A Novel Construction of 2-Benzazepine Scaffold Based on $TiCl_4$-Mediated Tandem *Mannich* Reaction–Aromatic Electrophilic Substitution

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A novel construction of 2-benzazepine derivatives based on $TiCl_4$-mediated tandem *Mannich* reaction of electron-rich benzyl iminium ions with alkenyl ethers and *Friedel–Crafts*-type alkylation is described. The protocol is amenable to provide the tricyclic furo[3,2-*d*][2]benzazepine and pyrano[3,2-*d*][2]benzazepine derivatives, respectively, with 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran as the substrates.

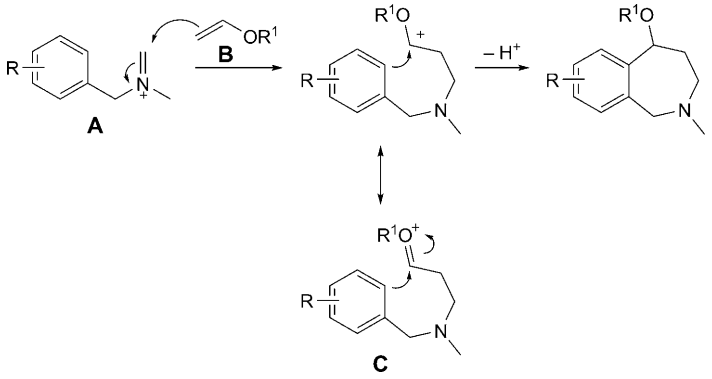
Introduction. – The 2-benzazepine motif is a core structure in a number of pharmacologically important compounds [1]. Several members of this class have been found to exhibit hypotensive, anticonvulsant, analgesic, and antiarrhythimic activities, and also have been proved to be useful as antagonists of muscarinic (M3) receptors and for the treatment of mental disorders and hypoxia [2][3]. Many naturally occurring molecules also contain a 2-benzazepine skeleton. For example, the alkaloids of the *Amaryllidaceae* group including galanthamine, lycoramine, and narwedine are tetrahydro-2-benzazepine derivatives [1][4][5]. In addition, many simpler synthetic analogues have been disclosed to possess a broad spectrum of biological activities [6]. Accordingly, considerable attention has been devoted to the development of convenient and efficient synthesis of families of this privileged heterocyclic ring system [1].

The most widely used methodologies involve *Pictet–Spengler* cyclization [7], the *Schmidt* reaction on tetralones [8], cyclization of benzyl amine and cinnamyl chloride [9], a ring-closing metathesis strategy [10], and transformation of the *Baylis–Hillman* adducts *via* tandem *Ritter* and *Houben–Hoesch* reactions [11]. A recent article by *Nagumo et al.* reported a novel construction of 2-benzazepines based on TMSOTf-promoted *7-endo Friedel–Crafts*-type reaction of vinyloxiranes [12]. However, these approaches require multistep sequences or expensive reagents.

Our strategy for developing a novel synthesis of 2-benzazepines is outlined in *Scheme 1*. We envisioned that the initial reaction of benzylic iminium ions **A** with vinyl ethers **B** may give rise to oxonium ions **C** with formation of a C–C bond. The intermediates **C** will be capable of concurrent *Friedel–Crafts*-type alkylation to give the *7-endo-trig* cyclization products, *i.e.*, 2-benzazepines, by formation of a new C–C bond. Remarkably, there is no precedent of this tandem synthesis of 2-benzazepines.

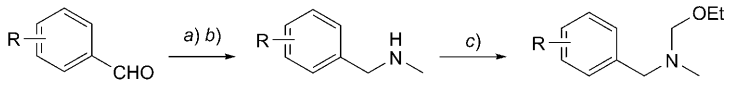
Results and Discussions. – To test our hypothesis, we firstly synthesized from **1a** *via* **2a** the aminoacetal **3a** as the precursor of the required benzyl iminium ion **4a**. Thus,

Scheme 1



benzaldehyde **1a** was subjected to reductive amination with $MeNH_2$ to afford *N*-benzylmethylamine **2a**, which was readily converted to **3a** by reaction with paraformaldehyde and anhydrous EtOH under basic conditions [13] (*Scheme 2*).

