A Synthesis of Mono- and Dimethoxy-1,2,3,4-tetrahydroisoquinolines *via* Pummerer Reaction: Effects of Methoxyl Groups on Intramolecular Cyclization

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A synthesis of 1,2,3,4-tetrahydroisoquinolines (TIQs) (23) with one and two methoxyl groups at various positions of the benzene ring was achieved *via* the intramolecular cyclization of *N*-(aryl)methyl-2-(phenylsulfinyl)ethylamines (9) using the Pummerer reaction as a key step. The reaction was carried out by using trifluoroacetic anhydride (TFAA) (method A) or TFAA–$BF_3 \cdot Et_2O$ (method B). The cyclization to 4-SPhTIQs (11) proceeded effectively when the reaction center at the benzene ring was electronically activated by a methoxyl group. In the reaction of the sulfoxide (9e) having two OMe groups at *ortho*- and *para*-positions a different cyclization reaction leading to a benzothiazepine (12) was observed, indicating that the high nucleophilicity of the benzene ring caused the unexpected reaction prior to the cyclization to 4-SPhTIQ (11e). The route starting from methoxylated benzaldehydes (5) was proved to provide an efficient and convenient method of TIQ synthesis which should be complementary to the well known Pictet–Spengler method.

Key words synthesis; 1,2,3,4-tetrahydroisoquinoline; benzothiazepine; Pummerer reaction; trifluoroacetic anhydride

1,2,3,4-Tetrahydroisoquinolines (TIQs) are widely distributed in the plant and animal kingdom and have received attention because of their biological activities.[1] Recently, we modified the Takano's TIQ synthesis[2] which utilizes sulfoxide-mediated electrophilic intramolecular cyclization (Pummerer reaction) and discovered a highly efficient method of preparing TIQs starting from aromatic aldehydes,[3] aromatic ketones,[4] and simple chiral amines.[5] In the investigations,[3,4] we explored two methods for the intramolecular cyclization of sulfoxides **1** and **2** (Chart 1); one is the reaction under a usual condition using trifluoroacetic anhydride (TFAA) in benzene at room temperature (method A) and the other involves sequential treatment with TFAA and $BF_3 \cdot Et_2O$ (method B). Method A is effective only for the synthesis of TIQs (**3**) possessing an OMe group in the benzene ring. On the other hand, method B is efficient for preparing TIQs (**4**) which do not possess an OMe group in the benzene ring. The use of $BF_3 \cdot Et_2O$ was proved to be essential for the cyclization of the sulfoxide **2**.[3,4] Furthermore, we found that the use of formamide for *N*-protection was very important for this intramolecular cyclization.[3] In this paper, we describe a synthesis of TIQs possessing one or two methoxyl groups at various positions of the benzene ring *via* intramolecular cyclization using Pummerer reaction, in order to obtain an information about the scope and limitations of this method of TIQ synthesis.

Results and Discussion

The sulfoxides **9**, substrates of the Pummolerer cyclization, were prepared from aromatic aldehydes **5** in excellent overall yields (60—88%) *via* the route shown in Chart 2. Condensation of **5** with 2-phenylthioethylamine[6] in the presence of acetic acid followed by $NaBH_4$ reduction of the resulting imines **6** gave *N*-(arylmethyl)-2-(phenylthio)ethylamines **7** in good yields. Formylation of **7** with 98—100% formic acid–acetic anhydride gave the *N*-formyl derivatives **8** in excellent yields. The products were oxidized with sodium metaperiodate to give *N*-formyl sulfoxides **9** in high yields, though the sulfones **10** were also produced in yields of a few percent.

Pummerer Reaction (Method A) As described in the

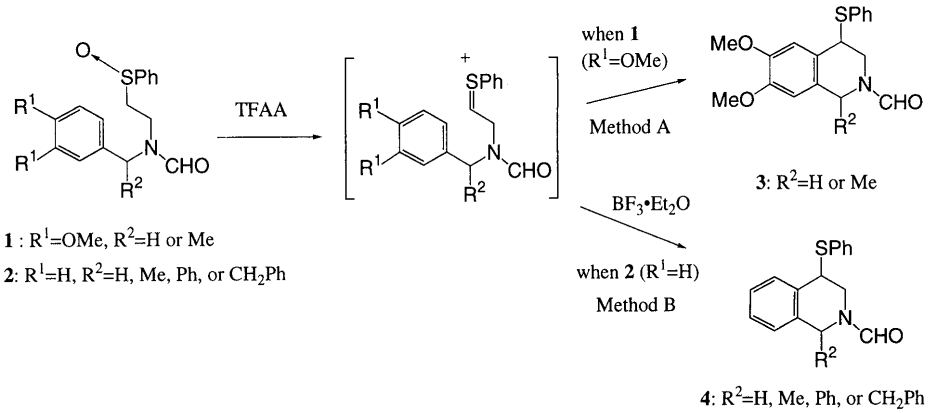

Chart 1

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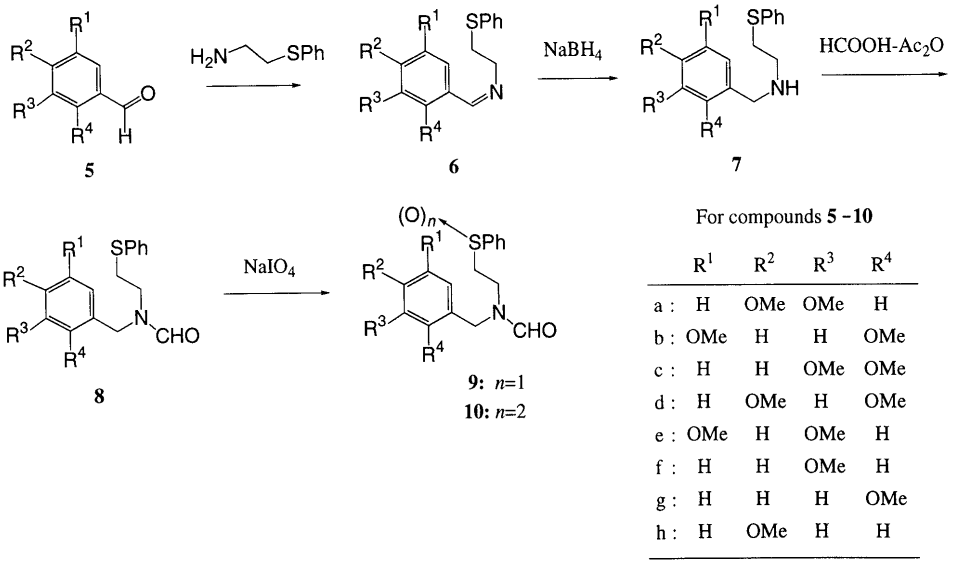


	R^1	R^2	R^3	R^4
a :	H	OMe	OMe	H
b :	OMe	H	H	OMe
c :	H	H	OMe	OMe
d :	H	OMe	H	OMe
e :	OMe	H	OMe	H
f :	H	H	OMe	H
g :	H	H	H	OMe
h :	H	OMe	H	H

Chart 2

previous paper,[3] the sulfoxide **9a** on treatment with TFAA in benzene at room temperature (method A) quantitatively cyclized to give 6,7-diOMe-4-SPh-*N*-formylTIQ (**11a**) in 97% yield. The sulfoxides **9b**—**9h** were treated with TFAA under the conditions of method A and the corresponding product, 4-SPh-*N*-formylTIQ **11**, was obtained in a pure form by column chromatography over SiO_2, and characterized by MS and ^{1}H-NMR analyses (see Experimental). The results are summarized in Table 1.

In the cases of dimethoxyl derivatives, the substrates **9a**—**9c** having at least one OMe group at *ortho* or *para* to the reaction center, which electronically facilitates the intramolecular cyclization, gave the corresponding TIQs **11a**—**11c** in good to excellent yields. The sulfoxide **9d** with two *meta* OMe groups which do not enhance the reactivity of the reaction center, as anticipated, did not give the TIQ **11d**. The sulfoxide **9e** having *ortho*- and *para*-OMe, both of which should facilitate the cyclization, gave the TIQ **11e** in only 27% yield in contrast to our expectation. A sulfenium salt **12** was obtained as the major product in about 60% yield [calculated as a trifluoroacetic acid (TFA) salt], although it could not be obtained as a pure form and the anion was therefore not identified. The evidence for the structure of **12** will be described later.

In the cases of the monomethoxyl derivatives, the sulfoxide **9f** with *para*-OMe smoothly cyclized to give the TIQ **11f** in 85% yield. On the other hand, the sulfoxide **9g** with *meta*-OMe did not give the TIQ **11g**. The results were consistent with expectation based on the electron donating effect of the OMe group. The sulfoxide **9h** with an OMe group at the other *meta*-position gave the TIQ **11h** in 10% yield, although the cyclization was electronically unfavored.

Pummerer Reaction (Method B) As described in the previous paper,[3] the sulfoxide **9j** lacking an OMe group in the benzene ring did not cause the cyclization under the conditions of method A. However, the cyclization occurred very effectively on sequential treatment with TFAA and $BF_3 \cdot Et_2O$ (method B) to give the TIQ **11j** in quantitative yield. This method was applied to the sulfoxides **9a**—**h** and the results are summarized in Table 1.

In the cases of dimethoxyl derivatives the product distribution and the yield of TIQs **11** were comparable to those obtained by method A. In the case of **9e** the benzothiazepine salt **12** and a SPh-substituted benzene derivative (**13a**) other than **11e** were obtained as major and minor product, respectively. On the other hand, in the cases of monomethoxy derivatives the results were significantly different from those obtained by method A. For example, the TIQ **11g** which was not formed at all under the conditions of method A, was obtained by method B although the yield was low (25%), and the yield of TIQ **11h** was dramatically improved in method B (84%). The sulfoxide **9f** under the conditions of method B caused the cyclization not only at the *para*-position but also at the *ortho*-position to give an inseparable mixture of TIQs **11f** and **11i** in the ratio of 3 : 1 (84 % yield) which, on reductive desulfurization and chromatography of the products over SiO_2, gave the *N*-formylTIQ (**21f**) (60%) and **21i** (24%) (Chart 5).

Next we will discuss the role of $BF_3 \cdot Et_2O$ in this reaction. In all cases which yield the TIQs **11**, the addition of $BF_3 \cdot Et_2O$ enormously accelerated the reaction. Formation of the TIQs **11** from the sulfoxides **9** can be explained as follows (Chart 3): i) trifluoroacetylation of the sulfoxide to yield an intermediate **14**, ii) rearrangement of the trifluoroacetoxy group to form **15**, iii) formation of a sulfenium cation **16** by elimination of CF_3COOH from the intermediate **15**, and iv) intramolecular cyclization of **16** by nucleophilic substitution of the aromatic ring. A Lewis acid seems to promote the elimination of CF_3COOH from **15** leading to the sulfenium cation **16**, since the reaction was completed within several hours irrespective of the structure of the aromatic moiety. Furthermore, the acid seems to facilitate the intramolecular cyclization of the cation **16** since a dramatic improvement of the yields upon adding $BF_3 \cdot Et_2O$ was observed with **9h** and **9j**.[3] This effect of the acid on the cyclization, although difficult to explain, may be attributable to enhancement of the electrophilic reactivity

Table 1. Pummerer Reaction of Sulfoxides **9**

Run	Sulfoxide (**9**)	Conditions[a]		Yield (%)		
		Reagent[b]	Time (h)	PhSTIQ (**11**)	Others	
1	**9a**	A	20	(**11a**) 97[c]		
2	**9a**	B	2	(**11a**) 86		
3	**9b**	A	151	(**11b**) 60		
4	**9b**	B	1	(**11b**) 79		
5	**9c**	A	22	(**11c**) 82		
6	**9c**	B	1	(**11c**) 86		
7	**9d**	A	147	—[d]		
8	**9d**	B	3	—[d]		
9	**9e**	A	20	(**11e**) 27	(**12**) 60	
10	**9e**	B	3	(**11e**) 27	(**12**) 49	(**13a**) 2
11	**9f**	A	18	(**11f**) 85		
12	**9f**	B	2	(**11f**, **11i**) 84[e]		
13	**9g**	A	18	—[d]		
14	**9g**	B	4	(**11g**) 25		
15	**9h**	A	120	(**11h**) 10		
16	**9h**	B	2	(**11h**) 84		
17	**9j**	A	20	—[d]		
18	**9j**	B	2.5	(**11j**) 99[c]		

a) In benzene at room temperature. *b*) A: TFAA. B: TFAA–$BF_3 \cdot Et_2O$. *c*) See reference 3. *d*) No characterizable products were obtained. *e*) An inseparable mixture of **11f** and **11i** in a ratio of about 3 : 1.

