

## Efficient Asymmetric Synthesis of (*S*)- and (*R*)-*N*-Fmoc-*S*-Trityl- $\alpha$ -methylcysteine Using Camphorsultam as a Chiral Auxiliary

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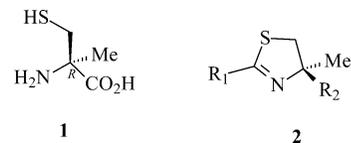
Received March 8, 2004

**Abstract:** (1*R*)-(+)-2,10- and (1*S*)-(–)-2,10-camphorsultam were acylated with ethyl 2-phenylthiazoline 4-carboxylate to afford (+)- and (–)-2-phenylthiazolinylcamphorsultam, which were stereoselectively alkylated with MeI in the presence of *n*-BuLi. Alkylation of these phenylthiazolinylcamphorsultams occurred from the  $\beta$ -face rather than  $\alpha$ -face, resulting in the formation of (*S*)- $\alpha$ -methylcysteine from (1*R*)-(+)-2,10-camphorsultam and (*R*)- $\alpha$ -methylcysteine from (1*S*)-(–)-2,10-camphorsultam after acidic hydrolysis. Subsequent protection of the side chain thiol group with trityl alcohol and  $\alpha$ -amine function with Fmoc-OSu furnished fully protected (*S*)- and (*R*)-*N*-Fmoc-*S*-trityl- $\alpha$ -methylcysteine in overall 20% yield.

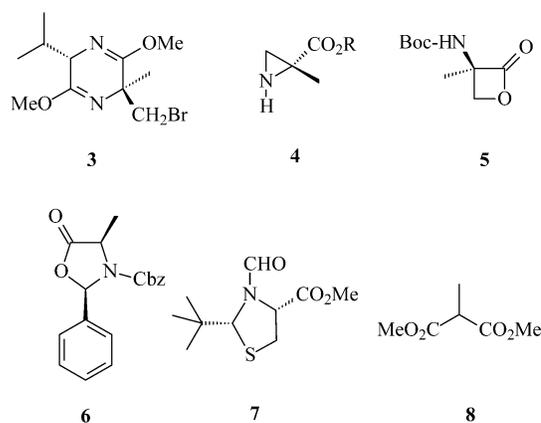
Optically pure modified amino acids are valuable building blocks for the preparation of biologically active peptidomimetics since they can be utilized to confer stability to peptides against enzymatic degradation.<sup>1</sup> In addition, C $^{\alpha}$ -alkylated amino acids are not prone to racemization under basic or acidic conditions because of a lack of abstractable or enolizable  $\alpha$ -hydrogen. Furthermore, C $^{\alpha}$ -alkylation severely restricts rotation around the N–C $^{\alpha}$  ( $\phi$ ) and C $^{\alpha}$ –C(O) ( $\psi$ ) bonds of the amino acid in a peptide sequence and stabilizes preferred conformations of the peptide backbone.<sup>2</sup>

Among C $^{\alpha}$ -alkylated amino acids,  $\alpha$ -methylcysteine (1) is an interesting molecule because it can impart constrained cyclic structure to the peptide via disulfide bridge formation. Furthermore,  $\alpha$ -methylcysteine occurs naturally in the thiazoline rings (2) of a number of natural products including mirabzoles,<sup>3,4</sup> tantazoles,<sup>5</sup> and thiangazole,<sup>6,7</sup> which exhibit antitumor and anti-HIV-1 activities.

