Chem. Pharm. Bull. 30(4)1322—1332(1982)

Stereoselective Transformation of the Alkaloid Lycorine to *O*-Demethylungiminorine and Ungiminorine[1)]

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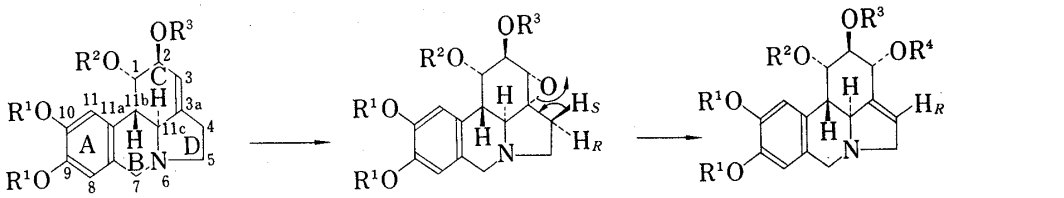
(Received September 28, 1981)

Diacetyllycorine, an Amaryllidaceae alkaloid, was transformed stereoselectively to the more heavily oxygenated congener, *O*-demethylungiminorine, by a route similar to that suggested for the biosynthesis of narcissidine. Similarly, acetylhippamine was converted to ungiminorine. A method of high yield conversion of lycorine to hippamine is also described.

The above transformations constitute a formal total synthesis of ungiminorine.

Keywords——Amaryllidaceae alkaloid; lycorine; hippamine; ungiminorine; *O*-demethylungiminorine; lycorine-chlorohydrin; permanganate oxidation; phosphoryl chloride; stereoselective hydroxylation; distorted boat conformation

Ungiminorine is an alkaloid isolated from *Ungernia minor* (Amaryllidaceae).[2a)] The structure **1** proposed by Russian workers[2b)] was suggested to be revised to **2** by Wildman *et al.*[3a)] on the basis of spectral analogy with narcissidine (**3**), the alkaloid of *Narcissus poeticus*,[3b)] the latter having been established by X-ray crystallographic analysis.[3a)] The alkaloid, parkacine,[4)] a constituent of *Amaryllis parkeri*, is also considered to be **4**[3a)] in view of the spectral resemblance to narcissidine. However, no direct structure proofs of ungiminorine and parkacine are so far available. Fuganti[5)] suggested that these three alkaloids of the most highly oxygenated lycorine-type may be biosynthesized from the corresponding lycorine alkaloids, hippamine (**5**), galanthine (**6**), and methylpseudolycorine (**7**), *via* the α-epoxide **9**, since he found that galanthine (**6**) was converted to narcissidine (**3**) in *Sempre avanti* daffodil



5 : $R^1-R^1=CH_2$, $R^2=H$, $R^3=Me$
6 : $R^1=R^3=Me$, $R^2=H$
7 : $R^1=Me$, $R^2=R^3=H$
8 : $R^1-R^1=CH_2$, $R^2=R^3=H$
10 : $R^1-R^1=CH_2$, $R^2=R^3=Ac$

9

2 : $R^1-R^1=CH_2$, $R^2=R^4=H$, $R^3=Me$
3 : $R^1=Me$, $R^2=R^4=H$, $R^3=Me$
4 : $R^1=Me$, $R^2=R^3=R^4=H$

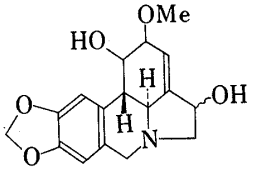


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Chart 1. A Proposed Biosynthetic Pathway from Lycorine Alkaloids to Ungiminorine Alkaloids

with stereospecific loss of *pro-S* hydrogen at C_4 (Chart 1). The proposed intermediate α-epoxide or its equivalent, however, has never been isolated nor prepared chemically. In this paper, we describe the chemical preparation of the α-glycols, **17** and **36**, the α-epoxide equivalent, from lycorine alkaloids and show that they are dehydrated in a regio- and stereoselective manner giving rise to ungiminorine alkaloids. These results not only confirm the structure of ungiminorine (**2**) but also provide strong chemical support for the suggested biosynthetic pathway.

Transformation of Lycorine to *O*-Demethylungiminorine

Introduction of an oxygen function at the double bond (C_3–C_{3a}) of lycorine (**8**) from the α-side is the crucial step in the transformation.

Lycorine (**8**) is well known to be vulnerable to various oxidizing agents. In most cases the products are oxyphenanthridinium betaines, **11** and **12**.[6] There is no report of a successful selective oxidation of its double bond. For example, an attempted oxidation with phthalmonoperacid to the oxide **9** only produced the *N*-oxide **13**.[7] Kotera[8] tried potassium permanganate oxidation of diacetyllycorine, but he could not isolate any characterizable product. In contrast, diacetyldihydrolycorine (**14**) gave the lactam **15** in high yield.[9a]

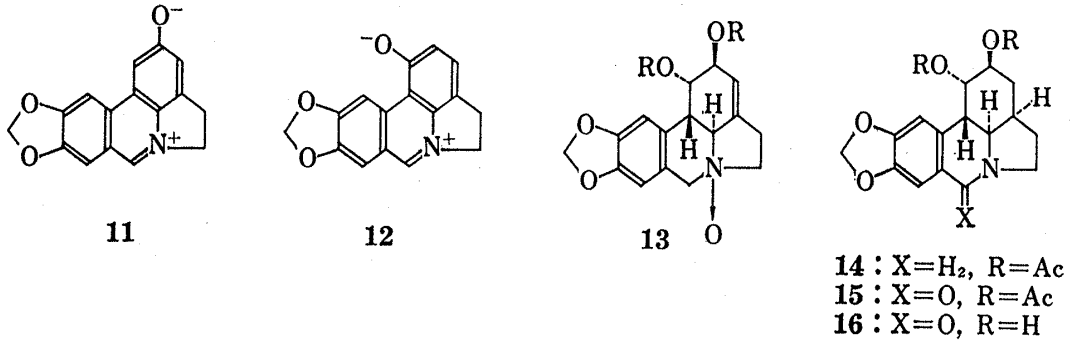


Chart 2. Oxidation Products of Lycorine and Dihydrolycorine

We found that very short oxidation of diacetyllycorine (**10**) with potassium permanganate in acetone–water under controlled conditions (0°C, 2 min) yielded three compounds, a lactam-glycol **17**, diacetyllycorine-lactam (**18**), and an aromatized compound **19**, in yields of 18, 0.5, and 1.5%, respectively. Diacetyllycorine-lactam (**18**) was identical with a synthetic specimen,[10] (except for the optical rotation) by infrared (IR), nuclear magnetic resonance (NMR), and thin layer chromatography (TLC) comparisons. Further oxidation of **18** with potassium permanganate afforded the lactam-glycol **17** in high yield. The ultraviolet (UV) spectrum of **17** was similar to that of dihydrolycorine-lactam (**16**)[9b] and its mass spectrum (MS) confirmed its molecular formula, $C_{20}H_{21}NO_9$, both indicating that the compound is a product of hydroxylation at the double bond.