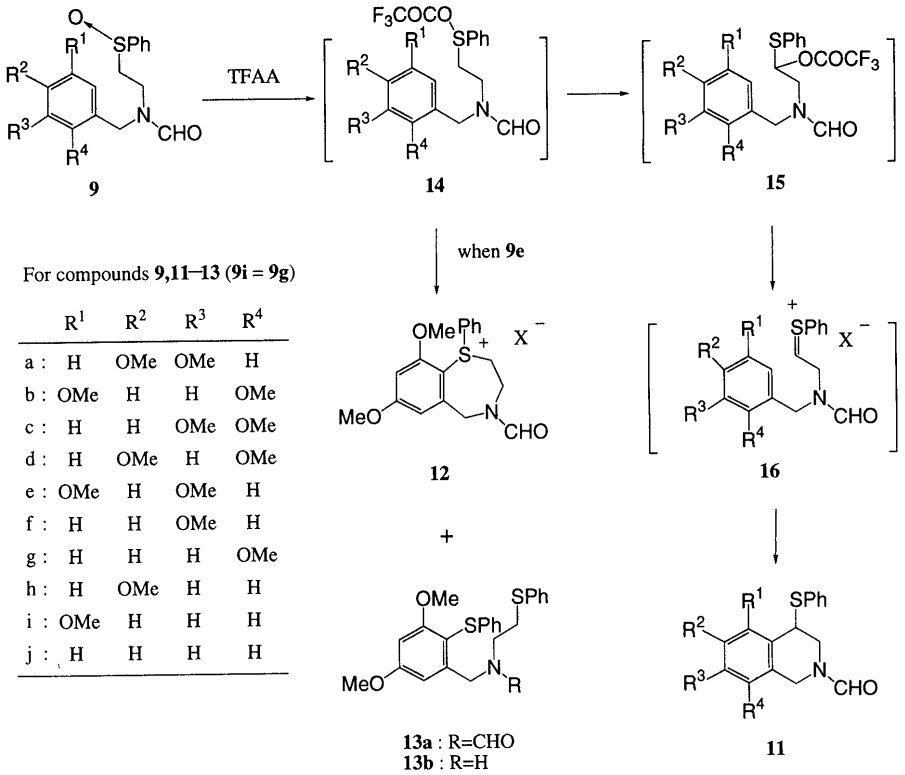


Chart 3

of the sulfenium cation **16** by the change of the counter anion (X^-) from CF_3COO^- to CF_3COO–BF_3^-.

Structure of the Benzothiazepine Salt 12 The Pummerer reaction of **9e** by either method A or B yielded a sulfenium salt **12** as a major product (about 50—60%) together with the TIQ **11e**. The salt **12** obtained by methods A and B showed significantly different physical features, suggesting that the anion (X^-) is different. The structure of the salt except the anion was deduced from the following chemical transformations. The crude material **12** isolated by SiO_2 column chromatography of the products obtained by method A, when allowed to stand at room temperature, gradually changed into less polar compounds. After standing overnight, the products were hydrolyzed with 10% HCl to give **18b** as a sole product in good yield. The ^{1}H-NMR and mass spectra of **18** were consistent with the assigned structure, with a SPh group and an OH group. The SPh group of **18** was resistant to reductive desulfurization with $NaBH_4$–$NiCl_2$, indicating that the SPh is positioned in the benzene ring, not in the side

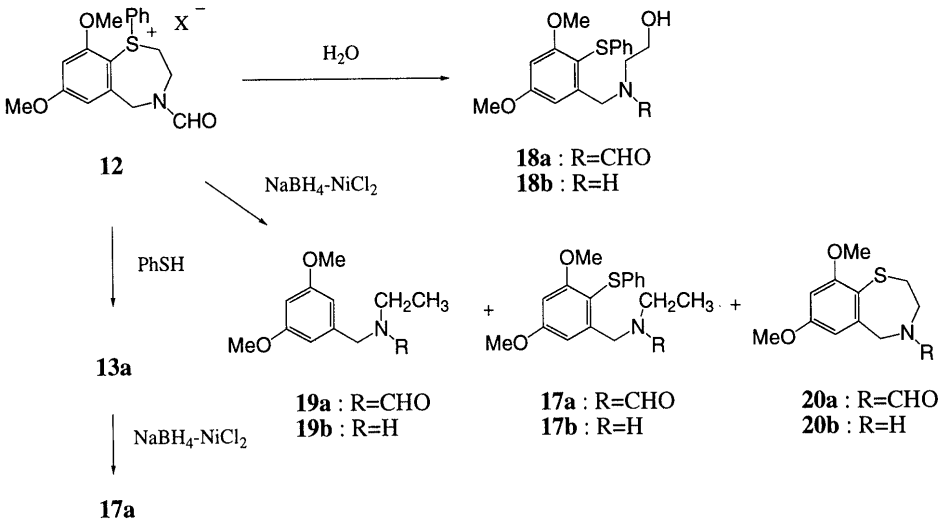
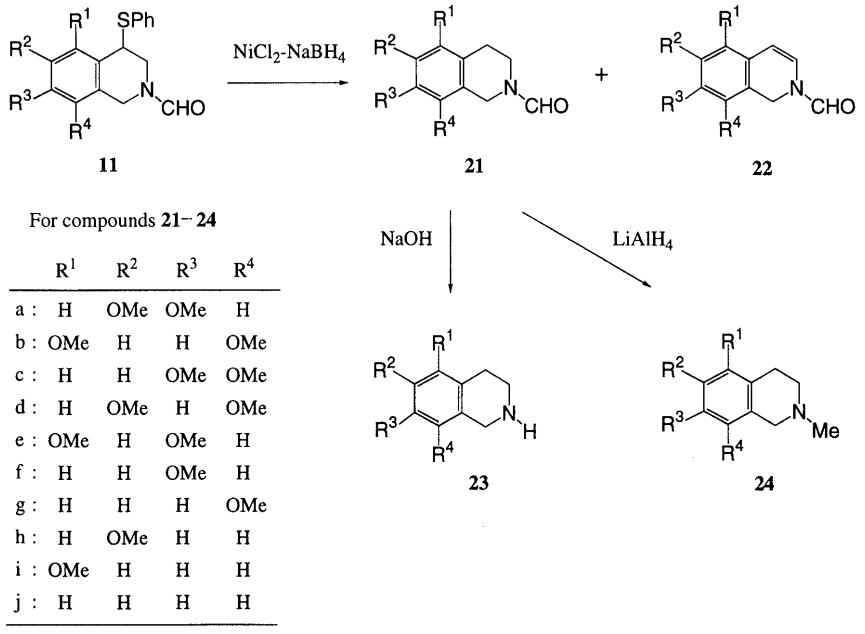


Chart 4



For compounds **21**–**24**

	R^1	R^2	R^3	R^4
a :	H	OMe	OMe	H
b :	OMe	H	H	OMe
c :	H	H	OMe	OMe
d :	H	OMe	H	OMe
e :	OMe	H	OMe	H
f :	H	H	OMe	H
g :	H	H	H	OMe
h :	H	OMe	H	H
i :	OMe	H	H	H
j :	H	H	H	H

Chart 5

chain. The PhS-substituted benzene derivative **18** should be formed by nucleophilic attack of water on the benzothiazepine ring.

Reduction of **12** with $NaBH_4$–$NiCl_2$ in MeOH–tetrahydrofuran (THF) gave three products **19a** (70%), **17a** (7%), and **20a** (<1%). Hydrolysis of **19a**, **17a**, and **20a** with 10% HCl in EtOH gave the corresponding deformates **19b**, **17b**, and **20b** in quantitative yield. Similar reduction of the salt **12** obtained by method B with $NaBH_4$–$NiCl_2$ gave the same products **19a**, **17a**, and **20a** in yields of 66%, 21%, and 9%, respectively, suggesting that this salt has the same structure as that obtained by method A. The structures of the derivatives were determined unambiguously from their spectral data as shown in Experimental. The chemical evidence, particularly the isolation of the benzothiazepine **20a**, strongly supported the conclusion that the product **12** is a sulfenium salt of benzothiazepine.

The minor product **13a** yielded from **9e** under the method B condition on hydrolysis with 10% HCl gave the deformate **13b** in 91% yield and on reduction with $NaBH_4$–$NiCl_2$ gave **17a** in 34% yield. The formation of **13a** may be rationalized in terms of nucleophilic attack of the thiophenol on the benzothiazepine ring of **12**.

The benzothiazepine salt **12** can be formed *via* intramolecular cyclization of the initially formed Pummerer intermediate **14** by the nucleophilic attack of the benzene ring on the sulfur atom as shown in Chart 3. This cyclization was observed only in the reaction of **9e**. Thus, only the sulfoxide **9e** caused two types of intramolecular cyclization, one leading to benzothiazepine and the other to TIQ, competitively. The participation of a radical species in this cyclization may be ruled out since the co-occurrence of a radical scavenger (1,1-diphenyl-2-picrylhydrazyl hydrate) in the reaction mixture did not affect the product distribution.

The benzene ring of the sulfoxide **9e** should be the most nucleophilic among the sulfoxides **9a**—**h** since it has two

Table 2. Total Yield of TIQs (**23**, **24**) from Aryl Aldehyde (**5**)

Aryl aldehyde (**5**)	Pummerer Reaction	Total Yield (%)	
		TIQs (**23**)	*N*-MeTIQs (**24**)
5a	A	(**23a**) 62	(**24a**) 54
5b	B	(**23b**) 33	(**24b**) 26
5c	B	(**23c**) 51	(**24c**) 53
5c	A, B	—	—
5e	A	(**23e**) 10	(**24e**) 11
5f	A	(**23f**) 32	(**24f**) 27
5g	B	(**23g**) 12	—
5h	B	(**23h**) 39	(**24h**) 37

electron-donating OMe groups *ortho* and *para* to the reaction center. Probably, this high nucleophilicity causes ring formation to benzothiazepine prior to the cyclization to TIQ. The results clearly indicated that the cyclization to benzothiazepine should not be favored in the Pummerer reaction, if the benzene ring is not sufficiently nucleophilic.

Preparation of TIQs Reductive removal of the phenylthio group of **11** readily proceeded on treatment with $NiCl_2$–$NaBH_4$[7] in MeOH–THF to give *N*-formyl-TIQs **21** in good yields, though 1,2-dihydroisoquinolines **22** were produced as a by-product in some cases. Deprotection of the *N*-formyl group was readily achieved by conventional methods. Alkaline hydrolysis of **21** gave the TIQs **23**. Reduction of **21** with $LiAlH_4$ gave *N*-methyl-TIQs **24** in good yields.

This route leading to TIQs is similar to that of Pomeranz–Fritsch TIQ synthesis, but seems to be more effective and convenient. As shown in Table 2, the synthesis using this route provides 6,7-diOMe- (**23a**) and 7,8-diOMeTIQ (**23c**) in excellent overall yields (51—62%), as well as 7-OMe- (**23f**), 6-OMe- (**23h**), and 5,8-diOMeTIQ (**23b**) in good overall yields (32—39%), and 8-OMe- (**23g**) and 5,7-diOMeTIQ (**23e**) in low overall yields (10—12%). The *N*-methyl TIQs (**24**) were obtained in similar total yields, as shown in Table 2. Among the TIQs thus prepared, the OMe groups of **23c**, **23e**, **23f**, and **23g** are arranged in electronically unfavored positions by the use of methods such as the Pictet–Spengler and Bischler–Napieralski reactions. The preparation of 7,8-diOMeTIQ (**23c**) constitutes a total synthesis of lemaireocereine, a simple isoquinoline alkaloid from the cactus species, whose total synthesis had been achieved in multiple steps.[8] Thus, it is concluded that the route explored here provides an efficient and convenient method of TIQ synthesis which should be complementary to the Pictet–Spengler synthesis.

Experimental

General Notes Unless otherwise noted, the following procedures were adopted. Melting points were taken on a Yanagimoto 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 JASCO FT/IR-5000 or a Horiba FT-170 spectrophotometer, and are given in cm^{-1}. NMR spectra were measured on JEOL JNM-EX 90 (^1H, 90 MHz) and JEOL JNM-AL 300 (^1H, 300 MHz ^{13}C, 75 MHz) spectrometers in $CDCl_3$ with tetramethylsilane as an internal standard, and the chemical shifts are given in δ values. The following abbreviations are used; s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, m = multiplet, and br = broad. LR-MS and HR-MS were taken on a JEOL JMS-AX 505H spectrometer at 70 eV [electron ionization MS (EI-MS)] or at 270 eV [chemical ionization MS (CI-MS, reactant gas: iso-butane)] using direct or GC/MS inlet systems, and figures in parentheses indicate the relative intensities. TLC was performed on Merck precoated Silica gel 60 F_{254} plates (Merck). Column chromatography was carried out with silica gel (Wakogel C-200). The organic extract from each reaction mixture was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to dryness. The known TIQs were also characterized by MS, IR, and ^1H-NMR examinations.

