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THE CONVERSION OF BICYCLO[3.3.0]OCTANE-3,7-DIONE TO BICYCLO[3.3.0]OCT-1-ENE-3,7-DIONE. SYMMETRY AS A COMPLICATING FACTOR IN SYNTHETIC ANALYSIS.†

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Summary: Both acid-catalyzed ketalization and base-mediated enolization of bicyclo[3.3.0]octane-3,7-dione tend to give statistical mixtures of products, which is a complicating factor in attempts to use this compound as a starting material for some targets.

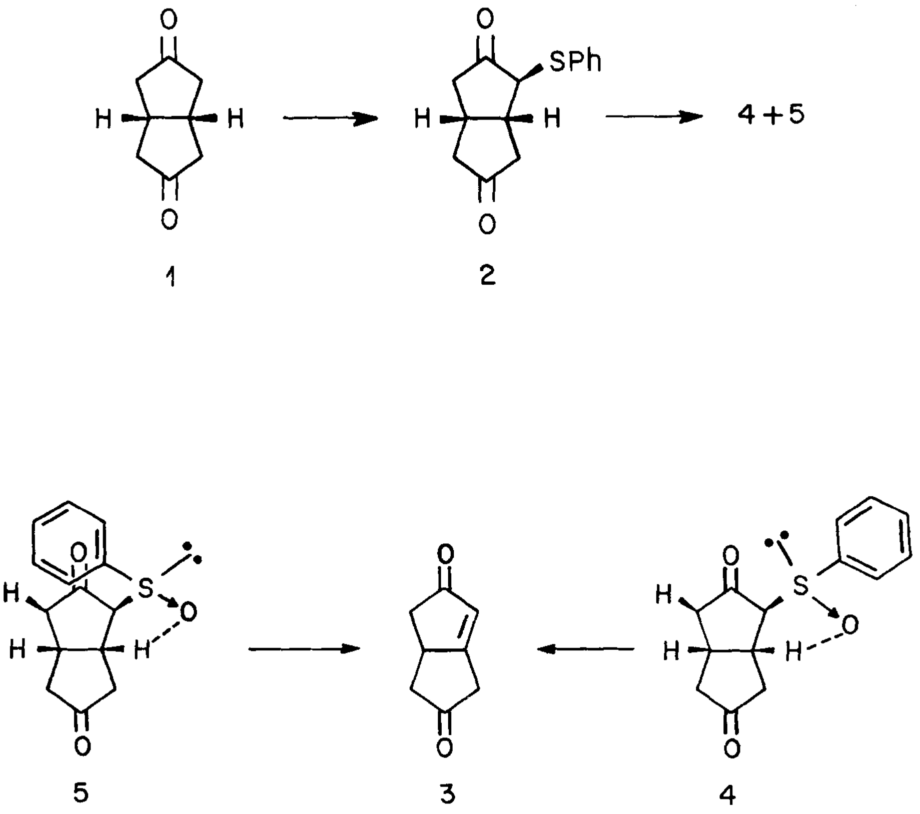
It has often been noted that symmetry is a simplifying factor in synthetic analysis;[1] thus chemists tend to assume this always to be the case. In fact, when the symmetry of a starting material must be broken on the way to the target, symmetry is usually a complicating factor, as illustrated by the difficulties associated with the use of bicyclo[3.3.0]octane-3,7-dione (**1**)[2] as a starting material for more complex polyquinanes. Examples will be given where the target has, alternatively, higher and lower symmetry than **1**.

Lok and Coward[3] have reported that the attempted monoketalization of **1** results in a mixture of unketalized **1** (13%), monoketal (40%), and bisketal (24%, isolated yields). We repeated this experiment with similar results. Nicolaou and co-workers have found that ca. 70% monoketal can be obtained from the partial hydrolysis of the bisketal under carefully controlled conditions.[4] The pure monoketal cannot be stored because it tends to disproportionate,[4] hampering this approach. If alkylation of the monoketal were then to proceed in 80% yield and the subsequent deprotection in 90%, the overall yield would be 50%, i.e. the same as a statistical alkylation of **1**. Therefore, in order to avoid the excess complexity[5] of protection-deprotection schemes, it was decided to try to optimize the direct generation and alkylation of the mono-enolate.

