Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: Org. Biomol. Chem., 2014, 12, 6507

Efficient asymmetric synthesis of *N*-protected-β-aryloxyamino acids *via* regioselective ring opening of serine sulfamidate carboxylic acid†

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Received 21st May 2014,
Accepted 19th June 2014

DOI: 10.1039/c4ob01047g

www.rsc.org/obc

First regioselective ring opening of serine derived cyclic sulfamidate by hard nucleophiles like ArONa is developed, where β-elimination of serine sulfamidate ester by stronger nucleophiles is overcome by reversal of the electronic effect of the carboxylate anion. This method provides easy and direct access to a variety of *N*-Boc- and *N*-PMB protected β-aryloxy-α-amino acids with complete retention of enantiopurity in moderate to high yields.

Introduction

β-Aryloxy-α-amino acids are important unnatural amino acids present in and precursor to many bioactive natural products[1,2] and pharmaceuticals.[3] Serine is commonly used as a chiral substrate for the synthesis of β-aryloxyamino acids and their derivatives. The nucleophilic substitution reaction of fluoronitroarenes with serine and its dipeptide has efficiently been utilized for the synthesis of cyclopeptide alkaloids with a β-aryloxyamino acid unit, where a number of additional steps are needed to remove the surplus nitro-group.[2] The Mitsunobu reaction of ArOH with *N*-protected serine ester provides low to moderate yields of β-aryloxy amino acid esters and it was found that N-protection is crucial to get the desired Mitsunobu products.[4] Regio- and stereoselective ring opening of aziridine with ArOH to obtain β-aryloxyamino acids has also been reported.[5]

Development of a general and direct method for the synthesis of unnatural amino acids from an easily accessible chiral precursor is highly desirable. Thus an alternative and efficient method could be regioselective ring opening of cyclic sulfamidates of serine. Though sulfamidates are synthetic equivalents to aziridines, the former is more advantageous over the latter in terms of reactivity and selectivity.[6] A wide variety of nucleophiles are used for the regioselective opening of the sulfamidate of serine.[6–11] Wei and Lubell studied the regioselective ring opening of serine derived cyclic sulfamidate ester with a variety of nucleophiles, where β-elimination and partial to complete loss of enantiopurity were the major problems.[8] Lanthionines were efficiently synthesized by Cobb and Vederas *via* regioselective ring opening of serine sulfamidate ester with *N*-protected cysteine ester.[9] Cohen and Halcomb reported the elegant synthesis of *S*-linked glycosyl amino acids from the serine derived cyclic sulfamidates with 1-thio-sugar.[10] Recently Varma *et al.* described the synthesis of a dithiocarbamate side chain containing unnatural α-amino acids by a one-pot reaction of *in situ* generated dithiocarbamate anions with serine derived sulfamidate ester.[11] Similarly regioselective ring opening of serine derived sulfamidate with ArOH may provide the aryloxyamino acids. However, ring opening of serine derived sulfamidates with oxy-nucleophiles like phenols has not been explored, may be due to the tendency for β-elimination. We have overcome the problem and thus describe here efficient and direct synthesis of *N*-protected-β-aryloxy-α-amino acids from the cyclic sulfamidate of serine with a free carboxylic acid group.

Results and discussion

A potential limitation of the serine derived sulfamidate **1** is the propensity to undergo elimination, affording compound **2′** (Scheme 1). It is almost exclusive in the case of strong nucleophiles. Thus sulfamidate **1** could not be utilized for the opening with stronger nucleophiles like oxy-anions. We also

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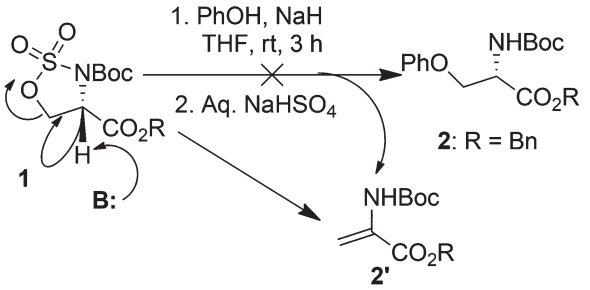
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra and LC-MS for all the compounds **1**, **4**, **6**, **9** and **10** and HPLC chromatograms of compounds **6a–6d**, **6h–6j**, **6l–6m**, **6o**, **10d**, **10j** and **10q**. See DOI: 10.1039/c4ob01047g



Scheme 1 β-Elimination of sulfamidate ester **1** with hard nucleophiles.

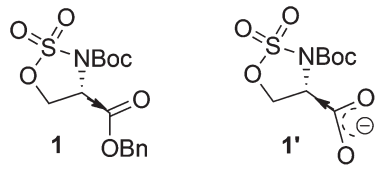
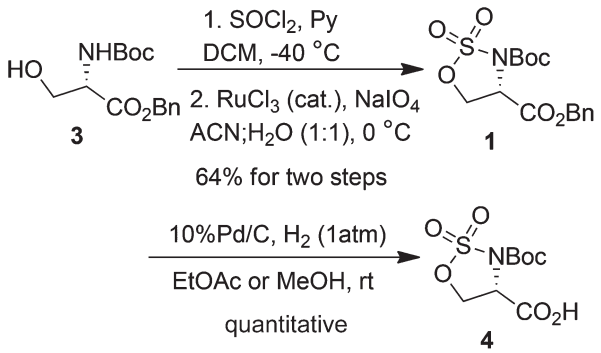


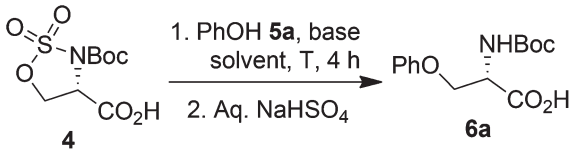
Fig. 1 Electronic effects of sulfamidate ester **1** and carboxylate anion **1′**.



Scheme 2 Synthesis of serine derived cyclic sulfamidate acid **4**.

found that when sulfamidate **1** (R = Bn) was reacted with sodium phenoxide generated from phenol in THF, it exclusively afforded the elimination product **2′** in 85% yield; no trace of compound **2** was detected. The combined electron-withdrawing effects of the ester and the sulfonyl unit attached to N, O might be making the α-methine proton of **1** more acidic. Thus a stronger nucleophile, in turn hard base, acts more like the latter and abstracts the proton resulting in elimination leading to **2′**. It is presumed that the electronic effect of the ester might be reversed if it transforms to a carboxylate ion **1′** (Fig. 1). We, therefore, intended to prepare the *N*-Boc-sulfamidate of L-serine with free carboxylic acid **4**. An EtOAc solution of serine sulfamidate ester **1** upon hydrogenation in the presence of Pd/C under 1 atm pressure gave compound **4**, which was directly used without any purification (Scheme 2). Instead of EtOAc, when the hydrogenation was carried out in MeOH, it showed a cleaner reaction profile as found in ^{1}H NMR spectrum analysis of the crude product. Sulfamidate **1** was prepared from *N*-Boc serine benzyl ester **3** (Scheme 2).[6,10]

Table 1 Screening of solvents, base and temperature for the ring opening of sulfamidate **4** with PhOH **5a**



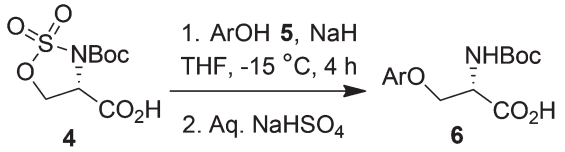
Entry	Base	Solvent	*T* (°C)	Yield[a] (%)	ee[b] (%)
1	NaH	THF	25	<5	ND
2	NaH	THF	0	49	>99
3	NaH	THF	−15	57	>99
4	K_2CO_3	THF	25	NR	—
5	Cs_2CO_3	THF	0	<5	—
6	NaH	Dioxane	25	40	ND
7	K_2CO_3	Dioxane	25	NR	—
8	Cs_2CO_3	Dioxane	25	20	ND

[a] Isolated yield of amino acid **6a** over two steps. [b] ee was determined by chiral HPLC. ND: not determined.

