A Synthesis of 3-Phenyl-1,2,3,4-tetrahydroisoquinoline and 2-Phenyl-1,2,4,5-tetrahydro-3*H*-3-benzazepine *via* Pummerer-Type Cyclization: Enhancing Effect of Boron Trifluoride Diethyl Etherate on the Cyclization

Toshiaki SAITOH, Tsuyoshi ICHIKAWA, Yoshie HORIGUCHI, Jun TODA, and Takehiro SANO*

Showa Pharmaceutical University, 3–3165, Higashi-tamagawagakuen, Machida, Tokyo 194–8543, Japan.
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A synthesis of 6,7-dimethoxy-3-phenyl-1,2,3,4-tetrahydroisoquinoline (14a) and 7,8-dimethoxy-2-phenyl-1,2,4,5-tetrahydro-3*H*-3-benzazepine (14b) was achieved *via* the cyclization of *N*-(3,4-dimethoxyphenyl)methyl-1-phenyl-2-(phenylsulfinyl)ethylformamide (6a) and *N*-2-(3,4-dimethoxyphenyl)ethyl-1-phenyl-2-(phenylsulfinyl)-ethylformamide (6b) using the Pummerer reaction as a key step, respectively. The Pummerer reaction of 6a,b under usual conditions using trifluoroacetic anhydride yielded the vinyl sulfides (8a, b), non-cyclized products, as a major product. The cyclization proceeded when boron trifluoride diethyl etherate was used as an additive reagent, thus giving rise to the corresponding cyclized products (7a) and (7b) in moderate yields. We propose that the enhancing effect of the Lewis acid on the cyclization may be attributable to the involvement of a dicationic intermediate, sulfonium-carbenium dication (23).

Key words 1,2,3,4-tetrahydroisoquinoline; 1,2,4,5-tetrahydro-3*H*-3-benzazepine; Pummerer reaction; boron trifluoride diethyl etherate; sulfonium-carbenium dication

In a series of papers we reported the syntheses of 1,2,3,4-tetrahydroisoquinolines,[1] 1,2,3,4-tetrahydroquinolines,[2] 2,3,4,5-tetrahydro-1*H*-3-benzazepines,[3] 2-quinolones,[4] erythrinan,[5] homoerythrinan,[6] isopavine and pavine alkaloids[7] using an aromatic cyclization of the sulfonium ion *in situ* formed from a sulfinyl precursor (Pummerer reaction). The aromatic cyclization in the reaction using trifluoroacetic anhydride (TFAA) smoothly proceeded at room temperature when the reactive center of the cyclizing benzene ring was activated by an electron-donating group. Furthermore, we found that the Pummerer substrate, which lacks an electron-donating group on the cyclizing benzene ring, requires boron trifluoride diethyl etherate ($BF_3 \cdot Et_2O$) as an additive reagent to induce the aromatic cyclization.[1,2] Thus, the investigations demonstrated that the Pummerer-type cyclization reaction is highly effective and widely applicable for the construction of six- and seven-membered nitrogen heterocycles.

In order to expand the utility of this methodology, we designed a synthesis of 1,2,3,4-tetrahydroisoquinoline and 1,2,4,5-tetrahydro-3*H*-3-benzazepine derivatives bearing a phenyl group on the nitrogen-containing ring. The compounds are expected to have some biological activities. For example, 3-substituted 1,2,3,4-tetrahydroisoquinolines are known to possess phencyclidine-like effects.[8]

Although the synthesis of 2-substituted 3-benzazepine derivatives was achieved by multi-steps using a ring expansion reaction of 1-substituted 1,2,3,4-tetrahydroisoquinoline derivatives as a key step,[9] a simple and short-step method has not been developed. The route *via* the Pummerer-type cyclization reaction shown in Chart 1 should provide a convenient method for preparing nitrogen heterocycles bearing a phenyl group because all the starting materials are readily available.

Results and Discussion

N-Formyl sulfoxides (**6a, b**), substrates of the Pummerer reaction, were prepared from (3,4-dimethoxyphenyl)methylamine (**1a**) and (3,4-dimethoxyphenyl)ethylamine (**1b**) as follows (Chart 2). Condensation of **1a**, **b** with phenylsulfanylacetophenone (**2**) in titanium (IV) isopropoxide[10] followed by $NaBH_4$ reduction of the resulting imines (**3a**, **b**) afforded the secondary amines (**4a**, **b**) in good yields. Formylation of **4a**, **b** and then oxidation of the resulting *N*-formate (**5a**, **b**) with sodium metaperiodate produced **6a**, **b** in good overall yields. All the products were characterized by MS, IR, and ^{1}H- and ^{13}C-NMR spectra (see Experimental).

Pummerer Reaction

The sulfoxide (**6a**) on treatment with TFAA in benzene at room temperature yielded two products, a vinyl sulfide (**8a**) as a major product (53%) and a 1,2,3,4-tetrahydroisoquinoline (**7a**) as a minor one (12%). The relative stereochemistry of the C3-phenyl and C4-SPh groups of **7a** was determined as *trans* by the ^{1}H-NMR spectral analysis. The spectrum exhibits complex signals attributable to the rotational isomerism of the N–CO bond. However, the pair of doublets appearing at δ 4.51 with J=16 Hz and δ 5.11 with J=17 Hz can be assigned to the C3-H, and the other pair of doublets at δ 4.00 with J=17 Hz and δ 4.17 with J=16 Hz to the C4-H. The large coupling constants indicated that the protons of C3 and C4 are arranged in *trans*-diaxial orientation. Thus, the C–C bond formation of **6a** proceeded in a highly stereo-selective manner.

The result obtained by the reaction of **6a** is in strong contrast to that of the Pummerer substrate lacking the phenyl group, *N*-(3,4-dimethoxyphenyl)methyl-2-(phenylsulfinyl)ethylformamide (**11**), which underwent the cyclization to give

