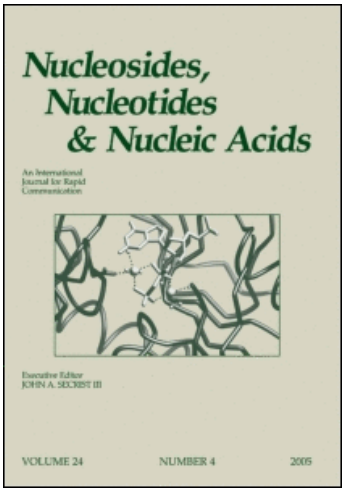

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Studies in the Synthesis and Biosynthesis of C-Nucleosides

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STUDIES IN THE SYNTHESIS AND BIOSYNTHESIS OF C-NUCLEOSIDES

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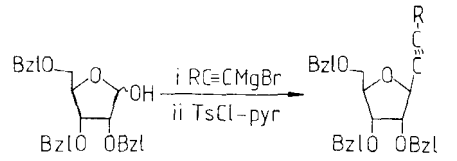
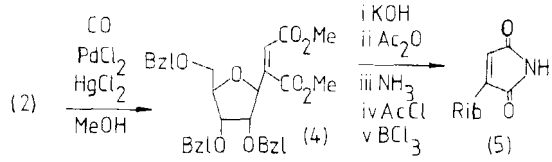
Heriot-Watt University, Riccarton, Edinburgh (G.B.).

The naturally occurring C-nucleosides[1] show marked antitumour and antiviral properties. We have developed, over a period of years, a general synthetic route to C-nucleosides by way of acetylenic intermediates. Tri-O-benzyl-D-ribofuranose (1) reacts with acetylenic Grignard reagents to give mixtures of D-allo and D-altro diols. The latter, on ring closure by means of toluene-p-sulphonyl chloride in pyridine, gives derivatives, (2) or (3), of β-D-ribofuranosylethyne in ~50% yield from (1).



The ethyne (2) was converted into showdomycin (5)[2] using a dicarbonylation reaction[3] to give the maleic diester (4), followed by elaboration of the imide ring and deprotection.



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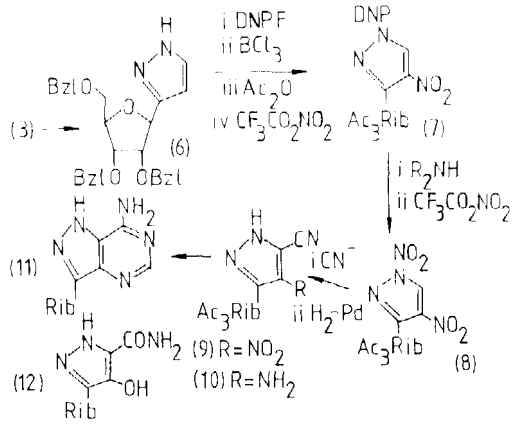
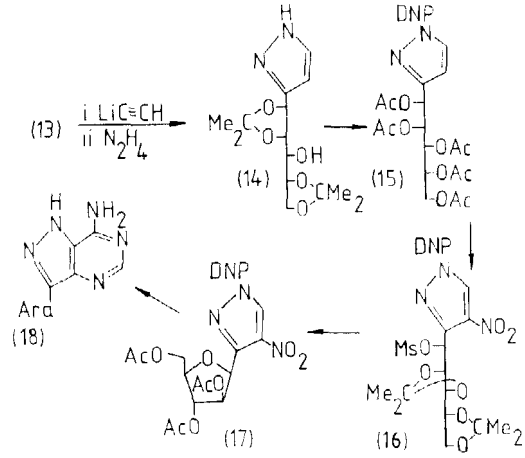


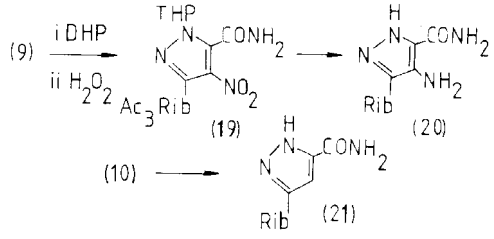
A major objective was a new synthesis of formycin (11)[4] and pyrazofurin (12)[5]. The ethyne (3) afforded the pyrazole (6) by treatment of the parent aldehyde with hydrazine[6]. The 4-nitrocompound (7) was obtained and gave, in turn, the 1,4-dinitrocompound (8). Cine substitution[7] of the N-nitro group in (8) gave the key nitropyrazole intermediate (9). The derived aminopyrazole (10) could be transformed into both formycin (11)[4] and pyrazofurin (12)[5].



