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Enantioselective Synthesis of α-Methyl-D-cysteine and Lanthionine Building Blocks via α-Methyl-D-serine-β-lactone

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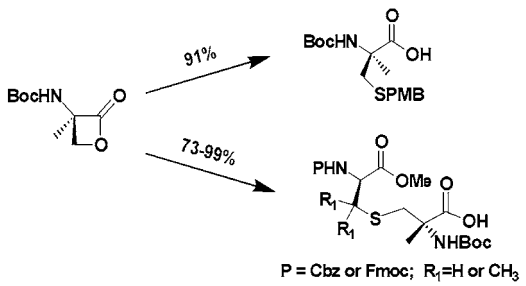
ABSTRACT



We report here the enantioselective synthesis of Boc-α-methyl-D-cysteine(PMB)-OH and lanthionine building blocks through the regioselective ring opening of key intermediate Boc-α-methyl-D-serine-β-lactone.

In our laboratory, we have been focused on the synthesis of constrained amino acid building blocks and their incorporation into biologically active peptidomimetics. In our opioid research program, we have been interested in the synthesis of α-methylcysteine disulfide and lanthionine enkephalin analogues. We previously reported the synthesis of α-methylcysteine via ring opening of a chiral aziridine.[1] While the ring opening with 4-methoxy-α-toluenethiol at the C-3 carbon in the presence of a Lewis acid proceeded efficiently, the yields were considerably lower with other thiols and different nucleophiles.[2] We therefore sought a more versatile and general approach to α-methylcysteine and α-methylcysteine-containing lanthionine building blocks.

Serine lactones are widely used intermediates in the enantioselective synthesis of β-substituted alanines yielding many unnatural amino acids and other chiral building blocks.[3] Vederas and co-workers opened serine lactones with various nucleophiles, including amines, thiols, halogens, and a variety of organometallic reagents.[4] Our laboratory has applied this chemistry to the synthesis of lanthionine derivatives by opening serine β-lactones with a variety of thiols in the presence of cesium carbonate.[5] In this paper, we extend this chemistry to the synthesis of α-methylcysteine and α-methyl lanthionine derivatives utilizing Boc-α-methyl-D-serine-β-lactone **9**.

The synthesis commenced with the preparation of Boc α-methyl-D-serine **8**. From the many syntheses of α-methyl-

(1) Shao, H.; Zhu, Q.; Goodman, M. *J. Org. Chem.* **1995**, *60*, 790−791.
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(3) Nelson, S. G.; Wan, Z.; Stan, M. A. *J. Org. Chem.* **2002**, *67*, 4680−4683.
(4) (a) Arnold, L. D. Kal.; T. H.; Vederas, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 7105−7109. (b) Arnold, L. D.; Drover, J. C. G.; Vederas, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 4649−4659. (c) Arnold, L. D.; May, R. G.; Vederas, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 2237−2241.
(5) Shao, H.; Wang, S. H. H.; Lee, C. W.; Osapay, G.; Goodman, M. *J. Org. Chem.* **1995**, *60*, 2956−2957.

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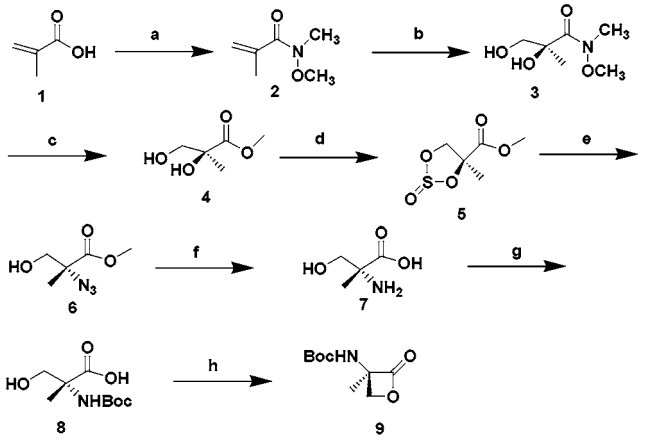
serines,[6] we chose to follow a procedure similar to that of Avenoza *et al.* because of the high yields and enantioselectivity.[7]

