Convenient Formation of 4-Hydroxyalk-2-en-1-one Functionality via A Knoevenagel-type Carbon Chain Elongation Reaction of Aldehyde with 1-Arylsulfinylalkan-2-one

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A highly functionalized four-carbon unit, 4-hydroxyalk-2-en-1-one functionality [$R^2CH(OH)CH{=}CHCOR^1$], was conveniently prepared by a reaction of an aldehyde (R^2CH_2CHO) with a 1-(arylsulfinyl)alkan-2-one [$ArS(O)CH_2COR^1$] in the presence of diethylamine (Knoevenagel condition). Other functional groups, such as carbonyl and hydroxy groups, in both of the alkyl chains (R^1, R^2) did not prevent this reaction. This reaction was used to conveniently prepare (±)-(11*E*)-13-hydroxy-10-oxooctadec-11-enoic acid (**14**), having cytotoxic activity, and its analogues from undec-10-enoic acid in good yield.

Introduction

The construction of the carbon skeleton through carbon−carbon (C−C) bond formation and the functionalization of an appropriate carbon atom to form functional groups are essential in organic synthesis. Subsequently, in many approaches to C−C bond formation, a variety of carbon-nucleophiles have been reacted with various carbonyl compounds (aldehydes and ketones). Among those, the Knoevenagel reaction[1] of aldehydes using active methylene compounds with a secondary amine are useful tools for convenient carbon chain elongation along with functionalization of the aldehyde to give α,*β*-unsaturated carbonyls or nitriles.

In the early 1980s, we discovered that a Knoevenagel-type reaction of aldehydes and ketones with 2-arylsulfinylacetonitrile **1** gave a highly functionalized four-carbon unit, 4-hydroxyalk-2-enenitrile **2**, in high yield.[2] This reaction is interesting in organic synthesis, because it gives a highly functionalized four-carbon (C_4) unit from normal aldehydes or ketones with two-carbon elongation of the carbonyls similar to a Horner−Wadsworth−Emmons (HWE) reaction.[3] However, unlike the HWE reaction, the C_4 unit can be obtained without using an α-hydroxyaldehyde or its synthetic equivalent, such as an α-triorganosilyloxyaldehyde. Similar reactions of alkyl 2-arylsulfinyl acetates **3** with aldehydes to give alkyl 4-hydroxyalk-2-enoates **4** were also reported[4] and employed for organic syntheses.[5] This is a useful functionality which occurs in the structure of some biologically attractive natural products, especially macrolides such as brefeldin A.[5a,b]

Among the reactions utilizing sulfinyl-activated methylene compounds, we are also very interested in the reaction of 1-arylsulfinylalkan-2-one **5** with aldehydes, because it is capable of introducing more than two carbons into the carbon chain of an aldehyde to give a wide variety of 4-hydroxyalk-2-en-1-ones [$R^2CH(OH)CH{=}CHCOR^1$] with various substituents (R^1), rather than **1** and **3**.[6] Here, we examine further the reaction of **5** with aldehydes in the synthesis of highly functionalized compounds having the 4-hydroxyalk-2-en-1-one unit **6**.

Results and Discussion

Various *β*-keto sulfoxides (1-arylsulfinylalkan-2-ones) **5** were conveniently prepared by employing well-known methods as follows (Figure 3):

(1) Oxidation of the corresponding sulfide (*β*-keto sulfide) **7a**,**b** to sulfoxide **5a**,**b**, with *m*CPBA.

(2) Reaction of dianion **8** derived from **5a**,**b** with alkylhalides and aldehyde to **5c**,**d** and **5e**, respectively.[7]

(3) Reaction of arylsulfinylcarbanion[8] **9** with carboxylic ester to **5f**−**i**.

(4) Oxidation of *β*-hydroxy sulfide **10** to *β*-hydroxy sulfoxide **11** via transition metal-catalyzed oxidation with hydrogen peroxide[9,10a] or *tert*-butyl hydroperoxide,[10b−d] or

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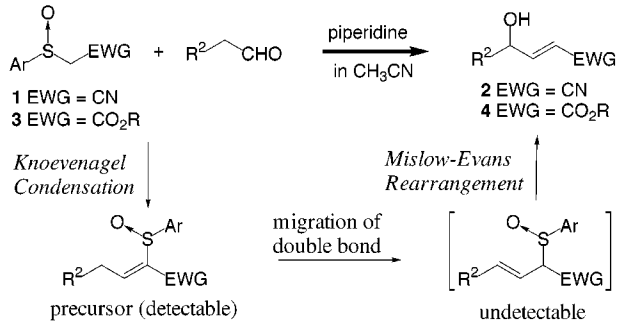


Figure 1. Two-carbon elongation of aldehydes by Knoevenagel reaction with sulfinyl-activated methylene compounds **1** and **3**.

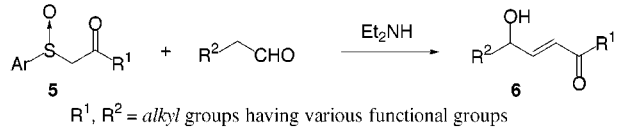


Figure 2. More than two carbons elongation of aldehydes by β-keto sulfoxides **5**.

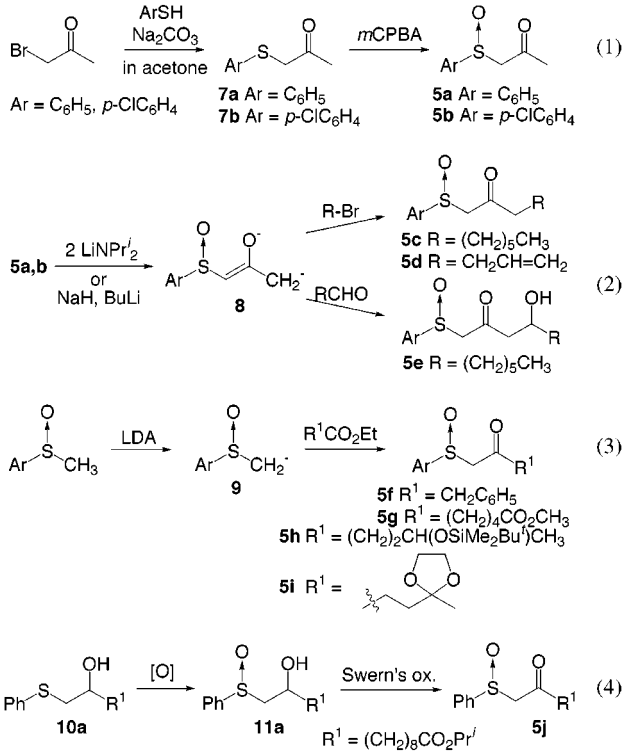


Figure 3. Synthetic methods for various β-keto sulfoxides **5**.

via conventional oxidation with *m*CPBA, followed by an improved Swern's oxidation[11] of β-hydroxy sulfoxide **11** to **5j**.

