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Synthesis of Lycorine-type Alkaloids. II. Synthesis of D,L-Lycorine

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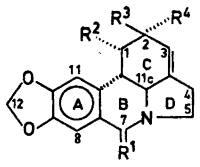
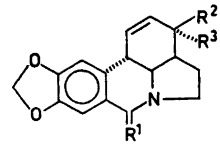
The procedures for preparation of the important intermediate *2a* were improved. Acid catalyzed rearrangement of *2a* gives *18b* which earlier has been transformed into *1a*; thus the present sequence of reactions constitutes a total synthesis of lycorine *1a*.

The structure of lycorine *1a* was elucidated by Japanese chemists over a period of several decades. The final stereostructure was presented in 1959 [1] and verified by an X-ray investigation.[2] The chemistry of lycorine and related alkaloids has been reviewed several times.[3] Lycorine is the most widely spread alkaloid of the family Amaryllidaceae and it holds a central position there because many of the other alkaloids have been related chemically to it. Several attempts have been launched on the synthesis [4–8] of the compound and to date several related structures such as dihydrolycorine,[9] 1-desoxylycorine,[10] dihydrocaranone,[11] and clividine [12] have been synthesized. Recently a route to 1-desoxylycorin-7-one, *1b*, and other lycorine-type derivatives suited for further transformations to naturally occurring alkaloids was presented in a preliminary note.[13] In continuation of this work we wish to report more details of the preparation of *1b* and *2a,b* and some newer developments which lead to the synthesis of D,L-lycorine. In the meantime a report on the synthesis of optically active lycorine has appeared.[14]

Methyl hexa-3,5-dienoate *4a* and 3,4-methylenedioxy-β-nitrostyrene *5* give the Diels-Alder adduct *6a* of correct stereostructure in the BCD-ring junctions for the α-dihydrolycorine series [4] (Scheme 1). The published synthesis [15] of *4a* is not suitable for larger preparations and gave unsatisfactory yields in our hands. According to Chiusoli *et al.*[16] methyl hexa-2,5-dienoate *7* can be prepared in large quantities *via* a tetracarbonylnickel process and can be rearranged to the amide *4b* in good yield.[17] The amide can be used for the Diels-Alder addition as well. Later other routes to *4a* were tested. It was anticipated that Cr^{2+} reduction of the NBS bromination product of methyl sorbate should yield *4a*. All our attempts to brominate *3* according to the published procedure [18] or variations thereof gave a complex mixture of products so this route was abandoned. However, when the method of Herrmann *et al.*[19] for deconjugation of α,β-unsaturated carbonyl compounds was tested on methyl sorbate, it was found that the compound could be converted into pure *4a* in a facile way. Thus, having access to simple routes for the starting materials, it was possible to prepare *6* in larger quantities. Selective reduction of *6a* or *b* with zinc and sulfuric acid in methanol/chloroform gave the hydroxamic acid *8* as the main product. Only small quantities of lactam *10* were formed. Upon further reduction of *8* with lithium aluminium hydride in ether at 40 °C, the hydroxylamine *9* was formed as the principal product and it became necessary to carry out a second separate reduction with iron powder and concentrated hydrochloric acid in methanol to obtain the amine *11*. Because of the large amounts of iron hydroxides formed during the work-up, we looked for simpler reduction methods. Electrolytic reduction of the hydroxylamine *9*, catalyzed by titanous ion, turned out to be more suitable,[20] but still the one-step reduction of *8* to *11* is desirable. This was finally accomplished by using a complex alkoxyhydride



