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Synthesis of Optically Active Methyl 12-Oxo-9,10-epoxyoctadecanoate*

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Abstract—The procedure for synthesizing optically active methyl 12-oxo-9,10-epoxyoctadecanoate (enantiomeric purity ~90%) was developed, starting from ricinolic acid methyl ester.

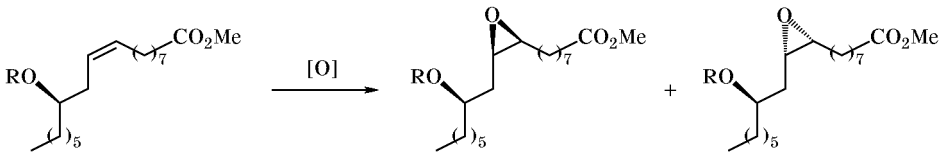
Derivatives of ricinolic [(9*Z*,12*R*)-12-hydroxy-9-octadecenoic] acid are known to exhibit a wide spectrum of biological activity [1–3]. One of the key compounds in the chemistry of ricinolic acid is methyl 12-oxo-9,10-epoxyoctadecanoate (**I**). Due to its high reactivity compound **I** can be used for preparation of a number of practically important substances [1, 4, 5]. Up to now, there were no published data on the synthesis of optically active ketoepoxy ester **I**.

The goal of the present study was to synthesize optically active compound **I** through intramolecular asymmetric induction of the chiral (*R*)-center at C^{12} in the molecule of methyl (9*S*,12*R*)-12-hydroxy-9-octadecenoate (**II**). The procedure was based on the epoxidation of the double C=C bond in ester **II**, followed by oxidation of the 12-hydroxy group to carbonyl (Scheme 1).

In the first stage compound **II** was treated with monoperoxyphthalic acid as epoxidating agent. The latter was taken in a 1.5–2-fold excess. The reaction afforded 95% of methyl 12-hydroxy-9,10-epoxyoctadecanoate which was formed as a mixture of two diastereoisomers, (9*S*,10*R*,12*R*) (**IIIa**) and (9*R*,10*S*,12*R*) (**IIIb**) at a ratio of 62 : 38; enantiomeric excess (ee) 24%; $[\alpha]_D^{20}$ –3.25°. Taking into account that neither ^{1}H nor ^{13}C NMR spectra of compounds **IIIa** and **IIIb** were reported, they were identified by epoxidation of hydroxy ester **II** with *tert*-butyl hydroperoxide in the presence of $VO(acac)_2$ [6], which leads to formation of (9*S*,10*R*,12*R*)-isomer **IIIa** as the major product (ee 90%). The configurations of **IIIa** and **IIIb** were thus determined by comparing the ^{1}H and ^{13}C NMR spectral parameters of the products obtained by the above two methods.

The reaction of methyl (9*Z*,12*R*)-12-acetoxy-9-octadecenoate (**IV**) with monoperoxyphthalic acid in diethyl ether showed that replacement of the hydroxy group by acetoxy did not change the stereoselectivity

Scheme 1.



II, IV **IIIa, Va** (9*S*,10*R*,12*R*) **IIIb, Vb** (9*R*,10*S*,12*R*)

II, **III**, R = H; **IV**, **V**, R = Ac.

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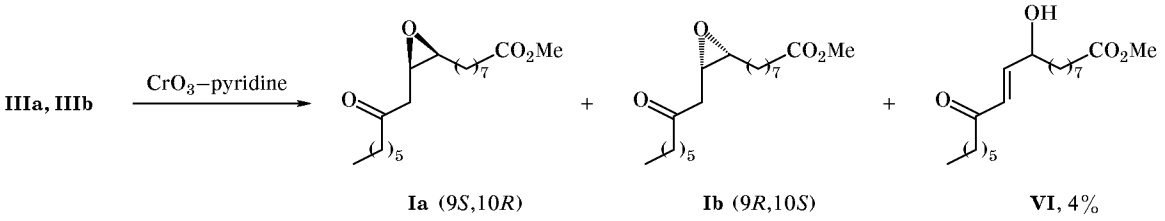
Scheme 2.



