Convenient synthesis of cytotoxic (11*E*)-13-hydroxy-10-oxooctadec-11-enoic acid from undec-10-enoic acid

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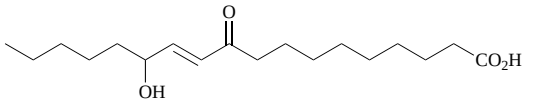
(11*E*)-13-Hydroxy-10-oxooctadec-11-enoic acid 1 is conveniently synthesized *via* a Knoevenagel-type reaction of isopropyl 11-phenylsulfinyl-10-oxoundecanoate 2a (itself easily derived from undec-10-enoic acid) with heptanal to form the γ-hydroxyenone functionality together with carbon chain elongation.

The title compound **1** was discovered in corn extract, and was also shown to be a stronger cytotoxic fatty acid than linoleic acid.[1] The first synthesis was accomplished by Matsushita *et al.* who showed it was also racemic.[2]†



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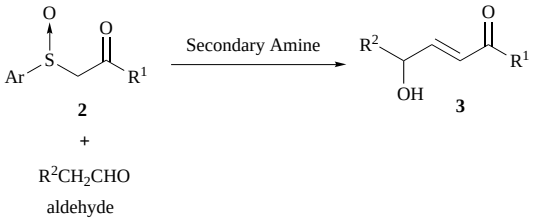
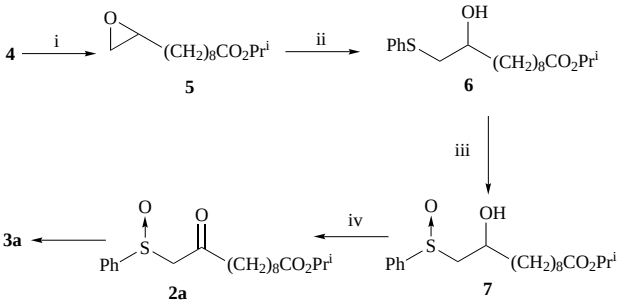
The notable antitumor activities of naturally occurring **1** shown by these pioneering works prompted us to synthesize it conveniently from an inexpensive fatty acid, undec-10-enoic acid, *via* a Knoevenagel-type reaction of a β-keto sulfoxide **2** with an aldehyde to form the γ-hydroxyenone functionality (Scheme 1).[3]



Scheme 1 Reaction of β-keto sulfoxide with aldehyde in the presence of secondary amine

Isopropyl 11-phenylsulfinyl-10-oxoundecanoate **2a** [Ar = Ph, $R^1 = (CH_2)_8CO_2Pr^i$ in **2**] was prepared from undec-10-enoic acid as follows (Scheme 2). Isopropyl undec-10-enoate **4**, derived from undec-10-enoic acid, was converted to the epoxide **5** by oxidation with *m*-chloroperbenzoic acid (MCPBA). Isopropyl 11-phenylsulfanyl-10-hydroxyundecanoate **6** was obtained by treatment of **5** with thiophenol and potassium carbonate in acetone, and converted to the corresponding sulfoxide **7** by MCPBA oxidation. The oxidation of the β-hydroxy sulfoxide **7** to β-keto sulfoxide **2a** was achieved by employing Swern oxidation[4] using an excess amount (20 equiv.) of dimethyl sulfoxide (DMSO). The key reaction of **2a** with heptanal (2 equiv.) was carried out in the presence of diethylamine (2 equiv.) and acetic acid (0.5 equiv.) in propiononitrile at 70 °C for 2 h to give the isopropyl ester **3a** [$R^1 = (CH_2)_8CO_2Pr^i$, $R^2 = (CH_2)_4CH_3$ in **3**] in 77% yield based on **2a**. The analogs **3b**–**e** were also prepared by a similar reaction of **2a** with various aldehydes, as shown in Table 1.



Scheme 2 *Reagents and conditions*: i, MCPBA, CH_2Cl_2, 0 °C–room temp., 5 h, 100%; ii, PhSH, K_2CO_3, acetone, 0 °C–room temp., 2 h, 88%; iii, MCPBA, CH_2Cl_2, 0 °C, 1 h, 96%; iv, DMSO (20 equiv.), $(COCl)_2$, Et_3N, CH_2Cl_2, −60 °C, 1 h, 82%

Hydrolysis of the isopropyl ester **3a** to the corresponding carboxylic acid **1** was performed enzymatically using lipase PS (Amano P) ‡ in a phosphate buffer (pH 7.0)–THF (8:1, v/v) at room temperature for 24 h, quantitatively.[2]

Experimental

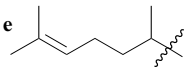
Isopropyl 11-phenylsulfinyl-10-oxoundecanoate 2a

