Synthesis of Vinyl *Threo*-9, 10-*Threo*-12, 13-Tetrahydroxystearates

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Abstract

Methyl esters from vernonia oil containing *cis*-12,13-epoxy-*cis*-9-octadecenoate were reacted with acetone in the presence of a boron trifluoride catalyst to yield *trans*-12,13-0-isopropylidene-9-ene derivative I. Epoxidation of the unsaturation followed by reaction with acetone gave the isomeric *trans,trans*-di-0-isopropylidene derivatives III of 9,10:12,13-tetrahydroxystearates. The carboxylic acids of III were converted to vinyl esters and subsequent hydrolysis of the isopropylidene groups with boric acid produced vinyl *threo*-9,10-*threo*-12,13-tetrahydroxystearates. By the same sequence of reactions monoepoxidized methyl linoleate yielded an optically inactive derivative which had identical refractive index, IR spectrum, and GLC data to III from vernonia methyl esters.

Introduction

Vinyl esters with differing functionalities along the carbon chain have been synthesized from fatty acids of vegetable oil origin for copolymerization with vinyl chloride to evaluate their effectiveness as internal plasticizers (8–10,12). Preparation of vinyl esters from hydroxy fatty acids by reaction with acetylene is complicated by side reactions and leads to poor yields of the desired product. Vinyl 9- and 12-hydroxystearates and 14-hydroxyeicosanoate have been prepared (8,12) by the ester interchange reaction with vinyl acetate (1). The reaction produces vinyl ester intermediates (containing no hydroxy groups) which must be decomposed by acid-washed alumina to the vinyl hydroxy products. Vinyl *threo*-9,10-dihydroxystearate has been prepared by hydration of the oxirane function in vinyl *cis*-9,10-epoxystearate with 25% fluoboric acid.

This work reports the preparation of vinyl tetrahydroxystearates via the ester interchange reaction of vinyl acetate with the di-0-isopropylidene derivative of 9,10:12,13-tetrahydroxystearic acid followed by boric acid hydrolysis of the 1,3-dioxolane groups (5).

Discussion

The sequence of reactions used to prepare vinyl tetrahydroxystearates from methyl esters of vernonia oil is shown in Fig. 1. Vernonia oil (containing about 75% *cis*-12,13-epoxyoleate) was transesterified to methyl esters. Reaction of the epoxide with acetone catalyzed by boron trifluoride-etherate complex yielded the 12,13–0-isopropylidene-9-ene derivative I. Straight-chain methyl ester components of vernonia oil were separated from the isopropylidene derivative by complexing with urea. Epoxidation of I with performic acid prepared in situ with 90% hydrogen peroxide and a catalytic amount of sulfuric acid yielded the 9,10-epoxy-12,13-0-isopropylidene derivative II. Reaction with acetone converted II to the di-0-isopropylidene derivative of methyl 9,10:12,13-tetrahydroxystearate III. The acid IV from saponification and controlled acidulation of III was subjected to the ester interchange reaction with vinyl acetate to form V. A second vinylation was necessary to insure that vinyl ester V would have a low acid value. A hexane solution of V was chromatographed on basic, washed, activated alumina to remove the last traces of acid.

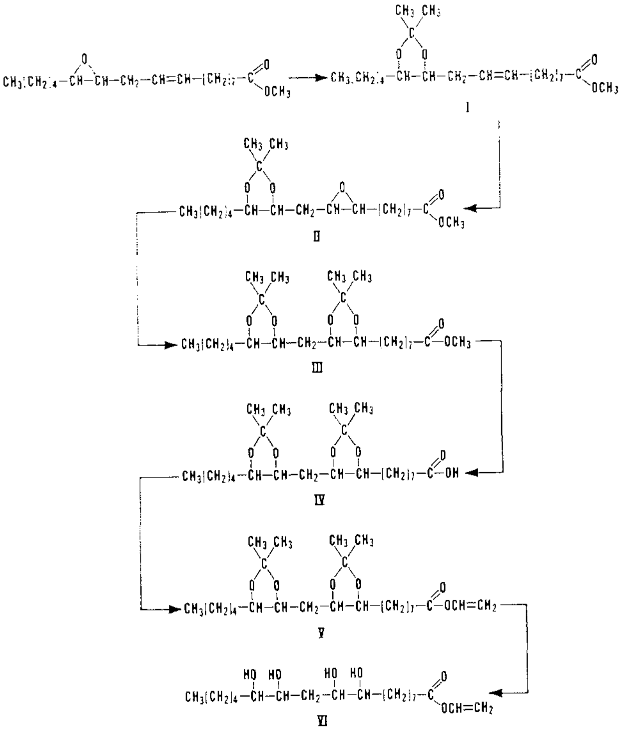

FIG. 1. Reaction scheme for preparing vinyl 9,10,12,13-tetrahydroxystearate from methyl 12,13-epoxy oleate.

