Photocyclization of Enamides. XXXII.[1] Alkaloid Synthesis Using Furopyridone as a Synthon: Synthesis of Key Intermediates for the Synthesis of (±)-Quinine, (±)-Ajmalicine, and (±)-7-Demethyltecomanine[2]

Takeaki NAITO,* Okiko MIYATA, Natsuko KIDA, Keiko NAMOTO, and Ichiya NINOMIYA

Kobe Women's College of Pharmacy, Motoyamakita, Higashinada, Kobe 658, Japan. *Received March 5, 1990*

Furopyridones 4a—c were shown to be available as synthons for alkaloid synthesis by their facile conversion to the key intermediates 13a, b, and 16 for the synthesis of quinine, ajmalicine, and 7-demethyltecomanine.

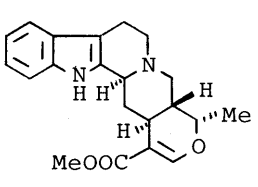
Keywords furopyridone; alkaloid synthesis; quinine; ajmalicine; tecomanine; photocyclization; enamide

Considering that loganin and secologanin are key biogenetic intermediates to monoterpenoid alkaloids,[3] we have focused our attention on an unnatural heterocycle, furopyridone, which might serve as a common synthetic intermediate for divergent syntheses of most monoterpenoid alkaloids. Although partially hydrogenated furopyridone is a bifunctional heterocycle since it contains enol-ether and lactam carbonyl groups in the structure, there has been no report of its use as a synthon.[4] We have now explored a general and divergent synthetic route to a large number of monoterpenoid alkaloids employing two types of furopyridones, **4a**—**c**, as common synthons which were prepared *via* reductive photocyclization[5] of enamides substituted with a methylthio group. The methylthio group was introduced into the enamide structure in order to facilitate photocyclization since α-unsubstituted enamides are resistant to photocyclization.[6]

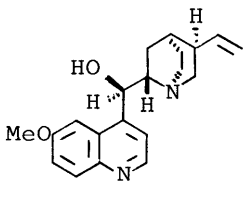
Preparation of the Methylthiofuropyridones 4a—c Treatment of the *N*-benzylacetamide and *N*-methylpropionamide with phosphorus pentasulfide gave the corresponding thioamides (**1a, b**)[7] in good yields, and **1a, b** were then alkylated with dimethyl sulfate to give the respective thioimidates **2a, b**[7] in comparable yields. They were found to be mixtures of two geometrical isomers, of which **2a** exhibited proton nuclear magnetic resonance (^{1}H-NMR) signals due to the methylthio group at δ 2.33 (1.8H) and 2.07 (1.2H) (each s). Acylation of the mixture of two geometrically isomeric thioimidates **2a** with 3-furoyl chloride in the presence of triethylamine afforded the unstable enamide **3a**,[7] which had already been prepared and its chemical reactivity investigated by Zeeh and Kiefer.[7] Similarly, acylation of the thioimidate **2b** with either 5-methyl-3-furoyl chloride[8] or 3-furoyl chloride gave the enamide **3b** or **3c**, both of which were also found to be separable 1 : 2 mixtures of two geometrical isomers, though their stereochemistries remained unclarified. Reductive photocyclization[5] of the unstable enamide **3a** in the presence of sodium borohydride in acetonitrile–methanol proceeded smoothly to give the hydrogenated lactam **4a** in 44% yield from the imidate **2a**. Similarly, reductive photocyclization of either the separated geometrical isomers **3b** and **3b'** or a mixture (**3b** and **3b'**) afforded a 4 : 5 mixture of two lactams **4b, c** in 89% combined yield. It has been suggested that photochemical isomerization of double bonds in the parent enamides **3b** and **3b'** occurs during the course of irradiation, since no photochemical isomerization between the photocyclized lactams **4b, c** has been observed under irradiation conditions used. Similarly, reductive photocyclization[5] of a mixture of two geometrically isomeric enamides **3c** gave two hydrogenated furopyridones **4d, e** in 36 and 28% yields, respectively. The structures of the five furopyridones **4a**—**e** were readily established from their spectral data. All the furopyridones **4a**—**e** showed molecular ion peaks at the expected positions, *i.e.*, two mass units larger than those of the parent enamides **3a**—**c** in their mass spectra (MS). All the products (**4a**—**e**) exhibited infrared (IR) absorption at around 1640 cm^{-1} due to a lactam carbonyl group. The stereostructures of these furopyridones **4a**—**e** were deduced from the ^{1}H-NMR signals of the hydrogens at the 3a-, 6-, 7-, and 7a-positions. Comparisons of the *J*-values (J = 10 Hz) between the 3a- and 7a-protons with those of related known furopyridones[1,9] suggested the 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[10] between the 2- and 7-protons, we deduced the relative configurations of the 3a-, 6-, 7-, and 7a-positions, including their conformations, as shown in Fig. 2. The configurations of the 7-methyl groups in **4b, c** were deduced by comparing the chemical shifts of their signals with those of **4d, e**.

Thus, we have prepared five methylthiofuropyridones (**4a**—**e**) as synthons for monoterpenoid alkaloids, as described below.

