Total Synthesis of (–)-γ-Lycorane Using Diastereoselective 5-*Endo*-*Trig* Radical Cyclization of *N*-Vinylic α-Halo Amides

Masazumi Ikeda,*[a] Shinji Ohtani,[a] Tatsunori Sato,[a] Hiroyuki Ishibashi*[b]

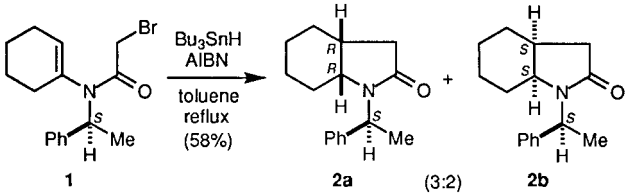
[a] Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607-8414, Japan
Fax +81(75)5954763; E-mail: ikeda@mb.kyoto-phu.ac.jp
[b] Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920-0934, Japan
Fax +81(76)2344476; E-mail: isibasi@dbs.p.kanazawa-u.ac.jp

Received 13 April 1998; revised 11 June 1998

Abstract: Bu_3SnH-mediated radical cyclization of α-iodo-*N*-(6-oxocyclohex-1-enyl)-*N*-[(*S*)-1-phenylethyl]acetamide **(6)** proceeded in a 5-*endo-trig* manner with moderate diastereoselectivity to give (3a*S*,7a*R*)-octahydroindole-2,7-dione **8a** as the major product, which was converted into (–)-γ-lycorane **(15)**.

Key words: asymmetric induction, 5-*endo-trig* cyclization, (–)-γ-lycorane, radical cyclization, tributyltin hydride

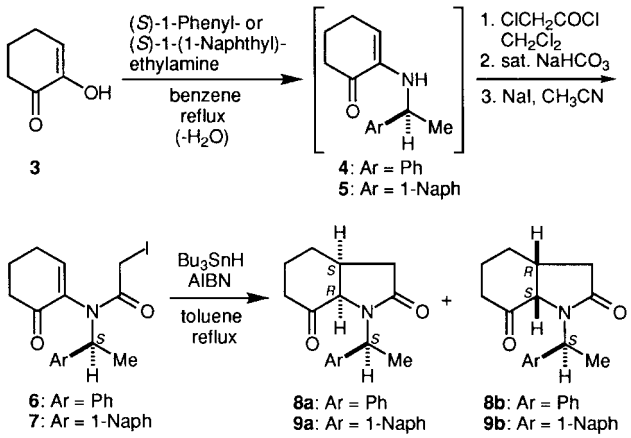
Great interest has recently been directed towards asymmetric induction in radical cyclizations induced by chiral auxiliary control.[1] In continuation of our studies on the asymmetric synthesis of natural products using radical cyclization of α-halo amides as the key step,[2] we reported that α-bromo-*N*-(cyclohex-1-enyl)acetamide **1** bearing an (*S*)-1-phenylethyl group on the nitrogen atom, upon treatment with Bu_3SnH in the presence of 2,2'-azobisisobutyronitrile (AIBN) in boiling toluene, underwent 5-*endo-trig* radical cyclization to give (3a*R*,7a*R*)-octahydroindol-2-one **2a** as the major product.[3,4] However, the diastereoselectivity for the products **2a** and **2b** was disappointingly low (ca. 3:2). Therefore, we turned our attention to the 6-oxo congener **6**, and found that the cyclization of **6** proceeded with a moderate degree of diastereoselectivity to give (3a*S*,7a*R*)-octahydroindole-2,7-dione **8a** as the major product. The present paper describes the application of this method to the total synthesis of (–)-γ-lycorane **(15)**.



Scheme 1

The radical precursor **6** was prepared by condensation of cyclohexane-1,2-dione **(3)** with (–)-(*S*)-1-phenylethylamine followed by treatment of the resulting enamine **4** with chloroacetyl chloride and then with sodium iodide. When a boiling solution of **6** in toluene was treated slowly with a toluene solution of 1.3 equivalents of Bu_3SnH containing a catalytic quantity of AIBN, an inseparable mixture of (3a*S*,7a*R*)- and (3a*R*,7a*S*)-octahydroindole-2,7-diones **8a** and **8b** was obtained in 84% combined yield.

