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Atropisomerism in the 2-Arylimino-*N*-(2-hydroxyphenyl)thiazoline Series: Influence of Hydrogen Bonding on the Racemization Process

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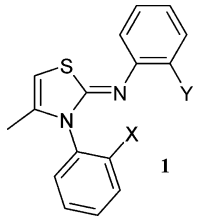

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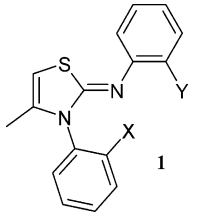
A series of original atropisomeric iminothiazolines **1** in which X = OH or (and) Y = OH were prepared from the corresponding methoxy precursors. The resolution of the atropisomeric enantiomers on chiral support is reported, and the barriers to enantiomerization are given. These barriers were determined either by off-line racemization studies or by treatment of the plateau-shape chromatogram during chromatography on chiral support. When X = OH, the barriers are quite low due to the development of a hydrogen bond between the proton of the OH group and the nitrogen of the imino group. For these compounds, plateau shape chromatograms were obtained during HPLC on chiral support. DFT calculations confirmed the occurrence of hydrogen bonding all along the rotation process and produced calculated barriers in close agreement with the experimental data. Compound **1i** (OH, OH) in which both X and Y are hydroxy groups was particularly easy to prepare by demethylation with BBr_3 of the dimethoxy precursor. Since the above-mentioned precursor is readily available from *N*,*N*′-bis(2-methoxyphenyl)thiourea and 1-chloropropan-2-one, **1i** (OH, OH) is a good candidate for further functionalization. Atropisomerism in a 12-membered bridged bisether prepared from **1i** (OH, OH) is reported as an illustrating example.

Introduction

Atropisomerism about the *N*-aryl bond has been the focus of considerable interest during the last two decades.[1−5] These studies were highly facilitated thanks to the development of liquid chromatography on chiral support during the same period. Particularly interesting are the cases in which the nitrogen atom of the *N*-aryl bond belongs to an amide, a carbamate, or their thio analogues. The nitrogen atom may either be included in a five-[6] or six-membered heterocyclic framework[7] or belong to open chain analogues.[8,9] The aryl group bears an ortho-substituent such as an alkyl, halogen, or methoxy group in order to fill the steric gap required to yield atropisomerism. To the best of our knowledge, very little attention has been paid to *N*-aryl ortho-substituents such as hydroxy or amino groups.[10] Atropisomerism in *N*-(2-hydroxy or 2-aminophenyl)thiazoline-2-(thi)ones has recently been reported.[11]

SCHEME 1. General Structure of 2-Arylimino-3-arylthiazoline Derivatives



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(**1a**) X = CH_3, Y = CH_3
(**1b**) X = OCH_3, Y = CH_3
(**1c**) X = CH_3, Y = OCH_3
(**1d**) X = OCH_3, Y = OCH_3

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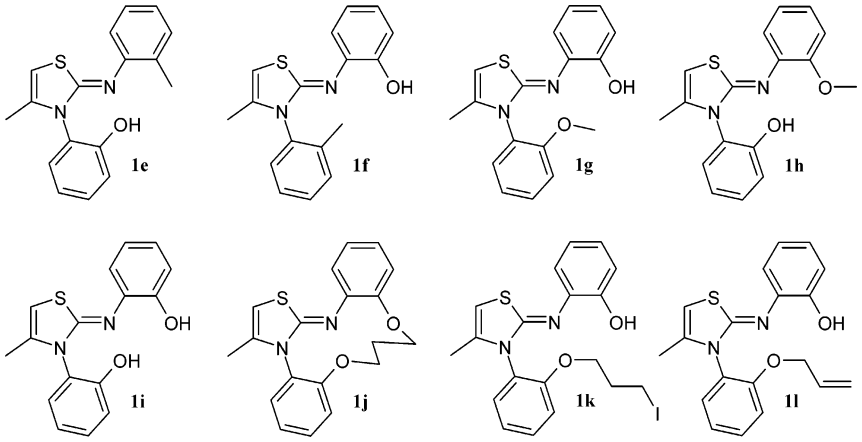
SCHEME 2. Structure of Atropisomers 1e−1l



2-Arylimino-*N*-arylthiazoline derivatives **1** are accessible thanks to a single-step reaction between a halogeno-ketone and an *N*,*N*′-diarylthiourea. This simple reaction involving readily available starting materials offers a large source of molecular diversity. When X and (or) Y are hydroxy groups, **1** may constitute an original framework (Scheme 1) in which, in addition to the highly basic nitrogen atom of the imino group, one or two oxygen binding sites are organized in a spatial arrangement suitable for binding. Ortho-substitution on the heterocyclic *N*-aryl group may lead to atropisomerism, and thus iminothiazolines **1** in which X and (or) Y are hydroxy groups might afford a chiral ligand.[12] Very little is known about atropisomerism in 2-arylimino-3-arylthiazoline derivatives. Limited information came from our previous paper which described the synthesis, the resolution on chiral support, and the stereodynamics of **1a** (X = Y = Me), **1b** (MeO, Me), **1c** (Me, MeO), and **1d** (MeO, MeO).[13]

A study has appeared recently which focuses on atropisomerism in a 2-arylimino-3-arylthiazolidine-4-one series. In that series, the substituents situated in the ortho-position of the rotating phenyl group were chlorine, methoxy, or methyl groups.[14]

We were interested in the transformation of the methoxy group into a hydroxy group in **1b** (MeO, Me), **1c** (Me, MeO), and **1d** (MeO, MeO) to produce better binding sites. **1b** (MeO, Me) and **1c** (Me, MeO) gave **1e** (OH, Me) and **1f** (Me, OH) respectively. **1d** (MeO, MeO) afforded **1g** (MeO, OH), **1h** (OH, MeO), and **1i** (OH, OH) in different ratios depending on the selectivity of the transformation. We report here the synthesis, resolution on chiral support, and stereodynamics of a focused series of atropisomeric iminothiazolines **1e−i** (Scheme 2). Compound **1i** (OH, OH) was used to prepare the cyclic ether **1j** ($OCH_2CH_2CH_2O$).

