

Thioalkylation of Enolates, II^[1] **α -Thioalkylation of Zinc Enolates to α,α -Disubstituted Ketones[☆]**

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An α -alkylation of the 2-methylcycloalkanones **1** and **4** at the higher substituted carbon can be achieved by thioalkylation of the corresponding zinc enolates with the α -chlorosulfides

3. The desulfurization can be carried out with either Raney nickel or lithium in diethylamine for compounds which contain double or triple bonds.

A fundamental C–C bond forming reaction in organic synthesis is the α -alkylation of carbonyl compounds by nucleophilic displacement of alkyl halides with enolates^[2]. However, under the influence of the highly basic alkali metal enolates, polyalkylation and a lack of regioselectivity has been observed^[3].

Besides the traditional procedure of using β -dicarbonyl compounds, a variety of methods have been developed for selective alkylation, which involve the use of azaenolates^[4], enol borates^[5] and silyl enol ethers^[3a,6].

These silyl enol ethers can be converted with methyl-lithium regioselectively into the corresponding lithium enolates^[7]. The shortcoming of the latter^[3a,6a,8], as well as their corresponding enol borates, is the low reactivity towards alkylating agents such as *n*-alkyl halides. However, alkylation can be achieved with reactive^[9] alkyl halides like benzyl bromide, allyl bromide or methyl iodide. Less reactive alkyl halides^[9] such as *n*-butyl iodide have in very few cases successfully been applied, but the alkylation of enolates with secondary alkyl halides generally fails.

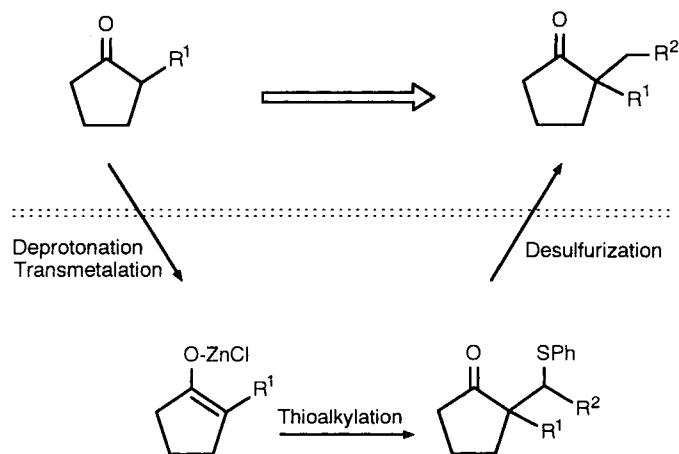
Even though azaenolates are more reactive towards alkylating agents, their use is limited since they are preferentially alkylated at the *less* substituted carbon^[4b].

Instead of using enolates from highly electropositive metals, it is more advantageous to use silyl enol ethers as a specific enol equivalent. Due to their covalent character and therefore weak nucleophilicity, they only react under the catalysis of a suitable Lewis acid^[10] such as TiCl₄ or ZnCl₂. These Lewis acids promote only the reaction of S_N1-active alkylating agents such as tertiary^[11], aryl-activated secondary^[12] and some reactive primary^[13] alkyl halides. However, the alkylation with nonactivated primary and secondary alkyl halides fails completely.

To extend this reaction to all primary and secondary halides, Fleming and Paterson^[14] suggested the use of α -phenylthio-activated S_N1-active halides for the alkylation of silyl enol ethers. Reetz was the first to report on the introduction of a secondary alkyl group by using this methodology^[15].

Our interest was the development of a method for the direct thioalkylation of metal enolates which would avoid

the synthesis of silyl enol ethers as they are not easily stored or handled. Subsequent desulfurization should yield the desired α,α -disubstituted ketones.



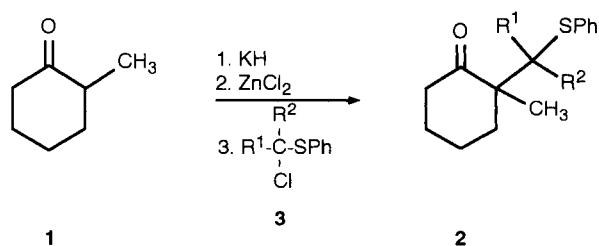
In 1974, Reich and Renga^[16] reported on the thioalkylation of lithium enolates with bromomethyl benzyl sulfide, but the yields were only moderate.

In order to achieve a S_N1-type reaction of an alkali enolate, it has to be transmetalated into a metal enolate which is stable towards a Lewis acid catalyzed thioalkylation. Besides boron, aluminium^[1] and titanium enolates, zinc enolates were the most suitable ones. Thus, the transmetalation was performed with an ethereal solution of zinc chloride. The zinc chloride catalyzed alkylation of these zinc enolates with α -chloroalkyl phenyl sulfides **3** afforded the β -(phenylthio) ketones **2** and **5** in 22–66% yield as a 1:1 mixture of their C-1' epimers.

It should be pointed out that the enolates of the ketones **1** and **4** and their corresponding regioisomers are generated in a 67:33 ratio for **1**^[17] and a 71:29 ratio for **4**^[7a]. Therefore, the maximum yield of the β -(phenylthio) ketones is limited by 67% and 71%. The potassium enolates of the ketones **1** and **4** were prepared by reaction of these ketones with potassium hydride (THF, 20°C). Usually, the deprotonation of 2-methylcyclopentanone (**4**) was completed within 20 min,

whereas the deprotonation of 2-methylcyclohexanone (**1**) proceeded significantly slower. After the evolution of hydrogen had ceased, 1.3 equivalents of an ethereal solution of ZnCl_2 was added at -40°C .

Transmetalation was completed within 20 min and 1 equivalent of the α -chloroalkyl phenyl sulfide^[18] **3** was added. The reaction temperature was chosen according to the structure of the α -chloroalkyl phenyl sulfide. In order to suppress elimination reactions in the case of **3e**, **3h** and **3i** the temperature was kept in the range of -30 to -10°C . Thioalkylation with the more stable α -chloroalkyl phenyl sulfides was completed after stirring at -20°C for 3 h and at 0 – 20°C for an additional 3–4 h. The thioalkylation with α -chloromethyl phenyl sulfide (**3a**) proceeded only sluggishly; after stirring at 0°C for 4 h TLC analysis showed no evidence for the formation of the desired product **2a**. After raising the temperature to 20°C , the reaction was completed within 10 h.



