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A SYNTHESIS OF (±)-Δ^2-α-LYCOREN-7-ONE, THE KEY INTERMEDIATE FOR THE TOTAL SYNTHESIS OF (±)-LYCORINE†

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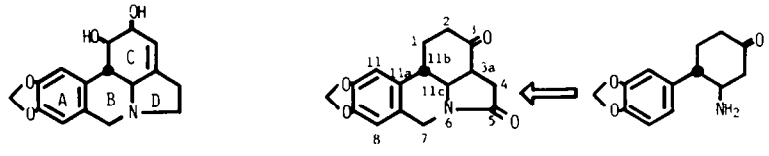
Abstract—(±)-α-Lycoran-3,5-dione (**14a**) was prepared from octahydrophenanthridin-3-one (**8b**) obtained by two methods starting from 5-aryl-4-nitrocyclohexene (**2**) and 1-hydroxy-2-aryl-5-oxo-cyclohexanecarboxylic acid (**10**), both of which were prepared by the Diels-Alder reaction of 3,4-methylenedioxy - ω - nitrostyrene with butadiene and the Robinson annelation of 3,4-methylenedioxy - phenylpyruvic acid (**9**) with methyl vinyl ketone, respectively. **14a** was converted into (±)-Δ^2-α-lycoren-7-one (**22b**), which has been transformed into (±)-lycorine (**1**) by Torssell *et al.*

The synthesis of lycorine (**1**) has long been a challenging problem for organic chemists,[1] because of its structural complexity with four asymmetric carbon atoms aligned contiguously in the C ring and of the significant biological activity.[2] For some years, we engaged in the construction of its skeleton, (±)-α-lycorane,[3] and the functionalization of (±)-α-lycoran-3,5-dione (**14a**), searching for an efficient route to the alkaloid.

Our original plan was to synthesize 3-amino-4-

†A part of this work has appeared as a preliminary communication: B. Umezawa, O. Hoshino, S. Sawaki, H. Sashida, and K. Mori, *Heterocycles* **12**, 1475 (1979).



1 **14a**

Fig. 1.

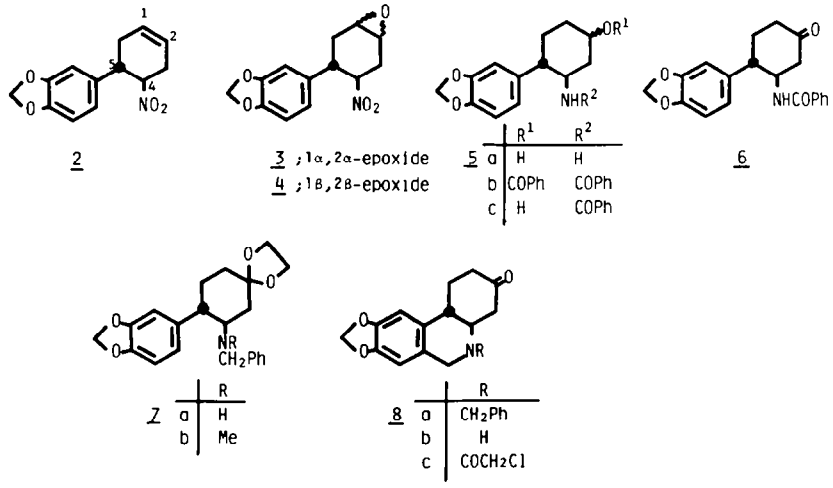


Fig. 2

(3,4-methylenedioxyphenyl)cyclohexanone or its equivalent (A–C ring of **1**), in which both amino and phenyl groups were trans disposed, because B–C ring juncture in **1** was trans. The present report deals with two routes, one involving the Diels–Alder reaction and the other the Robinson annelation, to aminoketone (**8b**), its transformation to **14a**, and functionalization of **14a** including a formal synthesis of **1**.

As the first method for preparation of **8b**, the Diels–Alder reaction of the requisite nitrostyrene with butadiene was carried out to give **2**.[4] Epoxidation of **2** with m-chloroperbenzoic acid (MCPBA) gave 1α,2α- and 1β,2β-epoxides (**3** and **4**) in a ratio of 1:1, structures of which were deduced by the finding that in the ^{1}H-NMR spectra the signals of C_4-αH in **3** and C_5-βH in **4** were shifted downfield by 0.19 and 0.21 ppm from those of the corresponding protons in **4** and **3**, respectively, by deshielding effect[5] of the oxygen atom of the epoxide ring and confirmed by the following chemical evidences. Hydrogenation over Raney Ni and subsequent reduction of the former (**3**) with $LiAlH_4$ gave **5a**. Benzoylation of **5a** gave N,O-dibenzoyl derivative (**5b**), which gave benzamide (**5c**) on hydrolysis with 5%KOH. CrO_3 oxidation of **5c** in pyridine gave **6**, ketalization of which followed by reduction with $LiAlH_4$ afforded **7a**. Deketalization of **7b**, obtained by N-methylation of **7a**, with 6N HCl gave α, β-unsaturated cyclohexenone, formed by β-elimination of the amino group due to the 1,3-relationship of the carbonyl and amino groups, and β,γ-unsaturated cyclohexenone, formed by isomerization of the former, respectively. However, the Pictet–Spengler reaction of **7a** with 35%CH_2O and 6N HCl afforded **8a**, hydrogenolysis of which with 10% Pd–C in acidic MeOH gave **8b**.

As the second method for preparation of **8b**, construction of the functionalized cyclohexane ring by the Robinson annelation[6] of a pyruvic acid (**9**) was carried out. The reaction of **9**[7] with methyl vinyl ketone led to **10**, dehydration of which with acid gave a mixture of unsaturated keto-acids (**11**). Hydrogenation of **11** with zinc powder in 70%AcOH gave cis-acid (**12a**). Transformation of cis-acid (**12a**) to trans-acid (**13c**) having the similar stereochemistry to that of the B–C ring juncture in **1** was performed as follows. Esterification followed by ketalization of **12a** gave cis-methyl ester (**12c**), epimerization of which with NaOMe in refluxing MeOH for 12 h gave trans-methyl ester (**13a**) and the unchanged **12c** in a ratio of 8:1 (GLC analysis). The reaction period for the epimerization was shortened by using KO*t*-Bu in refluxing *t*-BuOH (30 min) or NaOEt in refluxing EtOH (2.5 h). In the latter case, the product was a 3:1 mixture of trans-ethyl ester (**13b**) and trans-acid (**13c**). Thus, for a practical purpose, **13c** was obtained in a high yield on epimerization of **12c** with NaOEt and subsequent hydrolysis with 10%NaOH. While the Hofmann rearrangement of trans-amide (**13d**) failed to give the desired amine (**13g**), the Curtius rearrangement of the corresponding acid azide from **13c** gave trans-isocyanate (**13e**) in good yield. The signal of one proton double triplets (J = 5 and 11 Hz) at δ 3.73 due to C_1–H in its ^{1}H-NMR spectrum confirmed that no stereochemical change had occurred during the reaction.

Two routes to **8b** were next examined with a considerable success, one being a conventional transformation of **13e** to **8b** via methyl carbamate (**13f**) and amine (**13g**), and the Pictet-Spengler reaction of **13g**, and the other the dihydroisocarbostyril cyclization[8] and successive reduction.

Attachment of ring D to **8b** was achieved by intramolecular cyclization of **8c**. Acylation of **8b** with $ClCH_2COCl$ in pyridine gave chloroacetamide (**8c**),

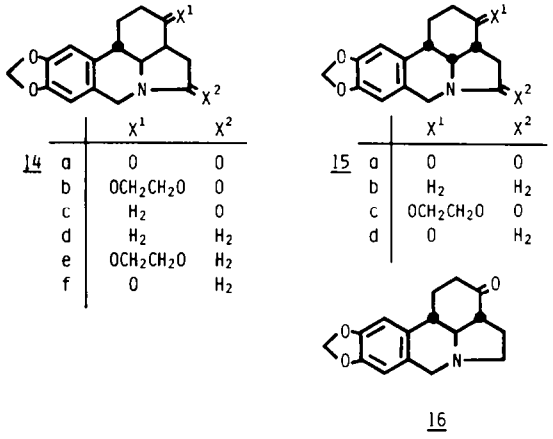


Fig. 4.

