A Synthesis of Heteroaromatic Analogues of 1-Methyl-1,2,3,4-tetrahydroisoquinoline Using the Pummerer-Type Cyclization Reaction: Observation of Tandem Cyclization Reaction

Yoshie HORIGUCHI,* Keita OGAWA, Toshiaki SAITOH, and Takehiro SANO

Showa Pharmaceutical University; 3–3165 Higashi-tamagawagakuen, Machida, Tokyo 194–8543, Japan.
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The sulfoxides 7b and 7d carrying thiophene or benzothiophene as heteroaromatic nucleophiles, when treated with trifluoroacetic anhydride at room temperature (Pummerer reaction), underwent an intramolecular alkylation in an exclusive manner to yield 4,5,6,7-tetrahydro-7-methyl-4-phenylsulfanylthieno[2,3-*c*]pyridine-6-carbaldehyde (10) and the corresponding benzothiophene derivative (12b) in high yields, respectively. Thus, this route provides biologically interesting nitrogen heterocycles (1b) and (2b). On the other hand, the sulfoxide (7c) carrying benzofuran as a nucleophile on reaction with TFAA yielded not only the Pummerer-type cyclization product (12a), but also the diastereoisomeric tandem cyclization products (13) and (14) having a noble 11-aza-2-oxa-7-thiatricyclo[4.3.3.0^{1,5}]dodecane ring system (B). The formation of these products can be readily rationalized by the intervention of the oxonium ion intermediate (21).

Key words pummerer reaction; thieno[2,3-*c*]pyridine; benzothieno[2,3-*c*]pyridine; benzofuro[2,3-*c*]pyridine; 11-aza-2-oxa-7-thiatricyclo[4.3.3.0^{1,5}]dodecane

In a series of papers we reported the synthesis of 1,2,3,4-tetrahydroisoquinolines,[1—6] 1,2,3,4-tetrahydroquinolines,[7] 2,3,4,5-tetrahydro-1*H*-3-benzazepines,[8] 2-quinolones[9] using an aromatic cyclization of the sulfonium ion *in situ* formed from a sulfinyl purecursor (Pummerer reaction). The aromatic cyclization in the reaction using trifluoroacetic anhydride (TFAA) as a sole reagent (method A) smoothly proceeded at room temperature when the reactive center of the cyclizing benzene ring was activated by the electron-donating substituent. Furthermore, we found that the Pummerer substrate which lacks an electron-donating substituent on the cyclizing benzene ring, requires boron trifluoride diethyl etherate ($BF_3 \cdot Et_2O$) as an additive reagent (method B) to induce the aromatic cyclization.[2,3] Thus, the investigations demonstrated that the Pummerer-type cyclization reaction is highly effective and widely applicable for the construction of aromatic condensed nitrogen heterocycles.[10]

In order to expand the utility of this methodology, we designed a synthesis of nitrogen heterocycles possessing furo- (**1a**), thieno- (**1b**), benzofuro- (**2a**) and benzothieno[2,3-*c*]pyridine (**2b**), which bear a methyl group on the nitrogen-containing ring. The compounds with the ring system are expected to have some biological activities related to parkinsonism because of their structural resemblance to 1-methyl-1,2,3,4-tetrahydroisoquinoline (**3**), endogenous amine present in the human brain,[11] which is considered to play an important role in the prevention of the onset of parkinsonism induced by the selective dopaminergic neurotoxin, 1-methyl-4-phenylpyridinium ion (MPP^+), and by other endogenous neurotoxins, 1,2,3,4-tetrahydroisoquinoline and 1-benzyl-1,2,3,4-tetrahydroisoquinoline.[12—14]

Results and Discussion

N-Formyl sulfoxides (**7a**—**d**), substrates of the Pummerer reaction, were prepared from 2-acetylfuran (**4a**), 2-acetylthiophene (**4b**), 2-acetylbenzofuran (**4c**), and 2-acetylbenzothiophene (**4d**) in three steps (Chart 2). Condensation of **4** with 2-phenylsulfanylethylamine in titanium(IV) isopropoxide followed by $NaBH_4$ reduction of the resulting imines afforded the amines **5** in good yields. Formylation of **5** and then oxidation of the resulting *N*-formates **6** with sodium metaperiodate produced the sulfoxides **7** in high yields, though the sulfones **8**, in some cases, were produced as a by-product.

Pummerer Reaction of the Sulfoxides 7a, b The sul-

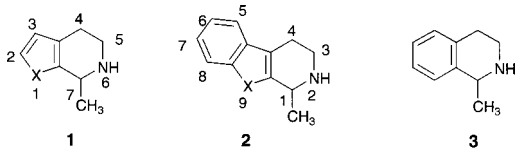

Chart 1

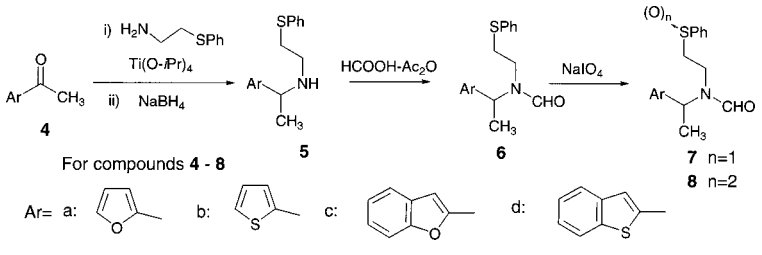

Chart 2

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

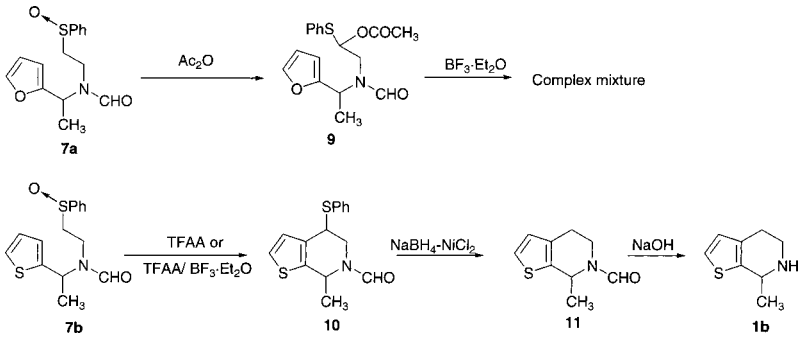

Chart 3

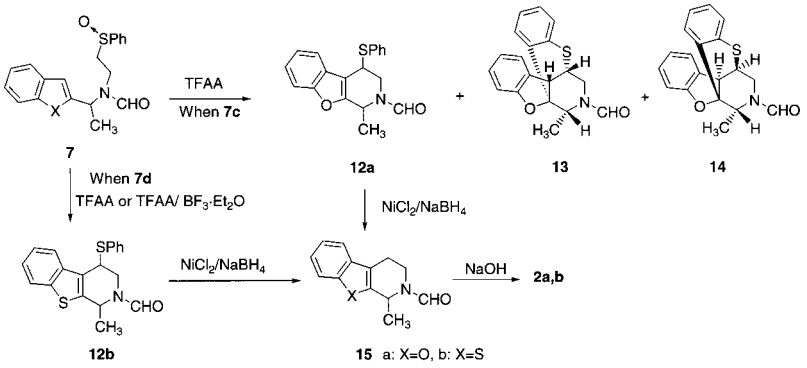

Chart 4

foxide **7a** possessing a furan ring as a nucleophilic aromatic ring, on treatment with trifluoroacetic anhydride (TFAA) in benzene at room temperature for 70 min, caused an extensive decomposition to yield no characterizable products. Even a reaction under more mild conditions (0 °C, 10 min) merely produced deep colored compounds. These facts suggest that the furan ring is highly vulnerable to trifluoroacetic acid (TFA) generated in the reaction. The treatment of **7a** with acetic anhydride at 80 °C for 14 d slowly induced a Pummerer rearrangement to give the α-acetoxyl sulfide **9** in 77% yield. Although this product is considered to be an intermediate of the Pummerer-type cyclization reaction, any attempt leading to the expected cyclization under acidic conditions was failed. For example, the reaction of **9** with $BF_3 \cdot Et_2O$ in benzene at room temperature gave no characterizable products.

