Pinacol Rearrangement of Jojoba Bis-epoxide

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ABSTRACT: Jojoba bis-epoxide (1.6 mmol) undergoes pinacol rearrangement upon reaction with the iodide ion (60 mmol) under slightly acidic conditions, *via* an iodohydrin as an intermediate, to yield bis-ketojojoba in high yield (92%) after 25 h reflux in THF; no hydroxy derivatives were detected. Since the nucleophilic opening of the epoxide ring is statistically equal on both sides, the rearranged product may have the two carbonyl groups on either side of the original carbon atoms of the two epoxide rings, both completely opened. MS of the rearranged products reveals that the ring opening is approximately equal on both sides of the epoxide ring. Other nucleophiles, such as acetate and amine, open the ring sluggishly without rearrangement.

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KEY WORDS: Epoxide, jojoba wax, mass spectra, pinacol rearrangement.

Jojoba liquid wax (jojoba "oil") is extracted from the evergreen desert shrub *Simmondsia chinensis*, which is indigenous to the southwestern United States and northern Mexico. The shrub is currently under cultivation in several countries, including Israel. The wax is used mainly in cosmetic products and to a small extent in lubrication applications. The liquid wax, unlike true plant oils and animal fats, does not contain glycerol and its derivatives but is a mixture of long-chain esters (compound **I**; Scheme 1). About 97–98% of the wax consists of esters consisting of C_{18}-, C_{20}-, C_{22}-, and C_{24}-chain monounsaturated acids and alcohols (1,2).

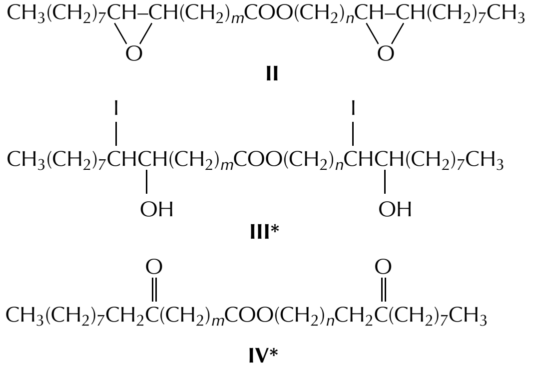
Jojoba wax is extremely hydrophobic and is insoluble in alcoholic and polar solvents. It is therefore desirable to increase the hydrophilicity of the wax for industrial applications. This can be achieved by introducing protic groups, such as hydroxyl and amino substituents, along the chain. Products containing these groups, either as tetrahydroxy- or tetraamino-jojoba derivatives, or as dihydroxy diamino-jojoba derivatives have been synthesized, and their solubilities in methanol are better than that of the underivatized wax (3). These compounds are slightly soluble in water but still exhibit good solubility in hydrocarbon solvents and ether. The appropriate starting material for the preparation of such derivatives is jojoba bis-epoxide (**II**; Scheme 2) (4). In the framework of an ongoing study of the chemistry of the wax, we have investigated the reactions of different nucleophiles with **II**. In this paper, we describe the reaction of the epoxide **II** [derived either from the natural *cis*- or the isomerized *trans*-jojoba (5)] with NaI in acid medium to yield an iodohydrin (**III**; Scheme 2), which then transforms to a bis-keto derivative (**IV**; Scheme 2) in almost quantitative yield. This reaction is considered as a modification of the well-established pinacol rearrangement (6). Most of those rearrangement studies were performed on short-chain molecules, although a few on long-chain molecules have been described in the literature. Thus, as early as the late 1940s (7), in a study of halogeno-hydroxy stearic acids, mercuric oxide was found to induce rearrangement of iodo-hydroxystearic acid to ketonic acids in low yield. A pinacol rearrangement of epoxy FA (8) produced a high yield of 10 (9)-ketostearic acids, after boiling in dioxane and BF_3·etherate for 3 h. Another procedure to produce ketoacids or esters was performed on methyl oleate and other acids (or their esters) by using a catalyst of $PdCl_2/CuCl_2$ and oxygen (9). A very recent procedure to convert cyclic and short-chain bromohydrins in high yield to ketones by free radical elimination of HBr with di-*tert*-butyl peroxyoxalate has appeared (10,11).

