

Antitumor Agents. III.¹⁾ A Novel Procedure for Inversion of the Configuration of a Tertiary Alcohol Related to Camptothecin

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As part of our attempts to employ the unnatural (*R*)-type compound (**8**), which was produced by optical resolution of the pyranoindolizine **6**, in the synthesis of natural (20*S*)-camptothecin, inversion of the configuration at the tertiary alcohol of the (4*R*)-pyranoindolizine **11** to give the (4*S*)-isomer **14** was achieved in 33% yield via the methanesulfonate **12**.

Keywords inversion; tertiary alcohol; (20*S*)-camptothecin; pyranoindolizine

Recently, clinical trials of 10-hydroxycamptothecin (**2**)²⁾ and a derivative of 7-ethyl-10-hydroxycamptothecin (**3**)³⁾ have commenced in China and Japan, respectively, and camptothecin (**1**)⁴⁾ itself is still one of the most potent antitumor substances available. There is an evident need for the development of practical synthetic routes to **1** and its analogues because of the scarcity of the natural source.

We have already reported a practical total synthesis of natural (20*S*)-camptothecin (**1**) by an efficient resolution of compound **6**, which was derived from **4** in two steps, as shown in Chart 2.⁵⁾ In this paper, we would like to present

detailed experimental data on this optical resolution process and on the recycling of the unnatural compound **8**, which is obtained at the optical resolution process, for the synthesis of natural camptothecin. As a part of this work we have achieved inversion of a tertiary alcohol by a novel procedure.

Many examples of inversion of the configuration of secondary alcohols are found in the literature,⁶⁾ but in the case of tertiary alcohol, no successful inversion by intermolecular nucleophilic displacement has been reported. Our first attempts at inversion of **11**, which was derived from **8** by alkaline hydrolysis, under the conditions of the Mitsunobu⁷⁾ reaction were not successful. For example, reaction of **11** with AcOH did not proceed in the presence of triphenylphosphine (PPh₃) and diethyl azodicarboxylate (DEAD). We then applied the conditions that have been used in a secondary alcohol inversion reaction by Huffman and Desai⁸⁾ and by Ikegami *et al.*⁹⁾ to our system. Mesylation of **11** with mesyl chloride and triethylamine gave a methanesulfonate **12**, which was treated with CsOAc in dimethylformamide (DMF) to afford an expected (4*S*)-acetate **13** in 33% yield in two steps. However, when

