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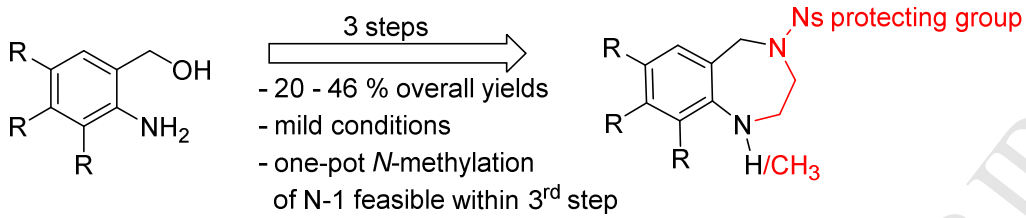

A new approach to monoprotected 1,4-benzodiazepines *via* a one-pot *N*-deprotection/reductive cyclization procedure

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Deprotection
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Abstract:

A novel approach to 2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepines starting from *N*-Boc-protected 2-aminobenzyl alcohols and *N*-nosyl-protected 2-aminoacetaldehyde dimethyl acetal is presented here. After connection of both building blocks under Mitsunobu conditions, a one-pot cyclization is accomplished with triethylsilane and trifluoroacetic acid. This conversion involves Boc deprotection and an intramolecular reductive N-alkylation. A consecutive methylation at N-1 can be accomplished by adding 1,3,5-trioxane to the reaction mixture. The resulting N4-monoprotected 1,4-benzodiazepines are versatile building blocks for the synthesis of variously substituted drug candidates.

1. Introduction

Lysine acetylation is a post-translational modification of DNA-binding proteins, which is involved in the regulation of chromatin structure. The *N*-acetylated lysines are docking sites for so-called bromodomains (epigenetic readers), which are small interaction modules found on diverse proteins. Inhibition of bromodomains has been investigated in the past few years intensively, since highly specific low-molecular inhibitors have the potential for opening new options for treatment of cancers, viral infections, inflammation and other diseases[1]. Numerous bromodomain inhibitors from different chemotypes (benzimidazoles, triazolothienodiazepines, benzodiazepines, benzotriazepines, isoxazoles, quinazolones, triazolophthalazines) have been published in the last decade.[1,2] Very recently, the benzoxazepine I-CBP112 (**A**) has been introduced as a novel inhibitor of CREBBP/p300 bromodomains.[2,3] A structure of I-CBP112 bound to CREBBP/p300 has been published (DOI: 10.2210/pdb4nr6/pdb) and reveals a number of interesting interactions with the *N*-acetyllysine binding pocket of the bromodomain. The *N*-propionyl moiety acts as a *N*-acetyllysine mimic forming a network of hydrogen bonds, further interactions of the aryl group at C-7 were detected. However, the role of the ring oxygen of the oxazepine ring for binding remains unexplored.

This prompted us to develop analogues of I-CBP112 (**A**) in which this ring oxygen is replaced by a nitrogen atom, ending up with 2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepines of type **B**.

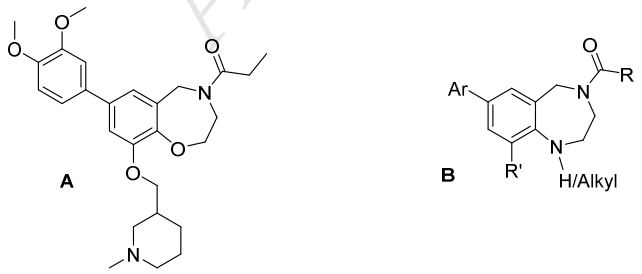

Figure 1: Structures of I-CBP112 (**A**) and the targeted 1,4-benzodiazepines (**B**).

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The 1,4-benzodiazepine scaffold has intensely been investigated over a number of decades, and has been assigned a "privileged scaffold" in drug development.[4,5] Depending on the degree of unsaturation of the diazepine ring and the substitution at both rings, compounds with a broad spectrum of pharmacological activities have been developed.[4] Consequently, a large number of approaches towards the 1,4-benzodiazepine ring system have been worked out in academia and pharmaceutical industry, for a comprehensive review, see ref. 5 & 6. Most of these approaches start from 2-aminobenzophenones (for 5-aryl-1,4-benzodiazepines) or anthranilic acid derivatives (for 5-unsubstituted 1,4-benzodiazepines).

For a short and flexible synthesis of 1,4-benzodiazepines of type **B** the following requirements had to be met: a) there has to be an option to obtain both a secondary or a tertiary amino function at N-1 (aromatic amine), b) there must be an option for introduction of various acyl groups at N-4 (aliphatic amino group), c) both C-2, C-3, and C-5 must be accessible as methylene units, and d) any steps in construction of the 1,4-benzodiazepine core had to be compatible with a broad spectrum of substituents (e.g. bromine at C-7 for introduction of the aryl residue by a Suzuki cross-coupling reaction) on the benzene ring.

A considerable number of sophisticated approaches to the 2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine ring system, including aziridine ring opening reactions[7], aminoalkylstannane-based routes[8], Pd-catalyzed cyclizations[9], metal-catalyzed hydrogen-transfer reactions[10], chlorosilane-promoted cyclizations of *N*,*O*-acetals[6] was not applicable here, since these protocols necessarily included undesired introduction of alkyl or aryl residues at either N-1, N-4, C-2 or C-3. Approaches starting from anthranilic or isatoic acid[11,12,13] through 1,4-benzodiazepine-2,5-diones or from 2-nitrobenzoic acids through 1,4-benzodiazepin-3,4-diones[14] typically require reduction of the dilactam moieties with lithium aluminum hydride or diborane under drastic conditions, and are poorly compatible with reducible residues at the benzene ring. An alternative approach starting from 2-nitrobenzaldehyde, requiring only mild reducing agents (potassium borohydride, zinc)[15], is hampered by the limited availability of substituted 2-nitrobenzaldehydes.

This prompted us to work out a novel approach to 2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepines of type **B**. In order to preserve flexibility concerning acyl substituents at N-4, we decided to introduce a readily removable protective group at N-4 first. This should enable us to introduce substituents at N-1 after completion of the ring system first (if necessary), and then remove the protective group at N-4, and introduce the acyl moiety here. Due to the higher nucleophilicity of N-4 (secondary aliphatic amine) compared to N-1 (secondary aromatic amine), selective functionalization of N-4 in presence of unsubstitited N-1 was not expected to be a challenge.[11]

We selected 2-aminobenzyl alcohols and *N*-(2,2-dimethoxyethyl)-2-nitrobenzenesulfonamide[16] (**1**) (Figure 2), all readily available, as starting materials. We selected the nosyl (2-nitrobenzenesulfonyl) protective group, since it is easier to remove than a tosyl group. The NH-acidic sulfonamide moiety of nosylamide **1** should allow construction of the prospective N-4/C-5 bond of the 1,4-benzodiazepine via Mitsunobu reaction with the alcohol moiety of the 2-aminobenzyl alcohol[17], and the acetal moiety of **1** was suitable for C-2/N-1 connection upon reductive amination with the primary aromatic amino group of the 2-aminobenzyl alcohol. For this final conversion the acetal group could either be hydrolized by aqueous acid to the corresponding aldehyde in a first step[18], or incorporated directly.

