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Enantioselective Synthesis, DFT Calculations and Preliminary Antineoplastic Activity of Dibenzo 1-Azaspiro[4.5]decanes on Drug Resistant Leukemias

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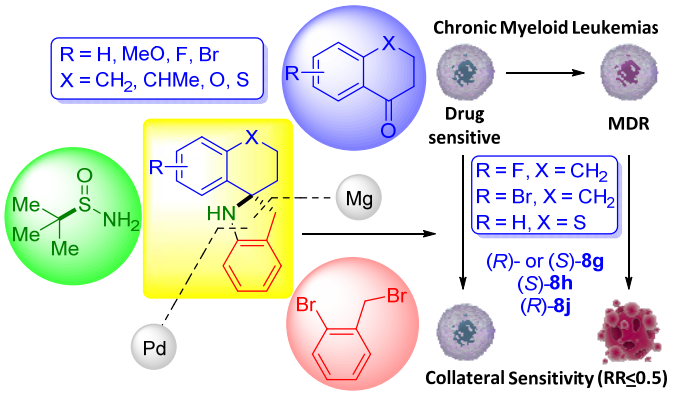


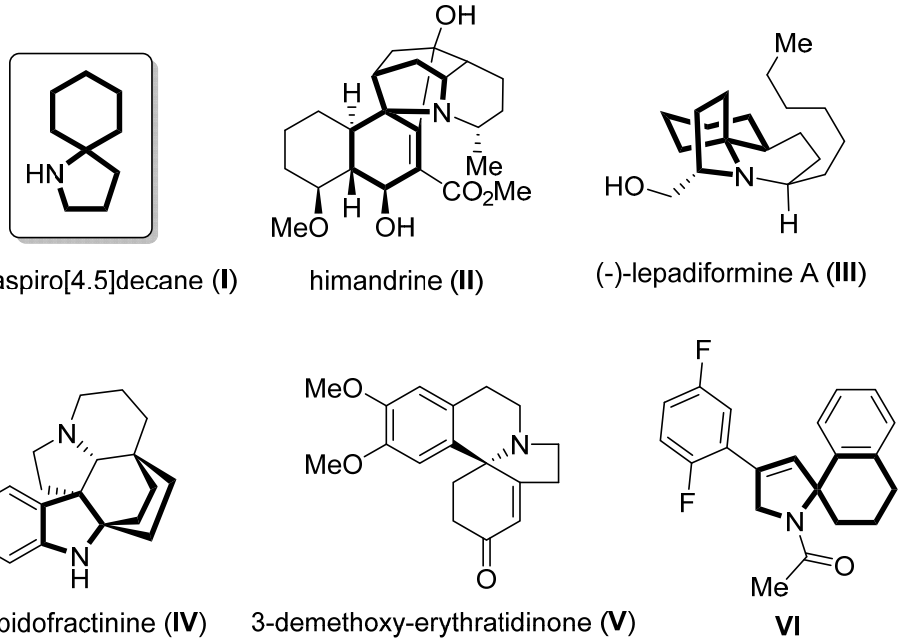
ABSTRACT. The addition of 2-bromobenzylmagnesium bromide to chiral *N*-*tert*-butanesulfinyl imines derived from tetralone type ketones proceeds with high levels of diastereocontrol. The resulting sulfinamide derivatives were transformed into dibenzoazaspiro compounds after a palladium catalyzed intramolecular *N*-arylation. DFT calculations have been performed to rationalize the stereochemical course of the reaction. Similar results have been obtained considering either diethyl ether or toluene as a solvent, in both cases in an excellent agreement with experimental findings. NCI topological calculations have also been used to evidence crucial non-covalent interactions. In addition, the azaspiro compounds reduced the viability chronic myeloid leukemia cells in the micromolar range. Notably, both the halogen-substituted **(*R*)-** and **(*S*)-8g** and **8h** as well as **(*R*)-8j** were at least two times more effective on a multidrug-resistant derivative than on the parental cell line, exerting a collateral sensitivity effect.

KEYWORDS. Chiral sulfinyl imines, tetralones, chromanone, thiochromanone, diastereoselective addition, *N*-arylation, 1-azaspiro[4.5]decanes, DFT calculations, multifactorial drug resistance, collateral sensitivity

INTRODUCTION

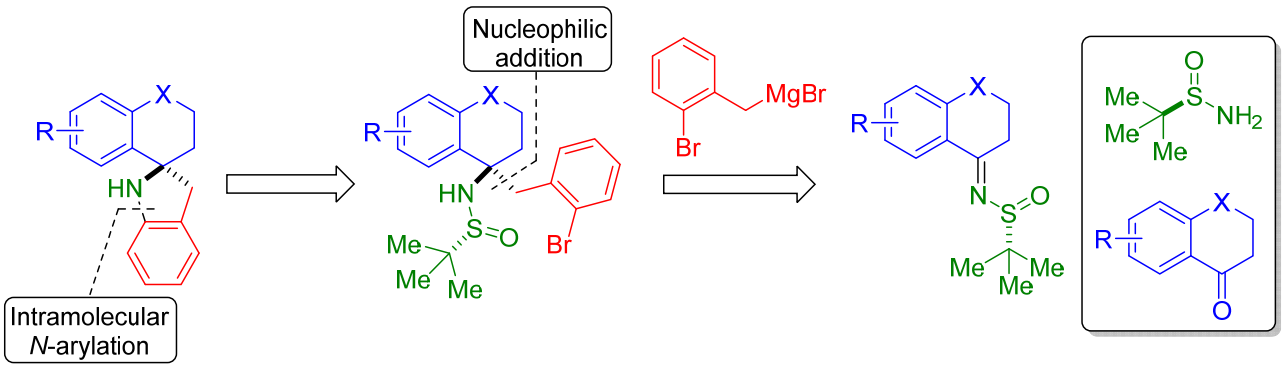
The 1-azaspiro[4.5]decane unit (**I**) is an important structural motif found in natural products and also in different synthetic molecules which display interesting pharmacological activities (Figure 1). Among the natural products, himandrine (**II**)[1] is an alkaloid isolated from the bark of *Galbulimima belgraveana* and *Galbulimima baccata* aromatic evergreen trees that grow in Papua New Guinea. These trees have been used as medicinal herbs by native tribes to induce sleep or relieve abdominal pains.[2] The azaspiro unit **I** was also found in marine alkaloids lepadiformine A (**III**) which was isolated from the tunicate Clavelina lepadiformis[3] (Figure 1). Interestingly, lepadiformine A (**III**) exhibits strong cardiovascular effects as well as moderate cytotoxicity.[4] Aspidofractinine (**IV**) and 3-demethoxyerythratidinone (**V**) were anothers examples of these natural products which were isolated respectively from the leaves of *Aspidosperma refractum*,[5] and *from Erythrina lithosperma* [6] as well as the leading compound of a large family of biological active alkaloids sharing the same basic hydrocarbon backbone (Figure 1). On the other hand, compounds with a benzo-1-azaspiro[4.5]decane unit, such as **VI** (Figure 1), were found to be inhibitors of kinesin spindle protein (KSP), a protein involved in mitosis, and potential therapeutic agents for treating cellular proliferative diseases associated with KSP.[7] In addition, there are several examples in literature of other type of azaspiro compounds which exhibit a wide range of biological activities, including anti-leishmanial,[8] antibacterial,[9] anti-convulsivant,[10] analgesic,[11] chronic neurologic disorders regulator[12] and anticancer[13] activities.

Figure 1. Representative natural products bearing the 1-azaspiro[4.5]decane unit



Being aware of the potential interest of dibenzo 1-azaspiro[4.5]decane derivatives with regard to antimitotic effect targeting the cytoskeleton, our interest in the study of the nucleophilic additions to *N*-*tert*-butanesulfinyl imines, and the influence of the stereogenic center on the stereochemical outcome of these reactions, we herein report our approach to the synthesis of these compounds through a successive addition of an organomagnesium compound to the corresponding chiral *tert*-butanesulfinyl imine and final intramolecular *N*-arylation (Scheme 1). Since the addition of Grignard reagents to these chiral imines proceeds in a diastereoselective manner, the two possible enantiomers are accessible by starting from the corresponding (R_S)- or (S_S)-sulfinyl imine. It is worth mentioning that chiral *N*-*tert*-butanesulfinyl imines[14] have attracted great attention for their potential uses in the stereoselective synthesis of amine derivatives containing a stereogenic center bonded to the nitrogen atom. For example, Chuang and co-works employed sulfinyl imine and organolithium in the synthesis of 3-demethoxyerythratidinone (4) (Figure 1)[15]. With regards to this, we have studied the stereoselective addition to these imines of different reagents, such as allyl[16] and propargyl[17] indium bromides in the presence of indium metal, nitrocompounds,[18] enolates[19] and Grignard reagents.[20]

Scheme 1. Retrosynthetic analysis of synthesis of dibenzo 1-azaspiro[4.5]decane derivatives



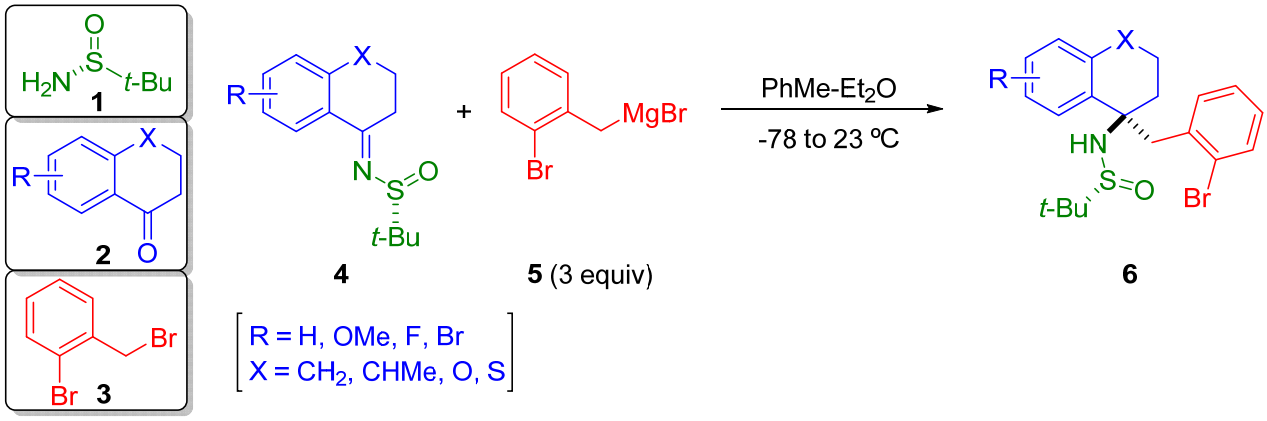
RESULTS AND DISCUSSION

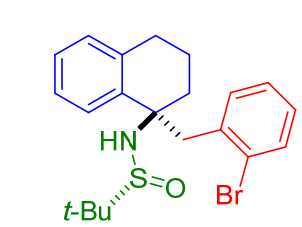
Synthetic studies

The synthesis of the target dibenzo 1-azaspiro[4.5]decanes started with the diastereoselective addition of 2-bromobenzylmagnesium bromide (**5**) to the corresponding chiral *N*-*tert*-butanesulfinyl imine (**4**). Chiral imines **4** were easily accessible by condensation of enantiomerically pure *tert*-butanesulfinamide **1**, and the corresponding tetralone (**2a-h**; X = CH_2 or CHMe; R = H, MeO, F, Br), chromanone (**2i**; X = O; R = H), or thiochromanone (**2j**; X = S; R = H) derivative in the presence of titanium tetraethoxide. The addition of Grignard reagents to *N*-*tert*-butanesulfinyl imines was studied for the first time by Ellman and co-workers and showed a remarkable dependence of diastereoselectivity using coordinating or non coordinating solvents, the best results being obtained in non coordinating solvents.[21] It was found that the attack of the Grignard reagent occurred on the *Si*-face of the imine with the *R* configuration at the sulfur atom. In previous studies, we observed that the highest diastereoselectivities in the addition of organomagnesium compounds to *N*-*tert*-butanesulfinyl imines were obtained in toluene and the lowest diastereoselectivities were reached in THF as solvent.[20] Based on that, we studied the reaction of a 1 M solution of 2-bromobenzylmagnesium bromide (**5**) in ether to the corresponding imine **4** in toluene (Table 1). The addition was carried out at -78 ºC, and after that the reaction was allowed to reach room temperature. Organomagnesium compound **5** was prepared from 2-bromobenzyl bromide (**3**) and magnesium powder, and in all cases, complete conversion was observed using three equivalents of the Grignard reagent **5**. The expected sulfinyl amine derivatives **6** were obtained in general in moderate yields. The highest yield was found for (R_S)-**6i** (92%), resulting from the addition of **5** to the imine **4i** derived from chromanone (**2i**) and (*R*)-*tert*-butanesulfinamide [(*R*)-**1**]. On the other hand, the imine **4a** was the model substrate that we took to study these transformations, and yield shown on Table 1 for compound (R_S)-**6a** corresponds to the highest yield we obtained after several reactions. The reaction conditions were not optimized for the rest of imines **4**, neither the reactions

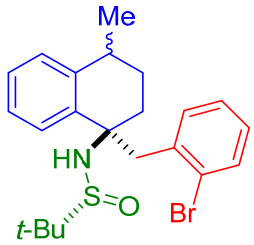
were repeated several times. It merits to be mentioned that high yields were also obtained for tetralone derivatives **6a** (80 and 70% for both enantiomers, Table 1). On the contrary, the lowest yields were attained for tetralone derivatives bearing a methoxy group at C6-position of the tetralone moiety, due probably to electronic effects (compounds **6d** and **6f**, Table 1). Unfortunately, compound (R_S)-**6b**, derived from 4-methyltetralone (**2b**), was obtained as a 1:1 mixture of epimers which differ in the configuration at C4-position of the tetralone moiety. All these reactions proceeded with high diastereoselectivities, and the diastereomeric ratios were easily determined by ^{1}H-NMR analysis of the crude reaction mixtures, with values over 90:10. In addition, the major diastereoisomer was isolated in all cases as a single compound after column chromatography purification. Concerning the configuration of the newly created stereogenic centre in compounds **6**, it was assigned after crystal X-ray analysis (see the Supporting Information) of the solid compound (R_S)-**6h**.[22] We assume that the nucleophilic attack took always place to the *Si*-face of the imines **4** with R_S configuration, and to the *Re*-face of the imines **4** with S_S configuration in compounds **6** (Table 1).

