# Highly Diastereoselective Hydrocyanation of β-Keto Sulfoxides: Synthesis of Enantiomerically Pure Cyanohydrin Derivatives

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

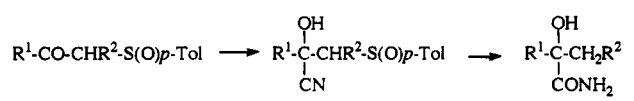
*Departamento de Química (C-1), Universidad Autónoma, Cantoblanco, 28049-Madrid, Spain*

*Received June 29, 1992*

The reactions of chiral β-keto sulfoxides, $R^1$-CO-CHR$^2$-SOTol ($R^1$ = Me, *n*-Pr, *i*-Pr, *t*-Bu, Ph; $R^2$ = H, Me) with $Et_2AlCN$ yield the corresponding sulfinyl cyanohydrins with high yields (85–96%) and de (>96%). The chirality induced at the hydroxylic carbon is controlled only by the sulfur configuration (1,3-induction), which is explained by assuming an intramolecular transfer of the CN group from a pentacoordinated aluminum intermediate with a trigonal bipyramidal structure. Controlled hydrolysis and desulfurization afforded optically pure α-alkyl-α-hydroxy carboxamides.

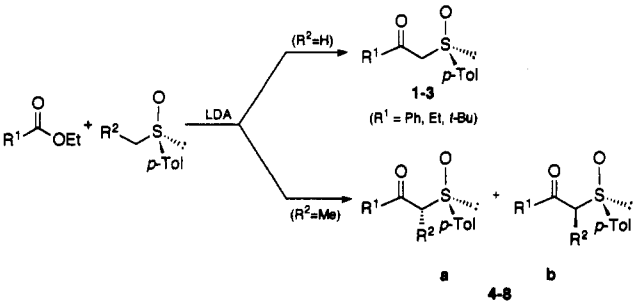
The easy transformation of cyanohydrins into biologically and pharmaceutically interesting organic groupings, such as α-hydroxy acids, vicinal diols, α-hydroxy ketones, ethanolamines, amino acids, etc.[1] renders those compounds as versatile starting materials in organic synthesis. Despite this interest, few methods have been reported about preparation of chiral non-racemic cyanohydrins,[1b,2] and none of them are adaptable to their α-methyl derivatives. The high stereoselectivity observed in DIBALH and DIBALH/$ZnCl_2$ reductions of β-keto sulfoxides[3] was related to the ability of the aluminum to associate with any of the unshared electron pairs at sulfinyl group, as a previous step to the intramolecular hydride transfer.[4] A similar mechanism can be invoked to explain the high stereoselectivity found in the reactions of 2-[(4-methylphenyl)sulfinyl]cycloalkanones with $Me_3Al$ and $ZnCl_2/Me_3Al$.[5] These results suggested to us the possibility of using the tricoordinated aluminium reagent $Et_2AlCN$ to control the stereoselectivity of the cyanide addition to the chiral β-keto sulfoxides. In this paper we report the results obtained in the reactions of the enantiomerically pure (*R*)-β-keto sulfoxides shown in Scheme I with $Et_2AlCN$ and the transformation of the resulting sulfinyl cyanohydrins into their corresponding α-alkyl-α-hydroxy carboxamides.[6]

**Scheme I**




| $R^1$ | $R^2$ | | | |
|---|---|---|---|---|
| Ph | H | 1 | 9 | 25 |
| Et | H | 2 | 10 | 26 |
| *t*-Bu | H | 3 | 11 | 27 |
| Me | Me | 4 | 12 | 28 |
| *n*-Pr | Me | 5 | 13 | 29 |
| *i*-Pr | Me | 6 | 14 | 30 |
| *t*-Bu | Me | 7 | 15 | 31 |
| Ph | Me | 8 | 16 | 32 |

**Scheme II**




## Results and Discussion

The syntheses of the starting (*R*)-β-keto sulfoxides 1–8 were carried out by reaction of (*R*)-(+)-alkyl (methyl or ethyl) *p*-tolyl sulfoxide with $R^1$-$CO_2Et$ in the presence of LDA (Scheme II). When the starting esters have no α-hydrogens ($R^1$ = *t*-Bu and Ph), the reaction conditions used to prepare compounds **1**, **3**, **7**, and **8**, were identical to those reported in the literature (LDA/$R^1CO_2Et$/alkyl *p*-tolyl sulfoxide in 2.3/1.2/1.0 molar ratio).[7] The syntheses of compounds **2** and **4–6**, derived from esters with α-hydrogens ($R^1$ = Et, Me, *n*-Pr, and *i*-Pr, respectively), required a decrease in the relative concentration of the base (LDA/$R^1CO_2Et$/alkyl *p*-tolyl sulfoxide in 1.0/1.2/1.0 molar ratio) to get satisfactory results (>85% yield).

The condensations of the ethyl *p*-tolyl sulfoxide with esters yield mixtures of the two possible diastereoisomers.[8] Therefore the α-methyl derivatives **4–8** were obtained as 40:60 mixtures of **a** and **b** epimers (see Scheme II) in ca. 85% yield. Only the *tert*-butyl derivatives **7a** and **7b** could be isolated by flash chromatography as diastereomerically

(1) Fuhrhop, J.; Penzlin, G. *Organic Synthesis, Concepts, Methods, Starting Materials*; Verlag Chemie: Weinheim, 1983; p 47. Brussee, J.; Van der Gen, A. *Eur. Pat. Appl.* EP 322,973 (Cl. C07C93/14), 5 July 1989.

(2) Brussee, J.; Roos, E. C.; Van der Gen, A. *Tetrahedron Lett.* 1988, *29*, 4485. Matthews, B. R.; Jackson, W. R.; Jayatilake, G. S.; Wilshire, C.; Jacobs, H. A. *Aust. J. Chem.* 1988, *41*, 1697. Brussee, J.; Loos, W. T.; Kruse, C. G.; Van der Gen, A. *Tetrahedron* 1990, *46*, 979 (and references cited herein). Brussee, J.; Dofferhoff, F.; Kruse, C. G.; Van der Gen, A. *Tetrahedron* 1990, *46*, 1653.

(3) Solladié, G.; Demailly, G.; Greck, C. *J. Org. Chem.* 1985, *50*, 1552.

(4) Carreño, C.; García Ruano, J. L.; Martín, A. M.; Pedregal, C.; Rodríguez, J. H.; Rubio, A.; Sanchez, J.; Solladié, G. *J. Org. Chem.* 1990, *55*, 2120.

(5) Bueno, A. B.; Carreño, M. C.; Fischer, J.; García Ruano, J. L.; Peña, B.; Peñas, L.; Rubio, A. *Tetrahedron Lett.* 1991, *32*, 3191.

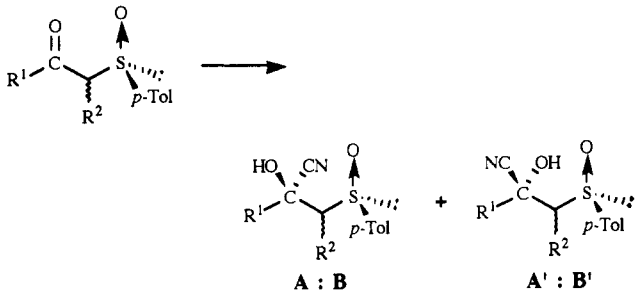
(6) A preliminary communication concerning the first studies about compounds 1–3 has been previously reported (García Ruano, J. L.; Martín-Castro, A. M.; Rodríguez, J. H. *Tetrahedron Lett.* 1991, *32*, 3195).

(7) (a) Solladié, G.; Frèchou, C.; Demailly, G.; Greck, C. *J. Org. Chem.* 1986, *51*, 1912. (b) Annunziata, R.; Cinquini, M.; Cozzi, F. *J. Chem. Soc. Perkin Trans. 1* 1979, 1687. In these references compounds 1 and 3 are reported.

(8) Bravo, P.; Piovosi, E.; Resnati, G. *Synthesis*, 1986, 579.

