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# A novel diastereoselective 1,3-dipolar cycloaddition approach to *cis*-fused bispyrrolidines

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ABSTRACT

The intramolecular cycloaddition reactions of non-stabilized azomethine ylides generated by the condensation of *N*-aryl glycines and an enantiopure *N*-allyl-tethered alkenyl aldehyde derived from (*S*)-phenyl alanine were investigated. The stereoselective reactions led to the formation of novel *cis*-fused enantiomerically pure octahydropyrrolo[3,4-*b*]pyrroles, and the strategy was expanded to the synthesis of enantiopure novel heterotricyclic skeletons, perhydrothiazolo[3′,4′-2,3]pyrrolo[4,5-*c*]pyrroles.

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## 1. Introduction

The pyrrolidine motif occurs in many families of biologically active molecules. Owing to the ease of substitution and modifications at several positions, many derivatives of pyrrolidines and pyrroles with varying properties have been synthesized.[1] Pyrrolidines and their fused derivatives, such as pyrrolizidines, indazolidines, and pyranoquinolines, have shown a wide spectrum of biological activities.[2] It has also been reported that the fused bispyrrolidines are the basic units of adenosine kinase inhibiting scaffolds for controlling neurodegeneration seizures, ischemia, inflammation, and pain.[3] Apart from this, pyrrolo[3,4-*b*]pyrrole derivatives are found to serve as useful intermediates in the synthesis of uracil-based antibacterials.[4] Moreover, these heterocycles have also been reported as h5-$HT_{1D}$ receptor agonists.[5] In view of the above-mentioned medicinal values of these heterocycles, we reported the synthesis of a series of pyrrolo[3,4-*b*]pyrroles.[6]

Of all the available synthetic tools for the construction of pyrrolidine-based heterocycles, an azomethine ylide cycloaddition methodology is the best suited for the synthesis of such heterocycles, and since these reactions follow a concerted pathway, it always results in retention of the geometries of the parent molecules.[7] Among the intra- and intermolecular versions of this cycloaddition protocol, the intramolecular variant has been used as a key step for the elegant synthesis of stereochemically defined heterocycles.[8–11] For instance, several polycyclic-fused pyrrolidine ring systems are synthesized by intramolecular cycloadditions of cyclic azomethine ylides with tethered dipolarophiles.[12] In many targeted syntheses, intramolecular 1,3-dipolar cycloaddition reactions have been used as the key step.[13] Moreover, this powerful tool has also been extensively employed for the synthesis of chiral heterocycles.[14] Many natural and unnatural compounds with the pyrrolidine skeleton have been synthesized stereoselectively.[15] Catalytic enantioselective variants of 1,3-dipolar cycloaddition reactions have also been reported.[16]

## 2. Results and discussion

As the octahydropyrrolo[3,4-*b*]pyrrole scaffolds promise potential bioactivities, the synthesis of a series of optically active pyrrolo[3,4-*b*]pyrrole derivatives was envisaged. Of the available methods for the induction of chirality in a molecule, subjecting a chiral molecule to some chemical transformations to obtain a target chiral product is one of the well-defined and best-suited methods. Thus, starting from a chiral substrate (*S*)-phenyl alanine **1**, a strategically positioned chiral alkenyl aldehyde **6** was synthesized. Azomethine ylides, generated by decarboxylative route,[17,18] were formed by the condensation of aldehyde **6** with various *N*-aryl glycines and 2-thiazolidine carboxylic acids, and were trapped by the tethered dipolarophile to yield a variety of enantiomerically pure octahydropyrrolo[3,4-*b*]pyrroles and perhydrothiazolo[3′,4′-2,3]pyrrolo[4,5-*c*]pyrroles, respectively.

### 2.1. Synthesis of enantiomerically pure *N*-alkenyl aldehyde

It is mandatory to have a strategically positioned aldehyde carbonyl component tethered to a dipolarophile for an effective intramolecular cycloaddition reaction. Hence for the construction of title enantiopure molecules, an allyl-tethered aldehyde built on chiral backbone is necessary. Aminoacids are the potential candidates on which wide ranges of modifications could be carried out, since they possess both basic and acidic functionalities. Hence, (*S*)-phenyl alanine **1** was chosen as the basic substrate and was subjected to a sequence of transformations as outlined in Schemes 1 and 2. Accordingly, **1** was converted to its ethyl ester

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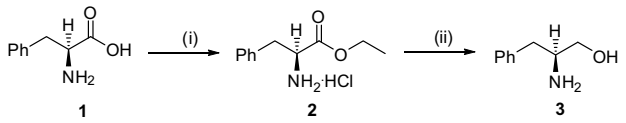
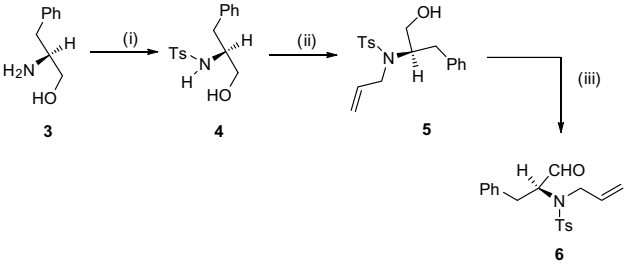
hydrochloride **2** by treatment with an excess of thionyl chloride in dry ethanol. The hydrochloride salt of the ester was then reduced by sodium borohydride in aqueous ethanolic solution to obtain the amino alcohol **3** in good yield {$[\alpha]_D^{26} = -24.1$ ($c$ 1, EtOH)}[19] (Scheme 1).




**Scheme 1.** Reagents and conditions: (i) $SOCl_2$, ethanol, 0 °C–rt–reflux, 5 h; (ii) $NaBH_4$, ethanol–water (1:1), reflux.

With the requisite amino alcohol **3** in hand, the protection of the amino group using *p*-toluenesulfonyl chloride was performed. As described earlier,[6b] the N-sulfonylation reaction was carried out under phase transfer catalysis condition to afford compound **4** in good yield (Scheme 2).




**Scheme 2.** Reagents and conditions: (i) TBAB, 10% NaOH/benzene, tosyl chloride, 0 °C–rt, 8 h, 90%; (ii) allyl bromide, $K_2CO_3$/acetone, 5 h; (iii) iodoxybenzoic acid, DMSO, 4 h, 94%.

