JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

Synthesis, Characterization, and Coupling Reactions of Six-Membered Cyclic P-Chiral Ammonium Phosphonite−Boranes; Reactive *H*-Phosphinate Equivalents for the Stereoselective Synthesis of Glycomimetics

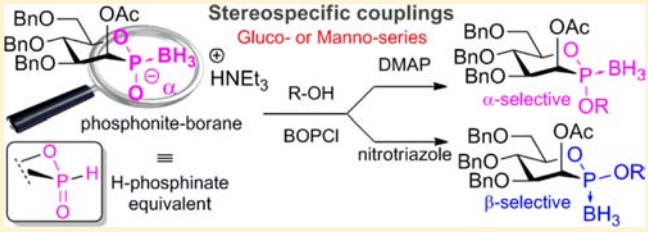
Angélique Ferry,[†] Xavier Guinchard,[†] Pascal Retailleau,[†] and David Crich*[,†,‡]

[†]Centre de Recherche de Gif, Institut de Chimie des Substances Naturelles, CNRS, Avenue de la Terrasse, 91198 Gif-sur-Yvette, France

[‡]Department of Chemistry, Wayne State University, 5101 Cass Avenue, Detroit, Michigan 48202, United States

Supporting Information

ABSTRACT: Stereoselective syntheses of P-chiral ammonium phosphonite-borane complexes in the *gluco*- and *manno*-like series have been developed from P(V) phostone derivatives. The coupling reactions of these phostone donors with alcohols have been investigated with particular emphasis on the influence of protecting groups and conditions on stereoselectivity. The phosphonite−borane complexes may be applied directly in the coupling reactions and the products oxidized in situ to give phostone-mimetics of disaccharides. On the basis of these studies, successful protocols were established for the synthesis of β-gluco and α- and β-manno-configured phostones of primary alcohols. Deprotection of the dimeric compounds leads to novel families of α- or β-(1→6)-linked glycomimetics.



INTRODUCTION

The efficient synthesis of oligosaccharides for applications in glycobiology[1] and in medicine depends critically on a number of factors including the yield and stereoselectivity of glycosidic bond formation.[2] Unfortunately, and despite the enormous advances made on this front in the last two decades, the current state of the art leaves much to be desired. That this is the case more than a hundred years after the advent of the Koenings−Knorr reaction[3] is an indication of the magnitude of the problem and an obvious indication of the need for renewed effort; it is also an indication that the parallel pursuit of alternative avenues, such as the development of oligosaccharide mimetics,[4] may be beneficial. This challenge was taken up by Vasella and co-workers[5] in the context of their investigation into the preparation of oligomeric glycosyl acetylenes, but in more recent years the preparation of oligosaccharide mimetics has been dominated by "Click" chemistry[6] methods.[7] In our laboratory, we have initiated a glycomimetic program[8] and explored the application of a novel ligation method based on the desulfurative allylic rearrangement of allylic disulfides[9] to the preparation of oligosaccharide mimetics,[10] but ultimately the goal must be to develop a system that provides the closest possible analogy to a native glycosidic bond. Phosphonosugars, or phostones,[11] in which the anomeric carbon of a furanose or pyranose ring is replaced by a phosphonate group have been advanced as potent therapeutic agents due to their close relation to glycosidic bonds and their potent ability to act as glycosidase inhibitors.[11d,g,12] Phostones differ from other phosphorus-containing glycomimetics based on the replacement of the ring oxygen by a P(V) atom, by virtue of the location of the phosphorus atom.[13] More recently, phosphinosugars, or phostines, closely related to phostones, have gained a renewed synthetic interest[14] and have shown anticancer activities.[14b,c] In addition to these potent activities, we considered that the phostone linkage might be a suitable surrogate of glycosidic bonds for application in oligosaccharide mimetics and, thus, embarked on the program of exploratory phostone chemistry and synthesis that we outline in this Article.

Numerous syntheses of simple phostones have been described in the literature[11b−g] en route to their development as glycosidase inhibitors. Despite this, only two actual disaccharide mimetics based on the gluco-phostone motif have been reported in the literature, in both of which the inter-residue phostone ester bond intended to mimic a glycosidic bond was prepared by esterification at the phosphorus V oxidation level. This strategy, however, relies on the achiral phosphonic acid function and furnishes mixtures of α- and β-glucophosphonates, with a predominance for the β-isomer;[11d] furthermore, nothing is known about the inherent diastereoselectivity of such a reaction in the manno-series. Taking note of the advantages of ease of reaction and yield conferred in oligonucleotide synthesis and related fields by the use of coupling reactions conducted at the phosphorus III rather than

Received: May 25, 2012
Published: June 29, 2012

   dx.doi.org/10.1021/ja305104b | J. Am. Chem. Soc. 2012, 134, 12289−12301

V oxidation level,[15] we have focused our attention on the synthesis of functionalized phostone esters via the intermediacy of P-chiral hydrogen phosphonites. To our knowledge, coupling reactions of alcohols with *H*-phosphinates[16] (Figure 1, iv), which possess one degree of oxidation less than *H*-

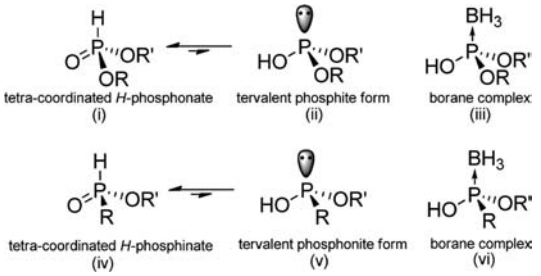


Figure 1. Tautomeric forms of *H*-phosphonates and *H*-phosphinates and their borane complexes.

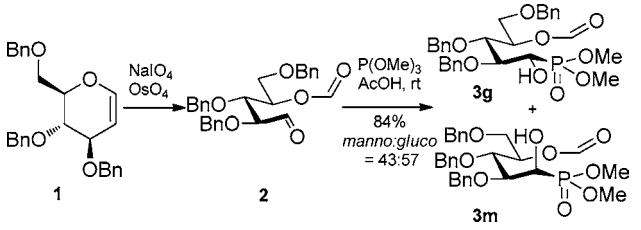
phosphonates (Figure 1, i),[15c,d,17] well-known for their reactions with alcohols[15a,18] and in particular in oligonucleotide synthesis,[19] have not been reported previously, outside the context of the Atherton–Todd reaction.[20] Conscious of the sensitivity of such P(III)-based tervalent substances toward aerial oxidation, we directed our attention more particularly at the use of hydrogen phosphonites protected in the form of their borane adducts (Figure 1, vi). The borane serves not only to protect the phosphorus center against oxidation,[21] but also provides an original means of blocking the *H*-phosphinate function (Figure 1, iv) in its tricoordinated P(III) state (Figure 1, v) rather than the tetra-coordinated P(IV) form[15d] that is likely to be largely favored by analogy with the hydrogen phosphite/*H*-phosphonate equilibrium,[15d,22] but which is not the reactive form in coupling with alcohols.

The synthesis and reactions of the diesters phosphonite-boranes ($RP(BH_3)(OR^1)(OR^2)$) have been studied,[23] but not their transformation to the borane adducts (Figure 1, vi). The acyclic borane complexes of the higher oxidation level phosphonates (Figure 1, iii) have recently been studied extensively by Wada and co-workers, who reported their preparation and uses,[24] and in particular on their coupling reactions with alcohols.[24a,c,25] As it was not an issue in these studies, the stereochemical course of these coupling reactions was mostly not investigated.[26] We describe herein the results of an extensive study into the synthesis and coupling reactions of carbohydrate-mimetic cyclic hydrogen or ammonium phosphonite–borane complexes, with particular emphasis on the stereoselectivity of the coupling reactions, of the subsequent oxidation step, the influence of the neighboring stereogenic center, and the affixed protecting groups on the yield and selectivity of the various processes.

RESULTS AND DISCUSSION

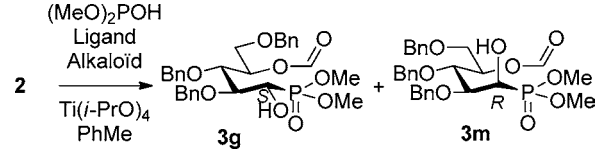
Diastereoselective Phostone Synthesis. We initially evaluated Drueckhammer's straightforward synthesis of six-membered cyclic phostones[11c] in which a glucal-derived aldehydo-formate ester is subjected to Abramov reaction[11a,b] with trimethylphosphite followed by base-catalyzed cyclization. Indeed, the first steps of this protocol (Scheme 1) proceeded in high yield to give the Abramov product as a 57:43 mixture of isomers in favor of what was subsequently assigned as the gluco-isomer.[27]

Scheme 1. Hydrophosphonylation with Simple Diastereoinduction

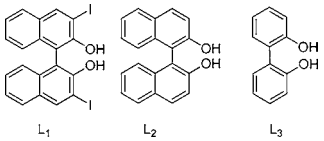


Crystallization from MTBE afforded the pure manno-isomer **3m** and enabled crystallographic confirmation of its configuration (see the Supporting Information), but did not provide a means of efficiently accessing the pure gluco-isomer **3g** from the otherwise difficulty separable mixture. Therefore, we investigated the possibility of enhancing diastereoselectivity through the use of an external chiral agent. Of the various systems developed recently for the asymmetric hydrophosphonylation of aldehydes,[28] we favored that of You[29] because of the relatively low catalyst loadings and its applicability to aliphatic aldehydes. Accordingly, reaction of aldehyde **2** and dimethyl phosphite, promoted with titanium tetraisopropoxide, was conducted in the presence of (*R*)-3,3′-diiodobinol and cinchonidine, as described by You for simple achiral aldehydes, resulting in a 57% yield of an improved 10:90 mixture of **3g** and **3m** (Table 1, entry 1). Changing the chirality and substitution

Table 1. Asymmetric Hydrophosphonylation



entry	ligand	alk.[a]	*T* (°C)	dr[b] (**3g**/**3m**)	conv. (yield[c])
1	(*R*)-L_1	CD	rt	10:90	100% (57%)
2	(*R*)-L_1	CD	−20	9:91	86% (59%)
3	(*R*)-L_1	CD	40	17:83	100% (59%)
4	(*R*)-L_1	CD	0	10:90	100% (89%)
5	(*R*)-L_1	C	0	47:53	67% (36%)
6	(*S*)-L_1	CD	0	62:48	75% (53%)
7	(*S*)-L_1	C	0	66:34	50% (29%)
8	(*R*)-L_2	CD	0	70:30	100% (77%)
9	(*R*)-L_2	C	0	56:44	65% (51%)
10	(*S*)-L_2	CD	0	61:39	79% (62%)
11	(*S*)-L_2	C	0	72:28	73% (64%)
12	(±)-L_3	CD	0	61:39	100% (80%)



[a]CD, cinchonidine; C, cinchonine. [b]Determined by HPLC. [c]Isolated yields for both diastereoisomers.