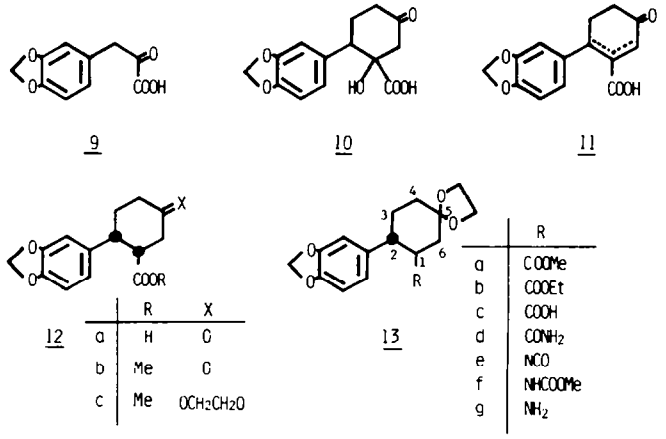


Fig. 3.

treatment of which with KO*t*-Bu in boiling t-BuOH at 120° (bath temp) for 10 min gave (±)-α- and (±)-γ-lycoran-3-one lactams (**14a** and **15a**) in 32 and 1.1% yields, respectively. The more convenient isolation of the α-isomer (**14a**) from the intramolecular cyclization mixture was carried out through ketalization of the reaction mixture followed by chromatographic purification and deketalization. For further confirmation of the stereochemistry, **14a** and **15a** were converted into (±)-α- and (±)-γ-lycoranes (**14d** and **15b**), respectively, by a sequence of reactions, i.e. ethylenethioketalization, desulfurization, and lactam reduction. The products were infrared spectroscopically indistinguishable with α- and γ-lycoranes,[4a,9] respectively, derived from natural lycorine.

Since heating of **14a** with KO*t*-Bu in boiling *t*-BuOH did not give even a trace of **15a**, formation of the γ-lycorane skeleton was most probably attributable to the retro-Michael and Michael reactions occurring partially before the ring closure.[10]

Prior to functionalization in the C ring, we examined the role of the lactam carbonyl group. Ketalization and deketalization of **14a** gave the starting material unchanged. However, removal of the lactam carbonyl group by a conventional method (ketalization, lactam reduction, and deketalization with 6N HCl) gave an inseparable mixture,[11] probably consisting of **14f** and **15d** or **16**. Accordingly, the presence of the lactam carbonyl group was proved to be indispensable to prevent the undesired epimerization.

Thus, we used **14a** as a key compound for further transformation and tried to introduce Δ^2-double bond to the α-lycorane skeleton starting from **14a**. $NaBH_4$ reduction of **14a** gave **17a**. Since hydride attack would have occurred preferentially from the convex α-face of **14a**, orientation of the OH group in **17a** must have been β and the assumption was substantiated as below. Acetylation of **17a** gave **17b**, the ^{1}H-NMR spectrum of which exhibited a broad singlet with a half-width of 24 Hz at δ5.13, pointing out that the substituent was β-equatorially oriented. Accordingly, syn-elimination was needed to make the Δ^2-double bond. However, the low yield of xanthate (**17c**) prohibited further examination.

Next, the Cope reaction of **17d**, prepared by reductive amination[12] of **14a** with Me_2NHHCl and $NaBH_3CN$, was undertaken. Oxidation of **17d** with

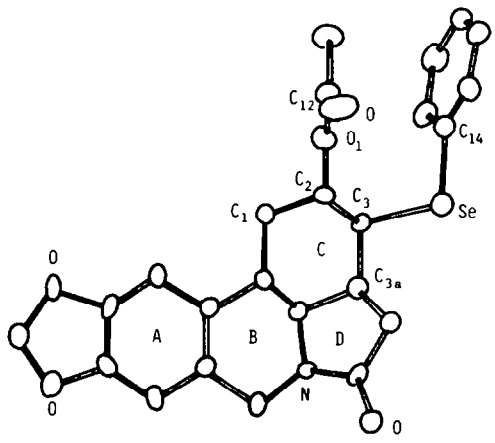


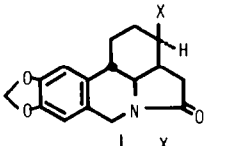
Fig. 6. A perspective drawing of **19** drawn by the ORTEP program [C. K. Johnson, ORTEP, report ORNL-3794, Oak Ridge National Laboratory, Tennessee (1965)].

MCPBA gave the N-oxide (**17e**), heating of which at 200° (bath temp) furnished the desired (±)-Δ^2-α-lycoran-5-one (**18**) in 73.1% yield. Structure of **18** was confirmed unequivocally by the following chemical transformations. Reaction of **18** with PhSeBr in the presence of KOAc[13] gave three kinds of selenides[14] in 57, 19, and 5% yields, respectively. The stereostructure of the major product was proved to be **19** by X-ray analysis.

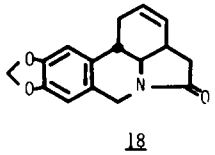
Contrary to the case of trans - 2 - acetoxycyclohexylphenylselenoxide,[13] heating of the selenoxide derived from **19** gave enol acetate (**20**) in addition to the deoxygenated product (**19**). Alkaline hydrolysis of **20** gave **21a**, non-identity of which with the isomeric 3,5-dione (**14a**) was apparent on the basis of GLC analysis.

Transformation of the lactam carbonyl group in **18** from C_5- to C_7-position would lead to (±)-Δ^2-α-lycoren-7-one (**22b**), which was Torssell's key compound[1c] for a formal synthesis of **1**. Thus, $LiAlH_4$ reduction of **18** gave **22a**, oxidation of which with active MnO_2 in $CHCl_3$ furnished the desired **22b**. IR and ^{1}H-NMR spectra of **22b** were superimposable to those of Torssell's sample.

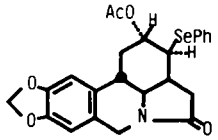
In conclusion, a formal synthesis of (±)-lycorine (**1**) was accomplished by the ring construction in the order of A→C→B→D.



17	X
a	OH
b	OAc
c	CCSSMe
d	NMe_2
e	$N(O)Me_2$



18



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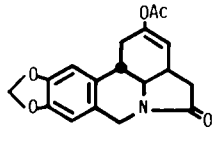

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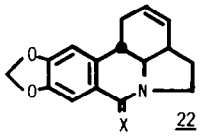
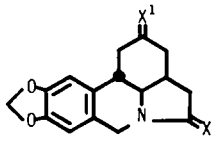


22

	X
a	H_2
b	O

Fig. 5



21	X^1	X^2
a	O	O
b	OCH_2CH_2O	O
c	OCH_2CH_2O	H_2

Fig. 7.

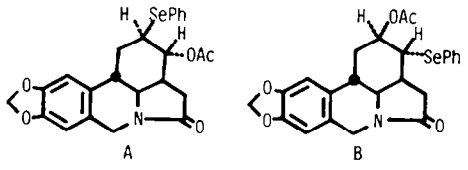


Fig. 8.

EXPERIMENTAL

M.ps are uncorrected. IR spectra were measured with one of the following instruments: (a) Koken Model DS-301: (b) Hitachi Model 225; and (c) Hitachi Model 215. UV spectra were obtained with a Hitachi Model EPS-2UV spectrometer. ^{1}H-NMR spectra were run on one of the following spectrometers: (a) Varian A-60 (60 MHz); (b) Hitachi R-24B (60 MHz): (c) JEOL Model NM-4H-100 (100 MHz); and (d) JEOL JNM FX-100 (100 MHz). ^{13}C-NMR spectra were taken with a JEOL JNM FX-100 spectrometer. Unless otherwise noted, Me_4Si was used as an internal standard in $CDCl_3$. Mass spectra were measured on a Hitachi RMU-7M spectrometer. GLC analysis was performed on a Shimadzu GC-4APF instrument.

