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Oligosaccharide Synthesis Based on Glycosyl Donors and Acceptors Carrying Phosphorus-Containing Leaving Groups

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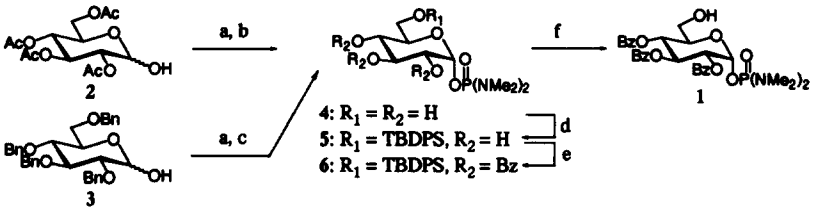
Abstract: *Efficient synthetic strategy for oligosaccharides has been developed by exploiting the difference in anomeric reactivity between glycosyl donors and acceptors carrying phosphorus-containing leaving groups, wherein the tetramethylphosphoroamidate group plays a pivotal role as anomeric protective group as well as leaving group.* © 1997 Elsevier Science Ltd.

The rapidly growing significance of oligosaccharides of cell surface-associated glycoconjugates as determinants for cell-cell recognition during many pathophysiological processes has spurred the development of a variety of innovative glycosidation strategies for the construction of oligosaccharides and their mimetics.[2,3] The major challenge to a convergent block synthesis of oligosaccharides is a facile construction of saccharide building blocks as well as their high-yielding and stereocontrolled assembly, wherein an anomeric protective group of glycosyl acceptors, after each glycosidation, has heretofore been converted into a leaving group for the next coupling under conditions that leave other protective groups on a saccharide block unaffected. In that these tedious interchange steps are no longer required, the "armed-disarmed" principle proposed by Fraser-Reid[4] is a notable recent landmark in this field, wherein a C2 benzyl-protected 4-pentenyl glycoside ("armed" donor) can be coupled chemoselectively to a benzoyl-protected 4-pentenyl glycoside ("disarmed" acceptor) and the disaccharide thus obtained can be directly glycosidated with a sugar alcohol. The "armed-disarmed" phenomenon due to the effect of protective groups on anomeric reactivity has been subsequently recognized with other, more established glycosyl donors such as thioglycosides,[5,6] glycals,[7] selenoglycosides,[8] and glycosyl fluorides.[9] The "armed-disarmed" glycosidation strategy is currently expanding into "active-latent",[10,11] "one-pot",[12-15] and "orthogonal"[16] glycosidation strategies, all of which focus on the chemoselective glycosidations based on the nature of leaving groups with different reactivities toward a given promoter.[17]

We have recently devised new glycosyl donors incorporating a variety of phosphorus-containing leaving groups, the glycosidations of which constitute mild and efficient methods for the highly stereocontrolled construction of 1,2-*trans*-β- and 1,2-*cis*-α-glycosidic linkages with or without a participating group on C2.[18] Herein, we wish to report a novel contribution of our glycosidation methods to the second-generation "armed-disarmed" strategy, a key feature of which is the fact that the tetramethylphosphoroamidate group plays a pivotal role as anomeric protective group as well as leaving group.

Of the glycosyl donors developed in our group, glycosyl tetramethylphosphoroamidates have been proven to be by far the most shelf-stable.[19a] Thus, we chose 2,3,4-tri-*O*-benzoyl-α-D-glucopyranosyl tetramethylphosphoroamidate **1**[20] as a "disarmed" acceptor, which was stereoselectively prepared from 2,3,4,6-tetra-*O*-acetyl- or benzyl-D-glucopyranose (**2** or **3**) by a series of routine functional and protective group manipulations

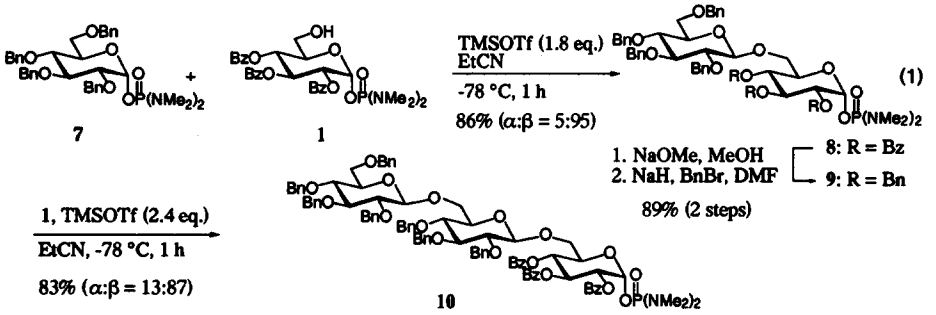


Reagents and conditions: a) *n*-BuLi, THF, -78 °C, 15 min, then $(Me_2N)_2P(=O)Cl$, HMPA, -10 °C, 2 h; b) Et_3N, MeOH, 2 d; c) H_2, $Pd(OH)_2/C$, MeOH, 2 d; d) TBDPSCl, imidazole, CH_3CN, -5 °C, 1 h; e) BzCl, DMAP, Py, 2 h; f) TBAF, AcOH, THF, 1 h.

