

A New Vinylic Organolithium Reagent : An Expedient C₁₀+C₁₀ Synthesis of Retinal

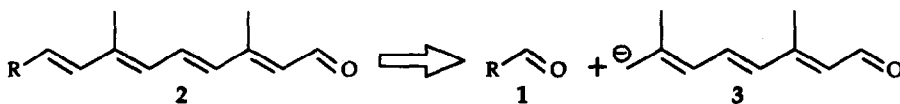
L. Duhamel*, P. Duhamel and Y. Le Gallic

Unité de Recherches Associé au CNRS
Faculté des Sciences et des Techniques de Rouen et IRCOF
BP 118 F-76134 Mont Saint Aignan-France

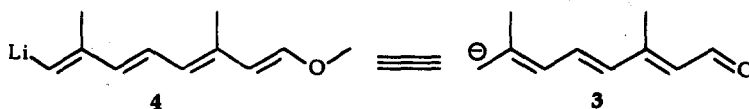
Abstract : 2,6-Dimethyl-8-methoxy-1-lithio-octatetra-1,3,5,7-ene **4** is prepared by bromine-lithium exchange from its readily accessible bromo precursor **8**. The lithio reagent **4** reacts with carbonyl compounds to give in one pot, after a mild acidic hydrolysis, the retinoid aldehydes **2**.

Various convergent synthesis of C₂₀ retinoid derivatives¹ involving either a C₁₃+C₇^{2,3b,c}, a C₁₅+C₅^{3a,4} or a C₁₄+C₆ route⁵ are known. On the contrary, only a few syntheses of retinoids using the C₁₀+C₁₀ approach have been published to date⁶. In these studies, the retinoids are obtained by multistep functional modifications after the construction of the C₂₀ skeleton.

We have studied a more convergent synthesis of retinoids through a C₁₀+C₁₀ route using aldehydes **1** as starting materials. Such an approach, which requires a synthetic equivalent of the anion **3**, would give a direct access to the polyenic aldehydes **2**.

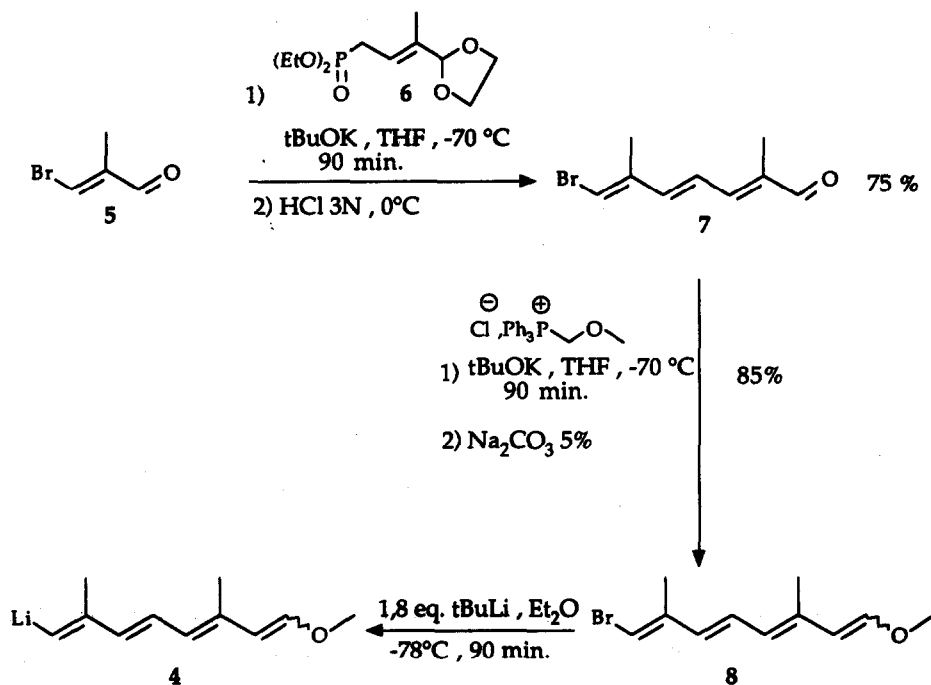


Thus, we have prepared a new organometallic vinylic compound with a masked aldehydic function, 2,6-dimethyl-8-methoxy-1-lithio-octatetra-1,3,5,7-ene **4**, synthetic equivalent of ω-lithio dehydrocital **3**.

