Stereoselective Reductions of 2-Keto Sulfoxides with Hydrides

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The results of reductions of some acyclic 2-keto sulfoxides ($ArC(O)CH_2S(O)R$; Ar = Ph, 2-Py, 4-Py, and R = Me, *p*-Tol) and flexible and rigid 2-sulfinylcyclohexanone diastereomers with various metal hydrides are reported. The configurational assignment and conformational preferences of these substrates have been inferred from their NMR parameters. The high stereoselectivity observed in i-Bu_2AlH reactions can be explained by assuming its association with the sulfinyl oxygen and intramolecular hydride transfer via chair-like transition states. In the presence of $ZnCl_2$ the hydride transfer evidently takes place intermolecularly on the half-chair conformation adopted by the chelated species formed by 2-keto sulfoxides and $ZnCl_2$. The reductions with $LiAlH_4$ involve lithium chelates to which hydride is intramolecularly transferred from associated AlH_4^- through the most stable transition state. In all cases, an important role of the stereoelectronic effects on the favored hydride approach is proposed.

Introduction

Considerable attention has been paid to the application of chiral 2-keto sulfoxides in asymmetric synthesis.[1] One of the most useful reactions has been their stereoselective reduction with i-Bu_2AlH and i-$Bu_2AlH/ZnCl_2$.[2] The model used to explain the stereoselectivity observed with i-Bu_2AlH (model I in Scheme I) is based on the assumption that the sulfoxides mainly adopt a conformation in which the electrostatic repulsion between oxygens is minimized. However, in the presence of $ZnCl_2$, the substrates adopt the conformation shown in model II, due to the formation of a chelated intermediate. Both models assume an intermolecular hydride attack whose favored approach is explained only on steric grounds. Therefore, the expected stereoselectivity for different hydrides should be determined only by the size of the reagents.

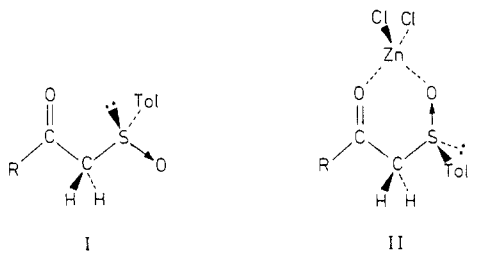
In a previous paper[3] we reported high stereoselectivity in i-Bu_2AlH reduction of oxisuran (2-PyC(O)CH_2S(O)Me), which disappeared when $NaBH_4$ was used as hydride donor. These results cannot be explained from model I, since the steric differences between the two hydrides should be minimal. We proposed that the sulfinyl oxygen should interact with i-Bu_2AlH before the attack of the hydride, since a similar interaction has been postulated with the less basic sulfonyl oxygens.[4] On the other hand, the stereoselectivity differences between $NaBH_4$ and i-Bu_2AlH in the reduction of 2-(methylthio)- and 2-(methylsulfonyl)cyclohexanones[4] had to be explained by assuming an important role of the stereoelectronic effects on the hydride approach.[5]

We hereby report the reduction of different acyclic and cyclic 2-keto sulfoxides (Schemes II and III) with several hydrides and propose new models to explain the observed stereochemical outcome, in which the role of stereoelectronic factors is strongly emphasized.

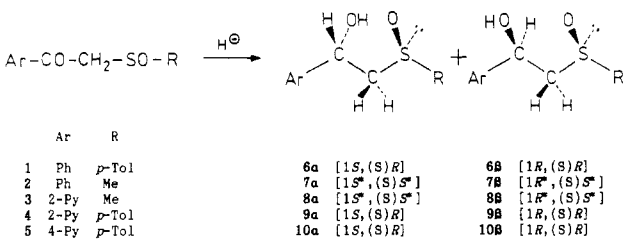
Synthesis and Configurational Assignments

Compounds **1**,[6a] **2**,[6b] and **3**[3] were prepared as described in the literature. The synthesis of compounds **4** and **5** was carried out by condensation of (*R*)-methyl *p*-tolyl sulfoxide and the corresponding aromatic ester $ArCO_2Et$, in the presence of lithium diisopropylamide. The reduction of these keto sulfoxides afforded mixtures of diastereomeric hydroxy sulfoxides (Scheme II), the ratio of which was determined from the ^1H NMR spectra of the crude products.

Scheme I

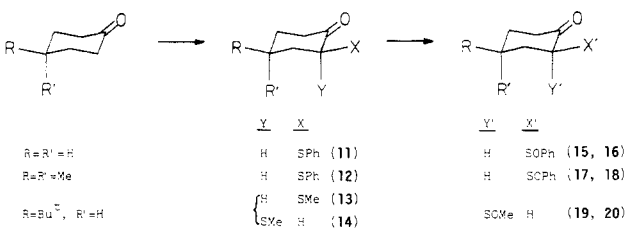


Scheme II



	Ar	R		
1	Ph	*p*-Tol	**6a** [1*S*,(S)*R*]	**6β** [1*R*,(S)*R*]
2	Ph	Me	**7a** [1*S**,(S)*S**]	**7β** [1*R**,(S)*S**]
3	2-Py	Me	**8a** [1*S**,(S)*S**]	**8β** [1*R**,(S)*S**]
4	2-Py	*p*-Tol	**9a** [1*S*,(S)*R*]	**9β** [1*R*,(S)*R*]
5	4-Py	*p*-Tol	**10a** [1*S*,(S)*R*]	**10β** [1*R*,(S)*R*]

Scheme III



	Y	X		Y'	X'	
R=R'=H	H	SPh	(11)	H	SOPh	(15, 16)
R=R'=Me	H	SPh	(12)	H	SOPh	(17, 18)
R=Bu^t, R'=H	H	SMe	(13)			
	SMe	H	(14)	SOMe	H	(19, 20)

Significant ^1H and ^{13}C NMR parameters used for the configurational assignment of **6–10** are summarized in

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(1) Posner, G. H. In *The Chemistry of Sulphones and Sulphoxides*; Patai, S., Rappoport, Z., Stirling, C. J. M., Eds.; Wiley: New York, 1988; p 823 and references cited therein.
(2) Solladié, G.; Demailly, G.; Greck, C. *Tetrahedron Lett.* **1985**, *26*, 435.
(3) Garcia Ruano, J. L.; Pedregal, C.; Rodriguez, J. H. *Tetrahedron* **1987**, *43*, 4407.
(4) Carreño, M. C.; Dominguez, E.; Garcia Ruano, J. L.; Rubio, A. *J. Org. Chem.* **1987**, *52*, 3619. A similar association has been proposed to rationalize the stereochemical results obtained in the reduction of a δ-keto sulfoxide (Iwata, C.; Moritani, Y.; Sugiyama, K.; Fujita, M.; Imanishi, M. *Tetrahedron Lett.* **1987**, *28*, 2255).
(5) A significant role of the stereoelectronic effects was suggested to explain the stereochemical results of the nucleophilic additions on vinyl sulfoxides (see: Kanh, S. D.; Doobs, K. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1988**, *110*, 4602).

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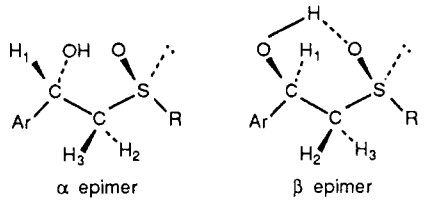
Table I. Significant NMR Parameters for the Configurational Assignment of the Hydroxy Sulfoxides Depicted in Scheme II



compd	$J_{1,2}/J_{1,3}$ $CDCl_3$	$J_{1,2}/J_{1,3}$ DMSO-d_6	^{13}C δ(C-OH)
1α	10.2/2.0	11.0/2.0	69.1
1β	9.9/2.5	7.7/5.8	71.3
2α	10.9/1.9	11.1/2.6	67.8
2β	9.5/2.9	7.4/5.6[a,b]	70.5
3α	10.2/2.4	11.1/2.4	68.5
3β	8.6/3.5	7.5/5.0	68.9
4α	10.4/1.8	10.4/2.4[a,c]	68.6
4β	9.5/2.7	8.7/3.9[a,c]	70.8
5α	10.5/1.9	10.9/2.4	66.1
5β	10.1/2.0	7.5/5.4	69.1

[a] Deceptively simple spectra in pure DMSO-d_6. [b] Data corresponding to OMe derivative. [c] 5:1 mixture of $CDCl_3$/DMSO-d_6 as solvent.

Table I. The α isomers exhibit larger $J_{1,2}$ and lower $J_{1,3}$ values than those of their corresponding β epimers in the ^1H NMR spectra, the difference ($J_{1,2} - J_{1,3}$) being higher in DMSO-d_6 than in $CDCl_3$. The ^{13}C NMR chemical shifts for the hydroxyl carbons show the opposite trend, suggesting that identical stereochemistry should be associated with the hydroxy sulfoxides with the same notation (α or β). The favored conformation for each diastereomer and their relative configuration, both depicted in Table I, can be inferred from the values of $J_{1,2}$ and $J_{1,3}$ obtained in $CDCl_3$ and DMSO-d_6.[7]

Keto sulfoxides **15–20** were obtained from the corresponding sulfides **11**, **12**, and **14** (Scheme III), which in their turn were prepared from cyclohexanone and its 4,4-dimethyl and 4-(1,1-dimethylethyl) derivatives following Trost's procedure[8] with diphenyl or dimethyl disulfide as sulfenylating agents. The 4-(1,1-dimethylethyl)-2-(methylthio)cyclohexanone was obtained as a mixture of cis (**13**) and trans (**14**) isomers,[4] whose separation[9] by chromatography afforded compound **14** diastereomerically pure.[10]

The oxidation of **11**, **12**, and **14** yielded the sulfoxides as diastereomeric mixtures (Scheme III), which could be separated by fractional crystallization at −20 °C.[11] Chromatographic separation was unsuccessful due to epimerization at C-2. The only compound that could not be isolated as a pure diastereomer was **20**, and its reduction was studied on an 83:17 mixture of **19**:**20**. Since the methylsulfinyl derivatives with structures similar to those of **15–18** could not be separated from their epimeric mixtures, the reduction studies were carried out on the corresponding phenyl derivatives.

