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Stereoselective Synthesis of Conjugated all-Trans-Tetraenes. Application to the Synthesis of β-Parinaric Acid Methyl Ester.

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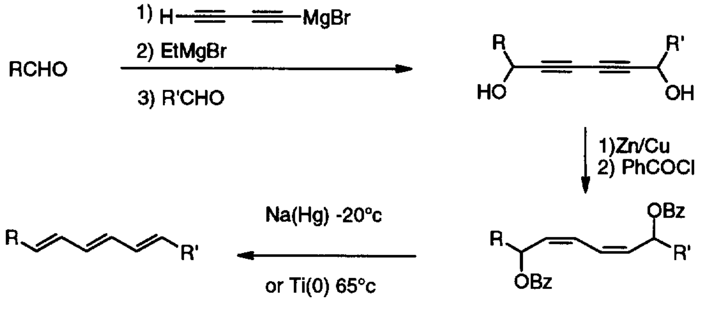
Abstract: in this paper is reported the stereoselective synthesis of all-trans-tetraenes by reductive elimination of 1,8-dibenzoate-2,4,6-trienes with sodium amalgam. The method was applied to the syntheses of 4E, 6E, 8E, 10E-heptatetraene and β–parinaric acid methyl ester.

Conjugated polyolefinic fragments are found in a wide variety of interesting and important organic compounds, including natural products such as : the polyene macrolides[1a], carotenoids[1b], leukotrienes[1c].

We recently reported[2,3] that all-trans trienes can be prepared stereoselectively and in high yield by Na(Hg) or low valent titanium reductive elimination of 1,6-dibenzoate-2,4 -dienes which are readily made by acetylene addition to aldehydes, followed by diyne reduction with Zn/Cu (Scheme 1).



Scheme 1

We published also the total syntheses of several natural products containing a trienic moiety made by this reductive elimination : 6(E)-5(S)-12(R) and 5(S)-12(R) leukotriene B_4[4] , cis and trans galbanolene[5], navenone B and lignarenone B[6].

We now report an efficient synthesis of all-trans tetraenes **1** based on the reductive elimination of 1,8-dibenzoate-2,4,6-trienes **2** obtained from the diol-diynes **3** which are obtained by a Chodkiewicz reaction[7]

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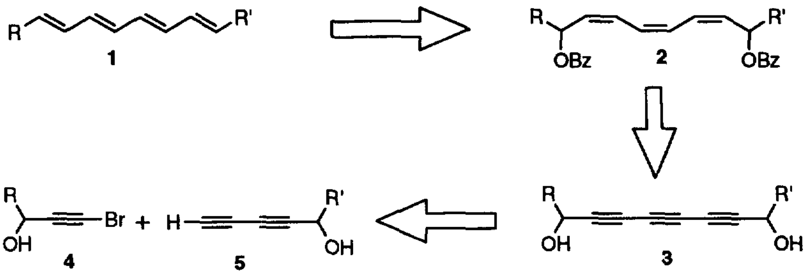
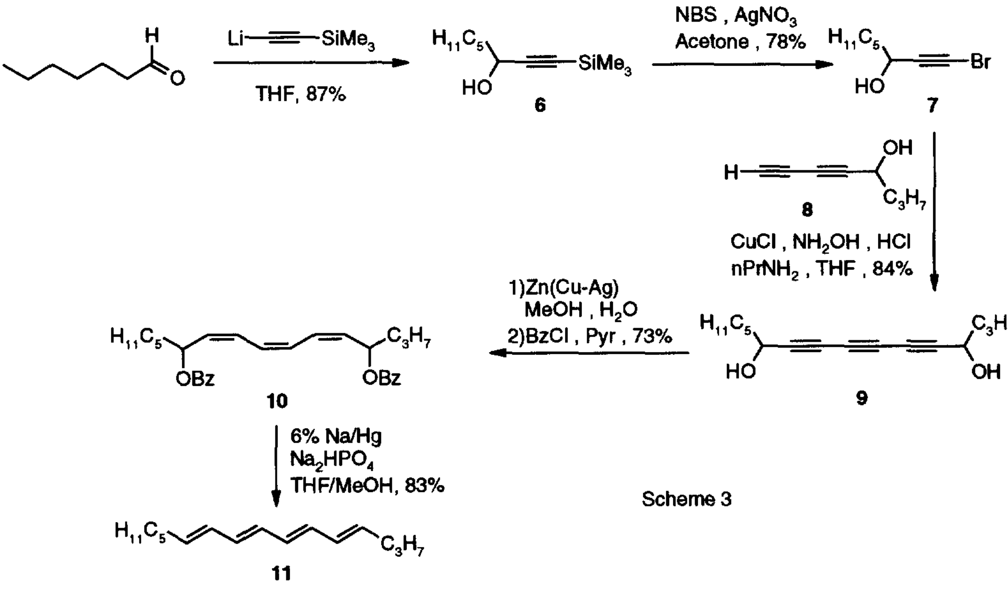
between the bromo-propargylic alcohol **4** and the diacetylenic alcohol **5** as shown on the retrosynthetic scheme (Scheme 2).



