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Synthesis of New Dopamine D1 Antagonist SCH 23390 Analogues by the Stereoselective Stevens Rearrangement

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A convenient synthesis for new SCH 23390 analogues bearing different substituents at the C-1 position has been developed by using the diastereoselective Stevens rearrangement. This procedure has provided a good number of new 1,2-disubstituted 1*H*-3-benzazepines, either through isolation of the isoquinolinium salts or directly by using a new one-pot *N*-alkylation–Stevens rearrangement reaction.

Introduction

The tetrahydro-1*H*-3-benzazepine ring system attracts a great deal of interest from medicinal chemists because of the phenetylamine substructure, which is common in nature and a wide variety of drugs. Furthermore, 1*H*-3-benzazepines are active in animal models of various neurological disorders such as Parkinson's disease[1] and Alzheimer's disease.[2] In particular, the synthesis of their 1-aryl derivatives has been an important dynamic area in the development of central nervous system drugs, mostly because of their potential dopaminergic activity.[3] The discovery of SCH 23390,[4] one of the first selective dopamine D1-like receptor antagonists, and its conformationally restricted analogue SCH 39166,[5] represented a major breakthrough in dopaminergic receptor research. In fact, SCH 39166, also known as ecopipam, has been subjected to several clinical trials for human diseases, including schizophrenia,[6] cocaine addiction[7] and obesity.[8] Although SCH 39166 improved the overall pharmacological profile with similar affinity and selectivity to SCH 23390 as a D1/D5 antagonist,[6a] both compounds showed low oral bioavailability.

On the basis of the importance and bioactivity of SCH 23390 and SCH 39166, there has been an increased interest in developing new analogues by numerous groups. In general, structural modification of SCH 23390 has focused on substitution at C-5 and/or C-6, isosteres of catechol (C-7 and/or C-8) and the study of conformational restrictions or substitution at the phenyl group (Figure 1).[3b,3c] Thus, a variety of analogues has been developed, such as NNC 756,[9] SCH 39166, D-ring-funtionalized SCH 39166[10] and fenoldopam,[11] which is currently employed in the treatment of hypertension (Figure 2). It is important to note that only a few examples of SCH 23390 analogues modified at the C-1 position have been reported to date (Figure 2).[12] However, to the best of our knowledge none of these has considered the substitution with different aromatic groups according to classic and nonclassic isosterism.

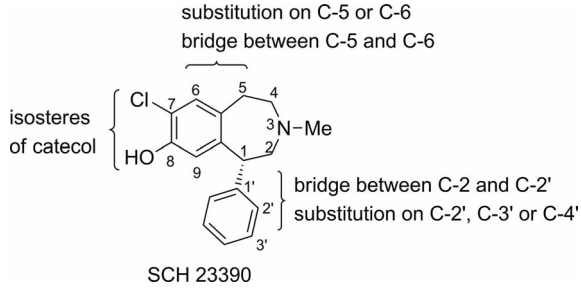

Figure 1. Common structural modifications of SCH 23390.

We have previously developed a short and efficient regio- and diastereoselective methodology based on the Stevens rearrangement to synthesize 1,2-disubstituted 1*H*-3-benzazepines,[13] in which the structural modification of SCH 23390 was introduced at the C-2 position. As a continuation of our study of the Stevens rearrangement in the synthesis of 1,2-disubstituted 1*H*-3-benzazepine analogues of SCH 23390, we have focused on the application of this methodology to obtain new analogues bearing different substituents at the C-1 position.

In this paper we report the influence of the substituent at the C-1 position of the starting isoquinolinium salts on the Stevens rearrangement. A fair number of isoquinolinium salts containing alkylic and benzylic groups as well as different aromatic substituents have been explored along with the development of a new one-pot *N*-alkylation–Stevens rearrangement reaction. This study has provided a

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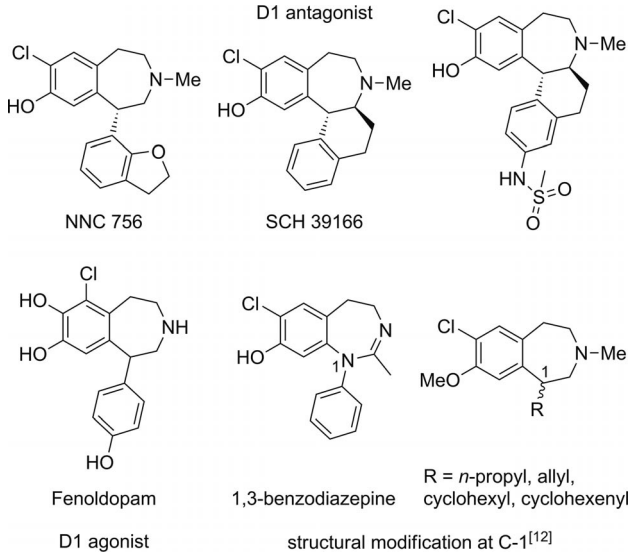
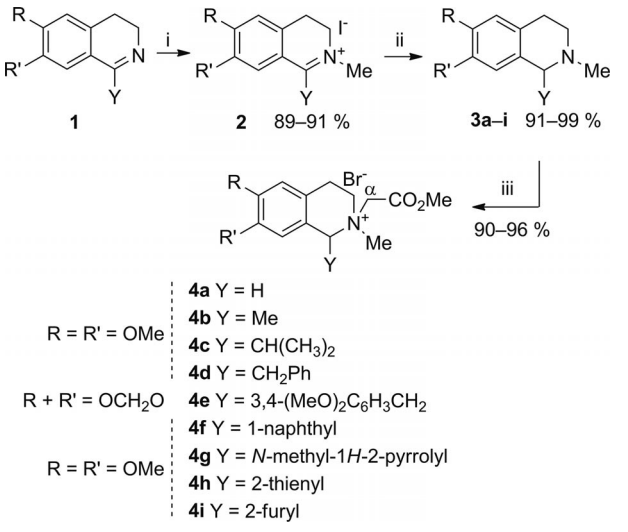


Figure 2. Relevant examples of analogues of SCH 23390.

collection of new isosteric analogues of SCH 23390, which could be used to help understand the structure–activity relationships in this family of compounds.

Results and Discussion

Isoquinolinium salts **4** were prepared from dihydroisoquinolines **1** following our standard method (Scheme 1),[13,14] with the exception of **4a** and **4b**, which were obtained directly from the corresponding tetrahydroisoquinolines **3a**[15] and **3b**.[16] Similarly, the enantiomerically pure **4e** was prepared from (+)-romneine (**3e**), a natural tetrahydroisoquinoline isolated in our laboratory from *Romneya coulteri*.[17] Given the satisfactory results attained in preceding work,[13] the (methoxycarbonyl)methyl group was chosen as the model alkylating agent.

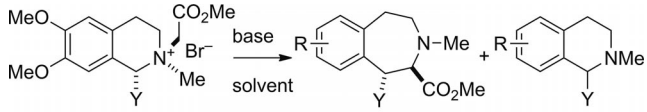


Scheme 1. Synthesis of **4a**–**i**: (i) CH_3I/acetone, reflux; (ii) $NaBH_4$/MeOH, room temp.; (iii) $BrCH_2CO_2Me$/acetone, room temp.

This procedure normally yielded a unique *trans* configured salt in excellent yields, except for **4h** and **4i**, which bear thienyl and furyl substituents at the C-1 position, respectively. The relative configuration between 1-H and the (methoxycarbonyl)methyl group was ascertained by both H,H-NOESY and NMR correlation data. Thus, the presence of an intense NOE effect between 1-H and a proton at the α position is fully consistent with a *trans* configuration. Conversely, a similar effect is observed between 1-H and *N*-Me in **4i**, which indicates a *cis* configuration. Interestingly, **4i** constitutes the unique example in which a *cis* configuration was detected as the only product. On the other hand, **4h** was obtained as a mixture of diastereoisomers in a *cis*/*trans* ratio of 1:4, and attempts to isolate both invariably failed. The higher content of the *trans* salt in the mixture was evidenced by NMR spectroscopy. Clear differences in the chemical shift of the signals arising from the *N*-Me group were observed for the two diastereoisomers. The *N*-Me signal arising from the *cis* isomer appeared at a higher shift than that of the *trans* isomer by ^{1}H NMR spectroscopy (δ_{cis} = 3.80 > δ_{trans} = 3.51 ppm), and the opposite effect was observed in the ^{13}C NMR spectra (δ_{cis} = 45.5 < δ_{trans} = 48.1 ppm). These data are in accordance with those previously described for similar isoquinolinium salts.[13,18]

The Stevens rearrangement of isoquinolinium salts bearing hydrogen, alkylic or benzylic substituents at the C-1 position was first examined. As shown in Table 1, the application of standard conditions to the Stevens rearrangement of **4a**–**c**, i.e. 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile at room temperature,[13] failed to give any reaction, and the starting materials were the only products recovered in all cases. Although stronger bases and different solvents were tried for **4a**, the Stevens rearrangement leading to the unsubstituted 1*H*-3-benzazepine did not take place (Table 1). Unlike **4a**, the ring enlargement of **4b** and **4c** to obtain 1-alkyl-1*H*-3-benzazepines **5b**-*trans* and **5c**-*trans* was achieved when a stronger base was employed (Table 1, Entries 1 and 2); in such cases, the respective tetrahydroisoquinolines **3b** and **3c** were also obtained from the dealkylation of the initial salt.

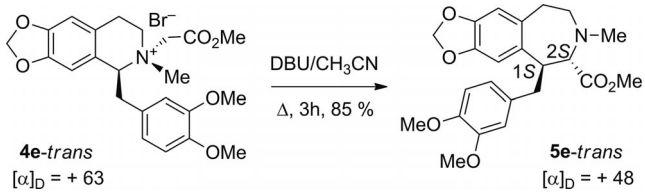
Table 1. Synthesis of **5b**–**d**.



Entry	Product	Y substituent	Base	Solvent	Time	Yield[a]
1	**5b**	CH_3	NaHMDS[b]	THF[c]	1 h	63%
2	**5c**	$CH(CH_3)_2$	NaHMDS	THF	1 h	76%
3	**5d**	CH_2Ph	DBU	CH_3CN	3 h[d]	86%

[a] Isolated yields after silica gel chromatography. [b] NaHMDS = sodium bis(trimethylsilyl)amide. [c] THF = tetrahydrofuran. [d] The reaction was carried out with heating to reflux for 3 h.

Conversely, **4d**, which contains a benzyl group at C-1, provided **5d** under standard Stevens rearrangement conditions (DBU in acetonitrile). In this case, dealkylation was not detected even though heating was needed (Table 1, Entry 3). Similarly, the Stevens rearrangement of the enantiomerically pure **4e** yielded **5e** regio- and diastereoselectively with a relative *trans* configuration and (1*S*,2*S*) absolute configuration (Scheme 2).

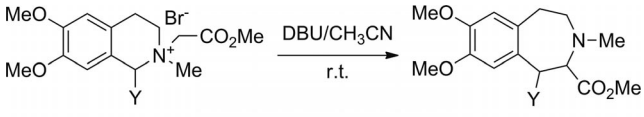


Scheme 2. Synthesis of **5e**-*trans*.

Although the 1-alkyl- and 1-benzylisoquinolinium salts required stronger reaction conditions to yield the desired compounds, the Stevens rearrangement occurred with complete retention of the initial configuration in all cases. H,H-NOESY data and ^{1}H NMR spectroscopic coupling constants were fully consistent with their *trans* configurations.[13,18]

Secondly, we evaluated the Stevens rearrangement using **4f**–**i**, which contain different aromatic groups at the C-1 position (Table 2). The application of standard Stevens rearrangement conditions, afforded the **5f**–**i** regio- and diastereoselectively in excellent yields, with a similar behaviour to that shown by the 1-phenyltetrahydroisoquinolinium salts previously described.[13] It is noteworthy that a shorter reaction time was required when isoquinolinium salts bearing aryl substituents at C-1 were employed. Similar to the other examples described above, the relative configuration between 1-H and 2-H in **5f**–**i** was confirmed by ^{1}H NMR coupling constants.

Table 2. Synthesis of **5f**–**i**.