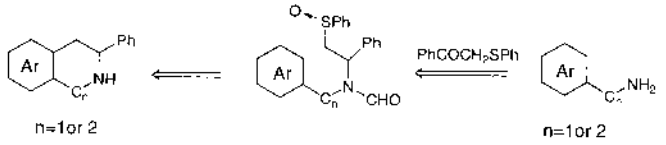

Chart 1

* To whom correspondence should be addressed. e-mail: t-sano@ac.shoyaku.ac.jp

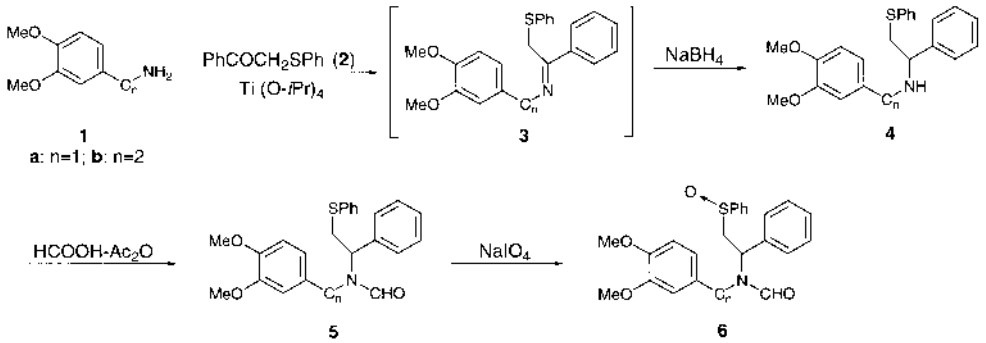

Chart 2

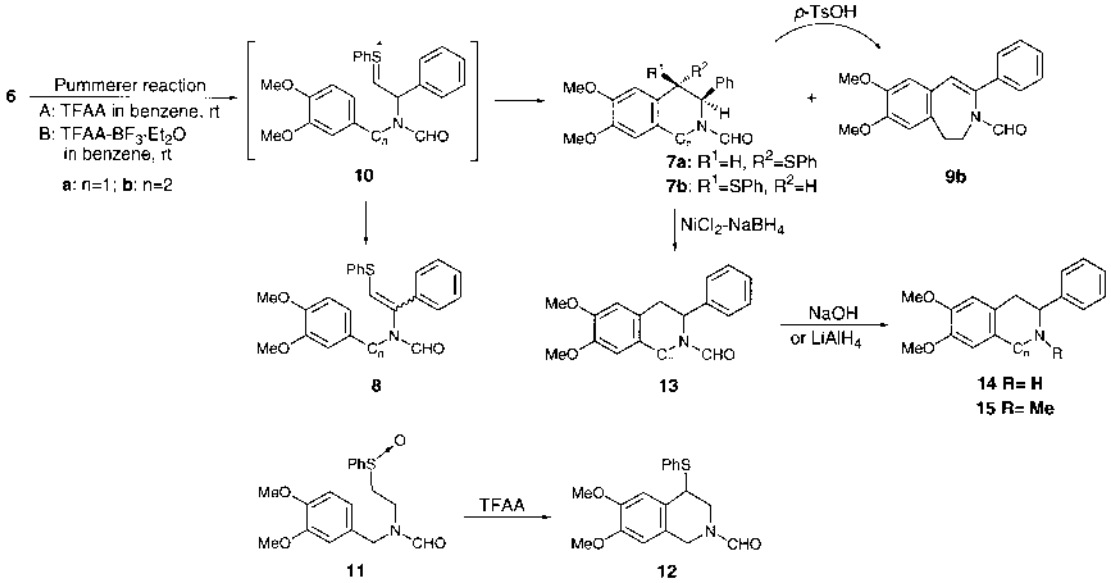

Chart 3

the 1,2,3,4-tetrahydroisoquinoline (**12**) in a quantitative yield.[1a] The undesired result, however, was improved when $BF_3 \cdot Et_2O$ was used as an additive reagent of the Pummerer reaction. That is, the sulfoxide (**6a**) was treated with TFAA in benzene at room temperature for 5 min, and then $BF_3 \cdot Et_2O$ was added to this solution. This mixture was allowed to react for a further 3 h at room temperature. Thus, the reaction produced **7a** in 62% yield, although **8a** still accompanied it as a minor product (3%).

The sulfoxide (**6b**), a homologous substrate of **6a**, when treated with TFAA in benzene at room temperature for 5.5 h, only produced the vinyl sulfide (**8b**) in 46% yield. No benzazepine derivative was obtained. However, this situation also changed when $BF_3 \cdot Et_2O$ was used as an additive reagent as described above. Thus, the sulfoxide (**6b**) underwent the cyclization to give 2-phenyl-1-phenylsulfanyl-3-benzazepine (**7b**) in 46% yield and 2-phenyl-4,5-dihydro-3-benzazepine (**9b**) in 8% yield. The relative stereochemistry of the C1-SPh and C2-phenyl groups of **7b** was determined as *cis* by the ^{1}H-NMR spectral analysis. The spectrum also exhibits complex signals attributable to the rotational isomerism of the N–CO bond. But the pair of doublets appearing at δ 4.48 with J=4.3 Hz and δ 4.93 with J=3.6 Hz can be assigned to the C1-H, and the other pair of doublets at δ 4.73 with J=4.3 Hz and δ 5.04 with J=3.6 Hz to the C2-H. The small coupling constants indicated that the protons of C1 and C2 are arranged in *cis* orientation. Thus, the C–C bond formation of **6b** also proceeded in a highly stereo-selective manner, which produced a stereochemical result different from that of **6a**. The compound (**7b**), on treatment with *p*-toluenesulfonic acid (*p*-TsOH) in benzene under heating for 1 h, gave **9b** in good yield, thus proving that **9b** is an elimination product of the phenylsulfanyl group from **7b**.

Reductive removal of the phenylsulfanyl group of **7a**, **b** proceeded on treatment with $NiCl_2$–$NaBH_4$ in MeOH–THF to give *N*-formyl derivatives (**13a**, **b**) in good yields. Deprotection of the *N*-formyl group was readily achieved by conventional methods. Alkaline hydrolysis of **13a**, **b** gave the 3-phenyl-1,2,3,4-tetrahydroisoquinoline (**14a**) and the 2-phenyl-3-benzazepine (**14b**), respectively. Reduction of **13a**, **b** with $LiAlH_4$ gave the corresponding *N*-methyl derivatives (**15a**, **b**), respectively.

