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[2,3] WITTIG REARRANGEMENT OF β'-HYDROXYETHYL BIS-ALLYLIC ETHERS: HIGHLY REGIOSPECIFIC ENTRY TO SINGLY DEHYDROXYLATED 19-NOR-1(OR 3),25-DIHYDROXYVITAMIN D_3

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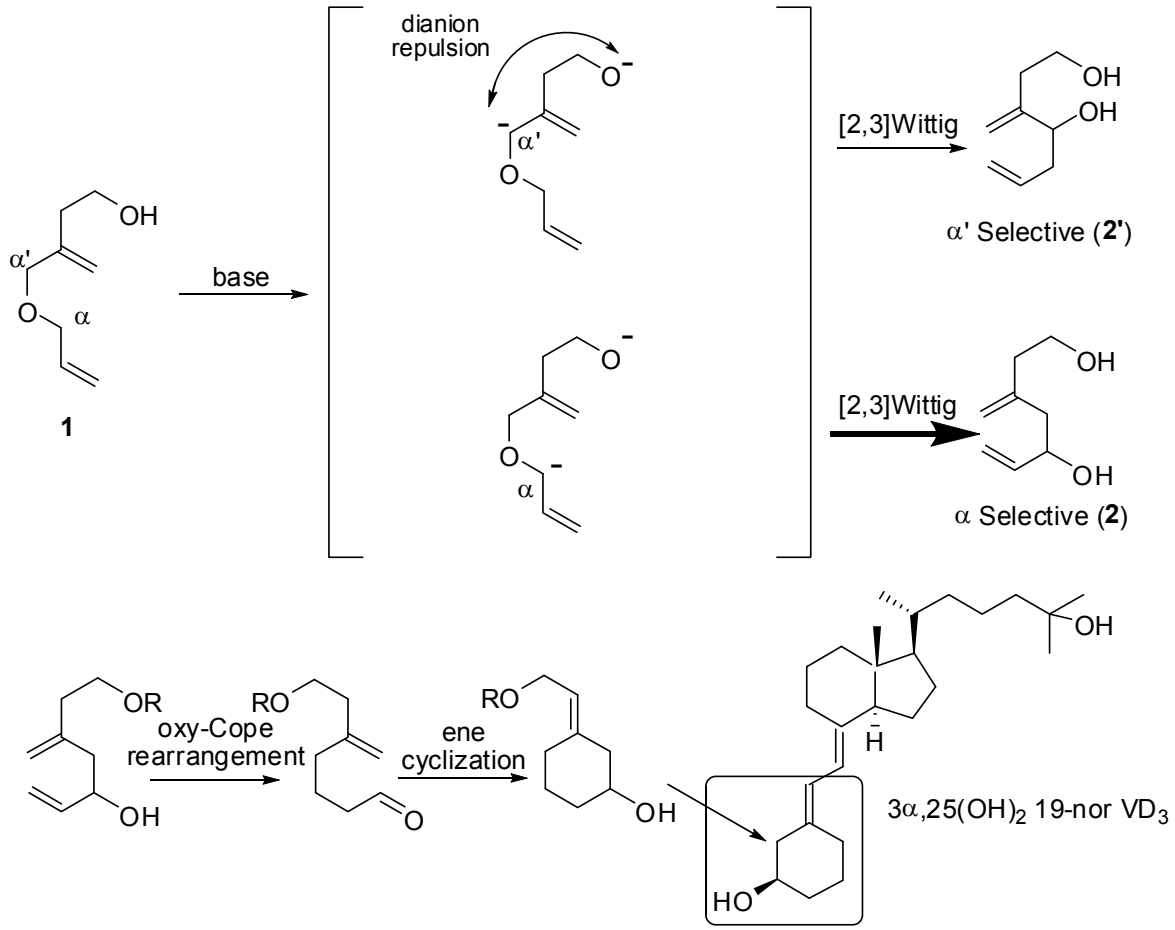
In the honor of the special issue for the 85th birthday of Professor Albert Eschenmoser, ETH Zurich.

