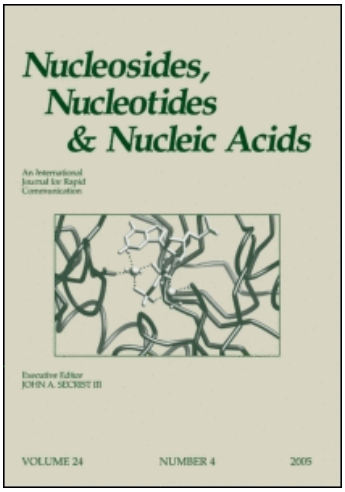

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The Synthesis of Enantiomerically Pure Pyrazolo[4,3-c]pyridine *Carbarzbo* C-Nucleoside

Barbara Mohar[a]; Jože Kobe[a]
[a] National Institute of Chemistry, Ljubljana, Slovenia

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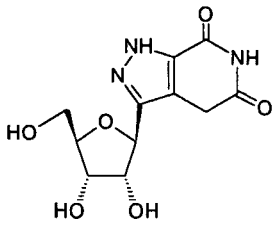
THE SYNTHESIS OF ENANTIOMERICALLY PURE PYRAZOLO[4,3-*c*]PYRIDINE *CARBARIBO C*-NUCLEOSIDE

Barbara Mohar and Jože Kobe*
National Institute of Chemistry, Hajdrihova 19, 1115 Ljubljana, Slovenia

Abstract: The synthesis of (-)-3-[(1*S*,2*S*,3*R*,4*R*)-2,3-dihydroxy-4-(hydroxymethyl) cyclopentan-1-yl]-1H-pyrazolo[4,3-*c*]pyridine-4,6(5H,7H)-dione **3** was accomplished *via* enantiomerically pure carbocyclic 5-(β-D-ribofuranosyl)tetrazole **4**.

Recent studies focused on non-standard base pairs possessing an expanding genetic alphabet patterns support a need for new xanthosine analogues with favourable pK_a values.[1] The pK_a values of xanthosine analogues are certainly the outcome of the number and positions of nitrogens in the base. In this respect, the dioxo derivatives of pyrazolo[3,4-*c*]pyridine[2] **1** and pyrazolo[4,3-*c*]pyridine[3] **2** families of *C*-nucleosides represent interesting and novel classes of compounds of this kind.



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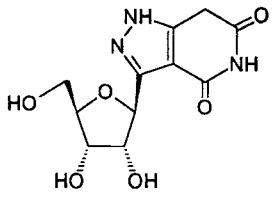

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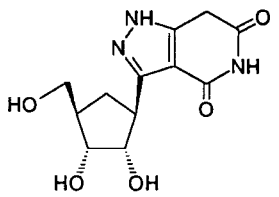
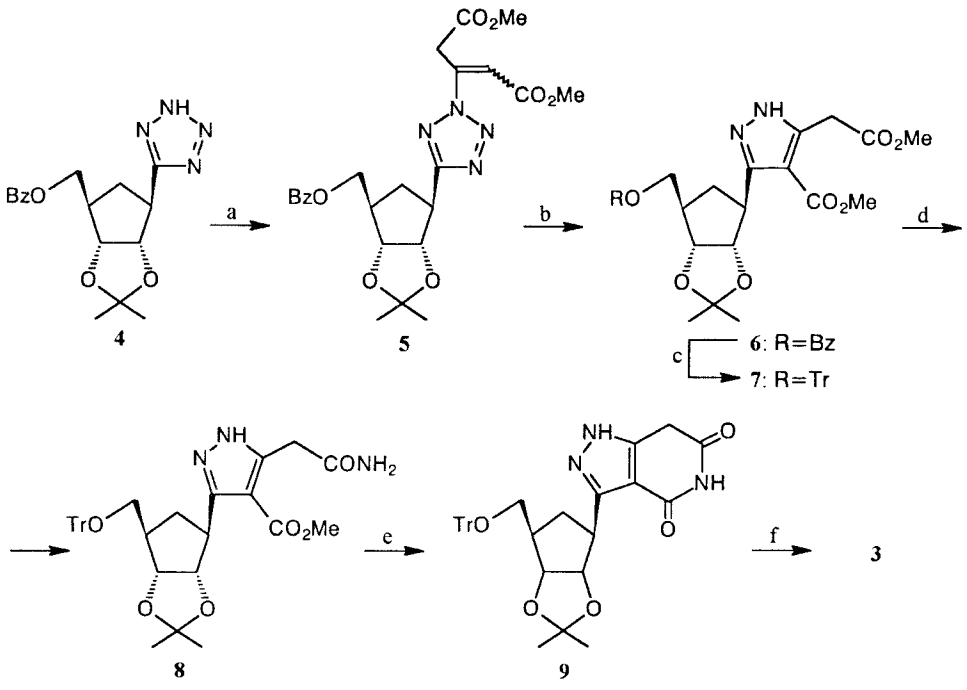


