

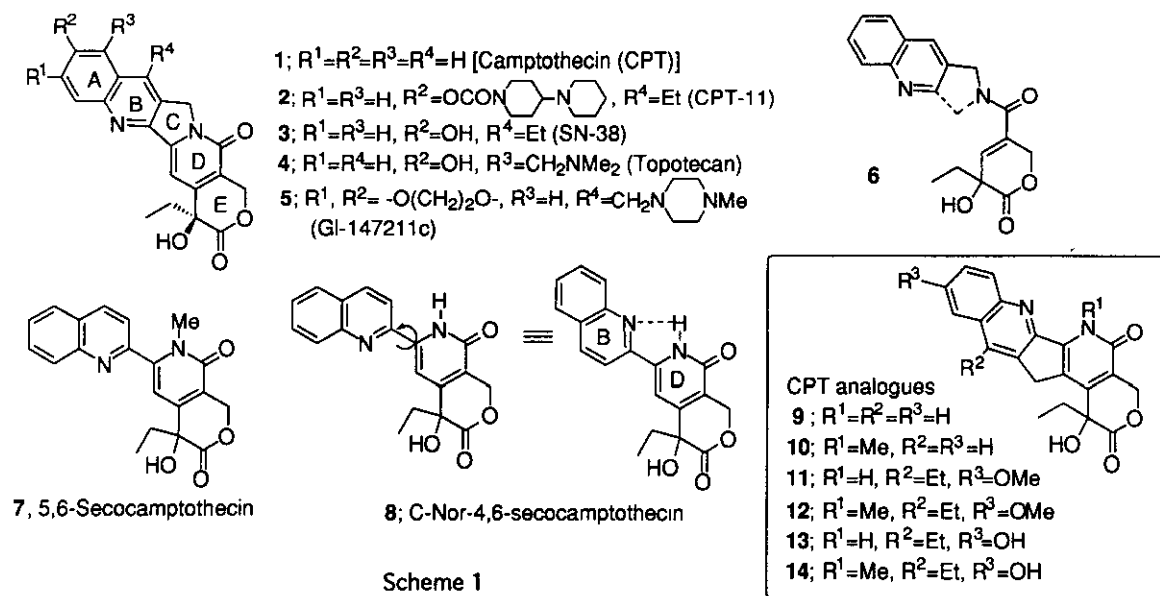
SYNTHESIS OF C-RING MODIFIED ANALOGUES OF CAMPTOTHECIN

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Abstract - Aiming at developing novel antitumor active compounds, we designed hexahydropyrano[3'', 4''; 3', 4']pyrido[5', 6'; 4, 5]cyclopenta[1, 2-*b*]quinoline which is a C-ring modified analogue of camptothecin. The compounds (9-14) were synthesized *via* Friedländer condensation and their *in vitro* cytotoxic activities were tested.

Camptothecin (CPT, 1), isolated from *Camptotheca acuminata* by Wall and co-workers¹ in 1966, is an antitumor agent due to the selective inhibition of DNA topoisomerase I² which is an essential enzyme for swiveling and relaxation of supercoiled DNA. The clinical utility of CPT as an anticancer agent³ was limited due to its toxicity and an extremely poor solubility profile. Thus, a number of water-soluble CPT derivatives such as irinotecan (CPT-11, 2),⁴ topotecan (4)⁵ and GI-147211c (5)⁶ have been synthesized and undergone extensive clinical trials. In 1994, CPT-11 (2) has been the first drug of CPT derivatives to be licensed for the treatment of lung, cervix, and ovary cancer in Japan (Scheme 1).

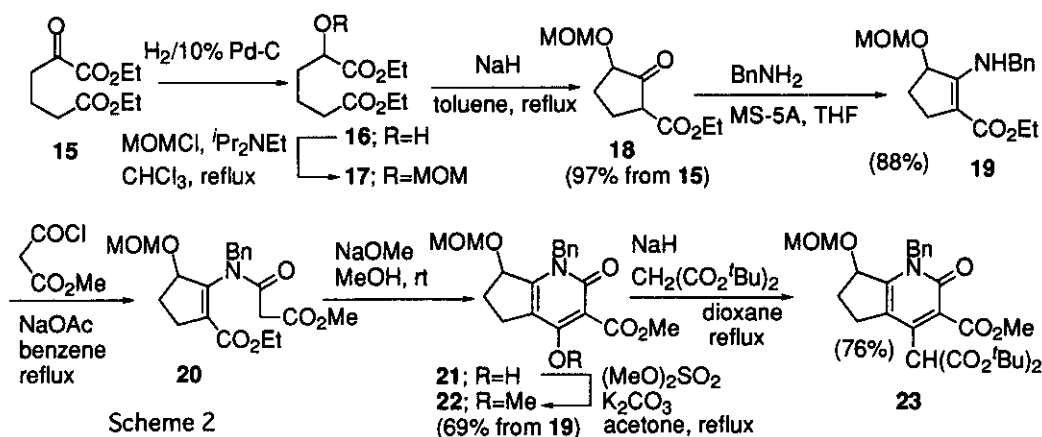


Scheme 1

On the other hand, the search for new derivatives with skeletal modification of CPT has extensively been carried out, especially the effects of modification of the A and E rings.⁷ Recently, Glaxo group⁸ reported the synthesis of the flexible analogues (**6**) of **1** in which the D-ring, or D- and C-rings are incomplete, and the lack of activity of compounds suggested the importance of the rigid camptothecin nucleus.

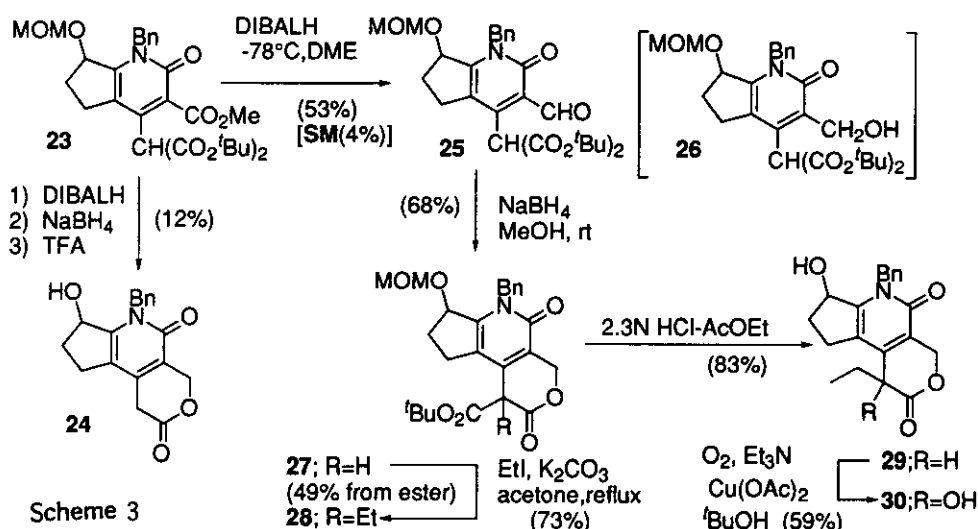
Previously, we reported the synthesis and biological evaluation of des-C-ring analogues of **1** such as 5,6-seccamptothecin (**7**), and C-nor-4,6-seccamptothecin (**8**), the latter of which make possible to retain a plane molecule by an intramolecular hydrogen bonding between the quinoline nitrogen atom and the N-H group of pyridone ring.⁹ The lack of activity of these compounds also showed the importance of the rigidity and planarity of the molecule. Therefore, we designed a rigid analogue of C-ring modified camptothecin, pyranopyridocyclopentaquinolines (**9-14**), which correspond to a conformationally restricted molecule of secocamptothecins (**7**, **8**).

Our synthesis started from cyclopentane ring formation. Catalytic hydrogenation of α -keto ester (**15**)¹⁰ on 10% Pd-C followed by subsequent protection of the hydroxyl group of **16** with MOMCl in the presence of Hünig base gave the ether (**17**) (Scheme 2). Dieckmann condensation of **17** with sodium hydride in refluxing toluene afforded the β -keto ester (**18**) in 97% overall yield from **15**. Treatment of **18** with benzylamine in the presence of 5A-molecular sieves (MS-5A) in THF gave the enamino ester (**19**) in 88% yield. Reaction of **19** with malonyl chloride in refluxing benzene did not go to completion. Use of sodium acetate as hydrogen chloride scavenger provided the best result (77%) to give the amide (**20**). Dieckmann cyclization (NaOMe) of **20** followed by methylation of the resulting hydroxypyridone (**21**) with dimethyl sulfate afforded the methoxypyridone (**22**) in 69% overall yield from **19**. Formation of the lactone ring (E ring) was then investigated based on our previous paper.⁹



