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A new approach to (+)-anisomycin☆

J. Santhosh Reddy, A. Ravi Kumar and B. Venkateswara Rao*

Organic Division III, Indian Institute of Chemical Technology, Hyderabad 500007, India

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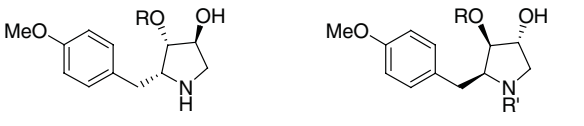
Abstract—An efficient approach to enantiomerically pure (+)-deacetylanisomycin **2a** and a formal synthesis of (+)-anisomycin **2** (11% overall yield in 10 steps) have been achieved through simple and good yielding reactions, starting from 1,2:3,4:5,6-tri-*O*-isopropylidene-D-mannitol **3**. Grignard reaction and intramolecular cyclisation reactions are key steps in the strategy.

1. Introduction

Anisomycin **1** is an antibiotic that was isolated from the fermentation broth filtrates of *Streptomyces griseolous* and *Streptomyces roseochromogens* by Sobin and Tanner at Pfizer, Inc. in 1954.[1] Its structure and relative stereochemistry were confirmed by chemical studies[2] and X-ray crystallographic analysis.[3] The absolute stereochemistry of this alkaloid (Fig. 1) were firmly established as (2*R*,3*S*,4*S*) by chemical correlation with L-tyrosine.[4]

Anisomycin **1** possesses a strong and selective activity against pathogenic protozoa and fungi, and has been used successfully in the clinics for the treatment of *Trichomonas vaginitis* and for amoebic dysentery.[5] Both anisomycin **1** and its deacetyl derivative **1a** have been used as fungicides in the eradication of bean mildew and for the inhibition of other pathogenic fungi in plants.[6] Anisomycin **1** was found to inhibit peptide bond formation on *eukaryotic ribosomes*.[7]



1 R=Ac
1a R=H

2 R=Ac, R'=H
2a R=R'=H
2b R=H, R'=Cbz

Figure 1. The structure of (−)-anisomycin **1** and (+)-anisomycin **2**.

2. Results and discussion

The diverse biological activity of anisomycin is due to the presence of a chiral pyrrolidine skeleton.[8] The activity and structural features of **1** has attracted the attention of several synthetic organic chemists.[9,10] Few routes have given good stereoselectivity, while others have an inherent problem in separating unwanted isomers. In continuation of our interest in the synthesis of biologically active chiral pyrrolidines,[11] we undertook the synthesis of the unnatural isomer, (+)-anisomycin **2**. Herein, we report a strategy where all the three centers of the (+)-anisomycin **2** were fixed from the inexpensive and readily available chiral pool starting material, D-mannitol. So far, three syntheses are reported for (+)-anisomycin **2**.[10] Two of the approaches[10a,b] are nonstereoselective and low yielding while the other[10c] prepared (+)-anisomycin, but with 88–90% ee. Previously, (+)-anisomycin **2** was synthesized from (+)-*N*-benzyloxycarbonyl deacetylanisomycin **2b** in three steps.[10c] Therefore, our approach mainly deals with the synthesis of (+)-(2*S*,3*R*,4*R*) deacetylanisomycin **2a** and its Cbz derivative **2b** as outlined below.

1,2:3,4:5,6-Tri-*O*-isopropylidene-D-mannitol **3**, a fully protected form of D-mannitol was treated with H_5IO_6 to give aldehyde[12] **4** and immediate reduction of the resultant crude aldehyde **4** with $NaBH_4$ gave arabinitol derivative **5**. Treatment of **5** with benzyl bromide/NaH furnished benzyl ether derivative **6**. Selective hydrolysis of **6** with 50% aq AcOH gave diol **7**. Regioselective tosylation of **7** gave **8**, which on further treatment with K_2CO_3/MeOH yielded epoxide **9**. Reaction of **9** with *p*-methoxyphenylmagnesium bromide in the presence of a catalytic amount of I_2/CuI gave **10**. Compound

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* Corresponding author. Tel.: +91 40 27160123x2614; fax: +91 40 27160512; e-mail: venky@iict.res.in

