A SYNTHESIS OF SOME TRIMETHOXYLATED 1,2,3,4-TETRAHYDROISOQUINOLINE ALKALOIDS *VIA* PUMMERER REACTION OF *N*-TRIMETHOXYBENZYL-*N*-[2-(PHENYLSULFINYL)ETHYL]FORMAMIDES

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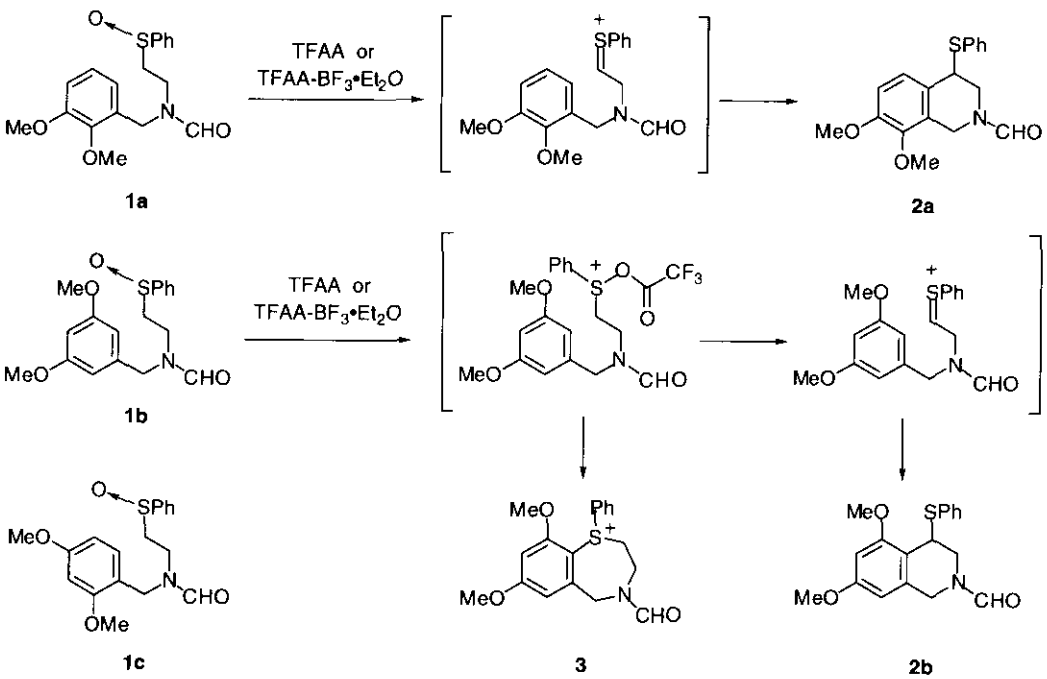
Abstract —— Pummerer reaction of *N*-trimethoxybenzyl-*N*-[2-(phenylsulfinyl)ethyl]formamides (**7**) gave *N*-formyl-1,2,3,4-tetrahydro-4-phenylsulfanylisoquinolines (**9**) which were converted into trimethoxylated 1,2,3,4-tetrahydroisoquinoline alkaloids in the family of Cactaceae, formylanhalinine (**10a**), nortehaunine (**12a**), anhalinine (**12b**), and tehaunine (**13a**).

We modified the Takano's 1,2,3,4-tetrahydroisoquinoline (TIQ) synthesis[1] which utilized Pummerer reaction and established the method as a general TIQ synthesis.[2] In the investigations, we demonstrated that the cyclization of *N*-(aryl)methyl-*N*-2-[(phenylsulfinyl)ethyl]formamides by the Pummerer reaction was affected by the position of methoxy group at the aryl ring. For example, the reaction of the sulfoxide (**1a**) with 2,3-dimethoxy groups gave the TIQ (**2a**) in an excellent yield. [2d] However, the reaction of the sulfoxide (**1b**) having 3,5-dimethoxy groups, in addition to the normal cyclization to the TIQ (**2b**), caused a C-S bond formation to give a benzothiazepine (**3**) as a major product.[2d] On the other hand, the sulfoxide (**1c**) with 2,4-dimethoxy groups did not undergo either cyclization and suffered an extensive decomposition.[2d] The findings indicated that the higher nucleophilicity at the ring-closing site prevented the TIQ formation.

Here, we describe the Pummerer reaction of the substrates with three OMe groups at the benzene ring in

order to disclose additional effects of OMe group on the ring formation.

