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A novel synthesis of α-(phenylthio)aldehydes

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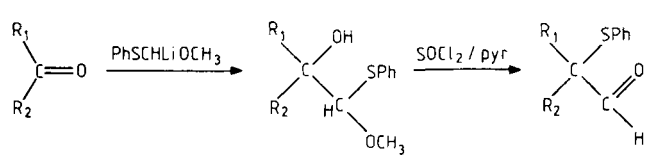
Abstract. Addition of methoxy(phenylthio)methyllithium to ketones, followed by rearrangement of the adducts, provides a new method for the preparation of α-(phenylthio)aldehydes. The rearrangement is stereospecific.

Methoxy(phenylthio)methyllithium is a good nucleophile, capable of addition to a variety of carbonyl compounds. For this reason, the reagent and the synthetic utilization of its adducts have been the subject of several recent investigations[1-9]. In our laboratory, a novel approach towards α-(phenylthio)aldehydes, starting from ketones, was developed using the reactions outlined in Scheme 1[2]. Addition of methoxy(phenylthio)methyllithium[1,7,8] to ketones gave the adducts which were rearranged to α-(phenylthio)aldehydes with $SOCl_2$ and pyridine.

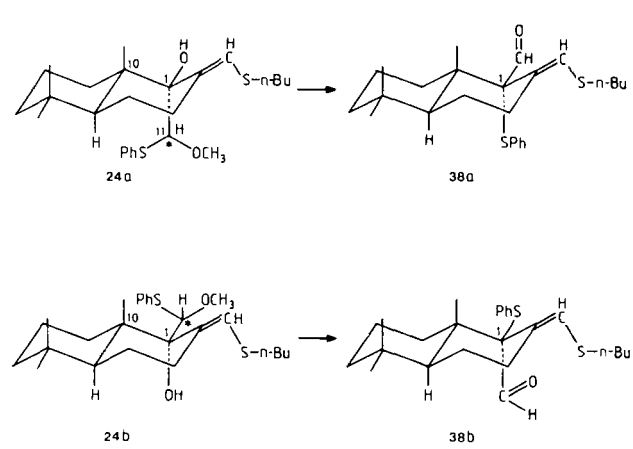
The addition of methoxy(phenylthio)methyllithium to aldehydes, ketones, α,β-unsaturated ketones and (aryl- or alkylthio)methylene ketones was straightforward and the adducts were obtained in high yields (see Table I). The separation of diastereomeric mixtures of adducts was not always possible, but did not prove to be a serious drawback for further transformations. The addition to the mono-protected oxo aldehyde **13** gave the deprotected aldehyde **28** as reaction product since the hydrolysis of the acetal could not be prevented.

The rearrangement was usually performed using $SOCl_2$ in pyridine at 0°C (entries 2–5). The adduct **16** did not rearrange under these conditions. The more complicated adducts gave better results at a lower reaction temperature of −30°C (entries 9, 10, 13–15). The adducts of the simple (*n*-butyl- or phenylthio)methylene ketones and the adducts of the cyclohexenones rearranged spontaneously or upon heating with or without acid (entries 6–8, 11 and 12). This was not unexpected since the olefinic bond provides additional stabilization for the presumed cationic-type intermediates. In two cases (entries 6 and 7), the adducts could not be isolated.

The rearrangement of the epimers of the adducts **24**, **25**, **28** and **30** gave more information about the mechanism of this reaction. The diastereomeric mixture of adducts **24** could be separated into two fractions **24a** and **24b** which, after rearrangement, both gave only one (phenylthio)aldehyde. In both cases, none of the epimeric (phenylthio)aldehyde was obtained. This not only proved that the fractions **24a** and **24b** were epimeric at C-1, but also revealed that the rearrangement was stereospecific. Since nucleophilic attack in decalones such as **9** preferably occurs from the α-side, it was assumed that the formation of the epimers **24a**, which were obtained in the highest yield, resulted from α-attack of the methox(phenylthio)methyllithium. This was confirmed by 2D NOE NMR spectroscopy which revealed a short distance between the OH proton and the protons of the methyl group on C-10 and between the OH proton and the olefinic proton. No NOE's could be found between H-11 and the protons of the C-10 methyl group or the olefinic proton[10]. Consequently, the structures of the epimers **24a** and **24b** were assigned as indicated in Scheme 2. Recently, sulphur participation in the synthesis of allyl sulphides from alcohols by phenylthio migration has been reported by *Aggarwal* and *Warren*[11]. A stereospecific migration of the phenylthio group, with inversion at the carbon atom bearing the leaving hydroxyl group, was observed by these authors.