Scheme 2



1a R = 3,4-$(MeO)_2$ **2a** R = 3,4-$(MeO)_2$ **3a** R = 3,4-$(MeO)_2$
1b R = 3-MeO **2b** R = 3-MeO **3b** R = 3-MeO
1c R = 2,3-$(MeO)_2$ **2c** R = 2,3-$(MeO)_2$ **3c** R = 2,3-$(MeO)_2$
1d R = H **2d** R = H **3d** R = H
1e R = 3-Me **2e** R = 3-Me **3e** R = 3-Me

a) $MeNH_2$, C_6H_6, reflux, 2 h; *b*) $NaBH_4$, EtOH, 3 h (80–85%); *c*) $(CH_2O)_n$, EtOH, K_2CO_3, 1–2 d (95%).

The aminoacetal **3a** and 2,3-dihydrofuran **5a** were selected as the substrates to screen the appropriate *Lewis* acid used for the generation of the benzyl iminium ion **4a** (*Scheme 3* and *Table 1*). If **4a** can be formed *in situ*, it should undergo an electrophilic addition with the pre-added **5a** to give the oxonium ion **6a**. Electrophilic aromatic substitution on the *ortho*-position of the Ph ring would afford the tricyclic furobenzazepine **7aa**. Examples of 2-benzazepines fused with an additional furan ring are rare (for a recent synthesis, see [14]). Otherwise, **6a** could lose a H-atom to furnish a trivial *Mannich* product **8aa**. As shown in *Table 1*, the use of $AlCl_3$ or $SbCl_5$ as the *Lewis* acid was proved to be unsuccessful for triggering the expected reaction (*Table 1*, *Entries 1* and *2*). Interestingly, switching the *Lewis* acid to both Me_2SiCl_2 and a mixture with $AlCl_3$ only led to **8aa** in comparable yields (*Table 1*, *Entries 3* and *4*). Finally, to our delight, by utilizing $TiCl_4$ as the *Lewis* acid, the reaction occurred smoothly to afford the desired product **7aa** as the only product in good yield (*Table 1*, *Entry 5*).

Having found the optimal *Lewis* acid for this reaction, it was necessary to optimize the reaction temperature. In our case, all reactions carried out from $-78°$ to the ambient temperature led to the formation of **7aa** (*Table 2*), but cooling with ice bath (-5 to $+5°$) was adopted in terms of easy operation and high yield of the product.

Scheme 3

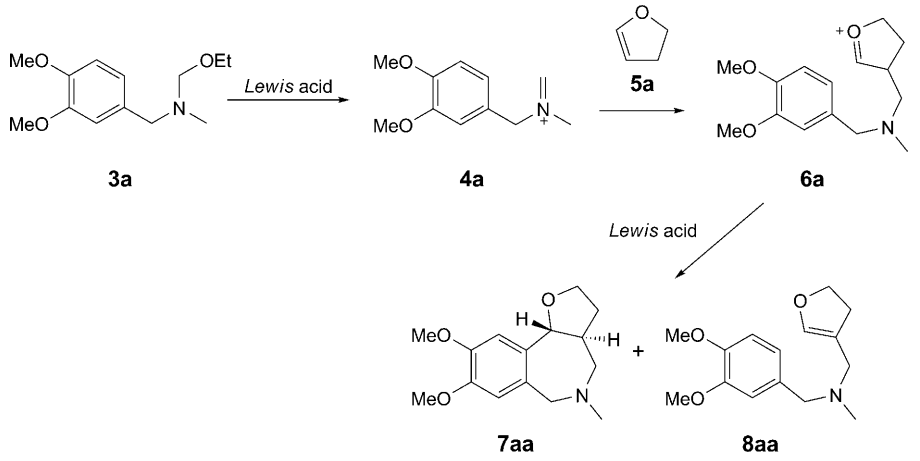


Table 1. *Screening for the Appropriate* Lewis *Acid for the Synthesis of* **7aa** *and* **8aa**[a])

Entry	*Lewis* acid	Yield of **7aa**[b]) [%]	Yield of **8aa**[b]) [%]
1	$AlCl_3$	0	0
2	$SbCl_5$	0	0
3	Me_2SiCl_2	0	65
4	Me_2SiCl_2/ $AlCl_3$ (1 : 1)	0	71
5	$TiCl_4$	81	0

[a]) Reaction conditions: **3a** (3 mmol), 2,3-dihydrofuran (**5a**; 3.9 mmol), *Lewis* acid (3 mmol), dry CH_2Cl_2 (7 ml), -5 to $+5°$, 3 h. [b]) Yields of products isolated by silica gel column chromatography.