On the other hand the sulfoxide **7b** having thiophene ring, when reacted with TFAA in benzene at room temperature for 6 h (method A), underwent the expected cyclization to produce 4,5,6,7-tetrahydro-7-methyl-4-phenylsulfanylthieno-[2,3-*c*]pyridine-6-carbaldehyde (**10**). This cyclization, on sequential treatment of **7b** using TFAA and $BF_3 \cdot Et_2O$ (method B), occurred more rapidly (1 h) to give **10** in an excellent yield (93%). Reductive removal of the phenylsulfanyl group of **10** with $NiCl_2$–$NaBH_4$ in THF produced 4,5,6,7-tetrahydro-7-methylthieno[2,3-*c*]pyridine-6-carbaldehyde (**11**) in 61% yield. Hydrolysis of **11** with NaOH solution gave the desired product, 4,5,6,7-tetrahydro-7-methylthieno[2,3-*c*]-pyridine (**1b**) in 79% yield.

Pummerer Reaction of the Sulfoxides 7c and 7d Treatment of the sulfoxide **7c** having benzofuran ring with TFAA in benzene at room temperature for 1.5 h (method A) yielded three products **12a**, **13**, and **14** in yields of 36%, 35%, and 16%, respectively (Chart 4). The use of $BF_3 \cdot Et_2O$ as an additional reagent (method B) facilitated the reaction to give the same products **12a** (30%), **13** (39%), and **14** (27%). In contrast the sulfoxide **7d** having benzothiophene ring, on the reaction by either the method A or B, gave **12b** in 94%, 99% yields, respectively.

The structures of **12a** and **12b** as the expected 4-phenylsulfanyl benzofuro and benzothieno[2,3-*c*]pyridine derivatives were confirmed by their spectral data and the following chemical transformations. Reductive removal of the phenylthio group of **12a** and **12b** with $NaBH_4$–$NiCl_2$ in EtOH produced **15a** and **15b** in 77% and 71% yields, respectively. Deprotection of the *N*-formyl group of **15a** and **15b** by alkaline hydrolysis yielded 1,2,3,4-tetrahydro-1-methylbenzo[4,5]furo- (**2a**) and 1,2,3,4-tetrahydro-1-methylbenzo-[4,5]thieno[2,3-*c*]pyridine (**2b**) in 98% and 83% yields, respectively.

Structures of Tandem Cyclization Products 13 and 14 The compounds **13** and **14** were identified as the products formed by two successive intramolecular alkylation reactions (tandem cyclization products) as follow. Their respective mass spectrum gave the same molecular peak at *m/z* 323 corresponding to the formula $C_{19}H_{17}O_2NS$, which is identical with that of **12a**. Their UV and NMR spectral data are very similar each other, but they are significantly different with those of **12a**; the facts indicating that the products **13** and **14** have a different skeletal ring system with that of **12a**. The ^{1}H- and ^{13}C-NMR spectra of **13** and **14** exhibited very complicated signals, thus suggesting that they are present in $CDCl_3$ as a mixture of two rotational isomers of N–CO bond. Therefore, accurate assignments of the NMR spectra were

difficult. Fortunately, we were able to clarify their structures including the stereochemistry by the spectral analysis of the *N*-deformyl derivatives **16** and **17** which were prepared by alkaline hydrolysis of **13** and **14** in 96% and 85% yields, respectively (Chart 5).

The gross structures of **16** and **17** were deduced from detailed analysis of the ^{1}H- and ^{13}C-NMR data aided by two-dimensional (2D) NMR experiments, H–H correlation spectroscopy (COSY), C–H COSY and heteronuclear multiple bond correlation (HMBC). Their ^{1}H- and ^{13}C-NMR data of **16** and **17** indicated that they possessed a same skeleton with twelve aromatic carbons, one quarternary carbon, three methines, one methylene, and one methyl group. All protons and carbons were unambiguously assigned from the 2D-NMR spectra analysis as shown in Table 1. HMBC correlations of **16** as shown in Fig. 1, H-9 to C-7 (δ_C 129.6), to C-3 (δ_C 157.6), to C-17 (δ_C 137.5), and to C-18 (δ_C 60.1), H-10 to C-1 (δ_C 98.4), and to C-8 (δ_C 133.6), H-6 to C-8, H-5 to C-3, H-14 to C12 (δ_C 129.9), and H-16 to C-12 indicated that **16** is not a derivative of furo[2,3-*c*]pyridine skeleton but a derivative of 19-aza-2-oxa-11-thiapentacyclo[8.7.3.0^{1,9}.0^{3,8}.0^{12,17}]icosa-3,5,7,12,14,16-hexaene skeleton (**A**). This ring system can be constructed by C–C bonding between the 9a-carbon of benzofuro[2,3-*c*]pyridine and the *ortho*-carbon of 4-phenylsulfanyl group. The other product **17** also exhibited HMBC correlations similar to those of **16**. Thus, the compounds **16** and **17** are assigned as stereoisomers possessing the skeleton of a unique tricyclic bridged ring system including nitrogen, oxygen, and sulfur atoms (11-aza-2-oxa-7-thiatricyclo[4.3.3.0^{1,5}]dodecane **B**).

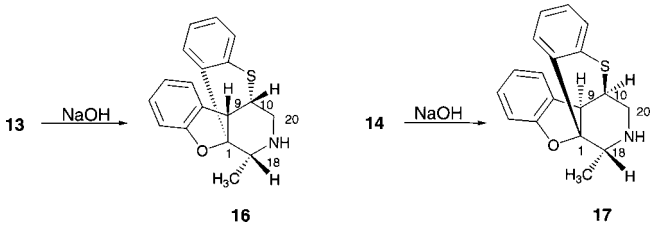

Chart 5

Table 1. ^{1}H- and ^{13}C-NMR Chemical Shifts (δ, ppm) of Products **16** and **17**

