

## Synthesis of Enantiomerically Pure Macroheterocycle Containing Ester and Hydrazide Groups from Ricinoleic Acid

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*Efficient two-stage synthetic method for potentially useful enantiomerically pure 34-member macrolide with hydrazide and ester fragments was developed based methyl ester of ricinoleic ((R,Z)-(+)-12-hydroxy-9-octadecenoic) acid.*

**Keywords:** Methyl ester of (R,Z)-(+)-12-hydroxy-9-octadecenoic acid, O,N-macroheterocycles, ester and hydrazide fragments, synthesis.

## Синтез энантиомерно чистого макрогетероцикла со сложноэфирными и гидразидными фрагментами из рицинолевой кислоты

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*Исходя из метилового эфира рицинолевой ((R,Z)-(+)-12-гидрокси-9-октадеценовой) кислоты разработан метод синтеза энантиомерно чистого потенциально полезного 34-членного макролида с гидразидными и сложноэфирными фрагментами.*

**Ключевые слова:** Метилловый эфир (R,Z)-(+)-12-гидрокси-9-октадеценовой) кислоты, O,N-макрогетероциклы, сложноэфирные и гидразидные фрагменты, синтез.

### Introduction

Only a small portion of several hundred thousands of secondary metabolites isolated from various natural sources described to date in the literature has a macrocyclic structure. However, it is among them were identified compounds with potent antibiotic (antimicrobial, antiviral, antiparasitic) and antitumor activity.<sup>[1]</sup> Modern practical medicine successfully employs pharmaceutical preparations with oxygen and nitrogen containing macrocyclic compounds as drug substances, therefore recently the synthesis of macroheterocycles is one of the areas of obtaining of the

materials with desired properties.<sup>[2]</sup> This is due to the relentless attention of chemists, biochemists and pharmacologists to this class of natural metabolites and synthetic derivatives, and the search for the optimal and efficient methods for the synthesis of optically active macrolide is relevant.

Availability of optically pure methyl (R,Z)-(+)-12-hydroxy-9-octadecenoic (ricinoleic) acid from castor oil,<sup>[3]</sup> as well as the presence of the Z-(C-9-C-10) double bond determine its widespread use as a promising substrate for chiral polyfunctional compounds. However, in the synthesis of macrocyclic compounds containing ester and hydrazide groups it has not yet been used.

## Experimental Procedure

IR spectra in thin layers were recorded on a Shimadzu Prestige-21 IR instrument. NMR spectra in CDCl<sub>3</sub> with TMS internal standard were recorded on a Bruker AM-300 spectrometer (operating frequency 300.13 MHz for <sup>1</sup>H; 75.47 MHz for <sup>13</sup>C) and Bruker Avance III 500 MHz spectrometer. Signals in the PMR spectra were assigned using homo- and heteronuclear correlation spectroscopy COSY H-H and COSY C-H. Chromatography was performed in Chrom-5 instrument [column length 1.2 m, silicone SE-30 stationary phase (5 %) on Chromatop N-AW-DMCS (0.16-0.20 mm), operating temperature 50-300 °C] with He carrier gas. Column chromatography used SiO<sub>2</sub> (70-230) (Lancaster, England). TLC monitoring used Sorbfil SiO<sub>2</sub> (Russia). Elemental analyses of all compounds agreed with those calculated. Optical rotation was measured on polarimeter «Perkin-Elmer-241-MC». Mass spectra were recorded on the device connections LC MS 2010 EV «Shimadzu» (syringe input, the sample solution in CH<sub>3</sub>CN at flow rate of 60 ml/min) using electrospray ionization (ESI) with simultaneous recording of positive and negative ions at the potentials of the capillary respectively, 4.5 kV and -3.5 kV. Capillary interface temperature 230°C. Nebulizer gas flow (dried nitrogen) 1.5 l/min. HPLC analyses were carried out in a Shimadzu-LC-20AD with an SPD-M20A diode-matrix detector (Shimadzu, Japan) using a Phenomenex column (250×4.6 mm) and Luna C18 sorbent with particle size 5 μm. The mobile phase was H<sub>2</sub>O:CH<sub>3</sub>CN at flow rate 1 ml/min. The analytical wavelength was 215 nm.

