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Simple and efficient synthesis of *allo*- and *threo*-3,3′-dimethylcystine derivatives in enantiomerically pure form

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ABSTRACT

A simple and efficient method for the synthesis of *allo*- and *threo*-3,3′-dimethylcystine derivatives is reported. Various tosyl and bromo derivatives of Cbz-, Boc-, and Fmoc- protected threonine methyl esters have been prepared and subjected to nucleophilic substitution with potassium thiocyanate in acetonitrile to yield the corresponding thiocyanate derivatives in moderate yield. The thiocyanates are readily converted to the corresponding *allo*- and *threo*-3,3′-dimethylcystine derivatives via reductive dimerization with benzyltriethylammonium tetrathiomolybdate.

1. Introduction

A complete understanding of the stereochemical requirement of the side chain of amino acid residues is important in peptide ligand–receptor interaction and also has a crucial role in the rational design of bioactive peptides and their non-peptide mimetics. This approach can be realized by the incorporation of conformationally constrained novel amino acids into peptide or non-peptide templates.[1] Among these, cystine and β-substituted cystine derivatives which are incorporated in many peptide sequences are known to possess diverse biological activities.[2,3] The introduction of an appropriate β-substituted cystine into a peptide sequence preserves the side chain orientation and restricts the C–S–S–C dihedral angle. Hence, there is a need for an efficient approach for the synthesis of β-substituted cystine and its diastereomers in enantiomerically pure form. There are number of reports in the literature for the synthesis of β-substituted cystines. Morell et al.[4] have reported that the displacement reaction of an *O*-tosyl threonine derivative with potassium thioacetate gave (*S*)-acetyl-3-methylcysteine, which was converted to 3,3′-dimethylcystine by hydrolysis and oxidation. However, this method is not very effective for making enantiomerically pure cysteine or 3,3′-dimethylcystine. Carter et al.[5] and Hoogmatens et al.[6] prepared 3-methylcysteine via addition of thiol to 2-phenyl 4-ethylidene-5(4*H*)-oxazoline. However, the procedure required a tedious resolution strategy to obtain the enantiomerically pure product. Wakamiya reported the synthesis of *threo*-3,3′-dimethylcystine via the ring opening reaction of an aziridine with thiobenzoic acid.[7] The major problem with this approach was competitive ring opening by oxygen, leading to the formation of a thionoester byproduct along with the desired product. Hydrogen sulfide has also been used as a nucleophile, but its high toxicity makes its use inconvenient, especially on a large-scale preparation.[8] Recently, VenNiewenhze[9] reported the synthesis of orthogonally protected 3-methylcysteine, where the ring opening reaction of an Ns-aziridine with alkyl thiols in the presence of $BF_3{\cdot}OEt_2$ was utilized. Deprotection of the Ns group and protection with Boc or Fmoc allowed them to use these compounds for peptide synthesis. The deprotection of the alkyl group followed by oxidation gave the desired cystine derivatives. However, the limitation of this procedure was that too many protection and deprotection steps were involved.

In our laboratory, we have utilized the chemistry of benzyltriethylammonium tetrathiomolybdate $[BnNEt_3]_2MoS_4$ **1** for the synthesis of structurally diverse molecules.[10] Previously, we reported the synthesis of cystine, selenocystine and their higher analogues using tetrathiomolybdate **1** as the key reagent.[11] Since, there is a growing interest for the synthesis of 3-alkyl cysteine and cystine derivatives, we decided to extend our methodology to the synthesis of 3,3′-dimethylcystine and its diastereomers from threonine; the results of this investigation are presented in this paper.

2. Results and discussion

We began our synthesis by treating the tosyl derivative of L-threonine[12] **3a** with **1** (1.2 equiv, CH_3CN, 28 °C, 24 h).

