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HIGHLY STEREOSELECTIVE SYNTHESIS OF VITAMIN A AND ALL-TRANS RETINOIC ACID BY LOW-VALENT TITANIUM INDUCED REDUCTIVE ELIMINATION

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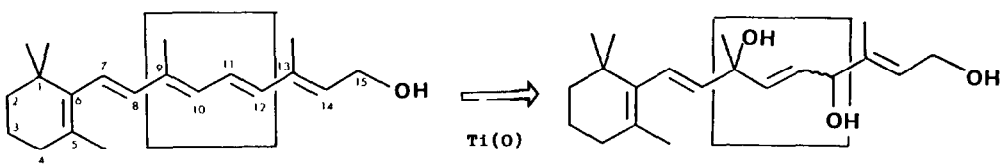
Abstract Application of the low-valent Titanium induced reductive elimination gave a new and highly stereoselective approach to Vitamin A and all-trans retinoic acid.

Since the first industrial synthesis of Vitamin A reported by Isler[1] at Hoffmann La Roche in 1947, many papers describing different approaches appeared[2]. The BASF industrial preparation[3] of all-trans retinoic acid featured Wittig condensations, while Hoffmann La Roche chemists[4] and Rhône-Poulenc Industries[5] developed efficient syntheses of Vitamin A by a sulfone coupling reaction, which was first reported by Julia[6].

During the last ten years, the discovery of new biological activities[7] of Vitamin A and retinoids, dependent on the geometry of the polyene chain and structural variation, stimulated the search of new methodologies for preparation of the pentaene derivatives[2].

We recently reported[8] the application of the low-valent Titanium induced reductive elimination[9] to the synthesis of the diene moiety of Vitamin D_3 analogues.

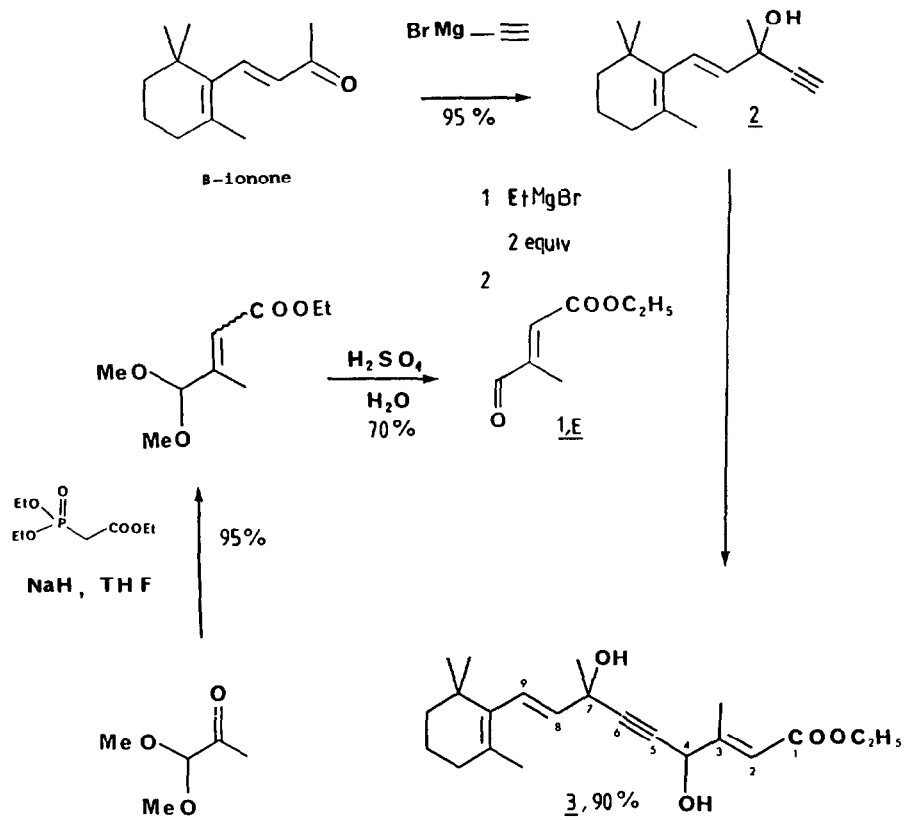
We describe now in this paper a highly stereoselective synthesis of Vitamin A based on the same methodology formation of the E,E-1,3-diene central unit of Vitamin A by Ti(0) induced reductive elimination of the corresponding allylic diol



Vitamin A

The synthesis of the parent allylic diol was performed in a few steps from β-ionone.