0022-3263/92/1957-7235$03.00/0 

**Table I. Results Obtained in the Hydrocyanation of Compounds 1–8 under Different Conditions**



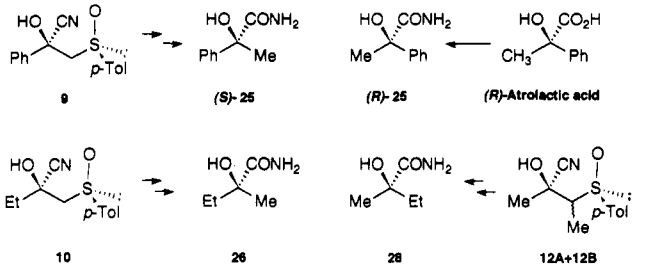

| | | diastereoisomer ratio[a] (yield,[b] %) | | |
|---|---|---|---|---|
| subs. | products | $Et_2AlCN$ | $Et_2AlCN/ZnX_2$ | $Et_2AlCN/MgX_2$ |
| 1 | 9 | (87) | (87) | (90) |
| 2 | 10 | (85) | (86) | (89) |
| 3 | 11 | (87) | (92) | (90) |
| **4a+4b** | **12A/12B** | 50:50 (87) | 43:57 (78) | 48:52 (85) |
| **5a+5b** | **13A/13B** | 42:58 (88) | 33:67 (93) | 38:62 (87) |
| **6a+6b** | **14A/14B** | 42:58 (91) | 35:65 (72) | 32:68 (88) |
| **7a+7b** | complex mixture | | | |
| **7a** | **15A/15A'** | 89:11 (96) | 97:3 (94) | 88:12 (86) |
| **7b** | **15B/15B'/15A** | 72:13:15 (89) | 57:0:43 (92) | 56:0:44 (89) |
| **8a+8b** | **16A/16B** | 40:60 (87) | 37:63 (85) | 33:67 (85) |

[a] Determined from the $^1$H-NMR spectra of the mixture. [b] Overall isolated yield.

pure compounds. Nevertheless, the significant $^1$H-NMR data for both epimers at C-$\alpha$ could be easily deduced from the spectra of their mixtures. From these data (see Experimental Section) it can be deduced that the minor epimers (designated as **a**) in all mixtures show a lower $\delta$ value for methyl and a higher $\delta$ for the proton at the chiral carbon than those corresponding to the major epimers (designated as **b**). The configurational assignment of these epimers ($R_2$,$R_S$ for the **a** epimers and $S_2$,$R_S$ for the **b** ones) had been previously made.[9]

The reaction of keto sulfoxides **1–8** with $Et_2AlCN$ in toluene at 0 °C afforded cyanohydrins **9–16**. The results are collected in Table I. Both the order of the addition of the reagents and the reaction time were critical to obtain good yields of cyanohydrins. Thus, when we used the experimental conditions initially reported for the reactions of $Et_2AlCN$,[10] the starting material was recovered as the major component of the crude reactions, but when we changed the order of the addition of the reagents (the keto sulfoxide must be added into the $Et_2AlCN$, see Experimental Section), the yields of cyanohydrins became higher than 85% (Table I). Additionally, the optimum reaction time for all these syntheses is 5 min at −78 °C for substrates **1–3** and less than 30 min at 0 °C for **4–8**. Longer reaction times cause significant changes in the composition of the reaction mixtures.[11] Contrary to the reduction of $\beta$-keto sulfoxides with DIBALH,[3] the addition of Lewis acids ($ZnX_2$ and $MgX_2$, X = Cl or Br) has little or no influence on the reaction because both stereochemical results and overall yields are almost identical to those

**Scheme III**




obtained in their absence. For this reason we have not specified in Table I the particular results for the different catalysts which have been used. It must be pointed out that in the preliminary communication[6] it was indicated that the presence of $ZnCl_2$ increased the rate of the reaction. This wrong conclusion was established because we thought that 2 h were needed to complete the reaction in the absence of the Lewis acid.

The hydrocyanation reaction is highly stereoselective. Starting from the optically pure $\beta$-keto sulfoxides **1–3**, only one cyanohydrin can be detected in the crude products by $^1$H NMR analysis (de > 96%). Similarly, the diastereomeric mixtures of the $\alpha$-methyl derivatives **4a + 4b**, **5a + 5b**, **6a + 6b** and **8a + 8b** gave the corresponding mixtures of only two cyanohydrins, **A** and **B**, whose ratio is quite similar to that of the epimeric starting products. This suggests that the hydrocyanation of both epimeric keto sulfoxides (**a** and **b**) is highly stereoselective yielding only one cyanohydrin (**A** and **B**, respectively).

The reaction of the mixture **7a + 7b** afforded a complex mixture of cyanohydrins. Therefore we isolated the epimers at C-$\alpha$ and then studied their behavior separately. After 30 min of reaction, the results obtained are those indicated in Table I. In the absence of Lewis acid, the stereoselectivity of the reaction of **7a** is high but lower than that observed for the other keto sulfoxides. The reaction time hardly affects the composition of the resulting mixture, but the presence of $ZnX_2$ considerably increases the stereoselectivity, **15A** being the only detected isomer in some trials. The behavior of **7b** is quite different. The epimerization at C-$\alpha$ is observed in all conditions, which led to the isolation of **15A** in all trials. When the reaction was performed with $Et_2AlCN$, the longer reaction time, the lower stereoselectivity, and the higher proportion of **15A** (a 52:22:26 mixture of **15B/15B'/15A** was obtained after 24 h). In the presence of Lewis acid, the degree of epimerization at C-$\alpha$ increases but the reactions of both keto sulfoxides are completely stereoselective. In order to confirm this result the reaction of the mixture **7a + 7b** with

(9) Barros, D.; Carreño, M. C.; García Ruano, J. L.; Maestro, M. C. *Tetrahedron Lett.* **1992**, *33*, 2733.

(10) Nagata, W.; Yoshioka, M. *Tetrahedron Lett.* **1966**, 1913. Nagata, W.; Yoshioka, M.; Murakami, M. *J. Am. Chem. Soc.* **1972**, *94*, 4654. Nagata, W.; Yoshioka, M.; Murakami, M. *Organic Syntheses*; Wiley: New York, 1972; Vol. *52*, 96.

(11) In some cases these changes only concern the yield, which decreases because a certain amount of the starting material is recovered (this fact is also observed when the temperature is increased), but frequently an increase in the reaction time also determines a decrease in the stereoselectivity. The following examples show the importance of the reaction time. (a) A 24% recovery of the starting products could be isolated from the reaction mixture of **4a + 4b** with $Et_2AlCN/ZnBr_2$ after 2 h of reaction (compare with the result indicated in Table II). (b) Treatment of keto sulfoxide **2** with $Et_2AlCN$ for 16 h yielded a mixture containing the starting product **2** (26%) and the cyanohydrin **10** (45%) and its epimer at C-2 **10'** (29%) (this epimer can be identified after 2 h of reaction, see ref 6). (c) When the reaction of **5a + 5b** was allowed to stand for 2 h, a 21% yield of the **13A'** (epimer of **13A** at C-2) could be identified in the crude, and after 24 h (or after 2 h in the presence of $MgCl_2$) a mixture of the starting keto sulfoxides and the four possible diastereoisomeric cyanohydrins were isolated. (d) When the reaction mixture of **6a + 6b** with $Et_2AlCN/ZnX_2$ was quenched after 2 h at 0 °C, ca. 25% of the starting product was recovered. (e) A 34:14:51 mixture of **16A:16A':16B** was isolated after 24 h from **8a + 8b**.

$ZnBr_2/Et_2AlCN$ was carried out and a mixture of **15A** + **15B** was obtained.

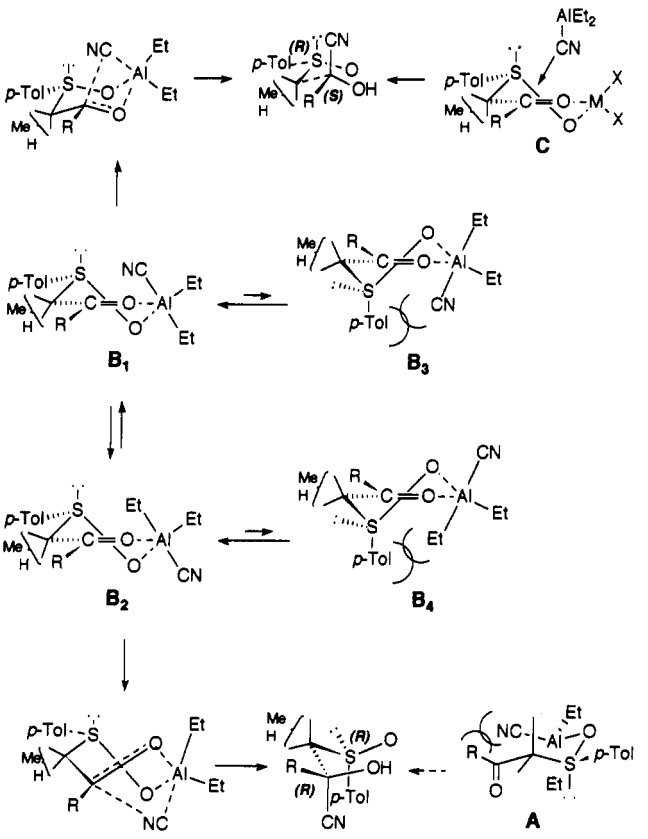
In order to assign the configuration of the new chiral center, a chemical correlation of the sulfinyl cyanohydrins with other products of known configuration was necessary. For such a purpose, the cyanohydrin **9** was correlated with atrolactic acid. Thus, the hydrolysis of compound **9** with HCl in diethyl ether followed by desulfurization with Raney nickel (vide infra) yielded the α-hydroxy amide **25** (Scheme III). The optical rotation of this compound is identical in magnitude but opposite in sign to that of the amide obtained from the enantiomerically pure (*R*)-atrolactic acid[12] (available from Aldrich Chemical Co). This fact establishes that the configuration of **25** (and therefore that of its precursor cyanohydrin **9** at C-2) must be (*S*). Bearing in mind the similar behavior of the substrates **1**, **2**, and **3** in the hydrocyanation reactions we can assume the same ($S_2R_S$) configuration for all these cyanohydrins.