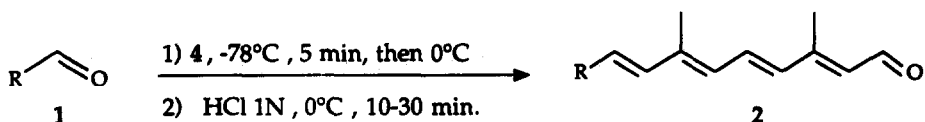


This lithio compound is readily accessible by bromine-lithium exchange from its bromo precursor **8** easily prepared by a Wittig reaction between the bromo-aldehyde **7** and methoxymethylene triphenylphosphorane. The aldehyde **7** was obtained from aldehyde E-5⁷ using the phosphono-

dioxolane **6**^{3c}. This is a new synthetic pathway to ω -bromo-polyenol alkyl ethers, since this type of molecules were precedently prepared ^{3b, 8} from the corresponding ω -bromoketals by a Miller and Mc Kean type alcohol elimination ⁹.

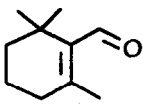
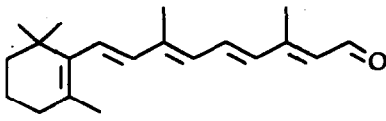
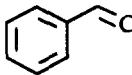
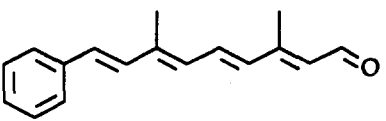
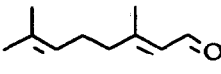
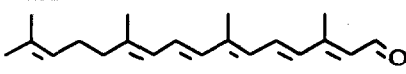
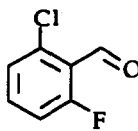
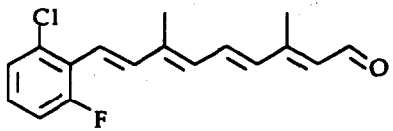


The lithio enoether **4** reacts readily with carbonyl compounds **1**, even at low temperature. After a mild hydrolysis of the non-isolated intermediate hydroxy polyenol ether, polyenic aldehydes **2** were obtained in good yields ¹⁰ (see table 1).



Synthesis of all-trans retinal **2a** starting from β -cyclo citral **1a** had already been achieved in eight steps, using a Mukaiyama reaction ¹¹, with an overall yield of 16%. The single-step procedure reported here increases the overall yield up to 68%. Aldehydes **2b** and **2d** were prepared from aldehydes **1b** and **1d** respectively in four steps, using a cyanophosphonate, with an overall yield ranging from 30 to 40% ¹³. Another multistep approach consisting in using an aldol condensation of a functionalized ketone in the key step has already been described ¹⁴.

Table 1. Examples of Retinoid Aldehydes **2** prepared from **1** and **4**

Aldehyde 1	Retinoid aldehyde 2	Yield ^{a)} (%)
 1a	 2a	68
 1b	 2b	75 45 ^{b)}
 1c	 2c	70
 1d	 2d	72

a) Isolated yield of purified product (flash chromatography)

b) Yield for pure all E isomer obtained by crystallisation in pentane.

In conclusion, we have developed a short access to a new vinylic organo lithio reagent, synthetic equivalent of ω -lithio dehydrocitral. This lithio reagent reacts easily with aldehydes and yields in an one step procedure the retinoid aldehydes in high yields. Further work on this type of reagent is currently in progress in our laboratory.

