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Efficient synthesis of protected sulfonopeptides from *N*-protected 2-aminoalkyl xanthates and thioacetates

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ABSTRACT

An efficient and convenient method was developed for the synthesis of protected sulfonopeptides via *N*-chlorosuccimide (NCS)/HCl oxidative chlorination of *N*-protected 2-aminoalkyl xanthates or thioacetates to the corresponding sulfonyl chlorides followed by aminolysis with amino esters. In the current method, sulfonopeptides containing 1- and 2-substituted taurines were prepared in satisfactory to good yields. It is a useful and efficient strategy for the synthesis of protected sulfonopeptides with functionalized side-chains.

1. Introduction

Peptides are important biological substances and have been widely used as drugs and prodrugs. However, their rapid enzymatic degradation in human body is one of their intrinsic properties that limit their utilization. Thus, different peptidomimetics, including peptides with D-amino acid residues, peptides containing non-coded amino acid residues, β-peptides, phosphonopeptides, and sulfonopeptides, have been developed.[1] Sulfonopeptides are one of the important peptidomimetics and show an abundant structural diversity[2] because α-aminoalkanesulfonic acids and their derivatives are unstable[3] and β-aminoalkanesulfonic acids are applied as building blocks in the synthesis of sulfonopeptides. β-Aminoalkanesulfonic acids can be 1-substituted or 2-substituted taurines as different sulfur analogs of naturally occurring amino acids and structurally diverse substituted taurines have been prepared efficiently.[4,5]

Sulfonopeptides are more stable analogs of naturally occurring or synthetic peptides than phosphonopeptides and have been used as enzyme inhibitors as well. The sulfonopeptides have been generally prepared via the reaction of *N*-protected aminoalkanesulfonyl chlorides and amino acid esters or peptide esters,[6] via the condensation of *N*-protected aminoalkanesulfinyl chlorides and amino esters or peptide esters followed by subsequent oxidation,[4e,f,7] or via the Mannich-type reaction of *N*-protected 2-aminoalkanesulfonamides, aldehydes, and aryldichlorophosphines, and subsequent aminolysis with amino esters.[8] Among the above mentioned methods, the sulfonyl chloride method is more practical one and has been widely applied in the synthesis of sulfonopeptides.

Generally, sulfonyl chlorides were prepared from the corresponding sulfonic acids via chlorination with thionyl chloride,[2b] oxalyl chloride,[8] phosgene,[6c] phosphorus pentachloride.[9] The reaction conditions are too harsh so that some protecting groups and functionalized groups in the side-chains of amino acids cannot survive during the chlorination. An alternative mild method for the synthesis of sulfonyl chlorides uses the corresponding disulfides as starting materials via chlorination with toxic gaseous chlorine in acetic anhydride[7] or in carbon tetrachloride.[6b,10] Both of these two methods are not convenient.

Recently, we worked on the synthesis of substituted taurines as sulfur analogs of naturally occurring amino acids and have developed several efficient routes to prepare structurally diverse substituted taurines.[5] Very recently, we synthesized 1-substituted taurines with different functionalized side-chains via the radical addition of various xanthates to *N*-allylphthalimide and subsequent oxidation with performic acid.[11] Herein, we reported the efficient and convenient synthesis of protected sulfonopeptides via the NCS/HCl oxidative chlorination of xanthates or thioacetates to the

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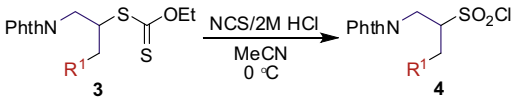
corresponding sulfonyl chlorides and subsequent aminolysis with amino esters.

2. Results and discussion

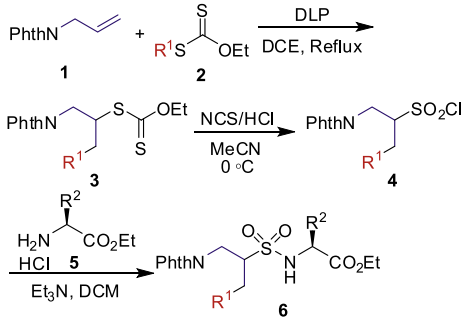
Firstly, different xanthates **2** and *N*-allylphthalimide (**1**) underwent radical addition with dilauroyl peroxide (DLP) as a radical initiator in refluxing 1,2-dichloroethane (DCE) to afford *S*-2-phthalimidoethyl xanthate derivatives **3** in good to excellent yields,[11] which were readily oxidized to the corresponding *N*-phthalimido-1-substituted ethanesulfonyl chlorides **4** in good to excellent yields with *N*-chlorosuccimide (NCS) and 2 mol/L hydrochloric acid in acetonitrile at 0 °C under Nishiguchi's conditions (Table 1).[12] The results indicate that steric bulky xanthates **3d** and **3i** generated the corresponding sulfonyl chlorides **4d** and **4i** in relative low yields (Table 1, entries 4 and 9) (Scheme 1).

Table 1
Synthesis of sulfonyl chlorides



Entry	Xanthate **3**	R^1	Chloride **4**	Isolated yield (%)
1	**3a**	$BnCH_2$	**4a**	83
2	**3b**	MeO_2C	**4b**	83
3	**3c**	EtO_2C	**4c**	95
4	**3d**	$(EtO_2C)_2CH$	**4d**	63
5	**3e**	$AcCH_2$	**4e**	84
6	**3f**	$PhCOCH_2$	**4f**	94
7	**3g**	$NCCH_2$	**4g**	84
8	**3h**	$C_4H_6O_2$[a]	**4h**	98
9	**3i**	$PhthNCH_2$	**4i**	60

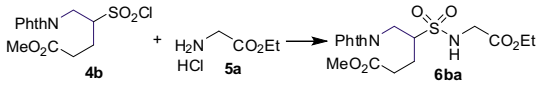
[a] 2-Oxotetrahydrofuran-3-yl.



Scheme 1. Synthesis of *N*-protected 2-aminoalkanesulfonopeptides **6**.

The reaction of 5-methoxyl-5-oxo-1-*N*-phthalimidopentane-2-sulfonyl chloride (**4b**) and ethyl glycinate hydrochloride (**5a**) was selected as a model reaction to optimize the synthetic conditions of protected sulfonopeptides **6**. It generated the desired sulfonopeptide **6ba** in 78% yield in the presence of triethylamine as a base in dichloromethane (DCM) when **4b** and **5a** were mixed and stirred for 12 h at room temperature (approximate 35 °C) (Table 2, entry 1). The yield was decreased from 78% to 42% when triethylamine was instead with potassium carbonate (Table 2, entry 2). Different solvents (such as THF, MeCN, and acetone) were evaluated. However, lower yields were obtained in all cases (Table 2, entries 3–5), indicating that DCM is suitable solvent and triethylamine is good base for the reaction. The yield was improved to 87% when sulfonyl chloride **4b** and ethyl glycinate hydrochloride (**5a**) were mixed at 0 °C and the resulting mixture was stirred for 12 h and allowed to warm to room temperature (Table 2, entry 6). No obvious effect was

Table 2
Optimizing reaction conditions for the synthesis of sulfonopeptide **6ba**[a]



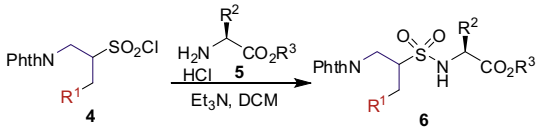
Entry	Solvent	Base	Time (h)	Temp (°C)	Yield[b] (%)
1	DCM	Et_3N	12	35	78
2	DCM	K_2CO_3	12	35	42
3	THF	Et_3N	12	35	59
4	MeCN	Et_3N	12	35	73
5	Me_2CO	Et_3N	12	35	61
6	DCM	Et_3N	12	0–35[c]	87
7	DCM	Et_3N	24	0–35[c]	86
8	DCM	Et_3N	6	0–35[c]	54

[a] Reaction was conducted with sulfonyl chloride **4b** (1 mmol), GlyOEt·HCl **5a** (1 mmol), and base (2.2 mmol).
[b] Isolated yield.
[c] Reaction was conducted at 0 °C and allowed to warm to 35 °C.

observed when the reaction time was extended to 24 h (Table 2, entry 7). However, the yield decreased from 87% to 54% when the reaction was shortened from 12 h to 6 h (Table 2, entry 8). The results reveal that it is optimal conditions that sulfonyl chloride and amino ester are mixed under stirring in the presence of triethylamine in DCM at 0 °C and the resulting mixture is further stirred for 12 h and allowed to warm to room temperature. In the current method, sulfonopeptides with functionalized side-chains were synthesized from simple starting materials.

Under the optimal conditions, a series of sulfonopeptides **6** was prepared from various *N*-protected 2-aminoalkanesulfonyl chlorides **4** with different functional groups, including ketone, ester, lactone, cyano, and imido groups, in their side-chains and amino ester hydrochlorides **5** (Table 3). The results indicate that different sulfonyl chlorides **4** show similar reactivity (Table 3). However, the product yield obviously depends on the steric hindrance of both aminoalkanesulfonyl chlorides and amino esters (Table 3, entries 4, and 8–14). Reactions of sulfonyl chlorides **4**, except for **4d**, **4h**, and **4i**, and ethyl glycinate hydrochloride show higher yields than reactions involving more steric sulfonyl chlorides (**4d**, **4h**, and **4i**) and amino esters salts, such as methyl (*S*)-2-alaninate (**5b**), ethyl (*S*)-phenylalaninate hydrochloride (**5c**), ethyl (*S*)-tyrosinate hydrochloride (**5d**), and methyl (*S*)-leucinate hydrochloride (**5e**). For sulfonopeptides involving sulfonyl chloride **4h** or optically pure amino esters **5b**–**e**, a pair of diastereomeric sulfonopeptides were