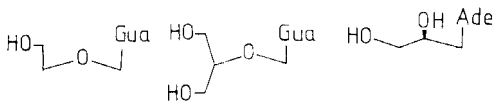
The acetylenic route could be applied to sugar analogues and this is exemplified by a synthesis of ara formycin[8]. The diacetonide (13) of D-mannonolactone reacted with lithium acetylide to give the lactol of an acetylenic ketone, transformed into the pyrazole (14) with hydrazine[9,10]. The derived dinitrophenyl derivative (15) could be

nitrated and further transformed into the sulphonate (16). Deacetonation of (16) was accompanied by ring closure and the triacetate (17) of the product was converted by the earlier methods into ara-formycin (18). Similar D-xylo intermediates are available[11] for elaboration into xylo formycin.

Other analogues are available from this general route. The nitronitrile (9) affords the tetrahydropyranyl derivative[12] which gives the nitroamide (19), convertible into the known aminoamide (20)[13]. 4-Deoxypyrazofurin (21) has been prepared by photolysis of the diazo compound derived from (10) in the presence of dioxan, followed by hydrolysis of the nitrile group and deprotection[12].

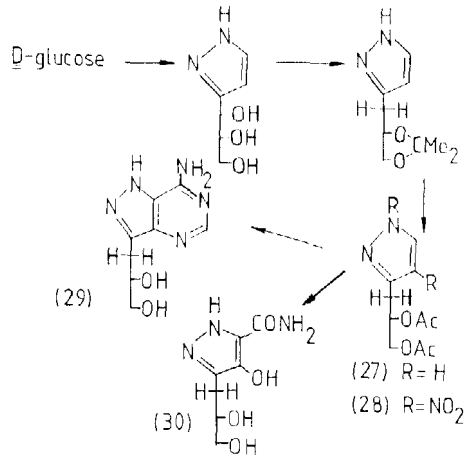


A major development in antiviral chemotherapy has been the recognition that potent antiviral activity is displayed by certain analogues of the normal nucleosides in which the ribose unit is replaced by a truncated acyclic residue. Examples are the guanine analogues acyclovir (22)[14] and DHPG (23)[15], and the adenosine analogue DHPA (24)[16]. We have synthesised the formycin analogue of DHPA containing a pyrazole ring using the methods already developed[17]. The trihydroxypropylpyrazole (25) is readily obtainable from D-glucose[18] and has been converted, via the 1'-deoxycompound (26), into

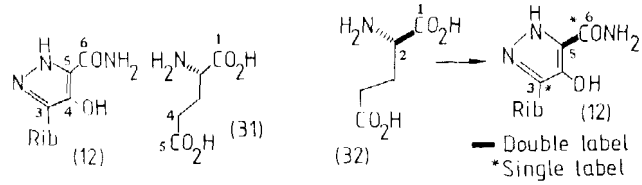


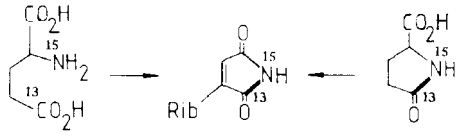
(22) (23) (24)

the analogues of formycin (29) and the pyrazofurin (30). A recent discovery is the direct nitration of the diacetate (27) to give the 1,4-dinitrocompound (28) using trifluoroacetyl nitrate[19].



