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A new enlargement methodology for the preparation of 2*H*-1- and 2*H*-3-benzazepin-2-one derivatives

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Abstract—An investigation of the one-carbon homologation of some 1-tribromomethyl-isoquinoline and 2-tribromomethyl-quinoline derivatives was conducted. Under the influence of an aqueous solution of silver nitrate in the presence of a nucleophilic species (MeOH, H_2O, $EtNH_2$), these derivatives led to the respective expanded heterocycles, 2*H*-1- and 2*H*-3-benzazepin-2-one derivatives. A mechanism for this novel ring enlargement involving initial formation of an aziridinium, and its subsequent opening to form a stabilized benzylic carbocation, is proposed to explain the results.
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1. Introduction

Compounds characterized by a 1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-one structure or a 1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-one core structure (**1** and **2**, respectively) have stimulated much synthetic effort due to their wide-ranging pharmacological activities (Scheme 1). For instance, compounds with a bicyclic core structure such as **1** have been shown to have activity against cyclin-dependent kinases (CDKs)[1] and the angiotensin-converting enzyme (ACE).[2] They also display activity as human growth hormone (hGH) secretagogues,[3] calcium channel blockers (CCBs),[4] and thrombin inhibitors.[5] On the other hand, compounds with core structure **2** have been reported to act as specific bradycardic agents[6] and γ-secretase inhibitors.[7]

1 **2**

Scheme 1.

Among the possible routes to a benzazepine structure, one consists in ring enlargement of a six-membered ring precursor.[8] This can be achieved either by insertion of a nitrogen atom in a carbacycle or by one-carbon homologation of an azacycle. Regarding the second and less frequently used approach, most of the reported examples rely on the intermediary formation of an aziridine or a transient aziridinium species[9] as pictured in general terms in Scheme 2 (X=halogen, OCOR). This approach, however, does not allow the direct formation of a benzazepinone structure such as **1** or **2**.[10] We reasoned that if the exocyclic carbon involved in the enlargement process were triply activated (for instance, as in **3**), the primary enlarged species **5** would lead to a 1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-one compound **6** after hydrolysis of its highly labile N–CX_2 moiety (Scheme 2, X=halogen, PG is a protecting group).[11]

In a retrosynthetic point of view (Scheme 3), the synthetic precursor to **6** could be prepared by 1,2-addition of a trihalomethane anion to an iminium species, which in turn could be prepared by quaternarization of the corresponding dihydroisoquinoline. Provided an additional reductive step is accomplished (i.e., **7**→**6**), an isoquinoline, rather than a dihydroisoquinoline species, is also a possible starting point to reach a 1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-one derivative. Of course, a compound such as **7** provides additional synthetic possibilities by chemical manipulation of its C_4–C_5 double bond. Finally, it is noteworthy that the above general procedure, when applied to a dihydroquinoline or

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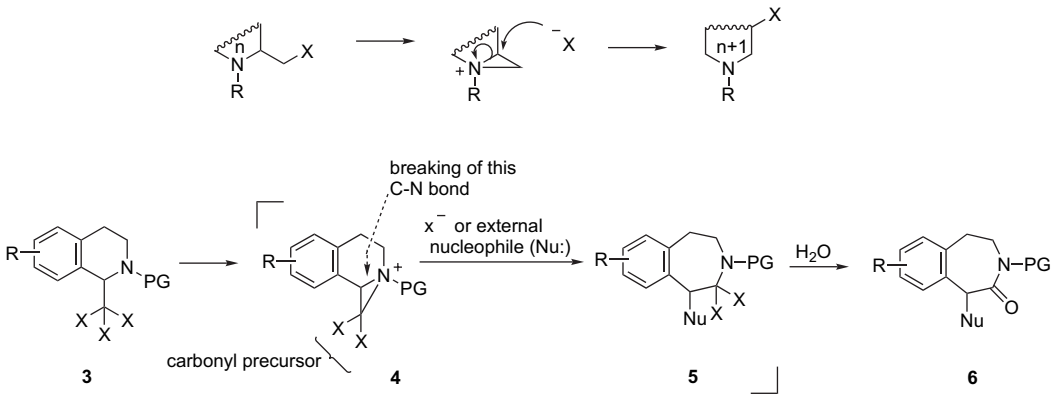


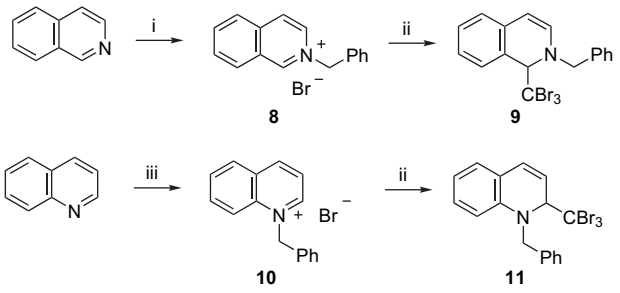
Scheme 2.

a quinoline species, would be expected to lead to a 1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-one derivative.

On the basis of the importance of structures **1** and **2** in medicinal chemistry and their presence in several natural products, there appeared to be a significant opportunity to study the possibility of ring enlargement of quinoline and isoquinoline derivatives following the sequence shown in Scheme 3. The realization of this goal would offer an attractive potential entry to a range of diverse 2*H*-1- and 2*H*-3-benzazepin-2-ones whose preparation following known methods is not always efficiently achieved. Herein, we describe our realization of that objective and also report results that shed light on some mechanistic aspects of these new ring expansion reactions.

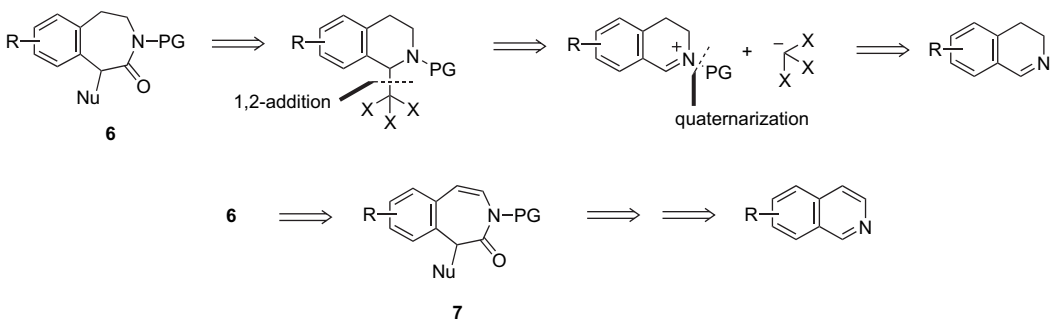
2. Results and discussion

Although trihalomethyl anions (X_3C^-, X=Cl, Br) are relatively good leaving groups, the negative charge being stabilized by the three halogen atoms, examples of their 1,2-addition to aromatic iminium salts have already been reported following different protocols.[12] After several preliminary experiments, it appeared to us that the most reliable and efficient way to reach the key intermediates **9** and **11** was by applying the protocol reported by Duchardt and Kröhnke.[12e] Thus, after quaternarization of isoquinoline and quinoline by treatment with benzyl bromide in methanol at reflux, the resultant salts **8**[13] and **10**,[14] vigorously stirred in aqueous acetonitrile at 20 °C, were sequentially treated with bromoform and an aqueous solution of potassium hydroxide to afford the tribromomethyl addition products **9** and **11**[15] in good yields (Scheme 4).

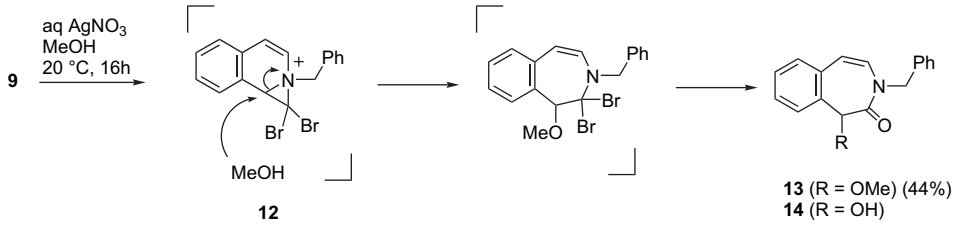


Scheme 4. Reagents and conditions: (i) BnBr, MeOH, reflux, two weeks (quantitative); (ii) $CHBr_3$, aq NaOH [45 min (**9**), 2 h (**11**)] (**9**: 89%; **11**: 80%); (iii) BnBr, MeOH, reflux, four days (71%).

