Pergamon

Tetrahedron Vol. 50, No. 25, pp. 7567-7578, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00380-7

Highly Diastereoselective Hydrocyanation of α-Sulfinyl Cycloalkanones

Ana Escribano, José L. García Ruano,* Ana M. Martín Castro, and Jesús H. Rodríguez*

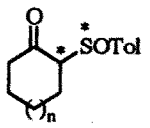
Departamento de Química (C-I), Universidad Autónoma de Madrid, Cantoblanco, 28049-Madrid, Spain

Abstract: Hydrocyanation of cyclic α-sulfinyl ketones under different conditions has been studied. The obtained results show that compounds derived from cyclohexanone react with Et_2AlCN yielding only sulfinyl cyanohydrins exhibiting different configurations at sulfur and at hydroxylic carbon. The stereoselectivity is slightly lower but also very high starting from α-sulfinyl cyclopentanones. The influence of Lewis acids as well as the stereochemical course of these reactions have also been discussed.

Chiral cyanohydrins can be easily transformed into numerous organic groupings, such as aminoalcohols,[1] acyloins,[2] or hydroxyacids.[3] Many of these groupings frequently occur in numerous natural products (antheacyclinones,[4] 17-α-hydroxyprogesterones,[5] spirostanes such as androstanone[6] or dilactoforbic acid[7]). This potential synthetic interest prompted us to develop a new method to afford chiral cyclic cyanohydrins.

Recently we have described the synthesis of enantiomerically pure cyanohydrin derivatives by hydrocyanation of acyclic α-sulfinyl ketones with Et_2AlCN.[8] The high stereoselectivity observed in these reactions was related to the ability of the aluminum to associate with both oxygens in the substrate, giving rise to a pentacoordinated species, as a previous step to the intramolecular cyanide transfer. It was interesting to see whether this methodology could be extended to the synthesis of chiral cyclic cyanohydrins by hydrocyanation of α-sulfinyl cycloalkanones. In addition to the synthetic interest represented by the highly stereoselective formation of the cyanohydrin moiety on cyclic structures, this study was also attractive from a mechanistic point of view because the more rigid nature of the cyclic carbon skeleton may have as a consequence a different stereochemical pathway of the reaction. This had been the case in the DIBAL reductions of α-sulfinyl alkanones.[9] Acyclic substrates always evolved through a chair-like TS, whichever was the configuration of the sulfinyl group. On the contrary, the stereochemical outcome of the α-sulfinyl cycloalkanones was dependent on the relative configurations of C-2 and sulfur (chair-like and twist-like TS's could be operative).

In this paper we report the results obtained in the reaction of the α-sulfinyl cycloalkanones shown in Scheme 1 with Et_2AlCN and propose models to explain the observed stereochemical outcome. Hydrocyanation with Et_2AlCN in the presence of Lewis acids is also investigated.



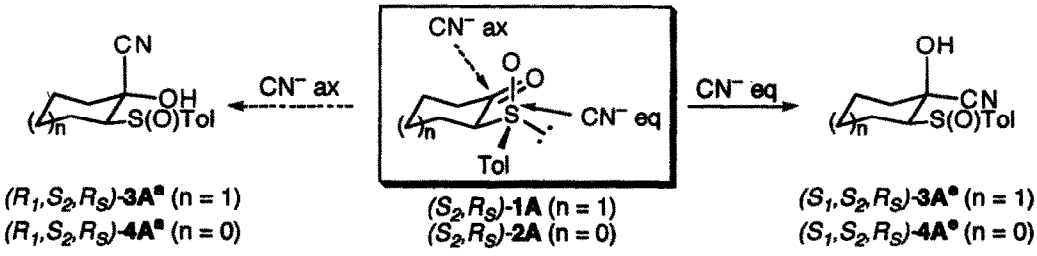
n = 1 **1A** (S_2,R_S), **1B** (R_2,R_S)
n = 0 **2A** (S_2,R_S), **2B** (R_2,R_S)

Scheme 1

RESULTS AND DISCUSSION

The syntheses of the starting α-sulfinyl cycloalkanones **1** and **2** have been previously described.[10] Enantiomerically pure (S_2,R_S)-**1A** could be isolated by crystallization of a mixture of epimers **1A** + **1B** from acetone–hexane (see ref 10). However the isolation of the optically pure isomer (S_2,R_S)-**2A** from a mixture of optically pure **2A** and **2B** was not possible under the same conditions, whereas racemic (S_2*,R_S*)-**2A*** could be crystallized from a mixture of racemic **2A*** and **2B*** (prepared by reaction of racemic methyl *p*-toluenesulfinate). Neither **1B** nor **2B** could be isolated as pure diastereomers due to epimerization at C-2 in solution, and their reactions with Et_2AlCN had to be studied on **A** + **B** mixtures.

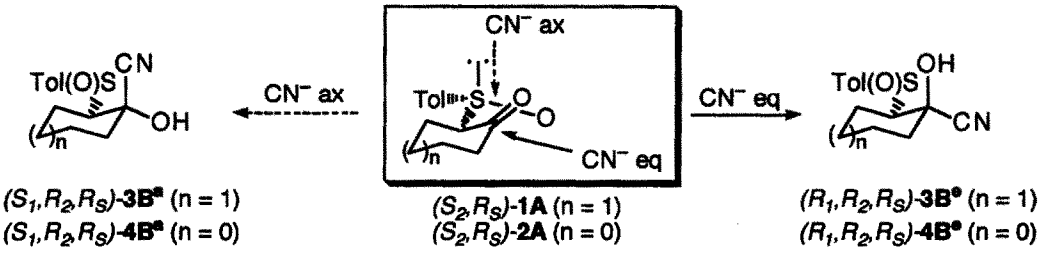
Scheme 2 shows the four possible sulfinyl cyanohydrins, epimeric at the hydroxylic carbon, resulting from axial and equatorial (superscripts [a] and [e], respectively) cyanide approach to the carbonyl group in sulfinyl ketones **A** and **B**, which adopt the foreseeable most stable conformation (sulfur moiety in *pseudo*-equatorial arrangement).



