Synthesis of Functionally Substituted α,β-Unsaturated Carbonyl Compounds[1]

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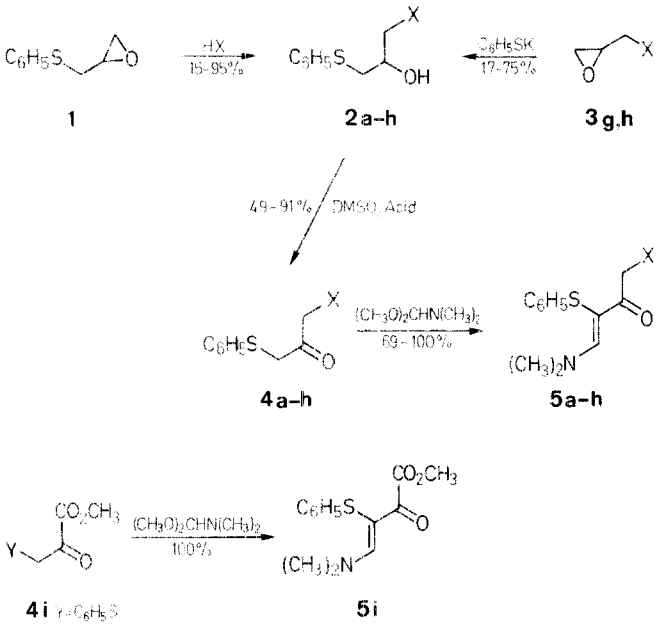
Epichlorohydrin and glycidol are transformed in a four step sequence into β-dimethylamino-α-phenylthio-substituted α,β-unsaturated carbonyl compounds **5**, possessing differently *O*-protected oxymethyl substituents at the carbonyl group. These compounds are of value as intermediates in inverse-type hetero-Diels-Alder reactions.

β-Acyloxy-α-phenylthio-substituted α,β-unsaturated carbonyl compounds possessing a benzyloxymethyl substituent at the carbonyl group are valuable 1-oxa-1,3-dienes in inverse-type hetero-Diels-Alder reactions with enol ethers as heterodienophiles.[2-4] The resulting dihydropyrans turned out to be versatile intermediates for efficient *de novo* syntheses of carbohydrates and related natural products.[2,4] Important aspects in this reaction are the reactivity of the α,β-unsaturated carbonyl compound, the *endo*/*exo*-diastereoselectivity in the cycloaddition step, and the stability of the dihydropyran product obtained (for the last two aspects, see subsequent paper[5]). It is now well known, that the reactivity of α,β-unsaturated carbonyl compounds in hetero-Diels-Alder reactions is increased by electron-withdrawing groups at the α-position.[6,7] This effect can be reached by an additional electron-withdrawing group at the α-position or by increasing the electron-withdrawing character of the substituted carbonyl group. Due to our interest in carbohydrate targets and related structural types with an oxymethyl substituent at the carbonyl group[4] we chose to rely on the second possibility. We planned to synthesize compounds **5** as useful intermediates for hetero-Diels-Alder reactions, because of the expected stability of the corresponding β-dimethylamino-α-phenylthio-derivatives (see subsequent paper[5]).

