SYNTHESES OF DEUTERATED METHYL 9,15-OCTADECADIENOATE AND METHYL 9,12,15-OCTADECATRIENOATE GEOMETRIC ISOMERS

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SUMMARY

Methyl 9,15-octadecadienoate-6,7-d_2 isomers (12) were obtained by Wittig coupling between methyl 9-oxononanoate-6,7-d_2 (6) and 6-nonenyltriphenylphosphonium bromide (11). Compound 11 was prepared from methyl 6-nonenoate (8) by reduction with sodium bis(2-methoxyethoxy)aluminum hydride, bromination with triphenylphosphine dibromide and further reaction with triphenylphosphine. Synthesis of compound 8 was achieved by Wittig coupling between propyltriphenylphosphonium bromide (7) and methyl 6-oxohexanoate (1) which was obtained by ozonolysis of cyclohexene. Compound 6 was prepared through the dimethoxy derivative from methyl 8-dioxanyloctanoate-6,7-d_2 (4) which was obtained by deuteration of methyl 8-dioxanyl-6-octenoate (3) with tris(triphenylphosphine)chlororhodium and deuterium gas. Compound 3 was obtained from compound 1 by chain extension with [2-(1,3-dioxan-2-yl)ethyl]triphenylphosphonium bromide (2). Chain extension of 6 with 2 yielded methyl 11-dioxanyl-9-undecenoate-6,7-d_2 (13). The latter was converted to methyl 12-oxo-9-dodecenoate-6,7-d_2 (15) which was treated with 3-hexenyltriphenylphosphonium bromide (16) and butyl lithium to give methyl 9,12,15-octadecatrienoate isomers (17). Geometric isomers formed during each of the Wittig reactions were separated by silver resin chromatography.

Key Words: Methyl 9,15-octadecadienoates-6,7-d_2; Methyl 9,12,15-octadecatrienoates-6,7-d_2; Wittig Reaction; Geometric Isomers; Silver resin chromatography; Carbon-13 NMR

INTRODUCTION

Methyl *cis*-9-,*cis*-15-octadecadienoate was prepared by hydrazine reduction of methyl linolenate and separated from its positional isomers by countercurrent distribution (CCD) (1). Isomerization of the *cis*-9, *cis*-15-isomer with selenium gave a mixture which was separated by CCD into the *cis*, *cis*, the *trans*, *trans*

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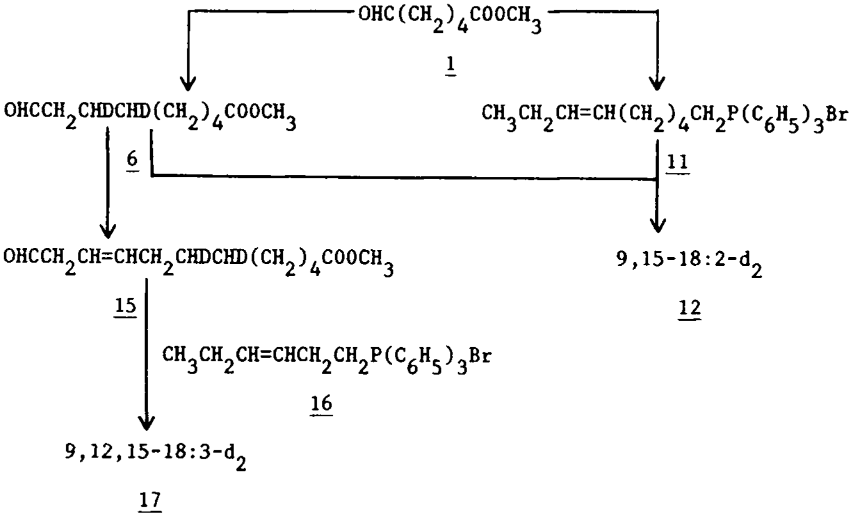
and a mixture of the *cis*, *trans* and *trans*, *cis* isomers (1). These compounds have been used as standards in a number of chromatographic (2) and hydrogenation studies (3). To date no one has prepared methyl 9,15-octadecadienoate isomers by synthesis from shorter chain precursors. In this report we describe a synthetic method for preparing any or all of the four geometric isomers of methyl 9,15-octadecadienoate and illustrate this method by the synthesis of methyl *cis*-9, *cis*-15- and *trans*-9, *cis*-15-octadecadienoate-6,7-d_2. We have prepared these deuterium-containing dienoates as part of our program for studying the metabolism in humans of isomeric fats formed during the hydrogenation of soybean oil (4,5).

