

On the Mechanism of the Meinwald Rearrangement of Electron Deficient Systems

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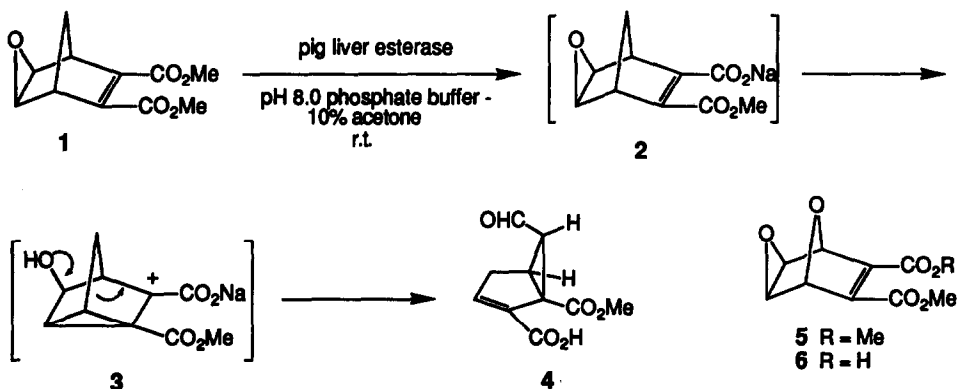
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epoxynorbornene; 2D-INADEQUATE;

Abstract; An alternative and plausible mechanism is proposed for the reaction pathway of
Meinwald rearrangement of electron deficient systems. This new reaction pathway involves
 α -lactone-type intermediate which is formed by intramolecular Michael addition of carboxylate anion.

Earlier, we reported that the epoxy diester **1** underwent a formal Meinwald rearrangement to produce the bicyclo[3.1.0]hex-2-ene-*endo*-carbaldehyde derivative **4** in quantitative yield by the treatment with pig liver esterase (PLE).³ This rearrangement was unexpected and also quite interesting because (1) the diester **1** involves the conjugated electron deficient system and (2) the similar treatment of 7-oxa analogue **5** with PLE afforded the expected unrearranged monoacid **6** in quantitative yield with 80~85% enantiomeric excess under the same reaction conditions. (Scheme 1)

Scheme 1



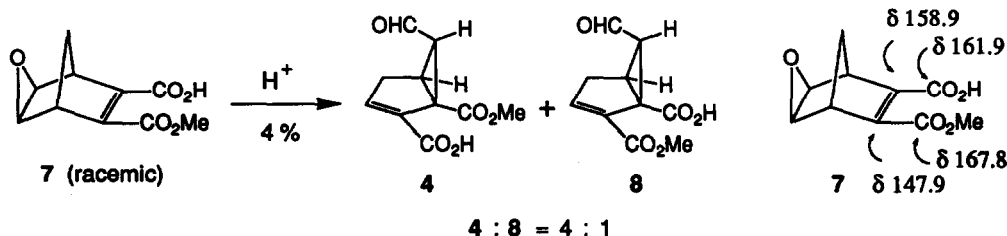
In the last paper, we assumed that this reaction mechanism was essentially the same as the Meinwald rearrangement,⁴ namely the acid-catalyzed mechanism, which proceeds through the cationic intermediate **3**. We considered a relative stability of carbocation neighboring the alkoxy carbonyl and the carboxyl group, and the

reason why the 7-oxa-analogue **5** does not cause this rearrangement was assumed to be due to the destabilization toward the carbocation by the inductive electron withdrawing effect of the allylic oxygen.

However, this assumption contains somewhat doubtful aspects in terms of electron localization such as cationic species neighboring the electron withdrawing group. We did not clarify the fundamental difference between the rearrangement of the electron deficient system of the diester **1** and the typical Meinwald rearrangement of epoxybornene. In terms of reaction condition, the most remarkable difference between them is that the Meinwald rearrangement occurs in an acidic medium while our rearrangement takes place under a basic condition. Here, we would like to propose an alternative α -lactone mechanism⁵ based on our further investigation. Our experiments present a clear distinction as described below.

