Glycosylation

DOI: 10.1002/ange.200602699

Dialkylphosphates as Stereodirecting Protecting Groups in Oligosaccharide Synthesis**

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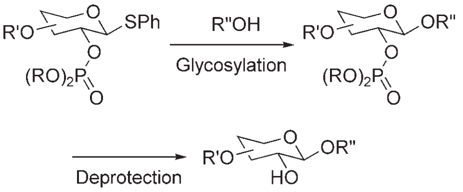
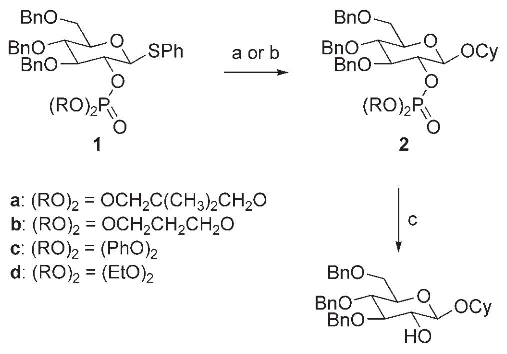
The stereoselective formation of the glycosidic linkage is one of the most important tasks in synthetic carbohydrate chemistry, because the glycoside structure plays a crucial role in many important biological processes involving oligosaccharides.[1] To date, 1,2-*trans*-glycosides have been prepared through the intramolecular participation of the acyl protecting groups at the neighboring C2 position.[2] However, this method has serious drawbacks owing to the formation of orthoester side products.[3] The formation cannot be completely surpressed even when sterically and electronically protected pivalates are used.[4] While the orthoester can be isomerized to give the 1,2-*trans*-glycoside, the isomerization frequently results in low efficiency[3f,j,k,5] or formation of the undesired stereoisomer.[3i,6] During our studies to develop an iterative glycosylation,[7,8] we faced the same problem, which limited the generality of the method. Therefore, the development of a general and high-yielding method for the synthesis of 1,2-*trans*-glycosides would considerably increase the generality of both the iterative as well as conventional glycosylations to access to certain complex oligosaccharides.

Here we report the first use of dialkylphosphates as stereodirecting groups for the synthesis of 1,2-*trans*-glycosides. As the phosphates can be removed after glycosylation, they can be used as stereodirecting protecting groups (Scheme 1). In addition, we found that these protecting groups can be used in iterative glycosylation reactions. Therefore, a variety of oligosaccharides that possess the 1,2-*trans*-glycosidic linkage can be synthesized under a set of glycosylation conditions. Although dialkylphosphinamides have been used for the protection of amines,[9] there is no report on the use of dialkylphosphates for the protection of alcohols. Furthermore, while there are a few examples of the use of diphenylphosphinamides as stereodirecting protecting groups in glucosamine synthesis,[10] their synthetic potential has not been well recognized.



Scheme 1. Dialkylphosphates as stereodirecting protecting groups.

Thioglycoside **1a**, which has a 2,2-dimethyltrimethylene (DMTM) phosphate group at the C2 position, was activated by treatment with benzenesulfenylpiperidine (BSP) and triflic anhydride (Tf_2O) in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) at −60°C,[11] and cyclohexanol was added to this reaction mixture. The desired 1,2-*trans*-glycoside β-**2a** formed as the sole product in 76% yield (Scheme 2). The formation of α-**2a** and the corresponding orthophosphorate product was not detected. The same glycosylation of **1a** by reaction with *N*-iodosuccinimide and triflic acid activators in the presence of cyclohexanol also afforded β-**2a** exclusively in 79% yield.[12] The DMTM phosphate group in **2a** was removed by treatment with sodium hydroxide (10 equiv) in an ethanol/water mixture at 60°C for 1.0 h to give the free alcohol **3** in 95% yield.



Scheme 2. Effects of dialkylphosphates. Reagents and conditions: a) **1** (1.0 equiv), BSP (1.1 equiv), Tf_2O (1.4 equiv), DTBMP (2.0 equiv), CH_2Cl_2, MS (4 Å), −60°C for 30 min, then cyclohexanol (1.5 equiv), −60°C for 30 min, **2a**; 76% (>99% β), **2b**; 84% (>99% β), **2c**; 77% (>99% β), **2d**; 84% (89% β). b) **1a** (1.0 equiv), NIS (1.1 equiv), TfOH (0.1 equiv), cyclohexanol (1.5 equiv), CH_2Cl_2, MS (4 Å), −45°C, 60 min, 79% (99% β). c) **2** (1.0 equiv), NaOH (10 equiv), EtOH/H_2O, 60°C, 1 h. Bn = benzyl, Cy = cyclohexyl, NIS = *N*-iodosuccinimide, Tf = trifluoromethylsulfonyl.

