An efficient one-pot protocol for the synthesis of dithiocarbonate-tethered peptidomimetics and neo-glycosylated amino acids has been described. This synthetic process involves *in situ* generation of a dithiocarbonate salt from the Nα-protected aminol substrate by reacting with CS₂ followed by addition of α-bromo amino acid/sugar bromide to form the desired product.

**Krishnamurthy Muniyappa**, Basavaprabhu, Sureshbabu, V.V. *Int. J. Pept. Res. Ther.* 2015, 21, 195-203
3.1. Introduction

Several classes of peptidomimetics have been prepared by replacing the native amide bond with various other tethers (carbamates, beta-carbamates, trithio-carbonate, thio-carbamate, dithio-carbamate and selenothio-carbamate) and are biologically scrutinized (Figure 3.1). Such non-amidic insertions would bring out shelf stability, alter the secondary structures and induce rigidity and thus would suffice the basic needs of a drug candidate. The importance of unnatural linkages in the peptide backbone and fruitful results being reported from biological screening of many types of molecules prompts one to explore this area of research. With a background of our group’s success in designing new peptidomimetics through incorporation of biologically active and valuable linkages into peptide backbone as well as developing simpler routes for the existing ones, the attention was focused towards another useful functionality namely dithiocarbonate.

FIGURE 3.1. Modification of peptide bond
Dithiocarbonates (xanthates) have a wide range of applications; they serve as radicals, intermediates in the synthesis of thiols, thiocarbonates, alkenes, alkanes, S-activated carbanions, photosensitizers and inhibitors of histone deacetylases (HDAC) in the treatment of cancer. They have also been used for enhanced technological, biological and synthetic applications. This functionality also serves as protecting group in the synthesis of natural products. It has been found that dithio-analogues are about ten times more potent rHDAC6 and rHDAC1 inhibitors than trithio-compounds.

S. Kakaei et al. reported the synthesis of different xanthates by treating potassium O-ethyl xanthate with various alkyl/aryl halo derivatives in the presence of acetone at 0 °C to room temperature (Scheme 3.1). The products were obtained in good yields.

![Scheme 3.1. Synthesis of dithiocarbonates starting from potassium O-ethyl xanthate](image)

Baptiste et al. synthesized dithiocarbonate esters by employing commercially available ethyl bromofluoroacetate through nucleophilic substitution of bromide ion with O-ethyl potassium dithiocarbonate in ethanol for about 1.5 h at r.t. This reaction proceeded smoothly, and the racemic dithiocarbonate was isolated in 80% yield (Scheme 3.2).
Scheme 3.2. Synthesis of dithiocarbonates from ethyl bromofluoroacetate

Jung et al.,\textsuperscript{21} reported the synthesis of dithiocarbonates by reacting corresponding alcohols with various primary and secondary halides in presence of CS$_2$, CS$_2$CO$_3$, and tetrabutylammonium iodide (TBAI) in DMF at 0 °C to r.t. The protocol gave good yields even when sterically hindered amines were employed (Scheme 3.3).

Scheme 3.3. Synthesis of dithiocarbonate esters

Ray et al., developed an efficient one-pot, three component reaction of alcohol, methyl iodide and Triton-B/CS$_2$ in dry DMSO resulting in dithiocarbonates in moderate to excellent yields (70-98%). Triton-B has been found to be an efficient and useful as a basic catalyst (Scheme 3.4).\textsuperscript{22} This protocol offers more general method for the formation of C-S bonds, essential for numerous organic reactions.
Katritzky et al., reported the synthesis of dithiocarbonates through benzotriazole and thiols (Scheme 3.5).\textsuperscript{23} The bis-(benzotriazol-1-yl)methanethione was made to react with alkyl alcohols and sodium ethoxide in dichloromethane at -78 °C to r.t. for about 4 h leading to an intermediate which was then subsequently treated with thiol and sodium hydroxide in THF for about 4 h to afford dithiocarbonate esters.

