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First asymmetric synthesis of (un)substituted bridged tetrahydro-2-benzazepines

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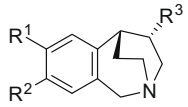
ABSTRACT

A new and flexible route for the asymmetric synthesis of a variety of alkylated bridged tetrahydro-2-benzazepines has been developed. The key steps are the highly diastereoselective Michael addition of metalated SAMP-hydrazones to α,β-unsaturated esters combined with cyclomethylenation/Mitsunobu coupling reactions to secure the formation of the seven-membered azaheterocycle and of the bridged unit, respectively.

1. Introduction

Seven-membered nitrogen heterocycles are constituents of a great variety of poly and diversely substituted models endowed with chemotherapeutic properties. As a result they have attracted the particular attention of medicinal chemists.[1] The benzo-annulated systems such as 2-benzazepine derivatives fall into this category and are known to display potent inhibitory activities against AchE and SERT,[2] broncho-relaxing activity,[3] and to promote skin epithelial cell migration and wound healing.[4] Many compounds containing this structure have also been found to interact with receptors for biogenic amines and to exhibit antipsychotic[5] and anticancer actions.[6] Several members of this class of azaheterocycles are also of significant interest as potent platelet anti-aggregatory drugs, CNS agents,[7] as specific ligands for serotonin and dopamine-receptor subtypes[7] and have also proved to be useful in the treatment of mental disorders and hypoxia.[8] A number of derivatives have been synthesized as non-peptide Arg-Gly-Asp (RGD) mimetic antagonist of the vitronectin, a receptor of glycoprotein assumed to play a pivotal role in cell–cell adhesion, signaling, and apoptosis.[9] The 2-benzazepine nucleus is also found in a number of *Cephalotaxus* and *Amaryllidaceae* bioactive alkaloids.[10] Due to this impressive range of exceptional bioactivities, the last few decades have witnessed a strong incentive toward the development of synthetic approaches to structurally sophisticated models and the interest in the chemistry of 2-benzazepines continues unabated.[11] In most cases, bioactive benzazepine-centered compounds comprise a benzofused azepine unit tailed with alkyl chains equipped with appropriate functionalities liable to act on the pharmacological profile. To the best of our knowledge, the assembly of conformationally constrained models has not elicited the interest of synthetic and pharmaceutical groups while benzofused bridged systems remain ignored by the scientific community in this series. This is notably the case for the azabicyclo[3.2.2]nonane derivatives **1** and **2** (Fig. 1) despite the fact that the bicyclic bridged scaffold is a common structural feature of structurally constrained analogues of balanol endowed with promising protein kinase inhibitor properties[12] and of heteroaromatic olefinic compounds that have been recently used as inhibitors of nicotinic cholinergic receptors.[13]



1 and **2**

Figure 1.

The benzofused analogues also represent the main structural unit of the communesins, an emerging class of biologically active *Penicillium* metabolites.[14] The lack of synthetic strategies to build up the rather constrained framework of **1** and **2** is probably due to the difficulties associated with the elaboration of parent compounds, which involve multi-steps,[15] a key problematic point hampering substitution of the azepine nucleus with appropriate functionalities to secure the required formation of the bridged unit. In this regard, the construction of models with additional stereocontrol of the carbon centers embedded in the bridged bicyclic unit becomes a very challenging synthetic task and we waited to face the challenge of preparing such stereopure polycyclic models.

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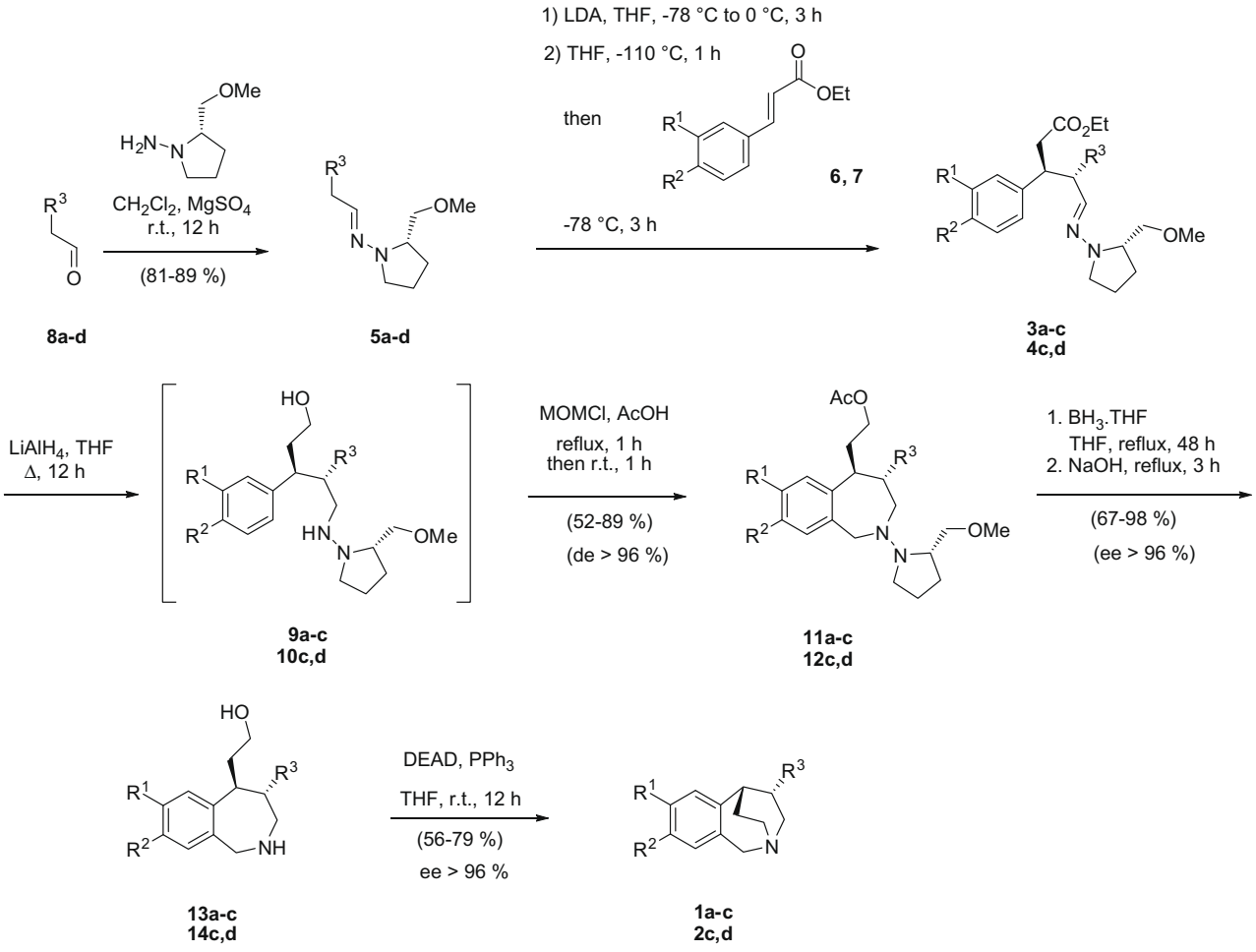
2. Results and discussion

We delineate in this paper a concise and conceptually new asymmetric approach to a variety of diversely substituted bridged tetrahydro-2-benzazepines **1**, **2** that is based upon strategic combinations of the highly diastereo- and enantioselective Michael addition of SAMP-hydrazones to α,β-unsaturated esters[16] followed by a reduction/cyclomethylenation sequence with an intramolecular Mitsunobu reaction. We surmised that the former sequence would provide the potential for an easy access to an opened precursor of the NH-free azepine ring system with the concomitant installation of a mandatory hydroxyalkylated chain.

