# STUDIES TOWARDS THE TOTAL SYNTHESIS OF STRYCHNINE (I)

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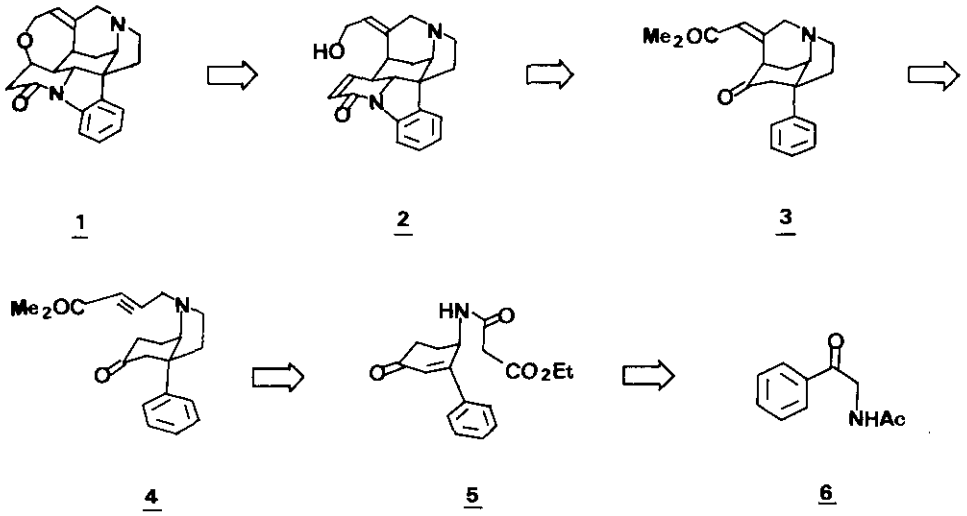
Abstract —— A stereoselective synthesis of a potential synthetic intermediate **12** for the synthesis of Strychnine is described, wherein a series of Michael reactions are key steps.

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

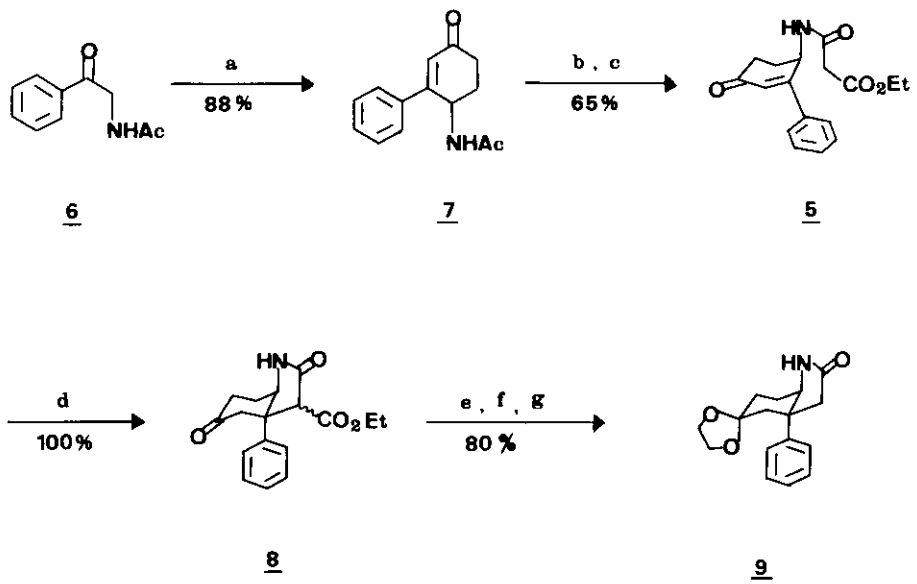



**1** **2** **3**

**4** **5** **6**

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 **6**[2] 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 reagent[5] 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 (protection[7], saponification, and decarboxylation).

SCHEME II

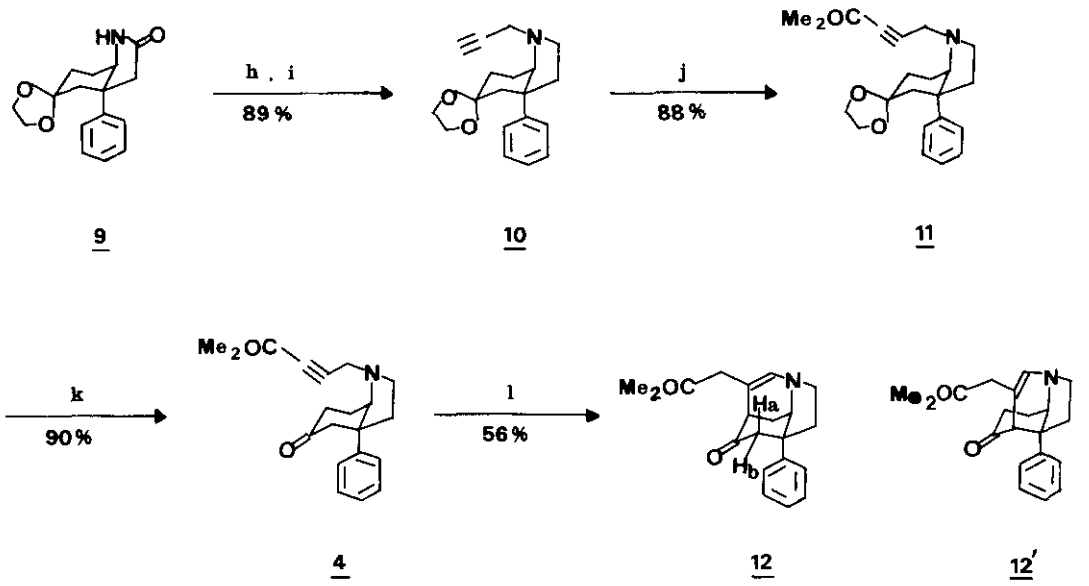



**6** **7** **5**

**8** **9**

(a) MVK, EtOH, NaOEt, -20°C-rt, 1 h. (b) Meerwein's reagent, $NaHCO_3$, $CH_2Cl_2$, rt, 24 h; HOAc, rt, 5 h. (c) $ClCOCH_2CO_2Et$, $CH_2Cl_2$, $NaHCO_3$, 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.

ACKNOWLEDGEMENT

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REFERENCES

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2. Prepared by acetylation of α -aminoacetophenone hydrochloride which is commericially available from Aldrich Chemical Co.
3. C-alkylation of α -amidoketones with reactive alkyl halides has been reported. M. Sekiya, J. Kawarabata and A. Hara, Chem. Pharm. Bull., 1970, 18, 2074.
4. All new compounds exhibited satisfactory spectroscopic data.
5. S. Hanessian, Tetrahedron Lett., 1967, 1549.
6. Conformational drawings of the bicyclic intermediates in the text do not necessarily represent the most stable conformation. For a similar cyclization see; H. Muxfeldt, R. S. Schneider and J. B. Mooberry, J. Am. Chem. Soc., 1966, 88, 3670.
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8. See the following for examples of conjugate addition to acetylenic Michael acceptors; R. B. Woodward and T. Singh, J. Am. Chem. Soc., 1950, 72, 494; G. Stork and M. Tomasz, J. Am. Chem. Soc., 1962, 84, 310; B. M. Trost, C. D. Shuey, F. DiNinno, Jr. and S. S. McElvain, J. Am. Chem. Soc., 1979, 101, 1284.
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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