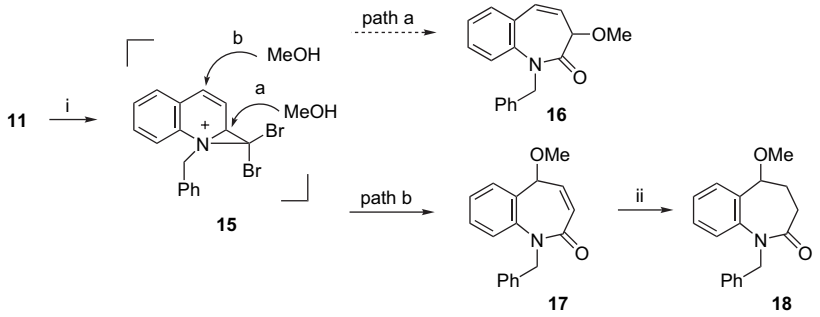
With the key compounds **9** and **11** in hand, we initially examined the ability for **9** to lead to ring expansion and formation of a 1,3-dihydro-2*H*-3-benzazepin-2-one derivative. Given the known halophile character of silver we thought to trigger the aziridinium formation by exposure of **9** to an aqueous solution of silver nitrate, hoping that the transient species **12** would be prone to evolve as shown in Scheme 2. We were thus pleased to observe that, in accordance with our expectations, a methanolic solution of the tribromomethyl derivative **9** led to the formation of the 2*H*-3-benzazepine-2-one **13** under the above conditions. The formation of **13** can be accounted for by the mechanism shown in Scheme 5 where methanol is the incoming nucleophile. It is worth noting that the 2*H*-3-benzazepinone **14** could not be detected in this experiment.



Scheme 3.



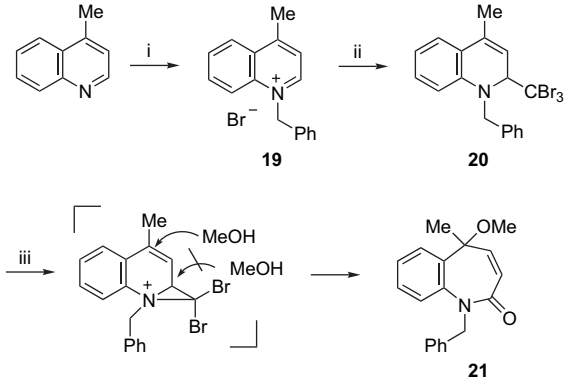
Scheme 5.



Scheme 6. Reagents and conditions: (i) **11** in methanol, aq $AgNO_3$, 20 °C, 3 h (50%); (ii) H_2, 5% Pd/C, MeOH, 20 °C (quantitative).

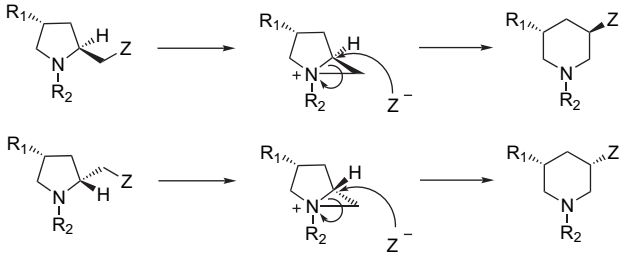
We next examined the behavior of **11** in the same experimental conditions as for **9**. The problem is more complex in that case because nucleophilic opening of the aziridinium species **15** may take place at two distinct positions, i.e., at carbon C_2 or at carbon C_4, to afford the 1,3-dihydro-2*H*-1-benzazepin-2-one **16** or the 1,3-dihydro-2*H*-1-benzazepin-2-one **17**, respectively (Scheme 6).

After being exposed to the action of $AgNO_3$, a methanol solution of the tribromo derivative **11** led to the formation of an expanded heterocycle which was thought to be **17** rather than **16** on the basis of its NMR data. Its structure was finally fully ascertained by comparison of its reduction product **18** with an authentic sample prepared following a more conventional route.[11a] Furthermore, when the whole sequence was performed starting from lepidine (4-Me-quinoline), the 1,3-dihydro-2*H*-1-benzazepin-2-one **21** was identified as the sole expanded product of the reaction. It thus appears that a methyl substituent does not provide a sufficient steric bias to prevent MeOH from approaching the benzylic carbon of the transient aziridinium species (Scheme 7).



Scheme 7. Reagents and conditions: (i) BnBr, MeOH, reflux, seven days (74%); (ii) $CHBr_3$, aq NaOH, 20 °C (60%); (iii) aq $AgNO_3$, MeOH, 20 °C, 4 h (29%).

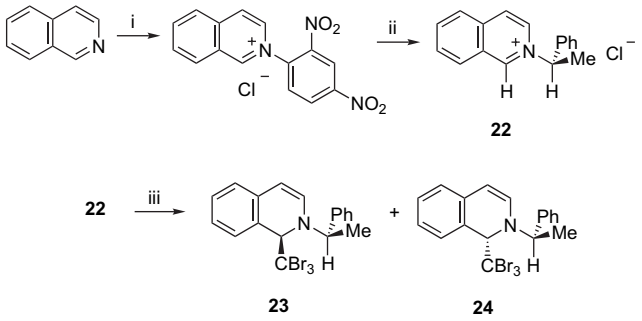
Many examples of ring expansion of substituted pyrrolidines via aziridinium species were shown to be stereospecific processes.[16] As pictured in general terms in Scheme 8, the reaction proceeds through an internal displacement of a good leaving group (Z) to generate an aziridinium salt that is subsequently opened by the nucleophile present in the reaction mixture (e.g., Z^-) following an S_N2-type displacement (Scheme 8). Because the stereochemical outcome for the related C6 to C7 enlargement is not yet known, we became much interested to know if the opening of the aziridinium intermediary shown in Scheme 2 is, or is not, a stereoselective process.



Scheme 8.

We restricted our study to the example of the isoquinoline enlargement and chose, as a model study, the chiral isoquinolinium salt **22** whose synthesis had been already reported[17] from isoquinoline by application of the Zincke reaction (Scheme 9).

When subjected to the action of bromoform in the presence of aqueous KOH, salt **22** led to the formation of two diastereomeric addition products, **23** and **24**, which could be routinely isolated in ca. 93% yield. The reaction was slightly selective (ca. 3:1 ratio of diastereomers) and significant amounts of the minor diastereomer could be obtained pure by fractional crystallization from ether. The structure of



Scheme 9. Reagents and conditions: (i) 1-chloro-2,4-dinitrobenzene, acetone, 60 °C, 2 h (82%); (ii) (*R*)-1-phenylethylamine, *n*-BuOH, reflux, 15 h (84%); (iii) $CHBr_3$, aq NaOH, 20 °C, 12 h (93%).

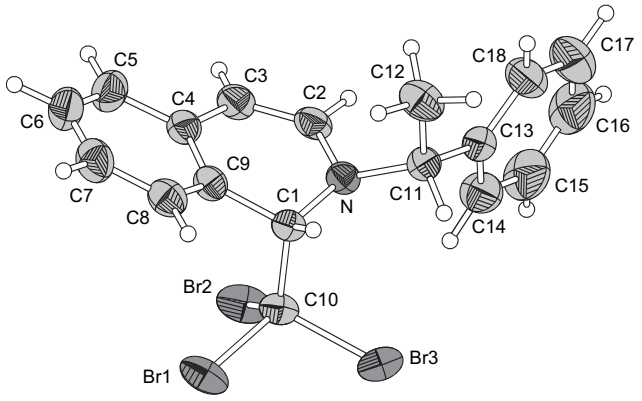


Figure 1. X-ray crystal structure of **24**.

