Resolution of a Configurationally Stable Hetero[4]helicene

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Abstract: We have developed an efficient chemical resolution of racemic hydroxy substituted dithia-aza[4]helicene (DTA[4]H 1(OH)) using enantiopure acids as resolving agents. The better diastereomeric separation was achieved on esters prepared with (1S)-(−)-camphanic acid. Subsequent simple manipulations produced highly optically pure (≥ 99% enantiomeric excess) (P) and (M)-1(OH) in good yields. The role of the position where the chiral auxiliary is inserted (cape vs bay zone) and the structure of the enantiopure acid used on successful resolution are discussed.

Keywords: heterohelicene; chirality; resolution; enantiomers; chiroptical; screw-shaped compounds

1. Introduction

Chirality is one of the most crucial assets of nature and is of paramount importance in several areas of science, technology and medicine. Molecular chirality has been recognized for a long time and has provided guidance in the design of drugs and functional materials. Furthermore, a smart combination of chiral phenomena and supramolecular chemistry resulted in an emerging interdisciplinary field called supramolecular chirality [1].

Helicenes are compounds with a screw-shaped skeleton formed by ortho-condensed (hetero)aromatic rings with a non-planar structure due to the steric superimposition of terminal rings or/and the substituents on these rings [2], which force the molecule to adopt a helical conformation (Figure 1). This important class of axially chiral compounds has a barrier of interconversion between M and P enantiomers increasing with the increase of the ring number forming the helicene backbone.

Circular dichroism (CD) and circularly polarized luminescence (CPL) are just a few of the chiroptical proprieties that make helicenes valuable in potential applications such as advanced optical information storage, circularly polarized organic light-emitting diodes (CP-OLEDs), circularly polarized light detecting organic field effect transistors (CP-OFETs), chirality-induced spin selectivity (CISS) devices and stereoselective sensing chiroptical probes in biological processes [3–14].

Recently, increased attention has focused on the binding of small molecules to specific DNA structures to inhibit the biological functions in which these structures participate. Indeed, helicenes enantioselectivity offered a way to rationally design Z-DNA depending inhibitors of biological functions [11].

Over the years, a variety of heterohelicenes and helical-shaped molecules, containing nitrogen, oxygen, sulfur, and other hetero-elements, have been synthesized and their unique properties studied. Great effort has been devoted to the setting of new simple and...
multi-gram synthetic procedures that allow for the isolation of helicenes in enantiopure form as required for various practical applications, including chirogenesis [7,15,16].

Figure 1. M and P enantiomers for a [6]carbohelicene.

Dithia-aza[4]helicenes (DTA[4]H) 1 (Scheme 1) can be described as bisphenothiazines with an aryl ring and a nitrogen atom in common forced into a helical shaped structure by the four long carbon–sulfur bonds. These [1,4]benzothiazino[2,3,4-kl]phenothiazines represent one of the attractive rare examples of geometrically stable [4]helicenes with racemization barriers higher than those measured for all carbon [5]helicenes.

DTA[4]H are obtained [17–21], as racemic mixture, from properly substituted triarylamines (TAA) 2 or N-aryl phenothiazines (PTZ) 3 (Scheme 1, pathway A and B respectively), through regioselective sulfonylation(s) with two or one equivalents of phthalimidesulfenyl chloride (PhtNSCl (4), Pht = phthaloyl). Reacting the resulting sulfonylated derivatives 5 or 6 with a Lewis Acid (L.A.), typically BF₃·OEt₂ or AlCl₃, causes two or one electrophilic intramolecular cyclization with formation of helicenes 1.

Scheme 1. Synthetic pathways (A or B) to dithia-aza[4]helicenes (DTA[4]H) 1.
Along with their peculiar helical-shaped structure, derivatives 1 show a very good one-electron donor ability, being easily, and reversibly, oxidized to the corresponding exceptionally stable crystalline chiral radical cations $1^{•+}$ [18,21] (Scheme 2). We have also demonstrated that the oxidative process is extremely sensitive to the medium, and under acidic conditions, molecular oxygen becomes an efficient single electron transfer (SET) oxidant, giving rise to the formation of $1^{•+}$. Furthermore, radical cations $1^{•+}$ can be generated also via irradiation at 240–400 nm of helicenes in the presence of PhCl [21] (Scheme 2).

![Scheme 2. Red-ox behavior of DTA[4]H 1.](image)

Indeed, we have also prepared, via ring-opening metathesis polymerization, dithia-aza[4]helicene functionalized polynorbornenes showing a pH depending reversible redox behavior as a new class of tunable material reversibly switchable by pH-triggered redox processes [22].

The availability of differently functionalized enantiomerically pure helicenes, avoiding the limitation associated with chiral HPLC resolution [17,23] is mandatory for the development of the appealing applications of these peculiar systems [21,22,24]. Therefore, in recent years we tried to set off regio-, stereo- and enantioselective synthetic approaches for the preparations of 1.

Actually, the synthetic procedure depicted in Scheme 1, while failing to control the absolute stereochemistry of the process, allowed for the control of the regiochemistry during ring closure as well as the possibility of inserting different substituents in specific positions. Thus, we have studied the chemical resolutions of 1 using the classical temporary insertion of chiral auxiliaries.

The DTA[4]H 1 derivatives requested for the above described applications require the insertion, as an anchoring unit, of a hydroxyl group in different positions of the helical backbone. Thus, we decided to take advantage of these phenolic groups for the introduction of chiral auxiliaries through esterification with enantiopure acids 7 and in order to verify whether the diastereoisomeric mixture of esters 8 obtained can be separated. Herein we report how the helicene topology and chiral auxiliary structure could be matched to allow the resolution of phenolic DTA[4]H 1(OH) (Scheme 3).

