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The Syntheses of Lamellarins and Isoindolobenzazepine Alkaloids

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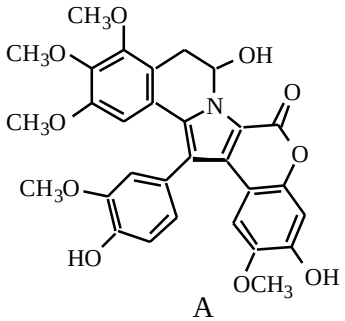
Abstract: Two efficient synthetic routes for the syntheses of lamellarin alkaloid and isoindolobenzazepine alkaloid are described.

Lamellarins are a group of marine natural products which were isolated from the prosobranch mollusc *Lamellaria sp* and the ascidians.



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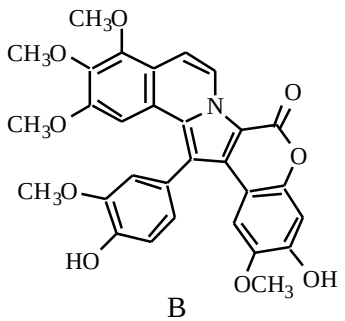

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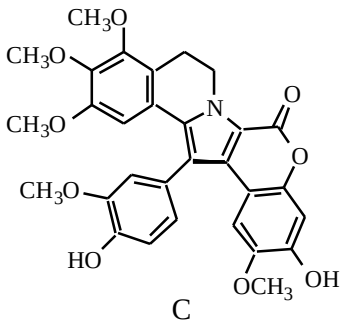

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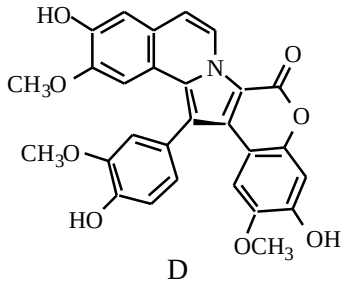

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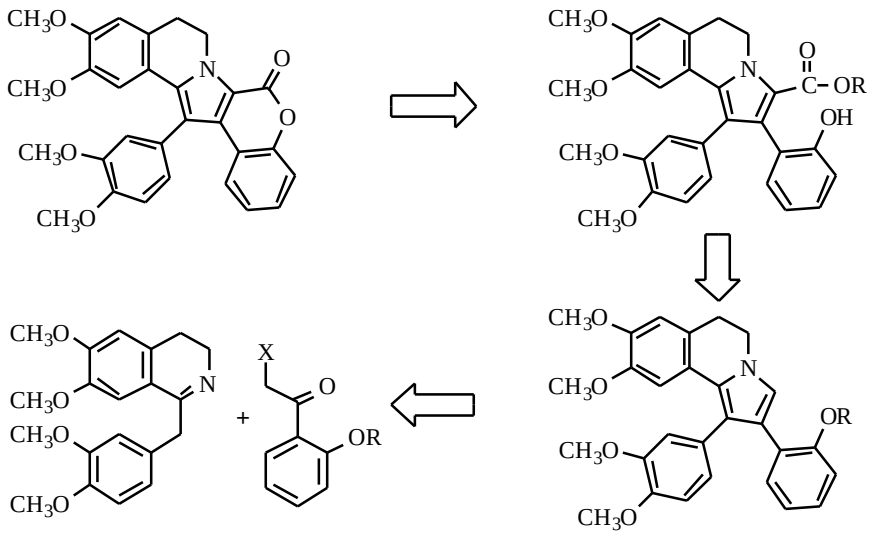
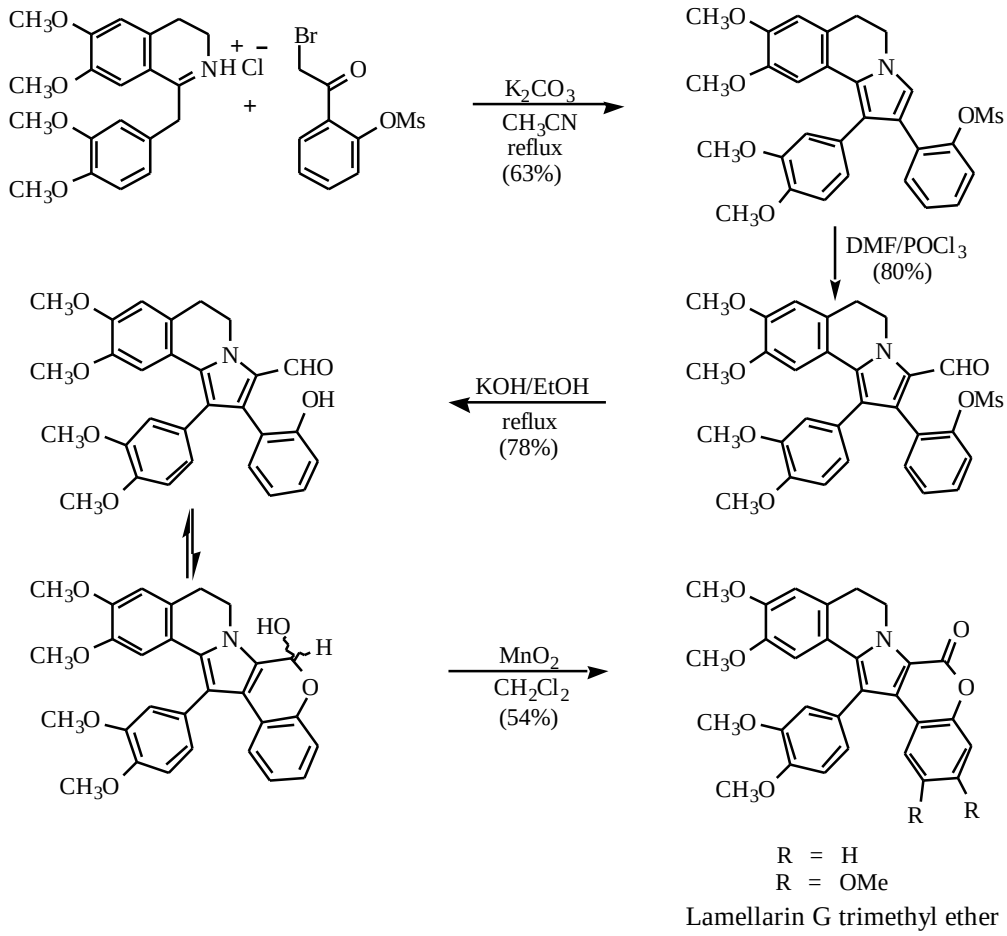
The first four lamellalins were isolated by Faulkner et al. in 1985 and named Lamellarins A, B, C, D. The structure of Lamellarin A was determined by X-ray crystallographic analysis and the structures of the remaining compounds were derived from spectroscopic data (1). More than twenty lamellarins have so far been isolated and identified (2). Some of these lamellarins exhibit interesting biological activities (3) including cell division inhibition, cytotoxicity, and immunomodulatory activity.

