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SYNTHESIS OF C-NUCLEOSIDES FROM NON-CARBOHYDRATE PRECURSORS. A 2,4-DIOXOIMIDAZOLIDIN-5-YL RIBOFURANOSIDE

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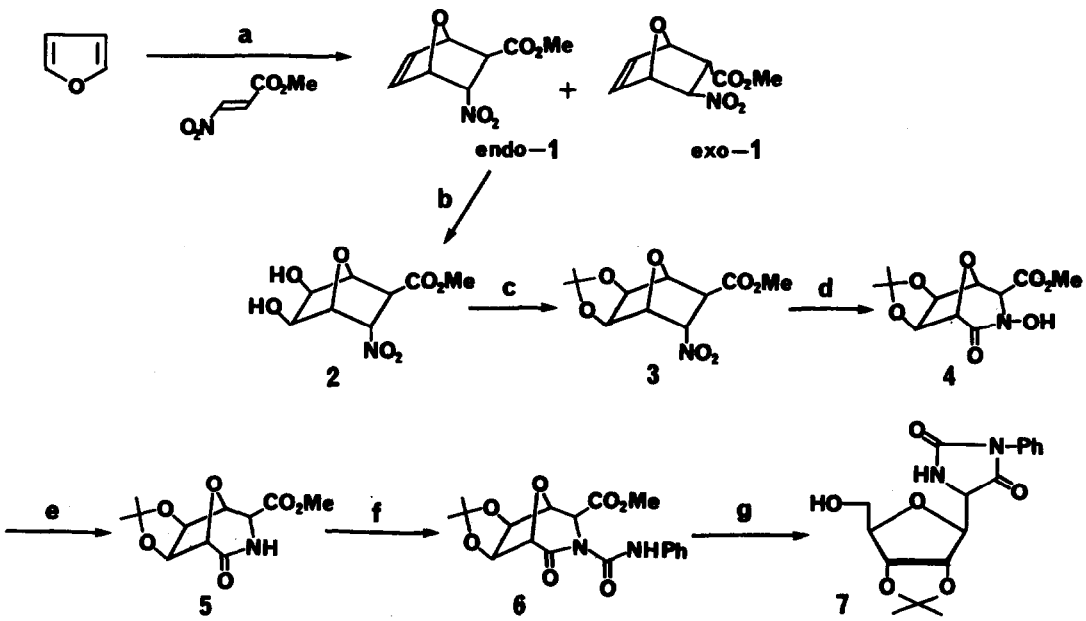
Summary: 3-Phenyl-2,4-dioxoimidazolidin-5-yl ribofuranoside (a hydantoin C-riboside) was synthesized from a Diels-Alder adduct of furan with methyl nitroacrylate.

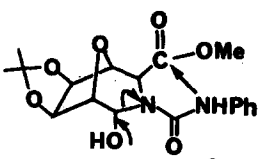
As a part of a program to synthesize C-nucleosides, we have recently reported that a high pressure reaction of furan with dialkyl acetoxymethylenemalonates gave corresponding Diels-Alder adducts,[1] and that the adducts were in turn converted to D,L- and β-D-ribofuranosyl malonates by subsequent hydroxylation and reductive retro aldol reactions.[2,3] It was therefore of interest to expand the scope of this strategy which allows an easy access to C-nucleosides.



Conditions: a, r.t., 14 hr (100 %); b. OsO_4-H_2O_2/acetone, r.t., 24 hr (70 %); c, p-TsOH-$Me_2C(OMe)_2$/ acetone, r.t., 5 hr (>95 %); d, NH_3/MeOH, hν , -10 °C, 3 hr (57 %); e, $TiCl_3$/ H_2O-MeOH, r.t., 1 hr (70 %); f, PhNCO-Et_3N/CH_2Cl_2, r.t., 2 hr (60%); g, $NaBH_4$/ MeOH, 0 °C, 0.5 hr (70 %).

Reaction of furan with methyl 3-nitroacrylate gave the known cycloadducts,[4] *endo*- and *exo*-1, in a ratio of 2:1. The adducts could be separated by chromatography. However, the adduct mixture was immediately hydroxylated with OsO_4 to yield a diol mixture, from which a 2-*endo*-nitro-5,6-*exo*-diol (2) was spontaneously crystallized out in a nearly pure state. After isopropylidenation, the product (3) was photoisomerized[5] to give an bicyclic hydroxamic acid (4) as a sole product. Treatment of 4 with $TiCl_3$ afforded a lactam derivative (5)[6]. The lactam 5 was found to resist to alkaline hydrolysis or reductive ($NaBH_4$) cleavage of the lactam ring. Accordingly introduction of an electron withdrawing group on the lactam N atom was carried out. Thus 5 was treated with phenyl isocyanate to give a urea derivative (6), and subsequent reduction of 6 with $NaBH_4$ proceeded smoothly to give 3-phenyl-2,4-dioxoimidazolidin-5-yl ribofuranoside (7)[7](a hydantoin C-riboside) in 70 % yield.

The formation of 7 was rationalized by taking account of following sequential reactions; a cleavage of the acetal linkage of the primary reduction product (8) gave rise to a C-ribofuranoside having a ureidoacetic acid ester aglycon, and then a nucleophilic ring closure occurred to accomplish the hydantoin aglycon.



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References and notes

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3. N. Katagiri, H. Akatsuka, C. Kaneko, and A. Sera, *Tetrahedron Lett.*, **29**, 5397 (1988).
4. G. Just, A. Martel, K. Grozinger, and M. Ramjeesingh, *Can. J. Chem.*, **53**, 131 (1975).
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6. 6,7-Isopropylidenedioxy-4-methoxycarbonyl-3-aza-8-oxabicyclo[3.2.1]octan-2-one (5): m.p., 167-168 °C; MS, (m/z) 242(M^+-CH_3); ^{1}H NMR ($CDCl_3$), δ 1.33 (s, Me), 1.49 (s, Me), 3.82 (s, Me), 3.87 (d, J=2.5 Hz, H_4), 4.41 (s, H_5), 4.81 (br s, $H_{1,6,7}$), 7.29 (br d, NH); IR (KBr), 1705 (NHC=O), 1740 cm^{-1},
7. 3-Phenyl-2,4-dioxoimidazolidin-5-yl 2,3-O-isopropylidene-β-ribofuranoside (7): m.p., 206-207 °C; MS (m/z), 348 (M^+); ^{1}H NMR (acetone-d_6), δ 1.32 (s, Me),1.50 (s, Me), 3.60-3.75 (m, H_5), 4.05-4.18 (br m, ring-H and OH), 4.35 (q, J= 4Hz, H_4), 4.50 (dd, J=1.5 and 4 Hz, H_1), 4.77 (dd, J=4 and 6.5Hz, H_2), 4.91 (dd, J=4 and 6.5Hz, H_3), 7.42 (s, Ar-H), 7.57 (br, NH); IR (KBr); 3500-3200 (OH), 1714 cm^{-1}(C=O).

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