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Stereoselective Synthesis of Unsaturated Very Long Chain Fatty Acid Methyl Esters

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Abstract : Very long chain fatty acids are isolated from many different natural sources. However their unsaturated and particularly their diunsaturated derivatives with a $\Delta^{n,n+4}$ pattern are almost exclusively encountered in marine organisms, until we found some derivatives in the botanical family of the Annonaceae. In this letter we present a very efficient synthesis of this family of products based on the new transition metal-catalyzed coupling reaction between an organomagnesium reagent and a functionalized vinyl bromide.

Key Words : acetogenins, olefins, lipids, Grignard reagents, transition metal catalysis.

Fatty acids with a very long aliphatic chain, possessing more than 20 carbon atoms (Very Long Chain Fatty Acid = VLCFA) have been isolated from vegetal or animal sources[1]. Among these fatty acids, those possessing a Δ^n and $\Delta^{n,n+4}$ pattern (e.g. $\Delta^{5,9}$, found mostly in marine invertebrates[2a-d] and more recently in *Allamanda cathartica* L. (Apocynaceae)[2e] flowers) are the more interresting. Recently we found, in the seeds of two different Annonaceae, several compounds derived from $\Delta^{15,19}$ diunsaturated and $\Delta^{15,19,23}$ triunsaturated VLCFA[3]. Furthermore, these natural products have shown interesting biological properties such as antimicrobial and cytotoxic activities[2,3]. Since these products are usually isolated in trace amounts, we wish to report in this communication a very efficient synthesis of unsaturated VLCFA, for instance methyl (Z)- Δ^{15} dotriacontadecenoate and methyl (*Z,E*)- $\Delta^{15,19}$ dotriacontadecadienoate. So far, the strategies used for the preparation of VLCFA are based on the low yielding Wittig procedures[4a-b], S_N2 halide displacement by a Grignard reagent[4b], or double alkylation of tosylmethyl isocyanide (TosMIC)[5] followed by reduction. However these approaches suffer either from the low yields or/and poor stereoselectivity in the formation of the double bonds of the unsaturated fatty acids, and/or a small scale procedure.

The strategy used therein (Figure 1) is based on the stereospecific transition metal-catalyzed cross-coupling reaction of a vinyl bromide with a Grignard reagent[6]. This approach required to prepare both fragments of the molecule with a good control of the geometry of the double bonds.

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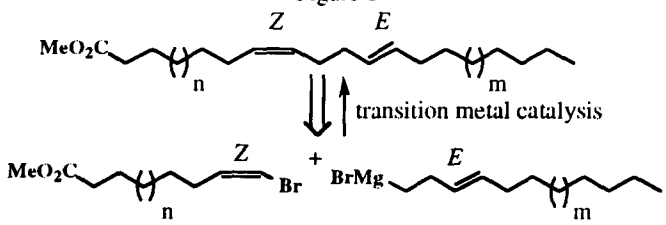
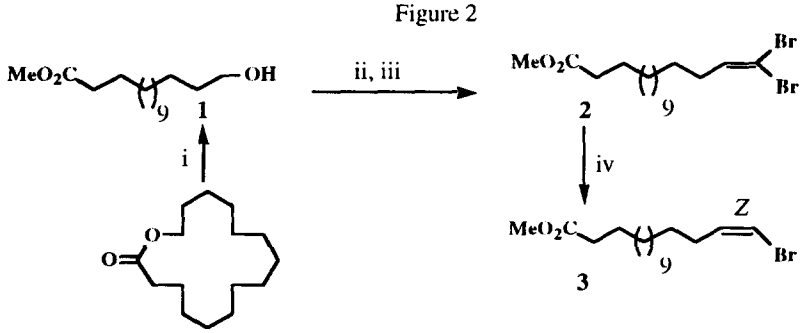
Figure 1



