Tetrahedron Letters, Vol.32, No.45, pp 6485-6488, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

AN EFFICIENT ROUTE TO C-4 LINKED IMIDAZOLE NUCLEOSIDES : SYNTHESIS OF 2-CARBAMOYL-4-(2'-DEOXY-β-D-RIBOFURANOSYL)IMIDAZOLE

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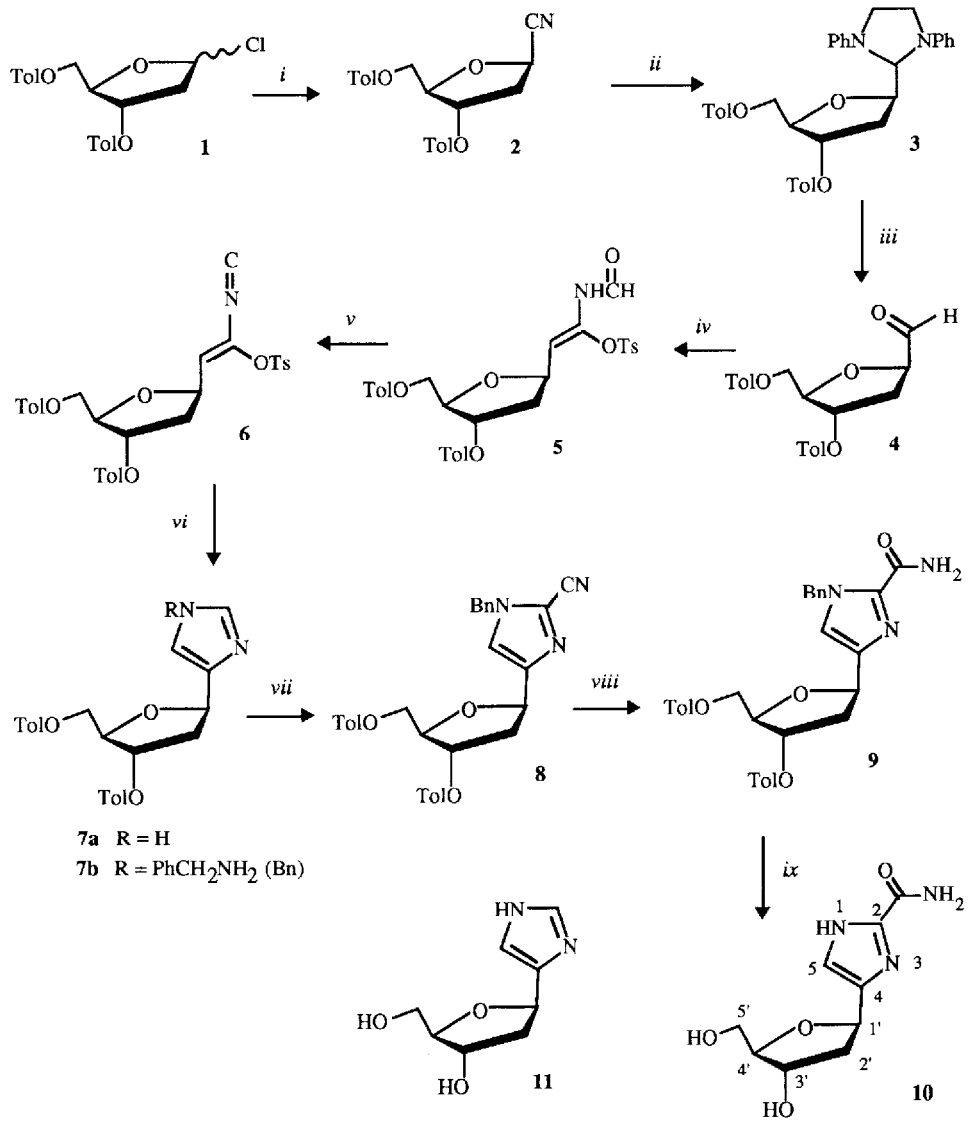
Summary: The first synthesis of an imidazole C-nucleoside linked through C-4, 2-carbamoyl-4-(2'-deoxy-β-D-ribofuranosyl)imidazole was achieved by way of a nine-step sequence starting from 2-deoxy-3,5-di-O-*p*-toluoyl-D-*erythro*-pentofuranosyl chloride.

Substituted imidazole nucleotides play a vital role in purine biosynthesis. At least five separate compounds of this class are found in the pathway leading from 1,6-ribosyldiphosphate to inosinic acid (1). A key structural feature of three of the intermediates is the presence of a carboxamide substituent on the imidazole. Numerous analogues containing different heterocyclic, five-membered rings have been synthesized and found to have biological activity. As examples, 2-β-D-ribofuranosylthiazole-4-carboxamide and 2-β-D-ribofuranosylselenazole-4-carboxamide are potent antitumor agents (2). Ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide) is a broad spectrum antiviral agent active particularly against many different RNA viruses (3).