The pure crystalline racemic epoxy monoester **7** was prepared³ and treated with diluted hydrochloric acid. This acid treatment for 2 hours resulted in the formation of two regio isomers **4** and **8** of which ratio is 4 to 1 in only 4% yield. (Scheme 2) Although **7** was heated in refluxing AcOEt as well, it resulted in a complex mixture containing a small amount of the rearranged products.

Scheme 2

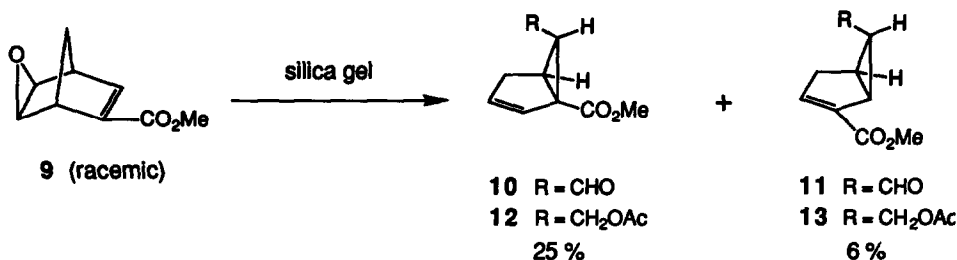


These results imply several important aspects. First, it is essentially unfavorable for electron deficient systems to cause this acid-catalyzed Meinwald type rearrangement. The result, that heating the monoester **7** did not accelerate the rearrangement, signifies that basically this process is not an exothermic electrocyclic rearrangement. Additionally, the acid-catalyzed mechanism would have to allow to generate the unreasonable carbocationic intermediate which would be rather destabilized by the electron withdrawing group.⁶ Furthermore, this process would not be regiospecific unlike the rearrangement we found. The formation of the two regioisomers in 4 to 1 ratio seems to reflect electron distribution on the two olefinic carbons of **7**. In ¹³C-NMR spectrum of the monoester **7**, considerably different chemical shifts, 147.9ppm and 158.9ppm, were observed for the two olefinic carbons that are attached to the methoxycarbonyl group and the carboxyl group. The connectivity of these four *sp*² carbons was unambiguously assigned by the 2D-INADEQUATE and the Long Range C-H COSY: One (167.8ppm) of the two carbonyl carbons was easily assigned as the methoxycarbonyl carbon by the Long Range C-H COSY, and the cross peaks in the 2D-INADEQUATE indicated that the olefinic carbon at the higher field connects to the methoxycarbonyl carbon as in Scheme 2. These chemical shifts imply that the carbon attached to the methoxycarbonyl group has higher electron density than the other olefinic carbon.⁷

As for the regiochemical problem, another experimental data of the monoester **9** provides with additional information in the acid catalyzed rearrangement. The monoester **9** involves a polarized system where π -electron is more localized on the carbon possessing -COOMe. Nevertheless the treatment of the monoester **9** with silica gel in CH₂Cl₂ accompanied the formation of **11**, which arose from the less stable carbocationic intermediate.

Since aldehydes **10** and **11** were found rather unstable, the rearranged products were isolated and characterized as acetates **12** and **13**, respectively. (Scheme 3)

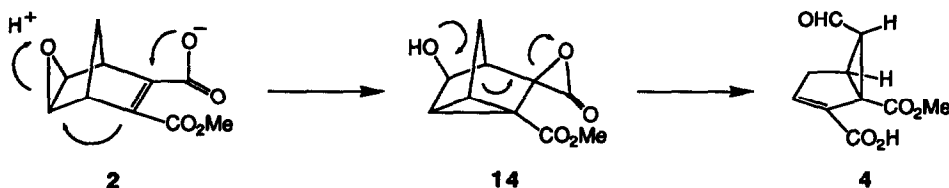
Scheme 3



In contrast to the above acid-catalyzed reactions, as was already described in the previous paper,³ when the racemic monoester **7** was stirred in phosphate buffer solution (pH 8.0) containing 10% acetone at room temperature, the rearrangement took place smoothly in an hour to give a single rearranged product **4** (racemic) in quantitative yield without accompanying the regio isomer **8**.

