Tetrahedron: *Asymmetry* 26 (2015) 186–194

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Synthesis of enantiomers of 3-methyl- and 3-phenyl-3,4-dihydro-2*H*-[1,4]benzothiazines and their 1,1-dioxides via an acylative kinetic resolution protocol

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ARTICLE INFO

Article history:
Received 26 November 2014
Accepted 8 January 2015

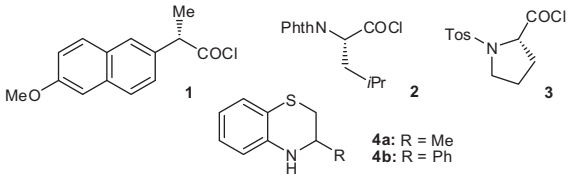
ABSTRACT

It has been found that acyl chlorides of (*S*)-naproxen, *N*-phthaloyl-(*S*)-leucine, and *N*-tosyl-(*S*)-proline are efficient chiral resolving agents for the acylative kinetic resolution of racemic 3-methyl- and 3-phenyl-3,4-dihydro-3-methyl-2*H*-[1,4]benzothiazines. Based on the experimental results, a preparative protocol comprising the acylative kinetic resolution followed by isolation of a single (major) diastereoisomeric amide and subsequent hydrolysis of amide bond was proposed. Using this approach with various chiral resolving agents, (*S*)- and (*R*)-enantiomers of 3,4-dihydro-3-methyl-2*H*-[1,4]benzothiazine (ee >99%) were obtained. The oxidation of the corresponding diastereoisomers of the amides followed by deacylation led to the (*S*)- and (*R*)-enantiomers of 3,4-dihydro-3-methyl-2*H*-[1,4]benzothiazine-1,1-dioxide (ee >97%). This method proved to be less suitable for the preparation of the (*S*)-enantiomer of 3,4-dihydro-3-phenyl-2*H*-[1,4]benzothiazine (ee up to 93%) and its sulfone (ee 82%) which were both obtained in low yields. The loss of enantioselectivity for (*S*)-3,4-dihydro-3-phenyl-2*H*-[1,4]benzothiazine and its sulfone occurred during hydrolysis of the corresponding diastereoisomerically pure amides.

1. Introduction

3-Substituted derivatives of 3,4-dihydro-2*H*-[1,4]benzothiazine and 3,4-dihydro-2*H*-[1,4]benzothiazine-1,1-dioxide are of special interest as the structural fragments of biologically active compounds.[1] However to date, a limited number of synthetic examples for enantiomerically pure 3-substituted 3,4-dihydro-2*H*-[1,4]benzothiazines have been described in the literature,[2] while the corresponding enantiopure sulfones are unreported.

Over the last few years, we have studied the acylative kinetic resolution of racemic amines[3] using acyl chlorides of 2-arylpropionic[4] and *N*-protected (*S*)-amino acids[4e,5] as chiral resolving agents. Thus, we have developed approaches for enantiopure heterocyclic amines with different structures, which are based on the acylative kinetic resolution with acyl chlorides of (*S*)-naproxen **1**,[4a,4b] *N*-phthaloyl-(*S*)-leucine **2**,[4e,5f] and *N*-tosyl-(*S*)-proline **3**[5a,5g] (Scheme 1). We have also demonstrated that a subsequent transformation of diastereoisomerically pure amides, the products of kinetic resolution can be used for the preparation of enantiopure functionalized amines.[5e]



Scheme 1. Resolving agents **1**–**3** and racemic benzothiazines **4a**,**b**.

Recently, we have demonstrated the possibility of the diastereoselective acylation of racemic amine **4a** with acyl chloride **3**.[5g] Herein our aim was to study the acylative kinetic resolution of racemic 3-methyl- **4a** and 3-phenyl-3,4-dihydro-2*H*-[1,4]benzothiazines **4b** with acyl chlorides **1**–**3** and to develop the preparative approaches to (*R*)- and (*S*)-enantiomers of these amines and corresponding sulfones.

2. Results and discussion

The starting racemic amines **4a** and **4b** were obtained from 2-aminothiophenol and appropriate chloroketone similar to the literature method.[6] In order to choose the most convenient

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http://dx.doi.org/10.1016/j.tetasy.2015.01.010
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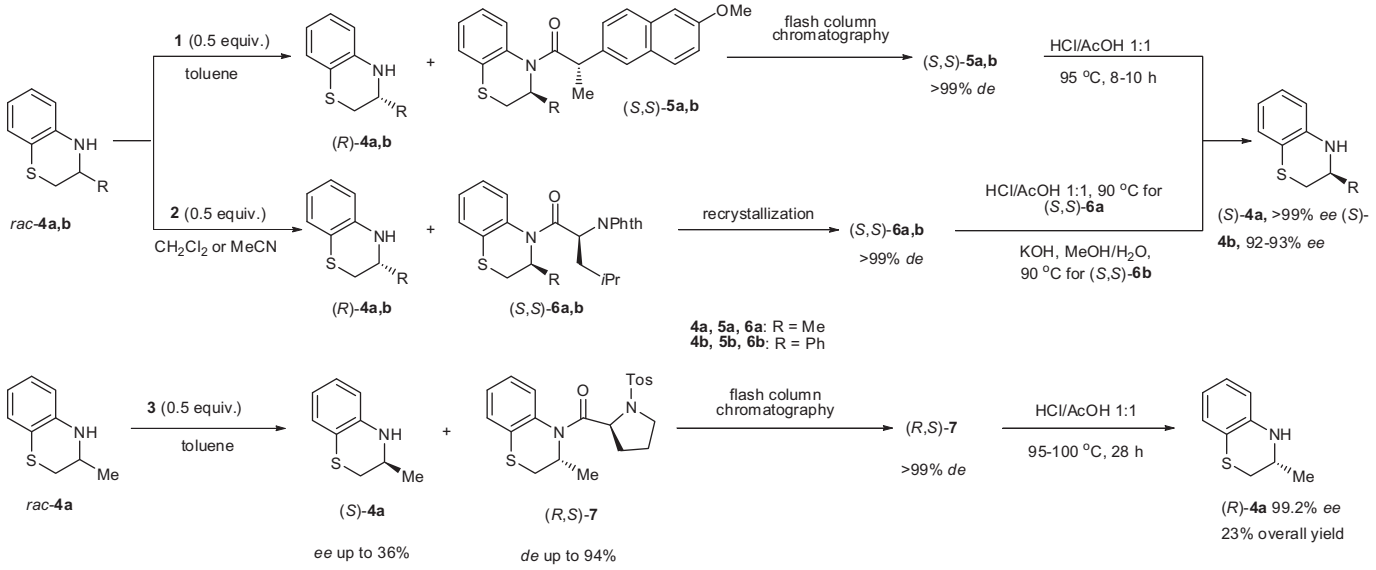


Scheme 2. Kinetic resolution of amines **4a**,**b** with acyl chlorides **1**–**3**.

reaction conditions for the preparation of enantiomers of amines **4a** and **4b**, we studied the acylative kinetic resolution with various chiral resolving agents. Diastereoselective acylation of racemic amines **4a** and **4b** with acyl chlorides **1**–**3** was carried out with a 2:1 amine–acyl chloride molar ratio in toluene, dichloromethane, or acetonitrile at various temperatures for 6 h (Scheme 2, Table 1). The initial concentration of racemic amine was 0.1 M. The choice of the solvent was based on the results of previous studies. Thus, it has been previously shown that in the acylative kinetic resolution of different heterocyclic amines with acyl chlorides **1**[4c,d] and **3**,[5g] a high stereoselectivity is achieved in toluene; when acyl chloride **2** is used as a chiral resolving agent, dichloromethane is the solvent of choice.[5e,f]

Diastereoselective acylation of amines **4a** and **4b** with acyl chlorides of (*S*)-naproxen **1** and *N*-phthaloyl-(*S*)-leucine **2** resulted in the predominant formation of (*S*,*S*)-amides **5a**,**b** and **6a**,**b**, while the unreacted amines were enriched with (*R*)-enantiomers (Table 1) similar to the acylation of racemic 2-methyl-1,2,3,4-tetrahydroquinoline and 2,3-dihydro-3-methyl-4*H*-[1,4]benzoxazine.[4a–c,5f] Diastereoselective acylation of amine **4a** with acyl chloride **3** led to the predominant formation of (*R*,*S*)-amide **7** recently shown.[5g] It should be emphasized that no diastereoisomeric amides were formed when the acylation of racemic amine **1b** with acyl chloride **3** was carried out in any of the abovementioned solvents at different temperatures (toluene from +20 to +80 °C, dichloromethane at +20 °C, acetonitrile from +20 to +50 °C). We consider that the phenyl substituent at the stereogenic center of the racemic amine probably gives rise to greater steric hindrances when compared with the methyl one.

The predominant diastereoisomeric amides (*S*,*S*)-**5a**,**b**, (*S*,*S*)-**6a**,**b**, and (*R*,*S*)-**7** (Scheme 2) were isolated from the reaction mixtures by recrystallization or flash column chromatography. The minor amides (*R*,*S*)-**6a** and (*S*,*S*)-**7** were also isolated from the reaction mixtures by flash column chromatography. In the case of crystalline amides (*S*,*S*)-**6a**, (*S*,*S*)-**6b**, and (*R*,*S*)-**7**, the absolute configuration was confirmed by X-ray diffraction from the known configuration of the acyl fragment (Figs. 1–3). Based on the data on which diastereoisomer, (*R*,*S*) or (*S*,*S*), of amides **6a**,**b** and **7** predominates in the kinetic resolution products, we determined in all cases the configuration of unreacted amines **4a** and **4b**. This made it possible to establish that the (*S*)-enantiomers of amines **4a**,**b** reacted faster than the (*R*)-enantiomers with acyl chloride **1** to afford (*S*,*S*)-amides **5a**,**b**, while the (*R*)-enantiomers remained unreacted.

