Asymmetric synthesis of *trans*-3,4-disubstituted tetrahydro-2-benzazepines

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Abstract

A convenient method for the synthesis of 3,4-disubstituted-2,3,4,5-tetrahydro-2-benz-azepines in high diastereoselective excess has been elaborated. The key steps are the highly stereoselective metallation/alkylation and nucleophilic 1,2-addition reaction on SAMP-hydrazones. Cyclomethylenation followed by N-N bond cleavage completes the synthesis of the titled compounds.

Keywords: Hydrazones, diastereoselective nucleophilic addition, diastereoselective alkylation, cyclization

Introduction

Compounds containing the benzazepine skeleton, mainly at the tetrahydro level have attracted the particular attention of medicinal chemists[1] because this ring system lies at the heart of a wide array of constitutionally diverse models exhibiting profound chemotherapeutic properties.[2] Benzo-annulated systems such as 2-benzazepines are indeed of special interest for the pharmaceutical industry since they have been found to be potent CNS agents[3] and specific ligands for serotonine and dopamine receptor sub-types[4] and to exhibit strong neuroleptic and neurotropic activities.[5] Compounds containing the 2-benzazepine skeleton have been also known to display potent broncho-relaxing activity,[6] to promote the healing of skin wounds[7] and are recommended for the treatment of stomach disorders.[8] The 2-benzazepine nucleus is also an integral part of many naturally occurring substances, namely those extracted from the *Amaryllidaceae*, which could be used in the treatment of schizophrenia and Alzheimer

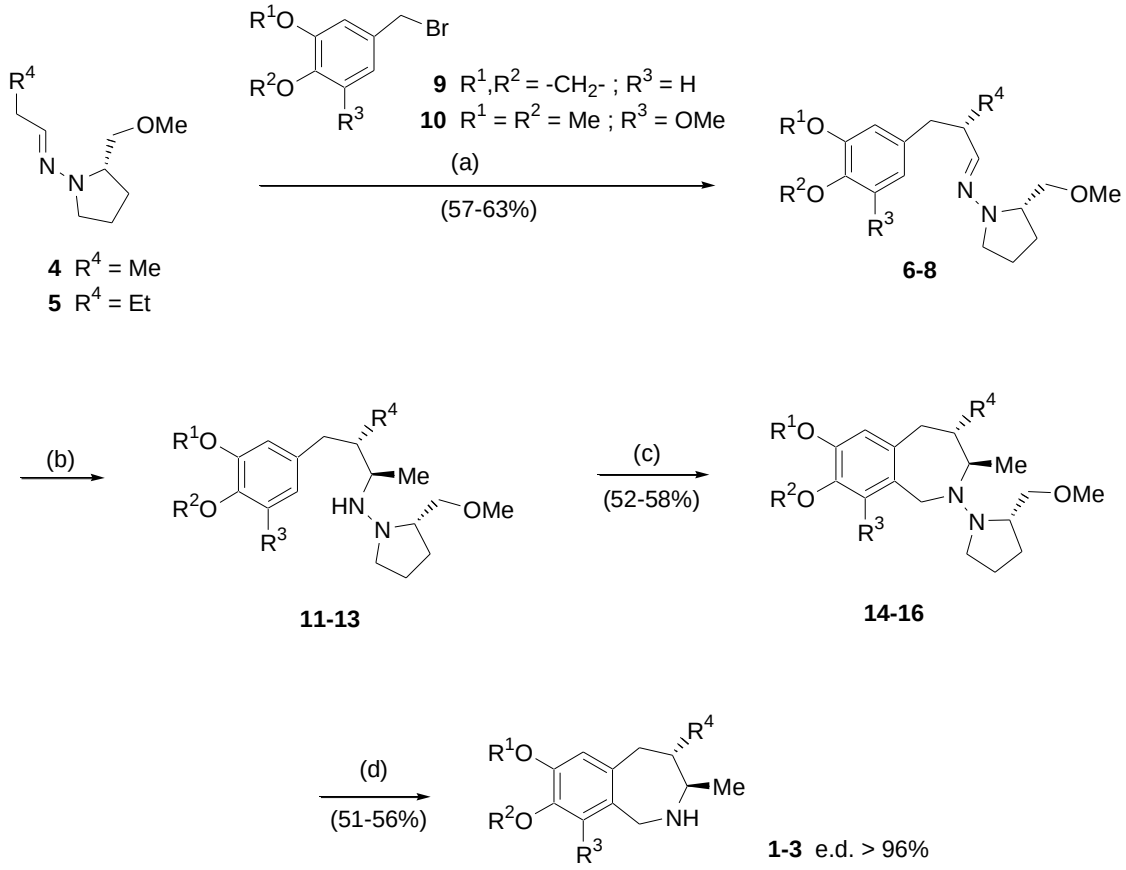
dementia.[9] Several synthetic strategies have been employed for the construction of 2-benzazepine ring systems based mainly on classical processes such as the Bischler-Napieralski[10] and Pictet-Spengler[11] reactions or miscellaneous methods such as intramolecular C-aryl coupling reaction[2] and ring expansion reactions applied to tetralones,[12] oxazepinones[13] and 1,2-dihydroisoquinolinones.[14] However their applicability is unsatisfactory mainly because of restricted choice for the substituents on the aromatic nucleus and on the azepine ring system as well. Furthermore none of these methods allows control of the stereogenic centers on the seven-membered azaheterocycle. Despite the great progress made in asymmetric synthesis in recent decades few flexible methods are indeed available for the assembly of substituted 2-benzazepines in high diastereoisomeric and enantiomeric excess.[15] Consequently the development of synthetic methodologies which may find great generality for constructing 2-benzazepine derivatives by stereoselective introduction of substituents at the carbon positions of azepine ring system, namely at C3 and C4 positions, constitutes an area of current interest.

