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The Synthesis of 11,11-Dideuterooleic Acid *

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SUMMARY

The synthesis of 11,11-dideuterooleic acid is described. The Wittig reaction is used to introduce the carbon-carbon double bond, giving a mixture of which better than 90 % is the desired cis-*isomer. Two alternative routes gave deuterium incorporation of 95 and >98 %* d_2.

INTRODUCTION.

Oleic acid (*cis*-9-octadecenoic acid) is the most widely distributed and most abundant fatty acid in nature. The synthesis of the labelled compound 11,11-dideuterooleic acid (1a, R = H) was undertaken so that this material could be used in enzymatic investigations.

$$CH_3(CH_2)_6CD_2CH = CH(CH_2)_7CO_2R$$

1a, R = H
1b, R = CH_3

DATA AND DISCUSSION.

Several routes for the stereospecific synthesis of unsaturated fatty acids and their derivatives have been reported [1]. Perhaps the simplest of these methods is that reported by Bergelson *et al.* [2, 3] in which the Wittig reaction

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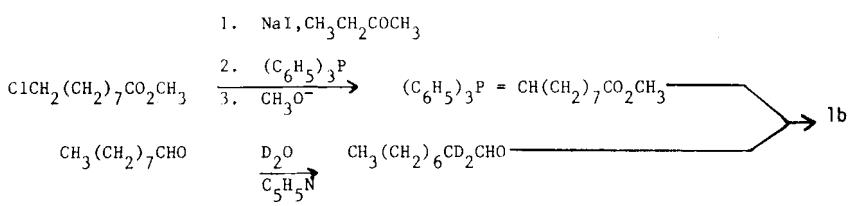
is employed to introduce the unsaturation. Although the Wittig reaction was generally considered to be non-stereospecific and to produce largely *trans* olefin [4, 5], it has been found possible to control the reaction to give predominantly the thermodynamically less stable *cis*-olefins [6, 7]. This is borne out by the present investigation in which *cis*-product is obtained in greater than 92 % yield *.

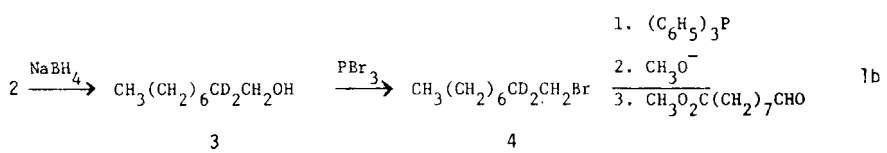
Corey's convenient modification of the Wittig reaction (methylsulfinyl carbanion-dimethylsulfoxide [8, 9] was not employed for the synthesis of the labelled oleic acid. Both Atkinson *et al.* [10] and Kinstle and Stark [11] found that with α-deuterated carbonyls or α-deuterated phosphonium salts, the Corey procedure results in extensive loss of the isotope prior to condensation **.

The Wittig reaction offers alternative paths to the desired olefin. In the preparation of oleic acid-11-d_2 (1a), the routes outlined in Schemes 1 and 2 (Methods A and B) were available.

Scheme 1 (Method A)



Scheme 2 (Method B)



* The synthesis of oleic acid through semihydrogenation of the acetylenic derivative, as reported in ref. 1, gave only about 1 % of the *trans*-isomer. However, the separation of the *cis*- and *trans*-products is a simple matter and does not, in the present case, represent a serious limitation to the Wittig route.

** KINSTLE and STARK [11], however, found that the use of a twice molar excess of phosphonium salt (with equimolar amounts of the sodium hydride and carbonyl) minimized the exchange.

Although both reaction sequences were used successfully for the preparation of 1b, the sequence of Scheme 2 gave a product with slightly higher isotopic purity (>98 % d_2) than did that of Scheme 1 (95 % d_2). In each sequence, 2,2-dideuterononanal (2) was an important intermediate. Preparation of 2 in 48 % yield was achieved by three equilibrations of nonanal with deuterium oxide in pyridine. In Scheme 1, 2 served as the carbonyl component in the Wittig condensation. Methyl 9-chlorononanoate was converted to the iodo compound which was used to prepare the phosphorus ylide. In Scheme 2, the deuterated nonanal was converted by standard procedures to the alcohol 3, and thence to the bromide 4. The bromide was then used to prepare the deuterated Wittig reagent which was condensed with methyl azelaaldehydate to give 1b. Because of the difficulty of obtaining accurate isotopic abundances for aliphatic aldehydes, alcohols, and bromides, mass spectral analyses of these intermediates were not reliable for establishing the degree of deuterium incorporation. Nuclear magnetic resonance spectroscopy, however, indicated that 2 was better than 95 % dideuterated and that the label was retained without scrambling in the formation of 3 and 4.

