DOI: 10.1002/ejoc.201000512

Diastereoselective Synthesis of 1,2-Disubstituted 2,3,4,5-Tetrahydro-1*H*-3-benzazepines by Means of the Stevens Rearrangement

María Valpuesta,*[a] Manuela Ariza,[a] Amelia Díaz,*[a] and Rafael Suau[a]

Dedicated to Professor Janine Cossy on the occasion of her 60th birthday

Keywords: Benzazepines / Rearrangement / Diastereoselectivity / Ylides / Isoquinolines

1,2-Disubstituted 2,3,4,5-tetrahydro-1*H*-3-benzazepines were conveniently obtained by making use of the regio- and diastereoselective Stevens rearrangement of the corresponding isoquinolinium salts with 1,8-diazabicyclo[5.4.0]undec-7-ene in acetonitrile. This procedure has provided a good number of novel analogue compounds of SCH 23390.

Introduction

Dopamine-mediated neurotransmission plays a role in several psychiatric and neurological disorders, and for this reason there has been great interest in the search for novel dopamine receptor agonists and antagonists.[1] The action of dopamine is mediated by five different receptor subtypes classified into two families: D1-like (D1 and D5) and D2-like (D2, D3, and D4).[2] During the last several decades, dopaminergic ligands have remained a very active area in the development of central-nervous-system pharmaceutical products.[3] In general, seven-membered nitrogen heterocycles are constituents of a number of compounds with remarkable pharmacological properties. The 2,3,4,5-tetrahydro-1*H*-3-benzazepine ring attracts a great deal of interest from a medicinal chemistry viewpoint, because it contains the phenethylamine substructure. Specifically, 1-aryl-substituted derivatives have been prepared and studied as dopamine receptor agonists and antagonists.[4] Moreover, 1*H*-3-benzazepines are active in animal models of various neurological disorders, for example, Parkinson's and Alzheimer's diseases. A significant example of a potent D1 receptor agonist is fenoldopam, which acts peripherally to produce selectively systemic vasodilation (Figure 1).[5] On the other hand, 1*H*-3-benzazepine SCH 23390 and its conformationally restricted analogue SCH 39166 are two classical highly potent and selective D1/D5 antagonists. In fact, compound SCH 39166 was developed for the treatment of a variety of diseases, including schizophrenia, cocaine addiction, and obesity, and it was studied in human clinical trials.[1,5a,6] However, both compounds displayed low plasma levels and poor oral bioavailability due to the rapid first-pass metabolism of the phenol moieties.

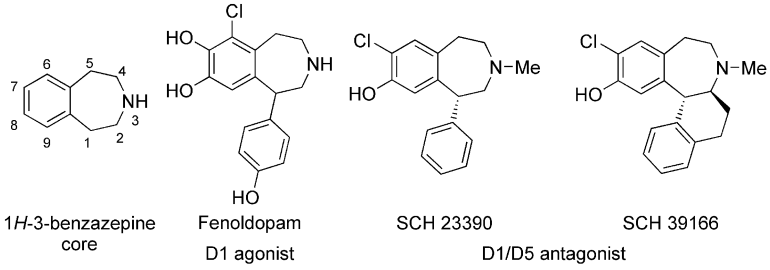


Figure 1. Relevant structures of 1*H*-3-benzazepines.

The preparation of 1*H*-3-benzazepine compounds is nowadays an object of considerable interest due to their potential dopaminergic activity. Synthetic approaches to 1*H*-3-benzazepines include different strategies, most of them based on two disconnections (Figure 2). Disconnection (a), which is the most common route, makes use of Friedel–

[a] Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Málaga
Campus de Teatinos s/n, 29071 Málaga, Spain
Fax: +34-952-131941
E-mail: mvalpuesta@uma.es

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000512.

Crafts-type reactions implying halogen,[7] alcohol,[8] or carbamate compounds.[4a] The cyclization process involved in these reactions requires an excess of acid and is poorly flexible in the selection of substituents. This disconnection may also exploit the intramolecular Heck reductive reaction[9] and the radical cyclization of highly reactive aryl radicals onto double and triple bonds.[10] Disconnection (b) consists of ring enlargement of a six-membered cyclic precursor via an aziridinium intermediate.[11] A parallel approach based on the Stevens rearrangement of tetrahydroisoquinolinium salts could be developed. This reaction has been employed by Padwa et al.[12] for the synthesis of isoindolo-benzazepines via carbenoid precursors. Nevertheless, the regioselective ylide formation was difficult to attain by this method.

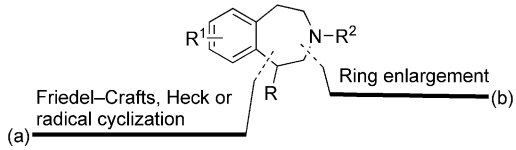


Figure 2. Strategies for the synthesis of 1*H*-3-benzazepines.

In previous work we have made use of the Stevens rearrangement for the synthesis of 8-(arylmethyl)berbine.[13] As a continuation of our exploratory study of the Stevens rearrangement as a highly efficient reaction to synthesize nitrogen-containing compounds, we have now extended this methodology to the synthesis of 1*H*-3-benzazepines.

In this paper we describe an effective and short synthesis of 1,2-disubstituted 1*H*-3-benzazepines by using the Stevens rearrangement in a regio- and diastereoselective approach. No alternative reaction, such as the Hofmann elimination and the Sommelet–Hauser rearrangement[12] were observed to take place under the applied conditions. Specifically, a collection of novel analogues of SCH 23390 and SCH 39166 were thus prepared. The aim was to generate new variants of 1*H*-3-benzazepines that could be used to help understand the structure/activity relationships in this family of compounds.

Results and Discussion

We hereby report the results obtained in the Stevens rearrangement of the 1-phenyltetrahydroisoquinolinium salts **5** (Figure 3). The regioselectivity of the ylide formation may be problematic if there is more than one acidic site in the precursor salt. In such a case, the Stevens rearrangement may afford two compounds: 1,2-disubstituted 1*H*-3-benzazepines **1**, if the exocyclic nitrogen ylide is formed at C-α, and the 1,1-disubstituted isoquinolines **6** with the endocyclic nitrogen ylide being the key intermediate. The reaction preference is largely dependent on the nature of the Z substituent so that electron-withdrawing groups exclusively yield 1*H*-3-benzazepines **1**.

We have chosen (±)-*trans*-6,7-dimethoxy-*N*-[(methoxycarbonyl)methyl]-*N*-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinolinium bromide (**5a**-*trans*) as a model compound to study the rearrangement reaction under different conditions (Scheme 1).

The synthesis of this isoquinolium salt **5a** is based on classical methods. We employed the Bischler–Napieralski cyclization of the corresponding amide followed by *N*-methylation and reduction to afford the isoquinoline intermediate **4**. The standard *N*-alkylation of this compound[14] yielded the *cis*/*trans* mixture of diastereoisomers **5a** in a

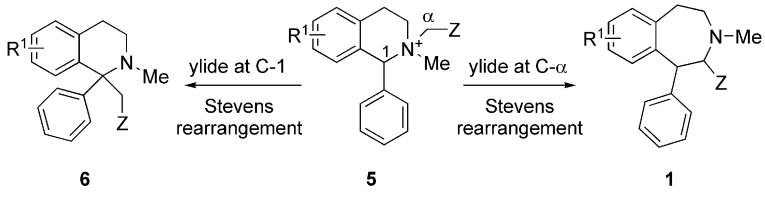
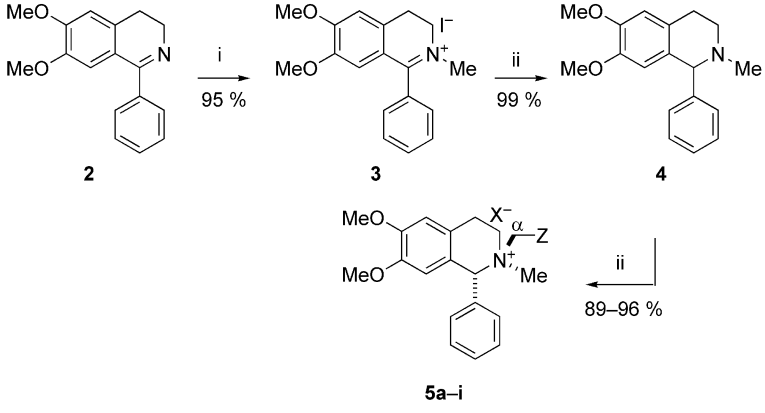


Figure 3. Stevens rearrangement of isoquinolinium salts.

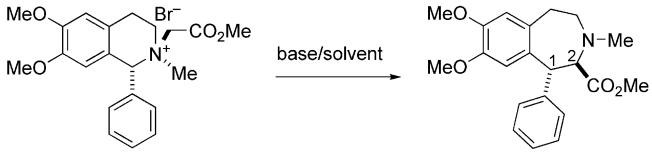


Scheme 1. Synthesis of salts **5a**–**i**: (i) CH_3I/acetone, reflux; (ii) $NaBH_4$/MeOH, r.t.; (iii) XCH_2Z/acetone, r.t.

5:95 ratio. The *trans* diastereoisomer was isolated from this mixture by fractional precipitation. The configuration of 1-H relative to the (methoxycarbonyl)methyl substituent was assessed by the occurrence of an intense NOE effect between 1-H and α-H in the H,H-NOESY spectra. However, several attempts to isolate the *cis* diastereoisomer failed due to the low proportion in this mixture.

