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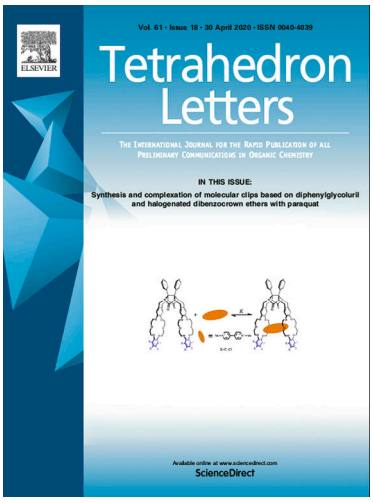

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A Concise and Scalable Synthesis of a Novel L-allo-Enduracididine Derivative

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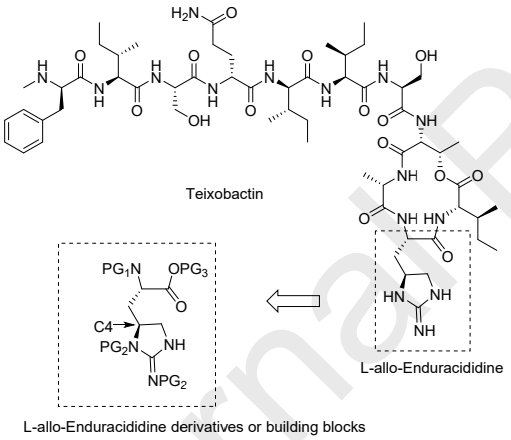
Introduction

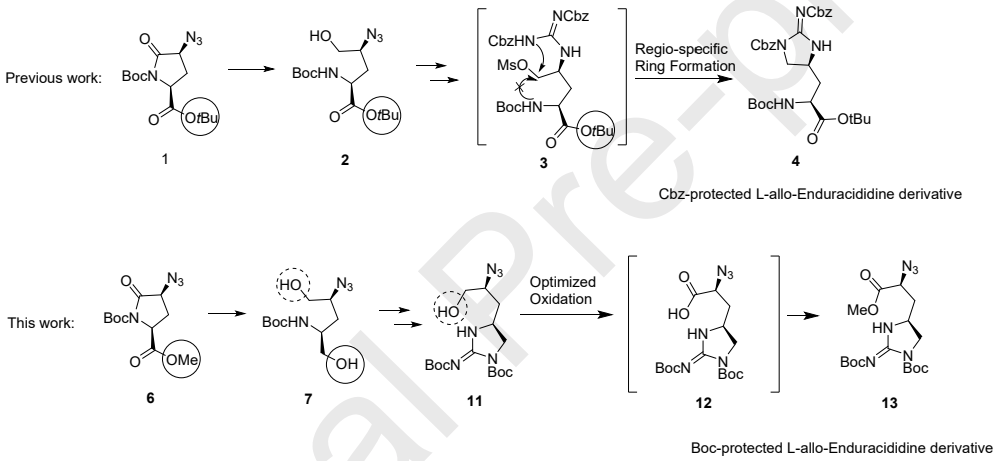
Antimicrobial resistance has become one of the biggest threats to human health. For example, multiresistant bacteria, particularly methicillin-resistant *S. aureus* (MRSA) have caused numerous hospital and community-acquired infections recently. Therefore, There is an urgent need for more efforts to develop efficient antimicrobial compound.[1] In early 2015, a nature publication described isolation and characterization of a novel peptidic natural product called Teixobactin (**Figure 1**), which exhibit excellent activities against multiple bacteria strains including MRSA by binding bacteria cell wall lipid-2 and lipid-3.[2a] Since the discovery, great attention has been paid to the synthesis and activities study of Teixobactin and its analogues.[2]



Figture 1. Teixobactin and L-allo-Enduracididine

Structurally, Teixobactin contains a 13-membered depsipeptide ring composed of 4 D-amino acids with an unusual amino acid L-allo-Enduracididine. Development of efficient methods to install L-allo-Enduracididine fragment is essential in the synthesis of Teixobactin and its analogues (**Figture 1**). However, only few examples were described for the synthesis of L-allo-Enduracididine building blocks or derivatives currently.[3] One of the main challenges is to establish the C4 chiral center in a highly stereoselective way. To address these challenges, our lab has been focused on this research area, and we have previously reported a highly stereoselective and scalable synthesis of L-allo-Enduracididine and its' building block from commercially available starting material *trans*-hydroxyproline. An excellent stereoselectivity (dr = >50:1) was achieved in this approach.[4] As is shown in **Scheme 1**, the reductive ring opening reaction is a key step. Amide **1** was selectively reduced to hydroxyl group in the presence of *tert*-butyl ester, of which the stability is essential to

