Photocyclization of Enamides. XXXVI.[1] Alkaloid Synthesis Using Furopyridone as a Synthon: Synthesis of Key Intermediates for the Synthesis of Eburnamine–Vincamine Alkaloids[2]

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The furopyridone 10 was shown to be a potential synthon for eburnamine–vincamine alkaloids, including cuanzine, by facile conversion to key intermediates 15, 18, and 22 for the synthesis of natural alkaloids.

Keywords alkaloid synthesis; eburnamine; eburnamonine; cuanzine; furopyridone; methylthio group; enamide; photocyclization

Eburnamine (**1b**) and vincamine (**2**) are pentacyclic indole alkaloids isolated from *Hunteria eburnea* PICHON (Apocynaceae)[3] and *Vinca minor* L. (Apocynaceae),[4] respectively. Because of their potent pharmacological activities, particularly the cerebral vasodilatory effects of vincamine (**2**), they have been the subject of intensive pharmacological and synthetic studies.[5] Cuanzine (**3a**) is a related hexacyclic indole alkaloid, first isolated from the roots of *Voacanga chalotiana* in the 1970s,[6] and structurally belongs to a subgroup of eburnanes having an oxygen atom bridging C_{15} to C_{18} in a D/F-*cis* ring junction.[7]

As an extension of our synthetic studies on alkaloid synthesis, we have explored a new synthetic method using furopyridone as a synthon[8] for the eburnamine–vincamine alkaloids, including cuanzine, which has emerged as a highly attractive synthetic target due to its unique hexacyclic structure including a tetrahydrofuran ring.

Preparation of the Furopyridones 10 and 15 Treatment of tryptamine with ethyl dithioacetate gave the thioamide **4**[9] in a quantitative yield, and it was alkylated with dimethyl sulfate to give the thioimidate **5**. It was found to be a 1:1 mixture of two geometrical isomers which exhibited proton nuclear magnetic resonance (^{1}H-NMR) signals due to the methylthio group a δ2.39 and 2.28 (each 1.5H, s). Acylation of the above mixture of isomeric

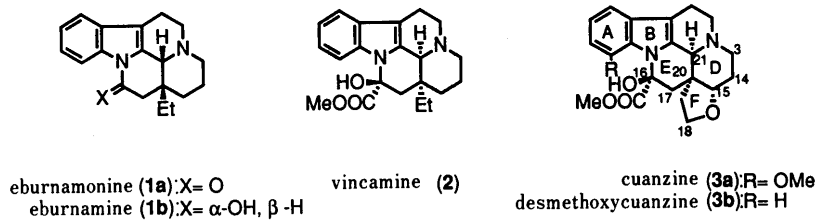

Fig. 1. Eburnamine–Vincamine Alkaloids

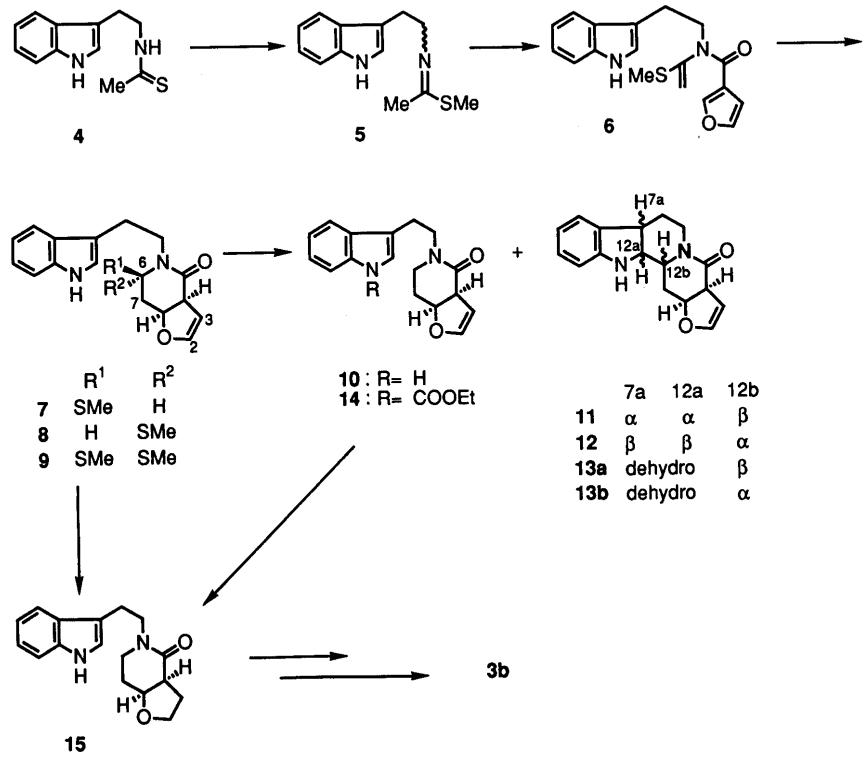

Chart 1

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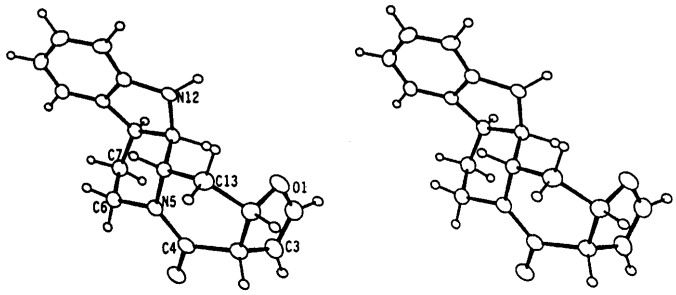

Fig. 2. X-Ray Crystal Structure of Compound **12**

thioimidates **5** with 3-furoyl chloride in the presence of triethylamine afforded the unstable enamide **6** in 50% yield, after purification by flash chromatography.

Reductive photocyclization of the enamide **6** in the presence of sodium borohydride in acetonitrile–methanol (9:1) proceeded smoothly to give four hydrogenated lactams **7**—**10** in 32, 1, 5, and 2% yields, respectively. The stereostructures of these furopyridones were deduced from the ^{1}H-NMR signals of hydrogens at the 3a-, 6-, 7-, and 7a-positions. Comparisons of J-values (J=10—11 Hz) between the 3a- and 7a-protons with those of the known furopyridone[8,10] suggested their 3a,7a-*cis* structure. From the signal patterns of the 6-proton, W-shaped long-range coupling between the 6- and 7a-protons and characteristic long-range coupling through five bonds[8] between the 2- and 7-protons, we deduced the relative configurations of the 3a-, 6-, and 7a-positions of the main product **7** to be as shown in Chart 1. Similarly, the relative configuration of the methylthio group of **8** was deduced by comparing the chemical shifts and signal patterns of the 3a-, 6-, 7-, and 7a-protons with those of **7**. Two lactams **9** and **10** were also characterized as geminal di(methylthio)- and des(methylthio)lactams, respectively, from their spectral data. In order to convert the two (methylthio)lactams **7** and **9** into the lactam **10**, we investigated reductive desulfurization reaction under three different conditions. Treatment of the (methylthio)lactam **7** with 2.5 eq of tributyltin hydride in the presence of azobisisobutyronitrile (AIBN) gave three products **10**—**12**, of which **10** is identical with the sample **10** obtained by reductive photocyclization of the enamide **6**. Although the stereostructure of the indoline **12** had been proposed as a different one in the preliminary communication,[2] it has now been revised to the structure **12** having 12a/12b-*anti* relationship based on X-ray analysis as shown in Fig. 2.