On the other hand, the identical but opposite optical rotation of hydroxy amides **26** and **28** (respectively obtained from cyanohydrins **10** and **12A** + **12B**, by hydrolysis and further desulfurization) demonstrates that both must exhibit opposite configuration. Therefore, we can conclude that the configuration of **28** must be (*R*), whereas the (*S*) one must be assigned to its precursor cyanohydrins (**12A** and **12B**) at C-2 (see Scheme III). The similar behavior of the different α-alkyl-substituted substrates and the spectroscopic parameters of the cyanohydrins[13] suggest an identical stereochemical course for all compounds, which means that the same (*S*) configuration must be assigned to the hydroxylic carbon of the cyanohydrins **13**, **14**, and **16**. As expected from the very high de of the cyanohydrins, the ee of the hydroxy amide **25** was determined to be greater than 96% by use of the chiral shift reagent Eu(tfc)$_3$.

All of these reactions are 1,3-induction processes. The configuration (*R*) at sulfinyl sulfur determines the (*S*) one at the hydroxylic carbon. This is specially significant in the case of the α-methyl derivatives, which have two chiral centers, C-2 and S, the first of which is nearer the reaction center than the sulfur. The complete predominance of the 1,3-induction (sulfur control) over the 1,2-induction (C-α control), which suggests that the reagent approach is not exclusively controlled by steric factors (the electronic effects must also play a decisive role), is very important from a synthetic point of view. Thus, in order to obtain optically pure cyanohydrins or their derivatives, which requires the elimination of the sulfur moiety at the end of the synthetic sequence, it is not necessary to separate the α-epimeric mixtures obtained in the reactions yielding the α-alkyl-β-keto sulfoxides (condensation of alkyl sulfoxides with esters or methylation of the β-keto sulfoxides), which is often very difficult.

The strong Lewis acid character of the $Et_2AlCN$ suggests its association with the sulfinylic oxygen to form a tetracoordinated species like that postulated in reaction of DIBALH with β-keto sulfoxides.[4] Nevertheless, the intramolecular cyanide transfer from such species (**A** in Scheme IV) would lead to the opposite configuration to that experimentally observed [(*R*) at sulfur would induce (*R*) at carbon instead of the observed (*S*)]. We postulate that the electron deficiency of the aluminum in the intermediate **A** (larger than that of the corresponding DIBALH intermediate, due to the presence of the electron-withdrawing group CN) would favor the formation of the pentacoordinated species **B** (Scheme IV), which exhibits a double association of the aluminum with both oxygens in the substrate, which is even more stable than **A**. There are four possible half-chain conformations for **B** with trigonal bipyramidal structure around the pentacoordinated aluminum (Scheme IV). The most stable of them, $\mathbf{B_1}$ and $\mathbf{B_2}$ (with the *p*-tolyl group in a pseudoequatorial arrangement), have the cyanide group in the apical position, the NC–Al bond being longer and weaker than usual and therefore easier to be transferred. The intramolecular transfer of the cyanide group from $\mathbf{B_1}$ is topologically easier than that from $\mathbf{B_2}$ (the CN group is nearer to the carbonyl carbon in the first case), and the TS of the first conformation (chair-like type) is more stable than that of the second one (twist-like type). The cyanohydrin obtained by assuming this intramolecular transfer has the right conformation.

**Scheme IV**




We have carried out a representative essay with a compound bearing (*S*)-configuration at sulfur, obtained from (*S*)-methyl *p*-tolyl sulfoxide. As expected, the reaction of (*S*)-**3** with $Et_2AlCN$ gave rise to the ($S_2R_S$)-**11** isomer (see Experimental Section).

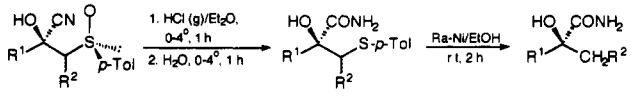
The lower stereoselectivity exhibited by the *tert*-butyl derivative **7** must be explained as a consequence of the large size of the *tert*-butyl group, which hinders the chelation (this was observed in reduction of **7a** with $ZnBr_2$/DIBAL[9]) and favors the retrohydrocyanation (mainly in the case of **7b**).

The fact that the configuration induced at carbonyl carbon during the hydrocyanation does not change in the

(12) The absolute configuration of this compound has been well established by different methods and reinforced by the asymmetric synthesis of (*S*)-(+)-atrolactic acid methyl ether (see Withman, C. P.; Craig, J. C.; Kenion, G. L. *Tetrahedron* **1985**, *41*, 1183 and references therein).

(13) The δ values (ppm) for the proton and the methyl group at C-2 in the **A′** isomers (epimers of **A** isomers at C-1) are, respectively, 0.35 and 0.1–0.3 ppm larger than those of the **A** isomers. Despite the high stereoselectivity observed in conditions of Table II, we have carried out a lot of experiments yielding the isomers **A′** as the minor components. On the contrary, **15B′** has been the only **B′** isomer detected.

**Scheme V**




| $R^1$ | $R^2$ | | | | | |
|---|---|---|---|---|---|---|
| Ph | H | 9 | 17 | (82%) | 25 | (65%) |
| Et | H | 10 | 18 | (80%) | 26 | (61%) |
| *t*-Bu | H | 11 | 19 | (42%) | 27 | (68%) |
| Me | Me | 12A+12B | 20A+20B | (92%) | 28 | (76%) |
| *n*-Pr | Me | 13A+13B | 21A+21B | (96%) | 29 | (79%) |
| *i*-Pr | Me | 14A+14B | 22A+22B | (87%) | 30 | (81%) |
| *t*-Bu | Me | 15A | 23A | (86%) | 31 | (76%) |
| Ph | Me | 16A+16B | 24A+24B | (95%) | 32 | (69%) |

presence of $ZnX_2$ or $MgX_2$ could be explained by assuming the attack of the reagent from the upper face of the chelated species **C** (Scheme IV), favored by stereoelectronic and steric effects in a similar way to the hydride approach in DIBALH/$ZnCl_2$ reductions.[4] The transformation of **C** species to **B** intermediates, presumably more stable, before the attack of the cyanide takes place, can also be invoked to explain the stereochemical results.

The elimination of the chiral auxiliary from the hydroxy sulfoxides **9–16** by hydrogenolysis of the C–S bond with Raney nickel did not give the expected desulfurized cyanohydrins. The hydrolysis of the CN group in compounds **9–16** by using an ether solution saturated with HCl(g)[14] resulted in the concomitant reduction of the sulfinyl group, yielding the sulfenyl hydroxy amides **17–24** (as mixtures of epimers at C-2, **A** and **B**, when $R^2$ = Me). In the reaction of compound **11**, the 3,3-dimethyl-2-hydroxy-2-[[(4-methylphenyl)sulfinyl]methyl]butanamide was isolated (35%) in addition to its corresponding sulfide **19**. Treatment of compounds **17–24** with Raney nickel afforded the desired optically pure α-hydroxy amides **25–32** (ee > 96%). The results obtained in these reactions are collected in Scheme V.

We can conclude that the hydrocyanation of chiral β-keto sulfoxides with $Et_2AlCN$ takes place in very mild conditions with very high stereoselectivity (de > 96%), making this reaction one of the best chemical methods to obtain derivatives of optically pure cyanohydrins derived from ketones. Now we are working to extend this methodology to synthesize amino acids and to apply it to the synthesis of different kinds of interesting compounds.

## Experimental Section

Details concerning the recording of NMR, IR, and MS spectra, the analytical instruments used, the determination of melting points, elemental analyses, diastereomeric ratios, enantiomeric purity, and chromatographic procedures (flash chromatography and TLC) have been previously described.[4,15] Dry THF and ethyl ether were distilled from sodium/benzophenone ketyl, and toluene was dried over $P_2O_5$. Eluting solvents for chromatography are indicated in brackets in the text. $^1H$ NMR (200.1 MHz) and $^{13}C$ NMR (50.3 MHz) spectra were measured in $CDCl_3$ solutions. Tol refers to 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. Yields and diastereomeric ratios of cyanohydrins are listed in Tables I and II.

**Preparation of Sulfinyl Ketones. General Procedure.** The syntheses of compounds **1–8** were carried out by following the procedure previously reported,[7] modified as follows: To a solution of LDA in 20 mL of THF at −78 °C was added dropwise (*R*)-(+)-alkyl *p*-tolyl sulfoxide in 20 mL of THF. The temperature was then allowed to reach 0 °C, and the mixture was stirred for 30 min. The temperature was lowered to −78 °C, and a solution of the corresponding ester in 20 mL of THF was added. The solution was stirred at this temperature for 2 h. The mixture was decomposed with 20 mL of a saturated $NH_4Cl$ solution. The organic layer was separated, and workup of the aqueous solution yielded a residue that was purified by chromatography. LDA/ester/alkyl *p*-tolyl sulfoxide molar ratio is shown in each case.

**(*R*)-2-[(4-Methylphenyl)sulfinyl]-1-phenylethanone (1)** was prepared from 180 mg of ethyl benzoate and 154 mg of methyl *p*-tolyl sulfoxide (1.0/1.2/1.0 LDA/ester/methyl *p*-tolyl sulfoxide molar ratio). It was purified by chromatography (ethyl acetate) (yield 193 mg, 75%) and crystallized from hexane: mp 82 °C; $[\alpha]^{20}_D$ +261° (acetone, *c* = 1.0) [lit.[7b] $[\alpha]^{20}_D$ +265° (acetone, *c* = 1.0)].

