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Synthesis of (E)-10-hydroxy-2-decenoic acid ethyl ester via a one-pot tandem oxidation-Wittig process

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Abstract: The synthesis of (E)-10-hydroxy-2-decenoic acid ethyl ester (10H2DA-EE) (**3**) was achieved via a one-pot, tandem oxidation-Wittig process from commercially available 1,8-octanediol (**1**), Wittig reagent ($Ph_3P{=}CHCO_2Et$) (**2**) and activated MnO_2. Subsequent hydrolysis with sodium hydroxide gave (E)-10-hydroxy-2-decenoic acid (10H2DA) (**4**).

Keywords: One-pot tandem oxidation-Wittig process; (E)-10-hydroxy-2-decenoic acid ethyl ester; (E)-10-hydroxy-2-decenoic.

1. Introduction

(E)-10-hydroxy-2-decenoic acid (10H2DA) is a biologically active fatty acid found in the royal jelly of honey bees that possesses a range of noteworthy pharmacological effects including anti-tumour [1], anti-bacterial [2], neurogenesis [3-4], angiogenesis inhibition [5], and oestrogen receptor modulation [6]. The synthesis of 10H2DA has been reported by several synthetic routes [7-13].

2. Background

In many cases, the α,β-unsaturated carbonyl component is formed through the Wittig or Horner-Wittig olefination reactions with 8-(hydroxy or acetyloxy)octanal to give the ester form of 10H2DA, which after hydrolysis yields the free acid (10H2DA). Synthesis of the 8-(hydroxy or acetyloxy)octanal precursor is a vital component of the whole process and involves a multistep procedure starting from compounds including 1,8-octanediol [8], cyclooctanone [7, 13], oleic acid [10], and 6-chlorohexanol [12]. In this work, the one-pot synthesis of (E)-10-hydroxy-2-decenoic acid ethyl ester (10H2DA-EE) and (E)-10-hydroxy-2-decenoic acid (10H2DA) were achieved.

3. Experimental

3.1. Chemistry

All chemicals and solvents were purchased from commercial suppliers and were used without further purification. Flash chromatography was performed using commercially available Grace-Resolv or Grace Reveleris HP Silica Flash Cartridges (40 g). Thin layer chromatography was performed using Grace-

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Reveleris Al-backed TLC Plates (UV254) and were visualised with UV 254 nm light and potassium permanganate stain (0.75 g $KMnO_4$, 5.0 g K_2CO_3, 0.6 mLof 10% (w/w) NaOH, 100 mL water). Infrared spectra were recorded on an Agilent Technologies Cary 630 FT-IR spectrometer. ^{1}H NMR, ^{13}C NMR, ^{1}H,^{1}H COSY and ^{1}H-^{13}C HSQC spectra were recorded on a Bruker Avance 300 NMR spectrometer at 300 MHz for ^{1}H (T=300K) and 75 MHz for ^{13}C respectively. All ^{1}H and ^{13}C NMR spectral results were recorded as chemical shifts (δ). Chemical shifts recorded in $CDCl_3$ are relative to the internal TMS (0 ppm) for ^{1}H spectra and solvent peak (77.1 ppm) for ^{13}C spectra. ^{1}H NMR multiplicities are expressed as singlet (s), broad singlet (bs) doublet (d), doublet of doublets (dd), triplet of doublets (td), triplet (t), doublet of triplets (dt), triplet of triplets (tt), quartet (q), doublet of quartets (dq), quintet(quin), and multiplet (m). Microanalysis was performed by Chemical and Microanalytical Services Pty Ltd in Belmont, Victoria.

*3.1.1. Synthesis of (E)-10-hydroxy-2-decenoic acid ethyl ester (10H2DA-EE) (**3**)*