The indoline **11** was characterized by comparing the spectral data with those of **12** and also by its chemical conversion to the lactam **13a** by the conventional oxidation reaction[11] of indoline to indole structure. The structure of **13a** was unambiguously established by comparison of the spectral data with those of the known lactam **13b**.[10a] The procedure for desulfurization was improved by employing excess of tributyltin hydride and AIBN. Treatment of the (methylthio)lactam **7** with tributyltin hydride (10 eq) and AIBN (8 eq) in refluxing benzene gave the desired lactam **10** in 85% yield. As a third procedure, desulfurization reaction of the lactam **7** over Raney-Ni (W-2) in refluxing tetrahydrofuran (THF) gave the desulfurized and hydrogenated tetrahydrofuran **15** in 8% yield. However, **15** was quantitatively prepared by catalytic hydrogenation of the

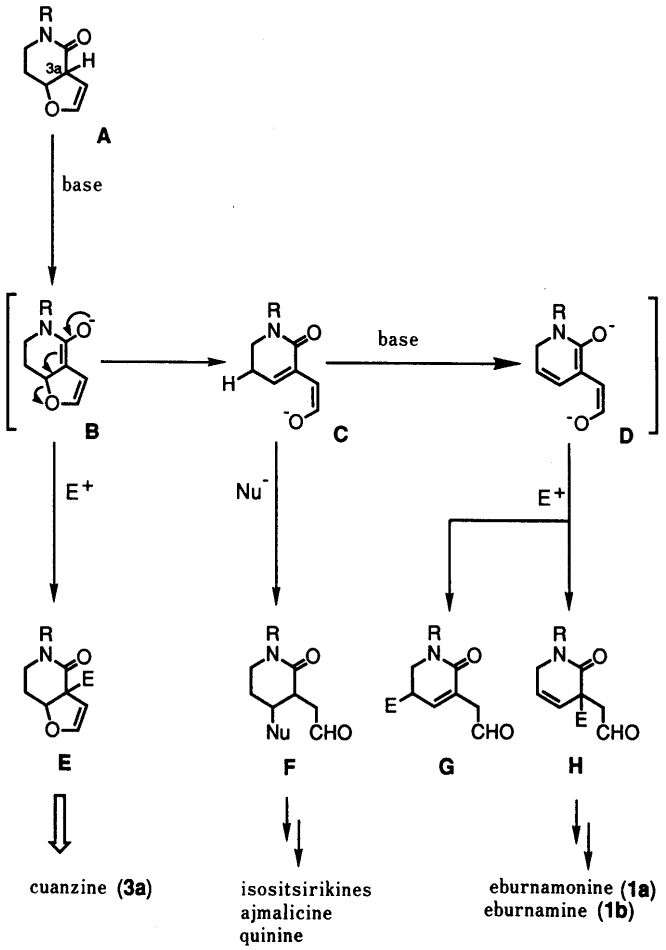

Chart 2

dihydrofuran **10** over platinum dioxide. Similarly, the other di(methylthio)lactam **9** was also desulfurized by treatment with tributyltin hydride (10 eq) in the presence of AIBN (8 eq) to give the lactam **10** in good yield.

Thus, we have prepared two furopyridones **10** and **15**. During the course of this study, Szántay *et al.*[12] have described the total synthesis of (±)-desmethoxycuanzine (**3b**) *via* the tetrahydrofuropyridone **15**. Therefore, our synthesis of **15** represents a formal total synthesis of (±)-desmethoxycuanzine (**3b**).

Potentiality of Furopyridone as a Synthon Since furopyridone has two functional groups, the enol ether and lactam carbonyl moieties, it can be effectively used as a synthon for alkaloid synthesis involving the elimination–addition reaction (**A**→**B**→**C**→**F**) as described previously.[10,13]

Considering the chemical reactivity of the functional groups in the furopyridone structure, we designed a synthetic strategy for eburnamine–vincamine alkaloids *via* a route involving two different reaction sequences as illustrated in Chart 2. Treatment of the furopyridone **A** with base results in β-elimination reaction of the enolate **B** to give the α,β-unsaturated lactam **C**, which is expected to be deprotonated when an excess of base is used. Then, if the resulting dienolate **D** is kinetically alkylated, we would obtain the 3,3-dialkylated lactam **H**, which is a potential intermediate for the synthesis of eburnamonine (**1a**) and eburnamine (**1b**). On the other hand, if alkylation of the enolate **B** proceeds prior to β-elimination, the alkylated

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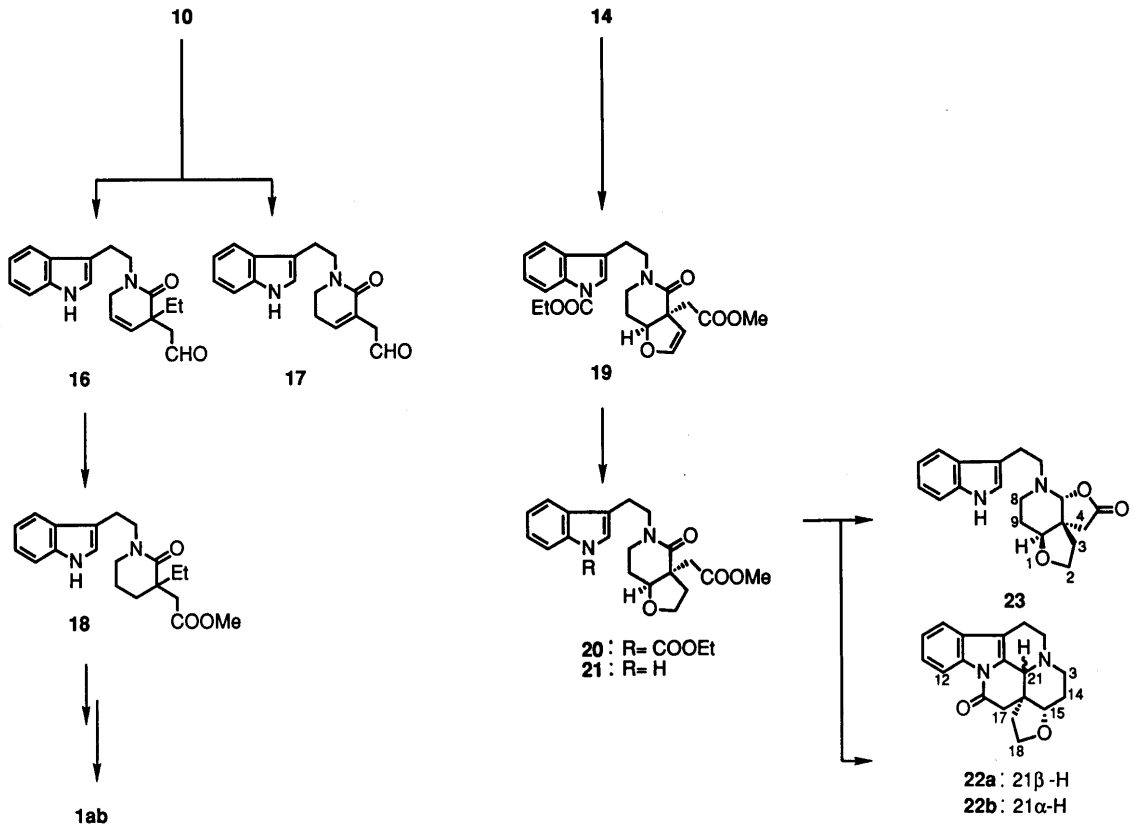

Chart 3

furopyridone **E** produced would be a potential intermediate for the synthesis of cuanzine (**3a**).

