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SYNTHESES OF PYRROLO- AND FURO-1,4-DIHYDRO-PYRIDINE DERIVATIVES

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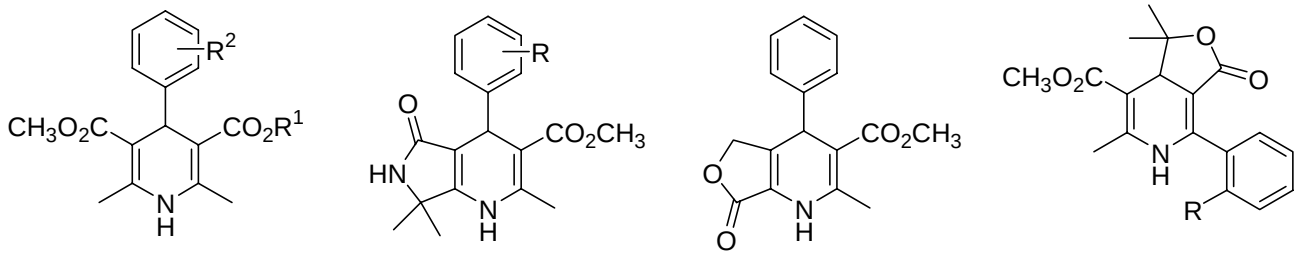
Abstract- Methyl 4-aryl-1,4,5,7-tetrahydro-2,7,7-trimethyl-5-oxo-6*H*-pyrrolo-[4,3-*b*]pyridine-3-carboxylates and methyl 1,4,5,7-tetrahydro-3-methyl-7-oxo-4-phenylfuro[3,4-*b*]pyridine-3-carboxylate were synthesized. Attempting synthesis of methyl 4-aryl-1,3,5,7a-tetrahydro-1,1,6-trimethyl-3-oxofuro[3,4-*c*]-pyridine-7-carboxylates failed.

1,4-Dihydropyridine derivatives, for example, nifedipine (**1**) and nicardipine (**2**), are used clinically for the treatment of angina pectoris, cerebrovascular disorders, hypertension and so on.[1] In the course of our synthetic studies on the biologically active heterocyclic compounds using tetronic acids, tetramic acids, thiotetronic acid and their analogs,[2] we planned to synthesize methyl 4-aryl-1,4,5,7-tetrahydro-2,7,7-trimethyl-5-oxo-6*H*-pyrrolo[4,3-*b*]pyridine-3-carboxylates (**3**), methyl 1,4,5,7-tetrahydro-3-methyl-7-oxo-4-phenylfuro[3,4-*b*]pyridine-3-carboxylate (**4**), and methyl 4-aryl-1,3,5,7a-tetrahydro-1,1,6-trimethyl-3-oxofuro[3,4-*c*]pyridine-7-carboxylates (**5**) expecting their biological activities (Figure 1).



1: Nifedipine
R^1= CH_3; R^2= 2-NO_2
2: Nicardipine
R^1=$CH_2CH_2N(CH_3)(CH_2C_6H_5)$
R^2=3-NO_2