Previous experience in the synthesis of the benzyloxy derivative of **5** (structure **5a**), X = $C_6H_5CH_2O$)[3] suggestd the possibility of synthesizing the desired derivatives with different O-protection *via* the corresponding α-oxy-α'-phenylthioacetone derivatives **4**, starting from the activated glycerol derivative epichlorohydrin, where both primary positions should be selectively accessible by nucleophilic attack. However, it became obvious that for regioselective nucleophilic attack both the reaction sequence and the reaction conditions are quite important. For instance, only when potassium thiophenoxide was reacted with a threefold excess of epichlorohydrin could good yields of the monophenylthio compound **1** be obtained. However, when epichlorohydrin was treated with more potassium thiophenoxide, an increasing amount of the disubstituted derivative **2e** was generated, which could be exclusively obtained with two equivalents of thiophenoxide. Epoxide **1** was readily transformed with potassium phenoxide and potassium *p*-nitrophenoxide into the required 2-hydroxypropane derivatives **2a** and **2b**, respectively (Table 1). Nucleophilic opening of the epoxide **1** with the poor nucleophile 2,2,2-trichloroethoxide gave, expectedly, only a modest yield (15%) of product **2d**. With benzoic acid and pivalic acid as nucleophiles in presence of tetrabutylammonium chloride as a catalyst, compounds **2e** and **2f** were obtained from the epoxide opening of **1** in modest (18%) and good (78%) yield, respectively. Fortunately, acyl migration could be prevented under these reaction conditions.

The *O*-(*N*,*N*-dimethylcarbamoyl) and the *O*-(tetrahydropyran-2-yl) derivatives **2g** and **2h** could not be obtained *via* this route. Therefore glycidol was used as a starting material. Reaction with dimethylaminocarbamoyl chloride under basic conditions and with dihydropyran under weak acid catalysis provided the required intermediates **3g** and **3h**, respectively. Epoxide opening of compound **3h** with potassium thiophenoxide readily provided the required compound **2h**. However, with compound **3g** the required compound **2g** was only a minor product. Due to the electron-withdrawing carbamoyl group, nucleophilic attack at the 2-position of compound **3g** and, in addition, decarbamoylation were favored.



2, 5	X
a	C_6H_5O
b	$4\text{-}O_2NC_6H_4O$
c	C_6H_5S
d	CCl_3CH_2O
e	$C_6H_5CO_2$
f	$t\text{-}C_4H_9CO_2$
g	$(CH_3)_2NCO_2$
h	THP-O

Transformation of the 2-propanol derivatives **2a–h** into the corresponding acetone derivatives **4a–h** was readily achieved with dimethyl sulfoxide in presence of a condensing agent, either acetic anhydride (Method A) or dicyclohexylcarbodiimide (DCC) (Method B) (Table 2). Since the CH-acidity next to a sulfur substituent is higher than next to an oxygen substituent, compounds **4a–h** gave the enamine derivatives **5a–h** regioselectively, when reacted with *N*,*N*-dimethylformamide dimethyl acetal. β-Dimethylamino-α-phenylthio-α,β-unsaturated ketones **5** are stable compounds, which could be characterized (Table 3). According to the ^{1}H-NMR chemical shift of the β-proton ($\delta \approx 8.2$), the (*Z*)-configuration was assigned to these compounds by comparison with literature reports.[4,8]

An even stronger electron-withdrawing effect at the carbonyl group is gained by replacing the *O*-activated oxymethyl group by an alkoxycarbonyl group. The corresponding compound **5i** could be readily synthesized starting from methyl bromopyruvate,[9] which gave the phenylthiopyruvate **4i** by reaction with pyridinium thiophenoxide. Again, reaction with *N,N*-dimethylformamide dimethyl acetal afforded compound **5i**,[10] which had the (*Z*)-configuration according to the ^{1}H-NMR shift of the β-proton.

1-Phenylthio-2,3-epoxypropane (1):

A solution of potassium thiophenoxide (148 g, 1 mol) in aqueous EtOH (1500 mL, 1:1) is added to epichlorohydrin (277 g, 3 mol) at 0–5 °C with stirring over a period of 1 h. The cooling bath is removed and stirring is continued for 0.5 h. Water (1500 mL) is added and the mixture is extracted with $CHCl_3$ (3 × 500 mL). The combined $CHCl_3$ phase is washed with water (1 × 500 mL), dried (Na_2SO_4) and concentrated. Vacuum distillation provides **1** as a colorless oil; yield: 130 g (78%); b.p. 82–85 °C/0.2 Torr.