Based on the values of diastereoisomeric excess (de) of amides (*S*,*S*)-**5a**,**b**, (*S*,*S*)-**6a**,**b**, and (*R*,*S*)-**7**, and the enantiomeric excess (ee) of the unreacted amine **4a** or **4b**, we calculated the conversion of starting racemate *C* and the selectivity factor *s*,[7] that is the ratio of the rate constants of enantiomers (Table 1).

Table 1
Stereochemical results of the acylative kinetic resolution of amines **4a** and **4b** with acyl chlorides **1**–**3** (the initial amine concentration 0.1 M, reaction time 6 h)[a]

Entry	Racemic amine	Resolving agent	Solvent	*T* (°C)	Amide, de[b] (%)	Unreacted amine, ee[c] (%)	Conversion, *C* (%)	Selectivity factor, *s*
1	**4a**	**1**	Toluene	+20	(*S*,*S*)-**5a**, 82.3	(*R*)-**4a**, 74.2	47	23
2	**4a**	**1**	Toluene	−20	(*S*,*S*)-**5a**, 89.7	(*R*)-**4a**, 65.2	42	37
3	**4a**	**2**	CH_2Cl_2	+20	(*S*,*S*)-**6a**, 51.4	(*R*)-**4a**, 40.5	44	4.6
4	**4a**	**2**	CH_2Cl_2	−20	(*S*,*S*)-**6a**, 61.7	(*R*)-**4a**, 23.7	27	5.2
5	**4a**	**2**	MeCN	+20	(*S*,*S*)-**6a**, 49.6	(*R*)-**4a**, 40.0	45	4.4
6	**4a**	**3**	Toluene	+20	(*R*,*S*)-**7**, 89.4	(*S*)-**4a**, 35.9	29	25[5g]
7	**4a**	**3**	Toluene	−20	(*R*,*S*)-**7**, 93.5	(*S*)-**4a**, 10.6	10	32[5g]
8	**4b**	**1**	Toluene	+20	(*S*,*S*)-**5b**, 82.4	(*R*)-**4b**, 66.0	44	20
9	**4b**	**1**	CH_2Cl_2	−20	(*S*,*S*)-**5b**, 71.6	(*R*)-**4b**, 71.6	50	13
10	**4b**	**2**	CH_2Cl_2	+20	(*S*,*S*)-**6b**, 53.1	(*R*)-**4b**, 13.8	21	3.8
11	**4b**	**2**	MeCN	+20	(*S*,*S*)-**6b**, 52.2	(*R*)-**4b**, 15.4	23	3.7

[a] Average values for 2–4 parallel runs are presented.
[b] Determined by HPLC (Phenomenex Luna C18(2) or ReproSil 100 Si, see Section 4).
[c] Determined by chiral HPLC (Chiralcel OD-H, see Section 4).

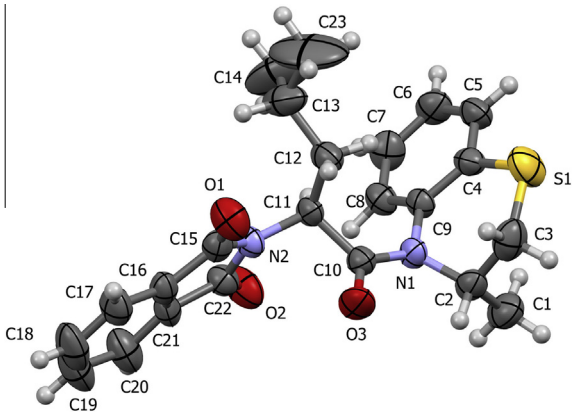


Figure 1. Structure of amide (*S*,*S*)-**6a** (thermal ellipsoids of 50% probability).

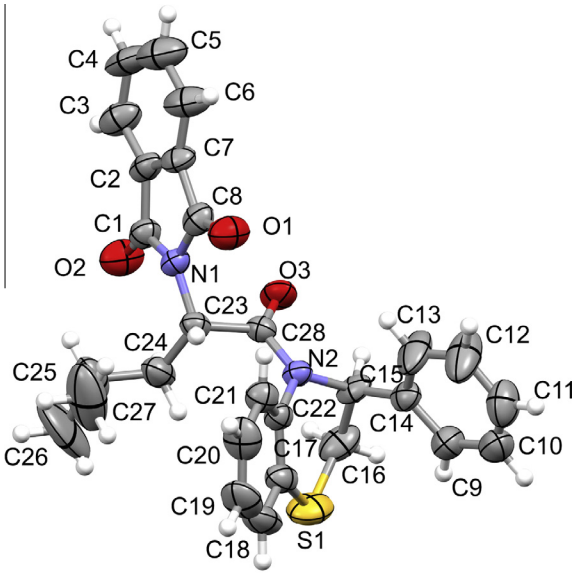


Figure 2. Structure of amide (*S*,*S*)-**6b** (thermal ellipsoids of 50% probability).

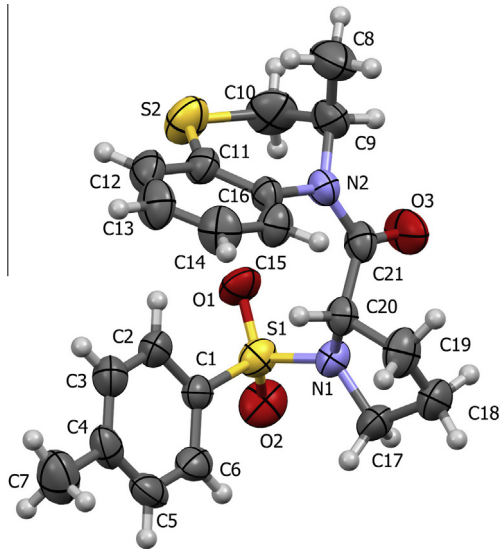


Figure 3. Structure of amide (*R*,*S*)-**7** (thermal ellipsoids of 50% probability).

From the data shown in Table 1 it can be seen that the highest selectivity of the acylation of racemic benzothiazine **4a** was observed when (*S*)-naproxen **1** and *N*-tosyl-(*S*)-prolyl **3** chlorides were used as chiral resolving agents, and the reaction was carried out in toluene at −20 °C (selectivity factor *s* was 37 and 32, respectively). However, the low reaction temperature (−20 °C) contributed to a decrease in conversion, which was most pronounced in the acylation with acyl chloride **3** (10% conversion).

In the case of diastereoselective acylation of racemic amine **4a** with acyl chloride **2**, the selectivity was moderate; the selectivity factor *s* was approximately 5 in dichloromethane and acetonitrile at 20 °C at rather high conversion of racemate (Table 1, entries 3 and 5).

It should be noted that the selectivity in the kinetic resolution of racemic 3,4-dihydro-3-methyl-2*H*-[1,4]benzothiazine **4a** with (*S*)-naproxen chloride **1** was as high as in the kinetic resolution of its oxygen-containing analogue, 3,4-dihydro-3-methyl-2*H*-[1,4]benzoxazine.[4e] In the case of the kinetic resolution with acyl chlorides of *N*-protected (*S*)-amino acids **2** and **3**, the acylation of benzothiazine **4a** was less selective than acylation of benzoxazine derivative.

When comparing the kinetic resolution processes of racemic 3,4-dihydro-3-phenyl-2*H*-[1,4]benzothiazine **4b** and amine **4a**, we can conclude that they occurred with a similar stereoselectivity. Thus, in the acylation of amines **4a** and **4b** with acyl chloride **1** in toluene at 20 °C, the selectivity factor *s* was 23 and 20, respectively (Table 1, entries 1 and 8). In the acylation of amines **4a** and **4b** with acyl chloride **2** in dichloromethane or MeCN at 20 °C, we also observed a similar stereoselectivity, but the acylation of phenyl-substituted amine **4b** proceeded at a significantly lower conversion, especially in MeCN (45% vs 23%; Table 1, entries 5 and 11). Prolonging this reaction in MeCN to 72 h led to an increase in the conversion of amine **4b** up to 47%.

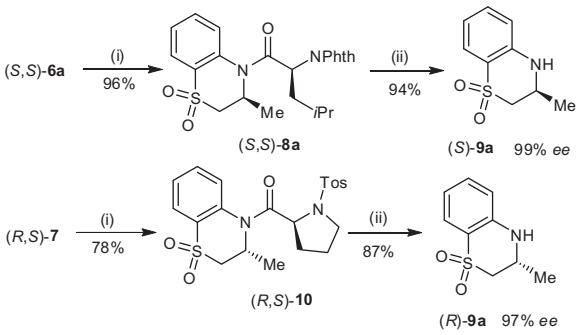
The results obtained formed the basis for the synthesis of enantiomerically pure (*S*)- and (*R*)-enantiomers of amines **4a** and (*S*)-enantiomer of amine **4b**.

In order to prepare (*S*)-**4a**, the kinetic resolution of the racemate can be carried out with either acyl chloride **1** or **2**. When the acylation of amine **4a** with acyl chloride **1** was carried out in toluene at 20 °C for 24 h, it resulted in amide (*S*,*S*)-**5a** (83.6% de) as a colorless oil in 91% yield (relative to acyl chloride **1**) and unreacted (*R*)-**4a** (79.2% ee; *s* 25). Flash column chromatography on silica gel gave individual (*S*,*S*)-**5a** (de >99%) in 55% overall yield (relative to acyl chloride **1**). The subsequent acidic hydrolysis of amide (*S*,*S*)-**5a** (Scheme 2) resulted in enantiopure amine (*S*)-**4a** (ee >99%) in 75% yield [relative to amide (*S*,*S*)-**5a**]. The overall yield of (*S*)-amine **4a** was 21% relative to the starting racemate.