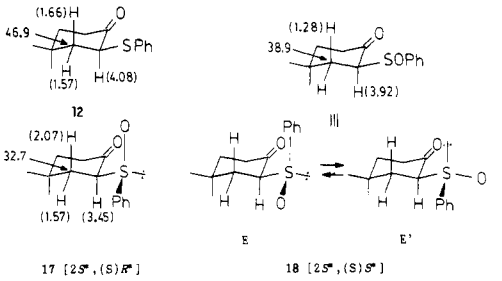
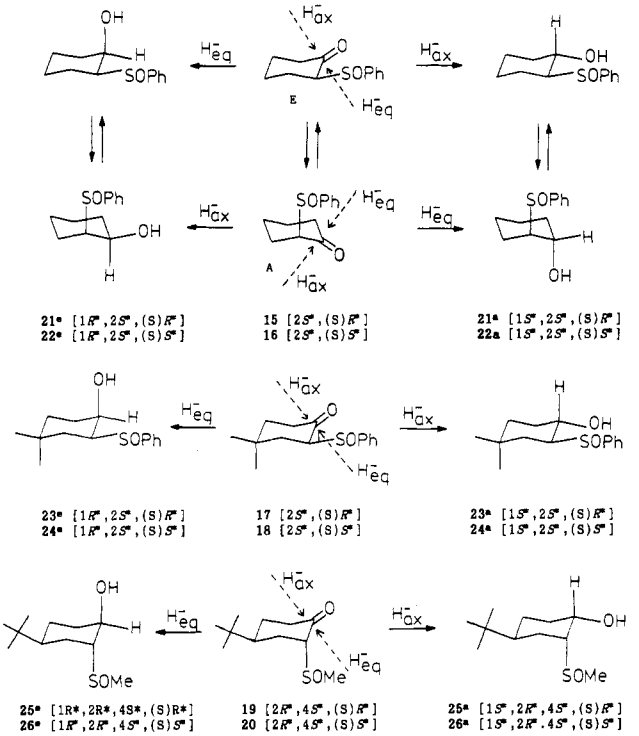


Figure 1. Significant ^1H and ^{13}C NMR chemical shifts for configurational assignment of **17** and **18**.

Scheme IV



The reduction of keto sulfoxides **15–20** afforded mixtures of hydroxy sufoxide epimers at C-1 resulting from axial and equatorial (superscripts [a] and [e], respectively) hydride approach (Scheme IV). Since the reduction of the sulfoxides **15–20** does not affect the configuration of the chiral centers at C-2, at sulfur, and at C-4 in **19** and **20**, this reaction chemically correlates hydroxy and keto sulfoxides with the same configuration at these centers. Therefore, the configurational assignment of all compounds with the same carbon skeleton can be made either on the ketones or on the corresponding hydroxy derivatives.

The configurational assignments of keto sulfoxides **17** and **18** are made by comparison of their ^1H and ^{13}C NMR parameters with those of the keto sulfide **12**. These parameters have been obtained at −105 °C in order to observe larger differences in the rotamer population around the C–S bond. Significant differences are depicted in Figure 1.

The shielding effect on β-carbons induced by oxidation of sulfides to sulfoxides has been previously reported.[12] In

(6) (a) Annunziata, R.; Cinquini, M.; Cozzi, F. *J. Chem. Soc., Perkin Trans. I* **1979**, 1687. (b) Becker, H. D.; Mikol, G. J.; Russell, G. A. *J. Am. Chem. Soc.* **1963**, *85*, 3410.

(7) The conformational behavior of different hydroxy sulfoxides had been established from the values of their vicinal coupling constants and correlated with the relative configuration of the substrates (see: Brunet E.; Garcia Ruano, J. L.; Hoyos, M. A.; Rodriguez, J. H.; Prados, P.; Alcudia, F. *Org. Magn. Reson.* **1983**, *23*, 643. Carretero, J. C.; Garcia Ruano, J. L.; Martinez, M. C.; Rodriguez, J. H. *Tetrahedron* **1985**, *41*, 2419).

(8) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.

(9) We have also prepared the corresponding *cis*- and *trans*-2-phenylsulfenyl derivatives, but their separation was not possible in our hands, and therefore they were not used in the reduction studies.

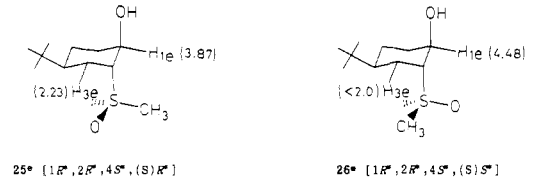
(10) As compound **13** could never be obtained free of its trans isomer **14** and the mixture **13** + **14** should yield four different keto sulfoxides by oxidation, whose separation should be very difficult, the behavior of substrate **13** was not investigated.

(11) Above 30 °C, pyrolytic elimination of the sulfoxide group was observed.

Table II. Diastereomeric Ratios Obtained in the Reductions of Substrates 1–5 with Different Hydrides in THF

substr	prod	n-Bu_4NBH_4[b]	$NaBH_4$[c]	$LiBH_4$[c]	i-Bu_2AlH[c]	i-$Bu_2AlH/ZnCl_2$[c]	$LiAlH_4$[c]
1	**6α:6β**	51:49	59:51[d]	43:57	≥95:5[e]	≤5:95[e]	16:84[e]
2	**7α:7β**	43:57	55:45[f]	47:53	84:16	20:80	36:64
3	**8α:8β**	44:56	50:50[g]	50:50[h]	92:8[g]	49:51	40:60
4	**9α:9β**	50:50	56:44	33:67	100:0	56:44	44:56
5	**10α:10β**	50:50	48:52	43:57	100:0	50:50	33:67[i]

[a] Obtained from the ^1H NMR spectra of the crude reaction. [b] Room temperature. [c] T = −78 °C. [d] 41:59 in the presence of $ZnCl_2$. [e] From ref 2. [f] 45:55 in the presence of $ZnCl_2$. [g] From ref 4. [h] Solvent 1:1 EtOH/THF. [i] Ratio [hydride]/[ketone] = 2:1.



25e [1R*,2R*,4S*,(S)R*] 26e [1R*,2R*,4S*,(S)S*]

Figure 2. Significant ^1H NMR parameters for configurational assignment of **25**[e] and **26**[e].

rigid substrates the magnitude of this effect is higher when the sulfinyl lone electron pair adopts an anti relationship with respect to the β-carbon (12–13 ppm in the ^{13}C NMR spectra) than in any other case (3–5 ppm). This fact has also been observed in 1,4-oxathianes[13] and 1,4-thiazanes.[14] The Δδ(C(3)) value (Δδ = $\delta_{sulfoxide} - \delta_{sulfide}$) observed for **17** (−14.2 ppm, Figure 1) indicates that this substrate exists in just one conformation with C(3) and the unshared pair in an anti relationship, whereas in **18** (Δδ(C(3)) = −8 ppm) one should consider the participation of at least two rotamers around the C–S bond, one of them possessing such a stereochemistry. Moreover, H_{2ax} in **17** is shielded (Δδ = −0.63 ppm) and H_{3ax} deshielded (Δδ = 0.41 ppm) with respect to the sulfide **12** (Figure 1). Both effects, which have also been reported in the literature,[15] suggest that the sulfinyl oxygen adopts the stereochemistry shown in Figure 1. Therefore we must assign the configuration 2*S**,(S)*R** to compound **17** and justify the shielding observed for H_{3eq} (Δδ = −0.45 ppm) as a consequence of the anisotropic effect of the aromatic ring in 1,3-parallel arrangement.

The Δδ values observed for **18** are consistent with the 2*S**,(S)*S** configuration assuming the participation of the rotamers **18E** and **18E′** (Figure 1) in its conformational equilibrium. The small value of Δδ(H_{2ax}) (−0.16 ppm) should come from the shielding of this proton in **18E** and its deshielding in **18E′**.[15] The shielding of H_{3ax} (Δδ = 0.38 ppm) should be due to the phenyl group in 1,3-parallel arrangement in **18E**, similar to that above-mentioned in the case of **17**.[16]

The most important conclusion reached from this conformational study is the fact that the favored rotamer in 2-keto sulfoxides is not always that exhibiting both oxygens in an anti relationship, as the model, so far accepted, requires one to explain the stereoselectivity in i-Bu_2AlH reductions of acyclic 2-keto sulfoxides.[2] A donor–acceptor interaction between the unshared electron pair on the carbonyl oxygen and the empty d orbital on sulfur, similar to that proposed in different 2-hetero-substituted sulfoxides,[17] could be responsible for the observed conformational preferences.

Table III. Diastereoisomeric Ratios Obtained in the Reductions of 15–20 with Different Hydrides

entry	hydride[a]	substr	b	b	substr	hydride	entry
			23e:23a	**24e:24a**			
1	A	**17**	64:36	31:69	**18**	A	1′
2	B	**17**	0:100	100:0	**18**	B	2′
3	C	**17**	61:39	13:87	**18**	C	3′
4	D	**17**	27:73	55:45	**18**	D	4′
5	E	**17**	67:33	5:95	**18**	E	5′
			21e:21a	**22e:22a**			
6	A	**15**	81:19	54:46	**16**	A	6′
7	B	**15**	0:100	94:6	**16**	B	7′
8	C	**15**	80:20	5:95	**16**	C	8′
9	E	**15**	82:18	26:74	**16**	E	9′
			25e:25a	**26e:26a**			
10	A	**19**	0:100				
11	B	**19**	55:45				
12	F	**19**	23:77	43:57	**20**[c]	F	12′
13	C	**19**	0:100				

[a] A, $NaBH_4$; B, i-Bu_2AlH; C, i-$Bu_2AlH/ZnCl_2$; D, $NaBH_4/ZnCl_2$; E, $LiAlH_4$; F, i-Bu_2AlH + MCBA (see text). [b] Diastereomer ratio from ^1H NMR of the crude reaction. [c] From a 17:83 mixture of **20**:**19**.

