A modular synthesis of dithiocarbamate pendant unnatural α- amino acids

Amit Saha#, R. B. Nasir Baig#, John Leazer, and Rajender S. Varma*

Sustainable Technology Division National Risk Management Research Laboratory, Environmental Protection Agency U.S. EPA, 26 West M.L.K. Dr. MS 443, Cincinnati, Ohio 45268, USA
E-mail: varma.rajender@epa.gov

# These authors contributed equally.

Supporting Information

Table of Contents

<table>
<thead>
<tr>
<th>Experimental Procedures and data</th>
<th>Page Number 1-12</th>
</tr>
</thead>
<tbody>
<tr>
<td>1H, and 13C NMR spectra of compounds</td>
<td>Page Number 13-52</td>
</tr>
</tbody>
</table>

Electronic Supplementary Material (ESI) for Chemical Communications
**General Methods.**

All the reactions were performed in oven dried apparatus and were stirred magnetically. Melting points and optical rotation values reported are uncorrected. Infrared spectra were recorded using an FTIR instrument, the frequencies are reported in wave numbers (cm⁻¹). ¹H and ¹³C spectra were recorded at 300 MHz and 75 MHz NMR instruments, respectively. Chemical shifts are reported in parts per million downfield from the internal reference, tetramethyilsilane (TMS). Multiplicity is indicated using the following abbreviations: s (singlet), d (doublet), dd (double doublet), t (triplet), m (multiplet), bs (broad singlet). elemental analysis has been performed using Perkin Elmer instrument. References for the compound reported previously are indicated against each of them along with the characterization data.
General Procedure for the Synthesis of \(N\)-Boc- and \(N\)-Cbz-, Sulfamidates.

Step I. A solution of \(\text{SOCl}_2\) (1.2 equiv) in dry \(\text{CH}_3\text{CN}\) under nitrogen was cooled to \(-40^\circ\text{C}\), and then \(\text{Boc-\text{Threo-OMe}}\) (1.0 equiv) in dry \(\text{CH}_3\text{CN}\) was added dropwise over 10 min and stirring continued for a further 45 min at the same temperature. Dry pyridine (4.0 equiv) was then added. The reaction mixture was further stirred for 1 h and then allowed to warm to room temperature. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic extract was washed with water, dried over anhydrous sodium sulfate (\(\text{Na}_2\text{SO}_4\)), and concentrated in vacuum to afford the crude sulfamidite. This was used without further purification in the next step.

Step II. To a cooled (ice bath) solution of crude (step I) sulfamidite in \(\text{MeCN}\) was added ruthenium- (III) chloride (5 mol %) followed by \(\text{NaIO}_4\) (1.2 equiv) and then water (\(\text{CH}_3\text{CN}:\text{H}_2\text{O}, 1:1\)). The mixture was stirred at \(\circ\text{C}\) for 1-3h and diluted with ether, and the phases were separated. The aqueous phase was extracted with ether. The combined organic portions were washed with \(\text{NaHCO}_3\) solution and then brine. The solution was dried over anhydrous \(\text{Na}_2\text{SO}_4\) and concentrated. The crude product was purified by silica gel (100-200 mesh) column chromatography.

Spectral Data.

\((4S,5R)-3\text{-benzyl 4-methyl 5-methyl-1,2,3-oxathiazolidine-3,4-dicarboxylate 2,2-dioxide}\): Yield 87 %; Gummy solid; \([\alpha]^{25}_D\) -30.51 (\(c = 1, \text{CHCl}_3\)); FT-IR (\(\text{cm}^{-1}\)), 2983, 1739, 1440, 1384, 1326, 1192, 1074, 1018, 751; \(^1\text{H NMR}\) (300 MHz, \(\text{CDCl}_3\)), \(\delta\) 7.61 (5H, m), 5.37 (1H, d, \(J = 12\) Hz), 5.35-5.25 (1H, m), 4.95-4.87 (1H, m), 4.55 (1H, d, \(J = 6\) Hz), 3.75 (3H, s), 1.70 (3H, d, \(J = 6\) Hz); \(^{13}\text{C NMR}\) (75 MHz, \(\text{CDCl}_3\)), \(\delta\) 166.5, 149.3, 134.1, 128.6, 128.5, 127.9, 77.8, 69.6, 63.7, 53.7, 18.8; Analysis calculated for \(\text{C}_{13}\text{H}_{15}\text{NO}_7\text{S}\): C, 47.41; H, 4.59; N, 4.25; O, 34.01; S, 9.74; Found C, 47.39; H, 4.57; N, 4.27; O, 34.04; S, 9.72.

