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Synthesis and characteristics of sugar-phosphoramidates: A spectroscopic study

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ABSTRACT

Phosphoramidate-incorporated scaffolds are structurally important targets owing to their diverse applications, particularly in medicinal chemistry. Herein we report the synthesis of several sugar phosphoramidates in excellent yields. NMR analyses were undertaken to examine their intramolecular H-bonding, stability under acidic conditions, and chemical shift effects.

Organophosphorus compounds are well known for their unique properties and significant biological functions [1], being present in many essential biomolecules [2] notably glycosyl phosphates, phospholipids and nucleic acids. Phosphoramidates may be considered as being derivatives of phosphoramidic acid where the nitrogen bound substituents = aryl, alkyl and heteroaryl [3]; or phosphates where an -*OR* moiety is replaced by -NR_2 [4]. These latter azaphosphane motifs are of particular interest owing to their diverse industrial applications [5,6].

Phosphoramidate moieties are present in many biologically and pharmaceutically important molecules. These include potent anticancer [7], anti-bacterial [8], insecticidal [9], anti-malarial [10], anti-protozoal [11] and anti-viral [12] agents. The Phosphoramidate ProTide strategy is becoming increasingly popular as it demonstrates exceptional promise in drug design [13]. The enhanced lipophilicity imparted improves cellular penetration of drugs; and the approach overcomes the rate limiting *in vivo* phosphorylation step of nucleosides [13,14]. An interesting example of a phosphoramidate containing drug involves brivudine (1) (BVdU) which is effective in inhibiting the *Herpes simplex virus type 1* (HSV-1) [15]. The inclusion of a benzyl derived phosphoramidate within the BVdU scaffold led to thymectacin (2), a selectively active anticancer prodrug (Fig. 1) [16].

Other selected examples include diphenyl phosphoramidate derivatives exhibiting twice the activity as the quinolone antibiotic, Ciprofloxacin [17]; as well as a dioxolane sugar phosphoramidate derivative possessing 1070-fold greater antiviral potency than its parent structure [18]. *Campylobacter jejuni*, a member of the epsilon † proteobacteria, is currently one of the leading causes of gastroenteritis worldwide [19].

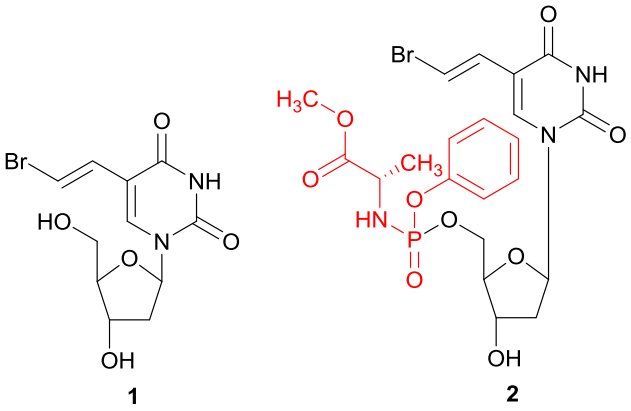

Fig. 1. Structure of brivudine (1) and thymectacin (2).

The capsular polysaccharides (CPSs) present on the surface of almost all *C. jejuni* strains consist of the *O*-methyl phosphoramidate functionality [19–21]. It has been speculated that the pathogenicity and virulence of the bacterium is significantly influenced by this portion of the CPSs [21]. Apart from their extensive contribution to the medicinal arena, phosphoramidates are also widely utilized as flame retardants due to the *P-N* bond synergistic effect [22]; chiral ligands for metal catalyzed reactions [23];

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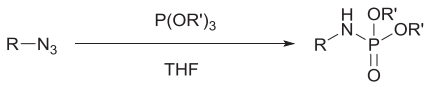
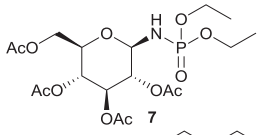
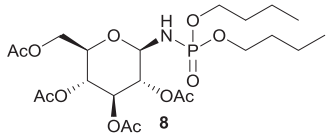
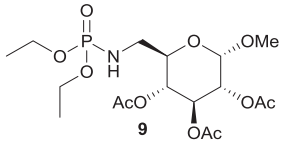
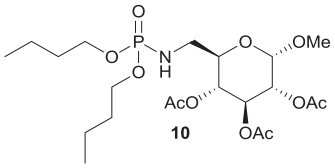
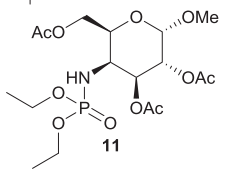
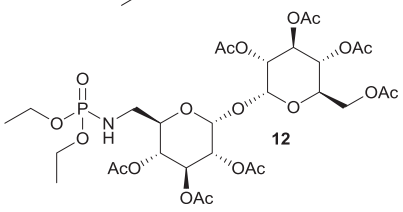
organocatalysts for several popular organic transformations [24]; antirust agents in lubricating oils [25]; and in mass spectrometry to improve ionization efficiency [26].

