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CHELATION AND NON-CHELATION CONTROLLED STEREOSELECTIVE REDUCTION OF α-METHOXY-α-PHENYLTHIO KETONES

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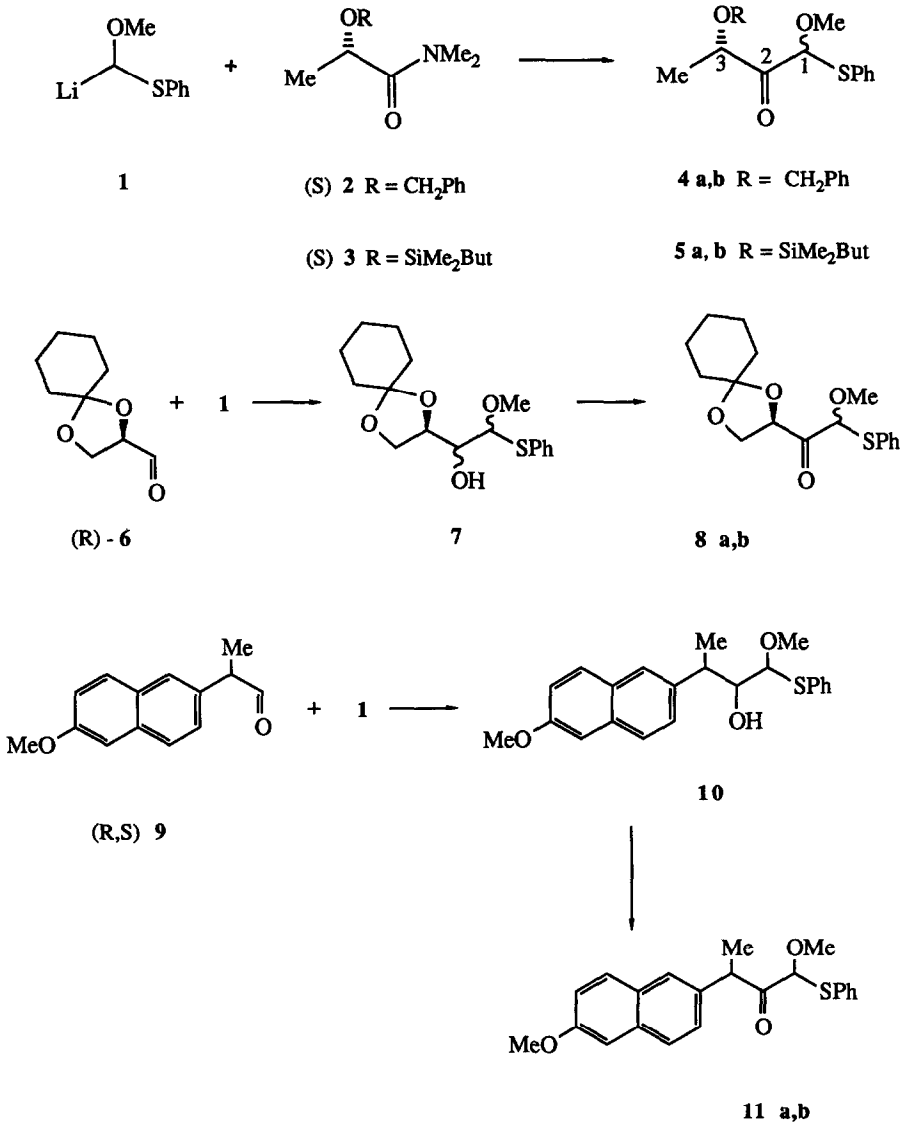
Abstract. A series of α-methoxy-α-phenylthio substituted ketones bearing an additional stereocenter in α'-position was prepared, and the reduction with chelating and non chelating reagents was studied. "Internal matched" pairs (leading to highly stereoselective processes) and "mismatched" pairs were identified, and possible transition structures were suggested.

The methoxy(phenylthio)methyl group is a versatile synthon for a variety of different classes of compounds including aldehydes, ketones, carboxylic acids, acetals, enolethers, furans, tetrahydrofurans, and allyl sulphides.[1] Notwithstanding this rich chemistry, its use as control element for stereoselective transformations has been very limited,[2] in spite of the presence of three ligands of well differentiated steric and stereoelectronic features. Enantiomerically pure alkoxy(alkylthio)methane derivatives, prepared from the "chiral pool", have been widely exploited as chiral auxiliaries by Eliel[3] for a number of stereocontrolled syntheses, that clearly showed the role of the oxygen- and sulphur-containing groups in determining the stereochemistry of the processes. In principle the insertion of the methoxy (phenylthio) methyl function into a chiral substrate could by-pass the synthesis of the chiral auxiliary and provide all the synthetic opportunities offered by this group. In this line we here report the preparation and the highly stereoselective reductions of some α-methoxy-α-phenylthio substituted ketones bearing an additional stereocenter in α'-position. Addition of methoxy(phenylthio)methyllithium **1**[1] to (S)-N,N-dimethyl-O-benzyllactamide **2** and to (S)-N,N-dimethyl-O-t-butyldimethylsilyllactamide **3** gave ketones **4a,b** and **5a,b**, respectively, as roughly 50:50 mixtures of epimers at C-1 (see Scheme 1 for numbering). Ketone **8a,b** was prepared by reaction of **1** with (R)-O,O-cyclohexylideneglyceraldehyde **6** to give **7** (as 37:31:19:13 mixture of four diastereoisomers) followed by oxidation. Ketone **11a,b** was obtained by the same route starting from racemic 2-(6-methoxy-2-naph-

Scheme 1.



thyl)-propionaldehyde **9**, that, when reacted with **1**, gave **10** as a 58:34:8 mixture of three isomers. Column chromatography allowed complete separation or substantial enrichment of the diastereoisomeric mixtures of the ketones. Yields, optical rotations (for enantiomerically pure materials) and diagnostic chemical shift values of HC-1 of

compounds **4a,b**, **5a,b**, **8a,b**, and **11a,b** are collected in Table 1.