![Scheme 3.5](image)

**Scheme 3.5.** Synthesis of dithiocarbonates employing benzotriazole and alcohols

A thorough literature survey revealed that the dithiocarbonate-tethered peptidomimetics were not reported earlier. Recently our group reported the synthesis of dithiocarbamates\textsuperscript{24} and trithiocarbonate tethered peptidomimetics.\textsuperscript{25} In this chapter, a straightforward and an efficient one-pot protocol for the synthesis of dithiocarbonate tethered peptidomimetics is delineated.
3.2. Present work

Initially, the synthesis of dithiocarbonates of the type 3.4 (Scheme 3.6) which can be accessed by employing a \(N^\alpha\)-protected aminol, NaH, CS\(_2\), and \(\alpha\)-bromo amino acid was undertaken. The Cbz/Boc-protected aminols\(^{26}\) 3.1, in brief, were prepared by the treatment of \(N^\alpha\)-protected amino acid with \(N, N\)-diisopropylethylamine (DIPEA), propylphosphonic anhydride (T3P) and NaBH\(_4\) in THF at 0 °C. The \(\alpha\)-bromo acid 3.2 was prepared starting from \(\alpha\)-amino acid through the diazotization followed by bromination under acidic conditions.\(^{27}\)

Having key components \(N^\alpha\)-protected aminols and \(\alpha\)-bromo acid in hand, we then started to synthesize the title compounds. In a typical experiment, Cbz-Ala-\(\psi\)[CH\(_2\)-OH] 3.1a (1.0 equiv.) in dry THF (5 mL) was treated with NaH (1.5 equiv.) and CS\(_2\) (1.5 equiv.), the reaction mixture was stirred for 10 min at r.t. to form dithiocarbonate salt. Then BrCH(CH\(_2\)C\(_6\)H\(_5\))COOH 3.2a (1.5 equiv.) was added. The reaction was found to be complete in about 3 h (as monitored by TLC analysis). A simple workup followed by purification of the crude product through column chromatography gave the pure product 3.4a in 79% yield (Scheme 3.6).

![Chemical structure](image)

**SCHEME 3.6.** Synthesis of dithiocarbonate-tethered peptidomimetics 3.4 and 3.5

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The above protocol was extended to prepare four dipeptidomimetics 3.4a-d employing several Cbz/Boc-protected aminols and α-bromo amino acid esters. All the compounds were obtained in moderate to good yields (Table 3.1). In the next part of the study, we extended the same protocol to prepare $N, N'$-orthogonally protected dithiocarbonate-tethered dipeptidomimetics. In a typical reaction, $N^\alpha$-protected aminol was reacted with NaI and CS$_2$ to afford the corresponding dithiocarbonate salt intermediate which was further treated with $N^\alpha$-protected amino alkyl iodide 3.3 to obtain $N, N'$-orthogonally protected dithiocarbonate-tethered dipeptidomimetics, 3.5a-c in good yield. A simple workup followed by purification through column chromatography resulted in pure products, which were characterized by mass spectrometry, $^1$H and $^{13}$C NMR analyses (Table 3.1).

**Table 3.1.** List of dithiocarbonate-tethered dipeptidomimetics

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reactant (3.1)</th>
<th>Reactant (3.2/3.3)</th>
<th>Product (3.4/3.5)</th>
<th>Yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>[\text{CbzHN} \text{OH} ]</td>
<td>[\text{Br} \text{COOH} ]</td>
<td>[\text{CbzHN} \text{O} \text{S} \text{COOH} ]</td>
<td>79</td>
</tr>
<tr>
<td>b</td>
<td>[\text{CbzHN} \text{OH} ]</td>
<td>[\text{Br} \text{COOH} ]</td>
<td>[\text{CbzHN} \text{O} \text{S} \text{COOH} ]</td>
<td>82</td>
</tr>
<tr>
<td>c</td>
<td>[\text{Boc} \text{OH} ]</td>
<td>[\text{Br} \text{COOH} ]</td>
<td>[\text{Boc} \text{O} \text{S} \text{COOH} ]</td>
<td>73</td>
</tr>
<tr>
<td>d</td>
<td>[\text{BocHN} \text{OH} ]</td>
<td>[\text{Br} \text{COOH} ]</td>
<td>[\text{BocHN} \text{O} \text{S} \text{COOH} ]</td>
<td>76</td>
</tr>
</tbody>
</table>
Chapter III  

Dithiocarbonate tethered peptidomimetics

a
BocHN \( \text{OH} \) \[ \text{NH} \text{Cbz} \] \[ \text{S} \] \[ \text{BocHN} \text{O} \text{S} \text{NH} \text{Cbz} \] 74

b
\(^{14}\text{BuO}\) BocHN \( \text{OH} \) \[ \text{NH} \text{Cbz} \] \[ \text{S} \] \[ \text{BocHN} \text{O} \text{S} \text{NH} \text{Cbz} \] 78

c
CbzHN \( \text{OH} \) \[ \text{NH} \text{Boc} \] \[ \text{S} \] \[ \text{CbzHN} \text{O} \text{S} \text{NH} \text{Boc} \] 77

*Yields correspond to the isolated pure dithiocarbonate-tethered peptidomimetics.

