SYNTHESES OF SOME DI-, TETRA-, AND HEXADEUTERIO-OCTADECENOATES

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SUMMARY

(E&Z)-10-Octadecenoic-13,14-d_2,   -14,15-d_2,   and
-14,14,15,15-d_4 acids were prepared by Wittig synthesis.
(E&Z)-11-Octadecenoic-14,14,15,15,17,18-d_6 acids were prepared
by Wittig synthesis and by synthesis and reduction of 11-
octadecynoic-14,14,15,15,17,18-d_6 acid. Overall yield in
11-octadecenoate-d_6 synthesis was better by the Wittig
procedure (25% vs. 15%). The Wittig-produced 11-octadecenoates
had higher hexadeuterio contents than the acetylenic sequence
products (85% vs. 70%) but the average isotopic purity was
similar (5.9 D/mole). The Wittig method appears better for
deuterium-labelled octadecenoate synthesis.

KEY WORDS: Methyl (E&Z)-10-octadecenoates-13,14-d_2, methyl (E&Z)-10-

octadecenoates-14,15-d_2,   methyl   (E&Z)-10-octadecenoates-14,14,15,15-d_4,

11-octadecynoic acid-14,14,15,15,17,18-d_6, methyl (E&Z)-11-octadecenoates-

14,14,15,15,17,18-d_6.

INTRODUCTION

A series of deuterated octadecenoic acids have been synthesized for

studies of the distribution of isomeric octadecenoic acids in human blood

fractions (1-5). With the synthesis reported here, the preparation of the

(E&Z)-isomers having double bonds in positions 8-13 and with 2, 4, or 6 deuterium

atoms has been completed.

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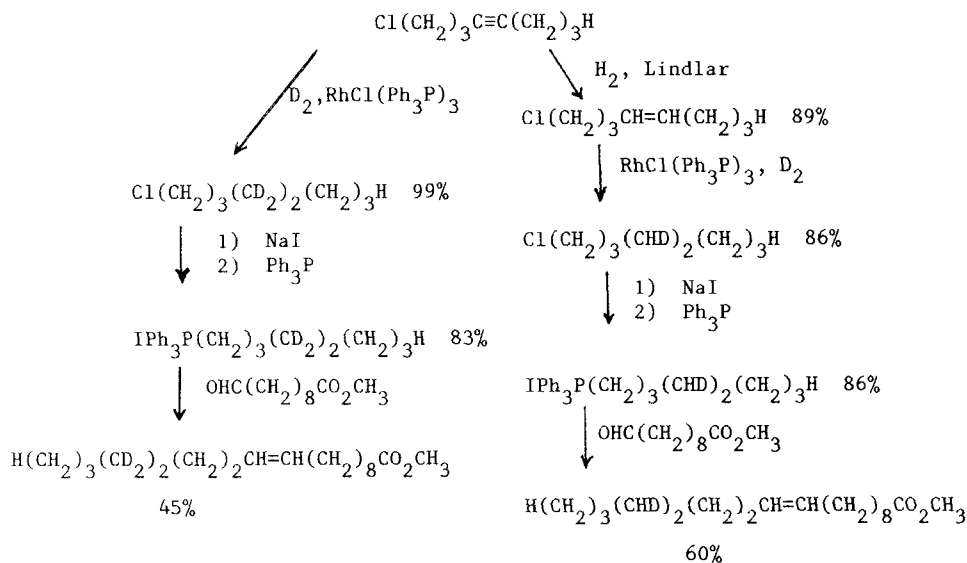or similar products not mentioned.

RESULTS AND DISCUSSION

Tetradeuterated methyl (E&Z)-10-octadecenoates were prepared from 1-chloro-4-octyne (Figure 1, left column). The chlorooctyne was saturated with deuterium gas employing tris(triphenylphosphine)chlororhodium. The resulting 1-chlorooctane-4,4,5,5-$\underline{d}_4$ was converted to the iodide and then to the corresponding triphenylphosphonium iodide. The phosphonium iodide by Wittig reaction with methyl 10-oxodecanoate gave methyl (E&Z)-10-octadecenoates of which 93% was the (Z)-isomer. The (E)-isomer was additionally obtained by stereoisomerization of the (Z)-isomer.

