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Note

The use of tri-*O*-acetyl-D-glucal and -D-galactal in the synthesis of ω-aminoalkyl 2-deoxy- and 2,3-dideoxy-D-hexopyranosides

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ABSTRACT

We report a simple, efficient, and mild method for the synthesis of ω-aminoalkyl 2-deoxy-D-*arabino/lyxo*-hexopyranoside and 2,3-dideoxy-α-D-*erythro*-hexopyranoside. The total synthesis is accomplished in two sequential reactions. The first step consists of an addition reaction of *N*-(ω-hydroxyalkyl)phthalimide and *N*-(ω-hydroxyalkyl)succinimide to peracetylated D-glycals, which is promoted by triphenylphosphine hydrobromide or borontrifluoride/diethyl etherate. The second step involves reacting the appropriate glycoside with methylamine.

The cyclic imides of dicarboxylic acids are versatile tools for introducing an amino group into a target molecule; in particular, phthalimide is a useful reagent for preparing several amino-deoxysaccharides, and it can also be used to synthesize nucleosides bearing amino groups.[1–3] Cyclic imides themselves exhibit interesting pharmacological properties. Thus, succinimide derivatives are used as anticonvulsants to control seizures in the treatment of epilepsy. These medicines act on the central nervous system (CNS) to reduce the number and severity of seizures.[4–6] Phthalimide derivatives possess a broad spectrum of biological activity. The N-substituted phthalimides exhibit cytostatic,[7] anti-inflammatory,[8] and hypolipidemic[9] activities. *N*-Arylphthalimdes can lower serum cholesterol and triglyceride levels,[10] and they have been reported to have antimicrobial activity.[11] The phthalimide moiety is present in thalidomide which inhibits tumor necrosis factor-α (TNF-α).[12,13]

As part of our research, we are interested in the synthesis of 1-(2-deoxy-D-hexopyranosyl)- and 1-(2,3-dideoxy-D-hexopyranosyl)-ω-aminoalkoxyalkanes. Previously, Petrig et al. reported the four-step synthesis of 2′-aminoethyl-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranoside toluene-4-sulfonic acid salt.[14] The first step of the synthesis is the glycosylation of tri-*O*-acetyl-D-glucal with ethylene glycol to give the corresponding alcohol of 2-deoxyglucose. Next, the 2-hydroxyethyl 3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucoside is tosylated to give the appropriate tosylated product, which is converted to an azide using NaN_3. Finally, the reduction of 2-azidoethyl 3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucoside yields the corresponding amine as a toluene-4-sulfonic acid salt.

D-Glycals react with simple alcohols in the presence of triphenylphosphine hydrobromide to produce glycosides,[15–18] and this reaction occurs without Ferrier rearrangement. We decided to apply this reaction strategy to the preparation of *N*-phthalimidoalkyl and *N*-succinimidoalkyl D-hexopyranosides, which are useful reagents for building heterocyclic rings on unmasked amino groups. Prior to the addition reaction, the amino alcohols **1a** and **1b** were transformed into the appropriate imide derivatives by refluxing with phthalic anhydride **2a** and succinic anhydride **2b**, respectively, in solvent-free medium, as described elsewhere.[19–21] After recrystallization from ethanol, the imide derivatives **3a–d** were obtained in satisfactory yield (Scheme 1).

The *N*-(ω-hydroxyalkyl)imides **3a–d** were coupled with the commercially available glycals 3,4,6-tri-*O*-acetyl-D-glucal **4a** and 3,4,6-tri-*O*-acetyl-D-galactal **4b**. Preliminary trials carried out using D-glucal **4a** and *N*-(2-hydroxyethyl)phthalimide **3a** as reagents indicated that the addition reaction proceeded efficiently when 1 equiv of unsaturated sugar **4a** was treated with 1.1 equiv of **3a** in the presence of 0.15 equiv of catalyst in anhydrous dichloromethane at room temperature (Scheme 2).

The product of addition, **5a**, was obtained in 89% yield (Table 1, entry 1). Inspection of ^1H NMR and ^{13}C NMR spectra revealed the predominant diastereomer to be the α-anomer. In all reactions involving imide substrates **3a–d** and glucal **4a**, the main products possess a trans configuration with respect to the acyl group present on carbon C-3 of the pyranosyl ring. The amounts of cis isomer vary between 10% and 18% (entries 2–4). In the case of D-galactal

