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Studies on the Total Synthesis of Hainanolide (VI)-The First Access to the Lactone Functionality

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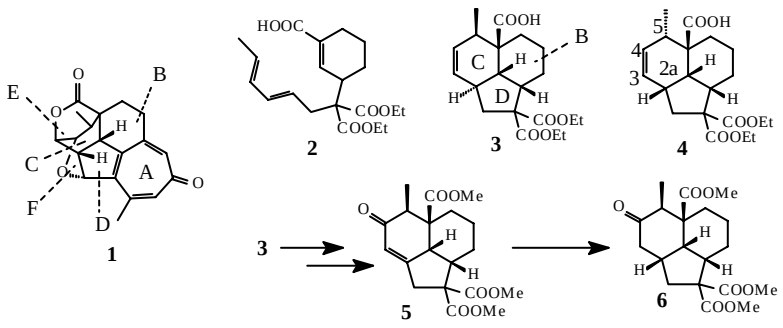
Abstract: C_{2a}-β-H ketone **6** was synthesized from the *exo*-IMDA-additive **4** with the aid of singlet oxygen, and ring E of hainanolide was assembled *via* kinetic enol ether of **6**.

Keyword: Hainanolide, *exo*-IMDA-additive, 1,4-lactone.

The intramolecular Diels-Alder reaction (IMDA) stands as the fundamental strategy in our total synthesis of hainanolide **1**, to assemble the tricyclic skeleton, ring B, C and D, as it was reported [1]. Cyclization of triene **2** afforded a mixture of *endo*-IMDA-additive **3** and *exo*-IMDA-additive **4**, the ratio of which varied with reaction conditions. Yet neither **3**, with the C_{2a} hydrogen at α position, nor **4**, with the C_5 methyl at α position, fits the configuration of that in the natural product. The stereochemistry of C_{2a}-α-H of *endo*-IMDA-additive **3** was successfully revised through six steps, as it was reported in our previous paper [2]. The α,β-unsaturated ketone **5** served a key intermediate in the process (**Scheme 1**).

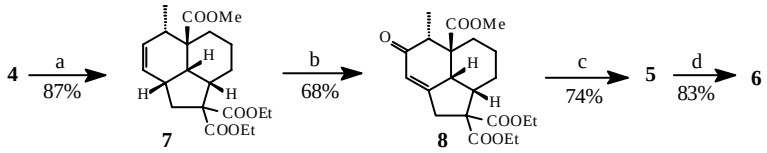
Scheme 1



Our recent study [3] on the ene-like mode reactivity of $^1O_2$ towards *exo*-IMDA-additive **4** suggested an effective procedure to obtain this compound, in convergence with the established approach. Furthermore, with **6** in hand, the introduction of a C_3 hydroxyl at the β position and the further access to the lactone

functionality, *e. g.* ring E of hainanolid, could be foreseeable, if a regio-specific enolization at C_3 of **6** could be achieved. The corresponding **scheme 2** and **scheme 3** were attempted and successful results have been obtained.

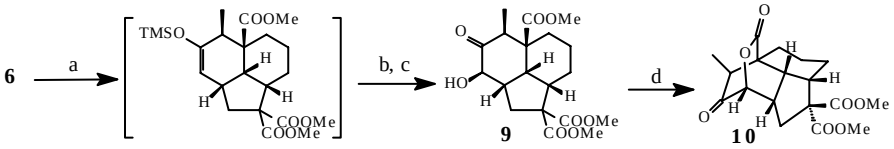
Scheme 2



a) CH_2N_2, Et_2O; b) O_2, Ac_2O, Py, TPP, hv; c) NaOMe, MeOH; d) H_2, Pd-C (10%), EtOAc.

Following **Scheme 2**, compound **4** was methylated and converted into α, β -unsaturated ketone **8** [4]. When compound **8** was treated with excessive sodium methoxide, epimerization of the methyl group at $C_{5\alpha}$ to $C_{5\beta}$ took place to give **5**, as the quartet peak at δ 2.69 in the ^{1}HNMR spectrum of **8** was found instead δ 2.49 in that of compound **5**. Hydrogenation of **5** gave the known ketone **6**, as it was reported [3].

Scheme 3



a) LDA, Me_3SiCl, THF, −78℃-r. t.; b) m-CPBA, hexane; c) n-$Bu_4N^+F^-$, THF, H_2O; d) K_2CO_3, MeOH.

For formation of ring E (**Scheme 3**), ketone **6** was kinetically enolized and the enolate trapped with chlorotrimethylsilane [5], and then exposed to m-CPBA [6] without purification. After subsequent desilylation, the expected ketone **9** with C_3 hydroxyl at β position was isolated in a total yield of 51%. Under basic condition, 1,4-lactonization of ketone **9** took place to form ring E and **10** was isolated in *c.a.* 40% yield. The structure of **10** was supported by ^{1}HNMR, MS and UV.

The above study constituted the first access to the 1,4-lactone, thus a four-ring skeleton of the target molecule was constructed. In addition, both the *endo*- and *exo*-IMDA-additive could be employed as intermediates in our total synthesis of hainanolide.

References

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