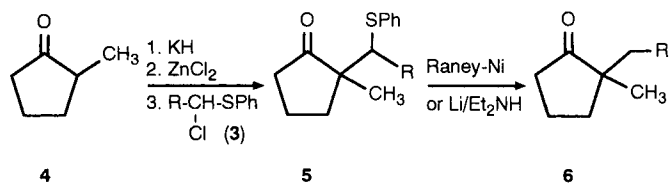
2, 3	R ¹	R ²	Yield of 2 (%)
a	H	H	49
b	CH ₃	H	66
c	(CH ₂) ₂ CH ₃	H	65
d	(CH ₂) ₂ COOC ₂ H ₅	H	49
e	CH ₂ COOC ₂ H ₅	H	22
f	C ₆ H ₅	H	52
g	CH(CH ₃) ₂	H	65
h	CH ₃	CH ₃	39

It should be noted that the thioalkylation with the α -chlorosulfides **3d** and **3e** did not lead to any detectable aldol product formation. Treatment of the zinc enolate of ketone **1** with the extremely base-sensitive α -chlorosulfide **3e** gave a remarkable 22% of the thioalkylation product **2e** as well as approximately 60% methyl β -phenylthioacrylate, the product of the competing elimination process. This result indicates the weak basicity of the employed zinc enolates.

Zinc enolates can also be thioalkylated with tertiary chlorosulfides although the yields are somewhat lower due to the strong tendency of these chlorosulfides to undergo an elimination. For example, the zinc enolate of ketone **1** was treated with α -chloroisopropyl phenyl sulfide **3h** to give the β -(phenylthio) ketone **2h** in 39% yield. The higher yields for the alkylation with the other α -chlorosulfides reflects their greater stability towards elimination. Since a 67:33 mixture of regioisomeric enolates was generated by deprotonation

with potassium hydride, a small amount (5–10%) of the regioisomeric alkylation product was obtained, which could easily be removed by column chromatography. In this context it is interesting to note that no evidence for the formation of any *O*-alkylated product was found.

Reductive desulfurization of the β -(phenylthio) ketones **2** and **5** can be achieved in almost quantitative yield either with moderately active Raney nickel^[19] or lithium in diethylamine yielding the α,α -disubstituted cyclopentanones **6** and 2-butyl-2-methyl-1-cyclohexanone. In contrast to Raney nickel, lithium in liquid diethylamine does not hydrogenate double or triple bonds.



5, 6	3	R	Yield of 5 (%)	Yield of 6 (%)
a	b	CH ₃	63	
b	c	(CH ₂) ₂ CH ₃	65	89
c	d	(CH ₂) ₂ COOC ₂ H ₅	53	86
d	i	(<i>E</i>)-CH ₂ CH=C(CH ₃)(CH ₂) ₃ CH ₃	32	82
e	j	CH ₂ CH ₂ C≡CH	57	

The described two-step method for the alkylation of ketones at the higher substituted carbon atom generally allows the introduction of primary and secondary alkyl groups by using α -chloroalkyl phenyl sulfides as the electrophilic reagent. This method has already been applied in a total synthesis of 3 β -hydroxyandrosta-5,7-diene-17-ones^[20], precursors of vitamin D.

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Experimental

Infrared (IR) spectra were recorded on a Perkin-Elmer 298 spectrometer. NMR spectra were measured with a Varian XL 200 or a VXR 200 spectrometer for ¹H and ¹³C NMR. Chemical shifts are given in parts per million (δ) by using tetramethylsilane as an internal standard for ¹H- and ¹³C-NMR spectroscopy. Mass spectra were recorded on Varian MAT 731 or 311 A spectrometers. TLC analyses were performed on Polygram Sil G/UV₂₅₄ silica gel plates. Silica gel (0.030–0.060 mm) from Baker was used for flash chromatography. Combustion analyses were carried out by the micro-analytical laboratory of the University of Göttingen. All reactions were carried out under argon except those involving desulfurization. All reagents were purified and dried before use if necessary. THF was freshly distilled from LiAlH₄ prior to use. CCl₄ was distilled from P₄O₁₀. The ethereal ZnCl₂ solution was purchased from Ald-

rich. The phenyl sulfides were prepared from the corresponding halides or mesylates with thiophenol and K_2CO_3 in acetone. The homoallylic alcohol, necessary for the synthesis of the α -chlorosulfide **3i**, was prepared according to ref.^[21]

α -Chlorosulfides 3. — *General Procedure:* Powdered *N*-chlorosuccinimide (4.41 g, 33 mmol) was added in a single portion to a stirred solution of the corresponding phenyl sulfide (30 mmol) in CCl_4 at $0^\circ C$. The reaction was finished when the succinimide was completely drifting on the surface of the solution. The mixture was cooled to $-20^\circ C$ and filtered under argon. The filtrate was concentrated in vacuo to afford the moisture-sensitive α -chlorosulfides in almost quantitative yield. These chlorosulfides were used after drying in vacuo ($0^\circ C$, 0.01 Torr) without further purification.

β -(Phenylthio) Ketones 2 and 5. — *General Procedure:* Potassium hydride (4.82 g of a 25% suspension in mineral oil, 30 mmol) was washed with three portions of THF (10 ml each) and suspended in THF (60 ml). 2-Methylcyclohexanone (**1**) (30 mmol, 3.37 g) or 2-methylcyclopentanone (**4**) (30 mmol, 2.95 g) was added at room temperature to this stirred suspension of potassium hydride. After the evolution of hydrogen had ceased (20–90 min), the resultant solution was cooled to $-40^\circ C$ and 39 mmol zinc chloride (39 ml of a 1.0 M solution in diethyl ether) was added. Upon the addition of 0.5 equivalents of $ZnCl_2$, the reaction mixture became viscous due to the formation of a white precipitate, which upon addition of a further 0.5 equivalents of $ZnCl_2$ afforded the soluble zinc enolate. After an additional 20 min, the α -chlorosulfide **3** was added and the mixture was stirred at $-20^\circ C$ for 3 h. Within a further 4 h, the reaction mixture was allowed to warm up to room temp. The solvent was evaporated in vacuo ($25^\circ C/20$ Torr) and the residue was diluted with 100 ml of diethyl ether and 40 ml of 1 N HCl. The ethereal layer was separated, washed with aqueous sodium hydrogen carbonate and water (50 ml each). It then was dried with $MgSO_4$, the solvent evaporated in vacuo and the residue — the crude β -(phenylthio) ketone — purified by chromatography on silica gel.

