# Total Synthesis of Darobactin A

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**ABSTRACT:** The total synthesis of darobactin A, a recently isolated antibiotic that selectively targets Gram-negative bacteria, has been accomplished in a convergent fashion with a longest linear sequence of 16 steps from D-Garner's aldehyde and L-serine. Scalable routes towards three non-canonical amino acids were developed to enable the synthesis. The closure of the bismacrocycle was realized through sequential, halogen-selective Larock indole syntheses, where the proper order of cyclizations proved crucial for the formation of the desired atropisomer of the natural product.

Antibiotic resistance is regarded as one of the biggest threats to global human health.[1] Many infections are becoming harder to treat, and this reality is being compounded by a stagnation in the discovery of new classes of antibiotics in recent years.[2,3] Infectious Gram-negative bacteria are especially challenging to treat because of their impenetrable outer membrane, and accordingly the World Health Organization has classified developing new treatments for drug-resistant Gram-negative organisms as a critical priority.[4] Therefore, it is of paramount importance to actively research the discovery and synthesis of new antibiotics, with the goal of overcoming common resistance pathways by developing a toolbox of diverse antibiotic agents that engage with multiple targets.

In 2019, the Lewis group disclosed darobactin A (**1**, Figure 1, top), a ribosomally synthesized and post-translationally modified bismacrocyclic heptapeptide natural product which was isolated from the *Photorhabdus* microbiome.[5] This molecule displays high potency against various strains of Gram-negative bacteria, while exhibiting no activity towards Gram-positive bacteria. This marked selectivity is achieved through a novel mechanism of action that serves to circumvent the impenetrable outer membrane. Namely, darobactin A binds to the bacterial insertase complex BamA, which is located on the outer membrane of the pathogen, thus resulting in interrupted folding and insertion of outer membrane proteins. Both macrocycles are required to hold the heptapeptide backbone in a conformation that mimics a β–sheet and decreases the entropic cost of binding to BamA.[6] This unprecedented mode of action can serve both to offer a

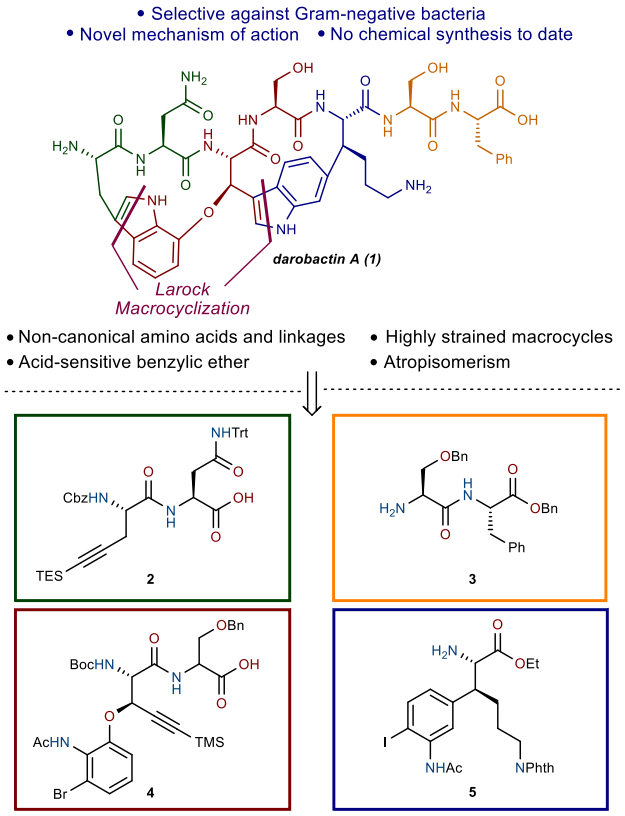



**Figure 1.** The structure of darobactin A (**1**) and the key synthetic building blocks (**2**–**5**).

new avenue for combating drug resistance, and to inspire the development of novel classes of robust antibiotics.

