# Total Synthesis of (+)-Lycoricidine and Its 2-Epimer from D-Glucose

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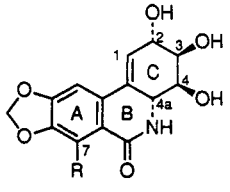
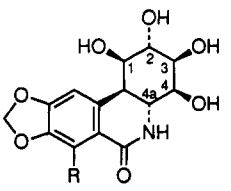
Stereoselective total synthesis of antimitotic alkaloid (+)-lycoricidine (1) and its 2-epimer (30) was accomplished starting from D-glucose. The key steps in this synthesis are (i) a catalytic version of the Ferrier rearrangement for the preparation of the optically active substituted cyclohexenone (the C-ring of lycoricidine) and (ii) a Pd-catalyzed intramolecular Heck-type reaction for construction of the phenanthridone skeleton. A preliminary biological assay revealed that the stereochemistry at the 2-position of lycoricidine plays an important role in its cytotoxic activity.

Because of the wide range of their biological activity[1] (for example, they have powerful cytotoxic and plant growth regulatory activity), the phenanthridone plant alkaloids lycoricidine (1),[2] narciclasine (2),[3] pancratistatin



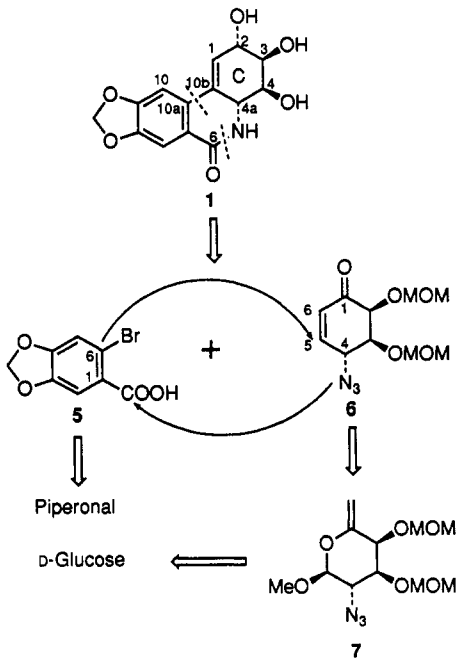
R = H: (+)-Lycoricidine (1)
R = OH: Narciclasine (2)



R = OH: Pancratistatin (3)
R = H: 7-Deoxypancratistatin (4)

(3),[4] and 7-deoxypancratistatin (4)[5] and their glucosides[4,5] have been the focus of considerable attention. The structures of these alkaloids, which have a phenanthridone skeleton with four or six contiguous asymmetric centers in the C-ring, are synthetically interesting and challenging. Several synthetic approaches[6] to these alkaloids have been reported to date, some of which culminated in total syntheses.[7] Herein, we detail our stereoselective total synthesis of (+)-lycoricidine (1) and its 2-epimer (30) starting from D-glucose.[8]

**Scheme I. Retrosynthetic Analysis**




**Synthetic Plan.** We reasoned that the phenanthridone skeleton might be constructed by C–C bond formation between C10a and C10b (phenanthridone numbering) and amide formation between the amino group at C4a and the carbonyl group at C6. This route dissects the phenanthridone skeleton into two subunits, 5 and 6 (Scheme I). The bromine atom located at C6 in subunit 5, easily available from piperonal, would serve as the key functionality for the generation of organometallic species, which would be utilized for the C–C bond formation between C6 in 5 and C5 in 6 by means of a 1,4-addition or a Pd-catalyzed coupling reaction. We expected that subunit 6 could be prepared in a homochiral form by means of Ferrier's carbocyclization[9] from enopyranoside 7, which in turn, was envisioned as arising from D-glucose.

## Results and Discussion

**Preparation of the C-Ring.** Ferrier's carbocyclization (Ferrier rearrangement) is one of the most efficient protocols for the preparation of substituted cyclohexane derivatives from aldohexoses.[9,10] A study in our laboratory

(1) For biological properties of phenanthridone alkaloids, see: (a) Okamoto, T.; Torii, Y.; Isogai, Y. *Chem. Pharm. Bull.* **1968**, *16*, 1860. (b) Ceriotti, G. *Nature (London)* **1967**, *213*, 595. (c) Pettit, G. R.; Gaddamidi, V.; Herald, D. L.; Singh, S. B.; Cragg, G. M.; Schmidt, J. M.; Boettner, F. E.; Williams, M.; Sagawa, Y. *J. Nat. Prod.* **1986**, *49*, 995. (d) Jimenez, A.; Sanchez, L.; Vazquez, D. *FEBS Lett.* **1975**, *55*, 53. (e) Mondon, A.; Krohn, K. *Chem. Ber.* **1975**, *108*, 445. (f) Ghosal, S.; Singh, S.; Kumar Y.; Srivastava, R. S. *Phytochemistry* **1989**, *28*, 611.

(2) For isolation and structure of lycoricidine and narciclasine, see: (a) ref 1a. For determination of the absolute structure of narciclasine, see: (b) Immirzi, A. *J. Chem. Soc., Chem. Commun.* **1972**, 240. Biosynthesis of narciclasine: (c) Fuganti, C.; Mazza, M. *Ibid.* **1972**, 239.

(3) Pettit, G. R.; Gaddamidi, V.; Cragg, G. M.; Herald, D. L.; Sagawa, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1693.

(4) For isolation of 7-deoxypancratistatine and its 2-*O*-$\beta$-glucoside, see ref 1f.

(5) For isolation of narciclasine 4-*O*-glucoside, see: Abou-Donia, A. H.; De Giulio, A.; Evidente, A.; Gaber, M.; Habib, A.-A.; Lanzetta, R.; Seif El Din, A. A. *Phytochemistry* **1991**, *30*, 3445.

(6) For a synthetic approach to pancratistatin and a synthesis of tetrabenzyllycoricidine, see: (a) Thompson, R. C.; Kallmerten, J. *J. Org. Chem.* **1990**, *55*, 6076. For a synthetic approach to lycoricidine, see: (b) Keck, G. E.; Boden, E.; Sonnewald, U. *Tetrahedron Lett.* **1981**, *22*, 2615. (c) Weller, T.; Seebach, D. *Ibid.* **1982**, *23*, 935. For a synthetic approach to pancratistatin, see: (d) Clark, R. D.; Souchet, M. *Tetrahedron Lett.* **1990**, *31*, 193.

(7) For a total synthesis of lycoricidine (racemic), see: (a) Ohta, S.; Kimoto, S. *Tetrahedron Lett.* **1975**, 2279; *Chem. Pharm. Bull.* **1976**, *24*, 2977. (b) Ugarkar, B. G.; DaRe, J.; Schubert, E. M. *Synthesis* **1987**, 715. Optically active: (c) Paulsen, H.; Stubbe, M. *Tetrahedron Lett.* **1982**, *23*, 3171; *Liebigs Ann. Chem.* **1983**, 535. (d) Hudlicky, T.; Olivo, H. F. *J. Am. Chem. Soc.* **1992**, *114*, 9694. For a total synthesis of racemic pancratistatine, see: (e) Danishefsky, S.; Lee, J. Y. *J. Am. Chem. Soc.* **1989**, *111*, 4829.

(8) For the preliminary communication of this work, see: Chida, N.; Ohtsuka, M.; Ogawa, S. *Tetrahedron Lett.* **1991**, *32*, 4525.

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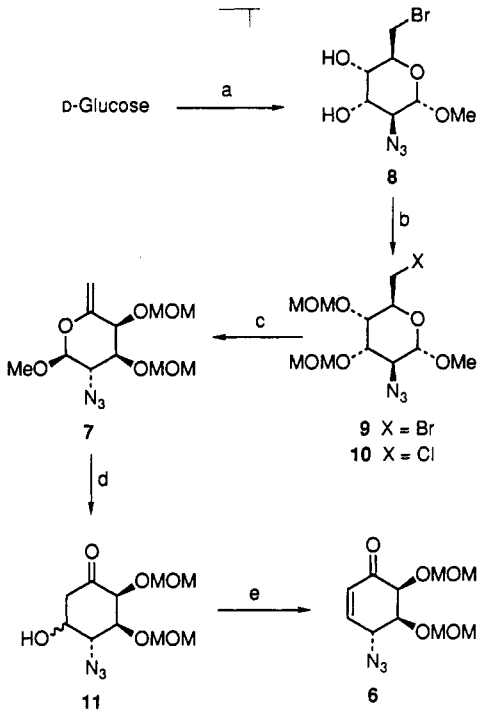
**Scheme II**[a]

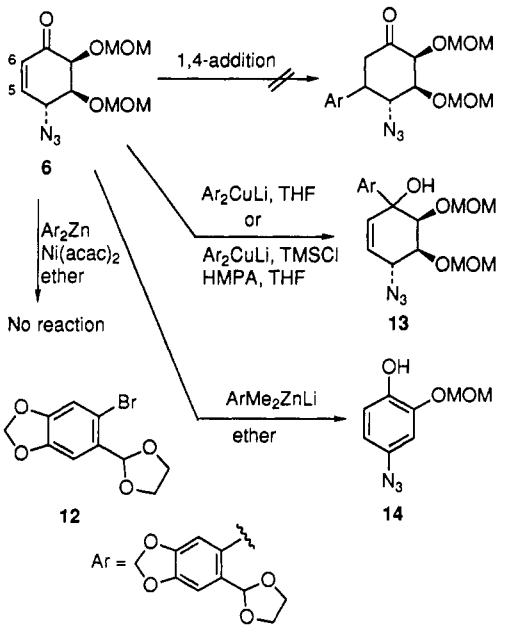



[a] MOM = $-CH_2OCH_3$. Key: (a) see ref 12; (b) MOMCl, *i*-$Pr_2NEt$, $CH_2Cl_2$; (c) DBU, toluene, reflux; (d) $Hg(OCOCF_3)_2$ (1 mol %), aqueous acetone, rt; (e) MsCl, $Et_3N$, $CH_2Cl_2$.

of the Ferrier rearrangement recently revealed that this cyclization proceeds effectively with a catalytic amount (less than 10 mol %) of mercury(II) trifluoroacetate at room temperature in a neutral solvent system.[11] This modified catalytic Ferrier rearrangement, which has been proved effective for a wide range of substrates,[11] was employed for the preparation of the C-ring of lycoricidine.