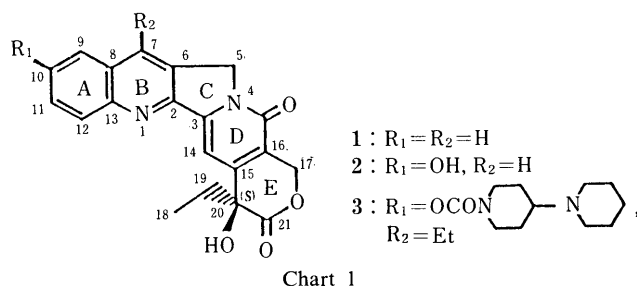


Chart 1

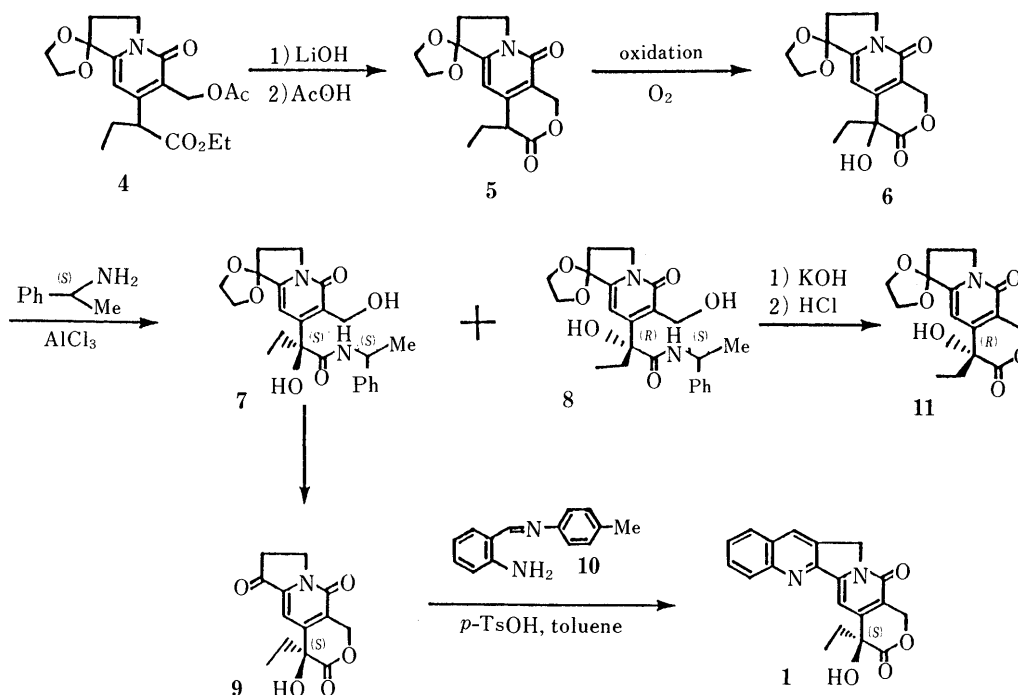


Chart 2

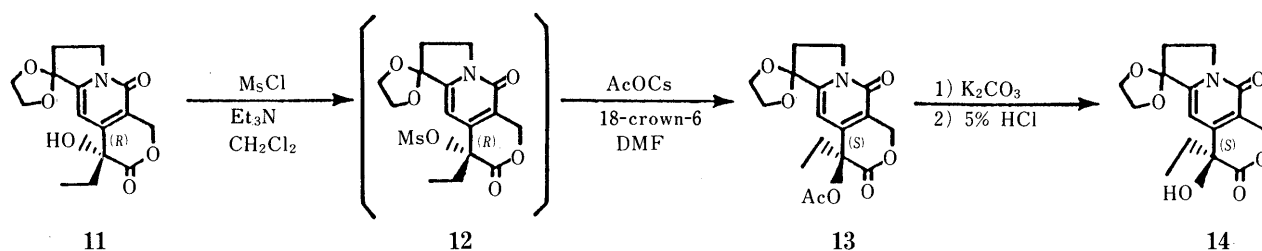


Chart 3

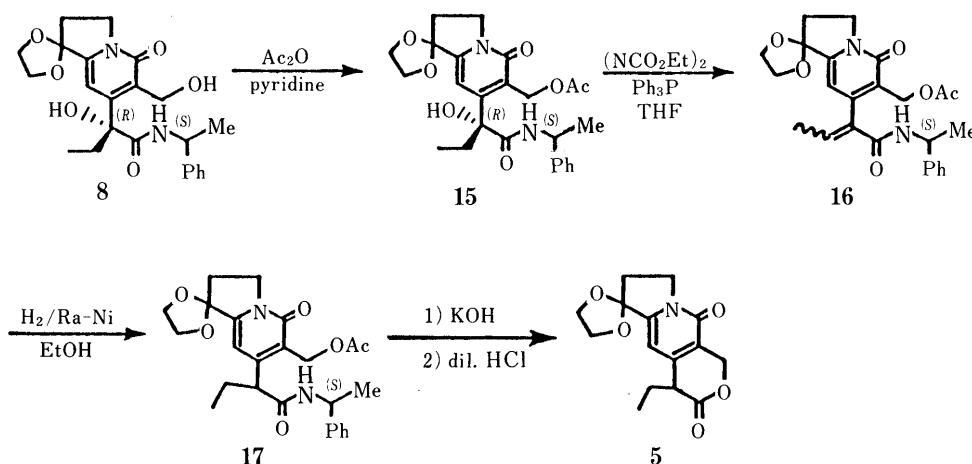


Chart 4

NaOAc or KOAc was used here instead of CsOAc, the reaction did not proceed. Hydrolysis of this acetate **13** with K_2CO_3 gave the (4*S*)-pyranoindolizine **14**, which was deketalized to afford **9** (Chart 3). The specific rotation, proton nuclear magnetic resonance (1H -NMR) spectrum and thin layer chromatographic (TLC) behavior of **9** were identical with those of the sample obtained from **7**. Thus, we have achieved inversion of the tertiary alcohol (**11**) by a novel intermolecular nucleophilic displacement procedure.