(R_1,S_2,R_S)-**3A**[a] (n = 1)
(R_1,S_2,R_S)-**4A**[a] (n = 0)

(S_2,R_S)-**1A** (n = 1)
(S_2,R_S)-**2A** (n = 0)

(S_1,S_2,R_S)-**3A**[e] (n = 1)
(S_1,S_2,R_S)-**4A**[e] (n = 0)



(S_1,R_2,R_S)-**3B**[a] (n = 1)
(S_1,R_2,R_S)-**4B**[a] (n = 0)

(S_2,R_S)-**1A** (n = 1)
(S_2,R_S)-**2A** (n = 0)

(R_1,R_2,R_S)-**3B**[e] (n = 1)
(R_1,R_2,R_S)-**4B**[e] (n = 0)

Scheme 2

The best results obtained in the reactions of **1A** and **2A***, as well as of **1A** + **1B** and **2A** + **2B** mixtures with Et_2AlCN in toluene are collected in Table 1. Like in the case of acyclic sulfinyl ketones, both the order of the

addition of the reagents (the sulfinyl ketone must be added into the Et_2AlCN, see Experimental Section) and the reaction time (the optimum reaction time for all these syntheses is 5 min) were critical to obtain good stereochemical results and high overall yields of cyanohydrins.

At -78 °C, with 2 eq of Et_2AlCN, **1A** yielded only one cyanohydrin **3A^e** (entry 1), thus demonstrating that hydrocyanation is totally stereoselective. When a smaller amount of Et_2AlCN was used, the reaction was not complete, despite the reaction time was increased. Starting from a **1A** + **1B** (3:1) mixture (entry 2) reaction with Et_2AlCN under the same conditions afforded a mixture of only two cyanohydrins **3A^e** + **3B^a**, the proportion of which is similar to that of the starting sulfinyl ketones. It suggests that under these conditions hydrocyanation of **1B** is also completely stereoselective and the equilibration **1A** ⇄ **1B** does not take place. An increase in the reaction temperature causes both the epimerization of the starting sulfinyl ketones and a decrease of stereoselectivity in the reaction of **1B**. Thus, the reaction of a **1A** + **1B** (75:25) mixture with Et_2AlCN at 0 °C (entry 3) yielded a 77:16:7 mixture of three cyanohydrins **3A^e**, **3B^a**, and **3B^e**. Likewise the reaction of pure **1A** at 0 °C (entry 4) afforded a mixture of the same three cyanohydrins.

Table 1. Results obtained in the Hydrocyanation of Cycloalkanones **1** and **2** with Et_2AlCN

Entry	Substrate (ratio)	T (°C)	[Substrate]: [Et_2AlCN]	Products (ratio)	Yield (%) (isolated)
1	**1A**	-78	1:2	**3A^e**	82
2	**1A** + **1B** (75:25)	-78	1:2	**3A^e** + **3B^a** (78:22)	79
3	**1A** + **1B** (75:25)	0	1:2	**3A^e** + **3B^a** + **3B^e** (77:16:7)	87
4	**1A**	0	1:2	**3A^e** + **3B^a** + **3B^e** (89:6:5)	89
5	**2A***	0	1:3	**4A^{e*}**	87
6	**2A** + **2B** (79:21)	0	1:3	**4A^e** + **4B^a** + **4B^e** (86:11:3)	82

Complete transformation of α-sulfinyl ketones **2** was achieved only at 0 °C with 3 eq of Et_2AlCN. Lower temperatures or a smaller amount of reagent determine the recover of perceivable amounts of the starting material. Under these conditions, reaction of **2A*** was completely stereoselective, giving rise only to cyanohydrin **4A^{e*}** (entry 5). However, **2B** (from a **2A** + **2B** mixture) yielded a 4:1 mixture of **4B^a** and **4B^e**, as could be deduced from the results obtained from a **2A** + **2B** mixture (entry 6). Epimerization of **2B** is also observed under these reaction conditions.

Contrary to the hydrocyanation of acyclic α-sulfinyl ketones with Et_2AlCN,[8] the addition of Lewis acids (MX_2, M = Zn, Mg and X = Cl, Br) caused significant influence on the reaction pathway of 2-(*p*-tolylsulfinyl)cyclohexanone. The results of the hydrocyanation at -78 °C with 2 eq of Et_2AlCN are shown in Table 2.

The composition of the resulting mixtures from **1A** (entries 1-8) clearly shows that partial epimerization of the starting ketones takes place under nearly all conditions. The rate of epimerization, which must happen during

the chelation process before the addition of the cyanide, depends not only on the temperature (the higher temperature, the higher increase in the rate), but also on the acid strength of the employed metallic salt. Hence the addition of a metallic salt to the reaction mixture of **1A** afforded a mixture of cyanohydrins **3A^e**, also obtained in the absence of a chelating agent, and **3B^a**, derived from the sulfinyl ketone epimer at C-2 **1B**. As the chelation temperature rises or the strength of the Lewis acid becomes higher, the degree of epimerization at C-2 increases, since the proportion of **3B^a** in the reaction mixture becomes higher. Nevertheless, the most significant difference induced by the presence of the Lewis acid is the totally stereoselective evolution of **1B** (regardless of the temperature and the used Lewis acid), yielding only **3B^a**, which contrasts with the results obtained in the absence of Lewis acids (see Table 1). This fact had also been observed in the hydrocyanation of acyclic sulfinyl ketones.[8]

Table 2. Results obtained in the reaction of **1** and **2** with Et_2AlCN (2 eq)/MX_2 (1.5 eq) at -78 °C (reaction time 5 min)

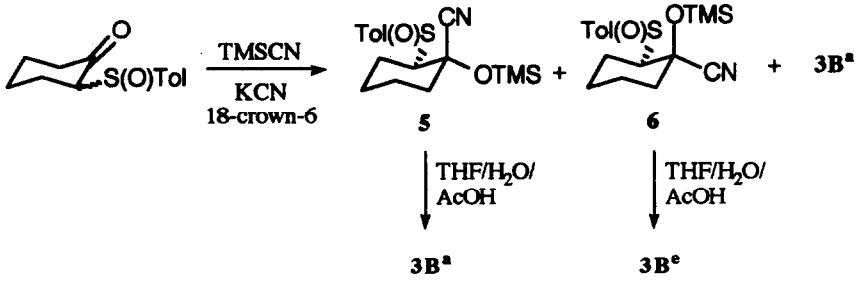
Entry	Compound	MX_2	Chelation temp. (°C)	Products (ratio)	Overall yield (%)
1	**1A**	$ZnCl_2$	+20	**3A^e**	77
2		$ZnBr_2$	–20	**3A^e** + **3B^a** (91:9)	60
3			+20	**3A^e** + **3B^a** (84:16)	54
4		$MgBr_2$	–20	**3A^e** + **3B^a** (90:10)	59
5			+20	**3A^e** + **3B^a** (30:70)	31
6		$MgCl_2$	–20	**3A^e**	65
7			+20	**3A^e** + **3B^a** (57:43)	75
8			+60	**3A^e** + **3B^a** (50:50)	55
9	**2A***	$ZnBr_2$	+20	**4A^{e*}**	87
10		$MgCl_2$	+20	**4A^{e*}** + **4B^{a*}** + **4B^{e*}** (82:14:4)	81
11	**2A** + **2B**	$ZnBr_2$	+20	**4A^e** + **4B^a** + **4B^e** (78:15:7)	76
12		$MgCl_2$	+20	**4A^e** + **4B^a** + **4B^e** (78:18:4)	81

The complete transformation of **2A*** in the presence of a Lewis acid required 6 eq of Et_2AlCN at 0 °C. In the presence of $MgCl_2$ the epimerization at C-2 of the starting sulfinyl ketone was also observed. The stereochemical results for this substrate were identical to those obtained in the absence of Lewis acid. Thus, the evolution of **2A** is totally stereoselective but **2B** yields a mixture of the two possible cyanohydrins **4B^a** and **4B^e**.

