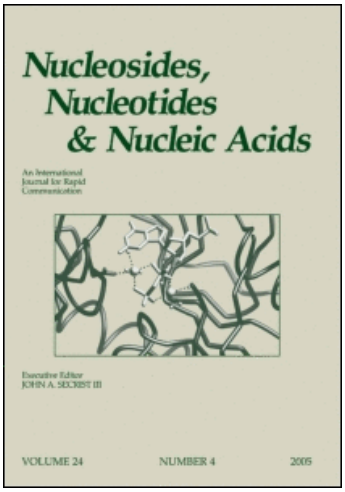

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C-Nucleosides via Glycosyl Alkynyl Ketones. Synthesis of 5(3)-Phenyl-3(5)-(β-D-ribofuranosyl) Pyrazole

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C-NUCLEOSIDES VIA GLYCOSYL ALKYNYL KETONES. SYNTHESIS OF 5(3)-PHENYL-3(5)-(β-D-RIBOFURANOSYL)PYRAZOLE.

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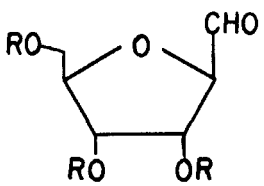
Abstract. A β-D-ribofuranosyl phenylethynyl ketone (3) has been synthesized and shown to be a suitable intermediate for heterocyclic elaboration to C-nucleosides. Cyclization of 3 with hydrazine hydrate produces the title C-nucleoside.

The discovery of C-nucleosides and their antibacterial and antitumor properties[2] has prompted considerable attention to the development of synthetic routes to this fascinating class of compounds.[3] Although a number of synthetic routes have been developed, there are few methods that appear to have the versatility for construction of a variety of heterocyclic systems. Among these are routes that employ heterocyclic elaboration upon glycosyl acetylenes,[4,5] 3-glycosyl acrylates,[6] and 2-glycosyl formylacetates.[7] Our approach to the synthesis of C-nucleosides has been to prepare C-glycosides containing functionalities such that they will be generally suited as intermediates for elaboration to a variety of heterocyclic systems. Herein, we describe one type of such intermediates and its elaboration to a C-nucleoside.

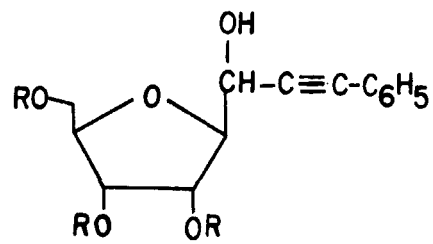
The facility with which acetylenic esters and ketones undergo nucleophilic additions and cyclizations [8-10] has prompted us to investigate the feasibility of synthesizing glycosyl alkynyl ketones and their suitability as versatile intermediates for C-nucleoside synthesis. The desired glycosyl alkynyl ketone was synthesized by the addition of an

alkynyllithium to an anhydroallose followed by oxidation of the resultant acetylenic alcohol. The 2,5-anhydroalloses (1) required for preparation of ribofuranosyl ketones are readily available[11] from 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl cyanide[12], which is a key intermediate in many C-nucleoside syntheses. Treatment of 1a with phenylethynyllithium in THF gave alcohol 2a as an epimeric mixture in 86% yield. The epimers can be separated at this point by chromatography on silica gel, but this is an unnecessary step since the chiral center giving rise to the epimers will be destroyed in the subsequent oxidation. A small sample of 2a was separated by chromatography to give a faster



