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Asymmetric synthesis of 3- or 4-alkyl or arylbenzo[*c*]azepines

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ABSTRACT

Two flexible routes for the stereoselective synthesis of a variety of 3- or 4-alkylated or arylated tetrahydrobenzazepines have been developed. The key steps are the highly diastereoselective metallation/alkylation reaction and 1,2-addition processes applied to stereopure SAMP hydrazones combined with a cyclomethylenation reaction.

1. Introduction

Benzazepines play an important role in heterocyclic chemistry because this ring system lies at the heart of a great variety of poly and diversely functionalized models endowed with profound chemotherapeutic properties.[1] Thus compounds containing the benzazepine skeleton, mainly at the tetrahydro level, display important physiological properties and are known to exhibit strong neuroleptic and neurotropic activities.[2] Some representatives have been found to display anti-HIV activity,[3] to promote healing of skin wounds[4] and to treat cardiovascular diseases, especially glaucoma and hypertension.[5] Compounds of this class are also used as antiarrythmic[6] and CNS agents,[7] as inhibitors of PNMT[8] and are recommended for the treatment of stomach disorders.[9] Finally the benzazepine nucleus represents the main structural unit of many naturally occurring molecules, namely those extracted from *Cephalotaxus Harringtonia*, *Papaveraceae* and the *Amaryllidaceae* alkaloids which could be used in the treatment of Alzheimer's disease,[10] the most common cause of elderly dementia. Due to the diverse biological activities of many of their derivatives the chemistry of 2-benzazepines has been the focus of new synthetic methodologies during the past decades[1] and organic chemists have at their disposal a great number of synthetic methods for the preparation of these azaheterobicyclic compounds.

Synthetic routes to the construction of these compounds can be cursorily classified into two main categories which mainly differ in the nature of the bond formed in the ultimate step. Thus the formation of the C–N bond a or b (Fig. 1) can be secured by cyclization of suitably *ortho*-disubstituted benzenes whereas the seven-membered heterocyclic ring has been accessed by creation of the c or d bond through intramolecular C-aryl coupling reactions.[1] Alternatively these compounds have also been obtained by a number of ring expansion methods applied to tetralones (Schmidt rearrangement),[11] oxazepinones,[12] benzopyranones[13] and by a cyclopropanation/ring enlargement of 1,2-dihydroisoquinolones.[14] All of these methods are simple but have been claimed to proceed with the varying degrees of success. Furthermore their applicability is unsatisfactory mainly because of restrictions in the choice of substituents, namely in their nature and position on the azepine ring system. Finally none of the annulation techniques allows control of stereogenic centres on the seven-membered azaheterocyclic unit. Despite the great progress made in asymmetric synthesis in recent decades few flexible methods are indeed available for the asymmetric synthesis of alkylated or arylated benzazepines in high enantiomeric excess. To our knowledge the 1-alkyl derivatives have been obtained by metallation/alkylation of chiral benzazepine formamidines[15] but this method could not be extended to the asymmetric synthesis of the 3- and 4-substituted analogues. Therefore the development of synthetic methodologies which may find generality for constructing a variety of benzo[*c*]azepines with alkyl or aryl appendages at C3 or C4 in a stereo and enantioselective manner constitutes an area of current interest.

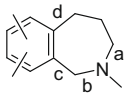

Figure 1.

2. Results and discussion

Herein we report on a straightforward, feasible and highly stereoselective route to 4- or 3-alkyl(aryl)benzo[*c*]azepines **1**, **2,** respectively. This new synthetic route which is depicted retrosynthetically in Scheme 1 hinges upon combinations of the highly diastereoselective metallation/alkylation reaction (paths a1 and a2)

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or nucleophilic 1,2-addition reaction (path b) to chiral aliphatic hydrazones **3**, **4** with a cyclomethylenation reaction. These processes should give access to the diastereochemically pure cyclic hydrazines **5**, **6**, which are suitable candidates for the asymmetric synthesis of the title compounds **1**, **2**, upon cyclization of the preliminary formed diastereopure hydrazines **7** and **8,** respectively. Stereopure hydrazines (*S*,*R*)-**7** or (*S*,*S*)-**7** would be in turn obtained by reduction of the corresponding hydrazones **9** which could be assembled through the reverse sequences depicted in synthetic pathways a1 and a2 (Scheme 1).

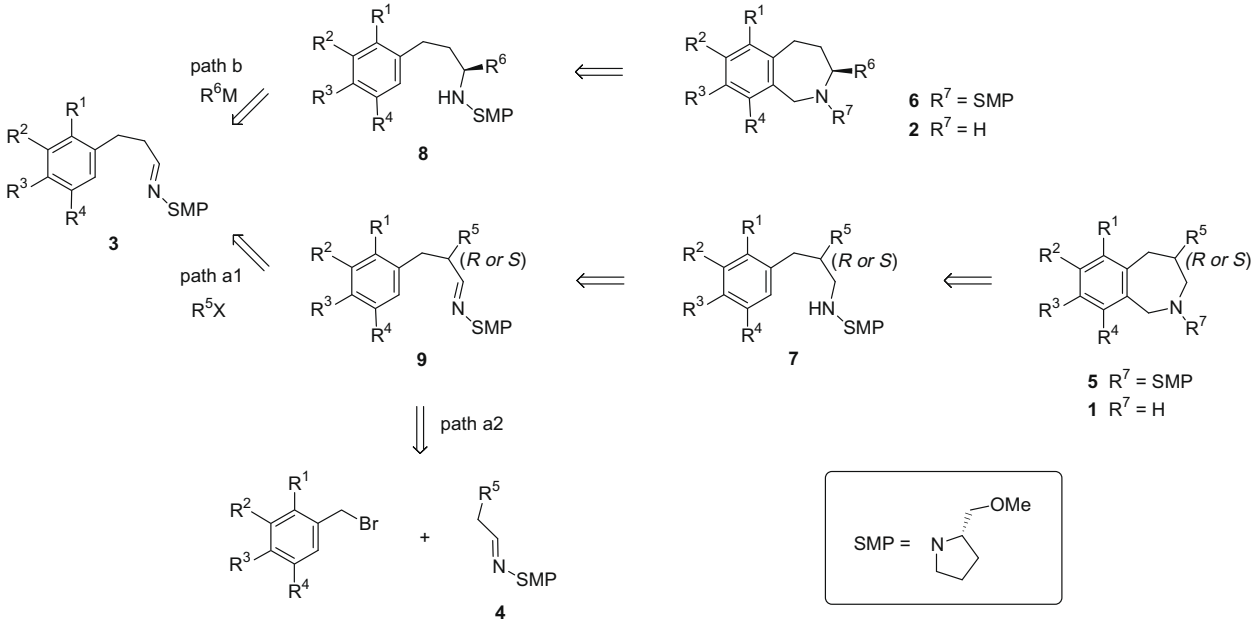
The first facet of the planned asymmetric synthesis of (*R*)-**1** or (*S*)-**1** was then the elaboration of the diastereochemically pure alkylated or arylated hydrazones **9**. Initially the appropriate aldehydes **10i**,**j** and **11d–g** were converted into the corresponding chiral hydrazones (*S*)-**3i**,**j** and (S)-**4d–g,** respectively, by simply mixing the enantiomerically pure hydrazine (*S*)-(−)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) with the easily accessible or commercially available aldehydes **10** and **11** (Scheme 2, Table 1). The next step was the creation of the stereogenic centre at the β-position to the nitrogen atom, that is, at C4 in the final compounds **1**, one of the major synthetic tasks in the synthesis of the targeted compounds. This operation was secured by taking advantage of the high level of diastereoselectivity observed upon the deprotonation/alkylation process α to the C=N bond of chiral hydrazones, a property aptly exploited by Enders.[16] Deprotonation of (*S*)-**3i**,**j** with lithium diisopropylamide (LDA) followed by alkylation with a variety of alkyl halides **13a–c** led to the diastereochemically enriched alkylated hydrazones (*R*,*S*)-**9a–d**. Alternatively the same reaction sequence involving hydrazones (*S*)-**4d–g** and benzyl bromides **12i–l** delivered excellent yields of the alkylated hydrazones (*S*,*S*)-**9d**,**f** and (*R*,*S*)-**9e**,**g** (Scheme 2, Table 1). SAMP derivatives of this type are usually converted into the corresponding α-substituted ketone as a reliable standard procedure for the determination of absolute configuration of chiral compounds.[17] The hydrazone precursors **9** were essentially obtained as a single diastereoisomer detectable by NMR (de ⩾ 96% after chromatographic treatment) making the high selectivity of the initial metallation/alkylation sequence evident.

For the synthesis of title compounds **1**, hydrazones (*R*,*S*)-**9a–d**,**e**,**g** or (*S*,*S*)-**9d**,**f** were subsequently reduced with $LiAlH_4$ to afford almost quantitative yields of the corresponding hydrazines (*R*,*S*)-**7a–d**,**e**,**g** or (*S*,*S*)-**7d**,**f** (Scheme 2). Owing to the sensitivity of these NH free hydrazines the reduced compounds were used in the next step without further purification. Cyclomethylenation of the unprotected alkyl hydrazines (*R*,*S*)-**7a–d**,**e**,**g** or (*S*,*S*)-**7d**,**f** proceeded smoothly by making use of chloromethylmethyl ether (MOMCl) in acetic acid[18] to provide moderate to good yields of the desired cyclic hydrazines (*R*,*S*)-**5a–d**,**e**,**g** and (*S*,*S*)-**5d**,**f** as the sole diastereoisomers detectable by NMR upon flash chromatographic treatment. The subsequent removal of the chiral auxiliary was readily achieved by basic treatment of the borane. THF complex of (*R*,*S*)-**5a-d**,**e**,**g** and (*S*,*S*)-**5d**,**f** effected N-N bond cleavage to deliver the virtually enantiopure (*R*)-**1a–d**,**e**,**g** or (*S*)-**1d**,**f** albeit in moderate yields (Scheme 2, Table 1).