Preparation of *N*-Arylmethyl-2-(phenylthio)ethylamines (7) A mixture of **5b—h** (5.0 g), 2-phenylthioethylamine[6] (1.5 mol eq), and acetic acid (1.5 mol eq) in EtOH (100 ml) was refluxed for 16—18 h under an Ar atmosphere. The reaction mixture was concentrated *in vacuo*, then the residue was dissolved in MeOH (100 ml). To this solution, $NaBH_4$ (1.5 mol eq) was added in small portions under ice-cooling. The reaction mixture was stirred at room temperature for 1 h, concentrated *in vacuo*, diluted with water, and extracted with $CHCl_3$. The crude product was dissolved in Et_2O (*ca.* 300 ml) and extracted with 10% HCl–H_2O. The aqueous layer and insoluble amine HCl salt were combined and basified with 10% NaOH–H_2O, and extracted with $CHCl_3$. The products (**7b—h**) were purified by column chromatography.

N-(2,5-Dimethoxyphenylmethyl)-2-(phenylthio)ethylamine (**7b**): Eluent for column chromatography: AcOEt. Yield: 7.3 g, 80% from **5b** (5.0 g, 30 mmol). Pale yellow oil. IR: 1499, 1462, 1223, 1047. ^1H-NMR: 2.72—2.92 (2H, m, $-SCH_2-$), 3.00—3.18 (2H, m, $-CH_2N=$), 3.76 (2H, s, $ArCH_2N=$), 3.75, 3.78 (each 3H, s, $2\times-OCH_3$), 6.70—6.90 (3H, m, Ar-H), 7.10—7.40 (5H, m, Ar-H). EI-MS *m/z*: 303 (M^+, 5), 301 (12), 180 (39), 178 (21), 151 (base peak), 121 (31). HR-MS: Calcd for $C_{17}H_{21}NO_2S$: 303.1293. Found: 303.1301.

N-(2,3-Dimethoxyphenylmethyl)-2-(phenylthio)ethylamine (**7c**): Eluent for column chromatography: AcOEt. Yield: 8.54 g, 94% from **5c** (5.0 g, 30 mmol). Pale yellow oil. IR: 1586, 1477, 1276. ^1H-NMR: 2.74—2.91 (2H, m, $-SCH_2-$), 3.01—3.17 (2H, m, $-CH_2N=$), 3.81 (2H, s, $ArCH_2N=$), 3.85, 3.86 (each 3H, s, $2\times-OCH_3$), 6.75—7.05 (3H, m, Ar-H), 7.10—7.40 (5H, m, Ar-H). EI-MS *m/z*: 303 (M^+, 13), 270 (6), 180 (59), 178 (20), 151 (base peak), 136 (47), 121 (18), 110 (11), 91 (23). HR-MS: Calcd for $C_{17}H_{21}NO_2S$: 303.1293. Found: 303.1258.

N-(2,4-Dimethoxyphenylmethyl)-2-(phenylthio)ethylamine (**7d**): Eluent for column chromatography: AcOEt. Yield: 8.93 g, 98% from **5d** (5.0 g, 30 mmol). Pale yellow oil. IR: 1613, 1589, 1508, 1460, 1290, 1209. ^1H-NMR: 2.70—2.90 (2H, m, $-SCH_2-$), 3.00—3.17 (2H, m, $-CH_2N=$), 3.74 (2H, s, $ArCH_2N=$), 3.79, 3.80, (each 3H, s, $2\times-OCH_3$), 6.34—6.45 (3H, m, Ar-H), 7.05—7.40 (5H, m, Ar-H). EI-MS *m/z*: 303 (M^+, 3), 288 (11), 178 (32), 151 (base peak), 137 (10), 124 (41), 121 (32), 109 (13), 91 (14). HR-MS: Calcd for $C_{17}H_{21}NO_2S$: 303.1294. Found: 303.1280.

N-(3,5-Dimethoxyphenylmethyl)-2-(phenylthio)ethylamine (**7e**): Eluent for column chromatography: AcOEt. Yield: 8.54 g, 94% from **5e** (5.0 g, 30 mmol). Pale yellow oil. IR: 1599, 1462, 1207, 1154. ^1H-NMR: 2.76—2.93 (2H, m, $-SCH_2-$), 3.02—3.18 (2H, m, $-CH_2N=$), 3.74 (2H, s, $ArCH_2N=$), 3.77 (6H, s, $2\times-OCH_3$), 6.32—6.49 (3H, m, Ar-H), 7.17—7.40 (5H, m, Ar-H). EI-MS *m/z*: 303 (M^+, 6), 301 (9), 193 (3), 180 (49), 151 (base peak), 137 (4), 121 (8), 109 (6), 91 (7). HR-MS: Calcd for $C_{17}H_{21}NO_2S$: 303.1293. Found: 303.1277.

N-(3-Methoxyphenylmethyl)-2-(phenylthio)ethylamine (**7f**): Eluent for column chromatography: $CHCl_3$–MeOH (95 : 5). Yield: 9.07 g, 90% from **5f** (5.0 g, 36.8 mmol). Pale yellow oil. IR: 1586, 1489, 1460, 1439, 1267. ^1H-NMR: 2.75—2.97 (2H, m, $-SCH_2-$), 3.02—3.40 (3H, m, $-CH_2N=$, $ArCHN=$), 3.70 (3H, s, $-OCH_3$), 3.83 ((1H, s, $ArCHN=$), 6.70—6.95 (3H, m, Ar-H), 7.15—7.45 (6H, m, Ar-H). EI-MS *m/z*: 273 (M^+, 19), 271 (7), 150 (69), 124 (21), 121 (base peak), 109 (4), 91 (11). HR-MS: Calcd for $C_{16}H_{19}NOS$: 273.1187. Found: 273.1225.

N-(2-Methoxyphenylmethyl)-2-(phenylthio)ethylamine (**7g**): Eluent for column chromatography: $CHCl_3$–MeOH (95 : 5). Yield: 8.50 g, 85% from **5g** (5.0 g, 36.8 mmol). Pale yellow oil. IR: 1589, 1493, 1483, 1243, 1104, 1050. ^1H-NMR: 2.75—2.90 (2H, m, $-SCH_2S-$), 3.00—3.18 (2H, m, $-CH_2N=$), 3.80 (2H, s, $ArCH_2N=$), 3.83 (3H, s, $-OCH_3$), 6.80—6.97 (2H, m, Ar-H), 7.10—7.40 (7H, m, Ar-H). EI-MS *m/z*: 273 (M^+, 10), 150 (73), 136 (6), 121 (base peak), 109 (3), 91 (25). HR-MS: Calcd for $C_{16}H_{19}NOS$: 273.1187. Found: 273.1146.

N-(4-Methoxyphenylmethyl)-2-(phenylthio)ethylamine (**7h**): Eluent for column chromatography: $CHCl_3$–MeOH (95 : 5). Yield: 9.27 g, 92% from **5h** (5.0 g, 36.8 mmol). Pale yellow oil. IR: 1611, 1584, 1514, 1439, 1247, 1178, 1036. ^1H-NMR: 2.75—2.95 (2H, m, $-SCH_2-$), 2.98—3.18

(2H, m, $-CH_2N=$), 3.72 (2H, s, $ArCH_2N=$), 3.78 (3H, s, $-OCH_3$), 6.83 (2H, dd, $J=2.0$, 6.5 Hz, Ar-H), 7.12—7.40 (7H, m, Ar-H). EI-MS *m/z*: 273 (M^+, 3), 271 (11), 150 (21), 148 (26), 136 (4), 121 (base peak), 110 (5), 91 (10). HR-MS: Calcd for $C_{16}H_{19}NOS$: 274.1187. Found: 273.1174.

Formylation of 7 A mixture of **7b—h** (6.0—16.8 g), 98—100% formic acid (30 mol eq) and acetic anhydride (10 mol eq) was heated at 70 °C for 1 h, then concentrated *in vacuo*, and the residue was extracted with $CHCl_3$. The products (**8b—h**) were purified by column chromatography.

N-(2,5-Dimethoxyphenylmethyl)-*N*-[2-(phenylthio)ethyl]formamide (**8b**): Eluent for column chromatography: AcOEt–*n*-hexane (1 : 1). Yield: 8.48 g, 98% from **7b** (7.90 g, 26.1 mmol). Pale yellow gum. IR: 1673 (=NCO–), 1584, 1504, 1226. ^{1}H-NMR: 2.85—3.10 (2H, m $-SCH_2-$), 3.25—3.55 (2H, m, $-CH_2N=$), 3.73, 3.76 (each 3H, each s, $2\times-OCH_3$), 4.36, 4.53 (total 2H, each s, $ArCH_2N=$), 6.59—6.81 (3H, m, Ar-H), 7.10—7.40 (5H, m, Ar-H), 8.09, 8.26 (total 1H, each s, =NCHO). EI-MS *m/z*: 331 (M^+, 35), 195 (base peak), 166 (27), 151 (64), 136 (9), 121 (25), 109 (6). HR-MS: Calcd for $C_{18}H_{21}NO_3S$: 331.1242. Found: 331.1230.

N-(2,3-Dimethoxyphenylmethyl)-*N*-[2-(phenylthio)ethyl]formamide (**8c**): Eluent for column chromatography: AcOEt–*n*-hexane (1 : 1). Yield: 13.57 g, 91% from **7c** (13.6 g, 44.9 mmol). Pale yellow gum. IR: 1673 (=NCO–), 1585, 1485, 1274. ^{1}H-NMR: 2.90—3.10 (2H, m, $-SCH_2-$), 3.25—3.55 (2H, m, $-CH_2N=$), 3.80, 3.81, 3.86 (total 6H, each s, $2\times-OCH_3$), 4.41, 4.56 (total 2H, each s, $ArCH_2N=$), 6.55—7.05 (3H, m, Ar-H), 7.10—7.40 (5H, m, Ar-H), 8.09, 8.28 (total 1H, each s, =NCHO). EI-MS *m/z*: 331 (M^+, 28), 302 (3), 222 (6), 195 (base peak), 166 (30), 151 (50), 136 (48), 109 (5), 91 (16). HR-MS: Calcd for $C_{18}H_{21}NO_3S$: 331.1242. Found: 331.1222.

N-(2,4-Dimethoxyphenylmethyl)-*N*-[2-(phenylthio)ethyl]formamide (**8d**): Eluent for column chromatography: AcOEt–*n*-hexane (1 : 1). Yield: 9.03 g, 95% from **7d** (8.7 g, 28.7 mmol). Pale yellow gum. IR: 1671 (=NCO–), 1613, 1589, 1510. ^{1}H-NMR: 2.85—3.06 (total 2H, m, $-SCH_2-$), 3.24—3.50 (total 2H, m, $-CH_2N=$), 3.76, 3.80 (each 3H, s, $2\times-OCH_3$), 4.31, 4.47 (total 2H, each s, $ArCH_2N=$), 6.32—6.43, 6.82—6.93 (total 3H, each m, Ar-H), 7.05—7.40 (total 5H, m, Ar-H), 8.06, 8.25 (total 1H, each s, =NCHO). EI-MS *m/z*: 331 (M^+, 16), 302 (4), 195 (67), 166 (7), 151 (base peak), 136 (6), 121 (19), 109 (4), 91 (7). HR-MS: Calcd for $C_{18}H_{21}NO_3S$: 331.1242. Found: 331.1276.

N-(3,5-Dimethoxyphenylmethyl)-*N*-[2-(phenylthio)ethyl]formamide (**8e**): Eluent for column chromatography: AcOEt–*n*-hexane (1 : 1). Yield: 17.0 g, 93% from **7e** (16.8 g, 55.5 mmol). Pale yellow gum. IR: 1671 (=NCO–), 1599, 1429, 1207, 1158. ^{1}H-NMR: 2.90—3.15 (2H, m, $-SCH_2-$), 3.25—3.58 (2H, m, $-CH_2N=$), 3.76 (6H, s, $2\times-OCH_3$), 4.34, 4.44 (total 2H, each s, $ArCH_2N=$), 6.25—6.40 (total 3H, m, Ar-H), 7.20—7.35 (5H, m, Ar-H), 8.12, 8.25 (total 1H, each s, =NCHO). EI-MS *m/z*: 331 (M^+, 18), 195 (base peak), 166 (6), 151 (53), 136 (10). HR-MS: Calcd for $C_{18}H_{21}NO_3S$: 331.1242. Found: 331.1256.

N-(3-Methoxyphenylmethyl)-*N*-[2-(phenylthio)ethyl]formamide (**8f**): Eluent for column chromatography: AcOEt–*n*-hexane (1 : 1). Yield: 6.92 g, 78% from **7f** (8.0 g, 29.3 mmol). Pale yellow gum. IR: 1678 (=NCO–), 1585, 1439, 1263, 1157, 1049. ^{1}H-NMR: 2.84—3.16 (2.5H, m, $-SCH_2-$, ArCHN=), 3.24—3.56 (2.5H, m, $-CH_2N=$, ArCHN=), 3.77 (3H, s, $-OCH_3$), 4.38, 4.47 (total 1H, each s, ArCHN=), 6.62—6.92 (3H, m, Ar-H), 7.10—7.38 (6H, m, Ar-H), 8.12, 8.26 (total 1H, each s, =NCHO). EI-MS *m/z*: 301 (M^+, 35), 192 (10), 178 (5), 165 (22), 136 (base peak), 121 (55), 109 (6), 91 (14). HR-MS: Calcd for $C_{17}H_{19}NO_2S$: 301.1136. Found: 301.1097.