Protein glycosylation is an ubiquitous process and is the complex protein modification which makes use of a plethora of enzymes to introduce structural diversity to the proteins. Glycosylation of peptides increases the absorption of peptides by increasing their membrane permeability.\(^{28}\) Our group reported several types of glycoconjugates such as trithiocarbonate linked glycosylated amino acids,\(^{25}\) urea tethered glycoconjugates\(^{29}\) and carbamate tethered glycosylated amino acids.\(^{30}\) With this background, we focused our attention towards dithiocarbonate-tethered glycosylated amino acids. At first glycosyl bromide 3.6, was prepared from glucose through established protocol using glucose pentaacetate.\(^{31}\) Subsequent reaction of this sugar bromide 3.6 with \(N^\text{H}\)-protected aminol 3.1 in the presence of NaH and CS\(_2\) yielded dithiocarbonate-tethered neo-glycosylated amino acid 3.7 (Scheme 3.7 & Table 3.2), which was isolated as pure product after column chromatography and characterized.
SCHEME 3.7. Synthesis of dithiocarbonate-tethered neo-glycosylated amino acids

Table 3.2. List of dithiocarbonate-tethered neo-glycosylated amino acids

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product 3.7</th>
<th>Yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>![Image]</td>
<td>65</td>
</tr>
<tr>
<td>b</td>
<td>![Image]</td>
<td>74</td>
</tr>
<tr>
<td>c</td>
<td>![Image]</td>
<td>69</td>
</tr>
</tbody>
</table>

aYields correspond to the isolated pure products.

On the other hand, the above protocol was employed to prepare dithiocarbonate-tethered tripeptidomimetics 3.9. In this case, N\textsuperscript{a}-protected dithiocarbonate-tethered dipeptide acids 3.4 were allowed to react with amino acid methyl ester 3.8 in presence of Et\textsubscript{3}N (1.2 equiv.) and ethyl chloroformate (1.2 equiv.) in dry THF (5 mL) at -15 °C to r.t. The reaction was complete in 2-3 h as monitored by TLC. A simple workup followed by column chromatography afforded pure N\textsuperscript{a}-protected dithiocarbonate-tethered tripeptidomimetic 3.9\textsuperscript{a} in 60% yield (Scheme 3.8). The generality of the protocol was demonstrated by employing Cbz/Boc-protected dithiocarbonate-
tethered dipeptide acids and amino acid methyl esters to obtain a series of tripeptidomimetics in moderate to good yields (Table 3.3). Thus the protocol works well for the chain extension of a peptide in N→C direction.

**Scheme 3.8.** Synthesis of dithiocarbonate-tethered tripeptidomimetic 21 through N→C terminal extension

**Table 3.3.** List of dithiocarbonate-linked tripeptidomimetics

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product 3.9</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td><img src="image.png" alt="Image" /></td>
<td>60</td>
</tr>
<tr>
<td>b</td>
<td><img src="image.png" alt="Image" /></td>
<td>68</td>
</tr>
<tr>
<td>c</td>
<td><img src="image.png" alt="Image" /></td>
<td>72</td>
</tr>
</tbody>
</table>

<sup>a</sup>Yields correspond to the isolated pure compounds.
3.2.1. Test for racemization

It was known that thiolysis/alcoholysis of any chiral α-bromo alkyl esters proceed through S_N2 mechanism with inversion of configuration at the stereocenter. Thus the coupling of α-bromo acids with thiols proceed with the inversion of configuration at the bromo derivative. Similarly, the formation of inverted product during the reaction of α-aminooxy esters with bromo esters and Cbz-NHOH was reported. In the present study, it is reasoned that the chiral carbon α to ester group of dipeptidomimetics will be of D-configuration due to inversion. The compounds 3.4b and 3.4b' were prepared through reacting Cbz-Phg-ψ(CH_2-OH) with the bromo acids derived from L- and D-Phe and subjected to RP-HPLC analysis. The study revealed the presence of diastereomers in 93:3 and 94:7 ratio respectively. The pure products 3.4b and 3.4b' showed single peaks at different R_t values 17.554 and 18.264 respectively. While the equimolar mixture of 3.4b and 3.4b' had two well separated peaks at R_t = 17.507 min and R_t = 18.420 min.