Position	**16**		**17**	
	^{1}H	^{13}C	^{1}H	^{13}C
1	—	98.4	—	95.1
3	—	157.6	—	158.8
4	7.17 (dd, *J*=8, 1 Hz)	124.7	7.12 (d, *J*=8 Hz)	124.7
5	7.09 (t, *J*=8 Hz)	128.8	7.09 (t, *J*=8 Hz)	128.9
6	7.06 (t, *J*=8 Hz)	126.7	7.06 (td, *J*=8, 1 Hz)	126.6
7	7.45 (d, *J*=8 Hz)	129.6	7.43 (dd, *J*=8, 1 Hz)	129.4
8	—	133.6	—	134.2
9	4.58 (s)	46.4	4.47 (s)	47.1
10	3.55 (dd, *J*=11, 8 Hz)	46.8	3.53 (dd, *J*=12, 8 Hz)	50.3
12	—	129.9	—	129.7
13	7.19 (d, *J*=8 Hz)	129.5	7.22 (dd, *J*=8, 1 Hz)	129.9
14	6.78 (td, *J*=8, 1 Hz)	120.7	6.76 (td, *J*=8, 1 Hz)	120.6
15	7.14 (td, *J*=8, 1 Hz)	126.2	7.16 (td, *J*=8, 1 Hz)	126.3
16	6.80 (d, *J*=8 Hz)	110.0	6.82 (d, *J*=8 Hz)	109.2
17	—	137.5	—	137.6
18	3.59 (q, *J*=7 Hz)	60.1	3.25 (q, *J*=7 Hz)	62.3
20	3.25 (dd, *J*=10, 11 Hz)	46.5	3.26 (dd, *J*=10, 11 Hz)	46.5
	3.42 (dd, *J*=10, 8 Hz)		3.41 (dd, *J*=10, 8 Hz)	
21	1.18 (d, *J*=7 Hz)	20.3	1.11 (d, *J*=7 Hz)	13.4

In order to clarify the formation mechanism of the Pummerer products **13** and **14**, we carried out some experiments. The treatment of **7c** with acetic anhydride at 80 °C for 9 d

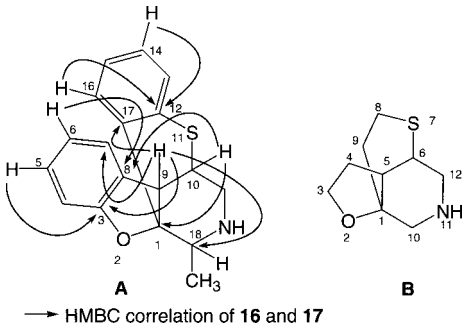

Fig. 1

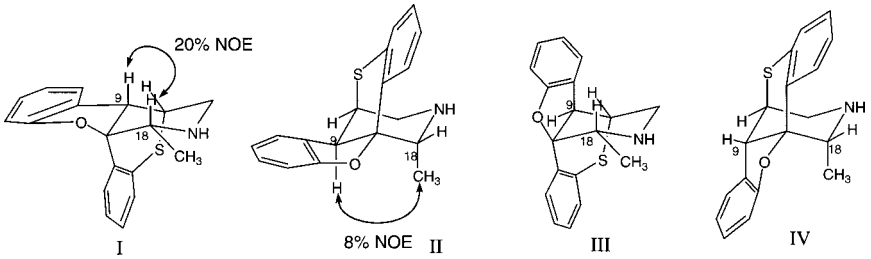

Fig. 2

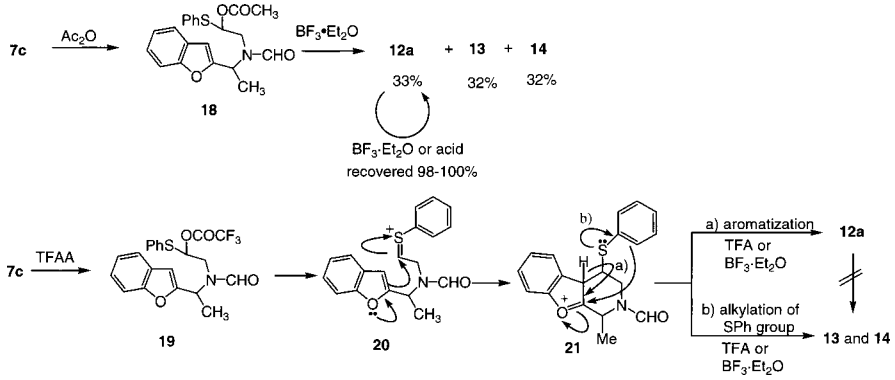

Chart 6

slowly caused the Pummerer-rearrangement reaction to afford the α-acetoxyl sulfide **18** in 87% yield. The treatment of **18** with $BF_3 \cdot Et_2O$ in benzene at room temperature for 7 d slowly induced the cyclization to yield **12a** (33%), **13** (32%), and **14** (32%), which were proved to be identical with the products obtained from the TFAA-induced Pummerer reaction of **7c** described above. On the other hand, acidic treatment of the Pummerer product **12a** with $BF_3 \cdot Et_2O$-TFAA, TFA-TFAA or *p*-TsOH-acetic anhydride did not cause any reaction and the starting material was recovered quantitatively (see experimental).

The formation mechanism of the products **12a**, **13**, and **14** is rationalized as shown in Chart 6. The formation of these products can be initiated by the generally accepted mechanism of the Pummerer reaction. The reaction involves two processes. One is a nucleophilic attack of the benzofuran ring on the cationic carbon atom of the sulfonium ion **20** followed by the aromatization reaction of the formed oxonium ion **21** leading to **12a**; the other involves the intramolecular alkylation of the C-9a carbon of **21** to the *ortho*-carbon of benzene ring of the phenylsulfanyl group. The two reactions should proceed in a competitive manner *via* the oxonium cation **21**, which, however, on treatment with $BF_3 \cdot Et_2O$ is not generated from **12a**. The compound with 11-aza-2-oxa-7-thiatricyclo[4.3.3.$0^{1,5}$]dodecane skeleton (**B**) seems to be hitherto unknown.

Experimental

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 measured as films for oils and gums, and KBr disks for solids with a HORIBA FT-710 spectrophotometer, and the values are given in cm^{-1}. NMR spectra were measured on a JEOL JNM-α-500 (^{1}H-NMR: 500 MHz, ^{13}C-NMR: 125 MHz) or a JEOL JNM-AL300 (^{1}H-NMR: 300 MHz, ^{13}C-NMR: 75 MHz) NMR spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard and the chemical shifts are given in δ values. Low-resolution electron impact ionization mass spectra (LR-EI-MS) were taken on JEOL JMS-AM20 mass spectrometer at 70 eV using direct inlet probe. High-resolution EI-MS (HR-EI-MS) and was taken on a JEOL JMS-D300 mass spectrometer at 70 eV using direct inlet system. FAB-MS spectra were recorded with JEOL-HX100A spectrometer using glycerol as a matrix. Elemental analyses were recorded on a Yanaco CHN-corder MT-3. TLC was performed on Merck precoated silica gel 60 F_{254} plates. Column chromatography was carried out with Wakogel C-200. Flash chromatography was carried out with silica gel 60 (Merck) or silica gel 60N (Kanto). The organic extract from each reaction mixture was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to dryness.

