SYNTHESIS OF INDOLIZIDINE DERIVATIVES TRIFLUOROMETHYLATED AT BRIDGEHEAD POSITION *VIA* ACYL IMINIUM ION INTERMEDIATES DERIVED FROM RING-CHAIN TAUTOMERISM OF 5,5,5-TRIFLUORO-4-OXOPENTANOYL ARYLETHYLAMIDES†

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Abstract- Acyliminium ion intermediates were generated from the stable cyclic form of 5,5,5-trifluoro-4-oxopentanoyl arylethylamides *via* acid catalyzed dehydration. Electrophilic cyclization of aryl group led to fused indolizidinones.

Preparation of trifluoromethylated heterocyclic compounds[1] is currently attracting wide interests because of their potential biological activities.[2] However, introduction of trifluoromethyl group into saturated nitrogen heterocycles such as pyrrolizidine, indolizidine, and quinolizidine has not been attracted much attention so far. There are many alkaloids with indolizidine skeleton known as biologically active compounds.[3] Introduction of trifluoromethyl group near the nitrogen atom may modify or newly produces the biological activity due to the inductive effect affecting the basicity of the tertiary amine. In this paper, we report a facile preparation method for such a new class of trifluoromethylated fused indolizidine derivatives *via* acid-catalyzed cyclization of 5,5,5-trifluoro-4-oxopentanoyl arylethylamides.

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†Dedicated to Professor Shigeru Oae on the occasion of his 77th birthday.

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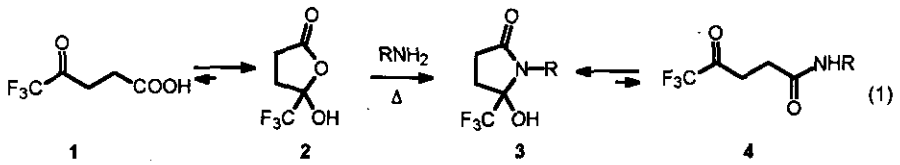
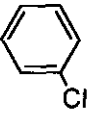
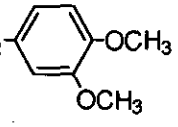
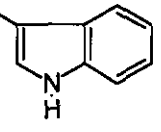
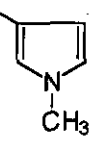
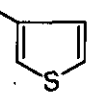
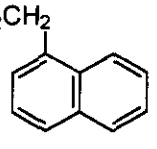


1 2 3 4

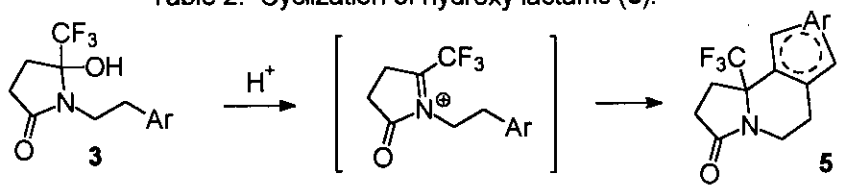
In the course of our study of preparation of fluorinated cyclic acyl imines,[4] we found that 5,5,5-trifluoro- 4- oxopentanoic acid (**1**)[5] exists as a cyclic form[6] of hydroxy lactone (**2**) due to highly electron-withdrawing effect of the CF_3 group which stabilized the hemiacetal structure. A facile reaction of **2** with phenethylamine gave hydroxy lactam (**3a**) (R = CH_2CH_2Ph) also as a stable

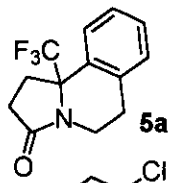
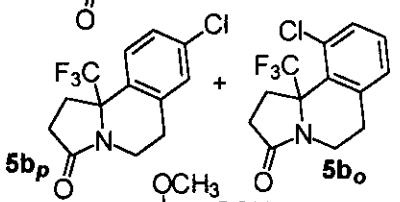
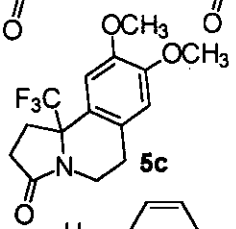
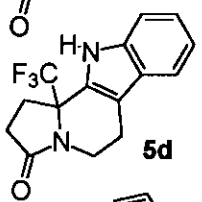
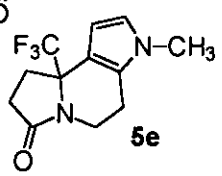
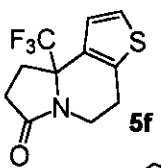
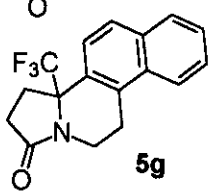
Table 1