The core skeleton of these lamellarins can be viewed as the linking of the pyrroloisoquinoline with the lactone unit and so far three synthetic routes have been reported for the synthesis of these skeletons (4-6). Our synthetic route is based on the retrosynthetic analysis as shown.



Breaking of the lactone ring leads to carboxy phenolic compound, this carboxy phenolic compound can in turn be generated from the phenolic pyrroloisoquinoline molecule. It is envisaged that the pyrroloisoquinoline unit can be derived from the reaction of 3,4-dihydroisoquinoline derivative and the phenacyl halide molecule.

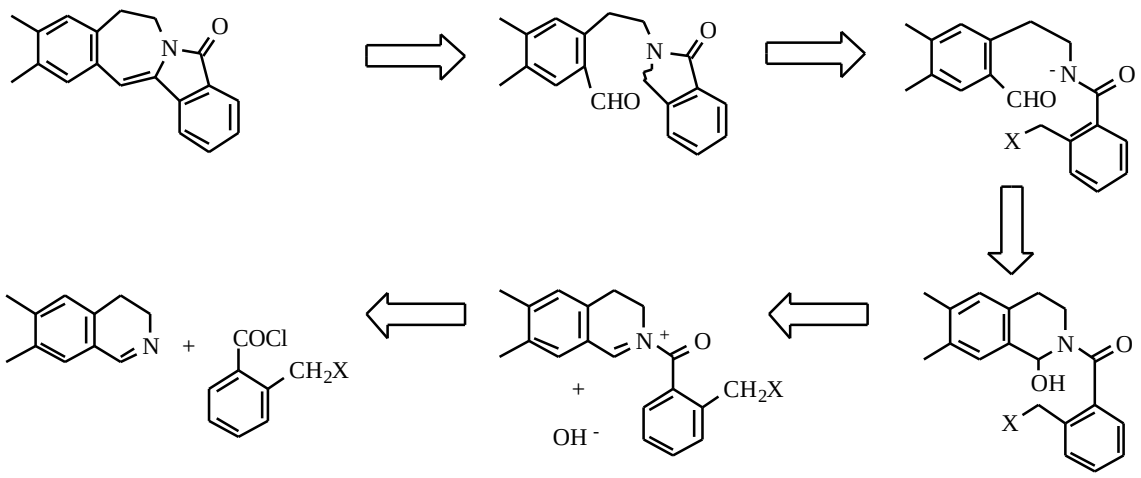
Indeed, the synthesis of the lamellarin skeleton can be accomplished via the above retrosynthetic analysis and this is shown in the scheme I.



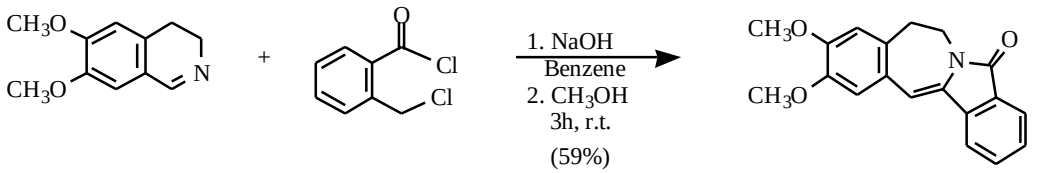
Scheme I

With the appropriate starting materials, Lamellamin G trimethyl ether was successfully synthesized.