Additionally, if we compare entry 6 of Table 1 with entries 10-12 of Table 2, we observe an almost identical composition of the reaction mixtures, which suggests that the chelation is not effective in the cyclopentanone derivative (at least in compound **2B**).

Configurational assignments. The configurational assignments of the chiral centers of the starting sulfinyl ketones **1** and **2** had been previously made.[10] Since hydrocyanation does not affect the configuration of the chiral center at sulfur, we had only to assign the configuration at both chiral carbons of the synthesized cyanohydrins.

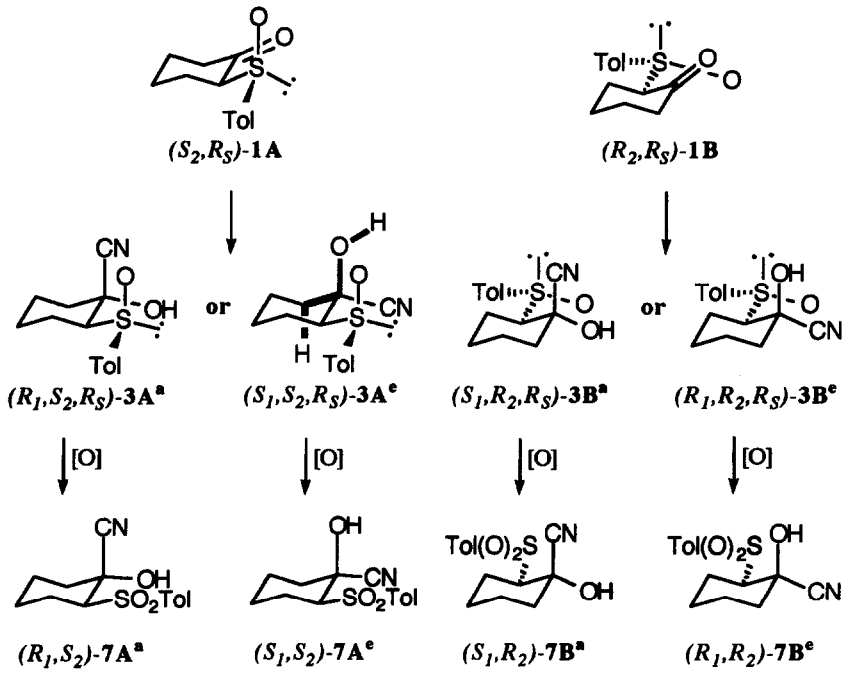
In order to obtain considerable amounts of the minor diastereoisomers of cyclohexane derivatives, we carried out the reaction of sulfinyl ketones with a presumably less stereoselective reagent, such as TMSCN/18-crown-6 ether/KCN.[11] Surprisingly, reaction of **1A** (or of a **1A** + **1B** mixture) with the reagent afforded a mixture of only the cyanohydrin $\mathbf{3B^a}$ and the *O*-trimethylsilylcyanohydrins **5** and **6**. Hydrolysis of **5** and **6** (previously separated by chromatography) with AcOH/THF/water[12] yielded cyanohydrins $\mathbf{3B^a}$ and $\mathbf{3B^e}$, respectively (Scheme 3).



Scheme 3

Configurational assignments of cyanohydrins $\mathbf{3A^e}$, $\mathbf{3B^a}$, and $\mathbf{3B^e}$ were based mainly on the ^{1}H NMR studies related to the existence of intramolecular hydrogen bonds. The high chemical shift observed for the hydroxylic proton of $\mathbf{3A^e}$ (obtained from **1A**) in pure $CDCl_3$ (5.57 ppm), which remains unaltered with dilution (from $95\cdot10^{-2}$ M to $1.9\cdot10^{-2}$ M), is indicative of an intramolecular association. Moreover, the signal of the hydroxylic proton appears as a doublet (J = 1.8 Hz), which demonstrates that the OH group adopts an axial disposition (W coplanar arrangement with H-6_{ax}). From Scheme 4 it can be inferred that this behaviour allows us to unequivocally assign the configuration (S_1,S_2,R_S) to compound $\mathbf{3A^e}$ (the other possible epimer resulting from **1A** has de OH in equatorial arrangement).