2-Methyl-2-(phenylthiomethyl)-1-cyclohexanone (2a): 1.20 g (30 mmol) of potassium hydride, 3.37 g (30 mmol) of 2-methylcyclohexanone (**1**), 39 ml (39 mmol) of a $ZnCl_2$ solution, and 4.73 g (30 mmol) of α -chloromethyl phenyl sulfide (**3a**) were allowed to react to yield 3.35 g (49%) of **2a**. — $R_f = 0.26$ (diethyl ether/petroleum ether, 1:10). — IR (neat): $\tilde{\nu} = 3060$ and 3040 (aromat. C—H), 1700 (C=O), 1575 (aromat. C=C), 745 and 685 cm^{-1} (δ_{CH} monosubst. aromat.). — 1H NMR ($CDCl_3$): $\delta = 1.24$ (s; 3H, C—CH₃), 1.61 – 1.99 (m; 6H, CH₂), 2.26 – 2.54 (m; 2H, CH₂—C=O), 3.14 and 3.21 (2 d, $J_{AB} = 12$ Hz; 2H, CH₂—SPh), 7.11 – 7.42 (m; 5H, C₆H₅). — ^{13}C NMR ($CDCl_3$): $\delta = 21.11$, 27.18 , 38.01 , 38.61 and 42.88 (CH₂), 22.68 (CH₃), 49.77 (C-2), 126.03 , 128.86 and 129.63 (aromat. CH), 137.65 (aromat. C), 213.91 (C=O). — MS (70 eV): m/z (%) = 234 (45) [M^+], 125 (100) [$M^+ - PhSH$].

$C_{14}H_{18}OS$ (234.3) Calcd. C 71.73 H 7.74
Found C 71.70 H 7.78

2-Methyl-2-[1-(phenylthio)ethyl]-1-cyclohexanone (2b): 0.38 g (9.6 mmol) of potassium hydride, 1.07 g (9.6 mmol) of 2-methylcyclohexanone (**1**), 12.8 ml (12.8 mmol) of a $ZnCl_2$ solution, and 1.98 g (11.5 mmol) of α -chloroethyl phenyl sulfide (**3b**) were allowed to react to yield 1.58 g (66%) of **2b**. — $R_f = 0.18$ (diethyl ether/petroleum ether, 1:10). — IR (neat): $\tilde{\nu} = 3060$, 3040 (aromat. C—H), 1690 (C=O), 1570 (C=C aromat.), 740 and 690 cm^{-1} (δ_{CH} monosubst. aromat.). — 1H NMR ($CDCl_3$): $\delta = 1.10$ and 1.17 (2 s; 3H, C—CH₃), 1.19 and 1.32 (2 d, $J = 7$ Hz; 3H, CH—CH₃), 1.41 – 2.63 (m; 8H, CH₂), 3.67 and 3.70 (2 q, $J = 7$ Hz; 1H, C-1'-CH), 7.18 – 7.55 (m; 5H, C₆H₅). — ^{13}C NMR ($CDCl_3$): $\delta = 16.87$

and 17.46 (C-2-CH₃), 19.08 and 20.66 (C-1'-CH₃), 20.62 and 20.63 , 27.21 and 27.32 , 36.16 and 36.42 , 38.75 and 38.95 (CH₂), 49.08 and 49.53 (C-1'), 53.01 and 53.17 (C-2), 127.03 , 127.21 , 128.96 , 128.99 , 132.11 and 132.68 (aromat. CH), 135.70 and 135.79 (aromat. C), 213.74 and 214.01 (C=O); signals of both diastereomers. — MS (70 eV): m/z (%) = 248 (40) [M^+], 139 (100) [$M^+ - SPh$], 69 (74) [$C_4H_5O^+$].

$C_{15}H_{20}OS$ (248.3) Calcd. C 72.52 H 8.12
Found C 72.63 H 8.17

2-Methyl-2-[1-(phenylthio)butyl]-1-cyclohexanone (2c): 0.57 g (14.2 mmol) of potassium hydride, 1.59 g (14.2 mmol) of 2-methylcyclohexanone (**1**), 17 ml (17 mmol) of a $ZnCl_2$ solution, and 2.85 g (14.2 mmol) of α -chlorobutyl phenyl sulfide (**3c**) were allowed to react to yield 2.55 g (65%) of **2c**. — $R_f = 0.23$ (diethyl ether/petroleum ether, 1:20). — IR (neat): $\tilde{\nu} = 3060$ and 3040 (aromat. CH), 1700 (C=O), 1580 (aromat. C=C), 740 and 690 cm^{-1} (δ_{CH} monosubst. aromat.). — 1H NMR ($CDCl_3$): $\delta = 0.88$ and 0.94 (2 t, $J = 7$ Hz; 3H, CH₂—CH₃), 1.10 and 1.16 (2 s; 3H, C-2-CH₃), 1.20 – 2.50 (m; 12H, CH₂), 3.50 and 3.51 (2 t, $J = 2.7$ Hz; 1H, C-1'-CH), 7.13 – 7.57 (m; 5H, C₆H₅). — ^{13}C NMR ($CDCl_3$): $\delta = 13.92$ and 14.00 (CH₂—CH₃), 19.07 and 21.85 (C-2-CH₃), 20.62 and 20.72 , 21.51 and 21.59 , 34.57 and 34.76 , 39.05 and 39.19 , 26.74 and 27.63 , 35.03 and 38.08 (CH₂), 54.45 and 54.95 (C-2), 56.31 and 56.35 (C-1'), 126.42 and 126.72 , 128.85 and 128.93 , 131.19 and 131.75 (aromat. CH), 137.78 and 137.82 (aromat. C), 214.15 and 214.84 (C=O); signals of both diastereomers. — MS (70 eV): m/z (%) = 276 (30) [M^+], 167 (80) [$M^+ - SPh$], 41 (100) [$C_3H_5^+$].