Table 1. Synthesis of ketones **4a,b**, **5a,b**, **8a,b**, **11a,b**.

Ketone	Yield %	**a** isomer[a] $[\alpha]_D^{22}$ c	**a** isomer[a] δ[d]	**b** isomer[b] $[\alpha]_D^{22}$ c	**b** isomer[b] δ[d]
4a,b	83[e]	-167.4	5.55	+131.5	5.40
5a,b	90[e]	-150.6	5.65	+ 84.9	5.60
8a,b	79[f]	+169.0	5.55	- 69.0	5.40
11a,b	84[f]	-	5.05	-	5.10

[a]First eluted isomer. [b]Second eluted isomer. [c]All rotations are for c 1 solution in $CHCl_3$. [d] ^1H 300 MHz nmr, in ppm downfield from TMS. [e]From the amide. [f]From the alcohol.

The choice of the reducing species was made using the known[4] α-methoxy-α-phenylthio-acetophenone **12** (Scheme 2) as model compound. Among the reagents reported[5] to give chelation controlled reduction of α-alkoxy carbonyls, $Zn(BH_4)_2$ gave the best result affording only alcohol **13a**. Di-isobutylaluminum hydride (DIBAL-H) was the non-chelating[3] reducing agent of choice giving a 74:26 mixtures of **13a** and **13b**.

The exclusive formation of anti **13a** with chelating $Zn(BH_4)_2$ can be rationalized by Cram's cyclic model **14**[3] where the methoxy group is the chelating ligand and the phenylthio group acts as the "large" substituent.[3,6]

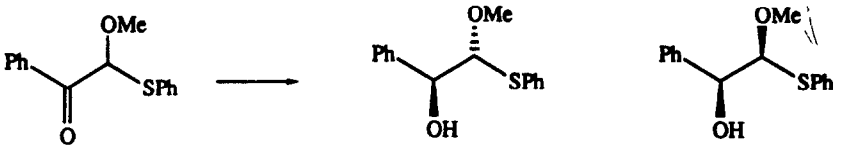
With non-chelating DIBAL-H the prevalent formation of the same isomer **13a** depends on the fact that transition structure **15** should be more favoured than **16**.

Indeed in the Felkin-Anh model[7] the "large" group is the one with the lowest lying σ^* orbital that in our case belongs to the C_α-S rather than to the C_α-O bond.[3,9]

We next examined the reduction of ketones **4a,b** and **5a,b**. In the former the carbonyl is flanked by two alkoxy groups both capable of chelation. In the latter only the alkoxy ligand can give rise to a substantial chelation.[10] The reaction of **4a,b** and **5a,b** with $Zu(BH_4)_2$ and DIBAL-H are summarized in Table 2. It must be noted that **4a** and **5a** (and hence **4b** and **5b**) feature the same configuration at C-1 as suggested by the optical rotations and by the chemical shift values of HC-1 (see Table 1), and as confirmed by

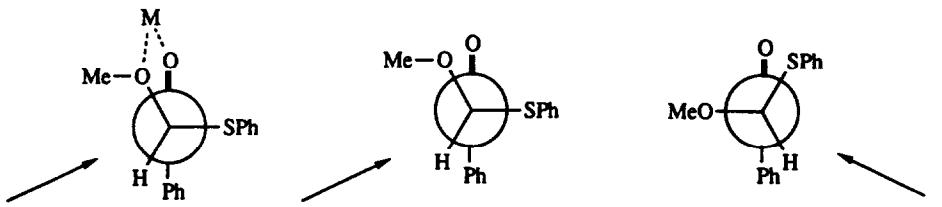
chemical correlation (see below).

Scheme 2.