Synthesis of  $\alpha$ -methylcysteine is rather challenging as a result of the labile nature of the sulfhydryl group.<sup>8</sup>



There are mainly three strategies for synthesizing  $\alpha$ -methylcysteine: (1) thiolation of bromomethyl bislactim ether **3**,<sup>9</sup> (2) regioselective ring opening of chiral aziridine **4**<sup>10</sup> or  $\beta$ -lactone **5**,<sup>11,12</sup> with thiolate nucleophile, and (3) utilization of Seebach's "self-reproduction of chirality" approach to thiomethylate oxazolidinone **6** derived from alanine<sup>13</sup> or methylate a thiazolidine derivative **7** of cysteine.<sup>14,15</sup> Recently,  $\alpha$ -methylcysteine has been synthesized from dimethyl 2-methylmalonate **8** via enzymatic resolution followed by Curtius rearrangement.<sup>16</sup>

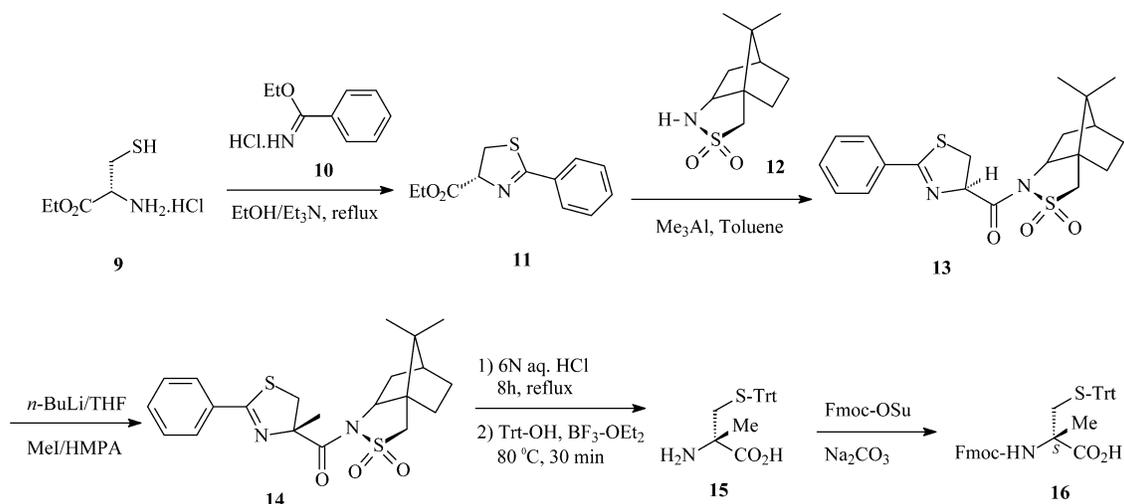


Several groups have utilized chiral auxiliaries to direct an incoming alkyl group stereoselectively.<sup>17–23</sup> In these reactions, alkylation occurs from the least shielded face of the enolate. Furthermore, in successive dialkylation reactions, the second alkyl group comes in from the opposite side of the sterically demanding group(s) present on the chiral auxiliary. In this publication, we report a short and efficient synthesis of  $\alpha$ -methylcysteine using Oppolzer's camphorsultam chiral auxiliary.<sup>21</sup> We chose

(1) Ma, J. S. *Chim. OGGI* **2003**, *21*, 65–68.  
 (2) Goodman, M.; Ro, S. In *Burger's Medicinal Chemistry and Drug Discovery*, 5th ed.; Wolff, M. E., Ed.; John Wiley & Sons: 1995; Vol. 1, Chapter 20, pp 803–861.  
 (3) Parsons, R. L.; Heathcock, C. H. *Tetrahedron Lett.* **1994**, *35*, 1379–1382.  
 (4) Parsons, R. L.; Heathcock, C. H. *Tetrahedron Lett.* **1994**, *35*, 1383–1384.  
 (5) Carmeli, S.; Paik, S.; Moore, R. E.; Patterson, G. M. L.; Yoshida, W. Y. *Tetrahedron Lett.* **1993**, *34*, 6680–6684.  
 (6) Parsons, R. L.; Heathcock, C. H. *J. Org. Chem.* **1994**, *59*, 4733–4734.  
 (7) Boyce, R. L.; Mulqueen, G. C.; Pattenden, G. *Tetrahedron Lett.* **1994**, *35*, 5705–5708.  
 (8) Jeanguenat, A.; Seebach, D. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2291–2298.