$C_{17}H_{24}OS$ (276.4) Calcd. C 73.86 H 8.75
Found C 73.96 H 8.70

Ethyl 4-(1-Methyl-2-oxocyclohexyl)-4-(phenylthio)butanoate (2d): 0.40 g (10 mmol) of potassium hydride, 1.12 g (10 mmol) of 2-methylcyclohexanone (**1**), 13 ml (13 mmol) of a $ZnCl_2$ solution, and 2.58 g (10 mmol) of ethyl 4-chloro-4-(phenylthio)butanoate (**3d**) were allowed to react to yield 1.64 g (49%) of **2d**. — $R_f = 0.38$ (diethyl ether/petroleum ether, 1:4). — IR (neat): $\tilde{\nu} = 3040$ (aromat. CH), 1720 and 1700 (C=O), 745 and 690 cm^{-1} (δ_{CH} monosubst. aromat.). — 1H NMR ($CDCl_3$): $\delta = 1.13$ and 1.19 (2 s; 3H, C—CH₃), 1.23 and 1.26 (2 t, $J = 7$ Hz; 3H, CH₂—CH₃), 1.39 – 2.88 (m; 12H, CH₂), 3.59 and 3.81 (2 dd, $J^1 = 11$ Hz, $J^2 = 3$ Hz; 1H, C—CH), 4.09 and 4.14 (q, $J = 7$ Hz; 2H, CH₂—CH₃), 7.18 – 7.58 (m; 5H, C₆H₅). — ^{13}C NMR ($CDCl_3$): $\delta = 14.22$ and 14.52 (CH₂—CH₃), 18.93 and 21.35 (C-2-CH₃), 20.69 , 20.71 , 26.98 , 27.43 , 27.50 , 27.63 , 31.83 , 32.50 , 35.28 , 38.15 , 39.03 and 39.12 (CH₂), 54.37 and 54.71 (C-2), 54.82 and 55.33 (C-1'), 60.36 and 60.39 (O—CH₂), 126.69 , 126.77 , 128.98 , 129.03 , 131.19 and 131.39 (aromat. CH), 137.15 and 137.28 (aromat. C), 173.18 and 173.37 (O—C=O), 213.66 and 214.61 (C=O); signals of both diastereomers.

$C_{19}H_{26}O_3S$ (334.5) Calcd. C 68.22 H 7.83
Found C 68.05 H 7.77

Ethyl 3-(1-Methyl-2-oxocyclohexyl)-3-(phenylthio)propanoate (2e): 0.40 g (10 mmol) of potassium hydride, 1.12 g (10 mmol) of 2-methylcyclohexanone (**1**), 13 ml (13 mmol) of a $ZnCl_2$ solution, and 2.45 g (10 mmol) of ethyl 3-chloro-3-(phenylthio)propanoate (**3e**) were allowed to react to yield 0.69 g (22%) of **2e**. — $R_f = 0.43$ (diethyl ether/petroleum ether, 1:4). — 1H NMR ($CDCl_3$): $\delta = 1.08$ and 1.18 (2 s; 3H, C—CH₃), 1.16 and 1.20 (2 t, $J = 7$ Hz; 3H, CH₂CH₃), 1.20 – 2.84 (m; 10H, CH₂), 3.80 – 4.19 (m; 3H, C—CH, CH₂), 7.14 – 7.63 (m; 5H, C₆H₅). — ^{13}C NMR ($CDCl_3$): $\delta = 14.09$ and 14.11 (CH₂—CH₃), 18.88 and 20.79 (C-2-CH₃), 20.43 and 20.71 , 27.54 and 27.23 , 37.89 and 36.23 , 27.79 and 38.09 , 38.95 and 39.09 (CH₂), 51.25 and 51.43 (C-1'), 53.58 and 54.08 (C-2), 60.81 and 60.82 (OCH₂—CH₃), 127.16 and 127.37 , 128.91 and 128.97 , 132.05 and

132.48 (aromat. CH), 135.70 and 135.78 (aromat. C), 171.75 and 171.83 (O=C=O), 213.17 and 214.29 (C=O); signals of both diastereomers. — MS (70 eV): m/z (%) = 320 (50) [M^+], 211 (30) [$M^+ - SPh$], 165 (100) [$M^+ - C_2H_5O$, — SPh].

$C_{18}H_{24}O_3S$ (320.5) Calcd. C 67.47 H 7.55
Found C 67.27 H 7.55

2-Methyl-2-[phenyl(phenylthio)methyl]-1-cyclohexanone (2f): 0.67 g (16.7 mmol) of potassium hydride, 1.87 g (16.7 mmol) of 2-methylcyclohexanone (**1**), 21.7 ml (21.7 mmol) of a $ZnCl_2$ solution, and 3.92 g (16.7 mmol) of α -chlorobenzyl phenyl sulfide (**3f**) were allowed to react to yield 2.67 g (52%) of **2f**. — R_f = 0.28 (diethyl ether/petroleum ether, 1:20). — 1H NMR ($CDCl_3$): δ = 1.01 and 1.11 (2 s; 3H, C- CH_3), 1.23–2.79 (m; 8H, CH_2), 4.72 (s; 1H, C-1'-CH), 7.03–7.50 (m; 10H, C_6H_5). — ^{13}C NMR ($CDCl_3$): δ = 19.30 and 23.85 (C-2- CH_3), 20.59, 21.15, 25.04, 28.13, 33.92, 38.52, 38.81 and 39.09 (CH_2), 53.28 and 53.99 (C-2), 57.24 and 59.86 (C-1'), 126.80, 126.85, 127.12, 127.47, 127.77, 127.90, 128.65, 128.73, 129.93, 130.23, 130.93 and 131.65 (aromat. CH), 135.62, 135.74, 138.16 and 139.49 (aromat. C), 213.98 and 214.71 (C=O); signals of both diastereomers. — MS (70 eV): m/z (%) = 310 (6) [M^+], 56 (100) [$C_4H_8^+$].