N-(2-Methoxyphenylmethyl)-*N*-[2-(phenylthio)ethyl]formamide (**8g**): Eluent for column chromatography: AcOEt–*n*-hexane (1 : 1). Yield: 6.08 g, 92% from **7g** (6.0 g, 22 mmol). Pale yellow gum. IR: 1672 (=NCO–), 1587, 1492, 1438, 1288, 1245, 1114, 1025. ^{1}H-NMR: 2.85—3.10 (2H, m, $-SCH_2-$), 3.28—3.51 (2H, m, $-CH_2N=$), 3.80 (total 3H, s, $-OCH_3$), 4.39, 4.55 (total 2H, each s, $ArCH_2N=$), 6.75—7.10 (4H, m, Ar-H), 7.10—7.40 (5H, m, Ar-H), 8.09, 8.27 (total 1H, each s, =NCHO). EI-MS *m/z*: 301 (M^+, 45), 272 (5), 192 (25), 165 (9), 136 (base peak), 121 (62), 109 (5), 91 (31). HR-MS: Calcd for $C_{17}H_{19}NO_2S$: 301.1136. Found: 301.1161.

N-(4-Methoxyphenylmethyl)-*N*-[2-(phenylthio)ethyl]formamide (**8h**): Eluent for column chromatography: AcOEt–*n*-hexane (1 : 1). Yield: 6.91 g, 90% from **7h** (7.0 g, 25.6 mmol). Pale yellow gum. IR: 1672 (=NCO–), 1612, 1513, 1439, 1248, 1176, 1031. ^{1}H-NMR: 2.82—3.10 (2H, m, $-SCH_2-$), 3.20—3.65 (2H, m, $-CH_2N=$), 3.78, 3.80 (total 3H, s, $-OCH_3$), 4.34, 4.44 (total 2H, each s, $ArCH_2N=$), 6.75—7.40 (9H, m, Ar-H), 8.10, 8.27 (total 1H, each s, =NCHO). EI-MS *m/z*: 301 (M^+, 33), 272 (3), 192 (6), 165 (59), 136 (59), 121 (base peak), 109 (7), 91 (6). HR-MS: Calcd for $C_{17}H_{19}NO_2S$: 301.1136. Found: 301.1110.

Oxidation of 8 with $NaIO_4$ A solution of sodium metaperiodate (1.5 mol eq) in H_2O (40—100 ml) was added to a solution of one of **8b—h** (3.0—16.9 g) in MeOH (150—350 ml), and the mixture was stirred at room temperature for 16 h. After removal of precipitated inorganic materials by filtration, the filtrate was concentrated *in vacuo*. The residue was extracted with $CHCl_3$. The products **9b—h** and **10b—h** were separated by column chromatography.

N-(2,5-Dimethoxyphenylmethyl)-*N*-[2-(phenylsulfinyl)ethyl]formamide (**9b**): Eluent for column chromatography: AcOEt. Yield: 8.28 g, 93% from **8b** (8.5 g, 25.7 mmol). mp 80—84 °C. Colorless needles (from AcOEt). IR: 1671 (=NCO–), 1504, 1228, 1046. ^{1}H-NMR: 2.70—3.30, 3.40—3.70 (each 2H, m, $-SOCH_2CH_2N=$), 3.74, 3.75, 3.78 (total 6H, each s, $2\times-OCH_3$), 4.42—4.53 (2H, each s, $ArCH_2N=$), 6.70—6.90 (3H, m, Ar-H), 7.40—7.80 (5H, m, Ar-H), 8.21, 8.25 (total 1H, each s, =NCHO). CI-MS *m/z*: 348 (MH^+, base peak), 332 (200, 222 (20), 151 (10).

N-(2,5-Dimethoxyphenylmethyl)-*N*-[2-(phenylsulfonyl)ethyl]formamide (**10b**): Eluent for column chromatography: AcOEt. Yield: 276 mg, 3% from **8b** (8.5 g, 25.7 mmol). mp 104—106 °C. Colorless plates (from AcOEt). IR: 1671 (=NCO–), 1508, 1305, 1151. ^{1}H-NMR: 3.10—3.40, 3.45—3.70 (each 2H, m, $-SO_2CH_2CH_2N=$), 3.73, 3.75, 3.77, 3.78 (total 6H, each s, $2\times-OCH_3$), 4.38 (2H, s, $ArCH_2N=$), 6.70—6.85 (3H, m, Ar-H), 7.50—7.95 (5H, m, Ar-H), 8.09, 8.18 (total 1H, each s, =NCHO). EI-MS *m/z*: 363 (M^+, 39), 334 (base peak), 192 (8), 166 (19), 151 (26), 121 (17). HR-MS: Calcd for $C_{18}H_{21}NO_5S$: 363.1141. Found: 363.1091.

N-(2,3-Dimethoxyphenylmethyl)-*N*-[2-(phenylsulfinyl)ethyl]formamide (**9c**): Eluent for column chromatography: AcOEt. Yield: 12.53 g, 92% from **8c** (13.0 g, 39.3 mmol). Pale yellow gum. IR: 1671 (=NCO–), 1589, 1485, 1274, 1085, 1046. ^{1}H-NMR: 2.70—3.30, 3.40—3.70 (each 2H, m, $-SOCH_2CH_2N=$), 3.82, 3.85, 3.87 (total 6H, each s, $2\times-OCH_3$), 4.47, 4.57 (total 2H, each s, $ArCH_2N=$), 6.70—7.15 (3H, m, Ar-H), 7.40—7.70 (5H, m, Ar-H), 8.23, 8.28 (total 1H, each s, =NCHO). CI-MS *m/z*: 348 (MH^+, base peak), 332 (7).

N-(2,3-Dimethoxyphenylmethyl)-*N*-[2-(phenylsulfonyl)ethyl]formamide (**10c**): Eluent for column chromatography: AcOEt. Yield: 885 mg, 6% from **8c** (13.0 g, 39.3 mmol). Pale yellow gum. IR: 1671 (=NCO–), 1589, 1485, 1307, 1152, 1087. ^{1}H-NMR: 3.10—3.20, 3.22—3.70 (each 2H, m, $-SO_2CH_2CH_2N=$), 3.77, 3.83, 3.85, 3.86 (total 6H, each s, $2\times-OCH_3$), 4.37, 4.42 (total 2H, each s, $ArCH_2N=$), 6.65—7.15 (3H, m, Ar-H), 7.45—7.95 (5H, m, Ar-H), 8.13, 8.19 (total 1H, each s, =NCHO). EI-MS *m/z*: 363 (M^+, 18), 334 (base peak), 304 (5), 192 (5), 166 (13), 151 (11), 136 (12). HR-MS: Calcd for $C_{18}H_{21}NO_5S$: 363.1140. Found: 363.1123.

N-(2,4-Dimethoxyphenylmethyl)-*N*-[2-(phenylsulfinyl)ethyl]formamide (**9d**): Eluent for column chromatography: AcOEt. Yield: 12.8 g, 94% from **8d** (13.0 g, 39.3 mmol). Pale yellow gum. IR: 1655 (=NCO–), 1615, 1510, 1042. ^{1}H-NMR: 2.65—3.15, 3.40—3.70 (each 2H, m, $-SOCH_2CH_2N=$), 3.76, 3.79, 3.81 (total 6H, each s, $2\times-OCH_3$), 4.36, 4.78 (total 2H, d, $J=1.0$ Hz, and s, $ArCH_2N=$), 6.35—6.55, 7.05—7.25 (total 3H, each m, Ar-H), 7.44—7.70 (total 5H, m, Ar-H), 8.17, 8.25 (total 1H, each s, =NCHO). CI-MS *m/z*: 348 (MH^+, base peak), 330 (7), 301 (15), 222 (12), 151 (76).

N-(2,4-Dimethoxyphenylmethyl)-*N*-[2-(phenylsulfonyl)ethyl]formamide (**10d**): Eluent for column chromatography: AcOEt. Yield: 570 mg, 4% from **8d** (13.0 g, 39.3 mmol). Pale yellow gum. IR: 1671 (=NCO–), 1615, 1591, 1510. ^{1}H-NMR: 3.10—3.39, 3.40—3.70 (each 2H, m, $-SO_2CH_2CH_2N=$), 3.76, 3.79, 3.82 (total 6H, each s, $2\times-OCH_3$), 4.33 (2H, s, $ArCH_2N=$), 6.35—6.52, 7.00—7.18 (total 3H, each m, Ar-H), 7.45—7.95 (total 5H, m, Ar-H), 8.06, 8.17 (total 1H, each s, =NCHO). EI-MS *m/z*: 363 (M^+, 13), 334 (base peak), 194 (10), 166 (19), 151 (30), 121 (15). HR-MS: Calcd for $C_{18}H_{21}NO_5S$: 363.1141. Found: 363.1094.

N-(3,5-Dimethoxyphenylmethyl)-*N*-[2-(phenylsulfinyl)ethyl]formamide (**9e**): Eluent for column chromatography: AcOEt. Yield: 16.12 g, 91% from **8e** (16.9 g, 51.1 mmol). mp 76—86 °C. Colorless plates (from AcOEt). IR: 1659 (=NCO–), 1603, 1431, 1357, 1296, 1209, 1164, 1040. ^{1}H-NMR: 2.70—3.30, 3.45—3.75 (each 2H, m, $-SOCH_2CH_2N=$), 3.77, 3.78 (total 6H, each s, $2\times-OCH_3$), 4.41, 4.54 (total 2H, each s, $ArCH_2N=$), 6.30—6.40 (3H, m, Ar-H), 7.45—7.60 (5H, m, Ar-H), 8.25, 8.27 (total 1H, each s, =NCHO). CI-MS *m/z*: 348 (MH^+, base peak), 222 (54).

N-(3,5-Dimethoxyphenylmethyl)-*N*-[2-(phenylsulfonyl)ethyl]formamide (**10e**): Eluent for column chromatography: AcOEt. Yield: 926 mg, 5% from **8e** (16.9 g, 51.1 mmol). mp 117—120 °C. Colorless needles

($CHCl_3$–*n*-hexane). IR: 1665 (=NCO–), 1603, 1431, 1296, 1210, 1164. ^{1}H-NMR: 3.30—3.70 (4H, m, $-SO_2CH_2CH_2N=$), 3.76, 3.79 (total 6H, each s, 2×$-OCH_3$), 4.33, 4.40 (total 2H, each s, $ArCH_2N=$), 6.31—6.41 (3H, m, Ar-H), 7.54—7.94 (5H, m, Ar-H), 8.18 (1H, s, =NCHO). EI-MS *m/z*: 363 (M^+, 56), 334 (89), 222 (40), 194 (19), 166 (30), 152 (90), 151 (base peak), 139 (7), 121 (8). HR-MS: Calcd for $C_{18}H_{21}NO_5S$: 363.1141. Found: 363.1182.

N-(3-Methoxyphenylmethyl)-*N*-[2-(phenylsulfinyl)ethyl]formamide (**9f**): Eluent for column chromatography: AcOEt–MeOH (95 : 5). Yield: 2.73 g, 86% from **8f** (3.0 g, 9.97 mmol). Pale yellow gum. IR: 1668 (=NCO–), 1600, 1490, 1444, 1263, 1036. ^{1}H-NMR: 2.65—3.20 (2H, m, $SOCH_2$–), 3.59 (2H, t, J=7.0 Hz, $-CH_2N=$), 3.79, 3.81 (total 3H, each s, $-OCH_3$), 4.46, 4.55 (total 2H, each s, $ArCH_2N=$), 6.65—6.95 (3H, m, Ar-H), 7.10—7.70 (6H, m, Ar-H), 8.26 (1H, s, =NCHO). CI-MS *m/z*: 318 (MH^+, base peak), 302 (47), 279 (25), 192 (50).

N-(3-Methoxyphenylmethyl)-*N*-[2-(phenylsulfonyl)ethyl]formamide (**10f**): Eluent for column chromatography: AcOEt–MeOH (95 : 5). Yield: 95 mg, 3% from **8f** (3.0 g, 9.97 mmol). mp 96—100 °C. Pale yellow needles (from AcOEt–*n*-hexane). IR: 1671 (=NCO–), 1603, 1444, 1265, 1046. ^{1}H-NMR: 3.10—3.40, 3.50—3.70 (each 2H, m, $-SO_2CH_2CH_2N=$), 3.78, 3.81 (total 3H, each s, $-OCH_3$), 4.37, 4.44 (total 2H, each s, $ArCH_2N=$), 6.65—7.95 (9H, m, Ar-H), 8.17, 8.19 (total 12H, each s, =NCHO). EI-MS *m/z*: 333 (M^+, 21), 304 (base peak), 162 (5), 136 (11), 121 (12). HR-MS: Calcd for $C_{17}H_{19}NO_4S$: 333.1035. Found: 333.1002.

