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Catalytic Cyclopropanation of Ricinolic Acid Derivatives with Diazomethane

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Abstract—The reaction of ricinolic acid methyl ester with diazomethane in the presence of $Co(BF_4)_2 \cdot 6H_2O$ results in selective methylation of the hydroxy group. Methyl (2*Z*,12*R*)-12-acetoxy-9-octadecenoate reacts with diazomethane in the presence of $Pd(acac)_2$, leading to formation of a mixture of *cis*-cyclopropanated (9*S*,10*S*,12*R*)- and (9*R*,10*R*,12*R*)-diastereoisomers at a ratio of 3:2 (overall yield 73%). Under similar conditions methyl (9*Z*)-12-oxo-9-octadecenoate gives rise to optically inactive methyl *cis*-8-[2-(2-oxooctyl)-cyclopropyl]octanoate.

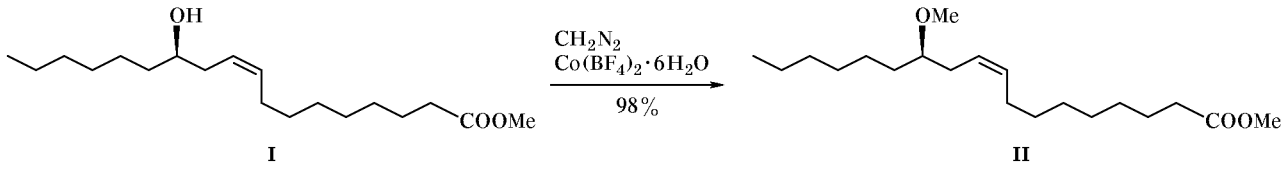
Due to its accessibility and the presence of a chiral *R*-center in position *12*, ricinolic acid [(9*Z*,12*R*)-12-hydroxy-9-octadecenoic acid] is a promising synthon for preparation of optically active polyfunctional compounds [1, 2]. Ricinolic acid derivatives also attract interest as suicidal lipoxygenase substrates [3]. Until present, there were almost no published data on the synthesis of cyclopropane-containing ricinolic acid derivatives. The procedure for Simmons–Smit cyclopropanation of ricinolic acid methyl ester was reported to occur with low regioselectivity; no data on optical activity of the products were given [4, 5]. We previously found [6] that catalytic [1+2]-cycloaddition of methylene species generated from diazomethane at double C=C bonds of unsaturated compounds is a convenient method of synthesis of cyclopropanes.

The present communication reports on the results of our study of the reaction of methyl (9*Z*,12*R*)-12-hydroxy-, (9*Z*,12*R*)-12-methoxy-, (9*Z*,12*R*)-12-acetoxy-, and (9*Z*)-12-oxo-9-octadecenoates **I**–**IV** with diazomethane, catalyzed by copper and palladium compounds. Methyl (9*Z*,12*R*)-12-methoxy-9-octadecenoate (**II**, $[\alpha]_D^{28}$ = +8.33°) was synthesized in 98% yield by reaction of ester **I** with 4-fold excess of diazomethane in pentane at 20°C in the presence of $Co(BF_4)_2 \cdot 6H_2O$ as catalyst. The insertion of CH_2 group into the O–H bond occurred with retention of the optically active *R*-center (Scheme 1).

Under the selected conditions [substrate-to-CH_2N_2-to-catalyst ratio 1:5:0.01; 0°C, Et_2O or CH_2Cl_2; catalyst = $Cu(CF_3SO_3)_2$, $Pd(OAc)_2$, or $Pd(acac)_2$], the double C=C bonds in olefins **I** and **II** were not involved, despite vigorous decomposition of CH_2N_2.

Diastereofacial differentiation, resulting from intramolecular asymmetric induction, was observed only in the cyclopropanation of methyl (9*Z*,12*R*)-12-acetoxy-9-octadecenoate (**III**) which reacted with diazomethane in the presence of $Pd(acac)_2$. The products were methyl *cis*-(9*S*,10*S*,12*R*)-12-acetoxy-9,10-methyleneoctadecanoate (**Va**) and *cis*-(9*R*,10*R*,12*R*)-

Scheme 1.