12 **13a** **13b**

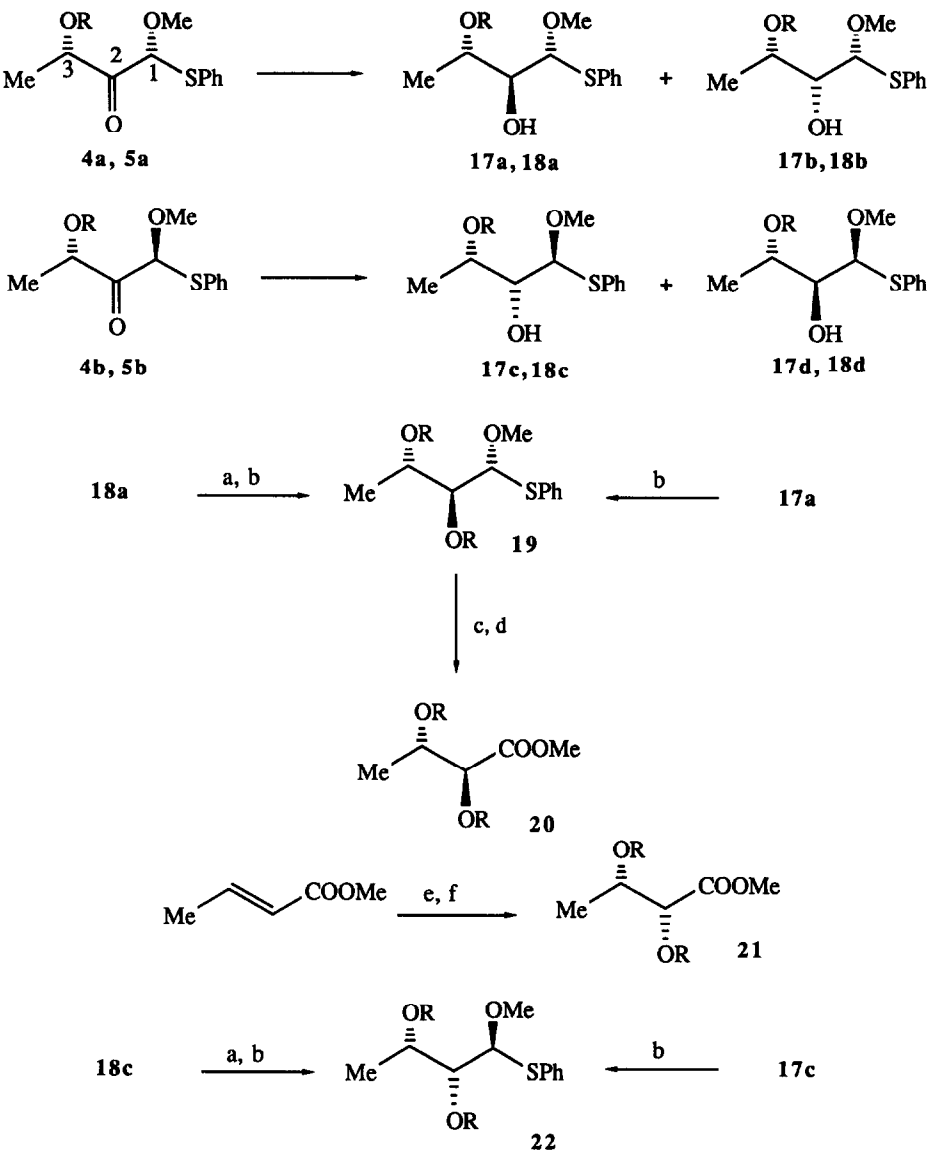
$Zn(BH_4)_2$	98	2
DIBAL-H	74	26



14 **15** **16**

The configurations of the various isomers of compounds **4**, **5**, **17**, and **18** are indicated in Scheme 3. $Zn(BH_4)_2$ reduction of **4a** and **5a** gave exclusively alcohols **17a** and **18a**, respectively. These two compounds have identical configuration as demonstrated by their conversion to **19** (that correlates also ketones **4a** and **5a**) and are likely to be generated by similar transition structure. The anti configuration at C-2 and C-3 was determined by transforming **19** into the anti-dialkoxy ester **20**, and showing that this compound was in a diastereoisomeric relationship with syn-ester **21**, obtained by osmylation of E-methylcrotonate followed by benzylation. The anti relative configuration at C-2 and C-3 could derive from a chelation controlled $Zn(BH_4)_2$ reduction that involves the carbonyl oxygen and the oxygen at C-3. However, as mentioned above, only the benzyloxy group of **4** and not the t-butyldimethylsilyloxy group of **5a** can be regarded as a chelating group. Therefore we think that is the methoxy group at C-1 the one involved in chelation for both **4a**[11] and **5a**, and thus we

Scheme 3.



4, 17, 19, 20, 21, 22 R = $PhCH_2$

5, 18 R = $SiMe_2Bu$-t

a) $Bu_4N^+F^-$ b) NaH, $PhCH_2Br$ c) CrO_3, H_2SO_4
d) CH_2N_2 e) OsO_4 f) Ag_2O, $PhCH_2Br$

Table 2. Reduction of **4a,b** and **5a,b** to **17a,b,c,d** and **18a,b,c,d**.

Ketone	Reducing agent	Alcohol	Yield %	Diastereoisomeric ratios a : b : c : d			
4a	$Zn(BH_4)_2$	**17**	90	⩾98	⩽2	-	-
4a	DIBAL-H	**17**	87	73	27	-	-
4b	$Zn(BH_4)_2$	**17**	91	-	-	78	22
4b	DIBAL-H	**17**	85	-	-	82	18
5a	$Zn(BH_4)_2$	**18**	91	⩾98	⩽2	-	-
5a	DIBAL-H	**18**	78	69	31	-	-
5b	$Zn(BH_4)_2$	**18**	89	-	-	63	37
5b	DIBAL-H	**18**	79	-	-	⩾98	⩽2

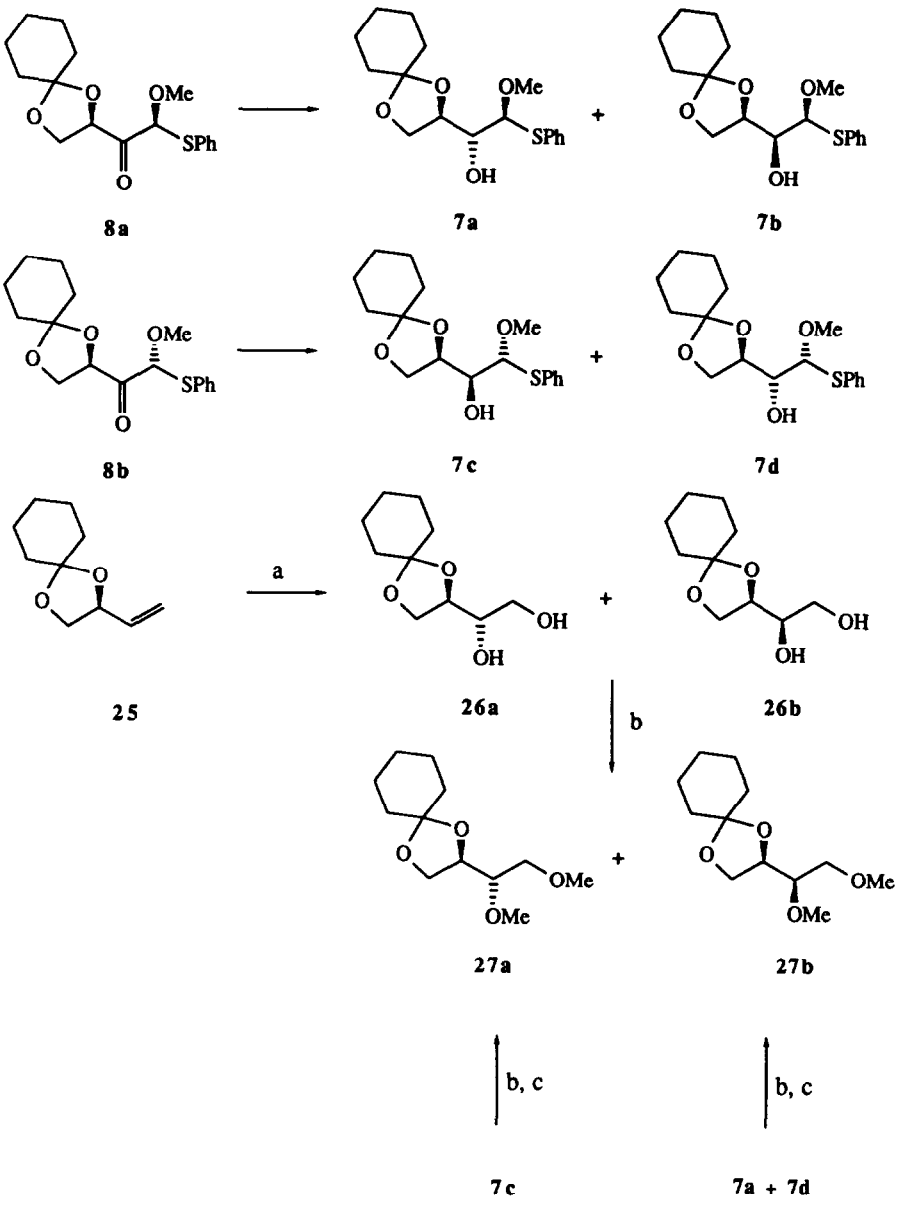
assign to **17a** and **18a** te 1,2-anti-2,3-anti configuration. On this basis we tentatively propose **23** as a possible transition structure for the highly diastereoselective $Zn(BH_4)_2$ reductions of **4a** and **5a**. In this model hydride attack occurs on the less hindered diastereoface of the carbonyl away from both the "large" phenylthio and alkoxy groups. In the DIBAL-H reductions the same isomers **17a** and **18a** predominate although with lower stereoselectivity.

