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Abstract

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Total Synthesis and Cytotoxicity Evaluation of Pareitropone and Analogues

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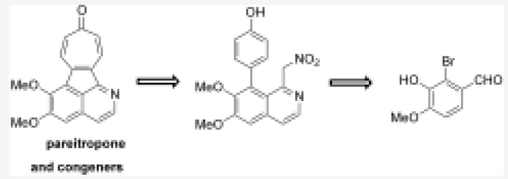
ABSTRACT: A concise synthesis of pareitropone by oxidative cyclization of a phenolic nitronate is delineated. The use of TMSOTf as an additive to promote the facile formation of a strained norcaradiene intermediate provides convenient access to highly condensed multicyclic tropones in high yields. This synthesis is modular, efficient, and scalable, highlighting the synthetic utility of radical anion coupling reactions in annulation reactions. This work is discussed in the context of total syntheses of the tropoloisoquinoline alkaloids. Also included are the preparation of several congeners and a brief description of their biological activities.



INTRODUCTION

The tropoloisoquinoline alkaloids **1**−**7** comprise a small group of secondary metabolites isolated from the plants of the tropical American genus *Abuta* (in the *Menispermaceae* family) (Figure 1).[1] Recently isolated from the genus *Acorus* was neotatarine (**7**).[2] These natural products are characterized by highly condensed aromatic heterocycles. The primary structural distinction among the tropoloisoquinoline alkaloids resides in the location and degree of polyoxygenation in the heterocycle nucleus. They possess close structural resemblance to colchicine (**8**), the most prominent tropolone natural product.[3] Their biosynthetic pathways may feature the intermediacy of fused cyclopropanes, which is congruent with the co-occurrence of the more abundant azafluoranthene alkaloids in the same *Abuta* plant sources.[4] Cytotoxic properties were reported for some of these alkaloids, in particular, pareitropone (**1**).[5] It is unknown whether its mode of action is linked to the well-established antimitotic (tubulin binding and microtubule assembly) activity of **8**, but **2** and **3** were reported to be inactive in a tubuline-binding activity.[6] Interestingly, neotatarine (**7**) was reported to display protective effect against Aβ_{25-35} (β-amyloid peptide)-induced neurotoxicity.[2]

The unique aromatic heterocycle core of the tropoloisoquinoline alkaloids and their bioactivity prompted synthetic studies, culminating in attractive syntheses of **1**−**5**.[6−9] Pareitropone (**1**) was reported to have the most potent cytotoxicity (against the leukemia P388 cell lines) despite its relatively uncommon tropone motif (compared to other tropolone members). Another impetus for launching a synthesis campaign was its scarcity from natural sources. It

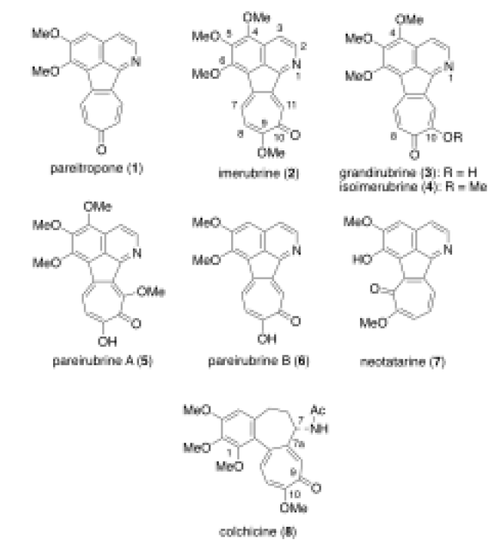


Figure 1. Tropoloisoquinoline alkaloids and colchicine.

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