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HIGHLY STEREOSELECTIVE SYNTHESIS OF 13-CIS RETINOIC ACID BY LOW-VALENT TITANIUM INDUCED REDUCTIVE ELIMINATION

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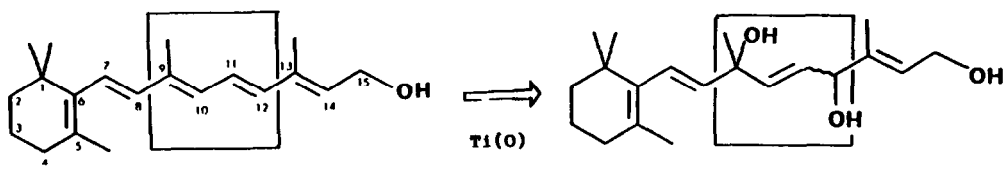
Abstract Application of the low-valent Titanium induced reductive elimination gave a new and highly stereoselective approach to 13-cis retinol and 13-cis retinoic acid.

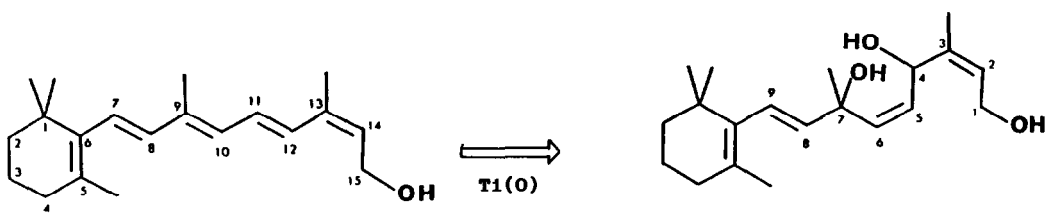
We reported in the preceeding paper[1] a highly stereoselective synthesis of Vitamin A by reductive elimination of the parent allylic diol 1 with Ti(0)



Vitamin A 1

It was shown that the E,E-1,3-diene central unit could be obtained with Ti(0) from the diol 1, whatever was the E or Z stereochemistry of the allylic diol. The E stereochemistry of the terminal double bond was maintained during the reaction.

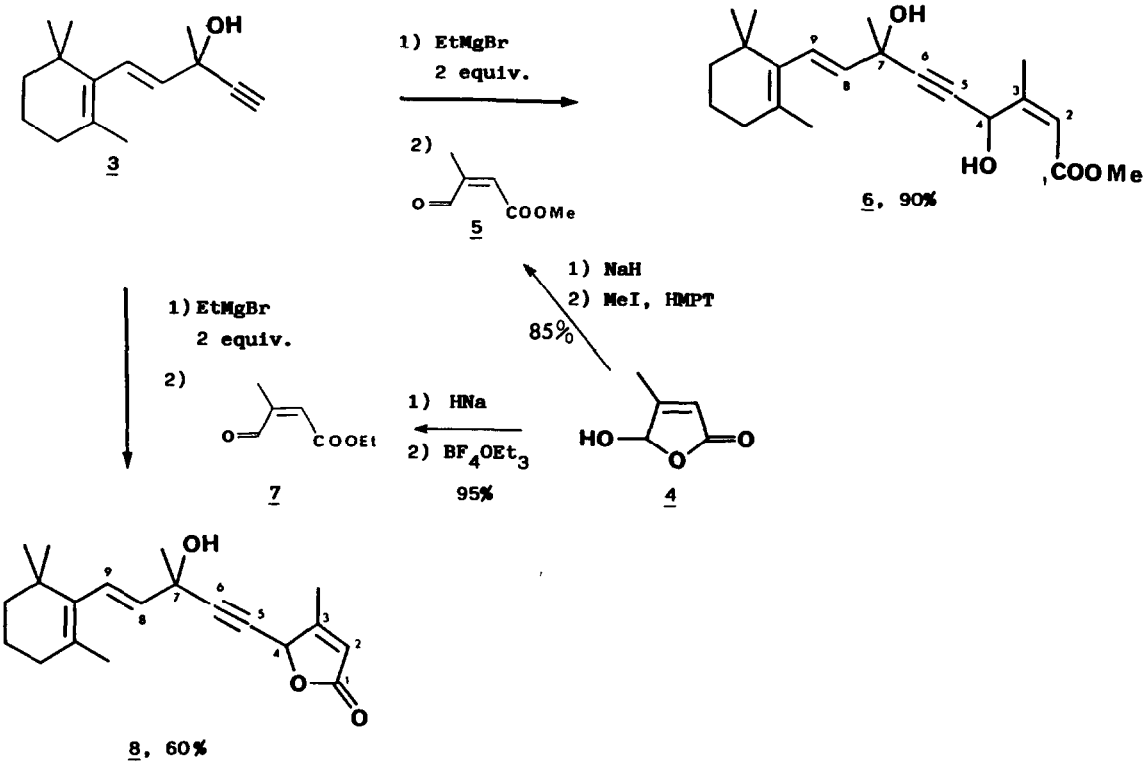
We describe now the synthesis of 13-cis retinol based on the same methodology · formation of the E,E-1,3 diene central unit from the parent allylic diol 2 by Ti(0) induced reductive elimination.