Results

Synthesis. We have previously described the synthesis of **1a** (Me, Me), **1b** (MeO, Me), **1c** (Me, MeO), and **1d** (MeO, MeO). Iminothiazolines **1a** (Me, Me) and **1d** (MeO, MeO) were issued from the respective symmetrical thioureas and were thus obtained as single compounds. Access to **1b** (MeO, Me) and **1c** (Me, MeO) required chromatographic separation since they were simultaneously obtained when dis-symmetrical *N*-(2-methoxyphenyl)-*N*′-(2-methylphenyl)thiourea was reacted with 1-chloropropan-2-one.[13] Access to iminothiazolines **1e−i** was designed through demethylation of the methoxy analogues.

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TABLE 1. Selected Chiral HPLC Chromatographic Data for Atropisomers 1e−1l

compound	X	Y	column	eluent	k_1	k_2	α	first eluted
1f	Me	OH	Chiralcel OJ	hexane/2-PrOH 80:20	2.46	3.12	1.26	(−)[a]
1g	MeO	OH	Chiralpak AD	hexane/2-PrOH 90:10	1.57	2.39	1.53	(−)[b]
1h	OH	MeO	Chiralcel OJ	hexane/EtOH 50:50		plateau at 10 °C		
1i	OH	OH	Chiralcel OD-H	hexane/2-PrOH 90:10		plateau at 10 °C		
1e	OH	Me	Chiralcel OD-H	hexane/2-PrOH 95:5		plateau at 10 °C		
1j	$OCH_2CH_2CH_2O$		Chiralpak AD	hexane/2-PrOH 90:10	1.10	3.27	2.99	(−)[b]
1k	$OCH_2CH_2CH_2I$	OH	Chiralpak AD	hexane/2-PrOH 90:10	1.81	2.29	1.27	(−)[b]
1l	$OCH_2CH{=}CH_2$	OH	Chiralpak AD	hexane/2-PrOH 90:10	1.43	1.86	1.30	(−)[b]

[a] Sign given by the circular dichroism at 254 nm. [b] Sign given by the polarimeter.

Several reagents for the demethylation of the methoxy group have been described in the literature.[15,16] Our main objective was to obtain the targeted samples for separation on chiral support followed by a racemization study; no special efforts were devoted to the optimization of the synthesis. Using $AlCl_3$/NaCl, **1c** (Me, MeO) afforded **1f** (Me, OH) in moderate conversion, whereas **1b** (MeO, Me) remained unchanged under these conditions, highlighting a large difference in reactivity for the methoxy group in **1c** (Me, MeO) and **1b** (MeO, Me). These conditions were applied to **1d** (MeO, MeO) but were not selective since **1g** (MeO, OH) (40%), **1h** (OH, MeO) (27%), and **1i** (OH, OH) (17%) were concomitantly obtained. It turned out that it was the only way to obtain **1h** (OH, MeO). Using $AlCl_3$/EtSH or BCl_3, **1d** (MeO, MeO) was selectively converted into **1g** (MeO, OH) in 66 or 92% isolated yield, respectively. Demethylation of **1d** (MeO, MeO) with BBr_3 selectively afforded **1i** (OH, OH). Demethylation of **1b** (MeO, Me) was successful with BCl_3 to give **1e** (OH, Me).

To sum up, the demethylation of the methoxy group situated on the heterocyclic *N*-phenyl was much more difficult than the demethylation of the methoxy group situated on the imino *N*-phenyl. It resulted that iminothiazoline **1h** (OH, MeO) was always obtained in an admixture and had to be isolated by semipreparative chromatography.

Having **1i** (OH, OH) in hand, it was tempting to obtain **1h** (OH, MeO) by selective methylation of the exocyclic phenol. Reaction of **1i** (OH, OH) with methyliodide in the presence of K_2CO_3 afforded **1g** (MeO, OH) and **1d** (MeO, MeO). The higher reactivity toward alkylation of the OH group on the heterocyclic *N*-aryl group was also confirmed during our attempts to prepare cyclic ethers from **1i** (OH, OH). Using 1,3-diiodopropane, **1i** (OH, OH) was transformed into the cyclic ether **1j** ($O-(CH_2)_3-O$). The isolated byproducts **1k** ($OCH_2CH_2CH_2I$, OH) and **1l** ($OCH_2CH{=}CH_2$, OH), which resulted from the elimination of HI in **1k**, confirmed the higher reactivity of the *N*-aryl hydroxy group.

HPLC on Chiral Support and Barriers to Racemization. We have already shown[13] that compounds **1a** (Me, Me), **1b** (MeO, Me), **1c** (Me, MeO), and **1d** (MeO, MeO) gave rise to atropisomerism and that the enantiomers could be separated by HPLC on chiral supports. Semipreparative isolation of the enantiomers allowed the determination of the first-order racemization rates and the barriers to rotation about the pivot *N*-aryl bond. All the new iminothiazolines **1e−1l** were submitted to HPLC on chiral support using a screening unit equipped with 10 commercially available chiral columns and chiroptical detection (CD or polarimeter). Our objective was to find suitable conditions for the isolation of the enantiomers in order to determine their configurational stability by measuring the barrier to racemization. In all cases, one or several columns allowed the clean separation of the enantiomers using a classical mobile phase composed of hexane and an alcoholic modifier. Selected examples are given in Table 1. The sign of the first eluted enantiomer reported in Table 1 is the sign given by the chirality detector in the mobile phase.[17]

Iminothiazolines **1** have to be sorted out in two classes: those in which X is an ether or a methyl group and those in which X is a hydroxy group. Two well-resolved peaks resulting from atropisomerism were observed at room temperature for the iminothiazolines of the former class; the enantiomers could be collected without racemization, allowing off-line determination of the barrier to racemization. The solvent was evaporated at low temperature to ensure configuration stability. For those of the latter class, plateau-shape chromatograms were obtained, indicating a racemization process on the column and thus a much lower barrier.[18] As usual, the height of the plateau increased with the temperature until the coalescence of the peaks occurred,