Compound **4** was characterized by spectroscopic data. The specific rotation of the compound was found to be −21.4 ($c$ 1, $CHCl_3$). Furthermore, the structure of the N-sulfonylated amino alcohol **4** was unambiguously corroborated by single crystal X-ray analysis[20] (Fig. 1).

The N-sulfonylated chiral alcohol **4** was then subjected to N-allylation using allylbromide with anhydrous potassium carbonate in dry acetone solvent to obtain the N-allylated alcohol **5** in good yield. The structure of chiral *N*-allyl-*N*-tosyl alcohol **5** was established on the basis of its spectroscopic data. The specific rotation of the compound **5** was found to be −1.2 ($c$ 1, $CHCl_3$).

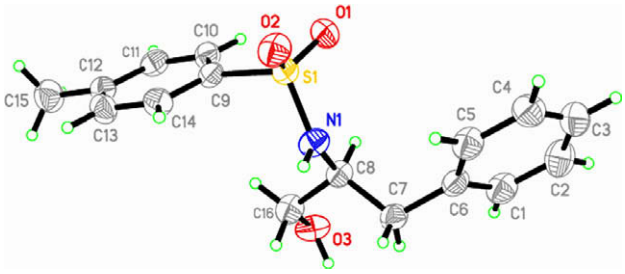


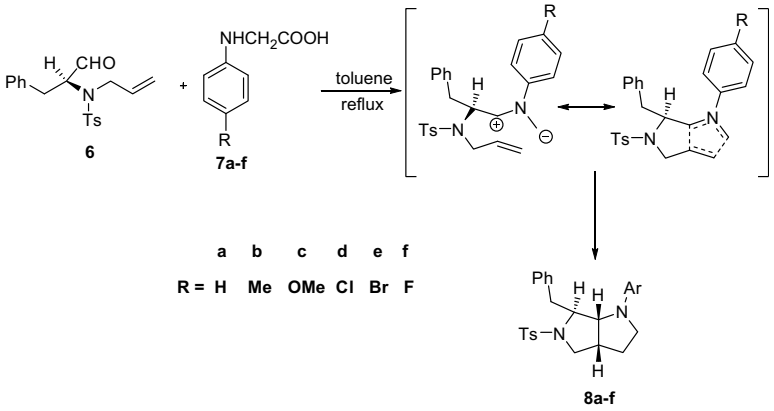

**Figure 1.** The molecular structure of compound **4**, showing 30% probability displacement ellipsoids.

Finally, attempts were made to oxidize alcohol **5** into aldehyde **6** with various oxidizing agents, such as PCC, PDC, and active $MnO_2$, under different reaction conditions. Successful oxidation was achieved by IBX. Thus, the alkenyl alcohol was oxidized quantitatively into the alkenyl aldehyde, (*S*)-2-(*N*-allyl-*N*-tosylamino)-3-phenylpropanal by stirring the suspension of IBX in DMSO with the alcohol for 4 h[21] (Scheme 2). The structure of alkenyl aldehyde **6** was confirmed on the basis of spectroscopic data. The specific rotation of the aldehyde was found to be −0.2 ($c$ 1, $CHCl_3$).

## 2.2. Synthesis of enantiopure octahydropyrrolo[3,4-*b*]pyrroles

Having synthesized the enantiomerically pure, strategically positioned alkenyl aldehyde **6** in good yield, an intramolecular azomethine ylide cycloaddition reaction was performed for the synthesis of enantiomerically pure cycloadducts. Thus, refluxing an equimolar mixture of the alkenyl aldehyde **6** and *N*-phenyl glycine **7e** in toluene under Dean–Stark conditions gave cycloadduct, (3a*R*,6*S*,6a*R*)-*cis*-1-(4-bromophenyl)-5-tosyl-6-benzyl- octahydropyrrolo[3,4-*b*]pyrrole, **8e** in 68% yield. The same reaction was extended to various substituted *N*-phenyl glycines **5a**–**f** for the synthesis of other cycloadducts **6a**–**f** (Scheme 3, Table 1, entries 1–6).

The structures of the cycloadducts were confirmed by spectroscopic data. All the cycloadducts were obtained as a single diastereomer and the specific rotation values were constant after repeated crystallizations. The cycloadduct **8e** as a typical example of the series with a specific rotation of +29.8 ($c$ 1, $CHCl_3$) exhibits a signal in the range $\delta$ 3.97–4.00 as a doublet of doublet ($J$ = 2.9 and 10.4 Hz), which is characteristic of *N*-methine proton at the ring junction. The large coupling constant value suggests a *cis* fusion at the ring junctions in analogy to the cycloadducts obtained in our earlier work.[6b] The formation of the cycloadducts **8e** was further confirmed by the mass spectrum showing a molecular




**Scheme 3.**

**Table 1**
Intramolecular azomethine ylide cycloadditions of compound **6** with secondary amino acids **7a–f** and **9a–f**

| Entry | Amino acid | Time (h) | Product | Yield (%) |
|---|---|---|---|---|
| 1 | **7a** | 3 | **8a** | 70 |
| 2 | **7b** | 4 | **8b** | 69 |
| 3 | **7c** | 3 | **8c** | 68 |
| 4 | **7d** | 2.5 | **8d** | 72 |
| 5 | **7e** | 2 | **8e** | 68 |
| 6 | **7f** | 3.5 | **8f** | 71 |
| 7 | **9a** | 3 | **10a** | 68 |
| 8 | **9b** | 4.5 | **10b** | 67 |
| 9 | **9c** | 5 | **10c** | 65 |
| 10 | **9d** | 3.5 | **10d** | 70 |
| 11 | **9e** | 3 | **10e** | 69 |
| 12 | **9f** | 3 | **10f** | 66 |

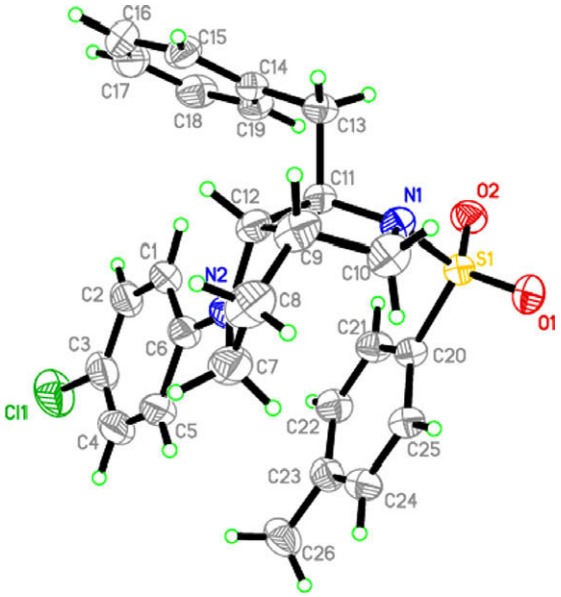



**Figure 2.** ORTEP diagram of **8d**.

ion peak at *m*/*z*, 513.16 ($M^+$). Moreover, the structure and stereochemistry of the cycloadducts **8d** and **8e** were established by the single crystal X-ray diffraction analysis[22,23] (Figs. 2 and 3).