The sulfamidate carboxylic acid **4** was reacted with phenol in the presence of different bases and with variation of solvents as well (Table 1). We are delighted to report that NaH (60% in oil) was found to work well in THF and dioxane at 0 °C and rt, respectively, and provided the desired *N*-Boc-β-phenoxyamino acid **6a** in moderate yields (entries 2 and 6). When the reaction in THF was performed at −15 °C, it afforded an improved yield of compound **6a** (entry 3). The reactions in DMF using three bases gave traces of product **6a** (not shown in Table 1). The optical purity of **6a** was determined by HPLC analysis, which showed complete retention of enantiopurity.

Having set the optimized reaction conditions, we explored the scope of this ring opening reaction with a panel of substituted phenols (Table 2). We are pleased to report that the majority of phenols work very well. In general sterically hindered and electron-deficient less reactive phenols were found to work well at 0 °C. Alkyl substituted phenols containing an ethyl group at the 3- or 4-position provided good yields of β-aryloxyamino acids **6b** and **6c**, respectively, at −15 °C (entries 2 and 3). The *ortho*-effect was not prominent for 2,3-dimethylphenol **5d** rather it gave the highest yield among the alkyl substituted phenols (entry 4). We are delighted to find that bulky *o-tert*-butylphenol also underwent smooth reaction and afforded the acid **6e** in 53% yield, but the corresponding *meta*-substituted phenol gave a lower yield (entries 5 and 6). A prominent *ortho*-steric effect was observed for 2,6-dimethylphenol **5g** and afforded the amino acid **6g** in low yield (entry 7). More electron rich substrates like alkoxy substituted phenols **5h–5j** were found to work very well and provided high yields of amino acids **6h–6j** (entries 8–10). α-Naphthol **5k** behaves similar to phenol and gave a moderate yield of the desired amino acid **6k** (entry 11). Electronically different substituents along with the *ortho*-steric effect did not affect the reaction of 4-chloro-2-methoxyphenol **5l** with sulfamidate **4** and acted more like an electron-rich substrate affording very good yield of **6l** (entry 12). Halogenated phenols **5m** and **5n** are compara-

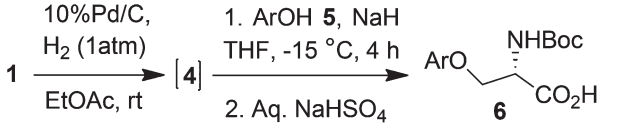
Table 2 Synthesis of *N*-Boc-β-aryloxyamino acids **6** from sulfamidate **4**



Entry	ArOH	5	Product 6	Yield[a] (%)	ee[b] (%)
1	PhOH	**5a**	**6a**	57	>99
2	3-EtC_6H_4OH	**5b**	**6b**	68	>99
3	4-EtC_6H_4OH	**5c**	**6c**	66	>99
4	2,3-$Me_2C_6H_3OH$	**5d**	**6d**	70	98
5[c]	2-^{t}BuC_6H_4OH	**5e**	**6e**	53	ND[e]
6[c]	3-^{t}BuC_6H_4OH	**5f**	**6f**	26	ND[e]
7[c]	2,6-$Me_2C_6H_3OH$	**5g**	**6g**	20	ND[e]
8	2,3-$(MeO)_2C_6H_3OH$	**5h**	**6h**	70	>99
9	2-EtOC_6H_4OH	**5i**	**6i**	66	>99
10	4-MeOC_6H_4OH	**5j**	**6j**	70	98.5
11	1-Naphthol	**5k**	**6k**	40	ND[e]
12	4-Cl-2-MeOC_6H_3OH	**5l**	**6l**	75	>99
13[c]	2-FC_6H_4OH	**5m**	**6m**	39	>99
14[c,d]	2-ClC_6H_4OH	**5n**	**6n**	51	ND[e]
15[c]	4-CNC_6H_4OH	**5o**	**6o**	52	>99
16	4-PhC_6H_4OH	**5p**	**6p**	53	ND[e]

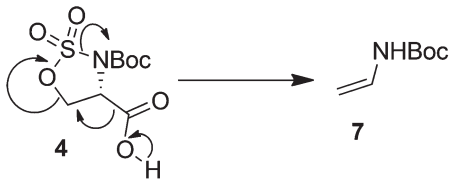
[a] Isolated yield of amino acid **6**. [b] ee was determined by chiral HPLC. [c] The reaction was performed at 0 °C. [d] *R*-Isomer, obtained from D-serine derived sulfamidate acid. [e] ND: not determined.

Table 3 One-pot synthesis of aryloxy amino acids **6**

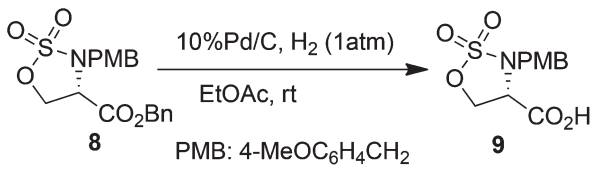


Entry	ArOH	5	Product 6	Yield[a] (%)	ee[b] (%)
1	PhOH	**5a**	**6a**	58	>99
2	4-EtC_6H_4OH	**5c**	**6c**	62	>99
3	2-EtOC_6H_4OH	**5i**	**6i**	70	>99
4[c,d]	2-ClC_6H_4OH	**5n**	**6n**	46	ND[e]

[a] Isolated yield of amino acid **6** over two steps. [b] ee was determined by chiral HPLC. [c] The reaction was performed at 0 °C. [d] Along with 8% of des-chloro product **6a**. [e] ND: not determined.



Scheme 3 Plausible route towards decomposition of sulfamidate **4**.



Scheme 4 Synthesis of *N*-PMB-sulfamidate carboxylic acid **9**.

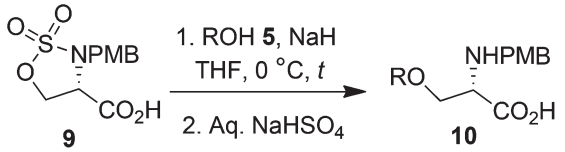
tively electron-deficient and react with sulfamidate **4** at 0 °C. Yields of the amino acids **6m** and **6n** increase from *o*-fluoro to *o*-chloro, respectively, probably due to the electronic effect (entries 13 and 14). We are delighted to report that electron-deficient 4-cyanophenol **5o** also underwent smooth reaction at 0 °C (entry 15) and 4-phenylphenol **5p** gave moderate yield of amino acid **6p** (entry 16). The formation of elimination products **2a′** (R = H) was noticed for the less reactive phenols and it enhances with the decrease in the reactivity of the phenols. Also to note is that no desired ring opening products were obtained for the highly sterically hindered 2,6-di-*tert*-butylphenol and electron-deficient pentachlorophenol (C_6Cl_5OH), rather the elimination product **2a′** was exclusively isolated (>80%; not shown in Table 2).

We also observed that the freshly prepared sulfamidate **4** always provided better yields of aryloxyamino acids **6**. Preservation of sulfamidate **4** for overnight at 5 °C reduces 20–30% of yields of **6**. Also to note is that evaporation of EtOAc and MeOH after hydrogenation must be done at rt or lower. The sulfamidate **4** undergoes decomposition at 40 °C and above to other compounds as found in ^{1}H NMR analysis. This impelled us to study a one-pot synthesis of the aryloxyamino acid *via in situ* generated sulfamidate **4**. For this purpose, a THF solution of sulfamidate **1** was hydrogenated in the presence of Pd/C under 1 atm pressure. After complete debenzylation, hydrogen was replaced with N_2 and the suspended mixture was successively treated with PhOH (1.0 equiv.) and NaH (60% in oil; 2.05 equiv.) at −15 °C. We are delighted to report that it provided the desired amino acid **6a** in 58% yield without any loss of enantiopurity. The one-pot method was generalized with a few phenols and gave moderate to good yields of amino acids **6** (Table 3). Chlorophenol also afforded the desired product **6n** along with a minor amount of the des-chloro product **6a**.