**(*R*)-1-[(4-Methylphenyl)sulfinyl]butan-2-one (2)** was prepared from 122.4 mg of ethyl propionate and 154 mg of methyl *p*-tolyl sulfoxide (1.0/1.2/1.0 LDA/ester/methyl *p*-tolyl sulfoxide molar ratio). It was purified by chromatography (ethyl acetate) (yield 97 mg, 92%) and crystallized from hexane, mp 78–79 °C; $[\alpha]^{20}_D$ +253° (acetone, *c* = 1.0); $^1H$ NMR δ 7.54 and 7.30 (AA′BB′ system, 4 H, $C_6H_4$), 3.89 and 3.77 (AB system, 2 H, *J* = 13.6, $CH_2S$), 2.51 (m, 2 H, $CH_2CH_3$), 2.42 (s, 3 H, $CH_3Ar$), 1.01 (t, 3 H, *J* = 7.2, $CH_3CH_2$). Anal. Calcd for $C_{11}H_{14}O_2S$: C, 62.83; H, 6.71. Found: C, 63.02; H, 6.80.

**(*R*)-3,3-Dimethyl-1-[(4-methylphenyl)sulfinyl]butan-2-one (3)** was prepared from 156 mg of ethyl pivaloate and 154 mg of methyl *p*-tolyl sulfoxide (2.3/1.2/1.0 LDA/ester/methyl *p*-tolyl sulfoxide molar ratio). It was purified by chromatography (ethyl acetate) (yield 218 mg, 89%) and crystallized from hexane, mp 108–109 °C (lit.[7a] 110–111 °C); $[\alpha]^{20}_D$ +163° ($CHCl_3$, *c* = 1.0) [lit.[7b] $[\alpha]^{20}_D$ +162° ($CHCl_3$, *c* = 1.0)].

**($R_3$,$R_S$)- and ($S_3$,$R_S$)-3-[(4-methylphenyl)sulfinyl]butan-2-one (4a + 4b)** were prepared as a 47:53 mixture from 106 mg of ethyl acetate and 168 mg of ethyl *p*-tolyl sulfoxide (1.0/1.2/1.0 LDA/ester/ethyl *p*-tolyl sulfoxide molar ratio). The mixture was purified by chromatography (ethyl acetate): yield 197 mg (92%) of an oil; $[\alpha]^{20}_D$ +113.7° ($CHCl_3$, *c* = 1.0); $^1H$ NMR δ 7.48 and 7.32 (AA′BB′ system, 4 H, $C_6H_4$(**a**)), 7.46 and 7.32 (AA′BB′ system, 4 H, $C_6H_4$(**b**)), 3.76 (q, 1 H, *J* = 7.1, C*H*(**a**)), 3.69 (q, 1 H, *J* = 7.1, C*H*(**b**)), 2.42 (s, 6 H, $CH_3Ar$(**a**) and $CH_3Ar$(**b**)), 2.24 (s, 3 H, $CH_3CO$(**a**)), 2.17 (s, 3 H, $CH_3CO$(**b**)), 1.35 (d, 1 H, *J* = 7.1, $CH_3CH$(**b**)), 1.27 (d, 1 H, *J* = 7.1, $CH_3CH$(**a**)).

**($R_2$,$R_S$)- and ($S_2$,$R_S$)-2-[(4-methylphenyl)sulfinyl]hexan-3-one (5a + 5b)** were prepared as a 40:60 mixture from 139 mg of ethyl butanoate and 168 mg of ethyl *p*-tolyl sulfoxide (1.0/1.2/1.0 LDA/ester/ethyl *p*-tolyl sulfoxide molar ratio). The mixture was purified by chromatography (hexane–ethyl acetate 1:1): yield 107 mg (90%) of an oil; HRMS calcd for $C_{13}H_{18}O_2S$ 238.1027, found 238.1030; $[\alpha]^{20}_D$ +102.8 ($CHCl_3$, *c* = 1.0); $^1H$ NMR δ 7.49 and 7.33 (AA′BB′ system, 4 H, $C_6H_4$(**a**)), 7.47 and 7.32 (AA′BB′ system, 4 H, $C_6H_4$(**b**)), 3.78 (q, 1 H, *J* = 7.1, C*H*(**a**)), 3.69 (q, 1 H, *J* = 7.0, C*H*(**b**)), 2.54 (m, 2 H, $CH_2CO$(**a**)), 2.36 (m, 2 H, $CH_2CO$(**b**)), 2.42 (s, 6 H, $CH_3Ar$(**a**) and $CH_3Ar$(**b**)), 1.56 (m, 2 H, $CH_2CH_3$(**b**)), 1.49 (m, 2 H, $CH_2CH_3$(**a**)), 1.39 (d, 3 H, *J* = 7.0, $CH_3CH$(**b**)), 1.21 (d, 3 H, *J* = 7.1, $CH_3CH$(**a**)), 0.90 (t, 3 H, *J* = 6.8, $CH_3CH_2$(**a**)), 0.84 (t, 3 H, *J* = 7.3, $CH_3CH_2$(**b**)).

**($R_4$,$R_S$)- and ($S_4$,$R_S$)-2-methyl-4-[(4-methylphenyl)sulfinyl]pentan-3-one (6a + 6b)** were prepared as a 43:57 mixture from 139 mg of ethyl 2-methylpropionate and 168 mg of ethyl *p*-tolyl sulfoxide (1.0/1.2/1.0 LDA/ester/ethyl *p*-tolyl sulfoxide molar ratio). The mixture was purified by chromatography (hexane–ethyl acetate 1:1): yield 106 mg (89%) of an oil; HRMS calcd for $C_{13}H_{18}O_2S$ 238.1027, found 238.1029; $[\alpha]^{20}_D$ +81.9° ($CHCl_3$, *c* = 1.0); $^1H$ NMR δ 7.51 and 7.34 (AA′BB′ system, 4 H, $C_6H_4$(**a**)), 7.48 and 7.31 (AA′BB′ system, 4 H, $C_6H_4$(**b**)), 4.01 (q, 1 H, *J* = 7.0, C*H*S(**a**)), 3.88 (q, 1 H, *J* = 7.0, C*H*S(**b**)), 2.77 (sep, 1 H, *J* = 6.9, $CH(CH_3)_2$(**a**)), 2.43 (s, 3 H, $CH_3Ar$(**a**)), 2.41 (s, 3 H, $CH_3Ar$(**b**)), 2.38 (sep, 1 H, *J* = 6.8, $CH(CH_3)_2$(**b**)), 1.50 (d, 3 H, *J* = 7.0, $CH_3CH$(**b**)), 1.14 (d, 3 H, *J* = 7.0, $CH_3CH$(**a**)), 1.13 and 1.12 (d and d, 3 H and 3 H, *J* = 6.9 and 6.9, $(CH_3)_2CH$(**a**)),

(14) We have tried many different hydrolysis conditions. The use of a saturated solution of HCl in $Et_2O$/MeOH (Herranz, R.; Castro-Pichel, J.; Vinuesa, S.; García Lopez, M. T. *J. Org. Chem.* **1990**, *55*, 2232) gave satisfactory results in some cases, but mixtures of sulfides and sulfoxides were also obtained in other trials.

(15) Carreño, M. C.; Domínguez, E.; García Ruano, J. L.; Pedregal, C.; Rodríguez, J. H. *Tetrahedron* **1991**, *47*, 10035.

1.01 and 0.79 (d and d, 3 H and 3 H, $J$ = 6.8 and 6.8, ($CH_3$)CH(b)).

**($R_4$,$R_S$)- and ($S_4$,$R_S$)-2,2-dimethyl-4-[(4-methylphenyl)sulfinyl]pentan-3-one (7a + 7b)** were prepared as a 40:60 mixture from 156 mg of ethyl pivaloate and 168 mg of ethyl *p*-tolyl sulfoxide (2.3/1.2/1.0 LDA/ester/ethyl *p*-tolyl sulfoxide molar ratio): yield 214 mg (85%) of an oil; HRMS (**7a + 7b**) calcd for $C_{14}H_{20}O_2S$ 252.1184, found 252.1184. Separation was achieved by chromatography (hexane–ethyl acetate 3:2). **Isomer 7a**: $R_f$ 0.7, $[\alpha]^{20}_D$ −11.3° ($CHCl_3$, $c$ = 0.15); $^1H$ NMR δ 7.58 and 7.34 (AA′BB′ system, 4 H, $C_6H_4$), 4.22 (q, 1 H, $J$ = 6.9, C*H*), 2.43 (s, 3 H, $CH_3$Ar), 1.23 (s, 9 H, $(CH_3)_3$C), 1.07 (d, 3 H, $J$ = 6.9, $CH_3$CH). **Isomer 7b**: $R_f$ 0.5; $[\alpha]^{20}_D$ −43.0° ($CHCl_3$, $c$ = 1.0); $^1H$ NMR δ 7.52 and 7.28 (AA′BB′ system, 4 H, $C_6H_4$), 4.02 (q, 1 H, $J$ = 7.0, C*H*), 2.40 (s, 3 H, $CH_3$Ar), 1.66 (d, 3 H, $J$ = 7.0, $CH_3$CH), 0.81 (s, 9 H, $(CH_3)_3$C).

