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Synthesis of amino thiols and isocysteines via regioselective ring opening of sulfamidates with tetrathiomolybdate

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ABSTRACT

Herein we present a simple and highly efficient method for the synthesis of β and γ-amino thiols via regioselective ring opening of sulfamidates with tetrathiomolybdate **1**. The generality of this methodology has been shown by synthesizing carbohydrate derived β-amino thiol. The scope and versatility of this methodology has been demonstrated by synthesizing biologically important unnatural amino acids like isocysteines in optically pure form.

1. Introduction

In the last few decades, there has been a significant interest in the synthesis and reactions of sulfamidates because of their very high reactivity and ability to function as carbon electrophiles. Sulfamidates and their derivatives are versatile synthetic intermediates for the synthesis of biologically important compounds.[1] Procedures for the synthesis of sulfamidates have been well developed and they are as readily available as aziridines.[2] Amino sulfides are compounds of synthetic interest in organic synthesis because of pharmaceutical importance.[3] Roques et al. found that β-amino thiols are selective inhibitors of aminopeptidase A (**APA**)[4] and would be an interesting probe to explore the physiological involvement of **APA** in the metabolism of neuropeptides. β-Amino thiols inhibit the zinc metallopeptidase activity of tetanus toxin[5] and of botulinum neurotoxin type B.[6] In addition, β-amino thiol functionality is present in some HIV protease inhibitors.[7] Catalytic quantities of β and γ-amino thiols have also been used for asymmetric addition of dialkylzinc to aldehydes[8] and have been shown to be effective ligands and catalysts in enantioselective conjugate addition of organocuprates to enones.[9] β-Amino thiols have also been used as a chiral auxiliaries for boron-mediated asymmetric aldol reactions[10] and the utility of β-amino thiols for the synthesis of polythiols and mercapto thio ethers has been demonstrated.[11] In spite of the importance of this class of compounds very few methods are reported in the literature for the synthesis of β-aminothiols.[12] The most straightforward route to β-amino thiols involves the acid catalyzed ring opening reaction of aziridines with hydrogen sulfide or sodium or potassium salt of thioacetic acid followed by deprotection of thioacetates to corresponding thiols.[12b] In addition, there are a number of methods available for the synthesis of β-amino sulfides via Lewis acid catalyzed aziridine ring opening with alkyl thiols.[13] Since the deprotection of *S*-alkyl or *S*-aryl group is non trivial, it makes these methods not very attractive for the synthesis of β-aminothiols.

Our investigation to understand the reactivity of benzyltriethylammonium tetrathiomolybdate, ($BnNEt_3MoS_4$) **1** as a reagent in organic synthesis led to the development of a number of useful methodologies.[14] Recently, we reported the synthesis of β-amino disulfides via ring opening of sulfamidates mediated by tetrathiomolybdate **1**.[15] During the course of our investigation we observed an unusual reactivity of tetrathiomolybdate **1** with sulfamidates derived from the corresponding diols using Burgess reagent **2** (Et_3NSO_2N-COOMe). In this report, we present a novel and versatile method for the synthesis β-amino thiols by utilizing the unusual reactivity of tetrathiomolybdate **1** with sulfamidates derived from the corresponding diols.

2. Results and discussion

Our ongoing study towards the ring opening reaction of sulfamidates with tetrathiomolybdate **1** led to the development of a very

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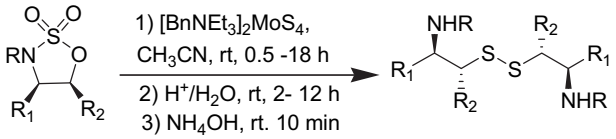
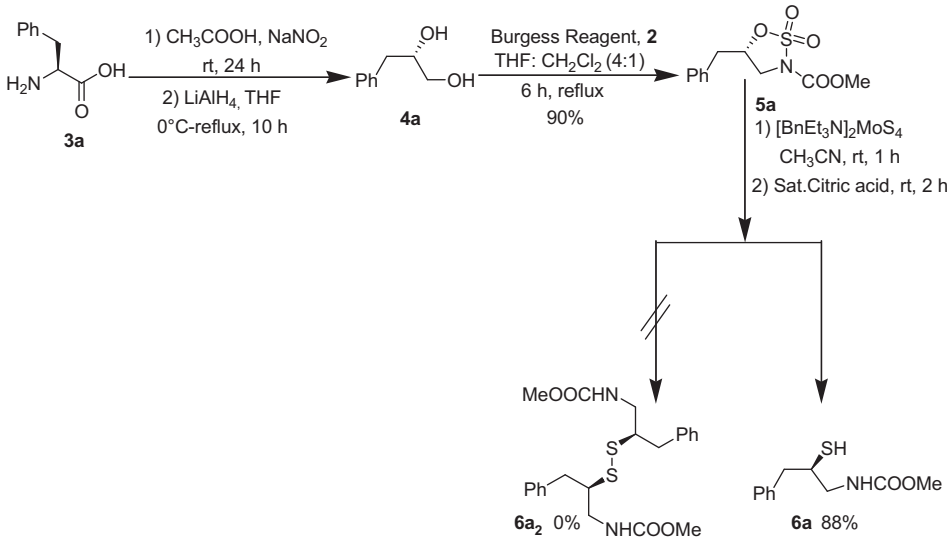
simple and efficient method for the synthesis of *N*-alkyl β-amino disulfides (Scheme 1).[15]



Scheme 1.