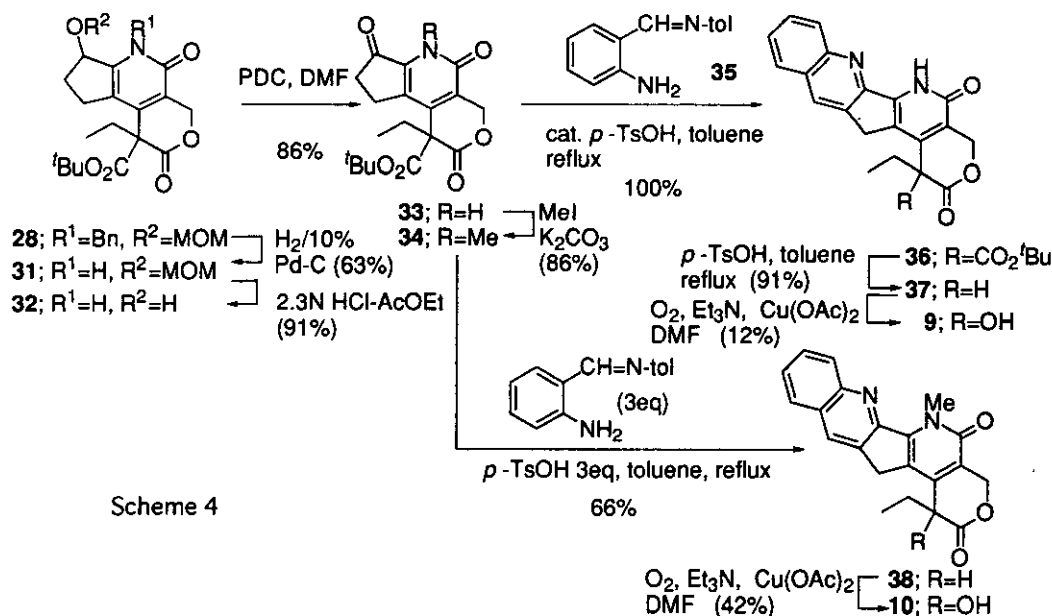
Reaction of **22** with di-*tert*-butyl malonate and sodium hydride in dioxane gave the malonate (**23**, 76%), which was treated in turn with DIBALH, NaBH₄, and TFA to give the lactone (**24**), but the yield was very poor (12% overall yield) (Scheme 3). Thus, a stepwise route was examined. Reduction of **23** with DIBALH in DME at -78°C followed by purification by SiO₂ column chromatography gave the aldehyde (**25**, 53%), together with the primary alcohol (**26**, 4%) and the starting material (**23**, 4%). Reduction of **25** with NaBH₄ in MeOH afforded the lactone (**27**) in 68% yield as a 1:1 mixture of diastereomers. Without

isolation of the aldehyde (**25**), the malonate (**23**) was directly converted to **27** in 49% overall yield.



Scheme 3

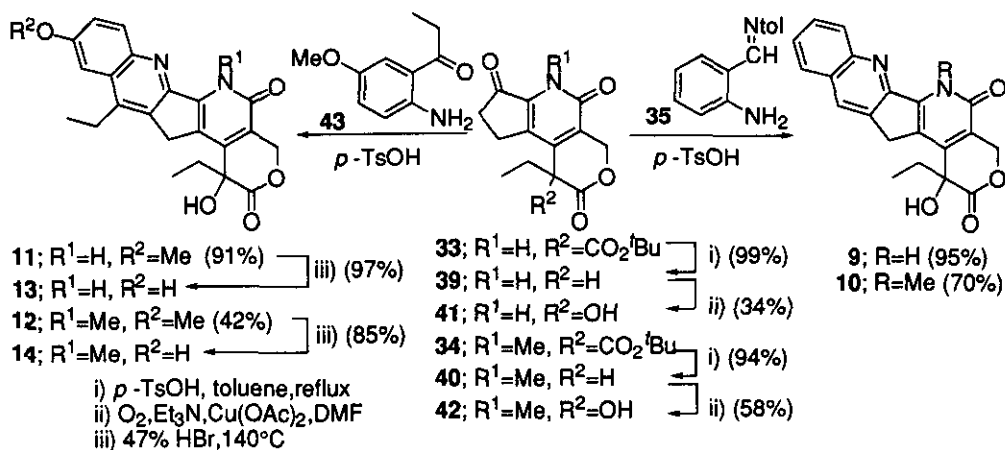
Ethylation (EtI/K₂CO₃) (73%) of **27** followed by treatment of **28** with HCl in EtOAc gave the alcohol (**29**) in 83% yield. Oxidation of **29** with an oxygen in the presence of Cu(OAc)₂ and triethylamine in *tert*-BuOH afforded the diol (**30**) in 59% yield. Even though the diol (**30**) was ultimately in hand, oxidation of the secondary hydroxy group of **30** resulted in a recovery of the starting material after several trials,



Scheme 4

probably due to the steric interaction with *N*-benzyl group in a *peri* position. Therefore, cleavage of *N*-benzyl group was investigated. Though debenzilation of **29** and **30** did not proceed, that of **28** by

catalytic hydrogenation (10% Pd/C-H₂) gave **31** (63%), which was successively transformed to the alcohol (**32**) (91%) keeping the *tert*-butoxycarbonyl group by treatment with HCl in EtOAc in this case (Scheme 4). PDC oxidation of **32** to the ketone (**33**) was conducted, in 86% yield, under standard conditions. Construction of quinoline ring was attained by Friedländer reaction of **33** with the imine (**35**)¹¹ in refluxing toluene in the presence of catalytic amounts of *p*-TsOH to give the pyranopyridocyclopentaquinoline (**36**) (100%), whose *tert*-butoxycarbonyl group was then cleaved by treatment with *p*-TsOH (1 equiv.) to lead **37** in 91% yield. The corresponding *N*-methyl derivative (**38**) was prepared by the method in analogy with the synthesis of **37**, wherein the Friedländer condensation of **34**, prepared by methylation (MeI/K₂CO₃) of **33**, with **35** barely proceeded by using three equivalents of *p*-TsOH to give **38** (66%) with *de-tert*-butoxycarbonylation. Finally, oxidative introduction of the hydroxyl group to **37** and **38** were performed by the described method for the preparation of **30** to give the target compounds [**9** (12%), **10** (42%)], but the yields were unsatisfactory because quinoline derivatives (**9**, **10**, **37**, and **38**) are extremely insoluble in organic solvents. Therefore, the another approach was examined. First, the lactones (**33**, **34**) were converted to **39** (99%) and **40** (94%) by treatment with *p*-TsOH, which were oxidized with O₂ followed by Friedländer condensation of the resulting alcohols [**41** (34%), **42** (58%)] with **35** to give **9** (95%) and **10** (70%), respectively (Scheme 5). Though the yields were not very improved, this method was preferred to the former method for the synthesis of A-ring substituted CPT analogues by using key intermediates **41** (**42**).



Scheme 5

CPT-11 (**2**) and SN-38 (**3**) having an ethyl group and an oxygen function in the quinoline ring are efficiently more potent than CPT (**1**). Thus, the methoxyquinolines (**11**) (91%) and (**12**) (42%) were prepared by treatment of **41** and **42** with amino ketone (**43**)¹² by the same procedure as that used for the preparation of **9** and **10**, respectively. Cleavage of methyl group of **11** and **12** were performed by treatment with 47% HBr solution in sealed tube at 140 °C to afford the hydroxy derivatives (**13**) (97%) and (**14**) (85%), whose ¹H-NMR spectra exhibited phenolic OH proton signals at δ 10.10 (s) and 10.18 (s), respectively.

The cytotoxic activities of compounds (**9-14**) synthesized in this study were investigated against P388

murine leukemia cells, CCRF-CEM human lymphoblastic leukemia cells, and Lu-99 human large cell lung carcinoma cells. All tested compounds exhibited weak cytotoxic activities. In particular, **14** inhibited the CCRF-CEM proliferation with the IC_{50} of 0.08 $\mu\text{g/mL}$, which is about 50 times less than that of CPT (**1**) (IC_{50} 0.0015 $\mu\text{g/mL}$). Consequently, this study would indicate that the plane and rigid molecule is essential for the activity in the case of C-ring modified analogues of CPT.

EXPERIMENTAL

General. Melting points (mp) were determined on a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-435 spectrophotometer. $^1\text{H-NMR}$ spectra were measured in CDCl_3 , unless otherwise stated, with Varian XL-300 and Varian Gemini-200 spectrometers; signals are given in ppm. Low-resolution and high-resolution mass spectra (HRMS) were recorded on a Hitachi M-4000H instruments. All reactions with air- and moisture-sensitive compounds were carried out under a nitrogen atmosphere. For column chromatography, SiO_2 (Merck Art 9385) was used.

Diethyl 2-Hydroxyhexane-1,6-dioate (16). A solution of **15** (21.6 g, 0.11 mol) in EtOH (70 mL) was hydrogenated with 10% Pd-C (1 g) at initial pressure of 2.5 kg/cm^2 for 16 h. The catalyst was removed by filtration through a Celite pad, and the filtrate was concentrated *in vacuo* to give pure **16** (21.8 g, 100%), bp 145 $^\circ\text{C}$ (7 mmHg). $^1\text{H-NMR}$: 1.24 and 1.33 (each t, each 3H, $J = 7.0$ Hz, $\text{COOCH}_2\text{CH}_3$), 1.78 (m, 4H, 3- H_2 , 4- H_2), 2.27 (t, 2H, $J = 6.5$ Hz, 5- H_2), 2.81 (d, 1H, $J = 5.0$ Hz, OH), 4.13 (q, 2H, $J = 7.0$ Hz, $\text{COOCH}_2\text{CH}_3$), 4.18 (m, 1H, 2-H), 4.26 (q, 2H, $J = 7.0$ Hz, $\text{COOCH}_2\text{CH}_3$). IR (neat) cm^{-1} : 3450 (OH), 1730 (C=O). CIMS m/z : 219 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{10}\text{H}_{18}\text{O}_5$: C, 55.03; H, 8.31. Found: C, 54.82; H, 8.40.