\((S)-3\text{-benzyl 4-methyl 1,2,3-oxathiazolidine-3,4-dicarboxylate 2,2-dioxide}\): Yield 84%; Gummy solid; FT-IR (\(\text{cm}^{-1}\)), 2981, 1736, 1442, 1377, 1259, 1187, 1150, 789, 784, 691, 657; \(^1\text{H NMR}\) (400 MHz, \(\text{CDCl}_3\)), \(\delta\) 7.42-7.27(5H, m), 5.40 (1H, d, \(J = 9\) Hz), 5.32 (1H, d, \(J = 9\) Hz), 4.89-4.73(3H, m), 3.82 (3H, s) \(^{13}\text{C NMR}\) (100 MHz, \(\text{CDCl}_3\)), \(\delta\) 167.1, 149.3, 134.2, 128.78, 128.71, 128.0, 69.8, 67.9, 57.7, 53.7; Analysis calculated for \(\text{C}_{12}\text{H}_{13}\text{NO}_7\text{S}\): C, 45.71; H, 4.16; N, 4.44; O, 35.52; S, 10.17; Found C, 45.73; H, 4.15; N, 4.41; O, 35.54; S, 10.15.
(S)-tert-butyl 4-benzyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide: Yield (87%) white solid; mp-138°C; [α]D25 -41.2 (c = 0.7%, CHCl3); FT-IR (cm-1), 2973, 2927, 1712, 1458, 1320, 1261, 1184, 1150, 1023, 838, 799, 784, 695, 657, 540; 1H NMR (300 MHz, CDCl3) δ 1.55 (9H, s), 2.92 (1H, dd, J = 9.9, 13.5), 3.36 (1H, dd, J = 3.3, 13.5), 4.28-4.34(1H, m), 4.40-4.48(2H, m), 7.21-7.37(5H, m); (75 MHz, CDCl3) δ 27.9, 37.8, 58.5, 68.7, 85.5, 127.4, 129.0, 129.4, 135.1, 148.4. Analysis calculated for C₁₄H₁₉NO₅S: C 53.66, H 6.11, N 4.47; Found C 53.63, H 6.13, N 4.45.

(S)-tert-butyl 4-((S)-sec-butyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide: Yield (91%) white solid; mp - 99°C; [α]D25 2.16 (c = 0.5%, CHCl3); FT-IR (cm -1), 2977, 2934, 1728, 1466, 1367, 1325, 1261, 1187, 1150, 1099, 968, 927, 826, 805, 653, 571, cm -1 ; 1H NMR (300 MHz, CDCl3) δH 0.96-1.04 (6H, m), 1.15-1.44( 2H, m), 1.57 (9H, s), 2.03-2.12(1H, m), 4.28-4.33( 1H, m), 4.39 (1H, dd, J = 2.4, 9.6), 4.57 (1H, dd, J = 9.3, 6.6); (75 MHz, CDCl3) δ 11.7, 13.0, 25.3, 27.9, 36.1, 60.8, 66.3, 85.3, 149.0. Analysis calculated for C₁₁H₂₁NO₅S: C 47.29, H 7.58, N 5.01; Found C 47.27, H 7.55, N 5.05.

Carbon disulfide (1.5 mmol) was added drop wise to a DMF (1 mL) solution of amine (1 mmol) at 0-5 °C. The mixture was stirred for 2-3 min. Sulfamidate (1 mmol) solution in DMF (1 mL) was added to the solution of dithiocarbamate at room temperature and was stirred for the required time period (TLC). The crude reaction mixture was extracted with ethyl acetate and was washed with water (three times). The organic layer was concentrated and was purified by column chromatography to obtain desired dithiocarbamate α-amino acid. The product was characterized by FT-IR, 1H and 13C NMR spectroscopy, elemental analysis and polarimetry.