In order to verify the biology and better understand the mechanism of action between darobactin A and BamA, meaningful quantities of the natural product are required. While gene expression is a viable route for accessing milligram quantities of the natural product, a chemical total synthesis of darobactin A could provide an adequate supply as well as prove useful in accessing other derivatives, and more broadly, macrocyclic peptides with complex architectures for use beyond antibiotics.[7] This is particularly important since several other darobactin-like molecules have been recently identified through genome mining and silent gene expression, but have been challenging to isolate and thus unambiguously determine their structures and biological activities.[8,9] In addition to the unique bioactivity, the unusual bicyclic peptide structure represents a major synthetic challenge not only through atom connectivity, but also the existence of atropisomerism arising from hindered rotation of the two indoles. Specifically, darobactin A contains two highly strained macrocycles with unconventional connectivity;[10,11] an alkyl–aryl ether between the benzylic and C7 position of the two tryptophan residues which forms the 15-membered western macrocycle,[12] and a C–C bond between the β–carbon of lysine and C6 of tryptophan that forms the 14-membered eastern macrocycle.[13] Herein, we report a total synthesis of darobactin A (**1**), featuring important lessons in non-canonical amino acid synthesis and atroposelective cyclizations that we expect to be useful in future polycyclic peptide synthesis.

Our successful synthetic strategy towards darobactin A relied on two Larock macrocyclizations, since this type of transformation has been successfully applied in the closure of several strained macrocyclic oligopeptides (Figure 1, top).[14–17] Initial studies revealed that the order of macrocyclizations had a significant influence on the atropisomeric outcome, with the eastern macrocycle having to be installed first to secure the required orientation of the central indole moiety (see SI for more details). To prepare the substrates for these two key cyclization reactions we needed to synthesize appropriately protected dipeptides **2-4** and non-canonical amino acid **5** (Figure 1, bottom).