We have reported the synthesis and characterization of all eight of the geometric isomers of methyl 9,12,15-octadecatrienoate(6). In this paper we describe a synthetic scheme for preparing deuterated methyl 9,12,15-octadecatrienoate isomers and illustrate it with the synthesis of methyl *cis*-9, *cis*-12, *cis*-15-, of *cis*-9, *trans*-12, cis-15-, and of *trans*-9, *cis*-12, *cis*-15-octadecatrienoates-6,7-d_2.

RESULTS AND DISCUSSION

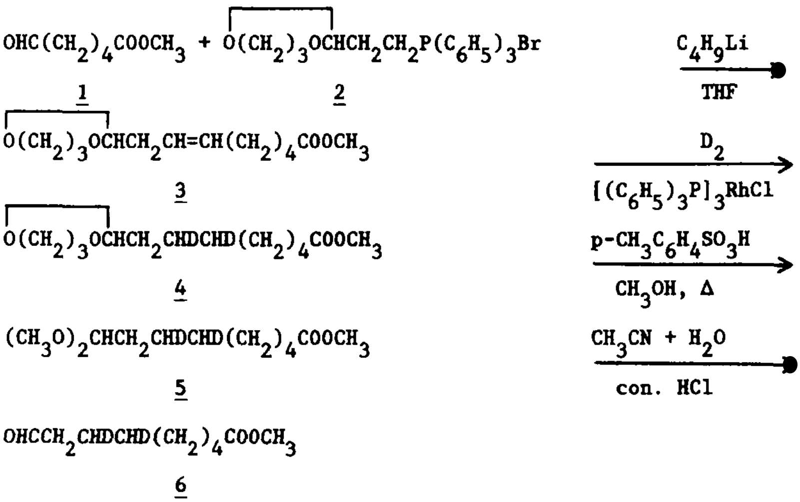
The syntheses of the 9,15-18:2-d_2 and the 9,12,15-18:3-d_2 compounds are summarized in Scheme 1.



Scheme 1

Methyl 9-oxononanoate-6,7-d_2 (6) is a common intermediate in both syntheses. When 6 is coupled via a Wittig reaction with 6-nonenyltriphenylphosphonium bromide (11) it yields the methyl 9,15-octadecadienoate-6,7-d_2 isomers (12). Alternatively it may be elongated, as described later, to form 15, methyl 12-oxo-9-dodecenoate-6,7-d_2, and then coupled in a Wittig reaction with 3-hexenyltriphenylphosphonium bromide (16) to yield the methyl 9,12,15-octadecatrienoate-6,7-d_2 isomers (17).

This scheme also shows another reagent common to the synthesis of both sets of compounds, namely methyl 6-oxohexanoate (1). This compound was obtained, through the aldehyde acid and acetal ester, from the ozonolysis of cyclohexene and was coupled, as shown in Scheme 2, via a Wittig reaction with



Scheme 2

[2-(1,3-dioxan-2-yl)ethyl]triphenylphosphonium bromide (2) with butyllithium in tetrahydrofuran (THF) to give 3, methyl 8-dioxanyl-6-octenoate as previously described (7). Deuterium gas was added at atmospheric pressure in the presence of Wilkinson's catalyst, $[(C_6H_5)_3P]_3RhCl$, by the method previously described (8) to give 4, methyl 8-dioxanyloctanoate-6,7-d_2 in 90% yield. Mass spectral analysis of 4 indicated a minimum of 95% d_2. Transacetalation of 4 with methanol and p-toluenesulfonic acid (9) gave 5, methyl 9,9-dimethoxynonanoate-

6,7-d_2 which was hydrolyzed to the aldehyde ester 6, methyl 9-oxononanoate-6,7-d_2 with concentrated HCl in aqueous acetonitrile by the method previously described (7).

The synthesis of compound 11, as diagramed in Scheme 3, started with

$$\underset{\underline{1}}{\mathrm{OHC(CH_2)_4COOCH_3}} + \underset{\underline{7}}{\mathrm{CH_3CH_2CH_2P(C_6H_5)_3Br}} \xrightarrow[\mathrm{THF}]{\mathrm{C_4H_9Li}} \underset{\underline{8}}{\mathrm{CH_3CH_2CH{=}CH(CH_2)_4COOCH_3}}$$

$$\xrightarrow{\mathrm{NaAlH_2(OCH_2CH_2OCH_3)_2}} \underset{\underline{9}}{\mathrm{CH_3CH_2CH{=}CH(CH_2)_4CH_2OH}} \xrightarrow{\mathrm{(C_6H_5)_3P{:}Br_2}}$$