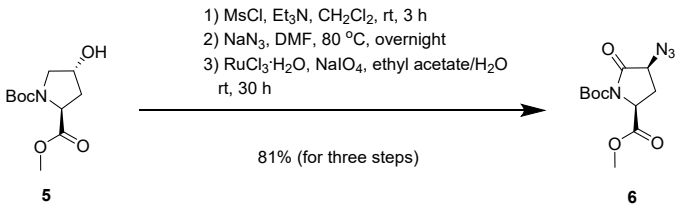
this strategy. Reduction reaction of Azide **2** followed by treatment with Goodman's reagent constructed the Cbz-protected guanidine moiety in excellent regioselectivity, delivering the L-allo-Enduracididine derivative **4** efficiently. Notably, it was found that trace of compound **7** was isolated when a methyl group (**6**) instead of *tert*-butyl group was used to mask the carboxylate during the study of the reductive ring opening reaction. Compound **7** contains two free hydroxyl group which may allow us to achieve the synthesis of a novel L-allo-Enduracididine derivative **12 or 13** bearing a Boc-protected guanidine moiety, meanwhile, simply using azido group as the amine protecting group. The oxidation reaction would be employed as a key manipulation to generate the carboxylic acid intermediate. To the best of our knowledges, synthesis of Boc-protected guanidine building block was rarely reported.[5] Herein, we report a novel synthesis of a L-allo-Enduracididine derivative bearing a Boc-protected guanidine moiety from commercially available *trans*-hydroxyproline. The reductive ring-opening reaction and oxidation reaction were the key steps in this synthesis. The chirality was achieved in a highly stereoselectivity. The oxidation/methylation condition was explored as well.



Scheme 1. Strategy of the Boc-protected L-allo-Enduracididine synthesis

Results and discussion

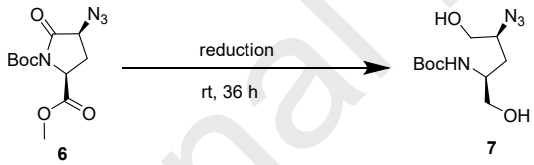
Our synthesis commenced with the transformation of hydroxyl functional group to azido group in **5** which is derived from commercially available *trans*-hydroxyproline by methylation (**Scheme 2**). Reaction of **5** with methanesulfonyl chloride in the presence of Et_3N gave the corresponding mesylate, which was treated with sodium azide without purification to inverse the chirality giving the corresponding azidoproline, and subsequent Sharpless oxidation worked well to deliver the lactam **6** as a single diastereomer (^{1}H NMR) in high yield over three steps.[6] The combined three steps are more efficient compared to our former work.[4]



Scheme 2. Installation of Lactam and Azido Functionalities

Reductive lactam ring-opening reaction is the key transformation in our synthesis (**Table 1**). Reduction of both lactam and methyl ester functionalities in one step was explored. The use of tetrahydrofuran or dioxane resulted in poor conversion. When EtOH was employed as the solvent, lactone product was formed as the major compound as reported in our previous work **(Entry 2 and 4**).[4] Fortunately, when 2.5 equivalents $NaBH_4$ was used in MeOH, trace of desired product was isolated successfully (**Entry 3**). More stronger reducing regents, such as $LiAlH_4$, was also tested to give a good conversion, however, the reaction delivered complicated mixtures (**Entry 1**). Increasing $NaBH_4$ to six equivalents delivered **7** in 88% yield as a single diastereomer (^{1}H NMR) (**Entry 8**). Decreasing the reaction time to 18 h resulted in a low conversion (**Entry 6**). Improving the reaction temperature resulted in more complicated transformation and a lower yield was obtained (**Entry 7**). It should be noted that the reduction using *t*-butyl ester derivative as the substrate resulted in a low conversion probably owing to the steric hindrance. Thus, all the chiral carbon centers required for the protocol were built successfully.

