

## Atropisomerism in the 2-arylimino-*N*-(2-aryl)-thiazoline series

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Dedicated to Professor Arlette Solladié-Cavallo on her 70<sup>th</sup> birthday

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### Abstract

An original atropisomeric tetradecyl-macrocyclic ether **3** is described, it was obtained by the sequence i) reaction of 1,3-bis-(2-methoxy-phenyl)-thiourea on a halogenoketone, demethylation of the resulting 2-arylimino-*N*-(2-aryl)-thiazoline bis-ether and macrocyclization with a ditosylate derivative. The resolution of the enantiomers on chiral support and stereodynamics of the macrocyclic ether and its precursors are reported.

**Keywords:** Atropisomerism, barrier to rotation, Dynamic chiral HPLC, N-aryl atropisomers

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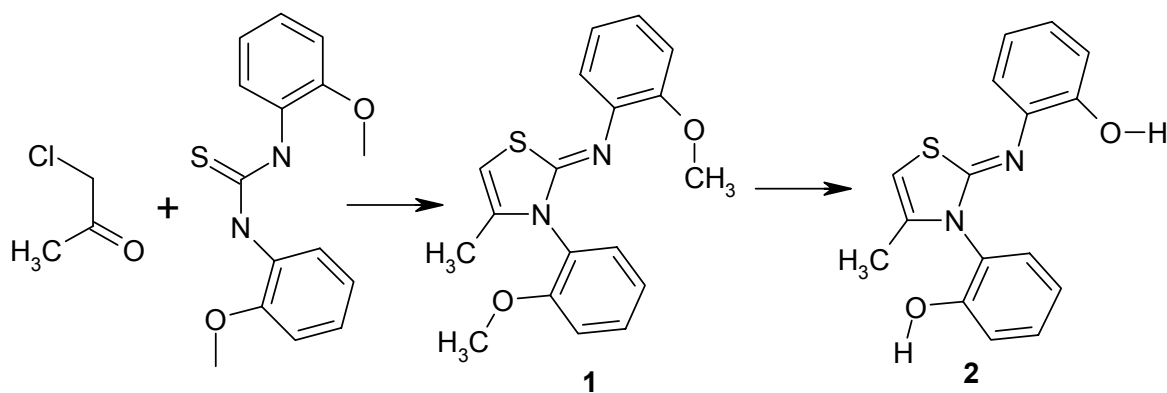
### Introduction

Atropisomerism is a fascinating domain of stereochemistry.<sup>1</sup> The fact that two enantiomers can be exchanged without bond breaking according to a unimolecular process had attracted a lot of interest.<sup>2,3</sup> Stable atropisomers have found outstanding applications as ligand for asymmetric catalysis<sup>4</sup> or as chiral scaffold in asymmetric synthesis.<sup>5</sup> Atropisomeric drugs such as Methaqualone and analogues have been developed<sup>6</sup> and the effect of axial chirality in bioactive compounds has been recently reviewed.<sup>7</sup> Optically pure atropisomeric crown ethers were in the beginning involved in the enantioselective extraction of protonated primary amines<sup>8</sup> and later as a chiral selector for liquid chromatography marketed as Crownpak CR(+).

The determination of the “steric” barrier is the cornerstone of all studies dealing with atropisomerism since the life-time of the enantiomers at room temperature is directly related to the barrier to rotation. The stability is conveniently expressed by the half-life of the species. The barriers to rotation ranging from 25 to 65 kJ/mole are estimated by Dynamic NMR,<sup>9</sup> the barriers