I **II**

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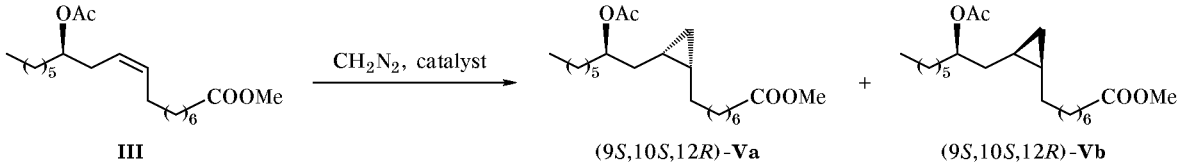
Scheme 2.



III (9*S*,10*S*,12*R*)-**Va** (9*S*,10*S*,12*R*)-**Vb**

Catalyst	Yield, %	Ratio **Va**:**Vb**
$Pd(acac)_2$	73	3:2
$Pd(OAc)_2$	5	3:2
$Cu(CF_3SO_3)_2$	25	4:5

12-acetoxy-9,10-methyleneoctadecanoate (**Vb**) at a ratio of 3:2, which we failed to separate (Scheme 2). The overall yield was 73%, $[\alpha]_D^{20}$ = +16.1°. With $Pd(OAc)_2$ or $Cu(CF_3SO_3)_2$ as catalyst the yield of compounds **Va** and **Vb** was reduced to 5–25%. Unlike $Pd(acac)_2$ and $Pd(OAc)_2$, $Cu(CF_3SO_3)_2$ favored predominant formation of isomer **Vb**.

The structure of products **Va** and **Vb** was confirmed by spectral data. Most proton signals in the ^{1}H NMR spectra were unresolved multiplets located in a narrow range. Two triplets at δ –0.33 and –0.29 ppm (^3J = 6.3 Hz) with an overall intensity corresponding to one proton belong to the *cis*-proton of the cyclopropane methylene group; the substituents in the cyclopropane ring are arranged *cis*. Splitting of the above signal is caused by diastereotopic effect. In the two-dimensional ^{1}H–^{1}H COSY spectrum we observed cross peaks resulting from spin–spin coupling between the upfield triplets (δ –0.33 and –0.29 ppm) and a three-proton multiplet in the region δ 0.5–0.7 ppm; the latter corresponds to one *trans*- and two *cis*-protons of the cyclopropane ring. The ^{13}C NMR spectrum recorded with broad-band decoupling from protons contained paired signals from the C^9–C^{13} atoms. The small difference in their chemical shifts ($\Delta\delta_C$ 0.1–0.5 ppm) suggests that magnetic nonequivalence of the corresponding nuclei is determined by diastereotopicity rather than by *cis*/*trans* isomerism, otherwise the difference between the chemical shifts of α-CH_2 (C^8 and C^{11}) would be as large as ~10 ppm. The diastereoisomeric configurations were derived from comparison of our spectral data with those published in [2, 7, 8]. The **Va**:**Vb** isomer ratio was determined from the ^{13}C NMR spectra.

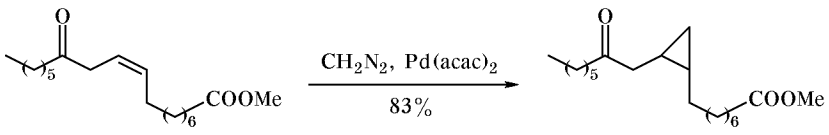
In order to prove that intramolecular asymmetric induction originates from the chiral *R*-center in position *12*, compound **I** was oxidized according to Collins [3] to obtain methyl (9*Z*)-12-oxo-9-octadecenoate (**IV**) which was then treated with diazomethane in the presence of $Pd(acac)_2$. We thus isolated 83% of methyl *cis*-8-[2-(2-oxooctyl)cyclopropyl]octanoate (**VI**) (Scheme 3). According to the spectral and chromatographic data, product **VI** was an individual optically inactive substance.