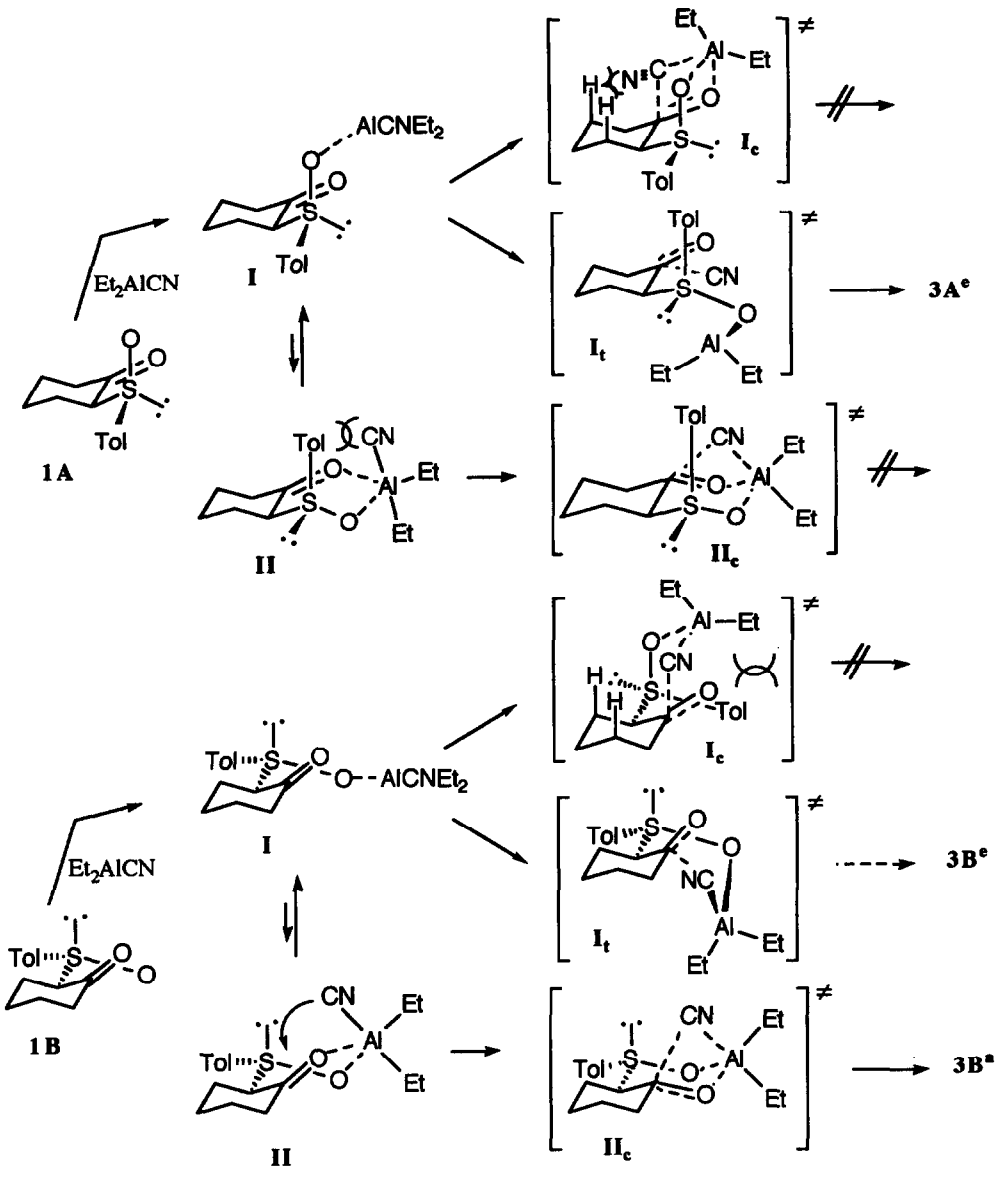
Additionally, oxidation of the sulfinyl cyanohydrins **3** with *m*-CPBA yielded the corresponding sulfones **7** (see Scheme 4).[13] The ^{1}H NMR spectra of the sulfones $\mathbf{7A^e}$ and $\mathbf{7B^e}$ (derived from $\mathbf{3A^e}$ and $\mathbf{3B^e}$, respectively) are identical, which demonstrates that they must be enantiomers. On the contrary, the spectrum of sulfone $\mathbf{7B^a}$ (resulting from $\mathbf{3B^a}$) is different, which proves that it must be diastereoisomer of the other two. As the configuration of $\mathbf{7A^e}$ must be (S_1,S_2) (it derives from $\mathbf{3A^e}$), its enantiomer $\mathbf{7B^e}$ must exhibit the configuration (R_1,R_2), which indicates that the precursory sulfoxide $\mathbf{3B^e}$ must exhibit the configuration (R_1,R_2,R_S) and, therefore, the configuration assigned to $\mathbf{3B^a}$ must be (S_1,R_2,R_S). In accordance with this assignment, cyanohydrin $\mathbf{3B^a}$ shows an intramolecular hydrogen bonding by ^{1}H NMR (the chemical shift of hydroxylic proton is 6.85 ppm, unchanging with dilution), but no long-range coupling constant.



Scheme 4

Configurations of cyanohydrins derived from α-sulfinyl ketones **2A** and **2B** were assigned following a similar method. Like the cyclohexane derivative **3A^e** (see Scheme 4), compound **4A^{e*}**, obtained from **2A***, shows an intramolecular hydrogen bond (δ_{OH} = 5.81 ppm, unchanging with dilution), the hydroxylic proton adopting a W coplanar arrangement with H-5$_{ax}$ (J = 1.4 Hz), which allows us to unequivocally assign the configuration ***(S1,S2,RS)*** to this compound. Additionally, elimination of chirality at sulfur by reduction of a **4A^e** + **4B^a** (89:11) mixture (attained by crystallization of a **4A^e** + **4B^a** + **4B^e** mixture from acetone–hexane (1:2), obtained from **2A** + **2B**) with $BF_3{\cdot}OEt_2$/NaI,[14] afforded an 82:18 mixture of two diastereoisomeric sulfenylcyanohydrins.[15] Accordingly, the actual configuration of **4B^a** must be ***(S1,R2,RS)*** and, therefore, the configuration ***(R1,R2,RS)*** must be assigned to the isomer **4B^e**. The NMR parameters of the major sulfenylcyanohydrin in this mixture were identical to those of the racemic sulfenylcyanohydrin **8***, derived from diastereoisomerically pure **4A^{e*}**.

Reaction mechanism. The stereochemical results obtained in the reactions of the cyclic α-sulfinyl ketones with Et_2AlCN can be rationalized by assuming that the Lewis acid character of the aluminum at Et_2AlCN determines the association of the reagent with the sulfinyl oxygen as a previous stage to the cyanide attack to the carbonyl group, which suggests that these reactions involve an intramolecular cyanide transfer. In Scheme 5 we have depicted all the possible situations for the case of the cyclohexanone derivatives.



Scheme 5

The initially formed tetracoordinated intermediates (I) could get equilibrated with the pentacoordinated ones (II), resulting in the further association of the aluminum with the carbonyl oxygen, the composition of the equilibrium being dependent on the relative stability of both species. The cyanide transfer can take place from the pentacoordinated species II (as it happens in the hydrocyanation of acyclic α-sulfinyl ketones[8]) and from tetracoordinated ones I (as it happens in DIBAL reductions[9]). In the last case two different transition states, chair-

like ($\mathbf{I_c}$) and twist-like ($\mathbf{I_t}$), can be involved, whereas only one ($\mathbf{II_c}$) is possible for the pentacoordinated intermediate.

Although the strong Lewis acid character of the Et_2AlCN suggested that the pentacoordinated species (**II**) would be more stable than the tetracoordinated ones (**I**) (it was the case for acyclic α-sulfinyl ketones[8]), the strain related to the bicyclic intermediates, generated from the cyclic sulfinyl ketones, could change the situation. Thus, starting from **1A**, the equilibrium **I**⇌**II** could shift even towards **I**, due to the steric interactions Tol/CN in **II**, both in *pseudo*-axial arrangement. Moreover, these interactions must increase considerably in TS $\mathbf{II_c}$, which precludes the evolution of **1A** through the pentacoordinated species. Strong steric interactions between the CN group and the axial protons at C(3) and C(5) also preclude the axial transfer of the CN group through the chair-like TS $\mathbf{I_c}$. Therefore the only possible evolution of the substrate must take place through the equatorial cyanide transfer through TS $\mathbf{I_t}$, yielding **3A**$^{\mathbf{e}}$, which explains the high stereoselectivity observed in the hydrocyanation of **1A** under all the experimental conditions. The situation must be identical starting from **2A**; the only expected difference could derive from the lower stability of the bicyclic pentacoordinated intermediate which would be formed in this case (the evolution of which does not take place in the six-membered rings), which would be now more strained.