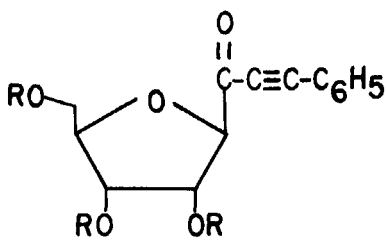
1a R = $C_6H_5CH_2$

1b R = C_6H_5CO

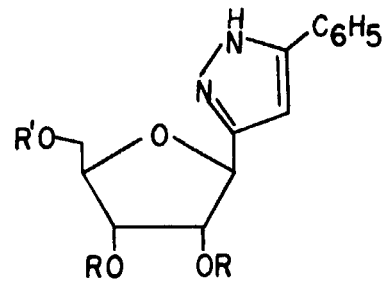


2a R = $C_6H_5CH_2$

2b R = C_6H_5CO



3 R = $C_6H_5CH_2$



4a R = R' = $C_6H_5CH_2$

4b R = R' = H

4c R' = H, R = Me_2C=

moving viscous syrup and a slower moving crystalline solid in a 3:1 ratio, respectively. However, we are uncertain as to which has the D-allo and which the D-altro configuration. Their 90 MHz ^1H NMR spectra show clear differences as typified by the H-8a and H-8b doublets of doublets (see Experimental).

The addition of phenylethynyllithium to 1b to give 2b would have been preferable since benzoyl protecting groups are easier to remove than benzyl protecting groups and the synthesis of 1b involves fewer steps than for 1a; however, all attempts to prepare 2b were unsuccessful. Evidently, there is insufficient difference in reactivity between the aldehyde carbonyl and the benzoate carbonyls in 1b; there is no evidence for the formation of 2b or any products derived therefrom, but NMR spectra of the crude reaction products clearly indicate that debenzoylation has occurred.

Oxidation of 2a to acetylenic ketone 3 in 78% and 68% yields was accomplished by using either the Pfitzner-Moffatt reagent (DMSO-DCC)[13] or the acetic anhydride modification [14] of the Ratcliffe-Rodehorst reagent ($CrO_3 \cdot 2C_5H_5N$-CH_2Cl_2)[15], respectively. Although the yields are generally higher with the Pfitzner-Moffatt reagent, shorter reaction times (1 versus 8h) and a much less involved isolation procedure accompany the modified Ratcliffe-Rodehorst reagent. Numerous other mild and selective oxidizing agents are presently available, and of these we have investigated the oxidation of 2a with $CrO_3 \cdot 2C_5H_5N$,[16] pyridinium chlorochromate,[17] pyridinium dichromate,[18] Jones reagent,[19] phase transfer with dichromate,[20] tetrabutylammonium permanganate,[21] barium manganate,[22] DMSO-oxalyl chloride,[23] and DMSO-trifluoroacetic anhydride.[24] However, all were vastly inferior to the previous two oxidants in our system in that if oxidation of 2a occurred at all, it occurred in less than 10% yield.

Although the instability of 2,5-anhydroaldoses toward eliminations is well-documented,[11b,25] we have not observed any problems with regard to the stability of anhydroketose 3. Based on our experience[26] with simple acetylenic ketones and their propensity towards self-reaction on prolonged storage, we recommend that ketones such as 3 be generated only shortly before use.

Ketose 3 was cyclized to 5(3)-phenyl-3(5)-(β-D-ribofuranosyl)pyrazole (4a) in 36% yield upon treatment with an ethanolic solution of hydrazine hydrate. Only one isomer was detected in the product mixture. Pyrazole 4a is presumed to be the β-isomer since only one isomer was isolated and the initial 2,5-anhydroallose 1a possessed the β configuration. Furthermore, no instances of epimerization have been ob-