$C_{20}H_{22}OS$ (310.5) Calcd. C 77.38 H 7.14
Found C 77.16 H 7.18

2-Methyl-2-[2-methyl-1-(phenylthio)propyl]-1-cyclohexanone (2g): 1.00 g (24.9 mmol) of potassium hydride, 2.79 g (24.9 mmol) of 2-methylcyclohexanone (**1**), 32.4 ml (32.4 mmol) of a $ZnCl_2$ solution, and 5.00 g (24.9 mmol) of α -chloroisobutyl phenyl sulfide (**3g**) were allowed to react to afford 4.47 g (65%) of **2g**. — R_f = 0.31 (diethyl ether/petroleum ether, 1:20). — IR (neat): $\tilde{\nu}$ = 3060, 3040 (aromat. CH), 1695 (C=O), 1570 (C=C), 740 and 695 cm^{-1} (δ_{CH} monosubst. aromat.). — 1H NMR ($CDCl_3$): δ = 1.05, 1.06, 1.10 and 1.11 [4 d, J_1 = 6.4 Hz, J_2 = 6.9 Hz; 6H, $CH(CH_3)_2$], 1.19 (s; 3H, C- CH_3), 1.20–2.52 [m; 9H, CH_2 and $CH(CH_3)_2$], 3.69 and 3.70 (2 d, J = 10 Hz; 1H, (C-1'-CH), 7.10–7.58 (m; 5H, C_6H_5). — ^{13}C NMR ($CDCl_3$): δ = 19.43 and 20.37 (C-2- CH_3), 20.57 and 24.58, 22.55 and 24.66 [$CH(CH_3)_2$], 20.73, 20.77, 26.70, 27.59, 34.92, 38.73, 39.05 and 39.44 (CH_2), 29.84 and 30.49 [$CH(CH_3)_2$], 55.27 and 55.87 (C-2), 61.93 and 61.98 (C-1'), 126.26, 126.52, 128.84, 128.90, 131.10 and 131.49 (aromat. CH), 138.25 and 138.35 (aromat. C), 213.89 and 214.99 (C=O); signals of both diastereomers. — MS (70 eV): m/z (%) = 276 (20) [M^+], 167 (100) [$M^+ - SPh$].

$C_{17}H_{24}OS$ (276.4) Calcd. C 73.86 H 8.75
Found C 73.69 H 8.68

2-Methyl-2-[1-methyl-1-(phenylthio)ethyl]-1-cyclohexanone (2h): 0.71 g (17.7 mmol) of potassium hydride, 1.98 g (17.7 mmol) of 2-methylcyclohexanone (**1**), 23 ml (23 mmol) of a $ZnCl_2$ solution, and 3.31 g (17.7 mmol) of α -chloroisopropyl phenyl sulfide (**3h**) were allowed to react to yield 1.82 g (39%) of **2h**. — R_f = 0.23 (diethyl ether/petroleum ether, 1:20). — IR (neat): $\tilde{\nu}$ = 3050, 3035 (aromat. CH), 1690 (C=O), 1570 (C=C), 745 and 690 cm^{-1} (δ_{CH} monosubst. aromat.). — 1H NMR ($CDCl_3$): δ = 1.24 (s; 3H, C-2- CH_3), 1.32 and 1.36 [2 s; 6H, $C(CH_3)_2$], 1.54–2.60 (m; 8H, CH_2), 7.24–7.60 (m; 5H, C_6H_5). — ^{13}C NMR ($CDCl_3$): δ = 19.78 (C-2- CH_3), 25.70 and 25.75 [$C(CH_3)_2$], 20.69, 24.28, 33.80 and 40.44 (CH_2), 54.35 (C-2), 55.95 [$C(CH_3)_2$], 128.35, 128.72 and 138.33 (aromat. CH), 132.06 (aromat. C), 214.60 (C=O). — MS (70 eV): m/z = 262 (5) [M^+], 153 (38) [$M^+ - SPh$], 43 (100) [$C_3H_7^+$].

$C_{16}H_{22}OS$ (262.4) Calcd. C 73.23 H 8.45
Found C 73.31 H 8.63

2-Methyl-2-[1-(phenylthio)ethyl]-1-cyclopentanone (5a): 0.36 g (9.0 mmol) of potassium hydride, 0.88 g (9.0 mmol) of 2-methylcyclopentanone (**4**), 11.7 ml (11.7 mmol) of a $ZnCl_2$ solution, and

1.55 g (9.0 mmol) of α -chloroethyl phenyl sulfide (**3b**) were allowed to react to yield 1.33 g (63%) of **5a**. — R_f = 0.20 (diethyl ether/petroleum ether, 1:10). — IR (neat): $\tilde{\nu}$ = 3040 (aromat. CH), 1730 (C=O), 1580 cm^{-1} (C=C). — 1H NMR ($CDCl_3$): δ = 1.05 and 1.27 (2 s; 3H, C- CH_3), 1.20 and 1.34 (2 d, J = 7 Hz; 3H, CH- CH_3), 1.72–2.52 (m; 6H, CH_2), 3.34 and 3.46 (2 q, J = 7 Hz, 1H, C-1'-CH), 7.15–7.48 (m; 5H, C_6H_5). — ^{13}C NMR ($CDCl_3$): δ = 17.91 and 18.14 (C-2- CH_3), 18.69, 18.79, 31.10, 32.39, 38.74 and 38.83 (CH_2), 21.46 and 23.03 (CH- CH_3), 50.44 and 50.71 (C-1'), 52.72 and 52.87 (C-2), 126.75, 127.13, 128.87, 129.91, 131.66 and 132.34 (aromat. C-H), 135.42 and 135.62 (aromat. C), 221.38 and 221.83 (C=O); signals of both diastereomers.

$C_{14}H_{18}OS$ (234.4) Calcd. C 71.75 H 7.74
Found C 71.78 H 7.73

2-Methyl-2-[1-(phenylthio)butyl]-1-cyclopentanone (5b): 0.34 g (8.5 mmol) of potassium hydride, 0.85 g (8.5 mmol) of 2-methylcyclopentanone (**4**), 11.1 ml (11.1 mmol) of a $ZnCl_2$ solution, and 1.70 g (8.5 mmol) of α -chlorobutyl phenyl sulfide (**3c**) were allowed to react to yield 1.67 g (65%) of **5b**. — R_f = 0.16 (diethyl ether/petroleum ether, 1:10). — IR (neat): $\tilde{\nu}$ = 3040 (aromat. CH), 1735 (C=O), 1580 cm^{-1} (C=C). — 1H NMR ($CDCl_3$): δ = 0.70–0.96 (m; 3H, [CH_2] $_2CH_3$), 1.06 and 1.16 (2 s; 3H, C-2- CH_3), 1.20–2.60 (m; 10H, CH_2), 3.10–3.34 (m; 1H, C-1'-CH), 7.10–7.60 (m; 5H, C_6H_5). — ^{13}C NMR ($CDCl_3$): δ = 13.78 and 13.90 (C-2- CH_3), 21.41 and 23.27 (CH_3), 18.35, 18.95, 20.39, 21.22, 31.64, 33.15, 34.64, 35.94, 38.63 and 38.90 (CH_2), 53.42 and 54.78 (C-2), 56.40 and 57.08 (C-1'), 126.23, 126.59, 128.73, 128.82, 130.62, 131.29, 137.20 and 137.99 (aromat. C), 220.96 and 222.13 (C=O); signals of both diastereomers. — MS (70 eV): m/z (%) = 262 (30) [M^+], 153 (57) [$M^+ - SPh$], 55 (100) [$C_4H_7^+$].