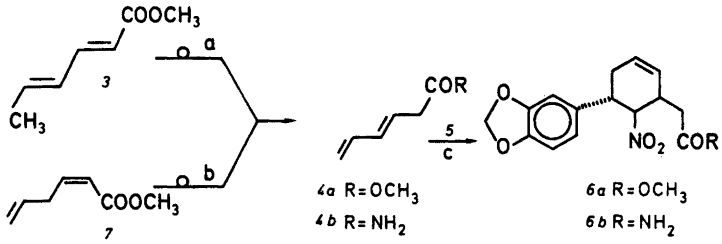


1a $R^1 = H_2$, $R^2 = OH$, $R^3 = OH$, $R^4 = H$; *2a* $R^1 = O$, $R^2 = H$, $R^3 = OH$

1b $R^1 = O$, $R^2 = H$, $R^3 = OH$, $R^4 = H$; *2b* $R^1 = O$, $R^2 = OH$, $R^3 = H$

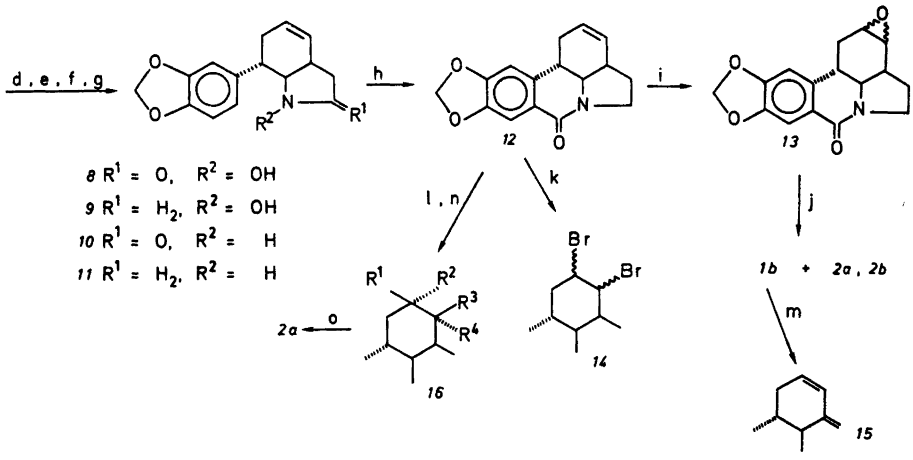
1c $R^1 = O$, $R^2 = H$, $R^3 = H$, $R^4 = OH$; *2c* $R^1 = O$, $R^2 = H$, $R^3 = OAc$

1d $R^1 = O$, $R^2 = H$, $R^3 = OAc$, $R^4 = H$; *2d* $R^1 = O$, $R^2 = OAc$, $R^3 = H$



4a R=OCH$_3$
4b R=NH$_2$

6a R=OCH$_3$
6b R=NH$_2$



8 $R^1 = O$, $R^2 = OH$
9 $R^1 = H_2$, $R^2 = OH$
10 $R^1 = O$, $R^2 = H$
11 $R^1 = H_2$, $R^2 = H$

16a $R^1 = SePh$, $R^2 = H$, $R^3 = H$, $R^4 = OH$

16b $R^1 = H$, $R^2 = SePh$, $R^3 = OH$, $R^4 = H$

16c $R^1 = H$, $R^2 = OH$, $R^3 = SePh$, $R^4 = H$

16d $R^1 = OH$, $R^2 = H$, $R^3 = H$, $R^4 = SePh$

16e $R^1 = SePh$, $R^2 = H$, $R^3 = H$, $R^4 = OAc$

Scheme 1. a. LiN(iPr)$_2$, HMPT. b. Conc. NH_4OH. c. Diels-Alder. d. Zn,H$^+$ (*8*). e. $LiAlH_4$ (*8*→*9*). f. Fe,H$^+$ or elec. red. (*9*→*11*). g. $LiAlH_2(OEt)_2$ (*8*→*11*). h. ClCOOEt, $POCl_3$. i. *m*-Cl-perbenzoic acid. j. $PhSe^-$, H_2O_2. k. Br_2. l. PhSeBr, HOAc. m. PBr_3, *t*-BuO^-. n. KOH. o. H_2O_2.

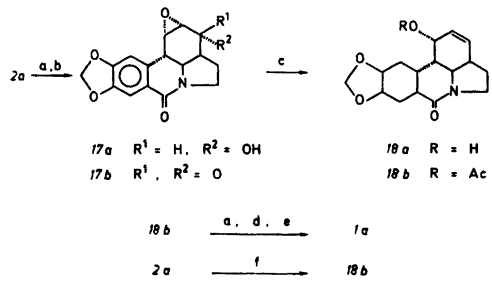
prepared by adding 2 equivalents of absolute ethanol to the suspension of lithium aluminium hydride in THF before addition of *8*. It is apparently essential that this complex alkoxyhydride first reduces the N–O bond and then the carbonyl function, since the complex does not reduce *9* to *11*.

The crude amine was treated with ethyl chloroformate and cyclized with phosphorus oxychloride to the lactam *12*. The carbonyl group protects the amino function and it can easily be reduced; we have *via* the olefinic bond an entry to further transformations of ring C and finally, we have correct ring junctions between the rings B, C, and D for conversions of *12* to derivatives of α-dihydrolycorine and the lycorine itself. The lycorine-type alkaloids have as a common feature always an oxygen function at C1, and often at C2. and a 3,3a olefinic bond (saturated in, *e.g.*, nartazine).

