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Michael addition reactions of chiral glycine Schiff base Ni (II)-complex with 1-(1-phenylsulfonyl)benzene

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Abstract

This work describes the first example of Michael addition reactions of chiral Ni (II)-complex of glycine Schiff base with 1-(1-(phenylsulfonyl)vinylsulfonyl) benzene. This approach was developed for asymmetric synthesis of 2-amino-4,4-bis (phenylsulfonyl)butanoic acid possessing various design-useful properties such as substantial steric bulk and lipophilicity. These properties are expected to provide for an improved binding to the apolar site of the various endogenous receptors. Fmoc derivative of the target amino acids ready for peptide coupling is described.

KEYWORDS

1(1-phenylsulfonyl)benzene, Michael additions, Ni (II)-complex of Schiff base, recyclable chiral auxiliary, tailor-made amino acids

1 | INTRODUCTION

Tailor-made amino acids (AAs), formerly referred to as "non-natural," "unusual," etc,[1] are essential components of modern medicinal chemistry and are becoming increasingly prominent in new drugs. In fact, over 25% of newly developed pharmaceuticals and medicinal formulations are containing at least one residue of tailor-made AA.[2] Furthermore, due to the increasing acceptance of peptides and modified peptides as drugs,[3] this trend is posed to grow, rendering asymmetric synthesis of tailor-made AAs an exciting area of research.[4] The stimulating potential of tailor-made AAs in modern drug design is associated with the rational control over key

biologically important properties such as, steric bulk, conformational constrains, lipophilicity, acidity/basicity, and reactivity towards biocatalytic transformations. For example, substitution of phenylalanine **1** in endogenous peptidic substrates, with a significantly bulkier and lipophilic beta-phenyl-phenylalanine (diphenyl-alanine) Dpa **2**, usually leads to improved binding to the apolar (lipophilic) site of the targeted receptors. Relative synthetic availability of Dpa **2** in both enantiomeric forms[5] allowed for wide-ranging studies of Dpa-modified peptidic drug-candidates showing encouraging biological profiles, in particular, in the areas of thrombin inhibitors,[6] angiotensin-converting enzyme (ACE) inhibitors,[7] HIV-protease inhibitors,[8] pain-related norepinephrine transporter inhibitors,[9] μ and δ opioid receptors,[10] and other types of peptidic substrate-receptor interactions.[11] Besides medicinal potential of this type of sterically bulky, lipophilic tailor-made AAs, there are numerous stimulating data on application of Dpa **2** and its analogs in the fields of bio-nano-materials, self-assembly, and drug delivery.[12]

However, the medicinal potential of tailor-made sterically bulky, lipophilic AAs is only in the initial stages of its exploration. Numerous advanced in silico studies have generated structural profiles of hundreds of AAs with rationally designed control over size, van der Waals, and electrostatic interactions influencing the peptide ligand binding affinity with endogenous receptors.[13] As part of our interest in various types of tailor-made AAs, including sterically constrained,[14] phosphorus-[15] and fluorine-containing derivatives,[16] we recently started a series of studies that focused on the design of new synthetic tripeptide-based inhibitors of ACE and thromboplastin; we became interested in 2-amino-4,4-bis (phenylsulfonyl) butanoic acid **3** possessing various design-useful properties. In this work, we report a convenient asymmetric synthesis of this new type of tailor-made AA in a form of its *N*-Fmoc derivative to be used for peptide synthesis (Figure 1).

Over the past decade, asymmetric synthesis of tailor-made AAs via Ni (II)-complexes of glycine Schiff base (Scheme 1) has emerged as a dominant methodology[17] for practical access to various types of enantiomerically pure α- and β-AAs.[18] In particular, Michael addition reactions of glycine Ni (II)-complex with various acceptors were extensively studied.[17d, 19] However, with exception of handful examples of additions with nitroalkenes,[20] vinylphosphonates,[21] and vinylsulfonic acid derivatives,[22] the previously reported Michael reactions represent 1,4-additions investigated using derivatives of α,β-unsaturated carboxylic acids.[23] Consequently, besides the practical need in tailor-made AA **3** (Figure 1), the addition of glycine Schiff base Ni (II)-complex (*S*)-**4** with 1-(1-(phenylsulfonyl)vinylsulfonyl)benzene **5** was of certain methodological interest as an example of new type of Michael addition reaction (Scheme 1).

