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Total Synthesis of (±)-α-Lycorane and 4,5-Dehydroanhydrolycorine

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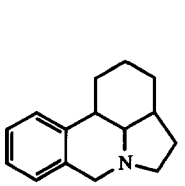
Summary: The total syntheses of (±)-α-lycorane and dehydroanhydrolycorine are described. The key intermediate in both approaches is the hydroindolone **5**, prepared from the [1+4] cycloaddition reaction of 1-isocyanatocyclohexene and cyclohexyl isocyanide. Alkylation of **5** with arylbromide **6** afforded **7**. Hydrolysis of enamide **7** followed by reduction of the resultant enol yielded **10** as a single diastereomer. Radical-based cyclization of this intermediate gave **11** possessing the requisite *trans*-fusion between rings B and C in good yield. Radical deoxygenation followed by reduction of the amide carbonyl function afforded (±)-α-lycorane. Similarly, alkylation of **5** with 6-(chloromethyl)-5-iodo-1,3-benzodioxole gave **14**. Treatment of **14** with $Pd(OAc)_2$ employing the Jeffery modification of the Heck reaction gave tetracycle **9**. Hydrolysis of **9** followed by oxidation with DDQ afforded **15**. Reduction of the two carbonyl functions in this material using lithium aluminum hydride afforded 4-hydroxyanhydrolycorine (**16**). Mesylation of the hydroxyl group led to rapid, spontaneous elimination producing anhydrodehydrolycorine.

The Amaryllidaceae alkaloids are a widely distributed and structurally diverse class of naturally occurring bases.[1] Compounds from this group possessing the tetracyclic galanthan ring system **1**, such as lycorine (**2**), continue to elicit considerable synthetic effort.[2] Much of this continuing interest can be



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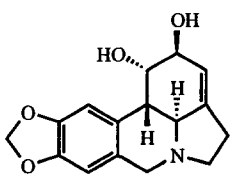

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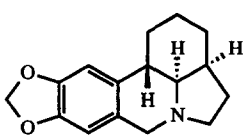

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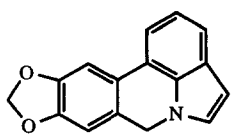

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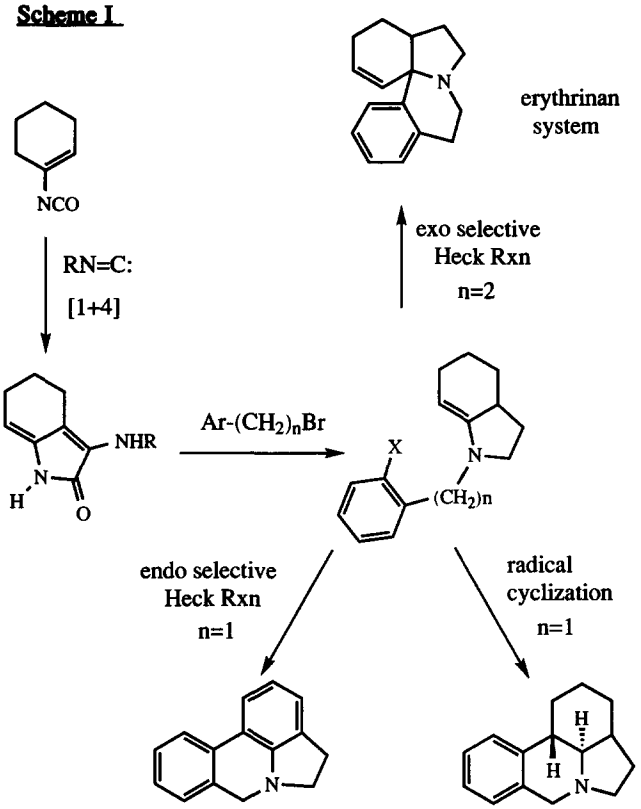
traced to the utility of ring system **1** as a proving ground for new synthetic methodology. In this vein, we have recently developed approaches for the construction of the galanthan ring system based on radical[3a,b] and Pd(0)-mediated[3d] cyclizations onto functionalized hydroindoles.

Scheme I

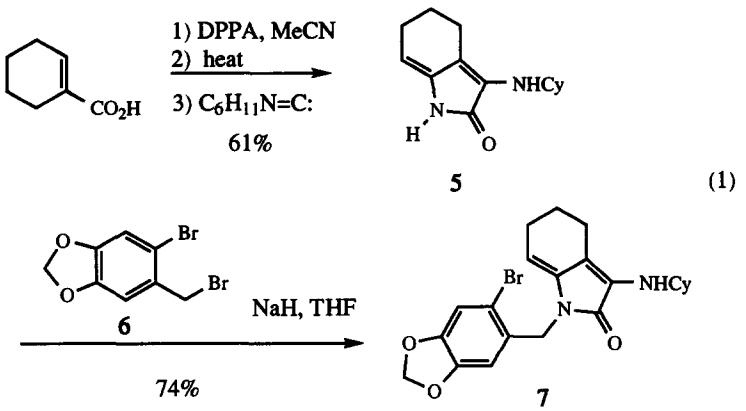


pyrrolophenanthridine system

The chemistry employed in these studies is based on a novel [1+4] cyclization between a vinyl isocyanate and an alkyl or aryl isocyanide that delivers a highly functionalized hydroindolone product.[3a] These intermediates, after tethering to appropriate aryl halide units, can be viewed as useful building blocks from which to assemble a range of alkaloid ring systems. An attractive feature of this methodology is that only minor modifications in tether length and reaction conditions could afford either the lycorane (galanthan)[2] or erythrinan[4] ring systems from essentially a common starting material (Scheme I). This aspect of the sequence has previously been brought to practice in model systems.[3] We now report the total syntheses of the amaryllidaceae alkaloids α-lycorane (**3**)[5] and dehydroanhydrolycorine (**4**)[6] employing radical and Pd(0)-based cyclizations, respectively, from hydroindolone precursors.

