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Base-Promoted 1,2-Shifts in α-Benzyloxy Ketones

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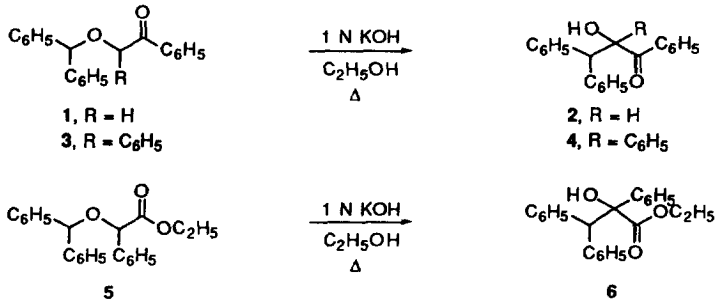
Abstract: Deprotonation of representative α-*p*-methoxybenzyl ketones results in the formation of rearranged α-benzylated α-hydroxy ketonic products. In the present examples, formal inversion of configuration at the carbanionic center is observed.

Keywords: rearrangements, carbanions, enolates, stereoselection, ketones

1,2-Anionic rearrangements involving α-metalated ethers have long been recognized to hold mechanistic and synthetic importance [1-5]. A great deal of research has been devoted to developing the [2,3]-Wittig shift in terms of its scope and stereochemistry [6,7]. The [1,2]-Wittig process has been scrutinized to a significantly lesser extent. Beyond the general adoption of a radical pair dissociation-recombination pathway for such reactions [8], several reports have documented its stereospecific nature involving retention at the migrating center and inversion of the lithium-bearing terminus [9-12]. Maleczka and Geng have recently confirmed that the normal predilection of an α-oxylithium species to react with configurational inversion can be overturned by intramolecular chelation [13].

A search of the literature revealed to us that a third variant of this subset of rearrangements, originally discovered by Curtin [14], has been accorded no further attention. These investigations demonstrated that the conversion of **1**, **3**, and **5** into their enolates by heating



1, R = H
3, R = C_6H_5

2, R = H
4, R = C_6H_5

5

6

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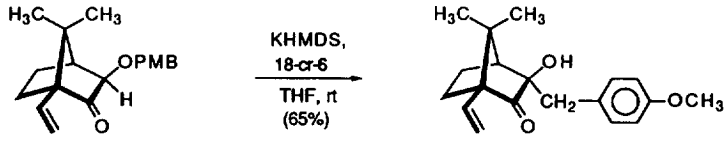
with 1 N ethanolic potassium hydroxide resulted in isomerization to **2**, **4**, and **6**, respectively. The harshness of these conditions induced further reactions of the initially-formed products, thereby complicating matters needlessly.

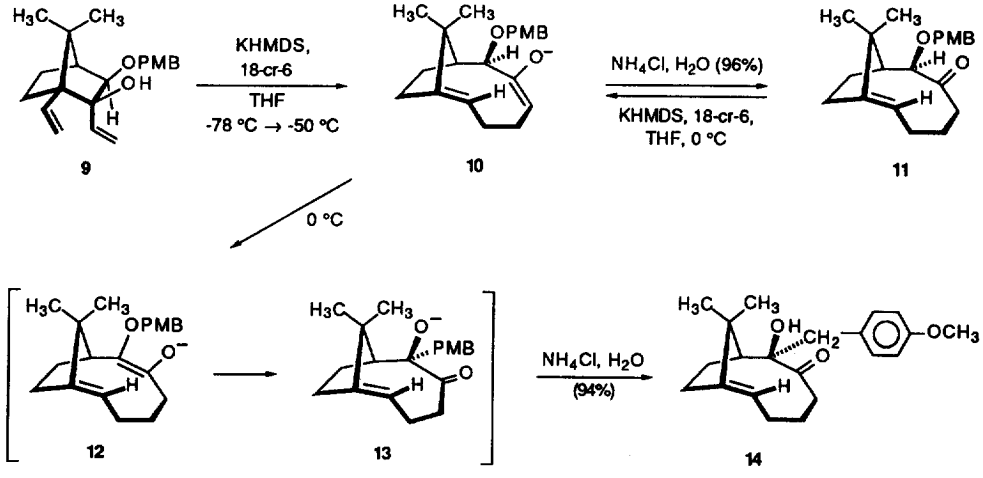
Our attention was drawn to these transformations while investigating the possibility of synthesizing C10-alkylated taxoids by tandem application of the anionic oxy-Cope and Curtin rearrangements. As a preclude to such studies, we took the opportunity to examine the potential of **7** to base-promoted isomerization. Indeed, stirring **7** with potassium hexamethyldisilazide and 18-crown-6 in THF at 20 °C for 5 min led to the isolation of **8** in an unoptimized 65% yield [15]. The endo orientation of the *p*-methoxybenzyl group was conveniently established by NOE measurements.



7 **8**

The astonishing ease and high stereoselectivity of this process led us to pursue its adaptation to the more complex scenario presented in Scheme 1. In line with expectations, generation of the potassium salt of **9** in THF containing 18-crown-6 at -78 °C to -50 °C resulted in rapid [3,3] sigmatropic shift via an endo-chair transition state [16] and generation of enolate anion **10**. Quenching of the reaction mixture with saturated NH_4Cl solution furnished **11** (96%). When the same process was repeated at 0 °C, no sign of **11** was found, this product being replaced by bicyclic ketone **14** (94%). At this more elevated temperature,

Scheme 1



9 **10** **11**

12 **13** **14**

the first-formed enolate **10** presumably equilibrates with **12**, thereby triggering a second-stage Curtin rearrangement to generate **13**. This conclusion was confirmed by the observation that **11** is transformed cleanly into **14** under identical conditions.

The structural features and stereochemistry of **14** were corroborated by X-ray crystallographic analysis (Figure 1). Thus, it is clear that formal inversion of configuration has once again (as in **8**) occurred at the enolate carbon. More extensive studies will be required to determine if this stereochemical course is customary and to clarify similar issues involving the migrating center.

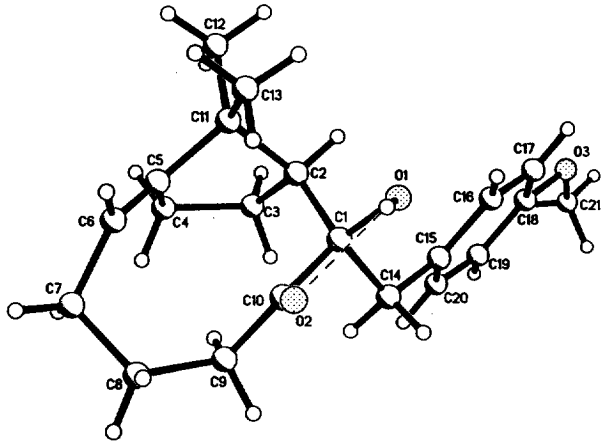


Figure 1

A surprising feature of the **7** → **8** and **10** → **14** conversions is that radical recombination proceeds regioselectively with respect to the (formally symmetric) ene-diolate intermediates. One must question why the selectivity is so high if the pair actually dissociates in this manner. In our view, such mechanistic analysis does not adequately account for the global observations.

Notwithstanding, we believe the present results to constitute compelling experimental support for the viability of base-promoted 1,2 α-benzyloxy ketone rearrangements in synthesis. Although reactivity patterns and stereochemical consequences remain to be defined, sufficient understanding is available to encourage the practitioner to make use of the Curtin rearrangement in their investigations.

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