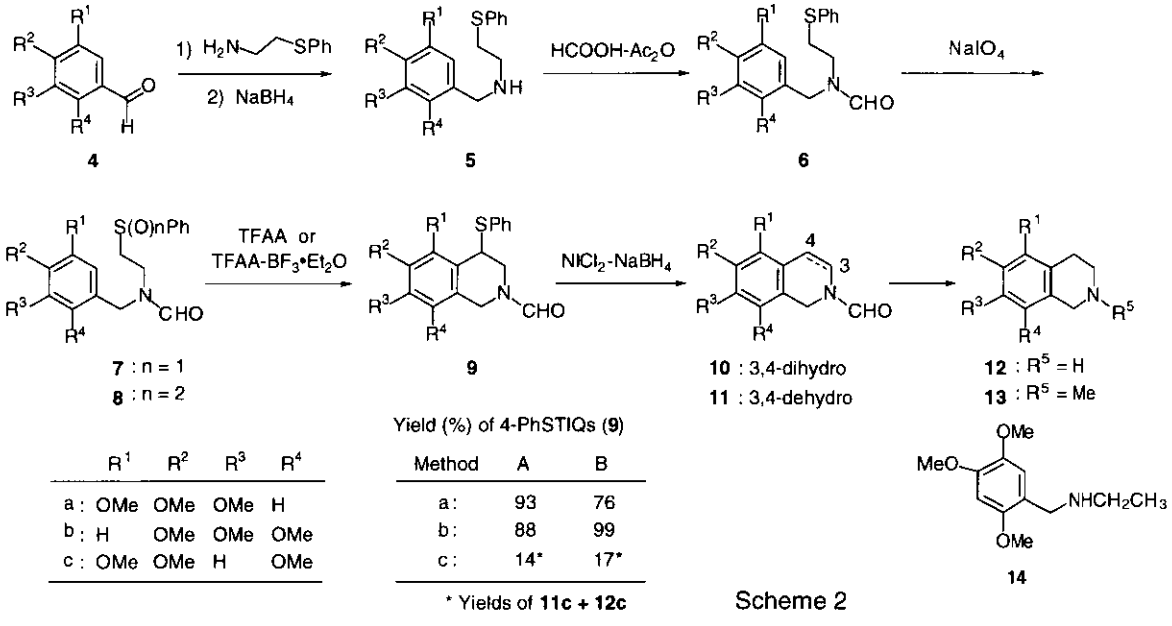


Scheme 1

Three sulfoxides (**7a-c**) were prepared from trimethoxybenzaldehydes (**4a-c**) in excellent overall yields *via* the route shown in Scheme 2 according to the method described in the previous papers.[2] The Pummerer reaction was carried out by using trifluoroacetic anhydride (TFAA) (method A) and TFAA-BF_3•Et_2O (method B).[2] The sulfoxide (**7a**) with 3,4,5-trimethoxy groups, when treated with TFAA in benzene at room temperature, slowly cyclized to give *N*-formyl-5,6,7-triOMe-4-PhSTIQ (**9a**) in 93% yield. Addition of BF_3•Et_2O to the reaction mixture remarkably accelerated the reaction to give the same TIQ (**9a**) in 76% yield.[3] The sulfoxide (**7b**) with 2,3,4-trimethoxy groups on similar treatments also underwent the cyclization to give *N*-formyl-6,7,8-triOMe-4-PhSTIQ (**9b**) in 88% yield by the method A and in 99% yield by the method B. However, the cyclization of the sulfoxide (**7c**) with 2,4,5-trimethoxy groups was difficult under either A or B conditions to give *N*-formyl-5,6,8-triOMe-4-PhSTIQ (**9c**) as a crude material in low yields. The crude **9c** on reductive desulfurization with $NaBH_4$-$NiCl_2$ followed by hydrolysis gave 5,6,8-triOMeTIQ (**12c**) in 13% and 16% yields (from **7c**) by the method A and method B, respectively. Together with **12c**, the amine (**14**), an uncyclized product, was formed in few percent yields.

The reaction of **7b** clearly indicates that the introduction of a 3-OMe between 2,4-diOMe groups remarkably

increases the nucleophilicity of the ring-closing site which furnished the TIQ (**9b**) in an excellent yield. On the other hand, the reaction of **7c** which gave the TIQ (**9c**) in low yield demonstrates that the enhancement of the reactivity by the 5-OMe is poor. In the case of **7a** the 4-OMe group present between the 3,5-diOMe groups probably decreases the nucleophilicity at the reaction site, and therefore retards the C-S bond formation observed in the reaction of **1b**, which results in the exclusive formation of the TIQ (**9a**).



	R1	R2	R3	R4
a :	OMe	OMe	OMe	H
b :	H	OMe	OMe	OMe
c :	OMe	OMe	H	OMe

Yield (%) of 4-PhSTIQs (**9**)

Method	A	B
a:	93	76
b:	88	99
c:	14*	17*

* Yields of **11c** + **12c**

Scheme 2

Reductive removal of the phenylthio group of the 4-PhSTIQs (**9a-b**) with $NiCl_2$-$NaBH_4$ gave the corresponding trimethoxylated *N*-formylTIQs (**10a-b**) in good yields, although the dihydroisoquinolines (**11a-b**) were produced in few percent yields. Alkaline hydrolysis of **10a-b** gave 5,6,7-trimethoxyTIQ (**12a**) and 6,7,8-trimethoxyTIQ (**12b**) and $LiAlH_4$ reduction of **10a-b** gave the *N*-methylTIQs (**13a-b**) in good yields, respectively. These compounds were identified as *N*-formylanhalinine (**10a**),[4] nortehaunine (**12a**),[5] anhalinine (**12b**),[6] and tehaunine (**13a**),[5] tetrahydroisoquinoline alkaloids from Cactus family, respectively. Thus, the synthesis of the alkaloids using the Pummerer reaction provides a useful alternative to the classical ones such as the Pictet-Spengler,[6,7] Bischler-Napieralski,[8] and the Pomeranz-Fritsch[9] cyclizations.

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 KBr disks with a JASCO FT/IR-5000 or a Horiba FT-170 spectrophotometer, and are given in

cm^{-1}. ^{1}H-NMR spectra were measured on a JEOL JNM-EX 90 (90 MHz) and ^{13}C-NMR on a JEOL JNM-a 300 (75 MHz) spectrometers in $CDCl_3$ with tetramethylsilane as an internal standard, and the chemical shifts are given in δ values. LRMS and HRMS were taken on a JEOL JMS-AX 505H or a JEOL JMS B-20 spectrometer at 70 eV [electron ionization MS (EIMS)] or at 270 eV [chemical ionization MS (CIMS, reactant gas: *iso*-butane)] using direct or GC/MS inlet system, and figures in parentheses indicate the relative intensities. The elemental analyses were recorded on a Yanagimoto CHN coder MT-3. TLC was performed on Merck precoated Silica gel 60 F_{254} plates (Merck). Unless otherwise stated, 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 ^{1}H-NMR indicated that all *N*-formyl derivatives (**6a-c**, **7a-c**, **8a-c**, **9a-b**, **10a-b**, and **11a-c**) are present in $CDCl_3$ as a mixture of two rotational isomers of the N-CO bond.