**Methyl (9*Z*,12*R*)-12-hydroxyoctadec-9-enoate (2).** <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ ppm: 0.89 (3H, t, *J* = 6.7, H-18), 1.21-1.38 (16H, m, H-4÷H-7, H-14÷H-17), 1.43-1.48 (2H, m, H-13), 1.57-1.61 (2H, m, H-3), 1.98-2.20 (2H, m, H-8), 2.18-2.23 (2H, m, H-11), 2.30 (2H, t, *J* = 6.5, H-2), 2.40 (2H, s, OH), 3.28-3.33 (H, m, H-12), 3.65 (3H, c, OCH<sub>3</sub>), 5.38 (H, dt, *J* = 10.8, 7.4, H-10), 5.58 (2H, dt, *J* = 10.8, 7.2, 1.4, H-9). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ ppm: 13.96 (q, C-18), 22.54 (t, C-17), 24.82 (t, C-3), 25.63 (t, C-14), 27.27 (t, C-8), 28.99 (t, C-6, C-15), 29.0 (t, C-7), 29.31, 29.48 (t, C-4, C-5), 31.78 (t, C-16), 33.93 (t, C-13), 35.28 (t, C-2), 36.76 (t, C-11), 51.25 (q, OCH<sub>3</sub>), 71.35 (d, C-12), 125.42 (d, C-10), 132.61 (d, C-9), 174.09 (s, C-1). IR (KBr) ν<sub>max</sub> cm<sup>-1</sup>: 1742 (O=C=O), 3420 (OH).

**Synthesis of tetraesters 3, 4. General method.** To the stirred solution of 0.94 g (3.0 mmol) methyl (9*Z*,12*R*)-12-hydroxyoctadec-9-enoate (2)<sup>[3]</sup> and 0.018 g (0.15 mmol) of 4-dimethylaminopyridine (DMAP) in 3 ml of abs. pyridine we added the solution of 1.5 mmol glutaric or adipic acid chloride in 1 ml of abs. diethyl ether. In 48 hours (with TLC control) the reaction mixture was diluted with 10 ml diethyl ether, sequentially rinsed with 5-*pc* HCl (3×1.5 ml) and saturated NaCl solution (3×1.5 ml), desiccated with MgSO<sub>4</sub> and sublimed. The residue was chromatographed (SiO<sub>2</sub>, petroleum ether – Et<sub>2</sub>O, 5:2), and the appropriate tetraester was prepared.

**Bis-((9*Z*,12*R*)-1-methoxy-1-oxooctadec-9-en-12-yl)-1,3-pentane dicarboxylate (3).** Yield 1.73 g (71 %), *R*<sub>f</sub> 0.75 (MTBE). [α]<sub>D</sub><sup>20</sup> +286° (c 0.06, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ ppm: 0.88 (6H, t, *J* = 6.6, H-18'), 1.22-1.37 (32H, m, H-4'÷H-7', H-14'÷H-17'), 1.43-1.48 (4H, m, H-13'), 1.57-1.61 (4H, m, H-3'), 1.98 (2H, t, *J* = 7.2, H-3), 1.99-2.07 (4H, m, H-8'), 2.18-2.23 (4H, m, H-11'), 2.30 (4H, t, *J* = 6.5, H-2'), 2.31 (4H, t, *J* = 7.2, H-2, H-4), 3.28-3.33 (2H, m, H-12'), 3.68 (6H, c, OCH<sub>3</sub>), 5.32 (2H, dt, *J* = 10.8, 7.4, H-10'), 5.46 (2H, dt, *J* = 10.8, 7.2, 1.4, H-9'). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ ppm: 13.98 (q, C-18'), 20.35 (t, C-3), 22.51 (t, C-17'), 24.85 (t, C-3'), 27.24 (t, C-8'), 29.05 (t, C-5'÷C-7', C-15'), 29.31 (t, C-4'), 29.43 (t, C-14'), 31.67 (t, C-16'), 33.56 (t, C-2, C-4), 34.35 (t, C-13'), 34.52 (t, C-11'), 36.80 (t, C-2'), 51.28 (q, OCH<sub>3</sub>), 73.85 (d, C-12'), 124.18 (d, C-10'), 132.50 (d, C-9'), 172.50 (s, C-1'), 174.07 (s, C-1, C-5). IR (KBr) ν<sub>max</sub> cm<sup>-1</sup>: 1734 (O=C=O). Mass spectrum (ESI), *m/z*, CH<sub>3</sub>CN/H<sub>2</sub>O – 95/5, (Scan+): 743 [M+Na]<sup>+</sup>, 759 [M+K]<sup>+</sup>.

