

PREPARATION OF CIS,CIS-, TRANS,CIS-, CIS,TRANS- AND TRANS,TRANS-12,15-OCTADECADIENOIC-9,10-D₂ ACIDS, METHYL ESTERS AND TRIGLYCERIDES

Henry Rakoff and Edward A. Emken
Northern Regional Research Center, Agricultural Research,
Science and Education Administration, U.S. Department of
Agriculture,* Peoria, Illinois 61604.

SUMMARY

Methyl cis,cis-, trans,cis-, cis,trans-, and trans,trans-12,15-octadecadienoates-9,10-d₂ were prepared by the Wittig Reaction between cis- or trans-3-hexenyltriphenylphosphonium bromide and methyl 12-oxododecanoate-9,10-d₂ with butyl lithium in ethyl ether. At room temperature, the Wittig Reaction gave a product mixture with 80-85% cis geometry in the double bond formed. When the reaction was run at -40°C, followed by protonation with methanol and slow warm-up to room temperature, the product mixture had 60-65% trans geometry in the double bond generated. Mixtures of the cis,cis and trans,cis and of the cis,trans and trans,trans isomers were separated by partial silver resin chromatography, and the individual pure fatty esters were converted to the triglycerides through the respective acid chlorides. Melting points and nuclear magnetic resonance chemical shifts are presented.

Key Words: Wittig Reaction, Geometric Isomers, 12,15-Octadecadienoic-d₂ Acids, Carbon-13 NMR, Triglycerides.

INTRODUCTION

The four geometric isomers of methyl 12,15-octadecadienoate labeled with two deuterium atoms were prepared for continuation of our program on the metabolism in humans (1,2) of isomeric fats formed during the hydrogenation of soybean oil. The synthesis of deuterium labeled lipids has been reviewed (3,4).

*The mention of firm names or trade products does not imply that they are endorsed or recommended by the U.S. Department of Agriculture over other firms or similar products mentioned.

The Wittig Reaction (5) has been used (6-14) for the preparation of a variety of unsaturated fatty esters. In compounds such as these that are generated from nonstabilized triphenylphosphonium ylids and aliphatic aldehyde esters, 80-90% of the double bonds formed during the Wittig Reaction have cis configuration. Consequently, synthetically useful amounts of the cis-12,cis-15- and cis-12,trans-15-isomers should be easily available from our starting materials. However, only small amounts of the trans-12,cis-15- and the trans-12,trans-15-isomers would be available through this same reaction scheme.

Several investigators have been able to alter the stereoselectivity of the Wittig Reaction, and their efforts have been reviewed (12-17). Much of the stereoselective work has been devoted to increasing the percentage of cis in the reaction mixture (18,19). Recently, Anderson and Henrick (11), proceeding from some observations of Schlosser and Christmann (20), have described their work on increasing the percentage of trans double bonds in the Wittig Reaction during the synthesis of insect pheromones. Their procedure involves partial equilibration of the relatively unstable betaine intermediate at -40 to -70°C in the presence of ethanol or methanol. We have been able to adapt this procedure to obtain 60-65% trans geometry in the double bond generated. Through this avenue, synthetically useful amounts of the trans-12,cis-15- and the trans-12,trans-15-isomers have been prepared. The success of our endeavor depended upon our ability to separate geometric isomers by silver resin chromatography (21-23) and by the fact that the cis-12,trans-15- and trans-12, cis-15-isomers, which are not separable by silver resin chromatography, are generated in separate reactions.

In recent years, several research groups have published on the ¹³C NMR spectroscopy of saturated, unsaturated and hydroxy fatty acids and esters (24-30), and some of this work has been reviewed (31). Chemical shift values for a complete series of geometrically isomeric

octadecadienoates have been reported (26,27) only for the 9,12 isomers. The ¹³C NMR shifts of the compounds prepared were determined to confirm further the configurations of these compounds and to provide data for a complete series of geometrically isomeric dienoates containing a double bond β, γ to a terminal methyl group.