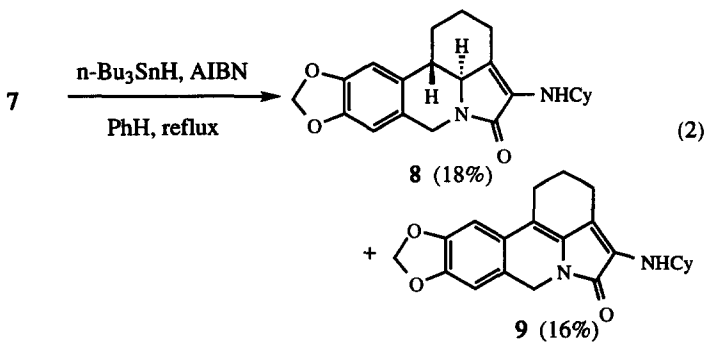
Results and Discussion

The synthesis of (±)-α-lycorane begins with the highly functionalized hydroindolone **5**, which is readily available in large quantities from the reaction between *in situ* generated 1-isocyanatocyclohexene (prepared from the corresponding α,β-unsaturated carboxylic acid and diphenyl phosphorazidate (DPPA)) and cyclohexyl isocyanide as reported previously.[3a,c] Selective alkylation with dibromide **6**[7] at the enamide nitrogen afforded the key intermediate **7** in good yield (Eq. (1)). Acquisition of this species sets the stage for an aryl radical-based 6-endo cyclization to deliver the desired galanthan ring system.

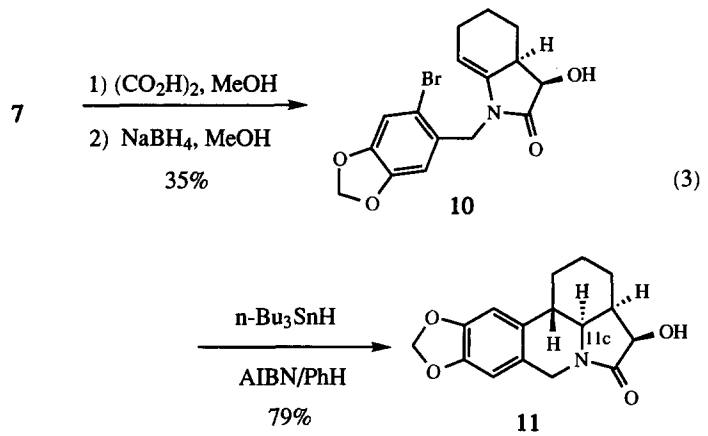


Cy=C_6H_{11}

Exposure of bromide **7** to n-Bu_3SnH in refluxing benzene in the presence of AIBN afforded the anticipated tetracyclic product **8** exhibiting the crucial trans BC ring fusion in moderate yield based on recovered starting material. This compound was accompanied by a lesser amount of the more highly unsaturated and vividly colored dienamide **9**.[8] Efforts to suppress the formation of **9** by simply changing reaction conditions proved futile, and our attention then turned to employing a functionally modified

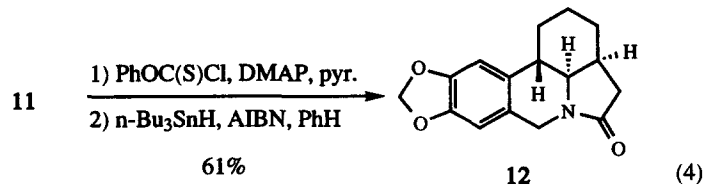


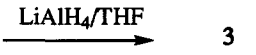
substrate for the key cyclization step. It was reasoned that the stability, and hence the lifetime, of the post-cyclization radical involved in the reaction of compound **7** may be an important contributing factor to the production of **9** at the expense of the reduced species and that altering the extent of conjugation in the enamide segment of the substrate would improve the efficiency of the desired reaction pathway. While appealing at one level, this potential solution raised concerns about the stereochemical course of the H-atom abstraction step by the reactive post-cyclization radical, since direct production of the trans BC ring fusion is an important aspect of this approach into these alkaloids.



(3)

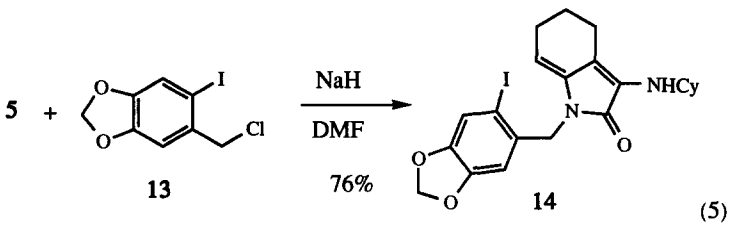
In the event, careful hydrolysis of the enamine function with oxalic acid followed by sodium borohydride reduction of the resultant keto-lactam afforded the corresponding α-hydroxylactam **10** in good overall yield and as a single diastereomer. While not necessarily pertinent to achieving our final synthetic objective, the relative stereochemistry of this material was assigned as shown in equation (3) based on coupling constant comparisons with a closely related hydroindolone system.[9] To our delight, reacting **10** under standard radical cyclization conditions as before yielded the desired galanthan product in 79% yield as a single diastereomer. The presence of the requisite trans-BC/cis-CD ring fusions in **11** was supported by the coupling constants observed for H_{11c} (J = 7.5, 10.5 Hz). The remote stereoinduction seen during the course of this reaction is also noteworthy. Presumably the extant stereogenic centers in **10** served to mediate facial selectivity at the enamide center in the cyclization event, since only one isomer of product was obtained. Models suggest that the α-face of the enamide double bond in compound **10** is sterically more accessible than the corresponding β-face, giving rise to the stereochemical arrangement observed in the product. The important issue of face selectivity during radical cyclization in these ring systems has received relatively little attention to date.[2e,10]