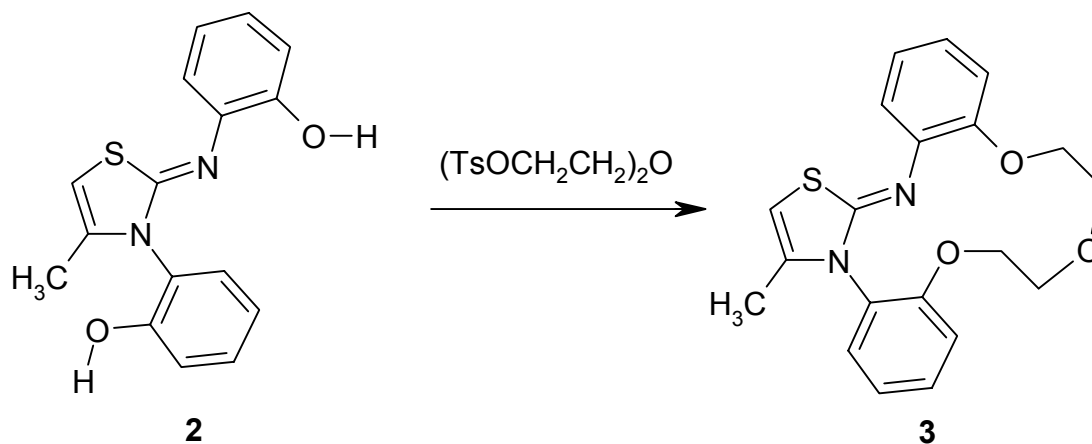
ranging from 65 to 100 kJ/mole could be attained by Dynamic HPLC or cryochromatography on chiral support, barriers larger than 100 kJ/mole can be determined by off-line racemization study of an optically enriched or optically pure enantiomer. The tremendous development of liquid chromatography on chiral support has been largely beneficial for studies dealing with atropisomerism.<sup>10</sup>

We have been involved in the last twenty years in the atropisomerism of N-aryl-heterocycles in which the rotating bond is the C-N bond linking a substituted aryl group to a heterocyclic framework.<sup>11</sup> Recently our interest focused on N-aryl-heterocycles in which functional groups are situated both on the aryl group and on the heterocycle.<sup>12</sup> Among these functional atropisomers, *rac*-2-[(2*Z*)-2-[(2-hydroxyphenyl)imino]-4-methyl-1,3-thiazol-3(2*H*)-yl]phenol **2** offered a very interesting and original scaffold which brings in a suitable spatial arrangement three binding groups composed of two oxygens and one imino-nitrogen. This scaffold is particularly attractive since it is prepared in high yield according to a two step synthesis from easily accessible starting material (Scheme 1). Among the various possible applications of bis-phenol **2**, it was interesting to explore the possibility to obtain macrocyclic ethers.



**Scheme 1**

We report here the synthesis and stereodynamic of a tetradecyl-macrocyclic ether **3** obtained by reaction of **2** with a commercially available bis-tosylate (Scheme 2).

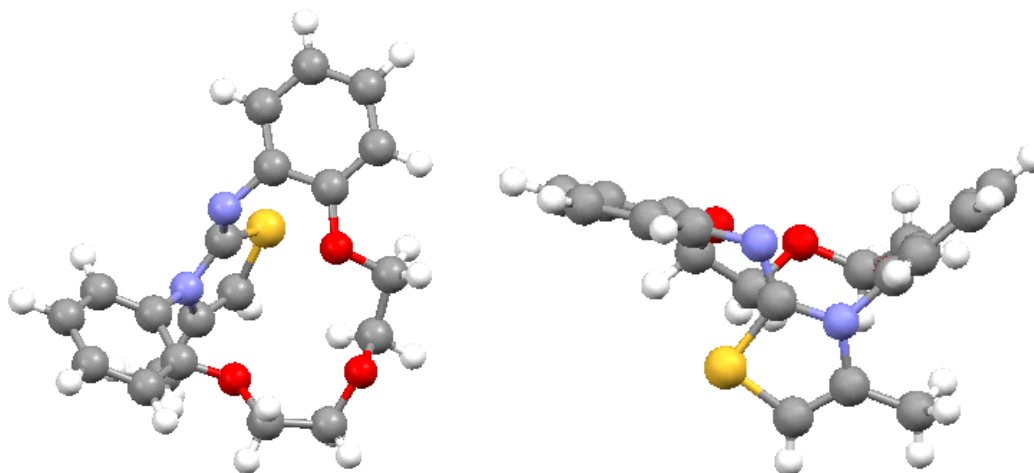


Scheme 2

## Results and Discussion

The reaction of the bis-tosylate with bis-phenol **2** proceeded smoothly yielding the expected macrocycle **3** together with traces of a bis-adduct **4**. Unreacted **2** and unreacted bis-tosylate were recovered. Pure **3** was easily obtained by flash chromatography on silica gel.