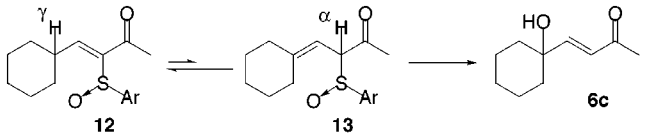


Figure 4. Reactivity of **12** to **6c**.

The β-keto sulfoxides **5a**−**j** obtained using the methods 1−4 were treated with aldehydes and diethylamine (in the presence or absence of a small amount of acetic acid) in propanenitrile to give 4-hydroxy-2-alkenones **6a**−**l**. In the presence of acetic acid, **6** was obtained in a shorter reaction time, thus giving a higher yield than that in the absence of acetic acid. This may be due to an acceleration of the dehydration step in the Knoevenagel reaction by the acid catalyst. The results are summarized in Table 1.[12] The results for **5j** are discussed later in the synthesis of the fatty acid **14**.

Although the reaction of 1-arylsulfinylpropan-2-one **5a**,**b** with hexanal and citronellal gave the corresponding 5-hydroxyalk-4-en-2-one **6a** and **6b** in good yield (entries 1−3), the reaction with cyclohexanecarboxaldehyde gave the desired **6c** in very poor yield (18%) together with its precursor **12** (35%), although **5b** was recovered in 31% (entry 4). This may have been caused by the remarkably slow rate of migration of the double bond from $\alpha\beta$ (**12**) to $\beta\gamma$ (**13**) due to a lower acidity of the methine proton at the γ-position of the sulfinyl group compared with that in other cases (Figure 4).

Carbonyl (ketone and ester) functionalities in both β-keto sulfoxide (R^1) and aldehyde (R^2) did not prevent the desired reaction (entries 5, 6, 11, and 14). Reaction of the compound having the free hydroxy group **5e** also gave the desired product **6h** without protection of the hydroxy group (entry 9). Some protecting groups, such as *tert*-butyldimethylsilyloxy[13] in **5h** and ketal (2,2-ethylenedioxy) in **5i**, were stable under the reaction conditions (entries 12 and 13).

We employed this reaction in the synthesis of the biologically attractive natural compound (fatty acid) from undec-10-enoic acid (**15**) as shown below.

Synthesis of (±)-(11*E*)-13-Hydroxy-10-oxooctadec-11-enoic Acid (14).[14] (±)-(11*E*)-13-Hydroxy-10-oxooctadec-11-enoic acid (**14**) was discovered in corn extract and was shown to be a stronger cytotoxic fatty acid than linoleic acid.[15] A retrosynthetic study of **14** based on our reaction suggested that undec-10-enoic acid (**15**) could be useful for this synthesis. That is, the terminal olefin will be easily convertible into 1-arylthioalkan-2-ol via 1,2-epoxide or 1,2-diol and then to β-keto sulfoxide. The synthesis of **14** was carried out as follows.

Undec-10-enoic acid (**15**) was converted to the corresponding 10,11-epoxy ester **16** by *m*CPBA-oxidation of

(10) Many methods have been developed for asymmetric oxidation of sulfides to optical active sulfoxides, in which hydrogen peroxide or *tert*-butyl hydroperoxide was used as an oxidant with a catalytic amount of chiral transition metal (Mn, Ti, Mo) complexes, for example: H_2O_2: (a) Palucki, M.; Hanson, P.; Jacobsen E. N. *Tetrahedron Lett*. **1992**, *33*, 7111−7114. *t*-BuOOH: (b) Kagan, H. B.; Pitchen, P. *Tetrahedron Lett*. **1984**, *25*, 1049−1052. (c) Pitchen, P.; Duñach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc*. **1984**, *106*, 8188−8193. (d) Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem*. **1993**, *58*, 4529−4533.

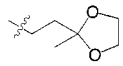
(11) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem*. **1978**, *43*, 2480−2482.

(12) Note that all of the reactions in the tables were not completely optimized. It is well-known that aldehydes are not very stable, especially in the case of α-methylene aldehyde, due to the high reactivities under basic and acidic conditions, at high temperature (undesired reactions such as aldol and/or Cannizzaro reactions take place very easily). Therefore, we had to choose the reaction conditions carefully to obtain the desired product in high yield. This means that the complete consumption of **5** did not always allow for the best yield and sometimes gave a large amount of byproducts due to side reactions of the aldehyde over the long reaction time, which resulted in a low yield by contamination of inseparable byproducts and decomposition of the desired product.

(13) Nokami, J.; Taniguchi, T.; Ogawa, Y. *Chem. Lett*. **1995**, 43−44.

(14) Preliminary report: Nokami, J.; Osafune, M.; Shiraishi, K.; Sumida, S.; Imai, N. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2947−2948.