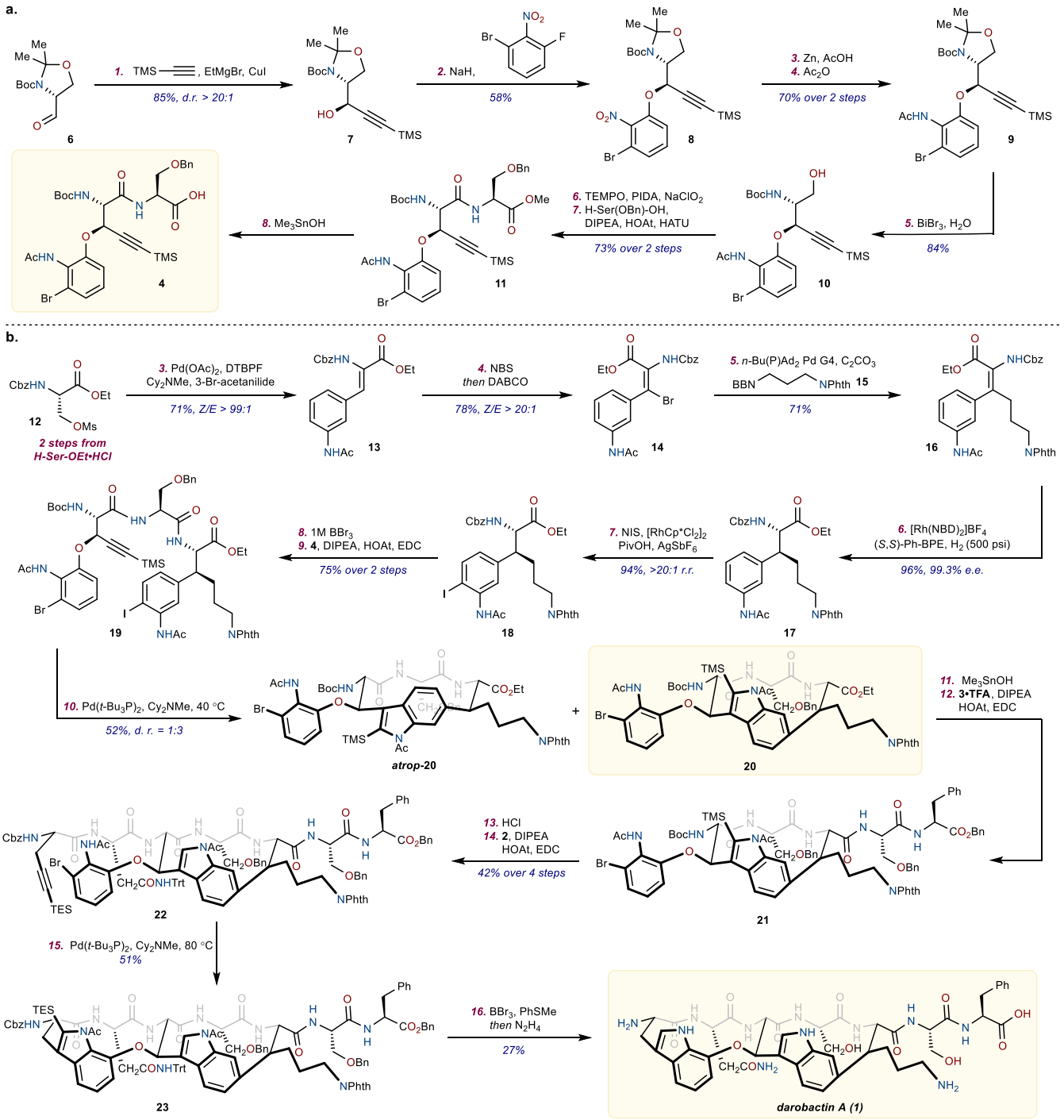
Synthesis of dipeptide **4** began with commercially available D–Garner's aldehyde (Scheme 1a, **6**).[18] Chelation-controlled addition of TMS-acetylene delivered alcohol **7** as a single diastereomer.[19] Nucleophilic aromatic substitution (**7→8**) installed an appropriately functionalized nitroarene on the propargylic alcohol, and the nitro group was subsequently reduced to the aniline and protected with neat acetic anhydride to provide acetanilide **9**. The use of base had to be avoided to prevent double acetylation of the aniline, and direct removal of acetic anhydride at room temperature was important to prevent acetonide deprotection and further decomposition of the product. Next, the *N*,*O*-acetal was removed with bismuth tribromide[20] to yield primary alcohol **10** which was directly oxidized to the carboxylic acid.[21,22] Overall, this specific reaction sequence ($S_NAr$/deprotection/oxidation) was necessary since β–elimination was observed as the major reaction pathway during the $S_NAr$ step when already operating at the ester oxidation state. Coupling of the acid with serine afforded **11**. Finally, mild hydrolysis of the ester[23] provided dipeptide **4** that was appropriately functionalized for downstream application.

The next goal of our synthetic campaign required the asymmetric synthesis of **5**, a β–disubstituted α–amino acid containing a rare aryl–lysine connectivity. Although past approaches to these motifs suffered from poor step economy[24,25] and stereoselectivity,[26–28] a concise and scalable route to the desired intermediate **5** was accomplished through enantioselective hydrogenation of tetrasubstituted enamide **16** (Scheme 1b).[29–32] Starting from Cbz-Ser(Ms)-OEt (**12**), *in situ* elimination followed by a Heck reaction with 3-bromoacetanilide installed the aryl group at the β–position with exclusive *Z* selectivity (**12→13**).[33] Bromination of enamide **13** (NBS and DABCO)[34] gave vinyl bromide **14** as a single alkene stereoisomer that was primed for a $C(sp^2)$-$C(sp^3)$ Suzuki-Miyaura cross-coupling. Thus, exposure of **14** to alkyl 9-BBN **15** delivered tetrasubstituted enamide **16** with the necessary substitution pattern for the ensuing asymmetric reduction. The challenging enantioselective hydrogenation was investigated using high-throughput experimentation to identify a suitable ligand–metal complex combination and optimal reaction conditions. Treatment with $[Rh(NBD)_2]BF_4$ and (*S*,*S*)-Ph-BPE at 500 psi provided intermediate **17** in 96% yield and 99.3% enantiomeric excess.[35] The use of high-throughput, high-pressure hydrogenation experimentation was paramount for rapid identification of these conditions (see SI for details).