Preparation of 5a. Typical Procedure A mixture of **4a** (6.00 g, 54.5 mmol), 2-phenylsulfanylethylamine (10.03 g, 66 mmol), and titanium(IV) isopropoxide (23.10 g, 81 mmol) was heated at 80 °C for 3 h under an argon atmosphere. After cooling, the reaction mixture was diluted with MeOH (100 ml). To this solution, $NaBH_4$ (2.48 g, 66 mmol) was added in small portions under ice-cooling. The reaction mixture was stirred at room temperature for 1 h and concentrated *in vacuo*. Water (*ca.* 40 ml) was added to the residue, and the mixture was diluted with MeOH (*ca.* 500 ml). After removal of precipitated inorganic materials by filtration, the filtrate was concentrated *in vacuo*. The residue was dissolved in water and acidified by 5% HCl solution and the mixture was extracted with $CHCl_3$. Purification by column chromatography (AcOEt : hexane=1 : 2) of the product gave (1-furan-2-yl)ethyl-(2-phenylsulfanylethyl)amine (**5a**) (13.04 g, 97%) as a yellow oil. IR: 1583. ^{1}H-NMR: 1.37 (3H, d, J=7 Hz, CH_3), 2.75 (2H, t, J=6 Hz, $SC\underline{H}_2CH_2N$), 3.02 (2H, t, J=6 Hz, $SCH_2C\underline{H}_2N$), 3.97 (1H, q, J=7 Hz, $C\underline{H}CH_3$), 6.09 (1H, d, J=3 Hz, Ar), 6.27 (1H, dd, J=2, 3 Hz, Ar), 7.1—7.3 (6H, m, Ar). ^{13}C-NMR: 20.3 ($CH\underline{C}H_3$), 34.4 ($S\underline{C}H_2CH_2N$), 45.4 ($SCH_2\underline{C}H_2N$), 50.9 ($\underline{C}HCH_3$), 105.3 (ArCH), 109.8 (ArCH), 126.2 (ArCH), 128.8 (ArCH×2), 129.8 (ArCH×2), 135.6 (ArC), 141.4 (ArCH), 157.5 (ArC). LR-EI-MS *m/z*: 247 (M^+). HR-EI-MS: Calcd for $C_{14}H_{17}NOS$: 247.1031. Found: 247.1069.

(2-Phenylsulfanylethyl)-(1-thiophen-2-ylethyl)amine (**5b**) (7.70 g, 81%) was obtained from 2-acetylthiophene (**4b**) (4.51 g, 36 mmol) after purification by column chromatography (AcOEt : hexane=1 : 1) as a colorless oil. IR: 1583. ^{1}H-NMR: 1.45 (3H, d, J=7 Hz, CH_3), 2.8—3.1 (4H, m, $SC\underline{H}_2C\underline{H}_2N$), 4.08 (1H, q, J=7 Hz, $C\underline{H}CH_3$), 6.9—7.3 (8H, m, Ar). LR-EI-MS *m/z*: 263 (M^+). HR-EI-MS: Calcd for $C_{14}H_{17}NS_2$: 263.0802. Found: 263.0806.

(1-Benzofuran-2-ylethyl)-(2-phenylsulfanylethyl)amine (**5c**) (5.37 g, 88%) was obtained from 2-acetylbenzofuran (**4c**) (3.01 g, 18.8 mmol) after purification by column chromatography (AcOEt : hexane=1 : 1) as a yellow oil. IR: 1583. ^{1}H-NMR: 1.59 (3H, d, J=6 Hz, CH_3), 2.79 (2H, t, J=6 Hz, $SC\underline{H}_2CH_2N$), 3.04 (2H, t, J=6 Hz, $SCH_2C\underline{H}_2N$), 3.97 (1H, q, J=6 Hz, $C\underline{H}CH_3$), 6.47 (1H, s, Ar), 7.1—7.5 (9H, m, Ar). ^{13}C-NMR: 20.5 ($CH\underline{C}H_3$), 34.5 ($S\underline{C}H_2CH_2N$), 45.4 ($SCH_2\underline{C}H_2N$), 51.4 ($\underline{C}HCH_3$), 102.4 (ArCH), 111.1 (ArCH), 120.7 (ArCH), 122.6 (ArCH), 123.7 (ArCH), 126.3 (ArCH), 128.3 (ArC), 128.8 (ArCH×2), 130.0 (ArCH×2), 135.3 (ArC), 154.7 (ArC), 160.2 (ArC). LR-EI-MS *m/z*: 297 (M^+). HR-EI-MS: Calcd for $C_{18}H_{19}NOS$: 297.1188. Found: 297.1218.

Formylation of 5a. Typical Procedure A solution of formic-acetic anhydride prepared from formic acid (74.6 ml, 1.96 mol) and acetic anhydride (46 ml, 0.49 mol), was added to **5a** (12.02 g, 49 mmol) at 0 °C in one portion and then the mixture was heated at 70 °C for 1 h. The reaction mixture was concentrated *in vacuo* and extracted with $CHCl_3$. The residue was chromatographed (AcOEt : hexane=1 : 2) to give *N*-(1-furan-2-ylethyl)-*N*-(2-phenylsulfanylethyl)formamide (**6a**) (12.97 g, 97%) as a yellow oil. IR: 1672. ^{1}H-NMR: 1.46, 1.54 (total 3H, each d, J=7 Hz, CH_3), 2.5—3.7 (4H, m, $SC\underline{H}_2C\underline{H}_2N$), 4.74, 5.68 (total 1H, each q, J=7 Hz, $C\underline{H}CH_3$), 6.2—6.4 (2H, m, Ar), 7.1—7.5 (total 6H, m, Ar), 8.09, 8.27 (total 1H, each s, NCHO). LR-EI-MS *m/z*: 275 (M^+). HR-EI-MS: Calcd for $C_{15}H_{17}NO_2S$: 275.0980. Found: 275.0974.

N-(2-Phenylsulfanylethyl)-*N*-(1-thiophen-2-ylethyl)formamide (**6b**) (6.96 g, 91%) was obtained from **5b** (7.00 g, 22.8 mmol) after purification by column chromatography (AcOEt : hexane=2 : 3) as a pale yellow oil. IR: 1672. ^{1}H-NMR: 1.57, 1.66 (total 3H, d, J=7 Hz, CH_3), 2.7—3.5 (4H, m, SCH_2CH_2N), 4.97, 5.90 (total 1H, q, J=7 Hz, $C\underline{H}CH_3$), 6.9—7.3 (8H, m, Ar), 8.09, 8.32 (total 1H, s, NCHO). LR-EI-MS *m/z*: 291 (M^+). HR-EI-MS: Calcd for $C_{15}H_{17}NOS_2$: 291.0752. Found: 291.0786.

N-(1-Benzofuran-2-ylethyl)-*N*-(2-phenylsulfanylethyl)formamide (**6c**) (5.25 g, 96%) was obtained from **5c** (5.00 g, 16.8 mmol) after purification by

column chromatography (AcOEt : hexane = 1 : 2) as a pale yellow oil. IR: 1672, 1583. ^{1}H-NMR: 1.56, 1.63 (total 3H, each d, J=7 Hz, CH_3), 2.6—3.1 (2H, m, SC$\underline{H}_2$CH_2N), 3.3—3.4 (2H, m, SCH$_2$C$\underline{H}_2$N), 4.86, 5.78 (total 1H, each q, J=7 Hz, C$\underline{H}$CH$_3$), 6.56, 6.62 (total 1H, each s, Ar), 7.1—7.6 (9H, m, Ar), 8.15, 8.35 (total 1H, each s, NCHO). LR-EI-MS m/z: 357 (M^+). HR-EI-MS: Calcd for $C_{19}H_{19}NO_2S$: 325.1134, Found: 325.1127.

N-[1-(Benzo[*b*]thiophen-2-yl)ethyl]-*N*-(2-phenylsulfanylethyl)formamide (**6d**) (7.26 g, 75%) was obtained from 2-acetylbenzo[*b*]thiophene (**4d**) (5.00 g, 28.4 mmol) followed by the formylation of crude resulting amine (**5d**) after purification by column chromatography (hexane : AcOEt=2:1) as a pale yellow oil. IR: 1672, 1583. ^{1}H-NMR: 1.63, 1.72 (total 3H, each d, J=7 Hz, CH_3), 2.8—3.5 (4H, m, SC$\underline{H}_2$C$\underline{H}_2$N–), 5.02, 5.94 (total 1H, each q, J=7 Hz, C$\underline{H}$CH$_3$), 7.1—8.0 (10H, m, Ar), 8.16, 8.37 (1H, each s, NCHO). LR-EI-MS m/z: 341 (M^+). HR-EI-MS: Calcd for $C_{19}H_{19}NOS_2$: 341.0908. Found: 341.0925.