Table 2. *Screening for the Optimal Reaction Temperature for the Synthesis of* **7aa**[a])

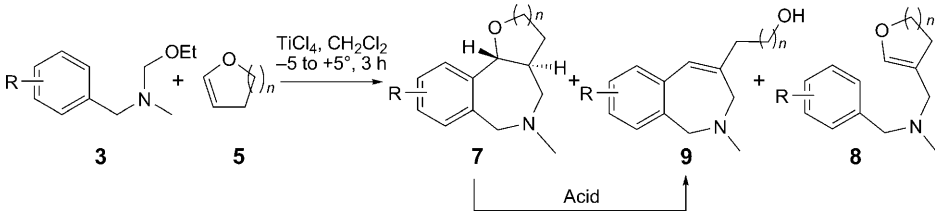
Entry	*T* [°]	Yield[b]) [%]
1	−78	40
2	−40	81
3	−10	82
4	20	71

[a]) Reagents and reaction conditions were the same as provided in the footnote of *Table 1*. [b]) Yields obtained after chromatography.

Having established the optimum conditions, a number of different combinations of substrates were used to probe the scope and feasibility of this methodology for preparation of 2-benzazepine derivatives (*Table 3*).

Depending on the electronic nature of the starting aminoacetal **3** (*Scheme 2*), the reaction sequence afforded either the tricylic 2-benzazepines **7** or a trivial uncyclized product **8**, or a mixture of 4-(hydroxyalkyl)-substituted 2,3-dihydro-2-benzazepines **9**. The formation of **9** may be accounted for by the acid-promoted ring opening of the

Table 3. *Preparation of 2-Benzoazepine Derivatives by $TiCl_4$-promoted Tandem* Mannich *Reaction and Electrophilic Aromatic Substitution*



Entry	**3**	R	**5**	*n*	Product	Yield[a]) [%]
1	**3a**	3,4-$(MeO)_2$	**5a**	1	**7aa**	82
2	**3a**	3,4-$(MeO)_2$	**5b**	2	**7ab**	68
3	**3b**	3-MeO	**5a**	1	**7ba**	25
					9ba	31
4	**3b**	3-MeO	**5b**	2	**8bb**	34
					9bb	35
5	**3c**	2,3-$(MeO)_2$	**5a**	1	**9ca**	[b])
6	**3c**	2,3-$(MeO)_2$	**5b**	2	**9cb**	[b])
7[c])	**3b**	3-MeO	**5a**	1	**9ba**	68
8[c])	**3b**	3-MeO	**5b**	2	**9bb**	72
9[c])	**3c**	2,3-$(MeO)_2$	**5a**	1	**9ca**	56
10[c])	**3c**	2,3-$(MeO)_2$	**5b**	2	**9cb**	[b])
11	**3d**	H	**5a**	1	**8da**	67
12	**3e**	3-Me	**5a**	1	**8ea**	70

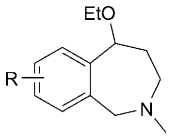
[a]) Yields of products isolated by silica gel column chromatography. [b]) Undetermined due to difficulty in purification. [c]) 2.0 Equiv. of $TiCl_4$ were employed.

