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# Synthesis of (*S*)-ricinoleic acid and its methyl ester with the participation of ionic liquid

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ABSTRACT

(*R*)-Ricinoleic acid methyl ester obtained from commercial castor oil was transformed in a three-step procedure into its *S*-enantiomer in overall 36% yield using ionic liquid (1-butyl-3-methylimidazolium acetate) in the key step process. The developed procedure provides easy access to (*S*)-ricinoleic acid and its methyl ester of over 95% enantiomeric excess. Optical rotations of the newly obtained compounds as well as their chromatographic and spectral characteristics are provided and discussed in the context of enantiopurity both of the substrate material and the final products.



## 1. Introduction

(*R*)-Ricinoleic acid or (*Z*)-(*R*)-12-hydroxyoctadec-9-enoic acid is a major constituent of castor oil from *Ricinus communis* seeds (Euphorbiaceae family) and comprises up to 87–92% of all fatty acids present in the oil (Broch-Jensen et al., 1997; Pradhan et al., 2012). Methyl (*R*)-ricinoleate is produced by transesterification of castor oil with methanol by chemical or enzymatic catalysis (Knothe et al., 2012; Baron et al., 2014; Goswami et al., 2013). Ricinoleic acid (castor oil) is widely exploited for industrial utilisation (Mutlu and Meier, 2010). This unusual hydroxy fatty acid has an *R*-configured carbon atom and an OH group in homoallylic position, which are the reasons for its multi-directional chemical and biochemical transformations (Behr et al., 2012; Kula et al., 2000; Braga and Belo, 2014). Its *S*-configured enantiomer or (*Z*)-(*S*)-12-hydroxyoctadec-9-enoic acid has not been reported, to the best of our knowledge, to occur in the plant kingdom, although there are several works describing the presence of ricinoleic acid (configuration not reported) in a family other than the large spurge family (Euphorbiaceae) (Parveen and Rauf, 2008; Katagi et al., 2011; Hosamani and Katagi, 2008). It is common knowledge that the biological activity of the chiral compound strongly depends on the configuration of its molecule. Enantiopure hydroxy fatty acids, including the only available (*R*)-ricinoleic acid, are desirable, for instance, to study their impact on the organisation of lipid membranes (Jenske et al., 2008). Taking into consideration the industrial importance of *R*-configured ricinoleic acid, its availability, wide range of application and our experience in the chemical transformation of this acid (Kula et al., 2000, 1996), we decided to attempt access to its *S*-configured enantiomer. In 1982 McGhie et al. (McGhie et al., 1982) tried to make an inversion of the configuration in (*R*)-ricinoleic acid to its optical antipode *via* the Mitsunobu reaction. However, the authors did not provide data on the reaction yield or on the purity of the products obtained. Moreover, the reagents used therein were hazardous and environmentally hostile, and separation of the product from two by-products, hydrazinedicarboxylate and phosphane oxide, is usually problematic (Dembinski, 2004; But and Toy 2006); hence the conclusion that inversion of chiral alcohol *via* the Mitsunobu reaction may not be suitable for large-scale preparations.

There are a number of papers on the $SN_2$ reaction of secondary alcohol sulfonates (mesylates) with the alkali metal salts of carboxylic acids, however, such a substitution has several drawbacks, especially if it were to be used on a larger scale, which was discussed in a recent work (Shi et al., 2010). The same authors also present an interesting protocol for the inversion of secondary alcohols using the complex of $R_3N$–RCOOH as a nucleophile providing excellent yields and enantiomer excess for several alcohols. The reaction is carried out in toluene at elevated temperature (60–110 °C), and 2–9 equivalents of the tunable amine-acid complex are necessary. We tried to apply this procedure to transform methyl (*R*)-ricinoleate into its optical antipode. The best result under the conditions tried (TEA–AcOH

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3:6 equiv., 70 °C, 15 h) allowed us to obtain the inverted product in ca. 25% yield (*R*-**1**–*S*-**1**). However, the optical purity of the sample, which was specially purified by column chromatography (99.6%, GC) was unsatisfactory, showing $[\alpha]_D = -2.40$ (c 8, $CHCl_3$) as compared to the optical rotation of the substrate ester, $[\alpha]_D = 3.03$ (*vide infra*). This may indicate that this homoallylic alcohol is very sensitive to the reaction conditions.

Recently, we turned our attention to the green protocol for the nucleophilic substitution reaction of sulfonate esters by recyclable ionic liquids as published by Yajun Liu (Liu et al., 2012) to develop the transformation of (*R*)-ricinoleic acid into its *S*-enantiomer.