In the case of the kinetic resolution of amine **4a** with acyl chloride **2**, the acylation was carried out in dichloromethane at +20 °C for 6 h. Recrystallization of the resulting amide afforded diastereoisomerically pure (*S*,*S*)-**6a** (de >99%) in 46% yield relative to the acylating agent **2**. After acidic hydrolysis of amide (*S*,*S*)-**6a** (Scheme 2), enantiopure amine (*S*)-**4a** (ee >99%) was obtained in 85% yield [relative to amide (*S*,*S*)-**6a**]. The overall yield of (*S*)-amine **4a** was about 20% relative to the starting racemate.

The approach that involves acylation of racemic amine **4a** with acyl chloride **2** is preferable compared to the use of acyl chloride **1**, since it is more convenient to purify amide (*S*,*S*)-**6a** by recrystallization.

In order to obtain enantiopure amine (*R*)-**4a**, we carried out the diastereoselective acylation of the racemate with acyl chloride **3** in toluene at 20 °C for 24 h. Diastereoisomerically pure amide (*R*,*S*)-**7** (de >99%) was isolated from the reaction mixture by flash column chromatography in 65% yield. The preparation of amine (*R*)-**4a** required a longer acidic hydrolysis (28 h) of amide (*R*,*S*)-**7** compared to the acidic hydrolysis of amides (*S*,*S*)-**5a** and (*S*,*S*)-**6a**.



Scheme 3. Preparation of (*R*)- and (*S*)-enantiomers of 3,4-dihydro-3-methyl-2*H*-[1,4]benzothiazine-1,1-dioxide **9a**.

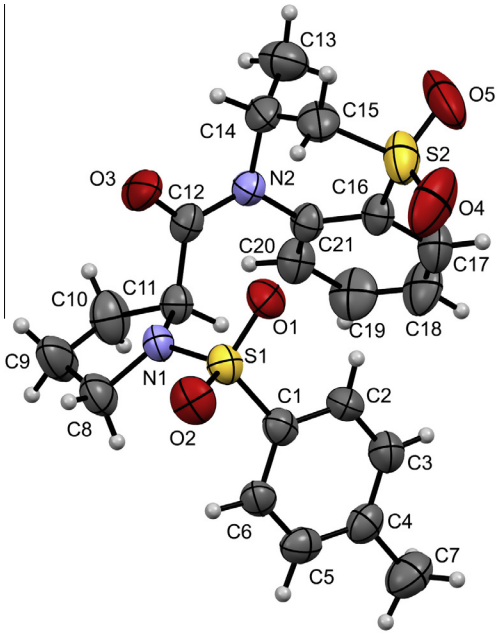


Figure 4. Structure of amide (*R*,*S*)-**10** (ellipsoids of 50% probability).

As a result we obtained enantiopure amine (*R*)-**4a** (ee >99%) in 23% overall yield relative to the racemate.

The derivatives of 3,4-dihydro-2*H*-[1,4]benzothiazine-1,1-dioxide with a free NH group are hard-to-obtain compounds; the oxidation of the corresponding dihydrobenzothiazines results in the formation of by-products of quinoid nature.[8] Our attempts to obtain racemic 3-methyl- and 3-phenyl-3,4-dihydro-2*H*-[1,4]benzothiazine-1,1-dioxides **9a**,**b** by the oxidation of amines **4a**,**b** in a way similar to the known approach[9] were unsuccessful. The target racemic sulfones **9a**,**b** were isolated in 18% and 24% yield, respectively.

Hence, we developed a synthetic approach for both enantiomers of sulfone **9a** based on the oxidation of diastereoisomerically pure amides (*S*,*S*)-**6a** and (*R*,*S*)-**7** resulting in amides (*S*,*S*)-**8a** and (*R*,*S*)-**10**, respectively (Scheme 3).

In this approach, the amides, the products of the kinetic resolution are subjected to oxidation and further transformation instead of amine **4a**. The oxidation of amides (*S*,*S*)-**6a** and (*R*,*S*)-**7** with hydrogen peroxide in a way similar to the literature[10] proceeded smoothly and led to amides (*S*,*S*)-**8a** and (*R*,*S*)-**10**, respectively (Scheme 3). Their structure and chemical purity were confirmed by the NMR spectroscopy and elemental analysis. In the case of amide (*R*,*S*)-**10**, the structure was confirmed by X-ray diffraction (Fig. 4).

The deacylation of amides (*S*,*S*)-**8a** and (*R*,*S*)-**10** with sodium methoxide in methanol at room temperature as described in the literature[8b,11] resulted in the enantiomeric sulfones (*S*)-**9a** (99% ee) and (*R*)-**9a** (97% ee), respectively, in high yields.

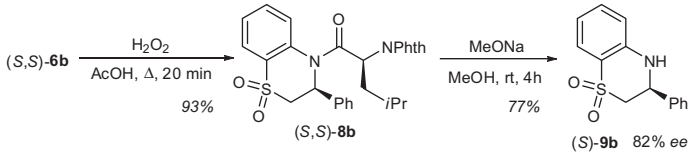
An attempt to obtain the individual (*S*)-enantiomers of 3-phenyl-benzothiazine **4b** and the corresponding sulfone **9b** in a similar way was not so successful. Preparative kinetic resolution of racemic amine **4b** with acyl chloride **1** in toluene at 20 °C followed by flash column chromatography (Scheme 2) afforded amide (*S*,*S*)-**5b** (de >99%) in 21% yield relative to the acylating agent. Subsequent acidic hydrolysis of amide (*S*,*S*)-**5b** proceeded in a moderate yield (61%) and was accompanied by partial racemization. The overall yield of enantiomerically enriched (*S*)-**4b** (93% ee) was 6.4% relative to the starting racemate.

In the case of the kinetic resolution of racemate **4b** with acyl chloride **2** (acetonitrile, +20 °C, 72 h), recrystallization of the kinetic resolution product gave amide (*S*,*S*)-**6b** (de >99%) in 41% yield. However, the acidic hydrolysis (heating in a mixture of concentrated HCl and AcOH) of amide (*S*,*S*)-**6b** failed. Hydrolysis of the amide bond in (*S*,*S*)-**6b** under the action of KOH in a MeOH–H_2O mixture resulted in the partially racemized amine (*S*)-**4b** (91% ee) in 37% yield. The overall yield was 7.6% relative to the starting racemate **4b**.

The oxidation of amide (*S*,*S*)-**6b** carried out in a similar manner to the preparation of sulfone (*S*)-**9a** smoothly afforded the corresponding amide (*S*,*S*)-**8b** (de >99% according to the ^{1}H NMR spectra) (Scheme 4). Deacylation of amide (*S*,*S*)-**8b** under the conditions described above for 3-methyl substituted analogue (*S*,*S*)-**8a** (NaOMe, MeOH, rt) resulted in (*S*)-**9b** (82% ee) in 77% yield. Such significant racemization of the target amine (*S*)-**4b** and sulfone (*S*)-**9b** is likely due to the effect of the phenyl substituent at the 3-position, since its presence facilitates the deprotonation at the stereogenic carbon atom under the conditions of deacylation of diastereoisomerically pure amides.

3. Conclusion

In conclusion, as a result of studying the acylative kinetic resolution of racemic 3,4-dihydro-3-methyl-2*H*-[1,4]benzothiazine with various chiral acyl chlorides, such as (*S*)-naproxen chloride, *N*-phthaloyl-(*S*)-leucyl chloride, and *N*-tosyl-(*S*)-prolyl chloride, we found conditions that gave the highest efficiency of the process. A synthetic sequence involving acylative kinetic resolution with subsequent isolation of the major diastereoisomeric amide followed by its deacylation made it possible to obtain enantiopure (*S*)- and (*R*)-enantiomers (ee >99%) of the titled compound. Oxidation of the corresponding diastereoisomerically pure amides followed by deacylation resulted in enantiopure (*S*)- and (*R*)-sulfones (ee from 97 to >99%). Application of the same approach for the preparation of enantiomers of 3,4-dihydro-3-phenyl-2*H*-



Scheme 4. Preparation of (*S*)-3,4-dihydro-3-phenyl-2*H*-[1,4]benzothiazine-1,1-dioxide **9b**.

[1,4]benzothiazine proved to be not so successful. The (*S*)-enantiomer of 3-phenyl-benzothiazine was obtained in a low yield and approximately 93% ee; the corresponding (*S*)-sulfone was obtained with 82% ee. The loss of enantiomeric purity took place during the deacylation step of corresponding amides.

4. Experimental

4.1. General

(*S*)-Naproxen chloride **1**,[12] *N*-phthaloyl-(*S*)-leucyl chloride **2**;[5e] *N*-tosyl-(*S*)-prolyl chloride **3**, racemic 3,4-dihydro-3-methyl-2*H*-[1,4]benzothiazine **4a**, (3*S*,2′*S*)-3,4-dihydro-3-methyl-4-(*N*′-tosylprolyl)-2*H*-[1,4]-benzothiazine (*S*,*S*)-**7**, and (3*R*,2′*S*)-3,4-dihydro-3-methyl-4-(*N*′-tosylprolyl)-2*H*-[1,4]-benzothiazine (*R*,*S*)-**7**[5g] were obtained as described in the literature. Other reagents are commercially available.

The solvents were purified according to standard methods.[13] Flash column chromatography was performed using Silica gel 60 (230–400 mesh) (Alfa Aesar, UK). Melting points were obtained on a SMP3 apparatus (Barloworld Scientific, UK) and are uncorrected. Optical rotations were measured on a Perkin Elmer M341 polarimeter. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 500 spectrometer operating at frequencies 500 MHz for ^{1}H and 126 MHz for ^{13}C with TMS as internal reference. The NMR spectra of amides **5a**,**b**, **6a**,**b**, **8a**,**b**, and **10** were recorded in DMSO-d_6 at 100 °C; the NMR spectra of amines **4a**,**b** and **9a**,**b** were recorded in $CDCl_3$ at ambient temperature. Elemental analysis was performed using Perkin Elmer 2400 II analyzer.