**Chiral HPLC particulars:** Agilent 1100 series having G1311B VWD at \( \lambda_{max} = 254 \text{ nm} \).

**Column Type:** Phenomenex made Lux, pore size-5u, Amylose-2.

**Column Dimensions:** diameter x length = 250 x 4.60 mm.

**Flow rate:** 0.5 mL/min, 30 min.

**Method:** n-hexane: 2-propanol (70:30).

**Detection limit:** 0.1 µg/mL.
FIGURE 3.2. RP-HPLC chromatogram of 3.4b

FIGURE 3.3. RP-HPLC chromatogram of 3.4b’
FIGURE 3.4. RP-HPLC chromatogram of 3.4b and 3.4b'
3.3. Experimental Section

All solvents were distilled prior to use according to the standard protocols. Amino acids were used as purchased from Sigma-Aldrich Company. $^1$H and $^{13}$C NMR spectra were recorded at 300, 400 MHz and 75, 100 MHz respectively, with DMSO-$d_6$ as an internal standard. Mass spectra were recorded using electrospray ionization mass spectrometry (ESI-MS) and the samples were dried under vacuum before analysis. All reactions were monitored using TLCs (Merck silica gel 60F254 precoated aluminium plates purchased from merck). Chiral HPLC analysis of isomers was carried out using Agilent 1100series, Lux 5µ amylase-2, and 250X4.60 nm

3.3.1 General procedure for the synthesis of dithiocarbonate-tethered dipeptidomimetics (3.4a-d): To a solution of $\text{N}^\text{a}$-Cbz/Boc-amino alcohol 3.1 (1.0 equiv.) in THF (5 mL) and NaH (1.5 equiv.) was added CS$_2$ (1.5 equiv.). After 10 min, a solution of α-bromo acid 3.2 (1.5 equiv.) in THF was added to the reaction mixture then stirred for 3 h. After completion of the reaction (TLC analysis), the solvent was removed under reduced pressure and the residue was diluted with ethyl acetate (20 mL). The organic layer was washed with 10% citric acid (10 mL), water (10 mL), brine (10 mL) and then dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to afford crude product 3.4, which was purified through silica gel column chromatography (100-200 mesh) using CHCl$_3$/MeOH as eluent (90:10).

3.3.2 General procedure for the synthesis of orthogonally protected $\text{N, N}^\text{a}$-dithiocarbonate-tethered dipeptidomimetics (3.5a-c): To a solution of $\text{N}^\text{a}$-Cbz/Boc-protected amino alcohol 3.1 (1.0 equiv.) in THF (5 mL) and NaH (1.5 equiv.) was added CS$_2$ (1.5 equiv.). After 10 min, a solution of $\text{N}^\text{a}$-protected amino alkyl iodide 3.3 (1.5 equiv.) in THF was added to the reaction
mixture and then stirred for 3 h. After completion of the reaction (TLC analysis), the solvent was removed under reduced pressure and the residue was diluted with ethyl acetate (20 mL). The organic layer was washed with 10% citric acid (10 mL), water (10 mL), brine (10 mL) and then dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to afford crude product 3.5, which was purified through silica gel column chromatography (100-200 mesh) using EtOAc/hexane as eluent (80:20).

3.3.3 General procedure for the synthesis of dithiocarbonate-tethered glycosylated amino acids (3.7a-c): To a solution of N\textsuperscript{α}-Cbz/Boc-amino alcohol 3.1 (1.0 equiv.) in THF (5 mL) and NaH (1.5 equiv.) was added CS\textsubscript{2} (1.5 equiv.). After 10 min, a solution of sugar bromide 3.6 (1.5 equiv.) in THF was added to the reaction mixture and then stirred for 3 h. After completion of the reaction (TLC analysis), the solvent was removed under reduced pressure and the residue was diluted with ethyl acetate (20 mL). The organic layer was washed with 10% citric acid (10 mL), water (10 mL), brine (10 mL) and then dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to afford crude product 3.7, which was purified through silica gel column chromatography (100-200 mesh) using EtOAc/hexane as eluent (70:30).

3.3.4 General procedure for the synthesis of dithiocarbonate-tethered tripeptidomimetics (3.9a-c): To a solution of N\textsuperscript{α}-protected dithiocarbonate-tethered dipeptide acid 3.4 (1.0 equiv.) in THF (5 mL) was added TEA (1.2 equiv.) and ECF (1.2 equiv.) at -15 °C. After 10 min, a deprotonated solution of α-amino acid methyl ester 3.8 (1.5 equiv.) in THF was added to the reaction mixture and then the whole mixture was stirred for 3-4 h. After completion of the reaction (TLC analysis), the solvent was removed under reduced pressure and the residue was diluted with ethyl acetate (20 mL). The organic layer was washed with 10% Na\textsubscript{2}CO\textsubscript{3} (10 mL), 10% citric acid (10 mL), water (10 mL), brine (10 mL) and then dried over anhydrous sodium
sulfate. The solvent was evaporated under reduced pressure to afford crude product 3.9, which was purified through silica gel column chromatography (100-200 mesh) using EtOAc/hexane as eluent (60:40).

