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Synthesis of Tripeptide Derivatives with Three Stereogenic Centers and Chiral Recognition Probed by Tetraaza Macrocyclic Chiral Solvating Agents Derived from D-Phenylalanine and (1*S*, 2*S*)-(+)-1,2-Diaminocyclohexane via ¹H NMR Spectroscopy

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Abstract

Enantiomers of a series of tripeptide derivatives with three stereogenic centers ($\pm$)-**G1–G9** have been prepared from D- and L- α -amino acids as guests for chiral recognition by ¹H NMR spectroscopy. In the meantime, a family of tetraaza macrocyclic chiral solvating agents (TAMCSAs) **1a–1d** has been synthesized from D-phenylalanine and (1*S*,2*S*)-(+)-1,2-diaminocyclohexane. Discrimination of enantiomers of ($\pm$)-**G1–G9** was carried out in the presence of TAMCSAs **1a–1d** by ¹H NMR spectroscopy. The results indicate that enantiomers of ($\pm$)-**G1–G9** can be effectively discriminated in the presence of TAMCSAs **1a–1d** by ¹H NMR signals of multiple protons exhibiting nonequivalent chemical shifts (δ) up to 0.616 ppm. Furthermore, enantiomers of ($\pm$)-**G1–G9** were easily assigned by comparing ¹H NMR signals of the split corresponding protons with those attributed to a single enantiomer. Different optical purities (ee up to 90%) of **G1** were clearly observed and calculated in the presence of TAMCSAs **1a–1d**, respectively. Intermolecular hydrogen bonding interactions were demonstrated through theoretical calculations of enantiomers of ($\pm$)-**G1** with TAMCSA **1a** by means of the hybrid functional theory with the standard basis sets of 3–21G of the Gaussian 03 program.

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b02212.

Crystallographic data for TAMCSAs **1a**·CHCl₃ and **1b** and their ORTEP diagrams, details of optimization of chiral discriminating conditions, determination of enantiomeric excesses of **G1** with different optical purities in the presence of TAMCSAs **1a–1d** and the stoichiometry of ($\pm$)-**G1** with TAMCSA **1a** (Job plots), energies and Cartesian coordinates (Å) of the complexes of **G1–1** and **G1–2** with TAMCSA **1a** obtained from B3LYP/3–21G structural optimization, copies of NMR and HRMS spectra of all new compounds, copies of ¹H NMR spectra of discrimination of enantiomers of ($\pm$)-**G1–G9**, and determination of enantiomeric excesses of **G1** (PDF)

X-ray data for TAMCSA **1a** (CIF)

X-ray data for TAMCSA **1b** (CIF)

Graphical Abstract

INTRODUCTION

During the last decades, chiral recognition methodologies have been rapidly developed due to the critical role of chiral differentiation in biological processes, analysis of optical purity of chiral drugs, assignment of absolute configuration, and determination of enantiomeric excess (ee) of products of catalytic asymmetric synthesis. In the process, several diagnostic techniques were employed and developed as more effective methods, separately or in tandem, such as high performance liquid chromatography (HPLC),¹ circular dichroism (CD),² mass spectrometry (MS),³ nuclear magnetic resonance (NMR),⁴ UV/vis,⁵ and fluorescence spectroscopy.⁶ Among them, NMR spectroscopy, as one of the most efficient analytical techniques, has been widely utilized for chiral recognition due to several advantages, including fast, accurate, and convenient application, as well as ubiquitous NMR instrumentation availability in nearly all chemical laboratories.⁷ So far, reported research relying on ¹H NMR spectroscopy largely implicates enantiomeric discrimination of chiral analytes with only one stereogenic center.^{4,7} In contrast, studies on enantiomeric discrimination of chiral analytes possessing two or more stereogenic centers have been rarely reported.⁸ Nevertheless, these chiral analytes often exist in natural products, biological systems, chiral drugs, and products of catalytic asymmetric synthesis.⁹ For example, it is well established that several oligopeptides or their derivatives, play a crucial role in the treatment of human diseases as clinical drugs or special dietary supplements, as exemplified by thyrotropin-releasing hormone (TRH) or its analogues,¹⁰ and aspartame,¹¹ which have been used clinically for the treatment of spinocerebellar degeneration and disturbance of consciousness in humans, as well as in special dietary supplements, respectively. Generally, peptides or their derivatives can be obtained by chemical or biological synthesis of related amino acids or their derivatives, or via microbial degradation of proteins. However, racemization of the stereogenic configuration of the chiral amino acid moiety may occur under certain severe reaction conditions. However, different stereoisomers or enantiomers may have different biological and pharmacological activities, and even result in the opposite physiological effects.¹² Therefore, analysis of optical purity and identification of enantiomers of these chiral analytes are very important contributors to the treatment of human diseases. Thus, in order to explore an effective methodology, enantiomers of a few tripeptide derivatives with three stereogenic centers, as one of the most representative oligopeptides, are synthesized and characterized from the corresponding D- and L- α -amino acids. In the meantime, we designed and synthesized tetraaza macrocyclic chiral solvating agents (TAMCSAs) **1a–1d** as chiral ¹H NMR auxiliaries to execute discrimination of enantiomers of these analytes as well as detection of their optical purity by ¹H NMR spectroscopy (Figure 1).

The molecular structures of TAMCSAs **1a–1d** contain two amide, two amino, and two phenolic hydroxyl groups as potential multiple hydrogen bonding sites with chiral analytes, as well as a 12-membered cavity and C_2 -symmetry. In addition, a conjugated effect and inductive effect between a phenyl group and Cl or Br atoms exist in the molecular structures of TAMCSAs **1b** and **1c**, but overall, the conjugated effect is stronger than the inductive effect and results in an increase of electron density of the phenyl group. However, chiral recognition is usually based on molecular interactions including hydrogen binding and π – π stacking. These outstanding structural features of TAMCSAs **1a–1d** are considered to be essential ingredients toward improving their chiral discriminating abilities against chiral analytes by ^1H NMR spectroscopy.

RESULTS AND DISCUSSION

Synthesis of TAMCSAs **1a–1d**.

N-Boc-D-phenylalanine diamide **3** was prepared by an amide reaction of *N*-Boc-D-phenylalanine with (1*S*,2*S*)-(+)-1,2-diaminocyclohexane in the presence of *N,N'*-dicyclohexylcarbodiimide (DCC) according to the procedure.¹³ Chiral diamine **4** was obtained by deprotection of **3** in trifluoroacetic acid (TFA), and the crude product was used without further purification in the next step. Condensation reactions of **4** with salicylaldehyde and its derivatives were carried out to afford chiral diimines **5a–5d**, respectively.¹⁴ TAMCSAs **1a–1d** were synthesized by reductive coupling reactions under suitably dilute conditions.¹⁵ They were purified by column chromatography on silica gel to afford TAMCSAs **1a–1d** in 18–24% overall yields via three steps, respectively (Scheme 1). Additionally, chiral compounds **2a–2d** were also obtained as known compounds, except **2c** as a new compound.¹⁶

Products were characterized by ^1H NMR, ^{13}C NMR, NOESY, HRMS, and IR methods. Among them, the absolute configurations of two newly generated chiral centers (Figure 1, C5 and C6, or Figure 2, C16 and C23) of TAMCSAs **1a** and **1b** in the intramolecular reductive C–C coupling reaction between two imino groups of **5a** and **5b** are assigned to possess *S* and *S* based on their X-ray crystallographic analysis (Figure 2).

Unfortunately, crystals of TAMCSAs **1c** and **1d**, suitable for X-ray diffraction analysis, were not obtained. Therefore, their 2D NOESY spectra were measured for characterization purposes (Figure 3).

As shown in Figure 3, the *CH* protons (α -H, Phe) of D-phenylalanine moieties of TAMCSAs **1c** and **1d** show NOESY correlated signals with *CH* protons of the newly generated chiral carbon atoms of the Ar*CHNH* groups. This result suggests that two types of protons (α -H and Ar*CHNH*) of TAMCSAs **1c** and **1d** are located on the same side of the macrocyclic framework. Based on the known absolute configuration (*R*) of α -H (Phe) and the C_2 -symmetric geometry, the absolute configurations of the two chiral carbon atoms of the newly generated Ar*CHNH* moieties of TAMCSAs **1c** and **1d** are assigned as *S,S*. This result is completely in line with the assignments of absolute configurations of the same moiety of TAMCSAs **1a** and **1b** by both their NOESY correlated signals of the corresponding protons and X-ray crystal diffraction analysis.

Synthesis of Enantiomers of Tripeptide Derivatives (G1–1–G9–2) and Their Chiral Recognition.

Usually, chiral analytes with a single stereogenic center, such as amines,¹⁷ alcohols,¹⁸ amino alcohols,¹⁹ carboxylic acids,²⁰ and amino acid or their derivatives,²¹ are often used for discrimination of enantiomers and determination of enantiomeric excess by ¹H NMR spectroscopy. However, chiral recognition of analytes with two or more stereogenic centers, which would be a challenging problem due to complicated stereogenic configurations, is rarely studied and reported.⁸ Herein, a series of enantiomers of tripeptide derivatives possessing three stereogenic centers were synthesized and utilized to probe their chiral recognition by ¹H NMR spectroscopy.

First, enantiomers of tripeptide derivatives (**G1–1–G4–2**) with three stereogenic centers were synthesized from the corresponding D/L-phenylglycine (Phg), phenylalanine (Phe), and alanine (Ala). *N*-Boc-D/L-Phg **7**, D/L-PheOBn **9**, and *N*-Ts-D/L-Ala **13** were initially prepared, respectively.²² Dipeptide derivatives (*N*-Boc-Phg-PheOBn) **10** were then derived from **7** and **9**.¹³ Finally, enantiomers **G1–1–G4–2** of tripeptide derivatives (*N*-Ts-Ala-Phg-PheOBn) were obtained by an amidation reaction of **11** and **13** in 34–78% yields (Scheme 2).¹³

As shown in Scheme 2, all stereoisomers **G1–1–G4–2** have highly similar chemical structures, possessing the same amino acid residue and sequence (*N*-Ts-Ala-Phg-PheOBn). The only difference is that **G1–1–G4–2** exhibit different stereogenic configurations (DLL and LDD, DDL and LLD, DDD and DLD and LDL).