Results and Discussion

In the present work we report a straightforward, feasible and highly stereoselective route to NH free 3,4-dialkylated-2,3,4,5-tetrahydro-2-benzazepines **1-3** using a proline derived chiral auxiliary. This new synthetic route which is depicted in Scheme 1 relies on combinations of the well established protocols for the α-alkylation and nucleophilic 1,2-addition of aldehyde SAMP-hydrazones[16] with a cyclomethylenation reaction followed by ultimate N-N bond cleavage.

The first stage of the synthesis was the elaboration of the diastereochemically pure SAMP-hydrazone precursors **4, 5**. These compounds were readily obtained by simply mixing the appropriate aliphatic aldehydes, i.e. propionaldehyde and butyraldehyde, with the enantiomerically pure hydrazine (*S*)-(–)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP). This condensation reaction delivered the desired chiral hydrazones **4, 5** with excellent yields (Table 1).

The next step was the assembly of the monosubstituted arylated hydrazones **6-8** allowing installation of the first stereogenic center at the β-position to the nitrogen atom, that is, at C4 in the final compounds **1-3**, one of the major synthetic tasks in the synthesis of the targeted compounds. For this purpose we envisaged taking advantage of the high level of diastereoselectivity observed upon the deprotonation/alkylation process α to the C=N bond of chiral hydrazones the so-called SAMP-RAMP methodology that have been elegantly developed by D. Enders.[16]



Scheme 1. Synthesis of target molecules **1-3**. *Reaction conditions* (a) LDA (1 equiv), benzyl bromide derivative **9** or **10**, THF, -90 ° then r.t., 12 h. (b) MeLi (3 equiv), THF, -78 °C then r.t., 3 h, then H_2O. (c) MOMCl (1 equiv), AcOH, reflux, 1 h. (d) BH_3 THF (10 equiv), THF, reflux, 48 h.

