Tetrahedron Vol. 49, No. 8, pp. 1571-1578, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

An Efficient Enantioselective Synthesis of Indicine *N*-Oxide, an Antitumor Pyrrolizidine Alkaloid

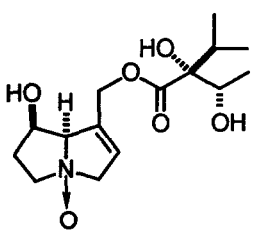
Takeshi Ogawa, Haruki Niwa,* and Kiyoyuki Yamada*

Department of Chemistry, Faculty of Science, Nagoya University, Chikusa, Nagoya 464, Japan

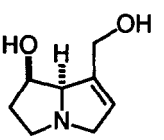
(*Received in Japan* 20 *November* 1992)

Abstract *— Indicine N-oxide (1), a pyrrolizidine alkaloid potentially useful for an anticancer drug was synthesized in the natural form through regioselective coupling of (+)-retronecine (2) and the protected necic acids 16a and 16b, the latter being efficiently prepared from the optically pure lactone 5.*

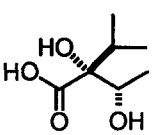
Pyrrolizidine alkaloids are known to display a wide range of biological activities.[1,2] Indicine *N*-oxide (**1**), the major pyrrolizidine alkaloid in the plant *Heliotropium indicum* L. (Boraginaceae),[3] is known to exhibit significant antitumor activity with little hepatotoxicity, and is the only pyrrolizidine alkaloid that has undergone clinical trials as an anticancer drug.[4] The potentiality as an anticancer drug coupled with the novel structure has made **1** an attractive synthetic target. Although there have been reported the results of several synthetic studies on **1**, rather limited progress has been achieved on the enantioselective synthesis of **1**.[5] Described herein is a full account of an enantioselective synthesis of indicine *N*-oxide (**1**) in the highly efficient manner.[6]



1 indicine *N*-oxide



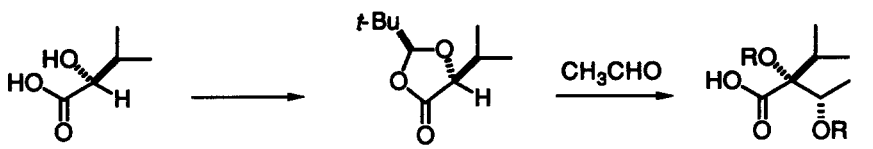
2 retronecine



3 trachelanthic acid

The synthesis of indicine *N*-oxide (**1**) in the natural form required (+)-retronecine (**2**) and (–)-trachelanthic acid (**3**). In the coupling stage the diol moiety in **3** should be protected with a suitable protecting group. We had already achieved the enantioselective synthesis of **2**.[7] Our efforts were therefore directed toward the enantioselective synthesis of **3** in the appropriately protected form **6**.[8] In 1984, Seebach and his co-workers reported a practical method for EPC (enantiomerically pure compounds) synthesis, in which an approach named "self-reproduction of chirality" was utilized.[9] We envisaged that this approach might be applicable to the efficient EPC synthesis of **6** involving the construction of the contiguous stereocenters as outlined in Scheme **1**.