The results clearly demonstrated that the reaction induced two irreversible pathways, the cyclization or the double bond migration, *via* the initially formed sulfonium ion (**10**) in a competitive manner (Chart 3). The phenyl group present at β position of the phenylsulfinyl group facilitated the double bond migration of **10** into **8** since the double bond is stabilized by conjugation with the phenyl group. As a result, the reaction retarded the aromatic cyclization leading to either

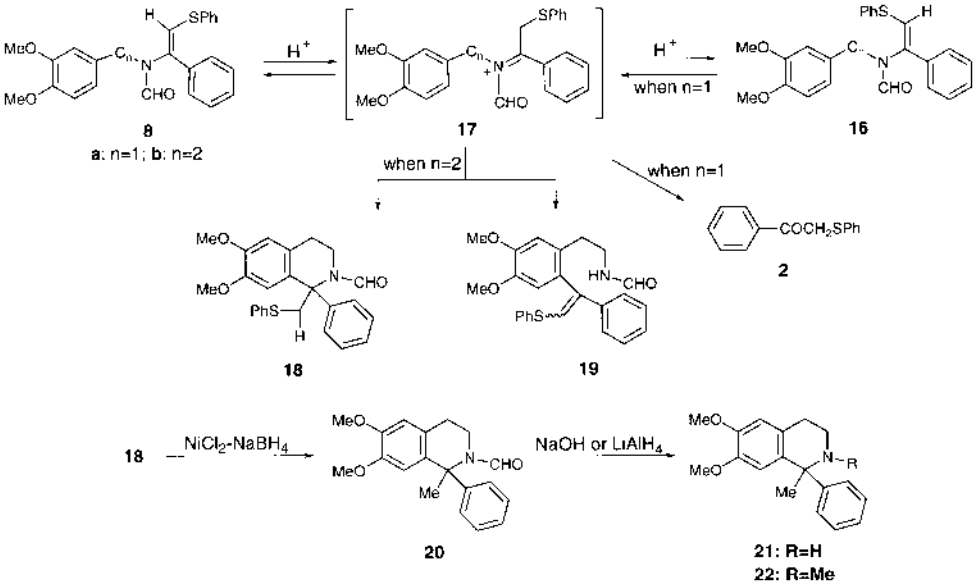

Chart 4

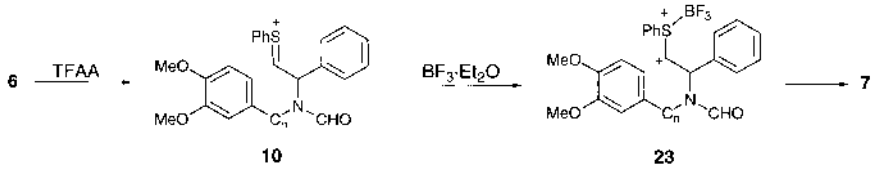

Chart 5

isoquinoline ring or benzazepine ring.

To examine whether the cyclized products (**7**) are formed through the corresponding vinyl sulfides (**8**) under the acidic conditions, we carried out acid-catalyzed reactions of **8** (Chart 4). Treatment of **8a** or **8b** with $BF_3 \cdot Et_2O$ in benzene at room temperature (the Pummerer reaction condition) for 24 h did not induce any reaction and the starting material was recovered almost quantitatively. Treatment of **8a** with *p*-TsOH in benzene under reflux yielded two products, an isomeric vinyl sulfide (**16a**) (50%) and **2** (36%), with recovery of the starting vinyl sulfide (**8a**) (6%). Compound **7a** was not yielded to any extent.

The vinyl sulfide (**8b**) on similar treatment with *p*-TsOH in benzene under reflux, produced the 1,2,3,4-tetrahydroisoquinoline derivative (**18**) (21%) and the seco-product (**19**) (53%), with recovery of the starting vinyl sulfide (**8b**) (21%). Neither benzazepine (**7b**) nor the isomeric vinyl sulfide (**16b**) was formed in this reaction. The structure of **18** was confirmed by the conversion to the 1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**21**)[11] by reductive elimination of the phenylsulfanyl group followed by hydrolysis of **20**. $LiAlH_4$ reduction of **20** yielded the corresponding *N*-methyl derivative (**22**). Thus, the results clearly demonstrated that the cyclized products (**7**) were not produced *via* the acid-catalyzed cyclization reaction of **8**.

The acid-catalyzed reactions of **8** are rationalized in terms of the intervention of immonium ions (**17**). The *E–Z* isomerization between **8a** and **16a** apparently occurs *via* the intermediate (**17a**). Compound **2** is produced by hydrolysis of the immonium moiety of **17a**. The aromatic cyclization of **17a** may be prohibited by steric hindrance since the anticipated cyclized product is a congested isoindole derivative with bulky groups. On the other hand, the immonium ion (**17b**) generated from **8b** induced a cyclization reaction different from the Pummerer-type cyclization to give the 1,2,3,4-tetrahydroisoquinoline derivative (**18**). The steric congestion in **19** due to two bulky substituents positioned at C-1 probably causes the ring cleavage to give the seco-derivative (**19**) as shown in Chart 4.

The stereo-structures of the vinyl sulfide (**8a**) and its geometric isomer (**16a**) were deduced as follows. The compound (**8a**) is a kinetic product of the Pummerer reaction since this was formed exclusively from the sulfonium ion (**10a**). On the other hand, the isomer (**16a**) is a thermodynamic product of the acid-catalyzed *E–Z* isomerization reaction since **8a** and **16a** are equilibrated in favor of the latter isomer. The heat of formation calculated by MNDO-PM3 showed that the *Z*-form (−5.12720 kcal/mol) is more stable than the corresponding *E*-form (−4.02976 kcal/mol), thus the stereo-structure of **8a** and **16a** was assigned as *E*-and *Z*-form, respectively.

Finally, we wish to discuss the role of $BF_3 \cdot Et_2O$ on the Pummerer-type cyclization reaction (Chart 5). This and previous results of our investigations[1a—d,2,3] showed that the Lewis acid of the additive reagent dramatically enhanced the cationic cyclization in the Pummerer reaction, in particular, when the nucleophilic benzene ring is not activated by the electron-donating group. This situation is reminiscent of superacid-catalyzed Friedel–Craft[12] and Pictet–Spengler reactions[13] reported by Shudo and his collaborators. In their kinetic studies, they clearly proved that the acceleration in the superacid-catalyzed reactions can be attributed to the in-

volvement of dicationic intermediates, and revealed that the true electrophiles inducing the cyclizations are dicationic super-electrophiles.

Thus, as a possible pathway we postulate that the $BF_3 \cdot Et_2O$-catalyzed cyclization of the Pummerer reaction can involve a dicationic intermediate. For example, the sulfonium-carbenium dication (**23**) can be generated by the coordination of the Lewis acid to the cationic sulfur atom of the sulfonium ion (**10**). The dicationic species that can act as a super-electrophile may be a true electrophile in the $BF_3 \cdot Et_2O$-catalyzed cyclization of the Pummerer reaction. Mechanistic studies of this cyclization are now under way.