3.3.5 Spectroscopic data of compounds 3.4, 3.5, 3.7 and 3.9

(S)-2-(((S)-2-(benzoylcarbonyl)propoxy)carbonothioylthio)-3-phenylpropanoic acid (3.4a) 
$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.31 (d, $J=5.4$ Hz, 3H), 3.41 (d, $J=3.8$Hz, 2H), 3.62 (d, $J=4.4$ Hz, 2H), 3.65-3.72 (m, 1H), 3.81-3.87 (m, 1H), 5.18 (s, 2H), 5.72 (br s, 1H), 7.10-7.35 (m, 10H), 9.25 (br s, 1H);

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 16.8, 42.8, 46.9, 51.9, 65.7, 70.9, 126.1, 127.2, 127.6, 127.7, 128.7, 129.0, 136.1, 139.2, 155.9, 173.4, 215.4 ppm;

HRMS: m/z [M+H]$^+$ calcd for C$_{31}$H$_{24}$NO$_3$S$_2$: 434.10; found: 434.09.

(R)-2-(((S)-2-(benzoylcarbonyl)-2-phenylethoxy)carbonothioylthio)-3-phenylpropanoic acid (3.4b)

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 3.30-3.48 (dd, 2H), 3.62 (d, $J=4.2$ Hz, 2H), 3.81-3.92 (m, 1H), 4.18-4.24 (m, 1H), 5.12 (s, 2H), 5.82 (br s, 1H), 6.96-7.55 (m, 15H), 9.10 (br s, 1H);

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 38.5, 48.6, 50.9, 62.3, 66.1, 125.0, 126.3, 127.0, 127.5, 127.6, 128.4, 140.6, 141.4, 143.6, 155.6, 171.2, 214.8 ppm;

HRMS: m/z [M+H]$^+$ calcd for C$_{26}$H$_{26}$NO$_3$S$_2$: 496.12; found: 496.13.
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(2R)-2-(((1-(tert-butoxycarbonyl)pyrrolidin-2-yl)methoxy)carbonothioylthio)-3-phenylpropanoic acid (3.4c)

\[ \text{NMR (400 MHz, CDCl}_3\text{): } \delta \text{ 1.58 (s, 9H), 1.94 (br s, 2H), 2.14 (br s, 1H), 2.41 (br s, 1H), 3.16 (dd, } J=13.6, 6.8 \text{ Hz, 1H), 3.34 (dd, } J=14.0, 5.8 \text{ Hz, 1H), 3.45-3.54 (br s, 2H), 3.60 (d, } J=4.4 \text{ Hz, 2H), 4.36-4.42 (m, 1H), 5.02 (br s, 1H), 7.25-7.45 (m, 5H), 9.08 (br s, 1H);} \]

\[ ^{13}\text{C NMR (100 MHz, CDCl}_3\text{): } \delta \text{ 23.4, 28.3, 30.7, 38.1, 46.9, 52.3, 52.7, 59.9, 66.0, 80.5, 127.1, 128.5, 129.3, 135.9, 154.5, 171.7, 214.9 \text{ ppm;}} \]

ESI-MS: \([M+H]^+ \text{ calcd for C}_{26}\text{H}_{38}\text{NO}_{5}\text{S}_{2}: 426.13; \text{ found: 426.09.} \]

(R)-2-(((S)-2-(tert-butoxycarbonyl)propoxy)carbonothioylthio)-4-methylpentanoic acid (3.4d)

\[ \text{NMR (400 MHz, CDCl}_3\text{): } \delta \text{ 0.91-0.92 (d, } J=5.6 \text{ Hz, 6H), 1.33-1.35 (d, } J=6.8 \text{ Hz, 3H), 1.43 (s, 9H), 1.52-1.56 (m, 1H), 1.62-1.65 (m, 2H), 3.59 (d, } J=4.4 \text{ Hz, 2H), 4.16-4.18 (m, 1H), 4.58-4.62 (m, 1H), 5.04 (br s, 1H), 9.13 (br s, 1H);} \]

\[ ^{13}\text{C NMR (100 MHz, CDCl}_3\text{): } \delta \text{ 17.9, 21.8, 22.9, 24.7, 28.3, 41.5, 49.9, 50.6, 52.3, 71.0, 80.1, 155.6, 172.4, 215.6 \text{ ppm;}} \]