4f-*trans* Y = 1-naphtyl
4g-*trans* Y = *N*-methyl-1*H*-2-pyrrolyl
4h (*cis*/*trans* 1:4) Y = 2-thienyl
4i-*cis* Y = 2-furyl

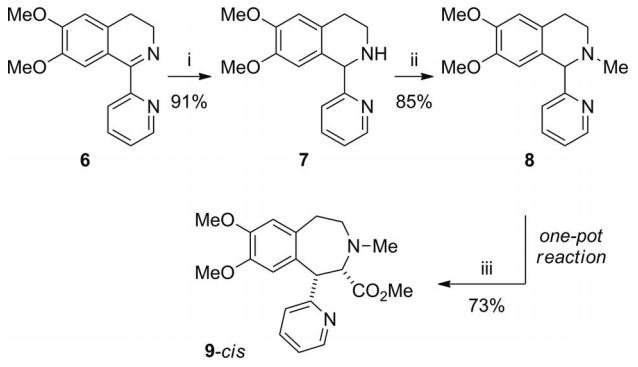
5f-*trans*
5g-*trans*
5h (*cis*/*trans* 1:4)
5i (*cis*/*trans* 1:1)

	Product	Y substituent	Time	Yield[a]	*cis*/*trans* ratio[b]
1	**5f**	1-naphthyl	30 min	91%	0:1
2	**5g**	*N*-methyl-1*H*-2-pyrrolyl	30 min	90%	0:1
3	**5h**	2-thienyl	30 min	93%	1:4
4	**5i**	2-furyl	30 min	91%	1:1

[a] Isolated yields after silica gel chromatography. [b] *cis*/*trans* ratio determined by GC–MS and from the quantity of compound isolated after silica gel chromatography.

As expected, benzazepines **5h** were obtained in a ratio similar to the *cis*/*trans* ratio of the starting salt **4h** according to the stereochemical control of the Stevens rearrangement (Table 2, Entry 3). Unlike most of the diastereomerically pure isoquinolinium salts, **4i**-*cis* afforded a mixture of benzazepines **5i** in a *cis*/*trans* ratio of 1:1 (Table 2, Entry 4). Owing to the diastereoselectivity of the Stevens rearrangement, this result suggests that **4i**-*cis* could have isomerized in solution to the *trans* compound. In fact, the ^{1}H NMR spectrum of **4i**-*cis* in CD_3CN, in the absence of base, showed both diastereoisomers in a *cis*/*trans* ratio of 1:1 after 30 min. This result is in agreement with the *cis*/*trans* ratio observed for **5i**, as the salts formed in situ yielded the corresponding benzazepines in the same proportion. Although the epimerization of isoquinolinium salts is not unprecedented,[18a] no other isoquinolinium salts studied here showed this behaviour even when heated.

Our next aim was to synthesize 1*H*-3-benzazepine **9**, which has a pyridyl substituent at the C-1 position. Given the presence of an electron lone pair in the pyridyl group, a new methodology was applied in order to avoid side reactions, such as *N*-alkylation of the pyridyl nitrogen atom. As shown in Scheme 3, tetrahydroisoquinoline **8** was prepared from dihydroisoquinoline **6** by sodium borohydride reduction and subsequent reductive amination with formaldehyde. The subsequent one-step reaction of **8** with methyl bromoacetate and DBU in acetonitrile afforded the rearranged product in good yield after silica gel purification. This is the first time that a one-pot reaction involving the Stevens rearrangement has been reported, in which a tetrahydroisoquinoline was directly converted into the corresponding 1*H*-3-benzazepine under mild conditions.



Scheme 3. One-pot reaction for the synthesis of **9**: (i) $NaBH_4$/MeOH, room temp.; (ii) CH_2O/$NaCNBH_3$/AcOH/CH_3CN, room temp.; (iii) $BrCH_2CO_2Me$/DBU/CH_3CN, room temp.

The ^{1}H NMR spectrum of **9** revealed the presence of a pair of unresolved doublets for 1-H and 2-H indicative of a relative *cis* configuration. Accordingly, the isoquinolinium salt formed in situ must also have a *cis* configuration in view of the stereochemical control of the Stevens rearrangement.

All these results suggest that the electronic effect exerted by the electronegative atom, which bears an electron lone pair at the aryl substituent, is decisive for the reaction out-

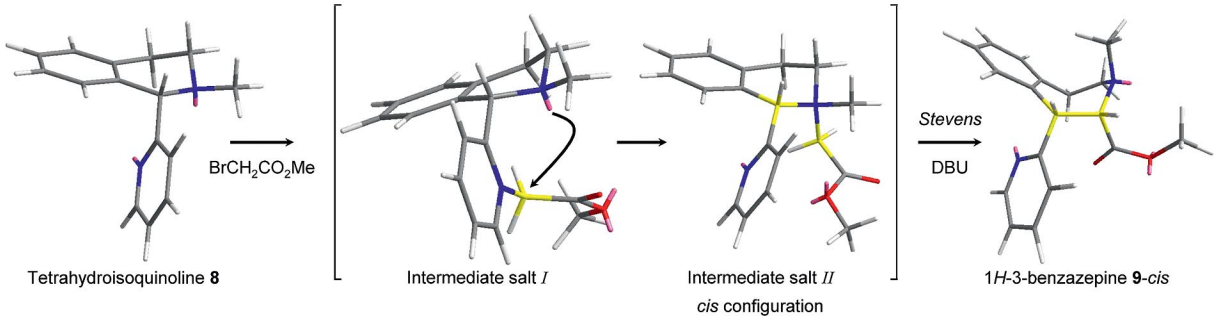
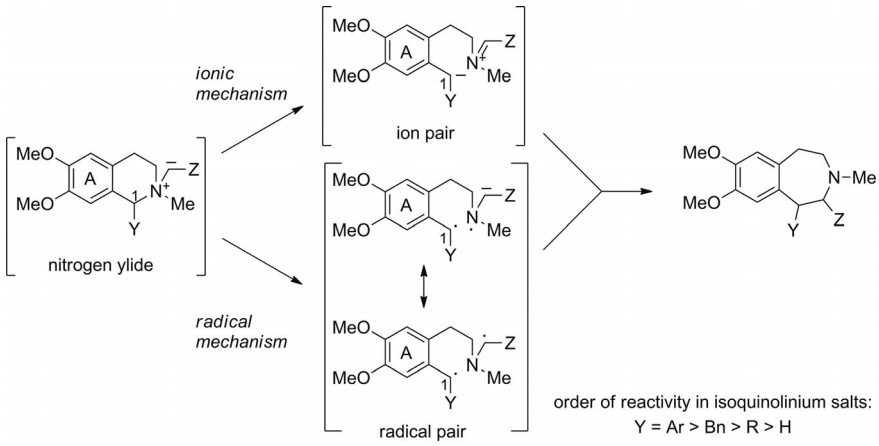


Figure 3. Proposed mechanism for the relative *cis* configuration in **9**-*cis*. 3D model structures of the most stable conformations.[19]



Scheme 4. Stevens rearrangement mechanism operating in the formation of 1,2-disubstituted 1*H*-3-benzazepines from isoquinolinium salts.

come. As can be seen from Figure 3, *N*-alkylation of the pyridyl nitrogen atom in the first step provides the intermediate salt I, which could assist the formation of salt II with a relative *cis* configuration. Similarly, the presence of an oxygen atom in **3i** would be responsible for the *cis* configuration observed in **4i**-*cis*. On the other hand, the less electronegative behaviour of the sulfur atom would justify a lower proportion of the *cis* diastereoisomer **4h** compared to the 1-furyl isoquinolinium salt **4i**-*cis*. When there were no heteroaromatic substituents at the C-1 position or the heteroatom was protected, e.g. **3g**, the reaction pathway rendered *trans*-benzazepine, either through salt formation and subsequent Stevens rearrangement or by a one-pot reaction.

These results give evidence for the stereoselectivity of the Stevens rearrangement, as once the relative configuration of the isoquinolinium salt was known, the configuration of the resulting 1*H*-3-benzazepine could be unequivocally assigned and vice versa. It has also emerged that the Stevens rearrangement is largely dependent on the nature of the substituent at the C-1 position, and aryl derivatives are the most favourable groups. A reasonable explanation for our experimental results is based on the influence exerted by the substituent on the stability of the ion pair or radical pair intermediate at C-1 that preceeds the formation of the benzazepine, as depicted in Scheme 4. According to the electronic effects expected for the different substituents, the ability of the intermediate charged species will increase as H < R < Bn < Ar with the subsequent increased ability to undergo the Stevens rearrangement.

Conclusions

Diastereoselective Stevens rearrangement has been conveniently applied to the synthesis of 1,2-disubstituted 1*H*-3-benzazepines bearing diverse substituents at the C-1 position such as alkylic, benzylic and different aromatic groups. In all cases the corresponding 1*H*-3-benzazepines were obtained in good or excellent yields. Furthermore, a new one-pot *N*-alkylation–Stevens rearrangement reaction has been developed, in which the tetrahydroisoquinoline is directly converted into the corresponding 1*H*-3-benzazepine, without isolation of the isoquinolinium salt. The broad applicability and versatility of this reaction was ascertained by the synthesis of a good number of new analogues of SCH 23390 modified at the C-1 position.

The application of this methodology to the synthesis of other 1*H*-3-benzazepines, SCH 23390 and SCH 39166 analogues, along with the evaluation of their bioactivity are currently underway.

Experimental Section

General Remarks: Melting points were determined with a Gallenkamp instrument. MS (EI) data were recorded with an HP–MS 5988A spectrometer operating at 70 eV and HRMS data with a VG Autospec spectrometer. GC were registered with a DB5 column using a initial temperature of 80 °C, a single ramp temperature of 20 °C/min and a final temperature of 250 °C. IR were obtained with an ATR accessory (MIRacle ATR, PIKE Technologies, USA) coupled to an FTIR spectrometer (FT/IR-4100, JASCO). All spectra were recorded in the range from 4000 to 600 cm^{-1} with a resolution of 4 cm^{-1}. NMR spectra were recorded with a Bruker AC 200 instrument operating at 200 MHz for ^1H and 50.3 MHz for ^{13}C NMR spectroscopy, or with Bruker ARX 400 or Bruker Avance III-Ultrashield plus 400 instruments operating at 400 MHz for ^1H and 100.6 MHz for ^{13}C NMR spectroscopy. Chemical shifts are given relative to residual $CHCl_3$ (δ = 7.24 ppm) and $CDCl_3$ (δ = 77.0 ppm). All solvents were dried and distilled prior to use. Reaction mixtures were magnetically stirred and monitored by TLC with silica gel 60 F_{254} (Merck) plates. Products were purified by column chromatography with 0.040–0.063 mm silica gel (Merck 9385).

Preparation of 3,4-Dihydroisoquinolines 1c–d, 1f–j and 6: A solution of $POCl_3$ (2.7 mL, 28 mmol) in CH_3CN (5 mL) was added dropwise to a solution of the corresponding amide (28 mmol) in CH_3CN (30 mL) under argon. The reaction mixture was heated to reflux for 2 h and concentrated to dryness. The crude material was dissolved in CH_2Cl_2 (30 mL) and washed with a saturated solution of $NaHCO_3$ (25 mL), NaOH (5%, 2 × 25 mL) and water. The organic layers were dried with $MgSO_4$ and concentrated under vacuum to obtain the corresponding isoquinoline.

1-Isopropyl-6,7-dimethoxy-3,4-dihydroisoquinoline (1c):[20] Isoquinoline **1c** (3.1 g, 95%) was obtained from the corresponding amide (3.5 g, 14 mmol) as a yellow oil. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 6.99, 6.64 (2 × s, 1 H each, 5-H, 8-H), 3.85, 3.84 (2 × s, 3 H each, 2 × OMe), 3.58 (t, J = 7.6 Hz, 2 H, 3-H), 3.15 [septet, J = 7.0 Hz, 1 H, C*H*(CH_3)$_2$], 2.54 (t, J = 7.6 Hz, 2 H, 4-H), 1.16 [d, J = 7.0 Hz, 6 H, CH(C*H*$_3$)$_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.1 (C-1), 150.5, 147.0 (C-6, C-7), 131.7 (C-8a), 120.8 (C-4a), 110.0, 108.4 (C-5, C-8), 55.8, 55.5 (2 × OMe), 45.9 (C-3), 31.4 [*C*H(CH_3)$_2$], 25.5 (C-4), 20.4 [CH(*C*H_3)$_2$] ppm. IR (neat): $\tilde{\nu}$ = 3020, 2961, 1603, 1568, 1510, 1462, 1379 cm^{-1}. Retention time, t_R = 6.52 min. EI-MS: m/z (%) = 234 (12), 233 (56) $[M]^+$, 232 (71), 218 (100), 205 (36), 202 (57), 190 (19). HRMS: calcd. for $C_{14}H_{19}NO_2$ $[M]^+$ 233.1416; found 233.1415.

1-Benzyl-6,7-dimethoxy-3,4-dihydroisoquinoline (1d):[21] Isoquinoline **1d** (3.9 g, 98%) was obtained from the corresponding amide[21] (4.2 g, 14 mmol) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.31–7.15 (m, 5 H, CH_2*Ph*), 6.96, 6.64 (2 × s, 1 H each, 5-H, 8-H), 4.12 (s, 2 H, C*H*$_2$Ph), 3.87, 3.70 (2 × s, 3 H each, 2 × OMe), 3.75 (t, J = 7.6 Hz, 2 H, 3-H), 2.69 (t, J = 7.6 Hz, 2 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 165.5 (C-1), 150.6, 146.9 (C-6, C-7), 137.6, 131.6 (C-1′, C-8a), 128.3, 128.2, 126.1 (CH CH_2*Ph*), 121.0 (C-4a), 110.0, 109.6 (C-5, C-8), 55.6, 55.5 (2 × OMe), 46.4 (C-3), 42.8 (*C*H_2Ph), 25.4 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3000, 2936, 1602, 1563, 1509, 1451, 1358 cm^{-1}. t_R = 8.31 min. EI-MS: m/z (%) = 282 (7), 281 (43) $[M]^+$, 280 (100), 264 (16), 250 (30). HRMS: calcd. for $C_{18}H_{20}NO_2$ $[M + H]^+$ 282.1494; found 282.1490.