Surprisingly it did not furnish the expected disulfide **5a**, instead the dehydroaminoacid **4** could be isolated in 15% yield and the starting material (80%) was recovered (Scheme 1). Since the attempt to prepare **5a** from **3a** was unsuccessful, we decided to convert tosylate **3a** to the corresponding thiocyanate **6a** (Scheme 2) via an S_N2 substitution reaction, which in turn can be converted

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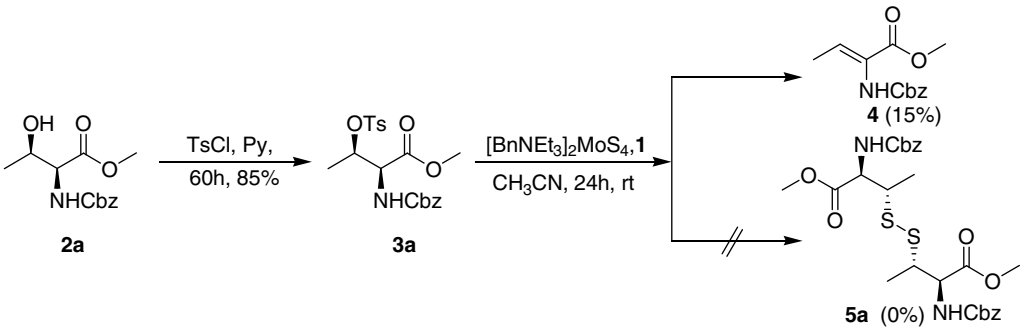
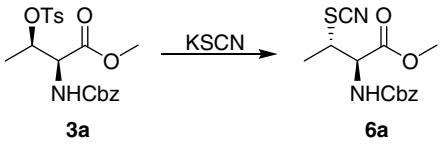


Scheme 1. Reaction of **3a** with **1**.



Scheme 2. Reaction of **3a** with KSCN.

to the corresponding disulfide **5a** using tetrathiomolybdate **1**.[13] Accordingly, the reaction of **3a** with excess KSCN (5 equiv) in different solvent systems was studied. The results of these studies are summarized in Table 1. The reaction of tosylate **3a** with KSCN in anhydrous acetone was unsuccessful as it did not furnish thiocyanate **6a** even after 30 h at reflux, whereas the reaction in methanol and THF gave the thiocyanate **6a** in very poor yields. In ethanol, compound **6a** was isolated in 40% yield. Acetonitrile and 1,4-dioxane were found to be the best solvents for this reaction as the thiocyanate **6a** was obtained in 60% and 58% yield, respectively.[14] The reactions of **3a** in DMF or DMSO (90 °C, 12 h) furnished **6a** in 52% and 48 % yield, respectively. After the successful isolation of thiocyanate **6a** in moderate yield, it was treated with tetrathiomolybdate **1** (1.2 equiv, CH_3CN, 28 °C, 10 h), and underwent reductive dimerization[13] to give 3,3′-dimethylcystine derivative **5a** in 92% yield without a loss in enantiomeric purity. This methodology could be extended to the synthesis of Boc- and Fmoc-protected 3,3′-dimethylcystine derivatives **5b** and **5c** with the same efficiency (Scheme 3). This demonstrates that the methodology can be used successfully when Boc or Fmoc are used for the protection of the amino group. With the successful synthesis of **5a–c**, we extended this methodology to the synthesis of *threo*-3,3′-dimethylcystine derivatives **9a–c**, where the configuration of the C_3 carbon atom is same as in L-threonine. The S_N2 displacement of the hydroxy group of **2a** with CBr_4/PPh_3[15] gave **7a** in 67% yield. Further treatment of **7a** with tetrathiomolybdate **1** (1.2 equiv CH_3CN, 28 °C, 24 h) gave the dehydroamino acid **4** instead of *threo*-3,3′-dimethylcystine derivative **9a** (Scheme 4). An alternate strategy was worked out to obtain the desired result. Compound **7a** was treated with an excess of KSCN which resulted in the formation of **8a** in 54% yield. Reductive dimerization of **8a** with tetrathiomolybdate **1** (1.2 equiv, CH_3CN, 28 °C, 10 h) gave the *threo*-3,3′-dimethylcystine derivative **9a** in excellent yield (90%) (Scheme 5). This methodology was extended further for the synthesis of Boc- and Fmoc-protected *threo*-3,3′-dimethylcystine derivatives **9b–c**.

Table 1
Reaction of **3a** with KSCN in different solvents

Entry	Solvents	Temperature	Time (h)	Yield[a] (%)
1	Acetone	Reflux	30	—
2	Methanol	Reflux	30	5
3	Ethanol	Reflux	24	40
4	THF	Reflux	30	8
5	Acetonitrile	Reflux	15	60
6	1,4-Dioxane	90 °C	15	58
7	DMF	90 °C	12	52
8	DMSO	90 °C	12	48

[a] Isolated yields.