Preparation of the Synthetic Key Intermediates 13a and 13b for (±)-Quinine, (±)-Akuammigine, and (±)-Ajmalicine Ajmalicine and quinine, representative of monoterpenoid indoles and related alkaloids, have been



ajmalicine



quinine

Fig. 1

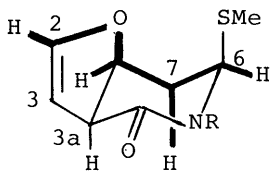


Fig. 2

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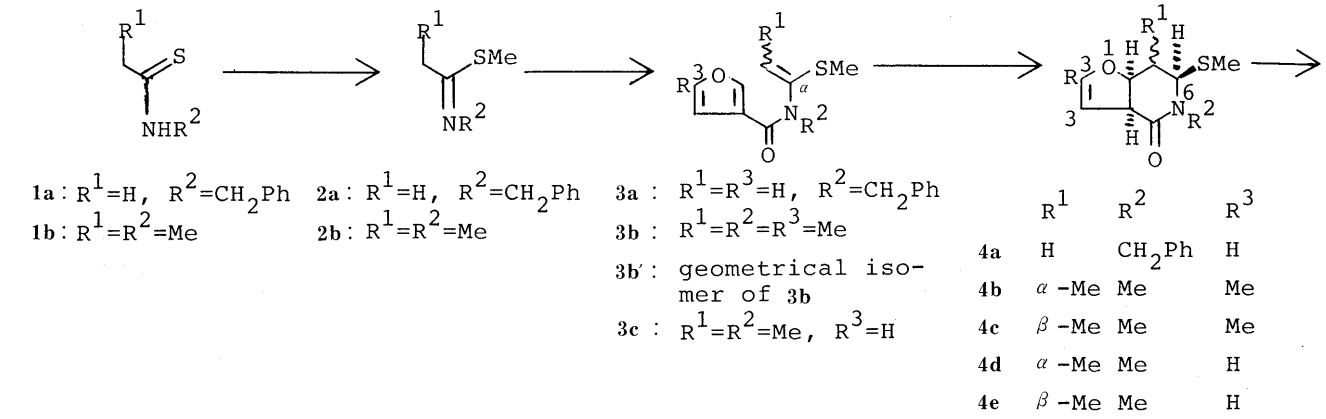
synthesized by many groups[1,11] because of their potent pharmacological activities. Many of the total syntheses have involved distinctive strategies for stereoselective synthesis of the *trans*- and *cis*-vinyl esters **13a, b**, since these simple piperidines were not readily obtainable through usual reactions. Thus, we have investigated the simple synthesis of these 3,4-disubstituted piperidines from the methylthiofuropyridone **4a**.

Reduction of the methylthiofuropyridone **4a** with tributyltin hydride and 2,2′-azobisisobutyronitrile[12] resulted in the formation of the desulfurized furopyridone **5a** in 90% yield, and this was subjected to catalytic hydrogenation over platinum dioxide under a hydrogen atmosphere to afford the tetrahydrofuran **5b** in 88% yield. The tetrahydrofuran **5b** was also prepared in one step from the methylthiofuropyridone **4a** by reduction in the presence of Raney-Ni (W-2). In order to introduce a two-carbon unit into the 4-position of the piperidone ring, the furopyridone **5b** was subjected to the elimination–addition reaction which has recently been developed and successively applied to the total syntheses of several indole alkaloids by our group.[1,9,13] According to the procedure,[1,13] lithiation of the furopyridone **5b** with lithium diisopropylamide followed by addition of the 2-lithioacetate gave the desired adducts **6a, b** as a 1:1 diastereomeric mixture in 89% yield. The two adducts **6a, b** were readily characterized by their MS, IR, and ^{1}H-NMR spectra except for their stereostructures, which were chemically established by the following conversions of **6a** into the known *cis*-intermediate **13a**[14,15] and of **6b** into the known *trans*-intermediate **13b**.[16]

Phenylselenylation of the ethylols **6a, b** with *o*-nitrophenylselenocyanate–tributylphosphine followed by oxidation of the corresponding selenides **7a, b** with *m*-chloroperbenzoic acid gave the vinyl esters **8a, b** in 76 and 53% yields, respectively, from the alcohols **6a, b**. The *cis*-lactam **8a** was converted into the known key intermediate **13a** for the syntheses of (±)-quinine, (±)-akuammigine, and (±)-tetrahydroalstonine by the following reaction sequence. Chemoselective reduction[17] of the lactam carbonyl group (AlH_3 at −50 °C) followed by transesterification ($MeOH–H_2SO_4$) gave the amino methyl esters **10a, b** in 53—70% yields; the yields were mainly dependent on the chemoselective reduction step. For the conversion of these two amines **10a, b** into the known benzoates **13a, b**, the benzyl group was replaced with a benzoyl group *via* the trichloroethylcarbamates **11a, b** according to the procedure developed by Reinecke and Daubert.[18] Treatment of the amine **10a** with trichloroethyl chloroformate in the presence of sodium bicarbonate gave the carbamate **11a** in 95% yield, and this was subjected to reductive elimination with zinc in acetic acid to afford the secondary amine **12a** in comparable yield. Benzoylation of the amine **12a** afforded the desired *cis*-*N*-benzoate **13a** in 59% yield from the carbamate **11a**. Spectral data of this benzoate **13a** were identical with those reported by Uskoković *et al.*[14,15]