The ^1H NMR spectrum showed the ratio of **8a**/**8b** to be ca. 2:1, indicating that the compound **6** proceeded with higher



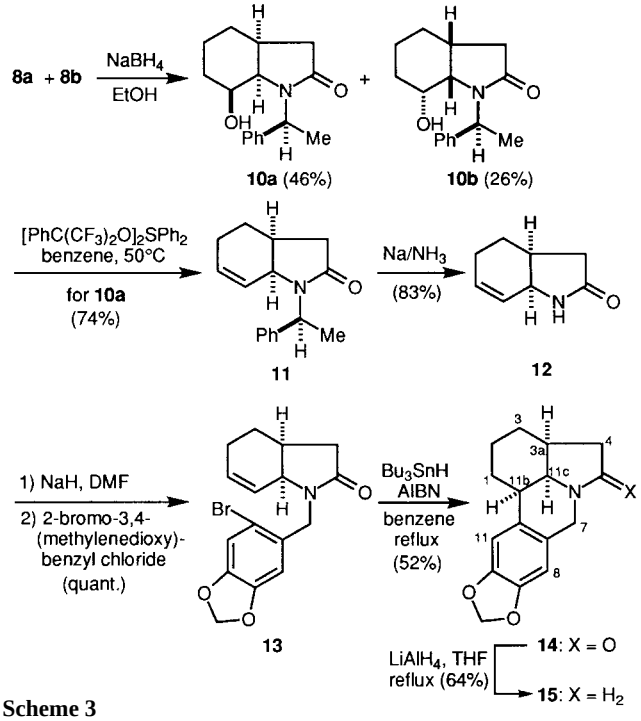
Scheme 2

diastereoselectivity than did **1**. The stereochemistry of **8a,b** was established by transforming **8a** to (–)-γ-lycorane **(15)** (vide infra). It is interesting to note that the absolute configuration of the *cis*-juncture of the major product **8a** [(3a*S*,7a*R*)] is opposite to that of **2a** [(3a*R*,7a*R*), note, there is a change of CIP priorities] in spite of using the same chiral auxiliary. The high combined yield (84%) of **8a,b** as compared to **2a,b** (58%) may be explained in terms of the capto-dative stabilizing effect[5] of the cyclized radical intermediates [-N–C•–C=O].

In an attempt to improve the diastereoselectivity in the cyclization, we also examined the reaction of **7** bearing a sterically more demanding 1-(1-naphthyl)ethyl group on the nitrogen atom. As expected, much higher diastereoselectivity was observed for the products **9a** and **9b** (3.2:1), but the combined yield was reduced to 42%.

Some of lycorine-class of *Amaryllidaceae* alkaloids display potentially useful biological properties including antiviral activity.[6] It is known that (–)-lycorine can be converted into (–)-γ-lycorane **(15)** through several chemical transformations.[7] Although γ-lycorane does not appear to possess any useful pharmacological properties, many attempts have been made to synthesize this compound[8] because its pentacyclic structure provides a means to demonstrate the utility of new synthetic methods. However, only a limited example has so far been reported for the synthesis of optically active γ-lycorane.[9] We envisioned that the major product **8a** obtained from **6** would be converted to optically active γ-lycorane through radical cyclization of **13** (Scheme 3).

In order to synthesize **13**, the regioselective formation of olefin **11** from **8a** was required. Reduction of **8a,b** with $NaBH_4$ gave a mixture of alcohols **10a** and **10b** in 76% combined yield, which could be separated by careful chromatography on silica gel to give pure **10a** in 46% yield. Compound **10a** was then treated with Martin sulfurane dehydrating agent[10] {$[PhC(CF_3)_2O]_2SPh_2$} {bis[α,α-bis(trifluoromethyl)benzenemethanolato]diphenylsulfur} to give **11** in 74% yield.



Scheme 3

Deprotection of the *N*-(1-phenylethyl) group of **11** was accomplished by treatment with sodium in liquid ammonia to give **12** in 83% yield. Subsequent *N*-alkylation of **12** with 2-bromo-4,5-(methylenedioxy)benzyl chloride provided quantitatively the requisite radical precursor **13**, which was treated with Bu_3SnH and AIBN in boiling benzene to give lycorane derivative **14** in 52% yield. Finally, reduction of lactam **14** with $LiAlH_4$ in boiling THF gave (–)-γ-lycorane **(15)** in 64% yield, whose spectral properties were virtually identical with those reported for (+)-γ-lycorane.[9] Thus, we established the absolute stereochemistry of the radical cyclization products **8a,b** and accomplished the first total synthesis of (–)-γ-lycorane **(15)**.

In summary, we revealed that the Bu_3SnH-mediated 5-*endo-trig* radical cyclization of α-iodo-*N*-(6-oxocyclohex-1-enyl)-*N*-[(*S*)-1-phenylethyl]acetamide **(6)** proceeded with moderate diastereoselectivity and the major product **8a** served as a useful intermediate for the synthesis of optically active lycorane alkaloids. Further work on the refinement of the chiral auxiliaries and an application of the method to the synthesis of more complex lycorine alkaloids is now in progress.