Diethyl 2-Methoxymethoxyhexane-1,6-dioate (17). A solution of **16** (2.0 g, 9.2 mmol), diisopropylamine (4.8 mL, 27.6 mmol), and MOMCl (2.1 g, 27.6 mmol) in CHCl_3 (10 mL) was refluxed for 90 min. The solution was removed by evaporation, and the residue was dissolved in Et_2O (300 mL). The solution was washed with water and brine, dried over MgSO_4 , and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc in hexane) to give **17** (2.40g, 100%) as an oil, bp 115 $^\circ\text{C}$ (0.5 mmHg). $^1\text{H-NMR}$: 1.24 and 1.33 (each t, each 3H, $J = 7.0$ Hz, $\text{COOCH}_2\text{CH}_3$), 1.79 (m, 4H, 3- H_2 , 4- H_2), 2.35 (m, 2H, 5- H_2), 3.40 (s, 3H, OCH_2OCH_3), 4.10 (q, 2H, $J = 7.0$ Hz, $\text{COOCH}_2\text{CH}_3$), 4.12 (m, 1H, 2-H), 4.23 (q, 2H, $J = 7.0$ Hz, $\text{COOCH}_2\text{CH}_3$), 4.66 (d, 1H, $J = 7.5$ Hz, OCHHO), 4.71 (d, 1H, $J = 7.5$ Hz, OCHHO). IR (neat) cm^{-1} : 1735 (C=O). CIMS m/z : 263 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{12}\text{H}_{22}\text{O}_6$: C, 54.95; H, 8.45. Found: C, 55.00; H, 8.46.

Ethyl 3-Methoxymethoxy-2-oxo-1-cyclopentanecarboxylate (18). Method A: A suspension of **17** (7.42 g, 28.3 mmol) and 60% NaH (2.04 g, 50.9 mmol) in toluene (20 mL) was refluxed for 10 min, then diluted with benzene (50 mL). The mixture was quenched with 10% HCl solution, and extracted with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by column chromatography (15% EtOAc in hexane) to give **18** (5.78 g, 95%) as an oil, bp 138 $^\circ\text{C}$ (9 mmHg). The $^1\text{H-NMR}$ spectrum

clearly showed that **18** exists as a mixture of keto and enol tautomers. $^1\text{H-NMR}$: 1.30 (m, 3H, $\text{COOCH}_2\text{CH}_3$), 1.80 (m, 1H, 5-H), 2.30 (m, 3H, 4-H₂, 5-H), 3.19 (t, 1H, $J = 11$ Hz, 3-H), 3.39 (s, 3/2H, OCH₃), 3.40 (s, 3/2H, OCH₃), 4.15 (m, 1/2H, COCHCO), 4.21 (m, 2H, $\text{COOCH}_2\text{CH}_3$), 4.70 (m, 1/2H, C=COH), 4.78 (m, 2H, OCH_2O). IR (neat) cm^{-1} : 1760, 1730, 1670 (C=O), 1630 (C=C). EIMS m/z : 216 (M^+). Anal. Calcd for $\text{C}_{10}\text{H}_{16}\text{O}_5$: C, 55.54; H, 7.46. Found: C, 55.34; H, 7.56.

Method B: Without isolation of the intermediate, **15** (71.2 g, 0.33 mol) was successively converted to **18** (69.4 g, 97%) after work up as described above.

Ethyl 2-Benzylamino-3-methoxymethoxycyclopent-1-ene-1-carboxylate (19). A mixture of **18** (23.9 g, 0.11 mol), benzylamine (15.4 g, 143.9 mmol), and MS-5A (40 g) in THF (130 mL) was allowed to stand for 10 days. The MS-5A was removed by filtration, and the filtrate was concentrated *in vacuo*, the residue was purified by column chromatography (5% EtOAc in hexane) to give **19** (29.7 g, 88%) as an oil, bp 174 °C (0.5 mmHg). $^1\text{H-NMR}$: 1.28 (t, 3H, $J = 7.0$ Hz, $\text{COOCH}_2\text{CH}_3$), 2.00 (m, 2H, 4-H₂), 2.43 (m, 1H, 5-H), 2.68 (m, 1H, 5-H), 3.41 (s, 3H, OCH₃), 4.18 (q, 2H, $J = 7.0$ Hz, $\text{COOCH}_2\text{CH}_3$), 4.54 (d, 2H, $J = 6.5$ Hz, CH_2Ph), 4.65 (d, 1H, $J = 7.0$ Hz, OCHHO), 4.75 (d, 1H, $J = 7.0$ Hz, OCHHO), 4.82 (m, 1H, 3-H), 7.31 (m, 5H, Ph), 7.52 (br s, 1H, NH). IR (neat) cm^{-1} : 3330 (NH), 1670 (C=O). EIMS m/z : 305 (M^+). Anal. Calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.92; H, 7.61; N, 4.72.

Ethyl 2-[N-Benzyl-N-(2-methoxycarbonyl-1-oxoethyl)]amino-3-methoxymethoxycyclopent-1-ene-1-carboxylate (20). Methyl malonyl chloride (2.22 g, 16.2 mmol) was added to a mixture of **19** (1.52 g, 5.0 mmol) and NaOAc (1.64 g, 19.9 mmol) in benzene (16 mL), and the whole was stirred for 2 h. The reaction was quenched with 10% HCl solution under ice cooling, and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by column chromatography (15% EtOAc in hexane) to give **20** (1.56 g, 77%) as an oil. The $^1\text{H-NMR}$ spectrum clearly showed that **20** exists as a mixture of *cis* and *trans*¹³ (ca. 5:1) of rotational isomers. $^1\text{H-NMR}$: 1.20 (m, 3H, $\text{COOCH}_2\text{CH}_3$), 1.82 (m, 2H, 4-H₂), 2.40 (m, 2H, 5-H₂), 3.33 (s, 5/2H, OCH₃), 3.46 (s, 1/6H, OCH₃), 3.58 (m, 2H, COCH_2CO), 3.74 (s, 5/2H, COOCH_3), 3.81 (s, 1/6H, COOCH_3), 4.00 (m, 2H, COOCH_3), 4.60 (m, 5H, CH_2Ph , OCH_2O , 7-H), 7.24 (m, 5H, Ph). IR (neat) cm^{-1} : 1740, 1710, 1660 (C=O). EIMS m/z : 405 (M^+). HRMS m/z : 405.1785 (calcd for $\text{C}_{21}\text{H}_{27}\text{NO}_7$: 405.1786).

Methyl 1-Benzyl-4-hydroxy-7-methoxymethoxy-2-oxo-2,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (21). A solution of **20** (4.33 g, 10.7 mmol) in MeOH (40 mL) was added to a solution of NaOMe [prepared from Na (370 mg, 16.0 mmol) and MeOH (20 mL)] under ice cooling, and the whole was stirred for 40 min. The reaction was quenched with water, and MeOH was removed by evaporation under reduced pressure. The residue was extracted with EtOAc, and the extract was washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by column chromatography (10% EtOAc in benzene) to give **21** (3.1 g, 81%), which was recrystallized from EtOH to give crystals, mp 118-121 °C. $^1\text{H-NMR}$: 2.20 (m, 2H, 6-H₂), 2.72 (m, 1H, 5-H), 2.91 (m, 1H, 5-H), 3.40 (s, 3H, OCH₃), 3.98 (s, 3H, COOCH_3), 4.65 (d, 1H, $J = 7.0$ Hz, OCHHO), 4.75 (d, 1H, $J =$

7.0 Hz, OCHHO), 4.92 (d, 1H, $J = 15$ Hz, CHHPh), 4.95 (m, 1H, 7-H), 5.71 (d, 1H, $J = 15$ Hz, CHHPh), 7.27 (m, 5H, Ph). IR (KBr) cm^{-1} : 3400 (OH), 1670 (C=O). EIMS m/z : 359 (M^+). Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.42; H, 5.94; N, 3.95.

Methyl 1-Benzyl-4-methoxy-7-methoxymethoxy-2-oxo-2,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (22) Method A: A suspension of **21** (591 mg, 1.58 mmol), K_2CO_3 (481 mg, 3.48 mmol), and dimethyl sulfate (399 mg, 3.16 mmol) in acetone (7 mL) was refluxed for 2 h. After evaporation of the solvent, 10% NH_3 solution (20 mL) was added to the residue, and the whole was vigorously stirred for 20 min. The mixture was neutralized with 10% HCl solution, and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by column chromatography (25% EtOAc in hexane) to give **22** (474 mg, 80%), which was recrystallized from EtOH to give crystals, mp 110–112 °C. 1H -NMR: 2.15 (m, 2H, 6- H_2), 2.67 (m, 1H, 5-H), 2.90 (m, 1H, 5-H), 3.42 (s, 3H, CH_2OCH_3), 3.92 (s, 3H, OCH_3), 3.96 (s, 3H, $COOCH_3$), 4.62 (d, 1H, $J = 7.0$ Hz, OCHHO), 4.72 (d, 1H, $J = 7.0$ Hz, OCHHO), 4.91 (d, 1H, $J = 15$ Hz, CHHPh), 4.93 (m, 1H, 7-H), 5.72 (d, 1H, $J = 15$ Hz, CHHPh), 7.28 (m, 5H, Ph). IR (KBr) cm^{-1} : 1730, 1650 (C=O). EIMS m/z : 373 (M^+). Anal. Calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.38; H, 6.23; N, 3.95.