1α,2α- and 1β, 2β-*Epoxy-trans*-4-*nitro*-5 - (3,4-*methylenedioxyphenyl*)*cyclohexanes* (**3** and **4**). A soln of MCPBA (85%, 1.2 g,) in CH_2Cl_2 (15 ml) was added to an ice-cooled soln of **2**[4] (1.18 g, 4.77 mmol) in CH_2Cl_2 (25 ml) and the whole was allowed to stand at 0° for 30 days. The resulting soln was successively washed with aq Na_2SO_3, 10% Na_2CO_3 and H_2O, and usual work-up gave a residue (1.2 g), which was crystallized from CH_2Cl_2–Et_2O to give colorless needles of **3** and **4** (1.0 g, 78%), mp 124–125°. Separation was achieved by preparative TLC (SiO_2, C_6H_6–AcOEt = 10:1; movility; **3** > **4**). **3**:colorless pillars (370 mg, 29.1%), m.p. 139.5–141° (CH_2Cl_2-MeOH); ^{1}H-NMR[a] δ:4.80 (1H, dt, J = 11.1, 4.8 Hz, 4-H), 3.06 (1H, dt, J = 11.1, 7.0 Hz, 5-H). (Found: C, 53.35; H, 5.09; N, 5.41. Calc. for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32%). **4**:colorless needles 392 mg, 30.7%), m.p. 145–147° (CH_2Cl_2-Et_2O); ^{1}H-NMR[a] δ:4.61(1H, ddd, J = 11.5, 10.0, 7.8 Hz, 4-H), 3.27 (1H, ddd, J = 11.5, 12.0, 4.5 Hz, 5-H). (Found: C, 59.38; H, 5.00; N, 5.42. Calc for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32%).

3 - *Amino* - 4 - (3,4 - *methylenedioxyphenyl*)*cyclohexanol* (**5a**). A soln of **3** (302 mg, 1.14 mmol) in EtOH (25 ml) was hydrogenated with Raney Ni (0.5 ml) at 50° under H_2 (40 atom) for 6 h. Usual work-up gave a product (270 mg), which was refluxed with $LiAlH_4$ (140 mg) in THF (4 ml)-Et_2O (18 ml) with stirring for 2 h. Usual work-up gave **5a** (190 mg, 70%) as colorless prisms, m.p. 178–179° (EtOH–AcOEt); (Found: C, 66.25; H, 7.20; N, 5.62. Calc for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95%).

3-*Benzamidio*-4-(3,4 - *methylenedioxyphenyl*)*cyclohexanol* (**5c**). A soln of PhCOCl (7.2 g, 51.2 mmol) in CH_2Cl_2 (20 ml) was added dropwise to an ice-cooled soln of **5a** (3 g, 12 mmol). After standing for 2 days at room temp the whole was refluxed for 4.5 h. Usual work-up and column chromatography (SiO_2, Woelm; 170 g; C_6H_6–$CHCl_3$) of the product gave **5b** (3.8 g, 67.2%), m.p. 182–183° ($CHCl_3$–EtOH); IR[a] ν (nujol): 3300, 1710, 1640 cm^{-1}; (Found: C, 73.10; H, 5.67; N, 3.14. Calc for $C_{27}H_{25}NO_5$: C, 73.12; N, 5.68; N, 3.16%). A mixture of **5b** (3.8 g, 8.57 mmol) and 5% KOH (44 ml) in MeOH (260 ml) was refluxed for 45 min. On cencentration of the reaction mixture to one-third of its original volume, H_2O was added and the product was taken up in $CHCl_3$. Usual work-up gave **5c** (2.8 g, 91.5%) as colorless needles, m.p. 187°; IR[a] ν(nujol): 1645 cm^{-1}; (Found: C, 69.15; H, 6.71; N, 3.58. Calc for $C_{20}H_{21}NO_4 \cdot H_2O$: C, 70.78; H, 6.24; N, 4.13%).

3 - *Benzamido* - 4 - (3,4-*methylenedioxyphenyl*)*cyclohexanone* (**6**)

(1) *Jones oxidation.* Jones reagent (331 ml) was added dropwise to an ice-cooled soln of **5c** (2.62 g, 7.33 mmol) in acetone (360 ml) over a period of 5 min. After stirring for 10 min, the whole was poured into ice-water and the product was extracted with CH_2Cl_2. Usual work-up of the extract gave **6** (1.5 g, 60.7%) as colorless needles, m.p. 210–212° (acetone); IR[a] ν(nujol): 3300, 1720, 1635 cm^{-1}. (Found: C, 71.18; H, 5.72; N, 4.14. Calc for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15%).

(2) *Oxidation with* CrO_3-*pyridine.* A soln of **5c** (11.2 g, 31.3 mmol) was added dropwise to a mixture of CrO_3 (13 g) and pyridine (130 g) and the whole was allowed to stand overnight at room temp. The reaction mixture was poured into AcOEt (500 ml) and stirred for 30 min. Inorganic salts were filtered off. The filtrate was purified through Al_2O_3 (200 g, Woelm) and celite (40 g) giving **6** (7.21 g, 68.2%).

3-*Benzylamino*-4-(3,4 - *methylenedioxyphenyl*) *cyclohexanone ethylene ketal*(**7a**). A mixture of **6** (1.11 g, 3.29 mmol), $HOCH_2CH_2OH$ (5.5 g, 98 mmol), and $BF_3 \cdot Et_2O$ (0.5 ml, 3.9 mmol) in THF (22 ml) was allowed to stand overnight at room temp. Cold H_2O (33 ml) was added to the reaction mixture and the resulting precipitate was collected to give ethylene ketal (1.12 g, 89.6%) as colorless silky fibres, m.p. 218° (MeOH); IR[a] ν(nujol): 3305, 1635 cm^{-1}; (Found: C, 69.25; H, 6.12; N, 3.54. Calc for $C_{22}H_{23}NO_5$: C, 69.27; H, 6.08; N, 3.67%). A soln of the above ketal (2.0 g, 5.2 mmol) in THF (190 ml) was refluxed with $LiAlH_4$ (1.0 g, 26.3 mmol) for 20 h. Usual work-up of the reaction mixture gave, after column chromatography on Al_2O_3 (60 g, Woelm II), **7a** (1.3 g, 71.8%) as colorless pillars, m.p. 87–88.5° (Et_2O-petroleum ether); (Found: C, 71.85; H, 6.90; N, 3.81. Calc for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; H, 3.81%).

Deketalization of **7b**. $NaBH_4$ (4 g, 105.8 mmol) was added portionwise to a mixture of **7a** (1.01 g, 2.75 mmol) and 37%CH_2O (4 ml, 53.3 mmol) in MeOH (20 ml) over a period of 1.5 h at room temp and the whole was stirred for 2 h at the same temp. After extraction with Et_2O and usual work-up, the residue was chromatographed on Al_2O_3 (30 g, Woelm II; C_6H_6-petroleum ether=1:1 and 2:1) gave pasty **7b** (563 mg, 53.7%); IR[a] ν(nujol): 2800, 1605 cm^{-1}. A stirred soln of **7b** (563 mg, 1.40 mmol) in 6N HCl (7 ml) was heated at 75° for 2 h. The reaction mixture was poured into H_2O and the product was extracted with Et_2O. Usual work-up followed by preparative TLC (SiO_2; C_6H_6–AcOEt=15:1) of the extract gave pasty β,γ-unsaturated ketone (134 mg, 44.1%; Rf=0.6) [IR[a] ν($CHCl_3$): 1675 cm^{-1}; UV λ (EtOH): 289.5 nm].