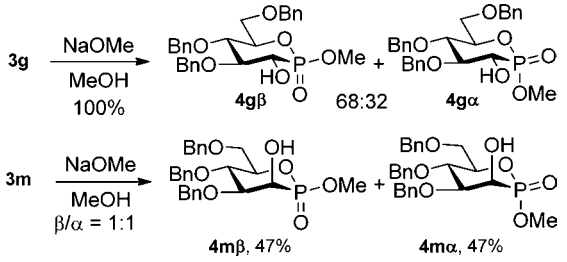
of the diol ligand, replacing cinchonidine by cinchonine, or both did not improve the diastereomeric ratio (Table 1), although operation at 0 °C did provide a 89% yield of the 10:90 gluco:manno mixture and therefore a practical functioning gram-scale synthesis of **3m** (Table 1, entry 4). In general, it was found (Table 1) that both chiral promoters were essential for high diasteroinduction and that while the ratio of diastereomers

dx.doi.org/10.1021/ja305104b | J. Am. Chem. Soc. 2012, 134, 12289–12301

could be reversed to favor moderately the gluco isomer (Table 1, entries 6−12) it was not possible to completely overcome the inherent preference of the arabino-configured aldehyde for formation of the manno-isomer **3m**. Nevertheless, despite the imperfect nature of the selectivity, the conditions of Table 1, entry 8 and use of preparative HPLC did afford a working gram-scale entry into the gluco-isomer **3g**.

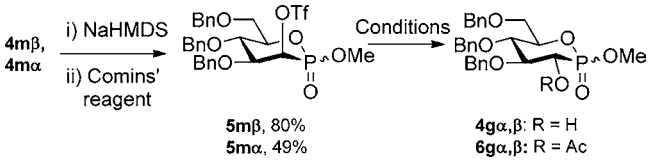
Treatment of **3g** with catalytic sodium methoxide in methanol promoted cyclization to the cyclic phostones **4g*α*** and **4g*β*** in quantitative yield as an inseparable 32:68 mixture of anomers (Scheme 2).[30] In the case of the manno-isomer **3m**, cyclization gave an equimolar mixture of the readily separable cyclic phostones **4m*α*** and **4m*β*** in excellent yield (Scheme 2).

Scheme 2. Conversion of Hydroxyphosphonates to Cyclic Phostones



The more facile synthesis of **3m** than of **3g** coupled with the ease of separation of **4m*α*** and **4m*β*** led us to investigate the inversion of the later pair as an alternative means of entry into the gluco-series. Attempts at Mitsunobu[31] inversion of **4m*α*** or **4m*β*** under a variety of conditions were unsuccessful, and therefore we focused on the displacement of sulfonate esters.[32] Accordingly, treatment of **4m*α*** and **4m*β*** with sodium hexamethyl disilamide followed by *N*,*N*-ditriflyl 5-chloro-2-pyridylamine (Comins' reagent[33]) afforded the triflate esters **5m*α*** and **5m*β*** in 49% and 80% yield, respectively. Treatment of **5m*β*** with potassium superoxide[34] resulted only in degradation, but the use of sodium or potassium nitrite as nucleophile[35] afforded the desired inverted alcohol **4g*β*** in modest yield (Table 2, entries 1−3). Sodium acetate proved to

Table 2. Inversion at C-2 in the manno-Phostones

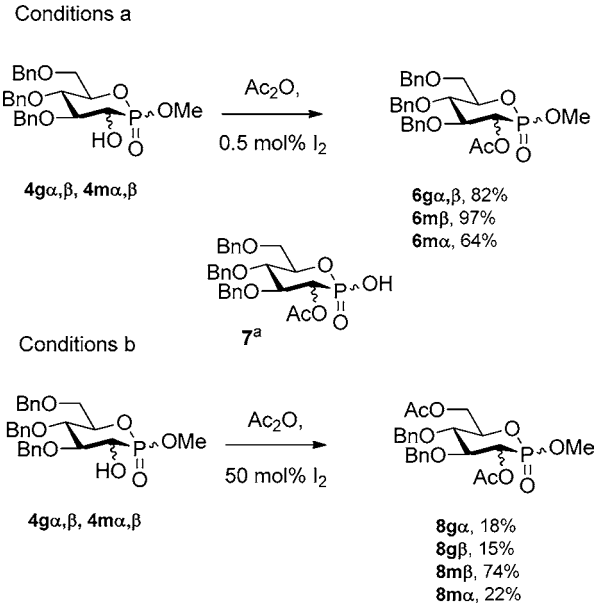


entry	triflate	conditions	yield
1	**5m*β***	KO_2 (3 equiv), 18-Cr-6, DMSO, rt	**4g*β***, 0%
2	**5m*β***	$NaNO_2$ (5 equiv), DMF, 50 °C, 2 h 30 min	**4g*β***, 28%
3	**5m*β***	KNO_2 (5 equiv), DMF, 50 °C, 2 h 30 min	**4g*β***, 22%
4	**5m*β***	AcONa (3 equiv), DMF, rt, 4 h 30 min	**6g*β***, 31%
5	**5m*α***	AcONa (3 equiv), DMF, rt, 6 h	**6g*α***, 63%

be marginally more successful and provided the inverted ester **6g*β*** in a still moderate 31% yield (Table 2, entry 4). Conversely, treatment of the stereoisomeric triflate **4m*α*** with sodium acetate proceeded more smoothly and afforded ester **6g*α*** in an acceptable 63% yield (Table 2, entry 5). Intriguingly, therefore, triflation of the alcohol antiperiplanar to the phosphoryl oxygen (and synclinal to the methoxy group) was favored, whereas the inversion reaction proceeded more rapidly with introduction of the nucleophile synclinal to the phosphoryl oxygen (and anti to the methoxy group). The preferential triflation anti to the phosphoryl oxygen is presumably the result of the strongly electron-withdrawing nature of the latter enhancing the acidity of the alcohol, whereas the lesser steric bulk of the P═O bond as compared to the P−OMe moiety explains the greater ease of substitution of a triflate group anti to the phosphoryl oxygen.

Acetylation of alcohols **4g*α*,*β*** and **4m*α*,*β*** under classical conditions with acetic anhydride in pyridine afforded the corresponding acetates **6g*α*,*β*** and **6m*α*,*β*** in moderate yield to good yield, typically accompanied by varying amounts of the corresponding phosphonic acids **7** resulting from base-mediated demethylation. Fortunately, the use of acetic anhydride as solvent in the presence of catalytic iodine proved equal to the task and provided the desired derivatives in excellent yield (Scheme 3, conditions a). With the exception of

Scheme 3. Acetylation of 4g*α*,*β* and 4m*α*,*β*



(a) Obtained as byproducts on acetylation with Ac_2O/pyridine.

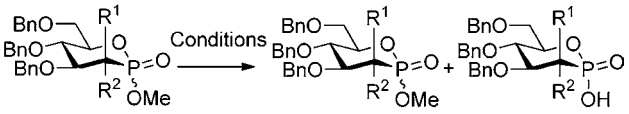
a single specific rotation,[36] the specific rotations and ^{31}P NMR chemical shifts of the four acetates **6g*α*,*β*** and **6m*α*,*β*** compared well with those provided earlier by Hanessian, thereby confirming the assignments of configuration at phosphorus. Interestingly, we found that increasing the amount of iodine from 0.5 to 50 mol % in these acetylation reactions resulted in the selective cleavage of a single benzyl ether at the 6-position with concomitant acetylation.[37] Although variable in terms of yield, these latter conditions (Scheme 3, conditions b) gave four diacetylated phostones **8g*α*,*β*** and **8m*α*,*β***, of which two (**8g*β*** and **8m*α***) were crystalline and whose X-ray crystallographic structures (see the Supporting Information) provided further confirmation of the configuration at phosphorus in the entire series.

The introduction of a fourth benzyl ether into phostones **4g*α*,*β*** and **4m*α*,*β*** to give the corresponding tetrabenzyl ethers **9g*α*,*β*** and **9m*α*** by the use of sodium hydride and benzyl bromide was successful, but was complicated by a competing demethylation reaction to give the corresponding phosphonic

dx.doi.org/10.1021/ja305104b | J. Am. Chem. Soc. 2012, 134, 12289−12301

acids **10** (Table 3, entries 1 and 2[38]). With alcohol **4mα** the use of heterogeneous conditions with 1 M aqueous sodium

Table 3. Benzylation of 4gα,β and 4mα,β



4gα,β: R^1 = H, R^2 = OH
4mα,β: R^1 = OH, R^2 = H

9gα,β: R^1 = H, R^2 = OBn
9mα,β: R^1 = OBn, R^2 = H

10

entry	alcohol	conditions	product	yield[a]
1	**4mα**	NaH, BnBr, DMF, rt, 6 h	**9mα**	31%
2	**4gα,β**	NaH, BnBr, THF, TBAI, rt, 6 h	**9gα,β**	30%[a]
3	**4mα**	BnBr, *n*-Bu_4NHSO_4, NaOH 1 N/ CH_2Cl_2, 1 h 30 min	**9mα**	80%
4	**4mβ**	BnBr, *n*-Bu_4NHSO_4, NaOH 1 N/ CH_2Cl_2, 3 h 30 min	**9mβ**	15%
5	**4gα**	BnBr, *n*-Bu_4NHSO_4, NaOH 1 N/ CH_2Cl_2, 3 h 30 min	**9gα**	1%
6	**4gβ**	BnBr, *n*-Bu_4NHSO_4, NaOH 1 N/ CH_2Cl_2, 6 h	**9gβ**	2%
7	**4mα**	$Cl_3CC(NH)OBn$, TfOH cat.	**9mα**	55%

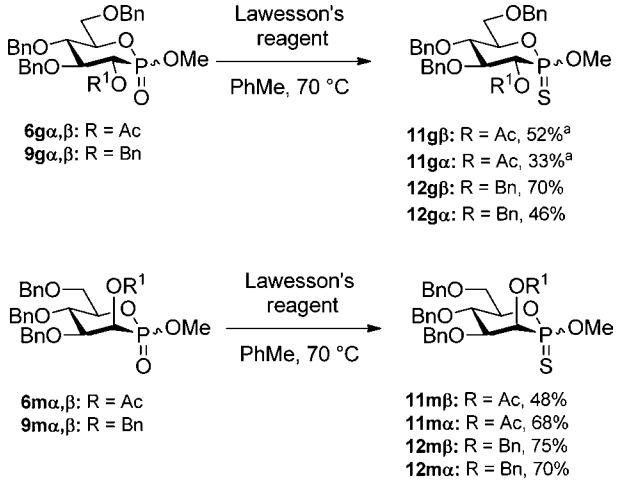
[a]Obtained as a 1/2.5 mixture of **9gβ**/**9gα**.

hydroxide and benzyl bromide in dichloromethane[39] was more successful and afforded **9mα** in 80% yield (Table 3, entry 3). Unfortunately, this success did not extend to the other members of the series when only disappointing results were obtained (Table 3, entries 4–6). It is noteworthy that the reactivity order in the diastereomeric pair **4mα,β** toward benzyl bromide and aqueous base, with the more reactive isomer having the phosphoryl group synclinal to the alcohol, is the opposite of that noted above for triflation of the same pair (Table 2). The Bronsted acid-catalyzed benzylation of **4mα** with benzyl trichloroacetimidate and triflic acid[11e] was also found to afford **9mα** in moderate yield (Table 3, entry 7), but these conditions were not extended to the other members of the series.