(9) Groth, U.; Schöllkopf, U. *Synthesis* **1983**, 37–38.  
 (10) Shao, H.; Zhu, Q.; Goodman, M. *J. Org. Chem.* **1995**, *60*, 790–791.  
 (11) Smith, N. D.; Goodman, M. *Org. Lett.* **2003**, *5*, 1035–1037.  
 (12) Fukuyama, T.; Xu, L. *J. Am. Chem. Soc.* **1993**, *115*, 8449–8450.  
 (13) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 5566–5568.  
 (14) Pattenden G.; Thom, S. M.; Jones, M. F. *Tetrahedron* **1993**, *49*, 2131–2138.  
 (15) Mulqueen, G. C.; Pattenden, G.; Whiting, D. A. *Tetrahedron* **1993**, *49*, 5359–5364.  
 (16) Kedrowski, B. L. *J. Org. Chem.* **2003**, *68*, 5403–5406.  
 (17) Williams, R. M. In *The Synthesis of Optically Active  $\alpha$ -Amino Acids*; Pergamon Press: Oxford, 1989, and references therein.  
 (18) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539–1650.  
 (19) Berkowitz, D. B.; Smith, M. K. *J. Org. Chem.* **1995**, *60*, 1233–1238.  
 (20) Seebach, D. Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708–2748.  
 (21) Oppolzer, W.; Moretti, R.; Zhou, C. *Helv. Chim. Acta* **1994**, *77*, 2363–2380.  
 (22) Myers, A. G.; Schnider, P.; Kwon, S.; Kung, D. W. *J. Org. Chem.* **1999**, *64*, 3322–3327.  
 (23) O'Donnell, M. J.; Drew, M. D.; Cooper, J. T.; Delgado, F.; Zhou, C. *J. Am. Chem. Soc.* **2002**, *124*, 9348–9349.

## SCHEME 1



this chiral auxiliary because of low cost, ease of attachment and removal, excellent enantioselectivity, and scalability. Furthermore, it was visualized that deprotonation of thiazolinyllcamphorsultam should result in a *Z*-enolate transition state, which upon alkylation with methyl iodide from the  $\alpha$ -face would afford (*R*)- $\alpha$ -methylcysteine from (1*R*)-(+)-2,10-camphorsultam and (*S*)- $\alpha$ -methylcysteine from (1*S*)-(–)-2,10-camphorsultam. However, our results indicated reverse stereochemical outcome.

As shown in Scheme 1, (*R*)-ethyl cysteine hydrochloride (9) was treated with ethyl benzimidate hydrochloride (10) in ethanol at reflux for 2 h to afford 2-phenylthiazoline (11) in 87% yield.<sup>24</sup> Thiazoline 11 has been previously synthesized using phosphorus pentachloride mediated cyclization in 80% yield.<sup>25</sup> Thiazolines are highly reactive molecules with a labile acidic proton at C-4 and undergo facile electrophilic alkylation to yield racemic 4-methylthiazolines, a precursor of  $\alpha$ -methylcysteine.<sup>24</sup> However, we exploited (+)-camphorsultam (12) as a chiral auxiliary to conduct alkylation, stereospecifically. Thus, camphorsultam 12 was acylated with thiazoline 11 in the presence of trimethylaluminum to afford 2-phenylthiazolinyllcamphorsultam 13 in 71% yield.<sup>21</sup> Some racemization (<10%) occurred during acylation possibly as a result of enolization of ester 11 prior to nucleophilic addition, which was easily separated by silica gel column chromatography.<sup>26</sup>

Alkylation of sultam 13 with methyl iodide in the presence of *n*-butyllithium afforded alkylated sultam 14. Enolate generation at –78 °C followed by quenching with methyl iodide at the same temperature and continuing the reaction either at –78 or –50 °C up to 24 h resulted in poor yield. Furthermore, use of lithium diisopropylamide or lithium bis(trimethylsilyl)amide as a base resulted in poor alkylated product. Treatment of 13 in tetrahydrofuran at –78 °C with *n*-butyllithium for 1 h, followed by quenching the resulting enolate with methyl iodide in hexamethylphosphoramide (both 3 molar equiv) at the same temperature and allowing the reaction to warm to ambient temperature over the period of 2 h gave the alkylated product 14 in 49% yield.

