Synthesis of Antibiotic Deoxynucleosides; β-D-Amicetosyl and β-D-Oxamicetosyl Cytosines

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Summary The stereoselective synthesis of β-D-amicetosyl and β-D-oxamicetosyl cytosines from the corresponding methyl α-D-amicetoside and methyl α-D-oxamicetoside are described.

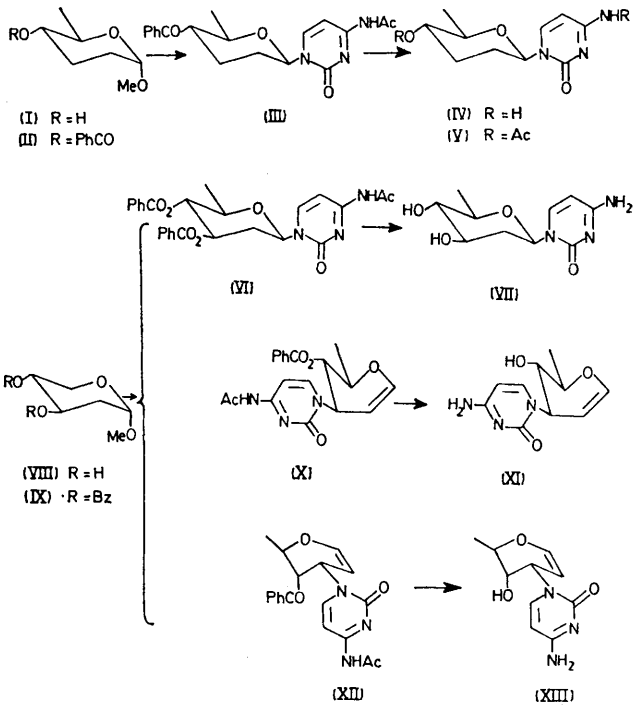
AMONG the nucleoside antibiotics, amicetin[1] and oxamicetin[2] have the unique deoxynucleoside units (IV) and (VII) in their structure. An unambiguous multistep synthesis of (IV) has been reported by Stevens *et al.*[3]

The difficulty in achieving a stereospecific synthesis of 2′-deoxynucleosides may be due to the absence of a 2′-substituent which could direct the stereochemical outcome of nucleoside formation through neighbouring-group participation,[4] and hitherto there has been no synthetic procedure to achieve this. By using 2′-deoxyhalogenoses, the stereochemistry of the nucleoside to be obtained is usually difficult to predict, mainly because of the unknown anomeric stereochemistry of the chemically unstable 2′-deoxyhalogenoses.[5]

Methyl 2′-deoxy-α-D-glycosides, which are easily available by standard methods, may be promising substrates for the synthesis of β-D-nucleosides through an S_N2-type reaction, if the reactivity of the glycosidic bond can be effectively enhanced. α-D-Nucleosides could be stereospecifically synthesized starting from methyl β-D-ribofuranoside through inversion of anomeric stereochemistry by employing boron trichloride as activating reagent,[6] but the reactivity of boron trichloride towards common protective groups reduces the general applicability of this method.

We now report the stereoselective synthesis of (IV) and (VII) from the corresponding methyl α-D-glycoside by using $SnCl_4$.

Benzoylation of methyl α-D-amicetoside (I)[7] gave the benzoate (II), $[\alpha]_D^{25}$ + 170·1° ($CHCl_3$). A solution of (II) and bistrimethylsilyl-*N*-acetylcytosine[8] in CH_2Cl_2 was treated with $SnCl_4$ (1 equiv.) at room temperature to give the nucleoside (III), m.p. 226—228 °C, $[\alpha]_D^{25}$ +82·0° ($CHCl_3$) in 41% yield (81% conversion†). Treatment of