Analytical HPLC of amides **5a**,**b** and **6a**,**b** was performed on an Agilent 1100 instrument using a Phenomenex Luna C18(2) column (250 × 4.6 mm, 5 μm) (Phenomenex Inc., USA), detection at 230 nm, 0.8 mL/min flow rate. Analytical HPLC of amide **7** was performed on a Knauer Smartline-1100 instrument using a ReproSil 100 Si column (250 × 4.6 mm, 5 μm) (Dr. Maisch GmbH, Germany), detection at 220 nm, 1 mL/min flow rate. Analytical HPLC of amines **4a**,**b** and **9a**,**b** was performed on a Knauer Smartline-1100 instrument using a Chiralcel OD-H column (250 × 4.6 mm) (Daicel Corp., Japan), detection at 220 nm, 1 mL/min flow rate.

The HRMS spectra were registered on 1200 Infinity (Agilent Technologies) instrument using 6540 Accurate-Mass Q-TOF (Agilent Technologies) detector operating in positive ion mode with ESI probe installed at N_2 flow rate 10 L/min, nebulizer pressure 40 psi. The probe voltage was set to 3.5 kV.

Crystallographic data for compounds (*S*,*S*)-**6a**, (*S*,*S*)-**6b**, (*R*,*S*)-**7**, and (*R*,*S*)-**10** have been deposited with the Cambridge Crystallographic Data Centre (CCDC Nos. 979743, 979744, 1035103, and 979745) Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (+44) 1223 336033; or e-mail: deposit@ccdc.cam.ac.uk].

4.2. (3*RS*)-3,4-Dihydro-3-phenyl-2*H*-[1,4]benzothiazine 4b

A solution of 2-aminothiophenol (5.56 g, 44.38 mmol) and chloroacetophenone (6.86 g, 44.38 mmol) in Et_2O (90 mL) was stirred at room temperature for 24 h in the dark, after which the precipitate was filtered off. The filtrate was successively washed with 1 M NaOH (2 × 40 mL) and water (2 × 40 mL), dried over Na_2SO_4 and evaporated to dryness. The residue and the precipitate were combined and dissolved in a 1:1 MeOH–AcOH mixture (120 mL); next $NaBH_4$ (10.49 g, 277.38 mmol) was added in several portions to the reaction mixture under stirring at 0 °C. The suspension was stirred at ambient temperature for 2 days then concentrated to half-volume under reduced pressure and poured into cold water (300 mL). The aqueous solution was alkalized with Na_2CO_3 (to pH 8–9) and extracted with CH_2Cl_2 (4 × 60 mL). The organic layers were washed with water (2 × 75 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by flash column chromatography (hexane to hexane–EtOAc 99:1 as an eluent) to give compound **4b** (2.42 g, 24%). Yellow crystals, mp 52–53 °C (lit.[14] mp 58–59 °C). HPLC (Chiralcel OD-H; hexane–*i*PrOH 5:1): $\tau_{(R)\text{-}\mathbf{4b}}$ 14.0 min, $\tau_{(S)\text{-}\mathbf{4b}}$ 15.0 min. NMR spectra were identical to the published for (*S*)-**4b**.[2d] Anal. Calcd for $C_{14}H_{13}NS$: C, 73.97; H, 5.76; N, 6.16; S, 14.11. Found: C, 73.82; H, 5.81; N, 5.91; S, 14.40.

4.3. Kinetic resolution of racemic amines 4a,b. General procedure

A solution of the appropriate acyl chloride (0.15 mmol) in an appropriate solvent (1.5 mL) was added to a solution of amine **4a** or **4b** (0.30 mmol) in the same solvent (1.5 mL) at specified temperature. The reaction mixture was kept at the appropriate temperature for 6 h, then washed with 4 M HCl (2 × 3 mL), saturated NaCl (3 × 3 mL), 5% $NaHCO_3$ (3 mL) and water (2 × 3 mL); in the case of the kinetic resolution in MeCN, the reaction mixture was diluted with 5 mL of EtOAc prior to work-up.

Work-up procedure for the kinetic resolution of amine **4a**: (i) the organic layers were separated, dried over $MgSO_4$, and evaporated under reduced pressure to give a mixture of diastereoisomeric amides **5a** (**6a** or **7**), which was then analyzed by HPLC; (ii) acidic washings were collected and alkalized with Na_2CO_3 up to pH 8–9 and extracted with $CHCl_3$ (2 × 3 mL); the organic layers were separated, dried over $MgSO_4$, and evaporated under reduced pressure to give the unreacted amine **4a**.

Work-up procedure for kinetic resolution of amine **4b**: the organic layers were separated, dried over $MgSO_4$, and evaporated under reduced pressure; the residue was subjected to flash column chromatography (10–30% hexane in EtOAc as an eluent) to give unreacted amine **4b** which was analyzed by chiral HPLC, and a mixture of diastereoisomeric amides **5b** or **6b** that was analyzed by HPLC.

4.4. Diastereoisomers of 3,4-dihydro-3-methyl-4-[2′-(6″-methoxynaphth-2″-yl)propionyl]-2*H*-[1,4]benzothiazine 5a

A solution of (*S*)-naproxen chloride **1** (0.77 g, 3.11 mmol) in toluene (42 mL) was added to a solution of amine **4a** (1.03 g, 6.22 mmol) in toluene (40 mL) at +20 °C. The reaction mixture was kept at +20 °C for 24 h, then successively washed with 4 M HCl (2 × 15 mL), saturated NaCl (3 × 20 mL), 5% aqueous $NaHCO_3$ (20 mL), water (2 × 20 mL), dried over $MgSO_4$ and evaporated. Diastereoisomeric mixture **5a** and amide (*S*,*S*)-**5a** (slow eluting diastereoisomer) were isolated by flash column chromatography using a 9:1 hexane–EtOAc mixture as an eluent.

4.4.1. (3*S*,2′*S*)-3,4-Dihydro-3-methyl-4-[2′-(6″-methoxynaphth-2″-yl)propionyl]-2*H*-[1,4]benzothiazine (*S*,*S*)-5a

Yield 0.65 g (55%). Colorless oil. $[\alpha]_D^{20}$ = +35.7 (*c* 1.07, $CHCl_3$). De >99.8%; HPLC (Phenomenex Luna C18(2), MeCN–H_2O 7:3): τ 18.3 min. ^{1}H NMR (DMSO-d_6, 100 °C): δ 0.92 (d, 3H, Me-3, *J* = 6.7 Hz), 1.46 (d, 3H, Me-2′, *J* = 6.8 Hz), 2.64 (dd, 1H, H-2B, *J* = 12.2, 4.4 Hz), 3.12 (dd, 1H, H-2A, *J* = 12.2, 5.9 Hz), 3.84 (s, 3H, OMe), 4.32 (q, 1H, H-2′, *J* = 6.8 Hz), 5.14 (qdd, 1H, H-3, *J* = 6.7, 5.9, 4.4 Hz), 6.96 (dd, 1H, H-7″, *J* = 8.9, 1.6 Hz), 7.04 (dd, 1H, H-8, *J* = 7.8, 1.4 Hz), 7.07 (dd, 1H, H-3″, *J* = 8.7, 2.5 Hz), 7.12 (td, 1H, H-7, *J* = 7.6, 1.4 Hz), 7.15–7.17 (m, 2H, H-1″ and H-5″), 7.22 (td, 1H, H-6, *J* = 7.6, 1.4 Hz), 7.39 (dd, 1H, H-5, *J* = 8.0, 1.4 Hz), 7.55 (d, 1H, H-4″, *J* = 8.7 Hz), 7.56 (d, 1H, H-8″, *J* = 8.9 Hz). ^{13}C NMR (DMSO-d_6, 100 °C): δ 16.61, 18.30, 33.60, 41.69, 45.03, 54.72, 105.79, 124.46, 124.70, 125.12, 125.68, 126.00, 126.40, 127.98, 128.03, 128.36, 130.54, 132.58, 134.51, 135.50, 156.68, 172.29. Anal. Calcd

for $C_{23}H_{23}NO_2S$: C, 73.18; H, 6.14; N, 3.71; S, 8.49. Found: C, 73.36; H, 6.22; N, 3.66; S, 8.34.

4.4.2. 3,4-Dihydro-3-methyl-4-[2′-(6″-methoxynaphth-2″-yl)propionyl]-2*H*-[1,4]benzothiazine 5a (diastereoisomeric mixture)

Yield 0.36 g (31%). Colorless oil. *S*,*S*/*R*,*S* 80:20, HPLC (Phenomenex Luna C18(2), MeCN–H_2O 7:3): $\tau_{(S,S)\text{-}\mathbf{5a}}$ 18.3 min, $\tau_{(R,S)\text{-}\mathbf{5a}}$ 24.3 min. ^{1}H NMR (DMSO-d_6, 100 °C): δ 0.92 (d, 2.4H, Me-3 (*S*,*S*), J = 6.7 Hz), 1.01 (d, 0.6H, Me-3 (*R*,*S*), J = 6.7 Hz), 1.32 (d, 0.6H, Me-2′ (*R*,*S*), J = 6.8 Hz), 1.46 (d, 2.4H, Me-2′ (*S*,*S*), J = 6.8 Hz), 2.65 (dd, 0.8H, H-2B (*S*,*S*), J = 12.3, 4.4 Hz), 2.74 (dd, 0.2H, H-2B (*R*,*S*), J = 12.2, 4.5 Hz), 3.12 (dd, 0.8H, H-2A (*S*,*S*), J = 12.3, 5.9 Hz), 3.21 (dd, 0.2H, H-2A (*R*,*S*), J = 12.2, 6.0 Hz), 3.84 (s, 2.4H, OMe (*S*,*S*)), 3.88 (s, 0.6H, OMe (*R*,*S*)), 4.04 (q, 0.2H, H-2′ (*R*,*S*), J = 6.8 Hz), 4.32 (q, 0.8H, H-2′ (*S*,*S*), J = 6.8 Hz), 5.14 (qdd, 0.8H, H-3 (*S*,*S*), J = 6.7, 5.9, 4.4 Hz), 5.22 (qdd, 0.2H, H-3 (*R*,*S*), J = 6.7, 6.0, 4.5 Hz), 6.95-7.78 (m, 10H, arom. H (*S*,*S*) + (*R*,*S*)). Anal. Calcd for $C_{23}H_{23}NO_2S$: C, 73.18; H, 6.14; N, 3.71; S, 8.49. Found: C, 73.03; H, 6.35; N, 3.67; S, 8.53.