One of the plausible routes towards decomposition of sulfamidate **4** might be decarboxylative ring opening (Scheme 3), where the electron-withdrawing Boc functionality might have facilitated the decomposition. Replacement of the Boc group with an electron-donating protecting group like *p*-methoxybenzyl (PMB) may reduce the propensity to undergo decarboxylative ring opening.

Thus the *N*-PMB sulfamidate **9** was prepared from *N*-PMB-serine sulfamidate ester **8** (Scheme 4).[10] The sulfamidate **9** was found to be quite stable at rt even for a month. Ring opening of the sulfamidate **9** was tested with 4-ethylphenol **5c** and NaH (60% in oil) under the standard developed conditions. It is found to work well at 0 °C and provided very good yield of amino acid **10c** (Table 4; entry 1). Ring opening reaction of **9** was generalized with electronically and sterically different phenols obtaining *N*-PMB protected aryloxyamino acids **10** in high yields (entries 2–7). Electron-rich phenols underwent

Table 4 Synthesis of *N*-PMB aryloxyamino acids **10**



Entry	ROH	5	Time (h)	Product 10	Yield[a] (%)	ee[b] (%)
1	4-EtC_6H_4OH	**5c**	4	**10c**	79	ND[c]
2	2,3-$Me_2C_6H_3OH$	**5d**	4	**10d**	80	>99
3	3-^{t}BuC_6H_4OH	**5f**	7	**10f**	54	ND[c]
4	2,6-$Me_2C_6H_3OH$	**5g**	7	**10g**	36	ND[c]
5	4-MeOC_6H_4OH	**5j**	4	**10j**	80	>99
6	2-FC_6H_4OH	**5m**	7	**10m**	51	ND[c]
7	4-CNC_6H_4OH	**5o**	7	**10o**	68	ND[c]
8	*n*-$C_8H_{17}OH$	**5q**	7	**10q**	16	>99

[a] Isolated yield of amino acid **10**. [b] ee was determined by chiral HPLC. [c] ND: not determined.

smooth reaction and provided high yields of *N*-protected aryloxyamino acids **10c**, **10d** and **10j** (entries 1, 2 and 5). Sterically hindered phenols **5f** and **5g** on reaction with sulfamidate **9** gave better yields (entries 3 and 4) than the sulfamidate **4** (Table 2; entries 6 and 7). Electron-deficient phenols **5m** and **5o** afforded moderate to good yields of aryloxyamino acids **10m** and **10o** (entries 6 and 7).

Regio-selective ring opening of the sulfamidates **4** and **9** were also tested with alkoxides generated from *n*-octanol, isopropanol and *tert*-butanol under standard reaction conditions. *N*-Boc-sulfamidate **4** led exclusively to the elimination product **2a′** (R = H). *N*-PMB-sulfamidate **9** showed 10–30% of the desired ring opening products in LC-MS along with a mixture of uncharacterised compounds. As branching of the alcohols increases the reactions become more and more messy. Only *n*-octyloxyamino acid **10q** could be isolated in pure form by preparative HPLC in 16% yield with complete retention of enantiopurity (Table 4; entry 8).

Conclusion

In summary, the electronic effect of the carboxylate anion and ester of serine derived cyclic sulfamidate plays a pivotal role towards their reactions with hard nucleophiles. This led us to develop the first regioselective ring opening of serine derived cyclic sulfamidate with phenols. The method provides easy and direct access to non-racemic *N*-protected-β-aryloxyamino acids in moderate to very good yields with complete preservation of enantiopurity. Both enantiomers of the unnatural amino acids can be obtained from sulfamidates derived from L- and D-serine. N-Protection of serine sulfamidate carboxylic acid takes a crucial role in the stability and reactivity. *N*-PMB-serine sulfamidate carboxylic acid **9** is more stable than the *N*-Boc compound **4**. In general the former gave better yields of aryloxyamino acids **6** and it also provided β-alkoxy amino acid too. A wide variety of substituted phenols were tested for the ring opening reaction, which showed a minute temperature effect. The method is also suitable for one-pot synthesis of these unnatural amino acids *via in situ* generated serine sulfamidate carboxylic acid.

Experimental

General

All reactions were conducted using oven-dried glassware under an atmosphere of argon (Ar) or nitrogen (N_2). Commercial grade reagents were used without further purification. Solvents were dried and distilled following usual protocols. Column chromatography was carried out using silica gel (100–200 mesh). TLC was performed on aluminium-backed plates coated with Silica gel 60 with F_{254} indicator. The ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra were recorded at 100 MHz using $CDCl_3$ and DMSO-d_6. ^{1}H NMR chemical shifts are expressed in parts per million (δ) relative to $CDCl_3$ (δ = 7.26) and DMSO-d_6 (δ = 2.49); ^{13}C NMR chemical shifts are expressed in parts per million (δ) relative to the $CDCl_3$ resonance (δ = 77.0) and DMSO-d_6 (δ = 39.7). High resolution mass spectra (HRMS) were measured with a QTOF I (quadrupole–hexapole TOF) mass spectrometer with an orthogonal Z-spray–electro-spray interface. HPLC analyses of compound **6** were done by Cellulose-2 (4.6 × 250 mm) and Chiralpak AD-H (4.6 × 250 mm) columns using SFC (Supercritical Fluid Chromatography) and that of compound **10** were done using a Cellulose-1 (4.6 × 250 mm) column. Specific optical rotation values were measured on a polarimeter. Sulfamidates **1** and **8** were prepared by following the literature procedures.[7,10]

4(*S*)-Benzyl-3-*tert*-butyl-1,2,3-oxathiazolidine-3,4-dicarboxylate-2,2-dioxide 1 [serine sulfamidate] (1). Dry CH_2Cl_2 (230 mL, 5.0 mL mmol^{-1}) and thionyl chloride (8.3 mL, 2.5 equiv.) were placed in a round-bottomed flask under an argon atmosphere. Then *N*-Boc benzyl ester of serine **3** (13.4 g, 45.37 mmol) in CH_2Cl_2 (450 mL, 10 mL mmol^{-1}) was dropwise added to the reaction mixture at −40 °C and stirring was continued for 30 min. Pyridine (18.7 mL, 5.1 equiv.) was added to the reaction mixture and slowly raised to rt. After 1 h, the reaction was quenched with ice-water (450 mL), washed with sodium bicarbonate (450 mL) and brine (450 mL) successively, dried over sodium sulfate, evaporated to get the crude sulfamidate (16.5 g), which was used for the next step. To the crude compound in acetonitrile (290 mL) were added $RuCl_3{\cdot}H_2O$ (0.220 g, 0.97 mmol, 0.02 equiv.), $NaIO_4$ (16.0 g, 74.8 mmol, 1.6 equiv.) and water (290 mL) at 0 °C and stirred. After 1 h, the reaction mixture was quenched with satd $NaHCO_3$ (300 mL), extracted with ethyl acetate (3 × 400 mL), washed with brine (500 mL), dried over sodium sulfate, and purified by column chromatography to get a white solid of sulfamidate **1** (10.43 g, 64%); m.p. 120–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.41–7.28 (m, 5H), 5.33 (d, J = 12.1 Hz, 1H), 5.24 (d, J = 12.1 Hz, 1H), 4.85–4.83 (m, 1H), 4.79–4.75 (m, 1H), 4.69–4.66

(m, 1H), 1.51 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): 166.9, 147.9, 134.3, 128.7 (2C), 128.6 (2C), 128.3, 86.2, 68.4, 67.4, 57.5, 27.7 (3C). LC-MS (ESI): 355.8 $[M - H]^+$, $[\alpha]_D^{25} = -26.3$ (*c* 0.51, DCM). HRMS (ESI): calcd for $C_{15}H_{19}NNaO_7S$, 380.0780 *m*/*z* $[M + Na]^+$, found 380.0780. From D-serine: white solid, m.p. 120–122 °C. $[\alpha]_D^{25} = +26.4$ (*c* = 0.51, DCM).