Sultam 14 was refluxed in 6 N aqueous HCl for 8 h, followed by treatment with trityl alcohol in the presence of boron trifluoride etherate<sup>27</sup> to afford (*S*)-*S*-trityl- $\alpha$ -methylcysteine (15) in 49% yield (isolated yield over two steps),  $[\alpha]_D^{24} = -32$  (*c* 0.5, MeOH). Protection of the  $\alpha$ -amino function of 15 with Fmoc-OSu in the presence of sodium carbonate<sup>28</sup> overnight afforded (*S*)-*N*-Fmoc-*S*-trityl- $\alpha$ -methylcysteine (16) in quantitative yield,  $[\alpha]_D^{24} = -29.3$  (*c* 0.15, MeOH).

It is important to note that alkylation of glycyllsultam under similar reaction conditions occurs via a kinetically controlled Li-chelated *Z*-enolate (17), which is attacked by the alkylating agent from the face opposite to the lone electron pair on the nitrogen atom. The stereospecific formation of *Z*-enolate occurs as a result of the presence of the bulky camphorsultam skeleton and sterically demanding SO<sub>2</sub> group.<sup>21,29</sup> However, in the present case, the *Z*-enolate derived from 2-phenylthiazolinyllcamphorsultam (18) was attacked by the electrophile from the  $\beta$ -face and furnished (*S*)- $\alpha$ -methylcysteine as confirmed by optical rotation. High performance liquid chromatography and NMR spectrometry were used to determine the diastereomeric excess (asymmetric induction) during the alkylation step. The <sup>1</sup>H NMR spectrum exhibited a relatively downfield shift for the  $\alpha$ -methyl protons (2.52 ppm) in agreement with the  $\beta$ -alkylation product (14). Compound 14 was the only alkylation product isolated from the reaction mixture, and there was no  $\alpha$ -alkylated product formed as checked by HPLC. Furthermore, the <sup>13</sup>C NMR spectrum exhibited resonances corresponding to a single isomer only.

To explain the unexpected stereochemical outcome on electrophilic alkylation of 13, it can be speculated that the enolate assumes *E*-configuration (19), which upon alkylation from the  $\alpha$ -face could result in the formation of product 14. However, in the *E*-enolate transition state (19) increased steric interactions between the camphor-

(24) Pattenden, G.; Thom, S. M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1629–1636.

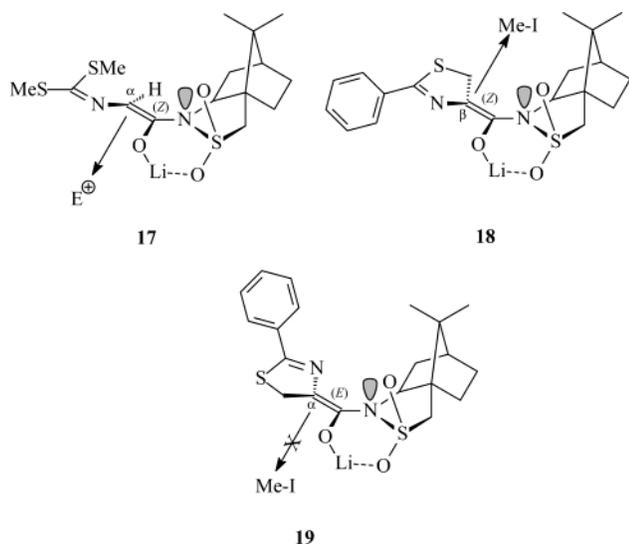
(25) Ino, A.; Murabayashi, A. *Tetrahedron* **1999**, *55*, 10271–10282.

(26) Martin, S. F.; Dwyer, M. P.; Lynch, C. L. *Tetrahedron Lett.* **1998**, *39*, 1517–1520.