Spectral Data.
(2R,3S)-methyl 2-(((benzyloxy)carbonyl)amino)-3-((piperidine-1-carbonothioyl)thio)butanoate, Table 2, Entry 1: Colorless viscous liquid, [α]D23= -18.2 (c = 0.28, CHCl3). FT-IR (cm⁻¹): 603, 667, 701, 755, 892, 975, 1005, 1031, 1077, 1205, 1227, 1241, 1270, 1307, 1357, 1386, 1434, 1468, 1508, 1718,
1744, 2944, 3362, 3431. 

\[ ^1\text{H NMR (300 MHz; CDCl}_3\text{)} \delta _\text{H} 1.38 (d, J = 7.2 Hz, 3H), 1.67 (bs, 6H), 3.78-3.84 (m, 5H), 4.25 (bs, 2H), 4.66-4.74 (m, 1H), 4.92 (dd, \text{J}_1 = 9\text{Hz}, \text{J}_2 = 3.6 \text{Hz, 1H}), 5.06-5.16 (m, 2H), 5.62 (d, J = 8.1 \text{Hz, 1H}), 7.28-7.32 (m, 5H). \]

\[ ^{13}\text{C NMR (75 MHz, CDCl}_3\text{)} \delta _\text{C} 16.62, 24.26, 25.76 (2C), 48.84, 51.60, 52.58, 52.99, 57.48, 67.05, 128.01, 128.08 (2C), 128.46 (2C), 136.30, 155.99, 170.89, 193.44. \]

Analysis calculated for C\textsubscript{19}H\textsubscript{26}N\textsubscript{2}O\textsubscript{4}S\textsubscript{2}: C, 55.58; H, 6.38; N, 6.82. Found: C, 55.55; H, 6.37; N, 6.80.

\[(2R,3S)-\text{methyl 2-(((benzyloxy)carbonyl)amino)-3-((pyrrolidine-1-carbonothioyl)thio)butanoate, Table 2, Entry 2}: \]

Colorless viscous liquid, \([\alpha]_{D}^{23} = -18.9 \ (c = 0.42, \text{CHCl}_3\text{)}. \)

\[ \text{FT-IR (cm}^{-1}\text{):} 579, 608, 670, 699, 749, 775, 869, 915, 955, 1004, 1034, 1078, 1090, 1159, 1207, 1269, 1304, 1349, 1384, 1438, 1509, 1718, 1744, 2953, 3363, 3425. \]

\[ ^1\text{H NMR (300 MHz; CDCl}_3\text{)} \delta _\text{H} 1.39 (d, J = 7.5 \text{Hz, 3H}), 1.93-2.06 (m, 4H), 3.58 (t, J = 6.3 \text{Hz, 2H}), 3.78 (s, 3H), 3.90 (t, J = 6.6 \text{Hz, 2H}), 4.66-4.74 (m, 1H), 4.88 (dd, \text{J}_1 = 9 \text{Hz}, \text{J}_2 = 3.6 \text{Hz, 1H}), 5.07-5.16 (m, 2H), 5.65 (d, J = 7.8 \text{Hz, 1H}), 7.28-7.32 (m, 5H). \]

\[ ^{13}\text{C NMR (75 MHz, CDCl}_3\text{)} \delta _\text{C} 16.92, 24.16, 25.95, 48.16, 50.72, 52.59, 55.07, 57.63, 67.08, 128.05, 128.09 (2C), 128.46 (2C), 136.27, 155.99, 170.81, 190.72. \]

Analysis calculated for C\textsubscript{18}H\textsubscript{24}N\textsubscript{2}O\textsubscript{4}S\textsubscript{2}: C, 54.52; H, 6.10; N, 7.06. Found: C, 54.53; H, 6.08; N, 7.05.

\[(2R,3S)-\text{methyl 2-(((benzyloxy)carbonyl)amino)-3-((diisopropylcarbamothioyl)thio)butanoate, Table 2, Entry 3}: \]

Pale yellow viscous liquid, \([\alpha]_{D}^{23} = -11.8 \ (c = 2.00, \text{CHCl}_3\text{)}. \)

\[ \text{FT-IR (cm}^{-1}\text{):} 583, 697, 734, 772, 851, 913, 960, 1026, 1085, 1142, 1193, 1212, 1313, 1370, 1439, 1476, 1508, 1720, 2968, 3348. \]

\[ ^1\text{H NMR (300 MHz; CDCl}_3\text{)} \delta _\text{H} 1.37 (d, J = 7.2 \text{Hz, 17H}), 3.78 (s, 3H), 4.79 (bs, 1H), 4.94 (dd, \text{J}_1 = 9\text{Hz, J}_2 = 3.6 \text{Hz, 1H}), 5.06-5.17 (m, 2H), 5.60 (d, J = 8.7 \text{Hz, 1H}), 7.30-7.35 (m, 5H). \]

\[ ^{13}\text{C NMR (75 MHz, CDCl}_3\text{)} \delta _\text{C} 16.18, 19.97 (4C), 47.44, 47.71, 52.54, 54.13, 57.36, 66.99, 128.00, 128.08 (2C), 128.47 (2C), 136.33, 156.00, 171.06, 198.06. \]