The configurational assignment of the sulfoxides **19** and **20** is based on the NMR parameters of hydroxy derivatives **25**[e] and **26**[e] depicted in Figure 2. Since the most stable conformation of the SOMe group in the axial orientation is that with the lone electron pair pointing toward the ring, the chemical shifts of the H_{1eq} and H_{3eq} in both epimers can be used for the assignment. The strong deshielding effect of the sulfinyl oxygen on the 1,3-parallel protons allows us to state that **25**[e] and **26**[e] exhibit H_{1eq} and H_{3eq}, respectively, in such an arrangement, fixing the relative configuration in both cases as shown in Figure 2.

Finally, the configuration 1*S**,2*S**,(S)*S** indicated in Scheme IV for compound **22**[a] (and hence the configuration of all sulfoxides **21** and **22**) has been established by X-ray diffraction.[18]

Results and Discussion

The results obtained in the reduction of acyclic (**1**–**5**) and cyclic (**15**–**20**) 2-keto sulfoxides are collected in Tables II and III.

The stereoselectivity observed in the reductions of **17** and **18** (selected as rigid models to study the role of the

(12) Frieze, D. M.; Hughes, P. F.; Merril, R. L.; Evans, S. A., Jr. *J. Org. Chem.* **1977**, *42*, 2206 and references therein.
(13) Rooney, R. P.; Evans, S. A., Jr. *J. Org. Chem.* **1980**, *45*, 180.
(14) Brunet, E.; Gallego, M. T.; Garcia Ruano, J. L.; Parellada, D.; Rodriguez, J. H.; Urbano, A. *Tetrahedron* **1988**, *44*, 1430.
(15) The Δδ values for protons on C-α are negative (shielding effect) when either sulfinyl oxygen or unshared electron pair are in anti relationship (slightly larger effect in the first case) and positive (deshielding effect) when none of them adopt such a disposition (Lett, R.; Marquet, A. *Tetrahedron* **1974**, *30*, 3379). The deshielding of the protons exhibiting an 1,3-parallel arrangement with respect to the sulfinyl oxygen is also well known (Foster, A. B.; Inch, T. D.; Qadir, M. H.; Weber, J. M. *J. Chem. Soc., Chem. Commun.* **1968**, 1086. Cook, M. J. *Kemia-Kemi* **1976**, *3*, 16).
(16) All these spectroscopic parameters could also be compatible with the preference of only one conformation exhibiting a promediated stereochemistry between those of **18E** and **18E′**.
(17) In connection with conformational preferences of 2-hetero sulfoxides, see the following. (a) 2-Oxygenated sulfoxides: Garcia Ruano, J. L.; Rodriguez, J. H.;f Alcudia, F.; Llera, J. M.; Olefirowicz, E. M.; Eliel, E. L. *J. Org. Chem.* **1987**, *52*, 4099 and references therein. (b) 2-Nitro-generated sulfoxides: Brunet, E.; Gallego, M. T.; Garcia Ruano J. L.; Alcudia, F. *Tetrahedron* **1986**, *42*, 1423. (c) 2-Halo sulfoxides: Carretero, J. C.; Garcia Ruano, J. L.; Martinez, M. C.; Rodriguez, J. H. *An. Quim.* **1987**, *83C*, 300 and references therein.
(18) S. Martinez and M. A. Hoyos, to be published.

equatorial sulfinyl function at C-2) with $NaBH_4$ (Table III) can be justified on the basis of their conformational behavior around the C–S bond (see Figure 1). Compound **17** gave a 64:36 mixture of hydroxy sulfoxides (entry 1), the major diastereomer **23**^{e} resulting from the equatorial hydride approach. The inversion of the expected stereoselectivity (preferential axial attack of small hydrides on cyclohexanones[19]) can be explained by assuming a strong stereoelectronic repulsive effect of the sulfinyl oxygen, which hinders the axial hydride attack on the favored rotamer for **17** (Figure 1). This effect has been previously suggested to explain the results obtained in the $NaBH_4$ reduction of *cis*-4-(1,1-dimethylethyl)-2-(methylsulfonyl)cyclohexanone[4] (yielding a 65:35 mixture of diastereomeric hydroxy sulfones), which bears one of the sulfonyl oxygens in a spatial arrangement identical with that of **17**. Reaction of **18** with $NaBH_4$ yielded a 31:69 mixture of **24**^{e}:**24**^{a} (entry 1′). The preference for axial attack on this substrate suggests that the stereoelectronic effect of the unshared electron pair in **18E**′ and the steric effect of the phenyl group in **18E** (see Figure 1) are less important than those of the sulfinyl oxygen in **17**. These effects can therefore only diminish the tendency of the small hydrides favoring the axial attack.[19]

The stereospecific $NaBH_4$ reduction of 2-keto sulfoxide **19** (Table III, entry 10) with axial SOMe only yielded **25**^{a}, which results from the axial hydride approach. The equatorial attack is probably inhibited by steric and stereoelectronic repulsion of the sulfinyl group. This is in agreement with the results obtained in the reduction of *trans*-4-(1,1-dimethylethyl)-2-(methylthio)[and 2-(methylsulfonyl)]cyclohexanone.[4]

The reduction of **15** and **16** with $NaBH_4$ (entries 6 and 6′) yielded a higher proportion of the *cis*-hydroxy sulfoxides **21**^{e} and **22**^{e} than that obtained from the rigid models **17** and **18**. This outcome may be explained by assuming the participation of conformations **15A** and **16A**[20] exhibiting the SOPh group in an axial position (Scheme IV) whose reductions must proceed stereospecifically yielding **21**^{e} and **22**^{e}.

The poor stereoselectivity observed in reduction of acyclic substrates **1–5** with $NaBH_4$ (Table II) can be explained by assuming that both the stereoelectronic repulsion of the sulfinyl lone electron pair and the steric effects control the hydride approach to the carbonyl. The effect of solvent polarity (the use of EtOH increased the proportion of β epimers) and the temperature (when it decreased, the proportion of α epimers increased) on the stereoselectivity of **1**, **2**, and **5** $NaBH_4$ reductions must be a consequence of changes in rotamer populations, suggesting a significant participation of conformers other than those depicted in Scheme I (model I).

The stereoselectivity observed in reductions of **1–5** with *i*-Bu_2AlH is much higher than that found with $NaBH_4$, although both hydrides have a similar size. The similar results obtained with $NaBH_4$, *n*-Bu_4NBH_4 (Table II), and

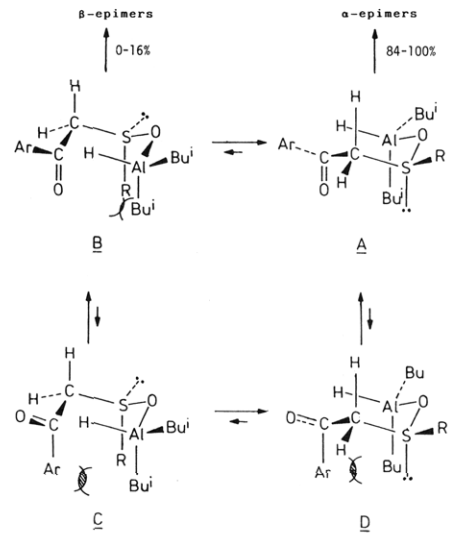


Figure 3. Possible chair-like transition states for intramolecular hydride transfer in *i*-Bu_2AlH reductions.

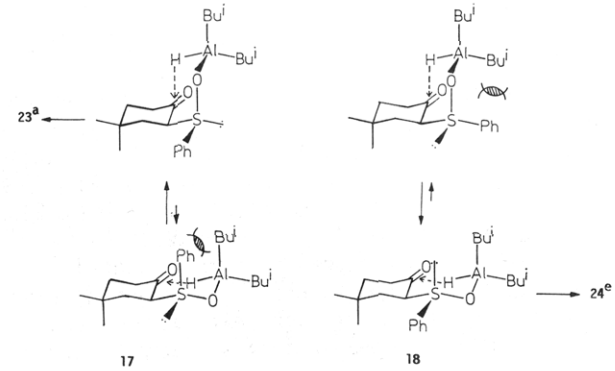


Figure 4. Possible transition states for intramolecular hydride transfer in *i*-Bu_2AlH reductions of **17** and **18**.

$NaBH_4$ in the presence of 18-crown-6 ether overrules a cation effect.[21] Therefore the steric control for the *i*-Bu_2AlH hydride attack, suggested by model I, is unable to explain the experimental results. We propose that the observed differences between BH_4^- and *i*-Bu_2AlH must be a consequence of the Lewis acid character of organoaluminium reagents, such as *i*-Bu_2AlH, which form an O–Al bond with the more basic sulfinyl oxygen. From this adduct, the intramolecular hydride transfer will take place through a chair-like transition state (TS). In acyclic substrates, four different TS A–D (Figure 3) can be postulated. The $(Ar/i\text{-}Bu)_{1,3\text{-diaxial}}$ interaction makes C and D quite unstable and will be disregarded. A and B would yield different epimers. The higher stability of A [the $(R/i\text{-}Bu)_{1,3\text{-diaxial}}$ interaction makes B unstable] enables us to explain the exclusive (R = *p*-Tol) or predominant (R = Me) formation of the α epimers in the reaction mixtures.

In *i*-Bu_2AlH reduction of **17** and **18** (entries 2 and 2′ in Table III) only one hydroxy sulfoxide is detected by ^1H NMR spectroscopy. Compound **18** gave **24**^{e}, whereas **17** only yielded **23**^{a}. The complete inversion of the favored hydride approach when the relative configuration of the starting keto sulfoxide is changed can be explained by considering the intramolecular hydride transfer in the *i*-Bu_2AlH–substrate complex derived from keto sulfoxides

(19) (a) Boone, I. R.; Ashby, E. C. *Top. Stereochem.* **1979**, *11*, 53. (b) Wigfield, D. C. *Tetrahedron* **1979**, *35*, 449. (c) Giddings, M. R.; Hudec, J. *Can. J. Chem.* **1981**, *59*, 459. (d) Cieplak, A. *J. Am. Chem. Soc.* **1981**, *103*, 4540. (e) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 579. (f) Cheung, C. K.; Tseng, L. T.f Lin, M. H.; Srivastava, S.; le Noble, V. J. *J. Am. Chem. Soc.* **1986**, *108*, 1598.

