*β-Selective Glycosidation*

# Direct and Stereoselective Synthesis of 2-Acetamido-2-deoxy-β-D-glycopyranosides by Using the Phosphite Method**

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2-Acetamido-2-deoxy-D-glycopyranosides occur as common and important structural units in oligosaccharides and glycoconjugates, such as glycolipids, glycoproteins, proteoglycans, and peptidoglycans, and are associated with a wide range of biological processes.[1] Whereas 2-acetamido-2-deoxy-α-D-galactopyranose residues are linked through a glycoside bond to the side-chain hydroxy groups of serine and threonine, the majority of 2-acetamido-2-deoxy-D-glycopyranosides are found as β-linked glycosides.

The most general and extensively developed strategy for the synthesis of 1,2-*trans*-β-glycosides of 2-amino-2-deoxysugars utilizes donors containing a participating group as the amino-protecting functionality, which is replaced by an acetyl group after the glycosidation event.[2,3] 2-Azido-2-deoxyglycosyl donors have also been used for this purpose.[4,5] Clearly, a direct glycosidation method by using donors with the natural *N*-acetyl function would constitute an ideal procedure in terms of efficiency and practicality. In practice, however, the reaction of these donors, **1**, generally leads to the predominant formation of oxazoline derivatives **3** through neighboring-group participation and the subsequent abstraction of a proton from the NH group (Scheme 1).[6,7] Although oxazolines can react with acceptor alcohols in the presence of Brønsted or Lewis acids to afford 2-acetamido-2-deoxy-β-glycosides **4** via oxazolinium ion intermediates **2** or **5** (that is, oxazoline method[8]), the harsh reaction conditions required for this conversion have precluded its wide application in the synthesis of complex oligosaccharides. As part of a program to extend the recently developed glycosidation method that capitalizes on diethyl phosphite as a leaving group,[9,10] we wish to report the stereoselective synthesis of 2-acetamido-2-deoxy-β-glycosides by a direct glycosidation that does not proceed via an oxazolinium ion intermediate.

At the outset of this study, we explored the trimethylsilyl trifluoromethanesulfonate (TMSOTf) promoted glycosidation of 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-glucopyr-

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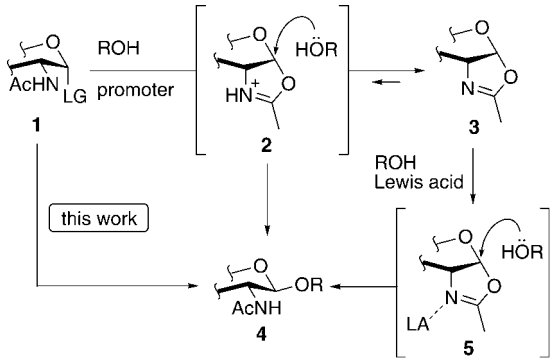
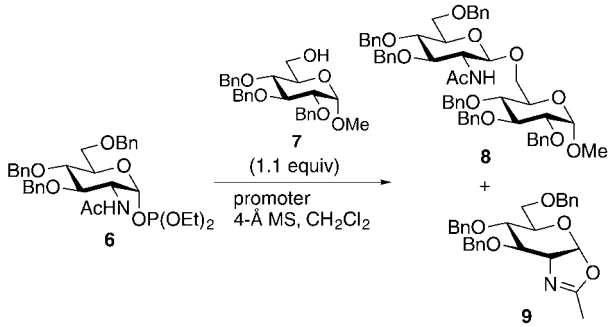



***Scheme 1.*** Glycosidation of 2-acetamido-2-deoxyglycosyl donors. Ac = acetyl, LA = Lewis acid, LG = leaving group.

anosyl diethyl phosphite (**6**)[11] with 6-*O*-unprotected glycoside **7** (1.1 equiv; Table 1). An initial experiment revealed that the donor **6** was completely consumed within 5 min at 0 °C, thereby affording a mixture of disaccharide **8** and oxazoline **9** in the ratio of 0.3:1 (Table 1, entry 1). To our surprise, an examination of the temperature profile of the reaction revealed a trend for the yield of disaccharide **8** to increase with descending temperature (entries 1–3). The temperature limit for a smooth reaction was −60 °C, at which disaccharide **8** was produced in 36 % yield (entry 3).[12] A number of other promoters were then examined for the reaction of diethyl phosphite **6** and alcohol **7**. Among a variety of Lewis acids that were screened (entries 3–6), $Hf(OTf)_4$[13] proved to be superior to TMSOTf; however, disaccharide **8** was still obtained in only 66 % yield (entry 6). Our interest was then directed to the use of promoters with Brønsted acidity.[10b,14] We found that the coupling of donor **6** with **7** in $CH_2Cl_2$ in the presence of TfOH proceeded even at −78 °C to give disaccharide **8** in 75 % yield (entry 7). It is interesting to note that the sulfonic acids with greater Brønsted acidity[15] resulted in higher yields of **8** (entries 7–9). The use of $HClO_4$ prepared from *t*BuBr and $AgClO_4$[16] also promoted the reaction at −78 °C, but a significantly longer time was required to reach completion (entry 10). Finally, we were gratified to find that a simple change in the counterion in super Brønsted acids from trifluoromethanesulfonate (triflate) to bis(trifluoromethanesulfonyl)imide (triflimide)[17] dramatically enhanced the reaction rate, without compromising product yield. Although the reason for this difference in reactivity is currently unclear, the use of $Tf_2NH$ provided disaccharide **8** rapidly (1 h) in 73 % yield (entry 11).[18] Eventually, the use of 2 equivalents of acceptor alcohol **7** led to an additional increase in the yield (84 %) of **8** (entry 12). When the reaction was carried out using 2 equivalents of donor **6**, disaccharide **8** was obtained in comparable (93 %) yield (entry 13).