served when 2,5-anhydroaldoses[6,11] and anhydroketoses[27] have been subjected to nucleophiles of varying basicity. None the less, further evidence for our β configurational assignment was desired. The H-1′, H-2′ coupling constant criterion[28,29] for C-1′ configurational assignment is obviated since $J_{1',2'}$ = 3.4 Hz in 4a. Therefore, 4a was debenzylated with iodotrimethylsilane[30] to give unprotected C-nucleoside 4b in 50% yield, which was then converted into its 2′,3′- O - isopropylidene derivative 4c by treatment with acetone and perchloric acid. The value of $J_{1',2'}$ for 4c is also inconclusive for C-1′ configurational assignment since $J_{1',2'}$ = 3.4 Hz; however the H-4′multiplicity criterion[31] for isopropylidene derivatives of nucleosides allows an assignment of the β configuration to C-1′ for 4c and thus for 4a and 4b. The H-4′ signal in 4c appears as an "apparent quartet" and is indicative of a β-nucleoside since β-nucleosides display a multiplicity greater than the "apparent triplets" of α-nucleosides. The ^{1}H NMR spectrum of 4c also exhibits a Δδ of 0.27 for the methyl resonances of the isopropylidene group, which is consistent with a β configuration according to the isopropylidene Δδ criterion[32] (Δδ>0.15 for β-nucleosides, Δδ<0.15 for α-nucleosides). Even though the Δδ for 4c in is the correct range for β-nucleosides, we believe the Δδ criterion, which was developed for N-nucleosides, should not be extended to C-nucleosides until a series of α,β-C-nucleoside pairs have been examined. In most of the instances where the Δδ criterion has been invoked for C-nucleosides, only one of the two possible isomers has been available (usually the β-isomer). Furthermore, at least one instance where an isopropylidene-α-C-nucleoside exhibits a Δδ>0.15 has been reported (Δδ = 0.20).[33]

We have also attempted to synthesize 3 in a more direct route by the action of copper(I) or silver acetylides on 3,4,6-tri-O-benzoyl-2,5-anhydro-D-allonyl chloride (5). Although acyl halides normally react with copper(I) and silver acetylides to give acetylenic ketones in good to excellent yields,[34-36] 5 is either unreactive or produces only trace amounts of the desired ketones. We attribute the lack of reactivity of 5 to a combination of the highly aggregated nature of copper(I) and silver acetylides and the somewhat congested nature, as apparent from space-filling models, of the carbonyl function in 5. That this is indeed the case seems to be borne out by the fact that treatment of 5

with silver acetylides of alkyl propiolates in methylene chloride results in the formation of the alkyl esters of 5 in about 40% yields.[37] Evidently the carbalkoxy groups of the acetylides are unencumbered so that ester cleavage by the acyl halide moiety of 5 occurs.

In summary, we have shown that glycosyl alkynyl ketones can be prepared and are suitable intermediates for C-nucleoside synthesis. We are currently looking into other routes to analogs of 3 since the present use of alkynyllithiums places limitations on the functionalities that can be present within the acetylene itself.

EXPERIMENTAL

n-Butyllithium was obtained as a 1.6 M hexane solution from Aldrich and was standardized by titration with 1-octanol using 1,10-phenanthroline as an indicator.[38] THF was freshly distilled from the sodium ketyl of benzophenone just prior to use. DMSO and pyridine were dried by distillation from CaH_2 and stored over 4A molecular sieves under N_2. Acetone and CH_2Cl_2 were dried by distillation from P_2O_5. Benzene was dried by distillation from Na and stored over 4A molecular sieves. All other reagents and solvents were commercial reagents and were used as received. All solvents were removed from reaction products on a rotary evaporator at 40°C or less. All column chromatography was performed on E. Merck silica gel 60 (7734) and all TLC was performed on E. Merck silica gel 60 plates (5539). IR spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. NMR spectra were recorded on a Varian EM390 spectrometer with Me_4Si as an internal standard. UV spectra were recorded on a Cary model 14 spectrophotometer. All new compounds gave acceptable (±0.4%) combustion analyses; all combustion analyses were by Galbraith Laboratories.

4,7-Anhydro-5,6,8-tri-O-benzyl-1,2-dideoxy-1-phenyl-D-glycero-D-allo (and D-altro)-oct-1-ynitol (2a). To a magnetically stirred solution of 755 mg (7.4 mmol) of phenylacetylene in 15 mL of THF at 0°C, under N_2, was added 4.6 mL (7.4 mmol) of n-BuLi via syringe. The solution was stirred at 0°C for 10 minutes and then a solution of 3.2 g (7.4 mmol) of anhydroallose 1a[11] in 10 mL of THF was added during 20 min. After 1 h at 0°C and 0.5 h at ambient temp, the THF was removed

and the residue was partitioned between CH_2Cl_2 and H_2O. The CH_2Cl_2 layer was washed with saturated NaCl solution and dried over anhyd $CaSO_4$. After filtration, the CH_2Cl_2 was removed to give 3.4 g (86%) of 2a as a colorless syrup: IR ($CHCl_3$) 3445 cm^{-1} (OH); NMR ($CDCl_3$) δ 3.33-4.90 (m, 14), 7.03-7.66 (m, 20, ArH).