**($R_2$,$R_S$)- and ($S_2$,$R_S$)-2-[(4-methylphenyl)sulfinyl]-1-phenylpropan-1-one (8a + 8b)** were prepared as a 40:60 mixture from 180 mg of ethyl benzoate and 168 mg of ethyl *p*-tolyl sulfoxide (2.3/1.2/1.0 LDA/ester/ethyl *p*-tolyl sulfoxide molar ratio). The mixture was purified by chromatography (hexane–ethyl acetate 1:9): yield 215 mg (79%) of an oil; HRMS calcd for $C_{16}H_{16}O_2S$ 272.0871, found 272.0874; $[\alpha]^{20}_D$ +13.9° ($CHCl_3$, $c$ = 0.3); $^1H$ NMR δ 8.01 (m, 2 H, aromatic protons (**b**)), 7.73 (m, 2 H, aromatic protons (**a**)), 7.63–7.16 (m, 14 H, aromatic protons (**a** and **b**)), 4.89 (q, 1 H, $J$ = 6.8, C*H*(**a**)), 4.62 (q, 1 H, $J$ = 7.1, C*H*(**b**)), 2.40 (s, 3 H, $CH_3$Ar(**b**)), 2.31 (s, 3 H, $CH_3$Ar(**a**)), 1.66 (d, 3 H, $J$ = 7.1, $CH_3$CH(**b**)), 1.30 (d, 3 H, $J$ = 6.8, $CH_3$CH(**a**)).

**Hydrocyanation.** The following procedures for the preparation of **($S_2$,$R_S$)-3,3-dimethyl-2-hydroxy-2-[[(4-methylphenyl)sulfinyl]methyl]butanenitrile (11)** were typical for all cyanohydrins:

(i) With **$Et_2AlCN$** (Method A). A solution of 238 mg (1 mmol) of (*R*)-**3** in 10 mL of toluene was dropwise added into a solution of 2 mmol of diethyl aluminum cyanide in 10 mL of toluene, and the mixture was stirred for 2 h (the results achieved at 0 °C, −20 °C, and −78 °C were similar). 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, concentrated below 40 °C (higher temperatures decompose the unstable cyanohydrins into the starting ketones) to afford pure (*R*)-**11** as a white solid. It was crystallized from acetone–hexane (1:2): mp 149–150 °C; $[\alpha]^{20}_D$ +220° ($CHCl_3$, $c$ = 0.5); $^1H$ NMR δ 7.61 and 7.40 (AA′BB′ system, 4 H, $C_6H_4$), 5.99 (s, 1 H, O*H*), 2.96 and 2.89 (AB system, 2 H, $J$ = 14.0, $CH_2$S), 2.45 (s, 3 H, $CH_3$Ar), 1.09 (s, 9 H, $(CH_3)_3$C). Anal. Calcd for $C_{14}H_{19}NO_2S$: C, 63.36; H, 7.22; N, 5.28. Found: C, 63.03; H, 6.98; N, 5.42.

The use of (*S*)-**3** isomer as starting material yielded ($S_2$,$R_S$)-**11**, $[\alpha]^{20}_D$ +219° ($CHCl_3$, $c$ = 0.5).

(ii) With **$Et_2AlCN/ZnX_2$ [or $MgX_2$]** (Method B). A solution of 238 mg (1 mmol) of **3** in 10 mL of toluene was added into a solution of 163 mg of $ZnCl_2$ (1.2 mmol) in 3 mL of THF. The mixture was stirred for 30 min at rt and then dropwise added into a stirred solution of 4 mmol of diethyl aluminum cyanide in 10 mL of toluene. The resulting mixture was stirred for 2 h at the corresponding temperature and then worked up as in method A, yield 244 mg (92%).

**($S_2$,$R_S$)-2-Hydroxy-3-[(4-methylphenyl)sulfinyl]-2-phenylpropanenitrile (9).** Hydrocyanation of **1** following methods A and B afforded pure **9** as a yellow syrup: $[\alpha]^{20}_D$ +85° ($CHCl_3$, $c$ = 1.0); $^1H$ NMR δ 7.64–7.57 (m, 4 H, aromatic protons), 7.46–7.28 (m, 5 H, aromatic protons), 3.18 and 3.11 (AB system, 2 H, $J$ = 13.5, $CH_2$), 2.41 (s, 3 H, $CH_3$).

**($S_2$,$R_S$)-2-Hydroxy-2-[[(4-methylphenyl)sulfinyl]methyl]butanenitrile (10).** Hydrocyanation of **2** following methods A and B afforded **10** (de ≥ 96%) as a white solid. It was crystallized from $Et_2O$–hexane (1:2): mp 68–69 °C; $[\alpha]^{20}_D$ +243° ($CHCl_3$, $c$ = 1.0); $^1H$ NMR δ, 7.59 and 7.39 (AA′BB′ system, 4 H, $C_6H_4$), 5.95 (s, 1 H, O*H*), 3.02 and 2.93 (AB system, 2 H, $J$ = 13.2, $CH_2$S), 2.45 (s, 3 H, $CH_3$Ar), 1.87 (m, 2 H, $CH_2CH_3$), 1.14 (t, 3 H, $J$ = 7.4, $CH_3CH_2$). Anal. Calcd for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.37; N, 5.90. Found: C, 61.09; H, 6.51; N, 5.81.

**($S_2$,$R_3$,$R_S$)- and ($S_2$,$S_3$,$R_S$)-2-Hydroxy-2-methyl-3-[(4-methylphenyl)sulfinyl]butanenitrile (12A + 12B).** Hydrocyanation of a 47:53 mixture of **4a** and **4b** following methods A and B afforded a white solid, which was characterized as a 43:57 mixture of diastereomers **12A** and **12B**: $[\alpha]^{20}_D$ +170° ($CHCl_3$, $c$ = 0.39); $^1H$ NMR δ 7.69 and 7.39 (AA′BB′ system, 4 H, $C_6H_4$(**A**)), 7.45 and 7.36 (AA′BB′ system, 4 H, $C_6H_4$(**B**)), 2.92 (q, 1 H, $J$ = 7.0, C*H*(**A**)), 2.78 (q, 1 H, $J$ = 6.7, C*H*(**B**)), 2.46 (s, 3 H, $CH_3$Ar(**A**)), 2.43 (s, 3 H, $CH_3$Ar(**B**)), 1.75 (s, 3 H, $CH_3$C(**B**)), 1.66 (s, 3 H, $CH_3$C(**A**)), 1.09 (d, 3 H, $J$ = 6.7, $CH_3$CH(**B**)), 1.08 (d, 3 H, $J$ = 7.0, $CH_3$CH(**A**)). Anal. Calcd for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.37; N, 5.90. Found: C, 60.65; H, 6.33; N, 5.54.

**($S_2$,$R_3$,$R_S$)- and ($S_2$,$S_3$,$R_S$)-2-Hydroxy-2-[1-[(4-methylphenyl)sulfinyl]ethyl]pentanenitrile (13A + 13B).** Hydrocyanation of a 40:60 mixture of **5a** and **5b** following methods A and B afforded a white solid, which was characterized as a 45:55 mixture of diastereomers **13A** and **13B** and crystallized from hexane–acetone (10:1): $[\alpha]^{20}_D$ +140.2° ($CHCl_3$, $c$ = 1.0); $^1H$ NMR δ 7.68 and 7.37 (AA′BB′ system, 4 H, $C_6H_4$(**A**)), 7.44 and 7.39 (AA′BB′ system, 4 H, $C_6H_4$(**B**)), 6.95 (s, 1 H, O*H*(**A**)), 4.92 (s, 1 H, O*H*(**B**)), 2.94 (q, 1 H, $J$ = 7.1, C*H*(**A**)), 2.73 (q, 1 H, $J$ = 6.7, C*H*(**B**)), 2.45 (s, 3 H, $CH_3$Ar(**A**)), 2.44 (s, 3 H, $CH_3$Ar(**B**)), 2.07–1.46 (m, 8 H, $CH_2CH_2$(**A**), $CH_2CH_2$(**B**)), 1.06 (d, 3 H, $J$ = 7.1, $CH_3$CH(**A**)), 1.05 (d, 3 H, $J$ = 6.7, $CH_3$CH(**B**)), 1.01 (t, 6 H, $J$ = 7.4, $CH_3CH_2$(**A**), $CH_3CH_2$(**B**)). Anal. Calcd for $C_{14}H_{19}NO_2S$: C, 63.36; H, 7.22; N, 5.28. Found: C, 63.45; H, 7.33; N, 5.38.