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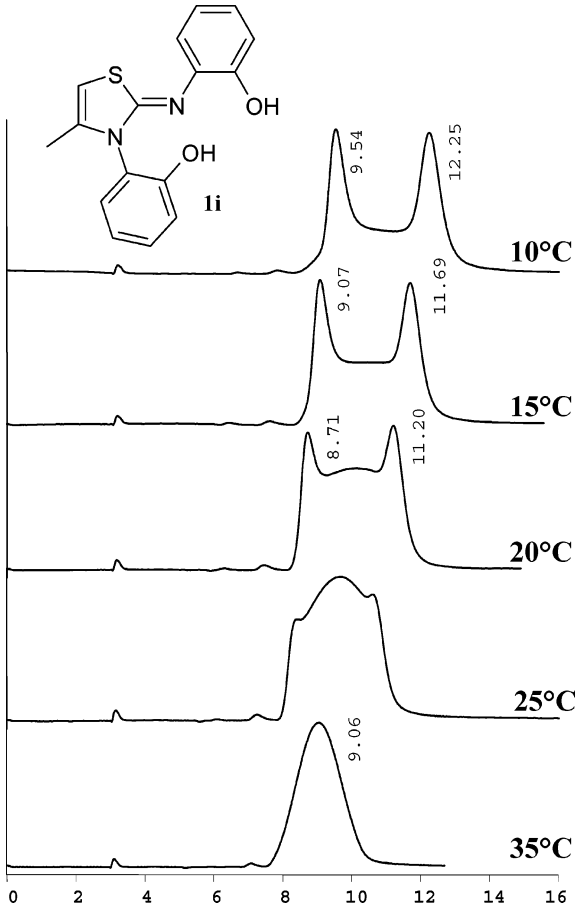

FIGURE 1. Evolution of the chromatographic profile of **1i** (OH, OH) atropisomers as a function of temperature: Chiralcel OD-H, hexane/2-PrOH (90:10), 1 mL/min, UV detection at 254 nm.

as illustrated in Figure 1 for compound **1i** (OH, OH). The CD traces (Figures 2 and 3) confirm that the plateau corresponds to the elution of a racemic mixture for compounds **1e** and **1h**, respectively.

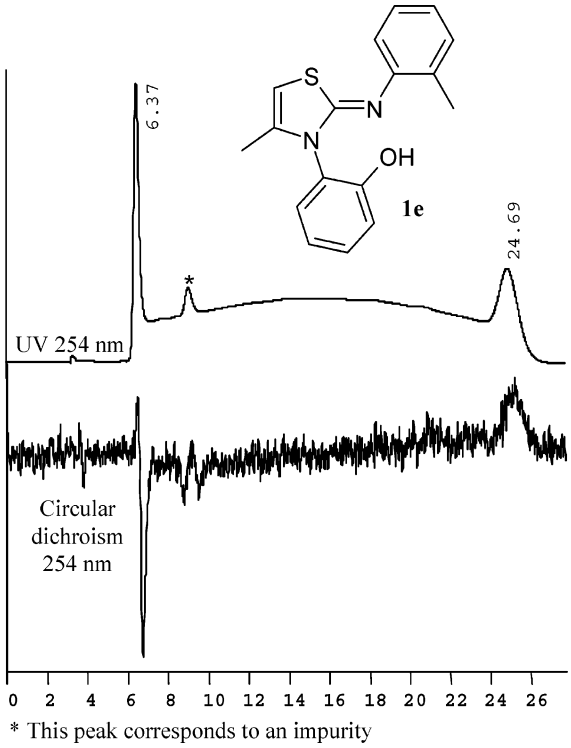

FIGURE 2. Plateau observed for **1e** (OH, Me) at 10 °C: Chiralcel OD-H, hexane/2-PrOH (95:5), 1 mL/min.

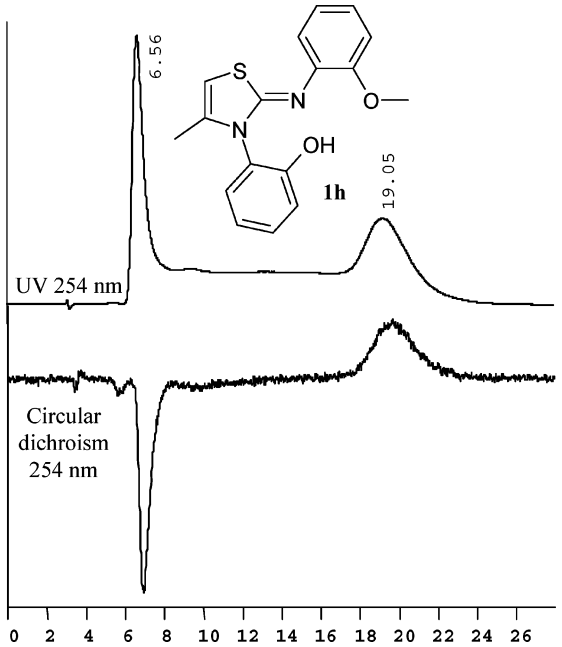

FIGURE 3. Plateau for **1h** (OH, MeO) at 10 °C: Chiralcel OJ, hexane/ethanol (1:1), 1 mL/min.

All the barriers to racemization were established using either classical off-line racemization kinetics[6a] or the equation developed by Trapp and Schurig in the case of a plateau.[19] The barriers to rotation (enantiomerization) are collected in Table 2. The enantiomerization rate corresponds to the racemization rate divided by a factor of 2. In Table 2, the barriers to rotation available from our previous studies are included for comparison.

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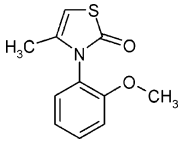
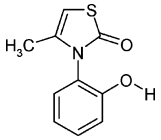
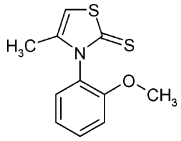
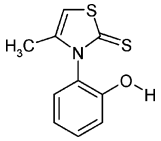
TABLE 2. Barriers to Rotation for Compounds 1a−1l

compound	X	Y	$\Delta G^{\ddagger}_{rot}$ (kJ/mol)	T (°C)	solvent	$t_{1/2}$
1a	Me	Me	122.3	78	EtOH	20 h, 28 min
1b	MeO	Me	109.7	58	EtOH	2 h, 49 min
1c	Me	MeO	121.8	78	EtOH	17 h, 30 min
1d	MeO	MeO	107.2	58	EtOH	1 h, 8 min
1f	Me	OH	112.4	78	EtOH	41 min
1g	MeO	OH	109.6	58	EtOH	2 h, 45 min
1h	OH	MeO	87.8	10	50:50 hexane/EtOH	15 min, 40 s
1i	OH	OH	86.5	10	90:10 hexane/2-PrOH	8 min, 47 s
1e	OH	Me	84.6	10	95:5 hexane/2-PrOH	2 min, 15 s
1j	$OCH_2CH_2CH_2O$		119.5	78	EtOH	7 h, 55 min
1k	$OCH_2CH_2CH_2I$	OH	111.5	58	EtOH	5 h, 18 min
1l	$OCH_2CH{=}CH_2$	OH	110.2	58	EtOH	3 h, 20 min
2a			110.5	58	EtOH	3 h, 47 min
2b			87.3	15	90:10 hexane/EtOH	6 min, 25 s
3a			135.8	118	2-pentanol	15 h, 51 min
3b			127.7	118	2-pentanol	1 h, 20 min

