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Short Synthesis of Octosyl Nucleosides

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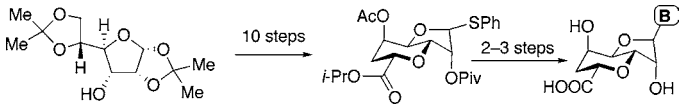
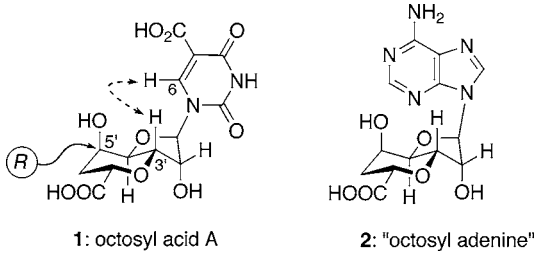
ABSTRACT



Commercial 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose was converted to a protected bicyclic octosyl acid thioglycoside donor by a 10-step sequence that features an intramolecular ester enolate alkylation. Glycosylation of *N*-benzoyladenine and methyl uridine-5-carboxylate followed by deprotection gave the respective nucleosides "octosyl adenine" and octosyl acid A.

Complex nucleoside antibiotics are diversely polyfunctional targets.[1] A synthetic strategy can either feature (a) "early glycosylation," which requires chain, ring, and functional group elaboration of a commercially available or early-route nucleoside, or (b) "late glycosylation," in which *N*-glycosylation of a purine/pyrimidine acceptor with a higher sugar donor occurs toward the end of the route. The challenges have been successfully met in a variety of instances, but other attractive synthetic approaches have foundered because seemingly basic steps such as glycosylation, C−C bond formation, and protecting group removal are more troublesome in these complex molecular settings than in simpler furanoside or nucleoside frameworks. The various approaches[2−11] to the synthesis of octosyl acid A (**1**, Figure 1)[12] illustrate the difficulties, particularly with respect to the timing of the introduction of the pyrimidine vs formation of the strained trans-fused 1,5-dioxabicyclo[4.3.0]nonane ring system. The three pioneering syntheses[2−4] of **1** made use of the chain extension at C-5′ and then intramolecular Williamson ether formation,[2,4] or an oxymercuration,[3] to fuse the tetrahydropyran ring onto an existing nucleoside. In no case was the pyrimidine introduced *after* formation of the bicyclic glycon, even though this might be considered a more convergent and versatile strategy.[13] A promising approach[5] to **1** described the prior assembly of a bicyclic glycon, but standard activation at C-1′ for Vorbrüggen coupling[14] to a pyrimidine was unsuccessful (Scheme 1), the failure being "attributed to the susceptibility of the 3,7-anhydrooctose skeleton to



1: octosyl acid A **2**: "octosyl adenine"

Figure 1. Octosyl nucleoside targets.

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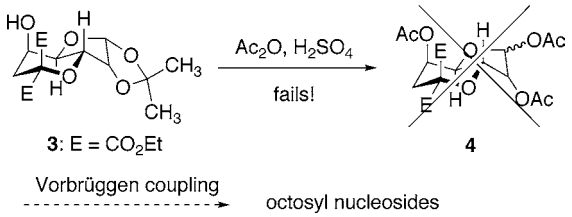
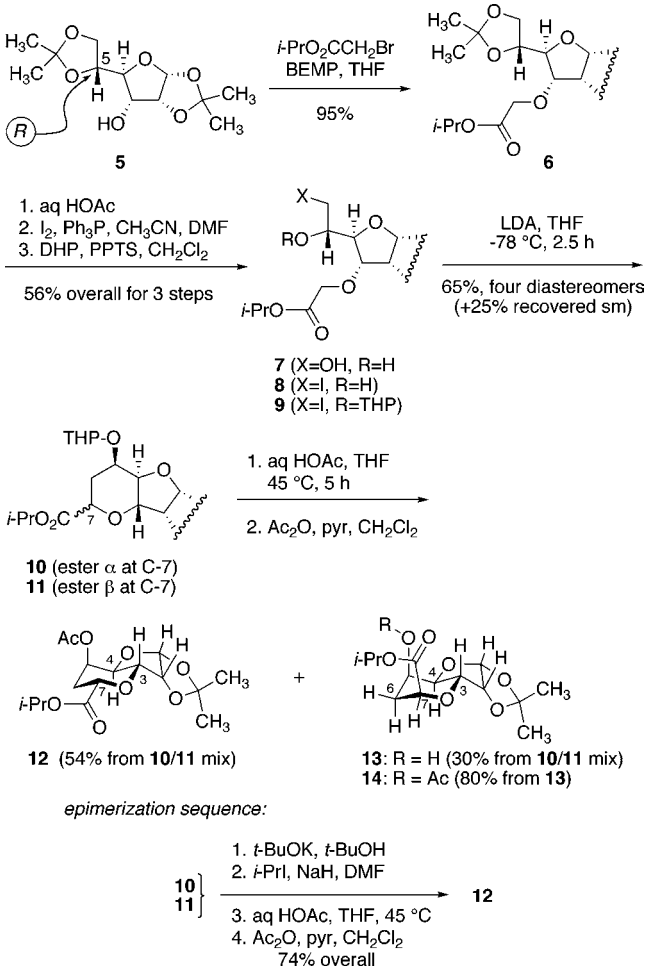
Scheme 1. Attempted Preparation of Octosyl Anomeric Acetate