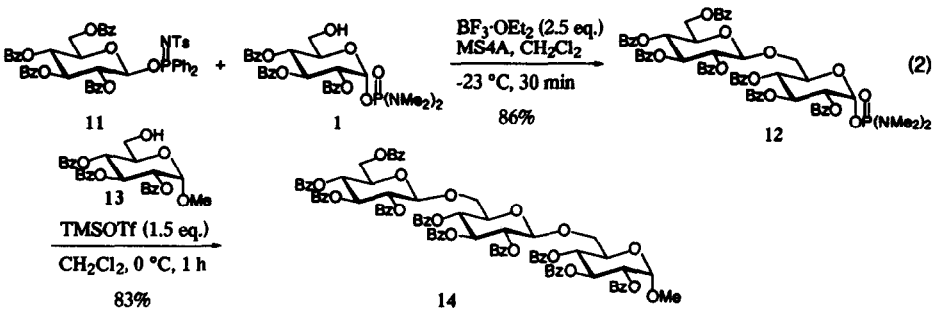
Scheme 1

(Scheme 1). Noteworthy is the fact that the anomeric tetramethylphosphoroamidate group is compatible with a variety of reaction conditions.

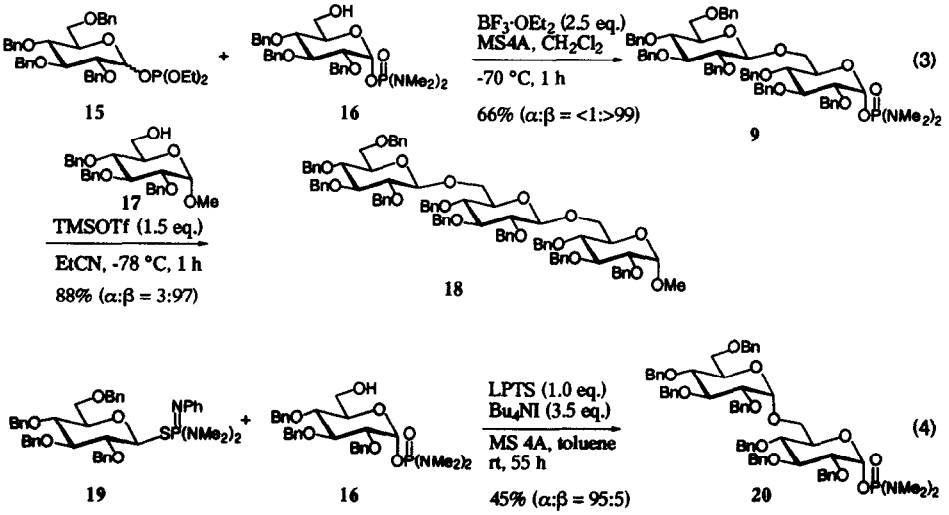
Patterned after the original work of Fraser-Reid,[4a] the initial phase of our study with **1** was focused on the feasibility of chemoselective glycosidation using the fully benzylated glycosyl tetramethylphosphoroamidate **7** as an "armed" donor (eq 1). As might be expected, trimethylsilyl trifluoromethanesulfonate (TMSOTf)-promoted coupling of **7** with **1** was found to proceed smoothly under the prescribed conditions (-78 °C, EtCN)[19a] to afford the disaccharide **8** with the α:β ratio of 5:95 and in 86% yield, no products arising from self-condensation of **1** being detected. According to the iterative protocol of Fraser-Reid, the benzoyl groups of the β-linked disaccharide **8** were quantitatively replaced with the benzyl groups *via* Zemplén debenzoylation and subsequent benzylation to provide the "armed" donor **9**, glycosidation of which with **1** led to the trisaccharide **10** as a 13:87 mixture of α- to β-anomers in 83% yield. Therefore, these results ensured that the tetramethylphosphoroamidate group could be "armed" or "disarmed" by the type of protective group on C2. It is also worthy of note that the tetramethylphosphoroamidate group was unaffected under the standard benzylation conditions.