6,7-Dimethoxy-1-(1-naphthyl)-3,4-dihydroisoquinoline (1f):[22] Isoquinoline **1f** (4.4 g, 98%) was obtained from the corresponding amide[22] (4.7 g, 14 mmol) as a pale yellow solid; m.p. 107–109 °C. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.92–7.84 (m, 2 H, 2′-H, 4′-H Ar), 7.72 (d, J = 7.3 Hz, 1 H, 8′-H Ar), 7.56–7.31 (m, 4 H, 3′-H, 5′-H, 6′-H, 7′-H Ar), 6.79, 6.37 (2 × s, 1 H each, 5-H, 8-H), 3.98–3.92 (m, 2 H, 3-H), 3.92, 3.42 (2 × s, 3 H each, 2 × OMe), 2.88 (t, J = 7.3 Hz, 2 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 166.7 (C-1), 151.0, 146.8 (C-6, C-7), 135.5, 132.9, 130.8, 130.7, 128.7, 127.6, 126.1, 125.6, 125.3, 125.0, 124.5, 121.9 (C-4a, C-8a, C_{quat}, CH Ar), 110.9, 109.7 (C-5, C-8), 55.3, 55.2 (2 × OMe), 46.5 (C-3), 25.0 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3053, 2935, 1602, 1561, 1508, 1461, 1352 cm^{-1}. t_R = 11.16 min. EI-MS: m/z (%) = 318 (18), 317 (88) $[M]^+$, 316 (100), 302 (22), 300 (38), 286 (25). HRMS: calcd. for $C_{21}H_{20}NO_2$ $[M + H]^+$ 318.1489; found 318.1478.

6,7-Dimethoxy-1-(1-methyl-1*H*-2-pyrrolyl)-3,4-dihydroisoquinoline (1g): Isoquinoline **1g** (3.7 g, 99%) was obtained from the corresponding amide (4.0 g, 14 mmol) as a yellow solid; m.p. 83–85 °C. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.14, 6.73 (2 × s, 1 H each, 5-H, 8-H), 6.75–6.73 (m, 1 H, 5′-H Ar), 6.33 (dd, J = 3.7, 1.5 Hz, 1 H, 3′-H Ar), 6.13 (dd, J = 3.7, 2.4 Hz, 1 H, 4′-H Ar), 3.92, 3.79 (2 × s, 3 H each, 2 × OMe), 3.84 (s, 3 H, *N*-Me), 3.74 (t, J = 7.6 Hz, 2 H, 3-H), 2.67 (t, J = 7.6 Hz, 2 H, 4-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 159.1 (C-1), 150.8, 147.0 (C-6, C-7), 132.5 (C-2′), 130.0 (C-8a), 126.7 (C-5′), 121.9 (C-4a), 114.6 (C-3′), 112.0, 110.1 (C-5, C-8), 107.2 (C-4′), 56.1, 56.0 (2 × OMe), 46.4 (C-3), 36.1 (*N-Me*), 25.8 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3050, 2936, 1599, 1558, 1509, 1460, 1350 cm^{-1}. t_R = 8.02 min. EI-MS: m/z (%) = 271 (13), 270 (73) $[M]^+$, 269 (100), 256 (15), 255 (90), 225 (16), 224 (28). HRMS: calcd. for $C_{16}H_{18}N_2O_2$ $[M]^+$ 270.1368; found 270.1367.

6,7-Dimethoxy-1-(2-thienyl)-3,4-dihydroisoquinoline (1h):[23] Isoquinoline **1h** (3.8 g, 99%) was obtained from the corresponding amide[24] (4.1 g, 14 mmol) as a yellow solid; m.p. 113–114 °C. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.48 (dd, J = 3.6, 1.2 Hz, 1 H, 3′-H Ar), 7.46 (dd, J = 4.8, 1.2 Hz, 1 H, 5′-H Ar), 7.22, 6.78 (2 × s, 1 H each, 5-H, 8-H), 7.11 (dd, J = 4.8, 3.6 Hz, 1 H, 4′-H Ar), 3.93, 3.82 (2 × s, 3 H each, 2 × OMe), 3.75 (t, J = 7.3 Hz, 2 H, 3-H), 2.70 (t, J = 7.3 Hz, 2 H, 4-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 160.6 (C-1), 151.7, 147.1 (C-6, C-7), 140.8, 133.0 (C-2′, C-8a), 130.0, 129.3, 127.4 (C-3′, C-4′, C-5′), 120.0 (C-4a), 111.4, 110.3 (C-5, C-8), 56.0, 55.9 (2 × OMe), 45.7 (C-3), 25.7 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3050, 2941, 1595, 1556, 1507, 1450, 1375 cm^{-1}. t_R = 8.36 min. EI-MS: m/z (%) = 274 (20), 273 (100) $[M]^+$, 272 (74), 258 (18). HRMS: calcd. for $C_{15}H_{15}NO_2S$ $[M]^+$ 273.0824; found 273.0831.

6,7-Dimethoxy-1-(2-furyl)-3,4-dihydroisoquinoline (1i):[23,25] Isoquinoline **1i** (3.6 g, 99%) was obtained from the corresponding amide[25] (3.9 g, 14 mmol) as a yellow solid; m.p. 108–110 °C. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.55 (d, J = 1.8 Hz, 1 H, 5′-H Ar), 7.24, 6.73 (2 × s, 1 H each, 5-H, 8-H), 6.85 (d, J = 3.7 Hz, 1 H, 3′-H Ar), 6.49 (dd, J = 3.7, 1.8 Hz, 1 H, 4′-H Ar), 3.90, 3.84 (2 × s, 3 H each, 2 × OMe), 3.76 (t, J = 7.3 Hz, 2 H, 3-H), 2.65 (t, J = 7.3 Hz, 2 H, 4-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 155.7 (C-1), 150.8, 150.7 (C-6, C-7), 146.7 (C-2′), 143.6 (C-5′), 132.2 (C-8a), 119.3 (C-4a), 112.8, 110.9, 110.4, 109.8 (C-5, C-8, C-3′, C-4′), 55.5, 55.3 (2 × OMe), 45.9 (C-3), 25.1 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3095, 2939, 1599, 1578, 1509, 1449, 1386 cm^{-1}. t_R = 7.64 min. EI-MS: m/z (%) = 258 (17), 257 (100) $[M]^+$, 256 (25), 242 (20). HRMS: calcd. for $C_{15}H_{15}NO_3$ $[M]^+$ 257.1052; found 257.1052.

6,7-Dimethoxy-1-(2-pyridyl)-3,4-dihydroisoquinoline (6):[26] Isoquinoline **6** (3.4 g, 90%) was obtained from the corresponding

amide[26] (3.9 g, 14 mmol) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.64 (d, J = 4.8 Hz, 1 H, 6′-H Ar), 7.85 (d, J = 7.5 Hz, 1 H, 3′-H Ar), 7.80 (t, J = 7.5 Hz, 1 H, 4′-H Ar), 7.34 (dd, J = 7.5, 4.8 Hz, 1 H, 5′-H Ar), 7.00, 6.73 (2× s, 1 H each, 5-H, 8-H), 3.91, 3.73 (2× s, 3 H each, 2× OMe), 3.85 (t, J = 7.5 Hz, 2 H, 3-H), 2.74 (t, J = 7.5 Hz, 2 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 165.3 (C-1), 156.8 (C-2′), 151.3, 147.1 (C-6, C-7), 148.5 (C-6′), 136.9 (C-4′), 132.6 (C-8a), 124.1, 124.0 (C-3′, C-5′), 120.5 (C-4a), 111.9, 110.1 (C-5, C-8), 56.0, 55.9 (2× OMe), 47.4 (C-3), 25.8 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3054, 2936, 1603, 1559, 1511, 1463, 1354 cm^{-1}. t_R = 8.33 min. EI-MS: m/z (%) = 269 (24), 268 (100) $[M]^+$, 267 (82), 253 (61), 251 (25). HRMS: calcd. for $C_{16}H_{16}N_2O_2$ $[M]^+$ 268.1212; found 268.1211.

Preparation of *N*-Methyl-3,4-dihydroisoquinolinium Salts 2c–d and 2f–i: To a solution of the appropriate dihydroisoquinoline (10 mmol) in dry acetone (50 mL) was added CH_3I (3.2 mL, 51 mmol) and the mixture was heated to reflux for 1 h. After this time, the yellow solid formed was filtered and the solution concentrated under vacuum to obtain the corresponding isoquinolinium salt.

1-Isopropyl-6,7-dimethoxy-*N*-methyl-3,4-dihydroisoquinolinium Iodide (2c):[27] Isoquinolium salt **2c** (3.6 g, 90%) was obtained from the isoquinoline **1c** (2.4 g, 10 mmol) as a pale yellow solid; m.p. 202–204 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.26, 6.89 (2× s, 1 H each, 5-H, 8-H), 4.14 (t, J = 7.5 Hz, 2 H, 3-H), 4.02, 3.98 (2× s, 3 H each, 2× OMe), 3.89 (s, 3 H, *N*-Me), 3.72 [septet, J = 7.2 Hz, 1 H, C*H*$(CH_3)_2$], 3.30 (t, J = 7.5 Hz, 2 H, 4-H), 1.60 [d, J = 7.2 Hz, 6 H, CH(C*H*$_3)_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 180.2 (C-1), 155.2, 147.3 (C-6, C-7), 133.7 (C-8a), 117.7 (C-4a), 111.4, 110.8 (C-5, C-8), 56.5, 56.2 (2× OMe), 53.5 (C-3), 46.2 (*N*-Me), 31.5 [*C*H$(CH_3)_2$], 25.6 (C-4), 20.3 [CH(*C*H$_3)_2$] ppm. IR (neat): $\tilde{\nu}$ = 3010, 2965, 1604, 1563, 1519, 1462, 1397 cm^{-1}. EI-MS: m/z (%) = 247(29) $[M - 1]^+$, 246 (38), 233 (48), 232 (100), 218 (45), 190 (32), 142 (95), 127 (69). HRMS: calcd. for $C_{15}H_{22}NO_2$ $[M]^+$ 248.1645; found 248.1637.

1-Benzyl-6,7-dimethoxy-*N*-methyl-3,4-dihydroisoquinolinium Iodide (2d): Isoquinolium salt **2d** (3.8 g, 91%) was obtained from the isoquinoline **1d** (2.9 g, 10 mmol) as a pale yellow solid; m.p. 120–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.36–7.26 (m, 3 H, CH_2*Ph*), 7.17, 6.89 (2× s, 1 H each, 5-H, 8-H), 7.13 (d, J = 7.0 Hz, 2 H, CH_2*Ph*), 4.69 (s, 2 H, C*H*$_2$Ph), 4.17 (t, J = 7.8 Hz, 2 H, 3-H), 3.98, 3.77 (2× s, 3 H each, 2× OMe), 3.84 (s, 3 H, *N*-Me), 3.37 (t, J = 7.8 Hz, 2 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 174.1 (C-1), 155.7, 147.9 (C-6, C-7), 133.1, 132.1 (C-1′, C-8a), 129.0, 127.8, 127.3 (CH CH_2*Ph*), 118.6 (C-4a), 112.2, 110.5 (C-5, C-8), 56.4, 56.0 (2× OMe), 52.9 (C-3), 45.5 (*N*-Me), 36.9 (C*H*$_2$Ph), 25.2 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3027, 2938, 1600, 1554, 1522, 1465, 1379 cm^{-1}. EI-MS: m/z (%) = 296 (19) $[M]^+$, 295 (100), 294 (91), 280 (25), 191 (14). HRMS: calcd. for $C_{19}H_{22}NO_2$ $[M]^+$ 296.1650; found 296.1645.

