Palladium-Mediated Asymmetric Synthesis of *Cis*-3,6-Disubstituted Cyclohexenes. A Short Total Synthesis of Optically Active (+)-γ-Lycorane

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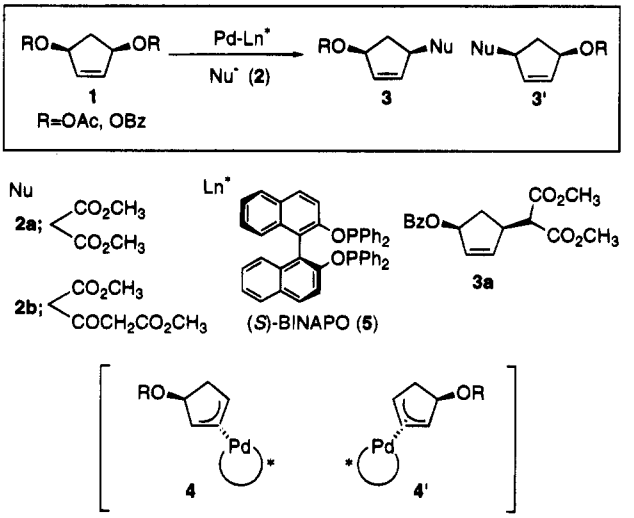
An asymmetric alkylation of the cyclohexenediol derivative **6** with **2c** or **2d** using a catalytic amount of $Pd(OAc)_2$ in the presence of (*S*)-BINAPO was achieved. The alkylation products **15** (49% ee, 53% yield) and **25** (40% ee, 63% yield) were further treated with a palladium catalyst to give the oxindole derivatives **14** and **26**. The absolute configuration of the monoalkylated product **15** was determined by the CD exiton method. From **6**, a total synthesis of (+)-γ-lycorane (**9**) was accomplished in five steps in 23% overall yield and 46% ee.

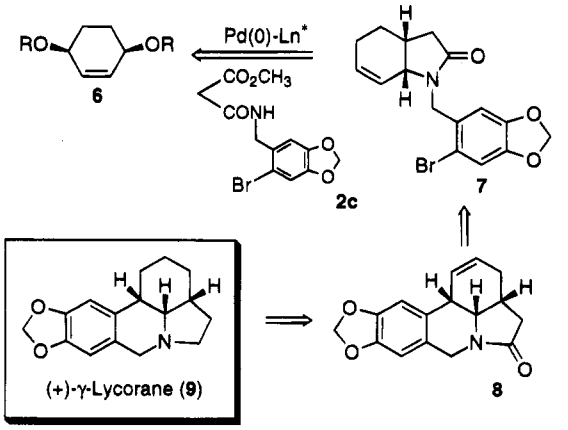
Transition metals have become important tools for carbon–carbon bond formation in synthetic organic chemistry.[1] Palladium-catalyzed allylic alkylation is a particularly useful method for the activation of allylic substrates,[2] and many asymmetric alkylations that employ the π-allyl palladium complex in the presence of a chiral ligand have been reported.[3] We have previously described[4] a catalytic asymmetric synthesis of cyclopentanoids **3** from the cyclopentenediol derivatives **1** using π-allyl palladium complex **4** with palladium(0) and (*S*)-BINAPO (**5**)[5] as a chiral ligand. Thus, the cyclopentene derivatives **13** and **3a** were obtained from **1** (R = COOPh) and **2b**, and **1** (R = COPh) and **2a**, in 72% yield with 55% ee, and in 38% yield with 57% ee, respectively.[4]

On the basis of these results, it was envisioned that treatment of cyclohexenediol derivative **6** with **2c** in the presence of a palladium(0) catalyst with a chiral phosphine ligand would afford an oxindole derivative **7**. The successful preparation of **7** could lead to the total synthesis of (+)-γ-lycorane (**9**). Namely, the palladium-catalyzed cyclization of compound **7** would stereoselectively construct the lycorane framework **8**, which may be converted into (+)-γ-lycorane (**9**).

Scheme 1



Scheme 2



Cyclohexene exists as the half-chair forms **IA** and **IB**, which interconvert *via* a half-boat form.[6] The low-valent palladium complex attacks at the back side of the leaving group[7] to produce a π-allyl palladium complex. The carbon nucleophile then attacks from the back side of the palladium complex. In the formation of the π-allyl

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(2) Trost, B. M. *Angew. Chem.* **1989**, *28*, 1173–1192 and references therein.
(3) (a) Hayashi,T.; Kumada, M. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press, Oxford, **1985**; Vol. 5, pp 147–169. Hayashi, T.; Hagihara, T.; Konishi, M.; Kumada, M. *J. Am. Chem. Soc.* **1983**, *105*, 7767–7768. Hayashi, T.; Yamamoto, A.; Ito, Y. *Tetrahedron Lett.* **1988**, *29*, 669–672. (b) Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1990**, *112*, 1261–1263. Trost B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143–1145. Trost, B. M.; Li, L.; Guile, S. D. *J. Am. Chem. Soc.* **1992**, *114*, 8745–8747. Trost, B. M.; Van Vranken, L.; Bingle, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327–9343. Trost, B. M.; Van Vranken D. L. *J. Am. Chem. Soc.* **1993**, *115*, 444–458. Trost, B. M.; Van Vranken D. L. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 228–230. (c) Mackenzie, P. B.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2046–2054. (d) Genet, J. P.; Ferroud, S.; Juge, S.; Montes, J. R. *Tetrahedron Lett.* **1986**, *27*, 4573–4576. (e) Reiser, O. *Angew. Chem. Int. Ed., Engl.* **1993**, *32*, 547–549. (f) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769–1772. (g) Fiaud, J-E.; Legros, J-Y. *J. Org. Chem.* **1990**, *55*, 4840–4846. (h) Kubota, H.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1993**, *34*, 8135–8138.
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(5) (a) Grubbs, R. H.; Devries, R. A. *Tetrahedron Lett.* **1977**, 1879–1880. (b) Trost, B. M.; Murphy, D. J. *Organometallics* **1990**, *4*, 1143–1146.
(6) Chiang, J. F.; Bauer, S. H. *J. Am. Chem. Soc.* **1969**, *91*, 1898–1901.

