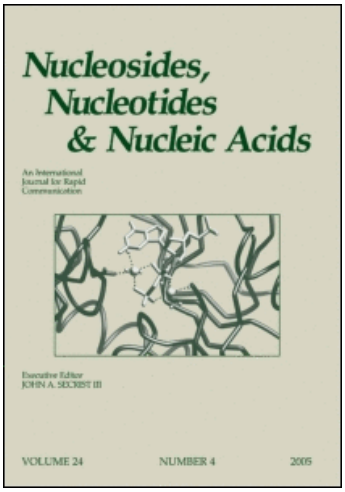

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DIRECT SYNTHESIS OF PYRROLE NUCLEOSIDES BY THE STEREOSPECIFIC SODIUM SALT GLYCOSYLATION PROCEDURE

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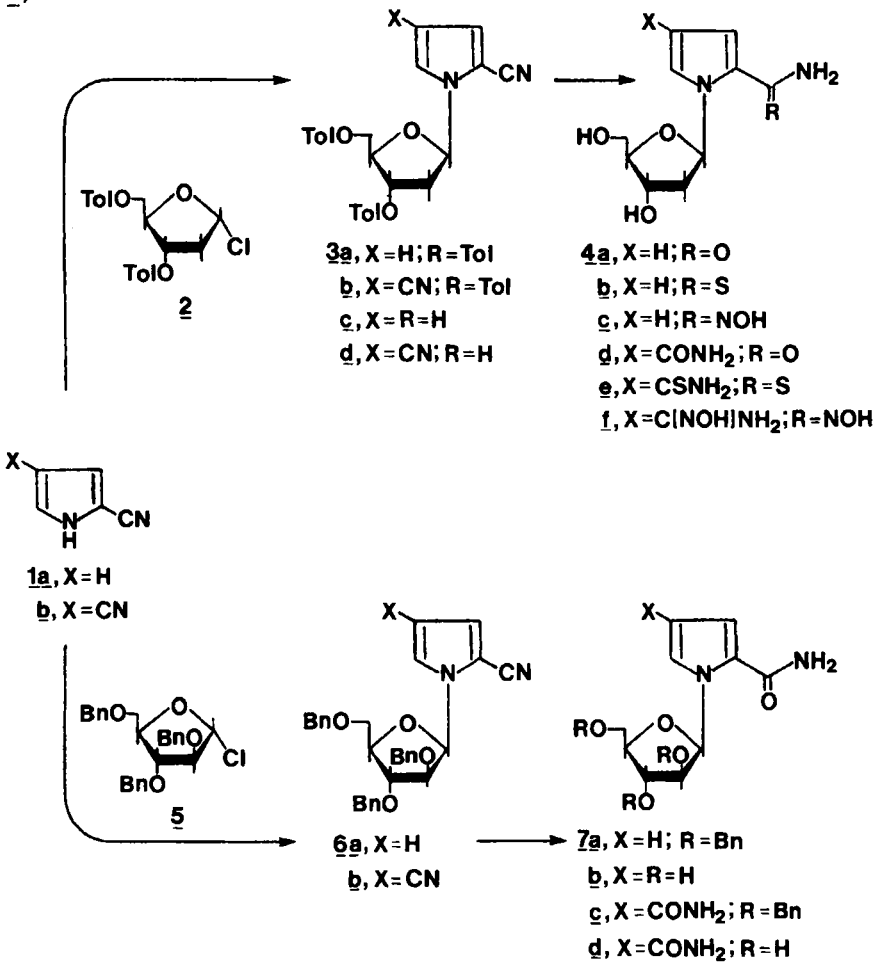
ABSTRACT: A number of 1-β-D-arabinofuranosyl and 1-(2-deoxy-β-D-erythro-pentofuranosyl) derivatives of substituted pyrroles have been prepared in good yields by the direct glycosylation of the sodium salt of a preformed fully aromatic pyrrole with an appropriate α-halogenose.

The stereospecific sodium salt glycosylation procedure for the synthesis of 2'-deoxyribonucleosides with β-anomeric configuration has been a part of our ongoing research program.[1-7] Application of this single-phase procedure for the synthesis of pyrrole nucleosides has now been found to be remarkably successful. Prior procedures for the preparation of pyrrole N-nucleosides[8] utilized partially hydrogenated pyrroles in the glycosylation reaction using the "indoline-indole" method.[9] However, our synthetic pathway involves the direct attachment of a glycon moiety (β-D-arabinofuranosyl and 2'-deoxy-β-D-ribofuranosyl) to a preformed fully aromatic pyrrole derivative.