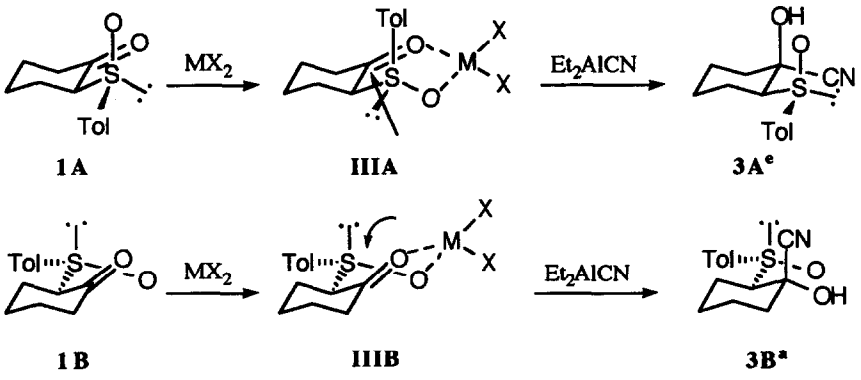
Starting from **1B** the situation is quite different. Now the equilibrium **I**⇌**II** must shift towards the corresponding pentacoordinated species **II**, which in this case is not sterically destabilized. The evolution of **II** through the chair-like TS $\mathbf{II_c}$ must be very easy (it must be favoured from an entropic point of view and does not exhibit any unstabilizing interaction), yielding compound **3B**$^{\mathbf{a}}$. This compound could also derive from the cyanide transfer through TS $\mathbf{I_c}$. Nevertheless, this evolution must be discarded because $\mathbf{I_c}$ must be strongly destabilized by the steric interactions of the CN group with the axial hydrogens at C(3) and C(5) and those of the Et group with the *p*-Tol one, both adopting a *syn*-diaxial arrangement. The equatorial cyanide transfer through $\mathbf{I_t}$ is also feasible, yielding cyanohydrin **3B**$^{\mathbf{e}}$. The high stereoselectivity observed in the hydrocyanation of **1B** at low temperature (only compound **3B**$^{\mathbf{a}}$ is formed) can be explained to a great extent by assuming the low stability of the twist-like transition states, $\mathbf{I_t}$, in comparison with that of the $\mathbf{II_c}$.

This assumption has been corroborated by reaction of a **1A** + **1B** mixture with 0.2 eq of Et_2AlCN. Only cyanohydrin **3B**$^{\mathbf{a}}$ and starting material could be isolated under these conditions, which demonstrates that the cyanide transfer from the pentacoordinated species must be easier than that from the tetracoordinated ones ($\mathbf{II_c}$ from **1B** must be more stable than the transition states $\mathbf{I_t}$**A** or $\mathbf{I_t}$**B**, derived from **1A** or **1B**) (see Scheme 5). This result justifies that the acyclic substrates, which can always form pentacoordinated species without any unstabilizing interaction (such as **II**, attained from **1B**), regardless of their relative configuration, yield only the products corresponding to the cyanide transfer from such chelated intermediates, although the marked shifting of the equilibrium **I**⇌**II** towards **II** could also be a contributing factor that cannot be disregarded.

The fact that **1B** can evolve through two different routes (one of them more favoured) would explain the decrease of the stereoselectivity observed when the temperature or the reaction time are increased (both factors favour the equilibration between reagents and products (see Table 1, entries 2 and 3). A similar situation is observed in the hydrocyanation of **2B**, where the higher temperature required (0°C) justifies the lower stereoselectivity observed in its evolution (see Table 1, entry 6).

The addition of Lewis acids causes some changes in the course of the hydrocyanations. In the case of the sulfinyl cyclohexanones the composition of the reaction mixtures is almost identical to that observed in the absence of Lewis acids. Except with $ZnCl_2$ (Table 2, entry 1), the other catalysts cause the epimerization of the

starting sulfoxides (a mixture of **3A**^{e} and **3B**^{a} was always isolated starting from **1A**, entries 2-8). The main difference induced by the Lewis acids is reflected in the highly stereoselective evolution of **1B**, which yields only **3B**^{a}, whichever temperature was used (in the absence of Lewis acid this behaviour is observed only at -78 °C, see Table 1, entry 2). These results can be explained by assuming the formation of chelates where the metal is joined to carbonyl and sulfinyl oxygens. As we can see in Scheme 6, the reagent attack must be now intermolecular. The axial approach of the CN group to the chelated species **IIA**, derived from **1A**, must be strongly hindered by the *p*-Tol group in *pseudo*-axial arrangement and thus, only equatorial attack can take place, yielding cyanohydrin **3A**^{e}. In the case of **IIIB**, derived from **1B**, the axial cyanide transfer must be favoured by both stereoelectronic (previous association of the aluminum with the lone electron pair at sulfur, see Scheme 6) and steric (chair-like TS, instead of the twist-like one, expected for the equatorial cyanide approach) factors.



Scheme 6

The results obtained from the cyclopentanone derivatives are practically identical to those observed in the absence of Lewis acids, which suggests that these are not able to achieve an efficient chelation of the sulfoxides.

From the obtained results, we must remark that the configuration induced at C(1) is controlled mainly by that of the sulfur (the influence of the configuration at C(2) is small or none) and thus, the major sulfinyl cyanohydrins always exhibit opposite configurations at both centers. If we take into account that the final step of these synthetic sequences (sulfinylation and hydrocyanation) would be the elimination of the sulfinyl group,[16] these results are of great importance because they suggest the possibility of affording cyanohydrins with high optical purity at the hydroxylic carbon starting from diastereoisomeric mixtures of sulfinyl cycloalkanones, epimers at C(2). This avoids the difficult and not always possible separation of such mixtures, which are always obtained in the sulfinylation reactions of cycloalkanones leading to the optically pure starting sulfinyl derivatives.

We can conclude that the hydrocyanation of cyclic α-sulfinyl ketones can be achieved in a highly stereoselective manner with Et_2AlCN, being completely controlled by the sulfur configuration. The addition of Lewis acids improves the stereoselectivity in the case of the six-membered rings.