(27) Bodanszky, M.; Bodanszky, A. In *The Practice of Peptide Synthesis*, 2nd ed.; Springer-Verlag: Berlin Heidelberg, Germany, 1994; pp 68–69.

(28) Atherton, E.; Sheppard, R. C. In *Solid-Phase Peptide Synthesis*; IRL Press: Oxford, England, 1989; p 61.

(29) Anne, C.; Turcaud, S.; Quancard, J.; Teffo, F.; Meudal, H.; Fournie-Zaluski, M.-C.; Roques, B. P. *J. Med. Chem.* **2003**, *46*, 4648–4656.



sultam skeleton and the phenylthiazoline ring, as well as electronic repulsions between the lone electron pair on the nitrogen atom of thiazoline ring and the lone pair electrons on the nitrogen and  $\text{SO}_2$  groups of camphorsultam moiety, are expected. On the contrary, the *Z*-enolate transition state (**18**) has minimum steric interactions. Furthermore, formation of the Li-chelated *Z*-enolate transition state under the similar reaction conditions has been demonstrated previously.<sup>21,29</sup> Therefore, deprotonation of **13** should result in the formation of the *Z*-enolate transition state (**18**), which upon alkylation from the  $\beta$ -face furnishes compound **14**.

Having realized the reverse stereochemical outcome from alkylation of enolate **18** and to confirm this finding, we utilized (1*S*)-(-)-2,10-camphorsultam (enantiomer of **12**) for alkylation of thiazoline **11**. As observed above, alkylation of the enolate derived from thiazolinylsultam **20** with methyl iodide occurred from the  $\beta$ -face and afforded the  $\beta$ -alkylated product **21** as shown in Scheme 2. The stereochemistry of alkylation was confirmed by checking the optical rotation. After treatment with 6 *N* aqueous HCl, protection of the side chain thiol group with trityl alcohol furnished *S*-trityl- $\alpha$ -methylcysteine (**22**;  $[\alpha]_D^{24} = +28.5$  (*c* 0.15, MeOH)), and protection of the  $\alpha$ -amino function then afforded (*R*)-*N*-Fmoc-*S*-trityl- $\alpha$ -methylcysteine (**23**;  $[\alpha]_D^{24} = +31.9$  (*c* 0.25, MeOH)) in overall good yield.

Thus, an efficient asymmetric synthesis of (*S*)- and (*R*)-*N*-Fmoc-*S*-trityl- $\alpha$ -methylcysteine (**16** and **23**) from the commercially available camphorsultam chiral auxiliaries was successfully accomplished with excellent optical purity (>95%) and in overall good yield (20%). Synthesis was easy to perform as reactions could be monitored by HPLC for transformation and diastereoselectivity. Furthermore, alkylation of 2-phenylthiazolinylcamphorsultams (**13** and **20**) occurred from the  $\beta$ -face. This reverse stereochemical outcome was completely unexpected. It is not known how other chiral auxiliaries will behave under similar conditions.

## Experimental Section

All reagents and solvents were used without further purification unless otherwise stated. Methyl iodide was freshly distilled. THF was dried over LAH and freshly distilled before use. HMPA was dried over 4Å molecular sieves.

HPLC was performed on a  $\text{C}_{18}$ , reversed phase column (Vydac, 250 mm  $\times$  4.6 mm, 5  $\mu$ ). A linear gradient from 5% buffer B to 95% buffer B in 45 min was used. Buffer A consisted of 0.1% TFA in water, and buffer B was MeCN containing 0.1% TFA. Flow rate was 1.5 mL/min.

The mass spectra of crude and purified samples were obtained using in-house MALDI-MS and ESI-MS.  $\alpha$ -Cyano-4-hydroxycinnamic acid (CCA) was used as matrix for MALDI-MS. ESI-MS spectra were collected from samples dissolved in methanol as a solvent. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were obtained at 600 MHz with  $\text{CDCl}_3$  or  $d_6$ -DMSO as solvent (Emory University, Atlanta, GA). Micro Analysis Inc. (Wilmington, DE) performed elemental analysis.