Therefore, the vinyl bromide derivative bearing the ester function at one terminus was prepared from the corresponding 1,1-dibromo-1-alkene, obtained after CBr_4 condensation with the desired aldehyde-ester (Figure 2). The commercially available ω-pentadecalactone was quantitatively opened up by refluxing in methanol containing a catalytic amount of APTS, to give methyl 15-hydroxypentadecanoate **1** which was oxidized with PDC (in 95 % yield based on the ^1H NMR data on the crude product) before Wittig homologation in the presence of PPh_3, CBr_4 and Zn (0) to afford, after purification, the vinyl *gem*-dibromo derivative **2** in 80 % yield for the two steps[7]. Then palladium ($Pd(PPh_3)_4$) catalyzed hydrogenolysis of 1,1-dibromo-1-alkene **2** with one equivalent of *n*-Bu_3SnH was performed[8], yielding the desired *Z* vinyl bromide **3** in 83 % yield.

Figure 2

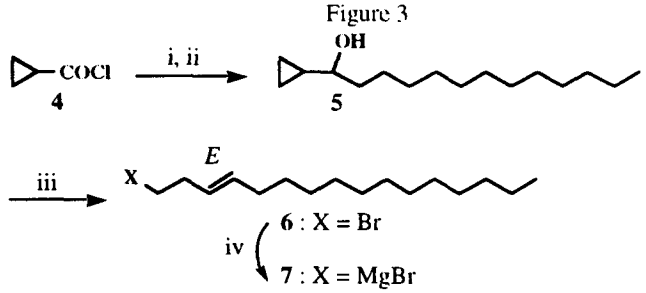


Reaction conditions : (i) MeOH, APTS cat.12h, reflux; (ii) PDC, CH_2Cl_2, (iii) PPh_3, CBr_4, Zn, THF, 80 % for the three steps; (iv) *n*-Bu_3SnH, $Pd(PPh_3)_4$, 83 %

The required organometallic reagent **7** was prepared from the corresponding alkyl bromide **6**, which was successfully obtained after Julia rearrangement of the cyclopropyl carbinolic derivative **5** (Figure 3). Thus, acylation at -78 °C in THF of dodecylmagnesium bromide with carboxylic acid chloride **4**, afforded the corresponding ketone in 68 % yield. $NaBH_4$ reduction of the latter in MeOH (24 h at room temperature) afforded the desired alcohol **5** in moderate yield (51 %). However when the $NaBH_4$ reduction was performed in THF/MeOH (99:1 v/v) in the presence of one equivalent of $MnCl_4Li_2$, both the kinetic and the yield were dramatically increased since the desired alcohol **5** was now obtained in 92 % yield after only 3 h of reaction[9]. Alcohol **5** was then pourred at room temperature into a concentrated aqueous solution of HBr (48 %) to yield the homoallylic alkyl bromide **6**, albeit in moderate yield (53 %)[10]. We found that when the reaction was performed with 7 equivalents of HBr and in the presence of 7 equivalents of $ZnBr_2$ *in pentane* at 20 °C, the desired rearranged product **6** was obtained in 78 % yield[11]. In both cases, geometry of the double bond was determined

as *E*, based on ^{1}H and ^{13}C NMR data (*E*:*Z* dr >97:3). Absence of the *Z* isomer was also conforted by ^{1}H NMR analysis of the crude reaction mixture.

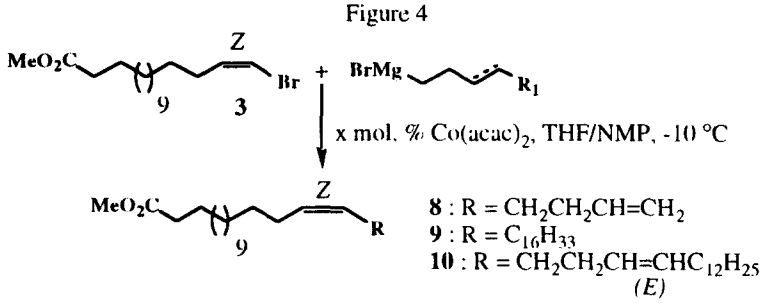
Figure 3



Reaction conditions : (i) $C_{12}H_{25}MgBr$, THF, -78 °C, 68 %; (ii) $NaBH_4$, $MnCl_4Li_2$, THF/MeOH (99/1), 20 °C, 92 %; (iii) HBr, $ZnBr_2$, pentane, 20 °C, 78 %; (iv) Mg, THF