8,9-*Methylenedioxy*-1,2,3,4,4a*α*,5,6,10*bβ* - *octahydrophenanthridin*-3-*one* (**8b**). 35%CH_2O (13 ml, 173 mmol) was added to efficiently stirred soln of **7a** (1.8 g, 5.01 mmol) in MeOH (6 ml) at room temp and the whole was stirred for 5 min, when a white paste was deposited. MeOH (5 ml) was added to the reaction mixture and the whole was poured into 6N HCl (400 ml) at room temp. After standing for 2 h at room temp, the reaction mixture was basified with Na_2CO_3 (powder) and the product was taken up in CH_2Cl_2. Usual work-up of the extract gave **8a** (1.47 g, 87.6%) as white needles, m.p. 212–215° (dec.) (CH_2Cl_2-MeOH); IR[a] ν(nujol): 1715 cm^{-1}; (Found: C, 74.94; H, 6.27; N, 4.13. Calc for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18%.) A mixture of **8a** (1.0 g, 2.98 mmol), 10%Pd–C (100 mg), and 6N HCl (1 ml) in MeOH (20 ml) was shaken in H_2 (1 atom) at 23° for 8 h. Usual work-up gave **8b** (450 mg, 61.5%) as colorless needles, m.p. 164–165.5° (EtOH); IR[a] ν($CHCl_3$): 1715 cm^{-1}; ^{1}H-NMR[d] δ: 3.93, 4.13 (each 1H, d, J = 16 Hz, 6-H_2), 5.88 (2H, s, OCH_2O), 6.49, 6.77 (each 1H, s, ar-H); (Found: C, 68.62; H, 6.14; N, 5.78. Calc for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71%).

2-(3,4-Methylenedioxyphenyl) - 5 - oxo-1-hydroxycyclohexanecarboxylic acid (**10**). A soln of $MeCOCH{=}CH_2$ (13.1 g, 0.19 mol) in MeOH (100 ml) was added dropwise to an ice-cooled, stirred soln of **9** (30 g, 0.14 mol) in 5%NaOH (200 ml) over a period of 1 h and the whole was allowed to stand overnight at room temp. Most of the solvent was removed *in vacuo* to leave a soln, which was acidified with

conc. HCl under ice-cooling to deposit crystals of **10** (34.4 g, 86%) as colorless needles, m.p. 194–196° (EtOH); IR^c ν(KBr): 3500, 1745, 1700 cm^{-1}; (Found: C, 60.33; H, 5.14. Calc for $C_{14}H_{14}O_6$: C, 60.43; H, 5.07%).

Cis-2-(3,4-*Methylenedioxyphenyl*) - 5 - *oxocyclohexanecarboxylic acid* (**10**). A mixture of **10** (6.95 g, 25 mmol) and conc. H_2SO_4 (0.32 ml) in 99%EtOH (250 ml) was refluxed for 4 h. The reaction mixture was basified with 5% $NaHCO_3$ under ice-cooling. After most of the solvent was removed *in vacuo*, H_2O was added to the residue. Usual work-up of the alkaline soln gave a mixture of $\Delta^{1,2}$- and $\Delta^{6,1}$-unsaturated acid (**11**) (5 g, 76.9%) as yellow needles, m.p. 184–187°. Analytical sample had m.p. 187–188.5° (EtOH); IR^c ν(KBr): 1720, 1645 cm^{-1}; ^{1}H-NMR^c δ (CF_3COOH): 4.25 (0.9 H, br s, 2-H), 5.91 (2H,s, OCH_2O), 6.00–6.80 (3H, m, ar-H), 7.17 (0.9H, s, 6-H); (Found: C, 64.41; H, 4.53. Calc for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65%). Zn powder (19.6 g) was added portionwise to a soln of **11** (14.5 g, 56 mmol) in 70% AcOH (520 ml) at room temp and stirring was continued for 2 h. Inorganic materials were filtered off and the filtrate was condensed to a volume of ca 100 ml to deposit on addition of ice-water crystals of **12a** which were filtered up. The filtrate was acidified with conc. HCl (10 ml) and extracted with Et_2O. Usual work-up of the extract gave an additional crop of **12a**. The combined yield of **12a** was 13.4 g (91.4%) as colorless prisms, m.p. 188–189° (EtOH); IR^c ν(KBr): 2950, 1720, 1690 cm^{-1}. (Found: C, 64.44; H, 5.25. Calc for $C_{14}H_{14}O_5$: C, 64.12; H, 5.38%.)

Methyl cis-2-(3,4-methylenedioxyphenyl)-5,5-ethylenedioxycyclohexanecarboxylate (**12c**). A mixture of **12a** (6.77 g, 25 mmol) and conc H_2SO_4 (2 g) in abs. MeOH (300 ml) was refluxed for 4 h. Usual work-up gave **12b** (6.85 g, 96.1%), m.p. 93–94° (*n*-hexane); IR^c ν(KBr): 1720 cm^{-1}; ^{1}H-NMR^b δ; 3.42 (3H,s, $COOCH_3$), 5,85 (2H, OCH_2O), 6.61 (3H, br s, ar-H); (Found: C, 65.15; H, 5.88. Calc for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84%.) Usual ketalization of **12b** (6.25 g, 23 mmol) with $HOCH_2CH_2OH$ (2.81 g, 45 mmol) gave **12c** (7.11 g, 98.1%), m.p. 105–105.5° (*n*-hexane); IR^b ν(KBr): 1740 cm^{-1}; ^{1}H-NMR^b δ: 3.45 (3H, s, $COOCH_3$), 3.85 (4H, s, OCH_2CH_2O), 5.81 (2H, s, OCH_2O), 6.55–6.85 (3H, m, ar-H); (Found: C, 63.56; H, 6.31. Calc for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29%.)

Epimerization of **12c**

(1) *With* KO*t*-Bu–*t*-BuOH. A mixture of **12c** (5.3 g, 17 mmol) and the reagent, prepared from K (645.9 mg) and abs. *t*-BuOH (50 ml), was refluxed for 0.5 h. On cooling, the solvent was removed below 40° (bath temp) *in vacuo* to give a residue, to which 5% $NaHCO_3$ was added. Extraction of the product with $CHCl_3$ followed by usual work-up gave **13a** (4.34 g, 81.8%), m.p. 145.5–146.5° (MeOH); IR$_C$ ν($CHCl_3$): 1730 cm^{-1}; ^{1}H-NMR^b δ :3.44 (3H,s, $COOCH_3$), 3.95 (4H, s, OCH_2CH_2O), 5.89 (2H, s, OCH_2O), 6.55–6.75 (3H, m, ar-H); (Found: C, 63.62; H, 6.28. Calc for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29%.) From the aqueous layer free acid (**13c**) (0.94 g, 18.7%), m.p. 192–204°, was obtained.

(2) *With* NaOEt–EtOH. A mixture of **12c** (318 mg, 0.99 mmol) and the reagent, prepared from Na (56.6 mg) and abs. EtOH (10 ml), was refluxed, for 2.5 h. Work-up as above gave **13b** (254 mg, 76.5%), m.p. 97–99.5° (EtOH–H_2O) and **13c** (70.2 mg, 23%), m.p. 199–202°. **13b**: IR^c ν($CHCl_3$): 1725 cm^{-1}; ^{1}H-NMR^b δ:1.03 (3H, t, J = 7 Hz, CH_2CH_3), 3.96 (2H, q, J = 7 Hz, CH_2CH_3), 4.00 (4H, s, OCH_2CH_2O), 5.91 (2H, s, OCH_2O), 6.65–6.90 (3H, m, ar-H); (Found: C, 64.87; H, 6.63. Calc for $C_{18}H_{22}O_6$: C, 64.65; H, 6.63%).

