CHEMISTRY LETTERS, pp. 413 - 416, 1985.

A NEW, GENERAL, AND STEREOSELECTIVE SYNTHESIS OF LONG CHAIN TETRAENOIC ACIDS EXAMPLIFIED BY β-PARINARIC ACID

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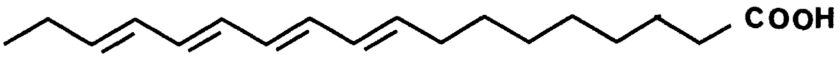
All trans-9,11,13,15-octadecatetraenoic acid was first synthesized in a stereoselective manner, using pentadienyl and allyl dithiocarbamates as the starting materials. This synthesis confirmed that β-parinaric acid has *all trans* configurations about the four double bonds.

General and facile synthetic methods for the stereoselective formation of conjugated polyene compounds play an increasingly important role in the arsenal of synthetic organic chemistry. Recent discovery of a number of long chain alcohols,[1) aldehydes,[2) ketones,[3) acids,[4) esters,[2) and macrolides[5) in various classes of natural products gives a major impetus to the development of these methods. We have explored a novel method for preparing *all trans*-trienes and tetraenes using pentadienyl dithiocarbamate **1** as the starting material, which has now been applied to the synthesis of a natural product having a tetraene unit.[6)

In this communication, we have selected β-parinaric acid as a representative of long chain natural products having a tetraene unit. Other tetraene natural products can be prepared by almost similar strategy.

α-Parinaric acid was first isolated from the kernels of *Parinarium Laurinum* as white crystals having mp 85-86 °C,[7) which can be converted into the β-form having mp 95-96 °C by treatment of iodine or UV irradiation. The structure of both the acids was determined to be 9,11,13,15-octadecatetraenoic acid. The IR studies suggested the *all trans* configuration for the β-form.[7d)



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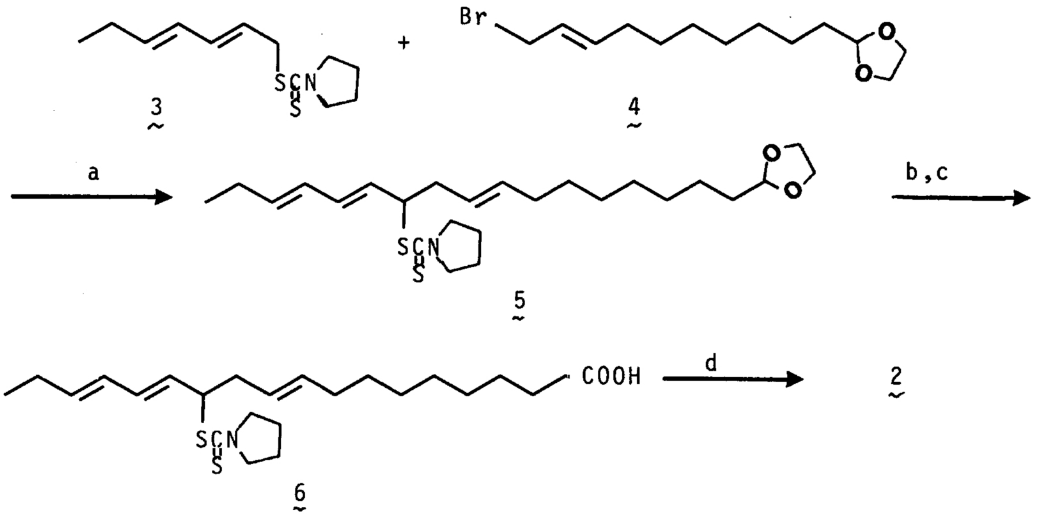
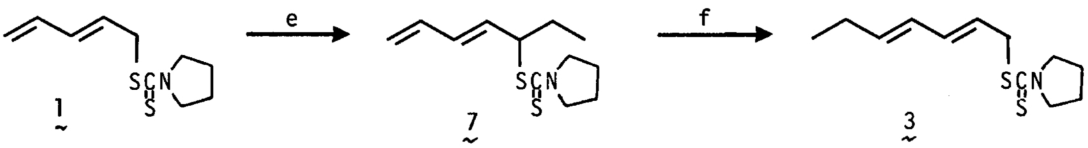
The convergent type synthesis[8) of this highly unsaturated fatty acid involves the coupling reaction between the right and left halves (**3** and **4**) as the key step, as shown in Scheme 1. The left half **3** was readily prepared from **1** according to the procedures previously described.[6) The lithium salt of **1** in THF reacted smoothly at -78 °C under argon with ethyl iodide to afford **7** in 79.7% yield. The contaminated regioisomers were removed by column chromatography using silica gel with hexane/EtOAc (9:1) as the solvent. Refluxing **7** in a toluene solution for 2.5 h provided **3** almost quantitatively through the double [3,3]-sigmatropic rearrangement.