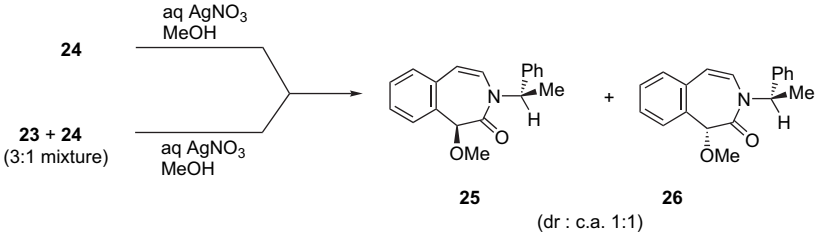
the minor diastereomer was firmly established as **24** by X-ray analysis (Fig. 1) and, by inference, structure **23** was thus attributed to the major diastereomer formed. The predominant formation of **23** may be accounted for by considering that the reactive conformation for **22** is the one that minimizes allylic 1,3-strain[18] (as shown in Scheme 9) and wherein Br_3C^- is approaching the less congested face of the iminium bond, i.e., the face opposite to the phenyl substituent of the attached chiral moiety.

The enlargement protocol was next applied to **24** and to a 3:1 mixture of diastereomers **23** and **24** to give, in each experiment, a 1 to 1 ratio of enlarged diastereomers **25** and **26** (Scheme 10), which could be separated by flash chromatography only with difficulty.

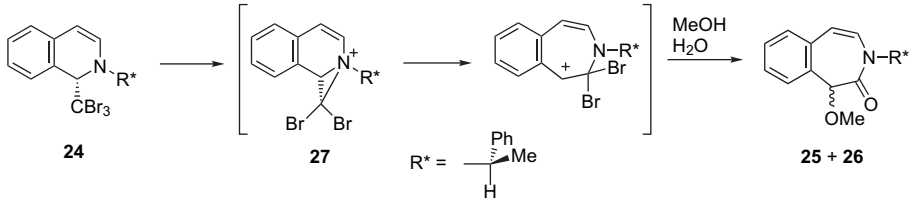
To rule out the possibility that the above 1:1 mixture was the result of an epimerization at C_1, we submitted compound **9** in MeOD to the action of a solution of $AgNO_3$ in D_2O.[19] The enlargement reaction took place without notable deuterium incorporation as judged from the ^1H and ^{13}C spectra of the crude enlarged product **13**. It thus appears that, in contrast to the stereochemical course of the C5 to C6 enlargement, opening of the transient aziridinium **27** does not take place via an S_N2-type displacement but merely involves its prior dissociation into a benzylic carbocation species (Scheme 11). By analogy we believe that such a mechanism is also relevant to the transformation **9**→**13** (**14**). Although not demonstrated, the formation of a transient benzylic carbocation is also probably involved in the transformations **11**→**17** and **20**→**21**.

We next focused our attention on the possibility of using nucleophiles other than methanol to promote, in association with $AgNO_3$, the C_6 to C_7 ring enlargement. In this regard, the above reported examples of ring enlargement were also studied in the presence of water and (or) ethylamine instead of methanol. In a general manner, reactions were less efficient in the presence of water, as compared to methanol, and we only got a synthetically useful result with the tribromomethyl derivative **29**, which was expanded to the 1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-one **30** in 71% yield (Scheme 12).

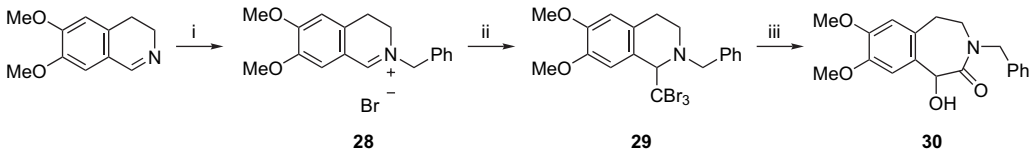
The ring enlargement of **29** was also studied in the presence of ethylamine in THF. We obtained results that greatly depended on the reaction conditions (Scheme 13). Thus, if the reaction was conducted in water or in a water/methanol mixture, compounds **30** and **31** were isolated, respectively. However, if the reaction was carried out in THF, the α-diketo derivative **32** was the sole expanded compound isolated from



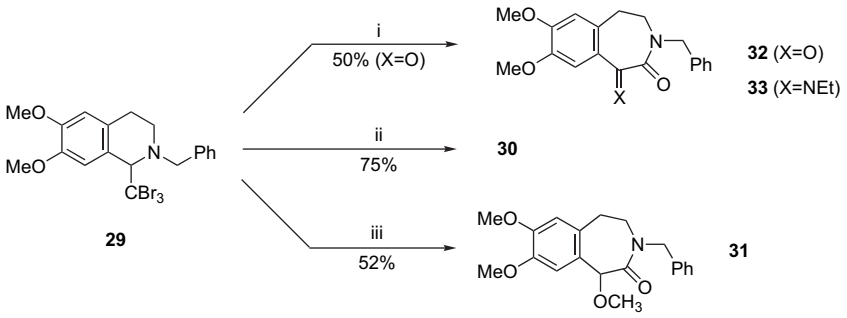
Scheme 10.



Scheme 11.



Scheme 12. Reagents and conditions: (i) BnBr, toluene, reflux, 5 h (74%); (ii) $CHBr_3$, aq NaOH, 20 °C, 8 h (73%); (iii) aq $AgNO_3$, −20 °C to 20 °C, 16 h (71%).



Scheme 13. Reagents and conditions: (i) **29** in THF, aq $AgNO_3$, $EtNH_2$ in THF, 20 °C, 12 h; (ii) aq $AgNO_3$, $EtNH_2$ in THF, 20 °C, 12 h; (iii) **29** in MeOH, aq $AgNO_3$, $EtNH_2$ in THF, −20 °C to 20 °C, 12 h.

the crude mixture. Because traces of the corresponding imine **33** were also detected when the reaction was carried out at a lower temperature, we believed that **32** was derived from **33** by hydrolysis. Interception of the transient carbocation by ethylamine followed by oxidation of the CH–NHEt moiety under the reaction conditions may explain the formation of imine **33**.

In summary, we have described a new procedure allowing the C6 to C7 enlargement of quinoline and isoquinoline to form 1,5-dihydro-2*H*-1-benzazepin-2-one and 1,3-dihydro-2*H*-3-benzazepin-2-one structures, respectively, in fair to good overall yields. The three-step sequence features a quaternarization reaction, a tribromomethyl anion addition and, as a key step, a silver-induced rearrangement. A reasonable mechanism based on the formation of a transient aziridinium species, its opening to form a stabilized benzylic cation (at least with isoquinoline derivatives) followed by its nucleophilic trapping with methanol (or water) has been offered to account for the results. This new methodology should be complementary to conventional routes in the preparation of 2*H*-1- and 2*H*-3-benzazepin-2-ones, which proved to be useful structural patterns in medicinal chemistry.

3. Experimental procedures

3.1. General methods

Melting points were determined using a Stuart Scientific SMP3 Tottoli apparatus. Microanalysis was carried out at the 'Services de Microanalyses de l'Université de Chatenay Malabry—France'. HRMS was carried out at the 'Centre régional de mesures physiques de l'Ouest, Rennes—France' or at the 'Centre commun de spectrométrie de masse-Université Claude Bernard Lyon 1, Villeurbanne—France'. IR spectra were recorded neat or as KBr pellets on an IRTF Bruker Vector 22 spectrometer. ^{1}H NMR spectra were recorded on a Bruker AC200 (or AC300) spectrometer at 200 MHz (respectively 300 MHz) or on a Bruker ARX400 spectrometer at 400 MHz. ^{13}C NMR spectra were recorded on a Bruker AC200 (or AC300) spectrometer at 50 MHz (respectively 75 MHz) or on a Bruker ARX400 spectrometer at 100 MHz. All NMR spectra used tetramethylsilane as the internal standard and were run in deuteriated solvents. Analytical thin-layer chromatography (TLC) was performed on silica gel aluminum plates precoated with a fluorescent indicator (Merck 5735 Kieselgel 60 F_{254}). Standard flash chromatography procedures were performed using 32–63 μm silica gel (Merck Geduran SI 60 Art. 11567). Reactions carried out under an inert atmosphere refer to the use of argon or nitrogen. Diethyl ether, tetrahydrofuran (THF), and toluene were dried by distilling from sodium and benzophenone. Dichloromethane and acetonitrile were dried by distillation from calcium hydride.