R	method[a]	product	yiled (%)
—$CH_2CH_2C_6H_5$	A	**3a**	74
	B	**3a**	81
—CH_2CH_2– 	B	**3b**	76
—CH_2CH_2– 	A	**3c**	74
	B	**3c**	79
—CH_2CH_2– 	A	**3d**	74[b]
—CH_2CH_2– 	B	**3e**	70[c]
—CH_2CH_2– 	B	**3f**	89
—CH_2CH_2– 	B	**3g**	91
—$CH_2C_6H_5$	A	**3h**	72

a) Method A: heated at 140 °C without solvent. Method B: refluxing benzene solution. *b*) (**5d**) (23 %) was also yielded. *c*) (**5e**) (26 %) was also yielded.

Table 2. Cyclization of hydroxy lactams (**3**).



substrate	conditions,[a] time	product	yield (%)
3a	A, 2d C, 1d D, 4d	 **5a**	85 100 0
3b	C, 7d	 **5b$_p$** + **5b$_o$**	100 (9 : 1)
3c	A, 1d C, 1d	 **5c**	97 97
3d[b]	A, 8h B, 4d C, 1d	 **5d**	57[c] 91[c] 77[c]
3e[d]	C, 2d	 **5e**	73[c]
3f	A, 1.5d C, 1d	 **5f**	77 33
3g	A, 1.5d	 **5g**	52

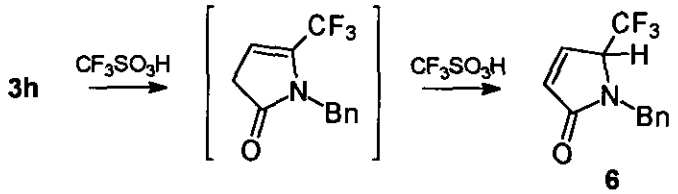
a) A: CF_3COOH (solvent), B: CF_3COOH (2eq) / CH_2Cl_2,
C: CF_3SO_3H (2eq) / CH_2Cl_2, D: 0.8M HCl / CH_3OH.
b) contaminated with 24% of (**5d**). *c*) yields based on ketoacid (**1**).
d) contaminated with 27% of (**5e**).

cyclic tautomer by just heating of the mixture at 140 °C (Method A) or refluxing of the benzene solution under neutral dehydration conditions (Method B) (eq. 1). Open- chain keto amide (**4a**) was not also observed in the reaction mixture unlike the corresponding acetyl derivative, which exists as open- chain structure as **4**.[7] Various aryl derivatives were obtained from acid (**1**) and arylethylamines and benzylamine in good yields as summarized in Table 1.

The structure of **3** is suitable for acid- catalyzed cyclization to indolizidinone skeletons (classical Pictet - Spengler conditions).[8] Unlike usual aliphatic hydroxy lactams,[7] (**3**) is considerably stable due to the electron- withdrawing effect of the CF_3 group and it could be treated with relatively strong acid such as CF_3COOH or CF_3SO_3H to dehydrate. For example, phenethylamide (**3a**) was treated with CF_3COOH as solvent at room temperature and led to tricyclic benzoindolizidinone (**5a**) in 85% yield (Table 2). Much better result was obtained by the reaction with 2- molar amount of CF_3SO_3H in CH_2Cl_2 at room temperature (quantitative yield). However, weaker 0.8 M HCl in methanol was not effective. Cyclized structure (**5a**) was readily assigned by the ^1H and ^{13}C nmr spectra and absence of OH absorption in the ir spectrum.

