UNSATURATED ACIDS AND MACROCYCLIC LACTONES

COMMUNICATION 9. PREPARATION OF CONJUGATED POLYENIC ALIPHATIC ACIDS WITH THE AID OF THE WITTIG REACTION, AND THE SYNTHESIS OF α-ELEOSTEARIC ACID *

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Conjugated polyenic aliphatic acids of general formula $CH_3(CH_2)_n(CH=CH)_m(CH_2)_7COOH$ (I) enter into the composition of the lipides of some of the higher plants. They include stereoisomeric octadecatrienoic acids (I; $m=3$, $n=4$): α-eleostearic acid (IX) (main fatty acid of tung oil) [4], its 9(cis), 11(trans), 13(cis)-isomer punicic acid (from the oil of pomegranate seeds and plants of the Trichosanthes family) [5-8], and its 9(trans), 11(trans), 13(cis)-isomer (from *Catalpa ovata*) [9], and also parinaric acid (I; $m=4$, $n=1$) (from seeds of *Parinarum Laurinum*) [10-12]. A close relation of these acids is 8,10,12-octadecatrienoic acid, which has been recently isolated from the seeds of *Calendula officinalis* [13].

A description has appeared of an eight-stage synthesis of α-eleostearic and punicic acids [8] based on the Reformatskii condensation of α,β-unsaturated aldehydes with 3-bromopropyne with subsequent dehydration and chain lengthening.

In our laboratory we recently developed a new method for the synthesis of natural cis-unsaturated fatty acids of type (III) [2] based on the condensation of alkyl ω-(triphenylphosphoranylidene)alkanoates (II) with saturated aldehydes under conditions that permitted the selective formation of cis olefins [1]:

$$CH_3(CH_2)_nCHO + \underset{(II)}{Ph_3P=CH(CH_2)_mCOOEt} \rightarrow \underset{(III)}{CH_3(CH_2)_n\overset{(cis)}{CH=CH}(CH_2)_mCOOH}$$

For the application of this method to the synthesis of polyenic acids of type (I) it was necessary to check to what extent the stereochemical relations established in the study of the Wittig reaction with saturated aldehydes [1] remain in force in the case of α,β-unsaturated aldehydes.

With this object we studied the stereochemistry of the reaction of crotonaldehyde with ethyl 9-(triphenylphosphoranylidene)nonanoate (IV). It was shown that in N,N-dimethylformamide in presence of iodide ions this reaction leads to the cis-trans-dienic ester (V), which after a short ultraviolet irradiation in presence of iodine is converted into the trans-trans isomer (VI):

$$\overset{(trans)}{CH_3CH=CHCHO} + \underset{(IV)}{Ph_3P=CH(CH_2)_7COOEt} \xrightarrow[I^-]{HCONMe_2}$$

$$\rightarrow \underset{(V)}{\overset{(trans)}{CH_3CH=CH}-\overset{(cis)}{CH=CH}(CH_2)_7COOEt} \rightarrow$$

$$\xrightarrow[I_2]{h\nu} \underset{(VI)}{\overset{(trans)}{CH_3CH=CH}-\overset{(trans)}{CH=CH}(CH_2)_7COOEt}$$

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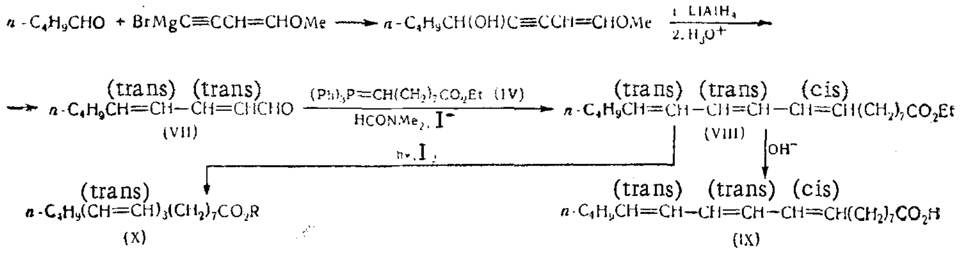
* Communication 4 of the series "Stereochemistry of the Wittig Reaction and its Use in Synthesis" (for Communications 1-3 see [1-3]).