3.2. 2-Benzyl-isoquinolinium bromide 8

A solution of isoquinoline (2.5 mL, 21.0 mmol) in anhydrous methanol (25 mL) was treated with benzyl bromide (2.50 mL, 23.1 mmol). The reaction was heated under reflux with stirring for 14 days and then cooled to rt. The solvent was removed in vacuo and the crude white solid was triturated in Et_2O. The suspension was filtered and afforded the desired isoquinolinium salt **8** as a white powder in quantitative yield (6.3 g, 21.0 mmol). Mp (MeOH)=112–113 °C (lit.[13] mp=108–110 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 11.05 (s, 1H), 8.91 (dd, 1H, J=6.8, 1.2 Hz), 8.52 (d, 1H, J=8.2 Hz), 8.22 (d, 1H, J=7.0 Hz), 8.05–7.85 (m, 2H), 7.80–7.65 (m, 3H), 7.20–7.10 (m, 3H), 6.28 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.8, 137.1, 136.9, 134.4, 133.2, 131.0, 130.9, 129.6, 129.4 (2C), 129.3 (2C), 127.5, 127.0, 126.2, 63.5; IR (KBr) 3005, 1641, 1397, 1106, 722 cm^{-1}; EIMS *m*/*z* (%) 220 (2), 129 (76), 102 (19), 91 (100), 65 (15).

3.3. 2-Benzyl-1-tribromomethyl-1,2-dihydro-isoquinoline 9

To a solution of the isoquinolinium salt **8** (500 mg, 1.66 mmol) in acetonitrile/water (1:1, 6 mL) were successively added bromoform (193 μL, 2.16 mmol) and an aqueous solution of KOH (1 mL, 115 mg, 2.05 mmol). The reaction mixture was vigorously stirred for 45 min. The resulting precipitate was filtered, rinsed with water, and dried under high vacuum to afford the desired compound **9** as a yellow solid in 89% yield (700 mg, 1.48 mmol). Mp (MeCN/H_2O)=101–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, 1H, J=7.6 Hz), 7.33 (td, 1H, J=7.6, 1.2 Hz), 7.10–7.20 (m, 5H), 6.90–7.0 (m, 2H), 6.38 (dd, 1H, J=7.2, 0.8 Hz), 5.74 (d, 1H, J=7.2 Hz), 5.23 (s, 1H), 4.77 and 4.97 (AB system, 2H, J=16.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 134.8, 134.4, 131.1, 129.0, 128.8 (2C), 127.6, 126.9 (2C), 125.1, 124.1, 121.9, 103.6, 77.5, 62.3, 59.8; IR (KBr) 1623, 1487, 1368, 1155, 770, 601, 549 cm^{-1}; EIMS m/z (%) 220 (87), 173 (8), 129 (12), 91 (100), 65 (11). Anal. Calcd for $C_{17}H_{14}NBr_3$: C, 43.26; H, 2.99; N, 2.97. Found: C, 43.26; H, 2.98; N, 2.95%.

3.4. 1-Benzyl-quinolinium bromide 10

A solution of quinoline (2.7 mL, 19.4 mmol) in anhydrous methanol (30 mL) was treated with benzyl bromide (2.6 mL, 21.3 mmol). The reaction was heated under reflux with stirring for seven days and then cooled to rt. The solvent was removed in vacuo and the crude white solid was triturated in CH_2Cl_2. The suspension was filtered and the operation was repeated twice to afford the desired quinolinium salt **10** as a white powder in 71% yield (4.2 g, 14.0 mmol). Mp (CH_2Cl_2)=183–184 °C (lit.[20] mp=188 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.57 (d, 1H, J=5.8 Hz), 9.25 (d, 1H, J=8.4 Hz), 8.57 (d, 1H, J=8.2 Hz), 8.37 (d, 1H, J=8.0 Hz), 8.20 (t, 1H, J=8.4 Hz), 8.11 (dd, 1H, J=8.0, 8.2 Hz), 7.88 (t, 1H, J=8.0 Hz), 7.50–7.40 (m, 2H), 7.30–7.15 (m, 3H), 6.71 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.5, 147.9, 138.0, 136.2, 132.8, 130.9, 130.3, 130.2, 129.4, 129.2, 127.6, 122.3, 119.5, 60.9; IR (KBr) 1529, 774, 765, 718 cm^{-1}.

3.5. 1-Benzyl-2-(tribromomethyl)-1,2-dihydroquinoline 11

To a solution of the quinolinium salt **10** (500 mg, 1.67 mmol) in acetonitrile/water (1:1, 6 mL) were successively added bromoform (179 μL, 2.0 mmol) and an aqueous solution of KOH (1 mL, 102.4 mg). The reaction mixture was vigorously stirred for 2 h producing a biphasic mixture. The more dense layer was separated and directly purified by silica gel chromatography (eluting with EtOAc/petroleum ether: 20:80) to afford the desired compound **11** as a yellow oil in 80% yield (630 mg, 1.34 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.05 (m, 7H), 6.97 (d, 1H, J=9.6 Hz), 6.88 (d, 1H, J=8.0 Hz), 6.27 (dt, 1H, J=1.0, 8.0 Hz), 6.23 (dd, 1H, J=5.8, 9.6 Hz), 5.34 and 5.02 (AB system, 2H, J=16.6 Hz), 4.81 (dd, 1H, J=1.0, 5.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 137.9, 130.8, 129.4, 128.7 (2C), 127.4, 127.3, 127.1 (2C), 123.6, 118.7, 118.4, 115.8, 75.4, 60.9, 59.8; IR (neat) 3028, 2923, 1636, 1600, 1488, 590 cm^{-1}; EIMS m/z (%) 220 (69), 129 (8), 91 (100), 65 (9); CIMS m/z 470 (M+H)$^+$; HRMS (LSIMS) m/z calcd for $C_{17}H_{15}NBr_3$ (M+H$^+$) 469.8755, found 469.876.

3.6. 3-Benzyl-1-methoxy-1,3-dihydro-benzo[*b*]azepin-2-one 13

An aqueous solution of silver nitrate (1 mL, 540 mg, 3.18 mmol) was added to a solution of the compound **9** (500 mg, 1.06 mmol) in MeOH (10 mL) cooled at −20 °C. The reaction was then stirred in the dark for 16 h while the temperature was allowed to rise to rt. The insoluble salts were filtered off through Celite, rinsed with CH_2Cl_2, and the filtrate was concentrated in vacuo. The crude product was diluted with CH_2Cl_2 (30 mL) and washed with water (2×20 mL) and brine (1×20 mL). The organic layer was dried ($MgSO_4$) and filtered. The solvent was removed in vacuo and the crude product was purified by silica gel chromatography (eluting with EtOAc/petroleum ether: 40:60) to afford the desired compound **13** as a yellow oil in 44% yield (130 mg, 0.46 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.65 (d, 1H, J=7.6 Hz), 7.44 (td, 1H, J=1.4, 7.6 Hz), 7.35–7.20 (m, 5H), 7.15–7.05 (m, 2H), 6.45 (d, 1H, J=9.2 Hz), 6.25 (d, 1H, J=9.2 Hz), 4.87 and 4.71 (AB system, 2H, J=15.0 Hz), 4.45 (br s, 1H), 3.59 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.9, 136.6, 133.7, 131.2, 129.0, 128.7 (2C), 128.4, 127.8 (2C), 127.7, 127.4, 127.0, 124.3, 117.3, 81.1, 58.3, 50.8; IR (neat) 1678, 1496, 1455, 1397, 1211, 1127, 785 cm^{-1}; EIMS m/z (%) 279 (42, M$^{+\bullet}$), 264 (9), 220 (19), 91 (100), 65 (18); HRMS (EI) m/z calcd for $C_{18}H_{17}NO_2$ (M$^{+\bullet}$) 279.1259, found 279.127.