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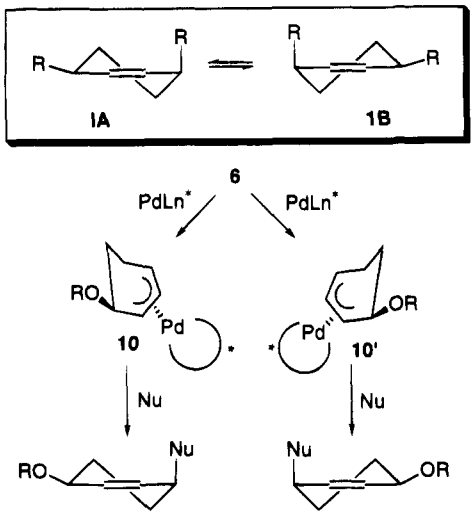
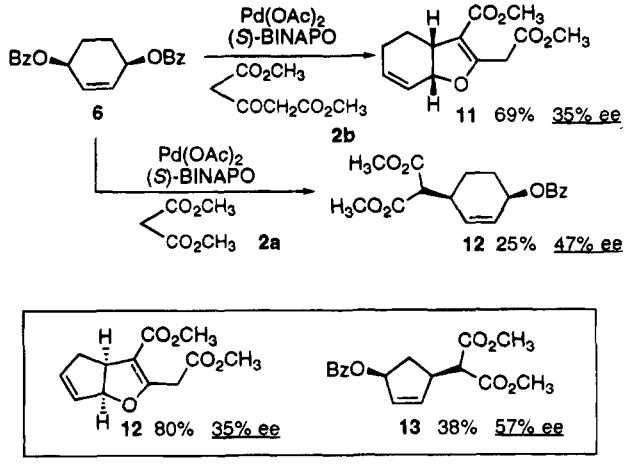
Scheme 3



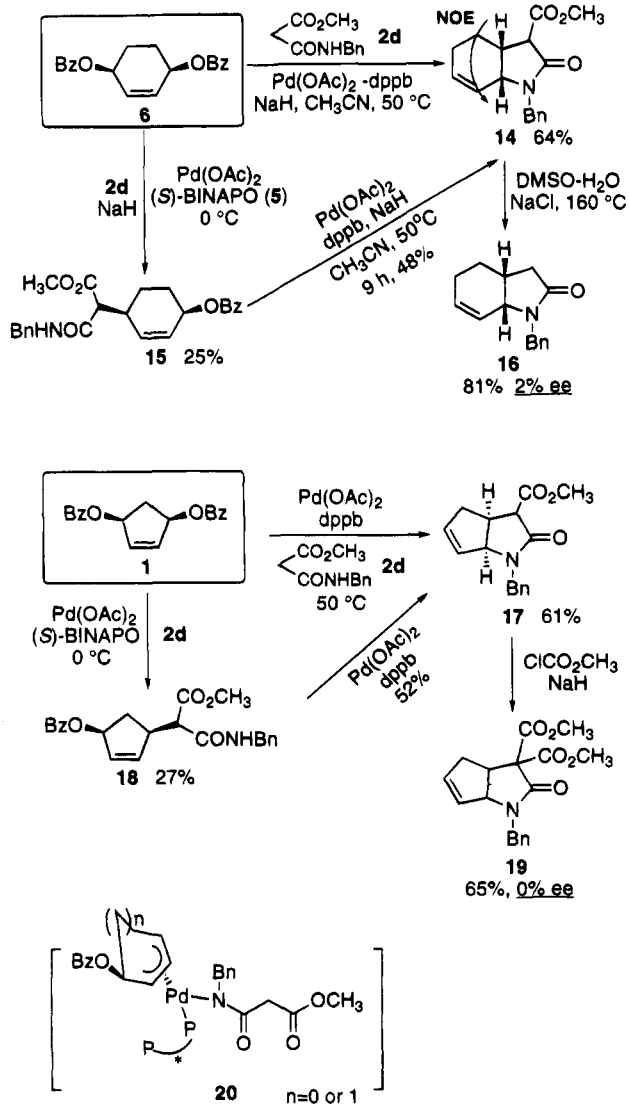
Scheme 4



palladium complex, a leaving group in the axial position of the cyclohexene ring, whose C–O bond is approximately parallel to the p-orbital of the C=C bond, is far more reactive toward the palladium complex than a leaving group in the equatorial position (orthogonal to that of the C=C bond).[8] As a result, the nucleophile is introduced in the same position formerly occupied by the leaving group, as shown in Scheme 3. If the palladium catalyst is coordinated by a chiral ligand, an asymmetric alkylation of the cyclohexene diol derivatives would be realized.

A Catalytic Asymmetric Synthesis of an Oxindole Derivative. As a preliminary study, the asymmetric alkylation of the cyclohexene derivative **6** with a palladium catalyst and a chiral ligand was examined. When an CH_3CN solution of **6**, the sodium salt of **2b**, $Pd(OAc)_2$ (5 mol %), and (*S*)-BINAPO (10 mol %) was stirred at room temperature, the cyclized product **11** was obtained in 69% yield (Scheme 4). The enantiomeric excess of **11**

Scheme 5



was determined to be 35% ee by HPLC using a chiral stationary phase column (CHIRALCEL OJ, hexane/iPrOH = 9/1). In a similar manner, compound **6** was treated with the sodium salt of dimethyl malonate **2a** to give monoalkylated product **12** in 25% yield with 47% ee. These ee values are almost the same as those of the products, **13** and **3a**, obtained by the reaction of the cyclopentenediol derivative **1** (R = COPh) and **2b** or **2a** in the presence of $Pd(OAc)_2$ and (*S*)-BINAPO under the same reaction conditions [**13**; 80% yield (35% ee), **3a**; 38% yield (57% ee)].[4] These results suggest that asymmetric alkylation can be successfully applied to the cyclohexenediol derivative **6**.

Subsequently, the synthesis of oxindole derivative **14** was examined by the reaction of cyclohexenediol derivative **6** with amide **2d** in the presence of a palladium catalyst. An CH_3CN solution of **6**, the sodium salt of **2d** (2.6 equiv), a catalytic amount of $Pd(OAc)_2$ (6 mol %), and dppb [1,4-bis(diphenylphosphino)butane, 12 mol %] in CH_3CN was warmed at 50 °C for 2 h. After the usual workup, the desired oxindole derivative **14** was obtained in 64% yield (Scheme 5). The structure of **14** was confirmed by the spectral data, and a NOE experiment suggested that the ring junction of the six- and five-membered rings in **14** is *cis*. The reaction was then investigated in the presence of (*S*)-BINAPO (**5**) as a chiral

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(8) Fiaud, J-C.; A-Zouioueche, L. *J. Chem. Soc., Chem. Commun.* **1986**, 390–392.