Table 1. Diastereoslective addition of 2-bromobenzylmagnesium bromide (**5**) to chiral imines **4**[a,b]

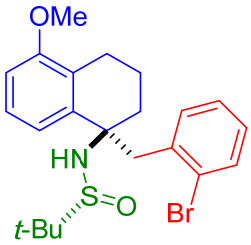




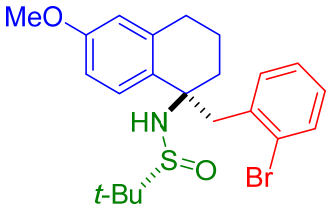
(*R*S)-**6a**: 80% (90:10 dr)
(*S*S)-**6a**: 70% (90:10 dr)



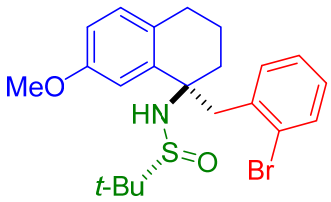
(*R*S)-**6b**: 47% (50:50 dr)



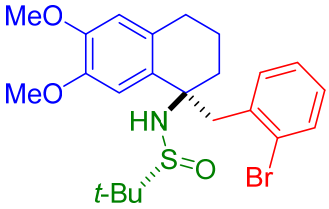
(*R*S)-**6c**: 50% (96:4 dr)
(*S*S)-**6c**: 46% (96:4 dr)



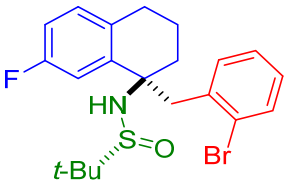
(*R*S)-**6d**: 30% (90:10 dr)
(*S*S)-**6d**: 35% (90:10 dr)



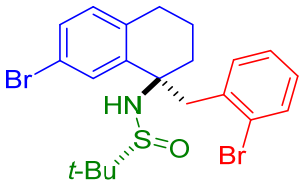
(*R*S)-**6e**: 61% (93:7 dr)
(*S*S)-**6e**: 52% (93:7 dr)



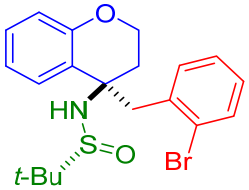
(*R*S)-**6f**: 52% (95:5 dr)
(*S*S)-**6f**: 43% (95:5 dr)



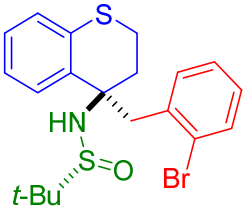
(*R*S)-**6g**: 65% (96:4 dr)
(*S*S)-**6g**: 75% (96:4 dr)



(*R*S)-**6h**: 51% (95:5 dr)
(*S*S)-**6h**: 60% (95:5 dr)



(*R*S)-**6i**: 92% (93:7 dr)
(*S*S)-**6i**: 85% (93:7 dr)



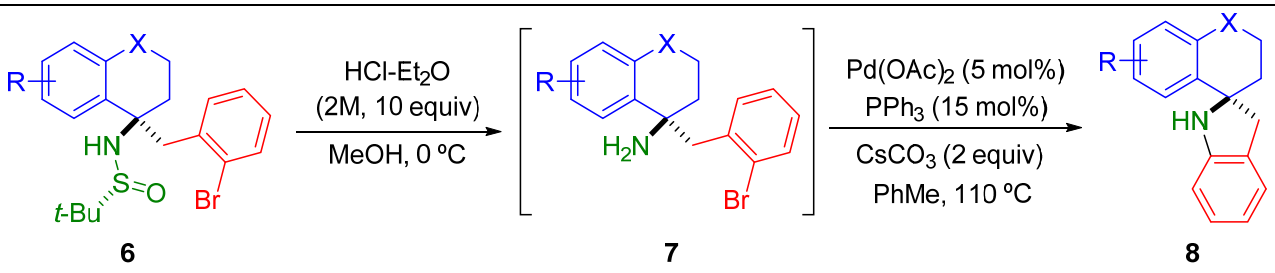
(*R*S)-**6j**: 56% (94:6 dr)
(*S*S)-**6j**: 68% (94:6 dr)

[a] Reactions were carried out starting from 1.0 mmol of the corresponding imine **4** in 5 mL of toluene. [b] Isolated yields after column chromatography purification. Diastereomeric ratios are given in parenthesis and were determined from ^{1}H-NMR spectrum of the crude reaction mixture.

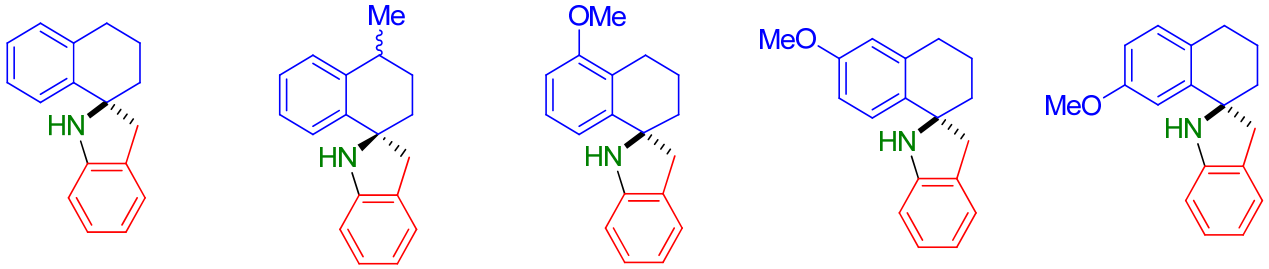
Finally, target spiro compounds **8** were obtained from benzyl amine derivatives **6** through a sequential removal of the *tert*-butanesulfinyl group under acidic conditions, and subsequent

intramolecular *N*-arylation of the resulting free amine **7** under palladium catalysis, using Cs_2CO_3 as a base in toluene, in a high pressure tube at 110 ºC for 20 hours (Table 2). Spiro compounds **8** were isolated in an enantiomerically pure form in yields ranging from 50% to 70% in most of the cases.

Table 2. Synthesis of spiro compounds **8** through a sequential desulfinylation and intramolecular *N*-arylation[a,b]



6 **7** **8**



(*S*)-**8a**: 66%
(*R*)-**8a**: 56%

(*S*)-**8b**: 32%

(*S*)-**8c**: 60%
(*R*)-**8c**: 57%

(*S*)-**8d**: 48%
(*R*)-**8d**: 58%

(*S*)-**8e**: 62%
(*R*)-**8e**: 65%

(*S*)-**8f**: 40%
(*R*)-**8f**: 49%

(*S*)-**8g**: 64%
(*R*)-**8g**: 54%

(*S*)-**8h**: 30%
(*R*)-**8h**: 22%

(*R*)-**8i**: 57%
(*S*)-**8i**: 55%

(*R*)-**8j**: 67%
(*S*)-**8j**: 72%

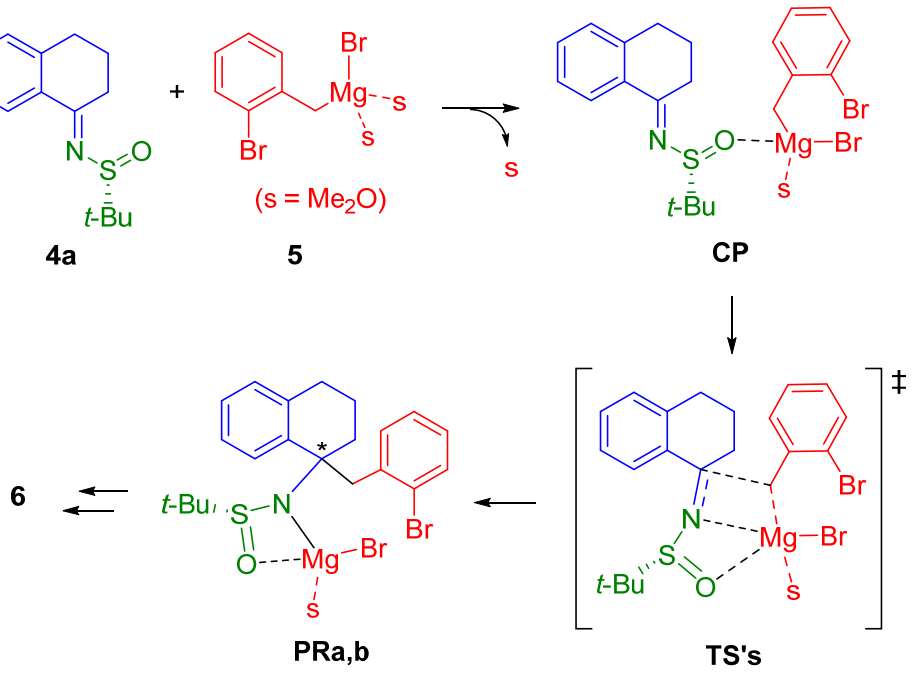
[a] Reactions were carried out starting from 0.5 mmol of the corresponding compound **6**. [b] Isolated yields after column chromatography purification.

Theoretical studies

We performed density-functional theory (DFT) calculations in order to understand the origins of the stereocontrol of the reaction between imines **4** and 2-bromobenzylmagnesium bromide (**5**). The nucleophilic addition reaction was studied at b3lyp-d3bj/def2svp level of theory to calculate geometries and then single point calculations at b3lyp-d3bj/def2tzvp/pcm=diethylether level of theory were performed for obtaining more accurate energy values; calculations in toluene were also performed for the purpose of comparison (for details see SI). Since the reaction was performed in a mixture of toluene-diethyl ether discrete molecules of dimethyl ether were added to complete the tetrahedral coordination sphere of magnesium when necessary. It has been reported that four-

membered rings formed through a Schlenk equilibrium control Grignard reactions,[23] but the presence of coordinating solvent molecules can displace the equilibrium towards the free Grignard reagent.[24] We have studied as a model reaction, the nucleophilic addition of Grignard reagent **5** to imine **4a** (R = H, X =CH_2) as illustrated in Scheme 2).

Scheme 2. General mechanism for the reaction between **4a** and **5**



Admittedly, nucleophilic additions of organometallic reagents, like Grignard reagents, to unsaturated systems capable of complexing the metal atom usually start with the formation of an initial complex. Typical examples are Grignard additions to carbonyl compounds[25] and nitrones.[26] In the particular case of sulfinyl imines, the sulphoxide group can displace a solvent molecule and form the initial complex **CP** as reported by Eisenstein and co-workers.[27] Although the (*E*)-imine is more stable than the (*Z*)-imine (by 5.1 kcal/mol), there is a rapid equilibrium between both isomers of sulfinyl imines[27] so, in agreement to Curtin-Hammett's principle,[28] the participation of the (*Z*)-isomer cannot be discarded *a priori.* In consequence, to locate possible transition structures **TS** we defined approaches for (*E*)- and (*Z*)-imines by *Re* and *Si* faces in which two possible orientations of the aryl Grignard reagents are possible due to the presence of the bromine atom, thus being a total of eight approaches leading to the two different diastereoisomers that can be obtained (Figure 2).[29] In the final products **PRa,b**, the magnesium atom is coordinated to both oxygen and nitrogen atoms of the sulfinyl amino group in agreement with previous studies.[27]

The analysis of the eight located transition structures **TSa-h** revealed that **TSa**, corresponding to the Grignard addition by the *Si* face of (*E*)-isomer and **TSg**, corresponding to the Grignard addition by the *Re* face of (*Z*)-isomer, present the lowest barriers with values of 14.3 and 15.4 kcal/mol,

respectively (for the complete energy profiles see SI). A Boltzmann distribution corroborated that **TSa** and **TSg** are essentially the only representative transition structures, with a very minor contribution of **TSh** (see SI). This analysis, obtained considering diethyl ether as a solvent, predict an 80:20 diastereomeric ratio for the products. Similar results were observed when toluene was considered as a solvent (13.8 and 15.0 kcal/mol for **TSa** and **TSg**, respectively), the corresponding Boltzmann distribution predicting a diastereomeric ratio of 83:17. These results are in a very good agreement with the experimentally observed 90:10 diastereomeric ratio.

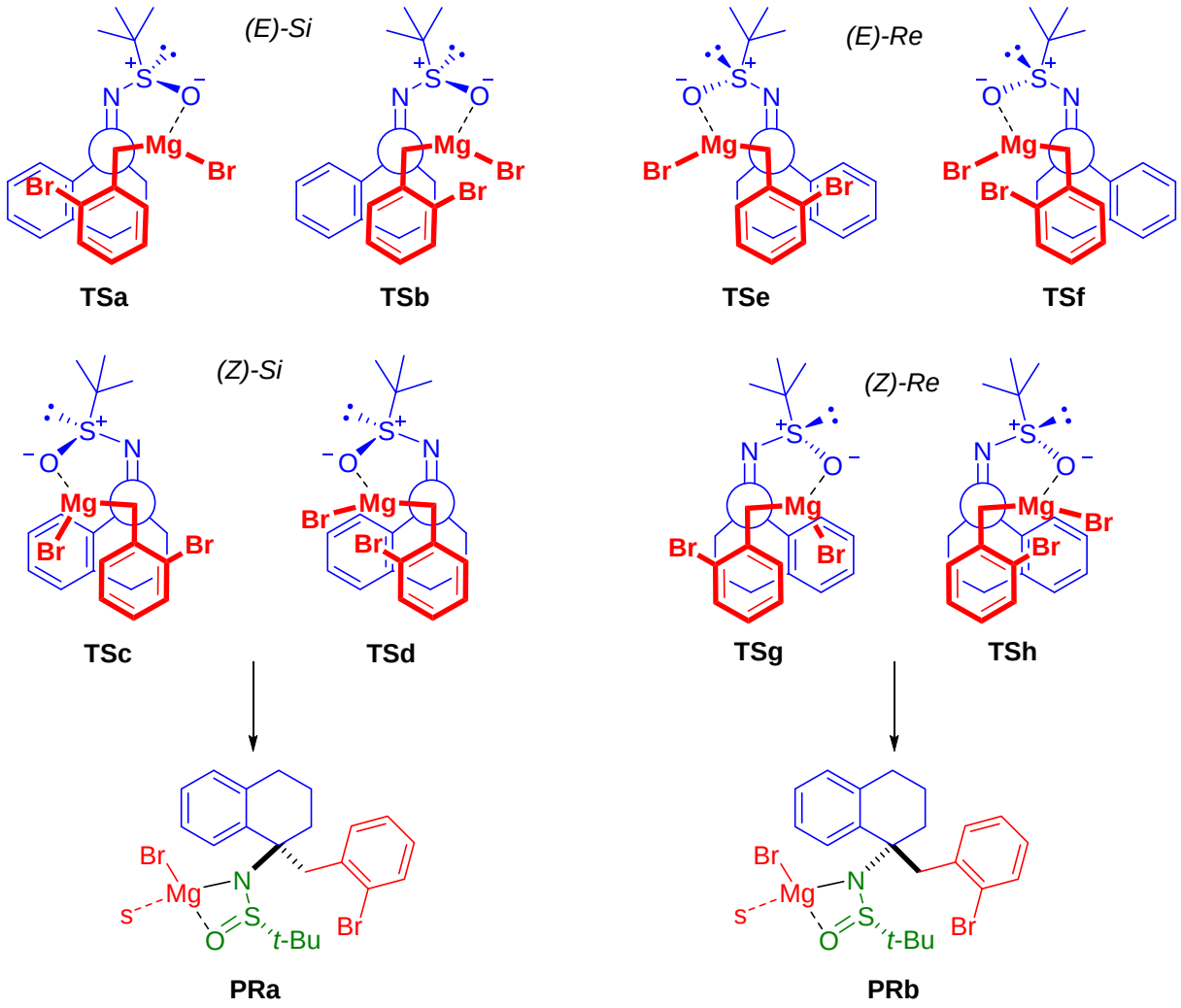


Figure 2. Approaches considered for the reaction between **4a** and **5**. Discrete solvent molecule (s = Me_2O) coordinated to Mg in **TSa-h** has been omitted for clarity. **TSa-d** and **TSe-h** correspond to attacks of **5** by *Si* and *Re* faces of **4**, respectively. **TSa,b,e,f** and **TSc,d,g,h** correspond to (*E*) and (*Z*)-imines, respectively. Couples **TSa/b**, **TSc/d**, **TSe/f** and **TSg/h** correspond to the different orientations (bromine atom inside/outside) of the aromatic residue of **5**.

The analysis of the optimized geometries of the transition structures revealed interesting features that justify the observed differences in energies. For the geometrical analysis we have only

considered the most stable transition structure for each attack *i.e*: **TSa** and **TSc** for *Si* attacks to (*E*)- and (*Z*)-isomers, respectively, and **TSe** and **TSg** for *Re* attacks to (*E*)- and (*Z*)-isomers, respectively (Figure 3). The transition structure **TSa** (*Si*-attack to (*E*)-isomer) corresponding to the lowest barrier, presents important London interactions between the two aromatic rings without remarkable steric requirements. On the other hand, **TSe,** corresponding to the attack by the other face of the same isomer is 9.1 kcal/mol higher in energy, despite the presence of CH-π and halogen-π interactions. The reason of such a difference is a steric clash between the entering benzyl group and the tert-butyl group, which causes a severe steric hindrance. A similar situation but from a different scenario is found for the (*Z*)-isomer. The transition structure **TSg**, corresponding to the *Re*-attack and only 1.2 kcal/mol higher in energy than **TSa**, is the one that presents fewer favorable non-covalent interactions but it has practically no steric hindrance in the approach of the benzyl group to the imine carbon. On the contrary, **TSc**, showing the highest barrier and corresponding to the attack by the *Si* face, should modify the attack angle because of the presence of the fused cyclohexane that, though might give rise to CH-π interactions, it also causes steric difficulties for the attack.