The use of 1 equiv. of $LiN(TMS)_2$ resulted in roughly statistical mixtures of products when the enolate was trapped using electrophiles such as phenylsulfenyl chloride or ethyl iodoacetate. Therefore, a deuteration study was conducted using the K enolate generated with $KN(TMS)_2$. Addition of 1 equiv. of this base to **1** at -30°C followed by quenching[6] with $DOAc/D_2O$ gave a distribution of products containing 49% **1**-d_1 (MS analysis). The K enolate was chosen so that the effect of 18-crown-6 could be tested. Inclusion of 1.1 equiv. of this complexing agent with the **1** shifted the amount of **1**-d_1 to 75% when the mixture was quenched after 1 min. In contrast, when the 18-crown-6 was added 15 min after the base, only 53% **1**-d_1 was observed. Therefore, the nonstatistical product distribution is a kinetic and not a thermodynamic effect. The negative charges of the bis-enolate must be far enough apart for coulombic interaction to be negligible. In fact, the bis-enolate may be favored by its insolubility. The deuteration experiments had to be run at concentrations of <0.004 M in THF to avoid errors due to precipitation of the bis-enolate, which was observed at 0.008 M. Practical difficulties encountered while trying to scale up this procedure and recycle the crown ether led to its abandonment in favor of the use of the Li enolate with recycling of the recovered **1**.

When **1** was treated with 1 equiv. of $LiN(TMS)_2$ at -90°C followed by 1 equiv. of PhSCl, a mixture of products resulted from which 2-phenylsulfenylbicyclo[3.3.0]octane-3,7-dione (**2**) was isolated in 31% yield after silica gel chromatography. A control experiment consisting of a second cycle of chromatography under the same conditions resulted in a 75% recovery of **2**, indicating that the original yield was ~40% (vide supra monoketalization yield). Up to 30% of **1** could also be isolated, along with 18% of disubstituted products (MS analysis), which were not characterized further. By painstaking optimization, Cook and

Scheme:



co-workers have been able to obtain a 50% yield of monoalkylation product using allyl iodide as the electrophile.[8] The 2-allyl derivative produced is an intermediate in a new synthesis of triquinacene. In this case the target has higher symmetry than the starting material; nevertheless, the symmetry of **1** must be broken in order to make triquinacene from it.

Sulfide **2** was quantitatively oxidized by _m_-chloroperbenzoic acid to a 1:1 mixture of two sulfoxides, the configurations of which at sulfur were assigned on the basis of their relative rates of elimination at 100°C to olefin **3**.[7] That the _R,S_-diastereomer (**4**)[7] should eliminate faster than the _S,S_-diastereomer (**5**)[7] is predicted by the model that has fewer nonbonded interactions in the transition state for elimination (see scheme). The yield of **3** in each case is nearly quantitative by ^{1}H-NMR; however, purification by HPLC gave only 30% (_vide infra_ **7**). While **3** is thermally stable, exposure to the atmosphere resulted in an insoluble yellow material. The sensitive nature of **3** makes it difficult to manipulate on a preparative scale. Belletire has circumvented this problem by preparing the α-enone ketal, monoketalizing the sulfoxides before elimination.[9]

In contrast to the sensitivity of **3**, the completely conjugated bicyclo[3.3.0]octane-1,5-diene-3,7-dione (**6**) is very stable. In fact, we first isolated **6** in low yield (~10%) from the attempted preparation of **3** _via_ the hydrolysis-decarboxylation of "Vossen's Red Salt." Docken[10] has reported an improved preparation from this starting material.

Pattenden and co-workers[11] have found that attempts to prepare bicyclo[3.3.0]oct-1-en-3-one (**7**) by an intramolecular Wadsworth-Emmons reaction led to either a "tarry mass" (60°C) or a crystalline dimer (25°C). On the other hand, Klipa and Hart[12] have prepared **7** in 38% yield by a pyrolytic decarboxylation reaction of the 5-carboxy derivative, which was prepared from the corresponding ethyl ester, a stable compound.[13] It may be posited that **3** and **7** are base sensitive and are best approached by thermal elimination reactions. Incredibly, Pattenden and co-workers[11] report that the 4-methyl derivative of **7** does not dimerize; in fact, in base it isomerizes to the 2-methyl derivative, which also does not dimerize. Similarly, Magnus and associates[14] have prepared 7,7-dimethyl-2-ethoxycarbonylbicyclo[3.3.0]oct-1-en-3-one by a Dieckmann reaction, and Trost and Curran[15] have synthesized 5-methyl-6-oxobicyclo[3.3.0]oct-1-en-3-one by an intramolecular Wittig reaction.

In conclusion, the stability of compounds in the bicyclo[3.3.0]oct-1-en-3-one series appears to be a very sensitive function of structure. From a synthetic viewpoint, the presence of symmetry in a starting material or intermediate (_e.g._ **1**) can be a complicating factor regardless of whether the target has lower (_e.g._ **3**) or higher (_e.g._ triquinacene) symmetry. Thus **1** is best suited to be a starting material for routes in which bis-functionalization is desired.[16]

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