$C_9H_{10}O_5$ (166.2) calc. C 65.02 H 6.06
found 64.64 6.27

^{1}H-NMR ($CDCl_3$/TMS, 250 MHz): δ = 2.45 (dd, 1 H, J = 2.4 Hz, 4.9 Hz); 2.70 (m, 1 H); 2.86 (dd, 1 H, J = 7.3 Hz, 15.2 Hz); 3.11 (m, 2 H); 7.12–7.37 (m, 5 H_{arom}).

1-Substituted 3-Phenylthio-2-Propanols 2a–h; General Procedures:

Method A (for **2a, b**): A solution of **1** (16.6 g, 100 mmol) in THF (50 mL) is added to a stirred solution of the potassium phenoxide (11.1 g, 75 mmol) in aqueous THF (150 mL, 2:1), and the mixture is stirred for 2 d. The THF is removed *in vacuo*, water is added and the mixture is extracted with $CHCl_3$ (2 × 100 mL). The $CHCl_3$ extract is dried (Na_2SO_4), concentrated and the residue is purified by flash chromatography using $CHCl_3$/petroleum ether (1:1) as eluent (Table 1).

Method B (for **2c**): Epichlorohydrin (23.5 mL, 0.3 mol) is added to a cooled (0–5 °C) and stirred solution of potassium thiophenoxide (88.9 g, 0.6 mol) in aqueous EtOH (500 mL, 1:1), and the resulting mixture is stirred at 0–5 °C for 0.5 h and at room temperature for 2 h. Water (400 mL) is added followed by extraction of the mixture with $CHCl_3$ (3 × 100 mL). The combined organic layer is washed with water (1 × 150 mL), dried (Na_2SO_4) and concentrated to yield the product (~ 99% pure), which is used in the next step without further purification (Table 1).

Method C (for **2d**): A solution of KOH (5.6 g, 100 mmol) in water (25 mL) is added to a solution of **1** (8.3 g, 50 mmol) and 2,2,2-trichloroethanol (14.9 g, 100 mmol) in THF (25 mL), and the resulting mixture is stirred at 70 °C for 3.5 d. Evaporation of the THF *in vacuo*, addition of water (25 mL), extraction with $CHCl_3$ (2 × 75 mL), drying of the extract (Na_2SO_4) and concentration affords a oily product, which is purified by flash chromatography ($CHCl_3$/petroleum ether, 1:1). A major unidentified by-product, having similar R_f value, is also formed (Table 1).

Method D (for **2e–f**): A solution of **1** (8.3 g, 50 mmol) in dry toluene (50 mL) is slowly added to a solution of the respective acid (51 mmol) and Bu_4NCl (1.5 g, 5 mmol) in dry toluene (50 mL), and the reaction mixture is refluxed with stirring under nitrogen atmosphere for 6 h (TLC control). Evaporation and flash chromatography of the residue (petroleum ether/EtOAc, 9:1) furnishes the alcohols (Table 1).

Glycidyl *N,N*-Dimethylcarbamate (3 g) and (3-Phenylthio-2-hydroxy)-propyl *N,N*-Dimethylcarbamate (2 g):

N,N-Dimethylcarbamoyl chloride (9.2 mL, 100 mmol) is added over a period of 10 min to a stirred solution of glycidol (7.6 mL, 100 mmol) in dry pyridine (20 mL) at −10 °C and stirring is continued at −10 °C for 4 h and at 10 °C for 20 h. The pyridine is removed *in vacuo*, and the residue is dissolved in $CHCl_3$ (150 mL), which is washed with brine (1 × 75 mL), dried (Na_2SO_4) and concentrated to give 5.1 g (35%) of the carbamate **3g** as a brown oil. The crude product, which is found to contain some by-product, is used as such in the next step.