Our results show that the reactivity of the *cis*-C=C bond increases on introduction of a carbonyl or carboxy group into the homoallylic position. Probably, such groups favor formation of intramolecular π-complexes of palladium with olefins **III** and **IV**. The result is that their coordinating activity increases. In keeping with the data of [6], just this factor is responsible for the reactivity of unsaturated compounds in cyclopropanation with diazomethane in the presence of palladium catalysts.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were taken on a Bruker AM-300 spectrometer in $CDCl_3$. The IR spectra were recorded on a Specord M-80 instrument from samples prepared as thin films. The mass spectra (electron impact, 70 and 12 eV) were obtained on an MKh-1300 spectrometer, batch inlet temperature 100°C. The products were analyzed on a Chrom-5

Scheme 3.



IV **VI**

chromatograph, flame-ionization detector, 1200 × 5-mm column packed with 5% of SE-30 on Inerton N-AW DMCS (0.125–0.160 mm), carrier gas helium. The optical rotations were measured on a Perkin–Elmer 241 MC spectropolarimeter. Compounds **Va**, **Vb**, and **VI** were isolated by preparative gas–liquid chromatography using a Perkin–Elmer F21 instrument; 5000 × 8-mm column packed with 5% of SE-30 on Inerton N-AW; oven temperature 220°C.

Methyl (9*Z*)-12-oxo-9-octadecenoate (**IV**) was synthesized by the procedure reported in [3].

Methyl (9*Z*,12*R*)-12-hydroxy-9-octadecenoate (I). A solution of 10 g of castor oil in 20 ml of toluene was added dropwise to 100 ml of a 0.5% solution of sodium methoxide in toluene. The mixture was stirred for 10 min at 50°C, evaporated by half, and neutralized with acetic acid. Water, 70 ml, was added, ester **I** was extracted into petroleum ether (bp 40–60°C), and the extract was washed with water, dried over Na_2SO_4, and evaporated. The residue was subjected to column chromatography on silica gel L (100/160 μm) with gradient elution by petroleum ether–diethyl ether (1 to 100% of the latter). We isolated 9.6 g (96%) of compound **I**, $[\alpha]_D^{20}$ = +4.98°.

Methyl (9*Z*,12*R*)-12-methoxy-9-octadecenoate (II). To a mixture of 0.2 g (0.64 mmol) of ester **I** and 4.36 mg (2 mol %) of $Co(BF_4)_2 \cdot 6H_2O$ in 2 ml of pentane we slowly added with stirring at 20°C a solution of 2.56 mmol of diazomethane prepared from 0.53 g (5.12 mmol) of *N*-methyl-*N*-nitrosourea in 5 ml of pentane. The mixture was kept for about 2 h until bright yellow color disappeared. It was then filtered and evaporated to obtain 0.2 g (98%) of ester **II**, $[\alpha]_D^{28}$ = +8.33° (*c* = 1.4, $CHCl_3$). IR spectrum, ν, cm^{-1}: 750, 1125 (C–O–C), 1190, 1455, 1480, 1740 (CO_2), 2875, 2945. ^{1}H NMR spectrum, δ, ppm: 0.83 t (3H, CH_3, *J* = 6.6 Hz), 1.12–1.45, 1.48–1.62 m (20H, CH_2), 1.96 q (2H, CH_2C=, *J* = 6.4 Hz), 2.18 t (2H, CH_2C=, *J* = 5.8 Hz), 2.35 t (2H, CH_2CO_2, *J* = 7.6 Hz), 3.10 m (1H, 12-H), 3.26 s (3H, CH_3O), 3.60 s (3H, CO_2CH_3), 5.45 m (2H, CH=CH, *J* = 5.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 14.08 q (C^{18}), 22.63 t (C^{17}), 24.93 t (C^3), 25.36 t (C^{14}), 27.39 t (C^{13}), 29.12 t (C^4, C^5, C^6), 29.50 t (C^7), 29.56 t (C^{15}), 31.06 t (C^8), 31.87 t (C^{16}), 33.57 t (C^2), 34.06 t (C^{11}), 51.39 q (CO_2**C**H_3), 56.54 q (CH_3O), 80.97 d (C^{12}), 125.43 d (C^{10}), 131.69 d (C^9), 174.23 s (C^1). Mass spectrum: *m*/*z* 326 $[M]^+$.