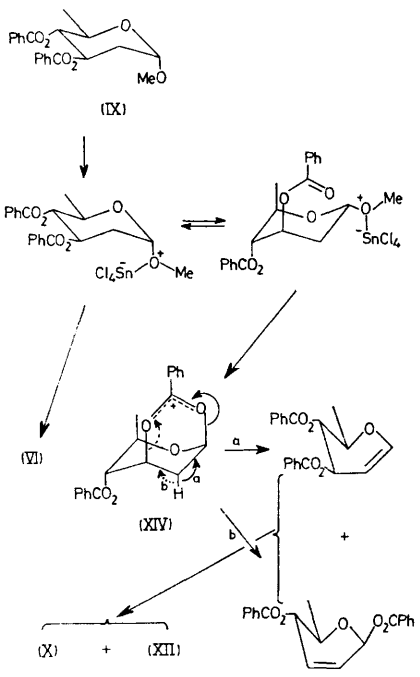
SCHEME 1

(III) with methanolic NH_3 at 0 °C gave β-D-amicetosylcytosine (IV), m.p. 265—267 °C, $[\alpha]_D^{25}$ −8·3°; δ (D_2O) for 1′-H, 5·67 [dd, $J(1'2'_{ax})$ 8 Hz, J $(1'2'_{eq})$ 4 Hz‡]. The

† The figures in parentheses are conversion yields.

‡ The J value reported herein were confirmed by decoupling experiments.

diacetate (V), m.p. 201—202 °C, $[\alpha]_D^{25}$ +124° ($CHCl_3$), obtained in the usual manner, was identical (i.r. comparison) with the natural product.



SCHEME 2

Benzoylation of methyl α-D-oxamicetoside (VIII)[9] gave the dibenzoate (IX), m.p. 80—83 °C, $[\alpha]_D^{25}$ −1·7° ($CHCl_3$), which, under the same conditions as for (II), afforded a mixture of nucleosides: (VI), $[\alpha]_D^{25}$ + 69·4°; (X), $[\alpha]_D^{25}$ −159·9° ($CHCl_3$), m.p. 255—257 °C; (XII), $[\alpha]_D^{25}$ − 128·0° ($CHCl_3$), m.p. 260—263 °C, in 10 (34†), 7 (23) and 5% (17%) isolated yields, respectively.

Deacylation in the usual manner of (VI) gave (VII) as a syrup, $[\alpha]_D^{25}$ − 8·7 (H_2O). Synthetic (VII) was identical with the natural product on ^1H n.m.r. comparison.

In order to elucidate the structure of the remaining two products (X) and (XII), these were deacylated to give the free nucleosides (XI) and (XIII) quantitatively. The structures of (XI), $[\alpha]_D^{25}$ − 12·5° (H_2O), and (XIII), $[\alpha]_D^{25}$ − 26·1° (H_2O), were assigned by ^1H n.m.r. spectroscopy (D_2O) as follows. The location of a C(1)–C(2) double bond in both compounds was evident from the 1′-H signals at δ 6·58 [dd, J(1′,2′) 6 Hz, J(1′,3′) 2 Hz) and at δ 6·62 [dd, J(1′,2′) 6 Hz, J(1′,3′) 2 Hz] in each case which are quite characteristic of glycal 1-H signals.[10] The stereochemistry of 3′-H was assigned from the coupling constant J(3′,4′). In the case of (XI), J(3′,4′) = 10 Hz, indicating a diaxial disposition of 3′- and 4′-H, but for (XIII) J(3′,4′) = 4 Hz, indicating a pseudoaxial and pseudoequatorial disposition. The attachment of the cytosine nucleus to the unsaturated sugar at N-1 was determined by u.v. spectroscopy: λ_{max} (0·1N HCl) 283 nm (ε 12,000), λ_{max} (0·1N NaOH) 275 nm (ε 8600) for (XIII); λ_{max} (0·1N HCl) 284 nm (ε 11,000), λ_{max} (0·1N NaOH) 275 nm (ε 8000) for (XI).[11]

The formation of (X) and (XII) can be explained in terms of a path *via* an intermediate benzoxonium ion (XIV)[12] (Scheme 2[13]).

In conclusion, we have shown that methyl 2-deoxy-α-D-glycosides could be promising substrates for the stereoselective synthesis of 2-deoxy-β-D-hexopyranosyl nucleosides through Lewis acid activation of the glycosidic bond.

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