An Unanticipated Ring-Opening of 2-Methyleneoxetanes: A Fundamentally New Approach to the Preparation of Homopropargylic Alcohols

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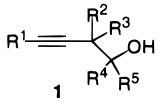
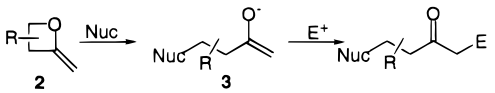
The alkyne functionality occupies a place of undisputed importance in organic synthesis.[1,2] The moiety is exceptionally versatile, open to ready regio- and stereoselective functionalization. In addition, numerous natural and synthetic products of biological significance contain the acetylenic unit.[3,4] One class of acetylenic compounds that has received wide attention because of its broad utility in organic synthesis is the homopropargylic alcohols **1**. Recently, in an ongoing investigation of the reactivity of 2-methyleneoxetanes **2**, we discovered a novel preparation of **1**. In this communication we describe our initial study of the scope of this procedure and delineate why it represents a fundamentally different and useful approach to the preparation of homopropargylic alcohols.



1

2-Methyleneoxetanes **2** are a largely unexplored class of heterocycles[5−7] that we believe will prove to be highly useful as synthetic intermediates. One attractive feature is that the precedented[5] ring opening of **2** affords an enolate **3**, which, potentially, could be captured by a variety of electrophiles.



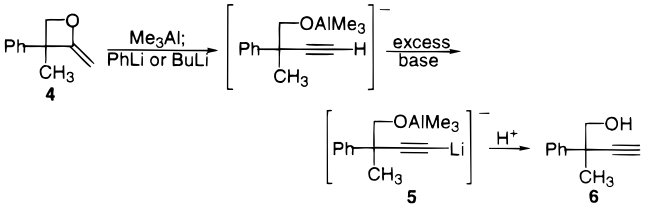
2 **3**

Our investigation of this versatile tandem sequence focused on ring-opening of **4** with carbanions. As shown in Table 1, neither *n*-butyllithium nor phenyllithium alone effected significant ring-opening. An attempt to boost the reactivity at C-4 by the addition of a Lewis acid produced an unanticipated outcome. Although boron trifluoride diethyl etherate did little to alter the course of the reactions, addition of trimethylaluminum to a solution of **4** in THF, followed by the addition of either *n*-butyllithium or phenyllithium, resulted in a single product **6**, isolated in 60−70% yield. Apparently, prior coordination of the oxygen with trimethylaluminum enhances the reactivity of the vinylic CH bond (Scheme 1). This reaction is largely unprecedented and should also be applicable to other methylene (or alkylidene) oxacycles. An analogous ring-opening of a 2-alkylidene tetrahydrofuran treated with LDA in the absence of trimethylaluminum has been previously observed, but only as a minor pathway.[8,9]

Table 1. Attempted Nucleophilic Ring-Opening of 2-Methyleneoxetane (4)

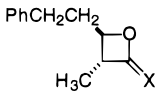
nucleophile	Lewis acid	conditions	results
n-BuLi		−95−0 °C, THF	**4** consumed no isolable product
n-BuLi	BF_3OEt_2	−95 −10 °C, THF	no isolable product recovery of some **4**
n-BuLi	$Al(CH_3)_3$	−95−0 °C, THF	**6**
PhLi		−78 °C−RT, THF	no reaction
PhLi	BF_3OEt_2	−78 °C−RT, THF	no reaction
PhLi	$Al(CH_3)_3$	−78 °C−RT, THF	**6**

Scheme 1

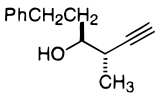


Intrigued by the conversion of **4** to **6** we decided to investigate the scope of this reaction. A range of 2-methyleneoxetanes **9** was prepared[7] by the reaction of the corresponding *β*-lactones **7** with dimethyltitanocene **8**.[10] The *β*-lactones were prepared either by the alkylation of 3-phenyl-2-oxetanone[11] or by the cyclization of *β*-hydroxy acids with benzenesulfonyl chloride. 2-Methyleneoxetanes **9** in THF were then added to a solution of lithium diisopropylamide (LDA) in THF at 0 °C. It is noteworthy that, when LDA was employed as the base, rather than *n*-butyllithium or phenyllithium, trimethylaluminum was not required for successful ring opening. The terminal homopropargylic alcohols **10a**−**d** were isolated in 48−88% yield. Presuming the intermediacy of **5**, we also examined the outcome of the addition of electrophiles other than water. As illustrated in Table 2, the syntheses of (trimethylsilyl)alkyne **10e** (electrophile = trimethylsilyl chloride) and internal alkyne **10f** (electrophile = iodomethane) were readily achieved.