Similarly, the *trans*-amine **10b** was converted into the



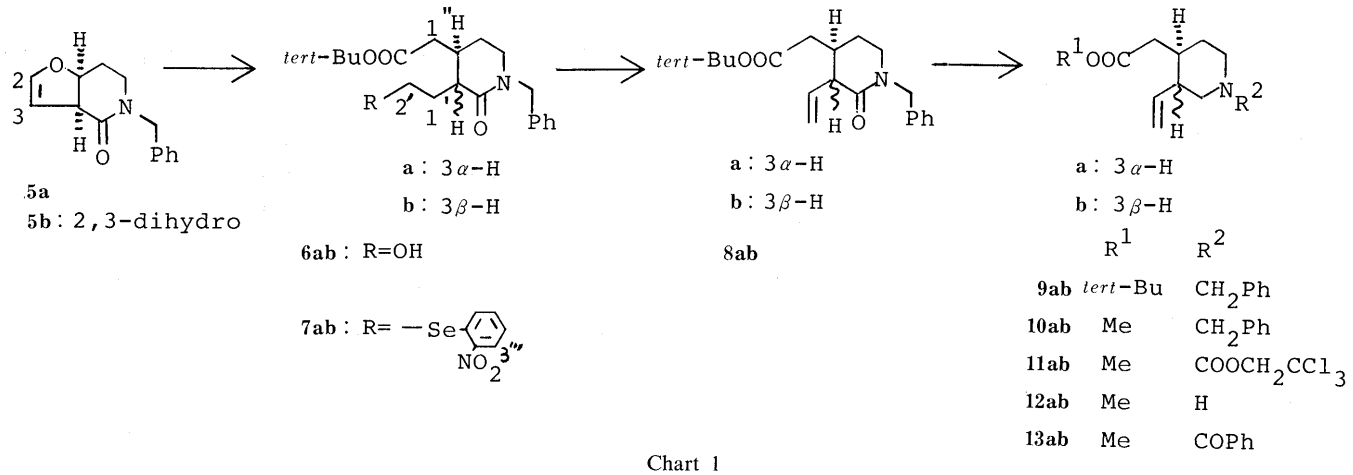


Chart 1

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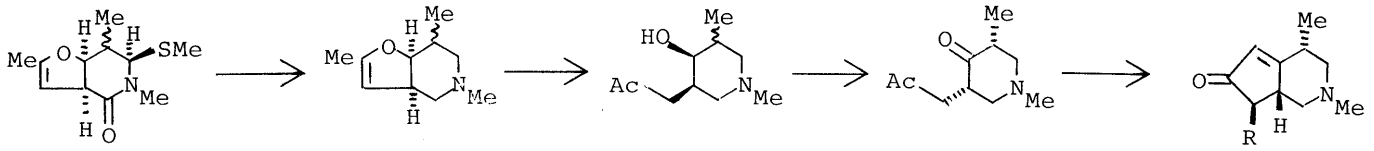

4b : α -Me
4c : β -Me

14a : α -Me
14b : β -Me

15a : α -Me
15b : β -Me

16

17a : R=Me
17b : R=H

Chart 2

known synthetic intermediate **13b** of (±)-ajmalicine, whose spectral data were identical with those reported by Uskoković *et al.*[16]

Preparation of the Synthetic Key Intermediate 16 for (±)-7-Demethyltecomanine Because of its powerful hypoglycemic activity,[19] tecomanine **17a**, a simple monoterpenoid alkaloid, has recently been synthesized by several groups.[20] The utility of the methylthiofuropyridones **4b, c** as synthons was visualized by their conversion into the known synthetic intermediate **16**[21] of 7-demethyltecomanine **17b**. Reduction of the methylthiolactams **4b, c** with lithium aluminum hydride in refluxing tetrahydrofuran resulted in the formation of the desulfurized amines **14a, b** in 91 and 88% yields. These amines were easily characterized on the basis of their spectral data as shown in Experimental. Both dihydrofurans **14a, b** were hydrolyzed with 10% hydrochloric acid to give the hydroxyketones **15a, b** in 82 and 94% yields, respectively. Jones' oxidation of the hydroxyketone **15b** gave the diketone **16** in quantitative yield. Compound **16** was also prepared by the same oxidation of the other hydroxyketone **15a** in 55% yield, presumably *via* isomerization at the 3- or 5-position of the resulting thermodynamically unstable 3,5-*trans*-diketone. Spectral data of the *cis*-diketone **16** were identical with those reported by Momose *et al.*,[21] who had accomplished the synthesis of (±)-7-demethyltecomanine (**17b**) from this diketone **16**.

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. 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 plate at 254 and 300 nm or by exposure to iodine vapor. Medium-pressure column chromatography (MCC) was undertaken on a 530-4-10V Yamazen) using a Lobar grosse B column (310-25, Lichroprep Si60, Merck). Short column chromatography (SCC) was undertaken on a short glass filter using Silica gel 60F-254 (Merck).

The *N*-Thioacetamides 1a, b Four 5.55 g portions of phosphorus pentasulfide (total 22.2 g) were added to a solution of *N*-benzylacetamide (74.6 g) in toluene (200 ml) at 80 °C with stirring. After being heated for 2 h, the hot reaction mixture was decanted and the solution was concentrated to give the thioacetamide **1a**[7] (72.7 g, 88%) as pale red-brown crystals, which were used for the following alkylation without purification. ^{1}H-NMR (60 MHz) δ: 7.30 (5H, s, Ph), 4.80 (2H, d, J=8 Hz, NHC$\underline{H}_2$), 2.57 (3H, s, CSMe). The other thioacetamide **1b**[7] was prepared similarly as a yellow oil (73%). ^{1}H-NMR (60 MHz) δ: 3.13 (3H, d, J=6 Hz, NH$\underline{Me}$), 1.33 (3H, t, J=8 Hz, CH$_2\underline{Me}$).

The Thioimidates 2a, b Dimethyl sulfate (54.9 g) was added dropwise to a solution of the thioacetamide **1a** (71.9 g) in tetrahydrofuran (THF) (50 ml) with stirring at room temperature during 0.5 h. The reaction mixture was then heated with stirring at 80 °C for 4 h. The resulting solution was cooled and made alkaline by the addition of saturated aqueous sodium carbonate, and then extracted with ether. The organic layer was washed with brine, dried, and evaporated to give a brown oil, which was distilled to afford the thioimidate **2a**[7] (45 g, 73.3%) as a pale yellow oil, bp 135—140 °C (11 mmHg). ^{1}H-NMR (60 MHz) δ: 4.57 (1.2H), 4.43 (0.8H) (each br s, NCH$_2$), 2.33 (1.8H), 2.07 (1.2H) (each s, SMe). Similarly, methylation of the thioamide **1b** with dimethyl sulfate followed by distillation of a crude oil gave the thioimidate **2b**[7] (34%) as a colorless oil, bp 75—80 °C (60 mmHg). ^{1}H-NMR (60 MHz) δ: 3.20 (1.7H), 3.13 (1.3H) (each s, NMe), 2.43 (1.7H), 2.20 (1.3H) (each s, SMe), 1.20 (1.7H), 1.13 (1.3H) (each t, J=8 Hz, CH$_2\underline{Me}$).