All the compounds studied bear a methyl group at position 4 and an imino group at position 2 of the heterocycle, and thus the substituent X in **1** is responsible for the differences observed in the barriers. The data may be sorted out in different families according to the nature of X. For compounds **1a** (Me, Me) and **1c** (Me, MeO) with a methyl group on the rotating phenyl (X = Me), the mean value of the barriers was 122.1 ± 0.3 kJ/mol at 78 °C in EtOH. This highlights the very low contribution of the remote Y on these rotation barriers when Y is not able to produce hydrogen bonding. **1f** (Me, OH) exhibited a barrier slightly lower than expected (the origin of that behavior has not been yet elucidated).

For compounds **1d**, **1b**, **1g**, **1k**, and **1l**, where X was either a methoxy, an allyloxyl, or a 3-iodopropyloxyl group, all the barriers were very comparable (109.6 ± 2 kJ/mol). In the case of **1j** ($OCH_2CH_2CH_2O$), in which the ether is part of a large cycle bridging X and Y, the barrier was higher (119.5 kJ/mol), offering the atropisomers a good stability at room temperature.

For the last class composed of three compounds **1e** (OH, Me), **1h** (OH, MeO), and **1i** (OH, OH), X was a hydroxy group. The barriers were much lower (86.3 ± 2 kJ/mol), and, as was said before, the barriers were derived from on-line plateau treatment.

Discussion

The barriers to atropisomerization depend on the interactions of the flanking substituents around the pivot bond in a near-planar transition state. For iminothiazolines **1**, two enantiomerization pathways are possible: either the X group interacts with the 4-methyl group or it interacts with the imino group.

It is well-established that, in the absence of particular conformational effect (in the case of the methoxy group) or

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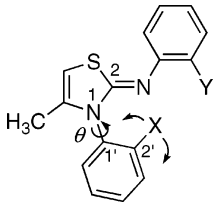
hydrogen bonding (in the case of the hydroxy group), MeO and OH exhibit the same steric requirement and are smaller than a CH_3. This is clearly recognized in various steric scales derived from conformational equilibrium[20] or rotational barrier studies. In the Sternhell'VdW scale derived from barrier to rotation in the biphenyl framework, the following order in size was obtained: Me(1.8) > OH(1.53) = MeO(1.52).[21] The same holds true for Taft's steric scale where Me(−1.24) > OH(−0.55) = MeO(−0.55).[22] In the iminothiazoline **1** model, substituents X rank in the following order: Me(122.1) > MeO(109.6) > OH-(85.3). The values in parentheses are the mean values of the experimental barriers. It is obvious that the contribution to the barrier is much lower for the OH group than for the methoxy group, contrary to what was expected on pure steric grounds. The barrier gap ($\Delta\Delta G^{\ddagger}$, ca. 24 kJ/mol) between MeO and OH demonstrates that an extra stabilization occurs in the quasi-planar transition state when X = OH. The OH group develops a stabilizing hydrogen bond with the imino group throughout the rotation process, the stabilizing effect being maximal in the near-planar transition state. The observed barrier gap due to the presence or the absence of hydrogen bonding is very similar to the one we have already observed when comparing the barriers in thiazolin-2-ones **2a** and **2b** ($\Delta\Delta G^{\ddagger}$ = 23.2 kJ/mol).[11]

TABLE 3. Results of the DFT Calculations (angles in degrees, barriers in kJ/mol)



compound	X	Y	θ min	θ TS	calcd barrier	exptl barrier
1a	CH_3	CH_3	78.4	9.7	114.3	122.3
1c	CH_3	OCH_3	78.8	8.3	112.8	121.8
average			78.6	9.0	113.5	122.0
1e	OH	CH_3	59.8	1.5	81.7	84.6
1h	OH	OCH_3	60.2	1.3	82.7	87.8
average			60.0	1.4	82.2	86.2

To evaluate the hydrogen bond hypothesis, calculations were performed on compounds **1a**, **1c**, **1e**, and **1h**. The calculations were carried out at the B3LYP/6-31G* level[23] using the facilities of the Gaussian 03 package.[24] The structures have been characterized as minima or transition state based on the number of imaginary frequencies (0 or 1). The results are gathered in Table 3 where the calculated barriers correspond to the rotation through the imino group. The torsion angles θ are defined by the 2−1−1′−2′ atoms; one corresponds to the energy minimum, θ min, and the other to the TS, θ TS.

The calculated values reproduce quite well the experimental values, both are linearly related (eq 1).

$$\text{exptl barrier} = -(7.8 \pm 3.9) + (1.14 \pm 0.04) \times \text{calcd barrier},\ n = 4,\ r^2 = 0.998 \quad (1)$$

The calculated barriers are related to the torsion angle of the minimum θ min defined as 2−1−1′−2′ by eq 2.

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$$\text{calcd barrier} = (119.3 \pm 0.8) - (148.6 \pm 4.4) \times \cos^2\theta \text{ min}, n = 4, r^2 = 0.998 \quad (2)$$

A hydrogen bond (HB) takes place between the OH (X = OH, **1e** and **1h**) and the nitrogen of the imino group both in the minimum and in the TS (pseudo-seven-membered ring). The HB "flattened" the dihedral angle in the ground state (from 78.6 to 60°).