Oxidation of 6a with $NaIO_4$. Typical Procedure A solution of **6a** (8.00 g, 29.1 mmol) and $NaIO_4$ (9.30 g, 43.65 mmol) in MeOH (200 ml) and H_2O (50 ml) was stirred at room temperature for 1.5 h. After removal of inorganic precipitates by filtration, the filtrate was concentrated *in vacuo*. The residue was extracted with $CHCl_3$. The product was chromatographed with AcOEt and AcOEt : MeOH=9 : 1 to give **7a** (6.23 g, 74%) and **8a** (1.67 g, 17%).

***N*-(1-Furan-2-ylethyl)-*N*-(2-phenylsulfinylethyl)formamide (7a)** A colorless oil. IR: 1670. ^{1}H-NMR: 1.41, 1.47, 1.56, 1.60 (total 3H, each d, J=7 Hz, CH_3), 2.2—4.8 (4H, m, SC$\underline{H}_2$C$\underline{H}_2$N), 4.76, 4.77, 5.62, 5.72 (total 1H, each q, J=7 Hz, C$\underline{H}$CH$_3$), 6.2—6.4 (2H, m, Ar), 7.3—7.6 (6H, m, Ar-H), 8.05, 8.22, 8.23, 8.24 (total 1H, each s, NCHO). LR-EI-MS m/z: 291 (M^+). HR-EI-MS: Calcd for $C_{15}H_{17}NO_3S$: 291.0948. Found: 291.0930.

***N*-(1-Furan-2-ylethyl)-*N*-(2-phenylsulfonylethyl)formamide (8a)** A colorless oil. IR: 1670. ^{1}H-NMR: 1.41, 1.56 (total 3H, each d, J=7 Hz, CH_3), 2.5—3.6 (4H, m, SC$\underline{H}_2$C$\underline{H}_2$N), 4.77, 5.61 (total 1H, each q, J=7 Hz, C$\underline{H}$CH$_3$), 6.2—6.4 (2H, m, Ar), 7.3—7.9 (total 6H, m, Ar), 8.08, 8.19 (total 1H, each s, NCHO). LR-EI-MS m/z: 307 (M^+). HR-EI-MS: Calcd for $C_{15}H_{17}NO_4S$: 307.0860. Found: 307.0876.

Oxidation of 6b **7b** (2.00 g, 94%) and **8b** (76 mg, 3%) were obtained from **6b** (2.00 g, 29.1 mmol) after purification by column chromatography (AcOEt : hexane=2 : 1 and AcOEt).

***N*-(2-Phenylsulfinylethyl)-*N*-(1-thiophen-2-ylethyl)formamide (7b)** An orange oil. IR: 1672. ^{1}H-NMR: 1.56, 1.59, 1.70, 1.75 (total 3H, each d, J=7 Hz, CH_3), 2.3—3.8 (4H, m, SC$\underline{H}_2$C$\underline{H}_2$N), 5.0—6.0 (total 1H, m, C$\underline{H}$CH$_3$), 6.9—7.6 (8H, m, Ar), 8.10, 8.24, 8.32 (total 1H, s, NCHO). LR-EI-MS: m/z: 323 (M^+). HR-EI-MS: Calcd for $C_{15}H_{17}NO_3S_2$: 323.0650. Found: 323.0643.

***N*-(2-Phenylsulfonylethyl)-*N*-(1-thiophen-2-ylethyl)formamide (8b)** An orange oil. IR: 1670. ^{1}H-NMR: 1.44, 1.61 (total 3H, each d, J=7 Hz, CH_3), 2.7—3.6 (total 4H, m, SC$\underline{H}_2$C$\underline{H}_2$N), 4.94, 5.80 (total 1H, m, C$\underline{H}$CH$_3$), 6.8—7.9 (total 8H, m, Ar), 8.10, 8.24, 8.32 (total 1H, s, NCHO). Chemical ionization (CI)-MS m/z: 308 (M^+).

Oxidation of 6c **7c** (3.06 g, 97%) and **8c** (32 mg, 1%) were obtained from **6c** (3.00 g, 9.24 mmol) after purification by column chromatography (AcOEt : hexane=2 : 1 and AcOEt).

***N*-(1-Benzofuran-2-ylethyl)-*N*-(2-phenylsulfinylethyl)formamide (7c)** Colorless oil. IR: 1670. ^{1}H-NMR: 1.55, 1.61, 1.71, 1.74 (total 3H, each d, J=7 Hz, CH_3), 2.6—3.2 (2H, m, SC$\underline{H}_2$CH$_2$N), 3.3—3.7 (2H, m, SCH$_2$C$\underline{H}_2$N), 4.8—6.7 (total 1H, m, C$\underline{H}$CH$_3$), 6.64, 6.67, 6.69 (total 1H, s, Ar), 7.1—7.6 (total 9H, m, Ar), 8.14, 8.31, 8.35 (total 1H, each s, NCHO). LR-EI-MS m/z: 341 (M^+). HR-EI-MS: Calcd for $C_{19}H_{19}NO_3S$: 341.1121. Found: 341.1086.

***N*-(1-Benzofuran-2-ylethyl)-*N*-(2-phenylsulfonylethyl)formamide (8c)** A colorless oil. IR: 1672. ^{1}H-NMR: 1.52, 1.68 (total 3H, each d, J=7 Hz, CH_3), 2.7—3.7 (4H, m, SC$\underline{H}_2$C$\underline{H}_2$N), 4.90, 5.73 (total 1H, each q, J=7 Hz, C$\underline{H}$CH$_3$), 6.59, 6.64 (total 1H, each s, Ar), 7.2—7.7 (9H, m, Ar), 8.16, 8.27 (total 1H, each s, NCHO). LR-EI-MS m/z: 357 (M^+). HR-EI-MS: Calcd for $C_{19}H_{19}NO_4S$: 357.1020. Found: 357.1008.

Oxidation of 6d *N*-[1-(Benzo[*b*]thiophen-2-yl)ethyl]-*N*-(2-phenylsulfinylethyl)formamide (**7d**) (1.55 g, 99%) was obtained from **6d** (1.50 g, 4.4 mmol) after purification by column chromatography (AcOEt : hexane=2 : 1) as a pale yellow oil. IR: 1655. ^{1}H-NMR: 1.63, 1.67, 1.78 (total 3H, each d, J=7 Hz, CH_3), 2.4—3.9 (4H, m, SC$\underline{H}_2$C$\underline{H}_2$N), 5.06, 5.95, 6.04 (total 1H, each q, J=7 Hz, C$\underline{H}$CH$_3$), 7.1—7.8 (10H, m, Ar), 8.16, 8.29, 8.36 (total 1H, s, NCHO). CI-MS m/z: 358 (MH^+).

