

A General Preparation of α -Alkoxyacroleins

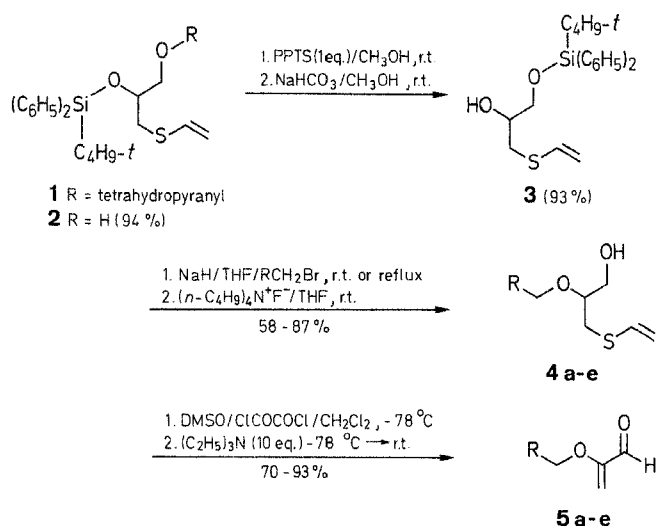
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Oxalyl chloride-dimethyl sulfoxide (Swern) oxidations of 3-ethenylthio-2-alkoxy-1-propanols provides a mild oxidation-elimination sequence for the synthesis of a series of functionalized α -alkoxyacroleins.

Acroleins are valuable reactants for a variety of processes including polymerizations, nucleophilic additions in 1,2 and Michael fashion, Wittig reactions, 1,3-dipolar additions, and Diels-Alder cycloadditions as either the dienophile or as a heterodiene. In light of continuing interest in the synthesis of highly oxygenated molecules, the general availability of α -alkoxyacroleins would stimulate new efforts toward unique and valuable targets. The only successful approach for the synthesis of these molecules utilizes a Mannich reaction of α -alkoxyacetaldehydes.¹ Although this route is straightforward for simple cases, it is not always amenable to situations wherein the α -alkoxy unit is associated with a high level of functionalization.² Our recent work has uncovered a mild preparation of α -alkoxyacroleins, affording good yields of these sensitive materials.

The generalized route for the synthesis of α -alkoxyacroleins **5** is illustrated in Scheme A. We have previously described an efficient preparation of a protected glycerol analog in the form of thioether **1**.³ Selective removal of the tetrahydropyranyl group of **1** is followed by treatment with a weak base, such as aqueous sodium bicarbonate, promoting a facile migration of the bulky *tert*-butyldiphenylsilyl moiety to the primary alcohol.⁴ The utilization of **3** under standard Williamson ether-synthesis conditions with primary alkyl halides (R-CH₂-X), and subsequent deprotection with *tetra-n*-butylammonium fluoride afforded the key intermediate alcohols **4** in yields ranging from 58% to 87% (Table 1).



PPTS = pyridinium *p*-toluenesulfonate

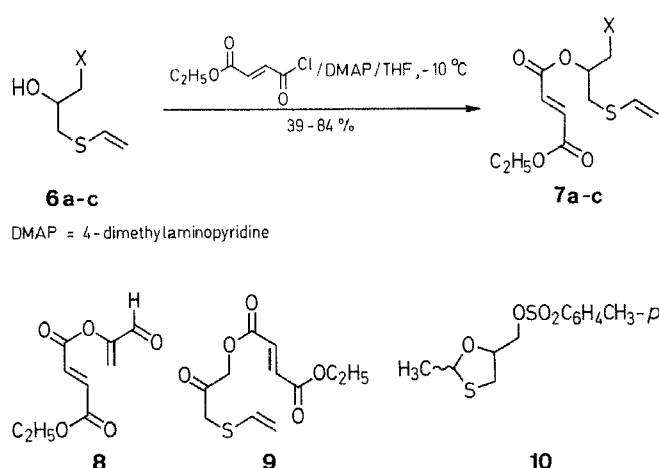
4, 5	R	4, 5	R
a	O(CH ₂) ₂ OCH ₃	d	(CH ₂) ₃ Br
b	CH=CH ₂	e	(CH ₂) ₃ N ₃
c			

Scheme A

Finally, oxalyl chloride-dimethyl sulfoxide (Swern) oxidation⁵ of the primary alcohols **4** at -78°C with addition of anhydrous triethylamine (10 equivalents) at -78°C resulted in production of the corresponding aldehydes of **4**.⁶ As the crude reaction mixtures were allowed to warm to ambient temperature with stirring (0.5 to 3 hr), β -elimination afforded the desired α -alkoxyaldehydes **5a-e** in good yields following purification by flash chromatography (see Table 2).