**Bis-((9*Z*,12*R*)-1-methoxy-1-oxooctadec-9-en-12-yl)-1,4-hexane dicarboxylate (4).** Yield 1.20 g (68 %), *R*<sub>f</sub> 0.75 (MTBE).

[α]<sub>D</sub><sup>20</sup> +130° (c 0.22, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ ppm: 0.87 (6H, t, *J* = 6.7, H-18'), 1.22-1.37 (32H, m, H-4'÷H-7', H-14'÷H-17'), 1.43-1.48 (4H, m, H-13'), 1.46-1.50 (4H, m, H-3, H-4), 1.57-1.61 (4H, m, H-3'), 1.90-1.98 (4H, m, H-8'), 2.18-2.23 (4H, m, H-11'), 2.15 (4H, t, *J* = 7.2, H-2, H-5), 2.21 (4H, t, *J* = 6.9, H-2'), 3.28-3.33 (2H, m, H-12'), 3.58 (6H, s, OCH<sub>3</sub>), 5.27 (2H, dt, *J* = 10.5, 6.3, H-10'), 5.38 (2H, dt, *J* = 10.8, 7.2, 1.4, H-9'). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ ppm: 13.77 (q, C-18'), 22.34 (t, C-17'), 24.65 (t, C-3, C-4), 25.30 (t, C-3'), 27.28 (t, C-8'), 29.05 (t, C-5', C-6', C-14'), 29.31 (t, C-15'), 29.46 (t, C-7'), 29.64 (t, C-4'), 31.50 (t, C-16'), 33.38 (t, C-13'), 33.57 (t, C-11'), 33.66 (t, C-2, C-5), 36.74 (t, C-2), 51.23 (q, OCH<sub>3</sub>), 73.38 (d, C-12'), 124.21 (d, C-10'), 132.43 (d, C-9'), 172.79 (s, C-1'), 174.00 (s, C-1, C-6). IR (KBr) ν<sub>max</sub> cm<sup>-1</sup>: 1741 (O=C=O). Mass spectrum (ESI), *m/z*, CH<sub>3</sub>CN/H<sub>2</sub>O – 95/5, (Scan+): 758 [M+Na+H]<sup>+</sup>, 774 [M+K+H]<sup>+</sup>.

