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Articles

Conversion of the Laboratory Synthetic Route of the *N*-Aryl-2-benzothiazolamine R116010 to a Manufacturing Method

Wim Aelterman,* Yolande Lang, Bert Willemsens, Ivan Vervest, Stef Leurs, and Fons De Knaep

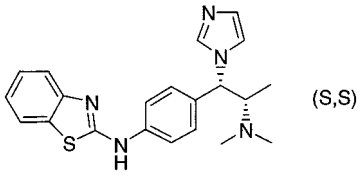
Chemical Process Research Department, Janssen Pharmaceutica, Turnhoutseweg 30, 2340 Beerse, Belgium

Abstract:

A facile and large-scale preparation of the antitumor agent R116010 has been developed. The new synthetic process requires four steps: (i) Friedel−Crafts reaction of *N*-phenyl-2-benzothiazolamine with 2-chloropropionyl chloride, (ii) conversion of the α-chloroketone into the corresponding α-(dimethylamino)ketone and resolution of the latter, (iii) reduction of the chiral aminoketone with resultant formation of the *β*-amino alcohol and finally (iv) conversion of the amino alcohol into the *β*-aminoimidazole R116010. The key strategic improvement is the crystallization-induced diastereomeric dynamic resolution of the aminoketone, leading to the chiral ketone in 90% yield and 90% enantiomeric purity. This new process improves the overall yield from 0.26 to 18.8% without tedious chromatographic separations and hazardous reaction conditions.

Introduction

All-*trans*-retinoic acid (RA), the biologically most active metabolite of vitamin A, plays a major role in cellular differentiation and proliferation of epithelial tissues.[1,2] Differentiating agents redirect cells towards their normal phenotype and therefore may reverse or suppress evolving malignant lesions or prevent cancer invasion. However, the therapeutic effects of RA are undermined by its rapid in vivo catabolism by cytochrome P450-dependent enzymes. Here, we will describe the synthesis and chemical development of R116010, a potent and selective inhibitor of the all-*trans*-retinoic acid metabolism (RAMBA).[3,4] This compound is an almost pure 4-hydroxylase inhibitor, lacking inhibition of other CYP450-mediated enzymes. It reduces tumour growth in breast and prostate cancer experimental models at dosages 10−20 times lower than liarozole fumarate (Liazal).[5−10] Given the results obtained in animal models, it seems R116010 may also have a cytotoxic/cytostatic potential.



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The Medicinal Chemistry Route

The medicinal chemistry route is outlined in Scheme 1. This route, which was successfully used for the delivery of early toxicology and clinical batches, could not be followed for the synthesis of larger quantities.

The major problems were encountered in the latter steps of the synthesis. For the preparation of the 2-aminobenzothiazole moiety, via a two-step sequence, from the arylamine **4**, toxic and highly flammable carbon disulfide was used in the first step, and DMSO was the solvent of choice for the second step. Moreover, methanethiol (ODOUR!) was evolved during this conversion and the benzothiazole compound **6** was only obtained in a poor yield (∼15%). Finally, to separate R116010 **1** (*S*,*S*) from its stereoisomers, two chromatographic purification steps, one of them on a chiral column, were necessary.

Route Used for the First Pilot-Plant Batch

Since the major problem of the medicinal chemistry route was the late-stage formation of the benzothiazole ring from the arylamine **4**, it was decided to start from a benzothiazole skeleton and introduce the (2-(dimethylamino)-1-imidazolyl)-propyl moiety (Scheme 2). *N*-phenyl-2-benzothiazolamine **14** was obtained via oxidative ring closure of 2,2′-diphenylthiourea **8** with bromine and 48% aqueous hydrobromic acid.[11] The aminobenzothiazole thus obtained was subsequently reacted with 2-chloropropionyl chloride, yielding the

* To whom correspondence should be addressed. Fax: 32 14605755. E-mail: waelterm@janbe.jnj.com.