Analysis calculated for C\textsubscript{20}H\textsubscript{36}N\textsubscript{2}O\textsubscript{4}S\textsubscript{2}: C, 56.31; H, 7.09; N, 6.57. Found: C, 56.28; H, 7.08; N, 6.57.
(2R,3S)-methyl 3-((benzylcarbamothioyl)thio)-2-(((benzyloxy)carbonyl)amino)butanoate, Table 2, Entry 4: Colorless viscous liquid, $[\alpha]_{23}^{23} = -10.3$ ($c = 2.80$, CHCl$_3$). FT-IR (cm$^{-1}$): 632, 666, 696, 751, 795, 932, 1028, 1086, 1215, 1339, 1379, 1437, 1454, 1494, 1509, 1707, 3033, 3276. $^1$H NMR (300 MHz; CDCl$_3$) $\delta$ H 1.37 (d, $J = 7.2$ Hz, 3H), 3.76 (s, 3H), 4.59-4.67 (m, 2H), 4.85-4.98 (m, 2H), 5.09 (s, 2H), 5.66 (bs, 1H), 7.24-7.38 (m, 10H), 7.64 (bs, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ C 16.3, 47.76, 51.16, 52.72, 57.63, 67.28, 127.58 (2C), 127.99, 128.20, 128.29 (2C), 128.52 (2C), 128.82 (2C), 136.11, 137.24, 156.15, 170.70, 196.01. Analysis calculated for C$_{21}$H$_{24}$N$_2$O$_4$S$_2$: C, 58.31; H, 5.59; N, 6.48. Found: C, 58.30; H, 5.60; N, 6.45.

(2R,3S)-methyl 2-(((benzyloxy)carbonyl)amino)-3-(((S)-1-phenylethyl)carbamothioyl)thio)butanoate, Table 2, Entry 5: Pale yellow viscous liquid, $[\alpha]_{23}^{23} = -55.8$ ($c = 2.42$, CHCl$_3$). FT-IR (cm$^{-1}$): 542, 600, 631, 697, 754, 845, 885, 913, 973, 1028, 1086, 1137, 1212, 1342, 1453, 1497, 1509, 1702, 2975, 3257. $^1$H NMR (300 MHz; CDCl$_3$) $\delta$ H 1.36 (d, $J = 7.2$ Hz, 3H), 1.60 (d, $J = 6.6$ Hz, 3H), 3.78 (s, 3H), 4.60-4.66 (m, 1H), 4.89 (dd, $J_1 = 8.7$ Hz, $J_2 = 3$ Hz, 1H), 5.13 (s, 2H), 5.67-5.78 (m, 2H), 7.29-7.38 (m, 10 H), 7.57 (bs, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ C 16.69, 20.73, 47.64, 52.70, 56.07, 57.74, 67.27, 126.53 (2C), 127.72, 128.09, 128.19 (2C), 128.52 (2C), 128.75 (2C), 136.17, 141.61, 156.12, 170.73, 194.72. Analysis calculated for C$_{22}$H$_{26}$N$_2$O$_4$S$_2$: C, 59.17; H, 5.87; N, 6.27. Found: C, 59.15; H, 5.85; N, 6.28.