Mps were determined using a Yanaco micromelting point apparatus and are uncorrected. IR spectra were recorded with a JASCO IR-A-100 spectrophotometer. ^1H (60 and 300 MHz) and ^{13}C NMR (75.4 MHz) spectra were measured on a JEOL JNM-PMX 60 or a Varian XL-300 spectrometer for solutions in $CDCl_3$. δ Values quoted are relative to TMS (0 ppm) and $CDCl_3$ (77.02 ppm) for ^1H and ^{13}C NMR, respectively. Optical rotations were measured with a JASCO DIP-360 polarimeter. Exact mass determinations were obtained with a JEOL-SX 102A instrument. Column chromatography was performed on silica gel 60 PF_{254} (Nacalai Tesque) under pressure.

2-Iodo-*N*-(6-oxocyclohex-1-enyl)-*N*-[(*S*)-1-phenylethyl]acetamide (6):
2-Chloro-*N*-(6-oxocyclohex-1-enyl)-*N*-[(*S*)-1-phenylethyl]acetamide

To a solution of cyclohexane-1,2-dione (1.22 g, 10.9 mmol) in benzene (50 mL) was added (–)-(*S*)-1-phenylethylamine (1.32 g, 10.88 mmol) and the mixture was heated under reflux for 2 h with azeotropic removal of the water thus formed. After the solvent had been evaporated off, the resulting enamine **4** was dissolved in CH_2Cl_2 (30 mL). Chloroacetyl chloride (1.60 g, 14.1 mmol) was added dropwise to the solution at 0 °C and the mixture was stirred at r.t. for 15 h. To the mixture was added sat. $NaHCO_3$ (30 mL) at 0 °C and it was then stirred for 10 min. The organic layer was separated, dried ($MgSO_4$) and concentrated. The residue was chromatographed (silica gel, hexane/EtOAc 2:1) to afford 2-chloro-*N*-(6-oxocyclohex-1-enyl)-*N*-[(*S*)-1-phenylethyl]acetamide (1.69 g, 53%); mp 136–137 °C (hexane/EtOAc).
IR (CCl_4): ν = 1740, 1695, 1660 cm^{-1}.
^1H NMR (60 MHz): δ = 1.38, 1.58 (both d, total 3H, J = 7.0 Hz, CH*Me*), 1.75–2.75 (m, 6H), 3.81 (s, 2H, $COCH_2Cl$), 5.52–6.32 (m, 2H), 7.30 (br s, 5H, ArH).
Anal. Calcd for $C_{16}H_{18}ClNO_2$: C, 65.86; H, 6.22; N, 4.80. Found: C, 65.95; H, 6.22; N, 4.93.

2-Iodo-*N*-(6-oxocyclohex-1-enyl)-*N*-[(*S*)-1-phenylethyl]acetamide (6):
The chloroacetamide (998 mg, 3.42 mmol) obtained above was dissolved in CH_3CN (20 mL), and NaI (5.43 g, 36.2 mmol) was added to the solution which then stirred at r.t. for 5 h. The insoluble material was filtered off and the filtrate concentrated. The residue was chromatographed (silica gel, hexane/EtOAc 2:1) to give **6** (1.20 g, 91%); mp 150–151 °C (hexane/EtOAc).
IR (CCl_4): ν = 1740, 1695 cm^{-1}.
^1H NMR (60 MHz): δ = 1.30, 1.53 (both d, total 3H, J = 7.0 Hz, CH*Me*), 1.6–2.7 (m, 6H), 3.22 and 3.60 (ABq, 1H each, J = 15.0 Hz, $COCH_2I$), 5.45–6.25 (m, 2H), 7.1–7.3 (m, 5H, ArH).
Anal. Calcd for $C_{16}H_{18}INO_2$: C, 50.15; H, 4.73; N, 3.65. Found: C, 50.28; H, 4.80; N, 3.42.