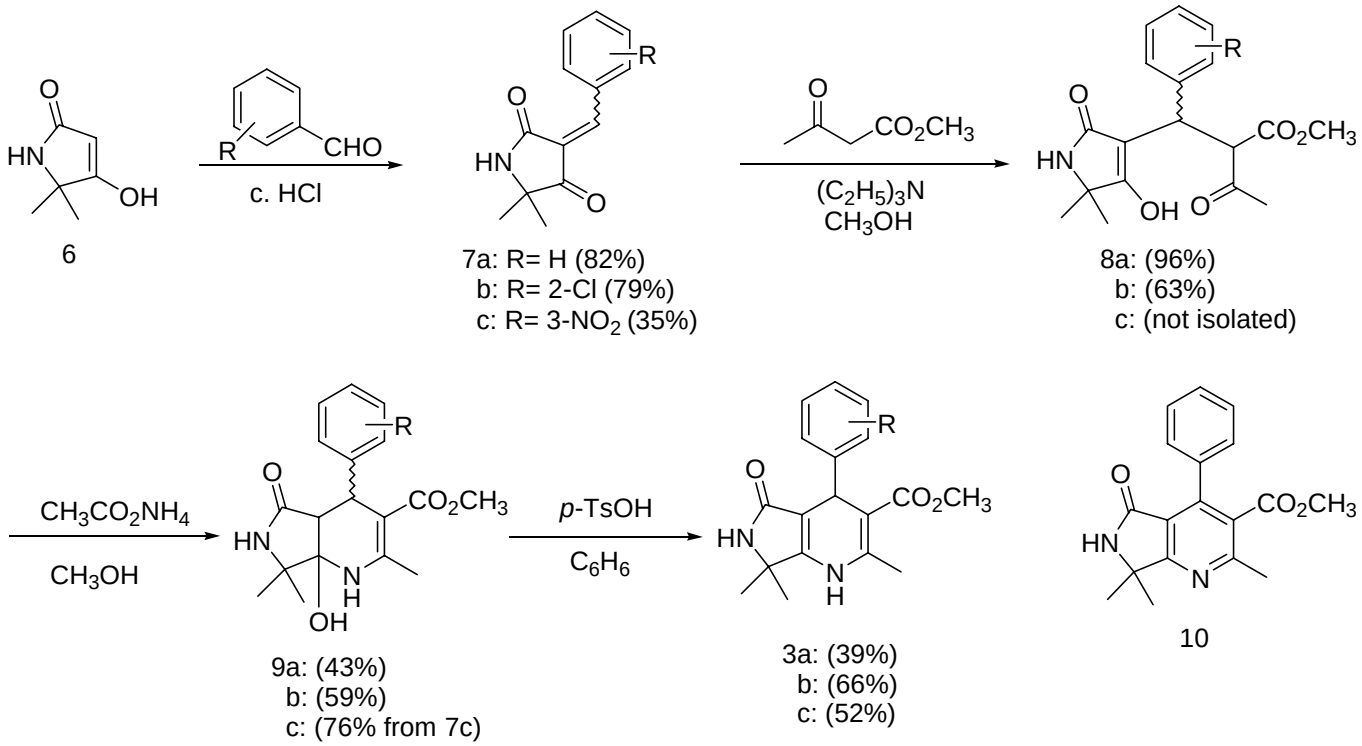
3a: R= H
b: R= 2-Cl
c: R= 3-NO_2

4

Figure 1

For the synthesis of methyl 4-aryl-1,4,5,7-tetrahydro-2,7,7-trimethyl-5-oxo-6*H*-pyrrolo[4,3-*b*]pyridine-3-carboxylates (**3**), 5,5-dimethyltetramic acid (**6**)[3] was used for the synthon. 3-Arylmethylene-5,5-

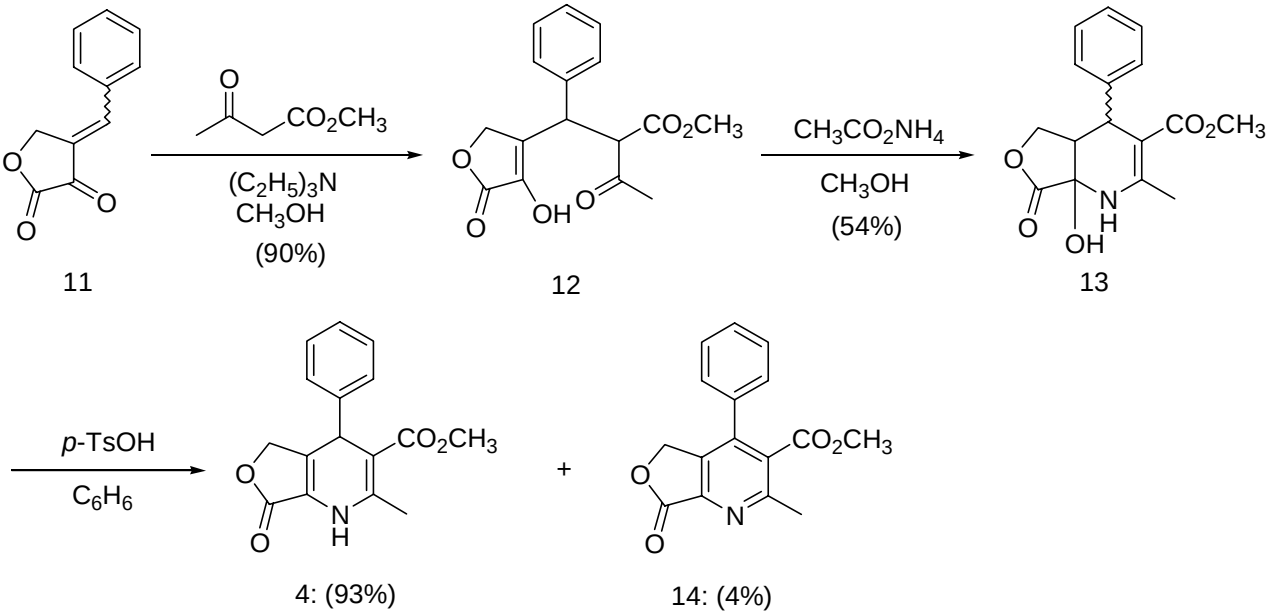
dimethyltetramic acids (**7a**∼**c**) were derived from **6** by treatment with the corresponding aryl aldehydes in the presence of conc. hydrochloric acid without solvents.[4] When 5,5-dimethyl-3-phenyl-methylenetetramic acid (**7a**) was treated with methyl acetoacetate in the presence of triethylamine in methanol at refluxing temperature, the Micheal adduct (**8a**) was obtained in 96% yield. Its ^{1}H-NMR spectrum showed that **8a** was a mixture of diastereoisomers. When **8a** was allowed to react with ammonium acetate in methanol at room temperature, the alcohol (**9a**) was isolated in 43% yield. Elemental analysis and MS spectral data supported the molecular formula of $C_{18}H_{22}N_2O_4$. In IR spectrum, the α,β-unsaturated ester and the five membered ring lactam appeared at 1670 cm^{-1}. The ^{1}H-NMR spectrum showed the benzylic methine proton signal at δ 4.98. For the following dehydration reaction, the alcohol (**9a**) was first heated with *p*-toluenesulfonic acid in benzene, but the isolated product in 41% yield was the undesired pyridine derivative (**10**). Therefore, the same reaction was repeated using a catalytic amount of *p*-toluenesulfonic acid. On this reaction, the desired dihydropyridine derivative (**3a**) was isolated in 39% yield. The structure of **3a** was fully characterized by IR, ^{1}H-NMR and MS spectral data. Other dihydropyridine derivatives (**3b**, R=2-Cl and **3c**, R=3-NO_2) were also prepared by similar reaction procedures to that used for **3a** in moderate yields (Scheme 1). In the preparation of **9c**, the intermediate (**8c**) was not isolated and used directly for the next reaction.