To a stirred solution of potassium thiophenoxide (5.2 g, 35 mmol) in aqueous EtOH (35 mL, 2:1) is added a solution of the above carbamate in 95% EtOH (15 mL) at 0–5 °C and the mixture is stirred at 0–5 °C for 2 h. The EtOH is removed *in vacuo*, and the remaining aqueous portion is saturated with NaCl and extracted with $CHCl_3$ (2 × 75 mL). The combined extract is washed with brine (1 × 75 mL), dried (Na_2SO_4) and

Table 1. 1-Substituted 3-Phenylthio-2-propanols **2a–h** Prepared

Product	Yield[a] (%)	m.p. (°C)[b]	R_f[c]	Molecular Formula[d]	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, J(Hz)
2a	95	oil	0.44	$C_{15}H_{16}O_2S$ (260.4)	2.74 (d, 1 H, J = 4.3, OH); 3.02–3.30 (m, 2 H, CH_2); 4.02–4.16 (m, 3 H, $CHCH_2$); 6.86–7.17, 7.22–7.42 (2m, 10 H_{arom})
2b	60	oil	0.41	$C_{15}H_{15}NO_4S$ (305.4)	2.73 (s, 1 H, OH); 3.17–3.31 (m, 2 H, CH_2); 4.09–4.18 (m, 3 H, $CHCH_2$); 6.90–6.96, 7.18–7.44, 8.15–8.22 (3m, 2 : 5 : 2, 9 H_{arom})
2c	95	oil	0.39	$C_{15}H_{16}O_2S_2$ (276.4)	2.83 (d, 1 H, J = 3.4, OH); 3.11 (dd, 2 H, J = 7.3, 13.7, CH_2SPh); 3.27 (dd, 2 H, J = 5, 13.7, CH_2SPh); 7.16–7.43 (m, 10 H_{arom})
2d	15	oil	0.32	$C_{11}H_{13}Cl_3O_2S$ (315.7)	2.66 (d, 1 H, J = 4.3, OH); 3.08 (dd, 1 H, J = 7, 14, HCH′); 3.20 (dd, 1 H, J = 5.5, 14, HCH′); 3.80–4.06 (m, 3 H, $CHCH_2$); 4.11 (s, 2 H, OCH_2CCl_3); 7.19–7.42 (m, 5 H_{arom})
2e	18	47–48	0.19	$C_{16}H_{16}O_3S$ (288.4)	2.81 (d, 1 H, J = 4 Hz, OH); 3.03–3.26 (m, 2 H, CH_2); 4.03–4.11 (m, 1 H, CH); 4.35–4.50 (m, 2 H, CH_2); 7.18–7.60, 8.01–8.05 (2m, 8 : 2, 10 H_{arom})
2f	78	oil	0.19	$C_{14}H_{20}O_3S$ (268.4)	1.21 (s, 9 H, t-C_4H_9); 2.64 (d, 1 H, J = 4.3, OH); 2.99 (dd, 1 H, J = 7.3, 13.7, HCH′); 3.13 (dd, 1 H, J = 5.2, 13.7, HCH′); 3.89–3.96 (m, 1 H, CH); 4.13–4.24 (m, 2 H, CH_2); 7.19–7.42 (m, 5 H_{arom})
2g	17	oil	0.51	$C_{12}H_{17}NO_3S$ (255.3)	2.91 [s, 6 H, $N(CH_3)_2$]; 3.01–3.10 (m, 2 H, CH_2); 3.48 (d, 1 H, J = 4, OH); 3.90–3.97 (m, 1 H, CH); 4.15–4.32 (m, 2 H, CH_2); 7.17–7.42 (m, 5 H_{arom})
2h	75	oil	0.30	$C_{14}H_{20}O_3S$ (268.4)	1.50–1.88 [m, 6 H, $(CH_2)_3$ of THP]; 3.00–3.18 (m, 2 H, CH_2); 3.28, 3.34 (2d, 1 : 1, 0.5 H each, J = 5.8, 3.7, OH); 3.48–3.57 (m, 1 H, OHCH′ of THP); 3.74–3.95 (m, 4 H, CH_2OTHP + OHCH′ of THP + CH); 4.49–4.58 (m, 1 H, OCHO of THP); 7.15–7.40 (m, 5 H_{arom})[f]

[a] Yield of pure, isolated product.