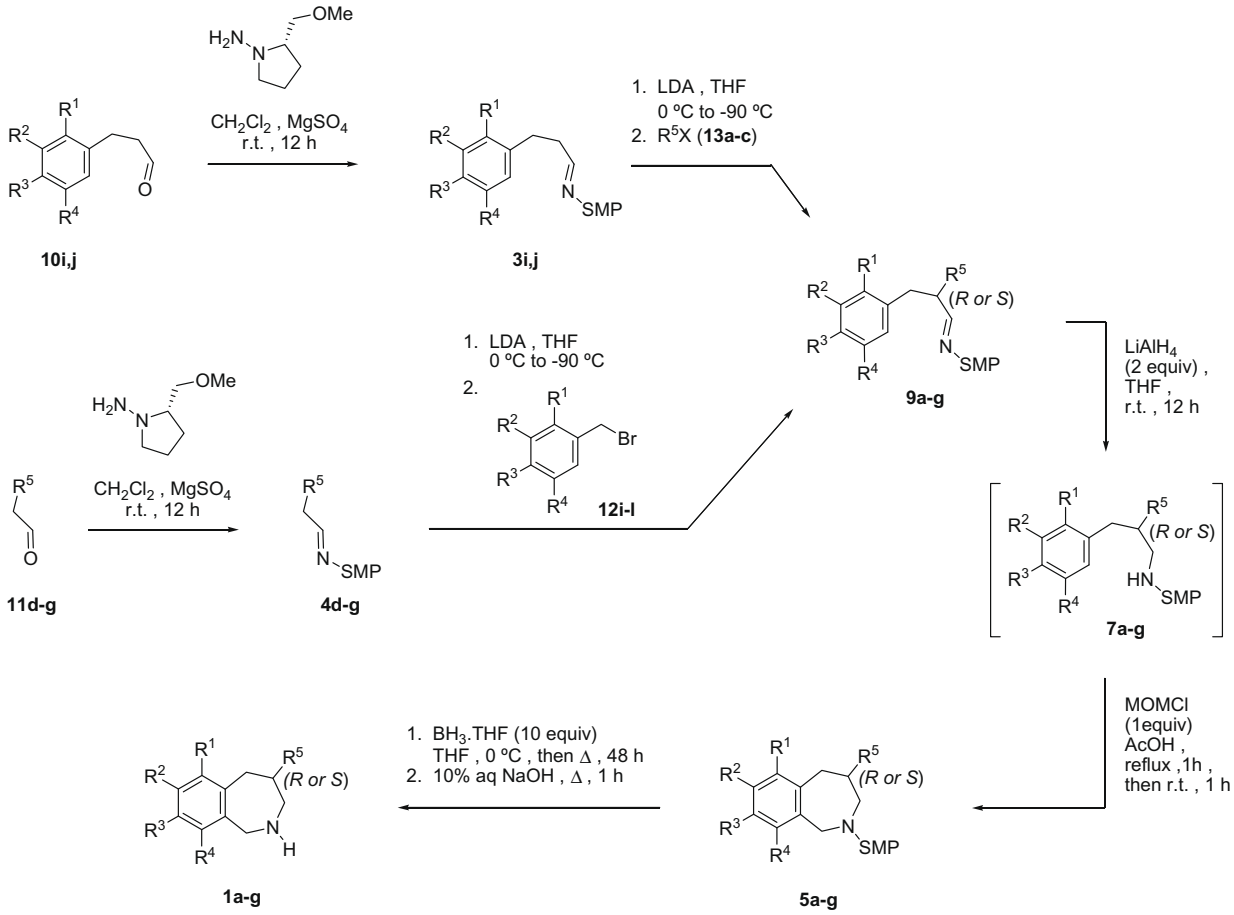
The synthetic route leading to the 3-substituted derivatives **2** (retrosynthetic Scheme 1, path b) was significantly shorter. The key step is based upon the nucleophilic 1,2-addition of organometallic reagents to SAMP hydrazones which are known to proceed in a highly stereoselective manner (de ⩾ 96%)[16,19] with the best results being obtained using organolithium or organocerium reagents.[16,20,21] The chiral hydrazones **3i**,**j** prepared as previously described were then allowed to react with methyl or hexyllithium to afford the diastereochemically enriched free NH hydrazines (*R*,*S*)-**8a**,**d**,**h** which were treated with MOMCl in AcOH to provoke the cyclomethylenation reaction. This operation gave rise to the diastereopure cyclic hydrazines (*R*,*S*)-**6a**,**d**,**h** (de ⩾ 96% after chromatographic treatment) making evident the high selectivity of the diastereofacial 1,2-addition process allowing introduction of the absolute stereochemistry at this stage of the sequence. Treatment of compounds **6a**,**d**,**h** with BH_3·THF triggered the release of the chiral appendage and this operation delivered very satisfactory yields of the virtually enantiopure NH free 3-alkylbenzazepines (*R*)-**2a**,**d**,**h** (Scheme 3, Table 2).

3. Conclusion

In conclusion we have devised a new, convenient and flexible method for the highly diastereo- and enantioselective synthesis of (*R*) and (*S*)-4-alkyl and aryl-2-benzazepines and of the (*R*)-3-



Scheme 1.



Scheme 2.

Table 1
Hydrazones **3**, **4**, **9** and benzazepines **5** and **1** prepared from **10** and **11** via paths a1 and a2

Path	R^1	R^2	R^3	R^4	R^5	Hydrazones **3**, **4** (yield %)	Halides **13**, **12**	Hydrazones **9** (yield %)[a]	Benzazepines **5** (yield %)[a,b]	Benzazepines[c] **1** (yield %)
a1	H	MeO	MeO	MeO	Me	(*S*)-**3i** (68)	**13a**	(*R*,*S*)-**9a** (57)	(*R*,*S*)-**5a** (50)	(*R*)-**1a** (58)
a1	H	MeO	MeO	MeO	Bn	(*S*)-**3i**	**13b**	(*R*,*S*)-**9b** (42)	(*R*,*S*)-**5b** (44)	(*R*)-**1b** (48)
a1	H	MeO	MeO	MeO	CH_2OMe	(*S*)-**3i**	**13c**	(*R*,*S*)-**9c** (51)	(*R*,*S*)-**5c** (53)	(*R*)-**1c** (49)
a1	H	MeO	MeO	H	Me	(*S*)-**3j** (74)	**13a**	(*R*,*S*)-**9d** (59)	(*R*,*S*)-**5d** (52)	(*R*)-**1d** (53)
a2	H	MeO	MeO	H	Me	(*S*)-**4d** (89)	**12j**	(*S*,*S*)-**9d** (62)	(*S*,*S*)-**5d** (54)	(*S*)-**1d** (55)
a2	H	MeO	MeO	MeO	Ph	(*S*)-**4e** (87)	**12i**	(*R*,*S*)-**9e** (47)	(*R*,*S*)-**5e** (46)	(*R*)-**1e** (48)
a2	MeO	MeO	H	H	C_5H_{11}	(*S*)-**4f** (85)	**12k**	(*S*,*S*)-**9f** (57)	(*S*,*S*)-**5f** (58)	(*S*)-**1f** (52)
a2	H	OCH_2O		H	$(CH_2)_2OBn$	(*S*)-**4g** (78)	**12l**	(*R*,*S*)-**9g** (55)	(*R*,*S*)-**5g** (42)	(*R*)-**1g** (51)

[a] Yield of isolated (*S*,*S*) or (*S*,*R*) diastereomer (de ⩾ 96%).
[b] Over two steps.
[c] Ee ⩾ 96% determined by chiral HPLC (Chiracel OD).

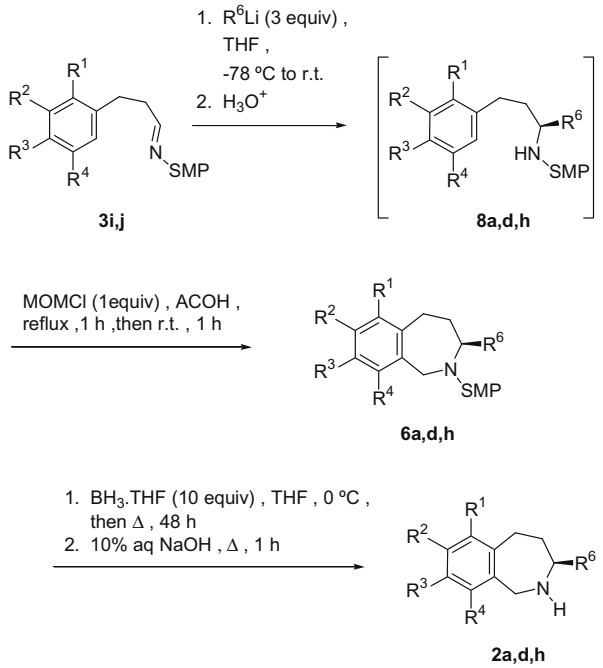
alkyl analogues. The key steps are the highly diastereoselective metallation/alkylation and nucleophilic 1,2-addition to SAMP hydrazones combined with a cyclomethylenation reaction to secure the formation of the azepine ring system. Owing to the availability of the RAMP chiral auxiliary we believe that this synthetic strategy should also allow for the assembly of both antipodes of these alkyl(aryl)ated benzazepines.