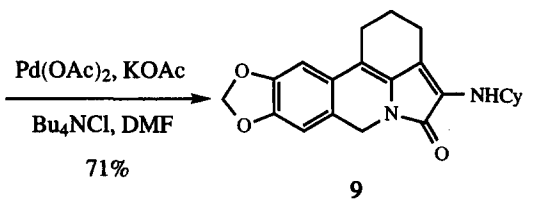




The synthesis of α-lycorane was completed by radical-mediated reductive deoxygenation of the D-ring hydroxyl group,[11] followed by lactam carbonyl group reduction with lithium aluminum hydride under standard conditions.[5a,12] The synthetic (±)-α-lycorane (**3**) exhibited melting point and ^{1}H NMR data identical to those described in the literature for the racemic material.[5]

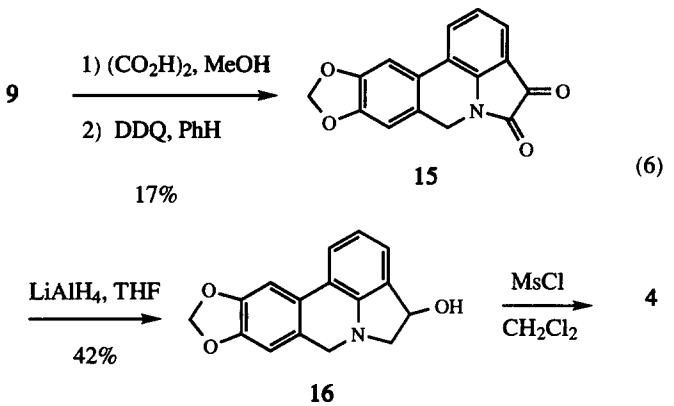
An approach complementary to the one described above was envisioned for producing the more fully unsaturated target 4,5-dehydroanhydrolycorine (**4**) from the same precursor. In this case we wished to exploit our recently described endo-selective Heck cyclization as the key B-ring assembly step.[3d] Previous experience indicated that the corresponding aryl iodide intermediate would be required for successful Pd(0)-promoted cyclization in this system.[3a] As a consequence, this synthesis commenced with the routine coupling of hydroindolone **5** with the known chloro-iodide **13**[13] to afford the requisite





cyclization precursor **14** in 76% yield. Treatment of this substrate under Pd(0)-mediated reaction conditions as originally described by Jeffery[14] afforded compound **9** in 71% isolated yield. Interestingly, this material is identical to the minor product obtained from the attempted radical cyclization of bromide **7**

(Eq. (2)). As described previously these modified Heck reaction conditions are known to provide endo-cyclization products exclusively in systems derived from hydroindolone **5**.[3d] In this instance, and in contrast to our needs in the previous investigation, the resultant extended dienamide in compound **9** was viewed as a convenient precursor to the C-aromatic ring portion of the target molecule. Toward that end the enamine function in **9** was hydrolyzed and the resultant dienol was dehydrogenated with DDQ to afford the C-aromatic intermediate **15** in modest, but serviceable yield. This dicarbonyl species was immediately taken on to the next step of the synthesis without thorough purification (Eq. (6)). Preparation



of the target molecule from this intermediate was finalized by routine amide reduction to give the hydroxyl species **16**, which has itself been isolated from natural sources,[15] followed by elimination of the hydroxyl group via the corresponding mesylate. The synthetic material exhibited melting point and ^1H NMR data identical to those reported for the authentic material.[6]

Acknowledgment: The authors wish to thank the National Science Foundation for their generous support of this research.

Experimental Section[16]

3-(Cyclohexylamino)-1,4,5,6-tetrahydro-2*H*-indol-2-one (5). To a well-stirred solution of cyclohexene-1-carboxylic acid (6.35 g; 60 mmol) in toluene (5 mL) was added Et_3N (5.0 g; (7 mL); 50 mmol) at room temperature. The resulting colorless solution was stirred for 20 min at which point it was cooled to 0 °C. To this solution was added diphenyl phosphorazidate (DPPA) (13.8 g; (11 mL); 50 mmol) neat over 20 min. The resulting green solution became blue as it was stirred at room temperature for 45 min. At this time the solution was applied directly to a silica gel column and eluted with 10:1 pentane:Et_2O to give a pale yellow liquid after removal of solvent *in vacuo*. This material was taken up in CH_3CN (500 mL) and to this solution was added in one portion cyclohexyl isocyanide (21.9 g; 217 mmol). The

resulting solution was heated at reflux for 3 h producing a bright yellow solution, which was then cooled to room temperature. The solvent was removed *in vacuo* to produce a yellow-green solid. Chromatography (6:1, Hexane EtOAc) yielded a yellow solid (8.52 g; 63%): mp. 144-145 °C (CH_3CN). IR (NaCl) υ 3373, 1682, 1663 cm^{-1}; ^1H NMR (300 MHz) δ 1.90-1.33 (m, 5H), 1.61 (m, 1H), 1.72 -1.81 (m, 4H), 1.95 (m, 2H), 2.24 (q, J = 5.4 Hz, 2H), 2.60 (dd, J = 6.0, 6.0 Hz, 2H), 3.29 (m, 1H), 3.94 (d, J = 9.3 Hz, 1H), exchangeable), 5.32 (t, J = 4.5 Hz, 1H), 7.73 (s, 1H), exchangeable); ^{13}C NMR (75 MHz) δ 22.5, 23.7, 23.8, 24.7, 25.7, 34.3, 52.1, 104.5, 106.5, 130.4, 136.6, 168.4; MS [m/e (rel. int.)] 232 (100), 189 (64), 150 (98). Anal. calcd. for $C_{14}H_{20}N_2O$: C, 72.39; H, 8.67; N, 12.06. Found: C, 72.38; H, 8.61; N, 12.09.

