# Synthesis of the *A/E/F* Tricyclic Section of the Norditerpenoid Alkaloid Methyllycaconitine, a Potent Inhibitor of Neurotransmission

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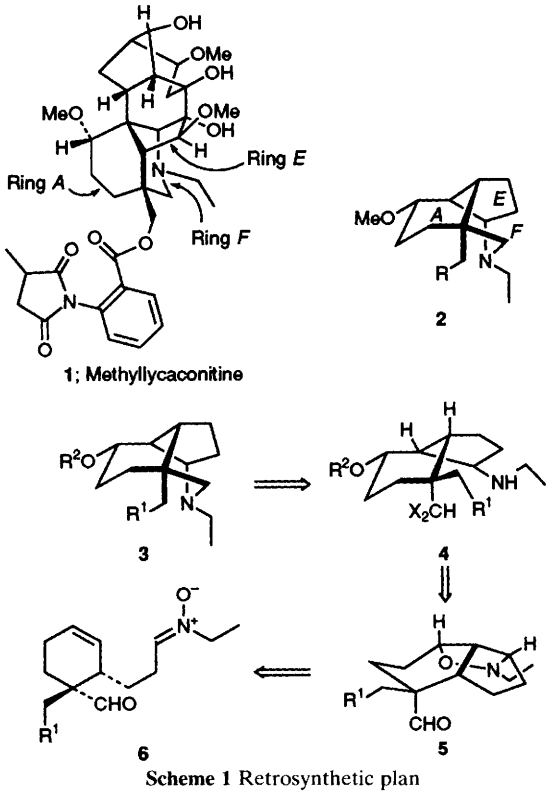
The tricyclic amine (±)-**2**; R = H, with five stereogenic centres, representing the *A/E/F* ring system of the norditerpene alkaloid methyllycaconitine, is synthesised from penta-1,4-dien-3-ol in nine steps, with overall yield 16%.

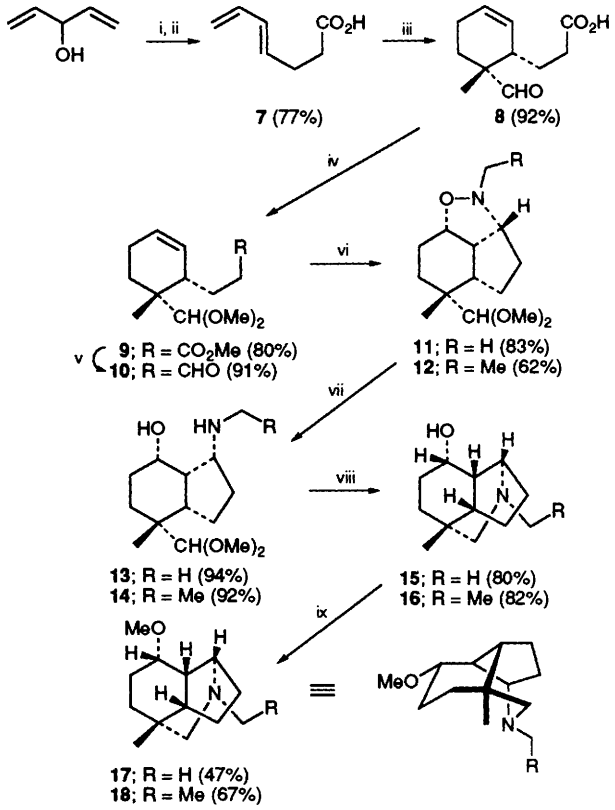
Methyllycaconitine **1** is a member of the $C_{19}$ diterpenoid alkaloid family, characteristic extractives of *Delphinium* and *Aconitum* species,[1,2] which show various biological activities, including high toxicity to mammals and insects. Methyllycaconitine, from *D. brownii* and *D. elatum*,[3,4] acts at the neuromuscular junction, inhibiting neurotransmission and inducing paralysis,[5] and it is stated to be the most potent non-protein antagonist of the neuronal nicotinic acetylcholine receptor yet found.[6]