Preparation of Phosphonite–Borane Complexes. With two sets of four diastereomeric phostones **6gα,β**, **6mα,β**, **9gα,β**, and **9mα,β** in hand, attention was focused on their reduction to the corresponding P(III) derivatives. None of the classical reduction protocols for the reduction of phosphoryl systems were satisfactory for our purposes. We focused instead on the initial conversion of the phosphoryl group to the corresponding thiophosphoryl system by means of equilibration with Lawesson's reagent, a transformation that is known to take place with retention of configuration at phosphorus.[11f] Thus, the fully protected phostones **6gα,β**, **6mα,β**, **9gα,β**, and **9mα,β** were heated to 70 °C in toluene with an excess of Lawesson's reagent resulting in the formation of what we dub the thiophostones (**11gα,β**, **11mα,β**, **12gα,β**, and **12mα,β**) in moderate to good yield (Scheme 4) with no loss of stereochemical integrity.[40] Gratifyingly, the isomers **11gα** and **11gβ** were readily separable by chromatography at this stage, making it possible to carry the much more difficultly separable glucosyl acetates to this stage as an anomeric mixture.

Reduction of the thiophostones **11gα,β**, **11mα,β**, **12gα,β**, and **12mα,β** was investigated using Raney-Ni[41] with immediate trapping of the reduced products in the form of phosphonite–borane adducts due to the high degree of sensitivity of the uncomplexed phosphonites to aerial oxidation. In the 2-*O*-acetyl series, three of the four available diastereomers were

Scheme 4. Synthesis of the Thiophostones 11gα,β, 11mα,β, 12gα,β, and 12mα,β



6gα,β: R = Ac
9gα,β: R = Bn

11gβ: R = Ac, 52%[a]
11gα: R = Ac, 33%[a]
12gβ: R = Bn, 70%
12gα: R = Bn, 46%

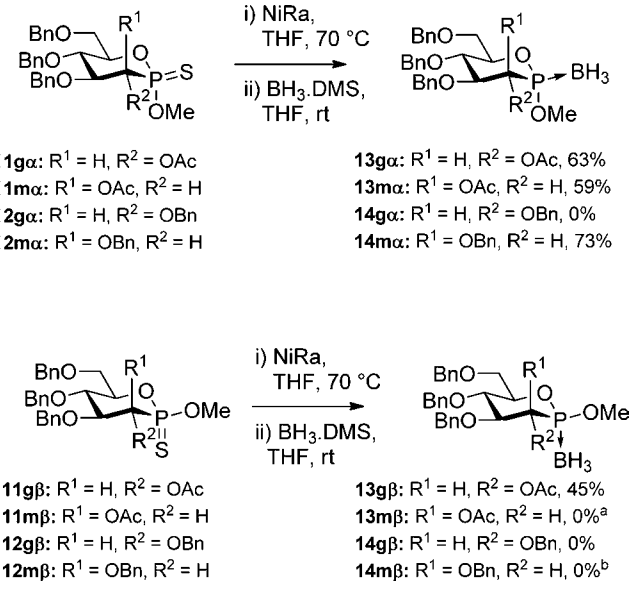
6mα,β: R = Ac
9mα,β: R = Bn

11mβ: R = Ac, 48%
11mα: R = Ac, 68%
12mβ: R = Bn, 75%
12mα: R = Bn, 70%

(a) From a mixture of **6gα,β**.

successfully reduced in this manner and afforded the corresponding phosphonite–boranes with full retention of stereochemistry (Scheme 5). The fourth such isomer, the 2-*O*-

Scheme 5. Reduction of Thiophostones to Phosphonite–Borane Complexes



11gα: R^1 = H, R^2 = OAc
11mα: R^1 = OAc, R^2 = H
12gα: R^1 = H, R^2 = OBn
12mα: R^1 = OBn, R^2 = H

13gα: R^1 = H, R^2 = OAc, 63%
13mα: R^1 = OAc, R^2 = H, 59%
14gα: R^1 = H, R^2 = OBn, 0%
14mα: R^1 = OBn, R^2 = H, 73%

11gβ: R^1 = H, R^2 = OAc
11mβ: R^1 = OAc, R^2 = H
12gβ: R^1 = H, R^2 = OBn
12mβ: R^1 = OBn, R^2 = H

13gβ: R^1 = H, R^2 = OAc, 45%
13mβ: R^1 = OAc, R^2 = H, 0%[a]
14gβ: R^1 = H, R^2 = OBn, 0%
14mβ: R^1 = OBn, R^2 = H, 0%[b]

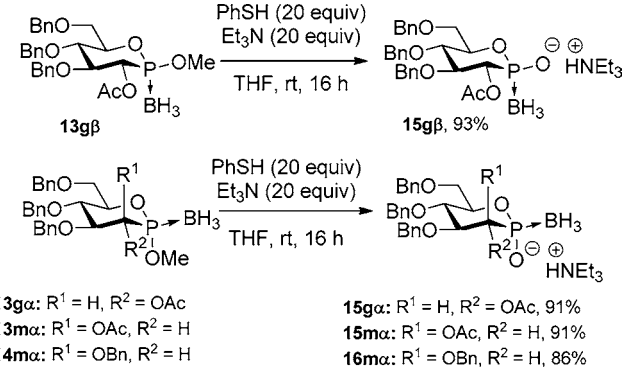
(a) 11% of a 2-deacetylated product. (b) 23% of a product with loss of phosphorus function was obtained (see the Supporting Information).

acetyl-β-manno system **11mβ**, did not afford the desired product but gave instead 11% of a desacetyl product. In contrast, in the tetra-*O*-benzyl series, only one of the four diastereomers, the 2-*O*-benzyl-α-manno system **12mα**, was amenable to reduction in this manner with the other three isomers either failing (**12gαβ**) to react or undergoing decomposition (**12mβ**) under the reaction conditions (Scheme 5). Previous workers had described the reaction of Raney Ni with sialyl derived-thiophostones to be completely ineffective.[42] Evidently, the success of the thiophostone reduction is strongly dependent on both the O2 protecting group and the stereochemistry at phosphorus. Benzyl ethers, with the one

exception, are generally detrimental, consistent with the failures reported earlier by other groups whereas acetate esters are acceptable except for the one case in which a fragmentation was observed.

Finally, in preparation for the coupling reactions, the phosphonite ester–borane complexes were cleaved to the corresponding phosphonite–borane complexes, which were conveniently isolated in the form of their triethylammonium salts. A number of conditions were investigated for this transformation including the use of sodium iodide[11c] and of bromotrimethylsilane[11d] to no avail. DABCO, whose successful use had been reported previously in a similar reaction[24e] and which is known to cleave phosphine–borane complexes effectively,[43] had no effect in the transformations at hand. The use of an excess of thiophenol and of triethylamine in THF at room temperature,[24a,c,44] however, proved to be effective and enabled the isolation of the ammonium phosphinates, in the form of their borane complexes in high yield following silica gel chromatography (Scheme 6). One isomer, the 2-*O*-acetyl-*β*-

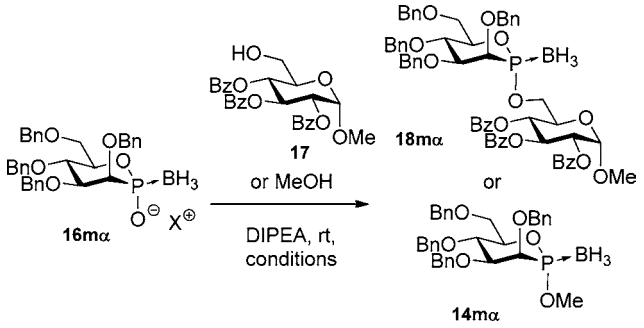
Scheme 6. Demethylation to Ammonium Phosphonite–Borane Complexes



gluco salt **15g*β***, provided crystals suitable for X-ray diffraction and hence confirmation of the stereochemical outcome of these processes (see the Supporting Information).

Coupling Reactions of Phosphonite–Borane Complexes. We first studied coupling with the per-*O*-benzyl protected mannosyl donor **16m*α*** so as to avoid all potential problems arising from the participation of protecting groups. Adopting conditions recommended by the Wada group in their work on phosphotriester synthesis with phosphonite–borane complexes,[24c] the protio form of **16m*α*** (as opposed to the triethylammonium salt) was coupled to the primary acceptor **17** by means of 3-nitro-1,2,4-triazolyl-1-yl-tris(pyrrolidin-1-yl)phosphonium hexafluorophosphate[45] (PyNTP) in the presence of diisopropylethylamine in acetonitrile at room temperature, giving rise to the formation of the disaccharide mimetic **18m*α*** with complete retention of configuration at phosphorus, albeit in only modest yield (Table 4, entry 1). The use of benzotriazol-1-yloxy-tris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP) under similar conditions (Table 4, entry 2) failed to give any of the desired compound, while the use of the closely related benzotriazol-1-yloxy-tris-(dimethylamino)phosphonium chloride (BOPCl) reagent in the presence of 3-nitro-1,2,4-triazole (NT),[24a] a critical component of the PyNTP system, gave the desired product **18m*α*** in 63% yield as a single diastereoisomer (Table 4, entry 3). The simple PyBOP system was again ineffective with the triethylammonium salt of **16m*α*** (Table 4, entry 4), whereas the

Table 4. Coupling of the Per-*O*-benzyl Donor 16m*α*



entry	X^+	conditions	product, % yield[a]
1	H	**17**, PyNTP, MeCN	**18m*α***, 26%
2	H	**17**, PyBOP, DMF	0%
3	H	**17**, BOPCl, NT, THF	**18m*α***, 63%
4	$HNEt_3$	**17**, PyBOP, DMF	0%
5	$HNEt_3$	**17**, BOPCl, NT, THF	**18m*α***, 82%[b]
6	$HNEt_3$	MeOH, BOPCl, NT, THF	**14m*α***, 74%
7	$HNEt_3$	**17**, BOPCl, DMAP, THF	**18m*αβ***, <35%[c]

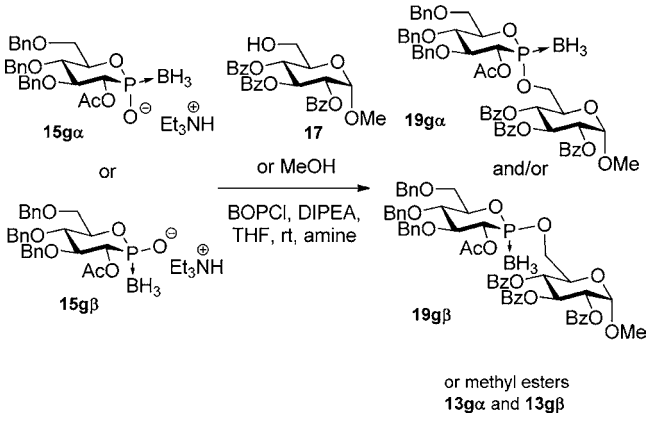
[a]Isolated yields. [b]0.8 equiv of alcohol **17** was used. [c]Obtained as a mixture of deborylated/borylated products. Following oxidation with *m*-CPBA, a 2:1 mixture of **21m*α*** and **21m*β*** was obtained.