![Scheme 3. Esterification with enantiopure acids 7.](image)
2. Results and Discussion

Selected DTA[4]H 1 can be resolved through HPLC in the chiral stationary phase as we previously reported [17,23]; however, this method is unsuitable to obtain enantiopure DTA[4]H in multigram scale. Instead, the diastereomeric process-based resolution has advantages in the the viewpoint of cost, generality and the amount of enantiopure products achieved. Thus, we decided to study the insertion of chiral auxiliaries, for example through esterification reactions, to verify whether the mixture of diastereomers obtained can be separated by flash chromatography allowing isolation of pure M and P DTA[4]H in relevant quantity.

We have demonstrated that N-arylphenothiazines PTZ 3 are suitable substrates for the synthesis of unsymmetrically hydroxy substituted helicenes 1(OH) [20]. We selected helicene 1a(OH) and 1b(OH) (Scheme 4) to prepare diastereoisomeric esters using enantiopure acid 7 (Scheme 5).

![Scheme 4. Synthesis of hydroxy substituted helicenes 1a(OH) and 1b(OH).](image)

Firstly, we planned the introduction of chiral auxiliaries in 2-hydroxy-substituted ADT[4]H 1a(OH) presenting a hydroxyl group in the 2-position (that we indicate as cape-zone) of the helicene, which was relatively easy to prepare [20].

Racemic 1a(OH) was esterified with different enantiopure acids 7a-h yielding a diastereomeric mixture (D1+D2) of esters 8a-h. Esterification reactions were carried out in presence of diisopropylcarbodiimide (DIC) and 4-dimethylaminopyridine (DMAP) as catalysts, in dry CH₂Cl₂ at room temperature (Scheme 5A).
Scheme 5. Esterification of helicenes 1a(OH) and 1b(OH), panels (A) and (B), respectively, with enantiopure acids 7.

Regardless, all chiral acids 7a–h (Scheme 5 panel A and Table 1) allowed the formation of diastereomeric esters 8a(a–h) (Scheme 5 panel A and Table 1) in good yields, in none of these cases it was possible to separate the diastereoisomeric mixtures by flash chromatography or crystallization.

We thought, as suggested by literature data [25–38], that functionalization of the cape-zone position keeps the chiral auxiliaries too far from the superimposition area of the terminal aryl rings vanishing separation. Thus, we moved to helicene 1b(OH), which allowed for the insertion of chiral auxiliaries on 1-position, ortho to the nitrogen atom, which we indicated as bay-zone, i.e., exactly in the area of terminal ring superimposition (Scheme 5B).

Using chiral acids 7d–h (Scheme 5 panel B and Table 1), the corresponding diastereomeric esters 8b(d–h) (Scheme 5 panel B and Table 1) were obtained in moderate yields generally lower than those of the corresponding esters prepared using phenol 1a(OH), indicating, as expected, a more difficult access to the OH group of 1b(OH) laying the bay-zone (Table 1). For several esters 8b it was possible to identify the presence of the two diastereomers (D1 and D2, chromatographic elution order) by $^1$H and $^{13}$C NMR, and, eventually, to reveal a slightly different chromatographic behavior on TLC (Figure 2).
Despite the introduction of the chiral auxiliary in the bay-zone diastereoisomeric esters D1 and D2 of 8b(d–f) were not separable by flash chromatography in spite of an accurate selection of eluent mixtures. However, esterification of 1b(OH) with N-boc pipecolic acid 7g allowed for the partial separation by flash chromatography on silica gel of diastereomers 8bgD1 and 8bgD2, which were characterized by $^1$H and $^{13}$C NMR. Optical rotation of 8bgD1 was: $[\alpha]_D^{20} = -157$ (c 0.1, CH$_2$Cl$_2$), while for 8bgD2 was: $[\alpha]_D^{20} = +49$ (c 0.1, CH$_2$Cl$_2$). $^1$H NMR spectra show that the product 8bgD1 was isolated as single diastereomer, while the product 8bgD2 was isolated as a roughly 3:1 mixture of the two diastereomers.

Esters 8bgD1 and 8bgD2 were hydrolysed with 3 eq. of NaOH in CH$_2$Cl$_2$/MeOH to give enantiomeric phenols (M)-1b(OH) and (P)-1b(OH). Phenols were analysed by HPLC in the chiral stationary phase in order to calculate the enantiomeric ratio. Chromatograms showed that product (M)-1b(OH) $[\alpha]_D^{20} = -161$ (c 0.1, CH$_2$Cl$_2$) was obtained as single enantiomer (e.e. ≥ 99%), while helicene (P)-1b(OH) $[\alpha]_D^{20} = +75$ (c 0.1, CH$_2$Cl$_2$) exhibits the enantiomeric ratio 72:28 (e.e. = 44%).
Table 1. Diastereomeric esters obtained from reaction of racemic phenols 1a(OH) or 1b(OH) with enantiopure acids 7a–h.

