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Synthesis of gibberellin derivatives with anti-tumor bioactivities

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ABSTRACT

A series of gibberellin based molecules were designed and synthesized. Gibberellin derivatives bearing two α,β-unsaturated ketone units showed strong anticancer activities in MTT assay towards a number of human cancer cell lines including HT29, A549, HepG2 and MKN28. The most potent gibberellin derivative (compound **10**, IC_{50} = 2.9 μM against HT29) inhibited completely the topoisomerase I activity at 8 μg/mL level.

Tetracyclic diterpenes constitute a large class of natural products isolated from plants, microorganisms and marine source.[1] Many of those compounds possess interesting biological activities, especially the gibberellin family and the *ent*-kaurenoid diterpenes. Representative structures of these two diterpenoid groups, ericalycin B (**1**), oridonin (**2**) and gibberellin GA_3 (**3**), are shown in Figure 1. These two families are closely related, gibberellins are biosynthetically from *ent*-kaurenes.[2] A number of *ent*-kaurene diterpenoids possess strong bioactivities against tumor cell lines[3] while gibberellins have been used as important plant growth regulators.[4] Ericalycin B and oridonin are two *ent*-kaurenoids with strong antitumor bioactivity by preventing NF-κB nuclear translocation and inducing IκBα cleavage.[5] A representative structure unit in both molecules is the α,β-unsaturated ketone, especially in the cyclopentane D ring system. Previous studies had well demonstrated that the α,β-unsaturated carbonyl unit incorporated in a cyclopentane or a γ-lactone system is responsible for anti-neoplastic activities.[6] Although gibberellins constitute a large number of compounds with more than 130 members being isolated, an α,β-unsaturated ketone moiety is rarely presented in gibberellin diterpenes. To the best of our knowledge, there is no report on antitumor gibberellins.[7] We were curious to know if such a system were incorporated into the structure of gibberellin GA_3 (**3**), would the resulting gibberellin derivatives bearing an α,β-unsaturated ketone unit display toxicities towards cancer cell lines? By the way, gibberellin GA_3 is abundant and commercially available in large quantities as a plant growth regulator. A research program aiming to assemble α,β-unsaturated ketone moiety to the tetracyclic ring system of gibberellins, especially the D ring, was thus initiated.

Starting from gibberellin GA_3 (**3**), the methyl ester (**4**) and benzyl ester (**5**) were prepared in high yield[8] as outlined in Scheme 1. Diacetate **6** was also prepared by treatment of alcohol **5** with acetic anhydride. With those three compounds (**4**, **5** and **6**) in hand, we initiated the key allylic oxidation to introduce a hydroxyl group to the D-ring of gibberellins. By treatment of substrates with selenium dioxide in the presence of *tert*-butyl hydroperoxide, allylic alcohols were obtained.[9] Having completed the synthesis of compound **7–9**, our attention was then focused on the oxidation of allylic alcohol **9**. To our disappointment, pyridinium dichromate as well as activated MnO_2 failed to promote the desire transformation. The goal was finally realized by a Swern oxidation and the gibberellin derivatives (**10**, **11** and **12**) that bear desired α,β-unsaturated ketone unit were obtained in good yields (see Scheme 2).[10] Carefully examination of the ^{13}C NMR spectrum of compound **10** and **11**, we noticed an unexpected tertiary carbon NMR signal at 65.9 ppm. This NMR signal is unlikely the resonance of a tertiary carbon bearing a hydroxyl group. We speculated that a chlorine atom rather than a hydroxyl group was attached to the C-13 position. The deduced structure was later confirmed by mass spectra (LRMS and HRMS) and further supported by conversion of compound **10** to C-13 hydroxyl compound **14** in the presence of

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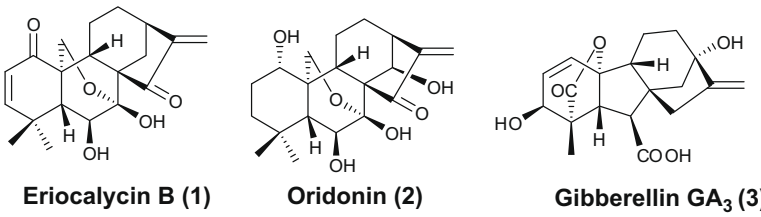