In order to demonstrate it as a modular method for the synthesis of β-amino disulfides we synthesized the chiral diol **4a** starting from phenylalanine **3a**. The diol **4a** was refluxed with Burgess reagent **2** in THF:CH_2Cl_2 (4:1) to give sulfamidate **5a** in 90% yield. Treatment of sulfamidate **5a** with tetrathiomolybdate **1** (1.2 equiv, CH_3CN, 28 °C, 1 h) resulted in a hitherto unreported reactivity of **1**. It gave β-amino thiol **6a** as the only product in very good yield instead of the anticipated β-amino disulfide **6a$_2$** (Scheme 2).



Scheme 2. Reaction of sulfamidate **5a** with tetrathiomolybdate **1**.

In order to examine the unusual reactivity of tetrathiomolybdate **1** with sulfamidates derived from 1,2 diols and Burgess reagent, we prepared a number of chiral and achiral sulfamidates **5a**–**l** by the reaction of the corresponding 1,2 diols with **2** employing the procedure described in Scheme 2. Treatment of sulfamidates **5a**–**j** with tetrathiomolybdate **1** (1.2 equiv, CH_3CN, 28 °C, 1 h) gave the corresponding β-amino thiols **6a**–**j** (Table 1) in good to excellent yields (78–96%). Results summarized in Table 1 illustrate that this method is general and is applicable to a variety of sulfamidates **5a**–**j**. Sulfamidate **5e** derived from methionine is the only exception as it gave a mixture of β-amino thiol **6e$_1$** and β-amino disulfide **6e$_2$** (3:7) in 83% yield. Sulfamidates **5k** and **5l** derived from achiral cycloheptane and cyclooctane 1,2 diols were found to be inert to the reaction with tetrathiomolybdate **1**.

2.1. Tentative mechanism for the formation of β-amino thiols

It is reasonable to visualize nucleophilic attack of **1** exclusively at the C–O bond of **5** in a highly stereospecific (S_N2) manner to give intermediate **7**. Elimination of MoS_3 followed by protonation gives intermediate **8**, which on hydrolysis leads to β-amino thiols **6** (Scheme 3).

2.2. Synthesis of isocysteine derivatives

In order to demonstrate the utility of this methodology for the synthesis of isocysteine derivatives, we converted the α,β-unsaturated ester **9** to the corresponding diol **10**.[16] The reaction of **10a**–**c** with excess of **2** (2.5 equiv) under reflux in THF:CH_2Cl_2 (4:1) gave sulfamidates **11a**–**c**, respectively, in very good yield (Scheme 4). Treatment of sulfamidates **11a**–**c** with tetrathiomolybdate **1** (1.2 equiv, CH_3CN, 28 °C, 45 min) led to the formation of the corresponding isocysteine derivatives **12a**–**c** in excellent yield (Table 2).

2.3. Synthesis of chiral isocysteine derivative 12d

In order to explore this methodology for the synthesis of enantiomerically pure isocysteine derivative, we synthesized the sulfamidate **11d** from chiral diol (2*R*, 3*S*)-ethyl 2,3-dihydroxy-3-phenylpropanoate, **10d**. The reaction of **11d** with tetrathiomolybdate **1** gave the optically pure isocysteine derivative **12d** in 89% yield (Scheme 5). The synthesis of **12d** in enantiomerically pure form illustrates that this methodology is general and can be extended easily for the synthesis of a variety of chiral isocysteine derivatives.

2.4. Synthesis of carbohydrate derived β-amino thiol 16

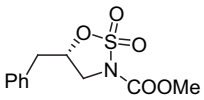
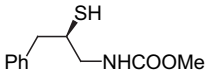
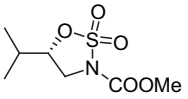
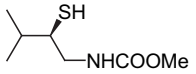
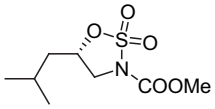
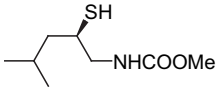
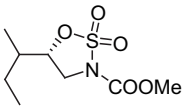
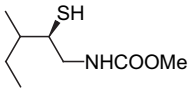
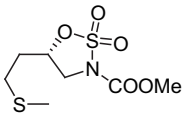
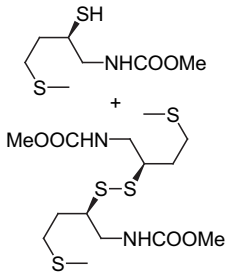
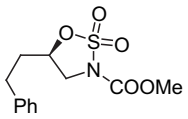
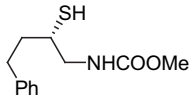
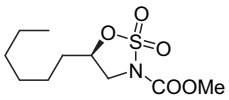
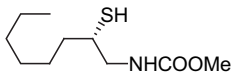
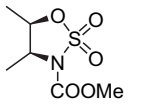
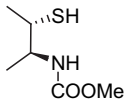
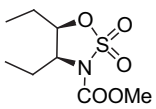
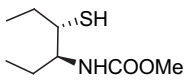
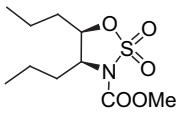
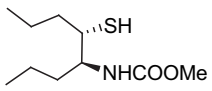
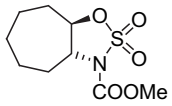
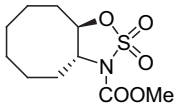
In continuation of our investigation to examine the efficacy of this methodology for the synthesis of β-amino thiols, we synthesized the diol **14** starting from α-D-glucose **13**.[17] The reaction of diol **14** with **2** gave sulfamidate **15** in 73% of yield.

