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Synthetic Studies on Lycoricidine and Related Compounds. II.[1] Total Synthesis of (±)-Lycoricidine

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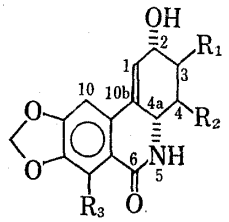
The first total synthesis of (±)-lycoricidine and confirmation of its full structure were established. In the synthesis of a key compound, 4*H-r*,1*H-trans*,2*H-cis*,10b*H-trans*,-1-(2′-tetrahydropyranyloxy)-2-hydroxy-8,9-methylenedioxy-1,2,4a,10b-tetrahydro-6(5*H*)-phenanthridone (**14**), Sharpless's procedure for preparation of allyl alcohols from epoxides using selenophenolate and hydrogene peroxide was applied.

The structure of lycoricidine[3] has been proposed as formula **2** on the basis of the closely analogous chemical behavior, biological activities and nuclear magnetic resonance (NMR) spectrum of its acetate with those of lycoricidinol,[3] whose structure has already been confirmed as **1** by X-ray analysis.[4] Attempt to synthesize the proposed structure (**2**) of lycoricidine was made and in the preceding paper,[1] synthesis of compound (**3**) lacking two hydroxyl groups at 3- and 4-position in the structure of **2** was reported. This paper deals with the first total synthesis of (±)-lycoricidine and confirmation of its structure.[5]

Hydrolysis of N-acetyl lactam (**4**)[1] with potassium hydroxide in dil. methanol afforded a lactam (**5**)[1] in 31% yield and a carboxylic acid (**6**) (mp 201°) in 67.8% yield, the structure of which was confirmed by presence of absorption bands of secondary amide group and by elemental analysis. It is considered that hydrolysis of the N-acetyl lactam (**4**) takes place through two ways, that is, hydrolysis at the benzamide side and at the acetamide side and cleavage at the former side preferred to that at the later. The fact corresponded to acidity of the acids participating in formation of the imide. To a suspension of **6** in anhydrous tetrahydrofuran (THF) was added N-bromosuccinimide (NBS) and the resulting compound had halogen atom and its NMR and infrared (IR) spectra showed the presence of an acetamide group and δ-lactone ring, so its structure may be a bromolactone (**7**), but the stereostructure will be discussed later. The bromolactone (**7**) was refluxed in pyridine in the presence of an equimolar amount of 1,8-diazabicyclo[5,4,0] undecene-7 (DBU) to give an olefinic lactone (**8**) (mp 267°), NMR spectrum of which showed formation of a double bond (δ 6.25—5.7, 2H, m). The olefinic lactone (**8**) was heated in aqueous sodium hydroxide to precipitate gradually as colorless needles (mp 280°) in 90% yield. IR spectrum of the crystals showed the presence of a hydroxyl group (3450 cm^{-1}) and reproduction of lactam ring (3170, 1655 cm^{-1}) and the NMR spectrum showed the presence of two vinylic protons (δ 5.83 as broad signal in DMSO-d_6). Its hydroxyl group should be in β-quassi-axial by consideration of *trans*-diaxial addition mechanism in formation of bromolactone from **6**. In order to confirm the presumption, it



1: $R_1=R_2=R_3=OH$
2: $R_1=R_2=OH$, $R_3=H$
3: $R_1=R_2=R_3=H$

Fig. 1

1) S. Ohta and S. Kimoto, *Chem. Pharm. Bull.* (Tokyo), **24**, 2969 (1976).
2) Location: *Misasagi-Nakauchi-cho, Yamashina-ku, Kyoto, 607, Japan.*
3) T. Okamoto, Y. Torii, and Y. Isogai, *Chem. Pharm. Bull.* (Tokyo), **16**, 1860 (1968).
4) A. Immirzi and C. Fuganti, *Chem. Commun.*, **1972**, 240.
5) Communication: S. Ohta and S. Kimoto, *Tetrahedron Letters*, **1975**, 2279.

was planned that the unsaturated alcohol (**9**) is converted to an ester (**11**) of the corresponding saturated alcohol and the NMR spectrum is examined. Thus, the acetate (**11**) was prepared by acetylation of **9** with acetic anhydride in pyridine gave **10** (mp 272°) followed by hydrogenation over platinum oxide. NMR spectrum of **11** showed one proton (>C<u>H</u>–$COOCH_3$) at δ 5.67 as broad signal (half band width ($W/2$)=8 Hz). Therefore, the acetoxyl group of **11** should be in β-axial and hence the ring juncture of the above mentioned bromolactone (**7**) and the olefinic lactone (**8**) should be in B/C *cis*.[6-8]