The *cis*-glycol structure and the stereochemistry of **17** were rigidly established by detailed analysis of ^{1}H-NMR spectra of **17** and its derived triacetate **20**.

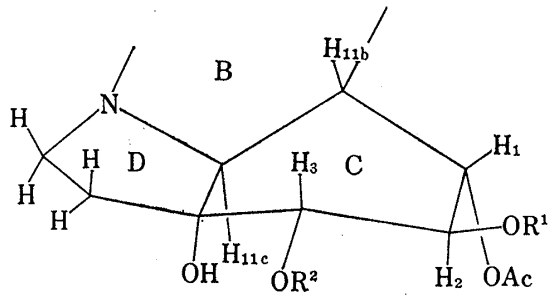
The dihedral angles between ring C protons obtained from Dreinding model of four possible orientational and conformational isomers and the anticipated qualitative magnitudes of their coupling constants are listed in Table I. The chemical shifts and the coupling constants of the protons on ring C were assigned as shown in Table II on the basis of a decoupling experiment. The observed coupling constants were consistent with those expected from α-orientation of the *cis*-glycol with a distorted boat conformation of ring C. Neither β-orientation of the *cis*-glycol function nor chair conformation of ring C would be consistent with the value given in Table II. Ring C is compelled to adopt a boat conformation, releasing the 1,3-diaxial interaction between C_1-acetoxyl and C_3-hydroxyl groups. The ^{13}C-NMR spectra of some related lactam derivatives were also assigned as shown in Table III.

Table I. Dihedral Angles of the Ring C Protons and the Expected Coupling Constants in Four Possible Orientational and Conformational Isomers of the *cis*-Glycols

Protons concerned	Coupling constants (Dihedral angles)			
	α-Chair	α-Boat	β-Chair	β-Boat
$H_{1,11b}$	S (65°)	S (60°)	S (60°)	L (5°)
$H_{1,2}$	S (60°)	S (55°)	S (60°)	L (180°)
$H_{2,3}$	S (65°)	L (175°)	S (57°)	S (55°)
$H_{11b,11c}$	L (180°)	L (180°)	L (180°)	L (180°)

S: small coupling expected. L: large coupling expected.

Table II. Analyses of the ^{1}H-NMR Spectra of **17**, **20**, and **38** (at 100 MHz)



17: R^1=Ac, R^2=H; **20**: R^1=R^2=Ac; **38**: R^1=Me, R^2=Ac

Chemical Shift (δ ppm)[a]

Compd.	H_1	H_2	H_3	H_{11b}	H_{11c}
17	5.58 (dd)	5.12 (dd)	3.88 (d)	3.09 (dd)	4.00 (d)
20	5.70 (dd)	5.30 (d)	5.30 (s)	3.35 (dd)	4.05 (d)
38	5.73 (dd)	3.67 (dd)	5.24 (d)	3.25 (dd)	4.02 (d)

First-Order Coupling Constants (Hz)

Compd.	$J_{1,2}$	$J_{2,3}$	$J_{1,11b}$	$J_{11b,11c}$
17	2.5	10.0	3.5	14.0
20	1.0	[b]	4	14.0
38	1.5	8.5	3.5	14.0

a) For other protons, see Experimental.
b) The coupling was not observed due to the coincidental identity of the chemical shifts of H_2 and H_3.

The spectral data of **19** (see Experimental) indicated that it has a phenanthridone structure carrying one acetoxyl group on ring C, whose aromatic protons appeared at δ 7.37 ppm (2H) as a singlet, thus establishing that it is 2-acetoxyanhydrolycorine-lactam. Although this structure formally corresponds to the dehydrated form of the *cis*-glycol (**17**) **17**, is not a precursor of **19**, since it was stable in acidic media. On treatment with 4% sulfuric acid in ethanol at room temperature for 18 h or heating at 80°C for 1 h, it was recovered unchanged. We consider that **19** might be the product of a *p*-glycol **25** (see below) which could be produced as a minor product and dehydrated smoothly under acid-catalyzed conditions.

Acetylation of the glycol-lactam **17** with acetic anhydride and pyridine gave the triacetate **20** (90%) and the tetraacetate **21** (6%). On treatment with excess thionyl chloride in pyridine,

TABLE III. ^{13}C-NMR Spectra of Some Lactam Derivatives (Solvent: $CDCl_3$)[a]

Carbon No.	15		17	20		22	
	δ_C ppm	J_{C-H} Hz	δ_C ppm	δ_C ppm	J_{C-H} Hz	δ_C ppm	J_{C-H} Hz
1	68.7 d	151	71.2 d	71.2 d	151	66.7 d	154
2	72.1 d	156	77.6 d	74.5 d	151	69.2 d	154
3	31.7 t	131	74.1 d	74.5 d	151	66.7 d	154
3a	34.5 d	121	79.5 s	79.4 s		133.4 s	
4	28.3 t	[b]	40.0 t	39.6 t	[b]	127.5 d	174
5	45.4 t	144	43.6 t	43.3 t	144	52.5 t	137
7	162.2 s		161.3 s	161.0 s		161.8 s	
7a	125.4 s		124.7 s	124.7 s		125.95 s	
8	108.7 d	168	108.7 d	108.7 d	169	109.0 d	166
9	146.8 s		147.2 s	147.1 s		147.2 s	
10	150.5 s		151.0 s	150.9 s		150.8 s	
11	103.8 d	163	104.4 d	104.2 d	163	103.1 d	163
11a	132.7 s		131.1 s	130.6 s		131.6 s	
11b	38.0 d	123	38.1 d	38.2 d	124	41.9 d	128
11c	55.4 d	147	63.6 d	64.1 d	151	59.6 d	148
12	101.6 t	174	101.8 t	101.7 t	174	101.7 t	174
$\underline{C}H_3CO-$	20.9 q	130	20.8 q	20.7 q	130	20.7 q	129
	21.1 q	130	21.0 q	20.7 q	130	20.9 q	129
				20.7 q	130	20.9 q	129
$CH_3\underline{C}O-$	169.6 s		170.3 s	169.7 s		168.4 s	
	170.0 s		170.9 s	169.7 s		168.9 s	
				170.2 s		169.7 s	

a) Assignments were confirmed by selective decoupling techniques.
b) J_{C-H} was uncertain.

20 afforded the dehydrated compound **22** in 91% yield. The appearance of a new olefinic proton signal at δ 6.06 ppm in **22** indicated the formation of a double bond at C_{3a}–C_4. This provides chemical support for the configuration of the glycol function, since E_2 elimination from the β-glycol **25** would easily give **26**, which would aromatize to **19** by further loss of two acetoxyl groups, during which process removal of the C_1-acetoxyl group produces a relief of steric interaction in the compound. Selective formation of **22** from **20** indicates that the *pro-S* hydrogen at C_4 was eliminated stereoselectively in an E_2 manner, and excludes the carbocation intermediate **27**. The compound **22** must therefore have the structure corresponding to triacetyl-*O*-demethylungiminorine-lactam.