Preparation of *N*-Arylmethyl-2-(phenylsulfanyl)ethylamines (5)

A mixture of **4a-c** (5-10 g), 2-phenylthioethylamine[10] (1.5 molar eq), and acetic acid (1.5 molar eq) in EtOH (100-200 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 (100-200 mL). To this solution, $NaBH_4$ (1.5 molar eq) was added in small portions under ice-cooling. The reaction mixture was stirred at rt 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. The aqueous layer and insoluble amine HCl salt were combined and basified with 10% NaOH, and extracted with $CHCl_3$. The products (**5a-c**) were purified by column chromatography with AcOEt.

***N*-(3,4,5-Trimethoxybenzyl)-2-(phenylsulfanyl)ethylamine (5a)**: Yield: 8.23g (97%) from **4a** (5 g). Pale yellow oil. IR (film): 1590, 1506, 1461, 1419, 1326, 1234, 1128. ^{1}H-NMR: 2.79-2.94 (2H, m, $-SCH_2-$), 3.04-3.20 (2H, m, $-CH_2N=$), 3.74 (2H, s, $ArCH_2N=$), 3.83, 3.85 (total 9H, each s, 3 x $-OCH_3$), 6.54 (2H, s, Ar-H), 7.16-7.40 (5H, m, Ar-H). EIMS *m/z*: 333 (M^+, 3), 209 (11), 181 (base peak), 148 (3), 137 (4), 109 (3). HRMS: Calcd for $C_{18}H_{23}NO_3S$: 333.1399. Found: 333.1395.

***N*-(2,3,4-Trimethoxybenzyl)-2-(phenylsulfanyl)ethylamine (5b)**: Yield: 7.87g (93%) from **4b** (5 g). Pale yellow oil. IR (KBr): 1602, 1583, 1468, 1417, 1279, 1099. ^{1}H-NMR: 2.75-2.90 (2H, m, $-SCH_2-$), 3.00-3.18 (2H, m, $-CH_2N=$), 3.73 (2H, s, $ArCH_2N=$), 3.85, 3.86, 3.90 (each 3H, s, 3 x $-OCH_3$), 6.60 (1H, d, *J*=8.5 Hz, Ar-H), 6.91 (1H, d, *J*=8.5 Hz, Ar-H), 7.10-7.40 (5H, m, Ar-H). EIMS *m/z*: 333 (M^+, 1), 210 (22), 181 (base peak), 166 (17), 136 (6), 109 (4). CIMS*m/z*: 334 (MH^+, base peak), 224, (24), 210 (17), 197 (11), 183 (33), 181 (96), 154 (18), 137 (14), 125 (12).

***N*-(2,4,5-Trimethoxybenzyl)-2(phenylsulfanyl)ethylamine (5c)**: AcOEt-hexane (9:1). Yield: 16.1g (94.7%) from **4c** (10 g). Pale yellow oil. IR (film): 1610, 1583, 1511, 1463, 1400, 1315, 1205, 1126, 1037. ^{1}H-NMR: 2.72-2.94 (2H, m, $-SCH_2-$), 2.96-3.20 (2H, m, $-CH_2N=$), 3.73 (2H, s, $ArCH_2-$), 3.79, 3.81, 3.87 (each 3H, s, 3 x $-OCH_3$), 6.51, 6.81 (each 1H, s, Ar-H), 7.10-7.40 (5H, m, Ar-H). EIMS *m/z*: 333 (M^+, 4), 210 (6), 181 (base peak), 151 (11), 136 (4), 109 (3). HRMS: Calcd for $C_{18}H_{23}NO_3S$: 333.1399. Found: 333.1438.

Formylation of 5

A mixture of **5a-c**, 98-100% formic acid (30 molar eq) and acetic anhydride (10 molar eq) was heated at 70℃ for 1 h, then concentrated *in vacuo*, and the residue was extracted with $CHCl_3$. The products (**6a-c**) were purified by column chromatography and eluted with AcOEt-hexane (2:1) for **6a-b**, and AcOEt to AcOEt-MeOH (9:1) for **6c**.

***N*-(3,4,5-Trimethoxybenzyl-*N*-[2-(phenylsulfanyl)ethyl]formamide (6a)**: Yield: 7.78g (96%) from **5a** (7.5 g). Pale yellow gum. IR (film): 1672 (=NCO-), 1592, 1506, 1462, 1419, 1328, 1239, 1126. ^{1}H-NMR: 2.85-3.15 (2H, m, -SCH_2-), 3.25-3.55 (2H, m, -CH_2N=), 3.80, 3.81, 3.82, 3.83 (total 9H, each s, 3 x -OCH_3), 4.36, 4.44 (total 2H, each s, ArCH_2N=), 6.31, 6.43 (total 2H, each s, Ar-H), 7.20-7.80 (5H, m, Ar-*H*), 8.14, 8.28 (total 1H, each s, =NCHO). EIMS *m/z*: 361 (M^+, 17), 225 (97), 182 (23), 181 (base peak), 148 (8), 137 (14), 109 (10). HRMS: Calcd for $C_{19}H_{23}NO_4S$: 361.1348. Found: 361.1384.