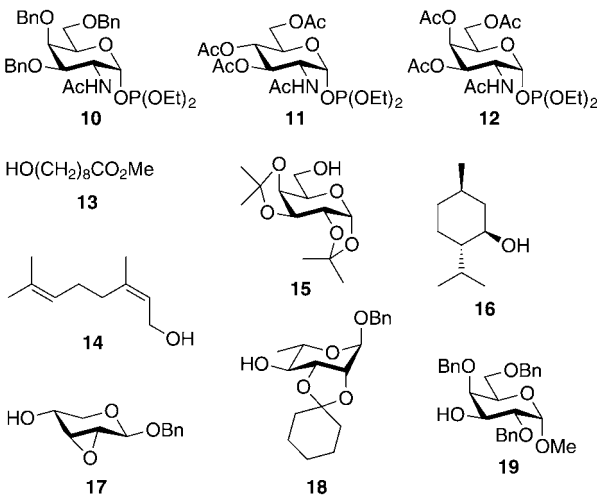
***Table 1:*** Effect of temperature and promoter on the glycosidation of **6** with **7**.[a]




| Entry | Promoter | *T* [°C] | *t* [h] | **8**:**9**[b] | Yield of **8** [%] |
|---|---|---|---|---|---|
| 1[c,d] | TMSOTf | 0 | 0.1 | 0.3:1 | 18 |
| 2[c,d] | TMSOTf | −23 | 0.1 | 0.4:1 | 24 |
| 3[c,d] | TMSOTf | −60 | 0.5 | 0.7:1 | 36 |
| 4 | $BF_3{\cdot}OEt_2$ | −60 | 4 | 2.0:1 | 39 |
| 5 | $Sn(OTf)_2$ | −60 | 1 | 1.6:1 | 46 |
| 6 | $Hf(OTf)_4$ | −60 | 1 | 2.9:1 | 66 |
| 7 | TfOH | −78 | 5 | 4.2:1 | 75 |
| 8 | TsOH | −78 | 1 | 1.8:1 | 51 |
| 9 | MsOH | −78 | 1 | 0.8:1 | 38 |
| 10 | $HClO_4$[e] | −78 | 12 | 2.2:1 | 59 |
| 11[d] | $Tf_2NH$ | −78 | 1 | 4.1:1 | 73 |
| 12[d,f] | $Tf_2NH$ | −78 | 1 | 7.8:1 | 84 |
| 13[g] | $Tf_2NH$ | −78 | 1 | – | 93 |

[a] The reaction was carried out on a 0.1 mmol scale with 1.1 equivalents of acceptor **7** and 1.5 equivalents of promoter in the presence of pulverized 4-Å molecular sieves (4-Å MS) in $CH_2Cl_2$, unless otherwise noted. Ts = *p*-toluenesulfonyl, MS = methanesulfonyl. [b] The ratio was determined by 500-MHz $^1$H NMR spectroscopic analysis of the crude mixture. [c] The reaction was performed in the absence of 4-Å MS. [d] The reaction was performed with 1.1 equivalents of promoter. [e] Prepared from *t*BuBr and $AgClO_4$. See ref. [16]. [f] The reaction was carried out by using 2.0 equivalents of **7**. [g] Donor/acceptor/$Tf_2NH$ molar ratio = 2.0:1.0:2.2. Bn = benzyl.