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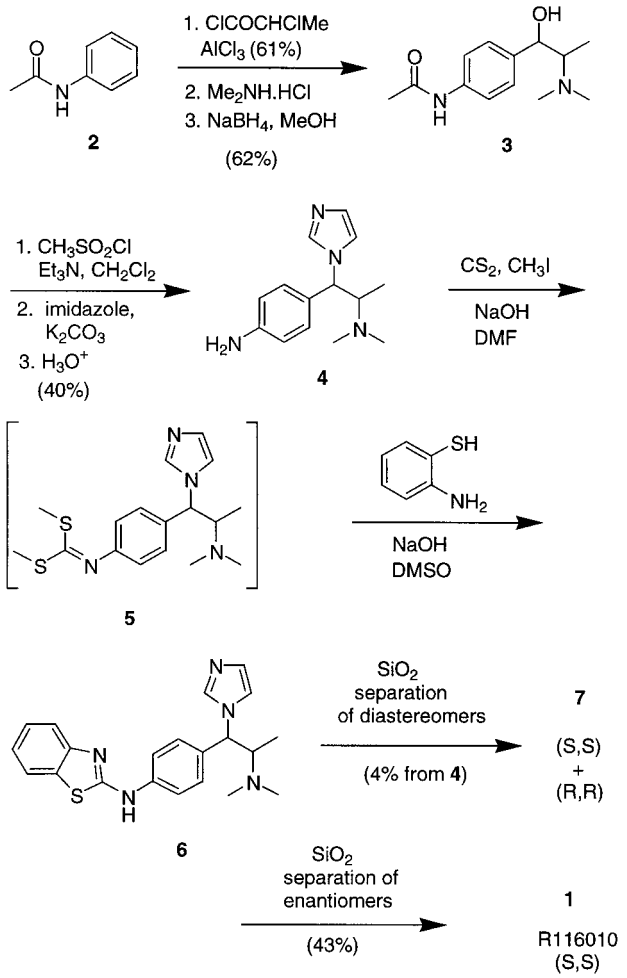
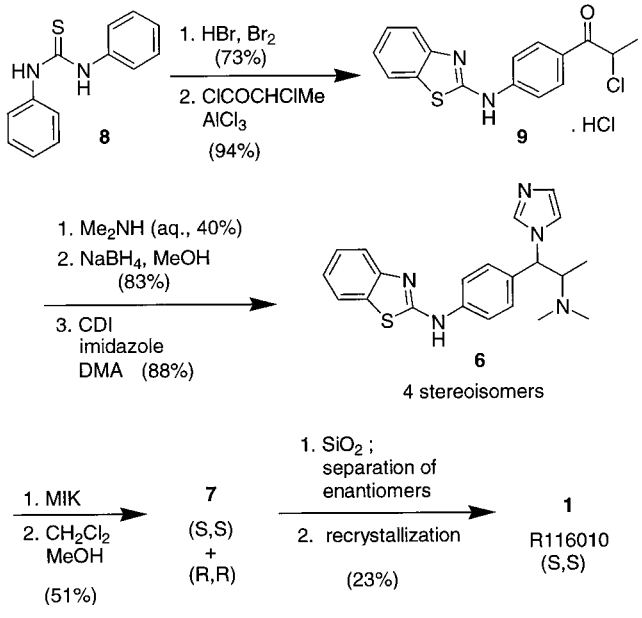
Scheme 1. **Medicinal chemistry route**