initially formed tricyclic products **7**. This illuminated that the attached additional furan or pyran ring of **7** did not tolerate acidic conditions. It was also shown that the amount of the employed $TiCl_4$ affected the product distribution. As shown by the representative results in *Table 3*, the substrate **3a** bearing two electron-donating groups reacted with both 2,3-dihydrofuran (**5a**) and 3,4-dihydro-2*H*-pyran (**5b**) using 1 equiv. of $TiCl_4$ as the *Lewis* acid to afford cleanly the tricyclic compounds **7aa** and **7ab** in 82 and 68% yield, respectively (*Table 3*, *Entries 1* and *2*). However, the use of **3b**, which holds only one MeO group, afforded a mixture of the tricyclic product **7ba** and the bicyclic product **9ba** in the case of **5a**, and **8bb** and **9bb** in the case of **5b** in essentially the same amount (*Table 3*, *Entries 3* and *4*). When using **3c** as substrate, the reaction gave intricate inseparable products (*Table 3*, *Entries 5* and *6*). Nevertheless, increasing the amount of the employed $TiCl_4$ to two equivalents, the reaction using **3b** afforded the bicyclic fused heterocycles **9ba** and **9bb** in good yields without the detection of the uncyclized products **8** (*Table 3*, *Entries 7* and *8*). This suggested that excessive *Lewis* acid is beneficial to the concurrent aromatic electrophilic substitution. This was further verified by the reaction of **3c** bearing two electron-donating MeO groups at the C(2) and C(3) positions, which delivered again the bicyclic compounds **9ca** and **9cb**, respectively, though not in quite as good yields (*Table 3*, *Entries 9* and *10*). At this

point, it may be concluded that the presence of electron-donating groups on the benzene ring is helpful to the electrophilic aromatic substitution thus leading to the formation of the 2-benzazepine core. Accordingly, the reaction of **3d** as well as **3e** lacking a strong electron-donating MeO group gave only the trivial uncyclized products **9da** and **9ea**, respectively, in good yields (*Table 3*, *Entries 11* and *12*), and increasing the amount of $TiCl_4$ to 2 equiv. did not give any cyclized products **7** or **9** (data not shown in *Table 3*).

The *trans* ring fusion between the attached furan or pyran ring, respectively, and the seven-membered ring in the tricyclic products **7aa**, **7ab**, and **7ba** has been tentatively assigned by inspection of the relatively large $^1H,^1H$-coupling constant (> 9 Hz) of H–C(3a)/C(4a) with H–C(10b)/C(11b). Further proof to this stereochemical assignment came from the fact that no NOE for **7ab** could be observed between the angular H-atoms H–C(11b) (apparent *d* at δ(H) 4.28, $J = 9.6$ Hz) and H–C(4a) (*m* centered at δ(C) 1.75).

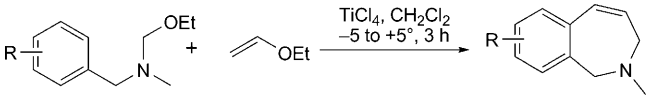
Finally, we applied the developed novel method with the open-chain enol ether **5c** as a substrate (*Table 4*). The reaction with aminoacetals **3a**–**3c** proceeded smoothly under similar conditions. Notably, the isolated products were 2,3-dihydro-1*H*-benzazepines **10a**–**10c**. The formation of **10** may be explained by invoking the 4-ethoxy-2,3,4,5-tetrahydro-1*H*-2-benzazepines **11** (*Figure*) as intermediates *via* subsequent elimination of a molecule of EtOH.



11

Figure. *The proposed structure of intermediate* **11**

Table 4. *Preparation of 2,3-Dihydro-1*H*-2-benzazepines* **10** *Using* **5c**[a])



3 **5c** **10**

Entry	**3**	R	Product	Yield[a]) [%]
1	**3a**	3,4-$(MeO)_2$	**10a**	71
2	**3b**	3-MeO	**10b**	67
3	**3c**	2,3-$(MeO)_2$	**10c**	55

[a]) 2.0 Equiv. of $TiCl_4$ were employed. [b]) Yields of products isolated by silica gel column chromatography.

In conclusion, an efficient tandem synthesis of pharmaceutically important 2-benzazepines was developed. The protocol relies on $TiCl_4$ mediated *Mannich*-type reaction of electron-rich benzyl iminium ions generated *in situ* from aminoacetals with alkenyl ethers such as 2,3-dihydrofuran, 3,4-dihydro-2*H*-pyran, or ethyl vinyl ether and concurrent *Friedel–Crafts*-type electrophilic substitution.

