Synthesis of the Tricyclic Nucleus of the Alkaloid Stemofoline: X-Ray Crystal Structure of (4*RS*,5*RS*,7*SR*,10*RS*)-10-Butyl-5-hydroxy-1-azatricyclo[5.3.0.0^{4,10}]decan-2-one

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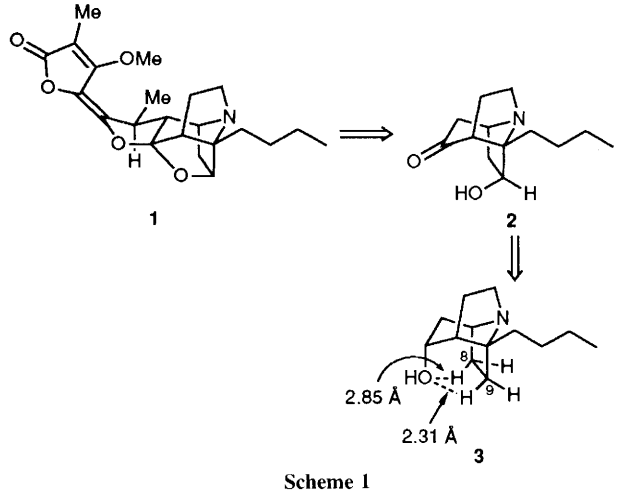
The tricyclic lactams **20** and **21** have been synthesized using iminium ion cyclisations and formation of the third ring *via* halogen metal exchange; oxidation of the lactam **22** using lead(IV) acetate gave the tetracyclic ether **27** regioselectively.

Stemofoline **1**, a complex alkaloid with insecticidal activity against silk worm larvae,[1,2] has not been synthesized despite its novel structure and biological activity. A key step in one possible approach to stemofoline was identified as the remote oxidation of alcohol **3**, since molecular modelling studies indicated that the tricyclic nucleus of the alcohol **3** is distorted so that the *endo*-hydrogen at C(9) is closer to the hydroxy group than the *endo*-hydrogen at C(8), 2.31 *vs.* 2.85 Å. Remote oxidation[3] of the alcohol **3** should, therefore, provide regioselective access to the hydroxyketone **2** (Scheme 1). We now report a synthesis of the tricyclic hydroxylactam **22**, and its oxidation to the tetracyclic ether **27** using lead(IV) acetate. The structure of this ether corresponds to the tetracyclic core of stemofoline.

Ketones **5** and **6** were prepared from 5-propenylpyrrolidinone **4**,[4,5] and were converted into the cyclic imines **7** and **8** using trifluoroacetic acid in dichloromethane. The imines were cyclised stereoselectively to the tropanones **9** and **10** by treatment with methyl or 2,2,2-trichloroethyl chloroformate and triethylamine (overall yields, 50–70%),[6–8] the structures, specifically the stereochemistry, of the products being established by spectroscopic methods and by an X-ray diffraction study of **10**.†

