Potential intermediate, (±)-di-*o*-acetyl-3α-phenylselanyl-3,3a-dihydro-B-nor-6,7a-secolycorin-5-one for synthesis of the *Amaryllidaceae* alkaloid lycorine: formal and total syntheses of (±)-lycorine[1]

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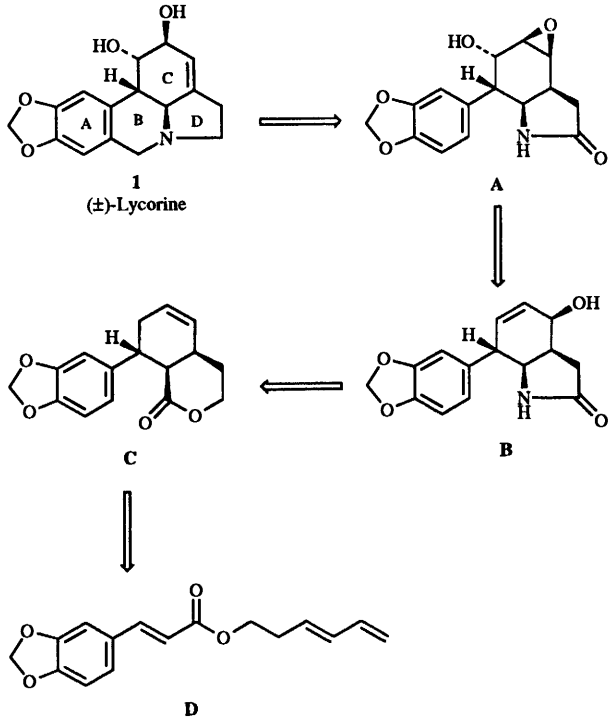
Formal and total syntheses of the *Amaryllidaceae* alkaloid, (±)-lycorine 1, were achieved by new synthetic routes *via* (±)-di-*o*-acetyl-3α-phenylselanyl-3,3a-dihydro-B-nor-6,7a-secolycorin-5-one 32. Namely, stereoselective intramolecular Diels–Alder reaction of triene ester 5 afforded, in good yield, the *cis*-lactone 6, which was converted into β(stereochemical)-hydroxy-γ-lactam 23. Oxidation of silyl ether 24 with *m*-chloroperbenzoic acid gave only β-(*tert*-butyldimethylsiloxy)-α-epoxide 25, the stereostructure of which was determined by its X-ray crystallographic analysis. Payne rearrangement of compound 25 and successive acetylation furnished α(stereochemical)-acetoxy-β(stereochemical)-epoxy γ-lactam 29, which was transformed into (±)-lycorine 1 by construction of the B ring. Formal total synthesis of (±)-lycorine 1 is also described.

Introduction

Lycorine **1**[2] is one of the important *Amaryllidaceae* alkaloids because of its many interesting and potential biological activities, in which antiviral[3a,b] and antineoplastic activity,[3c,d] growth inhibition in higher plants as well as in yeasts,[3e] and an effective antifeedant activity[3f,g] have been known. Moreover, it has been an attractive target for exploring new synthetic methodology, since its stereostructure bears four contiguous asymmetric centres arranged in all-*anti* relationships and a double bond in the C ring. Although many synthetic studies[4–8] on lycorine have appeared to date, in all the reports functionalization was performed after construction of the α-lycorane skeleton except for Boeckman's approach.[8] In this paper, we now report new formal and total syntheses of (±)-lycorine **1** by introduction of functional groups onto the C ring followed by construction of the B ring.[1]

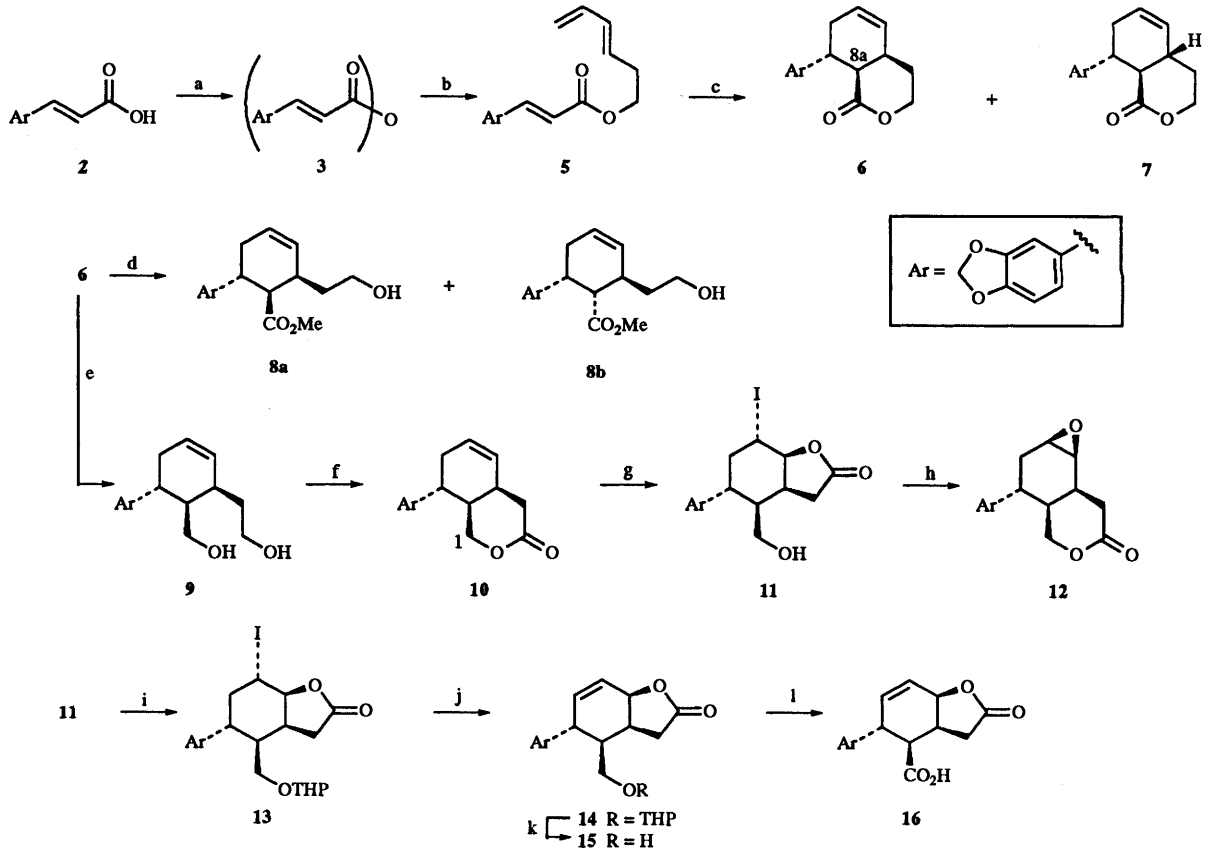
Our synthetic route to lycorine **1** is shown in Scheme 1. We decided to construct the C–D ring by intramolecular Diels–Alder reaction[9,10] of triene ester **D** leading to **C**, which could control two of the four stereocentres of lycorine. Then, introduction of functional groups onto the C ring by stereoselective epoxidation from the α-face of β(stereochemical)-hydroxy γ-lactam derivative **B** followed by Payne rearrangement[11] might afford an epoxy alcohol **A**, which could be converted into lycorine through construction of the B ring.



Scheme 1

Results and discussion

A solution of ester **5** derived from acid **2**[12] and hexa-3,5-dien-1-ol **4**[13] in *o*-dichlorobenzene (2% w/v) in a sealed tube was heated at 235 °C for 94 h to give *cis*-**6** and *trans*-lactone **7** in 86 and 5% yield, respectively (Scheme 2). When the reaction was carried out in more than 3% (w/v) *o*-dichlorobenzene solution of **5**, the yield of compound **6** decreased because of formation of intermolecular Diels–Alder product. The reaction using Et_2AlCl[14] as Lewis acid was also performed; however, the yield of compound **6** was less than 30%. Stereochemistry of δ-lactones **6** and **7** was assumed by ^1H NMR analysis. Namely, in the ^1H NMR (500 MHz) spectrum, the proton signal due to 8a-H of compound **6** appeared at δ 2.68 as a double doublet (J = 3, 7.5 Hz), whereas that of lactone **7** was at δ 2.78 as a triplet (J = 11 Hz). From inspection of Dreiding models, these spectral data could be explained reasonably by considering half-chair conformations of **6** and **7** as depicted in Fig. 1. Later, we confirmed stereochemistry of



Scheme 2 *Reagents and conditions:* a, Et_3N, $ClCO_2Et$, acetone, room temp., 15 h; b, hexa-3,5-dien-1-ol **4**, pyridine, DMAP, CH_2Cl_2, room temp.; c, *o*-DCB (2% w/v), 235 °C, 94 h; d, 10% aq., NaOH, MeOH, room temp. 3 h; CH_2N_2; e, $LiAlH_4$, THF, room temp. 0.5 h; f, Ag_2CO_3–Celite, benzene, reflux 2 h; g, aq. K_2CO_3, room temp. 1 h; I_2, aq. KI, room temp., 12.5 h; h, DBU, benzene, reflux, 1 h 40 min; i, DHP, *p*-TsOH, room temp., 4 h; j, DBU, benzene, reflux, 20 h; k, *p*-TsOH, MeOH, CH_2Cl_2, room temp., 6 h; l, Jones oxidation, acetone, 0 °C, 15 min

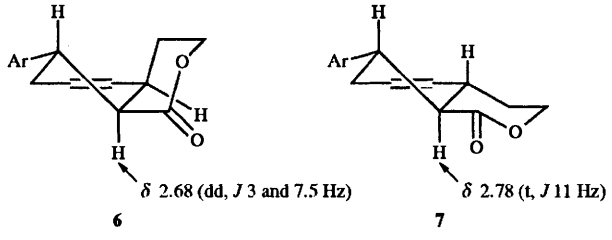


Fig. 1 Determination of the stereostructure of compounds **6** and **7**

lactones **6** and **7** by conversion of compound **6** into known lactam **19**[15] (*vide infra*).