3(*S*)-(*tert*-Butoxycarbonyl)-1,2,3-oxathiazolidine-4-carboxylic acid-2,2-dioxide (4). To the compound **1** (0.30 g, 0.84 mmol) in ethyl acetate (4.0 mL) was added 10% Pd/C (0.030 g) and the suspended mixture was stirred under a hydrogen balloon at rt for 30 min. The reaction mixture was filtered through a celite bed to remove the palladium and the filtrate was evaporated at rt under reduced pressure to get sulfamidate carboxylic acid **4** as a gummy liquid, which was directly used for the next step within an hour.

^{1}H NMR (400 MHz, DMSO-d_6): δ 13.83 (br s, 1H), 4.98 (dd, *J* = 8.8, 3.4 Hz, 1H), 4.89 (m, 2H), 1.50 (s, 9H); (400 MHz, d_6-acetone): δ 5.04 (dd, *J* = 6.8, 1.8 Hz, 1H), 4.97 (dd, *J* = 9.6, 6.8 Hz, 1H), 4.88 (dd, *J* = 9.6, 1.8 Hz, 1H), 1.50 (s, 9H).

Instead of EtOAc, hydrogenation was also carried out in MeOH. The ^{1}H NMR spectrum of the crude sulfamidate **4** showed a better reaction profile. ^{1}H NMR (400 MHz, MeOH-d_4): δ 4.91 (dd, *J* = 6.8, 1.6 Hz, 1H), 4.85 (dd, *J* = 9.5, 6.8 Hz, 1H, along with peak of HOD), 4.76 (dd, *J* = 9.5, 1.6 Hz), 1.52 (s, 9H). ^{13}C NMR (100 MHz, MeOH-d_4): 170.34, 149.8, 86.7, 69.7, 59.1, 28.2. ELSD-MS (ESI): 266.0 $[M - H]^-$. $[\alpha]_D^{25} = -24.3$ (*c* 0.53, MeOH). HRMS (ESI): calcd for $C_8H_{13}NNaO_7S$ 290.0310 *m*/*z* $[M + Na]^+$, found 290.0310.

General procedure for ring opening of sulfamidate acid 4 with phenol

To a suspended solution of NaH (60% in oil; 0.105 g, 2.6 mmol) in THF (3.0 mL), phenol **5a** (0.083 g, 0.88 mmol) was added at 0 °C. The reaction mixture was stirred for 10 min and then it was brought to −15 °C. Serine sulfamidate acid **4** (0.224 g, 0.84 mmol) in dry THF (1.0 mL) was slowly added to it at −15 °C. After 4 h, the reaction mixture was acidified (pH 2; monitored by pH paper) by addition of $NaHSO_4$. Then it was extracted with ethyl acetate (3 × 20 mL), the combined organic layers were washed with brine (100 mL), dried over sodium sulfate, and purified by column chromatography to get the β-phenoxy-α-amino acid **6a** (0.136 g, 57%).

General procedure for one pot synthesis of aryloxyamino acid 6

To the sulfamidate **1** (0.30 g, 0.84 mmol) in THF (4.0 mL) was added 10% Pd/C (0.030 g) and the reaction mixture was stirred under hydrogen (1 atm) at rt for 30 min. TLC shows complete consumption of starting **1**. The hydrogen balloon was replaced with N_2, phenol **5a** (0.083 g, 0.88 mmol) and NaH (60% in oil; 0.105 g, 2.6 mmol) were then successively added to the reaction mixture at −15 °C and stirred. After 4 h, the reaction mixture was acidified (pH 2 monitored by pH paper) by addition of $NaHSO_4$. Then it was filtered through a celite bed and the filtrate was extracted with ethyl acetate (3 × 20 mL), the combined organic layers were washed with brine (100 mL), dried over sodium sulfate, and purified by column chromatography to get the amino acid **6a** (0.138 g, 58%).

(*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-phenoxypropanoic acid (6a). Yield 57%; light yellow semi-solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.28 (t, *J* = 7.8 Hz, 2H), 7.12 (d, *J* = 8.1 Hz, 1H), 6.96–6.91 (m, 3H), 4.35–4.34 (m, 1H), 4.23–4.19 (m, 2H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.3, 158.0, 155.3, 129.4 (2C), 120.8, 114.5 (2C), 78.2, 67.2, 53.3, 28.0 (3C). LC-MS (ESI): 280.0 $[M - H]^-$. HPLC analysis: Cellulose-2 (4.6 × 250 mm) 5μ, (MeOH + 0.5% IPA) containing 82% CO_2, 2.0 mL min^{-1}, 220 nm, tr (major) 5.75, tr (minor) 6.98, >99% ee, $[\alpha]_D^{25}$ = +42.2 (*c* 1.02, MeOH). HRMS (ESI): calcd for $C_{14}H_{19}NNaO_5$ 304.1161 *m*/*z* $[M + Na]^+$, found 304.1161.

From D-serine: light yellow semi-solid; HPLC analysis: Cellulose-2 (4.6 × 250 mm) 5μ, (MeOH + 0.5% IPA) containing 82% CO_2, 2.0 mL min^{-1}, 220 nm, tr (major) 6.98, tr (minor) 5.77, >99% ee, $[\alpha]_D^{25} = -42.0$ (*c* 1.10, MeOH).

(*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-(3-ethylphenoxy)-propionic acid (6b). Yield 68%; light yellow solid; m.p. 78–80 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.86 (br s, 1H), 7.19–7.16 (m, 2H), 6.80–6.71 (m, 3H), 4.36–4.31 (m, 1H), 4.18–4.16 (m, 2H), 2.56 (q, *J* = 7.6 Hz, 2H), 1.38 (s, 9H), 1.16 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.5, 158.2, 155.4, 145.4, 129.3, 120.5, 114.2, 111.6, 78.3, 67.2, 53.4, 28.2 (3C), 28.1, 15.6 LC-MS (ESI): 308.2 $[M - H]^-$. HPLC analysis: Cellulose-2 (4.6 × 250 mm) 5μ, (MeOH + 0.5% IPA) containing 80% CO_2, 2 mL min^{-1}, 220 nm, tr (major) 4.98, tr (minor) 6.17, >98% ee, $[\alpha]_D^{25}$ = +33.7 (*c* 1.00, MeOH). HRMS (ESI): calcd for $C_{16}H_{23}NNaO_5$, 332.1474 *m*/*z* $[M + Na]^+$, found 332.1489. From D-serine: HPLC analysis: Cellulose-2 (4.6 × 250 mm) 5μ, (MeOH + 0.5% IPA) containing 80% CO_2, 2 mL min^{-1}, 220 nm, tr (major) 6.12, tr (minor) 5.07, >99% ee, $[\alpha]_D^{25} = -33.4$ (*c* 1.06, MeOH).