Allylic oxidation of *12* should give a hydroxyl function at C1; however, all our attempts to bring about reactions such as NBS bromination, $Pb(OAc)_4$ oxidation, CrO_3 or SeO_2 oxidations were unsuccessful. Either no reaction occurred, or a multitude of products were formed in the process or an aromatization of ring C occurred. *12* easily adds bromine and an epoxide *13* (mixture of isomers) can be prepared in good yields. Further elaborations of the dibromide *14* gave no useful products for further work.

It was next tried to rearrange the epimeric mixture of epoxides directly into allylic alcohols.[21,22] In this way the unsaturation can be shifted to the 1,2 or 3,3a position and an oxygen function is introduced at C3 or C2. Both sets of compounds, *i.e.* *2a,b* or *1b,c* are of interest for further transformations into naturally occurring lycorine-type alkaloids. Opening of the epoxide *13* by phenyl selenide and oxidation with hydrogen peroxide [23] led to a mixture of three allylic alcohols *1b* and *2a,b* which were separated by fractional crystallization, combined with preparative TLC. *1c* was not detected, which was expected, since selenic acid eliminations demand a *β-cis*-hydrogen. The yield was improved by using the phenylselenium bromide procedure [23] which gave the acetyl selenides. Hydrolysis and chromatography gave two fractions assigned *16a*, 33 %, and *16c* or *16d*, 56 %. Oxidation of *16a* gave an allylic alcohol in all respects identical to *2a*. The other fraction was not used further since it showed resistance to oxidation and elimination. A ketonic function appeared in the crude product on attempted oxidative elimination indicating that *16c* represents the structure. An X-ray investigation was carried out on *17a* confirming the assignments.[24]

By submitting *2a* to epoxidation, oxidation, and hydrazine reduction according to Wharton and Bohlen,[25] only traces of the desired *18a* were formed (Scheme 2). The last step of the



Scheme 2. a. *m*-Cl-perbenzoic acid (*17a*). b. $C_5H_5NHCrO_3Cl$ (*17a→17b*). c. NH_2NH_2 (*17b→18a*). d. $PhSe^-$,H_2O_2. e. $LiAlH_4$. f. Ac_2O, HOAc, H^+.

sequence proceeded in very poor yield. Primarily steric considerations coupled with the known preferred S_N2' substitution led us to test the simple acid catalyzed rearrangement. Thus, *2a* was treated with a small amount of acetic anhydride and sulfuric acid in acetic acid. The product turned out to consist mainly of *18b* and this product proved to be identical by IR and ^{1}N NMR spectral comparison to a sample prepared from naturally occurring lycorine.[26] Small amounts of acetylated *2a* and a phenanthridone derivative (ring C aromatic) were also isolated. Since the further steps, *18b* to *1a* are straightforward and have been performed in the natural series [14] and in the D,L-series as well [27] this constitutes formally also the total synthesis of lycorine *1a*. *1b* and *2a,b* gave the corresponding allylic bromides which on treatment with a *t*-butoxide gave the rearranged exocyclic diene system *15*.

EXPERIMENTAL

The IR spectra were recorded with a Perkin-Elmer Infracord and with a Beckman IR 18-A instrument. The UV spectra were recorded

with a Beckman DB spectrophotometer, and the NMR spectra with the Varian A-60 and CFT-20 instruments. The analyses were carried out by Mrs. Ilse Beetz, Mikroanal. Laboratorium, Kronach, West Germany, and Løvens Kemiske Fabrik, Ballerup, Denmark.

3,5-Hexadienamide, 4b, *and methyl 3,5-hexadienoate*, 4a. Methyl 2,5-hexadienoate * (150 g) was mixed with concentrated ammonia (160 ml) and stirred for 1 – 2 days in the dark. The amide separated as a crystalline mass. Addition of ice-water (200 ml) caused a more complete precipitation. The crystals were filtered off, pressed, and dried in a desiccator. The crude amide *4b* (110 g) was pure enough for further reactions. It was dissolved in 400 ml methanol containing 10 % dry hydrogen chloride and set aside at room temperature for 7 days. Half of the solvent was evaporated *in vacuo* and water (700 ml) and benzene (100 ml) were added. The water phase was extracted with benzene (50 ml) and the combined organic layers were washed with water and dried over sodium sulfate. After evaporation of the solvent, the residue was distilled *in vacuo*, b.p. 66 – 68 °C/17 mmHg (lit.[28] b.p. 71 – 72 °C/30 mmHg), yield 78 g of *4a*.