Table 1. Compounds prepared

R^1	R^2	R^3	R^4	Hydrazones (Yield %)	Benzazepine Derivatives (Yield %)	NH-Free Benzazepine Derivatives (Yield %)
-CH_2-		H	Me	(*S*,*S*)-**6** (63 %)	(*R*,*S*,*S*)-**14** (52 %)	(*R*,*S*)-**1** (56 %)
Me	Me	OMe	Me	(*S*,*S*)-**7** (57 %)	(*R*,*S*,*S*)-**15** (54 %)	(*R*,*S*)-**2** (51 %)
-CH_2-		H	Et	(*S*,*S*)-**8** (61 %)	(*R*,*S*,*S*)-**16** (58 %)	(*R*,*S*)-**3** (55 %)

Exposure of compounds **4, 5** to lithium diisopropylamide (LDA) followed by alkylation with diversely substituted benzyl bromides **9, 10** led to the diastereochemically enriched arylated

hydrazones (*S,S*)-**6-8** (Scheme 1, Table 1). These hydrazine precursors were essentially obtained as a single diastereoisomer detectable by NMR (de ≥ 96% after chromatographic treatment), a conclusive proof of the high selectivity of this metallation/alkylation process. The absolute configuration of the newly formed stereogenic center of the hydrazones **6-8** was assigned according to the previous results obtained in α-alkylation reaction of aldehyde SAMP-hydrazones.[16,17]

In the following step the second substituent was introduced by the nucleophilic 1,2-addition of an organometallic reagent to the C=N double bond. We surmised that the presence of the neighbouring stereogenic center in position α to the C=N bond in **6-8** could cooperatively increase the asymmetric induction originated by C2' in the pyrrolidine ring. Hydrazones **6-8** were then subsequently treated with excess MeLi (3 equiv) and reacted until consumption of the starting material.

Owing to the limited stability against oxidation usually exhibited by this type of hydrazines, compounds **11-13** were used in the next step without further purification. Interestingly we noticed that the efficiency of the nucleophilic 1,2-addition process was not significantly improved by employing the less basic and more nucleophilic organocerium derivative freshly prepared from $CeCl_3$ and MeLi following Imamoto's procedure[18] (Table 1).

Cyclomethylenation of the intermediate compounds **11-13** was performed by making use of chloromethylmethylether (MOMCl) in acetic acid to provide satisfactory yields of the cyclic hydrazides **14-16** (Scheme 1, Table 1).[19] This synthetic protocol offers several advantages over the standard Pictet-Spengler cyclization reaction. In particular it tolerates the presence of hydrazine units in the opened models and safeguards the regioselectivity of the annulation process. The *R* absolute configuration of the newly generated stereogenic center in **14-16** was assigned according to the previously confirmed mechanism for 1,2-addition to SAMP-hydrazones.[17,20] The desired tetrahydro-2-benzazepines were easily obtained after the N-N bond cleavage of hydrazines (*S,R,S*)-**14-16**. This was accomplished by treatment of compounds **14-16** with an excess of borane-tetrahydrofuran complex which triggered the release of chiral appendage to deliver rather satisfactory yields of the virtually diastereopure NH free *trans*-3,4-dialkylated-2,3,4,5-tetrahydro-2-benzazepines (*R,S*)-**1-3** (Scheme 1, Table 1) with de ≥ 96% after chromatographic treatment.

Conclusions

In summary we have developed a versatile and efficient asymmetric method for the highly diastereoselective synthesis of (*R,S*)-3,4-dialkylated-2,3,4,5-tetrahydro-2-benzazepines. The synthetic approach relies on the highly diastereoselective metallation/alkylation and nucleophilic1,2-addition procedures applied to enantio and diastereopure hydrazones respectively combined with a cyclomethylenation reaction to secure the formation of the diversely substituted azepine ring system.

Experimental Section

General. Tetrahydrofuran (THF) was pre-dried with anhydrous Na_2SO_4 and distilled over sodium benzophenone ketyl under Ar before use. CH_2Cl_2, Et_3N, and toluene were distilled from CaH_2. Dry glassware was obtained by oven drying and assembly under dry argon. The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. For flash chromatography, Merck silica gel 60 (40-63 μm; 230-400 mesh ASTM) was used. The melting points were obtained on a Reichert-Thermopan apparatus and are not corrected. Optical rotations were measured on a Perkin Elmer 343 polarimeter. Elemental analyses were obtained using a Carlo-Erba CHNS-11110 equipment. NMR spectra were recorded on a Bruker AM 300 (300 MHz and 75 MHz, for ^1H, and ^{13}C), $CDCl_3$ as solvent, TMS as internal standard.

