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Metalated Epoxides as Carbenoids. Stereospecific Synthesis of Functionalized Spiro Cyclopropanes via Highly Strained Tricyclic Intermediates

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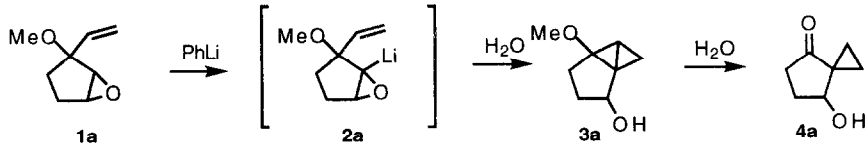
Abstract: Intramolecular cyclopropanation reaction of β,γ-unsaturated epoxides yields highly strained tricyclo[4,1,0,$0^{1,5}$]heptane compounds whose hydrolysis affords α-keto spiro cyclopropanes. Both steps of this one-pot reaction are stereospecific. © 1997 Elsevier Science Ltd.

Over the past three decades, the intramolecular formation of cyclopropyl moieties followed by subsequent manipulations of the cyclopropyl ring has become a general strategy for the synthesis of complex molecules.[1] Among the various methods which afford functionalized cyclopropanes, those involving carbenoid reagents (e.g. Simmons-Smith reaction[2] or decomposition of diazo compounds[3] catalyzed by a transition metal) are specially well-documented. On the other hand, the produced polycyclic intermediates have been cleaved by using several methods including radical-promoted reduction,[4] protonolysis,[5] hydrogenolysis,[6] or Lewis acid-induced ring opening.[7]

Recently,[8] we reported that carbenoid species are produced from the action of *n*-BuLi on α-hydroxy epoxides. We wish to describe herein a stereospecific intramolecular cyclopropanation of β,γ-unsaturated carbenoids leading to highly strained tricyclo[4,1,0,$0^{1,5}$]heptane intermediates[9] whose hydrolysis leads to α-keto cyclopropanes. This methodology is exemplified below in the case of substrate **1a** :



1a **2a** **3a** **4a**

This one-pot procedure involves: (i) the formation of carbenoid **2a** as a result of metalation[10] of epoxide **1a**, (ii) an intramolecular insertion of this carbenoid into the ethylenic double bond, and (iii) a water-mediated cleavage of the C_1-C_7 bond. As shown below in the case of substituted derivatives, all these steps are stereospecific.

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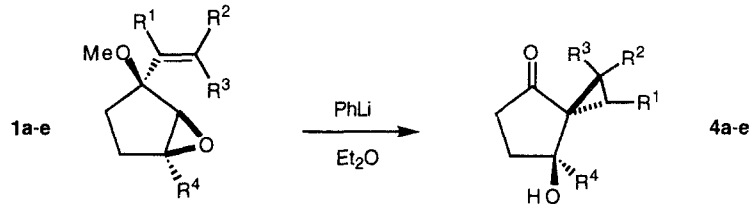
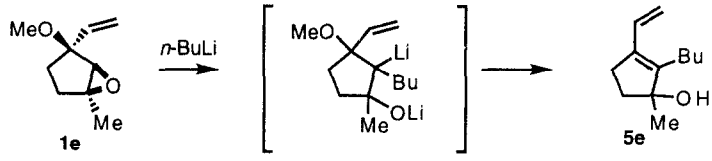
syn-Alkoxy epoxides **1a-e** were synthesized from the corresponding 2-cyclopentenones which were transformed into the corresponding keto epoxides (H_2O_2, NaOH). These compounds were then treated with the required alkenyllithium reagent. O-Methylation (NaH, MeI) followed by treatment of the resulting epoxides with phenyllithium (1.5 equiv., Et_2O) yielded tricyclic intermediates which were not isolated (except in one case: see below) but directly hydrolyzed. This procedure afforded racemic ketocyclopropanes **4a-e** in the single stereoisomeric form indicated hereafter.