**($S_2$,$R_3$,$R_S$)- and ($S_2$,$S_3$,$R_S$)-2-Hydroxy-3-[(4-methylphenyl)sulfinyl]-2-isopropylbutanenitrile (14A + 14B).** Hydrocyanation of a 43:57 mixture of **6a** and **6b** following methods A and B afforded a white solid, which was characterized as a 34:66 mixture of diastereomers **14A** and **14B** and crystallized from hexane–acetone (10:1): $[\alpha]^{20}_D$ +136.3° ($CHCl_3$, $c$ = 1.0); $^1H$ NMR δ 7.69 and 7.45 (AA′BB′ system, 4 H, $C_6H_4$(**A**)), 7.44 and 7.40 (AA′BB′ system, 4 H, $C_6H_4$(**B**)), 6.80 (d, 1 H, $J$ = 1.7, O*H*(**A**)), 5.22 (s, 1 H, O*H*(**B**)), 2.96 (q, 1 H, $J$ = 7.0, C*H*S(**A**)), 2.76 (q, 1 H, $J$ = 6.9, C*H*S(**B**)), 2.46 (s, 3 H, $CH_3$Ar(**A**)), 2.44 (s, 3 H, $CH_3$Ar(**B**)), 2.08 (sep, 1 H, $J$ = 6.7, C*H*$(CH_3)_2$(**B**)), 2.07 (m, 1 H, C*H*$(CH_3)_2$(**A**)), 1.26 (m, 9 H, $CH_3CHCH_3$(**A**) and C*H*$_3$)$_2$CH(**B**)), 1.04 (d, 3 H, $J$ = 7.0, $CH_3$CH(**A**)), 1.00 (d, 3 H, $J$ = 6.9, $CH_3$CH(**B**)), 0.94 (d, 3 H, $J$ = 6.6, $CH_3CHCH_3$(**A**)). Anal. Calcd for $C_{14}H_{19}NO_2S$: C, 63.36; H, 7.22; N, 5.28. Found: C, 63.75; H, 7.61; N, 5.12.

**($S_2$,$R_3$,$R_S$)-2-*tert*-Butyl-2-hydroxy-3-[(4-methylphenyl)sulfinyl]butanenitrile (15A).** Hydrocyanation of **7a** following method B ($Et_2AlCN/ZnBr_2$) afforded **15A** (de ca. 94%), which was obtained diastereomerically pure by crystallization from hexane of the crude mixture: mp 132–133 °C. $[\alpha]^{20}_D$ +61.9° ($CHCl_3$, $c$ = 1.0); $^1H$ NMR δ 7.69 and 7.38 (AA′BB′ system, 4 H, $C_6H_4$), 3.08 (q, 1 H, $J$ = 7.0, C*H*), 2.45 (s, 3 H, $CH_3$Ar), 1.16 (d, 3 H, $J$ = 7.0, $CH_3$CH), 1.15 (s, 9 H, $(CH_3)_3$C). Anal. Calcd for $C_{15}H_{21}NO_2S$: C, 64.48; H, 7.58; N, 5.01. Found: C, 64.12; H, 7.54; N, 5.09.

**($S_2$,$S_3$,$R_S$)- and ($R_2$,$S_3$,$R_S$)-2-*tert*-Butyl-2-hydroxy-3-[(4-methylphenyl)sulfinyl]butanenitrile (15B + 15B′).** Hydrocyanation of **7b** following method A afforded a yellow oil, which was characterized as a 85:15 mixture of diastereomers **15B** and **15B′**: $^1H$ NMR δ 7.57–7.28 (m and m, 8 H, $C_6H_4$(**B**) and $C_6H_4$(**B′**)), 5.80 (bs, 1 H, O*H*(**B′**)), 4.84 (bs, 1 H, O*H*(**B**)), 3.08 (q, 1 H, $J$ = 7.2, C*H*(**B′**)), 2.85 (q, 1 H, $J$ = 6.9, C*H*(**B**)), 2.44 (s, 6 H, $CH_3$Ar(**B** and $CH_3$Ar(**B′**)), 1.36 (d, 3 H, $J$ = 7.2, $CH_3$CH(**B′**)), 1.23 (s, 9 H, $(CH_3)_3$C(**B′**)), 1.21 (s, 9 H, $(CH_3)_3$C(**B**)), 1.13 (d, 3 H, $J$ = 6.9, $CH_3$CH(**B**)).

**($S_2$,$R_3$,$R_S$)- and ($S_2$,$S_3$,$R_S$)-2-Hydroxy-3-[(4-methylphenyl)sulfinyl]-2-phenylbutanenitrile (16A + 16B).** Hydrocyanation of a 40:60 mixture of **8a** and **8b** following methods A and B afforded a yellow oil, which was characterized as a 38:62 mixture of diastereomers **16A** and **16B**: $[\alpha]^{20}_D$ +86.2° ($CHCl_3$, $c$ = 0.66); $^1H$ NMR δ 7.74 (m, 2 H, aromatic protons(**A**)), 7.62 (m, 2 H, aromatic protons(**B**)), 7.57–7.34 (m, 14 H, aromatic protons), 7.11 (s, 1 H, O*H*(**A**)), 5.58 (s, 1 H, O*H*(**B**)), 3.05 (q, 1 H, $J$ = 7.1, C*H*(**A**)), 2.94 (q, 1 H, $J$ = 7.0, C*H*(**B**)), 2.44 (s, 3 H, $CH_3$Ar(**A**)), 2.42 (s, 3 H, $CH_3$Ar(**B**)), 0.77 (d, 3 H, $J$ = 7.0, $CH_3$CH(**B**)), 0.75 (d, 3 H, $J$ = 7.1, $CH_3$CH(**A**)).

**Hydrolysis of Cyanohydrins into Hydroxy Amides. General Procedure.** Ten milliliters of anhydrous $Et_2O$, previously saturated with HCl, were added into a flask containing

1 mmol of cyanohydrin, and the mixture was stirred at 0 °C for 1 h. Then ice–water (5 mL) was added, and the stirring was kept at 0 °C for 1 h. The reaction mixture was concentrated in vacuo and worked up.

**(*S*)-2-Hydroxy-3-[(4-methylphenyl)sulfenyl]-2-phenylpropanamide (17)** was prepared by hydrolysis of **9**, yield 82%. It was crystallized from hexane–toluene (2:1): mp 101–102 °C; HRMS calcd for $C_{16}H_{17}NO_2S$ 287.0980, found 287.0984; $[\alpha]^{20}_D$ −29.0° ($CHCl_3$, $c$ = 0.7); $^1$H NMR δ 7.59 and 7.03 (AA′BB′ system, 4 H, $C_6H_4$), 7.58 (m, 2 H, aromatic protons (Ph)), 7.27 (m, 3 H, aromatic protons (Ph)), 6.74 (bs, 1 H, N*H*), 5.52 (bs, 1 H, N*H*), 3.93 and 3.44 (AB system, 2 H, $J$ = 13.6, $CH_2S$), 3.85 (s, 1 H, O*H*), 2.28 (s, 3 H, $CH_3Ar$).

**(*S*)-2-Hydroxy-2-[[(4-methylphenyl)sulfenyl]methyl]butanamide (18)** was prepared by hydrolysis of **10**, yield 80%. It was crystallized from toluene, mp 74–75 °C; HRMS calcd for $C_{12}H_{17}NO_2S$ 239.0980, found 239.0975; $[\alpha]^{20}_D$ +22.0° ($CHCl_3$, $c$ = 0.275); $^1$H NMR δ 7.33 and 7.09 (AA′BB′ system, 4 H, $C_6H_4$), 6.69 (bs, 1 H, N*H*), 5.51 (bs, 1 H, N*H*), 3.55 and 3.16 (AB system, 2 H, $J$ = 13.8, $CH_2S$), 2.31 (s, 3 H, $CH_3Ar$), 1.76 (m, 2 H, $CH_2CH_3$), 0.93 (t, 3 H, $J$ = 7.4, $CH_3CH_2$).

**(*S*)-3,3-Dimethyl-2-hydroxy-2-[[(4-methylphenyl)sulfenyl]methyl]butanamide (19)** was prepared by hydrolysis of **11**, yield 42% (a 35% of ($S_2$,$R_S$)-3,3-dimethyl-2-hydroxy-2-[[(4-methylphenyl)sulfinyl]methyl]butanamide was also recovered). It was crystallized from hexane–toluene (2:1): mp 104–105 °C; HRMS calcd for $C_{14}H_{21}NO_2S$ 267.1293, found 267.1285; $[\alpha]^{20}_D$ −30.6° (MeOH, $c$ = 0.5); $^1$H NMR δ 7.32 and 7.09 (AA′BB′ system, 4 H, $C_6H_4$), 6.76 (bs, 1 H, N*H*), 5.83 (bs, 1 H, N*H*), 3.91 and 3.05 (AB system, 2 H, $J$ = 13.3, $CH_2S$), 3.39 (s, 1 H, O*H*), 2.31 (s, 3 H, $CH_3Ar$), 1.05 (s, 9 H, $(CH_3)_3C$).