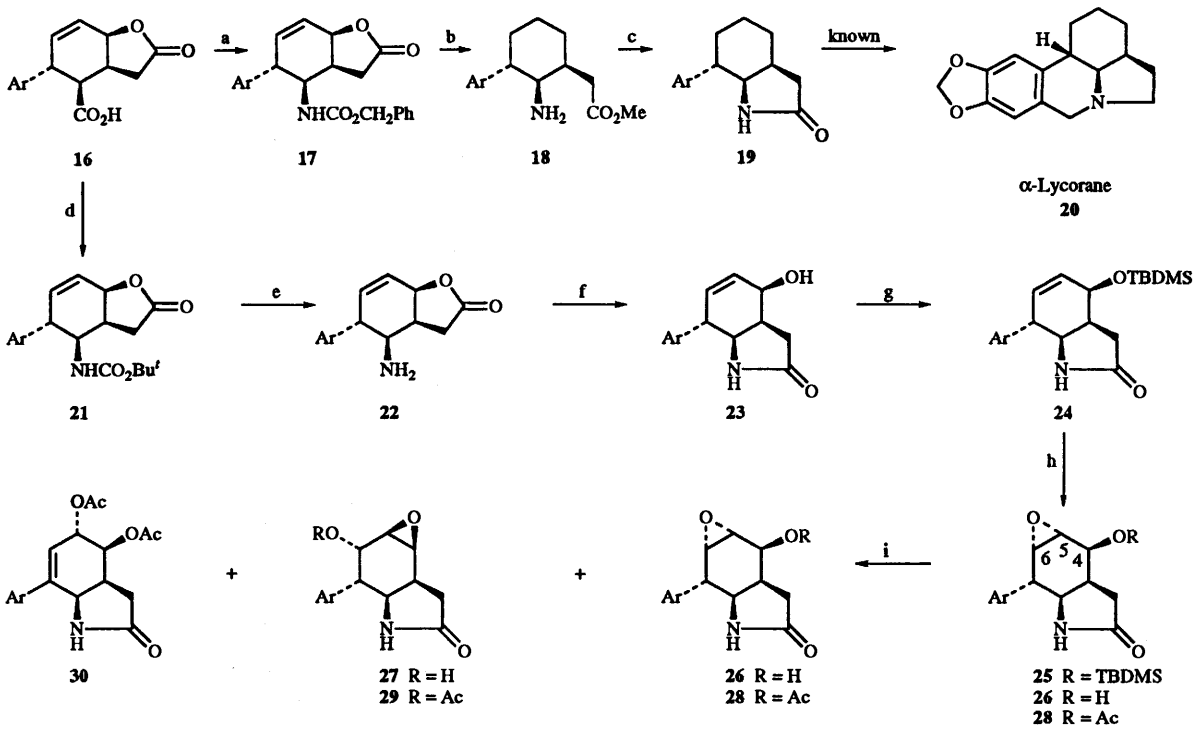
Next, hydrolysis of lactone **6** was attempted. Hydrolysis of compound **6** with methanolic aq. NaOH furnished hydroxy esters **8a** and **8b** in a 1 : 1 ratio, in which epimerization of C-8a in substrate **6** easily occurred. Unfortunately, attempts at hydrolysis of the lactone without epimerization failed. Thus, reduction of lactone **6** with $LiAlH_4$ in tetrahydrofuran (THF) at room temperature was performed to give a diol **9** in 97% yield. Although oxidation of diol **9** with Jones reagent or $NaBrO_2 \cdot 3H_2O$[16] afforded a mixture of δ-lactones **6** and **10** along with many by-products, with Fétizon's reagent[17] desired δ-lactone **10** was obtained as the sole product (98%).

Iodolactonization of lactone **10** seemed to be an effective method for introduction of functional groups on the C ring, and conversion into β(stereochemical)-hydroxy γ-lactam **23**. Thus, compound **10** was transformed into iodo lactone **11** in 92% yield. The reaction of iodo lactone with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave unexpectedly, in 94% yield, epoxy δ-lactone **12** instead of desired olefin **15**. Epoxy δ-lactone **12** would be formed by intramolecular attack of the hydroxy group to the lactone ring of iodohydrin **11**. To retard the undesired reaction, the reaction of compound **11** was conducted with dihydropyran (DHP) to give a tetrahydropyran-2-yl ether **13**, which was readily dehydroiodated with DBU to furnish olefin **14**. Furthermore, deprotection of ether **14** with *p*-TsOH in CH_2Cl_2–MeOH gave in 78% overall yield (from *iodo lactone* **11**) δ-lactone alcohol **15**, Jones oxidation of which in acetone afforded δ-lactonic acid **16** in 63% yield.†

As mentioned above, we assumed stereochemistry of the δ-lactone **6** to be *cis*. To confirm this assumption, conversion of lactone **16** into a known γ-lactam **19**[15] was performed. Thus, compound **16** was transformed into an azide in the usual manner ($ClCO_2Et$, Et_3N; NaN_3, water) followed by Curtius rearrangement with benzyl alcohol in boiling toluene to give the benzyl carbamate **17** in 72% yield. Reductive debenzylation of carbamate **17** and successive acid treatment afforded amino ester **18**, which was heated in EtOH for 10 h to furnish lactam **19** in 86% yield (Scheme 3). The ^1H NMR spectrum of synthetic lactam **19** was identical in all respects with that[15] of an authentic specimen. Thus, compound **6** was determined to be a 4a,8a-*cis*-δ-lactone. Since γ-lactam **19** has been converted into α-lycorane **20** by Hill *et al.*,[15a] a formal total synthesis of α-lycorane **20** was therefore newly accomplished.

For synthesis of (±)-lycorine, introduction of functional groups on the C ring in acid lactone **16** was the next important step. The *tert*-butyl carbamate **21** rather than the benzyl carbamate **17** seemed to be a potential candidate for transformation into functionalized γ-lactam **23**, because deprotection could easily occur. Treatment of acid **16** with diphenylphosphoryl azide (DPPA)[18] and Et_3N in boiling

† Attempted two-step transformation of alcohol **15** into δ-lactonic acid **16** *via* the corresponding aldehyde was unsuccessful, because conversion of the aldehyde into acid **16** under a variety of oxidation conditions was poor.



Scheme 3 *Reagents and conditions:* a, $ClCO_2Et$, Et_3N, 0 °C, 0.5 h; NaN_3, 0 °C, 3 h; $PhCH_2OH$, toluene, reflux, 9 h; b, 10% Pd-C/H_2, MeOH, room temp., 1.5 h; conc.-H_2SO_4, MeOH, room temp., 15 h; c, EtOH, reflux, 10 h; d, $ClCO_2Et$, 0 °C, 0.5 h; NaN_3, 0 °C, 3 h; Bu^{t}OH, reflux, 1.5 h or DPPA, Et_3N; Bu^{t}OH, reflux, 4 h; e, TFA, CH_2Cl_2, room temp., 1 h; f, NaOMe, MeOH, room temp., 3 h; g, TBDMSCl, imidazole, DMF, room temp., 8 h; h, MCPBA, CH_2Cl_2, room temp., 42 h; i, see Table 1; Ac_2O, py

Bu^{t}OH gave carbamate **21**‡ in 79% yield. The reaction of carbamate **21** with trifluoroacetic acid (TFA) in CH_2Cl_2 gave amine **22**, which reacted with NaOMe in MeOH to furnish expected β(stereochemical)-hydroxy γ-lactam **23** in 98% yield.

Tsuda *et al.*[4a,b] have reported that epoxidation of 1α-trimethysiloxy-2,3-didehydrolycorane proceeded only from the β-face. This finding encouraged us to try stereoselective epoxidation of a β(stereochemical)-hydroxy γ-lactam derivative to lead to the corresponding β(stereochemical)-hydroxy-α(stereochemical)-epoxy γ-lactam, Payne rearrangement of which could introduce hydroxy groups with stereochemistry similar to that of lycorine on the C ring. Thus, the *tert*-butyldimethylsilyl (TBDMS) group was chosen as a bulky protecting group in alcohol **23** for stereoselective epoxidation. The reaction of alcohol **23** with TBDMSCl and imidazole in dimethylformamide (DMF) gave silyl ether **24** in 98% yield, epoxidation of which with *m*-chloroperbenzoic acid (MCPBA) in CH_2Cl_2 afforded only the α(stereochemical)-epoxy γ-lactam **25** in 85% yield, as expected. Stereochemistry of product **25** was determined by ^1H NMR (400 MHz) analysis. Both coupling constants, between 4-H and 5-H, and between 5-H and 6-H were 4.4 Hz, whereas that between 7-H and 7a-H was 9.5 Hz. No spin–spin coupling between 6-H and 7-H was observed. From examination of the ^1H NMR spectrum coupled with Dreiding models, compound **25** was deduced to be an α(stereochemical)-epoxy γ-lactam, in which the cyclohexane ring exists in a boat conformation. This assumption was confirmed by X-ray crystallographic analysis (Fig. 2).[19]

Next, in order to rearrange the 5,6-α(sterochemical)-epoxy γ-lactam **26** into the 4,5-β(stereochemical)-epoxy γ-lactam **27**, a Payne rearrangement was carried out. Treatment of TBDMS-oxy-α-epoxy γ-lactam **25** with tetrabutylammonium fluoride (TBAF) in THF at room temperature for 30 min afforded a mixture of regioisomers **26** and **27**, recrystallization of which

‡ δ-Lactonic acid **16** was converted into the azide in the usual manner ($ClCO_2Et$, Et_3N; aq. NaN_3), which was refluxed in Bu^{t}OH to furnish the *tert*-butyl carbamate **21** in 65% yield.

