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Synthesis of Regioselectively Deuterated Hydroxy Conjugated Dienes

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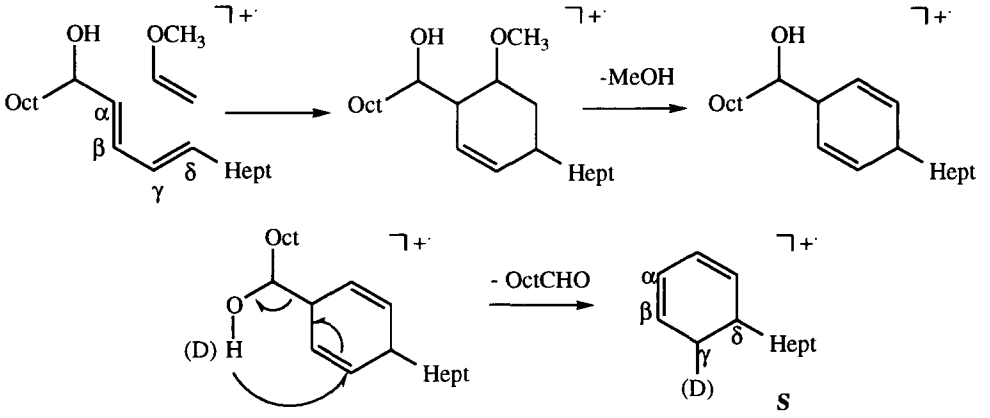
Abstract : A regioselective synthesis of deuterated dienic alcohols has been developed to provide labelled substrates in the frame of gas-phase ion-molecule reaction studies.

Key words : regioselective labelling, deuterated dienic alcohol, ion-molecule reaction.

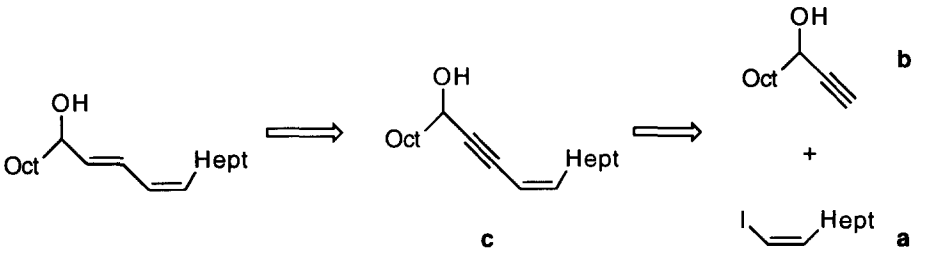
Dimorphecolic and coriolic acids[1], natural metabolites of linoleic acid, have been reported in rice plant as self defensive substances against diseases[2]. The tomato plant has also been investigated and shown[3] to produce some isomers of the corresponding methyl esters of dimorphecolic and coriolic acids as well. In order to improve the identification of such compounds or congeners characterized by an α-hydroxy conjugated diene system and often present as minute amounts in the extracts, we have explored[4] the capacities of gas-phase ion-molecule reactions associated with mass spectrometry. In principle, such reactions should be performed in the high pressure source of the instrument (*ie* conventional GC-MS) and give rise in this case to specific ion product(s) for the assignment and localization of the studied multifunctional system.

Vinyl ether radical cations (generated either from CH_2=$CHOCH_3$ or CH_2=$CHOC_2H_5$ or CH_2=$C(CH_3)OCH_3$ plasmas) were tested preliminarly[5,6] and shown to generate a number of characteristic ions. One of them is particularly interesting[4] since resulting apparently from an initial [4 + 2] cycloaddition reaction

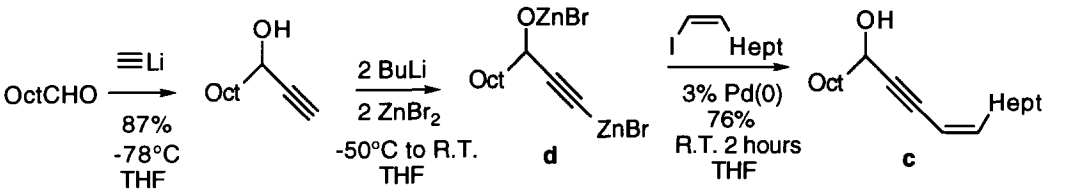
between *ie* the methyl vinyl ether radical cation and the dienic system. The intermediate adduct ion thus formed might then decompose by successive losses of methanol and an aldehyde *via* H (from the hydroxyle) rearrangement giving the diagnostic ion **S**.