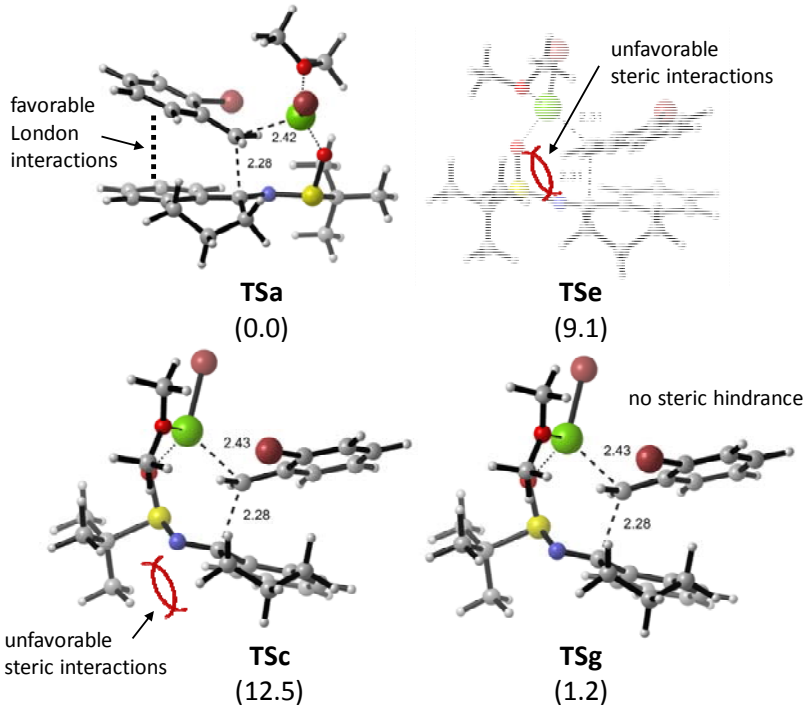


Figure 3. Preferred transition structures for each attack. **TSa** corresponds to the *Si* attack to (*E*)-isomer; **TSc** corresponds to the *Si* attack to (*Z*)-isomer; **TSe** corresponds to the *Re* attack to (*E*)-isomer and **TSg** corresponds to the *Re* attack to (*Z*)-isomer.

The above mentioned non-covalent interaction are evidenced by means of a topological NCI analysis[30] in which weak attractive non-covalent interactions are showed as green surfaces (for

details see SI). As an example, Figure 4 illustrates such an analysis for **TSa** and **TSe** in which London and π-halogen interactions, respectively, are shown.

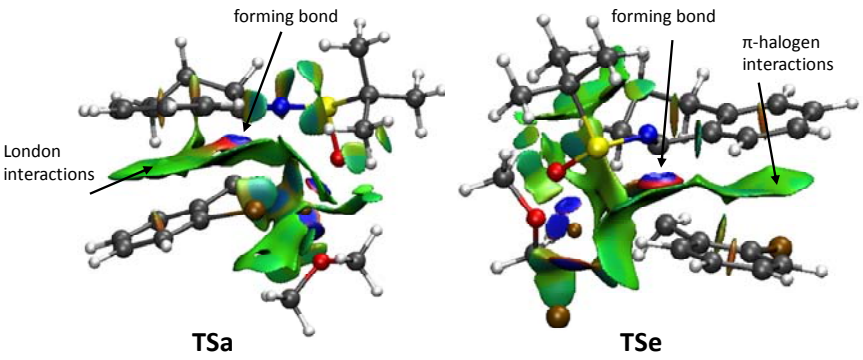


Figure 4. NCI analysis for **TSa** and **TSe.**

Studies on cancer cells

The development of new chemotherapeutics must take a set of factors into account since cancer cells often present intrinsic and acquired mechanisms to evade cytotoxicity. Increased cytoskeleton remodelling to support cell motility, mitosis and protein trafficking is a cancer hallmark[31] and, after a chemotherapy regimen, drug resistance may emerge due to selective killing of sensitive cells. The multidrug resistance phenotype (MDR) manifests due to cross-resistance to chemotherapeutic drugs with no structural nor functional relationship, markedly by increased activity of ABC superfamily transporters.[32] In regard to this, and considering that the benzo-1-azaspiro[4.5]decane motif is described to present antimitotic properties, all compounds were screened for toxicity towards MDA-MB-231, a model of an invasive, poorly differentiated and endocrine therapy-resistant breast ductal carcinoma. Results indicated compounds **(*S*)-8d**, **(*S*)-8g**, **(*S*)-8h**, **(*S*)-8i** and **(*R*)-8j** as potential candidates for further studies, since they reduced cell viability to at least 50% after treatment with 100 μM for 72 h. Taken these results into account, these compounds, along with their respective (*S*)- or (*R*)- enantiomers, were further evaluated on two models of human chronic myeloid leukemias. K562 cells present constitutive BCR/ABL tyrosine kinase activity leading to a highly proliferative status; FEPS is a K562/DNR derivative cell selected after continuous exposure of K562 to daunorubicin (**DNR**),[33] cross-resistant to a variety of natural and synthetic compounds owing to, but not limited to, its high efflux activity mediated by the ABC transporters ABCB1 (Pgp) and ABCC1 (MRP1).[33,34] The chemotherapeutic drugs vincristine (VCR), a tubulin-binding antimitotic alkaloid, and daunorubicin, a pro-oxidant, DNA-alkylating anthracycline were employed as controls. The antiproliferative effect of the various compounds on K562 and FEPS cells can be observed in Table 3.

Table 3. IC_{50} for the (*S*)- and (*R*)-azaspiro derivatives **8d**, **8g**, **8h**, **8i** and **8j**, as well as for the standards **VCR** and **DNR** toward human leukemias.

Compound	K562	FEPS
(*S*)-8d	123.17±9.45	149.20±17.19
(*R*)-8d	>200	>200
(*S*)-8g	>200	64.16±8.56
(*R*)-8g	142.42±23.51	70.86±16.41
(*S*)-8h	124.15±10.40	34.68±3.93
(*R*)-8h	59.72±4.23	31.85±3.00
(*S*)-8i	>200	>200
(*R*)-8i	>200	154.83±14.77
(*S*)-8j	77.58±5.76	47.07±7.08
(*R*)-8j	75.52±4.74	33.81±7.55
VCR*	57.70±9.55	922.25±107.87
DNR*	82.15±2.93	1543.40±134.42

Mean IC_{50} values ± SEM, in μM, obtained from a range of concentrations after three independent experiments, with each concentration evaluated in triplicate. Assays performed as described in the Experimental Section. *For VCR and DNR, mean IC_{50}± SEM is expressed in nM.

Results indicate that the evaluated compounds exerted cytotoxicity to both cell subtypes, most notably the 7'-bromo **(*R*)-8h** and the thiochromanes **(*S*)-** and **(*R*)-8j**. Moreover, the 7'-fluoro derivatives **(*S*)-** and **(*R*)-8g** and 7'-bromo **(*S*)-8h** were effective only on FEPS. The enantiomeric conformation produced little effect concerning the pharmacological effect, since only **(*R*)-8h** seemed to induce two-fold higher toxicity, and limited to K562. Disruption of the mitotic spindle is a well-recognized mechanism exerted by chemotherapeutic drugs such as VCR and paclitaxel,[35] and kinesin spindle proteins (KSP), motor proteins involved in anterograde protein transport and mitosis, are important for correct centrosome and chromosome segregation.[36] Kinesins have already been linked to multidrug resistance,[37] and its inhibition induced cell death on drug-resistant ovarian cancer[38] and lymphomas.[39] Since the benzo-1-azaspiro[4.5]decane motif was demonstrated to inhibit the KSP KIF11, FEPS present increased gene expression of KIF1A and KIF21B over K562,[40] and halogen modifications of known KSP inhibitors were shown to increase bioavailability[41] and to overcome ABC transporter-mediated efflux[42] this mechanism seems feasible. Intererstingly, all compounds but the 6'-methoxyl **(*S*)-** and **(*R*)-8d** and the chromane **(*S*)-8i**

presented higher toxicity to the MDR cell FEPS than to the parental K562. This profile is known as collateral sensitivity, and can be described as a hypersensitivity towards secondary drugs that arises from the development of resistance towards an unrelated primary agent.[43] Figure 5 shows that compounds **(*S*)-** and **(*R*)-8g**, **(*S*)-8h** and **(*R*)-8j** induced collateral sensitivity on FEPS, since they presented RR ≤ 0.5.[44] Of note, for the standard drugs VCR and DNR this ratio was higher than 2.0, indicative of drug resistance.

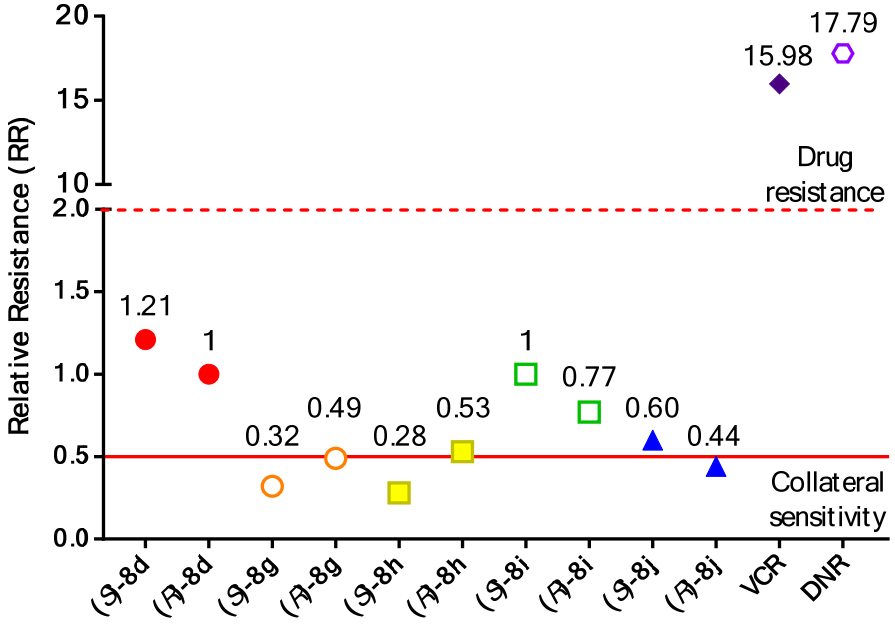


Figure 5. Relative resistance (RR) indexes for the azaspiro compounds evaluated on chronic myeloid leukemias. **RR = (IC_{50} resistant cell line, FEPS)/(IC_{50} parental cell line, K562)**. When IC_{50} exceeded the maximal tested concentration it was expressed as being higher than this concentration (e.g. >200), and this value, 200, was used for calculating the RR (e.g. RR of **(*R*)-8i**: IC_{50} FEPS / IC_{50} K562 = 154.83/200 = 0.77). Similar shapes and colors indicate each azaspiro (*S*)- or (*R*)- enantiomeric conformations, and the numbers above, the calculated RR for each compound.

Despite being poorly understood, mechanisms that govern collateral sensitivity may either rely on or be independent from MDR mechanisms. ATP depletion after a futile cycle of passive influx and active efflux of an ABCB1 transporter substrate, ABCC1-mediated extrusion of endobiotics such as glutathione, ROS production after metal-mediated redox cycling and perturbation of cellular bioenergetics and/or the plasma membrane fluidity were linked to collateral sensitivity.[45] Of note, the azaspiro compounds with the lowest RR presented a similar modification, the addition of the halogens fluorine or bromine. Halogenation has been previously linked to collateral sensitivity, as the addition of bromine,[46] chlorine[46] and iodine[47] on aza-carbapterocarpans produced similar outcomes on MDR leukemias. Halogen bonds are ubiquitous in nature, taking part in protein-ligand

interactions involving the carbonyl group present on the side chain of every aminoacid, and carboxylates in aspartate and glutamate.[48] Whether the observed collateral sensitization is a result of KSP inhibition, interaction with (or lack thereof) ABC proteins, targeting aminoacids such as the glutathione precursor glutamate, of simply by the increased bioavailability granted by the addition of halogens, this effect should undergo thorough investigation as it could foster the development of MDR-targeting azaspiro compounds.

CONCLUSIONS

Dibenzo-1-azaaspiro[4.5]decanes were prepared in a enantiomerically pure form from *tert*-butanesulfinamide, 2-bromobenzylbromide and tetralone type ketones. The methodology presented here comprised as key steps a diastereoselective addition of a benzylic organomagnesium compound to a chiral sulfinyl ketimine and an intramolecular palladium-catalyzed *N*-arylation. DFT calculations correctly predicted the observed experimental results evidencing that the reaction is under kinetic control and the two competitive transition structures resulted from the *Si* attack to the (*E*)-isomer and the *Re* attack to the (*Z*)-isomer. Whereas in the former, the preferred one, the presence of stabilizing London interactions contributes to the lowest barrier, in the latter it is the absence of any steric hindrance which causes the corresponding barrier to be only 1.2 kcal/mol higher in energy. The benzo-1-azaspiro[4.5]decane derivatives were effective on models of leukemias with diverse adaptations to evade cytotoxicity, depending on the pattern of substitutions on its molecular scaffold. The thiochromane compounds were the most promising, whereas the addition of bromine or fluorine produced collateral sensitivity to MDR cells. Our results highlight the azaspiro motif as an important lead for the development of new antineoplastic drugs targeted to chemo-refractory neoplasias, a sought after profile for the management of cancer.

EXPERIMENTAL SECTION

General Remarks: *tert*-Butanesulfinamides (*R* and *S*) were a gift of Medalchemy (> 99% ee by chiral HPLC on a Chiracel AS column, 90:10 *n*-hexane/*i*-PrOH, 1.2 mL/min, λ=222 nm). TLC was performed on silica gel 60 F_{254}, using aluminum plates and visualized with phosphomolybdic acid (PMA) stain. Flash chromatography was carried out on handpacked columns of silica gel 60 (230-400 mesh). Melting points are uncorrected. Optical rotations were measured using a polarimeter with a thermally jacketted 5 cm cell at approximately 20 ºC and concentrations (*c*) are given in g/100 mL. Infrared analyses were performed with a spectrophotometer equipped with an ATR component; wavenumbers are given in cm^{-1}. Low-resolution mass spectra (EI) were obtained at 70

eV; and fragment ions in *m/z* with relative intensities (%) in parentheses. High-resolution mass spectra (HRMS) were also carried out in the electron impact mode (EI) at 70 eV using a quadrupole mass analyzer or in the electrospray ionization mode (ESI) using a TOF analyzer. NMR Spectra were recorded at 300 or 400 MHz for ^{1}H NMR and 75 or 100 MHz for ^{13}C NMR, using $CDCl_3$ and CD_3OD as the solvents, and TMS as internal standard (0.00 ppm). ^{19} F NMR Spectrum for compound (R_S)-**6g** was recorded at 282 MHz, using $CDCl_3$ as the solvent, and CF_3CO_2H as internal standard (−75.66 ppm). The data are being reported as: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet or unresolved, br s = broad signal, coupling constant(s) in Hz, integration. ^{13}C NMR spectra were recorded with ^{1}H-decoupling at 100 MHz and referenced to $CDCl_3$ at 77.16 ppm. DEPT-135 experiments were performed to assign CH, CH_2 and CH_3.

General Procedure for the Synthesis of *N*-*tert*-Butanesulfinyl Imines 4a-h from Tetralones 2a-h and *tert*-Butanesulfinamide (1): The corresponding tetralone **2** (2.0 mmol), (*R*)- or (*S*)-*tert*-butanesulfinamide [(*R*)-**1** or (*S*)-**1**, 338.8 mg, 2.80 mmol], and $Ti(OEt)_4$ (912 mg, 0.84 mL, 4.0 mmol) were mixed and stirred under argon at room temperature. The reaction vessel was placed into the microwave reactor and heated to 70 °C (constant microwave irradiation at 40 W) for 90 min. After cooling to room temperature, the mixture was diluted with EtOAc (10 mL) and poured into 0.5 mL of brine while being rapidly stirred. The resulting suspension was filtered through a plug of Celite, and the filter cake was washed with EtOAc (20 mL). After evaporation of the solvent (15 Torr), the residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield products **4a-h**. Yields, physical and spectroscopic data follow.

