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Synthetic Application of Octalone Systems (I): Synthesis of β-Cyperone

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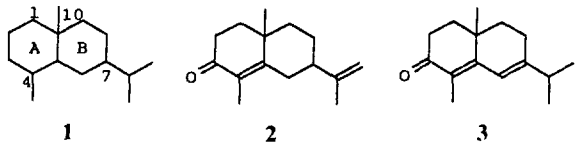
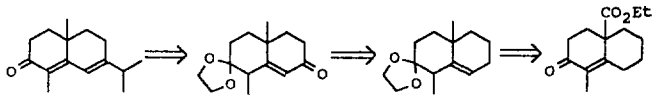
The eudasmain sesquiterpenoid is a group family of natural products that shares a carbobicyclic hydronaphtalene skeletons.[1] α-Cyperone[2] **2**, and β-cyperone[2] **3**, isolated from the tubers of *Cyperous rotundus*,[2] were members of this group and shown in Figure 1. Since β-cyperone **3** contained a dienone and an angular methyl group in an octalone skeleton, it is expected to serve as a useful starting meterial for synthesis of natural products. In addition, it is feasible to have a biological activity owing to its structure. In spite of a simple and well-known structure, total synthesis[3] and biological activity of it has not been reported well in the literature.

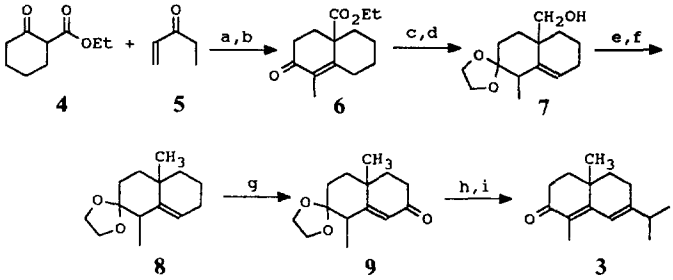


1 **2** **3**

Figure 1.



Scheme 1.



Reagents and Conditions: (a) 0.03 eq EtONa/EtOH, (b) 1.30 eq EtONa/EtOH, 0℃ →RT, (c) Ethylene glycol, TCA, Benzene, Reflux, (d) LAH, Ether, (e) *p*-TsCl, Pyridine, 0℃, (f) LAH, THF, (g) CrO_3, DMP, CH_2Cl_2, −23℃ →0℃, (h) $(CH_3)_2CHMgCl$, THF, (i) *p*-TsOH, Benzene.

Scheme 2.

Our continuing efforts to develop efficient synthetic routes for complex natural products utilizing an octalone[4] system, a general and flexible synthetic route for β-cyperone was investigated. Our retrosynthetic analysis is outlined in Scheme 1. Necessary functional groups are introduced in sequence to provide structure variations. Basic carbon skeleton was constructed by Robinson annulation[5] which was exclusively employed in our laboratory.

The strategy for the target compound was realized in Scheme 2. Robinson annulation of ethyl 2-cyclohexanonecarboxylate **4** and ethyl vinyl ketone **5** was conducted in two step sequences under the delicated condition. At first, Michael addition of keto ester **4** to enone **5** was facilitated by addition of a catalytic amount of sodium ethoxide at 0℃. Treatment of the resulting reaction mixture with stoichiometric amount of sodium ethoxide gave rise to an octalone **6** in 72% yield. Ketalization of compound **6** would enable us to protect a carbonyl group and to functionalize B ring by migration of a double bond. Under the standard condition[6]

(glycol and catalytic amount of *p*-toluenesulfonic acid in benzene), we were not able to get the desired compound in acceptable yield. After many failure, a reaction using trichloroacetic acid as a catalyst gave rise to 90% yield. We assumed that steric hindrance caused by methyl group at C-4 position required more drastic conditions. Before functionalizing B-ring, a carboethoxy group was converted to an angular methyl group by reduction, tosylation and substitution. In this substitution sequence, other derivatives were able to synthesize. Tosylation of the resulting alcohol **7** was also required a harsh condition because of 1, 3 diaxial interaction caused by methyl group at C-4 and hydrogens.

With all necessary carbons in place, B-ring was functionalized by allylic oxidation using Salmond procedure.[7] Treatment of compound **8** with chromium trioxide, Celite and 3,5-dimethylpyrazole under anhydrous condition afforded a key compound **9** in 63% yield. Addition of isopropylmagnesium chloride in THF followed by deketalization gave rise to the target compound in 38% yield. The spectral properties of this compound were in accordance with those reported.[3a]

In conclusion, we synthesized the β-cyperone **3** in **7** steps. Key steps are 1) Robinson annulation to construct a carbon skeleton 2) introduction of an angular methyl group at C-10 position 3) addition of isopropyl group by Grignard reaction followed by subsequent acidic hydrolysis to generate dienone moiety. This result will pave the way to prepare valuable starting materials from simple carbon skeletons. The development of synthetic routes for natural products and biologically active materials utilizing an octalone system are under investigation.

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Electron Transfer Process of Phenoxide Ion and α,β-Unsaturated Carbonyl Compounds

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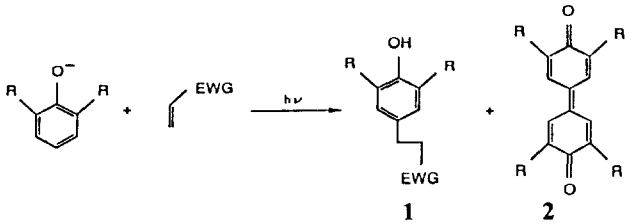
Nucleophilic substitution catalyzed by single electron trasfer (=S.E.T) process, *i.e.*, occurring along with a $S_{RN}1$ mechanism,[1] is now a well-known reaction. The electron transfer process has been proposed to proceed *via* various manners; electrochemically,[2] photochemically,[3] or by metal ions.[4] A large variety of nucleophiles has been demonstrated to react with aliphatic[5] or aromatic[6] nitro substrates *via* $S_{RN}1$ processes. It has also been found that alkyl radicals derived from alkyl mercury halide undergo Michael 1,4-addition reactions with α,β-unsaturated carbonyl compounds *via* single electron transfer process.[7] It is noteworthy that phenoxide and alkoxide ions do not seem to react as nucleophiles with α,β-unsaturated carbonyl compounds, Recently, Thiebault *et al.* have studied electron transfer initiated chain reaction of phenoxide ion under electrochemical conditions. They found phenoxy radicals derived from electrochemical electron transfer process of phenoxide ion were cross-coupled with halosulfonyl compounds, halopyridine, and 4-halobenzophenone *via* $S_{RN}1$.[8]

We wish to report our preliminary results that 2,6-di-*tert*-butyl phenoxy radical derived from the corresponding phenoxide ion reacts with α,β-unsaturated carbonyl compounds to produce Michael 1,4-addition adduct, **1**, as a major product and the dimer, **2**, of the phenoxy radical as a minor product. The results are summarized in Table 1[9] and plotted in Figure 1.



1 **2**

As shown in Table 1 and Figure 1, addition of 5 mole% of di-*tert*-butyl nitroxide or *m*-dinitrobenzene has shown a strong inhibitory effect on the final yield of Michael adduct and the dimer. In addition, either the presence of O_2 or the absence of UV inhibits the formation of Michael adduct. The bubbling of O_2 in the presence or the absence of methyl acrylate increases the formation of dimer, indicating that molecular oxygen would be the oxidant[10] in this reaction. The illumination of the reaction mixture with 254 nm or 350 nm UV light does not show a significant effect on the