Trans-2-(3,4-Methylenedioxyphenyl)-5,5 - ethylenedioxycyclohexanecarboxylic acid (**13c**). After epimerization of **12c** (20.8 g, 65 mmol) with NaOEt-EtOH as above, the product was directly refluxed with 10% NaOH (180 ml) for 1.25 h to give on acidification **13c** (18.9 g, 95%) as colorless needles, m.p. 208–209° (EtOH); IR^c ν(KBr): 1690 cm^{-1}; (Found: C, 62.76; H, 5.67. Calc for $C_{16}H_{18}O_6$: C, 62.74; H, 6.92%). GLC analysis [1.5% OV-17, column temp, 230°; N_2 (2 kg/cm^2)]: **12c**: Rt 7.05 min; **13c**: Rt 5.8 min; **13b**: Rt 6.45 min.

Trans-2-(3,4-Methylenedioxyphenyl)-5,5-ethylenedioxycyclohexanecarboxamide (**13d**). A soln of ClCOOEt (207.3 mg, 1.91 mmol) in dry $CHCl_3$ (3 ml) was added dropwise to a cooled (−19°) soln of **13c** (445 mg, 1.45 mmol) and Et_3N (198.7 mg, 2.0 mmol) in dry $CHCl_3$ (3 ml) over a period of 5 min and the whole was stirred for 0.5 h. NH_3 gas was passed for 5 min and stirring was continued for 0.5 h. H_2O was added to the reaction mixture and the product was taken up in $CHCl_3$. Usual work-up of the extract gave **13d** (407 mg, 91.9%) as colorless prisms, m.p. 226–228° (MeOH); IR^c ν(KBr): 3390, 3160, 1645 cm^{-1}; (Found: C, 62.60; H, 6.29; N, 4.47. Calc for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.24; N, 4.59%).

Trans-2-(3,4-Methylenedioxyphenyl)-5,5 - ethylenedioxycyclohexylamine (**13g**). A soln of Et_3N (1.0 g, 9.9 mmol) in acetone (7.5 ml) and successively a soln of ClCOOEt (1.2 g, 11.1 mmol) in acetone (7.5 ml) was added dropwise to an ice-cooled, stirred soln of **13c** (2.5 g, 8.17 mmol) in a mixture of acetone (48 ml) and H_2O (7.5 ml). After stirring for 40 min, a soln of NaN_3 (1.1 g, 16.9 mmol) in H_2O (3.8 ml) was added dropwise to the reaction mixture over a period of 5 min and the whole was stirred for 2 h. Ice-water was added to the reaction mixture and the product was taken up in Et_2O. After usual work-up, the solvent was removed below 30° (bath temp) *in vacuo* to give a residue, which was heated in boiling dry C_6H_6 (100 ml) for 1 h. Removal of the solvent gave isocyanate (**13e**) (2.26 g, 91.3%) as colorless needles, m.p. 88–88.5° (Et_2O–*n*-hexane); IR^b ν(KBr): 2255 cm^{-1}; ^{1}H-NMR^c δ: 2.45 (1H, dt, J = 5, 11 Hz, 2-H), 3.73 (1H, dt, J = 5, 11 Hz, 1-H), 3.96 (4H, s, OCH_2CH_2O), 5.92 (2H, s, OCH_2O), 6.60–6.85 (3H, m, ar-H); (Found: C, 63.35; H, 5.69; N, 4.71. Calc for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62%.) A stirred soln of **13e** (893 mg, 2.95 mmol) in abs. MeOH (30 ml) was refluxed for 1.5 h. The reaction mixture was condensed to a small volume and the residue was dissolved in Et_2O. Usual work-up of the Et_2O layer gave carbamate (**13f**) (936.2 mg, 97.5%), m.p. 123 – 125° (MeOH-H_2O); IR^c ν ($CHCl_3$): 3430, 1715 cm^{-1}; ^{1}H-NMR^b: δ: 3.48 (3H, s, $COOCH_3$), 3.92 (4H, s, OCH_2CH_2O), 4.42 (1H, br d, J = 10 Hz, 1 = H), 5.85 (2H, s, OCH_2O), 6.62 (3H, m, ar-H); (Found: C, 60.90; H, 6.29; N, 4.09. Calc for $C_{17}H_{21}NO_6$: C, 60.88; H, 6.31; N, 4.18%.) A mixture of **13f** (100 mg, 0.30 mmol) and 20% NaOH (3 ml) in $HOCH_2CH_2OH$ (3 ml) was refluxed for 1.5 h. The reaction mixture was poured into ice-water, acidified with 10% HCl under ice-cooling, and washed with Et_2O. After basification of the aqueous layer with K_2CO_3 (powder) under ice-cooling, the product was taken up in $CHCl_3$. Usual work-up of the extract gave amine (**13g**) (77.9 mg, 94.2%), m.p. 130–135°; IR^c ν(KBr): 3380, 3310 cm^{-1}; ^{1}H-NMR^b δ: 1.40 (2H, br s, disappeared on addition of D_2O, NH_2), 3.05 (1H, ddd, J = 4, 10, 13 Hz, 1-H), 3.94 (4H, s, OCH_2CH_2O), 5.86 (2H, s, OCH_2O), 6.67 (3H, br s, ar-H); (High MS: Found: 277.1318. Calc for $C_{15}H_{19}NO_4$: *m/z* 277.1314.

3,3-*Ethylenedioxy-8,9-methylenedioxy* - 1,2,3,4,4aα,5,6, 10bβ-*octahydrophenanthridine* (*ethylene ketal of* **8b**).

(1) *The Pictet–Spengler reaction of* **13g**. A mixture of **13g** (103.9 mg, 0.38 mmol) and 37%CH_2O (0.2 ml) in MeOH (3 ml) was stirred for 0.5 h at room temp and the reaction mixture was dissolved in Et_2O. After usual work-up, the solvent was removed below 30° (bath temp) to leave a colorless oil (110.2 mg), to which AcOH (3 ml) was added. The mixture was stirred at room temp for 1 h and then at 60° (bath temp) for 3 h. The reaction mixture was poured into ice-water, acidified with 10% HCl and washed with Et_2O. The ice-cold aqueous layer was basified with K_2CO_3 (powder) and the product was taken up in $CHCl_3$. Usual work-up of the extract gave a crystalline mass (91.6 mg), m.p. 74–75°, which was chromatographed on Al_2O_3 (5 g, $CHCl_3$) to give ethylene ketal of **8b** (70.6 mg, 65.1%), m.p. 126–127° (MeOH–H_2O); IR^b ν(KBr): 3290 cm^{-1}; ^{1}H-NMR^d

δ: 2.73 (1H, ddd, J = 4, 9.3, 12 Hz, 4a-H), 3.77, 4.26 (each 1H, d, J = 15.7 Hz, 6-H_2), 3.97 (4H, s, OCH_2CH_2O), 5.86 (2H, s, OCH_2O), 6.45, 6.71 (each 1H, s, ar-H); (Found: C, 65.66; H, 6.88; N, 4.73. Calc for $C_{16}H_{19}NO_4 \cdot 1/4\ H_2O$: C, 65.40; H, 6.69; N, 4.77%.)

(2) *Cyclization and subsequent* $LiAlH_4$ *reduction of* **13e**. A soln of **13e** (1.78 g, 5.87 mmol) in dry CH_2Cl_2 (1 ml) was added dropwise to a stirred anhydrous H_3PO_4, prepared from 85% H_3PO_4 (11.5 g) and P_2O_5 (8.5 g), and stirring was continued at room temp for 3 h. The reaction mixture was poured portionwise into an ice-cold, excess 10% Na_2CO_3 soln to give crystals (1.21 g). Reketalization of the crystals as usual gave ethylene ketal (1.18 g, 66.3%) as light brown crystals, m.p. 288–289° (dec.) ($CHCl_3$); IR[b] ν (KBr): 3190, 1670 cm^{-1}; (Found: C, 63.04; H, 5.72; N, 4.50. Calc for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62%.) Reduction of the ketal (10 g, 33 mmol) with $LiAlH_4$ (3.8 g) in boiling DME (140 ml) gave, after usual work-up, the ethylene ketal of **8b** (8.9 g, 93.3%), m.p. 122.5–124°, which was identical with the sample obtained in 1).