HRMS: \([M+H]^+ \text{ calcd for C}_{15}\text{H}_{28}\text{NO}_{5}\text{S}_{2}: 366.34; \text{ found: 366.32} \).
S-(R)-2-(benzyloxycarbonyl)-3-methylbutyl-O-(S)-2-(tert-butoxycarbonyl)propyl carbonodithioate (3.5a)

$^1$H NMR (300 MHz, CDCl$_3$): δ 0.98 (d, $J$=3.2 Hz, 6H), 1.39 (d, $J$=5.6 Hz, 3H), 1.44 (s, 9H), 2.11 (m, 1H), 3.55 (d, $J$=4.2 Hz, 2H), 3.62 (d, $J$=4.4 Hz, 2H), 3.91-4.01 (m, 1H), 4.44-4.62 (m, 1H), 5.12 (s, 2H), 5.05 (br s, 1H), 5.36 (br s, 1H), 7.25-7.46 (m, 5H);

$^{13}$C NMR (75 MHz, CDCl$_3$): δ 17.2, 18.7, 28.3, 32.4, 34.8, 53.3, 61.8, 67.6, 70.8, 80.1, 128.3, 128.4, 128.7, 129.0, 136.5, 154.4, 156.6, 214.5 ppm;

ESI-MS: m/z [M+H]$^+$ calcd for C$_{23}$H$_{35}$N$_2$O$_5$S$_2$: 471.19; found: 471.17.

S-2-(benzyloxycarbonyl)-4-methylpentyl-O-(S)-3-tert-butoxy-2-(tert-butoxycarbonyl)propyl carbonodithioate (3.5b)

$^1$H NMR (400 MHz, CDCl$_3$): δ 0.92-0.94 (dd, $J$=4.4, 6H), 1.20 (s, 9H), 1.45 (s, 9H), 1.54-1.57 (m, 1H), 1.61-1.68 (m, 2H), 2.96 (d, 2H), 3.64 (d, 2H), 3.79-3.81 (m, 2H), 4.18-4.21 (m, 1H), 4.61-4.63 (m, 1H), 5.24 (br s, 1H), 5.31 (s, 2H), 5.42 (br s, 1H), 7.22-7.39 (m, 5H);

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 21.9, 22.9, 24.7, 27.4, 28.3, 38.0, 41.8, 52.3, 54.0, 61.8, 65.0, 74.1, 80.0, 127.1, 127.8, 129.5, 135.9, 153.8, 155.5, 215.3 ppm;

ESI-MS: m/z [M+H]$^+$ calcd for C$_{27}$H$_{45}$N$_2$O$_6$S$_2$: 557.26; found: 557.22.
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O-(S)-2-(benzoxycarbonyl)-3-methylbutyl-S-(R)-2-(tert-butoxycarbonyl)propyl carbonodithioate (3.5c)

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 0.98 (d, $J=3.2$ Hz, 6H), 1.35 (d, $J=5.6$ Hz, 3H), 1.43 (s, 9H), 2.13 (m, 1H), 3.57 (d, $J=4.4$ Hz, 2H), 3.63 (d, $J=4.6$ Hz, 2H), 3.90-4.02 (m, 1H), 4.45-4.61 (m, 1H), 5.12 (s, 2H), 5.07 (br s, 1H), 5.38 (br s, 1H), 7.24-7.48 (m, 5H);

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 17.2, 18.7, 28.3, 32.4, 34.8, 53.3, 61.8, 67.6, 70.8, 80.1, 128.3, 128.4, 128.7, 129.0, 136.5, 154.1, 156.6, 214.5 ppm;

ESI-MS: m/z [M+H]$^+$ calcd for C$_{22}$H$_{33}$N$_2$O$_3$S$_2$: 471.19; found: 471.17.

(2S,3S,4R,5S,6R)-2-(acetoxyethyl)-6-(((S)-2-(((benzoxycarbonyl)amino)-3 methylbutoxy) carbonothioyl)thio) tetrahydro-2H-pyran-3,4,5-triyl triacetate (3.7a)

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 0.99 (d, $J=3.4$ Hz, 6H), 2.02 (s, 3H), 2.03 (s, 3H), 2.04 (s, 3H), 2.07 (s, 3H), 2.12 (m, 1H), 3.68 (d, $J=4.2$ Hz, 2H), 3.84 (ddd, $J=9.5$, 4.5, 2.0 Hz, 1H), 3.98-4.06 (m, 1H), 4.08 (dd, $J=12.5$, 2.0 Hz, 1H), 4.32 (dd, $J=12.5$, 4.5 Hz, 1H), 4.94 (t, $J=9.5$ Hz, 1H), 5.08 (t, $J=9.5$ Hz, 1H), 5.14 (s, 2H), 5.17 (br s, 1H), 5.28 (dd, $J=10$, 9.5 Hz, 1H), 5.32 (d, $J=9.5$ Hz, 1H), 7.33-7.36 (m, 5H);