Scheme 2

This methodology was first applied to the synthesis of (4E,6E,8E,10E) heptatetraene, **11**. The preparation of 1-bromo-3-hydroxyoctyne **7** started from commercially available hexanal (scheme 3) which was condensed with trimethylsilyl lithioacetylene to give the propargylic alcohol **6** in 87% yield. Bromoacetylene**7** was then obtained from **6** in Isobe conditions[8] (NBS,AgNO$_3$ in acetone, 78% yield). Chodkiewicz reaction[7] of the bromide **7** and the diyne **8** (prepared from lithiated diacetylene and butyraldehyde in 88% yield) gave the triynic diol **9** in 84% yield. The triple bonds of **9** were reduced with the activated Zn-Cu couple in MeOH/H$_2$O[9] and the diol converted to the trienic dibenzoate **10**. An overall yield of 73% was obtained for these two steps.

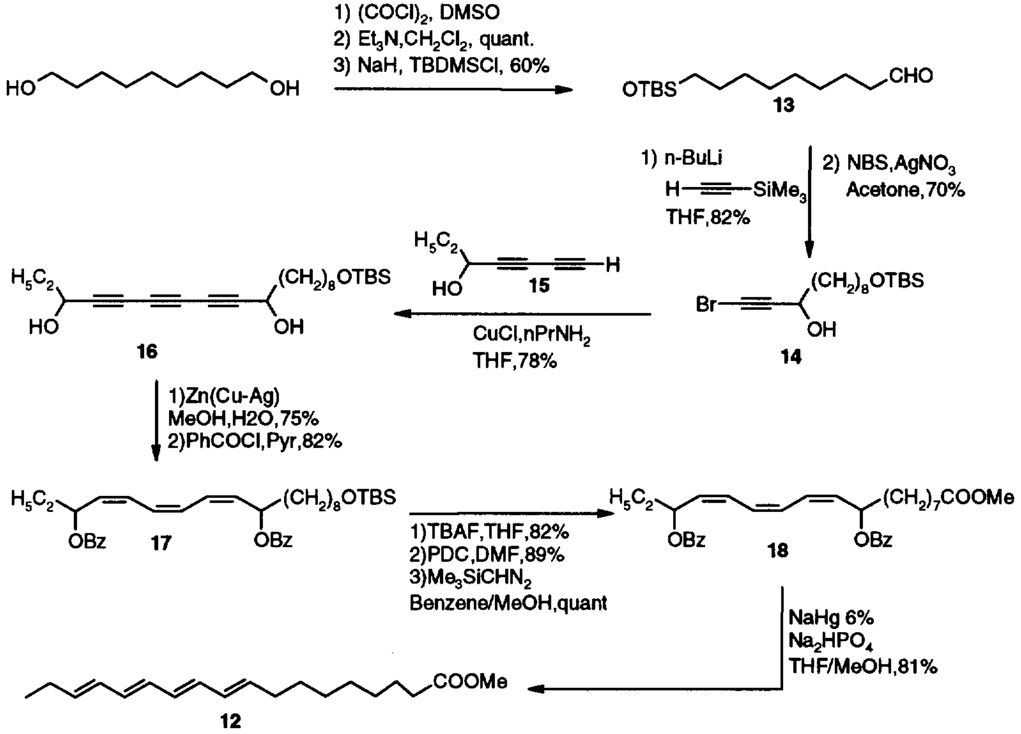


Scheme 3

Reaction of **10** with sodium amalgam in methanol at -20°C gave the all E tetraene **11** in 83% yield with more than 95% isomeric purity after column chromatography. We did not detected in the ^1H NMR spectra of the crude elimination product the characteristic signals of Z double bonds.[9]