The sulfamidate **15** was then treated with tetrathiomolybdate **1** (1.2 equiv, CH_3CN, 28 °C, 24 h) to give β-amino thiol derivative **16** as the only product in 78% yield (Scheme 6).

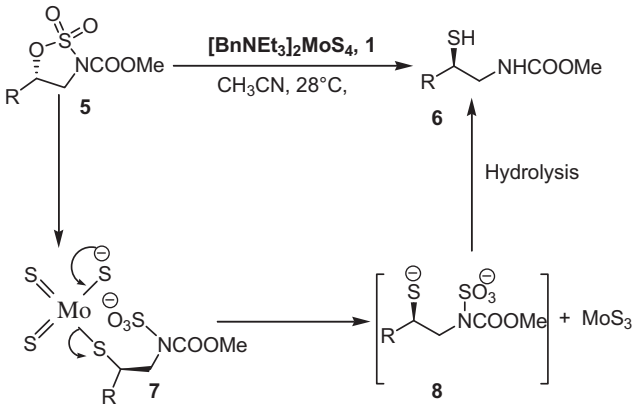
2.5. Synthesis of γ-amino thiols via regioselective ring opening of sulfamidates derived form (2*R*,4*R*) pentane diol

To explore this methodology further we treated (2*R*,4*R*) 2,4 pentane diol **17** with **2** to give sulfamidate **18** in 84% yield. The reaction of sulfamidate **18** with tetrathiomolybdate **1** (1.2 equiv, CH_3CN, 28 °C, 1 h) gave γ-amino thiol **19** in excellent yield (Scheme 7). This result indicates the potential utility of this method for the synthesis of a number of substituted γ-amino thiols.

Table 1
Synthesis of β-amino thiols by reaction sulfamidates with tetrathiomolybdate **1**

Entry	Sulfamidates	Time (h)	Product[c]	Yield (%)
1[a]	 **5a**	1	 **6a**	88
2[a]	 **5b**	1	 **6b**	87
3[a]	 **5c**	1	 **6c**	92
4[a]	 **5d**	1	 **6d**	95
5[a]	 **5e**	1	 **6e$_1$** + **6e$_2$**	83 (3:7)
6[b]	 **5f**	1	 **6f**	78
7[b]	 **5g**	1	 **6g**	92
8[a]	 **5h**	1	 **6h**	79
9[b]	 **5i**	1	 **6i**	95
10[b]	 **5j**	1	 **6j**	96
11[b]	 **5k**	1	—	—
12[b]	 **5l**	1	—	—

[a] Sulfamidates derived from chiral diols.
[b] Sulfamidates derived from racemic(±)diols.
[c] Reaction conditions: (i) $[BnEt_3N]_2MoS_4$ (1.2 equiv, CH_3CN, 28 °C, 1 h). (ii) Satd citric acid solution. 28 °C, 2 h.



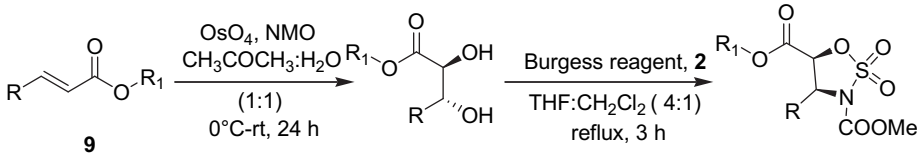
Scheme 3.

exemplified by synthesizing a carbohydrate derived β-amino thiol derivative. The reaction of sulfamidates derived form α,β-unsaturated esters leads to an efficient and modular method for the synthesis of isocysteine derivatives in optically pure form.

4. Experimental section

4.1. General methods

All the reactions were performed in oven dry apparatus and were stirred magnetically. Melting points and optical rotation values (recorded at 25 °C) reported are uncorrected. Infrared spectra were recorded using an FTIR instrument and the frequencies are reported in wave number (cm^{-1}) and intensities of the peak are denoted as s (strong), w (weak), m (medium), br (broad). ^1H and ^{13}C spectra were recorded at 300/400 MHz and at 75/100 MHz, respectively. Chemical shifts are reported in parts

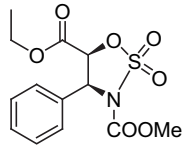
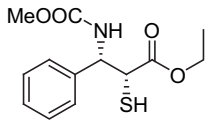
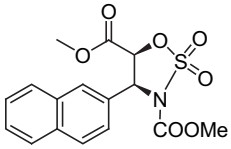
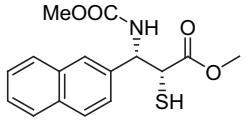
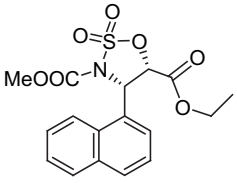
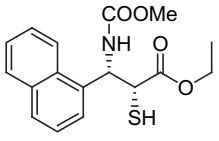


R = Ph, R_1 = Et, **10a**
R = 2-Nap, R_1 = Me, **10b**
R = 1-Nap, R_1 = Et, **10c**

R = Ph, R_1 = Et, **11a**
R = 2-Nap, R_1 = Me, **11b**
R = 1-Nap, R_1 = Et, **11c**

Scheme 4. Synthesis of sulfamidates from α, β-unsaturated esters.

