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Novel α-hydroxy phosphonic acids via castor oil☆

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ABSTRACT

Hydroxy fatty acids (HFAs) have found a number of uses in today's market, with uses ranging from materials to pharmaceuticals. Castor oil has served as a source of a versatile HFA; its principle component, ricinoleic acid, can be isolated from castor oil and has been modified extensively for a number of applications. Additionally, α-hydroxy phosphonates and their corresponding phosphonic acids are a functional moiety that have been shown to display a wide variety of biological activities, as enzyme inhibitors, pesticides, antibiotics and anti-cancer therapeutics. We were interested in combining these two functionalities, HFAs modified to produce α-hydroxy phosphonates and phosphonic acids, as potentially biologically active molecules. We have accomplished the synthesis of two families of α-hydroxy phosphonic acids based on ricinoleic acid: a family that retains the cis alkene found in ricinoleic acid to produce an unsaturated α-hydroxy phosphonic acid and one where the alkene has undergone hydrogenation to produce a saturated α-hydroxy phosphonic acid. These compounds have been produced in high yields and high purity, and the synthesis of these compounds is reported in this manuscript.

1. Introduction

Hydroxy fatty acids (HFAs) are a valuable commodity in today's market, used in the production of a variety of products, including industrial lubricants, nylon-11, plastics, drying agents, protective coatings, surfactants, cosmetics, and pharmaceuticals (Salywon et al., 2005; Glaser et al., 1992). The hydroxy functionality gives HFAs properties that make them more useful than typical fatty acids, such as increased viscosity, lubricity, and reactivity. The only HFA currently available in large enough quantities for commercial use is ricinoleic acid, from castor oil (Salywon et al., 2005). Castor oil comes from the seeds of *Ricinus communis*, more commonly referred to as castor. Native to Africa, castor is now grown throughout the world. An annual crop in temperate climates, castor is grown in conditions similar to those of cotton and corn and is known to contain over 50% oil by weight, with ricinoleic acid (18:1 hydroxy) accounting for 89% of the fatty acids present in this oil (S.C. Cermak et al., 2006).

Castor oil finds many industrial uses today, both direct and indirect (Glaser et al., 1992). It is used in products such as soaps, waxes, hydraulic fluids, cosmetics, and inks. Its derivatives, however, span an even greater array of applications. Its hydrogenated fatty acids are used in lubricating greases, while the dehydrated fatty acids are found in many inks and sealants. Ricinoleic acid has been derivatized to yield nylon-11, more resilient than the most common types of nylon, making it useful in high-performance applications. Castor oil and its derivatives are also known for their laxative and anti-inflammatory properties, making them viable starting materials for drug production (Vieira et al., 2000).

α-Hydroxy phosphonates and their corresponding phosphonic acids are widely recognized as an important structural moiety. They have been shown to exhibit a wide variety of biological activity as enzyme inhibitors of renin, enzyme 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase, human immunodeficiency virus (HIV) protease, and farnesyl protein transferase (FPTase) (Wiemer, 1997). They have also been utilized as pesticides, antibiotics and anticancer and antiviral agents (Wu et al., 2010). α-Hydroxy phosphonates have also shown use as synthetic intermediates in the synthesis of other α-substituted phosphonates and phosphonic acids, most commonly α-amino phosphonic acids, which have been shown to exhibit a wide variety of biological activity of their own (Kafarski and Lejczak, 1991).

It has been well documented in the literature that α-hydroxy phosphonates and their corresponding phosphonic acids have potentially interesting biological activity (D.M. Cermak et al., 1999; Pompliano et al., 1992). Coupling this with the fact that ricinoleic acid, the primary fatty acid present in castor oil, is a naturally occurring hydroxy fatty acid used in a wide variety of applications, including medicinal uses, we were interested in synthesizing a

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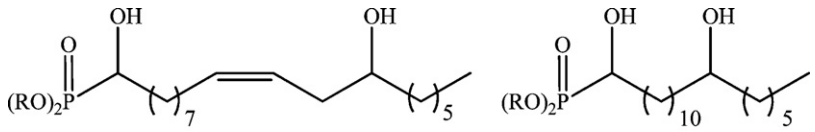

1a R = CH_3 **1b** R = CH_3
2a R = H **2b** R = H

Fig. 1. Monounsaturated and saturated α-hydroxy phosphonates and phosphonic acids.

family of castor-based α-hydroxy phosphonates. We thus set out to produce the monounsaturated and saturated phosphonates (**1a** and **1b**, respectively; see Fig. 1) and their corresponding phosphonic acids (**2a** and **2b**).

2. Materials and methods

2.1. Materials

Castor oil was obtained from Fisher Scientific Co. (Fairlawn, NJ). All other chemicals used were purchased from Aldrich Chemical Co. (Milwaukee, WI) and no further purification was necessary. Diethyl ether and tetrahydrofuran (THF) were obtained from Aldrich Chemical Co. (Milwaukee, WI) and were dried by VAC solvent purifier (Vacuum Atmospheres Co.). Dichloromethane was obtained from AAPER Alcohol and Chemical (Shelbyville, KY) and triethylamine was obtained from Aldrich Chemical Co. (Milwaukee, WI); both solvents were freshly distilled from calcium hydride. Methanol was obtained from Aldrich Chemical Co. (Milwaukee, WI) as an anhydrous solvent. All reactions in non-hydroxylic solvents were conducted in oven-dried glassware under a positive pressure of nitrogen. Solvents for extraction and flash-column chromatography were reagent grade or better and were used without further purification. Flash-column chromatography was carried out on SiliCycle 40–63 μm (230–400 mesh) silica gel obtained from SiliCycle Inc. (Quebec City, Quebec, Canada). Thin layer chromatography (TLC) was performed on Aldrich silica gel 60F254 pre-coated TLC plates of 0.2 mm thickness. TLC plates were visualized using ultraviolet light and phosphomolybdic acid (PMA) in ethanol. The acronyms used are defined as the following: DIBAL; diisobutylaluminum hydride; DMSO, dimethyl sulfoxide; TBDMS, *tert*-butyldimethylsilyl; TBAF, tetrabutylammonium fluoride; TMSBr, trimethylsilyl bromide.