Preparation of the Enamides 3a—c A solution of 3-furoyl chloride (2.8 g) in benzene (50 ml) was added to a solution of the imidate **2a** (3.6 g) and triethylamine (4 ml) in benzene (50 ml) with stirring at room temperature. After being stirred at 80 °C for 1.5 h, the reaction mixture was cooled and filtered. The filtrate was concentrated to give the unstable yellow-brown enamide **3a**, which was used for the following irradiation without purification. Similarly, other enamides **3b, c** were prepared from the imidate **2b** and the corresponding acid chlorides and also irradiated without purification. All the enamides (**3a—c**) were too unstable to be purified, and were characterized only by ^{1}H-NMR spectroscopy of the crude products. **3a**: (60 MHz) δ: 7.92 (1H, br s, 2-H), 7.25 (6H, s-like, Ph, 5-H), 6.70 (1H, br s, 4-H), 4.87, 4.83 (each 2H, s, NCH$_2$, CH$_2$=C), 2.17 (3H, s, SMe). The mixture of **3b** and **3b'** was readily separated by MCC (AcOEt : hexane = 1 : 1). **3b**: (60 MHz) δ: 7.75 (1H, s, 2-H), 6.33 (1H, br s, 4-H), 5.45 (1H, q, J=7 Hz, =C$\underline{H}$Me), 3.17 (3H, s, NMe), 2.27 (3H, s, 5-Me), 2.17 (3H, s, SMe), 1.77 (3H, d, J=7 Hz, CH$\underline{Me}$). **3b'**: (60 MHz) δ: 7.63 (1H, s, 2-H), 6.25 (1H, br s, 4-H), 5.63 (1H, q, J=7 Hz, =C$\underline{H}$Me), 3.17 (3H, s, NMe), 2.27 (3H, s, 5-Me), 2.07 (3H, s, SMe), 1.57 (3H, d, J=7 Hz, CH$\underline{Me}$). **3c**: (60 MHz) δ: 7.85, 7.73 (each 0.5H, br s, 2-H), 7.23 (1H, br s, 5-H), 6.70, 6.60 (each 0.5H, br s, 4-H), 5.60, 5.38 (each 0.5H, q, J=7 Hz, =C$\underline{H}$Me), 3.17 (3H, s, NMe), 2.17, 2.03 (each 1.5H, s, SMe), 1.73, 1.53 (each 1.5 Hz, d, J=7 Hz, CH$\underline{Me}$).

Reductive Photocyclization of the Enamides 3a—d Sodium borohydride (3 g) and methanol (100 ml) were added to a stirred solution of the crude unstable enamide **3a**, prepared from the imidate **1a** (3.6 g) and 3-furoyl chloride (2.8 g), in acetonitrile (900 ml) at 5 °C. After the added hydride agent had dissolved, the resulting solution was irradiated with a high-pressure mercury lamp (300 W) through a Pyrex filter at 5—10 °C for 9 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, the methylene dichloride-soluble part of which was purified by flash chromatography (AcOEt : hexane = 1 : 1) to give the methylthiofuropyridone **4a** (2.4 g, 44% from the imidate **1a** as a colorless solid. An analytical sample could not be obtained due to its instability during recrystallization. IR: 1644 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 6.43 (1H, br t, J=2.5 Hz, 2-H), 5.56 and 4.12 (2H, ABq, J=15 Hz, C$\underline{H}_2$Ph), 5.22 (1H, br t, J=3 Hz, 3-H), 5.00 (1H, br dt, J=10.5, 3.5 Hz, 7a-H), 4.40 (1H, ddd, J=5, 3, 1 Hz, 6-H), 3.88 (1H, dt, J=10.5, 2.5 Hz, 3a-H), 2.61 (1H, br dt, J=15, 2 Hz, 7-H$_{eq}$), 2.21 (1H, br dt, J=15, 5 Hz, 7-H$_{ax}$), 2.16 (3H, s, SMe). Irradiation at δ 6.43 (2-H), changed the signal pattern (br dt) of 7-H$_{ax}$ to a sharp double triplet and irradiation at δ 2.21 (7-H$_{ax}$) changed that (br t) of 2-H to a sharp triplet. Irradiation at δ 4.40 (6-H) changed the signal pattern (br dt) of 7a-H to a sharp double triplet and irradiation at δ 5.00 (7a-H) changed that (ddd) of 6-H to a double doublet (J=5, 3 Hz). High-resolution MS *m/z*: Calcd for $C_{15}H_{18}NO_2S$ (M^++1) 276.106. Found: 276.105. Similarly, reductive photocyclization of the other enamides (**3b, c**) proceeded smoothly to give the corresponding methylthiolactams (**4b—e**), after separation of the crude products by MCC. **4b** was obtained as an unstable colorless solid, mp

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83—86 °C. IR: 1636 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 4.76 (1H, br s, 3-H), 4.65 (1H, ddd, J=10, 3, 1 Hz, 7a-H), 4.24 (1H, dd, J=2.5, 1 Hz, 6-H), 3.72 (1H, br dm, J=10 Hz, 3a-H), 3.10 (3H, s, NMe), 2.71 (1H, m, 7-H), 2.27 (3H, s, SMe), 1.79 (3H, dd, J=2, 1 Hz, 2-Me), 1.15 (3H, d, J=7.5 Hz, 7-Me). MS m/z: 227 (M^+). **4c** was obtained as colorless crystals, mp 112—114 °C (Et_2O). IR: 1630 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 4.78—4.66 (2H, m, 7a- and 3-H), 4.21 (1H, dd, J=4, 1 Hz, 6-H), 3.73 (1H, br dm, J=10 Hz, 3a-H), 3.09 (3H, s, NMe), 2.50 (1H, m, 7-H), 2.28 (3H, s, SMe), 1.80 (3H, dd, J=2, 1 Hz, 2-Me), 1.37 (3H, d, J=7 Hz, 7-Me). *Anal.* Calcd for $C_{11}H_{17}NO_2S$: C, 58.12; H, 7.54; N, 6.16. Found: C, 57.99; H, 7.61: N, 6.00. Reductive photocyclization of either of the separated isomers **3b** and **3b'** or a mixture of the isomers afforded two lactams (**4b** and **4c**) in 40—41 and 48—50% yields, respectively. Upon irradiation under the same reaction conditions as above, the photocyclized lactams **4b, c** were quantitatively recovered.