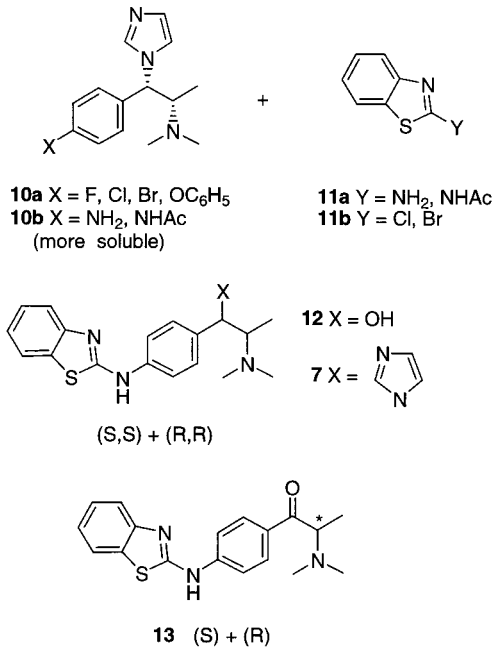


Scheme 2. **Original pilot-plant route**



α-chloroketone **9** as a hydrochloride salt in excellent yield. Conversion of ketone **9** to the final compound **1** was accomplished in an analogous manner as the medicinal chemistry route, that is, reaction with dimethylamine, sodium borohydride reduction, and conversion to the imidazole by reaction with 1,1′-carbonyldiimidazole in the presence of imidazole. The "*syn*" (*S,S* and *R,R*) and "*anti*" (*R,S* and *S,R*) stereoisomers of the β-aminoimidazole **6** could be separated by two subsequent recrystallizations, thus eliminating one of the chromatographic separations. The major problem associated with this improved method now became the separation of the enantiomers of **7** (*S,S* and *R,R*). Due to the low solubility of compound **7** in solvent systems typically used for chiral chromatography (e.g. hexane/ethanol) more than 4000 L of solvent was necessary to obtain 2 kg of enantiomerically pure drug substance **1**.

Scheme 3. **Alternative routes**



Alternative Routes

The alternative pathways investigated used two main strategies. First, a more convergent approach was tried by the coupling of optically pure [2-(dimethylamino)-1-(1H-imidazol-1-yl)propyl]aryl derivatives **10** with 2-substituted aminobenzothiazoles **11** (Scheme 3). This approach also offers more alternatives to synthesize the chiral segment of the molecule, for example from ephedrine or by classical resolution, than when the benzothiazole moiety is already attached, because of the low solubility of the latter. On one hand, coupling reactions between 2-aminobenzothiazoles **11a** and aryl derivatives **10a** bearing a leaving group and, on the other hand, between 2-halobenzothiazoles **11b** and para-substituted aromatic aminoderivatives **10b** were investigated. However, the use of Goldberg,[12] basic or Pd-catalyzed[13,14] conditions did not give satisfactory results. This was mainly due to the instability of the substituted arylamines **10b** at higher temperatures and the low nucleophilicity of the arylamines **10b** and 2-aminobenzothiazoles **11a**.

In a second approach, attempts to obtain the desired enantiomers via a classical resolution using chiral acids were

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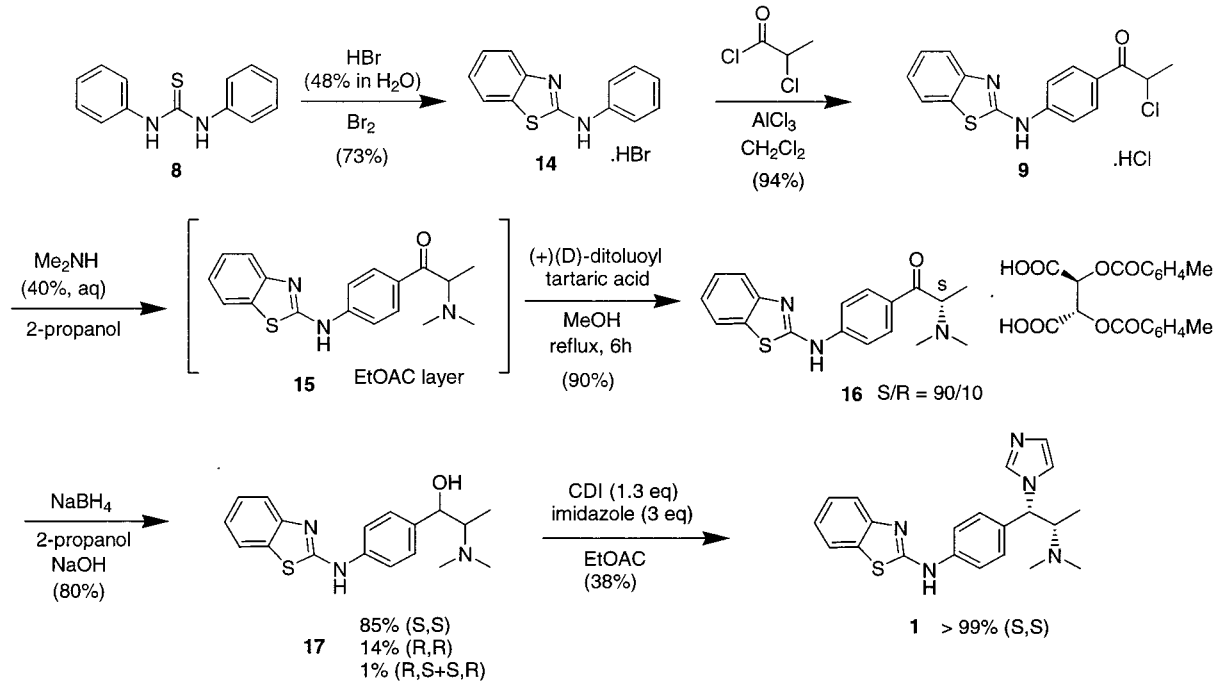
Scheme 4. **Commercial process**



