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Antibacterial activity of (−)-deoxypseudophrynaminol versus its racemate and derivatives

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Abstract—(−)-Deoxypseudophrynaminol **1** possesses 43-fold greater antibacterial potency than the racemate toward *Staphylococcus aureus*, indicating that the (−)-enantiomer is the biologically active isomer in this assay. Comparison of the percent growth inhibition by derivatives of **1** indicates that prenylation of N^8 and replacement of N^1-methyl by methyl carbamate are detrimental to antibacterial potency. (−)-**1** is a promising lead structure for the development of the novel hexahydropyrrolo[2,3-*b*]indole class of antibacterial agents.
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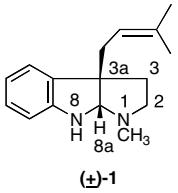
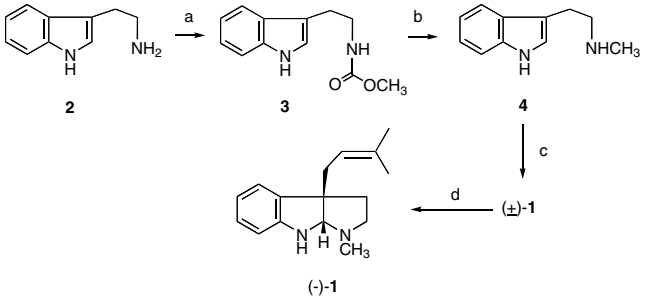
(±)-Deoxypseudophrynaminol **1** (Fig. 1) is a known antibacterial agent with MIC of 20–40 μg/mL versus vancomycin-resistant *Enterococci* and methicillin-resistant *Staphylococcus aureus*.[1] However, the antibacterial activity of the individual enantiomers of **1** is unreported. Other hexahydropyrrolo[2,3-*b*]indoles, natural products isolated from the marine bryozoan *Flustra foliacea*, also display antibacterial activity.[2] To improve our understanding of the structural requirements for antibacterial activity among the hexahydropyrrolo[2,3-*b*]indoles, we decided to obtain (−)-**1** via resolution of (±)-**1**, to prepare two derivatives of (±)-**1**, and to perform a colony count based assessment of antibacterial potency versus *S. aureus*.



(±)-1

Figure 1. (±)-Deoxypseudophrynaminol.



2 **3** **4**

Scheme 1. Reagents and conditions: (a) $ClCO_2Me$, DIEA, THF (81%); (b) $LiAlH_4$ (10 equiv), THF, reflux (79%); (c) MeMgBr, then prenyl bromide, Et_2O (25%); (d) dibenzoyl-D-tartaric acid then flash chromatography.

(±)-**1** was prepared by a three-step synthesis from tryptamine **2** (Scheme 1). Acylation of **2** with methyl chloroformate furnished carbamate **3** in 81% yield. Reduction of **3** with 10 eq lithium aluminum hydride under reflux followed a literature procedure [3] with the important modification of simple extraction with ethyl acetate to increase the yield of **4** from 50% to 79%. Alkylative cyclization of the indolyl Grignard of **4** with prenyl bromide provided (±)-**1** in 25% yield.[4] When we attempted to resolve (±)-**1** by combining it with equimolar dibenzoyl-D-tartaric acid to form solid diastereomeric salts of differing solubility, as per a known method for resolving hexahydropyrrolo[2,3-*b*]indoles,[5] only an intractable oil resulted in all tested solvents (hexanes,

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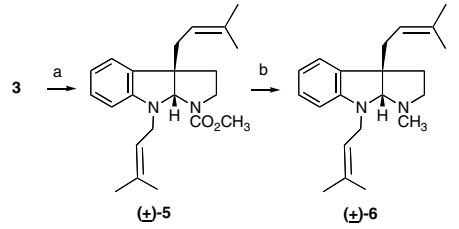
THF, CH_2Cl_2, $CHCl_3$, acetone, CH_3CN, and Et_2O). To our surprise, the diastereomeric salts separated cleanly by flash chromatography (2:1 EtOAc/CH_2Cl_2 to remove the dibenzoyl-D-tartrate salt of (+)-**1**, followed by methanol to isolate the dibenzoyl-D-tartrate salt of (−)-**1**). Unfortunately, the less polar dibenzoyl-D-tartrate salt of (+)-**1** was missed during UV monitoring of collected fractions due to extensive dilution by band broadening. The dibenzoyl-D-tartrate salt in the more polar methanolic fractions was concentrated in vacuo, basified with 10% NaOH (aq), and extracted with ethyl acetate to obtain (−)-**1** $[\alpha]_D^{20}$ −32.3 (*c* 0.0296, $CHCl_3$) spectroscopically identical to its racemate.[4] ^{1}H NMR spectra of the (*R*)-MTPA amide[6] of (−)-**1** versus that of (±)-**1** showed that (−)-**1** was homochiral (>95% ee). The absolute configuration assigned to (−)-**1** is consistent with that of all known (−)-hexahydropyrrolo[2,3-*b*]indoles.[2,5,7–9]