These results are consistent with the quantum mechanical calculations of the rotational barriers in *N*-arylthiazolones bearing a methoxy or a hydroxy group in the ortho-position of the aryl group, recently reported by Zheng and Kleier.[25] These calculations suggested that lower barriers in atropisomers bearing a hydroxy group instead of a methoxy group on the rotating aryl "are due to intramolecular hydrogen bonding that differentially stabilizes the near planar transition states compared to the twisted minimum energy structures".

In thiazolinethiones **3a** and **3b**, the barrier gap between a MeO and an OH is 10 kJ/mol, illustrating the difference in the hydrogen bonding abilities of the thiocarbonyl on one hand and of the carbonyl and the imino group on the other hand.[26]

The bridging of the hydroxy groups in **1j** ($OCH_2CH_2CH_2O$) resulted in rather stable atropisomers, whose optically pure forms might find applications in the enantioselective complexation of cations. Figure 4 reports the cartoon of the X-ray structure determination of the cyclic ether **1j** ($OCH_2CH_2CH_2O$), showing the topographic arrangement of the oxygen and nitrogen atoms in the 12-membered ring.

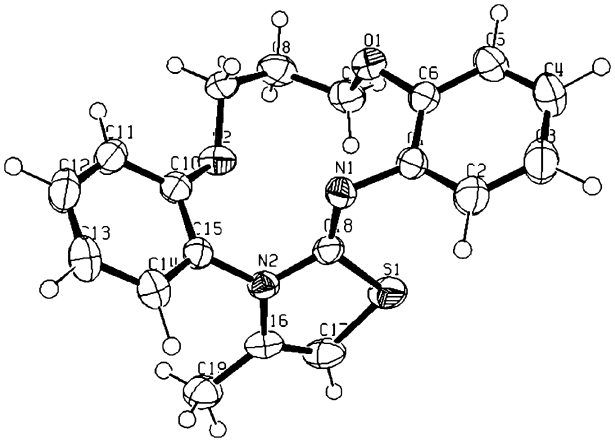

FIGURE 4. ORTEP drawing of bridged compound **1j**.

Conclusion

Atropisomeric iminothiazolines **1** in which X and (or) Y are hydroxy groups constitute an original class of chiral compounds. The enantiomers are easily separated by chromatography on chiral support on both analytical and semipreparative grounds. When X = OH, the barriers are quite low due to the development of a hydrogen bond between the proton of the OH group and the nitrogen of the imino group all along the rotation process. Plateau-shape chromatograms were obtained during HPLC on chiral support. Compound **1i** (OH, OH) was shown to be particularly easy to prepare by BBr_3 demethylation of the dimethoxy analogue, which is readily prepared from *N*,*N*′-bis-(2-methoxyphenyl)thiourea and 1-chloropropan-2-one. Bridging X = OH and Y = OH to form a macrocyclic ether including an imino group resulted in a large increase in the barrier to rotation. Compound **1i** (OH, OH) opens the way to a large diversity of stable atropisomeric chiral cyclic ethers. Further work in that direction is in progress.

Experimental Section

Synthesis. *N*-[(2*Z*)-4-Methyl-3-(2-methylphenyl)-1,3-thiazol-2(3*H*)-ylidene]-*N*-(2-methylphenyl)amine (**1a**) (Me, Me), *N*-[(2*Z*)-3-(2-methoxyphenyl)-4-methyl-1,3-thiazol-2(3*H*)-ylidene]-*N*-(2-methylphenyl)amine (**1b**) (MeO, Me), *N*-(2-methoxyphenyl)-*N*-[(2*Z*)-4-methyl-3-(2-methylphenyl)-1,3-thiazol-2(3*H*)-ylidene]amine (**1c**) (Me, MeO), *N*-(2-methoxyphenyl)-*N*-[(2*Z*)-3-(2-methoxyphenyl)-4-methyl-1,3-thiazol-2(3*H*)-ylidene]amine (**1d**) (MeO, MeO), 3-(2-methoxyphenyl)-4-methyl-1,3-thiazol-2(3*H*)-one (**2a**), 3-(2-hydroxyphenyl)-4-methyl-1,3-thiazol-2(3*H*)-one (**2b**), and 3-(2-methoxyphenyl)-4-methyl-1,3-thiazole-2(3*H*)-thione (**3a**), 3-(2-hydroxyphenyl)-4-methyl-1,3-thiazole-2(3*H*)-thione (**3b**) have already been described.[11,13] They were available for the present study.

Demethylation of Methoxy Groups in 1b, 1c, and 1d. *rac*-2-{[(2*Z*)-4-Methyl-3-(2-methylphenyl)-1,3-thiazol-2(3*H*)-ylidene]-amino}phenol (1f) (Me, OH). Compound **1c** (Me, MeO) (187 mg, 0.603 mmol, 1 equiv), $AlCl_3$ (804.3 mg, 6.03 mmol, 10 equiv), and NaCl (352 mg, 6.02 mmol, 10 equiv) were placed in CH_2Cl_2 (5 mL) and refluxed for 18 h. After cooling, the reaction mixture was treated with HCl solution (8.4 mL, 0.5 N), and the separated aqueous layer was extracted with CH_2Cl_2 (2 × 6 mL). The combined organic layers were washed (2 × 10 mL) with $NaHCO_3$ solution (2 × 10 mL, 1 N), dried on $MgSO_4$, and evaporated under vacuum to yield a mixture of **1f** and unreacted **1c** (141 mg). Chromatography gave 72 mg (40%) pure **1f**: R_f 0.86 (CH_2Cl_2/ethyl acetate 9:1), mp 86 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.4−6.8 (m, 8H), 6.54 (s, 1H, OH), 5.86 (q, 1H, J = 1.2 Hz), 2.17 (s, 3H), 1.84 (d, 3H, J = 1.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.5 (*C*═N), 150.2, 136.7, 136.6, 135.1, 134.5, 131.3, 129.3, 128.9, 127.3, 123.4, 119.2, 116.4, 112.9, 94.2 (*C*−H cycle), 17.3 (*C*H$_3$), 14.9 (*C*H$_3$ cycle). Anal. Calcd for $C_{17}H_{16}ON_2S$: C, 68.89; H, 5.44; N, 9.45; S, 10.82. Found: C, 68.84; H, 5.62; N, 9.40; S, 11.08.