(*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-(4-ethylphenoxy)-propionic acid (6c). Yield 66%; light yellow semi-solid, ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.13–7.09 (m, 3H), 6.82 (d, *J* = 8.5 Hz, 2H), 4.31–4.29 (m, 1H), 4.15–4.14 (m, 2H), 2.54 (q, *J* = 7.5 Hz, 2H), 1.38 (s, 9H), 1.13 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.5, 156.2, 155.4, 136.2, 128.7 (2C), 114.5 (2C), 78.3, 67.4, 53.4, 28.2 (3C), 27.3, 15.9. LC-MS (ESI): 308.2 $[M - H]^-$. HPLC analysis: Cellulose-2 (4.6 × 250 mm) 5μ, (MeOH + 0.5% IPA) containing 80% CO_2, 2 mL min^{-1}, 220 nm, tr (major) 5.13, tr (minor) 6.6, >98% ee, $[\alpha]_D^{25}$ = +38.4 (*c* 1.18, MeOH). HRMS (ESI): calcd for $C_{16}H_{23}NNaO_5$, 332.1474 *m*/*z* $[M + Na]^+$, found 332.1502. From D-serine: HPLC analysis: Cellulose-2 (4.6 × 250 mm) 5μ, (MeOH + 0.5% IPA) containing 80% CO_2, 2 mL min^{-1}, 220 nm, tr (major) 6.57, tr (minor) 5.08, >99% ee, $[\alpha]_D^{25} = -38.2$ (*c* 1.12, MeOH).

(*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-(2,3-dimethylphenoxy)-propionic acid (6d). Yield 70%; off white solid, m.p. 114–116 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.88 (br s, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.01 (t, *J* = 7.8 Hz, 1H), 6.77–6.74 (m, 2H), 4.43–4.38 (m, 1H), 4.18 (dd, *J* = 9.6, 4.0 Hz, 1H), 4.10 (dd, *J* = 9.6, 6.8 Hz, 1H), 2.19 (s, 3H), 2.03 (s, 3H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.4, 155.9, 155.3, 137.2, 125.8, 124.5, 122.3, 109.3, 78.2, 67.8, 53.3, 28.1 (3C), 19.5, 11.2.

LC-MS (ESI): 307.8 $[M - H]^-$. HPLC analysis: Chiralpak AD-H (4.6 × 250 mm) 5μ, (MeOH + IPA) containing 80% CO_2, 3.0 mL min^{-1}, 210 nm, tr (major) 2.12, tr (minor) 1.73; 98% ee. $[\alpha]_D^{25}$ = +43.4 (*c* 1.28, MeOH). HRMS (ESI): calcd for $C_{16}H_{23}NNaO_5$, 332.1474 *m*/*z* $[M + Na]^+$, found 332.1502. From D-serine: off white semi-solid, HPLC analysis: Chiralpak AD-H (4.6 × 250 mm) 5μ, (MeOH + IPA) containing 80% CO_2, 3.0 mL min^{-1}, 210 nm, tr (major) 1.7, tr (minor) 2.12, >99% ee, $[\alpha]_D^{25}$ = −44.5 (*c* 0.95, MeOH).

(*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-(2-*tert*-butylphenoxy)-propionic acid (6e). Yield 53%; light brown semi-solid; ^1H NMR (400 MHz, DMSO-d_6): δ 13.0 (br s, 1H), 7.20 (d, *J* = 6.6 Hz, 1H), 7.16 (t, *J* = 7.7 Hz, 1H), 7.07 (d, *J* = 8.3 Hz, 1H), 6.92 (d, *J* = 8.1 Hz, 1H), 6.87 (t, *J* = 7.7 Hz, 1H), 4.49–4.45 (m, 1H), 4.27 (dd, *J* = 9.5, 3.8 Hz, 1H), 4.15 (dd, *J* = 9.5, 7.1 Hz, 1H), 1.38 (s, 9H), 1.30 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.5, 156.6, 155.1, 137.2, 127.0, 126.2, 120.4, 111.9, 78.2, 67.0, 53.3, 34.3, 29.7 (3C), 28.1 (3C). LC-MS (ESI): 336.2 $[M - H]^-$. $[\alpha]_D^{25}$ = +33.2 (*c* 0.58, MeOH). HRMS (ESI): calcd for $C_{18}H_{27}NNaO_5$, 360.1787 *m*/*z* $[M + Na]^+$, found 360.1787.

(*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-(3-*tert*-butylphenoxy)-propionic acid (6f). Yield 26%; light brown solid, m.p. 108–110 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 12.90 (br s, 1H), 7.20 (t, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.89 (s, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 4.34 (m, 1H), 4.22–4.18 (m, 2H), 1.39 (s, 9H), 1.25 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): 171.3, 157.8, 155.2, 152.2, 128.9, 117.7, 112.2, 110.8, 78.1, 67.2, 53.3, 34.2, 30.9 (3C), 28.0 (3C). LC-MS (ESI): 336.2 $[M - H]^-$. $[\alpha]_D^{25}$ = +35.8 (*c* 1.04, MeOH). HRMS (ESI): calcd for $C_{18}H_{27}NNaO_5$, 360.1787 *m*/*z* $[M + Na]^+$, found 360.1816.

(*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-(2,6-dimethylphenoxy)-propionic acid (6g). Yield 20%; colourless semi-solid; ^1H NMR (400 MHz, DMSO-d_6): δ 12.9 (br s, 1H), 7.07 (d, *J* = 8.3 Hz, 1H), 7.01–6.99 (m, 2H), 6.93–6.89 (m, 1H), 4.32 (m, 1H), 4.01–3.95 (m, 2H), 2.21 (s, 6H), 1.36 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.4, 155.2, 154.5, 130.3 (2C), 128.6 (2C), 123.8, 78.2, 70.7, 54.1, 28.0 (3C), 15.6 (2C). LC-MS (ESI): 308.6 $[M - H]^-$. $[\alpha]_D^{25}$ = +25.4 (*c* 1.03, MeOH). HRMS (ESI): calcd for $C_{16}H_{23}NNaO_5$, 332.1474 *m*/*z* $[M + Na]^+$, found 332.1474.

(*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-(2,3-dimethoxyphenoxy)-propionic acid (6h). Yield 70%; light yellow semi-solid; ^1H NMR (400 MHz, DMSO-d_6): δ 12.93 (s, 1H), 7.15 (d, *J* = 8.3 Hz, 1H), 6.97 (t, *J* = 8.3 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 4.39–4.35 (m, 1H), 4.22 (dd, *J* = 9.8, 3.9 Hz, 1H), 4.15 (dd, *J* = 9.8, 7.2 Hz, 1H), 3.75 (s, 3H), 3.64 (s, 3H), 1.38 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.5, 155.4, 153.2, 151.9, 138.0, 123.6, 106.9, 106.0, 78.3, 68.3, 60.0, 55.8, 53.4, 28.2 (3C). LC-MS (ESI): 339.8 $[M - H]^-$. HPLC analysis: Chiralpak AD-H (4.6 × 250 mm) 5μ, (MeOH + IPA) containing 80% CO_2, 3.0 mL min^{-1}, 210 nm, tr (major) 3.88, tr (minor) 2.15, >99% ee. $[\alpha]_D^{25}$ = +40.0 (*c* 2.99, MeOH). HRMS (ESI): calcd for $C_{16}H_{23}NNaO_7$, 364.1372 *m*/*z* $[M + Na]^+$, found 364.1384. From D-serine: HPLC analysis: Chiralpak AD-H (4.6 × 250 mm) 5μ, (MeOH + IPA) containing 80% CO_2, 3.0 mL min^{-1}, 210 nm, tr (major) 2.13, tr (minor) 3.89, >99% ee, $[\alpha]_D^{25}$ = −40.1 (*c* 2.77, MeOH).