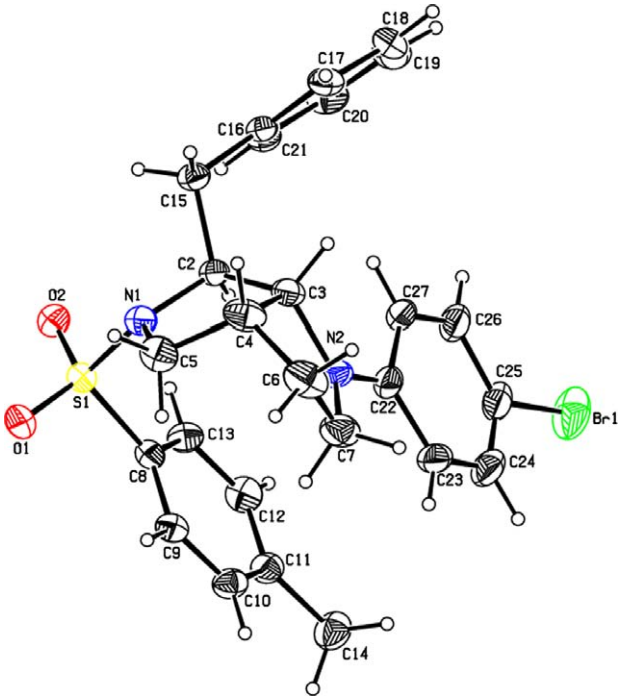
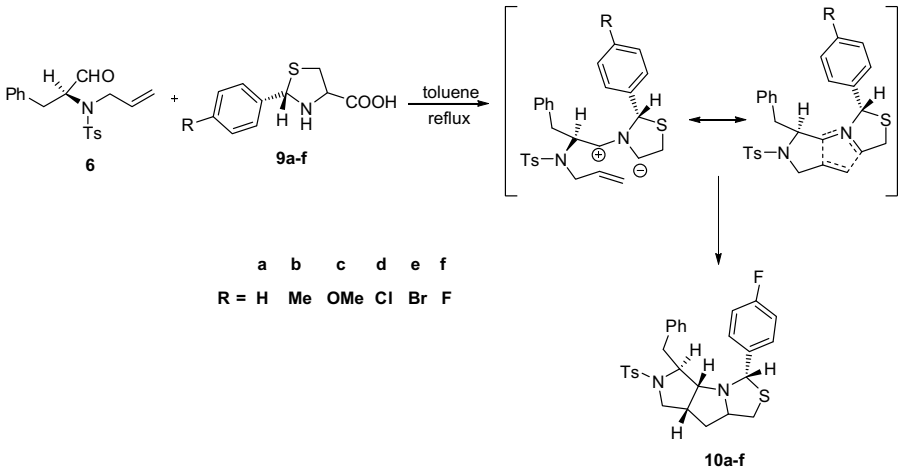



**Figure 3.** ORTEP diagram of **8e**.

## 2.3. Synthesis of enantiopure perhydrothiazolo[3′,4′-2,3]-pyrrolo[4,5-*c*]pyrroles

It is well documented in the literature that the thiazolidine ring has potential bioactivities such as anti-oxidizing, anti-amoebic, anti-diabetic and anti-inflammatory.[24] In order to extend the scope of this reaction for the synthesis of optically active heterotricycles with a pyrrolo[3,4-*b*]pyrrole moiety, the chiral alkenyl aldehyde **6** was reacted with 2-aryl-L-thiazolidine-4-carboxylic acids **9a–f** in refluxing toluene under Dean–Stark reaction conditions. The reaction afforded a series of optically active *cis*-2-aryl-4-benzyl-5-tosyl-perhydrothiazolo[3′,4′-2,3]pyrrolo[4,5-*c*]pyrroles **10a–f** in good yields (Scheme 4, Table 1, entries 7–12).

The specific rotation values of the cycloadducts were constant, even after several recrystallizations. The stereochemistry of the heterotricycles, (2*S*,3a*R*,4*S*,6a*R*,7a*R*)-2(aryl)-4-benzyl-5-tosyl-perhydrothiazolo[3′,4′-2,3]pyrrolo[4,5-*c*]pyrroles, **10a–f** were




**Scheme 4.**

determined on the basis of NMR experiments. The hydrogens at the ring junctions were *cis* to each other as the reaction between the cyclic α-amino acids and carbonyl compound results in an *anti*-dipole; the cycloaddition to the dipolarophile is highly stereoselective yielding only the *cis*-adducts.[25]

In the $^1$H NMR spectrum of the representative cycloadduct **10e**, the benzylic proton on the thiazolidine ring resonated as a singlet at $\delta$ 4.53. The *N*CH proton at the ring junction appeared as a doublet of doublet in the range $\delta$ 3.75–3.78 ($J$ = 2.9 and 9.8 Hz), confirming a *cis*-fused cycloaddition. It was observed from the NOESY experiments that the angular hydrogen atom next to the nitrogen is in a *trans*-position to those hydrogens present at the ring fusion. The high stereoselection of the cycloaddition reaction could be attributed to the selective addition of the *anti*-dipole to the tethered alkene through an *exo*-approach.[26]

In the $^{13}$C NMR spectrum, the methylene carbon displayed a signal at $\delta$ 34.07 and the benzylic carbon in the thiozolidine ring exhibited a signal at $\delta$ 74.72. Furthermore, the structure of the cycloadduct **10e** was confirmed by the mass spectrum exhibiting a molecular ion peak at *m/z* 570.08 ($M^+$). The specific rotation of the cycloadduct **10e** was found to be −13.8 (*c* 1, $CHCl_3$). The absolute stereochemistry of the tricyclic compound was established by single crystal X-ray diffraction analysis[27] (Fig. 4).