The preparation of the right half **4** begins with allyl dithiocarbamate **8**,[9) as



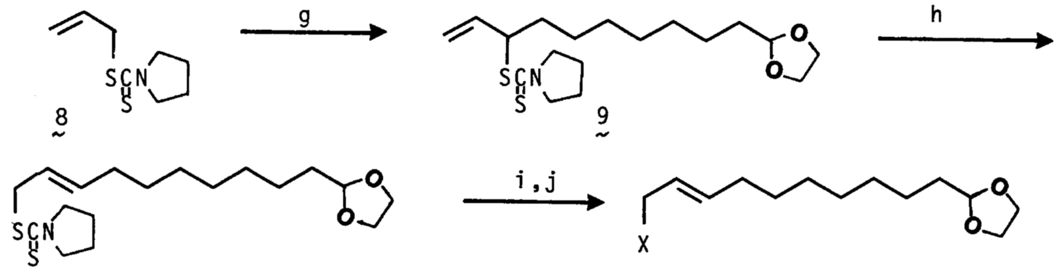
(a) LDA/THF, at -78 °C, 30 min; (b) 2.5% HCl/acetone, r.t., 24 h; (c) air, 5 °C, a week; (d) MeI/LiF/Li_2CO_3/DMF, r.t., 24 h.

Scheme 1.



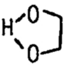
(e) LDA/THF, -78 °C, EtI, 30 min; (f) reflux in toluene, 2.5 h.

Scheme 2.



11, X= I

4, X= Br

(g) LDA/THF, -78 °C, I-$(CH_2)_7$-CH  ;(h) reflux in $CHCl_3$, 4.5 h; (i) MeI, 24 h; (j) NaBr/DMF, 50 °C, 24 h.

Scheme 3.

shown in Scheme 3. The lithium salt of 8 in THF reacted easily at -78 °C with acetal of ω-iodo-octanal to afford 9 in 85% yield, which was accompanied by 10% of the regioisomers. It was unnecessary to separate the α-isomer from other regioisomers. Refluxing 9 in a $CHCl_3$ solution for 4.5 h produced 10 almost quantitatively via the [3,3]-sigmatropic rearrangement. Treatment of 10 with methyl iodide in the dark under argon at room temperature overnight provided the iodide 11 in 75% yield. The isolation of 11 from the unreacted regioisomers of 10 was readily attained by column chromatography on silica gel using hexane/EtOAc (9:1) as solvent. The iodide 11 was then converted into the corresponding bromide 4 by the Finkelstein reaction,10) since the iodide is rather unstable, and further, in the reaction of allylic halides with thioallylic anions, the bromide gives a higher level of α-regioselectivity than the corresponding iodide.11)

The coupling reaction between the two components 3 and 4 was performed by the treatment of the lithium salt of 3 with a slight excess of 4 in THF at -78 °C under argon for 30 min, providing 5 in 85% yield, which was contaminated by 8% of the regioisomers. Purification of 5 was carried out by column chromatography on silica gel using hexane/EtOAc (9:1) as solvent. The acetal 5 was demasked by treating with excess acetone containing 2.5% HCl at room temperature overnight to give the corresponding aldehyde in 95% yield. The oxidation to the acid 6 was conducted by the air by allowing to stand in an open vessel in the air at 5 °C for a week, to afford 6 in 95% yield, which was purified by column chromatography on silica gel using hexane/EtOAc (7:3) as solvent. The oxidative desulfurization of 6 to 2 was achieved by treating with a mixture of MeI, LiF, and Li_2CO_3 in DMF in the dark under argon at room temperature12) to lead to the final product 2 in 75% yield as a faintly yellow solid, which was further purified by HPLC using silica gel column with hexane/EtOAc (9:1) as eluent, providing 2 as white crystals having mp 95-96 °C.

Immediately after the separation, the product was subjected to the physical measurements, because the acid is extremely vulnerable to the air and light. Therefore, care was taken to avoid oxidation and polymerization by performing the separation procedures under nitrogen atmosphere in the dark and lower temperature. The order in the reactions was also critical. When the oxidation desulfurization was performed before the oxidation process, the yield of the final product was reduced to a trivial level.

The mp and IR spectrum of the synthesized acid were in good agreement with those of β-parinaric acid.7c) The UV spectrum was almost the same as those of *all trans*-2,4,6,8-decatetraene and other tetraenes,6,13) but clearly different from that of α-parinaric acid.7b,14) The NMR, IR, and Mass spectra of the product15) agreed well with those of the expected structure. These facts support the result of the IR studies7d) that the β-form has *all trans*-configuration about the four double bonds.

This work constitutes the first synthetic study on the field of highly unsaturated long chain fatty acids. The extension of this methodology to the pentaene counterparts is currently in progress,

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14) UV spectrum of **2** (λ_{max}, hexane) 269(shoulder), 285, 299, and 314 nm.

15) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00(t, J=7.0 Hz, 3H, CH_3), 1.31(m, 8H, H_4,H_5,H_6,H_7), 1.40(m, 2H, H_3), 2.10(m, 4H, H_8,H_{17}), 2.40(t, 2H, H_2), 5.42(m, 2H, H_9,H_{16}), 6.04(m, 2H, H_{10},H_{15}), 6.19(m, 4H, H_{11},H_{14}), 6.50(m, 2H, H_{12},H_{13}) ppm.
Mass spectrum, m/e (relative intensity) 276(M^+, 23.5%), 274(94.0%), 231(M^+-CO_2H, 13.7%), 147($M^+-C_7H_{13}O_2$, 33.2%), 133(33.2%), and other many peaks.
IR spectrum (CS_2) 1795(νC=O) and 997 cm^{-1}($\delta\,{}^{H}\!\diagdown C{=}C\diagdown_{H}$).

(Received December 26, 1984)