The first facet of the synthesis which is depicted in Scheme 1 was the elaboration of the Michael adducts **3a–c**, **4c**,**d**. These compounds were readily assembled by the reaction of the azaenolates of SAMP-hydrazones **5a–d** acting as chiral nucleophiles on diversely substituted α,β-unsaturated esters **6**, **7**. Initially, the appropriate aliphatic carboxaldehydes were converted into the corresponding chiral hydrazones (*S*)-**5a–d** by simply mixing the enantiomerically pure hydrazine (*S*)-(−)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) with the commercially available aldehydes **8a–d** (Scheme 1, Table 1). The chiral hydrazones were allowed to react with lithium diisopropylamide (LDA) in THF at −78 °C followed by warming to 0 °C over a 3-h period. The (*E*)-esters **6**, **7** were then added at −100 °C to the lithium azaenolate generated, furnishing the crude Michael adducts (*R*,*S*)-**3a** and (*S*,*S*,*S*)-**3b**,**c or** (*S*,*S*,*S*)-**4c**,**d** which were purified by flash chromatography. In this way the ester-hydrazones **3**, **4** were obtained in good yields (Table 1) and high diastereoselectivity (de ⩾ 96%). The latter were determined by ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) and indicate the original asymmetric induction because no diastereomeric enrichment occurred during chromatography. The Michael adduct hydrazones **3**, **4** were obtained as the *E*-isomers exclusively based on the observed characteristic chemical shifts.[17] The (*S*,*S*)-absolute configuration of the newly generated stereogenic centers in **3b**,**c** and **4c**,**d** was assigned according to the previously confirmed mechanism for the asymmetric 1,4-addition of metalated aldehyde SAMP-hydrazones to enoate Michael acceptors.[16,18] SAMP-derivatives of this type are usually converted into the corresponding α,β-disubstituted ketones as a reliable procedure for the determination of the absolute configuration of chiral compounds.[19] For the synthesis of hydrazines **9a–c**, **10c**,**d**, suitable candidates for the planned cyclization reactions, hydrazones **3a–c**, **4c**,**d** were subsequently reduced with $LiAlH_4$. This operation delivered almost quantitative yields of the desired saturated compounds (*R*,*S*)-**9a**, (*S*,*S*,*S*)-**9b**,**c** and (*S*,*S*,*S*)-**10c**,**d**. As anticipated the reduction of the C=N double bond was accompanied with the conversion of the ester function into a hydroxyethyl appendage which should serve a role in synthetic planning. Owing to the limited stability and sensitivity usually exhibited by this type of NH-free hydrazines[16–18] the reduced compounds **9**, **10** were used in the next step without further purification. Cyclomethylenation of the unprotected arylalkylated hydrazones (*R*,*S*)-**9a**, (*S*,*S*,*S*)-**9b**,**c** and (*S*,*S*,*S*)-**10c**,**d** proceeded smoothly by making use of chloromethylmethyl ether (MOMCl) in acetic acid to provide satisfactory yields of the desired cyclic hydrazines (*R*,*S*)-**11a**, (*S*,*S*,*S*)-**11b**,**c** and (*S*,*S*,*S*)-**12c**,**d** as the sole diastereoisomer detectable by NMR upon flash chromatographic treatment. It is noteworthy that this simple operation did not spare the pendant hydroxyalkyl chain which was converted into the corresponding



Scheme 1.

Table 1
Compounds produced via Scheme 1

R^1	R^2	Michael adducts **3**, **4**[a] (yield %)	R^3	2-Benzazepine derivatives **11**, **12**[a,b] (yield %)	Hydroxyethyl 2-benzazepines **13**, **14**[c] (yield %)	Bridged **2** 2-benzazepines **1**, **2**[c] (yield %)
OMe	OMe	(*R*,*S*)-**3a** (51)	H	(*R*,*S*)-**11a** (61)	(*R*)-**13a** (88)	**1a** (64)
OMe	OMe	(*S*,*S*,*S*)-**3b** (48)	Me	(*S*,*S*,*S*)-**11b** (89)	(*S*,*S*)-**13b** (67)	(*S*,*S*)-**1b** (79)
OMe	OMe	(*S*,*S*,*S*)-**3c** (47)	Et	(*S*,*S*,*S*)-**11c** (55)	(*S*,*S*)-**13c** (98)	(*S*,*S*)-**1c** (62)
OCH_2O		(*S*,*S*,*S*)-**4c** (53)	Et	(*S*,*S*,*S*)-**12c** (59)	(*S*,*S*)-**14c** (73)	(*S*,*S*)-**2c** (59)
OCH_2O		(*S*,*S*,*S*)-**4d** (47)	n-C_5H_{11}	(*S*,*S*,*S*)-**12d** (52)	(*S*,*S*)-**14d** (76)	(*S*,*S*)-**2d** (56)

[a] Yield of isolated diastereoisomer (de ⩾ 96%).
[b] Over two steps.
[c] Yield of isolated virtually enantiopure isomer (ee ⩾ 96%).

acetate. However this undesirable reaction was not detrimental to the outcome of the synthetic process liable to give access to the diastereopure hydroxyalkylated benzazepine derivatives **13a–c**, **14c**,**d**, suitable candidates for the assembly of the title compounds. Indeed reductive N–N bond cleavage by the BH_3·THF complex triggered off the release of the chiral appendage with simultaneous regeneration of the hydroxy functionality and completed the synthesis of the virtually enantio- and diastereopure 5-hydroxyethyl NH-free tetrahydrobenzazepines (*R*)-**13a**, (*S*,*S*)-**13b**,**c** and (*S*,*S*)-**14c**,**d**, respectively. These amino-hydroxylated compounds were obtained in good yields with high enantio and diastereoisomeric excesses (ee ⩾ 96%, de ⩾ 96%; Table 1). With these compounds in hand, we were only one cyclization away from the title compounds since they possess the requisite structure and functional group location to be easily converted into the bridged seven-membered models under the agency of the Mitsunobu reaction. Thus treatment of **13a–c**, **14c**,**d** with diethyl azidodicarboxylate (DEAD) and triphenylphosphine delivered quite satisfactory yields of meso compound **1a** and of the virtually diastereopure benzofused bridged tetrahydroazepines (*S*,*S*)-**1b**,**c** and (*S*,*S*)-**2c**,**d** (Scheme 1, Table 1).