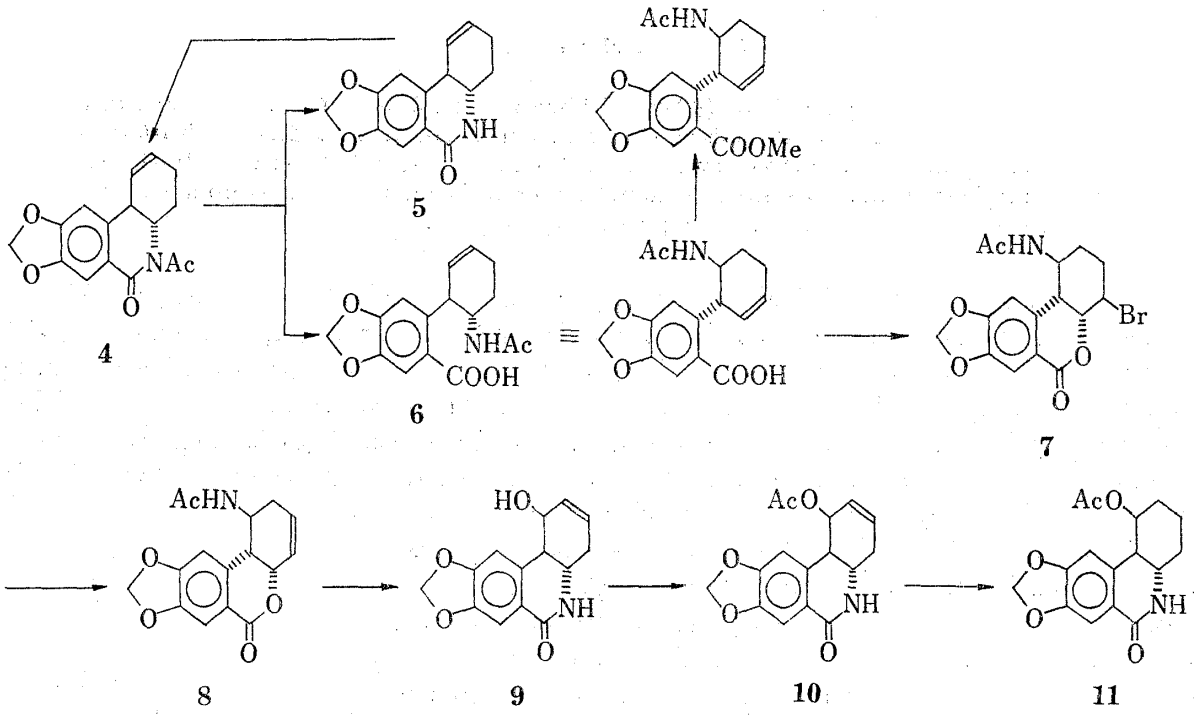


Chart 1

In order to synthesize lycoricidine, it would be better to introduce a double bond between 3- and 4-position in the lactam (**9**) using Sharpless's procedure,[9] which is an elegant method for preparation of allyl alcohols treating epoxides with selenophenolate and hydrogen peroxide. The olefinic alcohol (**9**) was heated in chloroform containing 2,3-dihydropyrane and *p*-toluenesulfonic acid (TsOH) to give the tetrahydropyranyl (THP) ether (**12**) (mp 220°) in 75.2% yield. The ether (**12**) was oxidized with *m*-chloroperbenzoic acid (CPBA) to give the epoxide (**13**) (mp 250°) in 84.2% yield. In the process of the epoxidation, it was considered that the reagent might attacked the double bond from the α-side of the molecule because the other side would be highly hindered by the presence of THP group.[8] If the epoxide **13** is α-form of the molecule,[8] an olefinic alcohol such as **14** may be formed by application of Sharpless's procedure on **13** under consideration of the reaction mechanism. Into a solution of diphenyl diselenide treated with sodium borohydride in ethanol was added the epoxide (**13**) and the solution was treated with 30% hydrogen peroxide. Work up of this reaction mixture yielded the olefinic diol monoether (**14**) (mp 232°) in 63% yield. Its NMR spectrum showed two vinylic protons and its IR spectrum showed the presence of a hydroxyl group.

The olefinic diol monoether (**14**) was acetylated and then, without purification of the intermediate (**15**), its THP protective group was hydrolyzed under a mild acidic condition to

6) R.U. Remiux, R.K. Kulling, H.J. Bernstein, and W.G. Sheider, *J. Am. Chem. Soc.*, **80**, 6098 (1958).
7) Y. Kawazoe, Y. Sato, T. Okamoto, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **11**, 328 (1963).
8) In this paper, the structure assigned in chart are used for stereochemical discussion.
9) K.B. Sharpless and R.F. Lauer, *J. Am. Chem. Soc.*, **95**, 2697 (1973).

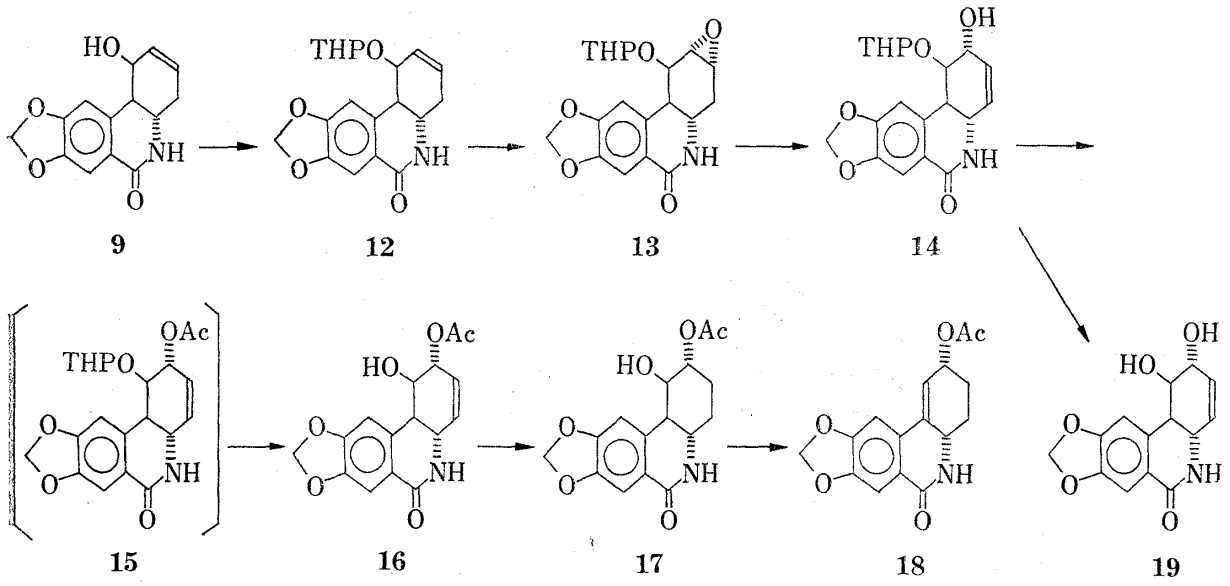


Chart 2

give the olefinic diol monoacetate (**16**) (mp 250°), IR and NMR spectra of which showed presence of a hydroxyl and an acetoxyl group. Steric configuration of C_2-acetoxyl group in **16** was clarified in the following manner. The olefinic diol monoacetate (**16**) was hydrogenated over platinum oxide to give the hexahydrodiol monoacetate (**17**) (mp 288°). According to the method of dehydration reported by Heymann and his colaborator,[10] dehydration of **17** with borontrifluoride etherate (BF_3·ether) in acetic acid (AcOH) at 25° resulted in recovery of the starting material, however, under refluxing condition was obtained the dehydrated product (**18**) (mp 290°), whose steric configuration of the hydroxyl group was already clarified in the preceding paper.[1] Therefore, the configuration of the substituent at 2-position of **14** and **16** should be in α-quassi-axial as was expected.

The olefinic diol (**19**) (mp 246°), having a similar structure as an alkaloid, lycorine, was prepared by hydrolysis of **14**, so as to examine its biological activity.