Furthermore, we were also able to recycle compound **8** by racemization. Treatment of **15**, derived from **8** on acetylation, with PPh_3 and DEAD gave a dehydrated compound (**16**) as a single isomer (*E* or *Z*) in good yield, and this was hydrogenated with hydrogen and Raney Ni to give the deoxygenated compound **17**. Hydrolysis of **17** with KOH in MeOH, followed by lactonization with AcOH resulted in the formation of the racemic tricyclic lactone **5**, which was identical with a sample obtained from **4**. Other attempts at reductive dehydration of **11** in the presence of Zn or $Me_2SiI_2^{10}$ were not successful (Chart 4).

In conclusion, we could utilize the unnatural compound **8** for the synthesis of natural camptothecin by two routes: one *via* inversion, and the other *via* racemization.

Experimental

Melting points were determined on a Yanagimoto apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 260-30 or 270-30 spectrometer. 1H -NMR spectra were recorded on a Hitachi R-40 or a JEOL JNM-FX90Q (90 MHz) instrument. Coupling constants are reported in hertz (Hz) and chemical shifts in ppm (δ units) downfield from internal tetramethylsilane. Mass spectra (MS) were recorded on a JEOL JMS-01SG-2 or a JMS-D300 mass spectrometer. Elemental analyses were made on a Heraeus instrument. Optical rotations were measured with a SEPA-200 polarimeter (Horiba) at 23 °C. All solvents and reagents were commercial products and were used without further purification. DMF

and toluene were dried over molecular sieves (4A) (Wako Chemicals). Column chromatographies were performed with Silica gel 60 F 254 (70–230 mesh) (Merck). Sodium sulfate was employed as a drying agent.

4-Ethyl-6,6-(ethylenedioxy)-7,8-dihydro-1*H*-pyrano[3,4-*f*]indolizine-3,10(4*H*)-dione (5) LiOH·H₂O (420 mg, 10 mmol) was added to a solution of tetrahydroindolizine **4**¹¹ (760 mg, 2 mmol) in a mixture of MeOH (15 ml) and water (5 ml), and the solution was stirred at room temperature for 2 h. Most of the MeOH was removed, and then the solution was treated with cold H₂O (10 ml) and AcOH (1.5 ml). After 22 h of stirring at room temperature, the organic material was extracted with CH₂Cl₂ (20 ml × 3), and the CH₂Cl₂ extracts were washed with H₂O, dried, and concentrated to give an oil, which was treated with CH₂Cl₂–hexane to give **5** as a white solid (535 mg, 92%), mp 130 °C. IR (KBr): 2972, 1732, 1608, 1466, 1278 cm⁻¹. 1H -NMR (CDCl₃) δ : 1.01 (3H, t, *J* = 7 Hz, CH₃), 1.95 (2H, m, CH₂CH₃), 2.37 (2H, t, *J* = 7 Hz, C₇-H), 3.43 (1H, t, *J* = 6 Hz, C₆-H), 4.12 (6H, m, C₈-H and OCH₂CH₂O), 5.21, 5.35 (2H, ABq, *J* = 17 Hz, C₁-H), 6.11 (1H, s, C₅-H). Anal. Calcd for C₁₅H₁₇NO₅: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.71; H, 5.85; N, 4.79.

4-Ethyl-6,6-(ethylenedioxy)-7,8-dihydro-4-hydroxy-1*H*-pyrano[3,4-*f*]indolizine-3,10(4*H*)-dione (6) Method A: Oxygen was bubbled through a solution of the pyranoindolizine **5** (300 mg, 1.03 mmol) in DMF (15 ml) containing Cu(OAc)₂ (352 mg, 1.94 mmol) and 50% aqueous dimethylamine (50 μ l) at room temperature. The reaction was continued for 1 h, then the DMF was removed *in vacuo* and the residue was extracted with CH₂Cl₂ (20 ml × 3). The CH₂Cl₂ extracts were washed with H₂O and dried. Removal of the solvent gave an orange oil, which was purified by column chromatography [benzene–AcOEt (1:1)] to give a solid. Recrystallization of this solid from CH₂Cl₂–hexane gave **6** as colorless needles (135 mg, 43%), mp 180 °C. IR (KBr): 3250, 1745, 1650 cm⁻¹. 1H -NMR (CDCl₃) δ : 0.96 (3H, t, *J* = 7 Hz, CH₃), 1.77 (2H, q, *J* = 7 Hz, CH₂CH₃), 2.38 (2H, t, *J* = 7 Hz, C₇-H), 4.12 (6H, m, C₈-H and OCH₂CH₂O), 5.12, 5.47 (2H, ABq, *J* = 16 Hz, C₁-H), 6.53 (1H, s, C₅-H). MS *m/z*: 307 (M⁺). Anal. Calcd for C₁₅H₁₇NO₆: C, 58.63; H, 5.58; N, 4.56. Found: C, 58.56; H, 5.57; N, 4.56.