of the process to an appreciable extent. Methyl (9*S*,10*R*,12*R*)- and (9*R*,10*S*,12*R*)-12-acetoxy-9,10-epoxyoctadecanoates **Va** and **Vb** were identified by acetylation of a 95:5 mixture of hydroxy derivatives **IIIa** and **IIIb** and subsequent comparison of the ^{1}H and ^{13}C NMR spectra. It should be noted that the reaction of **IV** with *tert*-butyl hydroperoxide in the presence of $VO(acac)_2$ [6] gave no epoxidation products. Optically active ketoepoxy derivative **I** was obtained by oxidation of a mixture of compounds **IIIa** and **IIIb** according to Collins (CrO_3–pyridine). The reaction afforded a mixture of methyl (9*S*,10*R*)- and (9*R*,10*S*)-12-oxo-9,10-epoxyoctadecanoates **Ia** and **Ib** in 52–56% yield. From diastereoisomeric mixture **IIIa**/**IIIb** enriched in **IIIa** (95:5) we obtained compound **I** with a high enantiomeric purity (ee 90%). In addition, methyl (10*E*)-9-hydroxy-12-oxo-10-octadecenoate (**VI**) was isolated as by-product; its yield did not exceed 4%.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C) using $CDCl_3$ as solvent which contained TMS as internal reference. The IR spectra were measured on a Specord M-80 instrument; samples were examined as thin films. The UV spectrum was obtained on a Specord M-400 spectrophotometer. The mass spectra were run on an MKh-1300 spectrometer. Samples were introduced through an inlet batch heated to 100°C; energy of ionizing electrons 12 and 70 eV. The optical rotations were measured on a Perkin–Elmer 241MS polarimeter.

Methyl (9*Z*,12*R*)-12-hydroxy-9-octadecenoate (II). To a 0.5% solution of sodium methoxide in toluene (100 ml) we added dropwise a solution of 10 g of castor oil in 20 ml of toluene. The mixture was stirred for 10 min at 50°C, evaporated by half, and neutralized with acetic acid. Water, 70 ml, was added, the mixture was extracted with petroleum ether, and the extract was washed with water, dried over Na_2SO_4, and evaporated to obtain 9.6 g of methyl esters derived from fatty acids of castor oil. By column chromatography on silica gel (L 100/160 μm, eluent petroleum ether containing 1 to 100% of diethyl ether) we isolated 7.8 g of ester **II**, $[\alpha]_D^{20}$ +4.98°.

Methyl (9*Z*,12*R*)-12-acetoxy-9-octadecenoate (IV) was synthesized by acetylation of ester **II** with AcCl in benzene in the presence of pyridine, following the procedure reported in [3], $[\alpha]_D^{20}$ +21.05°.

Epoxidation of ester II with monoperoxyphthalic acid. To a solution of 1.0 g (3.2 mmol) of ester **II** in 20 ml of diethyl ether we added dropwise with stirring at 0°C a solution of 0.9 g (4.8 mmol) of peroxyphthalic acid in 7 ml of diethyl ether. The mixture was kept for 3 h at 0°C and was left overnight at room temperature. It was then filtered, washed with saturated solutions of Na_2SO_3 (3 × 5 ml) and Na_2CO_3 (3 × 5 ml), dried over $MgSO_4$, and evaporated. By column chromatography on silica gel (L 100/250 μm, eluent petroleum ether–ethyl acetate, 15:1) we isolated 1 g (95%) of a mixture containing diastereoisomeric hydroxyepoxides **IIIa** and **IIIb** at a ratio of 62:38 (ee 24%, according to the ^{13}C NMR data), $[\alpha]_D^{20}$ –3.25° (*c* = 11.25, $CHCl_3$). IR spectrum, ν, cm^{-1}: 752 (C–O–C, epoxy group); 1172, 1740 (CO_2); 3448 (OH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.84 t (3H, $C^{18}H_3$, 7.0), 1.2–1.66 m (22H, CH_2), 1.67–1.73 m (2H, $C^{11}H_2$, **IIIb**), 1.77 t (1H, $C^{11}H$, **IIIa**, 4.0), 1.82 t (1H, $C^{11}H$, **IIIa**, 4.0), 2.28 t (2H, CH_2CO_2, 7.5), 2.87–2.98 m (1H, C^9H), 3.08–3.17 m (1H, $C^{10}H$), 3.65 s (3H, CO_2CH_3), 3.80–3.93 m (1H, $C^{12}H$). ^{13}C NMR spectrum of **IIIa**, δ_C, ppm: 13.98 (C^{18}), 22.51 (C^{17}), 24.76 (C^3), 25.43 (C^{14}), 26.28 (C^7), 27.77 (C^8), 28.89 (C^4), 29.04 (C^5), 29.16 (C^{15}), 29.20 (C^6), 31.72 (C^{16}), 33.90 (C^2), 34.73 (C^{11}), 37.30 (C^{13}), 51.34 ($CO_2\mathbf{C}H_3$), 55.18 (C^{10}), 56.27 (C^9), 70.53 (C^{12}), 174.18 (C^1). ^{13}C NMR spectrum of **IIIb**, δ_C, ppm: 13.98 (C^{18}), 22.51 (C^{17}), 24.76 (C^3), 25.51 (C^{14}), 26.30 (C^7), 27.89 (C^8), 28.89 (C^{14}), 29.04 (C^5), 29.16 (C^{15}), 29.20 (C^6), 31.72 (C^{16}), 33.90 (C^2), 35.14 (C^{11}), 37.70 (C^{13}), 51.34 ($CO_2\mathbf{C}H_3$), 54.48 (C^{10}), 57.11 (C^9), 69.71 (C^{12}), 174.18 (C^1). Mass spectrum, *m*/*z*: 328 $[M]^+$.