To the solution of the olefinic diol monoacetate (**16**) in pyridine was added an equimolar amount of osmium tetroxide and the mixture was kept standing overnight, and then the resulting osmate was decomposed with sodium bisulfite to convert only a tetraol monoacetate (**20**) (mp 258°) in 87.2% yield. Its IR spectrum showed a strong absorption band based on hydroxyl groups at 3450—3240 cm^{-1} and acetylation of **20** with acetic anhydride in pyridine gave the tetraacetate (**21**) (mp 300°), and hydrolysis of **20** with diluted potassium hydroxide methanolic solution gave the tetraol (**22**) (mp 305°). But the stereochemical relationship between substituents on 2- and 3-position or 4- and 4a-position could not be elucidated from NMR spectra of **20**, **21** and **22** because of complexity of signals. A mixture of tetraol (**22**), dimethylformamide (DMF), 2,2-dimethoxypropane and a catalytic amount of TsOH was refluxed to give an acetonide (**23**) (mp 286°) in 80% yield (TLC and NMR spectrum of the crude product showed presence of only one kind of acetonide). While, if structure of the tetraol may be represented as **24**, two kinds of monoacetonide should be given. In view of the experiment that only one kind of monoacetonide was obtained as mentioned above, it might be reasonable that the structure (**22**) was given for the tetraol (mp 305°). Beside, the tetraol monoacetate (**20**) gave the acetonide (**25**) (mp 258°) by the same method. Alkaline hydrolysis of the acetonide (**25**) also afforded **23**. The steric configuration of the hydroxyl groups at 3- and 4-position will be also described later in this paper by using an other evidence.

10) H. Heymann and L.F. Fieser, *J. Am. Chem. Soc.*, **73**, 5252 (1951).

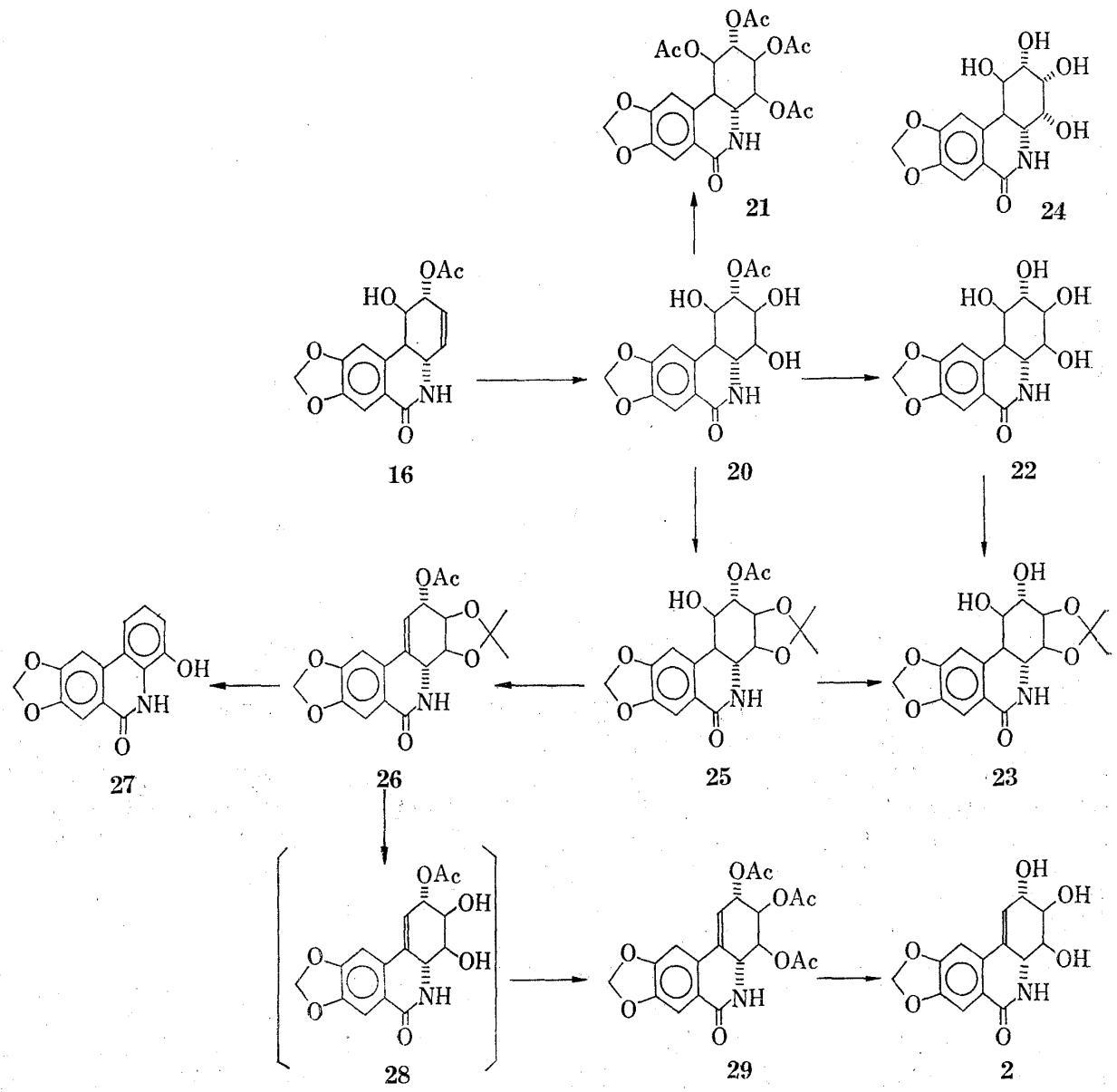


Chart 3

According to the method reported by Allen,[11] the acetonide (**25**) was successfully dehydrated with thionyl chloride in pyridine at 0° for ten hours to give the (±)-lycoricidine derivative (**26**) (mp 203°), whose NMR spectrum revealed one vinylic proton at δ 6.45 (broad) and ultraviolet (UV) spectrum was very similar to that of natural lycoricidine.[3] The isopropylidene protective group of the acetonide (**26**) could not be removed under a mild acidic condition at a room temperature. However, it has been known that natural lycoricidine was easily dehydrated under an acidic condition such as keeping it in methanolic concentrated hydrochloric acid for two days to convert to arolycoricidine (**27**).[3,12] In fact, treatment of **26** with concentrated hydrochloric acid in hot methanol afforded **27**, which was identified with the authentic sample by comparison of IR and UV spectra. Nevertheless, treatment of **26** with trifluoroacetic acid at a room temperature afforded a colorless needles after 10 minutes, which was filtered and acetylated with acetic anhydride in pyridine to give the (±)-lycoricidine triacetate (**29**) (mp 235°) in 70% yield.[13] NMR spectrum of **29** revealed one vinylic proton

