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

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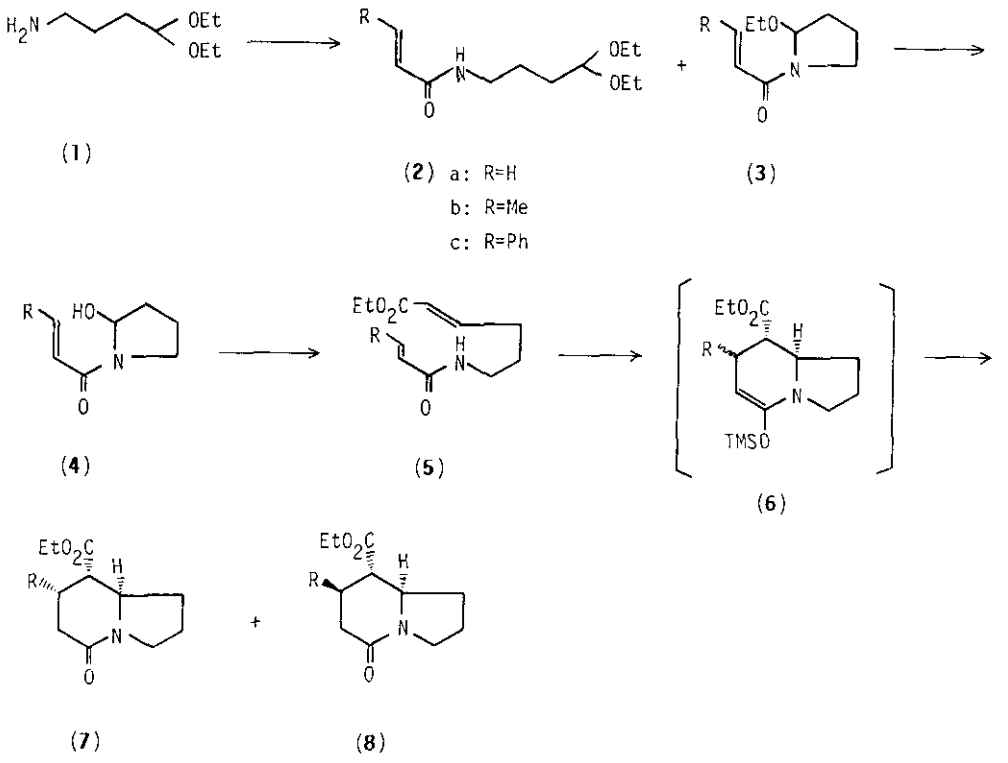
Abstract - Indolizidines and quinolizidines were synthesized through an intramolecular 1-aza-1,3-diene Diels-Alder reaction; the method provides an efficient route to (±)-epilupinine (**16**).

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 C_7 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.

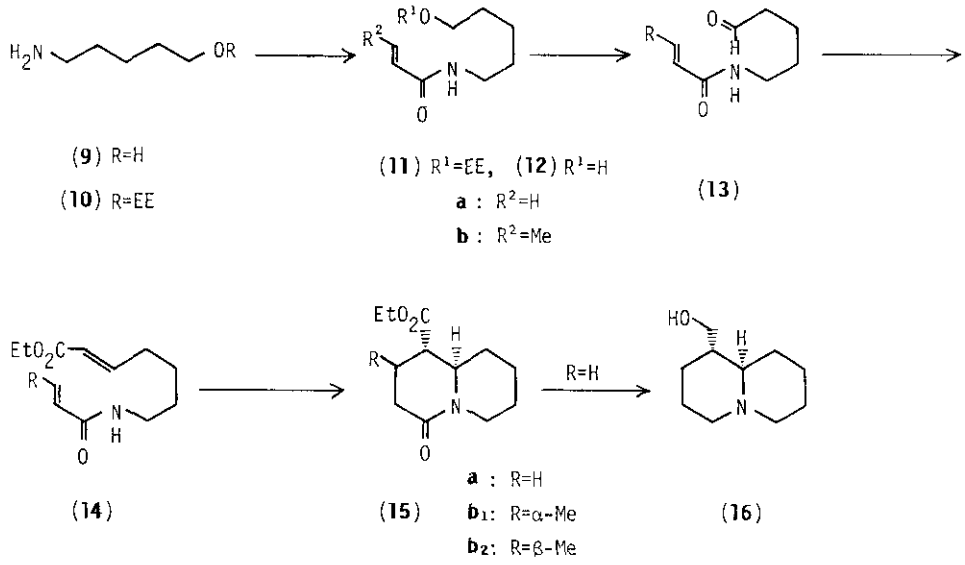


Scheme 1

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 dichloromethane[7] 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.



(**9**) R=H

(**10**) R=EE

(**11**) R^1=EE, (**12**) R^1=H

a : R^2=H

b : R^2=Me

(**13**)

(**14**)

(**15**) **a** : R=H; **b**$_1$: R=α-Me; **b**$_2$: R=β-Me

(**16**)

Scheme 2

ACKNOWLEDGEMENTS

We are grateful to Prof. Y. Ban and Prof. T. Wakamatsu, Hokkaido University for the spectral data of (±)-epilupinine. A part of this work was financially supported by Grant-in-Aid No. 59570884 from the Ministry of Education, Science and Culture, Japan, and by the fund from the Sendai Institute of Heterocyclic Chemistry.

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Received, 31st January, 1985