| Chiral auxiliary | Product | Yield | Resolution |
|------------------|---------|-------|------------|
| 7a (S)-(−)-Perillic acid | 8aaD1/8aaD2 | 60% | No resolution |
| 7b Camphorsulfonyl chloride | 8abD1/8abD2 | 56% | No resolution |
| 7c (−)-o,o’-Dibenzoyl-L-tartaric acid mono(dimethyl amide) | 8acD1/8acD2 | 56% | No resolution |
| 7d (1S)-(+) Ketopinic acid | 8adD1/8adD2 | 79% | No resolution |
| 7e (S)-(+)2-(6-Methoxy-2-naphthyl)propionic acid | 8aeD1/8aeD2 | 94% | No resolution |
| 7f (−)-mono-(1R)-Menthylphthalate | 8afD1/8afD2 | 54% | No resolution |
| 7g (S)-N-Boc pipecolic acid | 8agD1/8agD2 | 69% | No resolution |
| 7h (1S)-(−)-Camphanic acid | 8ahD1/8ahD2 | 57% | No resolution |

Esterification of 1b(OH) with (1S)-(−)-camphanic acid 7h provided, with our great satisfaction, diastereomers 8bhD1 and 8bhD2 that were successfully separated by flash chromatography and characterized by 1H and 13C NMR spectroscopy (Figure 3 and Supplementary Materials).
Figure 3. $^1$H-NMR spectra of diastereomers 8bhD1 and 8bhD2.

Optical rotation was measured and gave $[\alpha]^{20}_D -129$ (c 0.1, CH$_2$Cl$_2$) for 8bhD1 and $[\alpha]^{20}_D +126$, (c 0.1, CH$_2$Cl$_2$) for 8bhD2. Hydrolysis of diastereomeric esters provided helicenes (M)-1b(OH) and (P)-1b(OH), respectively. HPLC analysis with a chiral stationary phase showed that the first eluted product, (P)-1b(OH) $[\alpha]^{20}_D +166$ (c 0.1, CH$_2$Cl$_2$), exhibits an enantiomeric ratio = 98:2 (e.e. = 96%), while the second eluted product,
(M)-1b(OH) \([\alpha]_D^{20} -167 (c 0.1, \text{CH}_2\text{Cl}_2)\), was obtained as a single enantiomer (e.e. \(\geq 99\%\)), (Scheme 6).

Scheme 6. Chemical resolution of helicene (rac)-1b(OH).

The assignment of the absolute configuration of DTA[4]H 1 derivatives has been established as \(P-\) and \(M-\), which is typical for helicene systems; opposite assignment is quite unusual, as we have established in ref [17,19]. In this work the absolute configuration of 1b(OH) was validated by comparison of the electronic circular dichroism (ECD) spectra of the two optical enantiomers-\((+)-1b(OH)\) and \((-)-1b(OH)\), assigned to \((P)-1b(OH)\) and \((M)-1b(OH)\), with the calculated spectrum of the \(M\) structure.

In order to assign the configuration, DFT and TD-DFT calculations have been conducted with the Gaussian16 package [39]. Two orientations are possible for the hydroxyl-group; the two optimized structures in the \(M\) configuration are reported in Figure 4 with their Boltzmann populations. Two functionals have been considered; the two differing in the amount of the exact exchange included M06 with 27\% HF exchange and M06-2X with 54\% HF exchange [40]. The solvent has been treated at the iefpcm level. Structural results are similar for the two functionals.

![Figure 4](image)

**Figure 4.** Optimized 3D-structures for the two possible conformers of (M)-1b(OH). Percent population factors calculated at M06/cc-pvtz, iefpcm level; in parenthesis population factors calculated at M062X/cc-pvtz, iefpcm level.

CD and absorption spectra have been calculated at the same level of theory, a constant Gaussian 0.2 eV bandwidth was applied to each transition. The experimental CD
and absorption spectra have been recorded for the two enantiomers in 4.2 mM dichloromethane solution in a 0.1 mm quartz cuvette using a JASCO-815SE instrument.

The comparison of experimental data with calculations are presented in Figure 5. In order to compare with data, +4 nm shift has been applied to the results obtained with M06, +26 nm with M06-2X; calculation of similarity index between experimental and calculated spectra suggested the best shift for the best correspondence, as reported in the Supplementary Materials paragraph. It is also shown that the two conformers give very similar spectra, while in Figure 5 the Boltzmann weighed average is presented. Both functionals permit confirmation of the configuration as M-(−) (correspondingly P-(+)). This conclusion agrees with what was obtained for the parent molecule triarylamine hetero[4]helicene examined in reference [19].

Figure 5. CD (top) and absorption (bottom) experimental and calculated spectra with two choices for the DFT functional (see text); calculation performed on M-1b(OH). The calculated spectra are Boltzmann weighed averages of the two conformers A and B.

Overall, our results confirm that, on chemical resolution of helicenes, the position where the chiral auxiliaries are inserted is extremely important, being the bay-zone that allows for the higher effect on enantiomeric discrimination. At the same time we have confirmed previous studies reporting chromatographic resolutions of [7]carbo- and [7]hetero-helicenes by means of tetra- and monocamphanate esters [25–31]. In each of
these cases, the (1S)-camphanate of the (P)-helicenol moves more slowly upon chromatography on silica gel than the (1S)-camphanate of the (M)-helicenol [27].

3. Materials and Methods

1H and 13C NMR spectra were recorded with Varian Mercury Plus 400, Varian Inova 400, using CDCl3 as solvent. Residual CHCl3 at δ = 7.26 ppm and central line of CDCl3 at δ = 77.16 ppm were used as the reference of 1H-NMR spectra and 13C NMR spectra, respectively. FT-IR spectra were recorded with a Spectrum Two FT-IR Spectrometer. ESI-MS spectra were recorded with a JEOL MSStation JMS700. Melting points were measured with a Stuart SMP50 Automatic Melting Point Apparatus. Optical rotation measurements were performed on a JASCO DIP-370 polarimeter (JASCO, Easton, MD, USA) and the specific rotation of compounds was reported [41].