A couple of methods have been published for direct reductive amination of anilines with acetals, mostly using organosilanes in the presence[19,20,21] or absence[22] of trifluoroacetic acid.

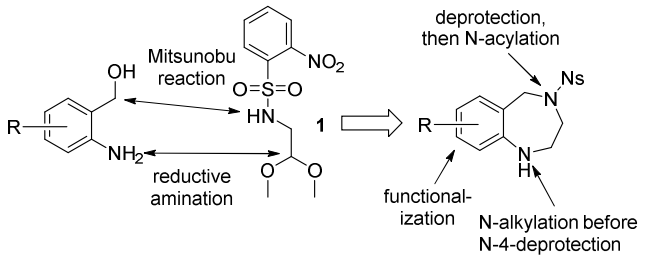
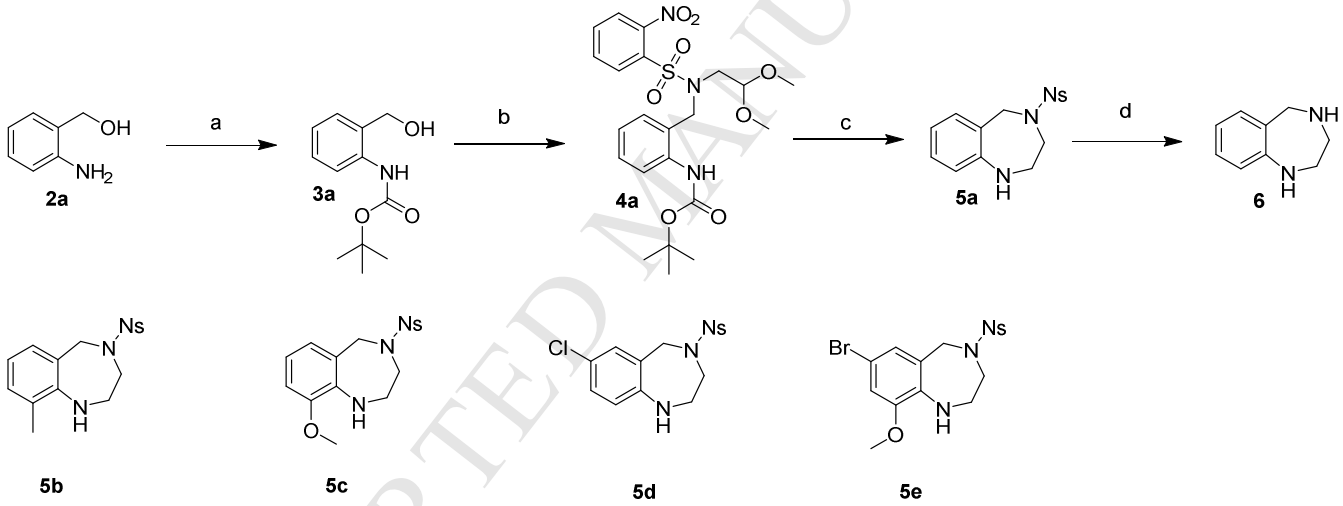


Figure 2: Strategy for construction and further functionalization of the 1,4-benzodiazepine ring system.

2. Results and Discussion

In a first approach we intended to perform a Mitsunobu coupling[23] of nosylamide **1** with unprotected 2-aminobenzyl alcohol (**2a**), but an inseparable mixture of products was obtained. So the amino function of **2a** was protected with the Boc group in almost quantitative yield[24,25]. With this new building block **3a** (Scheme 1) and after some experimentation an ultrasound-assisted[26] Mitsunobu reaction proceeded smoothly to give the desired product **4a** in 50% yield.

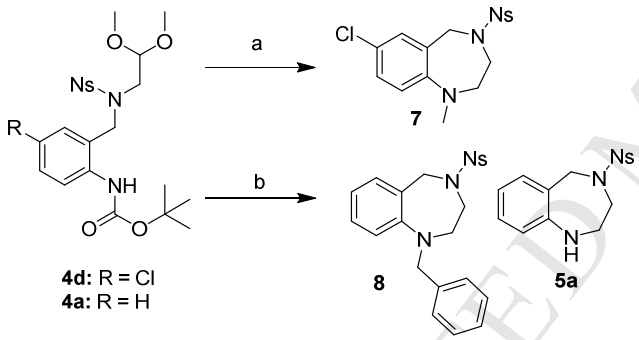


Scheme 1: Synthesis of the 1,4-benzodiazepines. (a) di-*tert*-butyl dicarbonate, THF, 40 °C; (b) PPh_3, DIAD, *N*-(2,2-dimethoxyethyl)-2-nitrobenzenesulfonamide, THF, RT; (c) TFA, Et_3SiH, DCM, RT; (d) thiophenol, K_2CO_3, MeCN, 50 °C.

The crucial step of this approach was the ring closure reaction. This required the removal of the *N*-Boc group and a reductive amination step. A three step protocol (deprotection with TFA, acetal hydrolysis with aqueous acid and spontaneous formation of the cyclic imine, reduction of the imine) has been reported for the construction of an annulated azepine[18]. Removal of the Boc protective group from **4a** under standard conditions (TFA/dichloromethane) gave the corresponding primary amine in disappointing isolated yield (<50%), so we decided to work out a one-pot procedure for deprotection and ring closure *via* reductive amination. Since Boc deprotection inevitably required strong acid, we selected a reduction protocol which also proceeds under acidic conditions. This brought us to the organosilane-trifluoroacetic acid couple, which is suitable for direct reductive amination of acetals[19,20,21]. In fact, treatment of intermediate **4a** with 2.5 equiv. of triethylsilane in a trifluoroacetic acid-dichloromethane mixture at ambient temperature gave the desired *N*-nosyl 1,4-benzodiazepine **5a** in 93% yield (overall yield over 3 steps: 46%). This clean conversion of the acetal to the 1,4-benzodiazepine was very pleasing, and we did not observe any evidence for a competing Pomeranz-