3. Conclusion

In conclusion we have devised a new and flexible method for the diastereoselective synthesis of a variety of diversely substituted bridged tetrahydro-2-benzazepines. The key steps are the highly diastereoselective Michael addition of metalated aldehyde hydrazones to aromatic enoates followed by a double reduction process to generate hydroxy and hydrazine functionalities combined with a cyclomethylenation reaction to secure the formation of the benzazepine ring system. Removal of the chiral auxiliary and an intramolecular Mitsunobu coupling reaction ensured the creation of the bridged unit to complete the assembly of the title compounds which were obtained with high de values.

4. Experimental

4.1. General

Melting points were determined on a Reichert-Thermopan apparatus and are uncorrected. NMR spectra were recorded on a Bruker AM 300 spectrometer. These 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.

SAMP-hydrazones **5a–d** were prepared according to a reported procedure.[20] The α,β-unsaturated esters **6**[21] and **7**[22] were synthesized following the literature methods.

4.2. Synthesis of the Michael adducts 3a–c and 4c,d. 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 and was then cooled to −78 °C. A solution of the appropriate hydrazone **5a–d** (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 3 h at 0 °C. The mixture was recooled to −110 °C and a solution of the appropriate α,β-unsaturated ester **6**, **7** (7.1 mmol) in dry THF (10 mL) was added slowly. After stirring for 1 h at −110 °C, the temperature was allowed to rise slowly to −78 °C and stirring was maintained for 3 h at this temperature. The reaction was then quenched with a saturated HCl ethereal solution (5 mL) and allowed to warm to rt. Water (10 mL) was then added, and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (20 mL) and water (20 mL), then dried ($MgSO_4$), concentrated, and purified by flash column chromatography on silica gel (ethyl acetate–hexanes, 30:70, as eluent) to yield the hydrazones **3a-c** and **4c**,**d** as a pale yellow to colorless oil.

4.2.1. (*R*)-3-(3,4-Dimethoxyphenyl)-5-[(*S*)-2-(methoxymethyl) pyrrolidin-1-ylimino]pentanoic ethyl ester 3a

1.42 g (51%); $[\alpha]_D^{25} = -57.7$ (*c* 0.87, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 (t, *J* = 7.2 Hz, 3H, CH_3), 1.71–2.02 (m, 4H, 2 × CH_2), 2.46–2.68 (m, 4H:2H, CH_2CHN + 1H, CH_2COO + 1H, CH_2N), 2.72 (dd, *J* = 3.9, 15.3 Hz, 1H CH_2CO_2Et), 3.29–3.45 (m, 4H:1H, CH_2N + 1H, CH + 1H, ArCH + 1H OCH_2), 3.37 (s, 3H, OCH_3), 3.47–3.60 (m, 1H, OCH_2), 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.03 (q, *J* = 7.2 Hz, 2H, $COOCH_2$), 6.46 (t, *J* = 5.4 Hz, 1H, CH=N), 6.67–6.84 (m, 3H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 (CH_3), 22.1 (CH_2), 26.5 (CH_2), 39.8 (CH_2), 40.4 (ArCH), 40.9 (CH_2), 50.2 (CH_2), 55.8 (2 × OCH_3), 59.2 (CH), 60.3 (OCH_2), 63.3 (OCH_3), 74.7 (OCH_2), 110.7 (CH), 111.0 (CH), 119.3 (CH), 135.6 (CH=N), 136.1 (C), 147.5 (C), 148.7 (C), 172.3 (CO) ppm. Anal. Calcd for $C_{21}H_{32}N_2O_5$: C, 64.26; H, 8.22; N, 7.14. Found: C, 64.32; H, 8.52; N, 7.05.

4.2.2. (3*S*,4*S*)-3-(3,4-Dimethoxyphenyl)-5-[(*S*)-2-(methoxymethyl) pyrrolidin-1-ylimino]-4-methylpentanoic ethyl ester 3b

1.38 g (48%); $[\alpha]_D^{25} = -68.4$ (*c* 1.18, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97–1.12 (m, 6H, 2 × CH_3), 1.65–1.95 (m, 4H, 2 × CH_2), 2.41–2.66 (m, 3H:1H, CH + 1H, CH_2COO + 1H, CH_2N), 2.74 (dd, *J* = 5.6, 15.5 Hz, 1H, CH_2COO), 3.11–3.41 (m, 4H:1H, CH_2N + 1H, CH + 1H, ArCH + 1H, OCH_2), 3.33 (s, 3H, OCH_3), 3.49 (dd, *J* = 3.8, 9.1 Hz, 1H OCH_2), 3.82 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.97 (dq, *J* = 2.2, 7.1 Hz, 2H, $COOCH_2$), 6.29 (d, *J* = 6.7 Hz, 1H, CH=N),

6.61–6.80 (m, 3H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3), 16.7 (CH_3), 22.1 (CH_2), 26.5 (CH_2), 38.1 (CH_2), 41.9 (CH), 45.9 (ArCH), 50.2 (CH_2N), 55.8 ($2 \times OCH_3$), 59.2 (CH), 60.2 (OCH_2), 63.4 (OCH_3), 74.6 (OCH_2), 110.6 (CH), 111.9 (CH), 120.5 (CH), 134.0 (C), 140.7 (CH=N), 147.4 (C), 148.3 (C), 172.5 (CO) ppm. Anal. Calcd for $C_{22}H_{34}N_2O_5$: C, 65.00; H, 8.43; N, 6.89. Found: C, 64.85; H, 8.45; N, 6.81.