Scheme 2. Synthesis of the 3,7-Anhydrooctulonate



acids".[5] Given that the adenine analogue of **1**, "octosyl adenine" (**2**) shows more pronounced biological activity than **1** (**2** competes with cAMP for cyclic AMP phosphodiesterases[15]), a late glycosylation approach to this class of complex nucleosides, in which the pyrimidine or purine could be varied, might have value.[13b] Furthermore, synthetic steps would be saved if commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**5**, Scheme 2), which already matches at C-5 the C-5′ stereochemistry of **1** and **2**, could be used as the starting material. We are pleased to report the syntheses of **1** and **2** by successful implementation of this late glycosylation strategy.

Alkylation of **5** at O-3 with isopropyl bromoacetate occurred smoothly in the presence of the strong soluble base 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine[16] (BEMP, Scheme 2). Selective hydrolysis of the 5,6-*O*-isopropylidene of **6** was followed by conversion of the primary hydroxyl to an iodide (**8**) and then protection of O-5 as the THP ether (**9**). Intramolecular alkylation of the ester lithium enolate[17] of **9** was successful in dilute solution (2.6 mM), whereas at higher concentrations intermolecular Claisen condensation siphoned away the starting material. The product was obtained as a mixture of two stereoisomers at C-7, **10** and **11** (each a mixture of THP diastereomers), along with recovered **9**. The stereochemical picture became clearer after conversion of **10**/**11** by hydrolysis and acetylation to the desired C-7 isomer **12** (54% yield from **10**/**11**) and the C-7 epimer **13** (30% from **10**/**11**), each of which was isolated and characterized. The hindered C-5 hydroxyl of **13** had not acetylated, but the acetyl group could be added in a followup step to provide **14**. First-order vicinal coupling constants, particularly those of the H-6 and H-7 protons, allow assignment of the configuration and conformation of **12** and **14**, as shown in Scheme 2. For example, H-7 for **12** appears as a dd (J = 2.7, 12.3 Hz), reflecting respective *ax-eq* and *ax-ax* couplings with the H-6's, whereas H-7 for **14** is a d (J = 6.8 Hz; < 1 Hz coupling to the *trans* H-6).

The modest stereoselectivity (**10**/**11** = 1.8:1) for the intramolecular ester enolate alkylation may be attributed to the availability of reasonably uncongested transition states A (chairlike) and B (boatlike) for the respective modes of cyclization (Figure 2). Fortunately, the undesired epimer **11** in the **10**/**11** mixture could be converted to the desired isomer **12** by an epimerization sequence (Scheme 2) that consists

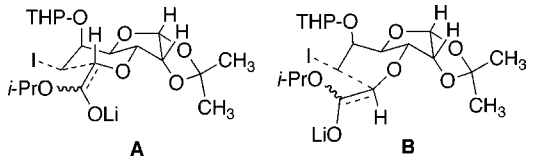


Figure 2. Stylized transition states for intramolecular alkylation.

