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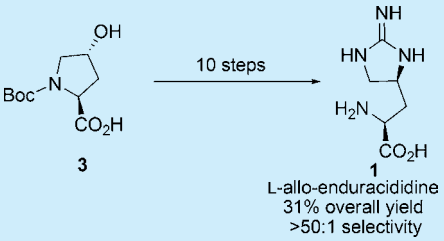
A Highly Stereoselective and Scalable Synthesis of L-allo-Enduracididine

William Craig, Janet Chen, David Richardson, Rondel Thorpe, and Yu Yuan*

Department of Chemistry, University of Central Florida, Orlando, Florida 32816, United States

Supporting Information

ABSTRACT: A highly stereoselective and scalable synthesis of L-allo-enduracididine from hydroxyproline derivative is described. Pyrrolidine oxidation and reductive ring opening are the key steps in the synthesis. Compared to previously reported approaches, the current route affords L-allo-enduracididine in 10 steps from **3** in 31% overall yield with >50:1 diastereoselectivity.



Antimicrobial resistance is one of the biggest threats to human health. In recent years, multiresistant bacteria, particularly methicillin-resistant *S. aureus* (MRSA), have caused numerous hospital and community-acquired infections and such infections will be difficult to treat without new antibiotics.[1] In the meantime, pharmaceutical industries have not kept pace with this alarming situation because increasing R&D costs and fast developing resistance limit their interest in antibiotic research. In this regard, novel antimicrobial compounds with distinct modes of action are in imminent demand. In early 2015, Lewis and co-workers disclosed a depsipeptide, teixobactin (Figure 1), which possesses excellent antibacterial activity against multiple bacteria strains including MRSA by binding bacterial cell wall lipid-2 and lipid-3.[2]

Since the molecular target of teixobactin is not an endogenous protein, no resistance was detected for *S. aureus* or *M. tuberculosis* when the bacteria were treated with sub-MIC levels of teixobactin over a period of 27 days. These encouraging results along with its toxicity and pharmacokinetic profiles make teixobactin a promising candidate for drug development.

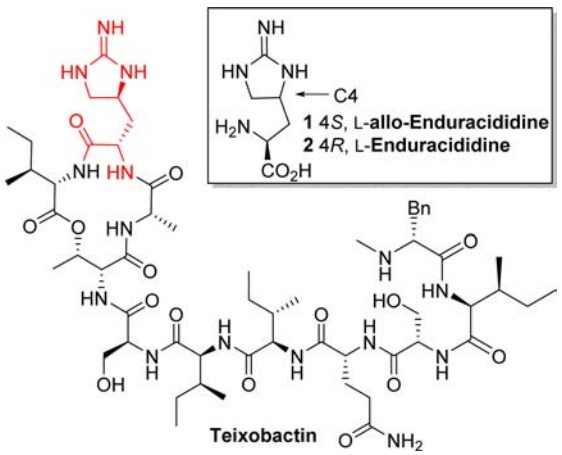


Figure 1. Teixobactin and enduracididines.

To improve its potency and understand its *in vivo* metabolism, our laboratories embarked on the total chemical synthesis of teixobactin. Given the peptidic nature of teixobactin, it is crucial to access all the amino acid residues in sufficient quantity and high stereochemical purity. A unique amino acid residue found in teixobactin is L-allo-enduracididine **1**, a stereoisomer of enduracididine **2**, which is derived from arginine by post-translational modification.[3] One of the challenges in allo-enduracididine synthesis is to establish a C4 center in a stereoselective manner. To date, there are several literature reports (Scheme 1) for the synthesis of **1** and **2**, but a highly selective and scalable route still needs to be developed. In an early example, hydrogenation of a histidine derivative was used to create the C4 center, but this method generated a 1:1 mixture of both isomers.[4] Dauban and Dodd reported an aziridination−ring opening approach to establish the nitrogen center: with 25 mol % of a Cu catalyst, a 1:3 diastereomeric ratio (dr) was achieved for the aziridination reaction, albeit in 16% yield.[5] Recently, Du Bois and co-workers disclosed an elegant synthesis of racemic enduracididine and allo-enduracididine by Rh catalysis, but the C4 selectivity problem remained unaddressed.[6] A relatively selective synthesis of enduracididines by scientists from Novobiotic Pharmaceuticals employed a 6:1 mixture of an aspartate derivative to set the C4 center, but the method to prepare this starting material was not specified.[7]