Ethyl γ-oxysenecionate 1,E was readily prepared from the dimethylacetal of pyruvaldehyde by a Wittig reaction giving a mixture of E and Z acetals which were hydrolyzed in acidic medium with complete isomerization to the pure E isomer 1. Further addition of the Grignard derived from ethynyl β-ionol 2 gave in high yield the diol 3 as a mixture of diastereoisomers



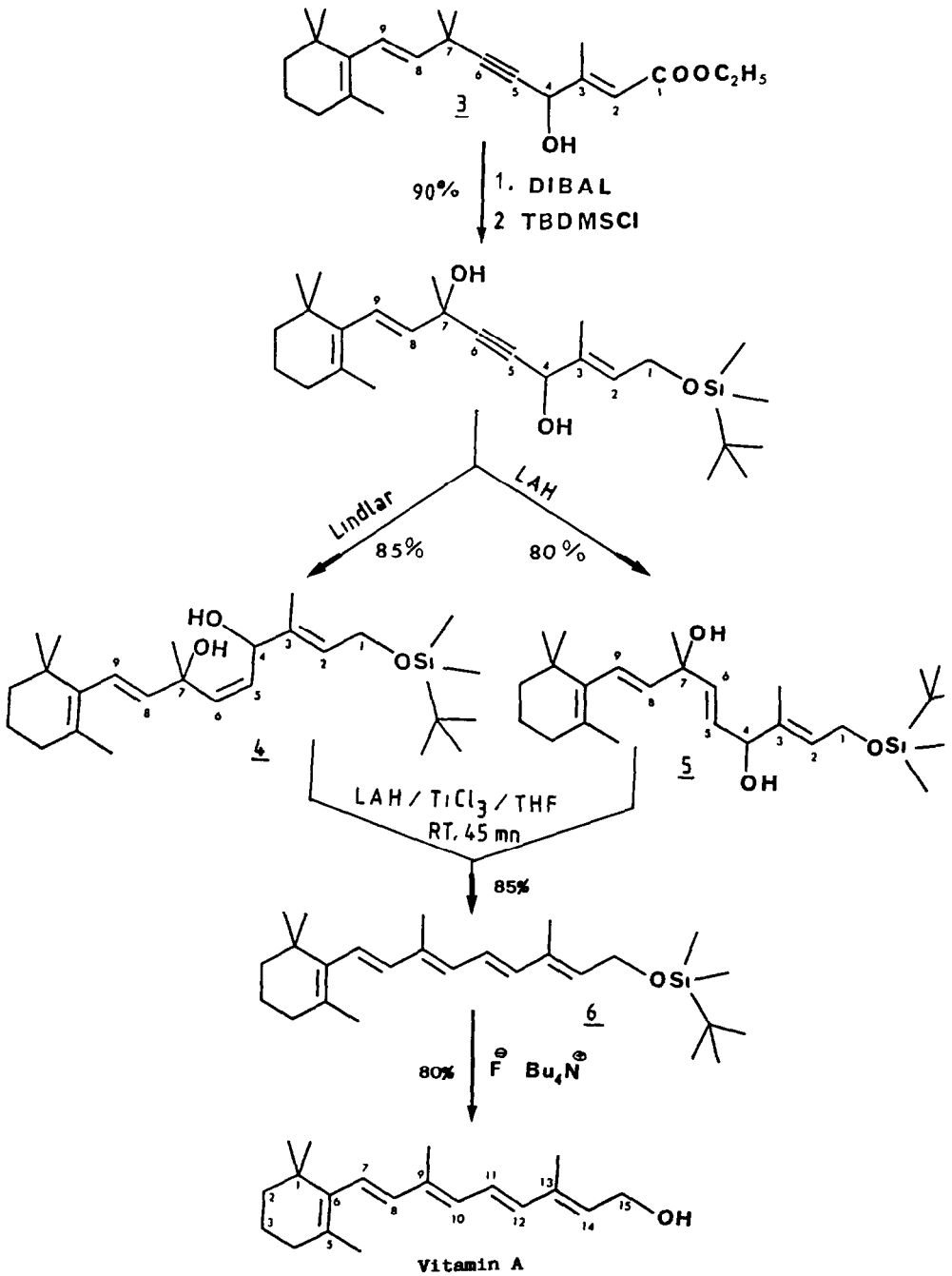
After the reduction of the ester function with DIBAL and protection of the resulting primary alcohol with a TBDMS group, the triple bond was reduced into a cis double bond with Lindlar catalyst and to a trans double bond with $LiAlH_4$.