Abstract – A conceptually new approach to regiospecific deprotonation at the α-position of β'-hydroxyethyl bis-allylic ethers is shown on the basis of the dianion repulsion with the β'-alkoxy anion, of which the [2,3] Wittig rearrangement product can be transformed to the A-rings of singly dehydroxylated 1(or 3),25-dihydroxy-19-nor-vitamin D_3 analogues to stimulate apoptosis or differentiation of HL-60 cancer cell.

Recently, the [2,3] Wittig rearrangement[1] of unsymmetrical bis-allylic ethers has enjoyed wide synthetic applications via highly regioselective deprotonation of an α- and/or a γ-substituted bis-allylic ether.[2] However, a β,β'-unsymmetrically substituted bis-allylic ether has still challenged regioselective α- or α'-deprotonation; We have already reported that the introduction of an anion stabilizing trialkylsilyl group at the γ-position leads to the highly regiocontrol in α-deprotonation[3] and that the introduction at the β-position has, however, essentially no effect[4] in regioselective deprotonation. Herein, we report a conceptually new approach to regiospecific deprotonation at the α-position by β'-hydroxyethyl bis-allylic ether (**1**) on the basis of the dianion repulsion with the "β'-alkoxy anion" (Scheme 1). The present synthetic method based on the highly regiospecific [2,3] Wittig rearrangement of unsymmetrical β'-hydroxyethyl bis-allylic ether can eventually lead to the A-rings of singly dehydroxylated[5] 1 (or

3),25-dihydroxy-19-nor[6]-vitamin D_3[7] analogues which stimulate apoptosis or differentiation of cancer cell line of HL-60, depending on the regio- and stereo-chemistries of the 1- or 3-hydroxy groups.



Scheme 1

Prior to the base treatment of the β'-hydroxyethyl unsymmetrical bis-allylic ether (**1**), the regioselectivity in deprotonation was deduced by DFT (RB3LYP) calculations implemented in GAUSSIAN 03[8] program package. The extended structures were calculated at the HF/6-31G(d,p) (*ab initio*) levels and DFT [RB3LYP/6-311+G(d,p)] method (Figure 1). Highly α-regioselective deprotonation is preferred over the regioisomeric α'-deprotonation by 19.74 kcal/mol energy difference, depending on the dianion repulsion in deprotonation at the α'-position of unsymmetrical bis-allylic ether substituted by β'-hydroxyethyl (alkoxy anion) group.