The success of this oxidation-elimination procedure is due to the facile and irreversible loss of thioacetaldehyde, which is subsequently destroyed under the reaction conditions. Our attempts to replace the vinyl sulfide moiety with the corresponding phenyl sulfides resulted in very poor yields of **5**, since the elimination produced a potent nucleophile, which could instigate self-condensation side reactions *via* conjugate addition to aldehydes **5**. Direct oxalyl chloride-dimethyl sulfoxide oxidation of bulky silyl ethers **2** (*t*-BuPh₂Si or *t*-BuMe₂Si) gave the corresponding aldehydes of **2** (90% yield) without giving rise to β -elimination, sulfur oxidation, or products derived from silyl migration.

Numerous attempts were initiated to provide ester derivatives, the α -acyloxyacroleins such as **8**, according to our general scheme. Our findings are illustrated for the mixed fumarates **7a-c** obtained *via* esterification of **6a-c** with ethyl fumaroyl chloride and 4-dimethylaminopyridine (1.2 equivalent) in anhydrous tetrahydrofuran at -10°C . All attempts for fluoride deprotection of **7a** led to a facile acyl migration to the primary site,⁷ and subsequent oxalyl chloride-dimethyl sulfoxide oxidation gave ketone **9**.⁸ Finally, to avoid the problems of internal acyl transfer, a Kornblum oxidation strategy⁹ was studied *via* esterification of the sensitive alcohols **6b** and **6c**. Products **7b** and **7c** were obtained by careful control of reaction temperature. Interestingly, reactions of **6b** conducted at 0°C with warming to room temperature gave only the 1,3-oxathiolane **10** in 89% isolated yield.¹⁰ Heating tosylate **7b** or iodide **7c** with anhydrous dimethylsulfoxide in the presence of sodium bicarbonate resulted only in the slow destruction of starting material.



DMAP = 4-dimethylaminopyridine

6, 7	X	Yield of 7 (%)
a	OSi(C ₆ H ₅) ₂ C ₄ H ₉ - <i>t</i>	78
b	OSO ₂ C ₆ H ₄ CH ₃ - <i>p</i>	84
c	I	39

Scheme B

In conclusion, we have described a route for the mild preparation of α -alkoxyacroleins in which the alkoxy chain may be elaborated with various functionalities. The process avoids the