A small sample of 2a was chromatographed on silica gel eluting with 7:3 (v/v) Hexane/$CHCl_3$ to give the separated epimers in a 3:1 ratio. The faster moving epimer was a colorless syrup: IR 3445 cm^{-1}; NMR ($CDCl_3$) δ 3.59 (dd, 1, $J_{8a,7}$ = 1 Hz, H-8a), 3.83 (dd, 1, $J_{8b,7}$ = 1.5 Hz, H-8b), 4.20-4.90 (m, 11, H-3, H-4, H-5, H-6, H-7, $ArCH_2$), 7.33 (m, 20, ArH). The slower moving epimer was a colorless crystalline solid: mp 75-77°C; IR 3445 cm^{-1}; NMR ($CDCl_3$) δ 3.50 (dd, 1, $J_{8a,8b}$ = 10.5 Hz, $J_{8a,7}$ = 3 Hz, H-8a), 3.72 (dd, 1, $J_{8b,7}$ = 3 Hz, H-8b), 4.00-4.70 (m, 11, H-3, H-4, H-5, H-6, H-7, $ArCH_2$), 7.29 (m, 20, ArH).

4,7-Anhydro-5,6,8-tri-O-benzyl-1,2-dideoxy-1-phenyl-oct-1-yn-3-ulose (3).

Method A: To a magnetically stirred solution of 1.27 g (16 mmol) of dry pyridine in 25 mL of dry CH_2Cl_2 was added 800 mg (8 mmol) of anhyd CrO_3. After 0.5 h, a solution of 1.10 g (2 mmol) of 2a (epimeric mixture) in 10 mL of CH_2Cl_2 was added to the deep red solution; the color of the solution turned to brown. Acetic anhydride (0.8 mL) was added and the mixture was stirred for an additional 1 h, at which time TLC indicated the oxidation was complete. The reaction mixture was transferred to a 4 x 25 cm column of silica gel and eluted with $CHCl_3$ to give 720 mg (68%) of 3 as a yellow syrup which was homogeneous by TLC: IR ($CHCl_3$) 2190 (C≡C), 1680 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.70 (d, 2, $J_{8,7}$ = 4.5 Hz, H-8), 3.80-4.90 (m, 10, H-4, H-5, H-6, H-7, $ArCH_2$), 6.98 (m, 20, ArH).

Method B: A solution of 310 mg (1.5 mmol) of dicyclohexylcarbodiimide and 1 mL of DMSO in 5 mL of dry benzene was magnetically stirred for 10 min, and then a solution of 265 mg (0.5 mmol) of 2a (epimeric mixture) in 5 mL of dry benzene and 5 mg of anhyd H_3PO_4 were added. TLC indicated the oxidation was complete after 8 h. The mixture was diluted with 10 mL of EtOAc followed by addition of 150 mg of oxalic acid dissolved in 5 mL of MeOH. After 0.5 h, the N,N'-dicyclohexylurea

was removed by filtration. The filtrate was washed with 5% of $NaHCO_3$ and H_2O and dried over anhyd Na_2SO_4. After filtration, the solvent was removed and the residue was treated with 8 mL of benzene. Filtration and evaporation of the filtrate to dryness gave 210 mg (78%) of 3 as a yellow viscous syrup identical in all respects to the product from Method A.