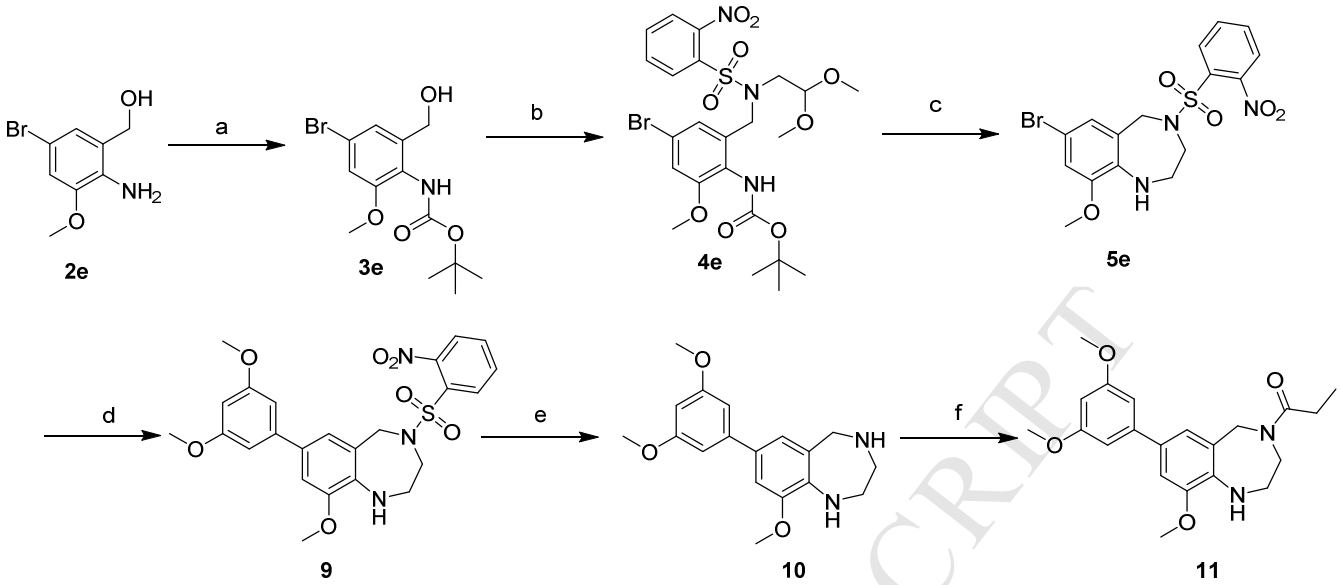
Fritsch-type cyclization[23,27] by acid-triggered electrophilic attack at C-3 of the aniline, which would eventually give 8-aminoisoquinoline.

Starting from ring-substituted 2-aminobenzyl alcohols **2b-e**, the corresponding 1,4-benzodiazepines **5b-e** bearing methyl, methoxy, chlorine, and bromine plus methoxy residues were obtained in the same manner. These monoprotected 1,4-benzodiazepines **5a-e** are versatile building blocks for further modification. Removal of the nosyl protective group from N-4 of **5a** was performed under standard conditions[17] with thiophenol and potassium carbonate to give the unsubstituted 1,4-benzodiazepine **6** (isolated as the hydrochloride). For *N*-methylation at N-1 of the monoprotected 1,4-benzodiazepines we worked out an extended one-pot protocol, utilizing the TTT system (triethylsilane, 1,3,5-trioxane, trifluoroacetic acid) we developed recently for the chemoselective *N*-methylation of aromatic amines[28]. Performing the deprotection/cyclization with triethylsilane in a trifluoroacetic acid-dichloromethane mixture for 24 hours as described above, followed by addition of 1,3,5-trioxane and additional triethylsilane gave the 1-methyl-4-nosyl-1,4-benzodiazepine **7** in 79% yield. We further intended to introduce benzyl residues at N-1 of intermediate **5a** in a similar one-pot procedure. The benzyl moiety was to be introduced using benzaldehyde, since related *N*-benzylations with 4-formylimidazole and triethylsilane-trifluoroacetic acid have been reported in literature.[29] Unfortunately, reductive cyclization of **4a**, followed by addition of benzaldehyde (and several portions of triethylsilane over considerable time) gave only 11% of the desired 1-benzyl-4-nosyl-1,4-benzodiazepine **8**, but 68% of non-benzylated product **5a** were isolated (Scheme 2). So the extended one-pot procedure seems not suitable for introduction of larger residues at N-1.



Scheme 2: Functionalization of 4-nosyl-1,4-benzodiazepines. (a) (i) TFA, Et_3SiH, DCM, RT; (ii) 1,3,5-trioxane, TFA, Et_3SiH, DCM, RT, 79 %; (b) (i) TFA, Et_3SiH, DCM, RT; (ii) benzaldehyde, TFA, Et_3SiH, DCM, RT, 11 % of **8** and 68 % of **5a**.

Having this new approach to substituted 1,4-benzodiazepines in hands, we prepared a 1,4-benzodiazepine analogue of the benzoxazepine-type CREBBP/p300 inhibitor I-CBP112 (**A**) (Figure 1). Introduction of the aryl residue at C-7 was to be performed with a Suzuki cross-coupling reaction, consequently the central intermediate **5e** of this synthesis contained a bromine substituent at C-7 (Scheme 3).



Scheme 3: Synthesis of the 1,4-benzodiazepine-type CREBBP/p300 inhibitor **11**. (a) di-*tert*-butyl dicarbonate, THF, 40 °C, 40 %; (b) PPh_3, DIAD, *N*-(2,2-dimethoxyethyl)-2-nitrobenzenesulfonamide, THF, RT, 36 %; (c) TFA, Et_3SiH, DCM, RT, 86 %; (d) 3,5-dimethoxyphenylboronic acid, $Pd(dppf)Cl_2$ * DCM, DIPEA, H_2O,1,4-dioxane, 95 °C, 68 %; (e) K_2CO_3, thiophenol, MeCN, 50 °C, 75 %; (f) propionyl chloride, DIPEA, DCM, 0 °C - RT, 56 %.

The appropriately substituted 2-aminobenzyl alcohol **2e** was prepared in two steps (bromination, reduction)[30] from commercial 2-amino-3-methoxybenzoic acid. Boc protection, subsequent Mitsunobu coupling with nosylamide **1**, and cyclization with triethylsilane-trifluoroacetic acid following the aforementioned protocol, gave 4-nosyl-1,4-benzodiazepine **5e** in 12% yield over three steps. Suzuki cross-coupling with 3,5-dimethoxybenzoic acid, followed by removal of the *N*-nosyl group with thiophenol gave the 7-aryl-1,4-benzodiazepine in good yield. Regioselective introduction of the propionyl residue at N-4 (and not at the aromatic amino group N-1)[11,12] to give amide **11** was easily accomplished with propionyl chloride.

Since testing of compound **11** on CREBBP/p300 bromodomains indicated that this compound is significantly less potent than its benzoxazepine analogue, no further effort was made to prepare additional 4-acyl-7-aryl-1,4-benzodiazepines for screening.

3. Conclusion

In conclusion, we have worked out a short and flexible approach to 2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepines starting from readily available building blocks, *N*-Boc-protected 2-aminobenzyl alcohols and *N*-nosyl-protected 2-aminoacetaldehyde dimethyl acetal. Due to the mild reaction conditions for both ring construction and deprotection a broad variety of substituents are tolerated. The resulting N4-monoprotected 1,4-benzodiazepines can be converted to advanced molecules via chemoselective functionalization at N-1 before N4-deprotection, and to 4-substituted products after N4-deprotection. Thus, this new approach provides an access to variously substituted drug candidates.