Method B: Without isolation of the intermediate, **19** (10.0 g, 33.8 mmol) was successively converted to **22** (9.5 g, 69%) after work up as described above.

Di-tert-butyl 1-Benzyl-3-methoxycarbonyl-7-methoxymethoxy-2-oxo-2,5,6,7-tetrahydro-1H-cyclopenta[b]pyridin-4-ylmalonate (23). Di-tert-butyl malonate (12.15 mL, 54.3 mmol) was added to a suspension of 60% NaH (2.17 g, 54.3 mmol) in dioxane (60 mL) with stirring at rt. Stirring was continued for 1 h, then a solution of **22** (11.57 g, 31.0 mmol) in dioxane (80 mL) was added, and the mixture was refluxed for 45 min. The reaction was quenched with water, and the solvent was removed by evaporation under reduced pressure. The residue was extracted with CH_2Cl_2 , and the extract was washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was recrystallized from isopropanol to give **23** (13.1 g, 76%), mp 139–141 °C. 1H -NMR: 1.49 [s, 18H, $2 \times C(CH_3)_3$], 2.15 (m, 2H, 6- H_2), 2.76 (m, 1H, 5-H), 2.92 (m, 1H, 5-H), 3.41 (s, 3H, OCH_3), 3.91 (s, 3H, $COOCH_3$), 4.58 [s, 1H, $CH(COOCtBu)_2$], 4.64 (d, 1H, $J = 7.0$ Hz, OCHHO), 4.74 (d, 1H, $J = 7.0$ Hz, OCHHO), 4.96 (m, 1H, 7-H), 5.01 (d, 1H, $J = 15$ Hz, CHHPh), 5.78 (d, 1H, $J = 15$ Hz, CHHPh), 7.29 (m, 5H, Ph). IR (KBr) cm^{-1} : 1740, 1730, 1725, 1650 (C=O). EIMS m/z : 557 (M^+). Anal. Calcd for $C_{30}H_{39}NO_9$: C, 64.61; H, 7.05; N, 2.51. Found: C, 64.53; H, 7.15; N, 2.58.

6-Benzyl-7-hydroxy-1,2,4,5,6,7,8,9-octahydrocyclopenta[b]pyrano[3,4-d]pyridine-2,5-dione (24). Method A: A 1 M solution of DIBALH in toluene (5.39 mL, 5.39 mmol) was added to a solution of **23** (1.0 g, 1.80 mmol) in DME (15 mL) at -78 °C, and the whole was stirred for 20 min. The reaction was quenched with water, and the solvent was removed *in vacuo*. The residue was diluted with $CHCl_3$ (100 mL), and dried over $MgSO_4$, then filtered through a Celite pad. The filtrate was concentrated *in vacuo*, and the residue was dissolved in MeOH (4 mL). $NaBH_4$ (271 mg, 71 mmol) was added to this

solution under ice-cooling, and the whole was stirred for 20 min. After evaporation of the solvent, TFA (12 mL) was added to the residue under ice-cooling, and the mixture was stirred at rt for 16 h. TFA was evaporated, neutralized with saturated NaHCO_3 solution, and extracted with CH_2Cl_2 . The extract was washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by column chromatography (25% EtOAc in hexane) to give **24** (66 mg, 12%) as an oil. $^1\text{H-NMR}$: 2.05 (m, 1H, 8-H), 2.50 (m, 2H, 8-H, 9-H), 2.70 (d, 1H, $J = 7.5$ Hz, OH), 2.86 (m, 1H, 9-H), 3.47 (s, 2H, 1- H_2), 5.07 (br s, 1H, 7-H), 5.24 (d, 1H, $J = 15$ Hz, CHHPh), 5.36 (s, 2H, 4- H_2), 5.70 (d, 1H, $J = 15$ Hz, CHHPh), 7.25 (m, 5H, Ph). IR (neat) cm^{-1} : 3350 (OH), 1745, 1660 (C=O). EIMS m/z : 311 (M^+). HRMS m/z : 311.1158 (calcd for $\text{C}_{18}\text{H}_{17}\text{NO}_4$: 311.1157).

Method B: TFA (2 mL) was added to **27** (28 mg, 0.06 mmol) under ice-cooling, and the whole was stirred for 18 h. After removal of TFA, saturated NaHCO_3 solution and CH_2Cl_2 was added to the residue. The separated organic layer was washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by column chromatography (25% EtOAc in hexane) to give **24** (4.8 mg, 25%), which was identical with **24** obtained by method A.

Di-tert-butyl 1-Benzyl-3-formyl-7-methoxymethoxy-2-oxo-2,5,6,7-tetrahydro-1H-cyclopenta[b]pyridin-4-ylmalonate (25) and Di-tert-butyl 1-Benzyl-3-hydroxymethyl-7-methoxymethoxy-2-oxo-2,5,6,7-tetrahydro-1H-cyclopenta[b]pyridin-4-ylmalonate (26).

A 1 M solution of DIBALH in toluene (2.64 mL, 2.64 mmol) was added to a solution of **23** (736 mg, 1.32 mmol) in DME (10 mL) at -78°C , and the whole was stirred for 10 min. The reaction was quenched with water, and the solvent was removed *in vacuo*. The residue was diluted with CHCl_3 (100 mL), and dried over MgSO_4 , then filtered through a Celite pad. The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography (10% EtOAc in hexane) to give **25** (278 mg, 53%) as an oil. $^1\text{H-NMR}$: 1.47 and 1.48 [each s, each 9H, $2\times\text{C}(\text{CH}_3)_3$], 2.14 (m, 2H, 6- H_2), 2.83 (m, 2H, 5- H_2), 3.39 (s, 3H, OCH_3), 4.63 (d, 1H, $J = 7.0$ Hz, OCH_2HO), 4.73 (d, 1H, $J = 7.0$ Hz, OCH_2HO), 4.98 (m, 1H, 7-H), 5.07 (d, 1H, $J = 15$ Hz, CHHPh), 5.76 (d, 1H, $J = 15$ Hz, CHHPh), 6.16 [s, 1H, $\text{CH}(\text{COOtBu})_2$], 7.27 (m, 5H, Ph), 10.48 (s, 1H, CHO). IR (neat) cm^{-1} : 1745, 1740, 1680, 1650 (C=O). EIMS m/z : 527 (M^+). HRMS m/z : 527.2520 (calcd for $\text{C}_{29}\text{H}_{37}\text{NO}_8$: 527.2517). The second eluate with the same solvent gave the starting material **23** (23 mg, 4% recovery). The third eluate with the same solvent gave **26** (19 mg, 4%) as an oil. $^1\text{H-NMR}$: 1.48 and 1.49 [each s, each 9H, $2\times\text{C}(\text{CH}_3)_3$], 2.17 (m, 2H, 6- H_2), 2.73 (m, 1H, 5-H), 2.96 (m, 1H, 5-H), 3.40 (s, 3H, OCH_3), 4.68 [m, 5H, CH_2OH , OCH_2O , $\text{CH}(\text{COOtBu})_2$], 4.98 (m, 1H, 7-H), 5.05 (d, 1H, $J = 15$ Hz, CHHPh), 5.75 (d, 1H, $J = 15$ Hz, CHHPh), 7.28 (m, 5H, Ph). IR (neat) cm^{-1} : 3410 (OH), 1740, 1730, 1640 (C=O). EIMS m/z : 529 (M^+). HRMS m/z : 529.2662 (calcd for $\text{C}_{29}\text{H}_{39}\text{NO}_8$: 529.2673).

tert-Butyl 6-Benzyl-2,5-dioxo-7-methoxymethoxy-1,2,4,5,6,7,8,9-octahydrocyclopenta[b]pyrano[3,4-d]pyridine-1-carboxylate (27). Method A: NaBH_4 (3 mg, 0.08 mmol) was added to a solution of **25** (44 mg, 0.08 mmol) in MeOH (2 mL) at 0°C , and the whole was stirred at rt for 30 min. The reaction was quenched with cold 10% HCl solution, and extracted with CH_2Cl_2 . The extract was washed with water and brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by

column chromatography (20% EtOAc in hexane) to give **27** (23 mg, 68%) as an oil. The $^1\text{H-NMR}$ spectrum clearly showed that **27** exists as a mixture of diastereomers (*ca.* 1:1). $^1\text{H-NMR}$: 1.45 [s, 9/2H, $\text{C}(\text{CH}_3)_3$], 1.46 [s, 9/2H, $\text{C}(\text{CH}_3)_3$], 2.22 (m, 2H, 8- H_2), 2.84 (m, 2H, 9- H_2), 3.40 (s, 3/2H, OCH_3), 3.42 (s, 3/2H, OCH_3), 4.46 (s, 1/2H, CHCOOtBu), 4.47 (s, 1/2H, CHCOOtBu), 4.64 (d, 1/2H, $J = 7.0$ Hz, OCHHO), 4.65 (d, 1/2H, $J = 7.0$ Hz, OCHHO), 4.74 (d, 1/2H, $J = 7.0$ Hz, OCHHO), 4.75 (d, 1/2H, $J = 7.0$ Hz, OCHHO), 5.02 (d, 1/2H, $J = 15$ Hz, CHHPh), 5.03 (m, 1H, 7-H), 5.06 (d, 1/2H, $J = 15$ Hz, CHHPh), 5.33 (d, 1/2H, $J = 15$ Hz, 4-H), 5.35 (d, 1/2H, $J = 15$ Hz, 4-H), 5.54 (d, 1/2H, $J = 15$ Hz, 4-H), 5.57 (d, 1/2H, $J = 15$ Hz, 4-H), 5.68 (d, 1/2H, $J = 15$ Hz, CHHPh), 5.81 (d, 1/2H, $J = 15$ Hz, CHHPh), 7.28 (m, 5H, Ph). IR (neat) cm^{-1} : 1750, 1730, 1660 (C=O). EIMS m/z : 455 (M^+). HRMS m/z : 455.1942 (calcd for $\text{C}_{25}\text{H}_{29}\text{NO}_7$; 455.1942).