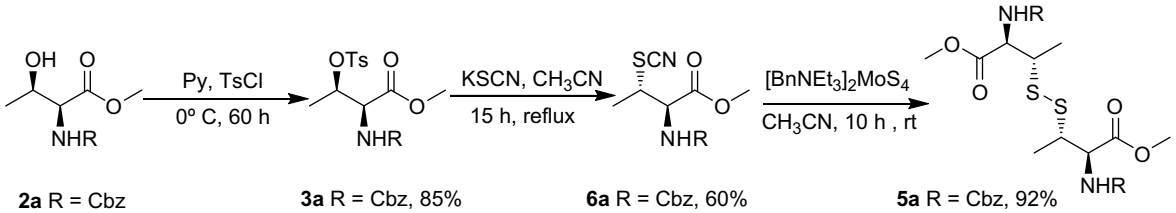
3. Conclusion

We have developed a simple and efficient methodology for the synthesis of *allo*-3,3′-dimethylcystine **5a–c** and *threo*-3,3′-dimethylcystine derivatives **9a–c** in enantiomerically pure form using L-threonine from the chiral pool and benzyltriethylammonium tetrathiomolybdate **1** as the key reagent.

4. Experimental

4.1. General

All reactions were performed in oven-dried apparatus and stirred magnetically. The 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



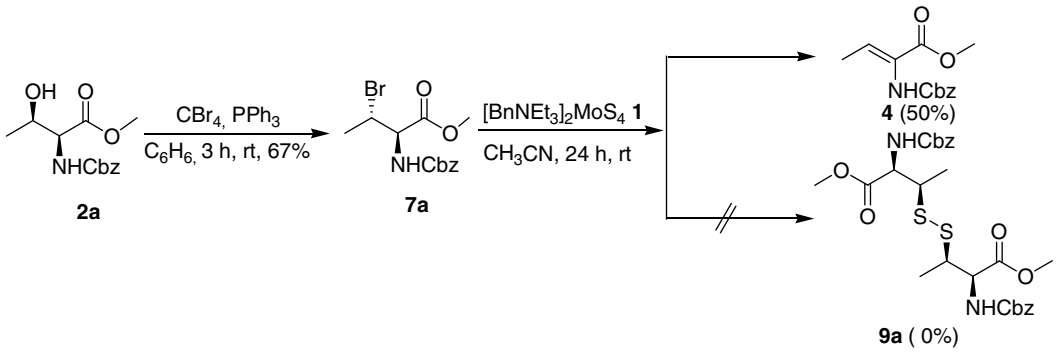
2a R = Cbz
2b R = Boc
2c R = Fmoc

3a R = Cbz, 85%
3b R = Boc, 81%
3c R = Fmoc, 77%

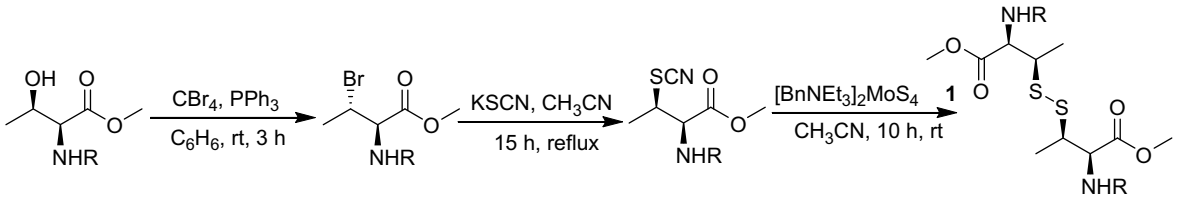
6a R = Cbz, 60%
6b R = Boc, 57%
6c R = Fmoc ,65%

5a R = Cbz, 92%
5b R = Boc, 90%
5c R = Fmoc, 94%

Scheme 3. Synthesis of *allo*-3,3′-dimethylcystine derivatives.



Scheme 4. Reaction of **7a** with **1**.