4d (36%) was obtained as colorless crystals mp 86—88 °C (Et_2O). IR: 1638 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 6.39 (1H, t, J=2.5 Hz, 2-H), 5.20 (1H, br t, J=3 Hz, 3-H), 4.64 (1H, ddd, J=11, 3, 1 Hz, 7a-H), 4.22 (1H, dd, J=3, 1 Hz, 6-H), 3.73 (1H, dt, J=11, 2.5 Hz, 3a-H), 3.12 (3H, s, NMe), 2.75 (1H, m, 7-H), 2.26 (3H, s, SMe), 1.20 (3H, d, J=7.5 Hz, 7-Me). *Anal.* Calcd for $C_{10}H_{15}NO_2S$: C, 56.31; H, 7.09; N, 6.57. Found: C, 56.01; H, 6.98; N, 6.64. **4e** was obtained as a pale yellow solid (28%). IR: 1636 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 6.38 (1H, br td, J=2, 1 Hz, 2-H), 5.17 (1H, t, J=3 Hz, 3-H), 4.73 (1H, ddd, J=10, 3, 1 Hz, 7a-H), 4.22 (1H, dd, J=5, 1 Hz, 6-H), 3.72 (1H, br dt, J=10, 3 Hz, 3a-H), 3.10 (3H, s, NMe), 2.60 (1H, m, 7-H), 2.27 (3H, s, SMe), 1.41 (3H, d, J=7.5 Hz, 7-Me). High-resolution MS m/z: Calcd for $C_{10}H_{15}NO_2S$ (M^+) 213.082. Found: 213.084. A W-shaped long-range coupling between the 6- and 7a-protons in **4b—d** and a long-range coupling through five bonds between the 2- and 7-protons in addition to the W-shaped coupling between the 6- and 7a-protons in **4e** were observed in the decoupling experiments on the lactams **4b—e**.

The Desulfurized THFs 5b Direct Method: A solution of the lactam **4a** (0.42 g) and Raney-Ni (W-2) (1 ml) in anhydrous THF (50 ml) was vigorously stirred under reflux for 2—3 h. The catalyst was filtered off from the hot solution and the filtrate was concentrated to give a residue, which was purified by MCC (AcOEt) to afford the saturated lactam **5b** (126 mg, 36%) as a colorless oil and the dihydrofuran **5a** (70 mg, 20%) as a colorless oil. **5b**: IR: 1630 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 4.68 and 4.59 (2H, ABq, J=13.5 Hz, C$\underline{H}_2$Ph), 4.24 (1H, dt, J=7, 3.5 Hz, 7a-H), 3.94 (1H, td, J=8, 5.5 Hz, 2-H), 3.75 (1H, td, J=8, 7 Hz, 2-H), 3.41 (1H, ddd, J=13, 9.5, 5 Hz, 6-H), 3.10 (2H, m, 3a- and 6-H), 2.47 (1H, m, 3-H), 2.22 (1H, dtd, J=13.5, 7, 5.5 Hz, 3-H), 1.94 (2H, m, 7-H_2). High-resolution MS m/z: Calcd for $C_{14}H_{17}NO_2$ (M^+) 231.126. Found: 231.126. **5a**: IR: 1640 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 6.48 (1H, t, J=2.5 Hz, 2-H), 5.18 (1H, t, J=2.5 Hz, 3-H), 4.97 (1H, br dt, J=10, 3 Hz, 7a-H), 4.68 and 4.20 (2H, ABq, J=16 Hz, C$\underline{H}_2$Ph), 3.85 (1H, dt, J=10, 3 Hz, 3a-H), 3.45 (1H, br ddd, J=12.5, 10, 3.5 Hz, 6-H), 3.10 (1H, br td, J=12.5, 4, 1.5 Hz, 6-H), 1.99 (2H, m, 7-H_2). High-resolution MS m/z: Calcd for $C_{14}H_{15}NO_2$ (M^+) 229.110. Found: 229.110.

Indirect Method: Azobisisobutyronitrile (AIBN) (50 mg) was added to a hot solution of a mixture of the methylthiolactam **4a** (0.5 g) and tributyltin hydride (1.26 g) in freshly distilled benzene (50 ml) with stirring. The solution was stirred under reflux for 3 h, then evaporated to half the initial volume to give a viscous solution, which was purified by SCC (AcOEt : hexane = 1 : 1) followed by MCC (AcOEt : hexane = 1 : 1) to give the desulfurized lactam **5a** (0.37 g, 90%), which was identical with the sample prepared above upon comparison of their *Rf* values and ^{1}H-NMR spectra. Catalytic hydrogenation of the lactam **5a** (0.33 g) over platinum dioxide (60 mg) in methanol (20 ml) under a hydrogen atmosphere at room temperature for 3 h and purification of the crude product by MCC (AcOEt : hexane = 1 : 2) gave the saturated lactam **5b** (0.3 g, 88%), which was identical with the sample prepared directly from **4a** based on a comparison of their *Rf* values and ^{1}H-NMR spectra.