Starting materials

Hydrazones **4** and **5** were prepared according to an already reported procedure.[21] Benzyl bromide derivatives **9**[22] and **10**[23] were synthesized following the literature methods.

Alkylation of the SAMP-hydrazones 4 and 5. General procedure

A solution of *n*-BuLi (4.42 mL, 7.08 mmol, 1.6 M solution in hexanes) was added dropwise to a stirred solution of diisopropylamine (715 mg, 1.0 mL, 7.08 mmol) in dry THF (5 mL) at 0 °C under Ar. The mixture was stirred for 15 min at 0 °C then cooled to -78 °C. A solution of the appropriate hydrazone **4** or **5** (7.08 mmol) in THF (5 mL) was slowly added and the mixture was stirred at -78 °C for 45 min. The mixture was allowed to warm to 0 °C and stirred for an additional 1 h at 0 °C. The mixture was recooled to -90 °C and a solution of the appropriate alkyl halide **9** or **10** (7.1 mmol) in dry THF (5 mL) was added dropwise. After stirring for 1 h at -90 °C, the temperature was allowed to rise to r.t. and stirring was maintained overnight. The mixture was then quenched with aqueous sat $NaHCO_3$ solution (20 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), and then dried over $MgSO_4$, concentrated. Purification by flash column chromatography on silica gel (ethyl acetate/hexanes, 30:70, as eluent) delivered the alkylated hydrazones **6-8** as pale yellow oil.

***N*-[(*S*)-3-Benzo[1,3]dioxol-5-yl-2-methylpropylidene]-[(*S*)-2-methoxymethylpyrrolidin-1-yl]amine (6).** 1.36g (63%); $[\alpha]_D^{25}$ = -42.4 (*c* 1.22, $CHCl_3$) {lit.[24] $[\alpha]_D^{24}$ = -44.7 (*c* 1.27, $CHCl_3$)}; ^1H NMR ($CDCl_3$): δ 0.99 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.67-2.01 (m, 4 H, 2 × CH_2), 2.44 (dd, *J* = 7.9, 12.9 Hz, 1 H, $ArCH_2$), 2.49-2.68 (m, 2 H: 1 H, CHMe + 1 H, NCH_2), 2.75 (dd, *J* = 7.1, 13.0 Hz, 1 H $ArCH_2$), 3.22-3.45 (m, 3 H: 1 H, OCH_2 + 1 H, NCH_2 + 1 H, NCH), 3.34 (s, 3 H, OCH_3), 3.52 (dd, *J* = 3.7, 8.9 Hz, 1 H, OCH_2), 5.87 (s, 2 H, OCH_2O), 6.50 (d, *J* = 5.7 Hz, 1 H, CH=N), 6.56-6.79 (m, 3 H, $H_{arom.}$) ppm; ^{13}C NMR ($CDCl_3$): δ 18.3 (CH_3), 22.1 (CH_2), 26.4 (CH_2), 38.8 (CH), 41.4 ($ArCH_2$), 50.3 (NCH_2), 59.1 (OCH_3), 63.4 (CH), 74.8 (CH_2O), 100.7 (OCH_2O), 107.9 (CH), 109.6 (CH), 122.0 (CH), 134.1 (C), 142.4 (CH=N), 145.6 (C), 147.4 (C) ppm.