3.7. 1-Benzyl-5-methoxy-1,5-dihydro-benzo[*b*]azepin-2-one 17

An aqueous solution of silver nitrate (1 mL, 680 mg, 3.99 mmol) was added to a solution of the compound **10** (630 mg, 1.33 mmol) in MeOH (10 mL). The reaction was then stirred in the dark for 3 h. The insoluble salts were filtered off through Celite, rinsed with EtOAc, and the filtrate was concentrated in vacuo. The crude product was diluted with EtOAc (20 mL) and washed with water (2×20 mL) and brine (1×20 mL). The organic layer was dried ($MgSO_4$) and filtered. The solvent was removed in vacuo and the crude product was purified by silica gel chromatography (eluting with EtOAc/petroleum ether: 50:50) to afford the desired compound **17** as a yellow oil in 50% yield (185 mg, 0.66 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.45–7.05 (m, 9H), 6.51 (dd, 1H, J=4.0, 11.2 Hz), 5.84 (d, 1H, J=11.2 Hz), 5.40 and 5.08 (AB system, 2H, J=15.2 Hz), 4.82 (br s, 1H), 3.40 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.5, 146.1, 138.4, 138.3, 137.7, 128.5 (2C), 127.5 (2C), 127.4, 127.3, 125.7, 123.1, 122.6, 121.1, 77.2, 57.7, 52.4; IR (KBr) 1659, 1615, 1595, 1488, 1382 cm^{-1}; EIMS m/z (%) 279 (8, M$^{+\bullet}$), 264 (19), 246 (30), 91 (100), 65 (18); HRMS (FAB) m/z calcd for $C_{18}H_{18}NO_2$ (M+H$^+$) 280.1338, found 280.134.

3.8. 1-Benzyl-5-methoxy-1,3,4,5-tetrahydro-benzo[*b*]-azepin-2-one 18

To a solution of the compound **17** (180 mg, 0.64 mmol) in anhydrous MeOH (5 mL) was added 30 mg of Pd/C (5%).

The suspension was stirred under a hydrogen atmosphere for 15 h. The reaction mixture was then filtered through Celite and concentrated to afford the title compound **18** as a white solid in quantitative yield (180.0 mg, 0.64 mmol). Mp (CH_2Cl_2)=69–70 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35–7.10 (m, 9H), 5.37 and 4.63 (AB system, 2H, J=14.4 Hz), 4.01 (dd, 1H, J=6.8, 10.4 Hz), 3.06 (s, 3H), 2.65–2.45 (m, 1H), 2.35–2.15 (m, 2H), 1.90–1.70 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.6, 140.5, 137.6, 135.9, 128.6 (2C), 128.5 (2C), 128.1, 127.5, 126.7, 124.6, 123.3, 77.5, 57.6, 51.3, 35.4, 31.8; IR (neat) 2980, 1667, 1601, 1456, 740 cm^{-1}; EIMS *m/z* (%) 281 (24, $M^{+\bullet}$), 253 (10), 221 (15), 194 (58), 130 (100), 91 (90), 77 (11), 65 (22), 51 (4); HRMS (FAB) *m/z* calcd for $C_{18}H_{20}NO_2$ $(M+H)^+$ 282.1494, found 282.149. Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.66; H, 6.96; N, 4.84%.

3.9. 1-Benzyl-4-methylquinolinium bromide 19

Benzyl bromide (1.1 mL, 9.2 mmol) was added to a solution of lepidine (1 mL, 7.6 mmol) in anhydrous methanol (12 mL). The reaction was heated under reflux with stirring for seven days and then cooled to rt. The solvent was removed in vacuo and the crude white solid was triturated in CH_2Cl_2. The suspension was filtered and the operation was repeated twice to afford the desired salt **19** as a white powder in 74% yield (1.7 g, 5.4 mmol). Mp (CH_3OH)=179–180 °C (lit.[21] mp=181–182 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.39 (d, 1H, J=6.0 Hz), 8.58 (d, 1H, J=8.5 Hz), 8.46 (d, 1H, J=8.5 Hz), 8.16 (t, 1H, J=8.5 Hz), 8.07 (d, 1H, J=6.0 Hz), 8.02 (t, 1H, J=8.5 Hz), 7.42–7.33 (m, 5H), 3.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 149.8, 139.0, 136.6, 134.8, 131.2, 130.7, 130.6 (2C), 130.3, 128.4 (3C), 124.1, 120.8, 61.8, 20.5.

3.10. 1-Benzyl-2-(tribromomethyl)-1,2-dihydro-4-methylquinoline 20

To a solution of the salt **19** (100 mg, 0.32 mmol) in acetonitrile/water (1:1, 1.2 mL) were successfully added, at 0 °C and in the dark, bromoform (86 μL, 0.96 mmol) and an aqueous solution of KOH (540 μL, 52.1 mg, 0.93 mmol). The reaction was stopped when the reaction mixture turned green. The mixture was then extracted with CH_2Cl_2 (2×10 mL), washed with water (1×10 mL) and with brine (1×10 mL). The organic layer was dried ($MgSO_4$) and filtered. The solvent was removed in vacuo and the crude product was purified by silica gel chromatography (eluting with EtOAc/petroleum ether: 70:30) to afford the desired compound **20** as a colored oil in 60% yield (93 mg, 0.19 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70–7.40 (m, 9H), 6.09 (d, 1H, J=6.1 Hz), 5.03 and 5.34 (AB system, 2H, J=16.4 Hz), 4.74 (d, 1H, J=6.1 Hz), 2.23 (s, 3H). The high instability of this compound only permitted the obtention of the ^{1}H NMR spectra.

3.11. 1-Benzyl-5-methoxy-5-methyl-1*H*-benzo[*b*]azepin-2(5*H*)-one 21

An aqueous solution of silver nitrate (110 μL, 66.1 mg, 0.39 mmol) was added to a solution of the compound **20** (63 mg, 0.13 mmol) in MeOH (1.1 mL). The reaction was then stirred in the dark for 4 h. The insoluble salts were filtered off through Celite, rinsed with CH_2Cl_2, and the filtrate was concentrated in vacuo. The crude product was diluted with CH_2Cl_2 (5 mL) and washed with water (2×5 mL) and brine (1×5 mL). The organic layer was dried ($MgSO_4$) and filtered. The solvent was removed in vacuo and the crude product was purified by silica gel chromatography (eluting with EtOAc/petroleum ether: 3:7) to afford the desired compound **21** as a colorless oil in 29% yield (11 mg, 0.04 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.14 (m, 9H), 6.48 (d, 1H, J=11.1 Hz), 6.01 (d, 1H, J=11.1 Hz), 5.10 and 5.37 (AB system, 2H, J=15.5 Hz), 3.09 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 147.3, 140.3, 139.3, 137.8, 128.7 (2C), 128.2, 127.6 (2C), 127.2, 125.2 (2C), 123.6 (2C), 76.4, 53.9, 51.0, 21.6; IR (neat) >3000, 1661, 1612 cm^{-1}; EIMS *m/z* (%) 293 (2, $M^{+\bullet}$), 278 (8), 261 (6), 170 (10), 91 (100); HRMS (EI) *m/z* calcd for $C_{19}H_{19}NO_2$ ($M^{+\bullet}$) 293.1416, found 293.140.

3.12. (+)-2-[(1*R*)-1-Phenethyl]isoquinolinium chloride 22

To a solution of 2-(2,4-dinitrophenyl)isoquinolinium chloride[17] (5 g, 15 mmol) in *n*-BuOH (100 mL) was added (+)-(1*R*)-1-phenylethylamine (1.83 g, 15 mmol), and this mixture was heated under reflux for 15 h. Removal of solvent under reduced pressure left a gum, which was dissolved in water and filtered. The aqueous phase was collected, basified with a few drops of concentrated ammonia, and washed twice with AcOEt in order to remove the remaining 2,4-dinitrophenylamine and the excess of phenylethylamine. Evaporation of water and subsequent filtration through a small column of silica gel (eluting with CH_2Cl_2/MeOH: 4:1) gave salt **22** as a pale pink gum in 84% yield (3.4 g, 12.6 mmol). The spectroscopic data correspond to the one described in the literature.[17a]

3.13. (*S*/*R*)-1-(Tribromoethyl)-1,2-dihydro-2-[(*R*)-1-phenylethyl]isoquinoline 23 and 24

To a solution of the isoquinolinium salt **22** (280 mg, 1.0 mmol) in acetonitrile/water (1:1, 4.5 mL) were successively added bromoform (280 μL, 3.1 mmol) and an aqueous solution of KOH (2.2 mL, 169 mg, 3.0 mmol). The reaction mixture was vigorously stirred for 12 h producing a biphasic mixture. The more dense layer was then diluted in EtOAc (10 mL) and washed with water (2×5 mL) and brine (1×5 mL). The organic layer was then dried ($MgSO_4$) and concentrated in vacuo to afford the two desired diastereomers **23** and **24** (3:1 ratio) as yellow crystals in 93% yield (470 mg, 0.97 mmol). A subsequent fractional crystallization in Et_2O under a nitrogen flow permitted the isolation of each diastereomer. *Compound **23***: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, 2H, J=7.2 Hz), 7.63 (d, 1H, J=7.3 Hz), 7.45–7.32 (m, 4H), 7.22 (td, 1H, J=1.3, 7.6 Hz), 7.10 (d, 1H, J=7.7 Hz), 6.04 (d, 1H, J=7.5 Hz), 5.75 (d, 1H, J=7.5 Hz), 5.36 (s, 1H), 5.03 (q, 1H, J=6.6 Hz), 1.38 (d, 3H, J=6.6 Hz). *Compound **24***: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.34 (m, 2H), 7.11–7.14 (m, 3H), 7.08–7.11 (m, 2H), 6.95–6.98 (m, 2H), 6.80 (d, 1H, J=7.4 Hz), 5.85 (d, 1H, J=7.5 Hz), 5.11 (s, 1H), 5.09 (q, 1H, J=7.0 Hz), 1.80 (d, 3H, J=7.0 Hz). The high instability of these compounds only permitted the obtention of the ^{1}H NMR spectra.