$CH_3(CH_2)_7CH{=}CH(CH_2)_mCOO(CH_2)_nCH{=}CH(CH_2)_7CH_3$

I

	m = 7, 9, 11, 13	*n* = 8, 10, 12, 14
Average composition (%)	11, 71, 14, 1	1, 45, 44, 9

SCHEME 1



$CH_3(CH_2)_7CH{-}CH(CH_2)_mCOO(CH_2)_nCH{-}CH(CH_2)_7CH_3$ (epoxide O bridging each CH–CH)

II

$$CH_3(CH_2)_7\overset{\displaystyle I}{\overset{|}{CH}}\underset{\displaystyle OH}{\underset{|}{CH}}(CH_2)_mCOO(CH_2)_n\overset{\displaystyle I}{\overset{|}{CH}}\underset{\displaystyle OH}{\underset{|}{CH}}(CH_2)_7CH_3$$

III*

$$CH_3(CH_2)_7CH_2\overset{\displaystyle O}{\overset{\|}{C}}(CH_2)_mCOO(CH_2)_nCH_2\overset{\displaystyle O}{\overset{\|}{C}}(CH_2)_7CH_3$$

IV*

*One of several possible isomers

SCHEME 2

EXPERIMENTAL PROCEDURES

Materials. Jojoba wax (Jojoba Israel Ltd., Hatzerim, Israel) was used as the crude oil (without bleaching); iodine number

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80.9 corresponds to a product with 94.7% diunsaturated esters in the liquid wax.

Solvents. Petroleum ether (60–80°C), CP grade (Frutarom, Haifa, Israel), was dried over $CaCl_2$ and distilled. THF, AR grade (Aldrich, Milwaukee, WI), was dried over KOH and distilled. Dimethyl formamide (DMF), 99.8% pure (Aldrich), was dried over A4 molecular sieves. Chloroform, dichloromethane, acetone, and ethyl acetate CP grade (Aldrich) were used without drying.

Reagents. *m*-Chloroperbenzoic acid (85%), glacial acetic acid, acetic anhydride, diethylamine, sodium iodide, and bromine AR grade (Aldrich) were used without any further purification.

Base. NaOH was CP grade (Frutarom).

Acids. HCl and H_2SO_4 were AR grade (Merck, Darmstadt, Germany).

Salts. NaCl, Na_2SO_4, $KHCO_3$, and $MgSO_4$ were AR grade (Merck), and K_2CO_3, $NaHCO_3$, $CaCl_2$, and KCl were CP grade (Frutarom).

General procedure. Crude products obtained after a particular chemical transformation were used in the subsequent step without further purification. The standard workup comprised pouring the reaction mixture into water, washing with $NaHCO_3$ solution (as well as with $NaHSO_3$ after the NaI reactions), extraction with petroleum ether, drying over anhydrous Na_2SO_4, filtration, and evaporation of the solvent to give the crude product. Separation of the pure products was performed either by column chromatography [silica gel 60, 70–230 mesh (Merck), or neutral aluminum oxide, 0.05–0.15 mm (Fluka Chemie GmbH, Buchs, Switzerland)] or by preparative TLC on prepared plates (Merck) in petroleum ether/ethyl acetate mixtures as eluant.

Elemental analyses. Elemental analyses, based on ASTM methods, were performed by the Analytical Laboratory of the Institutes for Applied Research (Ben-Gurion University of the Negev, Beer-Sheva, Israel).

IR spectra. IR spectra were obtained with a Nicolet (Madison, WI) 5ZDX FTIR spectrometer. All IR spectra (taken as neat in NaCl prisms) gave an intense carbonyl signal at 1735–1740 cm^{-1}, a signal at 1465–1466 cm^{-1}, and a broad intense signal of hydrogen-carbon bonds at 2800–3000 cm^{-1}.

^1H NMR spectra and analytical TLC. NMR spectra and analytical TLC were used to monitor the chemical changes occurring in each reaction. NMR (200 MHz) spectra were obtained on a Bruker DPX-200 instrument (Spectrospin AG, Sallenden, Switzerland) in $CDCl_3$ solution with Me_4Si as the internal reference. All NMR spectra gave a terminal CH_3 as a triplet at δ 0.92–0.94, an intense signal at 1.2–1.4 for all aliphatic hydrogens, a triplet at 2.20–2.26 for CH_2COO, and a triplet at 3.96–4.00 for CH_2OCO. All other signals are described below. Integration curves were consistent with the assignment of the different hydrogens, for an average of at least three experiments (±2%).