RESULTS AND DISCUSSION

For our syntheses, we treated cis- or trans-3-hexenyltriphenylphosphonium bromide (3a or 3b) with methyl 12-oxododecanoate-9,10-d₂ (5) to form the methyl 12,15-octadecadienoate-9,10-d₂ isomers (6) (see Reaction Scheme). Compounds 3a and 3b were prepared through the intermediary bromo compounds, 2a and 2b, from cis- or trans-3-hexenol (1a or 1b). Compound 5 was obtained by lead tetraacetate oxidation of methyl threo-12,13-dihydroxyoctadecanoate-9,10-d₂ which was obtained, in several steps, from Vernonia anthelmintica seed oil (21).

Complete reaction was not obtained between the ylid from 3 and the aldehyde ester 5 with sodium methoxide in dimethylformamide. Sodium methoxide in benzene or ethyl ether, however, gave isolated yields of 43-73% with about 90% cis geometry in the double bond generated.

The Wittig Reaction between 3 and 5 with butyl lithium in ethyl ether at room temperature gave isolated yields of 55-65% of isomers with about 80-85% cis geometry in the double bond generated. The reaction of 5 with the ylid generated from 3 and BuLi in Et₂O at -40°C, followed by equilibration with methanol and slow warm-up of the reaction mixture, gave 70-80% isolated yields of mixtures of isomers with 60-65% trans geometry about the double bond generated. Similar results were obtained at -78°C. If 5 is added to the ylid of 3 at 0°C, however, no equilibration to give more trans isomer occurs. Apparently, at temperatures below about -40°C, the equilibration proceeds more rapidly than the decomposition to products. At 0°C, the reverse appears to be true.

bond isomerization. Consequently, the methyl esters were converted to the corresponding triglycerides via their acid chlorides as described by Mattson and Volpenhein (32). Isolated yields of 80% (based on glycerol) or 64% overall yields (based on starting fatty ester) can be realized. An excellent review on acylglycerol synthesis has appeared (33).

The melting points of the isomeric acids, esters, and triglycerides are presented in Table 1.

The carbon-13 chemical shift values for all the carbons in the four isomers are listed in Table 2. The small effects the presence of deuterium would have on the spectra were not isolated and studied. The chemical shifts for the methoxy carbon and for C-1 through C-10 in the four isomers are the same, as would be expected (24). The values for C-11 and C-14 differ in the various isomers but are what would be expected (24,25) for carbons alpha to one (cis, δ 27; trans, δ 32.5) or two (cis,cis, δ 25.6; cis,trans, δ 30.5; trans,trans, δ 35.7) double

TABLE 1
Melting Points of Geometrically Isomeric 12,15-
Octadecadienoic-9,10-d₂ Acids, Their Methyl Esters, and
Triglycerides

Compound (18:2-9,10-d ₂)	Melting Point (°C)		
	Acid	Ester	Triglyceride
12- <u>cis</u> ,15- <u>cis</u>	17.5 ^a	-25.5	22
12- <u>trans</u> ,15- <u>cis</u>	28	-14	31
12- <u>cis</u> ,15- <u>trans</u>	22.5	-17	30
12- <u>trans</u> ,15- <u>trans</u>	44	-2.5	39

^a Literature (34) mp 18-18.5°C.

TABLE 2
Observed Chemical Shifts^a for the Isomeric Methyl 12,15-Octadecadienoates-9,10-d₂

Isomer ^b	Carbon Number																	
	1	2	3	4-10	11	12	13	14	15	16	17	18	OCH ₃					
12c,15c- 18:2	174.30	34.18	25.02	29.31-29.51	27.17	130.24	128.03	25.61	127.51	131.80	20.60	14.30	51.41					
12t,15c- 18:2	174.30	34.12	25.02	29.44-	32.43	130.83	128.36	30.35	127.25	132.06	20.47	14.30	51.34					
12c,15t- 18:2	174.30	34.18	25.02	29.31-29.57	27.04	130.50	127.84	30.48	127.51	132.38	25.61	13.84	51.41					
12t,15t- 18:2	174.30	34.18	25.02	29.31-29.96	32.50	131.15	128.68	35.68	127.77	132.58	25.61	13.91	51.41					

^a ppm Downfield from (CH₃)₄Si.

