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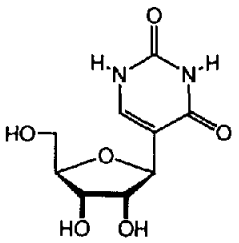
ERYTHROSE *SESQUI*-ACETALS AS ELECTROPHILES. 2-DEOXY-C-NUCLEOSIDES FROM D-GLUCOSE.

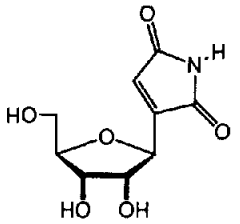
Robin Polt* and Thusitha Wijayaratne
Chemistry Department, University of Arizona, Tucson, Arizona 85721

Summary: *Cleavage of glucosides with $NaIO_4$ in MeOH furnishes sesqui-acetals (protected dialdehydes). Olefination of these substrates, followed by endocyclic oxymercuration-demercuration furnishes substituted tetrahydrofurans (1,2-dideoxy-1-aryl-D-ribofuranoses). Proper choice of protecting groups can affect the face selectivity of the oxymercuration step to provide only the desired β-C-anomer.*

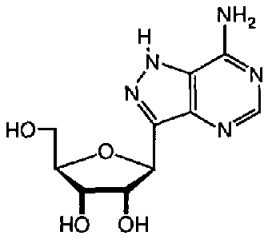
There has been considerable interest in C-nucleosides and various analogs as drugs, and for incorporation into DNA duplexes to examine the factors affecting helix stability.[1-3] Strong antibiotic, antitumor, and antiviral activities[4] have been associated with C-nucleosides which may replace essential metabolites[2] (inhibitors or anti-metabolites), or as substitutes for essential metabolites (RNA/DNA terminators). Many naturally occurring C-nucleoside analogs have been isolated and synthesized[5]- e.g. pseudouridine, showdowmycin, and formycin.



Pseudouridine



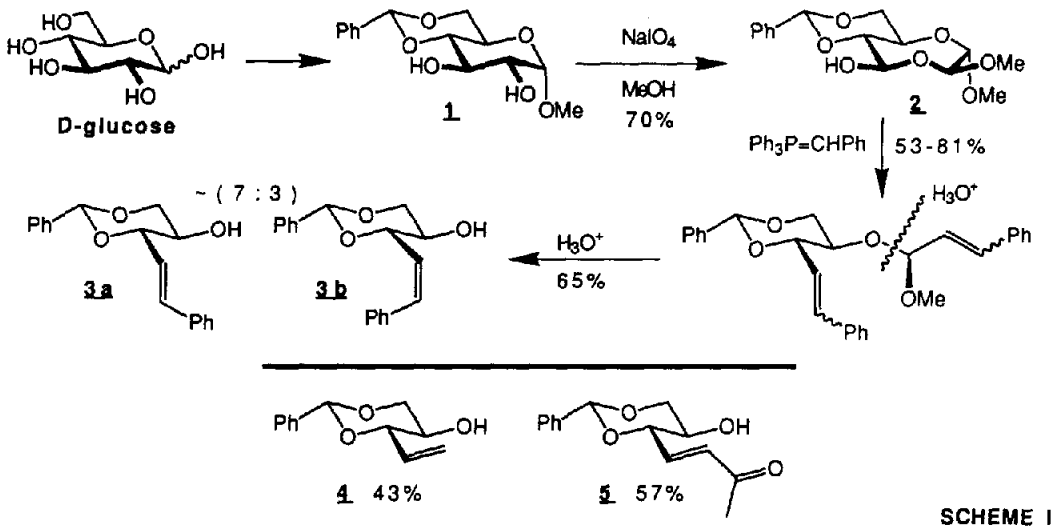
Showdowmycin



Formycin

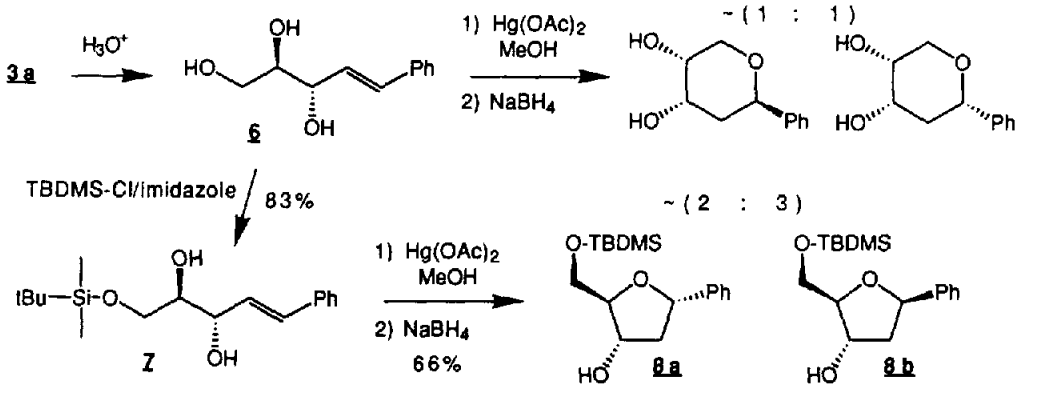
Our concern with this class of compounds stems from our interest in 4-carbon chiral building blocks.[6] Glucose provides access to D-erythrose compounds via oxidative removal of two carbons.[7] By retaining the two carbons which are oxidatively cleaved as a glyoxal acetal-*sesqui*-acetal (*c.f.* the related "dialdehydes"[8]), we have simplified the isolation of a fully-protected erythose derivative.