All the reactions were monitored by TLC on commercially available precoated plates (silica gel 60 F254) and the products were visualized with acidic vanillin solution. Silica gel 60 (230–400 mesh) was used for column chromatography. Dry solvents were obtained by The PureSolv Micro Solvent Purification System. Chloroform was washed with water several times and stored over calcium chloride. Pyridine and TEA were freshly distilled from KOH. Phthalimide sulfonyl chloride was prepared from the corresponding disulfide (purchased from Chemper snc) as reported elsewhere. Helicenes 1a and 1b were described elsewhere [17].

General Procedure for the synthesis of diastereomeric esters from 1 by Steglich esterification: To a solution of 1 in dry CHCl3 (roughly 0.03–0.04 M), the enantiopure acid 7 (1.2 eq), DMAP (0.1 eq) and DIC (1–1.2 eq) were added at 0 °C. The solution was stirred at room temperature under a nitrogen atmosphere for 2–29 h, then was diluted with CHCl3 (60 mL), washed with a saturated solution of NH4Cl (2 × 40 mL), with a saturated solution of NaHCO3 (3 × 40 mL) then with NH4Cl (3 × 40 mL). The organic layer was dried over Na2SO4, filtered and evaporated under reduced pressure. The crude was purified by flash chromatography on silica gel.

Diastereoisomers 8aaD1 and 8aaD2. (M/P)-3-methyl[1,4]benzothiazino[2,3,4-kf]phenothiazine-2-yl (S)-perilate. Following the general Steglich esterification procedure from 1a(OH) (60 mg, 0.18 mmol) and (S)-(−)-perilic acid 7a (36 mg, 0.22 mmol), kept for 22 h at rt. The crude was purified by flash chromatography on silica gel (petroleum ether/CHCl3 1:3, Rf 0.86) to afford the mixture of the two diastereomeric compounds 8aaD1 and 8aaD2 (52 mg, 60% yield) as a white solid (mp 105–115 °C). 1H NMR (400 MHz, CDCl3)* δ: 1.45–1.55 (m, 2H), 1.76 (s, 6H), 1.89–1.95 (m, 2H), 2.12 (s, 6H), 2.16–2.41 (m, 8H), 2.51–2.59 (m, 2H), 4.74 (bs, 2H), 4.78 (bs, 2H), 6.89 (bs, 2H) 6.92–7.05 (m, 8H), 7.06 (bs, 2H), 7.12–7.25 (m, 8H) ppm. 13C NMR (100 MHz, CDCl3)* δ: 15.8, 20.9, 24.76, 24.80, 27.1, 31.4, 40.1, 108.63, 108, 64, 110.0, 110.6, 114.7, 120.6, 124.1, 124.8, 125.0, 125.7, 125.75, 125.83, 126.0, 127.0, 127.3, 127.7, 128.0, 129.3, 129.5, 139.5, 141.2, 141.8, 142.5, 148.7, 149.2, 162.5, 165.3 ppm (34 signals for 58 different carbons). Elem. Anal. for C36H28NO5S: Calcld. C 72.02, H 5.21, N 2.90; found C 71.80; H 5.21, N 2.89.*Et2N was added to neutralize CHCl3 acidity.

Diastereoisomers 8abD1 and 8abD2. (M/P)-3-methyl[1,4]benzothiazino[2,3,4-kf]phenothiazine-2-yl (1S)-10-camphorsulfonate. To a solution of 1a(OH) (60 mg; 0.18 mmol) and TEA (22 mg, 0.22 mmol) in 4 mL of dry CH2Cl2, (1S)-(−)-10-camphorsulfonyl chloride 7b (51 mg, 0.20 mmol) is added at 0 °C. After 10 min the solution was allowed to warm at room temperature and was stirred for 18 h under a nitrogen atmosphere. The mixture was diluted with AcOEt (25 mL) and washed with water (3 × 20 mL). The organic layer was dried over Na2SO4, filtered, and then evaporated under reduced pressure. The crude was purified by flash chromatography on silica gel (petroleum ether/AcOEt 5/1, Rf 0.38) to afford the mixture of the two diastereomeric compounds 8abD1 and 8abD2 (55 mg, 56% yield) as a white solid (mp 190–195 °C). 1H NMR (400 MHz, CDCl3) δ: 0.87 (s, 3H), 0.88 (s, 3H), 1.11 (s, 6H), 1.40–1.47 (m, 2H), 1.64–1.72 (m, 2H), 1.92–1.98 (m, 2H), 2.00–
Diastereoisomers 8acD1 and 8acD2. (M/P)-3-methyl-[1,4]benzothiazino[2,3,4-kl]phenothiazine-2-yl o,o'-dibenzoyl-L-tartrate. Following the general procedure from 1a(OH) (85 mg, 0.25 mmol) and (+)-o,o'-dibenzoyl-L-tartaric acid mono(dimethyl amide) 7c (117 mg, 0.30 mmol), kept for 2 h at room temperature. The crude was purified by flash chromatography on silica gel (AcOEt/CHCl3:1/20, Rf 0.65) to afford the mixture of the two diastereomeric compounds 8acD1 and 8acD2 (99 mg, 56% yield) as a white solid (mp 102–106 °C). 'H NMR (400 MHz, CDCl3) δ: 2.09 (s, 3H), 2.10 (s, 3H), 2.92 (s, 3H), 3.17 (s, 3H), 3.30 (s, 3H), 6.16 (d, 1H, J = 4.8 Hz), 6.20 (d, 1H, J = 5.2 Hz), 6.31 (d, 1H, J = 4.8 Hz), 6.33 (d, 1H, J = 5.2 Hz), 6.83–7.20 (m, 18H), 7.44–7.54 (m, 8H), 7.54–7.58 (m, 4H), 7.99–8.08 (m, 8H) ppm. 13C NMR (100 MHz, CDCl3) δ: 15.61, 15.63, 36.27, 36.31, 37.2, 69.5, 69.6, 70.9, 113.8, 114.0, 120.35, 120.41, 124.8, 124.9, 125.0, 125.1, 125.5, 125.6, 125.72, 125.74, 125.86, 125.92, 126.75, 126.84, 126.9, 127.6, 127.7, 127.9, 128.0, 128.35, 128.43, 128.52, 128.53, 128.58, 128.59, 128.60, 129.0, 129.3, 129.5, 129.7, 129.8, 129.97, 130.0, 130.12, 130.15, 133.82, 133.86, 139.12, 139.13, 141.1, 141.2, 142.1, 142.3, 148.09, 148.10, 156.0, 165.1, 165.3, 165.43, 165.44, 165.45, 165.50 ppm (59 signals for 78 carbons). IR (ATR solid) ν: 3063, 2929, 1763, 1724, 1664, 1477, 1432, 1240 cm⁻¹. Elem. Anal. for C₃₀H₂₈N₂O₅S: Calcd. C 66.65, H 4.30, N 3.99; found C 66.61, H 4.28, N 4.00.