3.14. 1-Methoxy-3-[(*R*)-1-phenylethyl]-1*H*-benzo[*d*]-azepin-2(3*H*)-ones 25 and 26

An aqueous solution of silver nitrate (660 μL, 356.4 mg, 2.1 mmol) was added to a solution of the compound **23** (400 mg, 0.82 mmol) in anhydrous MeOH (8.0 mL). The reaction was then stirred in the dark for 16 h. The insoluble salts were filtered off through Celite, rinsed with CH_2Cl_2, and the filtrate was concentrated in vacuo. The crude product was diluted with CH_2Cl_2 (20 mL) and washed with water (2×10 mL) and brine (1×10 mL). The organic layer was dried ($MgSO_4$) and filtered. The solvent was removed in vacuo and the crude product was purified by silica gel chromatography (eluting with EtOAc/petroleum ether: 10:90) to afford a 1:1 mixture of the diastereomers **25** and **26** as a yellow oil in 34% yield (82 mg, 0.28 mmol). *First diastereomer*: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, 1H, J=7.9 Hz), 7.46 (t, 1H, J=7.3 Hz), 7.31 (t, 1H, J=7.3 Hz), 7.20 (m, 5H), 7.02 (br s, 1H), 6.40 (d, 1H, J=9.3 Hz), 6.18 (d, 1H, J=9.0 Hz), 6.06 (q, 1H, J=7.03 Hz), 4.47 (br s, 1H), 3.56 (s, 3H), 1.67 (d, 3H, J=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 140.5, 133.6, 131.4, 128.8 (2C), 128.5 (3C), 127.3 (2C), 127.0 (2C), 125.3, 117.8, 81.0, 58.2, 52.3, 17.2; IR (neat) 1670 cm^{-1}; EIMS *m/z* (%) 293 (18, $M^{+\bullet}$), 189 (28), 105 (100), 77 (37); HRMS (EI) *m/z* calcd for $C_{19}H_{19}NO_2$ ($M^{+\bullet}$) 293.1416, found 293.141. *Second diastereomer*: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.1–7.7 (m, 9H), 6.47 (d, 1H, J=9.4 Hz), 6.11 (q, 1H, J=7.1 Hz), 6.01 (d, 1H, J=9.2 Hz), 4.34 (br s, 1H), 3.62 (s, 3H), 1.38 (d, 3H, J=7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 139.7, 135.1, 133.9, 130.0, 128.8 (2C), 128.3, 127.9, 127.7 (2C), 127.3, 126.9, 125.2, 118.4, 80.8, 58.4, 51.8, 17.8.

3.15. 2-Benzyl-6,7-dimethoxy-3,4-dihydro-isoquinolinium bromide 28

A solution of 6,7-dimethoxy-3,4-dihydro-isoquinoline[22] (1.6 g, 8.4 mmol) in anhydrous toluene (32 mL) was treated with benzyl bromide (2 mL, 16.7 mmol). The reaction was heated under reflux with stirring for 5 h. The resulting suspension was filtered and the precipitate was washed with anhydrous diethyl ether. The crude solid was dissolved in a minimal amount of methanol and Et_2O was added dropwise leading to precipitation of the product. The product was then filtered, collected to afford the desired pure compound **28** as yellow crystals in 74% yield (2.3 g, 6.3 mmol). Mp (CH_3OH/Et_2O)=192–195 °C (lit.[23] mp=186–188 °C); ^{1}H NMR (300 MHz, CD_3OD) δ 10.3 (s, 1H), 7.67 (s, 1H), 7.58 (m, 2H), 7.36 (m, 3H), 6.84 (s, 1H), 5.50 (s, 2H), 3.91–3.98 (m, 2H), 3.98 (s, 3H), 3.91 (s, 3H), 3.18 (t, 2H, J=8.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 157.6, 148.8, 132.1, 131.4, 129.6, 129.5 (2C), 129.4 (2C), 117.2, 115.9, 110.7, 63.1, 56.8, 56.6, 47.4, 25.6.

3.16. 2-Benzyl-6,7-dimethoxy-1-tribromomehyl-1,2,3,4-tetrahydro-isoquinoline 29

The isoquinolinium salt **28** (2.2 g, 6.17 mmol) was dissolved in acetonitrile/water (1:1, 23 mL). A subsequent addition of bromoform (0.6 mL, 1.87 g, 7.4 mmol) and an aqueous solution of KOH (3.8 mL, 381 mg, 6.8 mmol) led to the formation of a precipitate. The reaction mixture was vigorously stirred for 8 h. The resulting precipitate was filtered, rinsed with water, and dried under high vacuum to afford the desired compound **29** as a white solid in 73% yield (2.4 mg, 4.50 mmol). Mp (CH_3CN/H_2O)=198–199 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.20 (m, 6H), 6.67 (s, 1H), 4.60 (s, 1H), 4.52 and 3.90 (d, 2H, J=13.7 Hz), 3.90 (s, 6H), 3.50–3.35 (m, 1H), 3.30–3.15 (m, 1H), 2.70–2.55 (m, 1H), 2.45–2.30 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.2, 146.4, 138.9, 131.0, 128.6, 128.5, 127.3, 123.0, 115.8, 111.1, 79.0, 63.5, 61.8, 56.3, 55.9, 47.3, 27.7; IR (KBr) 2943, 1517, 1277, 700 cm^{-1}; CIMS *m/z* 532 ($M+H^+$), 452, 374, 282; HRMS (CI^+) *m/z* calcd for $C_{19}H_{21}NO_2\ Br_3$ ($M+H^+$) 531.9123, found 531.912.

3.17. 3-Benzyl-4,5-dihydro-1-hydroxy-7,8-dimethoxy-1*H*-benzo[*d*]azepin-2(3*H*)-one 30

An aqueous solution of silver nitrate (1 mL, 280 mg, 1.68 mmol) was added to a solution of the compound **29** (300 mg, 0.56 mmol) in acetonitrile/water (2:8, 10 mL) cooled to −20 °C. The reaction was then stirred in the dark for 16 h while the temperature was allowed to rise to rt. The insoluble salts were filtered off through Celite, rinsed with CH_2Cl_2, and the filtrate was concentrated in vacuo. The crude product was diluted with CH_2Cl_2 (30 mL) and washed with water (2×20 mL) and brine (1×20 mL). The organic layer was dried ($MgSO_4$) and filtered. The solvent was removed in vacuo and the crude product was purified by silica gel chromatography (eluting with EtOAc/petroleum ether: 7:3) to afford the title compound as a yellow solid in 71% yield (130 mg, 0.40 mmol). Mp (AcOEt/hexanes)=131–132 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.35–7.15 (m, 5H), 6.49 (s, 1H), 5.76 (d, 1H, J=5.8 Hz), 4.84 and 4.53 (AB system, 2H, J=14.8 Hz), 4.55 (d, 1H, J=5.8 Hz), 4.10–3.90 (m, 1H), 3.91 (s, 3H), 3.82 (s, 3H), 3.40–3.25 (m, 1H), 3.10–2.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 148.1, 147.7, 136.6, 128.8 (2C), 128.6, 128.1 (2C), 127.9, 125.5, 112.9, 108.3, 67.9, 56.0 (2C), 50.9, 45.2, 31.4; IR (KBr) 3405, 1656, 1513, 1261, 1119 cm^{-1}; EIMS *m/z* (%) 327 (36, $M^{+\bullet}$), 297 (43), 206 (24), 91 (100), 77 (9), 65 (12); HRMS (EI) *m/z* calcd for $C_{19}H_{21}NO_4$ ($M^{+\bullet}$) 327.1471, found 327.147.