(20) Attempts to obtain $\Delta G°$ for conformational equilibria of **15** and **16** were unsuccessful because the ^{13}C NMR spectra of these compounds did not decoalesce on cooling at −130 °C. Nevertheless, the MM2 calculations suggest the participation of the two chair forms in the conformational equilibria of both keto sulfoxides ($\Delta G° < 1$ Kcal/mol) being **15E** and **16A**, depicted in Figure 5, the favored conformers. Once again, the donor–acceptor interaction, only possible in **11A**, can justify the differences in conformational behavior.

(21) In these reactions, the addition of 18-crown-6 ether to the medium does not modify the stereoselectivity significantly. The ratio of epimers changed at random in a range about 10%, which confirms the scarce participation of Na^+ in the course of reaction.

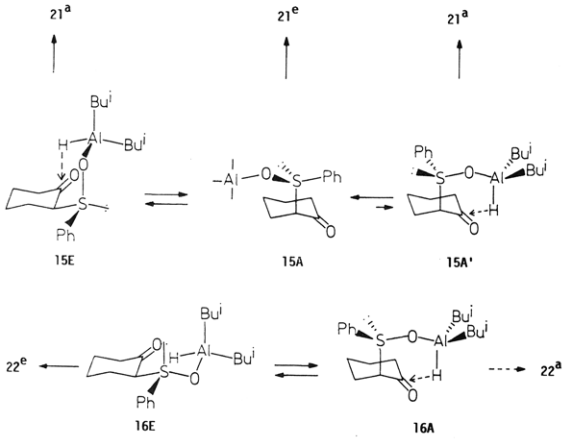


Figure 5. Possible transition states for hydride transfer in *i*-Bu_2AlH reductions of **15** and **16**.

17 and **18** through the TS depicted in Figure 4. In the case of **17** the axial attack must be strongly favored, since the $(Ph/i\text{-}Bu)_{1,3\text{-diaxial}}$ interaction makes the TS for the equatorial hydride approach unfavorable. The opposite is true for compound **18**.[22]

Reduction of **15** with *i*-Bu_2AlH (entry 7, Table III) yielded only **21a**. This result suggests that the intramolecular reaction of **15E** (Figure 5) should be faster than the intermolecular hydride attack on conformation **15A** yielding **21e**. The intramolecular evolution of the unstable conformation **15A′** (Figure 5) would also yield **21a**. The reaction of **16** with *i*-Bu_2AlH (entry 7′) yielded a 94:6 mixture of **22e**:**22a**. As the reduction of **16E** must be stereospecific (it was observed in the rigid model **18**), the low but significant proportion of **22a** can only be justified by considering the intramolecular hydride transfer from conformation **16A**, whose stability is clearly higher than that of **15A′** (Figure 5).

In order to confirm this explanation, which would be the best evidence of the SO–*i*-Bu_2AlH association prior to the hydride transfer,[23] we prepared compounds **19** and **20**.[9] Reaction of **14** with *m*-chloroperbenzoic acid (MCPBA) yielded a 33:7:60 mixture of **19**/**20**/MCBA (*m*-chlorobenzoic acid), from which it was possible to precipitate **19** diastereomerically pure.[24] The reaction of pure **19** with *i*-Bu_2AlH yielded a 55:45 mixture of **25e**/**25a**, which suggests that the intramolecular hydride transfer was only slightly preferred to the intermolecular one (cf. Figure 5). We were unable to isolate **20** diastereomerically pure,[25] but we attempted the reduction with *i*-Bu_2AlH of the crude 33:7:60 mixture of **19**/**20**/MCBA, obtained by oxidation of **14**. While compound **20** provided a 43:57 mixture of

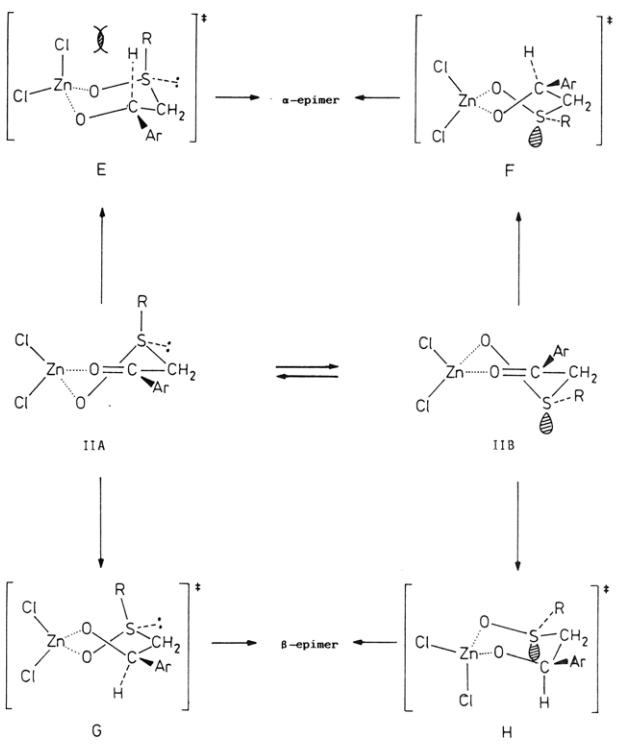


Figure 6. Proposed transition states for hydride reductions in the presence of $ZnCl_2$.

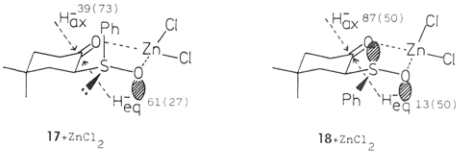


Figure 7. Stereoselectivity of *i*-Bu_2AlH and $NaBH_4$ (in parentheses) reductions in the presence of $ZnCl_2$.

26e/**26a**, **19** gave a different **25e**/**25a** ratio (23:77) compared to that obtained with pure **19** (45:55). The presence of acid appears to decrease **25e** (which comes from intramolecular hydride approach), probably by competing with *i*-Bu_2AlH in associating to **19** (the acid–substrate complex only may be *inter*molecularly attacked by hydride). In an independent run, pure **19** was doped with MCBA and reduced with *i*-Bu_2AlH. The result confirms the decrease in the amount of **25e** caused by the acid (compare entries 11 and 12).

The reactions of the acyclic keto sulfoxides with *i*-$Bu_2AlH/ZnCl_2$ afforded different results depending on the substrates (Table II). Reduction of compound **1** exhibited a high stereoselectivity, which slightly decreased in the case of **2**, the β alcohols being favored in both reactions. On the contrary, diastereomeric excesses were smaller in the reductions of pyridyl keto sulfoxides **3**–**5**. The result obtained for compound **1** cannot be explained by assuming an exclusively steric control in the hydride approach to the chelate indicated by model II (Scheme I), because the differentiation between the two carbonyl faces is not so obvious due to the conformational equilibrium involving IIA and IIB depicted in Figure 6.

Hydride approach to IIA and IIB gives rise to four possible TS, E–H. F and G are unstable flexible TS and will be disregarded.[26] The higher stability of chair-like H as compared to E $[(Cl/R)_{1,3\text{-diaxial}}$ interaction] justifies

(22) The reduction of **18** with *i*-Bu_2AlH is slower than that of **17** (the reduction of a mixture **17** + **18** with *i*-Bu_2AlH allowed us to reach this conclusion). This may be due to the more favorable approach of the hydride on the carbonyl group in **17** (almost orthogonal) as compared with that in **18**. In the latter, the chair-like TS must be deformed in order to reach a similar direction of approach, being possible to adopt a quasi-boat form.

(23) Other sulfur functions in the axial position hindered the equatorial hydride approach in cyclohexanone derivatives (see ref 4). At the begining, we thought that the sulfinyl group would exhibit the same behavior; hence the study of the rigid models with such a function in axial position had been disregarded. Nevertheless, the results obtained in the reduction of **16** prompted us to synthesize the substrates **19** and **20**.

(24) This compound slowly equilibrates with its trans diastereomer (epimerization at C-2) on standing in $CHCl_3$ solution. The composition of the equilibrium mixture is 3:1, with **19** being the major isomer, which is in accordance with the results obtained in MM2 calculations on (methylsulfinyl)cyclohexanones (see ref 19). Thus, the reduction studies must be carried out on **19** freshly prepared.

(25) All attempts to eliminate MCBA, by use of $NaCO_3H$, resulted in the epimerization at C-2. The reaction of **4** with $NaIO_4$ afforded a mixture of four epimeric keto sulfoxides.

(26) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; p 211.

the exclusive (R = *p*-Tol) or predominant (R = Me) formation of the β epimer in the reaction mixture.

In order to check the possible, additional role of stereoelectronic effects, reactions of **1** and **2** with $NaBH_4$ were performed in the presence of $ZnCl_2$. In both cases, the stereoselectivity was low [**1** yielded **6**α:**6**β (41:59, 90% yield) and **2** gave **7**α:**7**β (46:54, 92% yield)] in contrast to the results obtained with *i*-$Bu_2AlH/ZnCl_2$ (Table II). These marked stereoselectivity differences suggest that stereoelectronic effects, in addition to steric ones, are important in controlling the hydride approach to chelated keto sulfoxides. In order to evaluate their relative contribution, we reduced **17** and **18** (see Figure 7) with both *i*-$Bu_2AlH/ZnCl_2$ (Table III, entries 3 and 3′) and $NaBH_4/ZnCl_2$ (entries 4 and 4′). The resulting percentages of axial vs equatorial hydride attack (Figure 7) for *i*-Bu_2AlH and $NaBH_4$ (in parentheses) may be explained in the reduction of **17** by assuming that the lone electron pair at the sulfinyl oxygen facilitates or hampers, respectively, the equatorial attack of the electrophilic (*i*-Bu_2AlH) or nucleophilic hydride (BH_4^-). The results obtained from **18** (see Figure 7) suggest that the influence of the unshared pair at sulfur must be higher than that of the oxygen in the hydride approach, probably because the former is closer to the reaction center. Since **17** and **18** are epimers, the only differences presented by the corresponding chelates toward the approaching hydride are the position of the phenyl group and lone pair at sulfur (Figure 7). Therefore, the lower axial attack ratio observed in **18** (50:50) compared to **17** (73:27), even though Ph is axial in **17**, suggests the dominant repulsive stereoelectronic role of sulfur lone pair in **18** toward the approaching BH_4^-.