Scheme 1

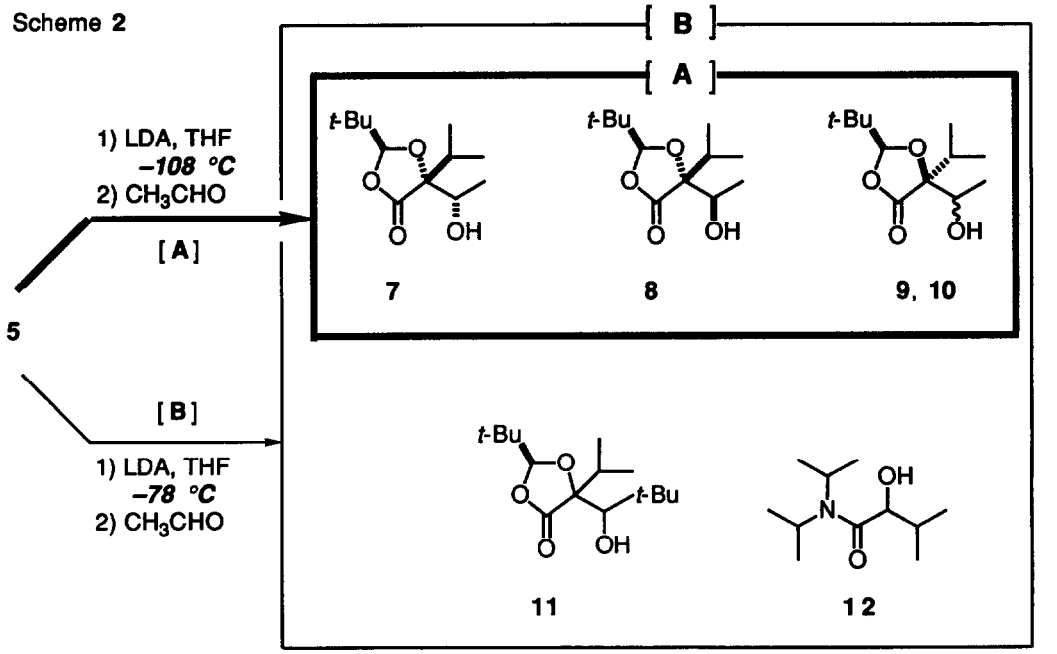


4 5 6

As the starting material for the synthesis of **6**, we chose (2*S*,5*S*)-2-(*t*-butyl)-5-isopropyl-1,3-dioxolan-4-one (**5**),[9,10,11] readily accessible from (*S*)-2-hydroxy-3-methylbutanoic acid (**4**).[12]

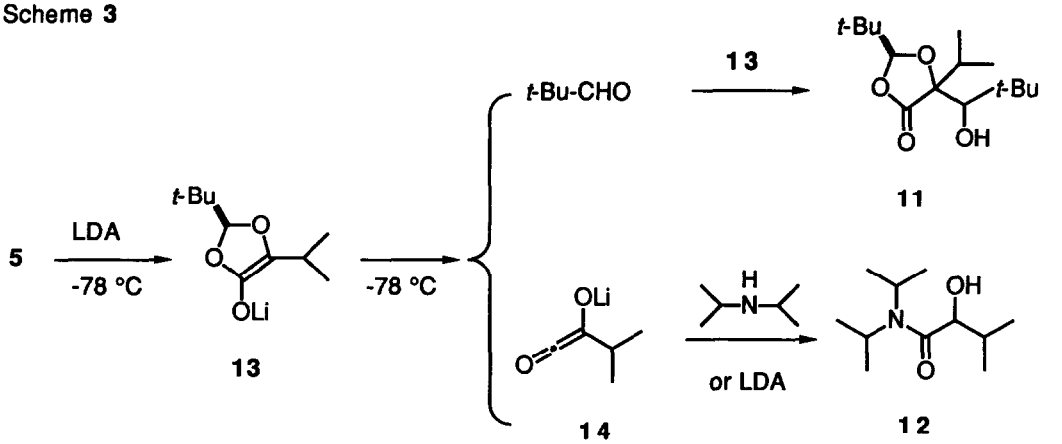
The enantiomerically and diastereomerically pure lactone **5** was converted into the corresponding enolate **13** by reaction with lithium diisopropylamide (LDA) in THF at –78 °C and subsequent reaction with acetaldehyde provided a 58:33:7:2 mixture[13] of the lactone alcohols **7** (desired stereoisomer), **8**, **9**,[14] and **10**[14] (41% yield) together with unexpected products, the lactone alcohol **11**[15] (20%) and the amide **12** (27%) (Scheme 2, conditions **B**). The plausible reaction pathway for the formation of these unexpected products **11**

Scheme 2



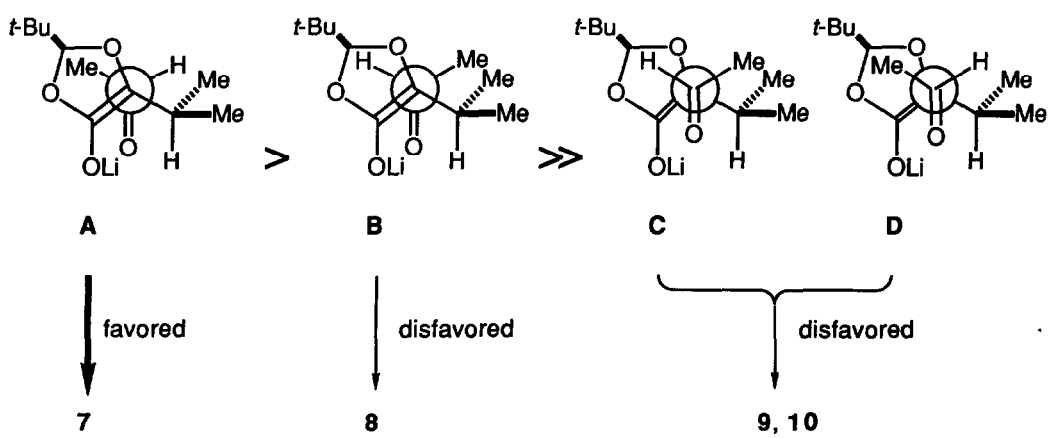
and **12** is shown in Scheme 3. At –78 °C, the enolate **13** was decomposed to some extent to pivalaldehyde and the ketene **14**. Pivalaldehyde thus formed reacted further with the remaining **13** to give the lactone alcohol **11**, while the ketene **14** was trapped with diisopropylamine (or LDA), providing the amide **12**. These results indicated that the enolate **13** was labile at –78 °C and the reaction of **13** with acetaldehyde proceeded with low diastereoselectivity. We anticipated that at the lower reaction temperature the collapse of the enolate **13** could be prevented and the diastereoselectivity of the aldol reaction might be increased. Thus, we conducted the