This method was also applied to the synthesis of the methyl ester of β-parinaric acid[10] **12**, methyl (9E,11E,13E,15E)-octadeca-9,11,13,15 tetranoate , an interesting fluorescent probe for biological menbrane microstructure[11] containing a tetraene unit. The (9Z,11E,13E,15Z) stereoisomer, called α-parinaric acid, was first isolated from the kernels of *Parinarum Laurinum*[12]. It can be converted into the all-trans β parinaric acid by treatment with iodine or using UV irradiation[13]. Only three reports have described the synthesis of β-parinaric acid[14-16] but in two of them [14,16] the ^1H NMR data showed vinylic protons at 6.5ppm which do not correspond to an all trans structure.[9,18]

The propargylic bromide **14** was obtained from 1,9-nonanediol *via* monoprotection with TBDMSCl, Swern oxidation to the aldehyde **13** , condensation with lithio trimethylsilyl-acetylene and bromination with NBS and $AgNO_3$ (Scheme 4). Chodkiewicz condensation[7] of **14** with the diynediol **15** (prepared in 74% yield from lithio acetylene and propanal) gave the triynediol **16** in 78% yield. Reduction with Zn/Cu gave the trienicdiol (75%yield), which was then dibenzoylated to **17** under standard conditions.



Scheme 4

Deprotection of the primary alcohol (82% yield), oxidation with pyridinium dichromate in DMF (89% yield) and esterification with trimethylsilyl diazomethane[17] afforded the methylester **18** in quantitative yield.

Reaction of **18** with 6% Na(Hg) in THF/MeOH (3/1) gave the β-parinaric methylester **12** in 81% yield (mp: 58-59°C, lit.[18] 58.5). The 500Mhz ^{1}H NMR shows the characteristic symmetrical signal of all-trans double bonds[9] and IR data are identical with those found in literature[10].

In conclusion these results provide an easy and stereoselective route to all-trans fonctionalized tetraenes. It is important to notice that for the first time the reductive elimination was carried out on a molecule containing a carboxylic ester.

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9) Boland, W. ; Schroer, N. ; Sieber, C. ; Feigel, N. *Helv. Chim. Acta*, **1987**, *70*, 1025: a Z double bond in these tetraenes gives at 500Mhz a signal near 6.5ppm. In the spectrum of our product we observed only two multiplets: one between 5.64 and 5.72ppm for the two external protons and one between 6 and 6.22ppm for the 6 other vinylic protons. This symmetrical signal is characteristic of all-trans tetraene.
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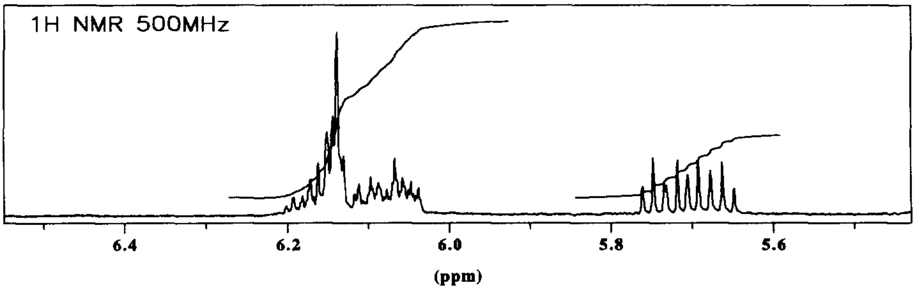
18) ^{1}H NMR ($CDCl_3$, 200MHz) : δ : 6.04-6.21 (m, 6H, H-10, 11, 12, 13, 14, 15), 5.65-5.76 (m, 2H, H-9, 16), 3.66 (s, 3H, OCH_3), 2.30 (t, 2H, J=7.5Hz, H-2), 2.60 (m, 4H, H-8, 17), 1.55 (m, 4H, H-3,7), 1.30 (m, 6H, H-4, 5, 6), 1.01 (t, 3H, J=7,4, H-18). ^{13}C NMR ($CDCl_3$) : 174.30, 136.55, 135.00, 132.54, 132.48, 130.93, 130.71, 129.72, 51.47, 34.13, 32.90, 29.31, 29.16, 29.05, 25.94, 24.99, 13.61. IR Spectrum (CS_2) v 3050-2840, 1740, 990 cm^{-1}



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