EXPERIMENTAL SECTION

Details concerning the recording of NMR, IR, MS spectra, the analytical instruments used, the determination of melting points, elemental analyses, and chromatographic procedures (flash chromatography and

TLC) have been previously described.[17] Dry THF and ethyl ether were distilled from sodium/benzophenone ketyl, and toluene and CH_2Cl_2 were dried over P_2O_5. Eluting solvents for chromatography are indicated in parentheses in the text. ^1H NMR (200.1 MHz) and ^{13}C NMR (50.3 MHz) spectra were measured in $CDCl_3$ solutions. *J* values are given in Hz. Tol refers to the tolyl group. HRMS were obtained in the electron impact (EI) mode at 70 eV. All compounds prepared were shown to be over 96% pure by NMR analysis. The syntheses of compounds **1** and **2** have been previously described.[10] Yields and diastereomeric ratios of cyanohydrins and ratios substrate/Et_2AlCN are listed in Tables 1 and 2.

General Procedures for Hydrocyanation.

(i) With **Et_2AlCN** (Method A). A solution of 1 mmol of α-sulfinyl ketone in 10 mL of toluene was dropwise added into a solution of Et_2AlCN in 10 mL of toluene, and the mixture was stirred for 5 min at the temperature indicated in Table 1. The reaction mixture was transferred by cannula (by applying a positive nitrogen pressure to the reaction flask) into a mixture of 25 mL of methanol and 15 mL of concentrated HCl, previously cooled at -78 °C. The resulting mixture was vigorously stirred at -78°C for 1 h, poured into a mixture of 20 mL of concentrated HCl and 30 mL of ice-water, and extracted with CH_2Cl_2. The extracts were washed with water (30 mL), dried, and concentrated below 40 °C (higher temperatures decompose the unstable cyanohydrins into the starting ketones).

(ii) With **Et_2AlCN/ZnX_2 [or MgX_2]** (Method B). A solution of 1 mmol of α-sulfinyl ketone in 10 mL of toluene was added into a solution of 1.2 mmol of ZnX_2 (or MgX_2) in 3 mL of THF. The mixture was stirred for 30 min at the temperature indicated in Table 2 and then dropwise added into a stirred solution of Et_2AlCN in 10 mL of toluene. The resulting mixture was stirred for 5 min at -78 °C and then worked up as in method A.

(iii) With **TMSCN/18-crown-6 ether/KCN**[11] (Method C). A solution of 30.0 mg (0.127 mmol) of α-sulfinyl ketone **1A** (or **1A** + **1B**) in 1.3 mL of CH_2Cl_2 was added into a solution of 3.4 mg (0.0127 mmol) of 18-crown-6 ether and 1.0 mg (0.0127 mmol) of KCN in 0.5 mL of CH_2Cl_2. The mixture was cooled at 0 °C and 31.4 mg (0.317 mmol) of TMSCN were added. The resulting mixture was stirred at rt for 18 h and concentrated in vacuo. The residue was purified by chromatography.

Hydrolysis of Trimethylsilylcyanohydrins into Cyanohydrins. A solution of 30.0 mg (0.089 mmol) of trimethylsilylcyanohydrin in 3 mL of a mixture of acetic acid-THF-water was stirred at rt for 15 h. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with water, dried, and concentrated in vacuo.

***(S1,S2,RS)*-1-Hydroxy-2-[(4-methylphenyl)sulfinyl]cyclohexanecarbonitrile (3A[e]).** Hydrocyanation of **1A** following methods A (-78 °C, Table 1) and B (in the presence of $ZnCl_2$ or $MgCl_2$, see Table 2) afforded pure **3A[e]** as a white solid. It was crystallized from hexane: mp 129-131 °C. HRMS calcd for $C_{14}H_{17}NO_2S$ 263.0980, found 263.0997. $[\alpha]^{20}_D$ +156.0 ($CHCl_3$, *c* = 1.0); ^1H NMR δ 7.44 and 7.38 (AA'BB' system, 4H, C_6H_4), 5.54 (bs, 1H, O*H*), 2.58 (dd, 1H, *J* = 12.4 and 3.6, C*H*SO), 2.45 (s, 3H, CH_3), 2.40-1.00 (m, 8H, $(CH_2)_4$). MS 263 (10) M^+, 236 (12), 140 (100), 92 (34). IR (KBr) 3500, 2240, 1450, 1030, 800. ^{13}C NMR δ 142.3 (*C-4* Tol), 134.9 (*C-1* Tol), 130.2 (*C-3* and *C-3'* Tol), 124.3 (*C-2* and *C-2'* Tol), 121.1 (*C*N), 70.2 (*C*-OH), 63.7 (*C*HSO), 38.5 (CH_2(6)), 24.0 (CH_2(4)), 21.5 (CH_3Ar), 18.8 (CH_2(5)), 15.6 (CH_2(3)).

***(S1,R2,RS)*-1-Hydroxy-2-[(4-methylphenyl)sulfinyl]cyclohexanecarbonitrile (3B[a])** was prepared by hydrolysis of *(S1,R2,RS)*-2-[(4-methylphenyl)sulfinyl]-1-trimethylsilyloxycyclohexanecarbonitrile **5** with a mixture of acetic acid-THF-water (8:1:1): yield 73% (oil); HRMS calcd for $C_{14}H_{17}NO_2S$ 263.0980, found 263.0974; $[\alpha]^{20}_D$ +48.0 ($CHCl_3$, *c* = 1.0); ^1H NMR δ 7.65 and 7.31 (AA'BB' system, 4H, C_6H_4), 6.84 (s, 1H, O*H*), 2.80 (dd, 1H, *J* = 12.7 and 4.4, C*H*SO), 2.46 (s, 3H, CH_3), 2.44-1.00 (m, 8H, $(CH_2)_4$). MS 263 (2) M^+, 236 (7), 140 (100), 92 (60), 69 (22). IR (film) 3300, 2240, 1460, 1060, 800. ^{13}C NMR δ 143.8 (*C-4* Tol), 137.6 (*C-1* Tol), 130.3 (*C-3* and *C-3'* Tol), 125.7 (*C-2* and *C-2'* Tol), 118.9 (*C*N), 73.1 (*C*-OH), 68.8 (*C*HSO), 38.7 (CH_2(6)), 24.2 (CH_2(4)), 22.9 (CH_2(5)), 22.2 (CH_2(3)), 21.6 (CH_3Ar).