BOPCl/NT system gave 82% of **18m*α*** as a single diastereoisomer (Table 4, entry 5). A further coupling of **16m*α*** was conducted with methanol as acceptor using the BOPCl/NT system, resulting in the formation of the *α*-methyl product **14m*α*** (Table 4, entry 6) and thereby confirming the retentive nature of these substitutions. A final coupling of **16m*α*** with **17** employing DMAP rather than NT was complicated by partial deborylation in the course of the reaction, resulting in a low yield (Table 4, entry 7) and difficulties in the assignment of anomeric stereochemistry. Nevertheless, after oxidation with *m*-CPBA, it was determined that a 2:1 ratio of anomers had been formed that favored the *β*-anomer. Given the evident importance of the nitrotriazole in these coupling reactions, the stereochemical outcome with overall retention of configuration is best rationalized in terms of an initial invertive displacement of the activated phosphonite by the heterocycle or its conjugate base followed its invertive displacement by the alcohol.

Application of the BOPCl/NT conditions to the coupling of the 2-*O*-acetyl gluco-configured donors **15g*α*** or **15g*β*** and acceptor **17** resulted in the formation of the two diastereomeric products **19g*β*** and **19g*α*** in 57:43 and 68:32 ratios, respectively, favoring in both cases the *β* product (Table 5, entries 1 and 2). Increasing the amount of NT employed significantly increased the yield of the coupling but had no effect on the stereoselectivity, whereas reducing the amount of NT employed led to an improved stereoselectivity but at the expense of the yield (Table 5, entries 3–5). Replacing NT by 4-dimethylaminopyridine (DMAP) gave the optimum results, a fully *β*-selective reaction and an isolated yield of 74% (Table 5, entry 6). Application of these later conditions to the anomeric donor **15g*β*** also resulted in the unique formation of the *β*-product in good yield (Table 5, entry 7). With donor **15g*β***, in the absence of either NT or DMAP, excellent selectivity was observed, but only a low yield of the product was obtained and the additional complication of competing deborylation was noted (Table 5, entry 8). On the other hand, with the isomeric donor **15g*α***, no coupling was observed in the absence of the

dx.doi.org/10.1021/ja305104b | J. Am. Chem. Soc. 2012, 134, 12289–12301

Table 5. Coupling of the 2-*O*-Acetyl Gluco Donors 15gα,β



entry	donor	ROH	amine (equiv)	% yield,[a] product ratio
1	**15gα**	**17**	NT (3)	54, **19gβ**:**19gα** = 57:43
2	**15gβ**	**17**	NT (3)	46, **19gβ**:**19gα** = 68:32
3	**15gβ**	**17**	NT (20)	83, **19gβ**:**19gα** = 56:44
4	**15gβ**	**17**	NT (1)	44, **19gβ**:**19gα** = 84:16
5	**15gβ**	**17**	NT (0.5)	21, **19gβ**:**19gα** = 84:16
6	**15gβ**	**17**	DMAP (3)	74, **19gβ**:**19gα** = 100:0
7	**15gα**	**17**	DMAP (3)	67, **19gβ**:**19gα** = 100:0
8	**15gβ**	**17**		25, **19gβ**:**19gα** = 100:0[b]
9	**15gα**	**17**		0, –
10	**15gβ**	MeOH[c]	DMAP (3)	82, **13gβ**:**13gα** = 66:34
11	**15gα**	MeOH[c]	DMAP (3)	69, **13gβ**:**13gα** = 85:15

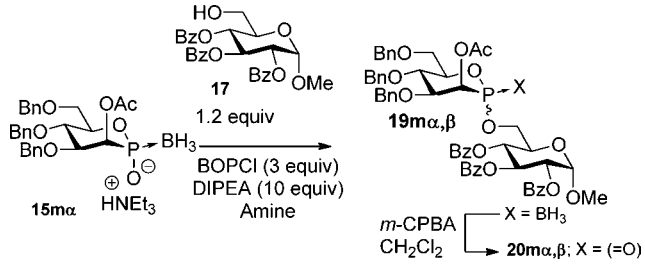
[a]Isolated yields. [b]Obtained as a 1:1 mixture with the deborylated product. [c]7.7 equiv of MeOH was used.

amine catalyst (Table 5, entry 9). Finally, both anomeric donors were coupled to methanol under the optimal conditions, resulting in good yields of the methyl esters **13gα** and **13gβ** in anomeric mixtures that favored the β-isomer in each case (Table 5, entries 10 and 11), possibly indicating a different mechanism for coupling to the more highly reactive alcohol.

The BOPCl coupling conditions were also applied to the mannosyl donor **15mα**, which bears a 2-*O*-acetyl protecting group. Both the NT and the DMAP promoter systems were assayed as were a variety of different solvents leading to the results presented in Table 6. Under certain conditions (Table 6, entries 1, 3, 4, and 5), to circumvent problems from partial deborylation of the products, the reaction mixtures were treated with *m*-CPBA before isolation so as to afford the more stable P(V) oxidation state, as both the oxidation deborylation process and the simple peracid oxidation of P(III) systems are known to proceed with retention of configuration. With nitrotriazole as nucleophilic partner in three different solvents, the axial product predominates, corresponding to a preponderance of retention of configuration (Table 6, entries 1–3). In contrast, with DMAP as promoter, the selectivity is solvent dependent with good to excellent α-selectivity being exhibited in dichloromethane and acetonitrile (Table 6, entries 6 and 7) and moderate to good β-selectivity in THF and toluene (Table 6, entries 4 and 5). In the absence of either NT or DMAP, no coupling product was formed (Table 5, entry 8).

Stereoselectivity of the Coupling Reaction. Concerning the mechanism of nucleophilic substitution at phosphorus,[46] the formal charge resident on phosphorus in the phosphonite–borane complexes studied inclines us to exclude the possibility of dissociative mechanisms and to focus instead on associative

Table 6. Coupling of the 2-*O*-Acetyl Manno Donor 15mα



entry	amine/solvent	**19mβ**/**19mα**	**20mβ**/**20mα**	yield[a]
1	NT/THF		9/91	62%[b]
2	NT/PhMe	0/100		96%
3	NT/CH_2Cl_2		10/90	98%[b]
4	DMAP/THF		80/20	49%[b]
5	DMAP/PhMe		60/40	73%[b]
6	DMAP/CH_2Cl_2	23/77		38%
7	DMAP/MeCN	0/100		91%
8	–/THF			0%

[a]Isolated yields. [b]Yield and ratio measured after oxidation.

processes. This choice is further guided by the obvious influence of the nucleophilic catalysts 3-nitro-1,2,4-triazole[47] and DMAP in the coupling process. An interesting feature of the nucleophilic catalysis observed concerns the charge state of the intermediate adducts. Thus, while the nitrotriazole with its pK_a of 5.19[47] must lead to a neutral adduct under the reaction conditions,[24a] the use of DMAP necessarily infers the close association of two at least formal positive charges, and it is interesting to speculate that such a system is stabilized by proximity to the hydride system (Figure 2). In these structures,

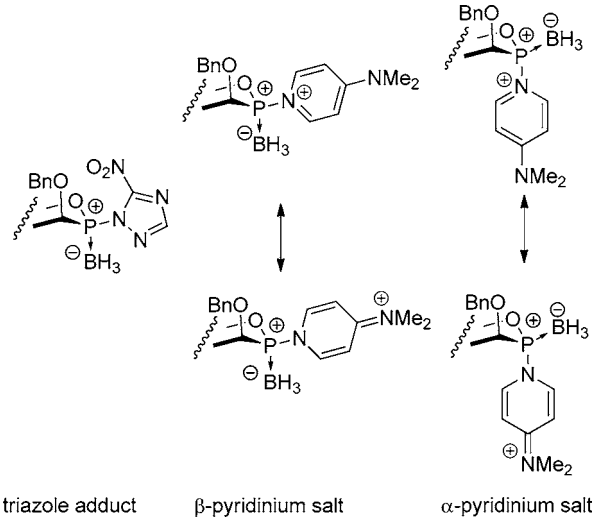


Figure 2. Hypothetical intermediate structures in the coupling reactions of **16mα** catalyzed by nitrotriazole and by DMAP. Counter ions have been omitted for clarity.

the amine may occupy the equatorial site, such as is typical in glycosyl imidazolinium[48] and pyridinium salts,[49] or the axial position. The equatorial preference of cationic substituents at the anomeric center is classically referred to as the reverse anomeric effect,[49a] for which the most reasonable current explanation simply revolves around the steric bulk of the solvated cation (and its associated anion), which causes it to occupy the least hindered site. The α-glycosyl pyridinium salts,

dx.doi.org/10.1021/ja305104b | J. Am. Chem. Soc. 2012, 134, 12289–12301

while sterically more demanding, are currently considered to benefit from the anomeric effect[50] due to the powerfully electron-withdrawing effect of the positively charged heterocycle.[51] For the pyridinium phosphinate−boranes proposed here, steric arguments favoring the equatorial system are less compelling due to the longer bonds of both the ring oxygen, C2, and the heterocyclic nitrogen to the phosphorus center than to the anomeric carbon in simple sugars.

In the case of the per-*O*-benzyl donor **16m*α***, which, with the nitrotriazole-based systems studied, affords exquisitely *α*-selective reactions (Table 4), it is evident that following initial activation the nucleophilic catalyst enters to give equatorial adducts of the type depicted in Figure 1 that are ultimately displaced by the incoming nucleophile to give the *α*-linked product. However, when NT was replaced by DMAP (Table 4, entry 7), a moderately *β*-selective reaction was observed albeit in only low yield. This latter result might be viewed as indicative of greater stability of the *α*-pyridinium salt versus its *β*-anomer or, conversely, of the operation of a Curtin−Hammett-type scenario in which the *α*- and *β*-pyridinium salts are in rapid dynamic equilibrium, with the less stable *α*-anomer being the more reactive of the two. In support of this argument, which draws on the Lemieux mechanism for the bromide anion catalyzed synthesis of *α*-glucosides,[52] we note that recent studies on the use of glucosyl pyridinium salts as glycosylating agents indicate that the *α*-isomer is the more reactive of the two anomers.[53] In a similar vein, we also note the recent proposal of *α*-glycosyl pyridinium salts as the reactive species in the DMAP catalyzed *β*-selective addition of alcohols to 2-nitroglycals.[54] With regard to the 2-*O*-acetyl donors studied (**15g*α*,*β***, **15m*α***, and **16m*α***), the situation is more complex, and it is evident that the acetate group influences the mechanism. Such a phenomenon closely parallels that seen in standard glycosyl donors and might be attributed to one or more of a combination of factors including neighboring group participation,[55] anchimeric assistance, and the simple electron-withdrawing (disarming) effect of the ester group. In the glucose series where both anomeric donors **15g*β*** and **15g*α*** are available for study, there is a clear preference for the formation of the *β*-anomeric product (Table 5) whatever the configuration of the donor employed except at higher concentrations of the nitrotriazole catalyst suggestive of neighboring group participation via a five-membered cyclic intermediate (Figure 3) following the initial activation. The difference in reactivity between the *α*- and *β*-donors **15g*α*** and **15g*β*** in the absence of nucleophilic catalysis is suggestive of anchimeric assistance to the departure of the leaving group by the trans-ester in the absence of the nucleophilic catalyst; evidence for such kinetic effects with a variety of classical donors is known even if their extent has recently been questioned.[56] However, the alternative possibility of the intervention of an *α*-glucosyl triazole or pyridinium salt, according to the additive employed, cannot be ruled out. In this respect, we note that glycosyl pyridinium salts are routinely prepared by the reaction of peracetylated glycosyl donors with pyridine; that is, the pyridinium salt is more stable than the cyclic dioxalenium ion. The reduced selectivity in the presence of greater amounts of the triazole catalyst is probably best explained by an increase in the equilibrium population of the covalently bound *β*-triazolyl species (Figure 3).