Scheme 1

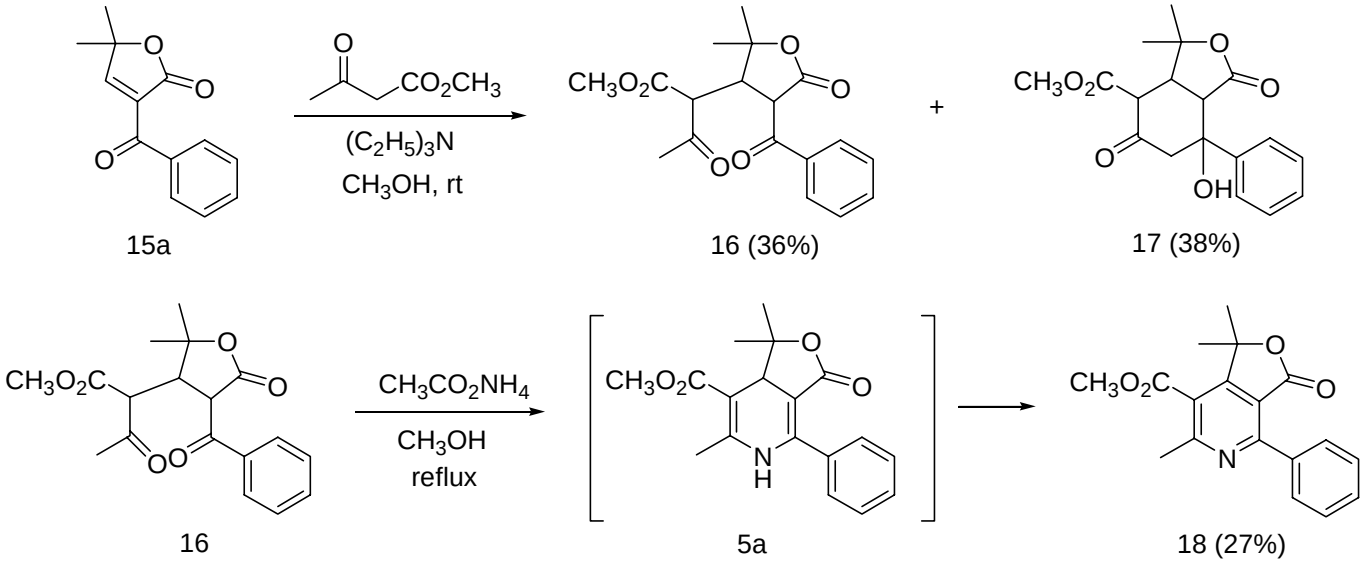
For the preparation of methyl 1,4,5,7-tetrahydro-3-methyl-7-oxo-4-phenylfuro[3,4-*b*]pyridine-3-carboxylate (**4**), 3-benzylidene-2-oxo-4-butanolide (**11**)[5] was treated first with methyl acetoacetate in methanol in the presence of triethylamine at reflux temperature to afford the Michael adduct (**12**) in 90% yield. The adduct (**12**) was then reacted with ammonium acetate in methanol at room temperature overnight to obtain the hydroxy ester (**13**) in 54% yield. When **13** was dehydrated by treatment with catalytic amount of *p*-TsOH in benzene, the desired furodihydropyridine derivative (**4**) was obtained in

93% yield accompanied with the furopyridine derivative (**14**) (4%) as a by-product (Scheme 2).



Scheme 2

For the synthesis of methyl 4-aryl-1,3,5,7a-tetrahydro-1,1,6-trimethyl-3-oxofuro[3,4-*c*]pyridine-7-carboxylates (**5a,** R=H or **5b**, R=Cl), 2-aroyl-4,4-dimethyl-2-buten-4-olides (**15**)[6] was used as the starting material. When 2-benzoyl-4,4-dimethyl-2-buten-4-olide (**15a**) was treated with methyl acetoacetate in the presence of triethylamine in methanol at room temperature, the Michael adduct (**16**) and the alcohol (**17**) were isolated in 36 and 38% yields, respectively.