Other arylethyllactams (**3b- g**) were also converted into the corresponding fused indolizidinones (**5b- g**) in the same manner as that used for the preparation of **5a** (Table 2). Usually CF_3SO_3H (2 equiv) was the best reagent to dehydrative cyclization. However, in some cases (**3d,f**), strong acidity of the acid affected the heterocyclic aromatic ring to lower the yields of the products. While homoveratryl derivative (**3c**) gave sterically less hindered **5c** regioselectively, *m*- chlorophenethyl derivative (**3b**) gave a mixture of regioisomers ($\mathbf{5b}_p$) and ($\mathbf{5b}_o$) in 9 : 1 ratio. The reaction of α- naphthyl derivative (**3g**) led to 13- azasteroidal skeleton (**5g**).

If this cyclization was applied to the benzylamide derivative such as **3h**, pyrrolizidine derivative which is also a biologically interesting group of alkaloid- related compounds[9] was expected to be obtained. However, **3h** unchanged under the similar reaction conditions (2 equiv CF_3SO_3H / CH_2Cl_2). When long reaction time (10 d) and high concentration of CF_3SO_3H (10 equiv) were

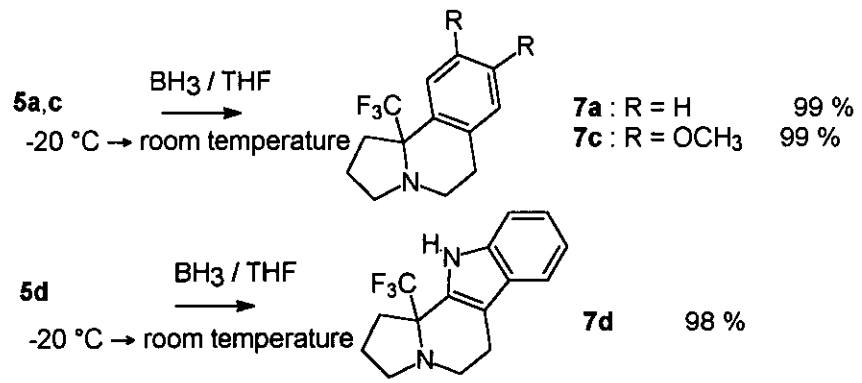


6 (2)

employed, dehydration and migration of a double bond led to pyrrolinone (**6**). The 5- *endo* cyclization of **3h** seems unlikely to occur (eq 2).[10]

Some of the obtained indolizidinones were readily converted into corresponding saturated tertiary amines (**7a**,**c**,**d**) with BH_3/THF complex[11] in good yields (Scheme 1).

Scheme 1



EXPERIMENTAL

^1H (200 MHz) and ^{13}C nmr (50 MHz) spectra were recorded on a Varian Gemini- 200 spectrometer. Other spectral data for the new compounds were satisfactorily obtained.

Amide formation of 5,5,5- trifluoro- 4- oxopentanoic acid (3). Method A: An amine (6.0 mmol) and **1** (850 mg, 5.0 mmol) was dissolved into Et_2O (15 ml), and the resulting mixture was allowed to stand overnight. The resulting precipitates were collected and washed with Et_2O several times. The collected solid was heated under Ar atmosphere at 140 °C for 2 h. Crude **3** was purified by recrystallization from Et_2O or SiO_2 column chromatography (1 : 1 hexane- EtOAc). Method B: An amine (6.0 mmol) and **1** (850 mg, 5.0 mmol) was dissolved into benzene (15 ml), and the resulting solution was refluxed with a Dean- Stark trap until deposition of water ceased. After removal of the solvent under reduced pressure, the residue was purified as above.