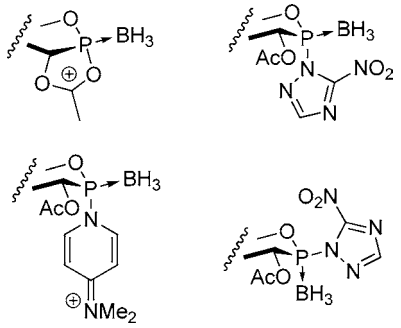


Figure 3. Hypothetical intermediates leading to the formation of *β*- and *α*-products from the donors **15g*α*** and **15g*β***. Partial charges at boron and phosphorus have been omitted for clarity.

With the *α*-manno-configured donor **15m*α***, a priori the most favorable system among those studied for the involvement of neighboring group participation, the situation appears more complex, and the selectivity was found to be dependent on solvent, at least with DMAP as the nucleophilic partner (Table 6). The *α*-anomeric product **19m*α*** or **20m*α*** that predominates under most conditions can be interpreted in terms of neighboring group participation with a cyclic dioxolenium ion intermediate as depicted in Figure 4, but the possibility of a *β*-pyridinium salt cannot be excluded particularly in view of the apparent requirement of DMAP for the formation of the coupling product. The preferential formation of the *β*-product **19m*β*** or **20m*β*** (Table 6, entries 4 and 5) and its formation to a significant extent in other cases (Table 6, entries 6 and 8) must be interpreted by the intervention of an *α*-adduct with DMAP (Figure 3) that is stabilized with respect to the corresponding more polar *β*-adduct or the polar dioxalenium ion in the less polar solvents in which the phenomenon occurs. In this context, it is important to note that the anomeric effect is larger in mannose than in glucose because of the antiperiplanar nature of the C2−O2 bond with respect to the axial glycosidic bond and, moreover, that the anomeric effect is greater in peracetylated mannose than in mannose itself.[57] Thus, the *α*-pyridinium salt can be expected to be more likely to play a role in the manno- rather than in the gluco-series, and this role is likely to be more important in the case of the acetylated mannosyl donor **15m*α*** than in that of the benzylated mannosyl donor **16m*α***.

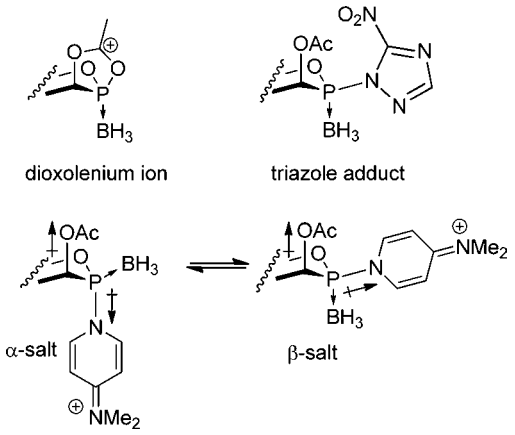


Figure 4. Hypothetical intermediates leading to the formation of *β*- and *α*-products from the donor **15m*α***. Partial charges at boron and phosphorus have been omitted for clarity.

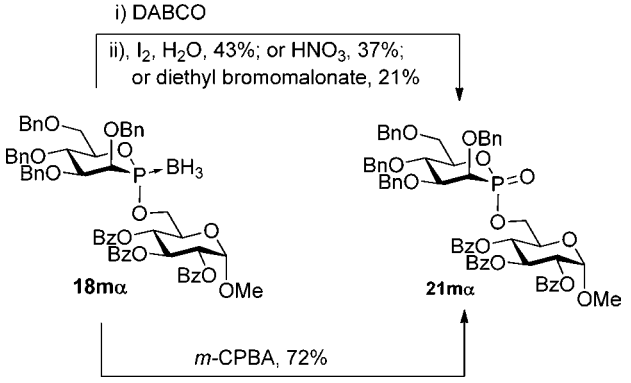
One final unknown is the extent to which, if any, dihydrogen bonding intervenes to direct the incoming nucleophile. Thus, a so-called dihydrogen bond between the hydridic hydrogen of

dx.doi.org/10.1021/ja305104b | J. Am. Chem. Soc. 2012, 134, 12289−12301

phosphine boranes and the acidic hydrogen of phenols has been advanced based on crystallographic evidence.[58] Accordingly, the possibility exists of such a dihydrogen bond between the incoming alcohol and the borane of one or more of the likely intermediates and that it directs the alcohol to the same face of the system as the borane moiety in a solvent-dependent manner. The possibility that donor−acceptor hydrogen bonding directs glycosylation reactions[59] has been raised in recent years and is a subject of ongoing discussion in the literature.[60]

Deborylation and Oxidative Deborylation. The ability to both deborylate the phosphonite−borane adducts following coupling and to oxidize the subsequent phosphonites to the P(V) oxidation in a predictable, stereospecific manner is a critical element in the overall protocol. Accordingly, we investigated a number of conditions for deborylation. Among the conditions assessed, tetrafluoroboric acid in dichloromethane,[23a] the dimethoxytrityl cation generated from dimethoxytrityl methyl ether with dichloroacetic acid,[61] and displacement with either trimethylphosphite or hexamethylphosphotriamide all were unsuccessful and left the starting material unchanged.[62] DABCO, which is reported to be the reagent of choice for deborylation of phosphine−boranes,[43] removed the borane moiety from the disaccharide **18mα** giving the corresponding phosphonite quantitatively, as determined by ^{31}P NMR spectroscopy; oxidative workup was then performed in situ to afford the corresponding phosphonate **21mα**. With I_2,[63] concentrated nitric acid,[64] and diethyl bromomalonate,[65] all reagents known to oxidize simple phosphines with inversion of configuration,[66] a single α-diastereomer that unexpectedly retained the configuration of the initial phosphonite−borane was obtained in 43%, 37%, and 21% yields, respectively (Scheme 7). Hydroxylamine, a further reagent known to oxidize phosphines with inversion of configuration,[67] was ineffective. The unexpected retention of configuration in these oxidations finds parallel in the work of Mikolajczyk who observed that oxidation of acyclic phosphonites with dimethyl selenoxide proceeds with inversion of configuration, but that of cyclic phosphonites with retention.[68] Direct oxidative deborylation of **18mα** with *m*-CPBA[24e,69] was found to be more convenient than the two step protocol and gave **21mα** in 72% yield with full retention of configuration consistent the literature on the oxidation of P(III) derivatives with peracids (Scheme 7).

Scheme 7. Conversion of the Phosphonite−Borane 18mα to the Phosphonate 21mα



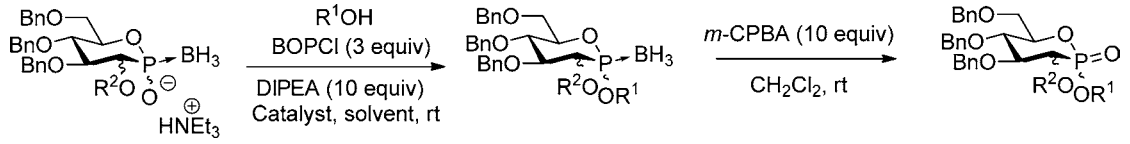
Assignment of Stereochemistry. The β-glucophostones **4gβ** and **6gβ** were obtained, respectively, by sodium nitrite and sodium acetic acetate displacement of the triflate group from **5mβ**, which itself was derived from **4mβ** by triflation (Table 2). Therefore, as the structure of **4gβ** was confirmed by X-ray crystallographic analysis (see the Supporting Information), the configurations of **4mβ**, **5mβ**, and **6gβ** are established by direct correlation and those of their anomers by default. The structures of compounds **8gβ** and **8mα** were also established crystallographically, which confirms by default those of their anomers **8gα** and **8mβ**. Subsequently, beyond the use of standard one and two-dimensional ^{1}H and ^{13}C methods for the assignment and verification of stereochemistry at C2 (gluco/manno) of the various phostone derivatives, we have relied on the use of $^2J_{H2-P}$ coupling constants for the determination of configuration at phosphorus, with spectral analysis being facilitated by the large (>100 Hz) $^1J_{P,C2}$ coupling constant and the consequent easy identification of H2. In the gluco-series, we found the $^2J_{H2-P}$ coupling constant to be consistently smaller for the α-series (1.7−4.6 Hz) in which the phosphoryl (P═O) bond is gauche to the C2−H2 bond than for the β-series (6.4−10.4 Hz) in which the P═O and C2−H2 bonds are antiperiplanar. The NMR-derived configurations are in full accord with those derived above crystallographically and by chemical correlation. These crystallographically supported correlations of $^2J_{H2-P}$ coupling constants with anomeric stereochemistry for the gluco-phostones agree neither with Drueckhammer who, in his pioneering work on the phostones,[11c] adduced the opposite rule, nor with Claesson and co-workers[42] who subsequently upheld Drueckhammer albeit without experimental support. At present, we are unable to rationalize this difference in interpretation. Correlation of the $^2J_{H2-P}$ coupling constants with anomeric stereochemistry is not applicable in the manno-series due to the gauche relationship of H2 to the P═O bond in both anomers.