As shown in Table 1, we first examined the reactivity of **5a**-*trans* with dimsylsodium in DMSO, since we have previously reported that no competitive reactions take place under such conditions.[13] This treatment gave a mixture of **1a** and **4** in a ratio 1:1, due to the initial salt dealkylation (Table 1, Entry 1). To improve this result a variety of bases were tried. Although the use of sodium hexamethyldisilazane or potassium *tert*-butoxide preferentially yields the benzazepine skeleton, the reaction did not cleanly proceed (Table 1, Entries 2 and 3). Despite the fact that the treatment of the **5a**-*trans* salt with potassium carbonate in THF led to a significant increase in yield, much longer periods of time were needed for a complete conversion (Table 1, Entry 4). The most advantageous procedure for the generation of the 1*H*-3-benzazepine **1a**-*trans* makes use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile; under these conditions the reaction proceeded with high stereoselectively so that the desired compound **1a**-*trans* was obtained in excellent yield (Table 1, Entry 5). A possible explanation for such a good result is that the use of a medium organic base in a highly polar solvent favored both the salt solubility and the intermediate ylide formation.

Table 1. Stevens rearrangement of the **5a**-*trans* salt with different bases.

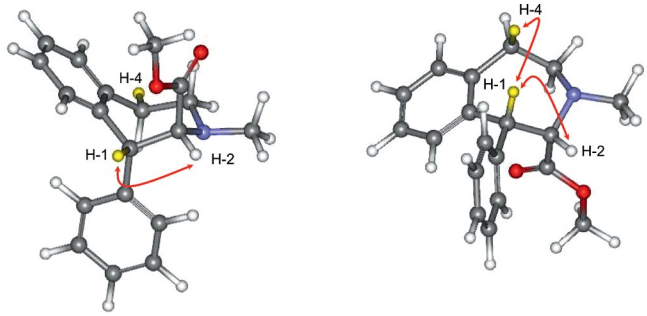


5a-*trans* **1a**-*trans*

Entry	Base	Solvent	*t*	Yield[a]
1	$NaCH_2SOCH_3$	DMSO	1 h	50%
2	NaHMDS	THF	1 h	70%
3	*t*BuOK	THF	2 h	72%
4	K_2CO_3	THF	48 h	80%
5	DBU	CH_3CN	30 min	95%

[a] The reaction was carried out at room temperature.

To corroborate the stereoselectivity of the reaction, we evaluated it with a mixture of diastereoisomers **5a**, enriched in **5a**-*cis*. The treatment of this mixture with DBU in acetonitrile yielded diastereoisomers **1a** in a ratio similar to the *cis*/*trans* ratio of the starting isoquinolinium salts confirming the stereochemical control of the Stevens rearrangement.[13] The relative configuration between 1-H and 2-H in the 1*H*-3-benzazepines **1a** was evidenced by both ^{1}H NMR and H,H-NOESY spectroscopic analysis. Clear differences in the coupling constant values were observed for the two diastereomers according to data previously reported for other 1,2-disubstituted 1*H*-3-benzazepines;[15] the stereoisomer **1a**-*trans* exhibits a large 1-H/2-H coupling constant ($J_{1,2}$ = 7.0 Hz), whereas in stereoisomer **1a**-*cis* 1-H and 2-H appear as a pair of broad unresolved doublets (with $J_{1,2}$ < 1.8 Hz). In the H,H-NOESY experiment, both diastereoisomers show NOE correlation between 1-H and 2-H, but only the stereoisomer **1a**-*cis* exhibits an NOE effect between 1-H and 4-H. The spectral differences observed between the two diastereoisomers are well supported by molecular modeling.[16] Owing to the presence of a seven-membered ring, the benzazepine molecule may adopt a number of different conformations. The relative spatial positions of 1-H/2-H/4-H in the preferred conformations for **1a**-*trans* and **1a**-*cis* benzazepines (Figure 4) are consistent with H,H-NOESY results. Furthermore, the calculated 1-H–2-H dihedral angles are in agreement with the coupling constant differences observed in the ^{1}H NMR spectra of *trans* and *cis* diastereoisomers.



1-H–2-H dihedral angle = 40° 1-H–2-H dihedral angle = 80°

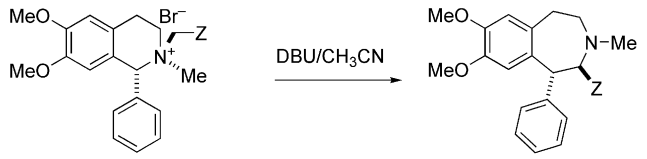
1,2-disubstituted 3-benzazepine **1a**-*trans* 1,2-disubstituted 3-benzazepine **1a**-*cis*

Figure 4. 3D model structures of the most stable conformations of **1a**-*trans* and **1a**-*cis* diastereoisomers with an indication of the NOE effects observed in each case.

The conditions optimized for the rearrangement of **5a** were then applied to the reaction of a set of tetrahydroisoquinolinium salts **5b**–**g** containing different electron-withdrawing substituents on the nitrogen atom. The synthesis of these salts was carried out according to the reaction route shown in Scheme 1, which afforded exclusively the *trans* diastereoisomer in all cases. The Stevens rearrangement of **5b**–**g** occurred regio- and diastereoselectively to yield exclusively the corresponding *trans*-benzazepine derivatives **1b**–**g** (Table 2). In fact, the H,H-NOESY data of these compounds were fully consistent with their *trans* configuration, and the ^{1}H NMR spectroscopic coupling constants were in accordance with the dihedral angles calculated by molecular modeling.[16]

Conversely, the application of the optimized conditions to the isoquinolium salts **5h**–**i** (Scheme 2) failed to give the ring enlargement toward the 1*H*-3-benzazepines, apparently due to the absence of the electron-withdrawing group in these compounds. Moreover, the use of a stronger base, such as potassium *tert*-butoxide in THF afforded regioselectively the 1,1-tetrahydroisoquinolines **6a**,**b** in good yield, derived from a nitrogen ylide at C-1.

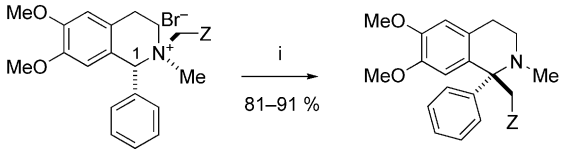
Table 2. Synthesis of 1*H*-3-benzazepines **1a**–**g** by the Stevens rearrangement.



5a–g **1a–g**

Entry	*trans*-Benzazepine	Z substituent	*t*	Yield[a]	$J_{1,2}$
1	**1a**	CO_2Me	30 min	95%	7.0 Hz
2	**1b**	$CONH_2$	1 h	85%[b]	5.0 Hz
3	**1c**	$CONMe_2$	1 h	90%[b]	9.1 Hz
4	**1d**	COMe	30 min	85%	7.8 Hz
5	**1e**	COPh	30 min	89%	7.5 Hz
6	**1f**	$C_6H_4NO_2$-4	2 h	84%	7.5 Hz
7	**1g**	$CH=CHCO_2Me$	30 min	85%	5.5 Hz

[a] Isolated yields after silica-gel chromatography. [b] The reaction was carried out under reflux for 1 h.



5h: Z = Ph
5i: Z = CH_2=CH

6a: Z = Ph
6b: Z = CH_2=CH

Scheme 2. Synthesis of 1,1-disubstituted isoquinolines **6a**,**b**: (i) *t*BuOK/THF, r.t.

Given the importance of a chlorine atom in the A ring of 1*H*-3-benzazepines SCH 23390 and SCH 39166 for their biological activity,[3,5a] our next aim was to synthesize the novel chloro-substituted 1*H*-3-benzazepine **11** by means of the Stevens rearrangement. As shown in Scheme 3, the isoquinolinium salt **10** was prepared from the dihydroisoquinoline **7** according to the standard procedure previously described for salts **5a**–**i**. The Stevens rearrangement of the diastereomerically pure *trans* salt **10** afforded stereoselectively the desired 1*H*-3-benzazepine **11** in excellent yield, with full retention of the initial salt configuration. The relative configuration between 1-H and 2-H in 1*H*-3-benzazepine **11** was also confirmed by ^{1}H NMR (coupling constant $J_{1,2}$ = 7.0 Hz) and H,H-NOESY spectroscopic analysis.

Conclusions

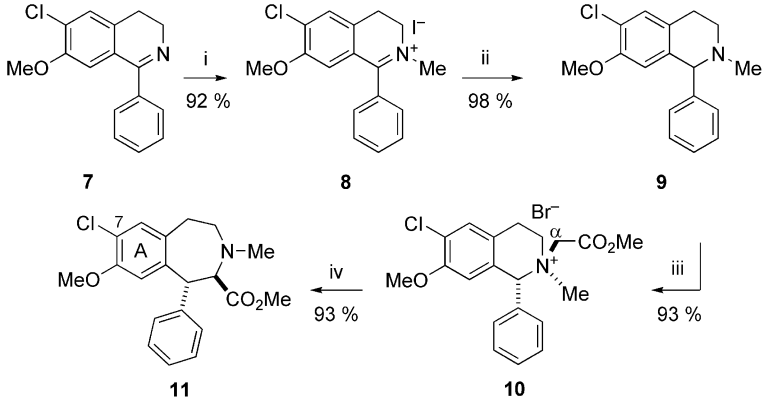
We have developed a short and efficient approach to the synthesis of 1,2-disubstituted 1*H*-3-benzazepines by using a diastereoselective Stevens rearrangement. The application of this methodology has provided a fair number of novel analogue compounds of SCH 23390. Furthermore, the adequate choice of the isoquinolinium salt allowed us to control the Stevens rearrangement to obtain exclusively either the 1*H*-3-benzazepines or the 1,1-disubstituted isoquinolines.