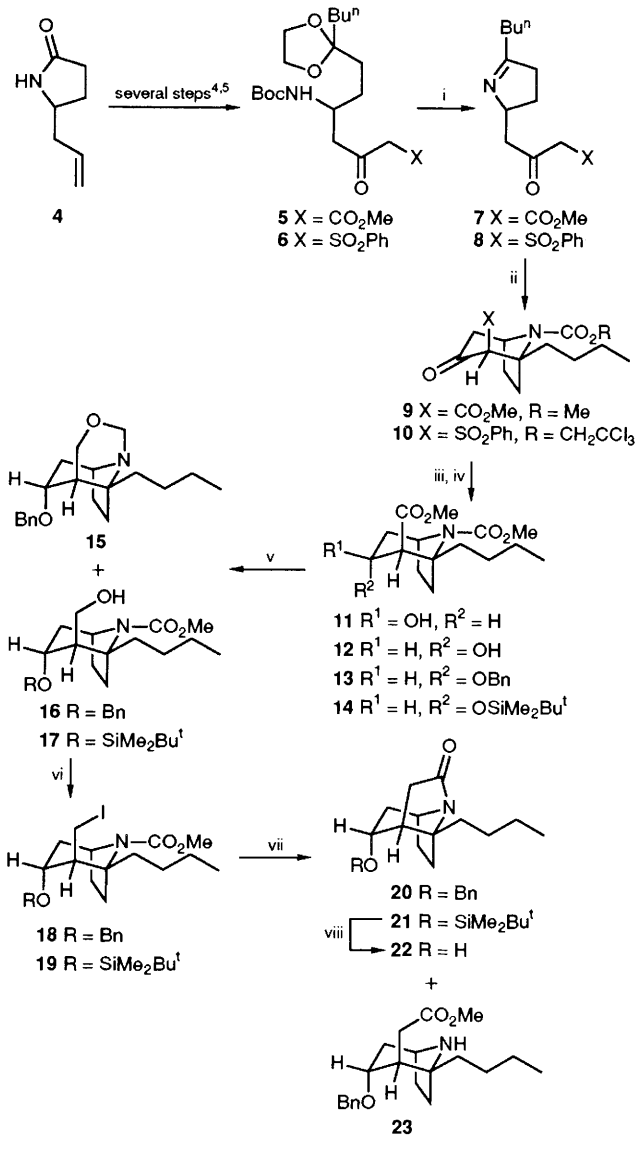
Reduction of the ketone **9** using zinc borohydride gave a mixture of the alcohols **11** and **12**, ratio 38 : 62. Protection of the axial alcohol and further reduction using an excess of diisobutylaluminium hydride (DIBAL-H), gave the alcohol **16** together with the tricyclic product **15** formed by reduction of the carbamate and interception of the intermediate iminium ion by the primary alcohol. The formation of the tricyclic product **15** could be avoided by use of lower temperatures and less reagent.



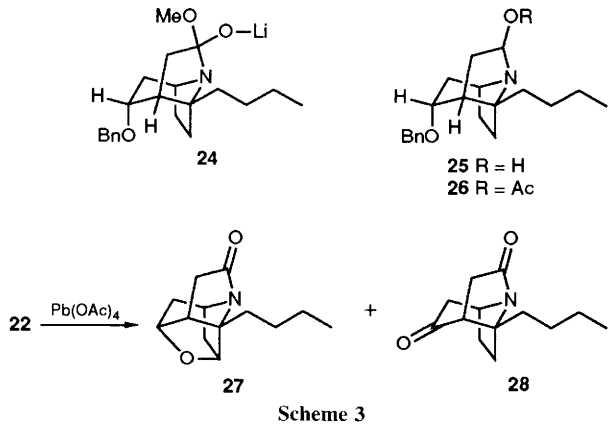
1 **2** **3**

Scheme 1

† The details of this X-ray structure will be reported in a full paper.



Scheme 2 *Reagents*: i, trifluoroacetic acid, CH_2Cl_2, 0 – 20 °C, 3 h; ii, methyl or 2,2,2-trichloroethyl chloroformate, CH_2Cl_2, −78 °C, 10 min, then triethylamine, −78 °C, 12 h (**9**, 71% from **5**: **10**, 51% from **6**); iii, $Zn(BH_4)_2 \cdot Et_2O$, 0 °C, 1 h (90%); iv, **13**, phenylmethyl 2,2,2-trichloroacetimidate, trifluoromethanesulfonic acid, cyclohexane, dichloromethane, 20 °C, 12 h (95%); **14**, *tert*-butyldimethylsilyl trifluoromethanesulfonate, lutidine, dichoromethane, 1 h (86%); v, DIBAL-H, hexane, −78 °C, 1 h (**16**, 75%; **17**, 78%); vi, iodine, triphenylphosphine, imidazole, dichloromethane, 3 h (**18**, 71%; **19**, 83%); vii, *tert*-butyllithium, tetrahydrofuran (THF), −78 °C; viii, tetrabutylammonium fluoride, THF, 12 h (100%) (Bn = $PhCH_2$)



