A New Chiral Synthesis of (−)-Anisomycin and its Demethoxy Analogue

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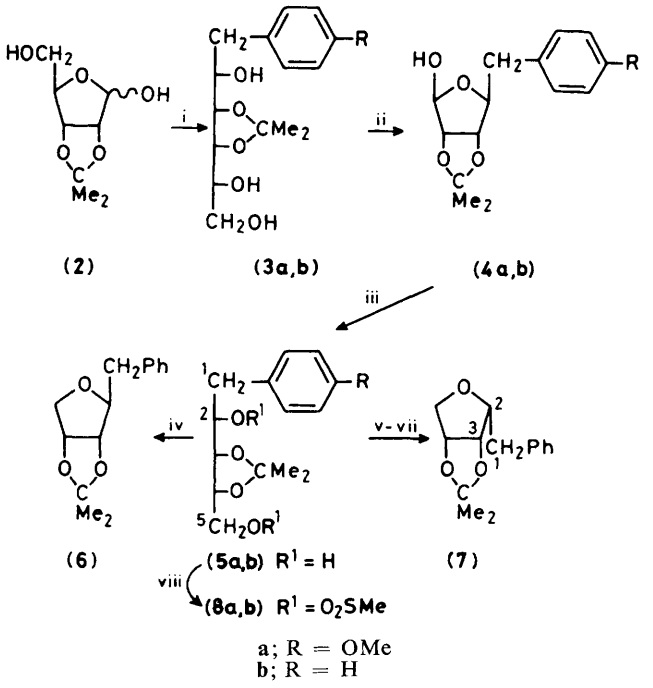
(−)-Anisomycin (**1a**) and its demethoxy-analogue (**1b**) have been prepared enantiospecifically and stereoselectively from D-ribose.

The antibiotic anisomycin (**1a**), with relative[1] and absolute[2] configuration as shown in Scheme 2, has been isolated from the culture filtrates of various species of *Streptomyces*; it possesses promising antiprotozoal activity, and has been shown to block ribosomal peptide synthesis.[3]

Early syntheses of anisomycin were non-stereoselective and

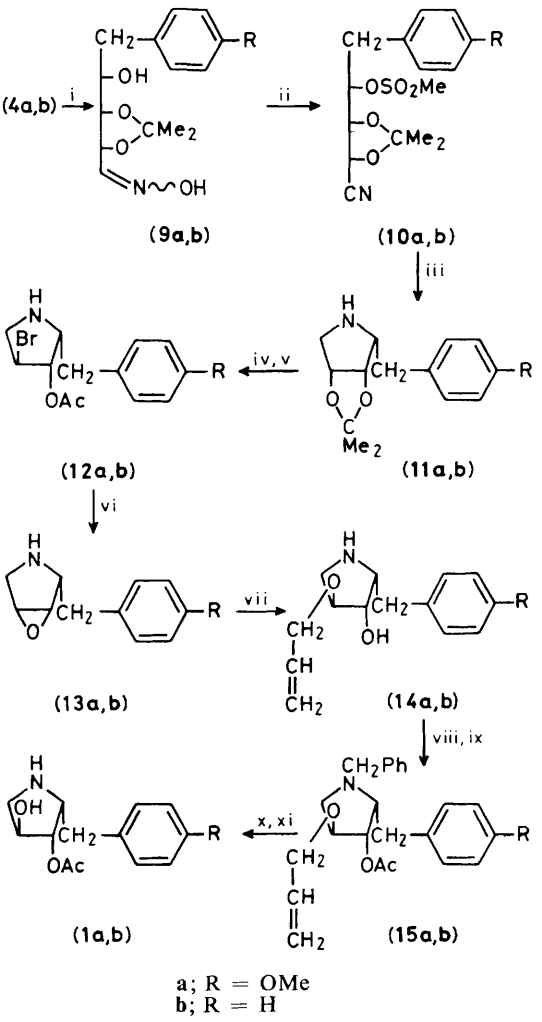


Scheme 1. i, $ArCH_2MgCl$, THF; ii, $NaIO_4$; iii, $NaBH_4$, EtOH; iv, $(CF_3SO_2)_2O$, C_5H_5N; v, PhCOCl, C_5H_5N; vi, *p*-$MeC_6H_4SO_2Cl$, C_5H_5N; vii, KOH, MeOH; viii, excess of $MeSO_2Cl$, C_5H_5N.

proceeded in poor overall yield.[4] Since then a much more efficient chiral synthesis of (−)-anisomycin (**1a**) has been reported,[5] and very recently Schumacher and Hall have announced a highly efficient and stereospecific synthesis of the racemate and two analogues including the racemic demethoxy-compound (**1b**).[6] We now report a new chiral and stereoselective synthesis of (−)-anisomycin (**1a**) and analogue (**1b**), proceeding from D-ribose in *ca.* 10% overall yield.