***(R1,R2,RS)*-1-Hydroxy-2-[(4-methylphenyl)sulfinyl]cyclohexanecarbonitrile (3B^{e})** was prepared by hydrolysis of *(R1,R2,RS)*-2-[(4-methylphenyl)sulfinyl]-1-trimethylsilyloxycyclohexanecarbonitrile **6** with a mixture of acetic acid-THF-water (8:8:1): yield 79% (oil); $[\alpha]^{20}_D$ +30.5 ($CHCl_3$, *c* = 0.69); ^1H NMR δ 7.60 and 7.40 (AA'BB' system, 4H, C_6H_4), 6.11 (bs, 1H, O*H*), 3.12 (dd, 1H, *J* = 11.9 and 2.1, C*H*SO), 2.45 (s, 3H, CH_3), 2.41-1.00 (m, 8H, $(CH_2)_4$). MS 263 (3) M^+, 236 (13), 140 (100), 92 (56), 69 (58). IR (film) 3300, 2240, 1460, 1060, 800.

(S1*,S2*,RS*)*-1-Hydroxy-2-[(4-methylphenyl)sulfinyl]cyclopentanecarbonitrile (4A^{e*}).** Hydrocyanation of **2A following methods A (0 °C, Table 1) and B (in the presence of $ZnBr_2$, see Table 2) afforded pure **4A^{e*}** as a white solid. It was crystallized from acetone–hexane (1:2): mp 125-126 °C; $[\alpha]^{20}_D$ +255.6 ($CHCl_3$, *c* = 0.5); ^1H NMR δ 7.47 and 7.36 (AA'BB' system, 4H, C_6H_4), 5.39 (bs, 1H, O*H*), 3.10 (dd, 1H, *J* = 10.3 and 8.7, C*H*SO), 2.43 (s, 3H, CH_3), 2.42-1.25 (m, 6H, $(CH_2)_3$). MS 249 (10) M^+, 233 (4), 222 (18), 206 (23), 140 (86), 139 (100), 123 (19), 111 (3), 91 (74), 83 (10). IR ($CHCl_3$) 3250, 2920, 2850, 2240, 1600, 1440, 1110, 1030, 870, 800. ^{13}C NMR δ 142.3 (*C-4* Tol), 136.9 (*C-1* Tol), 130.2 (*C-3* and *C-3'* Tol), 123.9 (*C-2* and *C-2'* Tol), 120.1 (*C*N), 74.3 (*C*-OH), 67.7 (*C*HSO), 41.1 (CH_2(5)), 21.4 (CH_3Ar), 20.3 (CH_2(4)), 18.9 (CH_2(3)). Anal. Calcd for $C_{13}H_{15}NO_2S$: C, 62.63; H, 6.06; N, 5.62. Found: C, 62.36; H, 6.26; N, 5.09.

***(S1,R2,RS)*- and *(R1,R2,RS)*-2-[(4-Methylphenyl)sulfinyl]-1-trimethylsilyloxycyclohexanecarbonitrile (5 and 6).** Addition of TMSCN to **1A** or to a **1A** + **1B** (75:25) mixture in the presence of 18-crown-ether and KCN, afforded a mixture of **5**, **6**, and **3B^{a}**. Isolation of **5** and **6** was achieved by flash chromatography using alumina as the stationary phase. **5** (oil): $[\alpha]^{20}_D$ +89.0 ($CHCl_3$, *c* = 1.77); ^1H NMR δ 7.51 and 7.32 (AA'BB' system, 4H, C_6H_4), 2.67 (dd, 1H, *J* = 10.3 and 4.4, C*H*SO), 2.41 (s, 3H, CH_3Ar), 2.33-1.10 (m, 8H, $(CH_2)_4$), 0.34 (s, 9H, $Si(CH_3)_3$). MS 335 (10) M^+, 320 (25), 236 (2), 212 (100), 196 (13), 139 (39). IR (film) 2240, 1260, 1120, 1030, 840. ^{13}C NMR δ 141.1 (*C-4* Tol), 140.9 (*C-1* Tol), 129.9 (*C-3* and *C-3'* Tol), 123.8 (*C-2* and *C-2'* Tol), 121.1 (*C*N), 71.2 (*C*-OH), 70.6 (*C*HSO), 38.2 (CH_2(6)), 23.0 (CH_2(4)), 21.3 (CH_3Ar), 20.0 (CH_2(5)), 17.0 (CH_2(3)), 1.0 ((CH_3)$_3$Si). **6** (oil): $[\alpha]^{20}_D$ +85.0 ($CHCl_3$, *c* = 1.0); ^1H NMR δ 7.47 and 7.42 (AA'BB' system, 4H, C_6H_4), 2.47 (dd, 1H, *J* = 11.6 and 4.7, C*H*SO), 2.41 (s, 3H, CH_3Ar), 2.21-1.00 (m, 8H, $(CH_2)_4$), 0.35 (s, 9H, $Si(CH_3)_3$). MS 335 (8) M^+, 212 (100), 196 (32), 139 (55). IR (film) 2240, 1270, 1120, 1040, 800. ^{13}C NMR δ 141.0 (*C-4* Tol), 140.9 (*C-1* Tol), 129.8 (*C-3* and *C-3'* Tol), 124.1 (*C-2* and *C-2'* Tol), 118.6 (*C*N), 73.1 (*C*-OH), 71.7 (*C*HSO), 41.3 (CH_2(6)), 23.9 (CH_2(4)), 22.8 (CH_2(5)), 21.4 (CH_3Ar), 19.2 (CH_2(3)), 1.4 ((CH_3)$_3$Si).

(S1*,S2*)*-Hydroxy-2-[(4-methylphenyl)sulfenyl]cyclopentanecarbonitrile (8*)** was prepared following the procedure described by Vankar:[14] A solution of 403.8 mg (2.85 mmol) of BF_3·OEt_2 in 2.5 mL of MeCN was added into a solution of 236.6 mg (0.95 mmol) of **4A^{e*}** and 498.4 mg (3.30 mmol) of NaI in 5 mL of MeCN, cooled at 0 °C. The resulting mixture was stirred at 0 °C for 1 h and decomposed with 2 mL of water. The aqueous layer was extracted with diethyl ether. The combined extracts were washed with an aqueous solution of sodium bisulfite, dried and concentrated in vacuo to afford pure *(S1*,S2*)*-**8: yield 191 mg (82%) of an oil; HRMS calcd for $C_{13}H_{15}NOS$ 233.0874, found 233.0874; $[\alpha]^{20}_D$ -24.6 ($CHCl_3$, *c* = 1.1); ^1H NMR δ 7.48 and 7.16 (AA'BB' system, 4H, C_6H_4), 3.73 (bs, 1H, O*H*), 3.71 (dd, 1H, *J* = 10.4 and 8.8, C*H*S), 2.55-1.54 (m, 6H, $(CH_2)_3$), 2.34 (s, 3H, CH_3). MS 233 (72) M^+, 206 (52), 150 (78), 135 (37), 124 (89), 123 (57), 110 (16), 105 (27), 98 (1), 91 (100), 83 (8), 77 (44). IR ($CHCl_3$) 3420, 2980, 2860, 2220, 1490, 1440, 1340, 800. ^{13}C NMR δ 139.1 (*C-4* Tol), 133.6 (*C-3* and *C-3'* Tol), 130.0 (C-2 and C-2' Tol), 128.0 (*C-1* Tol), 120.6 (*C*N), 71.6 (*C*-OH), 60.0 (*C*HS), 39.0 (CH_2(5)), 29.9 (CH_2(4)), 21.2 (CH_3Ar), 14.1 (CH_2(3)).