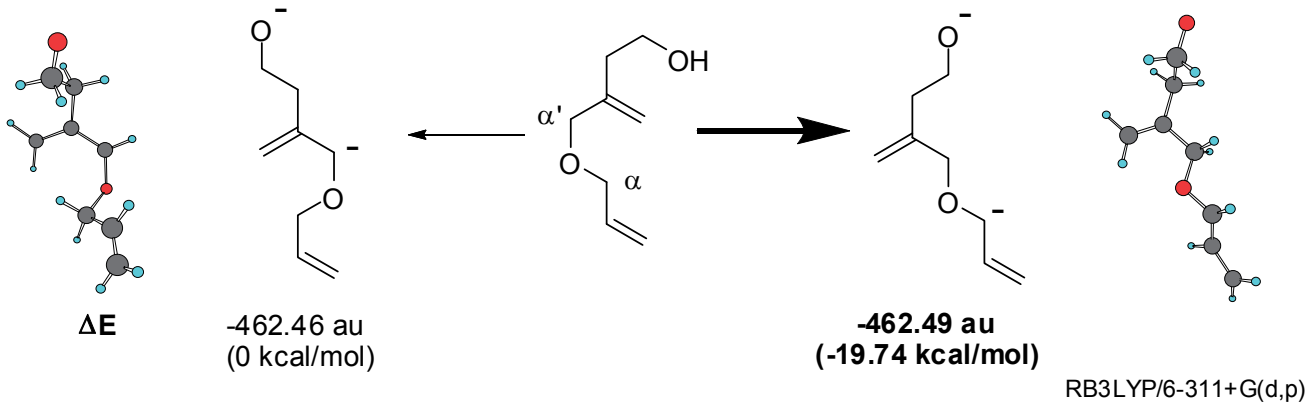


Figure 1

In order to examine the regiochemistry in deprotonation of the unsymmetrical bis-allylic ether (**1**), the various combination of metal/base species was scrutinized (Table 1). *n*-Butyllithium, the commonly employed base for the [2,3] Wittig rearrangement, did not give the highly regiospecific α-deprotonation/ rearrangement product but rather the regioisomeric mixture (entry 1: 60% α'-regioselectivity); The α'-[2,3] Wittig product was obtained via an α'-deprotonation, presumably via six-membered chelate with the lithiated β'-alkoxyethyl anion (Figure 2, **A**). Indeed, β'-hydroxypropyl substituent (**1"**) gave, in turn, the α-regioselective deprotonation/rearrangement product (entry 9: 81% α-regioselectivity), via dianion repulsion with the β'-"alkoxypropyl anion" (**B**), because seven-membered chelate (**C**) was less favorable than the six-membered chelate (**A**).

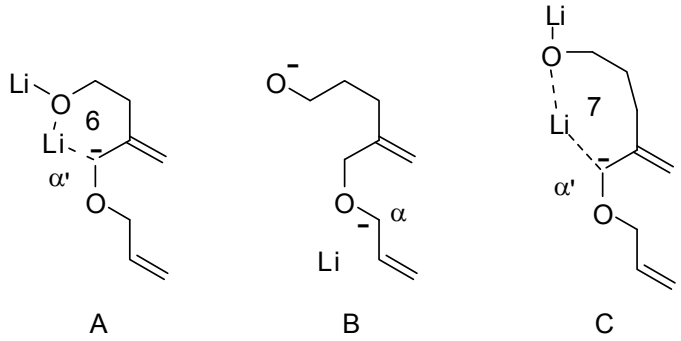
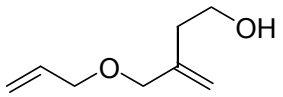
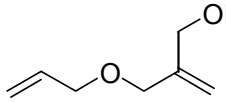
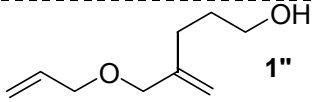
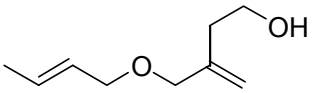
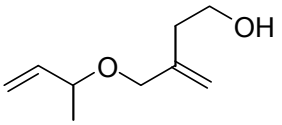


Figure 2

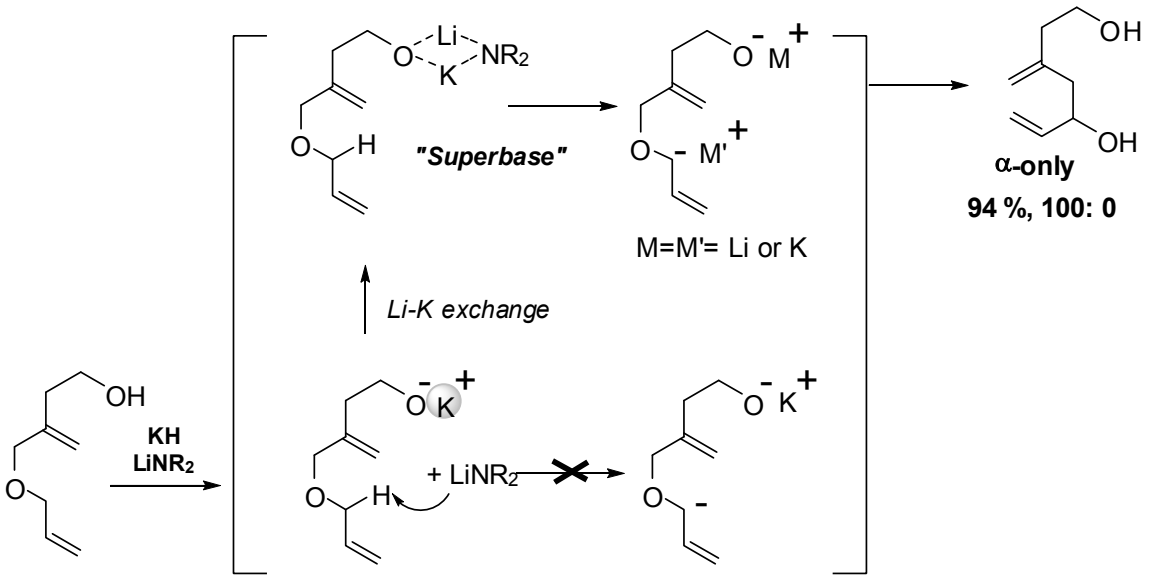
In a combination of *n*-butyllithium with sodium hydride, potassium *tert*-butoxide, or potassium hydride, the α-[2,3] Wittig rearrangement product was obtained in good-to-moderate (97-60%) combined yields via the α-deprotonation/rearrangement with n-BuLi, however, still as a regioisomeric mixture with α'-regioisomer (83:17 - 61:39) (entries 2, 3 and 4). Sterically demanding lithium amides in a