5-Chloroacetyl-8,9-methylenedioxy-1,2,3,4,4aα*,5,6,10b*β*-octahydrophenanthridin-3-one* (**8c**). A soln of the ketal of **8b** (610 mg, 2.11 mmol) in 6N HCl (40 ml) was stirred at room temp for 2 h. The reaction mixture was basified with 10% NaOH and the product was taken up in $CHCl_3$. Usual work-up of the extract gave **8b** (459 mg, 88.7%), m.p. 164–165.5° (EtOH–H_2O), which was identical with a sample obtained from **8a**. To an ice-cooled, stirred soln of **8b** (320 mg, 1.30 mmol) in pyridine (438 mg, 5.56 mmol) was added a soln of $ClCH_2COCl$ (300 mg, 2.65 mmol) in CH_2Cl_2 (4 ml) over a period of 20 min and the whole was stirred at room temp for 1.5 h. Usual work-up of the reaction mixture gave **8c** (316 mg, 75.2%) as colorless prisms, m.p. 188–189° (acetone); IR[a] ν(nujol): 1713, 1640 cm^{-1}; ^{1}H-NMR[b] δ: 4.05 (2H, s, $COCH_2Cl$), 4.22 (1H, d, J = 14 Hz, 6-H), 4.60 (1H, br d, J = 14 Hz, 6-H), 5.93 (2H, s, OCH_2O), 6.75 (2H, br s, ar-H); (Found: C, 59.59; H, 5.00; N, 4.26; Cl, 11.25. Calc for $C_{16}H_{16}NO_4Cl$: C, 59.72; H, 5.01; N, 4.35; Cl, 11.02%.)

(±)-α- and (±)-γ-Lycoran-3-one lactams (**14a** *and* **15a**)

(1) KO*t*-Bu (6.7 g, 59.7 mmol) was added under N_2 to a stirred soln of **8c** (6.1 g, 18.9 mmol) in hot *t*-BuOH (1000 ml) and stirring was continued at 120° (bath temp) for 10 min. After cooling, the reaction mixture was acidified with 10% HCl and the product was taken up in $CHCl_3$. The residue obtained after usual work-up of the extract was chromatographed on Al_2O_3 containing 5% H_2O to give a product mixture ($CHCl_3$–C_6H_6 = 1:1; 3.54 g), which was crystallized from CH_2Cl_2 to give **14a** (1.73 g, 32%) as fine prisms, m.p. 195–197° (dec); IR[a] ν($CHCl_3$): 1710, 1685 cm^{-1}; ^{1}H-NMR[d] δ: 3.33 (1H, dt, J = 10.6, 9.4 Hz, 3a-H), 3.84 (1H, dd, J = 9.4, 10.6 Hz, 11c-H), 4.23, 4.91 (each 1H, d, J = 17 Hz, 7-H_2), 5.23 (2H, s, OCH_2O), 6.57, 6.88 (each 1H, s, ar-H): ^{13}C-NMR δ: 22.7 (t, 2-C), 43.5 (d, 3a-C); (Found: C, 67.39; H, 5.23; N, 4.84. Calc for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91%.) The residue obtained from the mother liquors of **14a** was crystallized from acetone to give **15a** (60 mg, 1.1%) as colorless prisms, m.p. 246–248° (dec.); IR[a] ν($CHCl_3$): 1720, 1690 cm^{-1}; (Found: C, 67.36; H, 5.34; N, 4.88. Calc for $C_{16}H_{15}NO_4$: C, 67.36; H, 6.30; N, 4.91%.)

(2) A reaction mixture, **14a**:**15a** = 5:1 on the basis of GLC analysis (1.5% SE-30, column temp, 230°), (992.6 mg) prepared as above starting from **8c** (964.5 mg, 3 mmol) was ketalized with $HOCH_2CH_2OH$ (5.5 ml, 98 mmol) as usual to give a solid (1.05 g), which was chromatographed on SiO_2 (20 g, $CHCl_3$) to give **14b** (645 mg, 65.3%), m.p. 191–193° (acetone–MeOH); IR[c] ν($CHCl_3$): 1685 cm^{-1}; ^{1}H-NMR[b] δ: 3.35 (1H, dd, J = 6, 10 Hz, 11c-H), 3.92 (4H, s, OCH_2CH_2O), 4.23, 4.96 (each 1H, d, J = 17 Hz, 7-H_2), 5.87 (2H, s, OCH_2O), 6.56, 6.65 (each 1H, ar-H); ^{13}C-NMR δ: 22.1 (t, 2-C), 37.7 (t, 3a-C). Usual deketalization of **14b** with 10% HCl gave **14a** (386.4 mg, 45.2% overall yield from **8c**), m.p. 196–199° (acetone).

(±)-α-Lycorane (**14d**). A mixture of **14a** (150 mg, 0.52 mmol), $HSCH_2CH_2SH$ (0.5 ml, 5.97 mmol) and $BF_3 \cdot Et_2O$ (6 drops) in AcOH (4 ml) was allowed to stand for 18 h at room temp. 10% NaOH (35 ml) was added to the ice-cold reaction mixture and the product was taken up in CH_2Cl_2. Usual work-up of the extract gave a thioketal (146 mg, 76.8%) as fine prisms, m.p. 217–220° (CH_2Cl_2-acetone); IR[a] ν($CHCl_3$): 1680 cm^{-1}. A mixture of the thioketal (117 mg, 0.32 mmol) and Raney Ni (1 ml) in dioxane (12 ml) was refluxed for 2 h. Usual work-up of the reaction mixture gave **14c** (63 mg, 71.7%) as colorless needles, m.p. 153–154° (acetone); IR[a] ν($CHCl_3$): 1680 cm^{-1}; (Found: C, 70.95; H, 6.10; N, 5.25. Calc for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16%.) A soln of **14c** (32 mg, 0.12 mmol) was added dropwise to a suspension of $LiAlH_4$ (30 mg, 0.12 mmol) was added dropwise to a suspension of $LiAlH_4$ (30 mg, 0.79 mmol) in THF (1 ml) and stirring was continued at reflux for 4 h. Usual work-up of the reaction mixture gave **14d** (30 mg, 99%) as colorless needles, m.p. 93–94° (Et_2O–petroleum ether), which was identified with the authentic sample[9] (IR).

(±)-γ-Lycorane (**15b**). All operations were the same as described for **14d**. The corresponding thioketal (78.9%) as plates, m.p. 248–252° (dec.) (acetone). *(±)-γ-Lycoran-5-one*: 54.6% as colorless pillars, m.p. 128–136° (acetone). **15b**: 68% as colorless fine prisms, m.p. 99–101° (*n*-pentane). It was identified with the authentic sample[9] (IR).

Deketalization of **14b**, **14e**, *and* **15c**. (1) Ketalization of **14a** (184 mg, 0.64 mmol) as noted for **6** gave **14b** (175 mg, 82.4%) as plates, m.p. 194–195.5° (MeOH-acetone); IR[a] ν($CHCl_3$): 1680 cm^{-1}; (Found: C, 65.81; H, 5.81; N, 4.19. Calc for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.82; N, 4.25%.) A soln of **14b** (51 mg, 0.15 mmol) with p-TsOH (15 mg, 0.09 mmol) in acetone (5 ml) was refluxed for 2 h. Usual work-up gave **14a** (31 mg, 73.8%) as fine prisms, m.p. 195–197° (acetone), which was identified with the authentic sample (mixed m.p., IR).