Scheme 6

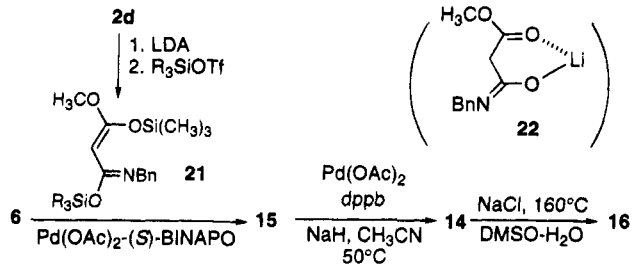


Table 1. Reaction of 6 with 2d[a]

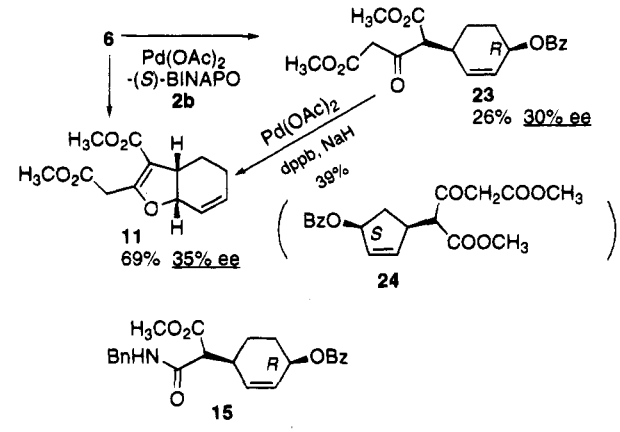
run	amide (equiv)	base (equiv)	additive	temp (°C)	time (h)	yield of 15 (%)	ee (%)
1	2.7	NaH (2.7)	–	0	92	25	2
2	2.7	LDA (2.7)	Et_3SiOTf	0	42	62	26
3	2.7	LDA (2.7)	$Me_2{}^tBuSiOTf$	0	42	54	26
4	2.6	LDA (2.6)	–	0	18	20	57
5	1.3	LDA (1.3)	–	0	19	53	49
6	1.1	LDA (1.1)	–	0	12	60	42
7	1.1	LDA (1.1)	–	−20	66	66	41

[a] All reactions were carried out in CH_3CN in the presence of $Pd(OAc)_2$ (5 mol %) and (*S*)-BINAPO (10 mol %).

ligand, at 0 °C. However, the desired oxindole derivative **14** did not result, and the monoalkylated product **15** was obtained in 25% yield. Compound **15** was further treated with NaH, $Pd(OAc)_2$, and dppb in CH_3CN at 50 °C for 9 h to give **14** in 64% yield. Decarbomethoxylation of compound **14** with NaCl in wet DMSO proceeded smoothly to give compound **16** in 81% yield. The enantiomeric excess of compound **16** was determined to be 2% by HPLC with a chiral stationary phase column (DAICEL CHIRALPAK AD, hexane/iPrOH = 9/1). Because the asymmetric alkylation of **6** with **2d** was unsuccessful, the asymmetric alkylation of the cyclopentenediol derivative **1** with **2d** was examined. An CH_3CN solution of **1** was warmed with **2d** in the presence of $Pd(OAc)_2$ and dppb at 50 °C to give compound **17** in 61% yield. A similar reaction was then carried out in the presence of (*S*)-BINAPO at 0 °C to give the monoalkylated product **18** in 27% yield, which was converted into **17** by palladium-catalyzed cyclization in 52% yield. In order to determine the enantiomeric excess of compound **18**, compound **17** was converted into **19** by treatment with NaH and ClCOOMe. However, compound **19** was found to be racemic product (DAICEL CHIRALPAK AD, hexane/iPrOH = 9/1).

The reason that the use of amide **2d** as the nucleophile did not give rise to asymmetric induction may be that the amide anion coordinates to the palladium catalyst, and partial dissociation of the chiral ligand occurs to give palladium species **20** (i.e. a function of the nature of the ion pair of the attacking nucleophile[9]). Initially, the reaction of cyclohexenediol derivative **6** with the amide protected by a silyl group was examined. A THF solution of compound **21**, which was prepared from **2d** by treatment with LDA and Et_3SiOTf[10] at −78 °C, was added to an CH_3CN solution of **6**, $Pd(OAc)_2$ and (*S*)-BINAPO, and the solution was stirred at 0 °C to give **15** in 62% yield (Scheme 6). The enantiomeric excess of **15** was determined by conversion of **15** into **16** to be 26% ee (Table 1, run 2). The amide protected by a $^tBuMe_2Si$ group afforded the desired product **15** in 54% yield with 26% ee (run 3). It was surprising that when the reaction was carried out in the presence of LDA without R_3SiOTf, **15** with 57% ee was obtained in 20% yield (run 4). The amount of LDA affects the ee of **15** (runs 4−6). Lower temperature did not affect the ee of **15** (run 7). So, the asymmetric alkylation was realized by use of disilylated amide **21**, which could not coordinate to the palladium catalyst. The lithium cation, formed from the amide **2d** and LDA, might also promote the asymmetric induction because the lithium cation would bind the enol-oxygen and be coordinated by the ester oxygen, making the intended nucleophile (see Scheme 6, **22**).

Scheme 7



Determination of the Absolute Configuration. The assignment of the absolute configuration of **15** was achieved by application of the CD exiton chirality method to its allyl benzoate.[11] The CD spectrum of allyl benzoate **15** at 230 nm showed a positive Cotton effect. Thus the absolute configuration of the carbon bearing the benzoyloxy group of **15** was determined to be *R*. The CD spectra of the allyl benzoates **3a** and **24** (which could be converted into **13**) at 230 nm showed negative Cotton effects.[3] Thus, the absolute configuration of **11** was determined as follows: the CD spectrum of compound **23**, which was obtained from **6** and **2b** in the presence of $Pd(OAc)_2$−(*S*)-BINAPO at 0 °C, showed a positive Cotton effect at 230 nm. This indicates that the absolute configuration of the carbon bearing the benzoyloxy group of **23** is *R*. Compound **23** was converted into **11** by treatment with $Pd(OAc)_2$−dppb in the presence of NaH (Scheme 7). The HPLC of the product **11**, obtained directly from **6** with palladium catalyst and (*S*)-BINAPO, showed behavior similar to that of the product obtained from **23**. Thus, the absolute configuration of compound **11** was also determined. These results are quite interesting because the opposite asymmetric inductions occur in the cyclopentenediol derivative **1** and in the cyclohexenediol derivative **6**, in spite of the use of same chiral ligand, (*S*)-BINAPO, in all of these reactions. Mechanistic studies of the asymmetric induction of the cyclopentenediol derivative **1** and the cyclohexenediol derivative **6** are now under way.

Total Synthesis of (+)-γ-Lycorane. γ-Lycorane (**9**) is representative of the lycorane class of Amaryllidaceae alkaloids.[12] All of the ring junctures of γ-lycorane are *cis*. The total synthesis of racemic γ-lycorane was

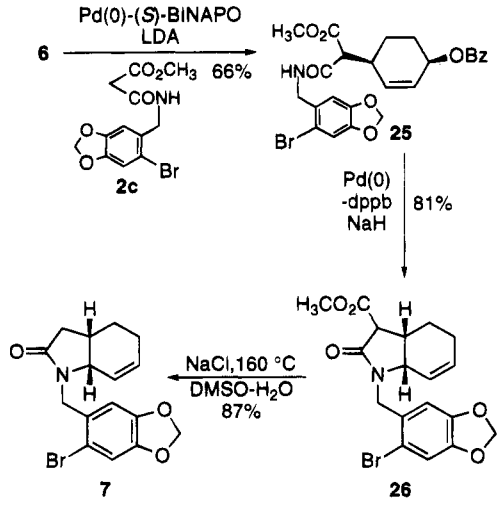
(9) Trost, B. M.; Bunt, R. C. *J. Am Chem. Soc.* **1994**, *116*, 4089−4090.