G1–1–G4–2 were characterized by ¹H NMR, C NMR, IR, and HRMS. However, some proton signals of them, including α -H (Phg) and NH protons of two CONH and TsNH groups, could not be properly assigned on this NMR evidence alone in a different degree, due to close chemical shifts, almost identical coupling constants and similar peak shapes. Thus, the H–H COSY and H–C HSQC spectra of one enantiomer (**GX–2**, X = 1, 2, 3, and 4) of **G1–G4** were measured in CDCl₃, and the assignments of the disputed proton signals were properly identified on the basis of the correlated information of H–H COSY and H–C HSQC spectra, for example, **G1–2** shown in Figure 4.

To explore discrimination of enantiomers of ($\pm$)-G1–G4 in the presence of TAMCSAs **1a–1d** by ¹H NMR spectroscopy, a sample of ($\pm$)-G1 (G1–1 (●) and G1–2 (○)) was prepared in the presence of TAMCSA **1a** in CDCl₃, and its ¹H NMR spectrum was measured. The result shows that the two enantiomers of ($\pm$)-**G1** were more clearly discriminated by the virtue of split ¹H NMR signals of five types of protons. The nonequivalent chemical shifts (δ) of the protons of CH₃, PhCH₃, TsNH, CONH (Phe), and ArH groups were found to be 0.007, 0.017, 0.090, 0.018, and 0.015 ppm, respectively.

TAMCSA **1a** has been preliminarily established to demonstrate chiral discriminating abilities toward ($\pm$)-**G1** by ¹H NMR spectroscopy. In order to obtain a better baseline resolution and more clearly distinguished ¹H NMR signals for chiral recognition, optimization of conditions was undertaken, with respect to solvent effect, concentration, and ratio of host and guest. These results suggest that CDCl₃ is the optimum solvent and that a

concentration of 5 mM along with a 1:1 ratio of host and guest are most suitable for chiral recognition by ^1H NMR spectroscopy (Supporting Information).

Under optimized conditions, all samples of ($\pm$)-**G1–G4** were prepared in the presence of TAMCSAs **1a–1d**, respectively, and then their ^1H NMR spectra were recorded on a 400 MHz spectrometer, with the exception of ($\pm$)-**G1**, which was examined only in the presence of TAMCSA **1a**. ^1H NMR signals of multiple protons of a pair of enantiomers of ($\pm$)-**G1–G4** were split in the presence of TAMCSAs **1a–1d**, respectively. Subsequently, the assignment of the enantiomers of ($\pm$)-**G1–G4** was achieved by comparing the featured ^1H NMR signals of each enantiomer separately under the same conditions. Nonequivalent chemical shift values (δ , up to 0.317 ppm) of selected protons of ($\pm$)-**G1–G4** featuring larger nonequivalent chemical shifts and better baseline separation, along with their partial ^1H NMR spectra, are summarized in Table 1.

The δ values of other split protons of ($\pm$)-**G1–G4** in the presence of **1a–1d** are summarized in Table 2, and their ^1H NMR spectra are available in the Supporting Information.

To further demonstrate the practicality of TAMCSAs **1a–1d** in discriminating enantiomers of tripeptide derivatives with three stereogenic centers, enantiomers **GX-1** ($X = 5-9$, DLL) and **GX-2** ($X = 5-9$, LDD) with the same stereogenic configuration, and different amino acid residues, were synthesized based on the above same procedure from the corresponding D- and L-amino acids. Their structures are shown in Chart 1.

Similarly, the H–H COSY and H–C HSQC spectra of enantiomers **GX-2** ($X = 5-9$) were measured in CDCl_3 for assignments of the aforementioned disputed protons.

Samples of ($\pm$)-**G5**, **G7**, and **G8** with TAMCSAs **1a–1d** (1:1, 5 mM) were prepared in CDCl_3 , respectively. Samples of ($\pm$)-**G6** and **G9** with TAMCSAs **1a–1d** (1:1) were prepared in lower concentrations (3 mM) due to their low solubility in CDCl_3 . ^1H NMR spectra of all samples were recorded on a 400 MHz NMR spectrometer. The results show that enantiomers of ($\pm$)-**G5–9** were effectively discriminated by split ^1H NMR signals of multiple type protons. The δ values (up to 0.616 ppm) and ^1H NMR spectra of representative protons of ($\pm$)-**G5–G9** in the presence of TAMCSAs **1a–1d** are summarized in Table 3.

Meanwhile, we find that nonequivalent chemical shift values of the separated protons of ($\pm$)-**G8** and ($\pm$)-**G9** are decreased in some sense, which maybe arise from an increase of steric hindrance due to a five-membered heterocycle in their molecules. The δ values of other split protons of the enantiomers of ($\pm$)-**G5–9** are shown in Table 4, and their ^1H NMR spectra are available in the Supporting Information.

Now that TAMCSAs **1a–1d** have been established to demonstrate excellent chiral discriminating abilities toward ($\pm$)-**G1–G9**, their practical applicability can be tested in determining enantiomeric excess (ee). As a typical example, samples containing **G1–2** with 90%, 70%, 50%, 30%, 10%, and 0% ee were prepared in the presence of TAMCSAs **1a–1d** in CDCl_3 , respectively, and their ^1H NMR spectra were recorded. Enantiomeric excess values of all samples were calculated based on the integration of ^1H NMR signals of *NH*

protons (TsNH group) of enantiomers **G1-1** and **G1-2**. Determination of optical purities of **G1-2** (up to 90% ee) was accurately executed by employing TAMCSAs **1a-1d**. Excellent linear correlations between the theoretical (X) and observed (Y) ee (%) values are obtained with the assistance of TAMCSAs **1a-1d** (Figure 5).

The aforementioned discriminating results show that not only larger nonequivalent chemical shift values of ($\pm$)-**G1-9** are obtained (up to 0.616 ppm) but also split ^1H NMR signals of the multiple hydrogen atoms are observed in the presence of TAMCSAs **1a-1d**. These indicate that TAMCSAs **1a-1d** have highly sensitive and effective chiral discriminating abilities toward the enantiomers of tripeptide derivatives ($\pm$)-**G1-9**.

In order to further reveal any underlying intermolecular hydrogen bonding interactions, theoretical calculations of TAMCSA **1a** with enantiomers (**G1-1** and **G1-2**) of ($\pm$)-**G1**, as a representative example, were performed by means of the hybrid density functional theory (B3LYP)²³ with the standard basis sets of 3-21G of the Gaussian 03 program.²⁴ The proposed models show that two hydrogen bonds were formed between TAMCSA **1a** and **G1-1** ((Ala) (NH)CO...HNCO (TAMCSA **1a**), 1.92 Å and (Ala) CONH... (H)OPh (TAMCSA **1a**), 1.86 Å, Figure 6a)). However, only one strong hydrogen bond ((TAMCSA **1a**) CONH... (NH)OC (Ala), 1.82 Å) was formed between **G1-2** and TAMCSA **1a** (Figure 6b), and hence the hydrogen bond network is more pronounced for the **G1-1/1a** combination.

The Cartesian coordinates (Å) and total energies (Hartree) of the complexes of **G1-1** and **G1-2** with TAMCSA **1a** obtained from B3LYP/3-21G structural optimization is available in the Supporting Information.

In addition, the calculated δ values of CH_3 protons (Ts group) of the enantiomers of ($\pm$)-**G1** in the presence of TAMCSA **1a** were obtained based on the above theoretically calculated models and were shown to be in agreement with the observed δ values (Table 5).

Moreover, Job plots of ($\pm$)-**G1** were carried out in the presence of TAMCSA **1a**. The Job plots of ($\pm$)-**G1** showed a maximum value ($X \times \delta = 0.045$ ppm) at a molar fraction of $X = 0.5$, which suggests that a pair of diastereoisomer complexes with 1:1 stoichiometry was established between ($\pm$)-**G1** and TAMCSA **1a** (Figure 7).

For further the demonstration of the formation of diastereomeric complexes of ($\pm$)-**G1** with TAMCSA **1a**, the stoichiometry of ($\pm$)-**G1** with TAMCSA **1a** was evaluated by electrospray ionization (ESI) mass spectroscopy. Indeed, the ESI mass spectrum of ($\pm$)-**G1** with TAMCSA **1a** exhibited a 1:1 complex [$(\pm)\text{-G1} + \text{1a} + \text{H}$](m/z 1232.5558) (Figure 8).

CONCLUSIONS

In conclusion, tetraaza macrocyclic chiral solvating agents (TAMCSAs) **1a-1d** were synthesized for chiral recognition by ^1H NMR spectroscopy. The enantiomers of tripeptide derivatives with three stereogenic centers ($\pm$)-**G1-G9** were prepared from corresponding D/L-amino acids and were successfully discriminated in the presence of TAMCSAs **1a-1d** by ^1H NMR spectroscopy. Enantiomeric excesses (ee) of **G1** with different optical

compositions were accurately calculated based on integrations of ^1H NMR signals of the proton (TsNH group) of **G1** in the presence of TAMCSAs **1a–1d**, respectively. Although determination of ee via ^1H NMR spectroscopy certainly has reportedly serious limitations for chiral analytes with a high optical purity, ee values ($>90\%$ ee) of **G1** can be clearly elucidated by ^1H NMR spectra. The chiral discriminating behavior of **G1** was further investigated by means of Job plots, theoretical calculations, and electrospray ionization mass spectroscopy. In summary, multiple lines of investigation (both experimental and computational) demonstrate that TAMCSAs **1a–1d** are especially suitable for chiral recognition of tripeptide derivatives with three stereogenic centers ($\pm$)-**G1–G9** by ^1H NMR spectroscopy, due to the unique structural features of TAMCSAs **1a–1d**, leading to a better baseline resolution, larger nonequivalent chemical shifts, and multiple detection windows. A practical strategy for chiral recognition of tripeptide derivatives with three stereogenic centers ($\pm$)-**G1–G9** has been effectively established by using TAMCSAs **1a–1d** via ^1H NMR spectroscopy. Therefore, it can be a powerful tool or method for chiral recognition of chiral analytes containing amino acid building blocks with two and more stereogenic centers.

EXPERIMENTAL SECTION

General.

NMR spectra were recorded on a Bruker Advance III spectrometer at 400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR. NOESY experiments of TAMCSAs were completed under a number of scans (**1a**, 8; **1b–1d**, 16), mixing time (**1a–1d** 0.30 s), and d1 (**1a**, 1.98 s; **1b**, 1.82 s; **1c**, 1.99 s; **1d**, 1.90 s). HRMS spectra were acquired on MicrOTOF-Q II 10260, FLEX-PC, and TripleTOF 5600 units. IR spectra were obtained on a Nicolet 360 Avatar IR spectrometer as KBr pellets. Optical rotations were measured with a PerkinElmer Model 343 polarimeter using the sodium D line at 589 nm. X-ray crystal structures were determined by a Smart Apex II Single Crystal diffractometer.