***N*-(2,3,4-Trimethoxybenzyl)-*N*-[2-(phenylsulfanyl)ethyl]formamide (6b)**: Yield: 7.43 g (98%) from **5b** (7.0 g). Pale yellow gum. IR (KBr): 1675 (=NCO-), 1601, 1583, 1494, 1467, 1417, 1278, 1099. ^{1}H-NMR: 2.88-3.12 (2H, m, -SCH_2-), 3.25-3.55 (2H, m, -CH_2N=), 3.83, 3.84, 3.82, 3.85, 3.86 (total 9H, each s, 3 x -OCH_3), 4.32, 4.47 (total 2H, each s, ArCH_2N=), 6.54, 6.59, 6.68, 6.92 (total 2H, each d, *J*=8.5 Hz, Ar-H), 7.15-7.38 (5H, m, Ar-H), 8.08, 8.26 (total 1H, each s, =NCHO). EIMS *m/z*: 361 (M^+, 9), 332 (3), 225 (82), 196 (12), 194 (26), 181 (base peak), 166 (38), 151 (5), 136 (15), 109 (10). HRMS: Calcd for $C_{19}H_{23}NO_4S$: 361.1348. Found: 361.1320.

***N*-(2,4,5-Trimethoxybenzyl)-*N*-[2-(phenylsulfanyl)ethyl]formamide (6c)**: Yield: 14.9 g (98.5%) from **5c** (14.0 g). Pale yellow gum. IR (KBr): 1651 (=NCO-), 1520, 1448, 1408, 1211, 1132, 1032. ^{1}H-NMR: 2.88-3.40 (2H, m, -SCH_2-), 3.24-3.60 (2H, m, -CH_2N=), 3.75, 3.77, 3.79, 3.89 (total 9H, each s, 3 x -OCH_3), 4.34, 4.50 (total 2H, each s, ArCH_2N=), 6.50, 6.53, 6.82 (total 2H, each s, Ar-H), 7.10-7.40 (5H, m, Ar-H), 8.07, 8.27 (total 1H, each s, =NCHO). EIMS *m/z*: 361 (M^+, 23), 225 (68), 210 (9), 196 (6), 194 (26), 181 (base peak), 151 (27), 136 (13), 109 (11). HRMS: Calcd for $C_{19}H_{23}NO_4S$: 361.1348. Found: 361.1356.

Oxidation of 6 with $NaIO_4$

A solution of sodium metaperiodate (1.5 molar eq) in H_2O (70 mL) was added to a solution of **6a-c** (7-13 g) in MeOH (250 mL), and the mixture was stirred at rt for 16 h. After removal of precipitated inorganic materials by filtration, the filtrate was concentrated *in vacuo*. The residue was extracted with $CHCl_3$ and chromatographed with AcOEt-MeOH (95:5) to give **7a-c** and **8a-c**, respectively.

***N*-(3,4,5-Trimethoxybenzyl)*N*-[2-(phenylsulfinyl)ethyl]formamide (7a)**: Yield: 7.2 g (94%) from **6a** (7.0 g). Pale yellow gum. IR (film): 1674 (=NCO-), 1593, 1506, 1464, 1423, 1329, 1240, 1124, 1041. ^{1}H-NMR: 2.65-4.30 (4H, m, -$SOCH_2CH_2N$=), 3.84, 3.85, 3.86 (total 9H, each s, 3 x -OCH_3), 4.30-4.80 (2H, m, ArCH_2N=), 6.43, 6.49, (total 2H, each s, Ar-H), 7.40-7.65 (5H, m, Ar-H), 8.28 (1H,

s, =NCHO). EIMS *m/z*: 377 (M^+, 29), 360 (40), 332 (43), 251 (6), 225 (12), 196 (15), 181 (base peak), 148 (9), 137 (65). CIMS *m/z*: 378 (MH^+, base peak), 362 (4), 252 (13), 181 (36).

***N*-(3,4,5-Trimethoxybenzyl)-*N*-[2-(phenylsulfonyl)ethyl]formamide (8a)**: Yield: 0.2 g (2%) from **6a** (7.0 g). Pale yellow gum. IR (film): 1672 (=NCO-), 1593, 1508, 1464, 1421, 1329, 1240, 1151. ^{1}H-NMR: 3.00-4.10 (4H, m, $-SO_2CH_2CH_2N=$), 3.83, 3.86, 3.87 (total 9H, each s, 3 x $-OCH_3$), 4.38, 4.44 (total 2H, each s, $ArCH_2N=$), 6.42, 6.60 (total 2H, each s, Ar-H), 7.50-7.95 (5H, m, Ar-H), 8.19, 8.21 (total 1H, each s, =NCHO). EIMS *m/z*: 393 (M^+, 48), 364 (78), 350 (16), 224 (17), 196 (24), 182 (34), 181 (base peak), 169 (10), 161 (11), 152 (11), 125 (16). HRMS: Calcd for $C_{19}H_{23}NO_6S$: 393.1246. Found: 393.1290.

***N*-(2,3,4-Trimethoxybenzyl)-*N*-[2-(phenylsulfinyl)ethyl]formamide (7b)**: Yield: 7.1 g (97%) from **6b** (7.0 g). Pale yellow gum. IR (film): 1673 (=NCO-), 1600, 1496, 1469, 1444, 1417, 1298, 1278, 1097, 1041. ^{1}H-NMR: 2.75-3.20, 3.30-3.70 (4H, m, $-SCH_2CH_2N=$), 3.83, 3.85, 3.87, 3.90 (total 9H, each s, 3 x $-OCH_3$), 4.38, 4.40, 4.48 (total 2H, each s, $ArCH_2N=$), 6.62, 6.90, 6.97 (total 2H, each d, *J*=8.5 Hz, Ar-H), 7.43-7.68 (5H, m, Ar-H), 8.20, 8.27 (total 1H, each s, =NCHO). EIMS *m/z*: 377 (M^+, 9), 360 (67), 332 (62), 252 (4), 220 (9), 197 (17), 181 (base peak), 166 (36), 137 (55). CIMS *m/z*: 378 (MH^+, base peak), 360 (11), 332 (6), 252 (11), 181 (61).