Inspection of nmr data brought some useful information on the stereochemistry of the macrocycle **3**. One interesting sensor for the dihedral angle between the 3-N-Aryl and the heterocycle is the chemical shift of the methyl group in position 4 of the heterocycle. That methyl group being situated in the shielding cone of the N-aryl group, the maximum shielding is attained when the plane of the heterocycle and the plane of the aryl group are nearly perpendicular. The observed chemical shift of the 4-methyl group is  $\delta = 1.78$  ppm in the bis-ether **1**,  $\delta = 1.97$  ppm in the bis-phenol **2** and  $\delta = 1.77$  ppm in the macrocycle **3**. Another interesting sensor is the chemical shift of the proton situated in position 5 of the heterocycle:  $\delta = 5.59$  ppm in the bis-ether **1**,  $\delta = 5.90$  ppm in the bis-phenol **2** and  $\delta = 5.60$  ppm in the macrocycle **3**. These chemical shifts militate in favor of a very similar dihedral angle in the open bis-ether **1** and in the macrocycle **3** whereas in the case of the dihydroxy analogue the occurrence of a hydrogen bond between the OH and the nitrogen of the imino group reduces the dihedral angle. The intramolecular hydrogen bond in the bis-phenol **2** is responsible for i) a lower barrier to racemization in **2** than in **1** and **3** (see below) ii) a deshielding of the heterocycle resulting in a deshielding of the 5-hydrogen atom. Aromatic induced shifts and hydrogen bonding both act in the same direction to produce a significant deshielding effect on both the 4-methyl group and 5-hydrogen in the bis-phenol **2**.



**Figure 1.** X-Ray structure of the macrocyclic polyether **3**. The two stereo views show the relative arrangement of the nitrogen and oxygen groups.

The X-ray structure of the racemic macrocycle revealed some interesting features (Figure 1). The heterocycle and the N-aryl group are situated in two planes with a dihedral angle of  $86.18^\circ$ . Interestingly, the N-imino-aryl plane and the imine plane form a dihedral angle of  $74^\circ$ , and the  $\text{CH}_2\text{CH}_2$  frameworks in the diethylene glycol chain are perfectly staggered. All these structural features reveal a particularly unstrained structure in the macrocycle. This is in agreement with the similarity in the chemical shift observed for the 4-Methyl group in the bis-ether **1** and in the macrocycle **3**. The N-aryl heterocycle accommodates the macrocyclization mainly through the rotation about the  $\text{N}_{(\text{imino})}$ -aryl bond without internal strain. X-ray provided also the relative orientation of the potentially binding sites. The imino group and two of the oxygen atoms are well situated for binding, the distance between the two oxygens is  $2.83 \text{ \AA}$ , the distances between the imino-nitrogen and the oxygen are  $2.70$  and  $4.80 \text{ \AA}$  respectively. The third oxygen points in the opposite direction and would not be involved in a cooperative binding in the conformation observed in the solid state.

Various chiral stationary phases were assayed under classical eluting conditions to resolve the enantiomers of the macrocyclic derivative in order to provide suitable conditions for semi-preparative separation. Derivatized cellulose (Chiralcel OD-H, OJ, OG and OC) and derivatized amylose (Chiralpak AS and AD) were screened as well as some non polysaccharide CSPs ((*S,S*)-Ulmo, Kromasil TBB, Sumichiral OA-2500, (*S,S*)-Whelk-O1) : the data are reported in Table 1. A very poor separation was observed on Chiralpak AD whereas an excellent baseline separation was achieved on Chiralcel OD-H. Noteworthy, an interesting separation was also observed on Chiralcel OC (Cellulose tris(phenylcarbamate) coated on silica), unfortunately the retentions were too large for preparative purpose. There was no evidence for a plateau-shape chromatogram (Figure 2). Chiralcel OD column ( $250 * 10 \text{ mm}$ ,  $10 \text{ }\mu\text{m}$ ) was selected for semi-preparative separation. The mobile phase was composed of a mixture 80:20 Hexane / 2-PrOH. 2 mg in  $500\mu\text{l}$