Table 3
Synthesis of sulfonopeptides **6**

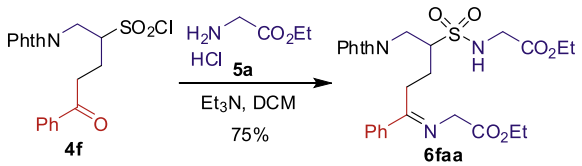


Entry	Chloride **4**	AA **5**	R^2	R^3	Peptide **6**	Yield[a] (%)	dr[b]
1	**4a**	**5a**	H	Et	**6aa**	81	
2	**4b**	**5a**	H	Et	**6ba**	87	
3	**4c**	**5a**	H	Et	**6ca**	77	
4	**4d**	**5a**	H	Et	**6da**	55	
5	**4e**	**5a**	H	Et	**6ea**	82	
6	**4f**	**5a**	H	Et	**6fa**	82	
7	**4g**	**5a**	H	Et	**6ga**	79	
8	**4h**	**5a**	H	Et	**6ha**	65	60:40
9	**4i**	**5a**	H	Et	**6ia**	58	
10	**4b**	**5b**	Me	Me	**6bb**	61	50:50
11	**4b**	**5c**	Bn	Et	**6bc**	56	54:46
12	**4b**	**5d**	4-$HOC_6H_4CH_2$	Et	**6bd**	60	50:50
13	**4b**	**5e**	Me_2CHCH_2	Me	**6be**	65	61:39
14	**4c**	**5d**	4-$HOC_6H_4CH_2$	Et	**6cd**	54	58:42

[a] Isolated yield.
[b] Determined on the basis of the integration of the ^1H NMR spectrum.

obtained in each of cases. For optically pure (*S*)-amino esters **5b**–**e**, (*R*,*S*)-diastereomers of the sulfonopeptides are major products due to kinetic preference in the coupling reaction. On the basis of the integration of their ^{1}H NMR spectra, diastereomeric ratios were determined and no obvious stereoselectivity was observed because the chiral center is too far away from the reactive center of sulfonyl chlorides.

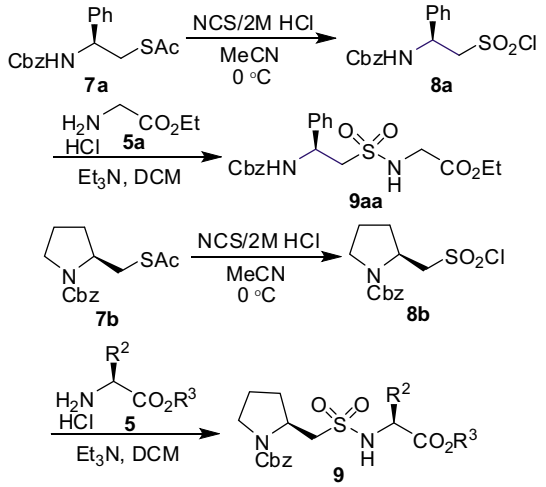
When the reaction of sulfonyl chloride **4f** and ethyl glycinate hydrochloride (**5a**) was conducted in a molar ratio of 1:2 (**4f**:**5a**), the first molecule of glycinate displaced the chloride in the sulfonyl group, while the second molecule of glycinate condensed with the keto group in the side-chain of the sulfonyl chloride to generate a sulfonopeptide **6faa** with an imino functionalized side-chain in 75% yield (Scheme 2).



Scheme 2. Synthesis of *N*-protected 2-aminoalkane-sulfonopeptide **6faa** with an imino functionalized side-chain.

After successful synthesis of sulfonopeptides from xanthates, we extended the method to 2-(*N*-Cbz protected amino)alkyl thioacetates **7**, which can be readily prepared from naturally occurring or synthetic optically active amino acids via the sodium borohydride–iodine reduction, Cbz protection, and esterification with thiolacetic acid.[5g] Thioacetates **7** were oxidized to the corresponding sulfonyl chlorides **8** in good yields with NCS/HCl, which were directly, without further purification, reacted with amino esters hydrochlorides **5** to afford sulfonopeptides **9** in good to excellent yields. Similarly, steric hindrance of both sulfonyl chlorides **8** and amino esters **5** affects the yield obviously. The current synthetic route provides an efficient pathway to prepare optically active sulfonopeptides as well from simple starting materials (Table 4).

Table 4
Synthesis of sulfonopeptides **9** from thioacetates **7**[a]



Entry	Thioacetate **7**	Chloride **8**	Yield (%)	AA **5**	Peptide **9**	Yield[b] (%)
1	**7a**	**8a**	87	**5a**	**9aa**	93
2	**7b**	**8b**	82	**5a**	**9ba**	85
3	**7b**	**8b**		**5c**	**9bc**	81
4	**7b**	**8b**		**5d**	**9bd**	73
5	**7b**	**8b**		**5e**	**9be**	60

[a] Reaction was conducted with sulfonyl chloride **8** (1 mmol), AAOEt·HCl **5** (1 mmol), and Et_3N (2.2 mmol).
[b] Isolated yield.

3. Conclusion

In conclusion, a series of protected sulfonopeptides with various functionalized side-chains were synthesized in good to excellent yields via the NCS/HCl oxidative chlorination of xanthates or thioacetates and subsequent aminolysis with amino esters. Sulfonopeptides containing α- and β-substituted taurine residues were prepared from xanthates and thioacetates, respectively. The current synthetic route is an efficient and convenient method for synthesis of protected sulfonopeptides from simple starting materials.

4. Experimental section

4.1. General

Melting points were determined on a melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 400 MHz in $CDCl_3$ with TMS as internal standard. ^{13}C NMR spectra were recorded at 100.6 MHz in $CDCl_3$ with $CDCl_3$ as internal standard. IR spectra were determined directly. HRMS spectra were performed on an LC/MSD TOF mass spectrometer. TLC analysis was performed on glass pre-coated silica gel plate. Spots were visualized with UV light or iodine. Column chromatography was performed on silica gel. Dichloromethane was refluxed with calcium hydride and freshly distilled prior to use.

4.2. General procedure for the synthesis of sulfonyl chlorides 4 with NCS/HCl as oxidants

NCS (4–4.67 g, 30–35 mmol) was dissolved in a mixture of 2 M HCl (6 mL) and MeCN (30 mL). The resulting solution was cooled to 10 °C. A solution of xanthate **3** (5 mmol) in MeCN (5 mL) was added dropwise to the cooled solution at 0 °C. The resulting solution was stirred at the same temperature for 15 min, and then diluted with isopropyl ether (25 mL). The organic layer was washed with aq NaCl (12%, 3×25 mL) and then dried over anhydrous Na_2SO_4. After concentration in vacuo, the crude residue was purified by flash column chromatography, eluting with ethyl acetate and petroleum ether (EA/PE) (0:10–1:10, *v*/*v*), to afford pure sulfonyl chloride **4** as colorless solid.

*4.2.1. 4-Phenyl-1-phthalimidobutane-2-sulfonyl chloride (**4a**).* Colorless solid, yield: 83%, mp 153–155 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85 (dd, J=5.4, 3.1 Hz, 2H, ArH), 7.75 (dd, J=5.4, 3.1 Hz, 2H, ArH), 7.21–7.09 (m, 5H, ArH), 4.39 (dd, J=12.6, 4.6 Hz, 1H in NCH_2), 4.10 (dddd, J=6.8, 6.7, 6.8, 4.6 Hz, 1H, SCH), 4.05 (dd, J=12.6, 6.7 Hz, 1H in NCH_2), 2.95 (ddd, J=14.1, 7.6, 6.9 Hz, 1H in CH_2), 2.89 (ddd, J=14.1, 7.6, 7.0 Hz, 1H in CH_2), 2.56 (dddd, J=14.6, 7.6, 6.9, 6.2 Hz, 1H in CH_2), 2.13 (dddd, J=14.6, 7.6, 7.0, 5.8 Hz, 1H in CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.4, 139.1, 134.4, 131.6, 128.7, 128.4, 126.6, 123.7, 70.9, 37.6, 32.5, 30.3. IR (ν_{max}, cm^{-1}) 3029.5, 2930.3, 1777.2, 1719.3, 1371.2, 1371.2, 1152.7. HRMS (ESI) calcd for $C_{18}H_{16}ClNNaO_4S$ m/z: 400.0381 $[M+Na]^+$; found 400.0372.

*4.2.2. 4-Methoxy-4-oxo-1-phthalimidobutane-2-sulfonyl chloride (**4b**).* Colorless solid, yield: 83%, mp 101–106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89 (dd, J=5.5, 3.1 Hz, 2H, ArH), 7.76 (dd, J=5.5, 3.1 Hz, 2H, ArH), 4.43 (dd, J=14.5, 6.2 Hz, 1H in CH_2N), 4.25 (dddd, J=6.9, 6.7, 6.2, 4.9 Hz, 1H, SCH), 4.05 (dd, J=14.5, 6.9 Hz, 1H in CH_2N), 3.65 (s, 3H, CH_3O), 2.76 (ddd, J=13.5, 7.9, 6.9 Hz, 1H in CH_2), 2.68 (ddd, J=13.5, 7.2, 6.2 Hz, 1H in CH_2), 2.43 (dddd, J=15.4, 6.9, 6.7, 6.2 Hz, 1H in CH_2), 2.21 (dddd, J=15.4, 7.9, 7.2, 4.9 Hz, 1H in CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.1, 167.6, 134.4, 131.6, 123.7, 70.9, 51.9, 37.6, 30.3, 23.7. IR (ν_{max}, cm^{-1}) 3038.1, 2952.9, 2923.8, 2846.9, 1775.3,

1716.2, 1610.7, 1400.4, 1371.5, 1160.3. HRMS (ESI) calcd for $C_{14}H_{15}ClNO_6S$ *m/z*: 360.0303 $[M+H]^+$; found 360.0309.