Methyl (9*Z*,12*R*)-12-acetoxy-9-octadecenoate (III). To a solution of 2 g (6.4 mmol) of ester **I** and 0.6 g (7.5 mmol) of pyridine in 10 ml of benzene we added with stirring and cooling to 0°C 0.6 g (7.5 mmol) of acetyl chloride in 2 ml of benzene. The mixture was refluxed for 2 h, cooled, and washed in succession with a saturated solution of $NaHCO_3$ (3 × 5 ml) and with water (5 ml). The benzene layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 3 ml). The combined extracts were dried over $MgSO_4$ and evaporated to isolate 2.2 g (98%) of ester **III**, $[\alpha]_D^{20}$ = +21.05°. IR spectrum, ν, cm^{-1}: 732, 760, 1024, 1184, 1244 (OAc), 1372, 1449, 1460, 1740 (CO_2), 2360, 2928. ^{1}H NMR spectrum, δ, ppm: 0.85 t (3H, CH_3, *J* = 7.9 Hz), 1.14–1.67 m (20H, CH_2), 1.90–1.98 m (4H, CH_2C=), 2.0 s (3H, CH_3CO_2), 2.28 t (2H, 2-H, *J* = 7.5 Hz), 3.65 s (3H, $COOCH_3$), 4.85 m (1H, 12-H, *J* = 6.2 Hz), 5.25–5.50 m (2H, CH=CH, *J* = 7.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 14.08 q (C^{18}), 21.28 q (CO**C**H_3), 22.59 t (C^{17}), 24.93 t (C^3), 25.37 t (C^{14}), 27.30 t (C^{13}), 29.10 t (C^4, C^5, C^6), 29.15 t (C^7), 29.50 t (C^{15}), 31.75 t (C^8), 31.92 t (C^{16}), 33.59 t (C^{11}), 34.06 t (C^2), 51.46 q (CO_2**C**H_3), 73.98 d (C^{12}), 124.23 d (C^{10}), 132.61 d (C^9), 170.83 s (CO), 174.29 s (C^1). Mass spectrum: *m*/*z* 354 $[M]^+$.

Cyclopropanation of ester III with diazomethane in the presence of $Pd(acac)_2$. *a*. To a mixture of 0.5 g (1.4 mmol) of ester **III** and 4.3 mg (1 mol %) of $Pd(acac)_2$ in 2 ml of Et_2O we added dropwise while stirring at 0°C a solution of 28 mmol of diazomethane, prepared from 5.8 g (56 mmol) of *N*-methyl-*N*-nitrosourea in 60 ml of diethyl ether. The mixture was stirred for 2 h at 0°C until bright yellow color disappeared and was left overnight at room temperature. It was then passed through a layer of Al_2O_3 and evaporated to obtain 0.68 g of a mixture containing, according to GLC data, 23% of unchanged ester **III** and 73% of methyl *cis*-(9*S*,10*S*,12*R*)- and *cis*-(9*R*,10*R*,12*R*)-12-acetoxy-9,10-methyleneoctadecanoates **Va** and **Vb** at a ratio of 3:2, $[\alpha]_D^{20}$ = +16.7° (*c* = 1.4, $CHCl_3$). IR spectrum, ν, cm^{-1}: 845, 1260 (OAc), 1750 (CO_2), 2875, 2940, 2970. ^{1}H NMR spectrum, δ, ppm: –0.33, –0.29 d.t (1H, *cis*-CH in cyclopropane ring, *J* = 6.3 Hz), 0.56–0.73 m (3H, *trans*-CH in cyclopropane ring, *cis*-9-H, *cis*-10-H), 0.82 t (3H, CH_3, *J* = 6.0 Hz), 1.03 m and 1.11–1.40 m (18H, CH_2), 1.44–1.72 m (6H, 8-H, 11-H, 13-H), 2.00 s (3H, $COCH_3$), 2.22 t (2H, CH_2CO_2, *J* = 7.5 Hz), 3.60 s (3H, CO_2CH_3), 4.81–4.95 m (1H, CHOC=O). Mass spectrum: *m*/*z* 368 $[M]^+$.

