

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 $\text{Co}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ results in selective methylation of the hydroxy group. Methyl (2*Z*,12*R*)-12-acetoxy-9-octadecenoate reacts with diazomethane in the presence of $\text{Pd}(\text{acac})_2$, 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.

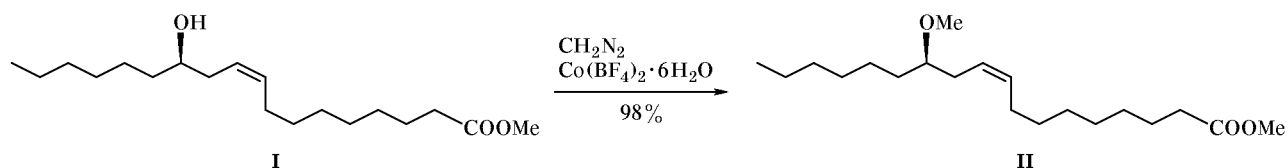
The present communication reports on the results of our study of the reaction of methyl (9*Z*,12*R*)-12-hydroxy-, (9*Z*,12*R*)-12-methoxy-, (9*Z*,12*R*)-12-acetoxy-, and (9*Z*)-12-oxo-9-octadecenoates **I–IV** with

diazomethane, catalyzed by copper and palladium compounds. Methyl (9*Z*,12*R*)-12-methoxy-9-octadecenoate (**II**, $[\alpha]_D^{28} = +8.33^\circ$) 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 $\text{Co}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ as catalyst. The insertion of CH_2 group into the O–H bond occurred with retention of the optically active *R*-center (Scheme 1).

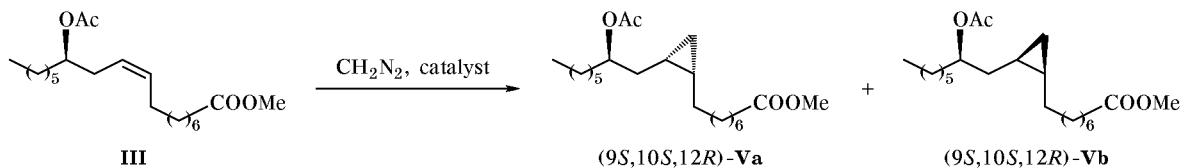
Under the selected conditions [substrate-to- CH_2N_2 -to-catalyst ratio 1:5:0.01; 0°C, Et_2O or CH_2Cl_2 ; catalyst = $\text{Cu}(\text{CF}_3\text{SO}_3)_2$, $\text{Pd}(\text{OAc})_2$, or $\text{Pd}(\text{acac})_2$], the double C=C bonds in olefins **I** and **II** were not involved, despite vigorous 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 $\text{Pd}(\text{acac})_2$. 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.



Scheme 2.



Catalyst	Yield, %	Ratio Va : Vb
$\text{Pd}(\text{acac})_2$	73	3:2
$\text{Pd}(\text{OAc})_2$	5	3:2
$\text{Cu}(\text{CF}_3\text{SO}_3)_2$	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%, $[\alpha]_{\text{D}}^{20} = +16.1^\circ$. With $\text{Pd}(\text{OAc})_2$ or $\text{Cu}(\text{CF}_3\text{SO}_3)_2$ as catalyst the yield of compounds **Va** and **Vb** was reduced to 5–25%. Unlike $\text{Pd}(\text{acac})_2$ and $\text{Pd}(\text{OAc})_2$, $\text{Cu}(\text{CF}_3\text{SO}_3)_2$ favored predominant formation of isomer **Vb**.

The structure of products **Va** and **Vb** was confirmed by spectral data. Most proton signals in the ^1H NMR spectra were unresolved multiplets located in a narrow range. Two triplets at $\delta -0.33$ 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 ^1H - ^1H COSY spectrum we observed cross peaks resulting from spin-spin coupling between the upfield triplets ($\delta -0.33$ and -0.29 ppm) and a three-proton multiplet in the region $\delta 0.5$ – 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 ($\Delta\delta_{\text{C}}$ 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 $\alpha\text{-CH}_2$ (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.

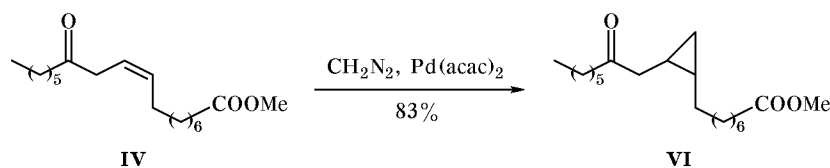
In order to prove that intramolecular asymmetric induction originates from the chiral *R*-center in position 12, compound **I** was oxidized according to Collins [3] to obtain methyl (9*Z*)-12-oxo-9-octadecenoate (**IV**) which was then treated with diazomethane in the presence of $\text{Pd}(\text{acac})_2$. 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 ^1H 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.



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 Na₂SO₄, 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**, $[\alpha]_D^{20} = +4.98^\circ$.