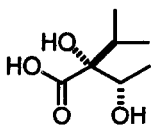
Scheme 3



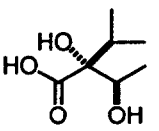
enolate formation from **5** and the reaction of the generated enolate **13** with acetaldehyde *at –108 °C* (Scheme 2, conditions A), providing, without formation of the undesired products **11** and **12**, a 77:13:6:4 mixture[13] of **7**, **8**, **9**, and **10** in 67% yield. Of the four possible diastereomers, the desired lactone alcohol **7** was formed predominantly. In Scheme 4 the stereochemical outcome of this aldol reaction is illustrated. With the diastereoface selectivity of the enolate **13**, the transition states **A** and **B** leading to **7** and **8**, respectively may be preferable to the transition states **C** and **D** leading to **9** and **10**, owing to the steric effect of the bulky *t*-butyl group in **13**. With the enantioface selectivity of acetaldehyde, the transition states **A** leading to **7** may be preferable to the transition states **B** leading to **8**, owing to the steric repulsion between the isopropyl group in **13** and the methyl group of acetaldehyde in the transition state **B**. Consequently, the transition state **A** leading to the desired **7** may be the most favorable one among the four possible transition states. The pure, desired lactone alcohol **7** (43%) and the diastereomer **8** (5.2%) could be isolated by repeated column chromatography. The stereochemistry of **7** and **8** was established unambiguously by transformation into (–)-trachelanthic acid

Scheme 4





3 trachelanthic acid

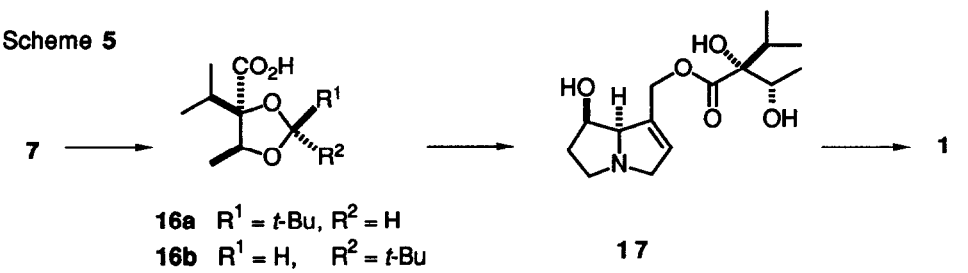


15 viridifloric acid

(**3**)[16a] and (+)-viridifloric acid (**15**),[16b] respectively, by acidic hydrolysis.[10]

In Scheme **5** the completion of the synthesis of (+)-indicine *N*-oxide (**1**) is shown. Acid-catalyzed isomerization (camphorsulfonic acid, benzene, reflux) of the lactone alcohol **7** furnished a separable mixture of the protected necic acids **16a** (62%) and **16b** (9.3%).[17] The optically active protected necic acids **16a** and **16b** required for the synthesis of indicine (**17**) were now in hand, and were subjected to coupling with retronecine (**2**). Thus, regioselective coupling of **2** and **16a** with DCC and DMAP (toluene, room temp.)[5a] gave protected indicine, which upon hydrolysis (1 M HCl, room temp.) provided **17** (two steps, 75%). Similarly, **17** was also obtained in 63% yield from **2** and **16b**. Finally, oxidation of **17** (*m*-CPBA, acetone, room temp.) furnished **1** (81%). Spectral and physical properties of synthetic **1** [mp 119–120 °C (MeOH–acetone), $[\alpha]_D^{19}$ +35.6° (*c* 0.85, EtOH)] were identical with those of natural **1**[5d] in all respects.