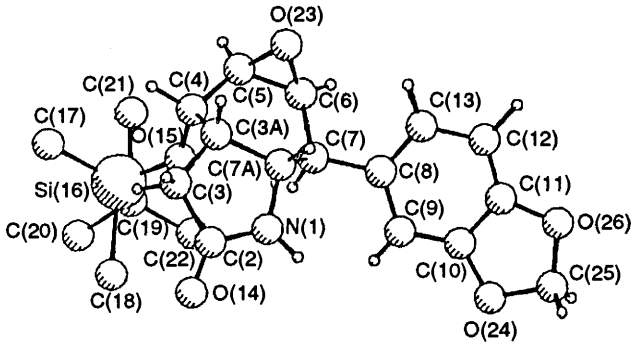
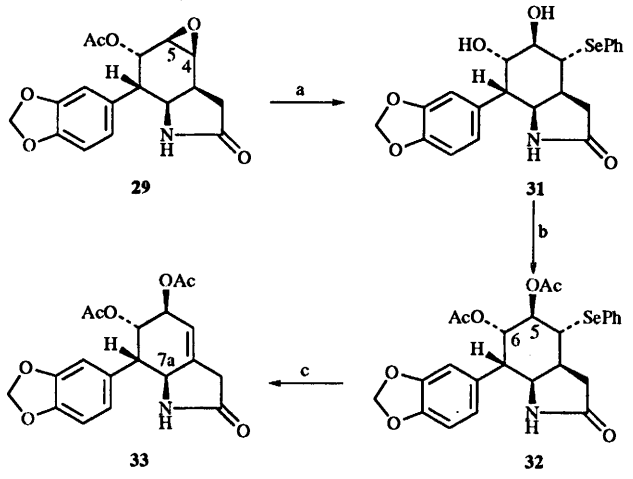


Fig. 2 X-Ray molecular structure of compound **25**

from MeOH gave only the δ,ε-epoxide **26**, in 38% yield. However, separation of isomers **26** and **27** was easily performed after acetylation. As shown in Table 1, the reaction of acetate **28** with 5% aq. K_2CO_3 in MeOH at room temperature was the best method for conversion of compound **26** into its regioisomer **27**. Thus, **29** was prepared from alcohol **23** in conventional procedures (silylation, epoxidation, deprotection, acetylation, base treatment and acetylation).

For introduction of a double bond at 4–5a positions on the C ring, the reaction of acetate **29** with diphenyl diselenide and $NaBH_4$[20] was investigated, and found to give phenylselanyl (PhSe) diol **31** in quantitative yield. After acetylation of diol **31**, structure of diacetate **32** was determined by ^1H NMR analysis using an irradiation method: namely, irradiation of 6-H or 5-H changed the triplet signal for 5-H or 6-H to a doublet, showing that two acetoxy groups are vicinal. Thus, phenylselanylation of epoxide **29** was shown to occur at the 4-position. Although oxidative dephenylselanylation of dihydro γ-lactam **31** with $NaIO_4$ or H_2O_2 did not occur, the reaction of the corresponding diacetoxy γ-lactam **32** with aq. $NaIO_4$ smoothly proceeded to give, in 88% yield, didehydro γ-lactam **33** bearing the same stereostructure as that concerning the C ring in lycorine (Scheme 4).

Finally, construction of the B ring was performed for the



Scheme 4 *Reagents and conditions:* a, $(PhSe)_2$, $NaBH_4$, EtOH, reflux, 15 min; b, Ac_2O, py, room temp., 21 h; c, $NaIO_4$, THF, aq. MeOH, 40 °C. 3.5 h

synthesis of lycorine by two routes; one was construction of the B ring followed by reduction of the γ-lactam (Route A) and the other was reduction of the γ-lactam followed by construction of the B ring (Route B) (Scheme 5).

For Route A, as attempts§ to cyclize compound **33** failed, the reaction of γ-lactam **32** with aq. Na_2CO_3 and 35% formalin followed by treatment with TFA in CH_2Cl_2 was performed to afford formation of the cyclization product **34**. Oxidative elimination of the PhSe group in compound **34** under reaction conditions similar to those described for selenide **32** furnished pentacycle **35** in 57% yield, the ^1H NMR spectrum of which was identical with that[4d] of an authentic sample. Since compound **35** has been converted into (±)-lycorine **1** by Sano *et al.*,[4d] the present results constitute a formal total synthesis of lycorine **1**.

A total synthesis of (±)-lycorine **1** was carried out according to Route B, though no unsaturated amine was employed as an intermediate. Reduction¶ of γ-lactam **32** with $NaAlH_2(OCH_2CH_2OCH_3)_2$ (Vitride®)[21] in boiling toluene gave the corresponding amine, which was immediately subjected to Pictet–Spengler reaction[22] using Eschenmoser's salt ($CH_2{=}N^+Me_2I^-$)[23] in THF to give pentacycle **36** in 44% yield. Finally, oxidative elimination of the PhSe group of compound **36** in a manner similar to that noted for compound **32** afforded (±)-lycorine **1**, the identification of which was performed after acetylation, by comparison (^1H NMR, IR, TLC) of (±)-di-*o*-acetyllycorine **37** with (−)-di-*o*-acetyllycorine. Thus, a total synthesis of (±)-lycorine **1** was accomplished (Scheme 6).

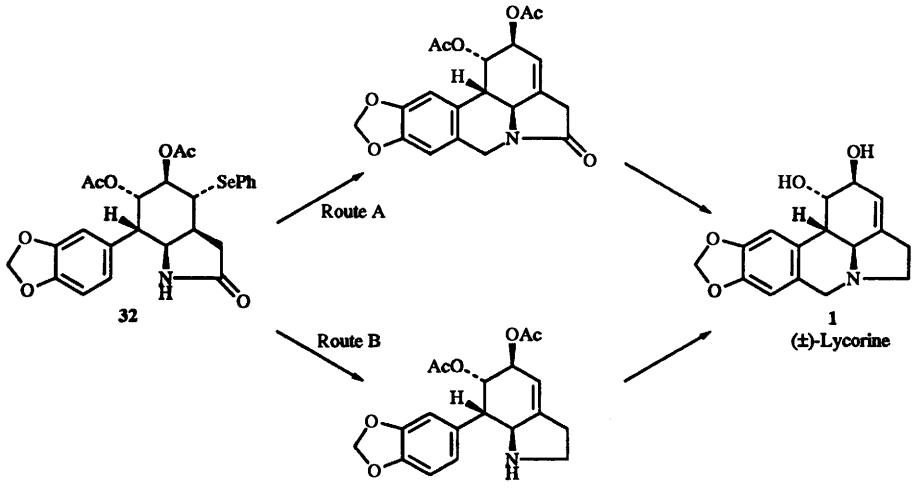
In conclusion, new formal and total syntheses of (±)-lycorine **1** were achieved by functionalization of the C ring followed by construction of the B ring.

Experimental

All mps were measured on a Büchi or a Yanagimoto (hot plate) melting point apparatus and are uncorrected. Unless otherwise noted, IR spectra were performed with a Hitachi 260-10 spectrometer for samples in $CHCl_3$ solution, and ^1H NMR spectra were taken with a JEOL JMX-FX100 (100 MHz) or a JEOL GSX-500 (500 MHz) spectrometer for samples in $CDCl_3$ solution with tetramethylsilane as internal standard. *J* Values are given in Hz. Mass spectra were measured on a Hitachi M-80

§ 1,4-Elimination of allylic acetate in compound **33** occurred.

¶ Reduction of selenide **32** with $LiAlH_4$ gave a complex mixture.

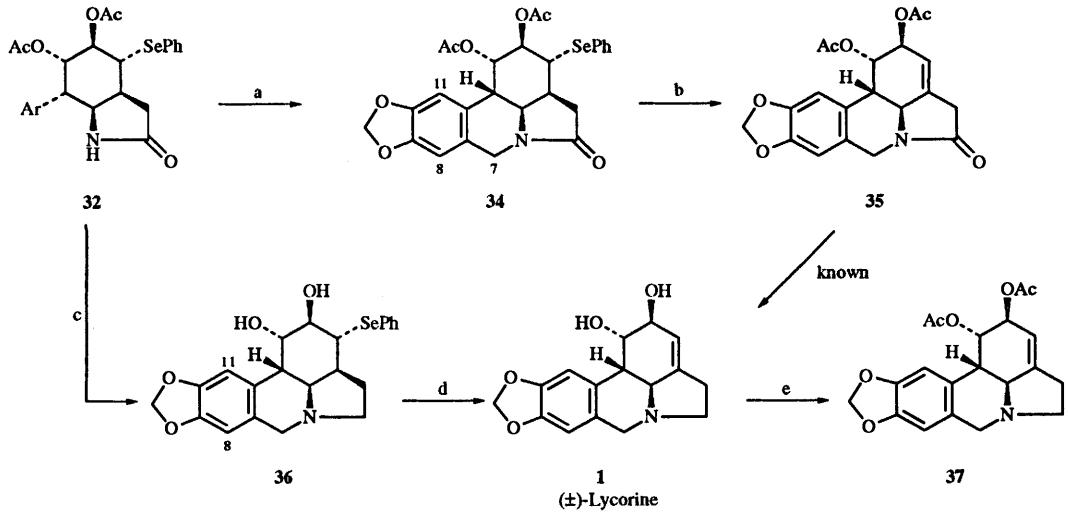


Scheme 5

Table 1 Payne rearrangement of epoxides **25**, **26** and **28**[a]

Entry	Substrate	Base	Reaction temp. (*T*/°C)	Reaction time (*t*/h)	Yield (%)[b] **28**	**29**	**30**
1	**25**	TBAF	rt[c]	0.5	77	11	*d*
2	**25**	TBAF	rt[c]	20	35	25	*d*
3	**25**	TBAF	40	8	30	26	*d*
4	**26**	NaH	40	9.5	10	61	5
5	**26**	NaH	reflux	9.5	*d*	21	35
6	**26**	KH	40	6.5	69	31	*d*
7	**26**	CaH_2	50	5	7	58	0
8[e]	**28**	5% aq. K_2CO_3	rt[c]	0.25	38	50	0
9[e]	**28**	5% aq. K_2CO_3	rt[c]	3	5	61	0

[a] All reactions were carried out in THF, unless otherwise stated. [b] Isolated yield. [c] Room temperature. [d] Not isolated. [e] In MeOH.



Scheme 6 *Reagents and conditions:* a, 35% aq. HCHO, sat. aq. Na_2CO_3, THF, room temp., 2 h; TFA, CH_2Cl_2, room temp., 15 min; b, $NaIO_4$, THF, aq. MeOH, 40 °C, 2 h; c, Vitride®, toluene, reflux, 0.5 h; $CH_2{=}N^+Me_2I^-$, THF, reflux, 1 h; d, $NaIO_4$, THF, aq. MeOH, 40 °C, 10 min; e, Ac_2O, py, room temp., 24 h

or a JEOL JMS D-300 spectrometer. Organic phase extract solutions were dried over Na_2SO_4 or $MgSO_4$ except for those organic phases containing an amine (K_2CO_3). Removal of the solvent was carried out under reduced pressure. Column chromatography was performed on silica gel. Preparative TLC (PLC) was run on Merck 5744 or Merck 7730 plates. Light petroleum refers to the fraction with distillation range 35–45 °C.