Epoxidation of ester II with *tert*-butyl hydroperoxide in the presence of $VO(acac)_2$ was carried

out according to the known procedure [6]. From 0.5 g (1.6 mmol) of ester **II** we obtained 0.51 g (98%) of a mixture of hydroxyepoxides **IIIa** and **IIIb** at a ratio of 95:5 (ee 90%, according to the ^{13}C NMR data), $[\alpha]_{80}^{20}$ –8.75° (*c* = 1.16, $CHCl_3$).

Epoxidation of ester IV with monoperoxyphthalic acid. Following the above procedure, from a solution of 1 g (2.8 mmol) of ester **IV** in 20 ml of diethyl ether and 1 g (5.6 mmol) of monoperoxyphthalic acid in 5.4 ml of diethyl ether we obtained 0.93 g (90%) of a mixture containing acetoxyepoxides **Va** and **Vb** at a ratio of 54:46 (ee 8%, according to the ^{13}C NMR data), $[\alpha]_D^{20}$ +13.88° (*c* = 11.00, $CHCl_3$). IR spectrum, ν, cm^{-1}: 760 (C–O–C, epoxy group); 1240, 1736 (CO_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.77 t (3H, $C^{18}H_3$, 6.6), 1.20–1.67 m (22H, CH_2), 1.68–1.75 m (2H, $C^{11}H_2$, **Vb**), 1.80 t (1H, $C^{11}H$, **Va**, 4.6), 1.83 t (1H, $C^{11}H$, **Va**, 4.5), 1.95 s (3H, CH_3CO_2), 2.19 t (2H, C^2H_2, 7.6), 2.71–2.91 m (2H, C^9H, $C^{10}H$), 3.55 s (3H, CO_2CH_3), 4.92–5.10 m (1H, $C^{12}H$). ^{13}C NMR spectrum of **Va**, δ_C, ppm: 14.02 (C^{18}), 21.20 ($\mathbf{C}H_3CO_2$), 22.56 (C^{17}), 24.86 (C^3), 25.20 (C^{14}), 26.47 (C^8), 27.94 (C^{15}), 29.01 (C^4), 29.06 (C^5, C^6), 29.15 (C^7), 31.69 (C^{16}), 32.76 (C^{13}), 34.06 (C^2), 34.33 (C^{11}), 51.41 (OCH_3), 53.65 (C^{10}), 56.10 (C^9), 72.39 (C^{12}), 170.60 (CO), 174.19 (C^1). ^{13}C NMR spectrum, δ_C, ppm: 14.02 (C^{18}), 21.20 ($\mathbf{C}H_3CO_2$), 22.68 (C^{17}), 24.86 (C^3), 25.34 (C^{14}), 26.47 (C^8), 27.94 (C^{15}), 29.01 (C^4), 29.06 (C^5, C^6), 29.15 (C^7), 31.69 (C^{16}), 32.62 (C^{13}), 34.06 (C^2), 34.33 (C^{11}), 51.41 ($CO_2\mathbf{C}H_3$), 53.86 (C^{10}), 56.76 (C^9), 72.39 (C^{12}), 170.77 (CO), 174.19 (C^1). Mass spectrum, *m*/*z*: 370 $[M]^+$.