1-(2-Bromo-4,5-methylenedioxybenzyl)-3-cyclohexylamino-4,5,6-trihydro-1*H*-indol-2-one (7). NaH (0.34 g; 8.5 mmol) was washed with 3 x 50 mL portions of pentane and dried under a stream of N_2, and DMF (30 mL) was then added. To the resulting suspension at room temperature was added, over a 10 min period, a solution of **5** (1.70 g; 7.3 mmol) in DMF (10 mL). The resulting red solution was allowed to stir for 25 min at which time a solution of **6** (2.54 g, 8.5 mmol) in DMF (10 mL) was added over 5 min. The resulting mixture was stirred for 45 min and poured onto ice-water (100 mL). This was extracted with EtOAc (3 x 100 mL) and the combined organic layers were washed with water (3 x 100 mL), brine (1 x 100 mL) and dried over anhydrous $MgSO_4$. Evaporation of the solvent *in vacuo* produced a yellow solid (3.94 g). Recrystallization from CH_3CN gave yellow crystals of **7** (2.39 g; 74% yield): mp 158-159 °C. IR (NaCl) υ 3327, 2926, 1685 cm^{-1}; ^1H NMR (300 MHz) δ 1.11-1.36 (m, 5H), 1.62 (m, 1H), 1.73-1.81 (m, 4H), 1.98 (m, 2H), 2.20 (q, J = 5.4 Hz, 2H), 2.62 (dd, J = 6.0, 6.0 Hz, 2H), 3.33 (m, 1H), 4.04 (br, s, 1H, exchangeable), 4.72 (s, 2H), 5.19 (t, J = 4.5 Hz, 1H), 5.91 (s, 2H), 6.48 (s, 1H), 6.96 (2, 1H); ^{13}C NMR (75 MHz) δ 22.5, 23.6, 24.7, 25.7, 34.3, 42.7, 52.2, 101.6, 103.5, 105.2, 107.9, 112.1, 112.4, 129.7, 129.9, 138.4, 147.3, 147.6, 166.9; MS [m/z (rel. int.)] 446 (10), 444 (M^+, 10), 365 (100), 283 (37), 255 (8); HRMS calcd. for $C_{22}H_{25}BrN_2O_3$: 444.1048. Found: 444.1054. Anal. calcd. for $C_{22}H_{25}BrN_2O_3$: C, 59.34; H, 5.66; N, 6.29. Found: C, 59.28; H, 5.67; N, 6.33.

4-(Cyclohexylamino)-9,10-(methylenedioxy)-[11b-(11bβ,11cα)]-2,3,7,11b,11c-pentahydro-1*H*-pyrrolo-[3,2,1-d,e]phenanthridin-5-one (8) and 4-(cyclohexylamino)-9,10-(methylenedioxy)-2,3,7-trihydro-1*H*-pyrrolo-[3,2,1-d,3]-phenanthridin-5-one (9). To a refluxing solution of **7** (200 mg; 0.45 mmol) and AIBN (11 mg; 0.06 mmol) in benzene (22.5 mL) was added slowly under N_2 a solution of n-Bu_3SnH (194.8 mg; 0.68 mmol) in benzene (1.5 mL). The resulting solution was heated at reflux for 16.5 h at which time the solvent was removed *in vacuo*. The residue was taken up in Et_2O (30 mL) and to this solution was added 60% aq. KF (30 mL). The mixture was stirred for 6 h, filtered and the residue washed with several portions of Et_2O. The combined washing

and filtrate were transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organics were washed with H_2O (3 x 50 mL), brine (1 x 50 mL) and dried over anhydrous $MgSO_4$ to obtain after solvent removal *in vacuo* a yellow oil. Chromatography (4:1 Hexanes:EtOAc) afforded recovered sm (129 mg), **8** (28.9 mg; 18%) and **9** (26.7 mg; 16%) **8**: mp 188-190 °C (MeOH/Et_2O). IR (NaCl) ν 3391, 1691 cm^{-1}; ^1H NMR (500 MHz) δ 1.08-1.42 (m, 5H), 1.48-1.77 (m, 5H), 1.98-2.12 (m, 4H), 2.24 (dt, J = 13.5, 5.0 Hz, 1H), 2.36 (dd, J = 13.0, 3.5 Hz, 1H), 2.86 (dd, J = 13.5, 3.5 Hz, 1H), 3.13 (d, J = 10.5 Hz, 1H), 3.24 (m, 1H), 3.80 (bs, 1H, exchangeable), 4.47 (d, J = 16.5 Hz, 1H), 4.81 (d, J = 16.5 Hz, 1H), 5.94 (m, 2H), 6.67 (s, 1H), 6.74 (s, 1H); ^{13}C NMR (125 MHz) δ 22.5, 24.9, 25.0, 25.9, 26.2, 27.0, 33.6, 33.8, 43.4, 44.8, 52.4, 60.5, 101.1, 104.6, 107.3, 115.7, 125.4, 130.2, 130.9, 146.3, 146.8, 168.4; Ms [m/e (rel. int.)] 366 (M^+, 44), 338 (10), 283 (12), 255 (21), 229 (21), 41 (100). HRMS calcd. for $C_{22}H_{26}N_2O_3$: 366.1943. Found: 366.1954.

