A Short Synthesis of γ-Lycorane using Ni/AcOH Mediated Radical Cyclisation

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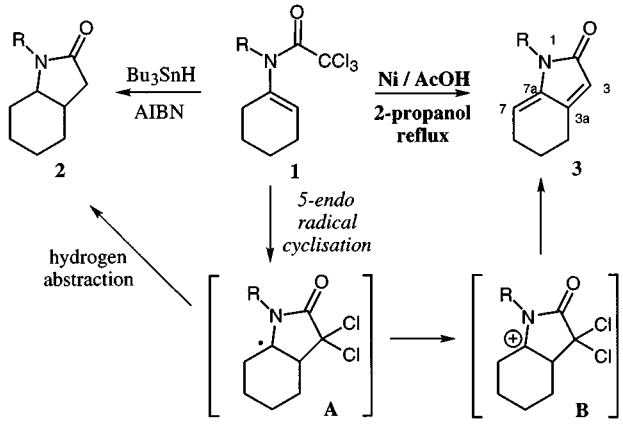
Abstract: A short synthesis of (±)-γ-lycorane **6** is described using two different radical cyclisations. The key step is the formation of tetrahydroindolone **9** by a nickel-promoted 5-endo radical cyclisation. This is followed by a tributylstannane-mediated 6-endo ring closure to the tetracyclic lactam **10** which is readily reduced to (±)-γ-lycorane **6**.

Key words: γ-lycorane, nickel, radical cyclisation

N-Alkenyl-trichloroacetamides **1** undergo unusual 5-*endo-trig* radical cyclisation when treated with Bu_3SnH and AIBN, affording saturated γ-lactams **2** (Scheme 1).[1] In contrast, we recently reported that unsaturated lactams **3** are formed when the same trichloroacetamides are treated with nickel powder and acetic acid in refluxing 2-propanol.[2] A 5-*endo* cyclisation of the radical derived from **1** is also involved, but the ensuing radical **A** is not reduced as in the Bu_3SnH-mediated cyclisation: a surprisingly easy oxidation occurs in this case giving the corresponding cation **B** which undergoes elimination, further reduction and a final elimination of HCl to give lactam **3**. This results in the one-step creation of a new carbon-carbon bond and the introduction of two double bonds.[3] The oxidation step is still not clear and occurs presumably via electron transfer to the starting trichloroacetamide **1** with the possible intervention of traces of cupric ions in the medium.



Scheme 1

A wide range of such tetrahydroindolones can therefore be obtained since the method is tolerant of many functional groups and requires simple starting materials. Moreover, the presence of the diene system in a structure such as **3** allows a great variety of further transformations. We have recently implemented this unusual radical chemistry in a short approach to *Erythrina* alkaloids[4] using an intramolecular Friedel-Crafts cyclisation between an electron-rich aromatic ring on the side chain R and the acyliminium arising from protonation of the diene moiety (connection at C-7a, indole numbering in compound **3**).[5] *Amaryllidaceae* alkaloids[6] are also ideal synthetic targets for our methodology. Ring closure at C-7 of the diene system using 6-*endo* radical cyclisation[7] or intramolecular Heck reaction[8] should allow the rapid construction of Lycorine-type alkaloids. On the other hand, connection at C-3 or C-3a could serve to construct Montanine-type or Crinane-type alkaloids.

Recently an asymmetric synthesis of (-)-γ-lycorane has been reported using a 5-*endo* radical cyclisation,[9] which prompts us to disclose our own results concerning the synthesis of this class of alkaloids.