Further application of this methodology to the synthesis of 1*H*-3-benzazepines SCH 23390 and SCH 39166 analogues along with the evaluation of the bioactivity of the newly synthesized compounds are currently underway.

Experimental Section

General Remarks: Melting points were determined with a Gallenkamp instrument and are uncorrected. MS (EI) data were recorded with an HP-MS 5988A spectrometer operating at 70 eV and HRMS data with a VG Autospec spectrometer. IR spectra 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 ^{1}H and 50.3 MHz for ^{13}C NMR spectroscopy, or with a Bruker ARX 400 instrument operating at 400 MHz for ^{1}H 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 0.063–0.200 mm silica gel (Merck 7734).

Preparation of 1-Phenyl-3,4-dihydroisoquinolines 2 and 7: A solution of $POCl_3$ (6.7 mL, 70.3 mmol) in CH_3CN (5 mL) was added dropwise to a solution of the corresponding amide (35.1 mmol) in



Scheme 3. Synthesis of the 1*H*-3-benzazepine **11**: (i) CH_3I/acetone, reflux; (ii) $NaBH_4$/MeOH, r.t.; (iii) $BrCH_2CO_2Me$/acetone, r.t.; (iv) DBU/CH_3CN, r.t.

CH_3CN (60 mL) under argon. The reaction mixture was refluxed for 2 h and then concentrated to dryness. The crude material was dissolved in CH_2Cl_2 (60 mL) and washed with a saturated solution of $NaHCO_3$ (50 mL), NaOH (5%, 2 × 50 mL), and water. The organic layers were dried with $MgSO_4$ and concentrated under vacuum to give the corresponding isoquinoline.

6,7-Dimethoxy-1-phenyl-3,4-dihydroisoquinoline (2):[17a] The isoquinoline **2** (9.3 g, 99%) was obtained from the corresponding amide[17] (10.0 g, 35.1 mmol) as a pale-yellow solid. M.p. 192–195 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.68 (d, J = 7.0 Hz, 2 H, Ph), 7.55–7.46 (m, 3 H, Ph), 6.82, 6.81 (2 × s, 1 H each, 5-H, 8-H), 3.95, 3.71 (2 × s, 3 H each, 2 × OMe), 3.89 (t, J = 7.5 Hz, 2 H, 3-H), 2.86 (t, J = 7.5 Hz, 2 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 166.8 (C-1), 151.0, 146.9 (C-6, C-7), 138.3, 132.5, 121.1 (C-1′, C-4a, C-8a), 129.4, 128.7, 128.0 (CH Ph), 111.5, 110.1 (C-5, C-8), 55.9, 55.8 (2 × OMe), 47.0 (C-3), 25.7 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3056, 3003, 2944, 1639, 1600, 1560, 1496, 1457, 1408, 1374 cm^{-1}. EI-MS: m/z (%) = 268 (14), 267 (64) $[M]^+$, 266 (100), 236 (17). HR-MS: calcd. for $C_{17}H_{17}NO_2$ 267.1259; found 267.1266.

6-Chloro-7-methoxy-1-phenyl-3,4-dihidroisoquinoline (7):[18] The isoquinoline **7** (0.4 g, 42%) was obtained from the corresponding amide[19] (1.0 mmol, 3.5 mmol) as a yellow oil, after purification by column chromatography (SiO_2; CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.60–7.55 (m, 2 H, Ph), 7.43–7.40 (m, 3 H, Ph), 7.26 (s, 1 H, 5-H), 6.80 (s, 1 H, 8-H), 3.79 (t, J = 7.3 Hz, 2 H, 3-H), 3.70 (s, 3 H, OMe), 2.67 (t, J = 7.3 Hz, 2 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 166.3 (C-1), 153.4 (C-7), 138.4, 131.8 (C-1′, C-8a), 129.5, 128.6, 128.2 (CH Ph), 128.9 (C-5), 127.7, 124.6 (C-4a, C-6), 111.8 (C-8), 56.2 (OMe), 47.6 (C-3), 25.0 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3055, 2938, 1593, 1556, 1489, 1443, 1390 cm^{-1}. EI-MS: m/z (%) = 273 (22), 272 (43), 271 (62) $[M]^+$, 270 (100), 240 (12), 192 (11). HR-MS: calcd. for $C_{16}H_{15}ClNO$ $[M + H]^+$ 272.0837; found 272.0827.

Preparation of *N*-Methyl-1-phenyl-3,4-dihydroisoquinolinium Salts 3 and 8: To a solution of the corresponding isoquinoline (18.7 mmol) in dry acetone (60 mL) was added CH_3I (6 mL, 96 mmol), and the reaction mixture was refluxed for 1 h. After this time, the yellow solid formed was filtered and the solution concentrated under vacuum to give the corresponding isoquinolinium salt.

6,7-Dimethoxy-*N*-methyl-1-phenyl-3,4-dihydroisoquinolinium Iodide (3):[20] The isoquinolium salt **3** (7.3 g, 95%) was obtained from the isoquinoline **2** (5.0 g, 18.7 mmol) as a yellow solid. M.p. 183–185 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.69–7.58 (m, 5 H, Ph), 6.97, 6.33 (2 × s, 1 H each, 5-H, 8-H), 4.47 (t, J = 8.1 Hz, 2 H, 3-H), 3.99, 3.70 (2 × s, 3 H each, 2 × OMe), 3.54 (s, 3 H, *N*-Me), 3.51 (t, J = 8.1 Hz, 2 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.7 (C-1), 156.3, 147.6 (C-6, C-7), 133.6 (C-1′), 131.6, 119.2 (C-4a, C-8a), 129.2, 128.8, 128.4 (CH Ph), 114.9, 110.8 (C-5, C-8), 56.7 (C-3), 55.6, 52.5 (2 × OMe), 46.6 (*N*-Me), 25.4 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3020, 2995, 2933, 1630, 1598, 1559, 1491, 1455, 1381 cm^{-1}. EI-MS: m/z (%) = 282 (4) $[M]^+$, 281 (8), 267 (78), 266 (100), 208 (22), 206 (20), 204 (20), 127 (24). HR-MS: calcd. for $C_{18}H_{20}NO_2$ 282.1494; found 282.1501.

6-Chloro-7-methoxy-*N*-methyl-1-phenyl-3,4-dihydroisoquinolinium Iodide (8): The isoquinolium salt **8** (1.1 g, 92%) was obtained from the isoquinoline **7** (780 mg, 2.9 mmol) as a yellow solid. M.p. 167–169 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.79 (d, J = 8.1 Hz, 2 H, Ph), 7.64–7.56 (m, 3 H, Ph), 7.38 (s, 1 H, 5-H), 6.40 (s, 1 H, 8-H), 4.53 (t, J = 8.1 Hz, 2 H, 3-H), 3.76 (s, 3 H, OMe), 3.55 (s, 3 H, *N*-Me), 3.46 (t, J = 8.1 Hz, 2 H, 4-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 174.1 (C-1), 154.3 (C-7), 132.5 (C-1′), 132.2 (C-5), 130.5, 130.4 (C-4a, C-8a), 129.8, 129.2, 129.0 (CH Ph), 126.6 (C-6), 116.0 (C-8), 56.1 (OMe), 53.5 (C-3), 48.0 (*N*-Me), 24.8 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3010, 2937, 1638, 1598, 1502, 1460, 1369 cm^{-1}. EI-MS: m/z (%) = 288 (3), 287 (7), 286 (10) $[M]^+$, 285 (16), 273 (9), 271 (24), 210 (33), 209 (12), 208 (92), 196 (36), 194 (100), 127 (17). HR-MS: calcd. for $C_{17}H_{17}ClNO$ 286.0993; found 286.0986.

Preparation of *N*-Methyl-1-phenyl-1,2,3,4-tetrahydroisoquinolines 4 and 9: $NaBH_4$ (220 mg, 5.8 mmol) was added dropwise over a period of 10 min to a solution of the corresponding salt (5.0 mmol) in MeOH (40 mL), 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 give the corresponding 1,2,3,4-tetrahydroisoquinoline.

6,7-Dimethoxy-*N*-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (4):[21] The isoquinoline **4** (1.4 g, 99%) was obtained from the salt **3** (2.0 g, 5.0 mmol) as a pale-yellow solid. M.p. 77–79 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.30–7.21 (m, 5 H, Ph), 6.58, 6.08 (2 × s, 1 H each, 5-H, 8-H), 4.16 (s, 1 H, 1-H), 3.82, 3.54 (2 × s, 3 H each, 2 × OMe), 3.20–3.05 (m, 2 H, 3-H, 4-H), 2.72 (dt, J = 15.6, 3.2 Hz, 1 H, 3′-H), 2.59 (dt, J = 10.7, 3.8 Hz, 1 H, 4′-H), 2.22 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 147.2, 146.9 (C-6, C-7), 143.7 (C-1′), 130.2, 126.4 (C-4a, C-8a), 129.4, 128.1, 127.2 (CH Ph), 111.3, 110.5 (C-5, C-8), 70.9 (C-1), 55.6, 55.5 (2 × OMe), 52.1 (C-3), 44.2 (*N*-Me), 28.9 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3058, 3009, 2976, 2834, 1609, 1513, 1489, 1453, 1365 cm^{-1}. EI-MS: m/z (%) = 288 (4), 283 (20) $[M]^+$, 282 (18), 207 (24), 206 (100). HR-MS: calcd. for $C_{18}H_{21}NO_2$ 283.1572; found 283.1574.