Method B: Triethyl phosphite (0.41 ml) was added to a solution of **5** (200 mg, 0.69 mmol) in DMF (15 ml) containing *tert*-BuOK (115.5 mg, 1.5 eq) at –40 °C. After dry oxygen had been bubbled through the solution for 40 min at the same temperature, the reaction mixture was poured into ice and H₂O. Concentrated aqueous HCl (1 ml) was added to the solution, and the mixture was then extracted with CH₂Cl₂ (20 ml × 6).

The combined organic layer was washed with H₂O and dried. Removal of the solvent gave a brown solid, which was purified by column chromatography [CHCl₃-MeOH (98:2)] to afford **6** as a colorless solid (167 mg, 79%), identical with the product prepared by method A.

(S) and (R)- α -Ethyl- α -hydroxy-1,1-(ethylenedioxy)-6-hydroxymethyl-5-oxo-1,2,3,5-tetrahydroindolizine-7-[N-(1S)-1-phenylethyl]acetamide (7) and (8) AlCl₃ (434 mg, 3.25 mmol) was added to a solution of **6** (1 g, 3.25 mmol) in CH₂Cl₂ (15 ml) containing (S)-(-)- α -methylbenzylamine (3 ml, 23.3 mmol) in a nitrogen atmosphere. After being heated under reflux for 15 h, the reaction mixture was diluted with CH₂Cl₂ (100 ml), and the solution was washed with 10% aqueous citric acid and H₂O. Drying and concentration of the resulting solution gave a yellow foam, which was crystallized from CH₂Cl₂-hexane to afford colorless needles. These crystals (1 g) were dissolved in hot benzene (70 ml) and the benzene solution was allowed to stand at room temperature for 15 h. The colorless needles that precipitated were collected by filtration and further recrystallized from CH₂Cl₂-hexane to afford **7** as colorless needles (380 mg, 38%), mp 115–116 °C, [α]_D –74.1° (*c* = 0.22, MeOH). IR (KBr): 3400, 1650, 1585 cm⁻¹. ¹H-NMR (CDCl₃) δ : 0.88 (3H, t, *J* = 7 Hz, CH₃CH₂), 1.50 (3H, d, *J* = 7 Hz, CH₃CH), 2.10 (2H, m, CH₂CH₂), 2.32 (2H, t, *J* = 7 Hz, C₂-H), 4.10 (6H, m, C₃-H and OCH₂CH₂O), 4.72, 5.04 (2H, ABq, *J* = 12.6 Hz, CH₂OH), 5.10 (1H, m, CHCH₃), 6.67 (1H, s, C₈-H), 7.32 (5H, s, Ar-H). Anal. Calcd for C₂₃H₂₈N₂O₄ · 1/4H₂O: C, 63.80; H, 6.63; N, 6.47. Found: C, 63.51; H, 6.69; N, 6.45.

On the other hand, the mother liquor of the above recrystallization was distilled off *in vacuo* to leave a white solid, which was recrystallized from CH₂Cl₂-hexane three times to afford **8** as colorless scales (370 mg, 37%), mp 119–120 °C, [α]_D –37.2° (*c* = 0.24, MeOH). IR (KBr): 3400, 1650, 1585 cm⁻¹. ¹H-NMR (CDCl₃) δ : 0.99 (3H, t, *J* = 7 Hz, CH₃CH₂), 1.52 (3H, d, *J* = 7 Hz, CH₃CH), 2.09 (2H, m, CH₂CH₂), 2.30 (2H, t, *J* = 7 Hz, C₂-H), 4.04 (6H, m, C₃-H and OCH₂CH₂O), 4.52, 4.82 (2H, ABq, *J* = 12.5 Hz, CH₂OH), 5.07 (1H, m, CHCH₃), 6.60 (1H, s, C₈-H), 7.29 (5H, s, Ar-H). Anal. Calcd for C₂₃H₂₈N₂O₄ · 1/4H₂O: C, 63.80; H, 6.63; N, 6.47. Found: C, 64.06; H, 6.67; N, 6.44.