$$\underset{\underline{10}}{\mathrm{CH_3CH_2CH{=}CH(CH_2)_4CH_2Br}} \xrightarrow[\mathrm{CH_3CN}]{\mathrm{(C_6H_5)_3P}} \underset{\underline{11}}{\mathrm{CH_3CH_2CH{=}CH(CH_2)_4CH_2P(C_6H_5)_3Br}}$$

$$\underline{11} + \underline{6} \xrightarrow[\mathrm{THF}]{\mathrm{C_4H_9Li}} \underset{\underline{12}}{\mathrm{CH_3CH_2CH{=}CH(CH_2)_4CH{=}CHCH_2CHDCHD(CH_2)_4COOCH_3}}$$

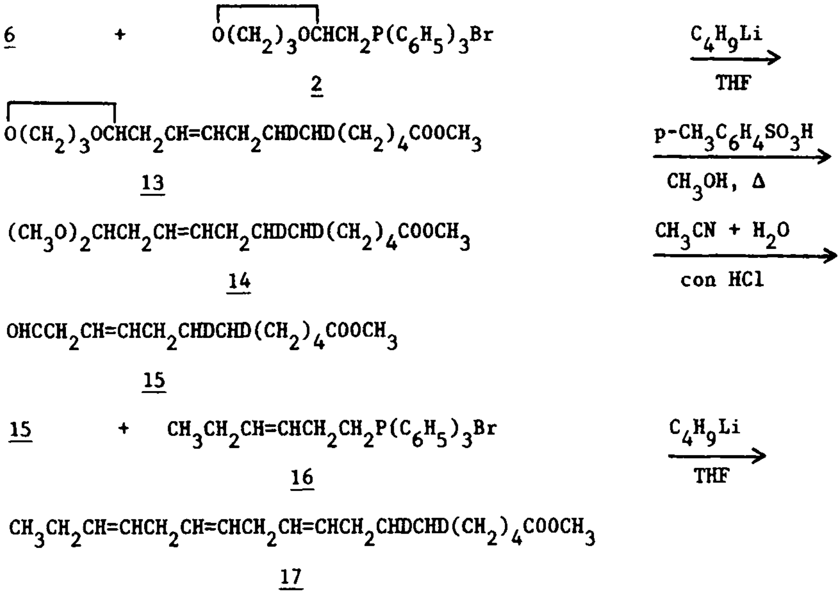
Scheme 3

methyl 6-oxohexanoate (1) which was coupled with propyltriphenylphosphonium bromide (7) via a Wittig reaction to give 8, methyl 6-nonenoate in 60% yield (80% cis, 20% trans). The cis and trans isomers were separated on a 100% Ag/H column.

Sodium bis(2-methoxyethoxy)aluminum hydride is a convenient reagent for reducing esters to alcohols. Its properties have been reviewed (10) and it is available commercially in toluene solution. As received, the solution is very viscous and was diluted with toluene for ease of handling. The cis and trans isomers of methyl 6-nonenoate (8) were individually reduced in 73% yield to the corresponding 6-nonenols (9) by this reagent.

Triphenylphosphine dibromide was used rather than phosphorus tribromide for conversion of 6-nonenol to 9-bromo-3-nonene (10) because it gave a much better yield (75% vs less than 50%). The bromide 10 was then converted to the phosphonium salt 11 with triphenylphosphine in acetonitrile in 85% yield. Compound 6 and compound 11 were then coupled via a Wittig reaction to give a mixture (54 to 46) of methyl trans-9, cis-15- and cis-9, cis-15-octadecadienoates-6,7-d_2 (12) containing over 95% d_2. These isomers were separated by silver resin chromatography on a 91% Ag/H column.

The carbon chain of 6 was extended three carbons, as shown in Scheme 4,



$$\mathbf{6} + \overline{O(CH_2)_3O}CHCH_2P(C_6H_5)_3Br\ (\mathbf{2}) \xrightarrow[THF]{C_4H_9Li}$$

$$\overline{O(CH_2)_3O}CHCH_2CH{=}CHCH_2CHDCHD(CH_2)_4COOCH_3\ (\mathbf{13}) \xrightarrow[CH_3OH,\ \Delta]{p\text{-}CH_3C_6H_4SO_3H}$$

$$(CH_3O)_2CHCH_2CH{=}CHCH_2CHDCHD(CH_2)_4COOCH_3\ (\mathbf{14}) \xrightarrow[con\ HCl]{CH_3CN + H_2O}$$

$$OHCCH_2CH{=}CHCH_2CHDCHD(CH_2)_4COOCH_3\ (\mathbf{15})$$

$$\mathbf{15} + CH_3CH_2CH{=}CHCH_2CH_2P(C_6H_5)_3Br\ (\mathbf{16}) \xrightarrow[THF]{C_4H_9Li}$$

$$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CHCH_2CHDCHD(CH_2)_4COOCH_3\ (\mathbf{17})$$