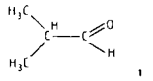
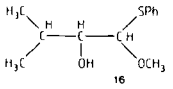
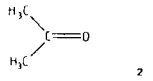
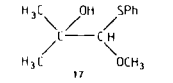
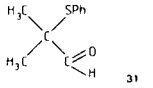
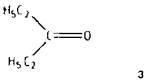
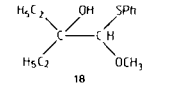
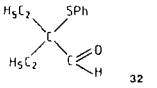
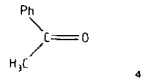
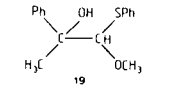
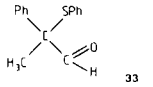
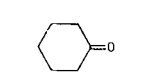
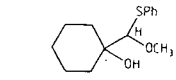
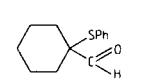
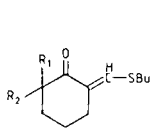
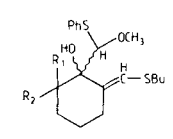
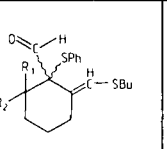
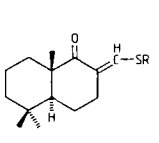
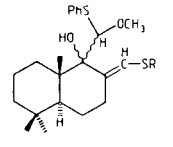
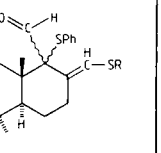
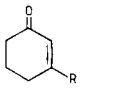
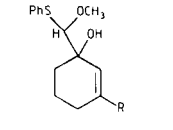
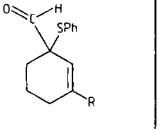
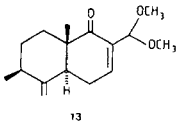
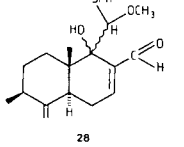
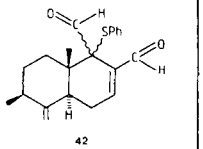
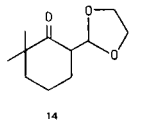
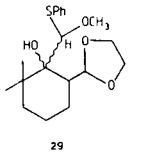
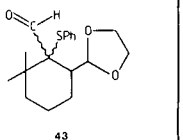
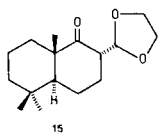
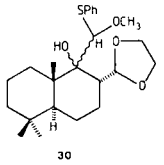
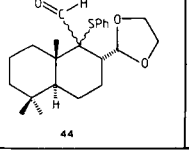


Scheme 1



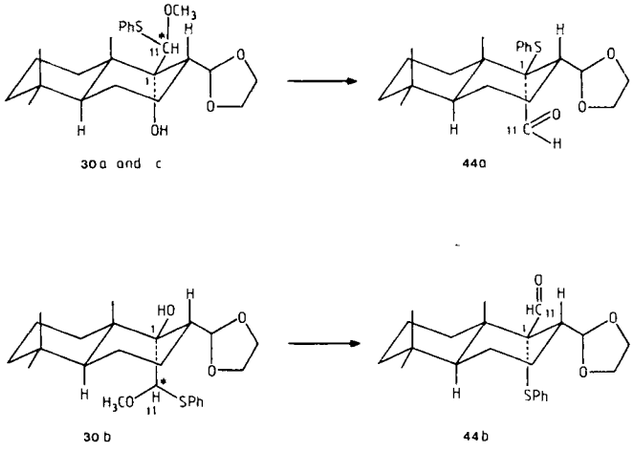
Scheme 2

Table I

	Substrate	Adduct	Yield (%)	(Phenylthio)aldehyde	Yield (%)
1	 1	 16	95		
2	 2	 17	92	 31	93
3	 3	 18	88	 32	95
4	 4	 19	96	 33	90
5	 5	 20	93	 34	83
					
6	6 $R_1 = R_2 = H$	21 $R_1 = R_2 = H$	—	35 $R_1 = R_2 = H$	80
7	7 $R_1 = H$, $R_2 = CH_3$	22 $R_1 = H$, $R_2 = CH_3$	—	36 $R_1 = H$, $R_2 = CH_3$	85
8	8 $R_1 = R_2 = CH_3$	23 $R_1 = R_2 = CH_3$	80	37 $R_1 = R_2 = CH_3$	82
					
9	9 R = n-Bu	24 R = n-Bu	88	38 R = n-Bu	66
10	10 R = Ph	25 R = Ph	94	39 R = Ph	91
					
11	11 R = H	26 R = H	76	40 R = H	75
12	12 R = CH_3	27 R = CH_3	—	41 R = CH_3	88
13	 13	 28	70	 42	70
14	 14	 29	84	 43	86
15	 15	 30	85	 44	75

A similar participation of sulphur in the rearrangement of the epimers **24a** and **24b** resulted in an inversion at C-1 and gave the aldehydes **38a** and **38b**, respectively. This was again confirmed by the 2D NOE NMR spectrum of **38a**. The same stereospecificity was observed in the rearrangement of the epimers of **25** and **28**.

The diastereomeric mixture of the adducts **30** could be separated into three fractions **30a,b** and **c**, with R_f values of 0.37, 0.22 and 0.15, respectively, on silica gel TLC using petroleum ether/5% ether as eluent. These were isolated in 27%, 25% and 18% yield, respectively. The rearrangement of the stereoisomers **30a** and **c** gave the same (phenylthio)aldehyde **44a**. The rearrangement of isomer **30b** afforded (phenylthio)aldehyde **44b**. In all three rearrangements, none of the C-1 epimeric (phenylthio)aldehydes could be detected. In this case, it may be concluded that the isomers **30a** and **c** are epimeric at C-11, that the isomers **30a** and **c** and the isomer **30b** are epimeric at C-1 and that the rearrangements are stereospecific. The 2D NOE NMR spectra of **30a** and **30b** indicated the positions of the substituents at C-1, although such evidence is not conclusive. The 2D NOE NMR spectra of **44a** and **44b** showed the relative positions of the carboxaldehyde and phenylthio groups to be as indicated in Scheme 3.