Scheme 3

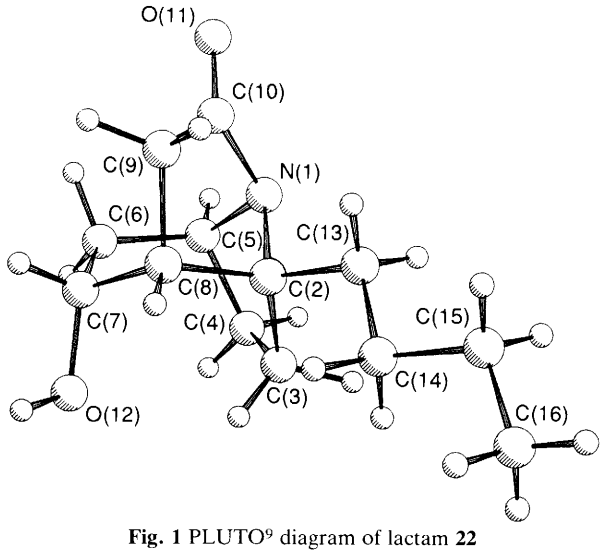


Fig. 1 PLUTO[9] diagram of lactam **22**

Treatment of the iodide **18**, available from the alcohol **16**, with *tert*-butyllithium at −78 °C, gave mixtures of the tricyclic lactam **20** and the bicyclic ester **23**. The yields of these products were found to depend upon the reaction time. If the reaction was quenched by the addition of acid after 1 min, the amino ester **23** was the major product (70%). However, if the reaction was left for 30 min at −78 °C before being quenched, the tricyclic lactam **20** was the major product (86%). These observations are consistent with the participation of the tricyclic alkyllithiumcarbamate adduct **24**, which on being quenched with acid gives the amino ester **23**. However, if addition of the acid is delayed, elimination of lithium methoxide takes place to give the tricyclic lactam. The silylated hydroxylactam **21** was similarly prepared (Scheme 2).

The structure of the hydroxylactam **22** was confirmed by an X-ray crystal structure determination, see Fig. 1.[9]‡ The amide functionality is significantly nonplanar, the nitrogen lone-pair being in the plane of the carbonyl group, and the carboxyl carbon–nitrogen bond length is 1.432 Å.[10] The predicted twist in the tropanone system is apparent with the oxygen of the hydroxy group being 2.97 and 2.32 Å from the *endo*-hydrogens at C(8) and C(9), respectively.

These structural features influence the spectroscopic and chemical properties of the tricyclic lactams. Their IR amide carbonyl stretching absorptions are at 1746 cm^{-1}, and reduction of **20** using lithium aluminium hydride gave the alcohol **25** as a single diastereoisomer, characterised as its acetate **26**. To test the regioselectivity of the proposed remote oxidation, the alcohol **22** was treated with lead(IV) acetate (Scheme 3).[11] This gave the bridged ether **27** (35%) together with a small amount of the ketone **28**. No product corresponding to oxidation at C(8) was isolated.

‡ *Crystal data* for **22**: $C_{13}H_{21}NO_2$, colourless, prismatic, m.p. 86–88 °C, crystal dimensions 0.280 × 0.280 × 0.560 mm, triclinic, a = 12.452(1), b = 16.234(1), c = 6.443(1) Å; α = 100.362(9), β = 90.57(1), γ = 98.543(6)°, U = 1266.1(2) Å^3, space group $P\bar{1}$ (No. 2), Z = 4, $F(000)$ = 488. ω–2θ scans of (1.21 + 0.30 tanθ)° were made at a speed of 32.0° min^{-1} at 297(1) K; 3958 reflections were collected with 0° < 2θ < 120.0°; of these, 3755 were unique and 2771 with $F > 3.0\sigma(F)$ were used in the analysis. The data were collected on a Rigaku AFC5R diffractometer using graphite monochromated Cu-Kα radiation. Lorentz, polarisation and linear intensity drift (maximum 0.99%) corrections were applied. The structure was solved by direct methods. Two crystallographically distinct molecules were found, but these differed only in the conformation of the butyl side-chain. The refinement converged with R = 0.063, R_w = 0.086. All calculations were performed using the TEXSAN crystallographic software package of Molecular Structure Corporation, 1985.[12] Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

The structure of the tetracyclic ether **27** corresponds to the tetracyclic core of stemofoline, and establishes the viability of the proposed remote oxidation for the regioselective introduction of the hydroxy substituent at C(9). This work is being continued to complete a synthesis of stemofoline.

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