Scheme 4

by Wittig reaction of 6 with 2 to give 13, methyl 11-dioxanyl-9-undecenoate-6,7-d_2 in 46% yield. When the reaction was run near room temperature, the product mixture was 75% cis and 25% trans. When the Wittig reaction was run at -60°C, by the method previously described (11), the product mixture was 80% trans and 20% cis.

Compound 13 was transacetalized to the dimethoxy ester 14, the geometric isomers of which were separated by silver resin chromatography (12) on a 100% Ag/H column.

Difficulty was encountered in hydrolyzing 14, methyl 12,12-dimethoxy-cis-9-dodecenoate-6,7-d_2 to the aldehyde ester 15, methyl 12-oxo-cis-9-dodecenoate-6,7-d_2 without conjugation of the double bond with the carbonyl group. Various reagents, e.g., aqueous acetic acid, tetrahydrofuran containing tartaric acid or acetic acid, aqueous acetonitrile containing oxalic acid or hydrochloric acid, aqueous acetone containing oxalic acid or acetic acid, etc. all gave some conjugation or reacted slowly or not at all. With slow reactions, products other than conjugated isomers also appeared on the gas chromatogram. Since deacetalation with hydrochloric acid in aqueous acetonitrile is fairly rapid, it was used even though the ratio of nonconjugated to conjugated isomers formed in this case was 65 to 35. This mixture was used in the Wittig reaction with *cis*-3-hexenyltriphenylphosphonium bromide (16) both at ice bath temperature and at -60° to give the various methyl 9,12,15-octadecatrienoate isomers (17). These isomers were separated from each other and the conjugated isomers present by silver resin chromatography on a 62% Ag/Na column (12).

Carbon-13 nuclear magnetic resonance chemical shifts for the dienoate and

Table 1. ^{13}C-NMR chemical shifts for octadecadienoate and trienoate isomers.

Carbon Number	Compound 9*c*,15*c*	9*t*,15*c*	9*c*,12*c*,15*c*	9*c*,12*t*,15*c*	9*t*,12*c*,15*c*
1	174.20	174.20	174.05	174.05	174.20
2	34.20	34.10	34.05	34.05	34.20
3	25.05	24.95	24.95	24.95	25.10
4- 7	28.10- 30.10	28.45- 29.20	28.30- 29.30	28.30- 29.30	28.25- 29.20
8	27.15	32.40	27.10	26.95	32.45
9	129.20	129.25	130.15	130.40	130.95
10	129.85	130.35	127.70	127.65	128.10
11	27.15	32.40	25.65	30.35	30.50
12	(28.10-	(28.45-	128.25	128.85	128.20
13	30.10)	29.20)	128.25	128.85	128.65
14	27.15	26.95	25.55	30.25	25.60
15	129.20	129.25	127.10	127.05	127.30
16	131.70	131.60	131.85	132.15	132.00
17	20.50	20.50	20.55	20.40	20.65
18	14.30	14.35	14.20	14.20	14.30
OCH_3	51.30	51.40	51.25	51.20	51.40

trienoate isomers prepared are recorded in Table 1. The values are what would be expected for these compounds. The values reported for the deuterated trienoates compare within experimental error with those previously reported (6) for the undeuterated isomers.

EXPERIMENTAL*

Reagents. [2-(1,3-Dioxan-2-yl)ethyl]triphenylphosphonium bromide, butyl lithium, propyltriphenylphosphonium bromide, sodium bis(2-methoxyethoxy) aluminum hydride (Red-Al) and Sudan Red were obtained from Aldrich Chemical Company. tris(Triphenylphosphine)chlororhodium was obtained from Strem Chemicals. cis-3-Hexenyltriphenylphosphonium bromide (16) was prepared from cis-3-hexenol as previously described (11). Methyl 8-dioxanyl-6-octenoate (3) and methyl 6-oxohexanoate (1) were prepared as previously described (7).

Procedures. A 50 m x 0.25 mm OV275 WCOT capillary GC column or a 50m x 0.25 mm CPS-2 capillary column was used for analyzing binary mixtures of geometric isomers. For other analyses a 6 ft. x 4 mm column packed with 3% EGSSX on 100/120 Gas Chrom Q or a 6 ft. x 4 mm column packed with 3% OV101 on 80/100 Supelcoport was employed.