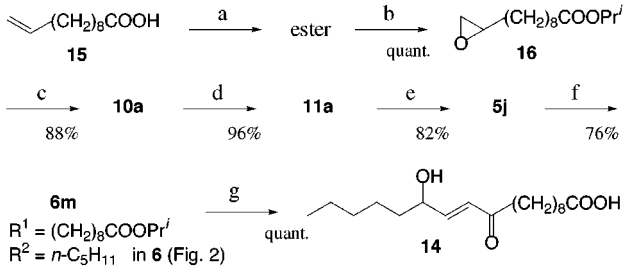
Table 1. Formation of 4-hydroxy-2-alkenone Unit by Reaction of 5 with Aldehydes 7[a]

entry	β-keto sulfoxide 5			R^2CH_2CHO 7	temp.	time	products 6		recovery
		Ar	R^1	R^2 [or aldehyde]	(°C)	(h)		yield (%)	of 5 (%)
1	**5a**	C_6H_5	CH_3	*n*-C_4H_9	r.t.	6	**6a**	82	7
2	**5b**	*p*-ClC_6H_4	CH_3	*n*-C_4H_9	r.t.	4	**6a**	76	13
3	**5b**	*p*-ClC_6H_4	CH_3	[citronellal]	r.t.	6	**6b**	84	5
4	**5b**	*p*-ClC_6H_4	CH_3	[*c*-$C_6H_{11}CHO$]	r.t.	90	**6c**	18[b]	31
5	**5b**	*p*-ClC_6H_4	CH_3	*n*-$C_5H_{11}CO(CH_2)_2$	70	2	**6d**	66	16
6	**5b**	*p*-ClC_6H_4	CH_3	$CH_3O_2C(CH_2)_7$	70	2	**6e**	51	25
7	**5c**	*p*-ClC_6H_4	$(CH_2)_6CH_3$	*n*-C_4H_9	70	2	**6f**	64	21
8	**5d**	*p*-ClC_6H_4	$(CH_2)_2CH{=}CH_2$	*n*-C_4H_9	70	2	**6g**	68	14
9	**5e**	C_6H_5	$CH_2CH(OH)(CH_2)_5CH_3$	*n*-C_5H_{11}	r.t.	6	**6h**	63	5
10	**5f**	C_6H_5	$CH_2C_6H_5$	*n*-C_4H_9	r.t.	4	**6i**	54	17
11	**5g**	C_6H_5	$(CH_2)_4CO_2CH_3$	*n*-C_4H_9	r.t.	6	**6j**	64	18
12	**5h**	C_6H_5	$(CH_2)_2CH(OTBDMS)CH_3$	*n*-C_5H_{11}	r.t.	6	**6k**	66	11
13[c]	**5i**	C_6H_5		*n*-C_4H_9	70	3	***6l***	69	14

[a] All reactions were performed with **5** (0.5−1.0 mmol), aldehyde (2.0 equiv), diethylamine (2.0 equiv), and acetic acid (0.5 equiv) in propanitrile, unless otherwise noted. [b] 3-(4-Chlorophenylsulfinyl)-4-cyclohexylbut-3-en-2-one **12** was obtained in 34% yield. [c] Reaction was performed in the absence of acetic acid.

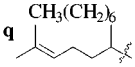
the ester. Treatment of **16** with thiol and a base (K_2CO_3) in acetone gave the β-hydroxy sulfide **10a** quantitatively. The β-hydroxy sulfide **10a** was converted to sulfoxide **11a** by *m*CPBA-oxidation and then to the corresponding β-keto sulfoxide **5j** by Swern's oxidation using an excess amount (20 equiv) of dimethyl sulfoxide.[16] Isopropyl 10-oxo-11-(phenylsulfinyl)undecanoate (**5j**) was allowed to react with heptanal (2 equiv) in the presence of diethylamine (2 equiv) and acetic acid (0.5 equiv) in propanenitrile at 70 °C for 2 h to give isopropyl 13-hydroxy-10-oxooctadec-11-enoate (**6m**) in 76% yield. Hydrolysis of the ester **6m** was carried out enzymatically by lipase PS (from *Pseudomonas cepacia*, Amano) in THF/phosphate buffer (1/8 v/v) to give the acid (±)-**14**, which was fully characterized by spectral data, e.g., IR spectra due to the carboxy group (COOH: 3500−2700 and 1709 cm^{-1}) and ^1H and ^{13}C NMR of the carbon skeleton (disappearance of the isopropyl group from **6m**).As shown above, this synthesis was very convenient, because undec-10-enoic acid (**15**) is inexpensive, and all of the reactions used here are very common and easy to handle. The total yield of **14** from **15** (seven steps) was 42%. Moreover, its analogues **6n**−**q** were easily prepared by the reaction of **5j** with various aldehydes (Table 2).

Scheme 1[a−g]



[a] Pr^iOH, H^+. [b] *m*CPBA. [c] PhSH, K_2CO_3. [d] *m*CPBA. [e] $(COCl)_2$, DMSO (20 equiv), Et_3N. [f] Heptanal, Et_2NH. [g] Lipase PS, phosphate buffer.

Table 2. Reaction of 5j with Various Aldehydes in the Presence of Diethylamine and Acetic Acid[a,b]

aldehyde equiv.	reaction time/h	product 6[c]			recovered
			R^2	yield/%	**5j**/%
heptanal 2.0	2 (2)	**m**	$CH_3(CH_2)_4$	76 (68)	10 (4)
propanal 2.0	2 (2)	**n**	CH_3	64 (51)	21 (23)
3-phenylpropanal 2.0	2 (4)	**o**	$PhCH_2$	67 (62)	8 (26)
nonanal 2.0	2 (4)	**p**		71 (63)	6 (23)
citronellal 4.0	4 (48)	**q**		58 (47)	22 (0)

[a] The reaction was performed in propionitrile at 70 °C. [b] The values in the parentheses show the result in the absence of acetic acid. [c] R1 = $(CH_2)_8CO_2Pr^i$ in **6** [$R^2CH(OH)CH{=}CHCOR^1$].

Experimental Section

General Methods. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHZ) spectra were obtained $CDCl_3$ unless noted otherwise. High-resolution mass spectra were obtained in the Analysis Center of our university. Elemental analyses were performed in our laboratory. Tetrahydrofuran (THF) and diethyl ether were distilled from benzophenone ketyl. Acetonitrile and propanenitrile were dried over phosphorus pentoxide and stored. Diethylamine and diisopropylamine were distilled from calcium hydride and stored over molecular sieves. Methanol and ethanol were distilled from $Mg(OMe)_2$ and $Mg(OEt)_2$, respectively. Commercially available reagents were used without further purification.