With both intermediates in hands we then decided to perform the key coupling reaction. We thus focused our attention on the $Co(acac)_2$-catalyzed coupling reaction between a Grignard reagent and a vinyl bromide as described by Cahiez[12], because of the stereoselectivity and good chemoselectivity observed in this reaction (e.g. unreactivity with an acetate function). Indeed, this reaction seems very attractive because of (i) stereoselectivity, (ii) chemoselectivity, (iii) unexpensive and safe reagents used, and (iv) easy experimental procedure (e.g. no low temperatures, usual solvents, and fast reaction). However model coupling reactions were first performed in order to study both the influence of the double bond in the Grignard reagent and the effect of a long aliphatic chain toward the coupling reaction (Figure 4). Thus, but-3-en-1-ylmagnesium bromide and hexadecylmagnesium bromide were prepared from the corresponding commercially available aliphatic bromides.

Figure 4



When but-3-en-1-ylmagnesium bromide (0.8 mol.L^{-1}, 1.6 equiv.) was mixed at -10 °C for 1 h with vinyl bromide **3** in the presence of 4 mol % of $Co(acac)_2$, and in a 1:3 mixture of NMP/THF, the corresponding coupling adduct **8** was obtained in 61 % yield (non optimized). When the coupling reaction was now performed with hexadecylmagnesium bromide, under the same reaction conditions but at lower concentration than above (0.25 mol.L^{-1}, 1.5 equiv.), methyl (*Z*)-dotriacontadec-15-enoate **9** was obtained in 46 % yield (non optimized). We thus decided to engage hexadec-3-en-1-ylmagnesium bromide **7** (0.4 mol.L^{-1}, 1.25 equiv.) with vinyl bromide **3** (5.8 mmol) in a 1:1 mixture of NMP/THF and in the presence of 6 mol % of $Co(acac)_2$, at -10 °C for

1 h and obtained our target compound, methyl (*Z,E*)- $\Delta^{15,19}$ dotriacontadecadienoate **10** (2.022 g)[13] in 71 % yield. Spectroscopic data (^1H and ^{13}C NMR) of compounds **8-10** are in accord with a complete retention of the configurations of the double bonds. Furthermore, it is worth of note that the desired coupled products were obtained on a gram scale.

In conclusion, the cobalt (II)-catalyzed coupling reaction between a Grignard reagent and a vinyl bromide is a synthetic useful reaction which allows us to prepare in *grams quantities* very long aliphatic chain fatty acids possessing either one or two double bonds with a perfect control of their geometries. These unusual natural products may serve furthermore as convenient intermediates in the total synthesis of more elaborate products[14].

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13 Selective spectroscopic data of methyl (*Z,E*)-$\Delta^{15,19}$ dotriacontadecadienoate **10**, $C_{33}H_{62}O_2$: ^1H NMR (200 MHz, $CDCl_3$, δ ppm) : 5.38 (m, 4H), 3.65 (s, 3H), 2,30 (t, J = 7.4 Hz, 2H), 2.03 (m, 8H), 1.62 (quin., J = 7.5 Hz, 2H), 1.26 (br. s, 40 H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) : 130.57, 130.18, 129.66, 129.12, 51.37, 34.11, 32.72, 32.60, 31.93, 29.66, 29.34, 29.27, 29.18, 27.41, 27.28, 26.95, 24.96, 22.69, 14.09; IR (solution in $CHCl_3$, ν cm^{-1}) : 3010, 2930, 2855, 1730, 1450; CIMS (CH_4, *m/z*) : 519 ($MH^+ + C_2H_5$, 13 %), 491 (MH^+, 78 %), 490 (M^+, 86 %), 459 (M-OCH_3, 100 %).

14 To be published