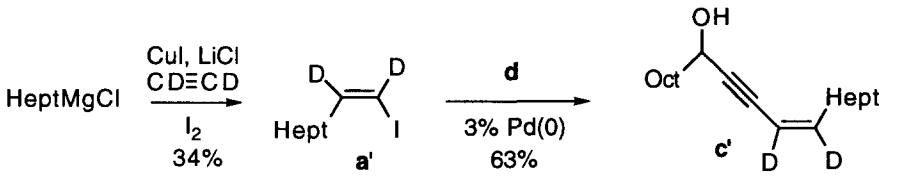
In order to demonstrate this mechanism and provide more confidence in the proposed ion for structural investigations, we have considered the synthesis of deuterium-labelled analogs of a model dienic alcohol. In view to compare their biological activities as phytoalexins, we had already synthesized[7] the four isomers of methyl dimorphecolate. In this paper, we have used a different approach. Our synthetic planning was to achieve the coupling[8] of two synthons **a** and **b** and to reduce[9] the triple bond to give the *E*-allylic alcohol required.



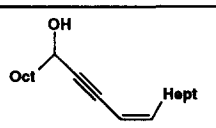
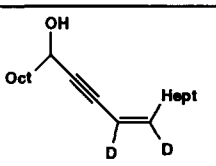
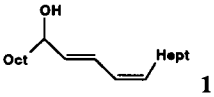
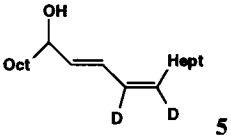
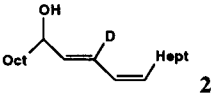
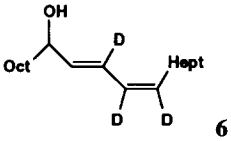
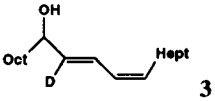
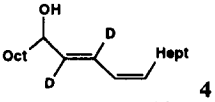
The reaction of di-heptyl cuprate with acetylene followed by iodination[10] gave **a** in 77% yield and 99% isomeric purity. Propargylic alcohol **b** was easily prepared in 87% yield by the reaction of the monolithioacetylene[11] on nonaldehyde. After deprotonation of the alkyne with BuLi (2eq.), transmetallation with 2 equivalents of zinc bromide and finally coupling with **a** with 3% tetrakistriphenylphosphine as catalyst, **c** was obtained in 76% yield.



In the case where we wanted to introduce deuterium on **c**', we needed to prepare the *Z* iodide **a**'. Carbocupration of D-labelled acetylene was best performed with heptyl copper in THF[12] due to the higher solubility of acetylene in this solvent. After addition of iodine, the isolated yield was 34%[13] and 99% of total deuterium incorporation. The coupling was realized on the same way with 63% yield[14].



The reduction of the triple bond of propargylic alcohols with $LiAlH_4$ is known to be stereo- and regioselective[9]. This, not only afforded the *E* isomer but also a regioselective D-labelling when the reaction was quenched with D_2O, or treated with $LiAlD_4$. Table 1 summarizes these results[15].

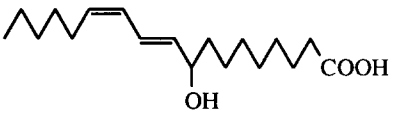
Starting enynol / Reagent (quench)		Yield %		Yield %
LAH, (H_2O)	 1	98	 5	99
LAH, (D_2O)	 2	69	 6	89
LAD, (H_2O)	 3	99		
LAD,(D_2O)	 4	78		

In conclusion, the described techniques are quite efficient for the selective D-labelling of *E,Z* dienols in a very high state of purity which allow the accurate ion-molecule reaction investigations.

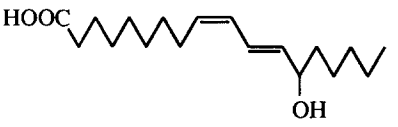
Acknowledgments : The authors wish to thank Professor J-F. Normant and Dr C. Descoins for helpful discussions.

References and notes :

1.