The configurations of the dienic esters (V) and (VI) were confirmed by a study of their ultraviolet and infrared spectra. The ultraviolet spectrum of the dienic ester (VI) (λ_{max} 228 mμ, ε 27300) differs from that of the isomeric diene (V) (λ_{max} 230 mμ, ε 25700) by a shift in the absorption maximum toward the short waves and an increase in the extinction coefficient, which is characteristic of a transition from cis-trans to trans-trans dienes [14-16]. The infrared spectrum of the dienic ester (V) contains a doublet in the region 1000-900 cm^{-1} which is characteristic for cis-trans dienes [15-17], whereas (VI), like other trans-trans dienes, has only one absorption maximum in this region, and this, moreover, is considerably more intense. Hence, in presence of Lewis bases (dimethylformamide, I^-) the reaction of the phosphoranylidenealkanoic esters (II) with α,β-unsaturated aldehydes leads, as in the case of saturated aldehydes [1], to the formation of a cis-ethylenic bond.

These results make it possible to effect the stereospecific synthesis of α-eleostearic acid (IX) in accordance with the scheme:



The 2,4-nonadienal (VII) required in this synthesis was prepared by the condensation of valeraldehyde with the magnesium derivative from 1-methoxy-1-buten-3-yne with subsequent reduction with lithium aluminum hydride and acid hydrolysis [18]. We modified somewhat the method of preparing the dienic aldehyde (VII) described in the literature by carrying out the acid treatment of the reduction product with tartaric instead of mineral acid, because the yield of aldehyde was then considerably higher.

The condensation of 2,4-nonadienal (VII) with ethyl 9-(triphenylphosphoranylidene)nonanoate lead to ethyl 9(cis),11(trans),13(trans)-octadecatrienoate (VIII), whose configuration was confirmed by its infrared spectrum (presence in the 1100-930 cm^{-1} region of an intense doublet characteristic for trans-trans-cis-trienes [8]). By the hydrolysis of the trienic ester (VIII) we obtained 9(cis),11(trans),13(trans)-octadecatrienoic acid (IX), whose melting point and ultraviolet maxima coincided satisfactorily with the corresponding constants of natural α-eleostearic acid (see table).

Acid	Natural [7]			Synthetic		
	m.p., °C	λ_{max}, mμ	ε · 10^{-3}	m.p., °C	λ_{max}, mμ	ε · 10^{-3}
α-Eleostearic	48	261	36.0	46.5-48	260	35.0
		271	47.0		270	45.6
		281	38.0		281	35.8
β-Eleostearic	72	259	47.0	70.5-72	259	44.5
		268	61.0		268	59.5
		279	49.0		279	47.6

EXPERIMENTAL

Ultraviolet spectra were determined in alcohol with an SF-4 spectrophotometer; infrared spectra of polyenic esters (in a thin layer) and acids (in mineral oil) were determined with a Zeiss UR-10 spectrophotometer*. Melting points (uncorrected) were determined in a Kofler block. Thin-layer chromatography was carried out on plates covered with an unbound layer of alumina (Grade II-III activity); for detection we used a 1% solution of potassium permanganate in 2 N sulfuric acid. All operations on the preparation and isolation of polyenic acids and their esters were carried out in an atmosphere of nitrogen.

2,4-Nonadienal. A solution of 6.97 g of 1-methoxy-1-buten-3-yne in 7 ml of tetrahydrofuran was added with stirring to a solution of ethylmagnesium bromide prepared from 1.86 g of magnesium and 8.33 g of ethyl bromide

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* The infrared spectra were determined by L. B. Senyavina and S.L. Portnova (Laboratory for Physicochemical Testing, Institute for the Chemistry of Natural Products, Academy of Sciences, USSR).

in 50 ml of tetrahydrofuran. The enyne was added at 30°, after which stirring was continued further for one hour at room temperature. The mixture was cooled with ice, and over a period of 40 minutes 6.25 g of freshly distilled valeraldehyde in 7 ml of tetrahydrofuran was added.