combination with potassium hydride afford the α-carbanion in a regiospecific manner (entry 5) by virtue of the (1) dianion repulsion and (2) highly sterically demanding nature of lithium amides/potassium alkoxides (*vide infra*). Among the lithium bases employed, the lithium dialkylamides gave the rearrangement product (**2**) in highly regiospecific manner. Significantly, lithium dicyclohexylamide (LDCHA) in a combination with potassium hydride gave the rearrangement product (**2**) in high yield and regiospecific manner (entry 5). However, LDCHA itself was totally ineffective (entry 6).

Table 1. Reactivity and regioselectivity of bis-allylic ethers in the [2,3] Wittig rearrangement

Entry	Substrate (**1**)	Base	T (^{o}C)	t (h)	%Yield (α : α')
1	 **1**	2 n-BuLi	-78	2	63 (40 : 60)
2		NaH / *n*-BuLi	-78	2	97 (61 : 39)
3		KO*t*-Bu / *n*-BuLi	-78	2	60 (80 : 20)
4		KH / *n*-BuLi	-78	2	95 (83 : 17)
5		KH / LDCHA	-78 ~ 0	6	94 (100 :0)
6		2 LDCHA	-78 ~ r.t.	24	trace
7	 **1'**	2 *n*-BuLi	-78	2	38 (50 : 50)
8		KH / *n*-BuLi	-78	2	85 (87 : 13)
9	 **1"**	2 *n*-BuLi	-78	2	37 (81 : 19)
10		KH / *n*-BuLi	-78	2	55 (80 : 20)
11		KH / LDCHA	-78 ~ r.t.	8	42 (33 : 67)
12		KO*t*-Bu / LDCHA	-78 ~ r.t.	8	54 (27 : 73)
13		KH / LDCHA	-78 ~ r.t.	8	92 (0 : 100)

The characteristic feature of Schlosser's superbase in a combination of lithium amides with potassium alkoxides[9] affects the reactivity and regioselectivity of unsymmetrically substituted bis-allylic ethers in the [2,3] Wittig rearrangement (Scheme 2). By virtue of the sterically demanding nature of lithium amides/potassium hydride (eventually as Schlosser's mixed-metal amide base showed in Scheme 2), the high yielding and regiospecific [2,3] Wittig rearrangement takes place (entry 5).



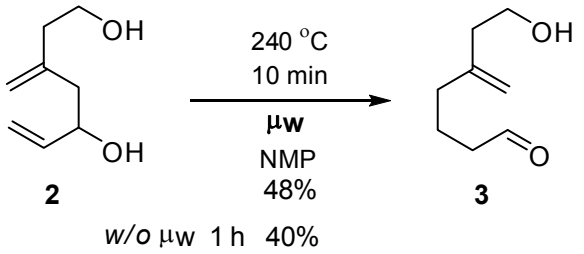
Scheme 2

The employment of highly sterically demanding and less nucleophilic lithium dialkylamides rather than the alkyllithium bases in a combination with β-potassium alkoxide (eventually as Schlosser's mixed-metal amide base) is thus the key for the highly α-regiospecific deprotonation/rearrangement sequence.