Scheme **5**



16a R^1 = *t*-Bu, R^2 = H
16b R^1 = H, R^2 = *t*-Bu

17

In conclusion, we have achieved an efficient enantioselective synthesis of indicine *N*-oxide (**1**), an antitumor pyrrolizidine alkaloid, from the lactone **5** in five steps and in 18% overall yield.

Experimental

Melting points are uncorrected. IR spectra were taken on a JASCO IR-810 spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL JNM-C675 (270 MHz) spectrometer: Chemical shifts (δ) are reported in ppm downfield from internal tetramethylsilane in chloroform-*d* ($CDCl_3$), and coupling constants (*J*) in Hz. Low-resolution (EIMS and CIMS) and high-resolution mass spectra (HREIMS and HRCIMS) were measured on a JEOL JMS-LG2000 instrument. Fuji-Davison silica gel BW-820 MH was used for column chromatography. Merck precoated silica gel 60 F_{254} plates, 0.25 mm thickness were used for analytical thin layer chromatography. Tetrahydrofuran (THF) was distilled from sodium–benzophenone ketyl under nitrogen. Toluene and benzene were distilled from sodium under nitrogen. Diisopropylamine was distilled from calcium hydride (CaH_2) under nitrogen. Unless otherwise stated, the organic solutions obtained by extractive workup

were washed with saturated aqueous sodium chloride (NaCl) solution, dried over anhydrous sodium sulfate (Na_2SO_4), and concentrated under reduced pressure by a rotary evaporator.

Aldol Reaction of (2*S*,5*S*)-2-(*t*-Butyl)-5-isopropyl-1,3-dioxolan-4-one (5) and Acetaldehyde at –108 °C. To a cooled (–78 °C), stirred solution of diisopropylamine (0.23 ml, 1.6 mmol) in THF (7 ml) under nitrogen was added dropwise a 1.7 M solution of *n*-butyllithium in hexane (0.92 ml, 1.5 mmol), and the mixture was stirred for 30 min. The resulting solution of LDA was cooled to –108 °C by using a liquid N_2-THF bath. To the cooled LDA solution was added dropwise a solution of **5**[9,10,11] (190 mg, 1.02 mmol) in THF (0.76 ml). After the mixture was stirred for 1 h at –108 °C, acetaldehyde (0.13 ml, 2.3 mmol) was introduced to the mixture. The reaction mixture was allowed to warm to room temperature with continuous stirring. After 1 h, the reaction was quenched by the addition of saturated NH_4Cl solution (2 ml). The aqueous mixture was extracted with ether (4 x 20 ml). The extracts were combined, dried, and concentrated. The residue was subjected to purification by column chromatography on silica gel (50 g, CH_2Cl_2) to give a 77:13:6:4 mixture[13] of **7**, **8**, **9**, and **10** (158 mg, 67%). The mixture of **7**, **8**, **9**, and **10** was separated by column chromatography on silica gel [30 g, ether/hexane (1/5)] to afford a mixture of **7** and **8** (134 mg, 57%), and an inseparable mixture of **9** and **10** (13.1 mg, 5.6%) as a colorless oil, respectively. Separation of the mixture of **7** and **8** by HPLC [Develosil ODS-10 (250 x 20 mm ID); solvent MeOH/H_2O (75/25); flow rate 8 ml/min; detection UV 215 nm; recycled twice] provided pure **7** (102 mg, 43%; t_R 54 min) as a colorless oil and **8** (12.2 mg, 5.2%; t_R 50 min) as crystals, respectively.

7: colorless oil; $[\alpha]_D^{16}$ +2.24° (*c* 0.980, $CHCl_3$); IR ($CHCl_3$) 3625, 3600–3300 (broad), 1780, 1165, 1090, and 980 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.00 (9 H, s), 1.06 (3 H, d, *J* = 6.9 Hz), 1.06 (3 H, d, *J* = 6.9 Hz), 1.33 (3 H, d, *J* = 6.6 Hz), 1.96 (1 H, d, *J* = 5.6 Hz, OH), 2.09 (1 H, qq, *J* = 6.9, 6.9 Hz), 4.31 (1 H, dq, *J* = 5.6, 6.6 Hz: on addition of D_2O; q, *J* = 6.6 Hz), and 5.42 (1 H, s); CIMS *m/z* (relative intensity) 231 [$(M + H)^+$, 15], 186 (49), 173 (10), 145 (11), and 87 (100) [HRCIMS. Found: 231.1587. $C_{12}H_{23}O_4$ [$(M + H)^+$] requires: 231.1596].