made. Although a wide variety of acids were screened, attempts to resolve the (*S*,*S*) and (*R*,*R*) enantiomers **7** of the drug substance by diastereomeric salt formation remained unsuccessful. The corresponding β-amino alcohols **12** also could not be separated in this way. Finally, it was decided to go back one step further in the synthesis and to try the resolution of the aminoketone **13**. By screening 22 chiral acids in numerous solvents, we found that it was possible to resolve the aminoketone **13** with ditoluoyltartaric acid in methanol. Moreover, after fine-tuning of the reaction conditions, the desired diastereomeric salt could be obtained in 90% yield (diastereomeric ratio 90/10) via a crystallization-induced diastereomeric resolution.[15−18] To our knowledge a crystallisation-based resolution of an α-tertiary amino ketone has not been reported before. The two enantiomers of the aminoketone **13** can equilibrate through the enol form. With literature analogies[19] showing that high stereocontrol is possible in the consequent reduction of the aminoketone and having established this very efficient and high yielding resolution procedure, prompted us to use this reaction sequence in the development of the final route towards R116010 **1**.

Commercial Process

The α-chlorinated propiophenone derivative **9**, isolated as its hydrochloric acid salt, was synthesized in two steps from diphenylthiourea **8** as previously described (Scheme 4). An excess of aluminium(III) chloride was used for the Friedel−Crafts reaction of *N*-phenyl-2-benzothiazolamine **14** with 2-chloropropionyl chloride. Possibilities to replace dichloromethane as solvent and to use a more environmentally friendly Friedel−Crafts catalyst are presently under investigation. The aminoketone **13** is a very viscous, foaming oil, even after further purification, and therefore very difficult to isolate as a free base. This problem was circumvented using an ethyl acetate solution of **13** directly in the next step. At this stage, excess dimethylamine and its hydrochloric acid salt could also be removed by washing the ethyl acetate layer with water. In the next step, the highest diastereomeric excess was achieved by using one equivalent of (+)-D-ditoluoyltartaric acid in methanol under reflux for 6 h. The diastereomeric salt **16** thus obtained was isolated in 90% yield, starting from the α-chloroketone **9**, and with 80% enantiomeric excess.

Subsequently, the diastereomeric salt **16** was reduced with an alkaline solution of 1 equiv of sodium borohydride in 2-propanol. After addition of water the *syn* diastereomers **17** (1*S*,2*S*) and (1*R*,2*R*) precipitated selectively from the reaction mixture, together with only a small amount (∼1%) of the *anti* epimers. It is known from the literature that erythro-rich products are obtained in the reduction of ketones having a functional group at α-position to the carbonyl group.[19] As derived from the percentages of the different stereoisomers, it would appear that less than 5% of base-promoted epimerisation occurred in this step.