The stereoselectivity observed in the reductions of **15** and **16** with *i*-$Bu_2AlH/ZnCl_2$ (entries 8 and 8′) was higher than that of **17** and **18**, respectively (entries 3 and 3′). Taking into account the results obtained in the reduction of **19** with this reagent (entry 13), the axial attack on **15A** (Scheme IV) would explain the increase in the proportion of the *cis*-hydroxyl sulfoxide **21**[e]. The intramolecular hydride transfer from **16A**, which cannot chelate to $ZnCl_2$, should be much easier than in the case of **15A** (Figure 5) and would justify the increase of the **22**[a] ratio.

The reductions of **3**–**5** with *i*-$Bu_iAlH/ZnCl_2$ (Table II) gave poor stereoselectivity. This should be attributed to the competing pyridyl nitrogen toward association with $ZnCl_2$. Thus, chelation cannot be complete[27] and the formation of the nonchelated species takes place with opposite stereoselectivity. On the other hand, the pyridine ring could also decrease the basicity of the carbonyl oxygen, making this group less able to participate in the chelation.[28]

The stereoselective reduction of acyclic keto sulfoxides with $LiAlH_4$ had been explained by assuming that Li^+ acts like $ZnCl_2$ does in the system *i*-$Bu_2AlH/ZnCl_2$ and its lower stereoselectivity was justified on the basis of the smaller chelating ability of Li^+.[2] Nevertheless, several results suggest that the situation is not that simple: (i) similar mixtures of hydroxy sulfoxides were obtained when **1** and **2** were reduced with $LiBH_4$ and $ZnCl_2/NaBH_4$ (Table II), indicating a similar chelating ability of both systems; (ii) the β/α ratio of epimeric hydroxy sulfoxides obtained from **1** and **2** is larger with $LiAlH_4$ than with $ZnCl_2/NaBH_4$ (Table II), despite the fact that both nucleophilic hydrides of similar size should act on similar chelated species. These facts suggest that the factors controlling AlH_4^- and BH_4^- attack must be different.

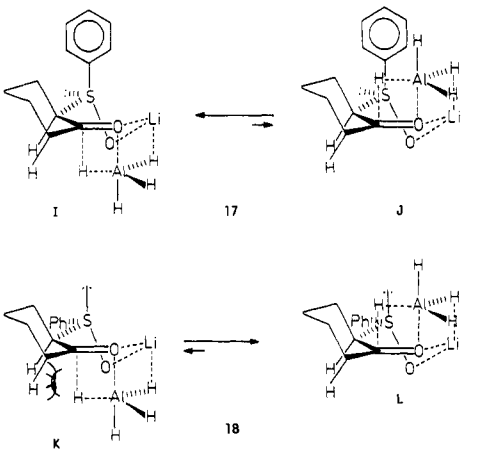


Figure 8. Proposed transition states for intramolecular hydride transfer in $LiAlH_4$ reductions.

When we used a 1:1 TMEDA/$LiAlH_4$ molar ratio, the reduction of **1**, **3**, **4**, and **5** was unsuccessful, whereas in the case of **2**, which forms the most stable chelate,[28] only 10% of starting product was recovered. This percentage became larger when more TMEDA was added and the reaction did not proceed at all when the molar ratio TMEDA/$LiAlH_4$ was 4:1. On the other hand, 2 mol of $LiAlH_4$ were needed for the reduction of **5** (the first mole of Li^+ should be consumed by the remote nitrogen). These findings suggest that the proximity of Li^+ to the reaction center is essential in the reducing role of this hydride.[19a]

The stereoselectivity in the reductions of cyclic compounds **17** and **18** with $LiAlH_4$ (entries 5 and 5′ in Table III) and $ZnCl_2/i$-Bu_2AlH (entries 3 and 3′) are similar, but very different from that observed with $NaBH_4/ZnCl_2$ (entries 4 and 4′). Once we have substantiated the influence of the stereoelectronic effects in controlling the hydride approach, again these results suggest that additional factors, different from those mentioned in the cases of $NaBH_4$ and *i*-$Bu_2AlH/ZnCl_2$, should be considered to complete the picture of the $LiAlH_4$ reductions. On the basis of Ashby's proposal,[20a] our model shown in Figure 8 justifies that, in the case of **17**, the formation of TS I should be quite favored as compared to J. This would determine a higher preference for the equatorial hydride attack in **17**. In its epimer **18**, the TS L, more stable than K, favors the axial approach (see Figure 8).

The reductions of **15** and **16** with $LiAlH_4$ (entries 9 and 9′) yielded a higher proportion of *cis*-hydroxy sulfoxides (**21**[e] and **22**[e]) than that observed in the reactions of the rigid substrates **17** and **18**. This may be easily explained from the expected stereospecific reduction of the axial conformations **15A** and **16A** (see above).

Conclusions

From this work we have drawn the following conclusions: (i) In the reductions of keto sulfoxides with *i*-Bu_2AlH, the hydride transfer takes place *intramolecularly* from SO–Al associated species. The relative stability of the proposed, chair-like TS determines the high diastereoselectivity observed. (ii) The hydride reductions in the presence of $ZnCl_2$ take place on the chelated species that adopt a half-chair conformation and pass through the most stable chair-like TS (favored with respect to the flexible forms).

(27) An excess of $ZnCl_2$ leads to the reduction of sulfoxides to thioethers.

(28) We have studied the NMR spectra of substrates **1**–**5** in the presence of $ZnCl_2$. We observed a decrease of methylene $\delta(^1H)$ values in the order **2** > **3** > **1** > **5** > **4** as expected from the basicity of sulfinyl and carbonyl oxygens. From the changes observed in the chemical shifts of the pyridyl protons in substrates **3**, **4**, and **5**, we have established using reference compounds (García Ruano, J. L.; Martín, A. M.; Rodríguez, J. H. *An. Quim.*, in press) that an important amount of $ZnCl_2$ is associated with the nitrogen, in accordance with the two formulated hypotheses.

(iii) The important role of the unshared electron pairs at sulfinyl oxygen and sulfur in controlling the approach of all hydrides is strongly indicated. Their interaction with electrophilic i-Bu_2AlH or nucleophilic hydrides, respectively, favors or hampers the hydride approach.

Experimental Section

Melting points were obtained in open capillary tubes and are uncorrected. Mass spectra were recorded at 70 eV. ^1H and ^{13}C NMR spectra were recorded at 200.1 and 50.3 MHz. Diastereomeric ratios were established by integration of well-separated signals of both diastereomers in the mixtures of the hydroxy sulfoxides resulting from hydrolysis. Thin layer chromatography was performed by using precoated sheets of silica gel 60 and flash column chromatography was performed with silica gel 60 (230–400 mesh) of Macherey-Nagel. Eluting solvents are indicated in the text. Dry THF was distilled from sodium/benzophenone ketyl and dichloromethane was dried over phosphorus pentoxide. Apparatus for all experiments was dried by flaming in a stream of dry argon and all reactions were carried out under an argon atmosphere and were monitored by TLC. Unless otherwise indicated, routine workup was as follows: The crude mixtures resulting from hydrolysis were extracted with methylene chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo. Diastereomeric ratios are listed in Tables II and III. Yields and reduction times are collected in Table IV.

Preparation of Acyclic Keto Sulfoxides. General Procedure. The synthesis of compounds **4** and **5** was carried out by following the procedure previously reported,[29] modified as follows: To a solution of LDA (24 mmol) in 50 mL of THF at −78 °C was added dropwise (*R*)-(+)-methyl *p*-tolyl sulfoxide (8 mmol) in 10 mL of THF. The temperature was then allowed to reach 0 °C and the mixture was stirred for 20 min. The temperature was lowered to −78 °C and a solution of 9 mmol of ester in 10 mL of THF was added dropwise. The resulting solution was stirred at −78 °C for the time indicated. The mixture was decomposed with 20 mL of a saturated ammonium chloride solution. The organic layer was separated and workup of the aqueous solution yielded a residue that was purified by chromatography or crystallization, as indicated.

2-[(4-Methylphenyl)sulfinyl]-1-(2-pyridyl)ethanone (4) was prepared from ethyl 2-pyridinecarboxylate: reaction time 15 min; yield 58%; purified by crystallization from hexane–acetone (1:1), mp 89–90 °C; $[\alpha]_D$ +142° (acetone, c = 0.6); MS, m/z (rel intensity) 259 (23) M^+, 211 (52), 210 (21), 139 (100), 120 (43), 91 (27), 78 (31); ^1H NMR δ 8.65 (dt, 1 H, J = 1.1 and 7.8 Hz), 8.03 (dt, 1 H, J = 1.7 and 9.3 Hz), 7.85 (td, 1 H, J = 1.1 and 9.3 Hz), 7.50 (ddd, 1 H, J = 1.7, 4.8, and 7.6 Hz), 7.59 and 7.28 (AA′BB′ system, 4 H), 4.82 and 4.60 (AB system, 2 H, J = 13.6 Hz), 2.39 (s, 3 H); IR (KBr) 1695, 1080, 1041 cm^{-1}. Anal. Calcd for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05; N, 5.40; S, 12.36. Found: C, 64.85; H, 5.36; N, 5.64; S, 12.44.

