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Molecular complexity and diversity from aromatics. Intramolecular cycloaddition of cyclohexa-2,4-dienones and sigmatropic shift in excited state: a unified approach towards synthesis of polycyclic frameworks related to crotogoudin, conidiogenol, and crinipellins

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ABSTRACT

Synthesis of polycyclic systems related to conidiogenol, crinipellin, and crotogoudin from simple aromatic precursor has been described. Oxidative dearomatization, tandem retro-Diels–Alder/Diels–Alder reaction, and photoreaction are the key features of our approach.

1. Introduction

Rapid creation of molecular complexity is one of the important aspects of contemporary design and development of methodology.[1] Generally, cascade or tandem reactions involving radicals, carbocations, carbanions, and pericyclic reactions are employed to achieve this objective.[1,2] Recently, chemistry of the reactive species such as *o*-cyclohexa-2,4-dienone ketals, α-acetoxycyclohexa-2,4-dienones, spiroepoxycyclohexa-2,4-dienones generated by oxidative dearomatization of phenols have gained increasingly more attention and methods based on these species have proved to be a powerful tool for efficient generation of molecular complexity.[2–4]

Nature continues to be a rich reservoir of wide variety of compounds having potent biological activity that often provide leads for drug discovery and development.[5] Recently, investigation on extract from madagascan plant *Croton goudotii* and *Croton barorum* led to isolation of diterpenoids crotogoudin **1a** and crotobarin **1b** (Fig. 1). These compounds exhibited strong cytotoxic activities against P388 murine lymphocytic leukemia cell line.[6] The diterpenoids **1a**,**b** belong to 3,4-secoatisane family and possess a unique molecular structure comprising complex tetracyclic network having several stereogenic centres, quaternary carbons and spiroannulated rings.

The unusually complex structural features of crotogoudin **1a** and crotobarin **1b** pose considerable synthetic challenge. Maier and Ushakhov first reported[7] synthesis of tricyclic ring system of crotogoudin, subsequently Carreira and Breitler disclosed an elegant synthesis of crotogoudin **1a** employing a radical cascade[8a] and we described an approach to tricyclic network of crotogoudin.[8b] Most recently, Jia and co-workers reported synthesis of tricyclic ring system of crotogoudin[8c] while total synthesis of crotogoudin and crotobarin has been achieved by Liu and co-workers.[8d]

Sterner and co-worker isolated two diterpenes from the extracts of fermentation broth of *Penicillium cyclopium* which were found to induce conidiogenesis in the producing organism. The diterpenes are identified as conidiogenol **2a** and conidiogenone **2b** (Fig. 1) which have unique tetracyclic molecular architecture containing linear triquinane annulated with a six membered ring.[9]

Crinipellins, a class of polyquinane diterpenoids, were isolated from various strains of *Crinipellis stipitaria*. Anke and Steglich reported the isolation of crinipellin A **3a** from the cultures of basidiomycete *C. stipitaria*, strain 7612, which was found to be active against Gram-positive bacteria.[10] Subsequent investigations by Steglich and co-workers on several strains of *C. stipitaria* led to the isolation of other related crinipellins such as crinipellin B **3b** and

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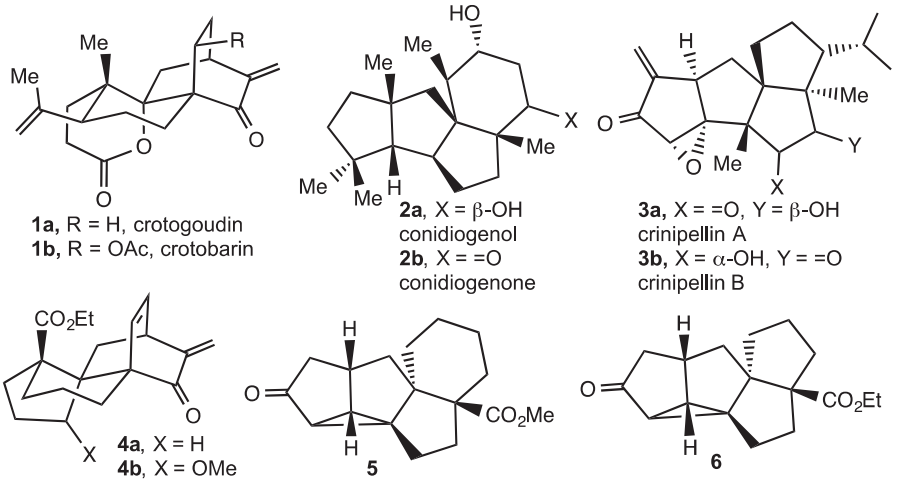