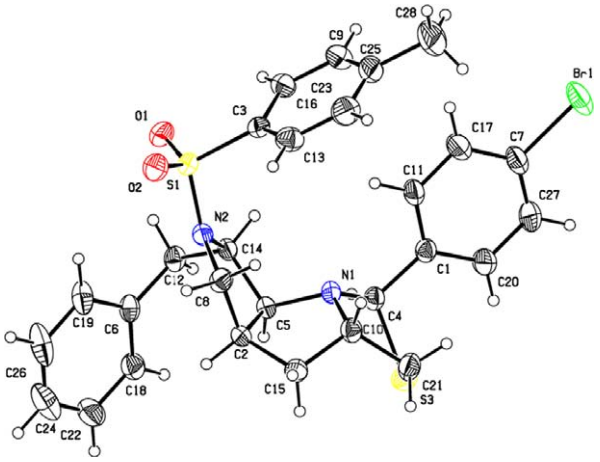



**Figure 4.** ORTEP diagram of **10e**.

## 3. Conclusion

In conclusion, the synthesis of enantiomerically pure N-tethered alkenyl aldehyde was accomplished in good yield from (*S*)-phenyl alanine. The enantiomerically pure alkenyl aldehyde was then successfully subjected to intramolecular cycloaddition reaction with *N*-aryl glycines and 2-aryl-L-thiazolidine-4-carboxylic acids to obtain a series of enantiopure octahydropyrrolo[3,4-*b*]pyrroles and perhydrothiazolo[3′,4′-2,3]pyrrolo[4,5-*c*]pyrroles, respectively. The cycloaddition reactions were found to be stereoselective and gave *cis*-fused cycloadducts.

## 4. Experimental

### 4.1. General

All melting points are uncorrected. IR spectra were recorded on a SHIMADZU IR-8300 series FT-IR spectrophotometer. $^1$H NMR and $^{13}$C NMR spectra were recorded on JEOL 400 MHz and JEOL 500 MHz instruments in $CDCl_3$ solvent with TMS as standard. Mass spectra were recorded by JEOL-DX303 HF mass spectrophotometer. Elemental analyses were carried out by Perkin–Elmer CHNS 2400 instrument. Single crystal X-ray diffraction analyses were performed by Bruker SMART APEX CCD area-detector diffractometer and Bruker SMART APEXII CCD area-detector diffractometer.

Column chromatography was performed on silica gel (ACME, 100–200 mesh). Routine monitoring of the reaction was done using thin layer chromatogram developed on glass plates coated with silica gel-G (ACME) of 25 mm thickness and visualized with iodine.

### 4.2. Preparation of (*S*)-2-amino-3-phenylpropan-1-ol, 3

(*S*)-2-Amino-3-phenylpropan-1-ol was prepared in two stages starting from (*S*)-phenyl alanine.[18]

#### 4.2.1. Stage 1: preparation of (*S*)-phenylalanine ethyl ester hydrochloride, 2

To a stirred, ice-cold suspension of (*S*)-phenylalanine (30 g, 0.182 mol) in absolute ethanol (800 mL), thionyl chloride (32.5 g, 0.273 mol) was added dropwise, and the reaction mixture was heated at reflux for 3.5 h. The pale yellow solution was allowed to stand overnight at room temperature, and the ethanol was evaporated in vacuo to obtain a colorless solid. The vacuum-dried (*S*)-phenylalanine ethyl ester hydrochloride was washed with dry diethyl ether, filtered, and dried in vacuo. The solid thus obtained was used as such in the next step.

#### 4.2.2. Stage 2: preparation of (*S*)-phenylalaninol from (*S*)-phenylalanine ethyl ester hydrochloride, 3

To a solution of sodium borohydride (28 g, 0.736 mol) in 50% aqueous ethanol (400 mL) was added dropwise a solution of (*S*)-phenylalanine ethyl ester hydrochloride (40 g, 0.176 mol) in 50% aqueous ethanol (400 mL), and the resulting mixture was refluxed for 4.5 h. Ethanol was evaporated in vacuum. The aqueous solution thus obtained was then extracted with ethyl acetate. The extract was washed with saturated brine solution and dried over anhydrous sodium hydroxide. Evaporation of the ethyl acetate under reduced pressure afforded (*S*)-phenyl alaninol **3** as a pale yellow solid. Pale yellow solid, 72% (19.16 g); $[\alpha]_D^{26} = -24.1$ (*c* 1, EtOH); Mp: 85–87 °C; IR (KBr): 2990 and 3452 cm$^{-1}$.

### 4.3. Synthesis of (*S*)-3-phenyl-2-(tosylamino)propan-1-ol, 4

To a solution of 15.10 g (0.1 mol) of (*S*)-2-amino-3-phenylpropan-1-ol in 100 mL benzene at 0 °C was added half a portion of 19.06 g (0.1 mol) *p*-toluenesulfonyl chloride. The reaction mixture was stirred vigorously, and after 10 min, 30 mL of benzene was added followed by the remaining portion of *p*-toluenesulfonyl chloride followed by a catalytic amount (500 mg) of the phase transfer catalyst, tetrabutylammonium bromide (TBAB). To this stirred mixture, a 25% solution of sodium hydroxide (0.1 mol) was added dropwise using an additional funnel, resulting in a thick flocculation. The temperature of the reaction mixture was raised to room temperature once the addition of sodium hydroxide was complete. After 8–10 h, the reaction mixture was diluted with 100 mL of water. It was then extracted with 100 mL of benzene and washed with brine solution. The organic layer was then dried over anhydrous sodium sulfate and concentrated in vacuum to yield crude N-sulfonylated-(*S*)-phenyl alaninol. The pure **4** was obtained by column chromatography using a 9:1 mixture of hexane–ethyl acetate. Colorless solid, 89% (27.18 g); $[\alpha]_D^{29} = -21.4$ (*c* 1, $CHCl_3$); Mp: 75–77 °C; IR (KBr): 1338, 1167, 1600, 3100 and 3452 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 2.01 (s, 1H, OH), 2.33 (s, 3H, Ar-$CH_3$), 2.64–2.65 (dd, 1H, $J_1$ = 6.8 Hz, $J_2$ = 13.0 Hz), 2.73–2.74 (dd, 1H, $J_1$ = 6.8 Hz, $J_2$ = 13.0 Hz), 3.48–3.58 (m, 3H), 5.85 (br

s, NH, 1H), 6.96–7.60 (m, 9H, Ar-H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 21.41, 37.61, 56.95, 63.73, 126.35, 126.89, 128.41, 128.53, 129.20, 129.59, 137.26, 137.29 and 143.12; Mass spectrum (EI, 70 eV): *m/z*, 305.40 ($M^+$). *Anal.* Calcd for $C_{16}H_{19}NO_3S$: C, 62.93, H, 6.27, N, 4.59. Found: C, 62.81, H, 6.20, N, 4.48.