6-Chloro-7-methoxy-*N*-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (9):[19] The isoquinoline **9** (340 mg, 98%) was obtained from the salt **8** (500 mg, 1.2 mmol) as a pale-yellow solid. M.p. 230–232 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.47–7.34 (m, 5 H, Ph), 7.11 (s, 1 H, 5-H), 6.14 (s, 1 H, 8-H), 4.17 (s, 1 H, 1-H), 3.55 (s, 3 H, OMe), 3.20–3.01 (m, 2 H, 3-H, 4-H), 2.75–2.50 (m, 2 H, 3′-H, 4′-H), 2.21 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 152.7 (C-7), 143.2 (C-1′), 138.0, 127.6 (C-4a, C-8a), 129.5 (C-5), 129.4, 128.3, 127.5 (CH Ph), 120.2 (C-6), 112.1 (C-8), 71.0 (C-1), 55.9 (OMe), 51.8 (C-3), 44.1 (*N*-Me), 28.2 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3023, 2976, 1624, 1601, 1492, 1452, 1396 cm^{-1}. EI-MS: m/z (%) = 289 (7), 288 (8), 287 (20) $[M]^+$, 286 (15), 212 (35), 210 (100). HR-MS: calcd. for $C_{17}H_{19}ClNO$ $[M + H]^+$ 288.1150; found 288.1149.

Preparation of *N*-Methyl-1-phenyl-1,2,3,4-tetrahydroisoquinolinium Salts 5a–i and 10: The corresponding halo derivative (2.1 mmol) was added to a solution of the corresponding isoquinoline (1.8 mmol) in dried acetone (20 mL) under argon. After the mixture had been stirred at room temperature for 24 h, a precipitate had formed that was filtered and washed with several portions of diethyl ether. The acetone solution was reduced to 10 mL, and diethyl ether was added to precipitate the remaining isoquinolinium salt.

(±)-*trans*-6,7-Dimethoxy-*N*-[(methoxycarbonyl)methyl]-*N*-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinolinium Bromide (5a): The isoquinolinium salt **5a** was obtained from the isoquinoline **4** (500 mg, 1.8 mmol). The ^{1}H NMR spectrum of the crude product indicated a mixture of stereoisomers **5a** in a *cis*/*trans* ratio of 5:95. The major diastereoisomer **5a**-*trans* (741 mg, 94%) was isolated by fractional precipitation with diethyl ether as a pale-yellow solid. M.p. 131–133 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.42–7.36 (m, 5

H, Ph), 6.93 (s, 1 H, 1-H), 6.68 (s, 1 H, 5-H), 6.32 (s, 1 H, 8-H), 5.64 (d, J = 17.5 Hz, 1 H, α-H), 4.62 (d, J = 17.5 Hz, 1 H, α′-H), 4.36 (dd, J = 13.2, 5.1 Hz, 1 H, 3-H), 3.85, 3.64 (2× s, 3 H each, 2× OMe), 3.76 (s, 3 H, COOMe), 3.70–3.64 (m, 1 H, 3′-H), 3.36 (s, 3 H, *N*-Me), 3.22–3.05 (m, 2 H, 4-H, 4′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 165.2 (CO), 149.2, 148.6 (C-6, C-7), 131.6 (C-1′), 130.5, 128.7 (CH Ph), 120.8, 120.1 (C-4a C-8a), 110.7, 110.1 (C-5, C-8), 73.7 (C-1), 57.1 (C-α), 55.7, 55.6 (2× OMe), 52.8 (COO*Me*), 51.8 (C-3), 47.8 (*N*-Me), 23.3 (C-4) ppm. IR (neat): ṽ = 3040, 2934, 1745, 1612, 1517, 1456, 1369 cm^{-1}. EI-MS: *m*/*z* (%) = 297 (15), 296 (72), 283 (28), 282 (67), 268 (66), 206 (100). HR-MS: calcd. for $C_{21}H_{26}NO_4$ 356.1862; found 356.1855.

(±)-*trans*-*N*-(Carbamoylmethyl)-6,7-dimethoxy-*N*-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinolinium Iodide (5b): The isoquinolinium salt **5b** (791 mg, 94%) was obtained from the isoquinoline **4** (500 mg, 1.8 mmol) as a white solid. M.p. 195–196 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.12 (s, 1 H, NH), 7.48–7.40 (m, 5 H, Ph), 6.73 (s, 1 H, 5-H), 6.51 (s, 1 H, 1-H), 6.27 (s, 1 H, 8-H), 6.18 (s, 1 H, NH), 4.85 (d, J = 14.2 Hz, 1 H, α-H), 4.73 (d, J = 14.2 Hz, 1 H, α′-H), 4.20–4.15 (m, 1 H, 3-H), 3.87, 3.65 (2× s, 3 H each, 2× OMe), 3.72–3.67 (m, 1 H, 3′-H), 3.46–3.38 (m, 1 H, 4-H), 3.26–3.20 (m, 1 H, 4′-H), 3.14 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 165.4 (CO), 149.7, 149.0 (C-6, C-7), 132.0 (C-1′), 131.0, 129.3 (CH Ph), 120.9, 120.6 (C-4a C-8a), 110.9, 110.5 (C-5, C-8), 74.3 (C-1), 59.1 (C-α), 56.0, 55.9 (2× OMe), 54.3 (C-3), 48.4 (*N*-Me), 23.6 (C-4) ppm. IR (neat): ṽ = 3427, 3351, 3008, 2965, 2929, 1698, 1610, 1515, 1461, 1369, 1316 cm^{-1}. EI-MS: *m*/*z* (%) = 341 (1) [M]$^+$, 340 (2), 283 (27), 282 (43), 268 (100), 206 (98), 127 (15). HR-MS: calcd. for $C_{20}H_{25}N_2O_3$ 341.1865; found 341.1869.

(±)-*trans*-6,7-Dimethoxy-*N*-[(*N*′,*N*′-dimethylcarbamoyl)methyl]-*N*-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinolinium Iodide (5c): The isoquinolinium salt **5c** (803 mg, 90%) was obtained from the isoquinoline **4** (500 mg, 1.8 mmol) as a pale-yellow solid. M.p. 187–189 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.34–7.26 (m, 5 H, Ph), 6.83 (s, 1 H, 1-H), 6.67 (s, 1 H, 5-H), 6.21 (s, 1 H, 8-H), 5.22 (d, J = 16.1 Hz, 1 H, α-H), 4.63–4.56 (m, 1 H, 3-H), 4.60 (d, J = 16.1 Hz, 1 H, α′-H), 3.76, 3.53 (2× s, 3 H each, 2× OMe), 3.56–3.49 (m, 1 H, 3′-H), 3.17–3.11 (m, 2 H, 4-H, 4′-H), 3.14 (s, 3 H, *N*-Me), 3.02, 2.83 (2× s, 3 H each, $CONMe_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 163.1 (CO), 149.2, 148.5 (C-6, C-7), 132.1 (C-1′), 130.4, 128.7 (CH Ph), 121.1, 120.5 (C-4a C-8a), 110.7, 110.2 (C-5, C-8), 73.3 (C-1), 57.0 (C-α), 55.8, 55.6 (2× OMe), 52.5 (C-3), 48.0 (*N*-Me), 37.4, 35.6 ($CONMe_2$), 23.5 (C-4) ppm. IR (neat): ṽ = 3006, 2971, 1649, 1612, 1518, 1459, 1318 cm^{-1}. EI-MS: *m*/*z* (%) = 283 (16), 282 (22), 268 (58), 206 (100), 127 (6). HR-MS: calcd. for $C_{22}H_{29}N_2O_3$ 369.2178; found 369.2186.

(±)-*trans*-*N*-(Acetylmethyl)-6,7-dimethoxy-*N*-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinolinium Iodide (5d): The isoquinolinium salt **5d** (789 mg, 94%) was obtained from the isoquinoline **4** (500 mg, 1.8 mmol) as a white solid. M.p. 185–187 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.48–7.40 (m, 5 H, Ph), 6.70, 6.69 (2× s, 1 H each, 1-H, 5-H), 6.31 (s, 1 H, 8-H), 5.78 (d, J = 18.8 Hz, 1 H, α-H), 4.99 (d, J = 18.8 Hz, 1 H, α′-H), 4.42 (dd, J = 10.7, 3.8 Hz, 1 H, 3-H), 3.89, 3.68 (2× s, 3 H each, 2× OMe), 3.67–3.59 (m, 1 H, 3′-H), 3.27 (s, 3 H, *N*-Me), 3.23–3.08 (m, 2 H, 4-H, 4′-H), 3.31 (s, 3 H, COMe) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 200.1 (CO), 149.6, 149.0 (C-6, C-7), 131.6 (C-1′), 130.9, 129.1 (CH Ph), 120.9, 120.3 (C-4a C-8a), 110.8, 110.5 (C-5, C-8), 73.7 (C-1), 64.0 (C-α), 56.0, 55.9 (2× OMe), 52.4 (C-3), 47.9 (*N*-Me), 29.5 (COMe), 23.6 (C-4) ppm. IR (neat): ṽ = 3007, 2911, 1723, 1612, 1520, 1494, 1463, 1373 cm^{-1}. EI-MS: *m*/*z* (%) = 297 (19), 296 (100), 283 (42), 282 (93), 206 (71). HR-MS: calcd. for $C_{21}H_{26}NO_3$ 340.1907; found 340.1900.