Formal Total Synthesis of (±)-Eburnamonine (1a) and (±)-Eburnamine (1b) There have been many synthetic studies[5] on eburnamine (**1b**) and vincamine (**2**), in which most chemists have employed the ester **18** or its homologue as a key intermediate, since the subsequent synthetic route to the final targets has been established. Therefore, we have investigated the formal total synthesis of these alkaloids by preparing the ester **18** from the furopyridone **10** *via* the route (**A**→**B**→**C**→**D**→**H**) illustrated in Chart 2.

Although treatment of the furopyridone **10** with lithium diisopropylamide (LDA) (2.5 eq) and then ethyl iodide (7 eq) gave exclusively the ring-opened product **17** in 58% yield, the elimination–addition reaction proceeded smoothly upon treatment of the furopyridone **10** with LDA (5 eq) and then ethyl iodide (10 eq) to give the desired ethyllactam **16** and the lactam **17** in 26 and 13% yields, respectively. These two products **16** and **17** were unambiguously characterized by their spectral data, particularly the absorptions of the formyl group at 1720—1725 cm^{-1} in their infrared (IR) spectra. Oxidation of the aldehyde **16** with silver dioxide, catalytic hydrogenation of the resulting unsaturated carboxylic acid, and finally conventional esterification of the saturated acid with methanol gave the ester **18** quantitatively from the aldehyde **16**. Spectral data of the ester **18** were identical with those reported by Schlessinger *et al.*,[14] who accomplished the total synthesis of (±)-eburnamonine (**1a**) and (±)-eburnamine (**1b**). Thus, we have succeeded in the formal total synthesis of both alkaloids.

Attempted Synthesis of (±)-Desmethoxycuanzine Next, we focused our attention to the synthesis of cuanzine (**3a**)[15,16] *via* the route (**A**→**B**→**E**) illustrated in Chart 2. Treatment of the furopyridone **10** with diethyl pyrocarbonate gave the carbamate **14** in 88% yield, and **14** was subjected to alkylation with methyl bromoacetate for the introduction of the C_2-unit at the 3a-position. In order to achieve selective alkylation at the 3a-position without opening of the furan ring, as shown in the formation of **16** and **17**, we investigated various reaction conditions by changing the temperature, amount of reagents, and also the order of addition of the reagents as follows. When LDA solution and methyl bromoacetate were concomitantly added to a THF solution of the furopyridone **14** at −78 °C, the alkylated furopyridone **19** was obtained in 34% yield in addition to 60% recovery of the starting furopyridone **14**. Catalytic hydrogenation of the furopyridone **19** over platinum dioxide under a hydrogen atmosphere followed by removal of the protective group by treatment with potassium carbonate gave the N-nortetrahydrofuran **21** in 52% yield from **19**. The stereostructure of **21** was firmly established by ^{1}H-NMR nuclear Overhauser enhancement and exchange spectroscopy (NOESY), which exhibited cross peaks between the 7a-proton and the newly introduced methylene protons. Therefore, the two lactams **19** and **20** were deduced to have the *cis*-ring juncture.

Bischler–Napieralski reaction of the lactam **21** with phosphorus oxychloride followed by reduction of the resulting iminium salt with sodium borohydride gave two compounds **22a** and **23** in 8 and 24% yields, respectively, after careful chromatographic separation of the crude products. The stereostructure of **22a** was deduced from the spectral data as follows. The mass spectrum (MS) showed the molecular ion peak at *m/z* 308, suggesting that

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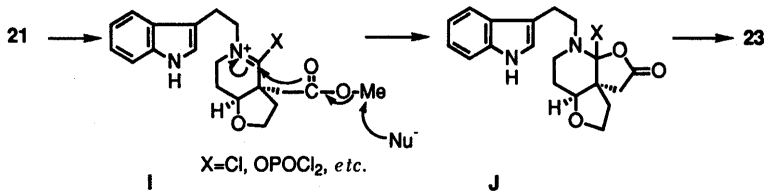

Chart 4

Bischler–Napieralski cyclization occurred with concomitant formation of the sixth ring E. The IR spectrum exhibited absorptions at 1704 cm^{-1} due to a lactam carbonyl group and also at 2745, 2800, and 2850 cm^{-1} due to Bohlmann bands. Compound **22a** exhibited ^{1}H-NMR signals at δ 8.33 (dm, J=7.5 Hz, 12-H), 3.24 (t, J=2.5 Hz, 21-H), 3.86 (dd, J=10, 7 Hz, 15-H), and 2.98 and 2.67 (ABq-like, J=16.5 Hz, 17-H_2). The Bohlmann bands in the IR spectrum and signals due to the 21- and 15-protons in the ^{1}H-NMR spectrum unambiguously suggested the presence of C/D-*trans*, D/E-*trans*, and D/F-*cis* ring junctures. Thus, **22a** is found to be epimeric in the stereochemistry at the 21-position of the basic skeleton of (±)-desmethoxycuanzine (**3b**).[12] The formation of **22a** would be reasonably explained *via* the route involving the attack of a hydride from the less hindered β-face and concomitant formation of six-membered lactam by dealcoholysis between the sterically close ester and indole ring. The other product **23** was also characterized from the spectral data. Formation of **23** would be explained as illustrated in Chart 4. The iminium salt **I**, formed by treatment of **21** with phosphorus oxychloride, would be attacked by the ester carbonyl group accompanying nucleophilic cleavage of the ester methoxyl group by chloride ion to form the intermediate **J**. Then reductive elimination of the phosphate group by sodium borohydride would give the product **23**. Aiming at the preparation of the hexacyclic compound **22b** having the desired stereochemistry for cuanzine synthesis, we have also investigated various reaction conditions involving combinations of the Bischler–Napieralski reaction and reduction of the intermediary iminium salt under different conditions (*e.g.* Zn–AcOH, LiAlH (*tert*-BuO)$_3$, and 10% Pd–C in 70% $HClO_4$–MeOH). However, all attempts have so far been unsuccessful.