The hydroxy groups of known diol 8,[12] prepared stereoselectively from D-glucose, were protected as the bis(methoxymethyl) ethers. During the protection reaction, substantial halide exchange occurred to give an inseparable mixture of compounds 9 and 10 in a ratio of 35:65 in 87% yield (Scheme II). Without isolation, the mixture of 9 and 10 was subjected to dehydrobromination (DBU in refluxing toluene) to afford 5-enopyranoside 7 in 73% yield. The catalytic Ferrier rearrangement of 7 with mercuric(II) trifluoroacetate (1 mol %)[11] in acetone–water (rt, 20 h) provided cyclohexanone derivative 11, which, without purification, was dehydrated (MsCl, $Et_3N$) to afford the desired enone 6, with the three contiguous chiral centers at C-3, 4, and 4a of lycoricidine, in 69% yield from 7.

**Scheme III**




**Construction of the Phenanthridone Skeleton: The Unsuccessful Intermolecular Approach.** With stereodefined cyclohexenone 6 in hand, we focused our attention on the introduction of an arene unit to the C5 position of compound 6 by means of a conjugate addition (Scheme III). However, treatment of enone 6 with lithium diarylcuprate,[13] generated from piperonal derivative 12[7c] by the action of *t*-BuLi and copper(I) iodide in THF, afforded only 1,2-adduct 13 in low yield (28%). Addition of TMSCl–HMPA to the reaction mixture to enhance the 1,4-addition reactivity[14] also resulted in the selective formation of the 1,2-adduct (20% yield). When 6 was treated with diarylzinc in the presence of Ni(II) catalyst,[15] the starting material was recovered, and the reaction of 6 with aryldimethylzincate[16] ($ArMe_2ZnLi$), generated from aryllithium and ethereal dimethylzinc,[17] afforded aromatized product 14 in low yield. Recognition of the poor reactivity of enone 6 toward 1,4-addition led us to the idea of constructing the phenanthridone by an intramolecular reaction.

**Construction of the Phenanthridone Skeleton: The Intramolecular Approach.** The pioneering work of Grigg[18] and Overman[19] on intramolecular Pd-catalyzed Heck arylation–cyclization of enamide derivatives suggested to us the possibility of using an intramolecular

(9) (a) Ferrier, R. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1455. (b) Blattner, R.; Ferrier, R. J.; Hains, S. R. *Ibid.* **1985**, 2413.

(10) For utilization of the Ferrier rearrangement in natural product synthesis, see: (a) Chida, N.; Ohtsuka, M.; Nakazawa, K.; Ogawa, S. *J. Org. Chem.* **1991**, *56*, 2976. (b) Barton, D. H. R.; Augy-Dorey, S.; Camara, J.; Dalko, P.; Delaumeny, J. M.; Gero, S. D.; Quiclet-Sire, B., Stütz, P. *Tetrahedron* **1990**, *46*, 215. (c) Blattner, R.; Ferrier, R. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1008. (d) Barton, D. H. R.; Gero, S. D.; Cleophax, J.; Mashado, A. S.; Quiclet-Sire, B. *Ibid.* **1988**, 1184. (e) Ferrier, R. J.; Stütz, A. E. *Carbohydr. Res.* **1990**, *200*, 237. (f) Miyamoto, M.; Baker, M. L.; Lewis, M. D. *Tetrahedron Lett.* **1992**, *33*, 3725. (g) Sakairi, N.; Kuzuhara, H. *Ibid.* **1982**, *23*, 5327. (h) Sugawara, F.; Kuzuhara, H. *Agric. Biol. Chem.* **1981**, *45*, 301. (i) Sakairi, N.; Hayashida, M.; Amano, A.; Kuzuhara, H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1301. (j) Takahashi, S.; Terayama, H.; Kuzuhara, H. *Tetrahedron Lett.* **1991**, *32*, 5123. (k) Sato, K.; Sakuma, S.; Muramatsu, S.; Bokura, M. *Chem. Lett.* **1991**, 1473. (l) Estevez, V. A.; Prestwich, G. D. *J. Am. Chem. Soc.* **1991**, *113*, 9885. (m) Dyong, I.; Hagedorn, H.-W.; Thiem, J. *Liebigs Ann. Chem.* **1986**, 551. (n) Fisher, M. J.; Myers, C. D.; Joglar, J.; Chen, S.-H.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 5826.

(11) Chida, N.; Ohtsuka, M.; Ogura, K.; Ogawa, S. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2118.

(12) Hanessian, S.; Masse, R. *Carbohydr. Res.* **1974**, *35*, 175.

(13) For reviews of 1,4-addition reactions of organocopper species, see: (a) Taylor, R. J. K. *Synthesis* **1985**, 364. (b) Lipshutz, B. H. *Ibid.* **1987**, 325.

(14) Matsuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* **1989**, *45*, 349.

(15) Greene, A. E.; Lansard, J.-P.; Luche, J.-L.; Petrier, C. *J. Org. Chem.* **1984**, *49*, 931.

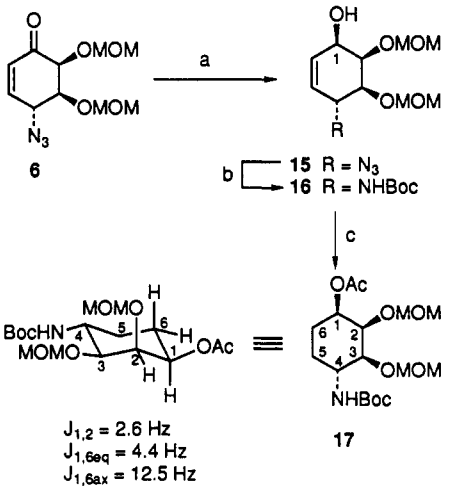
(16) (a) Isobe, M.; Goto, T. *Chem. Lett.* **1977**, 679. (b) Langer, W.; Seebach, D. *Helv. Chim. Acta* **1979**, *62*, 1710. (c) Soai, K.; Hayasaka, T.; Ugajin, S.; Yokoyama, S. *Chem. Lett.* **1988**, 1571. (d) Kjonaas, R. A.; Hoffer, R. K. *J. Org. Chem.* **1988**, *53*, 4133. (e) Jansen, J. F. G. A.; Ferringa, B. L. *J. Chem. Soc., Chem. Commun.* **1989**, 741. (f) Tückmantel, W.; Ohshima, K.; Nozaki, H. *Chem. Ber.* **1986**, *119*, 1581. (g) Morita, Y.; Suzuki, M.; Noyori, R. *J. Org. Chem.* **1989**, *54*, 1785.

(17) Luche, J.-L.; Petrier, C.; Lansard, J.-P.; Greene, A. E. *J. Org. Chem.* **1983**, *48*, 3837.

(18) (a) Grigg, R.; Sridharan, V.; Stevenson, P.; Worakan T. *J. Chem. Soc., Chem. Commun.* **1986**, 1697. (b) Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron* **1990**, *46*, 4003.

(19) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130.

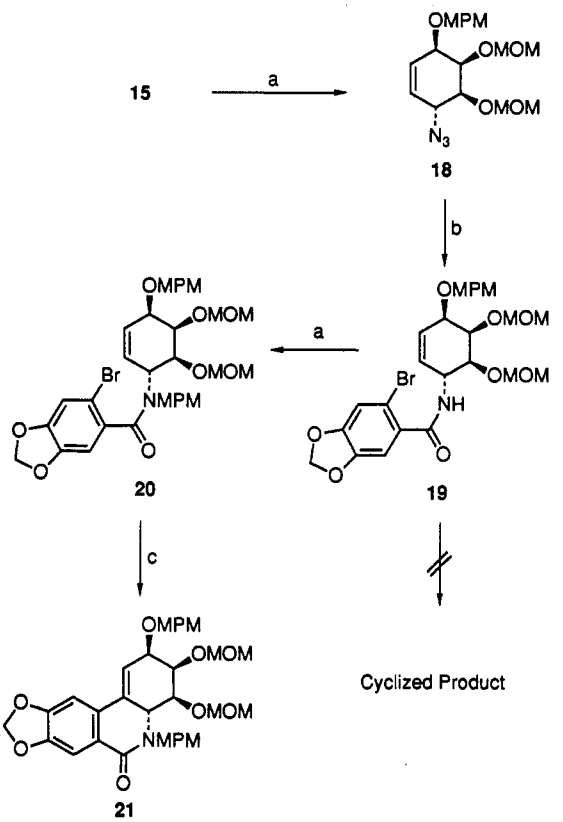
**Scheme IV**[a]




[a] Boc = –C(O)O*t*-Bu. Key: (a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C; (b) $LiAlH_4$, THF, $(Boc)_2O$, $Et_3N$, $CH_2Cl_2$; (c) $H_2$, $PtO_2$, EtOH, then $Ac_2O$, pyridine.