GC–MS. GC–MS analyses were performed on a Hewlett-Packard 5890 Series II gas chromatograph coupled with an AutoSpec E High Resolution mass spectrometer. The separation was performed with a 30 m × 0.32 mm × 0.25 μm DB-1 capillary column (J&W Scientific, Folsom, CA), temperature programmed from 150 (hold 1 min) to 270°C (hold 20 min) at 10°C/min. The mass spectra were obtained using chemical ionization (CI). The reagent gas used in CI was isobutane.

*Bis-iodohydrinjojoba (**III**).* A mixture of 1 g (1.6 mmol) of jojoba bis-epoxide (**II**) (4) in 60 mL of THF, 20 mL of acetone, 4 mL of glacial acetic acid, 0.5 mL of H_2O, and 9 g (0.06 mol) of NaI was stirred at 25°C under N_2 for 20 h to yield 0.6 g (53% yield, 85% purity) of semisolid **III**. IR, 3410 cm^{-1}; ^1H NMR, 4.2 [3.4H, $CH(J)CH(OH)$, *m*], 2.2–1.9 [7.5H, $CH_2CH(J)CH_2CH(OH)$, *m*]; calculated for I: 30.0%; found: 26.0%.

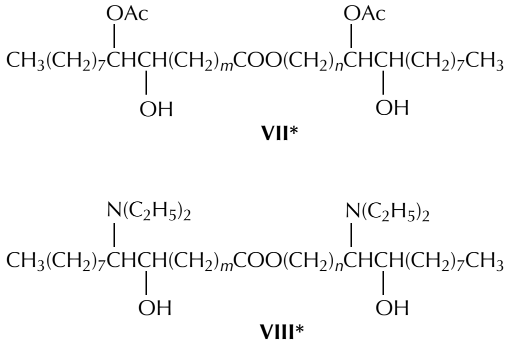
*Bis-ketojojoba (**IV**).* The above-described reaction mixture was refluxed for 25 h to yield 92% **IV**, which was purified by column chromatography, eluted with 5% ethyl acetate in petroleum ether, m.p. 68–69°C. IR, 2900, 2830, 1732, 1709 cm^{-1}; ^1H NMR, 2.32 (8H, CH_2COCH_2, *t, J* = 7 Hz). ^{13}C NMR, 211.6, 174.0, 64.3, 42.7, 34.3, 31.8, 29.4, 29.2, 28.6, 25.9, 24.9, 23.8, 22.6, 14.0.

*Methanolysis of bis-ketojojoba to methyl ketojojoboate (**V**) and ketojojoba alcohol (**VI**).* Acetyl chloride (0.6 mL, 6.4 mmol) was added dropwise to 15 mL of methanol at 5°C, and the resulting solution was then added to a solution of 1.1 g of **IV** (1.7 mmol) in 20 mL of toluene. The reaction mixture was refluxed for 4 h. The crude product was separated on a silica gel column to yield 0.31 g of **V** (eluted with 3% ethyl acetate in petroleum ether), m.p. 39–40°C. IR, 2900, 1732, 1709, 1150 cm^{-1}; ^1H NMR, 3.86 (3H, CH_3OCO, *s*), 2.37 (4H, CH_2COCH_2, *t, J* = 7 Hz), 2.28 (2H CH_2COO, *t, J* = 7 Hz). ^{13}C NMR, 211.8, 174.3, 64.6, 51.4, 42.8, 34.1, 32.7, 31.2, 30.3, 29.4, 29.2, 28.6, 25.9, 24.9, 23.8, 22.6, 14.1. High-resolution MS of the molecular ions (MH^+) of the methyl ketojojoboate esters are as follows: found 313.272522, calculated for $C_{19}H_{37}O_3$ 313.274270 (1.7% of total area in the GC chromatogram); found 341.300644, calculated for $C_{21}H_{41}O_3$ 341.305571 (60.3%); found 369.338661, calculated for $C_{23}H_{45}O_3$ 369.336871 (11.9%); found 396.356000 (M^+), calculated for $C_{25}H_{48}O_3$ 396.360346 (0.7%).

The ketoalcohol fraction (**VI**) was eluted by 20% ethyl acetate in petroleum ether to yield 0.28 g, m.p. 58–59°C. IR, 3387, 2900, 1709, 1064 cm^{-1}; ^1H NMR, 3.64 (2H, CH_2OH, *t, J* = 7 Hz), 2.38 (4H, CH_2COCH_2, *t, J* = 7 Hz). ^{13}C NMR, 211.4, 62.6, 42.4, 32.3, 31.4, 29.1, 29.0, 28.8, 25.3, 23.4, 22.2, 13.7. High-resolution MS of the molecular ions (MH^+) of the ketojojoba alcohols are as follows: found 313.313571, calculated for $C_{20}H_{41}O_2$ 313.310656 (40.5% of total area in the GC chromatogram); found 341.336426, calculated for $C_{22}H_{45}O_2$ 341.341956 (33.7%).