Synthesis of TAMCSAs **1a–1d**.

The chiral diimines **5** were derived from chiral substrate **3** based on the reported procedure. To a solution of chiral diimines **5** (1.2 mmol) in dried DMF (60 mL) were added zinc powder (0.78 g, 12 mmol) and MsOH (1.15 g, 12 mmol) in dried DMF (20 mL). The mixture was stirred for 24 h under a nitrogen atmosphere at $-18\text{ }^\circ\text{C}$. The reaction mixture was basified to pH = 9–10 with a saturated NaHCO_3 solution. The precipitate formed was filtered off and washed with CHCl_3 . The organic layer was separated from the filtrate. The water layer was extracted with CHCl_3 (15 mL $\times$ 3). The combined organic layer was dried over anhydrous Na_2SO_4 . The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel to afford TAMCSAs **1a–1d** and chiral products **2a–2d** as known compounds except **2c** as an unknown compound.

(3R,5S,6S,8R,10aS,14aS)-3,8-Dibenzyl-5,6-bis(2-hydroxyphenyl)-tetradecahydrobenzo[b][1,4,7,10]tetra-azacyclododecine-2,9-dione (TAMCSA **1a**):

24% overall yield; R_f = 0.2 (ethyl acetate/petroleum ether = 1:3); mp 205–207 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{20}$ +43.84 (c 0.025, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 0.90–0.92 (m, 2H), 1.11–1.16 (m,

2H), 1.20–1.25 (m, 2H), 1.63 (d, $J = 7.96$ Hz, 2H), 2.34 (br, 2H), 2.85 (dd, $J = 12.60$ Hz, $J = 5.28$ Hz, 2H), 2.91–2.96 (m, 2H), 3.24 (br, 2H), 3.73 (br, 2H), 4.43 (s, 2H), 5.78 (br, 2H), 6.43 (br, 2H), 6.62 (t, $J = 7.34$ Hz, 2H), 6.83 (d, $J = 7.96$ Hz, 2H), 7.03–7.07 (m, 6H), 7.13–7.18 (m, 6H), 9.90 (br, 2H); C{H} NMR (100 MHz, CDCl₃) δ 24.8 {2C, CH₂}, 31.7 {2C, CH₂}, 40.2 {2C, CH₂}, 52.8 {2C, CH}, 62.2 {2C, CH}, 66.8 {2C, CH}, 116.9 {2C, CH}, 119.5 {2C, CH}, 125.2 {2C}, 126.8 {2C, CH}, 128.4 {4C, CH}, 128.5 {4C, CH}, 129.4 {4C, CH}, 136.8 {2C}, 155.5 {2C}, 174.2 {2C}; IR (KBr) 3294, 2931, 1656, 748, 700 cm; HRMS (ESI-TOF) m/z calcd for C₃₈H₄₃N₄O₄ [M + H] 619.3284, found 619.3273.

(3R,5S,6S,8R,10aS,14aS)-3,8-Dibenzyl-5,6-bis(5-chloro-2-hydroxyphenyl)tetradecahydrobenzo[b][1,4,7,10]tetraazacyclododecine-2,9-dione (TAMCSA 1b):

19% overall yield; $R_f = 0.3$ (ethyl acetate/petroleum ether = 2:5); mp 201–203 °C; $[\alpha]_D^{20} +34.24$ (c 0.025, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.87–0.93 (m, 2H), 1.10–1.15 (m, 2H), 1.23 (d, $J = 13.40$ Hz, 2H), 1.62–1.65 (m, 2H), 2.13 (br, 2H), 2.84 (dd, $J = 12.64$ Hz, $J = 5.52$ Hz, 2H), 2.88–2.94 (m, 2H), 3.28 (br, 2H), 3.70 (br, 2H), 4.34 (s, 2H), 5.66 (br, 2H), 6.32 (br, 2H), 6.79 (d, $J = 8.64$ Hz, 2H), 7.05–7.07 (m, 5H), 7.15–7.23 (m, 7H), 9.75 (br, 2H); C{H} NMR (100 MHz, CDCl₃) δ 24.8 {2C, CH₂}, 31.8 {2C, CH₂}, 40.3 {2C, CH₂}, 52.8 {2C, CH}, 61.6 {2C, CH}, 66.7 {2C, CH}, 118.5 {2C, CH}, 124.6 {2C, CH}, 126.8 {2C}, 127.1 {2C, CH}, 127.8 {2C}, 128.5 {2C, CH}, 128.6 {4C, CH}, 129.5 {4C, CH}, 136.6 {2C}, 153.7 {2C}, 174.0 {2C}; IR (KBr) 3304, 2933, 1657, 1537, 1485, 700 cm; HRMS (ESI-TOF) m/z calcd for C₃₈H₄₁N₄O₄Cl₂ [M + H] 687.2505, found 687.2509.

(3R,5S,6S,8R,10aS,14aS)-3,8-Dibenzyl-5,6-bis(5-bromo-2-hydroxyphenyl)tetradecahydrobenzo[b][1,4,7,10]tetraazacyclododecine-2,9-dione (TAMCSA 1c):

21% overall yield; mp 204–206 °C; $R_f = 0.3$ (petroleum ether/ethyl acetate = 3:2); $[\alpha]_D^{20} +43.0$ (c 0.01, THF); ¹H NMR (400 MHz, CDCl₃) δ 0.90–0.93 (m, 2H), 1.10–1.15 (m, 2H), 1.24 (d, $J = 13.80$ Hz, 2H), 1.64 (d, $J = 8.64$ Hz, 2H), 2.84 (dd, $J = 12.70$ Hz, $J = 5.66$ Hz, 2H), 2.88–2.90 (m, 2H), 3.33–3.35 (m, 2H), 3.73 (br, 2H), 4.34 (s, 2H), 5.82 (br, 2H), 6.41 (br, 2H), 6.69 (d, $J = 8.64$ Hz, 2H), 7.05–7.07 (m, 4H), 7.14–7.23 (m, 8H), 9.79 (br, 2H); C{H} NMR (100 MHz, CDCl₃) δ 24.6 {2C, CH₂}, 31.6 {2C, CH₂}, 40.1 {2C, CH₂}, 52.5 {2C, CH}, 61.3 {2C, CH}, 66.4 {2C, CH}, 111.6 {2C}, 118.9 {2C, CH}, 126.9 {2C, CH}, 128.4 {4C, CH}, 129.4 {4C, CH}, 130.4 {2C}, 131.2 {2C, CH}, 136.5 {2C, CH}, 153.9 {2C}, 164.9 {2C}, 173.8 {2C}; IR (KBr) 3292, 2928, 2855, 2355, 1657, 1555, 1539, 1477, 1273, 704 cm; HRMS (MALDI-TOF) m/z calcd for C₃₈H₄₁Br₂N₄O₄ [M + H] 775.1496, found 775.1489.

(3R,5S,6S,8R,10aS,14aS)-3,8-Dibenzyl-5,6-bis(2-hydroxy-5-methoxyphenyl)tetradecahydrobenzo[b][1,4,7,10]tetraazacyclododecine-2,9-dione (TAMCSA 1d):

18% overall yield; $R_f = 0.3$ (ethyl acetate/petroleum ether = 1:2); mp 169–171 °C; $[\alpha]_D^{20} +37.92$ (c 0.025, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.91–0.93 (m, 2H), 1.11–1.16 (m,

2H), 1.25 (d, $J = 12.56$ Hz, 2H), 1.63 (d, $J = 8.08$ Hz, 2H), 2.16 (br, 2H), 2.84 (dd, $J = 12.68$ Hz, $J = 5.52$ Hz, 2H), 2.89–2.95 (m, 2H), 3.28–3.29 (m, 2H), 3.48 (s, 6H), 3.73 (br, 2H), 4.39 (s, 2H), 5.73 (br, 2H), 5.95 (br, 2H), 6.64 (dd, $J = 8.76$ Hz, $J = 2.72$ Hz, 2H), 6.78 (d, $J = 8.72$ Hz, 2H), 7.04–7.06 (m, 4H), 7.13–7.19 (m, 6H), 9.36 (br, 2H); C{H} NMR (100 MHz, CDCl₃) δ 24.9 {2C, CH₂}, 31.8 {2C, CH₂}, 40.3 {2C, CH₂}, 53.0 {2C, CH}, 55.9 {2C, CH₃}, 62.0 {2C, CH}, 67.1 {2C, CH}, 113.1 {2C, CH}, 115.1 {2C, CH}, 118.0 {2C, CH}, 126.1 {2C}, 126.9 {2C, CH}, 128.5 {4C, CH}, 129.5 {4C, CH}, 136.9 {2C}, 149.3 {2C}, 152.9 {2C}, 174.1 {2C}; IR (KBr) 3304, 2934, 1656, 1256, 701 cm; HRMS (ESITOF) m/z calcd for C₄₀H₄₇N₄O₆ [M + H] 679.3496, found 679.3491.

(2R,2'R)-N,N'-((1S,2S)-Cyclohexane-1,2-diyl)bis(2-((5-bromo-2-hydroxybenzyl)amino)-3-phenylpropan-amide) (2c):

18% yield; $R_f = 0.3$ (ethyl acetate/petroleum ether = 2:3); mp 179–180 °C; $[\alpha]_D^{20} +15.7$ (c 0.01, THF); ¹H NMR (400 MHz, CDCl₃) δ 0.88–0.94 (m, 2H), 1.18–1.23 (m, 2H), 1.66 (d, $J = 9.20$ Hz, 2H), 1.78 (d, $J = 12.68$ Hz, 2H), 2.86 (dd, $J = 13.46$ Hz, $J = 7.50$ Hz, 2H), 2.96 (dd, $J = 13.46$ Hz, $J = 7.10$ Hz, 2H), 3.27 (t, $J = 7.30$ Hz, 2H), 3.45–3.48 (m, 4H), 3.74 (d, $J = 13.36$ Hz, 2H), 6.37 (d, $J = 5.36$ Hz, 2H), 6.67 (d, $J = 8.56$ Hz, 2H), 6.86 (d, $J = 2.16$ Hz, 2H), 7.10–7.11 (m, 4H), 7.20–7.22 (m, 2H), 7.25–7.30 (m, 6H); C{H} NMR (100 MHz, DMSO-d₆) δ 25.6 {2C, CH₂}, 33.1 {2C, CH₂}, 40.7 {2C, CH₂}, 49.5 {2C, CH₂}, 53.7 {2C, CH}, 64.7 {2C, CH}, 112.0 {2C}, 118.3 {2C, CH}, 127.8 {2C, CH}, 128.0 {2C}, 129.6 {4C, CH}, 130.2 {4C, CH}, 132.3 {2C, CH}, 133.2 {2C, CH}, 138.5 {2C}, 156.9 {2C}, 175.6 {2C}; IR (KBr) 3294, 2926, 2855, 1643, 1535, 1483, 1414, 1265, 1179, 1117, 818, 704 cm; HRMS (MALDI-TOF) m/z calcd for C₃₈H₄₃Br₂N₄O₄ [M + H] 777.1653, found 777.1646.