2-Iodo-*N*-[(*S*)-1-(1-naphthyl)ethyl]-*N*-(6-oxocyclohex-1-enyl)acetamide (7):
2-Chloro-*N*-[(*S*)-1-(1-naphthyl)ethyl]-*N*-(6-oxocyclohex-1-enyl)-acetamide

According to the procedure described above for the preparation of **6**, the enamine **5** prepared from cyclohexane-1,2-dione (1.42 g, 12.6 mmol) and (–)-(*S*)-1-(1-naphthyl)ethylamine (2.16 g, 12.6 mmol) was treated with chloroacetyl chloride (1.85 g, 16.4 mmol) to give 2-chloro-*N*-[(*S*)-1-(1-naphthyl)ethyl]-*N*-(6-oxocyclohex-1-enyl)acetamide (2.77 g, 64%) as an oil.
IR (CCl_4): ν = 1690, 1665 cm^{-1}.
^1H NMR (60 MHz): δ = 1.6–2.6 (m, 6H), 1.50 (d, 3H, J = 7.0 Hz, CH*Me*), 3.76 (s, 2H, $COCH_2Cl$), 5.25–5.55 (m, 1H, C=CH), 6.64 (q, 1H, J = 7.0 Hz, C*H*Me), 7.1–8.3 (m, 7H, ArH).
HRMS: Calcd for $C_{20}H_{20}ClNO_2$, 341.1182; found *m/z* 341.1186.

2-Iodo-*N*-[(*S*)-1-(1-naphthyl)ethyl]-*N*-(6-oxocyclohex-1-enyl)acetamide (7):
The chloride (1.06 g, 3.09 mmol) obtained above was treated with NaI (2.32 g, 15.45 mmol) in a manner similar to that described above for the preparation of **6**. After workup, the crude material was chromatographed (silica gel, hexane/EtOAc 2:1) to give compound **7** (684 mg, 51%); mp 176–177 °C (hexane/EtOAc).
IR (CCl_4): ν = 1690, 1650 cm^{-1}.
^1H NMR (60 MHz): δ = 1.6–2.7 (m, 6H), 1.56 (d, 3H, *J* = 7.0 Hz, CH*Me*), 3.28 and 3.70 (ABq, 1H each, *J* = 10.0 Hz, $COCH_2I$), 5.4–5.6 (m, 1H, C=CH), 6.76 (q, 1H, *J* = 7.0 Hz, C*H*Me), 7.3–8.3 (m, 7H, ArH).
Anal. Calcd for $C_{20}H_{20}INO_2$: C, 55.44; H, 4.65; N, 3.23. Found: C, 55.56; H, 4.73; N, 3.04.

(3a*S*,7a*R*)- and (3a*R*,7a*S*)-1-[(*S*)-1-Phenylethyl]octahydroindole-2,7-diones (8a and 8b):
To a boiling solution of **6** (748 mg, 1.95 mmol) in toluene (200 mL) was added a solution of Bu_3SnH (737 mg, 2.54 mmol) and AIBN (64 mg, 0.39 mmol) in toluene (40 mL) via a syringe over 4 h, and the mixture was further heated under reflux for 3 h. After evaporation of the solvent, Et_2O (20 mL) and 8% aq KF (20 mL) were added to the residue, and the mixture was vigorously stirred at r.t. for 30 min. The organic layer was separated, dried ($MgSO_4$) and concentrated. The residue was chromatographed (silica gel, hexane/EtOAc 2:1) to give a mixture of **8a** and **8b** (421 mg, 84%) in a ratio of ca. 2:1 as an oil.
IR (CCl_4): ν = 1700 cm^{-1}.
^1H NMR (300 MHz): δ = 1.44–2.86 (m, 9H), 1.59 (d, 3H × 2/3, *J* = 7.2 Hz, CH*Me* for **8a**), 1.70 (d, 3H × 1/3, *J* = 7.3 Hz, CH*Me* for **8b**), 3.69 (d, 2/3H, *J* = 8.3 Hz, 7a-H for **8a**), 4.02 (d, 1/3H, *J* = 7.1 Hz, 7a-H for **8b**), 5.22 (q, 1/3H, *J* = 7.3 Hz, C*H*Me for **8b**), 5.45 (q, 2/3H, *J* = 7.2 Hz, C*H*Me for **8a**), 7.15–7.40 (m, 5H, ArH).
HRMS: Calcd for $C_{16}H_{19}NO_2$, 257.1416; found *m/z* 257.1424.