Preparation of 4a *from methyl sorbate*. To diisopropylamine (60.7 g) in tetrahydrofuran (500 ml) was added butyllithium (15 % in hexane, 389 ml) under stirring at – 70 °C. The temperature rose to *ca.* 0 °C but was lowered again, and HMPT (134.5 g) was added. The mixture was stirred for 30 min at – 70 °C and methyl sorbate (63 g) was added. The solution turned red. After a further 2 h at – 70 °C, the solution was hydrolyzed with water (1200 ml) and concentrated hydrochloric acid (200 ml). The organic phase was extracted with water (250 ml). Drying over magnesium sulfate and distillation *in vacuo* gave *4a*, b.p. 62 – 63 °C/12 mmHg, in a yield of 61 %. Traces of methyl sorbate were occasionally detected in the product by NMR spectroscopy.

Preparation of the Diels-Alder adduct, 6a. 3,4-Methylenedioxy-β-nitrostyrene (50 g), methyl 3,5-hexadienoate (40 g), hydroquinone (1 g), and toluene (150 ml) were refluxed for five days in the dark under N_2. The nitrostyrene passed slowly into the solution. The mixture was left at room temperature overnight whereby some nitrostyrene precipitated. After filtration and evaporation of 100 ml of the solvent, methanol (200 ml) was added. The adduct precipitated and was recrystallized from methanol, m.p. 115 – 118 °C (lit.[4] 117 – 118 °C). Yield 29 g.

A second product can be isolated from the mother liquors. The toluene-methanol filtrate from above was evaporated in vacuum until a thick, brown oil remained and methanol (20 ml) was added. On standing in a refrigerator a further crop of crystals precipitated. They were combined with the semi-solid product obtained by evaporation of the mother liquors from the recrystallization. Chromatography over silica (benzene) afforded nitrostyrene (yellow band) and immediately after this band a second product was eluted which proved to be an isomer of *6a*, m.p. 92 – 94 °C (from methanol).

Preparation of the Diels-Alder adduct, 6b. 3,4-Methylenedioxy-β-nitrostyrene (24 g), 3,5-hexadienamide, *4b*, (20 g), hydroquinone (1 g), and toluene (50 ml) were heated to 100 °C under nitrogen for 5 days with stirring. The adduct precipitated partly during that time. Half of the solvent was evaporated and ethanol (50 ml) was added. The oily mass became crystalline and was filtered off. The yield of crude *6b* was 19.6 g. A small amount was recrystallized from acetonitrile, m.p. 186 – 188 °C. (Found: C 59.12; H 5.32. Calc. for $C_{15}H_{16}N_2O_5$: C 59.20; H 5.31).

Reduction of 6a *or* 6b *with* Zn/H_2SO_4 *to* 8. *6b* (40 g, crude) was suspended in chloroform (300 ml) and methanol (220 ml). Zn powder (48 g) and $FeCl_3.6H_2O$ (30 g) were added and the mixture was cooled with dry ice. A mixture of conc. sulfuric acid (40 ml) and water (30 ml) was added under stirring so the reaction temperature was kept at *ca.* – 30 °C. The temperature was slowly raised to 20 °C over a period of 2 h and kept there for 16 h. The mixture was filtered and the filtrate was washed with water until neutral, dried over Na_2SO_4, and evaporated. To the resulting oily mass ethyl acetate was added which gave a crystalline precipitate. The crude yield was 26.3 g of the hydroxamic acid *8*. From the filtrate a further crop of 1.7 g *8* could be isolated. M.p. 150 – 152 °C (from ethyl acetate). (Found: C 66.15; H 5.87. Calc. for $C_{15}H_{15}NO_4$: C 65.94; H 5.87). From the product small amounts of the lactam *10* could be isolated by preparative TLC on silica gel. M.p. 205 – 206 °C. IR (KBr): 1690(s) cm^{-1}.

The ester *6a* was reduced in a similar way but without $FeCl_3$.