11) W.S. Allen and S. Bernstein, *J. Am. Chem. Soc.*, **77**, 1028 (1955); *idem ibid.*, **78**, 1028 (1956).
12) Y. Torii: His thesis at the University of Tokyo. The details were not described in ref. 3.
13) The triacetate (**29**) was also formed by refluxing a solution of **26** in $CHCl_3$–MeOH containing a small amount of TsOH followed by acetylation of the product with acetic anhydride in pyridine.

at δ 6.25—6.0 (m, complicated with signal of $-OC\underline{H}_2O-$) and three methyl groups of acetoxyl groups at δ 2.17—2.10, and mass spectrum (MS) showed a parent peak at 417 (*m/e*) and a base peak at 255 (*m/e*), and UV spectrum was very similar to that of natural lycoricidine.[3] Furthermore, these spectra (NMR, UV, MS) including IR spectrum (in $CHCl_3$) were superimposable with those of triacetate (mp 201°)[3] of natural lycoricidine.

By reinspection of NMR spectrum of the (±)-lycoricidine triacetate (**29**), the signal at δ 4.65 (unsharp doublet, 1H, J=10 Hz) can be assigned as 4a-proton coupled with 4-proton. Therefore, the steric relation between the two protons was reasonably considered to be in *trans*-diaxial (if in *cis*, coupling constant (J) would be estimated less than about 4 Hz according to Carplus's rule using bond angle=45°).

The (±)-triacetate (**29**) afforded (±)-lycoricidine (**2**) (mp<230° (decomp.)) by treating in methanolic ammonia.

Thus the total synthesis of (±)-lycoricidine and confirmation of its full structure were established.

Experimental[14]

4*H*-*r*,3*H*-*trans*,3-(3′,4′-Methylenedioxy-6′-carboxyphenyl)-4-acetylamino-1-cyclohexene[15] (6)——Powdered **4** (6 g) was suspended in MeOH (100 ml) and 1 N KOH solution (43 ml) and the resulting suspension was heated at 70° under stirring for ten min and then to give precipitate of **5**. The reaction mixture was concentrated to 40 ml *in vacuo* and the resulting precipitate of **5** was collected by filtration (1.5 g, 31.0%). The filtrate was acidified with conc. HCl and the resulting crystals were collected by filtration, dried and recrystallized from THF to give colorless needles, mp 198—201°. Yield, 4.36 g (67.8%). IR ν_{max}^{KBr} cm^{-1}: 3280 (NH), 2570—2330, 1677 (COOH), 1615 (NHCO).

The acid (**6**, 200 mg) was converted to the corresponding methyl ester with exess of CH_2N_2 by a usual manner. Recrystallization from MeOH gave colorless prisms, mp 173—175°. Yield, 175 mg (83.6%). *Anal.* Calcd. for $C_{17}H_{19}O_5N$: C, 64.34; H, 6.04; N, 4.41. Found: C, 64.40; H, 6.21; N, 4.20. IR ν_{max}^{KBr} cm^{-1}: 3240 (NH), 1720 (COOMe), 1630 (NHCO).

4a*H*-*r*,1*H*-*trans*,10b*H*-*cis*,4*H*-*trans*,1-Acetylamino-4-bromo-8,9-methylenedioxy-1,2,3,4,4a,10b-hexahydrodibenzo[*b*,*d*]pyrone-6 (7)——To a suspension of powdered **6** (7.10 g) in anhyd. THF (100 ml) was added NBS (4.30 g) at room temperature and the mixture was stirred until **6** was disappeared into solution. Thirty minutes later, precipitated crystals were collected by filtration. Yield, 8.61 g (96.2%). Recrystallization from DMF–ether gave colorless needles, mp 270—272°. *Anal.* Calcd. for $C_{16}H_{16}O_5NBr$: C, 50.28; H, 4.22; N, 3.86. Found: C, 50.39; H, 4.40; N, 3.86. IR ν_{max}^{KBr} cm^{-1}: 3320 (NH), 1695 (δ-lactone), 1655 (NHCO). NMR (in DMSO-d_6) δ: 8.05 (1H, d, N$\underline{H}$, J=9 Hz), 7.30 (1H, s, 7-position), 7.0 (1H, s, 10-position), 6.13 (2H, dd, $-OC\underline{H}_2O-$, J=2 Hz), 5.0—4.6 (2H, m, 4- and 4a-position), 4.0—3.4 (1H, broad, 1-position), 3.4—3.0 (1H, m, 10b-position), 2.3—1.5 (4H, 2- and 3-position), 1.70 (3H, s, $COC\underline{H}_3$).

4a*H*-*r*,1*H*-*trans*,10b*H*-*cis*,1-Acetylamino-8,9-methylenedioxy-1,2,4a,10b-tetrahydrodibenzo[*b*,*d*]pyrone-6 (8)——A mixture of **7** (10.5 g) and DBU (4.20 g) in pyridine (150 ml) was refluxed for 5 hr and was kept standing overnight to give colorless prisms. The crystals were collected by filtration. Recrystallization from pyridine gave colorless prisms, mp 263—267° (decomp.). Yield, 8.15 g (98.4%). *Anal.* Calcd. for $C_{16}H_{15}O_5N$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.66; H, 4.93; N, 4.91. IR ν_{max}^{KBr} cm^{-1}: 3320 (NH), 1695 (δ-lactone), 1638 (NHCO). NMR (DMSO-d_6) δ: 7.90 (1H, d, N$\underline{H}$, J=10 Hz), 7.28 (1H, s, 7-position), 6.93 (1H, s, 10-position), 6.11 (2H, dd, $-OC\underline{H}_2O-$, J=2.5 Hz), 6.25—5.7 (2H, m, $-C\underline{H}$=C$\underline{H}-$), 5.12 (1H, quartet, 10b-position, J=12 and 3.5 Hz), 2.43—2.1 (2H, m, 2-position), 1.68 (3H, s, $COC\underline{H}_3$).

