Anomeric Phosphorodithioates as Novel Glycosylating Agents

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Complex glycoconjugates carry detailed structural information that mediates a variety of biologically important events, including inflammation, immune response, and tumor metastasis at the level of cell−cell interactions.[1] The need for synthetic access to complex oligosaccharides and glycoconjugates has led to increased interest in the development of novel and powerful glycosylation reactions. Therefore, a wide range of anomeric groups, including anomeric trichloroacetimidates, sulfoxides, pentenyl glycosides, fluorides, and thioethyl glycosides, have been explored for their use as glycosyl donors.[2] In biosynthesis, glycosyl transferases utilize sugar-nucleotides such as UDP-glucose as substrates in glycosylation reactions where pyrophosphate acts as an anomeric leaving group.[3] Surprisingly, until recently phosphate-based glycosyl donors have received relatively little attention. Glycosyl phosphites[4] as well as glycosyl phosphates[5] and other phosphate analogues, including dimethylphosphinothioates,[6] phosphorimidates,[7] and phosphoramidimidates,[8] have been explored for their use as glycosylating agents. To create novel phosphate analogues of altered reactivity, the replacement of the oxygen bridging C1 and phosphorus would be particularly desirable since this change is expected to most profoundly influence the reactivity of the anomeric functionality toward different activators. 2-Deoxy-
sugar glycosyl phosphorodithioate donors that contain a bridging sulfur in place of oxygen have proven to be powerful donors for the formation of 2-deoxy glycosidic linkages.[9−11] While peracetylated phosphorodithioate glycosides have been prepared, their reactivity stood in stark contrast to that observed with phosphorodithioates in the 2-deoxy sugar series, and no successful glycosylation reactions involving these donors have been disclosed.[12] We now report an efficient, straightforward synthesis of differentially protected anomeric phosphorodithioates from glycal precursors. These stable glycosyl donors were applied to the selective and high-yielding construction of β-glucosidic linkages with a variety of glycosyl acceptors at ambient temperature, including acid-sensitive glycal acceptors.

To date, all protocols for the synthesis of anomeric phosphate-based glycosyl donors have relied on the phosphitylation or phosphorylation of an anomeric hydroxyl group following protection and deprotection protocols. The preparation of differentially protected monosaccharide glycosyl donors requires lengthy procedures in many cases. Glycals, on the other hand, allow for the facile differential protection of the hydroxyl functionalities and have been shown to be versatile starting materials for the synthesis of oligosaccharides and natural products.[13] Until now, the formation of β-glucosidic linkages involving glycal acceptors was only possible with thioethyl glycosides while the coupling conditions required for all other currently available glycosyl donors were too harsh. Ideally, glycals could be converted into stable glycosyl donors that could be selectively activated at room temperature to fashion glycosidic linkages with a variety of glycosyl donors including glycals to allow for the repetition of the process. Anomeric dithiophosphates fulfill these requirements.

Conversion of glycals to anomeric dithiophosphates was achieved by epoxidation of the glycal double bond of tribenzyl glucal **1** with dimethyldioxirane (DMDO) to furnish the 1,2-anhydrosugar (Scheme 1). Opening of the epoxide with diethyl dithiophosphate furnished a 1:1 mixture of α and β anomeric phosphorodithioates (**2** + **3**) in 82% yield, and purification by silica column chromatography allowed for separation of phosphorodithioates **2** and **3**. Anomeric phosphorodithioates are stable compounds that may be stored for several weeks at room temperature without decomposition. Purification of anomeric phosphorodithioates by silica column chromatography is not a problem.

Next, the introduction of different protecting groups on the C2-hydroxyl group was investigated. Participating acetyl and pivaloyl ester groups could be installed readily on C2. Reaction of **2** and **3** with acetic anhydride and DMAP yielded the C2-acetyl phosphorodithioates **4** (85%) and **5** (81%), while reaction with pivaloyl chloride in the presence of DMAP furnished glycosyl donors **6** and **7** in 83% and 80% yield, respectively. The formation of C2 ether protecting groups was unsuccessful. Benzylation of **2** with benzyl bromide and sodium hydride resulted in the formation of a single compound. Characterization of the reaction product revealed that instead of the desired protected anomeric phosphorodithioate, the benzyl C2-phosphorothioate thioglycoside **8** was obtained exclusively. Intramolecular nucleophilic attack of the C2 alkoxide on phosphorus displaced the anomeric sulfur, which was then benzylated, thus providing **8**. In the case of β-anomer **3,** the yield for the formation of the C2 phosphorothioate **9** was significantly lower (18%) than for the formation of **8** (49%) and accompanied by unidentified side products.