(±)-*trans*-*N*-(Benzoylmethyl)-6,7-dimethoxy-*N*-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinolinium Bromide (5e): The isoquinolinium salt **5e** (826 mg, 95%) was obtained from the isoquinoline **4** (500 mg, 1.8 mmol) as a pale-yellow solid. M.p. 139–140 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.12 (d, J = 8.1 Hz, 2 H, 2′′-H, 6′′-H COPh), 7.62 (t, J = 8.1 Hz, 1 H, 4′′-H COPh), 7.49 (t, J = 8.1 Hz, 2 H, 3′′-H, 5′′-H COPh), 7.47–7.41 (m, 5 H, Ph), 7.21 (s, 1 H, 1-H), 6.65 (s, 1 H, 5-H), 6.40 (s, 1 H, 8-H), 5.33–5.20 (m, 1 H, α-H), 4.69–4.66 (m, 2 H, 3-H, α′-H), 3.85, 3.69 (2× s, 3 H each, 2× OMe), 3.74–3.64 (m, 1 H, 3′-H), 3.39 (s, 3 H, *N*-Me), 3.20–3.13 (m, 2 H, 4-H, 4′-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 191.6 (CO), 149.3, 148.7 (C-6, C-7), 134.7, 132.0, 130.5, 128.8, 128.2 (CH Ph, CO*Ph*), 133.8, 132.6 (C-1′, C-1′′), 121.3, 120.3 (C-4a C-8a), 110.9, 110.1 (C-5, C-8), 74.0 (C-1), 61.7 (C-α), 55.7, 55.6 (2× OMe), 51.7 (C-3), 48.0 (*N*-Me), 23.6 (C-4) ppm. IR (neat): ṽ = 3032, 2975, 1683, 1597, 1583, 1495, 1451, 1370 cm^{-1}. EI-MS: *m*/*z* (%) = 297 (19), 296 (100), 283 (12), 282 (24), 206 (83), 105 (15). HR-MS: calcd. for $C_{26}H_{28}NO_3$ 402.2069; found 402.2072.

(±)-*trans*-6,7-Dimethoxy-*N*-methyl-*N*-(*p*-nitrobenzyl)-1-phenyl-1,2,3,4-tetrahydroisoquinolinium Bromide (5f): The isoquinolinium salt **5f** (846 mg, 94%) was obtained from the isoquinoline **4** (500 mg, 1.8 mmol) as a pale-yellow solid. M.p. 198–200 °C. ^{1}H NMR (400 MHz, $CDCl_3$ + CD_3OD, 25 °C): δ = 8.26 (d, J = 8.6 Hz, 2 H, 3′′-H, 5′′-H), 7.87 (d, J = 8.6 Hz, 2 H, 2′′-H, 6′′-H), 7.44–7.36 (m, 5 H, Ph), 6.79 (s, 1 H, 5-H), 6.34 (s, 1 H, 8-H), 6.10 (s, 1 H, 1-H), 5.39 (d, J = 12.9 Hz, 1 H, α-H), 5.00 (d, J = 12.9 Hz, 1 H, α′-H), 4.07–4.00 (m, 1 H, 3-H), 3.87, 3.67 (2× s, 3 H each, 2× OMe), 3.55–3.46 (m, 2 H, 3′-H, 4-H), 3.32–3.24 (m, 1 H, 4′-H), 2.91 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$ + CD_3OD, 25 °C): δ = 149.8, 149.1, 149.0 (C-6, C-7, C-4′′), 134.4 (C-2′′, C-6′′), 134.0 (C-1′′), 132.0 (C-1′), 130.9, 129.2 (CH Ph), 124.1 (C-3′′, C-5′′), 121.2, 120.4 (C-4a C-8a), 110.7, 110.6 (C-5, C-8), 73.5 (C-1), 61.9 (C-α), 55.9, 55.8 (2× OMe), 52.7 (C-3), 46.9 (*N*-Me), 23.5 (C-4) ppm. IR (neat): ṽ = 3082, 2997, 1607, 1524, 1453, 1346 cm^{-1}. EI-MS: *m*/*z* (%) = 283 (9), 206 (100), 136 (25). HR-MS: calcd. for $C_{25}H_{27}N_2O_4$ 419.1971; found 419.1968.

(±)-*trans*-6,7-Dimethoxy-*N*-[(methoxycarbonyl)allyl]-*N*-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinolinium Bromide (5g): The isoquinolinium salt **5g** (790 mg, 95%) was obtained from the isoquinoline **4** (500 mg, 1.8 mmol) as a white solid. M.p. 187–189 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.48–7.38 (m, 5 H, Ph), 6.95 (dt, J = 15.0, 7.5 Hz, 1 H, β-H), 6.70 (s, 1 H, 5-H), 6.65 (s, 1 H, 1-H), 6.58 (d, J = 15.0 Hz, 1 H, γ-H), 6.35 (s, 1 H, 8-H), 5.40 (dd, J = 14.0, 7.5 Hz, 1 H, α-H), 4.58 (dd, J = 14.0, 7.5 Hz, 1 H, α′-H), 3.88, 3.76, 3.67 (3× s, 3 H each, 3× OMe), 3.64 (m, 2 H, 3-H, 3′-H), 3.24 (m, 2 H, 4-H, 4′-H), 3.14 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 164.5 (CO), 149.4, 148.7 (C-6, C-7), 132.4, 131.9 (C-β, C-γ), 132.3 (C-1′), 130.6, 128.9 (CH Ph), 121.3, 120.1 (C-4a C-8a), 110.8, 110.3 (C-5, C-8), 73.4 (C-1), 60.0 (C-α), 55.8, 55.7 (2× OMe), 52.1 (C-3), 51.9 (COO*Me*), 47.5 (*N*-Me), 23.4 (C-4) ppm. IR (neat): ṽ = 3020, 3002, 2960, 1723, 1644, 1610, 1518, 1458, 1379 cm^{-1}. EI-MS: *m*/*z* (%) = 381 (1), 290 (15), 283 (11), 206 (100). HR-MS: calcd. for $C_{23}H_{28}NO_4$ 382.2013; found 382.2007.

(±)-*trans*-*N*-Benzyl-6,7-dimethoxy-*N*-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinolinium Bromide (5h): The isoquinolinium salt **5h** (727 mg, 89%) was obtained from the isoquinoline **4** (500 mg, 1.8 mmol) as a white solid. M.p. 186–188 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.66 (d, J = 6.7 Hz, 2 H, 2′′-H, 6′′-H), 7.49–7.34 (m, 8 H, 3′′-H, 4′′-H, 5′′-H, Ph), 6.78 (s, 1 H, 5-H), 6.45 (s,

1 H, 1-H), 6.36 (s, 1 H, 8-H), 5.31 (d, J = 12.9 Hz, 1 H, α-H), 5.09 (d, J = 12.9 Hz, 1 H, α′-H), 4.13–4.08 (m, 1 H, 3-H), 3.90, 3.69 (2× s, 3H each, 2× OMe), 3.56–3.41 (m, 2 H, 3′-H, 4-H), 3.26 (dd, J = 15.0, 5.9 Hz, 1 H, 4′-H), 2.96 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 149.3, 148.6 (C-6, C-7), 132.9 (C-2′′, C-6′′), 132.5 (C-1′), 130.4, 130.3, 129.0, 128.8 (CH Ph, C-3′′, C-4′′, C-5′′), 126.9 (C-1′′), 121.6, 120.4 (C-4a C-8a), 110.6, 110.4 (C-5, C-8), 72.7 (C-1), 63.2 (C-α), 55.8, 55.7 (2× OMe), 51.5 (C-3), 46.4 (*N*-Me), 23.5 (C-4) ppm. IR (neat): ṽ = 3055, 3001, 2983, 1608, 1519, 1500, 1458, 1374 cm^{-1}. EI-MS: *m*/*z* (%) = 283 (9), 206 (100), 91 (67). HR-MS: calcd. for $C_{25}H_{28}NO_2$ 374.2115; found 374.2109.

(±)-*trans*-*N*-Allyl-6,7-dimethoxy-*N*-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinolinium Bromide (5i): The isoquinolinium salt **5i** (700 mg, 96%) was obtained from the isoquinoline **4** (500 mg, 1.8 mmol) as a pale-yellow solid. M.p. 75–77 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.40–7.30 (m, 5 H, Ph), 6.70 (s, 1 H, 5-H), 6.39 (s, 1 H, 1-H), 6.29 (s, 1 H, 8-H), 6.09 (ddt, J = 16.7, 10.7, 7.2 Hz, 1 H, β-H), 5.74 (d, J = 16.7 Hz, 1 H, γ-H), 5.66 (d, J = 10.7 Hz, 1 H, γ′-H), 4.78 (dd, J = 13.4, 7.2 Hz, 1 H, α-H), 4.31 (dd, J = 13.4, 7.2 Hz, 1 H, α′-H), 3.82, 3.59 (2× s, 3 H each, 2× OMe), 3.73–3.67 (m, 1 H, 3-H), 3.58–3.50 (m, 1 H, 3′-H), 3.24–3.21 (m, 2 H, 4-H, 4′-H), 3.02 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 149.4, 148.7 (C-6, C-7), 132.7 (C-1′), 130.4, 128.9 (CH Ph), 129.7, 124.6 (C-β, C-γ), 121.7, 120.4 (C-4a C-8a), 110.9, 110.3 (C-5, C-8), 72.8 (C-1), 62.7 (C-α), 55.9, 55.8 (2× OMe), 51.5 (C-3), 47.4 (*N*-Me), 23.4 (C-4) ppm. IR (neat): ṽ = 3080, 3007, 2935, 1645, 1611, 1560, 1516, 1456, 1364 cm^{-1}. EI-MS: *m*/*z* (%) = 283 (12), 206 (100). HR-MS: calcd. for $C_{21}H_{26}NO_2$ 324.1958; found 324.1951.

