EFFICIENT AND CONCISE SYNTHESIS OF SPIRO-ISOXAZOLINE: FIRST TOTAL SYNTHESIS OF 11-DEOXYFISTULARIN-3

Prasanta Das and Ashton T. Hamme II

Department of Chemistry & Biochemistry, Jackson State University, Jackson, MS 39217, USA

Abstract: The natural occurrence and the discovery of new synthetic agents displaying antineoplastic activity is an important topic of research in medicinal chemistry. Since the first reports about the herbicidal and plant hormonal activity, spiroisoxazoline containing natural products and their analogues have stimulated much interest in medicinal chemistry. Among the broad spectrum of α-oximinotyrosine derived natural products isolated from marine sponges, in particular 11-deoxyfistularin-3, purealidin P and Q are cytotoxic against the MCF-7 breast cancer cell line (LD₅₀ = 17 mg/L), murine lymphoma K1210 (IC₅₀ 2.8 and 0.95 mg mL⁻¹ respectively) and human epidermal carcinoma KB (nasopharynx) (IC₅₀ 7.6 and 1.2 mg mL⁻¹ respectively) cell lines. The other members from the same family are also widely known for their diverse pharmacological activities including antiviral, antimicrobial, anti-HIV, antifungal, antifouling, Na⁺/K⁺ ATPase inhibition, HDAC inhibition, histamine H₃ antagonism, mycothiol S-conjugate amidase inhibition, isoprenylcysteine carboxy methyltransferase (Icmt) inhibition. Owing to the diverse biological activity along with structural diversity, many synthetic strategies mainly based on classical aromatic oxidation including toxic metal and electroorganic oxidation, NBS, and PIDA have been reported to these class of natural products so far. We herein reporting a concise and efficient base promoted Dickmann type keto-ester condensation strategy to generate the spiroisoxazoline moiety. The consecutive over bromination-elimination-bromination of the corresponding spiro-moiety has been successfully utilized to furnish the desired core structure of many bromotyrosine derived spiroisoxazoline natural products. The Bromo-spirocyclic acid was further coupled with hydroxymoloka’iamine to accomplish the first total synthesis of 11-deoxyfistularine-3. This strategy could be an efficient alternative of previously developed approaches that utilized an aromatic ring oxidation as the essential step to synthesize this class of natural products. In addition to the synthesis of the aforementioned natural product, our methodology was utilized for the construction of a series of dibromo-quinone derivatives of quinine-based spiroisoxazolines as novel analogues of biological interest.

Keywords: Isoxazoline ketoester, Dicmann Condensation, Bromination-elimination-bromination, Spiro-isoxazolines, Amide coupling, Natural products.

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