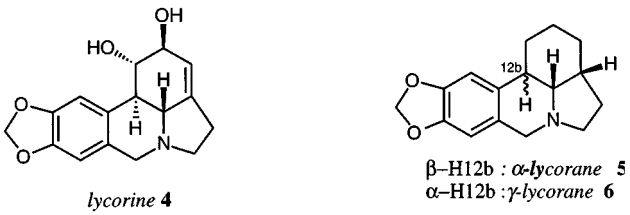
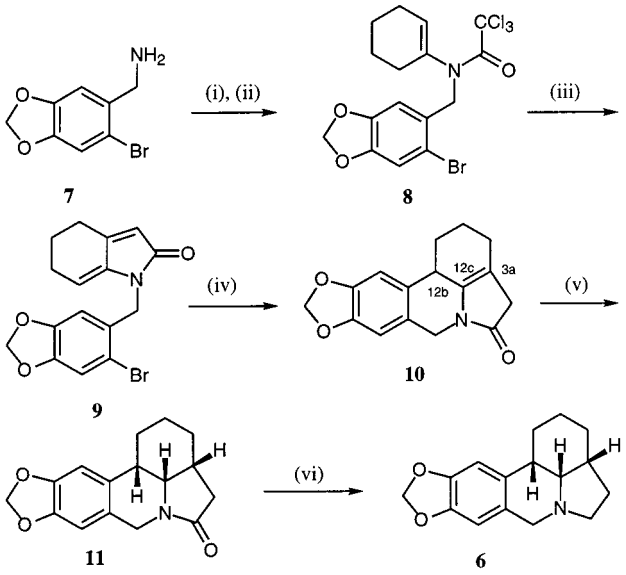


Figure 1

Lycorine **4** is representative of the large class of *Amaryllidaceae* alkaloids (Figure 1). Most synthetic efforts have been devoted to the total synthesis of this alkaloid and its reduced congeners, α- and γ-lycorane, **5** and **6**.[6] We present in this paper a very short synthesis of γ-lycorane **6**, as an illustration of our new methodology.[10,11]

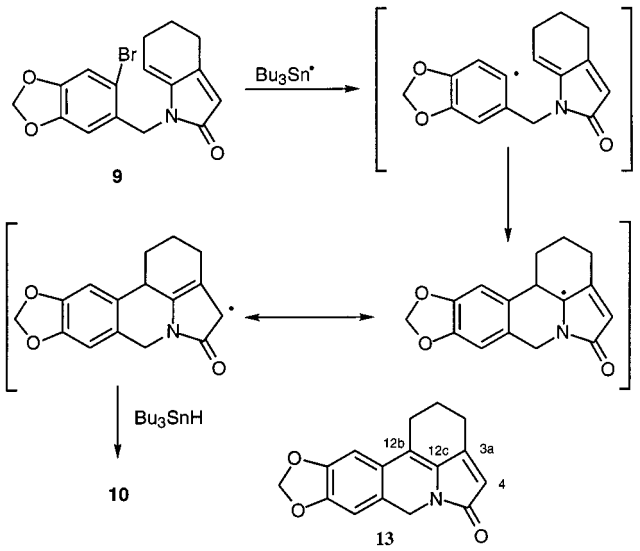
Condensation of cyclohexanone with the piperonal derived amine **7**[12] followed by acylation with trichloroacetyl chloride afforded trichloroacetamide **8**[13] in 73% yield. Subsequent treatment with nickel powder, acetic acid and sodium acetate in refluxing 2-propanol furnished tetrahydroindolone **9**[14] in 60% yield (Scheme 2). We next investigated the Bu_3SnH-mediated 6-*endo* radical cyclisation of arylbromide **9**. According to literature precedent,[7] we presumed this cyclisation would afford a trans-BC ring fused product. However, upon treatment with Bu_3SnH in

refluxing toluene in the presence of 1,1'-azobis(cyclohexanecarbonitrile), compound **9** was converted into lactam **10**[15] with the double bond at the ring junction.



Scheme 2 ***Reagents and conditions***: (i) cyclohexanone, toluene, reflux, 3h; (ii) $Cl_3CC(O)Cl$, Et_3N, toluene, 20°C, 4h (73% from **7**); (iii) Ni, AcOH, AcONa, 2-propanol, reflux, 10h (60%); (iv) Bu_3SnH, 1,1'-azobis(cyclohexanecarbonitrile), Toluene, reflux.12h; (v) $NaBH_3CN$, AcOH, 20°C, 24h (65% from 9); (vi) $LiAlH_4$, THF, reflux, 1h (88%).