8: mp 108–109 °C (pentane); $[\alpha]_D^{14}$ –39.0° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3600, 3450 (broad), 1780, 1170, 1100, and 980 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.98 (3 H, d, *J* = 6.9 Hz), 0.98 (3 H, d, *J* = 6.9 Hz), 1.00 (9 H, s), 1.39 (3 H, d, *J* = 6.6 Hz), 1.64 (1 H, d, *J* = 5.6 Hz, OH), 2.12 (1 H, qq, *J* = 6.9, 6.9 Hz), 4.23 (1 H, dq, *J* = 5.6, 6.6 Hz; on addition of D_2O: q, *J* = 6.6 Hz), and 5.55 (1 H, s); CIMS *m/z* (relative intensity) 231 [$(M + H)^+$, 11], 186 (66), 173 (15), 145 (12), and 87 (100) [HRCIMS. Found: 231.1581. $C_{12}H_{23}O_4$ [$(M + H)^+$] requires: 231.1596]. Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.92; H, 9.79.

A mixture of **9** and **10**: colorless oil; IR ($CHCl_3$) 3600, 1790, 1230, 1170, 1080, and 980 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) for the major diastereomer, δ 1.01 (9 H, s), 1.06 (3 H, d, *J* = 6.9 Hz), 1.09 (3 H, d, *J* = 6.9 Hz), 1.37 (3 H, d, *J* = 6.6 Hz), 2.13 (1 H, d, *J* = 5.0 Hz, OH), 2.27 (1 H, qq, *J* = 6.9, 6.9 Hz), 4.06 (1 H, dq, *J* = 5.0, 6.6 Hz: on addition of D_2O; q, *J* = 6.6 Hz), and 5.23 (1 H, s); ^1H NMR (270 MHz, $CDCl_3$) for the minor diastereomer, δ 1.00 (9 H, s), 1.08 (3 H, d, *J* = 6.9 Hz), 1.11 (3 H, d, *J* = 6.9 Hz), 1.30 (3 H, d, *J* = 6.6 Hz), 2.08 (1 H, d, *J* = 8.9 Hz, OH), 2.29 (1 H, qq, *J* = 6.9, 6.9 Hz), 4.09 (1 H, dq, *J* = 8.9, 6.6 Hz: on addition of D_2O; q, *J* = 6.6 Hz), and 5.26 (1 H, s); CIMS *m/z* (relative intensity) 231 [$(M + H)^+$, 100], 186 (47), 173 (21), 145 (19), and 87 (49) [HRCIMS. Found: 231.1603. $C_{12}H_{23}O_4$ [$(M + H)^+$] requires: 231.1596].

Aldol Reaction of 5 and Acetaldehyde at –78 °C. To a cooled (–78 °C), stirred solution of diisopropylamine (0.77 ml, 5.5 mmol) in THF (30 ml) under nitrogen was added dropwise a 1.62 M solution of *n*-butyllithium in hexane (3.24 ml, 5.25 mmol), and the mixture was stirred at –78 °C for 30 min. To the resulting solution of LDA was added dropwise a solution of **5**[9,10,11] (938 mg, 5.04 mmol) in THF (2 ml). After the mixture was stirred for 1 h at –78 °C, acetaldehyde (0.56 ml, 10 mmol) was introduced to the mixture. The reaction mixture was allowed to warm to room temperature with continuous stirring. After 1 h, the reaction was quenched by the addition of saturated NH_4Cl solution (10 ml). The aqueous mixture was extracted with ether (3 x 50 ml). The extracts were combined, dried, and concentrated. The residue was purified by column chromatography on silica gel (50 g, CH_2Cl_2) to give a 58:33:7:2 mixture[13] of **7**, **8**, **9**, and **10** (479 mg, 41%) together with **11**[15] (271 mg, 20%) and **12** (270 mg, 27%) as a colorless oil, respectively.
11:[15] colorless oil; IR ($CHCl_3$) 3620, 3530 (broad), 1780, 1180, 1160, 1090, and 980 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, the signals for the major diastereomer are shown) δ 1.00 (9 H, s), 1.03 (3 H, d, J = 6.9 Hz), 1.10 (9 H, s), 1.21 (3 H, d, J = 6.9 Hz), 2.22 (1 H, d, J = 5.9 Hz, OH) 2.33 (1 H, qq, J = 6.9, 6.9 Hz), 3.96 (1 H, d, J = 5.9 Hz; on addition of D_2O, s), and 5.41 (1 H, s); CIMS *m/z* (relative intensity) 273 [$(M + H)^+$, 60], 187 (100), 169 (44), 159 (49), and 87 (43) [HRCIMS. Found: 273.2052. $C_{15}H_{29}O_4$ [$(M + H)^+$] requires: 273.2066].
12: colorless oil; IR ($CHCl_3$) 3410 (broad), 1630, 1370, 1330, 1040, and 1025 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.78 (3 H, d, J = 6.6 Hz), 1.08 (3 H, d, J = 6.6 Hz), 1.21 (3 H, d, J = 6.6 Hz), 1.22 (3 H, d, J = 6.6 Hz), 1.40 (3 H, d, J = 6.6 Hz), 1.45 (3 H, d, J = 6.6 Hz), 1.81 (1 H, dqq, J = 2.3, 6.6, 6.6 Hz), 3.43 (1 H, qq, J = 6.6, 6.6 Hz), 3.87 (1 H, qq, J = 6.6, 6.6 Hz), and 4.16 (1 H, d, J = 2.3 Hz); CIMS *m/z* (relative intensity) 202 [$(M + H)^+$, 100], 183 (2), 158 (5), 128 (9), and 86 (9) [HRCIMS. Found: 202.1794. $C_{11}H_{24}NO_2$ [$(M + H)^+$] requires: 202.1807].