Lithium aluminum hydride reduction of **22** gave the base corresponding to *O*-demethylungiminorine **23** in 86% yield, and this formed the triacetate **24**. Its mass spectral fragmentation pattern (see Experimental) was in agreement with that expected from the reported fragmentation of narcissidine.[3c] Although the natural occurrence of this compound has not been reported so far, it might be found in the future.

Transformation of Lycorine to Hippamine

The above transformation suggests that ungiminorine (**2**) could be similarly synthesized from hippamine (2-*O*-methyllycorine) **5**, a minor alkaloid of *Hippeastrum sp.*[11] Conversion of lycorine (**8**) to hippamine has already been reported, though in very low yield. In 1958, Takeda *et al.*[12] obtained a chlorohydrin (**28**) in 10% yield from lycorine (**8**) by treatment with phosphoryl chloride and hydrochloric acid, together with the major formation of anhydrolycorinium chloride (**29**) (~70%). The chlorohydrin yielded hippamine on treatment with K_2CO_3–MeOH. Later, Wildman *et al.*[13] observed that the chlorohydrin is easily convertible, on chromatography over Florisil, to lycorene α-oxide (**30**), which also gave hippamine by the action of NaOMe. Therefore improvement of the yield of the chlorohydrin (**28**), to which

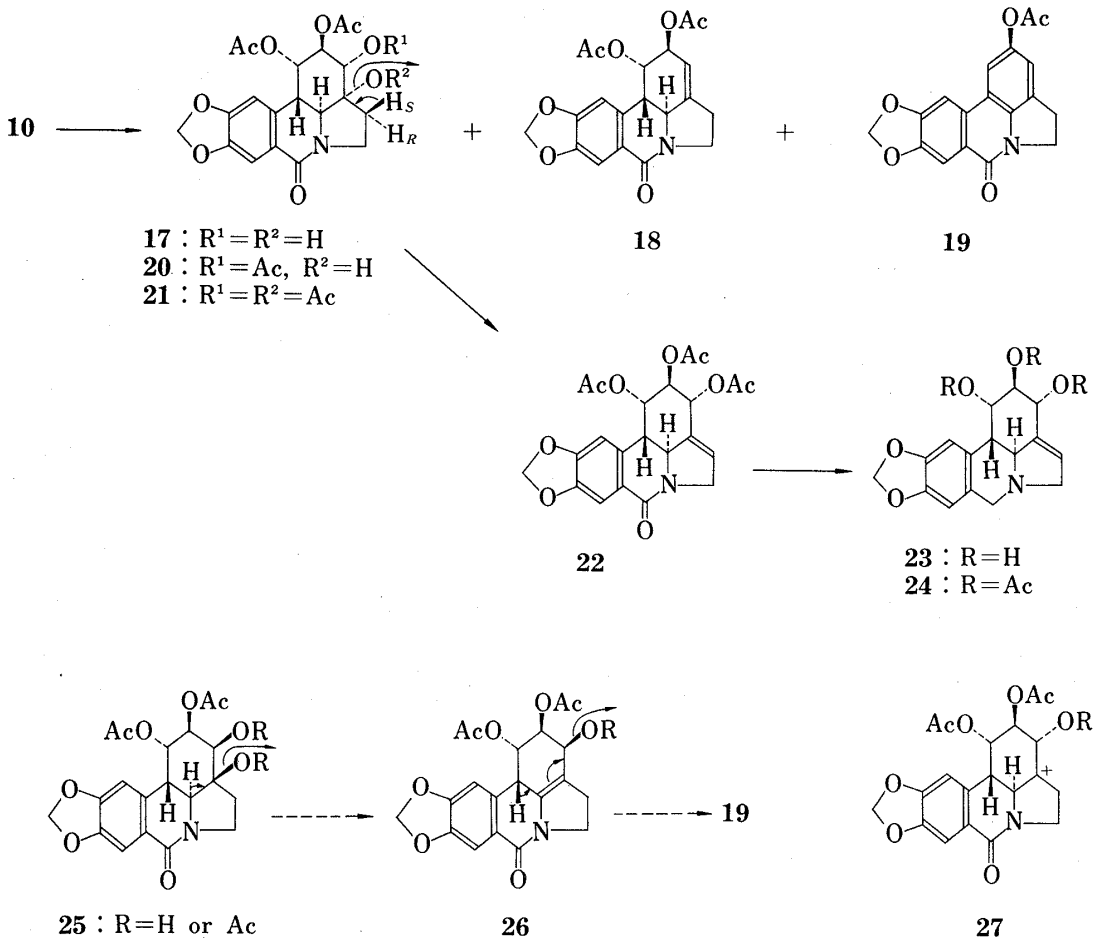


Chart 3. Synthesis of *O*-Demethylungiminorine

both authors gave the *cis*-configuration, as shown in **28a**, is the key to efficient synthesis of hippamine from lycorine.

We considered that aromatization of ring C leading to anhydrolycorinium chloride (**29**) may be the result of formation of the 1,2-di-*O*-phosphoryl ester (**32**) due to the use of excess

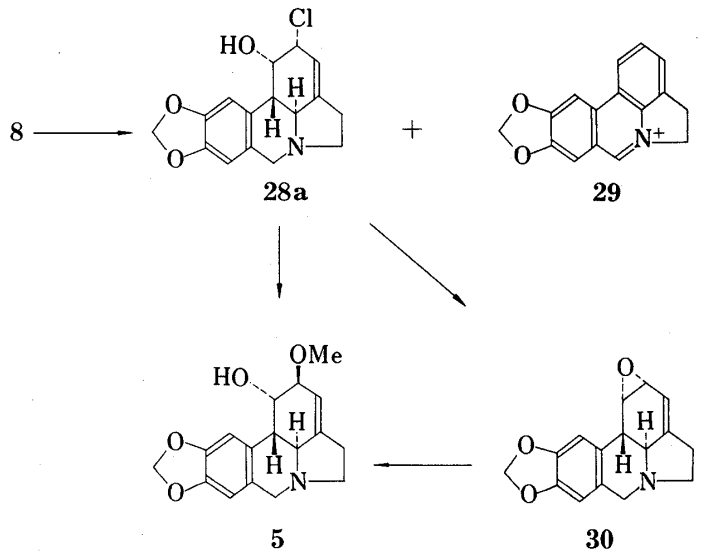


Chart 4. Transformation of Lycorine to Hippamine *via* the Chlorohydrin[12,13]