4.5. Diastereoisomers of 3,4-dihydro-3-phenyl-4-[2′-(6″-methoxynaphth-2″-yl)propionyl]-2*H*-[1,4]benzothiazine 5b

A solution of (*S*)-naproxen chloride **1** (0.22 g, 0.88 mmol) in toluene (9 mL) was added to a solution of amine **4b** (0.40 g, 1.76 mmol) in toluene (9 mL) at +20 °C. The reaction mixture was kept at +20 °C for 24 h, then successively washed with 5% aqueous $NaHCO_3$ (2 × 10 mL) and water (2 × 10 mL), dried over $MgSO_4$, and evaporated. Amides (*R*,*S*)-**5b** (fast eluting diastereoisomer) and (*S*,*S*)-**5b** (slow eluting diastereoisomer) were isolated by flash column chromatography using a 9:1 hexane–EtOAc mixture as an eluent.

4.5.1. (3*R*,2′*S*)-3,4-Dihydro-3-phenyl-4-[2′-(6″-methoxynaphth-2″-yl)propionyl]-2*H*-[1,4]benzothiazine (*R*,*S*)-5b

Yield 0.019 g (5%). Pale yellow oil. $[\alpha]_D^{20}$ = −298 (c 1.4, $CHCl_3$). De >99.8%; HPLC (Phenomenex Luna C18(2), MeCN–H_2O 8:2): τ 13.7 min; ^{1}H NMR (DMSO-d_6, 100 °C): δ 1.33 (d, 3H, Me-2′, J = 6.9 Hz), 3.14 (dd, 1H, H-2B, J = 13.0, 7.1 Hz), 3.61 (dd, 1H, H-2A, J = 13.0, 6.8 Hz), 3.88 (s, 3H, OMe), 4.04 (q, 1H, H-2′, J = 6.9 Hz), 6.18 (m, 1H, H-3), 7.06–7.29 (m, 10H, arom.), 7.33 (m, 1H, arom.), 7.42 (dd, 1H, arom., J = 8.5, 1.8 Hz), 7.69 m (1H, arom.), 7.76 m (2H, arom.). ^{13}C NMR (DMSO-d_6, 100 °C): δ 20.38, 34.43, 42.07, 54.81, 56.22, 105.95, 117.92, 124.93, 125.18, 125.72 (2C), 125.79, 125.96, 126.46 (2C), 127.69 (2C), 127.84, 128.07, 128.16, 128.55, 131.99, 132.78, 136.44, 136.66, 139.24, 156.93, 172.96. Anal. Calcd for $C_{28}H_{25}NO_2S$: C, 76.51; H, 5.73; N, 3.19; S, 7.29. Found: C, 76.75; H, 5.91; N, 3.02; S, 7.12.

4.5.2. (3*S*,2′*S*)-3,4-Dihydro-3-phenyl-4-[2′-(6″-methoxynaphth-2″-yl)propionyl]-2*H*-[1,4]benzothiazine (*S*,*S*)-5b

Yield 0.082 g (21%). Pale yellow oil. $[\alpha]_D^{20}$ = +132 (c 1.0, $CHCl_3$). De >99.8%; HPLC (Phenomenex Luna C18(2), MeCN–H_2O 8:2): τ 10.7 min. ^{1}H NMR (DMSO-d_6, 100 °C): δ 1.48 (d, 3H, Me-2′, J = 6.9 Hz), 3.03 (dd, 1H, H-2B, J = 13.0, 7.0 Hz), 3.41 (dd, 1H, H-2A, J = 13.0, 6.7 Hz), 3.84 (s, 3H, OMe), 4.38 (q, 1H, H-2′, J = 6.9 Hz), 6.07 (m, 1H, H-3), 6.94 (dd, 1H, arom., J = 8.4, 1.7 Hz), 7.02 (dd, 1H, arom., J = 7.8, 1.4 Hz), 7.05–7.26 (m, 10H, arom.), 7.49 m (1H, arom.), 7.54 m (2H, arom.). ^{13}C NMR (DMSO-d_6, 100 °C): δ 18.33, 33.99, 41.70, 54.72, 55.96, 105.80, 117.63, 124.78, 125.16, 125.27, 125.72, 125.87 (2C), 125.93, 126.32, 127.37, 127.57 (2C), 127.92, 128.31, 128.36, 132.55, 132.60, 135.33, 136.57, 139.24, 156.67, 173.05. Anal. Calcd for $C_{28}H_{25}NO_2S$: C, 76.51; H, 5.73; N, 3.19; S, 7.29. Found: C, 76.31; H, 6.01; N, 3.06; S, 7.12.

4.6. (3*S*,2′*S*)-3,4-Dihydro-3-methyl-4-(*N*′-phthaloylleucyl)-2*H*-[1,4]benzothiazine (*S*,*S*)-6a

A solution of *N*-phthaloyl-(*S*)-leucyl chloride **2** (2.02 g, 7.22 mmol) in CH_2Cl_2 (70 mL) was added to a solution of amine **4a** (2.39 g, 14.44 mmol) in CH_2Cl_2 (74 mL) at +20 °C. The reaction mixture was kept at +20 °C for 6 h, then successively washed with 4 M HCl (3 × 50 mL), saturated NaCl (4 × 70 mL), 5% aqueous $NaHCO_3$ (2 × 70 mL) and water (2 × 70 mL), dried over $MgSO_4$ and evaporated. The residue was recrystallized from hexane–EtOAc. Yield 1.36 g (46%). Colorless crystalline powder, mp 177–178 °C (hexane–EtOAc). $[\alpha]_D^{20}$ = +382 (c 0.94, $CHCl_3$). De >99%; HPLC (Phenomenex Luna C18; MeCN–H_2O 9:1): τ 8.1 min; ^{1}H NMR (DMSO-d_6, 100 °C): δ 0.33 (d, 3H, Me-4′, J = 6.6 Hz), 0.63 (d, 3H, Me-4′, J = 6.6 Hz), 0.96 (ddd, 1H, H-3′B, J = 13.9, 9.8, 3.7 Hz), 1.03 (d, 3H, Me-3, J = 6.6 Hz), 1.28 (m, 1H, H-4′), 2.56 (ddd, 1H, H-3′A, J = 13.9, 12.0, 3.9 Hz,), 2.76 (dd, 1H, H-2B, J = 12.5, 5.4 Hz,), 3.39 (dd, 1H, H-2A, J = 12.5, 6.5 Hz), 5.08 (qdd, 1H, H-3, J = 6.6, 6.5, 5.4 Hz), 5.39 (dd, 1H, H-2′, J = 12.0, 3.7 Hz), 7.29 (td, 1H, H-7, J = 7.5, 1.5 Hz), 7.32 (td, 1H, H-6, J = 7.5, 1.7 Hz), 7.42 (dd, 1H, H-8, J = 7.5, 1.7 Hz), 7.51 (dd, 1H, H-5, J = 7.5, 1.5 Hz), 7.86 (m, 4H, Phth). ^{13}C NMR (DMSO-d_6, 100 °C): δ 17.03, 19.51, 21.87, 24.17, 33.78, 34.85, 47.60, 51.91, 122.49 (2C), 125.51, 126.66, 127.28, 127.53, 130.88 (2C), 131.94, 134.03 (2C), 134.41, 167.66 (2C), 168.34. Anal. Calcd for $C_{23}H_{24}N_2O_3S$: C, 67.62; H, 5.92; N, 6.86; S, 7.85. Found: C, 67.50; H, 5.85; N, 7.13; S, 7.94.