[b] Melting points are taken from samples purified for elemental analysis by MPLC; measured on a Büchi (Switzerland) melting point apparatus; uncorrected.

[c] Petroleum ether/EtOAc, 4:1 (**2e**); $CHCl_3$/acetone, 4:1 (**2g**); benzene/EtOAc, 95:5 (**2a, 2c, 2d, 2f**); 4:1 (**2b, 2h**).

[d] Satisfactory microanalyses obtained: C ±0.27, H ±0.15, N ±0.14; except for **2d**.

[e] Obtained on a Bruker WM 250 spectrometer at 250 MHz.

[f] Mixture of diastereomers.

Table 2. 1-Substituted 3-Phenylthio-2-propanones **4a–i** Prepared

Product	Yield[a] (%)	m.p. (°C)[b]	R_f[c]	Molecular Formula[d]	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, J(Hz)	MS (70 eV)[f] *m/e* (%)
4a	49	oil	0.67	$C_{15}H_{14}O_2S$ (258.3)	3.86 (s, 2H, CH_2); 4.73 (s, 2H, CH_2); 6.81–7.40 (m, 10H$_{arom}$)	
4b	90	oil	0.47	$C_{15}H_{13}NO_4S$ (303.3)	3.84 (s, 2H, CH_2); 4.90 (s, 2H, CH_2); 6.81–6.86, 7.24–7.42, 8.10–8.17 (3m, 2 : 5 : 2, 9H$_{arom}$)	
4c	85	37–38	0.30	$C_{15}H_{14}OS_2$ (274.4)	3.84 [s, 4H, $(CH_2SPh)_2$]; 7.20–7.41 (m, 10H$_{arom}$)	
4d	50	oil	0.43	$C_{11}H_{11}Cl_3O_2S$ (313.6)	3.79 (s, 2H, CH_2); 4.13 (s, 2H, OCH_2CCl_3); 4.57 (s, 2H, CH_2); 7.24–7.40 (m, 5H$_{arom}$)	
4e	61	oil	0.56	$C_{16}H_{14}O_3S$ (286.3)	3.79 (s, 2H, CH_2); 5.08 (s, 2H, CH_2); 7.23–7.62, 8.04–8.10 (2m, 8 : 2, 10H$_{arom}$)	288 (1); 287 (4); 286 (M^+, 25)
4f	53	oil	0.57	$C_{14}H_{18}O_3S$ (266.4)	1.25 (s, 9H, t-C_4H_9); 3.71 (s, 2H, CH_2); 4.81 (s, 2H, CH_2); 7.23–7.39 (m, 5H$_{arom}$)	268 (2); 267 (7); 266 (M^+, 45)
4g	71	oil	0.26	$C_{12}H_{15}NO_3S$ (253.3)	2.93, 2.96 [2s, 3H each, $N(CH_3)_2$]; 3.73 (s, 2H, CH_2); 4.80 (s, 2H, CH_2); 7.23–7.40 (m, 5H$_{arom}$)	
4h	91	oil	0.51	$C_{14}H_{18}O_3S$ (266.4)	1.50–1.89 [m, 6H, $(CH_2)_3$ of THP]; 3.45–3.54, 3.76–3.89 (2m, 1H each, OCH_2 of THP); 3.81, 3.82 (2s, 1 : 1, 2H, CH_2); 4.27, 4.39 (2d, 1H each, J = 17, CH_2); 4.60–4.63 (m, 1H, OCHO of THP); 7.18–7.40 (m, 5H$_{arom}$)	
4i	64	oil	0.36	$C_{10}H_{10}O_3S$ (210.3)	3.80, 3.85 (2s, 3H, OCH_3; various amounts of the enol-compound); 3.98 (s, 2H, CH_2); 6.63 (s, 1H, –CH=); 7.25–7.58 (m, 5H$_{arom}$)	

