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STEREOSELECTIVE SYNTHESIS OF POLYENIC ALCOHOLS. A NEW ROUTE TO THE LEUKOTRIENES B.

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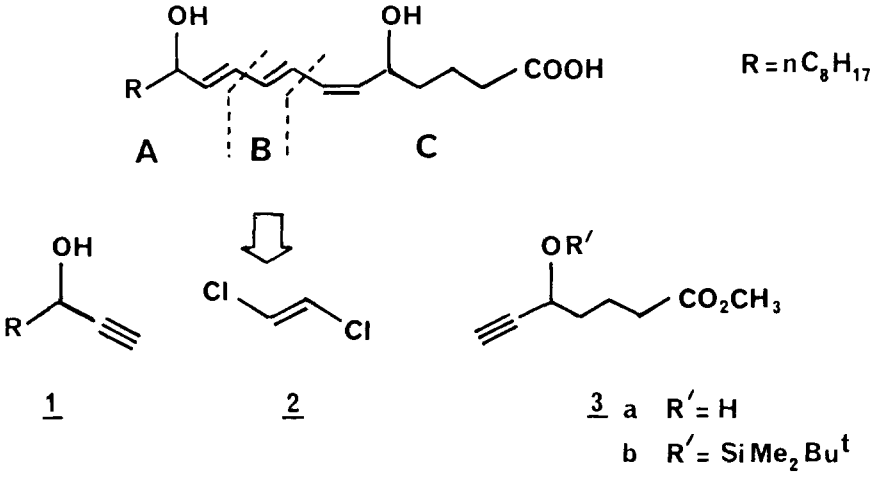
Summary : *A stereocontrolled synthesis of methyl (6Z, 8E, 10E) 5,15-dihydroxyeicosa-6,8,10-trienoate and several analogues of the LTB family is described.*

Since the discovery of leukotrienes by Borgeat and Samuelson in 1979,[1] a considerable chemical effort has been carried out to synthesise these new compounds arising from the lipoxygenase metabolism of arachidonic acid.

A characteristic structural feature of the leukotrienes is the presence of a conjugated triene system having a defined geometry. In every synthesis reported so far, the unsaturated system was generated by a Wittig reaction. However, a poor stereoselectivity was observed and the difficult separation of isomers by HPLC impeded the efficiency of the procedure.[2]

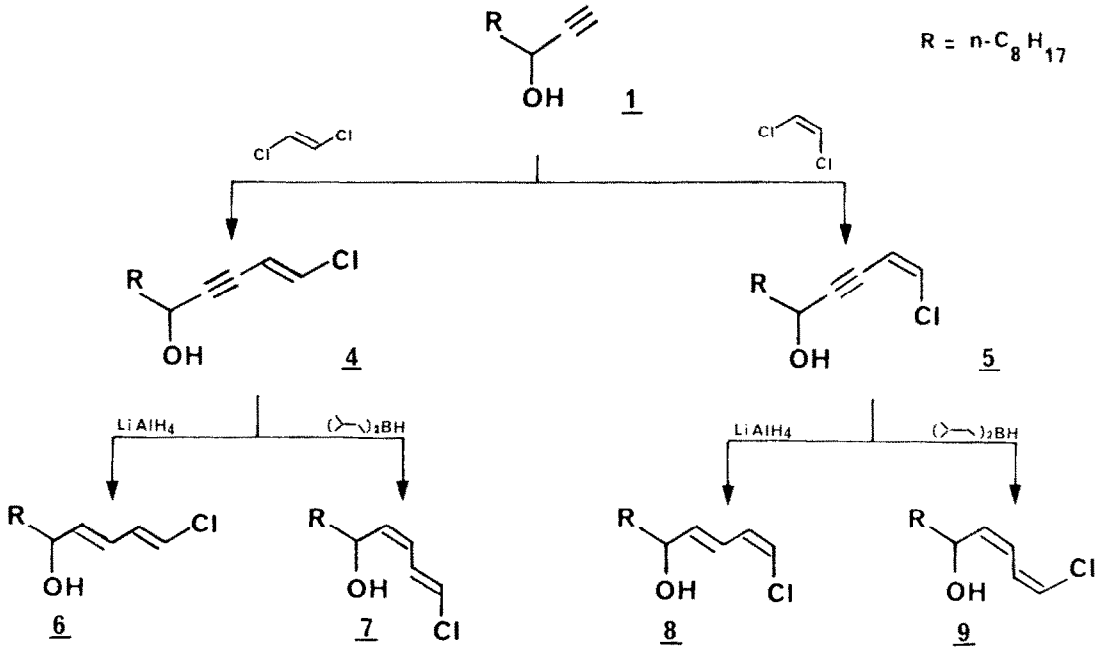
We now report a new route to the LTB family which avoids the Wittig reaction and generates the triene compounds by a stereoselective and flexible coupling reaction. A retrosynthetic analysis of the 14,15-dihydro leukotriene B_4 illustrates the synthesis of the (Z,E,E) 6,8,10-triene system :