Among naturally occurring C-ribonucleosides derived from five-membered ring heterocycles are showdomycin, bredinin (4-carbamoyl-1-β-D-ribofuranosylimidazolium-5-olate), pyrazofurin (3-(1-β-D-ribofuranosyl)-4-hydroxypyrazole-5-carboxamide) (4). Two of the compounds, showdomycin and pyrazofurin, are C-nucleosides. Although the synthetic chemistry of C-nucleosides has been extensively investigated (5), very few studies have been reported on the synthesis of imidazole C-nucleosides. These have been limited to C-2 substituted imidazoles (6,7,8). The synthesis reported here describes a carboxamide substituted imidazole deoxyribonucleoside, but the general approach should allow application to other sugars, including ribose, and also allow extensive imidazole modification late in the sequence in order to generate a wide variety of other analogues.

One criteria of a useful C-nucleoside synthesis is that a readily available stereochemistry pure starting material can be transformed to the final C-nucleoside without anomerization at C-1′. We have found that 4-(2'-deoxy-3',5'-di-O-toluoyl-β-D-ribofuranosyl)imidazole can be successfully synthesized from 2-deoxy-3,5-di-O-*p*-toluoyl-β-D-ribofuranosyl cyanide (**2**) (9), which is readily available from 2-deoxy-3,5-di-O-*p*-toluoyl-D-*erythro*-pentofuranosyl chloride (**1**, Scheme 1) (10). The cyanodeoxyribose **2** was converted to the aldehyde **4** via imidazolidine **3** following the procedure developed by Moffatt and coworkers for the preparation of 2,5-anhydro-3,4,6-tri-O-benzoyl-D-allose (11). As in Moffatt's case, the

Scheme 1



Reagents and Conditions: *i*, NaCN, 1,2-dimethoxyethane (DME); *ii*, Raney nickel, NaH_2PO_2, N,N'-diphenylethylenediamine, HOAc-Py-H_2O (1:2:1); *iii*, p-toluenesulfonic acid monohydrate, methylene chloride, and acetone; *iv*, tosylmethyl isocyanide, t-BuOK, DME (-35 to -30 °C); *v*, Et_3N, $POCl_3$, DME, - 5 °C; *vi*, NH_3 or $PhCH_2NH_2$ in methanol; *vii*, 4-(N,N-dimethylamino)pyridine, cyanogen bromide, DMF (45°C); *viii*, H_2O_2, methanol and water, pH = 10; *ix*, sodium, liquid ammonia.

aldehyde was used immediately following its generation by treatment of imidazolidine **3** with *p*-toluenesulfonic acid.

A decade ago Van Leusen and coworkers reported a method for synthesis of 4-substituted imidazoles from aldehydes via condensation with tosylmethyl isocyanide to give 1-formamido-1-tosylalkenes , which are easily transformed to imidazoles in two steps by reaction first with phosphorus oxychloride to dehydrate the formamide to an isocyanide moiety and then ring closed with ammonia to yield the imidazole(12). We have discovered that this is an excellent method for constructing an imidazole linked to a carbohydrate.

As described in scheme 1 aldehyde **4** reacted with tosylmethyl isocyanide and t-BuOK to yield formamide **5** in 51% yield. Dehydration of **5** by treatment with phosphorus oxychloride followed by addition of ammonia yielded 4-(2'-deoxy-3',5'-di-O-*p*-toluoyl-β-D-ribofuranosyl)imidazole in 86% yield. Characterization by IR, MS, ^{1}H NMR and ^{13}C NMR (13), confirmed the structure as compound **7a**. Throughout the synthesis, no isomerization at the anomeric carbon C-1´ was noted. Compound **7a** was anomerically pure as judged by ^{1}H NMR spectroscopy. The pattern of the methylene protons (H2´, H2´´) of the deprotected product, 4-(2´-deoxy-β-D-ribofuranosyl)imidazole (**11**) was consistent with the assignment (14). The signals for the two H-2' protons were centered at 2.086 and 2.218 ppm and spanned a total region of 0.181 ppm which is typical of a β anomer. The H-2' and H-2" protons of an α anomer would be expected to span a region of 1.0 ppm or greater. When benzylamine was used in step *vi* in place of ammonia the product was the benzyl protected imidazole **7b** which was readily converted to 1-benzyl-2-cyano-4-(2'-deoxy-3',5'-di-O-toluoyl-β-D-ribofuranosyl)imidazole (**8**) by treatment with 1-cyano-4-dimethylaminopyridinium bromide (15). Hydrolysis of the cyano group with basic hydrogen peroxide and protecting group removal with sodium in liquid ammonia yielded 2-carbamoyl-4-(2'-deoxy-β-D-ribofuranosyl)imidazole (**10**), which was confirmed to be the β-anomer by ^{1}H NMR.