Dimorphecolic acid



Coriolic acid

2. Kato, T.; Yamaguchi, Y. ; Hirano, T. ; Yokoyama, T. ; Uyehara, T. ; Namai, T. ; Yamanaka, S.; Harada, N. *Chem. Lett.*, **1984**, 409-412.
3. Vernenghi, A. ; Einhorn, J. ; Kunesch, G. ; Malosse, C. ; Ramiandrasoa, F. ; Ravisé, A. *Can. J. Bot.*, **1986**, *64*, 973-982.
4. Einhorn, J. ; *In* Therapeutic aspects and analytical methods in cancer research. Mass spectrometry in cancer research (proceedings), Ed. E. Constantin, Amudes, Strasbourg, France, 206/1-206/23.
5. Einhorn, J. ; Duffault, J-M. ; Virelizier, H. ; Tabet, J-C. *Rapid Commun. Mass Spectrom.*, **1988**, *2*, 112-115.
6. Einhorn, J. ; Duffault, J-M. ; Virelizier, H. ; Tabet, J-C. *Adv. Mass Spectrom.*, **1989**, *11A*, 550-551.
7. Duffault, J-M. ; Einhorn, J. ; Alexakis, A. *Tetrahedron Lett.*, **1991**, *32*, 3701-3705.
8. Negishi, E.I. *Acc.Chem. Res.*, **1982**, *15*, 340-348.
9. Malek, J. *Organic Reactions*, **1985**, *34*, 1-317.
10. Alexakis, A. ; Cahiez, G. ; Normant, J-F. *Org. Synth.*, **1984**, *62*, 1-9.
11. Midland, M.M. *J. Org. Chem.*, **1975**, *40*, 2250-2252.
12. Normant, J-F. ; Alexakis, A. *Synthesis*, **1981**, 841-870.
13. Labelling acetylene was flushed out by argon and so diluted.
14. The lower yield is ascribed to the purification technique which requires a careful distillation through a Vigreux column. The loss of material on small scale is therefore more important than in the same unlabelled reaction which was done in a much larger scale.
15. N.M.R.($CDCl_3$) data, δ(ppm), Bruker AC 200 MHz ;
Compound **1**, ^1H : C<u>H</u>OH 4.15 (1H, dt, J 5.9 Hz, J' 6.6 Hz), α 5.6 (1H, dd, J 15.2 Hz), β 6.5 (1H, dd, J 11 Hz), γ 5.9 (1H, dd, J 11.4 Hz), δ 5.4 (1H, dt, J 7.6 Hz).
^{13}C : <u>C</u>HOH 72.9, α 135.9, β 125.8, γ 127.8, δ 132.9.
Compound **2**, ^1H : C<u>H</u>OH 4.2 (1H, dt, J 5.9 Hz, J' 6.7 Hz), α 5.7 (1H, d), γ 6.0 (1H, d, J 11.4 Hz), δ 5.4 (1H, dt, J 7.6 Hz). ^{13}C : <u>C</u>HOH 72.9, α 136.0, γ 128.0, δ 132.9.
Compound **3**, ^1H : C<u>H</u>OH 4.2 (1H, t, J 5.9 Hz), β 6.5 (1H, d, J 11 Hz), γ 6.0 (1H, d, J 11.4 Hz), δ 5.4 (1H, dt, J 7.5 Hz). ^{13}C : <u>C</u>HOH 73.0, β 125.6, γ 128.0, δ 132.9.
Compound **4**, ^1H : C<u>H</u>OH 4.2 (1H, t, J 5.9 Hz), γ 6.0 (1H, d, J 11.4 Hz), δ 5.4 (1H, dt, J 7.6 Hz).
^{13}C : <u>C</u>HOH 73.0, γ 128.0, δ 132.8.
Compound **5**, ^1H : C<u>H</u>OH 4.2 (1H, dt, J 5.9 Hz, J' 6.7 Hz), α 5.7 (1H, dd, J 15.2 Hz), β 6.5 (1H, d).
^{13}C : <u>C</u>HOH 73.0, α 136.0, β 126.0.
Compound **6**, ^1H : C<u>H</u>OH 4.2 (1H, dt, J 5.9 Hz, J' 6.7 Hz), α 5.7 (1H, d).
^{13}C : <u>C</u>HOH 73.0, α 136.0.

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