Experimental

The ^{1}H-NMR spectra were measured with JEOL PMX-60 (60 MHz), Varian XL-200 (200 MHz) and VXR-500 (500 MHz) instruments for solutions in deuteriochloroform (with tetramethylsilane as an internal reference), and the IR spectra were measured with a Hitachi 215 machine for solutions in chloroform. MS were taken with a Hitachi M-80 spectrometer. All melting points were determined with a Kofler-type hot-stage apparatus. Extracts from the reaction mixture were washed with water and dried over anhydrous sodium sulfate. All reactions were carried out under an N_2 atmosphere unless otherwise stated. Thin layer chromatography (TLC) was performed on pre-coated Silica gel 60F-254 plates (0.25 mm thick, Merck) and preparative TLC (p-TLC) on pre-coated Silica gel 60F-254 plates (0.5 mm thick, Merck), and spots were detected by ultraviolet (UV) irradiation of the plates at 254 and 300 nm or exposure to iodine vapor. Medium-pressure column chromatography (MCC) was undertaken on a Yamazen 530-4-10V using a Lobar grösse B column (310-25, Lichroprep Si60, Merck). Flash column chromatography (FCC) was undertaken using Silica gel 60 (230—400 mesh, Merck). Short column chromatography (SCC) was undertaken on a short glass filter using Silica gel 60F-254 (Merck) under reduced pressure.

The Thioimidate 5 Dimethyl sulfate (3.78 g, 0.03 mol) was added dropwise to a solution of the thioamide **4**[9] (8.74 g, 0.04 mol) in THF (30 ml) with stirring at room temperature during 0.5 h. The reaction mixture was then heated with stirring at 50 °C for 3 h. The resulting solution was cooled and made alkaline by the addition of saturated aqueous sodium carbonate, and then extracted with methylene dichloride. The organic layer was washed with brine, dried and evaporated to give the thioimidate **5** (9.9 g, 99%) as a brown oil. IR: 3492 (NH), 1620 (C=N) cm^{-1}. ^{1}H-NMR (60 MHz) δ 8.10 (1H, brs, NH), 3.77—3.52 (2H, m, NCH_2CH_2), 3.31—2.80 (2H, m, NCH_2CH_2), 2.39 (1.5H, s, SMe), 2.28 (1.5H, s, SMe), 1.88 (3H, s, Me). High-resolution MS *m/z*: Calcd for $C_{13}H_{16}N_2S$ (M^+): 232.1033. Found: 232.1041.

Preparation of the Enamide 6 A solution of 3-furoyl chloride (1.15 g, 8.8 mmol) in benzene (20 ml) was added to a solution of the imidate **5** (1.86 g, 8 mmol) and triethylamine (1.2 g, 12 mmol) in benzene (160 ml) with stirring at room temperature. After being stirred at 100 °C for 4 h, the reaction mixture was cooled and filtered. The filtrate was concentrated to give the residue, which was purified by FCC (AcOEt : hexane = 1 : 1) to give the unstable enamide **6** (1.3 g, 50%). IR: 3484 (NH), 1620 (NCO) cm^{-1}. ^{1}H-NMR (60 MHz) δ: 8.36 (1H, brs, NH), 7.93 (1H, brs, 2-H), 7.30 (1H, brs, 5-H), 6.78 (1H, brs, 4-H), 5.13 and 4.97 (each 1H, brs, C=CH_2), 3.95 (2H, brt, J=6 Hz, 1′-H_2), 3.10 (2H, brt, J=6 Hz, 2′-H_2), 2.22 (3H, s, SMe).

Reductive Photocyclization of the Enamide 6 Sodium borohydride (0.49 g, 12.8 mmol) and methanol (20 ml) were added to a solution of the enamide **6** (0.52 g, 1.6 mmol) in acetonitrile (180 ml) at 0 °C. After the added hydride reagent had dissolved, the resulting solution was irradiated with a high-pressure mercury lamp (300 W) through a Pyrex filter at 0 °C for 3 h. After evaporation of the solvent at room temperature under reduced pressure, water was added to the residue to separate a viscous oil, which was extracted with methylene dichloride. The extract was washed, dried, and evaporated to give a residue, which was purified by MCC (AcOEt : hexane = 2 : 1 and then AcOEt) to give the furopyridones **7** (166 mg, 32%), **8** (5 mg, 1%), **9** (27 mg, 5%), and **10** (11 mg, 2%). **7** (pale yellow solid): IR: 3500 (NH), 1640 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 8.19 (1H, brs, NH), 7.69 (1H, brd, J=8 Hz, 4″-H), 7.40 (1H, brd, J=8 Hz, 7″-H), 7.23 (1H, brt, J=8 Hz, 5″- or 6″-H), 7.14 (1H, brt, J=8 Hz, 5″- or 6″-H), 7.05 (1H, d, J=2 Hz, 2″-H), 6.36 (1H, splitted t, J=2.5 Hz, 2-H), 5.18 (1H, t, J=2.5 Hz, 3-H), 4.86 (1H, brdt, J=11, 3 Hz, 7a-H), 4.26 (1H, ddd, J=13, 8, 5 Hz, 1′-H), 4.12 (1H, splitted dd, J=4.5, 3 Hz, 6-H), 3.77 (1H, dt, J=11, 2.5 Hz, 3a-H), 3.40 (1H, dt, J=13, 8 Hz, 1′-H), 3.26—2.96 (2H, m, 2′-H_2), 2.35 (1H, dt, J=15, 3 Hz, 7-H_{eq}), 2.06 (3H, s, SMe), 1.90 (1H, splitted dt, J=15, 4.5 Hz, 7-H_{ax}). High-resolution MS *m/z*: Calcd for $C_{18}H_{20}N_2O_2S$ (M^+): 328.1243. Found: 328.1224. *Anal.* Calcd for $C_{18}H_{20}N_2O_2S$: C, 65.85; H, 6.10; N, 8.54. Found: C, 65.56; H, 6.22; N, 8.28. **8** (pale yellow glass): IR: 3488 (NH), 1642 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 8.36 (1H, brs, NH), 7.68 (1H, brd, J=8 Hz, 4″-H), 7.38 (1H, brd, J=8 Hz, 7″-H), 7.21 (1H, brt, J=8 Hz, 5″- or 6″-H), 7.13 (1H, brt, J=8 Hz, 5″- or 6″-H), 7.02 (1H, d, J=2 Hz, 2″-H), 6.33 (1H, t, J=2.5 Hz, 2-H), 5.26 (1H, t, J=2.5 Hz, 3-H), 5.15 (1H, td, J=11, 6 Hz, 7a-H), 4.19 (1H, ddd, J=13, 7.5, 5 Hz, 1′-H), 4.08 (1H, t, J=3.5 Hz, 6-H), 3.88 (1H, dt, J=11, 2.5 Hz, 3a-H), 3.39 (1H, dt, J=13, 8 Hz, 1′-H), 3.21—3.04 (2H, m, 2′-H_2), 2.20 (1H, ddd, J=14, 6, 3.5 Hz, 7-H_{eq}), 2.00 (3H, s, SMe), 1.78 (1H, ddd, J=14, 11, 3.5 Hz, 7-H_{ax}). High-resolution MS *m/z*: Calcd for $C_{18}H_{20}N_2O_2S$ (M^+): 328.1244. Found: 328.1247. **9** (yellow glass): IR: 3490 (NH), 1635 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 8.19 (1H, brs, NH), 7.92 (1H, brd, J=7 Hz, 4″-H), 7.38 (1H, brd, J=7 Hz, 7″-H), 7.26—7.13 (2H, m, 5″-H, 6″-H), 7.09 (1H, d, J=2.5 Hz, 2″-H), 6.39 (1H, t, J=2.5 Hz, 2-H), 5.29 (1H, t, J=2.5 Hz, 3-H), 5.19 (1H, td, J=10, 6 Hz, 7a-H), 4.03 (1H, dt, J=10, 2.5 Hz, 3a-H), 4.00 (2H, t-like, J=9 Hz, 1′-H_2), 3.40—2.98 (2H, m, 2′-H_2), 2.70 (1H, dd, J=14, 6 Hz, 7-H_{eq}), 2.40 (1H, dd, J=14, 10 Hz, 7-H_{ax}), 2.26 (3H, s, SMe), 2.14 (3H, s, SMe). High-resolution MS *m/z*: Calcd for $C_{18}H_{19}N_2O_2S$ (M^+ − SMe): 327.1165. Found: 327.1158. **10** (colorless crystals, mp 102—103 °C (Et_2O–MeOH–hexane)): IR: 3488 (NH), 1632 (NCO) cm^{-1}. MS *m/z*:

