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Scalable Synthesis of Orthogonally Protected β-Methyllanthionines by Indium(III)-Mediated Ring Opening of Aziridines

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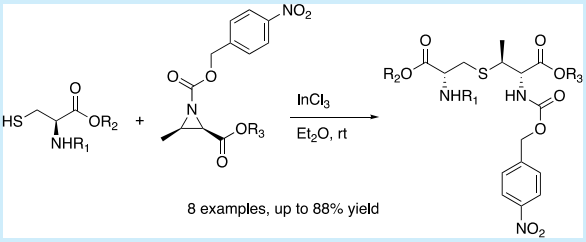
Supporting Information

ABSTRACT: Lantibiotics are a class of peptide antibiotics with activity against most Gram-positive bacteria. Lanthionine (Lan) and β-MeLan are unusual thioether-bridged, non-proteinogenic amino acids, which are characteristic features of lantibiotics. In this paper, we report the facile stereoselective synthesis of β-methyllanthionines with orthogonal protection by nucleophilic ring opening of aziridines. This method leads to an expedient access to β-methyllanthionines and allows production of over 30 g of β-methyllanthionine in a single batch.



Rapid outgrowth of multidrug-resistant bacteria poses a very serious threat to human health. Unfortunately, the weapons in our current antibiotic arsenal have become less and less effective in treating bacterial infections.[1] Discovering novel antibacterial agents, which are active against multiresistant bacteria, is a significant global health concern. In view of their unique modes of action,[2] lantibiotics such as nisin, mersacidin, lacticin, and gallidermin are promising candidates for the development of new antibiotics. Total syntheses of nisin A, lacticin 3147, and lacticin 481 have been accomplished.[3−5]

We have initiated a synthetic effort directed at the lantibiotic mersacidin (Figure 1), which is active against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE). Mersacidin is believed to inhibit the transglycosylation reaction, a key reaction that results in polymerization of the carbohydrate backbone, during the latter stages of the peptidoglycan biosynthetic pathway.[6]

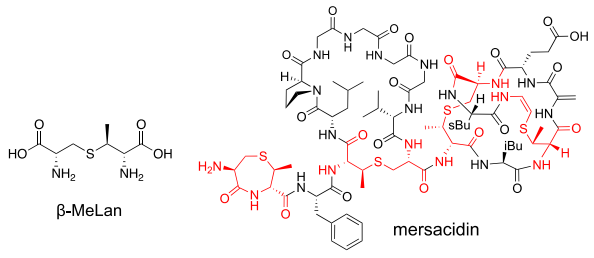
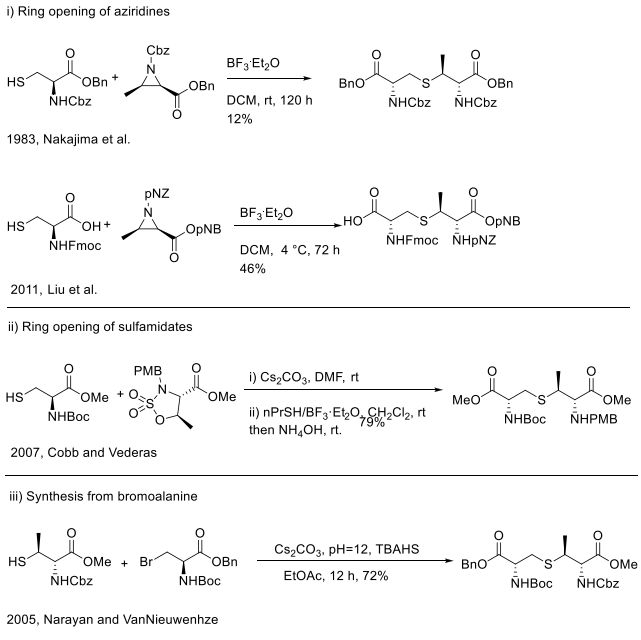


Figure 1. Structure of ββ-methyllanthionine and mersacidin.