Methyl (E&Z)-10-octadecenoates-14,15-$\underline{d}_2$ were prepared from 1-chloro-4-octyne by partial reduction to 1-chloro-4-octene and then application of a similar reaction sequence to that used in preparing the tetradeuterated isomers (Figure 1, right column).
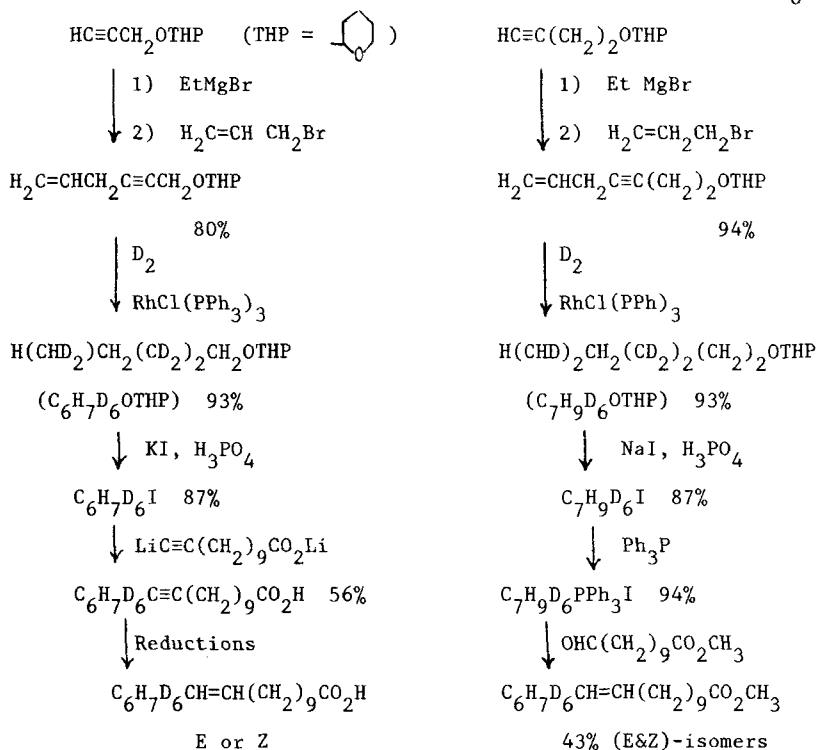
Figure 1

Preparation of Methyl (E&Z)-10-Octadecenoates-14,15-$\underline{d}_2$

and -14,14,15,15-$\underline{d}_4$

$$Cl(CH_2)_3C\equiv C(CH_2)_3H$$

D_2,RhCl(Ph$_3$P)$_3$ H_2, Lindlar

$$Cl(CH_2)_3CH=CH(CH_2)_3H \quad 89\%$$

$$Cl(CH_2)_3(CD_2)_2(CH_2)_3H \quad 99\%$$

RhCl(Ph$_3$P)$_3$, D$_2$

1) NaI
2) Ph$_3$P

$$Cl(CH_2)_3(CHD)_2(CH_2)_3H \quad 86\%$$

1) NaI
2) Ph$_3$P

$$IPh_3P(CH_2)_3(CD_2)_2(CH_2)_3H \quad 83\%$$

OHC(CH$_2$)$_8$CO$_2$CH$_3$

$$IPh_3P(CH_2)_3(CHD)_2(CH_2)_3H \quad 86\%$$

OHC(CH$_2$)$_8$CO$_2$CH$_3$

$$H(CH_2)_3(CD_2)_2(CH_2)_2CH=CH(CH_2)_8CO_2CH_3$$

45%

$$H(CH_2)_3(CHD)_2(CH_2)_2CH=CH(CH_2)_8CO_2CH_3$$

60%

Methyl (E&Z)-10-octadecenoates-13,14-$\underline{d}_2$ were prepared from the tetrahydropyranyl (THP) ether of 3-octyn-1-ol by Lindlar-catalyzed partial reduction followed by deuteration with $RhCl(Ph_3P)_3$ as catalyst. The resultant 2-(octyl-3,4-$\underline{d}_2$) tetrahydropyran was converted to the iodide and by subsequent Wittig synthesis to (E&Z)-10-octadecenoates 13,14-$\underline{d}_2$ in 42% yield.