9: Mp 204-205 °C (CH_3CN). IR (NaCl) ν 3371, 1675 cm^{-1}; ^1H NMR (500 MHz) δ 1.14-1.25 (m, 3H), 1.29-1.37 (m, 2H), 1.63 (dt, J = 13.0, 4.0 Hz, 1H), 1.76 (dt, J = 14.0, 4.0 Hz, 2H), 1.94-2.20 (m, 4H), 2.47 (t, J = 6.0 Hz, 2H), 2.65 (t, J = 6.0 Hz, 2H), 3.33 (m, 1H), 4.14 (bs, 1H, exchangeable), 4.73 (s, 2H), 5.94 (s, 2H), 6.61 (s, 1H), 6.73 (s, 1H); ^{13}C NMR (125 MHz) δ 21.9, 22.6, 23.6, 24.8, 25.7, 34.3, 42.6, 52.3, 101.2, 102.5, 102.6, 107.5, 110.0, 123.5, 126.3, 103.5, 132.8, 145.8, 147.1, 165.7; Ms [m/e (rel. int.)] 364 (M^+, 100), 282 (19), 281 (36). HRMS calcd. for $C_{22}H_{24}N_2O_3$: 364.1787. Found: 364.1794. Anal. calcd. for $C_{22}H_{24}N_2O_3$: C, 72.51; H, 6.64; N, 7.69. Found: C, 72.39; H, 7.03; N, 7.66.

1-(2-Bromo-4,5-methylenedioxybenzyl)-3-hydroxy-3,4,5,6-tetrahydro-1*H*-indol-2-one (10). To a stirred solution of **7** (1.61 g; 3.6 mmol) in THF (72 mL) was added a solution of oxalic acid (4.53 g; 36 mmol) in water (28 mL). The resulting solution was heated at reflux for 22 h. At this time, the solvent was evaporated *in vacuo* and the resulting suspension was diluted with water (30 mL) and the precipitated solids filtered to give 0.92 g of an off-white solid. Cooling of the filtrate gave a second crop of an off-white solid (0.46 g). Recrystallization from MeOH of the combined solids gave the product as a white crystalline solid (0.92 g; 70%): mp 248-250 °C. IR υ 3110, 1690, 1679 cm^{-1}. ^1H NMR (300 MHz), 1.78 (t, J = 6.0 Hz, 2H), 2.27 (d, J = 4.8 Hz, 1H), 2.58 (t, J = 6.0 Hz, 2H), 4.77 (s, 2H), 5.50 (t, J = 4.8 Hz, 1H), 5.95 (s, 2H), 6.23 (s, br, 1H), 6.50 (s, 1H), 6.99 (s, 1H); ^{13}C NMR 21.2, 22.0, 40.5, 100.2, 104.4, 105.8, 110.0, 110.5, 112.0, 128.0, 134.7, 136.0, 138.2, 145.8, 146.1, 163.6. Anal calcd. for $C_{16}H_{14}BrNO_4$: C, 52.77; H, 3.87; N, 3.85. Found: C, 52.56; H, 4.11; N, 3.88.

To a well-stirred suspension of the product from the above reaction (0.92 g, 2.5 mmol) in MeOH (15 mL) was added in one portion, $NaBH_4$ (0.96 g; 25.3 mmol) at 0 °C. The resulting suspension was stirred at room temperature for 5 days adding additional $NaBH_4$ (0.1 g; 2.6 mmol) each day. After this time

the solvent was removed *in vacuo* and the residue taken up in EtOAc (100 mL). This solution was washed with water (3x100 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated *in vacuo* to obtain a white solid. Chromatography (6:1 / 4:1 hexanes:EtOAc) gave starting material (0.07 g) and **10** (0.43 g; 46%): mp 183-184 °C (EtOAc/hexanes) IR (NaCl) υ 3375, 2920, 1682 cm^{-1}; ^1H NMR 1.41 (dq, J = 11.5 Hz, 2.5 Hz, 1H), 1.46-1.55 (m, 1H), 1.90 (gd, J = 10.0, 3.5 Hz, 1H), 1.99-2.15 (m, 2H), 2.27-2.31 (m, 1H), 2.63-2.70 (m, 1H), 3.88 (s, br, 1H, exchangeable), 4.16 (d, J = 9.0 Hz, 1H), 4.58 (d, J = 16.0 Hz, 1H), 4.70 (d, J = 16.0 Hz, 1H), 4.88 (dd, J = 4.0, 2.5 Hz, 1H), 5.95 (s, 2H), 6.53 (s, 1 H), 6.97 (s, 1H); ^{13}C NMR (125 MHz) 21.7, 23.2, 26.3, 43.4, 43.6, 74.6, 100.8, 101.8, 101.9, 107.6, 112.6, 113.0, 127.8, 136.5, 147.7, 147.1, 175.4; MS [m/e (rel. int.)] 367 (2), 365 (2), 286 (100), 215 (42), 213 (46). HRMS calcd. for $C_{16}H_{16}BrNO_4$: 365.0263. Found: 365.0275. Anal. calcd. for $C_{16}H_{16}BrNO_4$: C. 52.47; H, 4.40, N, 3.82. Found: C, 52.49; H, 4.40; N, 3.86.