4a*H*-*r*,1*H*-*trans*,1-Hydroxy-8,9-methylenedioxy-1,4,4a,10b-tetrahydro-6(5*H*)-phenanthridone (9)——A suspension of **8** (1.2 g) in 20% NaOH aqueous solution (3 ml) and EtOH (3 ml) was heated at 90—95°. A few milliliters of water was occasionally added to prevent from dryness. Several hours later, colorless needles were appeared. They were collected by suction and washed with water. The filtrate was heated again for several hours by the above mentioned manner. After the same procedure was repeated more than five times, the yield of the crystals was reached to 930 mg (90.1%). Recrystallization from AcOH–ether gave colorless prisms or needles, mp 265—280° (decomp.). *Anal.* Calcd. for $C_{14}H_{13}O_4N$: C, 64.86; H, 5.05; N, 5.40. Found:

14) All melting points were uncorrected. NMR were determined with Varian A-60A Analytical Spectrometer using TMS as an internal reference. Thin-layer chromatography (TLC) was carried out by using Silica-Layer G (Nakarai Chemicals) as solid phase, $CHCl_3$–MeOH (9: 1) as liquid phase and iodine for detection of spots.

15) *r*: reference
The steric expression of compounds in this paper is described according to IUPAC Tentative Rules for the Nomenclature of Organic Chemistry, Section E: Fundamental Stereochemistry.

C, 64.94; H, 5.19; N, 5.13. IR ν_{max}^{KBr} cm^{-1}: 3450 (OH), 3170 (NH), 1665(NHCO). NMR (in DMSO-d_6) δ: 7.72 (1H, broad, NH), 7.32 (1H, s, 7-position), 6.97 (1H, s, 10b-position), 6.04 (2H, s, $-OCH_2O-$), 5.83 (2H, broad, $-CH=CH-$), 4.65 (2H, broad, 1-position and OH), 4.1—3.4 (1H, m, 4a-position), 3.0—2.6 (1H, m, 10b-position), 2.9—2.0 (2H, m, 4-position).

4a*H*-*r*,1*H*-*trans*,10b*H*-*trans*,1-Acetoxy-8,9-methylenedioxy-1,4,4a,10b-tetrahydro-6(5*H*)-phenanthridone (10)——A mixture of the foregoing alcohol (**9**) (1.0 g) in pyridine (20 ml) and Ac_2O (2 ml) was heated at 90° for 30 min and the unreacted reagents were removed *in vacuo* to afford a crystalline mass, which was recrystallized from $CHCl_3$–ether to give colorless needles, mp 272° (decomp.). Yield, 990 mg (85.1%). *Anal.* Calcd. for $C_{16}H_{15}O_5N$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.21; H, 5.04; N, 4.74. IR ν_{max}^{KBr} cm^{-1}: 3170 (NH), 1720 ($OCOCH_3$), 1660 (NHCO). NMR (in DMSO-d_6) δ: 7.89 (1H, broad, 5-position), 7.87 (1H, s, 7-position), 6.65 (1H, s, 10-position), 6.08 (2H, dd, $-OCH_2O-$, J=1 Hz), 6.17—5.77 (2H, m, $-CH=CH-$), 4.0—3.5 (1H, m, 4a-position), 3.33—2.92 (1H, m, 10b-position), 2.5—2.1 (2H, m, 4-position), 1.87 (3H, s, $COCH_3$). TLC: Rf=0.71.

4a*H*-*r*,1*H*-*trans*,10b*H*-*trans*,1-Acetoxy-8,9-methylenedioxy-1,2,3,4,4a,10b-hexahydro-6(5*H*)-phenanthridone(11)——A solution of **10** (150 mg) in AcOH (10 ml) was hydrogenated over PtO_2 (40 mg) for 1 hr. After removal of the catalyst, the filtrate was evaporated *in vacuo* to give a crystalline mass, which was recrystallized from EtOH to yield colorless prisms, mp 257° (decomp.). Yield, 95 mg (63%). *Anal.* Calcd. for $C_{16}H_{17}O_5N$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.30; H, 5.84; N, 4.85. IR ν_{max}^{KBr} cm^{-1}: 3200 (NH), 1737 (OAc), 1667 (NHCO). NMR (in DMSO-d_6) δ: 7.78 (1H, broad, NH), 7.33 (1H, s, 7-position), 6.58 (1H, s, 10-position), 6.06 (2H, s, $-OCH_2O-$), 5.67 (1H, broad, 1-position, $W/2$=8 Hz), 3.83—3.33 (1H, m, 4a-position), 3.13—2.67 (1H, m, 10b-position), 2.2—1.3 (6H, m, $-(CH_2)_3-$), 1.93 (3H, s, $COCH_3$).

THP Ether (12) of 9——TsOH·H_2O (600 mg) was suspended in $CHCl_3$ (200 ml) and the solvent (50 ml) was distilled off in order to remove the crystalline water. To the solution was added powdered **9** (1 g) and then 2,3-dihydropyrane (1.0 g) and the resulting suspension was refluxed for 1 hr. After cooled, the solution was shaken with 10% NaOH (20 ml) and with water. The $CHCl_3$ layer was dried. After concentration of the solution to 20 ml of volume *in vacuo*, **9** (75 mg, 7.5%) precipitated was filtered off. The filtrate was concentrated to 5 ml of volume and to the solution was added ether (20 ml) to give precipitates. Yield, 1.00 g (75.2%). Recrystallization from $CHCl_3$–EtOH gave colorless needles, mp 270° (decomp.). *Anal.* Calcd. for $C_{19}H_{21}O_5N$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.06; H, 6.16; N, 4.17. IR ν_{max}^{KBr} cm^{-1}: 3190 (NH), 1662 (NHCO). TLC: Rf=0.65.

Epoxide (13) of 12——To the solution of **12** (290 mg) in $CHCl_3$ (3 ml) was added CPBA (290 mg) and the solution was kept standing for 2 days. The solution was washed successively with 10% $NaHSO_3$, 10% Na_2CO_3 and water. After dried the $CHCl_3$–layer, the solvent was removed *in vacuo* to give solid, which was recrystallized from $CHCl_3$–ether to afford colorless needles, mp 250° (decomp.). Yield, 255 mg (84.7%). *Anal.* Calcd. for $C_{19}H_{21}O_6N$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.12; H, 5.84; N, 4.08. IR ν_{max}^{KBr} cm^{-1}: 3200 (NH), 1686 (NHCO).