(*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-(2-ethoxyphenoxy)-propionic acid (6i). Yield 66%; light yellow semi-solid; ^1H NMR (400 MHz, DMSO-d_6): δ 12.88 (br s, 1H), 7.03 (d, *J* = 8.2 Hz, 1H), 6.99–6.96 (m, 2H), 6.94–6.90 (m, 1H), 6.89–6.85 (m, 1H), 4.32–4.29 (m, 1H), 4.18 (d, *J* = 5.2 Hz, 2H), 4.00 (q, *J* = 7.0 Hz, 2H), 1.39 (s, 9H), 1.31 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.5, 155.3, 148.8, 148.0, 122.1, 121.1, 115.7, 114.5, 78.3, 68.9, 64.1, 53.5, 28.1 (3C), 14.7. LC-MS (ESI): 324.0 $[M - H]^-$. HPLC analysis: Cellulose-2 (4.6 × 250 mm) 5μ, (MeOH + 0.5% IPA) containing 80% CO_2, 2.0 mL min^{-1}, 220 nm, tr (major) 6.14, tr (minor) 10.56, >99% ee, $[\alpha]_D^{25}$ = +23.6 (*c* 0.88, MeOH). HRMS (ESI): calcd for $C_{16}H_{23}NNaO_6$, 348.1423 *m*/*z* $[M + Na]^+$, found 348.1440. From D-serine: HPLC analysis: Cellulose-2 (4.6 × 250 mm) 5μ, (MeOH + 0.5% IPA) Containing 80% CO_2, 2.0 mL min^{-1}, 220 nm, tr (major) 10.59, tr (minor) 6.19, >99% ee. $[\alpha]_D^{25}$ = −23.4 (*c* 0.94, MeOH).

(*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-(4-methoxyphenoxy)-propionic acid (6j). Yield 70%; greenish semi-solid; ^1H NMR (400 MHz, DMSO-d_6): δ 12.87 (br s, 1H), 7.15 (d, *J* = 8.2 Hz, 1H), 6.85 (*AB quasi* t, *J* = 9.7 Hz, 4H), 4.34–4.30 (m, 1H), 4.16–4.12 (m, 2H), 3.69 (s, 3H), 1.38 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.4, 155.3, 153.6, 152.0, 115.6 (2C), 114.5 (2C), 78.2, 67.9, 55.2, 53.4, 28.1 (3C). LC-MS (ESI): 310.0 $[M - H]^-$. HPLC analysis: Chiralpak AD-H (4.6 × 50 mm) 5μ, (MeOH + IPA) containing 80% CO_2, 3.0 mL min^{-1}, 220 nm, tr (major) 2.45, tr (minor) 2.06, 98.5% ee, $[\alpha]_D^{25}$ = +33.7 (*c* 1.01, MeOH). HRMS (ESI): calcd for $C_{15}H_{21}NNaO_6$, 334.1267 *m*/*z* $[M + Na]^+$, found 334.1266. From D-serine: brown semi-solid, HPLC analysis: Chiralpak AD-H (4.6 × 250 mm) 5μ, (MeOH + IPA) containing 80% CO_2, 3.0 mL min^{-1}, 220 nm, tr (major) 2.06, tr (minor) 2.45, >99% ee, $[\alpha]_D^{25}$ = −33.8 (*c* 0.99, MeOH).

(*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-(naphthalen-1-yloxy)-propionic acid (6k). Yield 40%; brown semi-solid, ^1H NMR (400 MHz, DMSO-d_6): δ 8.20 (d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.53–7.34 (m, 5H), 6.94 (d, *J* = 7.5 Hz, 1H), 4.60 (m, 1H), 4.41–4.33 (m, 2H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): 171.4, 155.4, 153.6, 133.9, 127.2, 126.4, 126.1, 125.0, 124.8, 121.8, 120.1, 105.1, 78.2, 67.9, 53.3, 28.1 (3C). LC-MS (ESI): 330.2 $[M - H]^-$. $[\alpha]_D^{25}$ = +46.3 (*c* 1.30, MeOH). HRMS (ESI): calcd for $C_{18}H_{21}NNaO_5$, 354.1317 *m*/*z* $[M + Na]^+$, found 354.1349.

(*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-(4-chloro-2-methoxyphenoxy)-propionic acid (6l). Yield 75%; light yellow semi-solid; ^1H NMR (400 MHz, DMSO-d_6): δ 7.05–7.02 (m, 1H), 6.97 (d, *J* = 8.6 Hz, 1H), 6.91 (dd, *J* = 8.5, 2.2 Hz, 1H), 4.30–4.26 (m, 1H), 4.20–4.13 (m, 2H), 3.79 (s, 3H), 1.38 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.3, 155.3, 150.1, 146.6, 125.2, 120.1, 115.4, 112.7, 78.3, 68.6, 55.9, 53.4, 28.1 (3C). LC-MS (ESI): 344.0 $[M - H]^-$. HPLC analysis: Cellulose-2 (4.6 × 250 mm) 5μ, (MeOH + 0.5% IPA) containing 80% CO_2, 2.0 mL min^{-1}, 220 nm, tr (major) 6.27, tr (minor) 8.84, >98% ee, $[\alpha]_D^{25}$ = +35.7 (*c* 2.81, MeOH). HRMS (ESI): calcd for $C_{15}H_{20}ClNNaO_6$, 368.0877 *m*/*z* $[M + Na]^+$, found 368.0895. From D-serine: light yellow semi-solid, HPLC analysis: Cellulose-2 (4.6 × 250 mm)

5μ, (MeOH + 0.5% IPA) containing 80% CO_2, 2.0 mL min^{-1}, 220 nm, tr (major) 8.68, tr (minor) 6.3, >99% ee, $[\alpha]_D^{25}$ = −35.4 (*c* 2.54, MeOH).

(*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-(2-fluorophenoxy)-propionic acid (6m). Yield 39%; light yellow semi-solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.91 (br s, 1H), 7.22–7.09 (m, 4H), 6.98–6.94 (m, 1H), 4.36–4.34 (m, 1H), 4.31–4.21 (m, 2H), 1.36 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.2. 155.3, 151.7 (d, J = 242.5 Hz), 146.0 (d, J = 10.4 Hz), 124.7 (d, J = 3.8 Hz), 121.5 (J = 6.8 Hz), 116.0 (d, J = 17.8 Hz), 115.3, 78.3, 68.3, 53.3, 28.1. LC-MS (ESI): 298.2 $[M - H]^-$. HPLC analysis: Cellulose-2 (4.6 × 250 mm) 5μ, (MeOH + 0.5% IPA) containing 80% CO_2, 2.0 mL min^{-1}, 216 nm, tr (major) 4.97, tr (minor) 6.02, >99% ee; $[\alpha]_D^{25}$ = +28.1 (*c* 1.60, MeOH). HRMS (ESI): calcd for $C_{14}H_{18}FNNaO_5$, 322.1067 *m*/*z* $[M + Na]^+$, found 322.1077. From D-serine: HPLC analysis: Cellulose-2 (4.6 × 250 mm) 5μ, (MeOH + 0.5% IPA) containing 80% CO_2, 2.0 mL min^{-1}, 216 nm, tr (major) 6.02, tr (minor) 5.09, >99% ee, $[\alpha]_D^{25}$ = −27.9 (*c* 1.65, MeOH).

(*R*)-2-((*tert*-Butoxycarbonyl)amino)-3-(2-chlorophenoxy)-propionic acid (6n). Yield 51%; obtained from D-serine; yellow semi-solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.40 (d, J = 7.8 Hz, 1H), 7.27 (t, J = 8.1 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 8.1 Hz, 1H), 6.96 (t, J = 7.8 Hz, 1H), 4.44–4.39 (m, 1H), 4.32 (dd, J = 9.8, 3.8 Hz, 1H), 4.24 (dd, J = 9.8, 7.3 Hz, 1H), 1.38 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.1, 155.2, 153.5, 129.9, 128.2, 121.9, 121.6, 114.2, 78.3, 68.3, 53.2, 28.1 (3C). LC-MS (ESI): 314.2 $[M - H]^-$. $[\alpha]_D^{25}$ = −33.1 (*c* 1.01, MeOH). HRMS (ESI): calcd for $C_{14}H_{18}ClNNaO_5$, 338.0771 *m*/*z* $[M + Na]^+$, found 338.0771.