4.7. (3*R*,2′*S*)-3,4-Dihydro-3-methyl-4-(*N*′-phthaloylleucyl)-2*H*-[1,4]benzothiazine [(*R*,*S*)-6a]

The mother liquid after recrystallization of amide (*S*,*S*)-**6a** (see above) was evaporated to dryness, and the residue was purified by flash column chromatography (eluent benzene–EtOAc) to give amide (*R*,*S*)-**6a** as fast eluting diastereoisomer. Yield 0.17 g (5.7%). Amorphous solid. $[\alpha]_D^{20}$ = −215 (c 0.67, $CHCl_3$). De 94.6%; HPLC (Phenomenex Luna C18; MeCN–H_2O 9:1): τ 6.2 min. ^{1}H NMR (DMSO-d_6, 100 °C): δ 0.85 (d, 3H, Me-3, J = 6.6 Hz), 0.91 (d, 3H, Me-4′, J = 6.6 Hz,), 0.92 (d, 3H, Me-4′, J = 6.6 Hz,), 1.44 (m, 1H, H-4′), 1.79 (ddd, 1H, H-3′B, J = 14.1, 9.0, 5.2 Hz), 2.05 (ddd, 1H, H-3′A, J = 14.1, 8.5, 5.3 Hz), 2.69 (dd, 1H, H-2B, J = 12.0, 4.0 Hz), 3.30 (dd, 1H, H-2A, J = 12.0, 5.9 Hz), 5.11 (qdd, 1H, H-3, J = 6.6, 5.9, 4.0 Hz), 5.13 (dd, 1H, H-2′, J = 9.0, 5.3 Hz), 6.71 (dd, 1H, H-8, J = 7.8, 1.5 Hz), 6.88 (td, 1H, H-6, J = 7.7, 1.5 Hz), 7.04 (td, 1H, H-7, J = 7.7, 1.5 Hz), 7.25 (dd, 1H, H-5, J = 7.9, 1.5 Hz), 7.62 (m, 2H, Phth), 7.73 (m, 2H, Phth). ^{13}C NMR (DMSO-d_6, 100 °C): δ 16.43, 21.38, 22.33, 23.75, 33.58, 38.10, 45.43, 48.88, 122.13 (2C), 125.41, 125.52, 125.95, 126.44, 129.10, 130.47 (2C), 133.52, 133.56 (2C), 165.35 (2C), 167.28. Anal. Calcd for $C_{23}H_{24}N_2O_3S$: C, 67.62; H, 5.92; N, 6.86; S, 7.85. Found: C, 67.77; H, 6.05; N, 6.60; S, 7.66.

4.8. (3*S*,2′*S*)-3,4-Dihydro-3-phenyl-4-(*N*′-phthaloylleucyl)-2*H*-[1,4]benzothiazine (*S*,*S*)-6b

A solution of acyl chloride **2** (0.44 g, 1.57 mmol) in MeCN (16 mL) was added to a solution of amine **4b** (0.71 g, 3.14 mmol) in MeCN (16 mL) at +20 °C. The reaction mixture was kept at +20 °C for 72 h, then diluted with EtOAc (25 mL) and successively washed with 5% aqueous $NaHCO_3$ (2 × 25 mL) and water (2 × 25 mL), dried over Na_2SO_4, and evaporated. The residue was subjected to flash column chromatography (10–30% EtOAc in hexane) to separate crude amide (*S*,*S*)-**6b** which was then further purified by recrystallization from hexane–EtOAc. Yield 0.30 g (41%). Colorless powder, mp 184–185 °C (hexane–EtOAc). $[\alpha]_D^{20}$ = +476 (c 1.0, $CHCl_3$). De >99%; HPLC (Phenomenex Luna C18; MeCN–H_2O 7:3): τ 26.6 min. ^{1}H NMR (DMSO-d_6, 100 °C): δ 0.31 (d, 3H, Me-4′, J = 6.6 Hz), 0.63 (d, 3H, Me-4′, J = 6.7 Hz), 0.99 (ddd, 1H, H-3′B, J = 13.8, 9.9, 3.5 Hz), 1.22–1.32 (m, 1H, H-4′), 2.60 (ddd, 1H, H-3′A, J = 13.8, 12.0, 3.9 Hz), 3.09 (dd, 1H, H-2B, J = 13.2, 8.0 Hz,),

3.70 (dd, 1H, H-2A, J = 13.2, 7.2 Hz), 5.45 (dd, 1H, H-2′, J = 12.0, 3.5 Hz), 5.95 (dd, 1H, H-3, J = 8.0, 7.2 Hz), 7.14–7.18 (m, 1H, Ph), 7.21–7.25 (m, 4H, Ph), 7.26–7.30 (m, 1H, H-7), 7.34–7.38 (m, 1H, H-6), 7.46 (dd, 1H, H-8, J = 7.7, 1.5 Hz), 7.60 (d, 1H, H-5, J = 7.5 Hz), 7.83–7.87 (m, 4H, Phth). ^{13}C NMR (DMSO-d_6, 100 °C): δ 19.49, 21.86, 24.19, 33.84, 35.43, 51.96, 58.43, 122.51 (2C), 125.71 (2C), 126.30, 126.58, 126.66, 127.48, 127.76 (2C), 128.47, 130.85 (2C), 133.65, 134.04 (2C), 136.38, 139.18, 167.66 (2C), 169.07. Anal. Calcd for $C_{28}H_{26}N_2O_3S$: C, 71.46; H, 5.57; N, 5.95; S, 6.81. Found: C, 71.30; H, 5.64; N, 5.81; S, 6.81.

4.9. 3,4-Dihydro-3-phenyl-4-(*N*′-phthaloyl-(*S*)-leucyl)-2*H*-[1,4]benzothiazine 6b (diastereomeric mixture)

The mother liquor, after recrystallization of amide (*S*,*S*)-**6b** (see above), was evaporated to dryness, and the residue was purified by flash column chromatography (eluent hexane–EtOAc 9:1). Yield 0.17 g (23%). Amorphous yellowish solid. *R*,*S*/*S*,*S* 65:35; HPLC (Phenomenex Luna C18; MeCN–H_2O 7:3): $\tau_{(R,S)\text{-}\mathbf{6b}}$ 15.7 min, $\tau_{(S,S)\text{-}\mathbf{6b}}$ 26.6 min. ^{1}H NMR (DMSO-d_6, 100 °C): δ 0.31 (d, 1.05H, Me-4′ (*S*,*S*), J = 6.6 Hz), 0.63 (d, 1.05H, Me-4′ (*S*,*S*), J = 6.7 Hz), 0.92 (d, 1.95H, Me-4′ (*R*,*S*), J = 6.6 Hz), 0.99 (ddd, 0.35H, H-3′B (*S*,*S*), J = 13.8, 9.9, 3.5 Hz), 1.22–1.32 (m, 0.35H, H-4′ (*S*,*S*)), 1.41–1.49 (m, 0.65H, H-4′ (*R*,*S*)), 1.84 (ddd, 0.65H, H-3′B (*R*,*S*), J = 14.1, 9.2, 5.1 Hz), 2.07 (ddd, 0.65H, H-3′A (*R*,*S*), J = 14.1, 8.7, 5.2 Hz), 2.60 (ddd, 0.35H, H-3′A (*S*,*S*), J = 13.8, 12.0, 3.9 Hz), 3.07–3.13 (m, 1H, H-2B), 3.58 (dd, 0.65H, H-2A (*R*,*S*), J = 12.9, 6.5 Hz), 3.70 (dd, 0.35H, H-2A (*S*,*S*), J = 13.2, 7.2 Hz), 5.25 (dd, 0.65H, H-2′ (*R*,*S*), J = 9.2, 5.1 Hz), 5.45 (dd, 0.35H, H-2′ (*S*,*S*), J = 12.0, 3.5 Hz), 5.95–6.00 (m, 1H, H-3), 6.68 (dd, 0.65H, H-8 (*R*,*S*), J = 7.8, 1.3 Hz), 6.83 (ddd, 0.65H, H-6 (*R*,*S*), J = 7.6, 7.6, 1.3 Hz), 7.02–7.09 (m, 1.3H, H-7 (*R*,*S*) and Ph (*R*,*S*)), 7.12–7.17 (m, 1.65H, Ph), 7.20–7.25 (m, 2.7H, Ph), 7.26–7.44 (m, 1.35H, H-5 (*R*,*S*), H-6 (*S*,*S*) and H-7 (*S*,*S*)), 7.46 (dd, 0.35H, H-8 (*S*,*S*), J = 7.7, 1.5 Hz), 7.59–7.63 (m, 1.65H, H-5 (*S*,*S*) and Phth (*R*,*S*)), 7.70–7.74 (m, 1.3H, Phth (*R*,*S*)), 7.83–7.87 (m, 1.4H, Phth (*S*,*S*)); Anal. Calcd for $C_{28}H_{26}N_2O_3S$: C, 71.46; H, 5.57; N, 5.95; S, 6.81. Found: C, 71.38; H, 5.69; N, 5.93; S, 6.80.

4.10. Diastereoisomers of 3,4-dihydro-3-methyl-4-(*N*′-tosylprolyl)-2*H*-[1,4]benzothiazine 7

A solution of *N*-tosyl-(*S*)-prolyl chloride **3** (2.55 g, 8.87 mmol) in toluene (85 mL) was added to a solution of amine **4a** (2.93 g, 17.74 mmol) in toluene (90 mL) at +20 °C. The reaction mixture was kept at +20 °C for 24 h, then the organic solution was successively washed with 4 M HCl (3 × 70 mL), saturated NaCl (4 × 100 mL), 5% $NaHCO_3$ (2 × 100 mL), water (2 × 100 mL), dried over $MgSO_4$, and evaporated. Amides (*S*,*S*)-**7** (fast eluting diastereoisomer) and (*R*,*S*)-**7** (slow eluting diastereoisomer) were isolated by flash column chromatography using a hexane–EtOAc mixture as an eluent. The analytical data for amides (*S*,*S*)-**7** and (*R*,*S*)-**7** were published previously.[5g]

4.11. (3*S*)-3,4-Dihydro-3-methyl-2*H*-[1,4]benzothiazine [(*S*)-4a]

Method A: A solution of amide (*S*,*S*)-**5a** (0.276 g, 0.73 mmol) in a mixture of AcOH (5 mL) and concentrated HCl (5 mL) was heated at 92–96 °C for 10 h, then concentrated under reduced pressure to half-volume and poured into water (50 mL). The precipitate was filtered off and washed with water (2 mL). The combined filtrate was alkalized with Na_2CO_3 to pH 8–9 and then extracted with benzene (3 × 3 mL). The organic layers were washed with water (2 × 5 mL), dried over $MgSO_4$, and evaporated. The residue was purified by flash column chromatography on silica gel using hexane–benzene 3:7 mixture as an eluent. Yield 0.09 g (75%), colorless oil.