(R)-methyl 2-(((benzyloxy)carbonyl)amino)-3-((piperidine-1-carbonothioyl)thio)propanoate, Table 2, Entry 6: Colorless viscous liquid, $[\alpha]_{23}^{23} = +11.7$ ($c = 0.48$, CHCl$_3$). FT-IR (cm$^{-1}$): 614, 641, 718, 850, 895, 922, 973, 1019, 1052, 1130, 1151, 1175, 1221, 1274, 1432, 1524, 1682, 1735, 2947, 3336. $^1$H NMR (300 MHz; CDCl$_3$) $\delta$ H 1.69 (bs, 6H), 3.77 (s, 3H), 3.87-3.94 (m, 4H), 4.26 (bs, 2H), 4.63-4.70 (m, 1H), 5.12-5.13 (m, 2H), 5.87 (d, $J = 7.2$ Hz, 1H), 7.28-7.36 (m, 5H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ C 24.22, 25.46, 25.92, 38.30, 51.64, 52.67, 53.67, 54.00, 66.97, 128.02, 128.08 (2C), 128.46 (2C), 136.33, 155.93, 170.97, 194.25. Analysis calculated for C$_{18}$H$_{24}$N$_2$O$_4$S$_2$: C, 54.52; H, 6.10; N, 7.06. Found: C, 54.51; H, 6.07; N, 7.03.
(R)-methyl 2-(((benzyloxy)carbonyl)amino)-3-((pyrrolidine-1-carbonothioyl)thio)propanoate, Table 2, Entry 7: Colorless viscous liquid, \([\alpha]^{23}_{D}= +18.7\) (c = 0.50, CHCl\(_3\)). FT-IR (cm\(^{-1}\)): 545, 580, 623, 644, 699, 758, 742, 781, 799, 826, 865, 895, 919, 951, 975, 1022, 1055, 1157, 1178, 1227, 1242, 1277, 1319, 1343, 1388, 1434, 1456, 1528, 1681, 1737, 2946, 3329. \(^1\)H NMR (300 MHz; CDCl\(_3\)) \(\delta\) 1.93-2.13 (m, 4H), 3.65 (t, \(J = 6.9\) Hz, 2H), 3.78 (s, 3H), 3.90-3.94 (m, 4H), 4.63-4.70 (m, 1H), 5.08-5.17 (m, 2H), 5.91 (d, \(J = 7.2\) Hz, 1H), 7.31-7.38 (m, 5H). \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) C 24.21, 26.00, 37.58, 50.77, 52.67, 54.15, 55.49, 66.96, 128.02, 128.06 (2C), 128.45 (2C), 136.36, 155.97, 170.93, 191.48. Analysis calculated for C\(_{17}\)H\(_{22}\)N\(_2\)O\(_4\)S\(_2\): C, 53.38; H, 5.80; N, 7.32. Found: C, 53.40; H, 5.79; N, 7.33.

(R)-methyl 2-(((benzyloxy)carbonyl)amino)-3-((diethylcarbamothioyl)thio)propanoate, Table 2, Entry 8: Colorless viscous liquid, \([\alpha]^{23}_{D}= +24.4\) (c = 0.52, CHCl\(_3\)). FT-IR (cm\(^{-1}\)): 557, 577, 666, 697, 752, 832, 916, 982, 1006, 1028, 1055, 1144, 1205, 1269, 1301, 1343, 1380, 1420, 1438, 1455, 1490, 1514, 1719, 2934, 3340. \(^1\)H NMR (300 MHz; CDCl\(_3\)) \(\delta\) \(H\) 1.24-1.30 (m, 6H), 3.70-3.78 (m, 5H), 3.92 (d, \(J = 6.9\) Hz, 2H), 4.63-4.70 (m, 1H), 5.12-5.13 (m, 2H), 5.85 (d, \(J = 7.2\) Hz, 1H), 7.35-7.37 (m, 5H). \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) C 11.48, 12.54, 38.25, 46.99, 50.19, 52.66, 54.05, 66.94, 127.99, 128.06 (2C), 128.45 (2C), 136.35, 155.93, 170.95, 194.35. Analysis calculated for C\(_{17}\)H\(_{24}\)N\(_2\)O\(_4\)S\(_2\): C, 53.10; H, 6.29; N, 7.29. Found: C, 53.07; H, 6.29; N, 7.30.

