

CONSTRUCTION OF INDOLIZIDINE AND QUINOLIZIDINE RING SYSTEMS BY
AN INTRAMOLECULAR 1-AZA-1,3-DIENE DIELS-ALDER REACTION.
SYNTHESIS OF (±)-EPILOPININE

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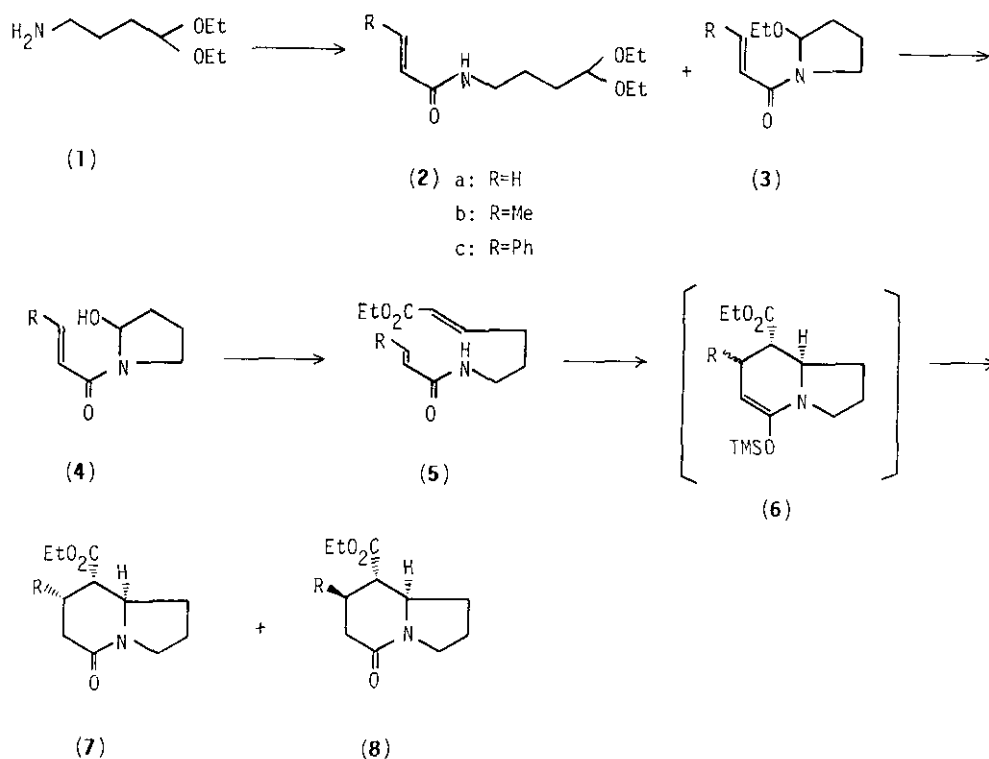
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Abstract - Indolizidines and quinolizidines were synthesized
through an intramolecular 1-aza-1,3-diene Diels-Alder reaction;
the method provides an efficient route to (±)-epilupinine (16).

Indolizidines and quinolizidines are common frameworks of a number of alkaloids and various synthetic methods have been devised. It is expected that intramolecular imino or 1-aza-1,3-diene Diels-Alder reaction can be used for the construction of these ring system. The former was successfully applied by Weinreb.¹ Although the latter route also seems attractive, only a few examples^{2,3} have been reported because of the difficult formation of the 1-aza-1,3-diene and its poor reactivity.⁴ We have recently demonstrated the effectiveness of an intramolecular Diels-Alder reaction of 1-aza-1,3-dienes derived *in situ* from enamides in the synthesis of benzo[a]- and indolo[a]quinolizidines.⁵ Here we would like to report the extension of this methodology and a facile synthesis of (±)-epilupinine (16).