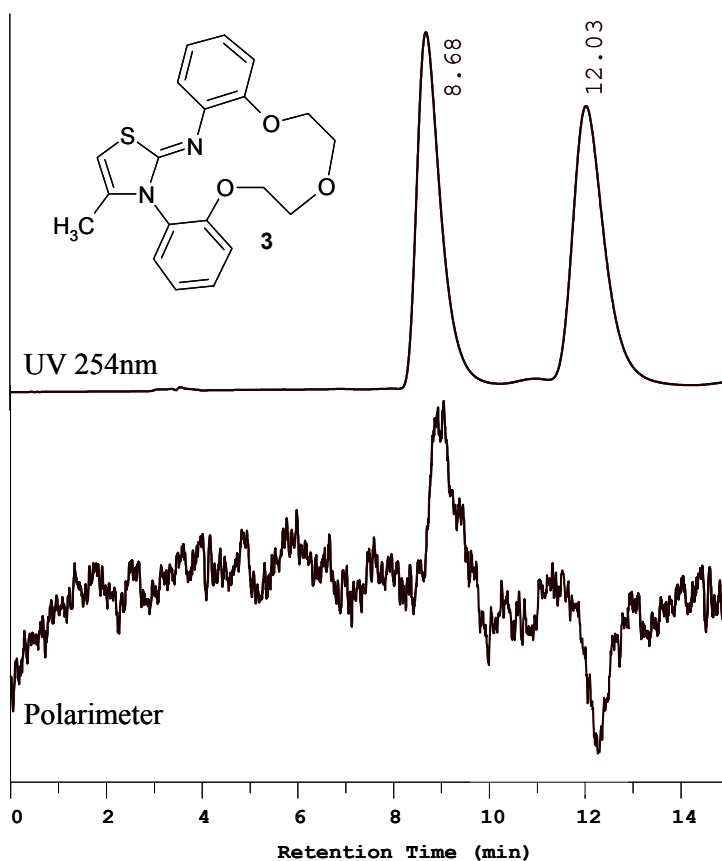
of the mobile phase were injected every 15 min at a flow rate of 4.5 ml/min. Baseline separation was observed, the first peak eluted at 10.45 min. and the second one at 15.35 min. The first eluting enantiomer on Chiralcel OD column was found to be the (+) enantiomer according to on line polarimetric detection in the mobile phase and off-line determination in CHCl<sub>3</sub>. [ $\alpha_D^{25} = 35.8$  (CHCl<sub>3</sub>, c= 0.48) for the first eluted enantiomer and  $\alpha_D^{25} = -35.7$  (CHCl<sub>3</sub>, c=0.625) for the second eluted].

**Table 1.** Chiral stationary phases screening results for macrocycle **3**, at 25°C with 1ml/min as flow-rate

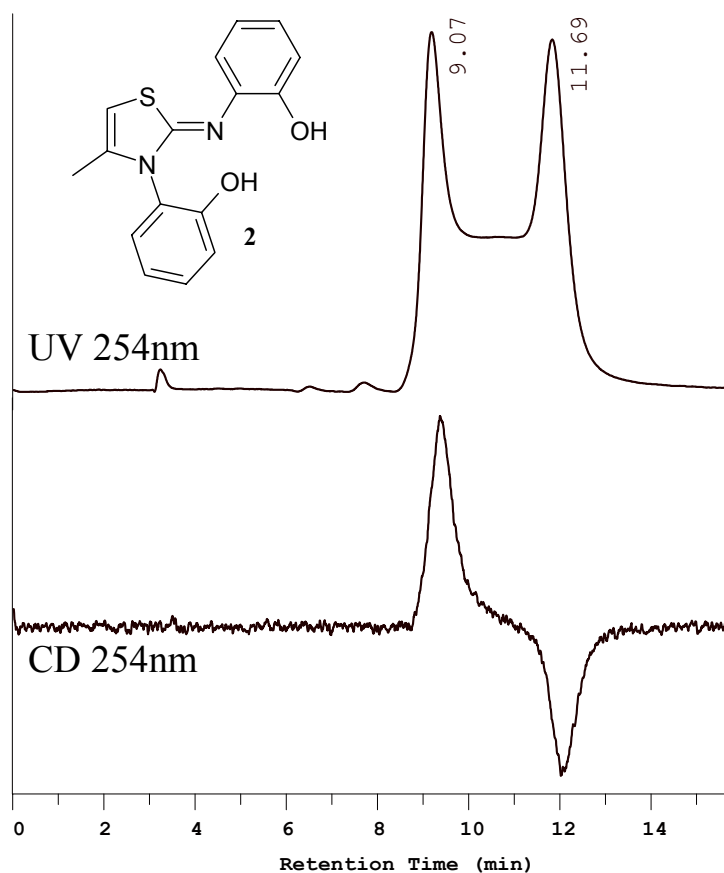
	Mobile phase	t <sub>1</sub> (min)	k <sub>1</sub>	t <sub>2</sub> (min)	k <sub>2</sub>	$\alpha$	Rs
Chiralpak AS	Hexane/2-PrOH 90/10	8.83	1.90	9.58	2.14	1.13	0.68
Chiralcel OD-H	Hexane/2-PrOH 80/20	8.68 (+)	1.85	12.03 (-)	2.94	1.59	3.22
Chiralcel OJ	Hexane/2-PrOH 60/40	9.07	2.20	14.60	4.16	1.31	1.31
Chiralcel OC	Hexane/2-PrOH 80/20	36.47	11.12	52.45	16.43	1.48	1.85
Chiralcel OG	Hexane/2-PrOH 60/40	9.98 (+)	2.27	11.91 (-)	2.91	1.28	0.73
Ulmo (S,S)	Ethanol	3.93	0.31			1	0
Chiralcel OB-H	Hexane/2-PrOH 80/20	17.53	4.83	41.43	12.77	2.65	1.77
Kromasil TBB	Hexane/2-PrOH 90/10	4.55	0.49			1	0
Chiralpak AD	Hexane/2-PrOH 70/30	19.13 (-)	5.36	19.83 (+)	5.59	1.04	
Sumichiral OA-2500	Hexane/Ethanol 50/50	5.04	0.68			1	0
Whelk-O1 (S,S)	Hexane/2-PrOH 70/30	5.22	0.73			1	0