The synthesis was initiated (Scheme 1) with methacrylic acid **1**, which was transformed into the Weinreb amide **2**

Scheme 1. Synthesis of Boc-α-Me-D-Serine-β-lactone[a]

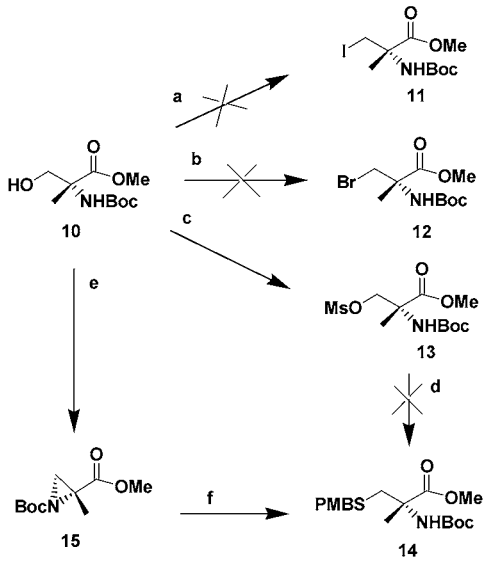


[a] Reaction conditions: (a) (i) $SOCl_2$, CH_2Cl_2; (ii) CH_3ONHCH_3·HCl, pyridine (94% overall). (b) Modified β-AD mix, 91%, >94% ee.[9] (c) (i) LiOH, H_2O/MeOH; (ii) AcCl, MeOH, reflux (94% overall). (d) $SOCl_2$, CCl_4, reflux, 88%. (e) NaN_3, DMF, 50 °C, 72%. The reactions (c−e) followed the methodology reported in ref 7. (f) (i) KOH, MeOH/H_2O; (ii) H_2/Pd−C, MeOH (quantitative overall). (g) Boc_2O, 10% aqueous Na_2CO_3, dioxane, quantitative. (h) DIAD, PPh_3, THF, 67%.

via displacement of the acid chloride with *N*,*O*-dimethylhydroxylamine hydrochloride. This substrate was chosen for the Sharpless asymmetric dihydroxylation on the basis of previous reports of high enantioselectivity from Avenoza et al.[7] A modified β-AD mix[8] that calls for a 5-fold increase of $(DHQD)_2$−PHAL and $K_2OsO_2(OH)_4$ as compared to the original mix was employed to obtain diol **3**. The diol was then saponified with lithium hydroxide and esterified with acidic methanol to form methyl ester **4**. The cyclic sulfite **5** was formed by refluxing the diol with thionyl chloride. The cyclic sulfite was then selectively opened with sodium azide at the tertiary carbon to give the azido alcohol **6**.[9] The regioselectivity of the attack of the azide at the tertiary carbon compared to the secondary carbon was found to be 4:1, and the minor isomer was easily removed by column chromatography. The methyl ester **6** was saponified with potassium hydroxide and the azide reduced with palladium on carbon to give completely unprotected α-methyl-D-serine **7** in a quantitative yield over the two steps. The zwitterion **7** was then protected with Boc-anhydride to give Boc-α-methyl-D-serine **8**.

Previously, we reported the synthesis of lanthionine building blocks from serine derivatives by iodination of the side chain and displacement of the iodine with the appropriate thiol.[10] This route was unsuccessful utilizing Boc-α-Me-D-Ser-OMe **10** (Scheme 2). Iodination and bromination with

Scheme 2. Attempted Synthesis of Boc-α-Me-D-Cys(PMB)-OH[a]



[a] Reaction conditions: (a) PPh_3, I_2, imidazole, CH_2Cl_2. (b) PPh_3, Br_2, imidazole, CH_2Cl_2. (c) MsCl, TEA, THF, 67%. (d) PMBSH, Cs_2CO_3, DMF. (e) PPh_3, DEAD, THF, 85%. (f) PMBSH, BF_3·OEt_2, CH_2Cl_2, 25%.