Reduction of the hydroxamic acid 8 *with lithium aluminium hydride. Preparation of* 9. To a suspension of $LiAlH_4$ (4 g) in ether (150 ml) was added *8* (25 g) in portions. When the first vigorous reaction had subsided, the mixture was stirred at 40 °C under N_2 overnight. The excess of $LiAlH_4$ was destroyed with $Na_2SO_4.10H_2O$/celite and the precipitate filtered and washed with chloroform. Evaporation of the solvent gave a viscous oil (20 g) of the hydroxylamine *9* which rapidly solidified. M.p. 122 °C (from methanol). (Found: C 69.09; H 6.44; N 5.57. Calc. for $C_{15}H_{17}O_3N$: C 69.48; H 6.60; N 5.40).

Preparation of the amine 11 *by iron reduction*. The hydroxylamine *9* (3.2 g) was reduced with Fe (6 g) in methanol (50 ml) by adding conc. hydrochloric acid (18 ml) in portions with

* A gift of Montedison, Novara, Italy.

stirring. The temperature was kept at 30 – 40°C for 12 h. Chloroform (50 ml) was added and the excess of acid was neutralized with sodium bicarbonate. Filtration, separation of the phases, and evaporation gave the amine *11* as an oily product (2.6 g) which was directly used for preparation of the lactam *12*.

Electrolytic reduction of *9* to *11* was performed according to the method of Feroci and Lund.[20]

Preparation of the amine 11 *by direct reduction of the hydroxamic acid* 8. $LiAlH_4$ (6.96 g) was suspended in dry THF and absolute ethanol (2 equiv., 16.82 g) was slowly added under nitrogen and with stirring keeping the mixture refluxing. This refluxing was continued for 1 h and then the suspension was cooled to 0 °C. Hydroxamic acid *8* (10 g, crude) was added in portions over 20 min. The stirring was continued at 0 °C for 3 h, then 16 h at 20 °C and finally by refluxing for 4 days. Excess reagent was destroyed with a mixture of $Na_2SO_4.10H_2O$ and celite. The precipitate was filtered and extracted once with boiling chloroform. The combined filtrate was dried over Na_2SO_4 and evaporated. A brown oil remained from which by addition of ethyl acetate 1.9 g of the lactam *10* could be separated. M.p., ^1H NMR, and IR spectra were identical with those of the minor product obtained by reduction of *6*. The filtrate was extracted four times with 4 N H_2SO_4 (20 ml). This water phase was made basic by NaOH and extracted three times with chloroform (25 ml). Drying over Na_2SO_4 and evaporation gave 6.43 g of the amine *11* as a brown oil. The lactam *10* could easily be reduced to the amine *11* in quantitative yield by $LiAlH_4$ in ether/THF (50:50 %) by refluxing for 16 h. ^1H NMR spectrum of *11*: δ 1.2 – 3.2 (9 H, m); 3.36 (1 H, br.dd, J 10 and 7 Hz), 5.74 – 5.85 (2 H, m); 5.89 (2 H, s); 6.73 (3 H, br.s). The same reaction could be performed by using 2 equiv. of aziridine instead of ethanol.

Preparation of the lactam 12. The amine *11* (18.8 g, crude) was dissolved in chloroform (120 ml), saturated $NaHCO_3$ solution (200 ml) and ethyl chloroformate (10.0 g) was added in portions and the mixture was stirred for 2 h. The organic phase was separated and the water phase extracted with chloroform (30 ml). The combined organic phases were dried (Na_2SO_4) and evaporated giving the urethane as a brown oil. IR ($CHCl_3$): 1680(s) cm^{-1}. This oil was dissolved in $POCl_3$ (50 ml), refluxed under N_2 for 4 h, and poured into ice water (220 ml). The water solution was decanted to remove the black oil. From the oil some unreacted urethane could be isolated by chromatography. After standing for a few hours, the water phase was made basic with NaOH and the precipitate was filtered. Yield: 10.4 g of the crude lactam *12*. M.p. 196 – 198 °C (from ethanol). MS: M+ 269. (Found: C 70.79; H 5.72. Calc. for $C_{16}H_{15}NO_3$: C 71.33; H 5.62). UV (ethanol): 223, 305 nm (ε 28 400, 6320). IR (KBr): 1645(s), 1616 (m) cm^{-1}. ^1H NMR: δ 1.3 – 3.9 (8 H, m); 4.21 (H11c, dd, J 11.4 and 7.4 Hz); 5.88 (H2, H3, br.s.); 5.98 (H12, s); 6.67 (H11, s); 7.47 (H8, s).

Bromination of 12. Bromine (160 mg) in chloroform (3 ml) was added slowly to *12* (270 mg) dissolved in chloroform (5 ml). After 30 min the solvent was evaporated and the epimeric mixture *14* was recrystallized from acetonitrile. Dec. *ca.* 180 °C. (Found: C 44.7; H 3.48. Calc. for $C_{16}H_{15}NO_3Br_2$: C 44.77; H 3.52). M.w. 429 (M+).