[a,b] See Table 1.
[c] Benzene/EtOAc, 95 : 5 **(4a, 4b, 4d–f, 4h, 4i)**; $CHCl_3$ **(4g)**; $CHCl_3$/petroleum ether, 1 : 1 **(4c)**.
[d] Satisfactory microanalyses obtained: C ±0.20, H ±0.41, N ±0.03; except for **4a**, **4b**, **4d** and **4i**, which decomposed during drying for analysis.
[e] See Table 1.
[f] Recorded on a Finnigan 312 spectrometer.

Table 3. 1-Substituted 4-Dimethylamino-3-phenylthio-butan-2-ones **5** Prepared

Product	Yield[a] (%)	m.p. (°C)[b]	R_f[c]	Molecular Formula[d]	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, J(Hz)	MS (70 eV)[f] *m/e* (%)
5a	87	115–116	0.62	$C_{18}H_{19}NO_2S$ (313.4)	3.26 [br s, 6H, $N(CH_3)_2$]; 5.07 (br s, 2H, CH_2); 6.78–6.91, 7.09–7.32 (2m, 3 : 7, 10H$_{arom}$); 8.26 (s, 1H, H$_{vinyl}$)	
5b	88	172–174	0.62	$C_{18}H_{18}N_2O_4S$ (358.4)	3.24, 3.36 [2br s, 3H each, $N(CH_3)_2$]; 5.18 (br s, 2H, CH_2); 6.77–6.82, 7.13–7.36, 8.07–8.12 (3m, 2 : 5 : 2, 9H$_{arom}$); 8.26 (s, 1H, H$_{vinyl}$)	358 (M^+, 62)
5c	69	91–93	0.25	$C_{18}H_{19}NO_2S_2$ (329.5)	3.24 [br s, 6H, $N(CH_3)_2$]; 4.11 (br s, 2H, CH_2); 7.07–7.33 (m, 10H$_{arom}$); 8.22 (s, 1H, H$_{vinyl}$)	329 (M^+, 25)
5d	100	oil	0.67	$C_{14}H_{16}Cl_3NO_2S$ (368.7)	3.26 [br s, 6H, $N(CH_3)_2$]; 4.20 (s, 2H, OCH_2CCl_3); 4.87 (s, 2H, CH_2); 7.08–7.14, 7.23–7.30 (2m, 3 : 2, 5H$_{arom}$); 8.23 (s, 1H, H$_{vinyl}$)	
5e	83	106–108	0.62	$C_{19}H_{19}NO_3S$ (341.4)	3.18, 3.29 [2br s, 3H each, $N(CH_3)_2$]; 5.30 (br s, 2H, CH_2); 7.09–7.56, 8.06–8.10 (2m, 8 : 2, 10H$_{arom}$); 8.24 (s, 1H, H$_{vinyl}$)	341 (M^+, 64)
5f	97	79–80	0.67	$C_{17}H_{23}NO_3S$ (321.4)	1.25 (s, 9H, t-C_4H_9); 3.23 [br s, 6H, $N(CH_3)_2$]; 5.08 (br s, 2H, CH_2); 7.07–7.32 (m, 5H$_{arom}$); 8.22 (s, 1H, H$_{vinyl}$)	
5g	89	92–94	0.30	$C_{15}H_{20}N_2O_3S$ (308.4)	2.93, 2.96 [2br s, 3H each, $N(CH_3)_2$]; 3.22 [br s, 6H, $N(CH_3)_2$]; 5.04 (br s, 2H, CH_2); 7.07–7.30 (m, 5H$_{arom}$); 8.21 (s, 1H, H$_{vinyl}$)	308 (M^+, 60)
5h	79	117–119	0.40	$C_{17}H_{23}NO_3S$ (321.4)	1.43–1.90 [m, 6H, $(CH_2)_3$ of THP]; 3.23 [s, 6H, $N(CH_3)_2$]; 3.37–3.46, 3.76–3.85 (2m, 1H each, OCH_2 of THP); 4.62–4.69 (m, 3H, CH_2 + OCHO of THP); 7.05–7.29 (m, 5H$_{arom}$); 8.20 (s, 1H, H$_{vinyl}$)	321 (M^+, 21)
5i	100	94–95	0.50	$C_{13}H_{15}NO_3S$ (265.3)	3.23, 3.37 [2s, 3H each, $N(CH_3)_2$]; 3.70 (s, 3H, OCH_3); 7.11–7.30 (m, 5H$_{arom}$); 8.14 (s, 1H, H$_{vinyl}$)	