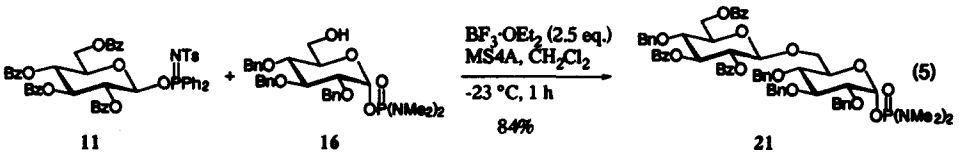
Encouraged by the observed selectivity, we next turned our attention to the feasibility of exploiting the difference in anomeric reactivity based on the phosphorus-containing leaving group itself without resorting to differential protection. To this end, coupling of two "armed" partners or two "disarmed" partners with identical protective group patterns was explored.[8a,17a,b,e] As expected from the fact that glycosidation of the fully benzoylated glycosyl diphenylphosphinimidates[19b] could be promoted with the aid of boron trifluoride etherate ($BF_3{\cdot}OEt_2$) even at -30 °C whereas at below 15 °C no glycosidation could be observed with the corresponding tetramethylphosphoroamidates,[19a] $BF_3{\cdot}OEt_2$-promoted glycosidation of the "disarmed" donor **11** with the "disarmed" acceptor **1** at -23 °C led to the exclusive formation of the β-linked disaccharide **12** in 86% yield (eq 2), no self-coupling of **1** being detected. The "disarmed" disaccharide **12** could be further coupled with the acceptor **13** using the more powerful TMSOTf to furnish the trisaccharide **14** as the sole product in 83% yield.



On the other hand, the fact that glycosidation of the fully benzylated glycosyl phosphites[19c] could be effected with the aid of BF_3·OEt_2 even at -78 °C to exhibit the highest 1,2-*trans*-β-selectivities known to date whereas the corresponding tetramethylphosphoroamidates[19a] were unreactive at below -10 °C suggested the possibility of selective activation of the "armed" donor **15** in the presence of the "armed" acceptor **16**[21] (eq 3). Indeed, this reaction proceeded uneventfully at -70 °C to afford the β-linked disaccharide **9** as virtually the single anomer in 66% yield, which could be further coupled with the acceptor **17** to give the trisaccharide **18** with the α:β ratio of 3:97 and in 88% yield. Apart from this, the intrinsically higher reactivity of the fully benzylated glycosyl phosphorodiamidimidothioates[19d] over the corresponding tetramethylphosphoroamidates toward lutidinium *p*-toluenesulfonate (LPTS) made it possible to couple the "armed" donor **19** with the "armed" acceptor **16** (eq 4), thereby producing the disaccharide **20** as mainly the α-anomer (α:β=95:5).



Finally, we investigated the possibility of reversing the normal "armed-disarmed" pattern.[11a,15,17a,d] By capitalizing on the aforementioned affinity of the fully benzoylated glycosyl diphenylphosphinimidates[19b] for BF_3·OEt_2, we were gratified to find that glycosidation of the "disarmed" donor **11** with the "armed" acceptor **16** at -23 °C led to the exclusive formation of the β-linked disaccharide **21** in 84% yield (eq 5), with no evidence of self-condensed products derived from **16**. Thus, the outstanding result achieved provides added flexibility in oligosaccharide synthesis.



11 16 21

In summary, we have demonstrated the effectiveness of chemoselective glycosidation methods based on glycosyl donors and acceptors carrying phosphorus-containing leaving groups in oligosaccharide synthesis, wherein the anomeric reactivity of glycosyl donors and acceptors can be regulated by varying the type of leaving groups as well as the nature of protective groups. Thus, the present stereocontrolled glycosidation strategy represents a significant and powerful addition to the existing convergent strategies for oligosaccharide synthesis.

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20. All new compounds exhibited satisfactory spectral (500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR) and high resolution mass spectral characteristics.
21. The "armed" acceptor **16** was prepared from allyl 2,3,4-tri-*O*-benzyl-D-glucopyranoside by the following sequence: (1) BzCl, DMAP, Py, 2 h; (2) $PdCl_2$, NaOAc, AcOH-H_2O (9:1), 70 °C, 2 h; (3) *n*-BuLi, THF, -78 °C, 15 min, then $(Me_2N)_2P(=O)Cl$, HMPA, -10 °C, 2 h; (4) K_2CO_3, MeOH, 1 h.

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