Experiments with non-labelled reactants showed that the conditions employed for the condensation led to olefin yields of about 75 %. Capillary gas-liquid chromatography and infrared analysis were used to determine that 92 $\pm$ 2 % of the olefin produced was the *cis*-isomer for each of six runs by Method A and for four runs by Method B. With the labelled compounds, Method A gave olefin in 91 % yield. The *cis*-product (1b) was found to comprise 93 % of the product mixture. The isotopic composition of 1b by this method was determined by mass spectrometry to be approximately 95 % d_2.

The final step of Method B provided an 82 % conversion to olefin, of which 93 % was methyl oleate (1b). Mass spectral analysis of this product showed its isotopic composition to be >98 % d_2. Separation of *cis-trans* isomers in these mixtures was conveniently carried out by argentation column chromatography [12] and 1a was obtained by saponification of the purified methyl ester. Oxidative cleavage [13] of 1a and mass spectral analysis of the cleavage products showed that the deuterium was located on carbon-11.

EXPERIMENTAL *.

9-Chlorononanonitrile.

1,8-Dichlorooctane (Columbia Organic Chemical Company) was purified by washing with concentrated sulfuric acid and then distillation. The material

* Nuclear magnetic resonance spectra were obtained in deuteriochloroform on a Varian HA-100 spectrometer. Mass spectral analyses were obtained on an AEI MS-12 mass spectrometer. Gas-liquid chromatography was performed on an F & M Model 700 gas chromatograph equipped with a flame ionization detector using a 4 foot 10 % ethylene glycol succinate column. Capillary gas-liquid chromatography employed a 150 foot column of polyphenyl ether.

collected boiled at 104-106°/4 torr, n_D^{25} 1.4572 (lit. [14] bp 115-116°/11 torr, n_D^{25} 1.4570) and was >98 % pure by gas-liquid chromatography. A mixture of 65 g (0.35 mole) 1,8-dichlorooctane and 21 g (0.42 mole) sodium cyanide in 150 ml ethanol-water (3 : 2 by volume) was refluxed and the progress of the reaction monitored by gas-liquid chromatography. After 16 hr the solvent was removed *in vacuo*, 200 ml water added to the residue, and the mixture extracted three times with 80 ml portions of ether. The ether extracts were combined, dried over magnesium sulfate, and the ether removed. Fractional distillation of the residue afforded 28 g of the desired product and allowed recovery of 25 g of dichlorooctane. The yield of 9-chlorononanonitrile (based on recovered starting material) was 73 %. The product boiled at 101°/0.3 torr, n_D^{25} 1.4521 (lit. [15] bp 105-106°/1.5 torr, n_D^{20} 1.4512).

Methyl 9-Chlorononanoate.

Conversion of 9-chlorononanonitrile to the chloroacid was accomplished by gentle heating of a mixture of 28 g (0.16 mole) of nitrile with 200 g of 75% sulfuric acid. The mixture began to darken almost immediately and was very dark when heating was stopped after 4 hr. The mixture was cooled, saturated with ammonium sulfate, and extracted three times with ether. The ether extracts were combined, washed with water, and dried over magnesium sulfate. Removal of the ether left a black, syrupy residue which was dissolved in 100 ml of dry methanol and the acids present converted to methyl esters by the addition of 10 ml boron fluoride-etherate and boiling for 2 min. Evaporation of the solvent and fractional distillation of the residue afforded 23.3 g (71 %) of crude methyl-4-chlorononanoate (90 % by glc). A second fractional distillation gave pure methyl 9-chlorononanoate, bp 90-91°/0.4 torr, n_D^{25} 1.4456 (lit. [16] bp 113-114/1 torr, n_D^{20} 1.4478).

Nonanal-2-d_2 (**2**).

A solution of 10 g (0.07 mole) of freshly distilled nonanal and 15 g (0.75 mole) of deuterium oxide (New England Nuclear, 99.7 % D_2O) in 75 ml dry pyridine under nitrogen was heated gently on the steam bath for 7 hr. After cooling, 800 ml of ice water was added and the mixture extracted twice with 80 ml portions of pentane. The combined pentane extracts were washed successively with water, 5 % hydrochloric acid, and water. The solution was dried over molecular sieves and after removal of the pentane the treatment of the aldehyde with deuterium oxide and pyridine was repeated twice more.

After the third treatment the residue was distilled to give 4.8 g (48 %) of nonanal-2-d_2, bp 74° (4 torr). This material was >99 % pure by glc and mass spectral analysis showed it had a minimal isotopic composition of 88 % d_2. Nuclear magnetic resonance spectroscopy indicated that both α-hydrogens had been replaced by deuterium.