***N*-(2,3,4-Trimethoxybenzyl)-*N*-[2-(phenylsulfonyl)ethyl]formamide (8b)**: Yield: 0.2 g (2%) from **6b** (7.0 g). Pale yellow gum. IR (film): 1670 (=NCO-), 1600, 1496, 1471, 1446, 1417, 1305, 1151, 1099. ^{1}H-NMR: 3.15-3.40, 3.45-3.75 (total 4H, each m, $-SO_2CH_2CH_2N=$), 3.83, 3.86, 3.87 (total 9H, each s, 3 x $-OCH_3$), 6.59, 6.62, 6.88, 6.96 (total 2H, each d, *J*=8.5 Hz, Ar-H), 7.40-8.00 (5H, m, Ar-H), 8.10, 8.19 (total 1H, each s, =NCHO). EIMS *m/z*: 393 (M^+, 11), 364 (base peak), 334 (11), 224 (6), 196 (21), 181 (26), 166 (24), 151 (6), 125 (7). HRMS: Calcd for $C_{19}H_{23}NO_6S$: 393.1246. Found: 393.1223.

***N*-(2,4,5-Trimethoxybenzyl)-*N*-[2-(phenylsulfinyl)ethyl]formamide (7c)**: Yield: 13 g (96%) from **6c** (13 g). Pale yellow gum. IR (KBr): 1668 (=NCO-), 1518, 1443, 1402, 1207, 1130, 1036. ^{1}H-NMR: 2.70-3.80 (4H, $-SOCH_2CH_2N=$), 3.78, 3.80, 3.86, 3.89, 3.90 (total 9H, each s, 3 x $-OCH_3$), 4.37, 4.40, 4.50 (total 2H, each s, $ArCH_2$-), 6.48, 6.51 (total 1H, each s, Ar-H), 6.78, 6.86 (total 1H, each s, Ar-H), 7.45-7.65 (5H, m, Ar-H), 8.16, 8.19, 8.26 (total 1H, each s, =NCHO). CIMS *m/z*: 378 (MH^+, 51), 360 (4), 252 (3), 181 (base peak).

***N*-(2,4,5-Trimethoxybenzyl)-*N*-[2-(phenylsulfonyl)ethyl]formamide (8c)**: Yield: 0.32 g (2.3%) from **6c** (13 g). Pale yellow gum. IR (KBr): 1670 (=NCO-), 1518, 1447, 1402, 1306, 1207, 1149, 1032. ^{1}H-NMR: 3.10-3.42, 3.43-3.70 (each 2H, m, $-SO_2CH_2CH_2N=$), 3.78, 3.81, 3.85, 3.88, 3.91 (total 9H, each s, 3 x $-OCH_3$), 4.34, 4.36 (total 2H, each s, $ArCH_2N=$), 6.46, 6.51 (total 1H, each s, Ar-H), 6.73, 6.78 (total 1H, each s, Ar-H), 7.40-7.75, 7.75-7.95 (total 5H, each m, Ar-H), 8.07, 8.19 (total 1H, each s, =NCHO). EIMS *m/z*: 393 (M^+, 61), 364 (base peak), 224 (13), 196 (32), 181 (69), 166 (11), 151 (31), 136 (14), 125 (12). HRMS: Calcd for $C_{19}H_{23}NO_6S$: 393.1246. Found: 393.1223.

Pummerer Reaction of Sulfoxides (7a-b)

i) Method A: TFAA (5 molar eq) was added to a solution of **7a-b** in dry benzene (100 mL) at rt, and the mixture was stirred for 17 h (**7a**) and 24 h (**7b**). The reaction mixture was concentrated *in vacuo*, and the product was purified by column chromatography with AcOEt-hexane (2:1) to give **9a** and **9b**, respectively.
ii) Method B: TFAA (5 molar eq) was added to a solution of **7a-b** in dry benzene (100 mL) at rt. After the mixture was stirred for 30 min, BF_3•Et_2O (3 molar eq) was added, and the reaction mixture was further stirred at the same temperature for further 30 min. The reaction mixture was washed with 5% NaOH. The products were purified by column chromatography with AcOEt-hexane (2:1) to give **9a** and **9b**, respectively.

2-Formyl-1,2,3,4-tetrahydro-5,6,7-trimethoxy-4-phenylsulfanylisoquinoline (9a): Yield: 2.65 g (93%) by method A from **7a** (3.0 g); 2.16 g (76%) by method B from **7a** (3.0 g). Colorless needles (from AcOEt-hexane). mp 103-106℃. IR (KBr): 1670 (=NCO-), 1600, 1581, 1496, 1457, 1346, 1282, 1236, 1143, 1120. ^{1}H-NMR: 3.55-4.75 (total 3H, m, -SCHCH_2N=), 3.86, 3.87, 4.11, 4.13 (total 9H, each s, 3 x -OCH_3), 4.12, 5.19 (each 2H, d, *J*=17.6 Hz, ArCH_2N=), 6.42 (1H, s, Ar-H), 7.25-7.62 (5H, m, Ar-H), 8.14, 8.47 (total 1H, each s, =NCHO). EIMS *m/z*: 250 (M-109, base peak), 235 (9), 219 (19), 190 (11), 176 (4), 110 (3), 109 (2). CIMS *m/z*: 360 (MH^+, 9), 252, (31), 251 (19), 250 (base peak), 220 (60), 167(6), 125 (12), 111 (14).