The formation of **10** can be rationalised by a 6-*endo* radical cyclisation of the aryl radical derived from **9**, giving an allylic radical which reacts with the stannane at the less hindered position (Scheme 3). Despite a clean conversion observed by TLC and NMR analysis of the crude product, the unsaturated lactam **10** was isolated in only 48% yield, due to partial degradation during chromatography. Upon standing in air, compound **10** underwent (possibly photo-induced) oxidation to give the highly conjugated lactam **13**[16] as a fluorescent yellow oil. This oxidation appears to be especially favourable since small quantities of **13** were even formed during the radical cyclisation (the solution became highly yellow coloured after a few hours). In addition, compound **10** proved to be sensitive to mild acidic conditions which caused the shifting of the olefinic bond from position 3a-12c to the more stable position 12b-12c. Following these observations, we decided to avoid the isolation of compound **10** to minimise such side reactions. Indeed, direct reduction with sodium cyanoborohydride in acetic acid of the crude product of the radical cyclisation furnished lactam **11**[17] in 65% yield from **9** (Scheme 2). Only the *cis*-ring fused product is formed during this ionic reduction which involves the intermediacy of an acyliminium species. Finally, γ-lycorane **6** was obtained in high yield following $LiAlH_4$ reduction according to literature procedure.



Scheme 3

In conclusion, the total synthesis of (±)-γ-lycorane has been accomplished in four operations and in 25% overall yield starting from 6-bromopiperonylamine. This represents perhaps the shortest and most efficient route to this substance and illustrates the synthetic potential of the Ni / AcOH mediated radical cyclisations. Incorporating substituents on the starting cyclohexanone should allow a similar access to the more complex members of the *Amaryllidaceae* alkaloids such as 1-deoxylycorine or lycorine itself. Work along these lines is under way.

References and Notes

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(13) Preparation of **8**: A solution of cyclohexanone (0.52 ml, 5 mmol) and 6-bromopiperonylamine (1.15 g, 5 mmol) in toluene (5 ml) was heated under reflux in a Dean-Stark apparatus for 3 hours. After evaporation of the solvant, the residue was dissolved in dry toluene (25 ml) and cooled to 0°C. Triethylamine (0.72 ml, 6 mmol) was added, followed by dropwise addition of trichloroacetyl chloride (0.61 ml, 5.5 mmol). The solution was then stirred for 3 hours at room temperature. Water was then added and the resulting mixture extracted with ether, the organic layer was dried over magnesium sulfate and concentrated in vacuo. The residue was cristallised from ethanol to give *N*-(6-bromo-3,4-dimethoxybenzyl)-*N*-(cyclohex-1-enyl)-2,2,2-trichloroacetamide **8** (1.66 g, 73%) as colourless needles (mp : 138-139°C, ethanol); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.56 (m, 2H, CH_2); 1.69 (m, 2H, CH_2); 2.02 (m, 2H, CH_2); 2.25 (m, 2H, CH_2); 4.55 (m, 1H, NCHH); 5.02 (m, 1H, NCHH); 5.65 (t, *J* = 3.6 Hz, 1H, C=CH); 5.98 (s, 2H, OCH_2O); 6.96 (s, 1H, CH Ar); 7.00 (s, 1H, CH Ar); IR (cm^{-1}) ν 1677; 1666; 1503; 1480. Anal. Calcd for $C_{16}H_{15}NO_3BrCl_3$: C: 42.39; H: 3.34. Found: C: 42.39; H: 3.35.