13-cis retinol 2

The main question concerning this synthetic approach was to determine if the Z stereochemistry of the terminal double bond in 2 could be preserved during the Ti(0) reductive elimination.

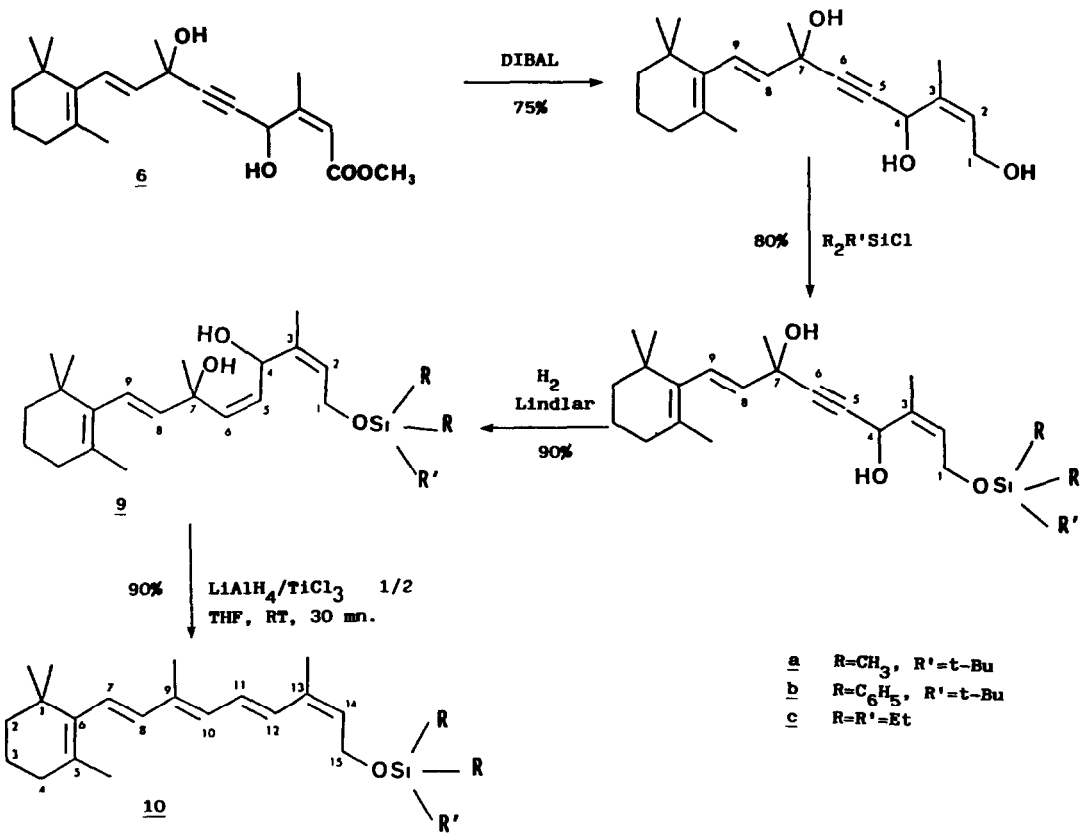
The synthesis of the diol 2 was performed in a few steps from ethynyl β-ionol 3.



The esters 5 and 7 were obtained in highly yield from the readily available[2] hydroxybutenolide 4. Condensation of the Grignard derived from ethynyl β-ionol 3 to the ester 5 gave in 90% yield the diol 6 while the condensation to the ester 7 gave in 60% yield the lactone 8.

It is interesting to point out that compound 8 was, after reduction of the triple bond with Lindlar catalyst, quite stable in presence of Ti(0) In sharp contrast the corresponding hydroxyester gave with Ti(0) a complex mixture of products which were not identified.

The ester 6 was reduced with DIBAL and the resulting primary alcohol was protected by a silicon containing protecting group. Our preceeding results[1] have shown the necessity of such protecting groups to get a stereoselective reductive elimination with Ti(0). Finally the triple bond was reduced with Lindlar catalyst.



The reductive elimination was conducted on compounds 9a-c in THF at room temperature using the mixture $LiAlH_4/TiCl_3$ in the ratio 1/2.