1 2 3 a R' = H
b R' = SiMe2But

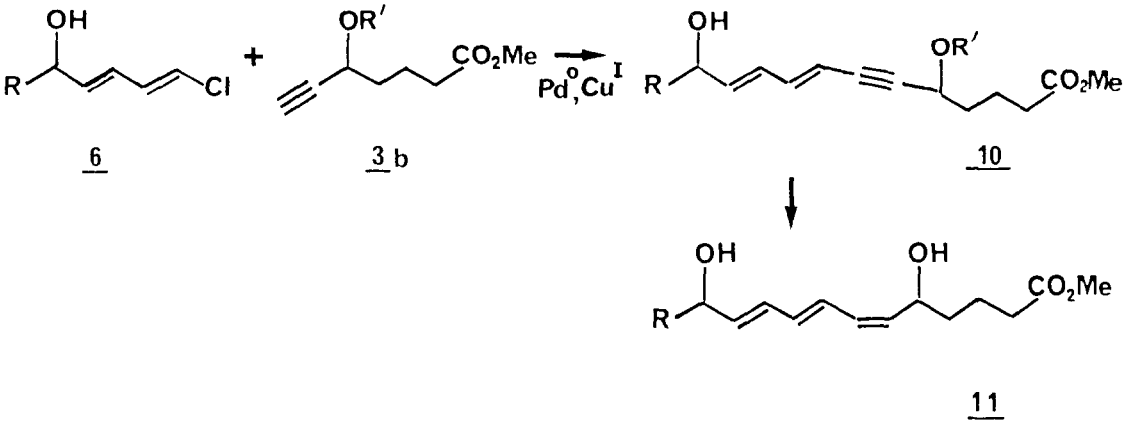
Disconnection of the central double bond C-8 C-9 from the two others, led to three fragments A, B, C. The fragments A and C are allylic alcohols whose precursors can be expected to be the propargyl alcohols 1 and 3a. The internal fragment B is a (E) double bond and we have previously shown that the two chlorine atoms of (E)-dichloroethylene can be substituted sequentially by acetylenes.[3]

Thus, when 1-undecyn-3-ol was treated with (E)-1,2-dichloroethylene (10 equiv.) in the presence of tetrakis (triphenyl phosphine) palladium (0.05 equiv.), copper iodide (0.1 equiv) in benzene containing n-butylamine (2 equiv.) at 25° for 10 h, 1-chloro-5-hydroxy-tridec-(1Z) en -3-yne 4 was obtained in 70 % yield.[4]