4. Experimental Section

General Procedures. Melting points were determined with a Büchi Melting Point B-540 and are uncorrected. IR spectra were recorded either with a Perkin Elmer FT-IR Spectrometer Paragon 1000 (oils as thin film on a NaCl plate or solids as KBr discs) or a JASCO FT-IR-4100 with ATR-PRO450S unit. ^{1}H and ^{13}C NMR spectra were recorded either with Avance III HD 400 MHz Bruker BioSpin or Avance III HD 500 MHz Bruker BioSpin spectrometers. Chemical shifts (δ) are given in ppm relative to TMS or residual undeuterated solvent, and coupling constants (*J*) are given in hertz (Hz). Splitting patterns are abbreviated as follows: s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublet; m = multiplet, br s = broad singlet. EI-Mass spectra were recorded at an ionization energy of 70eV either with a JMS GCmate II Jeol or a JEOL JMS-700 MStation. ESI-Mass spectra were recorded on a Thermo Finnigan LTQ FT at 4 kV. Purification by flash column chromatography (FCC) was performed using Silica Gel 60 from Merck KGaA.

***tert*-Butyl [2-({[*N*-(2,2-dimethoxyethyl)-2-nitrophenyl]sulfonamide}methyl)phenyl]carbamate (4a)**

To a vigorously stirred solution of 0.68 g (2.6 mmol) triphenylphosphine in 2.0 mL anhydrous THF under N_2 atmosphere, 0.48 mL (2.5 mmol) DIAD was added. When a homogenous white precipitate formed, 0.72 g (2.5 mmol) *N*-(2,2-dimethoxyethyl)-2-nitrobenzenesulfonamide[16] was added and the reaction mixture was treated in an ultrasonic bath. After 10 min a solution of 0.50 g (2.2 mmol) *tert*-butyl [2-(hydroxymethyl)phenyl]carbamate[24,25] in 0.5 mL anhydrous THF was added and the suspension was sonicated until a clear solution was obtained. The solvent was evaporated under reduced pressure and FCC with EtOAc and hexanes (1:3, Rf 0.3) followed by a second FCC with pure CH_2Cl_2 gave 0.65 g (1.3 mmol, 50 %) of **4a** as a colorless oil. IR (film): 3355, 3095, 2978, 2936, 1726, 1545, 1368, 1236, 1067, 1160 cm^{-1}. ^{1}H NMR (500 MHz, CD_2Cl_2) δ = 7.93 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.80 – 7.64 (m, 4H), 7.57 (br s, 1H), 7.28 (ddd, *J* = 8.5, 7.3, 1.7 Hz, 1H), 7.10 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.03 – 6.98 (m, 1H), 4.57 (s, 2H), 4.30 (t, *J* = 5.2 Hz, 1H), 3.31 (s, 6H), 3.27 (d, *J* = 5.2 Hz, 2H), 1.49 (s, 9H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ = 153.6, 148.4, 138.3, 134.3, 133.7, 132.3, 131.3, 129.5, 124.9, 124.7, 124.1, 122.8, 104.3, 80.5, 55.4, 49.4, 48.4, 28.5. MS (EI+): m/z calcd for ($C_{22}H_{29}N_3O_8S$) 495.1675, found 495.1669.

4-[(2-Nitrophenyl)sulfonyl]-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (5a)

To a solution of 0.50 g (1.0 mmol) **4a** in 2.0 mL CH_2Cl_2 under N_2 atmosphere, 1.0 mL trifluoroacetic acid and 0.40 mL (2.5 mmol) triethylsilane were added in rapid succession. After 24 h of stirring 2 M NaOH was added and the mixture extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. FCC with EtOAc and hexanes (1:2, Rf 0.3) gave 0.31 g (0.93 mmol, 93 %) of **5a** as a yellow solid. mp: 126 °C. IR (KBr): 3378, 3367, 3088, 3020, 2929, 1604, 1548, 1372, 1334, 1163, 766 cm^{-1}. ^{1}H NMR (500 MHz, CD_2Cl_2) δ = 7.91 – 7.85 (m, 1H), 7.70 – 7.62 (m, 1H), 7.65 – 7.55 (m, 2H), 7.20 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.12 (td, *J* = 7.6, 1.5 Hz, 1H), 6.87 (td, *J* = 7.4, 1.2 Hz, 1H), 6.73 (dd, *J* = 7.9, 1.2 Hz, 1H), 4.44 (s, 2H), 3.99 (br s, 1H), 3.64 – 3.58 (m, 2H), 3.25 – 3.19 (m, 2H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ = 150.0, 148.5, 133.9, 133.5, 132.0, 130.8, 130.4, 129.1, 128.0, 124.3, 121.3, 119.5, 52.8, 51.9, 48.8. MS (EI+): m/z calcd for ($C_{15}H_{15}N_3O_4S$) 333.0783, found 333.0782.

Yield over three steps: 46 %.

1-Benzyl-4-[(2-nitrophenyl)sulfonyl]-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (8)

To a solution of 0.15 g (0.30 mmol) **4a** in 0.6 mL CH_2Cl_2, 0.30 mL trifluoroacetic acid and 0.17 mL (1.1 mmol) triethylsilane were added in rapid succession and the resulting solution was stirred for 20 h at RT. Then 0.061 mL (0.61 mmol) benzaldehyde were added. After 1 d another equivalent of each benzaldehyde, TFA and TES were added. The reaction mixture was stirred for 2 d, then diluted with CH_2Cl_2 and washed with $NaHCO_3$. The phases were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine (1x 30 mL), dried over Na_2SO_4 and concentrated in vacuo. FCC with EtOAc and hexanes (1:4, Rf 0.2) gave 0.068 g (0.21 mmol, 68 %) of **5a** and 14 mg (33 µmol, 11 %) of **8** as a yellow oil. IR (KBr): 3028, 2920, 1599, 1543, 1495, 1371, 1357, 1163, 762. ^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.75 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.62 – 7.47 (m, 3H), 7.30 – 7.11 (m, 7H), 6.90 – 6.81 (m, 2H), 4.49 (s, 2H), 4.23 (s, 2H), 3.41 – 3.31 (m, 2H), 3.05 – 2.97 (m, 2H). ^{13}C NMR (101 MHz, CD_2Cl_2) δ = 150.9, 147.3, 138.0, 132.7, 132.2, 130.8, 129.7, 129.3, 128.3, 128.1, 127.7, 127.4, 126.4, 123.1, 120.7, 117.0, 56.9, 53.2, 52.9, 52.7, 52.4, 52.2, 52.1, 51.2, 48.9. MS (EI+): m/z calcd for ($C_{22}H_{21}N_3O_4S$) 423.1253, found 423.1252.