Experimental

General Notes Unless otherwise noted, the following procedures were adopted. Melting points were taken on a YANACO SP-M1 hot-stage melting point apparatus and are uncorrected. IR spectra were obtained as films for oils and gums, and KBr disks for solids with a HORIBA FT-710 spectrophotometer, and are given in cm^{-1}. NMR spectra were measured on a JEOL JNM-AL 300 (^1H, 300 MHz; ^{13}C, 75 MHz) or a JEOL JNM-α500 (^1H, 500 MHz; ^{13}C, 125 MHz) spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard, and the chemical shifts are given in δ values. LR-EIMS was obtained with a JEOL JMS-AM20 at 70 eV using a direct inlet system, and figures in parentheses indicate the relative intensities. HR-EIMS was taken on a JEOL JMS-D300 spectrometer at 70 eV using a direct inlet system. HR-FABMS was measured with a JEOL JMS-HX110A spectrometer (reactant gas: xenon, matrix: glycerol). Elemental analysis was recorded on a YANACO CHN Corder MT-3. The organic extract from each reaction mixture was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to dryness.

Materials Pre-coated silica gel glass plates [Merck Silica gel, Art5715] were used for analytical thin layer chromatography (TLC). Wakogel C-200 was used for column chromatography. 1-Phenylsulfanylacetophenone (**2**) was prepared according to the known method from phenacyl bromide and diphenyl disulfide.[14]

Preparation of 4a. Typical Procedure A mixture of **1a** (9 g, 53.9 mmol), **2** (12.3 g, 53.9 mmol), and titanium (IV) isopropoxide (20 g, 81 mmol) was heated at 80 °C for 3 h under an argon atmosphere. After cooling, the reaction mixture was diluted with MeOH (100 ml). To this solution, $NaBH_4$ (2 g, 53.9 mmol) was added in small portions under ice-cooling. The reaction mixture was stirred at room temperature for 1 h and concentrated *in vacuo*. Water (*ca*. 40 ml) was added to the residue, and the mixture was diluted with MeOH (*ca*. 500 ml). After removal of precipitated inorganic materials by filtration, the filtrate was concentrated *in vacuo*. The residue was dissolved in water and extracted with $CHCl_3$. Column chromatography of the product with hexane/ethyl acetate (6 : 1) gave **4a** (16 g, 79%) as a yellow gum.

***N*-(3,4-Dimethoxyphenyl)methyl-(1-phenyl-2-phenylsulfanyl)ethylamine (4a)** IR (film): 3309, 1513. ^1H-NMR: 1.96 (1H, br s, >NH), 2.8—4.1 (5H, m, $ArCH_2$–, $PhSCH_2CH<$), 3.84 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.77 (3H, s, ArH), 7.0—7.5 (10H, m, PhH×2). ^{13}C-NMR: 42.5 (t), 51.0 (t), 55.8 (q), 55.9 (q), 60.3 (d), 111.2 (d), 111.5 (d), 120.1 (d), 126.3 (d), 127.3 (d×2), 127.6 (d), 128.6 (d×2), 128.9 (d×2), 129.9 (d×2), 132.9 (s), 135.6 (s), 142.6 (s), 148.0 (s), 148.9 (s). HR-EIMS *m/z* (M^+): Calcd for $C_{23}H_{25}NO_2S$: 379.1607. Found: 379.1645.

***N*-2-(3,4-Dimethoxyphenyl)ethyl-1-phenyl-(2-phenylsulfanyl)ethylamine (4b)** From **1b** (4.76 g, 26.3 mmol) and **2** (6.0 g, 26.3 mmol); column chromatography (hexane/ethyl acetate 6 : 1) gave **4b** (8.92 g, 86%) as a yellow gum. IR (film): 3297, 1589, 1515. ^1H-NMR: 1.78 (1H, br s, >NH), 2.5—3.4 (6H, m, $ArCH_2CH_2$–, $PhSCH_2CH<$), 3.68 (1H, dd, J=4, 9 Hz, $PhSCH_2CH<$), 3.84 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 6.6—6.9 (3H, m, ArH), 7.2—7.3 (10H, m, PhH×2). ^{13}C-NMR: 35.7 (t), 42.3 (t), 48.9 (t), 55.7 (q), 55.9 (q), 61.5 (d), 111.3 (d), 112.0 (d), 120.6 (d), 126.3 (d), 127.1 (d×2), 127.4 (d), 128.4 (d×2), 128.8 (d×2), 129.9 (d×2), 132.6 (s), 135.5 (s), 142.6 (s), 147.4 (s), 148.9 (s). HR-FABMS *m/z* (MH^+): Calcd for $C_{24}H_{28}NO_2S$: 394.1841. Found: 394.1819.

Formylation of 4a. Typical Procedure To a solution of **4a** (15.8 g, 41.7 mmol) in formic acid (20 ml) was slowly added at 0 °C the mixed anhydride prepared from formic acid (50 ml) and acetic anhydride (66 ml), and then the mixture was heated at 60 °C for 1 h. The reaction mixture was concentrated *in vacuo* and extracted with $CHCl_3$. The residue was chromatographed with hexane/ethyl acetate (3 : 1) to give **5a** (16.4 g, 96%) as a pale yellow gum.

***N*-(3,4-Dimethoxyphenyl)methyl-1-phenyl-(2-phenylsulfanyl)ethylformamide (5a)** IR (film): 1668. ^1H-NMR: 3.0—4.2 (total 4H, m, $ArCH_2$–, $PhSCH_2CH<$), 3.74, 3.81, 3.86 (total 6H, each s, OCH_3×2), 4.3—4.7, 5.2—5.4 (total 1H, m, $PhSCH_2CH<$), 6.5—6.8 (total 3H, m, ArH), 7.0—7.5 (total 10H, m, PhH×2), 8.36, 8.44 (total 1H, each s, CHO). HR-EIMS *m/z* (M^+): Calcd for $C_{24}H_{25}NO_3S$: 407.1555. Found: 407.1565.

***N*-2-(3,4-Dimethoxyphenyl)ethyl-1-phenyl-(2-phenylsulfanyl)-ethylformamide (5b)** From **4a** (8.9 g, 22.6 mmol); column chromatography ($CHCl_3$) gave **5b** (9.6 g, 99%) as a pale yellow gum. IR (film): 1652, 1515. ^1H-NMR: 2.0—3.8 (total 6H, m, $ArCH_2CH_2$–, $PhSCH_2CH<$), 3.79, 3.82 (total 6H, each s, OCH_3×2), 4.5—4.8, 5.3—5.6 (total 1H, each m, $PhSCH_2CH<$), 6.4—6.8 (total 3H, m, ArH), 7.2—7.5 (total 10H, m, PhH×2), 8.01, 8.29 (total 1H, each s, CHO). HR-EIMS *m/z* (M^+): Calcd for $C_{25}H_{27}NO_3S$: 421.1709. Found: 421.1701.