[(*S*)-2-Methoxymethylpyrrolidin-1-yl]-*N*-[(*S*)-2-methyl-3-(3,4,5-trimethoxyphenyl)propylidene]amine (7).1.41g (57%); $[\alpha]_D^{25}$ -78.2(*c* 0.87, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.87 (d, *J* = 7.3 Hz, 3 H, CH_3), 1.63-2.02 (m, 4 H, 2 × CH_2), 2.49 (dd, *J* = 8.2, 13.2 Hz, 1 H, $ArCH_2$), 2.59-2.73 (m, 2 H: 1 H, CHMe + 1 H, NCH_2), 2.82 (dd, *J* = 6.3, 13.1 Hz, 1 H, $ArCH_2$), 3.30-3.48 (m, 3 H: 1 H, OCH_2 + 1 H NCH_2 + CH), 3.37 (s, 3 H, OCH_3), 3.56 (dd, 1 H, *J* = 3.7, 8.8 Hz, OCH_2), 3.82 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 6.40 (s, 2 H, H_{arom}), 6.55 (d, *J* = 6.0 Hz, 1 H, CH=N) ppm; ^{13}C NMR ($CDCl_3$): δ 18.5 (CH_3), 22.1 (CH_2), 26.6 (CH_2), 38.7 (CH), 42.1 ($ArCH_2$), 50.4 (NCH_2), 56.0 (2 × OCH_3), 59.2 (OCH_3), 60.9 (OCH_3), 63.5 (CH), 74.8 (CH_2O), 105.8 (CH), 106.0 (CH), 136.2 (2 × C), 142.7 (CH=N), 152.9 (2 × C) ppm. Anal. Calcd for $C_{19}H_{30}N_2O_4$: C, 65.12; H, 8.63; N, 7.99%. Found: C, 65.34; H, 8.49; N, 8.12%.

***N*-[(*S*)-2-Benzo[1,3]dioxol-5-ylmethylbutylidene]-(*S*)-2-methoxymethylpyrrolidin-1-amine (8).** 1.37g (61%); $[\alpha]_D^{25}$ -14.9 (*c* 1.39, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.89 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.31-1.55 (m, 2 H, CH_2), 1.73-1.99 (m, 4 H, 2 × CH_2), 2.31-2.46 (m, 1 H, $ArCH_2$), 2.55-2.77 (m, 3 H: 1 H, $ArCH_2$ + 1 H, CHMe + 1 H, NCH_2), 3.26-3.44 (m, 3 H: 1 H, OCH_2 + 1 H, NCH_2 + 1 H, CH), 3.36 (s, 3 H, OCH_3), 3.54 (dd, *J* = 3.5, 9.1 Hz, 1 H, OCH_2 , 5.91 (s, 2 H, OCH_2O), 6.47 (d, *J* = 6.7 Hz, 1 H, CH=N), 6.61 (dd, *J* = 1.6, 7.9 Hz, 1 H, H_{arom}), 6.64-6.73 (m, 2 H, H_{arom}) ppm; ^{13}C NMR ($CDCl_3$): δ 11.5 (CH_3), 22.1 (CH_2), 25.8 (CH_2), 26.5 (CH_2), 39.5 ($ArCH_2$), 45.7 (CH), 50.5 (NCH_2), 59.2 (OCH_3), 63.4 (CH), 74.7 (CH_2O), 100.7 (OCH_2O), 107.9 (CH), 109.7 (CH), 122.1 (CH), 134.2 (C), 142.1 (CH=N), 145.5 (C), 147.3 (C) ppm. Anal. Calcd for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80%. Found: C, 67.85; H, 8.49; N, 8.61%.

Synthesis of 3,4-disubstituted-2,3,4,5-tetrahydro-2-benzazepines (14-16). General procedure

Methyllithium (6.0 mmol, 3.75 mL, 1.6 M solution in diethyl ether) was added dropwise to a stirred solution of the appropriate hydrazone (**6-8**, 2.0 mmol) in THF (10 mL) at -78 °C under Ar. The mixture was then slowly allowed to warm to r.t. and stirred for 3 h. Water (10 mL) was added and the mixture was extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried ($MgSO_4$). Evaporation of the solvent afforded the corresponding crude hydrazine **11-13** as brown oil, which was used without further purification in the next step.