(2*S*,4*R*,5*S*)-2-(*t*-Butyl)-4-isopropyl-5-methyl-1,3-dioxolane-4-carboxylic Acid (16a) and (2*R*,4*R*,5*S*)-2-(*t*-Butyl)-4-isopropyl-5-methyl-1,3-dioxolane-4-carboxylic Acid (16b). A mixture of **7** (300 mg, 1.30 mmol) and camphorsulfonic acid (169 mg, 0.728 mmol) in benzene (30 ml) was heated under reflux for 72 h. After cooling, the reaction mixture was concentrated. The residue was dissolved in ether (10 ml) and extracted twice with 5% $NaHCO_3$ solution (10 ml and then 2 ml). The combined aqueous extracts were acidified to pH 1 with concd HCl (3 ml) and then were saturated with NaCl. The aqueous mixture was extracted with ether (4 x 20 ml). The ethereal extracts were combined, dried, and concentrated to give a 7:1 mixture[13] of **16a** and **16b** (221 mg, 74%), which was separated by column chromatography on silica gel [20 g, CH_2Cl_2→EtOAc/CH_2Cl_2 (1/10→1/5)] to provide **16a** (184 mg, 62%) and **16b** (27.8 mg, 9.3%) as colorless crystals, respectively.
16a: mp 107–108.5 °C (pentane); $[\alpha]_D^{14}$ +13.6° (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) 3600–2400 (broad), 1770, 1720, and 1100 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.97 (3 H, d, J = 6.9 Hz), 1.00 (9 H, s), 1.03 (3 H, d, J = 6.9 Hz), 1.49 (3 H, d, J = 6.6 Hz), 2.18 (1 H, qq, J = 6.9, 6.9 Hz), 4.14 (1 H, q, J = 6.6 Hz), and 4.51 (1 H, s); CIMS *m/z* (relative intensity) 231 [$(M + H)^+$, 8], 185 (25), 173 (28), 145 (12), and 87 (100) [HRCIMS. Found: 231.1569. $C_{12}H_{23}O_4$ [$(M + H)^+$] requires: 231.1596]. Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.49; H, 9.68.
16b: mp 66.5–68 °C (pentane); $[\alpha]_D^{14}$ +13.5° (*c* 0.850, $CHCl_3$); IR ($CHCl_3$) 3600–2400 (broad), 1770, 1720, and 1120 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.95 (9 H, s), 0.99 (3 H, d, J = 6.9 Hz), 1.08 (3 H, d, J = 6.9

Hz), 1.43 (3 H, d, J = 6.6 Hz), 2.25 (1 H, qq, J = 6.9, 6.9 Hz), 4.41 (1 H, q, J = 6.6 Hz), and 4.89 (1 H, s); CIMS m/z (relative intensity) 231 [$(M + H)^+$, 8], 185 (18), 173 (37), 145 (9), and 87 (100) [HRCIMS. Found: 231.1605. $C_{12}H_{23}O_4$ [$(M + H)^+$] requires: 231.1596]. Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.50; H, 9.62.

Indicine (17).