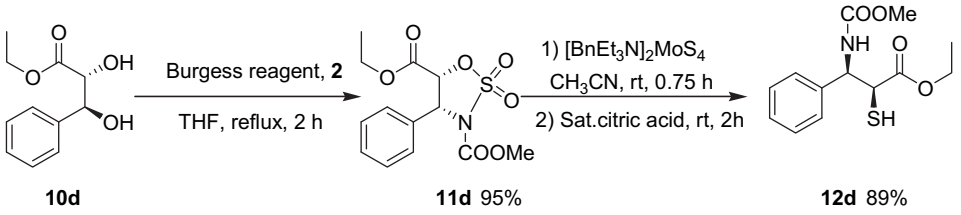
Table 2
Synthesis of isocysteine derivatives

Entry	Sulfamidates	Time[a] (h)	Product[b]	Yield (%)
1	 **11a**	0.75	 **12a**	93
2	 **11b**	0.75	 **12b**	88
3	 **11c**	0.75	 **12c**	87

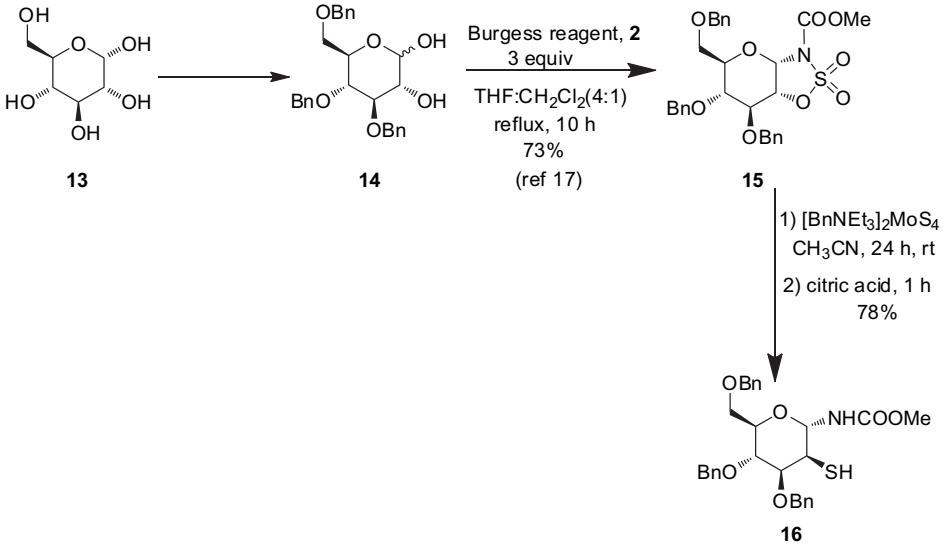
[a] Time required for the reaction of sulfamidate with **1**.
[b] Reaction conditions: (i) $[BnEt_3N]_2MoS_4$ (1.2 equiv, CH_3CN, 28 °C, 0.75 h). (ii) Satd citric acid solution. 28 °C, 2 h.

3. Conclusion

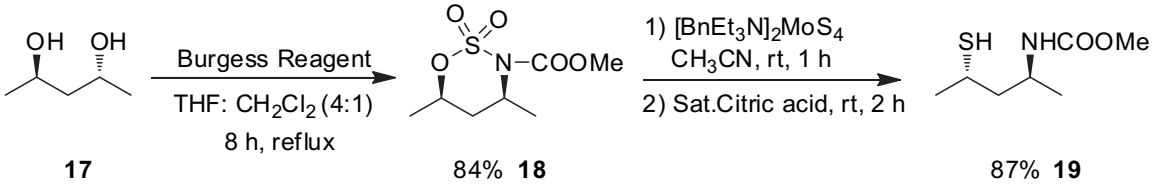
In summary, the unusual reactivity of tetrathiomolybdate leads to a simple and highly efficient method for the synthesis of β and γ-amino thiols via regioselective ring opening of sulfamidates derived from corresponding diols and Burgess reagent (Et_3NSO_2N-COOMe). The scope and generality of this methodology has been per million downfield from the internal reference, tetramethylsilane (TMS). Multiplicity is indicated using the following abbreviations: s (singlet), d (doublet), dd (double doublet) t (triplet), m (multiplet), br s (broad singlet). Mass spectra were recorded on Q-TOF electro-spray instrument. References for the compound reported previously are indicated against each of them along with the characterization data.



Scheme 5. Synthesis of chiral isocysteine derivative **12d**.



Scheme 6. Synthesis of carbohydrate derived β-amino thiol **16**.



Scheme 7. Synthesis of γ-amino thiol **19**.

4.2. General procedure for the synthesis of sulfamidates from diols

The appropriate diol (0.5 mmol, 1.0 equiv) was dissolved in THF/CH_2Cl_2 (4:1, 5 mL) and the Burgess reagent (1.25 mmol, 2.5 equiv) was added at 25 °C in a single portion. The resultant solution was immediately warmed to reflux (using a preheated oil bath) and stirred for 3–6 h. Upon completion, the reaction contents were cooled to 25 °C, poured into saturated aqueous NH_4Cl (25 mL), and extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were then washed with water (50 mL), dried over (Na_2SO_4), and concentrated. The resultant yellow residue was purified by flash column chromatography (silica gel) in an appropriate solvent system to give the desired product in high purity.