From these observations, although the original property of electron polarization on the two olefinic carbons could explain the observed regioselectivity to some extent, it is necessary to consider some additional contribution which pushes out electron exclusively from the 'COOMe side' to facilitate the rearrangement. We would like to propose here the most plausible intermediate, that is, an α -lactone type intermediate which would be formed by an intramolecular Michael addition of the carboxylate anion as shown in Scheme 4. In addition, since several other basic conditions in organic solvents did not facilitate the rearrangement of **7**,⁸ we further assume that the α -lactone formation is accelerated by the protonation to the epoxide oxygen.

Scheme 4



This reaction pathway would explain the regioselectivity which could not be elucidated from the acid-catalyzed mechanism. Concerned with this mechanism, *ab initio* single point calculations of the carboxylate with STO-3G basis set on the AM1 fully optimized geometries were carried out. The calculation provided a consistent data on stable conformational analysis of the two carbonyl groups. The most stable conformer is as follows; the carbonyl of COOMe is parallel to $\text{C}=\text{C}$ and that COO^- is perpendicular to $\text{C}=\text{C}$. This conformer would favorably enable the intramolecular Michael addition.

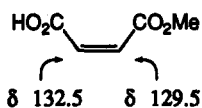
We have also carried out *ab initio* calculations of α -lactone **14** (as an alkoxide anion), its 7-oxa analogue, and **6** (as a carboxylate anion). The energy differences between the α -lactone type intermediate and the carboxylate anion for 7-carba series and that for 7-oxa series are 30.13kcal/mol and 33.39kcal/mol, respectively. These differences, although small in value, might reflect the different reactivity toward rearrangement. In a qualitative sense, α -lactone intermediate of the 7-oxa analogue seems to be destabilized by the repulsive

interactions between the lone pair electrons of oxygen at 7-position and either α -lactone oxygen or alkoxide oxygen.

As a conclusion, we have proposed that the new Meinwald-type rearrangement of an electron deficient system is a base-catalyzed reaction which proceeds through the α -lactone type intermediate which was formed by intramolecular Michael addition of the carboxylate anion. Furthermore, the present Meinwald-type rearrangement would provide a new example of the reaction which proceeds through an α -lactone intermediate.

References and Notes

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6. Concerned with these aspects, the diester **1** was also treated with several acids such as $\text{BF}_3\cdot\text{OEt}_2$, AcOH , silica gel, but the yields of the rearranged product were 8%, 31%, and 44%, respectively. Heating this compound does not accelerate the rearrangement either. Simple reflux of **1** in AcOEt afforded only 23% of the rearranged product. See also; Prinzbach, H.; Claus, M. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 276-278.
7. This electronic property seems unique to these rigid compounds (**6** also has the similar ^{13}C data; 156.4 and 145.7 ppm for $\underline{\text{C}}\text{-COOH}$ and $\underline{\text{C}}\text{-COOMe}$, respectively) since carboxyl and methoxycarbonyl groups have essentially almost the same electron-withdrawing character. In the case of monomethyl maleate, the difference of ^{13}C chemical shifts between two olefinic carbons are only ~3ppm as shown below.



8. For instance, triethylamine/ CDCl_3 slightly caused this rearrangement at room temperature, but this was extremely slow (more than 10 days). Treatment of **7** with $n\text{-BuLi}$ in THF resulted in only forming the lithium salt, and the starting monoester was recovered quantitatively. Potassium *tert*-butoxide in THF caused decomposition upon heating. Consequently, pH 8 phosphate buffer solution was found to be the excellent reaction media for this rearrangement.

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