(10) Because the halide ion would coordinate to the palladium catalyst, Et_3SiOTf or $^tBuMe_2SiOTf$ was used as the silylation reagent.

(11) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy - Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983.

(12) Review of the Amaryllidaceae alkaloids: Martin, S. F. In *The Alkaloids*; Brossi, A. Ed.; Academic Press: New York, 1987; Vol. 30, pp 251−376.

Scheme 8



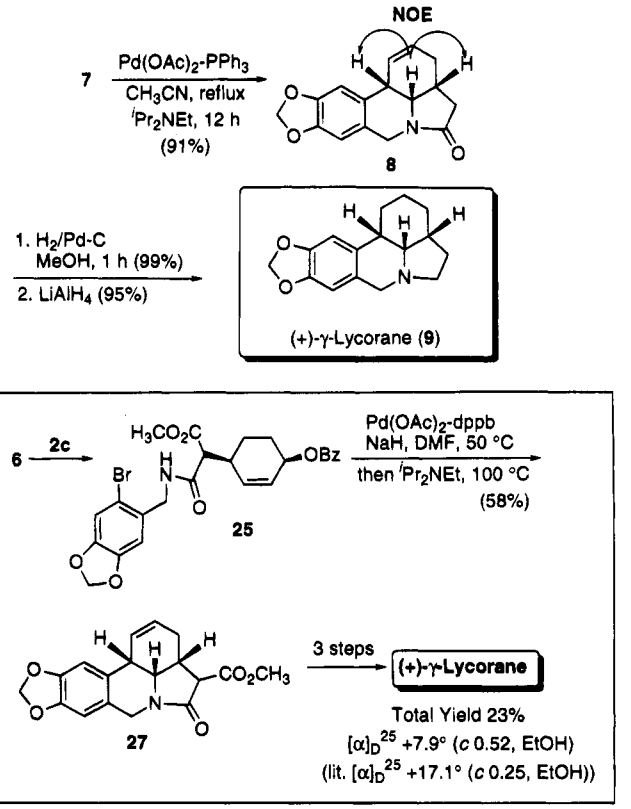
achieved by several groups,[13] and an effective total synthesis of γ-lycorane (**9**) has been recently reported.[13i] However, the total synthesis of optically active γ-lycorane has not yet been accomplished.

In order to synthesize (+)-γ-lycorane (**9**), the reaction of **6** with **2c** was carried out in the presence of $Pd(OAc)_2$ and (*S*)-BINAPO with LDA (1.1 equiv) as base. The desired monoalkylated product **25** was obtained in 66% yield, which was converted into **7** as shown in Scheme 8. The ee of **7** was determined by HPLC to be 40%. In this case, the amount of LDA also affected the ee (2.6 equiv of LDA; 54% ee, 30% yield) of **25**.

The final phase of the synthesis of (+)-γ-lycorane from **7** was carried out. An CH_3CN solution of compound **7**, a catalytic amount of $Pd(OAc)_2$, and PPh_3 were refluxed in the presence of $^iPr_2NEt$ for 12 h to give the tetracyclic compound **8** in 91% yield. The stereochemistry of compound **8** was determined from a NOE experiment. As expected, all ring junction protons are *cis*. Hydrogenation of compound **8** with palladium on charcoal in MeOH followed by treatment with $LiAlH_4$ provided (+)-γ-lycorane (**9**) in 94% yield in two steps. The spectral data of **9** agreed with those described in the literature.[13i] Thus, the total synthesis of (+)-γ-lycorane (**9**) was achieved using palladium-catalyzed alkylation followed by a palladium-catalyzed Heck reaction as the key steps, in 17% overall yield from **6**.

Finally, the short total synthesis of (+)-γ-lycorane was examined. A DMF solution of compound **25** was warmed with NaH, $Pd(OAc)_2$, and dppb in DMF at 50 °C for 2 h, and then $^iPr_2NEt$ was added to the solution. The solution was further warmed at 100 °C for 4 h to give tetracyclic compound **27** in 58% yield from **25** (Scheme 9). Decarbomethoxylation of compound **27** was carried out in the presence of NaCl in wet DMSO at 160 °C for 6 h to give compound **8** in 64% yield, and thus (+)-γ-lycorane was obtained in just more two steps. Consequently, the total synthesis of (+)-γ-lycorane from **6** has been accomplished in 5 steps in 23% overall yield and 46% ee [$[\alpha]_D$ +7.87 (*c* 0.52, EtOH), lit.[14] $[\alpha]_D$ +17.1 (*c* 0.25, EtOH)].

Scheme 9. Total Synthesis of (+)-γ-Lycorane



Experimental Section

All manipulations were performed under an argon atmosphere. Solvents were distilled under an argon atmosphere from sodium benzophenone (THF, ether) or CaH_2 [CH_3CN, CH_2Cl_2, diisopropylamine, diisopropylethlamine, DMF, DMSO]. All other reagents and solvents were purified when necessary using standard procedures. Column chromatography was performed on silica gel 60 (70–230 mesh, 60 Å) and flash chromatography was performed on silica gel 60 (230–400 mesh, 60 Å) using the indicated solvents.

General Procedure for the Palladium-Catalyzed Allylation. To a stirred solution of the nucleophile (1.1–2.6 equiv) and NaH (60% oil dispersion) or the other base in an appropriate solvent at 0 °C was added dropwise the solution of the substrate, $Pd(OAc)_2$ (2–6 mol %), and the ligand (4–12 mol %) at 0 °C. Then the solution was stirred for 10 h at an appropriate temperature. To the reaction mixture was added 5% HCl at 0 °C and the aqueous layer was extracted with Et_2O or AcOEt. The organic layer was washed successively with a solution of saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography to afford the product.