2-Formyl-1,2,3,4-tetrahydro-6,7,8-trimethoxy-4-phenylsufanylisoquinoline (9b): Yield: 2.51 g (88%) by method A from **7b** (3.0 g); 2.81g (99%) by method B from **7b** (3.0 g). Colorless prism (from AcOEt-hexane). mp 118-122℃. IR (KBr): 1664 (=NCO-), 1604, 1495, 1412, 1353, 1273, 1117. ^{1}H-NMR: 3.40-4.55 (total 3H, m, -SCHCH_2N=), 3.83, 3.86, 3.92, 3.94 (total 9H, each s, 3 x -OCH_3), 4.41, 5.04 (total 2H, each d, *J*=8.0 Hz, ArCH_2N=), 6.62, 6.72 (total 1H, each s, Ar-H), 7.20-7.65 (5H, m, Ar-H), 8.05, 8.35 (total 1H, each s, =NCHO). EIMS *m/z*: 250 (M-109, base peak), 235 (14), 219 (14), 206 (5), 205 (5), 191 (8), 190 (10), 109 (2). CIMS*m/z*: 360 (MH^+, 37), 252 (42), 251 (23), 250 (base peak), 220 (21), 167(8), 125 (11), 111 (13).*Anal.* Calcd for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90. Found: C, 63.32; H, 6.18; N, 3.77.

Reductive Desulfurization of 2-Formyl-4-phenylsufanyl-TIQs (9a-b)

$NaBH_4$ (10.5 molar eq) was added in small portions to a stirred solution of **9a-b** and $NiCl_2$•$6H_2O$ (3.5 molar eq) in MeOH-THF (3:1) (100 mL) under ice-cooling. The mixture was stirred at rt for a further 30 min, then filtered and the filtrate was concentrated *in vacuo*. The residue was suspended in water, acidified with 5% HCl, and extracted with $CHCl_3$. The products **10a-b** and **11a-b** were separated by column chromatography with AcOEt.

2-Formyl-1,2,3,4-tetrahydro-5,6,7-trimethoxyisoquinoline (10a): Yield: 1.83 g (65%) from **9a** (4.0 g). Colorless prisms (from AcOEt-hexane). mp 70-73℃. IR (KBr): 1655 (=NCO-), 1495, 1452, 1342, 1319, 1117, 1082. ^{1}H-NMR: 2.69-2.86 (total 2H, m, -CH_2-), 3.50-3.85 (total 2H, m, -CH_2N=), 3.84, 3.85, 3.86, 3.87 (total 9H, each s, 3 x -OCH_3), 4.61, 4.46 (total 2H, each s, ArCH_2N=), 6.40, 6.43

(total 1H, each s, Ar-H), 8.18, 8.23 (total 1H, each s, =NCHO). EIMS *m/z*: 251 (M^+, base peak), 236 (37), 220 (22), 208 (10), 194 (15), 179 (18), 151 (6). HRMS: Calcd for $C_{13}H_{17}NO_4$: 251.1157. Found: 251.1160. *Anal.* Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.89; H, 7.09; N, 5.50.

2-Formyl-1,2-dihydro-5,6,7-trimethoxyisoquinoline (11a): Yield: 0.29 g (10%) from **9a** (4.0 g). Colorless gum. IR (KBr): 1685 (=NCO-), 1633, 1496, 1346, 1236, 1191, 1118. ^{1}H-NMR: 3.85, 3.86, 3.88 (total 9H, each s, 3 x -OCH_3), 4.64-4.84 (total 2H, each s, m, $ArCH_2N$=), 6.10, 6.33 (total 1H, d and dd, *J*=8.0 Hz, and *J*=1.0, 8.0 Hz, olefinic-H), 6.43 (1H, s, Ar-H), 6.52, 7.04 (total 1H, d, and dd, *J*=8.0 Hz and *J*=1.0, 8.0 Hz, olefinic-H), 8.31 (1H, br s, =NCHO). EIMS *m/z*: 249 (M^+, base peak), 220 (10), 190 (11), 162 (16), 131 (13), 104 (62). HRMS: Calcd for $C_{13}H_{15}NO_4$: 249.1001. Found: 249.1010.

2-Formyl-1,2,3,4-tetrahydro-6,7,8-trimethoxyisoquinoline (10b): Yield: 2.41 g (76%) from **9b** (4.5 g). Colorless gum. IR (film): 1672 (=NCO-), 1604, 1496, 1433, 1354, 1311, 1192, 1119, 1088, 1034. ^{1}H-NMR: 2.65-2.90, 3.50-3.80 (total 4H, m, -CH_2CH_2N=), 3.84, 3.85, 3.92, 3.94 (total 9H, each s, 3 x -OCH_3), 4.46, 4.57 (total 2H, each s, $ArCH_2N$=), 6.41, 6.43 (total 1H, each s, , Ar-H), 8.19, 8.26 (total 1H, each s, =NCHO). EIMS *m/z*: 251 (M^+, base peak), 250 (35), 236 (21), 220 (24), 207 (8), 194 (19), 192 (12), 179 (23), 151 (6). HRMS: Calcd for $C_{13}H_{17}NO_4$: 251.1157. Found: 251.1181.

2-Formyl-1,2-dihydro-6,7,8-trimethoxyisoquinoline (11b): Yield: 0.23 g (7%) from **9b** (4.5 g). Colorless prism (from AcOEt-hexane). mp 99-101℃. IR (KBr): 1635 (=NCO-), 1498, 1459, 1427, 1402, 1356, 1317, 1113. ^{1}H-NMR: 3.85, 3.90, 3.92 (total 9H, each s, 3 x -OCH_3), 4.74, 4.86 (total 2H, each s, $ArCH_2N$=), 5.66, 5.93 (total 1H, each d and dd, *J*=8.0 Hz, and *J*=1.0, 8.0 Hz, olefinic-H), 6.34, 6.41 (total 1H, each s, Ar-H), 6.52, 7.06 (total 1H, each d, *J*=8.0 Hz, olefinic-H), 8.18, 8.32 (total 1H, each s, =NCHO). EIMS *m/z*: 249 (M^+, base peak), 248 (67), 234 (42), 220 (17), 204 (8), 190 (15), 173 (12), 162 (10), 159 (9), 146 (6), 119 (6). HRMS: Calcd for $C_{13}H_{15}NO_4$: 249.1001. Found: 249.1028.