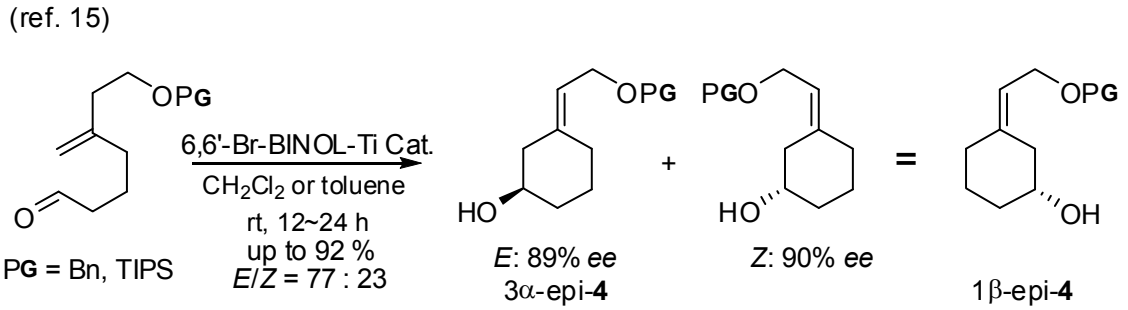
In sharp contrast to the highly regioselective α'-deprotonation of a γ-methyl substituted bis-allylic ethers,[2] β'-hydroxyethyl γ-methyl bis-allylic ether gave the deprotonation at the α-position of unsymmetrical bis-allylic ethers, though in 33% regioselectivity and 42% combined yield (entry 11); the S_N2' displacement product with base[10] was obtained due to the less favorable α-deprotonation process in the γ-methyl allylic ether. Indeed, β'-hydroxyethyl α-methyl bis-allylic ether gave the α'-[2,3] Wittig rearrangement product regioselectively in 92% yield (entry 13).

The highly regiospecific α-[2,3] Wittig rearrangement is, in principle, extended to the tandem anionic oxy-Cope rearrangement[11] of the α-[2,3] Wittig dianion rearrangement product (**2**) (Scheme 3); the tandem product (**3**) can be employed for the asymmetric catalytic ene cyclization[7e-f] leading to the A-ring of 19-nor-vitamin D_3 (Scheme 4). However, an attempted anionic oxy-Cope rearrangement of the α-[2,3] Wittig product in THF, DME, and DMSO with or without 18-crown-6 had not yet provided the oxy-Cope rearrangement aldehyde (**3**).[12] Simply upon isolation of the α-[2,3] Wittig rearrangement alcohol (**2**) followed by microwave-assisted thermal oxy-Cope rearrangement[13] in *N*-methyl-2-pyrrolidinone (NMP), the rearranged aldehyde (**3**) was obtained in 48% yield within only 10 min. Without microwave irradiation, the oxy-Cope rearrangement took 1 h in NMP to give lower (40%) yield (Scheme 3). The oxy-Cope rearrangement aldehyde (**3**) has already been reported via the

BINOL-Ti-catalyzed ene cyclization[14,15] to give the A-ring of 1β-epi- or 3α-epi-19-nor-vitamin D_3 that stimulate apoptosis of leukemia HL-60 cell and 1α- or 3β-19-nor analogues as potent differentiators of cancer cell line of HL-60 (Scheme 4).[15]



Scheme 3



Scheme 4

We have thus developed the new route to regiospecific deprotonation at the α-position of β'-hydroxyethyl bis-allylic ether by the dianion repulsion with the β'-alkoxy anion. The [2,3] Wittig rearrangement product can be transformed to the A-rings of singly dehydroxylated 1(or 3),25-dihydroxy-19-nor-vitamin D_3 analogues.

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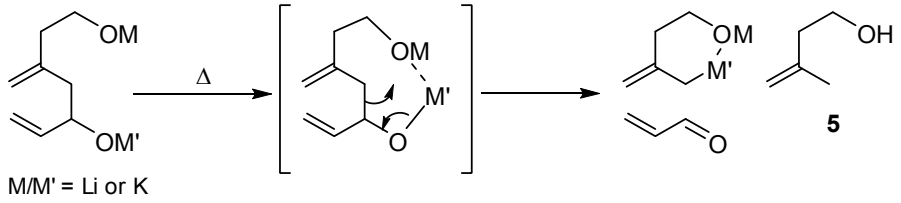

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