approach to the construction of the phenanthridone skeleton. For this purpose, amide **19** was prepared from enone **6**. Reduction of the carbonyl group in **6** with $NaBH_4$–$CeCl_3$[20] in methanol proceeded in a highly stereoselective manner to afford cyclohexene **15** in 86% yield as the sole product. Stereochemical assignment of the newly formed sterogenic center at C1 in **15** was based on the conversion of **15** into its saturated derivative **17** (Scheme IV); the $^1H$ NMR revealed that **17** has a chair conformation, and the coupling constants observed supported the assigned structure. After protection of the hydroxyl group in **15** as a *p*-methoxybenzyl ether (**18**, 69% yield), the azido function in **18** was reduced with $LiAlH_4$ to provide the corresponding amine, which was condensed with 6-bromopiperonylic acid (**5**)[21] under Shioiri conditions[22] to give **19** in 89% overall yield from **18**. With bromo enamide **19** in hand, the Pd-catalyzed arylation under the Overman conditions[19] [$Pd(OAc)_2$ (20 mol %), $Ph_3P$ (50 mol %), $Et_3N$ (2 equiv), in the presence or absence of $Ag_2CO_3$ (2 equiv), in $CH_3CN$, reflux] was attempted (Scheme V). However, none of the desired product was detected in the reaction mixture, and only unidentified aromatized products and the starting material were isolated. In their study of the preparation of the 3-spiro-2-oxindole system, Overman *et al.* had reported that secondary amides could not be cyclized satisfactorily.[19] We then turned to a cyclization reaction using *N*-protected derivative **20**. The amide nitrogen in **19** was alkylated with *p*-methoxybenzyl chloride in the presence of NaH to afford the fully protected tertiary amide **20** quantitatively. When compound **20** was subjected to the Grigg conditions[18] [$Pd(OAc)_2$ (10 mol %), $Ph_3P$ (20 mol %), $K_2CO_3$ (1.5 equiv) in $CH_3CN$, reflux, 78 h], cyclized product **21** was isolated, although in only 9% yield. Fortunately, it was found that this cyclization reaction proceeded in good yield (68%) under the modified Heck conditions using a thallium(I) salt as an additive, recently reported by Grigg.[23] Table I shows the results of the attempted cyclization of **20** under various reaction conditions.

**Scheme V**[a]




[a] MPM = $-CH_2C_6H_4(p\text{-}OCH_3)$. Key: (a) MPMCl, NaH, DMF; (b) $LiAlH_4$, ether, then 6-bromopiperonylic acid, $(EtO)_2P(O)CN$, $Et_3N$, DMF; (c) $Pd(OAc)_2$ (10 mol %), 1,2-bis(diphenylphosphino)-ethane (40 mol %), TlOAc (2 equiv), DMF, 140 °C.

**Table I. Palladium-Catalyzed Cyclization of 20**[a]

| phosphine (equiv) | additive (equiv) | solvent | time (h) | temp (°C) | yield of 21[b] (%) |
|---|---|---|---|---|---|
| $Ph_3P$ (1.0) | $K_2CO_3$ (2.0) | $CH_3CN$ | 78 | 70 | 9 (91) |
| $Ph_3P$ (1.0) | $K_2CO_3$ (2.0), *n*-$Bu_4NBr$ (1.0) | $CH_3CN$ | 68 | 70 | 7 (69) |
| $Ph_3P$ (0.2) | TlOAc (2.0) | DMF | 7 | 140 | 0 (85) |
| DPPE[c] (0.4) | $K_2CO_3$ (2.0) | DMF | 42 | 140 | trace (55) |
| DPPE (0.4) | $Ag_2CO_3$ (2.0) | DMF | 36 | 140 | 19 (25) |
| DPPE (0.4) | TlOAc (2.0) | DMF | 7 | 140 | 68 (8) |
| DPPE (0.2) | TlOAc (2.0) | $CH_3CN$ | 18 | 80 | 10 (85) |
| DPPE (0.2) | TlOAc (2.0) | anisole | 12 | 140 | 16 (51) |
| *n*-$Bu_3P$ (0.1) | none | THF | 90 | rt | 0 (84) |
| *n*-$Bu_3P$ (0.1) | TlOAc (2.0) | DMF | 12 | 140 | 8 (64) |

[a] All reactions were carried out in the presence of 10 mol % of palladium(II) acetate under Ar. [b] Isolated yields after silica gel chromatography, yields in parentheses are the amounts of recovered starting material **20**. [c] 1,2-Bis(diphenylphosphino)ethane.

It is noteworthy that the combination of dppe [1,2-bis-(diphenylphosphino)ethane] as ligand, thallium(I) acetate as additive, and DMF as solvent is essential for obtaining a high yield in this reaction. The use of other phosphines, such as *n*-$Bu_3P$,[24] and additives such as $Ag_2CO_3$[25] led to a dramatic decrease in the amount of cyclization product. It should be pointed out that this cyclization reaction gave only one diastereoisomer, **21**, as the sole product, and no other isomers, such as vinyl ether derivative **22** or the 2-hydroxyl epimer of compound **21**, were detectable. This result implies that the β-hydride elimination takes place formally with anti stereochemistry from anticipated

(20) Gemel, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
(21) Fales, H. M.; Warnhoff, E. W.; Wildman, W. C. *J. Am. Chem. Soc.* **1955**, *77*, 5885.
(22) Yamada, S.; Kasai, Y.; Shioiri, T. *Tetrahedron Lett.* **1973**, 1595.
(23) Grigg, R.; Loganathan, V.; Santhadumar, V.; Sridharan, V.; Teasdale, A. *Tetrahedron Lett.* **1991**, *32*, 687.
(24) Mandai, T.; Matsumoto, T.; Kawada, M.; Tsuji, J. *J. Org. Chem.* **1992**, *57*, 1326.
(25) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1991**, 324; *Tetrahedron Lett.* **1991**, *32*, 2121.

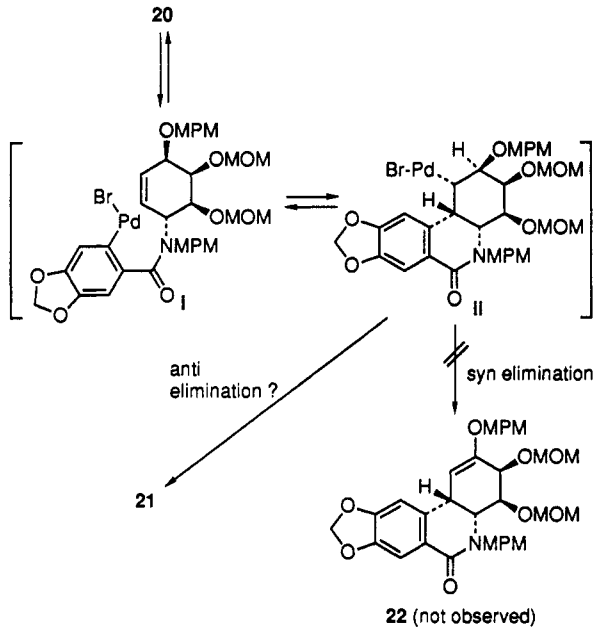
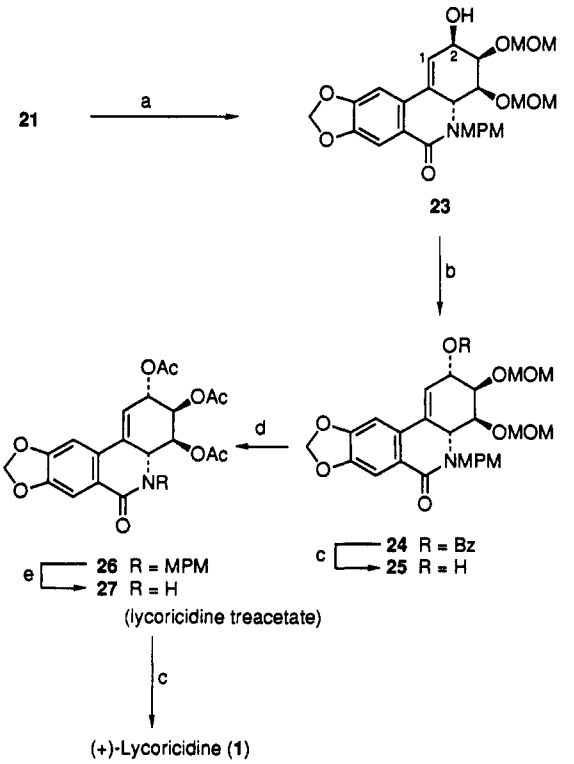



**Figure 1.**

intermediate **ii** (Figure 1). Since it is well-known that both the addition of an organopalladium species to a double bond and the β-elimination of palladium hydride normally occur with syn stereochemistry in the Heck reaction,[26,27] the expected product in the reaction of **20** would be vinyl ether **22**.[28] Although the detailed mechanism for the exclusive formation of the unexpected (but desired) product **21** is not clear,[29,30] this intriguing cyclization reaction proved to be very effective for the construction of the phenanthridone skeleton.[31]

**Total Synthesis of (+)-Lycoricidine.** With **21** possessing a phenanthridone skeleton in hand, we examined the final stage of the total synthesis (Scheme VI). Removal of the *O*-MPM group in **21** with DDQ[32] afforded a 53% yield of allyl alcohol **23**, which was subjected to the Mitsunobu reaction[33] using benzoic acid as a nucleophile to provide cleanly inverted benzoate **24** with the correct stereochemistry of the target in 78% yield. The benzoyl group in **24** was deprotected with sodium methoxide in methanol to give **25** (99% yield). The change in the coupling constant $J_{1,2}$ in the $^1$H NMR spectra of **23** and **25** (4.2 Hz for **23**, 1.8 Hz for **25**) clearly shows the inversion of the C2 stereochemistry. Acid hydrolysis of **25** (aqueous HCl in THF) followed by acetylation provided triacetate **26** in 51% yield. The *N*-MPM group in **26** was detached with trifluoroacetic acid in chloroform[34] to afford (+)-lycoricidine triacetate **27** (53% yield), whose physical properties were in full accord with those reported by Paulsen.[7c] Finally, removal of the acetyl group in **27** with sodium methoxide provided (+)-lycoricidine (**1**) in quantitative yield. The physical data for synthetic **1** were identical with those reported for the authentic compound.[1a,7c]

**Scheme VI**[a]




[a] Key: (a) DDQ, $CH_2Cl_2$–$H_2O$, rt; (b) benzoic acid, $Ph_3P$, diethyl azodicarboxylate, THF, rt; (c) MeONa–MeOH; (d) aqueous HCl–THF, 50 °C, then $Ac_2O$, pyridine; (e) TFA–$CHCl_3$, rt.