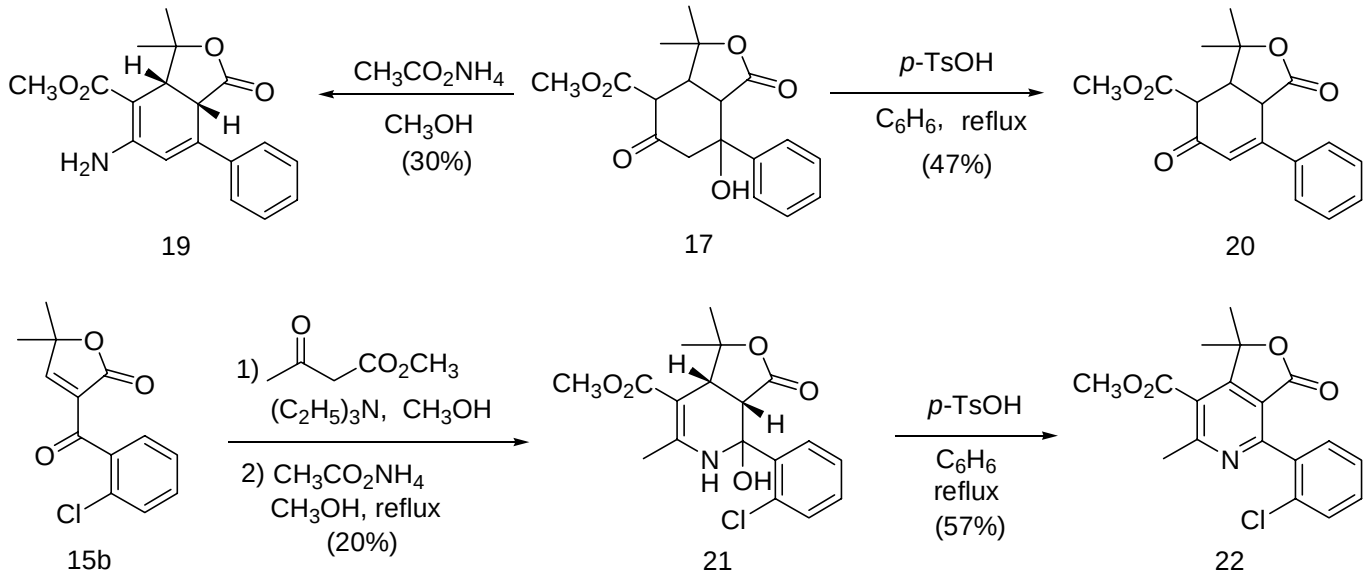


Scheme 3

The stereochemistry of α and β-positions of the γ-lactone in **16** supposed to be *cis*, because, in its ^{1}H-NMR spectrum, these two protons appeared at δ 4.85 (d, *J*=10.0 Hz) and 3.88 (t, *J*=10.0 Hz),

respectively. Expecting to obtain the dihydropyridine derivative (**5a**), successive treatment of the Michael adduct (**16**) with ammonium acetate in methanol at refluxing temperature resulted in the isolation of the pyridine derivative (**18**) in 27% yield. During the reaction, two spots supposed to be **5a** and **18** were observed on the TLC, but TLC analysis of the worked up crude products showed disappearance of the spot supposed to be **5a**. Therefore, the milder reaction conditions were employed next in the hope of isolation of **5a**. Thus, the same reaction was performed at room temperature, however no reaction took place (Scheme 3).

Since the structure of the by-product (**17**) in the above reaction was not clear at that stage, **17** was similarly treated with ammonium acetate in methanol at refluxing temperature. The product isolated in 30% yield was the amine (**19**), whose structure was confirmed by X-Ray crystallographic analysis. When **17** was reacted with *p*-TsOH in benzene, α,β-unsaturated ketoester (**20**) was obtained in 47% yield. These results indicate the structure of the by-product to be **17**.



Scheme 4

When 2-(2-chlorobenzoyl)-4,4-dimethyl-2-buten-4-olide (**15b**) was treated with methyl acetoacetate in the presence of triethylamine and successively with ammonium acetate, the alcohol (**21**) was obtained in 20% yield. The *cis* stereochemistry of the ring junction of **21** was attributed to the coupling constant (10 Hz) between those two methine protons. Dehydration reaction of **21** with *p*-TsOH in benzene at refluxing temperature in the hope of the isolation of the dihydropyridine derivative gave again the pyridine derivative (**22**) in 57% yield and **5b** was not isolated (Scheme 4).

In conclusion, methyl 4-aryl-1,4,5,7-tetrahydro-2,7,7-trimethyl-5-oxo-6*H*-pyrrolo[4,3-*b*]pyridine-3-carboxylates (**3a-c**) and methyl 1,4,5,7-tetrahydro-3-methyl-7-oxo-4-phenylfuro[3,4-*b*]pyridine-3-carboxylate (**4**) were synthesized. Attempting synthesis of methyl 4-aryl-1,3,5,7a-tetrahydro-1,1,6-trimethyl-3-oxofuro[3,4-*c*]pyridine-7-carboxylates (**5a, b**) failed and the product was the furopyridine derivatives (**18**, **22**).

EXPERIMENTAL

Melting points were determined using a Yanagimoto micro-melting point apparatus, model MP-S3, and are uncorrected. IR spectra were measured with a Hitachi 260-30 infrared spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-GSX270 (270 MHz) spectrometer using tetramethylsilane as the internal standard. High-resolution MS spectra (HRMS) were measured with a JEOL JMS-HX100 instrument at 70 eV.

Methyl 2-[1-(4,4-dimethyl-3-oxo-4-butanelactum-2-yl)-1-phenyl]methyl-3-oxobutanoate (8a)

Triethylamine (0.25 mL, 1.79 mmol) was added to a solution of methyl acetoacetate (0.546 g, 4.70 mmol) in MeOH (5 mL) and the solution was stirred for 10 min. To this solution was added dropwise a solution of **7a** (1.004 g, 4.66 mmol) in MeOH (12 mL), and the whole was heated under reflux for 5 h. After cooling the reaction mixture, the precipitates formed were collected by filtration and crystallized from MeOH to give **8a** (1.489 g, 96%). mp 147-152 ℃. IR (Nujol): 3350, 1710, 1660, 1590, 1240, 1010 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.13, 1.18 (each 3H, s, CH_3), 2.17 (3H, s, CH_3), 3.64 (3H, s, OCH_3), 4.47 (1H, d, *J*=12.0 Hz, CH), 4.99 (1H, d, *J*=12.0 Hz, CH), 7.2 (7H, m, ArH, OH, NH). HRMS (*m/z*) Calcd for $C_{18}H_{21}NO_5$: 331.1420. Found: 331.1423.