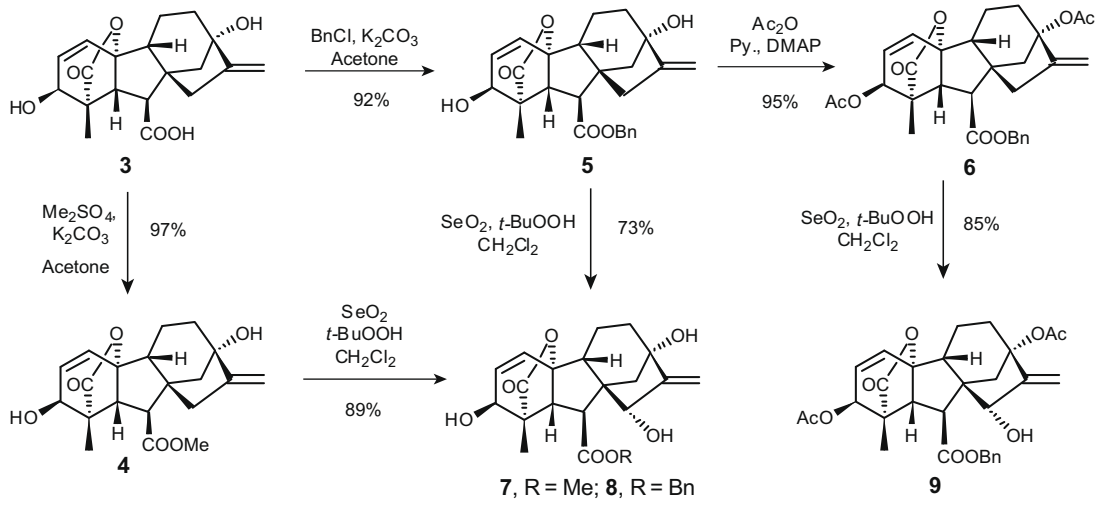
Figure 1. Representative tetracyclic diterpenes (**1–3**).

silver carbonate in wet acetone as indicated in Scheme 3.[11] The chloride compound (**10** and **11**) might be formed by a displacement of the hydroxyl group at C13 position with a chloride anion under the condition of Swern oxidation.[10]

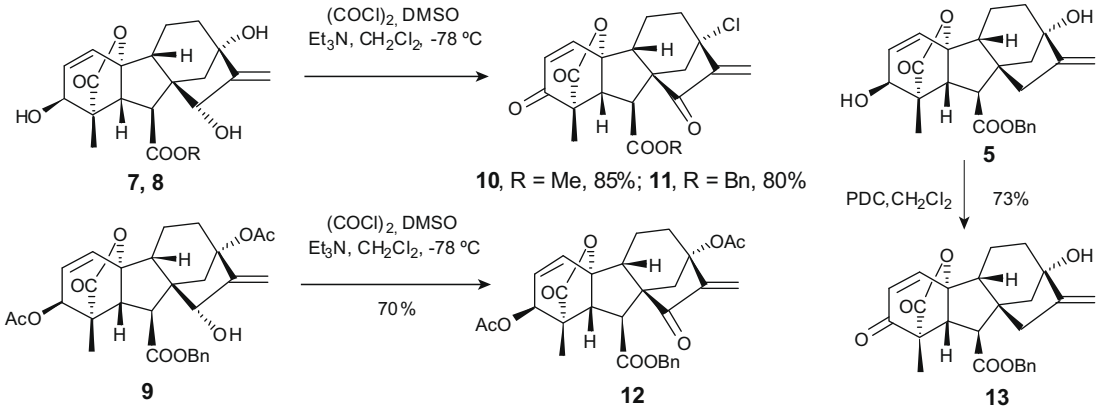
Having obtained gibberellin derivatives bearing a desired α,β-unsaturated ketone moiety, we then initiated a bioassay of these compounds. The cytotoxic potential of all synthesized gibberellin analogues was evaluated in vitro against two human tumor cell lines according to procedures described in the literature.[12] The tumor cell line panel consisted of human promyelocytic leukemia cell line (HL-60) and human bladder carcinoma cell line (BIU-87). Cisplatin (DDP) was used as the reference drug. The results of the cytotoxicity studies were indicated in Table 1 (IC_{50} value, defined as the concentration corresponding to 50% growth inhibition).

To our delight, two compounds (**10**, **11**) with α,β-unsaturated ketone substructure presented in both the D-ring and the A-ring showed strong toxicities toward tumor cells (see Table 1). For compounds without an α,β-unsaturated ketone unit, no cytotoxicities were observed in the bioassay. Only low level of activities was recorded for compounds with one α,β-unsaturated ketone functionality, either in the A-ring (**13**) or the D-ring (**12**) system. These results strongly suggested that both α,β-unsaturated ketone units are required for a better bioactivity.

To get further insight toward the structure and activity relationship, a number of C-13 substituted compounds were synthesized by displacement of the chloride at C-13 with corresponding anions (see Scheme 3). Although C-13 florides (**16**, **17**) and C-13 iodides (**18**, **19**) could be obtained in reasonable yields, we failed to



Scheme 1. Synthesis of 15-hydroxyl gibberellin derivatives.



Scheme 2. Synthesis of gibberellin derivatives bearing α,β-unsaturated ketone moiety.