(*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-(4-cyanophenoxy)-propanoic acid (6o). Yield 52%; brown semi-solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.98 (br s, 1H), 7.76 (d, J = 8.7 Hz, 2H), 7.29 (d, J = 8.1 Hz, 1H), 7.10 (d, J = 8.7 Hz, 2H), 4.40–4.36 (m, 1H), 4.32–4.29 (m, 2H), 1.38 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.0, 161.5, 155.3, 134.1 (2C), 118.9, 115.6 (2C), 103.1, 78.3, 67.7, 53.1, 28.1 (3C). LC-MS (ESI): 305.0 $[M - H]^-$. HPLC analysis: Cellulose-2 (4.6 × 250 mm) 5μ, (MeOH + 0.5% IPA) containing 80% CO_2, 2.0 mL min^{-1}, 246 nm, tr (major) 6.22, tr (minor) 7.15, >98% ee, $[\alpha]_D^{25}$ = +35.0 (*c* 1.06, MeOH). HRMS (ESI): calcd for $C_{15}H_{18}N_2NaO_5$, 329.1113 *m*/*z* $[M + Na]^+$, found 329.1113. From D-serine: HPLC analysis: Cellulose-2 (4.6 × 250 mm) 5μ, (MeOH + 0.5% IPA) containing 80% CO_2, 2.0 mL min^{-1}, 246 nm, tr (major) 7.09, tr (minor) 6.21, >99% ee, $[\alpha]_D^{25}$ = −34.8 (*c* 1.00, MeOH).

(*S*)-3-([1,1′-Biphenyl]-4-yloxy)-2-((*tert*-butoxycarbonyl)amino)-propanoic acid (6p). Yield 53%; light yellow solid, m.p. 124–126 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.91 (br s, 1H), 7.61–7.59 (m, 4H), 7.43 (t, J = 7.5 Hz, 2H), 7.31 (t, J = 7.4 Hz, 1H), 7.22 (d, J = 8.1 Hz, 1H), 7.02 (d, J = 8.6 Hz, 2H), 4.40–4.35 (m, 1H), 4.28–4.24 (m, 2H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 171.3, 157.7, 155.3, 139.6, 132.9, 128.7 (2C), 127.6 (2C), 126.6, 126.1 (2C), 114.9 (2C), 78.2, 67.4, 53.3, 28.1 (3C). LC-MS (ESI): 356.2 $[M - H]^-$. $[\alpha]_D^{25}$ = +44.2 (*c* = 0.99, MeOH). HRMS (ESI): calcd for $C_{20}H_{23}NNaO_5$, 380.1474 *m*/*z* $[M + Na]^+$, found 380.1474.

(4*S*)-*N*-(*p*-Methoxybenzyl)-2,2-dioxo-1,2,3-oxathiazolidione-4-carboxylic acid (9). To the protected sulfamidate **8** (0.30 g, 0.79 mmol) in ethyl acetate was added 10% Pd/C (0.070 g). The reaction mixture was stirred under a hydrogen balloon at rt for 1 h. The reaction mixture was filtered through a celite bed and the filtrate was evaporated under reduced pressure to get the sulfamidate carboxylic acid **9** as a sticky liquid, which was used for the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 4.67 (dd, J = 8.9, 4.1 Hz, 1H), 4.59 (quasi t, J = 8.2 Hz, 1H), 4.51 (d, J = 14.1 Hz, 1H), 4.41 (d, J = 14.1 Hz, 1H), 4.12–4.06 (m, 1H), 3.80 (s, 3H); ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.5 (br s, 1H), 7.31 (d, J = 8.5 Hz, 2H), 6.92 (d, J = 8.5 Hz, 2H), 4.76 (quasi t, J = 8.3 Hz, 1H), 4.67 (dd, J = 9.0, 4.6 Hz, 1H), 4.40 (d, J = 14.4, 1H), 4.41–4.29 (m, 1H), 4.30 (d, J = 14.4 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 159.9, 130.8 (2C), 125.1, 114.3 (2C), 67.4, 57.4, 55.3, 49.8. LC-MS (ESI): 286.3 $[M - H]^-$, $[\alpha]_D^{25}$ = −36.0 (*c* 1.01, MeOH).

General procedure of ring opening reaction of sulfamidate 9 with ArOH

To 4-methoxyphenol **5j** (0.104 g, 0.84 mmol, 1.05 equiv.) in dry THF (4.0 mL) was added NaH (60% in oil; 0.100 g, 2.5 mmol, 3.1 equiv.) at 0 °C and stirred for 5 min. Sulfamidate acid **9** (0.228 g, 0.79 mmol, 1.0 equiv.) in dry THF (2.0 mL) was added and stirring was continued at 0 °C. After 4 h, the reaction mixture was acidified (pH 2; monitored by pH paper) by addition of $NaHSO_4$ and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and purified by column chromatography using MeOH–DCM to give amino acid **10j** (0.21 g, 80%).

(*S*)-3-(4-Ethylphenoxy)-2-((4-methoxybenzyl)amino)-propanoic acid (10c). Yield 79%; white solid, m.p. 178–180 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.40 (d, J = 8.5 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.5 Hz, 1H), 8.86 (d, J = 8.4 Hz, 2H), 4.31 (d, J = 3.5 Hz, 2H), 4.11–4.06 (m, 2H), 3.92 (m, 1H), 3.75 (s, 3H), 2.53 (q, J = 7.6 Hz, 2H), 1.14 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.0, 159.6, 155.6, 136.7, 131.6 (2C), 128.6 (2C), 123.8, 114.5 (2C), 113.8 (2C), 65.8, 58.1, 55.1, 49.3, 27.2, 15.8. LC-MS (ESI): 330.2 $[M + H]^+$, HRMS (ESI): calcd for $C_{19}H_{23}NNaO_4$, 352.1525 *m*/*z* $[M + Na]^+$, found 352.1519. $[\alpha]_D^{25}$ = +23.0 (*c* 0.168, MeOH).

(*S*)-3-(2,3-Dimethylphenoxy)-2-((4-methoxybenzyl)amino)-propanoic acid (10d). Yield 80%; off white solid, m.p. 184–186 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.36 (d, J = 8.4 Hz, 2H), 7.01 (t, J = 7.8 Hz, 1H), 6.93 (d, J = 8.4 Hz, 2H), 6.78–6.75 (m, 2H), 4.25–4.20 (m, 2H), 4.01 (AB q, J = 13.0 Hz, 2H), 3.75 (s, 3H), 3.62 (m, 1H), 2.2 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.4, 159.2, 155.8, 137.4, 130.9 (2C), 126.2, 125.9, 124.5, 122.5, 113.9 (2C), 109.3, 67.7, 59.3, 55.1, 49.6, 19.7, 11.5. LC-MS (ESI): 330.3 $[M + H]^+$, HPLC analysis: Cellulose-1 (4.6 × 250 mm) 5μ, MeOH, 3.0 mL min^{-1}, 225 nm, tr (major) 2.78, tr (minor) 3.98, >99% ee, HRMS (ESI): calcd for $C_{19}H_{23}NNaO_4$, 352.1525 *m*/*z* $[M + Na]^+$, found 352.1525. $[\alpha]_D^{25}$ = +20.0 (*c* 0.252, MeOH). From D-serine: HPLC

analysis: Cellulose-1 (4.6 × 250 mm) 5μ, MeOH, 3.0 mL min^{-1}, 225 nm, tr (major) 3.95, tr (minor) 2.78, >99% ee.