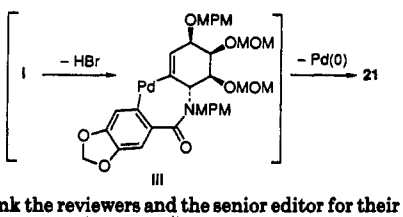
**Synthesis of (+)-Lycoricidine 2-Epimer and Cytotoxic Activities of (+)-Lycoricidine and Its 2-Epimer.** For a structure–activity relationship study, 2-*epi*-lycori-

(26) For reviews of the Heck reaction, see: Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 4, p 833. Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146. Heck, R. F. *Org. React.* **1982**, *27*, 345.

(27) Some cases of trans β-hydride elimination have been documented; see: Dieck, H. A.; Heck, R. F. *J. Organomet. Chem.* **1975**, *93*, 259 and ref 18b.

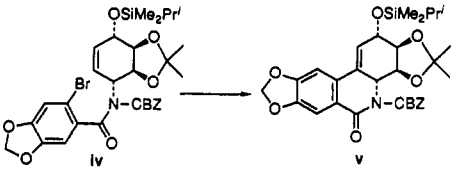
(28) Grigg suggested the possibility that the PdH elimination occurs via a conformation in which the dihedral angle between Pd and hydrogen is ca. 60°, even though they have an anti stereochemical relationship (see ref 23). This hypothesis could explain the formation of **21** from the intermediate **ii** (see Figure 1); however, it is still difficult to explain why vinyl ether **22** did not form at all.

(29) Although there is no experimental evidence for it, one of the plausible intermediates for this cyclization reaction is cyclopalladated compound **iii**, formed by the elimination of HBr from intermediate **i** (see Figure 1). This intermediate would afford **21** selectively via reductive elimination of Pd. Similar cyclopalladated intermediates have been recently proposed by Dyker and Rice in the intramolecular Pd-catalyzed arylation–cyclization reaction. See: Dyker, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1023. Rice, J. E.; Cai, Z.-W. *J. Org. Chem.* **1993**, *58*, 1415.




(30) We thank the reviewers and the senior editor for their suggestions on the mechanism of Pd-catalyzed cyclization reaction.

(31) After completion of our work, Hudlicky's group disclosed a synthesis of (+)-lycoricidine based on a similar modified Heck-type reaction of bromo enamide **iv** using dppe and Tl(OAc) (see ref 7d). Their cyclization reaction also selectively provided olefin **v**. Interestingly, the use of anisole as a solvent was crucial, and DMF was totally ineffective in their case. In our case, anisole was not a good solvent (Table I) for the cyclization reaction.

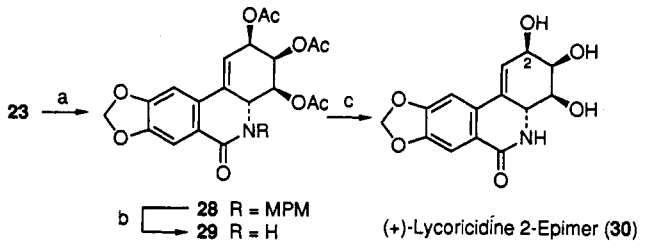



(32) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.

(33) Mitsunobu, O. *Synthesis* **1981**, 1.

(34) Smith, A. B., III; Rano, T. A.; Chida, N.; Sulikowski, G. A.; Wood, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 8008.

**Scheme VII**[a]




[a] Key: (a) aqueous HCl–THF, 50 °C, then $Ac_2O$, pyridine; (b) TFA–$CHCl_3$, rt; (c) MeONa–MeOH, rt.

**Table II. Cytotoxicity of Lycoricidine (1) and Its 2-Epimer (30) *in Vitro* against Murine P-388 Lymphocytic Leukemia**[a]

| compd | $IC_{50}$[b] (ng/mL) |
|---|---|
| lycoricidine (1) | 15 |
| lycoricidine 2-epimer (30) | 800 |
| adriamycin[c] | 11 |

[a] Determined by the MTT assay method after incubation for 72 h at 37 °C under 5% $CO_2$. [b] Concentrations required to cause 50% inhibition of growth. [c] Used as a control compound.

cidine (30) was prepared from synthetic intermediate 23 (Scheme VII). Acid hydrolysis of 23 with aqueous HCl in THF followed by acetylation afforded triacetate 28 in 92% yield. Removal of the *N*-MPM group and subsequent treatment of 29 with base provided 30 in 68% yield.

The cytotoxic activities of synthetic (+)-lycoricidine (1) and its 2-epimer 30 are shown in Table II. In accord with the previous report,[1] synthetic (+)-lycoricidine showed strong cytotoxicity against P-388 lymphocytic leukemia, almost comparable to that of adriamycin. The 2-epimer 30 showed weak activity (ca. 1/50 to lycoricidine), which suggested that the C2 stereochemistry is essential for the high cytotoxicity.

In summary, the stereoselective total synthesis of (+)-lycoricidine and its 2-epimer starting from D-glucose was accomplished. The success of this synthesis proved that our catalytic version of the Ferrier rearrangement is a powerful method for the preparation of optically active cyclohexanone derivatives from aldohexoses. The efficiency of the palladium-catalyzed cyclization reaction is also noteworthy for the construction of the skeleton of the phenanthridone alkaloids.

## Experimental Section

**General.** Melting points are uncorrected. $^1H$ NMR spectra were recorded at 90 or 270 MHz with tetramethylsilane as internal standard for solutions in $CDCl_3$, unless otherwise noted. $^{13}C$ NMR spectra were recorded at 67 MHz. High-resolution mass spectra were measured with the EI mode (70 eV). Optical rotations were measured in a 0.1-dm tube. Column chromatography was performed with Wakogel C-300 (Wako Pure Chemical, Osaka, Japan) or Katayama 60 (Katayama Chemical, Osaka, Japan). Analytical and preparative TLC were carried out on glass plates coated with Merck Kieselgel 60 Art 7734.

Unless otherwise noted, organic extracts were dried over anhydrous $Na_2SO_4$ and concentrated below 40 °C under reduced pressure. Solvents for reactions were dried and distilled before use (diethyl ether and THF from sodium benzophenone ketyl; $CH_2Cl_2$, HMPA, and DMF from $CaH_2$; pyridine from NaOH).

**Methyl 2-Azido-2,6-dideoxy-6-bromo-3,4-bis-*O*-(methoxymethyl)-α-D-altropyranoside (9) and Its 6-Chloro Derivative 10.** A mixture of methyl 2-azido-2,6-dideoxy-6-bromo-α-D-altropyranoside (8,[12] 9.51 g, 33.7 mmol), chloromethyl methyl ether (8.54 mL, 112 mmol), and *N*,*N*-diisopropylethylamine (39.1 mL, 225 mmol) in $CH_2Cl_2$ (90 mL) was heated at reflux for 15 h. The reaction mixture was diluted with $CH_2Cl_2$ and washed successively with 1 N HCl, saturated $NaHCO_3$ solution, and brine, dried, and concentrated to give a residue. Silica gel chromatography of the residue [150 g, EtOAc–toluene (1:10) eluent] afforded a syrupy, inseparable mixture of 9 and 10 (35:65, 10.4 g, 87% yield): IR (neat) 2100 $cm^{-1}$; $^1H$ NMR (270 MHz) δ 4.77 (m, 2 H), 4.76 (d, *J* = 7.0 Hz, 0.35 H), 4.75 (d, *J* = 7.0 Hz, 0.65 H), 4.71 (d, *J* = 7 Hz, 0.35 H), 4.70 (d, *J* = 7.0 Hz, 0.65 H), 4.65 (m, 1 H), 4.24 (m, 1 H), 3.94–3.85 (m, 3 H), 3.80 (dd, *J* = 11.7, 3.3 Hz, 0.65 H), 3.72 (dd, *J* = 11.7, 5.5 Hz, 0.65 H), 3.67 (dd, *J* = 11.0, 3.3 Hz, 0.35 H), 3.55 (dd, *J* = 11.0, 6.6 Hz, 0.35 H), 3.47 (s, 3 H × 0.35), 3.45 (s, 3 H × 0.35), 3.44 (s, 3 H × 0.65), 3.41 (s, 3 H × 0.65). Anal. Calcd for $C_{11}H_{20}N_3O_6Br_{0.35}Cl_{0.65}$: C, 38.71; H, 5.91; N, 12.31. Found: C, 38.91; H, 5.60; N, 12.31.