Methyl 1,4,4a,5,7-pentahydro-7a-hydroxy-2,7,7-trimethyl-5-oxo-4-phenyl-6*H*-pyrrolo[4,3-*b*]-pyridine-3-carboxylate (9a)

A solution of **8a** (3.802 g, 11.47 mmol) and ammonium acetate (4.409 g, 57.19 mmol) in MeOH (150 mL) was stirred at rt overnight. The mixture was concentrated under reduced pressure to give the residue, to which was added H_2O. The precipitates formed were collected by filtration and crystallized from AcOEt to give **9a** (1.623 g, 43%). mp 167-169 ℃. IR (Nujol): 3360, 3170, 1750, 1670, 1600, 1290, 1260, 1090 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.11, 1.17 (3H, s, CH_3), 2.34 (3H, s CH_3), 2.86 (1H, s CH), 3.39 (3H, s, OCH_3), 3.35 (3H, s, OCH_3), 4.28 (1H, s, OH), 4.98 (1H, s ArCH), 6.14 (1H, br s, NH), 7.15-7.25 (5H, ArH), 7.63 (1H, s, NH). *Anal*. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.31; H, 6.68; N, 8.53. MS (*m/z*): 330 (M^+), 312, 298, 235, 215.

Methyl 1,4,4a,5,7-pentahydro-7a-hydroxy-2,7,7-trimethyl-5-oxo-4-(2-chlorophenyl)-6*H*-pyrrolo-[4,3-*b*]pyridine-3-carboxylate (9b)

Triethylamine (0.55 mL, 3.94 mmol) was added to a solution of methyl acetoacetate (2.117 g, 18.23 mmol) in MeOH (50 mL) and the solution was stirred for 10 min. To this solution was added dropwise a solution of **7b** (4.571 g, 18.31 mmol) in MeOH (70 mL), and the whole was heated under reflux for 5 h. After concentration of the mixture under reduced pressure to give the residue, which was purified by SiO_2 column chromatography (acetone:hexane=1:2) to afford **8b** (4.223 g, 63%), after crystallization from 2-propanol-hexane. This Michael adduct (**8b**) (4.223 g, 11.54 mmol) was dissolved in MeOH (70 mL). To this solution was added ammonium acetate (2.661 g, 34.51 mmol), and the whole was stirred at rt overnight. After concentration, H_2O was added to the residue to form the precipitates, which were collected by filtration and then crystallized from DMSO-H_2O to give **9b** (2.471 g, 59%). mp 182-183 ℃. IR (Nujol): 3425, 3275, 1740, 1670, 1610, 1290, 1270, 1080 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.10, 1.17

(each 3H, s, CH_3), 2.38 (3H, s, CH_3), 2.86 (1H, s, CH), 3.34 (3H, s, OCH_3), 4.69 (1H, s, ArCH), 5.14 (1H, OH), 6.20 (1H, br s, NH), 7.10-7.36 (4H, m, ArH), 7.62 (1H, s, NH). HRMS (*m/z*) Calcd for $C_{18}H_{21}N_2O_4Cl$: 364.1190. Found: 364.1198.

Methyl 1,4,4a,5,7,7a-hexahydro-7a-hydroxy-2,7,7-trimethyl-5-oxo-4-(3-nitrophenyl)-6*H*-pyrrolo-[4,3-*b*]pyridine-3-carboxylate (9c)

Triethylamine (0.10 mL, 0.72 mmol) was added to a solution of methyl acetoacetate (0.225 g, 1.94 mmol) in MeOH (5 mL) and the solution was stirred for 10 min. To this solution was added dropwise a solution of **7c** (0.350 g, 1.34 mmol) in MeOH (24 mL), and the whole was heated under reflux for 2 h. Concentration of the mixture under reduced pressure gave the crude **8c** (0.70 g) as an oil, which was dissolved in MeOH (18 mL). To this solution was added ammonium acetate (0.505 g, 6.55 mmol), and the whole was stirred at rt for 5 h. After addition of ammonium acetate (0.207 g, 2.68 mmol), the mixture was stirred at rt overnight. After concentration, H_2O was added to the residue to form the precipitates, which were collected by filtration and then crystallized from MeOH to give **9c** (0.380 g, 76%). mp 189-193 ℃. IR (Nujol): 3290, 1720, 1660, 1600, 1270, 1250, 1210, 1190, 1100, 1060 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.09, 1.16 (each 3H, s, CH_3), 2.38 (3H, s, CH_3), 2.94 (1H, s, CH), 3.34 (3H, s, OCH_3), 4.35 (1H, s, OH), 5.51 (1H, s, ArCH), 6.56 (1H, s, NH), 7.51 (1H, t, *J*=8.0 Hz, ArH), 7.68 (1H, br d, *J*=8.0 Hz, ArH), 7.82 (1H, s, NH), 7.97 (1H, br d, *J*=8.0 Hz, ArH), 8.03 (1H, br s, ArH). HRMS (*m/z*) Calcd for $C_{18}H_{21}N_3O_6$: 375.1430. Found: 375.1445.

Methyl 5,7-dihydro-2,7,7-trimethyl-5-oxo-4-phenyl-6*H*-pyrrolo[4,3-*b*]pyridine-3-carboxylate (10)

p-TsOH・H_2O (0.431 g, 2.72 mmol) was added to a solution of **9a** (0.30 g, 0.908 mmol) in C_6H_6 (20 mL) and the reaction mixture was heated under reflux for 2 h, during the reaction, water formed was removed continuously. After cooling, the reaction mixture was concentrated under reduced pressure to give the residue, which was dissolved in $CHCl_3$. The solution was washed with saturated $NaHCO_3$ aqueous solution, H_2O, and brine, respectively and then dried over Na_2SO_4. Removal of the solvent gave the residue, which was crystallized from $CHCl_3$-hexane to afford **10** (0.115 g, 41%). mp 217-220 ℃. IR (Nujol): 3210, 1710, 1690, 1590, 1570, 1370, 1270, 1160, 1100 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.58 (6H, s, 2 x CH_3), 2.68 (3H, s, CH_3), 3.57 (3H, s, OCH_3), 6.31 (1H, s, NH), 7.36-7.42 (5H, m, ArH). *Anal*. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.72; H, 5.87; N, 9.04.