References and Notes

1. Isler, O. *Carotenoids*, Birkhauser Verlag, 1971 ; Liu, R.S.H.; Abato, A.E. *Tetrahedron* , 1984, 40, 1931-1969.
2. Fischli, A.; Mayer, H.; Simon, W.; Stoller, H.J. *Helv. Chim. Acta*, 1976, 59, 397-405 ; Organon, N.V.; Netherlands Patent, 6, 404, 175, 1965, C.A., 1966, 64, 1963
3. a) Duhamel, L.; Duhamel, P.; Lecouvé, J.P. *Tetrahedron*, 1987, 43, 4339-4348 ; b) Duhamel, L.; Duhamel, P.; Lecouvé, J.P. *Tetrahedron*, 1987, 43, 4349-4358 ; c) Duhamel, L.; Guillemont, J.; Le

- Gallic, Y.; Ple, G.; Poirier, J.M.; Ramondenc, Y.; Chabardes, P. *Tetrahedron Lett.*, **1990**, *31*, 3129-3132
4. see for example : Matsui, M.; Okano, S., Yamashita, K.; Miyano, M.; Kidamura, S.; Kobayashi, A.; Sato, S.; Mikami, R. *J. Vitaminol. (Kyoto)*, **1958**, *4*, 178 ; Pommer, H.; Sarnecki, W.; Ger. Pat.1 668 702 ; Cardillo, G.; Contento, M., Sandri, S. *J. Chem. Soc. Perkin Trans*, **1979**, 1729-1733 ; Chabardes, P.; Decor, J.P.; Varagnat, J. *Tetrahedron*, **1977**, *33*, 2799-2805 ; Duhamel, L.; Guillemonet, J.; Poirier, J.M.; Chabardes, P. *Tetrahedron Lett.*, **1991**, *32*, 4495-4498.
 5. Isler, O.; Huber, W. ; Ronco, A. ; Kofler, M. *Helv. Chim. Acta*, **1947**, *30*, 1911-1927.
 6. Otera, J.; Misawa, H.; Onishi, T.; Suzuki, S.; Fujita, Y. *J. Org. Chem.*, **1986**, *51*, 3834-3838; Pommer, H. *Angew. Chem.*, **1960**, 811-832 ; Mayer, H.; Bollag, W.; Hanni, R.; Ruegg, R. *Experientia*, **1978**, *34*, 1105-1119 ; Bestmann, H.J.; Ermann, P. *Liebigs Ann. Chem.*, **1984**, 1740-1745 ; Trost, B.M.; Fortunak, J.M.D. *Tetrahedron Lett.*, **1981**, *22*, 3459-3462 ; F. Chemla, Ph. D. Thesis, **1992**, Université Pierre et Marie Curie, Paris.
 7. Le Gallic, Y.; Ph. D. Thesis, Université de Rouen, **1992**
For an other synthesis of the E-5 see : Diez-Martin, D.; Grice, P.; Kolb, H.C.; Ley, S.V.; Madin, A. *Synlett*, **1990**, 326-328.
 8. Ancel, J.E.; Duhamel, L. *Tetrahedron*, in press ; Duhamel, L.; Ple, G.; Ramondenc, Y. *Tetrahedron Lett.*, **1989**, *30*, 7377-7380.
 9. Miller, R.D.; Mc Kean, D.R. *Tetrahedron Lett.*, **1982**, *23*, 323-326.
 10. Polyenic aldehydes **2** are obtained as a mixture of isomers that can be isomerized to the all trans compounds : see, for example, ref 11, 12 and 14
 11. Mukaiyama, T.; Ishida, T. *Chem. Lett.*, **1975**, 1201-1203
 12. Eastman Kodak Patent 1,098,521,C07c.
 13. Matsumoto, H.; Asato, A.E.; Denny, M.; Baretz, B.; Yen, Y.P.; Tong, D.; Liu, R.S.H. *Biochemistry*, **1980**, *19*, 4589-4594
 14. Akiyama, S.; Nakatsuji, S.; Eda, S.; Kataoka, M.; Nakagawa, N. *Tetrahedron Lett.*, **1979**, *22*, 2813-2816.

(Received in France 12 October 1992)