In the absence of chelation the Felkin-Anh model should be operative: in ketones **4a** and **5a** the configuration of the two stereocenters[12] is such that when they adopt a Felkin-Ahn conformation the two large groups shield opposite diastereofaces of the carbonyl, and this results in the low diastereoselection of these reductions.

In the case of ketones **4b** and **5b** again both reductions gave the same products, namely **17c** and **18c**, as predominant isomers; chemical correlation with **22** (see Scheme 3) showed that **17c** and **18c** have the same configuration, and conversion of **22** to ester **21** demonstrated that they feature the 2,3-syn stereochemistry.

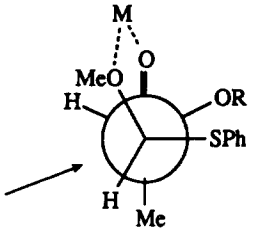
As for the extent of diastereoselection, the situation is reversed with respect to the reductions of ketones **4a** and **5a**. The chelation controlled $Zn(BH_4)_2$ reductions are poorly selective affording the 1,2-anti-2,3-syn alcohols **17c** and **18c** in low diastereoisomeric excess. With non-chelating DIBAL-H the configurations of the two stereocenters combine in promoting a highly selective reduction: indeed, both groups

Scheme 4.



a) OsO_4, Me_3NO b) NaH, CH_3I
c) Ni-Raney

can adopt a Felkin-Anh conformation with the two large ligands shielding the same diastereoface of the carbonyl, as depicted in the transition structure **24** that we propose for this reduction.



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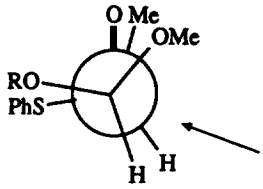

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The results of the reactions of ketones **8a** and **8b** are collected in Table 3. In analogy with the case of ketones **4** and **5** the configurations of these compounds are inferred (Table 1) from their optical rotations and from the chemical shift values of HC-1, and are assigned as syn for **8a** and anti for **8b** (Scheme 4).

Table 3. Reduction of **8a,b** to **7a,b,c,d.**

Ketone	Reducing agent	Yield %	Diastereoisomeric ratios **7a** : **7b** : **7c** : **7d**			
8a	$Zn(BH_4)_2$	90	93	7	-	-
8a	DIBAL-H	85	60	40	-	-
8b	$Zn(BH_4)_2$	92	-	-	$\geqslant 98$	$\leqslant 2$
8b	DIBAL-H	83	-	-	97	3

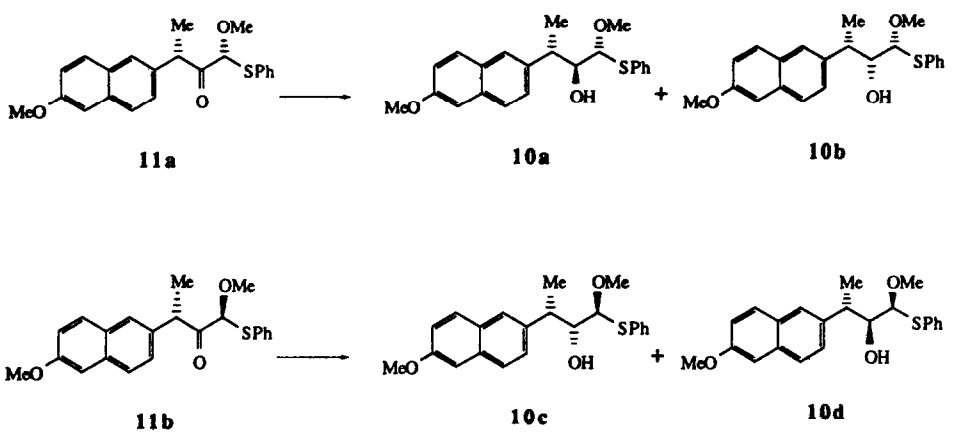
For both ketones the $Zn(BH_4)_2$ reductions are very stereoselective: we believe that they proceed via methoxy-chelated transition structures analogous to **23** that lead predominantly to 1,2-anti products **7a** and **7c** from **8a** and **8b**, respectively. The relative configuration at C-2/C-3 in these compounds was assigned by chemical correlation. Osmylation of **25** afforded a 70:30 mixture of diols **26a** and **26b**, the anti configuration being assigned to the major one **26a** according to Kishi's rule.[13] Methylation of **26a** and

26b gave the corresponding ethers anti **27a** and syn **27b**. Flash chromatography of the mixture obtained by reaction of **1** and **6** (see above) resulted in partial separation of the diastereoisomers **7**. Compound **7c** was isolated pure and subjected to methylation and subsequent Raney-Ni desulphurization to gave **27a**. The sequence was repeated on a 30:70 mixture of **7a** and **7d** to give **27b** as the only product (Scheme 4).