Hydrolysis of *N*-Formyl-TIQs (10a-b)

A solution of **10a** (0.7 g) and **10b** (0.8 g) in EtOH (10 mL)-10% NaOH-H_2O (5 mL) was refluxed for 1.5 h. 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 with $CHCl_3$-MeOH (9:1) to give **12a-b**.

1,2,3,4-Tetrahydro-5,6,7-trimethoxyisoquinoline (12a): Yield: 0.58 g (94%). Colorless prism (from AcOEt-hexane). mp 71-72℃ [lit.,[9] mp 71-72℃ (free base), lit.,[5] mp 260℃ (HCl salt)]. IR (KBr): 1604, 1585, 1492, 1457, 1411, 1342, 1222, 1191, 1124, 1033. ^{1}H-NMR: 2.66 (2H, t, *J*=5.5 Hz, -CH_2-), 3.10 (2H, t, *J*=5.5 Hz, -CH_2N=), 3.82, 3.85, 3.86, (total 9H, each s, 3 x -OCH_3), 3.92 (2H, s, $ArCH_2N$=), 6.34 (1H, s, Ar-H). ^{13}C-NMR: 22.97 (t), 43.38 (t), 48.00 (t), 55.68 (q), 60.11 (q), 60.58 (q), 104.68 (d), 120.66 (s), 131.21 (s), 140.02 (s), 151.19 (s), 151.32 (s). EIMS *m/z*: 223 (M^+, 77), 222 (71), 206 (23), 194 (91), 192 (base peak), 179 (95) 151 (28). HRMS: Calcd for $C_{12}H_{17}NO_3$: 223.1208. Found: 223.1192. *Anal.* Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.27; H, 7.96; N, 6.31.

1,2,3,4-Tetrahydro-6,7,8-trimethoxyisoquinoline (12b): Yield: 0.61 g (86%). Colorless prisms (from AcOEt-hexane). mp 62-65℃ [lit.,[6] mp 61-63℃; lit.,[7] 215-216℃ (HCl salt)]. IR (KBr): 1601, 1583, 1493, 1452, 1410, 1349, 1304, 1112. ^{1}H-NMR: 2.70 (2H, t, -CH_2-), 3.08 (2H, t, -CH_2N=), 3.83, 3.84, 3.86 (each 3H, each s, 3 x -OCH_3), 3.93 (2H, s, ArCH_2N=), 6.40 (1H, s, Ar-H). ^{13}C-NMR: 28.88 (t), 43.02 (t), 43.34 (t), 55.65 (q), 60.14 (q), 60.53 (q), 107.52, (d), 121.69 (s), 130.11 (s), 139.60 (s), 149.68 (s), 151.47 (s). EIMS *m/z*: 223 (M^+, 67), 222 (base peak), 206 (7), 194 (64), 192 (29), 179 (46), 151 (12). HRMS: Calcd for $C_{12}H_{17}NO_3$: 223.1208. Found: 223.1206. *Anal.* Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.41; H, 7.96; N, 6.31.

$LiAlH_4$ Reduction of *N*-Formyl-TIQs (10a-b)

$LiAlH_4$ (2 molar eq) was added to a solution of **10a** (0.7g) and **10b** (0.8g) in dry THF (30 mL) under ice-cooling, and the mixture was refluxed for 2 h. Et_2O, saturated with water, was added to the reaction mixture and insoluble material was removed by filtration. The products were purified by column chromatography with $CHCl_3$-MeOH (9:1) to give **13a-b**.

1,2,3,4-Tetrahydro-5,6,7-trimethoxy-2-methylisoquinoline (13a): Yield: 0.48 g (73%). Pale yellow gum, HCl salt: Colorless needles (from EtOH-Et_2O). mp 215-219℃ [lit.,[5] mp 219-221℃ (HCl salt)]. IR (KBr): 1604, 1496, 1459, 1376, 1349, 1321, 1118, 1084. ^{1}H-NMR: 2.44 (3H, s, =NCH_3), 2.60-2.90 (total 4H, m, -CH_2CH_2N=), 3.51 (2H, s, ArCH_2N=), 3.81, 3.84, 3.85, (each 3H, s, 3 x -OCH_3), 6.34 (1H, s, Ar-H). ^{13}C-NMR: 23.34 (t), 45.66 (q), 52.33 (t), 55.58 (q), 57.54 (t), 59.97 (q), 60.48 (q), 104.84 (d), 119.75 (s), 130.04 (s), 140.02 (s), 150.90 (s), 151.28 (s). EIMS *m/z*: 237 (M^+, 71), 236 (86), 220 (15), 206 (53), 194 (base peak), 179 (96) 151 (24). HRMS: Calcd for $C_{13}H_{19}NO_3$: 237.1365. Found: 237.1368.

1,2,3,4-Tetrahydro-6,7,8-trimethoxy-2-methylisoquinoline (13b): Yield: 0.67 g (88%). Pale yellow oil, HCl salt: Colorless gum [lit.,[7] mp 215-216℃ (HCl salt)]. IR (film): 1602, 1496, 1458, 1414, 1373, 1356, 1317, 1272, 1120, 1082. ^{1}H-NMR (90 MHz): 2.26 (3H, s, =NCH_3), 2.50-2.70, 2.70-2.95 (each 2H, m, -CH_2CH_2N=), 3.49 (2H, s, ArCH_2N=), 3.82, 3.83, 3.87, (each 3H, s, 3 x -OCH_3), 6.41 (1H, s, Ar-H). ^{13}C-NMR: 29.17 (t), 46.02 (q), 52.37 (t), 52.59 (t), 55.66 (q), 60.22 (q), 60.57 (q), 106.95 (d), 120.68 (s), 129.25 (s), 139.64 (s), 149.63 (s), 151.60 (s). EIMS *m/z*: 237 (M^+, 70), 236 (87), 220 (14), 206 (53), 194 (base peak), 179 (94) 151 (23). HRMS: Calcd for $C_{13}H_{19}NO_3$: 237.1365. Found: 237.1356.