Synthesis of Enantiomers of Tripeptide Derivatives with Three Stereogenic Centers G1–G9.

A typical procedure for the synthesis of enantiomers of **G1–G9** is exemplified with **G1–1**: N-TsD-Ala (0.24 g, 1 mmol) was added to a solution of L-Phg-L-PheOBn (0.39 g, 1 mmol) in dried ethyl acetate (15 mL). A solution of DCC (0.25 g, 1.2 mmol) in dried ethyl acetate (5 mL) was dropped into the above solution under a nitrogen atmosphere, and the mixture was kept in an ice bath; the reaction was carried out for 8 h. The reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel to afford the tripeptide derivative with three stereogenic centers **G1–1**.

(S)-Benzyl 2-((S)-2-((R)-2-(4-Methylphenylsulfonamido)propanamido)-2-phenylacetamido)-3-phenylpropanoate (G1–1):

33% yield; $R_f = 0.3$ (ethyl acetate/petroleum ether = 2:3); mp 125–126 °C; $[\alpha]_D^{20} +47.2$ (c 0.01, DMSO); ¹H NMR (400 MHz, CDCl₃) δ 1.21 (d, $J = 7.08$ Hz, 3H), 2.38 (s, 3H), 3.04 (dd, $J = 13.88$ Hz, $J = 6.08$ Hz, 1H), 3.11 (dd, $J = 13.88$ Hz, $J = 5.96$ Hz, 1H), 3.83–3.90 (m, 1H), 4.80–4.85 (m, 1H), 5.01 (d, $J = 12.08$ Hz, 1H), 5.06 (d, $J = 12.12$ Hz, 1H), 5.32 (d, $J = 6.80$ Hz, 1H), 5.58 (d, $J = 7.72$ Hz, 1H), 6.33 (d, $J = 7.72$ Hz, 1H), 6.95–6.97 (m, 2H), 7.16–7.25 (m, 12H), 7.33–7.34 (m, 3H), 7.39 (d, $J = 6.80$ Hz, 1H), 7.73 (d, $J = 8.28$ Hz, 2H); C{H} NMR (100 MHz, DMSO-d₆) δ 19.1 {CH₃}, 21.5 {CH₃}, 37.0 {CH₂}, 52.2 {CH},

54.4 {CH}, 55.7 {CH}, 66.5 {CH₂}, 126.9 {2C, CH}, 127.1 {CH}, 127.2 {2C, CH}, 127.9 {CH}, 128.3 {2C, CH}, 128.4 {CH}, 128.6 {2C, CH}, 128.8 {4C, CH}, 129.5 {2C, CH}, 130.0 {2C, CH}, 136.0 {C}, 137.2 {C}, 138.6 {C}, 138.9 {C}, 143.1 {C}, 169.8 {C}, 171.2 {2C}; IR (KBr) 3304, 1727, 1632, 1537, 1151, 974, 702 cm; HRMS (ESI-TOF) *m/z* calcd for C₃₄H₃₆N₃O₆S [M + H]614.2319, found 614.2329.

(R)-Benzyl 2-((R)-2-((S)-2-(4-Methylphenylsulfonamido)propanamido)-2-phenylacetamido)-3-phenylpropanoate (G1-2):

34% yield; *R_f* = 0.3 (ethyl acetate/petroleum ether = 2:3); mp 125–127 °C; [α]_D²⁰ –47.3 (*c* 0.01, DMSO); ¹H NMR (400 MHz, CDCl₃) δ 1.22 (d, *J* = 7.08 Hz, 3H), 2.38 (s, 3H), 3.04 (dd, *J* = 13.88 Hz, *J* = 6.12 Hz, 1H), 3.11 (dd, *J* = 13.88 Hz, *J* = 5.96 Hz, 1H), 3.83–3.90 (m, 1H), 4.80–4.85 (m, 1H), 5.01 (d, *J* = 12.12 Hz, 1H), 5.06 (d, *J* = 12.08 Hz, 1H), 5.31 (d, *J* = 6.84 Hz, 1H), 5.56 (d, *J* = 7.64 Hz, 1H), 6.32 (d, *J* = 7.72 Hz, 1H), 6.95–6.98 (m, 2H), 7.16–7.25 (m, 12H), 7.32–7.34 (m, 3H), 7.37 (d, *J* = 6.80 Hz, 1H), 7.73 (d, *J* = 8.00 Hz, 2H); C{H} NMR (100 MHz, CDCl₃) δ 19.1 {CH₃}, 21.6 {CH₃}, 37.7 {CH₂}, 52.4 {CH}, 53.6 {CH}, 57.4 {CH}, 67.3 {CH₂}, 127.2 {4C, CH}, 128.6 {9C, CH}, 129.1 {2C, CH}, 129.3 {2C, CH}, 129.8 {2C, CH}, 134.9 {C}, 135.4 {C}, 136.6 {C}, 136.9 {C}, 143.8 {C}, 169.2 {C}, 170.7 {C}, 170.9 {C}; IR (KBr) 3304, 1733, 1632, 1535, 1150, 975, 699 cm; HRMS (ESI-TOF) *m/z* calcd for C₃₄H₃₆N₃O₆S [M + H]614.2319, found 614.2340.

(S)-Benzyl 2-((R)-2-((R)-2-(4-Methylphenylsulfonamido)propanamido)-2-phenylacetamido)-3-phenylpropanoate (G2-1):

34% yield; *R_f* = 0.3 (ethyl acetate/petroleum ether = 2:3); mp 195–197 °C; [α]_D²⁰ –20.4 (*c* 0.01, DMSO); ¹H NMR (400 MHz, CDCl₃) δ 1.26 (d, *J* = 7.08 Hz, 3H), 2.35 (s, 3H), 2.96 (d, *J* = 5.64 Hz, 2H), 3.81–3.88 (m, 1H), 4.91 (dt, *J* = 5.60 Hz, 1H), 5.10 (d, *J* = 12.08 Hz, 1H), 5.15 (d, *J* = 12.08 Hz, 1H), 5.29 (d, *J* = 6.80 Hz, 1H), 5.31 (d, *J* = 7.40 Hz, 1H), 6.36 (d, *J* = 7.84 Hz, 1H), 6.54 (d, *J* = 7.16 Hz, 2H), 6.97–7.01 (m, 2H), 7.09–7.13 (m, 3H), 7.18–7.20 (m, 2H), 7.28–7.38 (m, 9H), 7.62 (d, *J* = 8.28 Hz, 2H); C{H} NMR (100 MHz, DMSO-d₆) δ 19.5 {CH₃}, 21.4 {CH₃}, 36.9 {CH₂}, 51.8 {CH}, 54.2 {CH}, 55.9 {CH}, 66.6 {CH₂}, 126.9 {2C, CH}, 127.1 {2C, CH}, 127.8 {CH}, 128.2 {2C, CH}, 128.5 {4C, CH}, 128.6 {2C, CH}, 128.9 {2C, CH}, 129.5 {2C, CH}, 129.8 {2C, CH}, 136.1 {C}, 137.2 {C}, 138.6, {C}, 138.7 {C}, 142.9 {C}, 170.0 {C}, 171.2 {C}, 171.5 {C}; IR (KBr) 3303, 1729, 1634, 1539, 1152, 974, 695 cm; HRMS (ESI-TOF) *m/z* calcd for C₃₄H₃₆N₃O₆S [M + H]614.2319, found 614.2332.

(R)-Benzyl 2-((S)-2-((S)-2-(4-Methylphenylsulfonamido)propanamido)-2-phenylacetamido)-3-phenylpropanoate (G2-2):

33% yield; *R_f* = 0.3 (ethyl acetate/petroleum ether = 2:3); mp 194–196 °C; [α]_D²⁰ +21.5 (*c* 0.01, DMSO); ¹H NMR (400 MHz, CDCl₃) δ 1.26 (d, *J* = 7.08 Hz, 3H), 2.36 (s, 3H), 2.96 (d, *J* = 6.16 Hz, 2H), 3.81–3.88 (m, 1H), 4.91 (dt, *J* = 5.60 Hz, 1H), 5.10 (d, *J* = 12.04 Hz, 1H), 5.15 (d, *J* = 12.04 Hz, 1H), 5.29 (d, *J* = 6.72 Hz, 1H), 5.32 (d, *J* = 7.36 Hz, 1H), 6.38 (d, *J* = 7.80 Hz, 1H), 6.53 (d, *J* = 7.08 Hz, 2H), 6.96–7.01 (m, 2H), 7.09–7.13 (m, 3H), 7.18–7.20 (m, 2H), 7.28–7.33 (m, 4H), 7.35–7.37 (m, 5H), 7.61 (d, *J* = 8.32 Hz, 2H); C{H} NMR

(100 MHz, CDCl₃) δ 19.8 {CH₃}, 21.6 {CH₃}, 37.4 {CH₂}, 52.4 {CH}, 53.3 {CH}, 57.3 {CH}, 67.5 {CH₂}, 126.9 {CH}, 127.1 {2C, CH}, 127.3 {2C, CH}, 128.4 {2C, CH}, 128.5 {CH}, 128.6 {2C, CH}, 128.7 {4C, CH}, 129.2 {3C, CH}, 129.7 {2C, CH}, 134.9 {C}, 135.0 {C}, 136.5 {C}, 137.3 {C}, 143.6 {C}, 168.8 {C}, 170.6 {C}, 170.8 {C}; IR (KBr) 3345, 3259, 1730, 1646, 1539, 1523, 1347, 1164, 695 cm; HRMS (ESI-TOF) m/z calcd for C₃₄H₃₆N₃O₆S [M + H]⁺ 614.2319, found 614.2317.