4.2.3. (3*S*,4*S*)-3-(3,4-Dimethoxyphenyl)-4-{[(*S*)-2-(methoxymethyl) pyrrolidin-1-yl-imino]methyl}hexanoic ethyl ester 3c

1.40 g (47%); $[\alpha]_D^{25} = -86.4$ (*c* 0.86, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, *J* = 7.3 Hz, 3H, CH_3), 1.08 (t, *J* = 7.2 Hz, 3H, CH_3), 1.20–1.38 (m, 1H, CH_2), 1.43–1.60 (m, 1H, CH_2), 1.68–1.96 (m, 4H, $2 \times CH_2$), 2.22–2.40 (m, 1H, CH), 2.49–2.69 (m, 2H:1H, CH_2COO + 1H, CH_2N), 2.74 (dd, *J* = 5.9, 15.3 Hz, 1H, CH_2COO), 3.18–3.39 (m, 4H:1H, CH_2N + 1H, CH + 1H, ArCH + 1H, OCH_2), 3.32 (s, 3H, OCH_3), 3.48 (dd, *J* = 3.8, 9.2 Hz, 1H, OCH_2), 3.82 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.97 (q, 2H, *J* = 7.0 Hz, $COOCH_2$), 6.18 (d, 1H, *J* = 7.6 Hz, CH=N), 6.57–6.81 (m, 3H, H_{arom}) pmm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.9 (CH_3), 14.1 (CH_3), 22.1 (CH_2), 24.6 (CH_2), 26.5 (CH_2), 38.7 (CH_2), 44.5 (CH), 48.9 (ArCH), 50.4 (CH_2N), 55.8 ($2 \times OCH_3$), 59.1 (CH), 60.1 (OCH_2), 63.4 (OCH_3), 74.7 (OCH_2), 110.5 (CH), 112.0 (CH), 120.8 (CH), 133.7 (C), 139.9 (CH=N), 147.5 (C), 148.3 (C), 172.5 (CO) ppm. Anal. Calcd for $C_{23}H_{36}N_2O_5$: C, 65.69; H, 8.63; N, 6.66. Found: C, 65.88; H, 8.39; N, 6.51.

4.2.4. (3*S*,4*S*)-3-Benzo[1,3]dioxol-5-yl-4-{[(*S*)-2-(methoxymethyl) pyrrolidin-1-ylimino]methyl}hexanoic ethyl ester 4c

1.43 g (53%); $[\alpha]_D^{25} = -90.4$ (*c* 4.58, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.81 (t, *J* = 7.3 Hz, 3H, CH_3), 1.05 (t, *J* = 7.1 Hz, 3H, CH_3), 1.18–1.32 (m, 1H, CH_2), 1.38–1.52 (m, 1H, CH_2), 1.64–1.94 (m, 4H, $2 \times CH_2$), 2.18–2.30 (m, 1H, CH), 2.47–2.61 (m, 2H:1H, CH_2COO + 1H, CH_2N), 2.67 (dd, *J* = 5.8, 15.6 Hz, 1H, CH_2COO), 3.13–3.36 (m, 4H:1H, CH_2N + 1H, CH + 1H, ArCH + 1H, OCH_2), 3.29 (s, 3H, OCH_3), 3.44 (dd, *J* = 3.1, 8.5 Hz, 1H, OCH_2), 3.94 (q, *J* = 7.0 Hz, 2H, $COOCH_2$), 5.84 (s, 2H, OCH_2O), 6.14 (d, *J* = 7.7 Hz, 1H, CH=N), 6.48–6.67 (m, 3H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.9 (CH_3), 14.1 (CH_3), 22.1 (CH_2), 24.6 (CH_2), 26.6 (CH_2), 38.8 (CH_2), 44.6 (CH), 48.9 (ArCH), 50.6 (CH_2N), 59.2 (CH), 60.2 (OCH_2), 63.4 (OCH_3), 74.7 (OCH_2), 100.8 (OCH_2O), 107.7 (CH), 109.1 (CH), 121.2 (CH), 134.9 (C), 139.7 (CH=N), 146.0 (C), 147.2 (C), 172.4 (CO) ppm. Anal. Calcd for $C_{22}H_{32}N_2O_5$: C, 65.32; H, 7.97; N, 6.93. Found: C, 65.12; H, 7.78; N, 6.87.

4.2.5. (3*S*,4*S*)-3-Benzo[1,3]dioxol-5-yl-4-{[(*S*)-2-(methoxymethyl) pyrrolidin-1-ylimino]methyl}nonanoic ethyl ester 4d

1.49 g (47%); $[\alpha]_D^{25} = -82.6$ (*c* 1.58, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.83 (t, *J* = 6.7 Hz, 3H, CH_3), 1.09 (t, *J* = 7.0 Hz, 3H, CH_3), 1.13–1.51 (m, 8H, $4 \times CH_2$), 1.65–1.98 (m, 4H, $2 \times CH_2$), 2.29–2.43 (m, 1H, CH), 2.49–2.65 (m, 2H:1H, CH_2COO + 1H, CH_2N), 2.72 (dd, *J* = 5.9, 15.6 Hz, 1H, CH_2COO), 3.12–3.40 (m, 4H:1H, CH_2N + 1H, CH + 1H, ArCH + 1H, OCH_2), 3.33 (s, 3H, OCH_3), 3.48 (dd, *J* = 3.5, 8.8 Hz, 1H, OCH_2), 3.98 (dq, *J* = 2.1, 7.2 Hz, 2H, $COOCH_2$), 5.87 (s, 2H, OCH_2O), 6.18 (d, *J* = 7.6 Hz, 1H, CH=N), 6.52–6.71 (m, 3H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 ($2 \times CH_3$), 22.1 (CH_2), 22.5 (CH_2), 26.5 (CH_2), 26.9 (CH_2), 31.7 (CH_2), 31.8 (CH_2), 38.8 (CH_2), 44.9 (CH), 47.1 (ArCH), 50.6 (CH_2N), 59.1 (CH), 60.1 (OCH_2), 63.4 (OCH_3), 74.7 (OCH_2), 100.8 (OCH_2O), 107.6 (CH), 109.0 (CH), 121.8 (CH), 134.9 (C), 139.9 (CH=N), 145.9 (C), 147.2 (C), 172.3 (CO) ppm. Anal. Calcd for $C_{25}H_{38}N_2O_5$: C, 67.24; H, 8.58; N, 6.27. Found: C, 67.12; H, 8.37; N, 6.51.

4.3. Synthesis of tetrahydrobenzazepine derivatives 11a–c, 12c,d. General procedure

A solution of Michael adduct **3a–c** or **4c**,**d** (4.0 mmol) in THF (10 mL) was slowly added to a stirred suspension of $LiAlH_4$ (419 mg, 12 mmol) in dry THF (5 mL) and the resulting mixture was refluxed overnight. After cooling, water (0.5 mL), 10% aqueous NaOH (0.5 mL), and water (1 mL) were successively added to the mixture. The precipitate was removed by filtration and was thoroughly washed with CH_2Cl_2 (2×5 mL) and Et_2O (2×5 mL). The filtrate was dried ($MgSO_4$) and concentrated under vacuum to afford the crude hydrazine **9a–c** or **10c**,**d** as a colorless oil which was used in the next step without further purification. MOMCl (161 mg, 0.15 mL, 2.0 mmol) was added to a stirred solution of the crude hydrazine **9a–c** or **10c**,**d** (2.0 mmol) in glacial acetic acid (10 mL) under Ar and the mixture was refluxed for 1 h and then stirred at rt for 1 h. The crude reaction mixture was poured onto crushed ice and neutralized with 50% aqueous NaOH and then was extracted with ethyl acetate (3×25 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), and 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 the expected tetrahydrobenzazepines **11a–c**, **12c**,**d** as yellow oil.