(*E*)-Hexa-3,5-dienyl 3′,4′-methylenedioxycinnamate 5

To an ice-cold, stirred suspension of carboxylic acid **2**[12] (60 g, 0.31 mol) and Et_3N (56 cm^3, 0.4 mol) in acetone (900 cm^3) was added $ClCO_2Et$ (15 cm^3, 0.155 mol). The mixture was stirred at 0 °C for 1 h and at room temperature for 15 h. The precipitate was filtered off and washed with hexane to give anhydride **3** (70 g) as crystals. To a mixture of anhydride **3** (55 g, 0.15 mol), 4-(dimethylamino)pyridine (DMAP) (6.1 g, 0.05 mol), and pyridine (60 cm^3, 0.75 mol) in CH_2Cl_2 (175 cm^3) was added a solution of diene alcohol **4**[13] (10 g, 0.1 mol) in CH_2Cl_2 (25 cm^3) at room temperature, and the mixture was stirred for 18 h. After suction filtration to remove the precipitate, the filtrate was acidified with 10% HCl. Then, the new precipitate was filtered off, and the organic phase was separated. The organic phase was washed successively with 5% aq. $KHCO_3$ and brine. Evaporation off of the solvent afforded a solid (42 g), which was recrystallized from hexane to furnish *title compound* **5** (29 g, 86% yield based on **4**) as crystals; mp 59–60.5 °C (from light petroleum); δ_H 7.54 (1 H, d, *J* 16, ArC*H*=CH), 6.86–7.04 (2 H, m, ArH × 2), 6.76 (1 H, d, *J* 8, ArH), 6.22 (1 H, d, *J* 16, ArCH=C*H*), 6.06–6.36 (2 H, m, olefinic H × 2), 5.96 (2 H, s, OCH_2O), 5.48–5.84 (1 H, m, olefinic H), 4.90–5.22 (2 H, m, olefinic H × 2), 4.22 (2 H, t, *J* 7.1, OCH_2CH_2) and 2.48 (2 H, q, *J* 7.1, OCH_2CH_2); ν_{max}/cm^{-1} 1700; *m*/*z* 272 (M^+) (Found: C, 70.5; H, 5.9. $C_{16}H_{16}O_4$ requires C, 70.57; H, 5.92%).

(4a*R,8*R**,8a*R**)-8-(3′,4′-Methylenedioxyphenyl)-3,4,4a,7,8a-hexahydroisocoumarin 6 and (4a*S**,8*R**,8a*R**)-8-(3′,4′-methylenedioxyphenyl)-3,4,4a,7,8a-hexahydroisocoumarin 7**

A solution of triene ester **5** (2.0 g, 7.4 mmol) and hydroquinone (0.040 g, 0.35 mmol) in *o*-dichlorobenzene (*o*-DCB) (100 cm^3) in a sealed tube was heated at 235 °C for 94 h under argon. The same reaction was repeated three times, independently. The four reaction mixtures were combined. Removal of the solvent gave a residue, which was purified by column chromatography and elution with (1:10 and then 1:7) AcOEt–hexane to furnish epimers **6** (6.88 g, 86.0%) and **7** (0.383 g, 4.8%).

Compound **6**; mp 128–129 °C (from $CHCl_3$–MeOH); δ_H(500 MHz) 6.81 (1 H, d, *J* 2, ArH), 6.76 (1 H, dd, *J* 2 and 8, ArH), 6.73 (1 H, d, *J* 8, ArH), 6.05 (1 H, ddt, *J* 2.5, 4.5 and 10, 5-H), 5.93 (2 H, s, OCH_2O), 5.63 (1 H, dd, *J* 2 and 10, 6-H), 4.24–4.30 (2 H, m, 3-H_2), 3.81 (1 H, q, *J* 3, 8-H), 2.68 (1 H, dd, *J* 3 and 7.5, 8a-H), 2.59 (1 H, ddt, *J* 3, 6.8 and 19, 7-H), 2.48 (1 H, br s, $w_{\frac{1}{2}}$ 14.5, 4a-H), 2.25 (1 H, ddd, *J* 2, 4 and 19, 7-H), 1.99–2.06 (1 H, m, 4-H), 1.78 (1 H, ddd, *J* 3.5, 4 and 14.5, 4-H); ν_{max}/cm^{-1} 1710; *m*/*z* 272 (M^+) (Found: C, 70.7; H, 5.9. $C_{16}H_{16}O_4$ requires C, 70.57; H, 5.92%).

Compound **7**; mp 151.5–152.5 °C (from $CHCl_3$–hexane); δ_H(500 MHz) 6.75 (1 H, d, *J* 11, ArH), 6.70 (1 H, d, *J* 2, ArH), 6.69 (1 H, dd, *J* 2 and 11, ArH), 5.92 and 5.91 (each 1 H, d, *J* 0.8, together OCH_2O), 5.76 (1 H, ddt, *J* 2.5, 5 and 10, 5-H), 5.64 (1 H, ddd, *J* 1.5, 4 and 10, 6-H), 4.36–4.39 (2 H, m, 3-H_2), 3.01 (1 H, dt, *J* 5 and 11, 8-H), 2.78 (1 H, t, *J* 11, 8a-H), 2.61 (1 H, dddt, *J* 2.5, 4, 11.5 and 21, 4-H), 2.31–2.43 (2 H, m, 4a- and 7-H), 2.12 (1 H, dddt, *J* 2.5, 5, 11.5 and 18.5, 7-H) and 1.69 (1 H, ddd, *J* 5, 10 and 21, 4-H); ν_{max}/cm^{-1} 1740; *m*/*z* 272 (M^+) (Found: C, 70.3; H, 5.8%).

(3*R,4*R**,5*R**)-3-(2-Hydroxyethyl)-4-hydroxymethyl-5-(3′,4′-methylenedioxyphenyl)cyclohexene 9**

To an ice-cold, stirred solution of ester **6** (0.539 g, 1.95 mmol) in THF (35 cm^3) was added $LiAlH_4$ (0.260 g, 6.84 mmol) in small portions. After being stirred at room temperature for 30 min, the reaction mixture was quenched with saturated aq. Na_2SO_4. The precipitate was filtered off and usual work-up of the filtrate gave a residue, which was subjected to column chromatography and elution with (30:1) $CHCl_3$–MeOH to afford *title compound* **9** (0.525 g, 97.0%); mp 114–115 °C (from $CHCl_3$–hexane); δ_H 6.48–6.80 (3 H, m, ArH × 3), 5.89 (2 H, s, OCH_2O), 5.58–5.90 (2 H, m, olefinic H × 2), 3.52–3.88 (2 H, m, CH_2OH), 3.28–3.48 (2 H, m, $CHCH_2OH$) and 1.68–2.76 (7 H, m); ν_{max}/cm^{-1} 3100–3650; *m*/*z* 276 (M^+) (Found: C, 69.5; H, 7.4. $C_{16}H_{20}O_4$ requires C, 69.59; H, 7.30%).

(4a*R,8*R**,8a*R**)-8-(3′,4′-Methylenedioxyphenyl)-3,4,4a,7,8,8a-hexahydroisochroman-3(1H)-one 10**

To a suspension of $AgNO_3$ (57.8 g, 0.34 mol) and Celite 545 (50 g) in distilled water (340 cm^3) was added a solution of Na_2CO_3 (18.0 g, 0.17 mol) in distilled water (510 cm^3). After the mixture had been stirred at room temperature for 1 h, the yellow precipitate was filtered off and was washed with distilled water until the filtrate was neutral to litmus paper. This precipitate was suspended in benzene (1020 cm^3), and water was removed as an azeotropic mixture using a Dean–Stark apparatus to prepare Fétizon reagent.[17] To the reagent was added a solution of diol **9** (4.50 g, 16 mmol) in benzene (100 cm^3). After the

mixture had been refluxed for 2 h, the precipitate was removed by suction filtration. Evaporation of the filtrate gave *lactone* **10** (4.22 g, 97.7%), mp 139–140 °C (from $CHCl_3$–hexane); δ_H 6.52–6.80 (3 H, m, ArH × 3), 5.92 (2 H, s, OCH_2O), 5.48–6.01 (2 H, m, olefinic H × 2), 3.87 and 4.12 (each 1 H, dd, *J* 4.8 and 12, together 1-H_2) and 2.04–2.96 (7 H, m, 4- and 7-H_2, 4a-, 8- and 8a-H); ν_{max}/cm^{-1} 1725; *m/z* 272 (M^+) (Found: C, 70.7; H, 5.9. $C_{16}H_{16}O_4$ requires C, 70.57; H, 5.92%).

(3a*S,4*S**,5*R**,7*S**,7a*S**)-4-Hydroxymethyl-7-iodo-5-(3′,4′-methylenedioxyphenyl)-2,3,3a,4,5,6,7,7a-octahydrobenzofuran-2-one 11**

A mixture of lactone **10** (13.8 g, 50.7 mmol) and K_2CO_3 (7.60 g, 55.1 mmol) in water (350 cm^3) was refluxed for 1 h. After the mixture had cooled to room temperature, a solution of I_2 (50.4 g, 0.2 mol) and KI (83 g, 0.5 mol) in water (350 cm^3) was added to the mixture, and the mixture was stirred for 12.5 h. The mixture was acidified with 3 mol dm^{-3} HCl and extracted with AcOEt. The organic extract was washed successively with 10% aq. $Na_2S_2O_3$ and brine. Usual work-up of the organic phase gave γ-lactone **11** (19.40 g, 91.9%) as an oil; δ_H 6.44–6.90 (3 H, m, ArH × 3), 5.92 (2 H, s, OCH_2O), 4.82 (1 H, dd, *J* 6.3 and 9.2, 7a-H), 3.97 (1 H, ddd, *J* 4.3, 9.2 and 12.3, 7-H), 2.80–3.56 (3 H, m) and 1.96–2.76 (5 H, m); ν_{max}/cm^{-1} 3150–3650 and 1775; *m/z* 416 (M^+).