N-(2-Methoxyphenylmethyl)-*N*-[2-(phenylsulfinyl)ethyl]formamide (**9g**): Eluent for column chromatography: AcOEt–MeOH (95 : 5). Yield: 5.0 g, 95% from **8g** (5.0 g, 16.6 mmol). mp 98—100 °C. Colorless needles (from AcOEt–*n*-hexane). IR: 1669 (=NCO–), 1657, 1495, 1441, 1400, 1249, 1048. ^{1}H-NMR: 2.80—3.25, 3.25—3.90 (each 2H, m, $-SOCH_2-CH_2N=$), 3.80, 3.82 (total 3H, each s, $-OCH_3$), 4.44, 4.56 (total 2H, each s, $ArCH_2N=$), 7.60—6.80 (9H, m, Ar-H), 8.21, 8.27 (total 1H, each s, =NCHO). CI-MS *m/z*: 318 (MH^+, base peak), 302 (54), 192 (22), 162 (36).

N-(4-Methoxyphenylmethyl)-*N*-[2-(phenylsulfinyl)ethyl]formamide (**9h**): Eluent for column chromatography: AcOEt–MeOH (95 : 5). Yield: 4.95 g, 94% from **8h** (5.0 g, 16.6 mmol). Pale yellow gum. IR: 1672 (=NCO–), 1612, 1513, 1442, 1249, 1039. ^{1}H-NMR: 2.65—3.30 (2H, m, $-SOCH_2$–), 3.54 (2H, t, J=7.0 Hz, $-CH_2N=$), 3.80, 3.81 (total 3H, each s, $-OCH_3$), 4.41, 4.48 (total 2H, each s, $ArCH_2N=$), 6.80—7.20 (4H, m, Ar-H), 7.40—7.70 (5H, m, Ar-H), 8.22, 8.26 (total 1H, each s, =NCHO). CI-MS *m/z*: 318 (MH^+, base peak), 302 (20), 192 (24).

N-(4-Methoxyphenylmethyl)-*N*-[2-(phenylsulfonyl)ethyl]formamide (**10h**): Eluent for column chromatography: AcOEt–MeOH (95 : 5). Yield: 165 mg, 3% from **8h** (5.0 g, 16.6 mmol). Pale yellow gum. IR: 1672 (=NCO–), 1612, 1514, 1446, 1306, 1250, 1151, 1086, 1032. ^{1}H-NMR: 3.10—3.40, 3.45—3.70 (each 2H, m, $-SO_2CH_2CH_2N=$), 3.80, 3.82 (total 3H, each s, $-OCH_3$), 4.33, 4.39 (total 2H, each s, $ArCH_2N=$), 6.75—7.20 (4H, m, Ar-H), 7.40—7.95 (5H, m, Ar-H), 8.14, 8.19 (total 1H, each s, =NCHO). EI-MS *m/z*: 333 (M^+, 13), 304 (base peak), 164 (9), 136 (7), 121 (18), 109 (4). HR-MS: Calcd for $C_{17}H_{19}NO_4S$: 333.1035. Found: 333.1053.

General Procedure for the Pummerer Cyclization of Sulfoxides (9) Method A TFAA (5 mol eq) was added to a solution of a sulfoxide (**9b—h**) (0.1—4.0 g) in dry benzene (10—100 ml) at room temperature, and the mixture was stirred for 18—150 h. The reaction mixture was concentrated *in vacuo*, and the product was purified by column chromatography. The sulfoxides **9b, c**, **9f**, and **9h** gave **11b, c**, **11f**, and **11h**, respectively, as a sole product and **9d** and **9g** gave intractable mixtures. In the case of **9e**, the products were separated by column chromatography with AcOEt–*n*-hexane (1 : 1) and $CHCl_3$–MeOH (7 : 3) to give **11e** in 27% yield and **12** in 60% yield. Compound **12**, when allowed to stand overnight at room temperature, yielded a mixture including **18a**.

Method B TFAA (5 mol eq) was added to a solution of the sulfoxides (**9a—h**) (0.1—4.55 g) in dry benzene (5—100 ml) at room temperature. After the mixture was stirred for 0.5—1 h, $BF_3 \cdot Et_2O$ (3 mol eq) was added, and the reaction mixture was further stirred at the same temperature for a further 1—4 h. The reaction mixture was washed with 5% NaOH–H_2O. The products were purified by column chromatography. The sulfoxides **9a**[3], **9b, c**, **9g**, and **9h** gave the corresponding TIQs (**11a**,[3] **11b, c**, **11g**, **11h**) as a sole product and **9f** gave an inseparable mixture of **11f** and **11i** (*ca.* 3 : 1) in 84% yield, while **9d** gave an intractable mixture. On the other hand, the sulfoxide **9e** gave **12** as a pale white powder in 49% yield (calculated as TFA salt) upon filtration of the reaction mixture, and chromatography of the filtrate with AcOEt–*n*-hexane (1 : 1) gave **11e** (27%) and **13a** (2%), respectively. Compound **12** did not change when allowed to stand overnight at room temperature.

2-Formyl-1,2,3,4-tetrahydro-5,8-dimethoxy-4-phenylthioisoquinoline (**11b**): Eluent for column chromatography: $CHCl_3$–MeOH (99 : 1). Yield: 151 mg, 60% by method A from **9b** (200 mg, 0.58 mmol); 1.87 g, 79% by method B from **9b** (2.5 g, 7.20 mmol). mp 133—135 °C. Colorless plates (from AcOEt). IR: 1676 (=NCO–), 1460, 1437, 1260. ^{1}H-NMR: 3.30—5.32 (5H, m, $-SCHCH_2-$, $ArCH_2N=$), 3.78, 3.80, 3.87, 3.88 (total 6H, each s, 2×$-OCH_3$), 6.74, 6.76 (total 2H, each s, Ar-H), 7.20—7.80 (5H, m, Ar-H), 8.11, 8.43 (total 1H, each s, =NCHO). EI-MS *m/z*: 329 (M^+, 7), 220 (base peak), 192 (18), 190 (15), 161 (22), 160 (19). HR-MS: Calcd for $C_{18}H_{19}NO_3S$: 329.1085. Found 329.1087. *Anal.* Calcd for $C_{18}H_{19}NO_3S$: C, 65.64; H, 5.82; N, 4.25. Found: C, 65.47; H, 5.90; N, 3.96.

2-Formyl-1,2,3,4-tetrahydro-7,8-dimethoxy-4-phenylthioisoquinoline (**11c**): Eluent for column chromatography: AcOEt–*n*-hexane (1 : 1). Yield: 3.19 g, 82% by method A from **9c** (4.0 g, 11.53 mmol); 3.27 g, 86% by method B from **9c** (4.0 g, 11.53 mmol). mp 157—160 °C. Colorless plates (from AcOEt). IR: 1682 (=NCO–), 1490, 1430, 1275. ^{1}H-NMR: 3.30—4.70 (m, $-SCHCH_2N=$, $ArCH_2N=$), 4.20, 5.17 (each d, J= 19.0 Hz, $ArCH_2N=$), 3.87, 3.88 (total 6H, each s, 2×$-OCH_3$), 6.84, 7.12 (total 2H, each d, J=8.5 Hz, Ar-H), 7.25—7.65 (5H, m, Ar-H), 8.04, 8.37 (total 1H, each s, =NCHO). EI-MS *m/z*: 329 (M^+, 2), 220 (base peak), 205 (6), 190 (11), 175 (10), 161 (21), 146 (6), 110 (10). HR-MS: Calcd for $C_{18}H_{19}NO_3S$: 329.1085. Found: 329.1071.

2-Formyl-1,2,3,4-tetrahydro-5,7-dimethoxy-4-phenylthioisoquinoline (**11e**): Eluent for column chromatography: AcOEt–*n*-hexane (1 : 1). Yield: 766 mg, 27% by method A from **9e** (3.0 g, 8.65 mmol); 258 mg, 27% by method B from **9e** (1.0 g, 2.88 mmol). mp 133—136 °C. Colorless plates (from AcOEt). IR: 1667 (=NCO–), 1605, 1437, 1363, 1205, 1149, 1094. ^{1}H-NMR: 2.95—4.75 (m, $-SCHCH_2N=$, $ArCH_2N=$), 3.80, 3.88 (total 6H, each s, 2×$-OCH_3$), 4.10, 5.22 (each d, J=17.8 Hz, $ArCH_2N=$), 6.25, 6.35 (each 1H, d, J=2.2 Hz, Ar-H), 7.25—7.70 (5H, m, Ar-H), 8.09, 8.39 (total 1H, each s, =NCHO). EI-MS *m/z*: 329 (M^+, 0.4), 220 (base peak), 190 (25), 175 (16), 161 (14), 146 (5), 110 (15). HR-MS: Calcd for $C_{18}H_{19}NO_3S$: 329.1086. Found: 329.1017.

N-[3,5-Dimethoxy-2-(phenylthio)phenylmethyl]-*N*-(2-hydroxyethyl)-formamide (**18a**): Eluent for column chromatography: AcOEt–*n*-hexane (2 : 1). Colorless gum. Yield: 128 mg, 38% from **12** (429 mg, 0.97 mmol, calculated as TFA salt). IR (KBr): 3388 (–OH), 1659 (=NCO–), 1595, 1460, 1437, 1323, 1203, 1166. ^{1}H-NMR: 3.10—3.70 (4H, m, $-OCH_2CH_2N=$), 3.81, 3.82, 3.86 (total 6H, each s, 2×$-OCH_3$), 4.66, 4.84 (total 2H, each s, $ArCH_2N=$), 6.45—6.65 (2H, m, Ar-H), 6.85—7.35 (5H, m, Ar-H), 8.19, 8.25 (total 1H, each s, =NCHO). EI-MS *m/z*: 347 (M^+, 22), 318 (5), 257 (17), 238 (base peak), 210 (62), 167 (16), 151 (5). HR-MS: Calcd for $C_{18}H_{21}NO_4S$: 347.1191. Found: 347.1159.

N-[3,5-Dimethoxy-2-(phenylthio)phenylmethyl]-*N*-[2-(phenylthio)-ethyl]formamide (**13a**): Eluent for column chromatography: AcOEt–*n*-hexane (1 : 1). Yield: 20 mg, 2% by method B from **9e** (1.0 g, 2.88 mmol). Pale yellow gum. IR: 1673 (=NCO–), 1595, 1458, 1437, 1323, 1203, 1164. ^{1}H-NMR: 2.90—3.60 (total 4H, m, $-SCH_2CH_2N=$), 3.81, 3.82, 3.86 (total 6H, each s, 2×$-OCH_3$), 4.67, 4.76 (total 2H, each d, J=13.0 Hz, $ArCH_2N=$), 6.30—6.70 (2H, m, Ar-H), 6.80—7.40 (10H, m, Ar-H), 8.08, 8.19, 8.24 (total 1H, each s, =NCHO). EI-MS *m/z*: 439 (M^+, 51), 330 (base peak), 302 (34), 259 (37), 257 (26), 244 (17), 194 (55), 182 (20). CI-MS *m/z*: 440 (MH^+, base peak), 297 (16). HR-MS: Calcd for $C_{24}H_{25}NO_3S_2$: 439.1276. Found: 439.1293.

2-Formyl-1,2,3,4-tetrahydro-7-methoxy-4-phenylthioisoquinoline (**11f**): Eluent for column chromatography: AcOEt–*n*-hexane (1 : 1). Yield: 846 mg, 85% by method A from **9f** (1.0 g, 3.15 mmol); 830 mg (mixture of **11f** and **11i**), 84% by method B from **9f** (1.0 g, 3.15 mmol). mp 112—115 °C. Colorless needles (from AcOEt–*n*-hexane). IR: 1676 (=NCO–), 1606, 1502, 1437, 1333, 1250, 1160, 1111, 1036. ^{1}H-NMR: 3.35—4.60 (m, $-SCHCH_2N=$, $ArCH_2N=$), 4.21, 5.15 (each d, J=17.7 Hz, $ArCH_2N=$), 6.60—6.90 (3H, m, Ar-H), 7.25—7.65 (5H, m, Ar-H), 8.04, 8.34 (total 1H, each s, =NCHO). EI-MS *m/z*: 299 (M^+, 3), 190 (base peak), 162 (19), 160 (18), 145 (9), 131 (9), 117 (6). CI-MS *m/z*: 300 (MH^+, 94), 190 (base peak).

2-Formyl-1,2,3,4-tetrahydro-8-methoxy-4-phenylthioisoquinoline (**11g**): Eluent for column chromatography: AcOEt–*n*-hexane (1 : 1). Yield: 240 mg, 25% by Method B from **9g** (1.0 g, 3.15 mmol). Pale yellow gum. IR (KBr): 1671 (=NCO–), 1589, 1471, 1437, 1267, 1091. ^{1}H-NMR: 2.90—4.80 (m, $-SCHCH_2N=$, $ArCH_2N=$), 4.11, 5.12 (each d, J=

18.6 Hz, $ArCH_2N=$), 3.84, 3.86 (total 3H, each s, $-OCH_3$), 6.70—7.70 (9H, m, Ar-H), 8.05, 8.37 (total 1H, each s, =NCHO). EI-MS *m/z*: 299 (M^+, 2), 190 (56), 189 (base peak), 162 (25), 145 (15), 131 (9). CI-MS *m/z*: 300 (MH^+, base peak), 190 (13).