***tert*-Butyl [2-(hydroxymethyl)-6-methylphenyl]carbamate (3b)**

To a solution of 1.7 g (7.7 mmol) di-tert-butyl dicarbonate in 16 mL anhydrous THF under N_2 atmosphere, 0.96 g (7.0 mmol) commercial (2-amino-3-methylphenyl)methanol was added and the resulting solution was stirred at 40 °C for 2 d. The solvent was evaporated under reduced pressure and FCC with EtOAc and hexanes (1:5, Rf 0.2) gave 1.0 g (4.2 mmol, 55 %) of **3b** as a white solid. mp: 123 °C. IR (KBr): 3406, 3265, 2980, 1688, 1516, 1279, 1176, 1056, 773 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.29 (br s, 1H), 7.32 – 7.27 (m, 1H), 7.18 – 7.07 (m, 2H), 5.04 (t, *J* = 5.6 Hz, 1H), 4.45 (d, *J* = 5.6 Hz, 2H), 2.16 (s, 3H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 153.6, 139.7, 135.1, 133.0, 128.2, 126.1, 124.0, 78.3, 59.4, 28.1, 17.7. MS (EI+): m/z calcd for ($C_{13}H_{19}NO_3$) 237.1365, found 237.1356.

***tert*-Butyl [2-({[*N*-(2,2-dimethoxyethyl)-2-nitrophenyl]sulfonamide}methyl)-6-methylphenyl]carbamate (4b)**

To a vigorously stirred solution of 0.55 g (2.1 mmol) triphenylphosphine in 2.0 mL anhydrous THF under N_2 atmosphere, 0.41 mL (2.1 mmol) DIAD was added. When a homogenous white precipitate formed, 0.60 g (2.1 mmol) *N*-(2,2-dimethoxyethyl)-2-nitrobenzenesulfonamide[16] was added and the reaction mixture was treated in an ultrasonic bath. After 10 min 0.44 g (1.9 mmol) **3b** was added and the suspension was sonicated until a clear solution was obtained. The solvent was evaporated under reduced pressure and FCC with EtOAc and hexanes (1:1, Rf 0.5) followed by a second FCC with pure CH_2Cl_2 gave 0.61 g (1.2 mmol, 63 %) of **4b** as a colorless oil. IR (ATR): 3330, 3019, 2936, 1710, 1543, 1158 cm^{-1}. ^1H NMR (400 MHz, CD_2Cl_2) δ = 7.92 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.73 – 7.56 (m, 3H), 7.18 – 7.10 (m, 1H), 7.12 – 6.99 (m, 2H), 6.69 (br s, 1H), 4.61 (s, 2H), 4.31 (t, *J* = 5.2 Hz, 1H), 3.33 – 3.24 (m, 8H), 2.21 (s, 3H), 1.49 (s, 9H). ^{13}C NMR (101 MHz, CD_2Cl_2) δ = 154.0, 148.2, 137.0, 135.2, 134.1, 133.8, 132.7, 132.1, 131.2, 130.7, 127.3, 127.2, 124.5, 104.3, 80.2, 55.3, 49.4, 49.4, 28.4, 18.4. MS (ESI-): m/z calcd for $[(C_{23}H_{30}N_3O_8S)^-]$ 508.1759, found 508.1764.

9-Methyl-4-[(2-nitrophenyl)sulfonyl]-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (5b)

To a solution of 0.42 g (0.82 mmol) **4b** in 1.6 mL CH_2Cl_2 under N_2 atmosphere, 0.80 mL trifluoroacetic acid and 0.33 mL (2.1 mmol) triethylsilane were added in rapid succession. After 48 h 2 M NaOH was added and the mixture extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. FCC with EtOAc and hexanes (1:3, Rf 0.4) gave 0.17 g (0.43 mmol, 53 %) of **5b** as a yellow solid. mp: 149 °C. IR (KBr): 3406, 3087, 2905, 1732, 1535, 1371, 1160, 1026, 938 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 7.77 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.58 – 7.50 (m, 1H), 7.50 – 7.39 (m, 2H), 7.02 (dd, *J* = 7.4, 1.6 Hz, 1H), 6.94 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.70 (dd, *J* = 7.7, 7.4 Hz, 1H), 4.43 (s, 2H), 3.81 (br s, 1H), 3.61 – 3.56 (m, 2H), 3.25 – 3.18 (m, 2H), 2.05 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 148.2, 147.6, 133.4, 133.3, 131.4, 130.8, 130.3, 128.6, 126.8, 125.5, 123.8, 120.6, 52.4, 51.4, 47.7, 17.7. MS (ESI+): m/z calcd for $[(C_{16}H_{18}N_3O_4S)^+]$ 348.1013, found 348.1015.

Yield over three steps: 18 %.

***tert*-Butyl [2-(hydroxymethyl)-6-methoxyphenyl]carbamate (3c)**

To a solution of 1.3 g (5.9 mmol) di-tert-butyl dicarbonate in 12 mL anhydrous THF under N_2 atmosphere, 0.83 g (5.4 mmol) (2-amino-3-methoxyphenyl)methanol[31] was added and the resulting solution was stirred at 40 °C for 20 h. The solvent was evaporated under reduced pressure and FCC with EtOAc and hexanes (1:3, Rf 0.6) gave 0.79 g (3.1 mmol, 58 %) of **3c** as a white solid. mp: 112 °C. IR (ATR): 3463, 3361, 3274, 3016, 2924, 1686, 1531, 1158 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 7.18 – 7.12 (m, 1H), 7.04 (dd, *J* = 7.8, 1.3 Hz, 1H), 6.79 (dd, *J* = 8.3, 1.3 Hz, 1H), 6.52 (br s, 1H), 4.50 (d, *J* = 5.8 Hz, 2H), 4.14 (br. s, 1H), 3.77 (s, 3H), 1.49 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 155.8, 153.1, 137.9, 126.8, 124.0, 122.3, 110.0, 80.7, 61.8, 55.6, 28.1. MS (EI+): m/z calcd for $(C_{13}H_{19}NO_4)$ 253.1314, found 253.1327.