4. Experimental

4.1. General

Melting points were determined on a Reichert-Thermopan apparatus and are uncorrected. NMR spectra were recorded on Bruker AM 300 spectrometer. They were referenced against internal tetramethylsilane; Coupling constants (*J*) are rounded to the nearest 0.1 Hz. Optical rotations were measured on a Perkin–Elmer 343 polarimeter. Elemental analyses were obtained using a Carlo-Erba CHNS-11110 equipment. The silica gel used for flash column chromatography was Merck Kieselgel of 0.040–0.063 mm particle size. Dry glassware was obtained by oven-drying and assembly under argon (Ar). Ar was used as the inert atmosphere and was passed through a drying tube to remove moisture. The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately before use.

Carboxaldehydes **10i**,[22] **10j**[23] and **11g**[24] were prepared according to reported procedures. The benzyl bromides **12i**,[25] **12j**,[26] **12k**[27] and **12l**[28] were synthesized following the literature methods.



Scheme 3.

4.2. Synthesis of the SAMP-hydrazones 3i,j and 4d–g

4.2.1. General procedure

A solution of the appropriate carboxaldehydes **10i,j** or **11d–g** (0.10 mmol), SAMP (1.56 g, 0.12 mmol) and $MgSO_4$ (500 mg) in CH_2Cl_2 (50 mL) was stirred at rt for 12 h. $MgSO_4$ was filtered off and the solvent was evaporated under vacuum. The crude residue was purified by flash column chromatography on silica gel (ethyl acetate/hexanes, 40:60, as eluent) to yield hydrazones **3i,j** as yellow viscous oil or **4d–g** as colourless viscous oil.

4.2.2. [(*S*)-2-Methoxymethylpyrrolidin-1-yl]-*N*-[3-(3,4,5-trimethoxyphenyl)propylidene]amine 3i

2.29 g (68%); $[\alpha]_D^{25} = -73.5$ (*c* 1.07, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.72–2.04 (m, 4H, 2 × CH_2), 2.47–2.63 (m, 2H, CH_2), 2.67–2.85 (m, 3H:2H, $ArCH_2$ + 1H, CH_2N), 3.39 (s, 3H, OCH_3), 3.29–3.50 (m, 3H, 2H; CH_2O + 1H, CH_2N), 3.51–3.65 (m, 1H, CH), 3.84 (s, 3H, OCH_3), 3.86 (s, 6H, 2 × OCH_3), 6.45 (s, 2H, H_{arom}), 6.68 (t, *J* = 5.2 Hz, 1H, CH=N); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.2 (CH_2), 26.6 (CH_2), 34.5 (CH_2), 34.9 ($ArCH_2$), 50.4 (CH_2N), 56.0 (2 × OCH_3), 59.2 (OCH_3), 60.9 (OCH_3), 63.5 (CH), 74.9 (CH_2O), 105.2 (2 × CH), 137.4 (2 × C), 137.5 (CH=N), 153.1 (2 × C)). Anal. Calcd for $C_{18}H_{28}N_2O_4$: C, 64.26; H, 8.39; N, 8.33. Found: C, 64.13; H, 8.44; N, 8.13.

4.2.3. *N*-[3-(3,4-Dimethoxyphenyl)propylidene]-[(*S*)-2-methoxymethylpyrrolidin-1-yl]amine 3j

2.27 g (74%); $[\alpha]_D^{25} = -69.8$ (*c* 1.01, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.63–2.04 (m, 4H, 2 × CH_2), 2.46–2.59 (m, 2H, CH_2), 2.65–2.84 (m, 3H:2H, $ArCH_2$ + 1H, CH_2N), 3.39 (s, 3H, OCH_3), 3.27–3.49 (m, 3H:2H, CH_2O + 1H, CH_2N), 3.51–3.76 (m, 1H, CH), 3.87 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.66 (t, *J* = 5.1, 1H, CH=N), 6.71–6.88 (m, 3H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.2 (CH_2), 26.6 (CH_2), 33.7 (CH_2), 35.1 ($ArCH_2$), 50.4 (CH_2N), 55.8 (OCH_3), 55.9 (OCH_3), 59.2 (OCH_3), 63.5 (CH), 74.8 (CH_2O), 111.1 (CH), 111.7 (CH), 120.2 (CH), 134.3 (C), 137.7 (CH=N), 147.1 (C), 148.7 (C). Anal. Calcd for $C_{17}H_{26}N_2O_3$: C, 66.64; H, 8.55; N, 9.14. Found: C, 66.47; H, 8.44; N, 8.88.

4.2.4. [(*S*)-2-Methoxymethylpyrrolidin-1-yl]-*N*-propylideneamine 4d

1.51 g (89%); $[\alpha]_D^{25} = -142.8$ (*c* 1.28, $CHCl_3$) {lit.:[29] $[\alpha]_D^{23} = -143.3$ (*c* 1.11, $CHCl_3$)}.

4.2.5. [(*S*)-2-Methoxymethylpyrrolidin-1-yl]-*N*-[2-phenylethylidene]amine (4e)[30]

2.02 g (87%); $[\alpha]_D^{25} = -115.7$ (*c* 0.99, $CHCl_3$).

4.2.6. *N*-Heptylidene-[(*S*)-2-methoxymethylpyrrolidin-1-yl]-amine 4f

1.92 g (85%); $[\alpha]_D^{25} = -105.3$ (*c* 1.42, $CHCl_3$) {lit.:[31] $[\alpha]_D^{22} = -106.6$ (neat)}.

4.2.7. *N*-(4-Benzyloxybutylidene)-[(*S*)-2-methoxymethylpyrrolidin-1-yl]amine 4g

2.27 g (78%); $[\alpha]_D^{25} = -83.0$ (*c* 0.79, $CHCl_3$) {lit.:[32] $[\alpha]_D^{25} = -84.0$ (*c* 3.80, $CHCl_3$)}.

4.3. Alkylation of the SAMP-hydrazones 3i,j and 4d–g (path a)

4.3.1. 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 hydrazones **3i,j** or **4d–g** (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 halides **13a–c** or **12i–l** (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 rt 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 brine (20 mL) and water (20 mL), then dried over $MgSO_4$, con-

Table 2
Benzazepines **6**, **2** prepared via path b

R^1	R^2	R^3	R^4	R^6	Hydrazones **3**	R^6Li	Benzazepines **6** (yield %)[a,b]	Benzazepines[c] **2** (yield %)
H	MeO	MeO	MeO	Me	(*S*)-**3i**	CH_3Li	(*R*,*S*)-**6a** (47)	(*R*)-**2a** (58)
H	MeO	MeO	H	Me	(*S*)-**3j**	CH_3Li	(*R*,*S*)-**6d** (48)	(*R*)-**2d** (53)
H	MeO	MeO	H	C_6H_{13}	(*S*)-**3j**	$C_6H_{13}Li$	(*R*,*S*)-**6h** (50)	(*R*)-**2h** (56)

[a] Yield of isolated (*R*,*S*) diastereomer (de ⩾ 96%).
[b] Over two steps.
[c] Ee ⩾ 96% determined by chiral HPLC (Chiracel OD).

centrated and purified by flash column chromatography on silica gel (ethyl acetate/hexanes, 30:70, as eluent).

4.3.2. [(*S*)-2-Methoxymethylpyrrolidin-1-yl]-*N*-[(*R*)-2-methyl-3-(3,4,5-trimethoxyphenyl)propylidene]amine 9a

1.41 g (57%); $[\alpha]_D^{25} = -122.3$ (*c* 1.09, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 1.00 (d, *J* = 6.5 Hz, 3H, CH_3), 1.59–1.96 (m, 4H, 2 × CH_2), 2.42–2.50 (m, 1H, $ArCH_2$), 2.51–2.84 (m, 3H:1H, CH_3 + 1H, CH_2 + 1H, NCH_2), 3.28–3.41 (m, 3H, CH_2O + CH), 3.31 (s, 3H, OCH_3), 3.43–3.56 (m, 1H, NCH_2), 3.79 (br s, 9H, 3 × OCH_3), 6.36 (s, 2H, H_{arom}), 6.50 (m, 1H, CH=N); ^{13}C NMR (75 MHz, $CDCl_3$): 18.5 (CH_3), 22.1 (CH_2), 26.6 (CH_2), 38.6 (CH), 42.1 ($ArCH_2$), 50.2 (NCH_2), 55.9 (2 × OCH_3), 59.1 (OCH_3), 60.8 (OCH_3), 63.4 (CH), 74.7 (CH_2O), 106.0 (2 × CH), 136.2 (2 × C), 142.4 (CH=N), 152.8 (2 × C). Anal. Calcd for $C_{19}H_{30}N_2O_4$: C, 65.12; H, 8.63; N, 7.99. Found: C, 65.01; H, 8.41; N, 8.15.