***rac*-2-[(2*Z*)-4-Methyl-2-[(2-methylphenyl)imino]-1,3-thiazol-3(2*H*)-yl]phenol (1e) (OH, Me).** To **1b** (MeO, Me) (100 mg, 0.322 mmol) in 10 mL of CH_2Cl_2 was added BCl_3 (2.6 mL, 2.6 mmol, 8 equiv, hexane) at −78 °C under nitrogen. After being stirred at −78 °C for 30 min, the mixture was refluxed for 20 h. Water (20 mL) and NaCl (5 g) were then added, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with 1 M $NaHCO_3$ solution (30 mL), dried on $MgSO_4$, filtered, and evaporated to yield 53.4 mg (60%) pure **1e** (OH, Me) after chromatography (silica gel, CH_2Cl_2/ethyl acetate 9:1): R_f 0.25 (CH_2Cl_2/ethyl acetate 9:1), mp 164 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.4−6.95 (m, 8H), 5.81 (q, 1H, J = 1.2 Hz), 2.23 (s, 3H, Me),

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2.01 (d, 3H, Me cycle, $J = 1.2$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 162.5 (C═N), 153.0, 148.4, 135.3, 131.0, 130.7, 129.7, 127.4, 127.1, 127.0, 124.2, 121.0, 120.7, 120.5, 96.9 (*C*−H cycle), 18.1 (CH_3), 16.0 (*C*H_3 cycle). Anal. Calcd for $C_{17}H_{16}ON_2S$: C, 68.89; H, 5.44; N, 9.45; S, 10.82. Found: C, 68.91; H, 5.51; N, 9.79; S, 10.93.

Note: Compounds **1f** (Me, OH) and **1e** (OH, Me) were also obtained by demethylation with BCl_3 of the crude mixture of isomers **1c** (Me, MeO) and **1b** (MeO, Me) resulting from the reaction between 1-chloropropan-2-one and *N*-(2-methoxyphenyl)-*N*′-(2-methylphenyl)thiourea. Separation by chromatography on silica gel was easy since **1f** (Me, OH) and **1e** (OH, Me) presented a large difference in R_f (0.25 and 0.86 in CH_2Cl_2/ethyl acetate 9:1).

rac-2-{[(2*Z*)-3-(2-Methoxyphenyl)-4-methyl-1,3-thiazol-2(3*H*)-ylidene]amino}phenol (**1g**) (MeO, OH), *rac*-2-{[(2*Z*)-2-[(2-methoxyphenyl)imino]-4-methyl-1,3-thiazol-3(2*H*)-yl]phenol (**1h**) (OH, MeO), and *rac*-2-{[(2*Z*)-2-[(2-hydroxyphenyl)imino]-4-methyl-1,3-thiazol-3(2*H*)-yl]phenol (**1i**) (OH, OH) were obtained concomitantly from demethylation of *rac*-*N*-(2-methoxyphenyl)-*N*-[(2*Z*)-3-(2-methoxyphenyl)-4-methyl-1,3-thiazol-2(3*H*)-ylidene]amine **1d** (MeO, MeO).

Compound **1d** (MeO, MeO) (500 mg, 1.53 mmol) in 10 mL of CH_2Cl_2, $AlCl_3$ (810 mg, 6.12 mmol, 4 equiv), and NaCl (358 mg, 6.12 mmol, 4 equiv) were placed in CH_2Cl_2 (10 mL) and refluxed under stirring for 23 h. After cooling, the reaction mixture was treated with HCl solution (22 mL, 0.5 N), and the separated aqueous layer was extracted with CH_2Cl_2 (5 × 30 mL). After being dried on $MgSO_4$, the combined organic phase was evaporated under vacuum to yield a crude reaction mixture (489 mg). It was dissolved in CH_2Cl_2 (10 mL) and treated with $NaHCO_3$ solution (8 mL, 1 N). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The pooled organic phases were dried ($MgSO_4$), filtered, and evaporated to yield a residue (359 mg). Flash chromatography (silica gel, petroleum ether/ethyl acetate 7:3) yielded unreacted **1d** (MeO, MeO) (44 mg, 9%, R_f 0.29), **1h** (OH, MeO) (101 mg, 21%, R_f 0.39), and **1g** (MeO, OH) (190 mg, 40%, R_f 0.53). The acidic aqueous phase was neutralized with $NaHCO_3$ solution (24 mL, 1 N). Extraction with CH_2Cl_2 (3 × 30 mL) afforded an organic phase which, after being dried, filtered, and evaporated, yielded **1i** (OH, OH) (77 mg, 17%).

***rac*-2-{[(2*Z*)-3-(2-Methoxyphenyl)-4-methyl-1,3-thiazol-2(3*H*)-ylidene]amino}phenol (1g) (MeO, OH):** R_f 0.82 (CH_2Cl_2/MeOH 9.8:0.2), mp 146 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.5−6.8 (m, 8H), 5.80 (q, 1H, $J = 1.2$ Hz), 3.84 (s, 3H), 1.87 (d, 3H, Me cycle, $J = 1.2$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.0 (*C*═N), 155.5, 149.9, 135.8, 135.3, 130.6, 130.3, 125.9, 123.5, 121.3, 119.3, 117.3, 113.0, 112.5, 937 (*C*−H cycle), 55.9 (*C*H_3−O), 14.7 (*C*H_3 cycle). Anal. Calcd for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.16; N, 8.97; S, 10.26. Found: C, 65.54; H, 5.21; N, 9.11; S, 10.47.

***rac*-2-[(2*Z*)-2-[(2-Methoxyphenyl)imino]-4-methyl-1,3-thiazol-3(2*H*)-yl]phenol (1h) (OH, MeO):** R_f 0.43(CH_2Cl_2/MeOH 9.8:0.2), mp 160 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.4−6.8 (m, 8H), 5.76 (q, 1H, $J = 1.4$ Hz), 3.87 (s, 3H, Me), 1.98 (d, 3H, Me cycle, $J = 1.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 162.6 (*C*═N), 152.9, 151.5, 139.1, 135.3, 129.7, 127.5, 126.7, 124.7, 121.7, 121.4, 121.1, 120.6, 111.3, 96.1 (*C*−H cycle), 55.6 (*C*H_3−O), 15.9 (*C*H_3 cycle). Anal. Calcd for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.16; N, 8.97; S, 10.26. Found: C, 65.45; H, 5.17; N, 9.17; S, 10.26.