*Bis-acetohydrinjojoba (**VII**; Scheme 3).* A solution of 1 g (1.6 mmol) of **II**, 4 mL of glacial acetic acid, 0.5 mL of H_2O, and 6 mL of acetic anhydride in 60 mL DMF was refluxed for 24 h to yield 89% of **VII** (70% pure), m.p. 50–51°C. IR, 3391, 1175 cm^{-1}; ^1H NMR, 4.9 [2.7H, $CH(OAc)CH(OH)$, *m*].

*Bis-aminohydrinjojoba (**VIII**; Scheme 3).* A solution of 1 g (1.6 mmol) of **II**, 4 mL of glacial acetic acid, 0.5 mL of H_2O, and 6 mL of diethylamine in 60 mL DMF was refluxed for



$CH_3(CH_2)_7\overset{OAc}{CH}\underset{OH}{CH}(CH_2)_mCOO(CH_2)_n\overset{OAc}{CH}\underset{OH}{CH}(CH_2)_7CH_3$

VII*

$CH_3(CH_2)_7\overset{N(C_2H_5)_2}{CH}\underset{OH}{CH}(CH_2)_mCOO(CH_2)_n\overset{N(C_2H_5)_2}{CH}\underset{OH}{CH}(CH_2)_7CH_3$

VIII*

*One of several possible isomers

SCHEME 3

24 h to yield 78% of semisolid **VIII**. IR, 3415, 1085 cm^{-1}; ^{1}H NMR, 5.1 [1.9H, CH(NEt$_2$)CH(OH), *m*]; calculated for N: 4.0%; found 2.4%.

RESULTS AND DISCUSSION

During our studies on the chemistry of jojoba bis-epoxide (**II**), we found that reactions of this material with the iodide ion do not proceed at low temperatures (below room temperature) with an acid catalyst, and after 24 h the starting material is collected unchanged. In contrast, short-chain epoxides react readily at low temperatures (5°C) under acid conditions, and care must be taken to isolate the resulting iodohydrin (12) before a pinacol rearrangement can take place (7).

In this study, warming was required for the reaction of iodide ion with **II**: only after 15 min at 35°C or 2–3 min at 56°C could we detect a reaction product having a lower R_f on TLC than that of **II**. The progress of the reaction is illustrated in Figure 1, which shows that the reaction leveled off after 2 h at 35°C or after 45 min at 56°C. By following the reaction carefully (by TLC and NMR), we found that the product of the first reaction started to convert to another product while the first reaction was still in progress.

A comprehensive workup was conducted on the two products isolated after the reaction had gone to completion (24 h at 35°C or 5 h at 56°C). TLC showed the first product to be the more polar of the two products. This product showed new signals in the NMR spectrum, δ 4.2–4.0 (3.4H, *m*, C*H*OH and C*H*I, 85% pure), but no epoxide hydrogens (δ 2.91). This product is the iodohydrin **III**, formed by the nucleophilic attack of I$^-$ on the epoxide.

The IR spectrum of the other product showed two carbonyl peaks at 1709 and 1732 cm^{-1}. The first peak is typical of a chain ketone (12) and the second peak of the original ester group of the jojoba chain. The ^{1}H NMR spectrum of this second product did not give a signal for epoxide hydrogens (δ 2.91) or any other hydrogens α to the oxygen atom. Instead, a new signal appeared at δ 2.32 (8 H), which is typical of a ketone group [CH_2C(O)R] (13). ^{13}C NMR confirmed the structure, showing new signals at δ 211.6 of the carbonyl carbon and at δ 42.7 of the α-carbon to the carbonyl (13). The epoxide carbons at 57.1 disappear. The carbon of the ester group appears at δ 174.0, and the alkoxy carbon at 64.3, as shown in the jojoba wax (**I**) and the epoxide (**II**). This product was therefore assigned as bis-keto-jojoba (**IV**). The progress of the rearrangement is shown in Figure 2. It is clear that the opening of the epoxide ring is faster than the rearrangement of the iodohydrin to the keto product. The reaction pathway is illustrated in Figure 3.