4*H*-*r*,1*H*-*trans*,2*H*-*cis*,10b*H*-*trans*,1-(2′-Tetrahydropyranyloxy)-2-hydroxy-8,9-methylenedioxy-1,2,4a,-10b-tetrahydro-6(5*H*)-phenanthridone (14)——To a solution of diphenyldiselenide (506 mg) in 10 ml of anhyd. EtOH was added sodium borohydride (130 mg). To the resulting colorless solution was added **13** (1.08 g) and the mixture was refluxed for 2 hr and followed by concentration until 5 ml of volume. To the solution was added THF (15 ml), then was added dropwise 30% H_2O_2 (5 ml) to afford a white precipitate, which was dissolved by refluxing the solution for 5—6 hr. The solvent was removed *in vacuo* to give a viscous oil, which was crystallized by soaking in a small amount of EtOH and recrystallized from EtOH to give colorless prisms, mp 232° (decomp.). Yield, 680 mg (63.0%). *Anal.* Calcd. for $C_{19}H_{21}O_6N$: C, 63.50; H, 5.89; N, 3.90. Found: C, 64.29; H, 5.98; N, 4.09. IR ν_{max}^{KBr} cm^{-1}: 3400—3200 (OH, NH), 1670 (NHCO). NMR (in DMSO-d_6) δ: 8.03—7.77 (1H, d, NH, J=15 Hz), 7.33 (1H, s, 7-position), 7.04 (1H, broad, 10-position), 6.3—5.7 (4H, m, $-OCH_2O-$ and $-CH=CH-$), 5.15 (1H, broad, OH), 5.05—4.6 (2H, broad, 2′- and 1-position), 4.5—4.0 (2H, m, 4a- and 2-position), 3.25—2.7 (1H, m, 10b-position), 1.7—1.1 (8H, broad, other protons).

4a*H*-*r*,1*H*-*trans*,2*H*-*cis*,10b*H*-*trans*,1-Hydroxy-2-acetoxy-8,9-methylenedioxy-1,2,4a,10b-tetrahydro-6-(5*H*)-phenanthridone (16)——The foregoing alcohol (**14**, 1.0 g) was heated at 80—90° in pyridine (10 ml) and Ac_2O (2 ml) for 15 min to give colorless needles of **15** (mp 257°). Without filtration, the reagents were removed *in vacuo* to afford pale yellow viscous oil, which was dissolved in $CHCl_3$, and the solution was shaken with 10% HCl, with 10% Na_2CO_3 and with water. After dried over Na_2SO_4, the solution was concentrated to 30 ml of volume. To the solution was added MeOH (5 ml), AcOH (5 ml) and TsOH (100 mg), then the resulting mixture was refluxed for 1.5 hr. After addition of 5 drops of pyridine, the solvent was removed *in vacuo* to give an oily residue, which was dissolved in MeOH to convert colorless prisms. Recrystallization from EtOH gave colorless prisms, mp 250° (decomp.). Yield, 740 mg (97.3%). *Anal.* Calcd. for $C_{16}H_{15}O_6N$: C, 60.56; H, 4.77; N, 4.41. Found: C, 60.27; H, 4.77; N, 4.40. IR ν_{max}^{KBr} cm^{-1}: 3430—3200 (OH, NH), 1720 (OAc), 1655 (NHCO). NMR (in DMSO-d_6) δ: 7.69 (1H, broad, NH), 7.30 (1H, s, 7-position), 6.90 (1H, s, 10-position), 6.05 (2H, s, $-OCH_2O-$), 5.3 (1H, broad, 1-position), 4.9 (1H, broad, 2-position), 4.35 (1H, broad, 1-position), 3.9—3.1 (1H, m, 4a-position), 2.95—2.6 (1H, m, 10b-position), 2.03 (3H, s, $COCH_3$).

4a*H*-*r*,1*H*-*trans*,2*H*-*cis*,10b*H*-*trans*,1-Hydroxy-2-acetoxy-8,9-methylenedioxy-1,2,3,4,4a,10b-hexahydro-6(5*H*)-phenanthridone (17)——A solution of **16** (300 mg) in AcOH (20 ml) and EtOH (20 ml) was shaken with

H_2 over PtO_2 (30 mg) for 1 hr. After removal of the catalyst by filtration, the solvent of the filtrate was removed *in vacuo* to give a solid, recrystallization of which from AcOH–MeOH gave colorless prisms, mp 288° (decomp.). Yield, 255 mg (84.5%). *Anal.* Calcd. for $C_{16}H_{17}O_6N$: C, 60.18; H, 5.37; N, 4.39. Found: C, 60.09; H, 5.78; N, 4.53. IR ν_{max}^{KBr} cm^{-1}: 3500 (OH), 3190 (OAc), 1667 (NHCO). NMR (in DMSO-d_6) δ: 7.67 (1H, broad, NH), 7.30 (1H, s, 7-position), 6.90 (1H, s, 10-position), 6.05 (1H, s, $-OCH_2O-$), 5.3 (1H, broad, OH), 4.9 (1H, broad, 2-position), 4.35 (1H, broad, 1-position), 3.9—3.1 (1H, m, 4a-position), 2.95—2.6 (1H, m, 10b-position), 2.03 (3H, s, $COCH_3$), 1.9—1.5 (4H, broad, $-(CH_2)_2-$).

4a*H*-*r*,2*H*-*cis*,2-Acetoxy-8,9-methylenedioxy-2,3,4,4a-tetrahydro-6(5*H*)-phenanthridone (18)——To a solution of **17** (50 mg) in AcOH (5 ml) was added BF_3·ether (0.1 g) and the resulting solution was refluxed for 2 hr, then the solvent was removed *in vacuo*. Water was added to the residue to give white precipitate, recrystallization of which from EtOH afforded colorless prisms, mp 290° (decomp.). This product was identified with **21**[1] by comparison of IR spectra.