Experimental Part

General. CH_2Cl_2 was dried by refluxing over CaH_2, and other reagents were commercially available and used without further purification. Flash column chromatography (FC): silica gel *60* (SiO_2; 230–400 mesh) with CH_2Cl_2/MeOH mixture for elution. IR Spectra: in CH_2Cl_2 or as KBr disc with a *Nicolet-360* spectrophotometer; absorptions given in cm^{-1}. ^{1}H-NMR Spectra: *JEOL ECA 400*; chemical shifts (δ) reported in ppm relative to TMS as internal standard; coupling constants (J) in Hz. GC/MS: 30 m *HP-5MS* cap. column on a *Hewlett-Packard 6890GC/5973MS* system. HR-ESI-MS: *SHIMADZU LCMS-IT-TOF.*

General Procedure for the Preparation of N-*Benzyl*-N-*methylamines* **2**. Gaseous $MeNH_2$ was bubbled into a soln. of benzaldehyde **1** (0.05 mol) in benzene (70 ml) for 1 h under stirring, then the resulting mixture was heated to reflux, and the produced H_2O was removed by azeotropic distillation. Upon completion of the reaction (2 h), the mixture was evaporated *in vacuo*. The residue was dissolved in 70 ml of EtOH, and $NaBH_4$ (2.27 g, 0.06 mol) was added in portions under stirring. After stirring at r.t. for 4 h, the solvent was removed *in vacuo*, the residue was dissolved in 200 ml of CH_2Cl_2, washed successively with H_2O and brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo* to give a yellow oil, which was subjected to vacuum distillation to afford the pure product **2**.

General Procedure for Preparation of Amino Acetals **3**. Anh. *N*-benzyl-*N*-methylamine **2** (10 mmol), dry EtOH (2.3 ml, 4.0 mol-equiv.), and anh. K_2CO_3 (1.51 g, 11 mmol, 1.1 mol-equiv.) were stirred at 0° for 15 min. Paraformaldehyde (0.33 g, 11 mmol, 1.1 mol-equiv.) was added in one portion, and the mixture was stirred at r.t. for 1 d. The reaction was monitored by TLC (CH_2Cl_2/MeOH 15:1). In case the reaction did not reach completion, an additional amount of paraformaldehyde (60 mg, 2 mmol) and 2 ml of anh. Et_2O were fed into the mixture, which then was stirred further overnight. The mixture was filtered, and the cake was washed several times with anh. Et_2O. The combined filtrate was concentrated *in vacuo* to give the product **3**, which could be used for the next step without purification. (Note: The products **3** are prone to decompose on exposure to moisture.)

General Experimental Procedure for the Tandem Mannich *and Aromatic Electrophilic Substitution Reactions.* To a soln. of **3** (3.0 mmol) in dry CH_2Cl_2 (7 ml) was added the alkenyl ether **5** (3.9 mmol, 1.3 equiv.). After cooling to −5°, anh. $TiCl_4$ (as specified in *Tables 3* and *4*) was added dropwise over 10 min. After stirring for 3 h, the temp. was allowed gradually to warm to r.t., then the mixture was poured into a sat. aq. $NaHCO_3$ soln. The org. phase was separated, the aq. phase was extracted with CH_2Cl_2 or AcOEt (3 × 60 ml). The org. phases were combined, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by CC (CH_2Cl_2/MeOH 1:1) to give the products **7**, **8**, **9**, or **10**.

*3,3a,4,5,6,10b-Hexahydro-8,9-dimethoxy-5-methyl-2*H-*furo[3,2-*d*][2]benzazepine* (**7aa**). Eluent CH_2Cl_2/MeOH 60:1. Colorless oil. Yield: 82%. IR (KBr): 3400, 2926, 1607, 1514, 1463, 1276, 1114, 1029. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.03 (*s*, 1 H); 6.57 (*s*, 1 H); 5.13 (*d*, J = 9.2, 1 H); 3.99–3.95 (*m*, 1 H); 3.81 (*s*, 3 H); 3.79 (*s*, 3 H); 3.73 (*d*, J = 13.3, 1 H); 3.70–3.63 (*m*, 1 H); 3.37 (*d*, J = 13.3, 1 H); 2.70–2.62 (*m*, 1 H); 2.54 (*dd*, J = 2.5, 12.6, 1 H); 2.22 (*s*, 3 H); 2.02–1.96 (*m*, 1 H); 1.90 (*t*, J = 12.1, 1 H); 1.33–1.24 (*m*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 148.4; 147.3; 131.9; 121.2; 113.1; 108.5; 79.5; 67.0; 56.1; 55.9; 55.8; 55.6; 43.2; 39.0; 31.9. GC/MS: 263 (M^+). HR-ESI-MS: 264.1662 ($[M+H]^+$, $C_{15}H_{22}NO_3^+$; calc. 264.1600).