3

Herein, we report on the use of the tetrazole synthon **4**[4] in the formation of sugar modified target *C*-nucleosides. The regiospecific linear synthesis of **2** which has been reported earlier[3] seemed adequate to extend on the enantiomerically pure compound **4** to yield a carbocyclic nucleoside **3** related to 7-substituted 3,7-deaza-8-azaxanthosine **2**.

Thus, tetrazole **4**[4] (Scheme) was transformed into 2-alkenyl tetrazole **5** by its conjugative addition to dimethyl 1,3-allenedicarboxylate.[5] The compound **5** was termally



(a) $MeOCOCH_2C(Cl)=CHCO_2Me$/ Et_3N/ THF, -5°C (η 73%)

(b) xylene, 140°C (η 61%)

(c) i, NaOMe/ MeOH; ii, Ph_3CCl/ Et_3N/ DMAP/ $(CH_2Cl)_2$, 50°C (η 86%)

(d) 25% NH_3 in MeOH (η 97%)

(e) 0.8M NaOMe in MeOH, reflux (η 60%)

(f) 60% aq. CH_3CO_2H (η 90%)

Scheme

rearranged in xylene into pyrazole **6** *via* the ring opening by loss of nitrogen and subsequent intramolecular cyclization. The diester **7** was ammonolyzed to give the monoamide **8**, which readily cyclized after treatment with sodium methylate in boiling methanol to pyrazolo[4,3-*c*]pyridine **9**. Deprotection of **9** with 60% aq. acetic acid furnished the target compound **3**.[6]

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(5) A mixture of tetrazole **4**, Et_3N (1.4 mole equiv.), and dimethyl 3-chloro-2-pentenedioate (1.2 mole equiv.) in THF is stirred at -5°C for 4 h, and concentrated. The residue is dissolved in EtOAc, washed with water, brine, and dried (Na_2SO_4). The concentrated residue is chromatographed on silica gel (eluent petroleum ether/ EtOAc 4:1) to furnish **5** as a light yellow syrup.

(6) Light amber solid, m.p. = 214-5°C (from abs. ethanol). $[\alpha]_D^{21}$ = -48.6 (c 0.5, H_20). ^1H NMR (299.94 MHz, D_2O/ TMS): δ 1.51 (m, 1H, H-5'a), 2.29 (m, 2H, H-4', H-5'b), 3.68 (m, 4H, CH_aH_bOH, H-7_a, H-7_b), 3.91 (m, 1H, H-1'), 3.99 (m, 1H, H-3'), 4.18 (m, 1H, H-2') ppm. ^{13}C NMR (75.43 MHz, Me_2SO-d_6): δ 30.07 (C-5'), 31.86 (br C-7), 40.57 (br C-1'), 46.89 (C-4'), 63.28 (CH_2OH), 73.18 (C-3'), 75.55 (C-2'), 106.23 (C-3a), 148.60 and 149.33 (br C-3, br C-7a), 162.18 (C-4), 171.33 (br C-6) ppm. IR (KBr): 3400 (NH, OH), 1704 (CO) cm^{-1}. FABMS m/z 282 (MH^+).