In the final step, the amino alcohol **17** was converted to the corresponding imidazole derivative by reaction with 1,1′-carbonyldiimidazole and imidazole. An excess of imidazole was necessary to reduce formation of a side product arising from the competitive attack of the exocyclic benzothiazole amino atom, instead of imidazole, on the intermediate

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imidazolide. The use of ethyl acetate for this final step gave major advantages. It not only offers the possibility to remove excess imidazole by washing with water, but also the desired enantiomer **1** crystallized selectively from ethyl acetate after seeding at 70 °C. The reaction mixture contained approximately 65% of the *syn* (*S*,*S* and *R*,*R*) β-imidazol-1-ylamine **7** and 28% of the *anti* (*R*,*S* and *S*,*R*) products, suggesting that the reaction proceeded with 30% inversion of configuration at C-2 (via a second-order nucleophilic substitution) and 70% retention due to the neighbouring group effect of the dimethylamino group.[20−22] Conversion of the amino alcohol **17** to the corresponding β-mesyloxy or β-chloro amine and treatment of the latter with imidazole resulted to a greater extent in the formation of the undesired *anti* products. Although currently the yield of the last reaction step is somewhat disappointing, the overall yield of the commercial route is 18.8%, a significant improvement on the original 0.26% yield of the discovery route. Taking into acount the low costs for raw materials and reagents and the low proposed dosage (1 mg a day) for R116010, this route seems to be highly suitable for the commercial production of the drug substance.

In conclusion, a safe and robust commercial route to R116010 **1** was developed; the number of isolated steps was reduced from 9 to 5, the overall yield improved from 0.26 to 18.8%, and all three chromatographic steps were eliminated.

Experimental Section

General. ^{1}H NMR spectra were measured on a Bruker AMX400 spectrometer in $CDCl_3$ or DMSO-d_6. The chemical purities were determined by HPLC quantitative and qualitative methods with a HP 1090 series II instrument using a Hypersil BDS−C18 column, 3 μm particle size (4.0 mm × 100 mm) and UV detection at 240 nm. Optical purities were determined by chiral HPLC and capillary electrophoresis. Enantiomeric purity of compound **16** was determined by chiral HPLC on a HP 1090 series using a Daicel chiralpak AD column and a mixture of hexanes−ethanol (90:10 + 1 mL TEA) as the mobile phase (isocratic flow of 1 mL/min and UV detector at 220 nm). The stereoisomers of compound **17** were analyzed by capillary electrophoresis on a TSP instrument (capillary: fused silica, 50 μm (i.d.) × 375 μm (o.d.) × 40 cm (34 cm effective separation length), detection: 200 nm; injection: 2.5 s; run voltage: 15 kV; run time: 20 min; polarity: positive; temperature: 15 °C; separation electrolyte: 100 mM phosphate, pH 2.5 with triethylamine, 10 mM heptakis (2,4,6-tri-*O*-methyl)-β-cyclodextrin). Enantiomeric purity of compound **1** was determined by capillary electrophoresis on a Beckman P/ACE 5500 series instrument (capillary: fused silica, 75 μm (i.d.) × 375 μm (o.d.) × 57 cm (50 cm effective separation length), detection: 200 nm; injection: 1 s; run voltage: 15 kV; run time: 35 min; polarity: positive; temperature: 20 °C; separation electrolyte: 100 mM phosphate, pH 2 with triethylamine, 5 mM heptakis (2,6-di-*O*-methyl)-β-cyclodextrin.

Compound **8** was supplied by Acros Chemicals (bulk).

***N*-Phenyl-2-benzothiazolamine Monohydrobromide (14).** A mixture of *N*,*N*′-diphenyl-thiourea (**8**) (36.5 kg, 160 mol) and an aqueous solution of 48% hydrobromic acid (478.4 kg, 2838 mol) was cooled to 0 °C. Bromine (28.45 kg, 178 mol) was added over 90 min, the batch temperature being maintained below 5 °C by cooling. The heterogeneous mixture was stirred at 0−5 °C for 17 h after which CH_2Cl_2 (368 L) was added. The mixture was warmed to 30 °C, and the layers were separated. The aqueous layer was again extracted with CH_2Cl_2 (368 L). The combined organic layers were concentrated by atmospheric pressure distillation to a residual volume of 150 L. 4-Methyl-2-pentanone (480 L) was added and the mixture was further distilled until a batch temperature of 115 °C was reached. The mixture was cooled to room temperature, and the formed precipitate was collected on a centrifuge and rinsed with 4-methyl-2-pentanone (16 L). The product was dried under reduced pressure to give **14** as off-white solid (35.8 kg, 73%)