^b The abbreviation for a given compound in this table follows the pattern pg-N:d where d is the number of double bonds in a fatty acid chain of N carbons while p is the position and g is the geometry (cis or trans) of the double bond(s).

bonds, respectively. The values for C-17 are different from those of C-11 because of the proximity of this carbon to the methyl end of the chain.

EXPERIMENTAL

Reagents. cis-3-Hexenol from Bedoukian Research, Inc., Danbury, Conn.; trans-3-hexenol from Farchan Division, Chemical Samples Co., Willoughby, Ohio; butyl lithium from Alfa Division, Ventron Corporation, Danvers, Mass.; sodium methoxide from Harshaw Chemical Company, Cleveland, Ohio; tris-triphenylphosphine chlororhodium from Strem Chemicals, Inc., Danvers, Mass.; methyl threo-12,13-dihydroxy-cis-9-octadecenoate from Vernonia anthelmintica seed oil as previously described (21).

Gas-Liquid Chromatography. For analyzing mixtures of geometric isomers, glass column, 14 ft x 1/4 in., 15% OV 275 on 100:120 mesh Chromosorb P-AW-DMCS. For other analyses, aluminum column, 10 ft x 1/4 in., 15% EGSSX on 100:120 mesh Gas Chrom P.

Proton NMR. Proton magnetic resonance spectra were determined on a Varian XL-100 spectrometer.

Carbon-13 NMR. The ¹³C NMR spectra were recorded in 10-mm tubes at ambient probe temperature with a Bruker WH-90 Fourier Transform spectrometer operating at 22.6 MHz. The spectra were obtained from solutions in CDCl₃, which also served as the internal deuterium lock. Chemical shifts are reported as δ values (ppm downfield from TMS). Sweep widths of 6024 Hz with 4096 plot data points were used to give chemical shift values to within ±1.5 Hz, i.e., ±0.1 ppm. A pulse width of 5 μsec (ca. 30°) was used, and the computer data memory size (8192 addresses) limited the data acquisition to 0.68 sec. No pulse delays were used.

Melting Points. Melting points were determined on a Perkin Elmer Differential Scanning Calorimeter, Model DSC 1B.

cis-1-Bromo-3-hexene (2a). Triphenylphosphine (262 g; 1 mole) was dissolved with stirring in dimethylformamide (750 ml) in a 3-liter, 3-necked flask equipped with a mechanical stirrer, a thermometer, and an addition funnel. Bromine (50 ml; 156 g; 0.97 mole) was added over 1 hr to the clear colorless solution while the temperature was maintained at $20 \pm 2^\circ\text{C}$ by intermittent use of an ice bath. Then cis-3-hexenol (1a) (96 g; 0.96 mole) in DMF (50 ml) was added over 30 min while the temperature was maintained at 20°C by intermittent cooling. Volatile material was separated from triphenylphosphine oxide by distillation through a Dry Ice cooled condenser into a Dry Ice cooled receiver under a pressure of 0.15 torr and a maximum pot temperature of 80°C (oil bath). The distillate was treated as previously described (6) and distilled under reduced pressure to yield 2a (116.8 g; 74.6% yield) bp $64\text{--}67^\circ\text{C}/35\text{--}38$ torr, n_D^{25} 1.4680. ^1H NMR: δ 0.96 [t, CH_3]; δ 2.03 [m, CH_2CH_2]; δ 2.58 [m, $\text{CH}_2\text{CH}_2\text{Br}$]; δ 3.32 [t, CH_2Br]; δ 5.38 [m, $\text{CH}=\text{CH}$]. Literature (35), bp $67\text{--}68^\circ\text{C}/38$ torr, n_D^{20} 1.4715.