(*S*)-3-(3-(*tert*-Butyl)phenoxy)-2-((4-methoxybenzyl)amino)-propanoic acid (10f). Yield 54%; white solid, m.p. 162–164 °C; ^{1}H NMR (400 MHz, DMSO): δ 7.39 (d, J = 8.4 Hz, 2H), 7.21 (t, J = 8 Hz, 1H), 6.99 (d, J = 8 Hz, 1H), 6.93 (d, J = 8.4 Hz, 2H), 6.90 (m, 1H), 6.75 (dd, J = 8.4 Hz, J = 2 Hz, 1H), 4.31 (d, J = 3.6 Hz, 2H), 4.11–4.03 (m, 2H), 3.74 (s, 3H), 3.72 (m, 1H), 1.25 (s, 9H), ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.1, 159.2, 157.6, 152.2, 130.9 (2C), 128.9, 125.6, 117.9, 113.7 (2C), 112.1, 110.9, 66.7, 58.9, 54.9, 49.3, 34.3, 30.9 (3C). LC-MS (ESI): 356.2 $[M - H]^-$, HRMS (ESI): calcd for $C_{21}H_{27}NNaO_4$, 380.1838 m/z $[M + Na]^+$, found 380.1838. $[\alpha]_D^{25}$ = +17.0 (c 0.10, MeOH).

(*S*)-3-(2,6-Dimethylphenoxy)-2-((4-methoxybenzyl)amino)-propanoic acid (10g). Yield 36%; white solid, m.p. 210–212 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.37 (d, J = 8.5 Hz, 2H), 7.0 (d, J = 7.4 Hz, 2H), 6.95–6.89 (m, 3H), 4.06–4.00 (m, 2H), 3.97–3.94 (m, 2H), 3.75 (s, 3H), 3.51 (m, 1H), 2.20 (s, 6H). ^{13}C NMR (100 MHz, DMSO + TFA): δ 168.0, 159.9, 153.5, 132.0 (2C), 130.4 (2C), 128.9 (2C), 124.6, 123.0, 114.0 (2C), 67.7, 58.6, 55.1, 49.3, 15.8 (2C). LC-MS (ESI): 328.2 $[M - H]^-$, HRMS (ESI): calcd for $C_{19}H_{23}NNaO_4$, 352.1525 m/z $[M + Na]^+$, found 352.1525.

(*S*)-2-((4-Methoxybenzyl)amino)-3-(4-methoxyphenoxy)-propanoic acid (10j). Yield 80%; white solid, m.p. 178–180 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.43 (d, J = 8.3 Hz, 2H), 6.97 (d, J = 8.3 Hz, 2H), 6.93–6.86 (m, 4H), 4.35 (m, 2H), 4.21–4.12 (m, 3H), 3.76 (s, 3H), 3.69 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.0, 159.8, 154.1, 151.5, 132.1 (2C), 123.3, 115.9 (2C), 114.6 (2C), 113.9 (2C), 66.1, 57.8, 55.4, 55.2, 49.2. LC-MS (ESI): 332.2 $[M + H]^+$, HPLC analysis: Cellulose-1 (4.6 × 250 mm) 5μ, MeOH, 3.0 mL min^{-1}, 225 nm, tr (major) 4.83, tr (minor) 5.16, >99% ee, $[\alpha]_D^{25}$ = +26.0 (c 0.127, MeOH). HRMS (ESI): calcd for $C_{18}H_{21}NNaO_5$, 354.1317 m/z $[M + Na]^+$, found 354.1317. From D-serine: HPLC analysis: Cellulose-1 (4.6 × 250 mm) 5μ, MeOH, 3.0 mL min^{-1}, 225 nm, tr (major) 5.18, tr (minor) 4.95, >99% ee.

(*S*)-3-(2-Fluorophenoxy)-2-((4-methoxybenzyl)amino)-propanoic acid (10m). Yield 51%; white solid, m.p. 169–171 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.36 (d, J = 8.5 Hz, 2H), 7.24–7.10 (m, 3H), 6.99–6.96 (m, 1H), 6.92 (d, J = 8.5 Hz, 2H), 4.39–4.29 (m, 2H), 4.04–3.97 (m, 2H), 3.75 (s, 3H), 3.31 (m, 1H), ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.1, 159.0, 151.7 (d, J = 251.5 Hz), 145.8 (d, J = 10.4 Hz), 130.6 (2C), 126.5, 124.7 (d, J = 2.5 Hz), 121.4 (d, J = 6.8 Hz), 115.9 (d, J = 17.8 Hz), 115.2, 113.7 (2C), 69.9, 59.9, 54.9, 49.5; LC-MS (ESI): 318.0 $[M - H]^-$, HRMS (ESI): calcd for $C_{17}H_{18}FNO_4Na$, 342.1118 m/z $[M + Na]^+$, found 342.1118. $[\alpha]_D^{25}$ = +21.0 (c 0.10, MeOH).

(*S*)-3-(4-Cyanophenoxy)-2-((4-methoxybenzyl)amino)-propanoic acid (10o). Yield 68%, white solid, m.p. 170–174 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.79 (d, J = 8.6 Hz, 2H), 7.39 (d, J = 8.6 Hz, 2H), 7.12 (d, J = 8.7 Hz, 2H), 6.94 (d, J = 8.7 Hz, 2H), 4.43 (m, 2H), 4.08 (AB q, J = 13.0 Hz, 2H), 3.90 (m, 1H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.7, 161.2, 159.4, 134.2 (2C), 131.3 (2C), 125.1, 119.0, 115.7 (2C), 113.9 (2C), 103.4, 67.0, 58.5, 55.1, 49.4. LC-MS (ESI): 325.4 $[M + H]^+$, HRMS (ESI): calcd for $C_{18}H_{18}N_2NaO_4$, 349.1164 m/z $[M + Na]^+$, found 349.1164. $[\alpha]_D^{25}$ = +25.0 (c 0.1006, MeOH).

(*S*)-2-((4-Methoxybenzyl)amino)-3-(octyloxy)-propanoic acid (10q). Yield 16%; white solid, m.p. 182–184 °C; ^{1}H NMR (400 MHz, MeOD): δ 7.40 (d, J = 8.6 Hz, 2H), 6.97 (d, J = 8.6 Hz, 2H), 4.19 (s, 2H), 3.83–3.79 (m, 2H), 3.64–3.61 (m, 1H), 3.45 (t, J = 6.6 Hz, 2H), 1.59–1.54 (m, 2H), 1.29 (m, 10H), 0.89 (t, J = 6.4, 3H), ^{13}C NMR (100 MHz, MeOD + $CDCl_3$): δ 169.7, 160.9, 131.5 (2C), 123.4, 114.4 (2C), 71.6, 68.4, 60.9, 54.8, 31.9, 29.5, 29.4, 29.3, 26.1, 22.6, 13.4. LC-MS (ESI): 336.2 $[M - H]^-$, HPLC analysis: Cellulose-2 (4.6 × 250 mm) 5μ, (MeOH) containing 20% CO_2, 1.999 mL min^{-1}, 232 nm, tr (major) 2.48, tr (minor) 3.1, >99% ee; HRMS (ESI): calcd for $C_{19}H_{31}NO_4Na$, 360.2151 m/z $[M + Na]^+$, found 360.2151. From D-serine: HPLC analysis: Cellulose-2 (4.6 × 250 mm) 5μ, (MeOH) containing 20% CO_2, 1.999 mL min^{-1}, 232 nm, tr (major) 3.11, tr (minor) 2.49, >99% ee.

Acknowledgements

We thank DBT (BIPP), New Delhi (sanction no. 102/IFD/SAN/1191/2009-2010) for providing financial support. The authors are thankful to the referees for their constructive scientific comments and suggestions.

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