(S)-2-((tert-butoxycarbonyl)amino)-3-phenylpropyl pyrrolidine-1-carbodithioate, Table 2, Entry 9: Pale yellow solid, Mp. 157-159 °C, \([\alpha]^{23}_{D}= +2.8\) (c = 0.34, CHCl\(_3\)). FT-IR (cm\(^{-1}\)): 657, 701, 745, 833, 857, 955, 1008, 1028, 1044, 1080, 1167, 1249, 1270, 1331, 1367, 1384, 1438, 1523, 1686, 2979, 3356. \(^1\)H NMR (300 MHz; CDCl\(_3\)) \(\delta\) \(H\) 1.41 (s, 9H), 1.93-2.13 (m, 4H), 2.84-2.91 (m, 1H), 3.02 (bs, 1H), 3.55 (d, \(J = 6\) Hz, 2H), 3.68 (t, \(J = 6.6\) Hz, 2H), 3.94 (t, \(J = 6.9\) Hz, 2H), 4.01-4.11 (m, 1H), 5.04 (bs, 1H), 7.22-7.32 (m, 5H). \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) C 24.27, 26.02, 28.38 (3C), 39.89, 40.89, 50.73, 52.42, 55.31, 79.11, 126.47, 128.44 (2C), 129.47 (2C), 137.75, 155.45, 192.78. Analysis calculated for C\(_{19}\)H\(_{28}\)N\(_2\)O\(_2\)S\(_2\): C, 59.96; H, 7.42; N, 7.36. Found: C, 59.97; H, 7.40; N, 7.35.
tert-butyl ((2S,3S)-1-((diethylcarbamothioyl)thio)-3-methylpentan-2-yl)carbamate, Table 2, Entry 10: Pale yellow solid, Mp. 104-105 °C, \([\alpha]_{D}^{23} = -56.8\) (c = 0.48, CHCl₃). FT-IR (cm⁻¹): 648, 744, 775, 835, 869, 918, 982, 1008, 1043, 1071, 1143, 1172, 1208, 1249, 1267, 1301, 1352, 1366, 1388, 1458, 1489, 1523, 1686, 2932, 2965, 3361. \(^1\)H NMR (300 MHz; CDCl₃) \(\delta_H 0.92-1.00 (m, 6H), 1.06-1.24 (m, 1H), 1.30 (t, \(J = 7.2\) Hz, 6H), 1.42 (s, 9H), 1.51-1.68 (m, 2H), 3.41-3.45 (m, 1H), 3.64-3.82 (m, 4H), 3.93-3.97 (m, 1H), 4.13-4.14 (m, 1H), 4.98 (d, \(J = 8.1\) Hz, 1H). \(^13\)C NMR (75 MHz, CDCl₃) \(\delta_C 11.58, 11.70, 12.48, 15.13, 25.37, 28.37 (3C), 38.98, 39.44, 46.82, 49.91, 55.10, 78.67, 155.92, 196.38. Analysis calculated for C₁₆H₃₂N₂O₂S₂: C, 55.13; H, 9.25; N, 8.04. Found: C, 55.10; H, 9.24; N, 8.05.

(S)-methyl 1-(((2S,3R)-3-(((benzyloxy)carbonyl)amino)-4-methoxy-4-oxobutan-2-yl)thio)carbonothioyl)pyrroloidine-2-carboxylate, Table 3, Entry 1: Colorless viscous liquid, \([\alpha]_{23}^{23} = -77.4\) (c = 2.18, CHCl₃). FT-IR (cm⁻¹): 561, 698, 751, 843, 888, 913, 957, 1013, 1042, 1086, 1170, 1205, 1341, 1413, 1516, 1735, 2954, 3360. \(^1\)H NMR (300 MHz; CDCl₃) \(\delta_H 1.38 (d, \(J = 7.5\) Hz, 3H), 2.03-2.28 (m, 4H), 3.71-3.77 (m, 8H), 4.59-4.63 (m, 1H), 4.91 (dd, \(J_1 = 8.7\) Hz, \(J_2 = 3.3\) Hz, 1H), 5.04-5.06 (m, 1H), 5.10-5.11 (m, 2H), 5.62 (d, \(J = 6\) Hz, 1H), 7.30-7.36 (m, 5H). \(^13\)C NMR (75 MHz, CDCl₃) \(\delta_C 16.38, 24.46, 29.03, 48.49, 50.95, 52.34, 52.62, 57.42, 66.20, 67.09, 127.98, 128.11 (2C), 128.47 (2C), 136.26, 156.03, 170.75, 171.02, 193.35. Analysis calculated for C₂₀H₂₆N₂O₆S₂: C, 52.85; H, 5.77; N, 6.16. Found: C, 52.82; H, 5.78; N, 6.18.