In order to understand the exact mechanism of action and in order to attempt tuning of biological activity through analog synthesis, we are currently pursuing the chemical synthesis of mersacidin. From a structural standpoint, ββ-methyllanthionine is embedded in all four rings of mersacidin. In addition, the (*Z*)-aminovinyl sulfide moiety is a derivative of ββ-methyllanthionine (Figure 1). In order to execute a total synthesis of mersacidin, large quantities of orthogonally-protected β-methyllanthionines were required.

As the characteristic component of lantibiotics, ββ-MeLan has attracted considerable interest from synthetic chemists. To date, several syntheses of orthogonally-protected ββ-MeLan have been reported.[7] In summary, synthesis of ββ-MeLan has been typically achieved through use of one of the following three approaches (Scheme 1): (i) Lewis acid mediated ring

Scheme 1. Previous Approaches to Orthogonally-Protected ββ-Methyllanthionine



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opening of *N*-carbobenzoxyaziridines with cysteine;[4,8] (ii) ring opening of cyclic sulfamidates with cysteine;[9] and (iii) S_N2 reactions of bromoalanine and β-methylcysteine.[10] However, each of the above methods have their drawbacks, which present difficulties for their application in a large-scale synthesis of β-methyllanthionine.

For example, nucleophilic ring opening of *N*-carbobenzoxyaziridines requires a large excess of $BF_3{\cdot}OEt_2$ (4−8 equiv). Furthermore, these reactions are typically sluggish (3−5 days), and the yields are frequently poor (e.g., 12%−46%). The cyclic sulfamidate method gives better yields, but it requires cleavage of the intermediate sulfamic acid, involving the use of propanethiol, after the nucleophilic ring-opening reaction.

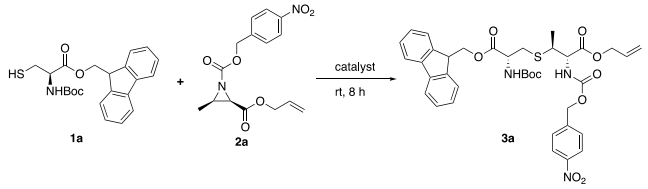
Additionally, the preparation of the sulfamidate precursors requires oxidative conditions that are not compatible with allyl and alloc protecting groups. The bromoalanine route requires multiple synthetic steps to prepare each of the reaction partners, and some of these reactions are plagued by low overall atom efficiencies. As a result, this method is also unsuitable for large-scale synthesis. To facilitate the total synthesis of mersacidin, we felt it was necessary to develop a new method for an efficient and scalable synthesis of orthogonally-protected $\beta\beta$-MeLan derivatives.

Direct construction of the carbon−sulfur bond in $\beta\beta$-MeLan through nucleophilic ring-opening of an orthogonally-protected *N*-carbobenzoxyaziridine with an orthogonally protected cysteine derivative is highly atom economical. Moreover, the preparation of the required cysteine- and aziridine-derived reaction partners is concise and well-established.[11] Various bases, as well as Lewis acids, have been successfully applied for aziridine ring-opening reactions with carbon, nitrogen, sulfur, oxygen, and halogen nucleophiles.[12,13] To the best of our knowledge, $BF_3{\cdot}OEt_2$ is the only Lewis acid that has ever been utilized in the attack of cysteine-derived nucleophile on aziridine. However, as mentioned above, since these reactions typically require large excesses of $BF_3{\cdot}OEt_2$, long reaction times, display intolerance toward acid labile protecting groups, and proceed in relatively poor yields, this reaction is unsuitable for large-scale synthesis of β-MeLan derivatives. These liabilities led us to investigate the development of an alternative method to enable an efficient and scalable synthesis of β-MeLan derivatives via ring opening of suitable protected aziridines by orthogonally-protected cysteine nucleophiles.

The protecting group on the aziridine nitrogen should be electron-withdrawing in order to activate the aziridine toward nucleophilic ring-opening. Given this limitation, our efforts focused on use of the *p*-nitrobenzyloxycarbonyl (*p*-NO_2-Cbz) protecting group. Compared to the Cbz protecting group frequently used in previously reported $\beta\beta$-MeLan syntheses, which is difficult to remove by catalytic hydrogenation due to the presence of the sulfur atom, *p*-NO_2-Cbz can be readily removed via catalytic hydrogenation or via reductive cleavage by sodium dithionite.[14] Therefore, cysteine derivative **1a** and aziridine derivative **2a** were chosen as model substrates for our initial investigation seeking suitable Lewis acids or bases that can facilitate the desired ring-opening reaction.