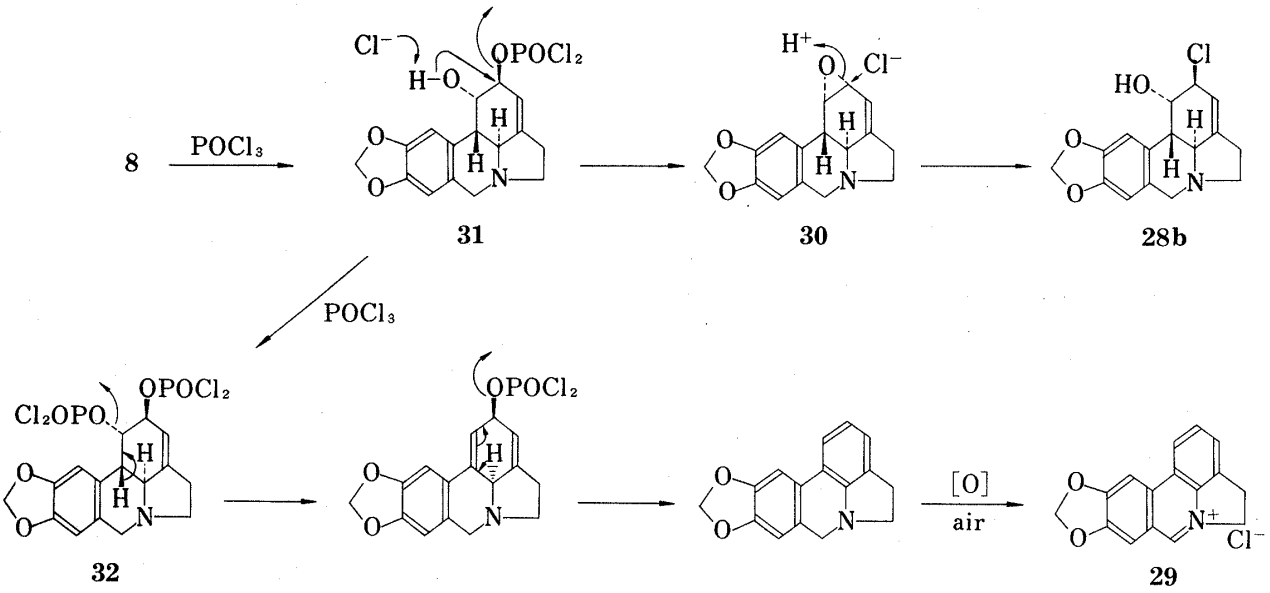


Chart 5. Mechanism of Formation of the Chlorohydrin and Anhydrolycorinium Chloride from Lycorine

phosphoryl chloride, as shown in Chart 5. The 2-*O*-phosphoryl ester (**31**) formed initially, if it is not further phosphorylated to the 1,2-di-*O*-phosphoryl ester (**32**), would give the oxide **30** which will be opened by chloride ion (from hydrochloric acid) to yield the chlorohydrin **28**. Thus the product should have *trans*-configuration as depicted in **28b**. In fact the previous authors suggested that HCl is essential for the formation of the chlorohydrin.[12] This mechanistic consideration led us to the idea that the dehydration to anhydrolycorinium chloride could be avoided by masking the C_1-hydroxyl group of lycorine. Thus, 1-*O*-monoacetyllycorine (**33**)[14] was subjected to the same treatment, giving rise to the chlorohydrin-acetate (**34**) in almost quantitative yield. On short treatment with NaOMe in MeOH at 0°C the chlorohydrin-acetate (**34**) smoothly afforded lycorene α-oxide (**30**), in accord with previous work.[13] On further treatment with the same reagent at 65°C, **34** directly gave hippamine (**5**) in 74% yield. Treatment of the epoxide (**30**) with dry hydrogen chloride gave the chlorohydrin (**28**), identical with the compound prepared by Takeda's procedure.[12] Acetylation of **28** regenerated the chlorohydrin-acetate (**34**) obtained above. These transformations, when coupled with the consideration that the chlorohydrin-acetate should be formed by neighboring group participation of the acetoxyl group as shown in Chart 6, strongly support our revision of its configuration to *trans* (**28b**). Final confirmation of the *trans* configuration of the chlorohydrin was obtained by *X*-ray analysis.[15]

Transformation of Hippamine to Ungiminorine

Short permanganate oxidation of acetylhippamine (**35**), as in the case of **10**, gave the lactam-glycol (**36**) and the aromatized compound (**37**) in yields of 26 and 3%, respectively. The latter was established as 2-methoxyanhydrolycorine-lactam (**37**) from its UV and NMR spectra. Acetylation of **36** gave the diacetate (**38**), and ^{1}H-NMR experiments again confirmed its structure and stereochemistry (Table II). Dehydration of **38** with thionyl chloride in pyridine gave diacetylungiminorine-lactam (**39**), the olefinic proton of which appeared at δ 6.08 ppm. Lithium aluminum hydride reduction of **39** furnished ungiminorine (**2**), mp 206—208°C (dec.), $[\alpha]_D$ −38.3, which formed a diacetate (**40**), mp 173—174°C, on acetylation. The synthetic ungiminorine gave mp and $[\alpha]_D$ identical with those reported for a natural specimen.[2] The NMR spectrum of the diacetate was also identical with the reported NMR spectrum of