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282 (M^+). ^{1}H-NMR (200 MHz) δ: 8.40 (1H, br s, NH), 7.66 (1H, br d, J=7.5 Hz, 4″-H), 7.47 (1H, br d, J=7.5 Hz, 7″-H), 7.21 (1H, td, J=7.5, 2.5 Hz, 5″- or 6″-H), 7.13 (1H, td, J=7.5, 2.5 Hz, 5″- or 6″-H), 7.02 (1H, d, J=2 Hz, 2″-H), 6.40 (1H, t, J=2.5 Hz, 2-H), 5.08 (1H, t, J=2.5 Hz, 3-H), 4.87 (1H, br dt, J=10, 4 Hz, 7a-H), 3.80—3.52 (2H, m, 1′-H_2), 3.76 (1H, dt, J=10, 2.5 Hz, 3a-H), 3.41 (1H, ddd, J=13, 11, 3.5 Hz, 6-H_{ax}), 3.02 (2H, t, J=7.5 Hz, 2′-H_2), 3.04—2.96 (1H, m, 6-H_{eq}), 2.08—1.70 (2H, m, 7-H_2). *Anal.* Calcd for $C_{17}H_{18}N_2O_2 \cdot 3/10MeOH$: C, 71.17; H, 6.63; N, 9.60. Found: C, 71.31; H, 6.42; N, 9.31.

Desulfurization of the (Methylthio)furopyridone 7 a) Using n-Bu_3SnH (2.5 eq) and AIBN (0.6 eq) A solution of AIBN (9.9 mg, 0.06 mmol) in n-Bu_3SnH (72 mg, 0.25 mmol) was added to a solution of the furopyridone **7** (33 mg, 0.1 mmol) in benzene (10 ml) with stirring. After being heated under reflux with stirring, the reaction mixture was concentrated to give the residue, which was purified by MCC (MeCN : CH_2Cl_2 = 1 : 1) to give the furopyridone **10** (12.3 mg, 40%), and the indolines **11** (5 mg, 17%) and **12** (12 mg, 38%). The furopyridone **10** was identical with the sample **10** obtained by reductive photocyclization of the enamide **6** as described above. **11** (colorless glass): IR: 3420 (NH), 1630 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 7.09 (2H, m, 8-H, 10-H), 6.80 (1H, td, J=8, 1 Hz, 9-H), 6.67 (1H, dd, J=8, 1 Hz, 11-H), 6.38 (1H, splitted t, J=2.5 Hz, 2-H), 5.11 (1H, t, J=2.5 Hz, 3-H), 4.94 (1H, dt, J=10, 3.5 Hz, 13a-H), 3.84—3.63 (4H, m, 6-H_{eq}, 3a-H, 7a-H, 12a-H), 3.55 (1H, td, J=10, 3 Hz, 12b-H), 3.44 (1H, td, J=13, 3.5 Hz, 6-H_{ax}), 2.42 (1H, br dt, J=14, 3.5 Hz, 13-H_{eq}), 2.36—2.26 (1H, m, 7-H_{eq}), 2.06—1.85 (1H, m, 7-H_{ax}), 1.74 (1H, splitted ddd, J=14, 10, 3.5 Hz, 13-H_{ax}). High-resolution MS m/z: Calcd for $C_{17}H_{18}N_2O_2$ (M^+): 282.1366. Found: 282.1358. **12** (colorless crystals, mp 223—225 °C (MeOH)): IR: 3416 (NH), 1628 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 7.10 (2H, m, 8-H, 10-H), 6.81 (1H, td, J=8, 1 Hz, 9-H), 6.68 (1H, dd, J=8, 1 Hz, 11-H), 6.37 (1H, t, J=2.5 Hz, 2-H), 5.30 (1H, t, J=2.5 Hz, 3-H), 4.88 (1H, br dt, J=10, 5 Hz, 13a-H), 4.00 (1H, ddd, J=13, 8, 5 Hz, 6-H_{eq}), 3.94 (1H, dd, J=10, 9 Hz, 12a-H), 3.71 (1H, br dt, J=10, 2.5 Hz, 3a-H), 3.60 (1H, br q, J=8 Hz, 7a-H), 3.39 (1H, br dt, J=10, 5 Hz, 12b-H), 3.25 (1H, ddd, J=13, 7, 5, 6-H_{ax}), 2.32—1.98 (4H, m, 7-H_2, 13-H_2). *Anal.* Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.28; H, 6.34; N, 9.82. X-ray crystallographic data: $C_{17}H_{18}N_2O_2$, M_r=282.33; orthorhombic; *Pabc*; a=17.296 (6); b=12.146 (3); c=13.136 (3) Å; V=2759 (1) Å^3; Z=8; D_c=1.3596 g·cm^{-3}.

The diffraction intensities were collected from a crystal of **12** with dimensions of 0.8 × 0.3 × 0.2 mm on a four-circle diffractometer (Rigaku AFC-5) using CuK_α radiation monochromated by means of a graphite plate. A total of 2345 reflections were measured within a 2θ range of 130°. These were used in the solution and refinement of the structure.