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(BF₄)₂ · 6H₂O 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**, $[\alpha]_D^{28} = +8.33^\circ$ (*c* = 1.4, CHCl₃). IR spectrum, ν , cm^{−1}: 750, 1125 (C–O–C), 1190, 1455, 1480, 1740 (CO₂), 2875, 2945. ¹H NMR spectrum, δ , ppm: 0.83 t (3H, CH₃, *J* = 6.6 Hz), 1.12–1.45, 1.48–1.62 m (20H, CH₂), 1.96 q (2H, CH₂C=, *J* = 6.4 Hz), 2.18 t (2H, CH₂C=, *J* = 5.8 Hz), 2.35 t (2H, CH₂CO₂, *J* = 7.6 Hz), 3.10 m (1H, 12-H), 3.26 s (3H, CH₃O), 3.60 s (3H, CO₂CH₃), 5.45 m (2H, CH=CH, *J* = 5.8 Hz). ¹³C NMR spectrum, δ_C , ppm: 14.08 q (C¹⁸), 22.63 t (C¹⁷), 24.93 t (C³), 25.36 t (C¹⁴), 27.39 t (C¹³), 29.12 t (C⁴, C⁵, C⁶), 29.50 t (C⁷), 29.56 t (C¹⁵), 31.06 t (C⁸), 31.87 t (C¹⁶), 33.57 t (C²), 34.06 t (C¹¹), 51.39 q (CO₂CH₃), 56.54 q (CH₃O), 80.97 d (C¹²), 125.43 d (C¹⁰), 131.69 d (C⁹), 174.23 s (C¹). 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 NaHCO₃ (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 MgSO₄ and evaporated to isolate 2.2 g (98%) of ester **III**, $[\alpha]_D^{20} = +21.05^\circ$. IR spectrum, ν , cm^{−1}: 732, 760, 1024, 1184, 1244 (OAc), 1372, 1449, 1460, 1740 (CO₂), 2360, 2928. ¹H NMR spectrum, δ , ppm: 0.85 t (3H, CH₃, *J* = 7.9 Hz), 1.14–1.67 m (20H, CH₂), 1.90–1.98 m (4H, CH₂C=), 2.0 s (3H, CH₃CO₂), 2.28 t (2H, 2-H, *J* = 7.5 Hz), 3.65 s (3H, COOCH₃), 4.85 m (1H, 12-H, *J* = 6.2 Hz), 5.25–5.50 m (2H, CH=CH, *J* = 7.2 Hz). ¹³C NMR spectrum, δ_C , ppm: 14.08 q (C¹⁸), 21.28 q (COCH₃), 22.59 t (C¹⁷), 24.93 t (C³), 25.37 t (C¹⁴), 27.30 t (C¹³), 29.10 t (C⁴, C⁵, C⁶), 29.15 t (C⁷), 29.50 t (C¹⁵), 31.75 t (C⁸), 31.92 t (C¹⁶), 33.59 t (C¹¹), 34.06 t (C²), 51.46 q (CO₂CH₃), 73.98 d (C¹²), 124.23 d (C¹⁰), 132.61 d (C⁹), 170.83 s (CO), 174.29 s (C¹). 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 Et₂O 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 Al₂O₃ 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, $[\alpha]_D^{20} = +16.7^\circ$ (*c* = 1.4, CHCl₃). IR spectrum, ν , cm^{−1}: 845, 1260 (OAc), 1750 (CO₂), 2875, 2940, 2970. ¹H 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, CH₃, *J* = 6.0 Hz), 1.03 m and 1.11–1.40 m (18H, CH₂), 1.44–1.72 m (6H, 8-H, 11-H, 13-H), 2.00 s (3H, COCH₃), 2.22 t (2H, CH₂CO₂, *J* = 7.5 Hz), 3.60 s (3H, CO₂CH₃), 4.81–4.95 m (1H, CHOC=O). Mass spectrum: *m/z* 368 [M]⁺.

Diastereoisomer Va. ¹³C NMR spectrum, δ_C , ppm: 11.01 t (CH₂, cyclopropane), 11.91 d (C¹⁰), 13.96 q (C¹⁸), 15.44 d (C⁹), 21.16 q (COCH₃), 22.50 t (C¹⁷), 24.84 t (C³), 25.28 t (C¹⁴), 28.78 t (C⁸), 29.12 t

(C⁴, C⁵, C⁶), 29.19 t (C⁷), 29.30 t (C¹¹), 29.90 t (C¹⁵), 31.67 t (C¹⁶), 33.14 t (C¹³), 33.94 t (C²), 51.25 q (CO₂CH₃), 74.91 d (C¹²), 170.68 s (CO), 174.06 s (C¹).

Diastereoisomer Vb. ¹³C NMR spectrum, δ_C, ppm: 10.80 t (CH₂, cyclopropane), 11.79 d (C¹⁰), 13.96 q (C¹⁸), 14.94 d (C⁹), 21.16 q (COCH₃), 22.50 t (C¹⁷), 24.84 t (C³), 25.23 t (C¹⁴), 29.12 t (C⁴, C⁵, C⁶), 28.67 t (C⁸), 29.19 t (C⁷), 29.30 t (C¹¹), 29.90 t (C¹⁵), 31.67 t (C¹⁶), 33.03 t (C¹³), 33.94 t (C²), 51.25 q (CO₂CH₃), 74.91 d (C¹²), 170.63 s (CO), 174.06 s (C¹).

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(CF₃SO₃)₂ in CH₂Cl₂ 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 (CO₂), 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, CH₃, J = 5.6 Hz); 1.15–1.60 m (20H, CH₂); 2.20 t (2H, CH₂CO₂, J = 7.5 Hz); 2.30–2.40 m (4H, CH₂CO); 3.57 s (3H, CO₂CH₃). ¹³C NMR spectrum, δ_C, ppm: 10.71 t (CH₂, cyclopropane ring), 10.88 d (C⁹), 13.90 q (C¹⁸), 15.20 d (C¹⁰), 22.37 t (C¹⁷), 23.64 t (C¹⁴), 24.79 t (C³), 28.80 t (C⁸), 28.98 t (C⁷), 29.13 t (C⁶), 29.21 t (C⁴, C⁵), 29.67 t (C¹⁵), 31.50 t (C¹⁶), 33.89 t (C²), 42.24 t (C¹¹), 42.32 t (C¹³), 51.25 q (CO₂CH₃), 174.06 s (C¹), 211.36 s (C¹²). Mass spectrum: m/z 324 [M]⁺.

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