General Procedure for Decarbomethoxylation. To a solution of the substrate in DMSO and H_2O was added NaCl and the mixture was heated at 160 °C. After cooling, H_2O was added and the aqueous solution was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4,

(13) (a) Ueda, N.;Tokuyama, T.; Sakan, T. *Bull Chem. Soc. Jpn.* **1966**, *39*, 2012–2014. (b) Irie, H.; Nishitani, Y.; Sugita, M.; Uyeo, S. *J. Chem. Soc., Chem. Commun.* **1970**, 1313–1314. Tanaka, H.; Nagai, Y.; Irie, H.; Uyeo, S.; Kuno, A. *J. Chem. Soc., Perkin Trans. 1* 1979, 874–878. (c) Genem, B. *Tetrahedron Lett.* **1971**, 4105–4108. (d) Hara, H.; Hoshino, O.; Umezawa, B. *Tetrahedron Lett.* **1972**, 5031–5034. Umezawa, B.; Hoshino, O.; Sawaki, S.; Sato, S.; Numao, N. *J. Org. Chem.*, **1977**, *42*, 4272–4275. (e) Iida, H.; Aoyagi, S.; Kibayashi, C. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2502–2506. Iida, H.; Yuasa, Y,; Kibayashi, C. *J. Am. Chem. Soc.* **1978**, *100*, 3598–3599. Iida, H.; Yuasa, Y.; Kibayashi, C. *J. Org. Chem.*, **1974**, *44*, 1074–1080. (f) Hwang, G.; Magnus, P. *J. Chem. Soc., Chem. Commun.* **1983**, 693–694. (g) Higashiyama, H.; Honda, T.; Otomasu, H.; Kametani, T. *Planta Med.* **1983**, *48*, 268271. (h) Sugiyama, N.; Narima, M.; Iida, H.; Kikuchi, T. *J. Hetrocycl. Chem.* **1988**, *25*, 1455–1457. (i) Bäckvall, J. E.; Anderson, P. A.; Stone, G. B.; Gogoll, A. *J. Org. Chem.* **1991**, *56*, 2988–2993. (j) Pearson, W. H.; Schkeryantz, J. M. *J. Org. Chem.* **1992**, *57*, 6783–6789. (k) Grotjahn, D. B.; Vollhardt, K. P. *Synthesis* **1993**, 579–609.

(14) Kotera, K. *Tetrahedron* **1961**, *12*, 248–261.

and concentrated. The residue was purified by column chromatography to afford the desired decarbomethoxylated product.

General Procedure for the Cyclization of Monoalkylation Product. To a stirred suspension of NaH (60% oil dispersion) in CH_3CN at 0 °C was added dropwise the solution of monoalkylation product in CH_3CN, and the solution was stirred at room temperature for 30 min. To the solution was added dropwise the solution of $Pd(OAc)_2$ and dppb in CH_3CN at 0 °C. Then the solution was stirred at 50 °C for 1.5 h. After a similar workup to that of the palladium-catalyzed allylation, the residue was purified by column chromatography to afford cyclized product.

(3a*R*,7a*S*)-2-[(Methoxycarbonyl)methyl]-3-(methoxycarbonyl)-3a,4,5,7a-tetrahydrobenzo[*b*]furan (11). The crude product, which was prepared from **6** (53.2 mg, 0.165 mmol), $Pd(OAc)_2$ (2.2 mg, 9.811 mmol), (*S*)-BINAPO (13.0 mg, 0.020 mmol), **2b** (65.5 mL, 0.449 mmol), and NaH (17.8 mg, 0.445 mmol) in CH_3CN (2.0 mL) at rt for 10 h, was purified by flash column chromatography (hexane–AcOEt, 3:1) to afford 28.7 mg of **10** (69%) as a colorless oil: IR (neat) 1745, 1700, 1640 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.8–2.3 (m, 3H), 2.9–3.2 (m, 1H), 3.4–4.0 (m, 2H), 3.72 (s, 6H), 4.7–4.9 (m, 2H), 5.8–6.0 (m, 1H), 6.1–6.3 (m, 1H); HRMS (EI, *m/z*) for $C_{13}H_{16}O_5$, calcd 252.2670, found 252.2681. Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 61.95; H, 6.50.

(1′*S*,4′*R*)-Dimethyl 2-[4′-(Benzoyloxy)-2′-cyclohexen-1′-yl]malonate (12). The crude product, which was prepared from **6** (47.6 mg, 0.148 mmol), $Pd(OAc)_2$ (2.0 mg, 8.92 mmol), (*S*)-BINAPO (11.6 mg, 0.018 mmol), **2a** (20.3 mL, 0.178 mmol), and NaH (7.1 mg, 0.178 mmol) in CH_3CN (2.0 mL) at 0 °C for 24 h, was purified by flash column chromatography (hexane–AcOEt, 5:1) to afford 12.1 mg (25%) of **11** as a colorless oil: IR (neat) 1750, 1735, 1710, 1600 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.6–2.2 (m, 4H), 2.9–3.1 (m, 1H), 3.40 (d, J = 9.0 Hz, 1H), 3.76 (s, 6H), 5.3–5.5 (m, 1H), 5.8–6.0 (m, 2H), 7.3–7.6 (m, 3H), 7.9–8.1 (m, 2H); MS (EI, *m/z*) 332 (M^+), 301, 273, 237, 227, 200, 150, 132, 118, 105, 91, 77; HRMS (EI, *m/z*) for $C_{18}H_{20}O_6$, calcd 332.1260, found 332.1248.

(3a*R,7a*S**)-1-Benzyl-3-(methoxycarbonyl)-3a,4,5,7a-tetrahydroindolin-2-one (14).** The crude product, which was prepared from **6** (80.6 mg, 0.250 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), dppb (10.7 mg, 0.025 mmol), NaH (26.0 mg, 0.65 mmol), and **2d** (134,7 mg, 0.65 mmol) in CH_3CN (10.5 mL) at 50 °C for 3 h, was purified by flash column chromatography (hexane–AcOEt, 3:1) to afford 45.3 mg (64%) of **14** as a colorless oil: IR (neat) 1735, 1690, 1600, 1490, 1430 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.50–2.20 (m, 4H), 2.78 (dddd, J = 4.4, 6.6, 6.6, 8.1 Hz, 1H), 3.33 (d, J = 6.2 Hz, 1H), 3.80 (s, 3H), 3.93–4.00 (m, 1H), 4.01 (d, J =15.0 Hz, 1H), 5.03 (d, J = 15.0 Hz, 1H), 5.67 (dddd, J = 1.8, 1.8, 3.6, 10.3 Hz, 1H), 5.96 (dddd, J = 1.3, 3.8, 3.8, 10.3 Hz, 1H), 7.24–7.35 (m, 5H); MS (EI, *m/z*) 285 (M^+), 254, 226, 194, 174, 162, 146, 91; HRMS (EI, *m/z*) for $C_{17}H_{19}NO_3$, calcd 285.1365, found 285.1385. Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.61; H, 6.72; N, 4.91. Found: C, 71.79; H, 6.99; N, 5.23.

(1′*S*,4′*R*)-Methyl 2-(4′-(Benzoyloxy)-2′-cyclohexen-1′-yl)-2-(*N*-benzylcarbamoyl)acetate (15). The crude product, which was prepared from **6** (200 mg, 0.62 mmol), $Pd(OAc)_2$ (7.0 mg, 0.03 mmol), (*S*)-BINAPO (42.8 mg, 0.06 mmol), **2d** (141 mg, 0.68 mmol), and LDA (1.1 equiv) in CH_3CN (8 mL) and THF (4 mL) at 0 °C for 12 h, was purified by flash column chromatography (hexane–AcOEt, 3:1) to afford 146.3 mg (60%) of **15** as a colorless oil: IR (neat) 3290, 1740, 1710, 1675, 1650, 1600 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.60–200.(m, 5H), 2.70–3.00 (m, 1H), 3.23 and 3.28 (d, J = 9.0 Hz, 1H), 3.72 and 3.75 (s, 3H) 4.43 and 4.49 (brs, 2H), 5.30–5.60 (m, 1H), 5.70–6.00 (m, 2H), 6.70–7.10 (m, 8H), 7.90–8.10 (m, 2H); HRMS (EI, *m/z*) for $C_{24}H_{25}NO_5$, calcd 407.4527, found 407.4521. Anal. Calcd for $C_{24}H_{25}NO_5$: C, 70.75; H, 6.18; N, 3.44. Found: 70.93; H, 6.24; N, 3.55.

