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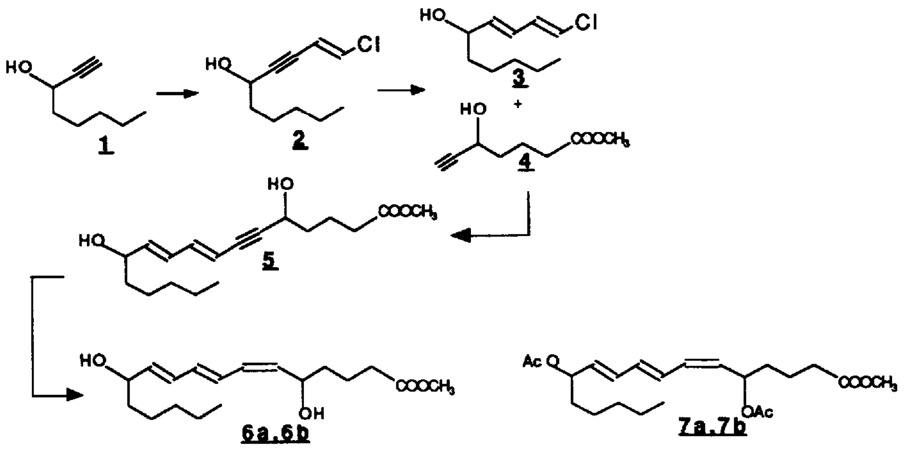
IMPROVED STEREOSELECTIVE REDUCTION OF A E,E, CONJUGATED DIENYNE TO A E,E,Z CONJUGATED TRIENE

M. Avignon-Tropis* and J.R.Pougny
Centre de Recherche de Biochimie et Génétique Cellulaires CNRS, 118 Route de Narbonne
31062 TOULOUSE Cedex (France)

Summary : *The stereoselective reduction of a functionalised E,E conjugated dienyne with Zn(Cu/Ag) in aqueous methanol produces a E,E,Z conjugated triene.*

A general strategy toward linear eicosanoids, based on palladium-copper coupling reactions was recently proposed [1-3]. While palladium/copper-catalyzed coupling [1,4] of terminal acetylenes with E-vinyl halides resulted in the exclusive formation of E-enynes with retention of stereochemistry, hydrogenation of the acetylene function into the desired Z-olefine was a very critical step and occured, in our hands, with rather low yields.
We now wish to report a synthesis of the E,E,Z conjugated trienic diol ester **6**, the Z double bond being obtained by a stereoselective reduction of a triple bond with activated Zn(Cu/Ag)[5].

The E-chloroenyne **2** was synthesized from (±) octyn-3-ol **1** by coupling with (E)-1,2-dichloroethylene using a palladium/copper catalyst [1]. It was further reduced to the chlorodiene **3** by hydrogenation with $LiAlH_4$[1]. Coupling of **3** with the propargylic hydroxyester **4** using a palladium/copper catalyst [1,4] affords the E,E conjugated dienyne system **5** (mixture of diastereomers not separated on TLC) [6].
The synthetic strategy demands a further stereoselective hydrogenation of the triple bond into a Z-double bond.
Several attempts of catalytic hydrogenation either were unsuccessful or gave low yields of **6**. Particularly, using the Lindlar's catalyst, a complex mixture was formed from which compound **6** was isolated in 30% yield only.
Attempts to reduce **5** either by hydrogenation over palladium on barium sulfate or by reduction with diisoamylborane were unsuccessful.



We found that **5** could be reduced using Cu/Ag activated zinc dust in methanol-water 1:1 [5] into a mixture of two compounds **6a** and **6b** in a 70% yield [7] , (Rf = 0,46 and 0,37 respectively on silicic acid TLC, using dichloromethane/ ethylacetate 6:4). These compounds were easily separated on silicic acid column chromatography. Their IR, MS and PMR spectra are identical [8]. It is thus likely that **6a** and **6b** are diastereomers .

The E, E, Z trienic system was characterized in both compounds by examination of the 300 MHz PMR spectrum of their diacetates **7a** and **7b**. The coupling constants $J_{10,11}$ and $J_{8,9}$ were identical and equal to 15 Hz. The same values were found in the diacetate of the dienyne **5** [6], thus characterizing the E,E conjugated dienic system. The Z double bond was identified by the coupling constant $J_{6,7}$ =11 Hz [8,9]. The complete system of intercoupling vinylic protons was resolved [8]. The racemic compound **6b** (lower Rf) possesses the same conjugated trienic system and the same relative configuration as leukotriene B4 by comparison of the TLC behaviour. The total synthesis of optically active leukotriene B4 is in progress.