4-Hydroxy-9,10-(methylenedioxy)-[3a-(3aα,11bβ,11cα)]-2,3,3a,4,5,7,11b,11c-octahydro-1*H*-pyrrolo[3,2,1-d,e]phenanthridin-5-one (11). To a refluxing solution of **10** (71.3 mg; 0.19 mmol) and AIBN (5.0 mg; 0.03 mmol) in benzene (3 mL) was added over 2 h a solution of Bu_3SnH (96.3 mg; 0.33 mmol) in benzene (1 mL). The resulting solution was heated at reflux for 4.5 h at which time the solvent was removed *in vacuo*. The residue was taken up in EtOAc (15 mL) and to this solution was added 60% aq. KF (10 mL). This mixture was stirred overnight, filtered and the residue washed with several portions of EtOAc. The combined washings and filtrate were transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics were washed with water (3 x 50 mL), brine (1 x 50 mL) and dried over anhydrous $MgSO_4$ to obtain a yellow solid after removal of solvent *in vacuo*. Chromatography (6:1 hexanes:EtOAc) afforded recovered starting material (18.1 mg) and **11** (43 mg; 79%) as a white solid: mp 226-227 °C (MeOH). IR (NaCl) υ 3322, 2928, 1677, 1483 cm^{-1}; ^1H NMR (500 MHz) δ 1.16-1.22 (m, 1H), 1.55-1.60 (m, 1H), 1.79-1.89 (m, 2H), 2.10-2.30 (m, 3H), 2.46-2.51 (m, 1H), 3.19 (dd, J = 10.5, 7.5 Hz, 1H), 3.85 (s, br, 1H), 4.21 (d, J = 10.5 Hz, 1H), 4.30 (d, J = 17.0 Hz, 1H), 4.92 (d, J = 17.0 Hz, 1H), 5.92 (dd, J = 4.5, 1.5 Hz, 2H), 6.59 (s, 1H), 6.68 (s, 1H); ^{13}C NMR (125 MHz) 21.7, 23.7, 24.8, 39.3, 40.8, 43.9, 56.7, 72.3, 101.1, 104.8, 106.7, 124.9, 131.8, 146.4, 146.6, 174.7; MS [m/e (rel. int.)] 287 (46), 226 (100); HRMS calcd. for $C_{16}H_{17}NO_4$: 287.1158. Found: 287.1152. Anal. calcd. for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.87. Found: C, 66.71; H, 6.04; N, 4.84.

9,10-(Methylenedioxy)-[3a-(3aα,11bβ,11cα)]-2,3,3a,4,5,7,11b,11c-octahydro-1*H*-pyrrolo-[3,2,1-d,e]phenanthridin-5-one (12). To a well-stirred suspension of **11** (36.8 mg 0.15 mmol), DMAP (8.5 mg, 0.07 mmol), and pyridine (20.5 mg; 0.26 mmol) in dry CH_2Cl_2 (2 mL) was added in one portion phenyl chlorothionoformate (44.0 mg; 0.26 mmol). The resulting solution was stirred at room temperature for 6.5 h. The solvent was evaporated *in vacuo* and the residue was directly applied to a

silica gel column. Chromatography (4:1 hexanes:EtOAc) yielded the product (46.9 mg, 85%) as a white solid: mp 189-190 °C (EtOAc/hexanes). IR (NaCl) υ 2923, 1712, 1203 cm^{-1}; ^1H NMR (500 MHz) δ 1.20-1.28 (m, 1H), 1.71-1.90 (m, 3H), 2.16-2.20 (m, 1H), 2.30-2.33 (m, 1H), 2.42-2.47 (m, 1H), 2.74-2.84 (m, 1H), 3.29 (dd, 7 = 11.0, 8.0 Hz, 1H), 4.34 (d, J = 17.0 Hz, 1H), 5.00 (d, J = 17 Hz, 1H), 5.94 (dd, J = 4.5, 1.5 Hz, 2H), 6.15 (d, J = 10.0 Hz, 1H), 6.16 (5, 1H), 6.71 (5, 1H), 7.18-7.20 (m, 2H), 7.29-7.32 (m, 1H), 7.41-7.45 (m, 2 H); ^{13}C NMR (125 MHz) 21.4, 23.9, 24.5, 38.17, 40.7, 44.0, 56.4, 81.3, 101.1, 104.8, 106.6, 121.8, 124.7, 126.7, 129.5, 131.3, 146.5, 146.7, 153.6, 168.7, 195.9; MS [m/e (rel. int.)] 269 (100, M^+- $C_6H_5C(S)OH$), 240 (43), 224 (9), 94 (30), HRMS calcd for $C_{16}H_{15}NO_3$ (M^+-154.00954) : 269.10550. Found: 269.10461. Anal. calcd for $C_{23}H_{21}NO_5S$: C, 65.23; H, 5.00; N, 3.31. Found: C, 65.17; H, 5.04; N, 3.26.

To a well-stirred refluxing solution of thioformate prepared above (34.5 mg; 0.08 mmol) in benzene (8 mL) was added dropwise over 50 min, a solution of AIBN (3.5 mg; 0.02 mmol) and n-Bu_3SnH (32.5 mg; 0.10 mmol) in benzene (1 mL). The resulting solution was heated at reflux for an additional 22 h. The solvent was removed *in vacuo* and the residue was directly applied to a column fitted with KF plug on top of the silica gel. Elution with 6:1 hexanes:EtOAc gave **12** as a white solid (15.6 mg; 72%): mp 155-156 °C (EtOAc/hexanes) [lit.[5a,f,11] mp 153-154 °C (acetone)]. IR (NaCl) υ 2927, 1689 cm^{-1}; ^1H NMR (500 MHz) δ 1.16-1.25 (m, 1H), 1.58-1.65 (m, 1H), 1.72-1.80 (m, 3H), 2.21-2.27 (m, 2H), 2.41 (dt, J = 11.5, 3.5 Hz, 2H), 2.50 (dd, J = 17.0, 9.0 Hz, 1H), 2.61-2.67 (m, 1H), 3.21 (dd, J = 10.5, 7.5 Hz, 1H), 4.19 (d, J = 17.10 Hz, 1H), 4.97 (d, J = 17.0 Hz, 1H), 5.91-5.93 (m, 2H), 6.59 (s, 1H), 6.69 (s, 1H); ^{13}C NMR (125 MHz) 21.0, 24.2, 25.5, 30.7, 35.2, 38.1, 43.3, 59.7, 100.9, 104.9, 106.6, 125.4, 132.1, 146.2, 146.4, 175.2; MS [m/e (rel. int.)] 2H (100, M^+), 270 (75), 43 (12). HRMS calcd. for $C_{16}H_{17}NO_3$: 271.1208. Found: 271.1203.