(R)-Benzyl 2-((R)-2-((R)-2-(4-Methylphenylsulfonamido)propanamido)-2-phenylacetamido)-3-phenylpropanoate (G3-1):

32% yield; R_f = 0.3 (ethyl acetate/petroleum ether = 2:3); mp 208–210 °C; $[\alpha]_D^{20}$ +18.7 (c 0.01, DMSO); ¹H NMR (400 MHz, CDCl₃) δ 1.27 (d, J = 7.08 Hz, 3H), 2.39 (s, 3H), 3.04 (dd, J = 13.88 Hz, J = 7.28 Hz, 1H), 3.19 (dd, J = 13.90 Hz, J = 5.54 Hz, 1H), 3.75–3.81 (m, 1H), 4.86–4.91 (m, 1H), 5.07 (d, J = 12.20 Hz, 1H), 5.11 (d, J = 4.48 Hz, 1H), 5.13 (d, J = 12.12 Hz, 1H), 5.32 (d, J = 7.04 Hz, 1H), 6.66 (d, J = 8.04 Hz, 1H), 7.04–7.06 (m, 4H), 7.12 (d, J = 7.08 Hz, 1H), 7.18–7.30 (m, 10H), 7.34–7.36 (m, 3H), 7.67 (d, J = 8.24 Hz, 2H); C{H} NMR (100 MHz, DMSO-d₆) δ 19.1 {CH₃}, 20.9 {CH₃}, 36.4 {CH₂}, 51.3 {CH}, 53.7 {CH}, 55.2 {CH}, 66.0 {CH₂}, 126.4 {2C, CH}, 126.5 {CH}, 126.9 {2C, CH}, 127.4 {CH}, 127.8 {2C, CH}, 127.9 {CH}, 128.1 {2C, CH}, 128.2 {2C, CH}, 128.3 {2C, CH}, 129.0 {2C, CH}, 129.3 {2C, CH}, 135.5 {C}, 136.7 {C}, 138.0 {C}, 138.2 {C}, 142.4 {C}, 169.4 {C}, 171.7 {2C}; IR (KBr) 3317, 3257, 1731, 1638, 1531, 1346, 1347, 1168, 693 cm; HRMS (ESI-TOF) m/z calcd for C₃₄H₃₆N₃O₆S [M + H]⁺ 614.2319, found 614.2331.

(S)-Benzyl 2-((S)-2-((S)-2-(4-Methylphenylsulfonamido)propanamido)-2-phenylacetamido)-3-phenylpropanoate (G3-2):

35% yield; R_f = 0.3 (ethyl acetate/petroleum ether = 2:3); mp 207–209 °C; $[\alpha]_D^{20}$ +20.0 (c 0.01, DMSO); ¹H NMR (400 MHz, CDCl₃) δ 1.27 (d, J = 7.08 Hz, 3H), 2.38 (s, 3H), 3.04 (dd, J = 13.82 Hz, J = 7.18 Hz, 1H), 3.19 (dd, J = 13.82 Hz, J = 5.50 Hz, 1H), 3.75–3.81 (m, 1H), 4.85–4.91 (m, 1H), 5.06 (d, J = 12.20 Hz, 1H), 5.12 (d, J = 6.52 Hz, 1H), 5.13 (d, J = 12.08 Hz, 1H), 5.32 (d, J = 7.04 Hz, 1H), 6.66 (d, J = 8.00 Hz, 1H), 7.03–7.05 (m, 4H), 7.12 (d, J = 7.04 Hz, 1H), 7.18–7.30 (m, 10H), 7.34–7.37 (m, 3H), 7.67 (d, J = 7.92 Hz, 2H); C{H} NMR (100 MHz, CDCl₃) δ 19.6 {CH₃}, 21.6 {CH₃}, 37.7 {CH₂}, 52.6 {CH}, 53.6 {CH}, 57.5 {CH}, 67.3 {CH₂}, 127.1 {CH}, 127.3 {4C, CH}, 128.5 {4C, CH}, 128.6 {4C, CH}, 129.1 {2C, CH}, 129.3 {2C, CH}, 129.8 {2C, CH}, 135.1 {C}, 135.7 {C}, 136.0 {C}, 136.6 {C}, 143.9 {C}, 169.1 {C}, 170.7 {C}, 170.8 {C}; IR (KBr) 3320, 3260, 1731, 1636, 1547, 1348, 1164, 693 cm; HRMS (ESI-TOF) m/z calcd for C₃₄H₃₆N₃O₆S [M + H]⁺ 614.2319, found 614.2305.

(R)-Benzyl 2-((S)-2-((R)-2-(4-Methylphenylsulfonamido)propanamido)-2-phenylacetamido)-3-phenylpropanoate (G4-1):

32% yield; R_f = 0.3 (ethyl acetate/petroleum ether = 2:3); mp 208–209 °C; $[\alpha]_D^{20}$ +52.0 (c 0.01, DMSO); ¹H NMR (400 MHz, CDCl₃) δ 1.23 (d, J = 7.04 Hz, 3H), 2.38 (s, 3H), 2.89–2.99 (m, 2H), 3.79–3.86 (m, 1H), 4.91 (dt, J = 5.36 Hz, 1H), 5.12 (d, J = 12.04 Hz, 1H), 5.17 (d, J = 11.92 Hz, 1H), 5.17 (d, J = 6.48 Hz, 1H), 5.26 (d, J = 7.72 Hz, 1H), 6.08 (d, J = 7.96

Hz, 1H), 6.46 (d, J = 7.16 Hz, 2H), 6.94–6.98 (m, 2H), 7.08–7.12 (m, 1H), 7.19–7.24 (m, 4H), 7.30–7.34 (m, 5H), 7.37–7.38 (m, 4H), 7.72 (d, J = 8.24 Hz, 2H); C{H} NMR (100 MHz, DMSO- d_6) δ 19.1 {CH₃}, 21.4 {CH₃}, 37.0 {CH₂}, 52.1 {CH}, 54.3 {CH}, 55.7 {CH}, 66.7 {CH₂}, 126.8 {2C, CH}, 126.9 {2C, CH}, 127.0 {CH}, 127.8 {CH}, 128.3 {2C, CH}, 128.5 {CH}, 128.6 {2C, CH}, 128.7 {2C, CH}, 128.9 {2C, CH}, 129.5 {2C, CH}, 130.0 {2C, CH}, 136.1 {C}, 137.1 {C}, 138.6 {C}, 138.9 {C}, 143.1 {C}, 170.0 {C}, 171.2 {C}, 171.6 {C}; IR (KBr) 3303, 1737, 1636, 1534, 1320, 1149, 694 cm; HRMS (ESI-TOF) m/z calcd for C₃₄H₃₆N₃O₆S [M + H] 614.2319, found 614.2324.

(S)-Benzyl 2-((R)-2-((S)-2-(4-Methylphenylsulfonamido)propanamido)-2-phenylacetamido)-3-phenylpropanoate (G4–2):

33% yield; R_f = 0.3 (ethyl acetate/petroleum ether = 2:3); mp 208–209 °C; $[\alpha]_D^{20}$ –53.3 (c 0.01, DMSO); ¹H NMR (400 MHz, CDCl₃) δ 1.23 (d, J = 7.04 Hz, 3H), 2.38 (s, 3H), 2.91 (dd, J = 13.90 Hz, J = 5.40 Hz, 1H), 2.96 (dd, J = 13.90 Hz, J = 5.46 Hz, 1H), 3.79–3.86 (m, 1H), 4.91 (dt, J = 5.36 Hz, 1H), 5.12 (d, J = 12.04 Hz, 1H), 5.16 (d, J = 4.88 Hz, 1H), 5.17 (d, J = 12.08 Hz, 1H), 5.24 (d, J = 7.68 Hz, 1H), 6.06 (d, J = 7.96 Hz, 1H), 6.45 (d, J = 7.08 Hz, 2H), 6.94–6.98 (m, 2H), 7.08–7.12 (m, 1H), 7.19–7.22 (m, 2H), 7.25–7.26 (m, 2H), 7.30–7.35 (m, 5H), 7.37–7.39 (m, 4H), 7.72 (d, J = 8.28 Hz, 2H); C{H} NMR (100 MHz, CDCl₃) δ 19.5 {CH₃}, 21.5 {CH₃}, 37.5 {CH₂}, 52.3 {CH}, 53.2 {CH}, 57.3 {CH}, 67.6 {CH₂}, 127.0 {2C, CH}, 127.2 {2C, CH}, 127.3 {2C, CH}, 128.5 {2C, CH}, 128.6 {2C, CH}, 128.7 {3C, CH}, 129.1 {2C, CH}, 129.3 {2C, CH}, 129.8 {2C, CH}, 134.8 {C}, 134.9 {C}, 136.7 {C}, 137.3 {C}, 143.8 {C}, 168.6 {C}, 170.5 {C}, 170.6 {C}; IR (KBr) 3257, 1731, 1643, 1525, 1338, 1164, 696 cm; HRMS (ESI-TOF) m/z calcd for C₃₄H₃₆N₃O₆S [M + H] 614.2319, found 614.2319.

(S)-Benzyl 2-((S)-2-((R)-3-Methyl-2-(4-methylphenylsulfonamido)butanamido)-2-phenylacetamido)-3 phenylpropanoate (G5–1):

63% yield; R_f = 0.3 (ethyl acetate/petroleum ether = 1:2); mp 172–174 °C; $[\alpha]_D^{20}$ +65.4 (c 0.01, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.73 (d, J = 6.84 Hz, 3H), 0.76 (d, J = 6.80 Hz, 3H), 1.98–2.06 (m, 1H), 2.36 (m, 3H), 3.05 (dd, J = 13.80 Hz, J = 6.20 Hz, 1H), 3.13 (dd, J = 13.80 Hz, J = 5.80 Hz, 1H), 3.55–3.59 (m, 1H), 4.78–4.83 (m, 1H), 5.02 (d, J = 12.08 Hz, 1H), 5.07 (d, J = 12.16 Hz, 1H), 5.11 (d, J = 6.16 Hz, 1H), 5.14 (d, J = 8.36 Hz, 1H), 6.02 (d, J = 7.68 Hz, 1H), 6.95–7.00 (m, 3H), 7.13–7.16 (m, 2H), 7.19–7.24 (m, 10H), 7.34–7.35 (m, 3H), 7.71 (d, J = 8.00 Hz, 2H); C{H} NMR (100 MHz, CDCl₃) δ 17.2 {CH₃}, 19.1 {CH₃}, 21.5 {CH₃}, 31.5 {CH}, 37.6 {CH₂}, 53.7 {CH}, 57.3 {CH}, 61.9 {CH}, 67.3 {CH₂}, 127.2 {3C, CH}, 127.3 {2C, CH}, 128.5 {4C, CH}, 128.6 {2C, CH}, 128.7 {2C, CH}, 129.0 {2C, CH}, 129.2 {2C, CH}, 129.6 {2C, CH}, 134.7 {C}, 135.4 {C}, 136.7 {C}, 136.9 {C}, 143.5 {C}, 169.1 {C}, 170.1 {C}, 170.5 {C}; IR (KBr) 3416, 3374, 3158, 2958, 1729, 1642, 1510, 1331, 1168, 700 cm; HRMS (ESI-TOF) m/z calcd for C₃₆H₄₀N₃O₆S [M + H] 642.2632, found 642.2671.