(R_S)-*N*-(*tert*-Butanesulfinyl)-3,4-dihydronaphthalen-1(2*H*)-imine [(R_S)-4a]:[49] The representative procedure was followed by using tetralone **2a** (731.0 mg, 0.665 mL, 5.00 mmol) and (*R*)-*tert*-butanesulfinamide [(*R*)-**1**, 847.0 mg, 7.00 mmol]. Purification by column chromatography (hexane/AcOEt, 4:1) yielded (R_S)-**4a** (510.5 mg, 2.05 mmol, 41%) as a yellow oil; $[\alpha]_D^{20} = -24.2$ (*c* = 0.56, CH_2Cl_2); R_f = 0.27 (hexane/EtOAc, 3:1); IR *ν* (neat) 2933, 2856, 1479, 1294, 1159, 1081, 1061, 781, 723 cm^{-1}; δ_H 8.17 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.39 (td, *J* = 7.5, 1.4 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 3.33–3.24 (m, 1H), 3.10–3.01 (m, 1H), 2.91–2.84 (m, 2H), 2.90–2.85 (m, 2H), 1.33 (s, 9H); δ_C 177.1 (C), 142.3 (C), 133.1 (C), 132.1 (CH), 129.0 (CH), 127.1 (CH), 126.6 (CH), 57.2 (C), 32.5 (CH_2), 29.6 (CH_2), 22.8 (CH_2), 22.6 (CH_3); LRMS (EI) *m*/*z* 249 (M^+, 0.2%), 194 (13), 193 (100), 145 (44), 144 (18), 117 (32), 116 (19), 57 (18).

(R_S)-*N*-(*tert*-Butanesulfinyl)-4-methyl-3,4-dihydronaphthalen-1(2*H*)-imine [(R_S)-4b]: The representative procedure was followed by using 4-methyltetralone **2b** (400.0 mg, 2.50 mmol) and (*R*)-*tert*-butanesulfinamide [(*R*)-**1**, 423.5 mg, 3.50 mmol]. Purification by column chromatography (hexane/AcOEt, 4:1) yielded (R_S)-**4b** (328.8 mg, 1.25 mmol, 50%) as a mixture of diastereoisomers

(1:1); yellow oil; R_f= 0.67 (hexane/EtOAc, 1:1); IR *v* (neat) 2959, 1685, 1456, 1360, 1294, 1159, 1072, 1054, 1011, 764, 721, 690 cm^{-1}; δ_H 8.16 (d, *J* = 7.5 Hz, 1H), 7.46–7.39 (m, 1H), 7.31–7.22 (m, 2H), 3.39–3.34 (m 2H), 3.06–3-02 (m, 2H), 2.16–2.10 (m, 1H), 1.77–1.72 (m, 1H), 1.34 (s, 9H); δ_C 177.3 (C), 147.0 (C), 132.4 (CH), 127.8 (CH), 127.2 (CH), 127.4 (CH), 127.2 (CH), 126.5 (CH), 57.1 (C), 32.6 (CH), 30.2 (CH_2), 30.0 (CH_2), 29.7 (CH_2), 29.3 (CH_2) 22.6 (CH_3), 20.9 (CH_3), 20,7 (CH_3); LRMS (EI) *m*/*z* 263 (M^+, 0.2%), 208 (13), 207 (100), 159 (14), 144 (33), 130 (15), 57 (12); HRMS (ESI-TOF) *m*/*z*: $(M+H)^+$ Calcd for $C_{15}H_{22}NOS$ 264.1422; Found 264.1424.

(R_S)-*N*-(*tert*-Butanesulfinyl)-5-methoxy-3,4-dihydronaphthalen-1(2*H*)-imine [(R_S)-4c]:[50] The representative procedure was followed by using 5-methoxytetralone **2c** (530.0 mg, 3.00 mmol) and (*R*)-*tert*-butanesulfinamide [(*R*)-**1**, 508.2 mg, 4.20 mmol]. Purification by column chromatography (hexane/AcOEt, 4:1) yielded (R_S)-**4c** (452.0 mg, 1.62 mmol, 54%) as a yellow solid; mp 88–92 ºC (hexane/CH_2Cl_2); $[\alpha]_D^{20}$ = −39.1 (*c* = 0.58, CH_2Cl_2); R_f = 0.35 (hexane/EtOAc, 1:1); IR *v* (neat) 3078, 2962, 2933, 1571, 1440, 1256, 1120, 1061, 790, 712 cm^{-1}; δ_H 7.79 (d, *J* = 7.3 Hz, 1H), 7.21 (t, *J* = 8.1 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 3.85 (s, 3H), 3.30–3.26 (m, 1H), 3.06–3.03 (m, 1H), 2.79–2.75 (m, 2H), 2.00–1.96 (m, 2H), 1.32 (s, 9H); δ_C 177.2 (C), 156.9 (C), 134.2 (C), 131.5 (C), 126.5 (CH), 118.9 (CH), 112.9 (CH), 57.3 (C), 55.7 (CH_3), 32.0 (CH_2), 22.6 (CH_3), 22.6 (CH_2), 22.1 (CH_2); LRMS (EI) *m*/*z* 279 (M^+, 0.2%), 223 (52), 175 (100), 147 (13), 57 (10).

(R_S)-*N*-(*tert*-Butanesulfinyl)-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-imine [(R_S)-4d]:[49] The representative procedure was followed by using 6-methoxytetralone **2d** (883.0 mg, 5.00 mmol) and (*R*)-*tert*-butanesulfinamide [(*R*)-**1**, 847.0 mg, 7.00 mmol]. Purification by column chromatography (hexane/AcOEt, 4:1) yielded (R_S)-**4d** (390.6 mg, 1.40 mmol, 28%) as a yellow oil; $[\alpha]_D^{20}$ = −11.0 (*c* = 0.32, CH_2Cl_2); R_f = 0.11 (hexane/EtOAc, 3:1); IR *v* (neat) 3059, 2962, 1575, 1469, 1440, 1256, 1178, 1061, 1032, 790 cm^{-1}; δ_H 8.16 (d, *J* = 8.9 Hz, 1H), 6.79 (dd, *J* = 8.9, 2.7 Hz, 1H), 6.65 (d, *J* = 2.6 Hz, 1H), 3.33–3.15 (m, 1H), 3.07–2.91 (m, 1H), 2.84 (t, *J* = 6.1 Hz, 2H), 2.14–1.88 (m, 2H), 1.31 (s, 9H); δ_C 176.9 (C), 162.7 (C), 144.6 (C), 129.3 (CH), 126.3 (C), 113.4 (CH), 112.7 (CH), 56.8 (C), 55.4 (CH_3), 32.4 (CH_2), 30.0 (CH_2), 22.8 (CH_2), 22.5 (CH_3); LRMS (EI) *m*/*z* 279 (M^+, 0.4%), 223 (69), 222 (15), 175 (100), 147 (39), 57 (10).

(R_S)-*N*-(*tert*-Butanesulfinyl)-7-methoxy-3,4-dihydronaphthalen-1(2*H*)-imine [(R_S)-4e]:[49] The representative procedure was followed by using 7-methoxytetralone **2e** (704.0 mg, 4.00 mmol) and (*R*)-*tert*-butanesulfinamide [(*R*)-**1**, 677.6 mg, 5.60 mmol]. Purification by column chromatography (hexane/AcOEt, 4:1) yielded (R_S)-**4e** (480.0 mg, 1.72 mmol, 43%) as a yellow oil; $[\alpha]_D^{20}$ = +12.4 (*c* = 0.53, CH_2Cl_2); R_f = 0.22 (hexane/EtOAc, 3:1); IR *v* (neat) 2942, 2865, 1556, 1488, 1226, 1072, 1032, 809, 702 cm^{-1}; δ_H 7.67 (d, *J* = 2.8 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 6.96 (dd, *J* = 8.4, 2.8 Hz, 1H), 3.79 (s, 3H), 3.24–3.19 (m, 1H), 2.99–2.95 (m, 1H), 2.79 (t, *J* = 6.1 Hz, 2H), 2.04–1.88 (m, 2H), 1.30 (s, 9H); δ_C 177.0 (C), 158.1 (C), 135.0 (C), 133.9 (C), 130.1 (CH), 119.6 (CH), 110.1

(CH), 57.3 (C), 55.4 (CH_3), 32.3 (CH_2), 28.8 (CH_2), 23.1 (CH_2), 22.6 (CH_3); LRMS (EI) *m*/*z* 279 (M^+, 0.4%), 223 (72), 175 (100), 174 (99), 146 (29), 145 (23), 57 (17).

(R_S)-*N*-(*tert*-Butanesulfinyl)-6,7-dimethoxy-3,4-dihydronaphthalen-1(2*H*)-imine [(R_S)-4f]:[51] The representative procedure was followed by using 6,7-dimethoxytetralone **2f** (338.0 mg, 2.80 mmol) and (*R*)-*tert*-butanesulfinamide [(*R*)-**1**, 474.3 mg, 3.92 mmol]. Purification by column chromatography (hexane/AcOEt, 4:1) yielded (R_S)-**4f** (251.0 mg, 0.81 mmol, 29%) as a yellow oil; $[\alpha]_D^{20}$ = +2.4 (*c* = 0.54, CH_2Cl_2); R_f = 0.20 (hexane/EtOAc, 1:1); IR *v* (neat) 2992, 2929, 1552, 1508, 1363, 1273, 1258, 1141, 1054, 1030, 805 cm^{-1}; δ_H 7.72 (s, 1H), 6.62 (s, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.30–3.17 (m, 1H), 3.0 –2.90 (m, 1H), 2.82 (t, *J* = 6.1 Hz, 2H), 2.10–1.91 (m, 2H), 1.31 (s, 9H); δ_C 176.6 (C), 152.8 (C), 147.7 (C), 137.0 (C), 125.7 (C), 110.5 (CH), 108.6 (CH), 56.9 (C), 55.0 (CH_3), 55.9 (CH_3), 32.0 (CH_2), 29.3 (CH_2), 23.1 (CH_2), 22.5 (CH_3); LRMS (EI) *m*/*z* 309 (M^+, 0.8%), 253 (72), 252 (33), 205 (100), 190 (22), 176 (23), 159 (19), 57 (13).

(R_S)-*N*-(*tert*-Butanesulfinyl)-7-fluoro-3,4-dihydronaphthalen-1(2*H*)-imine [(R_S)-4g]: The representative procedure was followed by using 7-fluorotetralone **2g** (450.0 mg, 2.70 mmol) and (*R*)-*tert*-butanesulfinamide [(*R*)-**1**, 457.4 mg, 3.78 mmol]. Purification by column chromatography (hexane/AcOEt, 4:1) yielded (R_S)-**4g** (510.0 mg, 1.91 mmol, 71%) as a yellow oil; $[\alpha]_D^{20}$ = –3.9 (*c* = 0.41, CH_2Cl_2); R_f = 0.18 (hexane/EtOAc, 3:1); IR *v* (neat) 2928, 2239, 1580, 1483, 1270, 1067, 902, 814, 727 cm^{-1}; δ_H 7.81 (dd, *J* = 10.1, 2.7 Hz, 1H), 7.22–7.00 (m, 2H), 3.27 (ddd, *J* = 17.6, 9.1, 4.8 Hz, 1H), 3.05 (ddd, *J* = 17.7, 7.2, 4.6 Hz, 1H), 2.84 (t, *J* = 6.1 Hz, 2H), 2.10–1.85 (m, 2H), 1.33 (s, 9H); δ_C 175.9 (C), 161.4 (d, *J* = 244.4 Hz, C), 137.9 (d, *J* = 2.8 Hz, C), 134.7 (C), 130.6 (d, *J* = 7.3 Hz, CH), 119.4 (d, *J* = 22.2 Hz, CH), 112.9 (d, *J* = 22.7 Hz, CH), 57.5 (C), 32.06 (CH_2), 28.9 (CH_2), 22.8 (CH_2), 22.6 (CH_3); LRMS (EI) *m*/*z* 267 (M^+, 1%), 211 (91), 163 (57), 135 (29), 134 (20), 57 (55), 43 (100); HRMS (ESI-TOF) *m*/*z*: $(M+H)^+$ Calcd for $C_{14}H_{19}FNOS$ 268.1171; Found 268.1163.

(R_S)-7-Bromo-*N*-(*tert*-butanesulfinyl)-3,4-dihydronaphthalen-1(2*H*)-imine [(R_S)-4h]:[49] The representative procedure was followed by using 7-bromotetralone **2h** (450.0 mg, 1.99 mmol) and (*R*)-*tert*-butanesulfinamide [(*R*)-**1**, 339.0 mg, 2.80 mmol]. Purification by column chromatography (hexane/AcOEt, 4:1) yielded (R_S)-**4h** (475.6 mg, 1.45 mmol, 73%) as a yellow solid; mp 95–98 ºC (hexane/CH_2Cl_2); $[\alpha]_D^{20}$ = +24.2 (*c* = 0.21, CH_2Cl_2); R_f = 0.19 (hexane/EtOAc, 3:1); IR *v* (neat) 2938, 1483, 1261, 1173, 1047, 902, 805, 727 cm^{-1}; δ_H 8.24 (d, *J* = 2.2 Hz, 1H), 7.48 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 1H), 3.27 (ddd, *J* = 17.6, 9.1, 5.0 Hz, 1H), 3.04 (ddd, *J* = 17.6, 7.3, 4.6 Hz, 1H), 2.81 (t, *J* = 6.1 Hz, 2H), 2.08–1.89 (m, 2H), 1.33 (s, 3H); δ_C 175.5 (C), 141.0 (C), 134.7 (C), 134.7 (CH), 130.8 (CH), 129.7 (CH), 120.5 (C), 57.5 (C), 32.1 (CH_2), 29.1 (CH_2), 22.5 (CH_3), 22.4 (CH_2); LRMS (EI) *m*/*z* 328 (M^+, 0.04%), 273 (100), 271 (98), 225 (48), 223 (50), 57 (38).

(S_S)-*N*-(*tert*-Butanesulfinyl)-3,4-dihydronaphthalen-1(2*H*)-imine [(S_S)-4a]:[49] The representative procedure was followed by using tetralone **2a** (600.0 mg, 0.540 mL, 4.10 mmol) and (*S*)-*tert*-butanesulfinamide [(*S*)-**1**, 694.5 mg, 5.74 mmol]. Purification by column chromatography (hexane/AcOEt, 4:1) yielded (S_S)-**4a** (418.5 mg, 1.68 mmol, 41%). Physical and spectroscopic data were found to be same than for (R_S)-**4a**. $[\alpha]_D^{20} = +22.7$ ($c = 0.51$, CH_2Cl_2).

(S_S)-*N*-(*tert*-Butanesulfinyl)-5-methoxy-3,4-dihydronaphthalen-1(2*H*)-imine [(S_S)-4c]:[50] The representative procedure was followed by using 5-methoxytetralone **2c** (600.0 mg, 3.40 mmol) and (*S*)-*tert*-butanesulfinamide [(*S*)-**1**, 576.0 mg, 4.76 mmol]. Purification by column chromatography (hexane/AcOEt, 4:1) yielded (S_S)-**4c** (436.3 mg, 1.56 mmol, 46%). Physical and spectroscopic data were found to be same than for (R_S)-**4c**. $[\alpha]_D^{20} = +14.9$ ($c = 0.38$, CH_2Cl_2).

(S_S)-*N*-(*tert*-Butanesulfinyl)-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-imine [(S_S)-4d]:[49] The representative procedure was followed by using 6-methoxytetralone **2d** (600.0 mg, 3.40 mmol) and (*S*)-*tert*-butanesulfinamide [(*S*)-**1**, 567.0 mg, 4.76 mmol]. Purification by column chromatography (hexane/AcOEt, 4:1) yielded (S_S)-**4d** (379.4 mg, 1.36 mmol, 40%). Physical and spectroscopic data were found to be same than for (R_S)-**4d**. $[\alpha]_D^{20} = +4.5$ ($c = 0.45$, CH_2Cl_2).