Oxidation of 5a with $NaIO_4$. Typical Procedure A solution of **5a** (15.6 g, 38.3 mmol) and $NaIO_4$ (13.0 g, 57.45 mmol) in MeOH (200 ml) and H_2O (50 ml) was stirred at room temperature for 1.5 h. After removal of inorganic precipitates by filtration, the filtrate was concentrated *in vacuo*. The residue was extracted with $CHCl_3$. The product was chromatographed with hexane/ethyl acetate (1 : 3) to give **6a** (15.8 g, 97%) as a yellow gum.

***N*-(3,4-Dimethoxyphenyl)methyl-1-phenyl-(2-phenylsulfinyl)ethylformamide (6a)** IR: 1670, 1515. ^1H-NMR: 2.9—4.6 (total 4H, m, $ArCH_2$–, $PhS(O)CH_2CH<$), 3.72, 3.75, 3.77, 3.85, 3.86, 3.87, 3.91 (total 6H, each s, OCH_3×2), 4.9—5.6 (total 1H, m, $PhS(O)CH_2CH<$), 6.4—7.8 (total 13H, m, ArH, PhH×2), 8.22, 8.46, 8.50, 8.75 (total 1H, each s, CHO). HR-EIMS *m/z* (M^+): Calcd for $C_{24}H_{25}NO_4S$: 423.1501. Found: 423.1483.

***N*-2-(3,4-Dimethoxyphenyl)ethyl-1-phenyl-(2-phenylsulfinyl)ethylformamide (6b)** From **5b** (9.6 g, 22.8 mmol); column chromatography (hexane/ethyl acetate 1 : 1) gave **6b** (9.6 g, 97%) as a yellow gum. IR: 1670, 1515. ^1H-NMR: 2.1—4.7 (total 6H, m, $ArCH_2CH_2$–, $PhSCH_2CH$–), 3.78, 3.81, 3.83, 3.85 (total 6H, each s, OCH_3×2), 4.3—5.5 (total 1H, m, $PhSCH_2CH$–), 6.4—6.9 (total 3H, m, ArH), 7.2—7.8 (total 10H, m, PhH×2), 7.79, 8.08, 8.36, 8.61 (total 1H, each s, CHO). HR-EIMS *m/z* (M^+): Calcd for $C_{25}H_{27}NO_4S$: 437.1661. Found: 437.1684.

Pummerer Reaction of 6a i) Method A: A solution of TFAA (2.59 g, 12.33 mmol) in benzene (5 ml) was added to a solution of **6a** (1.043 g, 2.47 mmol) in benzene (45 ml) at room temperature, and the mixture was stirred for 24 h under an argon atmosphere at room temperature. The reaction mixture was concentrated *in vacuo*, and the product was chromatographed with hexane/ethyl acetate (4 : 1) to give **7a** (124 mg, 12%) and **8a** (530 mg, 53%).

ii) Method B: A solution of TFAA (2.53 g, 12 mmol) in benzene (5 ml) was added to a solution of **6a** (1.02 g, 2.4 mmol) in benzene (40 ml), and the mixture was stirred at room temperature for 5 min under an argon atmosphere. To this mixture was slowly added $BF_3 \cdot Et_2O$ (1.03 g, 7.3 mmol) and the mixture was further stirred for 3 h. The reaction mixture was neutralized with 5% NaOH and extracted with $CHCl_3$. The product was chromatographed with hexane/ethyl acetate (6 : 1) to give **7a** (602 mg, 62%) and **8a** (33 mg, 2%).

(3*S,4*R**)-2-Formyl-6,7-dimethoxy-3-phenyl-4-phenylsulfanyl-1,2,3,4-tetrahydroisoquinoline (7a)** A pale yellow gum. IR (film): 1675, 1517. ^1H-NMR: 3.83, 3.84, 3.87 (total 6H, each s, OCH_3×2), 4.00, 4.17 (total 1H, each d, J=17, 16 Hz, C3-H), 4.51, 5.11 (total 1H, each d, J=16, 17 Hz, C4-H), 4.87, 4.90 (total 2H, each s, C1-H), 6.50, 6.55, 6.70, 6.81 (total 2H, each s, ArH), 6.9—7.7 (total 10H, m, Ph×2), 8.28, 8.46 (total 1H, each s, CHO). HR-EIMS *m/z* (M^+): Calcd for $C_{24}H_{23}NO_3S$: 405.1396. Found: 405.1363.

***N*-(3,4-Dimethoxyphenyl)methyl-*N*-[(*E*)-1-phenyl-2-(phenylsulfanyl)-ethenyl]formamide (8a)** A colorless gum. IR (film): 1683, 1515. ^1H-NMR: 3.80 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.52 (2H, s, $ArCH_2$–), 6.10 (1H, s, PhSCH=), 6.6—6.9 (3H, m, ArH), 7.0—7.5 (10H, m, PhH×2), 8.47 (1H, s, CHO). ^{13}C-NMR: 46.5 (t), 55.79 (q), 55.82 (q), 110.9 (d), 111.9 (d), 121.3 (d), 121.4 (d), 127.0 (d), 128.68 (d×2), 128.70 (d×2), 128.8 (s), 128.9 (d×2), 129.2 (d×2), 129.4 (d), 133.4 (s), 135.3 (s), 137.6 (s), 148.5 (s), 148.9 (s), 162.0 (d). HR-EIMS *m/z* (M^+): Calcd for $C_{24}H_{23}NO_3S$: 405.1395. Found: 405.1379.

Pummerer Reaction of 6b i) Method A: A solution of TFAA (204 mg, 0.97 mmol) in benzene (5 ml) was added to a solution of **6b** (85 mg, 0.195 mmol) in benzene (10 ml) at room temperature, and the mixture was stirred for 5.5 h under an argon atmosphere. The reaction mixture was concentrated *in vacuo*, and the product was chromatographed with $CHCl_3$ to give **8b** (37 mg, 46%) as a pale yellow gum.

ii) Method B: A solution of TFAA (4.77 g, 22.7 mmol) in benzene (5 ml) was added to a solution of **6b** (1.98 g, 4.53 mmol) in benzene (40 ml), and the mixture was stirred at room temperature for 5 min under an argon atmos-

phere. To this mixture was slowly added $BF_3 \cdot Et_2O$ (1.93 g, 13.6 mmol) and the mixture was further stirred for 1.5 h. The reaction mixture was neutralized with 5% NaOH and extracted with $CHCl_3$. The product was chromatographed with hexane/ethyl acetate (5 : 1) to give **7b** (870 mg, 46%) and **9b** (115 mg, 8%).