Methyl 1,4,5,7-tetrahydro-2,7,7-trimethyl-5-oxo-4-phenyl-6*H*-pyrrolo[4,3-*b*]pyridine-3-carboxylate (3a)

p-TsOH・H_2O(80 mg, 0.42 mmol) was added to a solution of **9a** (0.256 g, 0.775 mmol) in C_6H_6 (90 mL) and the reaction mixture was heated under reflux for 1 h, during the reaction, water formed was removed continuously. After cooling the reaction mixture, the precipitates formed were collected by filtration. Recrystallization of the precipitates from 2-propanol-hexane gave 95 mg (39%) of **3a**. mp 198-201 °C. IR (Nujol): 3300, 1710, 1660, 1610, 1220, 1090 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.29 and 1.31 (each 3H, s, CH_3), 2.32 (3H, s, CH_3), 3.47 (3H, s, OCH_3), 4.66 (1H, s, ArCH), 7.05-7.25 (5H, m, ArH), 7.29 (1H, s, CONH), 8.99 (1H, br s, NH). HRMS (*m/z*) Calcd for $C_{18}H_{20}N_2O_3$: 312.1474. Found: 312.1492.

Methyl 1,4,5,7-tetrahydro-2,7,7-trimethyl-5-oxo-4-(2-chlorophenyl)-6*H*-pyrrolo[4,3-*b*]pyridine-3-carboxylate (3b)

3b (0.565 g, 66%) was obtained from **9b** (0.90 g, 2.47 mmol) and *p*-TsOH・H_2O (94 mg, 0.493 mmol) by the same procedure used for **3a**. mp 285-289 ℃ (MeOH-hexane). IR (Nujol): 3200, 1700, 1660, 1640, 1270, 1210, 1170, 1080, 1040 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.28 and 1.32 (each 3H, s, CH_3), 2.30 (3H, s, CH_3), 3.41 (3H, s, OCH_3), 5.11 (1H, s, ArCH), 7.10 (1H, s, NH), 7.17-7.26 (4H, m, ArH), 9.02 (1H, s, NH). *Anal*. Calcd for $C_{18}H_{19}N_2O_3Cl$: C, 62.34; H, 5.52; N, 8.08. Found: C, 62.32; H, 5.58; N, 7.99

Methyl 1,4,5,7-tetrahydro-2,7,7-trimethyl-4-(3-nitrophenyl)-5-oxo-6*H*-pyrrolo[4,3-*b*]pyridine-3-carboxylate (3c)

3c (54 mg, 52%) was obtained from **9c** (0.110 g, 0.293 mmol) and *p*-TsOH・H_2O (11 mg, 0.058 mmol) by the same procedure used for **3a**. mp 173-176 ℃ (MeOH). IR (Nujol): 3280, 1710, 1680, 1640, 1610, 1340, 1220, 1190, 1090, 1030 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.30 and 1.32 (each 3H, s, CH_3), 2.33 (3H, s, CH_3), 3.48 (3H, s, OCH_3), 4.83(1H, s, ArCH), 7.42 (1H, s, NH), 7.50-8.02 (4H, m, ArH), 9.20 (1H, s, NH). HRMS (*m/z*) Calcd for $C_{18}H_{19}N_3O_5$: 357.1325. Found: 357.1317.

3-(2-Methoxycarbonyl-3-oxo-1-phenylbutyl)-2-oxo-4-butanolide (12)

To a solution of methyl acetoacetate (1.83 g, 15.76 mmol) and triethylamine (0.8 mL, 5.74 mmol) in MeOH (40 mL) was added drop wise a solution of **11** (2.0 g, 10.63 mmol) in MeOH (60 mL), and the whole was heated under reflux for 4.5 h. After cooling the reaction mixture, the precipitates formed were collected by filtration to give **12** (2.90 g, 90%). mp 137-138.5 ℃ (2-propanol-hexane). IR (Nujol): 3420, 1740, 1680, 1250, 1150, 1130, 1090, 1040, 1000 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.98 (3H, s, CH_3), 3.63 (3H, s, OCH_3), 4.40-4.80 (4H, m, ArCH, OCH_2, COCHCO), 7.27 (5H, m, ArH), 9.80 (1H, br s, OH). HRMS (*m/z*) Calcd for $C_{16}H_{16}O_6$: 304.0947. Found: 304.0921.

Methyl 1,4,4a,5,7,7a-hexahydro-7a-hydroxy-2-methyl-7-oxo-4-phenylfuro[3,4-*b*]pyridine-3-carboxylate (13)

A solution of **12** (0.20 g, 0.66 mmol) and ammonium acetate (0.26 g, 3.37 mmol) in MeOH (10 mL) was stirred at rt overnight. The mixture was concentrated under reduced pressure to give the residue, to which was added H_2O. The precipitates formed were collected by filtration to give **13** (0.107 g, 54%), which was crystallized from AcOEt. mp 185-188.5 ℃. IR (Nujol): 3350, 1760, 1675, 1590, 1290, 1220, 1120, 1100, 1000 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.34 (3H, s CH_3), 2.95 (1H, m OCH_2CH), 3.39 (3H, s, OCH_3), 3.75 (1H, dd, *J*=10.0, 8.0 Hz, OCH_2CH), 3.91 (1H, br s, ArCH), 4.44 (1H, t, *J*=8.0 Hz, OCH_2CH), 5.95 (1H, br s, OH), 7.21 (5H, m, ArH), 7.33 (1H, br s, NH). HRMS (*m/z*) Calcd for $C_{16}H_{17}NO_5$: 303.1107. Found: 303.1086.