5- Hydroxy- 1- (2- phenylethyl)- 5- trifluoromethyl- 2- pyrrolidinone (3a): mp 94 - 95 °C; ^1H nmr ($CDCl_3$) δ 1.93 - 2.07 (m, 1H), 2.42 - 2.62 (m, 3H), 2.80 (ddd, 1H, J= 13, 10, 5 Hz), 3.04 (ddd, 1H, J= 13, 10, 5 Hz), 3.39 (dddq, 1H, J= 14, 10, 7, 1 Hz), 3.64 (ddd, 1H, J= 14, 10, 5 Hz),

4.16 (brs, 1H), 7.15 - 7.36 (m, 5H); ^{13}C nmr ($CDCl_3$) δ 28.75, 29.79, 34.01, 42.42, 89.48 (q, J= 32 Hz), 124.11 (q, J= 285 Hz), 127.09, 129.07, 139.20, 175.82. Anal. Calcd for $C_{13}H_{14}NO_2F_3$: C, 57.14; H, 5.16; N, 5.13. Found: C, 56.95; H, 5.13; N, 5.18.

1- [2- (3- Chlorophenyl)ethyl]- 5- hydroxy- 5- trifluoromethyl- 2- pyrrolidinone (3b): mp 104 - 105°C; ^{1}H nmr ($CDCl_3$) δ 2.00 - 2.15 (m, 1H), 2.45 - 2.67 (m, 3H), 2.77 (ddd, 1H, J= 13, 10, 5 Hz), 2.99 (ddd, 1H, J= 13, 11, 6 Hz), 3.39 (ddd, 1H, J= 14, 10, 6 Hz), 3.58 (ddd, 1H, J= 14, 11, 5 Hz), 4.34 (s, 1H), 7.06 - 7.13 (m, 1H), 7.17 - 7.26 (m, 3H); ^{13}C nmr ($CDCl_3$) δ 28.68, 29.73, 33.84, 41.99, 89.52 (q, J= 33 Hz), 124.09 (q, J= 285 Hz), 127.23, 127.41, 129.38, 130.27, 141.06, 175.86. Anal. Calcd for $C_{13}H_{13}NO_2ClF_3$: C, 50.75; H, 4.26; N, 4.55. Found: C, 50.88; H, 4.30; N, 4.53.

1- [2- (3,4- Dimethoxyphenyl)ethyl]- 5- hydroxy- 5- trifluoromethyl- 2- pyrrolidinone (3c): mp 108 - 109 °C; ^{1}H nmr ($CDCl_3$) δ 1.94 - 2.08 (m, 1H), 2.43 - 2.63 (m, 3H), 2.74 (ddd, 1H, J= 13, 9, 5 Hz), 2.99 (ddd, 1H, J= 13, 10, 7 Hz), 3.37 (ddd, 1H, J= 14, 9, 7 Hz), 3.63 (ddd, 1H, J= 14, 10, 5 Hz), 3.85 (s, 3H), 3.86 (s, 3H), 6.71 - 6.83 (m, 3H); ^{13}C nmr ($CDCl_3$) δ 28.74, 29.79, 33.59, 42.48, 56.09, 56.14, 89.45 (q, J= 32 Hz), 111.82, 112.55, 121.19, 124.14 (q, J= 286 Hz), 131.78, 138.18, 149.48, 175.65. Anal. Calcd for $C_{15}H_{18}NO_4F_3$: C, 54.05; H, 5.44; N, 4.20. Found: C, 54.09; H, 5.44; N, 4.16.

5- Hydroxy- 1- (2- thienyl)- 5- trifluoromethyl- 2- pyrrolidinone (3f): mp 87 - 88 °C; ^{1}H nmr ($CDCl_3$) δ 1.97 - 2.12 (m, 1H), 2.44 - 2.47 (m, 3H), 3.01 (ddd, 1H, J= 14, 9, 5 Hz), 3.28 (ddd, 1H, J= 14, 9, 7 Hz), 3.45 (ddd, 1H, J= 14, 9, 7 Hz), 3.71 (ddd, 1H, J= 14, 9, 5 Hz), 6.85 (dd, 1H, J= 3, 1H), 6.95 (dd, 1H, J= 5, 3 Hz), 7.16 (dd, 1H, J= 5, 1 Hz); ^{13}C nmr ($CDCl_3$) δ 28.00, 28.78, 29.84, 42.42, 89.46 (q, J= 32 Hz), 124.10 (q, J= 285 Hz), 124.48, 125.93, 127.54, 141.32, 175.80. Anal. Calcd for $C_{11}H_{12}NO_2F_3S$: C, 47.31; H, 4.33; N, 5.02. Found: C, 47.54; H, 4.34; N, 4.96.