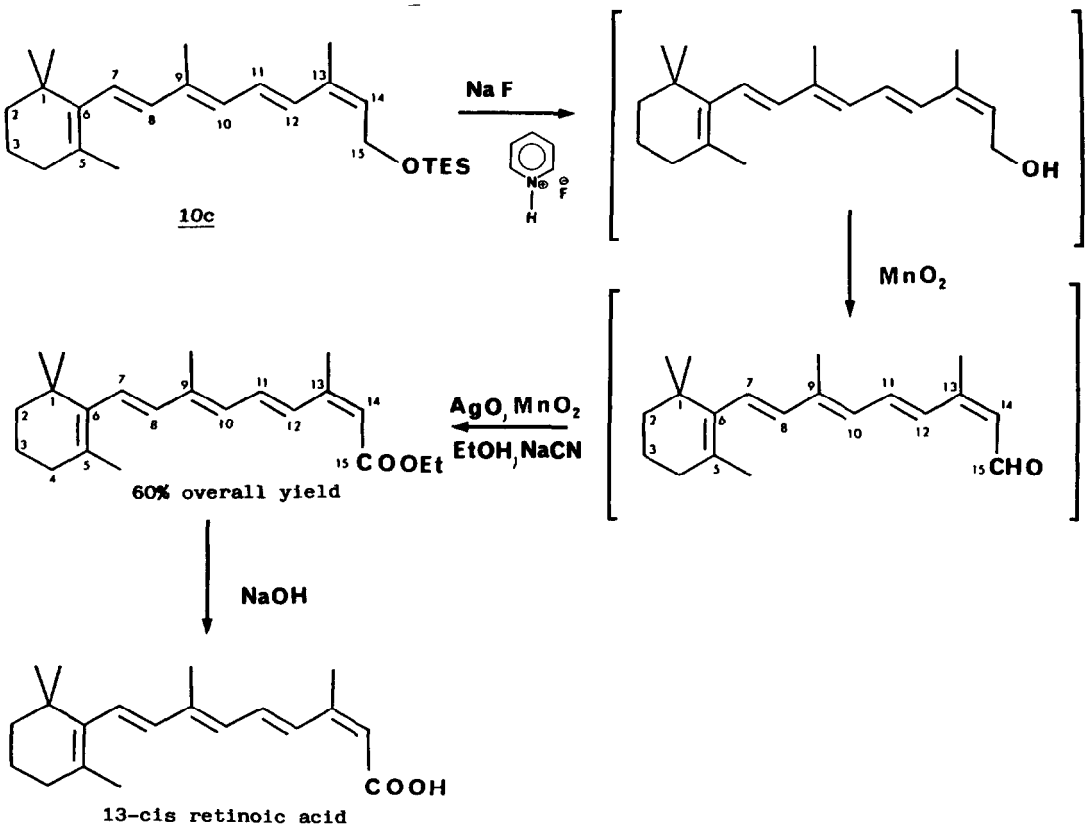
The allylic diols 9a-c gave in high yield only one single product 10a-c, as shown by the NMR spectrum (one set of signals for the vinylic hydrogen, consistent with the presence of only one stereoisomer).

Unfortunately, it was not possible to remove the protecting group in compounds 10a and 10b in smooth conditions without decomposition of the molecule.

However, the deprotection was achieved in the case of a triethylsilyl group with a mixture of sodiumfluoride and pyridiniumfluoride at room temperature, in quantitative yield.

13-cis retinol was then oxidized to 13-cis retinal with MnO_2 and to 13-cis ethylretinoate with a mixture of silver and manganous oxide in ethanol[3] with 60% overall yield.

Finally, this ester was purified by chromatography and saponified to 13-cis retinoic acid which was shown to be identical to an authentic sample and pure by HPLC[4,5]. In NMR at 200MHz, the main characteristic of the 13-cis stereoisomer is the deshielding of H_{12} at 7 75 ppm (6.31 ppm for the same proton in the all-trans isomer).



In conclusion, this Ti(0) methodology afforded a highly efficient synthesis of 13-cis retinoic acid, involving only one flash-chromatography at the final stage to remove impurities. The formation of other stereoisomers was never observed by 200MHz proton NMR.

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Bibliography

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3) E.J. Corey, N W. Gillman and B.E. Ganem, J. Am. Chem. Soc., 1968, 90, 5616.
4) m.p. 164-7°C (Lit.[6]) - ^{1}H NMR (200MHz, $CDCl_3$) δ 1.04 (s, 6H, $2CH_3$ at C_1) , 1.46-1.49 (m, 2H, CH_2 at C_2) , 1.60-1.66 (m, 2H, CH_2 at C_3) ; 1.72 (s, 3H, CH_3 at C_5) ; 2.01 (s, 3H, CH_3 at C_9) , 2 02-2 05 (m, 2H, CH_2 at C_4) , 2.11 (s, 3H, CH_3 at C_{13}) , 5.67 (s, 1H, H_{14}) ; 6.18 (d, 1H, H_8, J = 16Hz) ; 6 28 (d, 1H, H_{10}, J = 11.4Hz) ; 6.3 (d, 1H, H_7, J = 16.0Hz) ; 7.04 (dd, 1H, H_{11}, J = 15,3Hz, J = 11.4Hz) ; 7.75 (d, 1H, H_{12}, J = 15.3Hz).
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