2-Formyl-1,2,3,4-tetrahydro-6-methoxy-4-phenylthioisoquinoline (**11h**): Eluent for column chromatography: AcOEt–*n*-hexane (1 : 1). Yield: 44 mg, 10% by method A from **9h** (500 mg, 1.58 mmol) and 3.62 g, 84% by method B from **9h** (4.55 g, 14.35 mmol). Pale yellow gum. IR: 1670 (=NCO–), 1612, 1504, 1439, 1259, 1036. ^{1}H-NMR: 3.40—4.60 (m, $-SCHCH_2N=$, $ArCH_2N=$), 3.78 (3H, each s, $-OCH_3$), 4.23, 5.07 (each d, J=16.9 Hz, $ArCH_2N=$), 6.75—7.15 (4H, m, Ar-H), 7.30—7.65 (5H, m, Ar-H), 8.04, 8.33 (total 1H, each s, =NCHO). EI-MS *m/z*: 299 (M^+, 1), 190 (47), 189 (base peak), 188 (39), 162 (24), 160 (32), 145 (12), 117 (7). CI-MS *m/z*: 300 (MH^+, base peak), 190 (15).

Reductive Desulfurization of 2-Formyl-4-phenylthio-TIQs (11) $NaBH_4$ (10.5 mol eq) was added in small portions to a stirred solution of **11b, c**, **11e—i** (0.02—5.50 g) and $NiCl_2 \cdot 6H_2O$ (3.5 mol eq) in MeOH–THF (3 : 1) (8—320 ml) under ice-cooling. The mixture was stirred at room temperature for a further 30 min, then filtered and the filtrate was concentrated *in vacuo*. The residue was suspended in water, acidified with 5% HCl–H_2O, and extracted with $CHCl_3$. The compounds (**21b, c**, **21e—i**) and (**22b, c**, **22e—i**) were separated by column chromatography.

2-Formyl-1,2,3,4-tetrahydro-5,8-dimethoxyisoquinoline (**21b**): Eluent for column chromatography: AcOEt–*n*-hexane (1 : 1). Yield: 740 mg, 64% from **11b** (1.73 g, 5.26 mmol). mp 110—112 °C. Colorless plates (from AcOEt). IR: 1684 (=NCO–), 1603, 1485, 1429, 1257. ^{1}H-NMR: 2.65—2.90 (2H, m, $-CH_2-$), 3.50—3.70 (2H, m, $-CH_2N=$), 3.76, 3.78, 3.80 (total 6H, each s, $2\times-OCH_3$), 4.45, 4.59 (total 2H, each s and d, J=1.0 Hz, $ArCH_2N=$), 6.67 (2H, s, Ar-H), 8.19, 8.25 (total 1H, each s, =NCHO). EI-MS *m/z*: 221 (M^+, base peak), 206 (19), 190 (35), 178 (13), 164 (300, 162 (25), 149 (20). HR-MS: Calcd for $C_{12}H_{15}NO_3$: 221.1052. Found: 221.1071.

2-Formyl-1,2-dihydro-5,8-dimethoxyisoquinoline (**22b**): Eluent for column chromatography: AcOEt–*n*-hexane (1 : 1). Yield: 200 mg, 18% from **11b** (1.73 g, 5.26 mmol). mp 125—127 °C. Colorless plates (from AcOEt). IR: 1686 (=NCO–), 1640, 1593, 1491, 1350, 1261. ^{1}H-NMR: 3.77, 3.78, 3.80 (total 6H, each s, $2\times-OCH_3$), 4.75, 4.86 (total 2H, s, d, J=1.0 Hz, $ArCH_2N=$), 6.11, 6.37 (total 1H, d, dd, J=8.0 Hz, J=1.0, 8.0 Hz, olefinic-H), 6.54, 7.08 (total 1H, d, dd, J=8.0 Hz, J=1.0, 8.0 Hz, olefinic-H), 6.67, 6.70 (total 2H, each s, Ar-H), 8.17, 8.32 (total 1H, each s, =NCHO). EI-MS *m/z*: 219 (M^+, base peak), 218 (67), 204 (14), 190 (47), 175 (28), 160 (48). HR-MS: Calcd for $C_{12}H_{13}NO_3$: 219.0895. Found: 219.0914.

2-Formyl-1,2,3,4-tetrahydro-7,8-dimethoxyisoquinoline (**21c**): Eluent for column chromatography: AcOEt–*n*-hexane (1 : 1). Yield: 2.94 g, 80% from **11c** (5.50 g, 16.72 mmol). Pale yellow gum. IR: 1671 (=NCO–), 1495, 1437, 1282, 1087. ^{1}H-NMR: 2.70—2.90 (2H, m, $-CH_2-$), 3.50—3.80 (2H, m, $-CH_2N=$), 3.86, 3.87, 3.88 (total 6H, each s, $2\times-OCH_3$), 4.54, 4.68 (total 2H, each s, $ArCH_2N=$), 6.81, 6.83 (total 2H, each s, Ar-H), 8.20, 8.27 (total 1H, each s, =NCHO). EI-MS *m/z*: 221 (M^+, base peak), 206 (33), 190 (19), 178 (16), 164 (23), 149 (26), 135 (7), 121 (7). HR-MS: Calcd for $C_{12}H_{15}NO_3$: 221.1052. Found: 221.1013.

2-Formyl-1,2-dihydro-7,8-dimethoxyisoquinoline (**22c**): Eluent for column chromatography: AcOEt–*n*-hexane (1 : 1). Yield: 480 mg, 13% from **11e** (5.5 g, 16.72 mmol). mp 98—104 °C. Colorless plates (from $CHCl_3$–*n*-hexane). IR: 1636 (=NCO–), 1495, 1456, 1270. ^{1}H-NMR: 3.85, 3.86, 3.87 (total 6H, each s, $2\times-OCH_3$), 4.81, 4.94 (total 2H, s, d, J=1.0 Hz, $ArCH_2N=$), 5.71, 5.98 (total 1H, d, dd, J=7.8 Hz, J=1.3, 7.8 Hz, olefinic-H), 6.47, 7.00 (total 1H, d, dd, J=7.8 Hz, J=1.3, 7.8 Hz, olefinic-H), 6.73—6.90 (2H, m, Ar-H), 8.18, 8.33 (total 1H, each s, =NCHO). EI-MS *m/z*: 219 (M^+, base peak), 204 (16), 190 (31), 175 (23), 161 (23), 146 (12), 132 (9), 117 (4). HR-MS: Calcd for $C_{12}H_{13}NO_3$: 219.0895. Found: 219.0927.

2-Formyl-1,2,3,4-tetrahydro-5,7-dimethoxyisoquinoline (**21e**): Eluent for column chromatography: AcOEt–*n*-hexane (1 : 1). Yield: 500 mg, 62% from **11e** (1.20 g, 3.65 mmol). Pale yellow gum. IR: 1669 (=NCO–), 1601, 1439, 1205, 1147, 1096. ^{1}H-NMR: 2.62—2.80 (2H, m, $-CH_2-$), 3.50—3.72 (2H, m, $-CH_2N=$), 3.78, 3.79 (total 6H, each s, $2\times-OCH_3$), 4.47, 4.63 (total 2H, s, d, J=1.0 Hz, $ArCH_2N=$), 6.24, 6.32 (total 2H, each d, J=2.3 Hz, Ar-H), 8.18, 8.23 (total 1H, each s, =NCHO). EI-MS *m/z*: 221 (M^+, base peak), 206 (36), 192 (13), 176 (16), 164 (51), 149 (9), 135 (10), 121 (7). HR-MS: Calcd for $C_{12}H_{15}NO_3$: 221.1052. Found: 221.1059.

2-Formyl-1,2-dihydro-5,7-dimethoxyisoquinoline (**22e**): Eluent for column chromatography: AcOEt–*n*-hexane (1 : 1). Yield: 64 mg, 8% from **11e** (1.20 g, 3.65 mmol). mp 115—117 °C. Colorless needles (from AcOEt–*n*-hexane). IR: 1682 (=NCO–), 1644, 1613, 1593, 1504. ^{1}H-NMR: 3.80, 3.81 (total 6H, each s, $2\times-OCH_3$), 4.65, 4.86 (total 2H, each s, $ArCH_2N=$), 6.14, 6.46 (total 2H, each d, J=7.8 Hz, olefinic-H), 6.24, 6.32 (total 2H, each d, J=2.0 Hz, Ar-H), 8.12, 8.30 (total 1H, each s, =NCHO). EI-MS *m/z*: 219 (M^+, base peak), 204 (4), 190 (69), 175 (35), 147 (9), 132 (8). HR-MS: Calcd for $C_{12}H_{13}NO_3$: 219.0896. Found: 219.0875.

2-Formyl-1,2,3,4-tetrahydro-7-methoxyisoquinoline (**21f**): Eluent for column chromatography: AcOEt–*n*-hexane (1 : 1). Yield: 293 mg, 75% from **11f** (614 mg, 2.05 mmol); 227 mg, 46% from a mixture of **11f** and **11i** (*ca.* 3 : 1) (774 mg, 2.59 mmol). Pale yellow gum. IR (KBr): 1668 (=NCO–), 1506, 1440, 1278, 1263, 1039. ^{1}H-NMR: 2.65—2.95 (2H, m, $-CH_2-$), 3.63, 3.84 (total 2H, each t, J=6.0 Hz, $-CH_2N=$), 3.78 (3H, s, $-OCH_3$), 4.50, 4.66 (total 2H, each s, $ArCH_2N=$), 6.60—7.20 (3H, m, Ar-H), 8.18, 8.23 (total 1H, each s, =NCHO). EI-MS *m/z*: 191 (M^+, base peak), 176 (30), 162 (18), 146 (21), 134 (77), 119 (8), 104 (14), 91 (21). HR-MS: Calcd for $C_{11}H_{13}NO_2$: 191.0946. Found: 191.0971.

2-Formyl-1,2-dihydro-7-methoxyisoquinoline (**22f**): Eluent for column chromatography: AcOEt–*n*-hexane (1 : 1). Yield: 66 mg, 17% from **11f** (614 mg, 2.05 mmol); 54 mg, 11% from a mixture of **11f** and **11i** (*ca.* 3 : 1) (774 mg, 2.59 mmol). Yellow gum. IR: 1684 (=NCO–), 1637, 1506, 1442, 1253, 1035. ^{1}H-NMR: 3.79, 3.80 (total 3H, each s, $-OCH_3$), 4.69, 4.89 (total 2H, each s, $ArCH_2N=$), 5.79, 6.05 (total 1H, d, dd, J=7.90 Hz, J=1.50, 7.90 Hz, olefinic-H), 6.48 (0.8H, J=7.9 Hz, olefinic-H), 6.60—7.20 (3.2H, m, Ar-H and olefinic-H), 8.16, 8.30 (total 1H, each s, =NCHO). EI-MS *m/z*: 189 (M^+, base peak), 188 (60), 160 (84), 145 (24), 117 (41). HR-MS: Calcd for $C_{11}H_{11}NO_2$: 189.0790. Found: 189.0815.

2-Formyl-1,2,3,4-tetrahydro-8-methoxyisoquinoline (**21g**): Eluent for column chromatography: AcOEt–*n*-hexane (1 : 1). Yield: 102 mg, 68% from **11g** (250 mg, 0.84 mmol). mp 72—74 °C. Colorless prism (from AcOEt–*n*-hexane). Lit.[9] mp 74—76 °C. IR: 1654 (=NCO–), 1587, 1473, 1440, 1267, 1084. ^{1}H-NMR: 2.75—3.00 (2H, m, $-CH_2-$), 3.62, 3.77 (total 2H, each t, J=6.0 Hz, $-CH_2N=$), 3.83, 3.84 (total 3H, each s, $-OCH_3$), 4.47, 4.60 (total 2H, each s, $ArCH_2N=$), 6.68, 6.77 (total 2H, each s, Ar-H), 7.13 (total 1H, each d, J=0.9 Hz, Ar-H), 8.19, 8.26 (total 1H, each s, =NCHO). EI-MS *m/z*: 191 (M^+, base peak), 190 (33), 176 (12), 162 (21), 160 (18), 147 (28), 134 (19), 117 (6), 104 (14). HR-MS: Calcd for $C_{11}H_{13}NO_2$: 191.0946. Found: 191.0963.