(3a*S*,7a*R*)- and (3a*R*,7a*S*)-1-[(*S*)-1-(1-Naphthyl)ethyl]octahydroindole-2,7-diones (9a and 9b):
Following the procedure described above for the preparation of **8a,b**, compound **7** (684 mg, 1.58 mmol) was treated with Bu_3SnH (597 mg, 2.05 mmol) and AIBN (52 mg, 0.32 mmol) in toluene, and the crude material was purified by column chromatography (silica gel, hexane/EtOAc 2:1) to give a mixture of **9a** and **9b** (204 mg, 42%) in a ratio of ca. 3.2:1 as an oil.
IR (CCl_4): ν = 1695 cm^{-1}.
^1H NMR (300 MHz): δ = 1.13–1.94 (m, 6H), 1.75 (d, *J* = 6.9 Hz, CH*Me* for **9b**), 1.86 (d, *J* = 7.1 Hz, CH*Me* for **9a**), 2.06–2.38 (m, 2H), 2.50–2.65 (m, 1H), 3.15 (d, *J* = 8.3 Hz, 7a-H for **9a**), 4.04 (d, *J* = 7.1 Hz, 7a-H for **9b**), 6.06 (q, *J* = 7.3 Hz, C*H*Me for **9a**), 6.19 (q, *J* = 7.1 Hz, C*H*Me for **9b**), 7.35–7.94 (m, 7H, ArH).
HRMS: Calcd for $C_{20}H_{21}NO_2$, 307.1572; found *m/z* 307.1570.

(3a*S*,7*S*,7a*R*)-7-Hydroxy-1-[(*S*)-1-phenylethyl]octahydroindol-2-one (10a) and (3a*R*,7*R*,7a*S*)-7-Hydroxy-1-[(*S*)-1-phenylethyl]-octahydroindol-2-one (10b):
$NaBH_4$ (148 mg, 3.9 mmol) was added slowly to a solution of the mixture of **8a** and **8b** (333 mg, 1.3 mmol) and the mixture was stirred at r.t. overnight. After evaporation of the solvent, brine (10 mL) was added to the residue and it was extracted with EtOAc. The organic layer was dried ($MgSO_4$) and concentrated, and the residue was chromatographed (silica gel, EtOAc). The first fraction gave **10b** (88 mg, 26%) as an oil. The second fraction gave **10a** (155 mg, 46%); mp 141–142 °C (hexane/EtOAc).

10a:
IR (CCl_4): ν = 3400, 1670 cm^{-1}.
^1H NMR (300 MHz): δ = 1.20–1.96 (m, 7H), 1.68 (d, 3H, *J* = 7.3 Hz, CH*Me*), 2.15 (dd, 1H, *J* = 14.9, 8.3 Hz, one of 3-H_2), 2.21–2.34 (m, 1H, 3a-H), 2.66 (dd, 1H, *J* = 14.9, 12.7 Hz, one of 3-H_2), 3.02 (dd, 1H, *J* = 7.1, 3.8 Hz, 7a-H), 4.00 (br s, 1H, 7-H), 5.49 (q, 1H, *J* = 7.3 Hz, C*H*Me), 7.25–7.46 (m, 5H, ArH).
Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.08; H, 8.18; N, 5.55.

10b:
IR (CCl_4): ν = 3600, 1690 cm^{-1}.
^1H NMR (300 MHz): δ = 1.11–1.30 (m, 2H), 1.46–1.79 (m, 5H), 1.60 (d, 3H, *J* = 7.3 Hz, CH*Me*), 2.14 (dd, 1H, *J* = 15.0, 8.0 Hz, one of 3-H_2), 2.27–2.48 (m, 1H, 3a-H), 2.59 (dd, 1H, *J* = 14.9, 13.0 Hz, one of 3-H_2), 3.05–3.12 (m, 1H, 7-H), 3.47 (dd, 1H, *J* = 7.3, 3.7 Hz, 7a-H), 5.71 (q, 1H, *J* = 7.3 Hz, C*H*Me), 7.27–7.56 (m, 5H, ArH).
HRMS: Calcd for $C_{16}H_{21}NO_2$, 259.1572; found *m/z* 259.1570.

(3a*S*,7a*R*)-1-[(*S*)-1-Phenylethyl]-2,3,3a,4,5,7a-hexahydroindol-2-one (11):
Martin sulfurane (3.2 g, 4.75 mmol) was added to a solution of **10a** (308 mg, 1.19 mmol) in benzene (10 mL) and the mixture was heated to 50 °C for 2 h. Sat. $NaHCO_3$ (10 mL) was added to the mixture and it was extracted with Et_2O. The extract was dried ($MgSO_4$) and concentrated, and the residue was chromatographed (silica gel, hexane/EtOAc 3:1) to give **11** (211 mg, 74%) as an oil.
IR (CCl_4): ν = 1685 cm^{-1}.
^1H NMR (300 MHz): δ = 1.52–1.71 (m, 2H), 1.60 (d, 3H, *J* = 7.2 Hz, CH*Me*), 1.82–2.15 (m, 2H), 2.24–2.36 (m, 1H), 2.31 (dd, 1H, *J* = 17.8, 6.5 Hz, one of 3-H_2), 2.45 (dd, 1H, *J* = 17.8, 10.0 Hz, one of 3-H_2), 3.62–3.68 (m, 1H, 7a-H), 5.53–5.60 (m, 1H), 5.54 (q, 1H, *J* = 7.2 Hz, C*H*Me), 5.83–5.90 (m, 1H), 7.27–7.40 (m, 5H, ArH).
HRMS: Calcd for $C_{16}H_{19}NO$, 241.1467; found *m/z* 241.1464.