The 1,3-dioxolane groups of V were hydrolyzed with boric acid in methyl Cellosolve at 100C to yield vinyl tetrahydroxystearates VI. If the vinyl ester contained small amounts (ca. 1%) of free carboxylic acid, complete loss of the vinyl ester group resulted and only tetrahydroxystearic acids were isolated.

The same sequence of reactions shown in Fig. 1 was carried out on monoepoxidized methyl linoleate. The monoepoxidation performed according to the method of Swern reportedly yields equal amounts of the 9,10- and 12,13-monoepoxides (7,14). The 9,10(or 12,13)-0-isopropylidene-12(or 9)-ene derivatives from the monoepoxides were not resolved by GLC analysis, nor was any resolution observed when these isomers were mixed with 12,13-0-isopropylidene-9-ene derivative I. The 9,10:12,13-di-0-isopropylidene derivatives from methyl linoleate and methyl vernolate had identical refractive indices, infrared spectra and GLC analyses.

The di-0-isopropylidene derivatives of methyl 9,10:12,13-tetrahydroxystearates III were resolved into two peaks by GLC analysis (Fig. 2). When III was con-

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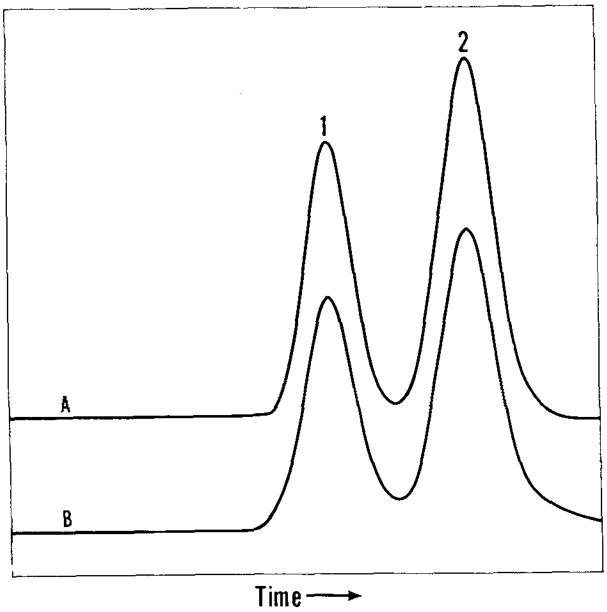

FIG. 2. Gas chromatograms of the isomeric methyl di-0-isopropylidene derivatives of *threo*-9,10-*threo*-12,13-tetrahydroxystearates from a glass column 4 ft × ¼ in., stationary phase 10% polyester succinate, temperature 195C.
A, synthesized from vernonia oil; B, synthesized from methyl linoleate.

verted to the tetrahydroxystearic acids and separated by the method of Bharucha and Gunstone (3), the melting points of the isomeric acids (122–123.5 and 147.5–148.5C) corresponded with those they obtained for authentic *threo*-9,10-*threo*-12,13-tetrahydroxystearic acids. Authentic samples of the *threo-threo* isomeric acids were converted to their respective di-0-isopropylidene methyl esters with 2,2-dimethoxypropane-methanol solution containing 1% hydrogen chloride. Subsequent GLC analysis identified the isopropylidene derivatives from the authentic low- and high-melting tetrahydroxystearic acids as identical to respective peaks 1 and 2 in the original mixture III.

As further evidence for the *threo* configuration, methyl oleate was epoxidized and reacted with acetone under the same conditions used for the preparation of tetrahydroxystearic acid. GLC analysis of the 9,10-0-isopropylidene derivative showed the presence of 90% *trans* isomer, 5% *cis* isomer and 5% unreacted oleate (confirmed by GLC analysis of a mixture containing known *cis* and *trans* isopropylidene derivatives). The 5% *cis* isomer was the result of elaidate impurity in the starting material (confirmed by IR analysis for methyl elaidate at 10.35 μ) rather than isomerization under the reaction conditions employed. When the 9,10-0-isopropylidene derivative prepared from methyl oleate was hydrolyzed with boric acid in methyl Cellosolve, a 75% yield of the known *threo*-dihydroxy acid (mp 94–95C) was obtained.