trans-1-Bromo-3-hexene (2b). In a manner similar to the conversion of 1a to 2a, trans-3-hexenol, (1b) was converted to 2b (bp $63\text{--}70^\circ\text{C}/35\text{--}38$ torr) in 64% yield. ^1H NMR: δ 0.98 [t, CH_3]; δ 2.02 [m, CH_2CH_2]; δ 2.54 [m, $\text{CH}_2\text{CH}_2\text{Br}$]; δ 3.37 [t, CH_2Br]; δ 5.50 [m, $\text{CH}=\text{CH}$]. Literature (36), bp $47^\circ\text{C}/20$ torr.

cis-3-Hexenyltriphenylphosphonium Bromide (3a). Xylene (10 ml) was added as an internal standard to triphenylphosphine (188.6 g; 0.72 mole), compound 2a (116.6 g; 0.715 mole), and acetonitrile (500 ml). The reaction mixture was heated at reflux for 30 hr, at which point only about 7% of the initial amount of 2a remained. The reaction mixture was worked up as described by Adlof and Emken (9) to give 3a (251 g; 82% yield) mp $165\text{--}166.5^\circ\text{C}$. ^1H NMR: δ 0.98 [t, CH_3]; δ 1.95 [m, CH_2CH_2]; δ 2.52 [m, $\text{CH}_2\text{CH}_2\text{P}$]; δ 3.53 [m, CH_2P]; δ 5.59 [m, $\text{CH}=\text{CH}$]; δ 7.94 [m, Ph_3]. Literature (35) mp $160\text{--}162^\circ\text{C}$.

trans-3-Hexenyltriphenylphosphonium Bromide (3b). In a manner similar to the conversion of 2a to 3a, 2b was converted to 3b in 84% yield, mp 167-168°C. ¹H NMR: δ0.85 [t, CH₃]; δ1.91 [m, CH₃CH₂]; δ2.37 [m, CH₂CH₂P]; δ3.83 [m, CH₂P]; δ5.49 [m, CH=CH]; δ7.76 [m, Ph₃].

Methyl threo-12,13-Dihydroxyoctadecanoate-9,10-d₂ (4). Methyl threo-12,13-dihydroxy-cis-9-octadecenoate (347 g; 1.06 mole) and [(C₆H₅)₃P]₃RhCl catalyst (10 g) in benzene (1 liter) were treated with deuterium gas as previously described (6). Removal of the benzene on a rotary evaporator gave a moist orange-red solid (375 g), which was dissolved in MeOH (750 ml) and filtered to remove spent catalyst. The MeOH was removed on a rotary evaporator to give a moist tan solid (326 g), mp 61-64°C. This material was washed with petroleum ether in portions (weight of compound/volume petroleum ether = 1:4) to give 4 as an off-white solid (251 g; 0.76 mole; 71% yield), mp 65-67°C.

¹H NMR: δ0.87 [m, CH₃CH₂]; δ1.25 [br.s., CH₂]; δ2.27 [t, CH₂COOCH₃]; δ3.35 [br.s., CHOH]; δ3.62 [s, COOCH₃]. A sample of this compound was converted to the dioxolane (37) with acetone and BF₃·MeOH and purified by passage with petroleum ether through a column of silica gel. Mass spectrometric analysis of the dioxolane of 4 showed 5.6% d₁, 90.3% d₂, and 3.4% d₃ (average number of deuterium atoms per molecule = 1.99).

Methyl 12-Oxododecanoate-9,10-d₂ (5). Compound 5, bp 118-128°C/0.16-0.25 torr, n_D²⁰ 1.4440, 2,4DNPH, mp 69.5-70.5°C, was obtained in 62% yield from compound 4 as previously described (6). The physical constants listed are close to those in the literature (38) for the undeuterated aldehyde ester.