After the mixture had stood overnight, 3.32 g of absolute alcohol was added. The mixture was cooled with ice while a solution of 2.87 g of lithium aluminum hydride in 50 ml of tetrahydrofuran was added dropwise over a period of 30 minutes. Stirring was continued for four hours at 20°, and the mixture was then left for 36 hours. The residue of lithium aluminum hydride was decomposed by the addition of 7 ml of ethyl acetate. The reaction mixture was acidified with aqueous tartaric acid solution, the organic layer was separated, and the aqueous layer was extracted four times with ether. The combined extract was washed with water and dried with magnesium sulfate. Solvent was vacuum-distilled off, and we then obtained 5.82 g (55%) of 2,4-nonadienal, b.p. 95-102° (10 mm) and n_D^{20} 1.5184; its 2,4-dinitrophenylhydrazone had m.p. 136-138° (from alcohol).

Ethyl 9(cis), 11(trans)-Tridecadienoate (V) and Ethyl 9(trans),11(trans)-Tridecadienoate (VI). A solution of 16.55 g of [8-(ethoxycarbonyl)octyl]triphenylphosphonium iodide [2] in 35 ml of N,N-dimethylformamide was added with stirring to a solution of 1.24 g sodium methoxide in 10 ml of N,N-dimethylformamide. Stirring was continued at room temperature until the reaction to phenolphthalein was neutral (two hours), after which 1.5 g of freshly distilled crotonaldehyde in 10 ml of N,N-dimethylformamide was added over a period of 20 minutes. The reaction mixture was stirred further for 15 hours, and then, after the addition of 50 ml of water, it was extracted with five 50-ml portions of petroleum ether. The extract was dried with anhydrous magnesium sulfate. Solvent was vacuum-distilled off, and we then obtained 4.11 g of oil, which was chromatographed in hexane on alumina (Grade II-III activity activity; pH 6). With the same solvent (150 ml) we eluted 2.90 g (60%) of ethyl 9(cis),11(trans)-tridecadienoate; b.p. 58-60° ($5 \cdot 10^{-2}$ mm), n_D^{20} 1.4818; d_4^{20} 0.9453. Found: C 75.57; H 10.74%. $C_{15}H_{26}O_2$. Calculated: C 75.58; H 11.00%.

In thin-layer chromatography of this dienic ester in hexane and in a 7 : 3 mixture of hexane and benzene only one spot was detected. Infrared spectrum (in a thin layer) (λ_{max}, cm^{-1}): 1740s (C=O), 986m, 948m (trans-CH=CH in conjugated cis-trans-diene); ultraviolet spectrum: λ_{max} 230 mμ (ε 25700).

1 ml of 0.005 N iodine in carbon disulfide was added to 45 ml of ethyl 9(cis),11(trans)-tridecadienoate, and the mixture was irradiated with an ultraviolet lamp for five minutes, after which it was washed with 0.5 ml of 5% sodium thiosulfate solution and with two 0.5-ml portions of water. Carbon disulfide was vacuum-distilled off, and the residue was dissolved in ether. The solution was dried with anhydrous magnesium sulfate, and after removal of solvent we obtained 10 mg of an almost colorless oil; λ_{max} 228 mμ (ε 27200). Infrared spectrum (in a thin layer) (ν_{max}, cm^{-1}): 1743s (C=O), 988s (trans-CH=CH), and a very weak band at 948 cm^{-1} due to slight cis-trans-diene impurity.

