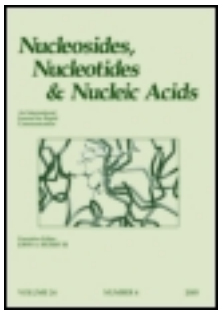

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A NOVEL SYNTHESIS OF MIZORIBINE® AND RELATED NUCLEOSIDES FROM ACYCLIC PRECURSORS

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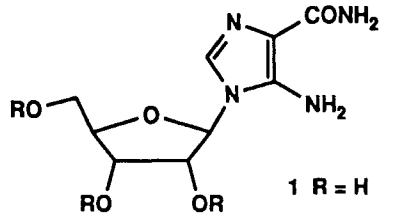
ABSTRACT

Mizoribine® (4-carbamoyl-1-β-D-ribofuranosylimidazolium-5-olate)(**13**β) and its 4-cyano analogue (**20**) were synthesized by formation of a malonamide from 2,3-isopropylidene-D-ribosylamine and a malonic acid derivative followed by amination, cyclisation and deprotection steps.

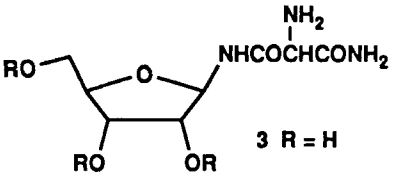
Mizoribine® (4-carbamoyl-1-β-D-ribofuranosylimidazolium-5-olate) is an imidazole nucleoside originally isolated from *Eupencillium brefeldianum* M-2166[1] and is currently in clinical use as an immunosuppressant for post transplant patients.[2] It has less side effects, but greater potency compared to azathioprine (Imuran®).[2,3,4] Mizoribine® has additional biological importance. It shows potential antitumour,[5,6,7] antiviral,[1] antimalarial,[8] and antiarthritic,[9,10] activities. This broad spectrum activity, and the unique imidazole structure of the aglycone (4-carbamoyl-imidazole-5-olate) make this compound and related 5-hydroxyimidazoles attractive targets for synthetic and enzyme inhibition studies. Notably mizoribine® is analogous to AICA-riboside (**1**), an intermediate in the *de novo* purine nucleotide pathway.

Two synthetic strategies for the synthesis of mizoribine® have been reported so far. The first involved the direct condensation of a 5-hydroxyimidazole base with an activated sugar.[11] This strategy has been used by various groups using different coupling methodologies, activated sugars and 5-hydroxyimidazoles.[12,13] An alternative strategy involved photolytic ring opening of **1** or its acetylated derivative **2** to give 2-amino-N-(β-D-ribofuranosyl)malondiamide **(3)** or the protected derivative **4,** respectively.[14,15] Each was cyclised with ethyl orthoformate to give mizoribine,® following deprotection as appropriate.

Herein we report a novel strategy in which the 5-hydroxyimidazole moiety of mizoribine® is formed by cyclisation of the D-ribofuranosylamine derivative **5**. This strategy is comparable with that devised by Shaw for 5-aminoimidazoles in which the