Pummerer Reaction of Sulfoxide 7b. Typical Procedure i) Method A: TFAA (2.27 ml, 16.3 mmol) was added to a solution of **7b** (1.00 g, 3.25 mmol) in benzene (60 ml) at room temperature, and the mixture was stirred for 6 h at the same temperature. The reaction mixture was concentrated *in vacuo*, and the residue was purified by column chromatography (AcOEt : hexane=1 : 2) to give **10** (841 mg, 89%).

ii) Method B: TFAA (2.27 ml, 16.3 mmol) was added to a solution of **7b** (1.00 g, 3.25 mmol) in benzene (60 ml) at room temperature. After the mixture was stirred for 0.5 h, $BF_3 \cdot Et_2O$ (0.41 ml, 3.25 mmol) was added, and the reaction mixture was further stirred at the same temperature for 1 h. The reaction mixture was diluted with H_2O and extracted with $CHCl_3$. Purification by column chromatography (AcOEt : hexane=1 : 2) of the product gave **10** (860 mg, 93%).

4,5,6,7-Tetrahydro-7-methyl-4-phenylsulfanylthieno[2,3-*c*]pyridine-6-carbaldehyde (10) Colorless oil. IR: 1670. UV: 220 (17700). ^{1}H-NMR: 1.41, 1.47, 1.49, 1.54 (total 3H, each d, J=7 Hz, CH_3), 3.0—4.7 (3H, m, 4-H and 5-H), 4.85, 4.91, 5.53, 5.60 (total 1H, q, J=7 Hz, 7-H), 6.9—7.6 (7H, m, Ar), 8.03, 8.05, 8.24, 8.39 (total 1H, each s, NCHO). LR-EI-MS m/z: 289 (M^+). HR-EI-MS: Calcd for $C_{15}H_{15}NOS_2$: 289.0595. Found: 289.0635.

Pummerer Reaction of 7a The reaction of **7a** with TFAA (5 mol eq) under the method A or B conditions described above merely yielded uncharacterable mixtures.

Pummerer Reaction of 7a with Acetic Anhydride A solution of **7a** (700 mg), Ac_2O (25 ml) and pyridine (0.5 ml) was heated at 80 °C for 14 d. The reaction mixture was concentrated *in vacuo*, the product was purified by column chromatography (AcOEt : hexane=1 : 2) to give acetic acid 2-[formyl-(1-furan-2-ylethyl)amino]-1-phenylsulfanylethyl ester (**9**) (685 mg, 86%) as colorless oil. IR: 1749, 1676. ^{1}H-NMR: 1.45, 1.46, 1.54, 1.59 (total 3H, each d, J=7 Hz, CH_3), 2.00, 2.04, 2.06, 2.09 (total 3H, each s, OAc), 3.2—3.7 (2H, m, NC$\underline{H}_2$CHS), 4.69, 4.70, 5.58, 5.64 (total 1H, each q, J=7 Hz, C$\underline{H}$CH$_3$), 5.05, 5.85, 6.10 (total 1H, each dd, J=3, 9 Hz, NCH$_2$C$\underline{H}$S), 6.2—6.3 (2H, m, Ar), 7.3—7.5 (6H, m, Ar-H), 8.00, 8.01, 8.23, 8.27 (total 1H, each s, NCHO). LR-EI-MS m/z: 334 (M^+). HR-FAB-MS: Calcd for $C_{17}H_{20}NO_4S$: 334.1116. Found: 334.1113.

Treatment of 9 with $BF_3 \cdot Et_2O$ A solution of **9** (333 mg) and $BF_3 \cdot Et_2O$ (0.13 ml) in benzene (16 ml) was allowed to react at rt for 17 h under stirring. The products obtained as dark reddish oil gave many spots on TLC.

Reductive Desulfurization of 10 $NaBH_4$ (610 mg, 18.1 mmol) was added in small portions to a stirred solution of **10** (509 mg, 1.76 mmol) and $NiCl_2 \cdot 6H_2O$ (1.26 g, 3.5 mmol) in EtOH (100 ml) under ice-cooling. The mixture was stirred at room temperature for a further 30 min. To the reaction mixture H_2O (10 ml) was added and filtered. The filtrate was diluted with H_2O and acidified by 5% HCl solution, and the mixture was extracted with $CHCl_3$. The residue was purified by flash chromatography (AcOEt : hexane=1 : 1) to give 4,5,6,7-tetrahydro-7-methylthieno[2,3-*c*]pyridine-6-carbaldehyde (**11**) (194 mg, 61%) as a colorless oil. IR: 1672. ^{1}H-NMR: 1.50, 1.59 (total 3H, d, J=7 Hz, CH_3), 2.7—4.6 (4H, m, 4-H and 5-H), 4.91, 5.57 (total 1H, q, J=7 Hz, 7-H), 6.7—7.2 (2H, m, Ar), 8.31, 8.35 (total 1H, s, NC$\underline{H}$O). LR-EI-MS m/z: 181 (M^+). HR-EI-MS: Calcd for $C_9H_{11}NOS$: 181.0561. Found: 181.0570.

Hydrolysis of 11 A solution of **11** (600 mg, 3.4 mmol) in EtOH (10 ml)–10% NaOH (10 ml) was refluxed for 16 h. The reaction mixture was diluted with H_2O and the mixture was extracted with $CHCl_3$. The product was purified by column chromatography ($CHCl_3$: MeOH=9 : 1) to give 4,5,6,7-tetrahydro-7-methylthieno[2,3-*c*]pyridine (**1b**)[15] (414 mg, 79%) as a pale yellow oil (lit (HCl salt: Colorless needles recrystallized from EtOH–Et_2O, mp 230—234 °C). IR: no carbonyl absorption. ^{1}H-NMR: 1.45 (3H, d, J=7 Hz, CH_3), 2.55—2.75, 2.80—3.45 (each 2H, m, 4-H and 5-H), 4.13 (1H, q, J=7 Hz, 7-H), 6.77 (1H, d, J=5 Hz, 2-H), 7.10 (1H, dd, J=1, 5 Hz, 3-H). ^{13}C-NMR: 23.5 (CH_3), 26.8 (C4), 42.9 (C5), 50.6 (C7), 121.9 (C2), 127.5 (C3), 133.8 (C7a), 140.4 (C3a). LR-EI-MS m/z: 153 (M^+). HR-EI-MS: Calcd for $C_8H_{11}NS$: 153.0612. Found: 153.0600.

Pummerer Reaction of 7c i) Method A: TFAA (4.11 ml, 22 mmol) was added to a solution of **7c** (1.50 g, 4.39 mmol) in dry benzene (75 ml) at room temperature, and the mixtrue was stirred for 1.5 h at the same temperature. The reaction mixture was diluted with H_2O and the mixture was extracted with $CHCl_3$. The residue was purified by column chromatography (AcOEt : hexane=1 : 2) to give **12a** (516 mg, 36%), **13** (496 mg, 35%), and **14** (230 mg, 16%).

ii) Method B: TFAA (1.02 ml, 7.33 mmol) was added to a solution of **7c** (500 mg, 1.47 mmol) in benzene (30 ml) at room temperature. After the mixture was stirred for 0.5 h, $BF_3 \cdot Et_2O$ (0.56 ml, 4.40 mmol) was added, and the reaction mixture was further stirred at the same temperature for 0.5 h. The reaction mixture was diluted with H_2O and extracted with $CHCl_3$. Purification by column chromatography (AcOEt : hexane=2 : 3) of the product gave **12a** (143 mg, 30%), **13** (187 mg, 39%) and **14** (127 mg, 27%).