(S_S)-*N*-(*tert*-Butanesulfinyl)-7-methoxy-3,4-dihydronaphthalen-1(2*H*)-imine [(S_S)-4e]:[49] The representative procedure was followed by using 7-methoxytetralone **2e** (600.0 mg, 3.40 mmol) and (*S*)-*tert*-butanesulfinamide [(*S*)-**1**, 576.0 mg, 4.76 mmol]. Purification by column chromatography (hexane/AcOEt, 4:1) yielded (S_S)-**4a** (417.4 mg, 1.47 mmol, 44%). Physical and spectroscopic data were found to be same than for (R_S)-**4e**. $[\alpha]_D^{20} = -7.2$ ($c = 0.35$, CH_2Cl_2).

(S_S)-*N*-(*tert*-Butanesulfinyl)-6,7-dimethoxy-3,4-dihydronaphthalen-1(2*H*)-imine [(S_S)-4f]:[51] The representative procedure was followed by using 6,7-dimethoxytetralone **2f** (600.0 mg, 2.91 mmol) and (*S*)-*tert*-butanesulfinamide [(*S*)-**1**, 363.0 mg, 3.00 mmol]. Purification by column chromatography (hexane/AcOEt, 4:1) yielded (S_S)-**4f** (269.7 mg, 0.873 mmol, 30%). Physical and spectroscopic data were found to be same than for (R_S)-**4f**. $[\alpha]_D^{20} = -1.5$ ($c = 0.43$, CH_2Cl_2).

(S_S)-*N*-(*tert*-Butanesulfinyl)-7-fluoro-3,4-dihydronaphthalen-1(2*H*)-imine [(S_S)-4g]: The representative procedure was followed by using 7-fluorotetralone **2g** (450.0 mg, 2.74 mmol) and (*S*)-*tert*-butanesulfinamide [(*S*)-**1**, 508.0 mg, 4.20 mmol]. Purification by column chromatography (hexane/AcOEt, 4:1) yielded (S_S)-**4g** (585.3 mg, 2.19 mmol, 80%). Physical and spectroscopic data were found to be same than for (R_S)-**4g**. $[\alpha]_D^{20} = +13.8$ ($c = 0.59$, CH_2Cl_2).

(S_S)-7-Bromo-*N*-(*tert*-butanesulfinyl)-3,4-dihydronaphthalen-1(2*H*)-imine [(S_S)-4h]:[49] The representative procedure was followed by using 7-bromotetralone **2h** (450.0 mg, 1.99 mmol) and (*S*)-*tert*-butanesulfinamide [(*S*)-**1**, 339.0 mg, 2.80 mmol]. Purification by column chromatography (hexane/AcOEt, 4:1) yielded (S_S)-**4h** (509.1 mg, 1.55 mmol, 78%). Physical and spectroscopic data were found to be same than for (R_S)-**4h**. $[\alpha]_D^{20} = -30.7$ ($c = 0.48$, CH_2Cl_2).

General Procedure for the Synthesis of *N*-*tert*-Butanesulfinyl Imines 4i,j from Chromanone (2i) and Thiochromanone (2j), and *tert*-Butanesulfinamide (1): A mixture of *tert*-butanesulfinamide [(*R*)-**1** or (*S*)-**1**, 339.0 mg, 2.8 mmol], the corresponding ketone **2** (2.0 mmol) and $Ti(OEt)_4$ (912 mg, 0.84 mL, 4.0 mmol) in THF (8 mL) was stirred for 12 h at 66 ºC. Then, the resulting mixture was hydrolyzed with brine (8 mL), extracted with EtOAc (3 × 10 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield products **4i**,**j**. Yields, physical and spectroscopic data follow.

(R_S)-*N*-(*tert*-Butanesulfinyl)chroman-4-imine [(R_S)-4i]:[49] The representative procedure was followed by using 4-chromanone **2i** (592.6 mg, 4.00 mmol) and (*R*)-*tert*-butanesulfinamide [(*R*)-**1**, 677.6 mg, 5.60 mmol]. Purification by column chromatography (hexane/AcOEt, 4:1) yielded (R_S)-**4i** (722.8 mg, 2.88 mmol, 72%) as a yellow oil; $[\alpha]_D^{20}$ = –75.3 (*c* = 0.56, CH_2Cl_2); R_f = 0.27 (hexane/EtOAc, 3:1); IR *v* (neat) 2982, 2913, 1611, 1587, 1454, 1306, 1258, 1214, 1077, 1055, 1041, 760 cm^{-1}; δ_H 8.04–7.96 (m, 1H), 7.42–7.34 (m, 1H), 7.01–6.88 (m, 2H), 4.43–4.25 (m, 2H), 3.56–3.44 (m, 1H), 3.34–3.21 (m, 1H), 1.33 (s, 9H); δ_C 169.7 (C), 159.3 (C), 134.3 (CH), 127.0 (CH), 121.4 (CH), 121.1 (C), 118.0 (CH), 65.6 (CH_2), 58.0 (C), 30.7 (CH_2), 22.7 (CH_3); LRMS (EI) *m*/*z* 251 (M^+, 0.2%), 195 (41), 147 (48), 57 (22), 43 (100).

(R_S)-*N*-(*tert*-Butanesulfinyl)thiochroman-4-imine [(R_S)-4j]:[49] The representative procedure was followed by using 4-thiochromanone **2j** (600.0 mg, 3.65 mmol) and (*R*)-*tert*-butanesulfinamide [(*R*)-**1**, 618.3 mg, 5.11 mmol]. Purification by column chromatography (hexane/AcOEt, 4:1) yielded (R_S)-**4j** (760.1 mg, 2.85 mmol, 78%) as a yellow solid; mp 76–79 ºC (hexane/CH_2Cl_2); $[\alpha]_D^{20}$ = −95.0 (*c* = 0.39, CH_2Cl_2); R_f = 0.23 (hexane/EtOAc, 3:1); IR *v* (neat) 2977, 2918, 1565, 1430, 1323, 1149, 1042, 761, 723, 678 cm^{-1}; δ_H 8.18 (d, *J* = 9.4 Hz, 1H), 7.33–7.07 (m, 3H), 3.73–3.60 (m, 1H), 3.51–3.37 (m, 1H), 3.10 (t, *J* = 6.4 Hz, 2H), 1.33 (s, 9H); δ_C 172.7 (C), 139.2 (C), 131.8 (CH_2), 131.4 C), 128.9 (CH_2), 128.1 (CH_2), 125.0 (CH_2), 58.0 (C), 32.5 (CH_2), 25.9 (CH_2), 22.7 (CH_3); LRMS (EI) *m*/*z* 267 (M^+, 0.7%), 211 (76), 163 (100), 135 (42), 57 (27).

(S_S)-*N*-(*tert*-Butanesulfinyl)chroman-4-imine [(S_S)-4i]:[49] The representative procedure was followed by using 4-chromanone **2i** (600.0 mg, 4.04 mmol) and (*S*)-*tert*-butanesulfinamide [(*S*)-**1**, 677.8 mg, 5.60 mmol]. Purification by column chromatography (hexane/AcOEt, 4:1) yielded (S_S)-**4i** (861.9 mg, 3.43 mmol, 85%). Physical and spectroscopic data were found to be same than for (R_S)-**4i**. $[\alpha]_D^{20}$ = +89.4 (*c* = 0.63, CH_2Cl_2).

(S_S)-*N*-(*tert*-Butanesulfinyl)thiochroman-4-imine [(S_S)-4j]:[49] The representative procedure was followed by using 4-thiochromanone **2j** (600.0 mg, 3.65 mmol) and (*S*)-*tert*-butanesulfinamide [(*S*)-**1**, 618.3 mg, 5.11 mmol]. Purification by column chromatography (hexane/AcOEt, 4:1) yielded

(S_S)-**4h** (760.0 mg, 2.85 mmol, 78%). Physical and spectroscopic data were found to be same than for (R_S)-**4j**. $[\alpha]_D^{20} = +89.2$ ($c = 0.34$, CH_2Cl_2).

General Procedure for the Reaction of 2-Bromobenzylmagnesium Bromide (5) 2 with *N*-*tert*-Butanesulfinyl Imines 4. Synthesis of Compounds 6: To a solution of the corresponding imine **4** (1.0 mmol) in dry toluene (4 mL) was added dropwise a 1M solution of 2-bromobenzylmagnesium bromide (**5**) in diethyl ether (3.0 mmol, 3.0 mL) at -78 ºC. The reaction mixture was allowed to reach room temperature for 12 h, and after that, it was cooled down to 0 ºC, hydrolyzed with water (5 mL) and extracted with EtOAc (4 × 15 mL). The organic layers were successively washed with water (15 mL), brine (10 mL) and then dried with anhydrous $MgSO_4$, and the solvent evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield products **6**. Yields are given on Table 1, physical and spectroscopic data follow.

(R_S,1*S*)-1-(2-Bromobenzyl)-*N*-(*tert*-butanesulfinyl)-1,2,3,4-tetrahydronaphthalen-1-amine [(R_S)-6a]: The representative procedure was followed by using imine (R_S)-**4a** (200.0 mg, 0.80 mmol). Purification by column chromatography (hexane/AcOEt, 2:1) yielded (R_S)-**6a** (268.1 mg, 0.64 mmol, 80%) as a yellow oil; $[\alpha]_D^{20} = -24.2$ ($c = 0.56$, CH_2Cl_2); $R_f = 0.37$ (hexane/EtOAc, 3:1); IR ν (neat) 2929,2869, 1469, 1241, 1731, 1043, 908, 761, 728 cm^{-1}; δ_H 7.57 (dd, $J = 7.9$, 1.1 Hz, 1H), 7.32 (d, $J = 7.8$ Hz, 1H), 7.22–7.01 (m, 7H), 3.63 (s, 1H), 3.49 (d, $J = 13.9$ Hz, 1H), 3.29 (d, $J = 13.9$ Hz, 1H), 2.97–2.84 (m, 1H), 2.73 (dt, $J = 16.6$, 4.9 Hz, 1H), 2.40 (ddd, $J = 14.1$, 10.8, 3.4 Hz, 1H), 2.22 (ddd, $J = 14.0$, 6.0, 2.6 Hz, 1H), 2.04–192 (m , 2H), 1.19 (s, 9H); δ_C 139.0 (C), 138.8 (C), 136.2 (C), 133.2 (CH), 132.9 (CH), 129.2 (CH), 128.9 (CH), 128.7 (CH), 127.2 (CH), 127.1 (CH), 126.6 (C), 125.6 (CH), 61.7 (C), 56.8 (C), 48.1 (CH_2), 36.6 (CH_2), 30.1 (CH_2), 22.9 (CH_3), 20.3 (CH_2); LRMS (EI) *m*/*z* 302 (M^+−*t*-$BuSONH_2$, 17%), 301 (97), 299 (100), 250 (30), 194 (65), 176 (35), 171 (51), 169 (51), 129 (49), 117 (88), 57 (26); HRMS (ESI-TOF) *m*/*z*: $(M+H)^+$ Calcd for $C_{21}H_{27}BrNOS$ 420.0997; Found 420.0991.

(R_S,1*S*,4*R)-1-(2-Bromobenzyl)-*N*-(*tert*-butanesulfinyl)-4-methyl-1,2,3,4-tetrahydronaphthalen-1-amine [(R_S)-6b]**: The representative procedure was followed by using imine (R_S)-**4b** (288.0 mg, 1.09 mmol). Purification by column chromatography (hexane/AcOEt, 2:1) yielded (R_S)-**6b** (221.8 mg, 0.51 mmol, 47%) as a mixture of diastereoisomers (1:1); yellow oil; $R_f = 0.72$ (hexane/EtOAc, 1:1); IR ν (neat) 2952, 2865, 1455, 1375, 1187, 1055, 1027, 1010, 771, 760 cm^{-1}; δ_H 7.57 (d, $J = 6.4$ Hz, 2H), 7.38–7.30 (m, 2H), 7.27–7.05 (m, 5H), 7.00 (dd, $J = 7.6$, 1.8 Hz, 1H), 3.58 (s, 1H), 3.56 (d, $J = 2.1$ Hz, 1H), 3.52 (s, 1H), 3.41 (d, $J = 13.9$ Hz, 1H), 3.32 (d, $J = 13.9$ Hz, 1H), 3.25 (d, $J = 13.9$ Hz, 1H), 3.04–2.87 (m, 2H), 2.67–2.54 (m, 1H), 2.40–2.22 (m, 2H), 2.20–2.04 (m, 4H), 1.81–1.63 (m, 3H), 1.42 (d, $J = 9.7$ Hz, 1H), 1.36 (d, $J = 7.2$ Hz, 3H), 1.20 (s, 8H), 1.18 (s, 10H); δ_C 138.7 (C), 138.3 (C), 133.2 (C), 133.1 (C), 131.0 (C), 130.9 (C), 128.0

(CH), 127.9 (CH), 127.7 (CH), 127.4 (CH), 123.6 (CH), 123.5 (CH), 123.4 (CH), 123.3 (CH), 122.5 (CH), 122.1 (CH), 122.1 (CH), 121.8 (CH), 121.7 (CH), 121.4 (C), 121.3 (C), 120.3 (CH), 120.2 (CH), 56.4 (C), 56.3 (C), 51.5 (C), 51.4 (C), 42.8 (CH_2), 42.6 (CH_2), 28.7 (CH_2), 27.6 (CH), 26.4 (CH_2), 23.1 (CH_2), 22.2 (CH_2), 18.1 (CH_3), 17.6 (CH_3), 16.6 (CH_3); LRMS (EI) *m*/*z* 316 (M^+–*t*-$BuSONH_2$, 19%), 171(45), 169 (47), 144 (29), 143 (44), 131(53), 57 (40); HRMS (ESI-TOF) *m*/*z*: $(M+H)^+$ Calcd for $C_{22}H_{29}BrNOS$ 434.1153; Found 434.1144.

(R_S,1*S*)-1-(2-Bromobenzyl)-*N*-(*tert*-butanesulfinyl)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-amine [(R_S)-6c]: The representative procedure was followed by using imine (R_S)-**4c** (390.0 mg, 1.39 mmol). Purification by column chromatography (hexane/AcOEt, 2:1) yielded (R_S)-**6c** (312.0 mg, 0.69 mmol, 50%) as a yellow oil; $[\alpha]_D^{20} = -69.8$ (*c* = 0.38, CH_2Cl_2); R_f = 0.21 (hexane/EtOAc, 3:1); IR *v* (neat) 2952, 2865, 1586, 1430, 1256, 1042, 7 23, 702 cm^{-1}; δ_H 7.58–7.52 (m, 1H), 7.22–6.95 (m, 5H), 6.74 (d, *J* = 8.0 Hz, 1H), 3.81 (s, 3H), 3.57 (s, 1H), 3.51 (d, *J* = 13.9 Hz, 1H), 3.30 (d, *J* = 13.9 Hz, 1H), 2.78–2.55 (m, 2H), 2.39–2.29 (m, 1H), 2.21–2.09 (m, 1H), 1.99–1.85 (m, 1H), 1.18 (s, 9H); δ_C 157.0 (C), 140.5 (C), 136.4 (C), 133.3 (CH), 133.1 (CH), 128.8 (CH), 128.2 (C), 127.2 (CH), 126.7 (C), 125.8 (CH), 120.8 (CH), 108.2 (CH), 61.6 (C), 56.9 (C), 55.4 (CH_3), 47.8 (CH_2), 36.0 (CH_2), 23.4 (CH_2), 23.0 (CH_3), 19.6 (CH_2); LRMS (EI) *m/z* 332 (M^+–*t*-$BuSONH_2$, 19%), 330 (22), 329 (100), 280 (27), 224 (58), 175 (38), 171 (38), 169 (40), 159 (46), 147 (78), 121 (40), 57 (24); HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{22}H_{29}BrNO_2S$ 450.1102; Found 450.1099.

