

THE SYNTHESIS OF (+)-14^D-HYDROXY-CIS-11-
EICOSENOIC (LESQUEROLIC) ACID

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In their proof that the structure of lesquerolic acid from the oil of Lesquerella seed is (+)-14-hydroxy-cis-11-eicosenoic acid, Smith and coworkers (1) suggested that this acid with $[\alpha]_D^{22} + 6.0$ was of the ^D-configuration by analogy with the known (+)-12^D-hydroxy-cis-9-octadecenoic acid (ricinoleic acid). Serck-Hanssen (2) earlier had established the absolute configuration of ricinoleic acid by synthesis of the enantiomorph of its reduction product, i.e., (-)-12^L-hydroxyoctadecanoic acid. Applewhite et al. (3) also obtained evidence suggesting that lesquerolic acid is of the ^D-configuration by comparison of the optical rotatory dispersion (ORD) spectra of the methyl esters of ricinoleic and lesquerolic acids and their saturated derivatives. This communication describes the

synthesis of methyl (+)-14D-hydroxy-cis-11-eicosenoate (methyl lesquerolate) from (+)-12D-hydroxy-cis-9-octadecenoic (ricinoleic) acid. Coupled with Serck-Hanssen's (2) configurational studies, this synthesis establishes the absolute configuration of lesquerolic acid. It also can be considered a total synthesis of lesquerolic acid since several total syntheses of (+)-ricinoleic acid have been reported (4,5,6).

Ricinoleic acid prepared by hydrolysis (7) of distilled methyl ricinoleate (8) was converted to the N,N-dimethylamide through the mixed carboxylic-carbonic anhydride (9). Ester traces were removed by mild alkaline hydrolysis and the chromatographically pure (thin layer chromatography (TLC) on chromatostrips (10)) amide was converted to the tetrahydropyranose ether with a two-fold excess of freshly distilled dihydropyran in the presence of a few drops of concentrated hydrochloric acid (11). The etherified dimethylamide (0.025 mole) was quantitatively reduced to the protected aldehyde with lithium triethoxyaluminumhydride (0.03 mole) (12) in diethyl ether. The freshly prepared crude aldehyde (0.0245 mole) (with characteristic aldehyde infrared bands at 2700 cm^{-1} and 1720 cm^{-1} ; strong ether band at 1025 cm^{-1} ; nuclear magnetic resonance (NMR) aldehyde triplet at $0.33\ \tau$; C-1 pyranose proton band at $4.6\ \tau$ relative to tetramethylsilane) was coupled in dimethoxyethane with the anion of trimethylphosphonoacetate (0.025 mole) (13) in high yield leading to methyl 14D-tetrahydropyraniloxy-trans-2-cis-11-eicosadienoate (characteristic α - β unsaturated ester infrared bands at 1730 and 1625 cm^{-1} ; NMR spectrum shows $> 95\%$ trans α - β unsaturated ester by typical 15 c.p.s. trans coupling at $3.12\ \tau$). The unsaturated ester was gently hydrolyzed with potassium carbonate in methanol-water, carefully acidified, and

reduced with a five-fold excess of sodium in boiling n-butanol according to the method of Arth and coworkers (14). The crude 14D-tetrahydropyranyloxy-cis-11-eicosenoic acid (infrared bands for acid at 1705 cm^{-1} and for ether at 1020 cm^{-1}) was warmed about one hour at 40-50°C in methanol with a few drops of concentrated hydrochloric acid to gain crude methyl 14D-hydroxy-cis-11-eicosenoate (about 90% purity as assessed by its far ultraviolet (15) and NMR spectra and by TLC). A pure sample (TLC and GLC analyses) was obtained by column chromatography on silica gel (ether:petroleum ether).

Anal. Calcd. for $\text{C}_{21}\text{H}_{40}\text{O}_3$: C, 74.1; H, 11.8. Found: C, 74.0; H, 11.7.

Synthetic methyl (+)-14D-hydroxy-cis-11-eicosenoate has infrared and NMR spectra identical to an authentic sample prepared from Lesquerella fendleri oil; synthetic ester $[\alpha]_D^{25} 5.4^\circ$ (C 1.8 methanol); natural ester $[\alpha]_D^{25} 5.4^\circ$ (C 3.9 methanol). The far ultraviolet spectra in cyclohexane were superimposable: synthetic product has $\lambda_{\text{max}} 183.5$, $\epsilon_{\text{max}} 13,700$; authentic material has $\lambda_{\text{max}} 183.5$, $\epsilon_{\text{max}} 13,600$ (15).

Hydrogenation of the synthetic material in acetic acid in the presence of platinum led to methyl (+)-14D-hydroxyeicosanoate. After one recrystallization from hexane the saturated compound had m.p. 60.1-60.8°C. Authentic material from reduced methyl lesquerolate has m.p. 59.9-61.0°C; $[\alpha]_D^{25} -0.23$ (3). A mixed sample showed an undepressed melting point.

Optical rotatory dispersion (ORD) curves of the synthetic and natural methyl lesquerolates and their saturated analogs were essentially superimposable to the limits of the instrumentation available. In addition to establishing the absolute configuration of lesquerolic acid, these results presented support the observations (3,16) that the absolute

configurations of long chain hydroxy acids can be assigned by examination of the ORD curves of their saturated derivatives. Extension of these studies to other positional isomers of naturally occurring long chain hydroxy acids is now in progress.

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