(±)-α-Lycorane (3) The synthesis of **3** was completed employing previously reported procedures[5a,c] compound **12** (10.4 mg; 0.04 mmol), $LiAlH_4$ (9.9 mg; 0.26 mmol) and THF (2 mL) afforded **3** (8.7 mg; 84%) as white solid. Recrystallization from Et_20/petroleum ether gave **3** as white prisms: mp 93-94 °C (lit.[5h,11] 93-94 °C, lit.[5c] 92-94 °C) IR (NaCl) υ 2923, 1481 cm^{-1}; ^1H NMR (500 MHz) 1.14-1.22 (m, 1H), 1.57-1.92 (m, 6H), 2.22-2.26 (m, 1H), 2.36-2.44 (m, 2H), 2.50 (dd, J = 10.5, 7.0 Hz, 1H), 2.84 (dt, J = 9.5, 3.0 Hz), 3.18 (dd, J = 18.0, 8.0 Hz, 1H), 3.76 (d, J = 15.5 Hz, 1H), 4.13 (d, J = 15.5 Hz, 1H), 5.90 (s, 2H), 6.60 (s, 1H), 6.70 (s, 1H), MS, m/e (rel. int.) 257 (35', M^+), 256 (100). HRMS Calcd. for $C_{16}H_{19}NO_2$: 257.1416. Found: 257.1409.

1-(2-Iodo-4,5-methylenedioxybenzyl)-3-cyclohexylamino-4,5,6-trihydro-1*H*-indol-2-one (14). To a suspension of NaH (0.73 g; 18.2 mmol) in DMF (50 mL) was added over 10 min a solution of **5** (3.02 g; 13.0 mmol) in DMF (15 mL) at room temperature. The resulting solution was stirred for 30 min at which time a solution of **13** (4.14 g; 13.0 mmol) in DMF (15 mL) was added over 5 min at room

temperature. The mixture was stirred for 2.5 h. Water (200 mL) was added and the suspension extracted with Et_2O (3 x 200 mL). The combined organic layers were washed with water (3 x 100 mL), brine (1 x 100 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated *in vacuo* to give a dark yellow solid. Recrystallization (CH_3CN) gave **14** (4.89 g; 76%) as yellow crystals: mp 169-170 °C. IR (NaCl) υ 3324, 2928, 1686 cm^{-1}; ^1H NMR (500 MHz) δ 1.15-1.25 (m, 3H), 1.29-1.37 (m, 2H), 1.63 (m, 1H), 1.78 (m, 4H), 1.99 (m, 2H), 2.21 (dd, J = 11.0, 6.0 Hz, 2H), 2.63 (t, J = 6.5 Hz, 2H), 3.33 (m, 1H), 4.10 (s, br, 1H), 4.65 (s, 2H), 5.15 (t, J = 5.0 Hz, 1H), 5.92 (s, 2H), 6.45 (s, 1H), 7.21 (s, 1H); ^{13}C NMR (125 MHz) 22.5, 23.6, 23.8, 24.8, 25.7, 34.4, 47.9, 52.3, 84.4, 101.6, 103.9, 107.8, 118.3, 129.7, 132.9, 138.4, 147.5, 148.8, 166.9; MS [m/e (rel. int.)] 492 (M^+, 5), 365 (100), 283 (74), 261 (36), 225 (24); HRMS calcd. for $C_{22}H_{25}IN_2O_3$: 492.0912. Found: 492.0903. Anal. calcd. for $C_{22}H_{25}N_2IO_3$: C, 53.67; H, 5.12; N, 5.69. Found: C, 53.98; H, 5.11; N, 5.95.

4-(Cyclohexylamino)-9,10-(methylenedioxy)-2,3,7-trihydro-1*H*-pyrrolo[3,2,1-d,e]-phenanthridin-5-one (9) *via* Pd(0)-mediated cyclization. To a suspension of **14** (3.01 g; 6.1 mmol), $Bu_4NCl•H_2O$ (3.61 g; 12.2 mmol), and KOAc (3.29 g, 33.6 mmol) in DMF (32 mL) was added in one portion $Pd(OAc)_2$ (136.9 mg; 0.6 mmol). The reaction mixture was heated to 100 °C and maintained at that temperature for 2 h. The resulting black mixture was poured onto water (50 mL) and this mixture was extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (2 x 100 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated *in vacuo* to provide an orange solid. Chromatography ($CHCl_3$) followed by recrystallization (EtOAc/hexanes) yielded **9** (1.58 g; 71%) as orange needles: mp 204-206 °C (CH_3CN). IR (NaCl) υ 3371, 3321, 2926, 1675 cm^{-1}; ^1H NMR (500 MHz) δ 1.14-1.37 (m, 5H), 1.63 (td, J = 13.0, 4.0 Hz, 1H), 1.76 (td, J = 14.0, 4.0 Hz, 2H), 1.94-2.00 (m, 4H), 2.47 (t, J = 6.0 Hz, 2H); 2.65 (t, J = 6.0 Hz, 2H), 3.33 (s, 1H), 4.14 (s, 1H), 4.73 (s, 2H), 5.94 (s, 2H), 6.61 (s, 1H), 6.73 (2, 1H); ^{13}C NMR (125 MHz) 21.9, 22.6, 23.6, 24.7, 24.9, 25.7, 34.2, 42.5, 52.3, 101.1, 102.5, 102.5, 107.4, 109.9, 123.5, 126.3, 130.5, 132.8, 147.8, 147.1; MS [m/e (rel. int.)] 267 (M^+, 100), 281 (36). HRMS calcd. for $C_{22}H_{24}N_2O_3$: 364.1787. Found: 364.1794. Anal. calcd. for $C_{22}H_{24}N_2O_3$: C, 72.51; H, 6.64; N, 7.69. Found: C, 72.39; H, 7.03; N, 7.66.

