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Development of cascade reactions for the synthesis of biologically active indole alkaloids

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Research Snippets

Nature produces numerous structurally complex and fascinating molecules that play an extremely supreme role in human health additionally as conjointly attract chemists to develop ways to access such biologically active compounds. Humankind has been used largely natural products as a source of traditional medicines for thousands of years and still represents the primary source of new drug development. The chemistry of Indole based alkaloids is one the most exciting research area owing to a wide range of biological activity and one of the prominent needs of medicinal chemistry.[1] Indole alkaloids are the classic example of structurally diverse architecture which shows the variety of biological activity. The synthesis of biologically active indole alkaloids is a challenging task that requires expertise in various aspects of organic synthesis. Numbers of synthesis designs and modifications already addressed various natural product scaffolds to serve humanity. Here, we highlight unique synthetic developments towards the construction of complexed biologically active scaffolds and application towards drug discovery using cascade approach to access biologically active indole-based alkaloids, the execution of cascade within the context of natural product synthesis with selected examples that address the future of this field. Cascade reactions (Domino or Tandem reactions) is an efficient methodology for the synthesizing core of structurally complex molecules therefore they received huge attention in a couple of decades. The continuously growing importance of cascade reactions impart synthetic chemists to achieve efficiency in synthesizing natural product scaffold. The cascade reactions have many benefits including atomic economy, time economy, resource management, besides this cascade process offers an economical and environmentally friendly approach for generating molecular complexity.[2][3] Because of their promising advantages, these reactions have found various applications in the synthesis of complex molecular frameworks such as in synthesizing natural products: (-)-3-O-methyl-10,11-demethoxychippiine, (-)-3-hydroxy-3,4-secocoronaridine, (-)-dippinine B, (+)- dippinine C, (-)-demethoxychippiine,[4] (-)-tubifoline, (+)-condyfoline, (+)-1,2-dehydroa-spidospermidine,[5] (Â±)-dehaloperophoramidine,[6] (âˆ')-jerantinines A,C,E, (âˆ')-16-methoxytabersonine, (+)-vinblastine,[7] lysergic acid,[8] (+)-tronocarpine,[9] and (+)-strychnine[10] etc. Introducing the total synthesis by cascade approach will empower the new thinking in organic synthesis and also provide a platform to approach a variety of scaffolds in total synthesis. Learning the unique approach to access structurally diverse natural products definitely can illuminate the area of chemistry of total synthesis. In the field of natural products and total synthesis, cascade reaction provides a great power of process to construct complex molecules and the core of the natural product in a single step.[11] Inspired by the distinctive biological activity of various indole-based alkaloids, like voacamine,[12] villalstonine,[13] toxiferine,[14] vinblastine,[15] ajmalicine[16] and catarantine,[17] our aim is to develop cascade methodology towards attempting the total synthesis of structurally complex molecules, along with discovery of novel potent drug candidates to cure mankind. To understand the basic evolution and early detection of disease, many attempts, clinical trials and potential strategies are being planned based on the immense interest in chemistry and biology. In this regard, a unified approach has been designed to synthesis effectively indole-based alkaloids and their simplified-designed analogues using a cascade approach incorporating well-known photochemical, cycloadditions, and Lewis-acid catalyzed reactions.

We have also developed a cascade approach to synthesize a bis-indole alkaloid yuchchukene natural product (antifertility and estrogenic activity) and its analogues (known for potent antiimplantation activity in rats as well as potential fertility regulatory agents), Yuremamine core (a new phytoindole),[18] pyrrolo[1,2-a]indoles and benzofuro[2,3-b]indulines motif utilizing Lewis-acid catalyzed cycloaddition. We extended our work for the total synthesis of recently isolated natural product such as shearilicine and paspalinine-13-ene along with previously reported paspalicine, paspalinine (low micromolar to nanomolar against various cancer cell lines).[19] Furthermore, our research group continuously looking forward to synthesis such promising scaffolds of the natural products of immense importance by the development of cascade approach.

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