2.2. Instrumentation

2.2.1. Nuclear magnetic resonance (NMR)

^{1}H, ^{13}C and ^{31}P NMR spectra were obtained on a Bruker ARX-500 (Karlsruhe, Germany) with a 5 mm dual proton/carbon probe (^{1}H at 500.11 MHz, ^{13}C at 125.77 MHz, ^{31}P at 202.44 MHz) using $CDCl_3$ as solvent unless otherwise noted. Chemical shifts for ^{1}H NMR spectra were reported in ppm relative to Me_4Si (δ 0.00), chemical shifts for ^{13}C NMR spectra (^{1}H decoupled) were reported in ppm relative to the center line of the triplet corresponding to $CDCl_3$ (δ 77.00), and chemical shifts for ^{31}P NMR spectra (^{1}H decoupled) were reported in ppm relative to phosphoric acid (δ −0.12). Splitting patterns for ^{1}H NMR spectral absorptions are denoted as follows: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bm, broad multiplet; dd, doublet of doublets; dt, doublet of triplets. Assignment of hydrogens and carbons are specified for esters **4a** and **4b** and hydroxy phosphonates **7a** and **7b**; other compounds are similar in assignment to these compounds and are thus not specified.

2.2.2. Gas chromatography/mass spectrometry (GC/MS)

A Hewlett-Packard 5890A GC with a 30 m × 0.20 mm i.d. SPB-1 column (Supelco, Bellefonte, PA, USA) and a Hewlett-Packard 5970 mass selective detector was used for GC–MS analysis. GC conditions: helium head pressure 15 psi (103 kPa) at 170 °C set for constant flow with varying pressure; split ratio 50:1; injector temperature set at 250 °C; transfer line temperature set at 250 °C; programmed ramp from 170 to 270 °C at 3 °C/min. MS conditions: mass range 50–550 amu; electron multiplier 200 V relative. MS data is reported as the major *m*/*z* fragments with the % abundance and possible fragment in parentheses.

2.3. Methods

2.3.1. Procedure for esterification of castor oil: preparation of ester 3a

A mixture of castor oil (1200 g, 1.29 mol) and BF_3 etherate (2 L, 0.5 M in methanol, 1 mol) was heated to reflux (∼60 °C) for 10 h. The mixture was then cooled to rt and washed with pH = 5 buffer (519 g NaH_2PO_4/4 L H_2O) until it reached pH 5. The reaction mixture was then dried (Na_2SO_4), filtered, and methanol was removed by rotary evaporation. The remaining mixture was then distilled via Kugelrohr up to a temperature of 180 °C (at 70 mTorr). The distillate contained ester **3a** (950 g, 88%) as a clear liquid: ^{1}H NMR ($CDCl_3$) δ 5.30–5.58 (m, 2H), 3.58 (s, 3H), 3.51 (quintet, *J* = 5.9 Hz, 1H), 2.21 (t, *J* = 7.5 Hz, 2H), 2.12 (t, *J* = 7.0 Hz, 2H), 1.95 (q, *J* = 6.9 Hz, 2H), 1.8 (br s, 1H), 1.50–1.55 (m, 2H), 1.15–1.40 (m, 18H), 0.79 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.3, 133.1, 125.3, 71.4, 51.4, 36.8, 35.3, 34.0, 31.8, 29.5, 29.3, 29.1 (2C), 27.3, 25.7, 24.9, 22.6, 14.1.

2.3.2. Hydrogenation of ester 3a: preparation of saturated ester 3b

Ester **3a** (10.1 g, 32.4 mmol) was dissolved in methanol (320 mL) and 10% Pd/C (0.860 g) was added in one portion. The flask was fit with a balloon containing H_2 and the mixture was stirred vigorously at rt. After stirring for 22 h under H_2 atmosphere, the solution was vacuum filtered over a pad of Celite, rinsed with ethyl acetate, and concentrated *in vacuo* to give compound **3b** as a white fluffy solid (10.1 g, 99%); mp: 37–39 °C; ^{1}H NMR ($CDCl_3$) δ 3.57 (s, 3H), 3.44–3.51 (m, 1H), 2.21 (t, *J* = 7.6 Hz, 2H), 1.79 (s, 1H), 1.47–1.58 (m, 2H), 1.18–1.39 (m, 26H), 0.79 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.3, 71.9, 51.4, 37.5, 34.1, 31.8, 29.7, 29.6, 29.5, 29.4, 29.2, 29.1, 25.6 (2C), 24.9, 22.6, 14.1.

2.3.3. Representative procedure for TBDMS protection of hydroxy-fatty acid esters 3a and 3b: preparation of TBDMS protected hydroxy-esters 4a and 4b

To a solution of ester **3a** (10.0 g, 32.1 mmol) in THF (200 mL) was added imidazole (5.43 g, 79.7 mmol) and TBDMSCl (5.73 g, 38.0 mmol) and the solution was heated to reflux for 22 h. The reaction mixture was cooled to rt and hexanes (250 mL) was added. The reaction mixture was washed with water (150 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (5% ethyl