*4.2.1. Compound **5e**.* Gummy solid; $[\alpha]_{D^{25}}$ −8.18 (*c* 1, $CHCl_3$); IR (Neat); 2960 (w), 2920 (w), 1744 (s), 1442 (s), 1375 (s), 1332 (s), 1192 (s), 1153 (w), 1018 (w), 835 (m), 760 (m), cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 5.16–5.10 (1H, m), 4.25 (1H, dd, *J*=5.6, 8 Hz), 3.97 (3H, s), 3.89 (1H, t, *J*=9.6 Hz), 2.75–2.67 9 (2H, m), 2.38–2.29 (1H, m), 2.19 (3H, s), 2.13–2.04 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$), δ 150.3, 78.5, 54.6, 50.4, 31.9, 29.0, 15.6; HRMS calcd for $C_7H_{13}NO_5S_2$ $[M+Na]^+$ 278.0133 found 278.0143.

*4.2.2. Compound **5h**.* Gummy solid; $[\alpha]_{D^{25}}$ −11.95 (*c* 1, $CHCl_3$); IR (Neat); 2961 (w), 1740 (s), 1442 (m), 1373 (s), 1324 (s), 1189 (s), 1057 (w), 1032 (w), 869 (m), 831 (m), 761 (m), 637 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 5.12–5.06 (1H, m), 4.40–4.35 (1H, m), 3.91 (3H, s), 1.47(3H, d, *J*=8 Hz), 1.39 (3H, d, *J*=8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), δ 150.0, 79.8, 58.1, 54.3, 14.0, 12.9; HRMS calcd for $C_6H_{11}NO_5S$ $[M+Na]^+$ 232.0256 found 232.0266.

*4.2.3. Compound **5k** (±).* Gummy solid; IR (Neat); 2947 (w), 2873 (w), 1738 (s), 1376 (s), 1333 (s), 1296 (s), 1185 (s), 1145 (w), 959 (s), 904 (m), 834 (m), 759 (m), 645 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ 4.66–4.58 (1H, m), 4.17–4.69 (1H, m), 3.90 (3H, s), 2.70–2.60 (1H, m), 2.43–2.33 (1H, m), 1.89–1.43 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$), δ 151.1, 83.6, 63.8, 54.8, 30.6, 30.0, 25.6, 25.0,

24.2; HRMS calcd for $C_9H_{15}NO_5S$ $[M+Na]^+$ 272.0569 found 272.0561.

4.2.4. Compound ***5l*** *(±).* White solid; mp 130 °C; IR (Neat); 2932 (s), 2868 (m), 1744 (s), 1593 (w), 1443 (m), 1382 (s), 1325 (s), 1302 (s), 1191 (s), 922 (m), 869(m), 762 (w), 646 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ 4.82–4.74 (1H, m), 4.34–4.26 (1H, m), 3.90 (3H, s), 2.53–2.46 (1H, m), 2.30–2.12 (1H, m), 1.90–1.35 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$), δ 150.3, 83.0, 62.0, 54.2, 33.0, 26.3, 21.4, 20.9; HRMS calcd for $C_{10}H_{17}NO_5S$ $[M+Na]^+$ 286.0725 found 286.0721.

4.2.5. Compound ***11b*** *(±).* White solid; mp 148 °C; IR (Neat); 3060 (w), 2960 (m), 1753 (s), 1440 (s), 1318 (s), 1196 (s), 1044 (s), 946 (s), 848 (s), 830 (s), 750 (m), 737 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.89–7.82 (4H, m), 7.53–7.48 (3H, m), 5.70 (1H, d, J=6.4 Hz), 5.64 (1H, d, J=6.4 Hz), 3.88 (3H, s), 3.36 (3H,s); ^{13}C NMR (100 MHz, $CDCl_3$), δ 162.6, 149.5, 133.5, 132.7, 130.2, 128.8, 128.2, 127.6, 127.0, 126.6, 123.9, 77.5, 63.1, 60.2, 54.8, 52.7; HRMS calcd for $C_{16}H_{15}NO_7S$ $[M+Na]^+$ 388.0467 found 388.0464.

4.2.6. Compound ***11c*** *(±).* White solid; mp 143 °C; IR (Neat); 3054 (w), 2963 (w), 1752 (s), 1442 (m), 1387 (s), 1320 (s), 1197 (s), 1035 (s), 952 (m), 927 (w), 839 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.67 (1H, d, J=8 Hz), 7.88–7.86 (3H, m), 7.61–7.50 (3H, m), 6.56 (1H, d, J=6.4 Hz), 5.7 (1H, d, J=6.4 Hz), 3.80 (3H, s), 3.63–3.59 (1H, m), 3.39–3.34 (1H, m), 0.46 (3H, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), δ 162.0, 149.6, 133.4, 130.7, 130.2, 129.0, 128.9, 126.7, 126.0, 125.5, 125.4, 122.1, 77.2, 62.4, 57.6, 54.9, 12.8; HRMS calcd for $C_{17}H_{17}NO_7S$ $[M+Na]^+$ 402.0623 found 402.0616.

4.2.7. Compound ***11d****.* Gummy solid; $[\alpha]_{D^{25}}$ +23.50 (c 1, $CHCl_3$); IR (Neat); 2969 (w), 2930 (w), 1749 (s), 1442 (m), 1388 (s), 1315 (s), 1194 (s), 1043 (s), 836 (s), 701 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ 7.46–7.36 (5H, m), 5.56 (1H, d, J=6.3 Hz), 5.53 (1H, d, J=6.3 Hz), 3.97–3.83 (5H, m), 0.93 (3H, t, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$), δ 162.1, 149.5, 132.9, 129.6, 128.7, 127.6, 77.4, 63.0, 62.5, 54.7, 13.4; HRMS calcd for $C_{13}H_{15}NO_7S$ $[M+Na]^+$ 352.0467 found 352.0461.