Determination of the Structure: The structure was solved by the direct method using MULTAN 84 and refined by the block-diagonal least-squares method. In the final refinement, anisotropic thermal parameters were used for non-hydrogen atoms. The final R factor was 0.0830.

b) Using n-Bu_3SnH (10 eq) and AIBN (8 eq) n-Bu_3SnH (11.7 g, 0.04 mol) and AIBN (5.26 g, 0.032 mol) were added to a solution of the (methylthio)furopyridone **7** (1.31 g, 0.004 mol) in benzene (50 ml) with stirring. After being heated under reflux with stirring for 2 h, the reaction mixture was concentrated to give the residue. SCC (hexane) to remove the reagent followed by MCC (MeCN : CH_2Cl_2 = 1 : 1) gave the desired furopyridone **10** (0.96 g, 85%), which was identical with the sample obtained by reductive photocyclization of the enamide **6** and also that obtained in a).

c) Using Raney-Ni (W-2) A mixture of the (methylthio)furopyridone **7** (100 mg, 0.3 mmol) and Raney-Ni (W-2) (0.5 ml) in anhydrous THF (10 ml) was stirred under reflux for 1 h. Then, additional Raney-Ni (0.5 ml) was added and the reaction was continued for 2 h. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to give the residue, which was purified by MCC (AcOEt and then AcOEt : MeOH = 98 : 2) to afford the hydrogenated furopyridone **15** (7 mg, 8%), mp 105.5—106.5 °C (lit.[12] brown glass) as colorless crystals from Et_2O–hexane. IR: 3488 (NH), 1626 (NCO) cm^{-1}. ^{1}H-NMR (500 MHz) δ: 8.10 (1H, br s, NH), 7.66 (1H, br d, J=8 Hz, 4″-H), 7.36 (1H, br d, J=8 Hz, 7″-H), 7.19 (1H, td, J=8, 1.5 Hz, 5″- or 6″-H), 7.12 (1H, td, J=8, 1.5 Hz, 5″- or 6″-H), 7.05 (1H, br d, J=2 Hz, 2″-H), 4.15 (1H, dt, J=7, 4 Hz, 7a-H), 3.83 (1H, td, J=8, 5.5 Hz, 2-H), 3.77 (1H, dt, J=13, 8 Hz, 1′-H), 3.63 (2H, m, 2-H, 1′-H), 3.40 (1H, ddd, J=13, 10.5, 4 Hz, 6-H_{ax}), 3.04 (2H, br t, J=8 Hz, 2′-H_2), 3.04—2.96 (2H, m, 6-H_{eq}, 3a-H), 2.42—2.35 (1H, m, 3-H), 2.12—2.05 (1H, m, 3-H), 1.86 (1H, dq, J=14, 4 Hz, 7-H_{eq}), 1.79 (1H, ddt, J=14, 10, 4 Hz, 7-H_{ax}). High-resolution MS m/z: Calcd for $C_{17}H_{20}N_2O_2$ (M^+) 284.1523. Found: 284.1528. The sample was identical with the sample prepared by catalytic hydrogenation of **10** as described below.

Desulfurization of the Di(methylthio)furopyridone 9 n-Bu_3SnH (150 mg, 0.5 mmol) and AIBN (10 mg, 0.06 mmol) were added to a solution of the di(methylthio)furopyridone **9** (37 mg, 0.1 mmol) in benzene (15 ml) with stirring. After being heated under reflux with stirring for 2 h, the reaction mixture was concentrated to give the residue. SCC (hexane) to remove the reagent followed by MCC (MeCN : CH_2Cl_2 = 1 : 1) gave the desired furopyridone **10** (12.1 mg, 43%), and the indolines **11** (11.6 mg, 41%) and **12** (5.4 mg, 19%). The furopyridone **10** was identical with the sample **10** obtained by reductive photocyclization of the enamide **6** as described above and desulfurization of the (methylthio)-furopyridone **7**. The indolines **11** and **12** were also identical with the samples obtained by desulfurization of the (methylthio)furopyridone **7** as described above.

Dehydrogenation of 11 with Benzeneseleninic Anhydride A mixture of the indoline **11** (13.5 mg, 0.048 mmol) and benzeneseleninic anhydride (10 mg, 0.028 mmol) in THF (4 ml) was treated in the presence of indole (18 mg, 0.15 mmol) at 40 °C for 1 h. The solvent was partially evaporated off, and 10% aqueous sodium carbonate was added to the residue. The extract was washed, dried, and evaporated to give a residue, which was purified by p-TLC (AcOEt) to afford the indole **13a** (9.4 mg, 70%) as a pale yellow glass. IR: 3240 (NH), 1624 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 7.56 (1H, splitted d, J=8 Hz, 8-H), 7.41 (1H, splitted d, J=8 Hz, 11-H), 7.20 (1H, td, J=8, 1.5 Hz, 9- or 10-H), 7.12 (1H, td, J=8, 1.5 Hz, 9- or 10-H), 6.56 (1H, splitted t, J=2.5 Hz, 2-H), 5.18 (1H, t, J=2.5 Hz, 3-H), 5.02 (3H, m, 6-H_{eq}, 12b-H, 13a-H), 3.82 (1H, dt, J=10, 2.5 Hz, 3a-H), 3.02—2.70 (4H, m, 7-H_2, 6-H_{ax}, 13-H_{eq}), 1.94 (1H, dddd, J=14, 12, 3, 1 Hz, 13-H_{ax}). High-resolution MS m/z: Calcd for $C_{17}H_{16}N_2O_2$ (M^+): 280.1211. Found: 280.1216.

The Hydrogenated Furopyridone 15 A solution of the furopyridone **10** (125 mg, 0.44 mmol) in methanol (100 ml) was catalytically hydrogenated in the presence of platinum dioxide (50 mg) under an H_2 atmosphere for 2 h. Usual work-up and MCC (AcOEt) of the crude product afforded the lactam **15** (105 mg, 83%).

The Carbamate 14 A solution of the furopyridone **10** (720 mg, 2.5 mmol), diethyl pyrocarbonate (2.03 g, 12.5 mmol), and 4-dimethylaminopyridine (DMAP) (10 mg) in MeCN (15 ml) was stirred at 60°C for 1 h. After the addition of water, the reaction mixture was extracted with methylene dichloride. The extract was washed, dried, and concentrated to give the residue, which was purified by MCC (AcOEt : CH_2Cl_2 = 1 : 1) to afford the carbamate **14** (0.8 g, 88%) as a colorless oil. IR: 1730 (NCOOEt), 1636 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 8.17 (1H, d, J=8 Hz, 7″-H), 7.62 (1H, br d, J=8 Hz, 4″-H), 7.26 (1H, br s, 2″-H), 7.36 (1H, br t, J=8 Hz, 5″- or 6″-H), 7.28 (1H, br t, J=8 Hz, 5″- or 6″-H), 6.40 (1H, t, J=2.5 Hz, 2-H), 5.08 (1H, t, J=2.5 Hz, 3-H), 4.89 (1H, dt, J=10, 3.5 Hz, 7a-H), 4.49 (2H, q, J=7 Hz, CH_2CH_3), 3.88—3.50 (3H, m, 3a-H, 1′-H_2), 3.44 (1H, br ddd, J=13, 11, 3.5 Hz, 6-H_{ax}), 3.02 (1H, dt, J=13, 4 Hz, 6-H_{eq}), 2.96 (2H, t, J=7.5 Hz, 2′-H_2), 1.76—2.07 (2H, m, 7-H_2), 1.44 (3H, t, J=7 Hz, CH_2CH_3). High-resolution MS m/z: Calcd for $C_{20}H_{22}N_2O_4$ (M^+): 354.1577. Found: 354.1569.