*4.2.3. 4-Ethoxy-4-oxo-1-phthalimidobutane-2-sulfonyl chloride (**4c**).* Colorless solid, yield: 95%, mp 76–79 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89 (dd, *J*=5.5, 3.1 Hz, 2H, ArH), 7.77 (dd, *J*=5.5, 3.1 Hz, 2H, ArH), 4.44 (dd, *J*=14.5, 6.3 Hz, 1H in CH_2N), 4.27 (dddd, *J*=6.8, 6.6, 6.3, 5.2 Hz, 1H, SCH), 4.12 (dq, *J*=10.7, 7.1 Hz, 1H in CH_2O), 4.08 (dq, *J*=10.7, 7.1 Hz, 1H in CH_2O), 4.05 (dd, *J*=14.5, 6.8 Hz, 1H in CH_2N), 2.74 (ddd, *J*=16.0, 7.6, 6.8 Hz, 1H in CH_2), 2.66 (ddd, *J*=16.0, 7.6, 6.6 Hz, 1H in CH_2), 2.43 (dddd, *J*=14.4, 6.8, 6.6, 6.6 Hz, 1H in CH_2), 2.20 (dddd, *J*=14.4, 7.6, 7.6, 5.2 Hz, 1H in CH_2), 1.21 (t, *J*=7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.6, 167.6, 134.4, 131.6, 123.7, 70.9, 60.9, 37.6, 30.5, 23.7, 14.1. IR (ν_{max}, cm^{-1}) 3034.6, 2926.7, 1775.5, 1717.4, 1641.2, 1400.4, 1371.3, 1160.4. HRMS (ESI) calcd for $C_{15}H_{17}ClNO_6S$ *m/z*: 374.0460 $[M+H]^+$; found 374.0415.

*4.2.4. 4-Ethoxy-3-ethoxycarbonyl-4-oxo-1-phthalimidobutane-2-sulfonyl chloride (**4d**).* Colorless solid, yield: 63%, mp 61–66 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.91 (dd, *J*=5.0, 3.0 Hz, 2H, ArH), 7.71 (dd, *J*=5.0, 3.0 Hz, 2H, ArH), 4.43 (dd, *J*=14.3, 5.9 Hz, 1H in CH_2N), 4.31 (dddd, *J*=7.1, 6.8, 5.9, 4.4 Hz, 1H, CHS), 4.24–4.22 (m, 2H, CH_2O), 4.18 (q, *J*=7.1 Hz, 2H, CH_2O), 4.09 (dd, *J*=14.3, 7.1 Hz, 1H, CH_2N), 3.88 (dd, *J*=9.6, 5.8 Hz, 1H, CH), 2.69 (ddd, *J*=15.1, 6.8, 5.8 Hz, 1H in CH_2), 2.42 (ddd, *J*=15.1, 9.6, 4.4 Hz, 1H in CH_2), 1.27 (t, *J*=7.1, 3H, CH_3), 1.25 (t, *J*=7.1, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.0, 167.7, 167.5, 134.4, 131.6, 123.7, 69.3, 62.14, 62.11, 48.9, 37.9, 27.4, 13.92, 13.89. IR (ν_{max}, cm^{-1}) 2978.3, 2933.4, 1777.2, 1719.3, 1469.8, 1370.9, 1159.1. HRMS (ESI) calcd for $C_{18}H_{20}ClNNaO_8S$ *m/z*: 468.0490 $[M+Na]^+$; found 468.0492.

*4.2.5. 5-Oxo-1-phthalimidohexane-2-sulfonyl chloride (**4e**).* Colorless solid, yield: 84%, mp 107–109 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89 (dd, *J*=5.5, 3.1 Hz, 2H, ArH), 7.77 (dd, *J*=5.5, 3.1 Hz, 2H, ArH), 4.41 (dd, *J*=14.3, 5.8 Hz, 1H in CH_2N), 4.19 (dddd, *J*=7.6, 7.3, 6.5, 5.8 Hz, 1H, SCH), 4.04 (dd, *J*=14.3, 7.3 Hz, 1H in CH_2N), 2.91 (ddd, *J*=14.7, 7.4, 7.3 Hz, 1H in CH_2), 2.81 (ddd, *J*=14.7, 6.3, 6.1 Hz, 1H in CH_2), 2.29 (dddd, *J*=15.3, 7.3, 6.5, 6.1 Hz, 1H in CH_2), 2.20 (dddd, *J*=15.3, 7.6, 7.4, 6.3 Hz, 1H in CH_2), 2.15 (s, 3H, CH_3CO). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.3, 167.6, 134.4, 131.6, 123.7, 71.1, 39.3, 37.6, 29.8, 22.1. IR (ν_{max}, cm^{-1}) 2922.8, 1774.8, 1716.8, 1400.3, 1370.1, 1158.2. HRMS (ESI) calcd for $C_{14}H_{14}ClNNaO_5S$ *m/z*: 366.0173 $[M+Na]^+$; found 366.0172.

*4.2.6. 5-Oxo-5-phenyl-1-phthalimidopentane-2-sulfonyl chloride (**4f**).* Colorless solid, yield: 92%, mp 189–192 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.90 (d, *J*=7.2 Hz, 2H, ArH_{ortho}), 7.89 (dd, *J*=5.5, 3.1 Hz, 2H, ArH), 7.76 (dd, *J*=5.4, 3.1 Hz, 2H, ArH), 7.58 (dd, *J*=7.6, 7.4 Hz, 1H, ArH_{para}), 7.44 (dd, *J*=7.6, 7.2 Hz, 2H, ArH_{meta}), 4.46 (dd, *J*=14.3, 5.8 Hz, 1H in CH_2N), 4.31 (dddd, *J*=7.3, 6.8, 5.8, 4.6 Hz, 1H, SCH), 4.14 (dd, *J*=14.3, 7.3 Hz, 1H in CH_2N), 3.45 (ddd, *J*=14.6, 7.8, 6.9 Hz, 1H in CH_2), 3.35 (ddd, *J*=14.6, 6.7, 6.6 Hz, 1H in CH_2), 2.49 (dddd, *J*=15.6, 6.9, 6.8, 5.8 Hz, 1H in CH_2), 2.41 (dddd, *J*=15.6, 7.8, 6.7, 4.6 Hz, 1H in CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.7, 167.7, 136.1, 134.4, 133.5, 131.7, 128.6, 127.9, 123.7, 71.3, 37.8, 34.7, 22.6. IR (ν_{max}, cm^{-1}) 3038.1, 2922.8, 1772.3, 1714.7, 1369.9, 1154.2. HRMS (ESI) calcd for $C_{19}H_{16}ClNNaO_5S$ *m/z*: 428.0330 $[M+Na]^+$; found 428.0304.

*4.2.7. 4-Cyano-1-phthalimidobutane-2-sulfonyl chloride (**4g**).* Colorless solid, yield: 80%, mp 122–125 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.90 (dd, *J*=5.5, 3.1 Hz, 2H, ArH), 7.79 (dd, *J*=5.5, 3.1 Hz, 2H, ArH), 4.46 (dd, *J*=14.5, 5.6 Hz, 1H in CH_2N), 4.19 (dddd, *J*=7.7, 7.1, 5.6, 4.8 Hz, 1H, CHS), 4.08 (dd, *J*=14.5, 7.1 Hz, 1H in CH_2N), 2.83 (ddd, *J*=14.4, 8.0, 6.1 Hz, 1H in CH_2CN), 2.74 (ddd, *J*=14.4, 7.9, 7.7 Hz, 1H in CH_2CN), 2.51 (dddd, *J*=15.6, 7.9, 7.7, 6.1 Hz, 1H in CH_2), 2.28 (dddd, *J*=15.6, 8.0, 7.7, 4.8 Hz, 1H in CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.5, 134.7, 131.4, 123.9, 117.6, 70.4, 37.3, 24.8, 15.1. IR (ν_{max}, cm^{-1}) 3020.8, 2923.8, 2251.3, 1774.7, 1717.6, 1620.4, 1400.9, 1371.1, 1159.6. HRMS (ESI) calcd for $C_{13}H_{12}ClN_2O_4S$ *m/z*: 327.0201 $[M+H]^+$; found 327.0202.

*4.2.8. 3-(2-Oxotetrahydrofuran-3-yl)-1-phthalimidopropane-2-sulfonyl chloride (**4h**).* Colorless solid, yield: 98%, mp 164–167 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89 (dd, *J*=5.3, 3.1 Hz, 2H, ArH), 7.76 (dd, *J*=5.3, 3.1 Hz, 2H, ArH), 4.58–4.51 (m, 1H in CH_2O), 4.49 (dd, *J*=14.2, 5.6 Hz, 1H in CH_2N), 4.39–4.35 (m, 1H in CH_2O), 4.21 (dddd, *J*=6.7, 6.0, 5.6, 2.9 Hz, 1H, CHS), 4.04 (dd, *J*=14.2, 6.7 Hz, 1H in CH_2N), 2.99 (dddd, *J*=11.9, 7.3, 6.5, 4.6 Hz, 1H, CHCO), 2.59 (ddd, *J*=13.9, 7.3, 6.0 Hz, 1H in CH_2CS), 2.38 (dddd, *J*=15.4, 6.6, 6.5, 6.4 Hz, 1H in CH_2CO) 2.24 (dddd, *J*=15.4, 7.2, 4.7, 4.6 Hz, 1H in CH_2CO), 2.02 (ddd, *J*=13.9, 11.2, 2.9 Hz, 1H in CH_2CS). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.4, 167.6, 134.6, 131.5, 123.9, 69.5, 66.4, 37.4, 36.3, 29.3, 28.9. IR (ν_{max}, cm^{-1}) 2917.4, 1768.5, 1718.3, 1370.4, 1160.1. HRMS (ESI) calcd for $C_{15}H_{14}ClNNaO_6S$ *m/z*: 394.0123 $[M+Na]^+$; found 394.0124.

*4.2.9. 1,4-Diphthalimidobutane-2-sulfonyl chloride (**4i**).* Colorless solid, yield: 60%, mp 166–169 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.71 (dd, *J*=5.5, 3.1 Hz, 4H, ArH), 7.64 (dd, *J*=5.5, 3.1 Hz, 4H, ArH), 4.46 (dd, *J*=14.2, 6.1 Hz, 1H in CH_2N), 4.22 (dddd, *J*=6.6, 6.3, 6.2, 6.1 Hz, 1H, CHS), 4.14 (dd, *J*=14.2, 6.6 Hz, 1H in CH_2N), 3.99 (t, *J*=6.7 Hz, 2H, CH_2N), 2.65 (dddd, *J*=13.1, 6.7, 6.7, 6.2 Hz, 1H in CH_2), 2.23 (dddd, *J*=13.1, 6.7, 6.7, 6.3 Hz, 1H in CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.9, 167.4, 134.4, 134.1, 131.6, 131.4, 123.6, 123.3, 69.4, 37.5, 35.1, 27.5. IR (ν_{max}, cm^{-1}) 2955.9, 2923.8, 1780.4, 1715.5, 1370.9, 1159.1. HRMS (ESI) calcd for $C_{20}H_{15}ClN_2NaO_6S$ *m/z*: 469.0232 $[M+Na]^+$; found 469.0231.

