

STUDIES TOWARDS THE TOTAL SYNTHESIS OF STRYCHNINE (I)

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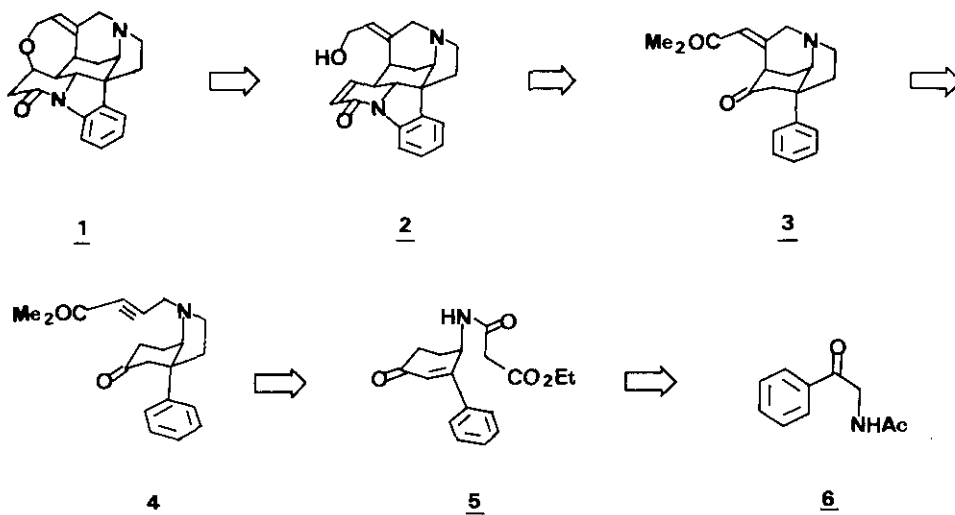
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Abstract — A stereoselective synthesis of a potential synthetic intermediate **12** for the synthesis of Strychnine is described, wherein a series of Michael reactions are key steps.

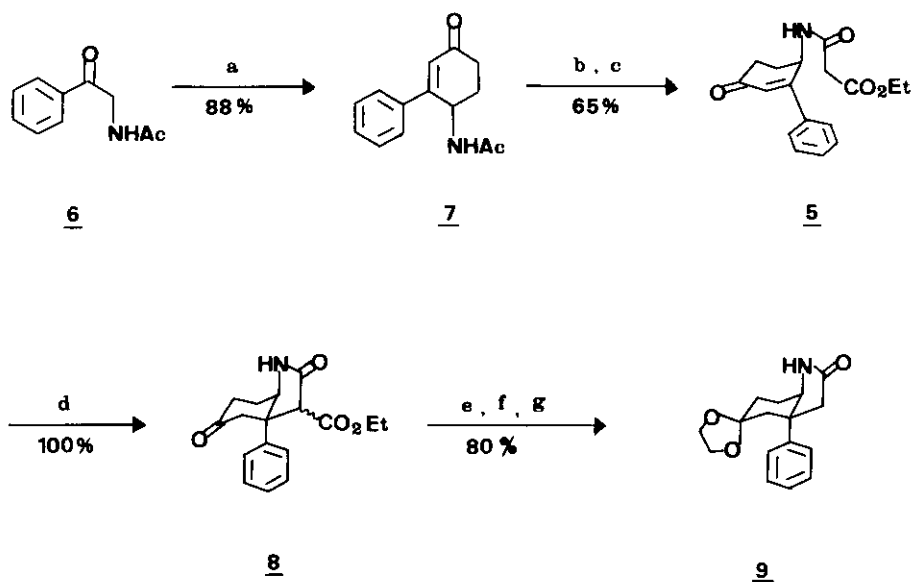
Our synthetic approach to strychnine **1**, a poisonous alkaloid from the Strychnos species, involves a series of inter- and intramolecular conjugate additions as key steps, as illustrated in Scheme I.¹ In this communication we wish to describe an efficient and stereoselective synthesis of the intramolecular Michael substrate **4** and its conjugate addition.

