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Low-Valent Titanium Reductive Elimination : a Direct and Highly Stereoselective Synthesis of Vitamin A Aldehyde.

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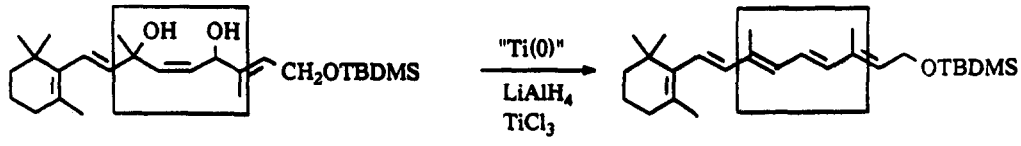
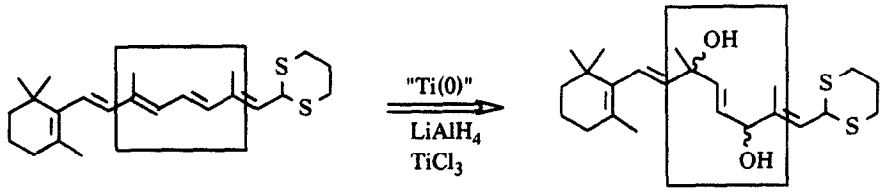
Abstract : It was shown that the low-valent titanium reductive elimination could be carried out in presence of a thioacetal group. An application to the synthesis of vitamin A aldehyde is described.

Low valent titanium, readily available by reduction of titanium trichloride with lithium aluminium hydride, was shown to be a powerful synthetic agent allowing the formation of a diene by reductive elimination of an allylic diol[1]. We have described already a highly stereoselective synthesis of the E, E-1,3-diene central unit of vitamin A and 13-cis retinol[2] from the corresponding allylic diol.



The reaction mechanism involves, at least in the first step, a one electron transfer from the titanium surface.

We report in this paper the application of this reaction to the preparation of vitamin A aldehyde, as shown on the retrosynthetic scheme. The aldehyde function in the starting allylic diol 2 had to be protected because of its sensitivity to electron transfer as shown by the pionneering work of Mc Murry[3] who described the carbonyl[1] reductive coupling to olefin monitored by Ti(0). We chose a thioacetal group as protecting group. It is known also that the C-S bond can be broken by a one electron transfer reaction but we expected that the competition would be in favor of the reductive elimination of the allylic diol.

