Synthesis of Methyl 9,12-Epoxyoctadecanoate from Castor Oil

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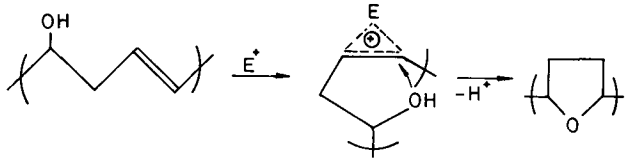
We report here the synthesis of methyl 9,12-epoxyoctadecanoate (2-[7-methoxycarbonyl-heptyl]-5-hexanyl-tetrahydrofuran). Methyl ricinoleate (methyl 12-hydroxy-9-*cis*-octadecenoate), isolated from castor oil methyl esters was isomerized with diphenyl disulfide as radical initiator under ultraviolet radiation to give the *trans* isomer, methyl ricinelaidate. The latter was cyclized by slow addition of 10% bromine solution in dichloromethane to give methyl 10-bromo-9,12-epoxyoctadecanoate, which on hydrogenation with Pd/C catalyst gave the title compound, methyl 9,12-epoxyoctadecanoate.

KEY WORDS: Castor oil derivative, cyclization, isomerization, methyl 9,12-epoxyoctadecanoate, methyl ricinelaidate, methyl ricinoleate.

Participation of neighboring groups is common in many reactions involving organic molecules. Homoallylic alcohols (β, γ-olefinic alcohol) have been used in many transformations to study this effect. The electrophilic attack on the olefinic bond, concerted with the intramolecular nucleophilic attack of the hydroxy group, leads to a tetrahydrofuran product (Scheme 1) (1,2). Thus, oxymercuration of, or halogen addition to, the double bond in a homoallylic alcohol yields a tetrahydrofuran derivative as one of the products (3,4). In such metal- or halogen-catalyzed reactions, the intermediates have been described as nonclassical carbonium ions.

Castor oil contains 85–90% ricinoleic acid (12-hydroxy-9-*cis*-octadecenoic acid) in triglyceride form. Ricinoleic acid is an eighteen-carbon homoallylic alcohol. In the literature, synthesis of C18-furan acids from methyl ricinoleate is well-documented (5,6), but the use of the homoallylic alcohol moiety to prepare a 2,5-dialkylated derivative of tetrahydrofuran is not reported. The synthesis of methyl 9,12-epoxyoctadecanoate (MEOD) from castor oil and its spectral characterization are reported in this communication.

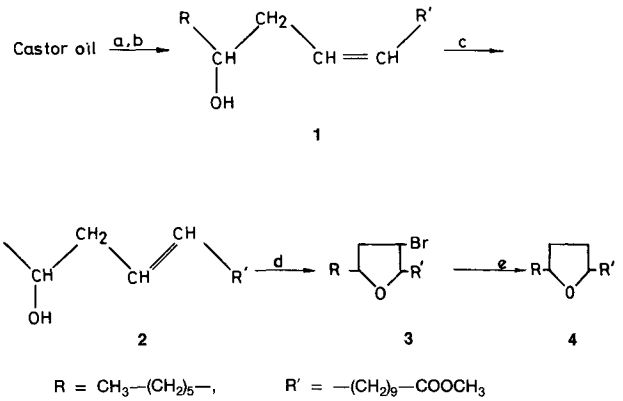


SCHEME 1

EXPERIMENTAL PROCEDURES

Analytical-grade reagents from Aldrich Chemical Co. (Milwaukee, WI) and solvents from Indian Drug and Pharmaceutical Ltd. (Hyderabad, India) were used. Dichloromethane (DCM) was dried by stirring over fused calcium chloride overnight and distilling under anhydrous conditions. Liquid bromine (3.2 mL) was added to dry DCM (100 mL) to give 10% (wt/vol) bromine solution. Silica gel (60–120 mesh) was obtained from ACME Synthetic Chemicals (Bombay, India). Castor oil (B.P. grade) was purchased from Jayant Oil Industries (Bombay, India).