4a*H*-*r*,1*H*-*trans*,2*H*-*cis*,10b*H*-*trans*,1,2-Dihydroxy-8,9-methylenedioxy-1,2,4a,10b-tetrahydro-6(5*H*)-phenanthridone (19)——To a suspension of powdered **14** (245 mg) in EtOH (10 ml) was added TsOH (20 mg) and the suspension was warmed at 60° under stirring for 1 hr. Removal of the solvent *in vacuo* gave a viscous residue, which was dissolved in a small amount of MeOH, and the solution was kept standing at a room temperature overnight to crystallize. Recrystallized from AcOH–ether to afford colorless prisms, mp 240° (decomp.). Yield, 110 mg (58.6%). *Anal.* Calcd. for $C_{14}H_{13}O_5N$: C, 61.09; H, 4.76; N, 5.09. Found: C, 61.13; H, 4.56; N, 5.03. IR ν_{max}^{KBr} cm^{-1}: 3430, 3275 (OH), 3170 (NH), 1650 (NHCO). NMR (in DMSO-d_6) δ: 7.95 (1H, s, NH), 7.33 (1H, s, 7-position), 6.97 (1H, s, 10-position), 6.07 (2H, s, $-OCH_2O-$), 5.86 (2H, broad, $-CH=CH-$), 5.19—4.9 (2H, m, OH), 4.46—3.8 (3H, m, 1-, 2-, and 10b-position), 2.88 (1H, d, 4a-position, $J=12$ Hz).

4a*H*-*r* 1*H*-*trans*, 2*H*-*cis*,3*H*-*trans*,4*H*-*trans*,10b*H*-*trans*,1,3,4-Trihydroxy-2-acetoxy-8,9-methylenedioxy-1,2,3,4,4a,-10b-hexahydro-6(5*H*)-phenanthridone (20)——To a solution of **16** (1.20 g) in pyridine was added OsO_4 (1.00 g) and the resulting solution was kept standing overnight. To the solution was added 10% $NaHSO_3$ (3 ml) and the mixture was stirred for 5 min. The mixture was filtered and the solvent of the filtrate was removed *in vacuo* (below 50°). To the residue was added pyridine (20 ml), and an insoluble material was filtered off, then the filtrate was evaporated *in vacuo* (below 50°) to give a red oily residue, which was dissolved in MeOH to convert colorless prisms, mp 258° (decomp.). Yield, 1.16 g (87.2%). *Anal.* Calcd. for $C_{16}H_{17}O_8N$: C, 54.70; H, 4.88; N, 3.99. Found: C, 54.39; H, 4.90; N, 3.93. IR ν_{max}^{KBr} cm^{-1}: 3450—3210 (OH, NH), 1727 (OAc), 1667 (NHCO). NMR (in DMSO-d_6) δ: 7.33 (1H, s, 7-position), 6.90 (1H, s, 10-position), 6.84 (1H, s, 5-position), 6.07 (2H, s, $-OCH_2O-$), 5.5—4.8 (4H, m, $3\times$OH, and 2-position), 4.6—4.25 (1H, broad, 4a-position), 4.0—3.62 (3H, m, 1-, 3-, and 4-position), 3.25—2.75 (1H, m, 10b-position), 2.04 (3H, s, $COCH_3$).

Acetonide (25)——A solution consisting of **20** (300 mg), TsOH (50 mg), 2,2-dimethoxypropane (5 ml) and DMF (5 ml) was refluxed for 2.5 hr. To the resulting solution was added pyridine (100 mg) and the volatile portion of the mixture was removed *in vacuo* to give viscous residue, which was soaked in a small amount of ether to crystallized. Recrystallization from EtOH gave colorless needles, mp 258° (decomp.). Yield, 280 mg (83.5%). *Anal.* Calcd. for $C_{19}H_{21}O_8N$: C, 58.31; N, 5.41; H, 3.58. Found: C, 58.31; H, 5.53; N, 3.82. IR ν_{max}^{KBr} cm^{-1}: 3360—3300 (OH, NH), 1743 (OAc), 1657 (NHCO). NMR (in DMSO-d_6) δ: 7.58 (1H, s, NH), 7.32 (1H, s, 7-position), 6.94 (1H, s, 10-position), 6.07 (2H, s, $-OCH_2O-$), 5.43—5.23 (1H, m, OH and 2-position), 4.57—3.58 (4H, m, 1-, 3-, 4-, and 4a-position), 3.08—2.7 (1H, m, 10b-position), 2.08 (3H, s, $COCH_3$), 1.41 (3H, s, $>C-CH_3$), 1.33 (3H, s, $>C-CH_3$).

4a*H*-*r*,1*H*-*trans*,2*H*-*cis*,3*H*-*trans*,4*H*-*trans*,10b*H*-*trans*,1,2,3,4-Tetrahydroxy-8,9-methylenedioxy-1,2,-3,4,4a,10b-hexahydro-6(5*H*)-phenanthridone (22)——A solution consisting of **20** (70 mg), MeOH (10 ml) and 1 N KOH solution (0.3 ml) was refluxed for 5 min. After removal of the solvent, was added one drop of AcOH and a small amount of MeOH to the residue to give colorless needles, recrystallization of which from AcOH gave colorless prisms, mp 305° (decomp.). Yield, 30 mg (48.7%). *Anal.* Calcd. for $C_{14}H_{15}O_7N$: C, 54.37; H, 4.89; N, 4.53. Found: C, 54.29; H, 4.68; N, 4.50. IR ν_{max}^{KBr} cm^{-1}: 3460—3100 (OH, NH), 1675 (NHCO).

The corresponding tetraacetate (**21**) was prepared by treating **20** with Ac_2O and pyridine in usual manner. The tetraacetate (**21**) melted at 300° under decomposition. Yield, 57.8%. *Anal.* Calcd. for $C_{22}H_{23}O_{11}N$: C, 55.34; H, 4.86; N, 2.93. Found: C, 55.50; H, 5.09; N, 3.05. IR ν_{max}^{KBr} cm^{-1}: 3375 (NH), 1757, 1735, 1250—1220 (OAc), 1667 (NHCO). NMR (low concentration in DMSO-d_6) δ: 8.15 (1H, s, NH), 7.38 (1H, s, 7-position), 6.62 (1H, s, 10-position), 6.10 (2H, s, $-OCH_2O-$), 5.68—4.84 (4H, m, 1-, 2-, 3-, and 4-position), 2.08, 2.01, and 1.94 ($3H\times4$, $s\times4$, $COCH_3\times4$). Signals of other protons were overlapped with those of solvent and H_2O.