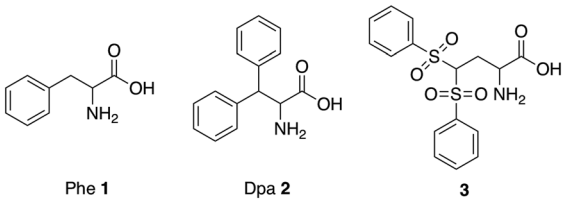
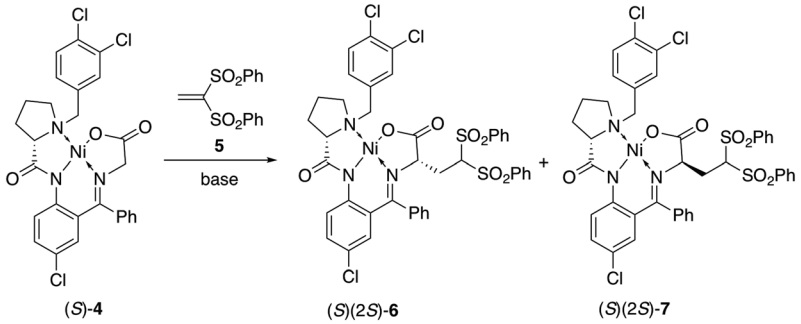


FIGURE 1 Phenylalanine **1**, and its bulkier, lipophilic and sterically constrained analogs, (diphenylmethy)alanine **2** and 2-amino-4,4-bis (phenylsulfonyl)butanoic acid **3**

2 | MATERIALS AND METHODS

2.1 | General information

All the commercial reagents including solvents were used directly without further purification. All the experiments were monitored by thin-layer chromatography (TLC) with ultraviolet (UV) light. The TLC employed 0.25-mm silica gel coated on glass plates. Column chromatography was performed with silica gel 60 (300-400 mesh). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 600-MHz spectrometer. Mass spectra (MS) were measured on Shimadzu LCMS-2020 with an electrospray ionization (ESI) probe operating in positive mode. Values



SCHEME 1 Michael addition reaction of glycine Schiff base Ni (II)-complex (*S*)-**4** with 1-(1-(phenylsulfonyl)vinylsulfonyl) benzene **5**

of optical rotation were measured on Automatic Polarimeter SGW-531 (see supporting information).

2.2 | Experiment procedure

Michael addition reaction of (*S*)-**4** with **5**: Into a 5-mL vial were taken (*S*)-**4** (0.05 mmol), **5** (1.1 equiv), base (4.0 equiv), and solvent (0.5 mL). The mixture was stirred at room temperature and monitored by TLC (dichloromethane:acetone = 3:1). After that, 10% AcOH aq. (2 mL) was added and stirred for another 1 hour. The precipitate was collected and washed with H_2O (5 mL × 3), then purified by column chromatography using dichloromethane/acetone (3:1, v/v) as eluent to afford the desired product.

Disassembly of (*S*)(2*S*)-**6**: Into a 50-mL flask were taken (*S*)(*2S*)-**6** (0.08 mmol), MeOH (3 mL), 6 N HCl aq. (1 mL). The mixture was stirred at 50°C for 2 hours. After removing the solvent MeOH, the mixture was extracted with dichloromethane (10 mL × 3). Then the aqueous layer was concentrated and MeCN (2 mL), EDTA (1.0 equiv) were added. After stirring at room temperature for 3 hours, 10 N NaOH aq. (pH = 8), Fmoc-OSu (1.0 equiv), Na_2CO_3 (1.3 equiv) were added and stirred for another 20 hours. After removing the solvent MeCN, the mixture was extracted with dichloromethane (10 mL × 3). The organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Toluene (2 mL) was added and stirred at room temperature overnight. The precipitate was then collected and dried in vacuo.