Method B: Without isolation of the intermediate, **23** (4.76 g, 8.55 mmol) was successively converted to **27** (1.91 g, 49%) after work up as described above.

tert-Butyl 6-Benzyl-2,5-dioxo-1-ethyl-7-methoxymethoxy-1,2,4,5,6,7,8,9-octahydro-cyclopenta[*b*]pyrano[3,4-*d*]pyridine-1-carboxylate (28). A suspension of **27** (1.0 g, 2.2 mmol), EtI (0.7 mL, 8.8 mmol), and K_2CO_3 (608 mg, 4.4 mmol) in acetone (30 mL) was refluxed for 16 h. After removal of the solvent, the residue was dissolved in a mixture of CH_2Cl_2 and water. The organic layer was washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by column chromatography (30% EtOAc in hexane) to give **28** (772 mg, 73%) as an oil. The $^1\text{H-NMR}$ spectrum clearly showed that **28** exists as a mixture of diastereomers (*ca.* 1:1). $^1\text{H-NMR}$: 0.80 (t, 3/2H, $J = 7.5$ Hz, CH_2CH_3), 0.82 (t, 3/2H, $J = 7.5$ Hz, CH_2CH_3), 1.38 [s, 9/2H, $\text{C}(\text{CH}_3)_3$], 1.44 [s, 9/2H, $\text{C}(\text{CH}_3)_3$], 2.15 (m, 3H, 8- H_2 , CHHCH_3), 2.54 (m, 2H, CHHCH_3 , 9-H), 2.82 (m, 1H, 9-H), 3.42 (s, 3H, OCH_3), 4.62 (d, 1/2H, $J = 7.0$ Hz, OCHHO), 4.63 (d, 1/2H, $J = 7.0$ Hz, OCHHO), 4.72 (d, 1/2H, $J = 7.0$ Hz, OCHHO), 4.73 (d, 1/2H, $J = 7.0$ Hz, OCHHO), 4.96 (m, 1H, 7-H), 5.03 (d, 1H, $J = 15$ Hz, CHHPh), 5.30 (d, 1/2H, $J = 17$ Hz, 4-H), 5.32 (d, 1/2H, $J = 17$ Hz, 4-H), 5.47 (d, 1/2H, $J = 17$ Hz, 4-H), 5.49 (d, 1/2H, $J = 17$ Hz, 4-H), 5.77 (d, 1/2H, $J = 15$ Hz, CHHPh), 5.78 (d, 1/2H, $J = 15$ Hz, CHHPh), 7.28 (m, 5H, Ph). IR (neat) cm^{-1} : 1750, 1730, 1660 (C=O). EIMS m/z : 483 (M^+). HRMS m/z : 483.2257 (calcd for $\text{C}_{27}\text{H}_{33}\text{NO}_7$; 483.2255).

6-Benzyl-1-ethyl-7-hydroxy-1,2,4,5,6,7,8,9-octahydrocyclopenta[*b*]pyrano[3,4-*d*]pyridine-2,5-dione (29). Compound (**28**) (228 mg, 0.47 mmol) was dissolved in 2.3 *N* HCl in EtOAc (20 mL) and the solution was stirred for 18 h. After removal of the solvent, the residue was neutralized with saturated NaHCO_3 solution and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by column chromatography (25% EtOAc in hexane) to give **29** (132 mg, 83%) as an oil. The $^1\text{H-NMR}$ spectrum clearly showed that **29** exists as a mixture of diastereomers (*ca.* 1:1). $^1\text{H-NMR}$: 1.08 (t, 3H, $J = 7.5$ Hz, CH_2CH_3), 1.93 (m, 2H, CH_2CH_3), 2.43 (m, 2H, 8- H_2), 2.67 (m, 1H, 9-H), 3.00 (m, 1H, 9-H), 3.49 (q, 1H, $J = 7.0$ Hz, 1-H), 4.89 (d, 1/2H, $J = 15$ Hz, CHHPh), 4.91 (d, 1/2H, $J = 15$ Hz, CHHPh), 5.10 (m, 1H, 7-H), 5.25 (d, 1H, $J = 16$ Hz, 4-H), 5.52 (d, 1/2H, $J = 16$ Hz, 4-H), 5.55 (d, 1/2H, $J = 16$ Hz, 4-H), 5.94 (d, 1/2H, $J = 15$ Hz, CHHPh), 6.02 (d, 1/2H, $J = 15$ Hz, CHHPh), 7.30 (m, 5H, Ph). IR (neat) cm^{-1} : 3420 (OH), 1740, 1660

(C=O). EIMS m/z : 339 (M^+). HRMS m/z : 339.1447 (calcd for $C_{20}H_{21}NO_4$: 339.1469).

6-Benzyl-1,7-dihydroxy-1-ethyl-1,2,4,5,6,7,8,9-octahydrocyclopenta[*b*]pyrano[3,4-*d*]-pyridine-2,5-dione (30). A stream of oxygen was bubbled into a stirred suspension of **29** (235 mg, 0.69 mmol), $Cu(OAc)_2 \cdot H_2O$ (28 mg, 0.14 mmol), and Et_3N (0.19 mL, 1.38 mmol) in *tert*-BuOH (15 mL) at rt for 5 h. After evaporation of the solvent *in vacuo*, the residue was dissolved in CH_2Cl_2 , and the mixture was washed with 10% HCl solution, water, and brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc in hexane) to give **30** (144 mg, 59%) as an oil. The 1H -NMR spectrum clearly showed that **30** exists as a mixture of diastereomers (*ca.* 1:1). 1H -NMR: 0.99 (t, 3/2H, $J = 7.5$ Hz, CH_2CH_3), 1.01 (t, 3/2H, $J = 7.5$ Hz, CH_2CH_3), 1.85 (m, 2H, CH_2CH_3), 2.38 (m, 2H, 8-H), 3.00 (m, 1H, 9-H), 3.35 (m, 1H, 9-H), 4.92 (d, 1/2H, $J = 15$ Hz, $CHHPh$), 4.95 (d, 1/2H, $J = 15$ Hz, $CHHPh$), 5.11 (m, 1H, 7-H), 5.19 (d, 1/2H, $J = 17$ Hz, 4-H), 5.20 (d, 1/2H, $J = 17$ Hz, 4-H), 5.64 (d, 1/2H, $J = 17$ Hz, 4-H), 5.69 (d, 1/2H, $J = 17$ Hz, 4-H), 5.95 (d, 1/2H, $J = 15$ Hz, $CHHPh$), 6.06 (d, 1/2H, $J = 15$ Hz, $CHHPh$), 7.25 (m, 5H, Ph). IR (neat) cm^{-1} : 3390 (OH), 1750, 1650 (C=O). EIMS m/z : 337 ($M^+ - 18$). HRMS m/z : 337.1312 (calcd for $C_{20}H_{21}NO_5 \cdot H_2O$: 337.1313).

***tert*-Butyl 2,5-Dioxo-1-ethyl-7-methoxymethoxy-1,2,4,5,6,7,8,9-octahydrocyclopenta[*b*]pyrano[3,4-*d*]pyridine-1-carboxylate (31).** A solution of **28** (373 mg, 0.77 mmol) in MeOH (30 mL) was hydrogenated with 10% Pd-C (100 mg) at initial pressure of 4.0 kg/cm² for 16 h. The catalyst was removed by filtration through a Celite pad, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (75% EtOAc in hexane) to give **31** (191 mg, 63%) as an oil. The 1H -NMR spectrum clearly showed that **31** exists as a mixture of diastereomers (*ca.* 1:1). 1H -NMR: 0.74 (t, 3/2H, $J = 7.5$ Hz, CH_2CH_3), 0.81 (t, 3/2H, $J = 7.5$ Hz, CH_2CH_3), 1.40 [s, 9H, $C(CH_3)_3$], 2.15 (m, 2H, 8-H, $CHHCH_3$), 2.51 (m, 3H, 8-H, 9-H, $CHHCH_3$), 2.80 (m, 1H, 9-H), 3.49 (s, 3/2H, OCH_3), 3.50 (s, 3/2H, OCH_3), 4.83 (m, 2H, OCH_2O), 4.95 (br s, 1H, 7-H), 5.33 (m, 2H, 4-H). IR (neat) cm^{-1} : 1750, 1730, 1660 (C=O). EIMS m/z : 393 (M^+). HRMS m/z : 393.1787 (calcd for $C_{20}H_{27}NO_7$: 393.1785).