Table 1. A General Reduction Condition[a]

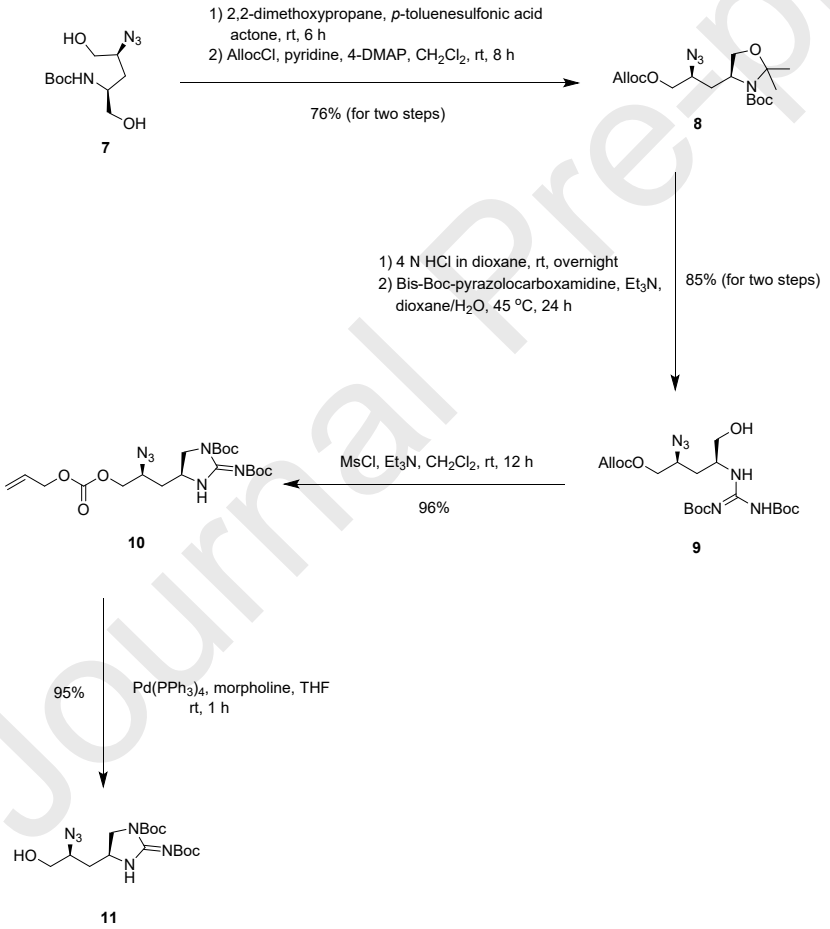


Entry	condition	**7** (%)[b]
1	2.5 equiv. $LiAlH_4$ in THF	-
2	2.5equiv. $NaBH_4$ in THF or dioxane	-
3	2.5equiv. $NaBH_4$ in MeOH	5
4	2.5equiv. $NaBH_4$ in EtOH	-
5	4 equiv. $NaBH_4$ in MeOH	51
6	6 equiv. $NaBH_4$ in MeOH[c]	45
7	4 equiv. $NaBH_4$ in MeOH[d]	36
8	6 equiv. $NaBH_4$ in MeOH	88

[a]*tert*-butyl group instead of methyl delivered trace desired product.

[b]isolated yield. [c]the reaction time is 18 h. [d]the temperature is 50 °C

In order to protect the hydroxyl group selectively, 2,2-dimethoxypropane was employed to give a five-membered ring in the presence of *p*-toluenesulfonic acid (**Scheme 3**). Subsequent protection of the other hydroxyl functional group using allyl chloroformate afforded **8** in 76% yield over two steps. To install the guanidine moiety in **9**, 4 N HCl was used to liberate the amine and hydroxyl functional groups, and the guanidinylation reaction was achieved after treatment with Bis-Boc-pyrazolocarboxamidine. An excellent conversion was realized to afford **9** in 85% yield. Cyclization reaction was performed employing methanesulfonyl chloride under basic condition, generating **10** in remarkable yield. Thus, the Boc-protected guanidine skeleton was successfully constructed in this approach. Deprotection reaction worked smoothly in the presence of palladium catalyst to generate hydroxyl group, delivering **11** in excellent yield.

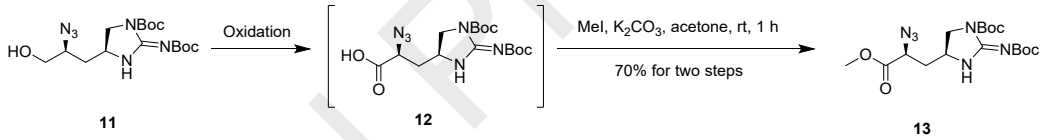


Scheme 3. Construction of the Boc-protected Guanidine Moiety

After establishing the requisite stereochemistry and guanidine fragment, we next tried to introduce the carboxylic acid functionality. The oxidation of hydroxyl group was the other key step for this strategy. However, it was found that the carboxylic acid intermediate was hard to purify by column