Several possible isomers may be obtained for the products jojoba bis-iodohydrin (**III**) and bis-ketojojoba (**IV**): The epoxide rings could be opened from either side to yield several isomers of **III**, and the hydrogen migrating to form the keto group could come from either side of a carbocation formed during the rearrangement.

The equal statistical probability of ring opening and hydride shift during the rearrangement taking place on either side of the epoxide ring is confirmed by the mass spectrum (MS) of the rearranged product. Transesterification of the rearranged product with acidic methanol to yield methyl esters of the ketojojoba acids (**V**) and the free ketoalcohols (**VI**) (Scheme 4), followed by preparative TLC separation, afforded a methyl ketojojoboate mixture consisting of 1.7% C$_{18}$ acid, 60.3% C$_{20}$ acid, 11.9% C$_{22}$ acid, and 0.7% C$_{24}$ acid (Table 1), and a ketoalcohol fraction containing two alcohols, C$_{20}$ (40.5%) and C$_{22}$ (33.7%). The methyl ketojojoboate ester

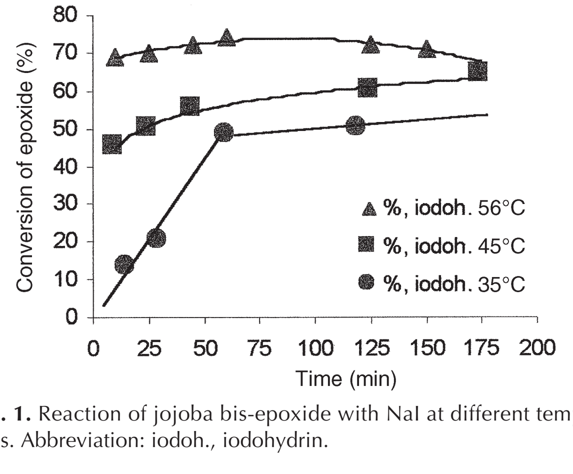


FIG. 1. Reaction of jojoba bis-epoxide with NaI at different temperatures. Abbreviation: iodoh., iodohydrin.

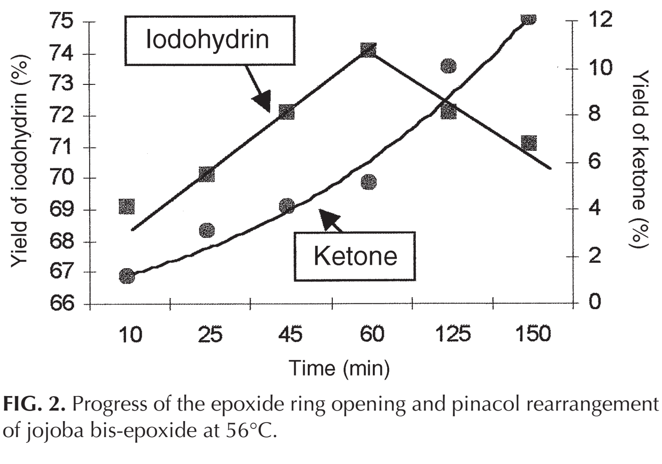
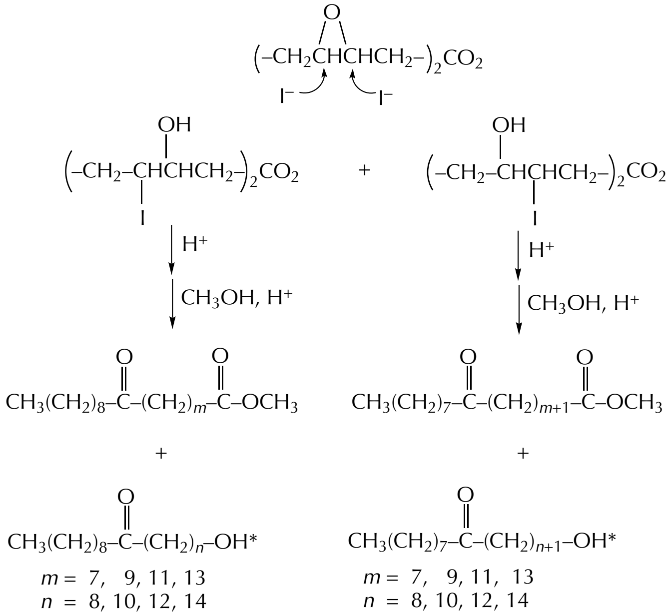


FIG. 2. Progress of the epoxide ring opening and pinacol rearrangement of jojoba bis-epoxide at 56°C.