(±)-*trans*-6-Chloro-7-methoxy-*N*-[(methoxycarbonyl)methyl]-*N*-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinolinium Bromide (10): The isoquinolinium salt **10** (409 mg, 93%) was obtained from the isoquinoline **9** (300 mg, 1.0 mmol) as a pale-yellow solid. M.p. 115–116 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.48–7.36 (m, 5 H, Ph), 7.29 (s, 1 H, 5-H), 7.16 (s, 1 H, 1-H), 6.44 (s, 1 H, 8-H), 5.76 (d, J = 17.4 Hz, 1 H, α-H), 4.47 (d, J = 17.4 Hz, 1 H, α′-H), 4.34 (dd, J = 13.1, 4.6 Hz, 1 H, 3-H), 3.70–3.60 (m, 1 H, 3′-H), 3.77 (s, 3 H, OMe), 3.67 (s, 3 H, COOMe), 3.38 (s, 3 H, *N*-Me), 3.19–3.06 (m, 2 H, 4-H, 4′-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 164.9 (CO), 154.2 (C-7), 131.1, 130.7 (C-1′, C-5), 129.7, 128.8 (CH Ph), 123.4 (C-6), 120.6, 120.5 (C-4a, C-8a), 111.7 (C-8), 73.5 (C-1), 57.2 (C-α), 55.9 (OMe), 52.9 (COO*Me*), 51.6 (C-3), 47.8 (*N*-Me), 22.6 (C-4) ppm. IR (neat): ṽ = 3025, 2924, 1747, 1605, 1536, 1498, 1457, 1403 cm^{-1}. EI-MS: *m*/*z* (%) = 303 (3), 302 (9), 301 (10), 300 (21), 289 (9), 288 (16), 287 (24), 286 (36), 274 (7), 272 (19), 212 (34), 210 (100), 209 (18), 208 (14). HR-MS: calcd. for $C_{20}H_{23}ClNO_3$ 360.1366; found 360.1364.

General Method for the Stevens Rearrangement: DBU (49 μL, 0.31 mmol) was added to a solution of the corresponding 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**)-7,8-Dimethoxy-2-(methoxycarbonyl)-*N*-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (1a-*trans*):** The benzazepine **1a**-*trans* (47 mg, 95%) was obtained from the salt **5a** (60 mg, 0.14 mmol) as a white solid. M.p. 122–124 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.31–7.17 (m, 5 H, Ph), 6.64 (s, 1 H, 6-H), 6.51 (s, 1 H, 9-H), 4.60 (d, J = 7.0 Hz, 1 H, 1-H), 4.16 (d, J = 7.0 Hz, 1 H, 2-H), 3.85, 3.73 (2× s, 3 H each, 2× OMe), 3.53 (s, 3 H, COOMe), 3.25 (dd, J = 13.4, 8.3 Hz, 1 H, 4-H), 2.80–2.63 (m, 3 H, 5-H, 4′-H, 5′-H), 2.50 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.5 (CO), 147.5, 146.8 (C-7, C-8), 140.4 (C-1′), 133.4, 131.0 (C-5a, C-9a), 128.2, 128.1, 126.3 (CH Ph), 114.1, 113.0 (C-6, C-9), 67.4 (C-2), 55.9, 55.8 (2× OMe), 51.6 (COO*Me*), 50.9 (C-1), 50.3 (C-4), 45.7 (*N*-Me), 34.4 (C-5) ppm. IR (neat): ṽ = 3085, 3058, 2990, 2957, 1720, 1608, 1579, 1509, 1459, 1447, 1383 cm^{-1}. EI-MS: *m*/*z* (%) = 355 (13) [M]$^+$, 297 (31), 296 (100). HR-MS: calcd. for $C_{21}H_{26}NO_4$ [M + H]$^+$ 356.1862; found 356.1872.

(1*R,2*S**)-7,8-Dimethoxy-2-(methoxycarbonyl)-*N*-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (1a-*cis*):** The benzazepine **1a**-*cis* (14 mg, 85%) was obtained from a mixture of diastereoisomers **5a** (*cis*/*trans* ratio 2:1; 30 mg, 0.07 mmol) as a white solid. M.p. 132–134 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.38–7.20 (m, 5 H, Ph), 6.68 (s, 1 H, 6-H), 6.19 (s, 1 H, 9-H), 4.83 (br. s, 1 H, 1-H), 4.07 (br. s, 1 H, 2-H), 3.87, 3.77 (2× s, 3 H each, 2× OMe), 3.57 (s, 3 H, COOMe), 3.36–3.10 (m, 2 H, 4-H, 5-H), 2.91–2.66 (m, 2 H, 4′-H, 5′-H), 2.53 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.5 (CO), 147.5, 146.8 (C-7, C-8), 140.4 (C-1′), 133.4, 130.9 (C-5a, C-9a), 129.0, 128.3, 126.6 (CH Ph), 112.5, 112.3 (C-6, C-9), 67.7 (C-2), 55.9, 55.8 (2× OMe), 51.6 (COO*Me*), 51.2 (C-1), 50.3 (C-4), 45.0 (*N*-Me), 34.4 (C-5) ppm. IR (neat): ṽ = 3080, 3050, 2990, 2960, 1719, 1608, 1579, 1509, 1459, 1445, 1373 cm^{-1}. EI-MS: *m*/*z* (%) = 355 (5) [M]$^+$, 297 (22), 296 (100). HR-MS: calcd. for $C_{21}H_{26}NO_4$ [M + H]$^+$ 356.1862; found 356.1872.

(1*R,2*R**)-2-Carbamoyl-7,8-dimethoxy-*N*-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (1b):** The benzazepine **1b** (38 mg, 85%) was obtained from the salt **5b** (60 mg, 0.13 mmol) after refluxing for 1 h as a pale-yellow solid. M.p. 195–197 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.28–7.16 (m, 5 H, Ph), 6.90 (br. s, 1 H, NH), 6.62 (s, 1 H, 6-H), 6.57 (s, 1 H, 9-H), 5.43 (br. s, 1 H, NH), 4.92 (d, J = 5.0 Hz, 1 H, 1-H), 4.01 (d, J = 5.0 Hz, 1 H, 2-H), 3.85, 3.73 (2× s, 3 H each, 2× OMe), 3.05–2.95 (m, 3 H, 4-H, 4′-H, 5-H), 2.81 (ddd, J = 15.0, 11.3, 5.4 Hz, 1 H, 5′-H), 2.27 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 175.2 (CO), 147.4, 147.1 (C-7, C-8), 142.6 (C-1′), 132.4, 129.9 (C-5a, C-9a), 128.3, 128.2, 126.1 (CH Ph), 115.2, 112.9 (C-6, C-9), 71.0 (C-2), 55.8, 55.7 (2× OMe), 51.0 (C-4), 50.8 (C-1), 45.4 (*N*-Me), 33.2 (C-5) ppm. IR (neat): ṽ = 3408, 3312, 3016, 2952, 1660, 1603, 1515, 1443, 1377, 1310 cm^{-1}. EI-MS: *m*/*z* (%) = 340 (1) [M]$^+$, 297 (22), 296 (100). HR-MS: calcd. for $C_{20}H_{25}N_2O_3$ [M + H]$^+$ 341.1865; found 341.1862.

(1*R,2*R**)-7,8-Dimethoxy-2-(*N*′,*N*′-dimethylcarbamoyl)-*N*-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (1c):** The benzazepine **1c** (40 mg, 90%) was obtained from the salt **5c** (60 mg, 0.12 mmol) after refluxing for 1 h as a pale-yellow solid. M.p. 103–105 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.33–7.20 (m, 5 H, Ph), 6.70 (s, 1 H, 6-H), 6.50 (s, 1 H, 9-H), 4.89 (d, J = 9.1 Hz, 1 H, 1-H), 4.14 (d, J = 9.1 Hz, 1 H, 2-H), 3.85, 3.64 (2× s, 3 H each, 2× OMe), 3.24–3.09 (m, 2 H, 4-H, 5-H), 2.93–2.86 (m, 2 H, 4′-H, 5′-H), 2.83, 2.78 (2× s, 3 H each, $CONMe_2$), 2.28 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.0 (CO), 147.3, 147.2 (C-7, C-8), 141.4 (C-1′), 131.9, 131.3 (C-5a, C-9a), 129.3, 128.5, 126.8 (CH Ph), 112.6, 112.4 (C-6, C-9), 64.3 (C-2), 55.9, 55.8 (2× OMe), 51.9 (C-4), 50.5 (C-1), 42.9 (*N*-Me), 37.2, 35.6 (CON*Me*$_2$), 33.1 (C-5) ppm. IR (neat): ṽ = 3010, 2931, 1635, 1512, 1450, 1398 cm^{-1}. EI-MS: *m*/*z* (%) = 368 (1), 337 (3), 297 (20), 296 (100). HR-MS: calcd. for $C_{22}H_{29}N_2O_3$ [M + H]$^+$ 369.2178; found 369.2158.