2-Formyl-1,2-dihydro-8-methoxyisoquinoline (**22g**): Eluent for column chromatography: AcOEt–*n*-hexane (1 : 1). Yield: 18 mg, 11% from **11g** (250 mg, 0.84 mmol). mp 80—85 °C. Colorless prism (from AcOEt–*n*-hexane). IR: 1676 (=NCO–), 1637, 1475, 1440, 1363, 1271. ^{1}H-NMR: 3.82, 3.85 (total 3H, each s, $-OCH_3$), 4.79, 4.89 (total 2H, each s, $ArCH_2N=$), 5.72, 5.98 (total 1H, d, dd, J=7.9 Hz, J=1.5, 7.9 Hz, olefinic-H), 6.55, 6.77 (1H, d, dd, J=7.9, J=1.5, 7.9 Hz, olefinic-H), 6.60—7.20 (total 3H, m, Ar-H), 8.18, 8.33 (total 1H, each s, =NCHO). EI-MS *m/z*: 189 (M^+, base peak), 188 (80), 160 (71), 145 (67), 130 (5), 117 (20). HR-MS: Calcd for $C_{11}H_{11}NO_2$: 189.0790. Found: 189.0751.

2-Formyl-1,2,3,4-tetrahydro-6-methoxyisoquinoline (**21h**): Eluent for column chromatography: AcOEt–*n*-hexane (1 : 1). Yield: 1.65 g, 65% from **11h** (4.0 g, 13.38 mmol). Pale yellow gum. IR (KBr): 1683 (=CO–), 1614, 1506, 1463, 1436, 1263, 1191, 1041. ^{1}H-NMR: 2.85, 2.87 (total 2H, each t, J=5.90 Hz, $-CH_2-$), 3.63, 3.77 (total 2H, each t, J=5.90 Hz, $-CH_2N=$), 3.78 (3H, s, $-OCH_3$), 4.4, 4.62 (total 2H, each s, $ArCH_2N=$), 6.60—7.15 (3H, m, Ar-H), 8.19, 8.24 (total 1H, each s, =NCHO). EI-MS *m/z*: 191 (M^+, base peak), 190 (58), 176 (5), 162 (38), 160 (34), 147 (22), 134 (14), 118 (7), 103 (8), 91 (17). HR-MS: Calcd for $C_{11}H_{13}NO_2$: 191.0944. Found: 191.0936.

2-Formyl-1,2-dihydro-6-methoxyisoquinoline (**22h**): Eluent for column chromatography: AcOEt–*n*-hexane (1 : 1). Yield: 202 mg, 8% from 11h (4.0 g, 13.38 mmol). Pale yellow gum. IR: 1670 (=NCO–), 1635, 1506, 1355, 1278, 1193, 1037. ^{1}H-NMR: 3.79 (3H, s, $-OCH_3$), 4.67, 4.86 (total 2H, each s, $ArCH_2N=$), 5.77, 6.02 (total 1H, d, dd, J=7.9 Hz, J=1.5, 7.9 Hz, olefinic-H), 6.50—7.20 (total 4H, m, Ar-H and olefinic-H), 8.10—8.30 (total 1H, each s, =NCHO). EI-MS *m/z*: 189 (M^+, 73), 188 (base peak), 160 (89), 145 (21), 129 (4), 117 (41). HR-MS: Calcd for $C_{11}H_{11}NO_2$: 189.0788. Found: 189.0772.

2-Formyl-1,2,3,4-tetrahydro-5-methoxyisoquinoline (**21i**): Eluent for column chromatography: AcOEt–*n*-hexane (1 : 1). Yield: 87 mg, 18% from a mixture of **11f** and **11i** (*ca.* 3 : 1) (774 mg, 2.59 mmol). Pale yellow

gum. IR: 1672 (=NCO–), 1589, 1441, 1263, 1090. ^{1}H-NMR: 2.65—2.95 (2H, m, $-CH_2-$), 3.63, 3.79 (total 2H, each t, $J=6.0$ Hz, $-CH_2N=$), 3.82 (3H, s, $-OCH_3$), 4.51, 4.67 (total 2H, each s, $ArCH_2N=$), 6.77 (2H, dd, $J=2.5$, 7.9 Hz, Ar-H), 7.19 (1H, t, $J=7.9$ Hz, Ar-H), 8.19, 8.24 (total 1H, each s, =NCHO). EI-MS *m/z*: 191 (M^+, base peak), 176 (23), 162 (16), 160 (15), 146 (22), 134 (30), 119 (3), 104 (24), 91 (12). HR-MS: Calcd for $C_{11}H_{13}NO_2$: 191.0946. Found: 191.0957.

2-Formyl-1,2-dihydro-5-methoxyisoquinoline (**22i**): Eluent for column chromatography: AcOEt–*n*-hexane (1 : 1). Yield: 19 mg, 4% from a mixture of **11f** and **11i** (*ca.* 3 : 1) (774 mg, 2.59 mmol). Yellow gum. IR: 1684 (=NCO–), 1635, 1577, 1473, 1265, 1087. ^{1}H-NMR: 3.79, 3.83 (total 3H, each s, $-OCH_3$), 4.69, 4.89 (total 2H, each s, $ArCH_2N=$), 6.22, 6.40 (total 1H, d, dd, $J=7.9$ Hz, $J=1.5$, 7.9 Hz, olefinic-H), 6.56 (0.75H, d, $J=7.9$ Hz, olefinic-H), 6.62—7.20 (3.25H, m, Ar-H and olefinic-H), 8.09, 8.31 (total 1H, each s, =NCHO). EI-MS *m/z*: 189 (M^+, base peak), 188 (67), 160 (74), 145 (59), 117 (27). HR-MS: Calcd for $C_{11}H_{11}NO_2$: 189.0790. Found: 189.0801.

Hydrolysis of *N*-Formyl-TIQs (21) A solution of an *N*-formyl-TIQ (**21b, c, 21e—i**) (0.075—1.0 g) in EtOH (10—20 ml)–10% NaOH–H_2O (2—10 ml) was allowed to stand at room temperature (4—7 h for **21b, c, 21e—f**) or refluxed for 4—15 h (4 h for **21h, i**, 15 h for **21g**). The reaction mixture was concentrated *in vacuo*, and the residue was diluted with water and extracted with $CHCl_3$. The products were purified by column chromatography to give TIQs (**23b, c, 23e—i**).

1,2,3,4-Tetrahydro-5,8-dimethoxyisoquinoline (**23b**): Eluent for column chromatography: $CHCl_3$–MeOH (9 : 1). Yield: 468 mg, 89% from **21b** (604 mg, 2.73 mmol). Pale yellow gum. HCl salt: mp 259—263 °C (from EtOH–Et_2O). Lit.[10] mp 258—259 °C (HCl salt).

1,2,3,4-Tetrahydro-7,8-dimethoxyisoquinoline (**23c**): Eluent for column chromatography: $CHCl_3$–MeOH (4 : 1). Yield: 821 mg, 94% from **21c** (1.0 g, 4.52 mmol). Pale yellow gum. HCl salt: mp 197—200 °C (from EtOH–Et_2O). Lit.[8] mp 198—200 °C; lit.[11] mp 180 °C; lit.[12] mp 194—195 °C (each HCl salt).

1,2,3,4-Tetrahydro-5,7-dimethoxyisoquinoline (**23e**): Eluent for column chromatography: $CHCl_3$–MeOH (4 : 1). Yield: 47 mg, 72% from **21e** (75 mg, 0.34 mmol). mp 92—95 °C. Colorless needles (from AcOEt–*n*-hexane). HCl salt: mp 283—287 °C (from EtOH–Et_2O). Lit.[9] mp 284—286 °C (HCl salt).

1,2,3,4-Tetrahydro-7-methoxyisoquinoline (**23f**): Eluent for column chromatography: $CHCl_3$–MeOH (8 : 2). Yield: 133 mg, 83% from **21f** (200 mg, 1.05 mmol). Pale yellow oil. HCl salt: mp 232—235 °C (from EtOH–Et_2O). Lit.[11] mp 228 °C; lit.[12] mp 231.5—232 °C; lit.[13] mp 232—233 °C; lit.[14] mp 231—232 °C (each HCl salt).

1,2,3,4-Tetrahydro-8-methoxyisoquinoline (**23g**): Eluent for column chromatography: $CHCl_3$–MeOH (8 : 2). Yield: 59 mg, 90% from **21g** (80 mg, 0.42 mmol). Pale yellow gum. HCl salt: mp 260—264 °C (from EtOH–Et_2O). Lit.[13] mp 259.7—261.2 °C; lit.[14] mp 261—262.5 °C (each HCl salt).

1,2,3,4-Tetrahydro-6-methoxyisoquinoline (**23h**): Eluent for column chromatography: $CHCl_3$–MeOH (8 : 2). Yield: 388 mg, 91% from **21h** (500 mg, 2.62 mmol). Pale yellow oil. HCl salt: mp 238—241 °C (from EtOH–Et_2O). Lit.[13] mp 242.6—244.1 °C; lit.[14] mp 238—239 °C (each HCl).

1,2,3,4-Tetrahydro-5-methoxyisoquinoline (**23i**): Eluent for column chromatography: $CHCl_3$–MeOH (8 : 2). Yield: 57 mg, 89% from **21i** (75 mg, 0.39 mmol). Colorless needles, mp 74—78 °C (from AcOEt–*n*-hexane). Lit.[13] mp 234.9—259.7 °C; lit.[14] mp 233—234 °C (each HCl salt).

$LiAlH_4$ Reduction of *N*-Formyl-TIQs (21) $LiAlH_4$ (2 mol eq) was added to a solution of *N*-formylTIQs (**11b, c, 21e—f**, and **21h**) (0.083—1.33 g) in dry THF (20 ml) under ice-cooling, and the mixture was refluxed for 1—2 h. Et_2O, saturated with water, was added to the reaction mixture and insoluble material was filtered off. The products were purified by column chromatography to give *N*-MeTIQs (**24b, c, 24e, f, 24h**).

1,2,3,4-Tetrahydro-5,8-dimethoxy-2-methylisoquinoline (**24b**): Eluent for column chromatography: $CHCl_3$–MeOH (9 : 1). Yield: 880 mg, 70% from **21b** (1.33 g, 6.02 mmol). Pale yellow gum. HCl salt: mp 216—219 °C (from EtOH–Et_2O). IR: 1485, 1379, 1342, 1257, 1087. ^{1}H-NMR: 2.47 (3H, s, $=NCH_3$), 2.50—2.90 (4H, m, $-CH_2CH_2N=$), 3.50 (2H, s, $ArCH_2N=$), 3.77 (6H, s, $2\times-OCH_3$), 6.62 (2H, s, Ar-H). ^{13}C-NMR: 24.1 (t), 46.2 (q), 52.0 (t), 52.9 (t), 55.6 (q), 55.7 (q), 106.9 (d), 107.2 (d), 124.5 (s), 125.2 (s), 150.0 (s), 151.3 (s). EI-MS *m/z*: 207 (M^+, 85), 206 (base peak), 191 (19), 176 (68), 164 (96), 149 (51), 134 (10), 121 (9). HR-MS: Calcd for $C_{12}H_{17}NO_2$: 207.1141. Found: 207.1200.

1,2,3,4-Tetrahydro-7,8-dimethoxy-2-methylisoquinoline (**24c**): Eluent for column chromatography: $CHCl_3$–MeOH (9 : 1). Yield: 740 mg, 98% from **21c** (800 mg, 3.62 mmol). Pale yellow gum. HCl salt: mp 174—176 °C (from EtOH–Et_2O). IR: 1495, 1458, 1278, 1230, 1087. ^{1}H-NMR: 2.52 (3H, s, $=NCH_3$), 2.60—3.00 (4H, m, $-CH_2CH_2N=$), 3.65 (2H, s, $ArCH_2N=$), 3.82, 3.83 (each 3H, s, $2\times-OCH_3$), 6.74, 6.84 (each 1H, d, $J=8.5$ Hz, Ar-H). ^{13}C-NMR: 28.0 (t), 45.6 (q), 52.2 (t), 52.7 (t), 55.8 (q), 60.0 (q), 111.0 (d), 123.7 (d), 126.6 (s), 127.9 (s), 145.2 (s), 150.1 (s). EI-MS *m/z*: 207 (M^+), 206 (base peak), 192 (16), 190 (25), 164 (73), 149 (67), 134 (7), 121 (11), 104 (10), 91 (6). HR-MS: Calcd for $C_{12}H_{17}NO_2$: 207.1259. Found: 207.1246.

1,2,3,4-Tetrahydro-5,7-dimethoxy-2-methylisoquinoline (**24e**): Eluent for column chromatography: $CHCl_3$–MeOH (9 : 1). Yield: 59 mg, 76% from **21e** (83 mg, 0.38 mmol). Pale yellow gum. HCl salt: mp 242—245 °C (from EtOH–Et_2O). IR: 1603, 1495, 1458, 1203, 1152, 1094. ^{1}H-NMR: 2.43 (3H, s, $=NCH_3$), 2.50—2.90 (4H, m, $-CH_2CH_2N=$), 3.51 (2H, s, $ArCH_2N=$), 3.76, 3.78 (each 3H, s, $2\times-OCH_3$), 6.16, 6.28 (each 1H, d, $J=2.3$ Hz, Ar-H). ^{13}C-NMR: 23.1 (t), 45.8 (q), 52.8 (t), 55.2 (q × 2), 58.1 (t), 96.2 (d), 101.9 (d), 115.3 (s), 136.3 (s), 158.1 (s), 158.6 (s). EI-MS *m/z*: 207 (M^+, 49), 190 (9), 176 (10), 164 (base peak), 149 (14), 135 (12), 121 (9). HR-MS: Calcd for $C_{12}H_{17}NO_2$: 207.1340. Found: 207.1250.