*One of several possible isomers

FIG. 3. Formation of iodohydrin, rearrangement to ketojojoba, and transesterification to methyl ketojojoboate and ketojojoba alcohol.

TABLE 1
Methyl Ketojojoboate Ester Mixture as Determined by GC–MS[a]

Ester	M.W.	% of total area
C_{18}: $m = 7$	312	1.7
C_{20}: $m = 8$	340	60.3
C_{22}: $m = 10$	368	11.9
C_{24}: $m = 12$	396	0.7

[a] For identification of m and $m + 1$, see Figure 3.

TABLE 2
MS Peaks for the First Set of Methyl Ketojoboate Esters (from Scheme 4)

Ester	y	MH^+	a	b	c	d	e	f
C_{18}	6	313	281	239	156	157	214	98
C_{20}	8	341	309	267	156	185	242	98
C_{22}	10	369	337	295	156	213	270	98
C_{24}	12	397	365	323	156	241	298	98

TABLE 3
MS Peaks for the Second Set of Methyl Ketojojoboate Esters (from Scheme 4)

Ester	y	MH^+	a_1	b_1	c_1	d_1	e_1	f_1
C_{18}	5	313	281	239	170	143	200	112
C_{20}	7	341	309	267	170	171	228	112
C_{22}	9	369	337	295	170	199	256	112
C_{24}	11	397	365	323	170	227	284	112

(**V**) fraction is, in fact, a mixture of isomers, namely, those that depend on the position of the carbonyl group in each of the ester chains. The carbonyl group could be located either at C_9 (first set, counted from the methyl end of the chain) or at C_{10} (second set), as expected from random ring opening and hydride shift. The two sets of ester isomers have structures shown in Scheme 4.

The corresponding MS peaks for the assigned cleavages are summarized in Tables 2 and 3. As can be seen from the Tables, cleavages c and f of the first set are 14 mass units smaller than the corresponding c_1 and f_1 cleavages of the second set. The completing cleavages d and e of the first set are larger by 14 mass units than d_1 and e_1. All the other peaks are identical in the two sets. This finding means that the difference between the two sets lies in one methylene group, namely, whether the carbonyl is located on C_9 or C_{10}. Since the intensities of the two sets of peaks is about 1:1, the two regional isomers were obtained in equal amounts, resulting from statistically even nucleophilic substitution on the epoxide ring by the iodide ion.

The same MS results were obtained for the ketoalcohol (**VI**) fraction (MS not shown), demonstrating that the process occurs on both sides of the long jojoba ester chain. It is important to note the relative abundance of the methyl ketojojoboate and the ketoalcohols in the rearranged products is in line with the natural composition of the acids and alcohols of jojoba wax.

The reaction of the bis-epoxide of *trans*-jojoba (5) was found to take place at a somewhat lower rate than that of the natural wax *cis*-jojoba. This finding means that there is small effect of the configuration of the epoxide ring on the reaction rate.

Two other nucleophiles were also reacted with the jojoba bis-epoxide—acetate and amine—giving bis-acetoxyhydrinjojoba (**VII**) and bis-diethylaminohydrinjojoba (**VIII**), respectively. The opening of the epoxide ring by these reagents was slower, and the yield was lower for the products vs. the iodide reaction. In addition, these products were not as pure as the iodohyrin products, since the opening of the two epoxide rings did not advance to completion, as can be seen from elemental analyses and NMR integration of the appropriate

(**V**)

First set of methyl ketojojoboate esters Second set of methyl ketojojoboate esters

SCHEME 4

signals. In many of the molecules, only one epoxide ring was opened, while the other remained intact. More drastic conditions are needed for complete conversion of both epoxide rings to the desired products (14).

Jojoba wax has promise as a renewable natural product component in cosmetic and other technological applications. It is likely that chemically modified wax—with new physical and chemical properties—will find new applications. Therefore, simple and efficient chemical procedures are being sought to transform the liquid wax into new chemical entities. As part of our ongoing studies on jojoba wax, we have now introduced a simple two-step process to convert the two olefinic bonds in the wax into keto groups. This reaction opens a new pathway to many potential derivatives, based on the carbonyl functional group. The reaction involves a pinacol rearrangement in the long-chain wax, even though it is much slower than that in short chains (Zeltser, I., and A. Shani, unpublished results). Its advantage is that no hydroxy derivatives are formed, in contrast to the classical pinacol rearrangement of long-chain epoxyacids and esters (8).

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