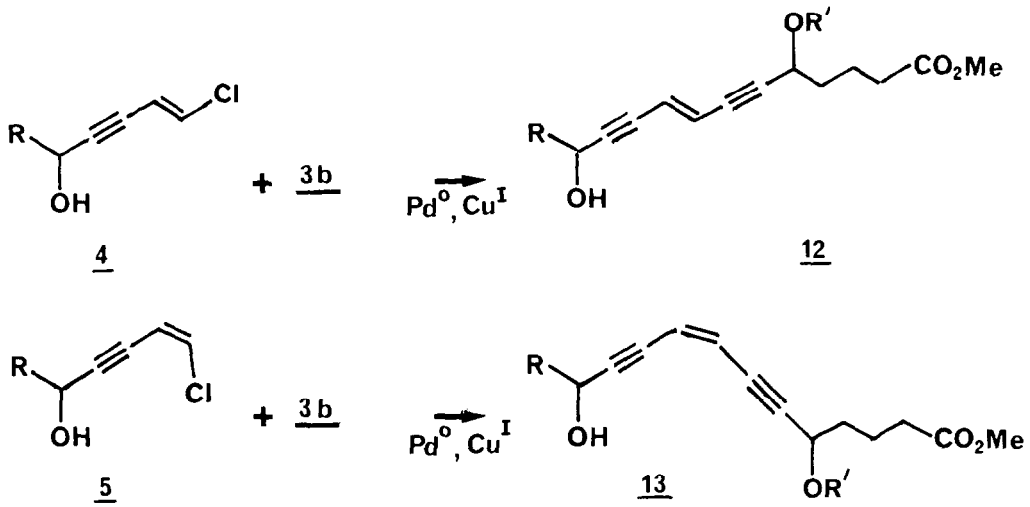


Reduction with lithium aluminium hydride in refluxing tetrathydrofuran gave the hydroxy (E,E)-chlorodiene 6 in 85 % yield.[5] The (E,Z)-isomer 7[6] was obtained (57 %) by reduction with diisoamylborane. The two other isomers 8 [7] and 9 [8] were obtained by a similar sequence from propargyl alcohol and (Z) dichloroethylene.[9]

Treatment of the hydroxy diene 6 with methyl 5- (t-butyl)dimethyl silyloxy -6-heptynoate 3b [2f] under palladium copper catalysis, gave the pure dienyne 10b [10] in 33 % yield (60 % of chlorodiene was recovered). Selective hydrogenation of 10b in the presence of Lindlar catalyst and desilylation led to the (Z,E,E) triene 11.[2f,g]



The Pd°-Cu^{I} strategy is very flexible since it allows the stereoselective preparation of isomers of the LTB family from a common synthon 3 and the chlorides 4 to 9. Thus, coupling of 3b with the hydroxychlorides 4 and 5 gave respectively the triunsaturated compounds 12 [11] and 13 [12] in 80 and 60 % yield.



This methodology will also enable the preparation of chiral leukotrienes from chiral compounds 1 and 3, the preparation of which is described in the following communication.[13]