### 4.4. Synthesis of (*S*)-2-(*N*-allyl-*N*-tosylamino)-3-phenylpropan-1-ol, 5

To a solution of 20 mmol of (*S*)-3-phenyl-2-(tosylamino)propan-1-ol in 100 mL of dry acetone under a nitrogen atmosphere was added 60 mmol of potassium carbonate. To this stirred solution, 20 mmol of allyl bromide in 50 mL of dry acetone was added. The stirring was continued for 8–10 h. After completion of the reaction, the solid was filtered off. The residue was washed several times with acetone and the filtrate was concentrated in vacuum and extracted with dichloromethane (100 mL) and water (100 mL). The organic extract was washed with brine solution and concentrated under reduced pressure. The crude product was subjected to column chromatography with hexane–ethyl acetate mixture (9:1) to obtain pure N-allylated (*S*)-3-phenyl-2-(tosylamino)propan-1-ol, **5**. Colorless oil, 80% (5.52 g); $[\alpha]_D^{29} = -1.2$ (*c* 1, $CHCl_3$); IR (KBr): 1330, 1169, 1600, and 3546 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 2.01 (br s, 1H, OH), 2.39 (s, 3H, Ar-$CH_3$), 2.65–2.67 (dd, 1H, $J_1$ = 6.8 Hz, $J_2$ = 13.0 Hz), 2.74–2.79 (dd, 1H, $J_1$ = 6.8 Hz, $J_2$ = 13.0 Hz), 3.58–3.66 (m, 2H), 3.85–4.07 (m, 3H), 5.15–5.29 (dd, 2H, $J_1$ = 9.8 Hz, $J_2$ = 17.0 Hz), 5.88–5.89 (m, 1H), 7.02–7.63 (m, 9H, Ar-H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 21.49, 36.32, 47.38, 61.91, 62.43, 117.89, 126.59, 127.27, 128.59, 129.00, 129.64, 135.82, 137.73, and 143.33; Mass spectrum (EI, 70 eV): *m/z*, 345.46 ($M^+$). Anal. Calcd for $C_{19}H_{23}NO_3S$: C, 66.06, H, 6.71, N, 4.05. Found: C, 66.25, H, 6.60, N, 4.15.

### 4.5. Synthesis of (*S*)-2-(*N*-allyl-*N*-tosylamino)-3-phenylpropanal, 6

To a stirred solution of 2-iodobenzoic acid, IBX (2.94 g, 0.010 mmol), dissolved in dimethyl sulfoxide, DMSO (10 mL), was added 2.07 g (0.006 mmol) of (*S*)-2-(*N*-allyl-*N*-tosylamino)-3-phenylpropan-1-ol, **5**. After 2 h of vigorous stirring, the reaction mixture was diluted with water and the precipitate formed was filtered and washed with ethyl acetate (20 mL). The filtrate was then extracted with ethyl acetate (2 × 20 mL). The organic layer was dried over anhydrous sodium sulfate and the solvent was distilled off at reduced pressure to obtain a brown colored crude aldehyde in quantitative yield. It was subjected to column chromatography (silica gel, 100–200 mesh) using hexane–ethyl acetate mixture (9:1) to obtain pure (*S*)-2-(*N*-allyl-*N*-tosylamino)-3-phenylpropanal, **6**. Yellow oil, 90% (1.86 g); $[\alpha]_D^{29} = -0.2$ (*c* 1, $CHCl_3$); IR (KBr): 1335, 1161, and 1735 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 2.40 (s, 3H, Ar-$CH_3$), 2.73–2.79 (dd, 1H, $J_1$ = 8.3 Hz, $J_2$ = 15.0 Hz), 3.36–3.41 (dd, 1H, $J_1$ = 5.8 Hz, $J_2$ = 15.0 Hz), 3.65–3.71 (dd, 1H, $J_1$ = 6.8 Hz, $J_2$ = 6.8 Hz), 3.78–3.84 (dd, 1H, $J_1$ = 6.3 Hz, $J_2$ = 6.3 Hz), 4.42–4.46 (dd, 1H, $J_1$ = 6.3 Hz, $J_2$ = 8.5 Hz), 5.10–5.18 (dd, $CH_2$, 2H, $J_1$ = 10 Hz, $J_2$ = 17.5 Hz), 5.66–5.72 (m, 1H, CH), 7.04–7.54 (m, 9H, Ar-H), 9.68 (s, 1H, CHO); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 21.50, 33.30, 49.19, 67.41, 120.33, 126.68, 127.33, 128.62, 129.02, 129.75, 133.31, 137.03, 137.17, 143.71 and 198.89; Mass spectrum (EI, 70 eV): *m/z*, 343.12 ($M^+$). Anal. Calcd for $C_{19}H_{21}NO_3S$: C, 66.45, H, 6.16, N, 4.08. Found: C, 66.52, H, 6.01, N, 3.97.

### 4.6. Synthesis of enantiopure *cis*-1-aryl-5-tosyl-6-benzyl octahydropyrrolo[3,4-*b*]pyrroles, 8a–f

A mixture of (*S*)-2-(*N*-allyl-*N*-tosylamino)-3-phenylpropanal **6** (1.0 mmol), and *N*-aryl glycine (1.5 mmol) in 30 mL of dry toluene was refluxed under Dean–Stark conditions until the completion of the reaction (3.5–5 h). The reaction mixture was then concentrated under reduced pressure. The residue was extracted with dichloromethane (2 × 20 mL) and water (2 × 20 mL). The organic layer was washed with brine solution (2 × 20 mL), dried over anhydrous sodium sulfate and concentrated in vacuum. The residue was then subjected to column chromatography (silica gel, 100–200 mesh) with hexane–ethyl acetate (8:2) to obtain the cycloadducts **8a–f**, (3a*R*,6*S*,6a*R*)-1-(aryl)-5-tosyl-6-benzyl-octahydropyrrolo [3,4-*b*]-pyrroles.

