A MODEL STUDY FOR THE CONCISE SYNTHESIS OF BROMOTYROSINE DERIVED SPIROISOXAZOLINE CORE STRUCTURES

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Abstract: The marine sponges (e.g. order Verongida and Suberea mollis) widely known to produce a series of α-oximinotyrosine derived monomeric and dimeric spiroisoxazolines as secondary metabolites. The structural diversity arising from a unique spiro linkage between a brominated cyclohexadiene, an isoxazoline along with a wide range of amine and diamine linkage, brings about a broad spectrum of 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, and antineoplastic properties. The purpose of this project was to find a model study towards the synthesis of α-hydroxyspiroisoxazolines resembling the core structure of bromotyrosine derived natural products. The model synthesis of spiroisoxazoline core mainly involved the multifunctionalization approach of a key 1,3-diketo-spiroisoxazoline. In our synthesis, the acyclic isoxazole derivative was treated with sodium hydride to afford the diketone spiroisoxazoline in 80% yield. We next investigated the optimal reaction conditions (5 mol% TiCl₄ in methanol, Et₃N) to synthesize the desired spiro-methoxyenone as a major product. With the anticipation of furnishing a conjugated double bond, we treated the predominant isomer with LiHMDS, PhSeCl followed by H₂O₂, which afforded the corresponding spiro-diene in 75% yield. However, our further efforts towards the dibromination were abortive after a number of attempts. In this context, we then decided to switch the electrophile used in the synthesis of spiro-diene from phenylselenium chloride to bromine. The major isomer was treated with excess (2.5 equiv.) LiHMDS followed by treatment with excess bromine to provide the allylic geminal dibromo compound via monobromination. Without further purification, the crude allylic geminal dibromo compound was reacted with DABCO in situ to afford mono bromo spiro-diene in 76% yield over two steps in one reaction vessel. Further bromination of the carbon adjacent to the carbonyl was achieved in 76% with NBS in the dark. Finally, the diastereoselective reduction of spiro-ketone with Zn(BH₄)₂ afforded the desired spiroisoxazoline core structures in a 4:1 diastereomeric ratio favoring the major isomer.

Key words: 1,3-Diketo-Spiroisoxazoline, Spiro-Methoxyenones, Dibromo Spiroisoxazoline

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