Diastereoisomers 8adD1 and 8adD2. (M/P)-3-methyl-[1,4]benzothiazino[2,3,4-kl]phenothiazine-2-yl (1S)-ketopinate. Following the general Steglich esterification procedure from 1a(OH) (60 mg, 0.18 mmol) and (1S)-(−)-ketopinic acid 7d (56 mg, 0.31 mmol), kept for 29 h at room temperature. The crude was purified by flash chromatography on silica gel (petroleum ether/CHCl3: 1/3, Rf 0.45) to afford the mixture of the two diastereomeric compounds 8adD1 and 8adD2 (71 mg, 79% yield) as a white solid (mp 130–133 °C). 'H NMR (400 MHz, CDCl3) δ: 1.14 (s, 6H), 1.21 (s, 3H), 1.22 (s, 3H), 1.42–1.48 (m, 2H), 1.88–1.97 (m, 3H), 2.01–2.10 (m, 3H), 2.13–2.15 (m, 2H), 2.18 (s, 3H), 2.19 (s, 3H), 2.40–2.48 (m, 2H), 2.54–2.60 (m, 2H), 6.85 (s, 1H), 6.87 (s, 1H), 6.94–7.06 (m, 10H), 7.12–7.23 (m, 6H) ppm. 13C NMR (100 MHz, CDCl3) δ: 16.2, 20.0, 21.50, 21.52, 26.49, 26.52, 26.7, 26.8, 44.02, 44.58, 44.61, 49.51, 49.56, 68.20, 68.24, 110.6, 114.70, 114.72, 120.41, 120.44, 124.6, 124.8, 124.9, 125.0, 125.72, 125.8, 126.1, 126.8, 127.2, 127.3, 127.5, 127.82, 128.1, 129.59, 129.61, 139.4, 140.9, 141.0, 142.66, 142.71, 148.8, 168.1, 210.3 ppm (44 signals for 58 different carbons). Elem. Anal. for C₃₀H₂₈N₂O₅S: Calcd. C 69.71, H 5.04, N 2.80; found: C 69.73, H 5.01, N 2.77. *EtN was added to neutralize CHCl₃ acidity.

Diastereoisomers 8aeD1 and 8aeD2. (M/P)-3-methyl-[1,4]benzothiazino[2,3,4-kl]phenothiazine-2-yl (S)-2-(6-methoxy-2-naphthyl) propionate. Following the general Steglich esterification procedure from 1a(OH) (60 mg, 0.18 mmol) and (S)-(−)-2-(6-methoxy-2-naphthyl) propionic acid 7e (50 mg, 0.22 mmol), kept for 20 h at room temperature. The crude was purified by flash chromatography on silica gel (petroleum ether/CHCl3: 1/3, Rf 0.80) to afford the mixture of the two diastereomeric compounds 8aeD1 and 8aeD2 (94 mg, 94% yield) as an orange solid (mp 132–136 °C). 'H NMR (400 MHz, CDCl3) δ: 1.39 (d, 6H, J = 6.5 Hz), 1.77 (s, 3H), 1.79 (s, 3H), 3.39 (s, 6H), 3.84 (q, 1H, J = 6.6 Hz), 4.12 (q, 1H, J = 6.7 Hz), 6.81 (bs, 2H), 6.91–7.05 (m, 10H), 7.10–7.20 (m, 10H), 7.44–7.47 (m, 2H), 7.67–7.73 (m, 6H) ppm. 13C NMR (100 MHz, CDCl3) δ: 15.46, 15.48, 18.5, 18.6, 20.6, 21.2, 22.7, 23.6, 42.3, 45.56, 45.59, 55.4, 105.7, 108.6, 110.6, 114.4, 114.5, 119.3, 120.5, 124.3, 124.8, 125.0, 125.7, 125.8, 125.96, 126.01, 126.3, 126.4, 126.9, 127.1, 127.2, 127.4, 127.7, 127.8, 127.98, 128.01,
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129.0, 129.4, 129.5, 133.9, 134.95, 134.99, 139.4, 141.0, 142.50, 142.54, 148.9, 157.9, 172.7 ppm (49 signals for 66 different carbons). Elem. Anal. for C_{25}H_{30}NO_S: Calcd. C 72.37, H 4.60, N 2.56; found C 72.29; H 4.58, N 2.57. *EtN was added to neutralize CHCl₃ acidity.