Methyl 1,4,5,7-tetrahydro-3-methyl-7-oxo-4-phenylfuro[3,4-*b*]pyridine-3-carboxylate (4) and Methyl 5,7-dihydro-3-methyl-7-oxo-4-phenylfuro[3,4-*b*]pyridine-3-carboxylate (14)

p-TsOH・H_2O (0.010 g, 0.05 mmol) was added to a solution of **13** (0.30 g, 0.99 mmol) in C_6H_6 (120 mL) and the reaction mixture was heated under reflux for 5 min, during the reaction, water formed was

removed continuously. After cooling, the reaction mixture was washed with saturated $NaHCO_3$ aqueous solution, H_2O, and brine, respectively and then dried over Na_2SO_4. Removal of the solvent gave the residue, which was crystallized from C_6H_6 to afford **4** (0.252 g). The filtrate was concentrated under reduced pressure and the residue was purified by SiO_2 PTLC (C_6H_6:AcOEt=4:1) to give **4** (11 mg, total 0.263 g, 93%) and **14** (10 mg, 4%). **4**: mp 198-200 ℃ (C_6H_6). IR (Nujol): 3300, 1740, 1710, 1640, 1590, 1500, 1260, 1100 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.42 (3H, s, CH_3), 3.55 (3H, s, OCH_3), 4.51, 4.68 (each 1H, dd, *J*=16.5, 1.8 Hz, OCH_2C), 4.94 (1H, br s, ArCH), 7.15-7.37 (5H, m, ArH). *Anal.* Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.33; H, 5.36; N, 4.83. **14**: mp 200-203 ℃ (C_6H_6). IR ($CHCl_3$): 1782, 1734, 1595, 1456, 1355, 1289, 1218, 1212, 1174, 1101, 1030 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.76 (3H, s, CH_3), 3.67 (3H, s, OCH_3), 5.27 (2H, s, OCH_2), 7.18-7.35 (5H, m, ArH). HRMS (*m/z*) Calcd for $C_{16}H_{13}NO_4$: 283.0845. Found: 283.0856.

2-Benzoyl-3-(1-methoxycarbonyl-2-oxopropyl)-4-methyl-4-pentanolide (16) and Methyl 1,3,3a,4,5,6,7,7a-octahydro-4-hydroxy-1,1-dimethyl-4-phenylisobenzofuran-7-carboxylate (17)

To a solution of methyl acetoacetate (0.787 g, 6.78 mmol) and triethylamine (0.4 mL, 2.87 mmol) in MeOH (10 mL) was added dropwise a solution of **15a** (1.008 g, 4.66 mmol) in MeOH (18 mL), and the whole was stirred at rt for 5 h. The precipitates formed were collected by filtration to give **17** (0.589 g, 38%). After concentration of the filtrate, the residue was crystallized from 2-propanol to give **16** (0.554 g, 36%). **16**: mp 114-120 ℃. IR (Nujol): 1755, 1730, 1715, 1675, 1595, 1580 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.38, 1.58 (each 3H, s, CH_3), 2.14 (3H, s, $COCH_3$), 3.54 (1H, d, *J*=10.0 Hz, $CHCO_2CH_3$), 3.77 (3H, s, CO_2CH_3), 3.88 (1H, t, *J*=10.0 Hz, $CHC(CH_3)_2$), 4.85 (1H, d, *J*=10.0 Hz, CHCOPh), 7.46-8.05 (5H, m, ArH). *Anal*. Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C, 65.10; H, 6.09. **17**: mp 210-212 ℃. IR (Nujol): 3400, 1765, 1750, 1710 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.33, 1.38 (each 3H, s, CH_3), 3.73, (3H, s, OCH_3), 5.96 (1H, br s, OH), 7.20-7.61 (5H, m, ArH). *Anal.* Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C, 64.92; H, 6.06.

Methyl 1,3-dihydro-1,1,6-trimethyl-3-oxo-4-phenylfuro[3,4-*c*]pyridine-7-carboxylate (18)

A solution of **16** (0.425 g, 1.28 mmol) and ammonium acetate (0.558 g, 7.24 mmol) in MeOH (17 mL) was stirred at rt for 6 h, and then heated under reflux for 2 h. The mixture was concentrated under reduced pressure to give the residue, to which was added H_2O. The mixture was extracted with $CHCl_3$ and the extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent afforded an yellow oil (0.422 g), 0.141 g of which was purified by SiO_2 column chromatography (ether:hexane=3:2) to give **18** (36 mg, 27%) as colorless crystals. mp 127-130 ℃ (ether). IR ($CHCl_3$): 1760, 1725, 1585, 1275, 1235, 1205, 1160, 1120, 1070, 1015 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.74 (6H, s, 2 x CH_3), 2.76 (3H, s, CH_3), 4.02 (3H, s, OCH_3), 7.46-7.94 (5H, m, ArH). *Anal*. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.36; H, 5.55; N, 4.40.