MOMCl (161 mg, 0.15 mL, 2.0 mmol) was added to a stirred solution of crude hydrazine (**11-13**, 2.0 mmol) in glacial acetic acid (10 mL) under Ar. The mixture was then refluxed for 1 h and stirring at r.t. was maintained for 1 h. The mixture was poured onto crushed ice and neutralized with 50% aqueous NaOH, then extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$). Evaporation of the solvent under vacuum afforded an oily residue, which was purified by flash column chromatography on silica gel (acetone/hexanes, 20:80, as eluent) to yield 2-benzazepines **14-16** as yellow oil.

(7*R*,8*S*)-6-[(*S*)-2-Methoxymethylpyrrolidin-1-yl]-7,8-dimethyl-6,7,8,9-tetrahydro-5*H*-[1,3]dioxolo[4,5-*h*][2]benzazepine (14). 346 mg (52 %); $[\alpha]_D^{25}$ -72.2 (*c* 0.49, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.02 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.21 (d, *J* = 6.1 Hz, 3 H, CH_3), 1.45-1.93 (m, 5 H: 4 H, 2 × CH_2 + 1 H, $ArCH_2C\underline{H}$), 2.50-2.67 (m, 2 H: 1 H, CH + 1 H, $ArCH_2$), 2.68-2.82 (m, 2 H: 1 H, NCH_2 + 1 H, $ArCH_2$), 2.83-2.93 (m, 1 H, CH), 2.94-3.05 (m, 1 H, NCH_2), 3.13 (t, *J* = 8.3 Hz, 1 H, CH_2O), 3.30 (s, 3 H, OCH_3), 3.49 (dd, *J* = 2.8, 8.8 Hz, 1 H, CH_2O), 3.68-3.83 (m, 2 H, $ArCH_2N$), 5.90 (s, 2 H, OCH_2O), 6.60 (s, 1 H, H_{arom}), 6.66 (s, 1 H, H_{arom}) ppm; ^{13}C NMR ($CDCl_3$): δ 19.0 (CH_3), 21.9 (CH_3), 22.0 (CH_2), 26.8 (CH_2), 40.0 (CH), 41.4 ($ArCH_2$), 42.5 (NCH_2), 54.0 ($ArCH_2N$), 59.0 (CH), 59.6 (OCH_3), 66.8 (NCH), 75.8 (CH_2O), 100.7 (OCH_2O), 108.6 (CH), 109.6 (CH), 133.3 (C), 134.6 (C), 144.2 (C), 146.4 (C) ppm. Anal. Calcd. for $C_{19}H_{28}N_2O_3$: C, 68.65; H, 8.49; N, 8.43%. Found: C, 68.82; H, 8.41; N, 8.56%.

(3*R*,4*S*)-7,8,9-Trimethoxy-2-[(*S*)-2-methoxymethylpyrrolidin-1-yl]-3,4-dimethyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine (15). 409 mg (54%); $[\alpha]_D^{25}$ -44.8 (*c* 1.97, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.02 (d, *J* = 6.9 Hz, 3 H, CH_3), 1.19 (d, *J* = 6.1 Hz, 3 H, CH_3), 1.49-1.93 (m, 5 H: 4 H, 2 × CH_2 + 1 H, $ArCH_2C\underline{H}$), 2.49-2.67 (m, 2 H: 1 H, CH + 1 H, $ArCH_2$), 2.70-2.95 (m, 3 H: 1 H, NCH_2 + 1 H, $ArCH_2$ + 1 H, CH), 3.07-3.18 (m, 2 H: 1 H, NCH_2 + 1 H, CH_2O), 3.27 (s, 3 H, OCH_3), 3.50 (dd, *J* = 2.3, 9.3 Hz, 1 H, CH_2O), 3.78-3.97 (m, 1 H, $ArCH_2N$), 3.83 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 4.27 (d, *J* = 14.2 Hz, 1 H, $ArCH_2N$), 6.42 (s, 1 H, H_{arom}) ppm; ^{13}C NMR ($CDCl_3$): δ 19.4 (CH_3), 21.9 (CH_2), 22.2 (CH_3), 26.9 (CH_2), 39.8 (CH), 41.9 ($ArCH_2$), 42.1 (NCH_2), 45.8 ($ArCH_2N$), 55.9 (OCH_3), 58.9 (OCH_3), 59.1 (OCH_3), 60.7 (CH), 61.0 (OCH_3), 67.3 (NCH), 75.9 (CH_2O), 108.2 (CH), 125.4 (C), 136.9 (C), 137.4 (C), 150.5 (C), 151.4 (C) ppm. Anal.Calcd.for $C_{21}H_{34}N_2O_4$: C, 66.64; H, 9.05; N, 7.40%. Found: C, 66.48; H, 8.83; N, 7.49%.