4.3.3. *N*-[(*R*)-2-Benzyl-3-(3,4,5-trimethoxyphenyl)propylidene]-[(*S*)-2-methoxymethylpyrrolidin-1-yl]amine 9b

1.27 g (42%); $[\alpha]_D^{25} = -52.9$ (*c* 0.83, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 1.69–1.98 (m, 4H, 2 × CH_2), 2.58–2.96 (m, 6H:1H, CH + 4H, 2 × $ArCH_2$ + 1H, NCH_2), 3.19–3.41 (m, 3H, OCH_2 + CH), 3.32 (s, 3H, OCH_3), 3.41–3.51 (m, 1H, NCH_2), 3.82 (s, 9H, 3 × OCH_3), 6.38 (s, 2H, H_{arom}), 6.48 (d, *J* = 5.8, 1H, CH=N), 7.12–7.20 (m, 3H, H), 7.21–7.30 (m, 2H, H); ^{13}C NMR (75 MHz, $CDCl_3$): 22.1 (CH_2), 26.6 (CH_2), 39.5 ($PhCH_2$), 40.0 ($ArCH_2$), 45.2 (CH), 50.3 (NCH_2), 56.0 (2 × OCH_3), 59.2 (OCH_3), 60.8 (OCH_3), 63.3 (CH), 74.7 (CH_2O), 106.1 (2 × CH), 125.9 (CH), 128.1 (2 × CH), 129.4 (2 × CH), 136.0 (2 × C), 140.1 (2 × C), 140.3 (CH=N), 152.9 (C). Anal. Calcd for $C_{25}H_{34}N_2O_4$: C, 70.40; H, 8.03; N, 6.57. Found: C, 70.72; H, 7.89; N, 6.55.

4.3.4. [(*S*)-2-Methoxymethylpyrrolidin-1-yl]-*N*-[(*R*)-2-methoxymethyl-3-(3,4,5-trimethoxyphenyl)propylidene]amine 9c

1.37 g (51%); $[\alpha]_D^{25} = -95.9$ (*c* 0.99, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 1.69–2.04 (m, 4H, 2 × CH_2), 2.68–2.88 (m, 4H:2H, $ArCH_2$ + 1H, CH + 1H, NCH_2), 3.21–3.46 (m, 5H, 2 × OCH_2 + CH), 3.32 (s, 3H, OCH_3), 3.33 (s, 3H, OCH_3), 3.51 (dd, *J* = 3.7, 8.3 Hz, 1H, NCH_2), 3.75–3.91 (m, 9H, 3 × OCH_3), 6.41 (s, 2H, H_{arom}), 6.53 (br s, 1H, CH=N); ^{13}C NMR (75 MHz, $CDCl_3$): 22.1 (CH_2), 26.6 (CH_2), 36.9 ($ArCH_2$), 44.2 (CH), 50.0 (NCH_2), 56.0 (2 × OCH_3), 58.9 (OCH_3), 59.2 (OCH_3), 60.8 (OCH_3), 63.2 (CH), 74.0 (CH_2O), 74.7 (CH_2O), 105.2 (2 × CH), 135.7 (2 × C), 138.0 (CH=N), 152.9 (2 × C). Anal. Calcd for $C_{20}H_{32}N_2O_5$: C, 63.13; H, 8.48; N, 7.36. Found: C, 62.79; H, 8.21; N, 7.54.

4.3.5. *N*-[(*R*)-3-(3,4-Dimethoxyphenyl)-2-methylpropylidene]-[(*S*)-2-methoxymethylpyrrolidin-1-yl]amine (*R*,*S*)-9d

1.34 g (59%); $[\alpha]_D^{25} = -124.0$ (*c* 0.72, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 0.97 (d, *J* = 6.8 Hz, 3H, CH_3), 1.61–1.94 (m, 4H, 2 × CH_2), 2.46 (dd, *J* = 7.9, 12.9 Hz, 1H, $ArCH_2$), 2.51–2.65 (m, 2H, CH + NCH_2), 2.77 (dd, *J* = 6.0, 12.8 Hz, 1H, $ArCH_2$), 3.22–3.45 (m, 3H, OCH_2 + CH), 3.36 (s, 3H, OCH_3), 3.53 (dd, *J* = 3.8, 8.9 Hz, 1H, NCH_2), 3.80 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 6.51 (d, *J* = 6.1 Hz, 1H, CH=N), 6.61–6.78 (m, 3H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): 18.4 (CH_3), 22.1 (CH_2), 26.6 (CH_2), 38.7 (CH), 41.8 ($ArCH_2$), 50.2 (NCH_2), 55.8 (OCH_3), 55.9 (OCH_3), 59.1 (OCH_3), 63.4 (CH), 74.6 (CH_2O), 110.8 (CH), 112.1 (CH), 121.3 (CH), 133.0 (C), 142.6 (CH=N), 147.4 (C), 148.1 (C). Anal. Calcd for $C_{18}H_{28}N_2O_3$: C, 67.47; H, 8.81; N, 8.74. Found: C, 67.51; H, 8.56; N, 8.64.

4.3.6. *N*-[(*S*)-3-(3,4-Dimethoxyphenyl)-2-methylpropylidene]-[(*S*)-2-methoxymethylpyrrolidin-1-yl]amine (*S*,*S*)-9d

1.41 g (62%); $[\alpha]_D^{25} = -37.0$ (*c* 1.22, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 0.99 (d, *J* = 6.6 Hz, 3H, CH_3), 1.66–1.97 (m, 4H, 2 × CH_2), 2.48 (dd, *J* = 8.0, 13.0 Hz, 1H, $ArCH_2$), 2.54–2.68 (m, 2H:1H, CH + 1H, NCH_2), 2.78 (dd, *J* = 6.0, 13.0 Hz, 1H, $ArCH_2$), 3.23–3.44 (m, 3H, OCH_2 + CH), 3.34 (s, 3H, OCH_3), 3.52 (dd, *J* = 3.7, 8.9 Hz, 1H, NCH_2), 3.81 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 6.52 (d, *J* = 6.0 Hz, 1H, CH=N), 6.62 6–6.79 (m, 3H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): 18.3 (CH_3), 22.1 (CH_2), 26.5 (CH_2), 38.8 (CH), 41.3 ($ArCH_2$), 50.3 (NCH_2), 55.7 (OCH_3), 55.8 (OCH_3), 59.2 (OCH_3), 63.4 (CH), 74.7 (CH_2O), 110.9 (CH), 112.3 (CH), 121.2 (CH), 132.9 (C), 142.9 (CH=N), 147.1 (C), 148.5 (C). Anal. Calcd for $C_{18}H_{28}N_2O_3$: C, 67.47; H, 8.81; N, 8.74. Found: C, 67.28; H, 8.66; N, 9.00.

4.3.7. [(*S*)-2-Methoxymethylpyrrolidin-1-yl]-*N*-[(*S*)-2-phenyl-3-(3,4,5-trimethoxyphenyl)propylidene]amine 9e

1.37 g (47%); $[\alpha]_D^{25} = -86.6$ (*c* 1.10, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 1.70–2.01 (m, 4H, 2 × CH_2), 2.74 (q, *J* = 8.0 Hz, 1H, NCH_2), 2.93 (dd, *J* = 5.3, 13.6 Hz, 1H, $ArCH_2$), 3.23 (dd, *J* = 6.6, 13.6 Hz, 1H, $ArCH_2$), 3.28–3.49 (m, 4H:2H, 2 × CH + 1H, NCH_2 + 1H, CH_2O), 3.35 (s, 3H, OCH_3), 3.56 (d, *J* = 5.1 Hz, 1H, CH_2O), 3.70 (s, 6H, 2 × OCH_3), 3.78 (s, 3H, OCH_3), 6.20 (s, 2H, H_{arom}), 6.76 (d, *J* = 5.7 Hz, 1H, CH=N), 7.07–7.34 (m, 5H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): 22.1 (CH_2), 26.6 (CH_2), 41.4 ($ArCH_2$), 50.1 (NCH_2), 50.8 (CH), 55.9 (2 × OCH_3), 59.2 (CH), 60.8 (OCH_3), 63.4 (OCH_3), 74.8 (CH_2O), 106.2 (2 × CH), 126.4 (CH), 128.2 (2 × CH), 128.4 (2 × CH), 135.8 (C), 135.9 (C), 139.1 (CH=N), 142.6 (C), 152.6 (2 × C). Anal. Calcd for $C_{24}H_{32}N_2O_4$: C, 69.88; H, 7.82; N, 6.79. Found: C, 69.95; H, 7.74; N, 6.96.