1,2,3,4-Tetrahydro-1-methyl-4-phenylsulfanylbenzo[4,5]furo[2,3-*c*]-

pyridine-2-carbaldehyde (12a) Colorless needles recrystallized from AcOEt–hexane, mp: 184—186 °C. UV: 248 (17000), 281 (3800). IR: 1668, 1662. ^{1}H-NMR: 1.50, 1.56 (total 3H, each d, J=7 Hz, CH_3), 3.25, 3.77 (total 1H, dd, J=3, 11 Hz, 3-H), 3.68, 4.75 (total 1H, dd, J=1, 14 Hz, 3-H), 4.4—4.6 (total 1H, m, 4-H), 4.83, 5.54 (total 1H, each d, J=7 Hz, 1-H), 7.2—7.7 (9H, m, Ar), 8.13, 8.42 (total 1H, each s, NCHO). LR-EI-MS m/z: 323 (M^+). HR-EI-MS: Calcd for $C_{19}H_{17}NO_2S$: 323.0981, Found: 323.0980. *Anal.* Calcd for $C_{19}H_{17}NO_2S$: C, 70.56; H, 5.30; N, 4.33. Found: C, 70.16; H, 5.26; N, 4.12.

(1*R,9*S**,10*S**,18*R**)-19-Formyl-18-methyl-19-aza-2-oxa-11-thiapentacyclo[8.7.3.0^{1,9}.0^{3,8}.0^{12,17}]icosa-3,5,7,12,14,16-hexaene (13)** Colorless plates recrystallized from $CHCl_3$–MeOH, mp: 258—260 °C. UV: 261 (8000), 281 (4300), 290 (3800). IR: 1662, 1655, 1597. ^{1}H-NMR: 1.35, 1.39 (total 3H, each d, J=7 Hz, CH_3), 3.6—3.8 (3H, m, 10-H and 20-H), 4.23, 4.43 (total 1H, each q, J=7 Hz, 18-H), 4.61, 4.65 (total 1H, each s, 9-H), 6.8—7.5 (8H, m, Ar), 8.34, 8.35 (total 1H, each s, NCHO). LR-EI-MS m/z: 323 (M^+). HR-EI-MS: Calcd for $C_{19}H_{17}NO_2S$: 323.0972, Found: 323.0978. *Anal.* Calcd for $C_{19}H_{17}NO_2S$: C, 70.56; H, 5.30; N, 4.33. Found: C, 70.27; H, 5.32; N, 4.15.

(1*S,9*R**,10*R**,18*R**)-19-Formyl-18-methyl-19-aza-2-oxa-11-thiapentacyclo[8.7.3.0^{1,9}.0^{3,8}.0^{12,17}]icosa-3,5,7,12,14,16-hexaene (14)** Colorless needles recrystallized from $CHCl_3$–MeOH, mp: 245—248 °C. UV: 260 (3900), 281 (2100), 290 (1900). IR: 1649, 1595. ^{1}H-NMR: 1.41, 1.43 (total 3H, each d, J=6 Hz, CH_3), 3.4—4.2 (3H, m, 10-H and 20-H), 3.89, 3.99 (total 1H, each q, J=6 Hz, 18-H), 4.54, 4.56 (total 1H, each s, 9-H), 6.8—7.4 (8H, m, Ar), 8.29, 8.36 (total 1H, each s, NCHO). LR-EI-MS m/z: 323 (M^+). HR-EI-MS: Calcd for $C_{18}H_{17}NO_2S$: 323.0952, Found: 323.0979. *Anal.* Calcd for $C_{19}H_{17}NO_2S$: C, 70.56; H, 5.30; N, 4.33. Found: C, 70.26; H, 5.29; N, 4.12.

Pummerer Reaction of 7d i) Method A: **12b** (893 mg, 94%) was obtained from **7d** (1.00 g, 2.81 mmol) after purification by column chromatography (AcOEt : hexane=1 : 2).

ii) Method B: **12b** (175 mg, 99%) was obtained from **7d** (187 mg, 0.523 mmol).

1,2,3,4-Tetrahydro-1-methylbenzo[4,5]thieno[2,3-*c*]pyridine-2-carbaldehyde (12b) Colorless needles recrystallized from AcOEt–hexane, mp: 173—175 °C. IR: 1672, 1664. UV: 227 (34300), 259 (13200), 297 (3400). ^{1}H-NMR: 1.35, 1.54, 1.62 (total 3H, each d, J=6 Hz, CH_3), 3.3—4.8 (3H, m, 3-H and 4-H), 4.86, 5.00, 5.53, 5.60 (total 1H, each q, J=6 Hz, 1-H), 7.3—7.9 (9H, m, Ar), 8.09, 8.17, 8.37, 8.47 (total 1H, s, NCHO). LR-EI-MS m/z: 339 (M^+). HR-EI-MS: Calcd for $C_{19}H_{17}NOS_2$: 339.0749, Found: 339.0748. *Anal.* Calcd for $C_{19}H_{17}NOS_2$: C, 67.22; H, 5.05; N, 4.13. Found: C, 66.97; H, 5.02; N, 3.94.

Reductive Desulfurization of 12a. Typical Experiment $NaBH_4$ (610 mg, 18.8 mmol) was added in small portions to a stirred solution of **12a** (607 mg, 1.88 mmol) and $NiCl_2 \cdot 6H_2O$ (1.38 g, 6.6 mmol) in EtOH (100 ml) under ice-cooling. The mixture was stirred at room temperature for a further 0.5 h. To the reaction mixture H_2O (10 ml) was added and filtered. The filtrate was diluted with H_2O and acidified by 5% HCl solution, and the mixture was extracted with $CHCl_3$. The residue was purified by flash chromatography (AcOEt : hexane=2 : 3) to give 1,2,3,4-tetrahydro-1-methylbenzo[4,5]-furo[2,3-*c*]pyridine-2-carbaldehyde (**15a**) (311 mg, 77%) as colorless needles recrystallized from AcOEt–hexane, mp 258—260 °C. IR: 1662, 1627. UV: 283 (3600), 277 (4200), 250 (16100). ^{1}H-NMR: 1.53, 1.60 (3H, each d, J=6 Hz, CH_3), 2.7—4.7 (4H, m, 3-H and 4-H), 4.48, 5.52 (total 1H, each q, J=7 Hz, 1-H), 7.2—7.5 (4H, m, Ar), 8.19, 8.34 (total 1H, s, NCHO). LR-EI-MS m/z: 323 (M^+). HR-EI-MS: Calcd for $C_{13}H_{13}NO_2$: 323.0982, Found: 323.0980.

1,2,3,4-Tetrahydro-1-methylbenzo[4,5]thieno[2,3-*c*]pyridine-2-carbaldehyde (**15b**) (383 mg, 71%) was obtained from **12b** (796 mg, 2.35 mmol) after purification by column chromatography (benzene : acetone=15 : 2) as a colorless oil. IR: 1670, 1654. UV: 229 (23900), 258 (6800), 287 (2100), 297 (1600). ^{1}H-NMR: 1.56, 1.65 (total 3H, d, J=7 Hz, CH_3), 2.7—4.7 (4H, m, 3-H and 4-H), 5.9—6.0 (1H, m, 1-H), 7.2—7.8 (4H, m, Ar), 8.20, 8.35 (total 1H, s, NCHO). LR-EI-MS m/z: 231 (M^+). HR-EI-MS: Calcd for $C_{13}H_{13}NOS$: 231.0718. Found: 231.0700.