During the course of our total synthesis, we realized that developing a scalable and stereoselective approach that led to adequate L-allo-enduracididine supplies was necessary for our synthetic endeavors. Thus, we proposed a new route to the amino acid from protected *trans*-hydroxyproline. As shown in Scheme 2, free L-allo-enduracididine **1** could be derived from

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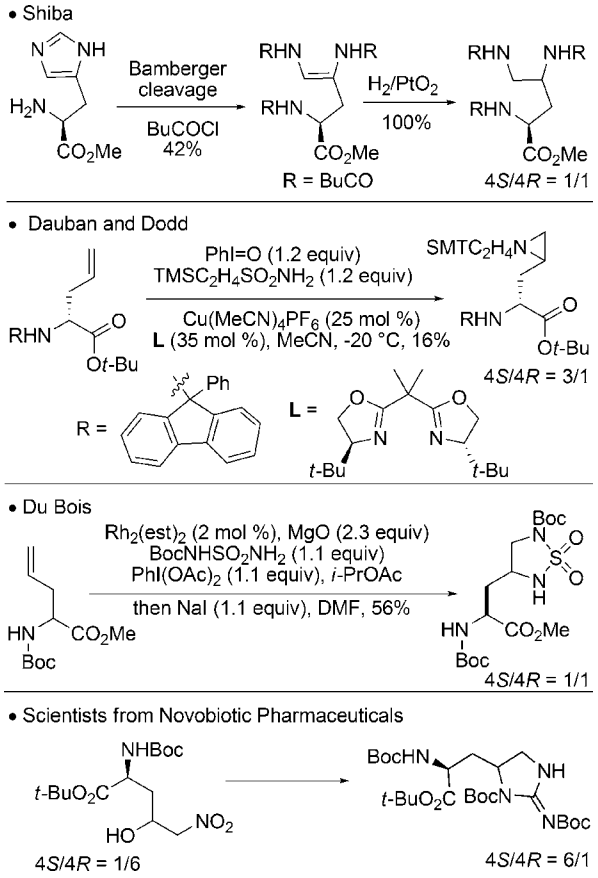
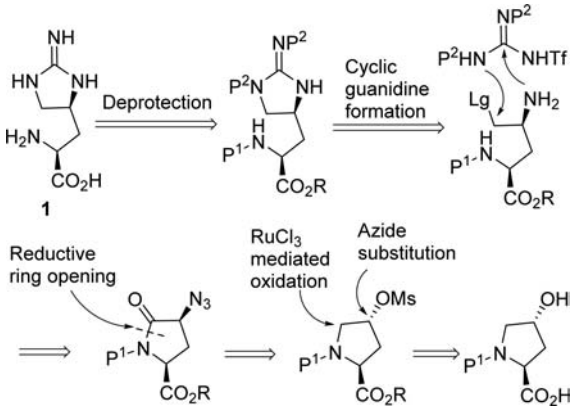
Scheme 1. Known Methods to Create C4 Chiral Center