The two peaks (Fig. 2) from the GLC analysis of III, synthesized from either vernonia oil or methyl linoleate, had approximately a 3:2 area ratio with the larger peak corresponding to the di-0-isopropylidene derivative of the higher melting tetrahydroxystearic acid (mp 147.5–148.5C). A similar phenomenon was reported by Maerker et al. (6) in their synthesis of methyl 9,10:12,13-diepoxystearate from vernonia oil and methyl linoleate. They found a 3:2 distribution of isomers in the diepoxides.

The vernonia oil derivatives were optically active (Table I). It has been reported that ring cleavage of (+) methyl vernolate with acetic acid proceeds with inversion to yield (−) *threo*-12,13 dihydroxy oleic acid. The mechanism involves preferential attack on the conjugate acid of the epoxide by the nucleophilic anion at the C_{13} position, due presumably to the influence of the C_9 double bond (3,11). Application of this mechanism to the reaction of methyl vernolate with acetone in the presence of boron trifluoride-etherate would give rise to a preponderance of one *trans* dioxolane enantiomer (Fig. 3). Conceivably each of these enantiomers could induce a stereo selective epoxidation at C_9 analogous to the formation of the diepoxy stearates (6). A second preferential attack by acetone on the epoxide at C_9 or C_{10} would yield unequal amounts of the two diastereoisomeric *trans,trans*-di-0-isopropylidene derivatives III.

TABLE I
Specific Rotations of Vernonia Oil Derivatives

Compound	$[\alpha]^{25}_{D}$ 10% ethanol	$[\alpha]^{25}_{D}$ Pure liquid
I	−6.9	−6.6
V	−7.6	−6.9
VI	−7.0	....

In Fig. 3 the 60:40 selectivity on epoxidation was used since that was the ratio of diastereoisomers formed in the synthesis of diepoxystearates. Then the ratio of diastereoisomeric di-0-isopropylidene derivatives approach 3:2 as the selectivity of the epoxide ring opening step approaches 100%.

Conclusion

The dioxolane derivative is effective in protecting the hydroxyl function in α-glycols during the preparation of vinyl esters via ester acid interchange reaction with vinyl acetate. Boric acid hydrolysis of the internal 1,3-dioxolane function was accomplished with negligible loss of vinyl ester. The reaction of an epoxide with acetone offers a facile synthesis for preparation of tetrahydroxystearates from vernonia

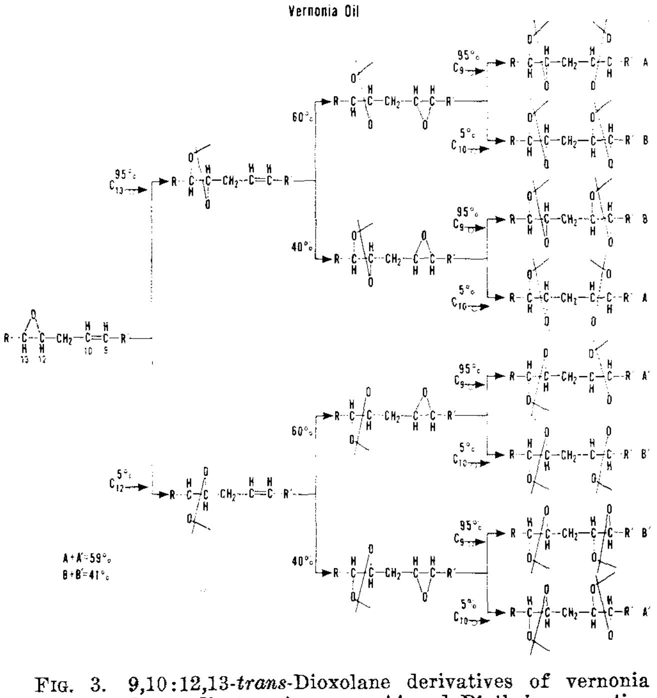

FIG. 3. 9,10:12,13-*trans*-Dioxolane derivatives of vernonia oil. A and B are diastereoisomers; A′ and B′ their respective enantiomers.

oil or other oils rich in linoleic acid. Analytically pure methyl tetrahydroxystearates were obtained in 52% yield from vernonia oil (based on epoxy oleate content). No difficulties were encountered when handling up to 300-g quantities in the synthesis. Conceivably, tetrahydroxystearates could be obtained more directly by hydroxylation of I according to Swern's procedure (13), followed by acid hydrolysis of both the dioxolane and formoxy groups.