Condensation of 4,4-diethoxybutylamine (1) with acryloyl chloride in a mixture of dichloromethane and saturated aqueous sodium bicarbonate at room temperature gave a mixture of the amide 2a and the pyrrolidine derivative 3a, which was subsequently treated with 1N hydrochloric acid in acetone at room temperature to afford the cyclic hydroxyl compound 4a in 85 % yield from 1. Wittig reaction of 4a with (carbethoxymethylene)triphenylphosphorane in acetonitrile formed α,β-unsaturated ester 5a in 86 % yield. Similarly, compounds 4b and 4c, obtained from 1 in 74 % and 75 % yields, respectively, were converted into esters 5b and 5c in 69 % and 88 % yields, respectively. Heating a mixture of 5a, trimethylchlorosilane, triethylamine and anhydrous zinc chloride^{5,6} in toluene in a sealed tube at 180-185 °C for 10 h produced cycloadduct 6a, which was easily hydrolyzed with dilute hydrochloric acid to indolizidine 7a. After purification by silica gel column chromatography, 7a was isolated as a single stereoisomer in 55 % yield. The reaction of 5b under the same conditions as above yielded two stereoisomers, 7b and 8b in 72 % and 8 % yields, respectively, after chromatographic purification. In the nmr spectra, the methyl groups at the C₇ position of 7b and 8b were observed at 0.99 and 1.06 ppm as doublets, respectively. Therefore the structure of the major product was assigned to 7b possessing the axially oriented methyl group.² Ester 5c was

also transformed into two stereoisomers, **7c** and **8c**, in 75 % and 11 % yields.

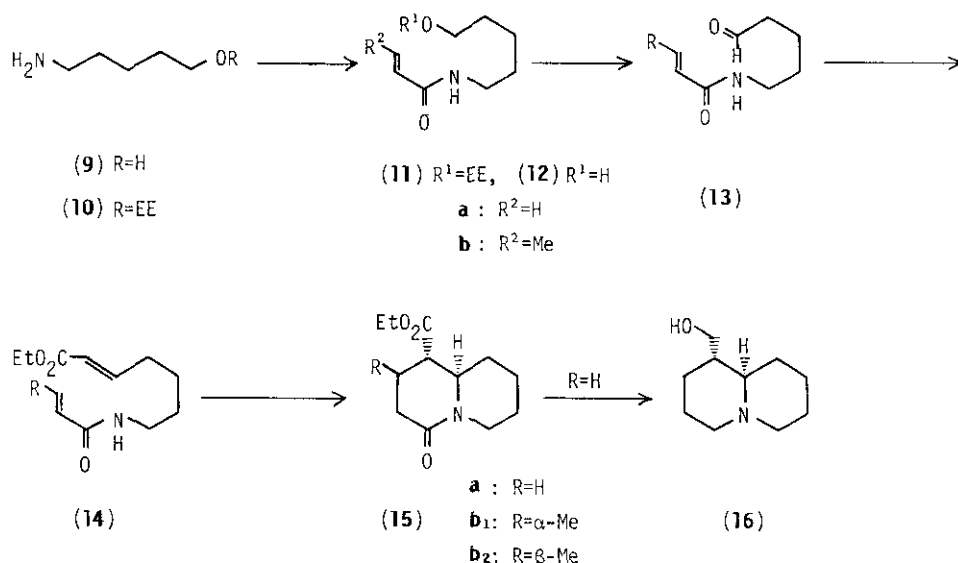


Scheme 1

An application of this reaction sequence to the synthesis of (±)-epilupinine (**16**) is shown in Scheme 2. Reaction of 5-amino-1-pentanol (**9**) with ethyl vinyl ether in the presence of a small excess of hydrogen chloride in dichloromethane at 4 °C gave a 95 % yield of the protected amine **10**. Treatment of **10** with acryloyl chloride in the presence of aqueous sodium bicarbonate afforded in 84 % yield enamide **11a** which was deprotected using acetic acid, tetrahydrofuran and water (3 : 2 : 1, v/v) to give labile alcohol **12a** in 83 % yield. Oxidation of **12a** using dipyridine-chromium (VI) oxide in dichloromethane⁷ followed by Wittig reaction of the resulting aldehyde **13a** furnished the α,β-unsaturated ester **14a** in 75 % yield from **12a**. Heating **14a** with trimethylchlorosilane, triethylamine and zinc chloride in toluene in a sealed tube at 180–185 °C for 7 h produced the quinolizidine **15a** in 56 % yield. Lithium aluminum hydride reduction of **15a** in refluxing tetrahydrofuran afforded in 77 % yield (±)-epilupinine (**16**),⁸ nmr and mass spectra of which were identical with those of the authentic compound. In related experiments, enamide **11b**, prepared in 83 % yield from **10** and crotonyl chloride, was deblocked in 82 % yield to give alcohol **12b**, which was converted into the ester **14b** in 62 % yield. The

intramolecular Diels-Alder reaction of **14b** under the same conditions as above furnished two stereoisomers, **15b** and **15b** in 58 % and 17 % yields, respectively. The stereochemistry of the products were deduced from the chemical shift of the methyl group.

Application of this methodology for syntheses of other alkaloids is in progress.



Scheme 2

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