(7*R*,8*S*)-8-Ethyl-6-[(*S*)-2-methoxymethylpyrrolidin-1-yl]-7-methyl-6,7,8,9-tetrahydro-5*H*-[1,3]dioxolo[4,5-*h*][2]benzazepine (16). 402 mg (58%); $[\alpha]_D^{25}$ -36.8 (*c* 0.61, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.85 (t, *J* = 6.6 Hz, 3 H, CH_3), 1.17 (d, *J* = 6.1 Hz, 3 H, CH_3), 1.29-1.93 (m, 7 H: 4 H, 2 × CH_2 + 2 H, CH_2 + 1 H, $ArCH_2C\underline{H}$), 2.47-2.63 (m, 2 H: 1 H, CH + 1 H, $ArCH_2$), 2.66-2.81 (m, 2 H: 1 H, NCH_2 + 1 H, $ArCH_2$), 2.82-2.91 (m, 1 H, CH), 2.93-3.02 (m, 1 H, NCH_2), 3.11 (t, *J* = 8.3 Hz, 1 H, CH_2O), 3.31 (s, 3 H, OCH_3), 3.48 (dd, *J* = 2.9, 8.7 Hz, 1 H, CH_2O), 3.67-3.84 (m, 2 H, $ArCH_2N$), 5.91 (s, 2 H, OCH_2O), 6.62 (s, 1 H, H_{arom}), 6.69 (s, 1 H, H_{arom}) ppm; ^{13}C NMR ($CDCl_3$): δ 11.5 (CH_3), 18.8 (CH_3), 21.8 (CH_2), 26.3 (CH_2), 27.1 (CH_2), 35.8 ($ArCH_2$), 44.1 (NCH_2), 46.0 (CH), 54.1 ($ArCH_2N$), 59.0 (OCH_3), 59.5 (CH), 61.4 (NCH), 75.7 (CH_2O), 100.6 (OCH_2O), 108.1 (CH), 110.1 (CH), 133.4 (2 × C), 144.2 (C), 146.4 (C) ppm.
Anal. Calcd. for $C_{20}H_{30}N_2O_3$: C, 69.33; H, 8.73; N, 8.09%. Found: C, 69.61; H, 8.95; N, 8.26%.

Removal of the chiral appendage. General procedure for synthesis of 3,4-disubstituted-2,3,4,5-tetrahydro-2-benzazepines (1-3)

Boran-tetrahydrofuran complex (BH_3·THF, 10 mL, 10 mmol, 1 M solution in THF) was slowly added to an ice-cooled stirred solution of benzazepine (**14-16**, 1.0 mmol) in dry THF (5 mL) under Ar and the resulting mixture was refluxed for 48 h. The mixture was concentrated under

reduced pressure, then made basic by addition of 10% aqueous NaOH (10 mL) and refluxed for 3 h. The combined organic layers were dried ($MgSO_4$), concentrated under vacuum and the residual colorless oil was purified by flash column chromatography on silica gel (acetone/MeOH, 90:1 as eluent) to afford the expected benzazepine **1-3**.