Conversion of 15 into 14. The crude product, which was prepared from **15** (31.4 mg, 0.08 mmol), NaH (3.4 mg, 0.008 mmol), $Pd(OAc)_2$ (1.0 mg, 0.004 mmol), and dppb (13.4 mg, 0.008 mmol) in CH_3CN (5 mL), was purified by flash column chromatography (hexane–AcOEt, 1:1) to afford 10 mg (48%) of **14** as a colorless oil.

(3a*R*,7a*S*)-1-Benzyl-3a,4,5,7a-tetrahydroindolin-2-one (16). The crude product, which was prepared from **14** (171.7 mg, 0.602 mmol) and NaCl (35.2 mg, 0.602 mmol) in DMSO (6 mL) and H_2O (21.7 μL, 1.206 mmol), was purified by flash column chromatography (hexane–AcOEt, 3:2) to afford 110.7 mg of **16** (81%): IR (neat) 1680, 1600 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.47–1.75 (m, 2H), 1.91–2.17 (m, 2H), 2.26 (d, J = 4.7, 15.8 Hz, 1H), 2.35–2.49 (m, 1H), 2.57 (dd, J = 7.9, 15.8 Hz, 1H), 3.76–3.84 (m, 1H), 3.98 (d, J = 15.2 Hz, 1H), 5.00 (d, J = 15.2 Hz, 1H), 5.72 (dddd, J = 2.1, 2.1, 4.2, 10.3 Hz, 1H), 5.98 (dddd, J = 1.2, 3.9, 3.9, 10.3 Hz, 1H), 7.22–7.37 (m, 5H); MS (EI, *m/z*) 227 (M^+), 199, 146, 136, 91, 79; HRMS (EI, *m/z*) for $C_{15}H_{17}NO$, calcd 227.1313, found 227.1310. Anal. Calcd for $C_{15}H_{17}NO$: C, 79.32; H, 7.54; N, 6.17. Found: C, 79.60; H, 7.66; N, 6.36.

(3a*R,6a*S**)-*N*-Benzyl-3-(methoxycarbonyl)-1-aza-3,3a,4,6a-tetrahydropentalen-2(1*H*)-one (17).** The crude product, which was prepared from **1** (76.1 mg, 0.247 mmol), $Pd(OAc)_2$ (3.3 mg, 0.0148 mmol), dppb (12.6 mg, 0.0330 mmol), **2d** (136.1 mg, 0.657 mmol), and NaH (126.3 mg, 0.657 mmol) in CH_3CN (6.5 mL) at 50 °C for 50 min, was purified by flash column chromatography (hexane–AcOEt, 3:1) to afford 41.2 mg (61%) of **17** as a colorless oil: IR (neat) 1740, 1689 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.28 (ddd, J = 17.0, 2.5, 2.5 Hz, 1H), 2.39–2.50 (m, 1H), 3.00–3.22 (m, 2H), 3.80 (s, 3H), 4.16 and 4.85 (ABq, J = 15.0 Hz, 2H), 4.45 (d, J = 7.0 Hz, 1H), 5.52–5.98 (m, 2H), 7.30 (m, 5H); MS (EI, *m/z*) 271 (M^+), 240, 212, 146: HRMS (EI, *m/z*) for $C_{16}H_{17}O_3N$, calcd 271.1207, found 271.1221.

(1′*R*,4′*S*)-Methyl 2-[4′-(Benzoyloxy)-2′-cyclopenten-1′-yl]-2-(*N*-benzylcarbamoyl)acetate (18). The crude product, which was prepared from **1** (222.7 mg, 0.722 mmol), $Pd(OAc)_2$ (9.7 mg, 0.043 mmol), (*S*)-BINAPO (56.7 mg, 0.087 mmol), **2d** (179.4 mg,0.866 mmol), and NaH (34.6 mg, 0.866 mmol) in CH_3CN (19.1 mL) at 0 °C for 90 h, was purified by flash column chromatography (hexane–AcOEt, 3:1) to afford 78.7 mg (27%) of **18** as a colorless oil: IR (neat) 3302, 1743, 1715, 1651 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.65 (ddd, J = 4.5, 4.5, 14.5 Hz, 1H), 2.60 (ddd, J = 7.6, 7.6, 14.5 Hz, 1H), 3.23 (d, J = 9.3 Hz, 1H), 3.28–3.39 (m, 1H), 3.65 (s, 3H), 4.38–4.56 (m, 2H), 5.78 (m, 1H), 5.85 (dd, J = 4.0, 8.5 Hz, 1H), 5.92–6.02 (m, 2H), 6.80–8.16 (m, 10H); MS (EI, *m/z*) 393 (M^+), 362, 272, 105, 91; HRMS (EI, *m/z*) for $C_{23}H_{23}O_5N$, calcd 393.1576, found 393.1597.

Conversion of 18 into 17. The crude product, which was prepared from **18** (40.5 mg, 0.103 mmol), $Pd(OAc)_2$ (2.3 mg, 0.010 mmol), dppb (8.8 mg, 0.021 mmol), and NaH (5.0 mg, 0.124 mmol) in CH_3CN (5.7 mL) at 50 °C for 2 h was purified by flash column chromatography (hexane–AcOEt, 3:1) to afford 14.4 mg (52%) of **17** as a colorless oil.

(3a*R,6a*S**)-*N*-Benzyl-3,3-bis(methoxycarbonyl)-1-aza-3,3a,4,6a-tetrahydropentalen-2(1*H*)-one (19).** To a suspension of NaH (2.4 mg, 0.060 mmol) in THF (0.3 mL) was added a solution of **17** (14.4 mg, 0.053 mmol) in THF (0.1 mL) at 0 °C. Then $ClCO_2CH_3$ (39 mL, 0.501 mmol) was added to the THF solution at 0 °C, and the solution was stirred at rt. Water was added, and the aqueous solution was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (hexane–Et_2O–CH_2Cl_2, 2:2:1) to afford **19** (10.8 mg, 65%) as a colorless oil: IR (neat) 1761, 1732, 1694 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.30–2.60 (m, 2H), 3.44–3.86 (m, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 4.10 (d, J = 15.0 Hz, 1H), 4.90 (d, J = 15.0 Hz, 1H), 4.37 (d, J = 7.0 Hz, 1H), 5.52–5.74 (m, 1H), 5.78–6.00 (m 1H), 7.08–7.46 (m, 5H); MS (EI, *m/z*) 329 (M^+), 298, 238, 91; HRMS (EI, *m/z*) for $C_{18}H_{19}O_5N$, calcd 329.1263, found 329.1256.