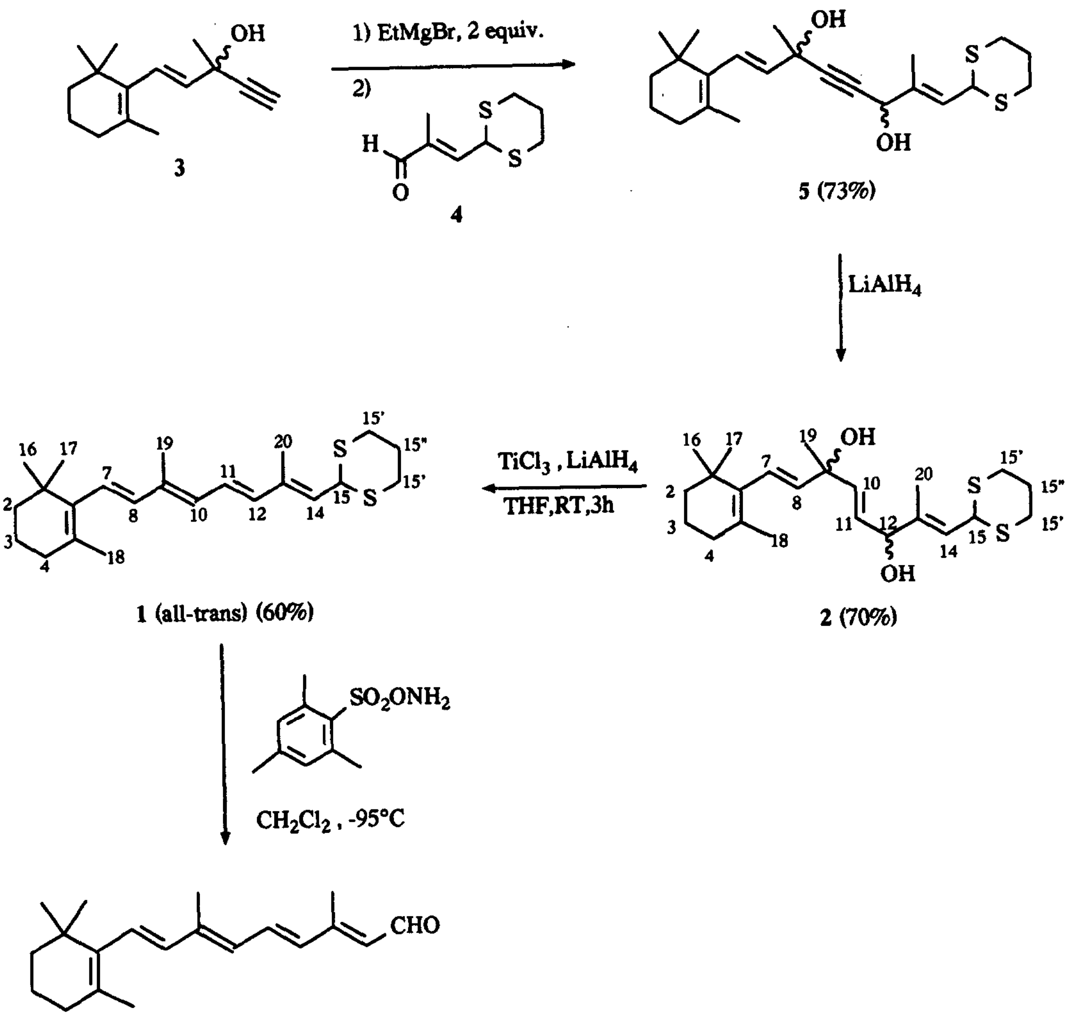


1 2

The allylic diol 2 was readily prepared from the well-known propargylic alcohol 3 derived from ß-ionone[2]. Condensation of the Grignard derivative of 3 with the C_5 aldehyde 4[4] gave propargylic diol 5 in 73% yield. Triple bond reduction with $LiAlH_4$ afforded the trans allylic diol 2[5] in 70% yield as a diastereomeric mixture. The reductive elimination was carried out in THF at room temperature for 3h using a 2 : 1 $LiAlH_4$: $TiCl_3$ mixture. Only one compound was isolated in 60% yield (after chromatography). This was shown by ^1H NMR to be the all-trans isomer of retinal thioacetal[6]. The stereochemistry of compound 1 was determined by ^1H NMR: a 16 Hz coupling constant between H-7 and H-8 and a 15 Hz one between H-11 and H-12 confirm the trans configuration. The ^{13}C chemical shifts of Me-18, Me-19 and Me-20 are totally consistent with an all-trans structure, as shown by the corresponding literature values[8] of chemical shifts for all the isomeric retinals (Table 1). Finally NOE experiments gave supplementary evidence : irradiation of CH_3-19 and CH_3-20 (having the same chemical shift) lead to a 15% NOE on H-15 and a 7% NOE on H-7 and H-11.

Table 1 : ^{13}C chemical shifts

Compound	Me-18	Me-19	Me-20
1	21.62	12.91	12.62
All-trans retinal	21.70	13.00	13.00
9-cis retinal	21.80	20.90	13.20
11-cis retinal	19.90	10.40	15.90
13-cis retinal	21.70	13.00	21.10



Retinal (90% , all trans / 13- cis = 93 / 7)

The hydrolysis of the thioacetal was attempted with many different reagents : mercury salts, oxidizing agents (NBS, I_2, NCS-$AgNO_3$, SO_2Cl_2), alkylating agents (MeI, Et_3OBF_4). In all these cases we observed the formation of degradation products as well as 20 to 30% of 13-cis retinal resulting from an isomerization of the terminal double bond. Finally, we have been able to avoid almost completely the double bond isomerization (7%) and to get all-trans retinal in 90% yield in using O-mesitylenesulfonyl hydroxylamine[7] (MSH), a sulfur aminating reagent which allowed to carry out the reaction at -95°. All-trans retinal and 13-cis retinal were identified from the ^1H and ^{13}C NMR spectra already described in the literature[8].

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5) ^1H NMR of **2** (200MHz, $CDCl_3$) : δ : 0.97 (s, 2x3H, Me-16 and Me-17) ; 1.42 (s, 3H, Me-18) ; 1.42-1.64 (m, 2x2H, CH_2-2 and CH_2-3) ; 1.64 (s, 3H, Me-19) ; 1.71 (d, 3H, J=1Hz, Me-20) ; 1.95 (t, 2H, CH_2-4) ; 1.79-2.17 (m, 2H, CH_2-15") ; 2.75-2.87 (m, 2H H_{eq}-15') ; 2.87-3.01 (m, 2H, H_{ax}-15') ; 4.55 (d, 1H, J=6Hz, H-12) ; 4.87 (d, 1H, J=10Hz, H-15) ; 5.51 (d, 1H, J=16Hz, H-7) ; 5.51 (dq, 1H J=10Hz, J=1Hz, H-14) ; 5.66 (dd, 1H, J=6Hz, J=15Hz, H-11) ; 5.90 (dt, 1H, J=1Hz, J=15Hz, H-10) ; 6.05 (d, 1H, J=16Hz, H-8).
6) m. p. 108-110°C ; ^1H NMR ($CDCl_3$, 200 MHz) : δ : 1,03 (s, 2x3H, Me-16 and Me-17) ; 1,44-1,66 (m, 2x2H, CH_2-2 and CH_2-3) ; 1, 72 (s, 3H, Me-18) ; 1,82-2,18 (m, 2H, CH_2-15") ; 1,95 (s, 2x3H, Me-19 and Me-20) ; 2,02 (t, 2H, J=6Hz, CH_2-4) ; 2,84 (m, 2H, H_{eq}-15') ; 2.98 (m, 2H, H_{ax} 15') ; 5.02 (d, 1H, J=10Hz, H-15) ; 5,44 (d, 1H, J=10Hz, H-14) ; 6,09 (d, 1H, 5=11Hz, H-10) ; 6,10 (d, 1H, J=16Hz, H-7) ; 6,20 (d, 1H, J=16Hz, H-8) ; 6,24 (d, 1H, J=15Hz, H-12) ; 6,64 (dd, 1H, J=11Hz, J=15Hz, H-11).
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