(1*R,2*R**)-2-Acetyl-7,8-dimethoxy-*N*-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (1d):** The benzazepine **1d** (61 mg, 86%) was obtained from the salt **5d** (100 mg, 0.21 mmol) as a pale-yellow solid. M.p. 99–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.30–7.16 (m, 5 H, Ph), 6.64 (s, 1 H, 6-H), 6.47 (s, 1 H, 9-H), 4.65 (d, J = 7.8 Hz, 1 H, 1-H), 3.93 (d, J = 7.8 Hz, 1 H, 2-H), 3.84, 3.68 (2× s, 3 H each, 2× OMe), 3.20–3.13 (m, 1 H, 4-H), 2.95–2.77 (m, 3 H, 4′-H, 5-H, 5′-H), 2.33 (s, 3 H, *N*-Me), 2.04 (s, 3 H, $COCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 209.6 (CO), 147.3, 147.1 (C-7, C-8), 141.3 (C-1′), 132.2, 131.4 0 (C-5a, C-9a), 128.6, 128.4, 126.5 (CH Ph), 113.6, 112.8 (C-6, C-9), 73.8 (C-2), 55.8, 55.7 (2× OMe), 51.9 (C-1), 49.6 (C-4), 44.1 (*N*-Me), 33.9 (C-5), 29.5 (CO*CH*$_3$) ppm. IR (neat): $\tilde{\nu}$ = 3070, 2938, 1706, 1604, 1515, 1497, 1449, 1382 cm^{-1}. EI-MS: *m*/*z* (%) = 297 (21), 296 (100). HR-MS: calcd. for $C_{21}H_{26}NO_3$ [M + H]$^+$ 340.1907; found 340.1904.

(1*R,2*R**)-2-Benzoyl-7,8-dimethoxy-*N*-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (1e):** The benzazepine **1e** (75 mg, 89%) was obtained from the salt **5e** (100 mg, 0.21 mmol) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.79 (d, J = 8.1 Hz, 2 H, 2′′-H, 6′′-H COPh), 7.48 (t, J = 8.1 Hz, 1 H, 4′′-H COPh), 7.37 (t, J = 8.1 Hz, 2 H, 3′′-H, 5′′-H COPh), 7.25–7.12 (m, 5 H, Ph), 6.68 (s, 1 H, 6-H), 6.34 (s, 1 H, 9-H), 4.91 (d, J = 7.5 Hz, 1 H, 1-H), 4.86 (d, J = 7.5 Hz, 1 H, 2-H), 3.86, 3.63 (2× s, 3 H each, 2× OMe), 3.28–3.22 (m, 1 H, 4-H), 3.03–2.96 (m, 2 H, 4′-H, 5-H), 2.92–2.85 (m, 1 H, 5′-H), 2.36 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 200.5 (CO), 147.3, 146.9 (C-7, C-8), 141.3, 137.7 (C-1′, C-1′′), 132.5, 128.4, 128.3, 127.8, 126.3 (CH Ph, CO*Ph*), 131.9, 131.4 (C-5a, C-9a), 113.6, 112.8 (C-6, C-9), 67.3 (C-2), 55.7, 55.6 (2× OMe), 51.5 (C-1), 49.7 (C-4), 43.5 (*N*-Me), 33.9 (C-5) ppm. IR (neat): $\tilde{\nu}$ = 3056, 2998, 1654, 1595, 1578, 1492, 1447, 1361 cm^{-1}. EI-MS: *m*/*z* (%) = 297 (20), 296 (100). HR-MS: calcd. for $C_{26}H_{27}NO_3$ 401.1991; found 401.1915.

(1*R,2*R**)-7,8-Dimethoxy-*N*-methyl-2-(*p*-nitrobenzyl)-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (1f):** The benzazepine **1f** (71 mg, 85%) was obtained from the salt **5f** (100 mg, 0.20 mmol) as a yellow solid. M.p. 194–196 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.03 (d, J = 9.1 Hz, 2 H, 3′′-H, 5′′-H), 7.26 (d, J = 9.1 Hz, 2 H, 2′′-H, 6′′-H), 7.24–7.13 (m, 5 H, Ph), 6.74 (s, 1 H, 6-H), 6.36 (s, 1 H, 9-H), 4.49 (d, J = 7.5 Hz, 1 H, 1-H), 4.40 (d, J = 7.5 Hz, 1 H, 2-H), 3.89, 3.62 (2× s, 3 H each, 2× OMe), 3.10–2.99 (m, 2 H, 5-H, 5′-H), 2.93 (ddd, J = 17.2, 11.9, 5.1 Hz, 1 H, 4-H), 2.72 (ddd, J = 11.9, 8.0, 5.1 Hz, 1 H, 4′-H), 2.13 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 148.3, 147.5, 147.0, 146.7 (C-1′′, C-7, C-8, C-4′′), 140.9 (C-1′), 132.2, 131.7 (C-5a, C-9a), 129.8 (C-2′′, C-6′′), 128.8, 128.3, 126.5 (CH Ph), 122.9 (C-3′′, C-5′′), 113.8, 112.8 (C-6, C-9), 70.3 (C-2), 55.9, 55.8 (2× OMe), 54.4 (C-1), 50.6 (C-4), 45.2 (*N*-Me), 34.0 (C-5) ppm. IR (neat): $\tilde{\nu}$ = 3019, 2934, 1602, 1513, 1460, 1449, 1377 cm^{-1}. EI-MS: *m*/*z* (%) = 419 (15), 418 (57) [M]$^+$, 362 (25), 328 (19), 327 (100). HR-MS: calcd. for $C_{25}H_{27}N_2O_4$ [M + H]$^+$ 419.1971; found 419.1978.

(1*R,2*R**)-7,8-Dimethoxy-2-[(methoxycarbonyl)allyl]-*N*-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (1g):** The benzazepine **1g** (70 mg, 84%) was obtained from the salt **5g** (100 mg, 0.22 mmol) as a pale-yellow solid. M.p. 89–91 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.31–7.13 (m, 5 H, Ph), 6.85 (dd, J = 15.7, 8.5 Hz, 1 H, β-H), 6.65 (s, 1 H, 6-H), 6.50 (s, 1 H, 9-H), 5.91 (d, J = 15.7 Hz, 1 H, α-H), 4.09 (d, J = 5.5 Hz, 1 H, 1-H) 4.07–4.00 (m, 1 H, 2-H), 3.87, 3.77, 3.68 (3× s, 3 H each, 3× OMe), 2.92–2.48 (m, 4 H, 4-H, 4′-H, 5-H, 5′-H), 2.31 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 166.2 (CO), 147.5, 147.0 (C-7, C-8), 145.3 (C-α), 140.9 (C-1′), 133.1, 130.8 (C-5a, C-9a), 128.2, 127.9, 126.2 (CH Ph), 123.7 (C-β), 114.8, 113.4 (C-6, C-9), 65.7 (C-2), 55.9, 55.8 (2× OMe), 54.9 (COO*Me*), 51.5 (C-1), 49.8 (C-4), 45.5 (*N*-Me), 35.1 (C-5) ppm. IR (neat): $\tilde{\nu}$ = 3038, 3010, 2951, 1720, 1606, 1515, 1495, 1444, 1375 cm^{-1}. EI-MS: *m*/*z* (%) = 382 (24), 381 (100) [M]$^+$, 350 (9), 322 (21), 290 (44), 253 (27), 252 (61), 140 (48). HR-MS: calcd. for $C_{23}H_{27}NO_4$ 381.1940; found 381.1956.

(1*R,2*R**)-7-Chloro-8-methoxy-2-(methoxycarbonyl)-*N*-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (11):** The benzazepine **11** (77 mg, 93%) was obtained from the salt **10** (100 mg, 0.23 mmol) as a white solid. M.p. 100–102 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.36–7.17 (m, 5 H, Ph), 7.11 (s, 1 H, 6-H), 6.55 (s, 1 H, 9-H), 4.65 (d, J = 7.0 Hz, 1 H, 1-H), 4.15 (d, J = 7.0 Hz, 1 H, 2-H), 3.74, 3.55 (2× s, 3 H each, 2× OMe), 3.24–3.15 (m, 1 H, 4-H), 2.75–2.61 (m, 3 H, 4′-H, 5-H, 5′-H), 2.49 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 172.2 (CO), 153.1 (C-8), 139.5, 139.0, 134.0 (C-1′, C-5a, C-9a), 130.7 (C-6), 128.3, 128.2, 126.6 (CH Ph), 120.3 (C-7), 114.2 (C-9), 67.4 (C-2), 56.1 (OMe), 51.7 (COO*Me*), 51.0, 50.0 (C-1, C-4), 45.6 (*N*-Me), 33.3 (C-5) ppm. IR (neat): $\tilde{\nu}$ = 3052, 2954, 1735, 1599, 1499, 1468, 1447, 1385 cm^{-1}. EI-MS: *m*/*z* (%) = 359 (2) [M]$^+$, 303 (7), 302 (37), 301 (24), 300 (100). HR-MS: calcd. for $C_{20}H_{23}ClNO_3$ [M + H]$^+$ 360.1366; found 360.1359.

General Procedure for the Synthesis of 1,1-Disubstituted Isoquinolines 6a,b: A solution of the corresponding salt **5** (0.23 mmol) and *t*BuOK (300 mg, 2.5 mmol) in dry THF (25 mL) was stirred at room temperature for 1 h. The solvent was evaporated in vacuo, and the residue obtained was dissolved in CH_2Cl_2 (20 mL) and washed with water. The organic layer was dried with anhydrous $MgSO_4$ and the solvent evaporated under vacuum. The crude reaction product was purified by column chromatography (SiO_2; CH_2Cl_2/MeOH) to yield the corresponding 1,1-disubstituted isoquinoline.