Silver Resin Chromatography. The macroreticular resin used for the separations was Rohm & Haas XN1010 sulfonic acid resin ground to the mesh sizes indicated. For the Ag/H columns, the indicated percentage of hydrogen ions was displaced by Ag ions (12). For the Ag/Na columns the hydrogen ions were displaced by sodium ions and then the indicated percentage of sodium ions was displaced by silver ions (13). The columns employed were: 100% Ag/H, 5 x 82 cm XN1010, 40/80 mesh; 91% Ag/H, 5 x 53 cm XN1010, 40/80 mesh; 62% Ag/Na, 0.76 x 70 cm XN1010, 80/120 mesh. Eluant was methanol.

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*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 not mentioned.

^{13}C-NMR. ^{13}C-NMR spectra were recorded with a Bruker WM 300 WB pulsed Fourier transform spectrometer operating at 75.5 MHz. Typically, 2500 transients were collected from solutions in $CDCl_3$, which served as both the internal lock and secondary reference, using 5 mm tubes. Sweep widths of 200 ppm and 8K real data points limited acquisition time to 0.54 s and were used to obtain chemical shift values to within ±1.85 Hz, i.e. ±0.05 ppm. A pulse width of 3 μs (40°) was employed with no delay between pulses. Decoupling power was held to approx. 1 W to provide adequate broadband decoupling power while minimizing sample heating. Chemical shifts [ppm downfield from $(CH_3)_4Si$] are 51.3 for the methyl ester carbon, 52.7 for the dimethyl acetal carbon and 66.8 and 25.9 for carbons α and β, respectively, to the oxygens of the dioxanyl group. Values for other carbons are presented in Table 1 or in the syntheses of the various intermediates.

Mass spectroscopy. Mass spectra were determined on a Nuclide 12-90-DF spectrometer with 70 eV ionizing energy.

6-Oxohexanoic Acid. A one-liter 3-neck flask was equipped with a mechanical stirrer, a low temperature thermometer, a condenser and a sparger. Into the flask were placed cyclohexene, (40.27 g, 50 ml, 490 mmol), glacial acetic acid (81 g, 77 ml, 1.35 mol), Sudan Red indicator solution (15 drops of 0.01 g Sudan Red in 10 g cyclohexane), and sufficient cyclohexane (*ca*. 750 ml) to fill the flask to the necks. The stirrer and sparger were set above the bottom of the flask to avoid plugging of the sparger or interference of stirring by the viscous material which forms. The pink solution was cooled to 3°C in an ice-salt bath with stirring. The sparger was connected to the output of a Welsbach ozone generator (117 v, 8 psi). A fog developed immediately. Three hours later, when the pink color had faded, the ozone flow was replaced by a flow of N_2 for about 5 min. Cyclohexane (*ca*. 700 ml) was decanted and acetic anhydride (190 ml) was added to the viscous mass, which eventually dissolved on stirring. Then 40 ml of 10% sodium acetate in glacial acetic acid was added slowly and carefully over 50 min while maintaining the temperature at 30-35°C with intermittent use of an ice bath. The reaction has an induction period and great care must be exercised at the beginning of the addition. When the exothermic reaction had subsided (ca. 30 min later) the product was transferred to a 500 ml round-bottom flask and distilled in batches at ca. 40 torr with a maximum oil bath temperature of 95°C. The distillate weighed 285 g and the material remaining in the flask, which weighed 81 g, was dissolved in ethyl ether (100 ml) and washed with H_2O (2 x 10 ml). The ether was removed on the rotary evaporator to give 76 g of liquid. Water (75 ml) was added and the mixture was heated by a boiling water bath for 1 hr. At ca. 40 torr a total of 81 g of distillate was obtained at the temperature of the boiling water bath. The orange liquid remaining in the flask (58.18 g) was distilled under reduced pressure to give 6-oxohexanoic acid (39.9 g, 62.5% yield) bp 100-117°C at 0.06 torr.