Reaction of β-Keto Sulfoxides 5 with Aldehydes in the Presence of Diethylamine

Reaction of 1-(Phenylsulfinyl)propan-2-one (5a) with Hexanal to 5-Hydroxynon-3-en-2-one (6a). To a solution of **5a** (100 mg, 0.55 mmol), diethylamine (94 μL, 1.10 mmol),

(15) (a) Kuga, H.; Ejima, A.; Mitui, I.; Sato, K.; Ishihara, N.; Fukuda, K.; Saito, F.; Uenakai, K. *Biosci. Biotech. Biochem.* **1993**, *57*, 1020−1021. (b) Hayashi, Y.; Ishihara, N.; Takahashi, M.; Fujii, E.; Uenakai, K.; Masada, S.; Ichimoto, I. *Biosci. Biotech. Biochem.* **1996**, *60*, 1115−1117. (c) Enantioselective syntheses of *R*- and *S*-**14** and their lactones *R*- and *S*-10-oxo-11(*E*)-octadecen-13-olide from linoleic acid via soybean lipoxygenase oxidation have been reported, in which it was also described that their in vitro cytotoxic activities (IC_{50} values against tumorial cell P388) were scarcely affected by their configurations; Matsushita, Y.; Sugamoto, K.; Nakama, T.; Matsui, T.; Hayashi, Y.; Uenakai, K. *Tetrahedron Lett.* **1997**, *38*, 6055−6058. (d) More recently, synthesis of *S*-**14** was reported; Sharma, A.; Chattopadhya, S. *Enantiomer* **1998**, *3*, 225−229.

(16) Although the same result was obtained when more than 20 equiv of DMSO was used, the use of less than 15 equiv of DMSO gave a TLC detectable amount of the corresponding β-keto sulfide.

and acetic acid (16 μL, 0.28 mmol) in propanenitrile (5 mL) was added hexanal (99 μL, 1.10 mmol) under nitrogen at room temperature. The reaction mixture was stirred for 6 h and then diluted with ethyl acetate (or chloroform). The mixture was washed with brine, dried, and concentrated under reduced pressure. The residue was column chromatographed on silica gel to give the oil **6a** (70 mg, 82%): ^{1}H NMR δ 0.92 (t, J = 7.0 Hz, 3H), 1.30−1.46 (m, 4H), 1.56−1.68 (m, 2H), 1.75 (br, 1H), 2.28 (s, 3H), 4.28−4.37 (m, 1H), 6.27 (dd, J = 16.0, 1.6 Hz, 1H), 6.77 (dd, J = 16.0, 5.2 Hz, 1H); ^{13}C NMR δ 14.0, 22.6, 27.3, 36.4, 71.1, 129.0, 149.6, 199.1; IR (neat) 3432, 2958, 2932, 2861, 1676, 1630, 981 cm^{-1}. Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.44; H, 10.57.

6,10-Dimethyl-5-hydroxyundeca-3,9-dien-2-one (6b): ^{1}H NMR δ 0.91 and 0.94 (d, J = 6.9 Hz for δ 0.91, d, J = 6.8 Hz for δ 0.94, 3H), 1.12−1.19 (m, 2H), 1.43−1.81 (m, 2H), 1.61 (s, 3H), 1.69 (s, 3H), 1.88−2.14 (m, 2H), 2.28 (s, 3H), 4.22 and 4.27 (m, 1H), 5.04−5.13 (m, 1H), 6.30 (d, J = 16.0 Hz, 1H), 6.77 (dd, J = 16.0, 4.9 Hz, 1H); ^{13}C NMR δ 14.4, 15.3, 18.0, 25.8, 25.9, 26.0, 27.7, 32.5, 33.2, 38.4, 38.7, 74.7, 75.5, 124.5, 130.0, 130.4, 132.1, 148.2, 149.0, 199.0; IR (neat) 3448, 2966, 2925, 2877, 2857, 1674, 1630, 983, 829 cm^{-1}; HMRS (EI) calcd for $C_{13}H_{22}O_2$ 210.1620, found 210.1609.

1-(3-Oxo-1-butenyl)cyclohexanol (6c) and 3-(4-Chlorophenylsulfinyl)-4-cyclohexylbut-3-en-2-one (12). 6c: ^{1}H NMR δ 1.20−1.36 (m, 2H), 1.50−1.72 (m, 8H), 1.60 (br, 1H), 2.28 (s, 3H), 6.31 (d, J = 16.0 Hz, 1H), 6.84 (d, J = 16.0 Hz, 1H); ^{13}C NMR δ 21.4, 25.1, 27.5, 36.9, 71.5, 127.0, 153.7, 199.2; IR (neat) 3427, 2933, 2857, 1674, 1625, 984 cm^{-1}; HMRS (EI) calcd for $C_{10}H_{16}O_2$ 168.1150, found 168.1102.

12: ^{1}H NMR (400 MHz) δ 1.15−1.43 (m, 6H), 1.60−1.83 (m, 4H), 2.27 (s, 3H), 2.85−2.90 (m, 1H); 6.78 (d, J = 10.4 Hz, 1H), 7.38−7.45 (m, 2H), 7.55−7.62 (m, 2H); IR (neat) 2929, 2853, 1692, 1662, 1052, 822 cm^{-1}.

5-Hydroxytridec-3-ene-2,8-dione (6d): ^{1}H NMR δ 0.89 (t, J = 6.9 Hz, 3H), 1.21−1.38 (m, 4H), 1.52−1.63 (m, 2H), 1.74−1.87 (m, 1H), 1.93−2.04 (m, 1H), 2.28 (s, 3H), 2.43 (t, J = 7.5 Hz, 2H), 4.35−4.43 (m, 1H), 6.31 (dd, J = 15.9, 1.8 Hz, 1H), 6.74 (dd, J = 15.9, 4.7 Hz, 1H); ^{13}C NMR δ 14.2, 22.7, 23.6, 27.7, 30.1, 31.6, 38.5, 43.2, 70.3, 129.4, 149.3, 199.2, 212.3; IR (neat) 3428, 2956, 2931, 2872, 2861, 1709, 1676, 1633, 982 cm^{-1}; HMRS (EI) calcd for $C_{13}H_{22}O_3$ 226.1569, found 226.1598.

