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Intramolecular Assistance to Metalation of a Dienol Ether

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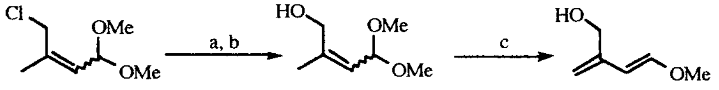
Abstract :
Functionalized dienol ethers **6** were obtained in one pot from hydroxyacetal **3**, via hydroxydienol ether **1** and anion **5**, when treating **3** with *n*-butyllithium. It was shown that the transient organometallic species **5** occured only when the electrophile was added.

Keywords: dienes; enol ethers; metalation; terpenes and terpenoids.

Our activity in the field of heterosubstituted dienol ethers [1] incited us to study hydroxy dienol ether **1**, a potential synthon in terpenic synthesis.
Reaction of chloroacetal **2** [2] with potassium acetate followed by saponification of the resulting acetoxyacetal lead to hydroxyacetal **3** with an overall yield of 86.5%. When treated with butyllithium (3 eq.), hydroxyacetal **3** undergoes deprotonation in γ of the acetal group with elimination of an alkoxyanion yielding hydroxydienol ether **1** with an *E* configuration and 76% yield (scheme 1).

Scheme1



2 (E/Z = 80/20) **3** (E/Z = 80/20) **1**

a) AcOK, MeOH, reflux, 24h. (95%) ; b) KOH, RT, 1h. (91%) ; c) i) *n*-BuLi (3 eq.), THF, -40°C, 4h. ; ii) H_2O (76%) or i) KH (1 eq.), THF, 15 min. ; ii) *n*-BuLi (2 eq.), -40°C, 1h. ; iii) H_2O (97%)

When **3** was prealably treated with KH (1 eq.), the yield was raised to 97%.
It is to be noted that the deprotonation occured exclusively on the methyl group in γ of the acetal function [1b,d; 3].

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In order to functionnalize dienol ether **1** we studied its metallation in α of the ether function. Metalation of monovinylic ethers has been explored using organosodium [4a] and organolithium reagents in THF [4b-d] or superbases (*n*-BuLi/TMEDA) [4e], (n-BuLi / *t*-*B*uOK) [4f] in hydrocarbons. Extension to dienic enol ethers was first reported by Venturello in 1992 [5] who related the metalation of *(E)*-alkoxybuta-1,3-diene with mixed superbase *s*-BuLi/*t*-BuOK in THF. In the case of dienol ether **1**, we observed a quantitative deprotonation using *n*-BuLi as evidenced by quenching anion **5** with D_2O (table 1). We postulate an intramolecular assistance of the alcoholate. As expected from the litterature concerning superbases [6], formation of the potassium alcoholate from hydroxy dienol ether **1** allowed an increase of the metalation rate (scheme 2; table 1: runs 1,3) [7].

Scheme 2

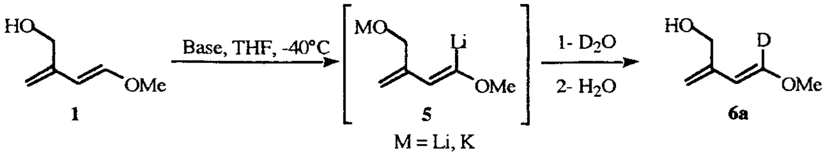
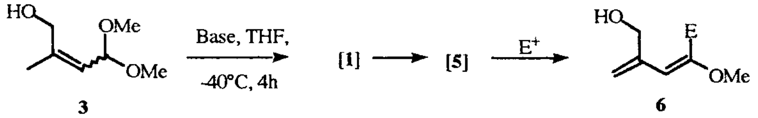


Table 1 : *Metalation of hydroxy dienol ether 1*

Run	*Conditions*	*6a %*
1	*n*-BuLi (2 eq.), 1h	80
2	*n*-BuLi (2 eq.), 4h	100
3	KH (1 eq.), 15 min. then *n*-BuLi (1 eq.), 1h	100

These results led us to acceed to anions **5** directly from hydroxyacetal **3** and to condense them with various electrophiles : D_2O, Me_3SiCl, alkyl halides (scheme 3; table 2).