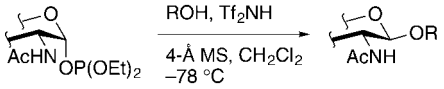
With the reaction conditions optimized, we then explored the glycosidation of **6** and **10**–**12**[11] for both the D-gluco and D-galacto series with a range of acceptor alcohols with different reactivities (Scheme 2, Table 2). The examples highlighted in Table 2 deserve some comments. In all cases, $-Tf_2NH$-promoted glycosidations in $CH_2Cl_2$ at −78 °C were found to offer a facile, efficient, and stereoselective route to 1,2-*trans*-β-linked glycosides. Under these conditions, secondary as well




***Scheme 2.*** Glycosyl donors and acceptor alcohols used for the reactions described in Table 2.

***Table 2:*** Glycosidation of **6**, **10**–**12**.[a]

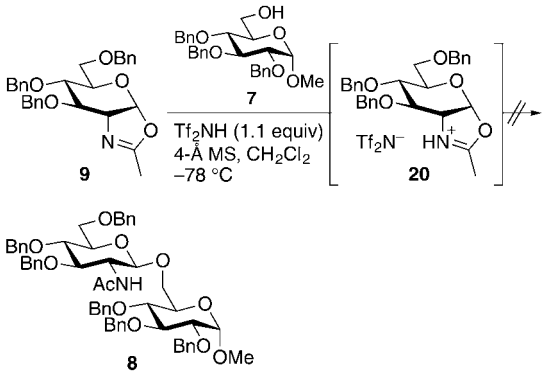



| Entry | Donor | Acceptor | *t* [h] | Yield [%][b] |
|---|---|---|---|---|
| 1[c] | **6** | **13** | 1 | 80 (83) |
| 2 | **6** | **15** | 1 | 89 (92) |
| 3 | **6** | **17** | 1 | 79 (78) |
| 4 | **6** | **18** | 1 | 57 (44) |
| 5 | **6** | **19** | 1 | 65 (64) |
| 6 | **10** | **7** | 1 | 83 (87) |
| 7[d] | **10** | **14** | 1 | 81 (79) |
| 8[c] | **10** | **16** | 1 | 74 (71) |
| 9 | **11** | **7** | 24 | 70 (72) |
| 10 | **12** | **15** | 24 | 67 (70) |
| 11 | **12** | **17** | 24 | 59 (59) |

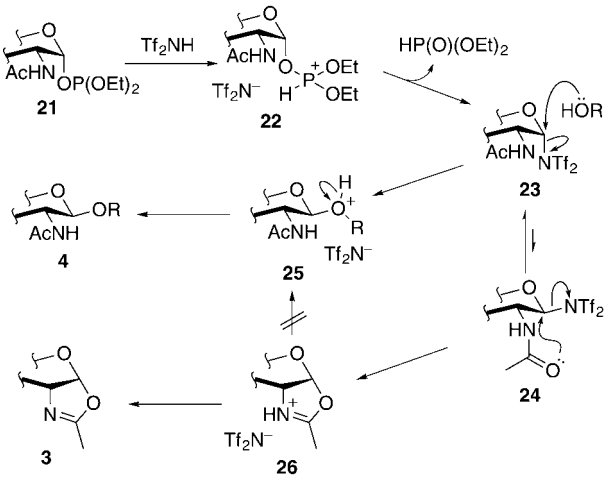
[a] Donor/acceptor/$Tf_2NH$ molar ratio = 1.0:2.0:1.1 unless otherwise noted. [b] Yields in parentheses were obtained when a donor/acceptor/$Tf_2NH$ molar ratio of 2.0:1.0:2.2 was used. [c] The reaction was carried out by using 1.5 equivalents of acceptor alcohol or, for the results in parentheses, 1.5 equivalents of donor. [d] The reaction was carried out by using 1.1 equivalents of acceptor alcohol or, for the results in parentheses, 1.1 equivalents of donor.

as primary alcohols could be employed and β-glycosides were obtained in good to high yields. It is also noteworthy that the alcohols bearing acid-sensitive acetal or epoxy groups could be safely glycosylated (entries 2–4, 10, and 11). The *O*-acetyl protective groups in **11** and **12** lowered the reactivities of these compounds relative to those with the fully benzylated donors **6** and **10** in a consistent and general trend,[19] but the β-glycosides were still produced in moderate to good yields (entries 9–11).[20]

To gain an insight into the mechanism of this glycosidation reaction, further experiments were performed to determine whether the glycosidation proceeded via an oxazolinium ion intermediate. The reaction of oxazoline **9** with **7** did not occur under the optimized conditions described above (Scheme 3).[21,22] This result, together with the finding that a prolonged reaction time (20 h) had no effect on the yield of disaccharide **8** in the reaction of **6** with **7**, suggests that the present reaction does not proceed via the intermediacy of an oxazolinium ion. In this context, it is interesting to note that Crich and Sun identified an anomeric mixture of glycosyl triflates as intermediates in the sulfoxide glycosidation reaction of Kahne et al.[23] when a participating acetyl group was present on the oxygen atom at position 2.[24,25] Based on this remarkable observation, a proposed reaction mechanism is outlined in Scheme 4. Diethyl phosphite **21** is activated by




***Scheme 3.*** Glycosidation of oxazoline **9** with **7** did not proceed via an oxazolinium ion intermediate **20** under the optimized conditions.