Acknowledgements

The National Institutes of Health is gratefully acknowledged for support of this research through NIH Grants AI20480 and AI26029. We also gratefully acknowledge the support by the Walther Cancer Institute.

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13. All intermediates (compounds **2**-**11**) were characterized by ^{1}H NMR, IR, and mass spectrometry. The spectral data for compounds **7** , **10**, and **11** are given below.

4-(2'-Deoxy-3',5'-di-O-*p*-toluoyl-β-D-ribofuranosyl)imidazole (7a)

IR (KBr), 3271, 3128, 1713, 1605, 1267, 1103, 749; ^{1}H NMR (500 MHz, acetone-d_6 / TMS,ppm), 2.389 (3H, s, methyl H), 2.413 (3H, s, methyl H), 2.450 (1H, m, 2´-H), 2.698 (1H, m, 2´-H), 4.443 (1H, dt, J = 6.0, 2.0 Hz, 4´-H), 4.534 (2H, dd, J = 4.8, 1.5 Hz, 5´-H), 5.305 (1H, dd, J = 10.5, 5.5, 1´-H), 5.649 (1H, dt, J = 6.0, 3´-H), 7.130 (1H, d, J = 0.5 Hz, 5-H), 7.321 (4H, m. aromatic H), 7.640 (1H, d, J = 1.0 Hz, 2-H), 7.980 (4H, d, J = 8.0 Hz, aromatic H); ^{13}C NMR (125 MHz, methanol-d_4 / TMS, ppm): 166.48 and 166.30 (C=O), 144.66, 144.40, 130.33, 130.28, 129.91 and 129.84 (aromatic C), 136.01 (2-C), 128.22 and 128.20 (4- and 5-C), 83.08 (5'-C), 78.03 and 75.87 (1' and 4'-C), 65.59 (3'-C), 38.96 (2'-C), 21.56 and 21.54 (methyl C); High Resolution FAB-MS: MH^+ (Fd. , 421.1768; Calc. , 421.1763).

2-Carboxamido-4-(2'-deoxy-β-D-ribofuranosyl)imidazole (10)

IR (KBr), 1673.0 cm^{-1}; ^{1}H NMR (500 MHz, methanol-d_4 / TMS, ppm), 2.147(1H, ddd, J=2, 5.5, 13.3 Hz, 2'-H_1), 2.225(1H, ddd, J=5.8, 10, 13.3 Hz, 2'-H_2), 3.625(1H, dd, J=4.8, 11.8Hz, 5'-H_1), 3.681(1H, dd, J=4.3, 11.8 Hz, 5'-H_2), 3.880 - 3.920(1H, m, 3'-H), 4.335 - 4.370(1H, m, 4'-H), 5.157(1H, dd, J=6.0, 10.0 Hz, 1'-H), 7.197(1H, s, 5-H); ^{13}C NMR (125 MHz, methanol-d_4 / TMS, ppm), 162.083(C=O), 141.900(2-C), 130.275(4-C), 129.252(5-C), 89.060(5'-C), 75.098(1'-C), 74.140(4'-C), 63.855(3'-C), 42.623(2'-C); High Resolution FAB-MS, MH^+(Fd. , 228.0985, Calc. , 228.0984).

4-(2'-Deoxy-β-D-ribofuranosyl)imidazole (11)

^{1}H NMR (500 MHz, methanol-d_4 / TMS, ppm) spectrum: 2.086 (1H, ddd, J = 1.5, 5.5, 13 Hz, 2'-H), 2.218 (1H, ddd, J = 6, 10.5, 13 Hz, 2'-H), 3.611 (1H, dd, J = 4.5, 12 Hz, 5'-H), 3.674 (1H, dd, J = 4.5, 12 Hz, 5'-H), 3.889 (1H, m, 4'-H), 4.351 (1H, m, 3'-H), 5.149 (1H, dd, J = 5.5, 10.5 Hz, 1'-H), 7.056 (1H, d, J ≤ 1 Hz, 2-H), 7.648 (1H, d, J ≤ 1 Hz, 4-H); ^{13}C NMR (125 MHz, methanol-d_4 / TMS, ppm), 139.273(2-C), 136.692(4-C), 117.649(5-C), 89.075(5'-C), 75.087(1'-C), 74.158(4'-C), 63.977(3'-C), 42.641(2'-C); High Resolution FAB-MS: MH^+ (Fd. , 185.0903; Calc. , 185.0926).

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(Received in USA 13 August 1991)