Figure 2

Preparation of (E&Z)-11-Octadecenoic-14,14,15,15,17,18-$\underline{d}_6$ Acids

Hexadeuterated methyl (E&Z)-11-octadecenoates were prepared by the two sequences shown in Figure 2. An acetylenic synthesis was carried out as indicated in the left column of the figure. A new synthesis was developed to prepare 11-dodecynoic acid (7). The acetylenic acid was alkylated (8,9) with hexadeuterio-1-iodohexane to give 11-octadecynoic-14,14,15,15,17,18-$\underline{d}_6$ acid which was reduced with Li in ammonia to hexadeuterated (E)-11-octadecenoic acid, $\underline{1}$, and with $Pd/BaSO_4$ or with Lindlar's catalyst to the (Z) isomer, $\underline{2}$.

An alternative synthesis of 11-octadecynoic-d_6 acid through hexadeuterio-1-octyne and its alkylation by 10-iododecanoic acid gave only 35% yield vs. 56% from alkylation of 11-dodecynoic acid. Attempts to alkylate 1-octyne-d_6 with the iodomagnesium salt of 10-iododecanoic acid gave low conversions.

Hexadeuterated (E&Z)-11-octadecenoates were also prepared by the Wittig sequence as indicated in the right-hand column of Figure 2. Alkylation of the bromomagnesium salt of the THP ether of 3-butyn-1-ol with allyl bromide gave the THP ether of 6-hepten-3-yn-1-ol which was deuterium-saturated and converted to 1-iodoheptane-3,3,4,4,6,7-d_6. Wittig reaction sequence with methyl 11-oxo-undecanoate gave a mixture of methyl esters of 1 and 2 (93% 2).

The hexadeuterio-contents (Table 1) of the methyl esters of 1 and 2 derived from the Wittig procedure were found to be higher than those of 1 and methylated 2 from reduction of 11-octadecynoic-d_6 acid. Furthermore, reduction products 1 and 2 of the acetylenic acid, showed inexplicable scatter over that found in their common precursor, the THP ether of 1-hexanol-d_6 (Table 1). The possibility of exchange is excluded by the relatively constant average deuterium per mole. Since 11-octadecynoic acid could not be analyzed for deuterium due to triple-bond migration, it was reduced with azodicarboxylic acid to a mixture of octadecanoic, octadecenoic, and octadecynoic acids. The octadecanoic-d_6 acid was separated by argentation chromatography for MS analysis which showed the acid to have scatter intermediate between hexyloxy-d_6 THP and that of 1 and 2. Thus, deuterium scatter appears to result during the alkylation and reduction steps. Based upon these results, it would appear that the better procedure for preparation of deuterium-labelled octadecenoates is the Wittig sequence.

TABLE 1

Deuterium distributions

| Octadecenoate | Number of deuterium atoms[a] | | | | | | | | | Average |
	0	1	2	3	4	5	6	7	8	
Methyl-10-[b]	2	1	3	4	85	0.3	1	1	0	3.9
Methyl-10-[b]	4	7	76	8	3	1	1	0	0	2.0
Methyl-10-[b]	6	2	89	1	1	0	0	0	0	1.9
Methyl-11-[b]	2	0	2	0	2	5	86	3	1	5.9
Methyl-(Z)-11[c]	0	0	1	1	3	8	71	10	4	6.0
(E)-11-acid[c]	0	0	2	1	4	8	71	9	3	5.9
2-(Hexyloxy) THP	0	0	0	0	1	6	88	5	0	5.9
Methyl octadecanoate[c]	1	1	1	1	2	8	75	10	1	5.9

[a] Table figures in percent, except under average.