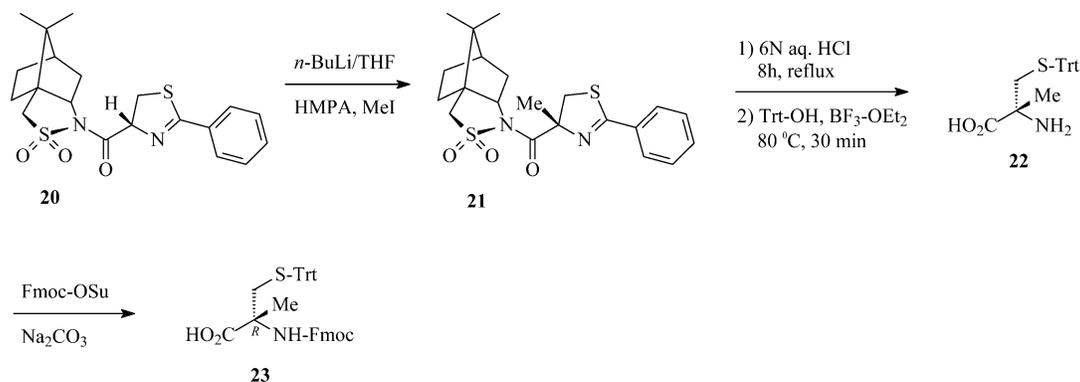
Diastereoisomeric excess (asymmetric induction) during the alkylation step was measured using HPLC and NMR spectrometry. Optical rotation measurements on purified samples were obtained from Bachem AG, Bubendorf, Switzerland.

**(4*R*)-Ethyl 2-phenyl-4,5-dihydrothiazole-4-carboxylate (11).** Triethylamine (21.21 g, 210 mmol) was added dropwise over the period of 15 min to a stirred solution of (*R*)-cysteine ethyl ester hydrochloride (**9**, 37.13 g, 200 mmol) and ethyl benzimidate hydrochloride (**10**, 37.13 g, 200 mmol) in EtOH (250 mL).<sup>24</sup> The mixture was refluxed for 2 h. The reaction mixture was diluted with isopropyl ether (500 mL) and washed with 0.5 *N* aqueous HCl (1  $\times$  150 mL), water (4  $\times$  150 mL), and brine (1  $\times$  150 mL). The organic layer was dried over  $\text{MgSO}_4$  and concentrated in vacuo to afford 41.0 g (87%) of light yellow oil. It was used in the next step without further purification. ESI-MS analysis gave a molecular ion peak at 236 ( $\text{C}_{12}\text{H}_{14}\text{NO}_2\text{S}$ ) ( $\text{M} + \text{H}$ )<sup>+</sup> and 258 ( $\text{M} + \text{Na}$ )<sup>+</sup>.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.86 (2H, d, *J* = 7.5 Hz), 7.47 (1H, m), 7.41 (2H, m), 5.27 (1H, t, *J* = 6.9 Hz), 4.29 (2H, q, *J* = 6.9 Hz), 3.71–3.64 (2H, m), 1.33 (3H, t, *J* = 6.9 Hz).