Methyl 6-amino-1,3,3a,7a-tetrahydro-1,1-dimethyl-3-oxo-4-phenylisobenzofuran-7-carboxylate (19)

A mixture of **17** (0.374 g, 1.13 mmol) and ammonium acetate (0.500 g, 6.49 mmol) in MeOH (20 mL) was heated under reflux for 3 h. After addition of further ammonium acetate (0.250 g, 3.24 mmol), the

mixture was heated under reflux for further 2 h. The mixture was concentrated under reduced pressure to give the residue, to which was added H_2O to form the precipitates. Purification of the products by SiO_2 column chromatography ($CHCl_3$) gave **19** (0.108 g, 30%) as yellow crystals. mp 183-185 ℃ (C_6H_6). IR (Nujol): 3450, 3330, 1755, 1665, 1605, 1535, 1280, 1235, 1190, 1095 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.29, 1.505 (each 3H, s, CH_3), 3.75 (3H, s, OCH_3), 3.82 (1H, d, *J*=11.5 Hz, $(CH_3)_2CCH$), 4.15 (1H, dd, *J*=11.5, 2.5 Hz, COCH), 5.99 (1H, d, *J*=2.5 Hz, =CH), 7.33-7.47 (5H, m, ArH). HRMS (*m/z*) Calcd for $C_{18}H_{19}NO_4$: 313.1314. Found: 313.1333. *Anal*. Calcd for $C_{18}H_{19}NO_4$: C, 69.00; H, 6.11; N, 4.47. Found: C, 68.98; H, 6.09; N, 4.48.

Methyl 1,3,3a,6,7,7a-hexahydro-1,1-dimethyl-3,6-dioxo-4-phenylisobenzofuran-7-carboxylate (20)

p-TsOH・H_2O(1.436 g, 7.55 mmol) was added to a solution of **17** (1.932 g, 5.81 mmol) in C_6H_6 (250 mL) and the reaction mixture was heated under reflux for 7 h, during the reaction, water formed was removed continuously. After cooling, the reaction mixture was washed with saturated $NaHCO_3$ aqueous solution, H_2O, and brine, respectively. The organic layer was dried over Na_2SO_4 and then concentrated under reduced pressure to give the brawn oil, which was crystallized from AcOEt-hexane to afford **20** (0.861 g, 47%) as colorless crystals. mp 115-120 ℃. IR (Nujol): 1765, 1740, 1660, 1610, 1260, 1155, 1120, 1010 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.39, 1.60 (each 3H, s, CH_3), 3.54 (1H, dd, *J*=11.5, 7.0 Hz, $CHC(CH_3)_2$), 3.61 (1H, d, *J*=11.5 Hz, COCHCO), 3.86 (3H, s, OCH_3), 4.47 (1H, dd, *J*=7.0, 1.0 Hz, ArCCH), 6.54 (1H, d, *J*=1.0 Hz, C=CH), 7.40-7.66 (5H, m, ArH). *Anal*. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77; N. Found: C, 68.72; H, 5.72.

Methyl 4-(2-chlorophenyl)-1,3,3a,4,5,7a-hexahydro-4-hydroxy-1,1,6-trimethyl-3-oxofuro[3,4-*c*]-pyridine-7-carboxylate (21)

To a mixture of methyl acetoacetate (0.412 g, 3.55 mmol) and triethylamine (0.2 mL, 1.44 mmol) in MeOH (15 mL) was added dropwise a solution of **15b** (0.540 g, 2.15 mmol) in MeOH (10 mL), and the whole was stirred at rt for 4 h. The reaction mixture was concentrated under reduced pressure to give an yellow oil (1.489 g), which was dissolved in MeOH (27 mL). Ammonium acetate (0.870 g, 11.3 mmol) was added to the mixture and the whole was heated under reflux for 3.5 h. After concentration under reduced pressure, the residue was dissolved in $CHCl_3$. The mixture was washed with H_2O and brine, and then dried over Na_2SO_4. Removal of the solvent gave an yellow oil (0.801 g), which was purified by SiO_2 column chromatography ($CHCl_3$) to afford **21** (0.156 g, 20%). mp 127-129.5 ℃ (C_6H_6). IR (Nujol): 3400, 3300, 1745, 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.35, 1.55 (each 3H, s, CH_3), 2.35 (3H, s, $=CCH_3$), 3.63 (3H, s, OCH_3), 3.43 (1H, d, *J*=10.0 Hz, $(CH_3)_2CCH$), 4.15 (1H, d, *J*=10.0 Hz, COCH), 5.15, 5.78 (each 1H, br s, NH, OH), 7.22-7.48 (4H, m, ArH). MS (*m/z*): 365, 310, 278, 261, 250, 132. HRMS (*m/z*) Calcd for $C_{18}H_{20}NO_5Cl$: 365.1030. Found: 365.1159.

Methyl 4-(2-chlorophenyl)-1,3-dihydro-1,1,6-trimethyl-3-oxofuro[3,4-*c*]pyridine-7-carboxylate (22)

p-TsOH・H_2O (54 mg, 0.284 mmol) was added to a solution of **21** (28 mg, 0.077 mmol) in C_6H_6 (10 mL) and the reaction mixture was heated under reflux for 4.5 h, during the reaction, water formed was removed continuously. After cooling, the reaction mixture was washed with saturated $NaHCO_3$ aqueous solution and brine, and then dried over Na_2SO_4. Removal of the solvent gave an oil which was purified by

SiO_2 TLC (ether:hexane=3:1) to give **22** (15 mg, 57%) as colorless crystals. mp 118-123 ℃ (C_6H_6). IR (Nujol): 1770, 1720, 1575, 1265, 1210, 1125, 1070, 1055, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.74 (6H, s, 2 x CH_3), 2.77 (3H, s, CH_3), 4.04 (3H, s, OCH_3), 7.35-7.54 (4H, m, ArH). HRMS (*m/z*) Calcd for $C_{18}H_{16}NO_4$ (M^+-Cl): 310.1079. Found: 310.1071.

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