[b] Wittig products (resp. 14,14,15,15-$\underline{d}_4$, 14,15-$\underline{d}_2$, 13,14-$\underline{d}_2$ and

14,14,15,15,17,18-$\underline{d}_6$.

[c] From 11-octadecynoic -$\underline{d}_6$ and reduction.

EXPERIMENTAL

The structures of synthesized compounds were confirmed by ^{1}H and ^{13}C NMR spectra and/or IR. Melting points are uncorrected. Preparative argentation separations were carried out on a 6 ft x 2 inch column packed with fully-silvered XN1010 ion exchange resin.

1-Chlorooctane-4,4,5,5-$\underline{d}_4$. 1-Chloro-4-octyne was reduced with D_2 using RhCl(Ph$_3$P)$_3$ by previously used method (1) in 99% yield.

2-Iodooctane-4,4,5,5-$\underline{d}_4$. Refluxing 1-chlorooctane-$\underline{d}_4$ with excess NaI in 2-butanone overnight gave a 93% yield.

1-Octyl-4,4,5,5-$\underline{d}_4$ triphenylphosphonium Iodide. Refluxing 1-iodooctane-$\underline{d}_4$ with excess Ph$_3$P in acetonitrile gave a 94% yield of phosphonium salt, m.p. 73-4°C.

Methyl (E&Z)-10-Octadecenoates-14,14,15,15-d_4. In a dry flask fitted with a N_2-inlet, stirrer, thermometer, and addition funnel protected by a drying tube were placed 120.9 g (0.24 mole) 1-octyltriphenylphosphonium iodide and 400 mL of dry DMF. The mixture was stirred under N_2 until the solid dissolved and then 12.9 g (0.239 mole) of freshly prepared NaOCH$_3$ was added. The orange slurry was stirred ½ hr and then 45.2 g (0.239 mole) methyl 10-oxodecanoate was added over 1 hr. The mixture was stirred 3/4 hr and then poured into 1 L pH 2 water. The product was taken up by extraction with 5, 100-mL portions of PE (35-60°C). The PE extracts were washed with 1 L water and dried over Na$_2$SO$_4$. The oily residue from evaporation of the PE was distilled to give 38.7 g of oil (bp. 120-160°C/0.05 mm Hg). GC analysis indicated the oil to consist largely of methyl 10-octadecenoates (83%) and methyl 10-oxodecanoate (14.6%). The aldehyde-ester was largely removed by extraction of an ether solution of the esters with two 100-mL portions of saturated NaHSO$_3$ solution. This procedure gave 29.8 g of 95% pure methyl 10-undecenoates. Finally purification and separation of the E&Z-isomers was effected by argentation chromatography to yield 24.2 g of pure (Z)-isomer and 2.7 g of pure (E) isomer in 34 and 4% yields, respectively.

Additional amounts of the (E)-isomer were prepared by isomerization (10). Thus, from 24.2 g of (Z)-isomer there were obtained 16.2 g (67%) of pure (E)-isomer and 3.5 g (14.6%) of (Z)-isomer following isomerization and argentation chromatography.

1-Chlorooctane-4,5-d_2. Deuteration of 88 g (0.6 mole) 1-chloro-4-octene with 7 g RhCl (Ph$_3$P)$_3$ catalyst in 1 L benzene by a previous procedure (1) gave 78.0 g 1-chlorooctane-4,5-d_2 of 99.6% GC purity, 86.3% yield.

(1-Octyl-4,5-d_2) triphenylphosphonium Iodide. 1-Chlorooctane-d_2 (60.3 g, 0.4 mole) was heated at reflux for 11 hr with 65 g (0.43 mole) NaI in 350 mL CH$_3$CN. Then 113 g (0.43 mole) Ph$_3$P was added and the mixture was filtered and the filtrate triturated with 1 L and two 500-mL portions of ether. Each portion of ether was decanted. The crystals which formed were filtered and

stirred with three 500-mL portions of ether. The yield was 188.5 g (93.4%)
m.p. 74-75°C.