**(1*R*)-(+)-2,10-*N*-(2-Phenylthiazoline-4-carbonyl)camphorsultam (13).** A 2 *M* solution of  $\text{Me}_3\text{Al}$  (35 mL, 70 mmol) was added dropwise to a suspension of sultam **12** (12.6 g, 58.6 mmol) in toluene (100 mL).<sup>21</sup> The mixture was heated to reflux. After 5 min of refluxing, the clear solution was allowed to cool to ambient temperature over the period of 30 min, and stirring was continued for additional 30 min. A solution of thiazoline **11** (21.3 g, 90.8 mmol) in toluene (60 mL) was added. The reaction mixture turned bright yellow immediately upon addition. It was stirred at  $55 \pm 5$  °C for 24 h. The mixture was cooled in an ice bath, and MeOH (50 mL) was added dropwise. After 30 min of stirring, water (40 mL) was added dropwise. After 60 min of stirring, the mixture was filtered through Celite and washed with EtOAc (750 mL). The filtrate and the washings were combined, dried over  $\text{MgSO}_4$ , and concentrated in vacuo to afford a syrup (30 g). Purification of the crude product by silica gel chromatography (EtOAc/hexane 5:95 to 20:80) afforded 16.8 g (71%) of white solid. Mp 174–175 °C. RP-HPLC:  $t_R = 28.65$  min.  $[\alpha]_D^{24} = +152.34$  (*c* 0.5, MeOH). ESI-MS analysis gave a molecular ion peak at 405 ( $\text{C}_{20}\text{H}_{25}\text{N}_2\text{O}_3\text{S}_2$ ) ( $\text{M} + \text{H}$ )<sup>+</sup>.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.90 (2H, d, *J* = 7.5 Hz), 7.48 (1H, m), 7.41 (2H, m), 5.86 (1H, t, *J* = 6.9 Hz), 3.99 (1H, m), 3.73 (1H, d, *J* = 7.2 Hz), 3.62–3.42 (3H, m), 2.18–2.06 (2H, m), 1.98–1.85 (3H, m), 1.50–1.42 (1H, m), 1.40–1.32 (1H, m), 1.17 (3H, s), 0.99 (3H, s).  $^{13}\text{C}$  NMR (600 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  170.3, 168.5, 132.1, 132.0, 128.9, 128.2, 64.2, 52.0, 48.7, 47.4, 44.5, 37.6, 31.8, 25.8, 20.1, 19.4. Anal. Calcd for  $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_3\text{S}_2$ : C, 59.40; H, 5.94; N, 6.90. Found: C, 59.04, H, 5.84; N, 6.50.

**(1*R*)-(+)-2,10-*N*-((4*S*)-Methyl-2-phenylthiazoline-4-carbonyl)camphorsultam (14).** A 1.6 *M* *n*-BuLi solution in hexane (28.5 mL, 45.6 mmol) was added over 30 min at  $-78$  °C to a stirred solution of **13** (12.85 g, 31.8 mmol) in dry THF (270 mL). After 90 min of stirring at the same temperature, a solution of MeI (5.94 mL, 94.5 mmol) and HMPA (16.6 mL, 94.5 mmol) in THF (25 mL) was added over 30 min. After an additional 90 min of stirring at  $-78$  °C, the reaction mixture was allowed to warm to ambient temperature over 2 h. After cooling in ice bath the reaction was quenched with 3.7 *M* aqueous  $\text{NH}_4\text{Cl}$  (50 mL). The mixture was taken in 1 L of EtOAc and successively washed with 10% aqueous citric acid (3  $\times$  250 mL), saturated aqueous  $\text{NaHCO}_3$  (3  $\times$  250 mL),  $\text{H}_2\text{O}$  (2  $\times$  250 mL), and brine (2  $\times$  250

## SCHEME 2



mL). The organic layer was dried over MgSO<sub>4</sub> and concentrated in vacuo to afford 13.0 g of a red oil. The crude mixture was purified by silica gel chromatography (EtOAc/hexane 5:95 to 20:80) to furnish 6.5 g (49%) of a white solid. Mp 135–136 °C. RP-HPLC:  $t_R$  = 30.65 min.  $[\alpha]^{24}_D$  = +51.07 (*c* 0.5, MeOH). ESI-MS analysis gave a molecular ion peak at 419 (C<sub>21</sub>H<sub>27</sub>N<sub>2</sub>O<sub>3</sub>S<sub>2</sub>) (M + H)<sup>+</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.95 (2H, d, *J* = 7.5 Hz), 7.44 (1H, m), 7.39 (2H, m), 4.18–4.10 (1H, m), 3.57–3.25 (3H, m), 2.93 (1H, m), 2.52 (3H, s), 1.94–1.80 (5H, m), 1.46–1.40 (1H, m), 1.25–1.21 (1H, m), 1.15 (3H, s), 0.91 (3H, s). <sup>13</sup>C NMR (600 MHz, DMSO-*d*<sub>6</sub>): δ 172.8, 126.2, 132.5, 131.6, 128.5, 128.4, 67.7, 49.5, 48.4, 47.2, 43.7, 34.0, 31.5, 27.1, 26.5, 20.0, 19.6. Anal. Calcd for C<sub>21</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>S<sub>2</sub>: C, 60.28; H, 6.22; N, 6.69. Found: C, 59.94, H, 6.02; N, 6.38.