(3a*S,4*S**,5*R**,7*S**,7a*S**)-7-Iodo-5-(3′,4′-methylenedioxyphenyl)-4-(tetrahydropyran-2-yloxymethyl)-2,3,3a,4,5,6,7,7a-octahydrobenzofuran-2-one 13**

A mixture of iodolactone alcohol **11** (0.0607 g, 0.15 mmol), DHP (67 × 10^{-3} cm^3, 0.73 mmol), and *p*-TsOH·H_2O (0.0011 g, 0.006 mmol) in CH_2Cl_2 (2 cm^3) was stirred at room temperature for 4 h. The mixture was diluted with Et_2O and washed successively with saturated aq. $NaHCO_3$ and brine. Work-up of the organic phase in usual way gave an oily residue, which was purified by PLC with (100:1) $CHCl_3$–MeOH as developing solvent to afford tetrahydropyranyl ether **13** (0.0631 g, 87%) as an oil; δ_H 6.46–6.76 (3 H, m, ArH × 3), 5.92 (2 H, s, OCH_2O), 4.77 (1 H, dd, *J* 7.2 and 10, 7a-H), 4.16–4.40 (1 H, m, OCHO), 3.94 (1 H, ddd, *J* 4.3, 10 and 12.5, 7-H), 3.24–3.80 (3 H, m), 2.80–3.17 (2 H, m), 2.08–2.76 (5 H, m) and 1.20–1.92 (7 H, m); ν_{max}/cm^{-1} 1780; *m/z* 500 (M^+).

(3a*S,4*S**,5*R**,7a*R**)-5-(3′,4′-Methylenedioxyphenyl)-4-(tetrahydropyran-2-yloxymethyl)-2,3,3a,4,5,7a-hexahydrobenzofuran-2-one 14**

A solution of iodolactone **13** (0.1698 g, 0.34 mmol) and DBU (0.25 cm^3, 1.7 mmol) in benzene (8 cm^3) was refluxed for 20 h. The mixture was diluted with Et_2O and washed successively with 2% aq. HCl and brine. Usual work-up of the organic phase gave an oily residue, which was purified by column chromatography and elution with (100:5:1) benzene–AcOEt–MeOH to afford *unsaturated lactone* **14** (0.1243 g, 98%) as an oil; δ_H 6.46–6.80 (3 H, m, ArH × 3), 5.93 (2 H, s, OCH_2O), 5.79 (2 H, d, *J* 1.6, olefinic H × 2), 5.08–5.22 (1 H, m, OCHO), 4.43 (1 H, br s, $w_{\frac{1}{2}}$ 5, 7a-H), 2.92–3.92 (5 H, m), 2.60 (1 H, d, *J* 5), 2.49 (1 H, dd, *J* 1.6 and 4.8), 1.92–2.32 (1 H, m) and 1.32–1.84 (5 H, m); ν_{max}/cm^{-1} 1760; *m/z* 372 (M^+); HRMS (Found: M^+, 372.1563. $C_{21}H_{24}O_6$ requires M, 372.1571).

(3a*S,4*S**,5*R**,7a*R**)-4-Hydroxymethyl-5-(3′,4′-methylenedioxyphenyl)-2,3,3a,4,5,7a-hexahydrobenzofuran-2-one 15**

A solution of tetrahydropyranyl ether **14** (2.60 g, 7.0 mmol) and *p*-TsOH·H_2O (0.310 g, 1.6 mmol) in a mixture of CH_2Cl_2 (40 cm^3) and MeOH (40 cm^3) was stirred at room temperature for 5 h. After removal of the solvent, the product was taken up in $CHCl_3$. Work-up of the organic phase in the usual way afforded the *hydroxy compound* **15** (1.85 g, 92%), mp 139–140 °C (from Et_2O); δ_H 6.48–6.80 (3 H, m, ArH × 3), 5.92 (2 H, s, OCH_2O), 5.79 (2 H, s, olefinic H × 2), 5.14 (1 H, ddd, *J* 0.8, 2.4 and 7.5, 7a-H), 3.63 [1 H, dd, *J* 4 and 10.5, C*H*(H)OH], 3.44 [1 H, dd, *J* 4 and 10.5, CH(*H*)OH], 3.24 (1 H, dd, *J* 2.5 and 10.5), 3.08 (1 H, dd, *J* 4 and 7.5), 2.58 (1 H, d, *J* 1), 2.48 (1 H, d, *J* 1) and 1.84–2.17 (1 H, m); ν_{max}/cm^{-1} 3450 and 1760; *m/z* 288 (M^+) (Found: C, 66.4; H, 5.5. $C_{16}H_{16}O_5$ requires C, 66.66; H, 5.59%).

(3a*S,4*S**,5*R**,7a*R**)-5-(3′,4′-Methylenedioxyphenyl)-2-oxo-2,3,3a,4,5,7a-octahydrobenzofuran-4-carboxylic acid 16**

To an ice-cold, stirred solution of alcohol **15** (0.310 g, 1.08 mmol) in acetone (14 cm^3) was added 2 mol dm^{-3} Jones reagent (0.54 cm^3, 1.08 mmol). After the mixture had been stirred for 15 min, cold water was added. The mixture was extracted with AcOEt. The organic phase was extracted with saturated aq. $NaHCO_3$. The aqueous phase was acidified with conc. HCl, and extracted with $CHCl_3$. Usual work-up of the organic phase afforded *acid* **16** (0.2045 g, 63%), mp 208–209 °C (from MeOH); δ_H 6.52–6.80 (3 H, m, ArH × 3), 5.90 (2 H, s, OCH_2O), 5.84 (2 H, s, olefinic H × 2), 5.20 (1 H, ddd, *J* 1.5, 2.6 and 5, 7a-H), 3.64–3.86 (1 H, m, 5-H), 3.00–3.36 (1 H, m, 4-H) and 2.28–2.96 (3 H, m, 3a-H and 3-H_2); ν_{max}/cm^{-1} 1770 and 1705; *m/z* 302 (M^+) (Found: C, 63.5; H, 4.7. $C_{16}H_{14}O_6$ requires C, 63.57; H, 4.67%).

(3a*S,4*S**,5*S**,7a*R**)-Benzyl 5-(3′,4′-methylenedioxyphenyl)-2-oxo-2,3,3a,4,5,7a-hexahydrobenzofuran-4-carbamate 17**

To an ice-cold, stirred solution of δ-lactonic acid **16** (0.0426 g, 0.14 mmol) and Et_3N (0.026 cm^3, 0.18 mmol) in acetone (3 cm^3) was added dropwise $ClCO_2Et$ (0.013 cm^3, 0.18 mmol). After this mixture had been stirred for 30 min, aq. NaN_3 (0.012 g, 0.18 mmol in 0.5 cm^3) was added to the mixture and the whole was stirred for 3 h. The reaction was quenched with cold water, and the mixture was extracted with Et_2O. The extract was washed with brine, and evaporated to give a residue, which was refluxed in a mixture of toluene (2 cm^3) and benzyl alcohol (0.1 cm^3) for 9 h. Evaporation off of the solvent afforded an oily residue, which was purified by column chromatography with (50:1) $CHCl_3$–MeOH as eluent to furnish carbamate **17** (0.0412 g, 72%) as an oil; δ_H 7.31 (5 H, br s, Ph), 5.93 (2 H, s, OCH_2O), 5.90–6.30 (2 H, m, olefinic H × 2), 5.03 (2 H, s, CH_2Ph), 4.75–5.10 (2 H, m, NH, 7a-H), 3.95–4.25 (1 H, m, 5-H) and 3.75–3.60 (1 H, m, 4-H); ν_{max}/cm^{-1} 3420, 1775 and 1715; *m/z* 407 (M^+); HRMS (Found: M^+, 407.1368. $C_{23}H_{21}NO_6$ requires M, 407.1368).

(3a*S,7a*S**,7a*S**)-7-(3′,4′-Methylenedioxyphenyl)-3a,4,5,6,7,7a-hexahydroindolin-2-one 19**

A suspension of the benzyl carbamate **17** (0.0689 g, 0.17 mmol) and 10% Pd–C (0.040 g) in MeOH (3 cm^3) was stirred for 1 h 50 min under H_2. After the catalyst had been filtered off, evaporation of the filtrate afforded crystals (0.0462 g, 98%). A solution of these crystals (0.042 g, 0.15 mmol) in MeOH (3 cm^3) was stirred with a catalytic amount of conc. H_2SO_4 at room temperature for 15 h. The mixture was diluted with $CHCl_3$ and extracted with 10% HCl. The aqueous phase was made alkaline with $NaHCO_3$ (powder), and extracted with $CHCl_3$. Usual work-up of the organic extract gave (1*S**,2*R**,3*S**)-methyl 2-amino-3-(3′,4′-methylenedioxyphenyl)cyclohexaneacetate **18** (0.0328 g, 74%) as an oil; δ_H 5.72 (2 H, s, OCH_2O) and 3.57 (3 H, s, CO_2Me); ν_{max}/cm^{-1} 3350 and 1720.

A solution of amino ester **18** (0.0328 g, 0.11 mmol) in EtOH (2 cm^3) was refluxed for 10 h. Removal of the solvent gave a residue, which was purified by column chromatography with (40:1) $CHCl_3$–MeOH as eluent to furnish compound **19** (0.0250 g, 86%), mp 192.5–193.5 °C (from $CHCl_3$–hexane) (lit.,[15b] 191.5–192.5 °C); δ_H 6.52–6.80 (3 H, m, ArH × 3), 5.91 (2 H, s, OCH_2O), 5.54 (1 H, br s, $w_{\frac{1}{2}}$ 8.6, NH), 3.40 (1 H, dd, *J* 7 and 10, 7a-H), 2.52–2.96 (1 H, m, 7-H), 2.06–2.20 (2 H, m, 3-H_2) and 1.16–2.96 (7 H, m, 3a-H, and 4-, 5- and 6-H_2); ν_{max}/cm^{-1} 3420 and 1690; *m/z* 259 (M^+); HRMS (Found: M^+,

Table 2 Crystal data for compound **25**

Compound	**25**
Formula, M_r	$C_{21}H_{29}NO_5Si$, 403.6
Crystal system	Monoclinic
Space group, Z	$P2_1/n$, 4
Lattice constant	
a (Å)	22.937(12)
b (Å)	6.957(7)
c (Å)	14.406(15)
β (°)	111.62(5)
V (Å^3)	2137
D_{calc} (g cm^{-1})	1.254

259.1208. $C_{15}H_{17}NO_3$ requires M, 259.1207). ^{1}H NMR spectral data of compound **19** were identical with those[15] of an authentic specimen.

