

A New Synthetic Route to Vindorosine

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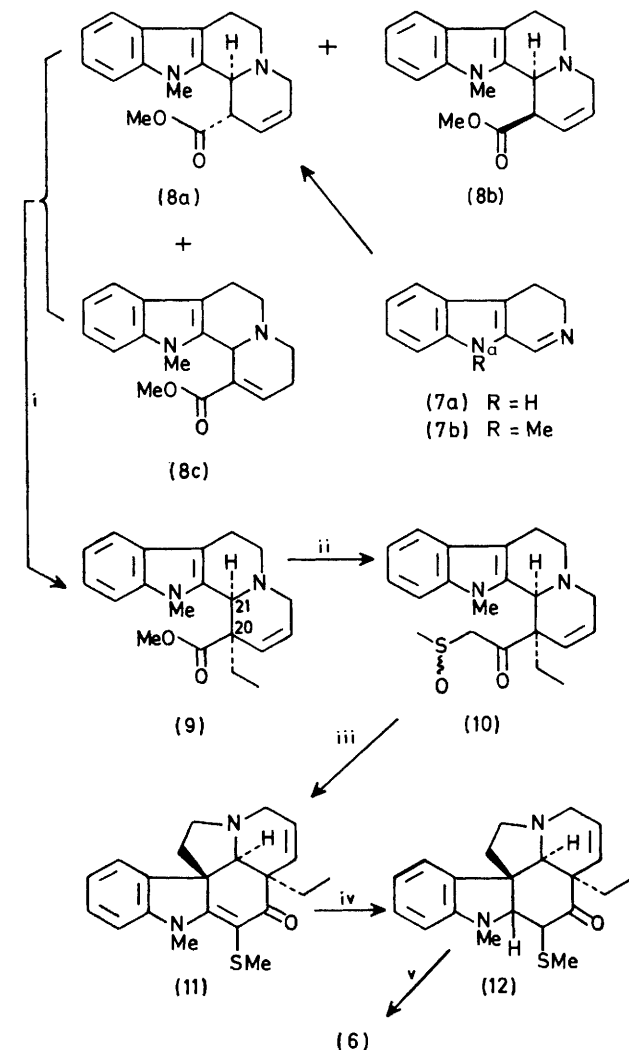
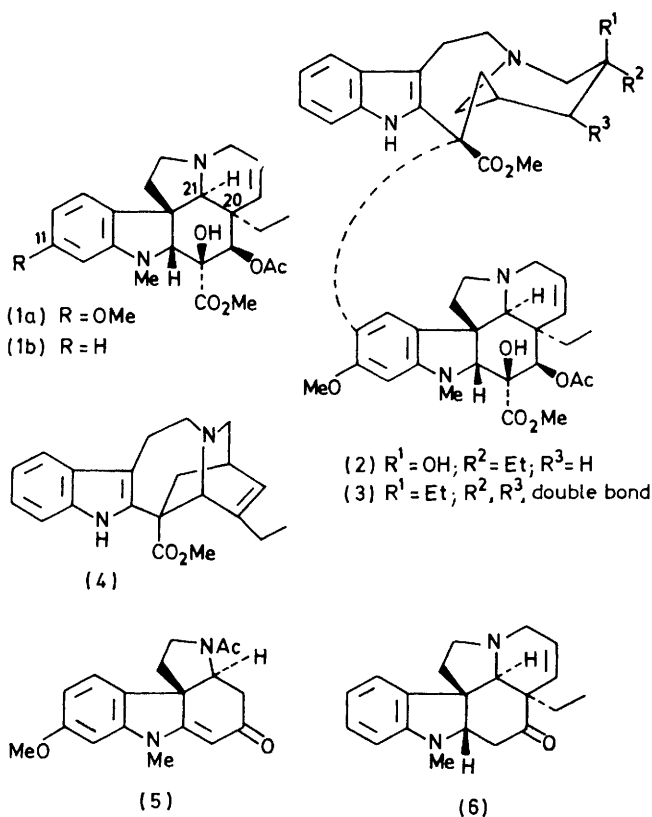
The pentacyclic ketone (**6**), a direct precursor of vindorosine (**1b**), has been synthesised with an overall yield of 41%, by a six-step sequence involving a Diels–Alder reaction, stereospecific alkylation, and Pummerer rearrangement coupled with electrophilic cyclisation.

The pentacyclic, highly functionalized aspidospermane alkaloid vindoline (**1a**)¹ is the dihydroindolic part of the anti-tumour alkaloid vinblastine (**2**).² The interest in a total synthesis of vindoline (**1a**) has been increased recently by our discovery of a semisynthetic route affording anhydrovinblastine (**3**)³ and vinblastine (**2**)⁴ from their biogenetic precursors⁵ vindoline (**1a**) and catharanthine (**4**).

Since the elegant synthesis of vindoline (**1a**)⁶ and vindorosine⁷ (11-demethoxyvindoline) (**1b**) by Büchi *et al.*, several improvements directed towards the synthesis of Büchi's tetracyclic intermediate (**5**) have appeared in the literature.^{8,9} We report here a high-yielding straightforward synthesis of the pentacyclic ketone (**6**), a direct synthetic precursor of vindorosine (**1b**).⁷

The classical preparation of *N*^α-methyl-dihydro- β -carboline (**7b**)^{10,11} has been by-passed by direct *N*^α-methylation of the corresponding dihydro- β -carboline (**7a**) (BuLi, THF, MeI, nearly quantitative yield). Compound (**7b**) subjected to a Diels–Alder type reaction in the presence of methyl pentadienoate gave rise to a mixture of indoloquinolizidines (**8a**), (**8b**), and (**8c**) (total yield 71%). Without further separation, this mixture was directly alkylated¹² [lithium di-isopropylamide-tetrahydrofuran(THF)-hexamethylphosphoric triamide, EtI] to afford the indoloquinolizidine (**9**) as a single

diastereoisomer (98%). This stereospecific alkylation gave rise to the correct relative configurations at C-20 and C-21. Compound (**9**) was treated with dimethyl-lithium¹³ in THF-dimethyl sulphoxide and afforded the corresponding β -oxo-sulphoxide (**10**) as a mixture of diastereoisomeric compounds in 75% yield. The rearrangement to the aspidospermane skeleton, a crucial step of this synthesis, was cleanly promoted by acidic treatment¹⁴ (toluene-*p*-sulphonic acid in THF-H₂O) and gave rise to the pentacyclic derivative (**11**) (78%) (Scheme 1). The synthesis was completed by a two-step sequence. The double bond of the vinylogous lactam (**11**) was reduced with sodium cyanoborohydride in MeOH.¹⁵ The resulting



Scheme 1. Reagents: i, LiNPr₂, THF-hexamethylphosphoric triamide, then EtI; ii, MeSOCH₂⁻ Li⁺, THF-Me₂SO; iii, *p*-Me-C₆H₄SO₃H, THF-H₂O; iv, NaBH₃CN, MeOH; v, Raney Ni, Me₂CO.

sulphide (12), after treatment with Raney-Ni in acetone,¹⁶ afforded the pentacyclic ketone (6), the direct synthetic precursor^{6,7} of vindorosine (1b) [overall yield of (6) from (7a); 41%].

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