$C_{16}H_{22}OS$ (262.4) Calcd. C 73.23 H 8.45
Found C 73.29 H 8.40

Ethyl 4-(1-Methyl-2-oxocyclopentyl)-4-(phenylthio)butanoate (5c): 0.20 g (5.0 mmol) of potassium hydride, 0.49 g (5.0 mmol) of 2-methylcyclopentanone (**4**), 6.5 ml (6.5 mmol) of a $ZnCl_2$ solution, and 1.29 g (5.0 mmol) of ethyl 4-chloro-4-(phenylthio)butanoate (**3d**) were allowed to react to yield 0.85 g (53%) of **5c**. — R_f = 0.27 (diethyl ether/petroleum ether, 1:2). — IR (neat): $\tilde{\nu}$ = 3040 (aromat. CH), 1730 (C=O), 1710 cm^{-1} (C=O). — 1H NMR ($CDCl_3$): δ = 1.10 and 1.19 (2 s; 3H, C-2- CH_3), 1.18 and 1.22 (2 t, J = 7 Hz; 3H, CH_2-CH_3), 1.56–2.85 (m; 10H, CH_2), 3.22 and 3.26 (2 dd, J^1 = 12 Hz, J^2 = 3 Hz; 1H, C-1'-CH), 4.02 and 4.08 (2 q, J = 7 Hz; 2H, O- CH_2-CH_3), 7.13–7.49 (m; 5H, C_6H_5). — ^{13}C NMR ($CDCl_3$): δ = 14.16 and 14.19 (CH_2-CH_3), 18.35, 18.97, 27.56, 28.51, 31.62, 31.76, 32.71, 33.02, 38.59 and 38.78 (CH_2), 21.31 and 23.05 (C-2- CH_3), 53.44 and 54.68 (C-2), 55.79 and 56.48 (C-1'), 60.32 and 60.38 (O- CH_2), 126.55, 126.83, 128.91, 128.99, 130.69, 131.20, 136.54 and 137.26 (aromat. C), 173.50 and 173.14 (O-C=O), 220.84 and 221.94 (C=O); signals of both diastereomers. — MS (70 eV): m/z (%) = 320 (5) [M^+], 211 (20) [$M^+ - SPh$], 98 (100) [$C_6H_{10}O^+$].

$C_{18}H_{24}O_3S$ (320.5) Calcd. C 67.47 H 7.55
Found C 67.33 H 7.61

2-Methyl-2-[(3E)-4-methyl-1-(phenylthio)-3-octenyl]-1-cyclopentanone (5d): 0.26 g (6.4 mmol) of potassium hydride, 0.63 g (6.4 mmol) of 2-methylcyclopentanone (**4**), 8.3 ml (8.3 mmol) of a $ZnCl_2$ solution, and 1.72 g (6.4 mmol) of 1-chloro-4-methyl-3-octenyl phenyl sulfide (**3i**) were allowed to react to yield 0.68 g (32%) of **5d**. — R_f = 0.25 (diethyl ether/petroleum ether, 1:10). — IR (neat): $\tilde{\nu}$ = 3040 (aromat. CH), 1740 (C=O), 1585 cm^{-1} (C=C). — 1H NMR ($CDCl_3$): δ = 0.85 (t, J = 7 Hz; 3H, CH_2-CH_3), 1.07 and 1.18 (2 s; 3H, C-2- CH_3), 1.00–1.40 (m; 4H, [CH_2] $_2CH_3$), 1.58 [d; 4J = 2 Hz; 3H, $C(CH_3)=CH$], 1.66–2.94 (m; 10H, CH_2),

3.23–3.36 (dd, $J_1 = 4$ Hz, $J_2 = 8$ Hz; 1H, C-1'-CH), 5.22 [tq, $J_1 = 2$ Hz, $^4J = 2$ Hz; 1H, CH=C(CH₃)], 7.00–7.50 (m; 5H, C₆H₅).

C₂₁H₃₀OS (330.6) Calcd. C 76.31 H 9.15
Found C 76.20 H 9.01

2-Methyl-2-[1-(phenylthio)-4-pentynyl]-1-cyclopentanone (5e): 0.40 g (10.0 mmol) of potassium hydride, 0.98 g (10.0 mmol) of 2-methylcyclopentanone (**4**), 12.0 ml (12 mmol) of a ZnCl₂ solution, and 2.32 g (11.0 mmol) of 1-chloro-4-pentynyl phenyl sulfide (**3j**) were allowed to react to yield 1.55 g (57%) of **5e**. — $R_f = 0.21$ (diethyl ether/petroleum ether, 1:10). — IR (neat): $\tilde{\nu} = 3280$ (C≡C-H), 3040 (aromat. CH), 2100 (C≡C), 1740 (C=O), 1585 cm⁻¹ (aromat. C=C). — ¹H NMR (CDCl₃): $\delta = 1.02$ and 1.10 (2 s; 3H, C-2-CH₃), 1.47–2.57 (m; 10H, CH₂), 1.83 and 1.91 (2 t, $^4J = 2$ Hz; 1H, C≡C-H), 3.29 and 3.35 (2 dd, $J_1 = 3$ Hz, $J_2 = 8$ Hz; 1H, C-1'-CH), 6.91–7.47 (m; 5H, C₆H₅). — ¹³C NMR (CDCl₃): $\delta = 16.36$, 17.06, 18.31, 18.84, 31.43, 31.97, 32.27, 33.14, 38.54, 38.77 (CH₂), 21.10 and 22.95 (C-2-CH₃), 53.28 and 54.55 (C-2), 55.30 and 56.11 (C-1'), 68.91 and 69.13 (C≡C-H), 83.43 and 83.63 (C≡C-H), 126.50, 126.80, 128.82, 128.91, 130.84 and 131.30 (aromat. CH), 136.40 and 137.16 (aromat. C), 220.63 and 221.74 (C=O); signals of both diastereomers.

