Stereoselective Reduction of Conjugated Homopropargylic Alcohols to (*E*)-Homoallylic Alcohols by Sodium Bis(2-methoxyethoxy) Aluminium Hydride

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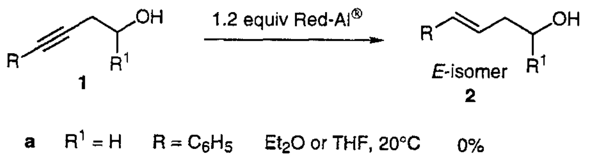
Abstract: The reduction of various conjugated homopropargylic alcohols with sodium bis(2-methoxyethoxy) aluminium hydride (Red-Al®) in ether or THF is described. The reaction takes place cleanly and rapidly, under mild conditions, to give (*E*)-homoallylic alcohols stereoselectively in good isolated yields.

Substituted homoallylic alcohols are important intermediates in organic synthesis and there is a continuous interest in the search of simple methods for the preparation of these compounds.[1] They are usually prepared by addition of allylic organometallic derivatives to carbonyl compounds;[2] however, this reaction is not stereoselective and gives a mixture of stereoisomeric alcohols. Reduction of homopropargylic alcohols to homoallylic alcohols by an aluminium hydride may be an attractive alternative. To our knowledge, only few examples using lithium aluminium hydride (LAH) have been reported in the literature.[3] The reaction requires an excess of reducing reagent (2 to 3.5 equiv), high temperatures (diglyme, 100° to 130°C), long reaction times (12 to 55h) and (or) gives a mixture of isomers. In this communication, we report an efficient and mild stereoselective reduction of homopropargylic alcohols to substituted (*E*)-homoallylic derivatives by using sodium bis(2-methoxyethoxy) aluminium hydride[4] (Red-Al®) in ether or THF.

Thus, when 4-phenyl-3-butyn-1-ol **1a** was treated with Red-Al® (1.2 equiv) at room temperature in Et_2O or THF, no reaction occurred. However, when performing the reduction in refluxing THF, an almost quantitative isolated yield (95%) of (3*E*)-4-phenyl-3-buten-1-ol **2a** was obtained within 2h (Scheme 1). The reaction can also be performed at reflux of ether in a 75% yield within 8h. It is worthwhile to note that the reduction proceeds stereoselectively providing exclusively the corresponding (*E*)-homoallylic alcohol. GLC analysis shows that the obtained (*E*)-homoallylic alcohol **2a** contains less than 1% of the corresponding (*Z*)-isomer.



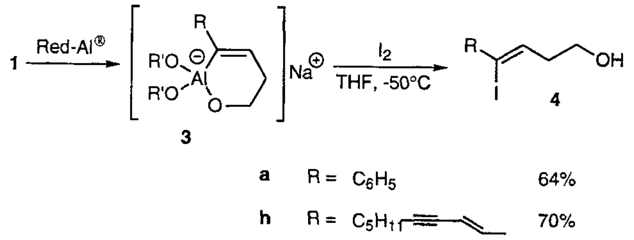
a	R^1 = H	R = C_6H_5	Et_2O or THF, 20°C	0%
a	R^1 = H	R = C_6H_5	Et_2O, 35°C, 8h	75%
a	R^1 = H	R = C_6H_5	THF, 66°C, 2h	95%
b	R^1 = H	R = C_2H_5	THF, 66°C	0%

Scheme 1

Attempts to reduce 3-hexyn-1-ol **1b** into (3*E*)-3-hexen-1-ol **2b**, under the same reaction conditions, were unsuccessful; only starting material was recovered. This reflects the higher reactivity of the triple bond bearing an aryl group in **1a** over the triple bond bearing an alkyl group in **1b**. Based on this observation, we decided to examine the reduction of conjugated homopropargylic alcohols **1c-l** (Table I).