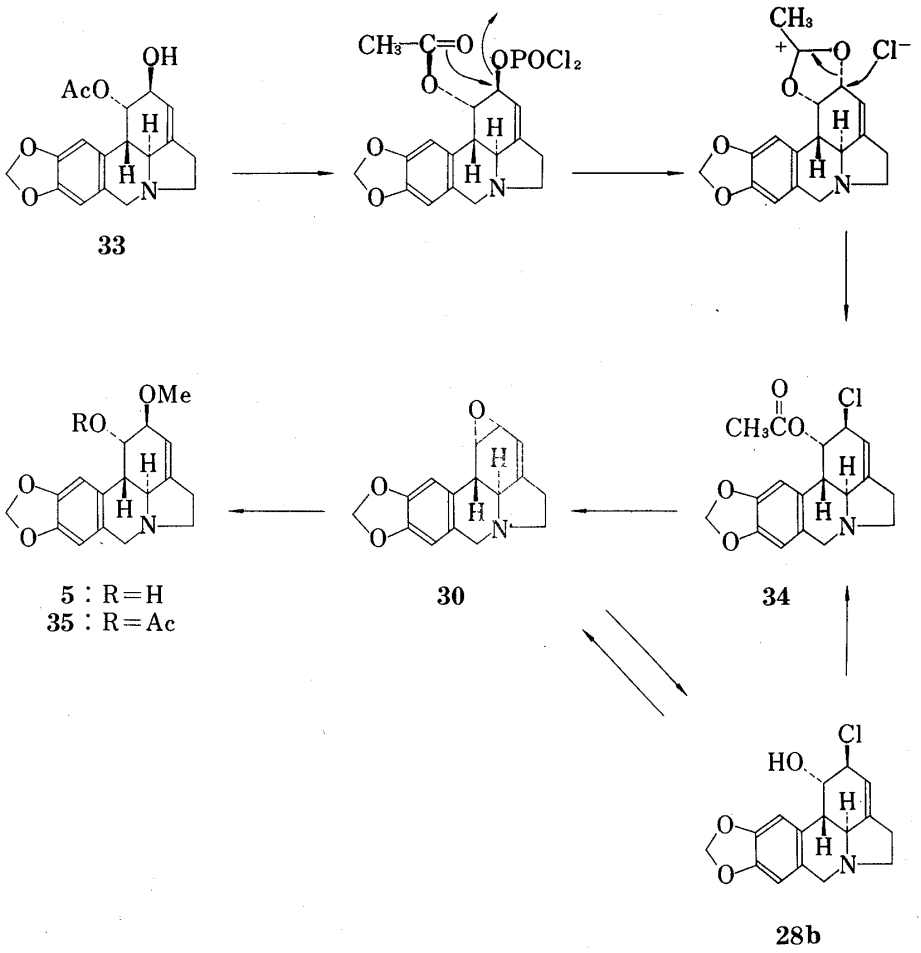


Chart 6. Formation of the Chlorohydrin-acetate from 1-*O*-Acetyllycorine and Its Transformation to Hippamine

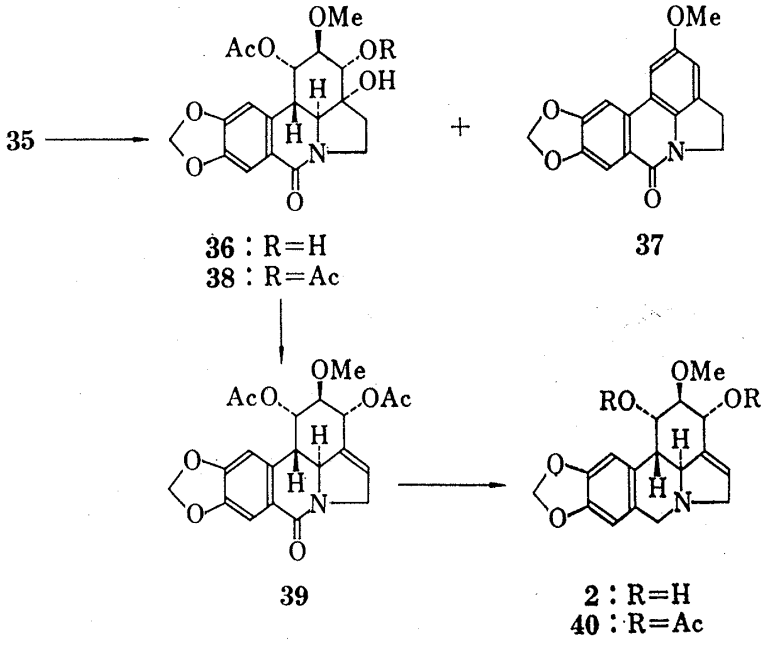


Chart 7. Synthesis of Ungiminorine

diacetylungiminorine,[2b] although direct comparison was not made, since a natural specimen was not available.

As lycorine (**8**) has already been synthesized,[10] the above transformation constitutes a formal total synthesis of the alkaloid ungiminorine.

Comment on the Biosynthesis of C_2-Oxyphenanthridinium Alkaloids

The above results support the suggested biosynthetic pathway of ungiminorine alkaloids from the lycorine alkaloids: α-face oxidation and E_2-elimination (or dehydration). A C_2-oxygenated phenanthridinium alkaloid, ungeremine (**11**), was found in *Ungernia minor*, as a minor constituent.[16] Co-occurrence of ungiminorine and ungeremine in the same plant is consistent with the chemical result that permanganate oxidation of diacetyllycorine produced the α-glycol-lactam and the C_2-oxyphenanthridone derivative. A C_1-oxygenated congener, which is always produced by other oxidative treatments of lycorine alkaloids as a major or appreciable product,[6] has never been isolated from natural sources, or from our oxidation procedure.

Therefore, although the alkaloids of ungiminorine-type and those of ungeremine-type could be produced by independent routes from the lycorine alkaloids, the authors consider that both alkaloids might be produced by a similar pathway differing only in the stereochemistry of oxidation at the double bond in lycorine alkaloids; α-face oxidation leads to ungiminorine and β-face oxidation to ungeremine. In the latter case the intermediate may be a β-glycol (or a β-epoxide).

Experimental

Unless otherwise stated, the following procedures were adopted. Melting points were taken on a Yanagimoto micro hot-stage mp apparatus and are uncorrected. IR spectra were taken in Nujol mulls with a Hitachi 215 spectrometer and are given in cm^{-1}. UV spectra were recorded in ethanol solutions with a Hitachi 200-10 spectrophotometer. ^{1}H-NMR spectra were taken in $CDCl_3$ solution with tetramethylsilane (TMS) as an internal standard on a Varian T-60 (60 MHz) or a JEOL JNM-PS-100 (100 MHz) spectrometer. High resolution mass spectra were taken with a JEOL JMS-D300 mass spectrometer. For column chromatography, Wakogel C-200 (silica gel) was used. All organic extracts were dried over $MgSO_4$ before concentration. Identities were confirmed by IR, NMR, and TLC comparisons.

Potassium Permanganate Oxidation of Diacetyllycorine (10)——i) A solution of potassium permanganate (2.5 g) in acetone (50 ml) and water (25 ml) was added in one portion to a mixture of **10** (2.7 g) and magnesium sulfate (2.7 g) in acetone (100 ml) and water (50 ml) under vigorous stirring at 0°C. After 2 min, excess permanganate was decomposed by addition of sodium bisulfite–sulfuric acid solution. The precipitate was removed by filtration and the filtrate was concentrated *in vacuo*, then the mixture was extracted with 1% MeOH–$CHCl_3$. Concentration of the extract gave a yellow oil (1.79 g) which was chromatographed in CH_2Cl_2 to give the starting material **10** (230 mg, 8.5%), followed by diacetyllycorine-lactam (**18**) (15 mg, 0.5%), mp>300°C (melted at 114°C and resolidified at 190°C), prisms from acetone. Further elution with the same solvent gave 2-acetoxyanhydrolycorine-lactam (**19**) (36 mg, 1.5%), mp 248—252°C, needles from MeOH. IR: 1750 (OAc), 1665 (lactam), 1620. ^{1}H-NMR (60 Hz) δ: 2.35 (3H, s, C$\underline{H}_3$CO), 3.38 (2H, t, J=8 Hz, $\underline{H}_2$-4), 4.47 (2H, t, J=8 Hz, $\underline{H}_2$-5), 6.13 (2H, s, –OC$\underline{H}_2$O–), 7.03 (1H, s), 7.37 (2H, s), 7.88 (1H, s) (each aromatic H). UV nm (ε): 243 (46900), 275 (19900), 345 (5400). MS m/z: Calcd for M^+ ($C_{18}H_{13}NO_5$): 323.0793. Found: 323.0770.