Methyl 12,15-Octadecadienoate-9,10-d₂ Isomers: I. Without Stereoselective Modification of the Wittig Reaction. trans-3-Hexenyltriphenylphosphonium bromide (63.6 g; 0.15 mole), (3b), was slurried with ethyl ether (500 ml, dried over Linde molecular sieve 3A)

in a 1-liter, 3-necked flask equipped with a mechanical stirrer, a thermometer, and inlet and outlet adapters. A stream of dry N_2 was maintained through the apparatus during the reaction. Butyl lithium (2.1 N in hexane, 72 ml, 0.15 mole) was added rapidly by means of disposable syringes but with the temperature controlled to 20–23°C by an ice bath. A blood-red solution formed. Freshly distilled methyl 12-oxododecanoate-9,10- d_2 (5) (22.68 g; 0.125 mole), in ethyl ether (25 ml) was added over 20 min with the temperature maintained at 20–24°C by occasional use of an ice bath. During addition of 5, the reaction mixture went from the clear red solution through various shades of orange and yellow to a pale white slurry. One hour later, the reaction mixture was treated with saturated NaCl solution (400 ml) and the clear liquid was separated from gummy solid by filtration through glass wool. The Et_2O layer was separated and dried over anhydrous Na_2SO_4 . Removal of the drying agent and solvent gave a mixture (46.85 g) of solid and liquid which was extracted with hexane (1 x 100 ml, 1 x 50 ml). The hexane was removed on the rotary evaporator to give a cloudy amber liquid (37.4 g) which was placed on a column (3 x 50 cm) of silica gel (125 g) in hexane. Elution with hexane and with hexane/ Et_2O (98:2) gave a mixture (24.25 g; 65% yield) which was shown by GLC on OV 275 to consist of 6d, the trans,trans isomer (16%), and 6c, the cis,trans isomer (84%). This mixture was separated by partial silver resin chromatography (23) to give 3.12 g of 6d, methyl trans-12,trans-15-, and 15.17 g of 6c, methyl cis-12,trans-15-octadecadienoates-9,10- d_2 . Mass spectrometric analysis of 6c gave 2.5% d_0 , 6.1% d_1 , 84.9% d_2 , 3.3% d_3 , 2.8% d_4 (average number of deuteriums/molecule = 1.99).

In a similar manner, 3a (63.6 g; 0.15 mole) was allowed to react with 5 (28.74 g; 0.125 mole) to give a mixture (20.53 g, 55% yield) of trans,cis (19%) and cis,cis (81%) isomers from the silica gel column. This mixture was separated by partial silver resin chromatography into

6b, methyl trans-12,cis-15 (2.31 g) and 6a, methyl cis-12,cis-15-octadecadienoates-9,10-d₂ (11.65 g).

II. With Stereoselective Modification of the Wittig Reaction.

cis-3-Hexenyltriphenylphosphonium bromide, (3a) (43.5 g; 0.102 moles) was treated with butyl lithium (2.1 N in hexane; 49 ml; 0.102 mole) as described in Section I. Twenty minutes later, the reaction vessel was cooled in a Dry Ice-acetonitrile bath to -45 to -50°C. Freshly distilled methyl 12-oxododecanoate-9,10-d₂, (5), (19.6 g; 0.085 mole) in ethyl ether (25 ml) was added over 25 min while the temperature was maintained at -45 ± 2°C. The reaction mixture became thick and yellow-orange in color. Thirty minutes later, a sample was taken and added to saturated NaCl solution. GLC analysis of the upper Et₂O layer on OV 275 showed it to contain the 12,15-octadecadienoate isomers in the ratio trans,cis/cis,cis = 20:80. About 1 hr later, methanol (100 ml) was added over a period of 45 min so that the temperature did not rise above -41°C. The reaction mixture became clear and amber in color when 90 ml of MeOH had been added. Thirty minutes later a sample was added to brine, and GLC analysis of the ether layer on OV 275 showed the trans,cis/cis,cis ratio now to be 35:65. One hour later, stirring and N₂ flow were discontinued and the reaction mixture (now at -42°C) was permitted to warm up slowly overnight. GLC analysis of a sample taken the next morning showed the trans,cis/cis,cis ratio to be 60:40. The reaction mixture was washed with saturated NaCl solution, dried, concentrated, and extracted into hexane. Removal of the hexane left an amber liquid (25.5 g) which was placed on a column (3 x 55 cm) packed with silica gel (175 g) in hexane. Elution with hexane and with hexane/Et₂O (98:2) gave a mixture (19.98 g; 79% yield) of 6a and 6b. The mixture was separated by silver resin chromatography (23) to give 10.53 g of 6b, methyl trans-12,cis-15- and 6.35 g of 6a, methyl cis-12,cis-15-octadecadienoate-9,10-d₂ isomers. Mass spectrometric