2a R=Cbz	**7a** R = Cbz, 67%	**8a** R = Cbz ,54%	**9a** R = Cbz, 90%
2b R=Boc	**7b** R = Boc, 60%	**8b** R = Boc, 50%	**9b** R = Boc, 91%
2c R=Fmoc	**7c** R = Fmoc, 75%	**8c** R = Fmoc, 61%	**9c** R = Fmoc, 96%

Scheme 5. Synthesis of *threo*-3,3′-dimethylcystine derivatives.

reported in wave number (cm^{-1}), and intensities of the peak are denoted as s (strong), w (weak), and m (medium). ^1H and ^{13}C spectra were recorded at 300 MHz at 75 MHz, respectively. Chemical shifts are reported in parts 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.

4.2. General procedure for the synthesis of bromoderivatives 7a–c

4.2.1. Synthesis of 7a

To a stirred solution of PPh_3 (0.393 g, 1.5 mmol) in anhydrous benzene (15 mL), CBr_4 (0.497 g, 1.5 mmol) was added and the reaction mixture was stirred for 1 h at room temperature. To this, compound **2a** (0.267 g, 1 mmol) was added and the reaction mixture was stirred for further 2 h. The reaction mixture was filtered through Celite, and washed with benzene (2 × 10 mL), after which the solvent was evaporated and the crude product was purified by silica gel (100–200 mesh) column chromatography EtOAc/hexane (1:9); Gummy liquid; yield 67%; IR (Neat) 3347 (br), 1727 (s), 1516 (m), 1213 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (s, 5H), 5.81 (d, J = 8.4 Hz, 1H), 5.11 (s, 2H), 4.61 (dd, J = 8.4, 3.6 Hz, 1H), 4.39–4.31 (m, 1H) 3.76 (s, 3H), 1.76 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 155.5, 135.8, 128.5, 128.2, 128.1, 67.3, 59.6, 52.7, 49.2, 22.7; m/z (HRMS) calcd for $C_{13}H_{16}BrNO_4$ + Na 352.0160; found 352.0158.

4.2.2. Boc-Thr(Br)-OMe, 7b

Gummy liquid; Purified by column chromatography EtOAc/hexane (1:9); yield 60%; IR (Neat) 3362 (br), 1747 (s), 1715 (s), 1506 (m), 1165 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.48 (d, J = 7.8 Hz, 1H), 4.54 (dd, J = 8.4, 3.6 Hz, 1H), 4.39–4.31 (m, 1H), 3.8 (s, 3H), 1.79 (d, J = 6.9 Hz, 3H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 154.8, 80.3, 59.2, 52.4, 49.5, 28.1, 22.7; m/z (HRMS) calcd for $C_{10}H_{18}BrNO_4$ + Na 318.0317; found 318.0315.

4.2.3. Fmoc-Thr(Br)-OMe, 7c

White solid; mp = 111 °C; Purified by column chromatography: EtOAc/hexane (1:9); yield 75%; IR (Neat) 3338 (br), 2951(w), 1734 (s), 1720 (s), 1508 (m), 1212 (m), 759 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 7.5 Hz, 2H), 7.59 (d, J = 7.2 Hz, 2H), 7.42–7.29 (m, 4H), 5.73 (d, J = 8.1 Hz, 1H), 4.61 (dd, J = 8.4 Hz, 3.9 Hz, 1H), 4.43–4.36 (m, 3H), 4.23 (t, J = 6.9 Hz, 1H), 3.87–3.81 (m, 1H), 3.81 (s, 3H), 1.80 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 155.5, 143.5, 141.2, 127.7, 127.0, 125.0, 119.9, 67.3, 59.30, 52.7, 49.1, 7.0, 2.7; m/z (HRMS) calcd for $C_{21}H_{20}N_2O_4S$ + Na 419.1041; found 419.1030.