Scheme 3

The examples shown in Table I illustrate the scope of this rearrangement reaction. The synthetic utility of the adducts and the rearranged (phenylthio)aldehydes will be the subject of further investigations.

Experimental

Boiling points and melting points are uncorrected. ^{1}H NMR spectra were determined on a Varian EM-390 or on an Hitachi Perkin-Elmer R-24B spectrometer. Chemical shifts are reported in δ units with reference to tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded using a Varian XL-100 or a Bruker CXP-300 spectrometer in the pulse FT mode with tetramethylsilane as the internal standard. Mass-spectral data and exact mass measurements were obtained using AEI MS 902 and VG micromass 7070F spectrometers. Unless indicated otherwise, the drying agent for organic solutions was $MgSO_4$. When no temperature is specified, the reaction was carried out at room temperature, *ca.* 20°C. The petroleum ether used for column chromatography had a boiling range of 40–60°C.

General procedure for the addition of methoxy(phenylthio)methyllithium to ketones

A three-necked flask equipped with a magnetic stirring bar, low-temperature thermometer, nitrogen inlet adaptor and a dropping funnel with a rubber septum was dried and kept under nitrogen. The flask was charged with 5.4 g (35 mmol) of methoxy(phenylthio)methane in 74 ml of dry THF and cooled to between −30° and −40°C. At this temperature, a solution of 23 ml of 1.5-M butyllithium in hexane (33 mmol) was added slowly and the reaction mixture was stirred at −35°C for 1 h. The solution was cooled to −78°C and a solution of 30 mmol of ketone in 10 ml of dry THF was added. The reaction mixture was stirred for 2 h at −78°C and then 30 ml of NH_4Cl solution was added. The mixture was extracted with ether and the combined organic fractions were sequentially washed with 5% $NaHCO_3$ solution and with brine. The solution was dried and the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography over silica gel.

1-Methoxy-3-methyl-1-(phenylthio)-2-butanol (**16**)

Isomer **16a** was obtained s a colourless oil in 40% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.85 d, *J* 6 Hz, 3H), 0.90 (d, *J* 6 Hz, 3H), 1.7–2.2 (m, 1H), 2.40 (br s, 1H), 3.15–3.40 (m, 1H), 3.40 (s, 3H), 4.45 (d, *J* 6 Hz, 1H), 7.1–7.5 (m, 5H). MS *(m/e):* 226 ($M^{+\bullet}$, 15); 153 (35); 117 (100); 99 (38); 85 (25); 73 (29); 45 (50).

Isomer **16b** was obtained as a colourless oil in 55% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.90 (d, *J* 6 Hz, 3H), 0.94 (d, *J* 6 Hz, 3H), 1.7–2.2 (m, 1H), 2.45 (br s, 1H), 3.25–3.45 (m, 1H), 3.47 (s, 3H), 4.49 (d, *J* 6 Hz, 1H), 7.1–7.5 (m, 5H). MS *(m/e):* 226 ($M^{+\bullet}$, 18); 153 (42); 117 (100); 110 (79); 99 (41); 85 (24); 73 (31); 45 (51).

1-Methoxy-2-methyl-1-(phenylthio)-2-propabol (**17**)

Compound **17** was obtained as a colourless oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.30 (s, 6H), 2.84 (s, 1H), 3.35 (s, 3H), 4.43 (s, 1H), 7.1–7.5 (m, 5H). MS *(m/e):* 212 ($M^{+\bullet}$, 20); 165 (8); 154 (26); 153 (33); 110 (45); 103 (100); 71 (54); 59 (23).

2-Ethyl-1-methoxy-1-(phenylthio)-2-butanol (**18**)

Compound **18** was obtained as a colourless oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.90 (t, 6H), 1.70 (dq, 4H), 2.38 (s, 1H), 3.32 (s, 3H), 4.66 (s, 1H), 7.1–7.5 (m, 5H). MSn *(m/e):* 240 ($M^{+\bullet}$, 11); 179 (28); 154 (47); 153 (23); 131 (100); 110 (83); 73 (40); 57 (96).

1-Methoxy-2-phenyl-1-(phenylthio)-2-propanol (**19**)

Isomer **19a** was obtained as a colourless oil in 81% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.68 (s, 3H), 2.95 (s, 1H), 3.35 (s, 3H), 4.64 (s, 1H), 7.1–7.5 (m, 10H). MS *(m/e):* 274 ($M^{+\bullet}$, 2); 154 (41); 153 (100); 133 (48); 121 (30); 110 (15); 105 (33).

Isomer **19b** was obtained as a colourless oil in 15% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.65 (s, 3H), 2.98 (s, 1H), 3.30 (s, 3H), 4.64 (s, 1H), 7.1–7.5 (m, 10H).