2-[(4-Methylphenyl)sulfinyl]-1-(4-pyridyl)ethanone (5) was prepared from ethyl 4-pyridinecarboxylate: reaction time 1 h; yield 71%; mp 78–80 °C (from 1:1 hexane–acetone); $[\alpha]_D$ +194° (acetone, c = 1.0); MS, m/z (rel intensity) 259 (20), 139 (100), 92 (6), 91 (16), 78 (15); ^1H NMR δ 8.81 and 7.67 (AA′BB′ system, 4 H), 7.55 and 7.32 (AA′BB′ system, 4 H), 4.47 and 4.30 (AB system, 2 H, J = 13.7 Hz), 2.41 (s, 3 H); IR (Nujol) 1686, 1085 cm^{-1}.

4,4-Dimethyl-2-(phenylthio)cyclohexanone (12). To a solution of LDA (34.5 mmol) in 50 mL of THF at −78 °C was added dropwise 2 g (25.5 mmol) of 4,4-dimethylcyclohexanone[30] in a mixture of THF (6 mL) and HMPA (17 mL). The resulting solution was stirred at −78 °C for 1 h, and the dry ice–methanol bath was replaced with an ice–water bath. After being stirred for 1 h at 0 °C and 35 min at room temperature, the mixture was cooled to 0 °C and 7.85 g (33 mmol) of diphenyl disulfide was added. The reaction mixture was then stirred for 15 min at 0 °C and 30 min at room temperature. The solution was poured into a separatory funnel containing ethyl acetate and 15% HCl. The separated organic layer was washed with a saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and concentrated to dryness. The crude material obtained (9.23 g of a yellowish solid) was a mixture of diphenyl disulfide and 4,4-dimethyl-2-(phenylthio)cyclohexanone (**12**). Most of the diphenyl disulfide was separated by crystallization from methanol. Flash column chromatography (CH_2Cl_2 eluent) afforded 2.52 g (68% yield) of **12** as a white solid, mp 57–58 °C (from hexane): MS, m/z (rel intensity) 236 (7) M^+, 234 (100), 177 (45), 136 (25), 123 (11), 110 (68), 97 (27), 55 (68); ^1H NMR δ 7.35 (m, 5 H), 404 (dd, 1 H, J = 12.0 and 6.0 Hz), 2.57–2.49 (m, 2 H), 2.03 (ddd, 1 H, J = 13.5, 6.0, and 2.7 Hz), 1.82–1.61 (m, 3 H), 1.17 (s, 3 H), 1.04 (s, 3 H); IR (Nujol) 1697, 737, 691 cm^{-1}. Anal. Calcd for $C_{14}H_{18}OS$: C, 71.79; H, 7.69; S, 13.67. Found: C, 71.59; H, 7.91; S, 13.96.

[2*S,(S)*R**]- and [2*S**,(S)*S**]-2-(Phenylsulfinyl)cyclohexanone (15 and 16).** A solution of *m*-chloroperbenzoic acid (10 mmol) in 20 mL of chloroform was added to a solution of sulfide **11** in 20 mL of chloroform at 0 °C. After 15 min the resulting solution was washed with several portions of saturated aqueous sodium bicarbonate solution until the washing aqueous phase remained alkaline. The organic phase was dried over anhydrous magnesium sulfate and concentrated in vacuo to yield a 67:33 mixture of **15** and **16** (yield 98%). Pure diastereomer **15** was obtained by fractional cyrstallization of the mixture from hexane–benzene as a white solid, mp 108–109 °C: MS, m/z (rel intensity) 222 (8) M^+, 125 (26), 97 (100), 69 (79), 41 (59); ^1H NMR δ 7.70–7.48 (m, 5 H), 3.37 (ddd, 1 H, J = 9.4, 5.6, and 1.2 Hz), 2.60–2.47 (m, 1 H), 2.44–1.55 (m, 7 H); IR (Nujol) 1700, 1020 cm^{-1}. From the mother liquors compound **16** was isolated pure by crystallization from hexane–acetone: mp 111–112 °C; MS, m/z (rel intensity) 222 (23) M^+, 174 (8), 125 (41), 97 (100), 69 (86), 41 (99); ^1H NMR δ 7.70–7.48 (m, 5 H), 3.56 (t, 1 H, J = 6.6 Hz), 2.62–2.37 (m, 2 H), 2.23–1.60 (m, 6 H); IR (Nujol) 1700, 1460, 1040, 760 cm^{-1}.

[2*S,(S)*R**]- and [2*S**,(S)*S**]-4,4-Dimethyl-2-(phenylsulfinyl)cyclohexanone (17 and 18).** Oxidation of **12** with *m*-chloroperbenzoic acid following the procedure described above afforded a 50:50 mixture of **17** and **18** (yield 95%). Compounds **17** and **18** were also obtained by oxidation with sodium metaperiodate as follows: sulfide **12** (6 g, 25.6 mmol) was dissolved in 20 mL of methanol and cooled in an ice bath prior to the dropwise addition of a solution of sodium metaperiodate (5.5 g, 25.6 mmol) in 10 mL of water. The solution was stirred for 4 h at 0 °C and overnight at room temperature. The reaction mixture was diluted with water and extracted with methylene chloride. Drying and evaporation of the organic solvent in vacuo afforded an 83:17 mixture of **17** and **18** (97% yield). From this mixture pure diastereomer **17** was obtained by fractional crystallization from acetone–hexane as a white solid: mp 108–109 °C; MS, m/z (rel intensity) 250 (22) M^+, 125 (93), 109 (40), 83 (23), 69 (34), 55 (100); ^1H NMR δ 7.72–7.47 (m, 5 H), 3.45 (dd, 1 H, J = 13.2, 6.1 Hz), 2.57–2.32 (m, 2 H), 2.07 (t, 1 H, J = 13.2 Hz), 1.72–1.65 (m, 2 H), 1.60–1.51 (m, 1 H), 1.08 (s, 3 H), 1.05 (s, 3 H); IR (Nujol) 1715, 1039 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_2S$: C, 67.20; H, 7.20; S, 12.80. Found: C, 67.12; H, 7.39; S, 13.04. Pure diastereomer **18** was isolated by fractional crystallization of a 50:50 mixture of **17** and **18** from acetone–hexane at 0 °C, mp 105–106 °C: MS, m/z (rel intensity) 250 (9) M^+, 125 (41), 109 (9), 83 (15), 69 (24), 55 (100); ^1H NMR δ 7.76–7.45 (m, 5 H), 3.93 (dd, 1 H, J = 13.0 and 6.0 Hz), 2.70–2.20 (m, 2 H), 1.82–1.38 (m, 3 H), 1.28 (t, 1 H, J = 13.0 Hz), 1.12 (s, 3 H), 0.97 (s, 3 H); IR (Nujol) 1707, 1036 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_2S$: C, 67.20; H, 7.20; S, 12.8. Found: C, 67.16; H, 7.27; S, 13.26.

[2*R,4*S**,(S)*R**]- and [2*R**,4*S**,(S)*S**]-4-(1,1-Dimethylethyl)-2-(methylsulfinyl)cyclohexanone (19 and 20).** A solution of 6 mmol of *m*-chloroperbenzoic acid in 25 mL of dry methylene chloride was added to a solution of *trans*-4-(1,1-dimethylethyl)-2-(methylthio)cyclohexanone (**14**) (6 mmol) in 25 mL of dry methylene chloride. After being stirred for 15 min at room temperature, the solvent was concentrated to 15 mL and the solution was cooled to −20 °C, crystallizing the *m*-chlorobenzoic acid (MCBA), which was filtered. The mother liquors were evaporated to yield a 83:17 mixture of **19** and **20** as a white solid (yield 95%). Pure diastereomer **19** was obtained by crystallization of the mixture from hexane–acetone, mp 98–99 °C: MS, m/z (rel intensity) 216 (7) M^+, 169 (10), 139 (13), 57 (100); ^1H NMR δ 3.45

(29) Solladié, G.; Demailly, G.; Greck, C. *J. Org. Chem.* **1985**, *50*, 1552.
(30) Bordwel, F. G.; Wellman, K. M. *J. Org. Chem.* **1963**, *28*, 1347.

Table IV. Reaction Times and Chemical Yields (in Parentheses) of Reductions of Substrates 1–5 and 15–19 with Different Hydrides in THF at −78 °C

substr	n-Bu_4NBH_4[a]	$NaBH_4$	DIBAL	DIBAL/$ZnCl_2$	$LiAlH_4$	$NaBH_4/ZnCl_2$
1	48 h	3 h (87)	3 h[b]	3 h[b]	3 h[b]	4 h[c] (90)
2	48 h	3 h (93)	3.5 h (100)	2.5 h (77)	10 min (97)	4 h[c] (92)
3	3 h	3 h (100)[d]	1 h (100)[d]	3 h (82)	3 h (90)	
4	3 h	3 h (91)	6 h (100)	3 h (93)	3 h (100)	
5	3 h	15 min (85)	6 h (95)	6 h (75)	3 h (95)[e]	
15		1 h (99)	1 h (97)	1 h (94)	1 h (68)	
16		1 h (90)	1 h (96)	1 h (84)	1 h (81)	
17		1 h (81)	1 h (87)	1 h (94)	1 h (98)	1 h (93)
18		1 h (72)	1 h (72)	1 h (91)	1 h (80)	1 h (91)
19		1 h (81)	1 h (99)	1 h (71)		

[a] Room temperature. [b] From ref 2. [c] 2 h at −78 °C and 2 h at room temperature. [d] From ref 4. [e] Ratio [hydride]/[ketone] = 2:1.

(m, 1 H), 2.73 (m, 1 H), 2.61 (s, 3 H), 2.55 (m, 1 H), 2.41–2.09 (m, 2 H), 1.95–1.75 (m, 2 H), 1.6 (m, 1 H), 0.97 (s, 9 H); IR (KBr) 1705, 1070, 1055 cm^{-1}. Pure diastereomer **20** could not be isolated and was characterized in a 33:7:60 mixture of **19**/**20**/MCBA: 3.62 (m, 1 H), 2.64 (s, 3 H), 2.85–1.40 (m, 7 H), 0.94 (s, 9 H).