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6 Characterization of 5 as its diacetylated derivative :
PMR (300 MHz, C6 D6) (d ppm) : 6.5 (1H, dd, $J_{9,10}$ = 10 Hz, $J_{9,8}$ = 15 Hz, H_9); 6.08 (1H, dd, $J_{10,11}$ = 15 Hz, $J_{10,9}$ = 10 Hz, H_{10}); 5.67 (1H, td, $J_{5,8}$ = 2 Hz, $J_{5,4}$ = 6 Hz, H5); 5.46 (1H, dd, $J_{8,9}$ = 15 Hz, $J_{8,5}$ = 2 Hz, H_8); 5.43 (1H, dd, $J_{11,10}$ = 15 Hz, $J_{11,12}$ = 7 Hz, H_{11}); 5.34 (1H, td, $J_{12,11}$ = 7 Hz, $J_{12,13}$ = 7 Hz, H_{12}); 3.31 (3H, s, OCH_3); 2.04 (4H, t, J = 7 Hz, H_4 and H_{13}); 1.69 and 1.63 (3H, s, OAc); 1.41-1.11 (10 H, m, aliphatics H); 0.84 (3H, t, $J_{17,16}$ = 7 Hz, CH_3-17).
MS spectrum, CI / ammonia : m/z 410 (M + NH4$^+$)
IR u max (film) : 2200 (C=C); 1730 (C=O); 1230 (-O-C=O) cm^{-1}.

7 The hydrogenation was run as follows : Copper-acetate-monohydrate (35 mg) was added to a suspension of zinc dust (350 mg) in 2 ml water and the mixture was stirred for 15 min. Silver nitrate (35 mg) was added and stirring was continued for 15 min. The suspension was filtered, washed successively with water (4 ml), methanol (4 ml), acetone (4 ml) and diethylether (4 ml) and resuspended into 1,4 ml of methanol-water 1:1. A solution of the dienyne 5 (60 mg) in methanol (0.2 ml) was poured into this suspension and the mixture was stirred overnight at room temperature. After dilution with methanol, the residue was filtered on Celite 545. To the clear solution, toluene was added for azeotropic distillation of water, and all solvents were removed under vacuum at room temperature. Compounds 6a and 6b were separated on silicic acid column chromatography using a dichloromethane/ethylacetate 6:4 mixture. The purity was checked on TLC plates, using the same solvent.

8 Characterization of the diastereomers 6 as their diacetylated derivatives 7a and 7b :
PMR (300 MHz, C6D6) (d ppm) : 6.75 (1H, dd, $J_{8,9}$ = 15 Hz,$J_{8,7}$ = 11 Hz, H_8); 6.30 (1H, dd, $J_{10,11}$ = 15 Hz, $J_{10,9}$ = 11 Hz, H_{10}); 6.08 (1H, dd, $J_{9,8}$ = 15 Hz, $J_{9,10}$ = 11 Hz, H_9); 5.98 (1H, dd, $J_{7,8}$ = 11 Hz, $J_{7,6}$ = 11 Hz, H_7); 5.85 (1H, m, H_5); 5.58 (1H, dd, $J_{11,12}$ = 7Hz, $J_{11,10}$ = 15 Hz, H_{11}); 5.44 (1H, q, $J_{12,11}$ = $J_{12,13}$ = 7 Hz, H_{12}); 5.28 (1H, dd, $J_{6,7}$ = 11 Hz, $J_{6,5}$ = 9,5 Hz, H_6); 3.30 (3H, s, OCH_3); 2.03 (4H, t, J = 7 Hz, H_4 and H_{13}); 1.71 and 1.64 (3H,s, OAc); 1.25-1.11 (10 H, m, aliphatics H); 0.84 (3H, t, $J_{17.16}$ = 7 Hz, CH_3-17).
MS spectrum : CI/ammonia m/z 412 (M + NH4$^+$)
IR u max (film) : 1730 (C=O); 1595 (C=C-C=C); 1230 (-O-C=O) cm-1

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