Catalytic hydrogenation of 12 over Pd/C in ethanol gave the saturated compound, m.p. 190 – 192 °C (lit.[4] 191 – 192 °C).

Epoxidation of 12, (1.0 g) with *m*-chloroperbenzoic acid (0.88 g, 85 %) in methylene chloride (16 ml) at + 5 °C for 2 days afforded *13* (0.89 g), m.p. 205 – 209 °C (from ethanol). M.w. 285 (M+). (Found: C 67.07; H 5.47. Calc. for $C_{16}H_{15}O_4N$: (285.3): C 67.35; H 5.30).

Rearrangement of the epoxide 13 *to the allyllic alcohols* 1b *and* 2a,b. To a solution of sodium selenophenolate, prepared from diphenyl diselenide (2.6 g) and sodium borohydride (0.65 g) in ethanol (55 ml), was added a crude, finely ground, epimeric mixture of the epoxide *13* (4.3 g). The mixture was refluxed for 2 h. The epoxide dissolved and after a short time the selenide adduct precipitated. The suspension was cooled to room temperature and filtered giving 4.3 g of *16a – d*. The filtrate was oxidized with hydrogen peroxide (8 ml, 30 %) at *ca.* 15 °C for 4 h. A white precipitate was formed. Icewater (50 ml) was added and the precipitate filtered, washed with hot water and crystallized from ethanol. 0.2 g of the isomer *2a*, m.p. 219 – 224 °C was obtained. MS: 283 (M+). ^1H NMR ($CDCl_3$, CD_3OD): δ 1.5 – 3.9 (7 H, m), 4.0 – 4.4 (H3, H11b, m), 6.03 (H12, s), 6.22 (H1, H2, s), 6.89 (H11, s), 7.51 (H8, s). From the filtrate a mixture of *2a* and *2b* (major), 0.2 g, was obtained by extracting with chloroform, evaporation, and precipitation with a few ml of ethanol in the cold. The isomers could be separated by preparative TLC (SiO_2, $CHCl_3$, 6 % CH_3OH). *2b* has the slightly higher R_F value, m.p. 208 – 212 °C from ethanol. MS: 285 (M+), 267, 266, 240, 241. ^1H NMR ($CDCl_3$): δ 1.5 – 4.3 (7 H, m), 4.5 (H3, H11b, m), 5.99 (H12, s), 6.39 (H1, H2, d), 6.79 (H11, s), 7.43 (H8, s).

The precipitate *16a – d* (4.3 g) was suspended in ethanol (80 ml) and oxidized with hydrogen peroxide (18 ml, 30 %) at *ca.* 15 °C for 5 h with stirring. The precipitate was filtered, washed with water, and recrystallized from ethanol. *1b* (0.8 g), m.p. 235 – 239 °C (after two crystallizations) was obtained. (Found: C 67.19; H 5.28, N 4.86. Calc. for $C_{16}H_{15}O_4N$: C 67.25; H 5.30; N 4.91). ^1H NMR ($CDCl_3$, CD_3OD): δ 1.5 – 4.0 (9 H, m), 4.52 (H2, m), 5.73 (H3, m), 6.02 (H12, s), 6.76 (H11, d, $J \sim 1$ Hz), 7.42 (H8, s). MS: 285 (M+), 267, 266, 241, 240, 226, 175.

The filtrate was diluted with water, extracted with chloroform, evaporated, and again precipitated with ethanol. A further crop of *1b* and *2b* (~1:1, 0.6 g) contaminated by some diphenyldiselenide was obtained and purified by TLC ($CHCl_3$, 6 % CH_3OH). *1b* has bluish and *2a,b* have brownish fluorescence in the UV.

Preparation of the diene 15. *1b* (0.32 g) was stirred with phosphorus tribromide (0.15 g) and pyridine (0.08 g) in methylene chloride (10 ml) for 2 h. The solution was extracted with water and the solvent dried and evaporated. The light yellow solid was suspended in DMSO (4 ml) and a suspension of potassium *t*-butoxide (0.2 g) in DMSO (4 ml) was added under nitrogen with stirring. After a few hours ice water (50 ml) was added and the oily precipitate filtered. TLC of the product gave *15* (80 mg) (SiO_2, $CHCl_3$, 3 % CH_3OH) as the only pure fraction, m.p. 232–240 °C dec. (Found: C 71.65; H 4.95. Calc. for $C_{16}H_{13}O_3N$: C 71.90; H 4.90). MS: M^+ 267. The exocyclic diene system was proved by selective decoupling. UV (EtOH): λ_{max} 225, 237 (sh), 274, 306 (ε 35 000, 19 000, 3500, 5400).