9,10-(Methylenedioxy)-7-hydropyrrolo[3,2,1-de]-phenanthridin-4,5-dione (15). To a stirred solution of **9** (1.57 g, 4.34 mmol) in THF (65 mL) was added a solution of oxalic acid (5.47 g, 43.4 mmol) in water (35 mL). The resulting solution was heated under reflux for 5 days producing a cloudy mixture. The excess solvent was evaporated *in vacuo* and the mixture diluted with water (150 mL). The precipitated solids were filtered to obtain a yellow solid. Recrystallization (EtOAc) gave pale yellow crystals of product (0.98 g; 80%): mp 256-258 °C. IR (NaCl) υ 3125, 2941, 1672 cm^{-1}; ^1H NMR 1.82 (apptt, J = 6.0 Hz, 2H), 2.44-2.49 (m, w/J = 6.0 Hz, 4H), 4.62 (s, 2H), 6.00 (s, 2H), 6.89

(s, 1H), 6.93 (s, 1H); ^{13}C 19.91, 22.48, 23.18, 42.45, 101.69, 103.40, 108.35, 111.55, 112.69, 124.97, 125.65, 130.68, 140.73, 147.21, 162.03, 164.29; MS [m/e (rel. int.)] 283 (78), 282 (100), 253 (19), 224 (23); HRMS calcd. for $C_{15}H_{13}NO_4$: 283.0844. Found: 283.0843. Anal. calcd. for $C_{16}H_{13}NO_4$: C, 67.88; H, 4.63; N, 4.95. Found: C, 67.71; H, 4.69; N, 4.93.

To a stirred suspension of the hydrolyzed product prepared above (0.67 g; 2.37 mmol) in benzene (30 mL) was added DDQ (1.18 g; 5.20 mmol). The resulting mixture was heated at reflux for 24 h. The suspension was filtered and the residue was washed with $CHCl_3$ (50 mL). The combined washings and filtrate were evaporated *in vacuo* and the residue taken up in $CHCl_3$ (100 mL). This was washed with 1% aqueous NaOH solution (5 x 100 mL), water (5 x 100 mL), dried over anhydrous $MgSO_4$ and evaporated *in vacuo* to afford a red solid. Passing this material though a plug of alumina (neutral) with 1:1 hexanes:EtOAc as eluent afforded **15** (0.14 g; 21%) as pale yellow solid: mp 186-186.5 °C (CH_3CN); IR (NaCl) υ 3325, 1780, 1670 cm^{-1}; ^1H NMR (500 MHz) 4.00 (s, 2H), 6.19 (s, 2H), 7.32 (s, 1H), 7.73 (t, J = 8.0 Hz, 1H), 7.87 (s, 1H), 8.23 (dd, J = 8.0, 1.5 Hz, 1H), 8.60 (dd, J = 8.0, 1.5 Hz, 1H); ^{13}C NMR (125 MHz) 52.7, 100.0, 102.2, 105.6, 123.1, 124.2, 126.4, 128.1, 129.7, 129.8, 132.4, 142.7, 148.8, 152.0, 165.7, 187.4. MS [m/e (rel. int.)] 250 (100), 222 (32), 164 (41).

4-Hydroxy-9,10-(methylenedioxy)-4,5,7-trihydropyrrolo[3,2,1-de]-phenanthridine (4-hydroxyanhydrolycorine) (16). To a well-stirred suspension of lithium aluminum hydride (127.7 mg, 3.36 mmol) in THF (6 mL) was added slowly a solution of **15** (69.8 mg; 0.25 mmol) in THF (6 mL) at room temperature. The resulting suspension was heated under reflux for 4.5 h, at which time it was cooled to room temperature. To this mixture was added dropwise water (2 mL), 10% aqueous NaOH solution (2 mL), then water (2 mL). The resulting suspension was stirred for 10 min then filtered through Celite. The residue was washed with EtOAc (50 mL). The combined filtrate and washings were dried over anhydrous $MgSO_4$ and the solvent removed *in vacuo* to give an orange solid. Chromatography (2:1/0:1 hexanes/EtOAc) gave **16** (28.5 mg; 42%) as a yellow solid: mp 165-167 °C (EtOAc/hexanes). IR (NaCl) υ 3290, 2900, 1603, 1490 cm^{-1}, ^1H NMR 2.96 (s, br, 1H), 3.86 (s, 2h), 3.87 (d, J = 7.0 Hz, 2H), 5.30 (dd, J = 7.0, 4.5 Hz, 1H), 6.14 (s, 2h), 7.28 (s, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.59 (d, J = 7.5 Hz, 1H), 7.85 (s, 1H); ^{13}C NMR (125 MHz) 67.5. 75.6. 100.1. 102.1. 105.5. 121.7. 122.5. 124.6. 126.5. 126.8. 130.7. 137.5. 141.8. 148.5. 149.9. 152.0. MS [m/e (rel. int.)] 178 (8), 144 (6).

Dehydroanhydrolycorine (4). To a well-stirred solution of **16** (25.9 mg; 0.1 mmol) in CH_2Cl_2 (2.5 mL) was added Et_3N (11.8 mg; 17 mL; 0.12 mmol) at 0 °C. The resulting solution was allowed to stir at 0 °C for 5 min at which time, MsCl (13.7 mg; 10 mL, 0.12 mmol) was added. The cloudy mixture was allowed to stir at room temperature for 15 min. The solvent was removed *in vacuo* to provide a yellow solid. Chromatography (6:1 hexanes:EtOAc) gave **4** (2.2 mg; 9%) as a white solid: mp 159-160 °C (MeOH) (lit.[6d] 159-161 °C; lit.[6b] 154-156°), ^1H NMR ($CDCl_3$, 500 MHz) δ 5.51 (s, 2H), 6.01 (s, 2H),

6.53 (d, J = 3.0 Hz, 1H), 6.65 (s, 1H), 7.05 (t, J = 8.0 Hz, 1H), 7.13 (d, J = 3.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.38 (s, 1H), 7.44 (d, J = 8.0 Hz, 1H).

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