(3a*S*,7a*R*)-2,3,3a,4,5,7a-Hexahydroindol-2-one (12):
Na (134 mg, 5.83 mmol) and a solution of **11** (281 mg, 1.16 mmol) in anhyd THF (3 mL) were added successively to liquid NH_3 (ca. 3 mL) at –78 °C, and the mixture was stirred at the same temperature for 1.5 h. The reaction was quenched by addition of NH_4Cl, and then allowed to warm to r.t. to remove any excess NH_3. The salts were filtered off and washed with Et_2O. The combined organic layer was concentrated and the residue was chromatographed (silica gel, hexane/EtOAc 1:2) to give **12** (132 mg, 83%); mp 103.5–105 °C (hexane/EtOAc); $[\alpha]_D^{22}$ +173.4 (*c* = 1.05, EtOH).
IR ($CHCl_3$): ν = 3480, 1690 cm^{-1}.
^1H NMR (300 MHz): δ = 1.51–1.76 (m, 2H, 4-H_2), 1.92–2.20 (m, 2H, 5-H_2), 2.13 (dd, 1H, *J* = 16.1, 4.6 Hz, one of 3-H_2), 2.48 (dd, 1H, *J* = 15.9, 8.1 Hz, one of 3-H_2), 2.50–2.62 (m, 1H, 3a-H), 4.00–4.06 (br, 1H, 7a-H), 5.65–5.72 (m, 1H), 5.91–5.99 (m, 1H), 6.78–7.02 (br, 1H, NH).
^{13}C NMR (75.4 MHz): δ = 22.3 (CH_2), 24.1 (CH_2), 33.0 (CH), 36.1 (CH_2), 51.5 (CH), 125.2, 130.7, 177.7 (CO).
Anal. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.01; H, 8.11; N, 10.49.

(3a*S*,7a*R*)-1-[2-Bromo-4,5-(methylenedioxy)benzyl]-2,3,3a,4,5,7a-hexahydroindol-2-one (13):
To a suspension of NaH (60% mineral oil dispersion) (58 mg, 1.44 mmol) [washed with anhyd pentane (3 × 3 mL) before use] in anhyd DMF (3 mL) was added dropwise a solution of **12** (132 mg, 0.96 mmol) in anhyd DMF (3 mL) at r.t., and the mixture was stirred at the same temperature for 30 min. A solution of 2-bromo-4,5-(methylenedioxy)benzyl chloride (240 mg, 0.96 mmol) was added and the mixture was stirred at r.t. for 30 min. The mixture was poured into water (10 mL) and extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed (silica gel, hexane/EtOAc 3:2) to give **13** (337 mg, quant.), whose spectral data were identical with those reported for the corresponding (3a*R*,7a*S*) enantiomer.[8]
IR ($CHCl_3$): ν = 1675 cm^{-1}.

^{1}H NMR (300 MHz): δ = 1.52–1.78 (m, 2H), 1.93–2.18 (m, 2H), 2.30 (dd, 1H, J = 15.1, 4.6 Hz, one of 3-H_2), 2.43–2.54 (m, 1H), 2.56 (dd, 1H, J = 15.1, 8.1 Hz, one of 3-H_2), 3.83–3.89 (m, 1H, 7a-H), 4.27 and 4.78 (ABq, 1H each, J = 15.5 Hz, NCH_2Ar), 5.70–5.78 (m, 1H), 5.93–6.01 (m, 1H), 5.97 (s, 2H, OCH_2O), 6.76 (s, 1H, ArH), 6.98 (s, 1H, ArH).