Compound (*S*)(2*S*)-**6**: red solid, mp 190-195°C, $[\alpha]_D^{25}$ = +2185.4 (*c* = 0.22 in MeOH). ^{1}H NMR (600 MHz, $CDCl_3$, δ): 8.89 (d, *J* = 2.4 Hz, 1H), 8.12 (d, *J* = 9.0 Hz, 1H), 7.84 (dd, *J* = 9.0, 1.8 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 2H), 7.63-7.55 (m, 6H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.44-7.38 (m, 3H), 7.34 (t, *J* = 7.8 Hz, 3H), 7.17 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.03-6.99 (m, 1H), 6.63 (d, *J* = 2.4 Hz, 1H), 5.62 (dd, *J* = 8.4, 1.8 Hz, 1H), 4.38 (q, *J* = 6.0 Hz, 1H), 4.30 (d, *J* = 12.6 Hz, 1H), 3.87-3.76 (m, 1H), 3.74-3.68 (m, 1H), 3.62-3.57 (m, 1H), 3.41 (q, *J* = 5.4 Hz, 1H), 3.25 (d, *J* = 12 Hz, 1H), 2.79-2.72 (m, 1H), 2.66-2.53 (m, 2H), 2.30-2.22 (m, 1H), 2.13-2.06 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$, δ): 206.96, 180.16, 177.59, 171.80, 140.79, 137.71, 137.51, 134.89, 134.19, 134.11, 133.60, 133.42, 133.58, 132.76, 132.42, 131.99, 131.09, 130.64, 130.00, 129.86, 129.59, 129.15, 129.02, 128.98, 128.83, 127.39, 127.16, 127.07, 125.87, 124.33, 71.50, 67.91, 62.99, 58.81, 30.98, 28.45, 23.92. MS (ESI, *m*/*z*): $[M + H]^+$ calcd for $C_{41}H_{34}Cl_3N_3NaNiO_7S_2^+$, 930.0; found 930.6.

Compound (*S*)(2*R*)-**7**: red solid, mp 135-140°C, $[\alpha]_D^{25}$ = −1297.9 (*c* = 0.05 in MeOH). ^{1}H NMR (600 MHz, $CDCl_3$, δ): 8.55 (d, *J* = 10.2 Hz, 1H), 8.23 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.88 (d, *J* = 2.4 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.72-7.66 (m, 2H), 7.65-7.55 (m, 5H), 7.52-7.44 (m, 2H), 7.36-7.29 (m, 4H), 7.25 (dd, *J* = 9.6, 1.8 Hz, 2H), 7.17 (d, *J* = 7.2 Hz, 1H), 6.76 (d, *J* = 3.0 Hz, 1H), 5.71 (dd, *J* = 9.0, 1.8 Hz, 1H), 4.57 (d, *J* = 13.2 Hz,1H), 4.50 (q, *J* = 6.0 Hz, 1H), 4.18-4.13 (m, 1H), 3.51 (q, *J* = 4.8 Hz,1H), 3.44 (d, *J* = 13.2 Hz, 1H), 3.33-3.26 (m, 1H), 2.75-2.66 (m, 2H), 2.65-2.59 (m, 1H), 2.30-2.14 (m, 2H), 2.08-2.01 (m, 1H), 2.01-1.94 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$, δ): 182.07, 178.39, 173.17, 141.63, 138.21, 137.29, 134.10, 134.00, 133.34, 133.21, 132.91, 132.76, 132.72, 131.82, 131.52, 130.50, 129.78, 129.73, 129.13, 128.98, 128.83, 128.73, 128.01, 126.57, 126.40, 125.68, 125.01, 99.99, 68.72, 67.80, 60.64, 58.71, 30.61, 29.70, 29.33, 27.92, 23.43. MS (ESI, *m*/*z*): $[M + H]^+$ calcd for $C_{41}H_{34}Cl_3N_3NaNiO_7S_2^+$, 930.0; found 930.1.