As in the case of ketones **4** and **5** the stereochemical outcome of the non-chelation controlled DIBAL-H reduction of **8a** and **8b** is dictated by the synergic effect of the configuration of the two stereocenters: clearly they cooperate only in the case of **8b** that gives exclusively alcohol **7c** via a transition structure similar to **24**.

Finally the reductions of racemic ketones **11a** and **11b** were examined. The results are summarized in Table 4. In this case only one stereocenter bears a group capable of chelation. As can be seen from the reported data ketone **11a** gave virtually a single isomeric alcohol **10a**, with $Zn(BH_4)_2$. The chelating nature of this reagent suggests the 1,2-anti configuration of **10a**. The assignment of relative stereochemistry at C-2/C-3 resides on the observation that **10a** was not produced by the condensation of **1** and **9** that gave a 58:34:8 mixture of **10b**, **10c**, and **10d**. This reaction should proceed by the Felkin-Anh model to give mainly 2,3-syn products.[14] Thus **10a** should feature the 1,2-anti-2,3-anti configuration depicted in Scheme 5, and accordingly **10b** is the 1,2-syn-2,3-syn isomer. Compound **10a** is the predominant alcohol also of the DIBAL-H reduction of **11a**, that occurs with fair diastereoselection.

Scheme 5.



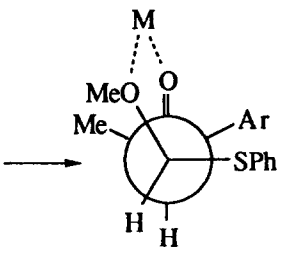
Starting with ketone **11b** both reductions gave **10c** as major isomer but with low stereocontrol. To this compound, that is the second most abundant product of the

addition of **1** to **9**, the 1,2-anti-2,3-syn configuration is assigned on the basis of the same considerations put forward before.

Table 4. Reduction of **11a,b** to **10a,b,c,d**.

Ketone	Reducing agent	Yield %	Diastereoisomeric ratios **10a** : **10b** : **10c** : **10d**			
11a	$Zn(BH_4)_2$	90	97	3	-	-
11a	DIBAL-H	85	81	19	-	-
11b	$Zn(BH_4)_2$	87	-	-	56	44
11b	DIBAL-H	86	-	-	71	29

As in the previous cases methoxy chelation is the factor mainly responsible of the stereochemical result in the reductions with $Zn(BH_4)_2$ of **11**. As for the ligands at C-3 the naphthyl residue must be regarded as the large group. Thus the highly selective reduction of **11a** with $Zn(BH_4)_2$ can be rationalized by transition structure **28** where hydride attack occurs away from the "large" substituents at C-1 and C-3; **11b** cannot adopt such a favoured conformation. The same holds for the non-chelation controlled DIBAL-H reductions that in the case of **11a** can take place on transition structure **29**, once again not available to **11b**.



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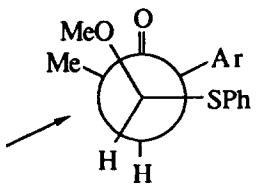

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In conclusion we have shown that the methoxy(phenylthio)methyl group can be used as an effective element of stereocontrol for nucleophilic addition reactions to a carbonyl.

The directing ability of its ligands can be exploited to override the intrinsic stereochemical preferences of other stereocenters present in the same molecule. The application of these findings to other stereoselective transformations will be the subject of future publications.

Table 5. Relevant ^{1}H NMR data for compounds **7, 10, 13, 17, 18, 19,** and **22.**

Compound	HC-1	HC-2	HC-3	$J_{1,2}$	$J_{2,3}$
13a	4.60	4.66	-	6.9	-
13b	4.61	4.74	-	7.5	-
17a	4.75	3.83	3.90	6.0	1.8
17b	4.81	3.58	4.05	7.0	3.0
17c	4.67	3.25	3.83	8.0	2.2
17d	4.70	3.80	3.83	5.0	8.0
18a	4.55	3.53	4.06	8.0	3.5
18b	4.65	3.45	4.31	7.8	2.8
18c	4.51	3.16	4.16	8.2	2.1
18d	4.72	3.33	4.08	6.8	1.9
19	5.01	3.79	3.91	3.8	6.0
22	4.89	3.55	3.87	6.7	3.8
7a	4.76	3.91	4.38	4.0	6.0
7b	4.75	3.66	4.56	7.0	3.0
7c	4.55	3.33	4.28	8.2	4.2
7d	4.83	3.78	4.15	2.8	7.0
10a	3.98	3.61	3.31	8.4	3.6
10b	4.39	3.91	3.34	4.4	7.2
10c	4.28	3.83	3.51	7.4	4.0
10d	4.54	3.91	3.35	5.6	6.0

Experimental.

^{1}H and ^{13}C NMR spectra were obtained on a Varian EM 390 and a Varian XL-300

spectrometer in $CDCl_3$ as solvent. Optical rotations were measured in $CHCl_3$ as solvent on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed with a Perkin-Elmer 240 instrument. Silica gel was used for analytical and flash chromatography. Organic extracts were dried over Na_2SO_4 and filtered before removal of the solvent under vacuum. Reactions employing dry solvents were run under Argon.