**Methyl 2-Azido-2,6-dideoxy-3,4-bis-*O*-(methoxymethyl)-α-D-*arabino*-5-enopyranoside (7).** A solution of a 35:65 mixture of 9 and 10 (10.3 g, 27.8 mmol) and DBU (12.5 mL, 83.5 mmol) in toluene (100 mL) was heated at reflux for 15 h. After cooling, the mixture was diluted with EtOAc and washed successively with 0.5 M $H_2SO_4$ solution, saturated $NaHCO_3$ solution, and brine, dried, and concentrated to give a residue. Silica gel chromatography of the residue [150 g, acetone–hexanes (1:15) eluent] gave 7 (5.85 g, 73%) as a colorless syrup: $[\alpha]^{22}_D$ +17° (*c* 2.7, $CHCl_3$); IR (neat) 2110, 1660 $cm^{-1}$; $^1H$ NMR (270 MHz) δ 4.86 (bs, 1 H), 4.81 (d, *J* = 7.0 Hz, 1 H), 4.79 (d, *J* = 6.6 Hz, 1 H), 4.77 (d, *J* = 6.6 Hz, 1 H), 4.62 (d, *J* = 7.0 Hz, 1 H), 4.61 (d, *J* = 1.1 Hz, 1 H), 4.32 (d, *J* = 3.3 Hz, 1 H), 4.22 (d, *J* = 7.7 Hz, 1 H), 3.88 (dd, *J* = 10.5, 7.7 Hz, 1 H), 3.61 (s, 3 H), 3.59 (dd, *J* = 10.5, 3.3 Hz, 1 H), 3.45 (s, 3 H), 3.39 (s, 3 H); HRMS *m/z* 289.1271 ($M^+$, calcd for $C_{11}H_{19}N_3O_6$ 289.1274). Anal. Calcd for $C_{11}H_{19}N_3O_6$: C, 45.67; H, 6.62; N, 14.53. Found: C, 45.58; H, 6.34; N, 14.33.

**2L-(2,3/4)-4-Azido-2,3-bis-*O*-(methoxymethyl)-2,3-dihydroxy-5-cyclohexen-1-one[35] (6).** A mixture of 7 (5.75 g, 19.9 mmol) and mercuric trifluoroacetate (84.8 mg, 0.199 mmol) in acetone–water (2:1, 90 mL) was stirred at rt for 20 h. The mixture was partially evaporated to remove acetone and then extracted with EtOAc. The organic layer was washed successively with aqueous 10% KI solution, aqueous 20% $Na_2S_2O_3$ solution, saturated $NaHCO_3$ solution, and brine and dried. Removal of the solvent afforded crude 11 (5.75 g) as a colorless syrup, which was used in the next reaction without purification. To a solution of crude 11 (5.75 g) in $CH_2Cl_2$ (90 mL) at 0 °C was added triethylamine (16.6 mL, 119 mmol) and methanesulfonyl chloride (4.62 mL, 59.5 mmol), and the resulting mixture was stirred at 0 °C for 1.5 h. The mixture was diluted with $CH_2Cl_2$ and then washed successively with 0.5 M $H_2SO_4$ solution, saturated $NaHCO_3$ solution, and brine, dried, and concentrated to give a residue. Silica gel chromatography of the residue [150 g, acetone–hexanes (1:5) eluent] gave 6 (3.52 g, 69%) as a colorless syrup: $[\alpha]^{22}_D$ −282° (*c* 0.9, $CHCl_3$); IR (neat) 2100, 1690 $cm^{-1}$; $^1H$ NMR (270 MHz) δ 6.74 (dd, *J* = 10.3, 2.9 Hz, 1 H), 6.11 (dd, *J* = 10.3, 1.8 Hz, 1 H), 4.85, 4.79, 4.76, and 4.74 (4d, *J* = 6.6 Hz, each 1 H), 4.59 (ddd, *J* = 6.6, 2.9, 1.8 Hz, 1 H), 4.38 (d, *J* = 2.6 Hz, 1 H), 4.07 (dd, *J* = 6.6, 2.6 Hz, 1 H), 3.44 and 3.40 (2s, each 3 H); HRMS *m/z* 258.1085 [$(M + H)^+$, calcd for $C_{10}H_{16}N_3O_5$ 258.1090].

**1L-(1,2,3/4)-4-Azido-2,3-bis-*O*-(methoxymethyl)-5-cyclohexene-1,2,3-triol[35] (15).** To a solution of 6 (120 mg, 0.466 mmol) in methanol (3 mL) at 0 °C was added cerium(III) chloride heptahydrate (261 mg, 0.700 mmol). After the mixture was stirred at 0 °C for 5 min, sodium borohydride (19.4 mg, 0.513 mmol) was added, and the resulting mixture was stirred at 0 °C for an additional 30 min. The reaction mixture was neutralized with acetic acid (30 μL, 0.513 mmol) and then concentrated to give a residue. The residue was dissolved in EtOAc, washed with saturated $NaHCO_3$ solution and brine, dried, and concentrated to give a residue. Silica gel chromatography of the residue [3 g, EtOAc–toluene (1:5) eluent] gave 15 (104 mg, 86%) as a colorless syrup: $[\alpha]^{25}_D$ −159° (*c* 1.2, $CHCl_3$); IR (neat) 3430, 2100 $cm^{-1}$; $^1H$ NMR (270 MHz) δ 5.77 (ddd, *J* = 10.3, 3.3, 1.8 Hz, 1 H), 5.63 (ddd, *J* = 10.3, 2.2, 2.2 Hz, 1 H), 4.86 (d, *J* = 6.6 Hz, 1 H), 4.83 (d, *J* = 7.0 Hz, 1 H), 4.81 (d, *J* = 6.6 Hz, 1 H), 4.76 (d, *J* = 7.0 Hz, 1 H), 4.26–4.23 (m, 2 H), 4.17 (ddd, *J* = 3.3, 2.2, 1.5 Hz, 1 H), 3.74 (dd, *J* = 8.3, 1.5 Hz, 1 H), 3.46 and 3.43 (2s, each 3 H). Anal. Calcd for $C_{10}H_{17}N_3O_5$: C, 46.33; H, 6.61; N, 16.21. Found: C, 46.24; H, 6.72; N, 15.90.

(35) The nomenclature and numbering of this compound follow IUPAC and IUB tentative rules for cyclitol nomenclature; see: *J. Biol. Chem.* 1968, *243*, 5809.

**1L-(1,2,3/4)-4-[(*tert*-Butoxycarbonyl)amino]-2,3-bis-*O*-(methoxymethyl)-5-cyclohexene-1,2,3-triol[35] (16).** To a stirred suspension of $LiAlH_4$ (21.9 mg, 0.576 mmol) in THF (0.5 mL) at 0 °C was added a solution of **15** (49.8 mg, 0.192 mmol) in THF (2 mL) dropwise. After the reaction mixture was stirred at 0 °C for 10 min, additional $LiAlH_4$ (11.3 mg, 0.298 mmol) was added. After being stirred for 15 min at 0 °C, the reaction was quenched with water. Insoluble material was removed by filtration through a bed of Celite, and the filtrate was concentrated and codistilled with ethanol several times to afford a residue. This residue was dissolved in $CH_2Cl_2$ (1 mL) and treated with di-*tert*-butyl dicarbonate (83.8 mg, 0.384 mmol) and triethylamine (54 μL, 0.384 mmol) at room temperature for 12 h. The mixture was concentrated to give a residue, which was purified by silica gel chromatography [6 g, EtOAc–toluene (1:2) eluent] to provide **16** (20.8 mg, 33%) as a crystalline residue: mp 134–135 °C (from toluene); $[\alpha]^{26}_D$ −124° (*c* 1.0, $CHCl_3$); IR (KBr) 3420, 1690 $cm^{-1}$; $^1H$ NMR (270 MHz) δ 5.75 (bd, *J* = 10.3 Hz, 1 H), 5.65 (ddd, *J* = 10.3, 2.6, 1.8 Hz, 1 H), 4.87, 4.81, 4.76 and 4.69 (4d, *J* = 7.0 Hz, each 1 H), 4.67 (m, 1 H), 4.40 (m, 1 H), 4.25 (bd, *J* = 9.3 Hz), 4.08 (bs, 1 H), 3.78 (bd, *J* = 7.3 Hz), 3.43 and 3.42 (2s, each 3 H), 3.26 (bd, *J* = 9.3 Hz), 1.45 (s, 9 H). Anal. Calcd for $C_{15}H_{27}NO_7$: C, 54.04; H, 8.16; N, 4.20. Found: C, 53.92; H, 7.84; N, 4.23.