Diastereoisomers 8afD1 and 8afD2. (M/P)-3-methyl[1,4]benzothiazino[2,3,4-kl]phenothiazine-2-y1 mono-(1R)-menthylphthalate. Following the general procedure from 1a(OH) (70 mg, 0.21 mmol) and (-)mono(1R)-menthylphthalate 7f (76 mg, 0.25 mmol), kept for 24 h at room temperature. The crude was purified by flash chromatography on silica gel (petroleum ether/CH₂Cl₂ 2/1, Rf 0.78) to afford the mixture of the two diastereomeric compounds 8afD1 and 8afD2 (70 mg, 54% yield) as a white solid (mp 140.8–146.8 °C). ¹H NMR (400 MHz, CDCl₃) δ: 0.73–0.89 (m, 6H), 0.83–0.89 (m, 14H), 0.97–1.16 (m, 4H), 1.36–1.51 (m, 4H), 1.64–1.71 (m, 4H), 1.85–1.98 (m, 2H), 2.05–2.11 (m, 2H), 2.21 (s, 3H), 2.22 (s, 3H), 4.82–4.89 (m, 2H), 6.93–7.00 (m, 6H), 7.03 (dd, 2H, J = 1.2 Hz, δ: 7.5 Hz), 7.08 (bs, 1H), 7.09 (bs, 1H), 7.11–7.16 (m, 2H), 7.18 (d, 2H, J = 7.7 Hz), 7.24–7.29 (m, 2H), 7.54–7.60 (m, 4H), 7.68–7.73 (m, 2H), 7.85–7.90 (m, 2H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ: 15.19, 16.0, 16.3, 16.5, 20.89, 20.93, 22.15, 22.18, 23.5, 23.6, 26.3, 26.4, 31.55, 31.57, 34.37, 34.41, 40.6, 40.7, 47.23, 47.25, 75.95, 75.95, 114.47, 114.49, 120.60, 120.64, 124.5, 124.6, 124.9, 125.0, 125.01, 125.71, 125.75, 125.77, 125.79, 126.07, 126.08, 126.95, 126.99, 127.33, 127.34, 127.71, 127.75, 127.98, 128.00, 128.09, 129.0, 129.51, 129.56, 129.60, 130.6, 130.89, 130.94, 131.0, 131.8, 131.9, 133.5, 133.7, 139.5, 141.2, 142.50, 145.22, 148.97, 149.98, 165.3, 165.4, 166.8, 166.9 ppm (68 signals for 74 different carbons). IR (ATR solid) ν: 2935, 2878, 1749, 1715, 1477, 1431, 1276, 1236 cm⁻¹. Elem. Anal. for C_{35}H_{39}NO_S: Calcd. C 71.47, H 5.67, N 2.25; found C 71.36, H 5.65, N 2.26.

Diastereoisomers 8agD1 and 8agD2. (M/P)-3-methyl[1,4]benzothiazino[2,3,4-kl]phenothiazine-2-y1 (S)-N-Boc pimoceline. Following the general procedure from 1a(OH) (61 mg, 0.18 mmol) and (S)-N-Boc pimocelic acid 7g (50 mg, 0.22 mmol) kept for 22 h at room temperature. The crude was purified by flash chromatography (CH₂Cl₂, Rf 0.51) on silica gel to afford the mixture of the two diastereomeric compounds 8agD1 and 8agD2 (70 mg, 69% yield) as a white solid (mp 108–117 °C). ¹H NMR (400 MHz, CDCl₃) δ: 1.37–1.44 (m, 2H), 1.65–1.80 (m, 8H), 2.13 (s, 6H), 2.29–2.33 (m, 2H), 2.93–3.09 (m, 2H), 3.89–3.95 (m, 1H), 4.04–4.09 (m, 2H), 4.92 (bs, 1H), 5.07 (bs, 1H), 7.21–7.67 (m, 18H) ppm. Elem. Anal. For C_{31}H_{34}N_{2}O_{3}: Calcd. C 65.91, H 5.53, N 5.12; found: C 65.35, H 5.31, N 4.98. *EtN was added to neutralize CHCl₃ acidity.