***tert*-Butyl [2-({[*N*-(2,2-dimethoxyethyl)-2-nitrophenyl]sulfonamide}methyl)-6-methoxyphenyl]carbamate (4c)**

To a vigorously stirred solution of 0.66 g (2.5 mmol) triphenylphosphine in 2.0 mL anhydrous THF under N_2 atmosphere, 0.51 mL (2.5 mmol) DIAD was added. When a homogenous white precipitate formed, 0.73 g (2.5 mmol) *N*-(2,2-dimethoxyethyl)-2-nitrobenzenesulfonamide[16] was added and the reaction mixture was treated in an ultrasonic bath. After 10 min a solution of 0.50 g (2.0 mmol) **3c** in 1.0 mL anhydrous THF was added and the suspension was sonicated until a clear solution was obtained. The solvent was evaporated under reduced pressure and FCC with EtOAc and hexanes (1:2, Rf 0.2) followed by a second FCC with pure CH_2Cl_2 gave 0.39 g (0.74 mmol, 37 %) of **4c** as a colorless oil. IR (ATR): 3011, 2936, 1718, 1543, 1366, 1160, 1068 cm^{-1}. ^1H NMR (400 MHz, CD_2Cl_2) δ = 7.97 – 7.91 (m, 1H), 7.71 – 7.57 (m, 3H), 7.11 (t, *J* = 8.1 Hz, 1H), 6.88 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.81 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.31 (br s, 1H), 4.64 (s, 2H), 4.32 (t, *J* = 5.3 Hz, 1H), 3.81 (s, 3H), 3.32 (d, *J* = 5.3 Hz, 2H), 3.22 (s, 6H), 1.48 (s, 9H). ^{13}C NMR (101 MHz, CD_2Cl_2) δ = 154.4, 154.3, 148.2, 134.1, 133.9, 133.8, 132.0, 131.2, 127.2, 125.3, 124.4, 120.5, 110.4, 103.7, 80.6, 56.2, 55.0, 49.6, 49.1, 28.4. MS (ESI-): m/z calcd for $[(C_{23}H_{30}{}^{35}ClN_3O_9S)^-]$ 524.1708, found 524.1707.

9-Methoxy-4-[(2-nitrophenyl)sulfonyl]-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (5c)

To a solution of 0.11 g (0.21 mmol) **4c** in 0.5 mL CH_2Cl_2 under N_2 atmosphere, 0.25 mL trifluoroacetic acid and 0.084 mL (0.53 mmol) triethylsilane were added in rapid succession. After 24 h 2 M NaOH was added and the mixture extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. FCC with EtOAc and hexanes (1:3, Rf 0.3) gave 0.065 g (0.18 mmol, 86 %) of **5c** as a yellow solid. mp: 132 °C. IR (ATR): 3361, 3013, 2920, 1532, 1158, 1074 cm^{-1}. ^1H NMR (500 MHz, CD_2Cl_2) δ = 7.85 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.69 – 7.54 (m, 3H), 6.91 – 6.68 (m, 3H), 4.74 (br s, 1H), 4.45 (s, 2H), 3.80 (s, 3H), 3.65 – 3.59 (m, 2H), 3.24 – 3.19 (m, 2H). ^{13}C NMR (126 MHz, CD_2Cl2) δ 149.6, 148.5, 139.6, 133.8, 133.5, 131.9, 130.8, 128.0, 124.2, 122.2, 120.4, 110.3, 56.2, 52.6, 52.0, 48.3. MS (ESI+): m/z calcd for $[(C_{16}H_{18}N_3O_5S)^+]$ 364.0962, found 364.0959.

Yield over three steps: 18 %.

***tert*-Butyl [4-chloro-2-(hydroxymethyl)phenyl]carbamate (3d)**

To a solution of 1.5 g (6.9 mmol) di-tert-butyl dicarbonate in 5 mL anhydrous THF under N_2 atmosphere, 1.0 g (6.3 mmol) commercial (2-amino-5-chlorophenyl)methanol was added and the resulting solution was stirred at 40 °C for 20

h. The solvent was evaporated under reduced pressure and FCC with EtOAc and hexanes (1:8, Rf 0.1) gave 0.84 g (3.3 mmol, 52 %) of **3d** as a white solid. mp: 89 °C. IR (ATR): 3423, 3354, 3006, 2984, 1694, 1515, 1163 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.85 (d, *J* = 8.8 Hz, 1H), 7.62 (br s, 1H), 7.25 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.14 (d, *J* = 2.5 Hz, 1H), 4.63 (d, *J* = 5.7 Hz, 2H), 2.31 (t, *J* = 5.7 Hz, 1H), 1.51 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 153.4, 136.7, 130.6, 129.0, 128.8, 128.1, 122.5, 81.0, 63.9, 28.5. MS (EI+): m/z calcd for ($C_{12}H_{16}{}^{35}ClNO_3$) 257.0819, found 257.0812.

***tert*-Butyl [4-chloro-2-({[*N*-(2,2-dimethoxyethyl)-2-nitrophenyl]sulfonamide}methyl)phenyl]carbamate (4d)**

To a vigorously stirred solution of 0.66 g (2.5 mmol) triphenylphosphine in 2.0 mL anhydrous THF under N_2 atmosphere, 0.51 mL (2.5 mmol) DIAD was added. When a homogenous white precipitate formed, 0.73 g (2.5 mmol) *N*-(2,2-dimethoxyethyl)-2-nitrobenzenesulfonamide[16] was added and the reaction mixture was treated in an ultrasonic bath. After 10 min a solution of 0.55 g (2.1 mmol) **3d** in 1.0 mL anhydrous THF was added and the suspension was sonicated until a clear solution was obtained. The solvent was evaporated under reduced pressure and FCC with EtOAc and hexanes (1:2, Rf 0.4) gave 0.46 g (0.86 mmol, 41 %) of **4d** as a colorless oil. IR (film): 3333, 2978, 1725, 1544, 1368, 1159 cm^{-1}. ^1H NMR (500 MHz, CD_2Cl_2) δ = 7.96 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.77 – 7.63 (m, 4H), 7.61 (br s, 1H), 7.21 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.97 (d, *J* = 2.5 Hz, 1H), 4.55 (s, 2H), 4.40 (t, *J* = 5.1 Hz, 1H), 3.38 (s, 6H), 3.32 (d, *J* = 5.1 Hz, 2H), 1.50 (s, 9H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ = 153.2, 147.8, 136.3, 133.9, 133.4, 131.8, 131.1, 130.5, 129.2, 128.7, 126.1, 124.4, 123.8, 104.3, 80.7, 55.3, 48.6, 48.1, 28.3. MS (ESI-): m/z calcd for ($C_{22}H_{27}{}^{35}ClN_3O_8S$) 528.1213, found 528.1218.

7-Chloro-4-[(2-nitrophenyl)sulfonyl]-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (5d)

To a solution of 0.15 g (0.28 mmol) **4d** in 0.50 mL CH_2Cl_2 under N_2 atmosphere, 0.25 mL trifluoroacetic acid and 0.11 mL (0.71 mmol) triethylsilane were added in rapid succession. After 24 h 2 M NaOH was added and the mixture extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. FCC with EtOAc and hexanes (1:1, Rf 0.3) followed by a second FCC with pure CH_2Cl_2 gave 0.099 g (0.27 mmol, 96 %) of **5d** as a yellow solid. mp: 141 °C. IR (ATR): 3408, 3097, 2930, 1531, 1495, 1352, 1126 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 7.96 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.72 – 7.56 (m, 3H), 7.21 (d, *J* = 2.4 Hz, 1H), 7.06 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.65 (d, *J* = 8.4 Hz, 1H), 4.39 (s, 2H), 3.91 (br s, 1H), 3.66 – 3.58 (m, 2H), 3.26 – 3.20 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 148.0, 148.0, 133.5, 133.2, 131.5, 130.8, 129.9, 129.2, 128.5, 125.9, 124.0, 120.5, 52.0, 51.3, 48.5. MS (ESI+): m/z calcd for [($C_{15}H_{15}{}^{35}ClN_3O_4S$)$^+$] 368.0466, found 368.0475.