(2) Reduction of **14b** (980 mg, 2.97 mmol) with $LiAlH_4$ (770 mg) in abs. THF (45 ml) was refluxed for 17 h. The product (875 mg) was filtered through Al_2O_3 (3.2 g; Et_2O–THF = 10:2) containing 5% H_2O to give **14e** (662 mg, 70.5%) as colorless pillars, m.p. 115° (dec.) (Et_2O-THF); (Found: C, 67.11; H, 6.56; N, 4.28. Calc for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44%.) A soln of **14e** (380 mg, 1.15 mmol) in 6N HCl (35 ml) was allowed to stand for 2.5 h at room temp. The reaction mixture was basified with Na_2CO_3 (powder) to give a mixture of **14f** and **15d** or **16** (263 mg, 84%) as colorless prisms, m.p. 143.5–144° (Et_2O); IR[a] ν($CHCl_3$): 2800, 1700 cm^{-1}; (Found: C, 71.01; H, 6.32; N, 4.90. Calc for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16%). Separation of the mixture was unsuccessful.

(3) Ketalization of **15a** (50 mg, 0.18 mmol) as above gave **15c** (46 mg, 79.7%) as colorless needles, m.p. 222–224° (acetone); IR[a] ν($CHCl_3$): 1680 cm^{-1}; (Found: C, 65.76; H, 5.87: N, 4.05. Calc for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.82; N, 4.25%.) Deketalization of **15c** (53 mg, 0.16 mmol) with p-TsOH (15 mg, 0.09 mmol) as above gave quantitatively **15a** as prisms, m.p. 240–243° (dec.) (acetone), which was identified with the authentic sample (mixed m.p., IR).

(±)-3β*-Acetoxy-α-lycoran-5-one* (**17b**). A soln of **14a** (90 mg, 0.31 mmol) in MeOH (20 ml) was treated with $NaBH_4$ (118 mg, 3.1 mmol) at room temp for 4 h to give, after usual work-up, a solid (**17a**) (82 mg, 90%); IR[c] ν(KBr): 3320, 1670 cm^{-1}. A mixture of **17a** (25.1 mg, 0.09 mmol) and Ac_2O (0.2 ml) in pyridine (2 ml) was stirred at room temp for 6 h. Usual work-up of the reaction mixture gave a solid (**17b**) (29 mg, 97.3%), m.p. 216–220°; IR[c] ν(KBr): 1730, 1700 cm^{-1}; ^{1}H-NMR[b] δ: 2.08 (3H, s, $COCH_3$), 4.15, 4.98 (each 1H, d, J = 17 Hz, 7-H_2), 5.13 (1H, br s, J(w/2) = 24 Hz, 3-H), 5.90 (2H, s, OCH_2O), 6.58, 6.65 (each 1H, s, ar-H); MS: m/z 329 (M^+).

(±)-3β*-N,N-Dimethylamino-α-lycoran-5-one* (**17d**). A mixture of **14a** (1.4 g, 4.91 mmol), Me_2NHHCl (2.0 g, 24.5 mmol), and $NaBH_3CN$ (360 mg, 5.71 mmol) in dry MeOH (420 ml) was stirred at room temp for 3 days. The

reaction mixture was consensed *in vacuo* to give a residue, the basic product of which was extracted with 10% HCl after dilution with $CHCl_3$. Usual work-up of the extract gave **17d** (654 mg, 43%) as colorless prisms, m.p. 204–205° (acetone); IR[b] ν(KBr): 1685 cm^{-1}; ^{1}H-NMR[c] δ: 2.30 [6H, s, $N(CH_3)_2$], 2.82[1H, m, J(w/2) = 22 Hz, 3-H], 3.15 (1H, dd, J = 6, 10 Hz, 11c-H), 4.18, 4.98 (each 1H, d, J = 17 Hz, 7-H_2), 5.88 (2H, s, OCH_2O), 6.57, 6.67 (each 1H, s, ar-H); (Found: C, 68.81; H, 6.95; N, 8.82. Calc for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91%.)

(±)-Δ^2-α-*Lycoren*-5-*one* (**18**). MCPBA (415 mg, 2.41 mmol) was added in portions to a cold soln of **17d** (584 mg, 1.86 mmol) in dry $CHCl_3$ (35 ml) over a period of 7 min at −18° (bath temp) and the whole was stirred for 1.5 h. The reaction mixture was chromatographed over Al_2O_3 (15 g) to give **17e** ($CHCl_3$-MeOH = 20:1) (588 mg, 95%), m.p. 175–176° (AcOEt-*n*-hexane); IR[b] ν(KBr): 1683 cm^{-1}; ^{1}H-NMR[c] δ (CD_3OD): 3.20 [6H, s, $N(CH_3)_2$], 4.20, 4.87 (each 1H, d, J = 16 Hz, 7-H_2), 5.90 (2H, s, OCH_2O), 6.65, 6.70 (each 1H, s, ar-H); MS: m/z 314 (M^+-16), 269 (M^+-61). Heating of **17e** (1.58 g, 47.9 mmol) under Ar at 200° (bath temp) was continued until the crystals were uniformly changed to an oil, when the whole was allowed to cool. Usual work-up of the reaction mixture gave **18** (950 mg, 73.1%), m.p. 148–150° (AcOEt-*n*-hexane); IR[c] ν($CHCl_3$): 1670 cm^{-1}; ^{1}H-NMR[c] δ: 3.42 (1H, dd, J = 7.7, 10 Hz, 11c-H), 4.20, 5.03 (each 1H, d, J = 18 Hz, 7-H_2), 5.70–6.15 (2H, m, 2- and 3-H), 5.90 (2H, s, OCH_2O), 6.59, 6.69 (each 1H, s, ar-H); MS: m/z 269 (M^+); (Found: C, 71.52; H, 5.54; N, 5.14. Calc for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20%.)

Reaction of **18** *with* PhSeBr *and* KOAc. A soln of PhSeBr (609 mg, 2.58 mmol) in AcOH (6 ml) was added dropwise to a stirred soln of **18** (139 mg, 0.49 mmol) and KOAc (253 mg, 2.58 mmol) in AcOH (7 ml) and stirring was continued at room temp for 3 h. The reaction mixture was slowly poured into sat. Na_2CO_3 to effect neutralization and the product was taken up in $CHCl_3$. Usual work-up of the extract gave a brown oil (482 mg), which was first purified by column chromatography over SiO_2 (15 g, $CHCl_3$). The eluate was further purified by preparative TLC (SiO_2, C_6H_6–*i*-PrOH=12:1) to give three products, **19**, *selenide A* and *selenide B* (moving rate: **19** > *selenide A* > *selenide B*). **19**: colorless prisms (142 mg, 57%), m.p. 228–229° (dec.) (acetone); IR[b] ν(KBr): 1735, 1690 cm^{-1}; ^{1}H-NMR[c] δ: 1.93 (3H, s, $COCH_3$), 3.65 (1H, dd, J = 7, 10 Hz, 2-H), 4.15, 4.98 (each 1H, d, J = 17.5 Hz, 7-H_2), 5.22 (1H, dt, J = 3, 10 Hz, 2-H), 5.91(2H, s, OCH_2O), 6.60(2H, br s, ar-H), 7.20 – 7.40(3H, m, SeC_6H_5), 7.50–7.70 (2H, m, SeC_6H_5); MS: m/z 485 (M^+); (Found: C, 59.51; H, 4.83; N, 2.93. Calc for $C_{24}H_{24}NO_5Se$: C, 69.50; H, 4.80; N, 2.89%.) *Selenide A*: a solid (47 mg, 19%); IR[c] ν($CHCl_3$): 1740, 1680 cm^{-1}; ^{1}H-NMR[d] δ: 2.00 (3H, s, $COCH_3$), 3.70 (1H, dt, J = 3, 5 Hz, 2-H), 4.19, 4.99 (each 1H, d, J = 17 Hz, 7-H_2), 5.38 (1H, dd, J = 3, 6 Hz, 3-H), 5.92 (2H, s, OCH_2O), 6.58, 6.62 (each 1H; s, ar-H), 7.20–7.70 (5H, m, SeC_6H_5); MS: m/z 485 (M^+). *Selenide B*: a solid (13 mg, 5%); IR[c] ν($CHCl_3$): 1750, 1685 cm^{-1}; ^{1}H-NMR[d] δ: 2.04 (3H, s, $COCH_3$), 3.62 (1H, t, J = 4 Hz, 3-H), 4.19, 4.94 (each 1H, d, J = 17 Hz, 7-H_2), 5.24 (1H, q, J = 4 Hz, 2-H), 5.92 (2H, s, OCH_2O), 6.59, 6.62 (each 1H, s. ar-H), 7.20–7.70 (5H, m, SeC_6H_5); MS: m/z 485 (M^+).