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References

1. P. Borgeat and B. Samuelson, J. Biol. Chem., 254, 2643 (1979)
2. a) E.J. Corey, A. Marfat, G. Goto and F. Brion, J. Am. Chem. Soc., 102, 7984 (1980) ; b) E.J. Corey, A. Marfat, J. Muroe, K.S. Kim, P.B. Hopkins and F. Brion, Tetrahedron Lett., 22, 1077 (1981) ; c) Y. Guindon, R. Zamboni, C.K. Lau and J. Rokach, Tetrahedron Lett., 23, 739 (1982) ; d) R. Zamboni and J. Rokach, Tetrahedron Lett., 23, 2631 (1982); e) L.S.Mills, and P.C. North, Tetrahedron Lett., 24, 409 (1983) ; f) K.C. Nicolaou, R.E. Zipkin, R.E. Dolle and B.D. Harris, J. Am. Chem. Soc., 106, 3548 (1984) ; g) B. Spur, A. Crea and W. Peters, Arch. Pharm. (Weinheim), 318, 225 (1985) ; h) C.Q. Han, D. Di Tullio, Y.F. Wang and C.J. Sih, J. Org. Chem., 51, 1253 (1986) ; i) Y. Le Merrer, C. Gravier, D. Languin-Micas and J.C. Depezay, Tetrahedron Lett., 27, 4161 (1986)
3. V. Ratovelomanana and G. Linstrumelle, Tetrahedron Lett., 22, 315 (1981) ; ibid. 25, 6001 (1984)
4. ^{1}H NMR ($CDCl_3$, 250 MHz) δppm : 0.88 (3H,t) ; 1.28-1.70 (14H,m) ; 4.48 (1H,m) ; 5.5 (1H,dd, J=2Hz, 13.5Hz) ; 6.56 (1H,d, J=13.5Hz)
5. ^{1}H NMR ($CDCl_3$, 250MHz) δppm vinylic protons : 5.74 (1H,dd, J=15 et 7Hz) ; 6.18 (1H,dd,J=15 et 10.5Hz) ; 6.20 (1H,d, J=12.5Hz) ; 6.48 (1H,dd, J=12.5 et 10.5Hz)
6. ^{1}H NMR ($CDCl_3$, 250MHz) δppm vinylic protons : 5.46 (1H,dd, J=11.25 et 7Hz) ; 5.58 (1H,t, J=11.25Hz) ; 6.26 (1H,d, J=13.5Hz) ; 6.78 (1H,dd, J=13.5 et 11.25hz)
7. ^{1}H NMR ($CDCl_3$, 250MHz) δppm vinylic protons : 5.88 (1H,dd, J=15 et 7Hz) ; 6.20 (1H,d, J=7.5Hz) ; 6.32 (1H,dd, J=10.5 et 7.5Hz) ; 6.64 (1H,dd, J=15 et 10.5Hz)
8. ^{1}H NMR ($CDCl_3$, 250MHz) δppm vinylic protons : 5.64 (1H,dd, J=10 et 7Hz) ; 6.14 (1H,d,J=7Hz) 6.50 (1H,dd, J=10 et 11Hz) ; 6.64 (1H,dd, J=11 et 7Hz)
9. ^{1}H NMR of 5 ($CDCl_3$, 250MHz) δppm : 0.88 (3H,t) ; 1.28-1.76 (14H,m) ; 4.58 (1H,m) ; 5.94 (1H,dd, J=2Hz, 7Hz) ; 6.42 (1H,d, J=7Hz)
10. ^{1}H NMR ($CDCl_3$, 250MHz) δppm : 0.1 (6H,s) ; 0.88 (3H,t,9H,s) ; 1.24 (14H,m) ; 1.7 (4H,m) ; 2.34 (2H,m) ; 3.7 (3H,s) ; 4.16 (1H,m) ; 4.5 (1H,m) ; 5.61 (H_8,dd, J=15 et 1Hz) ; 5.8 (H_{11},dd, J=15 et 7Hz) ; 6.25 (H_{10},dd, J=15 et 11Hz) ; 6.54 (H_9,dd, J=15 et 11Hz)
11. ^{1}H NMR ($CDCl_3$, 250MHz) δ ppm : 0.1 (6H,s) ; 0.90 (3H,t ; 9H,s) ; 1.28 (14H,m) ; 1.74 (4H,m); 2.36 (2H,m) ; 3.68 (3H,s) ; 4.52 (2H,m) ; 6.0 (2H,s)
12. ^{1}H NMR ($CDCl_3$, 250MHz) δ ppm : 0.1 (6H,s) ; 0.86 (3H,t ; 9H,s) ; 1.26 (14H,m) ; 1.72 (4H, m) ; 2.34 (2H,m) ; 3.66 (3H,s) ; 4.54 (2H,m) ; 5.86 (2H,s)
13. P. Pianetti, P. Rollin and J.R. Pougny, following communication.

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