A SHORT SYNTHETIC APPROACH TO ENANTIOMERICALLY PURE (-)-ANISOMYCIN

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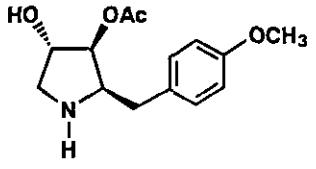
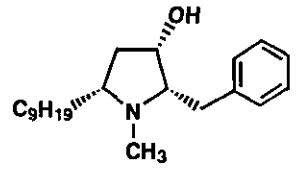
Abstract - A convenient enantiomerically pure route to an antibiotic, natural (-)-anisomycin has been developed in a short number of steps by featuring the stereocontrolled elaboration of the functionalized homochiral lactam derived from 2,3,5-tri-*O*-benzyl-β-L-arabinofuranose involving no separation of stereoisomers through the entire sequence.

Anisomycin (**1**), an antibiotic first isolated from fermentation broth filtrates of various species of *Streptomyces*[1] exhibits strong and selective activities against some pathogenic protozoa and fungi.[2] The structurally related antibiotic, (+)-preussin (**2**) possessing a pyrrolidine skeleton is also known to indicate the same type of activities.[3] Thus, the compound (**1**) has been used successfully in the clinic in the treatment of amebic dysentery and trichomonas vaginitis.[4] The structure of **1** was determined by X-ray crystallographic analysis[5] and the absolute configuration was established by chemical correlation studies.[6] Due to its interesting activities together with unique structural features it has attracted considerable attention and has been the subject of extensive synthetic efforts which have culminated in numerous syntheses of



1: (-)-Anisomycin

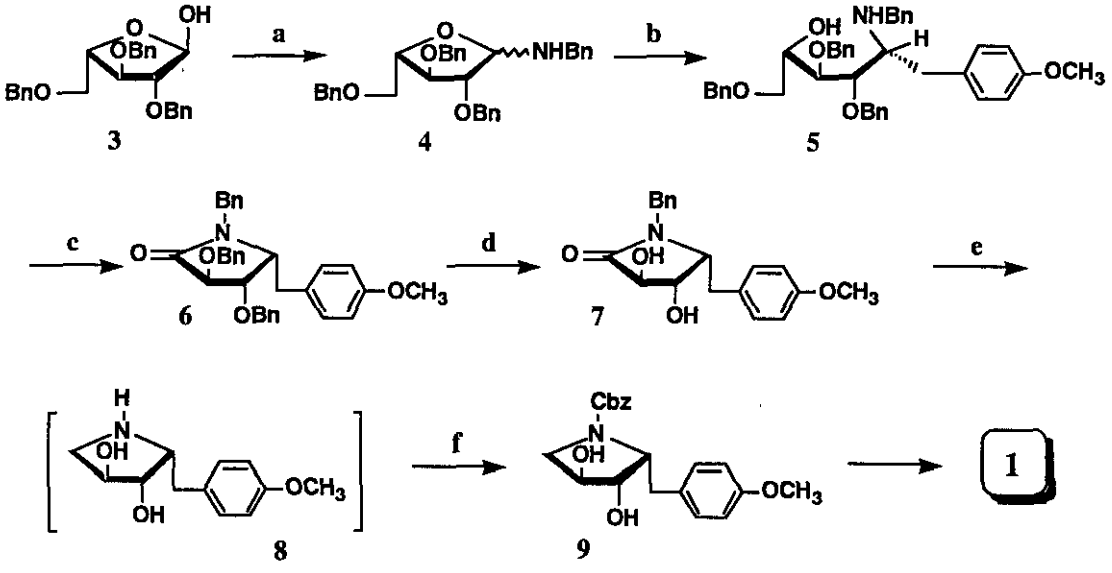


2: (+)-Preussin

racemic[7] and chiral forms.[8] However, these methods hitherto reported required generally multistage reactions including stereoisomer separation and were not necessarily satisfactory.

On the other hand, we recently detailed the unprecedented *trans*-selective (with respect to the C-4 substituent) lactam construction based on deoxygenation of the quaternary α-hydroxy lactams[9] and its application to the first total synthesis of natural antibiotic, lentiginosine.[10] The purpose of the present communication is to disclose a simple and short synthetic process to **1** without separation of its stereoisomers employing reversely the *cis*-selective lactam formation protocol.[11]

