Short Synthesis of γ-Hydroxy Octalone Utilizing an Unusual Decarboethoxylation

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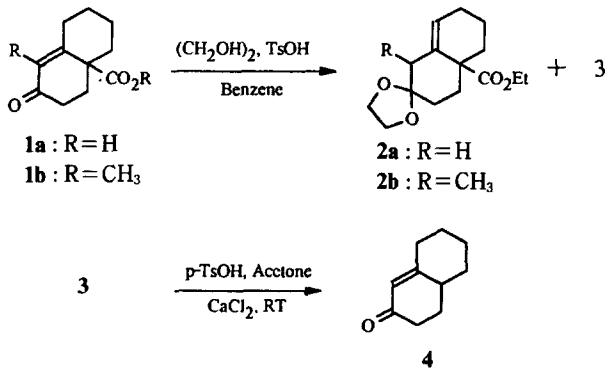
In connection with our continuing efforts to utilize an octalone system for synthesis of natural products, we wish to report an unexpected decarboethoxylation reaction and its application.

As part of a project directed toward synthesis of bruceantin[1] analogues, a ketal **2** was required in large quantity as a starting material. Ketalization of an octalone **1a**,[2] which was conducted in benzene containing ethylene glycol with a trace of *p*-toluenesulfonic acid, provided an unkown product **3** in addition to the desired ketal **2a** (Scheme 1).[3] At the early stage of research, **3** was regarded as a minor side product and discarded without any attention. Since the yields of ketalization reaction were inconsistant and not satisfatory for large scale preparation, **3** was fully reinvestigated for its exact structure in order to elucidate reaction mechanism and to improve reaction condition.

Proton NMR of **3** showed that vinyl and ethyl peaks were completely absent. However disappearance of purple color in bromine test strongly suggested that a double bond was still present in a molecule. In addition, the absence of peaks corresponding to an ester in IR of **3** revealed that an ester at a bridge head was removed. Treatment of **3** under standard deketalization conditions gave rise to an enone **4** within 5 minutes in near quantitative yield (Scheme 1).

Based on interpreting spectral data and reactivity, a noble structure of **3** was proposed as shown in Scheme 2. It has a double bond at a ring junction and no carboethoxy group. An unique feature and reactivity of this double bond would lead to functionalize bridge head positions to synthesize useful intermediates. It was suggested that an unexpected decarboethoxylation with formation of a double bond was triggered by a carbocation formed at a bridge head under the acidic reaction medium followed by fragmentation of an angular carboethoxy bond (Figure 1).

Treatment of an octalone **1b** with the same condition results in the only expected ketal **2b**. It shows that the unusual decarboethoxylation occurred under stringent steric requirements. From extensive literature survey, we found that a similar result[4] was reported only for octalones containing a carboxylate group under the strong basic condition.



Scheme 1.

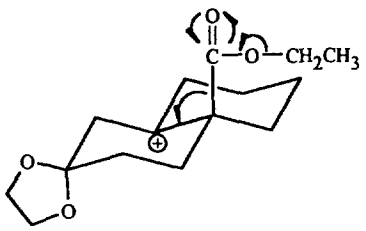
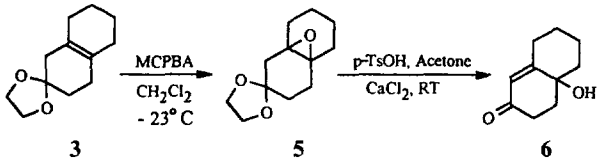


Figure 1.



Scheme 2.

With **3** available, a γ-hydroxy-enone **6** was synthesized[5] in order to elaborate it for further transformations in addition to confirmation of the structure of **3**. Exposure of **3** to MCPBA in methylene chloride at −23℃ gave rise to an epoxide **5** in 92.3% yield. The temperature control and purity of MCPBA[6] was important to this step. Treatment of the resulting epoxide **5** under standard deketalization condition afforded **6** in 53.0% yield (Scheme 2).

The octalone **6** containing an enone moiety with a hydroxyl group at a bridge head represents a useful intermediate for synthesis of natural products. Now several attempts to find optimized reaction conditions for conversion of **1a** or **2** to **3** are in progress.

In conclusion, we have developed a synthetic pathway to functionalize bridge heads in octalone systems which were not easily accessible by conventional methods.

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References

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2. D. L. Snitmam, R. J. Himmelsbach, and D. S. Watt, *J. Org. Chem.*, **43**, 4558 (1978).
3. The yields of 3 were variable up to 20%.
4. T. Oritani and K. Yamashita, *J. Org. Chem.*, **49**, 689 (1984).
5. G. F. Burkinshaw *et al.*, *J. Chem. Soc. (C).*, 3002 (1971).
6. MCPBA was carefully washed by buffer solution (pH 7.4) and then dried by azeotropic evaporation with benzene *in vacuo*. See O. Bortolini *et al.*, *J. Org. Chem.*, **52**, 5093 (1987).
7. All yields refer to isolated products and all new compounds gave satisfactory spectral data.