Infrared (IR) spectra were recorded in chloroform on a Nicolet 205 XB FTIR spectrophotometer (Nicolet Analytical Instruments Ltd., Madison, WI). Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained in $CDCl_3$ on a Bruker AC-F 200 spectrometer (Bruker Analytical Instruments, Fallanden, Switzerland). Mass spectra were recorded on a VG Micromass 7070 H mass spectrometer (VG Analytical Ltd., Manchester, England). A WOTAN ULTRA-VITALUX lamp (300 W; Osram GmbH, Munich, Germany), which gives radiation over the entire range of ultraviolet (UV), was used for sample irradiation. Gas chromatography (GC) was carried out on an SP-1000 packed column in a Shimadzu Gas Chromatograph GC-14B (Shimadzu Corporation, Tokyo, Japan). The column, injection port and the flame-ionization detector were maintained at 200, 290 and 290°C, respectively. Nitrogen was used as carrier gas at 1 mL/min. The route followed for the synthesis of MEOD (4) is shown in Scheme 2. The conditions employed are (a) $NaOCH_3$ (1%), methanol, reflux; (b) silica gel column chromatography; (c) diphenyl disulfide (1%), cyclohexane, UV radiation, 10 h; (d) bromine (10%) in DCM, DCM, 0°C, 2 h; (e) Pd/C (5%), ethanol, H_2 gas, room temperature.



SCHEME 2

Preparation of methyl ricinoleate (1). Castor oil was transesterified with methanol and sodium methoxide as catalysts. Methyl ricinoleate was obtained in 86% yield after purification on silica-gel chromatography (7).

Isomerization to methyl ricinelaidate (2). Compound 1 (10 mmol) was dissolved in cyclohexane (50 mL). Diphenyl disulfide (30 mg, 1% based on compound 1) was added, and the reaction mixture was stirred magnetically under the UV source. After 10 h of exposure, cyclohexane was removed on a rotary evaporator. The crude product (viscous liquid) was loaded on a 10% $AgNO_3$-incorporated silica-gel column and eluted with hexane/acetone (90:10, vol/vol)

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to give 2 in 83% yield. IR (cm^{-1}): 3500, 2850–2950, 1735, 965, 730. ^1H NMR (δ): 5.45 (*m*, 2H, -CH=CH-), 3.66 (*s*, 3H, $-OCH_3$), 3.59 (*m*, 1H, -CH-O), 2.3 (*t*, 2H, $-CH_2-CO$), 2.2 (*dd*, 1H, proton at 11th carbon), 2.0–2.1 (*m*, 3H, proton at 11th carbon and $=CH-CH_2-$), 1.65 (*m*, 2H, $-CH_2-$ beta to CO), 1.2–1.3 (*bs*, 18H, $[-CH_2-]_9$), 0.9 (*t*, 3H, $-CH_3$).

Synthesis of methyl 10-bromo-9,12-epoxyoctadecanoate (3). Compound 2 (10 mmol) was dissolved in dry DCM (30 mL) and cooled to 0°C. The solution was deaerated with nitrogen gas. The 10% bromine solution in DCM (30 mL) was added dropwise over a period of 1 h. After stirring for one more hour, the reaction mixture was treated with 5% $Na_2S_2O_3$ solution (30 mL) to quench the excess bromine. The organic layer was dried over sodium sulfate, and the solvent was evaporated. The crude product was separated on a silica-gel column with solvent hexane/acetone (98:2, vol/vol) to give compound 3 in 68% yield. IR (cm^{-1}): 2850–2950, 1735, 1250. ^1H NMR (δ): 3.95 (*m*, 2H, O-CH), 3.66 (*s*, 3H, $O-CH_3$), 2.63 (*m*, 1H, -CHBr-), 2.2 (*t*, 2H, $-CH_2-CO$), 1.96 (*m*, 2H, $-CH_2-CHBr$), 1.65 (*m*, 2H, $-CH_2-$ beta to CO), 1.2–1.3 (*bs*, 2OH, $[-CH_2-]_{10}$), 0.9 (*t*, 3H, $-CH_3$). Mass *m/z* (rel. int.): M^+ not observed, 311 (35.0), 279 (38.0), 233 and 235 (12.0), 225 (100), 69 (60.0).