4.3.1. Acetic acid 2-[(*R*)-7,8-dimethoxy-2-[(*S*)-2-(methoxymethyl) pyrrolidin-1-yl]-2,3,4,5-tetrahydro-1*H*-2-benzazepin-5-yl]ethyl ester 11a

495 mg (61%); $[\alpha]_D^{25} = -82.6$ (*c* 1.58, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.61–1.87 (m, 4H, $2 \times CH_2$), 1.88–2.10 (m, 3H:2H, CH_2 + 1H, CH_2), 2.06 (s, 3H, CH_3), 2.11–2.23 (m, 1H, CH_2), 2.68–2.82 (m, 1H, ArCH), 2.86–3.19 (m, 5H:4H, $2 \times CH_2N$ + 1H, CH), 3.21–3.36 (m, 1H, OCH_2), 3.31 (s, 3H, OCH_3), 3.46 (dd, 1H, *J* = 3.2, 9.0 Hz, 1H OCH_2), 3.79–3.97 (m, 2H, CH_2OAc), 3.84 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.04–4.22 (m, 2H, $ArCH_2N$), 6.64 (s, 1H, H_{arom}), 6.68 (s, 1H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0 (CH_3), 21.4 (CH_2), 26.3 (CH_2), 32.2 (CH_2), 32.7 (CH_2), 39.7 (ArCH), 44.0 (CH_2N), 44.2 (CH_2N), 51.8 (CH_2N), 56.0 ($2 \times OCH_3$), 59.0 (OCH_3), 59.1 (CH), 63.1 (CH_2OAc), 75.3 (OCH_2), 113.3 (CH), 113.4 (CH), 130.9 (C), 136.0 (C), 146.6 (C), 147.2 (C), 171.2 (CO) ppm. Anal. Calcd for $C_{22}H_{34}N_2O_5$: C, 65.00; H, 8.43; N, 6.89. Found: C, 64.87; H, 8.59; N, 6.75.

4.3.2. Acetic acid 2-{(4*S*,5*S*)-7,8-dimethoxy-2-[(*S*)-2-(methoxy methyl)pyrrolidin-1-yl]-4-methyl-2,3,4,5-tetrahydro-1*H*-2-benzazepin-5-yl}ethyl ester 11b

748 mg (89%); $[\alpha]_D^{25} = -86.0$ (*c* 1.40, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.93 (d, *J* = 6.9 Hz, 3H, CH_3), 1.59–1.85 (m, 4H, $2 \times CH_2$), 1.86–2.08 (m, 2H, CH_2), 2.03 (s, 3H, CH_3), 2.09–2.27 (m, 1H, CH), 2.54–2.69 (m, 1H, ArCH), 2.70–2.90 (m, 3H:2H, CH_2N + CH), 2.95–3.12 (m, 2H, CH_2N), 3.25–3.35 (m, 1H, OCH_2), 3.31 (s, 3H, OCH_3), 3.45 (dd, *J* = 3.1, 9.2 Hz, 1H, OCH_2), 3.78–3.92 (m, 1H, $ArCH_2N$), 3.84 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.98 (t, *J* = 6.1 Hz, 2H, CH_2OAc), 4.15 (d, *J* = 13.9 Hz, 1H, $ArCH_2N$), 6.54 (s, 1H, H_{arom}), 6.68 (s, 1H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.9 (CH_3), 21.0 (CH_3), 21.2 (CH_2), 25.6 (CH_2), 32.3 (CH_2), 35.5 (ArCH), 43.6 ($ArCH_2N$), 48.6 (CH), 51.8 (CH_2N), 51.9 (CH_2N), 55.8 (OCH_3), 55.9 (OCH_3), 58.9 (OCH_3), 59.2 (CH), 63.1 (CH_2OAc), 74.9 (OCH_2), 114.1 (CH), 115.1 (CH), 130.0 (C), 132.8 (C), 146.7 (C), 146.8 (C), 171.1 (CO) ppm. Anal. Calcd for $C_{23}H_{36}N_2O_5$: C, 65.69; H, 8.63; N, 6.66. Found: C, 65.41; H, 8.56; N, 6.56.

4.3.3. Acetic acid 2-{(4*S*,5*S*)-4-ethyl-7,8-dimethoxy-2-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]-2,3,4,5-tetrahydro-1*H*-2-benzazepin-5-yl}ethyl ester 11c

478 mg (55%); $[\alpha]_D^{25} = -55.8$ (*c* 1.46, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.85 (t, *J* = 7.3 Hz, 3H, CH_3), 1.12–1.46 (m, 2H, CH_2), 1.57–1.83 (m, 4H, $2 \times CH_2$), 1.87–1.98 (m, 1H, CH), 1.99–2.25 (m, 2H, CH_2), 2.02 (s, 3H, CH_3), 2.68–2.90 (m, 3H:2H, CH_2N + 1H, CH), 2.92–3.09 (m, 3H:2H, CH_2N + 1H, ArCH), 3.23–3.40 (m, 1H, OCH_2), 3.30 (s, 3H, OCH_3), 3.46 (dd, *J* = 2.9, 9.2 Hz, 1H, OCH_2),

3.82 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.88 (d, J = 13.7 Hz, 1H, $ArCH_2N$), 4.00 (t, 2H, J = 7.0 Hz, CH_2OAc), 4.16 (d, J = 13.7 Hz, 1H, $ArCH_2N$), 6.51 (s, 1H, H_{arom}), 6.66 (s, 1H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.3 (CH_3), 21.0 (CH_3), 21.1 (CH_2), 25.2 (CH_2), 25.6 (CH_2), 32.1 (CH_2), 42.8 (ArCH), 43.4 ($ArCH_2N$), 46.6 (CH), 49.4 ($2 \times CH_2N$), 55.8 (OCH_3), 55.9 (OCH_3), 59.0 (OCH_3), 59.2 (CH), 63.2 (CH_2OAc), 74.8 (OCH_2), 114.2 (CH), 115.0 (CH), 129.5 (C), 132.9 (C), 146.7 (C_a), 146.8 (C), 171.2 (CO) ppm. Anal. Calcd for $C_{24}H_{38}N_2O_5$: C, 66.33; H, 8.81; N, 6.45. Found: C, 66.51; H, 8.97; N, 6.53.