(3a*S,4*S**,5*S**,7a*R**)-*tert*-Butyl 5-(3′,4′-methylenedioxyphenyl)-2-oxo-2,3,3a,4,5,7a-hexahydrobenzofuran-4-carbamate 21**

A solution of δ-lactonic acid **16** (0.4455 g, 1.47 mmol), Et_3N (0.1561 g, 1.54 mmol), and DPPA[18] (0.4080 g, 1.48 mmol) in Bu^{t}OH (18 cm^3) was refluxed for 4 h. Evaporation off of the solvent gave a residue, which was taken up in AcOEt. The organic phase was washed successively with 5% HCl, water, saturated aq. $NaHCO_3$ and brine. Evaporation off of the solvent gave *title carbamate* **21** (0.4328 g, 78.6%), mp 213–215 °C (from $CHCl_3$–hexane); δ_H 6.50–6.80 (3 H, m, ArH × 3), 5.94–6.28 (2 H, m, olefinic H × 2), 5.92 (2 H, s, OCH_2O), 4.82–4.98 (1 H, m, 7a-H), 4.62 (1 H, d, J 10, NH), 3.92–4.12 (1 H, m, 5-H), 3.48 (1 H, t, J 4, 4-H), 2.72–2.98 (1 H, m, 3a-H), 2.48–2.62 (2 H, m, 3-H_2) and 1.40 (9 H, s, Bu^t); ν_{max}/cm^{-1} 3425, 1775 and 1700; m/z 373 (M^+) (Found: C, 64.1; H, 6.0; N, 3.7. $C_{20}H_{23}NO_6$ requires C, 64.33; H, 6.21; N, 3.75%).

(3a*S,4*S**,5*S**,7a*R**)-4-Amino-5-(3′,4′-methylenedioxyphenyl)-2,3,3a,4,5,7a-hexahydrobenzofuran-2-one 22**

A solution of carbamate **21** (0.4909 g, 1.3 mmol) and TFA (8.4 cm^3) in CH_2Cl_2 (25 cm^3) was stirred at room temperature for 1 h. The mixture was diluted with $CHCl_3$ and extracted with 10% HCl. The aqueous extract was made alkaline with $NaHCO_3$ (powder), and extracted with $CHCl_3$. Usual work-up of the organic phase furnished *compound* **22** (0.3528 g, 98%), mp 139–140 °C (from MeOH); δ_H 6.54–6.82 (3 H, m, ArH × 3), 5.93 (2 H, s, OCH_2O), 5.80–5.96 (2 H, m, olefinic H × 2), 5.11 (1 H, ddd, J 1.2, 2.8 and 6.8, 7a-H), 2.80–3.28 (3 H, m), 2.40–2.64 (2 H, m) and 1.32 (2 H, br s, $w_{\frac{1}{2}}$ 4, NH_2); ν_{max}/cm^{-1} 3350 and 1770; m/z 273 (M^+) (Found: C, 65.8; H, 5.4; N, 5.1. $C_{15}H_{15}NO_4$ requires C, 65.92; H, 5.53; N, 5.13%).

(3a*S,4*R**,7*S**,7a*S**)-4-Hydroxy-7-(3′,4′-methylenedioxyphenyl)-3a,4,7,7a-tetrahydroindolin-2-one 23**

A solution of amine **22** (0.3488 g, 1.28 mmol) and NaOMe (0.1077 g, 1.90 mmol) in MeOH (25 cm^3) was stirred at room temperature for 3 h. Evaporation off of the solvent left a residue, which was taken up in $CHCl_3$. Usual work-up of the organic phase afforded *lactam* **23** (0.3404 g, 97.6%), mp 147–148.5 °C (from AcOEt); δ_H 6.56–6.88 (3 H, m, ArH × 3), 6.15 (1 H, ddd, J 2.6, 4 and 10, olefinic H), 6.00 (2 H, s, OCH_2O), 5.92 (1 H, dd, J 4 and 10, olefinic H), 5.70 (1 H, br s, $w_{\frac{1}{2}}$ 10, NH), 4.48–4.68 (1 H, m, 4-H), 3.68 (1 H, t, J 8, 7a-H), 3.28–3.52 (1 H, m, 7-H) and 2.26–3.16 (3 H, m, 3-H_2 and 3a-H); ν_{max}/cm^{-1}, 3420 and 1690; m/z 273 (M^+) (Found: C, 65.8; H, 5.6; N, 5.2. $C_{15}H_{15}NO_4$ requires C, 65.92; H, 5.53; N, 5.13%).

(3a*S,4*R**,7*S**,7a*S**)-4-(*tert*-Butyldimethylsiloxy)-7-(3′,4′-methylenedioxyphenyl)-3a,4,7,7a-tetrahydroindolin-2-one 24**

A solution of hydroxy γ-lactam **23** (0.4199 g, 1.54 mmol), TBDMSCl (0.4545 g, 3.15 mmol) and imidazole (0.4526 g, 6.66 mmol) in DMF (10 cm^3) was stirred at room temperature for 8 h. Removal of the solvent afforded a residue, which was taken up in $CHCl_3$. The organic phase was washed successively with 1% HCl water and brine. Evaporation off of the solvent gave *compound* **24** (0.5868 g, 98.2%), mp 158–159 °C (from Et_2O–hexane); δ_H 6.56–6.86 (3 H, m, ArH × 3), 6.06 (1 H, ddd, J 2.8, 4 and 10.4, olefinic H), 5.98 (2 H, s, OCH_2O), 5.85 (1 H, dd, J 3.2 and 10.4, olefinic H), 5.78 (1 H, br s, $w_{\frac{1}{2}}$ 4, NH), 4.50 (1 H, br t, J 4.3, 4-H), 3.32–3.76 (2 H, m, 7- and 7a-H), 2.72–3.06 (1 H, m, 3a-H), 2.18–2.64 (2 H, m, 3-H_2), 0.91 (9 H, s, Bu^t) and 0.10 and 0.09 (each 3 H, s, $SiMe_2$); ν_{max}/cm^{-1} 3425 and 1695; m/z 387 (M^+) (Found: C, 64.75; H, 7.5; N, 3.6. $C_{21}H_{29}NO_4Si$ requires C, 65.08; H, 7.54; N, 3.61%).

(3a*S,4*S**,5*S**,6*S**,7*S**,7a*R**)-4-(*tert*-Butyldimethylsiloxy)-5,6-epoxy-7-(3′,4′-methylenedioxyphenyl)-3a,4,5,6,7,7a-hexahydroindolin-2-one 25**

A solution of compound **24** (0.5858 g, 1.52 mmol) and MCPBA (0.5210 g, 3.02 mmol) in CH_2Cl_2 (25 cm^3) was stirred at room temperature for 42 h (the reaction was monitored by GLC). The mixture was washed successively with 10% aq. $Na_2S_2O_3$, water, saturated aq. $NaHCO_3$ and brine. Removal of the solvent left a residue, which was purified by column chromatography with $CHCl_3$ as eluent to furnish epoxide **25** (0.5161 g, 84.8%), mp 145–145.5 °C (from AcOEt–hexane); δ_H (400 MHz) 6.86 (1 H, d, J 1.8, ArH), 6.80 (1 H, d, J 7.7, ArH), 6.74 (1 H, dd, J 1.8 and 7.7, ArH), 5.98 (2 H, s, OCH_2O), 5.29 (1 H, br s, NH), 4.39 (1 H, t, J 4.4, 4-H), 3.78 (1 H, t, J 9.5, 7a-H), 3.32 (1 H, t, J 4.4, 5-H), 3.28 (1 H, d, J 4.4, 6-H), 3.21 (1 H, d, J 9.5, 7-H), 2.79 (1 H, m, 3a-H), 2.56 (1 H, dd, J 6.6 and 17.2, 3-H), 2.37 (1 H, dd, J 11.4 and 17.2, 3-H), 0.96 (6 H, s, Me × 2) and 0.16 (9 H, s, Bu^t); ν_{max}/cm^{-1} 3420; m/z 403 (M^+) (Found: C, 62.7; H, 7.3; N, 3.5. $C_{21}H_{29}NO_5Si$ requires C, 62.50; H, 7.24; N, 3.47%).

X-Ray crystallographic analysis of TBDMS-oxy-epoxy γ-lactam 25

The X-ray study was carried out as follows. Intensities were measured on a Philips PW 1100 diffractometer using graphite-monochromated Cu-Kα radiation. A total of 2344 reflections were measured as above the 2σ(I) level out of 3649 reflections within the 2θ range 6–142°. The crystal structure was determined by direct methods and the atomic parameters were refined by the block-diagonal-matrix least-squares method to an R-value of 0.11. Some of the hydrogen atoms were included in the refinement with isotropic temperature factors but those which belong to the two methyl groups and to the tertiary butyl group bonded to silicon atom were not included because these groups exhibited very large anisotropic thermal deviations. This may be the consequence of some kind of disorder, possibly a rotational disorder about the bond including the silicon atom. The rather large value of R may result from the disorder. Crystal data are summarized in Table 2 and the PLUTO[19] drawing of the structure is shown in Fig. 2. Positional parameters are summarized in Table 3.[‖]

(3a*S,4*S**,5*R**,6*S**,7*S**,7a*R**)-5,6-Epoxy-4-hydroxy-7-(3′,4′-methylenedioxyphenyl)-3a,4,5,6,7,7a-hexahydroindolin-2-one 26**

A solution of epoxide **25** (0.385 2 g, 0.96 mmol) and TBAF (1 mol dm^{-3} in THF; 2.87 cm^3) in THF (9 cm^3) was stirred at room temperature for 30 min. Removal of the solvent afforded an oily residue, which was taken up in AcOEt. Usual work-up of the organic phase furnished a solid, which was recrystallized from MeOH (2 ×) to afford the *alcohol* **26** (0.1046 g, 38%), mp 193–

‖ Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1996, Issue 1.