4.2.8. Compound ***18****.* Gummy solid; $[\alpha]_{D^{25}}$ −21.7 (c 1, $CHCl_3$); IR (Neat); 2985 (m), 2962 (m), 2942 (m), 1738 (s), 1443 (m), 1380 (m), 1309 (m), 1187 (m), 1117 (m), 923 (m), 897 (m), 797 (m), 714 (w), 668 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ 5.06–4.98 (1H, m), 4.84–4.73 (1H, m), 3.91 (3H, s), 2.62–2.53 (1H, m), 1.81–1.73 (1H, m), 1.57 (3H, d, J=6.6 Hz), 1.49 (3H, d, J=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$), δ 152.5, 80.2, 54.5, 53.4, 35.2, 22.0, 21.7; HRMS calcd for $C_7H_{13}NO_5S$ $[M+Na]^+$ 246.0412 found 246.0393.

4.3. Synthesis of β-amino thiols

General procedure for the synthesis amino thiols: To a well-stirred solution of appropriate sulfamidate (0.50 mmol) in CH_3CN (6 mL) was added benzyltriethylammonium tetrathiomolybdate **1** (0.365 g, 0.6 mmol) in portions over a period of 5 min. The reaction mixture was stirred for further 55 min at room temperature. To this saturated citric acid solution (3 mL) was added and the stirring was continued for further 2 h at room temperature. Finally the reaction mixture was extracted with diethyl ether (20 mL×4). The combined organic extract was washed with brine, dried over anhydrous sodium sulfate, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (100–200 mesh).

4.3.1. Compound ***6a****.* Gummy solid; $[\alpha]_{D^{25}}$ −45.78 (c 1, $CHCl_3$); IR (Neat); 3329 (br), 3023 (w), 2945 (w), 2560 (w), 1705 (s), 1524 (s), 1254 (s), 1147 (w), 1070 (w), 997 (w), 770 (m), 753 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.33–7.19 (5H, m), 5.14 (1H, br s), 3.67 (3H, s), 3.56–3.50 (1H, m), 3.23–3.11 (2H, m), 2.99 (1H, dd, J=6, 14 Hz), 2.77 (1H, dd, J=8, 12 Hz), 1.40 (1H, d, J=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), δ 156.9, 138.0, 129.1, 128.4, 126.7, 62.2, 52.2, 47.5, 42.4; HRMS calcd for $C_{11}H_{15}NO_2S$ $[M+Na]^+$ 248.0721 found 248.0711.

4.3.2. Compound ***6b****.* Gummy solid; $[\alpha]_{D^{25}}$ −9.34 (c 1, $CHCl_3$); IR (Neat); 3332 (br), 2961 (m), 2565 (w), 1704 (w), 1528 (m), 1462 (w), 1260 (m), 1191 (w), 1021 (w), 775 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 5.18 (1H, br s), 3.68 (3H, s), 3.59–3.49 (1H, m), 3.10–3.03 (1H, m), 2.86–2.80 (1H, m), 1.97–1.85 (1H, m), 1.69 (1H, d, J=16 Hz), 1.02 (3H, d, J=8 Hz), 0.95 (3H, d, J=8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), δ 156.9, 52.1, 48.1, 46.5, 31.4, 17.7, 17.6; HRMS calcd for $C_7H_{16}NO_2S$ $[M+Na]^+$ 200.0721 found 200.0710.

4.3.3. Compound ***6c****.* Gummy solid; $[\alpha]_{D^{25}}$ −48.41 (c 1, $CHCl_3$); IR (Neat); 3339 (w), 2955 (w), 2560 (w), 1701 (m) 1522 (w), 1219 (m), 772 (s), 668 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 5.19 (1H, br s), 3.68 (3H, s), 3.50–3.48 (1H, m), 3.09–3.04 (1H, m), 2.97–2.94 (1H, m), 1.92–1.85 (1H, m), 1.44–1.35 (2H, m), 1.30 (1H, d, J=8 Hz), 0.93 (3H, d, J=8 Hz), 0.88 (3H, d, J=8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), δ 156.9, 52.1, 48.6, 44.9, 39.5, 25.4, 22.9, 21.5; HRMS calcd for $C_8H_{17}NO_2S$ $[M+Na]^+$ 214.0878 found 214.0861.

4.3.4. Compound ***6d****.* Gummy solid; $[\alpha]_{D^{25}}$ +28.94 (c 1, $CHCl_3$); IR (Neat); 3332 (br), 2962 (m), 2930 (w), 2575 (w), 1704 (s), 1530 (s), 1460 (w), 1260 (s), 1191 (w), 1015 (w), 773 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 5.17 (1H, br s), 3.68 (3H, s), 3.53–3.49 (1H, m), 3.12–3.06 (1H, m), 3.01–2.95 (1H, m), 1.71–1.61 (1H, m), 0.91–0.087 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$), δ 156.9, 52.1, 46.9, 45.9, 37.5, 27.4, 14.0, 11.5; HRMS calcd for $C_8H_{17}NO_2S$ $[M+Na]^+$ 214.0878 found 214.0861.