From **3**, two derivatives of (±)-**1** were also prepared (Scheme 2). Alkylative cyclization of **3** to furnish (±)-**5** was based on a quinine (35% yield) or quinidine (53% yield) modification of Ganesan's original approach with DIEA,[10] which did not work in our hands. Reduction of (±)-**5** with 10 equiv of lithium aluminum hydride produced racemic debromoflustramine B,[10] (±)-**6**, in 68–74% yield. As expected at room temperature, even though quinine and quinidine are homochiral amines, there was little enantiopreference (ca. 4% ee by optical rotation[8]), so **6** was nearly racemic.



Scheme 2. Reagents and conditions: (a) prenyl bromide, Bu_4NI, $Zn(OTf)_2$, quinine (35%) or quinidine (53%), toluene; (b) $LiAlH_4$ (10 equiv), THF, reflux (68–74%).

Figure 2 illustrates the effectiveness of each compound, averaging the data (see Table 1 in Supplementary Material). (±)-**6** has modest activity, reducing bacteria growth over 30 percent at 40 μg/mL. Carbamate (±)-**5** had no antibacterial effect. (±)-**1** had good antibacterial potency, reducing growth by almost 85 percent at 40 μg/mL but failed to have any significant effect at 10 μg/mL. (−)-**1** produced the most promising results, with over 99% reduction of bacteria at 40 μg/mL and 50% reduction at 10 μg/mL. Note that the micromolar concentration range for these different molecular weight compounds is narrow (0.113–0.165 μM at 40 mg/mL) and unlikely to contribute to the dramatic effects observed.

In this study, (±)-**1** produced moderate inhibition of the growth of *S. aureus*, while (−)-**1** gave an impressive 43-fold greater inhibition (see Table 2 in Supplementary Material). (−)-**1** is the eutomer. For antibacterial potency, hydrophobic substitutions at N^1 appear to be preferred over hydrophilic ones, both in this study and in previous work.[1,2] In contrast, much greater antibacterial potency was obtained when N^8 was unsubstituted (a hydrogen bond donor/acceptor). Future studies should also explore the relevance of substitutions on the benzene ring, the effect of different substituents at 3a, human cell toxicity, and the scope of antibacterial activity.

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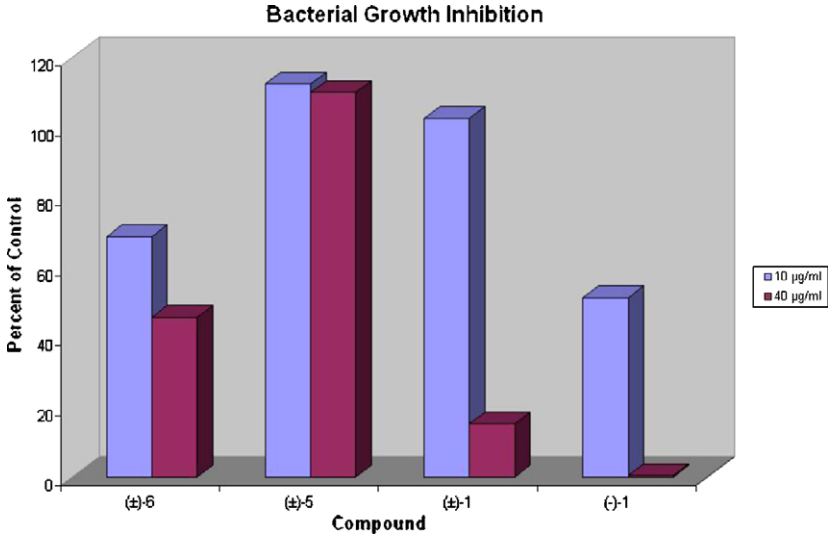

Figure 2. Percent inhibition of the growth of *Staphylococcus aureus* colonies at 10 and 40 μg/mL concentrations of inhibitors relative to DMSO control (100% growth).

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Supplementary Data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2006.01.093.

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