***tert*-Butyl 2,5-Dioxo-1-ethyl-7-hydroxy-1,2,4,5,6,7,8,9-octahydrocyclopenta[*b*]pyrano[3,4-*d*]pyridine-1-carboxylate (32).** Compound (**31**) (1.08 g, 2.75 mmol) was dissolved in 2.3 N HCl in EtOAc (40 mL), and the solution was stirred for 30 min. The mixture was treated as described for the preparation of **29** to give crude product. This was purified by column chromatography (20% EtOAc in hexane) to give **32** (874 mg, 91%) as an amorphous powder. The 1H -NMR spectrum clearly showed that **32** exists as a mixture of diastereomers (*ca.* 1:1). 1H -NMR: 0.74 (t, 3/2H, $J = 7.5$ Hz, CH_2CH_3), 0.82 (t, 3/2H, $J = 7.5$ Hz, CH_2CH_3), 1.40 [s, 9H, $C(CH_3)_3$], 2.10 (m, 2H, 8-H, $CHHCH_3$), 2.58 (m, 3H, 8-H, 9-H, $CHHCH_3$), 2.85 (m, 1H, 9-H), 5.25 (br s, 1H, 7-H), 5.35 (m, 2H, 4-H). IR (neat) cm^{-1} : 3400 (OH), 1750, 1730, 1660 (C=O). EIMS m/z : 349 (M^+). HRMS m/z : 349.1525 (calcd for $C_{18}H_{23}NO_6$: 349.1524).

***tert*-Butyl 1-Ethyl-2,5,7-trioxo-1,2,4,5,6,7,8,9-octahydrocyclopenta[*b*]pyrano[3,4-*d*]-pyridine-1-carboxylate (33).** PDC (3.10 g, 8.25 mmol) was added to a solution of **32** (1.44 g, 4.13 mmol) in DMF (4 mL), and the whole was stirred for 1 h. The mixture was agitated with EtOAc and water. The separated organic layer was washed with 10% HCl solution, water, and brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc: CHCl₃: hexane, 1: 2: 2) to give **33** (1.22 g, 86%), which was recrystallized from a mixture of EtOH and hexane to give crystals, mp 199-201 °C (decomp). ¹H-NMR: 0.83 (t, 3H, *J* = 7.5 Hz, CH₂CH₃), 1.43 [s, 9H, C(CH₃)₃], 2.24 (sextet, 1H, *J* = 7.5 Hz, CHHCH₃), 2.63 (sextet, 1H, *J* = 7.5 Hz, CHHCH₃), 2.72 (m, 2H, 8-H₂), 2.82 (m, 2H, 9-H₂), 5.37 (d, 1H, *J* = 18 Hz, 4-H), 5.50 (d, 1H, *J* = 18 Hz, 4-H). IR (KBr) cm⁻¹: 1750, 1730, 1710, 1670 (C=O). EIMS *m/z*: 347 (M⁺). Anal. Calcd for C₁₈H₂₁NO₆: C, 62.24; H, 6.10; N, 4.03. Found: C, 62.09; H, 6.03; N, 3.98.

***tert*-Butyl 1-Ethyl-6-methyl-2,5,7-trioxo-1,2,4,5,6,7,8,9-octahydrocyclopenta[*b*]pyrano-[3,4-*d*]pyridine-1-carboxylate (34).** A suspension of **33** (281 mg, 0.81 mmol), MeI (0.13 mL, 2.03 mmol), and K₂CO₃ (174 mg, 1.26 mmol) in acetone (30 mL) was refluxed for 90 min. After removal of the solvent, the residue was dissolved in a mixture of CH₂Cl₂ and water. The separated organic layer was washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc in hexane) to give **34** (250 mg, 86%), which was recrystallized from a mixture of EtOH and hexane to give crystals, mp 151-153 °C. ¹H-NMR: 0.80 (t, 3H, *J* = 7.5 Hz, CH₂CH₃), 1.43 [s, 9H, C(CH₃)₃], 2.20 (sextet, 1H, *J* = 7.5 Hz, CHHCH₃), 2.60 (sextet, 1H, *J* = 7.5 Hz, CHHCH₃), 2.72 (m, 2H, 8-H₂), 2.80 (m, 2H, 9-H₂), 3.88 (s, 3H, NCH₃), 5.33 (d, 1H, *J* = 17 Hz, 4-H), 5.49 (d, 1H, *J* = 17 Hz, 4-H). IR (KBr) cm⁻¹: 1750, 1730, 1700, 1660 (C=O). EIMS *m/z*: 361 (M⁺). Anal. Calcd for C₁₉H₂₃NO₆: C, 63.14; H, 6.42; N, 3.88. Found: C, 63.04; H, 6.31; N, 3.89.

***tert*-Butyl 1-Ethyl-1,2,4,5,6,13-hexahydropyrano[3'',4'':3',4']pyrido[5',6':4,5]cyclopenta[1,2-*b*]quinoline-1-carboxylate (36).** A solution of **33** (52 mg, 0.15 mmol) and **35** (63 mg, 0.30 mmol) in toluene (20 mL) was refluxed for 30 min with Dean-Stark water separator. *p*-TsOH (7 mg) was added to the reaction mixture, and the mixture was refluxed for an additional 90 min. After removal of the solvent, the residue was dissolved in a mixture of CH₂Cl₂ and saturated NaHCO₃ solution. The separated organic layer was washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (3% MeOH in CHCl₃) to give **36** (65 mg, 100%), which was recrystallized from a mixture of EtOH and hexane to give crystals, mp 211-213 °C (decomp). ¹H-NMR: 0.88 (t, 3H, *J* = 7.0 Hz, CH₂CH₃), 1.40 [s, 9H, C(CH₃)₃], 2.44 (q, 1H, *J* = 7.0 Hz, CHHCH₃), 2.68 (q, 1H, *J* = 7.0 Hz, CHHCH₃), 3.85 (s, 2H, 13-H₂), 5.50 (d, 1H, *J* = 18 Hz, 4-H), 5.60 (d, 1H, *J* = 18 Hz, 4-H), 7.61 (t, 1H, *J* = 8.5 Hz, 10-H), 7.77 (t, 1H, *J* = 8.5 Hz, 9-H), 7.89 (d, 1H, *J* = 8.5 Hz, 11-H), 8.13 (d, 1H, *J* = 8.5 Hz, 8-H), 8.24 (s, 1H, 12-H). IR (KBr) cm⁻¹: 1740, 1720, 1670 (C=O). EIMS *m/z*: 432 (M⁺). Anal. Calcd for C₂₅H₂₄N₂O₅: C, 69.43; H, 5.59; N, 6.48. Found: C, 69.28; H, 5.60; N, 6.51.

1-Ethyl-1,2,4,5,6,13-hexahydropyrano[3'',4'':3',4']pyrido[5',6':4,5]cyclopenta[1,2-*b*]quinoline-2,5-dione (37). A solution of **36** (65 mg, 0.15 mmol) and *p*-TsOH (27 mg, 0.15 mmol)

in toluene (50 mL) was refluxed for 5 h. After removal of the solvent, the residue was dissolved in a mixture of CH_2Cl_2 and MeOH (20: 1). The mixture was washed with saturated NaHCO_3 solution and brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was recrystallized from a mixture of CHCl_3 and MeOH to give **37** (45 mg, 91%), mp 265-268 °C (decomp). $^1\text{H-NMR}$: 1.15 (t, 3H, $J = 7.5$ Hz, CH_2CH_3), 2.08 (m, 2H, CH_2CH_3), 3.74 (t, 1H, $J = 7.5$ Hz, 1-H), 3.82 (s, 2H, 13- H_2), 5.35 (d, 1H, $J = 15$ Hz, 4-H), 5.65 (d, 1H, $J = 15$ Hz, 4-H), 7.61 (t, 1H, $J = 8.5$ Hz, 10-H), 7.78 (t, 1H, $J = 8.5$ Hz, 9-H), 7.90 (d, 1H, $J = 8.5$ Hz, 11-H), 8.14 (d, 1H, $J = 8.5$ Hz, 8-H), 8.28 (s, 1H, 12-H). IR (KBr) cm^{-1} : 1740, 1640 (C=O). EIMS m/z : 332 (M^+). Anal. Calcd for $\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_3 \cdot 1/5\text{H}_2\text{O}$: C, 71.50; H, 4.92; N, 8.34. Found: C, 71.69; H, 4.88; N, 8.34.