C₁₇H₂₀OS (272.2) Calcd. C 74.94 H 7.41
Found C 74.86 H 7.49

Desulfurization of the β-(Phenylthio) Ketones 2 and 5 with Raney Nickel. — *α,α-Disubstituted Cyclopentanones 6 and 2-Butyl-2-methyl-1-cyclohexanone*. — *General Procedure*: 50 g of Raney nickel W-2^[19] was rinsed with 100-ml portions of H₂O, until all alkali hydroxide had been removed. The metal was washed ten times with ethanol (96%, 50 ml each) and three times with anhydrous ethanol (50 ml each). The Raney nickel prepared according to this procedure could be stored in ethanol under argon for four months at 0°C without any significant loss of activity.

10 g of Raney nickel was stirred with 20 ml of anhydrous ethanol at room temp. To this suspension a solution of 5 mmol of the β-(phenylthio) ketone **2** or **5** in 5 ml of ethanol was added. According to a TLC analysis the desulfurization was completed within 10–15 min. The suspension was filtered through a short pad of silica gel in order to remove the Raney nickel. The silica gel was flushed with 200 ml of diethyl ether and immediately after this operation poured into 100 ml of 2 N HCl since the diethyl ether contaminated Raney nickel/silica gel mixture proved to be pyrophoric. The organic layers were combined and the solvent was removed at 20°C/12 Torr. The residue, i.e. the crude ketones **6**, was purified by silica gel chromatography using diethyl ether/petroleum ether (1:10) as the eluent.

2-Butyl-2-methyl-1-cyclohexanone: 0.56 g (2 mmol) of the β-(phenylthio) ketone **2c** was treated with 4 g of Raney nickel to afford 0.31 g (92%) of 2-butyl-2-methyl-1-cyclohexanone as a colorless oil. — $R_f = 0.29$ (diethyl ether/petroleum ether, 1:10). — IR (neat): $\tilde{\nu} = 1735$ cm⁻¹ (C=O). — ¹H NMR (CDCl₃): $\delta = 0.87$ (t, $J = 8$ Hz; 3H, CH₃), 1.04 (s; 3H, C-2-CH₃), 1.10–2.00 (m; 12H, CH₂), 2.25–2.45 (m; 2H, CO-CH₂). — ¹³C NMR (CDCl₃): $\delta = 14.03$ (CH₃), 22.65 (C-2-CH₃), 21.21, 23.49, 26.08, 27.65, 37.40, 38.79, 39.60 (CH₂), 48.55 (C-2), 214.75 (C=O).

C₁₁H₂₀O (168.2) Calcd. C 78.50 H 11.99
Found C 78.39 H 11.84

2-Butyl-2-methyl-1-cyclopentanone (6b): 0.71 g (2.7 mmol) of the β-(phenylthio) ketone **5b** was treated with 5 g of Raney nickel to afford 0.37 g (89%) of the ketone **6b** as a colorless oil. — $R_f = 0.36$ (diethyl ether/petroleum ether, 1:10). — IR (neat): $\tilde{\nu} = 1730$ cm⁻¹ (C=O). — ¹H NMR (CDCl₃): $\delta = 0.89$ (t, $J = 8$ Hz; 3H, CH₃),

0.98 (s; 3H, C-2-CH₃), 1.15–1.55 and 1.75–2.02 (2 m; 10H, CH₂), 2.16–2.38 (m; 2H, C-5-CH₂).

C₁₀H₁₈O (154.3) Calcd. C 77.87 H 11.76
Found C 77.84 H 11.81

Ethyl 4-(1-Methyl-2-oxocyclopentyl)butanoate (6c): 0.51 g (1.6 mmol) of the β-(phenylthio) ketone **5c** was treated with 3 g of Raney nickel to afford 0.29 g (86%) of the ketone **6c** as a colorless oil. — $R_f = 0.35$ (diethyl ether/petroleum ether, 1:2). — IR (neat): $\tilde{\nu} = 1720$ and 1705 cm⁻¹ (C=O). — ¹H NMR (CDCl₃): $\delta = 1.01$ (s; 3H, C-2-CH₃), 1.25 (t, $J = 7$ Hz; 3H, CH₂-CH₃), 1.35–2.22 (m; 10H, CH₂), 2.28 (t, $J = 7$ Hz; 2H, CH₂-C=O), 4.11 (q, $J = 7$ Hz; 2H, O-CH₂-CH₃). — ¹³C NMR (CDCl₃): $\delta = 14.26$ (CH₂-CH₃), 18.72, 19.89, 34.58, 35.55, 35.99, and 37.60 (CH₂), 21.65 (C-2-CH₃), 48.19 (C-2), 60.29 (O-CH₂), 173.36 (O-C=O), 223.25 (C=O). — MS (70 eV): m/z (%) = 212 (25) [M⁺], 98 (100) [C₆H₁₀O⁺].

C₁₂H₂₀O₃ (212.3) Calcd. C 67.89 H 9.50
Found C 67.89 H 9.52

Desulfurization of the β-(Phenylthio) Ketone 5d with Lithium in Diethylamine. — *2-Methyl-2-[(3E)-4-methyl-3-octenyl]-1-cyclopentanone (6d)*: In a 50-ml two-necked flask equipped with a dropping funnel containing a built-in sintered glass disk at the bottom and a dry ice condenser on the top, 42 mg (6 mmol) of lithium was deposited on the sintered glass disk in an inert atmosphere. At –20°C ethylamine was placed into the flask via a gas inlet tube. After 25 ml of ethylamine had condensed in the flask insertion was stopped and a solution of 0.53 g (1.6 mmol) of the β-(phenylthio) ketone **5d** in 3 ml of diethyl ether was added. The solution was kept under reflux at ≈20°C. The lithium was slowly dissolved by the condensing ethylamine and a blue solution of lithium in ethylamine dropped continuously into the reaction mixture. The addition of the lithium solution was stopped when the reaction mixture retained its dark blue color for more than 10 s. Then 0.54 g (10 mmol) of NH₄Cl and 20 ml of diethyl ether were added and the ethylamine was removed at 20–25°C within 20–30 min. Subsequently 30 ml of H₂O and 2 N HCl were added until the pH of the mixture was adjusted to 6. The layers were separated and the aqueous layer was extracted twice with diethyl ether (15 ml each). The combined organic layers were extracted twice with aqueous sodium carbonate, twice with H₂O (10 ml each) and then dried with MgSO₄. The solvent was removed in vacuo (20°C/12 Torr) and the crude ketone **6d** purified by silica gel chromatography (eluent: diethyl ether/petroleum ether, 1:10) to yield 0.29 g (82%) of **6d** as a colorless oil. — $R_f = 0.23$. — IR (neat): $\tilde{\nu} = 3050$ (C=C-H), 1735 (C=O), 1660 cm⁻¹ (C=C). — ¹H NMR (CDCl₃): $\delta = 0.88$ (t, $J = 7$ Hz; 3H, C-7'-CH₃), 1.02 (s; 3H, C-2-CH₃), 1.60 (d, $^4J = 2$ Hz; 3H, C-4'-CH₃), 1.70–2.04 and 2.10–2.40 (2 m; 16H, CH₂), 5.07 (tq, $J = 7$ Hz, $^4J = 2$ Hz; 1H, C-3'-CH). — ¹³C NMR (CDCl₃): $\delta = 14.04$ (C-7'-CH₃), 15.81 (C-2-CH₃), 22.35 (C-4'-CH₃), 18.75, 29.92, 30.15, 31.76, 35.69, 36.73, 37.77 and 39.36 (CH₂), 48.28 (C-2), 123.74 (C(CH₃)=CH), 135.67 (C(CH₃)=CH), 223.28 (C=O).