*2,3,4,4a,5,6,7,11b-Octahydro-9,10-dimethoxy-6-methylpyrano[3,2-*d*][2]benzazepine* (**7ab**). Eluent: CH_2Cl_2/MeOH 60:1. Colorless solid. Yield: 68%. IR (KBr): 3431, 2928, 2837, 1604, 1514, 1444, 1270, 1213, 1114, 1027, 821. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.31 (*s*, 1 H); 6.62 (*s*, 1 H); 4.28 (*d*, J = 9.6, 1 H); 4.20–4.14 (*m*, 1 H); 3.96 (*s*, 3 H); 3.85 (*s*, 3 H); 3.82–3.80 (*m*, 1 H); 3.53 (*d*, J = 14.2, 1 H); 3.45–3.39 (*m*, 1 H); 2.85 (*d*, J = 14.2, 1 H); 2.72–2.66 (*m*, 1 H); 2.22 (*s*, 3 H); 1.78–1.67 (*m*, 3 H); 1.62–1.59 (*m*, 1 H); 1.21–1.17 (*m*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 147.8; 146.7; 135.2; 127.5; 113.3; 109.0; 79.8; 67.5; 65.9; 61.4; 56.0 (2 MeO); 42.8; 36.2; 29.2; 25.5. HR-ESI-MS: 278.1744 ($[M+H]^+$, $C_{16}H_{24}NO_3^+$; calc. 278.1756).

*2,3,3a,4,5,6-Hexahydro-8-methoxy-5-methyl-2*H-*furo[3,2-*d*][2]benzazepine* (**7ba**). Eluent: CH_2Cl_2/MeOH 50:1. Colorless oil. Yield: 25%. IR (KBr): 3455, 2943, 2617, 1613, 1505, 1481, 1254, 1069. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.33 (*d*, J = 8.7, 1 H); 6.77 (*dd*, J = 2.3, 8.7, 1 H); 6.60 (*d*, J = 2.3, 1 H); 5.10 (*d*, J = 9.2, 1 H); 3.96–3.92 (*m*, 1 H); 3.83 (*d*, J = 13.5, 1 H); 3.70 (*s*, 3 H); 3.67–3.61 (*m*, 1 H); 3.46 (*d*, J = 13.5, 1 H); 2.74–2.69 (*m*, 1 H); 2.60 (*dd*, J = 2.3, 12.4, 1 H); 2.26 (*s*, 3 H); 2.03–1.96 (*m*, 1 H); 1.91 (*t*,

J = 12.4, 1 H); 1.35–1.29 (*m*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 158.7; 131.5; 129.5; 116.0; 115.9; 112.5; 79.5; 67.0; 56.2; 55.5; 55.3; 43.0; 39.2; 31.8. HR-ESI-MS: 234.1487 ($[M+H]^+$, $C_{14}H_{20}NO_2^+$; calc. 234.1494).

1-(4,5-Dihydrofuran-3-yl)-N-*(3,4-dimethoxybenzyl)*-N-*methylmethanamine* (**8aa**). Eluent: CH_2Cl_2/MeOH 80:1. Colorless oil. Yield: 71%. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.89 (*s*, 1 H); 6.80 (*s*, 2 H); 6.24 (*s*, 1 H); 4.35 (*t*, J = 9.6, 2 H); 3.88 (*s*, 3 H); 3.84 (*s*, 3 H); 3.41 (*s*, 2 H); 3.00 (*s*, 2 H); 2.64 (*t*, J = 9.6, 2 H); 2.17 (*s*, 3 H).