Relevant NMR data for compounds **7, 10, 13, 17, 18, 19,** and **22** are collected in Table 5. Compounds **2** was prepared as described.[15] Compound **3** was obtained as a colorless oil from (S)-N,N-dimethyllactamide[15] by standard silylation procedure ($tBuMe_2SiCl$, imidazole, DMF, RT; overnight) and purification by flash chromatography with a 50:50 hexane:ethylacetate mixture as eluant in 86% yield. Found: C, 57.18; H, 10.97; N, 6.00; $C_{11}H_{25}NO_2Si$ requires: C, 57.09; H, 10.89; N, 6.05. IR (thin film): ν 2930, 1640, 1455, 1250,1120, 830, 770, cm^{-1}. ^1H NMR: δ 4.60 (q, 1H, J 6.0 Hz); 3.20 and 3.00 (2 bs, 3H each); 1.40 (d, 3H, J 6.0 Hz); 0.95 (s, 9H); 0.15 (s, 6H). It had $[\alpha]_D^{22}$ (c 1). Aldehyde **6**[16] and **9**[14], ketone **12**[4] and alcohol **13**[4] were known compounds.

Synthesis of ketones **4** and **5**. To a stirred solution of methoxy(phenylthio)methane (0.456 ml, 3 mmol) in dry THF (15 ml) a 1.6 M solution of n-BuLi in hexane (1.9 ml, 3 mmol) was added dropwise. After an additional 1 h stirring at -78°C the reaction was quenched by addition of a saturated aqueous solution of NH_4Cl. The organic phase was separated and the aqueous phase extracted twice with diethylether. The combined organic phases were dried and concentrated in vacuo to give the crude products as roughly 1:1 mixtures of epimers at C-1 in the yields reported in Table 1. The diastereoisomers were separated by flash chromatography with a hexane:diethylether mixtures as eluants (70:30 for **4**; 85:15 for **5**). The optical rotations of diastereoisomerically pure ketones are reported in Table 1.

Compound **4**. Found: C, 68.47; H, 6.31; $C_{18}H_{20}O_3S$ requires: C, 68.33; H, 6.37; IR (thin film): ν 3060, 2940, 1735, 1445, 1115, 750, 700 cm^{-1}. **4a** was a thick oil; ^1H nmr:δ 7.10-7.40 (m, 10H); 5.55 (s, 1H); 4.55 (s, 2H); 4.35 (q, 1H, J 6.5 Hz); 3.60 (s, 3H); 1.30 (d, 3H, J 6.5 Hz). **4b** was a thick oil; ^1H nmr:δ 7.10-7.40 (m, 5H); 5.40 (s, 1H); 4.45 (s, 2H); 4.25 (q, 1H, J 7.0 Hz); 3.55 (s, 3H); 1.30 (d, 3H, J 7.0 Hz).

Copound **5**. Found: C, 60.04; H, 8.31; $C_{17}H_{28}O_3SSi$ requires: C, 59.96; H, 8.29; IR (thin film): ν 3050, 2940, 1735, 1450, 1120, 750, 700 cm^{-1}. **5a** was an oil; ^1H nmr:δ 7.10-7.45 (m, 5H); 5.65 (s, 1H); 4.55 (q, 1H, J 6.0 Hz); 3.60 (s, 3H); 1.30 (d, 3H, J 6.0 Hz); 1.00 (s, 9H); 0.15 and 0.10 (2s, 3H each). **5b** was an oil; ^1H nmr: δ 7.10-7.45 (m, 5H); 5.60 (s, 1H); 4.35 (q, 1H, J 6.0 Hz); 3.50 (s, 3H); 1.40 (d, 3H, J 6.0 Hz); 0.90 (s, 9H); 0.05 (s, 6H).

Synthesis of ketone **8**. This compound was prepared in two steps starting from aldehyde **6**. Reaction of **1** (prepared as described above, 8.82 mmol) with **6** (1.5 g, 8.82 mmol) in THF (50 ml) for 2h at -78°C followed by the usual work-up gave a mixture of four isomers **7a**, **7b**, **7c**, **7d**, in 31:19:13:37 ratio in 75% yield that was purified by flash chromatography with a 60:40 mixture of hexane:diethylether as eluant. The diastereoisomeric mixture (2.14 g, 6.6 mmol) was oxidized with PDC (7.15 g, 19 mmol) in dry CH_2Cl_2) (40 ml) in the presence of 4A molecular sieves (3 g) at room temperature for 15 h. The reaction mixture was filtered through a celite cake, concentrated, and purified by flash chromatography with a 65:35 hexane:diethylether mixture as eluant. Yield and optical rotations are reported in Table 1. Found: C, 63.21; H, 6.97; $C_{17}H_{22}O_4S$ requires: C, 63.33; H, 6.88. IR (thin film): ν 3050, 2940, 1735, 1450, 1115, 745, 700 cm^{-1}. Ketone **8a** was a thick oil. ^1H nmr: δ 7.20-7.50 (m, 5H); 5.55 (s, 1H); 4.00-4.80 (m, 1H + 2H); 3.60 (s, 3H); 1.40-1.80 (m, 10H). Keotne **8b** was a low melting material. ^1H nmr: δ 7.20-7.50 (m, 5H); 5.40 (s, 1H); 3.85-4.80 (m, 1H + 2H); 3.65 (s, 3H); 1.40-1.80 (m, 10H).

Synthesis of ketone **11**. This compound was prepared starting from (R,S)-**9** following the reaction sequence described for the synthesis of **8**. Condensation of **1** (3 mmol) with **9** (0.645 g, 3 mmol) in THF (15 ml) gave a 58:34:8 mixture of three diastereoisomeric alcohols **10** in 86% yield after flash chromatography (hexane: diethylether 70:30 mixture as eluant). These were oxidized with PDC as described above to give **11** in 84% yield. The two diastereoisomers were separated by flash chromatography with a 80:20 hexane:diethylether mixture as eluant. Found: C, 71.95; H, 6.00; $C_{22}H_{22}O_3S$ requires: C, 72.10; H, 6.05. IR (thin film): ν 3060, 3000, 2940, 1740, 1600, 1450, 1120, 750, 700 cm^{-1}. Ketone **11a** was a low melting material; ^1H nmr: δ 7.00-7.80 (m, 11H); 5.05 (s, 1H); 4.10 (q, 1H, J 6.3 Hz); 3.90 (s, 3H); 3.40 (s, 3H); 1.35 (d, 3H, J 6.3 Hz). Ketone **11b** was a waxeous solid: ^1H nmr: δ 7.00-7.80 (m, 1H); 5.10 (s, 1H); 4.05 (q, 1H, J 6.0 Hz); 3.90 (s, 3H); 3.35 (s, 3H); 1.30 (d, 3H, J 6.0 Hz).