4.3. General procedure for the synthesis of protected sulfonopeptides 6

A solution of sulfonyl chloride **4** (1.0 mmol) in 2 mL of DCM was added dropwise to a solution of amino ester hydrochloride salt **5** (1.0 mmol) and Et_3N (222 mg, 2.2 mmol) in 2 mL of DCM under N_2 atmosphere in an ice-water bath. The resulting mixture was stirred overnight and allowed to warm to rt. After dilution with DCM (10 mL), the mixture was washed with ice cooled 2 M HCl (2×10 mL), brine (2×10 mL), and saturated Na_2CO_3 (2×10 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography (DCM/MeOH 100:1–50:1, *v*/*v*) to afford sulfonopeptide **6**.

*4.3.1. Ethyl N-(4-phenyl-1-phthalimidobutane-2-sulfonyl)glycinate (**6aa**).* Colorless solid, yield: 81%, mp 156–159 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.96 (d, *J*=7.3 Hz, 2H, ArH_{ortho}), 7.85 (dd, *J*=5.5, 3.1 Hz, 2H, ArH), 7.73 (dd, *J*=5.5, 3.1 Hz, 2H, ArH), 7.56 (dd, *J*=7.6, 7.6 Hz, 1H, ArH_{para}), 7.45 (dd, *J*=7.6, 7.3 Hz, 2H, ArH_{meta}), 5.82 (dd, *J*=6.0, 5.6 Hz, 1H, NH), 4.30 (dd, *J*=14.9, 6.0 Hz, 1H in NCH_2), 4.28 (dd, *J*=14.9, 6.3 Hz, 1H in NCH_2), 4.22 (q, *J*=7.1 Hz, 2H, CH_2O), 4.09 (dd, *J*=18.3, 6.0 Hz, 1H in CH_2N), 4.00 (dd, *J*=18.3, 5.6 Hz, 1H in CH_2N), 3.61 (dddd, *J*=6.5, 6.3, 6.3, 6.0 Hz, 1H, SCH), 3.47 (ddd, *J*=18.2, 7.1, 6.8 Hz, 1H in CH_2), 3.33 (ddd, *J*=18.2, 6.7, 6.2 Hz, 1H in CH_2), 2.37 (dddd, *J*=14.7, 6.8, 6.7, 6.5 Hz, 1H in CH_2), 2.25 (dddd, *J*=14.7, 7.1, 6.3, 6.2 Hz, 1H in CH_2), 1.29 (t, *J*=7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.7, 169.9, 168.6, 136.6, 134.2, 133.2, 131.8, 128.6, 128.0, 123.6, 61.9, 60.1, 44.6, 37.3, 35.3, 21.7, 14.1. IR (ν_{max}, cm^{-1}) 3311.4, 2983.7, 2939.9, 1773.6, 1715.9, 1620.3, 1370.6, 1143.8. HRMS (ESI) calcd for $C_{22}H_{25}N_2O_6S$ *m/z*: 445.1428 $[M+H]^+$; found 445.1429.

*4.3.2. Ethyl N-(5-methoxy-5-oxo-1-phthalimidopentane-2-sulfonyl) glycinate (**6ba**).* Colorless solid, yield: 87%, mp 138–139 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85 (dd, *J*=5.3, 3.1 Hz, 2H, ArH), 7.73 (dd, *J*=5.3, 3.1 Hz, 2H, ArH), 5.85 (dd, *J*=6.0, 5.4 Hz, 1H, NH), 4.25 (dd, *J*=15.1,

6.2 Hz, 1H in CH_2N), 4.22 (q, J=7.1 Hz, 2H, OCH_2), 4.20 (dd, J=15.1, 5.1 Hz, 1H in CH_2N), 4.09 (dd, J=18.4, 6.0 Hz, 1H in CH_2N), 3.99 (dd, J=18.4, 5.4 Hz, 1H in CH_2N), 3.67 (s, 3H, OCH_3), 3.53 (dddd, J=6.2, 6.0, 5.8, 5.4 Hz, 1H, CHS), 2.77 (ddd, J=16.8, 7.2, 6.8 Hz, 1H in CH_2), 2.66 (ddd, J=16.8, 7.2, 6.4 Hz, 1H in CH_2), 2.29 (dddd, J=14.4, 6.8, 6.4, 5.8 Hz, 1H in CH_2), 2.01 (dddd, J=14.4, 7.2, 7.2, 6.0 Hz, 1H in CH_2), 1.30 (t, J=7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.9, 169.9, 168.5, 134.2, 131.8, 123.6, 61.8, 60.0, 51.7, 44.5, 36.9, 30.8, 22.6, 14.1. IR (ν_{max}, cm^{-1}) 3301.8, 2984.7, 1772.6, 1713.4, 1594.3, 1398.2, 1141.2. HRMS (ESI) calcd for $C_{18}H_{22}N_2NaO_8S$ m/z: 449.0989 $[M+Na]^+$; found 449.0992.

*4.3.3. Ethyl N-(5-ethoxy-5-oxo-1-phthalimidopentane-2-sulfonyl) glycinate (**6ca**).* Colorless solid, yield: 77%, mp 159–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85 (dd, J=5.4, 3.1 Hz, 2H, ArH), 7.73 (dd, J=5.4, 3.1 Hz, 2H, ArH), 5.85 (dd, J=6.2, 5.4 Hz, 1H, NH), 4.25 (dd, J=14.9, 6.1 Hz, 1H in CH_2N), 4.22 (q, J=7.1 Hz, 2H, OCH_2), 4.21 (dd, J=15.1, 5.1 Hz, 1H in CH_2N), 4.12 (q, J=7.1 Hz, 2H, OCH_2), 4.09 (dd, J=18.3, 6.2 Hz, 1H in CH_2N), 3.99 (dd, J=18.3, 5.4 Hz, 1H in CH_2N), 3.54 (dddd, J=7.6, 6.9, 6.9, 6.1 Hz, 1H, CHS), 2.75 (ddd, J=14.9, 7.6, 7.4 Hz, 1H in CH_2), 2.64 (ddd, J=14.9, 7.3, 7.1 Hz, 1H in CH_2), 2.29 (dddd, J=14.4, 7.6, 7.3, 6.9 Hz, 1H in CH_2), 2.03 (dddd, J=14.4, 7.6, 7.4, 7.1 Hz, 1H in CH_2), 1.29 (t, J=7.1 Hz, 3H, CH_3), 1.25 (t, J=7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.5, 169.9, 168.6, 134.2, 131.8, 123.6, 61.8, 60.7, 60.1, 44.5, 36.9, 31.1, 22.7, 14.12, 14.07. IR (ν_{max}, cm^{-1}) 3295.4, 2923.8, 1770.8, 1735.4, 1718.5, 1709.8, 1649.1, 1326.4, 1208.6, 1141.4. HRMS (ESI) calcd for $C_{19}H_{25}N_2O_8S$ m/z: 441.1326 $[M+H]^+$; found 441.1326.

*4.3.4. Ethyl N-(5-ethoxy-4-ethoxycarbonyl-5-oxo-1-phthalimidopentane-2-sulfonyl)glycinate (**6da**).* Colorless solid, yield: 55%, mp 89–91 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85 (dd, J=5.5, 3.1 Hz, 2H, ArH), 7.73 (dd, J=5.5, 3.1 Hz, 2H, ArH), 5.90–5.79 (s, br, 1H, NH), 4.25 (dd, J=13.8, 6.7 Hz, 1H in CH_2N), 4.22 (q, J=7.1 Hz, 6H, $3OCH_2$), 4.19 (dd, J=13.8, 6.9 Hz, 1H in CH_2N), 4.14–4.02 (m, 2H, CH_2N), 3.96 (dd, J=8.1, 6.8 Hz, 1H, CH), 3.58 (dddd, J=6.9, 6.9, 6.7, 6.0 Hz, 1H, CHS), 2.51 (ddd, J=14.6, 6.9, 6.8 Hz, 1H in CH_2), 2.31 (ddd, J=14.6, 8.1, 6.0 Hz, 1H in CH_2), 1.29 (t, J=7.1 Hz, 3H, CH_3), 1.26 (t, J=7.1 Hz, 6H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ: 169.9, 168.67, 168.63, 168.5, 134.2, 131.8, 123.6, 61.9, 61.8, 61.7, 58.6, 49.2, 44.6, 37.2, 26.5, 14.1, 13.94, 13.93. IR (ν_{max}, cm^{-1}) 3304.9, 2981.5, 2933.5, 1780.4, 1717.6, 1639.1, 1398.2, 1141.8. HRMS (ESI) calcd for $C_{22}H_{28}N_2NaO_{10}S$ m/z: 535.1357 $[M+Na]^+$; found 535.1356.

*4.3.5. Ethyl N-(5-oxo-1-phthalimidohexane-2-sulfonyl)glycinate (**6ea**).* Colorless oil, yield: 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85 (dd, J=5.2, 3.3 Hz, 2H, ArH), 7.73 (dd, J=5.5, 3.1 Hz, 2H, ArH), 5.82 (dd, J=5.9, 5.6 Hz, 1H, NH), 4.23 (dd, J=14.9, 4.1 Hz, 1H in CH_2N), 4.22 (q, J=7.1 Hz, 2H, OCH_2), 4.15 (dd, J=14.9, 5.2 Hz, 1H in CH_2N), 4.07 (dd, J=18.4, 5.9 Hz, 1H in CH_2N), 3.99 (dd, J=18.4, 5.6 Hz, 1H in CH_2N), 3.48 (dddd, J=7.1, 6.9, 5.2, 4.1 Hz, 1H, CHS), 2.93 (ddd, J=14.6, 7.1, 6.6 Hz, 1H in CH_2), 2.77 (ddd, J=14.6, 6.9, 6.6 Hz, 1H in CH_2), 2.17 (s, 3H, CH_3CO), 2.16 (dddd, J=14.0, 7.4, 7.1, 6.6 Hz, 1H in CH_2), 2.01 (dddd, J=14.0, 6.9, 6.9, 6.6 Hz, 1H in CH_2), 1.29 (t, J=7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 207.5, 169.9, 168.5, 134.2, 131.8, 123.5, 61.8, 59.9, 44.5, 39.9, 37.1, 29.9, 21.2, 14.1. IR (ν_{max}, cm^{-1}) 3295.4, 2949.5, 1774.0, 1738.8, 1715.6, 1607.5, 1398.7, 1134.2. HRMS (ESI) calcd for $C_{18}H_{22}N_2NaO_7S$ m/z: 433.1040 $[M+Na]^+$; found 433.1042.