The carbohydrate precursors arabinose,[9a] xylose,[9b] glucose,[5e,9c] glyceraldehyde,[9d,e] and ascorbic acid[9f] have been used previously for the synthesis of the deoxypentafuranose ring system. In 1979 Rapoport[10] synthesized 3,5-ethylidene 2-*deoxy*-ribose from 2,4-ethylidene erythrose. We have utilized a similar approach to produce 2-*deoxy*-C-nucleosides. Starting with the benzylidene glucoside **1**, $NaIO_4$ oxidation[11] *in anhydrous methanol* provided the crystalline *sesqui*-acetal **2** (m.p. 150-152°) in ~70% yield. (**Scheme I**)



SCHEME I

Treatment of **2** with the benzylidene Wittig generated in THF with $NaNH_2$ provided good yields of a mixture of isomeric bis-olefins. The exocyclic acetal, now allylic, underwent selective cleavage in aqueous acidic THF to yield the two styrene isomers **3a** and **3b** (**Scheme I**). Compounds **4** and **5** were prepared in a similar fashion from **2** using the methylene Wittig reagent, and the Horner-Emmons reagent prepared from dimethyl(2-oxopropyl)phosphonate in 43% and 57%, respectively. Olefination with more basic methoxy- and benzyloxy-substituted Wittig reagents failed due to β-elimination of the exocyclic acetal from the erythrose substrate.

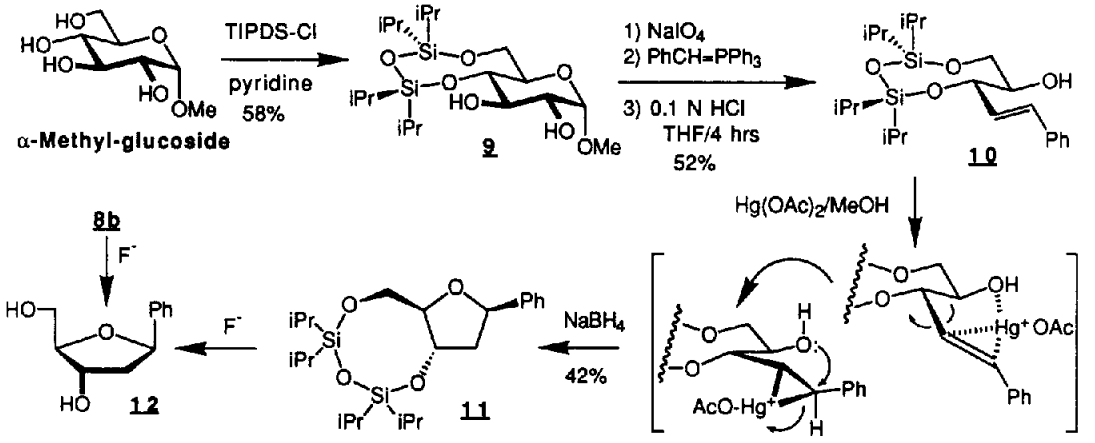


SCHEME II

Although Henbest reported a Hg^{++} promoted ring closure [5-endo-trig] of a bis-homo-allylic alcohol in 1959,[12] the intervening years provide almost no examples of such cyclizations.[13] Several attempts to cyclize **3a** using various solvents and Hg^{++} salts provided no trace of the desired C-nucleoside.

(**Scheme II**) Cleavage of the benzylidene ring provided the triol **6**, which yielded three of the four possible products arising from cyclization of the 1° alcohol upon treatment with $Hg(OAc)_2$ in MeOH. We therefore silylated the offending 1° alcohol, and proceeded. The olefinic siloxy diol **7** was treated with $Hg(OAc)_2$ in THF at 0°C for 30 minutes, followed by $NaBH_4$ to provide the desired ribofuranose compounds **8a** and **8b** in 66% yield as a 2:3 ratio of α/β anomers. The anomers were separated by flash and fully characterized (IR, ^1H, ^{13}C, MS & $[\alpha_D]$). Cleavage of the silyl group from **8b** provided the known[3] *deoxy*-C-nucleoside **12**. (see **Scheme III**)

Thus, in the absence of a more favorable cyclization pathway, the anti-Baldwin cyclization[14] proceeds without difficulty. We reasoned that a 1,3-diol protecting group more flexible than benzylidene might permit 5-endo-trig cyclization, *and influence the α/β anomer ratio* (**Scheme III**). Use of the tetraisopropyldisiloxane (TIPDS) protecting group[15] not only accomplished these goals, but increased the yield of the desired *trans*-olefin as well. (The *cis*-isomer does not cyclize.[12]) The glucoside **9** provided a *single* geometric isomer **10** upon oxidation, olefination, and selective hydrolysis. Cyclization as before provided a *single* cyclic product **11**, which also produced diol **12** upon desilylation.



SCHEME III

We attribute this dramatic change in α/β ratio to a decrease in the dihedral angle between the hydroxyl and the styryl group, coupled with decreased access to one face of the styrene double bond. In effect, the Hg^{++} ion may be directed to one face of the styrene double bond by the hydroxyl,[13] and away from the other face by the disiloxane moiety, resulting in the high diastereoselectivity.

It is noteworthy that the synthetic approach described in this paper is short and highly convergent. Work is presently underway to extend this methodology to more biologically relevant targets by using heterocyclic Wittig reagents.[1c,16]

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