Elimination–Addition Reaction of the Lactam 5b with Lithioacetate *tert*-Butyl acetate (1.05 ml) was added to a lithium diisopropylamide (LDA) solution, prepared from diisopropylamine (1.33 ml) and *n*-butyllithium (10% solution in hexane) (6.07 ml) at −78 °C. The mixture was stirred at −78 °C for 30 min, then a solution of the furopyridone **5b** (301 mg) in anhydrous THF (5 ml) was added to the resulting solution. The mixture was stirred at −30 °C for 1 h, then the reaction was quenched by the addition of water, and the mixture was extracted with methylene dichloride. The extract was dried and evaporated to give a yellow oil which was purified by MCC (AcOEt) to give the *cis*-adduct **6a** (208 mg, 46%) and the *trans*-adduct **6b** (195 mg, 43%), each as a colorless glass. **6a**: IR: 3380 (OH), 1720 (COO*tert*-Bu), 1618 (NCO) cm^{-1}. ^{1}H-NMR (500 MHz) δ: 4.62 and 4.57 (2H, ABq, J=14.5 Hz, C$\underline{H}_2$Ph), 3.81 (1H, ddd, J=11.5, 6.5, 4 Hz, 2'-H), 3.74 (1H, ddd, J=11.5, 8, 4 Hz, 2'-H), 3.26 (2H, m, 6-H_2), 2.73 (1H, br dt, J=10, 5 Hz, 3-H), 2.48 (1H, m, 4-H), 2.31 (1H, dd, J=15, 5.5 Hz, 1''-H), 2.12 (1H, dd, J=15, 10 Hz, 1''-H), 1.77 (4H, m, 5-H_2 and 1'-H_2), 1.44 (9H, s, *tert*-Bu). High-resolution MS m/z: Calcd for $C_{20}H_{29}NO_4$ (M^+) 347.209. Found: 347.208. **6b**: IR: 3400 (OH), 1720 (COO*tert*-Bu), 1614 (NCO) cm^{-1}. ^{1}H-NMR (500 MHz) δ: 4.63 and 4.58 (2H, ABq, J=14.5 Hz, C$\underline{H}_2$Ph), 3.82 (1H, br dt, J=11, 5 Hz, 2'-H), 3.75 (1H, br ddd, J=11, 8, 5 Hz, 2'-H), 3.23 (2H, m, 6-H_2), 2.42 (1H, m, 1''-H), 2.34 (1H, br td, J=7.5, 4.5 Hz, 3-H), 2.16 (2H, m, 4- and 1''-H), 1.96 (3H, m, 1'-H_2 and 5-H), 1.57 (1H, m, 5-H), 1.44 (9H, s, *tert*-Bu).

Preparation of the Olefins 8a, b Tributylphosphine (0.2 ml) and *o*-nitrophenylselenoisocyanate (183.1 mg) were successively added to a solution of the *cis*-adduct **6a** (198 mg) in THF (1 ml) at room temperature and the resulting red solution was stirred at room temperature for 1 h. The solvent was evaporated to give a residue, which was purified by SCC (AcOEt : hexane = 1 : 1) to afford the selenide **7a** (276 mg, 91%) as a yellow glass. IR: 1720 (COO*tert*-Bu), 1632 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 8.32 (1H, br d, J=8 Hz, 3'''-H), 7.75 (1H, br d, J=8 Hz, 6'''-H), 7.55 (1H, br t, J=8 Hz, 5'''-H), 7.34 (6H, m, 4'''-H and Ph), 4.62 (2H, s, C$\underline{H}_2$Ph), 3.40 (1H, m, 2'-H), 3.27 (1H, t, J=7 Hz, 6-H_2), 3.10 (1H, m, 2'-H), 2.68 (1H, br dt, J=9, 4.5 Hz, 3-H), 2.53 (1H, m, 4-H), 2.32 (1H, br dd, J=15, 5 Hz, 1''-H), 2.12 (1H, br dd, J=15, 10 Hz, 1''-H), 1.43 (9H, s, *tert*-Bu). Similarly, the *trans*-alcohol **6b** was converted into the selenide **7b** as a yellow brown glass in 70% yield. IR: 1720 (COO*tert*-Bu), 1628 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 8.32 (1H, br d, J=8 Hz, 3''-H), 7.77 (1H, br d, J=8 Hz, 6'''-H), 7.58 (1H, br t, J=8 Hz, 5'''-H), 7.32 (6H, m, 4'''-H and Ph), 4.68 and 4.60 (2H, ABq, J=15 Hz, C$\underline{H}_2$Ph), 3.25 (2H, t-like, J=6 Hz, 6-H_2), 3.08 (2H, m, 2'-H_2), 1.44 (9H, s, *tert*-Bu). *m*-Chloroperbenzoic acid (37.2 mg) was added to a stirred solution of the *cis*-selenide **7a** (88.7 mg) in methylene dichloride (5 ml) at 0 °C. The mixture was stirred at 0 °C for 1 h, then aqueous sodium hydrosulfite was added to quench the reaction. The reaction mixture was made alkaline by the addition of aqueous sodium bicarbonate and then extracted with methylene dichloride. The extract was washed, dried, and evaporated to give a residue which was purified by MCC (AcOEt : hexane = 1 : 1) to afford the *cis*-olefin **8a** (46 mg, 83%) as a colorless glass. IR: 1722 (COO*tert*-Bu), 1628 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 7.32 (5H, m, Ph), 5.48 (1H, ddd, J=17.5, 9.5, 8.5 Hz, C$\underline{H}$=CH$_2$), 5.29 (2H, m, C=C$\underline{H}_2$), 4.73 and 4.53 (2H, ABq, J=15 Hz, C$\underline{H}_2$Ph), 3.28 (1H, br dd, J=8.5, 4.5 Hz, 3-H), 3.24 (2H, m, 6-H_2), 2.46 (1H, m, 4-H), 2.32 (1H, dd, J=15, 6 Hz) and 2.16 (1H, dd, J=15, 8 Hz) (C$\underline{H}_2$COO*tert*-Bu), 1.76 (2H, m, 5-H_2), 1.44 (9H, s, *tert*-Bu). High-resolution MS m/z: Calcd for $C_{20}H_{27}NO_3$ (M^+) 329.199. Found: 329.200. Similarly, the *trans*-selenide **7b** was converted into the *trans*-olefin **8b** as a colorless glass in 75% yield. IR: 1720 (COO*tert*-Bu), 1628 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 7.30 (5H, m, Ph), 5.80 (1H, ddd, J=17, 10.5, 8 Hz, C$\underline{H}$=CH$_2$), 5.29 (2H, m, C=C$\underline{H}_2$), 4.68 and 4.56 (2H, ABq, J=15 Hz, C$\underline{H}_2$Ph), 3.24 (2H, m, 6-H_2), 2.81 (1H, br t, J=9 Hz, 3-H), 2.48 (1H, dd, J=15, 4 Hz) and 2.10 (1H, dd, J=15, 9 Hz) (C$\underline{H}_2$COO*tert*-Bu), 2.18 (1H, m, 4-H), 1.42 (9H, s, *tert*-Bu). High-resolution MS m/z: Calcd for $C_{20}H_{27}NO_3$ (M^+) 329.199. Found: 329.198.