Owing to their importance, various methods have been developed for the efficient synthesis of phosphoramidates. Conventional approaches include: the Atherton-Todd reaction [27] and the Staudinger-phosphite reaction [28]. More recently reactions involving: phosphoryl halides and amines [29]; amines and phosphonates [30]; nitroarenes and trialkyl phosphites [31]; halides and phosphites [32]; as well as the Ir catalyzed *C-H* amidation in generating the *C-N* linkage have been described [33,34].

There are only a few reports of sugar-based phosphoramidates. Carbohydrate methyl phosphoramidate derivatives have been synthesized and investigated under various deprotection conditions [35,36]. Another study describes the synthesis of symmetrical glycosyl phosphites which were then coupled with azido peptides and polyglycerols [37]. Most of these examples however, involve the sugar being one of the alkoxy substituents on the phosphorus atom. Herein we report the synthesis of six novel sugar-based phosphoramidates where the carbohydrate functions as an amine substituent (Table 1). These were prepared via the mild and chemoselective Staudinger-phosphite reaction using sugar-azido derivatives and triethyl/tributyl phosphite.

Table 1
Synthesis of phosphoramidates.



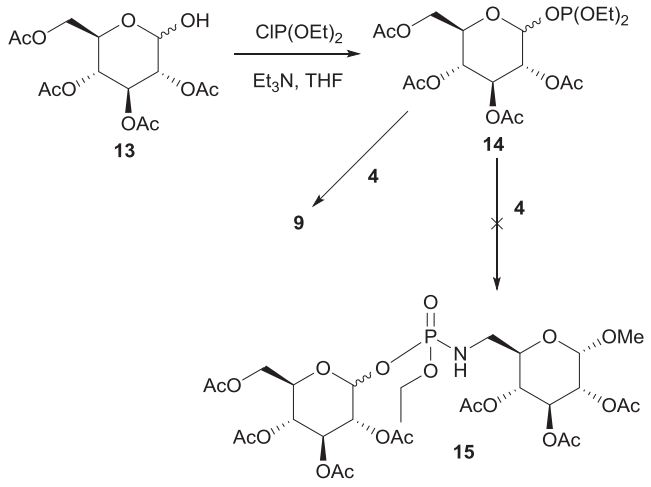
Substrate	Product	Yield (%)
3	 **7**	91 [38]
3	 **8**	90 [38]
4	 **9**	89
4	 **10**	87
5	 **11**	86
6	 **12**	89

The azides: 1-azido-1-deoxy-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside **3**, methyl 2,3,4, tri-*O*-acetyl-6-azido-6-deoxy-α-D-glucopyranoside **4**, methyl 2,3,6, tri-*O*-acetyl-4-azido-4-deoxy-α-D-galactopyranoside **5** and 2,3,4,6,2',3',4'-hepta-*O*-acetyl-6-azido-6-deoxy-trehalose **6** were synthesized via the S_N2 displacement of tosylates/bromides using NaN_3 [39,40]. These were then reacted with 1.5 eq. of the desired phosphite in THF for 24 h. Increasing the equivalents of the phosphites, as well as longer reaction times, had no impact on the yields. Table 1 illustrates the various products and their isolated yields. Excellent conversions (>85%) were obtained for all phosphoramidates **7**-**12**. We found that the reactivity of the anomeric azide under the required conditions were slightly higher than that at other positions. This is likely due to the endocyclic oxygen stabilizing the proximate reaction intermediate [41]. Attempts to synthesize an aromatic phosphoramidate derivative using triphenyl phosphite were futile even at elevated temperatures. This is probably as a result of the bulkiness of the aromatic ring which sterically shields the phosphorus core, thereby preventing initial attack on the azide.

We also investigated the possibility of constructing the phosphoramidate linked disaccharide shown in Scheme 1.

Compound **13** was reacted with 2 eq. of chlorodiethylphosphite and 1.5 eq. of triethylamine at 0 °C. Upon formation of the phosphite **14**, 1 eq. of the 6-azido derivative **4** was added and the reaction was allowed to warm to room temperature. The azide-phosphite reaction was done *in situ* due to the instability of **14**. Unfortunately we were unsuccessful in synthesizing **15**; instead, phosphoramidate **9** was unexpectedly formed**.** Scheme 2 illustrates our proposed mechanism for this result. The typical Staudinger reduction proceeds through an aza-ylide intermediate [42]. Hydrolysis of this intermediate results in the formation of the phosphoramidate as the stable product [43]. The final stage of the hydrolysis however requires one of the alkoxy substituents to depart in order to facilitate the stable phosphoryl bond formation as shown in intermediate **16**. The sugar alkoxide **17** would function as a better leaving group than its ethoxy counterpart **18**. This is suggested for two reasons: (i) the bulkiness of the sugar ring versus the ethyl moiety (departure releases steric strain) and (ii) the extra stabilization due to the resonance structures of mutarotation [44,45].

Intramolecular hydrogen bonding (IntraHB) within a molecule is known to impact on properties crucial to drug design including: permeability, lipophilicity, solubility and partition [46,47]. Interestingly, some of the N-*H* protons**,** appeared as a pseudo triplet. This is an indication of the coincidental similarity of N*H*-C$_1$*H* and



Scheme 1. Attempted synthesis of phosphoramidate-linked disaccharide.