(S)-4-Ethyl-7,8-dihydro-4-hydroxy-1H-pyrano[3,4-*f*]indolizine-3,6,10-(4H)-trione (9) A solution of the amide **7** (400 mg, 0.93 mmol) in 80% aqueous trifluoroacetic acid (10 ml) was stirred for 3 h at room temperature in a nitrogen atmosphere. Concentration of the reaction mixture under reduced pressure gave a yellow oil, to which cold H₂O (5 ml) was added. The aqueous mixture was extracted with CH₂Cl₂ (20 ml × 3), and the combined organic layer was washed with water and dried. The solvent was removed by evaporation to leave a yellow oil, which was triturated with a small amount of cold EtOH to give colorless crystals. They were collected by filtration, washed with cold EtOH, and dried to give **9** (228 mg, 93%) (>98% ee), [α]_D +120.6° (*c* = 0.62, CHCl₃), mp 176–177 °C (dec.). MS *m/z*: 263 (M⁺). Anal. Calcd for C₁₃H₁₃NO₅: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.18; H, 5.03; N, 5.28.

(20S)-Camptothecin (1) A solution of the tricyclic ketone **9** (45 mg, 0.2 mmol) and **10**⁽¹²⁾ (43 mg, 0.2 mmol) in toluene (10 ml) was heated to reflux in a nitrogen atmosphere. The reaction was continued for 30 min, then *p*-toluenesulfonic acid monohydrate (1 mg) was added and the mixture was heated under reflux for another 3 h using a Dean-Stark trap. The precipitate obtained after cooling was filtered and recrystallized from CH₃CN-MeOH to afford 50 mg (84%) of (20S)-camptothecin (>98% ee), mp 265–266 °C (dec.) [lit.⁽⁴⁾ mp 264–267 °C (dec.)], [α]_D +42.0° (*c* = 0.51, CHCl₃-MeOH, 4:1) [lit., [α]_D +40.7°⁽¹³⁾ +42.8°⁽¹⁴⁾] (CHCl₃-MeOH, 4:1). Anal. Calcd for C₂₀H₁₆N₂O₄: C, 68.96; H, 4.63; N, 8.04. Found: C, 68.81; H, 4.85; N, 7.95. The IR and NMR spectra of this compound were identical with those of the natural product.⁽⁴⁾

(R)-4-Ethyl-6,6-(ethylenedioxy)-7,8-dihydro-4-hydroxy-1H-pyrano[3,4-*f*]indolizine-3,10(4H)-dione (11) KOH (2.6 g, 46.4 mmol) was added to a solution of **8** (349 mg, 0.81 mmol) in a mixture of EtOH (21 ml), tetrahydrofuran (THF) (14 ml) and H₂O (3 ml), and the resulting reaction mixture was stirred at 50 °C for 2 h. After the solvent was removed, the residue was acidified by adding dilute aqueous HCl and the whole was extracted with CH₂Cl₂ (20 ml × 3). The combined organic layer was washed successively with H₂O, 5% aqueous NaHCO₃, and brine. After being dried and freed of solvent, the residue was purified by column chromatography (CHCl₃) to give a solid, which was then recrystallized twice from AcOEt to give **11** as colorless crystals (128 mg, 51.2%), [α]_D –105.7° (*c* = 0.28, CHCl₃) (>97% ee), mp 172–173 °C. Anal. Calcd for C₁₅H₁₇NO₆: C, 58.63; H, 5.58; N, 4.56. Found: C, 58.46; H, 5.54; N, 4.49. The TLC behavior and ¹H-NMR spectrum of **11** were identical with those of racemic **6**.