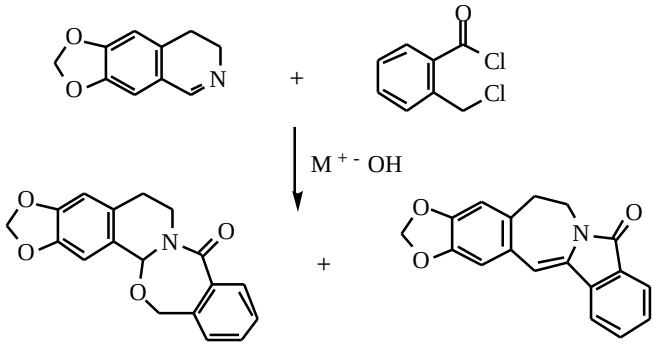
Our research group has also been interested in the synthesis of various benzylisoquinoline-derived alkaloids, including the isoindolobenzazepines (7). Our synthetic approach was based on the retrosynthetic analysis of the isoindolobenzazepine skeleton as shown.



Breaking of the carbon-carbon double bond of isoindolobenzazepine can lead to the aldehyde lactam intermediate. Disconnection of the carbon-nitrogen bond followed by condensation of amide anion with aldehyde group then gives the pseudobase. Pseudobase can be formed by the reaction of 3,4-dihydroisoquinoline with 2-halomethylbenzoyl chloride in the presence of hydroxide ion. This retrosynthetic analysis has been exploited for a one-pot synthesis of simple isoindolobenzazepine as shown.



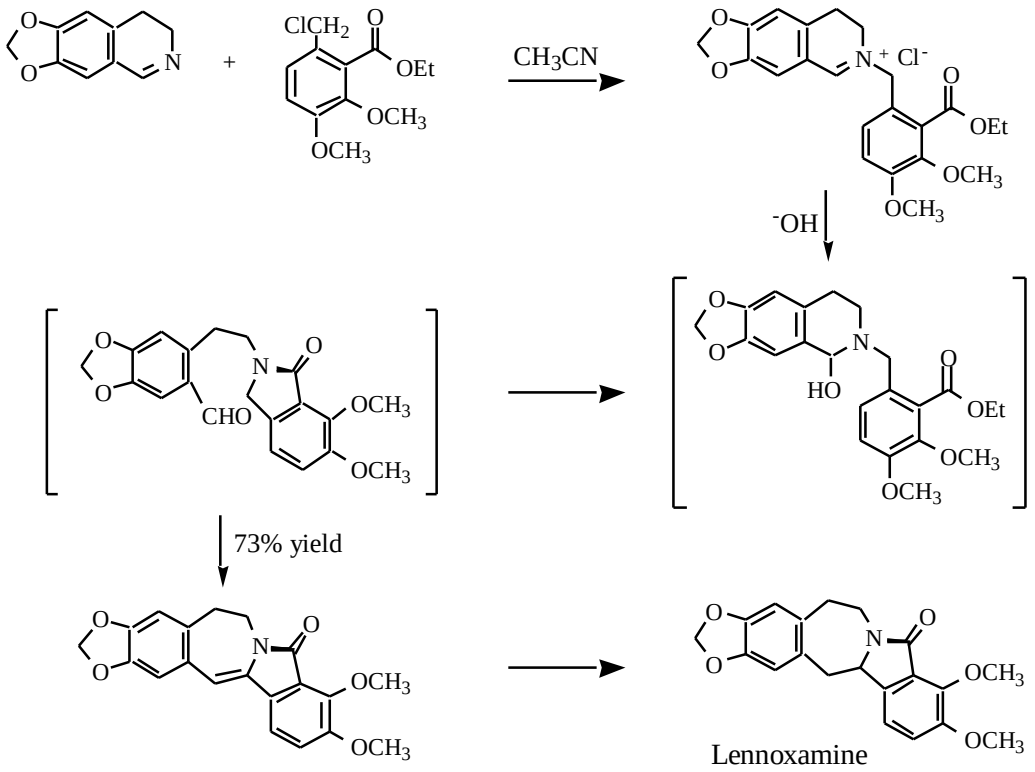
We have extended our study to the reaction of 2-chloromethylbenzoyl chloride with 3,4-dihydroisoquinoline and 3,4-dihydro-6,7-methylenedioxyisoquinoline in the presence of both sodium hydroxide and potassium hydroxide and these are shown.



	Cyclic ether		Benzazepine
For $M^+ = Na^+$	19 %	**Yield**	27 %
For $M^+ = K^+$	34 %	**Yield**	9 %

The above results suggested that while the approach is very efficient for the methoxylated isoquinoline, it cannot be efficiently utilized for the synthesis of isoindolobenzazepine containing

methylenedioxy group. However, we have successfully devised an alternative method for a very efficient synthesis of Lennoxamine, a natural product containing the methylenedioxy group, and the approach is as shown in scheme II.



Scheme II

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