Methyl 9-hydroxy-12-oxotridec-10-enoate (6e): ^{1}H NMR δ 1.28−1.36 (m, 4H), 1.55−1.66 (m, 4H), 1.85 (br, 1H), 2.28 (s, 3H), 2.31 (t, J = 7.2 Hz, 2H), 3.67 (s, 3H), 4.29−4.37 (m, 1H), 6.27 (dd, J = 16.0, 1.5 Hz, 1H), 6.77 (dd, J = 16.0, 5.0 Hz, 1H); ^{13}C NMR δ 25.1, 25.5, 27.6, 29.3, 29.5, 34.3, 36.9, 51.8, 71.3, 129.2, 149.8, 174.7, 199.2; IR (neat) 3448, 2932, 2857, 1736, 1677, 1631, 982 cm^{-1}; HMRS (EI) calcd for $C_{14}H_{24}O_4$ 256.1675, found 256.1674.

5-Hydroxypentadec-6-en-8-one (6f): ^{1}H NMR δ 0.86−0.94 (m, 6H), 1.27−1.45 (m, 14H), 1.57−1.62 (m, 3H), 2.55 (t, J = 7.4 Hz, 2H), 4.27−4.35 (m, 1H), 6.30 (dd, J = 15.8, 1.6 Hz, 1H), 6.79 (dd, J = 15.8, 4.8 Hz, 1H); ^{13}C NMR δ 14.3, 14.4, 22.9, 23.0, 24.5, 27.8, 29.4, 29.6, 32.0, 36.8, 41.1, 71.6, 128.3, 148.5, 201.5; IR (neat) 3435, 2957, 2929, 2858, 1670, 1632, 983 cm^{-1}; HMRS (EI) calcd for $C_{15}H_{28}O_2$ 240.2089, found 240.2089.

8-Hydroxydodeca-1,6-dien-5-one (6g): ^{1}H NMR δ 0.92 (t, J = 7.1 Hz, 3H), 1.26−1.46 (m, 4H), 1.54−1.70 (m, 2H), 1.74 (br, 1H), 2.38 (dt, J = 6.5, 7.4 Hz, 2H), 2.67 (t, J = 7.4 Hz, 2H), 4.29−4.37 (m, 1H), 4.99 (d, J = 10.2 Hz, 1H), 5.84 (ddt, J = 17.1, 10.2, 6.5 Hz, 1H), 6.32 (dd, J = 15.9, 1.6 Hz, 1H), 6.81 (dd, J = 15.9, 5.0 Hz, 1H); ^{13}C NMR δ 13.9, 22.5, 27.3, 27.9, 36.3, 39.6, 71.1, 115.2, 127.8, 137.0, 148.3, 199.9; IR (neat) 3435, 3079, 2958, 2932, 2861, 1667, 1634, 984 cm^{-1}; HMRS (EI) calcd for $C_{12}H_{20}O_2$ 196.1464, found 196.1442.

6,11-Dihydroxyhept-7-en-9-one (6h): ^{1}H NMR δ 0.84−0.91 (m, 6H), 1.25−1.45 (m, 14H), 1.50−1.75 (m, 4H), 1.70 (br, 1H), 2.65 (dd, J = 17.5, 8.9 Hz, 1H), 2.78 (dd, J = 17.5, 2.8 Hz, 1H), 3.12 (br, 1H), 4.03−4.13 (m, 1H), 4.28−4.38 (m, 1H), 6.31 (d, J = 15.9 Hz, 1H), 6.84 (dd, J = 15.9, 5.0 Hz, 1H); ^{13}C NMR δ 14.4, 14.4, 22.9, 23.0, 25.3, 25.8, 29.6, 32.0, 32.0, 32.1, 36.9, 47.1, 68.2, 71.4, 128.6, 150.0, 201.6; IR (neat) 3393, 2955, 2921, 2855, 1678, 1621, 997 cm^{-1}; Anal. Calcd for $C_{17}H_{32}O_3$: C, 71.79; H, 11.34. Found: C, 71.52; H, 11.37.

1-Phenyl-5-hydroxynon-3-en-2-one (6i): ^{1}H NMR δ 0.90 (t, J = 7.3 Hz, 3H), 1.26−1.39 (m, 4H), 1.52−1.66 (m, 2H), 1.55 (br, 1H), 3.85 (s, 2H), 4.25−4.33 (m, 1H), 6.35 (dd, J = 15.8, 1.5 Hz, 1H), 6.87 (dd, J = 15.8, 4.9 Hz, 1H), 7.19−7.37 (m, 5H); ^{13}C NMR δ 14.3, 22.9, 27.7, 36.7, 48.5, 71.6, 127.3, 127.4, 129.1, 129.8, 134.6, 149.6, 197.9; IR (neat) 3423, 3063, 2957, 2932, 2871, 2860, 1686, 1629, 984 cm^{-1}; HMRS (EI) calcd for $C_{13}H_{20}O_2$ 232.1463, found 232.1468.

Methyl 9-hydroxy-6-oxotridec-7-enoate (6j): ^{1}H NMR δ 0.92 (t, J = 6.8 Hz, 3H), 1.28−1.44 (m, 4H), 1.59 (br, 1H), 1.58−1.65 (m, 6H), 2.34 (t, J = 6.9 Hz, 2H), 2.59 (t, J = 6.8 Hz, 2H), 3.67 (s, 3H), 4.27−4.36 (m, 1H), 6.30 (dd, J = 15.9, 1.7 Hz, 1H), 6.80 (dd, J = 15.9, 4.9 Hz, 1H); ^{13}C NMR δ 13.8, 22.4, 23.3, 24.3, 27.3, 33.7, 36.3, 40.0, 51.4, 71.0, 127.7, 148.3, 173.9, 200.2; IR (neat) 3446, 2956, 2935, 2875, 1735, 1676, 1633, 986 cm^{-1}. Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.89; H, 9.68.