1-Ethyl-6-methyl-1,2,4,5,6,13-hexahydropyrano[3'',4'':3',4']pyrido[5',6':4,5]cyclopenta[1,2-*b*]quinoline-2,5-dione (38). A solution of **34** (100 mg, 0.28 mmol) and **35** (174 mg, 0.83 mmol) in toluene (50 mL) was refluxed for 1 h with Dean-Stark water separator. *p*-TsOH (148 mg, 0.83 mmol) was added to the reaction mixture, and the mixture was refluxed for an additional 48 h. After removal of the solvent, the residue was dissolved in a mixture of CH_2Cl_2 and saturated NaHCO_3 solution. The separated organic layer was washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by column chromatography (CHCl_3) to give **38** (63 mg, 66%), which was recrystallized from a mixture of CHCl_3 and MeOH to give crystals, mp 289-291 °C (decomp). $^1\text{H-NMR}$: 1.12 (t, 3H, $J = 7.5$ Hz, CH_2CH_3), 2.04 (m, 2H, CH_2CH_3), 3.72 (t, 1H, $J = 7.0$ Hz, 1-H), 3.75 (s, 2H, 13- H_2), 4.50 (s, 3H, NCH_3), 5.35 (d, 1H, $J = 16$ Hz, 4-H), 5.64 (d, 1H, $J = 16$ Hz, 4-H), 7.60 (t, 1H, $J = 7.5$ Hz, 10-H), 7.76 (t, 1H, $J = 7.5$ Hz, 9-H), 7.88 (d, 1H, $J = 7.5$ Hz, 11-H), 8.18 (d, 1H, $J = 7.5$ Hz, 8-H), 8.23 (s, 1H, 12-H). IR (KBr) cm^{-1} : 1740, 1650 (C=O). EIMS m/z : 346 (M^+). Anal. Calcd for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_3 \cdot 1/3\text{H}_2\text{O}$: C, 71.58; H, 5.34; N, 7.95. Found: C, 71.58; H, 5.17; N, 7.94.

1-Ethyl-1-hydroxy-1,2,4,5,6,13-hexahydropyrano[3'',4'':3',4']pyrido[5',6':4,5]cyclopenta[1,2-*b*]quinoline-2,5-dione (9). Method A: A stream of oxygen was bubbled into a stirred suspension of **37** (21 mg, 0.06 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (2.5 mg), and Et_3N (0.018 mL, 0.13 mmol) in DMF (70 mL) at 45 °C for 12 h. After removal of the solvent, the residue was dissolved in a mixture of CH_2Cl_2 and MeOH (20: 1). The mixture was washed with saturated NaHCO_3 solution and brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was recrystallized from a mixture of CHCl_3 and MeOH to give **9** (2.2 mg, 12%), mp 268-270 °C (decomp). $^1\text{H-NMR}$: 1.08 (t, 3H, $J = 7.5$ Hz, CH_2CH_3), 1.95 (m, 2H, CH_2CH_3), 3.90 (s, 1H, OH), 3.97 (d, 1H, $J = 22$ Hz, 13-H), 4.29 (d, 1H, $J = 22$ Hz, 13-H), 5.28 (d, 1H, $J = 17$ Hz, 4-H), 5.75 (d, 1H, $J = 17$ Hz, 4-H), 7.61 (t, 1H, $J = 8.5$ Hz, 10-H), 7.77 (t, 1H, $J = 8.5$ Hz, 9-H), 7.90 (d, 1H, $J = 8.5$ Hz, 11-H), 8.14 (d, 1H, $J = 8.5$ Hz, 8-H), 8.25 (s, 1H, 12-H). IR (KBr) cm^{-1} : 3490 (OH), 1740, 1650 (C=O). EIMS m/z : 348 (M^+). Anal. Calcd for $\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_4 \cdot 1/10\text{H}_2\text{O}$: C, 68.60; H, 4.66; N, 8.00. Found: C, 68.48; H, 4.56; N, 8.03.

Method B: A solution of **41** (16 mg, 0.08 mmol) and **35** (32 mg, 0.15 mmol) in toluene (60 mL) was refluxed for 20 min with Dean-Stark water separator. *p*-TsOH (4 mg) was added to the reaction mixture, and the mixture was refluxed for an additional 2 h. After removal of the solvent, the residue was treated as described above to give **9** (20 mg, 95%). This was identical with **9** obtained from **37**, based on

comparison of their $^1\text{H-NMR}$ spectra.

1-Ethyl-1-hydroxy-6-methyl-1,2,4,5,6,13-hexahydropyrano[3'',4'':3',4']pyrido[5',6':4,5]cyclopenta[1,2-*b*]quinoline-2,5-dione (10). Method A: A stream of oxygen was bubbled into a stirred suspension of **38** (6.4 mg, 0.02 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (2 mg), and Et_3N (0.002 mL, 0.03 mmol) in DMF (20 mL) at rt for 4 h. After evaporation of the solvent *in vacuo*, the residue was dissolved in CH_2Cl_2 , and the mixture was washed with water, and brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by column chromatography (CHCl_3) to give **10** (2.8 mg, 42%), which was recrystallized from a mixture of CHCl_3 and MeOH to give crystals, mp 269-271 °C (decomp). $^1\text{H-NMR}$: 1.06 (t, 3H, $J = 8.5$ Hz, CH_2CH_3), 2.94 (m, 2H, CH_2CH_3), 3.90 (s, 1H, OH), 3.94 (d, 1H, $J = 23$ Hz, 13-H), 4.29 (d, 1H, $J = 23$ Hz, 13-H), 4.56 (s, 3H, NCH_3), 5.28 (d, 1H, $J = 16$ Hz, 4-H), 5.76 (d, 1H, $J = 16$ Hz, 4-H), 7.60 (t, 1H, $J = 7.5$ Hz, 10-H), 7.76 (t, 1H, $J = 7.5$ Hz, 9-H), 7.88 (d, 1H, $J = 7.5$ Hz, 11-H), 8.18 (d, 1H, $J = 7.5$ Hz, 8-H), 8.23 (s, 1H, 12-H). IR (KBr) cm^{-1} : 3450 (OH), 1740, 1650 (C=O). EIMS m/z : 362 (M^+). Anal. Calcd for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_4$: C, 69.60; H, 5.00; N, 7.73. Found: C, 69.53; H, 4.99; N, 7.71.

Method B: A solution of **42** (67 mg, 0.24 mmol) was treated with **35** (153 mg, 0.73 mmol) and *p*-TsOH (42 mg, 0.24 mmol) as described for **9** (Method B) to give **10** (62 mg, 70%). This was identical with **10** obtained from **38**, based on comparison of their $^1\text{H-NMR}$ spectra.

1-Ethyl-1,2,4,5,6,7,8,9-octahydrocyclopenta[*b*]pyrano[3,4-*d*]pyridine-2,5,7-trione (39). A solution of **33** (96 mg, 0.28 mmol) and *p*-TsOH (47 mg, 0.28 mmol) in toluene (20 mL) was refluxed for 1 h. After removal of the solvent, the residue was neutralized with saturated NaHCO_3 solution and extracted with CH_2Cl_2 . The extract was washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by column chromatography (20% acetone in CHCl_3) to give **39** (68 mg, 99%), which was recrystallized from EtOH to give crystals, mp 248-250 °C (decomp). $^1\text{H-NMR}$: 1.09 (t, 3H, $J = 7.0$ Hz, CH_2CH_3), 2.00 (m, 2H, CH_2CH_3), 2.77 (m, 2H, 8- H_2), 2.93 (m, 2H, 9- H_2), 3.64 (t, 1H, $J = 7.0$ Hz, 1-H), 5.28 (d, 1H, $J = 18$ Hz, 4-H), 5.57 (d, 1H, $J = 18$ Hz, 4-H), 9.97 (br s, 1H, NH). IR (KBr) cm^{-1} : 1750, 1710, 1660 (C=O). EIMS m/z : 247 (M^+). Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{NO}_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.05; H, 5.33; N, 5.70.

1-Ethyl-6-methyl-1,2,4,5,6,7,8,9-octahydrocyclopenta[*b*]pyrano[3,4-*d*]pyridine-2,5,7-trione (40). The same procedure as described for the preparation of **39** provided a crude product from **34** (772 mg, 2.14 mmol) and *p*-TsOH (368 mg, 2.14 mmol), and this was purified by column chromatography (20% EtOAc in CHCl_3) to give **40** (525 mg, 94%), which was recrystallized from a mixture of EtOH and hexane to give crystals, mp 164-167 °C. $^1\text{H-NMR}$: 1.08 (t, 3H, $J = 7.0$ Hz, CH_2CH_3), 1.95 (m, 2H, CH_2CH_3), 2.80 (m, 4H, 8- H_2 , 9- H_2), 3.61 (t, 1H, $J = 7.0$ Hz, 1-H), 3.86 (s, 3H, NCH_3), 5.27 (d, 1H, $J = 18$ Hz, 4-H), 5.55 (d, 1H, $J = 18$ Hz, 4-H). IR (KBr) cm^{-1} : 1730, 1700, 1660 (C=O). EIMS m/z : 261 (M^+). Anal. Calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.27; H, 5.72; N, 5.40.

1-Ethyl-1-hydroxy-1,2,4,5,6,7,8,9-octahydrocyclopenta[*b*]pyrano[3,4-*d*]pyridine-2,5,7-trione (41). A stream of oxygen was bubbled into a stirred suspension of **39** (139 mg, 0.56 mmol), Cu(OAc)₂·H₂O (5 mg), and Et₃N (0.1 mL, 0.73 mmol) in DMF (10 mL) at rt for 2 h. Work up as described for the preparation of **10** (Method A) gave a crude product. This was purified by column chromatography (15% acetone in CHCl₃) to give **41** (51 mg, 34%), which was recrystallized from a mixture of CHCl₃ and MeOH to give crystals, mp 284-286 °C (decomp). ¹H-NMR: 1.02 (t, 3H, *J* = 7.5 Hz, CH₂CH₃), 1.87 (m, 2H, CH₂CH₃), 2.70 (t, 2H, *J* = 4.5 Hz, 8-H₂), 3.05 (dt, 1H, *J* = 18, 4.5 Hz, 9-H), 3.40 (dt, 1H, *J* = 18, 4.5 Hz, 9-H), 3.84 (s, 1H, OH), 5.21 (d, 1H, *J* = 18 Hz, 4-H), 5.67 (d, 1H, *J* = 18 Hz, 4-H), 9.65 (br s, 1H, NH). IR (KBr) cm⁻¹: 3470 (OH), 1740, 1700, 1660 (C=O). EIMS *m/z*: 263 (M⁺). Anal. Calcd for C₁₃H₁₃NO₅·1/4H₂O: C, 58.32; H, 5.08; N, 5.23. Found: C, 58.19; H, 4.98; N, 5.20.