triphenylphosphine and iodine or bromine gave no evidence of formation of product **11** or **12**. With methanesulfonyl chloride and triethylamine, the side chain alcohol was mesylated to form compound **13**, but this leaving group could not be displaced with 4-methoxy-α-toluenethiol to give Boc-α-Me-D-Cys(PMB)-OMe **14**. The added steric hindrance from the α-methyl group prevents displacement at the methylene carbon. We also attempted to ring open the α-methyl aziridine carboxylic acid methyl ester **15**, which was formed from Boc-α-Me-D-Ser-OMe **10** with triphenylphosphine and diethyl azodicarboxylate (DEAD). The opening of the aziridine gave low yields of the cysteine derivative **14** consistent with previous results.

The above results led us to explore the formation of Boc-α-Me-D-serine-β-lactone **9**, an analogue of the Vederas

(6) This list of references provides examples and is by no means complete: (a) Seebach, D.; Aebi, J. D. *Tetrahedron Lett.* **1984**, *25*, 2545−2548. (b) Ito, Y.; Sawamura, M.; Shirakawa, E.; Hayashizaki, K.; Hayashi, T. *Tetrahedron Lett.* **1988**, *29*, 235−238. (c) Colson, P. J.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 5918−5924. (d) Fukuyama, T.; Xu, L. *J. Am. Chem. Soc.* **1993**, *115*, 8449−8450. (e) Zembower, D. E.; Gilbert, J. A.; Ames, M. M. *J. Med. Chem.* **1993**, *36*, 305−313. (f) Wipf, P.; Venkatraman, S.; Miller, C. P. *Tetrahedron Lett.* **1995**, *36*, 3639−3642.

(7) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2001**, *12*, 949−957.

(8) Bennani, Y. L.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 2079−2082.

(9) Enantiomeric excess of azido alcohol **6** was determined to be greater than 94% by formation of Mosher's ester and subsequent ^{1}H NMR analysis. For comparison, the enantiomer of **6** was also transformed into Mosher's ester and analyzed by ^{1}H NMR (Supporting Information).

(10) Rew, Y.; Malkmus, S.; Svenssen, C.; Yaksh, T. L.; Chung, N. N.; Schiller, P. W.; Cassel, J. A.; DeHaven, R.; Goodman, M. *J. Med. Chem.* **2002**, *45*, 3746−3754.

lactone.[4] Boc-α-Me-D-serine-β-lactone **9** was formed from Boc-α-Me-D-serine **8** through a Mitsunobu reaction utilizing diisopropyl azodicarboxylate (DIAD) and triphenylphosphine[11] (Scheme 1). The resulting Boc-α-Me-D-serine-β-lactone was crystallized, and an X-ray crystal structure was obtained (Figure 1) to confirm the structure of this key building block.

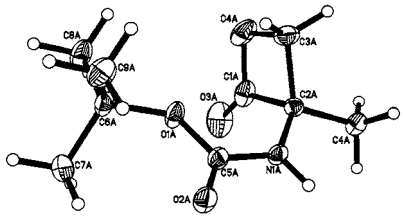
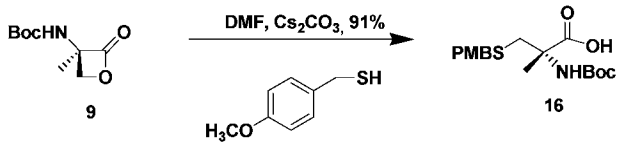


Figure 1. X-ray crystal structure of Boc-α-Me-D-serine-β- lactone **9**.

Boc-α-Me-D-serine-β-lactone **9** was regioselectively opened with 4-methoxy-α-toluenethiol at the β-methylene carbon resulting in *O*-alkyl fission (Scheme 3). The ring opening in

Scheme 3. Synthesis of Boc-α-Me-D-Cys(PMB)-OH



the presence of cesium carbonate was quantitative and gave a 91% yield of Boc-α-methyl-D-cysteine (PMB)-OH **16**. The remaining 9% was thioester formation resulting from *O*-acyl fission.