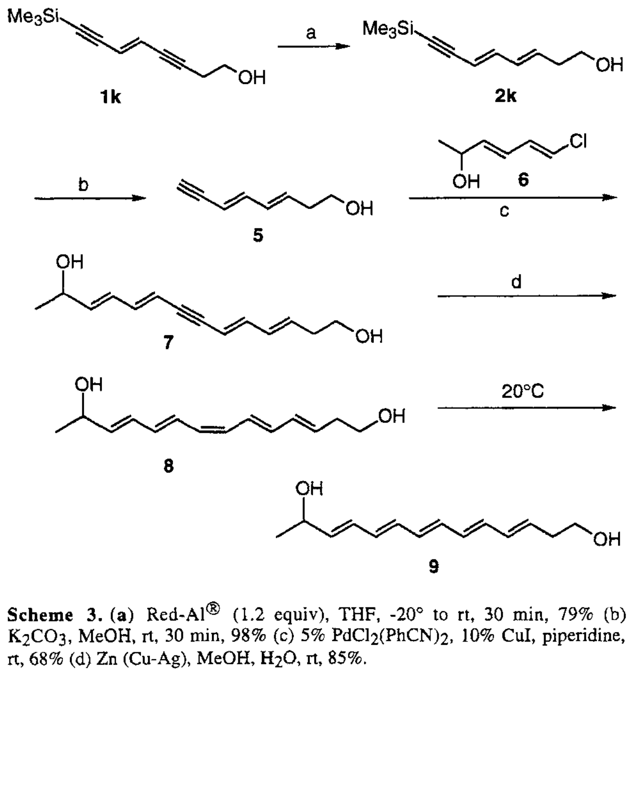
The reaction was successfully applied to a wide variety of conjugated homopropargylic alcohols. For example, diynols **1c-f** can be reduced stereoselectively by Red-Al® into (*E*)-enynols **2c-f** in good isolated yields (74-88%, entries 1 to 4). It may be pointed out that in the case of diynediols **1e** and **1f** (entries 3 and 4), the reduction of the second triple bond did not occur even in the presence of an excess of reducing reagent. In the case of **1f**, the allylic double bonds was also reduced. (*E,E*)-dienynol **1g** can also be reduced in good isolated yield (80%, entry 5) providing an efficient stereoselective route to (*E,E,E*)-β-hydroxytrienes.[8] In a similar way, (*E*)-enediynols **1h-j** react efficiently and give stereoselectively (*E,E*)-β-hydroxydienynes **2h-j** in good isolated yield (82-90%, entries 6,7 and 8).[9]

The high stereoselectivity observed in the reduction of homopropargylic alcohols **1a-f** by Red-Al® can be explained by the intermediate alkenyl aluminate **3** resulting from *trans* addition of aluminium-hydrogen to the triple bond. Thus, when homopropargylic alcohols **1a** and **1h** were treated with Red-Al® (1.2 equiv) in refluxing THF for 1 to 2h followed by addition of iodine at -78°C, the resulting alkenyl iodides **4a** and **4h** were obtained stereoselectively in 64 and 70% isolated yield respectively (Scheme 2).



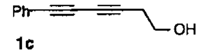
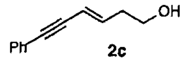
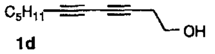
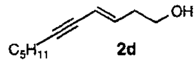
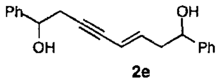
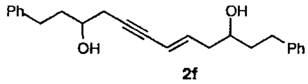
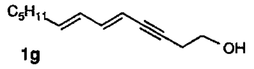
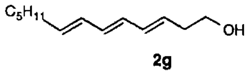
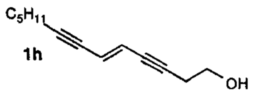
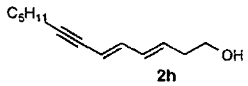
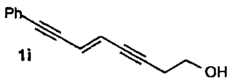
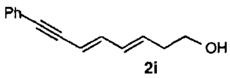
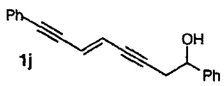
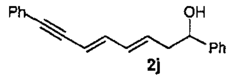
Scheme 2