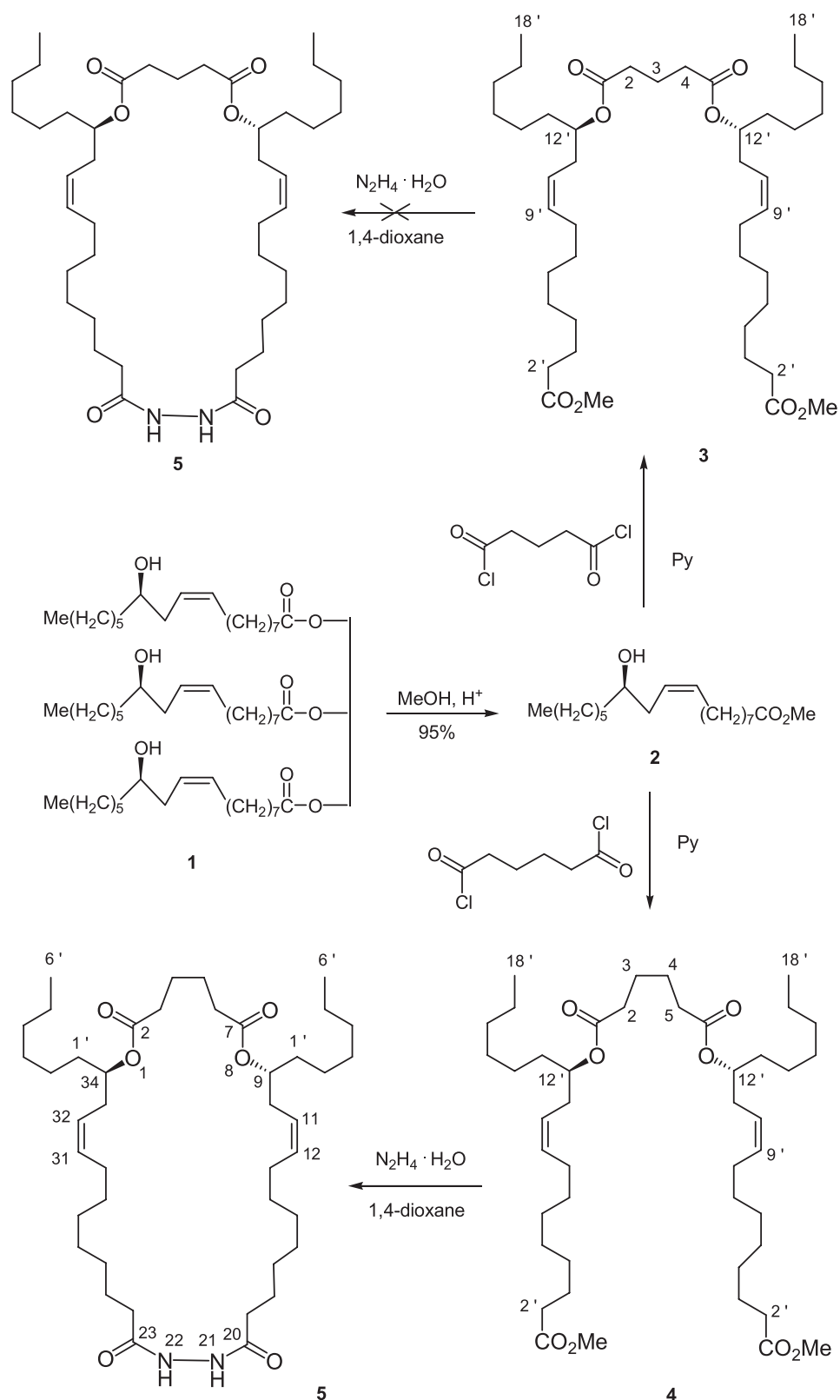
**(9*R*,11*Z*,31*Z*,34*R*)-9,34-dihexyl-1,8-dioxy-21,22-diazacyclotetracont-11,31-dien-2,7,20,23-tetraone (5).** To the solution of tetraester 4 (0.72 g, 1.0 mmol) in 8.5 ml of abs. dioxane we slowly added dropwise 0.05 g (1.0 mmol) 98-*pc* hydrazine hydrate under intensive stirring and stirred for 24 hours (with TLC control). Thereafter, dioxane was sublimed, and the residue was dissolved in 10 ml CH<sub>2</sub>Cl<sub>2</sub>, rinsed with water (3×3 ml), desiccated with MgSO<sub>4</sub> and sublimed. To the resultant residue we sequentially added 1 ml of abs. CH<sub>2</sub>Cl<sub>2</sub> and 10 ml of hexane under stirring and left to stand until the layers separated, the upper one being decanted. The remainder was rinsed with 3 ml of hexane and sublimed *in vacuo*. Yield 0.42 g (78 %). [α]<sub>D</sub><sup>20</sup> +98° (c 0.0273, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ ppm: 0.87 (6H, t, *J* = 6.8, H-6'), 1.20-1.34 (28H, m, H-14÷H-17, H-26÷H-29, H-2'÷H-4'), 1.38-1.50 (4H, m, H-5'), 1.46-1.55 (4H, m, H-1'), 1.40-1.47 (4H, m, H-18, H-25), 1.56-1.65 (4H, m, H-4, H-5), 1.90-1.98 (4H, m, H-13, H-30), 2.19 (4H, t, *J* = 7.0, H-19, H-24), 2.21 (4H, t, *J* = 7.1, H-3, H-6), 2.18-2.23 (4H, m, H-10, H-33), 4.81-4.90 (2H, m, H-9, H-34), 5.30 (2H, dt, *J* = 10.7, 6.4, H-11, H-32), 5.53 (2H, dt, *J* = 10.7, 6.1, H-12, H-31), 7.10 (2H, s, NH). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ ppm: 13.76 (q, C-6'), 22.22 (t, C-5'), 24.98 (t, C-4, C-5), 25.25 (t, C-18, C-25), 26.98 (t, C-13, C-30), 28.69 (t, C-17, C-26, C-2'), 28.78 (t, C-15, C-28), 28.93 (t, C-16, C-27), 29.05 (t, C-14, C-29), 29.17 (t, C-3'), 31.36 (t, C-4'), 33.03 (t, C-10, C-33), 33.88 (t, C-1'), 34.05 (t, C-3, C-6), 36.52 (t, C-19, C-24), 73.61 (d, C-9, C-34), 123.92 (d, C-11, C-32), 132.20 (d, C-12, C-31), 172.82 (s, C-20, C-23), 173.83 (s, C-2, C-7). IR (KBr) ν<sub>max</sub> cm<sup>-1</sup>: 1736 (O=C=O), 1672 (O=C=N). Mass spectrum (ESI), *m/z*, CH<sub>3</sub>CN/H<sub>2</sub>O – 95/5, (Scan+): 725 [M+Na]<sup>+</sup>, 741 [M+K]<sup>+</sup>; (Scan-): 701 [M-H]<sup>-</sup>.