Further elution with CH_2Cl_2–MeOH (10: 1) and crystallizations of the product from MeOH gave the lactam-glycol **17** (530 mg, 18%), mp 230—237°C, as needles; this compound was a hydrate. IR: 3440 (OH), 1740 (OAc), 1660 (lactam). ^{1}H-NMR (100 MHz) δ: 2.01, 2.18 (each 3H, s, C$\underline{H}_3$CO), 1.9—2.4 (2H, $\underline{H}_2$-4), 3.50, 4.17 (each 1H, $\underline{H}_2$-5), 5.97 (2H, s, –OC$\underline{H}_2$O–), 6.37, 7.42 (each 1H, s, aromatic H). UV nm (ε): 250 (2600), 262 (2400), 302 (3100). *Anal.* Calcd for $C_{20}H_{21}NO_9 \cdot H_2O$: C, 54.92; H, 5.30; N, 3.20. Found: C, 54.90; H, 4.86; N, 3.52. MS m/z: 419 (M^+).

In some instances, an anhydrous form crystallized as prisms from MeOH, giving mp 243°C (dec.). IR: 3350, 1735, 1635. *Anal.* Calcd for $C_{20}H_{21}NO_9$: C, 57.28; H, 5.08; N, 3.34. Found: C, 56.79; H, 5.02; N, 3.36. This was convertible to the hydrate on heating in CH_2Cl_2 containing MeOH. Both forms gave the same triacetate **20** on acetylation.

ii) Diacetyllycorine (1 g) was oxidized in the manner described above for 1 h at room temperature. On chromatography of the product (670 mg), 2-acetoxyanhydrolycorine-lactam (**19**) (58 mg) and the lactam-glycol **17** (212 mg) were isolated.

Potassium Permanganate Oxidation of Diacetyllycorine-lactam (18)——A solution of potassium permanganate (8 mg) in acetone (5 ml) and water (2.5 ml) was added in one portion to a mixture of diacetyllycorine-lactam (**18**) (15 mg) and magnesium sulfate (10 mg) in acetone (5 ml) and water (2.5 ml) under vigorous stirring at 0°C, and the mixture was stirred for a further 16 min. After work-up as above, the product was chromatographed in CH_2Cl_2. The first eluate gave the starting material (3 mg, 20%). Further elution with $CHCl_3$ afforded the lactam-glycol **17** (10 mg, 76.6%).

Acetylation of the Lactam-glycol (17)——The lactam-glycol **17** (410 mg) was acetylated with pyridine (6 ml) and Ac_2O (3 ml) overnight at room temperature. The mixture was concentrated to dryness *in vacuo* and the residue was chromatographed in CH_2Cl_2. The CH_2Cl_2 eluate gave the tetraacetate **21** (29 mg, 6%), mp 256—261°C, prisms from acetone. IR: 1765, 1745 (OAc), 1650 (lactam). ^{1}H-NMR (60 MHz) δ: 2.07 (3H, s, C$\underline{H}_3$CO), 2.13 (9H, s, 3×C$\underline{H}_3$CO), 2.33—2.90 (2H, m, $\underline{H}_2$-4), 3.45 (1H, dd, J=4 and 14 Hz, $\underline{H}$-11b), 3.90—4.20 (2H, m, $\underline{H}_2$-5), 4.43 (1H, d, J=14 Hz, $\underline{H}$-11c), 5.38, 5.47 (each 1H, br s, >C$\underline{H}$–OAc), 5.70 (1H, d, J=4 Hz, >C$^1\underline{H}$–OAc), 6.03 (2H, s, –OC$\underline{H}_2$O–), 6.06, 7.57 (each 1H, s, aromatic H). MS *m/z*: Calcd for M$^+$ ($C_{24}H_{25}NO_{11}$): 503.1428. Found: 503.1430.

Further elution with $CHCl_3$ gave the triacetate **20** as a colorless gum (405 mg, 90%). IR (CH_2Cl_2): 1760 (OAc), 1660 (lactam). ^{1}H-NMR (100 MHz) δ: 2.02, 2.10, 2.14 (each 3H, s, C$\underline{H}_3$CO), ~2.1 (2H, m, $\underline{H}_2$-4), ~3.4, ~4.1 (each 1H, m, $\underline{H}_2$-5), 5.97 (2H, s, –OC$\underline{H}_2$O–), 6.44, 7.47 (each 1H, s, aromatic H). MS *m/z*: Calcd for M$^+$ ($C_{22}H_{23}NO_{10}$): 461.1322. Found: 461.1362.

Dehydration of the Triacetate (20)——An excess of thionyl chloride (0.75 ml) was added to the triacetate **20** (80 mg) in pyridine (8 ml) at 0°C, and the mixture was kept overnight at room temperature. After dilution with $CHCl_3$, the mixture was washed with 5% HCl, 5% NH_4OH and water, and concentrated to give a residue which was passed in CH_2Cl_2 through a short silica gel column to give triacetyl-*O*-demethylungiminorine-lactam **22** (70 mg, 91%), mp 255—256°C (dec.), prisms from Et_2O–acetone. IR: 1770, 1760, 1740 (OAc), 1680 (lactam). ^{1}H-NMR (100 MHz) δ: 2.05 (3H, s, C$\underline{H}_3$CO), 2.10 (6H, s, 2×C$\underline{H}_3$CO), 3.28 (1H, dd, J=3.5 and 13 Hz, $\underline{H}$-11b), 4.2—4.8 (2H, m, $\underline{H}_2$-5), 4.80 (1H, m, $\underline{H}$-11c), 5.21 (1H, dd, J=2 and 3 Hz, >C$^2\underline{H}$–OAc), 5.50 (1H, d, J=2 Hz, >C$^3\underline{H}$–OAc), 5.59 (1H, dd, J=3 and 3.5 Hz, >C$^1\underline{H}$–OAc), 5.98 (2H, s, –OC$\underline{H}_2$O–), 6.06 (1H, dd, J=1.5 and 3.5 Hz, olefinic H), 6.51, 7.51 (each 1H, s, aromatic H). MS *m/z*: Calcd for M$^+$ ($C_{22}H_{21}NO_9$): 443.1217. Found: 443.1257.

Attempted Methanesulfonylation of the Triacetate (20)——On treatment of the triacetate **20** with methanesulfonyl chloride and Et_3N in CH_2Cl_2, at room temperature, the starting material was recovered unchanged.

***O*-Demethylungiminorine (23)**——The lactam **22** (100 mg) and an excess of lithium aluminum hydride (LAH) in tetrahydrofuran (THF) (20 ml) were heated under reflux for 5 h. After decomposition of excess hydride with water, the mixture was continuously extracted with $CHCl_3$ for 8 h. The combined organic extract was concentrated to dryness *in vacuo*. Crystallization of the residue from acetone gave *O*-demethylungiminorine (**23**) (59 mg, 86%) as prisms, mp 210°C (dec.). IR: 3400 (OH). MS *m/z*: Calcd for M$^+$ ($C_{16}H_{17}NO_5$): 303.1105. Found: 303.1082. 303 (M$^+$), 258, 268, 242, 214, 212 (base peak).