(1*R)-1-Benzyl-6,7-dimethoxy-*N*-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (6a):** The isoquinoline **6a** (75 mg, 91%) was obtained from the salt **5h** (100 mg, 0.22 mmol) as a pale-yellow solid. M.p. 95–97 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.29–7.19 (m, 5 H, Ph), 7.05–6.99 (m, 3 H, CH_2*Ph*), 6.83 (d, J = 8.1 Hz, 2 H, CH_2*Ph*), 6.35 (s, 1 H, 5-H), 6.29 (s, 1 H, 8-H), 3.84 (d, J = 13.4 Hz, 1 H, α-H), 3.80, 3.62 (2× s, 3 H each, 2× OMe), 3.23 (d, J = 13.4 Hz, 1 H, α′-H), 2.76 (ddd, J = 11.8, 10.2, 3.8 Hz, 1 H, 3-H), 2.56 (dt, J = 11.8, 4.8 Hz, 1 H, 3′-H), 2.43 (dt, J = 15.0, 4.8 Hz, 1 H, 4-H), 2.27 (ddd, J = 15.0, 10.2, 4.8 Hz, 1 H, 4′-H), 2.17 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 146.8, 146.6 (C-6, C-7), 145.3, 138.5 (C-1′, C-1′′), 132.5, 129.3 (C-4a C-8a), 130.9, 128.4, 127.3, 126.7, 126.2, 125.4 (CH Ph, CH_2*Ph*), 112.3, 109.7 (C-5, C-8), 66.6 (C-1), 55.8, 55.5 (2× OMe), 47.1 (C-3), 42.2 (*N*-Me), 38.9 (C-α), 29.4 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3055, 3001, 2980, 1607, 1510, 1494, 1462, 1367 cm^{-1}. EI-MS: *m*/*z* (%) = 283 (17), 282 (100) 91 (13). HR-MS: calcd. for $C_{25}H_{27}NO_2$ 373.2042; found 373.2056.

(1*R)-1-Allyl-6,7-dimethoxy-*N*-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (6b):** The isoquinoline **6b** (34 mg, 81%) was obtained from the salt **5i** (51 mg, 0.13 mmol) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.29–7.11 (m, 5 H, Ph), 6.57 (s, 1 H, 5-H), 6.28 (s, 1 H, 8-H), 5.62 (ddd, J = 17.1, 9.8, 7.3 Hz, 1 H, β-H), 5.00 (d, J = 17.1 Hz, 1 H, γ-H), 4.90 (d, J = 9.8 Hz, 1 H, γ′-H), 3.85, 3.61 (2× s, 3 H each, 2× OMe), 3.35 (dd, J = 14.6, 7.3 Hz, 1 H, α-H), 3.04–2.64 (m, 5 H, α′-H, 3-H, 3′-H, 4-H, 4′-H), 2.09 (s, 3 H, *N*-Me) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 147.1, 147.0 (C-6, C-7), 143.6 (C-1′), 135.9 (C-β), 132.5, 128.4 (C-

4a C-8a), 128.7, 127.2, 126.4 (CH Ph), 116.1 (C-γ), 111.5, 110.2 (C-5, C-8), 65.7 (C-1), 55.9, 55.6 (2× OMe), 47.0 (C-3), 40.7 (*N*-Me), 38.3 (C-α), 29.1 (C-4) ppm. IR (neat): $\tilde{\nu}$ = 3080, 3067, 2978, 1637, 1608, 1509, 1492, 1455, 1365 cm^{-1}. EI-MS: *m*/*z* (%) = 283 (30), 282 (100). HR-MS: calcd. for $C_{21}H_{26}NO_2$ $[M + H]^+$ 324.1963; found 324.1961.

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

Acknowledgments

Financial support of this work by the Ministerio de Educación y Ciencia (MEC) (MEC-07-CTQ-2007-60190) is gratefully acknowledged. A. B.-M. thanks the MEC for a predoctoral grant.

[1] W.-L. Wu, D. A. Burnett, R. Spring, W. J. Greenlee, M. Smith, L. Favreau, A. Fawzi, H. Zhang, J. E. Lachowicz, *J. Med. Chem.* **2005**, *48*, 680–693.
[2] a) H. H. M. Van Tol, J. R. Buznow, H. C. Guan, R. K. Sunahara, P. Seeman, H. B. Niznik, O. Civelli, *Nature* **1991**, *350*, 610–614; b) P. Sokoloff, B. Giros, M. P. Martres, M. L. Bouthenet, J. C. Schwartz, *Nature* **1990**, *347*, 146–151; c) R. K. Sunahara, H. C. Guan, B. F. O'Dowd, P. Seeman, L. G. Laurier, G. Ng, S. R. George, J. Torchia, H. H. M. Van Tol, H. B. Niznik, *Nature* **1991**, *350*, 614–619; d) K. Negash, D. E. Nichols, V. J. Watts, R. B. Mailman, *J. Med. Chem.* **1997**, *40*, 2140–2147.
[3] A. Zhang, J. L. Neumeyer, R. J. Baldessarini, *Chem. Rev.* **2007**, *107*, 274–302.
[4] a) J. Crecente-Campo, M. P. Vazquez-Tato, J. A. Seijas, *Tetrahedron* **2009**, *65*, 2655–2659; b) S. M. Husain, M. T. Heim, D. Schepmann, B. Wünsch, *Tetrahedron: Asymmetry* **2009**, *20*, 1383–1392.
[5] a) J. Zhang, B. Xiong, X. Zhen, A. Zhang, *Med. Res. Rev.* **2009**, *29*, 272–294; b) R. Feneck, *Drugs* **2007**, *67*, 2023–2044.
[6] L. Qiang, T. K. Sasikumar, D. A. Burnett, J. Su, H. Tang, Y. Ye, R. D. Mazzola, Z. Zhu, B. A. McKittrick, W. J. Greenlee, A. Fawzi, M. Smith, H. Zhang, J. E. Lachowicz, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 836–840.
[7] B. M. Smith, J. M. Smith, J. H. Tsai, J. A. Schultz, C. A. Gilson, S. A. Estrada, R. R. Chen, D. M. Park, E. B. Prieto, C. S. Gallardo, D. Sengupta, P. I. Dosa, J. A. Covel, A. Ren, R. R. Webb, N. R. A. Beeley, M. Martin, M. Morgan, S. Espitia, H. R. Saldana, C. Bjenning, K. T. Whelan, A. J. Grottick, F. Menzaghi, W. J. Thomsen, *J. Med. Chem.* **2008**, *51*, 305–313.
[8] S. W. Gerritz, J. S. Smith, S. S. Nanthakumar, D. E. Uehling, J. E. Cobb, *Org. Lett.* **2000**, *2*, 4099–4102.
[9] P. A. Donets, E. V. Van der Eycken, *Org. Lett.* **2007**, *9*, 3017–3020.
[10] A. Padwa, Q. Wang, *J. Org. Chem.* **2006**, *71*, 7391–7402.
[11] L. Jean-Gérard, M. Pauvert, S. Collet, A. Guingant, M. Evain, *Tetrahedron* **2007**, *63*, 11250–11259.
[12] a) J. A. Vanecko, H. Wan, F. G. West, *Tetrahedron* **2006**, *62*, 1043–1062; b) J. B. Sweeney, *Chem. Soc. Rev.* **2009**, *38*, 1027–1038.
[13] a) M. Valpuesta, M. Ariza, A. Diaz, G. Torres, R. Suau, *Eur. J. Org. Chem* **2010**, 638–645; b) M. Valpuesta, A. Díaz, R. Suau, G. Torres, *Eur. J. Org. Chem.* **2004**, 4313–4318.
[14] M. Valpuesta, A. Diaz, R. Suau, G. Torres, *Eur. J. Org. Chem* **2006**, 964–971.
[15] S. Smith Jr., V. Elango, M. Shamma, *J. Org. Chem.* **1984**, *49*, 581–586.
[16] Tinker software package, rev. 4: a) P. Ren, J. W. Ponder, *J. Phys. Chem. B* **2003**, *107*, 5933–5947; b) P. Ren, J. W. Ponder, *J. Comput. Chem.* **2002**, *23*, 1497–1506; c) R. V. Pappu, R. K. Hart, J. W. Ponder, *J. Phys. Chem. B* **1998**, *102*, 9725–9742; d) M. E. Hodsdon, J. W. Ponder, D. P. Cistola, *J. Mol. Biol.* **1996**, *264*, 585–602; e) C. E. Kundrot, J. W. Ponder, F. M. Richards, *J. Comput. Chem.* **1991**, *12*, 402–409; f) J. W. Ponder, F. M. Richards, *J. Comput. Chem.* **1987**, *8*, 1016–1024.
[17] a) M. Movassaghi, M. D. Hill, *Org. Lett.* **2008**, *10*, 3485–3488; b) C. Kuhakarn, N. Panyachariwat, S. Ruchirawat, *Tetrahedron Lett.* **2007**, *48*, 8182–8184.
[18] J. A. Christopher, F. L. Atkinson, B. D. Bax, M. J. B. Brown, A. C. Champigny, T. T. Chuang, E. J. Jones, J. E. Mosley, J. R. Musgrave, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2230–2234.
[19] I. Berenguer, N. El Aouad, S. Andújar, V. Romero, F. Suvire, T. Freret, A. Bermejo, M. D. Ivorra, R. D. Enriz, M. Boulouard, N. Cabedo, D. Cortes, *Bioorg. Med. Chem.* **2009**, *17*, 4968–4980.
[20] A. M. Taylor, S. L. Schreiber, *Org. Lett.* **2006**, *8*, 143–146.
[21] a) M. Chrzanowska, J. Sokołowska, *Tetrahedron: Asymmetry* **2001**, *12*, 1435–1440; b) D. L. Minor, S. D. Wyrick, P. S. Charifson, V. J. Watts, D. E. Nichols, R. B. Mailman, *J. Med. Chem.* **1994**, *37*, 4317–4328.

Received: April 14, 2010
Published Online: July 1, 2010