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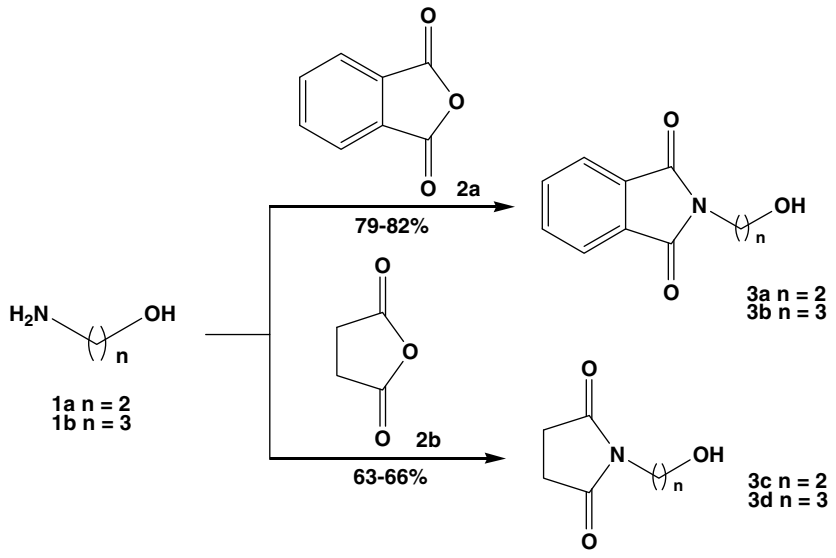
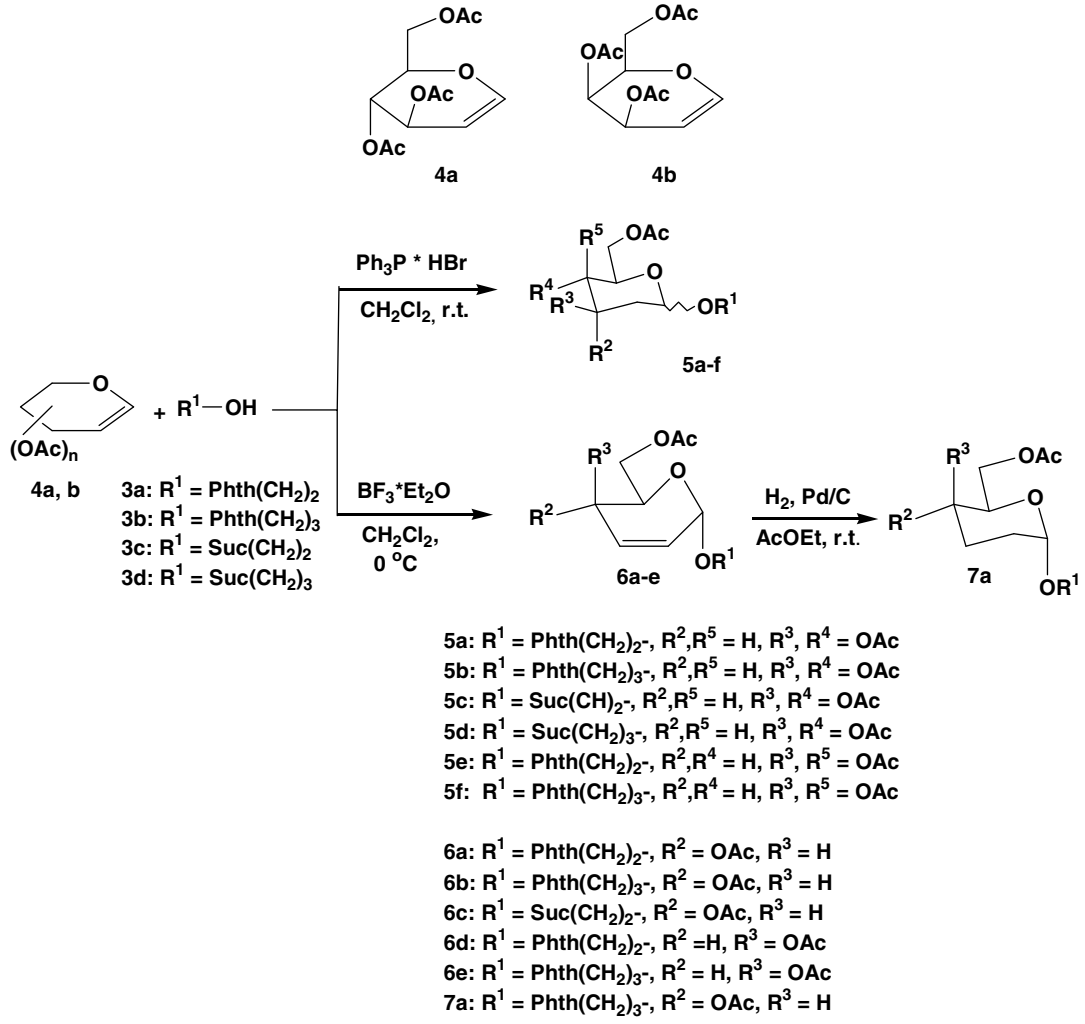


Scheme 1.



Scheme 2.

derivatives **5e**–**f**, only α-anomers were detected in the post-reaction mixture (entries 5 and 6). Attempts to separate the anomers were unsuccessful.

For comparison, we decided to repeat the reaction of the *N*-phthalimidoalkyl compounds **3a** and **3b** and *N*-succinimidoalkyl derivative **3c** with D-glycals **4a** and **4b** in the presence of borontri-