2-(*tert*-Butyldimethylsilyloxy)-9-hydroxytridec-6-en-5-one (6k): ^{1}H NMR δ 0.03 (s, 3H), 0.04 (s, 3H), 0.88 (s, 9H), 0.89 (t, J = 6.5 Hz, 3H), 1.14 (d, J = 6.1 Hz, 3H), 1.24−1.36 (m, 8H), 1.54−1.84 (br, 1H), 1.75 (m, 2H), 2.54−2.70 (m, 2H), 3.79−3.90 (m, 1H), 4.26−4.37 (m, 1H), 6.30 (dd, J = 15.9, 1.6 Hz, 1H), 6.79 (dd, J = 15.9, 5.0 Hz, 1H); ^{13}C NMR δ −4.8, −4.5, 13.9, 18.0, 22.5, 23.7, 24.9, 25.8, 31.6, 33.3, 36.6, 67.5, 71.1, 127.9, 148.0, 200.7; IR (neat) 3431, 2956, 2930, 2858, 1669, 1633, 1471, 986 cm^{-1}; HMRS (EI) calcd for $C_{19}H_{38}O_3Si$, 342.2592, found 342.2636.

2,2-Ethylenedioxy-8-hydroxyundec-6-en-5-one (6l): ^{1}H NMR δ 0.91 (t, J = 7.0 Hz, 3H), 1.33 (s, 3H), 1.28−1.44 (m, 4H), 1.53−1.71 (m, 2H), 1.70 (br, 1H), 2.02 (t, J = 7.7 Hz, 2H), 2.67 (t, J = 7.7 Hz, 2H), 3.88−3.99 (m, 4H), 4.28−4.36 (m, 1H), 6.31 (dd, J = 15.9, 1.6 Hz, 1H), 6.81 (dd, J = 15.9, 5.0 Hz, 1H); ^{13}C NMR δ 14.3, 22.9, 24.3, 27.7, 33.2, 35.5, 36.7, 65.0, 71.5, 109.7, 128.3, 148.5, 200.4; IR (neat) 3444, 2957, 2934, 2873, 1668, 1633, 1134, 1091, 1051, 984 cm^{-1}; HMRS (EI) calcd for $C_{14}H_{24}O_4$ 256.1675, found 256.1689.

Synthesis of (±)-(11*E*)-13-Hydroxy-10-oxooctadec-11-enoic Acid (14) from Undec-10-enoic Acid (15)

Isopropyl 10-Hydroxy-11-phenylthioundecanoate (10a). Undec-10-enoic acid (**15**) was treated with 2-propanol in the presence of a catalytic amount of *p*-toluenesulfonic acid in refluxing benzene with azeotropical removal of water to give isopropyl undec-10-enoate. A solution of *m*CPBA (9 g; ca. 80%, 42 mmol) in dichloromethane (70 mL) was added to a solution of the ester (4.0 g, 17.6 mmol) in dichloromethane (100 mL) at 0 °C. After stirring at room temperature for 5 h, saturated aqueous sodium thiosulfate (3 mL) was then added at 0 °C. The reaction mixture was washed with saturated aqueous sodium hydrogencarbonate (100 mL) and brine, dried, and concentrated to give isopropyl 10,11-epoxyundecanoate (**16**) (100% yield): ^{1}H NMR δ 1.23 (d, J = 6.3 Hz, 6H), 1.31−1.62 (m, 12H), 2.28 (t, J = 7.5 Hz, 2H), 2.60 (ddd, J = 5.0, 4.0, 2.7 Hz, 2H), 2.90 (m, 1H), 5.00 (m, 1H); ^{13}C NMR δ 22.4 (× 2), 25.5, 26.5, 29.6, 29.7, 29.9 (× 2), 33.0, 35.2, 47.6, 52.9, 67.8, 173.9; IR (neat) 2980, 2930, 2856, 1732, 1467, 1374, 1258, 1181, 1110, 961−700, 834, 756 cm^{-1}.

To a suspension of finely powdered potassium carbonate (3.84 g, 40 mmol) in acetone (30 mL) were added thiophenol (0.93 mL, 10 mmol) and a solution of **16** (2.42 g, 10 mmol) in acetone (15 mL) successively at 0 °C. After stirring at room temperature for 7 h, the mixture was filtered to remove excess potassium carbonate and concentrated. The resulting mixture was diluted with ethyl acetate (50 mL), washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give crude **10a**. Purification by column chromatography on silica gel (EtOAc/hexane = 1/5) afforded **10a** as a colorless solid (3.03 g, 86%): mp 29−31 °C; ^{1}H NMR δ 1.10 (d, J = 6.2 Hz, 6H), 1.27−1.61 (m, 12H), 2.25 (t, J = 7.5 Hz, 2H), 2.41 (br, 1H), 2.99 (ddd, J = 13.7, 3.4, 8.8 Hz, 2H), 3.66 (m, 1H), 5.00 (m, 1H), 7.21−7.40 (m, 5H); ^{13}C NMR δ 21.7 (× 2), 24.8, 25.5, 29.0, 29.1, 29.3, 34.5, 35.9, 41.9, 67.2, 69.2, 126.3, 128.9 (× 2), 129.7 (× 2), 135.4, 173.3; IR (Nujol mull) 3377, 1736, 1179, 1110, 761, 690 cm^{-1}; HMRS (EI) calcd for $C_{20}H_{32}O_3S$ 352.2074, found 352.2101.