Preliminary results indicate that isopropylidene derivatives offer a method for the identification and analysis of α-glycols and possibly epoxides. The oxirane values found for methyl 9,10-epoxystearate by the method of Durbetaki (4) and those calculated from the GLC analysis of the converted isopropylidene derivative were in close agreement; also, the relative amounts of *cis* and *trans* epoxides were determined.

Experimental

Starting Materials. Vernonia anthelmintica

A refined oil was provided by Krewson of the Eastern Utilization Research and Development Division, oxirane oxygen, 4.1%, I.V. (Wijs), 91.7.

Methyl linoleate (95%) was prepared by liquid-liquid extraction of safflower fatty acid in a Podbielniak centrifugal extractor (2). Other materials used were as follows: methyl oleate (Applied Science 99+%); vinyl acetate (Eastman's yellow label); boric acid (Reagent grade 99+%); methyl Cellosolve (purified by distillation); hydrogen peroxide (Becco's 90% concentrate); formic acid (90% grade).

Methyl Esters from Vernonia Oil

Oil (800 g) was added to 2200 ml of methanol containing 5.8 g sodium methoxide, and the mixture was kept for 16 hr at room temperature with occasional stirring. The resulting homogeneous solution was added to water and the esters were extracted with ether. Glacial acetic acid (4 g) was added to break the emulsion. The ether layer was washed repeatedly with water until neutral; the product amounted to 782 g containing 4.03% oxirane (4).

Methyl 12,13-0-isopropylidene-9-ene Derivative I

A 50% by weight solution (782 g) of vernonia oil methyl esters in acetone was added slowly to a stirred solution of 3200 g of acetone containing 16 ml of boron trifluoride-etherate. The reaction temperature rose to a maximum of 35C during addition. Upon cooling to room temperature, the solution was poured into a large volume of water. The separated oil was diluted with ether and washed until neutral. The organic layer was dried and the ether removed in vacuo to give 864 g of product I (96% yield based on epoxyoleate content).

Urea Fractionation

The 864 g of I was diluted with 1 liter of methanol and added, with stirring, to a warm solution of 590 g of urea in 3 liters of methanol. The solution was allowed to crystallize at −18C and filtered. The filtrate was poured into a large volume of water and the product extracted with ether. The filter cake was added to water and heated; the separated oil was extracted with ether. The ether extracts from both filtrate and filter cake were washed five times with water, dried and stripped in vacuo. GLC analysis: Filtrate (705 g) contained 95% I and 5% methyl linoleate; clathrate (95 g) contained 25% of I. The filtrate represents a 96.5% recovery of I.

Expoxidation of I

To 240 g I diluted with an equal weight of benzene was added 35 cc of 90% hydrogen peroxide containing 0.25 g concentrated sulfuric acid. This mixture was heated to 68C and 5.45 g 90% formic acid was added at a rate to maintain a reaction temperature of 68–72C while cooling with an ice bath. After the exothermic reaction subsided, heat was applied to maintain 72C for a total reaction time of 2 hr. The benzene solution was washed free of acid and peroxides and dried. Evaporation of the solvent in vacuo at 50C gave 242 g II, oxirane oxygen 3.7%. (Calc. 83% conversion of the olefin to oxirane.)

Preparation of III

Product II (342 g) was treated with acetone and BF_3 to give 372 g III; n_D^{30} 1.4520 (97% yield calc. from oxirane content).

Conversion of III to the Acid Derivative IV

Product III (372 g) was refluxed for ½ hr with 1400 ml 2 N alcoholic KOH. Ethanol was distilled from the flask while water was added to maintain an equivalent volume. The residue was diluted to 3 liters with water and 20% aqueous HCl added to pH 2. An ether solution of the acid was washed to neutral and dried. Evaporation of the solvent yielded 337 g of the acid: NE 406.

Vinylation of IV

A catalyst solution containing 3.02 g mercuric acetate, 0.12 g copper resinate and 0.775 g 100% sulfuric acid in 200 g vinyl acetate was added to a solution of 336 g of the acid in 520 g of vinyl acetate. The resulting solution was kept at room temperature in the dark for 65 hr. Sodium acetate trihydrate (3 g) was added with stirring and volatiles were removed in vacuo below 50C. The residue was diluted with hexane and washed once with saturated sodium chloride solution, once with 5% sodium bicarbonate and finally with water until neutral. The solution was dried, filtered and stripped in vacuo below 50C. The crude product contained about 20% free acid and was revinylated as above to yield a product with 3% acid. A 30% hexane solution was eluted through a column containing 100 g basic, washed, activated alumina; the eluate gave 280 g (79% yield) of acid-free vinyl ester V.