Methyl 6,6-Dimethoxyhexanoate. 6-Oxohexanoic acid (39.91 g, 307 mmol), trimethyl orthoformate (65.1 g, 67 ml, 614 mmol) and methanol (150 ml) were placed in a 500 ml round-bottom flask. Concentrated hydrochloric acid (10 drops) was added, the temperature rose to 38°C and the reaction mixture turned black. The flask was flushed with N_2 and capped. The next morning analysis by TLC on silica gel (Hexane: Ether: Acetic acid = 15:35: 6 drops) showed complete conversion to the acetal ester. The black liquid was concentrated to 56 g on a rotary evaporator, transferred to a separatory funnel with H_2O (100 ml) and extracted with ethyl ether (2 x 50 ml). The ether solution was washed with 5% $NaHCO_3$ (1 x 30 ml) and H_2O (2 x 30 ml) and dried (Na_2SO_4). Removal of the drying agent and solvent gave a black liquid (51 g) which was distilled at reduced pressure to give the title compound, (46 g, 79% yield) bp 62-65°C at 0.20 torr.

Methyl 8-Dioxanyloctanoate-6,7-d_2 (4). Methyl 8-dioxanyl-6-octenoate (3) (25.12 g, 104 mmol) was treated with deuterium gas in the presence of tris-(triphenylphosphine)chlororhodium by the method previously described (8) to give 22.9 g (90% yield) of compound 4, bp 110-120°C at 0.1 torr. Mass spectral analysis indicated a minimum of 95% d_2. ^{13}C NMR: 1, 173.9; 2, 34.9; 3, 24.8; 4-6, 28.6-28.8; 7, 23.2; 8, 33.9; 9, 102.2.

Methyl 9,9-Dimethoxynonanoate-6,7-d_2 (5) and Methyl 12,12-Dimethoxy-9-dodecenoate-6,7-d_2 (14). Compounds 5 and 14 were prepared by a method previously described (7) for the conversion of dioxanyl derivatives to dimethyl acetals. The geometric isomers of 14 were separated by silver resin chromatography on a 100% Ag/H column. ^{13}C NMR: Compound 5: 1, 174.2; 2, 34.1; 3, 25.0; 4-6, 28.0-29.6; 7, 25.0; 8, 32.5; 9, 104.8. Compound 14: 1, 174.2; 2, 34.1; 3, 25.0; 4-7, 28.2-29.1; 8*c*, 27.3; 8*t*, 32.5; 9*c*, 123.5; 9*t*, 124.3; 10*c*, 132.4; 10*t*, 133.6; 11*c*, 31.1; 11*t*, 36.3; 12, 104.5.

Methyl 9-Oxononanoate-6,7-d_2 (6). Compound 6 (b.p. 85-100° at 0.25 torr) was prepared in 67% yield by the method previously described (7). GC analysis on CPS-2 capillary column indicated 94.5% aldehyde ester, 2.4% dimethylacetal ester, and 1.6% dioxanyl ester. ^{13}C NMR: 1, 174.0; 2, 34.0; 3, 24.8; 4-6, 28.5-28.8; 7, 21.6; 8, 43.7; 9, 202.4.

Methyl 6-Nonenoates (8). Propyltriphenylphosphonium bromide (7) (19.25 g, 50 mmol) was slurried in tetrahydrofuran (150 ml) in a 500 ml 3-neck flask equipped with a mechanical stirrer, a thermometer and a nitrogen inlet and outlet. The reaction mixture was cooled in an ice bath and butyl lithium (2.5 M, 23 ml, 57.5 mmol) was added in portions. The temperature rose to 20°C and the reaction mixture became deep orange in color. Ninety minutes later methyl 6-oxohexanoate (1) (7.7 g, 53.4 mmol) was diluted with tetrahydrofuran (6 ml) and added to the reaction mixture. The temperature rose to 16° and the color faded to pale yellow. The ice bath was removed and 2 hr later the yellow liquid and solid were transferred to a separatory funnel and washed with saturated NaCl solution (100 ml). After separation, the aqueous layer was extracted with ethyl ether (2 x 25 ml) and dried (Na_2SO_4). The mixture was filtered and the solvent removed by distillation. Distillation under reduced pressure gave the product (5.17 g, 60% yield) bp 35-40°C at 0.1 torr (20% trans, 78% cis). This mixture can be separated by silver resin chromatography on 100% Ag/H column. ^{13}C NMR cis: 1, 174.0; 2, 34.1; 3, 24.7; 4, 29.3; 5, 26.8; 6, 128.6; 7, 132.1; 8, 20.6; 9, 14.2.