***N*-2-(3,4-Dimethoxyphenyl)ethyl-*N*-[(*E*)-1-phenyl-2-(phenylsulfanyl)-ethenyl]formamide (8b)** IR: 1673, 1515. ^{1}H-NMR: 2.77 (2H, t, J=7 Hz, $ArCH_2CH_2$–), 3.62 (2H, t, J=7 Hz, $ArCH_2CH_2$–), 3.79 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 6.15 (1H, s, PhSCH=C<), 6.6—6.8 (3H, m, ArH), 7.2—7.7 (10H, m, PhH×2), 8.40 (1H, s, CHO). ^{13}C-NMR: 33.4 (t), 44.4 (t), 55.8 (qx2), 111.1 (d), 111.9 (d), 120.7 (d), 121.1 (d), 127.3 (d), 128.6 (d×2), 128.7 (d×2), 128.9 (d), 129.3 (d×2), 129.4 (d×2), 130.7 (s), 133.4 (s), 135.1 (s), 137.1 (s), 147.6 (s), 148.8 (s), 162.3 (d). HR-EIMS *m/z* (M^+): Calcd for $C_{25}H_{25}NO_3S$: 419.1552. Found: 419.1537.

(1*S,2*S**)-3-Formyl-7,8-dimethoxy-2-phenyl-1-phenylsulfanyl-1,2,4,5-tetrahydro-3*H*-3-benzazepine (7b)** A pale yellow gum. IR: 1670. ^{1}H-NMR: 2.64—3.33 (total 2H, m, C4-H, C5-H), 3.50—4.53 (total 2H, m, C4-H, C5-H), 4.48, 4.93 (total 1H, each d, J=4.3, 3.6 Hz, C1-H), 4.73, 5.04 (total 1H, each d, J=4.3, 3.6 Hz, C2-H), 3.63, 3.72, 3.85 (total 6H, each s, OCH_3×2), 6.31, 6.37, 6.50, 6.60 (total 2H, each s, C6 or 9-H), 7.0—7.6 (total 10H, m, PhH×2), 8.28, 8.38 (total 1H, each s, CHO). HR-EIMS *m/z* (M^+): Calcd for $C_{25}H_{25}NO_3S$: 419.1552. Found: 419.1514.

3-Formyl-7,8-dimethoxy-2-phenyl-4,5-dihydro-3*H*-3-benzazepine (9b) Colorless prisms crystallized from Et_2O, mp 154—156 °C. IR: 1670, 1521. ^{1}H-NMR: 3.15 (2H, t, J=5 Hz, C5-H), 3.89 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.03 (2H, t, J=5 Hz, C4-H), 6.14 (1H, s, C1-H), 6.71 (1H, s, C6 or C9-H), 6.76 (1H, s, C6 or C9-H), 7.3—7.6 (5H, m, PhH), 8.22 (1H, s, CHO). ^{13}C-NMR: 36.6 (t), 42.0 (t), 55.9 (q), 56.0 (q), 113.2 (d), 115.3 (d), 118.4 (d), 126.2 (s), 127.8 (d×2), 128.6 (d), 128.8 (d×2), 131.2 (s), 138.1 (s), 138.7 (s), 147.1 (s), 147.9 (s), 162.4 (d). LR-EIMS *m/z*: 309 (M^+, 100). *Anal*. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.58; H, 6.30; N, 4.47.

Treatment of 7b with *p*-TsOH A solution of **7b** (176 mg, 0.42 mmol) and p-TsOH$\cdot H_2O$ (360 mg, 2.1 mmol) in benzene (20 ml) was heated under reflux for 1 h. The product was chromatographed with hexane/ethyl acetate (5 : 1) to give **9b** (99 mg, 76%).

Reductive Desulfurization of 7a. Typical Procedure $NaBH_4$ (980 mg, 25.79 mmol) was added in small portions to a stirred solution of **7a** (500 mg, 1.23 mmol) and $NiCl_2 \cdot 6H_2O$ (980 mg, 25.79 mmol) in MeOH–THF (3 : 1) (30 ml) under ice-cooling. The mixture was stirred at room temperature for 1 h. After removal of inorganic materials by filtration, the filtrate was concentrated *in vacuo*. The residue was extracted with $CHCl_3$. The product was chromatographed with hexane/ethyl acetate (1 : 1) to give **13a** (317 mg, 86%) as colorless prisms crystallized from Et_2O, mp 128—130 °C.

2-Formyl-6,7-dimethoxy-3-phenyl-1,2,3,4-tetrahydroisoquinoline (13a) IR: 1664, 1517. ^{1}H-NMR: 3.1—3.4 (total 2H, m, C4-H), 3.83, 3.87, 3.90 (total 6H, each s, OCH_3×2), 3.9—4.5, 4.9—5.2, 5.9—6.1 (total 3H, m, C1, C3-H), 6.50, 6.56, 6.66, 6.73 (total 2H, each s, ArH), 7.0—7.5 (total 5H, m, PhH), 8.34, 8.37 (total 1H, each s, CHO). LR-EIMS *m/z*: 297 (M^+, 33), 91 (100). *Anal*. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.62; H, 6.49; N, 4.70.

3-Formyl-7,8-dimethoxy-2-phenyl-1,2,4,5-tetrahydro-3*H*-3-benzazepine (13b) From **7b** (785 mg, 1.87 mmol); chromatography with hexane/ethyl acetate (1 : 3) gave **13b** (407 mg, 70%) as a pale yellow gum. IR: 1670. ^{1}H-NMR: 2.8—4.7 (total 6H, m, C1, C4, C5-H), 3.84, 3.87 (total 6H, each s, OCH_3×2), 4.8—5.0, 5.8—6.0 (total 1H, each m, C2-H), 6.62 (1H, d, J=2 Hz, C6 or C9-H), 6.74 (1H, d, J=2 Hz, C6 or C9-H), 7.2—7.4 (total 5H, m, PhH), 8.16, 8.20 (total 1H, each s, CHO). HR-EIMS *m/z* (M^+): Calcd for $C_{19}H_{21}NO_3$: 311.1519. Found: 311.1499.

Hydrolysis of 13a. Typical Procedure A 10% NaOH solution (6 ml) was added to a solution of **13a** (100 mg, 0.34 mmol) in EtOH (12 ml), and the mixture was heated under reflux for 20 h. The reaction mixture was concentrated *in vacuo*, and the residue was diluted with water, then extracted with $CHCl_3$. The product was chromatographed with hexane/ethyl acetate (1 : 5) to give **14a** (90 mg, 99%) as pale yellow prisms from Et_2O, mp 170—172 °C (lit.[15], mp 93—94 °C). The reason for the big difference in the melting point with that reported is unclear.