Compound (*S*)-**8**: white solid, mp 120-125°C, $[\alpha]_D^{25}$ = −14.0 (*c* = 0.09 in MeOH). ^{1}H NMR (600 MHz, $CDCl_3$, δ): 8.03 (d, *J* = 6.0 Hz, 2H), 7.89 (d, *J* = 7.2 Hz, 2H), 7.79 (d, *J* = 7.2 Hz, 2H), 7.68 (d, *J* = 6.6 Hz, 1H), 7.65-7.53 (m, 5H), 7.50-7.38 (m, 4H), 7.31 (dd, *J* = 16.2, 6.6 Hz, 2H), 5.68 (d, *J* = 5.4 Hz, 1H), 4.97 (brs, 1H), 4.68 (brs, 1H), 4.47-4.29 (m, 3H), 4.21 (brs, 1H), 2.87 (brs, 1H), 2.59 (t, *J* = 10.2 Hz,1H). ^{13}C NMR (150 MHz, $CDCl_3$, δ): 173.68, 156.69, 143.70, 143.44, 141.28, 141.25, 137.88, 137.54, 136.99, 134.82, 129.71, 129.68, 129.27, 129.22, 129.06, 128.25, 127.90, 127.86, 127.23, 127.19, 125.32, 125.21, 125.11, 120.06, 120.03, 79.21, 67.67, 52.37, 46.93, 28.69, 21.48. MS (ESI, *m*/*z*): $[M + H]^+$ calculated for $C_{31}H_{28}NO_8S_2^+$, 606.1; found 606.7.

3 | RESULTS AND DISCUSSION

As presented in Scheme 1, we decided to use glycine Schiff base complex (*S*)-**4** derived from the most advanced strategically tri-chlorinated[24] ligand available on over kilogram scale[25] and previously used for large-scale synthesis of several fluorinated tailor-made AAs.[26] Our initial attempts to conduct the Michael addition reaction in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave rather disappointing results, most likely related to very high electrophilicity and therefore exceptional reactivity of vinyl-disulfonyl Michael acceptor **5**.[27] Using medium-strength inorganic bases, such as sodium and potassium carbonates, we were able to control the reactivity and formation of the addition products **6** and **7**. As presented in Table 1 (entries 1-4), under similar conditions, the use of Na_2CO_3 (entries 1, 2) resulted in slower reactions and better stereochemical outcome as compared with the reactions catalyzed by a more basic K_2CO_3 (entries 3, 4). These results suggested that application of medium-strength organic bases might be a viable

TABLE 1 Optimization of the reaction conditions for Michael addition reaction of glycine Schiff base (*S*)-**4** with 1-(1-(phenyl sulfonyl) vinylsulfonyl)benzene **5**[a]

Entry	Solvent	Base	Temperature (°C)	Time (h)	Yield (%)[c]	Dr[d]
1	MeCN	Na_2CO_3	50	13	81	95:5
2	THF	Na_2CO_3	50	13	24	96:4
3	MeCN	K_2CO_3	50	13	86	81:19
4	*i*-PrOH	K_2CO_3	50	13	59	81:19
5	MeCN	TEA	rt	1	51	87:13
6	MeCN	TEA	rt	13	75	89:11
7	MeCN	TEA	50	1.5	68	89:11
8	MeCN	TEA	50	4	75	90:10
9	MeCN	TEA	50	13	79	96:4
10[b]	MeCN	TEA	50	13	86	93:7
11[b]	MeCN	TEA	50	13	99	93:7
12	MeCN	TEA	50	24	59	95:5
13	THF	TEA	50	7	44	84:16
14	MeCN	DIPEA	rt	12	70	96:4
15	MeCN	DIPEA	50	2	66	85:15
16	MeCN	DIPEA	50	4	73	88:12
17	THF	DIPEA	50	15	46	84:16

Abbreviations: DIPEA, di-(isopropyl)ethylamine; rt, room temperature; TEA, triethylamine.

[a]Reaction conditions: Gly-Ni (II) complex **4** (30 mg), 1,1-bis (phenylsulfonyl)ethylene **5** (17 mg, 1.1 equiv), solvent 0.5 mL, base (4.0 equiv).

[b]**5** was used 1.5 equiv. for entry 10 and 2.0 equiv. for entry 11. The reaction progress was monitored by TLC (CH_2Cl_2:acetone = 3:1); upon the reaction completion, 10% AcOH (aq.) (2 mL) was added and stirred at r.t. for 1 h, precipitate was collected and washed with H_2O; products **6**, **7** were purified by column chromatography, CH_2Cl_2 (or $CHCl_3$) /acetone = 3:1.