A 250 mL two-neck round bottom flask was attached with a condenser and purged under nitrogen for 10 minutes. 1,8-octandiol (2.00 g, 13.68 mmol), (Ethoxycarbonylmethylene)triphenylphosphorane **2** (5.96 g, 17.10 mmol), MnO_2 (11.89 g, 136.77 mmol)(Sigma Aldrich, technical, activated, ≥90%) and dichloromethane (100 mL) were added and allowed to stir under nitrogen bubbling for 10 minutes before refluxing under nitrogen for 48 hours. The MnO_2 was then filtered and washed with dichloromethane (3 x 20 mL). The filtrate evaporated to give an oily material, which was triturated with 1:9 (v:v) ethyl acetate – n-hexane (30 mL). The resulting triphenylphosphine oxide precipitate was removed by filtration then washed with additional 1:9 (v:v) ethyl acetate – n-hexane (3 x 10 mL). The filtrate was then evaporated to give an oil, which was subjected to flash chromatography (0:100 to 30:70 ethyl acetate:n-hexane) to give (E:Z-90:10)-10-hydroxy-2-decenoic acid ethyl ester (**3**) (2.25 g, 77%) as a pale yellow oil. IR (ATR): 3358 (broad)(w, OH st), 2928 (m, sp^3 C-H st), 2856 (m, sp^3 C-H st), 1718 (s, C=O st), 1653 (m, C=C st), 1264 (m C-O st), 1179 (s, C-O st), 1037 (s, C-O st), 977 (m, C=C bd) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.29 (t, 3H, H-12, *J* = 7.2 Hz), 1.33-1.48 (m, 8H, H-5, H-6, H-7, H-8), 1.56 (quin, 2H, H-9, *J* = 6.6 Hz), 2.05 (bs, 1H, OH), 2.20 (dq, 2H, H-4, *J* = 6.9 Hz, $J_{H4\text{-}H2}$ = 1.5 Hz), 3.62 (t, 2H, H-10, *J* = 6.6 Hz), 4.18 (q, 2H, H-11, *J* = 7.2 Hz), 5.81 (td, 1H, H-2, *J* = 15.6 Hz, *J* = 1.5 Hz), 6.96 (td, 1H, H-3, *J* = 15.6 Hz, *J* = 6.9 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.3 (C-3), 25.7 (C-8), 28.0 (C-5), 29.1 (C-6/C-7), 29.2 (C-6/C-7), 32.2 (C-4), 32.7 (C-9), 60.2 (C-11), 62.8 (C-10), 121.3 (C-2), 149.4 (C-3), 166.9 (C-1) ppm. $C_{12}H_{22}O_3$ (214.30): calcd. C 67.26, H 10.35; found. C 67.24, H 10.47.

*3.1. 2. Synthesis of (E)-10-hydroxy-2-decenoic acid (10H2DA) (**4**)*

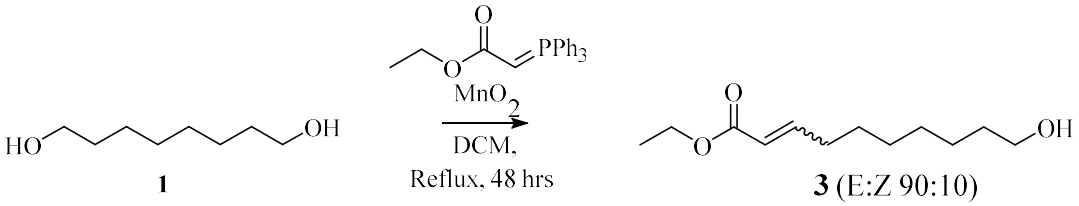
(E:Z-90:10)-10-hydroxy-2-decenoic acid ethyl ester **3** (2.00 g, 9.33 mmol), 1 M NaOH (15 mL) and ethanol (5 mL) were heated in a 50 mLround bottom flask at 100 °C for 20 minutes. The reaction mixture was then acidified with conc. HCl (pH ~2) and extracted with diethyl ether (3 x 20 mL). , The combined organic layers were washed with Brian water (20 ml), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting oil solidified upon cooling to give (E:Z-90:10)-10-hydroxy-2-decenoic acid **4** (1.65 g, 95%) as a white solid. Two recrystallizations from a co-solvent of diethyl ether and n-hexane gave (E:Z >99:1)-10-hydroxy-2-decenoic acid (**4**) (1.23 g, 71%) as a white solid. Mp = 64-66 °C (lit. mp = 64-65 °C [14]). IR (ATR): 3423 (m, OH st), 2927 (m, sp^3 C-H st), 1693 (s, C=O st), 1653 (s, C=C st), 980 (s, C=C bd) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.33-1.50 (m, 8H, H-5, H-6, H-7, H-8), 1.57 (quin, 2H, H-9, $J_{H9\text{-}H10}$ = $J_{H9\text{-}H8}$ = 6.6 Hz), 2.22 (dq, 2H, H-4, *J* = 6.9 Hz, $J_{H4\text{-}H2}$ = 1.2 Hz), 3.64 (t, 2H, H-10, *J* = 6.6 Hz), 5.82 (td, 1H, H-2, *J* = 15.6 Hz, *J* = 1.5 Hz), 6.88 (bs, 2H, OH), 7.06 (td, 1H, H-3, *J* = 15.6 Hz, *J* = 6.9Hz) ppm. ^{13}C NMR (75MHz, $CDCl_3$, T=300K): δ = 25.6 (C-5), 27.8 (C-8), 29.1 (C-6/C-7), 29.2 (C-6/C-7), 32.3 (C-4), 32.6 (C-9), 62.9 (C-10), 120.9 (C-2), 152.0 (C-3), 171.5 (C-1) ppm.

