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Recent progress toward the total synthesis of humulanolides

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ABSTRACT

The humulanolides are a series of sesquiterpene lactones, most of which have unique and challenging structure. The humulanolides have exhibited anticancer activity. The combinations of fascinating structural motifs and promising pharmacological properties have prompted significant interest in the synthetic community. In this review, we provide a summary of recent progress regarding the total synthesis of humulanolides.

Contents

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1. Introduction

The field of natural product total synthesis has evolved considerably since the pioneering work of Woodward in the 1940s.[1] A large number of natural products have been synthesized during the past eight decades, some of which have been marketed commercially as therapeutic agents to treat a variety of conditions. Natural products can be divided into specific chemical families depending on their structural characteristics that contain several other members.[2] It is therefore important for synthetic chemists to familiarize themselves with the diverse range of structural frameworks associated with different natural product classes, so that they can develop an understanding of the pathways responsible for the biosynthesis of these materials. This understanding can also benefit synthetic chemists in terms of assisting them in the design of increasingly efficient synthetic approaches.[3] In this review, we have provided a summary of recent work towards the total synthesis of humulanolides, including an overview of the synthetic strategies typically used to access these molecules, which will hopefully inspire future synthesis.

2. Isolation and bioactivity of humulanolides

The humulanolides are a structurally complex series of sesquiterpene lactones that consist of a bridged cyclic butenolide connected to an 11-membered ring or bicyclo[6.3.0]undecane ring, and several compounds belonging to this structural class have been reported to show excellent bioactivity (Fig. 1). One of the most important contributors to the field of humulanolide research was San Feliciano. The first member of the humulanolide family of natural products to be isolated and fully characterized was asteriscunolide A (**1**). This compound contains an 11-membered ring and was first isolated from *asteriscus aquaticus* in 1982.[4] Subsequent work involving the same plant species allowed for the isolation of asteriscunolides B (**2**), C (**3**) and D (**4**),[5] and the stereochemical characteristics of asteriscunolides A, B, C and D were later confirmed by X-ray diffraction analysis.[6] Following on from this early work, Bohlmann reported the isolation of a new compound containing a rather unusual bicyclo[6.3.0]undecane skeleton, which was subsequently named 6,7,9,10-tetradehydroasteriscanolide (**5**).[7] The saturated version of this compound, asteriscanolide (**6**), was isolated soon after.[8] Aquatolide (**8**) was first isolated in 1989 and assigned as a rare ladderane substructure; however, further isolation work and X-ray crystallographic analysis revealed this incorrect assignment, and the structure was subsequently revised to the uncommon bicyclo[2.1.1]hexane core shown in the figure.[9] 6,7,9,10-Tetrahydroasteriscunolide (**9**) was isolated in 2001 and its structure was initially established by two-dimensional NMR spectroscopy.[10] The structure of this material was later confirmed by X-ray diffraction analysis using synthetic material.[11] Naupliolide (**10**) was isolated as a novel tetracyclic skeleton in 2006, together with asteriscunolides A–D and 6,7,9,10-tetradehydroasteriscanolide.[12] Most recently, Triana et al. reported the isolation and characterization of several new members of the humulanolide family, namely 6β,7β-epoxyasteriscunolide A (**11**), 2α,3α-epoxyasteriscunolide C (**12**), 6β-hydroxy-asteriscunolide A (**13**), 6β-ethoxy-asteriscunolide A (**14**) and asteriscanolidenol (**15**).[13]

Several humulanolide compounds have been reported to exhibit anticancer activity. For example, asteriscunolide A (**1**) induces apoptosis in several human cancer cell lines,[14] whereas asteriscunolides A–D exhibit moderate cytotoxic activities against neoplastic cell lines, including A-549 (human lung carcinoma), HT-20 (human colon carcinoma), and MEL-28 (human melanoma) cells. Furthermore, asteriscunolide D (**4**) exhibits greater cytotoxicity than cisplatin.[15] To the best of our knowledge, there have been no reports pertaining to the biological activities of sesquiterpene lactones **5**, **6**, **8** and **10**, although it is envisaged that these molecules will exhibit some interesting biological properties. The newly isolated humulanolides (**11**–**15**) reported by Triana's group were assessed in terms of their cytotoxicity against HL-60 and MOLT-3

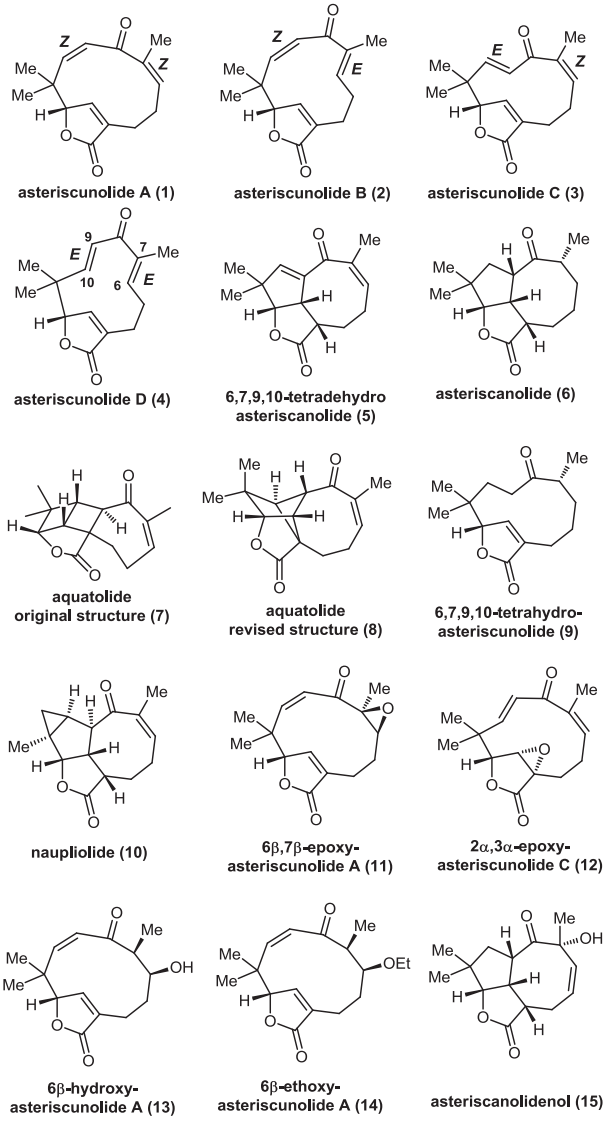

Fig. 1. Humulanolides.