***rac*-2-[(2*Z*)-2-[(2-Hydroxyphenyl)imino]-4-methyl-1,3-thiazol-3(2*H*)-yl]phenol (1i) (OH, OH):** R_f 0.28 (CH_2Cl_2/MeOH 9.8:0.2), mp 140 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.4−6.8 (m, 8H), 5.90 (q, 1H, $J = 1.4$ Hz), 1.97 (d, 3H, $J = 1.4$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.7 (*C*═N), 152.3, 149.7, 135.2, 135.1, 130.4, 128.4, 125.3, 124.5, 121.3, 119.8, 119.2, 117.9, 113.9, 96.0 (*C*−H cycle), 15.4 (*C*H_3 cycle). Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39; S, 10.75. Found: C, 64.12; H, 4.67; N, 9.57; S, 10.78.

Note: *rac*-2-{[(2*Z*)-3-(2-methoxyphenyl)-4-methyl-1,3-thiazol-2(3*H*)-ylidene]amino}phenol (1g) (MeO, OH) was obtained selectively from **1d** (MeO, MeO) using $AlCl_3$ in C_2H_5SH.[27] In an ice-cooled reactor (50 mL), $AlCl_3$ (318 mg, 2.4 mmol, 4 equiv) was suspended in C_2H_5SH (18 mL). Compound **1d** (MeO, MeO) (195 mg, 0.6 mmol) dissolved in CH_2Cl_2 (5 mL) was introduced with a syringe. The mixture was stirred for 45 min at room temperature. The reaction was monitored by TLC until the complete consumption of the starting material. The mixture was then washed with HCl solution (3 × 18 mL, 0.24 N), and the resulting aqueous phase was rinsed with CH_2Cl_2 (3 × 15 mL). The aqueous phase was neutralized with a $NaHCO_3$ solution (130 mL, 0.1 N) and then extracted with CH_2Cl_2 (3 × 100 mL). The pooled organic phase after being dried on $MgSO_4$, filtrated, and evaporated afforded pure **1g** (MeO, OH) (124 mg, 66%).

Note: *rac*-2-{[(2*Z*)-3-(2-methoxyphenyl)-4-methyl-1,3-thiazol-2(3*H*)-ylidene]amino}phenol (1g) (MeO, OH) was also obtained selectively from **1d** (MeO, MeO) using BCl_3. Compound **1d** (MeO, MeO) (100 mg, 0.307 mmol) in CH_2Cl_2 (10 mL) and BCl_3 (2.5 mL, 2.5 mmol, 8 equiv from a 1 M solution in CH_2Cl_2) were mixed at −78 °C under nitrogen for 1 h. The mixture was then refluxed for 22 h. After cooling, water (20 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The organic phase was washed with $NaHCO_3$ (1 N) solution (2 × 30 mL), dried on $MgSO_4$, filtered, and evaporated under vacuum to yield pure **1g** (MeO, OH) (88 mg, 92%).

Note: *rac*-2-[(2*Z*)-2-[(2-hydroxyphenyl)imino]-4-methyl-1,3-thiazol-3(2*H*)-yl]phenol (1i) (OH,OH) was also selectively obtained from **1d** (MeO, MeO) by demethylation using BBr_3.

Compound **1d** (MeO, MeO) (326 mg, 1 mmol) in CH_2Cl_2 (20 mL) and BBr_3 solution (7.56 mL of a 1 M solution in CH_2Cl_2) were mixed at −78 °C under nitrogen. The mixture was then refluxed for 21 h. The reactor was ice-cooled, and BBr_3 in excess was hydrolyzed with water (50 mL). The aqueous phase was neutralized with $NaHCO_3$ solution (50 mL, 1 N) and extracted with CH_2Cl_2 (3 × 40 mL). The organic phase was dried with $MgSO_4$, filtered, and evaporated under vacuum to yield **1i** (OH, OH) (231 mg, 81%).

Compounds from Alkylation of 1i (OH, OH). Alkylation with Methyl Iodide: To a solution of **1i** (OH, OH) (39.4 mg, 0.13 mmol) in acetone (0.5 mL) and K_2CO_3 (26.91 mg, 0.195 mmol, 1.5 equiv) was added methyl iodide with a syringe (12.14 μL, 0.195 mmol, 1.5 equiv). The mixture was refluxed for 3 h until **1i** (OH, OH) was totally consumed (TLC, petroleum ether/ethyl acetate 75:25, R_f 0.31). The solid was filtered, and the acetone phase was evaporated under vacuum to yield 24 mg of a mixture of **1d** (MeO, MeO) (23%) and **1g** (MeO, OH) (77%). Compound **1h** (OH, MeO) was not observed.

Alkylation with 1,3-Diiodopropane: To a solution of **1i** (OH, OH) (2 g, 6.7 mmol) in acetone (130 mL) containing K_2CO_3 (1.39 g, 10 mmol, 1.5 equiv) was added 1,3-diiodopropane (0.93 mL, 8.05 mmol, 1.2 equiv) dropwise with a syringe. The mixture was refluxed until all the starting **1i** (OH, OH) had been transformed. After elimination of the solid, the organic phase was evaporated under vacuum to yield 4.2 g of a complex mixture. The mixture was purified by chromatography (silica gel, petroleum ether/ethyl acetate 75:25), and the fraction with R_f 0.57 was collected (1.29 g). That fraction was composed of a mixture of **1k** (OCH_2CH_2-CH_2I, OH) and **1l** (OCH_2CH═CH_2, OH). **1k** ($OCH_2CH_2CH_2I$, OH) and **1l** (OCH_2CH═CH_2, OH) coeluted on silica, whatever the eluent. In order to obtain these compounds as pure samples for characterization, chiral separation, and racemization study, 50 mg was separated by semipreparative chromatography on chiral support (Chiralcel OD (25 × 1 cm) column, eluent hexane/2-PrOH 90:10, flow 4.5 mL/min, detection UV 254 nm, rt, 50 mg in 15 mL of 2-PrOH, injection 500 μL every 5 min). A first fraction (7.8−8.8 min) was collected, affording 6 mg of the mixture of the two enantiomers of **1l** (OCH_2CH═CH_2, OH). The second fraction (9.5−

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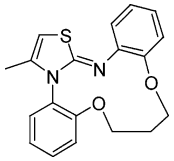
12 min) afforded **1k** ($OCH_2CH_2CH_2I$, OH) (44 mg) as a mixture of enantiomers.