cis-6-Nonenol (9). Red-Al [sodium bis(2-methoxyethoxy)aluminum hydride] (45.27 g) was diluted with toluene (76 ml) for ease of handling. This solution contains 1.25 mmol reagent per ml of solution. The diluted Red-Al solution (51.5ml, 64.4 mmol) was placed in a 100 ml 3-neck flask equipped with a magnetic stirrer, a thermometer, a dropping funnel, and a nitrogen inlet and outlet and immersed in a water bath. Methyl cis-6-nonenoate (8) (8.75 g, 51.5 mmol) dissolved in toluene (5 ml) was added dropwise over 10 min. The temperature rose to 50°C. One and one half hours later the reaction mixture was transferred to a beaker and treated with 9N H_2SO_4 (25 ml) and H_2O (10 ml) and cooled in an ice bath. The gelatinous precipitate was filtered with difficulty. The precipitate was extracted several times with toluene and the combined organic layers were washed with saturated $NaHCO_3$ solution and dried (Na_2SO_4). The toluene was removed by distillation at atmospheric pressure and compound 9 (5.33 g, 73% yield) was obtained, bp 54-60°C at 0.2 torr. The trans isomer was prepared in a similar manner. ^{13}C NMR cis: 1, 63.0; 2, 32.8; 3, 25.5; 4, 29.6; 5, 27.1; 6, 129.0; 7, 131.8; 8, 20.6; 9, 14.3.

9-Bromo-cis-3-nonene (10). Triphenylphosphine (10.48 g, 40 mmol) was dissolved in CH_2Cl_2 (25 ml) in a 100 ml 3-neck flask equipped with a mechanical stirrer, a low temperature thermometer, a burette and a nitrogen inlet and outlet. The solution was cooled in an ice bath and bromine (2 ml, 39 mmol) was added over 14 min. A white solid formed. The ice bath was removed and was replaced one hr later. Then cis-6-nonenol (9) (5.33 g, 37.5 mmol) dissolved in CH_2Cl_2 (5 ml) was added over 6 min at 10°C. About 2 hr later the clear yellow solution was diluted with hexane and a white solid that formed was filtered. More $(C_6H_5)_3$ PO was formed as solvent was removed on the rotary evaporator. The organic layer was distilled through a short path still to give 10 (5.77 g, 75% yield) bp 50-58°C at 0.35 torr. ^{13}C NMR cis: 1, 33.7; 2, 32.8; 3, 26.9; 4, 28.9; 5, 27.8; 6, 128.7; 7, 132.0; 8, 20.5; 9, 14.3.

cis-6-Nonenyltriphenylphosphoniumbromide (11). 9-Bromo-cis-3-nonene (5.77 g, 28.1 mmol) was added to a solution of triphenylphosphine (12 g, 45.8 mmol) in acetonitrile (100 ml) in a 250 ml round-bottom flask equipped with a reflux condenser and magnetic stirrer. Xylene (2 ml) was added as an internal standard and the reaction mixture was heated at reflux by an oil bath for 29 hr. The progress of the reaction was monitored by GC on 3% OV101. The acetonitrile was removed on the rotary evaporator and the liquid remaining was triturated numerous times with ethyl ether before a sticky solid formed. This sticky solid was spread on a porous clay plate and the resultant fine powder was washed twice with ethyl ether and placed in a vacuum desiccator. Compound 11 was obtained (11.11 g, 85% yield) as a white solid, mp 71-73°C.

Methyl 9,15-Octadecadienoate-6,7-d_2 (12). cis-6-Nonenyltriphenylphosphonium bromide (11) (4.58 g, 9.83 mmol) was suspended in tetrahydrofuran (25 ml) in a 100 ml 3-neck flask equipped with a mechanical stirrer, a low temperature thermometer and a nitrogen inlet and outlet. The reaction mixture was cooled to 4°C with an ice bath and butyl lithium (5 ml, 13 mmol, 2.6 M) was added. The temperature rose to 25°C and the reaction mixture adopted a deep orange color. The ice bath was removed and 1 hr later the reaction mixture was cooled to -50°C in a Dry Ice-isopropyl alcohol bath. Methyl 9-oxononanoate-6,7-d_2 (6) (2.46 g, 13.1 mmol) in tetrahydrofuran (3 ml) was added over 2 min and the orange color was discharged . Thirty minutes later a sample was added to saturated NaCl solution. GC analysis on CPS-2 capillary column indicated 20% tc and 80% cc isomers. Thirty minutes later methanol (10 ml) was added over 10 min while maintaining the temperature at -50±2°C. GC analysis of a sample 1 hr later indicated 30% tc and 70% cc. The reaction mixture was packed with Dry Ice and allowed to warm up slowly overnight from -70°C.

analysis of a sample the next morning indicated 54% tc and 46% cc. The yellow liquid was transferred to a separatory funnel with saturated NaCl solution (25 ml) and the layers were separated. The aqueous layer was extracted with ethyl ether (10 ml) and the combined organic layers were dried (Na_2SO_4). Removal of the drying agent and solvent gave an oil which was triturated several times with fresh portions of hexane. The hexane was removed on the rotary evaporator to yield a crude product (2.47 g, 85% yield) which analyzed on the CPS-2 capillary column as 92% diene (54% tc and 46% cc). The product was purified further by passage through a column of silica gel and the isomers were separated by silver resin chromatography on a 91% Ag/H column. Mass spectral analysis indicated 95.8% d_2 and 3.6% d_1.