3.18. 3-Benzyl-4,5-dihydro-1,7,8-trimethoxy-1*H*-benzo[*d*]azepin-2(3*H*)-one 31

An aqueous solution of silver nitrate (1 mL, 280 mg, 1.68 mmol) was added to a solution of the compound **29** (300 mg, 0.56 mmol) in MeOH (10 mL) cooled to −20 °C. The reaction was then stirred in the dark for 16 h while the temperature was allowed to rise to rt. The insoluble salts were filtered off through Celite, rinsed with CH_2Cl_2, and the filtrate was concentrated in vacuo. The crude product was diluted with CH_2Cl_2 (30 mL) and washed with water (2×20 mL) and brine (1×20 mL). The organic layer was dried ($MgSO_4$) and filtered. The solvent was removed in vacuo and the crude product was purified by silica gel chromatography (eluting with EtOAc/petroleum ether: 30:70) to afford the title compound as a yellow oil in 52% yield (99.4 mg, 0.29 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.25 (m, 5H), 6.95 (s, 1H), 6.52 (s, 1H), 5.02 (s, 1H), 4.76 and 4.58 (AB system, 2H, J=14.7 Hz), 4.26–4.32 (m, 1H), 3.90 (s, 3H), 3.82 (s, 3H), 3.55 (s, 3H),

3.48–3.41 (m, 1H), 2.94–2.81 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 149.2, 147.4, 137.6, 129.1, 128.7 (2C), 128.3 (2C), 127.6, 125.0, 113.5 (2C), 85.6, 57.8, 56.1, 56.0, 50.4, 43.7, 32.4; IR (KBr) 2933, 1653, 1517, 1456, 1251 cm^{-1}; EIMS *m*/*z* (%) 341 (65, $M^{+\bullet}$), 309 (17), 282 (36), 250 (79), 177 (35), 91 (100); HRMS (EI) *m*/*z* calcd for $C_{20}H_{23}NO_4$ ($M^{+\bullet}$) 341.1627, found 341.163.

3.19. 3-Benzyl-4,5-dihydro-7,8-dimethoxy-3*H*-benzo-[*d*]azepine-1,2-dione 32

An aqueous solution of silver nitrate (132 μL, 185 mg, 1.1 mmol) and a solution of $EtNH_2$ in THF (2 M, 1.9 mL, 3.7 mmol) were added to a solution of the compound **29** (200 mg, 0.37 mmol) in anhydrous THF (6 mL). The reaction was then stirred in the dark for 16 h. The insoluble salts were filtered off through Celite, rinsed with CH_2Cl_2, and the filtrate was concentrated in vacuo. The crude product was diluted with CH_2Cl_2 (20 mL) and washed with water (2×15 mL) and brine (1×15 mL). The organic layer was dried ($MgSO_4$) and filtered. The solvent was removed in vacuo and the crude product was purified by silica gel chromatography (eluting with EtOAc/petroleum ether: 1:1) to afford the title compound **32** as yellow crystals in 50% yield (60 mg, 0.185 mmol). Mp (AcOEt/hexanes)=221–222 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.20 (m, 6H), 6.52 (s, 1H), 4.65 (s, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.57 (m, 2H), 2.90 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.1, 167.3, 153.4, 148.2, 136.3, 135.6, 128.9 (2C), 128.6 (2C), 128.1, 126.7, 112.1 (2C), 56.1 (2C), 49.3, 45.5, 31.5; IR (KBr) 3100–2850, 1677, 1653, 1258 cm^{-1}; CIMS *m*/*z* 343 [(M+18)$^+$]; HRMS (EI) *m*/*z* calcd for $C_{19}H_{19}NO_4$ ($M^{+\bullet}$) 325.1314, found 325.132.

3.20. 3-Benzyl-1-(ethylimino)-4,5-dihydro-7,8-dimethoxy-1*H*-benzo[*d*]azepin-2(3*H*)-one 33

An aqueous solution of silver nitrate (132 μL, 185 mg, 1.1 mmol) and a solution of $EtNH_2$ in THF (2 M, 1.9 mL, 3.7 mmol) were added to a solution of the compound **29** (200 mg, 0.37 mmol) in anhydrous THF (6 mL) cooled to −20 °C. The reaction was then stirred in the dark for 72 h while the temperature was allowed to warm up to rt. The insoluble salts were filtered off through Celite, rinsed with CH_2Cl_2, and the filtrate was concentrated in vacuo. The crude product was diluted with CH_2Cl_2 (15 mL) and washed with water (2×15 mL) and brine (1×15 mL). The organic layer was dried ($MgSO_4$) and filtered. The solvent was removed in vacuo and the crude product was purified by silica gel chromatography (eluting with EtOAc/petroleum ether: 3:2) to afford the title compound **33** as a colorless oil in 3.2% yield (4.2 mg, 0.012 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.19 (m, 6H), 6.61 (s, 1H), 4.68 (s, 2H), 3.93 (s, 3H), 3.90 (s, 3H), 3.51 (m, 2H), 3.23 (q, 2H, *J*=7.2 Hz), 2.95 (m, 2H), 1.12 (t, 3H, *J*=7.2 Hz).

3.21. X-ray crystallographic study

Crystals of **24** used for X-ray diffraction analysis were grown at rt from **24**. A single crystal was glued at the tip of a Lindemann capillary by means of a solvent-free glue. The intensity measurement was carried out at rt on a Bruker-Nonius Kappa CCD diffractometer, using graphite-monochromatized Mo K-$L_{2,3}$ radiation (λ=0.71073 Å). Data were corrected for Lorentz-polarization effects and absorption corrections applied using a Gaussian integration. The structure was solved with the SIR2004 direct methods[24] and subsequent calculations were carried out with the JANA2006 program package.[25] All non-hydrogen atoms were refined anisotropically and hydrogen atoms were introduced with geometrical constraints and riding atomic displacement parameters. The absolute configuration was unambiguously determined by refining the inversion twin ratio.

CCDC 651575 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystal data for ***24***: $C_{18}H_{16}Br_3N$, M_r=486, monoclinic, $P2_1$, a=13.4635(5), b=6.1104(3), c=11.2325(6) Å, β=108.267(4), V=877.50(7) Å^3, Z=2, ρ_{calcd}=1.83894 g cm^{-3}, μ=6.892 mm^{-1}, F(000)=472, colorless needle, 0.32×0.08×0.06 mm^3, $2\theta_{max}$=60°, T=298 K, 20,995 reflections, 4563 unique (99% completeness), R_{int}=0.064, 198 parameters, GOF=1.64, *wR*2=0.0969, R=0.0397 for 3957 reflections with $I>2\sigma(I)$.

