

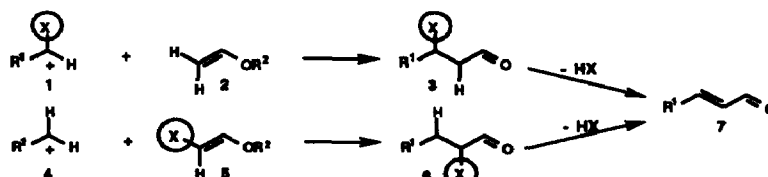
The OSM (Oxidation State Modification) Concept : Application to a New and Rapid Synthesis of Retinoids.

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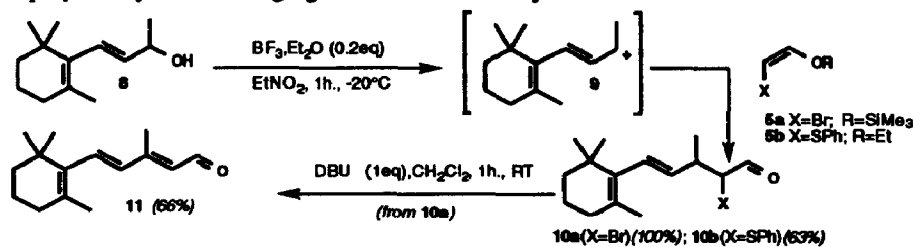
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Abstract : The OSM (oxidation state modification) concept for the elaboration of new synthetic pathways is demonstrated for the synthesis of β -ionylidene acetaldehyde 11 and retinal 13. According to this new scheme, electrophilic addition to α -heterosubstituted enol ethers 5 of the cationic species 9, generated from β -ionol led to aldehydic intermediates 10 which undergo easy elimination to β -ionylidene acetaldehyde 11. Similarly, retinal 13 was obtained from vinyl- β -ionol 14 and dienol ethers 12, via aldehydes 16.

In this paper, we propose, when planning a synthesis, to consider alternative routes resulting from an oxidation state modification (OSM) of each starting material, without changing of the overall balance of the reaction mixture. We illustrate our proposal by the well documented reaction of Muller-Cunradi, Picroh¹, according to which the electrophilic addition of the oxocation 1 derived from an acetal (X = OR), to the enol ether 2 leads via the aldehydic intermediate 3, to an α,β -unsaturated carbonyl compound 7. To exemplify the alternative OSM approach, we propose both decreasing the oxidation state of the electrophilic reagent by one unit providing cation 4 instead of 1, and increasing the oxidation state of the nucleophilic partner by one unit, using the enol ether 5 instead of 2 : this should give the same final product 7, via the intermediate 6.

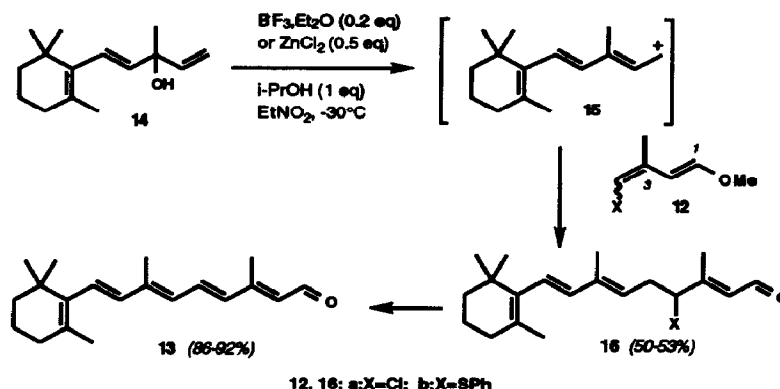


In order to establish the feasibility of this novel strategy, we describe in this paper a new and simple construction of polyenic systems belonging to the retinoid family.²



Condensation of β -ionol 8 with bromoenol ether 5a(Z)³ or phenylthioenol ether 5b(Z)⁴, catalyzed with boron trifluoride etherate (0.2 eq.) leads via the intermediate carbocationic species 9 to α -heterosubstituted aldehydes 10⁵. Aldehyde 10a was easily dehydrohalogenated to the C₁₅ aldehyde 11.

With a new synthesis of retinal 13 in mind, we studied the condensation of vinyl- β -ionol 14⁴ (via the carbocationic species 15) with dienol ethers 12a,b⁴ leading to aldehydes 16a,b⁵, precursors of retinal 13. In nitroethane, the reaction was catalyzed with boron trifluoride etherate or zinc dichloride and the yield of 16 was increased by about 10 % in the presence of one equivalent of *iso*-propanol.^{6, 7}



The dehydrohalogenation of 16a, leading to retinal 13 occurred using DBU / CH₂Cl₂ (50 °C, 2h ; yd : 86 %) or Li Cl / DMF (85 °C, 15 min ; yd : 75 %) whereas aldehyde 16b was easily transformed into retinal 13⁸ by oxidation with MCPBA in CH₂Cl₂ and spontaneous elimination of the sulfoxide moiety in CCl₄ (overall yield : 92 %).

In conclusion, the alternative OSM concept proved to be very fruitful and allowed us to disclose an unexplored, general, cheap and efficient synthetic route in the field of retinoids. This novel pathway opens a large range of possibilities concerning the nature and the site of the X substituent.

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References and Notes

- Muller-Cunradi, M ; Pieroh, K. *US Patent 1939*, 2 165 962 ; *CA 1939*, 33, 8210².
- (a) Ancel J.E. *Dr .Sc.Thesis*, Université de Rouen 1992.
(b) *French Patent Rhone-Poulenc 1991*, 14 699 ; *European Patent 1991*, 544 588.
- (a) Zembayashi, M. ; Tamao, K. ; Kumada, M. *Synthesis*, 1977, 422-423.
(b) Komarov, N.V. ; Lisovin, E. G. *Zh. Obshch. Khim.*, 1979, 49, 1673-1674 ; *CA 1979*, 91, 211474 z.
- Enol ethers 5b, 12a and 12b were obtained by cracking of the corresponding acetals by heating at 120°C (5b : 30% ; E/Z : 70:30; 12a : 85%; 1E,3E / 1E,3Z : 55 / 45; 12b : 80%; 1E,3E / 1E,3Z : 55 / 45. Vinyl β -ionol 14 and ω -chloroprenal dimethyl acetal are industrial intermediates.
- Aldehydes 10 and 16 were characterized by ¹H and ¹³C NMR and mass spectrometry. Aldehyde 16a is constituted of two geometric isomers : *all trans* / *9 cis* : 65/35.
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- Boron trifluoride etherate (75ml, 0.6 mmol) was quickly added to a solution of enol ether 12a (1E,3E/1E,3Z : 55/45 ; 3 mmol) and *iso*-propanol (3 mmol) in 6 ml of nitroethane cooled to -35°C. After stirring at this temperature for 10 min, a saturated NaHCO₃ solution (5ml) was added and the mixture was extracted with pentane (6ml). The organic phase was washed with water (2 X 1.5 ml), dried (MgSO₄) and concentrated. The residue was flash chromatographed on silicagel (Petroleum ether/Et₂O : 96/4).
- Retinal 13 was obtained as a mixture of isomers which can be transformed quantitatively into *all trans* 13 precursor of vitamin A, according to literature procedures : *U.S. Patent Eastman Kodak 1961*, 3, 013, 080 ; *Patent AEC 1,288, 972, CO7c*, *Patent AEC 1,291, 622, CO7c*.

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