Having in hand pure enantiomer of the macrocycle **3**, the barrier to rotation was determined in ethanol at 78°C (refluxing ethanol). The racemization was monitored by recording the changes in ratio of the enantiomers using chromatography on Chiralcel OD-H as a function of time. The rate constant for racemization was  $1.26 \cdot 10^{-5} \text{ s}^{-1}$ , the enantiomerization rate was  $0.63 \cdot 10^{-5} \text{ s}^{-1}$  corresponding to  $\Delta G_{\text{rot}}^{\ddagger} = 121.44 \text{ kJ}\cdot\text{mol}^{-1}$ ,  $t_{1/2} = 15.22 \text{ h}$  at 78°C. It pointed out that the enantiomers of **3** are stable several days at room temperature. The barrier to rotation in the open bis-ether **1** derivative was  $107.2 \text{ kJ}\cdot\text{mol}^{-1}$  in ethanol at 58°C corresponding to a  $t_{1/2} = 68 \text{ min}$ . The  $14 \text{ kJ}\cdot\text{mol}^{-1}$  gap which separated the barriers in the macrocycle **3** and in the open bis-ether **1** might come from a contribution of the eclipsing strain of the diethylene chains during rotation in addition to the strain associated with the rotation around the aryl-imino bond. The barrier in the bis-phenol precursor **2** ( $t_{1/2} = 520 \text{ s}$  at 10°C) is too low to allow a synthesis of the enantiomer of macrocycle **3** from optically pure atropisomer of **2**. On the other hand, the combination of a low barrier in the bis-phenol **2** and a high barrier in the resulting macrocycle **3** might open the way to the design of dynamic kinetic resolution technique in the presence of a chiral inductor. The chromatogram of the bis-phenol **2** on Chiralcel OD column at 15°C is reported in Figure 3. One observes a typical plateau shape arising from a fast racemization on the column.<sup>13</sup> CD detection

indicates that the first eluted enantiomer had a positive CD sign at 254 nm whereas the plateau is composed of a racemate. From this plateau shape chromatogram the enantiomerization barrier can be calculated<sup>14</sup>:  $\Delta G^{\ddagger}_{\text{rot}} = 87.0 \text{ kJ}\cdot\text{mol}^{-1}$  in 90:10 Hexane / 2-PrOH at 15°C.