*4.3.6. Ethyl N-(5-oxo-5-phenyl-1-phthalimidopentane-2-sulfonyl) glycinate (**6fa**).* Colorless solid, yield: 82%, mp 128–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97 (d, J=8.0 Hz, 2H, ArH_{ortho}), 7.85 (dd, J=5.2, 3.0 Hz, 2H, ArH), 7.73 (dd, J=5.2, 3.0 Hz, 2H, ArH), 7.56 (dd, J=7.2, 7.2 Hz, 1H, ArH_{para}), 7.45 (dd, J=8.0, 7.2 Hz, 2H, ArH_{meta}), 5.83 (dd, J=6.0, 5.6 Hz, 1H, NH), 4.30 (dd, J=14.9, 6.0 Hz, 1H in CH_2N), 4.24 (dd, J=14.9, 5.3 Hz, 1H in CH_2N), 4.22 (q, J=7.1 Hz, 2H, OCH_2), 4.09 (dd, J=18.2, 6.0 Hz, 1H in CH_2N), 4.00 (dd, J=18.2, 5.6 Hz, 1H in CH_2N), 3.53 (dddd, J=6.4, 6.2, 6.0, 5.3 Hz, 1H, CHS), 3.47 (ddd, J=12.8, 7.0, 6.8 Hz, 1H in CH_2), 3.33 (ddd, J=12.8, 7.2, 6.8 Hz, 1H in CH_2), 2.37 (dddd, J=14.6, 7.0, 6.8, 6.4 Hz, 1H in CH_2), 2.25 (dddd, J=14.6, 7.2, 6.8, 6.2 Hz, 1H in CH_2), 1.29 (t, J=7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.7, 169.9, 168.6, 136.6, 134.2, 133.2, 131.8, 128.6, 128.0, 123.6, 61.9, 60.1, 44.6, 37.3, 35.3, 21.7, 14.1. IR (ν_{max}, cm^{-1}) 3304.9, 3058.4, 2920.6, 2853.4, 1772.4, 1743.9, 1712.9, 1685.3, 1594.7, 1399.2, 1140.4. HRMS (ESI) calcd for $C_{23}H_{24}N_2NaO_7S$ m/z: 495.1196 $[M+Na]^+$; found 495.1200.

*4.3.7. Ethyl N-(5-ethoxycarbonylmethylimino-5-phenyl-1-phthalimidopentane-2-sulfonyl)glycinate (**6faa**).* Colorless solid, yield: 75%, mp 117–121 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97 (d, J=8.0 Hz, 2H, ArH), 7.60–7.57 (m, 2H, ArH), 7.53 (dd, J=5.1, 3.6 Hz, 2H, ArH), 7.46–7.44 (m, 1H, ArH), 7.44–7.40 (m, 1H, ArH), 7.26–7.21 (m, 1H, ArH), 6.31 (dd, J=6.0, 5.6 Hz, 1H, NH), 4.18 (q, J=7.1 Hz, 2H, OCH_2), 4.11 (q, J=7.1 Hz, 2H, OCH_2), 4.14–4.08 (m, 2H, CH_2N), 4.02 (dd, J=18.1, 6.0 Hz, 1H in CH_2N), 4.02–3.94 (m, 2H, CH_2N), 3.79 (dd, J=14.9, 6.3 Hz, 1H in CH_2N), 3.39 (dddd, J=6.9, 6.4, 6.3, 6.2 Hz, 1H, CHS), 3.37 (ddd, J=13.8, 7.1, 6.8 Hz, 1H in CH_2), 3.28 (ddd, J=13.8, 6.9, 6.8 Hz, 1H in CH_2), 2.39 (dddd, J=14.4, 6.9, 6.8, 6.4 Hz, 1H in CH_2), 2.17 (dddd, J=14.4, 7.1, 6.8, 6.2 Hz, 1H in CH_2), 1.27 (t, J=7.1 Hz, 3H, CH_3), 1.22 (t, J=7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 199.1, 170.4, 169.85, 169.76, 168.8, 136.5, 135.1, 134.1, 133.2, 130.6, 130.2, 128.6, 128.3, 128.0, 61.7, 61.5, 61.3, 44.2, 41.9, 39.1, 35.3, 21.3, 14.1, 13.9. IR (ν_{max}, cm^{-1}) 3344.9, 3156.8, 2955.5, 2876.7, 1789.1, 1772.3, 1766.7, 1695.1, 1604.2, 1409.1, 1448.6, 1200.1. HRMS (ESI) calcd for $C_{27}H_{32}N_3O_8S$ m/z: 580.1724 $[M+Na]^+$; found 580.1735.

*4.3.8. Ethyl N-(4-cyano-1-phthalimidohexane-2-sulfonyl)glycinate (**6ga**).* Colorless solid, yield: 79%, mp 156–159 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.86 (dd, J=5.4, 3.1 Hz, 2H, ArH), 7.54 (dd, J=5.4, 3.1 Hz, 2H, ArH), 6.1 (dd, J=7.4, 4.9 Hz, 1H, NH), 4.45 (dd, J=15.3, 4.3 Hz, 1H in CH_2N), 4.23 (q, J=7.1 Hz, 2H, OCH_2), 4.17 (dd, J=15.3, 4.6 Hz, 1H in CH_2N), 4.16 (dd, J=18.5, 7.4 Hz, 1H in CH_2N), 3.99 (dd, J=18.5, 4.9 Hz, 1H in CH_2N), 3.50 (dddd, J=7.1, 7.0, 4.6, 4.3 Hz, 1H, CHS), 2.82 (t, J=7.4 Hz, 2H, CH_2CN), 2.36 (dddd, J=14.5, 7.4, 7.4, 7.1 Hz, 1H in CH_2), 2.15 (dddd, J=14.5, 7.4, 7.4, 7.0 Hz, 1H in CH_2), 1.29 (t, J=7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.1, 168.8, 134.5, 131.6, 123.7, 118.6, 61.9, 59.9, 44.5, 36.6, 23.7, 15.2, 14.0. IR (ν_{max}, cm^{-1}) 3300.2, 2975.1, 2935.8, 2251.3, 1772.3, 1712.5, 1613.9, 1398.4, 1142.6. HRMS (ESI) calcd for $C_{17}H_{19}N_3NaO_6S$ m/z: 416.0887 $[M+Na]^+$; found 416.0885.

*4.3.9. Ethyl N-[4-(2-oxo-tetrahydrofuran-3-yl)-1-phthalimidobutane-2-sulfonyl]glycinate (**6ha**).* Colorless oil, yield: 65%, (Dr 60:40). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85–7.84 (m, 4H, ArH), 5.92 (dd, J=5.8, 5.8 Hz, 1H, NH), 4.38 (dd, J=14.8, 7.6 Hz, 1H in CH_2N), 4.28 (dd, J=14.8, 6.1 Hz, 1H in CH_2N), 4.24–4.19 (m, 4H, $2CH_2O$), 4.11 (d, J=18.4 Hz, 1H in CH_2N), 4.01 (d, J=18.4 Hz, 1H in CH_2N), 3.88 (dddd, J=6.8, 6.7, 6.1, 6.1 Hz, 1H, CHS), 3.08 (dddd, J=7.9, 7.9, 7.6, 7.6 Hz, 1H, CHCO), 2.56 (dddd, J=14.6, 7.6, 7.1, 7.0 Hz, 1H in CH_2), 2.17 (dddd, J=14.6, 7.6, 7.2, 6.9 Hz, 1H in CH_2), 2.09–2.01 (m, 1H in CH_2), 1.98 (ddd, J=14.9, 7.9, 6.4 Hz, 1H in CH_2), 1.29 (t, J=7.1 Hz, 3H, CH_3). Its diastereomer δ: 7.85–7.84 (m, 4H, ArH), 6.08 (dd, J=6.0, 5.7 Hz, 1H, NH), 4.39 (dd, J=14.4, 6.8 Hz, 1H in CH_2N), 4.17 (dd, J=14.4, 6.7 Hz, 1H in CH_2N), 4.24–4.19 (m, 4H, $2CH_2O$), 4.09 (d, J=18.4 Hz, 1H in CH_2N), 4.00 (d, J=18.4 Hz, 1H in CH_2N), 3.80 (dddd, J=7.6, 6.1, 5.8, 5.3 Hz, 1H, CHS), 3.24 (dddd, J=7.6, 7.6, 7.0, 6.6 Hz, 1H, CHCO), 2.61 (dddd, J=14.9, 6.6, 6.5, 6.3 Hz, 1H in CH_2), 2.56 (dddd, J=14.9, 7.0, 6.5, 6.3 Hz, 1H in CH_2), 2.44 (ddd, J=14.9, 7.6, 6.1 1H in CH_2), 1.87 (ddd, J=14.9, 7.6, 6.1 Hz, 1H in CH_2), 1.30 (t, J=7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.6, 169.9, 168.5, 134.25, 131.71, 123.56, 66.44, 61.9, 58.7, 44.51, 36.63, 36.2, 29.1, 28.6, 14.0. Its

diastereomer δ: 178.4, 170.0, 168.8, 134.31, 131.68, 123.61, 66.49, 61.9, 58.3, 44.56, 37.2, 36.63, 29.3, 28.2, 14.0. IR (ν_{max}, cm^{-1}) 3301.7, 2978.5, 2927.3, 1768.1, 1712.7, 1612.1, 1371.4, 1141.6. HRMS (ESI) calcd for $C_{19}H_{22}N_2NaO_8S$ *m/z*: 461.0989 $[M+Na]^+$; found 461.0990.