(2S,4R)-methyl 1-(((2S,3R)-3-(((benzyloxy)carbonyl)amino)-4-methoxy-4-oxobutan-2-yl)thio)carbonothioyl)-4-hydroxypyrroloidine-2-carboxylate, Table 3, Entry 2: Colorless viscous liquid, \([\alpha]_{D}^{23} = -32.2\) (c = 1.68, CHCl₃). FT-IR (cm⁻¹): 577, 667, 699, 752, 848, 897, 918, 975, 1014, 1040, 1081, 1176, 1210, 1336, 1414, 1522, 1735, 2954, 3349. \(^1\)H NMR (300 MHz; CDCl₃) \(\delta_H 1.31 (d, \(J = 6\) Hz, 3H), 2.04-2.14 (m, 1H), 2.39-2.45 (m, 1H), 3.36 (bs, 1H), 3.74 (s, 3H), 3.79 (s, 3H), 3.91-3.95 (m, 1H), 4.46 (bs, 1H), 4.52-4.58 (m, 1H), 4.99 (dd, \(J_1 = 9\) Hz, \(J_2 = 3\) Hz, 1H), 5.08-5.13 (m, 3H), 5.71 (d, \(J = 23\) Hz, 1H).
6 Hz, 1H), 7.31-7.37 (m, 5H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ C 14.54, 30.37, 48.40, 52.44, 52.81, 56.52, 59.18, 64.46, 67.28, 69.70, 127.83 (2C), 128.19, 128.55 (2C), 136.10, 156.55, 170.71, 171.20, 194.15. Analysis calculated for C$_{20}$H$_{26}$N$_2$O$_7$S$_2$: C, 51.05; H, 5.57; N, 5.95. Found: C, 51.03; H, 5.58; N, 5.93.

(S)-1-((((2S,3R)-3-(((benzyloxy)carbonyl)amino)-4-methoxy-4-oxobutan-2-yl)thio)carbonothioyl)pyrrolidine-2-carboxylic acid, Table 3, Entry 3: Colorless viscous liquid, $[\alpha]^{23}_D = -69.7$ (c = 1.68, CHCl$_3$). FT-IR (cm$^{-1}$): 667, 697, 751, 795, 829, 920, 959, 1013, 1039, 1086, 1183, 1215, 1342, 1412, 1522, 1717, 2954, 3329. $^1$H NMR (300 MHz; CDCl$_3$) $\delta$ H 1.38 (d, $J = 7.2$ Hz, 3H), 2.02-2.33 (m, 4H), 3.65-3.79 (m, 5H), 4.59-4.63 (m, 1H), 4.94 (dd, $J_1 = 8.7$ Hz, $J_2 = 3$ Hz, 1H), 5.07-5.16 (m, 3H), 5.66 (d, $J = 8.7$ Hz, 1H), 7.31-7.35 (m, 5H), 8.84 (bs, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ C 16.28, 24.46, 28.94, 48.54, 50.96, 52.72, 57.36, 66.05, 67.22, 128.05, 128.15 (2C), 128.49 (2C), 136.20, 156.18, 170.84, 174.94, 193.73. Analysis calculated for C$_{19}$H$_{24}$N$_2$O$_6$S$_2$: C, 51.80; H, 5.49; N, 6.36. Found: C, 51.78; H, 5.48; N, 6.37.

(5R,6S,10R)-methyl 9-benzyl-10-((S)-1-hydroxyethyl)-5-(methoxycarbonyl)-6-methyl-3-oxo-1-phenyl-8-thioxo-2-oxa-7-thia-4,9-diazaundecan-11-oate, Table 3, Entry 4: Pale yellow viscous liquid, $[\alpha]^{23}_D = +11.4$ (c = 1.62, CHCl$_3$). FT-IR (cm$^{-1}$): 567, 698, 753, 771, 915, 1002, 1085, 1168, 1214, 1380, 1437, 1455, 1498, 1516, 1719, 2956, 3353. $^1$H NMR (300 MHz; CDCl$_3$) $\delta$ H 3.80 (s, 6H), 4.67-4.71 (m, 1H), 5.07-5.18 (m, 3H), 5.27-5.45 (m, 2H), 5.61 (bs, 1H), 7.28-7.42 (m, 10H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ C 15.87, 23.11, 49.46, 52.62, 52.74, 54.15, 56.99, 57.40, 67.32, 70.34, 128.05 (2C), 128.16 (2C), 128.49, 128.55 (2C), 128.59, 130.16, 136.00, 156.65, 169.51, 170.94, 198.10. Analysis calculated for C$_{26}$H$_{32}$N$_2$O$_7$S$_2$: C, 56.92; H, 5.88; N, 5.11. Found: C, 56.90; H, 5.85; N, 5.12.
(S)-methyl 1-(((R)-2-(((benzyloxy)carbonyl)amino)-3-methoxy-3-oxopropyl)thio)carbonothioyl)pyrrolidine-2-carboxylate, Table 3, Entry 5: Colorless viscous liquid, $[\alpha]_{D}^{23} = -56.9 \ (c = 0.58, \text{CHCl}_3)$. FT-IR (cm$^{-1}$): 577, 667, 699, 752, 841, 890, 914, 958, 1013, 1046, 1087, 1170, 1209, 1266, 1341, 1415, 1515, 1720, 1736, 2957, 3346. $^1$H NMR (300 MHz; CDCl$_3$) $\delta$H 2.05-2.28 (m, 4H), 3.70-3.77 (m, 7H), 3.82-4.00 (m, 3H), 4.66-4.72 (m, 1H), 5.03-5.05 (m, 1H), 5.13 (s, 2H), 5.77 (d, J = 7.6 Hz, 1H), 7.33-7.37 (m, 5H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C 24.52, 29.12, 38.06, 51.03, 52.35, 52.72, 53.80, 66.68, 67.07, 128.05, 128.10 (2C), 128.46 (2C), 136.29, 156.32, 170.77, 170.79, 194.00. Analysis calculated for C$_{19}$H$_{24}$N$_2$O$_6$S$_2$: C, 51.80; H, 5.49; N, 6.36. Found: C, 51.82; H, 5.48; N, 6.34.