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References and notes

1. Schultz, C.; Link, A.; Leost, M.; Zaharevitz, D. W.; Gussio, R.; Sausville, E. A.; Meijer, L.; Kunick, C. *J. Med. Chem.* **1999**, *42*, 2909–2919.
2. (a) Blaser, H. U.; Boyer, S.; Pittelkow, U. *Tetrahedron: Asymmetry* **1991**, *2*, 721–732; (b) Boyer, S. K.; Pfund, R. A.; Portmann, R. E.; Sedelmeier, G. H.; Wetter, H. F. *Helv. Chim. Acta* **1988**, *71*, 337–343; (c) Watthey, J. W. H.; Stanton, J. L.; Desai, M.; Babiarz, J. E.; Finn, B. M. *J. Med. Chem.* **1985**, *28*, 1511–1516.
3. (a) Zheng, N.; Armstrong, J. D., III; Eng, K. K.; Keller, J.; Liu, T.; Purick, R.; Lynch, J.; Hartner, F. W.; Frederick, W.; Volante, R. P. *Tetrahedron: Asymmetry* **2003**, *14*, 3435–3446; (b) DeVita, R.; Bochis, R.; Frontier, A. J.; Kotliar, A.; Fisher, M. H.; Schoen, W. R.; Wyvratt, M. J.; Cheng, K.; Chan, W. W.-S.; Butler, B.; Smith, R. G.; Jacks, T. M.; Hickey, G.; Schleim, K. D.; Leung, K.; Chen, Z.; Chiu, S.-H. L.; Feeney, W. P.; Cunningham, P. K. *J. Med. Chem.* **1998**, *41*, 1716–1728; (c) Hansen, T. H.; Thøgersen, H.; Hansen, B. S. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2951–2954; (d) Ok, H. O.; Szumiloski, J. L.; Doldouras, G. A.; Schoen, W. R.; William, R.; Cheng, K.; Chan, W. W. S.; Butler, B.; Smith, R. G.; Fisher, M. H.; Wyvratt, M. J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 3051–3056; (e) Bhupathy, M. B.; McNamara, J. J.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 9445–9448; (f) Wells, K. M.; Rossen, K.; Askin, D.; Hartner, F. W., Jr.; Volante, R. P.; Reider, P. J. *Synth. Commun.* **1995**, *25*, 2197–2202; (g)

Schoen, W. R.; Pisano, J. M.; Prendergast, K.; Wyvratt, M. J., Jr.; Fisher, M. H.; Cheng, K.; Chan, W. W.-S.; Butler, B.; Smith, R. G.; Ball, R. G. *J. Med. Chem.* **1994**, *37*, 897–906.

4. (a) Das, J.; Floyd, D. M.; Kimball, D. S.; Duff, K. J.; Truc, C. V.; Lago, M. W.; Moquin, R. V.; Lee, V. G.; Gougoutas, J. Z.; Malley, M. F.; Moreland, S.; Brittain, R. J.; Hedberg, S. A.; Cucinotta, G. G. *J. Med. Chem.* **1992**, *35*, 773–780; (b) Das, J.; Floyd, D. M.; Kimball, D. S.; Duff, K. J.; Lago, M. W.; Krapcho, J.; White, R.; Ridgewell, R.; Obermeier, M. T.; Moreland, S.; McMullen, D.; Normandin, D.; Hedberg, S. A.; Schaeffer, T. *J. Med. Chem.* **1992**, *35*, 2610–2617.
5. Ho, J. Z.; Gibson, T. S.; Semple, J. E. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 743–748.
6. (a) Bisi, A.; Rampa, A.; Budriesi, R.; Gobbi, S.; Belluti, F.; Ioan, P.; Valoti, E.; Chiarini, A.; Valenti, P. *Bioorg. Med. Chem. Lett.* **2003**, *11*, 1353–1361; (b) *Drugs Future* **1997**, *22*, 933–934.
7. Lewis, H. D.; Pérez Revuelta, B. I.; Nadin, A.; Neduvelil, J. G.; Harrison, T.; Pollack, S. J.; Shearman, M. S. *Biochemistry* **2003**, *42*, 7580–7586.
8. For reviews, see: (a) Kantorowski, E. J.; Kurth, M. J. *Tetrahedron* **2000**, *56*, 4317–4353; (b) Molander, G. A. *Acc. Chem. Res.* **1998**, *31*, 603–609.
9. (a) Zheng, L.; Xiang, J.; Bai, X. *J. Heterocycl. Chem.* **2006**, *43*, 321–324; (b) Koseki, Y.; Ozawa, H.; Kitahara, K.; Kato, I.; Sato, H.; Fukaya, H.; Nagasaka, T. *Heterocycles* **2004**, *63*, 17–22; (c) Koseki, Y.; Katsura, S.; Kusano, S.; Sakata, H.; Sato, H.; Monzene, Y.; Nagasaka, T. *Heterocycles* **2003**, *59*, 527–540; (d) Li, W.-D. Z.; Wang, Y.-Q. *Org. Lett.* **2003**, *5*, 2931–2934; (e) Koseki, Y.; Sato, H.; Watanabe, Y.; Nagasaka, T. *Org. Lett.* **2002**, *4*, 885–888; (f) Koseki, Y.; Kusano, S.; Sakata, H.; Nagasaka, T. *Tetrahedron Lett.* **1999**, *40*, 2169–2172; (g) Blasko, G. *Acta Chim. Hung.* **1991**, *128*, 819–822; (h) Pfister, J. R. *Heterocycles* **1986**, *24*, 2099–2103.
10. To the best of our knowledge it was solely reported that the dichlorocyclopropyl adduct resulting from the action of dichlorocarbene onto a 1,2-dihydroisoquinoline could be converted to a 1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-one on treatment with water in ca. 50–60% yield (cyclopropanation–ring enlargement process). Khlebnikov, A. F.; Nikiforova, T. Y.; Novikov, M. S.; Kostikov, R. R. *Russ. J. Org. Chem.* **1997**, *33*, 885–895.
11. Aspects of this work have been previously disclosed: (a) Pauvert, M.; Dupont, V.; Guingant, A. *Synlett* **2002**, 1350–1352; (b) Pauvert, M.; Collet, S.; Guingant, A. *Tetrahedron Lett.* **2003**, *44*, 4203–4206.
12. (a) Marek, R.; Seckarova, P.; Hulova, D.; Marek, J.; Dostal, J.; Sklenar, V. *J. Nat. Prod.* **2003**, *66*, 481–486; (b) Grignon-Dubois, M.; Diaba, F.; Grellier-Marly, M.-C. *Synthesis* **1994**, 800–804; (c) Maeda, M. *Chem. Pharm. Bull.* **1990**, *38*, 2577–2580; (d) Gündel, W. H.; Berenbold, H. J. *Ann.* **1978**, 1536–1539; (e) Duchardt, K. H.; Kröhnke, F. *Chem. Ber.* **1977**, *110*, 2669–2679.
13. Katritzky, A. R.; Millet, G. H.; Noor, H. M.; Yates, F. S. *J. Org. Chem.* **1978**, *43*, 3957–3960.
14. Kröhnke, F.; Dickhäuser, H.; Vogt, I. *Ann.* **1961**, *644*, 93–108.
15. Compound **11** was formed along with ca. 10% of the 1,4-addition product.
16. For reviews, see: (a) Cossy, J.; Gomez Pardo, D. *Targets in Heterocyclic Systems: Chemistry and Properties*; Società Chimica Italiana: Rome, 2002; Vol. 6, pp 1–26; (b) Cossy, J.; Gomez Pardo, D. *Chemtracts: Org. Chem.* **2002**, *15*, 1–28; For a recent communication, see: Mena, M.; Bonjoch, J.; Gomez Pardo, D.; Cossy, J. *J. Org. Chem.* **2006**, *71*, 5930–5935.
17. (a) Barbier, D.; Marazano, C.; Das, B. C.; Potier, P. *J. Org. Chem.* **1996**, *61*, 9596–9598; (b) Génisson, Y.; Marazano, C.; Mehmandoust, M.; Gnecco, D.; Das, B. C. *Synlett* **1992**, 431–434.
18. Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860.
19. We thank Prof. J. Lebreton for suggesting us this control experiment.
20. Lee, I. S. H.; Lee, C. K.; Han, I. S. *Org. Prep. Proced. Int.* **1988**, *20*, 302–305.
21. Gutsulyak, B. M.; Chuchina, V. N. *Khim. Geterot. Soedin.* **1979**, *11*, 1505–1507.
22. Warrener, R. N.; Liu, L.; Russell, R. A. *Tetrahedron* **1998**, *54*, 7485–7496.
23. (a) Beaumont, D.; Waigh, R. D.; Sunbhanich, M.; Nott, M. W. *J. Med. Chem.* **1983**, *26*, 507–515; (b) Chapman, J. H.; Holton, P. G.; Ritchie, A. C.; Walker, T.; Webb, G. B.; Whiting, K. D. E. *J. Chem. Soc.* **1962**, 2471–2479.
24. Burla, M. C.; Caliandro, R.; Camalli, M.; Carrozzini, B.; Cascarano, G. L.; De Caro, L.; Giacovazzo, C.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **2005**, *38*, 381–388.
25. Petricek, V.; Dusek, M.; Palatinus, L. *JANA2006, The Crystallographic Computing System*; Institute of Physics, Academy of Sciences of the Czech Republic: Prague, Czech Republic, 2006.