Table 3 Positional parameters for compound **25**

No.	Atom	$10^4 X$	$10^4 Y$	$10^4 Z$
1	N(1)	2784(3)	4608(9)	−1017(5)
2	C(2)	2196(3)	4923(12)	−1665(6)
3	C(3)	1901(4)	2988(13)	−2027(7)
4	C(3A)	2341(3)	1482(11)	−1359(6)
5	C(4)	2092(4)	476(12)	−648(6)
6	C(5)	2602(4)	−738(13)	88(7)
7	C(6)	3208(4)	179(13)	584(6)
8	C(7)	3287(3)	2275(11)	327(6)
9	C(7A)	2971(3)	2598(11)	−815(6)
10	C(8)	3970(3)	2905(11)	707(6)
11	C(9)	4112(3)	4812(12)	1011(7)
12	C(10)	4723(4)	5380(12)	1306(6)
13	C(11)	5192(3)	4138(13)	1316(7)
14	C(12)	5076(4)	2280(14)	1034(8)
15	C(13)	4440(4)	1658(12)	723(7)
16	O(14)	1958(3)	6494(8)	−1933(5)
17	O(15)	1906(2)	1836(9)	−72(4)
18	Si(16)	1244(1)	2310(8)	40(3)
19	C(17)	577(4)	1012(20)	−850(8)
20	C(18)	1094(8)	5286(19)	−323(16)
21	C(19)	1321(6)	2710(43)	1200(13)
22	C(20)	723(5)	3550(27)	1379(10)
23	C(21)	1393(8)	−105(24)	1469(12)
24	C(22)	1904(6)	3848(34)	1852(11)
25	O(23)	3134(3)	−1254(8)	−189(5)
26	O(24)	4971(3)	7150(9)	1640(9)
27	C(25)	5628(4)	7022(15)	1834(8)
28	O(26)	5760(2)	5073(10)	1655(5)

195 °C; δ_H([$^2H_5$]pyridine) 6.72–7.06 (3 H, m, ArH × 3), 5.95 and 5.93 (each 1 H, d, *J* 2, together OCH_2O), 4.56 (1 H, dd, *J* 4.3 and 8, 4-H), 4.12 (1 H, br t, *J* 8.9, 7a-H), 3.65 (1 H, d, *J* 8.9, 7-H), 3.63 (1 H, t, *J* 4.3, 5-H), 3.39 (1 H, d, *J* 4.3, 6-H) and 2.44–3.27 (3 H, m, 3-H_2 and 3a-H); ν_{max}/cm^{-1}: 3270 and 1675; *m*/*z* 289 (M^+) (Found: C, 62.3; H, 5.0; N, 4.9. $C_{15}H_{15}NO_5$ requires C, 62.28; H, 5.23; N, 4.84%).

Payne rearrangement

(a) With TBAF (Table 1, entries 1–3). A solution of silyl ether **25** (1 mol equiv.) and TBAF (3 mol equiv.) in THF (0.12 mol dm^{-3}) was stirred at room temperature. Removal of the solvent under cooling left a residue, which was taken up in AcOEt. The organic phase was washed successively with water and brine. Evaporation off of the solvent gave a mixture of epoxy alcohols **26** and **27**, which was treated with Ac_2O and pyridine at room temperature for 16 h. The reaction was quenched with 10% HCl, and the mixture was extracted with $CHCl_3$. Usual work-up of the extract left a residue, PLC of which with (5:1) $CHCl_3$–MeOH as developing solvent afforded acetates **28** and **29**.

(b) With metal hydride (Table 1, entries 4–7). A mixture of regioisomeric alcohols **26** and **27** (1 mol equiv.) with metal hydride (NaH, KH or CaH_2, 3 mol equiv.) in THF (0.33 mol dm^{-3}) was heated at an appropriate temperature. The reaction mixture was quenched with saturated aq. NH_4Cl, and extracted with AcOEt. Usual work-up of the organic phase furnished a mixture of epoxy alcohols **26** and **27**, which was converted into the acetates **28** and **29** in a manner similar to that described in (**a**). In the reaction with NaH in THF at reflux, compounds **29** and **30** were obtained after acetylation.

(c) With aq. K_2CO_3 (Table 1, entries 8, 9). A mixture of acetate **28** (1 mol equiv.) and 5% aq. K_2CO_3 (1.2 mol equiv.) in MeOH (0.30 mol dm^{-3}) was stirred at room temperature. After addition of water, the mixture was extracted with AcOEt. Work-up of the organic phase in the usual manner afforded a mixture of epoxy alcohols **26** and **27**, which was converted into the acetates **28** and **29** in a manner similar to that described in (**a**).

(3aS*,4S*,5S*,6S*,7S*,7aR*)-5,6-*Epoxy*-7-(3′,4′-*methylenedioxyphenyl*)-2-*oxo*-3a,4,5,6,7,7a-*hexahydroindolin*-4-*yl acetate* **28**, mp 238–240 °C (from AcOEt); δ_H(400 MHz) 6.84 (1 H, d, *J* 1.8, ArH), 6.79 (1 H, d, *J* 8.1, ArH), 6.74 (1 H, dd, *J* 1.8 and 8.1, ArH), 5.96 (2 H, s, OCH_2O), 5.50 (1 H, br t, *J* 4, 4-H), 5.34 (1 H, br s, NH), 3.82 (1 H, t, *J* 9.5, 7a-H), 3.48 (1 H, t, *J* 4, 5-H), 3.28 (1 H, d, *J* 4, 6-H), 3.11 (1 H, d, *J* 9.5, 7-H), 2.94–3.02 (1 H, m, 3a-H), 2.44 (1 H, dd, *J* 11.4 and 17.6, 3-H), 2.30 (1 H, dd, *J* 7 and 17.6, 3-H) and 2.16 (3 H, s, Ac); ν_{max}/cm^{-1} 3420, 1735 and 1690; *m*/*z* 331 (M^+); HRMS (Found: M^+, 331.1052. $C_{17}H_{17}NO_6$ requires M, 331.1054).

(3aS*,4S*,5S*,6S*,7S*,7aR*)-4,5-*Epoxy*-7-(3′,4′-*methylenedioxyphenyl*)-2-*oxo*-3a,4,5,6,7,7a-*hexahydroindolin*-6-*yl acetate* **29**, mp 180–181 °C (from AcOEt–hexane); δ_H(270 MHz) 6.75 (1 H, d, *J* 7.9, ArH), 6.70 (1 H, d, *J* 1.6, ArH), 6.64 (1 H, dd, *J* 1.6 and 7.9, ArH), 5.96 (2 H, s, OCH_2O), 5.40 (1 H, t, *J* 3.3, 6-H), 5.30 (1 H, br s, $w_{\frac{1}{2}}$ 8.4, NH), 4.04 (1 H, dd, *J* 8.1 and 11.7, 7a-H), 3.51 (1 H, apparent t, *J* 3.3, 5-H), 3.37 (1 H, t, *J* 3.3, 4-H), 3.09–3.22 (1 H, m, 3a-H), 2.97 (1 H, dd, *J* 3.2 and 11.7, 7-H), 2.67 (1 H, dd, *J* 10.9, and 17.0, 3-H), 2.52 (1 H, dd, *J* 9.6 and 17.0, 3-H) and 2.08 (3 H, s, Ac); ν_{max}/cm^{-1} 3430, 1750 and 1700; *m*/*z* 331 (M^+) (Found: C, 61.75; H, 5.3; N, 4.2. $C_{17}H_{17}NO_6$ requires C, 61.63; H, 5.17; N, 4.23%).

(3aS*,4S*,5S*,7aR*)-7-(3′,4′-*Methylenedioxyphenyl*)-2-*oxo*-3a,4,5,7a-*tetrahydroindoline*-4,5-*diyl diacetate* **30**, mp 71–72 °C (from $CHCl_3$–hexane); δ_H 6.64–6.86 (3 H, m, ArH × 3), 5.97 (2 H, s, OCH_2O), 5.84 (1 H, dd, *J* 1 and 2.9, 6-H), 5.64 (1 H, br s, $w_{\frac{1}{2}}$ 10.4, NH), 5.56 (1 H, ddd, *J* 1.4, 2.9 and 7.2, 5-H), 5.24 (1 H, dd, *J* 4.9 and 7.2, 4-H), 4.69 (1 H, d, *J* 7.2, 7a-H), 3.04–3.56 (1 H, m, 3a-H), 2.25–2.62 (2 H, m, 3-H_2) and 2.08 and 2.07 (each 3 H, s, Ac); ν_{max}/cm^{-1} 3430, 1740 and 1700; *m*/*z* 373 (M^+); HRMS (Found: M^+, 373.1163. $C_{19}H_{19}NO_7$ requires M, 373.1160).

(3a*S,4*R**,5*R**,6*S**,7*S**,7a*S**)-5,6-Dihydroxy-7-(3′,4′-methylenedioxyphenyl)-4-phenylselanyl-3a,4,5,6,7,7a-hexahydroindolin-2-one 31**

To a stirred solution of $(PhSe)_2$ (0.0364 g, 0.113 mmol) in EtOH (2.2 cm^3) under argon was added $NaBH_4$ (0.0094 g, 0.25 mmol) in one portion. After the yellow solution became colourless, stereochemically β-epoxide **29** (0.050 g, 0.15 mmol) was added to the mixture and the whole was refluxed for 15 min. Then the reaction was quenched with water, and the mixture was extracted with AcOEt. Usual work-up of the organic phase gave a residue, which was purified by PLC with (20:1) $CHCl_3$–MeOH as developing solvent to furnish the *selenide* **31** (0.0665 g, 98.7%), mp 84–86 °C; δ_H 7.44–7.67 (2 H, m, ArH × 2), 7.12–7.44 (3 H, m, ArH × 3), 6.64 (1 H, d, *J* 8, ArH), 6.61 (1 H, d, *J* 2, ArH), 6.42 (1 H, dd, *J* 2 and 8, ArH), 5.91 (2 H, s, OCH_2O), 5.44 (1 H, br s, $w_{\frac{1}{2}}$ 4.3, NH), 3.85–4.11 (2 H, m), 3.52–3.75 (1 H, m) and 2.52–3.16 (5 H, m); ν_{max}/cm^{-1} 3150–3600 and 1680; *m*/*z* 447 (M^+); HRMS (Found: M^+, 447.0593. $C_{21}H_{21}NO_5Se$ requires M, 447.0583).