analysis of 6a gave 1.5% d_0 , 5.8% d_1 , 86.9% d_2 , 3.6% d_3 , and 1.9% d_4 (average number of deuteriums/molecule = 1.99).

In a similar manner, 3b (46.6 g; 0.109 mole) was permitted to react with 5 (21.1 g; 0.09 mole) to give a mixture (18.78 g; 69% yield) of cis,trans (35%) and trans,trans (65%) isomers from the silica gel column. This mixture was separated on the silver resin column to give 4.41 g of 6c, methyl cis-12,trans-15- and 10.36 g of 6d, methyl trans-12,trans-15-octadecadienoate-9,10- d_2 isomers.

Proton Magnetic Resonance. All of the methyl 12,15-octadecadienoate-9,10- d_2 isomers showed the following signals: δ 0.95 [t, CH_3]; δ 1.26 [m, $(\text{CH}_2)_n$]; δ 1.95 [m, $\text{CH}_2\text{C}=\text{C}$]; δ 2.26 [t, $\text{CH}_2\text{C}=\text{O}$]; δ 3.60 [s, OCH_3]; δ 5.53 [m, $\text{CH}=\text{CH}$]. The signal for the CH_2 group between the two double bonds (C-14) appeared at δ 2.73 in the cis,cis-, at δ 2.68 in the cis,trans- and trans,cis- and at δ 2.62 in the trans,trans- isomers, confirming previous observations of Frost and Gunstone (39). Principal features of the ^1H NMR of the undeuterated cis,cis- isomer have been published (34).

Triglyceride of cis-12,trans-15-Octadecadienoic-9,10- d_2 Acid. Methyl cis-12,trans-15-octadecadienoate-9,10- d_2 (13.77 g; 0.046 mole) was saponified with KOH in aqueous ethanol to the acid (12.46 g; 95% yield). The acid was treated with freshly distilled oxalyl chloride for 24 hr and the acid chloride (12.4 g; 88% yield) was isolated as described by Mattson and Volpenhein (32). The acid chloride (0.039 mole) was added in portions to glycerol (1.17 g; 0.013 mole) and pyridine (3.2 ml; 3.1 g; 0.039 mole) in CH_2Cl_2 (25 ml). Twenty-four hours later, the reaction mixture was diluted with a mixture of equal volumes of hexane and ethyl ether, washed with HCl and with H_2O , and dried over anhydrous Na_2SO_4 . Removal of the drying agent and solvent gave a product (11.97 g), which was placed on a column (3 x 30 cm) of Florisil (Baker, 100-200 mesh, 100 g) in hexane. The column was eluted

with 500 ml portions of hexane, hexane/ethyl ether (98:2, 95:5, and 90:10) and with 100% ethyl ether. TLC analyses (100% Et₂O) showed triglyceride in the hexane/ethyl ether fractions and several components in the ether fraction. Yield of triglyceride was 8.47 g (80.6% based on glycerol, 64% overall based on ester).

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