1-[Methoxy(phenylthio)methyl]-1-cyclohexanol (**20**)

Compound **20** was obtained as a colourless oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.4–1.8 (m, 10H), 2.35 (s, 1H), 3.35 (s, 3H), 4.45 (s, 1H), 7.1–7.5 (m, 5H). MS *(m/e):* 252 ($M^{+\bullet}$, 12); 154 (31); 153 (11); 143 (100); 111 (42); 110 (40); 99 (11).

2-[(n-Butylthio)methylene]-6,6-dimethyl-1-[methoxy(phenylthio)-methyl]-1-cyclohexanol (**23**)

Compound **23** was obtained as white crystals, m.p. 48–50°C. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.99 (s, 3H), 1.02 (s, 3H), 1.2–1.9 (m, 11H), 2.2–2.6 (m, 2H), 2.70 (t, 2H), 2.82 (s, 1H), 3.32 (s, 3H), 5.00 (s, 1H), 6.02 (s, 1H), 7.2–7.5 (m, 5H). MS *(m/e):* 380 ($M^{+\bullet}$, 1); 239 (16); 227 (100); 153 (17); 121 (15); 110 (16); 95 (27). Anal. $C_{21}H_{32}S_2O_2$: calcd. C 66.27, H 8.48; found C 66.43, H 8.64.

trans-2-[(n-Butylthio)methylene]-1α-[(phenylthio)methoxymethyl]-5,5,8a-trimethylperhydro-1β-naphtalenol (**24**)

The (*n*-butylthio)methylene ketone **9** was obtained as described in the literature[12,13]. The epimers **24** were obtained as described in the general procedure. The epimers were separated in two fractions **a** and **b** by chromatography over silica gel using petroleum ether/2% ether as eluent.

Epimers **24a** were obtained in 53% yield as white crystals, m.p. 116–117°C. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.85 and 0.97 (CH_3 signals), 1.05–1.95 (m, 18H), 2.70 (t, *J* 7 Hz, 2H), 2.95 (s, 1H), 3.30

(s, 3H), 5.14 (s, 1H), 5.97 (br s, 1H), 7.15–7.6 (m, 5H). Anal. $C_{25}H_{38}O_2S_2$ calcd.: C 69.07, H 8.81; found: C 69.41, H 8.94%.
Epimers **24b** were obtained in 35% yield as a colourless oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.85 and 0.87 (CH_3 signals), 1.04–2.0 (m, 18H), 2.67 (t, *J* 7 Hz, 2H), 3.02 (br s, 1H), 3.32 (s, 3H), 5.18 (s, 1H), 6.04 (s, 1H), 7.15–7.6 (m, 5H).

trans-2-[(Phenylthio)methylene]-5,5,8a-trimethylperhydro-1(2H)--naphthalenone (**10**)

5,5,8a-Trimethylperhydro-1-naphthalenone was formylated as described[14]. The formyl ketone was converted into (**10**), following the procedure of *Ireland* and *Marshall*[15]. The (phenylthio)methylene ketone **10** was obtained in 92% yield as a white crystalline compound, m.p. 65–66°C. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.92, 0.95 and 1.11 (CH_3 signals), 1.2–2.8 (m, 11H), 7.2–7.5 (m, 5H), 7.55 (t, *J* 2.5 Hz, 1H). MS *(m/e):* 314 ($M^{+\bullet}$, 100); 205 (56); 177 (36); 137 (67); 95 (40); 81 (33); 69 (29). Anal. $C_{20}H_{26}O_5$ calcd.: C 76.38, H 8.33, *m/e* 314.1705; found: C 76.49, H 8.58%, *m/e* 314.1705.

trans-1α-[(Phenylthio)methoxymethyl]-2-[(phenylthio)methylene]--5,5,8a-trimethylperhydro-1β-naphthalenol (**25**)

The epimers **25** were prepared as described in the general procedure. Evaporation of the solvent *in vacuo* gave an oil, which was chromatographed on silica gel using petroleum ether/1% ether as eluent. A total yield of 94% of the epimers **25** was obtained, which was separated into two fractions:
Epimers **25a**: ^{1}H NMR ($CDCl_3$) δ (ppm): 0.92 and 1.07 (CH_3 signals), 1.1–3.0 (m, 11H), 3.36 (s, 3H), 5.16 (s, 1H), 6.30 (s, 1H), 7.2–7.5 (m, 10H). MS *(m/e):* 436 [$(M-32)^{+\bullet}$, 1], 326 (79), 315 (26), 249 (87), 189 (45), 110 (100).
Epimers **25b**: ^{1}H NMR ($CDCl_3$) δ (ppm): 0.90, 0.95 and 1.00 (CH_3 signals), 1.3–2.3 (m, 9H), 2.85–3.15 (m, 2H), 3.40 (s, 3H), 5.23 (s, 1H), 6.43 (s, 1H), 7.1–7.6 (m, 10H). MS *(m/e):* no significant differences between epimers **25a** and **b** were observed.