4.3.8. *N*-[(*S*)-2-(2,3-Dimethoxybenzyl)heptylidene]-[(*S*)-2-methoxymethylpyrrolidin-1-yl]amine 9f

1.52 g (57%); $[\alpha]_D^{25} = -29.8$ (*c* 1.09, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 0.85 (t, *J* = 6.3 Hz, 3H, CH_3), 1.14–1.51 (m, 8H, 4 × CH_2), 1.67–2.02 (m, 4H, 2 × CH_2), 2.49–2.68 (m, 2H:1H, $ArCH_2$ + 1H, CH), 2.70–2.83 (m, 2H:1H, $ArCH_2$ + 1H, NCH_2), 3.29–3.42 (m, 3H, OCH_2 + CH), 3.34 (s, 3H, OCH_3), 3.52 (dd, *J* = 3.5, 9.1 Hz, 1H, NCH_2), 3.80 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 6.51 (d, *J* = 6.6 Hz, 1H, CH=N), 6.59–6.80 (m, 2H, H_{arom}), 6.88–6.99 (m, 1H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): 14.1 (CH_3), 22.0 (CH_2), 22.6 (CH_2), 26.4 (CH_2), 26.8 (CH_2), 31.9 (CH_2), 33.4 (CH_2), 33.7 (CH_2), 43.3 (CH), 50.3 (NCH_2), 55.6 (OCH_3), 55.7 (OCH_3), 59.1 (OCH_3), 63.4 (CH), 74.7 (CH_2O), 110.0 (CH), 122.8 (CH), 123.4 (CH), 134.3 (C), 143.1 (CH=N), 147.4 (C), 152.6 (C). Anal. Calcd for $C_{22}H_{36}N_2O_3$: C, 70.18; H, 9.64; N, 7.44. Found: C, 69.91; H, 9.54; N, 7.67.

4.3.9. *N*-[(*R*)-2-Benzo[1,3]dioxol-5-ylmethyl-4-benzyloxybutylidene]-[(*S*)-2-methoxymethylpyrrolidin-1-yl]amine 9g

1.65 g (55%); $[\alpha]_D^{25} = -43.2$ (*c* 0.87, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 1.65–2.04 (m, 6H, 3 × CH_2), 2.59–2.85 (m, 4H:1H, CH + 2H, $ArCH_2$ + 1H, NCH_2), 3.23–3.64 (m, 6H:2H, OCH_2 + 1H, CH + 2H, CH_2OBn + 1H, NCH_2), 3.38 (s, 3H, OCH_3), 4.49 (s, 2H, OCH_2Ph), 5.91 (s, 2H, OCH_2O), 6.50 (d, *J* = 5.4, 1H, CH=N), 6.58–6.67 (m, 1H, H_{arom}), 6.68–6.76 (m, 2H, H_{arom}), 7.26–7.41 (m, 5H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): 22.1 (CH_2), 26.5 (CH_2), 32.9 (CH_2), 40.1 ($ArCH_2$), 41.3 (CH), 50.3 (NCH_2), 59.2 (OCH_3), 63.4 (CH), 68.6 (CH_2O), 73.0 ($PhCH_2O$), 74.7 (CH_2O), 100.7 (OCH_2O), 107.9 (CH), 109.8 (CH), 122.2 (CH), 127.5 (2 × CH), 127.7 (2 × CH), 128.3 (CH), 133.8 (C), 138.6 (C), 140.8 (CH=N), 145.7 (C), 147.4 (C). Anal. Calcd for $C_{25}H_{32}N_2O_4$: C, 70.73; H, 7.60; N, 6.60. Found: C, 70.54; H, 7.47; N, 6.45.

4.4. Synthesis of the 4-substituted benzo[*c*]azepines 5a–g

4.4.1. General procedure

A solution of hydrazones **9a–g** (4.0 mmol) in THF (10 mL) was slowly added to a stirred suspension of lithium aluminium hydride (349 mg, 10 mmol) in dry THF (5 mL). The resulting

mixture was refluxed for 6 h then stirring at rt was maintained overnight. Water (0.5 mL), 10% aqueous sodium hydroxide (0.5 mL) and water (1 mL) were successively added to the mixture. The precipitate was removed by filtration and thoroughly washed with Et_2O and CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$). After evaporation of the solvent, the crude hydrazines **7a–g**, obtained as a pale yellow oil, were used in the next step without further purification. MOMCl (161 mg, 0.15 mL, 2.0 mmol) was added to a stirred solution of crude hydrazines **7a–g** (2.0 mmol) in glacial acetic acid (10 mL) under Ar. The mixture was then refluxed for 1 h and stirring at rt was maintained for 1 h. The mixture was poured onto crushed ice, neutralized with 50% aqueous NaOH and then extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL) and then 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).

4.4.2. (*R*)-7,8,9-Trimethoxy-2-[(*S*)-2-methoxymethylpyrrolidin-1-yl]-4-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine 5a

364 mg (50%); $[\alpha]_D^{25} = -46.8$ (*c* 0.71, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 0.93 (d, *J* = 6.7 Hz, 3H, CH_3), 1.59–1.99 (m, 5H, 2 × CH_2 + CH), 2.56–2.88 (m, 4H, $ArCH_2$ + CH_2N), 2.98–3.11 (m, 2H:1H, CH + 1H, OCH_2), 3.13–3.27 (m, 2H:1H, NCH_2 + 1H, OCH_2), 3.29 (s, 3H, OCH_3), 3.48 (dd, *J* = 3.1, 8.9 Hz, 1H, NCH_2), 3.76–3.97 (m, 11H, 3 × OCH_3 + $ArCH_2N$), 6.42 (s, 1H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): 19.8 (CH_3), 21.4 (CH_2), 26.6 (CH_2), 33.1 (CH), 42.6 ($ArCH_2$), 44.8 (NCH_2), 48.9 ($ArCH_2N$), 55.9 (OCH_3), 58.3 (CH), 59.1 (OCH_3), 60.8 (OCH_3), 61.3 (OCH_3), 65.7 (CH_2N), 75.7 (CH_2O), 109.1 (CH), 125.1 (C), 136.9 (C), 140.1 (C), 150.9 (C), 151.3 (C). Anal. Calcd for $C_{20}H_{32}N_2O_4$: C, 65.91; H, 8.85; N, 7.69. Found: C, 66.14; H, 8.56; N, 7.38.

4.4.3. (*R*)-4-Benzyl-7,8,9-trimethoxy-2-[(*S*)-2-methoxymethylpyrrolidin-1-yl]-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine 5b

388 mg (44%); $[\alpha]_D^{25} = -37.8$ (*c* 0.72, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 1.59–1.95 (m, 4H, 2 × CH_2), 2.13–2.37 (m, 1H, CH), 2.46–2.70 (m, 3H: 1H, $ArCH_2$ + 1H, CH_2N + 1H, NCH_2), 2.77–2.93 (m, 2H:1H, $ArCH_2$ + 1H, CH_2N), 2.95–3.23 (m, 4H:1H, NCH_2 + 1H, CH + 2H, $ArCH_2$), 3.33 (s, 3H, OCH_3), 3.49–3.71 (m, 2H, OCH_2), 3.80 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.04–4.29 (m, 2H, $ArCH_2N$), 6.29 (s, 1H, H_{arom}), 7.08–7.36 (m, 5H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): 21.3 (CH_2), 26.5 (CH_2), 39.5 (CH), 39.6 ($PhCH_2$), 42.9 ($ArCH_2$), 43.7 (NCH_2), 47.8 ($ArCH_2N$), 55.9 (OCH_3), 58.8 (CH), 59.1 (OCH_3), 60.8 (OCH_3), 61.3 (OCH_3), 64.4 (CH_2N), 75.5 (CH_2O), 109.6 (CH), 124.7 (C), 125.8 (CH), 128.2 (2 × CH), 129.3 (2 × CH), 136.2 (C), 140.2 (C), 140.9 (C), 150.9 (C), 151.3 (C). Anal. Calcd for $C_{26}H_{36}N_2O_4$: C, 70.88; H, 8.24; N, 6.36. Found: C, 70.89; H, 8.44; N, 6.27.

4.4.4. (*R*)-7,8,9-Trimethoxy-4-methoxymethyl-2-[(*S*)-2-methoxymethylpyrrolidin-1-yl]-2,3,4,5-tetrahydro-1*H*-benzo[*c*]-azepine 5c

418 mg (53%); $[\alpha]_D^{25} = -44.0$ (*c* 0.61, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 1.54–1.92 (m, 4H, 2 × CH_2), 2.05–2.16 (m, 1H, CH), 2.63–2.90 (m, 3H:1H, $ArCH_2$ + 1H, CH_2N + 1H, NCH_2), 2.96–3.11 (m, 3H:1H, $ArCH_2$ + 1H, CH_2N + 1H, CH), 3.13–3.39 (m, 4H, OCH_2 + -CH_2OMe), 3.28 (s, 3H, OCH_3), 3.30 (s, 3H, OCH_3), 3.46 (d, *J* = 6.6 Hz, 1H, NCH_2), 3.65 (d, *J* = 12.5 Hz, 1H, $ArCH_2N$), 3.78–3.98 (m, 9H, 3 × OCH_3), 4.09 (d, *J* = 13.1 Hz, 1H, $ArCH_2N$), 6.46 (s, 1H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): 21.4 (CH_2), 26.3 (CH_2), 37.4 ($ArCH_2$), 38.1 (CH), 43.9 (NCH_2), 48.4 ($ArCH_2N$), 55.9 (OCH_3), 58.7 (OCH_3), 59.1 (OCH_3 + CH), 60.8 (OCH_3), 61.2 (OCH_3), 61.5 (CH_2N), 74.8 (OCH_2), 75.4 (CH_2O), 109.2 (CH), 125.0 (C), 136.1 (C), 140.2 (C), 150.8 (C), 151.3 (C). Anal. Calcd for $C_{21}H_{34}N_2O_5$: C, 63.93; H, 8.69; N, 7.10. Found: C, 63.82; H, 8.72; N, 6.89.