General Procedures for Hydride Reductions. Method A. *i*-Bu_2AlH. A solution of 0.23 mmol of 2-keto sulfoxide in 1 mL of THF was added to a mixture of 0.25 mL (0.25 mmol) of a 1 M hexane solution of *i*-Bu_2AlH and 1 mL of THF was added at −78 °C. The resulting solution was stirred and upon completion (Table IV), the mixture was decomposed with 3 mL of methanol. The solvents were evaporated in vacuo, and the residue was diluted with a 10% aqueous sodium hydroxide solution.

Method B. $NaBH_4$. A solution of 0.25 mmol of 2-keto sulfoxide in 3 mL of THF or ethanol was added to a solution of sodium borohydride at −78 °C in 3 mL of the same solvent. The resulting mixture was stirred upon completion (Table IV) and decomposed with 3 mL of saturated ammonium chloride solution.

Method C. *n*-Bu_4NBH_4. A solution of 2-keto sulfoxide (0.25 mmol) in 2 mL of methylene chloride or THF was added to a solution of tetra-*n*-butylammonium borohydride (1 equiv) in 3 mL of the same solvent. The mixture was stirred at room temperature upon completion and washed with 10 mL of a 3% hydrogen peroxide solution and then with 5 mL of a 10% aqueous sodium hydroxide solution. The aqueous solution was extracted with methylene chloride (3 × 10 mL) and the organic layer was washed with a saturated sodium sulfite solution (1 × 10 mL) and worked up as usual. The crude product was taken up in anhydrous diethyl ether, the insoluble tetrabutylammonium salts were removed by filtration, and the solvent was evaporated under reduced pressure. Yields in pure hydroxy sulfoxides could not be determined.

Method D. *i*-$Bu_2AlH/ZnCl_2$. A solution of 2-keto sulfoxide (0.23 mmol) and anhydrous zinc chloride (0.23 mmol) in 2 mL of THF (or methylene chloride for **1–5**) was stirred for 30 min at room temperature. A 1 M solution of *i*-Bu_2AlH in hexane (0.28 mmol for **1–5** and 0.55 mmol for **15–20**) was added to the cooled (−78 °C) solution. The reaction mixture was stirred until completion of the reaction (Table IV) and then worked up as in method A.

Methods E ($LiAlH_4$) and F ($LiBH_4$). A solution of 0.25 mmol of 2-keto sulfoxide in 3 mL of THF was added to a suspension of the hydride (0.25 mmol) in 3 mL of THF at −78 °C. After completion of the reaction, the mixture was decomposed with 2 mL of a saturated ammonium chloride solution.

Method G. $NaBH_4/ZnCl_2$. A solution of the 2-keto sulfoxide (0.25 mmol) and anhydrous zinc chloride (0.25 mmol) in 3 mL of THF was stirred at room temperature for 30 min and then cooled at −78 °C. The resulting solution was cannulated over a suspension of sodium borohydride (0.25 mmol) in 3 mL of THF and stirred until completion (Table IV). The mixture was decomposed by addition of 3 mL of a saturated ammonium chloride solution.

1-(2-Pyridyl)-2-[(4-methylphenyl)sulfinyl]ethanol (9α and 9β). Reduction of **4** following methods A–F afforded a yellow oil, which was characterized as a mixture of diastereomers **9α** and **9β** (Table II). Method A afforded pure **9α** as a white solid, mp 100–102 °C (from hexane): $[\alpha]_D$ +97° (acetone, c = 1.6); MS, m/z (rel intensity) 261 (8) M^+, 199 (20), 139 (22), 122 (100), 91 (40), 79 (29), 78 (44); ^1H NMR δ 8.7 (m, 1 H), 7.68 (m, 1 H), 7.55 (m, 1 H), 7.58 and 7.34 (AA'BB' system, 4 H), 7.19 (m, 1 H), 5.71 (br s, 1 H), 5.32 (m, 1 H), 3.18 (m, 2 H), 2.39 (s, 3 H); IR (KBr) 3200, 1080, 1060, 1040 cm^{-1}. Compound **9β** was not obtained diastereomerically pure: ^1H NMR δ 8.51 (m, 1 H), 7.72 (m, 1 H), 7.58 and 7.34 (AA'BB' system, 4 H), 7.52 (m, 1 H), 7.32 (m, 1 H), 5.38 (m, 1 H), 4.95 (br s, 1 H), 3.25 (m, 2 H), 2.39 (s, 3 H). Anal. Calcd for $C_{14}H_{15}NO_2S$: C, 64.34; H, 5.78; N, 5.36. Found: C, 64.27; H, 6.06; N, 5.64.

1-(4-Pyridyl)-2-[(4-methylphenyl)sulfinyl]ethanol (10α and 10β). Reduction of **5** following methods A–F afforded a yellow oil, which was characterized as a mixture of diastereomers **10α** and **10β** (Table II). Method A afforded pure **10α** as a white solid, mp 73–74 °C (from 2:1 hexane–acetone): $[\alpha]_D$ +164° (acetone, c = 1); MS, m/z (rel intensity) 261 (7) M^+, 140 (81), 139 (47), 122 (100), 106 (14), 92 (90), 91 (57), 78 (33), 77 (32); ^1H NMR δ 8.53 and 7.26 (AA'BB' system, 4 H), 7.56 and 7.37 (AA'BB' system, 4 H), 5.27, 3.17 and 2.84 (ABX system, 3 H, J = 13.5, 10.5, and 1.9 Hz), 2.44 (s, 3 H); IR (Nujol) 3465, 1099, 1075, 1043 cm^{-1}. Pure **10β** was isolated by flash chromatography from the mixture obtained by method B [eluent 5:35:60 ammonium hydroxide (0.92 specific gravity)–ethanol–diethyl ether] as a yellow oil: MS, m/z (rel intensity) 261 (1) M^+, 140 (26), 139 (87), 123 (21), 106 (100), 92 (34), 91 (59), 78 (73), 77 (42); ^1H NMR δ 8.57 and 7.18 (AA'BB' system, 4 H), 7.58 and 7.39 (AA'BB' system, 4 H), 5.45, 3.09 and 2.94 (ABX system, 3 H, J = −13.3, 10.1, and 2.0 Hz), 2.44 (s, 3 H); IR (film) 3360, 1032 cm^{-1}.

[1*S,2*S**,(S)*R**]- and [1*R**,2*S**,(S)*R**]-2-(Phenylsulfinyl)cyclohexanol (21[a] and 21[e]).** Reduction of compound **15** following methods B, D, and E afforded a white solid, which was characterized as a mixture of diastereomers **21[a]** and **21[e]** (Table III). Method A yielded pure diastereomer **21[a]** as a white solid, mp 135–136 °C (from hexane–acetone): MS, m/z (rel intensity) 224 (3) M^+, 126 (100), 97 (19), 77 (25); ^1H NMR δ 7.72–7.42 (m, 5 H), 4.16 (d, 1 H, J = 3.0 Hz), 3.92 (dt, 1 H, J = 10.2 and 3.5 Hz), 2.69 (ddd, 1 H, J = 11.8, 10.2, and 3.9 Hz), 2.16–2.02 (m, 1 H), 1.75–1.02 (m, 7 H); IR (Nujol) 3300, 1070, 1020 cm^{-1}. Pure diastereomer **21[e]** was obtained by crystallization of the mixture resulting from method D carbon tetrachloride–methylene chloride), mp 138–139 °C: MS, m/z (rel intensity) 224 (1) M^+, 126 (100), 97 (15), 81 (51), 78 (59); ^1H NMR δ 7.65–7.50 (m, 5 H), 4.45 (m, 1 H), 3.30 (dd, 1 H, J = 2.0 and 1.4 Hz), 2.50 (ddd, 1 H, J = 12.5, 3.7, and 2.0 Hz), 2.15–1.06 (m, 8 H); IR (Nujol) 3300, 1030, 990 cm^{-1}.

[1*S,2*S**,(S)*S**]- and [1*R**,2*S**,(S)*S**]-2-(Phenylsulfinyl)cyclohexanol (22[a] and 22[e]).** Reduction of compound **16** following procedures A, B, D, and E yielded a white solid, which was characterized as a mixture of diastereomers **22[a]** and **22[e]** (Table III). Pure **22[a]** was obtained by crystallization (hexane–acetone) of the mixture resulting from method D, mp 156–157 °C: MS, m/z (rel intensity) 224 (6) M^+, 149 (12), 126 (100), 97 (60), 77 (74); ^1H NMR δ 7.72–7.52 (m, 5 H), 5.11 (d, 1 H, J = 1.0 Hz), 4.14 (dt, J = 9.8 and 5.1 Hz), 2.75 (ddd, 1 H, J = 11.8, 9.8, and 4.5 Hz), 2.21–2.08 (m, 1 H), 1.82–0.97 (m, 7 H); IR (Nujol) 3300, 1070, 990 cm^{-1}. Crystallization (hexane–acetone) of the mixture obtained by method B afforded pure **22[e]**, mp 140–142 °C: MS, m/z (rel intensity) 224 (2) M^+, 126 (100), 99 (14), 78 (30); ^1H NMR δ 7.72–7.45 (m, 5 H), 4.46 (t, 1 H, J = 1.9 Hz), 4.35 (m, 1 H), 2.46–2.35 (ddd, 1 H, J = 12.8, 3.2, and 2.1 Hz), 2.34–2.14 (m, 1 H), 1.94–1.68 (m, 4 H), 1.50–1.16 (m, 3 H); IR (Nujol) 3300, 1020, 990 cm^{-1}.