Treatment of 2,3-*O*-isopropylidene-D-ribose (**2**)[7] with a large excess of the appropriate Grignard reagent in tetrahydrofuran (THF) gave (**3a**) (77%) and (**3b**) (70%) (see Scheme 1). In each case a single stereoisomer was produced, which was assigned the D-*allo*-configuration shown on the basis of earlier work,[8] and this was confirmed as described below. Periodate oxidation of (**3a,b**) gave the crystalline hemiacetals (**4a,b**) readily reduced with borohydride to diols (**5a,b**). Treatment of (**5b**) with trifluoromethanesulphonic anhydride caused cyclisation to the tetrahydrofuran derivative (**6**), whilst monobenzoylation, toluene-*p*-sulphonylation, and subsequent base treatment gave the all-*cis*-isomer (**7**). Examination of ^{13}C n.m.r. spectra of (**6**) and (**7**) confirmed the stereochemistry of the initial Grignard reaction; on the basis of earlier work,[9,10] one would predict upfield shifts for C-1, C-2, and C-3, as well as the carbons of the isopropylidene group, in the all-*cis*-arrangement (**7**) as compared with β-isomer (**6**). Such an upfield shift was observed for all six carbon atoms.

Diols (**5a,b**) were readily converted into dimesylates (**8a,b**); we had hoped that reaction of (**8a,b**) with ammonia or a primary amine would give an all-*cis* pyrrolidine, but these dimesylates were surprisingly unreactive with a variety of nitrogen nucleophiles,† and an alternative route was sought (Scheme 2).



Scheme 2. i, $NH_2OH{\cdot}HCl$,C_5H_5N; ii, excess of $MeSO_2Cl$,C_5H_5N; iii, $LiAlH_4$, ether; iv, HCl,MeOH,H_2O, reflux; v, HBr, HOAc, 10 °C; vi, KOH, MeOH, H_2O; vii, allyl alcohol, $HClO_4$, $CHCl_3$, 60 °C; viii, $PhCH_2Br$, Et_3N, $CHCl_3$; ix, Ac_2O, C_5H_5N; x, Pd/C, MeOH, dil. HCl, reflux; xi, Pd/C, H_2, MeOH, HCl.

Hemiacetals (**4a,b**) were converted into the oximes (**9a,b**) (95%, mixture of *E*- and *Z*-isomers, *ca.* 70:30). Treatment of these with mesyl chloride in pyridine formed the *O*-mesyl nitriles (**10a,b**), which without purification were reduced with lithium aluminium hydride to give pyrrolidines (**11a,b**) isolated as their crystalline hydrochlorides [60% from (**4a,b**)]. Hydrolysis, and subsequent treatment of the diol hydrochlorides with HBr in glacial acetic acid[11] gave, presumably *via* the 3,4-acetoxonium ion, mixtures of *trans*-bromoacetates in which (**12a,b**) predominated;‡ treatment of the mixed bromoacetates with base gave epoxides (**13a,b**) [68% from (**11a,b**)], (**13a**) proving identical with material produced from (−)-anisomycin.[12]

Regioselective acid-catalysed ring opening with allyl alcohol‡ then gave alcohols (**14a,b**) (*ca.* 65%); *N*-benzylation and subsequent *O*-acetylation yielded (**15a,b**), which were deprotected by palladium-catalysed rearrangement and hydrolysis

† Examination of a molecular model indicates considerable hindrance to either the incoming nucleophile, or the departing leaving group, for displacement at C-5 of (**8**). Forcing conditions produced 1,2-elimination products.

‡ The regioselectivity in this reaction is predictable from results obtained during structural work on anisomycin (refs. 1a, 2, and 12); the regioselectivity is lost if the nitrogen is substituted (refs. 4b and 4c).

of the allyl group, followed by hydrogenolysis, to give (−)-anisomycin (**1a**), identical with natural material, and the demethoxy-analogue (**1b**) [70% from (**14a,b**)]. The synthetic (−)-anisomycin (**1a**) had identical activity towards *Trichomonas vaginalis* compared with the natural product, whilst (**1b**) had about one sixth of this activity.

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