(A) From 16a. A mixture of **16a** (10.7 mg, 0.0465 mmol), **2** (7.6 mg, 0.049 mmol), dicyclohexylcarbodiimide (22.0 mg, 0.107 mmol), and 4-(dimethylamino)pyridine (1.8 mg, 0.015 mmol) in toluene (0.38 ml) under nitrogen was stirred at room temperature. After 6 days, the reaction mixture was concentrated. The residue was dissolved in 1 M HCl (10 ml), and the mixture was stirred at room temperature for 22 h. The reaction mixture was made basic (pH ca. 10) with concd NH_3 aq (4 ml), and the aqueous mixture was extracted with ether (9 x 20 ml). The ethereal extracts were combined, dried, and concentrated. The residue was purified by column chromatography on silica gel [5 g, concd NH_3 aq/MeOH/$CHCl_3$ (1/10/100→1/10/50)] to give **17** (10.5 mg, 75%) as a colorless oil: $[\alpha]_D^{18}$ +20.0° (c 0.40, EtOH); [lit.[5d] $[\alpha]_D^{22}$ +19.5° (c 1.2, EtOH)]; IR ($CHCl_3$) 3500 (broad), 1725, 1160, 1110, 1030, and 1000 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.93 (3 H, d, J = 6.9 Hz), 0.96 (3 H, d, J = 6.9 Hz), 1.19 (3 H, d, J = 6.3 Hz), 1.9–2.1 (2 H, m), 2.15 (1 H, qq, J = 6.9, 6.9 Hz), 2.75 (1 H, m), 3.30 (1 H, m), 3.45 (1 H, br dd, J = 5.6, 15.8 Hz), 3.97 (1 H, br d, J = 15.8 Hz), 4.05 (1 H, q, J = 6.3 Hz), 4.21 (1 H, br s), 4.30 (1 H, br s), 4.60 (1 H, d, J = 12.9 Hz), 5.12 (1 H, d, J = 12.9 Hz), and 5.94 (1 H, br s); EIMS m/z (relative intensity) 299 (M^+, 8), 254 (1), 156 (10), 138 (100), and 93 (91) [HREIMS. Found: 299.1704. $C_{15}H_{25}NO_5$ (M^+) requires: 299.1733].

(B) From 16b. A mixture of **16b** (21.8 mg, 0.0948 mmol), **2** (16.5 mg, 0.106 mmol), dicyclohexylcarbodiimide (45.3 mg, 0.220 mmol), and 4-(dimethylamino)pyridine (3.7 mg, 0.030 mmol) in toluene (0.83 ml) under nitrogen was stirred at room temperature. After 6 days, the reaction mixture was concentrated. The residue was dissolved in 1 M HCl (5 ml), and the mixture was stirred at room temperature for 28 h. The reaction mixture was made basic (pH ca. 10) with concd NH_3 aq (4 ml), and the aqueous mixture was extracted with ether (6 x 20 ml). The ethereal extracts were combined, dried, and concentrated. The residue was purified by column chromatography on silica gel [7 g, concd NH_3 aq/MeOH/$CHCl_3$ (1/10/100→1/10/50)] to give **17** (17.8 mg, 63%) as a colorless oil.

Indicine *N*-Oxide (1).

To a solution of **17** (29.0 mg, 0.0970 mmol) in acetone (1.75 ml) was added *m*-chloroperoxybenzoic acid (22.7 mg, 0.131 mmol) and the mixture was stirred at room temperature for 2 h. The reaction mixture was directly subjected to purification by column chromatography on silica gel (5 g, acetone→MeOH), providing **1** (24.6 mg, 81%) as colorless crystals: mp 119–120 °C (MeOH-acetone); $[\alpha]_D^{19}$ +35.6° (c 0.850, EtOH) [lit.[5d] mp 118–119 °C (MeOH–acetone); $[\alpha]_D^{21}$ +35° (c 0.9, EtOH)]; IR ($CHCl_3$) 3200 (broad), 1730, 1140, 1020, and 1000 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.92 (3 H, d, J = 6.9 Hz), 0.96 (3 H, d, J = 6.9 Hz), 1.19 (3 H, d, J = 6.6 Hz), 1.92 (1 H, qq, J = 6.9, 6.9 Hz), 2.03 (1 H, m), 2.64 (1 H, m), 3.7–3.9 (2 H, m), 4.13 (1 H, q, J = 6.6 Hz), 4.45 (2 H, s), 4.6–4.8 (3 H, m), 5.13 (1 H, d, J = 13.2 Hz), and 5.85 (1 H, br s); EIMS m/z (relative intensity) 299 [$(M - O)^+$, 2], 297 (6), 279 (4), 170 (4), 153 (21), 136 (100), and 117 (93) [HREIMS. Found: 299.1722. $C_{15}H_{25}NO_5$ [$(M - O)^+$] requires: 299.1733].

Acknowledgement: We are grateful to Dr. Yoshio Nishimura, Institute of Microbial Chemistry, Japan for providing us with the authentic samples and spectral data of natural indicine and indicine *N*-oxide.