The Reaction of the Furopyridone 10 with Ethyl Iodide a) Using 2.5 eq of LDA A solution of the furopyridone **10** (141 mg, 0.5 mmol) in THF (5 ml) was added to a LDA solution, prepared from diisopropylamine (0.19 ml, 1.25 mmol) and n-butyllithium (10% solution in hexane) (0.81 ml, 1.25 mmol) at −78°C, with stirring at the same temperature under an N_2 atmosphere, and stirring was continued for 30 min. After the addition of ethyl iodide (546 mg, 3.5 mmol) to the reaction mixture, the temperature was gradually raised to 0 °C with monitoring of the reaction by TLC. Stirring was continued at 0 °C for 15 min, then the reaction was quenched by adding water and the mixture was extracted with methylene dichloride. The extract was dried and concentrated to give the residue, which was purified by MCC (AcOEt) to afford the aldehyde **17** (82 mg, 58%) as a pale yellow glass. IR: 3488 (NH), 1725 (CHO), 1620 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 9.77 (1H, t, J=2 Hz, CHO), 8.13 (1H, br s, NH), 7.68 (1H, br d, J=8 Hz, 4″-H), 7.40 (1H, br d, J=8 Hz, 7″-H), 7.24 (1H, br t, J=8 Hz, 5″- or 6″-H), 7.17 (1H, br t, J=8 Hz, 5″- or 6″-H), 7.10 (1H, br d, J=2 Hz, 2″-H), 6.42 (1H, t, J=4 Hz, 4-H), 3.77 (2H, t, J=7.5 Hz, 1′-H_2), 3.36 (2H, s, CH_2CHO), 3.32 (2H, t, J=7.5 Hz, 6-H_2), 3.08 (2H, t, J=7.5 Hz, 2′-H_2), 2.26 (2H, br q, J=6 Hz, 5-H_2). High-resolution MS m/z: Calcd for $C_{17}H_{18}N_2O_2$ (M^+): 282.1366. Found: 282.1355.

b) Using 5 eq of LDA Under similar reaction conditions to those used in a) except for the use of 5 eq of LDA, prepared from diisopropylamine

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(0.35 ml, 2.5 mmol), *n*-butyllithium (1.6 ml, 2.5 mmol) and ethyl iodide (780 mg, 5 mmol), the furopyridone **10** (141 mg, 0.5 mmol) gave the aldehyde **17** (37 mg, 13%) and the alkylated lactam **16** (40 mg, 26%) as a pale yellow glass. IR: 3484 (NH), 1722 (CHO), 1626 (NCO) cm^{-1}. ^{1}H-NMR (60 MHz) δ: 9.55 (1H, dd, J=2, 1 Hz, CHO), 8.40 (1H, br s, NH), 5.73 (1H, dt, J=10, 3 Hz, 5-H), 5.33 (1H, dt, J=10, 2 Hz, 4-H), 1.80 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$). High-resolution MS m/z: Calcd for $C_{19}H_{22}N_2O_2$ (M^+): 310.1679. Found: 310.1673.

The Methyl Ester 18 The conventional oxidation of the aldehyde **16** (28 mg) with silver oxide, catalytic hydrogenation of the dihydrofuran ring in the presence of platinum dioxide (5 mg) under an H_2 atmosphere, and finally esterification in 15% H_2SO_4 in MeOH (2 ml) gave the ester **18** (31 mg, 99%) after purification by p-TLC. The spectral data of the ester **18** were identical with those of the known ester.[14] IR: 3484 (NH), 1730 (COOMe), 1626 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 8.36 (1H, br s, NH), 7.71 (1H, br d, J=8 Hz, 4″-H), 7.39 (1H, br d, J=8 Hz, 7″-H), 7.21 (1H, td, J=8, 2 Hz, 5″- or 6″-H), 7.12 (1H, td, J=8, 2 Hz, 5″- or 6″-H), 7.07 (1H, d, J=2 Hz, 2″-H), 3.65 (3H, s, OMe), 3.65 (2H, t-like, J=8 Hz, 1′-H_2), 3.38 and 3.22 (each 1H, m, 6-H_2), 3.04 (2H, t-like, J=8 Hz, 2′-H_2), 2.96 and 2.38 (2H, ABq, J=15.5 Hz, $C\underline{H}_2$COOMe), 2.06—1.60 (6H, m, 4-H_2, 5-H_2, $C\underline{H}_2CH_3$), 1.88 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$). High-resolution MS m/z: Calcd for $C_{20}H_{26}N_2O_3$ (M^+): 342.1941. Found: 342.1928.

Alkylation of the Furopyridone 14 An LDA solution was prepared from diisopropylamine (0.19 ml, 1.27 mmol) and *n*-butyllithium (10% solution in hexane) (0.8 ml, 1.27 mmol) at −78 °C. The solution of LDA thus prepared and a solution of methyl bromoacetate (0.2 ml, 1.27 mmol) in THF (2 ml) were carefully and simultaneously added dropwise to a solution of the furopyridone **14** (224 mg, 0.63 mmol) in THF (5 ml) with stirring at −78 °C. The reaction was monitored by TLC, and at a stage before many spots appeared on TLC, the reaction was quenched by adding saturated aqueous ammonium chloride, and the mixture was extracted with methylene dichloride. The extract was dried and concentrated to give the residue, which was purified by MCC (AcOEt : CH_2Cl_2 = 1 : 1) to afford the alkylated furopyridone **19** (92 mg, 34%) as a pale yellow glass and the starting lactam **14** (35 mg, 60%). **19**: IR: 1730 (NCOOEt + COOMe), 1642 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 8.19 (1H, br d, J=8 Hz, 7″-H), 7.65 (1H, br d, J=8 Hz, 4″-H), 7.50 (1H, s, 2″-H), 7.37 (1H, td, J=8, 1 Hz, 5″- or 6″-H), 7.29 (1H, td, J=8, 1 Hz, 5″- or 6″-H), 6.42 (1H, d, J=3 Hz, 2-H), 4.84 (1H, d, J=3 Hz, 3-H), 4.77 (1H, t, J=4 Hz, 7a-H), 4.49 (2H, q, J=7.5 Hz, $C\underline{H}_2CH_3$), 3.82 (1H, dt, J=13, 7.5 Hz, 1′-H), 3.70—3.40 (2H, m, 6-H_{ax}, 1′-H), 3.68 (3H, s, OMe), 3.46 and 2.48 (2H, ABq, J=17 Hz, $C\underline{H}_2$COOMe), 3.18 (1H, dt, J=12.5, 4.5 Hz, 6-H_{eq}), 2.95 (2H, t, J=7 Hz, 2′-H_2), 2.28 (1H, ddt, J=14.5, 11, 4.5 Hz, 7-H_{ax}), 1.92 (1H, dq, J=14.5, 4 Hz, 7-H_{eq}), 1.47 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$). High-resolution MS m/z: Calcd for $C_{23}H_{26}N_2O_6$ (M^+): 426.1789. Found: 426.1823.