5- Hydroxy- 1- [2- (1- naphthyl)ethyl]- 5- trifluoromethyl- 2- pyrrolidinone (3g): mp 132 - 134 °C; ^{1}H nmr ($CDCl_3$) δ 1.83 - 2.09 (m, 1H), 2.43 - 2.63 (m, 3H), 3.17 - 3.33 (m, 1H), 3.43 - 3.62 (m, 2H), 3.66 - 3.81 (m, 1H), 7.35 (dd, 1H, J= 12, 7 Hz), 7.35 (d, 1H), 7.41 - 7.56 (m, 2H), 3.66 - 3.81 (m, 1H), 7.31 - 7.40 (m, 2H), 7.41 - 7.56 (m, 2H), 7.73 (dd, 1H, J= 7, 3 Hz), 7.81 - 7.86 (m, 1H), 8.19 - 8.24 (m, 1H); ^{13}C nmr ($CDCl_3$) δ 28.52, 29.90, 31.36, 41.86, 89.48 (q, J= 33 Hz), 124.15 (q, J= 286 Hz), 124.15, 125.93, 126.20, 127.44, 127.85, 129.14, 132.34, 134.21, 135.40,

175.94. Anal. Calcd for $C_{17}H_{16}NO_2F_3$: C, 63.15; H, 4.99; N, 4.33. Found: C, 63.32; H, 4.34; N, 4.34.

1- Benzyl- 5- hydroxy- 5- trifluoromethyl- 2- pyrrolidinone (3h): *mp* 101 - 103 °C; ^{1}H *nmr* ($CDCl_3$) δ 2.01 - 2.13 (m, 1H), 2.37 - 2.55 (m, 3H), 4.36 (d, 1H, *J*= 16 Hz), 4.69 (d, 1H, *J*= 16Hz), 7.20 (s, 5H); ^{13}C nmr ($CDCl_3$) δ 28.46, 29.15, 43.78, 90.00 (q, *J*= 33Hz), 124.23 (q, *J*= 286Hz), 127.86, 128.24, 128.85, 137.31, 176.37. Anal. Calcd for $C_{12}H_{12}NO_2F_3$: C, 55.60; H, 4.67; N, 5.40. Found: C, 55.67; H, 4.59; N, 5.40.

Acid- catalyzed cyclization of hydroxy lactams (3). Lactam (**3**) (0.5 mmol) was dissolved in CH_2Cl_2 (3 ml), and CF_3SO_3H (0.09 ml, 1.0 mmol) was added. The resulting mixture was stirred for the period given in Table 2 at room temperature. The solution was neutralized by saturated aq $NaHCO_3$ and extracted with Et_2O. The solution was dried over $MgSO_4$. After removal of the solvent under reduced pressure, recrystallization of the residual solid from Et_2O or SiO_2 column chromatography (1:1 hexane - EtOAc) gave pure cyclization product (**5**). When CF_3COOH as the solvent was used, just removal of the solvent under reduced pressure and purification as above was done.

1,5,6,10b- Tetrahydro- 10b- trifluoromethylpyrrolo[2,1- *a*]isoquinolin- 3(2*H*)- one (5a): mp 113 - 114 °C; ^{1}H nmr ($CDCl_3$) δ 2.20 (dtq, 1H, *J*= 13, 10, 1 Hz), 2.47 (dd- pentaplet, 1H, *J*= 17, 10, 1 Hz), 2.66 - 3.09 (m, 4H), 3.27 - 3.43 (m, 1H), 4.41 (dddq, 1H, *J*= 13, 7, 4, 1 Hz), 7.16 - 7.38 (m, 4H); ^{13}C nmr ($CDCl_3$) δ 27.48, 29.43, 30.38, 35.30, 65.14 (q, *J*= 34 Hz), 126.85, 127.02 (q, *J*= 288 Hz), 127.34, 129.12, 129.84, 132.82, 134.71, 174.37. Anal. Calcd for $C_{13}H_{12}NOF_3$: C, 61.17; H, 4.74; N, 5.49. Found: C, 61.19; H, 4.69; N, 5.35.