1,2,3,4-Tetrahydro-7-methoxy-2-methylisoquinoline (**24f**): Eluent for column chromatography: $CHCl_3$–MeOH (9 : 1). Yield: 133 mg, 72% from **21f** (200 mg, 1.05 mmol). Pale yellow gum. HCl salt: mp 208—211 °C. Lit.[12] mp 207—208 °C; lit.[14] mp 208—210 °C.

1,2,3,4-Tetrahydro-6-methoxy-2-methylisoquinoline (**24h**): Eluent for column chromatography: $CHCl_3$–MeOH (9 : 1). Yield: 407 mg, 87% from **21h** (500 mg, 2.62 mmol). Pale yellow oil. HCl salt: mp 168—172 °C. Lit.[14] mp 165—168 °C; lit.[15] mp 170—171 °C (each HCl salt).

Reductive Desulfurization of 12 $NaBH_4$ (3.45 g, 91.3 mmol) was added in small portions to a stirred solution of the salt **12** (2.31 g, 5.21 mmol, from method A) and $NiCl_2\cdot6H_2O$ (7.20 g, 30.3 mmol) in MeOH–THF (3 : 1) (200 ml) under ice-cooling. The mixture was stirred at room temperature for 30 min. Chromatography of the products gave **17a** (152 mg, 9%), **19a** (817 mg, 70%) and **20a** (8 mg, 0.6%).
The salt **12** (500 mg, 1.13 mmol, from method B) was treated in the same manner to give **17a** (77 mg, 21%), **19a** (167 mg, 66%) and **20a** (25 mg, 9%).

Hydrolysis of 17a, 19a and 20a A solution of **17a** (110 mg, 0.33 mmol), **19a** (375 mg, 1.68 mmol), and **20a** (20 mg, 0.08 mmol) in EtOH (5—20 ml)–10% HCl–H_2O (5—10 ml) was refluxed for 20—24 h. The reaction mixture was concentrated *in vacuo*, and the residue was diluted with water, basified with 10% NaOH–H_2O and extracted with $CHCl_3$. The products were purified by column chromatography to give **17b** (84 mg, 83%), **19b** (324 mg, 99%), and **20b** (17.5 mg, 98%).

Hydrolysis of 13a and 18a A solution of **13a** (75 mg, 0.17 mmol) and **18a** (66 mg, 0.19 mmol) in EtOH (10 ml)–10% HCl–H_2O (5 ml) was refluxed for 22—24 h (24 h for **13a**, 22 h for **18a**). The reaction mixture was purified by column chromatography to give **13b** (64 mg, 91%) and **18b** (60 mg, 98%).

Reductive Desulfurization of 13a $NaBH_4$ (34 mg, 0.90 mmol) was added in small portion to a stirred solution of **13a** (38 mg, 0.087 mmol) with $NiCl_2\cdot6H_2O$ (72 mg, 0.30 mmol, 3.5 mol eq) in MeOH–THF (3 : 1) (8 ml) under ice-cooling. The mixture was stirred at room temperature for 30 min, then purified by column chromatography to give **17a** (11 mg, 34%).

N-[(3,5-Dimethoxy-2-(phenylthio)phenylmethyl]-*N*-ethylformamide (**17a**): Eluent for column chromatography: AcOEt–*n*-hexane (2 : 1). Pale yellow gum. IR: 1671 (=NCO–), 1595, 1458, 1437, 1323, 1202, 1164. ^{1}H-NMR: 0.97, 1.04 (total 3H, each t, $J=7.3$ Hz, $-CH_3$), 3.12, 3.24 (total 2H, each q, $J=7.3$ Hz, $=CH_2-$), 3.79, 3.81, 3.82, 3.84 (total 6H, each s, $2\times-OCH_3$), 4.58, 4.80 (total 2H, each s, $ArCH_2N=$), 6.40—6.60 (2H, m, Ar-H), 6.85—7.60 (5H, m, Ar-H), 8.15, 8.19 (total 1H, each s, =NCHO). EIMS *m/z*: 331 (M^+, 19), 302 (7), 257 (13), 243 (4), 222 (base peak), 194 (50), 167 (16), 151 (6). HR-MS: Calcd for $C_{18}H_{21}NO_3S$: 331.1242. Found: 331.1229.

N-(3,5-Dimethoxyphenylmethyl)-*N*-ethylformamide (**19a**): Eluent for column chromatography: AcOEt–*n*-hexane (2 : 1). Colorless gum. IR: 1671 (=NCO–), 1599, 1462, 1429, 1207, 1160, 1067. ^{1}H-NMR: 1.08, 1.15 (total 3H, each t, $J=7.0$ Hz, $-CH_3$), 3.23, 3.31 (total 2H, each q, $J=7.0$ Hz, $-CH_2N=$), 3.77, 3.78 (each 3H, s, $2\times-OCH_3$), 4.32, 4.48 (total 2H, each s, $ArCH_2N=$), 6.30—6.45 (2H, m, Ar-H), 8.29 (1H, s, =NCHO). EI-MS *m/z*: 223 (M^+, base peak), 194 (22), 180 (6), 166 (32),

152 (70), 139 (24), 123 (16), 91 (14). HR-MS: Calcd for $C_{12}H_{17}NO_3$: 223.1208. Found: 223.1208.

2,3,4,5-Tetrahydro-7,9-dimethoxy-1,4-benzothiazepine-4-carbaldehyde (**20a**): Eluent for column chromatography: AcOEt–*n*-hexane (2 : 1). Colorless gum. IR: 1671 (=NCO–), 1597, 1460, 1325, 1205, 1164, 1096. ^{1}H-NMR: 2.65—2.85 (2H, m, $-SCH_2-$), 3.75—4.10 (2H, m, $-CH_2N=$), 3.82, 3.85, 3.87 (total 6H, each s, $2\times-OCH_3$), 4.62, 4.72 (total 2H, each s, $ArCH_2N=$), 6.41, 6.44, 6.51, 6.76 (total 2H, each d, $J=2.6$ Hz, Ar-H), 8.00, 8.21 (total 1H, each s, =NCHO). EI-MS *m/z*: 253 (M^+, base peak), 225 (14), 210 (10), 192 (18), 182 (48), 166 (15), 151 (12), 139 (7). HR-MS: Calcd for $C_{12}H_{15}NO_3S$: 253.0773. Found: 253.0802.

N-[3,5-Dimethoxy-2-(phenylthio)phenylmethyl]ethylamine (**17b**): Eluent for column chromatography: $CHCl_3$–MeOH (9 : 1). Pale yellow oil. IR: 1593, 1458, 1323, 1201, 1162. ^{1}H-NMR: 0.99 (3H, t, $J=7.0$ Hz, $-CH_3$), 2.59 (2H, t, $J=7.0$ Hz, $-CH_2N=$), 3.78, 3.87 (each 3H, s, $2\times-OCH_3$), 3.92 (2H, s, $ArCH_2N=$), 6.84, 6.71 (each 1H, d, $J=2.6$ Hz, Ar-H), 6.85—7.35 (5H, m, Ar-H). ^{13}C-NMR: 15.0 (q), 43.3 (t), 52.7 (t), 55.2 (q), 56.0 (q), 97.8 (d), 106.6 (d), 109.3 (s), 124.5 (d), 125.3 (d×2), 128.6 (d×2), 138.7 (s), 147.6 (s), 161.8 (s), 161.9 (s). EI-MS *m/z*: 303 (M^+, 93), 274 (86), 257 (base peak), 243 (11), 226 (16), 192 (19), 182 (19), 151 (14). HR-MS: Calcd for $C_{17}H_{21}NO_2S$: 303.1293. Found: 303.1253.

N-(3,5-Dimethoxyphenylmethyl)ethylamine (**19b**): Eluent for column chromatography: $CHCl_3$–MeOH (9 : 1). Pale yellow oil. IR: 1599, 1464, 1207, 1156, 1067. ^{1}H-NMR: 1.13 (3H, t, $J=7.0$ Hz, $-CH_3$), 2.67 (2H, q, $J=7.0$ Hz, $-CH_2N=$), 3.74 (2H, s, $2\times-OCH_3$), 6.30—6.50 (3H, m, Ar-H). ^{13}C-NMR: 15.1 (q), 43.4 (t), 53.9 (t), 55.1 (q), 55.2 (q), 98.7 (d), 105.7 (d×2), 142.7 (s), 160.7 (s×2). EI-MS *m/z*: 195 (M^+, 2), 194 (8), 164 (3), 152 (base peak), 137 (4), 121 (8), 91 (7). CI-MS *m/z*: 196 (MH^+, base peak), 152 (12).

2,3,4,5-Tetrahydro-7,9-dimethoxy-1,4-benzothiazepine (**20b**): Eluent for column chromatography: $CHCl_3$–MeOH (9 : 1). Colorless gum. IR (KBr): 1593, 1577, 1458, 1319, 1201, 1163, 1095, 1041. ^{1}H-NMR: 2.70 (2H, t, $J=4.9$ Hz, $-SCH_2-$), 3.37 (2H, $J=4.9$ Hz, $-CH_2N=$), 3.80, 3.86 (each 3H, s, $2\times-OCH_3$), 4.15 (2H, s, $ArCH_2N=$), 6.39, 6.45 (each 1H, d, $J=2.6$ Hz, Ar-H). ^{13}C-NMR: 36.5 (t), 52.8 (t), 55.3 (t), 55.4 (q), 56.2 (q), 97.5 (d), 106.5 (d), 116.2 (s), 148.9 (s), 159.7 (s), 160.0 (s). EI-MS *m/z*: 225 (M^+, base peak), 210 (96), 197 (87), 192 (55), 181 (74), 151 (63), 138 (54), 121 (42), 109 (43). HR-MS: Calcd for $C_{11}H_{15}NO_2S$: 225.0823. Found: 225.0846.

N-[3,5-Dimethoxy-2-(phenylthio)phenylmethyl]-2-(phenylthio)ethylamine (**13b**): Eluent for column chromatography: $CHCl_3$. IR: 1591, 1454, 1319, 1201, 1160. ^{1}H-NMR: 2.56—3.10 (4H, m, $-SCH_2CH_2N=$), 3.78, 3.85 (each 3H, s, $2\times-OCH_3$), 3.90 (2H, s, $ArCH_2N=$), 6.47, 6.69 (each 1H, d, $J=2.6$ Hz, Ar-H), 6.90—7.40 (10H, m, Ar-H). ^{13}C-NMR: 34.1 (t), 47.7 (t), 52.4 (t), 55.5 (q), 56.2 (q), 98.1 (d), 106.6 (d), 109.5 (s), 124.7 (d), 125.5 (d×2), 126.1 (d), 128.8 (d×2), 128.9 (d×2), 129.6 (d×2), 135.9 (s), 138.7 (s), 147.5 (s), 162.1 (s×2). EI-MS *m/z*: 411 (M^+, 7), 302 (13), 288 (95), 259 (base peak), 244 (20), 228 (14), 137 (17), 109 (11). HR-MS: Calcd for $C_{23}H_{25}NO_2S_2$: 411.1327. Found: 411.1283.

2-[(3,5-Dimethoxy-2-(phenylthio)phenylmethylamino]-1-ethanol (**18b**): Eluent for column chromatography: $CHCl_3$–MeOH (9 : 1). Pale yellow gum. IR (KBr): 3307, 1592, 1457, 1321, 1203, 1163. ^{1}H-NMR: 2.70 (2H, t, $J=5.0$ Hz, $=NCH_2-$), 3.53 (2H, t, $J=5.0$ Hz, $-CH_2O-$), 3.78, 3.87 (each 3H, s, $2\times-OCH_3$), 3.92 (2H, s, $ArCH_2N=$), 6.49, 6.68 (each 1H, d, $J=2.6$ Hz, Ar-H), 6.85—7.30 (5H, m, Ar-H). ^{13}C-NMR: 50.2 (t), 52.2 (t), 55.4 (q), 56.2 (q), 60.7 (t), 98.0 (d), 106.9 (d), 109.6 (s), 124.7 (d), 125.4 (d×2), 128.7 (d×2), 138.6 (s), 147.1 (s), 162.0 (s), 163.0 (s). EI-MS *m/z*: 319 (M^+, 42), 301 (6), 288 (60), 274 (23), 259 (base peak), 244 (26), 228 (18), 182 (7). HR-MS: Calcd for $C_{17}H_{21}NO_3S$: 319.1243. Found: 319.1233.

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