## 2. Materials and methods

Methyl (*R*)-ricinoleate *R*-**1** was prepared by common transesterificarion of commercial castor oil with methanol in the presence of sodium methoxide to deliver a product (b.p. 173–177 °C/1.5 Torr) of 92% purity (GC). Triethylamine, methanesulfonyl chloride and ion liquid, 1-butyl-3-methylimidazolium acetate (BMIM-OAc), were purchased from Sigma–Aldrich.

Flash chromatography: silica gel for TLC. GC–MS was performed with a Trace GC Ultra chromatograph coupled with a DSQII mass spectrometer (Thermo Scientific) equipped with a Rxi-1ms capillary column (60 m long, 0.25 mm inside diameter, 0.25 mm film thickness), temperature program 50–310 °C at 4 °C/min. Chiral-GC–MS was performed with a Trace GC Ultra chromatograph coupled with an ISQ mass spectrometer (Thermo Scientific) equipped with an RT-BetaDEX-sm capillary column (30 m long, 0.32 mm inside diameter, 0.25 mm film thickness), temperature program 50–140 °C at 4 °C/min (held for 47 min), then to 230 °C at 20 °C/min. $^1$H NMR (250 MHz) and $^{13}$C NMR (62.90 MHz) were recorded using $CDCl_3$ solutions with TMS as internal standard (Bruker DPX-250 Avance). $^{13}$C NMR multiplicity was determined using DEPT experiments. Purity of the products was confirmed by both GC and TLC analyses. Optical rotations were measured with an Autopol IV polarimeter (Rudolph Research) and IR spectra were obtained with the FT-IR spectrometer Nicolet 6700 (Thermo Scientific).

### 2.1. Preparation of (Z)-(R)-12-methanesulfonyloksy-octadec-9-enoic acid methyl ester (mesylate 2)

Methyl (*R*)-ricinoleate (*R*-**1**) (37.5 g, 110 mmol) was dissolved in dichloroethane (230 mL), and triethylamine (24.2 g, 239.9 mmol) was added. The mixture was cooled to −5 °C and methanesulfonyl chloride (20.7 g, 180.2 mmol) was dropped carefully during agitation, maintaining the temperature below +5 °C. Then the reagents were stirred for 3 h at room temperature and acidified with hydrochloric acid (230 mL, 2 M HCl). The organic layer was separated and washed twice with other portions of hydrochloric acid (2 × 100 mL, 2 M) and then three times with water (3 × 60 mL). After the organic solution was dried over anhydrous $MgSO_4$, the solvent was removed by a rotavapor to give a brown product, which was preliminarily purified by passing through a silica gel (20 g) column using hexane/acetone (80:20 v/v) as eluent to furnish crude mesylate **2** (43 g, 91% yield). A sample of the crude material (0.8 g) was purified by flash chromatography on silica gel column using hexane/acetone (90:10) as eluent to afford pure mesylate **2** (0.41 g). $[\alpha]_D = +16.33$ (c 5.0, $CHCl_3$). IR (cm$^{-1}$, neat): 2927, 2855, 1737, 1172, 905, 725. $^1$H NMR ($CDCl_3$, $\delta$ ppm): 5.51 (m, 1H), 5.38 (m, 1H), 4.67 (qn $J$ = 6.25 Hz, 1H-12), 3.65 (s, 3H-MeO), 2.98 (s, 3H-MeS), 2.44 (m, 2H), 2.29 (dd, $J$ = 7.25 and 7.75 Hz 2H), 2.01 (m, 2H), 1.65 (m, 4H), 1.29 (m, 16H), 0.87 (t, $J$ = 6.6 Hz, 3H). $^{13}$C NMR ($CDCl_3$): 174.28 (s, C1), 133.76 (d, C9), 123.01 (d, C10), 83.59 (d, C12), 51.42 (q, MeO), 38.64 (q, MeS), 34.21 (t), 34.04 (t), 32.50 (t), 31.60 (t), 29.35 (t), 29.05 (t, 22.51 (t), 2 × $CH_2$), 28.98 (t), 27.38 (t), 25.00 (t), 24.88 (t), 14.00 (q).