REFERENCES AND NOTES

1. (a) Smith, L. W.; Culvenor, C. C. J. *J. Nat. Prod.* **1981**, *44*, 129–152. (b) Robins, D. J. *Fortschr. Chem. Org. Naturst.* **1982**, *41*, 115–203. (c) Robins, D. J. *Nat. Prod. Rep.* **1984**, *1*, 235–243; **1985**, *2*, 213–220; **1986**, *3*, 297–305; **1987**, *4*, 577–590; **1989**, *6*, 221–230; **1989**, *6*, 577–589; **1990**, *7*, 377–386; **1991**, *8*, 213–221; **1992**, *9*, 313–321.
2. Mattocks, A. R. *Chemistry and Toxicology of Pyrrolizidine Alkaloids*; Academic Press: London, 1986.
3. (a) Mattocks, A. R.; Schoental, R.; Crowley, H. C.; Culvenor, C. C. J. *J. Chem. Soc.* **1961**, 5400–5403. (b) Kugelman, M.; Liu, W.-C.; Axelrod, M.; McBride, T. J.; Rao, K. V. *J. Nat. Prod.* **1976**, *39*, 125–128.
4. Suffness, M.; Cordell, G. A. In *The Alkaloids*; Brossi, A. Ed; Academic Press: New York, 1985; Vol. 25, Chapter 1, pp 21–38.
5. (a) Piper, J. R.; Kari, P.; Shealy, Y. F. *J. Labelled Compd. Radiopharm.* **1981**, *18*, 1579–1591. (b) Vedejs, E.; Larsen, S.; West, F. G. *J. Org. Chem.* **1985**, *50*, 2170–2174. (c) Zalkow, L. H.; Glinski, J. A.; Gelbaum, L. T.; Fleischmann, T. J.; McGowan, L. S.; Gordon, M. M. *J. Med. Chem.* **1985**, *28*, 687–694. (d) Nishimura, Y.; Kondo, S.; Takeuchi, T.; Umezawa, H. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4107–4113.
6. Preliminary communication: Niwa, H.; Ogawa, T.; Yamada, K. *Tetrahedron Lett.* **1989**, *30*, 4985–4986.
7. (a) Niwa, H.; Okamoto, O.; Miyachi, Y.; Uosaki, Y.; Yamada, K. *J. Org. Chem.* **1987**, *52*, 2941–2943. (b) Niwa, H.; Miyachi, Y.; Okamoto, O.; Uosaki, Y.; Kuroda, A.; Ishiwata, H.; Yamada, K. *Tetrahedron* **1992**, *48*, 393–412.
8. During our investigation, the efficient synthesis of **3** by a different route was reported: Sato, T.; Kato, R.; Gokyu, K.; Fujisawa, T. *Tetrahedron Lett.* **1988**, *29*, 3955–3958.
9. Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313–1324.
10. Niwa, H.; Ogawa, T.; Yamada, K. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3707–3709.
11. The compound **5** prepared according to the procedure reported in the literature[9] contained a small amount (<5%) of the 2*R*-isomer of **5**. Enantiomerically and diastereomerically pure **5** was obtained by low-temperature (–78 °C) recrystallization of crude **5** from ether–pentane. Pure **5**: $[\alpha]_D^{24}$ –1.66° (*c* 3.07, $CHCl_3$), bp 104 °C (21 mmHg); >99% ee by ^1H NMR spectral analysis using a shift reagent $Eu(hfc)_3$.[10]
12. Fischer, E.; Scheibler, H. *Chem. Ber.* **1908**, *41*, 2891–2902.
13. The ratio was determined by the ^1H NMR spectral analysis of the mixture.
14. The stereochemistry was not determined.
15. This material was a 10:1 mixture[13] of diastereomers.
16. (a) Synthetic **3**: mp 88.5–89.5 °C (benzene–hexane), $[\alpha]_D^{14}$ –4.46° (*c* 1.01, EtOH); lit.[5d] mp 89.5-90 °C (benzene–hexane), $[\alpha]_D^{25}$ –4.8° (*c* 0.51, EtOH). (b) Synthetic **15**: mp 117–118 °C (ether–hexane), $[\alpha]_D^{19}$ +1.92° (*c* 0.73, H_2O); lit.[18] mp 117–119 °C (ether–petroleum ether), $[\alpha]_D^{25}$ +1.8° (*c* 2.73, H_2O)
17. The stereochemistry of **16a** and **16b** was determined by the NOE experiments.
18. Ladner, W. *Chem. Ber.* **1983**, *116*, 3414–3426.