(3a*S*,11b*R*,11c*R*)-9,10-(Methylenedioxy)-1,2,3,3a,4,5,11b,11c-octahydropyrrolo[3,2,1-*de*]phenanthridin-5-one (14):
A solution of Bu_3SnH (125 mg, 0.43 mmol) and AIBN (9 mg, 0.05 mmol) in benzene (20 mL) was added to a boiling solution of **13** (100 mg, 0.29 mmol) in benzene (30 mL) over a period of 2 h via a syringe, and the mixture was further heated under reflux for 1 h. After workup as described above for the preparation of **8a,b**, the crude material was chromatographed (silica gel, hexane/EtOAc 3:2) to give **14** (40 mg, 52%), whose spectral data were identical to those reported for the corresponding (3a*R*,11b*S*,11c*S*) enantiomer.[9]
IR ($CHCl_3$): ν = 1670 cm^{-1}.
^{1}H NMR (300 MHz): δ = 1.08–1.44 (m, 3H), 1.67–1.82 (m, 3H), 2.09 (d, 1H, J = 16.1 Hz), 2.38–2.47 (m, 1H), 2.58 (dd, 1H, J = 16.1, 6.8 Hz), 2.75 (dt, 1H, J = 12.5, 4.2 Hz), 3.77 (t, 1H, J = 4.6 Hz), 4.32 and 4.54 (ABq, 1H each, J = 17.4 Hz, NCH_2Ar), 5.92 (d, 1H, J = 1.4 Hz), one of OCH_2O), 5.94 (d, 1H, J = 1.4 Hz, one of OCH_2O), 6.59 (s, 1H, ArH), 6.62 (s, 1H, ArH).
^{13}C NMR (75.4 MHz): δ = 23.6 (CH_2), 27.8 (CH_2), 30.3 (CH_2), 33.0 (CH), 39.8 (CH_2), 40.3 (CH), 42.7 (CH_2), 55.7 (CH), 101.0 (CH_2), 106.6 (CH), 108.5 (CH), 123.2, 131.6, 146.6, 147.7, 175.7 (CO).

(–)-γ-Lycorane (15):
To a suspension of $LiAlH_4$ (28 mg, 0.74 mmol) in anhyd THF (3 mL) was added dropwise a solution of **14** (100 mg, 0.23 mmol) in anhyd THF (4 mL) at 0 °C and the mixture was stirred at r.t. for 1.5 h. The mixture was poured into Et_2O and made alkaline with 5% aq NH_4OH. The resulting precipitate was filtered off and the filtrate was washed with brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed (silica gel, $CHCl_3$/MeOH 20:1) to give **15** (24 mg, 64%) as an oil, whose spectral data were identical with those reported for (+)-γ-lycorane;[9] $[\alpha]_D^{22}$ –14.8 (c = 0.99, EtOH) {Lit.[7] $[\alpha]_D^{20}$ –17.1 (c = 0.25, EtOH)}.
IR ($CHCl_3$): ν = 2950, 1480 cm^{-1}.
^{1}H NMR (300 MHz): δ = 1.23–1.54 (m, 4H), 1.59–1.81 (m, 3H), 1.95–2.07 (m, 1H), 2.09–2.24 (m, 2H), 2.37 (t, 1H, J = 4.8 Hz, 11c-H), 2.70–2.78 (m, 1H, 11b-H), 3.21 (d, 1H, J = 14.4 Hz, one of 7-H_2), 3.38 (ddd, 1H, J = 9.3, 9.2, 3.8 Hz, one of 5-H_2), 4.02 (d, 1H, J = 14.4 Hz, one of 7-H_2), 5.88 and 5.89 (ABq, 1H each, J = 1.4 Hz, OCH_2O), 6.49 (s, 1H, ArH), 6.61 (s, 1H, ArH).
^{13}C NMR (75.4 MHz): δ = 25.2 (CH_2), 29.3 (CH_2), 30.4 (CH_2), 31.7 (CH_2), 37.4 (CH), 39.5 (CH), 53.7 (CH_2), 57.1 (CH_2), 62.9 (CH), 100.7 (CH_2), 106.3 (CH), 108.3 (CH), 127.3, 133.2, 145.6, 146.0.

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture of Japan and Ciba-Geigy Foundation (Japan) for the Promotion of Science (H.I.)