[a,b] See Table 1.
[c] $CHCl_3$/acetone, 9 : 1 **(5a, 5b, 5d–i)**; benzene/EtOAc, 95 : 5 **(5c)**.
[d] Satisfactory microanalyses obtained: C ±0.34, H ±0.28, N ±0.12; except for **5b** (C–1.43), **5c** (C –0.92), **5e** (C –0.69, H –0.47), **5g** (C –0.42) and **5h** (C –0.51), which showed correct molecular ion peaks in their MS (see above).
[e] See Table 1.
[f] See Table 2.

concentrated to give a brown oil, which is purified by flash chromatography (petroleum ether/EtOAc, 85:15), to give **3g** as a light yellow viscous oil; yield: 1.5 g (17%) (Table 1).

Besides the above product, two major side products are also formed: *(3-hydroxy-2-phenylthio)propyl N,N-dimethylcarbamate*, as a colorless viscous oil; yield: ~10%

$C_{19}H_{17}NO_3S$	calc.	C 56.44	H 6.79	N 5.49
(255.3)	found	56.51	6.97	5.50

^{1}H-NMR ($CDCl_3$/TMS, 250 MHz): δ = 2.81 (m, 4H, OH + NCH_3); 2.89 (s, 3H, NCH_3); 3.12–3.28 (m, 2H, CH_2); 3.82 (m, 2H, CH_2); 4.89 (m, 1H, $H_{methine}$); 7.15–7.45 (m, 5H_{arom});
and *3-phenylthiopropan-1,2-diol*, as a white solid; yield: ~10%; m.p. 67–68°C (EtOAc/petroleum ether);

$C_9H_{12}O_2S$	calc.	C 58.66	H 6.57
(184.3)	found	58.89	6.77

^{1}H-NMR ($CDCl_3$/TMS, 250 MHz): δ = 2.26 (bs, 1H, OH); 2.90 (bs, 1H, OH); 2.94–3.14 (m, 2H, CH_2); 3.65 (m, 1H, $H_{methine}$); 3.80 (m, 2H, CH_2); 7.20–7.45 (m, 5H_{arom}).

1-(2-Tetrahydropropyranyloxy)-2,3-epoxypropane (3h) and 1-Phenylthio-3-(2-tetrahydropyranyloxy)-2-propanol (2h):
To a solution of glycidol (15.2 mL, 200 mmol) and 3,4-dihydro-2*H*-pyran (27.3 mL, 300 mmol) in dry CH_2Cl_2 (400 mL) is added, at 0–5°C, pyridinium *p*-toluenesulfonate (5 g, 20 mmol), and the mixture is stirred at 0–5°C for 5 h and at room temperature for 4 h. The solution is washed with brine (3 × 200 mL), dried (Na_2SO_4) and concentrated to give 15.6 g (49%) of the crude glycidyl ether **3h**, which is used in the next step without further purification.