Table 1. 2-Alkoxy-3-ethenylthio-1-propanols **4** Prepared

Product	Yield ^a (%)	R _f ^b (solvent)	IR (neat) ^c ν (cm ⁻¹)	¹ H-NMR (CDCl ₃ /TMS) ^d δ, J (Hz)
4a	87	0.13 (40% EtOAc/ hexanes)	3425, 3080, 2920, 2880, 1585, 1400, 1025	2.88 (AB of ABX, 2H, J = 13.7, 7.8, 7.5, Δν = 22.0 Hz); 3.12 (t, 1H, J = 6.1, OH); 3.40 (s, 3H); 3.85–3.55 (m, 7H); 4.84 (AB, 2H, J = 7.4, Δν = 16.8 Hz); 5.17 (d, 1H, J = 16.7); 5.21 (d, 1H, J = 10.1); 6.35 (dd, 1H, J = 16.7, 10.1)
4b	84	0.07 (CH ₂ Cl ₂)	3410, 3085, 2925, 2870, 1590, 1425, 1050	2.21 (br s, 1H, OH); 2.87 (AB of ABX, 2H, J = 13.8, 6.7, 5.4, Δν = 20.6 Hz); 3.79 (m, 1H); 4.13 (AB of ABX, 2H, J = 12.4, 6.3, 5.8, Δν = 21.5 Hz, J _{allylic} = 1.3); 5.17 (d, 1H, J = 16.8); 5.20 (obscured ddd, 1H, J = 10.2, additional coupling obscured); 5.21 (d, 1H, J = 9.4); 5.30 (ddd, 1H, J = 17.2, 3.1, 1.6); 5.93 (m, 1H); 6.35 (dd, 1H, J = 16.8, 10.2)
4c^e	58	0.07 (25% EtOAc/ hexanes)	3420, 2995, 2920, 2880, 1585, 1075	2.40 (br s, 1H, OH); 2.65 (m, 0.5H); 2.76–2.96 (m, 3.5H); 3.19 (m, 1H); 3.40–4.04 (m, 5H); 5.25 (m, 2H); 6.38 (m, 1H)
4d	79	0.20 (25% EtOAc/ hexanes)	3450, 2940, 2880, 1589, 1105, 1050	1.75 (m, 3H); 2.0 (m, 2H); 2.87 (AB of ABX, 2H, J = 13.6, 7.37, 5.9, Δν = 25.0 Hz); 3.47 (t, 2H, J = 6.4); 3.51–3.69 (m, 4H); 3.80 (A of AMX, 1H, J = 11.5, 3.6); 5.17 (d, 1H, J = 16.7); 5.22 (d, 1H, J = 10.1); 6.35 (dd, 1H, J = 16.7, 10.1)
4e	75	0.18 (25% EtOAc/ hexanes)	3410, 2940, 2880, 2100, 1590, 1260, 1110	1.70 (m, 4H); 1.93 (br s, 1H); 2.87 (AB of ABX, 2H, J = 13.6, 6.9, 5.5, Δν = 21.9 Hz); 3.33 (t, 2H, J = 6.2); 3.51–3.69 (m, 4H); 3.79 (A of AMX, 1H, J = 11.5, 3.6); 5.17 (d, 1H, J = 16.7); 5.22 (d, 1H, J = 10.1); 6.36 (dd, 1H, J = 16.7, 10.1)

^a Overall yield from **3**.^b Determined on E. Merck, silica gel 60 F-254, 0.25 thickness.^c Recorded on a Perkin-Elmer 298 Infrared spectrophotometer.^d Obtained on a Nicolet NT-360 (360 MHz) NMR spectrometer.^e Mixture of two diastereomers.**Table 2.** α-Alkoxyacroleins **5** Prepared

Product	Yield ^a (%)	IR (neat) ^b ν (cm ⁻¹)	¹ H-NMR (CDCl ₃ /TMS) ^c δ, J (Hz)	Molecular Formula HRMS (20 eV) ^d	
				calc.	found
5a	70	3070, 2830, 2750, 1709, 1620	3.38 (s, 3H); 3.55 (m, 2H); 3.78 (m, 2H); 5.19 (s, 2H); 5.49 (AB, 2H, J = 2.7, Δν = 135.2 Hz); 9.28 (s, 1H)	C ₇ H ₁₂ O ₄ 160.0735	105.0552
5b	78	3080, 2840, 1690, 1610, 1305	4.40 (d, 2H, J = 5.5); 5.18 (AB, 2H, J = 2.7, Δν = 29.7 Hz); 5.30 (ddd, 1H, J = 10.5, 3.2, 1.0); 5.38 (ddd, 1H, J = 17.2, 3.2, 1.7); 5.99 (ddt, 1H, J = 17.2, 10.5, 5.3); 9.26 (s, 1H)	C ₆ H ₈ O ₂ 112.0524	112.0532
5c	83	3000, 2850, 1705, 1615, 1310	2.65 (A'B' of A'B'X, 2H, J = 4.7, 4.2, 2.7, Δν = 165.8 Hz); 3.35 (m, 1H); 3.96 (AB of ABX, 2H, J = 11.3, 5.7, 3.3, Δν = 91.7 Hz); 5.24 (AB, 2H, J = 3.2, Δν = 42.2 Hz); 9.31 (s, 1H)	C ₆ H ₈ O ₃ 128.0473	128.0476
5d	81	3050, 2850, 1710, 1615	1.9–2.1 (m, 4H); 3.47 (t, 2H, J = 6.4); 3.84 (t, 2H, J = 5.9); 5.15 (AB, 2H, J _{AB} = 2.9, Δν = 39.7 Hz); 9.24 (s, 1H)	C ₇ H ₁₁ BrO ₂ 205.9942	206.9855
5e	93	3050, 2850, 2100, 1705, 1615	1.77 (m, 2H); 1.90 (m, 2H); 3.35 (t, 2H, J = 6.6); 3.84 (t, 2H, J = 6.1); 5.15 (AB, 2H, J _{AB} = 2.9, Δν = 38.3 Hz); 9.28 (s, 1H)	C ₇ H ₁₁ N ₃ O ₂ 169.0851	169.0869