(R_S,1*S*)-1-(2-Bromobenzyl)-*N*-(*tert*-butanesulfinyl)-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-amine [(R_S)-6d]: The representative procedure was followed by using imine (R_S)-**4d** (367.0 mg, 1.31 mmol). Purification by column chromatography (hexane/AcOEt, 2:1) yielded (R_S)-**6d** (175.1 mg, 0.39 mmol, 30%) as a yellow oil; $[\alpha]_D^{20} = -6.5$ (*c* = 0.51, CH_2Cl_2); R_f = 0.31 (hexane/EtOAc, 1:1); IR *v* (neat) 2928, 2831, 1606, 1464, 1439, 1243, 1024, 756, 818 cm^{-1}; δ_H 7.57 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.24–7.14 (m, 2H), 7.14–7.01 (m, 2H), 6.78–6.68 (m, 1H), 6.62 (d, *J* = 2.7 Hz, 1H), 3.81 (s, 4H), 3.55 (s, 1H), 3.45 (d, *J* = 13.9 Hz, 1H), 3.26 (d, *J* = 13.9 Hz, 1H), 2.96–2.84 (m, 1H), 2.70 (dt, *J* = 16.6, 5.0 Hz, 1H), 2.44–2.29 (m, 1H), 2.25–2.12 (m, 1H), 2.02–1.87 (m, 2H), 1.19 (s, 9H); δ_C 158.5 (C), 140.4 (C), 136.5 (C), 133.3 (CH), 133.1 (CH), 131.1 (C), 130.4 (CH), 128.8 (CH), 127.2 (CH), 126.7 (C), 113.0 (CH), 112.6 (CH), 61.4 (C), 56.8 (C), 55.2 (CH_3), 48.3 (CH_2), 37.0 (CH_2), 30.6 (CH_2), 23.0 (CH_3), 20.5 (CH_2); LRMS (EI) *m/z* 332 (M^+–*t*-$BuSONH_2$, 19%), 331 (99), 330 (28), 329 (100), 280 (45), 224 (67), 176 (85), 175 (42), 159 (40), 147 (58), 57 (22); HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{22}H_{29}BrNO_2S$ 450.1102; Found 450.1101.

(R_S,1*S*)-1-(2-Bromobenzyl)-*N*-(*tert*-butanesulfinyl)-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-amine [(R_S)-6e]: The representative procedure was followed by using imine (R_S)-**4e** (397.0 mg, 1.42 mmol). Purification by column chromatography (hexane/AcOEt, 2:1) yielded (R_S)-**6e** (388.9 mg, 0.86 mmol, 61%) as a yellow oil; $[\alpha]_D^{20} = -93.5$ (*c* = 0.20, CH_2Cl_2); R_f = 0.41 (hexane/EtOAc;

1:1), IR *v* (neat) 2943, 2865, 1734, 1466, 1266, 1236, 1040, 761, 732 cm^{-1}; δ_H 7.57 (d, *J* = 8.0 Hz, 1H), 7.20 (t, *J* = 8.1 Hz, 1H), 7.14–7.00 (m, 3H), 6.77 (d, *J* = 8.1 Hz, 2H), 3.66 (s, 3H), 3.59 (s, 1H), 3.47 (d, *J* = 13.8 Hz, 2H), 3.26 (d, *J* = 13.8 Hz, 1H), 2.89–2.78 (m, 1H), 2.69 (dt, *J* = 16.1, 4.7 Hz, 1H), 2.43 (ddd, *J* = 14.3, 11.1, 3.5 Hz, 1H), 2.27–2.16 (m, 2H), 2.04–1.90 (m, 2H), 1.20 (s, 9H); δ_C 157.4 (C), 139.8 (C), 136.4 (C), 133.3 (CH),133.2 (CH), 131.1 (C), 130.3 (CH), 128.8 (CH),127.2 (CH), 126.8 (C), 114.1 (CH), 113.4 (CH), 62.0 (C), 56.9 (C), 55.2 (CH_3), 48.3 (CH_2), 37.1 (CH_2), 29.4 (CH_2), 23.1 (CH_3), 20.6 (CH_2); LRMS (EI) *m/z* 332 (M^+–*t*-$BuSONH_2$, 19%), 331 (98), 330 (23), 329 (100), 224 (48), 206 (22), 175 (20), 174 (41), 159 (40), 57 (21); HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{22}H_{29}BrNO_2S$ 450.1102; Found 450.1106.

(R_S,1*S*)-1-(2-Bromobenzyl)-*N*-(*tert*-butanesulfinyl)-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-amine [(R_S)-6f]: The representative procedure was followed by using imine (R_S)-**4f** (119.0 mg, 0.38 mmol). Purification by column chromatography (hexane/AcOEt, 2:1) yielded (R_S)-**6f** (94.6 mg, 0.197 mmol, 52%) as a yellow oil; $[\alpha]_D^{20}$ = –55.9 (*c* = 0.27, CH_2Cl_2); R_f = 0.20 (hexane/EtOAc, 1:1); IR *v* (neat) 3011, 2923, 1615, 1509, 1463, 1353, 1254, 1213, 1024, 791 cm^{-1}; δ_H 7.55 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.19 (td, *J* = 7.4, 1.2 Hz, 1H), 7.08 (ddd, *J* = 24.7, 7.7, 1.8 Hz, 2H), 6.59 (d, *J* = 13.7 Hz, 2H), 3.88 (s, 3H), 3.77 (s, 1H), 3.63 (s, 3H), 3.48 (d, *J* = 13.9 Hz, 1H), 3.24 (d, *J* = 13.9 Hz, 1H), 2.88–2.82 (m, 1H), 2.70–2.65 (m, 1H), 2.48–2.42 (m, 1H), 2.27–2.22 (m, 1H), 2.09–1.98 (m, 2H), 1.21 (s, 9H); δ_C 148.3 (C), 146.6 (C), 136.5 (C), 133.2 (CH), 133.3 (CH), 131.6 (C), 130.0 (C), 128.7 (CH), 127.2 (CH), 126.8 (C) 111.8 (CH), 111.3 (CH), 61.8 (C), 56.8 (C), 55.8 (CH_3), 55.6 (CH_3), 48.4 (CH_2), 37.8 (CH_2), 29.9 (CH_2), 23.0 (CH_3), 20.8 (CH_2); LRMS (EI) *m/z* 362 (M^+–*t*-$BuSONH_2$, 22%), 361(98), 360 (32), 359 (100), 310 (70), 254 (59), 206 (43), 205 (50), 204 (35), 190 (66), 57 (26); HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{23}H_{31}BrNO_3S$ 480.1208; Found 480.1207.

(R_S,1*S*)-1-(2-Bromobenzyl)-*N*-(*tert*-butanesulfinyl)-7-fluoro-1,2,3,4-tetrahydronaphthalen-1-amine [(R_S)-6g]: The representative procedure was followed by using imine (R_S)-**4g** (513.0 mg, 1.92 mmol). Purification by column chromatography (hexane/AcOEt, 2:1) yielded (R_S)-**6g** (545.3 mg, 1.24 mmol, 65%) as a colourless oil; $[\alpha]_D^{20}$ = –54.7 (*c* = 0.45, CH_2Cl_2); R_f = 0.30 (hexane/EtOAc, 3:1); IR *v* (neat) 2947, 1610, 1483, 1251, 1047, 912, 727 cm^{-1}; δ_H 7.59 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.28–7.19 (m, 1H), 7.11 (p, *J* = 7.7 Hz, 3H), 7.00–6.85 (m, 2H), 3.61 (s, 1H), 3.41 (d, *J* = 13.9 Hz, 1H), 3.25 (d, *J* = 13.9 Hz, 1H), 2.90–2.69 (m, 2H), 2.48–2.17 (m, 2H), 2.03 (d, *J* = 8.8 Hz, 2H), 1.21 (s, 9H); δ_C 160.8 (d, *J* = 242.8 Hz, C), 141.0 (d, *J* = 6.3 Hz, C), 135.7 (C), 134.4 (d, *J* = 2.7 Hz, C), 133.4 (CH), 133.0 (CH), 130.6 (d, *J* = 7.6 Hz, CH), 129.0 (CH), 127.2 (CH), 126.5 (CH), 115.21 (d, *J* = 22.0 Hz, CH), 114.6 (d, *J* = 21.3 Hz, CH), 61.6 (C), 57.0 (C), 47.9 (CH_2), 36.4 (CH_2), 29.3 CH_2), 22.9 (CH_3), 20.4 (CH_2); δ_F –116.84 (1F); LRMS (EI) *m/z* 320 (M^+–*t*-$BuSONH_2$,

18%), 319 (98), 318 (20), 317 (100), 212 (68), 171 (77), 169 (78), 147 (44), 135 (74), 57 (38); HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{21}H_{26}BrFNOS$ 438.0903; Found 438.0902.

(R_S,1*S*)-7-Bromo-1-(2-bromobenzyl)-*N*-(*tert*-butanesulfinyl)-1,2,3,4-tetrahydronaphthalen-1-amine [(R_S)-6h]: The representative procedure was followed by using imine (R_S)-**4h** (481.0 mg, 1.46 mmol). Purification by column chromatography (hexane/AcOEt, 2:1) yielded (R_S)-**6h** (370.0 mg, 0.74 mmol, 51%) as a white solid; mp 130–132 ºC (hexane/CH_2Cl_2); $[\alpha]_D^{20} = -59.5$ (c = 0.38, CH_2Cl_2); R_f = 0.30 (hexane/EtOAc, 3:1); IR ν (neat) 2947, 1474, 1270, 1037, 912, 737, 707 cm^{-1}; δ_H 7.59 (d, J = 8.0 Hz, 1H), 7.30 (s, 1H), 7.28–7.20 (m, 1H), 7.15 (d, J = 7.8 Hz, 1H), 7.08–6.96 (m, 1H), 3.64 (s, 1H), 3.40 (d, J = 13.9 Hz, 1H), 3.24 (d, J = 13.9 Hz, 1H), 2.62–2.92 (m, 2H), 2.47–2.32 (m, 1H), 2.31–2.14 (m, 1H), 2.02 (d, J = 9.7 Hz, 2H), 1.20 (s, 9H); δ_C 141.1 (C), 137.6 (C), 135.7 (C), 133.2 (CH), 132.2 (CH), 130.9 (CH), 130.2 (CH), 129.0 (CH), 127.2 (CH), 126.6 (CH), 119.0 (C), 61.6 (C), 57.2 (C), 48.0 (CH_2), 36.8 (CH_2), 29.6 (CH_2), 23.0 (CH_3), 20.4 (CH_2); LRMS (EI) *m/z* 381 (M^+–*t*-BuSONH$_2$, 50%), 380 (20), 379 (100), 377 (52), 197 (35), 195 (36), 171 (82), 169 (86), 57 (39); HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{21}H_{26}Br_2NOS$ 498.0102; Found 498.0101.

(R_S,4*R*)-4-(2-Bromobenzyl)-*N*-(*tert*-butanesufinyl)chroman-4-amine [(R_S)-6i]: The representative procedure was followed by using imine (R_S)-**4i** (340.0 mg, 1.35 mmol). Purification by column chromatography (hexane/AcOEt, 2:1) yielded (R_S)-**6i** (522.8 mg, 1.24 mmol, 92%) as a yellow solid; mp 52–54 ºC (hexane/CH_2Cl_2); $[\alpha]_D^{20} = -17.8$ (c = 0.60, CH_2Cl_2); R_f = 0.26 (hexane/EtOAc, 1:1); IR ν (neat) 2952, 1488, 1459, 1216, 1061, 1032, 761, 742 cm^{-1}; δ_H 7.57 (dd, J = 7.9, 1.4 Hz, 1H), 7.23–7.03 (m, 5H), 7.00–6.78 (m, 2H), 4.46–4.21 (m, 2H), 3.69 (s, 1H), 3.59 (d, J = 13.9 Hz, 1H), 3.36 (d, J = 13.9 Hz, 1H), 2.57 (ddd, J = 14.5, 8.3, 3.6 Hz, 1H), 2.41–2.24 (m, 1H), 1.20 (s, 9H); δ_C 156.0 (C), 135.7 (C), 133.5 (CH), 132.8 (CH), 129.3 (CH), 129.0 (CH), 128.9 (CH), 127.3 (CH), 126.7 (C), 124.4 (C), 120.4 (CH), 117.7 (CH), 63.4 (CH_2), 57.6 (C), 56.9 (C), 48.2 (CH_2), 35.6 (CH_2), 23.0 (CH_3); LRMS (EI) *m/z* 304 (M^+–*t*-BuSONH$_2$, 17%), 303 (97), 302 (19), 301 (100), 196 (33), 171 (16), 169 (17), 57 (21); HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{20}H_{25}BrNO_2S$ 422.0789; Found 422.0781.

(R_S,4*R*)-4-(2-Bromobenzyl)-*N*-(*tert*-butanesufinyl)thiochroman-4-amine [(R_S)-6j]: The representative procedure was followed by using imine (R_S)-**4j** (490.0 mg, 1.83 mmol). Purification by column chromatography (hexane/AcOEt, 2:1) yielded (R_S)-**6j** (447.8 mg, 1.02 mmol, 56%) as a colourless oil; $[\alpha]_D^{20} = -44.2$ (c = 0.36, CH_2Cl_2); R_f = 0.30 (hexane/EtOAc, 3:1); IR ν (neat) 3049, 1474, 1430, 1256, 1042, 732, 712 cm^{-1}; δ_H 7.58–7.54 (m, 1H), 7.21–7.09 (m, 5H), 6.95 (d, J = 8.1 Hz, 1H), 6.82 (dd, J = 7.4, 2.0 Hz, 1H), 3.79 (s, 1H), 3.50 (d, J = 14.0 Hz, 1H), 3.32 (d, J = 14.0 Hz, 1H), 3.29–3.11 (m, 2H), 2.77 (t, J = 14.5 Hz, 1H), 2.59–2.51 (m, 1H), 1.20 (s, 9H); δ_C 135.3 (C), 135.1 (C), 134.7 (C), 133.1 (CH), 133.0 (CH), 129.8 (CH), 128.8 (CH), 128.5 (CH), 127.6 (CH),

127.1 (CH), 126.5 (C), 123.5 (CH), 60.44 (C), 57.23 (C), 46.95 (CH_2), 37.24 (CH_2), 23.50 (CH_2), 23.05 (CH_3); LRMS (EI) *m/z* 320 (M^+–*t*-BuSONH$_2$, 18%), 319 (99), 318 (19), 317 (100), 238 (26), 212 (27), 135 (63), 57 (27); HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{20}H_{25}BrNOS_2$ 438.0561; Found 438.0563.

(*S*$_S$,1*R*)-1-(2-Bromobenzyl)-*N*-(*tert*-butanesulfinyl)-1,2,3,4-tetrahydronaphthalen-1-amine [(*S*$_S$)-6a]: The representative procedure was followed by using imine (*S*$_S$)-**4a** (338.0 mg, 1.35 mmol). Purification by column chromatography (hexane/AcOEt, 2:1) yielded (*S*$_S$)-**6a** (396.0 mg, 0.94 mmol, 70%). Physical and spectroscopic data were found to be same than for (*R*$_S$)-**6a**. $[\alpha]_D^{20}$ = +53.1 (*c* = 0.43, CH_2Cl_2).

(*S*$_S$,1*R*)-1-(2-Bromobenzyl)-*N*-(*tert*-butanesulfinyl)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-amine [(*S*$_S$)-6c]: The representative procedure was followed by using imine (*S*$_S$)-**4c** (331.0 mg, 1.18 mmol). Purification by column chromatography (hexane/AcOEt, 2:1) yielded (*S*$_S$)-**6c** (243.7 mg, 0.54 mmol, 46%). Physical and spectroscopic data were found to be same than for (*R*$_S$)-**6c**. $[\alpha]_D^{20}$ = +29.8 (*c* = 0.64, CH_2Cl_2).