Isopropyl 10-Hydroxy-11-phenylsulfinylundecanoate (11a). To a solution of the β-hydroxy sulfide **10a** (1.2 g, 3.16 mmol) in dichloromethane (20 mL) was added a solution of *m*CPBA (0.68 g, 3.16 mmol) in 10 mL of dichloromethane at 0 °C. After stirring at 0 °C for an additional 1.5 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (1 mL) and then saturated aqueous sodium hydrogencarbonate (20 mL). The organic phase was separated, and the water phase was extracted with chloroform. The combined extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by chromatography on silica gel (EtOAc/hexane = 1/2) to give **11a** as a colorless solid (1.12 g, 96%): mp 39−42 °C; ^{1}H NMR δ 1.10 (d, J = 6.3 Hz, 6H), 1.28−1.61 (m, 12H), 2.24 (dt, J = 7.4, 3.0 Hz, 2H), 2.68 (dd, J = 13.5, 1.8 Hz, 0.5H), 2.80 (dd, J = 13.0, 2.4 Hz, 0.5H), 2.96 (dd, J = 13.0, 9.3 Hz, 0.5H), 3.06 (dd, J = 13.5, 9.8 Hz, 0.5H), 3.90 (br, 1H), 4.15 (m, 0.5H), 4.32 (m, 0.5H), 5.00 (m, 0.5H), 7.53−7.66 (m, 5H); ^{13}C NMR δ 21.8 (× 2), 24.9, 25.0, 28.9, 29.1, 29.2, 29.3, 34.6, 37.0, 37.1, 62.2, 62.6, 66.3, 67.3, 68.6, 123.8, 123.9, 129.3, 129.4, 130.9, 131.3, 143.0, 143.8, 173.3; IR ($CHCl_3$) 3377, 3014, 2932, 2856, 1720, 1467, 1444, 1375, 1108, 1032, 691 cm^{-1}; HMRS (EI) calcd for $C_{20}H_{32}O_4S$ 368.2023, found 368.2025.

Isopropyl 10-Oxo-11-phenylsulfinylundecanoate (5j). To a solution of oxalyl chloride (0.3 mL, 3.47 mmol) in dichloromethane (16 mL) was added 4.5 mL (63.2 mmol) of dimethyl sulfoxide (DMSO) at −60 °C. After 5 min, to the stirred solution was added the β-hydroxy sulfoxide **11a** (1.16 g, 3.16 mmol) in dichloromethane (5 mL) over 2 min, the stirring was continued for an additional 1 h at −60 °C, and then triethylamine (2.2 mL, 15.8 mmol) was added. Following this, the temperature was slowly raised to room temperature by removal of the cooling bath. The reaction mixture was washed with water, and the water layer was extracted with chloroform. The combined extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by chromatography on silica gel (EtOAc/hexane = 1/1) and recrystalization from ether−hexane gave a colorless solid **5j** (0.95 g, 82%): mp 66−67 °C; ^{1}H NMR δ 1.23 (d, J = 6.3 Hz, 6H), 1.26−1.30 (m, 12H), 1.47−1.62 (m, 4H), 2.25 (t, J = 7.6 Hz, 2H), 2.39−2.54 (m, 2H), 3.82 (dd, J = 37.8, 13.6 Hz, 2H), 5.00 (m, 1H), 7.53−7.68 (m, 5H); ^{13}C NMR δ 21.8 (× 2), 22.9, 24.9, 28.76, 28.94, 28.95, 29.04, 34.6, 45.0, 67.3, 68.1, 124.0 (× 2), 129.4 (× 2), 131.6, 143.0, 173.4, 201.7; IR ($CHCl_3$) 2983, 2933, 2857, 1717, 1467, 1445, 1375, 1108, 1045, 690 cm^{-1}; HMRS (EI) calcd for $C_{20}H_{30}O_4S$ 366.1866, found 366.1856.

Isopropyl 13-Hydroxy-10-oxooctadec-11-enoate (6m). To a solution of the β-keto sulfoxide **5j** (100 mg, 0.27 mmol) in propanenitrile (5 mL) were added diethylamine (57 μL, 0.55 mmol), acetic acid (8 μL, 0.14 mmol), and heptanal (76 μL, 0.54 mmol) under nitrogen. After stirring for 2 h at 70 °C, the mixture was cooled to 0 °C and diluted with chloroform and washed with brine. The organic layer was separated, and the water layer was extracted with chloroform. The combined extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residual oil was purified by column chromatography on silica gel (EtOAc/hexane=1/4) to give **6m** as a pale yellow oil (74 mg, 76%): ^{1}H NMR δ 0.89 (t, J = 6.6 Hz, 3H), 1.10 (d, J = 6.3 Hz, 6H), 1.26−1.63 (m, 20H), 2.04 (br, 1H), 2.25 (t, J = 7.5 Hz, 2H), 2.55 (t, J = 7.4 Hz, 2H), 4.32 (m, 1H), 5.00 (m, 1H), 6.30 (dd, J = 15.9, 1.4 Hz, 1H), 6.80 (dd, J = 15.9, 5.1 Hz, 1H); ^{13}C NMR δ 14.0, 21.8 (× 2), 22.5, 24.1, 24.89, 24.92, 28.96, 29.0 (× 2), 29.1, 31.6, 34.6, 36.7, 40.7, 67.3, 71.3, 127.9, 147.8, 173.4, 200.8; IR ($CHCl_3$) 3449, 2978, 2931, 2857, 1731, 1676, 1632, 1467, 1374, 1110, 754, 725 cm^{-1}; HMRS (EI) calcd for $C_{21}H_{38}O_4$ 354.5303, found 354.5321.

Isopropyl 13-hydroxy-10-oxotetradec-11-enoate (6n): ^{1}H NMR δ 1.23 (d, J = 6.2 Hz, 6H), 1.30 (m, 8H), 1.35 (d, J = 6.6 Hz, 3H), 1.60 (m, 4H), 2.00 (br, 1H), 2.25 (t, J = 7.5 Hz, 2H), 2.55 (t, J = 7.4 Hz, 2H), 4.502 (ddq, J = 6.6, 4.8, 1.6 Hz, 1H), 5.00 (m, 1H), 6.29 (dd, J = 15.9, 1.6 Hz, 1H), 6.79 (dd, J = 15.9, 4.7 Hz, 1H); ^{13}C NMR δ 22.5 (× 2), 22.4, 24.7, 29.6 (× 2), 29.7, 29.8, 35.3, 41.3, 67.8, 68.1, 128.1, 149.4, 174.2, 201.7; IR ($CHCl_3$) 3448, 2980, 2931, 2856, 1727, 1663, 1635, 1466, 1374, 1109, 978, 755 cm^{-1}. Anal. Calcd for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13. Found: C, 68.55; H, 10.30.