^a Isolated yields. Aldehydes could be stored at -78 °C under argon for approximately two weeks without detectable decomposition.^b Recorded on a Perkin-Elmer 298 Infrared spectrophotometer.^c Obtained on a Nicolet NT-360 (360 MHz) NMR.^d Measured on a Kratos GC/MS 80 RFA spectrometer.

introduction of nucleophiles, which are known to facilitate the polymerization of these sensitive aldehydes. The corresponding acyl derivatives were not available by this methodology owing to a facile acyl migration.

2-tert-Butyldiphenylsiloxy-3-ethenylthio-1-propanol (2):

Freshly recrystallized pyridinium *p*-toluenesulfonate (4.52 g, 18.2 mmol) is added to a solution of 2-tert-butyldiphenylsiloxy-3-ethenylthio-1-tetrahydropyranloxypropane³ (**1**; 8.22 g, 18.2 mmol) in dry MeOH (1 L). After vigorous stirring at room temperature for 24 h, solvent is removed under reduced pressure at ambient temperature, and the residue is immediately submitted to flash chromatography¹¹ (40 g silica gel Kieselgel 60 H; E. M. Merck). Elution with EtOAc/hexanes

(ratio 2:98 by volume, 500 mL; ratio 4:96, 500 mL; ratio 1:5, 500 mL) affords the primary alcohol **2** as a colorless oil; yield: 6.3 g (94%); R_f = 0.41 (1:3 EtOAc/hexanes).

IR (neat): ν = 3430, 1583, 1104, 1063, 1034, 957, 817, 733, 697 cm⁻¹.

¹H-NMR (CDCl₃/TMS_{int}): δ = 1.09 (s, 9H); 1.86 (dd, 1H, J = 7.3 Hz, 5.8 Hz); 2.75 (AB of ABX, 2H, J = 13.6 Hz, 9.0 Hz, 4.5 Hz, Δν = 70.0 Hz); 3.68 (m, 2H); 3.89 (m, 1H); 4.87 (d, 1H, J = 16.7 Hz); 4.97 (d, 1H, J = 10.0 Hz); 5.87 (dd, 1H, J = 16.7 Hz, 10.0 Hz); 7.40 (m, 6H); 7.67 (m, 4H).

Extended reaction times or heating lead to the acid-catalyzed addition of MeOH to vinyl sulfide **2** producing 2-tert-butyldiphenylsiloxy-3-(*α*-methoxyethyl)thio-1-propanol as a mixture of two diastereoisomers.

IR (neat): ν = 3460, 1587, 1104, 1074, 817, 734, 698 cm⁻¹.

$^1\text{H-NMR}$ ($\text{CDCl}_3/\text{TMS}_{\text{int}}$): $\delta = 1.03$ (s, 9H); 1.28 (d, 3H, $J = 6.4$ Hz); 2.05 (bt, 1H, $J = 6.2$ Hz, 1-OH); 2.75–2.47 (m, 2H); 3.12 (s, 1.5H); 3.13 (s, 1.5H); 3.62 (m, 2H); 5.84 (m, 1H); 4.24 (q, 0.5H, $J = 6.4$ Hz); 4.33 (q, 0.5H, $J = 6.4$ Hz); 7.34 (m, 6H); 7.63 (m, 4H).

1-*tert*-Butyldiphenylsiloxy-3-ethenylthio-2-propanol (3):

Migration of the silyl ether is accomplished by addition of NaHCO_3 (1.13 g, 13.5 mmol) to a solution of **2** (250 mg, 0.672 mmol) in dry MeOH (5 mL). After removal of solvent at reduced pressure, the crude product is purified by column chromatography (silica gel, 8% EtOAc/hexanes), affording pure alcohol **3**; yield: 240 mg (93%); $R_f = 0.43$ (CH_2Cl_2).

IR (neat): $\nu = 3430, 3060, 2930, 2860, 1590, 1105 \text{ cm}^{-1}$.