**1L-(1,2,3/4)-1-*O*-Acetyl-4-[(*tert*-butoxycarbonyl)amino]-2,3-bis-*O*-(methoxymethyl)-5-cyclohexane-1,2,3-triol[35] (17).** A mixture of **16** (19.5 mg, 0.0584 mmol) and platinum oxide (10 mg) in ethanol (0.5 mL) was hydrogenolyzed under 1 atm of $H_2$ at rt for 3 h. The catalyst was removed by filtration, and the filtrate was concentrated to give a residue, which was treated with acetic anhydride (0.5 mL) and pyridine (0.5 mL) at rt for 4 h. After the addition of methanol, the mixture was concentrated and purified by silica gel chromatography [1 g, acetone–toluene (1:1) eluent] to provide **17** (18.4 mg, 83%) as a crystalline residue: mp 110–112 °C (from ether–hexane); $[\alpha]^{26}_D$ −6° (*c* 0.9, $CHCl_3$); IR (KBr) 3370, 1740, 1720 $cm^{-1}$; $^1H$ NMR (270 MHz), δ 4.78 (d, *J* = 6.6 Hz, 1 H), 4.73 and 4.70 (2d, *J* = 4.8 Hz, each 1 H), 4.65 (ddd, *J* = 12.5, 4.4, 2.6 Hz, 1 H), 4.58 (d, *J* = 6.6 Hz, 1 H), 4.16 (bs, 1 H), 3.80 (m, 1 H), 3.42 and 3.41 (2s, each 3 H), 3.32 (dd, *J* = 10.6, 2.6 Hz, 1 H), 2.19 (m, 1 H), 2.06 (s, 3 H), 1.94 (dddd, *J* = 13.6, 12.5, 4.4, 4.4 Hz), 1.66 (m, 1 H), 1.43 (s, 9 H), 1.18 (dddd, *J* = 13.6, 13.6, 12.1, 4.0 Hz, 1 H). Anal. Calcd for $C_{17}H_{31}NO_8$: C, 54.10; H, 8.28; N, 3.71. Found: C, 54.20; H, 7.82; N, 3.81.

**1L-(1,2,3/4)-4-Azido-1-*O*-(4-methoxybenzyl)-2,3-bis-*O*-(methoxymethyl)-5-cyclohexene-1,2,3-triol[35] (18).** To a stirred solution of **15** (2.01 g, 7.75 mmol) in DMF (40 mL) at 0 °C was added NaH (60% dispersion in oil, 558 mg, 14.0 mmol). After the mixture was stirred at 0 °C for 30 min, 4-methoxybenzyl chloride (1.86 mL, 14.0 mmol) was added, and the resulting mixture was stirred at rt for 18 h. The reaction mixture was poured into ice-cold saturated $NaHCO_3$ solution and extracted with EtOAc. The extract was washed with saturated $NaHCO_3$ solution and brine, dried, and concentrated to give a residue, which was purified by silica gel chromatography [100 g, EtOAc–toluene (1:12) eluent] to afford **18** (2.04 g, 69%) as a colorless syrup: $[\alpha]^{22}_D$ −150° (*c* 1.8, $CHCl_3$); IR (neat) 2100 $cm^{-1}$; $^1H$ NMR (270 MHz) δ 7.26 and 6.86 (2d, *J* = 8.8 Hz, each 1 H), 5.77 (ddd, *J* = 10.3, 4.5, 1.8 Hz, 1 H), 5.66 (ddd, *J* = 10.3, 2.6, 2.2 Hz, 1 H), 4.86 (d, *J* = 7.1 Hz, 1 H), 4.83 (s, 2 H), 4.72 (d, *J* = 7.1 Hz, 1 H), 4.62 (d, *J* = 11.7 Hz, 1 H), 4.55 (d, *J* = 11.7 Hz, 1 H), 4.39 (m, 1 H), 4.31 (ddd, *J* = 8.8, 4.5, 2.2 Hz, 1 H), 4.07 (m, 1 H), 3.81 (s, 3 H), 3.65 (dd, *J* = 8.8, 1.8 Hz, 1 H), 3.48 and 3.42 (2s, each 3 H). Anal. Calcd for $C_{18}H_{25}N_3O_6$: C, 56.98; H, 6.64; N, 11.07. Found: C, 57.02; H, 6.44; N, 10.94.

**1L-(1,2,3/4)-4-[(6-Bromopiperonyloyl)amino]-1-*O*-(4-methoxybenzyl)-2,3-bis-*O*-(methoxymethyl)-5-cyclohexene-1,2,3-triol[35] (19).** To a stirred suspension of $LiAlH_4$ (152 mg, 4.00 mmol) in $Et_2O$ (3 mL) at 0 °C was added a solution of **18** (506 mg, 1.33 mmol) in $Et_2O$ (10 mL) dropwise. After being stirred at 0 °C for 30 min, the reaction was quenched with water at 0 °C, and the product was extracted with EtOAc. The extract was concentrated to give the crude amine. To a solution of this crude amine and 6-bromopiperonylic acid[21] (**5**, 358 mg, 1.37 mmol) in DMF (20 mL) at 0 °C were added diethyl cyanophosphonate (245 μL, 1.61 mmol) and triethylamine (393 μL, 2.82 mmol). After being stirred at 0 °C for 15 min, the reaction mixture was diluted with EtOAc, washed with brine, dried, and concentrated to give a residue. Silica gel chromatography of the residue [30 g, acetone–toluene (1:5) eluent] gave **19** (692 mg, 89%) as a crystalline residue: mp 180–182 °C (from toluene); $[\alpha]^{22}_D$ −160° (*c* 0.5, $CHCl_3$); IR (KBr) 1660, 1510 $cm^{-1}$; $^1H$ NMR (270 MHz) δ 7.29 (d, *J* = 8.8 Hz, 2 H), 7.07 (s, 1 H), 6.99 (s, 1 H), 6.88 (d, *J* = 8.8 Hz, 2 H), 6.18 (d, *J* = 8.1 Hz, 1 H), 6.01 (s, 2 H), 5.80 (m, 1 H), 5.76 (m, 1 H), 4.93 (m, 1 H), 4.91, 4.85, 4.78 and 4.66 (4d, *J* = 7.0 Hz, each 1 H), 4.64 and 4.57 (2d, *J* = 11.8 Hz, each 1 H), 4.41 (m, 1 H), 4.14 (m, 1 H), 3.81 (s, 3 H), 3.77 (dd, *J* = 9.2, 1.5 Hz, 1 H), 3.44 and 3.35 (2s, each 3 H). Anal. Calcd for $C_{26}H_{30}NO_9Br$: C, 53.80; H, 5.21; N, 2.41. Found: C, 53.72; H, 5.21; N, 2.45.

**1L-(1,2,3/4)-4-[(6-Bromopiperonyloyl)(4-methoxybenzyl)-amino]-1-*O*-(4-methoxybenzyl)-2,3-bis-*O*-(methoxymethyl)-5-cyclohexene-1,2,3-triol[35] (20).** To a stirred solution of **19** (2.09 g, 3.60 mmol) in DMF (40 mL) at 0 °C was added NaH (60% dispersion in oil, 288 mg, 7.20 mmol). After the reaction mixture stirred at 0 °C for 30 min, 4-methoxybenzyl chloride (1.46 mL, 10.8 mmol) was added, and the resulting mixture was stirred at rt for 5 h. The reaction mixture was poured into an ice-cold saturated $NaHCO_3$ solution and extracted with EtOAc. The extract was washed with saturated $NaHCO_3$ solution and brine, dried, and concentrated to give a residue. Silica gel chromatography of the residue [120 g, EtOAc–toluene (1:5) eluent] gave **20** (2.71 g, 100%) as a colorless syrup: $[\alpha]^{21}_D$ −141° (*c* 0.3, $CHCl_3$); IR (neat) 1630, 1610 $cm^{-1}$; $^1H$ NMR (270 MHz) δ 7.40 and 7.23 (2d, *J* = 8.4 Hz, each 2 H), 6.90 (d, *J* = 8.8 Hz, 2 H), 6.85 (s, 2 H), 6.82 (d, *J* = 8.8 Hz, 2 H), 5.95 (d, *J* = 1.3 Hz, 1 H), 5.89 (d, *J* = 1.3 Hz, 1 H), 5.62 (s, 2 H), 4.93 (d, *J* = 15.2 Hz, 1 H), 4.67 (m, 1 H), 4.65 (d, *J* = 7.1 Hz, 1 H), 4.59 (s, 2 H), 4.53 (s, 2 H), 4.28 (m, 1 H), 4.24 (d, *J* = 15.2 Hz, 1 H), 4.22 (s, 1 H, *J* = 7.1 Hz, 1 H), 4.04 (dd, *J* = 3.3, 3.3 Hz, 1 H), 3.80 and 3.79 (2s, each 3 H), 3.72 (dd, *J* = 9.5, 1.5 Hz, 1 H), 3.41 and 3.17 (2s, each 3 H). Anal. Calcd for $C_{34}H_{38}NO_{10}Br$: C, 58.29; H, 5.47; N, 2.00. Found: C, 58.18; H, 5.39; N, 1.96.

**(2*R*,3*R*,4*S*,4a*R*)-5-(4-Methoxybenzyl)-2-[(4-methoxybenzyl)oxy]-3,4-bis[(methoxymethyl)oxy]-3,4,4a,5-tetrahydro[1,3]dioxolo[4,5-*f*]phenanthridin-6(2*H*)-one (21).** A mixture of **20** (156 mg, 0.223 mmol), palladium(II) acetate (10.0 mg, 0.0445 mmol), 1,2-bis(diphenylphosphino)ethane (35.5 mg, 0.0891 mmol), and thallium(I) acetate (117 mg, 0.445 mmol) in DMF (5 mL) under Ar was heated at 140 °C for 7 h. After cooling, the reaction mixture was diluted with EtOAc, and insoluble material was removed by filtration. The filtrate was concentrated to give a residue, which was purified by silica gel chromatography [5 g, EtOAc–toluene (1:7) eluent] to afford **21** (93.8 mg, 68%) as a colorless syrup: $[\alpha]^{22}_D$ −32° (*c* 0.7, $CHCl_3$); IR (neat) 1650, 1610 $cm^{-1}$; $^1H$ NMR (270 MHz) δ 7.53 (s, 1 H), 7.30 and 7.11 (2d, *J* = 8.8 Hz, each 2 H), 6.02 and 6.01 (2d, *J* = 1.3 Hz, each 1 H), 5.99 (m, 1 H), 5.19 and 4.97 (2d, *J* = 16.1 Hz, each 1 H), 4.77 (s, 2 H), 4.74 (d, *J* = 6.8 Hz, 1 H), 4.72 (m, 1 H), 4.67 and 4.59 (2d, *J* = 11.7 Hz, each 1 H), 4.49 (d, *J* = 6.8 Hz, 1 H), 4.37 (m, 1 H), 4.14 (m, 1 H), 3.99 (dd, *J* = 7.7, 1.8 Hz, 1 H), 3.81, 3.76, 3.38, and 3.38 (4s, each 3 H). Anal. Calcd for $C_{34}H_{37}NO_{10}$: C, 65.90; H, 6.02; N, 2.26. Found: C, 65.33; H, 5.89; N, 2.23. Further elution afforded starting material **20** (11.8 mg, 8%).

