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Efficient synthesis of the siderophore petrobactin via antimony triethoxide mediated coupling

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ABSTRACT

Chemical synthesis of petrobactin, a siderophore for *Bacillus anthracis*, has been achieved via $Sb(OEt)_3$-mediated ester–amide exchange.

Introduction

Infections caused by *Bacillus* bacteria are often life threatening and consequently remain a worldwide health concern. *Bacillus anthracis* and *Bacillus cereus* are two such *Bacillus* species that remain in the public eye, because they can emerge in the human population via transmission from animals, contaminated food, or bioterrorism.[1,2]

Bacillus species, like most other pathogenic bacteria, have developed a mechanism to obtain the iron required for their proliferation by releasing an iron chelating agent called a siderophore into their environment. After iron chelation, the resulting iron–siderophore complex is retrieved by association with a siderophore-specific receptor expressed on the microbial cell surface, which then internalizes and delivers the ferric chelate complex into the cell cytoplasm. Because ferric iron is essential for bacterial survival,[3] the human immune system attempts to suppress bacterial growth by sequestering all extracellular iron immediately upon detection of bacterial components.[4,5] Survival of the pathogen in its host thus depends on the pathogen's ability to outcompete the host for extracellular iron. Not surprisingly, the affinities of most siderophores for iron are in the subpicomolar range, and the affinities of the iron–siderophore complexes for their cognate bacterial receptors are similarly high.[6–9]

Because of the high affinities and specificities of siderophores for their cognate pathogens,[10] siderophore–antibiotic conjugates have been recently exploited as a tool for the selective killing of the source pathogen.[11–13] *Bacillus* species, including *B. anthracis* and *B. cereus*, recognize the 3,4-catecholate siderophore called petrobactin (Fig. 1).[14] Petrobactin–iron chelate complexes in turn bind cell surface receptor-like proteins, FpuA, FatB, and YclQ, and are transported into the bacteria.[15,16] In order to examine whether petrobactin might be similarly exploited for the selective therapy of *Bacillus* infections, we sought to synthesize the siderophore in quantifiable amounts. While some chemical and enzymatic syntheses have been established in the literature,[7,17–20] they have proven to be inadequate in providing sufficient yield for subsequent use in large scale combinatorial screening for therapeutic use. Recently, high-yielding $Sb(OEt)_3$-mediated ester–amide transformation has been outlined in the literature,[21–23] prompting us to apply the same coupling conditions for the synthesis of petrobactin. Herein, we report $Sb(OEt)_3$-mediated coupling enables the high yield production of preclinical quantities of petrobactin (Scheme 1–3).

Results and discussion

Total synthesis of petrobactin, **1**, begins with the synthesis of intermediate **6**, which was prepared in 3 steps, starting from a commercially available *N*-dibenzyl-aminoalcohol, **2** (Scheme 1).

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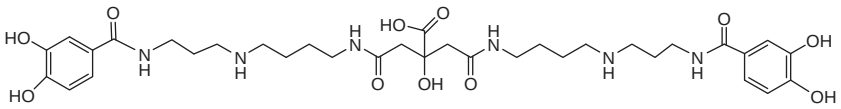
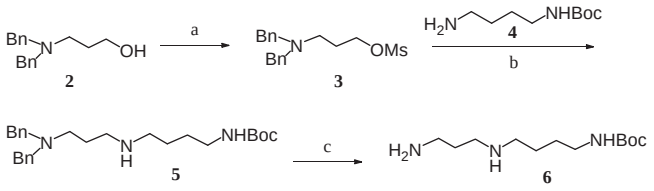


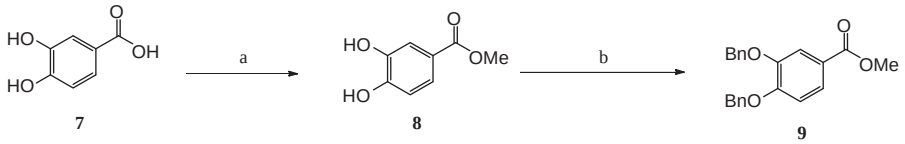
Figure 1. Structure of petrobactin, **1**.