(1′*S*,4′*R*)-Dimethyl 2-[4′-(Benzoyloxy)-2′-cyclohexen-1′-yl]-3-oxoglutarate (23). The crude product, which was prepared from **6** (94.9 mg, 0.294 mmol), $Pd(OAc)_2$ (4.0 mg, 0.015 mmol), (*S*)-BINAPO (24.1 mg, 0.029 mmol), **2b** (54.2 mL, 0.369 mmol), and NaH (14.7 mg, 0.367 mmol) in CH_3CN (4.0 mL) at 0 °C for 7.5 h, was purified by flash column chromatography (hexane–AcOEt, 3:1) to afford 28.6 mg (26%) of **23**

as a colorless oil and 7.6 mg (10%) of **10** and 40 mg of **6** (42%). **23**: IR (neat) 1744, 1740 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.6–2.1 (m, 4H), 2.8–3.2 (m, 1H), 3.5–3.8 (m, 2H), 3.72 (s, 3H), 3.75 (s, 3H), 5.3–5.5 (m, 2H), 5.7–6.1 (m, 2H), 7.3–7.6 (m, 3H), 7.9–8.1 (m, 2H); MS (EI, *m/z*) 278 (M^+, bp), 247, 229; HRMS (EI, *m/z*) for $C_{20}H_{22}O_7$, calcd 278.3940, found 278.3951.

Conversion of 23 into 10. The crude product, which was prepared from **23** (15 mg, 0.04 mmol), $Pd(OAc)_2$ (1 mg, 0,004 mmol), dppb (3.4 mg, 0.008 mmol), and NaH (3.2 mg, 0.08 mmol) in CH_3CN (3.5 mL) at 0 °C for 3 h was purified by flash column chromatography (hexane–AcOEt, 3:2) to afford 4 mg (39%) of **10** as a colorless oil.

(1′*S*,4′*R*)-Methyl 2-[4′-(Benzoyloxy)-2′-cyclohexen-1′-yl]-2-[*N*-(6′-bromopiperonyl)carbamoyl]acetate (25). The crude product, which was prepared from **6** (100.1 mg, 0.310 mmol), $Pd(OAc)_2$ (3.5 mg, 0.016 mmol), (*S*)-BINAPO (21.0 mg, 0.031 mmol), **2c** (265.0 mg, 0.806 mmol), and LDA (2.6 equiv) in CH_3CN (2.0 mL) and THF (2 mL) at 0 °C for 1 h, was purified by flash column chromatography (hexane–AcOEt, 2:1) to afford 91.2 mg (66%) of **25** as a colorless oil: IR (neat) ν_{max} 3340, 1740, 1711, 1675, 1650, 1602 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.55–2.06.(m, 5H), 2.79–2.95 (m, 1H), 3.23 and 3.28 (d, J = 9.0 Hz, 1H), 3.72 and 3.75 (s, 3H) 4.43 and 4.49 (brs, 2H), 5.30–5.60 (m, 1H), 5.80–5.90 (m, 2H), 5.93–6.05 (m, 1H), 5.97 (s, 2H), 6.90 and 7.00 (s, 1H) 7.40-7.60 (m, 3H), 8.00–8.10 (m, 2H). Anal. Calcd for $C_{25}H_{24}BrNO_7$: C, 56.62; H, 4.56; N, 2.64; Br, 15.07. Found: C, 56.65; H, 4.70; N, 2.56; Br, 14.99.

(3a*R,7a*S**)-1-(6′-Bromopiperonyl)-3-(methoxycarbonyl)-3a,4,5,7a-tetrahydroindolin-2-one (26).** The crude product, which was prepared from **25** (55.4 mg, 0.104 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), dppb (4.4 mg, 0.010 mmol), NaH (9.2 mg, 0.229 mmol), and **2c** (47.5 mg, 0.229 mmol) in DMF (2.5 mL) at 50 °C for 9 h was purified by flash column chromatography (hexane–AcOEt, 3:1) to afford 35.3 mg (81%) of **26** as a colorless oil: IR (neat) 1735, 1695 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.58–1.87 (m, 2H), 1.96–2.20 (m, 2H), 2.78–2.91 (m, 1H), 3.36 (d, J = 6.8 Hz, 1H), 3.82 (s, 3H), 4.01–4.05 (m, 1H), 4.30 (d, J = 15.5 Hz, 1H), 4.84 (d, J = 15.5 Hz, 1H), 5.70–5.76 (m, 1H), 5.93–6.02 (m, 1H), 5.98 (s, 2H), 6.86 (s, 1H), 6.99 (s, 1H). Anal. Calcd for $C_{18}H_{18}BrNO_5$: C, 52.96; H, 4.44; N, 3.43; Br, 19.57. Found: C, 53.07; H, 4.50; N, 3.31; Br, 19.68.

(3a*R*,7a*S*)-1-[6-Bromo-3,4-(methylenedioxy)benzyl]-3a,4,5,7a-tetrahydroindolin-2-one (7). The crude product, which was prepared from **26** (29.3 mg, 0.072 mmol) and NaCl (4.2 mg, 0.072 mmol) in DMSO (0.6 mL) and H_2O (2.6 mL, 0.144 μmol) was purified by flash column chromatography (hexane–AcOEt, 3:2) to afford **7** (9.4 mg, 87%) as colorless crystals: mp 113–115 °C; IR (KBr) 1695 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.50–1.80 (m, 4H), 1.91–2.20 (m, 2H), 2.20–2.60 (m, 3H), 3.84 (brs, 1H), 4.24 (d, J = 15.7 Hz, 1H), 5.70–5.80 (m, 1H), 5.89–5.99 (m, 1H), 5.95 (s, 2H), 6.73 (s, 1H), 6.96 (s, 1H); MS (EI, *m/z*) 350, 348 ($M^+ - 1$), 302, 270 ($M^+ - Br$), 215, 213, 192, 190, 162, 151, 135; HRMS (EI, *m/z*) for $C_{15}H_{17}NO$, calcd 351.0314, found 351.0293; Anal. Calcd for $C_{16}H_{16}BrNO_3$: C, 54.87; H, 4.60; N, 4.00; Br, 22.82. Found: C, 54.82; H, 4.60; N, 3.99; Br, 22.89.