Diastereoisomer Va. ^{13}C NMR spectrum, δ_C, ppm: 11.01 t (CH_2, cyclopropane), 11.91 d (C^{10}), 13.96 q (C^{18}), 15.44 d (C^9), 21.16 q (CO**C**H_3), 22.50 t (C^{17}), 24.84 t (C^3), 25.28 t (C^{14}), 28.78 t (C^8), 29.12 t

(C^4, C^5, C^6), 29.19 t (C^7), 29.30 t (C^{11}), 29.90 t (C^{15}), 31.67 t (C^{16}), 33.14 t (C^{13}), 33.94 t (C^2), 51.25 q ($CO_2\mathbf{C}H_3$), 74.91 d (C^{12}), 170.68 s (CO), 174.06 s (C^1).

Diastereoisomer Vb. ^{13}C NMR spectrum, δ_C, ppm: 10.80 t (CH_2, cyclopropane), 11.79 d (C^{10}), 13.96 q (C^{18}), 14.94 d (C^9), 21.16 q ($CO\mathbf{C}H_3$), 22.50 t (C^{17}), 24.84 t (C^3), 25.23 t (C^{14}), 29.12 t (C^4, C^5, C^6), 28.67 t (C^8), 29.19 t (C^7), 29.30 t (C^{11}), 29.90 t (C^{15}), 31.67 t (C^{16}), 33.03 t (C^{13}), 33.94 t (C^2), 51.25 q ($CO_2\mathbf{C}H_3$), 74.91 d (C^{12}), 170.63 s (CO), 174.06 s (C^1).

b. Following the above procedure, from 0.3 g (0.85 mmol) of compound **III** and an ether solution of 4.25 mmol of diazomethane in the presence of 1.9 mg (1 mol %) of $Pd(OAc)_2$ we obtained 0.3 g of a mixture containing (GLC) 5% of isomers **Va** and **Vb** and 90% of unchanged ester **III**.

c. Following the above procedure, from 0.3 g (0.85 mmol) of compound **III**, an ether solution of 4.25 mmol of diazomethane, and 1.9 mg (1 mol %) of $Cu(CF_3SO_3)_2$ in CH_2Cl_2 we obtained 0.3 g of a mixture containing (GLC) 25% of isomers **Va** and **Vb** and 60% of unchanged ester **III**.

Methyl *cis*-12-oxo-9,10-methyleneoctadecanoic acid (VI). Following the above procedure, from 0.3 g (0.97 mmol) of ketone **IV**, an ether solution of 19.4 mmol of diazomethane, and 2.9 mg (1 mol %) of $Pd(acac)_2$ we obtained 0.38 g of a mixture containing (GLC) 83% of ester **VI**. IR spectrum, ν, cm^{-1}: 728, 1024, 1168, 1364, 1432, 1460, 1712 (C=O), 1736 (CO_2), 2856, 2928. ^1H NMR spectrum, δ, ppm: –0.33 to –0.25 m, 0.51–0.52 m, and 0.88–1.10 m (4H, cyclopropane ring); 0.82 t (3H, CH_3, J = 5.6 Hz); 1.15–1.60 m (20H, CH_2); 2.20 t (2H, CH_2CO_2, J = 7.5 Hz); 2.30–2.40 m (4H, CH_2CO); 3.57 s (3H, CO_2CH_3). ^{13}C NMR spectrum, δ_C, ppm: 10.71 t (CH_2, cyclopropane ring), 10.88 d (C^9), 13.90 q (C^{18}), 15.20 d (C^{10}), 22.37 t (C^{17}), 23.64 t (C^{14}), 24.79 t (C^3), 28.80 t (C^8), 28.98 t (C^7), 29.13 t (C^6), 29.21 t (C^4, C^5), 29.67 t (C^{15}), 31.50 t (C^{16}), 33.89 t (C^2), 42.24 t (C^{11}), 42.32 t (C^{13}), 51.25 q ($CO_2\mathbf{C}H_3$), 174.06 s (C^1), 211.36 s (C^{12}). Mass spectrum: *m*/*z* 324 $[M]^+$.

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