Hydrolysis of 15a. Typical Experiment A solution of **15a** (201 mg, 1.08 mmol) in EtOH (20 ml)–10% NaOH (10 ml) was refluxed for 1.5 h. The reaction mixture was diluted with H_2O and the mixture was extracted with $CHCl_3$. The product was purified by column chromatography (AcOEt) to give 1,2,3,4-tetrahydro-1-methylbenzo[4,5]furo[2,3-*c*]pyridine (**2a**) (171 mg, 98%) as a colorless oil. IR: no carbonyl absorption. UV: 244 (13000), 273 (2600), 280 (2200). ^{1}H-NMR: 1.46 (3H, d, J=7 Hz, CH_3), 2.5—3.3 (4H, m, 3-H and 4-H), 4.0—4.1 (1H, m, 1-H), 7.2—7.25 (2H, m, Ar-H), 7.4—7.42 (2H, m, Ar-H). ^{13}C-NMR: 19.2 (CH_3), 22.8 (C4), 42.0 (C3), 48.4 (C1), 111.0 (C8), 111.1 (C4a), 118.6 (C5), 122.3 (C6), 123.3 (C7), 128.3 (C4b), 154.1 (C8a), 156.0 (C9a). LR-EI-MS m/z: 187 (M^+). HR-EI-MS: Calcd for $C_{12}H_{13}NO$: 187.1000. Found: 187.0997.

1,2,3,4-Tetrahydro-1-methylbenzo[4,5]thieno[2,3-*c*]pyridine (**2b**) (86 mg, 83%) was obtained from **17b** (118 mg, 0.51 mmol) after purification by column chromatography (AcOEt : MeOH=6 : 1 and 4 : 1) as a colorless oil (lit[16]: HCl salt mp: 256—258 °C) (lit[17]: (*S*)-1,2,3,4-tetrahydro-1-methylbenzo[4,5]thieno[2,3-*c*]pyridine HCl salt mp: 240—242 °C). IR: no carbonyl absorption. UV: 227 (22500), 265 (6400), 298 (1700). ^{1}H-NMR: 1.50 (3H, d, J=7 Hz, CH_3), 2.7—2.8 (2H, m, 4-H), 3.11 (1H, ddd, J=14, 13, 7 Hz, 3-H), 3.44 (1H, td, J=13, 5 Hz, 3-H), 4.23 (1H, qt, J=7, 2 Hz, 1-H), 7.28 (1H, ddd, J=7.6, 7.3, 1 Hz, 6-H or 7-H), 7.35 (1H, ddd, J=7.6, 7.3, 1 Hz, 6-H or 7-H), 7.58 (1H, d, J=7 Hz, 8-H), 7.79 (1H,d, J=7 Hz, 5-H). ^{13}C-NMR: 23.1 (CH_3), 25.0 (C4), 42.3 (C3), 50.6 (C1), 120.7 (C8), 122.4 (C5), 124.0 (C6 and C7), 128.2 (C4a), 138.3 (C9a), 139.5 (C8b), 141.6 (C4b). LR-EI-MS m/z: 204 (M^+). HR-EI-MS: Calcd for $C_{12}H_{13}NS$: 204.0835. Found: 204.0847.

Hydrolysis of 13. Typical Prcedure A solution of **13** (200 mg) in EtOH (30 ml) and 10% NaOH (10 ml) was heated under reflux for 1.5 h. The reaction mixture was diluted with H_2O and the mixture was extracted with $CHCl_3$. Recrystallyzation of the product from AcOEt–hexane gave (1*R**,9*S**,10*S**,18*R**)-18-methyl-19-aza-2-oxa-11-thiapentacyclo-[8.7.3.0^{1,9}.0^{3,8}.0^{12,17}]icosa-3,5,7,12,14,16-hexaene (**16**) (175 mg, 96%) as colorless plates, mp: 139—142 °C. UV: 261 (7900), 281 (4400), 290 (3700). IR: 1597. LR-EI-MS m/z: 295 (M^+). HR-EI-MS: Calcd for $C_{18}H_{17}NOS$: 295.1071. Found: 295.1031.

(1*S**,9*R**,10*R**,18*R**)-18-Methyl-19-aza-2-oxa-11-thiapentacyclo-[8.7.3.0^{1,9}.0^{3,8}.0^{12,17}]icosa-3,5,7,12,14,16-hexaene (**17**) (28 mg, 85%) was obtained from **14** (36 mg) as colorless needles recrystallized from AcOEt–hexane, mp: 169—170 °C. IR: 1597, 1479. UV: 260 (6600), 282 (3700), 289 (3200). LR-EI-MS m/z: 295 (M^+). HR-EI-MS: Calcd for $C_{18}H_{17}NOS$: 295.1068. Found: 295.1032.

Pummerer Reaction of 7c with Acetic Anhydride A solution of **7c** (702 mg, 2.06 mmol) in Ac_2O (10 ml) was allowed to react at 80 °C for 9 d. Column chromatography of the product (AcOEt/hexane 1 : 2) gave acetic acid 2-[(1-benzofuran-2-ylethyl)formylamino]-1-phenylsulfanylethyl ester (**18**) (691 mg, 87%) as colorless oil. IR: 1749, 1676. ^{1}H-NMR: 1.56, 1.57, 1.66, 1.69 (total 3H, each d, J=7 Hz, CH_3), 1.82, 2.02, 2.03, 2.07 (total 3H, each s, $OCOCH_3$), 3.3—3.8 (2H, m, NCH_2CHS), 5.46, 6.01, 6.26, 6.28 (total 1H, each dd, J=4, 9 Hz, NCH_2CHS), 4.79—4.87, 5.67—5.77 (1H, m, $CHCH_3$), 6.5—6.6 (1H, m, Ar), 7.1—7.6 (9H, m, Ar-H), 8.06, 8.09, 8.32, 8.36 (total 1H, each s, NCHO).

Reaction of 20 with $BF_3 \cdot Et_2O$ A solution of **18** (279 mg, 0.72 mmol) in benzene (15 ml) was treated with $BF_3 \cdot Et_2O$ (0.27 ml, 2.18 mmol) at room temperature for 7 d. Column chromatography of the product (AcOEt : hexane=2 : 3) gave **12a** (78 mg, 33%), **13** (76 mg, 32%), and **14** (76 mg, 32%).

Treatment of 12a under Acidic Conditions i) A solution of **12a** (302 mg, 0.93 mmol), TFAA (0.71 ml, 5.11 mmol) in benzene (20 ml) was treated with $BF_3 \cdot Et_2O$ (0.39 ml, 3.06 mmol) at room temperature for 17 h. Column chromatography of the residue (AcOEt : hexane=1 : 1) recovered the starting material **12a** (295 mg, 98%).

ii) A solution of **12a** (300 mg, 0.93 mmol) TFAA (0.64 ml, 4.65 mmol) in benzene (20 ml) was treated with TFA (106 mg, 0.93 mmol) at room temperature for 18 h. After treatment in the same manner as described above, recovered the starting material **12a** (300 mg, 100%).

iii) Treatment of **12a** (300 mg, 0.93 mmol) in benzene (20 ml) with TFAA (0.64 ml, 4.65 mmol), $BF_3 \cdot Et_2O$ (0.39 ml, 3.06 mmol) and TFA (106 mg, 0.93 mmol) at room temperature for 18 h recovered **12a** (300 mg, 100%).

iv) Treatment of **12a** (300 mg, 0.93 mmol) in benzene (20 ml) with acetic anhydride (0.46 ml, 4.65 mmol) and *p*-TsOH (160 mg, 0.93 mmol) at 80 °C for 18 h recovered **12a** (300 mg, 100%).

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