The Tetrahydrofuran 20 The conventional catalytic hydrogenation of the acetate **19** (246 mg) in MeOH (200 ml) in the presence of platinum dioxide (70 mg) under an H_2 atmosphere at room temperature for 1.5 h and purification of the crude product gave the tetrahydrofuran **20** (166 mg, 67%) as a pale yellow glass. IR: 1730 (NCOOEt + COOMe), 1632 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 8.14 (1H, br d, J=8 Hz, 7″-H), 7.63 (1H, br d, J=8 Hz, 4″-H), 7.48 (1H, br s, 2″-H), 7.32 (1H, br t, J=8 Hz, 5″- or 6″-H), 7.24 (1H, br t, J=8 Hz, 5″- or 6″-H), 4.44 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.05 (1H, t, J=4.5 Hz, 7a-H), 3.88 (1H, td, J=8.5, 4 Hz, 2-H), 3.72—3.61 (3H, m, 2-H, 1′-H_2), 3.62 (3H, s, OMe), 3.40 (1H, ddd, J=13, 9, 3.5 Hz, 6-H_{ax}), 3.26 and 2.56 (2H, ABq, J=17 Hz, $C\underline{H}_2$COOMe), 3.25—3.12 (1H, m, 6-H_{eq}), 2.95 (2H, t, J=7.5 Hz, 2′-H_2), 2.16—1.99 (3H, m, 7-H_{ax}, 3-H_2), 1.78 (1H, br dq, J=14, 5 Hz, 7-H_{eq}), 1.41 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$). High-resolution MS m/z: Calcd for $C_{23}H_{28}N_2O_6$ (M^+): 428.1945. Found: 428.1963.

The Lactam 21 A mixture of the tetrahydrofuran **20** (89 mg) and K_2CO_3 (304 mg) in MeOH (13 ml) was stirred at room temperature for 3 h. Water was added to the reaction mixture, which was then extracted with methylene dichloride. The extract was dried and concentrated to give the residue, which was purified by MCC (AcOEt) to afford the deprotected indole **21** (57 mg, 77%) as a pale yellow glass. IR: 3520 (NH), 1741 (COOMe), 1640 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 8.18 (1H, br s, NH), 7.67 (1H, br d, J=8 Hz, 4″-H), 7.35 (1H, br d, J=8 Hz, 7″-H), 7.18 (1H, td, J=8, 2 Hz, 5″- or 6″-H), 7.12 (1H, td, J=8, 2 Hz, 5″- or 6″-H), 7.07 (1H, br d, J=2 Hz, 2″-H), 4.07 (1H, t, J=5 Hz, 7a-H), 3.87 (1H, ddd, J=9, 8, 4 Hz, 2-H), 3.79 (1H, dt, J=14, 7.5 Hz, 1′-H), 3.69 (1H, td, J=9, 6.5 Hz, 2-H), 3.66 (3H, s, OMe), 3.65—3.62 (1H, m, 1′-H), 3.41 (1H, ddd, J=12.5, 9, 3 Hz, 6-H_{ax}), 3.30 and 2.57 (2H, ABq, J=17 Hz, $C\underline{H}_2$COOMe), 3.18 (1H, dt, J=12.5, 5 Hz, 6-H_{eq}), 3.03 (2H, t, J=7.5 Hz, 2′-H_2), 2.15—1.99 (3H, m, 7-H_{ax}, 3-H_2), 1.78 (1H, dtd, J=14, 6, 3.5 Hz, 7-H_{eq}). In NOESY, a cross peak was observed between 7a-H (δ 4.07) and $C\underline{H}_2$COOMe (δ 3.30 and 2.57). High-resolution MS m/z: Calcd for $C_{20}H_{24}N_2O_4$ (M^+): 356.1735. Found: 356.1752.

The Bischler-Napieralski Cyclization of the Tetrahydrofuropyridone 21 and Reduction of the Resulting Iminium Salt A solution of the furopyridone **21** (58 mg, 0.16 mmol) and $POCl_3$ (0.24 ml, 2.55 mmol) in anhydrous MeCN (8 ml) was stirred under reflux for 8 h until the spot due to the starting material disappeared on TLC. The solvent was evaporated off to give the residue, which was dissolved in MeOH (8 ml), and then $NaBH_4$ (120 mg, 3.18 mmol) was added. The mixture was left at room temperature overnight, then water was added and the whole was extracted with methylene dichloride. The extract was dried and concentrated to give the residue, which was purified by MCC (MeCN) to afford the hexacyclic product **22a** (4 mg, 8%) as a pale yellow glass and the lactone **23** (13 mg, 24%) as a yellow glass. **22a**: IR: 2850, 2800, 2745 (Bohlmann bands), 1704 (NCO) cm^{-1}. ^{1}H-NMR (500 MHz) δ: 8.33 (1H, dm, J=7.5 Hz, 12-H), 7.41 (1H, dm, J=7.5 Hz, 9-H), 7.31 (1H, td, J=8, 1.5 Hz, 10- or 11-H), 7.28 (1H, td, J=8, 1.5 Hz, 10- or 11-H), 4.05—4.02 (2H, m, 18-H_2), 3.86 (1H, dd, J=10, 7 Hz, 15-H), 3.24 (1H, t, J=2.5 Hz, 21-H), 3.16 (1H, dt, J=11, 5.5 Hz, 5-H_{eq}), 3.01 (1H, br ddd, J=12, 5, 2.5 Hz, 3-H_{eq}), 2.98 (1H, d, J=16.5 Hz, 17-H_{eq}), 2.89 (1H, dddd, J=15.5, 11, 5.5, 2.5 Hz, 6-H_{ax}), 2.72—2.68 (1H, dm, J=15.5 Hz, 6-H_{eq}), 2.67 (1H, dd, J=16.5, 2.5 Hz, 17-H_{ax}), 2.59 (1H, td, J=11, 4.5 Hz, 5-H_{ax}), 2.38 (1H, br ddd, J=12.5, 12, 3 Hz, 3-H_{ax}), 2.37—2.30 (1H, m, 19-H), 1.92 (1H, br ddt, J=13.5, 7, 2.5 Hz, 14-H_{eq}), 1.81 (1H, br tdd, J=13.5, 10, 5 Hz, 14-H_{ax}), 1.28 (1H, ddd, J=12.5, 7, 4 Hz, 19-H). High-resolution MS m/z: Calcd for $C_{19}H_{20}N_2O_2$ (M^+): 308.1522. Found: 308.1515. **23**: IR: 3484 (NH), 1774 (lactone) cm^{-1}. ^{1}H-NMR (500 MHz) δ: 7.99 (1H, br s, NH), 7.60 (1H, br d, J=8 Hz, 4″-H), 7.36 (1H, br d, J=8 Hz, 7″-H), 7.19 (1H, br t, J=7 Hz, 5″- or 6″-H), 7.11 (1H, br t, J=7 Hz, 5″- or 6″-H), 7.01 (1H, br s, 2″-H), 4.41 (1H, br s, 6a-H), 4.40 (1H, br t, J=7 Hz, 9a-H), 3.94—3.85 (2H, m, 2-H_2), 3.09—3.20 (1H, m, 1′-H), 2.95—2.92 (3H, m, 1′-H, 2′-H_2), 2.83 (1H, br t, J=12 Hz, 8-H_{ax}), 2.69 and 2.30 (2H, ABq, J=17 Hz, 4-H_2), 2.63 (1H, dt, J=12, 6 Hz, 8-H_{eq}), 2.19—2.09 (2H, m, 3-H, 9-H), 1.88 (1H, dt, J=12, 8 Hz, 3-H), 1.81—1.74 (1H, m, 9-H). High-resolution MS m/z: Calcd for $C_{19}H_{22}N_2O_3$ (M^+): 326.1628. Found: 326.1623.

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