4.3.4. Acetic acid 2-{(8*S*,9*S*)-8-ethyl-6-[(*S*)-2-(methoxymethyl) pyrrolidin-1-yl]-6,7,8,9-tetrahydro-5*H*-1,3-dioxa-6-azacyclohepta[*f*]inden-9-yl}ethyl ester 12c

494 mg (59%); $[\alpha]_D^{25} = -54.0$ (c 0.69, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, J = 7.2 Hz, 3H, CH_3), 1.11–1.44 (m, 2H, CH_2), 1.59–1.86 (m, 4H, $2 \times CH_2$), 1.84–1.97 (m, 1H, CH), 2.02–2.21 (m, 2H, CH_2), 2.01 (s, 3H, CH_3), 2.69–2.93 (m, 3H:2H, CH_2N + CH), 2.91–3.06 (m, 3H:2H, CH_2N + 1H, ArCH), 3.21–3.39 (m, 1H, OCH_2), 3.31 (s, 3H, OCH_3), 3.44 (dd, J = 2.8–9.1 Hz, 1H, OCH_2), 3.86 (d, J = 13.5 Hz, 1H, $ArCH_2N$), 4.03 (t, J = 7.1 Hz, 2H, CH_2OAc), 4.17 (d, J = 13.5 Hz, 1H, $ArCH_2N$), 5.91 (d, J = 11.5 Hz, 2H, OCH_2O), 6.51 (s, 1H, H_{arom}), 6.64 (s, 1H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.1 (CH_3), 21.0 (CH_3), 21.2 (CH_2), 25.1 (CH_2), 25.6 (CH_2), 32.2 (CH_2), 42.4 (ArCH), 43.3 ($ArCH_2N$), 46.7 (CH), 49.2 ($2 \times CH_2N$), 59.0 (OCH_3), 59.1 (CH), 63.2 (CH_2OAc), 75.1 (OCH_2), 99.9 (OCH_2O), 107.6 (CH), 108.1 (CH), 134.2 (C), 138.5 (C), 145.7 (C), 146.6 (C), 171.1 (CO) ppm. Anal. Calcd for $C_{23}H_{34}N_2O_5$: C, 66.00; H, 8.19; N, 6.69. Found: C, 65.87; H, 8.36; N, 6.77.

4.3.5. Acetic acid 2-{(8*S*,9*S*)-6-[(*S*)-2-(methoxymethyl)pyrrolidin-1-yl]-8-pentyl-6,7,8,9-tetrahydro-5*H*-1,3-dioxa-6-azacyclohepta[*f*]inden-9-yl}ethyl ester 12d

479 mg (52%); $[\alpha]_D^{25} = -53.4$ (c 0.52, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.72–0.91 (m, 3H, CH_3), 0.93–1.45 (m, 8H, $4 \times CH_2$), 1.49–1.83 (m, 4H, $2 \times CH_2$), 1.85–2.28 (m, 3H:1H, CH + 2H, CH_2), 2.04 (s, 3H, CH_3), 2.64–2.87 (m, 3H:2H, CH_2N + 1H, CH), 2.88–3.04 (m, 3H:2H, CH_2N + 1H, ArCH), 3.21–3.41 (m, 1H, OCH_2), 3.31 (s, 3H, OCH_3), 3.46 (dd, J = 2.9, 9.2 Hz, 1H, OCH_2), 3.63–3.72 (m, 1H, $ArCH_2N$), 3.81–4.04 (m, 2H, CH_2OAc), 4.06–4.20 (m, 1H, $ArCH_2N$), 5.92 (d, J = 11.6 Hz, 2H, OCH_2O), 6.51 (s, 1H, H_{arom}), 6.63 (s, 1H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3), 21.0 (CH_3), 21.1 (CH_2), 22.4 (CH_2), 22.6 (CH_2), 25.7 (CH_2), 26.2 (CH_2), 28.3 (CH_2), 32.0 (CH_2), 41.2 (ArCH), 43.3 ($ArCH_2N$), 47.6 (CH), 49.4 (CH_2N), 49.6 (CH_2N), 58.9 (OCH_3), 59.2 (CH), 63.2 (CH_2OAc), 75.3 (OCH_2), 99.7 (OCH_2O), 107.5 (CH), 108.2 (CH), 134.2 (C), 138.6 (C), 145.6 (C), 146.5 (C), 171.2 (CO) ppm. Anal. Calcd for $C_{26}H_{40}N_2O_5$: C, 67.80; H, 8.75; N, 6.08. Found: C, 68.07; H, 8.92; N, 6.76.

4.4. Synthesis of hydroxyethyltetrahydro-2-benzazepines 13a–c and 14c,d. 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 benzazepine derivative **11a–c**, **12c**,**d** (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. After cooling to rt, water (10 mL) was added and the mixture was extracted with ethyl ether (3×25 mL). The combined organic layers were washed with water (2×5 mL), brine (5 mL), and then dried ($MgSO_4$). Concentration under vacuum afforded a pale yellow oil which was purified by flash column chromatography on silica gel (acetone–MeOH–Et_3N, 80:10:10, as eluent) to yield the expected benzazepines **13a–c**, **14c**,**d**.

4.4.1. 2-[(*R*)-7,8-Dimethoxy-2,3,4,5-tetrahydro-1*H*-2-benzazepin-5-yl]ethanol 13a

221 mg (88%); $[\alpha]_D^{25} = -15.5$ (c 1.51, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.42–1.91 (m, 5H:4H, $2 \times CH_2$ + 1H, NH + 1H, OH), 1.92–2.11 (m, 1H, CH_2), 2.69–3.21 (m, 3H:2H, CH_2N + 1H, ArCH), 3.42–3.67 (m, 2H, CH_2O), 3.69–3.99 (m, 2H, $ArCH_2N$), 3.77 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 6.56 (s, 1H, H_{arom}), 6.64 (s, 1H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.1 (CH_2N), 34.6 (CH_2), 37.3 (ArCH), 52.7 ($ArCH_2N$), 54.2 (CH_2N), 54.9 (OCH_3), 55.1 (OCH_3), 59.7 (CH_2OH), 109.5 (CH), 110.1 (CH), 132.8 (C), 135.9 (C), 145.4 (C), 146.3 (C) ppm. Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 67.09; H, 8.45; N, 5.82.