Preparation of the α-keto-epoxide from the allylic alcohol 2a; *attempted hydrazine reduction to* 18a. The allylic alcohol *2a* (739 mg; crude) was suspended in methylene chloride (35 ml), cooled to 0 °C and 85 % *m*-Cl-perbenzoic acid (579 mg) was added. The mixture was stirred for 3 days at 0 °C. Methanol (15 ml) was added and the mixture washed (2 M NaOH), dried (Na_2SO_4) and evaporated giving 439 mg of the α-hydroxy-epoxide *17a*, m.p. (methanol) 245–248 °C. MS: (M^+) 301. ^1H NMR ($CDCl_3$, CD_3OD): δ 1.6–2.7 (H3a, H4, m), 3.0–3.6 (H1, H2, H5, m), 3.7–4.2 (H3, H11b,c, m), 6.01 (H12, s), 6.96 (H11, s), 7.43 (H8, s). (Found: C 63.43; H 4.95. Calc. for $C_{16}H_{15}NO_4$ C 63.77; H 5.03).

Pyridinium-chlorochromate [29] (511 mg) was suspended in dry methylene chloride (20 ml). The α-hydroxyepoxide *17a* (284 mg, crude) in methylene chloride (25 ml) was added and the mixture was stirred under N_2 at 20 °C for 3 h. The reaction was followed by TLC. The reaction mixture was then extracted once by 4 N HCl (50 ml) and the resulting water phase was extracted with methylene chloride (20 ml). The combined organic phases were dried over Na_2SO_4 and evaporated. Preparative TLC (SiO_2, $CHCl_3$, 5 % CH_3OH) gave 139 mg of *17b*, m.p. 215–216 °C. MS: (M^+) 299. ^1H NMR ($CDCl_3$): δ 1.6–2.5 (H4, m), 3.0–3.4 (H3a,5, m), 3.62 (H2, d, *J* 5 Hz), 3.9–4.4 (H1, 11b, 11c, m), 6.01 (H12, s), 6.92 (H11, s), 7.49 (H8, s). IR ($CHCl_3$): 1730(s), 1650(s), 1605(m).

The eliminative reduction of the α-keto-epoxide *17b* was carried out by suspending the α-ketoepoxide (58 mg) in hydrazine hydrate (10 ml) and stirring for 1½ h. Gas evolution could be seen, and the substrate was slowly dissolved. The reaction was followed by TLC. After 1½ h water (10 ml) was added. The organic phase was separated and the water phase extracted once with chloroform. The combined organic phase was dried over Na_2SO_4 and evaporated. ^1H NMR and TLC showed that it was a mixture of several compounds and it was not possible to crystallize the product. It was directly treated with acetic anhydride (6 ml) and pyridine (3 ml) for 20 h. The workup gave a brown oil which by preparative TLC (SiO_2, $CHCl_3$, 5 % CH_3OH) gave a fraction (*ca.* 2 mg) of the same R_F value and spectral properties as *18b*.