[c]Isolated yield.

[d]Determined by ^1H NMR.

option. Indeed, using triethylamine (TEA) as a base and acetonitrile as a solvent, we observed the desired addition reaction taking place even at an ambient temperature (entries 5, 6). Further optimization of the equivalent of **5**, reaction temperature, time, and solvent (entries 7-13) revealed that synthetically acceptable levels of diastereoselectivity, about 95/5, can be achieved in acetonitrile solvent at elevated temperature at 50°C. Especially, use of 2.0 equivalent of **5** gave the corresponding products in 99% yield. We posited that the kinetically controlled diastereoselectivity may be influenced by the base-catalyst steric bulk and conducted a series of experiments using di-(isopropyl)ethylamine (DIPEA). However, the stereochemical outcome in these reactions (entries 14-17) was quite similar to that obtained in the TEA-catalyzed reactions. It should be noted that while the Michael addition reactions are catalytic in base, the low reaction rates required relatively large amounts of the base. Considering the results obtained, we selected the conditions presented in entry 11 as optimal for practical synthesis of the target AA (Table 1).

Diastereomeric products **6** and **7** were isolated in pure form by column chromatography and fully characterized. The absolute configuration of the major diastereomer **6** was determined to be (*S*)(2*S*) by single crystal X-ray analysis (Figure 2, view A). Consequently, the stereochemistry of minor diastereomer **7** was deduced to be (*S*)(2*R*). It is interesting to note that, as shown in Figure 2 view B, one can clearly see the parallel displaced type of aromatic interactions between *o*-amino-benzophenone and Pro *N*-benzyl rings. It was demonstrated[24] that this type of aromatic interactions is responsible for the preference of α-(*S*) absolute configuration of the newly created stereogenic center, in the case of (*S*)-**4** and correspondingly, α-(*R*) when (*R*)-**4** is used (Figure 2).

Major product (*S*)(2*S*)-**6** was conveniently purified by column chromatography to diastereomerically pure state taking advantage of its bright-red color simplifying the collection of the desired fraction. Disassembly of Ni (II)-complex (*S*)(2*S*)-**6** was performed under standard acidic conditions as presented in Scheme 2. Upon completion of the disassembly procedure, as indicated by disappearance of the bright-red color, the reaction mixture was cooled to ambient temperature resulting in precipitation of