Six hundred milligrams of the mixture **1k** ($OCH_2CH_2CH_2I$, OH) and **1l** ($OCH_2CH{=}CH_2$, OH) in CH_3CN (600 mL) and K_2CO_3 (276 mg, 2 mmol) was stirred at room temperature for 8 days and then refluxed for 24 h. Filtration of the solid and evaporation under vacuum of the organic phase afforded 450 mg of a mixture composed of pure **1j** ($OCH_2CH_2CH_2O$) (120 mg) and a mixture of **1k** ($OCH_2CH_2CH_2I$, OH) and **1l** ($OCH_2CH{=}CH_2$, OH) (330 mg) after chromatography (silica gel, petroleum ether/ethyl acetate 90:10).

***rac*-2-{[(2*Z*)-3-[2-(Allyloxy)phenyl]-4-methyl-1,3-thiazol-2(3*H*)-ylidene]amino}phenol (1l) ($OCH_2CH{=}CH_2$, OH):** R_f 0.57 (petroleum ether/ethyl acetate 75:25), mp 96−97 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−6.80 (m, 8H), 6.0−5.83 (m, 1H), 5.80 (q, 1H, J = 0.9 Hz), 5.31−5.17 (m, 2H), 4.57 (d, 2H), 1.88 (d, 3H, J = 0.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9 (*C*=N), 154.4, 149.9, 135.7, 135.2, 132.4, 130.4, 126.4, 123.4, 121.5, 119.3, 117.3, 117.2, 114.1, 112.9, 93.6 (*C*−H cycle), 69.2 (O−*CH*$_2$−CH=CH_2), 14.7 (*C*H_3 cycle). Anal. Calcd for $C_{19}H_{18}N_2O_2S$: C, 67.43; H, 5.36; N, 8.28; S, 9.48. Found: C, 67.21; H, 5.41; N, 8.22; S, 9.46.

***rac*-2-{[(2*Z*)-3-[2-(3-Iodopropoxy)phenyl]-4-methyl-1,3-thiazol-2(3*H*)-ylidene]amino}phenol (1k) ($OCH_2CH_2CH_2I$, OH):** R_f 0.57 (petroleum ether/ethyl acetate 75:25), mp 70−72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.5−6.8 (m, 8H), 5.81 (q, 1H, J = 1.2 Hz), 4.13−4.01 (m, 2H, O−C*H*$_2$−CH_2−CH_2−I), 3.19−3.15 (dd, 2H, O−CH_2−CH_2−C*H*$_2$−I, J = 5.7, 7.2 Hz), 2.23−2.01 (m, 2H, O−CH_2−C*H*$_2$−CH_2−I), 1.88 (d, 3H, J = 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9 (*C*=N), 154.4, 149.8, 135.6, 135.3, 130.5, 130.3, 126.5, 123.5, 121.7, 119.3, 117.2, 113.7, 112.9, 93.6 (*C*−H cycle), 67.9 (O-*C*H_2−CH_2−CH_2−I), 32.3 (O−CH_2-*CH*$_2$-CH_2−I), 15.0 (*C*H_3 cycle), 2.4 (O−CH_2−CH_2-*C*H_2−I). Anal. Calcd for $C_{19}H_{19}IN_2O_2S$: C, 48.94; H, 4.11; N, 6.01; S, 6.88. Found: C, 48.99; H, 4.15; N, 6.02; S, 6.94.



***rac*-1j ($OCH_2CH_2CH_2O$) Bridged Compound:** R_f 0.44 (petroleum ether/ethyl acetate 9:1), mp 174−176 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−6.9 (m, 8H), 5.60 (q, 1H, J = 1.2 Hz), 4.5−3.85 (m, 4H, O−C*H*$_2$−CH_2−C*H*$_2$−O), 2.3−2.0 (2H, O−CH_2−C*H*$_2$−CH_2−O), 1.89 (d, 3H, CH_3 cycle, J = 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1 (*C*=N), 156.0, 151.5, 145.7, 135.3, 130.1, 129.3, 126.3, 124.7, 124.0, 123.1, 122.5, 121.3, 115.6, 92.9 (*C*−H cycle), 69.6 (O−*C*H_2), 65.5 (O−*C*H_2), 29.4 (CH_2−*C*H_2−CH_2), 15.5 (*C*H_3 cycle). Anal. Calcd for $C_{19}H_{18}N_2O_2S$: C, 67.43; H, 5.36; N, 8.28; S, 9.48. Found: C, 67.26; H, 5.42; N, 8.34; S, 9.37.

Liquid Chromatography on Chiral Supports. The analytical chiral HPLC experiments were performed on a unit composed of a Merck D-7000 system manager, Merck-Lachrom L-7100 pump, Merck-Lachrom L-7360 oven, Merck-Lachrom L-7400 UV-detector, and on-line Jasco OR-1590 polarimeter or Jasco CD-1595 circular dichroism spectrometer. Hexane, isopropanol, and ethanol, HPLC grade, were degassed and filtered on a 0.45 μm membrane before use.

Retention times, Rt, in minutes, and retention factors $k_i = (Rt_i - Rt_0)/Rt_0$ are given. Rt_0 was determined by injection of tri-tertiobutyl benzene. The sign given by the on-line polarimeter or on-line CD detectors is the sign of the product in the solvent used for the chromatographic separation.

The columns (analytical 250 × 4.6 mm and semipreparative 250 × 10 mm) were Chiralpak AD, Chiralcel OJ and Chiralcel OD−H from Chiral Technologies Europe (Illkirch, France).

The analyses were performed at 25 °C, with 1 mL/min as flow rate, detection by UV at 254 nm and by the appropriate chirality detector.

Semipreparative separations were performed on a unit composed of a Merck D-7000 system manager, Merck-Hitachi L-6000 pump, Rheodyne valve with a 500 μL loop and a Merck-Hitachi L-4000 UV-detector.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra, chromatographic data on chiral supports, optical rotation of enantiomers, kinetic data for racemization for compounds **1e**−**1l**, X-ray crystallographic file (CIF) for compound **1j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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