*4.3.10. Ethyl N-(1,4-diphthalimidobutane-2-sulfonyl)glycinate (**6ia**).* Colorless solid, yield: 58%, mp 71–75 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.80 (dd, *J*=5.5, 3.1 Hz, 4H, ArH), 7.71 (dd, *J*=5.5, 3.1 Hz, 4H, ArH), 5.87 (dd, *J*=5.7, 5.6 Hz, 1H, NH), 4.38 (dd, *J*=15.1, 5.7 Hz, 1H in CH_2N), 4.31 (dd, *J*=15.1, 4.7 Hz, 1H in CH_2N), 4.17 (q, *J*=7.1 Hz, 2H, OCH_2), 4.13–3.96 (m, 4H, $2CH_2N$), 3.49 (dddd, *J*=6.7, 6.4, 5.6, 4.8 Hz, 1H, CHS), 2.42 (dddd, *J*=14.2, 7.4, 6.9, 6.7 Hz, 1H in CH_2), 2.05 (dddd, *J*=14.2, 7.0, 6.6, 6.0 Hz, 1H in CH_2), 1.26 (t, *J*=7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.9, 168.6, 168.2, 134.2, 133.9, 131.9, 131.7, 123.5, 123.3, 61.8, 58.7, 44.6, 36.7, 35.4, 26.5, 14.1. IR (ν_{max}, cm^{-1}) 3298.6, 2949.5, 2923.8, 2872.6, 1774.0, 1711.8, 1396.5, 1140.8. HRMS (ESI) calcd for $C_{24}H_{24}N_3O_8S$ *m/z*: 536.1098 $[M+Na]^+$; found 536.1100.

*4.3.11. Methyl (S)-N-(methoxy-5-oxo-1-phthalimidopentane-2-sulfonyl)alaninate (**6bb**).* Colorless oil, yield: 61%, (Dr=50:50). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.84–7.81 (m, 4H, ArH), 5.94 (d, *J*=8.3 Hz, 1H, NH), 4.29 (dd, *J*=14.7, 7.3 Hz, 1H in CH_2N), 4.26 (dd, *J*=14.7, 7.2 Hz, 1H in CH_2N), 4.19 (dd, *J*=15.0, 5.1 Hz, 1H, CHN), 3.76 (s, 3H, CH_3O), 3.74 (s, 3H, CH_3O), 3.48 (dddd, *J*=8.0, 7.2, 6.4, 6.4 Hz, 1H, CHS), 2.75 (ddd, *J*=16.9, 8.0, 7.5 Hz, 1H in CH_2CO), 2.72–2.67 (m, 1H in CH_2CO), 2.26 (dddd, *J*=14.3, 8.0, 8.0, 6.4 Hz, 1H in CH_2), 2.04 (dddd, *J*=15.0, 7.8, 7.8, 6.8 Hz, 1H in CH_2), 1.51 (d, *J*=4.1 Hz, 3H, CH_3). Its diastereomer δ: 7.72–7.70 (m, 4H, ArH), 5.73 (d, *J*=8.6 Hz, 1H, NH), 4.26 (dd, *J*=14.7, 7.2 Hz, 1H in CH_2N), 4.10 (dd, *J*=15.0, 5.3 Hz, 1H, CHN), 3.92 (dd, *J*=14.7, 6.1 Hz, 1H in CH_2N), 3.63 (s, 3H, CH_3O), 3.62 (s, 3H, CH_3O), 3.48 (dddd, *J*=7.2, 7.2, 6.4, 6.1 Hz, 1H, CHS), 2.68–2.66 (m, 1H in CH_2CO), 2.65–2.57 (m, 1H in CH_2CO), 2.18 (dddd, *J*=14.3, 7.5, 7.2, 6.4 Hz, 1H in CH_2), 1.97 (dddd, *J*=15.0, 7.4, 7.4, 6.8 Hz, 1H in CH_2), 1.49 (d, *J*=4.1 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 173.2, 172.8, 168.5, 134.1, 131.6, 123.4, 59.64, 52.60, 51.9, 51.6, 36.9, 30.7, 22.4, 19.9. Its diastereomer δ: 173.0, 172.8, 168.1, 134.1, 131.6, 123.4, 59.6, 52.59, 51.8, 51.6, 36.8, 30.6, 22.4, 19.8. IR (ν_{max}, cm^{-1}) 3299.0, 2927.1, 2843.8, 1741.9, 1712.4, 1399.3, 1139.9. HRMS (ESI) calcd for $C_{19}H_{25}N_2O_8S$ *m/z*: 441.1326 $[M+H]^+$; found 441.1327.

*4.3.12. Ethyl (S)-N-(methoxy-5-oxo-1-phthalimidopentane-2-sulfonyl)phenylalaninate (**6bc**).* Colorless oil, yield: 56%, (Dr 54:46). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.86–7.83 (m, 2H, ArH), 7.73–7.71 (m, 2H, ArH), 7.35–7.25 (m, 5H, ArH), 5.64 (d, *J*=9.2 Hz, 1H, NH), 4.50 (ddd, *J*=9.2, 7.2, 4.8 Hz, 1H, CHN), 4.21 (q, *J*=7.2 Hz, 2H, OCH_2), 4.03 (dd, *J*=14.8, 7.2 Hz, 1H in CH_2N), 3.95 (dd, *J*=14.8, 6.0 Hz, 1H in CH_2N), 3.66 (s, 3H, CH_3O), 3.34 (dddd, *J*=7.2, 6.4, 6.4, 6.0 Hz, 1H, CHS), 3.23–3.18 (m, 2H, CH_2Ar), 2.65 (ddd, *J*=16.8, 7.6, 7.6 Hz, 2H, CH_2CO), 2.57 (ddd, *J*=16.8, 7.2, 7.2 Hz, 1H in CH_2CO), 2.13 (dddd, *J*=14.8, 7.6, 7.6, 6.4 Hz, 1H in CH_2), 1.89 (dddd, *J*=14.8, 7.2, 7.2, 7.2 Hz, 1H in CH_2), 1.26 (t, *J*=7.2 Hz, 3H, CH_3). Its diastereomer δ: 7.86–7.83 (m, 2H, ArH), 7.73–7.71 (m, 2H, ArH), 7.35–7.25 (m, 5H, ArH), 5.51 (d, *J*=9.3 Hz, 1H, NH), 4.45 (ddd, *J*=9.3, 7.2, 4.8 Hz, 1H, CHN), 4.19 (q, *J*=7.2 Hz, 2H, CH_2O), 4.00 (dd, *J*=14.8, 5.2 Hz, 1H in CH_2N), 3.75 (dd, *J*=14.8, 5.2 Hz, 1H in CH_2N), 3.66 (s, 3H, CH_3O), 3.24 (dddd, *J*=7.2, 6.4, 5.2, 5.2 Hz, 1H, CHS), 3.13 (dd, *J*=7.2, 4.8 Hz, 1H in CH_2Ar), 3.09 (dd, *J*=7.2, 4.8 Hz, 1H in CH_2Ar), 2.65 (ddd, *J*=16.8, 7.6, 7.6 Hz, 2H, CH_2CO), 2.53 (ddd, *J*=16.8, 7.2, 7.2 Hz, 1H in CH_2CO), 2.05 (dddd, *J*=14.8, 7.6, 7.6, 6.4 Hz, 1H in CH_2), 1.76 (dddd, *J*=14.8, 7.2, 7.2, 6.4 Hz, 1H in CH_2), 1.26 (t, *J*=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ: 172.81, 171.6, 168.4, 135.52, 134.2, 131.8, 129.6, 128.7, 127.3, 123.5, 61.9, 59.8, 57.6, 51.71, 39.5, 36.9, 30.9, 22.47, 14.0. Its diastereomer δ: 172.84, 171.4, 168.2, 135.48, 134.2, 131.8, 129.6, 128.6, 127.3, 123.5, 61.9, 60.0, 57.4, 51.71, 39.8, 36.8, 30.8, 22.52, 14.0. IR (ν_{max}, cm^{-1}) 3288.9, 2949.5, 2930.3, 2872.6, 1777.2, 1741.9, 1715.9, 1610.7, 1339.5, 1144.0. HRMS (ESI) calcd for $C_{25}H_{29}N_2O_8S$ *m/z*: 517.1639 $[M+H]^+$; found 517.1640.

*4.3.13. Ethyl (S)-N-(methoxy-5-oxo-1-phthalimidopentane-2-sulfonyl)tyrosinate (**6bd**).* Colorless oil, yield: 60%, (Dr 50:50). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.85–7.83 (m, 2H, ArH), 7.73–7.71 (m, 2H, ArH), 7.11 (d, *J*=8.5 Hz, 2H, ArH), 7.01 (d, *J*=8.5 Hz, 2H, ArH), 5.65 (d, *J*=9.2 Hz, 1H, NH), 5.59 (s, 1H, OH), 4.45–4.40 (m, 1H, CHN), 4.40 (dd, *J*=15.2, 6.8 Hz, 1H in CH_2N), 4.22 (q, *J*=7.1 Hz, 2H, CH_2O), 3.66 (s, 3H, CH_3O), 3.78 (dd, *J*=15.2, 5.2 Hz, 1H in CH_2N), 3.31 (dddd, *J*=7.1, 6.8, 6.3, 5.2 Hz, 1H, CHS), 3.17–3.09 (m, 2H, CH_2Ar), 2.66–2.59 (m, 2H, CH_2CO), 2.14 (dddd, *J*=15.2, 7.3, 6.9, 6.3 Hz, 1H in CH_2), 1.78 (dddd, *J*=15.2, 7.7, 7.2, 7.1 Hz, 1H in CH_2), 1.27 (t, *J*=7.1 Hz, 3H, CH_3). Its diastereomer δ: 7.85–7.83 (m, 2H, ArH), 7.73–7.71 (m, 2H, ArH), 6.78 (d, *J*=7.0 Hz, 2H, ArH), 6.76 (d, *J*=7.0 Hz, 2H, ArH), 5.59 (s, 1H, OH), 5.54 (d, *J*=9.4 Hz, 1H, NH), 4.41–3.97 (m, 1H, CHN), 4.19 (q, *J*=7.1 Hz, 2H, CH_2O), 4.07 (dd, *J*=14.8, 7.1 Hz, 1H in CH_2N), 3.62 (dd, *J*=14.8, 5.3 Hz, 1H in CH_2N), 3.66 (s, 3H, CH_3O), 3.24 (dddd, *J*=7.1, 7.1, 6.4, 5.3 Hz, 1H, CHS), 3.06–3.99 (m, 2H, CH_2Ar), 2.59–2.51 (m, 2H, CH_2CO), 2.06 (dddd, *J*=14.5, 7.9, 6.4, 6.4 Hz, 1H in CH_2), 1.89 (dddd, *J*=14.5, 7.4, 7.3, 7.1 Hz, 1H in CH_2), 1.24 (t, *J*=7.1 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 173.02, 171.7, 168.5, 155.1, 134.22, 131.8, 130.8, 127.34, 123.65, 115.7, 61.9, 60.1, 57.8, 51.83, 38.9, 36.9, 30.91, 22.6, 14.1. Its diastereomer δ: 172.98, 171.6, 168.3, 155.1, 134.21, 131.8, 130.8, 127.25, 123.59, 115.6, 61.9, 59.9, 57.6, 51.78, 38.7, 36.9, 30.85, 22.5, 14.1. IR (ν_{max}, cm^{-1}) 3474.7, 3295.4, 2952.7, 2936.7, 1777.2, 1716.1, 1617.1, 1399.9, 1143.5. HRMS (ESI) calcd for $C_{25}H_{28}N_2NaO_9S$ *m/z*: 555.1408 $[M+Na]^+$; found 555.1409.