As an illustration of the synthetic interest of the procedure outlined above, the pentaenediol all (*E*) **9** has been synthesized (Scheme 3). This structure is found in various biologically active compounds (e.g., macrolide antibiotics).[10]



Scheme 3. (a) Red-Al® (1.2 equiv), THF, -20° to rt, 30 min, 79% (b) K_2CO_3, MeOH, rt, 30 min, 98% (c) 5% $PdCl_2(PhCN)_2$, 10% CuI, piperidine, rt, 68% (d) Zn (Cu-Ag), MeOH, H_2O, rt, 85%.

Table I. Reduction of conjugated homopropargylic alcohols[a] with Red-Al®

Entry	Homopropargylic alcohols 1[b]	Solvent	Conditions	homoallylic alcohols 2[c]	Isolated yield (%)
1	 1c	Et_2O	36°C, 0.5h	 2c	74[d]
2	 1d	Et_2O	36°C, 1h	 2d	83[d]
3	 1e	THF	20°C, 1h	 2e	88[e]
4	 1f	THF	20°C, 1h	 2f	77[e]
5	 1g	THF	66°C, 1h	 2g	80
6	 1h	THF	66°C, 1h	 2h	82
7	 1i	THF	20°C, 0.5h	 2i	90
8	 1j	THF	20°C, 1h	 2j	90

a/ Unless otherwise stated, 1.2 equiv of Red-Al was used. b/ Symmetrical 1,3-diynes **1e** and **1f** were prepared from the corresponding 1-alkynes see ref 5.; unsymmetrical 1,3-diynes were synthesized according to ref 6.; dienyne **1g** was prepared according to ref 7d.; enediynes **1h-j** were synthesized from 1,2-dichloroethylene and 1-alkynes see: ref 7. c/ Satisfactory spectral data were obtained for all new compounds. d/ 1.6 equiv of Red-Al was used. e/ 4 equiv of Red-Al were used.

Thus, (*E*)-enediynol **1k** was stereoselectively reduced by Red-Al® into (*E,E*)-dienynol **2k** in 79% yield.[11] Desilylation and coupling with chlorodiene[12] **6** in the presence of $PdCl_2(PhCN)_2$ and CuI in piperidine[13] gave the diol **7**[14] in 68% yield. The pentaene **8** , with one *Z*-double bond, obtained by selective reduction[15] of **7**, was not stable at room temperature and isomerized quantitatively into the pure pentaene all (*E*) **9**.[16]

In conclusion, the reduction of conjugated homopropargylic alcohols by Red-Al® takes place rapidly to give stereoselectively (*E*)-homoallylic alcohols in good isolated yields.

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4. Red-Al® is an efficient reagent for the reduction of propargylic alcohols into (*E*)-allylic alcohols see: Denmark, S.E.; Jones, T.K. *J. Org. Chem.* **1982**, *47*, 4595. For a review see: Gugelchuk, M. *Sodium Bis(2-methoxyethoxy)aluminium Hydride* in *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L.; Ed., Wiley, Chichester **1995**, 7, 4518.
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8. **2g:** ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.07 (4H, m), 5.66 (1H, dt, J = 14.7 and 6.9 Hz), 5.59 (1H, dt, J = 14.6 and 7.3 Hz), 3.63 (2H, t, J = 6.3 Hz), 2.33 (2H, q, J = 6.7 Hz), 2.06 (2H, q, J = 7.0 Hz), 1.64 (1H, s), 1.36 (2H, quint, J = 7.1 Hz), 1.33 to 1.20 (4H, m), 0.85 (3H, t, J = 6.7 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 135.40, 133.40, 132.05, 130.15, 130.00, 129.10, 61.95, 36.15, 32.75, 31.35, 29.00, 22.50, 14.00.
9. *Typical procedure: preparation of (3E,5E)-8-phenyl-3,5-octadien-7-yn-1-ol (2i, Table I, entry 7):* To a stirred solution of Red-Al® (0.612 mmol, 3.4N in toluene) in anhydrous THF (3 mL), under an argon atmosphere, was added dropwise, at -20°C, a solution of homopropargylic alcohol **1i** (0.51 mmol, 100 mg) in 2 mL of THF. After stirring at room temperature for 30 min, the reaction was hydrolysed, at -20°C, with aqueous hydrochloric acid (1M, 5 mL) and extracted with Et_2O (2 x 10 mL). The organic extract was dried over $MgSO_4$ and the solvent was removed *in vacuo*. Filtration through silica gel (eluent: petroleum ether: ethyl acetate, 7:3) gave 97 mg (90%) of pure dienyne **2i**: ^{1}H