### 2.2. Synthesis of (Z)-(S)-12-acetoxy-octadec-9-enoic acid methyl ester (3)

Crude mesylate **2** (42 g, 99 mmol) and 1-butyl-3-methylimidazolium acetate (20.2 g, 102 mmol) were stirred at 40 °C for 48 h. Then water (80 mL) was added and the product was extracted with hexane (3 × 100 mL), washed with water (100 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated to obtain a brown liquid (34 g) which was preliminarily purified by flash chromatography (silica gel, hexane/acetone 90:10) to get rid of the unreacted mesylate (monitored by TLC and $^1$H NMR) and a little of unsaturated esters. After solvent evaporation, crude diester **3** (26.8 g), 78% pure (GC), was obtained. A sample of the crude material (0.8 g) was purified by flash chromatography on silica gel column using hexane/acetone (95:5) as eluent to afford 97% pure diester **3** (0.38 g). $[\alpha]_D = -21.8$ (c 2.3, $CHCl_3$). IR (cm$^{-1}$, neat): 2925.8, 2854.9, 1738.1, 1239.5, 1196.6, 1170.8, 1022.7, 724.9. $^1$H NMR ($CDCl_3$, $\delta$ ppm): 5.45 (m, 1H), 5.34 (m, 1H), 4.86 (m, 1H), 3.66 (s, 3H), 2.30 (m, 4H), 2.02 (s, 3H), 1.99 (m, 2H), 1.57 (m, 4H), 1.29 (m, 16H), 0.87 (t, $J$ = 6.5 Hz, 3H). GC–MS (EI, 70 eV), $m/z$): 294 ($M^+ - 60$), 43 (100%), 262 (5), 207 (5), 150 (8), 124 (9), 96 (20), 81 (24), 67 (40), 55 (37).

### 2.3. Methanolysis of diester 3

A mixture of crude diester **3** (26 g, 47 mmol) and anhydrous methanol (100 mL) containing sodium methoxide (0.216 g, 0.004 mmol) was refluxed for 2.5 h, then the methanol was distilled off (60 mL). Water (50 mL) and concentrated hydrochloric acid (4 mL) were added to the residue and the product was extracted with hexane (3 × 25 mL). The combined extracts were washed neutral with water and dried over anhydrous $MgSO_4$ to give, after solvent evaporation, crude hydroxy ester *S*-**1** (22.2 g, purity 77% by GC), which was subjected to silica gel flash chromatography (hexane/acetone 94:6) to get 99.6% pure (GC) hydroxy ester *S*-**1** (12.45 g, 36% total yield based on pure *R*-**1**). $[\alpha]_D = -2.81$ (c 5.0, $CHCl_3$). IR (cm$^{-1}$, neat): 3422.5, 2925.8, 2854.6, 1740.9, 1197.3, 1172.3, 725.5. $^1$H NMR ($CDCl_3$, $\delta$ ppm): 5.53 (m, 1H), 5.42 (m, 1H), 3.66 (s, 3H), 3.60 (m, 1H), 2.29 (t, $J$ = 7.5 Hz, 2H), 2.20 (t, $J$ = 6.5 Hz, 2H), 2.04 (m, 2H), 1.51 (M, 3H), 1.45 (m, 3H), 1.29 (m, 15H), 0.87 (t, $J$ = 6.5 Hz, 3H). $^{13}$C NMR ($CDCl_3$): 174.24 (s), 133.21 (d), 125.20 (d), 71.42 (d), 51.37 (t), 36.79 (t), 35.30 (t), 34.01 (t), 31.78 (t), 29.51 (t), 29.30 (t), 29.02 (t, 2 × $CH_2$), 27.31 (t), 25.66 (t), 24.85 (t), 22.56 (t), 14.02 (q). GC–MS (EI, 70 eV), $m/z$): 294 [$M^+ - 18$ (3)], 55 (100), 198 (24), 124 (48), 98 (45), 96 (53), 84 (58), 82 (43), 74 (73), 69 (50).

### 2.4. Hydrolysis of hydroxy ester S-1 to (S)-ricinoleic acid

A mixture of hydroxy ester *S*-**1** (2 g), methanol (20 mL) and KOH (2.5 g) dissolved in water (10 mL) was refluxed for 2 h. Then methanol was distilled off (10 mL) and the mixture was acidified with concentrated hydrochloric acid (2.5 mL). The product was extracted with ethyl acetate (3 × 20 mL), washed with water (2 × 15 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated to obtain (*S*)-ricinoleic acid (1.98 g, 100% pure by TLC and $^1$H NMR). $[\alpha]_D = -3.54$ (c 2.89, $CHCl_3$). IR (cm$^{-1}$, neat): 3337.3, 2968.7, 2928.1, 2856.8, 1709.3, 1160.5, 1128.0, 950.5, 816.2. $^1$H NMR ($CDCl_3$, $\delta$ ppm): 6.20 (br.m, 1H), 5.52 (m, 1H), 5.40 (m, 1H), 3.62 (qn, $J$ = 6.25 Hz, 1H), 2.33 (t, $J$ = 7.40 Hz, 2H), 2.21 (t, $J$ = 7.0 Hz, 2H), 2.03 (m, 2H), 1.62 (m, 2H), 1.46 − 1.28 (m, 19H), 0.87 (t, $J$ = 6.75 Hz, 3H).). $^{13}$C NMR ($CDCl_3$): 179.49 (s), 133.26 (d), 125.14 (d), 71.62 (d), 26.70