**($S_2$,$R_3$)- and ($S_2$,$S_3$)-2-hydroxy-2-methyl-3-[(4-methylphenyl)sulfenyl]butanamide (20A + 20B)** were prepared as a 38:62 mixture by hydrolysis of a 43:57 mixture of **12A** and **12B**, yield 92%. Both isomers were isolated by chromatography (hexane–ethyl acetate 1:4). **Isomer 20A** ($R_f$ 0.5): crystallized from $CH_2Cl_2$, mp 96–97 °C; $[\alpha]^{20}_D$ −14.1° (MeOH, $c$ = 0.1); $^1$H NMR δ 7.36 and 7.11 (AA′BB′ system, 4 H, $C_6H_4$), 6.75 (bs, 1 H, N*H*), 5.41 (bs, 1 H, N*H*), 3.63 (q, 1 H, $J$ = 7.0, C*H*), 2.45 (s, 1 H, O*H*), 2.32 (s, 3 H, $CH_3Ar$), 1.50 (s, 3 H, $CH_3C$), 1.34 (d, 3 H, $J$ = 7.0, $CH_3CH$). **Isomer 20B** ($R_f$ 0.4): crystallized from $CH_2Cl_2$, mp 162–163 °C; $[\alpha]^{20}_D$ −4.8° (MeOH, $c$ = 0.15); $^1$H NMR δ 7.37 and 7.10 (AA′BB′ system, 4 H, $C_6H_4$), 6.71 (bs, 1 H, N*H*), 5.44 (bs, 1 H, N*H*), 3.61 (q, 1 H, $J$ = 7.1, C*H*), 2.42 (bs, 1 H, O*H*), 2.33 (s, 3 H, $CH_3Ar$), 1.43 (s, 3 H, $CH_3C$), 1.37 (d, 3 H, $J$ = 7.1, $CH_3CH$). Anal. Calcd for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16; N, 5.85. Found: C, 60.21; H, 7.24; N, 5.74.

**($S_2$,$R_3$)- and ($S_2$,$S_3$)-2-hydroxy-2-[[1-(4-methylphenyl)sulfenyl]ethyl]pentanamide (21A + 21B)** were prepared as a 39:61 mixture by hydrolysis of a 45:55 mixture of **13A** and **13B**: yield 96%; HRMS calcd for $C_{14}H_{21}NO_2S$ 267.1293, found 267.1293; $[\alpha]^{20}_D$ −13.6° (MeOH, $c$ = 0.5); $^1$H NMR δ 7.35 and 7.08 (AA′BB′ system, 4 H, $C_6H_4$(**B**)), 7.34 and 7.08 (AA′BB system, 4 H, $C_6H_4$(**A**)), 6.87 (bs, 2 H, N*H*(**A** and **B**)), 6.37 (bs, 2 H, N*H*(**A** and **B**)), 3.57 (q, 1 H, $J$ = 6.8, C*H*(**A**)), 3.55 (q, 1 H, $J$ = 6.9, C*H*(**B**)), 3.48 (bs, 2 H, O*H*(**A** and **B**)), 2.31 (s, 6 H, $CH_3Ar$(**A** and **B**)), 1.97–1.68 (m, 4 H, $CH_2C$(**A** and **B**)), 1.68–1.12 (m, 4 H, $CH_2CH_3$(**A** and **B**)), 1.34 (d, 3 H, $J$ = 6.9, $CH_3CH$(**B**)), 1.31 (d, 3 H, $J$ = 6.8, $CH_3CH$(**A**)), 0.88 (t, 3 H, $J$ = 6.9, $CH_3CH_2$(**B**)), 0.85 (t, 3 H, $J$ = 7.0, $CH_3CH_2$(**A**)).

**($S_2$,$R_3$)- and ($S_2$,$S_3$)-2-hydroxy-3-(4-methylphenyl)sulfenyl)-2-isopropylbutanamide (22A + 22B)** were prepared as a 29:71 mixture by hydrolysis of a 34:66 mixture of **14A** and **14B**: yield 87%; $[\alpha]^{20}_D$ −27.1° (MeOH, $c$ = 0.5); $^1$H NMR δ 7.37 and 7.12 (AA′BB′ system, 8 H, $C_6H_4$(**A**) and $C_6H_4$(**B**)), 6.73 (bs, 2 H, N*H*(**A** and **B**)), 5.90 (bs, 1 H, N*H*(**B**)), 5.75 (bs, 1 H, N*H*(**A**)), 3.71 (bs, 1 H, O*H*(**B**)), 3.64 (q, 1 H, $J$ = 6.8, $CHCH_3$(**A**)), 3.56 (q, 1 H, $J$ = 6.9, $CHCH_3$(**B**)), 2.78 (bs, 1 H, O*H*(**A**)), 2.33 (s, 6 H, $CH_3Ar$(**A**), $CH_3Ar$(**B**)), 2.24 (sep, 2 H, $J$ = 6.7, $CH(CH_3)_2$(**A**), $CH(CH_3)_2$(**B**)), 1.37 (d, 3 H, $J$ = 6.9, $CH_3CH$(**A**)), 1.28 (d, 3 H, $J$ = 7.1, $CH_3CH$(**B**)), 1.00 and 0.98 (d and d, 3 H and 3 H, $J$ = 6.8 and 6.8, $(CH_3)_2CH$(**A**)), 0.92 (d, 6 H, $J$ = 6.8, $(CH_3)_2CH$(**B**)).

**($S_2$,$R_3$)-2-*tert*-Butyl-2-hydroxy-3-[(4-methylphenyl)sulfenyl]butanamide (23A)** was prepared by hydrolysis of diastereomerically pure **15A**: yield 86%; crystallized from hexane–acetone (1:1), mp 108–109 °C; $[\alpha]^{20}_D$ −76.8° (MeOH, $c$ = 0.45); $^1$H NMR δ 7.34 and 7.12 (AA′BB′ system, 4 H, $C_6H_4$), 6.82 (bs, 1 H, N*H*), 5.53 (bs, 1 H, N*H*), 3.83 (q, 1 H, $J$ = 6.8, C*H*), 2.33 (s, 3 H, $CH_3Ar$), 1.29 (d, 3 H, $J$ = 6.8, $CH_3CH$), 1.21 (s, 9 H, $(CH_3)_3C$).

**($S_2$,$R_3$)- and ($S_2$,$S_3$)-2-hydroxy-3-[(4-methylphenyl)sulfenyl]-2-phenylbutanamide (24A + 24B)** were prepared as a 33:67 mixture by hydrolysis of a 38:62 mixture of **16A** and **16B**, yield 95%. Anal. Calcd for $C_{17}H_{19}NO_2S$: C, 67.74; H, 6.35; N, 4.65. Found: C, 67.70; H, 6.31; N, 4.04. Chromatography (hexane–ethyl acetate 4:1) of the crude afforded diastereomerically pure **24B** as a white solid. **Isomer 24A** (characterized from a mixture of **24A** + **24B**): $^1$H NMR δ 7.55 (m, 2 H, aromatic protons), 7.40 and 7.16 (AA′BB′ system, 4 H, $C_6H_4$), 7.31 (m, 3 H, aromatic protons), 6.69 (bs, 1 H, N*H*), 5.19 (bs, 2 H, N*H*), 4.03 (q, 1 H, $J$ = 7.0, C*H*), 3.58 (bs, 1 H, O*H*), 2.39 (s, 3 H, $CH_3Ar$), 1.85 (d, 3 H, $J$ = 7.0, $CH_3CH$). **Isomer 24B**: crystallized from hexane–acetone (1:3), mp 183–184 °C; $[\alpha]^{20}_D$ −4.0° (MeOH, $c$ = 0.4); $^1$H NMR δ 7.65 (m, 2 H, aromatic protons), 7.46 and 7.12 (AA′BB′ system, 4 H, $C_6H_4$), 7.30 (m, 3 H, aromatic protons), 6.70 (bs, 1 H, N*H*), 5.28 (bs, 1 H, N*H*), 4.34 (q, 1 H, $J$ = 7.2, C*H*), 3.61 (bs, 1 H, O*H*), 2.34 (s, 3 H, $CH_3Ar$), 0.97 (d, 3 H, $J$ = 7.2, $CH_3CH$). Anal. Calcd for $C_{17}H_{19}NO_2S$: C, 67.74; H, 6.35; N, 4.65. Found: C, 67.04; H, 5.94; N, 4.48.

**Raney Nickel Desulfurization of Sulfenyl Hydroxy Amides. General Procedure.** One millimole of sulfenyl hydroxy amide was dissolved in 20 mL of anhydrous ethanol, and an excess of Raney nickel (previously activated by washing the commercial reagent with ethanol) was added. The mixture was vigorously stirred under argon at room temperature for 2 h. The nickel was removed by filtration and washed with ethanol. The solvent was evaporated, and the residue was washed with boiling hexane to yield the corresponding hydroxy amide.

**(*S*)-2-Hydroxy-2-phenylpropanamide (25)** was prepared from **17**: yield 65%; crystallized from toluene, mp 71–72 °C; HRMS calcd for $C_9H_{11}NO_2$ 165.0790, found 165.0792; $[\alpha]^{20}_D$ −5.9° (acetone, $c$ = 0.63); $^1$H NMR δ 7.57 (m, 2 H, aromatic protons), 7.32 (m, 3 H, aromatic protons), 6.40 (bs, 1 H, N*H*), 5.80 (bs, 1 H, N*H*), 3.54 (bs, 1 H, O*H*), 1.80 (s, 3 H, $CH_3$). Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.69; H, 6.74; N, 8.02.