C₁₅H₂₆O (222.4) Calcd. C 81.02 H 11.79
Found C 81.05 H 11.68

* Dedicated to Professor Ulrich Schöllkopf on the occasion of his 65th birthday.

[1] For part I see: U. Groth, T. Köhler, T. Taapken, *Tetrahedron* **1991**, *47*, 7583.

[2] Reviews: [2a] D. Caine, R. L. Augustine, *Carbon-Carbon Bond Formation*, vol. I, Marcel Dekker, New York, **1979**, p. 85. — [2b] J. A. March, *Advanced Organic Chemistry*, 3rd ed., Wiley, New York, **1985**, p. 411. — [2c] H. O. House, *Modern Synthetic Reactions*, 2nd ed., W. A. Benjamin, Menlo Park, CA, **1972**, Chapters 9–11.

- [3] ^[3a] H. O. House, M. Gall, H. D. Olmstead, *J. Org. Chem.* **1971**, *36*, 2361. — ^[3b] G. H. Posner, J. J. Sterling, C. E. Whitten, C. M. Lentz, D. J. Brunelle, *J. Am. Chem. Soc.* **1975**, *97*, 107.
- [4] For metalated dimethylhydrazones, see: ^[4a] E. J. Corey, D. Enders, *Chem. Ber.* **1978**, *111*, 1337. — For metalated oximes, see: ^[4b] W. G. Kofron, M. K. Yeh, *J. Org. Chem.* **1976**, *41*, 439. — For metalated ketimines, see: ^[4c] T. Cuvigny, M. Larcheveque, H. Normant, *Liebigs Ann. Chem.* **1975**, *719*. — ^[4d] Review: D. Enders in J. D. Morrison: *Asymmetric Synthesis*, Academic Press, New York **1984**, vol. 3, p. 275.
- [5] ^[5a] E. I. Negishi, M. J. Idacavage, *Tetrahedron Lett.* **1979**, 845. — ^[5b] E. I. Negishi, R. A. John, *J. Org. Chem.* **1983**, *48*, 4098.
- [6] ^[6a] H. O. House, L. J. Czuba, M. Gall, H. D. Olmstead, *J. Org. Chem.* **1969**, *34*, 2324. — ^[6b] J. K. Rasmussen, *Synthesis* **1977**, *91*.
- [7] ^[7a] G. Stork, P. F. Hudrlik, *J. Am. Chem. Soc.* **1968**, *90*, 4462. — ^[7b] G. Stork, P. F. Hudrlik, *ibid.* **1968**, *90*, 4464.
- [8] ^[8a] H. O. House, B. M. Trost, *J. Org. Chem.* **1965**, *30*, 2502. — ^[8b] H. O. House, D. S. Crumrine, A. Y. Teranishi, H. D. Olmstead, *J. Am. Chem. Soc.* **1973**, *95*, 3310.
- [9] ^[9a] P. F. Hudrlik, A. M. Hudrlik, T. Yimenu, M. A. Waugh, G. Nagendrappa, *Tetrahedron* **1988**, *44*, 3791. — ^[9b] R. M. Williams, M.-N. Im, *J. Am. Chem. Soc.*, **1991**, *113*, 9276.
- [10] T. Mukaiyama, *Angew. Chem.* **1977**, *89*, 858; *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 817.
- [11] ^[11a] T. H. Chan, I. Paterson, J. Pinsonnault, *Tetrahedron Lett.* **1977**, 4183. — ^[11b] M. T. Reetz, W. F. Maier, *Angew. Chem.* **1978**, *90*, 50; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 48. — ^[11c] M. T. Reetz, I. Chatziiosifidis, U. Löwe, W. F. Maier, *Tetrahedron Lett.* **1979**, 1427.
- [12] M. T. Reetz, S. Hüttenhain, P. Walz, U. Löwe, *Tetrahedron Lett.* **1979**, 4971.
- [13] ^[13a] I. Paterson, *Tetrahedron Lett.* **1979**, 1519. — ^[13b] See ref. ^[12].
- [14] ^[14a] I. Paterson, I. Fleming, *Tetrahedron Lett.* **1979**, 993. — ^[14b] I. Paterson, I. Fleming, *ibid.* **1979**, 995. — ^[14c] I. Paterson, I. Fleming, *ibid.* **1979**, 2179. — ^[14d] I. Paterson, *Tetrahedron* **1988**, *44*, 4207.
- [15] ^[15a] See ref. ^[12]. — ^[15b] M. T. Reetz, A. Giannis, *Synth. Comm.* **1981**, 315.
- [16] H. J. Reich, J. M. Renga, *J. Chem. Soc., Chem. Comm.* **1974**, 135.
- [17] C. A. Brown, *J. Org. Chem.* **1974**, *39*, 3913.
- [18] ^[18a] D. L. Tuleen, T. B. Stephens, *Chem. Ind.* **1966**, 1555. — ^[18b] B. M. Dilworth, M. A. McKervey, *Tetrahedron* **1986**, *42*, 3731.
- [19] For the preparation of W2-Raney Nickel, see: ^[19a] R. Mozingo, *Org. Synth.*, Coll. Vol. III, **1955**, p. 181. — ^[19b] R. E. Ireland, J. A. Marshall, *J. Org. Chem.* **1962**, *27*, 1615.
- [20] U. Groth, N. Richter, *Angew. Chem.* **1993**, in print.
- [21] U. Groth, N. Richter, *Synthesis* **1993**, in print.

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