Yield over three steps: 20 %.

2,3,4,5-Tetrahydro-1H-1,4-benzodiazepin-4-ium chloride (6)

To a solution of 0.20 g (0.60 mmol) **5a** in 1.5 mL acetonitrile were added 0.33 g (2.4 mmol) K_2CO_3 and 0.18 mL (1.8 mmol) thiophenol. The mixture was stirred at 50 °C for 24 h. Then 2 M NaOH was added. The mixture was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated, and the residue dissolved in methanol. A 4 M solution of HCl in 1,4-dioxane was added and the mixture cooled to -18 °C overnight. The obtained precipitate was washed with diethyl ether to give 67 mg (0.36 mmol, 61 %) of **6** as a white solid. mp: 233 °C. IR (KBr): 3433, 3057, 2926, 2617, 2074, 1977, 1416, 778 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ = 9.58 (s, 2H), 7.37 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.27 (td, *J* = 7.7, 1.5 Hz, 1H), 7.18 (d, *J* = 7.7 Hz, 1H), 7.03 – 6.97 (m, 1H), 4.28 – 4.20 (m, 2H), 3.35 – 3.26 (m, 4H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 147.6, 131.8, 129.6, 123.6, 122.3, 120.1, 49.1, 47.5, 44.0. MS (ESI+): m/z calcd for [($C_9H_{13}N_2$)$^+$] 149.1073, found 149.1073.

7-Chloro-1-methyl-4-[(2-nitrophenyl)sulfonyl]-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (7)

To a solution of 0.15 g (0.28 mmol) **4d** in 0.50 mL CH_2Cl_2 under N_2 atmosphere, 0.25 mL trifluoroacetic acid and 0.11 mL (0.71 mmol) triethylsilane were added in rapid succession. After 24 h further 0.33 mL (2.1 mmol) triethylsilane and 0.076 g trioxane (0.84 mmol) were added and stirred for further 24 h. 2 M NaOH was added and the mixture extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. FCC with EtOAc and hexanes (1:1, Rf 0.6) gave 0.081 g (0.21 mmol, 79 %) of **7** as a yellow oil. IR (ATR): 3009, 2860, 1737, 1546, 1494, 1355, 1165, 1084 cm^{-1}. ^1H NMR (400 MHz, CD_2Cl_2) δ = 7.80 – 7.74 (m, 1H), 7.62 – 7.56 (m, 1H), 7.54 – 7.48 (m, 2H), 7.14 – 7.06 (m, 2H), 6.69 (d, *J* = 8.4 Hz, 1H), 4.34 (s, 2H), 3.54 – 3.47 (m, 2H), 3.07 – 2.99 (m, 2H), 2.74 (s, 3H). ^{13}C NMR (101 MHz, CD_2Cl_2) δ = 151.2, 148.6, 134.2, 133.3, 132.1, 131.0, 130.2, 130.2, 128.9, 125.9, 124.4, 118.1, 56.7, 52.0, 50.0, 42.8. MS (ESI+): m/z calcd for [($C_{16}H_{17}{}^{35}ClN_3O_4S$)$^+$] 382.0623, found 382.0630.

***tert*-Butyl [4-bromo-2-(hydroxymethyl)-6-methoxyphenyl]carbamate (3e)**

To a solution of 2.3 g (11 mmol) di-tert-butyl dicarbonate in 20 mL anhydrous THF under N_2 atmosphere, 2.3 g (9.9 mmol) (2-amino-5-bromo-3-methoxyphenyl)methanol[30] was added and the resulting solution was stirred at 40 °C for 2 d. The solvent was evaporated under reduced pressure and FCC with EtOAc and hexanes (1:5, Rf 0.2) gave 1.6 g (4.8 mmol, 48 %) of **3e** as a white solid. mp: 136 °C. IR (KBr): 3462, 3327, 3009, 2981, 2944, 1695, 1509, 1275, 1164, 1043 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 7.20 (d, *J* = 2.1 Hz, 1H), 6.89 (d, *J* = 2.1 Hz, 1H), 6.19 (br s, 1H), 4.42 (s, 2H), 3.77 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (RT, 126 MHz, $CDCl_3$) δ = 155.8, 153.6, 139.3, 125.8, 123.5, 119.9, 113.7, 81.6, 61.8, 56.2, 28.3. MS (EI+): m/z calcd for ($C_{13}H_{18}{}^{79}BrNO_4$) 331.0419, found 331.0431.

***tert*-Butyl [4-bromo-2-({[*N*-(2,2-dimethoxyethyl)-2-nitrophenyl]sulfonamide}methyl)-6-methoxyphenyl]carbamate (4e)**

To a vigorously stirred solution of 0.55 g (2.1 mmol) triphenylphosphine in 2.0 mL anhydrous THF under N_2 atmosphere, 0.33 mL (1.7 mmol) DIAD was added. When a homogenous white precipitate formed, 0.48 g (1.7 mmol) *N*-(2,2-dimethoxyethyl)-2-nitrobenzenesulfonamide[16] was added and the reaction mixture was treated in an ultrasonic bath. After 10 min 0.50 g (1.5 mmol) **3e** was added and the suspension was sonicated until a clear solution was obtained. The solvent was evaporated under reduced pressure and FCC with EtOAc and hexanes (1:2, Rf 0.4) followed by a second FCC with pure CH_2Cl_2 gave 0.46 g (0.76 mmol, 36 %) of **4e** as a colorless oil. IR (film): 3095, 2936, 2837, 1720, 1544, 1368, 1161, 1070, 779 cm^{-1}. ^1H NMR (500 MHz, CD_2Cl_2) δ = 7.93 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.76 – 7.57 (m, 3H), 7.02 – 6.95 (m, 1H), 6.92 (d, *J* = 2.1 Hz, 1H), 6.26 (br s, 1H), 4.62 (s, 2H), 4.35 (t, *J* = 5.2 Hz, 1H), 3.80 (s, 3H), 3.35 (d, *J* = 5.2 Hz, 2H), 3.27 (s, 6H), 1.47 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 154.9, 154.3, 148.3, 135.7, 134.3, 134.0, 132.2, 131.3, 124.7, 124.7, 123.4, 120.3, 114.1, 104.2, 81.1, 56.7, 55.3, 50.4, 49.1, 28.5. MS (EI+): m/z calcd for ($C_{23}H_{30}{}^{79}BrN_3O_9S$) 603.0886, found 603.0881.