After having established a straightforward and high-yielding synthetic route for the preparation of differentially protected anomeric phosphorodithioates, a variety of activation protocols were screened for use with glycosyl phosphorodithioate donors. Ideally, glycosylation conditions would allow for the selective formation of glycosidic linkages in high yield at ambient temperature in solution and in solid support synthesis paradigms. First, a number of thiophiles that had been successfully employed as activators of phosphorodithioate 2-deoxyglycosides were tested (Table 1). Silver salts such as silver fluoride, requiring prolonged reaction times of 48 h,[9] and iodonium perchlorate as well as *N*-iodosuccinimide

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Scheme 1

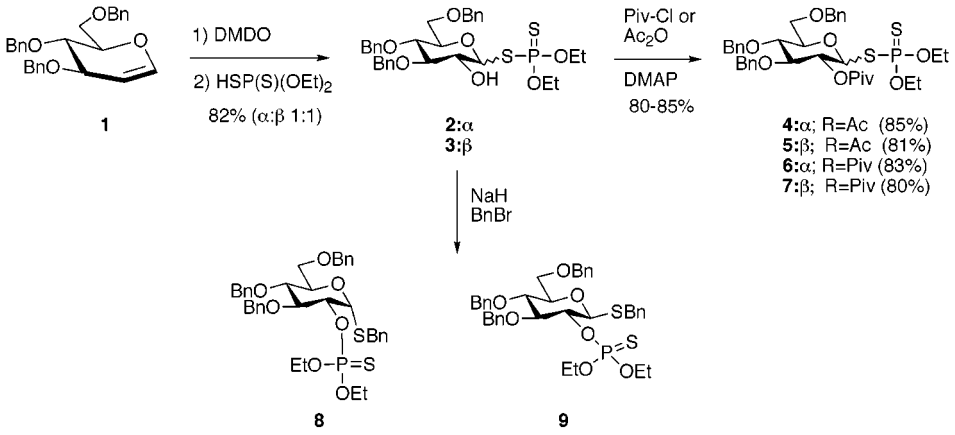
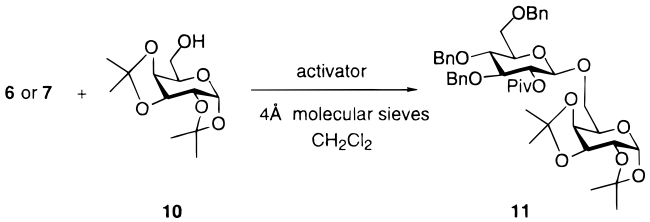


Table 1



activator	*T* (°C)	reaction time (h)	yield (%)
NIS	rt	20	<5
NIS/TfOH	rt	1	–
$I(coll)_2ClO_4$	rt	20	15
$I(coll)_2ClO_4$	rt	10	<5
AgF	rt	10	–
$AgClO_4$	rt	10	35
MeOTf	0→rt	16	70

Table 2

Acceptor	Product	Isolated Yield (%)
10	**11**	70
12	**13**	65
14	**15**	59
16	**17**	55
18	**19**	58
20	**21**	18

(NIS)[11] were not successful in activating phosphorodithioate glycosyl donors and resulted in slow and low-yielding reactions. Activation with silver perchlorate succeeded in the formation of glycosidic linkages but resulted in anomeric mixtures.

Phosphorodithioate glycosides **4** and **5** equipped with a C2-acetyl group failed to yield any of the desired disaccharide under the activation conditions tested but instead produced a mixture of side products. Activation of anomeric phosphorodithioates **6** and **7** with methyl triflate produced exclusively the *β*-glycosidic linkage by virtue of the participating pivaloyl ester functionality on C2.[14] The yield as well as the rate of reaction were indistinguishable when either the α- or the *β*-phosphorodithioate was used. The coupling of **6** and **7** with a variety of glycosyl acceptors revealed that these novel glycosyl donors also selectively furnished the *β*-glucosidic linkage with hindered acceptors in good yield (Table 2). Acid-sensitive glycal acceptors could successfully be accommodated in coupling reactions when a base such as di-*tert*-butylpyridine was included without requiring prolonged reaction times. The couplings to form *β* (1→3) disaccharide **13**, *β* (1→4) disaccharide **15**, and *β* (1→6) disaccharide **17** proceeded in good yields with complete stereoselectivity. Other acceptors containing secondary hydroxyl moieties (e.g., **18**) could also be coupled in good yields using methyl triflate activation while reactions with tertiary alcohol **20** as acceptor proceeded in low yield (18%).

In summary, we have developed a straightforward synthesis of anomeric phosphorodithioates from glycal precursors. This novel synthetic scheme can be employed in the facile synthesis of differentially protected glycosyl donors. We have demonstrated that these anomeric phosphorodithioates can be activated by methyl triflate to serve as glycosyl donors in reactions with a variety of glycosyl acceptors, including acid-sensitive glycals. Currently, we are expanding this concept to the formation of other glycosidic linkages in solution and on the solid support. Other phosphate analogues, which are now easily accessible from glycals using the described synthetic protocols, are presently being evaluated for their potential use as glycosyl donors.

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Supporting Information Available: Detailed experimental procedures and compound characterization data, including ^1H, ^{13}C, and ^{31}P NMR spectra for all compounds in this study (45 pages).

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