Chemoselective Reduction of the Lactams 8a, b A solution of aluminum hydride in a mixture of THF (5 ml) and ether (10 ml), prepared from lithium aluminum hydride (273 mg) and anhydrous aluminum trichloride (300 mg), was carefully added to a stirred solution of the ester **8a** (129 mg) in THF (10 ml) at −50 °C by monitoring the reaction by TLC. The mixture was stirred at −50 °C for 1.5 h, then water was carefully added and the whole was extracted with methylene dichloride. The extract was dried and evaporated to give a yellow oil, which was purified by SCC (AcOEt) to afford the amine **9a** (117 mg, 70%) as a colorless glass. IR: 1718 (COO*tert*-Bu) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 7.33 (5H, m, Ph), 6.19 (1H, ddd, J=17, 11, 9.5 Hz, C$\underline{H}$=CH$_2$), 5.08 (2H, m, CH=C$\underline{H}_2$), 3.54 and 3.46 (2H, ABq, J=14 Hz, C$\underline{H}_2$Ph), 1.44 (9H, s, *tert*-Bu). High-resolution MS m/z: Calcd for $C_{20}H_{29}NO_2$ (M^+) 315.220. Found: 315.221. Similarly, the *trans*-lactam **8b** was converted into the amine **9b** in 53% yield in addition to the starting lactam **8b**. **9b** was obtained as a colorless glass. IR: 1720 (COO*tert*-Bu) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 7.32 (5H, m, Ph), 5.56 (1H, ddd, J=17.5, 10, 9 Hz, C$\underline{H}$=CH$_2$), 5.08 (2H, m, CH=C$\underline{H}_2$), 3.56 and 3.52 (2H, ABq, J=13 Hz, C$\underline{H}_2$Ph), 1.42 (9H, s, *tert*-Bu). High-resolution MS m/z: Calcd for $C_{20}H_{29}NO_2$ (M^+) 315.220. Found: 315.220. The yield in chemoselective reduction of the two lactams **8a, b** was dependent on the activity of the freshly prepared aluminum hydride.

Transesterification of the *tert*-Butyl Esters 9a, b A solution of the *cis-tert*-butyl ester **9a** (112 mg) in 10% sulfuric acid–methanol solution

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(10 ml) was stirred at room temperature overnight, then poured into ice-cooled aqueous sodium bicarbonate and extracted with methylene dichloride. The extract was washed, dried and evaporated to give the methyl ester **10a** (95 mg, 98%) as a pale yellow oil. IR: 1730 (COOMe) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 7.38 (5H, br s, Ph), 6.10 (1H, br, 1'-H), 5.12 (2H, m, 2'-H_2), 3.68 (3H, s, COOMe). High-resolution MS *m/z*: Calcd for $C_{17}H_{23}NO_2$ (M^+) 273.173. Found: 273.172. Similarly, the *trans*-*tert*-butyl ester **9b** was converted into the methyl ester **10b** as a pale yellow oil in quantitative yield. IR: 1730 (COOMe) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 7.40 (5H, br s, Ph), 5.54 (1H, br dt, J=17, 9 Hz, 1'-H), 5.13 (2H, m, 2'-H_2), 3.66 (3H, s, COOMe). High-resolution MS *m/z*: Calcd for $C_{17}H_{23}NO_2$ (M^+) 273.173. Found: 273.172.

Debenzylation of the Amines 10a, b Trichloroethyl chloroformate (36.5 mg) was added to a stirred mixture of the *cis*-amine **10a** (31.5 mg), sodium bicarbonate (150 mg), and acetone (2 ml) and the mixture was stirred at room temperature overnight. Water was added and then the whole was extracted with methylene dichloride. The extract was washed, dried, and evaporated to give a residue, which was purified by SCC (AcOEt : hexane = 1 : 2) to afford the carbamate **11a** (39 mg, 95%) as a pale yellow glass. ^{1}H-NMR (60 MHz) δ: 4.70 (2H, s, $COOCH_2CCl_3$). Similarly, the *trans*-amine **10b** was converted into the carbamate **11b** as a yellow glass in quantitative yield. ^{1}H-NMR (60 MHz) δ: 4.72 (2H, s, $COOCH_2CCl_3$). Both carbamates **11a, b** were characterized by ^{1}H-NMR spectra and were used for the following reduction without further purification.