Although the possibility of racemization at the propargylic position cannot be ignored, if the postulated mechanism in Scheme 1 is correct, the stereochemical integrity at this position should remain intact. Consequently, homochiral *β*-lactones should result in homochiral homopropargylic alcohols. To confirm this, 2-methyleneoxetane **11b** was prepared from diastereomerically pure *β*-lactone **11a**.[12]



11a X=O
11b X=CH$_2$



12

Compound **11b** was readily converted to homopropargylic alcohol **12**, as a single diastereoisomer, in 81% yield.

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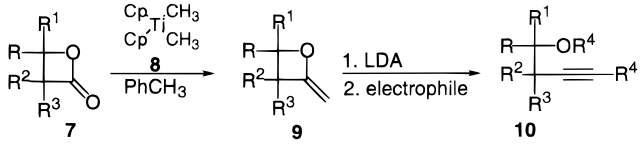
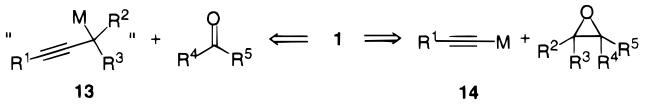
Table 2. Preparation of Homopropargylic Alcohols (10a−f) from 2-Methyleneoxetanes



7 9 10

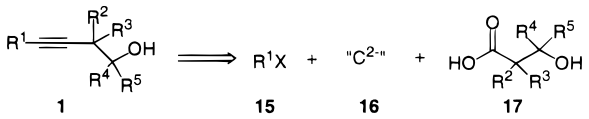
entry	lactone **7**	isolated yield **9**, %	R^4	isolated yield **10**, %
a	R, R^1 = H; R^2, R^3 = Ph, CH_2CHCH_2	74	H	85
b	R, R^1 = CH_3; R^2 = H; R^3=$(CH_2)_3OSi$*t*-BuPh$_2$	60	H	48
c	R, R^1 = $(CH_2)_5$; R^2,R^3 = H,CH_3	60	H	86
d	R, R^1 = H; R^2, R^3 = Ph,CH_3	76	H	88
e	**7d**		$(CH_3)_3Si$[a]	87
f	**7d**		CH_3[b]	74

[a] Electrophile = $(CH_3)_3SiCl$. [b] Electrophile = CH_3I.



13 14

Figure 1. Common approaches to homopropargylic alcohols **1**.



1 15 16 17

Figure 2.

The conversion of **7** to **10** represents a novel protocol for the preparation of homopropargylic alcohols. The two most widely used approaches to **1** are illustrated in Figure 1. One strategy exploits propargylic anion equivalents **13** in reactions with carbonyl compounds. Historically, this approach has been hampered by problems of regioselection with many propargyl anion equivalents giving mixtures of **1** and allenyl alcohols.[13] However, some of the more recent methodologies centered on **13** are regiospecific and high yielding, although their syntheses are not always trivial.[14−26] With substituted propargyl anions (**13** R^2 and/or $R^3 \neq$ H) that produce diastereomeric alcohols (**1** $R^4 \neq R^5$),[18−26] a major drawback is that, with one exception,[24] diastereoselectivities tend to be quite variable. More importantly, of these examples only Marshall et al. examine the issue of the enantioselectivity of the addition when the propargyl anion equivalent is chiral.[25,26] It should be noted that efficient asymmetric syntheses of **1** from unsubstituted **13** (R^1, R^2, R^3 = H) are available.[27−30] The other widely used approach to **1** involves the reaction of acetylenic anions **14** with epoxides.[31−34] The regioselectivity of the ring-opening reaction can be problematic, but the variety of asymmetric epoxidation procedures available[35−37] makes this an attractive protocol. Obviously, the versatility of any synthetic methodology must be evaluated by the accessibility of key intermediates.

In evaluating the utility of 2-methyleneoxetanes as precursors for **1**, it is important to recognize that *β*-hydroxy acids are common precursors for *β*-lactones. When combined with the many approaches,[38,39] both racemic and enantioselective, to *β*-hydroxy acids, the protocol outlined in this communication represents a fundamentally different way of considering the retrosynthesis of homopropargylic alcohols, as shown in Figure 2. The retrons are an alkyl halide **15**, a "C^{2-}" synthon **16** and a *β*-hydroxy acid **17**.[40]

In conclusion, the one-step conversion of 2-methyleneoxetanes to homopropargylic alcohols is an unusual, useful, and largely unprecedented reaction. Further, the conversion represents a fundamentally new approach to the preparation of homopropargylic alcohols.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds, as well as proton NMR's for compounds **7b**, **9a**,**b**, **10a**−**f** (16 pages).

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