We next examined the structural effects of the phosphates on the selectivity and deprotection efficiency. Trimethylene phosphate **1b** reacted with similar efficiencies to **1a** in both the glycosylation (84%, >99% β) and the deprotection (84%). Diphenyl phosphate **1c** also showed high glycosylation efficiencies (77%, >99% β), but the deprotection was

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[**] This work was supported in part by a Shiseido Grant for Science Research. The authors thank Prof. Kawabata of Kyoto University for the measurement of optical rotation.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

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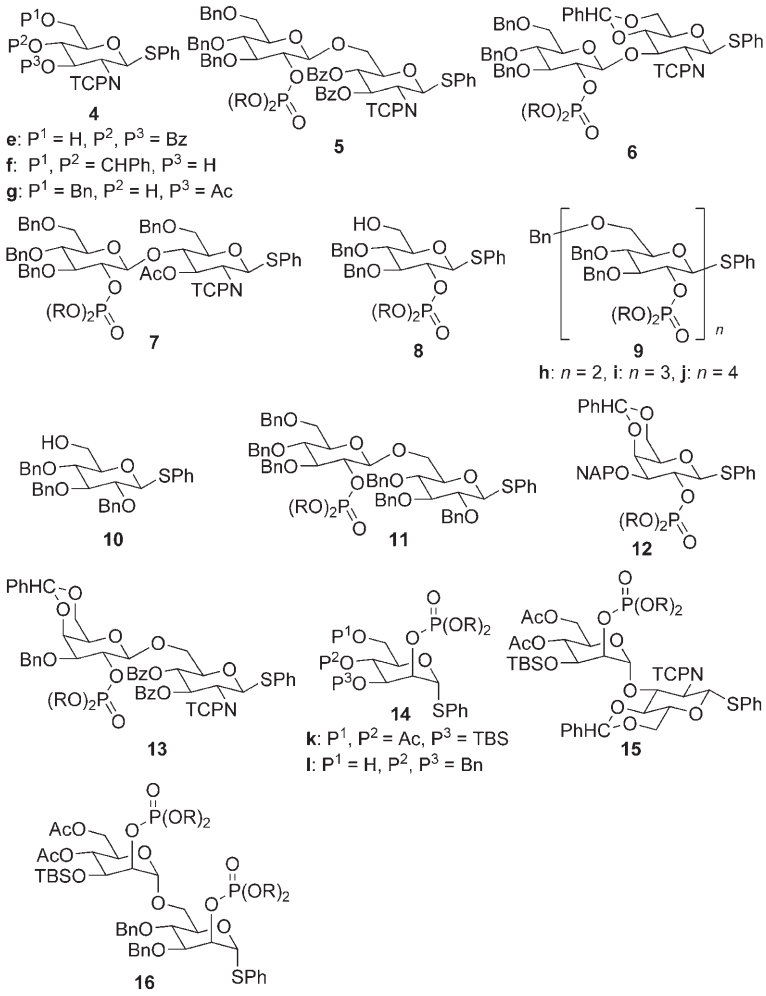
sluggish (< 30 % yield). The selectivity eroded in the glycosylation of diethyl phosphate **1d** (89 % β). We selected DMTM phosphate for the following studies since in the protection of the C2 hydroxy group it was more efficient than the corresponding trimethylene analogue (see the Supporting Information).

The synthetic scope of the current phosphate protecting group has been examined by changing the structure of donors as well as acceptors (Table 1, Scheme 3). We employed a binary activation system using BSP and Tf_2O[11] because these conditions could be applied for the iterative glycosylation of thioglycosides derived from 2-deoxy-2-aminoglycosides.[7a,b] The glycosylation of **1a** with **4e**, which has a hydroxy group at C6, proceeded smoothly and afforded the desired *O*-glycoside with complete β selectivity in quantitative yield (entry 1, Table 1). The glycosylation of **1a** with **4f** and **4g**, which have the sterically hindered hydroxyl groups at C3 and C4, respectively, also afforded **6** and **7** in good yields (entries 2 and 3, Table 1). While small quantities of the 1,2-*cis* isomers were formed in both cases, sufficiently high levels of selectivity were observed (> 96 %). Thioglycosides with a DMTM protecting group at C2 could also be used as glycosyl acceptors. Thus, the coupling of **1a** with **8** afforded β-**9h** in quantitative yield (entry 4, Table 1). Iterative glycosylation using **9h** as a donor and **8** as an acceptor afforded trisaccharide **9i** (entry 5, Table 1), which was further glycosylated with **8** to give tetrasaccharide **9j** (entry 6, Table 1). The desired 1,2-*trans*-glycosides formed in good yields with excellent selectivities in all cases. As the glycosyl donor was activated prior to the coupling reaction, the armed glycoside **10** could be used as a glycosyl acceptor (entry 7, Table 1).[13,14] As all the products are thioglycosides, they could be directly used for the next iterative or armed–disarmed glycosylation reaction as glycosyl donors.



