J. Chem. Research (S), 2003, 62
J. Chem. Research (M), 2003, 0264–0276

Activation of ethynyl-β-ionol by Lewis acid catalysts: synthesis of a novel branched C_{20} molecule[†]

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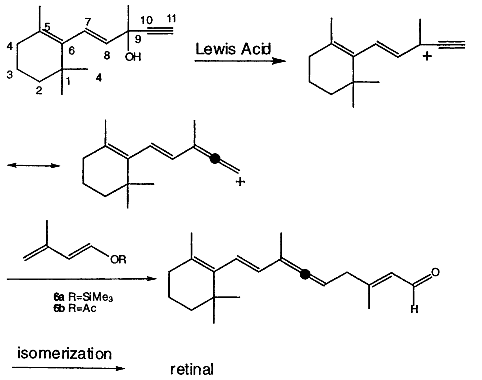
A condensation C_{15} + C_5 between ethynyl-β-ionol and a derivative of prenal was performed at low temperature in the presence of a Lewis acid. The coupling occurs at position 7 of ethynyl-β-ionol and led to the efficient synthesis of a new C_{20} molecule rather than the expected retinal.

Keywords: retinoid, Vitamin A, C15 + C5 coupling, Lewis acid

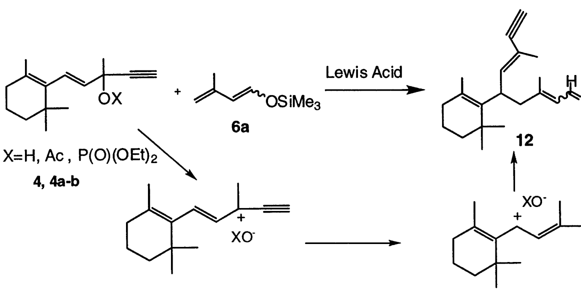
Carotenoids and retinoids are important families of biomolecules.[1] Vitamin A aldehyde (retinal) is the subject of much interest because of its crucial role in a wide variety of biological function mainly in the vision process.[2] Among many syntheses of Vitamin A aldehyde,[3] one efficient method involves the coupling a C_{15} sulfone **1** (containing 15 carbons) and the allylic chloride **2**.[4]

Another approach would consist in using a C_{15} and a C_5 component with inverted polarity.[6]



(1)

Properly activated ethynyl-β-ionol **4** (or a derivative such as **4a** or **4b**) would generate a carbocation on which the condensation of an enol ether (**6a** or **6b**) should take place and lead to the synthesis of retinal after isomerization. Indeed, it has been shown in the literature that a carbinol (or derivatives) could be activated as described in the presence of Lewis acids, especially copper based catalysts.[7]



(2)

For this purpose derivatives **4a** and **4b** were synthesised and evaluated in the coupling reaction.

Table 1 Results of the coupling in the presence of various Lewis acids.

Entry	C_{15}	Lewis Acid	Yield of **12**/% ^1H NMR (isolated)	Ratio *E/Z* (%)	Yield of **9**/% ^1H NMR (isolated)
1	**4**	$LiClO_4$	52	90/10	22
2	**4**	$TiCl_4$	53	86/14	0
3	**4**	$CuOTf.(C_6H_6)_{0.5}$	33	85/15	13
4	**4a**	$LiClO_4$	100	90/10	0
5	**4a**	$TiCl_4$	100	86/14	0
6	**4a**	$ZnCl_2.Et_2O$	77(55)	85/15	0
7	**4b**	$FeCl_3$	(40)	90/10	(20)

It was found that by using careful conditions (low temperature, dilution), it was possible to couple ethynyl-β-ionol (or a derivative) with C_5 unit **6a**.

The most striking feature of this reaction is that **4** or **4a-b** did not react at the expected position 11 or 9 but rather at position 7 to yield **12** a novel regioisomer of Vitamin A aldehyde **12**. To our knowledge such a reactivity from a β-ionol derivative is unknown in the literature.

Techniques used ^1H NMR, IR, UV, chromatography

References 24

Schemes 5

Tables 2

Received 28 October 2002; accepted 12 January 2003
Paper 02/1648

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[†] Dedicated to Professor Marc Julia on the occasion of his 80th birthday