*4.3.14. Methyl (S)-N-(methoxy-5-oxo-1-phthalimidopentane-2-sulfonyl)leucinate (**6be**).* Colorless oil, yield: 65%, (Dr 61:39). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.87–7.85 (m, 2H, ArH), 7.74–7.72 (m, 2H, ArH), 5.89 (d, *J*=9.1 Hz, 1H, NH), 4.26 (ddd, *J*=9.1, 5.6, 5.5 Hz, 1H, CHN), 4.12 (dd, *J*=14.2, 7.3 Hz, 1H in CH_2N), 4.10 (dd, *J*=14.2, 4.9 Hz, 1H in CH_2N), 3.76 (s, 3H, CH_3O), 3.67 (s, 3H, CH_3O), 3.40 (dddd, *J*=6.4, 6.3, 5.0, 4.9 Hz, 1H, CHS), 2.71 (ddd, *J*=16.5, 7.8, 7.8 Hz, 1H in CH_2CO), 2.63 (ddd, *J*=16.5, 7.8, 6.8 Hz, 1H in CH_2CO), 2.11–2.02 (m, 1H in CH_2), 1.92–1.87 (m, 1H in CH_2), 1.85–1.77 (m, 1H, CH), 1.73–1.66 (m, 2H, CH_2), 0.97–0.94 (m, 6H, $2CH_3$). Its diastereomer δ: 7.87–7.85 (m, 2H, ArH), 7.74–7.72 (m, 2H, ArH), 5.59 (d, *J*=9.4 Hz, 1H, NH), 4.35 (dd, *J*=14.8, 4.9 Hz, 1H in CH_2N), 4.22 (ddd, *J*=9.4, 5.9, 5.8 Hz, 1H, CHN), 3.95 (dd, *J*=14.8, 5.4 Hz, 1H in CH_2N), 3.79 (s, 3H, CH_3O), 3.68 (s, 3H, CH_3O), 3.47 (dddd, *J*=6.2, 6.1, 5.9, 5.8 Hz, 1H, CHS), 2.80 (ddd, *J*=15.2, 7.5, 7.5 Hz, 1H in CH_2CO), 2.29 (ddd, *J*=15.2, 6.8, 6.6 Hz, 1H in CH_2CO), 2.17 (dddd, *J*=14.2, 6.7, 6.5, 6.3 Hz, 1H in CH_2), 1.95 (dddd, *J*=14.2, 7.4, 6.9, 6.9 Hz, 1H in CH_2), 1.85–1.77 (m, 1H, CH), 1.65–1.58 (m, 2H, CH_2), 0.99–0.97 (m, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 173.6, 172.9, 168.8, 134.26, 131.8, 123.6, 60.2, 54.8, 52.56, 51.7, 42.4, 36.8, 30.9, 24.4, 22.8, 22.62, 21.46. Its diastereomer δ: 173.6, 172.9, 168.3, 134.23, 131.8, 123.6, 60.2, 55.1, 52.61, 51.8, 42.8, 37.1, 30.9, 24.4, 22.72, 22.65, 21.54. IR (ν_{max}, cm^{-1}) 3292.2, 2949.5, 2869.4, 1777.2, 1736.2, 1716.4, 1614.3, 1398.8, 1139.3. HRMS (ESI) calcd for $C_{21}H_{29}N_2O_8S$ *m/z*: 469.1639 $[M+H]^+$; found 469.1648.

*4.3.15. Ethyl (S)-N-(ethoxy-5-oxo-1-phthalimidopentane-2-sulfonyl) tyrosinate (**6cd**).* Colorless oil, yield: 54%, (Dr 58:42). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.86–7.83 (m, 2H, ArH), 7.73–7.71 (m, 2H, ArH), 7.12 (d, *J*=8.4 Hz, 2H, ArH), 7.09 (d, *J*=8.4 Hz, 2H, ArH), 5.62 (d, *J*=9.2 Hz, 1H, NH), 5.19 (s, 1H, OH), 4.48–4.43 (m, 1H, CHN), 4.15–4.09 (m, 4H, $2CH_2O$), 4.00 (dd, *J*=14.8, 7.2 Hz, 1H in CH_2N), 3.78 (dd, *J*=14.8, 5.3 Hz, 1H in CH_2N), 3.33 (dddd, *J*=7.2, 6.1, 5.9, 5.3 Hz, 1H, CHS), 3.24 (d, *J*=13.6 Hz, 1H in CH_2Ar), 3.21 (d, *J*=13.6 Hz, 1H in CH_2Ar), 2.66–2.59 (m, 2H, CH_2CO), 2.06 (dddd, *J*=14.6, 6.6, 6.5, 6.4 Hz, 1H in CH_2), 1.78 (dddd, *J*=14.6, 7.7, 7.3, 7.3 Hz, 1H in CH_2),

1.27 (t, J=7.1 Hz, 3H, CH_3), 1.26 (t, J=7.1 Hz, 3H, CH_3). Its diastereomer δ: 7.86–7.83 (m, 2H, ArH), 7.73–7.71 (m, 2H, ArH), 6.79 (d, J=8.0 Hz, 2H, ArH), 6.77 (d, J=8.0 Hz, 2H, ArH), 5.52 (d, J=9.4 Hz, 1H, NH), 5.19 (s, 1H, OH), 4.48–4.43 (m, 1H, CHN), 4.21 (q, J=7.1 Hz, 2H, CH_2O), 4.19 (q, J=7.1 Hz, 2H, CH_2O), 4.00 (d, J=6.3 Hz, 1H, CHN), 3.38–3.34 (m, 1H in CH_2N), 3.27–3.22 (m, 1H, CHS), 3.64–3.55 (m, 2H, CH_2Ar), 2.59–2.49 (m, 2H, CH_2CO), 2.13 (dddd, J=14.4, 6.5, 6.4, 6.4 Hz, 1H in CH_2), 1.89 (dddd, J=14.4, 7.4, 7.2, 7.1 Hz, 1H in CH_2), 1.27 (t, J=7.1 Hz, 3H, CH_3), 1.26 (t, J=7.1 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 172.68, 171.6, 166.5, 165.0, 134.19, 131.8, 130.8, 127.1, 123.7, 115.7, 61.9, 60.68, 59.9, 57.8, 38.7, 37.78, 36.87, 31.2, 22.5, 14.09. Its diastereomer δ: 172.64, 171.7, 166.3, 164.9, 134.2, 131.8, 130.8, 127.1, 123.7, 115.6, 61.9, 60.75, 60.1, 57.6, 39.0, 37.84, 36.9, 31.1, 22.6, 14.14. IR (ν_{max}, cm^{-1}) 3449.1, 3282.6, 2981.5, 2949.5, 2929.6, 1777.2, 1715.9, 1610.7, 1399.1, 1190.6. HRMS (ESI) calcd for $C_{26}H_{31}N_2O_9S$ m/z: 547.1745 $[M+H]^+$; found 547.1748.

4.4. General procedure for synthesis of *N*-benzyloxycarbonyl-protected sulfonopeptides 9

NCS (534 mg, 4 mmol) was dissolved in a mixture of 2 M HCl (0.8 mL) and MeCN (4 mL). The resulting solution was cooled to 10 °C. A solution of thiolacetate **7** (1 mmol) in MeCN (1 mL) was added dropwise to the cooled solution at below 20 °C. The resulting solution was stirred at the same temperature for 30 min, and then diluted with isopropyl ether (5 mL). The organic layer was washed with aq NaCl (12%, 3×5 mL) and then dried over anhydrous Na_2SO_4. After concentration in vacuo, the crude sulfonyl chloride **8** was obtained as colorless solids or pale yellow oil, and used directly without further purification. The sulfonyl chloride **8** was dissolved in dry dichloromethane (2 mL) and the resulting solution was added dropwise into a solution of amino ester hydrochloride salt **5** (1 mmol) and triethylamine (222 mg, 2.2 mmol) in DCM (1 mL) under stirring at 0–5 °C in an ice-water bath. After addition, the resulting mixture was stirred for another 12 h at the same temperature and was allowed to warm to room temperature. The solution was concentrated in vacuo to afford the crude product **9**. Further recrystallization from ethanol gave rise to *N*-Cbz-protected sulfonopeptide as colorless crystals or chromatography gave rise to colorless oil.