Diastereoisomers 8ahD1 and 8ahD2. (M/P)-3-methyl[1,4]benzothiazino[2,3,4-kl]phenothiazine-2-y1 (1S)-camphanate. Following a Steglich esterification procedure from 1a(OH) (60 mg, 0.18 mmol) and (1S)-(−)-camphanic acid 7h (43 mg, 0.22 mmol), kept for 17 h at room temperature. The crude was purified by flash chromatography on silica gel (petroleum ether/AcOEt/diethyl ether: 10:1.3, Rf 0.43) to afford the mixture of the two diastereomeric compounds 8ahD1 and 8ahD2 (52 mg, 57% yield) as a white solid (mp 170 °C dec). ¹H NMR (400 MHz, CDCl₃) δ: 1.04 (s, 3H), 1.06 (s, 3H), 1.11 (s, 6H), 1.13 (s, 3H), 1.14 (s, 3H), 1.69–1.77 (m, 2H), 1.92–1.99 (m, 2H), 2.11–2.19 (m, 8H), 2.45–2.54 (m, 2H), 6.84 (s, 1H), 6.86 (s, 1H), 6.93–7.00 (m, 6H), 7.02–7.08 (m, 4H), 7.12–7.21 (m, 6H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ: 9.78, 9.81, 16.0, 16.2, 16.94, 16.96, 17.01, 17.04, 29.0, 31.2, 31.3, 53.6, 54.6, 54.97, 55.00, 90.89, 90.94, 114.16, 114.21, 120.4, 120.5, 125.0, 125.1, 125.24, 125.27, 125.6, 125.8, 125.9, 126.0, 126.1, 126.2, 126.52, 126.9, 127.0, 127.8, 128.1, 129.0, 139.3, 141.2, 141.3, 142.4, 142.5, 148.1, 148.2, 165.8, 165.9, 177.8 ppm (47 signals for 58 different carbons). Elem. Anal. for C_{39}H_{34}N_{2}O_{2}: Calcd. C 67.55, H 4.89, N 2.72; found C 67.49, H 4.88, N 2.72. *EtN was added to neutralize CHCl₃ acidity.

Diastereoisomers 8bdD1, 8bdD2. (M/P)-1,3,7-trimethyl[1,4]benzothiazino[2,3,4-kl]phenothiazine-2-y1 (1S)-ketopinate. Following procedure from 1b(OH) (40 mg, 0.11 mmol) and (1S)-(−)-ketopinic acid 7d (20 mg, 0.11 mmol), kept for 18 h at room
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Diastereoisomers 8beD1 and 8beD2. (M/P)-1,3,7-trimethyl[1,4]benzothiazino[2,3,4-k]phenothiazine-2-yl (S)-(2-(6-methoxy-2-naphthyl) propionic acid 7e (28 mg, 0.13 mmol), kept for 12 h at room temperature. The crude was purified by flash chromatography on silica gel (petroleum ether/CHCl₃ 1/2, Rf 0.74)) to afford the mixture of the two diastereomeric compounds 8beD1 and 8beD2 (43 mg, 58% yield) as a white solid (mp 250 °C dec). ¹H NMR (400 MHz, CDCl₃) δ: 1.23 (d, 3H, J = 7.2 Hz), 1.39 (d, 3H, J = 7.2 Hz) 2.208 (s, 3H), 2.214 (s, 3H), 2.22 (s, 3H), 2.23 (s, 3H), 2.29 (s, 3H), 2.33 (s, 3H), 3.10 (q, 1H, J = 7.3 Hz), 3.20 (q, 1H, J = 7.2 Hz), 3.91 (s, 3H), 3.92 (s, 3H), 6.52 (bs, 1H), 6.65 (bs, 1H), 6.75–6.94 (m, 10H), 6.99 (bs, 1H), 7.04 (bs, 1H), 7.09–7.17 (m, 5H), 7.27–7.30 (m, 1H), 7.39 (bs, 1H), 7.53 (bs, 1H), 7.64–7.71 (m, 4H) ppm. Elem. Anal. for C₉H₇NOS: Calcd: C 70.56, H 5.54, N 2.43; found C 70.48, H 5.55, N 2.64.

Diastereoisomers 8bfD1 and 8bfD2. (M/P)-1,3,7-trimethyl[1,4]benzothiazino[2,3,4-k]phenothiazine-2-yl mono(1R)-menthylphthalate. Following the general procedure from 1b(OH) (40 mg, 0.11 mmol) and (S)-mon(1R)-menthylphthalate 7f (33 mg, 0.11 mmol), kept for 18 h at room temperature. The crude was purified by flash chromatography on silica gel (petroleum ether/CHCl₃ 1/2, Rf 0.63)) to afford the mixture of the two diastereomeric compounds 8bfD1 and 8bfD2 (32 mg, 45% yield) as a white solid (mp 180–190 °C). ¹H NMR (400 MHz, CDCl₃) δ: 0.66 (d, 3H, J = 6.9 Hz), 0.78–0.90 (m, 17H), 0.98–1.11 (m, 4H), 1.40–1.53 (m, 4H), 1.65–1.71 (m, 4H), 1.90–1.99 (m, 2H), 2.05–2.26 (m, 14H), 2.53 (s, 6H), 4.85–4.93 (m, 2H), 6.70–6.85 (m, 10H), 6.95–7.00 (m, 4H), 7.07 (bs, 2H), 7.26–7.30 (m, 2H), 7.44–7.54 (m, 4H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ: 16.1, 16.4, 20.5, 20.6, 20.90, 20.92, 21.02, 22.1, 22.2, 23.4, 23.5, 26.2, 26.3, 31.5, 31.6, 34.4, 34.5, 40.5, 40.7, 47.3, 47.4, 75.7, 118.45, 118.50, 123.35, 123.40, 125.7, 125.76, 125.77, 125.79, 125.9, 126.26, 126.34, 126.4, 127.0, 127.46, 127.48, 128.05, 128.12, 128.16, 128.3, 129.50, 129.53, 129.6, 129.75, 129.77, 130.15, 130.18, 130.7, 130.8, 131.4, 131.5, 133.6, 133.9, 134.1, 134.7, 134.8, 135.36, 135.40, 138.1, 138.2, 141.45, 141.52, 141.98, 142.01, 163.82, 163.84, 167.28, 167.33 ppm (56 signals for 78 different carbons). Elem. Anal. for C₂₁H₁₇N₂O₃: Calcd. C 72.08, H 6.05, N 2.16; found C 71.89, H 6.06, N 2.15.