#### 4.6.1. (3a*R*,6*S*,6a*R*)-*cis*-1-Phenyl-5-tosyl-6-benzyl-octahydropyrrolo[3,4-*b*]pyrrole, 8a

Colorless solid, 70% (0.302 g); $[\alpha]_D^{28} = +6.6$ (*c* 1, $CHCl_3$); Mp: 142–145 °C; IR (KBr): 1339 and 1169 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 1.55–1.80 (m, 2H, $CH_2$), 2.32 (s, 3H, Ar-$CH_3$), 2.57–2.92 (m, 3H), 3.22–3.26 (dd, 1H, *J* = 2.6, 10.1 Hz), 3.66–3.68 (m, 2H), 3.97-4.10 (dd, 1H, *J* = 2.8, 10.2 Hz), 5.47 (d, 2H, *J* = 8.0 Hz), 6.58–7.40 (m, 14H, Ar-H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 21.47, 27.61, 30.92, 41.54, 42.41, 46.73, 51.94, 65.10, 65.80, 112.73, 116.25, 126.92, 127.06, 128.58, 129.37, 130.16, 133.95, 137.67, 142.91, and 145.44; Mass spectrum (EI, 70 eV): *m/z*, 432.19 ($M^+$). Anal. Calcd for $C_{26}H_{28}N_2O_2S$: C, 72.19, H, 6.52, N, 6.48. Found: C, 72.08, H, 6.61, N, 6.40.

#### 4.6.2. (3a*R*,6*S*,6a*R*)-*cis*-1-(4-Methyl)-phenyl-5-tosyl-6-benzyl-octahydropyrrolo[3,4-*b*]pyrrole, 8b

Colorless solid, 69% (0.307 g); $[\alpha]_D^{29} = 27.5$ (*c* 1, $CHCl_3$); Mp: 140–142 °C; IR (KBr): 1337 and 1169 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 1.63–1.72 (m, 2H, $CH_2$), 2.34 (s, 3H, Ar-$CH_3$), 2.41 (s, 3H, Ar-$CH_3$), 2.54–2.89 (m, 3H), 3.25–3.27 (dd, 1H, *J* = 2.8, 10.2 Hz), 3.75–3.77 (m, 2H), 3.98–4.02 (dd, 1H, *J* = 2.7, 10.4 Hz), 5.48 (d, 2H, *J* = 8.0 Hz), 6.80–7.43 (m, 13H, Ar-H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 21.44, 21.84, 27.50, 30.87, 41.51, 42.53, 46.87, 51.06, 64.19, 65.02, 113.34, 121.09, 127.23, 128.87, 128.27, 129.33, 130.00, 133.07, 137.29, 143.03, and 143.85; Mass spectrum (EI, 70 eV): *m/z*, 446.20 ($M^+$). Anal. Calcd for $C_{27}H_{30}N_2O_2S$: C, 72.61, H, 6.77, N, 6.27. Found: C, 72.50, H, 6.69, N, 6.36.

#### 4.6.3. (3a*R*,6*S*,6a*R*)-*cis*-1-(4-Methoxy)-phenyl-5-tosyl-6-benzyl-octahydropyrrolo[3,4-*b*]pyrrole, 8c

Colorless solid, 68% (0.314 g); $[\alpha]_D^{29} = +24.6$ (*c* 1, $CHCl_3$); Mp: 145–147 °C; IR (KBr): 1337 and 1169 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 1.65–1.72 (m, 2H, $CH_2$), 2.39 (s, 3H, Ar-$CH_3$), 2.59–2.88 (m, 3H, *N*$CH_2$), 3.25–3.28 (dd, 1H, *J* = 2.8, 10.3 Hz), 3.74–3.77 (m, 2H), 3.78 (s, 3H, Ar-$OCH_3$), 3.97–4.00 (dd, 1H, *J* = 2.7, 10.4 Hz), 5.47 (d, 2H, *J* = 8.1 Hz), 6.83–7.45 (m, 13H, Ar-H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 21.94, 27.09, 30.87, 37.34, 41.87, 42.59, 46.12, 51.77, 64.18, 65.72, 113.55, 121.83, 127.89, 128.07, 128.87, 129.53, 130.70, 133.67, 137.22, 143.03, and 143.58; Mass spectrum (EI, 70 eV): *m/z*, 462.52 ($M^+$). Anal. Calcd for $C_{27}H_{30}N_2O_3S$: C, 70.10, H, 6.54, N, 6.06. Found: C, 69.92, H, 6.63, N, 6.17.

#### 4.6.4. (3a*R*,6*S*,6a*R*)-*cis*-1-(4-Chloro)-phenyl-5-tosyl-6-benzyl-octahydropyrrolo[3,4-*b*]pyrrole, 8d

Colorless solid, 72% (0.336 g); $[\alpha]_D^{28} = +27.0$ (*c* 1, $CHCl_3$); Mp: 147–149 °C; IR (KBr): 1337 and 1166 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 1.62–1.74 (m, 2H, $CH_2$), 2.35 (s, 3H, Ar-$CH_3$), 2.59–2.88 (m, 3H), 3.25–3.28 (dd, 1H, *J* = 2.8, 10.3 Hz), 3.70–3.74 (m, 2H), 3.99–4.00 (dd, 1H, *J* = 2.8, 10.4 Hz), 5.49 (d, 2H, *J* = 8.0 Hz), 6.84–7.43 (m, 13H, Ar-H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 21.47, 27.59, 30.90, 41.53, 42.50, 46.91, 51.86, 64.93, 65.75, 113.73, 121.05, 127.03, 128.23, 128.67, 129.38, 130.05, 133.95, 137.59, 143.03, and 143.95; Mass spectrum (EI, 70 eV): *m/z*, 466.80 ($M^+$). Anal. Calcd for $C_{26}H_{27}ClN_2O_2S$: C, 66.87, H, 5.83, N, 6.00. Found: C, 66.70, H, 5.97, N, 5.89.