Methyl (E&Z)-10-Octadecenoates-14,15-$\underline{d}_2$. Wittig synthesis between 141 g
(0.28 mole) 1-octyl-4,5-$\underline{d}_2$-triphenylphosphonium iodide and 60 g (0.3 mole)
methyl 10-oxo-decanoate as described above for preparation of 10-octadecenoates-
14,14,15,15-$\underline{d}_4$ gave 31.9 g (60%) of (E&Z)-10-octadecenoates-$\underline{d}_2$. The isomers
were separated by argentation chromatography to give 18.4 pure (Z)-isomer and
1.9 g (E)-isomer. Isomerization (10) of 18.5 g of a mixture of the (E&Z)-
isomers followed by argentation chromatography gave 12.3 g of the (E)-isomer.

2-(3-Octenyloxy)tetrahydropyran. Hydrogenation of 2(3-octynyloxy)
tetrahydropyran over Lindlar's catalyst gave a quantitative yield of 2-(3-
octenyloxy)tetrahydropyran (pure by GC).

2-(Octyl-3,4-$\underline{d}_2$)tetrahydropyran. Deuteration by previous method ($\underline{1}$) gave
98% yield of 2-(octyl-3,4-$\underline{d}_2$) tetrahydropyran.

1-Iodooctane-3,4-$\underline{d}_2$. Treatment of the previous product with H_3PO_4-KI
(12) gave 1-iodooctane-3,4-$\underline{d}_2$ in 73% yield.

1-Octyl-3,4-$\underline{d}_2$ triphenylphosphonium iodide. The previous product refluxed
in acetonitrile overnight with 10% excess Ph_3P gave a 99% yield of the phosphonium
salt (m.p. 75-77°C) following purification by trituration in ether.

Methyl (E&Z)-10-Octadecenoates. Wittig synthesis between 1-octyl-3,4-$\underline{d}_2$
triphenylphosphonium iodide and methyl 10-oxodecanoate as for 10-octadecenoate-
$\underline{d}_4$ above gave a 42% yield of (Z&E)-10-octadecenoates-13,14-$\underline{d}_2$ (90% Z) which
were separated by argentation chromatography.

2-(5-Hexene-2-ynyloxy)tetrahydropyran. This compound was prepared by a
published method (11) in 80% yield.

2-(Hexyloxy-2,2,3,3,5,6-$\underline{d}_6$)tetrahydropyran. The deuteration of 2-(5-
hexen-2-ynyloxy)tetrahydropyran was achieved by use of RhCl $(Ph_3P)_3$ (1) after
20 hr in 93% yield.

1-Iodohexane-2,2,3,3,5,6-$\underline{d}_6$. Treatment of 2-(hexyloxy-$\underline{d}_6$) tetrahydropyran
with H_3PO_4-NaI (12) gave 87% of the corresponding iodide.

10-Hydroxydecanoic Acid. A flask fitted with gas-dispersion tube, mechanical
stirrer, thermometer, and reflux condenser and cooled with a Dry Ice bath was
charged with a solution of 198.3 g (1.0 mole) methyl 10-undecenoate in 1.5 L
methanol. At 10°C 3% ozone in oxygen was bubbled through at 3 L/min. After
4 hr, the ozone flow was stopped and the solution was sparged for 15 min with
N_2. Sodium borohydride (45 g) was added in portions at 5-10°C. The solution
was allowed to stand for 13 hr and then heated at reflux with 200 mL 5N aq.
KOH. About 1 L methanol was evaporated and the residue was taken up in 1.5 L
H_2O and acidified with 5N H_2SO_4. The product was extracted with 6, 150 mL
portions of ether, washed with saline, and dried over Na_2SO_4. The ether
solution was filtered, concentrated to 400 mL and diluted with 600 mL PE. The
separated crystals (211.8 g) had m.p. 70-2°C. Recrystallization from PE-ether
gave 155.3 g (77%) colorless solid, m.p. 71-3°C (reported 75-6°C) (13). GC
analysis of a methylated sample showed a purity of 93%, sufficient for further
synthesis.