7-Bromo-9-methoxy-4-[(2-nitrophenyl)sulfonyl]-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (5e)

To a solution of 0.85 g (1.4 mmol) **4e** in 3.4 mL CH_2Cl_2 under N_2 atmosphere, 1.7 mL trifluoroacetic acid and 0.56 mL (3.5 mmol) triethylsilane were added in rapid succession. After 48 h 2 M NaOH was added and the mixture extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. FCC with EtOAc and hexanes (1:1, Rf 0.4) gave 0.51 g (1.2 mmol, 86 %) of **5e** as a yellow solid. mp: 68 °C. IR (KBr): 3420, 3092, 2936, 1629, 1542, 1488, 1372, 1341, 1162, 1029 cm^{-1}. ^1H NMR (500 MHz, CD_2Cl_2) δ = 7.89 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.71 – 7.57 (m, 3H), 6.97 (d, *J* = 2.1 Hz, 1H), 6.88 (d, *J* = 2.1 Hz, 1H), 4.70 (br s), 4.39 (s, 2H), 3.80 (s, 3H), 3.64 – 3.59 (m, 2H), 3.25 – 3.20 (m, 2H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ = 150.2, 148.4, 138.9, 134.0, 133.3, 132.0, 130.9, 129.1, 124.7, 124.3, 113.5, 111.7, 56.5, 52.0, 51.9, 48.2. MS (EI+): m/z calcd for ($C_{16}H_{16}{}^{79}BrN_3O_5S$) 440.9994, found 440.9998.

Yield over three steps: 15 %.

7-(3,5-Dimethoxyphenyl)-9-methoxy-4-[(2-nitrophenyl)sulfonyl]-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (9)

To a solution of 0.30 g (0.68 mmol) **5e**, 0.18 g (1.0 mmol) 3,5-dimethoxyphenylboronic acid, and 0.051 g (0.070 mmol) [1.1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) in a mixture of 1.0 mL H_2O and 4.0 mL 1,4-dioxane, were added 0.47 mL (2.8 mmol) DIPEA. The mixture was heated to 95 °C for 3.5 h. After cooling water was added and the mixture was extracted with CH_2Cl_2 three times. The combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. FCC with with EtOAc and hexanes (1:1, Rf 0.3) gave 0.22 g (0.44 mmol, 65 %) of **9** as a yellow oil. IR (ATR): 3380, 3004, 2934, 1589, 1544, 1463, 1342, 1158 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 7.93 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.67 – 7.50 (m, 3H), 7.07 (d, *J* = 1.9 Hz, 1H), 6.94 (d, *J* = 1.9 Hz, 1H), 6.68 (d, *J* = 2.2 Hz, 2H), 6.44 (t, J = 2.2 Hz, 1H), 4.75 (br s, 1H), 4.54 (s, 2H), 3.89 – 3.83 (m, 9H), 3.73 – 3.65 (m, 2H), 3.32 – 3.24 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 161.0, 149.1, 148.1, 143.2, 138.7, 133.3, 133.3, 133.2, 131.3, 130.8, 127.3, 123.9, 120.8, 108.7, 105.2, 98.6, 55.9, 55.5, 52.4, 51.5, 47.9. MS (ESI+): m/z calcd for [($C_{24}H_{26}N_3O_7S$)$^+$] 500.1486, found 500.1489.

7-(3,5-Dimethoxyphenyl)-9-methoxy-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (10)

To a solution of 0.32 g (0.64 mmol) **9** in 1.6 mL MeCN, 0.36 g (2.9 mmol) K_2CO_3 and 0.20 mL (1.9 mmol) thiophenol were added and the mixture was warmed under N_2 atmosphere to 50 °C for 12 h. The solvent was evaporated, and the residue dissolved in a mixture of EtOAc and 2 M NaOH. This mixture was extracted with EtOAc five times and the combined organic layers were concentrated in vacuo. FCC on a short column with CH_2Cl_2 with 1→10 % MeOH (Rf 0.1) gave 0.15 g (0.48 mmol, 75 %) of **10** as a colorless oil. IR (ATR): 3377, 2936, 2837, 1586, 1461, 1153 cm^{-1}. ^1H NMR (500 MHz, CD_2Cl_2) δ = 6.99 – 6.95 (m, 2H), 6.68 (d, *J* = 2.2 Hz, 2H), 6.40 (t, *J* = 2.2 Hz, 1H), 4.84 (br s, 1H), 3.93 (s, 2H), 3.89 (s, 3H), 3.82 (s, 6H), 3.15 – 3.09 (m, 2H), 3.09 – 3.02 (m, 2H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ = 161.5, 149.7, 143.7, 139.9, 132.8, 131.5, 121.0, 108.4, 105.2, 98.8, 56.4, 55.8, 54.2, 51.8, 50.0. MS (ESI+): m/z calcd for [($C_{18}H_{23}N_2O_3$)$^+$] 315.1703, found 315.1705.

1-[7-(3,5-Dimethoxyphenyl)-9-methoxy-1,2,3,5-tetrahydro-4*H*-1,4-benzodiazepin-4-yl]propan-1-one (11)

To a solution of 0.050 g (0.16 mmol) **10** in 1.0 mL CH_2Cl_2 under N_2 atmosphere was added 0.080 mL (0.47 mmol) DIPEA and the mixture was cooled to -78 °C. Then 0.014 mL (0.16 mmol) propionyl chloride were added. After warming to RT, 10 mL 2 M NaOH was added and the mixture was extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. FCC with EtOAc and hexanes (1:1, Rf 0.1) gave 0.030 g (0.09 mmol, 56 %) of **11** as a yellow oil. IR (ATR): 3384, 3000, 2937, 1639, 1585, 1461, 1154, 751 cm^{-1}. ^1H NMR (RT, mixture of rotamers, 500 MHz, $CDCl_3$) δ = 7.20 (d, *J* = 1.9 Hz, 0.3H), 6.99 – 6.93 (m, 1.7H), 6.70 (d, *J* = 2.2 Hz, 0.7H), 6.68 (d, *J* = 2.2 Hz, 1.3H), 6.44 (t, *J* = 2.2 Hz, 0.7H), 6.41 (t, *J* = 2.2 Hz, 0.3H), 4.90 – 4.77 (m, 1H), 4.64 (s, 0.7H), 4.51 (s, 1.3H), 3.92 – 3.82 (m, 10.3H), 3.76 – 3.69 (m, 0.7H), 3.29 – 3.19 (m, 2H), 2.46 (q, *J* = 7.4 Hz, 1.3H), 2.33 (q, *J* = 7.4 Hz, 0.7H), 1.16 – 1.07 (m, 3H). ^{13}C NMR (RT, 126 MHz, $CDCl_3$) δ = 173.2, 172.4, 161.1, 160.9, 149.4, 149.0, 143.4, 143.3, 138.8, 138.2, 133.1, 132.7, 128.8, 127.7, 121.5, 120.2, 108.6, 108.2,

105.3, 105.1, 98.8, 98.3, 56.0, 55.9, 55.5, 55.5, 52.3, 51.1, 49.3, 48.5, 48.1, 47.2, 27.0, 26.7, 9.3. MS (ESI+): m/z calcd for $[(C_{21}H_{27}N_2O_4)^+]$ 371.1965, found 371.1969.

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Supplementary Data

NMR-Spectra are available as supplementary data.

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