The potentially powerful insecticidal activity of methyllycaconitine and its relatives makes it a very attractive subject for agrochemical research, and there is an urgent need for structure–activity relationships to be investigated. While some approaches have employed partial synthesis,[7] we considered that synthetic work on selected substructures was essential, and we chose for our first target the tricycle **2** comprising the *A/E/F* ring system. In this communication we report the synthesis of the cyclic amine **2**; R = H in a short sequence showing high regio- and stereo-specificity and which offers the potential both for enantioselectivity and for access to the hydroxylated analogue **2**; R = OH. The synthetic analysis (Scheme 1) involved an initial C–N bond disconnection from **3** to a *cis*-fused 6,5 bicarbocycle **4**, in which the N and ether O were envisaged as relating to the isoxazolidine **5**. The heterocycle **5** can now be viewed as the product of 1,3-dipolar cycloaddition from the nitrone **6**, derivable in its turn from a Diels–Alder reaction.

Scheme 2 displays the synthetic sequence in practice. *E*-Hepta-4,6-dienoic acid **7** was prepared by heating penta-1,4-dienol with triethyl orthoacetate containing catalytic propionic acid, followed by alkaline hydroysis of the resulting ester.[8] Diels–Alder reaction of the sodium salt of the diene acid **7** with methacrolein in water[9] at room temp. for 24 h afforded the *endo* cyclohexene acid **8** as the major stereoisomer (15 *endo*:1 *exo*). Simultaneous acetalisation and esterification was carried out by refluxing with trimethyl orthoformate and methanol, with toluene-*p*-sulfonic acid catalyst, providing the ester **9**, which was reduced by diisobutyl aluminium hydride directly to the aldehyde **10**. This aldehyde reacted with both methyl- and ethyl-hydroxylamines in refluxing benzene to yield the isoxazolidines **11** and **12**, respectively. Efficient cleavage of the N–O bond was achieved using nickel chloride–sodium borohydride. The heterocyclic ring was then closed by a one-pot reductive amination procedure,[10] in which the amines **13** and **14** were treated with 5 mol $dm^{-3}$ hydrochloric acid, the solution was buffered to pH 5.5, and reduction of the resulting cyclic imine intermediate was effected with sodium cyanoborohydride, to afford the tricycles **15** and **16** in excellent yield. Finally *O*-methylation was achieved by treatment of the corresponding alkoxide with




**Scheme 1** Retrosynthetic plan




**Scheme 2** *Reagents and conditions*: i, $MeC(OEt)_3$, $EtCO_2H$, 142 °C, 3.5 h; ii, KOH, MeOH; iii, 4 equiv. $CH_2{=}C(Me)CHO$, $H_2O$, $NaHCO_3$, room temp., 24 h; iv, $HC(OMe)_3$, MeOH, PTSA; v, DIBAL, toluene, −80 °C; vi, MeNHOH·HCl or EtNHOH·TFA, $Et_3N$, benzene, reflux, 3.5 h; vii, $NiCl_2{\cdot}6H_2O$, $NaBH_4$, MeOH; viii, *a*, 5 mol $dm^{-3}$ HCl; *b*, buffer pH 5.5; *c*, $NaCNBH_3$; ix, NaH, THF, MeI

methyl iodide. Molecular models indicate that competing *N*-alkylation in this step is inhibited by steric compression of the resulting quaternary ammonium salts, and in agreement the yields of *O*-methyl ether were significantly greater for the *N*-ethyl compound than for the *N*-methyl relative.†

The *endo* stereochemistry of the adduct **8** is demonstrated by the subsequent successful reductive amination, and the remaining stereochemistry in the final product is controlled by the nitrone cycloaddition. As an additional check, single crystal X-ray analysis[11] of the oxazolidine **11** was carried out, and confirmed the assignments given here.

Thus, the synthesis of the desired tricyclic amine **2**; R = H, modelling the *A/E/F* ring system of methyllycaconitine and containing five stereogenic centres, has been effected in nine steps from the commercially available penta-1,4-dien-3-ol, with overall yield 16%. Future work will focus on the extension of this route to provide homochiral products through an enantioselective cycloaddition process, and to introduce an additional hydroxy to form the tricycle **2**; R = OH, and hence appropriate esters related to the natural product.

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## Footnote

† All new compounds gave satisfactory spectroscopic and analytical data.

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