1-[Methoxy(phenylthio)methyl]-2-cyclohexen-1-ol (**26**)

A 75% yield of a mixture of diastereoisomers was isolated as a colourless oil, which could not be separated by column chromatography.
Major isomer, 44% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.5–2.1 (m, 6H), 2.60 (s, 1H), 3.46 (s, 3H), 4.58 (s, 1H), 5.6–6.1 (m, 2H), 7.1–7.6 (m, 5H).
Minor isomer, 31% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.5–2.1 (m, 6H), 2.55 (s, 1H), 3.46 (s, 3H), 4.61 (s, 1H), 5.6–6.1 (m, 2H), 7.1–7.6 (m, 5H). MS *(m/e):* 250 ($M^{+\bullet}$, 1); 141 (100); 140 (17); 110 (13); 109 (20); 81 (54); 67 (12). Acc. mass. $C_{14}H_{18}O_2S$ calcd.: 250.1028; found: 250.1023.

trans-1-Hydroxy-1-[(phenylthio)methoxymethyl]-6β,8a-dimethyl-5--methylene-1,4-4a,5,6,7,8a-octahydro-2-naphthalenecarboxaldehyde (**28**)

The starting ketone **13** was prepared as described in the literature[8]. The epimers **28** were prepared as described in the general procedure. The epimers were purified by column chromatography using petroleum ether/5% ethyl acetate as eluent. The yield was 44% for the major epimers and 19% for the minor epimers.
Major epimers: ^{1}H NMR ($CDCl_3$) δ (ppm): 0.80 (s, 3H), 1.09 (d, 3H), 1.4–2.5 (m, 8H), 3.48 (s, 3H), 4.70 (br s, 1H), 4.85 (br s, 1H), 5.18 (s, 1H), 6.92 (dd, 1H), 7.2–7.7 (m, 5H), 9.54 (s, 1H).
Minor epimers: ^{1}H NMR ($CDCl_3$) δ (ppm): 0.80 (s, 3H), 1.10 (d, 3H), 1.5–2.5 (m, 8H), 3.30 (s, 3H), 4.68 (br s, 1H), 4.85 (br s, 1H), 5.18 (s, 1H), 6.91 (dd, 1H), 7.2–7.5 (m, 5H), 9.48 (s, 1H).

6,6-Dimethyl-2-(1,3-dioxolan-2-yl)-1-[(phenylthio)methoxymethyl]-1--cyclohexanol (**29**)

The starting ketone **14** was prepared as described for compound **15**. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.05 (s, 3H), 1.20 (s, 3H), 1.4–2.5 (m, 7H), 3.88 (s, 4H), 5.15 (d, 1H). MS *(m/e):* 198 ($M^{+\bullet}$, 17); 73 (100); 70 (28); 55 (16); 45 (38).
The stereoisomers **29** were prepared as described in the general procedure. The stereosiomers were separated by column chromatography over silica gel. Elution with petroleum ether/5% ether initially gave **29a** in 6% yield as a colourless oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.91 (s, 6H), 1.3–2.0 (m, 6H), 2.4–2.7 (m, 1H), 3.40 (s, 3H), 3.65 (s, 1H), 3.7–4.1 (m, 4H), 4.91 (s, 1H), 5.06 (br s, 1H), 7.2–7.7 (m, 5H).
The second isomer **29b** was obtained in 9% yield as white crystals, m.p. 99–100°C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.00 (s, 3H), 1.16 (s, 3H), 1.2–2.3 (m, 7H), 3.34 (s, 3H), 3.7–4.2 (m, 4H), 4.26 (s, 1H), 5.09 (d, *J* 7 Hz, 1H), 5.20 (s, 1H), 7.2–7.7 (m, 5H). Anal. $C_{19}H_{28}O_4S$ calcd.: C 64.73, H 8.01; found: C 64.77, H 7.72%.
The third fraction contained a mixture of two isomers **29c** and **d** and was obtained as a colourless oil in 29% yield.
Major isomer: ^{1}H NMR ($CDCl_3$) δ (ppm): 1.03 (s, CH_3), 1.17 (s, CH_3), 1.3–2.1 (m), 2.3–2.6 (m), 3.35 (s, $O-CH_3$), 3.40 (s, OH), 3.8–4.0 (m), 5.01 (s, 1H), 5.47 (d, *J* 3 Hz), 7.2–7.6 (m).
Minor isomer: ^{1}H NMR ($CDCl_3$) δ (ppm): 1.12 (s, CH_3), 1.29 (s, CH_3), 1.3–2.1 (m), 2.3–2.6 (m), 3.28 (s, OCH_3), 3.8–4.0 (m), 5.18 (d, *J* 2 Hz), 5.40 (s, 1H), 7.2–7.6 (m).

trans-2α-(1,3-Dioxolan-2-yl)-3,4,4a, 5,6,7,8,8a-octahydro-5,5,8a--trimethyl-1(2H)-naphthalenone (**15**)