(*S*$_S$,1*R*)-1-(2-Bromobenzyl)-*N*-(*tert*-butanesulfinyl)-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-amine [(*S*$_S$)-6d]: The representative procedure was followed by using imine (*S*$_S$)-**4d** (254.0 mg, 0.91 mmol). Purification by column chromatography (hexane/AcOEt, 2:1) yielded (*S*$_S$)-**6d** (143.0 mg, 0.32 mmol, 35%). Physical and spectroscopic data were found to be same than for (*R*$_S$)-**6d**. $[\alpha]_D^{20}$ = +39.2 (*c* = 0.21, CH_2Cl_2).

(*S*$_S$,1*R*)-1-(2-Bromobenzyl)-*N*-(*tert*-butanesulfinyl)-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-amine [(*S*$_S$)-6e]: The representative procedure was followed by using imine (*S*$_S$)-**4e** (278.0 mg, 0.99 mmol). Purification by column chromatography (hexane/AcOEt, 2:1) yielded (*S*$_S$)-**6e** (231.1 mg, 0.51 mmol, 52%) Physical and spectroscopic data were found to be same than for (*R*$_S$)-**6e**. $[\alpha]_D^{20}$ = +49.6 (*c* = 0.42, CH_2Cl_2).

(*S*$_S$,1*R*)-1-(2-Bromobenzyl)-*N*-(*tert*-butanesulfinyl)-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-amine [(*S*$_S$)-6f]: The representative procedure was followed by using imine (*S*$_S$)-**4f** (160.0 mg, 0.51 mmol). Purification by column chromatography (hexane/AcOEt, 2:1) yielded (*S*$_S$)-**6f** (105.0 mg, 0.22 mmol, 43%). Physical and spectroscopic data were found to be same than for (*R*$_S$)-**6f**. $[\alpha]_D^{20}$ = +34.3 (*c* = 0.36, CH_2Cl_2).

(*S*$_S$,1*R*)-1-(2-Bromobenzyl)-*N*-(*tert*-butanesulfinyl)-7-fluoro-1,2,3,4-tetrahydronaphthalen-1-amine [(*S*$_S$)-6g]: The representative procedure was followed by using imine (*S*$_S$)-**4g** (444.0 mg, 1.66 mmol). Purification by column chromatography (hexane/AcOEt, 2:1) yielded (*S*$_S$)-**6g** (544.0 mg, 1.24 mmol, 75%). Physical and spectroscopic data were found to be same than for (*R*$_S$)-**6g**. $[\alpha]_D^{20}$ = +50.6 (*c* = 0.64, CH_2Cl_2).

(S_S,1*R*)-7-Bromo-1-(2-bromobenzyl)-*N*-(*tert*-butanesulfinyl)-1,2,3,4-tetrahydronaphthalen-1-amine [(S_S)-6h]: The representative procedure was followed by using imine (S_S)-**4h** (317.0 mg, 0.96 mmol). Purification by column chromatography (hexane/AcOEt, 2:1) yielded (S_S)-**6h** (282.2 mg, 0.57 mmol, 60%). Physical and spectroscopic data were found to be same than for (R_S)-**6h**. $[\alpha]_D^{20} = +47.7$ ($c = 0.54$, CH_2Cl_2).

(S_S,4*S*)-4-(2-Bromobenzyl)-*N*-(*tert*-butanesufinyl)chroman-4-amine [(S_S)-6i]: The representative procedure was followed by using imine (S_S)-**4i** (400.0 mg, 1.60 mmol). Purification by column chromatography (hexane/AcOEt, 2:1) yielded (S_S)-**6i** (572.5 mg, 1.36 mmol, 85%). Physical and spectroscopic data were found to be same than for (R_S)-**6i**. $[\alpha]_D^{20} = +21.5$ ($c = 0.90$, CH_2Cl_2).

(S_S,4*S*)-4-(2-Bromobenzyl)-*N*-(*tert*-butanesufinyl)thiochroman-4-amine [(S_S)-6j]: The representative procedure was followed by using imine (S_S)-**4j** (490.0 mg, 1.83 mmol). Purification by column chromatography (hexane/AcOEt, 2:1) yielded (S_S)-**6j** (543.8 mg, 1.24 mmol, 68%). Physical and spectroscopic data were found to be same than for (R_S)-**6j**. $[\alpha]_D^{20} = +40.3$ ($c = 0.32$, CH_2Cl_2).

General Procedure for the Synthesis of Spiro compounds 8 from Sulfinamides 6: To a solution of the corresponding sulfinamide **6** (0.5 mmol) in MeOH (5.0 mL) was added a 2M solution of HCl in Et_2O (2.5 mL, 5.0 mmol). The reaction mixture was stirred at 23 ºC for 2 h. Removal of the *tert*-butanesulfinyl group with concomitant formation of the free amine hydrochloride was followed by TLC. Solvents were evaporated (15 Torr) and the resulting residue was treated with CH_2Cl_2 (20 mL) and saturated aqueous solution of $NaHCO_3$ (15 mL). The organic layer was dried over with anhydrous $MgSO_4$, and the solvent evaporated (15 Torr). The resulting free amine **7** was transferred to a high pressure flask, and triphenylphosphine (19.7 mg, 0.075 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), Cs_2CO_3 (325 mg, 1.0 mmol) and toluene (5 mL) were successively added. The reaction mixture was stirred at 110 ºC for 20 h. After that it was cooled down to room temperature and hydrolyzed, first with 3M HCl (3.0 mmol, 1 mL), then with 2M NaOH (8.0 mmol, 4 mL), and extracted with EtOAc (4 × 15 mL). The organic layers were successively washed with brine (15 mL) and then dried with anhydrous $MgSO_4$, and concentrate under vacuum (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield products **8**. Yields are given on Table 2, physical and spectroscopic data follow.

(*S*)-3',4'-Dihydro-2'*H*-spiro[indoline-2,1'-naphthalene] [(*S*)-8a]: The representative procedure was followed by using (R_S)-**6a** (86.0 mg, 0.20 mmol). Purification by column chromatography (hexane/AcOEt, 20:1) yielded (*S*)-**8a** (31.0 mg, 0.132 mmol, 66%) as a yellow solid; mp 75–77 ºC (hexane/CH_2Cl_2); $[\alpha]_D^{20} = -15.0$ ($c = 0.45$, CH_2Cl_2); $R_f = 0.50$ (hexane/EtOAc, 9:1); IR ν (neat) 3375, 2933, 2851, 1606, 1484, 1433, 1258, 1104, 1024, 767, 745 cm^{-1}; δ_H 7.62–7.49 (m, 1H), 7.09

(dt, *J* = 27.6, 7.5 Hz, 5H), 6.73 (t, *J* = 7.4 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 3.28 (d, *J* = 16.1 Hz, 1H), 3.22 (d, *J* = 16.1 Hz, 1H), 2.89–2.74 (m, 2H), 2.16–2.06 (m, 1H), 1.90 (t, *J* = 7.4 Hz, 3H); δ_C 149.8 (C), 143.3 (C), 136.3 (C), 128.8 (CH), 127,6 (CH) 127.4 (C), 126.9 (CH), 126.7 (CH) 126.5 (CH), 124.8 (CH), 118.8 (CH), 109.0 (CH), 64.9 (C), 46.4 (CH_2), 37.7 (CH_2), 29.7 (CH_2), 20.3 (CH_2); LRMS (EI) *m/z* 235 (M^+, 100%), 234 (34), 220 (43), 207 (34), 206 (54), 106 (51); HRMS (EI) *m/z*: M^+ Calcd for $C_{17}H_{17}N$ 235.1361; Found 235.1362.

(2*S*,4'*R)-4'-Methyl-3',4'-dihydro-2'*H*-spiro[indoline-2,1'-naphthalene] [(*S*)-8b]**: The representative procedure was followed by using (R_S)-**6b** (113.0 mg, 0.26 mmol). Purification by column chromatography (hexane/AcOEt, 20:1) yielded (*S*)-**8b** (20.7 mg, 0.083 mmol, 32%) as a mixture of diastereoisomers (1:1); yellow solid; mp 60–63 ºC (hexane/CH_2Cl_2); R_f = 0.51 (hexane/EtOAc, 9:1); IR *v* (neat) 3392, 2924, 1725, 1607, 1484, 1463, 1261, 1018, 743 cm^{-1}; δ_H 7.59 (t, *J* = 5.1 Hz, 2H), 7.34–6.99 (m, 12H), 6.86–6.47 (m, 2H), 3.30 (d, *J* = 3.5 Hz, 2H), 3.27 (s, 2H), 2.99 (dd, *J* = 13.6, 7.7 Hz, 2H), 2.32–2.05 (m, 6H), 1.97–1.84 (m, 1H), 1.78–1.58 (m, 3H), 1.38 (d, *J* = 1.9 Hz, 3H), 1.36 (d, *J* = 2.1 Hz, 3H); δ_C 141.4 (C), 141.1 (C), 128.3 (CH), 127.7 (CH), 127.6 (CH), 127.2 (CH), 126.7 (CH), 126.5 (CH), 126.5 (CH), 124.8 (CH), 118.8 (CH), 109.1 (CH), 65.1 (C), 60.4 (C), 46.3 (CH_2), 36.0 (CH_2), 33.7 (CH_2), 32.8 (CH_3), 32.3 (CH_3), 29.7 (CH_2), 29.0 (CH_2) 28.2 (CH_2), 23.2 (CH_3), 22.4 (CH_3); LRMS (EI) *m/z* 249 (M^+, 100%), 248 (30), 234 (74), 106 (53); HRMS (EI) *m/z*: M^+ Calcd for $C_{18}H_{19}N$ 249.1517; Found 249.1511.

(*S*)-5'-Methoxy-3',4'-dihydro-2'*H*-spiro[indoline-2,1'-naphthalene] [(*S*)-8c]: The representative procedure was followed by using (R_S)-**6c** (143.0 mg, 0.32 mmol). Purification by column chromatography (hexane/AcOEt, 20:1) yielded (*S*)-**8c** (50.8 mg, 0.192 mmol, 60%) as a yellow solid; mp 104–107 ºC (hexane/CH_2Cl_2); $[\alpha]_D^{20} = -1.3$ (*c* = 0.76, CH_2Cl_2); R_f = 0.48 (hexane/EtOAc, 9:1); IR *v* (neat) 3392, 2918, 2854, 1604, 1582, 1458, 1435, 1247, 1031, 780, 742 cm^{-1}; δ_H 7.20–7.08 (m, 4H), 6.81–6.65 (m, 3H), 3.85 (s, 3H), 3.34–3.18 (m, 2H), 2.74–2.69 (m, 2H), 2.06 (d, *J* = 12.1 Hz, 1H), 1.95–1.83 (m, 3H); δ_C 158.0 (C), 152.3 (C), 146.2 (C), 128.6 (C) 128.4 (CH), 127.4 (CH), 126.2 (C), 125.4 (CH), 119.5 (CH), 119.1 (CH), 109.6 (CH), 108.7 (CH), 65.6 (C), 55.8 (CH_3), 47.4 (CH_2), 38.1 (CH_2), 24.2 (CH_2), 20.6 (CH_2); LRMS (EI) *m/z* 265 (M^+, 100%), 264 (36), 250 (42), 106 (56); HRMS (EI) *m/z*: M^+ Calcd for $C_{18}H_{19}NO$ 265.1467; Found 265.1462.

(*S*)-6'-Methoxy-3',4'-dihydro-2'*H*-spiro[indoline-2,1'-naphthalene] [(*S*)-8d]: The representative procedure was followed by using imine (R_S)-**6d** (30.4 mg, 0.067 mmol). Purification by column chromatography (hexane/AcOEt, 20:1) yielded (*S*)-**8d** (8.5 mg, 0.032 mmol, 48%) as a yellow solid; mp 96–98 ºC (hexane/CH_2Cl_2); $[\alpha]_D^{20} = -50.1$ (*c* = 0.71, CH_2Cl_2); R_f = 0.30 (hexane/EtOAc, 9:1); IR *v* (neat) 3397, 2940, 2924, 1604, 1482, 1464, 1242, 1226, 1034, 1021, 837, 744 cm^{-1}; δ_H 7.45 (d, *J* = 8.7 Hz, 1H), 7.18–7.07 (m, 2H), 6.94–6.67 (m, 3H), 6.61 (s, 1H), 3.77 (s, 3H), 3.31 (d, *J* = 24.4 Hz, 2H), 2.83 (d, *J* = 20.1 Hz, 2H), 2.12–1.84 (m, 4H); δ_C 159.7 (C), 152.2 (C), 138.7 (C),

137.3 (C), 128.8 (CH), 128.7 (C), 128.4 (CH), 125.4 (CH), 119.1 (CH), 113.6 (CH), 113.6 (CH), 109.7 (CH), 65.5 (C), 55.5 (CH_3), 47.5 (CH2), 38.8 (CH_2), 31.1 (CH_2), 21.5 (CH_2); LRMS (EI) *m/z* 265 (M^+, 100%), 264 (40), 250 (48), 237 (29); HRMS (EI) *m/z*: M^+ Calcd for $C_{18}H_{19}NO$ 265.1467; Found 265.1481.

(*S*)-7'-Methoxy-3',4'-dihydro-2'*H*-spiro[indoline-2,1'-naphthalene] [(*S*)-8e]: The representative procedure was followed by using imine (R_S)-**6e** (195.0 mg, 0.42 mmol). Purification by column chromatography (hexane/AcOEt, 20:1) yielded (*S*)-**8e** (69.0 mg, 0.26 mmol, 62%) as a yellow solid; mp 100–103 ºC (hexane/CH_2Cl_2); $[\alpha]_D^{20} = -18.7$ (*c* = 0.83, CH_2Cl_2); R_f = 0.40 (hexane/EtOAc, 9:1); IR *v* (neat) 3392, 2918, 2854, 1604, 1582, 1487, 1458, 1435, 1247, 1031, 780, 742 cm^{-1}; δ_H 7.18 (d, *J* = 2.7 Hz, 1H), 7.14–6.98 (m, 3H), 6.80–6.72 (m, 2H), 6.67 (d, *J* = 4.8 Hz, 1H), 3.73 (s, 3H), 3.26 (s, 2H), 2.79 (d, *J* = 6.3 Hz, 2H), 2.19–2.08 (m, 1H), 1.94–1.88 (m, 3H) ; δ_C 158.2 (C), 150.0 (C), 144.5 (C), 129.8 (CH), 128.7 (C), 127.7 (CH), 127.4 (CH), 124.9 (CH), 118.8 (CH), 113.8 (CH), 111.2 (CH), 109.1 (CH), 65.4 (C), 55.4 (CH_3), 46.4 (CH_2), 37.4 (CH_2), 20.5 (CH_2); LRMS (EI) *m/z* 265 (M^+, 100%), 264 (29), 250 (37), 237 (38), 236 (44), 192 (19), 159 (26), 144 (22), 115 (24), 106 (52); HRMS (EI) *m/z*: M^+ Calcd for $C_{18}H_{19}NO$ 265.1467; Found 265.1452.

(*S*)-6',7'-Dimethoxy-3',4'-dihydro-2'*H*-spiro[indoline-2,1'-naphthalene] [(*S*)-8f]: The representative procedure was followed by using imine (R_S)-**6f** (40.9 mg, 0.085 mmol). Purification by column chromatography (hexane/AcOEt, 20:1) yielded (*S*)-**8f** (10.1 mg, 0.034 mmol, 40%) as a yellow solid; mp 120–121 ºC (hexane/CH_2Cl_2); $[\alpha]_D^{20} = -23.7$ (*c* = 0.44, CH_2Cl_2); R_f = 0.12 (hexane/EtOAc, 9:1); IR *v* (neat) 3060, 2928, 2852, 1608, 1509, 1462, 1253, 1217, 1125, 746 cm^{-1}; δ_H 7.13 (s, 1H), 7.12–7.03 (m, 2H), 6.88–6.64 (m, 2H), 6.55 (s, 1H), 3.86 (s, 3H), 3.74 (s, 3H), 3.23 (d, *J* = 4.3 Hz, 2H), 2.76 (d, *J* = 5.6 Hz, 2H), 2.13 (d, *J* = 9.8 Hz, 1H), 1.90 (d, *J* = 5.1 Hz, 3H); δ_C 152.3 (C), 149.3 (C), 148.7 (C), 137.1 (C), 130.3 (C), 128.7 (C), 128.5 (CH), 125.5 (CH), 119.1 (CH), 112.6 (CH), 111.1 (CH), 109.7 (CH), 65.9 (C), 56.3 (CH_3), 56.2 (CH_3), 47.3 (CH_2), 38.2 (CH_2), 30.3 (CH_2), 21.6 (CH_2); LRMS (EI) *m/z* 295 (M^+, 100%), 280 (28), 264 (46), 189 (38), 180 (28), 108 (29), 106 (32); HRMS (EI) *m/z*: M^+ Calcd for $C_{19}H_{21}NO_2$ 295.1572; Found 295.1571.