Methyl 11-Dioxanyl-9-undecenoate-6,7-d_2 (13). Compound 13 was prepared in 46% yield from [2-(1,3-dioxan-2-yl)ethyl]triphenylphosphonium bromide and methyl 9-oxononanoate-6,7-d_2 (6) by the method previously described (7). It boiled at 135-146°C at 0.05 torr. When the reaction was run at ice bath temperature the product mixture was 75% cis and 25% trans and when it was run at -60°C the product mixture was 20% cis and 80% trans. ^{13}C NMR: 1, 174.2; 2, 34.3; 3, 25.0; 4-7, 28.3-29.2; 8c, 27.3; 8t, 32.5; 9c, 123.2; 9t, 124.0; 10c, 132.5; 10t, 133.6; 11c, 33.6; 11t, 38.8; 12, 102.2.

Methyl 12-Oxo-cis-9-dodecenoate-6,7-d_2 (15). Methyl 12,12-dimethoxy-cis-9-dodecenoate-6,7-d_2 (14) (4.03 g, 14.6 mmol) was dissolved in water (10 ml) and acetonitrile (32 ml). Then concentrated HCl (10 drops) was added and the reaction was monitored by shaking a sample with saturated $NaHCO_3$ solution and extracting with CH_2Cl_2. This extract was then analyzed on a 3% EGSSX column. After 135 min of stirring at room temperature the reaction mixture was transferred to a separatory funnel with saturated $NaHCO_3$ solution (15 ml) extracted into CH_2Cl_2 and dried (Na_2SO_4). GC analysis indicated the ratio of non-conjugated to conjugated isomers was about 65 to 35. This mixture was used in the Wittig reaction.

Methyl 9,12,15-Octadecatrienoate-6,7-d_2 (17). cis-3-Hexenyltriphenylphosphonium bromide (16) (7 g, 16.5 mmol) was suspended with stirring in tetrahydrofuran (75 ml) in a 250 ml 3-neck flask equipped with a mechanical stirrer, a low temperature thermometer and a nitrogen inlet and outlet. The reaction mixture was cooled to 5°C with an ice bath and butyl lithium (12 ml, 30 mmol, 2.5 M) was added. The temperature rose to 26°C and the mixture assumed a deep red-orange color. The reaction mixture was cooled to -63°C in a Dry Ice-isopropyl alcohol bath and impure methyl 12-oxo-cis-9-dodecenoate-6,7-d_2 (3 g, 13.2 mmol) in tetrahydrofuran (5 ml) was added over 2 min. The temperature rose to -58°C and the color changed to light tan. Thirty minutes later a sample was treated with saturated sodium chloride solution. GC analysis on the CPS-2 column showed numerous peaks, probably representing several conjugated isomers as well as the desired methylene interrupted isomers. The 9c12t15c and 9c12c15c isomers (about 32% of the mixture) were in the ratio of 6 to 94. Thirty minutes later methanol (10 ml) was added over 2 min while the temperature rose from -67 to -60°C. The reaction flask was packed with Dry Ice and allowed to warm up slowly overnight. The amber liquid containing a small amount of fine white solid was shaken with saturated NaCl solution (50 ml) and the layers were separated. The aqueous layer was extracted with ethyl ether (10 ml), the combined organic layers were dried (Na_2SO_4) and filtered and the solvent was removed on the rotary evaporator. The thick oil remaining was triturated several times with fresh portions of hexane. GC analysis on the CPS-2 column showed the ctc and ccc isomers (about 57% of the mixture) in the ratio 46 to 54. The ratios of the other peaks also changed indicating they also had undergone isomerization. The hexane solution was passed through a column of silica gel. The product eluted with hexane and hexane/ethyl ether = 98/2 weighed 0.71 g and analysis on the CPS-2 column indicated the isomers in the same ratio as before and comprising about 63% of the mixture. The mixture was separated in approximately 200 μl portions on a 62% Ag/Na column (0.76 x 70 cm, 80/120 mesh XN1010). Mass spectral analysis indicated 94% d_2, 4.7% d_1.

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