9 : 1 Mixture of 8- and 10- chloro- 1,5,6,10b- tetrahydro- 10b- trifluoromethylpyrrolo[2,1- *a*]isoquinolin- 3(2*H*)- one (5b). ^{1}H Nmr ($CDCl_3$) δ 2.15 (dtq, 0.9H, *J*= 13, 10, 1 Hz), 2.39 - 2.60 (m, 1H), 2.65 - 3.07 (m, 4H), 3.23 - 3.40 (m, 1H), 4.30 - 4.40 (m, 0.1H), 4.41 (dddq, 0.9H, *J*= 13, 7, 3, 1 Hz), 7.13 (ddt, 0.1H, *J*= 8, 2, 1 Hz), 7.19 - 7.36 (m, 3H); ^{13}C nmr ($CDCl_3$) δ 27.42, 29.38, 30.29, 34.93, 64.87 (q, *J*= 28 Hz), 126.42 (q, *J*= 250 Hz), 127.71, 128.29 (q, *J*= 2 Hz), 129.71, 131.29, 135.12, 136.78, 174.20; minor peaks: 27.91, 28.90, 30.02, 34.63, 130.15, 130.80, 135.4. Anal. Calcd for $C_{13}H_{11}NO_2ClF_3$: C, 53.90; H, 3.83; N, 4.84. Found: C, 53.57; H, 3.91; N, 4.77.

1,5,6,10b-Tetrahydro-8,9-dimethoxy-10b-trifluoromethylpyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (5c): mp 69 - 71 °C; ^{1}H nmr ($CDCl_3$) δ 2.09 - 2.25 (m, 1H), 2.39 - 2.53 (m, 1H), 2.65 - 3.01 (m,

4H), 3.22 - 3.38 (s, 6H), 4.35 - 4.46 (m, 1H), 6.63 (s, 1H), 6.77 (q, J= 1 Hz); ^{13}C nmr ($CDCl_3$) δ 27.15, 29.38, 30.38, 35.30, 56.00, 56.28, 64.92 (q, J= 28 Hz), 109.27 (q, J= 2 Hz), 111.7, 124.29, 127.07(q, J= 288 Hz), 127.28, 148.45, 149.79, 174.32. Anal. Calcd for $C_{15}H_{16}NO_3F_3$: C, 57.14; H, 5.12; N, 4.44. Found: C, 57.27; H, 5.14; N, 4.47.

1,5,6,9b- Tetrahydro- 9b- trifluoromethylindolizino[8,7- *b*]indol-3(2 *H*)- one (5d). The reaction of tryptamine with acid (1) gave a mixture of **3d** and **5d**. The mixture was treated as above: mp 221 - 222 °C; ^{1}H nmr ($CDCl_3$) δ 2.16 - 2.33 (m, 1H), 2.50 (ddq, 1H, J= 15, 10, 1 Hz), 2.70-2.93 (m, 4H), 3.26 - 3.41 (m, 1H), 4.61 (ddd, 1H, J= 14, 5, 3 Hz), 7.16 (ddd, J= 8, 7, 1 Hz), 7.27 (ddd, 1H, J= 8, 7, 1 Hz), 7.40 (ddd, 1H, J= 8, 1, 1 Hz), 7.54 (ddd, 1H, J= 8, 1, 1 Hz), 8.31 (brs, 1H); ^{13}C nmr ($CDCl_3$) δ 20.67, 27.93, 30.41, 36.60, 63.76 (q, J= 30Hz), 111.71, 117.36, 120.59, 123.86, 126.36, 126.58 (q, J= 287Hz), 127.62, 137.09, 174.61. Anal. Calcd for $C_{15}H_{13}N_2OF_3$: C, 61.22; H, 4.45; N, 9.52. Found: C, 61.46; H, 4.41; N, 9.33.