Acknowledgement. We thank Dirección General de Investigación Científica y Técnica (Grant PB92-0162) for financial support.

REFERENCES AND NOTES

1. Evans, D. A.; Carrol, G. L.; Truesdale, L. M. *J. Org. Chem.* **1974**, *39*, 914. Midland, M. M.; Lee, P. E. *J. Org. Chem.* **1985**, *50*, 3237. Cainelli, G.; Mezzina, E.; Panunzio, M. *Tetrahedron Lett.* **1990**, *31*, 3481. Effenberger, F.; Gutterer, B.; Ziegler, T. *Liebigs Ann. Chem.* **1991**, 269. Cainelli, G.; Panunzio, M.; Contento, M.; Giacomini, D.; Mezzina, E.; Giovagnoli, D. *Tetrahedron* **1993**, *49*, 3809.
2. Elphimoff-Felkin, I. *Bull. Soc. Chim. Fr.* **1955**, 784. Elphimoff-Felkin, I.; Verrier, M. *Bull. Soc. Chim. Fr.* **1967**, 1047. Krepski, L. R.; Heilmann, S. M.; Rasmussen, J. K. *Tetrahedron Lett.* **1983**, *24*, 4075. Brussee, J.; Roos, E. C.; Van der Gen, A. *Tetrahedron Lett.* **1988**, *29*, 4485. Brussee, J., Van der Gen, A., Eur. Pat. Appl. EP 322,973 (1990).
3. Effenberger, F.; Hörsch, B.; Weingart, F.; Ziegler, T.; Kühner, S. *Tetrahedron Lett.* **1991**, *32*, 2605.
4. Arcamone, F. in "Doxorubicin Anticancer Antibiotics"; Ed. Academic Press, New York, 1981. Krohn, K., Erkundi, V. S. in "Total Synthesis of Enantiomerically Pure Anthracyclinones"; Ed. H. E. J. Atta-ur-Rahman, Elsevier, Amsterdam, 1989.
5. Livingston, D. A.; Petre, J. E.; Bergh, C. L. *J. Amer. Chem. Soc.* **1990**, *112*, 6449.
6. Orduña, A.; Zepeda, L. G.; Tamariz, J. *Synthesis* **1993**, 375.
7. Bernatek, E.; Nordal, A.; Oguer, G. *Acta Chem. Scand.* **1963**, *17*, 2375. Nordal, A.; Krogh, A.; Oguer, G. *Acta Chem. Scand.* **1965**, *19*, 1705. Rosenqvist, E. *Acta Chem. Scand.* **1971**, *25*, 3111.
8. García Ruano, J. L.; Martín Castro, A. M.; Rodríguez, J. H. *J. Org. Chem.* **1992**, *57*, 7235.
9. Carreño, M. C.; García Ruano, J. L.; Martín, A. M.; Pedregal, C.; Rodríguez, J. H.; Rubio, A.; Sánchez, J.; Solladié, G. *J. Org. Chem.* **1990**, *55*, 2120.
10. Carreño, M. C.; García Ruano, J. L.; Pedregal, C.; Rubio, A. *J. Chem. Soc. Perkin Trans. I* **1989**, 1335.
11. Evans, D. A.; Truesdale, L. K. *Tetrahedron Lett.* **1973**, *14*, 4929.
12. Greene, T. W.; Wuts, P. G. M. "Protective Groups in Organic Synthesis"; Ed. Wiley, New York, 1991, p 71 and references cited therein.
13. The reaction was carried out in an NMR tube in order to be monitored by ^{1}H NMR. A solution of 0.057 mmol of *m*-CPBA in 0.3 mL of $CDCl_3$ was added into a solution of 0.38 mmol of cyanohydrin in 0.3 mL of $CDCl_3$ until the signals of the starting material were not observed by ^{1}H NMR. No 2-[(4-methylphenyl)sulfonyl]cyanohydrin was isolated since the basic conditions required for the workup decomposed the cyanohydrin. Hence, ^{1}H NMR parameters are those deduced from the spectra of the reaction mixtures. *(S$_1$,S$_2$)*-1-Hydroxy-2-[(4-methylphenyl)sulfonyl]cyclohexanecarbonitrile (**7A^e**) was prepared by oxidation of *(S$_1$,S$_2$,R$_S$)*-**3A^e**: δ 4.87 (s, 1H, O*H*), 3.29 (dd, 1H, *J* = 11.7 and 4.8, C*H*SO$_2$), 2.47 (s, 3H, C*H*$_3$). *(S$_1$,R$_2$)*-1-Hydroxy-2-[(4-methylphenyl)sulfonyl]cyclohexanecarbo-nitrile (**7B^a**) was prepared by oxidation of *(S$_1$,R$_2$,R$_S$)*-**3B^a**: δ 5.88 (bs, 1H, O*H*), 3.15 (dd, 1H, *J* = 12.8 and 3.6, C*H*SO$_2$), 2.47 (s, 3H, C*H*$_3$).
14. Vankar, Y. D.; Trinadha Rao, C. *Tetrahedron Lett.* **1985**, *26*, 2717.
15. In this case, diastereomerically pure samples of **4B^a** and **4B^e** were not available for their study. Additionally, oxidation of **4A^e** and **4A^e** + **4B^a** to sulfone with *m*-CPBA did not solved the problem of the configurational assignment, since the signals corresponding to the proton at C(2) in the ^{1}H NMR spectra of the crude reaction of a **4A^e** + **4B^a** mixture with *m*-CPBA (which would enable us to identify diastereoisomers) are not quite separate.
16. Reductive desulfinylation (via hydrolysis of the sulfinyl cyanohydrin and further desulfenylation of the resulting sulfenyl hydroxyamide, see ref 8) of compounds **3** and **4**, would yield achiral compounds due to the symmetrical character of our model sulfinyl cycloalkanones. Therefore, in these cases other elimination processes, such as the pyrolitic elimination of the sulfinyl group (see Linney, D. L.; Tye, H.; Wills, M. *Tetrahedron Lett.* **1994**, *35*, 1785) must be undertaken.
17. See ref 8 and references cited therein.

(*Received in UK* 16 *February* 1994; *revised* 27 *April* 1994; *accepted* 29 *April* 1994)