General procedure for the $Zn(BH_4)_2$ and DIBAL-H reductions. To a stirred solution of ketone (1-3 mmol) in dry CH_2Cl_2 (5-15 ml) cooled at -78°C a 0.16 M ethereal solution of $Zn(BH_4)_2$[17] (1-3 mmol) or a 1M hexane solution of DIBAL-H (2-6 mmol) was added dropwise. When the reaction was complete (TLC monitoring, usually 1-4 h) it was quenched by addition of a saturated aqueous solution of NH_4Cl and allowed to warm up to room temperature. The organic phase was separated and dried and the crude product analyzed by ^1H nmr to evaluate the diastereoisomeric excess. Purification of the crude products by flash chromatography with the same eluants used for the corresponding ketones gave

the alcohols as oils or waxeous solids. Yields and diastereoisomeric excesses are reported in Tables 2-4.

Alcohol **7**. Found: C, 63.07; H, 7.51; $C_{17}H_{24}O_4S$ requires: C, 62.93; H, 7.46. IR (thin film): ν 3500, 2940, 1445, 1105, 920, 745 cm^{-1}.

Alcohol **10**. Found: C, 71.70; H, 6.66; $C_{22}H_{24}O_3S$ requires: C, 71.71; H, 6.57. IR (thin film): ν 3520, 2940, 1605, 1440, 1390, 1260, 1120, 860, 740 cm^{-1}.

Alcohol **17**. Found: C, 67.99; H, 7.03; $C_{18}H_{22}O_3S$ requires: C, 67.89; H, 6.96. IR (thin film): ν 3490, 2930, 1440, 1080, 740, 700 cm^{-1}.

Alcohol **18**. Found: C, 59.47; H, 8.96; $C_{17}H_{30}O_3SSi$ requires: C, 59.60; H, 8.83. IR (thin film): ν 3480, 2930, 1465, 1440, 1255, 1080, 830, 780 cm^{-1}.

Synthesis of **19** from **17a**. To an oil free suspension of NaH (0.33 mmol) in THF (2 ml) cooled at 0°C compound **17a** (0.106 g, 0.33 mmol) in THF (1 ml) was added dropwise. After 30 min stirring at 0°C a spatule tip of tetrabutylammonium iodide was added followed by benzyl bromide (0.055 ml, 0.45 mmol). The mixture was refluxed overnight and quenched by addition of a saturated aqueous solution of NH_4Cl. The organic phase was separated, dried, and evaporated to give the crude product that was purified by flash chromatography with a 90:10 hexane:diethylether mixture as eluant. Compound **19** was obtained an an oil in 81% yield. Found: C, 73.41; H, 6.83; $C_{25}H_{28}O_3S$ requires: C, 73.50; H, 6.91. IR (thin film): ν 2940, 1580, 1455, 1080, 730, 700 cm^{-1}.

To a stirred solution of **18a** (0.185 g, 0.54 mmol) in THF (10 ml) tetrabutylammonium fluoride monohydrate (0.513 g, 1.63 mmol) was added portionwise. The reaction was stirred at RT overnight. Water and diethylether were added, the organic phase was separated, dried and concentrated to give the crude product in nearly quantitative yield (by nmr). This was benzylated as described above (with twice the amount of NaH and benzylbromide) to give **19** in 80% overall yield from **18a**.

Synthesis of **20** from **19**. To a stirred solution of **19** (0.085 g, 0.21 mmol) in acetone (3 ml), cooled at 0°C, 0.2 ml of Jones reagent were added dropwise. After overnight stirring at room temperature acetone was evaporated and the aqueous phase was extracted twice with diethylether. The organic phase was dried and evaporated to give the crude and that upon treatment with diazomethane in THF gave the ester in 61% yield as an oil after flash chromatography with a 70:30 hexane:diethylether mixture as eluant. Found: C, 72.47; H, 6.97; $C_{19}H_{22}O_4$ requires: C, 72.59; H, 7.05. IR (thin film): ν 2940, 1740, 1455, 1100, 730, 700 cm^{-1}. ^1H nmr (relevant data): δ 4.02 (d, 1H, J 5.0 Hz); 3.88 (m, 1H).

Synthesis of **21**. To a stirred solution of (E)-methyl crotonate (1.0 g, 10 mmol) in

THF:H_2O 9:1 (10 ml) a 0.005 M solution of OsO_4 in t-BuOH (20 ml, 0.1 mmol) was added followed by trimethylamine N oxide dihydrate (2.44 g, 22 mmol). After overnight stirring at room temperature the reaction was quenched by addition of solid $NaHSO_3$. The mixture was filtered and most of the solvent was evaporated. The residue was extracted with methylene chloride and the organic phase dried and evaporated to give the crude product. This was benzylated with benzyl bromide in refluxing dry diethyl ether in the presence of Ag_2O (15 h) to give **21** in 81% overall yield after purification by flash chromatography. Found: C, 72.63; H, 7.00; $C_{19}H_{22}O_4$ requires: C, 72.59; H, 7.05. ^1H nmr (relevant data): δ 4.00 (d, 1H, J 4.3 Hz); 3.96 (m, 1H).

Synthesis of **22** from **17c**. Following the procedure described above **22** was obtained in 82% yield.

Synthesis of **22** from **18c**. Following the procedure described above **22** was obtained in two steps from **18c** in 75% overall yield.

Synthesis of **21** from **22**. Following the procedure described above **21** was obtained from **22** in 58% yield.