	R¹	R²	R³	R⁴	yields (%)
a	H	H	H	H	70
b	Me	H	H	Me	71
c	H	Me	H	Me	75
d	H	H	Me	Me	83
e	H	H	H	Me	88

Phenyllithium emerged as the choice reagent for the production of carbenoid species from epoxides **1a-e** since insertion of the produced carbenoid into the carbon-lithium bond of the organometallic reagent is, in this case, not detrimental to the expected reaction. For instance, the following side-reaction was observed[11] when using *n*-butyllithium:



Tricyclic compound **3b** turned out to be more stable than its analogs. Treatment of the reaction mixture resulting from intramolecular carbenoid insertion within molecule **2b** allowed product **3b** to be isolated. This compound was purified and fully characterized.[12] The structure of such a tricyclo[4,1,0,$0^{1,5}$]heptane intermediate, shown in the opposite figure, was obtained from optimization of the geometry by AM1 calculations.[13] Compound **3b** was submitted to the action of water (THF-H_2O solution) in the presence of silicagel. This reaction afforded ketocyclopropane **4b** quantitatively.

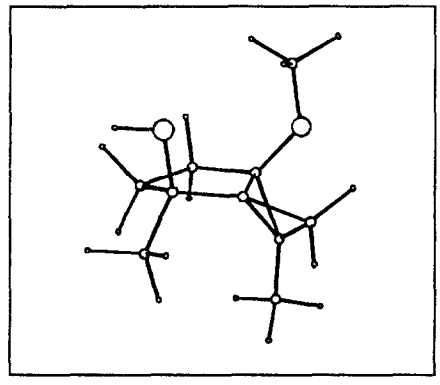
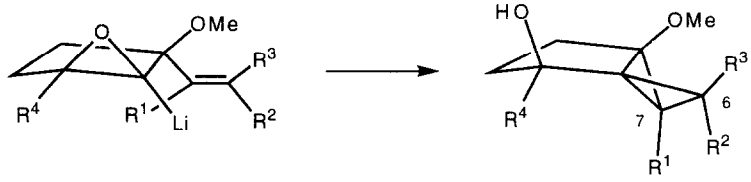


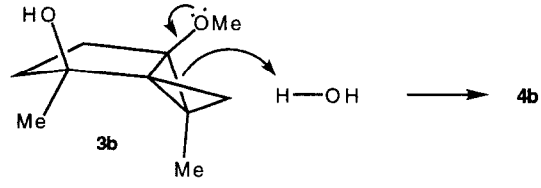
Figure 1. AM1 Structure of compound **3b**

Configurations of the stereocenters present in the cyclopropyl moieties of products **4b-4d** were determined by using ^{1}H NMR measurements[14] at 500 MHz performed on compounds **4b** and **4c**. Difference NOE experiments resulted in enhancements as shown below. Such determinations were not feasible with compound **4d** because, in this case, both methyl substituents did not appear as sufficiently distinct signals. However since products **4c** and **4d** (respectively obtained from the *E* or *Z* structure of the ethylenic linkage in substrates **1c** and **1d**) clearly show a diastereomeric relationship, the relative configuration of the stereocenters existing in **4d** can be assigned.

As regards the stereochemistry of the above carbenoid insertion into the ethylenic double bond, it is worth noting that results in this area are very scarce. Though such kind of C-C bond formation is well-known since the pioneering work by Crandall and Lin,[14] the stereoselectivity of related formations of bicyclo[n.1.0]alcanes was addressed but only in few reports.[15] In the present cases, the formation of tricyclic compounds **3c** and **3d** is stereospecific: the relative configuration of the produced stereocenters at C-6 and C-7 is directly related to the *E* or *Z* geometry of the reactive double bond.



On the other hand, the hydrolytic cleavage of the C_1-C_7 bond in tricyclic intermediate **3b** occurred with complete retention. The position of the newly created C-H bond in **4b** (obtained as a single diastereomer) corresponds to the cleaved C_1-C_7 bond in **3b**. Tentatively, the mechanistic hypothesis depicted in the following scheme can be put forward; the observed ring opening would therefore result from an S_E2 process at the C_7 center.[16]



Many spirocyclic cyclopropyl ketones show important biological properties[17] and their synthesis has attracted considerable interest. The methodology reported here offers a new access to such appealing compounds from common unsaturated ketones; this procedure has two main assets: a limited number of steps and the stereospecificity of the whole process.

Acknowledgment

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