As noted in Table 1, $ZnCl_2$, $Ag(cod)_2PF_6$, $LiClO_4$, $In(OTf)_3$, and DABCO failed to afford the desired product **3a** (Table 1, entries 1−4 and 6). $BiCl_3$ and $InBr_3$ gave **3a** in yields of 20% and 36%, respectively (Table 1, entries 5 and 7). When the mixture of **1a** and **2a** was treated with $InCl_3$ in DCM at room temperature, product **3a** was obtained in 52% yield (Table 1, entry 8). When the reaction was performed in Et_2O, the yield improved to 62% (Table 1, entry 10). Based on the reaction monitoring by TLC, the improved yield was attributed to suppressed Boc protecting group cleavage when the reaction was carried out in Et_2O relative to DCM. A reduction of the amount of $InCl_3$ (Table 1, entries 9 and 11) resulted in increased reaction times and increased product decomposition. This trend was further exacerbated when catalytic amounts of $InCl_3$ were employed. Further experimentation revealed that 1 molar equiv of $InCl_3$ in Et_2O at room temperature provided the optimal conditions for the desired aziridine ring-opening reaction.

Table 1. Optimization of the Reaction Conditions for Nucleophilic Ring-Opening of 2a with 1a[a]



entry	catalyst	solvent	yield (%)
1	DABCO	DCM	0
2	$ZnCl_2$	DCM	0
3	$Ag(cod)_2PF_6$	DCM	0
4	$LiClO_4$	DCM	0
5	$BiCl_3$	DCM	20
6	$In(OTf)_3$	DCM	0
7	$InBr_3$	DCM	36
8	$InCl_3$	DCM	52
9	$InCl_3$	DCM	46[b]
10	$InCl_3$	Et_2O	62
11	$InCl_3$	Et_2O	56[b]

[a] **1a** (1 equiv), **2a** (1 equiv), catalyst (1 equiv). [b] $InCl_3$ (30 mol %), 16 h

With the optimal conditions identified in our model reaction system, the substrate scope was subsequently investigated. As shown in Scheme 2, a variety of cysteine derivatives performed well in the $InCl_3$-mediated aziridine ring-opening reactions to provide $\beta\beta$-MeLan derivatives (e.g., **3a**−**c**,**e**,**f**) in good yields. To our delight, the reaction also worked well when the C-terminal cysteine carboxyl group was not protected; **3g** and **3h** were obtained in yield of 88% and 50%, respectively. These products can be directly utilized for further peptide assembly or for direct preparation of unusual *S*-[(*Z*)-2-aminovinyl]-(3*S*)-3-methyl-D-cysteine (AviMeCys)—an important unit of several lantibiotics (including mersacidin) with highly potent biological activities—via diphenylphosphoryl azide (DPPA)-mediated decarboxylation[15] or Ni-promoted decarbonylation of amino acid thioesters.[16] In general, our data appear to support the notion that better yields are obtained in reactions that do not utilize reaction partners with acid-labile protecting groups (e.g., Boc, *tert*-butyl).

After the exploration of the substrate scope, we tested our optimized substrates and reaction conditions for a large-scale synthesis of $\beta\beta$-MeLan (Scheme 3). To our delight, the yields remained consistent with those observed in our model systems when the reactions were carried out on a small scale. For example, reactions 1 and 2 (Scheme 3) proceeded smoothly to deliver over 30g of $\beta\beta$-MeLan **3g** and **3b** in yields of 86% and 62%, respectively.