Diastereoisomers 8bgD1 and 8bgD2. (M/P)-1,3,7-trimethyl[1,4]benzothiazino[2,3,4-k]phenothiazine-2-yl (S)-N-Boc pipecolate. Following the general procedure from 1b(OH) (40 mg, 0.11 mmol) and (S)-N-Boc pipecolic acid 7g (25 mg, 0.11 mmol), kept for 3 h at room temperature. The crude was purified by flash chromatography on silica gel (petroleum ether/CHCl₃ 1/3, D1 Rf 0.27, D2 Rf 0.20) to afford the product 8bgD1 (17 mg, 28% yield) as a white solid (mp 79–82 °C) and the product 8bgD2 (9 mg, 15% yield) as a white solid (mp 121–125 °C). 8bgD1: ¹H NMR (400 MHz, CDCl₃) δ: 1.10–1.21 (m, 1H), 1.26–1.53 (m, 14H), 2.21 (s, 3H), 2.28 (s, 3H), 2.29 (s, 3H), 2.29–2.95 (m, 1H), 3.79–3.96 (m, 1H), 4.40–4.47 (m, 1H), 6.78–6.91 (m, 6H), 7.00 (bs, 1H) ppm. ¹³C NMR (100 MHz,
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Diastereomers 8bhD1 and 8bhD2. (M/P)-1,3,7-trimethyl[1,4]benzothiazino[2,3,4-kl]phenothiazine-2-yl (15)-camphanate. Following the general procedure from 1b(OH) (259 mg, 0.71 mmol) and (15)-(−)-camphamic acid 7 (170 mg, 0.86 mmol), kept for 22 h at room temperature. The crude was purified by flash chromatography on silica gel (petroleum ether/CHCl3:1/3, D1 Rf 0.37, D2 Rf 0.26) to afford product 8bhD1 (143 mg, 37% yield) as a white solid (mp 70 °C) and product 8bhD2 (126 mg, 33% yield) as a white solid (mp 86–88 °C). 8bhD1: 1H NMR (400 MHz, CDCl3) δ: 0.97–0.99 (m, 1H), 1.26–1.45 (m, 1H), 2.14–2.29 (m, 9H), 2.46–2.94 (m, 1H), 3.65–3.92 (m, 1H), 4.39–4.63 (m, 1H), 6.78–6.91 (m, 6H), 7.00–7.02 (m, 1H) ppm. 13C NMR (100 MHz, CDCl3) δ: 20.1, 20.2, 20.5, 20.6, 20.70, 20.74, 20.8, 21.0, 24.7, 24.9, 26.0, 26.1, 28.4, 28.6, 41.0, 42.0, 54.4, 55.3, 80.0, 80.3, 115.2, 118.1, 118.2, 122.7, 122.9, 125.5, 125.8, 125.8, 125.8, 125.8, 125.9, 126.1, 126.3, 127.5, 128.0, 128.2, 128.9, 129.5, 131.5, 133.8, 134.9, 135.6, 138.1, 142.5, 155.7, 169.7, 169.9, ppm. [α]D +129 (c 0.1, CHCl3).

General Procedure for the hydrolysis: To a solution of ester 8 in CHCl3/MeOH: 10/1 (roughly 0.05 M) 3 eq. of NaOH was added, and the solution was stirred for 4–6 h at room temperature. The solution was diluted with water and HCl (1 M) was added until the pH was neutral, then the mixture was extracted with CHCl3 (3 × 5 mL). The organic layer was dried over Na2SO4, filtered, and then evaporated under reduced pressure. The crude was purified by flash chromatography on silica gel (Petroleum Ether/CHCl3:1/3) to afford the products (M)-1b(OH) or (P)-1b(OH) as a white solid in quantitative yield. (M)-1b(OH) [α]D 156 (c 0.1, CHCl3) and (P)-1b(OH) [α]D 166 (c 0.1, CHCl3).

Experimental HPLC Analytical (250 × 4.6 mm) column packed with Chiralpak IA chiral stationary phase was purchased from Chiral Technologies Europe. The HPLC resolution of products was performed on a HPLC Waters Alliance 2695 equipped with a 200 μL loop injector and a spectrophotometer UV Waters PDA 2996. The mobile phase, delivered at a flow rate of 1.2 mL/min, was hexane/CHCl3: 70/30 v/v + 1% MeOH.

4. Conclusions

In this paper we have reported that the fine matching of the structures of the chiral auxiliaries used and, above all, the topology of their insertion on the helical skeleton, bay-zone vs cape-zone, allow for the chemical resolution of DTA[4]H 1. Helicene 1b(OH) allowed for the insertion of the chiral auxiliary on the 1-position, the area of terminal ring superimposition that we indicated as the bay-zone. Esterification of 1b(OH) with (15)-(−)-camphamic acid 7 provided diastereomers 8bhD1 and 8bhD2 which were successfully separated by flash chromatography and hydrolyzed providing enantiopure helicenes (M)-1b(OH) and (P)-1b(OH), respectively.
Supplementary Materials: The following supporting information is available online: HPLC Analysis, NMR spectra, DFT calculations of compound 1b(OH). Optimized structures’ coordinates

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Sample Availability: Samples of the compounds are available from the authors.

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