**(S)-S-Trityl-α-methylcysteine (15).** Sultam **14** (4.7 g, 11.24 mmol) was refluxed in 6 N HCl (85 mL) for 8 h. The mixture was washed with EtOAc (3 × 50 mL) and evaporated under reduced pressure. The syrup was taken in EtOH and treated with MTBE to yield a white solid (5.1 g). Without further purification, the solid was treated with trityl alcohol (3.12 g, 12 mmol) and BF<sub>3</sub>·OEt<sub>2</sub> (1.72 mL) in glacial acetic acid (30 mL) at 80 ± 5 °C for 30 min according to reported procedure.<sup>27</sup> After workup and purification by silica gel chromatography, 2.2 g of a white solid (49% over two steps) was obtained. Mp 188 °C. RP-HPLC:  $t_R$  = 21.01 min.  $[\alpha]^{24}_D$  = –32.0 (*c* 0.5, MeOH). ESI-MS analysis gave a molecular ion peak at 378 (C<sub>23</sub>H<sub>24</sub>NO<sub>2</sub>S) (M + H)<sup>+</sup>. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 7.40–7.15 (15H, m), 2.40 (1H, d,

*J* = 6.0 Hz) 2.33 (1H, d, *J* = 6.0 Hz), 1.13 (3H, s). Anal. Calcd for C<sub>23</sub>H<sub>23</sub>NO<sub>2</sub>S: C, 73.21; H, 6.10; N, 3.71. Found: C, 73.01, H, 5.94; N, 3.38. <sup>13</sup>C NMR (600 MHz, DMSO-*d*<sub>6</sub>): δ 170.3, 144.2, 129.1, 128.0, 126.7, 65.6, 58.9, 22.1.

**(S)-N-Fmoc-S-trityl-α-methylcysteine (16).** Compound **15** (2.1 g, 5.57 mmol) was treated with Fmoc-OSu (2.27 g, 6.68 mmol) in the presence of Na<sub>2</sub>CO<sub>3</sub> (1.5 g, 14 mmol) in a water/dioxane mixture overnight according to reported procedure.<sup>28</sup> After workup, 3.2 g (96%) of a white solid was obtained. Mp 192 °C. RP-HPLC:  $t_R$  = 35.4 min.  $[\alpha]^{24}_D$  = –29.3 (*c* 0.15, MeOH). ESI-MS analysis gave a molecular ion peak at 600 (C<sub>38</sub>H<sub>34</sub>NO<sub>4</sub>S) (M + H)<sup>+</sup>. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 7.90–7.85 (2H, m), 7.72–7.67 (2H, m), 7.40–7.35 (2H, m), 7.28 (15H, s), 7.22–7.15 (2H, m), 4.30–4.15 (3H, br, m), 2.88–2.68 (2H, m), 1.47 (3H, s). <sup>13</sup>C NMR (600 MHz, DMSO-*d*<sub>6</sub>): δ 174.4, 154.7, 144.4, 143.8, 140.7, 129.1, 127.9, 127.6, 127.1, 127.0, 126.7, 125.3, 120.1, 65.6, 65.5, 57.6, 46.6, 22.6. Anal. Calcd for C<sub>38</sub>H<sub>33</sub>NO<sub>4</sub>S: C, 76.12; H, 5.50; N, 2.33. Found: C, 75.92, H, 5.39; N, 2.13.

Compounds **20–23** were prepared using similar procedures as described above.

**Supporting Information Available:** Experimental procedures including characterization data for compounds **20–23**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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