4. Present Study

The trans 10H2DA was involved in the treatment of prophylaxis of neurological diseases [4]. In this communication the trans10H2DA was synthesised and used in a previously reported patent by one of the authors (Wah Chin Boon)[4], which was found to be useful in the treatment of prophylaxis Therefore it was important to develope a simple, scalable and high yielding synthetic procedure for 10H2DA to support the in vivo and preclinical future treatment of prophylaxis of neurodevelopmental disorders in mammals.

4. 1. Synthesis of 10H2DA-EE

The need to synthesize the 8-(hydroxy or acetyloxy)octanal intermediate is a limiting step in the preparation of 10H2DA (**4**). However, the ability to carry out a number of synthetic steps in a one-pot process would circumvent the need to prepare and isolate intermediates. From literature review, an efficient tandem process for the synthesis of terminal-hydroxy-2-alkenoic acid ethyl esters has indeed been reported by via a tandem oxidation-Wittig process involving terminal alkanediols, Wittig reagent ($Ph_3P{=}CHCO_2Et$, **2**) and MnO_2 [15]. However, the synthesis of 10H2DA-EE (**3**) was not included in the study as the longest chain reported was 8-hydroxy-2-octenoic acid ethyl ester. In this publication, we disclose the extension of this procedure to the synthesis of 10H2DA-EE (**3**) followed by base-catalysed hydrolysis to give 10H2DA (**4**). Careful choice of the MnO_2 grade was crucial owing to the varied oxidative capacity among the various grades that are commercially available [15]. We tested three grades of MnO_2 (Table 1) which revealed that the yield of 10H2DA-EE (**3**) was highest when activated MnO_2 (Sigma Aldrich, technical, ≥90%) was employed (Entries 3, Table 1).



Scheme 1. Synthesis of 10H2DA-EE (**3**) by a tandem oxidation-Wittig process.

Table 1. Determining the most suitable grade of MnO_2 for the synthesis of 10H2DA-EE (**3**).

Entry*	MnO_2 grade[#]	Yield (%)	E:Z ratio
1	*ReagentPlus*, ≥99%	trace	90:10
2	10μm, ≥90%	7	90:10
3	activated, ≥90%	39	90:10

*20x MnO_2, 2.4x Wittig (**2**), DCM, 25ºC, 24 hours. [#]Purchased from Sigma Aldrich.

Table 2. Refining the conditions to optimise the yield of 10H2DA-EE (**3**).

Entry	Solvent	Wittig (2) Eq	MnO_2 Eq.	Time (h)	Yield (%)	E:Z ratio
4	DCM	1.5	10	24	42	90:10
5	DCM	1.5	10	48	62	90:10
6	DCM	1.25	10	48	58	90:10
7	DCM	1.25	10	72	58	90:10
8	DCM	1.25	6	48	43	90:10
9*	DCM	1.25	10	48	45	95:5
10**	DCM	1.25	10	48	57	92:8
11	THF	1.25	10	72	trace	90:10
12[#]	Toluene	1.25	10	72	37	90:10
13[##]	DCM	1.25	10	48	77	90:10

*0.3x Benzoic acid added; **0.1x Benzoic acid added;
[#]Reaction performed at 60ºC; [##]Reaction mixture purged with nitrogen.