Acetylation of **23** with acetic anhydride and pyridine afforded the triacetate **24**, mp 216—218°C (dec.), prisms from acetone. IR: 1760, 1745, 1730. ^{1}H-NMR: (60 MHz) δ: 2.02, 2.07, 2.10 (each 3H, s, C$\underline{H}_3$CO), 2.8—3.1 (1H, $\underline{H}$-11b), 3.72, 4.18 (each 1H, d, J=14 Hz, benzylic H), 4.5—4.8 (1H, $\underline{H}$-11c), 5.2—5.3 (1H, >C$\underline{H}$–OAc), 5.5—5.7 (2H, 2×>C$\underline{H}$–OAc), 5.95 (2H, s, –OC$\underline{H}_2$O–), 6.03 (1H, m, olefinic H), 6.57, 6.73 (each 1H, s, aromatic H). MS *m/z*: Calcd for M$^+$ ($C_{22}H_{23}NO_8$): 429.1422. Found: 429.1340.

1-*O*-Acetyllycorine (33)——1-*O*-Acetyllycorine was prepared by partial hydrolysis of diacetyllycorine (**10**) in 46% yield as described previously.[14] mp 227.5—229°C (dec.) [lit.[14] mp 215—216°C]. IR: 3200 (OH), 1740 (OAc). ^{1}H-NMR (60 MHz) δ: 1.93 (3H, s, C$\underline{H}_3$CO), 4.17 (1H, m, >C$\underline{H}$–OH), 5.53 (1H, m, olefinic H), 5.60 (1H, br s, >C$\underline{H}$–OAc), 5.92 (2H, s, –OC$\underline{H}_2$O–), 6.57, 6.65 (each 1H, s, aromatic H).

Lycorine-chlorohydrin-acetate (34)—— A mixture of 1-*O*-acetyllycorine (**33**) (215 mg) and phosphoryl chloride (2 g) was warmed at 30°C. After 10 min, one drop of conc. HCl was added to this mixture from a capillary tube and the temperature was gradually raised to 40°C over a period of 10 min. At this point the reaction mixture became clear. It was keep at 40°C for a further 10 min, then several pieces of ice were added to the mixture, which was basified with 10% NaOH (6 ml) followed by 10% Na_2CO_3 (30 ml), and extracted with ether. The ethereal layer was washed with water, and concentrated to give the chlorohydrin-acetate (**34**) (194 mg) which crystallized in needles from benzene, mp 185—187°C (dec.). IR: 1745 (OAc). ^{1}H-NMR (60 MHz) δ: 1.97 (3H, s, C$\underline{H}_3$CO), 4.60 (1H, m, >C$\underline{H}$–Cl), 5.55 (1H, m, olefinic H), 5.90 (1H, m, >C$\underline{H}$–OAc), 5.92 (2H, s, –OC$\underline{H}_2$O–), 6.57, 6.72 (each 1H, s, aromatic H). MS *m/z*: Calcd for M$^+$ ($C_{18}H_{18}$-^{35}ClNO$_4$): 347.0923. Found: 347.0920. Extraction of the aqueous layer with chloroform gave a further crop of **34** (30 mg) (total yield 96.9%).

Lycorene-oxide (30) from the Chlorohydrin-acetate (34)——The chlorohydrin-acetate (**34**) (200 mg) in 3% MeONa–MeOH (30 ml) was stirred for 20 min at 0°C. The mixture was diluted with $CHCl_3$, washed with water, and concentrated to dryness. Chromatography of the residue in benzene on alumina and crystallization of the eluate from benzene–Et_2O gave lycorene-oxide (**30**) (95 mg, 70.9%) as prisms, mp 152—154°C [lit.[13] mp 148—150°C] ^{1}H-NMR (60 MHz) δ: 5 72 (1H, m, olefinic H), 5 92 (2H, s, –OC$\underline{H}_2$O–), 6.57, 7.00 (each 1H, s, aromatic H).

The Chlorohydrin (28b) and Its Acetate (34) from Lycorene-oxide (30)——i) Anhydrous HCl gas was introduced into a stirred solution of lycorene-oxide (**30**) (100 mg) in $CHCl_3$ (20 ml) at 0°C. A precipitate separated out and then gradually dissolved in the solution after 40 min. The clear reaction mixture was stirred for a further 20 min at 0°C. Then the solvent was evaporated off *in vacuo*. Crystallization of the residue from Et_2O–acetone gave the chlorohydrin (**28b**) (30 mg, 26.4%) as prisms, mp 143—148°C. This product was identical with the chlorohydrin prepared from lycorine by Takeda's method[12] (mp 150°C, dec.). ^{1}H-NMR ($CDCl_3$–DMSO-d_6, 60 MHz) δ: 3.48, 4.02 (each 1H, d, J=14 Hz, benzylic H), ~4.7 (2H, m, H-1 and H-2), 5.53 (1H, m, olefinic H), 5.92 (2H, s, $-OCH_2O-$), 6.58, 6.83 (each 1H, s, aromatic H).

ii) Acetylation of the above residue (from 100 mg of lycorene-oxide (**30**)) with pyridine (2 ml) and acetic anhydride (1 ml) overnight in a refrigerator and usual work-up of the mixture gave the chlorohydrin-acetate (**34**) (109 mg, 84.5%), mp 184—186°C (dec.), which was identical with the specimen obtained in a foregoing experiment.

iii) A crude chlorohydrin (**28b**) (73 mg) obtained by Takeda's method was acetylated with pyridine (5 ml) and acetic anhydride (2.5 ml) overnight at room temperature. On work-up as usual, the acetate (29 mg, 35%), mp 180—183°C (dec.), was obtained and found to be identical with **34**.

The Reaction of Chlorohydrin-acetate (34) with K_2CO_3 in MeOH–H_2O——The chlorohydrin-acetate (**34**) (220 mg) and K_2CO_3 (300 mg) in MeOH (30 ml)–H_2O (6 ml) were heated under reflux for 30 min. After cooling, the mixture was diluted with H_2O, concentrated *in vacuo* to one-third volume and then extracted with Et_2O–benzene. The organic layer was washed with water and concentrated, and the residue was chromatographed. The first eluate with CH_2Cl_2 gave lycorene-oxide (**30**) (41 mg, 23.3%), the second eluate with 1% MeOH–CH_2Cl_2 gave hippamine (**5**) (92 mg, 48.4%) and the following eluate with MeOH–CH_2Cl_2 (1: 1) afforded lycorine (**8**) (34 mg, 18.7%).

