A New Asymmetric Route to Bridged Indole Alkaloids: Formal Syntheses of (−)-Suaveoline, (−)-Raumacline and (−)-N^b-Methylraumacline

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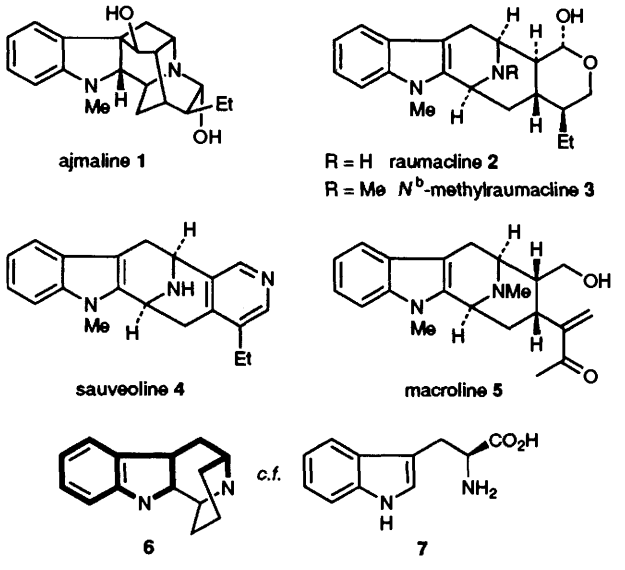
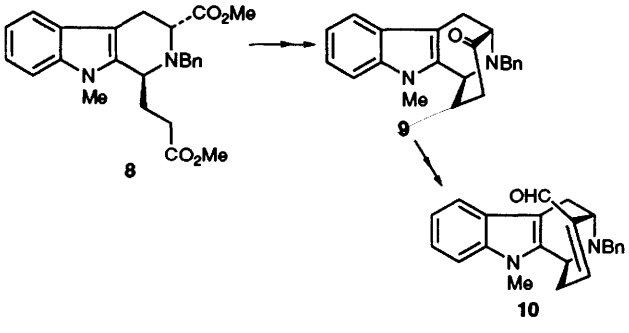
When the homologated nitrile **11** derived from L-tryptophan undergoes a modified Pictet–Spengler reaction with methyl propynoate, the resulting *cis*-tetrahydro-β-carboline **12a** is ideally functionalised for cyclisation to the bridged ketonitrile **14**; simple functional group modifications *via* the nitrile **15** (structure confirmed by X-ray crystallography) allow convergence with the tetracyclic α,β-unsaturated aldehyde **10**, which is an advanced intermediate for the synthesis of a range of bridged indole alkaloids.

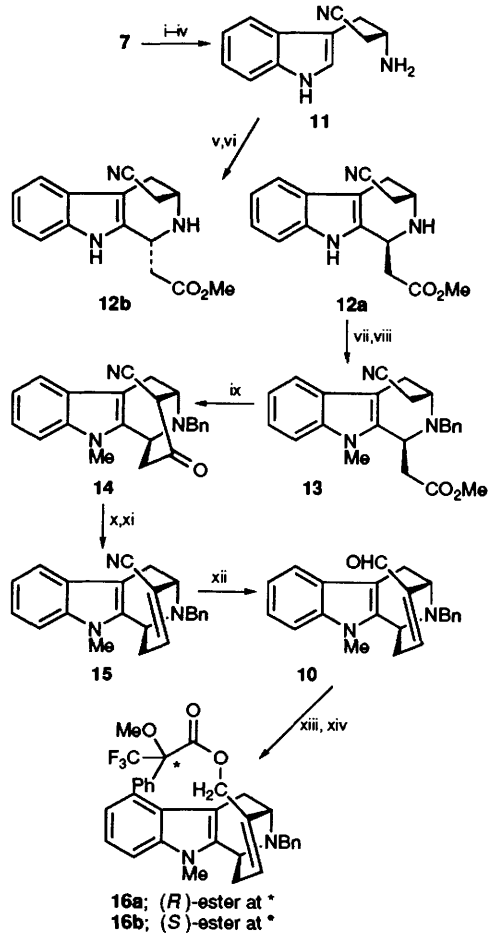
Indole alkaloids of the ajmaline-sarpagine family (*e.g.* **1–5**) have long been at the forefront of synthetic endeavour,[1] both because of their diverse biological properties, and because of their structural complexity. This large family of alkaloids all possess the bridged substructure **6** in which the skeleton of L-tryptophan **7** can be discerned. Although the stereochemistry is not derived from this source in the biosynthesis,[2] L-tryptophan is a logical building block for the asymmetric synthesis of these compounds.



Starting from D-tryptophan, Cook *et al.* have achieved the synthesis of a range of these alkaloids, for which the α,β-unsaturated aldehyde **10** is a common advanced intermediate.[3] Key steps involve the stereospecific formation of the *trans* tetrahydro-β-carboline **8**, followed by epimerisation of the C-3 chiral centre during Dieckmann cyclisation[4] to give (after hydrolysis/decarboxylation) the bridged ketone **9**. A similar initial strategy has been employed by Magnus *et al.* in the elegant synthesis of kopsinine alkaloids.[5]



Our own development of the *cis*-selective Pictet–Spengler reaction has allowed us to achieve asymmetric syntheses of bridged indole alkaloids starting from cheaper proteinogenic L-tryptophan, again *via* the bridged ketone **9**.[6] However, conversion of this to the α,β-unsaturated aldehyde **10** is not trivial, and a more direct route would be a great advantage.