NMR (200 MHz, $CDCl_3$) δ 7.41 (2H, m), 7.28 (3H, m), 6.65 (1H, dd, J = 15.5 and 11 Hz), 6.21 (1H, dd, J = 15 and 11 Hz), 5.80 (1H, dt, J = 15 and 7 Hz), 5.74 (1H, d, J = 15.5 Hz), 3.65 (2H, t, J = 6.5 Hz), 2.34 (2H, q, J = 6.5 Hz), 2.30 (1H, s); ^{13}C NMR (63 MHz, $CDCl_3$) δ 141.45, 133.40, 132.10, 131.25, 128.15, 127.90, 123.25, 109.70, 91.55, 88.85, 61.55, 36.00.

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11. In the presence of $LiAlH_4$, at 0°C, the reduction of **1k** was not stereoselective and led directly to desilylated compounds **5** as a mixture of stereoisomers (63%, *3E,5Z/3E,5E* : 89/11).

12. Prepared by reaction of 1-butyn-3-ol with (*E*)-1,2-dichloroethylene and subsequent reduction with $LiAlH_4$.[7c]

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14. **7:** ^1H NMR (400 MHz, $CDCl_3$) δ 6.60 (1H, dd, J = 15.0 and 11.0 Hz), 6.59 (1H, dd, J = 15.0 and 11.0 Hz), 6.31 (1H, dd, J = 15.0 and 11.0 Hz), 6.25 (1H, dd, J = 15.0 and 11.0 Hz), 5.88 (1H, dd, J = 15.0 and 6.0 Hz), 5.83 (1H, dt, J = 15.0 and 7.5 Hz), 5.79 (1H, dd, J = 15.0 and 2.0 Hz), 5.72 (1H, dd, J = 15.0 and 2.0 Hz), 4.43 (1H, quint, J = 6.0 Hz), 3.75 (2H, t, J = 7.0 Hz), 2.44 (2H, q, J = 7.0 Hz), 1.58 and 1.43 (2H, s), 1.35 (3H, d, J = 6.0 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 141.25, 140.50, 139.55, 133.20, 132.45, 128.70, 111.65, 110.10, 92.00, 91.35, 68.20, 61.70, 36.10, 23.20. UV: (CH_2Cl_2) λ = 311 nm (ε = 49000).

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16. **9:** ^1H NMR (400 MHz, $CDCl_3$) δ 6.35 to 6.10 (8H, m), 5.70 (2H, m), 4.35 (1H, m), 3.68 (2H, q, J = 7 Hz), 2.35 (2H, q, J = 7 Hz), 1.50 (1H, d, J = 7 Hz), 1.35 (1H, t, J = 7 Hz), 1.28 (3H, d, J = 7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.35, 133.40, 133.35, 133.30, 132.90, 132.65, 132.00, 131.80, 130.75, 129.85, 68.60, 61.95, 36.25, 23.30. UV: (CH_2Cl_2) λ = 311 nm (ε = 34300), λ = 318 nm (ε = 45600), λ = 322 nm ($ε_{max}$ = 49500); mp : 118-120°C.