1-Ethyl-1-hydroxy-6-methyl-1,2,4,5,6,7,8,9-octahydrocyclopenta[*b*]pyrano[3,4-*d*]pyridine-2,5,7-trione (42). The same procedure as described for the preparation of **41** provided a crude product from **40** (525 mg, 2.01 mmol), Cu(OAc)₂·H₂O (20 mg), and Et₃N (0.34 mL, 2.41 mmol), and this was purified by column chromatography (10% acetone in CHCl₃) to give **42** (320 mg, 58%), which was recrystallized from a mixture of EtOH and hexane to give crystals, mp 214-216 °C (decomp). ¹H-NMR: 1.02 (t, 3H, *J* = 7.5 Hz, CH₂CH₃), 1.87 (m, 2H, CH₂CH₃), 2.70 (t, 2H, *J* = 5.0 Hz, 8-H₂), 3.00 (dt, 1H, *J* = 18, 5.0 Hz, 9-H), 3.37 (dt, 1H, *J* = 18, 5.0 Hz, 9-H), 3.84 (s, 1H, OH), 3.87 (s, 3H, NCH₃), 5.20 (d, 1H, *J* = 18 Hz, 4-H), 5.67 (d, 1H, *J* = 18 Hz, 4-H). IR (KBr) cm⁻¹: 3430 (OH), 1750, 1710, 1650 (C=O). EIMS *m/z*: 277 (M⁺). Anal. Calcd for C₁₄H₁₅NO₅: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.46; H, 5.45; N, 5.06.

1,12-Diethyl-1-hydroxy-10-methoxy-1,2,4,5,6,13-hexahydropyrano[3'',4'':3',4']pyrido[5',6':4,5]cyclopenta[1,2-*b*]quinoline-2,5-dione (11). The same procedure as described for the preparation of **9** (Method B) provided a crude product from **41** (27 mg, 0.1 mmol), **43** (37 mg, 0.2 mmol), and *p*-TsOH (18 mg, 0.1 mmol), and this was recrystallized from dioxane to give **11** (38 mg, 91%), as crystals, mp 276-278 °C (decomp). ¹H-NMR (DMSO-*d*₆): 0.91 (t, 3H, *J* = 7.5 Hz, CH₂CH₃), 1.32 (t, 3H, *J* = 7.5 Hz, ArCH₂CH₃), 1.95 (m, 2H, CH₂CH₃), 3.18 (q, 2H, *J* = 7.5 Hz, ArCH₂CH₃), 3.95 (d, 1H, *J* = 21 Hz, 13-H), 3.97 (s, 3H, OCH₃), 4.10 (d, 1H, *J* = 21 Hz, 13-H), 5.36 (s, 2H, 4-H₂), 6.47 (s, 1H, OH), 7.43 (d, 1H, *J* = 9.0 Hz, 8-H), 7.46 (s, 1H, 11-H), 8.03 (d, 1H, *J* = 9.0 Hz, 9-H). IR (KBr) cm⁻¹: 3420 (OH), 1730, 1660 (C=O). EIMS *m/z*: 406 (M⁺). Anal. Calcd for C₂₃H₂₂N₂O₅·1/2H₂O: C, 66.50; H, 5.58; N, 6.74. Found: C, 66.74; H, 5.65; N, 6.49.

1,12-Diethyl-1,10-dihydroxy-1,2,4,5,6,13-hexahydropyrano[3'',4'':3',4']pyrido[5',6':4,5]cyclopenta[1,2-*b*]quinoline-2,5-dione (13). A mixture of **11** (13 mg, 0.03 mmol) in 47% HBr solution (8 mL) was heated in a sealed tube at 140 °C for 4 h. The reaction mixture was neutralized with 6 *N* NaOH solution, and the resulting precipitate was collected by filtration. Recrystallization from a mixture of DMF and water to give **13** (13 mg, 97%), mp 270-274 °C (decomp). ¹H-NMR (DMSO-*d*₆): 0.92 (t, 3H, *J* = 7.5 Hz, CH₂CH₃), 1.31 (t, 3H, *J* = 7.5 Hz, ArCH₂CH₃), 1.96 (m, 2H, CH₂CH₃), 3.08

(q, 2H, $J = 7.5$ Hz, ArCH_2CH_3), 3.93 (d, 1H, $J = 20$ Hz, 13-H), 4.10 (d, 1H, $J = 20$ Hz, 13-H), 5.36 (s, 2H, 4- H_2), 6.47 (s, 1H, OH), 7.35 (d, 1H, $J = 8.0$ Hz, 8-H), 7.38 (s, 1H, 11-H), 7.99 (d, 1H, $J = 8.0$ Hz, 9-H), 10.10 (s, 1H, ArOH). IR (KBr) cm^{-1} : 3420, 3240 (OH), 1730, 1650 (C=O). EIMS m/z : 392 (M^+). Anal. Calcd for $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_5 \cdot 3/2\text{H}_2\text{O}$: C, 63.00; H, 5.53; N, 6.68. Found: C, 62.77; H, 5.23; N, 6.87.

1,12-Diethyl-1-hydroxy-10-methoxy-6-methyl-1,2,4,5,6,13-hexahydropyrano[3'',4'':3',4']pyrido[5',6':4,5]cyclopenta[1,2-*b*]quinoline-2,5-dione (12). The same procedure as described for the preparation of **10** (Method B) provided a crude product from **42** (146 mg, 0.53 mmol), **43** (283 mg, 1.58 mmol), and *p*-TsOH (91 mg, 0.53 mmol), and this was purified by column chromatography (10% EtOAc in hexane) to give **12** (94 mg, 42%), which was recrystallized from a mixture of CHCl_3 and MeOH to give crystals, mp 272-274 °C (decomp). $^1\text{H-NMR}$: 1.06 (t, 3H, $J = 7.5$ Hz, CH_2CH_3), 1.39 (t, 3H, $J = 7.5$ Hz, ArCH_2CH_3), 1.95 (m, 2H, CH_2CH_3), 3.18 (q, 2H, $J = 7.5$ Hz, ArCH_2CH_3), 3.84 (d, 1H, $J = 22$ Hz, 13-H), 3.92 (s, 1H, OH), 4.00 (s, 3H, OCH_3), 4.19 (d, 1H, $J = 22$ Hz, 13-H), 4.51 (s, 3H, NCH_3), 5.27 (d, 1H, $J = 17$ Hz, 4-H), 5.76 (d, 1H, $J = 17$ Hz, 4-H), 7.32 (d, 1H, $J = 2.5$ Hz, 11-H), 7.40 (dd, 1H, $J = 9.0, 2.5$ Hz, 8-H), 8.08 (d, 1H, $J = 9.0$ Hz, 9-H). IR (KBr) cm^{-1} : 3420 (OH), 1750, 1640 (C=O). EIMS m/z : 420 (M^+). Anal. Calcd for $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_5 \cdot 1/4\text{H}_2\text{O}$: C, 67.83; H, 5.81; N, 6.59. Found: C, 67.94; H, 5.81; N, 6.61.

1,12-Diethyl-1,10-dihydroxy-6-methyl-1,2,4,5,6,13-hexahydropyrano[3'',4'':3',4']pyrido[5',6':4,5]cyclopenta[1,2-*b*]quinoline-2,5-dione (14). The same procedure as described for the preparation of **13** provided a crude product from **12** (36 mg, 0.085 mmol) and 47% HBr solution (6 mL), and this was purified by recrystallized from a mixture of DMF and water to give **12** (29 mg, 85%), mp >300 °C. $^1\text{H-NMR}$ ($\text{DMSO}-d_6$): 0.92 (t, 3H, $J = 7.0$ Hz, CH_2CH_3), 1.30 (t, 3H, $J = 7.0$ Hz, ArCH_2CH_3), 1.98 (m, 2H, CH_2CH_3), 3.08 (q, 2H, $J = 7.0$ Hz, ArCH_2CH_3), 3.94 (d, 1H, $J = 23$ Hz, 13-H), 4.14 (d, 1H, $J = 23$ Hz, 13-H), 4.35 (s, 3H, NCH_3), 5.41 (s, 2H, 4- H_2), 6.50 (s, 1H, OH), 7.36 (d, 1H, $J = 8.0$ Hz, 8-H), 7.39 (s, 1H, 11-H), 7.98 (d, 1H, $J = 8.0$ Hz, 9-H), 10.18 (br s, 1H, ArOH). IR (KBr) cm^{-1} : 3430, 3240 (OH), 1740, 1640 (C=O). EIMS m/z : 406 (M^+). Anal. Calcd for $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_5 \cdot \text{H}_2\text{O}$: C, 65.08; H, 5.70; N, 6.60. Found: C, 64.88; H, 5.41; N, 6.69.

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