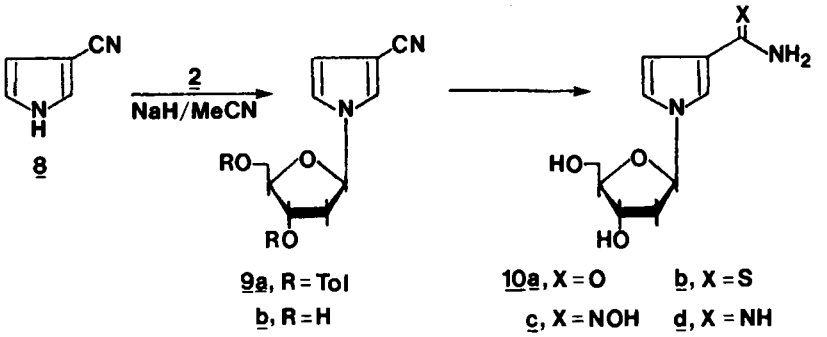
In the present work we first selected pyrrole-2-carbonitrile[10] (1a) for glycosylation studies. The sodium salt of 1a, produced in situ by NaH in CH_3CN, was treated with 1-chloro-2-deoxy-3,5-di-O-p-toluoyl-α-D-erythro-pentofuranose[11](2). A clean reaction was observed at room temperature, and the desired 1-(2-deoxy-3,5-di-O-p-toluoyl-β-D-erythro-pentofuranosyl)pyrrole-2-carbonitrile (3a) was isolated in 67% yield. No formation of the α-anomer was detected. When 3a was treated with $MeOH/NH_3$ at room temperature, deprotection of the glycon moiety occurred to give almost quantitative yield of 1-(2-deoxy-β-D-erythro-pentofuranosyl)pyrrole-2-carbonitrile (3c). The carbonitrile function of 3c was available for further transformation reactions to

obtain 1-(2-deoxy-β-D-erythro-pentofuranosyl)pyrrole-2-carboxamide (4a), as well as the corresponding 2-thiocarboxamide (4b) and 2-carboxamidoxime (4c) derivatives. Similarly, glycosylation of the sodium salt of pyrrole-2,4-dicarbonitrile[10] (1b) with 2 gave a 68% yield of the corresponding blocked nucleoside (3b), which on deprotection with MeOH/NH_3 afforded 1-(2-deoxy-β-D-erythro-pentofuranosyl)-pyrrole-2,4-dicarbonitrile (3d). Compound 3d served as a versatile starting material to obtain 2,4-disubstituted pyrrole nucleosides (4d-f).

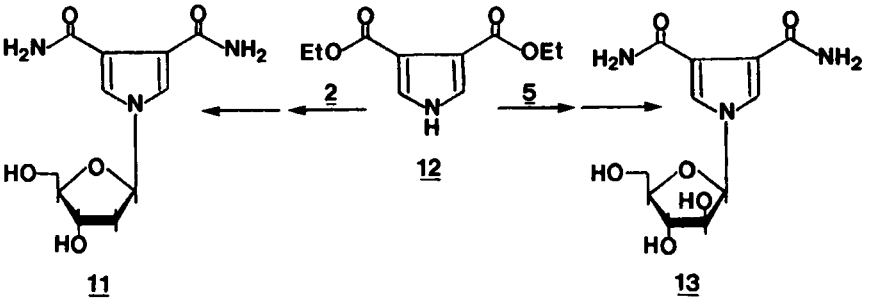


This general synthetic procedure has been found to be applicable equally well to the preparation of β-D-arabinofuranosyl derivatives of certain pyrroles. Glycosylation of the sodium salt of either 1a or 1b

with 1-chloro-2,3,5-tri-O-benzyl-α-D-arabinofuranose[12] (5) in CH_3CN furnished the corresponding protected nucleosides (6a) and (6b), which on subsequent functional group manipulation gave 1-β-D-arabinofuranosylpyrrole-2-carboxamide (7b) and 1-β-D-arabinofuranosylpyrrole-2,4-dicarboxamide (7d), respectively.



The other pyrroles that were employed for glycosylation studies were pyrrole-3-carbonitrile[10] (8) and diethyl pyrrole-3,4-dicarboxylate[13] (12). Compound 8 was particularly chosen since brunfelsamidine, a novel convulsant isolated recently from the roots and bark of **Brunfelsiagrandiflora** is identified as pyrrole-3-carboxamidine.[14] Reaction of the protected halogenose 2 with the sodium salt of 8 gave a 62% yield of 1-(2-deoxy-3,5-di-O-p-toluoyl-β-D-erythro-pentofuranosyl)pyrrole-3-carbonitrile (9a). As in the case of 3a, no formation of the α-anomer of 9a in this reaction was observed. Deprotection of the blocking groups of the glycon moiety of 9a was accomplished by the treatment with $MeOH/NH_3$ to yield 1-(2-deoxy-β-D-erythro-pento-



furanosyl)pyrrole-3-carbonitrile (9b), in which the nitrile function was available for further transformation reactions.

Glycosylation of the sodium salt of 12 with 2 and subsequent ammonolysis of the reaction product gave 1-(2-deoxy-β-D-erythro-pento-

furanosyl)pyrrole-3,4-dicarboxamide (11). Similar reaction of 12 with 5, followed by catalytic debenzylation and ammonolysis furnished 1-β-D-arabinofuranosylpyrrole-3,4-dicarboxamide (13). The anomeric configuration of the isolated pyrrole nucleosides was assigned as β on the basis of ^{1}H NMR studies.[15,16]

Thus, the stereospecific attachment of β-D-arabinofuranosyl and 2-deoxy-β-D-ribofuranosyl moieties via the sodium salt of a preformed aromatic pyrrole represents a direct route to pyrrole nucleosides.

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