(3a*R*,11b*S*,11c*S*)-3,3a,4,5,11b,11c-Hexahydro-9,10-(methylenedioxy)pyrrolo[3,2,1-*de*]phenanthridin-5-one (8). A DMF solution (0.5 mL) of $Pd(OAc)_2$ (4.6 mg, 0.021 mmol) and PPh_3 (21.6 mg, 0.082 mmol) was added to a DMF solution (3.5 mL) of **7** (144.4 mg, 0.412 mmol) and $^iPr_2NEt$ (150 μL, 0.840 mmol). The mixture was stirred at 100 °C for 7.5 h. After cooling, H_2O (1.0 mL) was added to the reaction mixture, and the aqueous layer was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (hexane–AcOEt; 2:1, then only AcOEt) to afford 79.6 mg of **8** (72%) as colorless crystals: mp 161.5–162.5 °C; IR (KBr) 1680 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.04–2.28 (m, 3H), 2.67 (ddd, J = 1.4, 10.5, 17.0 Hz, 1H), 2.82–2.96 (m, 1H), 3.39 (brs, 1H), 4.06 (brdd, J = 3.5, 5.5 Hz, 1H), 4.11, (d, J = 17.4 Hz, 1H), 4.79 (d, J = 17.4 Hz, 1H), 5.62–5.69 (m, 1H), 5.89–5.99 (m, 1H), 5.96 (s, 2H), 6.59 (s, 1H), 6.67 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 27.3, 29.1, 38.5, 38.8, 42.1, 56.5, 101.1, 106.1, 108.8, 124.3, 126.7, 129.7, 132.5, 146.8, 146.9, 174.3; MS (EI, *m/z*) 269 (M^+), 268 ($M^+ - 1$), 240, 226, 199, 187, 174; HRMS (EI, *m/z*) for $C_{16}H_{15}NO_3$, calcd 269.1052, found 269.1063.

(3a*R*,11b*S*,11c*S*)-3-(Methoxycarbonyl)-3,3a,4,5,11b,11c-hexahydro-9,10-(methylenedioxy)pyrrolo[3,2,1-*de*]-phenanthridin-5-one (27). To a stirred suspension of NaH (13.2 mg, 0.330 mmol) in DMF (4.0 mL) was added a solution of **25** (133.1 mg, 0.300 mmol). After stirring the mixture for 20 min, a DMF solution of $Pd(OAc)_2$ (3.4 mg, 0.015 mmol) and dppb (12.8 mg, 0.030 mmol) was added to the mixture at 0 °C. The mixture was stirred at 50 °C for 2 h. Then $^iPr_2NEt$, (0.600 mmol, 104.5 μL) was added to the reaction mixture, and the solution was stirred at 100 °C for 5 h. After usual workup, the residue was purified by flash column chromatograhy (hexane–AcOEt, 1:1) to afford 57.4 mg of **27** (58%, two steps): IR (neat) 1734, 1690 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.23–2.50 (m, 2H), 3.19–3.24 (m, 3H), 3.79 (s, 3H), 4.16 (d, J = 17.4 Hz, 1H), 4.21–4.25 (m, 1H), 4.85 (d, J = 17.2 Hz, 1H), 5.70–5.73 (m, 1H), 5.90–6.02 (m, 1H), 5.96 (s, 2H), 6.59 (s, 1H), 6.67 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 26.8, 34.4, 38.3, 42.4, 52.8, 55.6, 55.5, 101.2, 106.0, 108.9, 124.1, 126.8, 128.3, 128.6, 129.3, 132.2, 133.8, 147.0, 147.1, 168.7, 170.7; MS (EI, *m/z*) 327 (M^+, bp), 296, 277, 268, 226, 213, 185, 174, 128, 91; HRMS (EI, *m/z*) for $C_{18}H_{17}NO_5$, calcd 327.1107, found 327.1087.

Decarbomethoxylation of 27. The crude product which was prepared from **27** (57.4 mg, 0.18 mmol), and NaCl (15.3 mg, in DMSO(3.0 mL) and H_2O (6.5 μL) was purified by column chromatography on alumina (AcOEt–hexane, 1:2) to give **8** (31.1 mg, 64%).

(+)-γ-Lycorane (9). A suspention of **8** (10.5 mg, 0.039 mmol) and 5% Pd on charcoal (8.2 mg) in MeOH (1.5 mL) was stirred under hydrogen for 2 h. The palladium catalyst was filtered off, and the filtrate was concentrated. The residue was purified by flash column chromatography (AcOEt) to afford 10.5 mg (99%) of hydrogenation product as colorless crystals: IR ($CHCl_3$) 1670, 1600 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.06–1.46 (m, 3 H), 1.66–1.83 (m, 3H), 2.09 (d, J = 16.1 Hz, 1 H), 2.42 (dddd, J = 5.5, 5.5, 5.5, 11.0 Hz, 1 H), 2.57 (dd, J = 6.8, 16.1 Hz, 1 H), 2.74 (ddd, J = 4.4, 4.4, 12.5 Hz, 1 H), 3.76 (dd, J = 4.4, 4.4 Hz, 1 H), 4.32 (d, J = 17.2 Hz, 1 H), 4.54 (d, J = 17.2 Hz, 1 H), 5.92 (d, J = 2.6 Hz, 2 H), 6.59 (s, 1 H), 6.61 (s, 1 H); MS (EI, *m/z*) 271 (M^+, bp), 270 ($M^+ - 1$), 241, 174; HRMS (EI, *m/z*) for $C_{16}H_{17}NO_3$, calcd 271.1208 found 271.1184. A solution of the hydrogenation product (30.5 mg, 0.112 mmol) in THF (3 mL) was added to the THF suspension of $LiAlH_4$ (21.3 mg, 0.561 mmol) at 0 °C, and the THF suspension was refluxed for 1 h. $Na_2SO_4 \cdot 10H_2O$ was added, and the mixture was stirred overnight. The precipitate was removed by filtration, and the filtrate was concentrated. The residue was purified by flash column chromatography (Et_2O) to afford 24.9 mg (86%) of γ-lycorane (**9**): IR ($CHCl_3$) 1600 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.23–1.55 (m, 6H), 1.57–1.80 (m, 3H), 1.94–2.25 (m, 3H), 2.37 (dd, J = 4.8, 4.8 Hz, 1H), 2.74 (ddd, J = 4.4, 4.4, 9.2 Hz, 1H), 4.01 (d, J = 14.3 Hz, 1H), 5.88 (d, J = 1.5 Hz, 1H), 5.89 (d, J = 1.5 Hz, 1H), 6.49 (s, 1H), 6.61 (s,1H); ^{13}C NMR ($CDCl_3$) δ 25.2, 29.1, 30.4, 31.7, 37.4, 39.5, 53.7, 57.1, 62.9, 100.6, 106.2, 108.3, 127.4, 133.2, 145.7, 146.0; MS (EI, *m/z*) 257 (M^+), 256 ($M^+ - 1$); HRMS (EI, *m/z*) for $C_{16}H_{19}NO_2$, calcd 257.1415, found 257.1390; $[\alpha]_D$ +7.9° (*c* 0.52, EtOH) [lit.[14] $[\alpha]_D$ +17.1° (c 0.25, EtOH)].

Supplementary Material Available: Copies of ^1H NMR spectra of **11**, **17–19**, and **23** and copies of ^{13}C NMR spectra of **8**, **9**, and **27** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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