SCHEME I



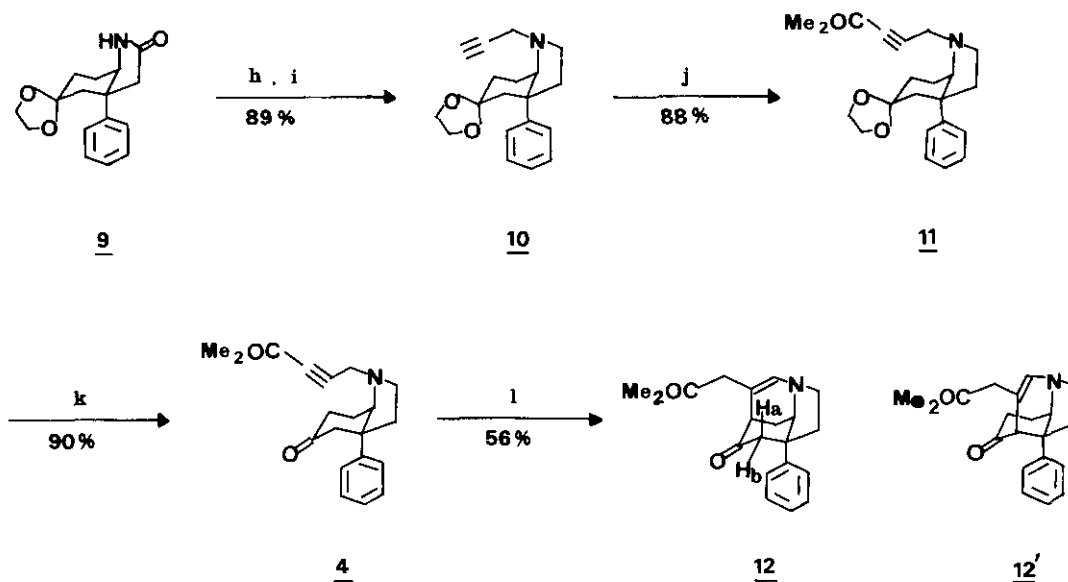
Stereoselective construction of the cis-fused bicyclic lactam 9 starts with a highly efficient one-step synthesis of the cyclohexenone 7 from the readily available N-phenacyl amide 6² by Robinson annulation. Thus, slow addition of MVK to an ethanolic solution of the ketone 6 in the presence of NaOEt directly afforded 7 in 88% yield.^{3,4} Reaction of the amide 7 with Meerwein's reagent⁵ and in situ hydrolysis of the resulting imino ether followed by carboethoxyacetylation under a Schotten-Baumann condition provided the second conjugate addition substrate 5 in 65% overall yield. Upon treatment of NaH in refluxing THF compound 5 underwent smooth cyclization to give a quantitative yield of Michael adduct 8 whose cis stereochemistry was dictated by the nature of ring closure.⁶ The ester 8 was converted to the lactam 9 in an overall yield of 80% by the three-step sequence (protection⁷, saponification, and decarboxylation).

SCHEME II



(a) MVK, EtOH, NaOEt, -20°C-rt, 1 h. (b) Meerwein's reagent, NaHCO₃, CH₂Cl₂, rt, 24 h; HOAc, rt, 5 h. (c) ClCOCH₂CO₂Et, CH₂Cl₂, NaHCO₃, rt, 5 h. (d) NaH, THF, reflux, 30 min. (e) Ethylene glycol, PTSA, PhH, reflux, 24 h. (f) 1N-NaOH, MeOH, reflux, 2 h; 2N-HCl. (g) LiI, Diglyme, reflux, 4 h.

SCHEME III



(h) LAH, THF, reflux, 10 h. (i) Propargyl bromide, Na_2CO_3 , EtOH, rt, 30 h. (j) LDA, THF, -78°C , 30 min; ClCO_2Me , -78°C -rt, 1 h. (k) PTSA, acetone, rt, 72 h. (l) Triton B, DME, -20°C , 1 h.

Reduction of the lactam **9** with LAH in refluxing THF followed by alkylation with propargyl bromide gave the tertiary amine **10** in 89% overall yield after chromatographic purification. The propargylic amine **10** was carbomethoxylated by successive treatment with LDA and methyl chloroformate in THF to give the ester **11** in 88% yield. Hydrolysis of the ketal protecting group in **11** produced a 90% yield of the ketone **4**, which sets up the third and crucial intramolecular conjugate addition to an acetylenic Michael acceptor.⁸

After a considerable amount of experimentation it was found that treatment of the intramolecular Michael substrate **4** with Triton B in DME at -20°C for 1 h produced the tricyclic compound **12** as a single product in 56% yield. Careful analysis of the spectral data, especially an absorption at 1743 cm^{-1} in IR spectrum, strongly suggested the migration of double bond to an enamine structure.⁹

In summary we have demonstrated the feasibility of our synthetic approach to strychnine which involves a series of Michael additions as key steps. Transformation of the potential key intermediate 12 to strychnine itself is under active investigation in our laboratories.

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9. The presence of signal for two methylene protons H_a and H_b at δ 2.7 in the NMR spectrum strongly supports the tricyclic compound has the structure of 12 rather than regioisomeric 12'.

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