Preparation of 16a, c *with PhSeBr as reagent.* Diphenyldiselenide (4.69 g) was added with stirring to a solution of Br_2 (0.76 ml) in acetic acid (80 ml). After 0.5 h the lactam *12* (8 g, crude) and anhydrous potassium acetate (5.84 g) were added. The mixture was stirred for 4 h. Water (80 ml) and chloroform (80 ml) were added. The organic phase was separated and the water phase extracted twice with chloroform (30 ml). The combined organic phase was washed twice with 10 % K_2CO_3, dried (Na_2SO_4) and evaporated. This gave a white solid (15.1 g) which according to ^1H NMR was a mixture of mainly two isomers (~1:2). It was not possible to separate these isomers by TLC. The crude product was dissolved in chloroform (100 ml) and methanol (200 ml), and crushed KOH pellets (4.1 g) were added and the solution stirred for half an hour. The precipitate was filtered [6.3 g assigned *16c*; δ 6.67 (H8)] and to the filtrate was added chloroform (100 ml) and water (280 ml). The organic phase was separated and the water phase extracted with chloroform (100 ml). The combined organic phase was washed with water until neutral and dried (Na_2SO_4). Evaporation gave a white solid consisting mainly of two isomers [δ 6.67 and 6.53, respectively, (2 H8)], which were separated by preparative TLC (SiO_2, $CHCl_3$, 5 % CH_3OH) giving 4.4 g of an isomer m.p. 213–215 °C (methanol) assigned structure *16a* and a further crop of *16c* (1.0 g). ^1H NMR of *16a* ($CDCl_3$): δ 1.65–4.05 (11 H, m), 4.14 (1 H, br.dd, *J* 12 and 7 Hz), 5.98 (H12, s), 6.53 (H11, s), 7.20–7.43 (4 H, m). 7.52–7.78 (2 H, m). IR (KBr): 3400 (br.s), 1650(s), 1610(m) cm^{-1}. MS: (M^+) 443. Acetylation of the latter isomer, m.p. 253–254 °C, with acetic anhydride/pyridine gave a mono-acetate, m.p. 220–222 °C. ^1H NMR ($CDCl_3$): δ 1.25–3.9 (9 H, m), 1.89 (acetyl, s), 4.19 (H3, br.dd, *J* 12 and 6 Hz), 5.25 (H2, br. d, t, *J* 9.5 and 4 Hz), 6.01 (H12, s), 6.59 (H11, s), 7.15–7.5 (4 H, m), 7.5–7.8 (2 H, m). IR (KBr): 1740(s), 1650(s), 1610(m) cm^{-1}. This isomer was resistant to oxidative elimination that indicates that *16c* represents the structure.

Preparation of 2a *from* 16a. *16a* (2 g) was suspended in methylene chloride (80 ml) and pyridine (3.5 ml), and H_2O_2 (3.8 ml, 35 %) were added. The mixture was stirred at 20 °C for 1 h and then refluxed for 5 h. The originally

found precipitate disappeared and the elimination was completed (followed by TLC). Water (20 ml) and methanol (20 ml) were added, the organic phase was separated, and the water phase extracted with methylene chloride (20 ml). The combined organic phase was washed with potassium carbonate (20 ml), 10 % aqueous soln.) and then with hydrochloric acid (20 ml, 4 M), dried (Na_2SO_4) and evaporated. It gave 0.74 g of a crystalline compound identical with that obtained by the other route and assigned *2a*.

Allylic rearrangement of 2a *to* 18b. The allylic alcohol assigned *2a* (166 mg, crude) was dissolved in acetic acid (6 ml) and heated to 50 °C. A mixture of acetic anhydride (2 ml) and conc. sulfuric acid (10 drops) was added, and the reaction mixture was stirred at 50 °C for 15 min. Ice water (25 ml) and methylene chloride (50 ml) were added. The organic phase was separated and the water phase extracted twice with methylene chloride (25 ml). The combined organic phase was washed with saturated $NaHCO_3$ solution and dried over Na_2SO_4. Evaporation gave a yellow oil which was separated by preparative TLC (SiO_2, $CHCl_3$) into *18b* (55 mg), *2c* (12 mg) and 6 mg of a phenanthridone formed by aromatization of ring C. *18b*, recrystallized from ether, melted at 211–212 °C. ^1H NMR ($CDCl_3$): δ 1.91 (acetyl, s), 1.4–2.3 (H4, m), 2.7–3.5 (H3a, 5, m), 3.9–4.3 (H11b, 11c, m), 5.53 (H1, br.t, J 4 Hz), 5.90 (H12, s), 5.97–6.10 (H2, 3, m), 6.45 (H11, s), 7.40 (H8, s). IR ($CHCl_3$): 3685(m), 3625(m), 3420(br.m), 3015(s), 2895(m), 1740(s), 1650(4 bands, s), 1615(s), 1510(m), 1490(s), 1470(s), 1420(s), 1390(w), 1380(s), 1350(w), 1340(m), 1185(w), 1130(w), 1005(w), 995(w), 985(w), 950(s), 910(w), 895(m), 855(w), 850(w), 630(w). These spectra are identical with the spectra of a sample prepared from natural lycorine.[26] *2c* was identified by its ^1H NMR spectrum and it was identical to the product obtained by direct oxidative elimination of *16e*. ^1H NMR of the phenanthridone: δ 3.32 (H4, t, J 8 Hz), 4.39 (H5, t, J 8 Hz), 6.01 (H12, s), 6.95–7.72 (H1, H2, H3, m), 7.45 (H11, s), 7.81 (H8, s).

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