Efficient Synthesis of Novel Jolkinolides and Related Derivatives Starting from Stevioside

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Abstract: Jolkinolides are naturally occurring tetracyclic diterpene from *Euphorbia* genus, which exhibit promising antitumor and other biological activity. Efficient syntheses of the 19-carboxy derivative of jolkinolide A and 19-hydroxyjolkinolide E have been accomplished in 13 steps with a total yield of 7.8% starting from the easily available and low-cost sweetener stevioside, and some related derivatives have also been synthesized.

Key words: jolkinolides, Euphorbiaceae, stevioside, antitumor

Natural products are interesting sources of novel leading compounds for the design of new drugs. 'Lang-du' serving as a kind of traditional Chinese medicine with various biological activity was first described ~2,000 years ago. It is the root of dried *Euphorbia Fischeriana Steud* (*Euphorbiaceae*) and has been used in folk medicine for the treatment of cancer, edema, inflammation, tuberculosis, and ascites.[1] Many scientists have paid close attention to the active components of this herb, and many investigations have reported that it mainly contained diterpenoids, triterpenoids, tannins, and steroids.[2] Abietane lactone-type diterpenoids are the main components in *Euphorbia* genus, and this kind of carbon skeleton is commonly tetracyclic with a γ-ylidenbutenolide functionality in ring D and some oxidation function groups in ring C, such as an unsaturated bond and hydroxy, carbonyl, and epoxy groups.[3] Jolkinolides A, B, D, and E (Figure 1) are the representative compounds of the abietane lactones and exhibit significant antitumor activity with IC_{50} values ranging from 7.1 nM to 0.5 μM.[4] It was reported that the molecular target and mode of action of abietane lactones were inhibition the activation of NF-κB signaling pathway and JAK/STAT signaling pathway, and induced apoptosis of tumor cells.[5]

Katsumura et al.[6] carried out the total synthesis of (±)-jolkinolides A, B, and E starting from 10-(methoxycarbonyl)-β-ionone through a synthetic route of almost twenty reaction steps and bearing a low yield to obtain the target compounds. Herein, we simply modified the synthetic route using easily available and low-cost stevioside as our starting material, and developed a facile access to obtain the target compounds (Scheme 1).

Stevioside was hydrolyzed by a literature method[7] to give the steviol **4** in 70% yield (Scheme 2). Selective esterification of **4** with chloromethyl methyl ether and *N*,*N*-diisopropylethylamine gave **5** in good yield (95%).[8] Treatment of **5** with selenium oxide and *tert*-butyl hydroperoxide led to **6** (85%), which was subsequently oxidized with pyridinium dichromate to afford **7** (75%).[9] Ozone oxidation of **7** at –78 °C gave a mixture of **8** and **9**.[10] In normal ozonolysis, only the double bond is cleaved, but during this reaction, the C_{13}–C_{16} and C_{15}–C_{16} single bonds are both cleaved. We proposed that the Criegee rearrangement may have occurred.[11]

As shown in Scheme 3, during the ozone oxidation process, the C_{16}–C_{17} double bond of **7** was transformed to 1,2,3-trioxacyclopentane intermediate **I**, which then rearranged to the more stable ozonide intermediate **III**, and further rearrangement of intermediate **III** with the loss of methanal provided **8**, some of which was decarboxylated to afford compound **9**. We attempted to modify the reaction conditions (e.g. time, temperature, ozone quantity) to increase the yield of **9**, but the products of ozonolysis were still a mixture of **8** and **9**. Next we examined the transformation of **8** to **9**, several conventional decarboxylation methods [e.g., $Pb(OAc)_4$, $NaIO_4$] were attempted, but failed. However, when we treated **8** with pyridinium

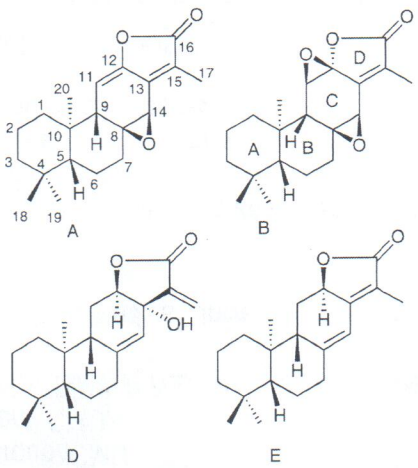

Figure 1 Structures of jolkinolides A, B, D, and E

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