The formylation of *trans*-3,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethylnaphthalene-1(2*H*)-one was performed as described in the literature[12,14]. The formyl ketone was converted into **15** in the following way: A solution of 3.95 g (17.8 mmol) of formyl ketone, 1.29 g (19.4 mmol) of ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid in 150 ml of benzene was refluxed for 14 h in a Dean Stark apparatus. The reaction mixture was cooled and 1 ml of triethylamine was added. The benzene solution was extracted with water and brine, dried and evaporated *in vacuo*. The residue was chromatographed over silica gel using petroleum ether/15% ether as eluent. The dioxolane **15**, 3.31 g (70%), was obtained as a white crystalline compound, m.p. 72–74°C. ^{1}H NMR ($CDCl_3$): δ 0.94, 0.96, 1.20 (CH_3 signals), 1.2–2.0 (m, 10H), 2.0–2.3 (m, 1H), 2.7–3.1 (m, 1H), 3.95 (s, 4H), 5.15 (d, *J* 4 Hz, 1H). Anal. $C_{16}H_{26}O_3$ calcd.: C 72.14, H 9.84; found: C 72.03, H 10.01%.

trans-2α-(1,3-Dioxolan-2-yl)-1-[(phenylthio)methoxymethyl]-5,5,8a--trimethylperhydro-1-naphthalenol (**30**)

The epimers **30** were obtained from **15** as described in the general procedure. Evaporation of the solvent gave an oil, which was chromatographed on silica gel using petroleum ether/5% ether as eluent. A total yield of 1.7 g (85%) of adducts **30** was obtained and was separated in three fractions. The isomer **30a** was first eluted in 18% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.85, 0.90 and 0.95 (CH_3 signals), 1.3–1.9 (m, 11H), 2.56 (dd, *J* 12 Hz and *J* 6 Hz, 1H), 3.4 (s, 3H), 3.72 (s, 1H), 3.7–3.9 (m, 4H), 4.93 (s, 1H), 5.02 (d, *J* 2 Hz, 1H), 7.2–7.6 (m, 5H). Anal. $C_{24}H_{36}O_4S$ calcd.: C 68.53, H 8.63; found: C 68.75, H 8.81%.
The isomer **30b** was eluted as the second compound in 24% yield, m.p. 114–115°C. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.90 and 1.22 (CH_3 signals), 1.1–2.4 (m, 12H), 3.34 (s, 3H), 3.8–4.1 (m, 4H), 4.36 (s, 1H), 5.09 (d, *J* 8 Hz), 5.38 (s, 1H), 7.2–7.7 (m, 5H). Anal. $C_{24}H_{36}O_4S$ calcd.: C 68.53, H 8.63; found: C 68.21, H 8.77%.
The isomer **30c** was eluted as the third compound in 27% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.87, 0.90 and 1.27 (CH_3 signals), 1.0–2.0 (m, 11H), 2.3–2.8 (m, 1H), 3.27 (s, 3H), 3.35 (s, 1H), 3.7–3.9 (m, 4H), 5.01 (s, 1H), 5.4 (d, *J* 2 Hz, 1H), 7.2–7.7 (m, 5H). Acc. mass calc. for $C_{24}H_{36}O_4S$: 420.2334; found: 420.2255. $C_{23}H_{32}O_3S$ calcd.: 388.2072; found: 388.2073.

General procedure for the rearrangement to the α-(phenylthio)aldehydes

A solution of 2 mmol of the adduct in 5 ml of pyridine was cooled to 0°C and 0.3 ml of thionyl chloride was added dropwise and with stirring. The reaction mixture was stirred for $\frac{1}{2}$ h at 0°C and then poured on to crushed ice. Acidification was performed with 3 ml of conc. HCl. The water solution was extracted five times with 15 ml of dichloromethane and the organic solution was washed with water, brine and dried. The solvent was evaporated and, when necessary, the residual pyridine was removed by azeotropic distillation with toluene. The residue was purified by column chromatography on silica gel.

2-Methyl-2-(phenylthio)propanal (**31**)

Compound **31** was obtained as a colourless oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.30 (s, 6H), 7.25 (s, 5H), 9.23 (s, 1H). MS *(m/e):* 180

($M^{+\bullet}$, 23); 151 (100); 123 (15); 111 (17); 110 (20); 109 (18); m.p. of the 2,4-DNPH: 153–154°C. Anal. of the 2,4-DNP $C_{16}H_{16}N_4O_4S$ calcd.: C 53.32, H 4.48; found: C 53.58, H 4.47%.

2-Ethyl-2-(phenylthio)butanal (**32**)

Compound **32** was obtained as a colourless oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.92 (t, *J* 7 Hz, 6H), 1.70 (dq, 4H), 7.1–7.4 (s, 5H), 9.23 (s, 1H). MS *(m/e):* 208 ($M^{+\bullet}$, 28); 179 (100); 123 (26); 110 (42); 109 (17); m.p. of the 2,4-DNPH: 144–145°C. Anal. of the 2,4-DNPH $C_{18}H_{20}N_4O_4S$ calcd.: C 55.66, H 5.19; found: C 55.56, H 5.09%.