6,7-Dimethoxy-*N*-methyl-1-(1-naphthyl)-3,4-dihydroisoquinolinium Iodide (2f): Isoquinolium salt **2f** (4.1 g, 91%) was obtained from the isoquinoline **1f** (3.2 g, 10 mmol) as a pale yellow solid; m.p. 188–190 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.11–7.96 (m, 3 H, Ar), 7.71–7.40 (m, 4 H, Ar), 7.05, 6.21 (2× s, 1 H each, 5-H, 8-H), 4.83–4.68 (m, 1 H, 3-H), 4.60–4.42 (m, 1 H, 3′-H), 4.00, 3.33 (2× s, 3 H each, 2× OMe), 3.82–3.73 (m, 1 H, 4-H), 3.62–3.55 (m, 1 H, 4′-H), 3.57 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 173.0 (C-1), 156.9, 148.0 (C-6, C-7), 133.6, 132.8, 131.8, 128.9, 128.8, 127.5, 127.4, 126.4, 125.1, 123.9, 123.8, 119.4 (C-4a, C-8a, C_{quat}, CH Ar), 114.6, 111.2 (C-5, C-8), 56.9, 55.7 (2× OMe), 52.8 (C-3), 46.5 (*N*-Me), 25.8 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3080, 2932, 1602, 1557, 1518, 1460, 1376 cm^{-1}. EI-MS: m/z (%) = 318 (8), 317 (7) $[M - 15]^+$, 142 (100), 127 (66). HRMS: calcd. for $C_{22}H_{22}NO_2$ $[M]^+$ 332.1650; found 332.1657.

6,7-Dimethoxy-*N*-methyl-1-(1-methyl-1*H*-2-pyrrolyl)-3,4-dihydroisoquinolinium Iodide (2 g): Isoquinolium salt **2g** (3.7 g, 91%) was obtained from the isoquinoline **1g** (2.9 g, 10 mmol) as an orange solid; m.p. 113–115 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.02 (dd, J = 2.4, 1.5 Hz, 1 H, 5′-H Ar), 6.93, 6.40 (2× s, 1 H each, 5-H, 8-H), 6.69 (dd, J = 3.8, 1.5 Hz, 1 H, 3′-H Ar), 6.40–6.38 (m, 1 H, 4′-H Ar), 4.44–4.38 (m, 1 H, 3-H), 4.16–4.10 (m, 1 H, 3′-H), 4.02–3.93 (m, 1 H, 4-H), 4.01, 3.67 (2× s, 3 H each, 2× OMe), 3.93 (s, 3 H, *N*-Me Ar), 3.57 (s, 3 H, *N*-Me), 3.11 (dt, J = 16.8, 5.0 Hz, 1 H, 4′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 163.5 (C-1), 156.1, 148.0 (C-6, C-7), 134.2, 130.1 (C-2′, C-8a), 121.0, 119.7, 119.2, 114.2 (C-3′, C-4′, C-5′, C-4a), 110.9, 110.1 (C-5, C-8), 56.7, 56.0 (2× OMe), 52.3 (C-3), 46.7 (*N*-Me), 36.7 (*N*-*Me* Ar), 25.7 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3060, 2931, 1601, 1558, 1514, 1462, 1380 cm^{-1}. EI-MS: m/z (%) = 285 (7) $[M]^+$, 284 (21), 271 (20), 270 (92), 269 (100), 204 (29), 142 (75), 127 (35). HRMS: calcd. for $C_{17}H_{21}N_2O_2$ $[M]^+$ 285.1597; found 285.1598.

6,7-Dimethoxy-*N*-methyl-1-(2-thienyl)-3,4-dihydroisoquinolinium Iodide (2h):[28] Isoquinolium salt **2h** (3.7 g, 89%) was obtained from the isoquinoline **1h** (2.8 g, 10 mmol) as a yellow solid; m.p. 168–170 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.92 (dd, J = 3.7, 1.2 Hz, 1 H, 3′-H), 7.82 (dd, J = 4.9, 1.2 Hz, 1 H, 5′-H), 7.27 (dd, J = 4.9, 3.7 Hz, 1 H, 4′-H), 6.97, 6.58 (2× s, 1 H each, 5-H, 8-H), 4.37 (t, J = 7.6 Hz, 2 H, 3-H), 3.96, 3.83 (2× s, 3 H each, 2× OMe), 3.60 (s, 3 H, *N*-Me), 3.39 (t, J = 7.6 Hz, 2 H, 4-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 166.8 (C-1), 156.3, 147.5 (C-6, C-7), 135.9, 133.0, 127.8 (C-3′, C-4′, C-5′), 134.0, 133.9 (C-2′, C-8a), 119.8 (C-4a), 115.2, 110.6 (C-5, C-8), 56.8, 55.7 (2× OMe), 53.1 (C-3), 47.1 (*N*-Me), 25.4 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3036, 2937, 1600, 1558, 1511, 1461, 1378 cm^{-1}. EI-MS: m/z (%) = 288 (13) $[M]^+$, 287 (47), 286 (20), 274 (14), 273 (55), 272 (67), 205 (12), 204 (100), 188 (21), 142 (26), 127 (28). HRMS: calcd. for $C_{16}H_{18}NO_2S$ $[M]^+$ 288.1053; found 288.1051.

6,7-Dimethoxy-1-(2-furyl)-*N*-methyl-3,4-dihydroisoquinolinium Iodide (2i): Isoquinolium salt **2i** (4.1 g, 90%) was obtained from the isoquinoline **1i** (2.6 g, 10 mmol) as an orange solid; m.p. 113–115 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.92 (d, J = 1.8 Hz, 1 H, 5′-H), 7.42 (d, J = 3.7 Hz, 1 H, 3′-H), 7.02, 6.78 (2× s, 1 H each, 5-H, 8-H), 6.80 (dd, J = 3.7, 1.8 Hz, 1 H, 4′-H), 4.26 (t, J = 7.6 Hz, 2 H, 3-H), 3.97, 3.96 (2× s, 3 H each, 2× OMe), 3.71 (s, 3 H, *N*-Me), 3.35 (t, J = 7.6 Hz, 2 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 159.3 (C-1), 156.3, 147.6 (C-6, C-7), 148.9 (C-5′), 141.3 (C-2′), 134.9, 126.2, 114.8, 113.3, 111.0 (C-8a, C-3′, C-4′, C-5, C-8), 117.9 (C-4a), 56.8, 55.9 (2× OMe), 53.5 (C-3), 47.1 (*N*-Me), 25.8 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3080, 2999, 1599, 1563, 1518, 1446, 1371 cm^{-1}. EI-MS: m/z (%) = 272 (15) $[M]^+$, 271 (55), 270 (37), 257 (81), 256 (100), 204 (90), 198 (45), 142 (39), 127 (45). HRMS: calcd. for $C_{16}H_{18}NO_3$ $[M]^+$ 272.1281; found 272.1282.

Preparation of 1,2,3,4-Tetrahydroisoquinolines 3c–d, 3f–i and 7: To a solution of the appropriate starting material (5.0 mmol) in MeOH (40 mL) was added $NaBH_4$ (220 mg, 5.8 mmol) dropwise over a period of 10 min and the mixture was stirred for 2 h. The solvent was evaporated under vacuum, and the residue obtained was dissolved in CH_2Cl_2 (30 mL) and washed with water. The organic layer was dried with anhydrous $MgSO_4$, and the solvent evaporated under vacuum to obtain the corresponding 1,2,3,4-tetrahydroisoquinoline.

1-Isopropyl-6,7-dimethoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (3c):[29] Isoquinoline **3c** (1.2 g, 98%) was obtained from the salt **2c** (2.0 g, 5.0 mmol) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.54, 6.51 (2× s, 1 H each, 5-H, 8-H), 3.81, 3.80 (2× s, 3 H each, 2× OMe), 3.14 (dd, J = 12.1, 4.6 Hz, 1 H, 3-H), 3.08 (d, J = 6.9 Hz, 1 H, 1-H), 2.71–2.54 (m, 3 H, 3′-H, 4-H, 4′-H), 2.40 (s, 3 H, *N*-Me), 1.86 [octet, J = 6.9 Hz, 1 H, C*H*$(CH_3)_2$], 0.96 [d, J = 6.9 Hz, 3 H, CH(C*H*$_3)_2$], 0.83 [d, J = 6.9 Hz, 3 H, CH-(C*H*$_3)_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 146.6, 146.0 (C-6, C-7), 128.2, 126.9 (C-4a, C-8a), 111.4, 110.6 (C-5, C-8), 68.7 (C-1), 55.2, 55.0 (2× OMe), 47.7 (C-3), 43.5 (*N*-Me), 33.8 [*C*H$(CH_3)_2$], 28.4 (C-4), 19.5 [CH(*C*H$_3)_2$] ppm. IR (neat): $\tilde{\nu}$ = 3020, 2934, 1608, 1569, 1511, 1462, 1375 cm^{-1}. t_R = 6.43 min. EI-MS: *m*/*z* (%) = 207 (37), 206 (100) [M – 43]$^+$, 191 (26), 190 (45), 162 (13). HRMS: calcd. for $C_{15}H_{24}NO_2$ [M]$^+$ 250.1802; found 250.1793.

1-Benzyl-6,7-dimethoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (3d): Isoquinoline **3d** (1.5 g, 99%) was obtained from the salt **2d** (2.1 g, 5.0 mmol) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.30–7.15 (m, 3 H, CH_2*Ph*), 7.08 (d, J = 7.0 Hz, 2 H, CH_2*Ph*), 6.54, 5.87 (2× s, 1 H each, 5-H, 8-H), 3.87–3.83 (m, 1 H, 1-H), 3.81, 3.46 (2× s, 3 H each, 2× OMe), 3.78–3.74 (m, 1 H, C*H*$_2$Ph), 3.29–3.19 (m, 2 H, 3-H, 4-H), 2.85–2.75 (m, 2 H, 3′-H, C*H*$_2$Ph), 2.63 (dd, J = 11.4, 3.5 Hz, 1 H, 4′-H), 2.54 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 146.8, 145.7 (C-6, C-7), 139.1 (C-1′), 129.3, 127.5, 125.4 (CH CH_2*Ph*), 128.1, 124.9 (C-4a, C-8a), 110.7, 110.5 (C-5, C-8), 64.2 (C-1), 55.1, 54.8 (2× OMe), 46.0 (C-3), 41.8 (*N*-Me), 40.3 (*C*H$_2$Ph), 24.7 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3050, 2933, 1603, 1561, 1511, 1452, 1372 cm^{-1}. t_R = 8.07 min. EI-MS: *m*/*z* (%) = 207 (19), 206 (100), 190 (17). HRMS: calcd. for $C_{19}H_{24}NO_2$ [M]$^+$ 298.1807; found 298.1807.

6,7-Dimethoxy-*N*-methyl-1-(1-naphthyl)-1,2,3,4-tetrahydroisoquinoline (3f): Isoquinoline **3f** (1.6 g, 95%) was obtained from the salt **2f** (2.2 g, 5.0 mmol) as a pale yellow solid; m.p. 140–142 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 8.27 (d, J = 8.2 Hz, 1 H, 8′-H Ar), 7.83–7.75 (m, 2 H, 2′-H, 4′-H Ar), 7.43–7.29 (m, 4 H, 3′-H, 5′-H, 6′-H, 7′-H Ar), 6.63, 6.04 (2× s, 1 H each, 5-H, 8-H), 4.74 (s, 1 H, 1-H), 3.83, 3.37 (2× s, 3 H each, 2× OMe), 3.33–3.15 (m, 2 H, 3-H, 4-H), 2.85–2.60 (m, 2 H, 3′-H, 4′-H), 2.20 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 147.2, 147.0 (C-6, C-7), 139.0, 134.2, 130.3, 126.0, 128.5, 128.4, 128.3, 128.1, 125.4, 125.3, 125.2, 124.8 (C-4a, C-8a, C_{quat}, CH Ar), 110.7, 110.4 (C-5, C-8), 70.3 (C-1), 55.6, 55.4 (2× OMe), 52.7 (C-3), 44.3 (*N*-Me), 28.4 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3050, 2948, 1609, 1558, 1512, 1462, 1391 cm^{-1}. t_R = 9.99 min. EI-MS: *m*/*z* (%) = 333 (5) [M]$^+$, 207 (13), 206 (100), 190 (10), 127 (22). HRMS: calcd. for $C_{22}H_{23}NO_2$ [M]$^+$ 333.1792; found 333.1792.

6,7-Dimethoxy-*N*-methyl-1-(1-methyl-1*H*-2-pyrrolyl)-1,2,3,4-tetrahydroisoquinoline (3g): Isoquinoline **3g** (1.4 g, 99%) was obtained from the salt **2g** (2.1 g, 5.0 mmol) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 6.56, 6.19 (2× s, 1 H each, 5-H, 8-H), 6.50 (dd, J = 2.4, 1.5 Hz, 1 H, 5′-H Ar), 6.07–5.98 (m, 2 H, 3′-H, 4′-H Ar), 4.27 (s, 1 H, 1-H), 3.83, 3.60 (2× s, 3 H each, 2× OMe), 3.26 (s, 3 H, *N*-Me Ar), 3.13–2.95 (m, 2 H, 3-H, 4-H), 2.74–2.43 (m, 2 H, 3′-H, 4′-H), 2.24 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 147.3, 147.2 (C-6, C-7), 131.9, 128.8, 126.5 (C-2′, C-4a, C-8a), 123.1 (C-5′), 111.3, 110.7, 110.4, 105.7 (C-3′, C-4′, C-5, C-8), 64.4 (C-1), 55.8, 55.7 (2× OMe), 52.6 (C-3), 44.2 (*N*-Me), 34.3 (*N-Me* Ar), 28.4 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3054, 2938, 1604, 1550, 1512, 1461 cm^{-1}. t_R = 7.42 min. EI-MS: *m*/*z* (%) = 287 (19), 286 (100) [M]$^+$, 285 (55), 271 (10), 243 (19), 242 (15), 228 (24), 207 (15), 206 (42). HRMS: calcd. for $C_{17}H_{22}N_2O_2$ [M]$^+$ 286.1681; found 286.1678.