4.3. General procedure for the synthesis of thiocyanates (6a–c and 8a–c)

4.3.1. Synthesis of 6a

To a solution of tosyl derivative **3a** (0.421 g, 1 mmol) in anhydrous acetonitrile, KSCN (0.486 g, 5 mmol) was added and the solution was refluxed for 15 h. The reaction mixture was allowed to come to room temperature and acetonitrile was removed under vacuum. The residue was extracted with DCM (3 × 20 mL) and filtered through Na_2SO_4. The crude thiocyanate **6a** was then purified by silica gel (100–200 mesh) column chromatography EtOAc/hexane (3:7); Gummy liquid; yield 60%; $[\alpha]_D$ = +70 (c 1, $CHCl_3$); IR (Neat) 3342 (br), 2154 (m), 1727 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (s, 5H), 5.76 (d, J = 7.5 Hz, 1H), 5.13 (s, 2H), 4.71(dd, J = 3.6 Hz, 7.5 Hz, 1H), 3.81 (s, 3H), 3.75–3.73 (m, 1H), 1.56 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 155.6, 135.6, 128.5, 128.3, 128.1, 110.1, 67.5, 57.7, 53.0, 46.6, 17.6; m/z (HRMS) calcd for $C_{14}H_{16}N_2O_4S$ + Na 331.0728; found 331.0714.

4.3.2. (*allo*) Boc-Thr(SCN)-OMe, 6b

Gummy liquid; Purified by column chromatography: EtOAc/hexane (2:8); yield 57%; $[\alpha]_D$ = +97 (*c* 1, $CHCl_3$); IR (Neat) 3361 (br), 2960 (w), 2155 (m), 1741 (s), 1513 (m), 1163 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.45 (d, *J* = 6.9 Hz, 1H), 4.66 (dd, *J* = 3.3 Hz, 7.5 Hz, 1H), 3.83 (s, 3H), 3.79–3.73 (m, 1H), 1.57 (d, *J* = 6.9 Hz, 3H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 154.9, 110.3, 81.0, 57.3, 53.0, 46.9, 28.1, 17.7; *m*/*z* (HRMS) calcd for $C_{11}H_{18}N_2O_4S$ + Na 297.0885; found 297.0884.

4.3.3. (*allo*) Fmoc-Thr(SCN)-OMe, 6c

White solid; mp = 106 °C; Purified by column chromatography: EtOAc/hexane (2:8); yield 65%; $[\alpha]_D$ = +56.0 (*c* 1, $CHCl_3$); IR (Neat) 3339 (br), 2953 (w), 2154 (m), 1724 (s), 1513 (m), 1221 (m), 740 (m) cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.6 Hz, 2H), 7.5 (d, *J* = 7.2 Hz, 2H), 7.40 (t, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 5.72 (d, *J* = 7.6 Hz, 1H), 4.69 (dd, *J* = 8 Hz, 3.6 Hz, 1H), 4.5 (dd, *J* = 10.4 Hz, 7.2 Hz, 1H), 4.40 (dd, *J* = 10.4 Hz 7.2 Hz, 1H), 4.2 (t, *J* = 6.8 Hz, 6.4 Hz, 1H), 3.83 (s, 3H), 3.76–3.72 (m, 1H), 1.57 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 155.7, 143.5, 141.3, 127.8, 127.1, 124.9, 120.0, 110.0, 67.4, 57.8, 53.0, 47.1, 46.6, 17.7; *m*/*z* (HRMS) calcd for $C_{21}H_{20}N_2O_4S$ + Na 419.1041; found 419.1030.

4.3.4. (*threo*) Cbz-Thr(SCN)-OMe, 8a

Gummy liquid; Purified by column chromatography: EtOAc/hexane (3:7); yield 54%; $[\alpha]_D$ = +25.6 (*c* 1, $CHCl_3$); IR (Neat) 3332 (br), 2956 (w), 2155 (m), 1725 (s), 1520 (m), 1216 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (s, 5H), 5.68 (d, *J* = 8.4 Hz, 1H), 5.059 (s, 2H), 4.68 (dd, *J* = 9 Hz, 3.3 Hz, 1H), 3.84–3.79 (m, 1H), 3.78 (s, 3H), 1.46 (d, *J* = 6.9 Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 156.1, 135.6, 128.4, 128.2, 128.0, 110.1, 67.2, 58.1, 53.0, 47.0, 18.5; *m*/*z* (HRMS) calcd for $C_{14}H_{16}N_2O_4S$ + Na 331.0728; found 331.0714.

4.3.5. (*threo*) Boc-Thr(SCN)-OMe, 8b

Gummy liquid; Purified by column chromatography: EtOAc/hexane (3:7); yield 50%; $[\alpha]_D$ = +15.1 (*c* 1, $CHCl_3$); IR (Neat) 3338 (br), 2155 (m), 1728 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.34 (d, *J* = 6.9 Hz, 1H), 4.69 (dd, *J* = 2.7, 9.3 Hz, 1H), 3.92–3.89 (m, 1H), 3.83 (s, 3H), 1.55 (d, *J* = 6.9, 3H), 1.54 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 155.4, 110.2, 80.8, 57.70, 52.9, 47.4, 28.1, 18.6; *m*/*z* (HRMS) calcd for $C_{11}H_{18}N_2O_4S$ + Na 297.0885; found 297.0883.