1-Nonanol-2-d_2 (**3**) [17].

A solution of 720 mg (5 mmoles) of nonanal-2-d_2 in 3 ml of methanol was added dropwise to a cold (0°) solution of 200 mg (5.3 mmoles) of sodium borohydride in 4 ml of methanol. The solution was stirred cold for 5 min and then allowed to warm to room temperature. After addition of an equal volume of water the mixture was extracted twice with 20 ml portions of pentane, the extracts were combined, washed three times with water, and dried. Evaporation of the solvent gave 700 mg (96 %) of the alcohol, essentially pure by glc.

1-Bromononane-2-d_2 (**4**).

A solution of 1.30 g (9 mmoles) of 1-nonanol-2-d_2 (**3**) in 5 ml of dry ether containing 6-8 drops of pyridine was cooled to 0° and 1.36 g (5 mmoles) of freshly distilled phosphorus tribromide was added. The mixture was stirred cold for 2 hr and then at room temperature for 5 hr. After cooling and diluting with an additional 10 ml of ether, 10 ml of ice water was carefully added. The ether layer which separated was washed three times with water and dried. Evaporation of the solvent and distillation of the residue gave 1.60 g (86 %) of the desired bromide. Mass spectral analysis indicated a minimal incorporation of 1.95 atoms of deuterium.

Methyl Oleate (**1b**) *via the Wittig Reaction.*

Method A. From Nonanal and 9-Carbomethoxynonyltriphenylphosphonium Iodide. — The procedure outlined below is a modification of that of Bergelson [3]. A mixture of 1.13 g (7.5 mmoles) of sodium iodide and 8 ml of dry methyl ethyl ketone was heated at 80° for 30 min; 1.04 g (5.0 mmoles) of methyl 9-chlorononanoate was added and the mixture refluxed for 9 hr. After evaporation of the solvent, the residue was taken up in 10 ml of benzene and the solution washed with water, 5 % sodium thiosulfate, again with water, and then dried over molecular sieves. The dried solution of the iodoester was transferred to a tared flask, 1.57 g (6 mmoles) of triphenylphosphine was added, and the mixture was refluxed under nitrogen and with vigorous stirring for 10 hr. The mixture was cooled and the product forced from solution by the addition of ether. After washing thoroughly with ether three times by decantation the viscous phosphonium salt was dried in a vacuum desiccator and the amount of product obtained determined. The yields by this procedure ranged from 80-85 %.

Under nitrogen, a solution of 9-carbomethoxynonyltriphenylphosphonium iodide (4.0 mmoles) in 8 ml of dry dimethyl formamide was cooled to 0°; 175 mg (3.2 mmoles) of sodium methoxide (Matheson Coleman & Bell) was added and the mixture stirred at 0° for 2 hr. After this time the orange-red

solution was treated with 355 mg (2.5 mmoles) of freshly distilled nonanal and the mixture kept at 0° overnight. After diluting the solution with 50 ml of water, the mixture was extracted twice with 25 ml of pentane. The extracts were combined, washed three times with water, dried, and the crude product obtained by evaporation of the solvent. This material was analyzed by gas-liquid chromatography to determine both the amount of total unsaturated ester present and the relative amounts of *cis-* to *trans* isomers. The average yield for six reactions was 76 % (based on aldehyde), 92 ± 2 % of which was the *cis*-isomer.

When nonanal-2-d_2 (**2**) was used in this procedure, olefin was produced in 91 % yield. Capillary gas-liquid chromatography and infrared analysis showed this mixture to be 93 % **1b**. Separation of **1b** from the mixture was accomplished by argentation column chromatography [14]. Mass spectral analysis showed the isotopic composition by this method to be approximately 95 % d_2.

Method B. From Methyl Azelaaldehydate and Nonyltriphenylphosphonium Bromide. — Nonyltriphenylphosphonium bromide was prepared in yields of 80 to 90 % by refluxing a solution of 1.04 g (5 mmoles) of 1-bromononane and 1.57 g (6 mmoles) of triphenylphosphine in 7 ml of dry xylene under nitrogen for 16 hr. The product precipitated upon cooling and was washed thoroughly with ether several times by decantation.

The procedure from this point is essentially the same as that outlined in part A except that equivalent amounts of phosphonium salt, sodium methoxide, and methyl azelaaldehydate were employed. Yields again averaged 75 % and the amount of *cis-* isomer was 92 ± 2 % that of the total unsaturated esters.

When 1-bromononane-2-d_2 (**4**) was used in this procedure, olefin was produced in 82 % yield of which 93 % was methyl oleate (**1b**). This product had the isotopic composition of >98 % d_2 as determined by mass spectrometry.

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