6,7-Dimethoxy-*N*-methyl-1-(2-thienyl)-1,2,3,4-tetrahydroisoquinoline (3h):[28] Isoquinoline **3h** (1.4 g, 98%) was obtained from the salt **2h** (2.1 g, 5.0 mmol) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.23 (d, J = 4.9 Hz, 1 H, 5′-H Ar), 6.98 (d, J = 3.8 Hz, 1 H, 3′-H Ar), 6.93 (dd, J = 4.9, 3.8 Hz, 1 H, 4′-H Ar), 6.57, 6.34 (2× s, 1 H each, 5-H, 8-H), 4.64 (s, 1 H, 1-H), 3.83, 3.65 (2× s, 3 H each, 2× OMe), 3.09 (dt, J = 11.0, 5.1 Hz, 1 H, 3-H), 3.01 (ddd, J = 15.8, 8.3, 5.1 Hz, 1 H, 4-H), 2.77 (dt, J = 15.8, 5.1 Hz, 1 H, 4′-H), 2.63 (ddd, J = 11.0, 8.3, 5.1 Hz, 1 H, 3′-H), 2.34 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 147.6, 146.9, 144.6 (C-6, C-7, C-2′), 127.5, 125.9, 125.8 (C-3′, C-4′, C-5′), 127.4, 124.7 (C-4a, C-8a), 110.5, 110.3 (C-5, C-8), 63.7 (C-1), 55.4, 55.3 (2× OMe), 49.4 (C-3), 42.8 (*N*-Me), 26.9 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3080, 2977, 1610, 1513, 1461, 1445, 1364 cm^{-1}. t_R = 7.76 min. EI-MS: *m*/*z* (%) = 290 (21), 289 (90) [M]$^+$, 288 (68), 274 (19), 246 (60), 231 (19), 215 (33), 207 (14), 206 (100), 190 (18). HRMS: calcd. for $C_{16}H_{19}NO_2S$ [M]$^+$ 289.1137; found 289.1138.

6,7-Dimethoxy-1-(2-furyl)-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (3i):[23,25] Isoquinoline **3i** (1.4 g, 99%) was obtained from the salt **2i** (2.1 g, 5.0 mmol) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.34 (s, 1 H, 5′-H Ar), 6.57, 6.30 (2× s, 1 H each, 5-H, 8-H), 6.28 (d, J = 3.1 Hz, 1 H, 3′-H Ar), 6.13 (d, J = 3.1 Hz, 1 H, 4′-H Ar), 4.51 (s, 1 H, 1-H), 3.81, 3.66 (2× s, 3 H each, 2× OMe), 3.08–2.56 (m, 4 H, 3-H, 3′-H, 4-H, 4′-H), 2.33 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 153.0 (C-2′), 147.4, 146.7 (C-6, C-7), 142.0 (C-5′), 125.3, 125.2 (C-4a, C-8a), 110.4, 109.8, 109.7, 109.4 (C-5, C-8, C-3′, C-4′), 61.2 (C-1), 55.1, 55.0 (2× OMe), 48.9 (C-3), 42.4 (*N*-Me), 26.8 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3050, 2937, 1609, 1561, 1514, 1462, 1369 cm^{-1}. t_R = 7.22 min. EI-MS: *m*/*z* (%) = 274 (6), 273 (31) [M]$^+$, 272 (17), 231 (15), 230 (100), 206 (29). HRMS: calcd. for $C_{16}H_{19}NO_3$ [M]$^+$ 273.1365; found 273.1370.

6,7-Dimethoxy-1-(2-pyridyl)-1,2,3,4-tetrahydroisoquinoline (7):[30] Tetrahydroisoquinoline **7** (1.2 g, 91%) was obtained from the dihydroisoquinoline **6** (1.3 g, 5.0 mmol) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.58 (d, J = 4.3 Hz, 1 H, 6′-H Ar), 7.61 (t, J = 8.1 Hz, 1 H, 4′-H Ar), 7.20–7.15 (m, 2 H, 3′-H, 5′-H Ar), 6.62, 6.34 (2× s, 1 H each, 5-H, 8-H), 5.21 (s, 1 H, 1-H), 3.84, 3.66 (2× s, 3 H each, 2× OMe), 3.17–3.04 (m, 2 H, 3-H, 4-H), 2.90–2.79 (m, 2 H, 3′-H, 4′-H), 2.57 (sa, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 159.3 (C-2′), 149.5, 148.5, 147.6 (C-6, C-7, C-6′), 137.1 (C-4′), 126.2, 124.6, 123.5, 123.2 (C-4a, C-8a, C-3′, C-5′), 111.5, 110.6 (C-5, C-8), 60.1 (C-1), 55.9, 55.8 (2× OMe), 40.3 (C-3), 27.0 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3500–3400, 3033, 2932, 1608, 1568, 1512, 1462, 1355 cm^{-1}. t_R = 8.08 min. EI-MS: *m*/*z* (%) = 270 (6) [M]$^+$, 254 (14), 253 (74), 238 (17), 192 (100). HRMS: calcd. for $C_{16}H_{18}N_2O_2$ [M]$^+$ 270.1368; found 270.1373.

6,7-Dimethoxy-*N*-methyl-1-(2-pyridyl)-1,2,3,4-tetrahydroisoquinoline (8): $NaBH_3CN$ (200 mg, 3.2 mmol) was added to a stirred solution of the isoquinoline **7** (500 mg, 1.8 mmol) and 37% aqueous formaldehyde (6.5 mL, 23 mmol) in acetonitrile (10 mL). The mixture was stirred for 25 min, and acetic acid was added dropwise until the solution tested neutral. Stirring was continued for additional 4 h, and the solvent was evaporated under vacuum. The residue obtained was dissolved in CH_2Cl_2 (20 mL) and washed with NaOH (5%, 2× 10 mL). The organic layer was dried with anhydrous $MgSO_4$, the solvent evaporated in vacuo and the crude reaction mixture purified by column chromatography (SiO_2; CH_2Cl_2/MeOH, 9.6:0.4) to obtain the isoquinoline **8** (434 mg, 85%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.55 (d, J = 4.8 Hz, 1 H, 6′-H Ar), 7.59 (t, J = 7.5 Hz, 1 H, 4′-H Ar), 7.28 (d, J = 7.5 Hz, 1 H, 3′-H Ar), 7.16 (dd, J = 7.5, 4.8 Hz, 1 H, 5′-H

Ar), 6.58, 6.21 (two s, 1 H each, 5-H, 8-H), 4.43 (s, 1 H, 1-H), 3.81, 3.56 (2× s, 3 H each, 2× OMe), 3.21–3.07 (m, 2 H, 3-H, 4-H), 2.72–2.61 (m, 2 H, 3′-H, 4′-H), 2.26 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 164.2 (C-2′), 148.2 (C-6′), 147.4, 147.0 (C-6, C-7), 136.8 (C-4′), 128.9, 126.2 (C-4a, C-8a), 123.3, 122.2 (C-3′, C-5′), 110.7, 110.6 (C-5, C-8), 72.1 (C-1), 55.7, 55.6 (2× OMe), 51.9 (C-3), 44.2 (*N*-Me), 29.0 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3048, 2939, 1588, 1566, 1512, 1463, 1368 cm^{-1}. t_R = 7.76 min. EI-MS: *m*/*z* (%) = 284 (6) [M]$^+$, 254 (18), 253 (91), 238 (28), 206 (100), 190 (28). HRMS: calcd. for $C_{17}H_{20}N_2O_2$ [M]$^+$ 284.1525; found 284.1523.

Preparation of *N*-Methyl-1,2,3,4-tetrahydroisoquinolinium Salts 4a–i: The appropriate halo derivative (2.1 mmol) was added to a solution of the corresponding isoquinoline (1.8 mmol) in dry acetone (20 mL) under argon. After stirring at room temperature for 24 h, a precipitate formed, which was collected by filtration and washed with several portions of diethyl ether. The acetone solution was reduced by half, and diethyl ether was added to precipitate the remaining isoquinolinium salt.

6,7-Dimethoxy-*N*-[(methoxycarbonyl)methyl]-*N*-methyl-1,2,3,4-tetrahydroisoquinolinium Bromide (4a):[31] Isoquinolinium salt **4a** (583 mg, 90%) was obtained from the isoquinoline **3a**[15] (360 mg, 1.8 mmol) as a white solid; m.p. 193–195 °C. ^{1}H NMR (400 MHz, DMSO, 25 °C): δ = 6.88, 6.81 (2× s, 1 H each, 5-H, 8-H), 4.72 (d, *J* = 15.2 Hz, 1 H, α-H), 4.65 (d, *J* = 15.2 Hz, 1 H, α′-H), 4.52 (d, *J* = 15.2 Hz, 1 H, 1-H), 4.46 (d, *J* = 15.2 Hz, 1 H, 1′-H), 4.06–3.81 (m, 2 H, 3-H, 3′-H), 3.79, 3.76, 3.73 (3× s, 3 H each, 3× OMe), 3.26 (s, 3 H, *N*-Me), 3.16–3.08 (m, 2 H, 4-H, 4′-H) ppm. ^{13}C NMR (100 MHz, DMSO, 25 °C): δ = 165.1 (CO), 148.8, 148.0 (C-6, C-7), 121.4, 117.9 (C-4a, C-8a), 111.6, 109.9 (C-5, C-8), 61.7 (C-1), 60.1 (C-α), 58.4 (C-3), 55.6, 55.5 (2× OMe), 53.2 (CO*OMe*), 47.8 (*N*-Me), 22.8 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3033, 2952, 1741, 1612, 1519, 1480, 1462, 1366 cm^{-1}. EI-MS: *m*/*z* (%) = 265 (5), 220 (12), 207 (40), 206 (100), 164 (51). HRMS: calcd. for $C_{15}H_{22}NO_4$ [M]$^+$ 280.1549; found 280.1542.

(±)-*trans*-6,7-Dimethoxy-*N*-[(methoxycarbonyl)methyl]-1-methyl-*N*-methyl-1,2,3,4-tetrahydroisoquinolinium Bromide (4b-*trans*): Isoquinolinium salt **4b**-*trans* (774 mg, 90%) was obtained from the isoquinoline **3b**[16] (500 mg, 2.3 mmol) as a pale yellow solid; m.p. 178–180 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 6.59, 6.58 (2× s, 1 H each, 5-H, 8-H), 5.73 (c, *J* = 6.7 Hz, 1 H, 1-H), 5.16 (d, *J* = 17.7 Hz, 1 H, α-H), 4.72 (d, *J* = 17.7 Hz, 1 H, α′-H), 4.56 (dt, *J* = 12.8, 4.3 Hz, 1 H, 3-H), 3.84, 3.83 (2× s, 3 H each, 2× OMe), 3.77 (s, 3 H, CO*OMe*), 3.72 (s, 3 H, *N*-Me), 3.66–5.56 (m, 1 H, 3′-H), 3.04 (m, 2 H, 4-H, 4′-H), 1.73 (d, *J* = 6.7 Hz, 3 H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 165.0 (CO), 149.1, 148.7 (C-6, C-7), 123.3, 119.3 (C-4a, C-8a), 110.6, 109.7 (C-5, C-8), 67.2 (C-1), 57.5 (C-α), 55.9, 55.7 (2× OMe), 53.0, 52.9 (C-3, CO*OMe*), 48.0 (*N*-Me), 23.3 (C-4), 18.7 (*Me*) ppm. IR (neat): $\tilde{\nu}$ = 3032, 1742, 1614, 1520, 1471, 1459, 1375 cm^{-1}. EI-MS: *m*/*z* (%) = 264 (33), 207 (13), 206 (100), 190 (23). HRMS: calcd. for $C_{16}H_{24}NO_4$ [M]$^+$ 294.1705; found 294.1708.