Boc-α-Me-D-serine-β-lactone **9** was then ring opened with Cbz- and Fmoc-protected cysteine and penicillamine derivatives resulting in the orthogonally protected lanthionine building blocks (Table 1). The primary thiol of Cbz-cysteine-OEt showed some *O*-acyl fission resulting in thioester formation. It is important to note that the α-methyl group of the β-lactone plays a key role in the suppression of *O*-acyl fission as compared to the unmethylated serine β-lactones when utilizing the less hindered cysteine nucleophile. The ratio of *O*-acyl fission to *O*-alkyl fission was 17:83 (Table 1, entry 1) as compared to 50:50 with unmethylated serine β-lactone in DMF.[5] The corresponding tertiary thiol of Cbz-penicillamine gave a nearly quantitative yield of the lanthionine analogue (Table 1, entry 4).

Replacing the Cbz protecting group with the larger Fmoc group eliminated the formation of the thioester but led to

(11) One of the difficulties in the formation of serine lactones is the separation of the lactone from the hydrazine of DIAD by column chromatography. This was not the case with the Boc-α-Me-D-serine-β-lactone where the two compounds could easily be separated by column chromatography.

Scheme 4. Synthesis of Lanthionine Derivatives

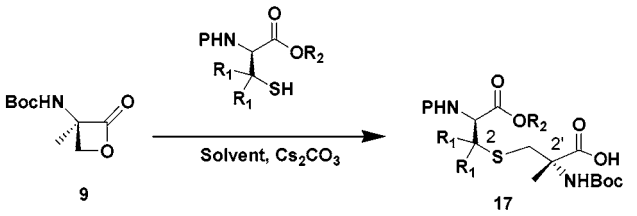


Table 1. Ring Opening of Boc-α-Me-D-Serine-β-lactone **9** to Form Lanthionine Building Blocks

entry	cysteine derivatives	solvent	product (yield, %)	% *O*-acyl fission
1	P = Cbz; R_1 = H; R_2 = Et	DMF	**17a** (83)	17
2	P = Cbz; R_1 = H; R_2 = Et	CH_3CN	**17a**[1] (76)	24
3	P = Fmoc R_1 = H; R_2 = Me	DMF	**17b** (78)	0
4	P = Cbz; R_1 = CH_3; R_2 = Me	CH_3CN	**17c** (99)	0
5	P = Fmoc; R_1 = CH_3; R_2 = Me	CH_3CN	**17d** (80)	0
6	P = Fmoc; R_1 = CH_3; R_2 = Me	DMF	**17d**[1] (73)	0

somewhat lower yields because of cleavage of the Fmoc group under basic conditions with cesium carbonate. To determine if carbonate was responsible for the Fmoc cleavage, test reactions were run with Fmoc-Phe-OMe with 1.2 equiv of cesium carbonate or sodium carbonate in DMF. After 3 h, the Fmoc protecting group was completely removed. This is an important observation that has not been previously reported. To minimize the cleavage of the Fmoc protecting group, the reaction was quenched with ammonium chloride immediately upon disappearance of Boc-α-Me-D-serine-β-lactone **9** resulting in very good yields (Table 1, entries 3, 5, and 6). It is also interesting to note that the reactions proceeded faster in CH_3CN but with slightly reduced regioselectivity (see Table 1, entries 1 and 2). In the case where the tertiary thiol of penicillamine controls the regioselectivity, it was beneficial to use CH_3CN in order to decrease the reaction time, thereby minimizing Fmoc cleavage (see Table 1, entries 5 and 6).

In summary, we have developed an efficient and versatile route to Boc-α-Me-D-Cys(PMB)-OH **16** and lanthionine building blocks through the key intermediate Boc-α-Me-D-serine-β-lactone **9**. This intermediate is currently being explored as a precursor to a variety of α-methyl amino acids and amino acid building blocks by opening of the α-Me-serine-β-lactone with a wide range of nucleophiles.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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