3(5)-(2,3,5-Tri-O-benzyl-β-D-ribofuranosyl)-5(3)-phenylpyrazole (4a)

To a magnetically stirred solution of 400 mg (0.75 mmol) of 3 in 10 mL of absolute EtOH was added 0.3 mL of 99% hydrazine hydrate. After 20 h, the solvent was removed and the residue was chromatographed on a 5 x 30 cm column of silica gel, eluting with $CHCl_3$, to give 140 mg (36%) of a colorless syrup which was homogeneous by TLC: UV λ_{max}^{MeOH} 250.5 (ε_{mM}1.18), 256 (1.08) 263 (9.40), 270 nm (7.46); NMR ($CDCl_3$) δ 3.55 (dd, 1, $J_{5'a,5'b}$ = 10.5 Hz, $J_{5'a,4}$ = 2.3 Hz, H-5'a), 3.77 (dd, 1, $J_{5'b,4}$ = 3 Hz, H-5'b), 3.95-4.70 (m, 9, H-2', H-3', H-4', $ArCH_2$), 5.23 (d, 1, $J_{1'2'}$ = 3.4 Hz, H-1'), 6.35 (s, 1, H-4), 7.10-7.70 (m, 20, ArH).

5(3)-Phenyl-3(5)-(β-D-ribofuranosyl)pyrazole (4b). To a magnetically stirred solution of 450 mg (0.82 mmol) of 4a in 8 mL of $CHCl_3$, under N_2, was added 0.5 mL (730 mg, 3.65 mmol) of Me_3SiI via syringe. After 6 h, an additional 0.2 mL of Me_3SiI was added and the mixture was allowed to stand overnight. After the mixture had been stirred for 0.5 h with MeOH, the solvent was removed and the residue was dissolved in H_2O. Extraction of the H_2O solution with CH_2Cl_2 removed most of the iodine color. The H_2O was removed and the residue was chromatographed on a 2 x 25 cm column of silica gel, eluting with 85:15 (v/v) $CHCl_3$/MeOH, to give 110 mg (50%) of 4b as a pale yellow syrup. The syrup was further purified by dissolving it in 85:15 $CHCl_3$/MeOH and passing it through a Waters Associates SEP-PAK™ silica cartridge. There was negligible loss of material and 4b was obtained as a homogeneous (TLC) colorless syrup: UV λ_{max}^{MeOH} 251 nm (ε_{mM} 9.61); NMR ($(CD_3)_2SO$) δ 3.47-3.66 (m, 2, H-5'), 3.70-4.20 (m, 3, H-2', H-3', H-4'), 4.72 (d, 1, $J_{1',2'}$ = 5.3 Hz, H-1'), 6.67 (s, 1, H-4), 7.20-7.60 (m, 3, ArH), 7.67-7.93 (m, 2, ArH).

3(5)-(2,3-O-Isopropylidene-β-D-ribofuranosyl)-5(3)-phenyl pyrazole (4c). Treatment of 4b with anhyd acetone and 70% $HClO_4$ followed by chromatography on a 2 x 25 cm column of silica gel, eluting with 97:3 (v/v) $CHCl_3$/MeOH gave 85 mg (74%) of 4c as a pale yellow syrup. Isopropylidene 4c was further purified as for 4b with negligible loss to give a homogeneous (TLC) colorless syrup: UV λ_{max}^{MeOH} 250.5 nm (ϵ_{mM} 14.7); NMR ($CDCl_3$) δ 1.30 (s, 3, exo-CH_3), 1.57 (s, 3, endo-CH_3), 3.67 (dd, 1, $J_{5'a,5'b}$ = 12 Hz, $J_{5'a,4'}$ = 3.6 Hz, H-5'a), 3.93 (dd, 1, $J_{5'b,4'}$ = 2.4 Hz, H-5'b), 4.30 ("apparent q", J_{app} = 3 Hz, H-4'), 4.79 (dd, 1, $J_{2',3'}$ = 6.5 Hz, $J_{1',2'}$ = 3.4 Hz, H-2'), 4.89 (dd, 1, $J_{3',4'}$ = 2.6 Hz, H-3'), 5.15 (d, 1, $J_{1',2'}$ = 3.4 Hz, H-1'), 6.47 (s, 1, H-4), 7.20-7.46 (m, 3, ArH), 7.50-7.70 (m, 2, ArH).

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