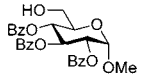
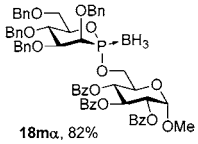
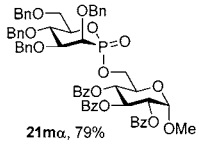
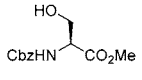
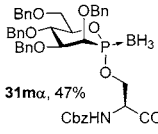
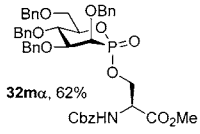
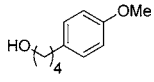
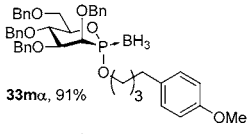
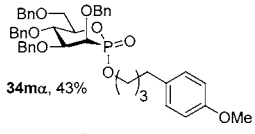
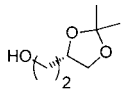
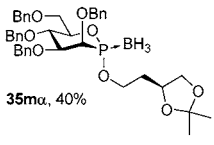
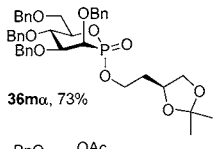
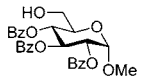
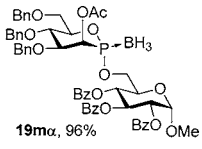
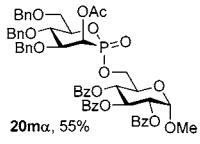
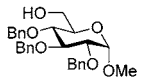
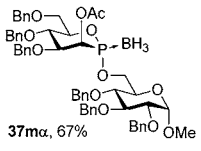
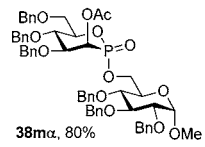
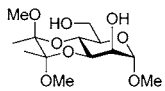
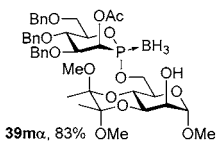
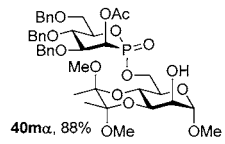
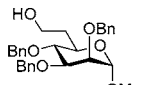
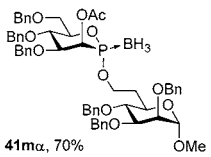
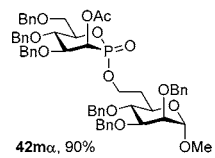
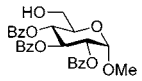
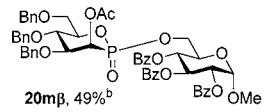
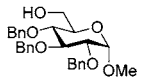
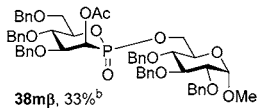
In many cases, supporting data may also be gleaned from the ^{31}P chemical shift of the phostones with the axial P−OMe group resonating some 2−4 ppm more upfield than the corresponding equatorial P−OMe moiety.[11e] We found this rule to apply in the **4**, **6**, and **9** series; a larger chemical shift difference of 8−14 ppm was observed in the thiophostones **11** and **12**. This effect is less pronounced in the *manno* series than in the *gluco* series, and is reduced to zero for **11mα** and **11mβ**. We also noted a consistently higher value for the $^3J_{P,OMe}$ coupling constant for the equatorial P−OMe groups than for the axial P−OMe systems, with the sole exception of the two *manno* derivatives **4mα** and **4mβ**. IR spectroscopy gave a final confirmation of the anomeric configuration of all compounds. As described by Thiem,[11a] we observed the axial P═O bonds to have a γ_{max} of 1260 cm^{-1}, whereas the equatorial P═O bond has γ_{max} 1290 cm^{-1}.

In the solid state, all of the compounds analyzed crystallographically exhibit a well-defined chair conformation, even those with an axial P−-OMe group, although it had been suggested previously that such compounds may also adopt a twist boat conformation.[11e,70] The crystallographically observed chair conformations persist in solution as their $^2J_{H2,P}$ coupling constants were typically <5 Hz, whereas they are known to be in the range of 30−35 Hz for six-membered cyclic phosphonates that adopt boat or twist-boat conformations.[11a,42]

Exploration of Acceptor Scope and Limitations and Final Deprotection. The couplings of donors **15gα,β**, **15mα**, and **16mα** were explored with a range of primary alcohols (**17**,

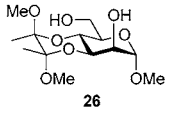
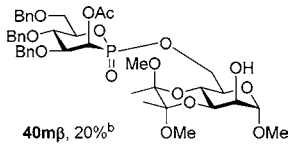
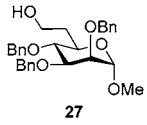
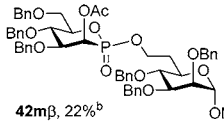
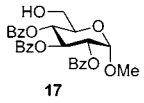
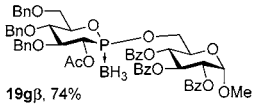
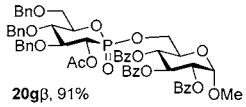
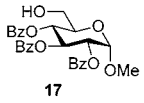
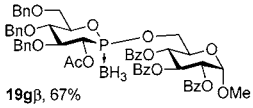
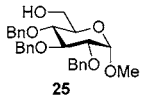
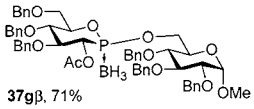
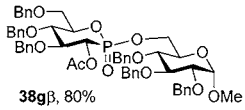
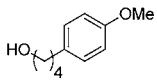
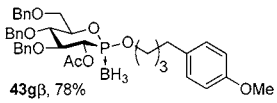
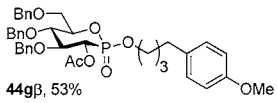
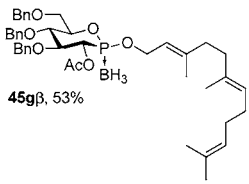
Table 7. Coupling Reactions of Ammonium Boranophosphonites and Subsequent Oxidation and Deprotection



entry	donor	Cata-lyst/solvent	acceptor	coupled product, yield[a]	oxidized product, yield[a]
1	**16mα**	NT/THF	 **17**	 **18mα**, 82%	 **21mα**, 79%
2	**16mα**	NT/THF	 **22**	 **31mα**, 47%	 **32mα**, 62%
3	**16mα**	NT/THF	 **23**	 **33mα**, 91%	 **34mα**, 43%
4	**16mα**	NT/THF	 **24**	 **35mα**, 40%	 **36mα**, 73%
5	**15mα**	NT/PhMe	 **17**	 **19mα**, 96%	 **20mα**, 55%
6	**15mα**	NT/MeCN	 **25**	 **37mα**, 67%	 **38mα**, 80%
7	**15mα**	NT/MeCN	 **26**	 **39mα**, 83%	 **40mα**, 88%
8	**15mα**	NT/MeCN	 **27**	 **41mα**, 70%	 **42mα**, 90%
9	**15mα**	DMAP/THF	 **17**	-	 **20mβ**, 49%[b]
10	**15mα**	DMAP/THF	 **25**	-	 **38mβ**, 33%[b]

dx.doi.org/10.1021/ja305104b | J. Am. Chem. Soc. 2012, 134, 12289−12301

Table 7. continued

11	**15mα**	DMAP/THF	 **26**	-	 **40mβ**, 20%[b]
12	**15mα**	DMAP/THF	 **27**	-	 **42mβ**, 22%[b]
13	**15gβ**	DMAP/THF	 **17**	 **19gβ**, 74%	 **20gβ**, 91%
14	**15gα**	DMAP/THF	 **17**	 **19gβ**, 67%	
15	**15gα**	DMAP/THF	 **25**	 **37gβ**, 71%	 **38gβ**, 80%
16	**15gβ**	DMAP/THF	 **23**	 **43gβ**, 78%	 **44gβ**, 53%
17	**15gβ**	DMAP/THF	Farnesol, **28**	 **45gβ**, 53%	-

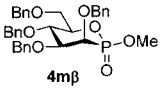
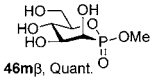
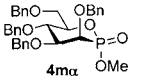
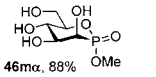
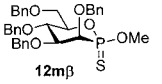
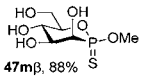
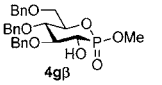
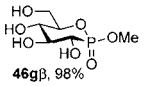
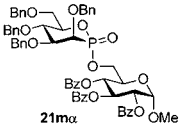
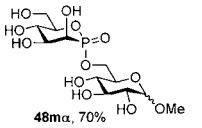
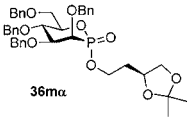
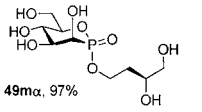
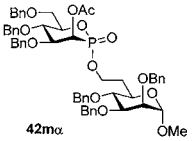
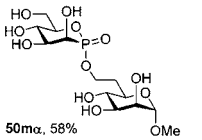
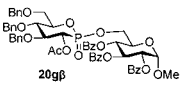
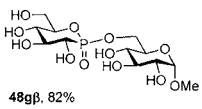
[a]Isolated yields. [b]Anomeric ratio of 1:4 α:β determined by ^{1}H NMR on the crude reaction mixture; the yield is for the pure isolated β-isomer.

22–**28**), prepared by standard means, leading to the results reported in Table 7. The coupled products either were isolated and characterized and subsequently oxidized to the phosphonates with *m*-CPBA (Table 7, entries 1–8, 13–16) or were engaged directly in the oxidative deborylation without intermediate purification (Table 7, entries 9–12). A final example (Table 7, entry 17) was not subjected to deborylation or oxidation because of the olefinic character of the aglycone. Each of these coupling reactions proceeded with moderate to good yield and with excellent stereoselectivity consistent with the patterns established in the exploratory phase of the investigation (vide supra). The only exception to this rule was couplings conducted with donor **15mα** under conditions optimized for formation of the β-anomer (Table 7, entries 9 and 10) when approximately 4:1 mixtures of diastereomers were observed in which the desired β-anomer nevertheless predominated. Attempts to extend the various coupling reactions to the use of secondary alcohols as acceptors such as menthol or methyl 2,3-*O*-isopropylidene-L-rhamnopyranoside were, however, generally unsuccessful giving only low yields of disaccharides, presumably for steric reasons arising from the presence of the borane moiety at the reaction center. All oxidation reactions proceeded with clean retention of configuration at phosphorus.