$^1\text{H-NMR}$ ($\text{CDCl}_3/\text{TMS}_{\text{int}}$): $\delta = 1.08$ (s, 9H); 2.59 (d, 1H, $J = 5.0$ Hz, OH); 2.86 (AB of ABX, 2H, $J = 13.7$ Hz, 7.6 Hz, 6.5 Hz, $\Delta\nu = 26.8$ Hz); 3.72 (AB of ABX, 2H, $J = 10.3$ Hz, 3.5 Hz, 1.5 Hz, $\Delta\nu = 5.9$ Hz); 3.88 (m, 1H); 5.16 (d, 1H, $J = 16.7$ Hz); 5.19 (d, 1H, $J = 10.0$ Hz); 6.32 (dd, 1H, $J = 16.7$ Hz, 10.0 Hz); 7.41 (m, 6H); 7.65 (m, 4H).

MS (20 eV) for $\text{C}_{21}\text{H}_{28}\text{O}_2\text{SSi}$: $m/e = 315.088$ ($\text{M}^+ - \text{C}_4\text{H}_6$); calc. for $\text{C}_{17}\text{H}_{19}\text{O}_2\text{SSi}$: 315.0875.

2-Alkoxy-3-ethenylthio-1-propanols (4); General Procedure:

A suspension of sodium hydride (68 mg, 1.68 mmol, 57% oil dispersion) in anhydrous THF (10 mL) is cooled to 0°C under argon, and a solution of alcohol **3** (400 mg, 1.08 mmol) in THF (20 mL) is added dropwise. After the reaction mixture has warmed to room temperature with stirring (30 min), a solution of freshly distilled alkyl bromide (2.16 mmol) in THF (10 mL) is added, and stirring is continued for 10 h (examples **4d** and **4e** require heating at reflux for 4–6 h). The reaction is quenched by addition of aqueous NH_4Cl (100 mL). Extraction with Et_2O (3×25 mL), drying (MgSO_4) and removal of solvent under reduced pressure give a crude residue which is purified by column chromatography (silica gel) using EtOAc/hexanes. Yields of the corresponding 2-alkoxy-1-*tert*-butyldiphenylsiloxy-3-ethenylthio-1-propanols range from 78 to 96%.

Tetrabutylammonium fluoride (0.44 mL, 0.438 mmol, 1.0 molar solution in THF, Aldrich) is added *via* syringe to a solution of the appropriate *tert*-butyldiphenylsilyl ether (0.29 mmol) in dry THF (10 mL). After stirring at room temperature for 1 h, silica gel (~ 200 mg) is added, and solvent is removed under reduced pressure. The preabsorbed reaction mixture is chromatographed through a column of silica gel (EtOAc/hexanes) to give the alcohols **4** as clear, colorless oils. Yields range from 74 to 92% (Table 1).

2-Alkoxy-2-propenals 5; General Procedure:

Dimethyl sulfoxide (97 mg, 0.088 mL, 1.24 mmol) is dissolved in dry CF_2Cl_2 (0.1 mL), and added *via* syringe to a solution of freshly distilled oxalyl chloride (100 mg, 0.074 mL, 0.844 mmol) in CH_2Cl_2 (1 mL) at -78°C under argon atmosphere. After stirring for 5 min, a solution of primary alcohol **4** (0.40 mmol) in CH_2Cl_2 (1 mL) is added *via* syringe. The resulting mixture is stirred at -78°C for 30 min. Freshly distilled triethylamine (490 mg, 0.67 mL, 4.8 mmol) is added to the cloudy mixture, and the reaction is allowed to warm to ambient temperature. The reaction is closely monitored by analytical TLC with observation of the disappearance of the corresponding aldehydes of **4**, producing the less polar α,β -unsaturated aldehydes **5**, as the reaction mixture is continuously stirred at room temperature (0.5 to 3 hr). After addition of H_2O (25 mL) and extraction with CH_2Cl_2 (3×10 mL), the combined organic phase is washed with aqueous NaCl (15 mL), dried (MgSO_4), and concentrated under reduced pressure to a yellow oil. Crude materials are immediately submitted to flash chromatography¹¹ or preparative thin-layer chromatography (EtOAc/hexanes) (Table 2).

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