Boc-deprotection of the compound, A (entry 9, Table 2):

Compound, A (30 mg, 0.08 mmol) was dissolved in DCM (1.5 mL). Trifluoroacetic acid (TFA) (45 mg, 0.4 mmol) was added to the solution at 0 °C followed by stirring at room temperature for 12 h. After completion of the reaction (monitored by TLC), DCM and excess of TFA were removed under vacuum.
The crude product, B obtained was directly used in the next step of peptide coupling reaction without any purification.

**Peptide coupling of B with Boc-protected (S)-phenylalanine(N-Boc(S)-Phe):**

Compound, B obtained from the previous step and N-Boc(S)-Phe (24 mg, 0.09 mmol) were dissolved in THF (2 mL). Triethylamine (32 mg, 0.32 mmol) was added to the solution. The reaction mixture was cooled to 0 °C. N-Hydroxybenzotriazole (HOBt) (16 mg, 0.12 mmol) and 3-(ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine (EDC) (18 mg, 0.12 mmol) were added drop wise to the solution followed by stirring for 1 h at 0 °C. The reaction mixture was continued to stir for 14 h at room temperature. After completion of the reaction (monitored by TLC), THF was removed under vacuum. The product was extracted using ethyl acetate and was washed with water. The organic layer was dried over anhydrous Na₂SO₄. The crude product was purified using column chromatography.

![Scheme 1 Synthesis of dithiocarbamate bearing peptide](image-url)
(S)-2-((S)-2-((tert-butoxycarbonyl)amino)-3-phenylpropanamido)-3-phenylpropyl pyrrolidine-1-carbodithioate: White solid, Mp. 164-165 °C, [α]$_{D}^{23}$ = -37.7 (c = 0.38, CHCl$_3$). FT-IR (cm$^{-1}$): 657, 701, 857, 833, 870, 955, 1008, 1044, 1154, 1167, 1249, 1270, 1438, 1523, 1687, 2930, 2979, 3349, 3356. $^1$H NMR (300 MHz; CDCl$_3$) δ$_{H}$ 1.40 (s, 9H), 1.82-2.13 (m, 4H), 2.75-2.83 (m, 1H), 2.92-2.94 (m, 1H), 3.00-3.16 (m, 2H), 3.35 (dd, J$_1$ = 3.9 Hz, J$_2$ = 14.4 Hz, 1H), 3.60-3.74 (m, 3H), 3.90 (t, J = 6.3 Hz, 2H), 4.22-4.35 (m, 2H), 5.01 (bs, 1H), 7.01 (d, J = 6.6 Hz, 1H), 7.16-7.34 (m, 10H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ$_{C}$ 24.18, 25.95, 28.29, 38.16, 38.76, 40.80, 50.87, 52.65, 55.58, 79.70, 126.65, 126.67, 128.40, 128.55, 129.46, 129.48, 136.71, 137.38, 155.16, 171.07, 193.04. Analysis calculated for C$_{28}$H$_{37}$N$_{3}$O$_{3}$S$_{2}$: C, 63.72; H, 7.07; N, 7.96. Found: C, 63.74; H, 7.05; N, 7.93.