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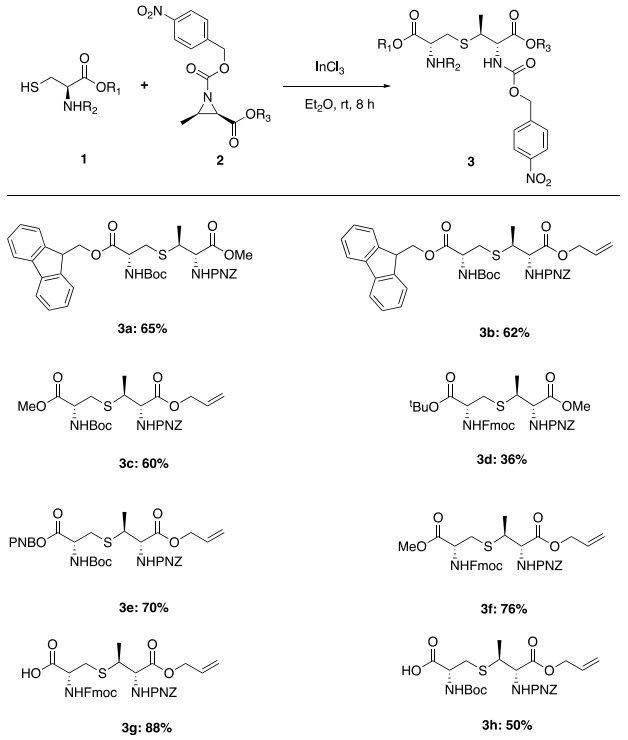
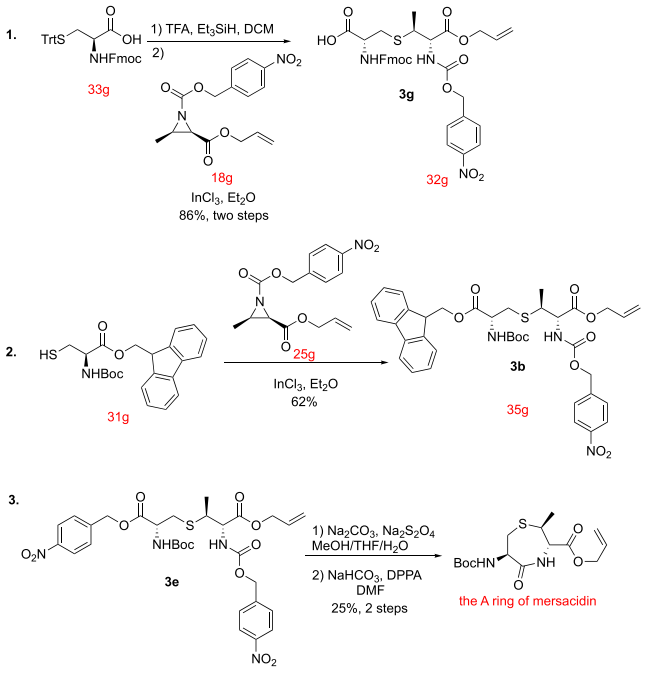
Scheme 2. Substrate Scope of the $InCl_3$-Mediated Ring-Opening Reaction of Cysteines and Aziridines[a]



[a]All reactions were carried out with **1** (2.5 mmol), **2** (2.5 mmol), and $InCl_3$ (1.0 equiv) in Et_2O (25 mL) at 25 °C.

Scheme 3. Thirty-Gram Scale Synthesis of ββ-MeLan and Synthesis of the A Ring of Mersacidin



To further demonstrate the utility of this chemistry, ββ-MeLan derivative **3e** was readily converted into the A-ring of mersacidin. Cleavage of the *p*-NO_2-Cbz group and the *p*-nitrobenzyl group in ββ-MeLan **3e**, via reductive cleavage with sodium dithionite, followed by cyclization of the resulting amino acid through activation with diphenylphosphoryl azide afforded the orthogonally protected A-ring of mersacidin in 25% yield over the two-step sequence.

In summary, we have developed a rapid and efficient synthesis of orthogonally-protected ββ-methyllanthionines via indium(III)-mediated nucleophilic ring opening of aziridines under mild conditions. The reaction conditions tolerated various protecting groups schemes, and large quantities of ββ-methyllanthionines can be produced in a single batch. The development of this efficient method to quickly access ββ-methyllanthionines, in quantity, will substantially assist efforts directed at the total synthesis of mersacidin and other lantibiotics. Our own efforts in this area will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00125.

Experimental procedures, spectroscopic data of the obtained compounds and copies of ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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