4.4.5. (*R*)-7,8-Dimethoxy-2-[(*S*)-2-methoxymethylpyrrolidin-1-yl]-4-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine (*S*,*R*)-5d

348 mg (52%); $[\alpha]_D^{25} = -38.8$ (*c* 0.51, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 0.95 (d, *J* = 6.9 Hz, 3H, CH_3), 1.49–1.97 (m, 5H, 2 × CH_2 + CH), 2.52–2.83 (m, 4H, $ArCH_2$ + CH_2N), 2.97–3.11 (m, 2H:1H, CH + 1H, OCH_2), 3.17 (d, *J* = 11.4 Hz, 1H, NCH_2), 3.22–3.30 (m, 1H, OCH_2), 3.32 (s, 3H, OCH_3), 3.51 (dd, *J* = 3.4, 9.1 Hz, 1H, NCH_2), 3.73–3.81 (br s, 2H, $ArCH_2N$), 3.85 (s, 6H, 2 × OCH_3), 6.62 (s, 1H, H_{arom}), 6.70 (s, 1H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): 20.6 (CH_3), 21.4 (CH_2), 26.4 (CH_2), 33.7 (CH), 42.3 ($ArCH_2$), 44.2 (NCH_2), 55.9 (OCH_3), 56.0 (OCH_3), 57.9 ($ArCH_2N$), 59.1 (CH), 59.2 (OCH_3), 65.4 (CH_2N), 75.3 (CH_2O), 112.8 (CH), 113.1 (CH), 131.2 (C), 133.3 (C), 146.6 (C), 147.2 (C). Anal. Calcd for $C_{19}H_{30}N_2O_3$: C, 68.23; H, 9.04; N, 8.38. Found: C, 68.53; H, 8.98; N, 8.23.

4.4.6. (*S*)-7,8-Dimethoxy-2-[(*S*)-2-methoxymethylpyrrolidin-1-yl]-4-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine (*S*,*S*)-5d

361 mg (54%); $[\alpha]_D^{25} = -32.6$ (*c* 0.58, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 0.93 (d, *J* = 6.8 Hz, 3H, CH_3), 1.47–1.99 (m, 5H, 2 × CH_2 + CH), 2.51–2.77 (m, 4H, $ArCH_2$ + CH_2N), 2.93–3.04 (m, 2H:1H, CH + 1H, OCH_2), 3.16 (d, *J* = 11.4 Hz, 1H, NCH_2), 3.19–3.27 (m, 1H, OCH_2), 3.33 (s, 3H, OCH_3), 3.41–3.58 (m, 1H, NCH_2), 3.71–3.83 (br s, 2H, $ArCH_2N$), 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 6.63 (s, 1H, H_{arom}), 6.69 (s, 1H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): 20.5 (CH_3), 21.4 (CH_2), 26.4 (CH_2), 33.8 (CH), 42.2 ($ArCH_2$), 44.2 (NCH_2), 55.9 (OCH_3), 56.0 (OCH_3), 57.8 ($ArCH_2N$), 59.1 (CH), 59.3 (OCH_3), 65.6 (CH_2N), 75.5 (CH_2O), 112.9 (CH), 113.3 (CH), 131.1 (C), 133.2 (C), 146.6 (C), 147.1 (C). Anal. Calcd for $C_{19}H_{30}N_2O_3$: C, 68.23; H, 9.04; N, 8.38. Found: C, 68.44; H, 9.22; N, 8.65.

4.4.7. (*R*)-7,8,9-Trimethoxy-2-[(*S*)-2-methoxymethylpyrrolidin-1-yl]-4-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine 5e

392 mg (46%); $[\alpha]_D^{25} = -58.3$ (*c* 1.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 1.53–1.95 (m, 4H, 2 × CH_2), 2.72–2.88 (m, 2H:1H, NCH_2 + 1H, $ArCH_2$), 2.92–3.18 (m, 4H:1H, $ArCH_2$ + 2H, CH_2N + 1H, CH), 3.20–3.47 (m, 3H:1H, NCH_2 + 1H, CH + 1H, CH_2O), 3.33 (s, 3H, OCH_3), 3.57 (dd, *J* = 3.1, 8.8 Hz, 1H, CH_2O), 3.74–3.98 (m, 1H, $ArCH_2N$), 3.83 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.49 (d, *J* = 14.6 Hz, 1H, $ArCH_2N$), 6.47 (s, 1H, H_{arom}), 7.05–7.43 (m, 5H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): 21.5 (CH_2), 26.5 (CH_2), 41.7 ($ArCH_2$), 43.5 (NCH_2), 45.8 (CH), 46.9 ($ArCH_2N$), 55.9 (OCH_3), 59.1 (OCH_3), 59.2 (OCH_3), 60.8 (OCH_3), 61.3 (CH), 63.9 (CH_2N), 75.6 (CH_2O), 108.6 (CH), 125.0 (C), 126.9 (CH), 127.0 (2 × CH), 128.5 (2 × CH), 137.4 (C), 140.4 (C), 145.7 (C), 151.1 (C), 151.7 (C). Anal. Calcd for $C_{25}H_{34}N_2O_4$: C, 70.39; H, 8.03; N, 6.57. Found: C, 70.44; H, 7.92; N, 6.80.

4.4.8. (*S*)-6,7-Dimethoxy-2-[(*S*)-2-methoxymethylpyrrolidin-1-yl]-4-pentyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine 5f

453 mg (58%); $[\alpha]_D^{25} = -48.2$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 0.89 (t, *J* = 6.7 Hz, 3H, CH_3), 1.12–1.53 (m, 8H, 4 × CH_2), 1.59–1.95 (m, 5H, 2 × CH_2 + CH), 2.41–2.64 (m, 1H, $ArCH_2$), 2.70–2.93 (m, 2H:1H, NCH_2 + 1H, $ArCH_2$), 2.94–3.22 (m, 4H:1H, CH,+ 2H, CH_2N + 1H, NCH_2), 3.22–3.43 (m, 1H, CH_2O), 3.33 (s, 3H, OCH_3), 3.52 (d, *J* = 6.5 Hz, 1H, CH_2O), 3.66–4.00 (m, 2H, $ArCH_2N$), 3.86 (s, 6H, 2 × OCH_3), 6.53–6.77 (m, 2H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): 14.2 (CH_3), 21.4 (CH_2), 22.7 (CH_2), 26.3 (CH_2), 26.9 (CH_2), 30.2 (CH_2), 32.1 (CH_2), 38.0 (CH), 43.8 ($ArCH_2$), 43.9 (NCH_2), 47.8 ($ArCH_2N$), 55.6 (OCH_3), 59.1 (OCH_3), 59.4 (OCH_3), 60.9 (CH), 63.2 (CH_2N), 75.2 (CH_2O), 107.4 (CH), 119.4 (CH), 126.6 (C), 133.2 (C), 142.8 (C), 145.4 (C). Anal. Calcd for $C_{23}H_{38}N_2O_3$: C, 70.73; H, 9.81; N, 7.17. Found: C, 70.84; H, 9.80; N, 7.35.

4.4.9. (*R*)-8-(2-Benzyloxyethyl)-6-[(*S*)-2-methoxymethylpyrrolidin-1-yl]-6,7,8,9-tetrahydro-5*H*-1,3-dioxa-6-azacyclohepta-[*f*]indene 5g

368 mg (42%); $[\alpha]_D^{25} = -46.6$ (*c* 0.67, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 1.42–1.87 (m, 7H, 3 × CH_2 + CH), 2.51–3.11 (m, 7H, $ArCH_2$ + 2 × CH_2N + CH), 3.24 (t, *J* = 8.8 Hz, 1H, CH_2O), 3.31 (s, 3H, OCH_3), 3.40–3.58 (m, 3H:2H, CH_2OBn + 1H, CH_2O), 3.75 (dd, *J* = 9.1, 13.6 Hz, 2H, $ArCH_2N$), 4.49 (s, 2H, OCH_2Ph) 5.89 (s, 2H, OCH_2O), 6.51 (s, 1H, H_{arom}), 6.64 (s, 1H, H_{arom}), 7.22–7.41 (m, 5H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): 21.3 (CH_2), 26.1 (CH_2), 34.8 (CH), 39.9 (CH_2), 43.9 ($ArCH_2$), 44.0 (NCH_2), 55.8 ($ArCH_2N$), 59.2 (OCH_3), 59.2 (CH), 62.6 (CH_2N), 68.1 (CH_2OBn), 73.0 (OCH_2Ar), 75.3 (CH_2O), 100.7 (OCH_2O), 109.6 (CH), 110.3 (CH), 127.6 (2 × CH), 127.8 (2 × CH), 128.4 (CH), 132.6 (C), 133.8 (C), 138.5 (C), 145.4 (C), 145.9 (C). Anal. Calcd for $C_{26}H_{34}N_2O_4$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.02; H, 7.58; N, 6.45.