A solution of the above crude product (~10 mmol) in 95% EtOH (5 mL) is added to a stirred and cooled (0–5°C) solution of potassium thiophenoxide (10 mmol) [prepared from thiophenol (1.02 mL, 10 mmol) and KOH (0.56 g, 10 mmol)] in aqueous EtOH (10 mL, 3:1). The reaction mixture is stirred at 0°C for 1 h and at room temperature for 24 h. The EtOH is removed *in vacuo*, and the residue is diluted with water (30 mL) and extracted with $CHCl_3$ (3 × 30 mL). The combined extract is dried (Na_2SO_4), concentrated and purified by flash chromatography ($CHCl_3$/petroleum ether, 2:1) to give a light-brown oil; yield: 2 g (75%) (Table 1).

1-Substituted 3-Phenylthio-2-propanones 4a–h; General Procedures:

Method A (for **4a, e, f**): A solution of **2** (10 mmol) in dry DMSO (30 mL) and dry Ac_2O (20 mL) is stirred at room temperature for 24 h. The mixture is concentrated *in vacuo* (0.2 Torr) at a bath temperature of 60°C. The oily residue thus obtained is purified by flash chromatography using $CHCl_3$ or 5–10% EtOAc in petroleum ether as eluent (Table 2).

Method B (for **4b, c, d, g, h**): To a stirred solution of **2** (2 mmol) in dry DMSO (10 mL) is added DCC (6 mmol) followed by a catalytic amount of H_3PO_4 (~0.2 mmol), and the resulting mixture is stirred at room temperature for 15 h. A solution of oxalic acid (0.6 g, 6.6 mol) in MeOH (1.5 mL) is added dropwise and stirring is continued for 1 h at room temperature. The mixture is diluted with acetone (50 mL), the dicyclohexylurea is removed by suction through a pad of silica gel. The precipitate is washed with acetone (25 mL), and the combined filtrate is concentrated *in vacuo* (0.2 Torr) at a bath temperature of 60°C. The residue is redissolved in $CHCl_3$ (100 mL), the $CHCl_3$ solution is washed with water (1 × 30 mL), halfsaturated Na_2CO_3 solution (1 × 30 mL), dried (Na_2SO_4) and concentrated. The crude ketones are purified by flash chromatography using 5–10% EtOAc in petroleum ether as eluent (Table 2).

Methyl 2-oxo-3-phenylthiopropionate (4i):
To a mechanically stirred solution of methyl 3-bromo-2-oxopropionate[9] (70 g, 386 mmol) in dry Et_2O (250 mL) is added thiophenol (37 mL, 368 mmol) at 0–5°C under a nitrogen atmosphere followed by the dropwise addition of dry, degassed pyridine (31 mL, 386 mmol) in dry Et_2O (50 mL). The mixture is stirred at 0–5°C for 30 min, then poured on ice (200 g) and 2N HCl (200 mL) and extracted with Et_2O (3 × 100 mL). Washing of the combined extracts with brine (3 × 80 mL), drying ($MgSO_4$), evaporating and distilling gives **4i** as a yellow oil; yield: 52 g (64%); b.p. 135–155°C/0.1 Torr.

The product, which is contaminated with a small amount of phenyldisulfide, is used as such for the next step (Table 2).

1-Substituted 4-dimethylamino-3-phenylthiobut-3-en-2-ones 5a–h; General Procedure:
A mixture of **4** (1 equiv) and *N,N*-dimethylformamide dimethyl acetal (1.1 equiv) is stirred at 70°C for 1.5 h. The liberated MeOH is evaporated *in vacuo* and the dark-brown residue is purified by flash chromatography using $CHCl_3$ or 15–20% EtOAc in petroleum ether as eluent to give the enamines **5** (Table 3).

Methyl 4-Dimethylamino-2-oxo-3-phenylthio-3-butenoate (5i):
To a solution of **4i** (6.5 g, 31 mmol) in dry toluene (40 mL) is added *N,N*-dimethylformamide dimethyl acetal (6 mL, 42 mmol) at 0–5°C. The mixture is stirred at room temperature for 1.5 h and evaporated. Flash chromatography (petroleum ether/EtOAc = 1:1) affords **5i** as a yellow solid (Table 3).

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