[1S*,2S*,(S)R*]- and [1R*,2S*,(S)R*]-4,4-Dimethyl-2-(phenylsulfinyl)cyclohexanol (23[a] and 23[e]). Reduction of compound **17** following methods B, D, E, and G afforded a mixture of diastereomers **23[a]** and **23[e]** (Table I). Method A yielded pure **23[a]**, mp 154-155 °C (from hexane-ethyl acetate): MS, *m/z* (rel intensity) 252 (1) M^+, 127 (10), 126 (100), 109 (20), 78 (18); ^1H NMR δ 7.65-7.42 (m, 5 H), 4.60-4.35 (m, 1 H), 3.87 (dt, 1 H, *J* = 10.7 and 5.1 Hz), 2.78 (ddd, 1 H, *J* = 13.0, 10.7, and 3.8 Hz), 1.95 (ddd, 1 H, *J* = 13.2, 5.1, and 3.8 Hz), 1.66 (ddd, 1 H, *J* = 13.2, 10.7, and 4.1 Hz), 1.40-1.10 (m, 3 H), 0.94 (ddd, 1 H, *J* = 13.2, 3.8, and 2.7 Hz), 0.86 (s, 3 H), 0.80 (s, 3 H); IR (Nujol) 3220, 1012 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_2S$: C, 66.66; H, 7.94, S, 12.70. Found: C, 66.79; H, 8.24; S, 13.10. Fractional crystallization (hexane-acetone) of the mixture obtained by method E afforded pure **23[e]**, mp 150-151 °C: MS, *m/z* (rel intensity) 252 (1) M^+, 126 (100), 109 (4), 78 (3); ^1H NMR δ 7.70-7.45 (m, 5 H), 4.32 (c, 1 H, *J* = 2.2 Hz), 3.20 (m, 1 H), 2.63 (ddd, 1 H, *J* = 13.3, 3.8, and 2.2 Hz), 1.93 (t, 1 H, *J* = 13.3 Hz), 1.84-1.50 (m, 3 H), 1.30-1.00 (m, 2 H), 0.96 (s, 3 H), 0.78 (s, 3 H); IR (Nujol) 3339, 1012 cm^{-1}.

[1S*,2S*,(S)S*]- and [1R*,2S*,(S)S*]-4,4-Dimethyl-2-(phenylsulfinyl)cyclohexanol (24[a] and 24[e]). Reduction of compound **18** following methods B, D, E, and G yielded a mixture of diastereomers **24[a]** and **24[e]** (Table III). Crystallization of the 95:5 mixture obtained with $LiAlH_4$ (method E) from hexane-acetone afforded pure diastereomer **24[a]** mp 172-173 °C: MS, *m/z* (rel intensity) 252 (1) M^+, 126 (100), 109 (22), 78 (32), 67 (22); ^1H NMR δ 7.80-7.50 (m, 5 H), 4.40 (br s, 1 H), 4.09 (dt, 1 H, *J* = 10.0 and 5.2 Hz), 2.93 (ddd, 1 H, *J* = 12.9, 10.0, and 4.6 Hz), 1.98 (m, 1 H), 1.80-0.92 (m, 5 H), 0.91 (s, 3 H), 0.78 (s, 3 H); IR (Nujol) 3388, 1015 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_2S$: C, 66.66; H, 7.94; S, 12.70. Found: C, 66.57; H, 8.03; S, 12.86. Pure diastereomer **24[e]** was obtained by following method B, mp 167-168 °C (from hexane-ethyl acetate); MS, *m/z* (rel intensity) 252 (1) M^+, 126 (100), 109 (23), 78 (31), 67 (23); ^1H NMR δ 7.80-7.35 (m, 5 H), 4.26 (m, 1 H), 4.12 (br s, 1 H), 2.44 (ddd, 1 H, *J* = 13.9, 3.7, and 2.2 Hz), 2.07 (t, 1 H, *J* = 13.9 Hz), 1.76-1.58 (m, 2 H), 1.36 (ddd, 1 H, *J* = 13.9, 3.7, and 2.7 Hz), 1.27-1.16 (m, 1 H), 1.08-0.97 (m, 1 H), 0.93 (s, 3 H), 0.75 (s, 3 H); IR (Nujol) 3304, 1019 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_2S$: C, 66.66; H, 7.94, S, 12.70. Found: C, 66.60; H, 7.84; S, 12.97.

[1S*,2R*,4S*,(S)R*]- and [1R*,2R*,4S*,(S)R*]-4-(1,1-Dimethylethyl)-2-(methylsulfinyl)cyclohexanol (25[a] and 25[e]). Reduction of compound **19** following method A yielded mixtures of diastereomers **25[a]** and **25[b]** (Table III). Method B afforded pure **25[a]**, mp 182-183 °C (from hexane-acetone): MS, *m/z* (rel intensity) 218 (4) M^+, 109 (4), 81 (31), 57 (100); ^1H NMR δ 4.02 (td, 1 H, *J* = 10.7 and 4.8 Hz), 3.70 (br s, 1 H), 3.22 (c, 1 H, *J* = 4.8 Hz), 2.79 (s, 3 H), 2.45 (m, 1 H), 2.00-1.70 (m, 3 H), 1.52-1.05 (m, 3 H), 0.88 (s, 9 H); IR (KBr) 3340, 1100, 1060, 1015 cm^{-1}. Column chromatography of the mixture obtained by method A (eluent acetone) afforded pure **25[e]** as a white solid, mp 109-110 °C (from hexane-acetone): MS, *m/z* (rel intensity) 218 (1) M^+, 137 (24), 109 (3), 95 (15), 81 (54), 57 (100); ^1H NMR δ 3.88 (c, 1 H, *J* = 3.3 Hz), 3.15 (br s, 1 H), 2.95 (m, 1 H), 2.63 (s, 3 H), 2.23 (m, 1 H), 1.93-1.30 (m, 6 H), 0.90 (s, 9 H); IR (KBr) 3400, 1035, 1025, 1005 cm^{-1}.

[1S*,2R*,4S*,(S)S*]- and [1R*,2R*,4S*,(S)S*]-4-(1,1-Dimethylethyl)-2-(methylsulfinyl)cyclohexanol (26[a] and 26[e]). Reduction of a 33:7:60 mixture of compounds **19**, **20**, and *m*-chlorobenzoic acid following method A afforded a 66:8:20:6 mixture of **25[a]**/**26[a]**/**25[e]**/**26[e]** and the acid (**26[a]**/**26[e]** ratio: 57:43, see Table III), which was chromatographed (eluent acetone) to give pure **25[a]** and **25[e]**. The minor diastereomers could not be isolated pure and **26[a]** was characterized in a 84:16 mixture of **25[a]** and **26[a]**: MS, *m/z* (rel intensity) 218 (2) M^+, 95 (10), 81 (52), 57 (100); ^1H NMR δ 4.02 (td, 1 H, *J* = 10.7 and 4.8 Hz), 3.32 (dc, 1 H, *J* = 3.6 and 1.8 Hz), 2.72 (s, 3 H), 2.20-1.05 (m, 8 H), 0.85 (m, 9 H); IR (KBr) 3340, 1100, 1080, 1060, 1010 cm^{-1}. Diastereomer **26[e]** was identified in a 79:21 mixture of **26[e]** and **25[e]**: MS, *m/z* (rel intensity) 218 (3), 137 (14), 95 (7), 81 (53), 57 (100); ^1H NMR δ 4.48 (c, 1 H, *J* = 3.4 Hz), 2.95 (m, 1 H), 2.64 (s, 3 H), 2.00-1.00 (m, 8 H), 0.86 (s, 9 H); IR (KBr) 3300, 1370, 1110, 1100, 1020 cm^{-1}.

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Registry No. **1**, 52154-24-2; **2**, 124992-49-0; **3**, 124992-50-3; **4**, 124992-51-4; **5**, 124992-52-5; **6α**, 39201-99-5; **6β**, 39201-98-4; **7α**, 94661-72-0; **7β**, 94661-73-1; **8α**, 124733-62-6; **8β**, 124733-63-7; **9α**, 125074-79-5; **9β**, 125074-87-5; **10α**, 125074-80-8; **10β**, 125074-88-6; **11**, 110452-14-7; **12**, 124992-53-6; **14**, 124992-54-7; **15**, 124992-55-8; **16**, 124992-56-9; **17**, 124992-57-0; **18**, 124992-58-1; **19**, 125074-81-9; **20**, 125074-82-0; **21[a]**, 125074-83-1; **21[e]**, 125074-89-7; **22[a]**, 125074-84-2; **22[e]**, 125074-90-0; **23[a]**, 124992-59-2; **23[e]**, 125074-91-1; **24[a]**, 125074-85-3; **24[e]**, 125074-92-2; **25[a]**, 124992-60-5; **25[e]**, 125074-93-3; **26[a]**, 125074-86-4; **26[e]**, 125074-94-4; (*R*)-(+)-4-$MeC_6H_4S(O)Me$, 1519-39-7; PhSSPh, 882-33-7; ethyl 2-pyridinecarboxylate, 2524-52-9; ethyl 4-pyridinecarboxylate, 1570-45-2; 4,4-dimethylcyclohexanone, 4255-62-3.

Supplementary Material Available: Listing of ^{13}C NMR spectral data of all studied compounds (4 pages). Ordering information is given on any current masthead page.

Asymmetric Total Syntheses of Elaeokanines A and B via α-Sulfinyl Ketimine[1]

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α-Lithiated (+)-(*R*)-4,5-dihydro-2-[[(4-methylphenyl)sulfinyl]methyl]-3*H*-pyrrole (**4**) underwent annulation with 1,3-diiodopropane to give (-)-(SS)-1,2,3,5,6,7-hexahydro-8-[(4-methylphenyl)sulfinyl]indolizine (**6**), which was converted into (-)-elaeokanine B (three steps) and (+)-elaeokanine A (four steps).

Introduction

The in-situ 1,4-addition/ring closure reactions of chiral α-sulfinyl ketimine anions[3] occur in useful yield and offer a unique, convenient route for the construction of chiral indolizidine alkaloids. Beside 1,4-addition, α-sulfinyl ketimine anions also undergo annulation with 1,3-diiodopropane;[4] the resulting cyclic chiral β-sulfinyl enamines can be transformed into various indolizidine alkaloids such

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