4.3.6. (*threo*) Fmoc-Thr(SCN)-OMe, 8c

White solid; mp = 127 °C; Purified by column chromatography: EtOAc/hexane (2:8); yield 61%; $[\alpha]_D$ = +13.7 (*c* 1, $CHCl_3$); IR (Neat) 3337 (br), 2953 (w), 2154 (m), 1718 (s), 1521 (m), 1521 (m), 1220, 759, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.2 Hz, 2H), 7.59 (d, *J* = 6.3, 2H), 7.42–7.72 (m, 4H), 5.73 (d, *J* = 8.1, 1H), 4.75 (dd, *J* = 3 Hz, 8.1 Hz, 1H), 4.51–4.35 (m, 2H) 4.22 (t, *J* = 6.9 Hz, 1H), 3.87–3.81 (m, 1H), 3.75 (s, 3H), 1.52 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 156.1, 143.3, 141.2, 127.7, 127.0, 124.9, 119.9, 110.9, 67.4, 58.2, 53.0, 47.0, 46.8, 18.5; *m*/*z* (HRMS) calcd for $C_{21}H_{20}N_2O_4S$ + Na 419.1041; found 419.1030.

4.4. General procedure for the synthesis of 3,3′-dimethylcystine derivatives: 5a–c and 9a–c

4.4.1. Synthesis of 5a

To the solution of thiocyanate **6a** (0.308 g, 1 mmol,) in acetonitrile (5 mL), tetrathiomolybdate **1** (0.730 g, 1.2 mmol) was added and the reaction mixture was stirred for 10 h. The solvent was removed under vacuum, after which the solid residue was extracted with (3:7) DCM/Et_2O (5 × 10 mL), filtered through Celite and concentrated. The crude product was purified by silica gel (100–200 mesh) column chromatography EtOAc/hexane (3:7); Gummy liquid: yield 92%; $[\alpha]_D$ = −98.4 (*c* 1, $CHCl_3$); IR (Neat) 3350 (br) 1724 (s), 1526 (m), 1216 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (s, 5H), 5,45 (d, *J* = 8.7 Hz, 1H), 5.11 (s, 2H), 4.79 (dd, *J* = 9 Hz, 3.6 Hz, 1H), 3.75 (s, 3H), 3.37–3.35 (m, 1H), 1.25 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.85, 155.98, 136.01, 128.5, 128.19, 128.13, 67.25, 56.80, 52.64, 48.08, 15.68; *m*/*z* (HRMS) calcd for $C_{26}H_{32}N_2O_8S_2$ + Na 587.1498; found 587.1490.

4.4.2. *N,N′*-Bis(*tert*-butoxycarbonyl)-*allo*-3,3′-dimethyl-L-cystine dimethyl ester 5b

Gummy liquid; Purified by column chromatography: EtOAc/hexane (3:7); yield 90%; $[\alpha]_D$ = −54.9 (*c* 4.38, $CHCl_3$); lit.[7b] = +52.9 for the enantiomer of **5b** at 17 °C (*c* 1.14, $CHCl_3$); IR (Neat) 3366 (br), 2977, 1741, 1715, 1508, 1367, 1163 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.15 (d, *J* = 7.2 Hz 1H), 5.70 (br s, 1H), 3.77 (s, 3H), 3.36 (br s, 1H), 1.45 (s, 9H), 1.27 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 155.1, 80.2, 56.4, 52.5, 48.2, 28.2, 15.9; *m*/*z* (HRMS) calcd for $C_{20}H_{36}N_2O_8S_2$ + Na 519.1811; found 519.1808.