***N*-Benzoylmeroquinene Methyl Ester 13a and Its *trans*-Congener 13b** A mixture of the *cis*-carbamate **11a** (55.7 mg), freshly washed zinc powder (600 mg), and acetic acid (12 ml) was vigorously stirred at room temperature overnight. The reaction mixture was filtered and the filtrate was made alkaline by the addition of aqueous potassium carbonate and then extracted with methylene dichloride. The extract was washed, dried, and evaporated to give the crude secondary amine **12a** (25 mg) as a pale yellow oil, which was directly used for the following benzoylation without purification. Benzoylation of the *cis*-amine **12a** with benzoyl chloride in the presence of triethylamine in benzene in a usual manner and purification of the crude product by p-TLC (AcOEt : hexane = 5 : 1) afforded the *cis*-benzoate **13a** as a colorless glass (26.3 mg, 59% from the carbamate **11a**). IR: 1730 (COOMe), 1620 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 7.42 (5H, s, Ph), 5.90 (1H, ddd, J=17, 11, 8 Hz, 1'-H), 5.16 (2H, m, 2'-H_2), 3.67 (3H, s, COOMe). High-resolution MS *m/z*: Calcd for $C_{17}H_{21}NO_3$ (M^+) 287.152. Found: 287.152. Similarly, the *trans*-carbamate **11b** was converted into the corresponding *N*-benzoate **13b** as a colorless glass in 55% yield *via* the secondary amine **12b**. **13b**: IR: 1730 (COOMe), 1620 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 7.40 (5H, s, Ph), 5.50 (1H, br dt, J=17.5, 9 Hz, 1'-H), 5.14 (2H, m, 2'-H_2), 3.66 (3H, s, COOMe). High-resolution MS *m/z*: Calcd for $C_{17}H_{21}NO_3$ (M^+) 287.152 (M^+). Found: 287.151. Spectral data of these two benzoates **13a, b** were identical with those reported.[14-16]

The Hydroxyketones 15a, b Lithium aluminum hydride (500 mg) was carefully added to a stirred solution of the lactam **4b** (430 mg) in a mixture of THF and ether (1 : 1) (150 ml). The mixture was refluxed for 8 h. Usual work-up gave the unstable amine **14a** (288 mg, 91%) as a pale yellow oil. ^{1}H-NMR (60 MHz) δ: 4.60 (1H, br s, 3-H), 3.92 (1H, dd, J=8, 6 Hz, 7a-H), 2.20 (3H, s, NMe), 1.70 (3H, split s, 2-Me), 1.00 (3H, d, J=7 Hz, 7-Me). MS *m/z*: 167 (M^+). A solution of the amine **14a** (230 mg) in a mixture of methanol (20 ml) and 10% hydrochloric acid (4 ml) was stirred at room temperature for 1.5 h. After evaporation of the solvent, the mixture was made alkaline by the addition of saturated aqueous potassium carbonate and then extracted with methylene dichloride. The extract was dried and evaporated to give the hydroxyketone **15a** (208 mg, 82%) as a yellow oil. IR: 3424 (OH), 1706 (CO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 3.35 (1H, dd, J=9, 5 Hz, 4-H), 2.92 (1H, dd, J=17, 7 Hz, 2-H_{eq}), 2.70 (1H, dd, J=17, 5.5 Hz, 2-H_{ax}), 2.20 (3H, s, Me), 2.18 (3H, s, Me), 0.98 (3H, d, J=6.5 Hz, 5-Me). High-resolution MS *m/z*: Calcd for $C_{10}H_{19}NO_2$ (M^+) 185.142. Found: 185.142. Similarly, reduction of the lactam **4c** with lithium aluminum hydride followed by acid hydrolysis of the resulting unstable **14b**. ^{1}H-NMR (60 MHz) δ: 4.73 (1H, br s, 3-H), 4.17 (1H, br dd, J=6, 3 Hz, 7a-H), 2.20 (3H, s, NMe), 1.82 (3H, s, 2-Me), 1.08 (3H, d, J=6 Hz, 7-Me)) gave the hydroxyketone **15b** as a yellow oil in 83% yield from the lactam **4c**. **15b**: IR: 3424 (OH), 1706 (CO) cm^{-1}: ^{1}H-NMR (200 MHz) δ: 3.68 (1H, br s, 4-H), 2.33 (3H, s, Me), 2.18 (3H, s, Me), 1.52 (1H, t, J=12 Hz, 6-H_{ax}), 0.95 (3H, d, J=6.5 Hz, 5-Me).

The Diketone 16 Oxidation of the two hydroxyketones **15a, b** (110 mg) in acetone (5 ml) with Jones' reagent (0.08 ml) and purification of the crude product by p-TLC (AcOET : MeOH = 1 : 1) gave the same diketone **16** (103 mg, 95%) as a pale brown oil. IR: 1712 (CO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 3.28 (1H, m, 3-H), 3.20—3.14 (2H, m, 6-H_{eq} and 2-H_{eq}), 2.95 (1H, dd, J=17, 7 Hz, 1'-H), 2.80 (1H, m, 5-H), 2.38 (3H, s, Me), 2.22 (3H, s, Me), 2.12 (1H, dd, J=17, 5 Hz, 1'-H), 2.08 (1H, br t, J=12 Hz, 2-H_{ax}), 2.06 (1H, t, J=12 Hz, 6-H_{ax}), 0.98 (3H, d, J=6.5 Hz, 5-Me). High-resolution MS *m/z*: Calcd for $C_{10}H_{17}NO_2$ (M^+) 183.126. Found: 183.127. Spectral data of the diketone **16** were identical with those reported.[21]

Acknowledgements This work was supported by a Grant-in-Aid for Scientific Research (C) (No. 01571171) from the Ministry of Education, Science and Culture of Japan. The authors are grateful to Misses T. Kato, N. Kitade, M. Fukui, and S. Hira for technical assistance.

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