(±)-*trans*-1-Isopropyl-6,7-dimethoxy-*N*-[(methoxycarbonyl)methyl]-*N*-methyl-1,2,3,4-tetrahydroisoquinolinium Bromide (4c-*trans*): Isoquinolinium salt **4c**-*trans* (745 mg, 93%) was obtained from the isoquinoline **3c** (500 mg, 2.0 mmol) as a yellow solid; m.p. 143–145 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.62, 6.40 (2× s, 1 H each, 5-H, 8-H), 5.11 (br. s, 1 H, 1-H), 4.85 (d, *J* = 16.5 Hz, 1 H, α-H), 4.62 (d, *J* = 16.5 Hz, 1 H, α′-H), 4.55–4.50 (m, 1 H, 3-H), 3.77, 3.76 (2× s, 3 H each, 2× OMe), 3.76–3.70 (m, 1 H, 3′-H), 3.67 (s, 3 H, CO*OMe*), 3.64 (s, 3 H, *N*-Me), 3.07–3.03 (m, 2 H, 4-H, 4′-H), 2.65 [septet, *J* = 6.7 Hz, 1 H, C*H*(CH$_3$)$_2$], 1.23 [d, *J* = 6.7 Hz, 1 H, CH(C*H*$_3$)$_2$], 0.53 [d, *J* = 6.7 Hz, 1 H, CH(C*H*$_3$)$_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 165.6 (CO), 149.8, 148.2 (C-6, C-7), 120.6, 120.1 (C-4a, C-8a), 111.0, 110.6 (C-5, C-8), 75.5 (C-1), 58.3 (C-α), 56.2, 56.0 (2× OMe), 54.0 (C-3), 52.9 (CO*OMe*), 49.1 (*N*-Me), 28.3 [*C*H(CH$_3$)$_2$], 24.4 [CH(*C*H$_3$)$_2$], 23.4 (C-4), 20.0 [CH(*C*H$_3$)$_2$] ppm. IR (neat): $\tilde{\nu}$ = 3033, 2965, 1744, 1610, 1517, 1442, 1357 cm^{-1}. EI-MS: *m*/*z* (%) = 322 (21) [M]$^+$, 321 (26), 318 (47), 264 (49), 206 (100), 190 (17). HRMS: calcd. for $C_{18}H_{28}NO_4$ [M]$^+$ 322.2013; found 322.2010.

(±)-*trans*-1-Benzyl-6,7-dimethoxy-*N*-[(methoxycarbonyl)methyl]-*N*-methyl-1,2,3,4-tetrahydroisoquinolinium Bromide (4d-*trans*): Isoquinolinium salt **4d**-*trans* (759 mg, 94%) was obtained from the isoquinoline **3d** (540 mg, 1.8 mmol) as a white solid; m.p. 162–165 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.28–7.24 (m, 3 H, CH$_2$*Ph*), 6.94 (d, *J* = 7.3 Hz, 2 H, CH$_2$*Ph*), 6.62 (s, 1 H, 5-H), 5.96 (d, *J* = 17.8 Hz, 1 H, α-H), 5.43 (s, 1 H, 8-H), 5.28 (dd, *J* = 10.9, 3.5 Hz, 1 H, 1-H), 5.00 (d, *J* = 17.8 Hz, 1 H, α′-H), 4.89 (dd, *J* = 12.8, 6.3 Hz, 1 H, 3-H), 4.04–3.96 (m, 2 H, 3′-H, 4-H), 3.90, 3.84 (2× s, 3 H each, 2× OMe), 3.63 (s, 3 H, CO*OMe*), 3.52 (dd, *J* = 12.5, 3.5 Hz, 1 H, C*H*$_2$Ph), 3.27 (s, 3 H, *N*-Me), 3.16 (dd, *J* = 18.3, 6.3 Hz, 1 H, 4′-H), 2.92 (dd, *J* = 12.5, 10.9 Hz, 1 H, C*H*$_2$Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 165.9 (CO), 149.4, 146.8 (C-6, C-7), 134.9 (C-1′), 130.3, 128.7, 127.4 (CH CH$_2$*Ph*), 120.6, 120.0 (C-4a, C-8a), 111.5, 110.7 (C-5, C-8), 71.1 (C-1), 61.0 (C-α), 55.9, 55.2 (2× OMe), 53.2, 53.1 (C-3, CO*OMe*), 47.1 (*N*-Me), 38.8 (*C*H$_2$Ph), 23.2 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3050, 2954, 1741, 1611, 1522, 1494, 1466, 1358 cm^{-1}. EI-MS: *m*/*z* (%) = 370 (27) [M]$^+$, 369 (100), 310 (14), 264 (99), 206 (54). HRMS: calcd. for $C_{22}H_{28}NO_4$ [M]$^+$ 370.2018; found 370.2009.

(+)-*trans*-*N*-[(Methoxycarbonyl)methyl]romneinium Bromide (4e-*trans*): Isoquinolinium salt **4e**-*trans* (604 mg, 94%) was obtained from the (+)-romneine (**3e**)[17] (440 mg, 1.3 mmol) as a pale yellow solid; m.p. 150–152 °C. $[\alpha]_D$ = +63 (*c* = 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.78–6.72 (m, 2 H, 2′-H, 5′-H Ar), 6.60 (s, 1 H, 5-H), 6.51 (dd, *J* = 8.1, 2.1 Hz, 1 H, 6′-H Ar), 5.88 (s, 2 H, OC*H*$_2$O), 5.87 (br. s, 1 H, 1-H), 5.82 (s, 1 H, 8-H), 5.11 (d, *J* = 17.5 Hz, 1 H, α-H), 4.73 (d, *J* = 17.5 Hz, 1 H, α′-H), 4.60 (br. d, *J* = 14.0 Hz, 1 H, 3-H), 3.83, 3.82 (2× s, 3 H each, 2× OMe), 3.84–3.73 (m, 1 H, C*H*$_2$Ar), 3.74 (s, 3 H, CO*OMe*), 3.68–3.64 (m, 1 H, 3′-H), 3.60 (s, 3 H, *N*-Me), 3.01–2.97 (m, 2 H, 4-H, C*H*$_2$Ar), 2.95–2.89 (m, 1 H, 4′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 165.2 (CO), 148.9, 148.2, 148.1, 146.2, (C-6, C-7, C-3′, C-4′), 126.5 (C-1′), 122.3, 122.1, 121.5 (C-2′, C-5′, C-6′), 113.0, 111.0 (C-4a, C-8a), 108.6, 108.0 (C-5, C-8), 101.2 (O*C*H$_2$O), 71.5 (C-1), 57.8 (C-α), 56.2, 55.6 (2× OMe), 53.5 (C-3), 52.9 (CO*OMe*), 49.3 (*N*-Me), 37.3 (*C*H$_2$Ar), 23.7 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3052, 2908, 1745, 1613, 1515, 1483, 1449, 1396 cm^{-1}. EI-MS: *m*/*z* (%) = 414 (10) [M]$^+$, 413 (41), 248 (80), 190 (100), 148 (52). HRMS: calcd. for $C_{23}H_{28}NO_6$ [M]$^+$ 414.1917; found 414.1910.

(±)-*trans*-6,7-Dimethoxy-*N*-[(methoxycarbonyl)methyl]-*N*-methyl-1-(1-naphthyl)-1,2,3,4-tetrahydroisoquinolinium Bromide (4f-*trans*): Isoquinolinium salt **4f**-*trans* (678 mg, 93%) was obtained from the isoquinoline **3f** (500 mg, 1.5 mmol) as a yellow solid; m.p. 158–160 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.10 (d, *J* = 8.2 Hz, 1 H, 8′-H Ar), 7.97–7.95 (m, 2 H, 2′-H, 4′-H Ar), 7.87 (t, *J* = 8.2 Hz, 1 H, 6′-H Ar), 7.65 (t, *J* = 8.2 Hz, 1 H, 7′-H), 7.42 (t, *J* = 8.2 Hz, 1 H, 3′-H), 7.31 (s, 1 H, 1-H), 7.09 (d, *J* = 8.2 Hz, 1 H, 5′-H), 6.77, 6.22 (2× s, 1 H each, 5-H, 8-H), 5.79 (d, *J* = 17.5 Hz, 1 H, α-H), 4.95–4.88 (m, 2 H, α′-H, 3-H), 3.90, 3.85 (2× s, 3 H each, 2× OMe), 3.90–3.85 (m, 1 H, 3′-H), 3.63–3.60 (m, 1 H, 4-H), 3.61 (s, 3 H, CO*OMe*), 3.29 (dd, *J* = 18.3, 5.7 Hz, 1 H, 4′-H), 3.20 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 165.9

(CO), 149.7, 148.9 (C-6, C-7), 133.5, 133.0, 132.1, 131.7, 129.2, 128.4, 128.3, 126.5, 124.7, 123.1 (C_{quat}, CH Ar), 121.5, 120.4 (C-4a, C-8a), 110.5, 110.2 (C-5, C-8), 67.2 (C-1), 57.8 (C-α), 55.9, 55.6 (2× OMe), 53.4 (C-3), 53.1 (CO*OMe*), 48.5 (*N*-Me), 23.3 (C-4) ppm. IR (neat): ṽ = 3033, 2951, 1742, 1613, 1517, 1440, 1375 cm^{-1}. EI-MS: *m*/*z* (%) = 405 (1), 333 (24), 332 (32), 318 (55), 264 (32), 206 (100). HRMS: calcd. for $C_{25}H_{28}NO_4$ $[M]^+$ 406.2018; found 406.1997.

(±)-*trans*-6,7-Dimethoxy-*N*-[(methoxycarbonyl)methyl]-*N*-methyl-1-(1-methyl-1*H*-2-pyrrolyl)-1,2,3,4-tetrahydroisoquinolinium Bromide (4g-*trans*): Isoquinolinium salt **4g**-*trans* (590 mg, 96%) was obtained from the isoquinoline **3g** (400 mg, 1.4 mmol) as a yellow solid; m.p. 128–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.79 (br. s, 1 H, 5′-H Ar), 6.70 (s, 1 H, 3′-H Ar), 6.64, 6.36 (2× s, 1 H each, 5-H, 8-H), 6.13 (m, 1 H, 4′-H Ar), 5.83 (br. s, 1 H, 1-H), 5.49 (d, *J* = 17.4 Hz, 1 H, α-H), 4.89 (d, *J* = 17.4 Hz, 1 H, α′-H), 4.50–4.46 (m, 1 H, 3-H), 4.00–3.93 (m, 1 H, 3′-H), 3.86, 3.85, 3.78, 3.73 (4× s, 3 H each, 3× OMe, *N*-*Me* Ar), 3.86–3.77 (m, 1 H, 4-H), 3.26 (s, 3 H, *N*-Me), 3.13–3.09 (m, 1 H, 4′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 165.6 (CO), 149.4, 148.6 (C-6, C-7), 126.5, 123.2, 121.5, 119.6, 116.0 (C-4a, C-8a, C-2′, C-3′, C-5′), 111.0, 110.3 (C-5, C-8), 108.7 (C-4′), 67.2 (C-1), 56.7 (C-α), 55.8, 55.7 (2× OMe), 53.0 (CO*OMe*), 52.1 (C-3), 46.2 (*N*-Me), 36.0 (*N*-*Me* Ar), 23.2 (C-4) ppm. IR (neat): ṽ = 3051, 2938, 1743, 1612, 1516, 1439, 1366 cm^{-1}. EI-MS: *m*/*z* (%) = 360 (7), 286 (21), 255 (85), 254 (100), 206 (17). HRMS: calcd. for $C_{20}H_{27}N_2O_4$ $[M]^+$ 359.1971; found 359.1968.

(±)-*trans*-6,7-Dimethoxy-*N*-[(methoxycarbonyl)methyl]-*N*-methyl-1-(2-thienyl)-1,2,3,4-tetrahydroisoquinolinium Bromide (4h-*trans*): Isoquinolinium salt **4h**-*trans* (699 mg, 93%) was obtained from the isoquinoline **3h** (500 mg, 1.7 mmol). The ^{1}H NMR spectrum of the crude product indicated a mixture of stereoisomers **4h** in a *cis*/*trans* ratio of 1:4. Spectroscopic data of the major *trans* diastereoisomer was determined from the mixture. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.96 (d, *J* = 3.5 Hz, 1 H, 3′-H Ar), 7.48 (d, *J* = 4.8 Hz, 1 H, 5′-H Ar), 7.40 (s, 1 H, 1-H), 7.08 (dd, *J* = 4.8, 3.5 Hz, 1 H, 4′-H Ar), 6.46, 6.39 (2× s, 1 H each, 5-H, 8-H), 5.58 (d, *J* = 16.9 Hz, 1 H, α-H), 4.55 (d, *J* = 16.9 Hz, 1 H, α′-H), 4.42–4.37 (m, 1 H, 3-H), 3.87, 3.79 (2× s, 3 H each, 2× OMe), 3.72 (s, 3 H, CO*OMe*), 3.74–3.69 (m, 1 H, 3′-H), 3.51 (s, 3 H, *N*-Me), 3.19–3.07 (m, 2 H, 4-H, 4′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 165.4 (CO), 149.7, 148.9 (C-6, C-7), 135.1, 134.7, 130.8, 127.6, (C-2′, C-3′, C-4′, C-5′), 121.9, 119.4 (C-4a, C-8a), 110.3, 110.2 (C-5, C-8), 69.5 (C-1), 56.7 (C-α), 55.8, 55.7 (2× OMe), 53.1 (CO*OMe*), 52.2 (C-3), 48.1 (*N*-Me), 23.5 (C-4) ppm.