4.3.5. Compound ***6e₁****.* Gummy solid; $[\alpha]_{D^{25}}$ +38.75 (c 1, $CHCl_3$); IR (Neat); 3330 (br), 2918 (m), 2852 (w), 2542 (w), 1704 (s), 1520 (m), 1434 (w), 1366 (w), 1222 (s), 1145 (w), 1015 (w), 847 (w), 776 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 5.14(1H, br s), 3.68 (3H, s), 3.50–3.42 (1H, m), 3.22–2.15 (1H, m), 3.08–3.04 (1H, m), 2.76–2.61 (2H, m), 2.10 (3H, s), 2.02–1.93 (1H, m), 1.72–1.65 (1H, m), 1.35 (1H, d, J=8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), δ 157.7, 52.7, 48.6, 40.7, 35.4, 31.9, 15.9; HRMS calcd for $C_7H_{15}NO_2S2$ $[M+Na]^+$ 232.0442 found 232.0450.

4.3.6. Compound ***6e₂****.* Gummy solid; $[\alpha]_{D^{25}}$ +103.82 (c 1, $CHCl_3$); IR (Neat); 3328 (br), 2940 (w), 2915 (w), 2842 (w), 1703 (s), 1529 (m), 1434 (w), 1257 (s), 1191 (w), 1021 (w), 775 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 5.46 (1H, br s), 3.69 (3H, s), 3.42–3.36 (2H, m), 3.02 (1H, m), 2.71–2.60 (2H, m), 2.10 (3H, s), 1.92–1.77 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$), δ 157.2, 52.2, 50.2, 44.3, 31.3, 30.4, 15.3; HRMS calcd for $C_{14}H_{28}N_2O_4S_4$ $[M+Na]^+$ 439.0830 found 439.0826.

4.3.7. Compound ***6f*** *(±).* Gummy solid; IR (Neat); 3329 (br), 3023 (w), 2945 (w), 2561 (w), 1705 (s), 1524 (s), 1254 (s), 1147 (w), 1070 (w), 997 (w), 770 (m), 753 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ 7.31–7.10 (5H, m), 5.15 (1H, br s), 3.67 (3H, s), 3.20–3.11 (1H, m), 2.93–2.68 (3H, m), 2.09–1.91 (1H, m), 1.78–1.66 (1H, m), 1.36 (1H, d, J=6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), δ 156.9, 136.4, 129.5, 128.5, 125.7, 52.1, 48.2, 40.8, 37.5, 33.0; HRMS calcd for $C_{12}H_{17}NO_2S$ $[M+Na]^+$ 262.0878 found 262.0880.

4.3.8. Compound ***6g*** *(±).* Gummy solid; IR (Neat); 3342 (br), 2929 (s), 2857(m), 2552 (w), 1711 (s), 1533 (m), 1463 (w), 1378 (w), 1288 (m), 1075 (w), 778 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ 5.19 (1H, br s), 3.68 (3H, s), 3.54–3.44 (1H, m), 3.13–3.04 (1H,

m), 2.94–2.83 (1H, m), 1.70–1.28 (1H, m), 0.88 (3H, t, J=6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$), δ 156.9, 52.1, 48.3, 41.4, 35.8, 31.6, 28.8, 26.8, 22.5, 13.9; HRMS calcd for $C_{10}H_{21}NO_2S$ $[M+Na]^+$ 242.1190 found 242.1198.

4.3.9. Compound ***6h***. Gummy solid; $[\alpha]_{D^{25}}$ −12.0 (c 1, $CHCl_3$); IR (Neat); 3329 (br), 2973 (m), 2931 (w), 2560 (w), 1702 (s), 1524 (s), 1454 (m), 1249 (m), 1194 (w), 1077 (w), 1018 (w), 777 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 4.91 (1H, br s), 3.86 (1H, br m), 3.67 (3H, s), 3.08–3.06 (1H, br m), 1.35 (1H, d, J=8 Hz), 1.31 (3H, d, J=6.8 Hz), 1.17 (3H, d, J=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), δ 156.6, 52.0, 51.4, 40.7, 21.6, 19.2; HRMS calcd for $C_6H_{13}NO_2S$ $[M+Na]^+$ 186.0565 found 186.0557.

4.3.10. Compound ***6i*** *(±).* Gummy solid; IR (Neat); 3332 (br), 2965 (m), 2935 (m), 2877 (w), 2561 (w), 1709 (s), 1515 (s), 1460 (m), 1379 (w), 1355 (w), 1238 (m), 1105 (w), 776 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$), δ 4.88 (1H, d, J=8.7 Hz), 3.81–3.73 (1H, m), 3.67 (3H, s), 2.90–2.82 (1H, m), 1.78–1.42 (4H, m), 1.15 (1H, d, J=6.9 Hz), 1.04 (3H, t, J=7.5 Hz), 0.93 (3H, t, J=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$), δ 157.0, 55.4, 52.0, 46.9, 29.1, 27.2, 12.2, 10.5; HRMS calcd for $C_8H_{17}NO_2S$ $[M+Na]^+$ 214.0878 found 214.0877.