Method B: A solution of amide (*S*,*S*)-**6a** (1.30 g, 3.21 mmol) in a mixture of AcOH (12 mL) and concentrated HCl (12 mL) was heated at 90–92 °C for 16 h, then concentrated under reduced pressure to a half-volume and poured into water (100 mL). The resulting mixture was alkalized with Na_2CO_3 and extracted with benzene (3 × 25 mL). The organic layers were washed with water (2 × 25 mL), dried over $MgSO_4$, and evaporated. The residue was purified by flash column chromatography on silica gel using hexane–benzene 3:7 mixture as an eluent. Yield 0.45 g (85%). Colorless oil. $[\alpha]_D^{20}$ = −79.0 (*c* 1.2, $CHCl_3$). Ee 99.4%; HPLC (Chiralcel OD-H; hexane–*i*PrOH–MeOH 100:1.5:1.5): τ 13.8 min. ^{1}H NMR (DMSO-d_6): δ 1.21 (d, 3H, Me-3, J = 6.3 Hz), 2.67 (dd, 1H, H-2B, J = 12.3, 7.9 Hz), 2.90 (ddd, 1H, H-2A, J = 12.3, 2.8, 1.0 Hz), 3.54 (dqdd, 1H, H-3, J = 7.9, 6.3, 2.8, 1.7 Hz), 5.91 (s, 1H, NH), 6.44 (ddd, 1H, H-7, J = 7.7, 7.2, 1.3 Hz), 6.52 (dd, 1H, H-5, J = 8.1, 1.3 Hz), 6.80 (ddd, 1H, H-6, J = 8.1, 7.2, 1.4 Hz), 6.84 (dd, 1H, H-8, J = 7.7, 1.4 Hz). ^{13}C NMR (DMSO-d_6): δ 21.83 (Me), 31.13 (C-2), 46.03 (C-3), 113.48 (C-8a), 114.68 (C-5), 116.14 (C-7), 125.18 and 126.69 (C-6 and C-8), 142.60 (C-4a). HRMS (ESI) calcd for $C_9H_{12}NS$ $[M+H]^+$: 166.0685; found: 166.0686.

4.12. (3*R*)-3,4-Dihydro-3-methyl-2*H*-[1,4]benzothiazine (*R*)-4a

A solution of amide (*R*,*S*)-**7** (1.06 g, 2.54 mmol) in a mixture of AcOH (10 mL) and concentrated HCl (10 mL) was heated at 95–100 °C for 28 h, then concentrated under reduced pressure to a half-volume and poured into water (100 mL). The resulting mixture was alkalized with Na_2CO_3 and extracted with benzene (3 × 15 mL). The organic layers were washed with water (2 × 20 mL), dried over $MgSO_4$, and evaporated. The residue was purified by flash column chromatography on silica gel using hexane–benzene 3:7 mixture as an eluent. Yield 0.30 g (70%). Colorless oil. $[\alpha]_D^{20}$ = +78.7 (*c* 1.2, $CHCl_3$). Ee 99.2%; HPLC (Chiralcel OD-H; hexane–*i*PrOH–MeOH 100:1.5:1.5): τ 12.6 min. ^{1}H and ^{13}C NMR spectra were identical to those of (*S*)-**4a**. HRMS (ESI) calcd for $C_9H_{12}NS$ $[M+H]^+$: 166.0685; found: 166.0686.

4.13. (3*S*)-3,4-Dihydro-3-phenyl-2*H*-[1,4]benzothiazine (*S*)-4b

The title compound was obtained as described for amine (*S*)-**4a** (Method A) starting from amide (*S*,*S*)-**5b** (97 mg, 0.22 mmol), AcOH (3 mL), and concentrated HCl (3 mL). Yield 30.6 mg (61%). Yellowish oil. $[\alpha]_D^{20}$ = +55.9 (*c* 1.0, $CHCl_3$). Ee 92.6%, HPLC (Chiralcel OD-H; hexane–*i*PrOH 5:1): τ 15.0 min. Anal. Calcd for $C_{14}H_{13}NS$: C, 73.97; H, 5.76; N, 6.16; S, 14.11. Found: C, 73.79; H, 5.94; N, 5.87; S, 14.22. NMR spectra were identical to those of racemic compound **4b**.

4.14. Oxidation of racemic 3-substituted 3,4-dihydro-2*H*-[1,4]benzothiazines

30% aqueous H_2O_2 solution (2.83 mL, 24.8 mmol) was added to a solution of amine **4a** or **4b** (6.2 mmol) in AcOH (18 mL). The reaction mixture was refluxed for 40 min, then cooled, concentrated under reduced pressure to a volume of 7 mL and poured into water (100 mL). The solution was alkalized with Na_2CO_3 and extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were washed with water (2 × 20 mL), dried over $MgSO_4$, and evaporated. The product was purified by flash column chromatography using a benzene–EtOAc mixture as an eluent.

4.14.1. (3*RS*)-3,4-Dihydro-3-methyl-2*H*-[1,4]benzothiazine-1,1-dioxide (*RS*)-9a

Yield 0.22 g (18%). Colorless solid, mp 159 °C. HPLC (Chiralcel OD-H; hexane–*i*PrOH 5:1): $\tau_{(R)\text{-}\mathbf{9a}}$ 19.1 min, $\tau_{(S)\text{-}\mathbf{9a}}$ 22.5 min. ^{1}H NMR (DMSO-d_6): δ 1.34 (d, 3H, Me-3, J = 6.5 Hz), 3.12 (dd, 1H, H-2B, J = 13.4, 12.6 Hz), 3.46 (ddd, 1H, H-2A, J = 13.4, 2.4, 1.2 Hz), 3.90 (dqd, 1H, H-3, J = 12.6, 6.5, 2.4 Hz), 6.68 (ddd, 1H, H-7, J = 8.0, 7.0, 1.0 Hz), 6.78 (dd, 1H, H-5, J = 8.5, 1.0 Hz), 6.92 (s, 1H,

NH), 7.27 (ddd, 1H, H-6, J = 8.5, 7.0, 1.5 Hz), 7.48 (dd, 1H, H-8, J = 8.0, 1.5 Hz). ^{13}C NMR (DMSO-d_6): δ 20.16 (Me), 46.53 (C-3), 53.30 (C-2), 115.73 and 115.82 (C-6 and C-7), 120.58 (C-8a), 123.04 (C-8), 133.23 (C-6), 144.56 (C-4a). Anal. Calcd for $C_9H_{11}NO_2S$: C, 54.80; H, 5.62; N, 7.10; S, 16.26. Found: C, 54.81; H, 5.46; N, 6.97; S, 16.08.

4.14.2. (3*RS*)-3,4-Dihydro-3-phenyl-2*H*-[1,4]benzothiazine-1,1-dioxide (*RS*)-9b

Yield 0.39 g (24%). Colorless solid, mp 134 °C (lit. mp 184 °C,[15a] 184–186 °C[15b]). HPLC (Chiralcel OD-H, hexane–*i*PrOH 2:1): $\tau_{(R)\text{-}\mathbf{9b}}$ 9.3 min (*R*), $\tau_{(S)\text{-}\mathbf{9b}}$ 14.4 (*S*). ^{1}H NMR ($CDCl_3$, 25 °C): δ 3.31–3.34 (m, 1H, H-2B), 3.47–3.52 (m, 1H, H-2A), 4.51 (s, 1H, NH), 5.16 (dd, 1H, H-3, J = 12.7, 2.4 Hz), 6.68 (m, 1H, H-5), 6.88 (m, 1H, H-7), 7.33 (ddd, 1H, H-6, J = 7.3, 7.3, 1.3 Hz), 7.40–7.48 (m, 5H, Ph), 7.78 (dd, 1H, H-8, J = 8.0, 1.3 Hz). ^{13}C NMR ($CDCl_3$, 25 °C): δ 54.99, 56.11, 116.17, 118.39, 122.01, 124.07, 126.84 (2C), 129.37 (3C), 133.87, 138.84, 143.29. Anal. Calcd for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05; N, 5.40; S, 12.36. Found: C, 64.77; H, 4.92; N, 5.32; S, 12.56.

4.15. Oxidation of amides (*S*,*S*)-6a,b and (*R*,*S*)-7

30% aqueous H_2O_2 (0.6 mL, 5.3 mmol) was added to a solution of amide (*S*,*S*)-**6a**, (*S*,*S*)-**6b**, or ,(*R*,*S*)-**7** (1.54 mmol) in AcOH (3 mL). The reaction mixture was refluxed for 20 min, then cooled to room temperature, and poured into water (70 mL). The solution was neutralized with Na_2CO_3 and extracted with $CHCl_3$ (3 × 15 mL). Organic layers were washed with water (2 × 20 mL), dried over $MgSO_4$, and evaporated to give amides (*S*,*S*)-**8a**, (*S*,*S*)-**8b**, or (*R*,*S*)-**10**, respectively.