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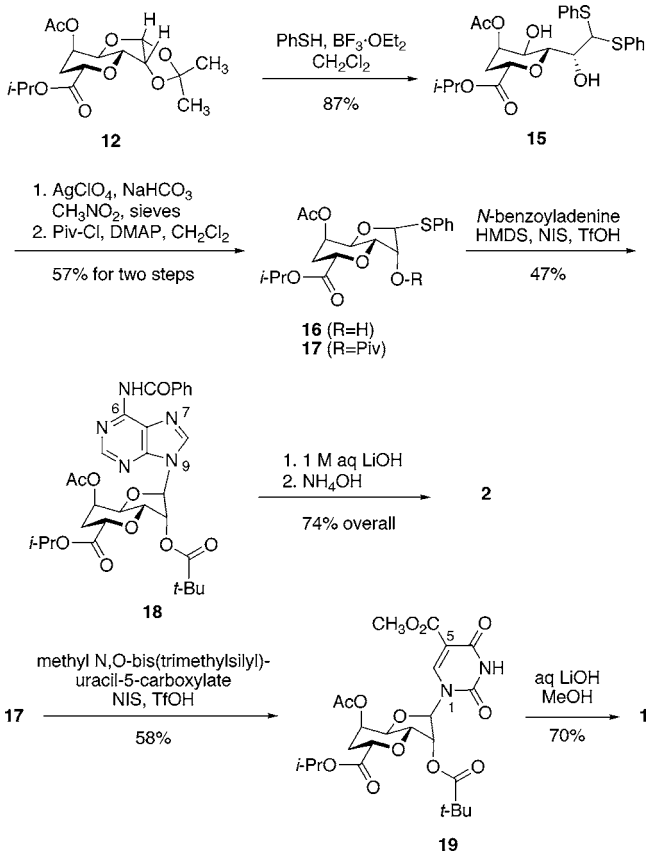
of treatment of the mixture with *tert*-butoxide, replacement of any isopropyl lost to hydrolysis by carboxylate *O*-alkylation, hydrolysis of the *O*-THP at C-5, and then acetylation. In this way, **12** could be produced from **10**/**11** in 74% overall yield, 48% from **9** (64% based on recovered **9**). The synthetic route to 3,7-anhydroocturonic ester **12** is relatively short and efficient, but of little use if C-1 cannot be activated for nucleosidation.

In converting **12** to a donor for *N*-glycosylation, we employed the Lewis acid mediated acetal exchange reaction of acetonides with mercaptans.[18] Thus, **12** was converted to the ring-opened bis(phenylthio)acetal **15** (Scheme 3), and

Scheme 3. Donor Preparation, Glycosylations, and Deprotection



then **15** was closed to the thioglycoside **16** with promotion by Ag(I)[19] and participation of O-4. Although the anomeric stereochemistry was not determined with certainty, **16** was obtained as a single isomer. Subsequent pivaloylation at O-2 to give **17** proceeded very slowly, suggesting that the nearby (*cis*?) phenylthio substituent hinders acylation, as had been observed with a related thioglycoside.[20] As thioglycosides of either stereochemistry are effective donors for *N*-glycosylation,[21,22] **17** ought to serve as a precursor to a variety of octosyl nucleosides, including **1** and **2**, differing only in the identity of the nucleobase.

Both glycosylations proved successful (Scheme 3). Treatment of a mixture of **17** and silylated N_6-benzoyladenine with *N*-iodosuccinimide and triflic acid[22] led to the protected nucleoside **18** along with a small amount of an isomer, probably N-7 glycosylated. Deprotection with aqueous lithium hydroxide removed the acetyl and pivaloyl groups and hydrolyzed the isopropyl ester, but not the *N*-benzoyl, which promotes deprotonation at N-6 under these conditions.[23] Subsequent ammonolysis, however, removed the remaining protecting group, and the product **2** was isolated and characterized by its mass spectrum and fully assigned proton and carbon NMR spectra. In particular, the singlet for H-1′ of **2** is diagnostic for octosyl nucleosides of the desired stereochemistry, and the respective chemical shifts for C-4 and C-5 (148.5 and 119.1 ppm) match those of adenosine (149.2 and 119.5) but not 7-(β-D-ribofuranosyl)-adenine (160.7 and 110.2).[24] A literature description of **2** (which was prepared by a nucleoside transglycosylation sequence starting with **1**)[25] includes chemical shifts for H-1′, H-2, and H-8 that match our values.

The option to activate the anomeric center of **12** for *N*-glycosylation as a thioglycoside, rather than the more usual anomeric acetate, was crucial to the success of this route. The question[26] has been posed: "Why not use the protected 1-*O*-acyl or 1-*O*-alkyl sugars for nucleoside synthesis instead of the corresponding 1-phenylthio sugars, which entail additional reaction steps and bad smelling thiophenols?" The syntheses of **1** and **2** and several additional targets[13b,21,27,28] provide the answer: In a complex synthetic undertaking, the thioglycoside is often a more effective way to prepare the anomeric center for late *N*-glycosylation.

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Supporting Information Available: Experimental details and spectral characterization of new compounds, including copies of ^{13}C and ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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