Hydrolysis of the 1,3-Dioxolane Groups in V

To a flask fitted with an air condenser, thermometer, stirrer and gas inlet tube for nitrogen was added 47 g V and 500 ml methyl Cellosolve containing 84 mg of copper resinate. The contents were heated to 100C and 168 g of powdered boric acid added. The reaction was monitored by TLC with silicic acid plates using 10% ethyl acetate in ether as a developing solvent. Five spots were observed. The spot with the smallest R_f value was VI; the one with the largest R_f value was starting material; two of the intermediate spots could be due to the partially cleaved derivatives and the minor fifth spot resulted from the copper resinate. After 1 hr reaction time at 100C, V and two of the intermediate spots diminished to nil whereas VI showed a corresponding increase in size and intensity. The contents were cooled to ca. 40C and poured into ice water. Separated solids were filtered, extracted with hot hexane and the residual solids twice crystallized from 200 ml methanol at −18C gave 22 g (52% yield). Found: C, 64.27; H, 10.25. Theory: C, 64.14; H, 10.23. I.V. 68, theory 68.1.

Preparation of Di-0-isopropylidene Derivative of III from Methyl Linoleate

Methyl linoleate (31 g) was epoxidized, according to the method of Swern, to yield 30.7 g of monoepoxidized product, 4.05% oxirane oxygen, I.V. 87.5.

The epoxidized product (29 g) was treated with acetone as previously described to yield 31.5 g of isopropylidene derivative. GLC analysis: 60% mono-0-isopropylidene, 3.6% di-0-isopropylidene, 31.5% unreacted methyl linoleate, 1.4% 0-isopropylidene derived from methyl oleate, 0.7% oleate and 2.1% palmitate.

The isopropylidene derivatives were concentrated by urea fractionation as above. GLC analysis: 91% mono-0-isopropylidene, 6% di-0-isopropylidene, 1% methyl linoleate and 3% 0-isopropylidene derived from methyl oleate.

Epoxidation of 22.5 g by the method described yielded 23 g product, oxirane oxygen 2.7%.

The epoxidized product (22.1 g) was treated with acetone to yield 23 g of di-0-isopropylidene derivative of methyl 9,10:12,13-tetrahydroxystearates III; n_D^{30} 1.4522. IR spectra and GLC chromatogram were identical to III from methyl vernolate.

Threo-9,10-Dihydroxystearic Acid

Methyl oleate, 15 g (Applied Science grade 99+, weak IR absorption for *trans* isolated bonds at 10.35 μ) was epoxidized with 4.8 g of 70% hydrogen peroxide and 0.8 g of 90% formic acid under the same conditions used in the preparation of II to give 14.9 g of product, oxirane oxygen 4.7%.

Acetonization of 14 g of the epoxide was performed as in the preparation of I; 14.7 g of product resulted. GLC analysis: methyl oleate 4.8%, *cis*-0-isopropylidene 5.1%, and 90.2% *trans*-0-isopropylidene.

The isopropylidene (12 g) was treated with 40 g boric acid in 120 ml of methyl Cellosolve as previously described. Saponification and acidulation yielded 10 g of crude 9,10-dihydroxystearate, mp 90–92C. Crystallization twice from 50 cc of 95% ethanol at 0C gave 7.7 g, mp 94–95C; mixed melting point with authentic *threo* acid, 94–95C; overall yield, 75%.

Methyl 9,10:12,13-Tetrahydroxystearates

The hydrolysis was performed as before with 12 g IV, 120 ml methyl Cellosolve and 40 g boric acid. The crude product was crystallized from 50 ml of methanol at −18C to give 6 g of methyl tetrahydroxystearates. Found: C, 62.87; H, 10.34. Theory: C, 62.95; H, 10.57. Overall yield, calculated from epoxy oleate content of vernonia oil, was 52.4%.

Conversion of Hydroxy Acids to Their Respective Di-0-isopropylidene Derivatives

Hydroxy acid (0.2 to 0.3 g) was added to a solution containing 2.2 g of 2,2-dimethoxypropane, 0.3 g of methanol and 1% hydrogen chloride, and the mixture was kept in the dark at room temperature for 24 hr. The solution was eluted with hexane through a column containing 3 g basic, washed, activated alumina. Removal of volatiles in vacuo yielded the di-0-isopropylidene derivatives.

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