(1) Porter, N. A.; Lacher, B.; Chang, V. H.-T.; Magnin, D. R. *J. Am. Chem. Soc.* **1989**, *111*, 8309.
Curran, D. P.; Shen, W.; Zhang, J.; Heffner, T. A. *J. Am. Chem. Soc.* **1990**, *112*, 6738.
Takano, S.; Suzuki, M.; Kijima, A.; Ogasawara, K. *Tetrahedron Lett.* **1990**, *31*, 2315.
Stack, J. G.; Curran, D. P.; Geib, S. J.; Rebek, J. Jr.; Ballester, P. *J. Am. Chem. Soc.* **1992**, *114*, 7007.
Zahouily, M.; Journet, M.; Malacria, M. *Synlett* **1994**, 366.
Curran, D. P.; Shen, W.; Zhang, J.; Geib, S. V.; Lin, C.-H. *Heterocycles* **1994**, *37*, 2315.
Cardillo, B.; Galeazzi, R.; Mobbili, G.; Orena, M.; Rossetti, M. *Heterocycles* **1994**, *38*, 2663.
Curran, D. P.; Geib, S. J.; Lin, C.-H. *Tetrahedron: Asymmetry* **1994**, *5*, 199.
Nishida, M.; Ueyama, E.; Hayashi, H.; Ohtake, Y.; Yamaura, Y.; Yanaginuma, E.; Yonemitsu, O.; Nishida, A.; Kawahara, N. *J. Am. Chem. Soc.* **1994**, *116*, 6455.
Nishida, M.; Hayashi, H.; Yamaura, Y.; Yanaginuma, E.; Yonemitsu, O.; Nishida, A.; Kawahara, N. *Tetrahedron Lett.* **1995**, *36*, 269.
Nishida, M.; Hayashi, H.; Yonemitsu, O.; Nishida, A.; Kawahara, N. *Synlett* **1995**, 1045.
Nishida, M.; Nobuta, M.; Nakaoka, K.; Nishida, A.; Kawahara, N. *Tetrahedron: Asymmetry* **1995**, *6*, 2657.
Nishida, M.; Hayashi, H.; Nishida, A.; Kawahara, N. *J. Chem. Soc., Chem. Commun.* **1996**, 579.
Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron* **1996**, *52*, 1069.
Galeazzi, R.; Geremia, S.; Mobbili, G.; Orena, M. *Tetrahedron: Asymmetry* **1996**, *7*, 3573.
Katsumata, A.; Iwaki, T.; Fukumoto, K.; Ihara, M. *Heterocycles* **1997**, *46*, 605.
Lee, E.; Jeong, J.-W.; Yu, Y. *Tetrahedron Lett.* **1997**, *38*, 7765.
(2) Ishibashi, H.; Kameoka, C.; Iriyama, H.; Kodama, K.; Sato, T.; Ikeda, M. *J. Org. Chem.* **1995**, *60*, 1276.
Ishibashi, H.; Kameoka, C.; Kodama, K.; Ikeda, M. *Tetrahedron* **1996**, *52*, 489.
Ishibashi, H.; Kodama, K.; Kameoka, C.; Kawanami, H.; Ikeda, M. *Tetrahedron* **1996**, *52*, 13867.
Ishibashi, H.; Kawanami, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 817.
Ishibashi, H.; Kameoka, C.; Kodama, K.; Kawanami, H.; Hamada, M.; Ikeda, M. *Tetrahedron* **1997**, *53*, 9611.
(3) Ishibashi, H.; Fuke, Y.; Yamashita, T.; Ikeda, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2531.
(4) Absolute configuration of **2a** and **2b** was deduced from the results with the *N*-[(*S*)-1-(1-naphthyl)ethyl] congener of **1**, which gave the corresponding (3a*R*,7a*R*)-octahydroindol-2-one as the major product.
(5) Viehe, H. G.; Merenyi, R.; Stella, L.; Janousek, Z. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 917.
(6) For a review, see: Martin, S. F. In *The Alkaloids*; Brossi, A. Ed.; Academic: New York, **1987**; Vol. 30, pp 251–376.
(7) Kotera, K. *Tetrahedron* **1961**, *12*, 248.
(8) For recent syntheses of racemic γ-lycorane, see:
Bäckvall, J.-E.; Andersson, P. G.; Stone, G. B.; Gogoll, A. *J. Org. Chem.* **1991**, *56*, 2988.
Pearson, W. H.; Schkeryantz, J. M. *J. Org. Chem.* **1992**, *57*, 6783.
Grotjahn, D. B.; Vollhardt, K. P. C. *Synthesis* **1993**, 579.
Banwell, M. G.; Wu, A. W. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2671.
Angle, S. R.; Boyce, J. P. *Tetrahedron Lett.* **1995**, *36*, 6185.
(9) Synthesis of (+)-γ-lycorane has been reported by Mori and coworkers. See:
Yoshizaki, H.; Satoh, H.; Sato, Y.; Nukui, S.; Shibasaki, M.; Mori, M. *J. Org. Chem.* **1995**, *60*, 2016.
(10) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 2341.
For a recent example of the use of Martin sulfurane in total synthesis, see:
Paquette, L. A.; Sun, L.-Q.; Friedrich, D.; Savage, P. B. *J. Am. Chem. Soc.* **1997**, *119*, 8438.