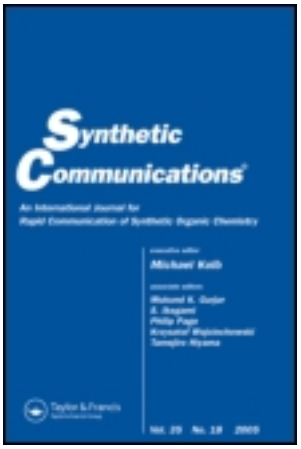

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CONCISE SYNTHESIS OF XIMENYNIC ACID

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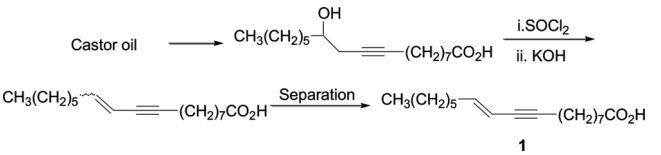
GRAPHICAL ABSTRACT



Abstract *An improved synthesis of ximenynic acid (**1**) starting from castor oil has been developed with the direct chlorination of ricinstearolic acid as the key step. By this modification, the synthetic route was more concise and economic. The separation of geometric somers was achieved by repeated urea fractionation.*

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Keywords Chlorination; synthesis; ximenynic acid

INTRODUCTION

Ximenynic acid [(11*E*)-octadecen-9-ynoic acid, **1**, Fig. 1], also known as santalbic acid, is a C18 conjugated enyne fatty acid isolated from the sandalwood oil from the shrub *Santalum spicatum*.[1] Similar to other natural conjugated enyne fatty acids, a variety of biological activities have been reported for ximenynic acid. Ximenynic acid has been extensively used in formulations to improve hair vitality by stimulating the microvasculokinetic activity of the scalp.[2] It has also been reported to possess anti-inflammatory and anticarcinogenic activities.[3]

The total synthesis of ximenynic acid was reported by Crombie and Jacklin from n-heptaldehyde and propargyl bromide with seven steps early in 1950s.[4] Recently, Jie and coworkers developed a nice approach to prepare ximenynic acid from methyl ricinoleate.[5] Methyl ricinoleate was first converted into ricinstearolic acid by bromination and dehydrobromination. Ricinstearolic acid was then esterified with BF_3/methanol, followed by the sulfonylation of the 12-hydroxy group with

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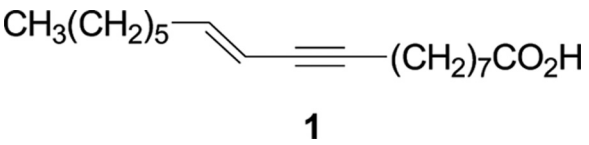

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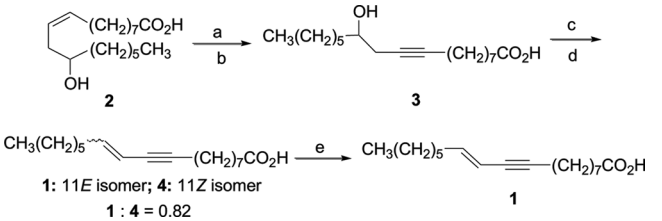
Figure 1. Structure of ximenynic acid (**1**).

methanesulfonyl chloride and elimination to afford a mixture of ximenynic acid and its 11*Z*-isomer. Pure ximenynic acid was separated by urea fractionation with a total yield of 20%.

Here we report an improved synthesis of ximenynic acid from castor oil with the following advantages. First, our synthesis exploits castor oil as the starting material, which is more inexpensive and accessible. Second, the chlorination of 12-hydroxy was directly performed for ricinstearolic acid instead of methyl ricinstearolate, which avoids the protection of carboxylic group and later deprotection, thus providing a more concise and economic synthetic route.

Scheme 1 delineates the improved synthesis of ximenynic acid developed in our laboratories. Castor oil (**2**) was brominated first, followed by the elimination of hydrobromide, to provide ricinstearolic acid (**3**) with a modified literature method.[4,6] Ricinstearolic acid (**3**) was then chlorinated with $SOCl_2$, followed by the elimination of hydrochloride under aqueous KOH to yield a mixture of ximenynic acid (**1**) and its (*Z*)-isomer (**4**). What should be mentioned here is that the elimination provided the double bond only in the 11-position, and no 12-double bond product was isolated, as proposed by Liu.[7] The separation of ximenynic acid isomers was then achieved by repeated urea fractionation and geometrically pure ximenynic acid was yielded, with a comparable overall yield with literature[5] (16% from castor oil for our method compared to 20% from pure methyl ricinoleate for Jie's approach). The melting point and ^{1}H NMR spectrum of **1** were in good agreement with those described in the literature.[5]

In summary, we have successfully developed a concise synthetic route to prepare ximenynic acid from easily available castor oil with a comparable yield. The key steps involved the chlorination for 12-hydroxy of ricinstearolic acid and the subsequent elimination of hydrochloride for 12-chlorooctadec-9-ynoic acid. A mixture of (11*E* and *Z*)-octadecen-9-yonic acids ($E/Z = 0.82$) was thus obtained



Scheme 1. Reagents and conditions: (a) Br_2/ EtOH/ −5 °C; (b) KOH/H_2O/80 °C/10 h; (c) $SOCl_2$/ 60 °C/ 3 h; (d) KOH/EtOH/ 80 °C/24 h; and (e) urea/CH_3OH.

and the pure *E*-enyonic acid (i.e., ximenynic acid), was then separated by repeated urea fractionation. The route is convenient and economical.