Scheme 1 *Reagents and conditions*: i, $LiAlH_4$, THF, heat; ii, TsCl, py, 0 °C; iii, KCN, MeOH, heat; iv, Na/liq. NH_3, −78 °C; v, $HC{\equiv}CCO_2Me$, $CHCl_3$, heat; vi, TFA, 0 °C; vii, BnBr, $NaHCO_3$, $CHCl_3$, heat; viii, MeI, NaH, DMF, 0 °C; ix, Et_2NLi, THF, −78 °C; x, $NaBH_4$, MeOH, room temp.; xi, $POCl_3$, py, PhH, heat; xii, DIBAL, CH_2Cl_2, −78 °C then H_3O^+; xiii, $NaBH_4$, MeOH, room temp.; xiv, (*R*)- or (*S*)-PhC(OMe)(CF_3)COCl, py, CH_2Cl_2, room temp.

We therefore studied the feasibility of introducing the additional carbon at the first step in the synthesis.

Our successful synthesis† (Scheme 1) started from L-tryptophan, which was converted into the homologated nitrile **11** in four steps (50% overall yield), following the procedure of Kutney *et al.*[7] Extensive modifications of the experimental detail allowed us to process the tryptophan in batches of >100 g, for which recrystallisation of the cyanosulfonamide was the only purification required, prior to quantitative removal of the *N*-tosyl protective group.

The tetrahydro-β-carboline ring system was formed using a modified Pictet–Spengler reaction, in which the conventional aldehyde is replaced by an alkyne conjugated to a carbonyl group.[8] Thus, reaction of **11** with methyl propynoate gave the enamine ester, and the addition of TFA under conditions of kinetic control generated a mixture of the cyanoesters (60%) in which the *cis*-isomer **12a** predominated (**12a** : **12b** = 77 : 23).

Efficient acylation of the N^b-nitrogen was easy, but this led to ring opening at the Dieckmann/Thorpe cyclisation stage.[9] Instead, N^b-benzylation was achieved in 50% total yield for the *cis*/*trans* mixture, with recycling of the starting material necessary because of the sluggish reaction of the *cis* isomer. Separation of the *cis*/*trans* isomers was readily achieved by flash chromatography, and subsequent N^{in}-methylation of the *cis*-isomer gave the fully protected cyanoester **13** in 92% yield. The key Dieckmann/Thorpe cyclisation was effected using lithium diethylamide at −78 °C. The reaction occurred exclusively *via* the α-cyanoenolate, to give the bridged ketonitrile **14** in 90% yield. With the required skeleton intact, only simple functional group interconversions remained. Thus, sodium borohydride reduction of the ketone gave the corresponding hydroxynitrile (90% yield),[10] dehydration of which gave the α,β-unsaturated nitrile **15** (87% yield) whose structure was confirmed by single crystal X-ray diffraction studies (Fig. 1).‡ inally, DIBAL reduction of **15** gave the α,β-unsaturated aldehyde (−)-**10** (99% yield), which had been previously prepared by Fu and Cook from D-tryptophan.[3] The optical purity of (−)-10§ was determined to be >97% e.e. by reduction of **10** to the alcohol, followed by analysis of the ^{19}F NMR spectra of the (*R*)- and (*S*)-Mosher's esters **16a/b**.[11] As (−)-**10** has been used in the synthesis of the title alkaloids [(−)-suaveoline, (−)-raumacline and (−)-N^b-methylraumacline],[3] our work constitutes a formal synthesis of these natural products, and represents a particularly efficient approach for accessing alkaloids of the ajmalinesarpagine family.

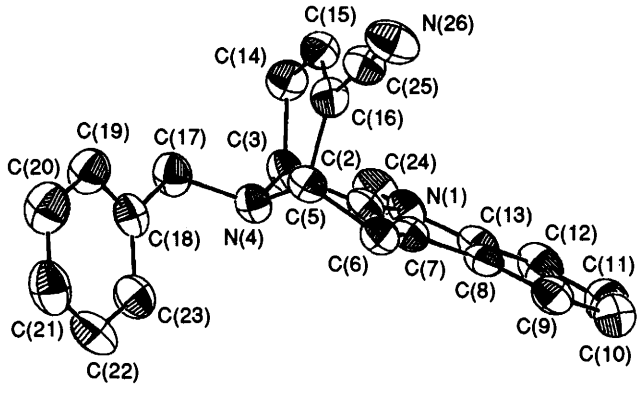


Fig. 1 X-Ray crystal structure of the α,β-unsaturated nitrile **15**, showing the crystallographic numbering system. The position of the double bond was confirmed by the C(15)–C(16) bond length of 1.332(8)Å.‡

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Footnotes

† Satisfactory analyses (elemental or HRMS), NMR (^1H and ^{13}C), IR and MS data were obtained for all new compounds.

‡ *Crystal data* for **15**: $C_{23}H_{21}N_3$, M_r = 339.44, crystal dimensions 0.30 × 0.40 × 0.60 mm. Orthorhombic, space group $P2_12_12_1$, a = 10.777(4), b = 18.682(3), c = 8.927(6) Å, V = 1997(1) Å^3, Z = 4, D_c = 1.254 g cm^{-3}, Mo-Kα radiation (graphite monochromator), λ = 0.71069 Å, μ = 0.75 cm^{-1}, F(000) = 720. Total of 4616 reflections collected at 296 K in an ω scan of which 1854 were unique. A polynomial absorption correction was applied. The structure was solved by direct methods (SHELX 86) and refinement converged with R_w = 0.051. All hydrogen atoms were placed at calculated positions. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

§ Optical rotation of **10**: $[\alpha]_D^{20}$ − 282 (*c* = 0.33, $CHCl_3$) {lit.[3] $[\alpha]_D^{24}$ −310.5 (*c* = 0.55, $CHCl_3$)}. Importantly, ^{19}F NMR analysis of Mosher's esters **16a/b** confirmed the high optical purity of our compounds (e.e. > 97%).

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