**(2*R*,3*R*,4*S*,4a*R*)-2-Hydroxy-5-(4-methoxybenzyl)-3,4-bis[(methoxymethyl)oxy]-3,4,4a,5-tetrahydro[1,3]dioxolo[4,5-*f*]phenanthridin-6(2*H*)-one (23).** To a stirred mixture of **21** (1.24 g, 2.00 mmol) in $CH_2Cl_2$ (36 mL) and water (2 mL) at 0 °C was added DDQ (681 mg, 3.00 mmol), and the mixture was stirred at 0 °C for 3 h. To the reaction mixture was added 10% aqueous sodium sulfite solution, and the product was extracted with $CH_2Cl_2$. The organic layer was washed three times with saturated $NaHCO_3$ solution and brine, dried, and concentrated to give a residue. Silica gel chromatography of the residue [40 g, EtOAc–toluene (1:2) eluent] gave **23** (530 mg, 53%) as a colorless syrup: $[\alpha]^{21}_D$ +32° (*c* 1.5, $CHCl_3$); IR (neat) 3400, 1640, 1610 $cm^{-1}$; $^1H$ NMR (270 MHz) δ 7.59 (s, 1 H), 7.15 (d, *J* = 8.4 Hz, 2 H), 6.92 (s, 1 H), 6.85 (d, *J* = 8.4 Hz, 2 H), 6.10 (dd, *J* = 4.2, 1.6 Hz, 1 H), 6.05 and 6.03 (2d, *J* = 1.4 Hz, each 1 H), 5.09 and 4.89 (2d, *J* = 16.1 Hz, each 1 H), 4.75, 4.62 and 4.57 (3d, *J* = 7.0 Hz, each 1 H), 4.47 (m, 1 H), 4.42 (m, 2 H), 4.31 (d, *J* = 7.0 Hz, 1 H), 3.97 (m, 1 H), 3.77, 3.41, and 3.29 (3s, each 3 H); HRMS *m/z* 499.1851 ($M^+$, calcd for $C_{26}H_{29}NO_9$ 499.1842).

**(2*S*,3*R*,4*S*,4a*R*)-2-(Benzoyloxy)-5-(4-methoxybenzyl)-3,4-bis[(methoxymethyl)oxy]-3,4,4a,5-tetrahydro[1,3]dioxolo-**

**[4,5-*f*]phenanthridin-6(2*H*)-one (24).** To a solution of **23** (266 mg, 0.533 mmol), triphenylphosphine (279 mg, 1.07 mmol), and benzoic acid (130 mg, 1.07 mmol) in THF (12 mL) under Ar at rt was added diethyl azodicarboxylate (168 μL, 1.07 mmol) dropwise. After being stirred at room temperature for 15 min, the reaction mixture was concentrated to give a residue, which was purified by silica gel chromatography [30 g, 2-butanone–toluene (1:10) eluent] to afford **24** (251 mg, 78%) as a colorless syrup: $[\alpha]^{26}_D$ +121° (*c* 1.6, $CHCl_3$); IR (neat) 1740, 1650, 1610 $cm^{-1}$; $^1H$ NMR (270 MHz) δ 8.02 (m, 2 H), 7.63 (s, 1 H), 7.57–7.41 (m, 3 H), 7.22 (d, *J* = 8.4 Hz, 2 H), 6.89 (s, 1 H), 6.87 (d, *J* = 8.4 Hz, 2 H), 6.04 and 6.02 (2d, *J* = 1.1 Hz, each 1 H), 5.99 (m, 2 H), 5.52 (d, *J* = 15.4 Hz, 1 H), 4.69 and 4.60 (2d, *J* = 7.0 Hz, each 1 H), 4.57–4.51 (m, 2 H), 4.30–4.26 (m, 2 H), 4.22 (d, *J* = 7.0 Hz, 1 H), 4.02 (dd, *J* = 7.7, 1.8 Hz, 1 H), 3.78, 3.38 and 3.18 (3s, each 3 H); HRMS *m/z* 603.2096 ($M^+$, calcd for $C_{33}H_{33}NO_{10}$ 603.2104). Anal. Calcd for $C_{33}H_{33}NO_{10}·H_2O$: C, 63.76; H, 5.68; N, 2.25. Found: C, 63.58; H, 5.52; N, 2.41.

**(2*S*,3*R*,4*S*,4a*R*)-2-Hydroxy-5-(4-methoxybenzyl)-3,4-bis[(methoxymethyl)oxy]-3,4,4a,5-tetrahydro[1,3]dioxolo[4,5-*f*]phenanthridin-6(2*H*)-one (25).** To an ice-cooled solution of **24** (28.5 mg, 0.0472 mmol) in methanol–THF (5:1, 1.2 mL) was added sodium methoxide (1 mg, 0.019 mmol). After being stirred at room temperature for 1.5 h, the reaction mixture was neutralized with acidic resin [Amberlite IR-120B ($H^+$ form)]. The resin was removed by filtration, and the filtrate was concentrated to give a residue. Silica gel chromatography of the residue [3 g, EtOAc–toluene (2:3) eluent] gave **25** (23.4 mg, 99%) as a colorless syrup: $[\alpha]^{25}_D$ +74° (*c* 1.1, $CHCl_3$); IR (neat) 3400, 1630, 1610 $cm^{-1}$; $^1H$ NMR (270 MHz) δ 7.59 (s, 1 H), 7.22 and 6.86 (2d, *J* = 8.6 Hz, each 2 H), 6.85 (s, 1 H), 6.05 and 6.04 (2d, *J* = 1.3 Hz, each 1 H), 5.95 (dd, *J* = 1.8, 1.5 Hz, 1 H), 5.07 and 4.80 (2d, *J* = 15.8 Hz, each 1 H), 4.60 (d, *J* = 6.6 Hz, 1 H), 4.58–4.52 (m, 3 H), 4.32 (d, *J* = 6.6 Hz, 1 H), 4.29 (m, 1 H), 4.19 (m, 1 H), 3.77 (s, 3 H), 3.54 (bs, 1 H), 3.42 (s, 3 H), 3.27 (dd, *J* = 8.4, 2.0 Hz, 1 H), 3.20 (s, 3 H). Anal. Calcd for $C_{26}H_{29}NO_9$: C, 62.52; H, 5.85; N, 2.80. Found: C, 61.96; H, 5.69; N, 2.80.

**(2*S*,3*R*,4*S*,4a*R*)-2,3,4-Triacetoxy-5-(4-methoxybenzyl)-3,4,4a,5-tetrahydro[1,3]dioxolo[4,5-*f*]phenanthridin-6(2*H*)-one (26).** A solution of **25** (246 mg, 0.493 mmol) in THF (4 mL) and 1 N aqueous HCl (2 mL) was stirred at 50 °C for 23 h. The resulting mixture was concentrated and codistilled several times with ethanol to give a residue, which was then treated with acetic anhydride (2 mL) and pyridine (3 mL) at rt for 3 h. The mixture was concentrated to give a residue, which was purified by silica gel chromatography [20 g, EtOAc–toluene (1:7) eluent] to provide **26** (135 mg, 51%) as a colorless syrup: $[\alpha]^{25}_D$ +154° (*c* 0.6, $CHCl_3$); IR (neat) 1740, 1640, 1610 $cm^{-1}$; $^1H$ NMR (270 MHz) δ 7.62 (s, 1 H), 7.17 (d, *J* = 8.8 Hz, 2 H), 6.89 (s, 1 H), 6.82 (d, *J* = 8.8 Hz, 2 H), 6.06 and 6.05 (2d, *J* = 1.3 Hz, 2 H), 5.96 (dd, *J* = 2.9, 1.5 Hz, 1 H), 5.91 (dd, *J* = 4.0, 2.6 Hz, 1 H), 5.57 (ddd, *J* = 7.0, 2.9, 1.5 Hz, 1 H), 5.45 (d, *J* = 16.1 Hz, 1 H), 5.12 (dd, *J* = 7.0, 2.6 Hz, 1 H), 4.60 (d, *J* = 16.1 Hz, 1 H), 4.29 (ddd, *J* = 4.0, 1.5, 1.5 Hz, 1 H), 3.77, 2.09, 2.05 and 1.88 (4s, each 3 H); HRMS *m/z* 537.1631 ($M^+$, calcd for $C_{28}H_{27}NO_{10}$ 537.1635).