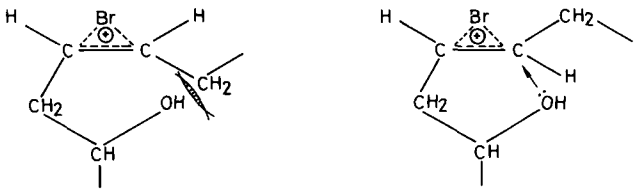
Synthesis of MEOD (4). To compound 3 (5 mmol) in distilled ethanol (20 mL), Pd/C (200 mg, 1% based on 3) was added. The reaction mixture was stirred for 24 h under hydrogen gas at atmospheric pressure. The reaction mixture was filtered, and ethanol was evaporated. Purification of the product was carried out on a silica-gel column with hexane/acetone (98:2, vol/vol) to give MEOD (4) in 80% yield. IR (cm^{-1}): 2850–2950, 1735, 730. ^1H NMR (δ): 3.95 (*m*, 2H, O-CH), 3.66 (*s*, 3H, $O-CH_3$), 2.30 (*t*, 2H, $-CH_2-CO$), 1.96 (*m*, 4H, $-CH_2-$ of tetrahydropyran ring), 1.65 (*m*, 2H, $-CH_2-$ beta to C=O), 1.2–1.3 (*bs*, 20H, $[-CH_2-]_{10}$), 0.9 (*t*, 3H, $-CH_3$). Mass *m/z* (rel. int.): 312 (5.0), 281 (30.0), 227 (100.0), 70 (50.0).

RESULTS AND DISCUSSION

Methyl ricinoleate conformed with the reported spectral data and gave a single peak in GC.

Isomerization of methyl ricinoleate (1) to methyl ricinelaidate (2) was examined with various catalysts such as I_2, acetophenone and diphenyl disulfide under UV exposure. The best yield of 84% was obtained with 1% diphenyl disulfide in cyclohexane under UV exposure for 10 h. This method reportedly affects geometric isomerization without positional isomerization (8). The isomerized product was separated on silica gel, impregnated with $AgNO_3$, to yield pure methyl ricinelaidate (2). The IR spectrum showed absorption at 965 cm^{-1}, relating to the *trans* double bond, and the NMR spectrum showed peaks similar to methyl ricinoleate, except that the peaks for two protons at the 11th carbon atom appeared at 2.04 δ and 2.2 δ. The downfield shift of one of the protons by 0.16 δ apparently is due to the chirality of the hydroxyl group at 12th carbon atom and the *trans* double bond between carbons 9 and 10. The olefinic *J* coupling constant of 15.2 Hz for the peak at 5.46 δ confirmed the *trans* nature of double bond.

An attempt at cyclization, by adding 10% bromine solution in DCM to methyl ricinoleate, yielded only traces of cyclized product. The major product was the dibrominated derivative, methyl 9,10-dibromo-12-hydroxy octadecanoate. That steric hindrance is the reason for noncyclization can be ascertained by viewing molecular models of the transition states. The *cis* olefin transition state model revealed that the alkyl chain (R') hinders the attack of the hydroxyl group because both lie on the same side of the *cis* double bond (Scheme 3). Isomerization of the double bond from *cis* to *trans* (unhindered) positions the hydroxyl group favorably for attack on the bridged bromonium ion to yield the cyclized product. Isolation of the cyclized product, methyl 10-bromo-9,12-epoxyoctadecanoate (3) in 68% yield from methyl ricinelaidate supports this hypothesis. The cyclization of methyl ricinelaidate was also attempted with NBS/CCl_4 without any success. The NMR spectrum of compound 3 showed a multiplet at 3.95 δ for tertiary protons, a doublet of triplets at 2.63 δ for -CH-Br and a multiplet at 1.96 δ for the methylene protons of the tetrahydrofuran ring. The singlet at 3.66 δ ($-OCH_3$ of ester) and broad singlet at 1.2 δ (methylenes of alkyl chains) were also seen. The mass spectrum did not show M^+, but showed peaks at *m/z* 311 (M − Br), 279 (M − HBr − OCH_3), 233 (M − R') and 69 (tetrahydrofuran ring). All these data confirm the structure of 3.



cis: hindered *trans*: unhindered

SCHEME 3

The debromination of compound 3 was tried by hydrogenation in the presence of Pd/C catalyst. The dehalogenation did occur at room temperature but only after a long reaction time of 24 h. The 80% yield of MEOD (4) was obtained after purification on a silica gel column. The NMR spectrum of A showed no peak at 2.63 δ (-CHBr-) but one additional proton at 1.96 δ (methylenes of tetrahydrofuran ring) compared to the NMR spectrum of 3. The mass spectrum showed expected fragmentation of *m/z* 312 (M^+), 281 (M − OCH_3), 227 (M − R) and 70 (tetrahydrofuran ring). These data support the assigned structure of 4 as methyl 9,12-epoxyoctadecanoate. Thus, this synthetic approach allows access to 2,5-dialkylated derivatives of tetrahydrofuran from fatty acids containing a homoallylic secondary alcohol moiety.

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