(3a*S,4*R**,5*R**,6*S**,7*R**,7a*S**)-7-(3′,4′-Methylenedioxyphenyl)-2-oxo-4-phenylselanyl-3a,4,5,6,7,7a-hexahydroindoline-5,6-diyl diacetate 32**

A solution of diol **31** (0.025 g, 0.56 mmol) and Ac_2O (0.1 cm^3) in pyridine (1 cm^3) was stirred at room temperature for 21 h. After 10% HCl was added to the mixture, the aqueous phase was extracted with AcOEt. Treatment of the extract in the usual manner gave *diacetate* **32** (0.0292 g, 98.3%), mp 223 °C (from $CHCl_3$–hexane); δ_H 7.48–7.62 (2 H, m, ArH × 2), 7.16–7.44 (3 H, m, ArH × 3), 6.69 (1 H, d, *J* 8, ArH), 6.60 (1 H, d, *J* 1.2, ArH), 6.54 (1 H, dd, *J* 1.2 and 8, ArH), 5.92 (2 H, s, OCH_2O), 5.48 (1 H, br s, $w_{\frac{1}{2}}$ 4, NH), 5.26 (1 H, dd, *J* 3.1 and 8.3, H-5), 5.07 (1 H, t, *J* 3.1, 6-H), 4.16 (1 H, dd, *J* 6.9 and 9.7, 7a-H), 3.29 (1 H, t, *J* 8.3, 4-H), 3.07 (1 H, dd, *J* 3.1 and 9.7, 7-H), 2.70–2.92 (1 H, m, 3a-H), 2.51–2.66 (2 H, m, 3-H_2) and 1.96 and 2.05 (each 3 H, s, Ac); ν_{max}(KBr)/cm^{-1} 1750, 1735 and 1700; *m*/*z* 531 (M^+); HRMS (Found: M^+, 531.0827. $C_{25}H_{25}NO_7Se$ requires M, 531.0794).

(5*S,6*S**,7*S**,7a*S**)-7-(3′,4′-Methylenedioxyphenyl)-2-oxo-5,6,7,7a-tetrahydroindoline-5,6-diyl diacetate 33**

A solution of selenide **32** (0.0252 g, 0.048 mmol) and $NaIO_4$ (0.0203 g, 0.095 mmol) in a mixture of THF (1.3 cm^3), MeOH (0.7 cm^3), and water (0.3 cm^3) was stirred at room temperature for 30 min and at 40 °C for 3 h. The precipitate was filtered off and the filtrate was treated in the usual way and gave a residue, which was purified by PLC with (10:1) AcOEt–hexane as developing solvent to furnish *compound* **33** (0.0156 g, 87.9%), mp 206–208 °C (from $CHCl_3$–hexane); δ_H 6.60–6.82 (3 H, m, ArH × 3), 5.95 (2 H, s, OCH_2O), 5.64 (1 H, br s, $w_{\frac{1}{2}}$ 8, 5- or 6-H), 5.46 (1 H, br s, $W_{\frac{1}{2}}$ 4.8, 6- or 5-H), 5.08–5.24 (2 H, m, 4-H and NH), 4.64 (1 H, br d, *J* 11.4, 7a-H), 3.00–3.47 (2 H, m, 3-H_2), 2.89 (1 H, dd, *J* 2 and 11.4, 7-H) and 2.05 and 2.12 (each 3 H, s, Ac); ν_{max}(KBr)/cm^{-1} 1745, 1720 and 1695; *m*/*z* 373 (M^+); HRMS (Found: M^+, 373.1154. $C_{19}H_{19}NO_7$ requires M, 373.1159).

(1*S,2*R**,3*R**)-Di-*o*-acetyl-3-phenylselanyldihydrolycorin-5-one 34**

A solution of γ-lactam **32** (0.019 g, 0.036 mmol), 35% formalin (0.1 cm^3), and saturated aq. Na_2CO_3 (0.02 cm^3) in THF (1 cm^3) was stirred at room temperature for 2 h. Then, saturated aq. NH_4Cl was added to the mixture, which was extracted with CH_2Cl_2. The residue (0.0203 g) obtained by the usual work-up of the organic phase was treated with TFA (0.2 cm^3) in CH_2Cl_2 (2 cm^3) at room temperature for 15 min under stirring. After addition of water, the product was taken up in $CHCl_3$. Usual work-up of the organic phase gave a residue, which was purified by PLC with (50:1) $CHCl_3$–MeOH as developing solvent to furnish *pentacycle* **34** (0.0154 g, 79.4%), mp 256–257.5 °C; δ_H 7.44–7.64 (2 H, m, ArH × 2), 7.22–7.38 (3 H, m, ArH × 3), 6.28 and 6.35 (each 1 H, s, 8- and 11-H), 5.89 (2 H, s, OCH_2O), 5.74 (1 H, t, *J* 3.1, 1-H), 5.18 (1 H, dd, *J* 3.1 and 9.7, 2-H), 4.92 and 4.15 (each 1 H, d, *J* 17.1, 7-H_2), 3.81 (1 H, dd, *J* 8.3 and 12, 11c-H), 3.30 (1 H, t, *J* 9.7, 3-H), 3.10 (1 H, dd, *J* 3.1 and 12, 11b-H), 2.22–2.94 (3 H, m, 3a-H and 4-H_2) and 1.96 and 2.06 (each 3 H, s, Ac); ν_{max}/cm^{-1} 1745 and 1685; *m*/*z* 543 (M^+); HRMS (Found: M^+, 543.0812. $C_{26}H_{25}NO_7Se$ requires M, 543.0794).

(±)-Di-*o*-acetyllycorin-5-one 35

To a stirred solution of selenide **34** (0.0079 g, 0.015 mmol) in a mixture of THF (0.4 cm^3) and MeOH (0.21 cm^3) was added aq. $NaIO_4$ (0.0078 g, 0.036 mmol in 0.09 cm^3). After being stirred at 40 °C for 2 h, AcOEt was added. The filtrate obtained by removal of the precipitate was treated with the usual manner and gave a residue, which was purified by PLC with (50:1) $CHCl_3$–MeOH as developing solvent to furnish title compound **35** (0.0032 g, 57.0%), mp 242–244 °C (lit.,[4d] 244–245 °C); δ_H(500 MHz) 6.67 and 6.68 (each 1 H, s, together 8- and 11-H), 5.89 (2 H, s, OCH_2O), 5.80 (1 H, br s, $w_{\frac{1}{2}}$ 5.3, 1-H), 5.60–5.63 (1 H, m, 3-H), 5.29–5.32 (1 H, m, 2-H), 4.44 and 4.76 (each 1 H, d, *J* 17, together 7-H_2), 4.14 (1 H, d, *J* 10.2, 11c-H), 3.12 and 3.38 (each 1 H, dd, *J* 19.3, together 4-H_2), 2.82 (1 H, d, *J* 10.2, 11b-H) and 2.01 and 2.11 (each 3 H, s, Ac); ν_{max}/cm^{-1} 1745, 1705 and 1685; *m*/*z* 385 (M^+): HRMS (Found: M^+, 385.1164. Calc. for $C_{20}H_{19}NO_7$; M, 385.1160). The ^1H NMR spectrum of compound **35** was identical with that[4d] of an authentic specimen.

(1*S,2*R**,3*R**)-3-Phenylselanyldihydrolycorine 36**

A solution of γ-lactam **32** (0.0403 g, 0.086 mmol) and Vitride® (0.1 cm^3, 0.32 mmol) in toluene (2 cm^3) was refluxed for 30 min. The reaction mixture was quenched with 3 mol dm^{-3} NaOH (0.05 cm^3) and water. The aqueous phase was extracted with $CHCl_3$. The extract was dried (K_2CO_3), and evaporated to give an amine (0.0336 g). After a mixture of the amine (0.0329 g) and Eschenmoser's salt (0.047 g, 0.25 mmol) in THF (5 cm^3) had been refluxed for 1 h, 3 mol dm^{-3} NaOH (0.1 cm^3) and water were added. The mixture was extracted with AcOEt. Work-up of the organic phase as usual gave a residue, which was purified by PLC with (8:1) $CHCl_3$–MeOH as developing solvent to afford title diol **36** (0.0164 g, 43.5%), mp 99–100 °C; δ_H($CDCl_3$–CD_3OD) *inter alia* 7.48–7.76 (2 H, m, ArH × 2), 7.12–7.38 (3 H, m, ArH × 3), 6.52 and 6.78 (each 1 H, s, together 8- and 11-H) and 5.88 (2 H, s, OCH_2O); ν_{max}/cm^{-1} 3200–3625 and 1680; *m*/*z* 445 (M^+); HRMS (Found: M^+, 445.0804. $C_{22}H_{23}NO_4Se$ requires M, 445.0791).

(±)-Di-*o*-acetyllycorine 37

A solution of selenide **36** (0.0248 g, 0.056 mmol) and $NaIO_4$ (0.0274 g, 0.128 mmol) in a mixture of THF (1 cm^3), water (0.5 cm^3), and MeOH (1 cm^3) was stirred at 40 °C for 10 min. Water was added and the product was taken up in AcOEt. Treatment of the organic phase as usual gave (±)-lycorine **1** (0.0138 g, 86.3%).

The reaction of lycorine **1** with Ac_2O (0.06 cm^3) in pyridine (0.2 cm^3) at room temperature for 24 h and usual work-up gave a residue, PLC of which with (50:1) $CHCl_3$–MeOH as developing solvent furnished title diacetate **37** (0.0085 g, 41.1% from **36**), mp 216–217 °C (lit.,[4d] 217–218 °C); δ_H(500 MHz) 6.74 and 6.58 (each 1 H, s, together 8- and 11-H), 5.92 (2 H, s, OCH_2O), 5.74 (1 H, br s, $w_{\frac{1}{2}}$ 4.6, 1-H), 5.54 (1 H, br s, $w_{\frac{1}{2}}$ 7.6, 3-H), 5.25 (1 H, br s, $w_{\frac{1}{2}}$ 6.5, 2-H), 4.15 and 3.56 (each 1 H, d, *J* 13.5, together 7-H_2), 3.37 (1 H, br s, $w_{\frac{1}{2}}$ 18.9, 11c-H), 2.89 (1 H, d, *J* 10.5, 11b-H), 2.81 (1 H, br s, $w_{\frac{1}{2}}$ 27.4, 4- or 5-H), 2.66 (2 H, br s, $w_{\frac{1}{2}}$ 17.9, 2 × 4- or 5-H), 2.41 (1 H, br s, $w_{\frac{1}{2}}$ 31.6, 4- or 5-H) and 2.08 and 1.95 (each 3 H, s, Ac); ν_{max}/cm^{-1} 1740; *m*/*z* 371 (M^+); HRMS (Found: M^+, 371.1398. Calc. for $C_{20}H_{21}NO_6$: M, 371.1401). (±)-Di-*o*-acetyllycorine **37** was identical in all respects with (−)-di-*o*-acetyllycorine.

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