X-Ray crystallographic analysis of (±)-2α-*acetoxy*-3β-*benzeneselenenyl*-α-*lycoran*-5-*one* (**19**). The lattice constants and intensities were collected on a Philips PW 1100 diffractometer using graphite monochromated CuKα radiation. The crystal structure was solved by the heavy atom method and refined by a block-diagonal least-squares procedure. The crystal data are as follows. $C_{24}H_{23}NO_5Se$ (mol. wt. = 484.41), monoclinic, spare group $P2_1/n$, a = 14.883(7), b = 24.151(10), c = 5.908(3)Å, β = 91.60(40)°, U = 2122.8Å, Z = 4, Dx = 1.516 g cm^{-3}, μ (for CuKα) = 27.4 cm^{-1}.

The analysis was carried out for a crystal of colorless thin plate grown from an aq. MeOH soln. A total of 1723 reflections out of 3240 theoretically possible ones were measured as above the 2σ(I) level within 2θ angle of 120°. The size of the crystal was approximately. 0.01 × 0.06 × 0.4 mm. The final R value was 0.068 without hydrogen atom contributions. The bond lengths and angles are consistent with the chemical structure if allowance is made for the standard deviations. They are estimated to be σ(Se–C) = 0.011 Å, σ(C–C) = 0.017 Å, σ(C–Se–C) = 0.4°, and σ(C–C–C) = 1.0°. The length of C(14)–Se is shorter than that of C(3)-Se owing to the effect of the phenyl group. As is commonly observed, the plane of Ac group is perpendicular to the six membered ring and bisecting the angle C(1)–C(2)–C(3). The phenyl group, on the other hand, is situated at approximately trans position to one of the endocyclic bonds. Thus, the torsion angles, C(3a)–C(3)–Se–C(14) and C(2)–C(3)–Se–C(14) are 162° and −74°, respectively, while those for the Ac group C(3)–C(2)–O(1)–C(12) and C(1)–C(2)–O(1)–C(12) are −138° and 105°. It is clearly seen that ring C adopts a regular chain conformation and ring B is distorted half-chair. The five-membered ring D takes an envelope form with a flat at C(3a).

(±)-α-*Lycoran*-2,5-*dione* (**21**). 35% H_2O_2 (1.5 ml) was added dropwise to a cold, stirred soln of **19** (120 mg, 0.25 mmol) in THF (20 ml) and stirring was continued at room temp for 3 h. H_2O was added to the whole and the product was taken up in $CHCl_3$. Usual work-up gave a selenoxide (112 mg, 91%), m.p. 103–105° (dec.); IR[c] ν(KBr): 1740, 1680 cm^{-1}; ^{1}H-NMR[b] δ ($CDCl_3$–CD_3OD): 1.95 (3H, s, $COCH_3$), 5.35 (1H, m, 3-H), 5.85 (2H, s, OCH_2O), 6.53 (2H, s, ar-H), 7.40–7.90 (5H, m, SeC_6H_5). Heating of the above selenoxide (73 mg) at 120° (bath temp) under Ar and usual work-up gave an oil (59 mg), which was subjected to column chromatography (SiO_2, 2 g) to give two products, one (C_6H_6–AcOEt = 15:1) being the starting **19** (12 mg, 17%) and another (C_6H_6–AcOEt = 10:1) **20** (27 mg, 57%); IR[c] ν ($CHCl_3$): 1745, 1675 cm^{-1}; ^{1}H-NMR[b] δ: 2.10 (3H, s, $COCH_3$), 4.12, 4.93 (each 1H, d, J = 17 Hz, 7-H_2), 5.50 (1H, br s, 3-H), 6.57 (2H, s, ar-H); MS: m/z 327 (M^+). A mixture of **20** (34 mg, 0.10 mmol) and 10% NaOH (1 ml) in DME (6 ml) was stirred at room temp for 16.5 h. The reaction mixture was extracted with $CHCl_3$ and usual work-up of the extract gave **21a** (15 mg, 51%), m.p. 250–252° (dec.) (acetone); GLC (1.5% SE-30, column temp, 210°: Rt 17.8 min; *cf.* **14a**: Rt 18.35 min); IR[c] ν ($CHCl_3$): 1720, 1680 cm^{-1}; ^{1}H-NMR[b] δ: 5.80 (2H, s, OCH_2O), 6.47 (2H, s, ar-H); MS: m/z 285 (M^+); (Found: C, 67.39; H, 5.31; N, 4.94. Calc for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91%.)

(±)-Δ^2-α-*Lycoren*-7-*one* (**22b**). Reduction of **18** (80 mg, 0.297 mmol) with $LiAlH_4$ (66 mg, 1.78 mmol) in dry DME (10 ml) followed by usual work-up gave **22a** (73.2 mg, 96.5%) as colorless prisms, m.p. 93–95° (MeOH-H_2O); IR[c] ν($CHCl_3$): 1510, 1490 cm^{-1}; ^{1}H-NMR[d] δ: 3.20 (1H, ddd, J = 6.3, 8.6, 9.7 Hz, 11c-H), 3.77, 4.23 (each 1H, d, J = 15 Hz, 7-H_2), 5.60–6.00 (2H, m, 2- and 3-H), 5.88 (2H, s, OCH_2O), 6.57, 6.69 (each 1H, s, ar-H); (High MS: Found: 255.1249. Calc for $C_{16}H_{17}NO_2$: m/z 255.1250). Active MnO_2 (525 mg) was added to a soln of **22a** (52.5 mg, 0.21 mmol) in $CHCl_3$ (10 ml) and the whole was stirred at reflux for 4 h. On further adding MnO_2 (250 mg), stirring was continued for 1.5 h. Usual work-up of the $CHCl_3$ soln gave brown crystals, which were chromatographed over SiO_2 (1 g, $CHCl_3$) to give **22b** (13.3 mg, 24%) as colorless needles, m.p. 194.5–196° (EtOH) (lit.[1c] 196–198°); IR[c] ν(KBr): 1630, 1602 cm^{-1}; ^{1}H-NMR[b] δ: 4.18 (1H, dd, J = 7, 12 Hz, 11c-H), 5.87 (2H, br s, 2- and 3-H), 5.97 (2H, s, OCH_2O), 6.66 (1H, s, 11-H), 5.87 (2H, br s, 2- and 3-H), 5.97 (2H, s, OCH_2O), 6.66 (1H, s, 11-H), 7.46 (1H, s, 8-H); ^{1}H-NMR[d] δ: 1.62 (1H, dd, J = 8.6, 12.3 Hz, 2-H), 4.19 (1H, dd, J = 7.1, 11.4 Hz, 11c–H), 5.80–5.94 (2H, m, 2- and 3-H), 5.99 (2H, s, OCH_2O), 6.65 (1H, d, J = 1 Hz, 11-H), 7.46 (1H, s, 8-H); MS: m/z 269 (M^+); (Found: C, 71.52; H, 5.74; N, 5.24. Calc for $C_{16}H_{15}NO_3$: C, 71.36; N, 5.61; N, 5.20%.) Identity of **22b** with Torssell's sample was confirmed by comparison of each spectral data [IR and ^{1}H-NMR (60 MHz)].

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