2-Phenyl-2-(phenylthio)propanal (**33**)

Compound **33** was obtained as white crystals, m.p. 75°C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.54 (s, 3H), 7.1–7.5 (m, 10H), 9.56 (s, 1H). MS *(m/e):* 242 ($M^{+\bullet}$, 11); 213 (100); 133 (19); 110 (33); 109 (16); 103 (39). Anal. $C_{15}H_{14}OS$ calcd.: C 74.34,;H 5.82; found: C 74.58, H 5.87%.
M.p. of the 2,4-DNPH $C_{21}H_{18}N_4O_4S$ calcd.: C 59.70, H 4.29; found: C 59.85, H 4.15%.

1-(Phenylthio)-1-cyclohexanecarboxaldehyde (**34**)

Compound **34** was obtained as a colourless oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.1–2.0 (m, 10H), 5.25 (s, 5H), 9.15 (s, 1H). MS *(m/e):* 220 ($M^{+\bullet}$, 22); 191 (100); 123 (24); 110 (31); 81 (72); m.p. of the 2,4-DNPH: 194–195°C. Anal. of the 2,4-DNPH $C_{19}H_{20}N_4O_4S$ calcd.: C 56.98, H 5.03; found: C 56.96, H 5.13%.

2-[(n-Butylthio)methylene]-1-(phenylthio)-1-cyclohexanecarboxaldehyde (**35**)

The adduct **21** was prepared following the general procedure. Evaporation of the solvent and purification by column chromatography using petroleum ether/5% ether as eluent did not give the adduct, but rather the rearranged α-(phenylthio)aldehyde (**35**), which was obtained as a colourless oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.9–1.2 (m, 3H), 1.0–1.8 (m, 6H), 2.0–2.3 m, 2H), 2.72 (t, 2H), 5.59 (s, 1H), 7.2–7.4 (m, 5H), 9.49 (s, 1H). MS *(m/e):* 320 ($M^{+\bullet}$, 1); 291 (1); 211 (43); 155 (100); 110 (5); 77(3).

2-[(n-Butylthio)methylene]-6-methyl-1-(phenylthio)-1-cyclohexanecarboxaldehyde (**36**)

The adduct **2** was prepared following the general procedure. Acidification of the THF solution afforded the aldehyde **36** as a colourless oil and as a mixture of stereoisomers.
Major isomer: ^{1}H NMR $CDCl_3$) δ (ppm): 0.8–2.0 (m, 17H), 2.5–2.9 (m, 2H), 5.71 (s, 1H), 7.1–7.3 (m, 5H), 9.63 (s, 1H).
Minor isomer: ^{1}H NMR ($CDCl_3$) δ (ppm): 0.8–2.0 (m, 17H), 2.5–2.9 (m, 2H), 5.71 (s, 1H), 7.1–7.3 (m, 5H), 9.50 (s, 1H). MS *(m/e):* 334 ($M^{+\bullet}$, 2); 305 (3); 224 (78); 168 (100); 110 (95); 105 (24).

2-[(n-Butylthio)methylene]-6,6-dimethyl-1-(phenylthio)-1-cyclohexanecarboxaldehyde (**37**)

The adduct **23** was dissolved in dioxane and treated with a few drops of concentrated hydrochloric acid. After 2 h, the reaction mixture was poured into water and extracted with ether.The extract was washed with brine and dried. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel with petroleum ether/10% ether as eluent. Compound **37** was obtained as a colourless oil. 1H NMR ($CDCl_3$) δ (ppm): 1.00 (s, 3H), 1.10 (s, 3H), 0.9–1.9 (m, 11H), 2.3–2.9 (m, 4H), 5.78 (s, 1H), 7.1–7.5 (m, 5H), 9.48 (s, 1H). MS *(m/e):* 348 ($M^{+\bullet}$, 1); 291 (1); 239 (100); 183 (92); 135 (56); 110 (96).

trans-*2-[(n-Butylthio)methylene]-1-(phenylthio)-5,5,8-trimethylperhydro-1-napthalenecarboxaldehyde* (**38**)

The rearrangement of epimers **24a** was performed at −30°C following the general procedure. The crude product **38a** was purified by chromatography over silica gel using petroleum ether/3% ether as eluent. The (phenylthio)aldehyde **38a** was obtained in 66% yield as a colourless oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.87, 0.94 and 1.02 (CH_3 signals), 0.9–2.1 (m, 16H), 2.1–2.8 (m, 2H), 2.80 (t, 2H), 5.78 (s, 1H), 7.1–7.5 (m, 5H), 9.37 (s, 1H).

trans-*1-(Phenylthio)-2-[(phenylthio)methylene]-5,5,8-trimethylperhydro-1-naphthalenecarboxaldehyde* (**39**)

The rearrangement of epimers **25** was performed at −30°C as described in the general procedure. An unstable mixture of two aldehydes was obtained in 91% yield as a colourless oil. ^{1}H NMR of **39** (one epimer) ($CDCl_3$) δ (ppm): 0.84, 0.90 and 1.00 (CH_3 signals), 1.1–2.1 (m, 9H), 2.2–3.0 (m, 2H), 6.10 (s, 1H), 7.1–7.5 (m, 10H), 9.37 (s, 1H).