and decomposed slowly in solution, probably owing to the instabilities caused by the interaction between carboxylic acid and Boc-protecting group. Therefore, methyl iodide was employed to trap the acid to form the methyl ester derivative. Hence, we optimized the reaction conditions for these two steps. It was found that the oxidation reaction was sensitive to oxidants and solvents. When the reaction was performed in the presence of quantitative TEMPO and NaClO under basic condition, only 10 % target product was delivered (**Table 1, Entry 1**). After an organic oxidant (trichloroisocyanuric acid) was used, the reaction gave more desired product while no product was monitored under buffer conditions (**Entry 2, 8**).[7] The use of *Jones* reagent or $RuCl_3{\cdot}xH_2O$ failed to generate the target ester derivative. In addition, DMP was explored aiming to generate aldehyde, however, no desired product was found. Fortunately, when the reaction condition was switched to $NaClO_2$/NaClO in presence of a catalytic amount of TEMPO, 31% methyl ester derivative was isolated after 30 mins (**Entry 5**).[8] Increasing the reaction time to 1 h gave **12** in 72% yield while 1.5 h resulted in a lower yield (**Entry 6, 7**). This optimized condition enables the generation of the carboxylate functionality through an oxidation strategy, where sensitive moieties such as *Boc*-protected guanidine can be tolerated. It should be noted that all these synthetic routes are gram-scale processes. Thus, we accomplished the synthesis of a Boc-protected L-allo-Enduracididine derivative efficiently. Further research is ongoing to apply this derivative in the synthesis of Teixobactin analogues.

Table 2. Optimization of Oxidation Conditions



Entry	Oxidation condition	The yield of methyl ester derivative **13**[a]
1	TEMPO (1.1 eq.)/NaOCl/KBr/$NaHCO_3$/acetone	10%
2	TEMPO (cat.)/**A**/NaBr/$NaHCO_3$/acetone[b]	15%
3	Jones reagent	-
4	$RuCl_3{\cdot}xH_2O$/$NaIO_4$/CCl_4/CH_3CN/H_2O	-
5	TEMPO (cat.)/$NaClO_2$/NaClO/buffer/30 min	31%
6	TEMPO (cat.)/$NaClO_2$/NaClO/buffer/1 h	72%
7	TEMPO (cat.)/$NaClO_2$/NaClO/buffer/1.5 h	49%
8	TEMPO (cat.)/**A**/NaBr/buffer/acetone	-
9	DMP or DMP/$NaHCO_3$ then Pinnick Oxidation[c]	-

[a]isolated yield. [b]A = trichloroisocyanuric acid. [c]no aldehydes product was formed.

Conclusion

we report a novel synthesis of a L-allo-Enduracididine derivative bearing a *Boc*-protected guanidine moiety from commercially available *trans*-hydroxyproline. The reduction reaction and oxidation reaction were the key steps in the synthesis. The chirality was achieved in a highly stereoselectivity. The oxidation/methylation condition was explored as well.

Acknowledgment

This work is supported by the University of Central Florida.

Appendix A. Supplementary data

Supplementary data to this article can be found online

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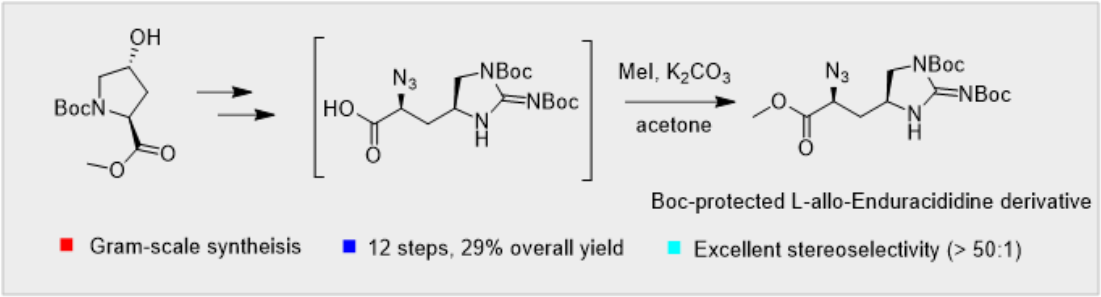

Highlights

- 12 steps and 29% overall yield to a novel Boc-protected L-allo-Enduracididine derivative
- Gram-scale synthesis for all steps
- Excellent stereoselectivity starting from methylated *trans*-hydroxyproline