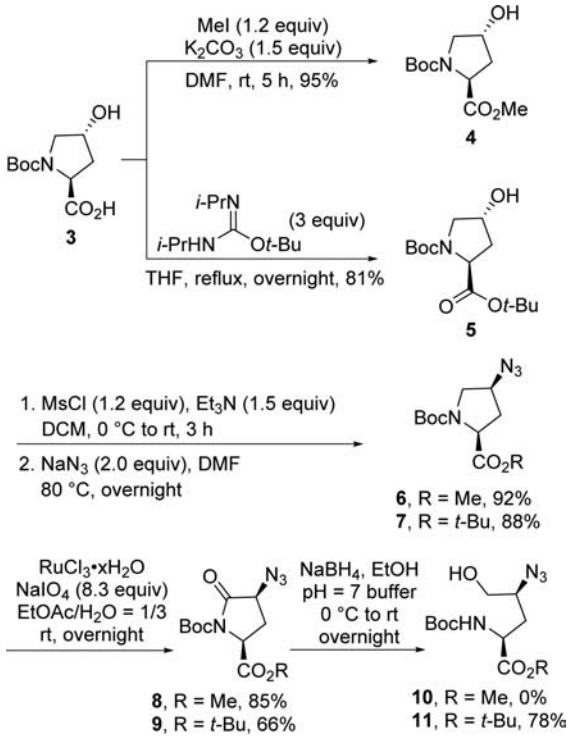
Scheme 2. Retrosynthetic Analysis



the protected precursor, and the cyclic guanidine moiety could potentially be constructed by an intramolecular nucleophilic substitution reaction. In our case, the C4 chiral center would be established by inverting the hydroxyl group stereochemistry in the starting material, and subsequent oxidation−reduction would convert the cyclic substrate to a linear intermediate.

Our synthesis commenced with protection of the carboxylate group in *trans*-hydroxyproline (Scheme 3). Reaction of **3** with iodomethane in the presence of K_2CO_3 afforded methyl ester **4** in 95% yield, and then the methyl ester was treated with methanesulfonyl chloride and Et_3N to give the corresponding mesylate. The crude product was pure enough for the inversion reaction, and the mesylate group was cleanly replaced by an azido group in DMF at 80 °C to generate the azidoproline **6** in

Scheme 3. Synthesis of the Acyclic Skeleton



92% yield. The dr was difficult to determine at this stage because rotamers of **6** complicated the NMR analysis. The dr was measured after azidoproline **6** was oxidized to lactam **8** by $RuCl_3{\cdot}xH_2O/NaIO_4$,[8] and the *cis* relationship of the azido group and the carboxylate group was confirmed by NOE. The key step in our synthesis was the conversion of **8** into the fully functionalized L-allo-enduracididine skeleton by a reductive ring opening reaction without the newly generated hydroxyl group attacking the carboxylate under the reaction conditions. We carefully controlled the pH of the reaction media and the amount of reducing agent, but a clean ring opening product was not able to be isolated from the reaction mixture. The reason we chose a methyl group to mask the carboxylate is that the methyl group is easily removed by saponification and a Boc group on the α nitrogen would be compatible with basic hydrolysis. This protective group orthogonality would allow us to use the demethylation product in solid phase peptide synthesis. The less sterically demanding methyl group was prone to form lactone during the ring opening reaction, so we decided to replace it with a more bulky *tert*-butyl group. The synthesis of the *tert*-butyl ester was accomplished by mixing Boc-*trans*-Hyp-OH with *O*-*tert*-butyl-*N*,*N*′-diisopropylisourea in THF at reflux; the resulting *tert*-butyl ester underwent smooth mesylation, azide substitution, and Ru oxidation to afford lactam **9** in good overall yield and high dr. Reduction of the lactam **9** in ethanol/pH = 7 buffer by $NaBH_4$ successfully provided the ring opening product **11** in 78% yield, and no lactone was detected by LC-MS.[9]

After establishing all the requisite chiral centers, we turned our attention to the guanidine moiety (Scheme 4). To liberate the free amino group, azide **11** was reduced by Pd catalyzed hydrogenation and the guanidinylation was effected by treatment of **12** with Goodman's reagent.[10] The advantage of a *tert*-butyl ester was further demonstrated in the guanidinylation reaction: when free amine **12** was heated at 45 °C for 24