6,7-Dimethoxy-3-phenyl-1,2,3,4-tetrahydroisoquinoline (14a) IR: 3397, 1517. ^{1}H-NMR: 1.80 (1H, s, >NH), 2.88 (2H, br d, J=4 Hz, C4-H), 3.6—4.4 (3H, m, C1, C3-H), 3.85 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.59 (2H, br s, ArH), 7.1—7.6 (5H, m, PhH). ^{13}C-NMR: 37.1 (t), 48.8 (t), 56.0 (q×2), 58.6 (d), 109.2 (d), 111.9 (d), 126.5 (d×2), 126.8 (s), 127.0 (s), 127.3 (d), 128.5 (d×2), 144.3 (s), 147.5 (s), 147.6 (s). HR-EIMS *m/z* (M^+): Calcd for $C_{17}H_{19}NO_2$: 269.1414. Found: 269.1414.

7,8-Dimethoxy-2-phenyl-1,2,4,5-tetrahydro-3*H*-3-benzazepine (14b) From **13b** (200 mg, 0.64 mmol); heating for 25 h under reflux and chromatography with hexane/ethyl acetate (1 : 10) gave **14b** (131 mg, 72%) as a colorless gum (lit.,[9a] HCl salt, mp 172—174 °C). IR (film): 3320, 1517. ^{1}H-NMR: 1.87 (1H, br s, >NH), 2.6—4.0 (7H, m, C1, 2, 4, 5-H), 3.84 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 6.64 (1H, s, C6 or 9-H), 6.68 (1H, s, C6 or 9-H), 7.2—7.5 (5H, m, PhH). ^{13}C-NMR: 38.5 (t), 46.6 (t), 49.0 (t), 55.9 (q×2), 63.8 (d), 113.3 (d), 113.7 (d), 126.3 (d×2), 127.0 (d), 128.4 (d×2), 132.9 (s), 134.5 (s), 146.1 (s), 146.6 (s), 146.8 (s). HR-EIMS *m/z* (M^+): Calcd for $C_{18}H_{21}NO_2$: 283.1572. Found: 283.1582.

$LiAlH_4$ Reduction of 13a. Typical Procedure $LiAlH_4$ (26 mg, 0.68 mmol) was added to a solution of **13a** (100 mg, 0.34 mmol) in dry THF (15 ml), and the mixture was heated under reflux for 30 min. Et_2O, saturated with water, was added to the reaction mixture and insoluble material was filtered off. The product was chromatographed with $CHCl_3$ to give **15a** (86 mg, 91%) as a pale yellow gum.

6,7-Dimethoxy-2-methyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline (15a) IR (film): 1519. ^{1}H-NMR: 2.17 (3H, s, >NCH_3), 2.8—4.1 (5H, m, C1, C3, C4-H), 3.83 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 6.57 (2H, s, ArH), 7.2—7.5 (5H, m, PhH). ^{13}C-NMR: 37.7 (t), 43.3 (q), 55.85 (q), 55.92 (q), 58.2 (t), 66.5 (d), 108.9 (d), 110.7 (d), 126.20 (s), 126.24 (s), 127.3 (d), 127.9 (d×2), 128.5 (d×2), 142.6 (s), 147.3 (s), 147.6 (s). HR-EIMS *m/z* (M^+): Calcd for $C_{18}H_{21}NO_2$: 283.1570. Found: 283.1565.

7,8-Dimethoxy-3-methyl-2-phenyl-1,2,4,5-tetrahydro-3*H*-3-benzazepine (15b) From **13b** (200 mg, 0.64 mmol); chromatography with hexane/ethyl acetate (1 : 4) gave **15b** (166 mg, 87%) as colorless plates crystallized from hexane–Et_2O, mp 112–114 °C (lit.,[9b] mp 156—157 °C from MeOH). IR: 1517. ^{1}H-NMR: 2.06 (3H, s, >NCH_3), 2.2—4.0 (7H, m, C1, C2, C4, C5-H), 3.81 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 6.59 (1H, s, C6 or C9-H), 6.68 (1H, s, C6 or C9-H), 7.2—7.4 (5H, m, PhH). ^{13}C-NMR: 35.1 (t), 44.1 (t), 45.5 (q), 56.0 (qx2), 57.8 (t), 71.0 (d), 112.4 (d), 113.4 (d), 127.0 (d), 127.1 (d×2), 128.5 (d×2), 132.4 (s), 134.2 (s), 145.7 (s), 146.9 (s), 147.2 (s). HR-EIMS *m/z* (M^+): Calcd for $C_{19}H_{23}NO_2$: 297.1729. Found: 297.1755.

Reaction of 8a with *p*-TsOH A solution of **8a** (108 mg, 0.27 mmol) and p-TsOH$\cdot H_2O$ (187 mg, 1.1 mmol) in benzene (15 ml) was heated under reflux for 7 h using a Dean-Stark water separator. The reaction mixture was concentrated *in vacuo*, and the residue was extracted with $CHCl_3$. The product was chromatographed with hexane/ethyl acetate (1 : 1) to give **2** (22 mg, 36%), **16a** (54 mg, 50%), and the starting material **8a** (7 mg, 6%).

***N*-(3,4-Dimethoxyphenyl)methyl-*N*-[(*Z*)-1-phenyl-2-phenylsulfanylethenyl]formamide (16a)** A pale yellow gum. IR (film): 1670, 1515. ^{1}H-NMR: 3.74 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.60 (2H, s, $ArCH_2$–), 6.54 (1H, s, PhSCH=), 6.6—6.9 (3H, s, ArH), 7.0—7.5 (10H, m, PhH×2), 8.38 (1H, s, CHO). ^{13}C-NMR: 46.3 (t), 55.7 (q), 55.8 (q), 110.6 (d), 112.5 (d), 121.7 (d), 123.1 (d), 126.3 (d×2), 127.3 (d), 128.3 (s), 128.91 (d×2), 128.92 (d), 129.2 (d×2), 129.6 (d×2), 134.6 (s), 135.6 (s), 138.6 (s), 148.5 (s), 148.6 (s), 163.1 (d). HR-EI-MS *m/z* (M^+): Calcd for $C_{24}H_{23}NO_3S$: 405.1399. Found: 405.1411.

Reaction of 8b with *p*-TsOH A solution of **8b** (91 mg, 0.22 mmol) and p-TsOH$\cdot H_2O$ (187 mg, 1.1 mmol) in benzene (15 ml) was heated under reflux for 2.5 h using a Dean-Stark water separator. The reaction mixture was concentrated *in vacuo*, and the residue was extracted with $CHCl_3$. The product was chromatographed with hexane/ethyl acetate (1 : 1) to give **18** (19 mg, 21%), **19** (48 mg, 53%), and the starting material (**8b**) (19 mg, 21%).