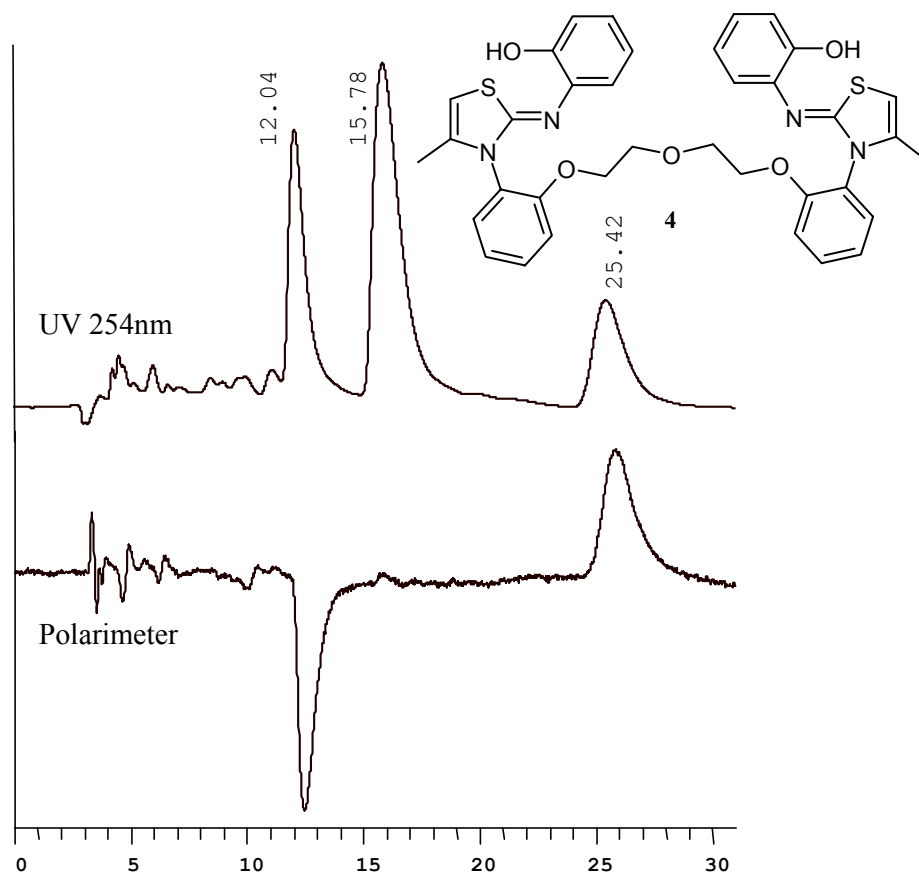
**Figure 2.** Chromatogram of macrocycle 3 on Chiralcel OD-H column at 25°C (Eluent 80:20 Hexane / 2-PrOH).



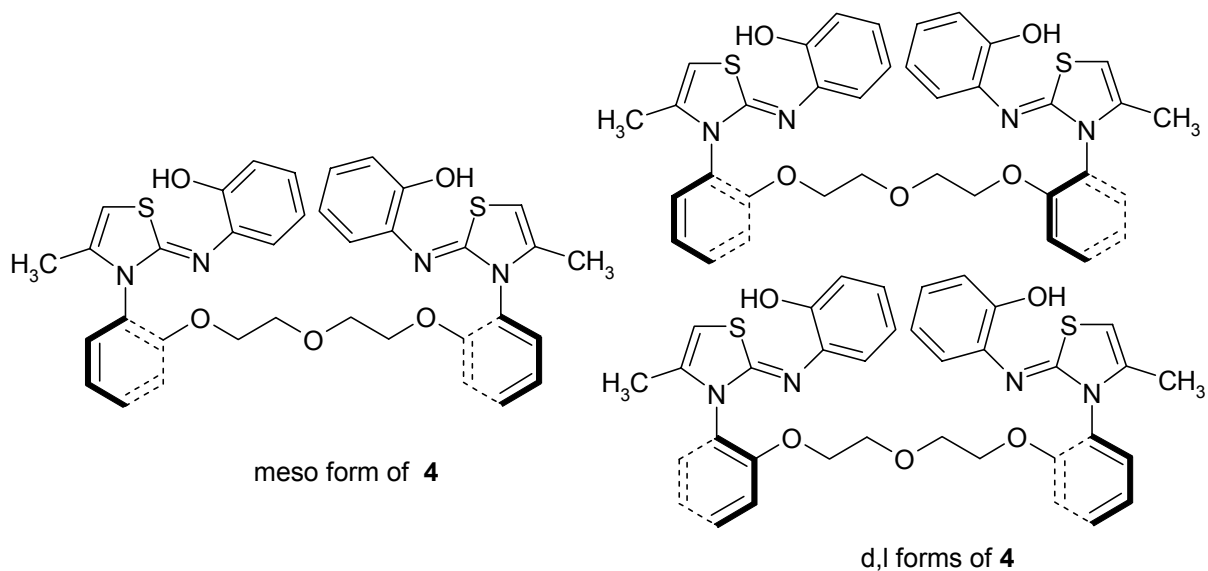
**Figure 3.** Chromatogram of bis-phenol **2** on Chiralcel OD-H column at 15°C (Eluent 90:10 Hexane / 2-PrOH).