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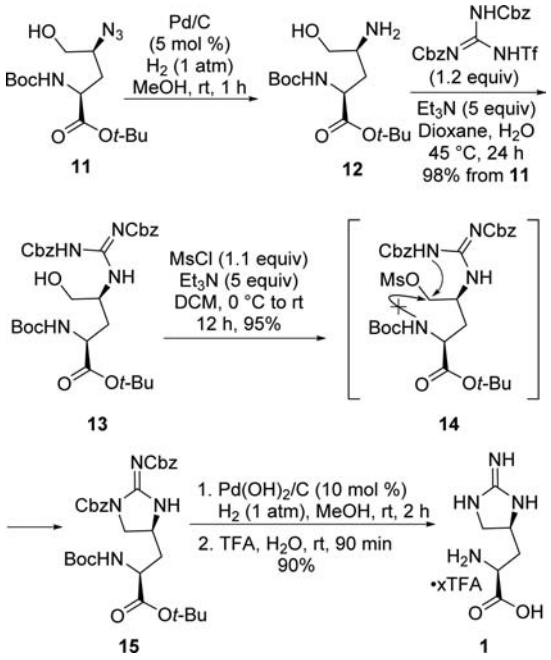
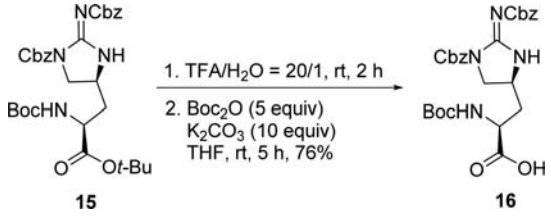
Scheme 4. Completion of L-allo-Enduracididine



h in the presence of Et_3N, no lactam formation was observed as determined by LC-MS analysis. The final ring closure was achieved by a nucleophilic substitution reaction of the pendant guanidine moiety after the hydroxyl group was converted to a mesylate. Although the nitrogen atom in the α amino group is also five atoms away from the mesylate and two different five-membered rings can be potentially formed, the more nucleophilic guanidine should dominate the substitution reaction. Indeed, when **13** was treated with methanesulfonyl chloride under basic conditions, only one product was formed in the reaction mixture and NMR analysis confirmed the product identity as **15**. Furthermore, we prepared the other possible ring closure product from **7** by sequential reduction and guanidinylation, and ^{1}H NMR analysis of the resulting product further supported our assignment of **15**.[11] At this stage, HPLC analysis of crude **15** could achieve good resolution on the stereoisomers and the dr of the analytical sample was determined to be >50:1. Finally, the benzyloxycarbonyl groups were removed by $Pd(OH)_2$ catalyzed hydrogenation in MeOH and trifluoroacetic acid (TFA) mediated final deprotection afforded L-allo-enduracididine **1** in 90% yield as its TFA salt. The spectroscopic data (^{1}H NMR, HRMS) of synthetic **1** are in good agreement with literature reports.[6,7,11]

In the total synthesis of teixobactin, a properly protected L-allo-enduracididine building block is required. Such an amino acid is conveniently prepared by a deprotection−reprotection sequence from **15**. As illustrated in Scheme 5, when fully protected L-allo-enduracididine was treated with a mixture of TFA and water, followed by reprotection of the α amino group with Boc_2O, amino acid **16**, a suitable building block for solid phase peptide synthesis, was produced in 76% yield.

Scheme 5. Synthesis of L-allo-Enduracididine Building Block



In summary, we have developed a highly practical route to prepare L-allo-enduracididine from commercially available Boc-*trans*-Hyp-OH. Our current approach is highlighted by its excellent stereoselectivity (dr = >50:1) and scalability (31% overall yield). The application of the properly protected **16** in the total synthesis of teixobactin 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.5b02362.

Experimental details and spectral data for **1**, **5**, **7**, **9**, **11**, **13**, **15**, and **16** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yu.yuan@ucf.edu.

Notes

The authors declare no competing financial interest.

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