HPLC: 99.63%. ^{1}H NMR: (DMSO-d_6, 400 MHz) δ 7.07 (t, 1H, J = 7.5 Hz), 7.17 (dt, 1H, J = 7.5, 0.88 Hz), 7.33 (t, 1H, J = 8.6 Hz), 7.38 (t, 2H, J = 8.6 Hz), 7.59 (d, 1H, J = 7.5 Hz), 7.77 (dd, 2H, J = 8.6, 0.88 Hz), 7.81 (dd, 1H, J = 7.5, 0.88 Hz).

1-[4-(2-Benzothiazolylamino)phenyl]-2-chloro-1-propanone Hydrochloride (9). To a suspension of **14** (70 kg, 227.9 mol) in dichloromethane (500 L), aluminum chloride (91.2 kg, 683.1 mol) was added at 0 °C. The reaction mixture was stirred for 0.5 h, during which time the batch temperature was allowed to rise to 23 °C. 2-Chloropropionyl chloride (29 kg, 228 mol) was added over a period of 1 h maintaining the temperature below 30 °C. The reaction mixture was stirred for 18 h at room temperature and then was slowly added to 2 N aqueous hydrochloric acid (250 L). The solvent was removed by distillation, and water (600 L) was added. The precipitate was filtered, washed with water (3 × 20 L), and dried to yield 75.2 kg of product **9** (94%) as a light yellow solid.

HPLC: 86.3%; ^{1}H NMR: (DMSO-d_6, 400 MHz) δ 1.64 (d, 3H, J = 6.6 Hz), 5.76 (q, 1H, J = 6.6 Hz), 7.23 (t, 1H, J = 7.5 Hz), 7.39 (t, 1H, J = 7.5 Hz), 7.71 (d, 1H, J = 7.5 Hz), 7.88 (d, 1H, J = 7.5 Hz), 7.88 (d, 2H, J = 8.9 Hz), 8.09 (d, 2H, J = 8.9 Hz).

1-[4-(2-Benzothiazolylamino)phenyl]-2-(dimethylamino)-1-propanone (+)(D)-Ditoluoyl Tartaric Acid Salt (16). To a suspension of **9** (176 g, 0.5 mol) in 2-propanol (1 L) was added dropwise an aqueous solution of dimethylamine (40%) (0.23 L, 2 mol) at room temperature. The mixture was heated at 50 °C for 16 h. After cooling to room temperature, ethyl acetate (1 L) and water (1 L) were added, the mixture was stirred for 10 min, and the layers were separated. The water layer was again extracted with ethyl acetate (400 mL). The organic phases were combined, and a solution of (+)(D)-ditoluoyl tartaric acid (212.3 g, 0.55 mol) in methanol (0.96 L) was added dropwise at 50 °C. Crystallisation occurred when three-quarters of the methanolic solution was added.

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The suspension was kept at 50 °C for 7 h, stirred at room-temperature overnight, and filtered. The solid was washed with methanol (2 × 100 mL) and water (2 × 100 mL) and dried to give (*S*)-**16** (284 g, 92%) as a white solid.

Ee (chiral HPLC): 80.2%; HPLC: 98.5%; ^{1}H NMR: (DMSO-d_6, 400 MHz) δ 1.33 (d, 3H, J = 6.6 Hz).,), 2.37 (s, 6H), 2.57 (s, 6H), 4.79 (q, 1H, J = 6.6 Hz), 5.73 (s, 2H), 7.23 (t, 1H, J = 7.5 Hz), 7.39 (t, 1H, J = 7.5 Hz), 7.70 (d, 1H, J = 7.5 Hz), 7.87 (d, 4H, J = 8 Hz), 7.88−7.85 (m, 5H), 7.96 (d, 2H, J = 9.1 Hz), 8.05 (d, 2H, J = 9.1 Hz).

