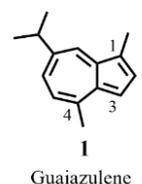


Synthesis of guaiazulene carboxylic acid derivatives utilizing unique reactivity

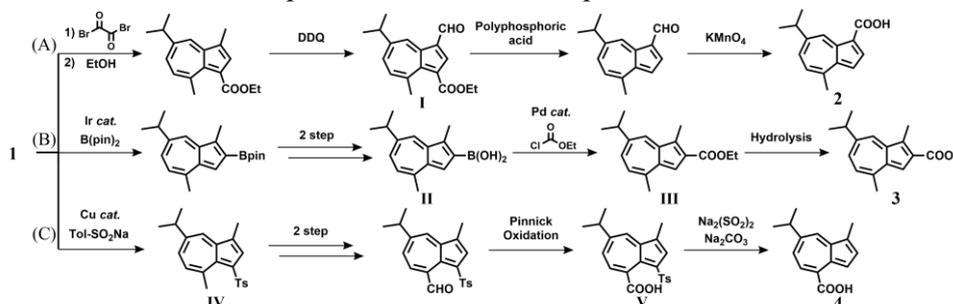
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Azulene conjugates are impacting the development of useful materials in a variety of research fields.¹ Guaiazulene (**1**) has attracted particular attention in the medical and cosmetic field as a natural compound that can be extracted from fungi and corals of the genus *Lactarius*.² Chemical transformations to introduce a substituent into **1** have been very limited by its unique reactivity arising from the polarized π -electron system and the alkyl substituents of **1**, therefore, the number of their derivatives is still small. To enable the development of a wider range of materials, there is a need to establish synthetic routes for their various derivatives. In this study, we report the synthesis of guaiazulene derivatives with carboxyl groups in various positions using **1** as a starting material, focusing on the carboxyl group, which can be converted into various molecules and is of high synthetic value.



In the synthesis of **2**, the selective oxidation of C1 methyl group in **1** was attained by protecting **1** with an ester group from side reaction at the C3-position (**1**→**I**). Subsequently, **2** was synthesized *via* decarboxylation and oxidation reaction (**Scheme 1A**). To synthesize **3**, boronic acid **II** was prepared by the Ir-catalyzed direct borylation³ at the C2-position. Then, the Pd-catalyzed coupling reaction of ethyl chloroformate with **II** afforded **III**. The subsequent hydrolysis of **III** gave **3** (**Scheme 1B**). Selective oxidation of the C4 methyl group required Cu-catalyzed tosylation at the C3-position as a precursor. Finally, the synthesis of **4** was achieved by oxidation of the C4 methyl group to a carboxyl group (**IV**→**V**) and removal of the tosyl group (**Scheme 1C**). In this presentation, the details of the reaction and the optical properties of the obtained compounds will be further explained.



Scheme 1. Syntheses of guaiazulene carboxylic acid derivatives

References: 1) a) K. Tsurui *et al.*, *Adv. Funct. Mater.* **2014**, *24*, 7338. b) T. Shoji *et al.*, *J. Org. Chem.* **2018**, *83*, 6690. 3) M. Fujinaga *et al.*, *Synthesis* **2008**, *37*, 45. 2) D. Chen *et al.*, *J. Agric. Food Chem.* **2012**, *60*, 112.