***Scheme 4.*** Plausible mechanism of the glycosidation of 2-acetamido-2-deoxyglycosyl diethyl phosphites.

protonation of the phosphorus atom[26] and the phosphite group cleaves to produce an equilibrium mixture of α- and β-glycosyl triflimide intermediates **23** and **24**. An $S_N2$-like displacement by the acceptor alcohol at the anomeric carbon atom of the α-glycosyl triflimide **23** affords β-glycoside **4** via intermediate **25**. On the other hand, the β-glycosyl triflimide **24** undergoes an intramolecular attack by the acetamido group, thereby generating the oxazolinium ion **26**,[27] from which the oxazoline **3** is formed by the elimination of a proton from the NH group.

In conclusion, we have demonstrated herein that $Tf_2NH$-promoted glycosidations of 2-acetamido-2-deoxyglycopyranosyl diethyl phosphites with a variety of acceptor alcohols in $CH_2Cl_2$ at −78 °C give 1,2-*trans*-β-linked glycosides in good to high yields with perfect stereoselectivity. This protocol represents the first example of the direct glycosidation of 2-acetamido-2-deoxyglycosyl donors that does not proceed via an oxazolinium ion intermediate. Spectroscopic investigations to support the proposed mechanism, as well as further studies aimed at expanding the synthetic utility of this protocol, are in progress.

## Experimental Section

A representative procedure for glycosidation of 2-acetamido-2-deoxyglycopyranosyl diethyl phosphite (entry 12 in Table 1): A 1M solution of $Tf_2NH$ in EtCN (0.11 mL, 0.11 mmol) was added to a mixture of donor **6** (61.2 mg, 0.1 mmol), acceptor **7** (92.9 mg, 0.2 mmol), and pulverized 4-Å molecular sieves (61.2 mg) in

$CH_2Cl_2$ (1 mL) at −78 °C. After stirring at this temperature for 1 h, the reaction was quenched by addition of $Et_3N$ (0.15 mL), and the whole mixture was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic extract was washed with brine and dried over anhydrous $Na_2SO_4$. Filtration and evaporation in vacuo furnished the crude products, whose ratio was determined to be 7.8:1 by 500-MHz $^1H$ NMR spectroscopic analysis. For easy purification, a solution of the crude mixture in EtOAc (12 mL) and $CH_2Cl_2$ (2 mL) was vigorously stirred with 10% aqueous HCl (2 mL) for 10 min, during which time the oxazoline **9** was completely hydrolyzed to form the corresponding glycopyranose. The whole mixture was extracted with EtOAc, and the organic extract was washed successively with saturated aqueous $NaHCO_3$ and brine, then dried over anhydrous $Na_2SO_4$. Filtration and evaporation in vacuo followed by flash column chromatography (silica gel, toluene/acetone 7:1) afforded disaccharide **8** (77.2 mg, 84%) as a white solid.

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[11] 2-Acetamido-2-deoxy-D-glycopyranosyl diethyl phosphites were readily prepared from the corresponding glycopyranoses by using a previously reported procedure[10a] ($ClP(OEt)_2$, $Et_3N$, $CH_2Cl_2$, 0 °C).

[12] With the lone exception of THF, where oxazoline **9** was exclusively produced, the product ratio (**8**:**9** = 0.7:1) was nearly the same in the other solvents tested (EtCN/$CH_2Cl_2$ (1:1) and toluene/$CH_2Cl_2$ (1:1)), although the low solubility of donor **6** in EtCN and toluene precluded a direct comparison.

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[18] The $TMSNTf_2$-promoted glycosidation of **6** with **7** proceeded at −60 °C to give **8** in 35% yield (reaction time 1 h, **8**/**9** = 0.7:1).
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[20] The limitation of the present method was encountered with unreactive acceptor alcohols, such as 4- or 2-*O*-unprotected glucosides.
[21] $^1$H NMR spectral data (400 MHz) clearly revealed that oxazoline **9** was protonated upon treatment with $Tf_2NH$ in $CD_2Cl_2$ at −78 °C to form oxazolinium ion **20** (**9**, $\delta = 5.91$ (d, $J = 7.2$ Hz, H1), 4.20 (m, H2), 1.95 ppm (s, $CH_3$); **20**, $\delta = 6.63$ (d, $J = 8.0$ Hz, H1), 4.51 (m, H2), 2.39 ppm (s, $CH_3$)).
[22] The reaction of glycosyl diethyl phosphites with alcohols is accompanied by the formation of $HP(O)(OEt)_2$. However, the addition of $HP(O)(OEt)_2$ was not effective for the $Tf_2NH$-promoted reaction of oxazoline **9** with alcohol **7**, which proceeded at temperatures above approximately 5 °C.
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