4.15.1. (3*S*,2′*S*)-3,4-Dihydro-3-methyl-4-(*N*′-phthaloylleucyl)-2*H*-[1,4]benzothiazine-1,1-dioxide (*S*,*S*)-8a

Yield 0.65 g (96%). Colorless foam. $[\alpha]_D^{20}$ = +415 (c 1.3, $CHCl_3$). ^{1}H NMR (DMSO-d_6, 100 °C): δ 0.32 (d, 3H, Me-4′, J = 6.6 Hz), 0.63 (d, 3H, Me-4′, J = 6.6 Hz), 1.17 (ddd, 1H, H-3′B,, J = 14.2, 9.8, 3.4 Hz), 1.18 (d, 3H, Me-3, J = 6.7 Hz), 1.26 (m, 1H, H-4′), 2.54 (ddd, 1H, H-3′A, J = 14.2, 12.0, 3.6 Hz), 3.20 (dd, 1H, H-2B, J = 14.6, 7.4 Hz), 4.04 (dd, 1H, H-2A, J = 14.5, 7.9 Hz), 5.09 (ddq, 1H, H-3, J = 7.9, 7.4, 6.7 Hz), 5.39 (dd, 1H, H-2′, J = 12.0, 3.4 Hz), 7.67 (td, 1H, H-7, J = 7.6, 1.0 Hz), 7.76 (dd, 1H, H-5, J = 8.0, 1.0 Hz), 7.85–7.89 (m, 5H, H-6 and Phth), 7.95 (dd, 1H, H-8, J = 7.7, 1.5 Hz). ^{13}C NMR (DMSO-d_6, 100 °C): δ 18.80, 19.50, 21.81, 24.14, 33.70, 48.38, 51.61, 57.05, 122.59 (2C), 124.20, 127.56, 127.79, 130.82 (2C), 133.87, 134.11 (2C), 134.41, 135.43, 167.56 (2C), 168.43. Anal. Calcd for $C_{23}H_{24}N_2O_5S$: C, 62.71; H, 5.49; N, 6.36; S, 7.28. Found: C, 62.80; H, 5.48; N, 6.42; S, 7.03.

4.15.2. (3*S*,2′*S*)-3,4-Dihydro-3-phenyl-4-(*N*′-phthaloylleucyl)-2*H*-[1,4]benzothiazine-1,1-dioxide (*S*,*S*)-8b

Obtained starting from amide (*S*,*S*)-**6b** (0.25 g, 0.53 mmol) as described above. Yield 0.248 g (93%). Colorless solid, mp 123–125 °C. $[\alpha]_D^{20}$ = +417 (c 0.64, $CHCl_3$). ^{1}H NMR (DMSO-d_6, 100 °C): δ 0.31 (d, 3H, Me-4′, J = 6.4 Hz), 0.63 (d, 3H, Me-4′, J = 6.5 Hz), 1.16–1.32 (m, 2H, H-3′B and H-4′), 2.57 (ddd, 1H, H-3′A, J = 14.2, 12.0, 3.5 Hz), 3.15 (dd, 1H, H-2B, J = 14.7, 9.2 Hz,), 4.41 (dd, 1H, H-2A, J = 14.7, 8.0 Hz), 5.43 (dd, 1H, H-2′, J = 12.0, 3.4 Hz), 6.03 (m, 1H, H-3), 7.19–7.23 (m, 3H, Ph), 7.25–7.28 (m, 2H, Ph), 7.69 (ddd, 1H, H-7, J = 7.7, 7.6, 1.0 Hz), 7.83–7.85 (m, 5H, H-5 and Phth), 7.91 (ddd, 1H, H-6, J = 7.8, 7.6, 1.4 Hz), 7.99 (dd, 1H, H-8, J = 7.7, 1.4 Hz). ^{13}C NMR (DMSO-d_6, 100 °C): δ 19.48, 21.79, 24.13, 33.59, 51.67, 55.64, 56.41, 122.59 (2C), 124.41, 125.70 (2C), 127.11, 127.67, 127.84, 128.01 (2C), 130.75 (2C), 134.10 (2C), 134.22, 134.73, 136.38, 138.61, 167.52 (2C), 169.02. Anal. Calcd for $C_{28}H_{26}N_2O_5S$: C, 66.91; H, 5.21; N, 5.57; S, 6.38. Found: C, 66.95; H, 5.44; N, 5.24; S, 6.30.

4.15.3. (3*R*,2′*S*)-3,4-Dihydro-3-methyl-4-(*N*′-tosylprolyl)-2*H*-[1,4]benzothiazine-1,1-dioxide (*R*,*S*)-10

Yield 0.54 g (78%) after flash column chromatography (eluent benzene–EtOAc). Yellowish solid, mp 182–184 °C (dec). $[\alpha]_D^{20}$ = −294 (c 1.1, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 100 °C): δ 1.30 (d, 3H, Me-3, J = 6.9 Hz), 1.64 (m, 1H, H-4′B), 1.98 (m, 1H, H-4′A), 2.08–2.13 (m, 2H, 2 × H-3′), 2.36 (s, 3H, Me-Tos), 3.30 (ddd, 1H, H-5′B, J = 9.8, 7.3, 6.6 Hz), 3.43 (ddd, 1H, H-5′A, J = 9.8, 7.2, 5.7 Hz), 3.45 (dd, 1H, H-2B, J = 14.1, 5.2 Hz), 3.96 (dd, 1H, H-2A, J = 14.1, 6.2 Hz), 4.38 (t, 1H, H-2′, J = 6.5 Hz), 5.28 (qdd, 1H, H-3, J = 6.9, 6.2, 5.2 Hz), 7.26 (d, 2H, H*m*-Tos, J = 8.4 Hz), 7.29 (dd, 1H, H-5, J = 7.9, 1.0 Hz), 7.40 (d, 2H, H*o*-Tos, J = 8.4 Hz), 7.57 (td, 1H, H-7, J = 7.7, 1.0 Hz), 7.65 (ddd, 1H, H-6, J = 7.9, 7.6, 1.6 Hz), 7.91 (dd, 1H, H-8, J = 7.9, 1.6 Hz). ^{13}C NMR (DMSO-d_6, 100 °C): δ 17.28, 20.25, 23.76, 30.62, 47.44, 48.49, 56.71, 57.38, 123.47, 126.34 (2C), 126.81, 127.09, 128.97 (2C), 132.51, 133.57, 134.48, 134.52, 142.67, 170.39. Anal. Calcd for $C_{21}H_{24}N_2O_5S_2$: C, 56.23; H, 5.39; N, 6.25; S, 14.30. Found: C, 56.36; H, 5.64; N, 6.28; S, 14.22.

4.16. (3*S*)-3,4-Dihydro-3-methyl-2*H*-[1,4]benzothiazine-1,1-dioxide (*S*)-9a

A solution of amide (*S*,*S*)-**8a** (0.575 g, 1.31 mmol) in MeOH (30 mL) was added to a solution of sodium methoxide (4.78 mmol) in MeOH (30 mL). The reaction mixture was stirred for 4 h at room temperature, and then poured into 0.5 N NaOH (200 mL). The resulting solution was extracted with $CHCl_3$ (3 × 25 mL). Organic layers were washed with water (3 × 50 mL), dried over $MgSO_4$, and evaporated to give sulfone (*S*)-**9a** (0.243 g, 94%) as a colorless solid, mp 144–146 °C. $[\alpha]_D^{20}$ = −177 (c 1.1, $CHCl_3$). Ee 99%; HPLC (Chiralcel OD-H; hexane–*i*PrOH 5:1): τ 22.5 min. ^{1}H and ^{13}C NMR spectra were identical to those of racemic amine (*RS*)-**9a**. HRMS (ESI) calcd for $C_9H_{12}NO_2S$ $[M+H]^+$: 198.0583; found: 198.0584.

4.17. (3*R*)-3,4-Dihydro-3-methyl-2*H*-[1,4]benzothiazine-1,1-dioxide (*R*)-9a

A solution of amide (*R*,*S*)-**10** (0.476 g, 1.06 mmol) in MeOH–CH_2Cl_2 5:1 mixture (25 mL) was added to a solution of sodium methoxide (3.56 mmol) in MeOH (25 mL). The reaction mixture was stirred for 4 h at room temperature, and then poured into 0.5 M NaOH (200 mL) and the resulting solution was extracted with $CHCl_3$ (3 × 25 mL). The organic layers were washed with water (3 × 50 mL), dried over $MgSO_4$, and evaporated. The residue was purified by flash column chromatography using benzene–EtOAc 8:2 mixture as an eluent. Yield 0.182 g (87%). Colorless solid, mp 143–146 °C. $[\alpha]_D^{20}$ = +170 (c 1.0, $CHCl_3$). Ee 97%; HPLC (Chiralcel OD-H; hexane–*i*PrOH 5:1): τ 19.1 min. ^{1}H and ^{13}C NMR spectra were identical to those of racemic amine (*RS*)-**9a**. Anal. Calcd for $C_9H_{11}NO_2S$: C, 54.80; H, 5.62; N, 7.10; S, 16.26. Found: C, 55.00; H, 5.46; N, 6.89; S, 16.30.

4.18. (3*R*)-3,4-Dihydro-3-phenyl-2*H*-[1,4]benzothiazine-1,1-dioxide (*R*)-9b

Obtained starting from amide (*S*,*S*)-**8b** (0.20 g, 0.40 mmol) in a way similar to that described for compound (*S*)-**9a**. Yield 0.080 g (77%). Colorless solid, mp 169–172 °C (subl.). $[\alpha]_D^{20}$ = −54.8 (c 0.6, $CHCl_3$). Ee 82%; HPLC (Chiralcel OD-H, hexane–*i*PrOH 2:1): $\tau_{(R)\text{-}\mathbf{9b}}$ 9.4 min, $\tau_{(S)\text{-}\mathbf{9b}}$ 14.5 min. NMR spectra were identical to those of racemic amine (*RS*)-**9b**. Anal. Calcd for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05; N, 5.40; S, 12.36. Found: C, 64.46; H, 5.23; N, 5.39; S, 12.43.

Acknowledgments

The authors thank Dr. Pavel A. Slepukhin for performing X-ray diffraction. The work was financially supported by the Russian Scientific Foundation (grant 14-13-01077) in the part of studies on 3,4-dihydro-3-phenyl-2*H*-[1,4]benzothiazine and its derivatives, and the Russian Foundation for Basic Research (grant 13-03-00674) in the part of studies on 3,4-dihydro-3-methyl-2*H*-[1,4]benzothiazine and its derivatives.

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