Finally, we turned to the deprotection of selected examples with the goal of identifying conditions suitable for the removal of both acid and base labile protecting groups without detriment to the cyclic phosphonate functionality. To this end, working with the simple methyl phosphonates, we determined that exposure to BCl_3 in dichloromethane followed by workup with MeOH in the standard manner[71] is a convenient and suitable method for the removal of benzyl ethers without concomitant cleavage of the phosphonate group (Table 8, entries 1 and 2). This protocol was also applicable to the methyl thiophosphonate **12mβ** (Table 8, entry 3) giving the fully deprotected thiophostone **47mβ**. Hydrogenolysis over palladium on charcoal was also found to be suitable for the removal of benzyl ethers (Table 8, entry 4).[71] With respect to the removal of carboxylate esters, careful treatment with sodium methoxide in methanol was found to be suitable provided that the reaction was carefully monitored and quenched before the onset of the slower transesterification of the phosphonate group. Thus, phostone **21mα** was exposed to sodium methoxide to remove the three benzoate esters followed, after extractive workup, by BCl_3 resulting overall in the phostone **48mα** in 70% overall yield (Table 8, entry 5). Unfortunately, the methyl glucoside moiety of **48mα** was scrambled during the course of the methanolic workup of BCl_3 (Table 8, entry 5). Treatment with BCl_3 followed by MeOH was effective for the removal of the acetonide group in **36mα** concomitant with cleavage of the benzyl ethers (Table 8, entry 6). Transesterification with sodium methoxide in methanol followed hydrogenolysis in a mixture of acetic acid and aqueous THF was found to be suitable for the complete deprotection of **42mα** giving phostone **50mα** in 58% yield for the two steps (Table 8, entry 7). Finally, transesterification and hydro-

dx.doi.org/10.1021/ja305104b | J. Am. Chem. Soc. 2012, 134, 12289–12301

Table 8. Deprotection of Phostones

entry	substrate	conditions	product, % yield
1	 **4mβ**	BCl_3	 **46mβ**, Quant.
2	 **4mα**	BCl_3	 **46mα**, 88%
3	 **12mβ**	BCl_3	 **47mβ**, 88%
4	 **4gβ**	H_2, Pd/C, THF:H_2O :AcOH	 **46gβ**, 98%
5	 **21mα**	i) NaOMe, MeOH; ii) BCl_3	 **48mα**, 70%
6	 **36mα**	BCl_3	 **49mα**, 97%
7	 **42mα**	i) NaOMe, MeOH ii) H_2, Pd/C, THF:H_2O :AcOH	 **50mα**, 58%
8	 **20gβ**	i) NaOMe, MeOH ii) H_2, Pd/C, THF:H_2O :AcOH	 **48gβ**, 82%

genolysis converted **20gβ** to phostone **48gβ** in 82% yield (Table 8, entry 8).

CONCLUSION

Asymmetric hydrophosphonylation methodology enables optimization of the Drueckhammer synthesis of six-membered phostones for the formation of the manno-isomer, of which inversion affords ready access to the gluco-series. Subsequent conversion to the thiophostones with Lawesson's reagents enables reduction to the P(III) oxidation level with Raney nickel enabling formation, after demethylation, of the formation of a series of phostone donors that may be readily protected and stored in the form of their borane adducts. The direct application of these phosphonite−boranes in coupling to primary alcohols, followed by oxidation with *m*-CPBA, affords phostone mimetics with yields and stereoselectivities that differ as a function of the stereochemistry of the donor at both phosphorus and the adjacent carbon (C2). The nature of the O2 protecting group, ester or ether, also impinges on the selectivity of the coupling process as does the absence or presence of a nucleophilic catalyst. Overall, protocols were established for the preparation of three series of protected diastereomeric phostones, the *β*-gluco, and *α*- and *β*-manno-mimetics of the pyranoside sugars for which suitable deprotection conditions were established. Further work will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Full characterization data and copies of spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

dcrich@chem.wayne.edu

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

A.F. thanks the ICSN for financial support.

REFERENCES

(1) (a) Seeberger, P. H. *Nat. Chem. Biol.* **2009**, *5*, 368−372. (b) Stallforth, P.; Lepenies, B.; Adibekian, A.; Seeberger, P. H. *J. Med. Chem.* **2009**, *52*, 5561−5577.

(2) (a) Demchenko, A. V. *Handbook of Chemical Glycosylation: Advances in Stereoselectivity and Therapeutic Relevance*; Wiley-VCH: Weinheim, 2008. (b) Crich, D. *Acc. Chem. Res.* **2010**, *43*, 1144−1153.

(3) Koenigs, W.; Knorr, E. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 957−981.

(4) Roy, R. *Glycomimetics: Modern Synthetic Methodologies*; American Chemical Society: Washington, DC, 2005.

(5) Bruno, B.; Vasella, A. In *Acetylene Chemistry*; Diederich, F., Stang, P. J., Tykwinski, R. R., Eds.; Wiley-VCH: Weinheim, 2005; pp 173−231.

(6) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952−3015.

(7) (a) Dedola, S.; Nepogodiev, S. A.; Field, R. A. *Org. Biomol. Chem.* **2007**, *5*, 1006−1017. (b) Dondoni, A. *Chem. Asian J.* **2007**, *2*, 700−708. (c) Nicotra, F.; Cipolla, L.; Peri, F.; La Ferla, B.; Redaelli, C. *Adv. Carbohydr. Chem. Biochem.* **2007**, *61*, 353−398. (d) Györgydeák, Z.; Thiem, J. *Adv. Carbohydr. Chem. Biochem.* **2006**, *60*, 103−182. (e) Pieters, R. J.; Rijkers, D. T. S.; Liskamp, R. M. J. *QSAR Comb. Sci.* **2007**, *26*, 1181−1190. (f) Santoyo-Gonzalez, F.; Hernandez-Mateo, F. *Top. Heterocycl. Chem.* **2007**, *7*, 133−177. (g) Hanson, S. R.; Greenberg, W. A.; Wong, C.-H. *QSAR Comb. Sci.* **2007**, *26*, 1243−1252. (h) Wilkinson, B. L.; Bornaghi, L. F.; Houston, T. A.; Poulsen, S.-A. In *Drug Design Research Perspectives*; Kaplan, S. P., Ed.; Nova Science Publishers: Hauppauge, NY, 2007; pp 57−102.

(8) Malik, G.; Guinchard, X.; Crich, D. *Org. Lett.* **2012**, *14*, 596−599.

(9) (a) Crich, D.; Subramanian, V.; Karatholuvhu, M. *J. Org. Chem.* **2009**, *74*, 9422−9427. (b) Crich, D.; Krishnamurthy, V.; Brebion, F.; Karatholuvhu, M.; Subramanian, V.; Hutton, T. K. *J. Am. Chem. Soc.* **2007**, *129*, 10282−10294. (c) Crich, D.; Zou, Y.; Brebion, F. *J. Org. Chem.* **2006**, *71*, 9172−9177.

(10) Subramanian, V.; Moumé-Pymbock, M.; Hu, T.; Crich, D. *J. Org. Chem.* **2011**, *76*, 3691−3709.

(11) (a) Thiem, J.; Günther, M.; Paulsen, H.; Kopf, J. *Chem. Ber.* **1977**, *110*, 3190−3200. (b) Thiem, J.; Günther, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **1984**, *20*, 67−79. (c) Darrow, J. W.; Drueckhammer, D. G. *J. Org. Chem.* **1994**, *59*, 2976−2985. (d) Hanessian, S.; Galéotti, N.; Rosen, P.; Oliva, G.; Babu, S. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2763−2768. (e) Harvey, T. C.; Weiler, L.; Withers, S. G. *J. Org. Chem.* **1997**, *62*, 6722−6725. (f) Polozov, A. M.; Cremer, S. E.; Fanwick, P. E. *Can. J. Chem.* **1999**, *77*, 1274−1280. (g) Hanessian, S.; Rogel, O. *J. Org. Chem.* **2000**, *65*, 2667−2674. (h) Stoianova, D. S.; Hanson, P. R. *Org. Lett.* **2001**, *3*, 3285−3288. (i) Stoianova, D. S.; Whitehead, A.; Hanson, P. R. *J. Org. Chem.* **2005**, *70*, 5880−5889. (j) Bisseret, P.; Boiteau, J.-G.; Eustache, J. *Tetrahedron Lett.* **2003**, *44*, 2351−2354.

(12) Darrow, J. W.; Drueckhammer, D. G. *Bioorg. Med. Chem.* **1996**, *4*, 1341−1348.

(13) (a) Hanaya, T.; Tsukui, H.; Igi, N.; Noguchi, A.; Kawamoto, H.; Yamamoto, H. *Heterocycles* **2007**, *72*, 411−420. (b) Hanaya, T.; Koga, Y.; Kawamoto, H.; Yamamoto, H. *Heterocycles* **2007**, *73*, 581−591. (c) Hanaya, T.; Sugiyama, K.; Kawamoto, H.; Yamamoto, H. *Carbohydr. Res.* **2003**, *338*, 1641−1650. (d) Hanaya, T.; Fujii, Y.; Ikejiri, S.; Yamamoto, H. *Heterocycles* **1999**, *50*, 323−332. (e) Hanaya, T.; Yamamoto, H. *J. Synth. Org. Chem. Jpn.* **1993**, *51*, 377−387. (f) Hanaya, T.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1154−1156. (g) Hanaya, T.; Noguchi, A.; Armour, M. A.; Hogg, A. M.; Yamamoto, H. *J. Chem. Soc., Perkin Trans. 1* **1992**, 295−301. (h) Hanaya, T.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2320−2327. (i) Yamamoto, H.; Hanaya, T.; Kawamoto, H.; Inokawa, S.; Yamashita, M.; Armour, M. A.; Nakashima, T. T. *J. Org. Chem.* **1985**, *50*, 3516−3521.

(14) (a) Cristau, H.-J.; Monbrun, J.; Schleiss, J.; Virieux, D.; Pirat, J.-L. *Tetrahedron Lett.* **2005**, *46*, 3741−3744. (b) Pirat, J.-L.; Virieux, D.; Clarion, L.; Volle, J.-N.; Bakalara, N.; Mersel, M.; Montbrun, J.; Cristau, H.-J. WO 2009004096A1 I, 2009. (c) Clarion, L.; Jacquard, C.; Sainte-Catherine, O.; Loiseau, S.; Filippini, D.; Hirlemann, M.-H.; Volle, J.-N.; Virieux, D.; Lecouvey, M.; Pirat, J.-L.; Bakalara, N. *J. Med. Chem.* **2012**, *55*, 2196−2211.

(15) (a) Stawinski, J.; Stömberg, R. *Trends Org. Chem.* **1993**, *4*, 31. (b) Stawinski, J. In *Handbook of Organophosphorus Chemistry*; Engel, R., Ed.; Marcel Dekker: New York, 1992; pp 377−434. (c) Kraszewski, A.; Stawinski, J. *Pure Appl. Chem.* **2007**, *79*, 2217−2227. (d) Stawinski, J.; Kraszewski, A. *Acc. Chem. Res.* **2002**, *35*, 952−960.

(16) (a) Yudelevich, V. I.; Sokolov, L. B.; Ionin, B. I. *Russ. Chem. Rev.* **1980**, *49*, 46−58. (b) Montchamp, J.-L. *J. Organomet. Chem.* **2005**, *690*, 2388−2406. (c) Bravo-Altamirano, K.; Coudray, L.; Deal, E. L.; Montchamp, J.-L. *Org. Biomol. Chem.* **2010**, *8*, 5541−5551.

(17) *Chemistry and Application of H-Phosphonates*; Troev, K. D., Ed.; Elsevier: New York, 2006.

(18) Kraszewski, A.; Stawinski, J. *Trends Org. Chem.* **2003**, *10*, 1−19.

(19) (a) Wada, T.; Sato, Y.; Honda, F.; Kawahara, S.-i.; Sekine, M. *J. Am. Chem. Soc.* **1997**, *119*, 12710−12721. (b) Sobkowski, M.; Stawinski, J.; Kraszewski, A. *Tetrahedron: Asymmetry* **2008**, *19*, 2508−2518. (c) Lavéna, G.; Stawinski, J. *ARKIVOC* **2009**, 20−27. (d) Sobkowski, M.; Stawinski, J.; Kraszewski, A. *Tetrahedron: Asymmetry* **2010**, *21*, 410−419.