4.4.3. *N,N′*-Bis(9-fluorenylmethoxycarbonyl)-*allo*-3,3′-dimethyl-L-cystine dimethyl ester 5c

White solid; mp = 172 °C; Purified by column chromatography: EtOAc/hexane (3:7); yield 94%; $[\alpha]_D$ = −44.0 (*c* 1, $CHCl_3$); IR (Neat) 3346 (br), 1723 (s), 1513 (m), 1216 (m), 758 (m), 740 (m) cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.2 Hz, 2H), 7.59 (d, *J* = 7.2 Hz, 2H), 7.47–7.26 (m, 4H), 5.48 (d, *J* = 9.3 Hz, 1H), 4.82 (dd, *J* = 9.3 Hz, 3.6 Hz, 1H), 4.59 (d, *J* = 7.5 Hz, 2H), 4.22 (t, *J* = 7.2 Hz, 1H), 3.77 (s, 3H), 3.40 (br s, 1H), 1.29 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 156.0, 143.6, 141.2, 127.7, 127.0, 125.0, 119.9, 67.3, 56.8, 52.7, 48.1, 47.0, 15.83; *m*/*z* (HRMS) calcd for $C_{40}H_{40}N_2O_8S_2$ + Na 763.2124; found 763.2126.

4.4.4. *N,N′*-Bis(benzyloxycarbonyl)-*threo*-3,3′-dimethyl-L-cystine dimethyl ester 9a

White solid; mp = 107 °C; Purified by column chromatography: EtOAc/hexane (3:7); yield 90%; $[\alpha]_D$ = +172.1 (*c* 0.44, $CHCl_3$); lit.[7a] −167 for the enantiomer of **9a** at 18 °C (*c* 1, $CHCl_3$); IR (Neat) 3336 (br), 1724 (s), 1521 (m), 1216 (m) cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 7.31 (s, 5H); 5.62 (d, *J* = 8.7 Hz, 1H), 5.12 (s, 2H), 4.59 (dd, *J* = 8.7 Hz, 3.3 Hz, 1H), 3.73 (s, 3H), 3.57–3.48 (br s, 1H), 1.3 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 156.2, 136.0, 128.5, 128.2, 128.0, 67.25, 57.4, 52.5, 48.6, 17.8; *m*/*z* (HRMS) calcd for $C_{26}H_{32}N_2O_8S_2$ + Na 587.1498; found 587.1478.

4.4.5. *N,N′*-Bis(*tert*-butoxycarbonyl)-*threo*-3,3′-dimethyl-L-cystine dimethyl ester 9b

Gummy liquid; Purified by column chromatography: EtOAc/hexane (3:7); yield 91%; $[\alpha]_D$ = +145 (*c* 1, $CHCl_3$); IR (Neat) 3368 (br), 2978 (w), 1746 (s), 1718 (s), 1502 (m), 1164 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.35 (d, *J* = 9 Hz 1H), 4.51 (dd, *J* = 9 Hz, 2.7 Hz, 1H), 3.76 (s, 3H), 3.54–3.46 (m, 1H), 1.45 (s, 9H), 1.33 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 155.5, 80.2, 57.0, 52.3, 49.1, 28.2, 18.0; *m*/*z* (HRMS) calcd for $C_{20}H_{36}N_2O_8S_2$ + Na 519.1811; found 519.1807.

4.4.6. *N,N′*-Bis(9-fluorenylmethoxycarbonyl)-*threo*-3,3′-dimethyl-L-cystine dimethyl ester 9c

White solid; mp = 181 °C; Purified by column chromatography: EtOAc/hexane (3:7); yield 94%; $[\alpha]_D$ = +75.6 (*c* 1, $CHCl_3$); IR (Neat) 3342 (br), 2952 (w), 1723 (s), 1513 (m), 1215 (m), 756 (m) cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.5 Hz, 2H), 7.6 (d, *J* = 6.9 Hz, 2H), 7.42–7.25 (m, 4H), 5.6 (d, *J* = 9 Hz, 1H), 4.62 (dd, *J* = 8.7 Hz, 3.3 Hz, 1H), 4.43–4.38 (m, 2H), 4.23 (t, *J* = 6.9 Hz, 1H), 3.75 (s,

3H), 3.59–3.50 (m, 1H), 1.32 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 156.3, 143.7, 141.4, 127.8, 127.1, 125.1, 120.0, 67.3, 57.6, 52.6, 48.8, 47.2, 17.9; m/z (HRMS) calcd for $C_{40}H_{40}N_2O_8S_2$ + Na 763.2124; found 763.2136.

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