1-(Phenylthio)-2-cyclohexene-1-carboxaldehyde (**40**)

The rearrangement was performed in acetone with 3 ml 1-N hydrochloric acid at room temperature. Compound **40** was obtained as a colourless oil. ^{1}H NMR ($CDCl_3$) δ 1ppm): 1.50–2.10 (m, 6H), 5.52 (d, *J* 11 Hz, 1H), 6.02 (m, 1H), 7.2–7.4 (m, 5H), 9.34 (s, 1H). MS *(m/e):* 218 ($M^{+\bullet}$, 8); 189 (100); 109 (20). Acc. mass $C_{13}H_{14}OS$ calcd.: 218.0765; found: 218.0762.

3-Methyl-1-(phenylthio)-2-cyclohexene-1-carboxaldehyde (**41**)

The addition of methoxy(phenylthio)methyllithium to 3-methyl-2-cyclohexenone (**12**) was performed as described in the general procedure. The rearrangement of the adduct occurred during the column chromatography on silica gel. The aldehyde **41** as obtained as white crystals, m.p. 61–62°C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.5–1.8 (m, 4H), 1.75 (s, 3H), 1.9–2.1 (m, 2H), 5.25 (br s, 1H), 7.35 (br s, 5H), 9.30 (s, 1H). MS *(m/e):* 232 ($M^{+\bullet}$, 5); 204 (17); 203 (100); 123 (69); 110 (16); 109 (13); 95 (32); 93 (39). Anal. $C_{14}H_{16}SO$ calcd.: C 72.37, H 6.94; found: C 72.21, H 6.90%.

trans-*1-(Phenylthio)-6β,8a-dimethyl-5-methylene-1,4,4a,5,6,7,8,8a-octahydro-1,2-naphthalenedicarboxaldehyde* (**42**)

The rearrangement of **28** was performed at −30°C following the general procedure. Compound **42** was obtained as a colourless oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.87 (s, 3H), 1.10 (d, 3H), 1.4–2.5 (m, H), 4.73 (br s, 1H), 4.92 (br s, 1H), 6.92 (dd, 1H), 7.1–7.5 (m, 5H), 8.70 (s, 1H), 9.68 (s, 1H). MS *(m/e):* 340 ($M^{+\bullet}$, 4); 322 (21); 311 (14); 263 (28); 231 (70); 230 (62); 215 (60); 131 (55); 110 (100); 105 (84); 91 (88); 77 (61).

2-(1,3-Dioxolan-2-yl)-1-(phenylthio)-6,6-dimethyl-1-cyclohexanecarboxaldehyde (**43**)

The rearrangement of a mixture of diastereomers of **29** was performed at −20°C following the general procedure. A mixture of isomers **43** was obtained as a colourless oil and was separated by column chromatography on silica gel using petroleum ether/5% ether as eluent.
Major isomer ^{1}H NMR ($CDCl_3$) δ (ppm): 1.10 (s, 3H), 1.30 (s, 3H), 1.4–2.0 (m, 6H), 2.55–2.80 (m, 1H), 3.5–3.9 (m, 4H), 4.82 (d, *J* 4 Hz, 1H), 7.1–7.6 (m, 5H), 9.55 (s, 1H). Acc. mass $C_{18}H_{24}O_3S$ calcd.: 320.1446; found: 320.1451.
Minor isomer ^{1}H NMR ($CDCl_3$) δ (ppm): 1.17 (s, 3H), 1.22 (s, 3H), 1.5–2.2 (m, 7H), 3.80 (br s, 4H), 5.48 (d, *J* 3 Hz, 1H), 7.1–7.6 (m, 5H), 9.59 (s, 1H). Acc. mass $C_{18}H_{24}O_3S$ calcd: 320.1446; found: 320.1457.

trans-*2α-(1,3-Dioxolan-2-yl)-1-(phenylthio)-5,5,8a-trimethylperhydro-1-naphthalenecarboxaldehyde* (**44**)

A solution of 1.5 g (3.6 mmol) of adduct **30a** or **30c** in 1.5 ml pyridine was cooled to −30°C and 0.15 ml of thionyl chloride was added dropwise. The reaction mixture was stirred for 40 min at −30°C and then 50 ml of water was added. The water solution was extracted five times with 1.5 ml of dichloromethane. The organic solution was washed with water, brine and dried. The solvent was evaporated *in vacuo* and the pyridine was removed via azeotropic distillation with toluene. The residue was chromatographed on silica gel using petroleum ether/5% ether as eluent. In both reactions, the same aldehyde **44a** was obtained as a colourless oil in 70–75% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.88, 0.89 and 1.24 (CH_3 signals), 1.1–2.0 (m, 11H), 2.43 (dd, *J* 13 Hz and *J* 4 Hz, 1H), 3.8–3.95 (m, 4H), 5.8 (br s, 1H), 7.2–7.6 (m, 5H), 9.60 (s, 1H). The same procedure was used for the rearrangement of adduct **30b**, which gave a 66% yield of aldehyde **44b** as a colourless oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.85, 0.95 and 1.07 (CH_3 signals), 1.2–1.9 (m, 11H), 2.5–2.9 (m, 2H), 3.5–3.9 (m, 4H), 4.85 (d, *J* 4 Hz, 1H), 7.2–7.7 (m, 5H), 9.30 (s, 1H).

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