*1-(3,4-Dihydro-2*H*-pyran-5-yl)*-N-*(3-methoxybenzyl)*-N-*methylmethanamine* (**8bb**). Eluent: CH_2Cl_2/MeOH 80:1. Colorless oil. Yield: 34%. IR (KBr): 2940, 2782, 1667, 1601, 1488, 1264, 1155, 1051, 877. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.99 (*d*, J = 8.2, 1 H); 6.67 (*dd*, J = 8.2, 2.3, 1 H); 6.59 (*d*, J = 2.3, 1 H); 6.24 (*s*, 1 H); 3.73 (*s*, 3 H); 3.68 (*s*, 2 H); 3.56 (*t*, J = 6.4, 2 H); 3.28 (*s*, 2 H); 2.31 (*s*, 3 H); 2.13 (*t*, J = 7.6, 2 H); 1.71–1.67 (*m*, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 158.1; 139.1; 138.3; 131.3; 129.6; 126.2; 114.8; 112.2; 61.9; 61.3; 60.5; 55.3; 42.6; 34.6; 32.0.

*2-(2,3-Dihydro-8-methoxy-2-methyl-1*H*-2-benzazepin-4-yl)ethanol* (**9ba**). Eluent: CH_2Cl_2/MeOH 20:1. Yellow oil. Yield: 68%. IR (KBr): 3394, 2939, 1609, 1504, 1466, 1254, 1043. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.09 (*d*, J = 8.7, 1 H); 6.78 (*dd*, J = 2.7, 8.7, 1 H); 6.68 (*d*, J = 2.7, 1 H); 6.41 (*s*, 1 H); 3.79 (*s*, 3 H); 3.76 (*t*, J = 6.0, 2 H); 3.70 (*s*, 2 H); 3.16 (*s*, 2 H); 2.41 (*t*, J = 6.0, 2 H); 2.40 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 158.4; 137.9; 137.1; 130.9; 130.0; 128.8; 115.2; 112.4; 62.5; 60.1; 60.0; 55.4; 43.1; 41.3. HR-ESI-MS: 234.1490 ($[M+H]^+$, $C_{14}H_{20}NO_2^+$; calc. 234.1494).

*3-(2,3-Dihydro-8-methoxy-2-methyl-1*H*-2-benzazepin-4-yl)propan-1-ol* (**9bb**). Eluent: CH_2Cl_2/MeOH 25:1. Yellow oil. Yield: 72%. IR (KBr): 3411, 2934, 1608, 1501, 1278, 1248, 1034. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.05 (*d*, J = 8.7, 1 H); 6.74 (*dd*, J = 1.8, 8.7, 1 H); 6.65 (*d*, J = 1.8, 1 H); 6.30 (*s*, 1 H); 3.78 (*s*, 3 H); 3.75 (*s*, 2 H); 3.64 (*t*, J = 6.4, 2 H); 3.34 (*s*, 2 H); 2.37 (*s*, 3 H); 2.20 (*t*, J = 7.8, 2 H); 1.79–1.73 (*m*, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 158.1; 139.1; 138.3; 131.3; 129.6; 126.2; 114.8; 112.2; 61.9; 60.5; 55.3; 42.6; 34.6; 32.0.

*2-(2,3-Dihydro-8,9-dimethoxy-2-methyl-1*H*-2-benzazepin-4-yl)ethanol* (**9ca**). Eluent: CH_2Cl_2/MeOH 20:1. Yellow oil. Yield: 56%. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.89 (*d*, J = 8.7, 1 H); 6.85 (*d*, J = 8.7, 1 H); 6.56 (*s*, 1 H); 3.93 (*s*, 2 H); 3.84 (*s*, 3 H); 3.80 (*t*, J = 7.9, 2 H); 3.78 (*s*, 3 H); 3.14 (*s*, 2 H); 2.55 (*s*, 3 H); 2.46 (*t*, J = 7.9, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 151.6; 147.5; 136.3; 131.5; 131.4; 126.3; 124.8; 112.2; 61.4; 57.3; 55.9; 50.2; 46.0; 42.6; 40.8.