(7*R*,8*S*)-7,8-Dimethyl-6,7,8,9-tetrahydro-5*H*-1,3-dioxa-6-azacyclohepta[*f*]indene (1). 123 mg (56%); $[\alpha]_D^{25}$ -49.2 (*c* 0.82, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.00 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.18 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.26-1.47 (m, 1 H, $ArCH_2CH$), 2.47-2.77 (m, 3 H: 1 H, NH + 1 H, CH + 1 H, $ArCH_2$), 2.86 (dd, *J* = 4.0, 10.4 Hz, 1 H, $ArCH_2$), 3.82 (d, J_{AB} = 14.6 Hz, 1 H, $ArCH_2N$), 3.94 (d, J_{AB} = 14.6 Hz, 1 H, $ArCH_2N$), 5.90 (s, 2 H, OCH_2O), 6.64 (s, 1 H, H_{arom}), 6.67 (s, 1 H, H_{arom}) ppm; ^{13}C NMR ($CDCl_3$): δ 21.0 (CH_3), 21.9 (CH_3), 40.4 (CH), 43.0 ($ArCH_2$), 52.3 ($ArCH_2N$), 63.5 (NCH), 100.7 (OCH_2O), 108.7 (CH), 110.3 (CH), 134.9 (C), 135.0 (C), 144.8 (C), 145.1 (C) ppm. Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39%. Found: C, 70.96; H, 7.65; N, 6.58%.

(3*R*,4*S*)-7,8,9-Trimethoxy-3,4-dimethyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine (2). 135 mg (51%;); $[\alpha]_D^{25}$ -19.5 (*c* 2.38, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.94 (d, *J* = 6.9 Hz, 3 H, CH_3), 1.11 (d, *J* = 6.3 Hz, 3 H, CH_3), 1.33-1.47 (m, 1 H, $ArCH_2CH$), 2.46-2.71 (m, 3 H: 1 H, NH + 1 H, CH + 1 H, $ArCH_2$), 2.80 (dd, *J* = 4.1, 10.4 Hz, 1 H, $ArCH_2$), 3.59 (d, J_{AB} = 14.8 Hz, 1 H, $ArCH_2N$), 3.74 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 4.30 (d, *J* = 14.8 Hz, 1 H, $ArCH_2N$), 6.43 (s, 1 H, H_{arom}) ppm; ^{13}C NMR ($CDCl_3$): δ 20.9 (CH_3), 21.5 (CH_3), 39.8 (CH), 43.4 (CH_2), 43.5 (CH_2), 56.0 (OCH_3), 60.8 (OCH_3), 61.6 (OCH_3), 63.5 (NCH), 109.2 (CH), 136.6 (C), 137.4 (C), 140.2 (C), 150.7 (C), 151.7 (C) ppm. Anal. Calcd. for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28%. Found: C, 67.99; H, 8.98; N, 5.35%.

(7*R*,8*S*)-8-Ethyl-7-methyl-6,7,8,9-tetrahydro-5*H*-1,3-dioxa-6-azacyclohepta[*f*]indene (3). 128 mg, (55%); $[\alpha]_D^{25}$ -35.5 (*c* 0.37, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.88 (t, *J* = 6.7 Hz, 3 H, CH_3), 1.09 (d, *J* = 6.3 Hz, 3 H, CH_3), 1.21-1.49 (m, 3 H: 2 H, CH_2 + 1 H, $ArCH_2CH$), 2.43-2.75 (m, 3 H: 1 H, NH + 1 H, CH + 1 H, $ArCH_2$), 2.81 (dd, *J* = 4.0, 10.4 Hz, 1 H, $ArCH_2$), 3.81 (d, J_{AB} = 14.5 Hz, 1 H, $ArCH_2N$), 3.93 (d, J_{AB} = 14.5 Hz, 1 H, $ArCH_2N$), 5.91 (s, 2 H, OCH_2O), 6.66 (s, 1 H, H_{arom}), 6.69 (s, 1 H, H_{arom}) ppm; ^{13}C NMR ($CDCl_3$): δ 13.2 (CH_3), 21.0 (CH_3), 22.7 (CH_2), 39.1 (CH), 42.8 ($ArCH_2$), 51.9 ($ArCH_2N$), 63.1 (NCH), 100.9 (OCH_2O), 106.9 (CH), 109.7 (CH), 134.7 (C), 135.3 (C), 144.9 (C), 145.2 (C) ppm. Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00%. Found: C, 72.28; H, 8.05; N, 6.24%.

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