*4.4.1. Ethyl N-[(S)-N-benzyloxycarbonyl-2-amino-2-phenylethanesulfonyl]glycinate (**9aa**).* Colorless solid, yield: 93%, mp 122–125 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.38–7.26 (m, 10H, ArH), 6.07 (s, br, 1H, NH), 5.61 (s, br, 1H, NH), 5.55–5.51 (m, 1H, CHN), 5.09 (s, 2H, CH_2O), 4.21 (q, J=7.1 Hz, 2H, OCH_2), 3.95–3.88 (m, 2H, CH_2N), 3.57 (dd, J=14.6, 10.3 Hz, 1H in CH_2SO_2), 3.43–3,47 (m, 1H in CH_2SO_2), 1.27 (t, J=7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ: 170.4, 156.2, 139.6, 136.2, 129.0, 128.4, 128.1, 126.2, 67.1, 61.9, 58.1, 51.5, 44.4, 14.1. IR (ν_{max}, cm^{-1}) 3317.8, 3295.7, 2984.7, 2939.9, 2917.4, 1743.0, 1689.1, 1536.2, 1371.5, 1140.5. HRMS (ESI) calcd for $C_{20}H_{25}N_2O_6S$ m/z: 421.1428 $[M+H]^+$; found 421.1434.

*4.4.2. Ethyl N-[(S)-N-benzyloxycarbonylpyrrolidine-2-ylmethanesulfonyl]glycinate (**9ba**).* Colorless oil, yield: 85%. Two different rotamers exist in a molar ration of approximate 4:1 in solution due to rigid proline residue. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.43–7.31 (m, 5H, ArH), 5.90 [5.15 (Rotamer)] (s, br, 1H, NH), 5.12 (s, 2H, CH_2O), 4.49 [4.31 (Rotamer)] (m, 1H, CHN), 4.24–4.21 (m, 3H, OCH_2 & 1H in CH_2N), 3.98–3.90 (m, 1H in CH_2N), 3.57 (dd, J=14.0, 4.9 Hz, 1H in CH_2SO_2), 3.45 (t, J=6.4 Hz, 2H, CH_2N), 3.05 (dd, J=14.0, 7.4 Hz, 1H in CH_2SO_2), 2.17–1.99 (m, 2H, CH_2), 1.96–1.83 (m, 2H, CH_2), 1.28 (t, J=6.9 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.8 [169.7 (Rotamer)], 155.34 [155.26 (Rotamer)], 136.5, 128.5 [128.4 (Rotamer)], 128.1 [127.9 (Rotamer)], 127.7, 67.2 [66.9 (Rotamer)], 61.8 [61.7 (Rotamer)], 56.0 [55.4 (Rotamer)], 53.7 [53.0 (Rotamer)], 46.5 [46.0 (Rotamer)], 44.2 [43.9 (Rotamer)], 30.7 [30.6 (Rotamer)], 23.5 [22.8 (Rotamer)], 14.0. IR (ν_{max}, cm^{-1}) 3288.2, 2980.4, 2936.7, 2875.8, 1746.9, 1698.3, 1492.2, 1332.6, 1139.2. HRMS (ESI) calcd for $C_{17}H_{25}N_2O_6S$ m/z: 385.1428 $[M+H]^+$; found 385.1434.

*4.4.3. Methyl (S)-N-[(S)-N-benzyloxycarbonylpyrrolidine-2-ylmethanesulfonyl]alaninate (**9bb**).* Colorless oil, yield: 73%. Two different rotamers exist in a molar ration of approximate 2:1 in solution due to rigid proline residue. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.38–7.30 (m, 5H, ArH), 5.94 [5.03 (Rotamer)] (d, J=8.2 Hz, 1H, NH), 5.13 [5.10 (Rotamer)] (s, 2H, CH_2O), 4.56–4.49 [4.40–4.32 (Rotamer)] (m, 1H, CHN), 4.24 [4.00–3.93 (Rotamer)] (dddd, J=7.5, 7.5, 6.2, 6.2 Hz, 1H, CHN), 3.76 [3.69 (Rotamer)] (s, 3H, CH_3O), 3.49 (dd, J=13.8, 6.2 Hz, 1H in CH_2SO_2), 3.44 (t, J=7.2 Hz, 2H, CH_2N), 2.99 [2.23 (Rotamer)] (dd, J=13.8, 7.5 Hz, 1H in CH_2SO_2), 2.14–2.07 (m, 1H in CH_2), 2.05–1.98 (m, 1H in CH_2), 1.95–1.89 [1.88–1.82 (Rotamer)] (m, 2H, CH_2), 1.51 [1.29 (Rotamer)] (d, J=7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.4, 155.4, 136.6, 128.6 [128.5 (Rotamer)], 128.2 [128.02 (Rotamer)], 128.08 [127.8 (Rotamer)], 67.2 [67.0 (Rotamer)], 56.2 [55.6 (Rotamer)], 54.0 [53.7 (Rotamer)], 53.1 [52.7 (Rotamer)], 51.8 [51.5 (Rotamer)], 46.6 [46.1 (Rotamer)], 30.6 [30.4 (Rotamer)], 23.5 [23.5 (Rotamer)], 19.7. IR (ν_{max}, cm^{-1}) 3281.2, 3029.5, 2978.3, 2954.6, 2883.6, 1744.1, 1697.2, 1498.1, 1336.0, 1134.43. HRMS (ESI) calcd for $C_{17}H_{25}N_2O_6S$ m/z: 385.1428 $[M+H]^+$; found 385.1434.

*4.4.4. Ethyl (S)-N-[(S)-N-benzyloxycarbonylpyrrolidine-2-ylmethanesulfonyl]tyrosinate (**9bd**).* Colorless oil, yield: 60%. Two different rotamers exist in a molar ration of approximate 3:2 in solution due to rigid proline residue. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.43–7.30 (m, 5H, ArH), 7.04 [6.92 (Rotamer)] (d, J=7.8 Hz, 2H, ArH), 6.72 [6.70 (Rotamer)] (d, J=7.8 Hz, 2H, ArH), 5.69 [5.22 (Rotamer)] (s, 1H, OH), 5.12 [5.05–4.94 (Rotamer)] (s, 2H, CH_2O), 4.38 (s, br, 1H, NH), 4.17 [4.13 (Rotamer)] (q, J=7.1 Hz, 2H, CH_2O), 3.45–3.37 (m, 3H, 2CHN & 1H in CH_2SO_2), 3.10–2.96 (m, 2H, CH_2N), 2.76 (dd, J=13.4, 7.9 Hz, 1H in CH_2SO_2), 2.24–2.15 (m, 2H, CH_2), 2.05–1.95 (m, 2H, CH_2), 1.91–1.72 (m, 2H, CH_2), 1.25 [1.24 (Rotamer)] (t, J=7.1 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 171.7 [171.4 (Rotamer)], 155.2 [155.1 (Rotamer)], 136.5 [136.3 (Rotamer)], 130.9 [130.8 (Rotamer)], 128.6 [128.5 (Rotamer)], 128.2 [128.0 (Rotamer)], 127.9 [127.1 (Rotamer)], 115.7 [115.5 (Rotamer)], 67.2 [67.0 (Rotamer)], 62.0 [61.8 (Rotamer)], 57.5 [57.2 (Rotamer)], 56.1 [55.4 (Rotamer)], 53.6 [52.8 (Rotamer)], 46.2 [46.1 (Rotamer)], 38.8 [38.6 (Rotamer)], 30.1, 23.4 [22.6 (Rotamer)], 14.1 [14.0 (Rotamer)]. IR (ν_{max}, cm^{-1}) 3285.5, 2981.9, 2,91.9, 2933.1, 2878.7, 1736.8, 1696.9, 1613.3, 1338.4, 1146.1. HRMS (ESI) calcd for $C_{24}H_{31}N_2O_7S$ m/z: 491.1846 $[M+H]^+$; found 491.1854.

*4.4.5. Methyl (S)-N-[(S)-N-benzyloxycarbonylpyrrolidine-2-ylmethanesulfonyl]leucinate (**9be**).* Colorless oil, yield: 81%. Two different rotamers exist in a molar ration of approximate 3:1 in solution due to rigid proline residue. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.36–7.31 (m, 5H, ArH), 5.92 [4.79 (Rotamer)] (d, J=9.2 Hz, 1H, NH), 5.14 [5.15 (Rotamer)] (s, 2H, CH_2O), 4.58 [4.40 (Rotamer)] (ddd, J=9.2, 6.5, 6.0 Hz, 1H, CHN), 4.19 [3.99 (Rotamer)] (dddd, J=8.6, 8.6, 6.9, 6.9 Hz, 1H, CHN), 3.75 [3.66 (Rotamer)] (s, 3H, CH_3O), 3.45 (t, J=7.4 Hz, 2H, CH_2N), 3.39 (dd, J=13.7, 6.7 Hz, 1H in CH_2SO_2), 2.97 (dd, J=13.7, 6.9 Hz, 1H in CH_2SO_2), 2.16–2.05 [2.24–2.17 (Rotamer)] (m, 2H, CH_2), 1.95–1.92 (m, 2H, CH_2), 1.88–1.83 (m, 1H, CH), 1.65–1.61 (m, 2H, CH_2), 0.97–0.93 (m, 6H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.7, 155.43 [155.42 (Rotamer)], 136.6, 128.5 [128.4 (Rotamer)], 128.1 [127.9 (Rotamer)], 127.8 [127.7 (Rotamer)], 67.0, 56.3 [55.7 (Rotamer)], 54.6 [54.4 (Rotamer)], 53.6, 52.9 [52.5 (Rotamer)], 46.4 [45.9 (Rotamer)], 42.2 [42.1 (Rotamer)], 30.7 [30.4 (Rotamer)], 24.4 [24.3 (Rotamer)], 23.43 [23.36 (Rotamer)], 22.78 [22.68 (Rotamer)], 21.6 [21.4 (Rotamer)]. IR (ν_{max}, cm^{-1}) 3272.9, 3032.7, 2956.6, 2874.4,

1744.4, 1698.7, 1492.2, 1336.0, 1139.4. HRMS (ESI) calcd for $C_{20}H_{31}N_2O_6S$ *m*/*z*: 427.1897 $[M+H]^+$; found 427.1906.

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Supplementary data

Copies of the ^1H NMR and ^{13}C NMR spectra of all key intermediates and final products. Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2013.08.028. These data include MOL files and InChiKeys of the most important compounds described in this article.

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