#### 4.6.5. (3a*R*,6*S*,6a*R*)-*cis*-1-(4-Bromo)-phenyl-5-tosyl-6-benzyl-octahydropyrrolo[3,4-*b*]pyrrole, 8e

Colorless solid, 68% (0.348 g); $[\alpha]_D^{29} = +29.8$ (*c* 1, $CHCl_3$); Mp: 145–147 °C; IR (KBr): 1337 and 1166 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.60–1.75 (m, 2H, $CH_2$), 2.33 (s, 3H, Ar-$CH_3$), 2.53–2.85 (m, 3H), 3.24–3.28 (dd, 1H, *J* = 2.9, 10.0 Hz), 3.66–3.73 (m, 2H), 3.97–4.00 (dd, 1H, *J* = 2.9, 10.4 Hz), 5.43 (d, 2H, *J* = 8.7 Hz), 6.96–7.43 (m, 13H, Ar-H); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 21.46, 27.56, 41.49, 42.47, 46.84, 51.83, 64.84, 65.69, 108.18, 114.26, 126.82, 127.95, 128.20, 128.44, 129.65, 130.02, 131.07, 133.10, 137.56, 141.65, 143.04, and 144.30; Mass spectrum (EI, 70 eV): *m/z*, 513.16 ($M^+$). Anal. Calcd for $C_{26}H_{27}BrN_2O_2S$: C, 61.05, H, 5.32, N, 5.48. Found: C, 61.14, H, 5.24, N, 5.57.

#### 4.6.6. (3a*R*,6*S*,6a*R*)-*cis*-1-(4-Fluoro)-phenyl-5-tosyl-6-benzyl-octahydropyrrolo[3,4-*b*]pyrrole, 8f

Colorless solid, 71% (0.320 g); $[\alpha]_D^{27} = +2.5$ (*c* 1, $CHCl_3$); Mp: 148–150 °C; IR (KBr): 1337 and 1168 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.64–1.75 (m, 2H, $CH_2$), 2.34 (s, 3H, Ar-$CH_3$), 2.59–2.86 (m, 3H), 3.25–3.28 (dd, 1H, *J* = 2.6, 10.4 Hz), 3.69–3.73 (m, 2H), 3.99–4.02 (dd, 1H, *J* = 2.8, 10.4 Hz), 5.51 (d, 2H, *J* = 8.0 Hz), 6.63–7.44 (m, 13H, Ar-H); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 21.46, 27.55, 30.92, 41.59, 42.48, 47.29, 51.92, 65.05, 65.93, 113.14, 113.22, 114.76, 114.98, 127.07, 128.64, 129.34, 130.08, 133.95, 137.68, 142.01, 142.94, 153.84, and 156.17; Mass spectrum (EI, 70 eV): *m/z*, 450.59 ($M^+$). Anal. Calcd for $C_{26}H_{27}FN_2O_2S$: C, 69.31, H, 6.04, N, 6.22. Found: C, 69.43, H, 6.10, N, 6.10.

### 4.7. Synthesis of enantiopure perhydrothiazolo[3′,4′-2,3]-pyrrolo[4,5-*c*]pyrroles, 10a–f

A mixture of (*S*)-2-(*N*-allyl-*N*-tosylamino)-3-phenylpropanal **6** (1.0 mmol) and 2-aryl-thiazolidine-4-carboxylic acids **9a–f** (1.5 mmol) in 30 mL of dry toluene was refluxed under Dean–Stark conditions until the completion of the reaction (2.5–4 h). The reaction mixture was then concentrated under reduced pressure. The concentrate was extracted with dichloromethane (2 × 20 mL) and water (2 × 20 mL). The organic layer was washed with brine solution (2 × 20 mL), dried over anhydrous sodium sulfate, and concentrated in vacuum. The residue was then subjected to column chromatography (silica gel, 100–200 mesh) with hexane–ethyl acetate (8:2) to obtain the cycloadducts **10a–f**, (2*R*,3a*R*,4*S*,6a*R*,7a*R*)-*cis*-2-aryl-4-benzyl-5-*N*-(*p*-methyl)-benzenesulfonyl-perhydrothiazolo[3′,4′-2,3]pyrrolo[4,5-*c*]pyrroles.

#### 4.7.1. (2*S*,3a*R*,4*S*,6a*R*,7a*R*)-*cis*-2-Phenyl-4-benzyl-5-*N*-(*p*-methyl)-benzenesulfonyl perhydrothiazolo[3′,4′-2,3]-pyrrolo[4,5-*c*]pyrrole, 10a

Brownish viscous liquid, 68% (0.333 g); $[\alpha]_D^{29} = -10.6$ (*c* 1, $CHCl_3$); IR (KBr): 1335 and 1165 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.68–1.70 (m, 1H), 1.87–1.85 (m, 1H), 2.43 (s, 3H), 2.66–2.76 (m, 3H), 3.07–3.10 (m, 1H), 3.25–3.30 (m, 2H), 3.47–3.49 (m, 1H), 3.69–3.72 (m, 1H), 3.74–3.78 (dd, 2H, *J* = 2.9, 9.8 Hz), 4.54 (s, 1H), 6.74–7.73 (m, 14H, Ar-H); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 21.89, 27.37, 41.77, 42.07, 46.14, 51.93, 64.81, 65.09, 108.68, 114.08, 126.02, 127.05, 128.67, 129.53, 129.08, 130.02, 133.19, 137.06, 141.25, 143.54, and 144.16; Mass spectrum (EI, 70 eV): *m/z*, 490.54 ($M^+$). Anal. Calcd for $C_{28}H_{30}N_2O_2S_2$: C, 68.54, H, 6.16, N, 5.71. Found: C, 68.47, H, 6.08, N, 5.77.

#### 4.7.2. (2*S*,3a*R*,4*S*,6a*R*,7a*R*)-*cis*-2-(*p*-Methyl)-phenyl-4-benzyl-5-*N*-(*p*-methyl)-benzenesulfonyl perhydrothiazolo[3′,4′-2,3]-pyrrolo[4,5-*c*]pyrrole, 10b

Brownish viscous liquid, 67% (0.338 g); $[\alpha]_D^{29} = -14.8$ (*c* 1, $CHCl_3$); IR (KBr): 1335 and 1170 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.69–1.73 (m, 1H), 1.79–1.84 (m, 1H), 2.43 (s, 3H), 2.45 (s, 3H), 2.65–2.79 (m, 3H), 3.05–3.08 (m, 1H), 3.25–3.31 (m, 2H), 3.46–3.49 (m, 1H), 3.66–3.73 (m, 1H), 3.74–3.78 (dd, 2H, *J* = 2.9, 9.8 Hz), 4.52 (s, 1H), 6.97–7.74 (m, 13H, Ar-H); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 21.57, 21.89, 27.79, 41.85, 42.37, 46.47, 51.37, 64.04, 65.19, 108.12, 114.98, 126.12, 127.15, 128.46, 129.89, 129.65, 130.86, 133.11, 137.76, 141.87, 143.43, and 144.76; Mass spectrum (EI, 70 eV): *m/z*, 504.71 ($M^+$). Anal. Calcd for $C_{29}H_{32}N_2O_2S_2$: C, 69.01, H, 6.39, N, 5.55. Found: C, 69.07, H, 6.29, N, 5.50.