10-Iododecanoic Acid. Treatment of 10-hydroxydecanoic acid with H_3PO_4-KI
(12) gave 95% 10-iododecanoic acid, m.p. 46-9°C (m.p. 49-50°C) (14).

11-Dodecynoic Acid. Treatment of 11-iododecanoic acid with lithium
acetylide ethylenediamine (6) gave 86% of 11-dodecynoic acid, m.p. 44-45°C
(reported 44-46°C) (15).

11-Octadecynoic-14,14,15,15,17,18-d_6 Acid. Alkylation (8,9) of 11-
dodecynoic acid with 1-iodohexane-2,2,3,3,5,6-d_6 gave the d_6-acid in 46%
yield, crystals from PE-ether, m.p. 45-46°C (reported 45.5-46.5°C for undeuterated
acid) (17).

(E)-11-Octadecenoic-14,14,15,15,17,18-d_6 Acid (1). This acid was obtained
in 77% yield by reduction with Li in liquid ammonia according to Barve &
Gunstone (17), m.p. 43-43.5°C identical to that of the undeuterated isomer.

(Z)-11-Octadecenoic-14,14,15,15,17,18-d_6 Acid (2). A sample (0.5 g) of
11-octadecynoic-d_6 acid was reduced in 10 mL benzene over 0.1 g. Lindlar's

of the PE gave 2.0 g which was partially separated by argentation chromatography.
The methyl octadecanoate fraction was analyzed by MS.

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catalyst and 0.1 g dry quinoline. The hydrogenation was monitored with an automatic manometer and gave theoretical uptake in ½ hr. GC analysis of a methylated sample showed 2.2% acetylenic acid remaining and 1.5% of 1.

A similar sample (0.5 g) of 11-octadecynoic-d_6 acid was reduced in 10 ml pyridine with 0.1 g 5% Pd/BaSO$_4$. Reduction was completed in ¼ hr. Analysis by argentation chromatography and GC indicated ca. 8.1% stearate and 8.5% 1 were present. A sample was purified by argentation chromatography for MS.

2-(6-Hepten-3-ynyloxy)tetrahydropyran. Treatment of 2(3-butynyloxy) tetrahydropyran with ethylmagnesium bromide and then allyl bromide (11) gave an 84% yield, purity 98% (GC).

2-(1-Heptyloxy-3,3,4,4,6,7-d_6)tetrahydropyran. Deuteration of hepten-3-ynyloxytetrahydropyran by previous method (1) gave a 93% yield.

1-Iodoheptane-3,3,4,4,6,7-d_6. Treatment of 2-(1-heptyloxy-d_6)tetrahydropyran with H$_3$PO$_4$-NaI (3) gave 87% of the corresponding iodide.

1-Heptyl-3,3,4,4,6,7-d_6 triphenylphosphonium Iodide. The phosphonium salt was obtained in 94% yield (2), m.p. 129-132°C, by refluxing the previous product with 10% excess Ph$_3$P as for octyl-d_4 phosphonium salt above.

Methyl 11-Oxoundecanoate. Methyl 11-hydroxyundecanoate was oxidized (18) to give the aldehyde-ester in 80 to 96% yields.

Methyl (E&Z)-11-Octadecenoates-14,14,15,15,17,18-d_6. Wittig synthesis between methyl 11-oxoundecanoate and heptyl-d_6 phosphonium salt gave 43% of a mixture of (E&Z)-isomers (93% Z). The octadecenoates were separated by argentation chromatography. Methyl (E)-11-octadecenoate-d_6 was additionally prepared by isomerization of the (Z)-isomer (10).

Methyl Octadecanoate-14,14,15,15,17,18-d_6. A flask fitted with magnetic stirrer, N$_2$-inlet, drying tube and addition funnel was charged with 2.0 g (10.3 mmole) potassium diazodicarboxylate. A solution of 0.19 g (0.65 mmole) methyl octadecynoate-d_6 in 30 ml dry pyridine was added. The resultant slurry was vigorously stirred under N$_2$ for 2 hr while 2 ml (35 mmole) acetic acid was added. The mixture was decomposed in water and extracted with PE. Evaporation