The original method regarding terminal-hydroxy-2-alkenoic acid ethyl ester synthesis utilised a very large excess of Wittig reagent (**2**) (2.4 equ) and MnO_2 (20 x equ) relative to the terminal-alkanediol [15]. Through our investigation, we found such an excess to be superfluous, and often complicated the workup and purification. Reducing the excess of Wittig reagent (**2**) and MnO_2 (Table 2) was generally found to have only minimal impact on the isolated yield while also facilitating workup and purification. Interesting, a notable yield increase was observed when performing the reaction under nitrogen (Entry 13). However the utilising of THF as the solvent was extremely deleterious as only a trace amount of compound **3** was isolated

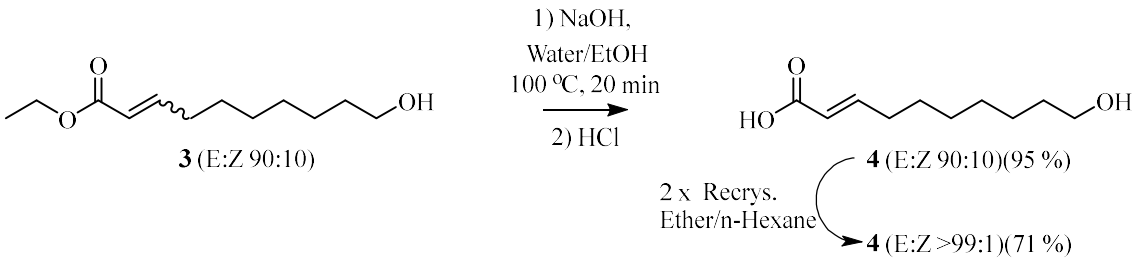
(Entry 11). Similarly, toluene was inferior to DCM (Entry 12), although the effect was not as profound as THF, and with no improvement in the E:Z ratio.

10H2DA-EE (**3**) synthesized in this investigation (Scheme 1) was a mixture of the trans (E) and cis (Z) isomers with a ratio of 90:10 respectively as shown by ^{1}H NMR spectroscopy. Since it is (E)-10H2DA (**4**) that occurs naturally in royal jelly, we sought to increase the proportion of the E isomer. The addition of reagents such as salts and benzoic acid have a profound effect on the reaction rate and/or the E:Z ratio of alkenes formed through Wittig or Wittig-Horner reactions [16-17]. We observed that the addition of a 0.3 x stoichiometric equivalent of benzoic acid (Entry 9) improved the E:Z ratio from 90:10 to 95:5, but also unacceptably reduced the yield from 58% (Entry 6) to 45%. A lower 0.1 x stoichiometric equivalent (Entry 10) gave only a modest improvement in the E:Z ratio from 90:10 to 92:8. Overall, the observed increase in the E:Z ratio did not recompense the reduction in yield.

Additionally, complete separation of the trans (E) and cis (Z) isomers by flash column chromatography was generally cumbersome as multiple runs were required (typically three) to achieve a E:Z ratio of ~99:1. Although employing high performance 20 µM-silica flash cartridges in our procedure (Grace Reveleris HP) did provide a noticeable improvement over standard 60 µM silica.

4.1.2. Hydrolysis of 10H2DA-EE to give the free acid 10H2DA.

The hydrolysis of the (E:Z-90:10)-10H2DA-EE (**3**) (Scheme 3) with aqueous NaOH followed by acidification with HCl gave (E:Z-90:10)-10H2DA (**4**) in a 95% yield as a white, waxy solid.



Scheme 2. Synthesis of 10H2DA (**4**) by hydrolysis of 10H2DA-EE (**3**) with sodium hydroxide.

Interestingly, flash chromatography was not required for the separation of the E and Z isomers because a single recrystallization from a co-solvent of diethyl ether and hexane yielded (E:Z~96:4)-10H2DA (**4**) as seen by ^{1}H NMR; a second recrystallization gave (E:Z>99:1)-10H2DA (**4**). Therefore, it is much easier and less cumbersome to enrich the E-isomer after formation of the 10H2DA free acid.

The structures of the new products **3** and **4** were confirmed by the analysis of their IR, ^{1}H NMR and ^{13}C NMR spectra in addition to the C and H microanalysis. The assignments of the ^{1}H NMR spectra of compounds **3** and **4** were achieved using ^{1}H-^{1}H correlation spectroscopy (COSY), while the protonated signals of the ^{13}C NMR spectra were assigned using heteronuclear single quantum coherence spectroscopy (HSQC) and using the assigned proton NMR spectra

5. Conclusion

The one pot synthesis of (E)-10-hydroxy-2-decenoic acid ethyl ester was described. Then the E:Z-90:10)-10H2DA-EE was hydrolysed and purified and gave E:Z-99:1)-10H2DA in 71% yield.

It is worth noting that this method has the potential to be a scalable process for the synthesise to produce the biologically important (E)-10-hydroxy-2-decenoic acid.

Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/organic-communications

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