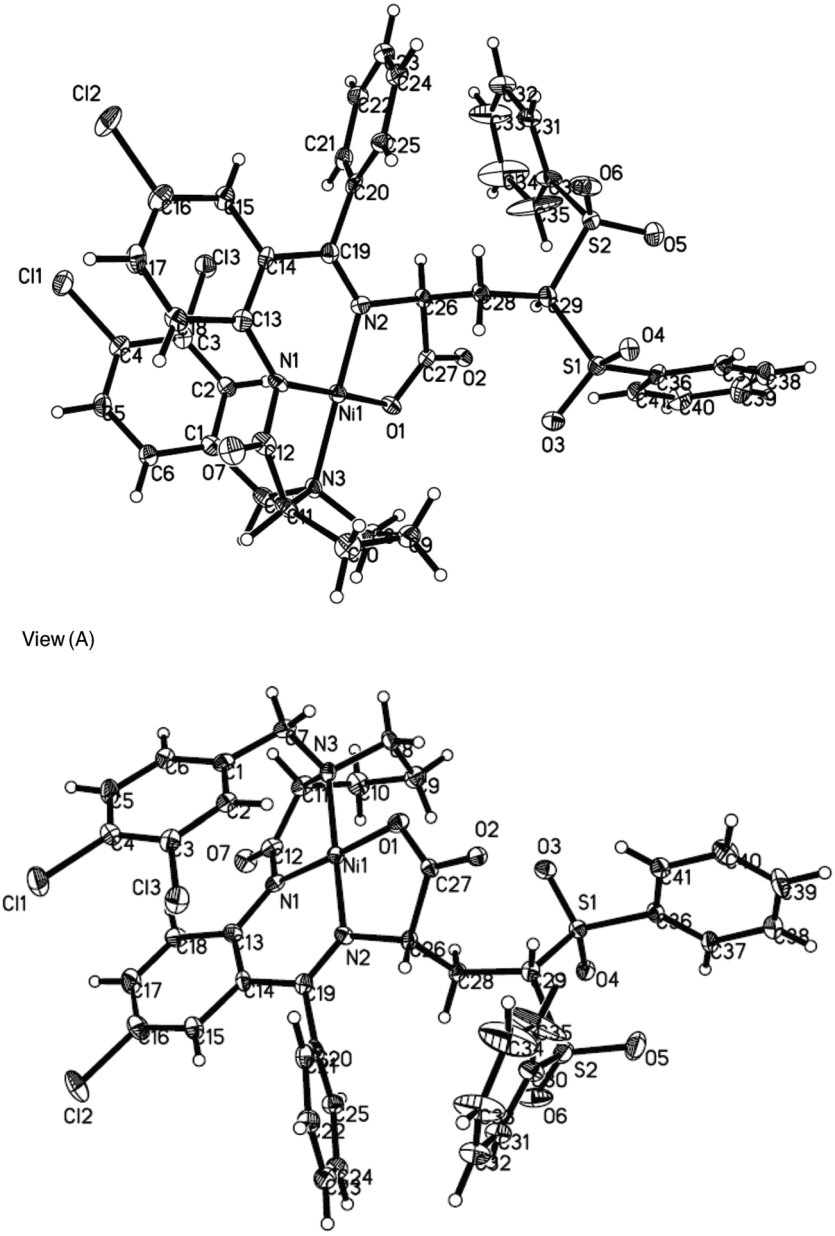
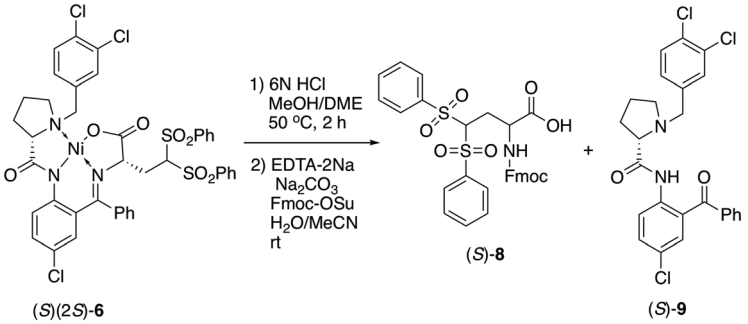


FIGURE 2 Crystal structure of major diastereomer (*S*)(2*S*)-**6**: absolute configuration of the α-stereogenic center (view A); the parallel displaced type of aromatic interactions between *o*-amino-benzophenone and Pro *N*-benzyl rings (view B)

hydrochloric salt of ligand (*S*)-**9**, which was collected by simple filtration. It should be noted that chiral tridentate ligand (*S*)-**9** was recycled and reused for preparation of stating Ni (II)-complex of glycine Schiff base (Scheme 1).[25b] Using recently established procedure,[26] the intermediate AA was transformed in situ to target Fmoc derivative (*S*)-**8**, which was isolated via extraction by organic solvent (CH_2Cl_2) (Scheme 2).



SCHEME 2 Disassembly of major diastereomer (*S*)(2*S*)-**6**; preparation of target Fmoc-derivative of AA (*S*)-**8** and recycling of chiral auxiliary (*S*)-**9**

4 | CONCLUSION

In conclusion, in this work, we successfully performed the first example of Michael addition reactions between chiral Ni (II)-complex of glycine Schiff base with 1-(1-(phenylsulfonyl)vinylsulfonyl)benzene. The reactions were found to proceed under relatively mild conditions in the presence of medium-strength organic bases, such as TEA and DIPEA. The diastereoselectivity of the reactions favors the corresponding (2*S*) product (~95/5), which can be purified to diastereomerically pure state via routine column chromatography on silica gel. Acidic disassembly of the major diastereomer and in situ protection of the intermediate AA afforded the target Fmoc-derivative of 2-amino-4,4-bis (phenylsulfonyl)butanoic acid possessing various design-useful properties to be used in the preparation of new synthetic tripeptide-based enzyme inhibitors.

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