1,5,6,9b- Tetrahydro- 7- methyl- 9b- trifluoromethylpyrrolo[2,3- *g*]indolizin- 3(2*H*)- one (5e). The reaction of 2- (2- aminoethyl)pyrrole with **1** gave a mixture of **3e** and **5e**. The mixture was treated as above: mp 115 - 116 °C; ^{1}H nmr ($CDCl_3$) δ 1.93 - 2.16 (m, 1H), 2.36 - 2.47 (m, 1H), 2.56 - 2.79 (m, 4H), 3.16 - 3.33 (m, 1H), 3.51 (s, 3H), 4.49 - 4.59 (m, 1H), 6.06 (dq, J= 3, 1 Hz), 6.59 (m, 1H); ^{13}C nmr ($CDCl_3$) δ 20.97, 29.42, 30.64, 33.19, 35.59, 64.30 (q, J= 29 Hz), 104.28, 114.63, 122.28, 126.94, 127.16 (q, J= 286 Hz), 174.98. Anal. Calcd for $C_{12}H_{13}N_2OF_3$: C, 55.81; H, 5.07; N, 10.85. Found: C, 55.70; H, 5.09; N, 10.73.

1,5,6,9b- Tetrahydro- 9b- trifluoromethylindolizino[7,8- *b*]thiophen- 3(2*H*)-one (5f) : ^{1}H Nmr ($CDCl_3$) δ 1.96 - 2.20 (m, 1H), 2.37 - 2.55 (m, 1H), 2.64 - 2.84 (m, 2H), 2.92 (dd, 1H, J= 8, 4 Hz), 3.21 - 3.37 (m, 1H), 4.54 (dt, 1H, J= 13, 2 Hz), 6.96 (dq, 1H, J= 5, 2 Hz), 7.23 (dq, 1H, J= 5, 1 Hz); ^{13}C nmr ($CDCl_3$) 24.11, 28.60, 30.41, 35.81, 64.90 (q, J= 29 Hz), 124.55 (q, J= 2 Hz), 124.70, 126.66 (q, J= 287 Hz), 130.94, 137.06, 174.52. Anal. Calcd for $C_{11}H_{10}NOF_3S$: C, 50.57; H, 3.86; N, 5.36. Found: C, 50.50; H, 3.94; N, 5.23.

1,5,6,12b- Tetrahydro- 12b- trifluoromethylnaphtho[1,2- *g*]indolizin- 3(2*H*)- one (5g): mp 146 - 149 °C; ^{1}H nmr ($CDCl_3$) δ 2.21 (dtq, 1H, J= 12, 11, 1 Hz), 2.49 (dd- pent, 1H, J= 16, 10, 1 Hz), 2.69 - 2.88 (m, 1H), 2.99 (ddd, 1H, J= 13, 9, 2 Hz), 3.10 - 3.54 (m, 3H), 4.58 - 4.69 (m, 1H), 7.43 (dq, 1H, J= 9, 2 Hz), 7.52 - 7.47 (m, 2H), 7.79 - 7.89 (m, 2H), 7.95 - 8.02 (m, 1H); ^{13}C nmr ($CDCl_3$) δ 24.00, 29.36, 30.43, 34.62 (q, J= 2 Hz), 65.24 (q, J= 28 Hz), 123.62 (q, J= 3 Hz),

123.72, 127.17 (q, J= 288 Hz), 127.43, 127.98,129.02, 129.70, 130.84, 131.84, 133.35, 174.05. Anal. Calcd for $C_{17}H_{14}NOF_3$: C, 66.88; H, 4.62; N, 4.59. Found: C, 66.85; H, 4.75; N, 4.49.

1- Benzyl- 5- trifluoromethylpyrrol- 2(5*H*)-one (6) : ^{1}H Nmr ($CDCl_3$) δ 4.12 (d, 1H, J= 15 Hz), 4.37 (ddq, 1H, J= 6, 2, 1 Hz), 5.35 (d, 1H, J= 15 Hz), 6.44 (dd, 1H, J= 6, 2 Hz), 6.97 (dd, 1H, J = 6, 1 Hz), 7.19 - 7.40 (m, 5H); ^{13}C NMR δ 44.99, 61.92 (q, J= 33 Hz), 123.69 (q, J= 282 Hz), 128.52, 129.34, 131.71, 136.53, 139.27 (q, J= 3 Hz), 171.86. Anal. Calcd for $C_{12}H_{10}NOF_3$: C, 59.75; H, 4.18; N, 5.81. Found: C, 59.75; H, 4.17; N, 5.81.