4.5. Synthesis of the 3-substituted 2-benzo[*c*]azepines 6a,d,h (path b)

Methyllithium (6.0 mmol, 3.75 mL, 1.6 M solution in diethylether) or hexyllithium (6.0 mmol, 2.6 mL, 2.3 M solution in hexane) was added dropwise to a stirred solution of the appropriate hydrazones **3i,j** (2.0 mmol) in THF (10 mL) at −78 °C under Ar. The mixture was then allowed to warm to rt 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 hydrazines **8a**,**d**,**h** as brown oil, which was used without further purification in the reaction with MOMCl as previously described for the synthesis of **5a–g**. Purification by flash column chromatography on silica gel (acetone/hexanes, 20:80, as eluent) delivered the benzazepines **6a**,**d**,**h** as a foam.

4.5.1. (*R*)-7,8,9-Trimethoxy-2-[(*S*)-2-methoxymethylpyrrolidin-1-yl]-3-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine 6a

343 mg (47%); $[\alpha]_D^{25} = -43.8$ (*c* 1.25, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 1.13 (d, *J* = 6.0 Hz, 3H, CH_3), 1.39–1.54 (m, 1H, CH_2), 1.55–1.82 (m, 3H:1H, CH_2 + 2H, CH_2), 1.83–2.00 (m, 2H:2 × 1H, 2 × CH_2), 2.66 (dd, *J* = 7.4, 6.9 Hz, 1H, CH_2N), 2.73–2.99 (m, 4H:1H, CH_2N + 2H, $ArCH_2$ + 1H, CH), 3.06–3.22 (m, 2H:1H, CH + 1H, CH_2O), 3.28 (s, 3H, OCH_3), 3.35 (d, *J* = 13.6 Hz, 1H, $ArCH_2N$), 3.53 (d, *J* = 6.7 Hz, 1H, CH_2O), 3.83 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.34 (d, *J* = 13.6 Hz, 1H, $ArCH_2N$), 6.44 (s, 1H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): 21.9 (CH_3), 22.0 (CH_2), 27.1 (CH_2), 33.3 ($ArCH_2$), 36.6 (CH_2), 40.5 (NCH), 45.4 ($ArCH_2N$), 55.9 (OCH_3), 58.9 (CH), 59.1 (OCH_3), 60.7 (OCH_3), 61.0 (OCH_3), 62.5 (CH), 76.1 (CH_2O), 107.7 (CH), 125.1 (C), 139.3 (C), 139.9 (C), 151.1 (C), 151.5 (C). Anal. Calcd for $C_{20}H_{32}N_2O_4$: C, 65.91; H, 8.85; N, 7.69. Found: C, 66.09; H, 8.58; N, 7.89.

4.5.2. (*R*)-7,8-Dimethoxy-2-[(*S*)-2-methoxymethylpyrrolidin-1-yl]-3-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine 6d

321 mg (48%); $[\alpha]_D^{25} = -50.3$ (*c* 0.31, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 1.15 (d, *J* = 6.2, 3H, CH_3), 1.40–1.56 (m, 1H, CH_2), 1.57–1.82 (m, 3H:1H, CH_2 + 2H, CH_2), 1.83–2.01 (m, 2H:2 × 1H, 2 × CH_2), 2.67 (dd, *J* = 7.5, 6.9 Hz, 1H, CH_2N), 2.71–2.96 (m, 4H:1H, CH_2N + 2H, $ArCH_2$ + 1H, CH), 2.97–3.13 (m, 2H:1H, CH + 1H CH_2O), 3.30 (s, 3H, OCH_3), 3.55 (dd, *J* = 2.2, 5.4 Hz, 1H, CH_2O), 3.73 (q, *J* = 13.6 Hz, 2H, $ArCH_2N$), 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.64 (s, 1H, H_{arom}), 6.70 (s, 1H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): 21.8 (CH_3), 22.1 (CH_2), 27.3 (CH_2), 32.5 ($ArCH_2$), 36.8 (CH_2), 40.8 (NCH_2), 54.0 ($ArCH_2N$), 55.9 (OCH_3), 56.1 (OCH_3), 58.9 (CH), 59.7 (OCH_3), 62.4 (CH), 76.1 (CH_2O), 112.2 (CH), 112.6 (CH), 131.5 (C), 135.2 (C), 146.6 (C), 147.2 (C). Anal. Calcd for $C_{19}H_{30}N_2O_3$: C, 68.23; H, 9.04; N, 8.38. Found: C, 68.53; H, 8.98; N, 8.23.

4.5.3. (*R*)-3-Hexyl-7,8-dimethoxy-2-[(*S*)-2-methoxymethylpyrrolidin-1-yl]-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine 6h

404 mg (50%); $[\alpha]_D^{25} = -46.3$ (*c* 0.49, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 0.91 (t, *J* = 6.7 Hz, 3H, CH_3), 1.05–1.41 (m, 8H, 4 × CH_2), 1.43–1.80 (m, 4H, 2 × CH_2), 1.81–2.13 (m, 4H, 2 × CH_2), 2.68–2.83 (m, 2H, CH_2N), 2.84–2.95 (m, 1H, CH), 2.98–3.18 (m, 3H, CH + $ArCH_2$), 3.21–3.39 (m, 1H, CH_2O), 3.30 (s, 3H, OCH_3), 3.55 (dd, *J* = 2.2, 5.7 Hz, 1H, CH_2O), 3.75 (q, *J* = 15.2 Hz, 2H, $ArCH_2N$), 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.63 (s, 1H, H_{arom}), 6.69 (s, 1H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): 14.2 (CH_3), 22.0 (CH_2), 22.7 (CH_2), 26.4 (CH_2), 27.3 (CH_2), 29.8 (CH_2), 31.9 (CH_2), 32.0 (CH_2), 32.9 ($ArCH_2$), 33.3 (CH_2), 41.5 (NCH_2), 53.4 ($ArCH_2N$), 55.9 (OCH_3), 56.1 (OCH_3), 58.9 (CH), 59.7 (OCH_3), 66.6 (CH), 76.0 (CH_2O), 112.2 (CH), 112.5 (CH), 131.6 (C), 135.1 (C), 146.5 (C), 147.1 (C). Anal. Calcd for $C_{24}H_{40}N_2O_3$: C, 71.25; H, 9.97; N, 6.92. Found: C, 70.99; H, 9.87; N, 7.10.

4.6. Removal of the chiral appendage. Synthesis of the targeted benzazepines 1a–g and 2a,d,h

4.6.1. General procedure

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 benzazepines **5a–g** or **6a**,**d**,**h** (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 adding 10% aqueous NaOH (10 mL) and refluxed for 3 h. The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum for afford a colourless oil, which was purified by flash column chromatography on silica gel (acetone/MeOH, 90:10, as eluent).

4.6.2. (*R*)-7,8,9-Trimethoxy-4-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine 1a

146 mg (58%); $[\alpha]_D^{25} = -39.4$ (*c* 0.72, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 0.92 (d, *J* = 6.8 Hz, 3H, CH_3), 1.65–1.79 (m, 1H, CH), 2.58–2.73 (m, 3H:2H, $ArCH_2$ + 1H, CH_2N), 3.08–3.21 (m, 1H, CH_2N), 3.74–4.01 (m, 2H, $ArCH_2N$), 3.84 (s, 6H, 2 × OCH_3), 3.88 (s, 3H, OCH_3), 6.44 (s, 1H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): 19.8 (CH_3), 33.8 (CH), 42.9 ($ArCH_2$), 48.7 ($ArCH_2N$), 55.9 (OCH_3), 56.0 (OCH_3), 58.7 (OCH_3), 60.3 (CH_2N), 108.6 (CH), 126.1 (C), 136.6 (C), 139.8 (C), 150.6 (C), 151.2 (C). Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 67.02; H, 8.54; N, 5.58.

4.6.3. (*R*)-4-Benzyl-7,8,9-trimethoxy-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine 1b

157 mg (48%); $[\alpha]_D^{25} = -72.8$ (*c* 0.39, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 2.06–2.23 (m, 1H, CH), 2.52–2.91 (m, 4H, $PhCH_2$ + CH_2N), 2.96–3.09 (m, 2H, $ArCH_2$), 3.78–3.96 (m, 2H, $ArCH_2N$), 3.86 (s, 6H, 2 × OCH_3), 3.88 (s, 3H, OCH_3), 6.39 (s, 1H, H_{arom}), 7.02–7.27 (m, 5H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): 38.9 (CH), 39.4 (CH_2), 42.6 (CH_2), 48.1 ($ArCH_2N$), 55.9 (OCH_3), 56.1 (OCH_3), 58.6 (OCH_3), 61.9 (CH_2N), 109.3 (CH), 124.6 (C), 125.4 (CH), 128.3 (2 × CH), 129.4 (2 × CH), 136.1 (C), 140.7 (C), 140.9 (C), 151.0 (C), 151.2 (C). Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.25; H, 7.58; N, 4.50.

4.6.4. (*R*)-7,8,9-Trimethoxy-4-methoxymethyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine 1c

138 mg (49%); $[\alpha]_D^{25} = -44.2$ (*c* 0.41, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 2.05–2.18 (m, 1H, CH), 2.63–2.98 (m, 4H, $ArCH_2$ + CH_2N), 3.26–3.39 (m, 2H, CH_2OMe), 3.29 (s, 3H, OCH_3), 3.76–4.02 (m, 2H, $ArCH_2N$), 3.86 (s, 6H, 2 × OCH_3), 3.88 (s, 3H, OCH_3), 6.42 (s, 1H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): 38.2 (CH_2), 38.9 (CH), 48.1 ($ArCH_2N$), 55.9 (OCH_3), 56.4 (OCH_3), 60.8 (OCH_3), 61.2 (OCH_3), 61.9 (CH_2N), 74.6 (OCH_2), 108.4 (CH), 125.1 (C), 136.3 (C), 140.2

(C), 150.9 (C), 151.2 (C). Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98. Found: C, 63.94; H, 8.23; N, 5.12.