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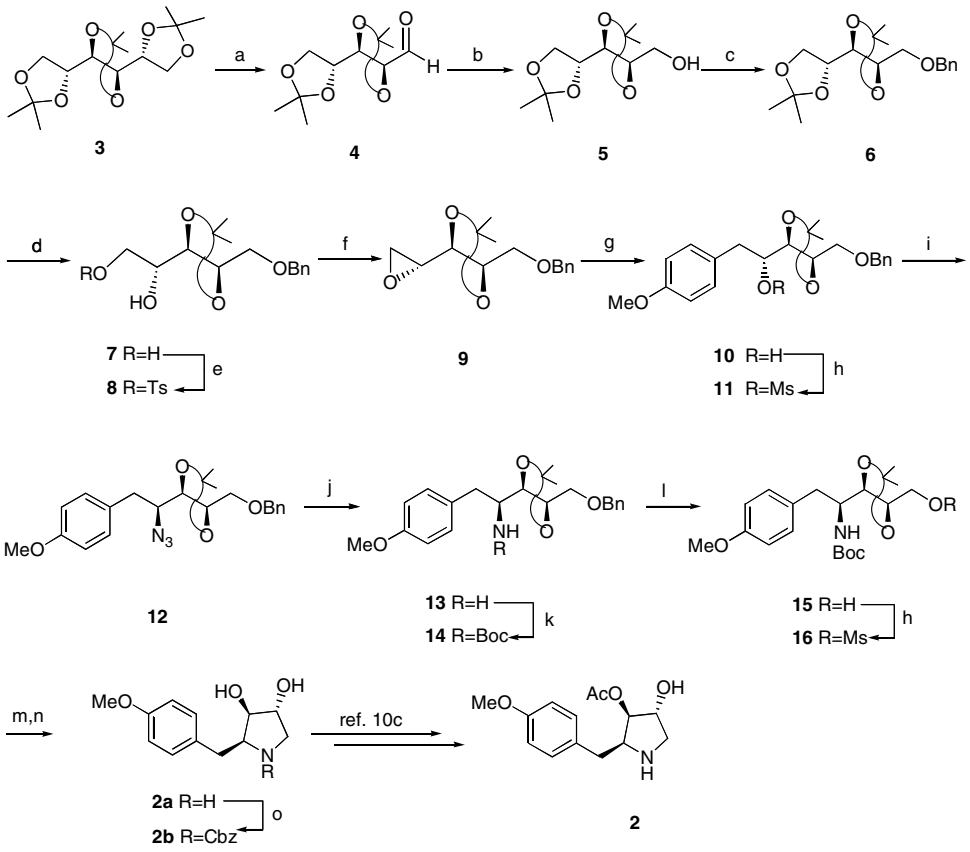

Reagents and conditions: (a) ref. 12; (b) $NaBH_4$, MeOH, rt, 3 h, 67% for two steps; (c) NaH, BnBr, DMF, 0 °C–rt, overnight, 84%; (d) 50% aq. AcOH, rt, overnight, 84%; (e) *p*-TsCl, Et_3N, DCM, 0 °C, 16 h; (f) K_2CO_3, MeOH, 30 min, 71% for two steps; (g) 4-Bromo anisole, Mg, I_2/CuI (cat.), 0 °C–rt, overnight, 86%; (h) MsCl, Et_3N, DCM, rt, 1 h; (i) NaN_3, [18-Crown-6], DMSO, 65 °C, 24 h, 83% for two steps; (j) $LiAlH_4$, THF, 0 °C– rt, overnight; (k) $(Boc)_2O$, Et_3N, THF, rt, 6 h, 81% for two steps; (l) Li/liq.NH_3, -78 °C, 30 min, 83%; (m) TFA, DCM, 0 °C–rt, 10 h; (n) Et_3N, MeOH, 0 °C– rt, 5 h; (o) Cbz-Cl, Na_2CO_3, THF, 2 h, 69% for four steps.

10 on treatment with MsCl/Et_3N gave **11**, which on further treatment with NaN_3/[18-crown-6] in DMSO[13] yielded azido derivative **12**. Reduction of the azido functionality with $LiAlH_4$/THF gave amine **13**, which on in situ treatment with $(Boc)_2O$/Et_3N afforded compound **14**. Removal of benzyl group in **14** was achieved using Li/liq. NH_3 to give **15**. Compound **15** was converted to corresponding mesyl derivative **16** with MsCl/Et_3N, which without purification treated with TFA followed by Et_3N to give (+)-deacetyl anisomycin **2a**. Further treatment of **2a** with Cbz–Cl gave (+)-*N*-benzyloxycarbonyl deacetylanisomycin **2b**,[9a,c,e,k] whose melting point, ^1H NMR and IR were in agreement with the reported values. The specific rotation of (+)-*N*-benzyloxycarbonyl deacetylanisomycin **2b** is $[\alpha]_D^{25} = +7.9$ (*c* 0.45, MeOH) {lit.[9e] for (−)-isomer is $[\alpha]_D^{25} = -8.2$ (*c* 5.97, MeOH)}.

3. Conclusion

Since **2b** had previously been transformed into (+)-anisomycin **2**,[10c] the present work offers an alternative route to the enantiomerically pure unnatural isomer **2**. A good yielding approach to the synthesis of (+)-deacetylanisomycin **2a**, has been achieved from D-mannitol, which also helps in making compound **2** in good quantities for the complete evaluation of its biological activity.

4. Experimental

TLC was performed on Merck Kiesel gel 60, F254 plates (layer thickness 0.25 mm). Column chromatography was performed on silica gel (60–120 mesh) using ethyl acetate and hexane mixture as eluent. Melting points were determined on a Fisher John's melting point apparatus and are uncorrected. IR spectra were recorded on a Thermo Nicolet nexus 670 FT-IR systems. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on Bruker Avance-300 MHz spectrometer. ^1H NMR (400 MHz) spectra were recorded on a Varian Unity-400 MHz spectrometer. Optical rotations were measured with Horiba-SEPA-300 digital polarimeter. FABMS were recorded on a VG AUTOSPEC M251 (Micromass) at 70 eV using a direct inlet system. EI-mass spectrum was recorded on a VG 7070 H (Micromass) spectrometer. HRMS were recorded on a Q STAR XL HYBRID (PE SEIEX) spectrometer. Chiral