(S)-4-Acetyloxy-4-ethyl-6,6-(ethylenedioxy)-7,8-dihydro-1H-pyrano[3,4-

***f*]indolizine-3,10(4H)-dione (13)** Et₃N (0.28 ml, 2.00 mmol) and methanesulfonyl chloride (0.21 ml, 1.55 mmol) were added to a solution of **11** (123 mg, 0.40 mmol) in CH₂Cl₂ (1 ml) at 0 °C. After being stirred for 0.6 h at the same temperature, the solution was diluted with cold CH₂Cl₂ (30 ml) and washed successively with 10% aqueous citric acid, 5% aqueous NaHCO₃ and brine. The residue was dried, freed of solvent, and purified by column chromatography [AcOEt-CH₂Cl₂ (1:2)] to give crude **12** as a colorless oil (164 mg). Next AcOH (0.41 ml, 7.16 mmol) was added to a solution of Cs₂CO₃ (392 mg, 1.2 mmol) in MeOH (20 ml) and the reaction mixture was stirred for 1 h at room temperature. The solution was concentrated *in vacuo* and the unchanged AcOH was removed by azeotropic distillation with dry toluene. The residual white powder was dried *in vacuo* for 2 h. To this white powder, a solution of crude **12** (164 mg) and 18-crown-6 (106 mg, 0.40 mmol) in DMF (9 ml) was added, and the resulting mixture was stirred at 100 °C for 4 h. The solution was poured into H₂O, and the aqueous mixture was acidified with 10% aqueous citric acid to pH 2 and extracted with CH₂Cl₂ (20 ml × 5). The combined organic layer was washed with H₂O, dried, and concentrated to give an oil, which was purified by column chromatography [AcOEt-benzene (1:2)] to afford **13** as a yellow oil (46 mg, 33% based on **11**). ¹H-NMR (CDCl₃) δ : 0.91 (3H, t, *J* = 7 Hz, CH₃CH₂), 2.04 (2H, q, *J* = 7 Hz, CH₂CH₃), 2.14 (3H, s, COCH₃), 2.36 (2H, t, *J* = 7 Hz, C₂-H), 4.13 (4H, s, OCH₂CH₂O), 5.25, 5.52 (2H, ABq, *J* = 17 Hz, C₁-H), 6.08 (1H, s, C₅-H).

(S)-4-Ethyl-6,6-(ethylenedioxy)-7,8-dihydro-4-hydroxy-1H-pyrano[3,4-*f*]indolizine-3,10(4H)-dione (14) A reaction mixture consisting of **13** (46 mg, 0.13 mmol), K₂CO₃ (30 mg, 0.22 mmol), MeOH (3 ml) and water (0.6 ml) was stirred for 1 h at room temperature. The solution was poured into 5% aqueous HCl (4 ml) and extracted with CH₂Cl₂ (6 ml × 4). The combined organic layer was washed with H₂O, dried and concentrated *in vacuo*. The residue was purified by column chromatography [CHCl₃-MeOH (100:1)] to give a solid, which was recrystallized from AcOEt to afford **14** as colorless crystals (26 mg, 64.2%), [α]_D +106.6° (*c* = 0.30, CHCl₃) (>98% ee), mp 172–173 °C. The TLC and ¹H-NMR spectrum of compound **14** obtained here were identical with those of racemic **6**.

[7-[(1R)-1-[(1S)-1-Phenylethyl]carbamoyl-1-hydroxypropyl]-1,1-(ethylenedioxy)-5-oxo-1,2,3,5-tetrahydroindolizine-6-yl]methyl Acetate (15) A reaction mixture consisting of **8** (550 mg, 1.28 mmol), Ac₂O (262 mg, 2.57 mmol) and pyridine (11 ml) was stirred at room temperature for 24 h. The solution was diluted with CH₂Cl₂ (70 ml) and washed successively with dilute aqueous HCl, 5% aqueous NaHCO₃, and brine. After being dried, the solvent was removed to give **15** as a pale yellow solid (630 mg, 100%), mp 235–235.5 °C. IR (KBr): 1728, 1648, 1625, 1604 cm⁻¹. ¹H-NMR (CDCl₃) δ : 0.86 (3H, t, *J* = 7 Hz, CH₃CH₂), 1.48 (3H, d, *J* = 7 Hz, CH₃CH), 1.7–2.2 (2H, m, CH₂CH₂), 2.05 (3H, s, COCH₃), 2.36 (2H, t, *J* = 7 Hz, C₂-H), 3.9–4.3 (6H, m, C₃-H and OCH₂CH₂O), 4.8–5.2 (2H, m, CHCH₃ and NH), 5.36, 5.65 (2H, ABq, *J* = 11 Hz, CH₂OAc), 6.62 (1H, s, C₈-H), 7.31 (5H, s, Ar-H). MS *m/z*: 470 (M⁺), 452 (M⁺ – 18). Anal. Calcd for C₂₅H₃₀N₂O₇: C, 63.82; H, 6.43; N, 5.95. Found: C, 63.75; H, 6.37; N, 5.98.