4.6.5. (*R*)-7,8-Dimethoxy-4-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine (*R*)-1d

117 mg (53%); $[\alpha]_D^{25} = -56.5$ (*c* 0.63, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 0.90 (d, *J* = 6.9, 3H, CH_3), 1.61–1.78 (m, 1H, CH), 2.63–2.84 (m, 3H:2H, $ArCH_2$ + 1H, CH_2N), 3.23 (d, *J* = 13.1 Hz, 1H, CH_2N), 3.71–4.04 (m, 2H, $ArCH_2N$), 3.85 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 6.68 (s, 2H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): 19.9 (CH_3), 34.5 (CH), 43.3 (CH_2), 54.0 ($ArCH_2N$), 56.0 (2 × OCH_3), 60.1 (CH_2N), 112.2 (CH), 113.6 (CH), 133.3 (C), 134.2 (C), 146.5 (C), 147.3 (C). Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.45; H, 8.55; N, 6.21.

4.6.6. (*S*)-7,8-Dimethoxy-4-methyl-2,3,4,5-tetrahydro-1*H*-2-benzo[*c*]azepine (*S*)-1d

115 mg (55%); $[\alpha]_D^{25} = +53.6$ (*c* 0.52, $CHCl_3$).

4.6.7. (*R*)-6,7-Dimethoxy-4-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine 1e

Yield: 48% (150 mg); $[\alpha]_D^{25} = +24.3$ (*c* 0.38, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 2.42 (br s, 1H, NH), 2.78–2.97 (m, 2H, $ArCH_2$), 3.04–3.21 (m, 1H, CH), 3.38–3.53 (m, 2H, CH_2N), 3.67 (d, *J* = 14.5 Hz, 1H, $ArCH_2N$), 3.83 (s, 3H, OCH_3), 3.88 (s, 6H, 2 × OCH_3), 4.54 (d, *J* = 14.8 Hz, 1H, $ArCH_2N$), 6.53 (s, 1H, H), 7.16–7.45 (m, 5H, H_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): 41.2 (CH_2), 45.2 (CH), 46.8 ($ArCH_2N$), 55.9 (OCH_3), 59.1 (OCH_3), 60.6 (OCH_3), 62.9 (CH_2N), 108.8 (CH), 124.9 (C), 126.8 (CH), 126.9 (2 × CH), 128.6 (2 × CH), 137.3 (C), 140.6 (C), 145.6 (C), 150.9 (C), 151.8 (C). Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 73.07; H, 7.54; N, 4.45.

4.6.8. (*S*)-6,7-Dimethoxy-4-pentyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine 1f

144 mg (52%); $[\alpha]_D^{25} = -6.8$ (*c* 0.47, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 0.89 (t, *J* = 6.7 Hz, 3H, CH_3), 1.03–1.65 (m, 9H, 4 × CH_2 + CH), 2.51–2.99 (m, 3H:1H, NH + 1H, CH_2N + 1H from $ArCH_2$), 3.05–3.33 (m, 2H:1H, CH_2N + 1H, $ArCH_2$), 3.70–3.99 (m, 8H, 2 × OCH_3 + $ArCH_2N$), 6.54–6.72 (m, 2H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): 14.1 (CH_3), 22.6 (CH_2), 26.7 (CH_2), 30.9 (CH_2), 32.0 (2 × CH_2), 38.8 (CH), 54.3 ($ArCH_2N$), 56.0 (2 × OCH_3), 58.6 (CH_2N), 107.2 (CH), 123.3 (CH), 136.5 (2 × C), 143.4 (C_a), 145.8 (C). Anal. Calcd for $C_{17}H_{27}NO_2$: C, 73.61; H, 9.81; N, 5.05. Found: C, 73.73; H, 9.98; N, 5.21.

4.6.9. (*R*)-8-(2-Benzyloxyethyl)-6,7,8,9-tetrahydro-5*H*-1,3-dioxa-6-azacyclohepta[*f*]indene 1g

166 mg: (51%); $[\alpha]_D^{25} = -12.6$ (*c* 0.61, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 1.52 (q, *J* = 6.4 Hz, 2H, CH_2), 1.78–1.93 (m, 1H, CH), 2.72 (dd, *J* = 8.6, 14.4, 1H, $ArCH_2$), 2.80–3.01 (m, 2H:1H, $ArCH_2$ + 1H, CH_2N), 3.25 (dd, *J* = 2.2, 11.4 Hz, 1H, CH_2N), 3.53 (t, *J* = 6.3 Hz, 2H, CH_2O), 3.62 (br s, 1H, NH), 3.86 (s, 2H, $ArCH_2N$), 4.51 (s, 2H, OCH_2), 5.91 (s, 2H, OCH_2O), 6.59 (s, 1H, H_{arom}), 6.64 (s, 1H, H_{arom}), 7.25–7.44 (m, 5H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): 32.8 (CH_2), 35.3 (CH), 40.6 (CH_2), 53.8 ($ArCH_2N$), 57.5 (CH_2N), 67.9 (OCH_2), 73.0 (OCH_2), 100.9 (OCH_2O), 109.3 (CH), 110.7 (CH), 127.6 (2 × CH), 127.7 (2 × CH), 128.4 (CH), 134.0 (C), 134.2 (C), 138.4 (C), 145.5 (C), 146.3 (C). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.51; H, 7.08; N, 4.25.

4.6.10. (*R*)-7,8,9-Trimethoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine 2a

146 mg (58%); $[\alpha]_D^{25} = -81.1$ (*c* 0.54, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 1.17 (d, *J* = 6.3 Hz, 3H, CH_3), 1.22–1.45 (m, 1H, CH_2), 1.81–2.02 (m, 1H, CH_2), 2.49–2.88 (m, 2H, CH_2), 2.89–3.15 (m, 2H, CH + NH), 3.57 (d, *J* = 14.6 Hz, 1H, $ArCH_2N$), 3.84 (s, 9H, 3 × OCH_3), 4.46 (d, *J* = 14.5 Hz, 1H, $ArCH_2N$), 6.50 (s, 1H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): 23.4 (CH_3), 34.9 (CH_2), 36.7 (CH_2), 44.0 ($ArCH_2N$), 56.0 (OCH_3), 58.9 (OCH_3), 60.8 (OCH_3), 61.6 (CH), 108.8 (CH), 127.0 (C), 138.7 (C), 140.7 (C), 151.0 (C), 151.7 (C). Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 67.07; H, 8.67; N, 5.78.

4.6.11. (*R*)-7,8-Dimethoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine 2d

117 mg (53%); $[\alpha]_D^{25} = -69.7$ (*c* 0.41, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 1.23 (d, *J* = 6.3 Hz, 3H, CH_3), 1.42–1.51 (m, 1H, CH_2), 1.88–2.07 (dd, *J* = 6.8, 7.0 Hz, 1H, CH), 2.76 (dd, *J* = 6.6, 14.6 Hz, 1H, CH_2), 2.97 (t, *J* = 13.7 Hz, 1H, CH_2), 3.07–3.23 (m, 1H, CH), 3.75–4.04 (m, 2H, $ArCH_2N$), 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.70 (s, 1H, H_{arom}), 6.73 (s, 1H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): 22.8 (CH_3), 33.8 (CH_2), 36.3 (CH_2), 52.1 ($ArCH_2N$), 56.0 (OCH_3), 56.1 (OCH_3), 58.5 (CH), 112.9 (2 × CH), 132.1 (C), 134.7 (C), 146.7 (C), 147.2 (C). Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.46; H, 8.51; N, 6.14.

4.6.12. (3*R*)-7,8-Dimethoxy-3-hexyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine 2h

163 mg (56%); $[\alpha]_D^{25} = -29.6$ (*c* 0.73, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 0.89 (t, *J* = 6.6 Hz, 3H, CH_3), 1.18–1.49 (m, 11H:10H, 5 × CH_2 + 1H, CH_2), 1.77–2.03 (m, 2H:1H, CH_2 + NH), 2.74 (dd, *J* = 6.6, 14.5 Hz, 1H, $ArCH_2$), 2.79–2.91 (m, 1H, CH), 2.97 (t, *J* = 13.6 Hz, 1H, $ArCH_2$), 3.77–4.03 (m, 2H, $ArCH_2N$), 3.86 (s, 6H, 2 × OCH_3), 6.69 (s, 1H, H_{arom}), 6.70 (s, 1H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): 14.1 (CH_3), 22.6 (CH_2), 26.2 (CH_2), 29.5 (CH_2), 31.8 (CH_2), 34.3 (CH_2), 35.8 (CH_2), 38.0 (CH), 53.4 ($ArCH_2N$), 56.0 (2 × OCH_3), 63.4 (CH), 112.4 (CH), 113.1 (CH), 134.5 (C), 134.9 (C), 146.5 (C), 147.3 (C). Anal. Calcd for $C_{18}H_{29}NO_2$: C, 74.18; H, 10.03; N, 4.81. Found: C, 74.45; H, 9.78; N, 4.62.

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