(±)-*cis*-6,7-Dimethoxy-1-(2-furyl)-*N*-[(methoxycarbonyl)methyl]-*N*-methyl-1,2,3,4-tetrahydroisoquinolinium Bromide (4i-*cis*): Isoquinolinium salt **4i**-*cis* (728 mg, 95%) was obtained from the isoquinoline **3i** (500 mg, 1.8 mmol) as a white solid; m.p. 160–162 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.46 (d, *J* = 1.5 Hz, 1 H, 5′-H Ar), 6.69, 6.36 (2× s, 1 H each, 5-H, 8-H), 6.69–6.66 (m, 1 H, 3′-H Ar), 6.60 (s, 1 H, 1-H), 6.44 (dd, *J* = 3.0 Hz, 1.5 Hz, 1 H, 4′-H Ar), 5.26 (d, *J* = 17.4 Hz, 1 H, α-H), 4.88 (dd, *J* = 12.2 Hz, 6.1 Hz, 1 H, 3-H), 4.06 (d, *J* = 17.4 Hz, 1 H, α′-H), 3.87, 3.82 (2× s, 3 H each, 2× OMe), 3.78 (s, 3 H, *N*-Me), 3.73 (s, 3 H, CO*OMe*), 3.73–3.63 (m, 1 H, 3′-H), 3.45–3.06 (m, 2 H, 4-H, 4′-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 164.6 (CO), 149.3, 148.2 (C-6, C-7), 145.3, 145.2 (C-2′, C-5′), 120.4, 118.1, 117.1 (C-4a, C-8a, C-3′), 111.0, 110.3, 109.9 (C-5, C-8, C-4′), 66.3 (C-1), 59.8 (C-α), 55.5, 55.4 (2× OMe), 54.5 (C-3), 52.7 (CO*OMe*), 45.3 (*N*-Me), 22.6 (C-4) ppm. IR (neat): ṽ = 3090, 2950, 1747, 1612, 1515, 1496, 1457, 1369 cm^{-1}. EI-MS: *m*/*z* (%) = 346 (4) $[M]^+$, 345 (9), 287 (19), 286 (99), 273 (36), 272 (73), 259 (17), 258 (100). HRMS: calcd. for $C_{19}H_{24}NO_5$ $[M]^+$ 346.1649; found 346.1643.

Preparation of 1-Alkyl-2,3,4,5-tetrahydro-1*H*-3-benzazepines 5b and 5c: NaHMDS (0.34 mL, 1 M in THF, 0.34 mmol) was added to a solution of the appropriate isoquinolinium salt (0.25 mmol) in dry THF (25 mL), and the mixture was stirred at room temperature for 1 h. The solvent was evaporated in vacuo, and the crude reaction mixture was purified by column chromatography (SiO_2; cyclohexane/EtOAc) to yield the benzazepine.

(1*R,2*R**)-7,8-Dimethoxy-2-(methoxycarbonyl)-1-methyl-*N*-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (5b-*trans*):** Benzazepine **5b**-*trans* (50 mg, 63%) was obtained from the salt **4b**-*trans* (100 mg, 0.27 mmol) as a pale yellow solid; m.p. 60–61 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.65, 6.61 (2× s, 2 H, 6-H, 9-H), 3.83, 3.82, 3.63 (3× s, 3 H each, 3× OMe), 3.36 (q, *J* = 7.2 Hz, 1 H, 1-H), 3.25 (d, *J* = 7.2 Hz, 1 H, 2-H), 3.22–3.16 (m, 1 H, 4-H), 3.00–2.93 (m, 1 H, 5-H), 2.89–2.82 (m, 1 H, 4′-H), 2.69–2.65 (m, 1 H, 5′-H), 2.40 (s, 3 H, *N*-Me), 1.39 (d, *J* = 7.2 Hz, 3 H, *Me*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.9 (CO), 147.1, 147.0 (C-7, C-8), 133.1, 132.3 (C-5a, C-9a), 112.7, 111.1 (C-6, C-9), 70.6 (C-2), 56.0, 55.8 (2× OMe), 50.9, 50.4 (C-1, CO*OMe*), 45.7 (C-4), 40.1 (*N*-Me), 33.9 (C-5), 17.3 (*Me*) ppm. IR (neat): ṽ = 3020, 2936, 1732, 1603, 1516, 1467, 1381 cm^{-1}. t_R = 7.23 min. EI-MS: *m*/*z* (%) = 293 (19) $[M]^+$, 235 (26), 234 (100), 219 (24). HRMS: calcd. for $C_{16}H_{24}NO_4$ $[M + H]^+$ 294.1700; found 294.1701.

(1*R,2*R**)-7,8-Dimethoxy-1-isopropyl-2-(methoxycarbonyl)-*N*-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (5c-*trans*):** Benzazepine **5c**-*trans* (61 mg, 76%) was obtained from the salt **4c**-*trans* (100 mg, 0.25 mmol) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 6.51, 6.43 (2× s, 2 H, 6-H, 9-H), 3.81, 3.78 (2× s, 3 H each, 2× OMe), 3.76 (d, *J* = 6.7 Hz, 1 H, 2-H), 3.46 (t, *J* = 6.7 Hz, 1 H, 1-H), 3.45 (s, 3 H, CO*OMe*), 3.36–3.17 (m, 1 H, 4-H), 2.76–2.64 [m, 1 H, C*H*$(CH_3)_2$], 2.62–2.38 (m, 3 H, 4′-H, 5-H, 5′-H), 2.56 (s, 3 H, *N*-Me), 1.03 [d, *J* = 6.0 Hz, 3 H, CH(C*H*$_3)_2$], 0.65 [d, *J* = 6.0 Hz, 3 H, CH(C*H*$_3)_2$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 171.8 (CO), 146.9, 146.2 (C-7, C-8), 132.6, 132.2 (C-5a, C-9a), 115.6, 113.5 (C-6, C-9), 65.2 (C-2), 57.6 (C-1), 56.1, 55.7 (2× OMe), 50.5 (C-4), 50.3 (CO*OMe*), 46.7 (*N*-Me), 35.9 [*C*H$(CH_3)_2$], 26.5 (C-5), 21.9, 21.5 [CH(*C*H$_3)_2$] ppm. IR (neat): ṽ = 3025, 2957, 1735, 1606, 1512, 1462, 1381 cm^{-1}. t_R = 7.32 min. EI-MS: *m*/*z* (%) = 321 (7) $[M]^+$, 263 (18), 262 (100), 219 (45). HRMS: calcd. for $C_{18}H_{28}NO_4$ $[M + H]^+$ 322.2013; found 322.2007.

General Method for the Stevens Rearrangement: DBU (49 μL, 0.31 mmol) was added to a solution of the appropriate salt (0.23 mmol) in CH_3CN (10 mL), and the resulting mixture was stirred at room temperature for 30 min. After this time, the solvent was evaporated in vacuo, and the crude reaction mixture was purified by column chromatography (SiO_2; cyclohexane/EtOAc) to yield the benzazepine.

(1*R,2*R**)-1-Benzyl-7,8-dimethoxy-2-(methoxycarbonyl)-*N*-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (5d-*trans*):** Benzazepine **5d**-*trans* (70 mg, 86%) was obtained from the salt **4d**-*trans* (100 mg, 0.22 mmol) after heating to reflux for 3 h as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.26–7.15 (m, 5 H, CH_2*Ph*), 6.56 (s, 1 H, 6-H), 6.41 (br. s, 1 H, 9-H), 3.82, 3.72 (2× s, 3 H each, 2× OMe), 3.44 (s, 3 H, CO*OMe*), 3.44–3.37 (m, 5 H, 1-H, 2-H, 4-H, 4′-H, 5-H), 2.96–2.75 (m, 2 H, C*H*$_2$Ph, 4′-H), 2.64–2.54 (m, 1 H, C*H*$_2$Ph), 2.53 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.3 (CO), 147.2, 146.7 (C-7, C-8), 140.7 (C-1′), 132.9, 132.1 (C-5a, C-9a), 129.2, 128.2, 126.0 (CH CH_2*Ph*), 114.5, 113.7 (C-6, C-9), 70.6 (C-2), 66.2 (C-1), 56.1, 55.8 (2×

OMe), 52.0 (CO*OMe*), 50.6, 50.5 (C-4, *C*H_2Ph), 46.6 (*N*-Me), 37.4 (C-5) ppm. IR (neat): $\tilde{\nu}$ = 3050, 2930, 1732, 1605, 1514, 1494, 1452, 1382 cm^{-1}. t_R = 9.40 min. EI-MS: *m*/*z* (%) = 369 (7), 311 (21), 310 (100), 219 (76). HRMS: calcd. for $C_{22}H_{28}NO_4$ $[M + H]^+$ 370.2018; found 370.2012.

(1*S*,2*S*)-1-(3′,4′-Dimethoxybenzyl)-7,8-methylenedioxy-2-(methoxycarbonyl)-*N*-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (5e-*trans*): Benzazepine **5e**-*trans* (70 mg, 85%) was obtained from the salt **4e**-*trans* (100 mg, 0.20 mmol) after heating to reflux for 3 h as a pale yellow oil. $[a]_D$ = +48, (*c* = 1.3, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.78–6.68 (m, 3 H, CH_2Ar), 6.54 (s, 1 H, 6-H), 6.47 (br. s, 1 H, 9-H), 5.88 (s, 2 H, OCH_2O), 3.84, 3.83 (2× s, 3 H each, 2× OMe), 3.46 (s, 3 H, CO*OMe*), 3.40–3.31 (m, 4 H, 1-H, 4-H, 4′-H, 5-H), 3.33 (d, *J* = 9.9 Hz, 1 H, 2-H), 2.92–2.75 (m, 2 H, CH_2Ar, 5′-H), 2.62–2.58 (m, 1 H, CH_2Ar), 2.52 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.3 (CO), 148.6, 147.4, 146.0, 145.6 (C-7, C-8, C-3′, C-4′), 134.1, 133.5, 133.1 (C-1′, C-5a, C-9a), 121.1 (C-6′), 112.6, 111.2, 110.8, 110.5 (C-2′, C-5′, C-6, C-9), 100.7 (OCH_2O), 65.9 (C-2), 59.8 (C-1), 55.8, 55.7 (2× OMe), 52.1, 50.7, 50.4 (C-4, CO*OMe*, *C*H_2Ar), 46.5 (*N*-Me), 36.7 (C-5) ppm. IR (neat): $\tilde{\nu}$ = 3033, 2932, 1733, 1613, 1513, 1485, 1450, 1368 cm^{-1}. t_R = 13.71 min. EI-MS: *m*/*z* (%) = 414 (3), 413 (14) $[M]^+$, 355 (22), 354 (100), 262 (7), 203 (25), 151 (65). HRMS: calcd. for $C_{23}H_{28}NO_6$ $[M + H]^+$ 414.1917; found 414.1909.

(1*R,2*R**)-7,8-Dimethoxy-2-(methoxycarbonyl)-*N*-methyl-1-naphthyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (5f-*trans*):** Benzazepine **5f**-*trans* (74 mg, 91%) was obtained from the salt **4f**-*trans* (100 mg, 0.27 mmol) as a white solid; m.p. 70–72 °C. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.87–7.78 (m, 3 H, 2′-H, 4′-H, 8′-H Ar), 7.58–7.33 (m, 4 H, 3′-H, 5′-H, 6′-H, 7′-H Ar), 6.75 (s, 1 H, 6-H), 6.11 (s, 1 H, 9-H), 5.40 (d, *J* = 8.8 Hz, 1 H, 1-H), 4.12 (d, *J* = 8.8 Hz, 1 H, 2-H), 3.85, 3.54 (2× s, 3 H each, 2× OMe), 3.32 (s, 3 H, CO*OMe*), 3.46–3.09 (m, 2 H, 4-H, 5-H), 2.96–2.74 (m, 2 H, 4′-H, 5′-H), 2.44 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 172.5 (CO), 147.3, 146.9 (C-7, C-8), 134.2, 131.6, 131.1, 128.8, 127.9, 126.5, 125.8, 125.4, 125.1, 125.0, 124.8, 124.7 (C-5a, C-9a, C_{quat}, CH Ar), 112.3, 112.0 (C-6, C-9), 68.3 (C-2), 55.7, 55.5 (2× OMe), 51.9 (C-1), 51.0 (CO*OMe*), 49.7 (C-4), 45.1 (*N*-Me), 32.9 (C-5) ppm. IR (neat): $\tilde{\nu}$ = 3052, 2934, 1725, 1598, 1508, 1449, 1398 cm^{-1}. t_R = 14.20 min. EI-MS: *m*/*z* (%) = 405 (9) $[M]^+$, 347 (23), 346 (100), 289 (19). HRMS: calcd. for $C_{25}H_{28}NO_4$ $[M + H]^+$ 406.2013; found 406.2003.