4.3.11. Compound ***6j*** *(±).* Gummy solid; IR (Neat); 3333 (br), 2959 (s), 2872 (s), 2559 (w), 1710 (s), 1512 (s), 1463 (m), 1253 (s), 1193 (w), 1109 (m), 1067 (m), 1022 (w), 776 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$), δ 4.88 (1H, d, J=9.6 Hz), 3.85–3.80 (1H, m), 3.67 (3H, s), 2.93–2.90 (1H, m), 1.86–1.25 (8H, m), 1.16 (1H, d, J=6.9 Hz), 0.95–0.88(6H, m); ^{13}C NMR (75 MHz, $CDCl_3$), δ 156.9, 53.9, 52.0, 45.0, 37.9, 36.4, 20.5, 19.2, 13.8, 13.6; HRMS calcd for $C_{10}H_{21}NO_2S$ $[M+Na]^+$ 242.1191 found 242.1190.

4.3.12. Compound ***12b*** *(±).* Gummy solid; IR (Neat); 3342 (br), 3059 (w), 2852 (w), 2563 (w), 1733 (s), 1701 (s), 1511 (s), 1511 (s), 1260 (w), 1046 (m), 827 (w), 758 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.84–7.75 (4H, m), 7.05–7.46 (3H, m), 5.75 (1H, d, J=9.2 Hz), 5.49 (1H, br s), 4.05 (1H, t, J=8 Hz), 3.70 (3H, s), 3.68 (3H, s), 1.95 (1H, d, J=8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), δ 170.6, 156.3, 133.0, 132.9, 128.7, 128.0, 127.6, 126.4, 126.3, 15.7, 124.1, 116.0, 57.1, 53.0, 52.5, 48.4; HRMS calcd for $C_{16}H_{17}NO_4S$ $[M+Na]^+$ 342.0776 found 342.0787.

4.3.13. Compound ***12c*** *(±).* Gummy solid; IR (Neat); ^{1}H NMR (300 MHz, $CDCl_3$), δ 8.10 (1H, d, J=8.1 Hz), 7.81–7.20 (2H, m), 7.55–7.34 (4H, m), 6.15 (1H, dd, J=4.8, 9 Hz), 5.72 (1H, d, J=9 Hz), 4.15–4.09 (3H, m), 3.67 (3H, s), 1.77 (1H, d, J=5.7 Hz), 1.17 (3H, t, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), δ 170.0, 156.2, 134.6, 133.9, 133.0, 129.1, 128.8, 126.9, 125.9, 124.9, 123.6, 122.4, 62.3, 52.7, 52.4, 48.4, 13.9; HRMS calcd for $C_{17}H_{19}NO_4S$ $[M+Na]^+$ 356.0932 found 356.0923.

4.3.14. Compound ***12d***. Gummy solid; $[\alpha]_{D^{25}}$ −3.21 (c 1, $CHCl_3$); IR (Neat); 3327 (br), 3059 (w), 2955 (w), 2874 (w), 2563 (w), 1371 (s), 1695 (s), 1537 (m), 1455 (w), 1370 (w), 1291 (w), 1253 (w), 1160 (w), 1046 (m), 1023 (m), 758 (w), 701 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.37–7.25 (5H, m), 5.63 (1H, d, J=9 Hz), 5.30(1H, dd, J=6, 8.7 Hz), 4.13 (2H, q, J=6 Hz), 3.91(1H, t, J=6 Hz), 3.66 (3H, s), 1.94 (1H, d, J=9 Hz), 1.19 (3H, t, J=6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$), δ 170.0, 156.2, 138.9, 128.6, 128.0, 126.6, 62.1, 57.1, 52.4, 48.6, 13.8; HRMS calcd for $C_{13}H_{17}NO_4S$ $[M+Na]^+$ 306.0776 found 306.0781.

4.3.15. Compound ***16***. Gummy solid; $[\alpha]_{D^{25}}$ +28.70 (c 1, $CHCl_3$); 3332 (br), 3028 (w), 2928 (m), 2568 (w), 1732 (s), 1714 (s), 1518 (m), 1454 (s), 1359 (m), 1260 (m), 1092 (s), 1023 (s), 748 (m), 698 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.30–7.25 (1H, m), 5.38 (1H, d, J=9 Hz), 5.28 (1H, t, J=7.8 Hz), 5.59–5.25 (7H, m), 4.08 (1H, m), 3.84–3.73(3H, m), 3.69 (3H, s), 3.27–3.21 (1H, m), 1.97 (1H, d, J=9.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$), δ 156.0, 138.1, 137.6, 137.1, 128.5, 128.4, 128.3, 128.0, 127.9, 127.6, 127.5, 78.6, 74.7, 73.4, 72.7, 72.6, 72.1, 68.1, 52.4, 41.5; HRMS calcd for $C_{29}H_{33}NO_6S$ $[M+Na]^+$ 546.1926 found 546.1907.

4.3.16. Compound ***19***. Gummy solid; $[\alpha]_{D^{25}}$ −3.21 (c 1, $CHCl_3$); IR (Neat); 3334 (br), 2929 (s), 2856 (m), 2558 (w), 1713 (s), 1699 (s), 1537 (m), 1455 (m), 1261 (s), 1103 (s), 1036 (s), 864 (w), 800 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$), δ 4.90 (1H, br s), 3.97 (1H, br s), 3.66 (3H, s), 3.05–2.93(1H, m), 1.68(1H, d, J=12 Hz), 1.60–1.56 (2H, m), 1.33 (3H, d, J=6.9 Hz), 1.17 (3H, d, J=6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$), δ 156.5, 51.9, 48.6, 45.4, 32.2, 25.4, 21.6; HRMS calcd for $C_7H_{15}NO_2S$ $[M+Na]^+$ 200.0721 found 200.0723.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.02.074.

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