Synthesis of **27** from **25**. A 0.05 M solution of osmium tetroxide in t-butanol (5 ml, 0.022 mmol) was added at 0°C to a solution of **25**[18] (0.375 g, 2.23 mmol) and trimethylamine N-oxide (0.55 g, 5 mmol), and the mixture was stirred at room temperature overnight. To the crude product, isolated by the usual work-up, were added 15 ml of THF and, at 0°C, 5 mmol of NaH. After 30 min. at 0°C the mixture was treated with CH_3I (10 mmol) and stirred for 1 h at room temperature. Standard work-up afforded in 90% yield a 70:30 mixture of ethers **27a** and **27b**, purified by flash chromatography with a 65:35 hexane:diethylether mixture as eluant. Found: C, 62.66; H, 9.70; $C_{12}H_{22}O_4$ requires: C, 62.54; H, 9.63. ^1H NMR (relevant data) of **27a**: δ 4.06 (m, 1H, J 6.2 Hz); 3.27 (m, 1H, J 6.2 Hz); of **27b**: δ 4.17 (m, 1H, J 7.0 Hz); 3.33 (m, 1H, J 7.0 Hz).

Synthesis of **27** from **7**. Diastereoisomer **7c** (0.088 g, 0.27 mmol) was added to an oil-free suspension of NaH (0.27 mmol) in dry THF (2 ml) and the mixture stirred for 30 min. at 0°. CH_3I (0.4 mmol) was added and stirring continued for 1h at room temperature. The usual work-up and flash chromatography with a 85:15 hexane: diethylether mixture afforded in 70% yield the product which was subjected to Raney-Nickel desulphurization (THF, 24h) to give in 45% yield **27a**. Similarly a 30:70 mixture of diastereoisomers **7a** and **7d** was converted into the methyl ether (70% yield) and desulphurized (51% yield) to give **27b**.

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References and Notes.

1) Review: J. Otera, Synthesis, 95, 1988. Recent reports: T. Sato, H. Okazani, J. Otera, H. Nozaki, J. Am. Chem. Soc., **110**, 5209, 1988; T. Sato, M. Inoue, S. Kobara, J. Otera, H. Nozaki, Tetrahedron Lett., 91, 1989; T. Sato, Y. Hiramura, J. Otera, H. Nozaki, Tetrahedron Lett., 2821, 1989; T. Sato, J. Otera, H. Nozaki, J. Org. Chem., **54**, 2780, 1989; J.L. Marco, Tetrahedron, **45**, 1475, 1989; C.A. Broka, T. Shen, J. Am. Chem.Soc., **111**, 2981, 1989.
2) J.L. Marco, B. Rodriguez, Synth. Commun., **19**, 1025, 1989.
3) Review: E.L. Eliel, Asymmetric Synthesis, J.D. Morrison, Ed.; vol. 2, p.1 25, 1985. Recent reports: S.V. Frye, E.L. Eliel, J. Am. Chem. Soc., **110**, 484, 1988, and references cited therein. See also: K. Utimoto, A. Nakamura, S. Matsubara, J. Am. Chem. Soc., **112**, 8189, 1990.
4) V.H. Raiwal, M. Akiba, M.P. Cava, Synth. Commun., **14**, 1129, 1984.
5) See inter alia: T. Takahashi, M. Miyazawa, J. Tsuji, Tetrahedron Lett., 5137, 1985; H. Iide, N. Yamazaki, C. Kibayashi, J. Org. Chem., **51**, 3769, 1986.
6) When both alkoxy and alkylthio groups are present chelation controlled nucleophilic additions to carbonyls have been shown to involve alkoxy group chelation; see ref. 3 and : G. Guanti, L. Banfi, E. Narisano, J. Chem. Soc., Chem. Commun., 136, 1986, and references therein. The chelating ability of an aryl- or alkylthio group seems to depend largely on the nature of the metal: M. Shimagaki, T. Maeda, Y. Matsuzaki, I. Hori, T. Nakata, T. Oishi, Tetrahedron Lett., 4775, 1984; M. Shimagaki, H. Takubo, T. Oishi, Tetrahedron Lett., 6235, 1985.
7) N.T. Anh, Top. Curr. Chem., Springer-Verlag, Berlin, 1980, p. 145.
8) F. Bernardi, A. Bottoni, A. Venturini, A. Mangini, J. Am. Chem. Soc., **108**, 8171, 1986.
9) It is worth mentioning that the $Zn(BH_4)_2$ reduction of the keto-sulphone derived from **12** by in CPBA oxidation was less anti selective (86:14 isomer ratio) likely because of competing chelation of methoxy- and sulphonyl-oxygens with the carbonyl oxygen. The possibility of such a chelation is well recognized; see, inter alia. W. Oppolzer, Tetrahedron, **43**, 1969, 1987. The reduction with DIBAL-H was almost stereorandom, since both the methoxy and phenylsulphonyl groups can act as "large" in the Felkin model.
10) M.T. Reetz, M. Hüllmann, J. Chem. Soc., Chem. Commun., 1600, 1986.
11) It must be noted that **4a** can also give rise to a chair-like six-membered chelate involving methoxy and benzyloxy group. However inspection of the molecular model of this chelate leads to the prediction of the preferential formation of **17b**.
12) For a review that illustrates principles and applications of double stereoselection see: S. Masamune, W. Chang, J.S. Petersen, L.R. Sita, Angew. Chem., Int. Ed. Engl.; **24**, 1, 1985.
13) J.K. Cha, W.J. Christ, Y. Kishi, Tetrahedron, **40**, 2255, 1984.
14) For an example of highly syn-selective sulphur stabilized carbanion addition to **9** see: R. Annunziata, M. Cinquini, F. Cozzi, L. Raimondi, S. Stefanelli, Tetrahedron, **42**, 5443, 1986.
15) Y. Kobayashi, M. Takase, Y. Ito, S. Terashima, Bull. Chem. Soc. Jpn., **62**, 3038, 1989.
16) M. Grauert, U. Schöllkopf, Liebigs Ann. Chem., 1817, 1985.
17) W.J. Gensler, F.A. Johnson, A.D.B. Sloan, J. Am. Chem. Soc., **82**, 60, 1960.
18) V. Jäger, R. Schohe, E.F. Paulus, Tetrahedron Lett., 5501, 1983.