Hippamine (5)——i) The chlorohydrin-acetate (**34**) (740 mg) in 3% MeONa–MeOH (50 ml) was heated under reflux for 10 min. The reaction mixture was concentrated *in vacuo*, diluted with ice-water, and extracted with Et_2O–benzene (1: 1). Concentration of the organic layer and crystallization of the residue (720 mg) from ether gave hippamine (**5**) (665 mg, 73.5%) as prisms, mp 167.5—170°C [lit.[11] mp 162—163°C]. ^{1}H-NMR (60 MHz) δ: 3.48 (3H, s, CH_3O), 3.80 (1H, m, >CH–OCH_3), 4.57 (1H, br s, >CH–OH), 5.58 (1H, m, olefinic H), 5.93 (2H, s, $-OCH_2O-$), 6.60, 6.83 (each 1H, s, aromatic H).

ii) Treatment of lycorene-oxide (**30**) (81 mg) with 3% MeONa–MeOH (5 ml) in a manner similar to that described above afforded hippamine (**5**) (40 mg, 44.1%).

Acetylation of hippamine (**5**) with acetic anhydride–pyridine gave the acetate **35**, as prisms from ether–acetone, mp 204—206°C. IR: 1730 (OAc). ^{1}H-NMR (60 MHz) δ: 1.95 (3H, s, CH_3CO), 3.58 (3H, s, CH_3O), 3.72 (1H, m, >CH–OCH_3), 5.53 (1H, m, olefinic H), 5.80 (1H, br s, >CH–OAc), 5.95 (2H, s, $-CH_2O-$), 6.58, 6.75 (each 1H, s, aromatic H).

Potassium Permanganate Oxidation of Acetylhippamine (35)——Potassium permanganate (630 mg) in acetone (50 ml)–water (25 ml) was added in one portion to a solution of acetylhippamine (**35**) (345 mg) and magnesium sulfate (630 mg) in acetone (60 ml)–water (30 ml) under vigorous stirring. The mixture was stirred for 8 min at room temperature, then excess permanganate was decomposed by $NaHSO_3$–H_2SO_4 solution and the precipitated manganese dioxide was filtered off. The filtrate was concentrated under reduced pressure, basified with NH_4OH, and extracted with $CHCl_3$. The extract was washed with water and concentrated to give a gummy residue (343 mg), which was chromatographed in CH_2Cl_2 to give 2-methoxyanhydrolycorine-lactam (**37**) (8 mg, 2.7%), mp 278—279°C, needles from CH_2Cl_2–MeOH. IR: 1640, 1620. ^{1}H-NMR (100 MHz, DMSO-d_6) δ: 3.23 (3H, s, CH_3O), 3.34, 4.33 (each 2H, t, J=8 Hz), 6.21 (2H, s, $-OCH_2O-$), 7.00, 7.53, 7.66, 7.99 (each 1H, s, aromatic H). UV nm (ε): 242 (48400), 282 (23400), 343 (7900), 358 (7300). MS m/z: Calcd for M^+ ($C_{17}H_{13}NO_4$): 295.0844. Found: 295.0848.

Elution of the column with CH_2Cl_2–MeOH (10: 1) and crystallization of the eluate from MeOH gave the glycol **36** (103 mg, 26.2%) as needles, mp 276—278°C (dec.). IR: 3400 (OH), 1740 (OAc), 1640 (lactam). MS m/z: Calcd for M^+ ($C_{19}H_{21}NO_8$): 391.1267. Found: 391.1261.

Acetylation of the *cis*-Glycol (36)——The glycol **36** (53 mg) was acetylated with pyridine (6 ml) and acetic anhydride (3 ml) overnight at room temperature, and worked up as usual. Purification of the product in CH_2Cl_2 by passage through a short column gave the acetate **38** (42 mg, 73%), mp 230—231°C, prisms from benzene. IR: 1740 (OAc), 1650 (lactam). ^{1}H-NMR (60 MHz) δ: 2.05, 2.18 (each 3H, s, CH_3CO), 3.52 (3H, s, CH_3O), 6.02 (2H, s, $-OCH_2O-$), 6.58, 7.47 (each 1H, s, aromatic H). MS m/z: Calcd for M^+ ($C_{21}H_{23}NO_9$): 433.1373. Found: 433.1365.

Dehydration of the Diacetate (38)——Thionyl chloride (1 ml) was added to the diacetate **38** (62 mg) in pyridine (20 ml) at 0°C, and the mixture was kept overnight in a refrigerator. After addition of dil.NH_4OH, the mixture was extracted with 1% MeOH–$CHCl_3$ and the extract was washed with water, and concentrated to give the residue, which was chromatographed in $CHCl_3$. Crystallization of the eluate from Et_2O afforded diacetylungiminorine-lactam (**39**) (44 mg, 74%) as prisms, mp 226—229°C (dec.). IR: 1740 (OAc), 1650 (lactam). ^{1}H-NMR (60 MHz) δ: 2.03, 2.07 (each 3H, s, CH_3CO), ~3.30 (1H, m, H-11b), 3.53 (3H, s, CH_3O), 3.80 (1H, m, >CH–OCH_3), 4.38—4.73 (2H, m, H_2-5), 4.85 (1H, m, H-11c), 5.70 (2H, m, 2×>CH–OAc), 6.02 (2H, s, $-OCH_2O-$), 6.08 (1H, m, olefinic H) 6.55, 7.52 (each 1H, s, aromatic H). MS m/z: Calcd for M^+ ($C_{21}H_{21}NO_8$): 415.1267. Found: 415.1270.

Ungiminorine (2)——The lactam **39** (60 mg) and LAH (100 mg) in THF (20 ml) were heated under reflux for 5 h. After decomposition of excess hydride with water, the mixture was extracted with $CHCl_3$ and the extract was washed with water, and concentrated to give a crystalline residue (43 mg). Crystallization of this from acetone gave pure ungiminorine (**2**) as needles, mp 206—208°C (dec.). $[\alpha]_D^{22} = -38.3°$ (in $CHCl_3$, $c=0.25$). [lit.[2a] mp 206—208°C (dec.), $[\alpha]_D = -28.8°$]. MS *m/z*: 317 (M^+), 299, 268 (base peak), 250, 242, 214, 212.

Acetylation of this compound with pyridine and acetic anhydride gave diacetylungiminorine (**40**), mp 173—174°C [lit.[2a] mp 173—174°C]. ^{1}H-NMR (60 MHz) δ: 2.00, 2.05 (each 3H, s, $C\underline{H}_3CO$), 3.53 (3H, s, $C\underline{H}_3O$), 5.70 (2H, $2\times>C\underline{H}$–OAc), 5.93 (3H, olefinic H and $-OC\underline{H}_2O-$), 6.53, 6.70 (each 1H, s, aromatic H). MS *m/z*; Calcd for M^+ ($C_{21}H_{23}NO_7$): 401.1475. Found: 401.1477.

Acknowledgement A part of this work was supported by a Naito Research Grant (1978), for which we would like to express our appreciation.

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