(R)-Benzyl 2-((R)-2-((S)-3-Methyl-2-(4-methylphenylsulfonamido)butanamido)-2-phenylacetamido)-3-phenylpropanoate (G5-2):

56% yield; R_f 0.3 (ethyl acetate/petroleum ether = 1:2); mp 172–173 °C; $[\alpha]_D^{20}$ –62.1 (*c* 0.01, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.73 (d, *J* = 6.84 Hz, 3H), 0.76 (d, *J* = 6.80 Hz, 3H), 1.98–2.06 (m, 1H), 2.36 (m, 3H), 3.05 (dd, *J* = 13.80 Hz, *J* = 6.20 Hz, 1H), 3.13 (dd, *J* = 14.00 Hz, *J* = 6.00 Hz, 1H), 3.56–3.59 (m, 1H), 4.78–4.83 (m, 1H), 5.02 (d, *J* = 12.00 Hz, 1H), 5.07 (d, *J* = 12.40 Hz, 1H), 5.11 (d, *J* = 6.00 Hz, 1H), 5.18 (d, *J* = 8.40 Hz, 1H), 6.05 (d, *J* = 7.68 Hz, 1H), 6.95–6.97 (m, 2H), 7.02 (d, *J* = 6.20 Hz, 1H), 7.13–7.16 (m, 2H), 7.20–7.25 (m, 10H), 7.34–7.35 (m, 3H), 7.71 (d, *J* = 8.40 Hz, 2H); C{H} NMR (100 MHz, CDCl₃) δ 17.2 {CH₃}, 19.1 {CH₃}, 21.5 {CH₃}, 31.5 {CH}, 37.6 {CH₂}, 53.7 {CH}, 57.3 {CH}, 61.9 {CH}, 67.3 {CH₂}, 127.2 {3C, CH}, 127.3 {2C, CH}, 128.5 {4C, CH}, 128.6 {2C, CH}, 128.7 {2C, CH}, 129.0 {2C, CH}, 129.2 {2C, CH}, 129.6 {2C, CH}, 134.9 {C}, 135.4 {C}, 136.7 {C}, 136.9 {C}, 143.5 {C}, 169.1 {C}, 170.1 {C}, 170.6 {C}; IR (KBr) 3417, 3329, 3252, 2963, 1731, 1643, 1512, 1325, 1160, 696 cm; HRMS (ESI-TOF) *m/z* calcd for C₃₆H₄₀N₃O₆S [M + H]⁺ 642.2632, found 642.2646.

(S)-Benzyl 2-((S)-2-((R)-5-Amino-2-(4-methylphenylsulfonamido)-5-oxopentanamido)-2-phenylacetamido)-3-phenylpropanoate (G6-1):

30% yield; R_f 0.3 (methol/petroleum ether = 1:3); mp 200–201 °C; $[\alpha]_D^{20}$ +39.5 (*c* 0.01, DMSO); ¹H NMR (400 MHz, CDCl₃) δ 1.87–1.94 (m, 1H), 2.04–2.11 (m, 1H), 2.14–2.21 (m, 1H), 2.36 (s, 3H), 2.39–2.46 (m, 1H), 3.05 (dd, *J* = 13.74 Hz, *J* = 6.86 Hz, 1H), 3.13 (dd, *J* = 13.80 Hz, *J* = 5.72 Hz, 1H), 3.80–3.85 (m, 1H), 4.82–4.87 (m, 1H), 5.04 (d, *J* = 12.16 Hz, 1H), 5.09 (d, *J* = 12.12 Hz, 1H), 5.26 (d, *J* = 6.88 Hz, 1H), 5.86 (br, 1H), 5.98 (br, 1H), 6.56 (d, *J* = 7.88 Hz, 1H), 6.78 (d, *J* = 7.00 Hz, 1H), 7.02–7.04 (m, 2H), 7.07–7.10 (m, 2H), 7.19–7.27 (m, 11H), 7.34–7.35 (m, 3H), 7.47 (d, *J* = 6.92 Hz, 1H), 7.70 (d, *J* = 8.24 Hz, 2H); C{H} NMR (100 MHz, DMSO-*d*₆) δ 21.5 {CH₃}, 29.1 {CH₂}, 31.6 {CH₂}, 37.0 {CH₂}, 54.4 {CH}, 55.8 {CH}, 56.5 {CH}, 66.5 {CH₂}, 126.9 {2C, CH}, 127.1 {CH}, 127.3 {2C, CH}, 127.9 {CH}, 128.3 {2C, CH}, 128.4 {CH}, 128.6 {2C, CH}, 128.8 {4C, CH}, 129.5 {2C, CH}, 129.9 {2C, CH}, 136.0 {C}, 137.2 {C}, 138.6 {C}, 138.8 {C}, 142.9 {C}, 169.8 {C}, 170.4 {C}, 171.2 {C}, 174.0 {C}; IR (KBr) 3357, 3266, 1730, 1651, 1534, 1338, 1158, 697 cm; HRMS (ESITOF) *m/z* calcd for C₃₆H₃₉N₄O₇S [M + H]⁺ 671.2534, found 671.2537.

(R)-Benzyl 2-((R)-2-((S)-5-Amino-2-(4-methylphenylsulfonamido)-5-oxopentanamido)-2-phenylacetamido)-3-phenylpropanoate (G6-2):

32% yield; R_f 0.3 (methol/petroleum ether = 1:3); mp 200–202 °C; $[\alpha]_D^{20}$ –37.3 (*c* 0.01, DMSO); ¹H NMR (400 MHz, CDCl₃) δ 1.88–1.94 (m, 1H), 2.04–2.12 (m, 1H), 2.14–2.21 (m, 1H), 2.36 (s, 3H), 2.39–2.46 (m, 1H), 3.05 (dd, *J* = 13.80 Hz, *J* = 6.80 Hz, 1H), 3.13 (dd, *J* = 13.80 Hz, *J* = 5.72 Hz, 1H), 3.81–3.85 (m, 1H), 4.82–4.87 (m, 1H), 5.04 (d, *J* = 12.12 Hz, 1H), 5.09 (d, *J* = 12.12 Hz, 1H), 5.26 (d, *J* = 6.92 Hz, 1H), 5.93 (br, 1H), 6.01 (br, 1H), 6.58 (d, *J* = 7.84 Hz, 1H), 6.80 (d, *J* = 6.96 Hz, 1H), 7.01–7.04 (m, 2H), 7.07–7.10 (m, 2H), 7.18–7.28 (m, 11H), 7.34–7.35 (m, 3H), 7.50 (d, *J* = 6.76 Hz, 1H), 7.70 (d, *J* = 8.24 Hz, 2H); C{H} NMR (100 MHz, DMSO-*d*₆) δ 21.5 {CH₃}, 29.1 {CH₃}, 31.6 {CH₃}, 37.0 {CH₂}, 54.4 {CH}, 55.8 {CH}, 56.5 {CH}, 66.5 {CH₂}, 126.9 {2C, CH}, 127.1 {CH}, 127.3 {2C,

CH}, 127.9 {CH}, 128.3 {2C, CH}, 128.4 {CH}, 128.6 {2C, CH}, 128.8 {4C, CH}, 129.5 {2C, CH}, 129.9 {2C, CH}, 136.0 {C}, 137.2 {C}, 138.6 {C}, 138.8 {C}, 142.9 {C}, 169.8 {C}, 170.4 {C}, 171.2 {C}, 174.0 {C}; IR (KBr) 3426, 3211, 1724, 1664, 1637, 1540, 1158, 694 cm; HRMS (ESITOF) m/z calcd for $C_{36}H_{39}N_4O_7S$ [M + H] 671.2534, found 671.2545.

(S)-Benzyl 2-((S)-3-Methyl-2-((R)-2-(4-methylphenylsulfonamido)propanamido)butanamido)-3-phenylpropanoate (G7-1):

28% yield; R_f = 0.3 (ethyl acetate/petroleum ether = 2:3); mp 178–180 °C; $[\alpha]_D^{20}$ –27.1 (c 0.01, $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) δ 0.83 (d, J = 6.84 Hz, 3H), 0.87 (d, J = 6.76 Hz, 3H), 1.21 (d, J = 7.08 Hz, 3H), 2.01–2.10 (m, 1H), 2.41 (s, 3H), 3.09 (d, J = 6.00 Hz, 2H), 3.76–3.83 (m, 1H), 4.14–4.18 (m, 1H), 4.87–4.92 (m, 1H), 5.10 (d, J = 12.08 Hz, 1H), 5.13 (d, J = 6.24 Hz, 1H), 5.15 (d, J = 11.92 Hz, 1H), 6.26 (d, J = 8.00 Hz, 1H), 6.76 (d, J = 8.56 Hz, 1H), 7.00–7.02 (m, 2H), 7.21–7.23 (m, 3H), 7.27–7.31 (m, 4H), 7.35–7.37 (m, 3H), 7.75 (d, J = 8.24 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9 {CH₃}, 19.0 {CH₃}, 19.3 {CH₃}, 21.5 {CH₃}, 31.0 {CH}, 37.9 {CH₂}, 52.6 {CH}, 53.3 {CH}, 58.5 {CH}, 67.3 {CH₂}, 127.1 {2C, CH}, 128.5 {2C, CH}, 128.6 {2C, CH}, 128.6 {4C, CH}, 129.3 {2C, CH}, 129.9 {2C, CH}, 135.0 {C}, 135.5 {C}, 136.9 {C}, 143.8 {C}, 170.6 {C}, 171.1 {C}, 171.7 {C}; IR (KBr) 3312, 2969, 1729, 1642, 1543, 1336, 1161, 1090, 697 cm; HRMS (ESI-TOF) m/z calcd for $C_{31}H_{38}N_3O_6S$ [M + H] 580.2475, found 580.2478.