1,2,3,5,6,10b- Hexahydro- 10b- trifluoromethylpyrrolo[2,1- *a*]isoquinoline (7a). To a THF solution (15 ml) of (**5a**) (765 mg, 3.00 mmol), BH_3- THF (1.0 M, 30 ml, 30 mmol) was added dropwise at - 20°C, and the resulting solution was stirred for 3 h. To the solution, MeOH (8ml) was added, and then the solvents were removed under reduced pressure. The residue was chromatographed on SiO_2 column (1 : 1 hexane - EtOAc) to give colorless oil which was treated with HCl (g) to form hydrochloride as colorless solid (633 mg, 100 %): mp 169 - 170 °C; ^{1}H nmr (free amine, $CDCl_3$) δ 1.73 - 2.17 (m, 3H), 2.64 - 2.91 (m, 5H), 3.26 - 3.36 (m, 1H), 3.52 (m, 1H), 7.12 - 7.37 (m, 4H); ^{13}C nmr (free amine, $CDCl_3$) δ 23.86, 26.50, 36.83, 47.09, 54.78, 67.50 (q, J= 26 Hz), 127.78 (q, J= 284 Hz), 127.89, 128.53, 128.78, 135.25, 137.58. Anal. Calcd for $C_{13}H_{14}NF_3$·HCl: C, 56.22; H, 5.44; N, 5.04. Found: C, 56.13; H, 5.34; N, 5.21.

1,2,3,5,6,10b- Tetrahydro- 8,9- dimethoxy- 10b- trifluoromethylpyrrolo[2,1- *a*]isoquinoline (7c). ^{1}H Nmr ($CDCl_3$) δ 1.75 - 2.14 (m, 3H), 2.58 - 2.96 (m, 3H), 2.58 - 2.96 (m, 5H), 3.25 (ddd, 1H, J= 9, 6, 2 Hz), 3.40 (ddd, 1H, J= 13, 9, 5 Hz), 3.87 (s, 3H), 3.88 (s, 3H), 6.62 (s, 1H), 6.82 (q, 1H, J= 1 Hz); ^{13}C nmr ($CDCl_3$) δ 23.75, 25.12, 36.98, 46.33, 54.05, 55.95, 56.26, 66.93 (q, J= 27 Hz), 111.07, 111.59 (q, J= 285 Hz), 126.74, 129.80, 147.96, 148.85. Hydrochloride: mp 30 °C (decomp.). Anal. Calcd for $C_{15}H_{18}NF_3$·HCl: C, 53.34; H, 5.67; N, 4.15. Found: C, 53.03; H, 6.00; N, 4.13.

1,2,3,5,6,11b- Tetrahydro- 11b- trifluoromethyl- (1*H*)- indolizino[8,7- *b*]indole (7d): mp 105 - 107 °C; ^{1}H nmr ($CDCl_3$) δ 1.75 - 2.08 (m, 3H), 2.49 - 2.65 (m, 2H), 2.95 (ddd, 2H, J= 16, 10, 7 Hz), 3.08 - 3.16 (m, 1H), 3.31 - 3.38 (m, 2H), 7.13 (ddd, 1H, J= 8, 7, 1 Hz), 7.22 (ddd, 1H, J= 8, 7, 1 Hz), 7.36 (ddd, 1H, J= 8, 1, 1 Hz), 7.55 (ddd, 1H, J= 8, 1, 1 Hz), 7.91 (br s, 1H); ^{13}C nmr ($CDCl_3$) δ 15.96, 23.78, 35.34, 44.26, 51.38, 63.77 (q, J= 28 Hz), 111.40, 111.81, 119.10, 120.07, 123.14, 126.80, 127.49 (q, J= 284 Hz), 130.71, 136.78. Anal. Calcd for $C_{15}H_{15}N_2F_3$: C, 64.28;

H, 5.39; N, 9.99. Found: C, 64.33; H, 5.50; N, 9.82. Hydrochloride: mp 120 °C (decomp.).

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