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 18.7, 20.4, 20.5, 20.6, 28.4, 53.3, 61.9, 65.8, 67.6, 68.3, 70.3, 72.9, 73.3, 79.8, 128.3, 128.3, 128.4, 128.6, 129.0, 136.6, 156.7, 169.8, 170.0, 170.9, 171.1, 215.4 ppm;

ESI-MS: m/z [M+H]$^+$ calcd for C$_{28}$H$_{38}$NO$_{12}$S$_2$: 644.18; found: 644.15.
(2S,3S,4R,5S,6R)-2-(acetoxyethyl)-6-(((S)-2-(((benzyloxy)carbonyl)amino)-2-phenylethoxy) carbonothioyl)thio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (3.7b)

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.97 (s, 3H), 2.01 (s, 3H), 2.02 (s, 3H), 2.06 (s, 3H), 3.61 (d, $J$= 4.4 Hz, 2H), 3.77 (ddd, $J$=10, 4.5, 2 Hz, 1H), 4.07 (dd, $J$=12.5, 2 Hz, 1H), 4.19-4.25 (m, 1H), 4.31 (dd, $J$=12.5, 4.5 Hz, 1H), 4.86 (t, $J$=9.5 Hz, 1H), 5.04 (t, $J$=9.5 Hz, 1H), 5.10 (s, 2H), 5.14 (t, $J$=9.5 Hz, 1H), 5.19 (br s, 1H), 5.27 (t, $J$=9.5 Hz, 1H), 7.25-7.36 (m, 10H);

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 20.4, 20.5, 20.6, 50.9, 61.8, 67.2, 68.3, 70.5, 72.9, 73.1, 80.0, 126.3, 127.0, 127.2, 127.7, 128.6, 129.0, 140.6, 143.6, 155.6, 169.7, 170.1, 170.8, 171.0, 215.6 ppm;

HRMS: m/z [M+H]$^+$ calcd for C$_{31}$H$_{36}$NO$_{12}$S$_2$: 678.16; found: 678.15.

(2S,3S,4R,5S,6R)-2-(acetoxyethyl)-6-(((S)-2-((tert-butoxycarbonyl)aminopropoxy)
carbonothioyl)thio) tetrahydro-2H-pyran-3,4,5-triyl triacetate (3.7c)

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.34 (s, 9H), 1.36 (d, $J$=5.7 Hz, 3H), 2.01 (s, 3H), 2.03 (s, 3H), 2.04 (s, 3H), 2.05 (s, 3H), 3.63-3.66 (m, 2H), 3.79 (ddd, $J$=10.5, 4.5, 2 Hz, 1H), 3.84-3.91 (m, 1H), 4.07 (dd, $J$=13, 2 Hz, 1H), 4.29 (dd, $J$=13, 4.5 Hz, 1H), 4.89 (t, $J$=10 Hz, 1H), 5.05 (t, $J$=10 Hz, 1H), 5.12 (br s, 1H), 5.28 (t, $J$=10 Hz, 1H), 5.48 (t, $J$=6 Hz, 1H);

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 17.0, 20.4, 20.5, 20.6, 28.3, 44.1, 61.8, 67.1, 68.2, 70.5, 72.9, 79.7, 80.1, 156.4, 169.7, 170.0, 170.8, 171.1, 215.3 ppm;

ESI-MS: m/z [M+H]$^+$ calcd for C$_{32}$H$_{38}$NO$_{12}$S$_2$: 582.65; found: 582.61.
(S)-methyl-2-((R)-2-(((S)-2-(benzoxycarbonyl)-4-methylpentyloxy)carbonothioylthio)-3-methyl butanamido)-3-methyl butanoate (3.9a)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.85-0.92 (m, 18H), 1.51-1.64 (m, 3H), 2.02-2.08 (m, 1H), 2.13-2.19 (m, 1H), 3.60 (d, $J$=4.4 Hz, 2H), 3.70 (s, 3H), 4.31-4.35 (m, 1H), 4.41-4.45 (m, 1H), 4.53-4.57 (m, 1H), 5.09 (s, 2H), 5.82 (br s, 1H), 7.17 (br s, 1H), 7.28-7.32 (m, 5H);

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 18.5, 18.7, 24.8, 28.0, 30.2, 42.9, 50.1, 51.7, 55.3, 60.5, 66.2, 68.6, 127.1, 127.5, 128.9, 135.8, 155.5, 159.2, 171.6, 215.3 ppm;

HRMS: m/z [M+H]$^+$ calcld for C$_{26}$H$_{41}$N$_2$O$_6$S$_2$: 541.23; found: 541.18.