Acetonide (23)——i) From **22**: The procedure, described in the preparation of **25**, was used. Yield, 79.7%. **23** was recrystallized from pyridine–ether to afford colorless needles, mp 286° (decomp.). *Anal.* Calcd. for $C_{17}H_{19}O_7N$: C, 58.45; H, 5.48; N, 4.01. Found: C, 58.37; H, 5.52; N, 4.04. IR ν_{max}^{KBr} cm^{-1}: 3360 (NH, OH), 1660 (NHCO). NMR (in DMSO-d_6) δ: 7.40 (1H, broad, NH), 7.32 (1H, s, 7-position), 6.92 (1H, s, 10-position), 6.07 (2H, s, $-OCH_2O-$), 5.35 (1H, broad, OH), 4.83 (1H, broad, OH), 4.53—3.6 (5H, m, 1-, 2-, 3-, 4-, and 10b-position), 3.1—2.65 (1H, m, 4a-position), 1.38 (3H, s, $>C-CH_3$), 1.32 (3H, s, $>C-CH_3$). TLC: $Rf=0.47$ ($CHCl_3$: MeOH=9: 1), 0.61 (AcOEt: MeOH=9: 1).

ii) From **25**: Acetonide (**25**) (20 mg) was hydrolyzed in a solution of 1 N KOH (0.1 ml) and MeOH (2 ml). This product was identified with the authentic sample by comparison of IR spectra.

4a*H*-*r*,2*H*-*cis*,3*H*-*trans*,4*H*-*trans*,2-Acetoxy-3,4-isopropylidenedioxy-8,9-methylenedioxy-2,3,4,4a-tetrahydro-6(5*H*)-phenanthridone (26)——To a solution of **25** (100 mg) in pyridine (1 ml) was added $SOCl_2$ (150 mg) under cooling, then the solution was kept standing in a refrigerator (0°) for 10 hr. The reaction mixture was shaken with $CHCl_3$ and water. The $CHCl_3$ layer was shaken with 10% HCl, with water and dried. The solvent of the solution was removed *in vacuo* to give a viscous oil, which was soaked in a small amount of MeOH to give colorless needles. Yield, 55 mg (57.8%). Recrystallization from MeOH afforded colorless needles, mp 203° (decomp.). *Anal.* Calcd. for $C_{19}H_{19}O_7N$: C, 61.12; H, 5.13; N, 3.75. Found: C, 60.56; H, 5.07; N, 3.89. IR ν_{max}^{KBr} cm^{-1}: 3380 (NH), 1740 (OAc), 1677 (NHCO). UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 247.5 (4.45), 308 (4.04). NMR (in DMSO-d_6) δ: 7.97 (1H, broad, NH), 7.38 (1H, s, 7- or 10-position), 7.37 (1H, s, 10- or 7-position), 6.45 (1H, broad, 1-position), 6.11 (2H, s, $-OCH_2O-$), 5.30 (1H m, 2-position), 4.4—4.13 (3H, m, 3-, 4-, and 4a-position), 2.14 (3H, s, $COCH_3$), 1.47 (3H, s, $>C-CH_3$), 1.33 (3H, s, $>C-CH_3$).

Arolycoricidine (27)——A solution of **26** (25 mg), MeOH (2.5 ml) and conc. HCl (1 ml) was refluxed for 3 hr, then volatile portion of the solution was removed *in vacuo* to give solid, which was recrystallized from AcOH to give colorless needles, mp >285° (decomp.). Yield, 11.5 mg (67.3%). This product was identified with the authentic sample of arolycoricidine by comparison of IR and UV spectra.

(±)-Lycoricidine Triacetate (29)——The acetonide (**26**) (100 mg) was dissolved in trifluoroacetic acid (1 ml) at 0° to precipitate colorless needles (mp 207° (decomp.)) 10 min later, which was filtered and washed with ether. To the crystals was added pyridine (3 ml) and Ac_2O (1 ml) and the mixture was heated at 70—80° for 30 min. After removal of the reagents *in vacuo*, the residue was dissolved in $CHCl_3$ and the solution was shaken with 10% HCl, with water and dried over anhyd. Na_2SO_4. Removal of $CHCl_3$ *in vacuo* gave a viscous oil, which was soaked in a small amount of MeOH to give colorless fine prisms, recrystallized from $CHCl_3$–MeOH, mp 233—235°. Yield, 85 mg (70.3%). *Anal.* Calcd. for $C_{20}H_{19}O_9N$: C, 57.55; H, 4.59; N, 3.36. Found: C, 57.37; H, 4.21; N, 3.49. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3410, 3200 (NH), 1750, 1240—1200 (OAc), 1667 (NHCO). UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 244.5 (4.49), 306 (3.93). NMR (in $CDCl_3$) δ: 7.51 (1H, s, 7-position), 7.43 (1H, broad, NH), 7.00 (1H, s, 10-position), 6.25—6.0 (3H, broad and s, $-CH=C<$ and $-OCH_2O-$), 5.55—5.17 (3H, m, 2-, 3-, and 4-position), 4.65 (1H, unsharp d, 4a-position, J=10 Hz), 2.17, 2.11, and 2.10 (3H×3, s×3, $COCH_3$×3). Mass Spectrum *m/e*: 417 (M^+), 357 (M^+-60), 297 (M^+-120), 255 (base peak). These spectral data were really superimposable with those of triacetate (mp 201°) of natural lycoricidine.

(±)-Lycoricidine (2)——A solution of **29** (60 mg) in MeOH (10 ml) was saturated with NH_3 and the resulting solution was kept standing at a room temperature for 2 days. After removal of the solvent *in vacuo* (below 40°), the residue was soaked in a small amount of MeOH to give colorless prisms. Yield, 35 mg (84.4%). Recrystallization from MeOH gave 25 mg of colorless prisms, mp <230° (decomp.). *Anal.* Calcd. for $C_{14}H_{13}O_6N$: C, 57.73; H, 4.56; N, 4.82. Found: C, 57.74; H, 5.16; N, 4.34. IR ν_{max}^{KBr} cm^{-1}: 3500—3050 (OH, NH), 1650 (NHCO). UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 243.5 (4.48), 305 (3.95). NMR (measured in pyridine-d_5 with JNM-PS-100 Spectrometer) δ: 8.4 (1H, broad, NH), 7.94 (1H, s, 7-position), 7.22 (1H, s, 10-position), 6.6 (1H, m, $>C=CH-$), 6.5—6.0 (3H, broad, OH), 5.98 (2H, d, $-OCH_2O-$, J=3 Hz), 5.2—4.6 (4H, m, 2-, 3-, 4-, and 4a-position). These spectra were very similar as those of natural lycoricidine.

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