2-Formyl-6,7-dimethoxy-1-phenyl-1-phenylsulfanylmethyl-1,2,3,4-tetrahydroisoquinoline (18) A colorless gum. IR (film): 1652, 1515. ^{1}H-NMR (500 MHz): 2.78, 2.82 (total 1H, each t, J=4 Hz, C4-H), 2.96, 2.99 (total 1H, each dd, J=5, 10 Hz, C4-H), 3.0—3.2 (total 1H, m, C3-H), 3.53, 3.57, 3.85, 3.86 (total 6H, each s, OCH_3×2), 3.74 (1H, d, J=14 Hz, $PhSCH_2$–), 4.13 (1H, d, J=14 Hz, $PhSCH_2$–), 4.26, 4.29 (total 1H, each t, J=5 Hz, C3-H) 6.13, 6.17 (total 1H, each s, ArH), 6.58, 6.59 (total 1H, each s, ArH), 7.1—7.6 (total 10H, m, PhH×2), 8.08, 8.16 (total 1H, each s, CHO). HR-EIMS *m/z* (M^+): Calcd for $C_{25}H_{25}NO_3S$: 419.1553. Found: 419.1511.

***N*-2-{4,5-Dimethoxy-2-[1-phenyl-2-(phenylsulfanyl)ethenyl]phenyl}-ethylformamide (19)** A pale yellow gum. IR (film): 3355, 1683, 1511. ^{1}H-NMR: 2.5—2.7 (total 2H, m, $ArCH_2CH_2$–), 3.0—3.7 (total 2H, m, $ArCH_2CH_2$–), 3.88, 3.89, 3.92 (total 6H, each s, OCH_3×2), 6.53, 6.70, 6.79, 6.83 (total 2H, each s, ArH), 7.07 (1H, s, PhSCH=C<), 7.2—7.5 (total 10H, m, PhH×2), 7.92 (1H, br s, CHO). HR-EIMS *m/z* (M^+): Calcd for $C_{25}H_{25}NO_3S$: 419.1555. Found: 419.1577.

Reductive Desulfurization of 18 $NaBH_4$ (900 mg, 23.7 mmol) was added in small portions to a stirred solution of **18** (480 mg, 1.15 mmol) and $NiCl_2 \cdot 6H_2O$ (1.9 g, 23.7 mmol) in MeOH–THF (3 : 1) (30 ml) under ice-

cooling. The mixture was stirred at room temperature for 1 h. After removal of inorganic materials by filtration, the filtrate was concentrated *in vacuo*. The residue was extracted with $CHCl_3$. The product was chromatographed with hexane/ethyl acetate (3 : 1) to give **20** (346 mg, 97%) as colorless prisms from hexane, mp 109—111 °C.

2-Formyl-6,7-dimethoxy-1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (20) IR: 1654. ^{1}H-NMR: 2.04 (3H, s, CH_3), 2.7—3.0 (2H, m, C4-H), 3.4—3.6 (1H, m, C3-H), 3.64 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.1—4.2 (1H, m, C3-H), 6.26 (1H, s, C5 or C8-H), 6.62 (1H, s, C5 or C8-H), 7.2—7.5 (5H, m, PhH), 8.11 (1H, s, CHO). ^{13}C-NMR: 28.5 (t), 29.2 (q), 36.0 (t), 55.8 (q), 56.0 (q), 62.7 (s), 110.7 (d), 110.9 (d), 126.4 (s), 127.3 (d×2), 127.6 (d), 128.7 (d×2), 133.5 (s), 145.5 (s), 147.7 (s), 147.9 (s), 163.0 (d). LR-EIMS *m/z*: 311 (M^+, 30), 296 (100). *Anal*. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.08; H, 6.91; N, 4.43.

Hydrolysis of 20 A 10% NaOH solution (5 ml) was added to a solution of **20** (100 mg, 0.32 mmol) in EtOH (10 ml), and the mixture was heated under reflux for 45 h. The reaction mixture was concentrated *in vacuo*, and the residue was diluted with water, then extracted with $CHCl_3$. The product was chromatographed with hexane/ethyl acetate (4 : 1) to give **21** (73 mg, 80%) as colorless prisms from Et_2O, mp 101—103 °C (lit.,[11]) HCl salt, mp 260—262 °C).

6,7-Dimethoxy-1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (21) IR: 3326, 1513. ^{1}H-NMR: 1.86 (3H, s, CH_3), 2.04 (1H, br s, >NH), 2.6—3.1 (4H, m, C3, C4-H), 3.75 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 6.53 (1H, s, C5 or C8-H), 6.62 (1H, s, C5 or C8-H), 7.1—7.3 (5H, m, PhH). ^{13}C-NMR: 29.5 (t), 30.3 (q), 39.0 (t), 55.8 (q), 56.0 (q), 58.9 (s), 110.9 (d), 111.6 (d), 126.5 (d), 127.2 (d×2), 127.4 (s), 127.9 (d×2), 133.8 (s), 147.1 (s), 147.6 (s), 148.6 (s). LR-EIMS *m/z*: 283 (M^+, 100). *Anal*. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 75.99; H, 7.59; N, 4.87.

$LiAlH_4$ Reduction of 20 $LiAlH_4$ (24 mg, 0.63 mmol) was added to a solution of **18** (97 mg, 0.31 mmol) in dry THF (15 ml), and the mixture was heated under reflux for 2.5 h. Et_2O, saturated with water, was added to the reaction mixture and insoluble material was filtered off. The product was chromatographed with $CHCl_3$ to give **22** (82 mg, 88%) as a colorless gum.

6,7-Dimethoxy-1,2-dimethyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (22) IR (film): 1511. ^{1}H-NMR: 1.70 (3H, s, C-CH_3), 2.15 (3H, s, >NCH_3), 2.7—3.2 (4H, m, C3, C4-H), 3.59 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 6.18 (1H, s, C5 or C8-H), 6.56 (1H, s, C5 or C8-H), 7.1—7.4 (5H, m, PhH). ^{13}C-NMR: 20.0 (q), 28.8 (t), 38.5 (q), 47.0 (t), 55.6 (q), 55.8 (q), 63.3 (s), 110.5 (d), 111.8 (d), 126.0 (s), 126.4 (d), 127.6 (d×2), 128.1 (d×2), 135.8 (s), 146.9 (s), 147.1 (s), 147.6 (s). HR-EIMS *m/z* (M^+): Calcd for $C_{19}H_{23}NO_2$: 297.1729. Found: 297.1754.

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