EXPERIMENTAL

Reagents were purchased from commercial sources and used without further purification unless otherwise indicated. Melting points were determined with an XT-4 melting-point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV-300 (300 MHz) or AV-500 (500 MHz) instruments with $CDCl_3$ as the solvents, and mass spectra were performed on a Waters Q-TOF Micro.

12-Hydroxyoctadec-9-ynoic Acid (3)

Bromine (11.6 g, 67.5 mmol) was added dropwise to a solution of castor oil (**2,** 20 g, 67 mmol, containing ~17 g of ricinoleic acid) in ethyl alcohol (12 mL) at −5 °C with stirring. When addition was complete, the product was refluxed with potassium hydroxide (24 g) in water (16 g) for 10 h. The mixture was poured into water (120 mL), acidified with sulfuric acid (5 M, 60 mL), extracted with diethyl ether (3 × 100 mL), and dried over anhydrous sodium sulfate. Removal of ether gave ricinstearolic acid (20 g). Recrystallization of the crude from petroleum ether gave 12-hydroxyoctadec-9-ynoic acid **3** (12.9 g, 65% yield). Mp 51–53 °C [lit.[4] 52 °C]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, 3H, $J = 6.6$ Hz), 1.29–1.52 (m, 18H), 1.60–1.67 (m, 2H), 2.17 (t, 2H, $J = 6.9$ Hz), 2.22–2.44 (m, 4H), 3.65–3.73 (m, 1H); ^{13}C NMR (1D + DEPT, 125 MHz, $CDCl_3$): δ 14.0 (CH_3), 18.7 (CH_2), 22.6 (CH_2), 24.6 (CH_2), 25.6 (CH_2), 27.7 (CH_2), 28.6 (CH_2), 28.7 (CH_2), 28.8 (CH_2), 28.9 (CH_2), 29.2 (CH_2), 31.8 (CH_2), 33.9 (CH_2), 36.2 (CH_2), 70.3 (CH), 76.2 (C), 83.1(C), 179.2 (C); MS (ESI, negative ion mode): $m/z = 295.1$ $[M - H]^-$; HRMS (ESI, negative ion mode) calcd. for $C_{18}H_{31}O_3$, m/z: 295.2273 $[M\text{-}H]^-$; found, m/z: 295.2278.

(11*E*/*Z*)-Octadecen-9-ynoic Acid (1 and 4)

Thionyl chloride (10 g, 84 mmol) was added to a mixture of ricinstearolic acid (**3**) (5.0 g, 16.9 mmol) and pyridine (0.5 mL) with stirring at rt. The mixture was heated at 60 °C for 3 h, and excess thionyl chloride was removed under reduced pressure. Water (30 mL) was added to the residue and the mixture was extracted with diethyl ether (3 × 30 mL), and the organic extract was washed with water (3 × 30 mL) and then dried over anhydrous sodium sulfate. Removal of ether gave the crude (6.8 g). It was used for next step without further purification.

The crude was refluxed with potassium hydroxide (6.8 g) and water (6.8 mL) in ethyl alcohol (136 mL) for 24 h, acidified with sulfuric acid (5 M), extracted with diethyl ether (3 × 100 mL), and dried over anhydrous sodium sulfate. After the solvent was evaporated, the residue was purified by column chromatography with petroleum ether and ethyl acetate (75:25, vol/vol) as eluent to yield a mixture of (*Z*)- and (*E*)-enynoic acids (2.65 g, 57% yield) with 45% (*E*)-isomer. The ratio of *E* to *Z* isomers (**1** and **4**) was determined by the signals of 12-H at their ^{1}H NMR spectrum.

(11*E*)-Octadecen-9-ynoic Acid (1)

The mixture of the crude acids (0.61 g), urea (2.61 g), and methanol (8 mL) was warmed to dissolve the urea crystals. The solution was then kept at 5 °C for 4 h. The solution was filtered to recover the solid urea adduct. The collected urea adduct was dissolved in diethyl ether (3 × 10 mL) and then dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was refractionated to yield pure ximenynic acid **1** (0.25 g, 41% yield). Mp 38–39 °C [lit.[5] 39 °C]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, 3H, $J = 6.9$ Hz), 1.25–1.34 (m, 14H), 1.46–1.54 (m, 2H), 1.59–1.66 (m, 2H), 2.03–2.14 (m, 2H), 2.27 (t, 2H, $J = 6.9$ Hz), 2.35 (t, 2H, $J = 7.5$ Hz), 5.45 (d, 1H, $J = 15.9$ Hz), 6.04 (dt, 1H, $J = 15.6$, 7.2 Hz); ^{13}C NMR (1D +DEPT, 125 MHz, $CDCl_3$): δ 14.0 (CH_3), 19.3 (CH_2), 22.6 (CH_2), 24.6 (CH_2), 28.6 (CH_2), 28.74 (CH_2), 28.77 (CH_2), 28.8 (CH_2), 28.9 (CH_2), 29.7 (CH_2), 31.7 (CH_2), 32.9 (CH_2), 34.0 (CH_2), 79.3 (C), 88.5 (C), 109.8 (CH), 143.4 (CH), 180.1 (C); MS (ESI, negative ion mode): $m/z = 277.3$ $[M - H]^-$; HRMS (ESI, negative ion mode) calcd. for $C_{18}H_{29}O_2$, m/z: 277.2168 $[M - H]^-$; found, m/z: 277.2170.

ACKNOWLEDGMENT

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