Scheme 3



Runs 1-4 (table 2) emphasize the importance of the basicity of the organometallic reagent for the elimination-metalation steps : more basic is the reagent, higher is the ratio of deuterated **6a** [8].

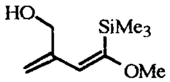
Table 2 : *Access to products 6 and 7 in one pot from hydroxyacetal 3*

Run	*Conditions*	*Electrophile*	*Product*	*Yield^a (%)*
1	*n*-BuLi (3 eq.)	D_2O (10 eq.)	**6a**	80^b
2	*s*-BuLi (3 eq.)	D_2O (10 eq.)	**6a**	90^b
3	*t*-BuLi (3 eq.)	D_2O (10 eq.)	**6a**	100^b
4	KH (1 eq.) then *n*-BuLi (1 eq.)^c	D_2O (10 eq.)	**6a**	100^b
5	*n*-BuLi (3 eq.)	Me_3SiCl (3 eq.)	**6b**	62
6	*n*-BuLi (3 eq.)	Me_3SiCl (6 eq.)	**7**	47
7	KH (1 eq.) then *n*-BuLi (1 eq.)^c	Me_3SiCl (6 eq.)	**7**	60
8	*n*-BuLi (3 eq.)	 (4.6 eq.)	**6c**	60^d
9	*n*-BuLi (3 eq.)	$PhCH_2Br$ (4.9 eq.)	**6d**	57

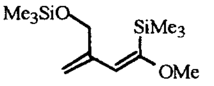
a) yield of chromatographed product
b) **6a** / (**1** + **6a**) ; overall yield >80%
c) contact time after addition of *n*-BuLi : 1h
d) yield determinated by ^1H NMR of the crude material

Silylation of **5** with trimethylchlorosilane led to monosilylated product **6b** but the disilylated product **7** was obtained when using a large excess of silylating agent (table 2: runs 5-7; figure 1).

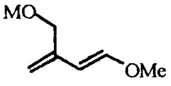
Figure 1



6b



7



8 a: M = Li ; **b**: M = K

Alkylation with alkyl- and benzyl- bromides yielded in our conditions to the mono-C-alkylated products **6c** and **6d** [9].

Finally, in order to obtain information about the carbanionic species **5**, we studied alcoholates **8a** and **8b** (figure 1) in the presence of *n*-BuLi (1 eq.) in THF-d_8 by ^1H NMR (500 MHz). At -70 and -40°C we don't detect the anions **5** (the ^1H signal was remaining) [10]. although the deuterated species **6a** was observed after addition of D_2O at -40°C. Thus we suggest that **8** and *n*-BuLi form a mixed aggregate and that the very transient anions **5** occur during the electrophilic addition. These observations are in agreement with a recent litterature report [11].

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[7] At T= -70°C, deprotonation of **1** was very slow. At T> -40°C, degradation by-products were observed. Thus -40°C seems to be the optimal deprotonation temperature.

[8] Control experiments have shown that liberated MeOLi in the formation of **1** from **3** had no significative influence in the metalation step.

[9] Typical experimental procedure for the formation of **6** : To a cold (-40°C) solution of **3** in THF was added 2,5 eq. of *n*-BuLi (2.5 M in hexanes). The reaction mixture was then stirred at -40°C for 4 h. Freshly distilled trimethylchlorosilane (3 eq.) was added and the temperature raised to room temperature. Treating the reaction mixture with water and purification of the crude by flash chromatography afforded pure **6b**.

[10] Addition of one eq. of n-BuLi to **1** (formation of **8a**) led to a shift toward the low fields (+ 0.37 ppm) for one methylenic hydrogen. Addition of a second eq. of n-BuLi don't lead to any significant modification after one hour (the ^{1}H signal was always detected)

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