N-*Benzyl-1-(4,5-dihydrofuran-3-yl)*-N-*methylmethanamine* (**8da**). Eluent: CH_2Cl_2/MeOH 80:1. Colorless oil. Yield: 67%. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.29–7.21 (*m*, 5 H); 6.22 (*s*, 1 H); 4.32 (*t*, J = 9.4, 2 H); 3.44 (*s*, 2 H); 3.00 (*s*, 2 H); 2.63 (*t*, J = 9.4, 2 H); 2.14 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 143.1; 139.5; 129.0; 128.3; 127.0; 112.7; 70.4; 61.4; 53.7; 42.4; 31.6. GC/EI-MS: 203.1 (M^+).

1-(4,5-Dihydrofuran-3-yl)-N-*methyl*-N-*(3-methylbenzyl)methanamine* (**8ea**). Eluent: CH_2Cl_2/MeOH 80:1. Colorless oil. Yield: 70%. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.20–7.05 (*m*, 4 H); 6.25 (*s*, 1 H); 4.36 (*t*, J = 9.6, 2 H); 3.43 (*s*, 2 H); 3.03 (*s*, 2 H); 2.69–2.64 (*m*, 2 H); 2.35 (*s*, 3 H); 2.17 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 143.2; 139.3; 137.9; 129.7; 128.2; 127.7; 126.0; 112.7; 70.5; 61.4; 53.8; 42.4; 31.6; 21.5. GC/EI-MS: 217.2 (M^+).

*2,3-Dihydro-7,8-dimethoxy-2-methyl-1*H*-2-benzazepine* (**10a**). Eluent: CH_2Cl_2/MeOH 60:1. Yellow oil. Yield: 71%. IR (KBr): 3393, 2968, 1604, 1520, 1466, 1353, 1274, 1116. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.70 (*s*, 1 H); 6.64 (*s*, 1 H); 6.37 (*d*, J = 12.4, 1 H); 5.70 (*dt*, J = 3.7, 12.4, 1 H); 3.88 (*s*, 3 H); 3.86 (*s*, 3 H); 3.78 (*s*, 2 H); 3.51 (*s*, 2 H); 2.41 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 147.7; 147.6; 131.1; 129.4; 129.1; 129.0; 113.8; 112.5; 61.1; 59.8; 56.1 (2 MeO); 43.3. HR-ESI-MS: 220.1312 ($[M+H]^+$, $C_{13}H_{18}NO_2^+$; calc. 220.1337).

*2,3-Dihydro-8-methoxy-2-methyl-1*H*-2-benzazepine* (**10b**). Eluent: CH_2Cl_2/MeOH 70:1. Yellow oil. Yield: 67%. IR (KBr): 3402, 2958, 2524, 1608, 1504, 1466, 1258, 1031, 874. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.09 (*d*, J = 8.2, 1 H); 6.72 (*dd*, J = 2.3, 8.2, 1 H); 6.65 (*d*, J = 2.3, 1 H); 6.36 (*d*, J = 10.5, 1 H); 5.64–5.59 (*m*, 1 H); 3.82 (*s*, 2 H); 3.79 (*s*, 3 H); 3.52 (*s*, 2 H); 2.39 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 158.6; 140.0; 132.0; 129.2; 129.1; 128.2; 114.8; 111.8; 61.7; 60.2; 55.3; 43.3. HR-ESI-MS: 190.1242 ($[M+H]^+$, $C_{12}H_{16}NO^+$; calc. 190.1232).

*2,3-Dihydro-8,9-dimethoxy-2-methyl-1*H*-2-benzazepine* (**10c**). Eluent: CH_2Cl_2/MeOH 70:1. Yellow oil. Yield: 55%. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.90 (*d*, J = 8.2, 1 H); 6.75 (*d*, J = 8.2, 1 H); 6.39 (*d*,

$J = 11.9$, 1 H); 5.68–5.63 (*m*, 1 H); 3.90 (*s*, 2 H); 3.85 (*s*, 3 H); 3.78 (*s*, 3 H); 2.19 (*s*, 2 H); 2.48 (*s*, 3 H). GC/EI-MS: 219.2 (M^+).

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