Ethyl 9(cis),11(trans),13(trans)-Octadecatrienoate (α-Eleostearate) (VIII). Under the above-stated conditions from 16.55 g of [8-(ethoxycarbonyl)octyl]triphenylphosphonium iodide, 1.24 g of sodium methoxide, and 2 g of trans-trans-2,4-nonadienal (VII) we obtained a neutral product (4.85 g), which was dissolved in hexane and chromatographed on a column (30 × 1300 mm) filled with 750 g of alumina (Grade III activity; pH 7). The column was eluted with a 2 : 1 mixture of petroleum ether and benzene. The first fractions (90 ml) of the eluate contained 0.28 g of triphenylphosphine. From the succeeding fractions (110 ml) we obtained 1.12 g of a yellow oil consisting, according to thin-layer chromatography, of the trienic ester (VIII) containing triphenylphosphine impurity. Further elution gave 1.3 g of a colorless oil (n_D^{20} 1.5093), which was homogeneous according to the results of thin-layer chromatography (R_f 0.53 and 0.51 in the systems 2 : 1 petroleum ether and benzene and 20 : 1 petroleum ether and ethyl acetate, respectively). Distillation of this product at a bath temperature of 135° (residual pressure $5 \cdot 10^{-5}$ mm) gave ethyl α-eleostearate as a colorless oil; λ_{max}(mμ) 261 (ε 35000), 269.5 (ε 45600), 280.5 (ε 35300). Infrared spectrum (ν_{max}, cm^{-1}): 1744s (C=O), 993s, 965m (trans-CH=CH in trans-trans-cis-triene). Found: C 78.15, H 11.09%. $C_{20}H_{34}O_2$. Calculated: C 78.38; H 11.18%.

9(cis),11(trans),13(trans)-Octadecatrienoic (α-Eleostearic) Acid (IX). A solution of 0.083 g of NaOH in 1.7 ml of alcohol was added to 0.3 g of ethyl α-eleostearate. The mixture was left overnight, alcohol was removed in a vacuum, and the residue was acidified with 5% sulfuric acid and extracted with four 20-ml portions of ether; the ether extract was dried with anhydrous magnesium sulfate. When solvent was distilled off, the residue (0.21 g) crystallized out and was recrystallized from petroleum ether of b.p. 30-50°; m.p. 46.5-48°, λ_{max}(mμ) 260 (ε 35500), 270 (ε 45500), 281 (ε 35800); infrared spectrum (ν_{max}, cm^{-1}): 1705s (C=O), 995s, and 970m (trans-CH=CH in a conjugated trans-trans-cis-triene).

Ethyl 9(trans),11(trans),13(trans)-Octadecatrienoate (β-Eleostearate) (X; R = C_2H_5). Under the above-stated isomerization conditions from 0.46 g of ethyl α-eleostearate we obtained 0.3 g of ethyl β-eleostearate; b.p. 150° (bath temperature) ($5 \cdot 10^{-5}$ mm); λ_{max} (mμ) 259 (ε 41000), 268 (ε 55000), 279 (ε 44600); infrared spectrum (ν_{max}, cm^{-1}): 1743s, 994s, and a band of very low intensity at 966 cm^{-1}.

9(trans),11(trans),13(trans)-Octadecatrienoic (β-Eleostearic) Acid (X; R = H). Under the conditions used in the hydrolysis of α-eleostearic ester, from 0.28 g of ethyl β-eleostearate we obtained 0.19 g of β-eleostearic acid; m.p. 70.5-72° (from alcohol); λ_{max}(mμ) 259 (ε 44500), 268 (ε 59500), 279 (ε 47700); infrared spectrum (ν_{max}, cm^{-1}): 1710s C=O), 990s (trans-CH=CH in a conjugated trans-trans-trans-triene). Found: C 77.70; H 10.97%. $C_{18}H_{30}O_2$. Calculated: C 77.65; H 10.86%.

SUMMARY

1. The condensation of alkylidenetriphenylphosphoranes with α, β-unsaturated aldehydes in N,N-dimethylformamide in presence of iodide ions leads to cis-trans-dienes.

2. A description is given of a stereospecific method based on the Wittig reaction for the synthesis of conjugated polyenic factty acids.

3. A new total synthesis of α-eleostearic acid was carried out.

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