As shown in Scheme 1, furanosylamine (**4**) obtained from amination of commercially available 2,3,5-tri-*O*-benzyl-β-L-arabinofuranose (**3**) was smoothly reacted at low temperature with *p*-methoxybenzylmagnesium chloride prepared *in situ* to provide the adduct (**5**) exclusively in high yield. The reaction would proceed based on Cram's chelation structure model.[12] No other stereoisomer was detected in the ^{13}C nmr analysis of the reaction mixture under these conditions. Treatment of **5** with PCC in the presence of molecular sieves 4A degraded oxidatively to afford desired *cis*-functionalized lactam (**6**), $[\alpha]_D^{24}$ +116.4° (c 1.23, MeOH) with respect to the C-4 substituent. Removal of the *O*-benzyl protecting groups from **6** was effected with 4% HCOOH-MeOH on Pd(black) to furnish the diol **7**, $[\alpha]_D^{18}$+134.4° (c 2.08, MeOH) in a quantitative yield. The complete absence of its diastereomer was ascertained again at this stage precisely in



Scheme 1. Reagents and conditions: (a) $BnNH_2$, CH_2Cl_2, MS 4A; quant.; (b) *p*-$MeOPhCH_2MgCl$, -78-0 °C, THF; 78%; (c) PCC, MS 4A, CH_2Cl_2; 63%; (d) Pd(black), HCOOH, MeOH; 99%; (e) 1 $LiAlH_4$, THF; 91%; 2 Pd(black), HCOOH, MeOH; (f) CbzCl, $NaHCO_3$, MeOH; 77% (2 steps).

the chiral hplc analysis[13] employing the crude material (**7**) without chromatographic separation through the entire sequence from **3** by comparison with the retention time of *trans*-lactam.[14]

Thus, **7** was successively submitted to reduction with $LiAlH_4$ in THF at room temperature and hydrogenation again on Pd(black) to yield the corresponding amino alcohol intermediate (**8**). Subsequent treatment of **8** with CbzCl in MeOH protected the amino function selectively leading to the known compound (**9**), $[\alpha]_D^{24}$-7.2° (c 1.22, MeOH), mp 129-130 °C [lit.,$[\alpha]_D^{20}$-8.0° (c 0.661), mp 129-130 °C;[8b] $[\alpha]_D^{20}$-8.2° (c 5.97, MeOH), mp 127-129 °C[8e]], in 77% yield based on **7** after separation by silica gel column chromatography. The spectral data of the synthetic **9** were identical with those of reported compound.[8b,e]

Since conversion of **9** into natural anisomycin (**1**) has been accomplished by two groups efficiently,[8b,e] the present work formally constitutes a new and completely stereospecific synthesis of this antibiotic.

In summary, a short and efficient method for the synthesis of anisomycin involving no separation of stereoisomers has been developed. We anticipate that this procedure will find application in the synthesis other polyhydroxylated biologically active alkaloids. Work along this line is in progress.

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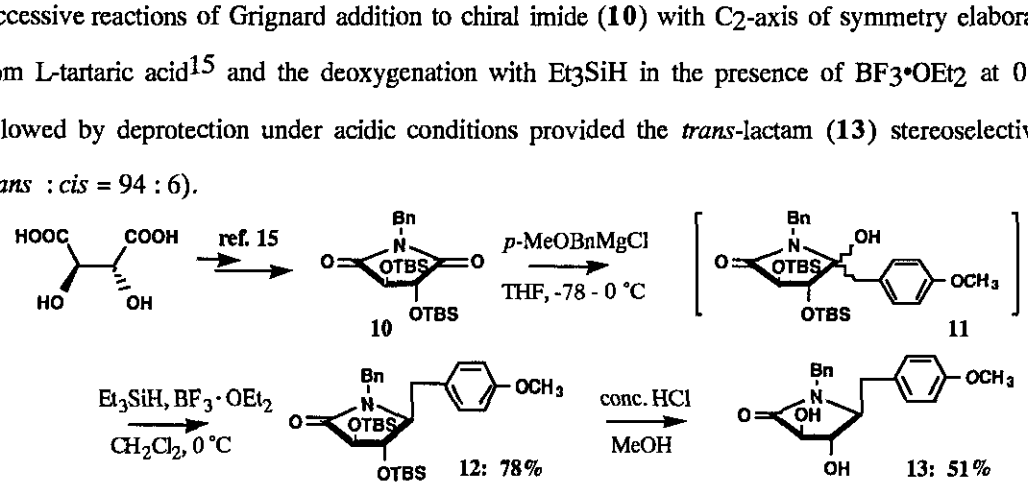
13. Hplc conditions were as follows. Column: Daicel Chiralpak AS, 4.6x250 mm. Eluent: hexane-2-propanol (80 : 20), 1.0 ml/min. Detection: UV at 284 nm. *cis*-lactam (**7**) 9.2 min., *trans*-lactam (**13**) 11.7 min.
14. *trans*-Lactam (**13**) was obtained according to the reaction conditions as shown below.[9] Thus, successive reactions of Grignard addition to chiral imide (**10**) with C_2-axis of symmetry elaborated from L-tartaric acid[15] and the deoxygenation with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$ at 0 °C followed by deprotection under acidic conditions provided the *trans*-lactam (**13**) stereoselectively (*trans* : *cis* = 94 : 6).



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