(*S*)-7'-Fluoro-3',4'-dihydro-2'*H*-spiro[indoline-2,1'-naphthalene] [(*S*)-8g]: The representative procedure was followed by using imine (R_S)-**6g** (140.0 mg, 0.32 mmol). Purification by column chromatography (hexane/AcOEt, 20:1) yielded (*S*)-**8g** (51.8 mg, 0.205 mmol, 64%) as a yellow solid; mp 65–68 ºC (hexane/CH_2Cl_2); $[\alpha]_D^{20} = -21.9$ (*c* = 0.96, CH_2Cl_2); R_f = 0.44 (hexane/EtOAc, 9:1); IR *v* (neat) 3364, 2925, 2843, 1718, 1609, 1484, 1466, 1261, 1220, 1024, 875, 743 cm^{-1}; δ_H 7.31–7.22 (m, 1H), 7.04 (dd, *J* = 16.9, 6.7 Hz, 3H), 6.81 (d, *J* = 36.9 Hz, 2H), 6.69 (s, 1H), 3.23 (s, 2H), 2.79 (d, *J* = 11.7 Hz, 2H), 2.12 (d, *J* = 19.9 Hz, 1H), 1.92–1.83 (m, 3H); δ_C 161.2 (d, *J* = 242.1 Hz, C), 150.7 (C), 146.0 (d, *J* = 6.3 Hz, C), 137.1 (C), 129.9 (d, *J* = 7.7 Hz, CH), 127.2 (CH), 126.6 (C), 124.1 (CH), 117.8 (CH), 113.3 (d, *J* = 21.8 Hz, CH), 112.2 (d, *J* = 21.7 Hz, CH), 108.2 (CH),

64.5 (C), 46.1 (CH_2), 36.4 (CH_2), 28.5 (CH_2), 19.9 (CH_2); LRMS (EI) *m/z* 253 (M^+, 100%), 252 (28), 238 (37), 225 (30), 224 (44), 106 (39); HRMS (EI) *m/z*: M^+ Calcd for $C_{17}H_{16}FN$ 253.1267; Found 253.1257.

(*S*)-7'-Bromo-3',4'-dihydro-2'*H*-spiro[indoline-2,1'-naphthalene] [(*S*)-8h]: The representative procedure was followed by using imine (R_S)-**6h** (100.0 mg, 0.20 mmol). Purification by column chromatography (hexane/AcOEt, 20:1) yielded (*S*)-**8h** (18.8 mg, 0.060 mmol, 30%) as a yellow solid; mp 131–134 ºC (hexane/CH_2Cl_2); $[\alpha]_D^{20}$ = –30.2 (*c* = 0.98, CH_2Cl_2); R_f = 0.47 (hexane/EtOAc, 9:1); IR *v* (neat) 3368, 2928, 2861, 1719, 1606, 1482, 1464, 1262, 1020, 815, 744, 708 cm^{-1}; δ_H 7.78 (s, 1H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.10 (d, *J* = 7.6 Hz, 2H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.82 (d, *J* = 7.3 Hz, 1H), 3.25 (s, 2H), 2.79 (t, *J* = 6.2 Hz, 2H), 2.15 (d, *J* = 9.4 Hz, 1H), 1.94–1.87 (m, 3H); δ_C 152.0 (C), 147.7 (C), 136.6 (C), 131.6 (CH), 130.7 (CH), 130.6 (CH), 128.6 (CH), 127.8 (C), 125.5 (CH), 120.5 (C), 119.2 (CH), 109.6 (CH), 65.7 (C), 47.5 (CH_2), 37.7 (CH_2), 30.0 (CH_2), 21.0 (CH_2); LRMS (EI) *m/z* 315 (M^+, 96%), 313 (100), 300 (29), 298 (32), 204 (39), 106 (61); HRMS (EI) *m/z*: M^+ Calcd for $C_{17}H_{16}BrN$ 313.0466; Found 313.0455.

(*R*)-Spiro[chromane-4,2'-indoline] [(*R*)-8i]: The representative procedure was followed by using imine (R_S)-**6i** (224.0 mg, 0.53 mmol). Purification by column chromatography (hexane/AcOEt, 20:1) yielded (*R*)-**8i** (71.6 mg, 0.30 mmol, 57%) as a yellow solid; mp 110–112 ºC (hexane/CH_2Cl_2); $[\alpha]_D^{20}$ = –30.1 (*c* = 0.91, CH_2Cl_2); R_f = 0.30 (hexane/EtOAc, 9:1); IR *v* (neat) 3370, 3046, 1606, 1482,1448, 1248, 1226, 1052, 1033, 761, 746 cm^{-1}; δ_H 7.49 (d, *J* = 7.8 Hz, 1H), 7.23–7.10 (m, 3H), 6.87 (m, 3H), 6.75 (d, *J* = 7.8 Hz, 1H), 4.33 (d, *J* = 28.0 Hz, 2H), 3.52–3.42 (m, 1H), 3.23 (d, *J* = 16.1 Hz, 1H), 2.24 (d, *J* = 10.7 Hz, 2H); δ_C 153.8 (C), 150.5 (C), 129.3 (C), 128.0 (CH), 127.2 (CH), 126.7 (C), 126.5 (CH), 124.1 (CH), 120.2 (CH), 118.0 (CH), 116.2 (CH), 108.5 (CH), 63.5 (CH_2), 60.6 (C), 45.6 (CH_2), 35.7 (CH_2); LRMS (EI) *m/z* 237 (M^+, 100%), 238 (18), 236 (58), 210 (47), 180 (49), 131 (32), 89 (32), 77 (32); HRMS (EI) *m/z*: M^+ Calcd for $C_{16}H_{15}NO$ 237.1154; Found 237.1137.

(*R*)-Spiro[indoline-2,4'-thiochromane] [(*R*)-8j]: The representative procedure was followed by using imine (R_S)-**6j** (258.0 mg, 0.61 mmol). Purification by column chromatography (hexane/AcOEt, 20:1) yielded (*R*)-**8j** (103.8 mg, 0.41 mmol, 67%) as a yellow solid; mp 103–105 ºC (hexane/CH_2Cl_2); $[\alpha]_D^{20}$ = –44.3 (*c* = 0.92, CH_2Cl_2); R_f = 0.40 (hexane/EtOAc, 9:1); IR *v* (neat) 3370, 2944, 1066, 1482, 1448, 1259, 1248, 1052, 761 cm^{-1}; δ_H 7.54 (d, *J* = 8.2 Hz, 1H), 7.16–6.94 (m, 5H), 6.86–6.65 (m, 2H), 3.34–3.27 (m, 4H), 2.46–2.19 (m, 2H); δ_C 150.6 (C), 140.4 (C), 132.3 (C), 127.2 (CH), 126.7 (CH), 126.6 (CH), 126.4 (CH), 125.8 (CH), 124.1 (CH), 123.8 (CH), 117.8 (CH), 108.1 (CH), 63.4 (C), 44.7 (CH_2), 35.3 (CH_2), 22.8 (CH_2); LRMS (EI) *m/z* 253 (M^+, 100%), 226 (52), 223 (38), 147 (34); HRMS (EI) *m/z*: M^+ Calcd for $C_{16}H_{15}NS$ 253.0925; Found 253.0919.

(*R*)-3',4'-Dihydro-2'*H*-spiro[indoline-2,1'-naphthalene] [(*R*)-8a]: The representative procedure was followed by using imine (S_S)-**6a** (178.0 mg, 0.42 mmol). Purification by column chromatography (hexane/AcOEt, 20:1) yielded (*R*)-**8a** (55.3 mg, 0.235 mmol, 56%). Physical and spectroscopic data were found to be same than for (*S*)-**8a**. $[\alpha]_D^{20} = +16.5$ ($c = 0.53$, CH_2Cl_2).

(*R*)-5'-Methoxy-3',4'-dihydro-2'*H*-spiro[indoline-2,1'-naphthalene] [(*R*)-8c]: The representative procedure was followed by using imine (S_S)-**6c** (80.0 mg, 0.17 mmol). Purification by column chromatography (hexane/AcOEt, 20:1) yielded (*R*)-**8c** (25.7 mg, 0.097 mmol, 57%). Physical and spectroscopic data were found to be same than for (*S*)-**8c**. $[\alpha]_D^{20} = +2.5$ ($c = 0.83$, CH_2Cl_2).

(*R*)-6'-Methoxy-3',4'-dihydro-2'*H*-spiro[indoline-2,1'-naphthalene] [(*R*)-8d]: The representative procedure was followed by using imine (S_S)-**6d** (135.0 mg, 0.30 mmol). Purification by column chromatography (hexane/AcOEt, 20:1) yielded (*R*)-**8d** (46.2 mg, 0.174 mmol, 58%). Physical and spectroscopic data were found to be same than for (*S*)-**8d**. $[\alpha]_D^{20} = +47.7$ ($c = 0.54$, CH_2Cl_2).

(*R*)-7'-Methoxy-3',4'-dihydro-2'*H*-spiro[indoline-2,1'-naphthalene] [(*R*)-8e]: The representative procedure was followed by using imine (S_S)-**6e** (160.0 mg, 0.35 mmol). Purification by column chromatography (hexane/AcOEt, 20:1) yielded (*R*)-**8e** (60.3 mg, 0.227 mmol, 65%). Physical and spectroscopic data were found to be same than for (*S*)-**8e**. $[\alpha]_D^{20} = +22.3$ ($c = 0.93$, CH_2Cl_2).

(*R*)-6',7'-Dimethoxy-3',4'-dihydro-2'*H*-spiro[indoline-2,1'-naphthalene] [(*R*)-8f]: The representative procedure was followed by using imine (S_S)-**6f** (98.3 mg, 0.20 mmol). Purification by column chromatography (hexane/AcOEt, 20:1) yielded (*R*)-**8f** (29.6 mg, 0.10 mmol, 49%). Physical and spectroscopic data were found to be same than for (*S*)-**8f**. $[\alpha]_D^{20} = +20.8$ ($c = 0.66$, CH_2Cl_2).

(*R*)-7'-Fluoro-3',4'-dihydro-2'*H*-spiro[indoline-2,1'-naphthalene] [(*R*)-8g]: The representative procedure was followed by using imine (S_S)-**6g** (289.0 mg, 0.65 mmol). Purification by column chromatography (hexane/AcOEt, 20:1) yielded (*R*)-**8g** (88.8 mg, 0.351 mmol, 54%). Physical and spectroscopic data were found to be same than for (*S*)-**8g**. $[\alpha]_D^{20} = +31.0$ ($c = 0.94$, CH_2Cl_2).

(*R*)-7'-Bromo-3',4'-dihydro-2'*H*-spiro[indoline-2,1'-naphthalene] [(*R*)-8h]: The representative procedure was followed by using imine (S_S)-**6h** (250.0 mg, 0.50 mmol). Purification by column chromatography (hexane/AcOEt, 20:1) yielded (*R*)-**8h** (34.4 mg, 0.11 mmol, 22%). Physical and spectroscopic data were found to be same than for (*S*)-**8h**. $[\alpha]_D^{20} = +64.8$ ($c = 0.92$, CH_2Cl_2).

(*S*)-Spiro[chromane-4,2'-indoline] [(*S*)-8i]: The representative procedure was followed by using imine (S_S)-**6i** (158.0 mg, 0.37 mmol). Purification by column chromatography (hexane/AcOEt, 20:1) yielded (*S*)-**8i** (48.2 mg, 0.203 mmol, 55%). Physical and spectroscopic data were found to be same than for (*R*)-**8i**. $[\alpha]_D^{20} = +31.2$ ($c = 0.93$, CH_2Cl_2).

(*S*)-Spiro[indoline-2,4'-thiochromane] [(*S*)-8j]: The representative procedure was followed by using imine (S_S)-**6j** (140.0 mg, 0.32 mmol). Purification by column chromatography

(hexane/AcOEt, 20:1) yielded (*S*)-**8j** (58.3 mg, 0.23 mmol, 72%). Physical and spectroscopic data were found to be same than for (*R*)-**8j**. $[\alpha]_D^{20} = +49.4$ (c = 0.98, CH_2Cl_2).

Cell Culture Methods

The chronic myeloid leukemia cell lines K562 and FEPS were cultured in RPMI-1640 medium (Sigma-Aldrich, St Louis, MO, USA) supplemented with 25 mM HEPES adjusted to pH 7.4 with NaOH, 60 $mg.L^{-1}$ penicillin and 100 $mg.L^{-1}$ streptomycin (all obtained from Sigma-Aldrich). Dr. Vivian M. Rumjanek kindly donated FEPS cells. Briefly, K562 cells were exposed to increasing concentrations of the chemotherapeutic drug daunorubicin hydrochloride (DNR) (Sigma-Aldrich), as described before[32]. FEPS (K562/DNR) cells were cultured in the presence of 500 nM DNR in order to maintain the MDR phenotype. For subcultures, cells were harvested every three days followed by washing with cold phosphate-buffered saline, and maintained at 37 ºC in 5% CO_2. All media was supplemented with 10% fetal bovine serum (FBS) (Thermo Fischer Scientific, Waltham, MA, USA) inactivated at 56 °C for 1 h prior to use.

***In vitro* cell viability**

Cell viability was determined with the tetrazolium salt 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium (MTT; Sigma-Aldrich). Prior to the experiments, the MDR FEPS cells were cultured free of DNR to avoid additive effect. Briefly, 10^4 mL^{-1} leukemia cells were treated with compounds at a range of concentrations and incubated for 72 h at 37 ºC. Negative controls were prepared with DMSO 0.1% (Vetec Química Fina, Duque de Caxias, RJ, Brasil), and positive ones with VCR or DNR. Then, media was replaced with fresh RPMI supplemented with 10% FBS, 20 µL MTT (5 $mg.mL^{-1}$) was added to each well and plates were kept at 37 °C in 5% CO_2 for 3 h. Plates were then centrifuged, and 200 µL DMSO was added to dissolve the formazan crystals formed after MTT reduction. Absorbance was measured on a Beckman Coulter AD340S spectrophotometer microplate reader (Beckman Coulter, Brea, CA, USA) at 570 nm. The percentage of viable cells was determined in comparison to the control wells. The half-maximal inhibitory concentrations (IC_{50}) were calculated by non-linear regression using the GraphPad Prism version 7.0 program (GraphPad Software, San Diego, CA, USA). The relative resistance (RR) was calculated using the formula **(RR) = (IC_{50} resistant cell line, FEPS) / (IC_{50} parental cell line, K562)**. When IC_{50} exceeded the maximal tested concentration it was expressed as being higher than this concentration (e.g. >200), and this value, 200, was used for calculating the RR (e.g. RR of **(*R*)-8i**: IC_{50} FEPS / IC_{50} K562 = 154.83/200 = 0.77). If RR ≤ 0.5, the compound exerted collateral sensitivity[44], and cells were considered resistant when RR ≥ 2.0.

ASSOCIATED CONTENT

Supporting Information. Copies of ^{1}H, ^{13}C NMR and DEPT spectra for all the reported compounds, ^{19}F NMR for compound R_S)-**6g**, X-ray structure of compound (R_S)-**6h** (Figure S1), as well as computational methods, transitions structures, energy values, energy profiles, NCI calculations and cartesian coordinates.

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