To form the desired atropisomer of darobactin A, the eastern macrocycle had to be closed first; however, as both indoles were to be formed using Larock indole synthesis, it was necessary to establish chemoselectivity between two different *ortho*-halogenated acetanilides to properly sequence their reaction. Accordingly, we installed an iodide on the eastern arene. Our hypothesis was that oxidative addition into an aryl iodide would occur much faster and at a lower temperature than insertion into an aryl bromide, as established in traditional Pd-catalyzed coupling chemistry.[36–39] This strategy would allow for selective formation of the eastern macrocycle while maintaining a handle for the western macrocyclization without the need for a late-stage functionalization of an elaborate oligopeptide.

In practice, acetanilide-directed C–H iodination was realized on **17** with conditions adapted from the Glorius group.[40] Using $[RhCp^*Cl_2]_2$, $AgSbF_6$, pivalic acid and *N*-iodosuccinimide, the *ortho*-iodo acetanilide **18** could be isolated as a single regioisomer. Removal of the Cbz group was accomplished using boron tribromide,[41] delivering free amine **5**, which was elaborated to Larock macrocyclization precursor **19** through peptide coupling with **4.** The key Larock macrocyclization proceeded at 40 °C to deliver the desired eastern macrocycle **20** and its unnatural atropisomer ***atrop*–20** (52% yield, *d.r.* = 3:1). The lower reaction temperature permitted by the aryl iodide left the aryl bromide intact without any detectable debromination. Characteristic ROESY cross-peaks present in the natural atropisomer confirmed the topology of the macrocycle (see SI for details).

**Scheme 1. (a) Synthesis of dipeptide 12; and (b) total synthesis of darobactin A (1)[a]**




[a]See the Supporting Information for detailed procedures and characterization data.

With the first macrocycle established, installation of the Ser-Phe sidechain **3** was accomplished through hydrolysis of the ethyl ester followed by peptide coupling with **3•TFA** (see SI for the synthesis of **3•TFA**) to provide **21**. The TMS and Boc groups were then removed simultaneously by HCl, and alkynyl dipeptide **2** (see SI for the synthesis of **2**) was coupled onto the eastern macrocycle to yield heptapeptide **22**. A second Larock macrocyclization delivered protected darobactin **23** in 51% yield. At this stage, ROESY analysis again confirmed the desired orientation of both macrocycles (see SI for details). Deprotection of the nine remaining protecting groups was achieved in a single pot by first employing $BBr_3$ to remove Trt, TES, Cbz and three benzyl groups, followed by addition of hydrazine which deacetylated the two indoles and deprotected the phthalimide to deliver darobactin A (**1**). The sequence of protecting group removal and peptide couplings after the first Larock cyclization had to be carefully choreographed to preserve the stability of late-

stage intermediates. For example, attempted ethyl ester hydrolysis on a substrate that lacks the TMS group at C2 of the eastern indole resulted in simultaneous deacetylation. This led to highly acid sensitive intermediates, due to the presence of a benzylic ether next to an electron-rich indole, which rendered deprotection steps that proceed under acidic conditions unfeasible. The finding that no decomposition was detected during the $BBr_3$ mediated deprotection in Scheme 1 further reinforces the importance of having electron-withdrawing protecting groups on the indoles to modulate their reactivity during acid-mediated deprotection steps.

In conclusion, we have achieved the total synthesis of darobactin A (**1**) in 16 steps (LLS) from commercially available starting materials. This synthesis demonstrates the utility of the halogen-selective Larock indole synthesis as a method for controlled formation of bismacrocycles, and the ability to control atroposelectivity of macrocyclization events through a properly timed cyclization sequence. The described synthetic route should enable access to the synthesis of other darobactin-like natural products, as well as provide insight into the syntheses of complex macrocyclic peptide scaffolds, which have been so far challenging to isolate.

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### Notes

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