Isopropyl 13-hydroxy-10-oxo-14-phenyltetradec-11-enoate (6o): ^{1}H NMR δ 1.22 (d, J = 6.4 Hz, 6H), 1.29 (m, 8H), 1.59 (m, 4H), 1.84 (br, 1H), 2.25 (t, J = 7.5 Hz, 2H), 2.52 (t, J = 7.4 Hz, 2H), 2.88 (ddd, J = 13.6, 8.1, 5.1 Hz, 2H), 4.53 (m, 1H), 5.00 (m, 1H), 6.30 (dd, J = 15.9, 1.7 Hz, 1H), 6.83 (dd, J = 15.9, 4.7 Hz, 1H), 7.28 (m, 5H); ^{13}C NMR δ 21.8 (× 2), 24.0, 24.9, 28.9, 29.0 (× 2), 29.1, 34.6, 40.8, 43.3, 67.3, 71.8, 126.9, 128.3, 128.6 (× 2), 129.4 (× 2), 136.8, 146.5, 173.4, 200.6; IR ($CHCl_3$) 3448, 2980, 2931, 2856, 1727, 1663, 1635, 1455, 1370, 1109, 984, 751, 700 cm^{-1}. Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 74.09; H, 8.98.

Isopropyl 13-hydroxy-10-oxoicos-11-enoate (6p): ^{1}H NMR δ 0.88 (t, J = 6.6 Hz, 3H), 1.23 (d, J = 6.4 Hz, 6H), 1.30 (m, 14H), 1.59 (m, 6H), 2.00 (br, 1H), 2.25 (t, J = 7.5 Hz, 2H), 2.55 (t, J = 7.4 Hz, 2H), 4.31 (ddt, J = 5.5, 5.5, 1.5 Hz, 1H), 5.00 (m, 1H), 6.29 (dd, J = 15.9, 1.5 Hz, 1H), 6.79 (dd, J = 15.9, 5.0 Hz, 1H); ^{13}C NMR δ 14.0, 21.8 (× 2), 22.6, 24.0, 24.9, 25.2, 28.9, 29.0 (× 2), 29.1 (× 2), 29.4, 31.7, 34.6, 36.7, 40.7, 67.3, 71.2, 127.9, 147.9, 173.4, 200.8; IR ($CHCl_3$) 3454, 2978, 2929, 2856, 1732, 1677, 1632, 1466, 1374, 1181, 1109, 981, 756 cm^{-1}**;** Anal. Calcd for $C_{23}H_{42}O_4$: C, 72.21; H, 11.07. Found: C, 72.38; H, 10.98.

Isopropyl 14,18-dimethyl-13-hydroxy-10-oxononadeca-11,17-dienoate (6q): (mixture of diastereomers, ca. 1:1) ^{1}H NMR δ 0.90 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 1.23 (d, J = 6.5 Hz, 6H), 1.30 (m, 8H), 1.60 (s, 3H), 1.69 (s, 3H), 2.00 (br, 1H), 2.00 (m, 1H), 2.25 (t, J = 7.5 Hz, 2H), 2.55 (t, J = 7.4 Hz, 2H), 4.20 (dt, J = 5.2, 1.5 Hz, 0.5H), 4.26 (dt, J = 4.4, 1.6 Hz, 0.5H), 5.00 (m, 1H), 5.09 (m, 1H), 6.32 (dt, J = 15.9, 1.5 Hz, 1H), 6.80 (dd, J = 15.9, 5.0 Hz, 1H); ^{13}C NMR δ 14.0 and 15.0, 21.8 (× 2), 22.6, 24.1, 24.9, 25.5 and 25.6, 25.7, 28.96, 29.01, 29.11, 29.14, 32.1 and 32.8, 34.6, 38.0 and 38.4, 40.8, 67.3, 74.5 and 75.3, 124.1, 128.7 and 129.2, 131.8, 146.1 and 147.0, 173.4, 200.5; IR ($CHCl_3$) 3446, 2965, 2930, 2856, 1731, 1668, 1633, 1456, 1375, 1181, 1109, 984, 824, 756 cm^{-1}. Anal. Calcd for $C_{24}H_{42}O_4$: C, 73.05; H, 10.73. Found: C, 73.29; H, 10.68.

13-Hydroxy-10-oxooctadec-11-enoic Acid (14). To a suspension of lipase PS (from *Pseudomonas cepacia*, 400 mg) in THF (0.5 mL) and a phosphate buffer of pH 7.0 (4 mL) was added the ester **6n** (200 mg, 0.28 mmol). After stirring at room temperature for 24 h, Selite 545 (2 g) was added to the mixture. The insoluble materials were filtered off, and the filtrate was acidified by hydrochloric acid (2 N, 3 mL) and then extracted with chloroform twice. The combined extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give a crude solid. Recrystallization from chloroform−hexane gave **14** as a white solid (145 mg, 82%): mp 58−60 °C [lit. 64 °C];[15b] ^{1}H NMR δ 0.89 (t, J = 6.6 Hz, 3H), 1.30−1.63 (m, 21H), 2.34 (t, J = 7.4 Hz, 2H), 2.55 (t, J = 7.4 Hz, 2H), 4.32 (m, 1H), 6.30 (dd, J = 15.9, 1.4 Hz, 1H), 6.80 (dd, J = 15.9, 5.10 Hz, 1H); ^{13}C NMR δ 13.9, 22.5, 24.1, 24.6, 24.9, 28.8, 28.9, 29.0 (× 2), 31.6, 33.9, 36.6, 40.6, 71.2, 127.9, 148.0, 179.4, 201.2; IR ($CHCl_3$) 3400, 3019, 2932, 2858, 1709, 1674, 1632, 1466, 1410, 1143, 1079 cm^{-1}.

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Supporting Information Available: Spectroscopic data (^{1}H and ^{13}C NMR, IR, HRMS, and elemental analysis) and experimental details of β-keto sulfoxides **5a**−**i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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