#### 4.7.3. (2*S*,3a*R*,4*S*,6a*R*,7a*R*)-*cis*-2-(*p*-Methoxy)-phenyl-4-benzyl-5-*N*-(*p*-methyl)-benzenesulfonyl perhydrothiazolo[3′,4′-2,3]-pyrrolo[4,5-*c*]pyrrole, 10c

Brownish viscous liquid, 65% (0.338 g); $[\alpha]_D^{29} = -15.8$ (*c* 1, $CHCl_3$); IR (KBr): 1336 and 1168 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.68–1.73 (m, 1H), 1.80–1.85 (m, 1H), 2.46 (s, 3H), 2.65–2.77 (m, 3H), 3.04–3.07 (m, 1H), 3.20–3.30 (m, 2H), 3.45–3.49 (m, 1H), 3.67–3.71 (m, 1H), 3.74–3.77 (dd, 2H, *J* = 2.9, 9.8 Hz), 3.79 (s, 3H, Ar-OMe), 4.54 (s, 1H), 6.98–7.80 (m, 13H, Ar-H); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 21.67, 27.89, 37.67, 41.23, 42.65, 46.38, 51.73, 64.76, 65.91, 108.43, 114.59, 126.41, 127.01, 128.09, 129.98, 129.33, 130.09, 133.52, 137.34, 141.09, 143.09, and 144.98; Mass spectrum (EI, 70 eV): *m/z*, 520.77 ($M^+$). Anal. Calcd for $C_{29}H_{32}N_2O_3S_2$: C, 66.89, H, 6.19, N, 5.38. Found: C, 66.75, H, 6.27, N, 5.30.

#### 4.7.4. (2*S*,3a*R*,4*S*,6a*R*,7a*R*)-*cis*-2-(*p*-Chloro)-4-benzyl-5-*N*-(*p*-methyl)-benzenesulfonyl perhydrothiazolo[3′,4′-2,3]-pyrrolo[4,5-*c*]pyrrole, 10d

Brownish viscous liquid, 70% (0.366 g); $[\alpha]_D^{29} = -12.8$ (*c* 1, $CHCl_3$); IR (KBr): 1338 and 1170 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.68–1.72 (m, 1H), 1.81–1.85 (m, 1H), 2.47 (s, 3H), 2.66–2.78 (m, 3H), 3.05–3.08 (m, 1H), 3.24–3.31 (m, 2H), 3.46–3.49 (m, 1H), 3.66–3.70 (m, 1H), 3.75–3.79 (dd, 2H, *J* = 2.9, 9.8 Hz), 4.50 (s, 1H), 6.87–7.79 (m, 13H, Ar-H); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 21.89, 27.89, 41.43, 42.49, 46.38, 51.83, 64.23, 65.90, 108.43, 114.44, 126.11, 127.91, 128.09, 129.43, 129.66, 130.09, 133.80, 137.54, 141.69, 143.24, and 144.70; Mass spectrum (EI, 70 eV): *m/z*, 524.14 ($M^+$). Anal. Calcd for $C_{28}H_{29}ClN_2O_2S_2$: C, 64.04, H, 5.57, N, 5.33. Found: C, 64.12, H, 5.50, N, 5.41.

#### 4.7.5. (2*R*,3a*R*,4*S*,6a*R*,7a*R*)-*cis*-2-(*p*-Bromo)-phenyl-4-benzyl-5-*N*-(*p*-methyl)-benzenesulfonyl perhydrothiazolo[3′,4′-2,3]-pyrrolo[4,5-*c*]pyrrole, 10e

Colorless solid, 69% (0.393 g); $[\alpha]_D^{29} = -13.8$ (*c* 1, $CHCl_3$); Mp: 162–164 °C; IR (KBr): 1339 and 1166 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.69–1.72 (m, 1H), 1.80–1.85 (m, 1H), 2.45 (s, 3H), 2.64–2.79 (m, 3H), 3.06–3.08 (m, 1H), 3.24–3.30 (m, 2H), 3.47–3.49 (m, 1H), 3.66–3.71 (m, 1H), 3.75–3.78 (dd, 2H, *J* = 2.9, 9.8 Hz), 4.53 (s, 1H), 6.66–7.74 (m, 13H, Ar-H); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 21.69, 34.07, 39.23, 40.36, 41.48, 54.23, 67.71, 68.70, 72.73, 74.72, 120.55, 126.71, 127.74, 128.12, 128.62, 129.62, 130.81, 134.42, 137.81, 141.92, and 143.22; Mass spectrum (EI, 70 eV): *m/z*, 570.08 ($M^+$). Anal. Calcd for $C_{28}H_{29}BrN_2O_2S_2$: C, 59.04, H, 5.13, N, 4.92. Found: C, 59.12, H, 5.05, N, 5.00.

#### 4.7.6. (2*S*,3a*R*,4*S*,6a*R*,7a*R*)-*cis*-2-(*p*-Fluoro)phenyl-4-benzyl-5-*N*-(*p*-methyl)-benzenesulfonyl perhydrothiazolo[3′,4′-2,3]-pyrrolo[4,5-*c*]pyrrole, 10f

Brownish viscous liquid, 66% (0.335 g); $[\alpha]_D^{29} = -15.6$ (*c* 1, $CHCl_3$); IR (KBr): 1338 and 1170 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.68–1.72 (m, 1H), 1.79–1.85 (m, 1H), 2.46 (s, 3H), 2.63–2.78 (m, 3H), 3.07–3.09 (m, 1H), 3.23–3.32 (m, 2H), 3.47–3.55 (m, 1H), 3.66–3.71 (m, 1H), 3.74–3.79 (dd, 2H, *J* = 2.9, 9.8 Hz), 4.55 (s, 1H), 6.64–7.68 (m, 13H, Ar-H); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 21.37, 27.16, 41.88, 42.54, 46.98, 51.87, 64.00, 65.21,

108.06, 114.78, 126.21, 127.70, 128.00, 129.20, 129.76, 130.02, 133.09, 137.45, 141.98, 143.09, and 159.07; Mass spectrum (EI, 70 eV): *m/z*, 508.17 ($M^+$). Anal. Calcd for $C_{28}H_{29}FN_2O_2S_2$: C, 66.11, H, 5.75, N, 5.51. Found: C, 66.20, H, 5.64, N, 5.59.

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