(1*R,2*R**)-7,8-Dimethoxy-2-(methoxycarbonyl)-*N*-methyl-1-(1-methyl-1*H*-2-pyrrolyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (5g-*trans*):** Benzazepine **5g**-*trans* (74 mg, 90%) was obtained from the salt **4g**-*trans* (100 mg, 0.23 mmol) as a yellow oil. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 6.68 (s, 1 H, 6-H), 6.57 (dd, *J* = 2.4, 1.5 Hz, 1 H, 5′-H Ar), 6.19 (dd, *J* = 3.7, 2.4 Hz, 1 H, 3′-H Ar), 6.10 (t, *J* = 3.7 Hz, 1 H, 4′-H Ar), 6.06 (s, 1 H, 9-H), 4.64 (d, *J* = 10.1 Hz, 1 H, 1-H), 3.84, 3.63, 3.60 (3× s, 3 H each, 3× OMe), 3.75 (d, *J* = 10.1 Hz, 1 H, 2-H), 3.30–3.20 (m, 1 H, 4-H), 3.25 (s, 3 H, *N*-Me Ar), 3.09–2.99 (m, 1 H, 5-H), 2.86–2.60 (m, 2 H, 4′-H, 5′-H), 2.36 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 172.0 (CO), 147.3, 147.2 (C-7, C-8), 130.7, 130.6, 130.2 (C-2′, C-5a, C-9a), 122.2 (C-5′), 111.8, 110.6, 107.4, 106.5 (C-6, C-9, C-3′, C-4′), 67.3 (C-2), 55.7, 55.6 (2× OMe), 51.0 (CO*OMe*), 48.8 (C-1), 44.9 (C-4), 41.0 (*N*-Me), 33.5 (*N*-*Me* Ar), 32.2 (C-5) ppm. IR (neat): $\tilde{\nu}$ = 3031, 1722, 1607, 1508, 1462, 1376 cm^{-1}. t_R = 8.79 min. EI-MS: *m*/*z* (%) = 359 (9), 358 (38) $[M]^+$, 300 (23), 299 (100), 257 (36), 256 (81), 242 (48). HRMS: calcd. for $C_{20}H_{27}N_2O_4$ $[M + H]^+$ 359.1965; found 359.1964.

7,8-Dimethoxy-2-(methoxycarbonyl)-*N*-methyl-1-(2-thienyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (5h): A mixture of isomers of **5h** (77 mg, 93%) were obtained in a *cis*/*trans* ratio 1:4 from the salts **4h** (*cis*/*trans* 1:4, 100 mg, 0.23 mmol). Both isomers of **5h** were isolated by colunm chromatography (SiO_2; cyclohexane/EtOAc, 6:4) to yield **5h**-*trans* (62 mg, 75%) and **5h**-*cis* (15 mg, 18%).

5h-*trans*: Pale yellow solid; m.p. 83–85 °C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.16 (d, *J* = 4.9 Hz, 1 H, 5′-H Ar), 6.89 (dd, *J* = 4.9, 3.5 Hz, 1 H, 4′-H Ar), 6.69 (d, *J* = 3.5 Hz, 1 H, 3′-H Ar), 6.63, 6.59 (2× s, 1 H each, 6-H, 9-H), 4.76 (d, *J* = 5.9 Hz, 1 H, 1-H), 4.09 (d, *J* = 5.9 Hz, 1 H, 2-H), 3.83, 3.79 (2× s, 3 H each, 2× OMe), 3.56 (s, 3 H, CO*OMe*), 3.27 (ddd, *J* = 12.9, 10.4, 2.7 Hz, 1 H, 4-H), 2.94 (ddd, *J* = 14.2, 10.4, 3.5 Hz, 1 H, 5-H), 2.71 (ddd, *J* = 12.9, 6.2, 3.5 Hz, 1 H, 4′-H), 2.57 (s, 3 H, *N*-Me), 2.57–2.51 (m, 1 H, 5′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.5 (CO), 147.6, 146.7, 144.8 (C-7, C-8, C-2′), 133.5, 130.8 (C-5a, C-9a), 126.2, 125.1, 123.9 (C-3′, C-4′, C-5′), 113.8, 113.2 (C-6, C-9), 68.0 (C-2), 55.9, 55.6 (2× OMe), 50.8 (CO*OMe*), 50.1 (C-1), 48.8 (C-4), 45.9 (*N*-Me), 34.7 (C-5) ppm. IR (neat): $\tilde{\nu}$ = 3006, 2934, 1736, 1607, 1513, 1448, 1381 cm^{-1}. t_R = 9.18 min. EI-MS: *m*/*z* (%) = 361 (9) $[M]^+$, 303 (19), 302 (100). HRMS: calcd. for $C_{19}H_{24}NO_4S$ $[M + H]^+$ 362.1420; found 362.1410.

5h-*cis*: Pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.21 (d, *J* = 4.9 Hz, 1 H, 5′-H Ar), 7.10 (d, *J* = 3.5 Hz, 1 H, 3′-H Ar), 6.97 (dd, *J* = 4.9, 3.5 Hz, 1 H, 4′-H Ar), 6.62, 6.48 (2× s, 1 H each, 6-H, 9-H), 5.03 (br. s, 1 H, 1-H), 4.00 (br. s, 1 H, 2-H), 3.83, 3.65 (2× s, 3 H each, 2× OMe), 3.54 (s, 3 H, CO*OMe*), 3.25–3.17 (m, 2 H, 4-H, 5-H), 2.84–2.73 (m, 2 H, 4′-H, 5′-H), 2.51 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.0 (CO), 147.2, 146.8, 144.4 (C-7, C-8, C-2′), 132.6, 132.5 (C-5a, C-9a), 126.5, 126.4, 124.5 (C-3′, C-4′, C-5′), 112.5, 112.3 (C-6, C-9), 69.2 (C-2), 55.9, 55.8 (2× OMe), 51.4 (C-1), 51.0 (CO*OMe*), 47.6 (C-4), 44.6 (*N*-Me), 34.6 (C-5) ppm. IR (neat): $\tilde{\nu}$ = 3068, 2932, 1735, 1607, 1461, 1449, 1377 cm^{-1}. t_R = 9.43 min. EI-MS: *m*/*z* (%) = 361 (9) $[M]^+$, 303 (19), 302 (100). HRMS: calcd. for $C_{19}H_{24}NO_4S$ $[M + H]^+$ 362.1420; found 362.1432.

7,8-Dimethoxy-1-(2-furyl)-2-(methoxycarbonyl)-*N*-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (5i): A mixture of isomers of **5i** (74 mg, 92%) were obtained in a *cis*/*trans* ratio 1:1 from the salt **4i**-*cis* (100 mg, 0.23 mmol). Both isomers of **5i** were isolated by colunm chromatography (SiO_2; cyclohexane/EtOAc, 6:4) to yield **5i**-*trans* (37 mg, 46%) and **5i**-*cis* (37 mg, 46%).

5i-*trans*: Yellow oil. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.34 (d, *J* = 1.8 Hz, 1 H, 5′-H Ar), 6.60, 6.50 (2× s, 1 H each, 6-H, 9-H), 6.26 (dd, *J* = 3.0, 1.8 Hz, 1 H, 4′-H Ar), 5.94 (d, *J* = 3.0 Hz, 1 H, 3′-H Ar), 4.60 (d, *J* = 6.7 Hz, 1 H, 1-H), 4.13 (d, *J* = 6.7 Hz, 1 H, 2-H), 3.82, 3.75, 3.56 (3× s, 3 H each, 3× OMe), 3.27–2.95 (m, 2 H, 4-H, 5-H), 2.73–2.56 (m, 2 H, 4′-H, 5′-H), 2.47 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 171.6 (CO), 153.9 (C-2′), 147.6, 146.8 (C-7, C-8), 141.3 (C-5′), 133.3, 128.9 (C-5a, C-9a), 113.6, 113.0, 110.1, 107.4 (C-6, C-9, C-3′, C-4′), 66.3 (C-2), 55.8, 55.7 (2× OMe), 50.9 (CO*OMe*), 50.0 (C-1), 47.2 (C-4), 45.5 (*N*-Me), 34.3 (C-5) ppm. IR (neat): $\tilde{\nu}$ = 3080, 2933, 1734, 1607, 1512, 1461, 1450, 1381 cm^{-1}. t_R = 8.25 min. EI-MS: *m*/*z* (%) = 346 (7), 345 (30) $[M]^+$, 287 (32), 286 (100). HRMS: calcd. for $C_{19}H_{24}NO_5$ $[M + H]^+$ 346.1649; found 346.1649.

5i-*cis*: Yellow oil. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.33 (br. s, 1 H, 5′-H Ar), 6.61 (br. s, 1 H, 4′-H Ar), 6.33, 6.32 (2× s, 1 H each, 6-H, 9-H), 6.24 (br. s, 1 H, 3′-H Ar), 4.80 (br. s, 1 H, 1-H), 3.98 (br. s, 1 H, 2-H), 3.81, 3.64, 3.52 (3× s, 3 H each, 3× OMe), 3.27–3.05 (m, 2 H, 4-H, 5-H), 2.87–2.72 (m, 2 H, 4′-H, 5′-H), 2.45 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 170.8

(CO), 154.7 (C-2′), 147.3, 146.8 (C-7, C-8), 141.1 (C-5′), 133.0, 130.6 (C-5a, C-9a), 112.6, 112.0, 110.2, 107.9 (C-6, C-9, C-3′, C-4′), 67.1 (C-2), 55.9, 55.7 (2× OMe), 51.6 (C-4), 51.0 (CO*OMe*), 46.1 (C-1), 43.9 (*N*-Me), 34.2 (C-5) ppm. IR (neat): $\tilde{\nu}$ = 3080, 2933, 1735, 1607, 1511, 1450, 1377 cm^{-1}. t_R = 8.38 min. EI-MS: *m*/*z* (%) = 346 (5), 345 (23) $[M]^+$, 287 (28), 286 (100). HRMS: calcd. for $C_{19}H_{24}NO_5$ $[M + H]^+$ 346.1649; found 346.1658.

One-pot Procedure for the Stevens Rearrangement: Methyl bromoacetate (0.11 mL, 1.4 mmol) was added to a solution of the appropriate tetrahydroisoquinoline (1.4 mmol) and DBU (0.21 mL, 1.4 mmol) in CH_3CN (10 mL), and the resulting mixture was stirred at room temperature for 1 h. The solvent was evaporated in vacuo, and the crude reaction mixture was purified by column chromatography (SiO_2; CH_2Cl_2/MeOH, 9.8:0.2) to yield the benzazepine.

(1*R,2*S**)-7,8-Dimethoxy-2-(methoxycarbonyl)-*N*-methyl-1-(2-pyridyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (9-*cis*):** Benzazepine **9**-*cis* (390 mg, 73%) was obtained from the tetrahydroisoquinoline **8** (400 mg, 1.4 mmol) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.62 (d, *J* = 4.8 Hz, 1 H, 6′-H Ar), 7.52 (t, *J* = 7.7 Hz, 1 H, 4′-H Ar), 7.11 (dd, *J* = 7.7, 4.8 Hz, 1 H, 5′-H Ar), 6.87 (d, *J* = 7.7 Hz, 1 H, 3′-H Ar), 6.65, 6.49 (2× s, 1 H each, 6-H, 9-H), 4.73, 4.72 (2× s, 1 H each, 1-H, 2-H), 3.86, 3.73, 3.56 (2× s, 3 H each, 3× OMe), 3.30–3.25 (m, 1 H, 4-H), 2.86–2.80 (m, 1 H, 5-H), 2.69–2.64 (m, 2 H, 4′-H, 5′-H), 2.48 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.6 (CO), 159.9 (C-2′), 149.1 (C-6′), 147.6, 146.9 (C-7, C-8), 136.3 (C-4′), 133.6, 129.5 (C-5a, C-9a), 122.8, 121.3 (C-3′, C-5′), 114.4, 113.1 (C-6, C-9), 66.7 (C-2), 55.9, 55.7 (2× OMe), 54.8 (C-1), 50.9 (CO*OMe*), 50.1 (C-4), 45.9 (*N*-Me), 35.1 (C-5) ppm. IR (neat): $\tilde{\nu}$ = 3048, 2933, 1732, 1606, 1568, 1515, 1463, 1382 cm^{-1}. t_R = 9.29 min. EI-MS: *m*/*z* (%) = 356 (6) $[M]^+$, 298 (42), 297 (100), 240 (45), 121 (81). HRMS: calcd. for $C_{20}H_{25}N_2O_4$ $[M + H]^+$ 357.1809; found 357.1810.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra of compounds described in the Experimental Section.

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