4.4.2. 2-[(4*S*,5*S*)-7,8-Dimethoxy-4-methyl-2,3,4,5-tetrahydro-1*H*-2-benzazepin-5-yl]ethanol 13b

177 mg (67%); $[\alpha]_D^{25} = -14.7$ (c 1.26, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (d, J = 7.1 Hz, 3H, CH_3), 1.80–2.02 (m, 2H, CH_2), 2.05–2.23 (m, 1H, CH), 2.53–2.87 (m, 3H:1H, NH + 1H, ArCH + 1H, OH), 2.95 (dd, J = 2.9, 14.2 Hz, 1H, CH_2N), 3.34 (dd, J = 2.2, 14.3 Hz, 1H, CH_2N), 3.44–3.65 (m, 2H, CH_2O), 3.74 (d, J = 15.2 Hz, 1H, $ArCH_2N$), 3.84 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.05 (d, J = 15.2 Hz, 1H, $ArCH_2N$), 6.59 (s, 1H, H_{arom}), 6.66 (s, 1H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.9 (CH_3), 35.7 (ArCH), 36.1 (CH_2), 49.1 (CH), 52.0 ($ArCH_2N$), 54.1 (CH_2N), 55.9 (OCH_3), 56.1 (OCH_3), 60.9 (CH_2OH), 113.3 (CH), 115.6 (CH), 132.6 (C), 134.0 (C), 146.6 (C), 147.0 (C) ppm. Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 68.12; H, 8.89; N, 5.52.

4.4.3. 2-[(4*S*,5*S*)-7,8-Dimethoxy-4-ethyl-2,3,4,5-tetrahydro-1*H*-2-benzazepin-5-yl]ethanol 13c

273 mg (98%); $[\alpha]_D^{25} = -13.5$ (c 1.33, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, J = 7.2 Hz, 3H, CH_3), 1.15–1.31 (m, 2H, CH_2), 1.81–2.02 (m, 2H, CH), 2.08–2.23 (m, 1H, CH), 2.25–2.49 (br s, 2H, OH + NH), 2.81–2.96 (m, 1H, ArCH), 3.08 (d, J = 12.0 Hz, 1H, CH_2N), 3.27 (d, J = 14.3 Hz, 1H, CH_2N), 3.49–3.67 (m, 2H, CH_2O), 3.73 (d, J = 15.2 Hz, 1H, $ArCH_2N$), 3.83 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.07 (d, J = 15.2 Hz, 1H, $ArCH_2N$), 6.58 (s, 1H, H_{arom}), 6.66 (s, 1H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.0 (CH_3), 24.2 (CH_2), 36.0 (CH_2), 43.0 (ArCH), 47.2 (CH), 49.7 ($ArCH_2N$), 54.5 (CH_2N), 55.9 (OCH_3), 56.1 (OCH_3), 61.1 (CH_2OH), 113.3 (CH), 115.5 (CH), 133.9 (C), 134.0 (C), 146.6 (C), 147.0 (C) ppm. Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 68.97; H, 8.78; N, 5.23.

4.4.4. 2-[(8*S*,9*S*)-8-Ethyl-6,7,8,9-tetrahydro-5*H*-1,3-dioxa-6-azacyclohepta[*f*]inden-9-yl]ethanol 14c

192 mg (73%); $[\alpha]_D^{25} = -10.6$ (c 0.80, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, J = 7.1 Hz, 3H, CH_3), 1.16–1.34 (m, 2H, CH_2), 1.83–2.01 (m, 2H, CH_2), 2.07–2.23 (m, 1H, CH), 2.24–2.51 (br s, 2H, OH + NH), 2.83–2.99 (m, 1H, ArCH), 3.07 (d, J = 12.1 Hz, 1H, CH_2N), 3.28 (d, J = 12.1 Hz, 1H, CH_2N), 3.49–3.69 (m, 2H, CH_2O), 3.74 (d, J = 15.1 Hz, 1H, $ArCH_2N$), 4.06 (d, J = 15.1 Hz, 1H , $ArCH_2N$), 5.92 (s, 2H, OCH_2O), 6.61 (s, 1H, H_{arom}), 6.66 (s, 1H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.2 (CH_3), 24.1 (CH_2), 36.0 (CH_2), 42.8 (ArCH), 47.1 (CH), 49.8 ($ArCH_2N$), 54.2 (CH_2N), 61.0 (CH_2OH), 100.9 (OCH_2O), 108.2 (CH), 108.6 (CH), 135.9 (C), 137.2 (C), 145.8 (C), 146.2 (C) ppm. Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.53; H, 7.94; N, 5.21.

4.4.5. 2-[(8*S*,9*S*)-8-Pentyl-6,7,8,9-tetrahydro-5*H*-1,3-dioxa-6-azacyclohepta[*f*]inden-9-yl]ethanol 14d

232 mg (76%); $[\alpha]_D^{25} = -6.9$ (c 1.63, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.83 (t, J = 7.0 Hz, 3H, CH_3), 0.98–1.49 (m, 6H, $3 \times CH_2$), 1.51–1.68 (m, 2H, CH_2), 1.69–1.83 (m, 1H, CH), 1.86–2.12 (m, 4H:2H, CH_2 + 1H, OH + 1H, NH), 2.71–2.97 (m, 1H, ArCH), 3.31–3.67 (m, 4H:2H, CH_2N + 2H, CH_2O), 3.69–3.86 (m, 1H, $ArCH_2N$),

4.02–4.21 (m, 1H, $ArCH_2N$), 5.93 (s, 2H, OCH_2O), 6.64 (s, 1H, H_{arom}), 6.67 (s, 1H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3), 22.6 (CH_2), 26.7 (CH_2), 27.2 (CH_2), 31.7 (CH_2), 35.8 (CH_2), 38.9 (CH), 42.1 (ArCH), 45.6 ($ArCH_2N$), 51.7 (CH_2N), 61.9 (CH_2OH), 100.8 (OCH_2O), 107.9 (CH), 108.5 (CH), 135.8 (C), 137.1 (C), 145.7 (C), 146.2 (C) ppm. Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.86; H, 9.12; N, 4.34.

4.5. Synthesis of the bridged tetrahydro-2-benzazepines 1a–c, 2c,d. General procedure

A solution of the appropriate hydroxyethyl-tetrahydro-2-benzazepine **13a–c**, **14c**,**d** (0.5 mmol) in dry THF (5 mL) was slowly added to a stirred solution of triphenylphosphine (PPh_3, 184 mg, 0.7 mmol) and DEAD (0.27 mL, 40% in toluene, 0.6 mmol) in dry THF (5 mL) at rt under Ar. The solution was stirred overnight at rt, water (2 mL) was then added and the resulting mixture was concentrated under reduced pressure. The oily residue was purified by flash column chromatography on silica gel (acetone–MeOH–Et_3N, 85:5:10, as eluent) to yield the bridged tetrahydrobenzazepine **1a–c**, **2c**,**d** as foam.

4.5.1. 4,5-Dimethoxy-9-aza-tricyclo[7.2.2.0^{2,7}]trideca-2,4,6-triene 1a

74 mg (64%); ^1H NMR (300 MHz, $CDCl_3$): δ 1.97–2.14 (m, 4H, 2 × CH_2), 2.83–2.92 (m, 1H, CH), 3.00–3.17 (m, 2H, CH_2N), 3.18–3.32 (m, 2H, CH_2N), 3.85 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.33 (s, 2H, $ArCH_2N$), 6.59 (s, 1H, H_{arom}), 6.60 (s, 1H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.0 (2 × CH_2), 35.4 (CH), 46.0 (CH_2N), 46.3 (CH_2N), 55.9 (2 × OCH_3), 61.2 ($ArCH_2N$), 110.4 (CH), 111.7 (CH), 128.9 (C), 136.9 (C), 147.3 (C), 147.4 (C) ppm. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.89; H, 8.12; N, 5.88.