1 R = H
2 R = Ac

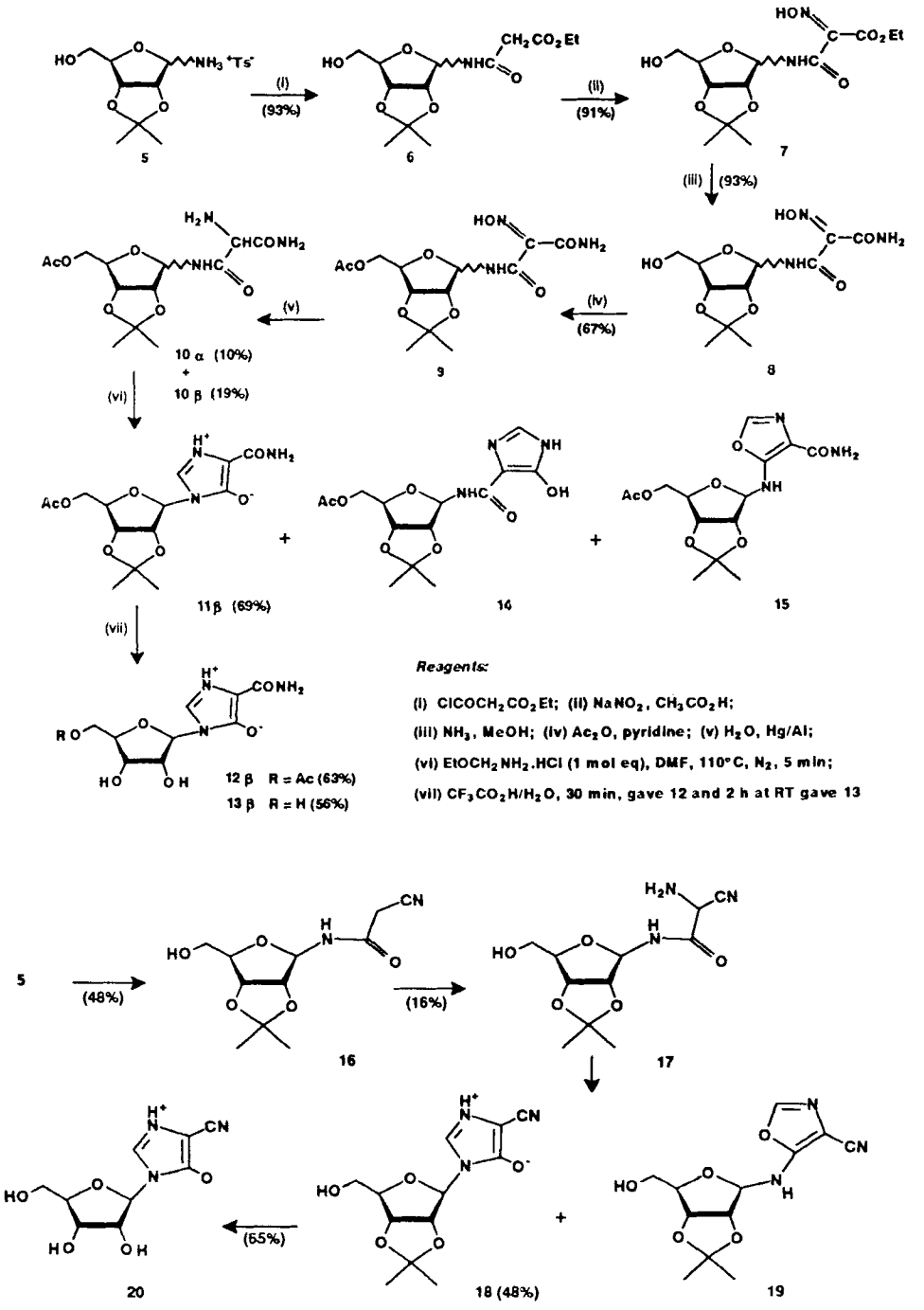


3 R = H
4 R = Ac

heterocycle is formed from acyclic intermediates.[16] This strategy has the advantage that the reagents employed are relatively inexpensive and can be easily modified to introduce a wide variety of substituents at positions **1**, **2** and **4** of the 5-hydroxyimidazole and hence provide a route to a large number of mizoribine® analogues.

2,3-*O*-Isopropylidene-D-ribofuranosylamine toluene-p-sulphonate (**5**) was reacted with ethyl malonyl chloride in NEt_3 and CH_2Cl_2 to give an anomeric mixture of ethyl N-(2,3-*O*-isopropylidene-D-ribofuranosyl)malonamate (**6**)(93%). Reaction of **6** in aqueous sodium nitrite and acetic acid gave an anomeric mixture of ethyl 2-hydroxy-imino-N-(2,3-*O*-isopropylidene-D-ribofuranosyl)malonamate (**7**)(81%) which with ethanolic ammonia (4°C, 18h) gave 2-hydroxyimino-N-(2,3-*O*-isopropylidene-D-ribo-furanosyl)malondiamide (**8**)(93%). To facilitate chromatographic purification of later products in this route the oxime **8** was acetylated (Ac_2O in pyridine) to give the corresponding 5-*O*-acetyl derivative **9**, which was reduced with aluminium/mercury amalgam to give a separable (silica gel column chromatography eluted with $CHCl_3$-MeOH) anomeric mixture of 2-amino-N-(5-*O*-acetyl-2,3-*O*-isopropylidene-D-ribofuranosyl)malondiamide (**10**α)(10%) and (**10**β) (19%). Compound **10**β is analogous to **3** and **4**, previously obtained by photochemical cleavage[14,15] of **1** and **2**, respectively. The low yield of **10**β was probably due to its adsorption on the solid residue produced by the reagent. An alternative route to **10**β was investigated by treating **6** with *O*-mesitylenesulphonylhydroxylamine but this was unsuccessful.

The reaction conditions required for clean cyclisation without by-products were highly specific. Thus **10**β was reacted with ethylformimidate hydrochloride (1 mol eq) in DMF at 110°C for 5 min under nitrogen to give the 5-hydroxyimidazole **11**β (69%). It was noted that when an excess (1.3 mol eq) of ethyl formimidate hydrochloride was used competition between the different modes of cyclisation was



evident, resulting in the formation of 11β, 14β and 15β. The analogous synthesis of α-mizoribine® did not demonstrate a similar selectivity since the reaction using 1 mol equivalent of ethyl formimidate hydrochloride resulted in a mixture which contained 11α, 14α and 15α.

In a parallel study to synthesise **20,** the 4-cyano analogue of mizoribine® cyano N-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)acetamide **(16)** was obtained stereoselectively as the β-anomer by condensation of the ribosylamine **5** with cyanoacetyl chloride. In contrast to the ester analogue **6** the cyano compound **16**(48%) reacted with *O*-mesitylenesulphonylhydroxylamine to give the amine **17**(16%) which with ethylformimidate hydrochloride (1 mol eq) in DMF at 110°C after 5 min cyclised to give the 5-hydroxyimidazole **18**(48%) and a small amount of the oxazole by-product **19** resulting from the alternative cyclisation. Deprotection of **18** was effected with trifluoroacetic acid to give the β-nucleoside **20** 65%.

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