(R)-Benzyl 2-((R)-3-Methyl-2-((S)-2-(4-methylphenylsulfonamido)propanamido)butanamido)-3-phenylpropanoate (G7-2):

39% yield; R_f = 0.3 (ethyl acetate/petroleum ether = 2:3); mp 178–180 °C; $[\alpha]_D^{20}$ +27.7 (c 0.01, $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) δ 0.83 (d, J = 6.76 Hz, 3H), 0.87 (d, J = 6.68 Hz, 3H), 1.21 (d, J = 7.04 Hz, 3H), 2.01–2.09 (m, 1H), 2.41 (s, 3H), 3.09 (d, J = 5.88 Hz, 2H), 3.77–3.84 (m, 1H), 4.15–4.19 (m, 1H), 4.87–4.92 (m, 1H), 5.10 (d, J = 12.16 Hz, 1H), 5.15 (d, J = 12.12 Hz, 1H), 5.19 (d, J = 7.24 Hz, 1H), 6.23 (d, J = 7.96 Hz, 1H), 6.79 (d, J = 8.64 Hz, 1H), 7.00–7.02 (m, 2H), 7.21–7.23 (m, 3H), 7.26–7.31 (m, 4H), 7.36–7.37 (m, 3H), 7.75 (d, J = 8.04 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9 {CH₃}, 19.0 {CH₃}, 19.3 {CH₃}, 21.5 {CH}, 31.0 {CH}, 37.9 {CH₂}, 52.6 {CH}, 53.3 {CH}, 58.5 {CH}, 67.3 {CH₂}, 127.1 {2C, CH}, 128.5 {2C, CH}, 128.6 {2C, CH}, 128.6 {4C, CH}, 129.3 {2C, CH}, 129.9 {2C, CH}, 135.0 {C}, 135.5 {C}, 136.9 {C}, 143.8 {C}, 170.5 {C}, 171.1 {C}, 171.6 {C}; IR (KBr) 3309, 2971, 1730, 1639, 1548, 1333, 1166, 1091, 699 cm; HRMS (ESI-TOF) m/z calcd for $C_{31}H_{38}N_3O_6S$ [M + H] 580.2475, found 580.2480.

(S)-Benzyl 3-Phenyl-2-((S)-2-phenyl-2-((R)-1-tosylpyrrolidine-2carboxamido)acetamido)propanoate (G8-1):

64% yield; R_f = 0.4 (ethyl acetate/petroleum ether = 1:1); mp 132–134 °C; $[\alpha]_D^{20}$ +121.7 (c 0.01, $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) δ 1.61–1.66 (m, 2H), 1.77–1.85 (m, 1H), 2.14–2.20 (m, 1H), 2.43 (s, 3H), 3.08 (dd, J = 13.86 Hz, J = 5.78 Hz, 1H), 3.15 (dd, J = 13.80 Hz, J = 5.76 Hz, 1H), 3.16–3.24 (m, 1H), 3.58–3.63 (m, 1H), 4.08–4.13 (m, 1H), 4.88 (dt, J = 5.84 Hz, 1H), 5.04 (d, J = 12.12 Hz, 1H), 5.10 (d, J = 12.08 Hz, 1H), 5.39 (d, J = 7.04 Hz, 1H), 6.20 (d, J = 7.68 Hz, 1H), 6.97–7.00 (m, 2H), 7.21–7.24 (m, 5H), 7.30–7.36 (m, 10H),

7.71 (d, J = 8.24 Hz, 2H), 7.78 (d, J = 7.08 Hz, 1H); C{H} NMR (100 MHz, CDCl₃) δ 21.6 {CH₃}, 24.4 {CH₂}, 30.3 {CH₂}, 37.7 {CH₂}, 49.9 {CH₂}, 53.5 {CH}, 57.7 {CH}, 62.4 {CH}, 67.3 {CH₂}, 127.1 {CH}, 127.3 {2C, CH}, 127.9 {2C, CH}, 128.5 {2C, CH}, 128.6 {6C, CH}, 129.1 {2C, CH}, 129.3 {2C, CH}, 129.9 {2C, CH}, 133.0 {C}, 134.9 {C}, 135.4 {C}, 136.4 {C}, 144.3 {C}, 169.2 {C}, 170.7 {C}, 171.0 {C}; IR (KBr) 3331, 1736, 1650, 1516, 1344, 1156, 699 cm; HRMS (ESI-TOF) m/z calcd for C₃₆H₃₈N₃O₆S [M + H] 640.2476, found 640.2498.

(R)-Benzyl 3-Phenyl-2-((R)-2-phenyl-2-((S)-1-tosylpyrrolidine-2-carboxamido)acetamido)propanoate (G8-2):

67% yield; R_f = 0.4 (ethyl acetate/petroleum ether = 1:1); mp 132–134 °C; $[\alpha]_D^{20}$ –120.7 (c 0.01, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 1.60–1.66 (m, 2H), 1.77–1.88 (m, 1H), 2.14–2.20 (m, 1H), 2.43 (s, 3H), 3.07 (dd, J = 13.88 Hz, J = 5.76 Hz, 1H), 3.15 (dd, J = 13.92 Hz, J = 5.92 Hz, 1H), 3.18–3.23 (m, 1H), 3.57–3.62 (m, 1H), 4.08–4.11 (m, 1H), 4.85–4.89 (m, 1H), 5.04 (d, J = 12.08 Hz, 1H), 5.09 (d, J = 12.04 Hz, 1H), 5.38 (d, J = 7.04 Hz, 1H), 6.17 (d, J = 7.52 Hz, 1H), 6.98–7.00 (m, 2H), 7.21–7.23 (m, 5H), 7.30–7.38 (m, 10H), 7.71 (d, J = 8.20 Hz, 2H), 7.77 (d, J = 6.96 Hz, 1H); C{H} NMR (100 MHz, CDCl₃) δ 21.6 {CH₃}, 24.4 {CH₂}, 30.3 {CH₂}, 37.7 {CH₂}, 49.9 {CH₂}, 53.5 {CH}, 57.7 {CH}, 62.4 {CH}, 67.3 {CH₂}, 127.1 {CH}, 127.3 {2C, CH}, 127.9 {2C, CH}, 128.5 {2C, CH}, 128.6 {6C, CH}, 129.1 {2C, CH}, 129.4 {2C, CH}, 129.9 {2C, CH}, 133.0 {C}, 134.9 {C}, 135.5 {C}, 136.4 {C}, 144.3 {C}, 169.2 {C}, 170.7 {C}, 171.0 {C}; IR (KBr) 3329, 1743, 1656, 1514, 1345, 1154, 702 cm; HRMS (ESITOF) m/z calcd for C₃₆H₃₈N₃O₆S [M + H] 640.2476, found 640.2497.

(S)-Benzyl 2-((S)-2-((R)-5-Oxopyrrolidine-2-carboxamido)-2-phenylacetamido)-3-phenylpropanoate (G9-1):

50% yield; R_f = 0.2 (methol/petroleum ether = 1:4); mp 209–210 °C; $[\alpha]_D^{20}$ –8.1 (c 0.01, DMSO); ¹H NMR (400 MHz, CDCl₃) δ 2.07–2.16 (m, 1H), 2.23–2.31 (m, 1H), 2.34–2.49 (m, 2H), 3.04 (dd, J = 14.00 Hz, J = 6.00 Hz, 1H), 3.11 (dd, J = 13.92 Hz, J = 5.92 Hz, 1H), 4.12–4.16 (m, 1H), 4.79–4.84 (m, 1H), 4.99 (d, J = 12.12 Hz, 1H), 5.06 (d, J = 12.04 Hz, 1H), 5.44 (d, J = 7.00 Hz, 1H), 6.33 (br, 1H), 6.40 (br, 1H), 6.94–6.96 (m, 2H), 7.19–7.20 (m, 6H), 7.26–7.27 (m, 5H), 7.32–7.34 (m, 3H); C{H} NMR (100 MHz, DMSO-d₆) δ 25.8 {CH₂}, 29.6 {CH₂}, 37.0 {CH₂}, 54.4 {CH}, 55.7 {CH}, 55.8 {CH}, 66.5 {CH₂}, 127.1 {CH}, 127.4 {2C, CH}, 127.9 {CH}, 128.2 {2C, CH}, 128.4 {CH}, 128.6 {2C, CH}, 128.7 {2C, CH}, 128.8 {2C, CH}, 129.6 {2C, CH}, 136.0 {C}, 137.3 {C}, 138.8 {C}, 170.0 {C}, 171.2 {C}, 172.3 {C}, 177.9 {C}; IR (KBr) 3286, 1743, 1717, 1654, 1537, 1241, 697 cm; HRMS (ESI-TOF) m/z calcd for C₂₉H₃₀N₃O₅ [M + H] 500.2180, found 500.2171.

(R)-Benzyl 2-((R)-2-((S)-5-Oxopyrrolidine-2-carboxamido)-2-phenylacetamido)-3-phenylpropanoate (G9-2):

52% yield; R_f = 0.2 (methol/petroleum ether = 1:4); mp 209–210 °C; $[\alpha]_D^{20}$ +37.8 (c 0.01, DMSO); ¹H NMR (400 MHz, CDCl₃) δ 2.11–2.17 (m, 1H), 2.27–2.32 (m, 1H), 2.36–2.48 (m, 2H), 3.04 (dd, J = 13.88 Hz, J = 5.92 Hz, 1H), 3.12 (dd, J = 13.90 Hz, J = 5.90 Hz, 1H),

4.12–4.15 (m, 1H), 4.79–4.84 (m, 1H), 5.01 (d, J = 12.08 Hz, 1H), 5.07 (d, J = 12.12 Hz, 1H), 5.41 (d, J = 7.00 Hz, 1H), 6.19 (br, 1H), 6.23 (d, J = 7.60 Hz, 1H), 6.94–6.97 (m, 2H), 7.20–7.21 (m, 6H), 7.26–7.30 (m, 5H), 7.33–7.35 (m, 3H); ^1H NMR (100 MHz, CDCl_3) δ 25.7 {CH₂}, 29.3 {CH₂}, 37.6 {CH₂}, 53.7 {CH}, 56.8 {CH}, 57.1 {CH}, 67.3 {CH₂}, 127.1 {CH}, 127.4 {2C, CH}, 128.5 {2C, CH}, 128.6 {6C, CH}, 129.1 {2C, CH}, 129.3 {2C, CH}, 134.9 {C}, 135.4 {C}, 136.7 {C}, 169.3 {C}, 170.6 {C}, 171.7 {C}, 178.9 {C}; IR (KBr) 3283, 1747, 1723, 1645, 1544, 1239, 701 cm; HRMS (ESITOF) m/z calcd for $\text{C}_{29}\text{H}_{30}\text{N}_3\text{O}_5$ [M + H] 500.2180, found 500.2183.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Structures of TAMCSAs **1a–1d**.