4.5.2. (1*S*,11*S*)-4,5-Dimethoxy-11-methyl-9-azatricyclo[7.2.2.0^{2,7}]trideca-2,4,6-triene 1b

97 mg (79%); $[\alpha]_D^{25} = -2.3$ (*c* 0.92, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.75 (d, *J* = 6.7 Hz, 3H, CH_3), 2.03–2.22 (m, 3H:2H, CH_2 + 1H, CH), 2.41 (dd, *J* = 8.8, 13.4 Hz, 1H, CH_2N), 2.53–2.69 (m, 1H, CH_2N), 2.98–3.14 (m, 2H:1H, ArCH + 1H, CH_2N), 3.32 (dd, *J* = 8.5, 13.6 Hz, 1H, CH_2N), 3.81 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.21 (d, J_{AB} = 17.1 Hz, 1H, $ArCH_2N$), 4.31 (d, J_{AB} = 17.1 Hz, 1H, $ArCH_2N$), 6.50 (s, 1H, H_{arom}), 6.55 (s, 1H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.5 (CH_3), 30.8 (CH_2), 33.2 (CH), 42.1 (ArCH), 46.6 (CH_2N), 53.6 (CH_2N), 55.8 (OCH_3), 56.0 (OCH_3), 61.6 ($ArCH_2N$), 110.2 (CH), 113.4 (CH), 129.0 (C), 133.7 (C), 146.9 (C), 147.3 (C) ppm. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.69; H, 8.42; N, 5.83.

4.5.3. (1*S*,11*S*)-4,5-Dimethoxy-11-ethyl-9-azatricyclo[7.2.2.0^{2,7}]trideca-2,4,6-triene 1c

81 mg (62%); $[\alpha]_D^{25} = -1.6$ (*c* 1.36, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, *J* = 7.3 Hz, 3H, CH_3), 1.02–1.19 (m, 2H, CH_2), 1.81–1.99 (m, 1H, CH), 2.00–2.23 (m, 2H, CH_2), 2.48 (dd, *J* = 8.3, 13.6 Hz, 1H, CH_2N), 2.71–2.81 (m, 1H, CH_2N), 3.01–3.16 (m, 2H:1H, ArCH + 1H, CH_2N), 3.34 (dd, *J* = 8.6, 13.7 Hz, 1H, CH_2N), 3.83 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.22 (d, J_{AB} = 17.1 Hz, 1H, $ArCH_2N$), 4.31 (d, J_{AB} = 17.1 Hz, 1H, $ArCH_2N$), 6.52 (s, 1H, H_{arom}), 6.56 (s, 1H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.8 (CH_3), 26.6 (CH_2), 30.9 (CH_2), 39.7 (CH), 40.6 (CH), 46.0 (CH_2N), 52.7 (CH_2N), 55.8 (OCH_3), 56.0 (OCH_3), 61.6 ($ArCH_2N$), 110.2 (CH), 113.1 (CH), 129.1 (C), 133.9 (C), 146.9 (C), 147.2 (C) ppm. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.58; H, 8.85; N, 5.12.

4.5.4. (1*S*,11*S*)-4,5-Methylenedioxy-11-ethyl-9-azatricyclo[7.2.2.0^{2,7}]trideca-2,4,6-triene 2c

72 mg (59%); $[\alpha]_D^{25} = -1.1$ (*c* 0.83, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.1 Hz, 3H, CH_3), 1.01–1.17 (m, 2H, CH_2), 1.83–1.99 (m, 1H, CH), 2.01–2.24 (m, 2H, CH_2), 2.49 (dd, *J* = 8.2, 13.4 Hz, 1H, CH_2N), 2.73–2.83 (m, 1H, CH_2N), 3.00–3.19 (m, 2H:1H, ArCH + 1H, CH_2N), 3.33 (dd, *J* = 8.6, 13.7 Hz, 1H, CH_2N), 4.11 (d, J_{AB} = 17.2 Hz, 1H, $ArCH_2N$), 4.18 (d, J_{AB} = 17.2 Hz, 1H, $ArCH_2N$), 5.92 (d, *J* = 6.0 Hz, 2H, OCH_2O), 6.52 (s, 1H, H_{arom}), 6.56 (s, 1H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.0 (CH_3), 26.8 (CH_2), 31.2 (CH_2), 39.9 (CH), 40.8 (CH), 46.2 (CH_2N), 52.8 (CH_2N), 61.9 ($ArCH_2N$), 100.6 (OCH_2O), 107.2 (CH), 110.2 (CH), 132.1 (C), 135.2 (C), 145.8 (C), 146.1 (C) ppm. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.59; H, 7.69; N, 5.62.

4.5.5. (1*S*,11*S*)-4,5-Methylenedioxy-11-pentyl-9-azatricyclo[7.2.2.0^{2,7}]trideca-2,4,6-triene 2d

80 mg (56%); $[\alpha]_D^{25} = +2.2$ (*c* 0.63, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, *J* = 7.0 Hz, 3H, CH_3), 0.97–1.41 (m, 8H, 4 × CH_2), 1.87–2.15 (m, 3H:1H, CH + 2H, CH_2), 2.44 (dd, *J* = 8.5, 13.6 Hz, 1H, CH_2N), 2.63–2.77 (m, 1H, CH_2N), 2.91–3.14 (m, 2H:1H, ArCH + 1H, CH_2N), 3.27 (dd, *J* = 8.8, 13.6 Hz, 1H, CH_2N), 4.15 (d, J_{AB} = 17.4 Hz, 1H, $ArCH_2N$), 4.23 (d, J_{AB} = 17.4 Hz, 1H, $ArCH_2N$), 5.92 (d, *J* = 6.0 Hz, 2H, OCH_2O), 6.51 (s, 1H, H_{arom}), 6.54 (s, 1H, H_{arom}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3), 22.6 (CH_2), 26.8 (CH_2), 31.4 (CH_2), 32.0 (CH_2), 33.9 (CH_2), 39.0 (CH), 40.6 (CH), 46.9 (CH_2N), 53.0 (CH_2N), 62.1 ($ArCH_2N$), 100.8 (OCH_2O), 107.1 (CH), 110.0 (CH), 131.9 (C), 135.3 (C), 145.6 (C), 146.0 (C) ppm. Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.07; H, 8.56; N, 5.02.

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