**(*S*)- and (*R*)-2-Hydroxy-2-methylbutanamide (26 and 28).** (*S*)-enantiomer (**26**) was prepared from **18** (oil): yield 61%; $[\alpha]^{20}_D$ −5.2° (acetone, $c$ = 0.6); $[\alpha]^{20}_D$ −5.3° (MeOH, $c$ = 0.7); HRMS calcd for $C_5H_{11}NO_2$ 117.0790, found 117.0790. (*R*)-enantiomer (**28**) was prepared from a mixture of **20A** and **20B** (oil): yield 76%; $[\alpha]^{20}_D$ +5.6° (MeOH, $c$ = 2.0); HRMS calcd for $C_5H_{11}NO_2$ 117.0790, found 117.0789; $^1$H NMR δ 6.59 (bs, 1 H, N*H*), 5.68 (bs, 1 H, N*H*), 2.48 (s, 1 H, O*H*), 1.76 (m, 2 H, $CH_2$), 1.44 (s, 3 H, $CH_3C$), 0.94 (t, 3 H, $J$ = 7.4, $CH_3CH_2$).

**(*S*)-2-Hydroxy-2,3,3-trimethylbutanamide (27)** was prepared from **19**: yield 68%; crystallized from toluene, mp 116–117 °C; $[\alpha]^{20}_D$ −5.4° (acetone–water (2:3), $c$ = 0.7); $^1$H NMR δ 6.58 (bs, 1 H, N*H*), 5.64 (bs, 1 H, N*H*), 1.42 (s, 3 H, $CH_3COH$), 1.04 (s, 9 H, $(CH_3)_3C$).

**(*S*)-2-Ethyl-2-hydroxypentanamide (29)** was prepared from a 39:61 mixture of **21A** and **21B**: yield 79%; crystallized from toluene, mp 66–67 °C; HRMS calcd for $C_7H_{16}NO_2$ [M + H]$^+$ 146.1181, found 146.1179; $[\alpha]^{20}_D$ +4.4° (MeOH, $c$ = 2.45); $^1$H NMR δ 6.73 (bs, 1 H, N*H*), 6.29 (bs, 1 H, N*H*), 3.18 (s, 1 H, O*H*), 1.95–1.13 (m, 9 H, $CH_3CH_2CH_2$ and $CH_2C$), 0.91 (t, 3 H, $J$ = 7.3, $CH_3$).

**(*S*)-2-Hydroxy-2-isopropylbutanamide (30)** was prepared from a 29:71 mixture of **22A** and **22B**: yield 81%; crystallized from toluene, mp 89–90 °C; HRMS calcd for $C_7H_{15}NO_2$ 145.1103, found 145.1112; $[\alpha]^{20}_D$ −13.0° (MeOH, $c$ = 0.6); $^1$H NMR δ 6.49 (bs, 1 H, N*H*), 5.86 (bs, 1 H, N*H*), 2.41 (bs, 1 H, O*H*), 2.00 (sep, 1 H, $J$ = 6.7, C*H*), 1.72 (m, 2 *H*, $CH_2$), 0.95 (d, 3 H, $J$ = 6.7, $CH_3CH$), 0.92 (d, 3 H, $J$ = 6.7, $CH_3CH$), 0.91 (t, 3 H, $J$ = 7.4, $CH_3CH_2$).

**(*S*)-2-*tert*-Butyl-2-hydroxybutanamide (31)** was prepared from **23A**: yield 76%; crystallized from hexane–acetone (1:1), mp 123–124 °C; $[\alpha]^{20}_D$ −17.3° (MeOH, $c$ = 0.3); $^1$H NMR δ 6.53 (bs, 1 H, N*H*), 5.57 (bs, 1 H, N*H*), 2.29 (s, 1 H, O*H*), 2.05 and 1.56 (m, 2 H, $CH_2$), 1.04 (s, 9 H, $(CH_3)_3C$), 0.91 (t, 3 H, $J$ = 7.4, $CH_3CH_2$).

**(*S*)-2-Hydroxy-2-phenylbutanamide (32)** was prepared from a 33:67 mixture of **24A** and **24B**: yield 69%; $[\alpha]^{20}_D$ −3.1° (MeOH,

$c$ = 0.4); $^1$H NMR $\delta$ 7.63-7.55 (m, 2 H, aromatic protons), 7.43-7.29 (m, 3 H, aromatic protons), 6.36 (bs, 1 H, NH), 5.40 (bs, 1 H, NH), 3.09 (s, 1 H, OH), 2.21 (m, 2 H, $CH_2$), 0.98 (t, 3 H, $J$ = 7.4, $CH_3$).

**Acknowledgment.** We are indebted to the DGICYT for financial support (Grant PB88/176). We thank Dr. F. Alcudia from Universidad de Sevilla (Spain) for performance of the HRMS.

**Supplementary Material Available:** MS, IR, and $^{13}$C NMR data for **2-32** and $^1$H NMR spectra of **17-32** (23 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

# Structural Investigation and Anti-HIV Activities of High Molecular Weight ATA Polymers

Mark Cushman,*,† Pinglang Wang,† Joseph G. Stowell,† Dominique Schols,‡ and Erik De Clercq‡

*Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907, and Rega Institute for Medical Research, Katholieke Universiteit Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium*

*Received August 4, 1992*

Aurintricarboxylic acid (ATA) was prepared from salicylic acid, formaldehyde, sulfuric acid, and sodium nitrite using a prolonged reaction time in order to favor the production of high molecular weight polymers. The resulting material was fractionated on the basis of molecular weight into nine fractions by equilibrium dialysis and ultrafiltration. Comparison of the NMR spectral data of these polymer fractions with the NMR spectra of low molecular weight ATA components provided a revised schematic representation of the structures of the ATA polymers used in the present study. The low molecular weight components were previously obtained from an ATA sample prepared using a limited reaction time. The anti-HIV activities of the ATA fractions were also investigated. The assays included prevention of the cytopathic effect of HIV-1 and HIV-2 in MT-4 cells, prevention of the cytopathic effect of HIV-1 in CEM cells, cytotoxicity in MT-4 cells, inhibition of syncytium formation between MOLT-4 cells and either HIV-1- or HIV-2-infected HUT-78 cells, and inhibition of HIV-1 binding to MT-4 cells. The potencies of the fractions in preventing the cytopathic effects of HIV-1 and HIV-2 increased as the average molecular weights of the fractions increased up to a dialysis molecular weight range of 7000-12 000 Da, which had weight average and number average molecular weights ($M_w$ and $M_n$) of approximately 2937 and 2547, respectively. Further increase in the molecular weight beyond this point did not result in a further increase in potency, and the highest molecular weight fractions displayed decreased potencies for prevention of the cytopathic effects of HIV-1 and HIV-2 in MT-4 cells as well as for inhibition of syncytium formation between MOLT-4 cells and HIV-1 or HIV-2-infected HUT-78 cells.

Aurintricarboxylic acid (ATA) is a heterogeneous, polymeric substance that forms when a mixture of salicylic acid and formaldehyde is treated with sulfuric acid and sodium nitrite.[1-3] Interest in ATA has been stimulated by the observation that it prevents the cytopathic effect of HIV-1 in ATH8, MT-4, and HUT-78 cell cultures.[4,5] We recently fractionated ATA by a combination of equilibrium dialysis, ultrafiltration, and gel permeation chromatography and established a correlation between the average molecular weights of the ATA fractions and their potencies in preventing the cytopathic effects of HIV-1 and HIV-2 in several different cell cultures.[6] The molecular weights also correlated with activities in a number of related assays, including inhibition of syncytium formation between HIV-1- or HIV-2-infected HUT-78 cells and uninfected MOLT-4 cells, prevention of the binding of the OKT4A monoclonal antibody to the CD4 receptor, inhibition of binding of anti-gp120 monoclonal antibody to gp120, inhibition of the attachment of HIV-1 virions to cells, and inhibition of HIV-1 reverse transcriptase.[6] In all of these assays, the higher the average molecular weight, the higher the activity.[6]

The ATA sample used in these previous studies was prepared at 0 °C for 15 min, conditions which favor the formation of lower molecular weight material. In addition, the highest molecular weight cutoff value of the dialysis tubing used was 12 000 Da. An obvious and important question posed by these results is how far the correlation of molecular weight with activity would hold if fractions were obtained having higher average molecular weights. In order to obtain these higher molecular weight fractions for the present study, the polymerization reaction used to prepare ATA was performed for 64 h instead of 15 min, and additional dialysis membranes were used having molecular weight cutoff values greater than 12 000 Da. The potencies of the fractions in preventing the cytopathic effects of HIV-1 in CEM cell cultures as well as the cy-

† Purdue University.
‡ Katholieke Universiteit Leuven.

(1) Caro, N. *Chem. Ber.* **1892**, *25*, 939-949.
(2) González, R.; Blackburn, B. J.; Schleich, T. *Biochim. Biophys. Acta* **1979**, *562*, 534-545.
(3) Cushman, M.; Kanamathareddy, S. *Tetrahedron* **1990**, *46*, 1491-1498.
(4) Balzarini, J.; Mitsuya, H.; De Clercq, E.; Broder, S. *Biochem. Biophys. Res. Commun.* **1986**, *136*, 64-71.
(5) Baba, M.; Schols, D.; Pauwels, R.; Balzarini, J.; De Clercq, E. *Biochem. Biophys. Res. Commun.* **1988**, *155*, 1404-1411.
(6) Cushman, M.; Wang, P.; Chang, S.; Wild, C.; De Clercq, E.; Schols, D.; Goldman, M. E.; Bowen, J. A. *J. Med. Chem.* **1991**, *34*, 329-342.

0022-3263/92/1957-7241$03.00/0 