(14) Synthesis of tetrahydroindolone **9**: To a solution of *N*-alkenyl trichloroacetamide **8** (990 mg, 2.2 mmol) in dry 2-propanol (25 ml) were added acetic acid (2.5 ml, 44 mmol), sodium acetate (535 mg, 6.6 mmol) and nickel powder (3.82 g, 66 mmol); the resulting mixture was stirred under reflux in an inert atmosphere for 10 h, then cooled to room temperature, diluted with ether and filtered through Celite. Water was added to the filtrate which was subsequently neutralised with saturated aqueous sodium bicarbonate, washed with water, brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography (heptane / ethyl acetate 9/1) to give 1-(6-bromo-3,4-dimethoxybenzyl)-1,4,5,6-tetrahydro-indol-2-one **9** (453 mg, 60%) as a white solid (mp : 124-125°C, ether); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.83 (tt, *J* = 6.5, 5.9 Hz, 2H, CH_2); 2.29 (td, *J* = 5.9, 4.8 Hz, 2H, CH_2); 2.66 (td, *J* = 6,5, 1,6 Hz, 2H, CH_2); 4.75 (s, 2H, NCH_2); 5.55 (dt, *J* = 4.8, 1.6 Hz, 1H, C=CH); 5.84 (m, 1H, CHCO); 5.94 (s, 2H, OCH_2O); 6.51 (s, 1H, CH Ar); 6.99 (s, 1H, CH Ar); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 23.5, 24.3, 24.4, 42.5, 101.8, 108.2, 111.4, 112.4, 112.5, 115.6, 129.8, 139.4, 147.5, 147.9, 148.0, 170.3. IR (cm^{-1}) ν 1692, 1656, 1502, 1480; Anal. Calcd for $C_{16}H_{14}NO_3Br$: C: 55.33; H: 4.07. Found: C: 54.96; H: 3.82.

(15) Data for **10** : ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.25-1.90 (m, 3H, CH_2); 2,03-2.16 (m, 2H, CH_2); 2.48-2.59 (m, 1H, CH_2); 2.95 (dm, *J* = 22.8 Hz, 1H, COCHH); 3.10 (dm, *J* = 22.8 Hz, 1H, COCHH); 3.50 (m, 1H, CHAr); 4.22 (d, *J* = 15.6 Hz, 1H, NCHH); 4.79 (d, *J* = 15.6 Hz, 1H, NCHH); 5.94 (s, 2H, OCH_2O); 6.64 (s, 1H, CH Ar); 6.79 (s, 1H, CH Ar). ^{13}C-NMR (50 MHz, $CDCl_3$) δ 22.5, 22.9, 27.7, 33.0, 40.7, 41.8, 101.2, 105.6, 107.2, 108.0, 125.7, 130.1, 136.5, 146.1, 147.3, 175.4; IR (cm^{-1}) ν 2927, 1706, 1678, 1486.

(16) Data for **13** : ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.02 (q, J = 6.1 Hz, 2H, CH_2); 2.57 (t, J = 6.1 Hz, 2H, CH_2); 2.70 (td, J = 6.1, 1.5 Hz, 2H, CH_2); 4.84 (s, 2H, NCH_2); 5.82 (t, J = 1.5 Hz, 1H, C=CH); 6.00 (s, 2H, OCH_2O); 6.72 (s, 1H, CH Ar); 6.83 (s, 1H, CH Ar); IR (cm^{-1}) ν 1667, 1508, 1489, 1466.

(17) Preparation of **11** : A solution of Bu_3SnH (1.2 ml, 4.5 mmol) and 1,1'-azobis(cyclohexanecarbonitrile) (220 mg, 0.9 mmol) in toluene (10 ml) was slowly added (2 hours) to a refluxing solution of **9** in toluene (20 ml). The resulting mixture was refluxed for 15 h. The solvent was evaporated and the residue immediately dissolved in acetic acid (10 ml). Sodium cyanoborohydride (710 mg, 11.2 mmol) was added and the mixture stirred for 24 h under argon. The solution was poured into water, neutralised with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The organic layer was dried, concentrated, and the residue purified by silica gel column chromatography (heptane / ethyl acetate 7/3) to give **11** (398 mg, 65%) whose spectroscopic data (^{1}HNMR, ^{13}CNMR, IR) were identical to those reported in ref 10b.