In parallel with synthetic studies we have examined the biosynthesis of the C-nucleoside antibiotics pyrazofurin (12) and showdomycin (5). We have shown[20] that in the biosynthesis of pyrazofurin (12) by Streptomyces candidus the ribose ring is derived from D-ribose, presumably as 5-phosphoribosylpyrophosphate (PRPP). This was established using 1-^{14}C-D-ribose, and more specifically by means of 5-$^{2}H_{1}$-D-ribose. The heterocyclic portion is derived from L-glutamate (31), shown by feeding U-^{14}C-L-glutamate,[20] 1-^{14}C-L- and D-glutamate and 1- and 5- ^{13}C-DL-glutamate.[21] C-6 in pyrazofurin becomes ^{13}C-labelled from both 1- and 5- ^{13}C-glutamate. This may be due to the operation of the Krebs tricarboxylic acid cycle where C-5 of ketoglutarate, derived from glutamate by transamination, can become C-1 after one turn of the cycle. A recent experiment using 1,2-$^{13}C_{2}$-glutamic acid (32) shows that satellites are present in the signals for C-5 and C-6 in the ^{13}C-n.m.r. spectrum of the pyrazofurin. In addition a single label is present at C-3 and C-6. The latter may be





(33) (5) (34)

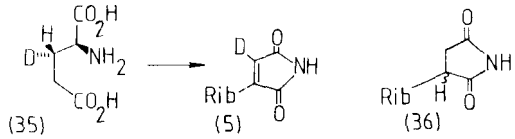
due to the operation of the Krebs cycle, but the former is not readily explained on present hypotheses.[20,22]

A reinterpretation[20] of earlier data[23] indicates that glutamic contributes four continguous carbon atoms in the biosynthesis of formycin (11).

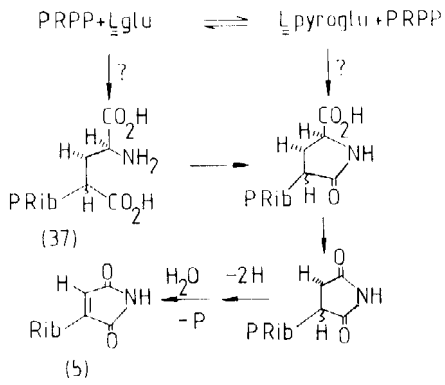
The biosynthesis of showdomycin (5) by S. showdoensis was first studied by Suhadolnik[23] who showed that D-ribose and the carbon skeleton of glutamic acid were the major precursors. We have fully confirmed these results and extended them in several details.[21] 5-$^{2}H_{1}$-D-Ribose is specifically incorporated into the ribose portion, and 5-^{14}C-L-glutamic acid is incorporated much more efficiently than the D-isomer. 5-^{13}C-Glutamic acid is converted into showdomycin labelled only at C-1. 5-^{13}C, ^{15}N-glutamic acid (33) gives showdomycin whose ^{13}C n.m.r. spectrum shows satellite signals due to ^{13}C-^{15}N coupling of C-1, demonstrating clearly that the amino group is also incorporated.

Experiments have also been carried out with 5-^{13}C,^{15}N-pyroglutamic acid (34). This gave a very similar result to the glutamic acid, leading to satellite signals for C-1 in showdomycin. Since glutamate and pyroglutamate are enzymically interconvertible this experiment does not show whether glutamate or pyroglutamate is the more direct precursor of the maleimide ring.

Experiments in collaboration with Dr. Douglas Young of the University of Sussex have shown that the deuterium atom in (2S,3S)-[3-^{2}H]-glutamic acid (35) is retained as the vinyl hydrogen in showdomycin, whereas the corresponding 3-pro-R hydrogen is lost.



(35) (5) (36)



Radioactive showdomycin, obtained by feeding 1-^{14}C acetate was hydrogenated to give 2,3-dihydroshowdomycin as a mixture of diastereomers (36). When this was fed to S. showdoensis the specific incorporation into the resulting showdomycin was 12.9%.

The following partial scheme is suggested for showdomycin biosynthesis. The intermediate (37) is that previously suggested for general C-nucleoside biosynthesis,[20,22] in which decarboxylation of C-1 led to showdomycin and decarboxylation of C-5 led to pyrazofurin. Our recent findings for pyrazofurin do not appear to be consistent with the idea of a common pathway. Further work is in progress.

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