The reductive elimination was conducted on compounds 4 and 5 in THF at room temperature using the mixture $LiAlH_4/TiCl_3$ in the ratio 1/2.

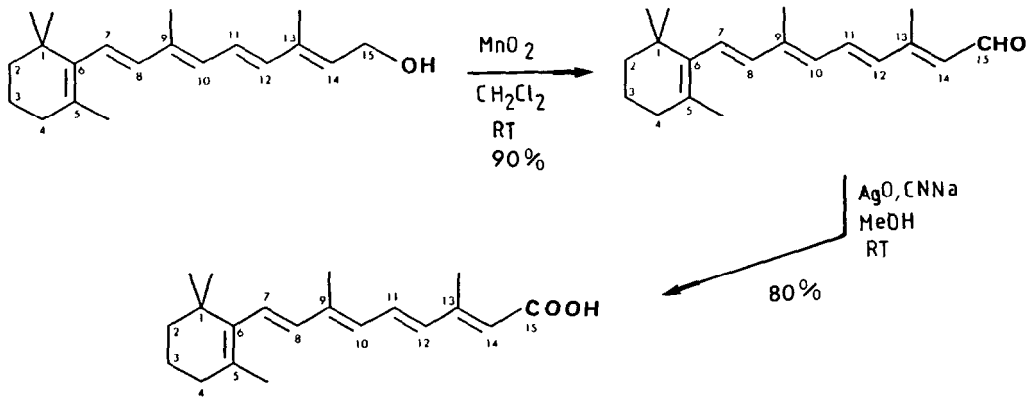
Both Z and E isomers 4 and 5 gave only one product 6 in 85% yield which afforded, after removing the protection group and purification by flash chromatography, Vitamin A (80% yield) identical in all respect to an authentic sample[10].

Therefore, this reductive elimination with Ti(0) affords a highly stereoselective route to Vitamin A from cis or trans allylic diols as long as the protecting group of the primary alcohol is a silyl group If this primary hydroxyle is protected as an acetate, the reductive elimination with Ti(0) gave indeed a mixture of E and Z isomers.

Finally all-trans retinoic acid was prepared from Vitamin A in 2 steps by oxidation with activated MnO_2[11] to retinal and subsequent oxidation with argentic oxid in presence of cyanide ion as catalyst[12] leading in 80% overall yield to a compound identical in all respect to an authentic sample[13,2].


COOC2H5
OH
90%
1. DIBAL
2 TBDMSCI
OH
OSi
OH
Lindlar
85%
LAH
80 %
HO
OH
OSi
4
OH
OSi
OH
5
LAH / TiCl3 / THF
RT. 45 mn
85%
OSi
6
80%
F⊖ Bu4N⊕
OH

Vitamin A



All-Trans Retinoic acid

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m p. 179-180°C (Lit.[14] 179-180°C) - ^1H NMR (200MHz, $CDCl_3$) δ 1.03 (s, 6H, $2CH_3$ at C_1) , 1.44 - 1.62 (m, 4H, CH_2 at C_2 and C_3) , 1.72 (s, 3H, CH_3 at C_5) , 2.01 - 2.06 (broad s, 5H, CH_2 at C_4 and CH_3 at C_9) , 2.37 (s, 3H, CH_3 at C_{13}) ; 5 80 (s, 1H, H_{14}) ; 6.14 (d, 1H, H_8, J = 16Hz) , 6.15 (d, 1H, H_{10}, J = 11Hz) ; 6.23 (d, 1H, H_7, J = 16Hz) ; 6.31 (d, 1H, H_{12}, J = 15Hz) , 7.05 (dd, 1H, H_{11}, J = 15Hz, J = 11Hz)
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