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A Short Synthesis of Oxazolidinone Derivatives Linezolid and Eperezolid : A New Class of Antibacterials

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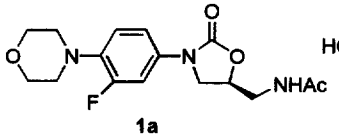
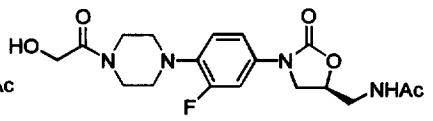
Abstract: Oxazolidinone derivatives such as Linezolid and Eperazolid, which are a new class of antibacterials, have been synthesized from 1,2,5,6-dianhydro-3,4-isopropylidine-D-mannitol in good yield.

Keywords : 1,2,5,6-diahydrosugar, Linezolid, Eperezolid, antibacterials.

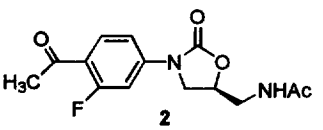
The increasing incidence of bacterial resistance to a large number of antibacterial agents such as β-lactam antibiotics, macrolides, quinolones and vancomycin is becoming a major issue [1]. For the past several years, vancomycin has been considered the last line of defence against Gram-positive infections and there is no suitable therapy available for treating diseases that have become resistant to vancomycin [2].



1a
Linezolid-(U-100766)



1d
Eperezolid-(U-100592)



2
DUP-721

Scientists from Pharmacia & Upjohn [3] have discovered a number of antibacterial oxazolidinones, based on the lead compound of Dupont, DUP-721 (2) [4]. Recently, we have reported a very simple and efficient synthesis of bis-epoxide **3** [5] from readily available *D*-mannitol. We wanted to utilize this bis-epoxide for an efficient synthesis of Linezolid **1a** and other chiral oxazolidinone derivatives **1b** - **1d**. The synthetic strategy is shown in Scheme-1.The C_2-symmetric bis-epoxide **3** reacted readily with 3-fluoro-4-substituted aniline in isopropyl alcohol at 80-85 °C and the resultant crude adduct was allowed to react with carbonyldiimidazole in dichloromethane at room temperature to furnish the bis-oxazolidinone **4** in 61 - 70 % yields.

Removal of the acetonide group was achieved in quantitative yields with 2N HCl at room temperature to furnish diol **5**. Oxidative cleavage of diol **5** was carried out with lead tetraacetate in tetrahydrofuran at 0 °C

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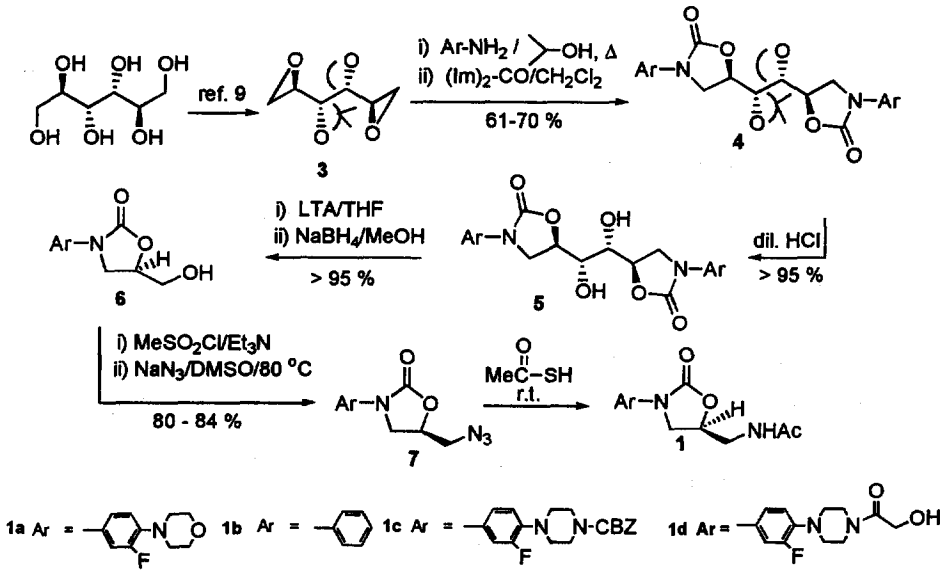

Scheme-1

[6] and the resultant aldehyde was reduced immediately to alcohol **6** in quantitative yield with sodium borohydride in methanol at 0 °C. Following the known procedure [3], the alcohol **6** was converted into the corresponding azide **7** in two steps, in 80 - 84% yields. The azide **7a** was converted to Linezolid **1a** in 86% yield with thioacetic acid [7].

In conclusion, we have achieved a general and very reliable synthesis of chiral oxazolidinones starting from a cheap and readily available *D*-mannitol.

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