[7-1-[(1S)-1-Phenylethyl]carbamoyl-1-propenyl]-1,1-(ethylenedioxy)-5-oxo-1,2,3,5-tetrahydroindolizine-6-yl]methyl Acetate (16) A reaction mixture consisting of **15** (300 mg, 0.64 mmol), Ph₃P (503 mg, 1.92 mmol), diethyl azodicarboxylate (0.3 ml, 1.95 mmol) and THF (20 ml) was stirred for 6 h at 50 °C. After the solution had been concentrated at reduced pressure, the residue was purified by column chromatography [CHCl₃-MeOH (100:2)] to give a colorless foam, which was crystallized from AcOEt-hexane to afford **16** as colorless needles (262 mg, 91%), mp 167.5–168.5 °C. IR (KBr): 1728, 1658, 1624, 1604 cm⁻¹. ¹H-NMR (CDCl₃) δ : 1.47 (3H, d, *J* = 6.7 Hz, CH₃CHPh), 1.97 (3H, s, COCH₃), 1.98 (3H, d, *J* = 7 Hz, CH₃CH), 2.38 (2H, t, *J* = 6.7 Hz, C₂-H), 3.95–4.30 (6H, m, C₃-H and OCH₂CH₂O), 5.00–5.34 (3H, m, CH₃CH and CH₂O), 6.27 (1H, s, C₈-H), 6.73 (1H, q, *J* = 7 Hz, CH₃CH=C), 6.74 (1H, d, *J* = 6.7 Hz, NH), 7.28 (5H, s, Ar-H). MS *m/z*: 452 (M⁺), 392 (M⁺ – 60).

4-Ethyl-6,6-(ethylenedioxy)-7,8-dihydro-1H-pyrano[3,4-*f*]indolizine-3,10(4H)-dione (5) A solution of **16** (302 mg, 0.67 mmol) in a mixture of AcOH (0.05 ml) and EtOH (30 ml) was hydrogenated in the presence of Raney Ni (200 mg) at room temperature for 11 h at a pressure of 1 atm. During the reaction, the flask was irradiated with a 100 W tungsten lamp. The catalyst was removed by filtration and the solvent was concentrated *in vacuo* to give **17** as a colorless foam (290 mg). ¹H-NMR (CDCl₃) δ : 0.80, 0.87 (3H, each t, *J* = 7 Hz, CH₃CH₂), 1.29, 1.44 (3H, each d, *J* = 4 Hz, CH₃CH), 1.2–1.8 (2H, m, CH₂CH₂), 1.96, 1.99 (3H, each s, COCH₃), 2.38, 2.40 (2H, each t, *J* = 7 Hz, C₂-H), 3.7–4.3 (7H, m, C₃-H, OCH₂CH₂O and CHCO), 4.96, 5.04 (1H, each t, *J* = 7 Hz, CH₃CHPh), 5.19, 5.34 (2H, ABq, *J* = 11 Hz, CH₂O), 6.41, 6.59 (1H, each s, C₇-H), 6.84

(1H, br d, $J=7$ Hz, C₇-H), 7.31, 7.37 (5H, each s, Ar-H). Then, a mixture consisting of **17** (290 mg), KOH (330 mg, 5.89 mmol), MeOH (6 ml) and H₂O (2 ml) was stirred for 5 h at 100 °C. After being cooled, the solution was poured into H₂O and washed with AcOEt (10 ml × 2). The aqueous layer was acidified with dilute aqueous HCl and extracted with CH₂Cl₂ (20 ml × 6). The combined organic layer was dried and concentrated *in vacuo* to afford **5** as a white solid (97 mg, 50% base on **16**), mp 130 °C, $[\alpha]_D^{20}$ 0° ($c=0.31$, CHCl₃). The TLC, IR data and ¹H-NMR spectrum of **5** obtained here were identical with those of **5** prepared from **4**.

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