Chiral chromatography is the best method to obtain the enantiomers of the macrocycle **3**. As said before, a by-product **4** was obtained in low yield during the reaction of the bis-tosylate with the bis-phenol **2**. NMR showed that the compound resulted from the condensation of two bis-phenols with one tosylate. The chromatogram at 25°C on Chiralpak AD (Amylose tris(3,5-dimethylphenylcarbamate) coated on silica) is reported in Figure 4.

UV detection showed three peaks eluting at 12.04, 15.78 and 25.42 min respectively. Polarimetric detection revealed that the first and the last peak corresponded to enantiomers and that the second peak was achiral. This behavior is consistent with the occurrence of a *d,l* and a *meso* form for the bis-adduct **4**. (Scheme 3) The absence of plateau and the known preferred reactivity of the hydroxyl group of the N-(heterocyclic)-aryl firmly established the structure of the compounds. A few milligrams of each isomer were collected by semi-preparative chiral HPLC to confirm this assignment by the determination of the barrier to rotation in ethanol at 58°C  $\Delta G_{\text{rot}}^{\ddagger} = 109.3 \text{ kJ}\cdot\text{mol}^{-1}$ , which is in close agreement with the barrier of the bis-ether **1** ( $107.2 \text{ kJ}\cdot\text{mol}^{-1}$ ). The yield in the bis-adduct could be improved by changing the operating set-up.



**Figure 4.** Chromatogram of bis-adduct **4**, *meso* and *d,l* forms, on Chiralpak AD column (Eluent 50:50 Hexane / ethanol).



**Scheme 3.** *meso* and *d,l* forms of the bis-adduct **4**.



## Conclusions

The macrocyclic ether **3** was prepared in an efficient way from easily accessible starting materials. The resolution of **3** by HPLC on chiral support was achieved using classical mobile phase, the separation could be easily scaled-up to obtain pure enantiomer in larger quantities. The determination of the enantiomerization barrier showed that the resolved enantiomers are stable at room temperature for several days. All these observations open the way to the design of a focused library of analogues for binding studies aiming at the enantioselective recognition of chiral  $\alpha$ -hydroxy acid derivatives.

## Experimental Section

**General Procedures.**  $^1\text{H}$ -NMR spectra were recorded at 300 or 200 MHz and  $^{13}\text{C}$ -NMR spectra at 75 or 50 MHz on Bruker Avance DPX-300 or 200. Chemical shifts are reported in ppm with the signal for residual solvent as internal standard.  $J$  values are reported in Hz. Melting points were measured using a Kofler hot stage apparatus and are uncorrected. Flash column chromatography was performed with silica gel 60 (230-400 mesh). TLC were carried out on Merck 60F<sub>254</sub> silica plates. The optical rotatory powers were measured on a 241 MC Perkin-Elmer polarimeter with a sodium lamp and a double-jacketed cell at 25°C.

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. Hexane, 2-PrOH and ethanol, HPLC grade from SDS (Peypin-France), were degassed and filtered on a 0.45  $\mu\text{m}$  membrane before use. Retention times  $R_t$  in minutes, retention factors  $k_i = (R_{t_i} - R_{t_0}) / R_{t_0}$  are given.  $R_{t_0}$  was determined by injection of tri-tertio-butyl 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.<sup>15</sup> Analytical columns (250 x 4.6 mm) Chiralpak AD, Chiralcel OJ, Chiralcel OD-H, Chiralcel OC and Chiralcel OG were from Chiral Technologies Europe (Illkirch, France), Sumichiral OA-2500 was from Sumika (Yokohama, Japan), Ulmo (S,S) and Whelk-o1 (S,S) were from Regis (Morton Grove, USA), Kromasil TBB was from EKA-Nobel (Molnå, Sweden). 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. Semi-preparative separations on Chiralcel OD column (250 x 10 mm) were performed on a unit composed of Merck D-7000 system manager, Merck-Hitachi L-6000 pump, Rheodyne valve with a 500  $\mu\text{L}$  loop and a Merck-Hitachi L-4000 UV-detector.