Figure 2.

X-ray crystal structures of TAMCSAs **1a**· CHCl_3 (a) and **1b** (b) drawn at 30% probability thermal ellipsoids.

Figure 3.
NOESY spectra of TAMCSAs **1c** and **1d**.

Figure 4.
 ^1H - ^1H COSY (a) and HSQC (b) spectra of tripeptide derivative **G1-2** in CDCl_3 .

Figure 5.

Determination of enantiomeric excesses of **G1**, $ee(\%) = \{(\mathbf{G1-2} - \mathbf{G1-1})/(\mathbf{G1-2} + \mathbf{G1-1})\} \times 100\%$. Overlaid ¹H NMR spectra of the TsNH proton of **G1-1** and **G1-2** in the presence of an equal amount of TAMCSAs **1a** (a), **1b** (b), **1c** (c), and **1d** (d), respectively. [**G1**] = 5 mM. Linear correlation between the theoretical (X) and observed (Y) ee (%) values of **G1** with TAMCSAs **1a** (a), **1b** (b), **1c** (c), and **1d** (d), respectively.

Figure 6. Proposed bonding models for the hydrogen bonding interactions between TAMCSA **1a** and the enantiomers **G1-1** (a) and **G1-2** (b).

Figure 7.

Job plots for complexes of (±)-**G1** and TAMCSA **1a**. δ stands for chemical shift change of the *NH* proton (Ts*NH* group) of **G1-1** and **G1-2** in the presence of TAMCSA **1a**. X stands for the molar fraction of (±)-**G1**, ($X = [(\pm)\text{-G1}]/[(\pm)\text{-G1} + \text{TAMCSA } 1a]$).

Figure 8.

ESI mass spectrum of (a) [(±)-**G1** + H]: calcd for C₃₄H₃₆N₃O₆S [M + H] 614.2319, found 614.2322; (b) [**1a** + H] calcd for C₃₈H₄₃N₄O₄ [M + H] 619.3278, found 619.3275; (c) [(±)-**G1** + **1a** + H] calcd for C₇₂H₇₈N₇O₁₀S [M + H] 1232.5525, found 1232.5558.

Scheme 1.
Synthesis of TAMCSAs 1a–1d

Scheme 2.
Synthesis of G1-1-G4-2

Chart 1.
Structures of Enantiomers of Tripeptide Derivatives G5–1–G9–2

Table 1.

Nonequivalent Chemical Shifts (δ , ppm) of the Representative Protons of ($\pm$)-G1–G4 and Their Partial ^1H NMR Spectra in the Presence of TAMCSAs 1a–1d in CDCl_3 at Room Temperature, Respectively (400 MHz)^a

	TsNH(Ala, ($\pm$)-G1)/1a	TsNH(Ala, ($\pm$)-G1)/1b	TsNH(Ala, ($\pm$)-G1)/1c	TsNH(Ala, ($\pm$)-G1)/1d
α -H(Phe, ($\pm$)-G2)/1a		TsNH(Ala, ($\pm$)-G2)/1b	TsNH(Ala, ($\pm$)-G2)/1c	CONH(Phe, ($\pm$)-G2)/1d
CONH(Phe, ($\pm$)-G3)/1a		TsNH(Ala, ($\pm$)-G3)/1b	TsNH(Ala, ($\pm$)-G3)/1c	ArH(($\pm$)-G3)/1d
TsNH(Ala, ($\pm$)-G4)/1a		TsNH(Ala, ($\pm$)-G4)/1b	TsNH(Ala, ($\pm$)-G4)/1c	TsNH(Ala, ($\pm$)-G4)/1d

^a[Guest] = 5×10^{-3} M, H/G = 1:1.

Table 2.

Nonequivalent Chemical Shifts (δ , ppm) of Other Split Protons of ($\pm$)-G1–G4 in the Presence of TAMCSAs 1a–1d in CDCl₃ at Room Temperature, Respectively (400 MHz)^a

	proton	δ	proton	δ
1a/(±)-G1	CH ₃ (Ala)	0.007	ArH	0.020
	CH ₃ (Ts)	0.017	1c/(±)-G3	CONH (Phe)
	CONH (Phe)	0.018	ArH	0.020
1b/(±)-G1	ArH	0.015	1d/(±)-G3	CONH (Phe)
	CH ₃ (Ts)	0.017	1a/(±)-G4	CH ₃ (Ala)
	α -H (Phg)	0.014	CH ₃ (Ts)	0.017
	CONH (Phe)	0.014	CONH (Phe)	0.091
	ArH	0.018	ArH	0.019
1c/(±)-G1	CH ₃ (Ts)	0.020	1b/(±)-G4	CH ₃ (Ala)
	α -H (Phg)	0.011	CH ₃ (Ts)	0.015
	CONH (Phe)	0.022	α -H (Phg)	0.173
	ArH	0.020	CONH (Phe)	0.276
	CH ₃ (Ts)	0.016	ArH	0.021
1a/(±)-G2	ArH	0.014	1c/(±)-G4	CH ₃ (Ala)
	CH ₃ (Ts)	0.011	CH ₃ (Ts)	0.016
	ArH	0.029	α -H (Phg)	0.180
1b/(±)-G2	ArH	0.022	CONH (Phe)	0.187
1c/(±)-G2	ArH	0.023	ArH	0.022
1d/(±)-G2	TsNH (Ala)	0.042	1d/(±)-G4	CH ₃ (Ala)
	ArH	0.022	CH ₃ (Ts)	0.015
	ArH	0.020	CONH (Phe)	0.083
1b/(±)-G3	CONH (Phe)	0.048	ArH	0.016

^a[Guest] = 5×10^{-3} M, H/G = 1:1.

Nonequivalent Chemical Shifts (δ , ppm) of the Representative Protons of ($\pm$)-G5–G9 and Their Partial ^1H NMR Spectra in the Presence of TAMCSAs 1a–1d in CDCl_3 at Room Temperature, Respectively (400 MHz)^a

TsNH(Val, ($\pm$)-G5)/1a	TsNH(Val, ($\pm$)-G5)/1b	TsNH(Val, ($\pm$)-G5)/1c	TsNH(Val, ($\pm$)-G5)/1d
PhCH ₂ O(($\pm$)-G6)/1a ^b	CONH(Ph, ($\pm$)-G6)/1b ^b	CONH(Ph, ($\pm$)-G6)/1c ^b	PhCH ₂ O(($\pm$)-G6)/1d ^b
TsNH(Ala, ($\pm$)-G7)/1a	TsNH(Ala, ($\pm$)-G7)/1b	TsNH(Ala, ($\pm$)-G7)/1c	TsNH(Ala, ($\pm$)-G7)/1d
α -H(Phg, ($\pm$)-G8)/1a	α -H(Phg, ($\pm$)-G8)/1b	α -H(Phg, ($\pm$)-G8)/1c	α -H(Phg, ($\pm$)-G8)/1d
α -H(Phg, ($\pm$)-G9)/1a ^b	α -H(Phg, ($\pm$)-G9)/1b ^b	α -H(Phg, ($\pm$)-G9)/1c ^b	α -H(Phg, ($\pm$)-G9)/1d ^b

^a[Guest] = 5×10^{-3} M, H/G = 1:1.

^b[Guest] = 3×10^{-3} M, H/G = 1:1.

Table 4

Nonequivalent Chemical Shifts (δ , ppm) of Other Split Protons of ($\pm$)-G5–G9 in the Presence of TAMCSAs 1a–1d in CDCl₃ at Room Temperature, Respectively (400 MHz)^a

	proton	δ	proton	δ
1a/($\pm$)-G5	<i>α</i> -H (Phg)	0.017	<i>α</i> -H (Ala)	0.089
	CONH (Phe)	0.018	CONH (Phe)	0.044
1b/($\pm$)-G5	CH ₃ (Ts)	0.007	CONH (Val)	0.021
	<i>α</i> -H (Phg)	0.030	ArH	0.050
1c/($\pm$)-G7	CONH (Phe)	0.035	CH ₃ (Ala)	0.033
	ArH	0.007	CH ₃ (Ts)	0.032
	CH ₃ (Ts)	0.007	PhCH ₂ (Phe)	0.014
	<i>α</i> -H (Phg)	0.030	<i>α</i> -H (Ala)	0.090
1d/($\pm$)-G9	CONH (Phe)	0.033	CONH (Phe)	0.040
	ArH	0.007	CONH (Val)	0.062
	<i>α</i> -H (Phg)	0.016	ArH	0.049
	CONH (Phe)	0.019	CH ₃ (Ala)	0.018
1a/($\pm$)-G6	CH ₃ (Ts)	0.007	CH ₃ (Ts)	0.022
	TsNH (Glu)	0.177	CONH (Val)	0.018
1b/($\pm$)-G6	CH ₃ (Ts)	0.004	ArH	0.033
	TsNH (Glu)	0.016	CONH (Phe)	0.047
1c/($\pm$)-G8	CH ₃ (Ts)	0.005	CONH (Phe)	0.036
	TsNH (Glu)	0.014	CONH (Phe)	0.024
1d/($\pm$)-G9	CH ₃ (Ts)	0.005	PhCH ₂ O	0.020
	CONH (Glu)	0.033		0.016
1a/($\pm$)-G7	CH ₃ (Ala)	0.016	PhCH ₂ O	0.013
	CH ₃ (Ts)	0.027		0.008
1b/($\pm$)-G7	ArH	0.040	PhCH ₂ O	0.010
	CH ₃ (Ala)	0.033		0.014
1d/($\pm$)-G9	CH ₃ (Ts)	0.032	PhCH ₂ O	0.017

$[\text{Guest}] = 5 \times 10^{-3} \text{ M}$, H/G = 1:1.
 $[\text{Guest}] = 3 \times 10 \text{ M}$, H/G = 1:1.

δ	0.020
proton	
δ	0.014
proton	PhCH ₂ (Phe)

Table 5.

Calculated and Observed δ and δ (ppm) Values for the CH₃ (Ts) of G1–1 and G1–2 in the Presence of TAMCSA 1a

	δ^{G1-1}	δ^{G1-2}	$\delta^{G1-1/G1-2}$
calcd values	2.726	2.701	0.025
obsd values	2.395	2.379	0.016