4-(2-Benzothiazolylamino)-α-[1-(dimethylamino)ethyl]-benzenemethanol (17). A 5 L flask, under nitrogen atmosphere, was charged with **16** (120 g, 0.168 mol), water (0.36 L), and 2-propanol (1.2 L). Sodium hydroxide (13.5 g, 0.336 mol) was added to the suspension. The homogeneous mixture was heated to 40 °C. A borohydride solution was prepared (6.6 g, 0.168 mol $NaBH_4$ in 12.3 mL of 50% NaOH and 210 mL water) and was added to the reaction mixture. The heterogeneous reaction mixture was stirred overnight at 40 °C and cooled to room temperature, and the excess borohydride was quenched with acetone (37.2 mL, 0.504 mol). Water was added (1.68 L), and the reaction mixture was stirred at room temperature for 16 h and filtered. The solid was washed with water and dried to yield **17** as a white solid (45 g, 81%).

CE: 85.05% (1*S*,2*S*); 14.1% (1*R*,2*R*); 0.85% (1*R*,2*S* + 1*S*,2*R*); ^{1}H NMR: (DMSO-d_6, 400 MHz) δ 0.65 (d, 3H, J = 6.6 Hz), 2.25 (s, 6H), 2.59−2.51 (m, 1H), 4.22 (d, 1H, J = 9.3 Hz), 4.84 (s, OH), 7.15 (t, 1H, J = 7.5 Hz), 7.34−7.30 (m, 3H), 7.59 (d, 1H, J = 7.5 Hz), 7.72 (d, 2H, J = 8.4 Hz), 7.80 (d, 1H, J = 7.5 Hz), 10.43 (s, NH),

***(1S,2S)*-*N*-[4-[2-(Dimethylamino)-1-(1H-imidazol-1-yl)]-propyl]phenyl]-2-benzothiazol-amine (1).** Compound **17** (90 g, 0.273 mol) was added to a 5 L flask containing ethyl acetate (1.1 L), 1,1′-carbonyldiimidazole (58.5 g, 0.36 mol), and imidazole (55.2 g, 0.81 mol). The heterogeneous mixture was heated to reflux for 1 h. The reaction mixture was quenched with water (0.6 L) and stirred at 70 °C for 10 min. The layers were maintained at 70 °C, and the water layer was removed. Ethanol (1.1 L) was added to the organic phase at 70 °C. After the homogeneous mixture cooled to 50 °C, charcoal was added, and the mixture was refluxed for 10 min and filtered through Celite. The filtrate was partially evaporated to a batch temperature of 72 °C. The residue was seeded with pure **1**, allowed to cool to room temperature, and stirred for 16 h. The crystals were filtered, rinsed with ethanol (100 mL), and dried under reduced pressure to give (*S*,*S*)-**1** (39.6 g, 38%) with a diastereomeric purity of 99.1%.

CE: 99.1% (1*S*,2*S*); <0.1% (1*R*,2*R*); 0.9% (1*R*,2*S* + 1*S*,2*R*). Anal. Calcd for $C_{21}H_{23}N_5S$: C, 66.81; H, 6.14; N, 18.55. Found: C, 66.50; H, 6.24; N, 18.44. ^{1}H NMR: (DMSO-d_6, 400 MHz) δ 0.69 (d, 3H, J = 6.6 Hz), 2.15 (s, 6H), 3.68−3.57 (m, 1H), 5.18 (d, 1H, J = 11.1 Hz), 6.80 (s, 1H), 7.16 (t, 1H, J = 7.5 Hz), 7.35−7.32 (t, 1H, J = 7.5 Hz, s), 7.50 (d, 1H, J = 8.6 Hz), 7.61 (d, 1H, J = 7.5 Hz), 7.75 (d, 1H, J = 8.6 Hz), 7.79 (s, 1H), 7.80 (d, 1H, J = 7.5 Hz), 10.53 (s, NH).

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