***rac-N-(2-Methoxyphenyl)-N-[(2Z)-3-(2-methoxyphenyl)-4-methyl-1,3-thiazol-2(3H)-ylidene]amine (1)***. Already described.<sup>12b</sup>

***rac-2-[(2Z)-2-[(2-Hydroxyphenyl)imino]-4-methyl-1,3-thiazol-3(2H)-yl]phenol (2)***. Under N<sub>2</sub> atmosphere and stirring, BBr<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> (50 mL, 0.05 mol) was added dropwise to a solution of **1** (4.075 g, 12.5 mmol) in 10 mL CH<sub>2</sub>Cl<sub>2</sub> at -78°C and then the mixture was gradually warmed to room temperature. The mixture was reacted for 1 h and then refluxed for 21 h. Under cooling in ice bath, H<sub>2</sub>O (100 mL) was added. The mixture was carefully neutralized with NaHCO<sub>3</sub> and a white gummy product was collected. Soxhlet continuous extraction with dichloromethane yielded pure **2** (3.32 g, 89%) after evaporation. R<sub>f</sub> = 0.28 [CH<sub>2</sub>Cl<sub>2</sub>-MeOH (9.8:0.2)], mp: 140°C. <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>): δ 7.4-6.8 (m, 8H), 5.90 (q, 1H, J=1.4 Hz), 1.97 (d, 3H, J=1.4 Hz); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>): 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 (CH<sub>3</sub> cycle). Anal. Calcd for C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>S: 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.

***rac-(16Z)-19-Methyl-6,7,9,10-tetrahydroibenzo[b,g][1,3]thiazolo[3,2-d][1,9,12,4,6]-trioxadiazacyclotetradecine (3)***. A solution of **2** (0.5 g, 1.68 mmol) in acetonitrile (50 mL) was added to a solution of diethyleneglycol ditosylate (0.73 g, 1.76 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.58 g, 4.2 mmol) in acetonitrile (100 mL). The mixture was refluxed for 72 h. After cooling to room temperature the salts were filtered off and the solvent evaporated under vacuum. The resulting crude reaction mixture (0.788 g) was purified by column chromatography [SiO<sub>2</sub>, CHCl<sub>3</sub>-ethyl acetate (5:5)] to yield pure **3** (0.311 g, 50%), unreacted ditosylate (0.137 g), unreacted bis-phenol **2** (0.104 g) and by-product **4** (0.06 g).<sup>16</sup> R<sub>f</sub> 0.22 [CHCl<sub>3</sub>-ethyl acetate (7:3)], mp 150°C. <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 7.37-6.91 (m, 8H), 5.60 (q, 1H, J = 1.2 Hz), 4.37-3.73 (m, 8H), 1.77 (d, 3H, J = 1.2 Hz); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>) δ 162.3 (C=N), 155.3, 150.6, 143.2, 135.3, 131.2, 130.3, 126.9, 123.6, 123.4, 122.2, 121.6, 115.5, 114.1, 93.1 (C-H cycle), 70.6, 69.6, 69.3, 68.6, 14.84 (CH<sub>3</sub> cycle); Anal. Calcd for C<sub>20</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>S: C, 65.20; H, 5.47; N, 7.60; S, 8.70. Found: C, 65.01; H, 5.52; N, 7.42; S, 8.79.

***2-[[[(2-Hydroxyphenyl)imino]-4-methyl-1,3-thiazol-3(2H)-yl]phenoxy]ethoxy]ethoxy]phenyl)-4-methyl-1,3-thiazol-3(2H)-ylidene]amino)phenol (4)*** (mixture of *meso* and *d,l* forms). R<sub>f</sub> 0.76 [CHCl<sub>3</sub>-ethyl acetate (7:3)], mp 64°C for the *meso* and 75°C for each enantiomer. The *meso* and the *d,l* forms presented identical <sup>1</sup>H and <sup>13</sup>C-NMR spectra at 200 MHz and 50 MHz respectively. <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 7.39-6.85 (m, 18H), 5.69 (q, 2H, J = 1.2 Hz), 3.99 (m, 4H), 3.63 (m, 4H), 1.81 (6H); <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>) δ 159.7 (C=N), 154.8, 149.9, 135.67, 135.3, 130.5, 130.3, 126.5, 123.5, 121.6, 119.3, 117.1, 114.1, 113.0, 93.6 (C-H cycles), 69.67, 68.9, 14.67 (CH<sub>3</sub> cycles). HRMS Calcd (C<sub>36</sub>H<sub>34</sub>N<sub>4</sub>O<sub>5</sub>S<sub>2</sub>+H)<sup>+</sup> : 667.2043. Found: 667.2048 for the *meso* form and 667.2049 for the (-)-enantiomer.

## Supplementary Information Available

CCDC-662723 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/conts/retrieving.html](http://www.ccdc.cam.ac.uk/conts/retrieving.html) (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336033; or [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk)).

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