(20) (a) Atherton, F.; Openshaw, A.; Todd, A. *J. Chem. Soc.* **1945**, 660−663. (b) Zhou, Y.; Wang, G.; Saga, Y.; Shen, R.; Goto, M.; Zhao, Y.; Han, L.-B. *J. Org. Chem.* **2010**, *75*, 7924−7927. (c) Wang, G.; Shen, R.; Xu, Q.; Goto, M.; Zhao, Y.; Han, L.-B. *J. Org. Chem.* **2010**, *75*, 3890−3892.

(21) Staubitz, A.; Robertson, A. P. M.; Sloan, M. E.; Manners, I. *Chem. Rev.* **2010**, *110*, 4023−4078.

(22) (a) Guthrie, J. P. *Can. J. Chem.* **1979**, *57*, 236−239. (b) Doak, G. O.; Freedman, L. D. *Chem. Rev.* **1961**, *61*, 31−44.

(23) (a) Belabassi, Y.; Antczak, M. I.; Tellez, J.; Montchamp, J.-L. *Tetrahedron* **2008**, *64*, 9181−9190. (b) Antczak, M. I.; Montchamp, J.-L. *Org. Lett.* **2008**, *10*, 977−980.

(24) (a) Wada, T.; Shimizu, M.; Oka, N.; Saigo, K. *Tetrahedron Lett.* **2002**, *43*, 4137−4140. (b) Higashida, R.; Oka, N.; Kawanaka, T.; Wada, T. *Chem. Commun.* **2009**, 2466−2468. (c) Sato, K.; Oka, N.; Fujita, S.; Matsumura, F.; Wada, T. *J. Org. Chem.* **2010**, *75*, 2147−2156. (d) Enya, Y.; Nagata, S.; Masutomi, Y.; Kitagawa, H.; Takagaki, K.; Oka, N.; Wada, T.; Ohgi, T.; Yano, J. *Bioorg. Med. Chem.* **2008**, *16*, 9154−9160. (e) Matsumura, F.; Oka, N.; Wada, T. *Org. Lett.* **2008**, *10*, 1557−1560.

(25) Shimizu, M.; Wada, T.; Oka, N.; Saigo, K. *J. Org. Chem.* **2004**, *69*, 5261−5268.

(26) However, in the course of the stereoselective synthesis of P-chiral nucleotides analogues, other strategies have been studied, see: Oka, N.; Wada, T. *Chem. Soc. Rev.* **2011**, *40*, 5829−5843.

(27) In accordance with the designated use of the phostones as sugar mimetics, we have adopted standard carbohydrate nomenclature throughout this Article.

(28) Zhao, D.; Wang, R. *Chem. Soc. Rev.* **2012**, *41*, 2095−2108.

(29) Yang, F.; Zhao, D.; Lan, J.; Xi, P.; Yang, L.; Xiang, S.; You, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 5646−5649.

(30) Continuing the use of carbohydrate-based nomenclature, we apply a modification of the Rosanoff convention to describe the stereochemistry at phosphorus in the cyclic phostones. Thus, for the D-configured sugars studied that essentially adopt the $^4C_1$ chair conformation, the equatorial ester mimicking the glycosidic bond is termed the β-anomer, while its axial counterpart is named as the α-anomer.

(31) Swamy, K. C. K.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. V. P. P. *Chem. Rev.* **2009**, *109*, 2551−2651.

(32) Oxidation/selective reduction strategies such as the one described by Virieux and Pirat have not been investigated, see: Filippini, D.; Loiseau, S.; Bakalara, N.; Dziuganowska, Z. A.; Van der Lee, A.; Volle, J.-N.; Virieux, D.; Pirat, J.-L. *RSC Adv.* **2012**, *2*, 816−818.

(33) Comins, D. L.; Dehghani, A.; Foti, C. J.; Joseph, S. P. *Org. Synth.* **1977**, *74*, 77−80.

(34) San Filippo, J.; Chern, C.-I.; Valentine, J. S. *J. Org. Chem.* **1975**, *40*, 1678−1680.

(35) Dong, H.; Pei, Z.; Ramström, O. *J. Org. Chem.* **2006**, *71*, 3306−3309.

(36) Hanessian reports $[\alpha]_D$ of −16.9° for **6m*α***, whereas we find +14.8°, both with c = 1 in $CHCl_3$.

(37) Lewis or Bronsted acid-based debenzylations are known with reagents other than iodine, see: Greene, T. H.; Wuts, P. G. M. *Prot. Groups Org. Chem.* **2007**, 111−113.

(38) Faul, M. M.; Winneroski, L. L.; Krumrich, C. A. *J. Org. Chem.* **1999**, *64*, 2465−2470.

(39) Sajiki, H.; Hirota, K. *Tetrahedron* **1998**, *54*, 13981−13996.

(40) Interestingly, and confirming the necessity for protection of position 2, with the corresponding 2-hydroxy compounds **4g*αβ*** and **4m*αβ***, no reaction was observed with Lawesson's reagent.

(41) Jiang, B.; Lei, Y.; Zhao, X.-L. *J. Org. Chem.* **2008**, *73*, 7833−7836.

(42) Molin, H.; Norèn, J.-O.; Claesson, A. *Carbohydr. Res.* **1989**, *194*, 209−221.

(43) Brisset, H.; Gourdel, Y.; Pellon, P.; Le Corre, M. *Tetrahedron Lett.* **1993**, *34*, 4523−4526.

(44) (a) Fujita, S.; Oka, N.; Matsumura, F.; Wada, T. *J. Org. Chem.* **2011**, *76*, 2648−2659. (b) Daub, G. W.; Van Tamelen, E. E. *J. Am. Chem. Soc.* **1977**, *99*, 3526−3528.

(45) Oka, N.; Shimizu, M.; Saigo, K.; Wada, T. *Tetrahedron* **2006**, *62*, 3667−3673.

(46) (a) van Bochove, M. A.; Swart, M.; Bickelhaupt, F. M. *ChemPhysChem* **2007**, *8*, 2452−2463. (b) van Bochove, M. A.; Swart, M.; Bickelhaupt, F. M. *Phys. Chem. Chem. Phys.* **2009**, *11*, 259−267.

(47) Nurminen, E. J.; Mattinen, J. K.; Lönnberg, H. *Helv. Chim. Acta* **2003**, *86*, 2005−2008.

(48) Lemieux, R. U. *Pure Appl. Chem.* **1971**, *25*, 527−548.

(49) (a) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2205−2213. (b) Hosie, L.; Marshall, P. J.; Sinnott, M. L. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1121−1131. (c) Dauben, W. G.; Köhler, P. *Carbohydr. Res.* **1990**, *203*, 47−56.

(50) (a) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer: New York, 1983. (b) Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019−5087.

(51) Perrin, C. L.; Young, D. B. *Tetrahedron* **1995**, *51*, 11901−11935.

(52) (a) Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056−4062. (b) Kaeothip, S.; Yasomanee, J. P.; Demchenko, A. V. *J. Org. Chem.* **2012**, *77*, 291−299.

(53) Smoot, J. T.; Demchenko, A. V. *J. Org. Chem.* **2008**, *73*, 8838−8850.

(54) Xue, W.; Sun, J.; Yu, B. *J. Org. Chem.* **2009**, *74*, 5079−5082.

(55) (a) Winstein, S.; Buckles, R. E. *J. Am. Chem. Soc.* **1942**, *64*, 2780−2786. (b) Nukada, T.; Berces, A.; Zgierski, M. Z.; Whitfield, D. M. *J. Am. Chem. Soc.* **1998**, *120*, 13291−13295. (c) Bérces, A.; Enright, G.; Nukada, T.; Whitfield, D. M. *J. Am. Chem. Soc.* **2001**, *123*, 5460−5464.

(56) Heuckendorff, M.; Pedersen, C. M.; Bols, M. *Org. Lett.* **2011**, *13*, 5956−5959.
(57) Lemieux, R. U. In *Molecular Rearrangements*; Mayo, P. D., Ed.; Interscience: New York, 1964; Vol. *2*, pp 709−769.
(58) Wawrzyniak, P.; Kindermann, M. K.; Heinicke, J. W.; Jones, P. G. *Eur. J. Org. Chem.* **2011**, *2011*, 593−606.
(59) Whitfield, D. M. In *Advances in Carbohydrate Chemistry and Biochemistry*; Horton, D., Ed.; Academic Press: New York, 2009; Vol. *62*, pp 83−159.
(60) (a) Crich, D.; Sharma, I. *Org. Lett.* **2008**, *10*, 4731−4734. (b) Huang, M.; Garrett, G. E.; Birlirakis, N.; Bohé, L.; Pratt, D. A.; Crich, D. *Nat. Chem.* **2012**, DOI: 10.1038/NCHEM.1404. (c) Whitfield, D. M. *Carbohydr. Res.* **2012**, *356*, 191−195.
(61) Shimizu, M.; Tamura, K.; Wada, T.; Saigo, K. *Tetrahedron Lett.* **2004**, *45*, 371−374.
(62) A number of other reagents for deborylation have also been described. *N*-Methylpiperazine and diethylamine: (a) Antczak, M. I.; Montchamp, J.-L. *Org. Lett.* **2008**, *10*, 977−980. (b) Bisseret, P.; Eustache, J. *Tetrahedron Lett.* **2001**, *42*, 8451−8453. EtOH: (c) Ortial, S. P.; Thompson, D. A.; Montchamp, J.-L. *J. Org. Chem.* **2010**, *75*, 8166−8179. (d) Belabassi, Y.; Gushwa, A. F.; Richards, A. F.; Montchamp, J.-L. *Phosphorus, Sulfur Silicon Relat. Elem.* **2008**, *183*, 2214−2228.
(63) Horner, L.; Winkler, H. *Tetrahedron Lett.* **1964**, *5*, 175−179.
(64) Michalski, J.; Okruszek, A.; Stec, W. *J. Chem. Soc., Chem. Commun.* **1970**, 1495−1497.
(65) Denney, D. B.; Adin, N. G. *Tetrahedron Lett.* **1966**, *7*, 2569−2572.
(66) Pietrusiewicz, K. M.; Zablocka, M. *Chem. Rev.* **1994**, *94*, 1375−1411.
(67) Stec, W. J.; Okruszek, A. *J. Chem. Res.* **1977**, 142.
(68) Mikolajczyk, M.; Luczak, J. *J. Org. Chem.* **1978**, *43*, 2132−2138.
(69) Imamoto, T.; Hirose, K.; Amano, H. *Main Group Chem.* **1996**, *1*, 331−338.
(70) Gorenstein, D. G. *Chem. Rev.* **1987**, *87*, 1047−1077.
(71) Greene, T. H.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 4th ed.; John Wiley & Sons: Hoboken, NJ, 2007.

■ NOTE ADDED AFTER ASAP PUBLICATION

After ASAP publication on July 16, 2012, references to forms iv and v in Figure 1 near the end of the second paragraph were corrected. The corrected version reposted July 25, 2012.