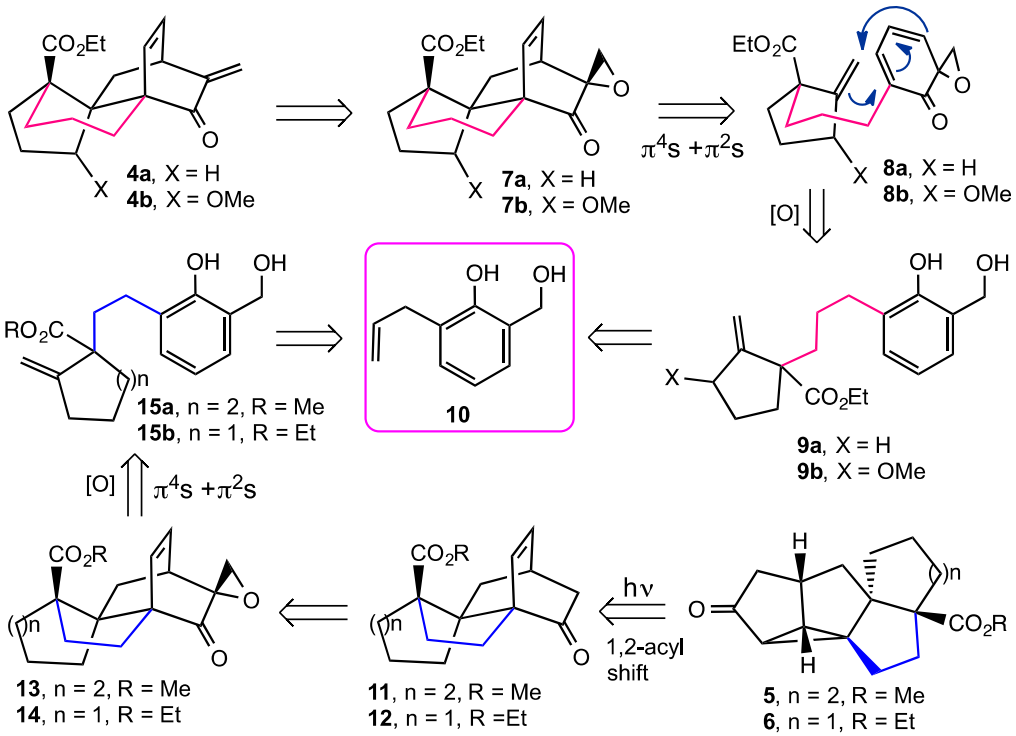
Fig. 1. Structure of crotogoudin, crotobarin, crinipellins, conidiogenol, conidiogenone and compounds **4**–**6**.

others that were found to exhibit antibiotic activity.[11] Recently, Shen and Li reported isolation of several other crinipellins which exhibited moderate antitumor activity against HeLa cells.[12] The crinipellins are the first group of natural products to contain a tetraquinane framework that incorporates both a linear *cis*:*anti*:*cis* triquinane as well as an angular triquinane ring systems.

There has been longstanding interest in the synthesis of polyquinanes,[13–15] however, studies directed towards synthesis of architecturally more complex crinipellins are limited.[16] Piers and Renaud reported synthesis of crinipellin B.[16f] Recently, Lee and coworkers reported a total synthesis of crinipellin A.[16i] Though there are no syntheses of conidiogenol, there are a few reports on the synthesis of the tetracyclic system of conidiogenol.[17]

We have been interested in the development of new methodology for creating molecular complexity employing oxidative dearomatization of *o*-hydroxymethyl phenols, cycloaddition, and photochemical reactions.[4,18] In view of the above and in order to extend the scope of our methodology, we considered exploring a common route to polycyclic compounds **4a**,**b** related to crotogoudin and polyquinanes **5** and **6** (Fig. 1) containing tetracyclic network of conidiogenol and crinipellins, respectively, and wish to report our results herein.

Our general strategy is delineated in the Scheme 1. It was contemplated that compound **4** having exocyclic alkene moiety may be easily derived from keto-epoxide **7** by manipulation of the oxirane ring. The ketoepoxide **7** was considered amenable from aromatic precursor **9** via oxidative dearomatization to spiroepoxycyclohexa-2,4-dienone **8** followed by intramolecular cycloaddition. The precursor **9** would be easily derived from 3-allyl salicyl alcohol **10**.



Scheme 1. Retrosynthetic scheme.

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