**(2*S*,3*R*,4*S*,4a*R*)-2,3,4-Triacetoxy-3,4,4a,5-tetrahydro[1,3]dioxolo[4,5-*f*]phenanthridin-6(2*H*)-one [(+)-Lycoricidine Triacetate] (27).** A solution of **26** (66.3 mg, 0.123 mmol) in TFA (0.75 mL) and chloroform (0.75 mL) was stirred at rt for 1.5 h. The reaction mixture was concentrated, and the residual TFA was removed by coevaporation with several portions of $CHCl_3$ to give a residue. Silica gel chromatography of the residue [4 g, EtOAc–toluene (1:4) eluent] gave **27** (27.3 mg, 53%) as a crystalline residue: mp 233–235 °C (from $CH_2Cl_2$–hexane) (lit.[7c] mp 236–237 °C); $[\alpha]^{24}_D$ +238° (*c* 0.1, $CHCl_3$) [lit.[7c] $[\alpha]^{24}_D$ +214° (*c* 0.45, $CHCl_3$)]; $^1H$ NMR (270 MHz, acetone-$d_6$) δ 7.43 (s, 1 H), 7.25 (s, 1 H), 6.28 (ddd *J* = 4.8, 2.6, 1.1 Hz, 1 H), 6.15, 6.13 (2d, *J* = 1.1 Hz, each 1 H), 5.44 (ddd, *J* = 2.6, 2.6, 1.1 Hz, 1 H), 5.36 (ddd, *J* = 4.8, 2.6, 1.1 Hz, 1 H), 5.18 (dd, *J* = 9.0, 2.6 Hz, 1 H), 4.70 (ddd, *J* = 9.0, 2.6, 1.1 Hz, 1 H), 2.09, 2.09 and 2.07 (3s, each 3H); $^{13}C$ NMR (67 MHz, $CDCl_3$, $^{13}CDCl_3$ = 77.0 ppm) δ 170.3, 169.8, 169.5, 164.1, 151.9, 149.3, 133.9, 130.3, 122.2, 117.3, 107.7, 103.4, 102.1, 71.4, 68.5, 68.1, 50.2, 20.9, 20.9, 20.8: HRMS *m/z* 417.1067 ($M^+$, calcd for $C_{20}H_{19}NO_9$ 417.1060). The $^1H$ and $^{13}C$ NMR data of **27** were identical with those reported in the literature.[7c]

**(+)-Lycoricidine (1).** To an ice-cooled solution of **27** (3.1 mg, 7.2 μmol) in methanol–THF (5:1, 0.6 mL) was added sodium methoxide (0.5 mg, 0.01 mmol). After being stirred at room temperature for 1 h, the reaction mixture was neutralized with acidic resin [Amberlite IR-120B ($H^+$ form)]. The resin was removed by filtration, and the filtrate was concentrated to give a residue. Silica gel chromatography of the residue [0.5 g, triethylamine–methanol–$CH_2Cl_2$ (1:8:43) eluent] gave **1** (2.1 mg, 100%) as a crystalline residue: mp 217–221 °C dec (from methanol) (lit.[7c] mp 224–226 °C dec); $[\alpha]^{24}_D$ +204° (*c* 0.21, pyridine) [lit.[7c] $[\alpha]^{24}_D$ +180° (*c* 0.21, pyridine)]; $^1H$ NMR (270 MHz, $CD_3OD$) δ 7.40 (s, 1 H), 7.16 (s, 1 H), 6.17 (ddd, *J* = 4.9, 2.5, 1.0 Hz, 1 H), 6.07 (bs, 1 H), 6.05 (bs, 1 H), 4.39 (ddd, *J* = 8.3, 2.5, 1.5 Hz, 1 H), 4.24 (ddd, *J* = 4.9, 2.5, 1.5 Hz, 1 H), 3.94–3.90 (m, 2 H); $^{13}C$ NMR (67 MHz, $CD_3OD$, $^{13}CD_3OD$ = 49.0 ppm) δ 166.6, 153.5, 150.1, 133.4, 132.7, 123.4, 122.8, 107.7, 104.4, 103.6, 74.4, 70.9, 70.9, 53.9; HRMS *m/z* 291.0774 ($M^+$, calcd for $C_{14}H_{13}NO_6$ 291.0743). The $^1H$ and $^{13}C$ NMR data were identical with those reported in the literature.[7c]

**(2*R*,3*R*,4*S*,4a*R*)-2,3,4-Triacetoxy-5-(4-methoxybenzyl)-3,4,4a,5-tetrahydro[1,3]dioxolo[4,5-*f*]phenanthridin-6(2*H*)-one (28).** A solution of **23** (200 mg, 0.400 mmol) in THF (4 mL) and 1 N aqueous HCl (2 mL) was stirred at 50 °C for 20 h. The resulting mixture was concentrated and codistilled several times with ethanol to give a residue, which was then treated with acetic anhydride (2 mL) and pyridine (3 mL) at rt for 3 h. The mixture was concentrated to give a residue, which was purified by silica gel chromatography [20 g, EtOAc–toluene (1:7) eluent] to provide **28** (198 mg, 92%) as a crystalline residue: mp 168–169.5 °C (from toluene); $[\alpha]^{27}_D$ +7° (*c* 0.5, $CHCl_3$); IR (KBr) 1745, 1650, 1610 $cm^{-1}$: $^1H$ NMR (270 MHz) δ 7.60 (s, 1 H), 7.00 (d, *J* = 8.8 Hz, 2 H), 6.98 (s, 1 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 6.07 and 6.05 (2d, *J* = 1.1 Hz, 2 H), 5.93 (m, 1 H), 5.73 (m, 1 H), 5.60 (m, 1 H), 5.42 (dd, *J* = 8.1, 2.6 Hz, 1 H), 5.05 (d, *J* = 16.9 Hz, 1 H), 4.80 (ddd, *J* = 8.1, 2.6, 2.6 Hz, 1 H), 4.59 (d, *J* = 16.9 Hz, 1 H), 3.77, 2.09, 2.07 and 1.70 (4s, each 3 H). Anal. Calcd for $C_{28}H_{27}NO_{10}$: C, 62.56; H, 5.06; N, 2.61. Found: C, 62.85; H, 5.04; N, 2.58.

**(2*R*,3*R*,4*S*,4a*R*)-2,3,4-Triacetoxy-3,4,4a,5-tetrahydro[1,3]dioxolo[4,5-*f*]phenanthridin-6(2*H*)-one (29).** A solution of **28** (149 mg, 0.274 mmol) in TFA (0.75 mL) and $CHCl_3$ (0.75 mL) was stirred at rt for 1.5 h. The reaction mixture was concentrated, and the residual TFA was removed by coevaporation with several portions of chloroform to give a residue. Silica gel chromatography of the residue [6 g, EtOAc–toluene (1:4) eluent] gave **29** (90.5 mg, 79%) as a crystalline residue: mp 222–224 °C (from $CH_2Cl_2$–hexane); $[\alpha]^{27}_D$ −33° (*c* 0.3, $CHCl_3$); $^1H$ NMR (270 MHz) δ 7.54 (s, 1 H), 7.00 (s, 1 H), 6.43 (bs, 1 H), 6.07, 6.05 (2d, *J* = 1.1 Hz, each 1 H), 5.90 (bs, 1 H), 5.82 (m, 1 H), 5.76 (m, 1 H), 5.12 (dd, *J* = 9.3, 2.2 Hz, 1 H), 4.73 (ddd, *J* = 9.3, 3.3, 2.9 Hz, 1 H), 2.15, 2.12, and 2.09 (3s, each 3H); $^{13}C$ NMR (67 MHz, $CDCl_3$, $^{13}CDCl_3$ = 77.0 ppm) δ 170.2, 170.1, 169.6, 164.6, 151.7, 148.9, 131.0, 130.3, 122.1, 119.7, 107.4, 103.2, 102.0, 72.4, 68.1, 67.5, 50.7, 20.9, 20.7, 20.7. Anal. Calcd for $C_{20}H_{19}NO_9$: C, 57.56; H, 4.59; N, 3.36. Found: C, 57.33; H, 4.67; N, 3.30.

**(2*R*,3*R*,4*S*,4a*R*)-2,3,4-Trihydroxy-3,4,4a,5-tetrahydro[1,3]dioxolo[4,5-*f*]phenanthridin-6(2*H*)-one [(+)-Lycoricidine 2-Epimer] (30).** To an ice-cooled solution of **29** (81.2 mg, 0.195 mmol) in methanol–THF (5:1, 2 mL) was added sodium methoxide (5 mg, 0.093 mmol). After being stirred at room temperature for 2 h, the reaction mixture was neutralized with acidic resin [Amberlite IR-120B ($H^+$ form)]. The resin was removed by filtration, and the filtrate was concentrated to give a residue. Silica gel chromatography of the residue [3 g, triethylamine–methanol–$CH_2Cl_2$ (1:8:43) eluent] gave **30** (36.6 mg, 86%) as a crystalline residue: mp 215–220 °C dec (from methanol); $[\alpha]^{24}_D$ +33° (*c* 0.1, pyridine); $^1H$ NMR (270 MHz, $CD_3OD$) δ 7.38 (s, 1 H), 7.11 (s, 1 H), 6.06, 6.04 (2d, *J* = 1.1 Hz, each 1H), 6.00 (m, 1 H), 4.44 (m, 2 H), 4.10 (m, 1 H), 3.74 (dd, *J* = 9.0, 2.0 Hz, 1 H); $^{13}C$ NMR [67 MHz, DMSO-$d_6$, $(^{13}CH_3)_2SO$ = 39.7 ppm] δ 163.4, 151.2, 147.8, 131.7, 127.9, 126.8, 122.1, 106.4, 103.2, 102.1, 72.5, 71.9, 67.8, 53.2; HRMS *m/z* 291.0728 ($M^+$, calcd for $C_{14}H_{13}NO_6$ 291.0743).

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