Pummerer Reaction of 7c

i) Method A: TFAA (11.2 g, 53 mmol) was added to a solution of **7c** (4 g, 10.16 mmol) in dry benzene (100 mL) at rt, and the mixture was stirred for 96 h. The reaction mixture was concentrated *in vacuo*, and the product was purified by column chromatography with AcOEt-hexane (2:1) to give crude **9a** (1.86 g). To a solution of crude **9c** and $NiCl_2$•$6H_2O$ (4.30 g, 35 mmol) in MeOH-THF (3:1) (50 mL) $NaBH_4$ (2.1 g, 110 mmol) was slowly added at rt and the mixture was stirred for 30 min at the same temperature. After

removal of insoluble material by filtration, the filtrate was concentrated *in vacuo*, diluted with water, acidified with 5% HCl, and extracted with $CHCl_3$. The product was chromatographed over SiO_2 with AcOEt to give an eluate (810 mg) and **11c** (22 mg, 1%). A solution of the eluate (810 mg) in EtOH (10 mL) and 5% NaOH (5 mL) was refluxed for 2 h. The product was chromatographed over SiO_2 with $CHCl_3$-MeOH (3:1) to give **12c** (290 mg, 13%) and **14** (74 mg, 3%), respectively.

ii) Method B: TFAA (19.5 g, 93 mmol) was added to a solution of **7c** (7 g, 18.57 mmol) in dry benzene (200 mL) at rt. After the mixture was stirred for 30 min, BF_3•Et_2O (7.92 g, 56 mmol) was added, and the reaction mixture was further stirred at the same temperature for further 1.5 h. The reaction mixture was washed with 5% NaOH. The products were purified by column chromatography with AcOEt to give crude **9c** (4.0 g) and **11c** (39 mg, 1%). This crude **9c** was hydrolysed as described above to give **12c** (622 mg, 16%) and **14** (187 mg, 4.6%).

2-Formyl-1,2-dihydro-5,6,8-trimethoxyisoquinoline (11c). Pale yellow plate (from AcOEt-hexane), mp 138-141℃. IR (KBr): 1687 (=NCO-), 1641, 1496, 1354, 1331, 1240, 1093, 1053. ^{1}H-NMR: 3.76, 3.80, 3.83, 3.87 (total 3H, each s, 3 x -OCH_3), 4.69, 4.79 (total 2H, each s, ArCH_2N=), 6.09, 6.32 (total 1H, d and dd, *J*=8.0 Hz and *J*=1.0, 8.0 Hz, olefinic-H), 6.35, 6.39 (total 1H, each s, Ar-H), 6.59, 7.12 (total 1H, each d, *J*=8.0 Hz, olefinic-H), 8.17, 8.33 (total 1H, each s, =NCHO). EIMS *m/z*: 249 (M^+, base peak), 248 (80), 234 (42), 220 (21), 205 (17), 190 (36), 176 (19), 162 (15). HRMS: Calcd for $C_{13}H_{15}NO_4$: 249.1001. Found: 249.1033.

1,2,3,4-Tetrahydro-5,6,8-trimethoxyisoquinoline (12c): Colorless oil, HCl salt: Colorless needles (from EtOH-Et_2O). mp 265-268℃. IR (KBr): 1603, 1483, 1437, 1340, 1317, 1236, 1213, 1105, 1082, 1049. ^{1}H-NMR: 2.72 (2H, t, *J*=5.7 Hz, -CH_2-), 3.05 (2H, t, *J*=5.7 Hz, -CH_2N=), 3.75, 3.78, 3.86 (total 11H, each s, 3 x -OCH_3, ArCH_2N=), 6.35 (1H, s, Ar-H). ^{13}C-NMR: 23.94 (t), 43.08 (t), 55.51 (q), 56.12 (q), 60.17 (q), 94.44 (d), 117.20 (s), 129.99 (s), 140.44 (s), 150.62 (s), 152.21 (s). EIMS *m/z*: 223 (M^+, 57), 222 (91), 206 (14), 194 (24), 192 (base peak), 179 (50), 151 (22). HRMS: Calcd for $C_{12}H_{17}NO_3$: 223.1208. Found 223.1214.

***N*-(2,4,5-Trimethoxybenzyl)ethylamine (14)**: Colorless gum. IR (KBr): 1610, 1514, 1466, 1400, 1317, 1205, 1128, 1038. ^{1}H-NMR (90MHz): 1.12 (3H, t, *J*=7.0 Hz, -CH_2CH_3), 2.66 (2H, q, *J*=7.0 Hz, -CH_2CH_3), 3.72 (2H, s, ArCH_2N=), 3.81, 3.84, 3.88 (each 3H, s, 3 x -OCH_3), 6.53, 6.84 (each 1H, s, Ar-H). EIMS *m/z*: 225 (M^+, 47), 224 (33), 194 (60), 181 (base peak), 165 (13), 151 (48), 136 (14). HRMS: Calcd for $C_{12}H_{19}NO_3$: 225.1365. Found: 225.1384.

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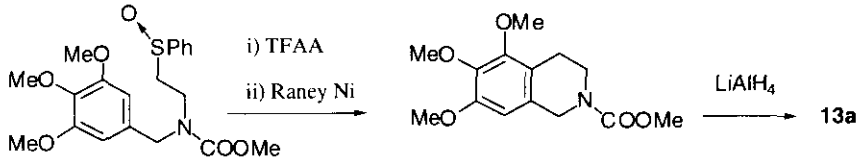

15 **16**

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