Acetylation of hydroxyperoxides IIIa and IIIb. A solution of hydroxyepoxides **IIIa** and **IIIb** (0.5 g, 1.53 mmol) at a ratio of 95:5, freshly distilled acetic anhydride (0.16 g, 1.53 mmol), and pyridine (0.15 g, 1.84 mmol) in benzene (5 ml) was refluxed for 3 h. The mixture was cooled and poured into ice water (10 ml), and the products were extracted into Et_2O (2 × 1 ml). The extract was washed with 5% hydrochloric acid (2 × 2 ml) and water (2 × 2 ml), dried over $MgSO_4$, and evaporated to obtain 0.54 g (97%) of a mixture of acetoxyepoxides **Va** and **Vb** at a ratio of 95:5 (ee 90%, according to the ^{13}C NMR data), $[\alpha]_D^{20}$ +11.24° (*c* = 10.0, $CHCl_3$).

Oxidation of hydroxyepoxides IIIa/IIIb with Collins' reagent. To a mixture of 2.75 g (34.7 mmol) of pyridine and 18 ml of CH_2Cl_2 we added on cooling to 0°C 1.6 g (16 mmol) of CrO_3 in small portions, and the mixture was stirred for 2 h until its color changed from yellow to red. To the resulting Collins' reagent we added 0.88 g (2.68 mmol) of a mixture of hydroxyepoxides **IIIa** and **IIIb** (ratio 62:38) in 3 ml of CH_2Cl_2, and the mixture was stirred for 30 min at 20°C. It was then passed through a layer of Al_2O_3, the sorbent was washed with $CHCl_3$, the solvent was evaporated, and pyridine was removed under reduced pressure on heating to ~50°C. The residue, 0.55 g, was subjected to column chromatography on silica gel (L 40/100 μm; eluent petroleum ether–ethyl acetate, 10:1) to isolate 0.29 g (52%) of a mixture of ketoepoxides **Ia** and **Ib** and 0.02 g (4%) of ester **VI**. Mixture **Ia**/**Ib**, $[\alpha]_D^{20}$ +2.12° (*c* = 1.00, $CHCl_3$). The IR, ^1H and ^{13}C NMR, and mass spectra of compound **I** were consistent with those reported previously [4].

Ester VI. UV spectrum (ethanol), λ_{max}, nm (log ε): 223.4 (3.70). IR spectrum, ν, cm^{-1}: 976 (*trans*-C=C); 1072, 1472 (OH); 1176, 1732 (CO_2); 1376, 1676 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.77 t (3H, $C^{18}H_3$, 6.7), 1.12–1.63 m (20H, CH_2), 2.21 t (2H, C^2H_2, 7.5), 2.47 t (2H, $C^{13}H_2$, 7.4), 2.90 br.s (1H, OH), 3.57 s (3H, CO_2CH_3), 4.21 q (1H, C^9H, 6.7), 6.21 d (1H, $C^{11}H$, 15.9), 6.71 d.d (1H, $C^{10}H$, 15.9 and 4.9). ^{13}C NMR spectrum, δ_C, ppm: 13.67 (C^{18}), 22.16 (C^{17}), 23.85 (C^3), 24.53 t (C^7), 24.86 (C^{14}), 28.63 t (C^{15}), 28.69 (C^6), 28.78 (C^4), 28.95 (C^5), 31.27 (C^{16}), 33.70 (C^2), 36.40 (C^8), 40.33 (C^{13}), 51.08 ($CO_2\mathbf{C}H_3$), 70.72 (C^9), 127.70 (C^{11}), 148.02 (C^{10}), 173.98 (C^1), 200.72 (C^{12}). Mass spectrum, *m*/*z*: 326 $[M]^+$.

From a mixture of hydroxyepoxides **IIIa** and **IIIb** (0.34 g, 1.04 mmol; ratio **IIIa**:**IIIb** 95:5) oxidized with Collins' reagent by a similar procedure we obtained 0.34 g of a nonvolatile residue. By column chromatography we isolated 0.19 g (56%) of **Ia**/**Ib**, $[\alpha]_D^{20}$ +10.60° (*c* = 1.0, $CHCl_3$).

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