## Results and Discussion

We have previously developed<sup>[4]</sup> enantiopure methyl and isopropyl-substituted 21-membered macrolide with hydrazide (-C(O)-NH-NH-C(O)-) and ester fragments on the basis of *l*-menthol using sequential [2+1]-condensation reactions of (3*R*,6*S*)-6-hydroxy-3,7-dimethyl octanoic methyl ether with glutaric dichloranhydride and [1+1]-condensation reaction with hydrazine hydrate. The synthesis of a macrocycle containing a similar hydrazide fragment on the basis of isosteviol was given in<sup>[5]</sup>.

This paper considers a short-time expedient synthesis method for enantiopure 34-membered macrolide 5 from ricinoleic methyl ether obtained through re-etherification of castor oil with methanol. The macrolide contains a hydrazide function, two double bonds and two ether groups and has potential biological activity and complex-forming properties.

By means of [2+1]-condensation of ricinoleic methyl ether (2) produced from castor oil upon interaction with



glutaric or adipic chloranhydrides, we have produced, with high yields, *bis*-derivatives **3**, **4**, in which two hydroxyether carbon skeletons (**2**) at the C-12 position are linked together via diether spacers. The [1+1]-condensation of tetraesters (**3**, **4**) with hydrazine hydrate was carried out at room temperature under high-rate dissolution conditions in 1,4-dioxane. In the case of using *bis*-derivative **4**,

the reaction was accompanied by the formation of the macrocycle **5** with two ester and hydrazone fragments. Nevertheless, tetraester (**3**) cyclization has not met with success.

The structures of the obtained products (**3**, **4**) and the macrolide (**5**) have been confirmed by IR, <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy and chromato-mass spectrometry.

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