(S)-methyl-2-(((S)-3-(((S)-3-tert-butoxy-2-(tert-butoxycarbonyl)propxoxy)carbonothioylthio)-2-methylpropanamido)-3-methylbutanoate (3.9b)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.99 (d, $J$=3.6 Hz, 6H), 1.19 (s, 9H), 1.37-1.39 (d, $J$=7.2 Hz, 3H), 1.45 (s, 9H), 2.12-2.19 (m, 1H), 3.36-3.42 (m, 1H), 3.61 (d, $J$=4.6 Hz, 2H), 3.74 (s, 3H), 3.78-3.81 (m, 1H), 4.18 (br, 1H), 4.47-4.54 (m, 2H), 5.43 (br s, 1H), 7.18 (br s, 1H);

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 16.1, 18.9, 28.3, 29.6, 30.7, 34.3, 41.2, 50.0, 53.2, 60.8, 65.0, 66.9, 74.8, 79.5, 82.2, 155.3, 159.8, 171.2, 215.4 ppm;

ESI-MS: m/z [M+H]$^+$ calcld for C$_{23}$H$_{43}$N$_2$O$_7$S$_2$: 523.24; found: 523.21.
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(S)-methyl-2-((R)-2-(((S)-2-(benzyloxy carbonyl)-3-methylbutoxy)carbonothioylthio)propanamido)propanoate (3.9c)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.98 (d, $J$=3.2 Hz, 6H), 1.35 (d, $J$=5.6 Hz, 6H), 2.11 (m, 1H), 3.58 (d, $J$=4.2 Hz, 2H), 3.69 (s, 3H), 3.91-3.95 (m, 2H), 4.41-4.62 (m, 1H), 5.12 (s, 2H), 5.36 (br s, 1H), 6.68 (br s, 1H), 7.24-7.36 (m, 5H);

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 17.8, 18.1, 19.8, 29.7, 44.8, 48.3, 51.8, 57.4, 61.0, 65.9, 127.3, 127.5, 128.9, 141.0, 155.5, 159.7, 171.8, 215.2 ppm;

ESI-MS: $m/z$ [M+H]$^+$ calcd for C$_{21}$H$_{31}$N$_2$O$_6$S$_2$: 471.15; found: 471.11.
FIGURE 3.5. HRMS of (S)-2-(((S)-2-(benzyloxycarbonyl)propoxy)carbonothioylthio)-3-phenylpropanoic acid (3.4a)
FIGURE 3.6. $^1$H NMR of (S)-2-(((S)-2-(benzyloxycarbonyl)propoxy)carbonothioylthio)-3-phenylpropanoic acid (3.4a)
FIGURE 3.7. HRMS of (R)-2-(((S)-2-(benzyloxy carbonyl)-2-phenylethoxy)carbonothioylthio)-3-phenylpropanoic acid (3.4b)
FIGURE 3.8. $^1$H NMR of (R)-2-((S)-2-(benzyloxy carbonyl)-2-phenylethoxy)carbonothioylthio)-3-phenylpropanoic acid (3.4b)
FIGURE 3.9. $^{13}$C NMR of (R)-2-((S)-2-(benzyloxy carbonyl)-2-phenylethoxy)carbonothioylthio)-3-phenylpropanoic acid (3.4b)
FIGURE 4.0. HRMS of (R)-2-(((S)-2-(tert-butoxycarbonyl)propoxy)carbonothioylthio)-4-methylpentanoic acid (3.4d)
FIGURE 4.1. HRMS of (S)-methyl-2-((S)-3-((3-tert-butoxy-2-(tert-butoxycarbonyl)propoxy)carbonothioylthio)-2-methylpropanamido)-3-methylbutanoate (3.5b)
FIGURE 4.2. HRMS of (2S,3S,4R,5S,6R)-2-(acetoxymethyl)-6-(((S)-2-(((benzyloxy)carbonyl)amino)-2-phenylethoxy) carbonothioyl)thio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (3.7b)
FIGURE 4.3. HRMS of (S)-methyl-2-((R)-2-((((S)-2-(benzylcarbonyl)-4-methylpentyl)oxy)carbonothioylthio)-3-methyl butanamido)-5-methyl butanoate (3.9a)
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3.4. References


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