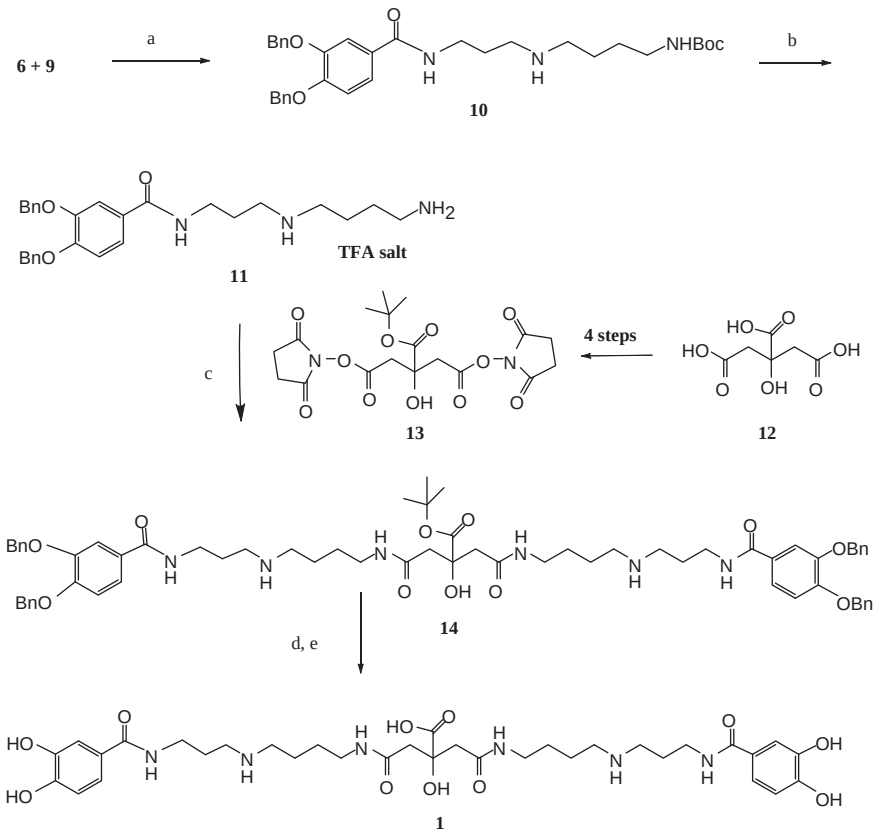
Scheme 1. Reagents and conditions: (a) MsCl, TEA, DCM, 0 °C to rt, 3 h, 85%; (b) **4** (1.5 equiv), DIPEA (15 equiv), DMSO, 70 °C, 24 h, 75%; (c) Pd/C, H_2, EtOH, reflux 4 h, 95%.

The hydroxyl group was mesyl (Ms) protected to provide compound **3** with an 85% yield. Nucleophilic displacement of O-Ms with amine, **4**, provided **5** with a 75% yield of the isolated product. Formation of a diamine byproduct was observed in 5–10% abundance during this nucleophilic substitution reaction. Debenzylation was quantitatively achieved under H_2-Pd/C conditions in ethanol to yield **6**. Separately, compound **9** was prepared from commercially available 3,4-dihydroxybenzoic acid in 2 steps with an 85% yield (Scheme 2). Esterification of **7** was achieved using H_2SO_4 and methanol under reflux conditions, followed by benzyl protection of the catechol unit without any purification.

Ester–amide exchange was carried out with amine **6** and acid **9** under neat conditions using $Sb(OEt)_3$ to produce **10** with a 75% yield. The *N*-Boc group was removed from **10** by treatment with trifluoroacetic acid (TFA) to give amine **11** as a TFA salt. A separate component for the coupling reaction, **13**, was prepared as an activated NHS ester by a reported literature procedure.[24]



Scheme 2. Reagents and conditions: (a) MeOH, H_2SO_4 (cat), reflux 8 h, quantitative; (b) K_2CO_3 (6 equiv), BnBr (4 equiv), DMF, 120 °C, 36 h, 85%.



Scheme 3. Reagents and conditions: (a) $Sb(OEt)_3$ (1 equiv), neat, 80 °C, 24 h, 75%; (b) TFA, DCM, 0 °C, 0.5 h, 93%; (c) **13** (1 equiv), TEA, dioxane, DCM, 1.5 h, 82%; (d) TFA, DCM/H_2O (100:1), 0 °C to rt, 2 h; (e) H_2, $PdCl_2$, AcOH/H_2O (20:1), 2 h, 65%.

Coupling of **11** and **13** was achieved using triethylamine (TEA) to give protected petrobactin, **14**, with an 82% conversion. The *t*-butyl protecting group was removed from the citric acid moiety of compound **14** under TFA conditions. After completion, the reaction mixture was concentrated using high vacuum without heating to avoid intramolecular imine formation between amide bonds and tertiary acid groups of citric acid moieties.[17,24] **14** was debenzylated using H_2-$PdCl_2$ conditions to provide petrobactin, **1**, with a 65% yield (Scheme 3). The physical and spectroscopic data of petrobactin were in full agreement with the literature data.[17]

Conclusion

We have shown the application of antimony triethoxide-mediated ester–amide exchange for the chemical synthesis of petrobactin from commercially available starting materials in 8 steps with good overall yield (22.5%).

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