To a solution of $(COCl)_2$ (0.3 ml, 3.47 mmol) in CH_2Cl_2 (16 ml) at −60 °C was added dimethyl sulfoxide (4.5 ml, 63.2 mmol). A solution of isopropyl 11-phenylsulfinyl-10-hydroxyundecanoate **7** (1.16 g, 3.16 mmol) in CH_2Cl_2 (5 ml) was added dropwise to the above solution over a period of 2 min at −60 °C. After stirring for 1 h, the mixture was treated with triethylamine (2.2 ml, 15.8 mmol) then was slowly warmed to room temperature by removal of the cooling bath. The reaction mixture was poured into water and extracted with chloroform. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystallised from diethyl ether–hexane to afford isopropyl 11-phenylsulfinyl-10-oxoundecanoate **2a** (952 mg, 82%); mp 66–67 °C; ν_{max}(neat)/cm^{-1} 2983, 2933, 2857, 1717, 1467, 1445, 1375, 1108, 1045 and 690; δ_H 1.23 (6 H, d, *J* 6.3), 1.26–1.30 (12 H, m), 1.47–1.62 (4 H, m), 2.25 (2 H, t, *J* 7.6), 2.39–2.54 (2 H, m), 3.76 (1 H, d, *J* 13.6), 3.88 (1 H, d, *J* 13.6), 5.00 (1 H, tt, *J* 6.3, 6.3) and 7.53–7.68 (5 H,

† The optically active **1** and its 14-membered lactone were prepared by Matsushita *et al. via* lipoxygenase-catalyzed highly enantio- and regioselective oxygenation at C-13 (the allylic carbon) of linoleic acid in 33% overall yield. They reported that each of the $[\alpha]_D^{25}$ values of naturally occurring **1** and its 14-membered lactone was almost zero and therefore they were racemic by comparison with the $[\alpha]_D^{25}$ values of (*R*) and (*S*)-**1** and the corresponding (*R*) and (*S*) lactones (−12.7, +15.8, +48.8 and −49.0 respectively) prepared by them.

‡ Commercially available (10 000 yen kg^{-1}). It was used 1 wt. equiv. to the ester **3a**.

Table 1 Reaction of **2a** with various aldehydes in the presence of diethylamine and acetic acid[a,b]

Aldehyde equiv.	Reaction time/h	Product **3**[c] R^2	Yield/%	Recovered **2a**/%
heptanal 2.0	2 (2)	**a** $(CH_3(CH_2)_4$	77 (68)	10 (4)
propanal 2.0	2 (2)	**b** CH_3	64 (51)	21 (23)
3-phenyl-propanal 2.0	2 (4)	**c** $PhCH_2$	67 (62)	8 (26)
nonanal 2.0	2 (4)	**d** $CH_3(CH_2)_6$	71 (63)	6 (23)
citronellal 4.0	4 (48)	**e** 	58 (47)	22 (0)

[a] Carried out in propiononitrile at 70 °C. [b] The values in the parentheses show the result in the absence of acetic acid. [c] $R^1 = (CH_2)_8CO_2Pr^i$.

m);§ δ_C 21.8, 22.9, 24.9, 28.8, 28.9, 29.0, 34.6, 44.9, 67.3, 68.0, 124.0, 129.4, 131.6, 143.0, 173.3 and 200.7.

Isopropyl (11*E*)-13-hydroxy-10-oxooctadec-11-enoate 3a

To a solution of **2a** (100 mg, 0.27 mmol) with diethylamine (57 μl, 0.55 mmol) and acetic acid (8 μl, 0.13 mmol) in propiononitrile (5 ml) was added heptanal (76 μl, 0.54 mmol) at 70 °C. After stirring was continued for 2 h at 70 °C, chloroform (5 ml) and saturated aqueous ammonium chloride (1 ml) were added to the reaction mixture at 0 °C. The aqueous layer was extracted with chloroform, and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (Merck, silica gel 60 or Fuji Silysia, silica gel BW-300) with 25% ethyl acetate in hexane as the eluent to provide **3a** (75 mg, 77%); ν_{max}(neat)/cm^{-1} 3449, 2978, 2931, 2857, 1731, 1676, 1632, 1467, 1374, 1110, 754 and 725; δ_H 0.89 (3 H, t, *J* 6.6), 1.22 (6 H, d, *J* 6.3), 1.26–1.63 (20 H, m), 2.25 (2 H, t, *J* 7.5), 2.55 (2 H, t, *J* 7.4), 4.32 (1 H, m), 5.00 (1 H, tt, *J* 6.3, 6.3), 6.30 (1 H, dd, *J* 1.4, 15.9) and 6.80 (1 H, dd, *J* 5.1, 15.9); δ_C 21.8, 22.5, 24.1, 24.9, 29.0, 29.1, 31.6, 34.6, 36.7, 40.7, 67.3, 71.3, 127.9, 147.8, 173.4 and 200.8. (Found: M^+, 354.5321. $C_{21}H_{38}O_4$ requires *M*, 354.5303).

§ *J* Values are given in Hz.

Acknowledgements

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