Scheme 3. Examples of donors and acceptors used in the glycosylation and the resulting products; see Table 1. Bz = benzoyl, NAP = 2-naphthylmethyl, $(RO)_2 = OCH_2C(CH_3)_2CH_2O$, TCPN = *N*-tetrachlorophthalimide, TBS = *tert*-butyldimethylsilyl.

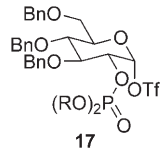
Table 1: Stereoselective glycosylation of thioglycosides.[a] For structures see Scheme 3.

Entry	Donor	Acc.	Prod.	Yield [%]	Sel. (α:β)
1	**1a**	**4e**	**5**	98	1:>99
2	**1a**	**4f**	**6**	75	2:98
3	**1a**	**4g**	**7**	71	4:96
4	**1a**	**8**	**9h**	100	1:>99
5	**9h**	**8**	**9i**	80	1:99
6	**9i**	**8**	**9j**	80	1:>99
7	**1a**	**10**	**11**	85	2:98
8	**12**	**4e**	**13**	100	2:98
9	**14k**	**4f**	**15**	81	99:1
10	**14k**	**14l**	**16**	76	96:4

[a] Donor (1.0 equiv), BSP (1.1 equiv), Tf_2O (1.4 equiv), DTBMP (2.0 equiv), CH_2Cl_2, MS (4 Å), −60 °C, 10–30 min, then acceptor (1.5 equiv) at −60 °C, 15–60 min.

This method could be extended to the use of glycosides other than glucose derivatives. Galactose derivative **12** afforded exclusively β isomer **13** (entry 8, Table 1). Mannose donor **14k** gave exclusively α isomers **15** and **16** upon coupling with acceptors **4f** and **14l**, respectively, as a result of the 1,2-*trans*-directing effect of the axial DMTM group at C2 (entries 9 and 10, Table 1).

Potential intermediates in the current glycosylation reaction were analyzed to understand the remarkable 1,2-*trans* selectivity. Thus, **1a** was activated by BSP and Tf_2O in CD_2Cl_2 at −80 °C, and the resulting reaction mixture was analyzed by ^1H, ^{13}C, and ^{31}P NMR spectroscopy at the same temperature. We were surprised to find that the α-glycosyl triflate **17** formed as the sole product.[15] The anomeric carbon in **17** resonates at $\delta =$ 105 ppm in the ^{13}C NMR spectra, which strongly indicates the formation of a neutral species rather than a cationic species.[15,7a] The α stereochemistry was suggested by the ^1H NMR spectra, in which the



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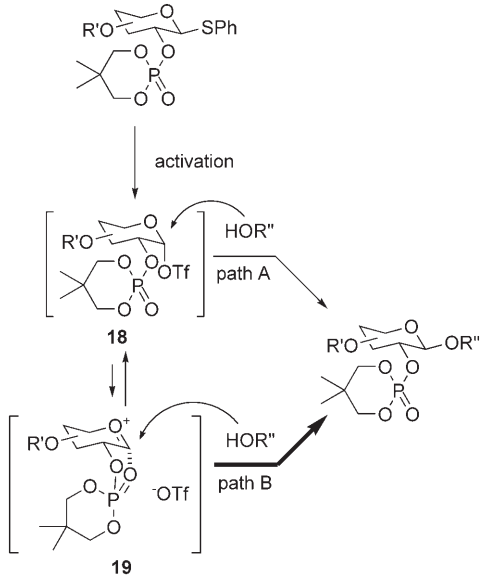
C1 proton gives rise to a doublet at $\delta = 6.40$ ppm with a coupling constant of 2.4 Hz. The phosphorus signal in **17** occurs at $\delta = -8.9$ ppm, a chemical shift virtually identical to that of **1a** ($\delta = -8.8$ ppm). The results clearly indicate that the phosphorus atom in **17** does not bear a positive charge.[16] These results are in sharp contrast to the formation of the orthoester cation intermediate in C2 acyl-protected glycosyl donors.[17] Therefore, the lack of the formation of orthophosphate product must be attributed to the lack of positive charge on the phosphorus atom in **17**.

A possible explanation for the observed 1,2-*trans* selectivity is the "S_N2-like" attack of the acceptor alcohol on the α-triflate intermediate (Scheme 4, path A) in analogy to the β-mannoside synthesis developed by Crich.[15] However, Crich



Scheme 4. Plausible mechanism.

also reported that α-triflate intermediates, which possess a nonparticipative protecting group at C2, show low or moderate 1,2-*trans* selectivity.[18] We also reported that a β-triflimide intermediate of *N*-phthaloyl-protected glucosamine exclusively afforded the β-glycosides,[7a] suggesting that the α-triflates do not always react in an "S_N2-like" manner. An alternative and more plausible mechanism involves intermediate **19**, which would arise through neighboring group participation of the phosphorus ester. This intermediate would be short-lived and exist in equilibrium with **18**. The alcohol reacts at less hindered side in **19** to give 1,2-*trans*-glycoside (path B). While there is no direct evidence for the involvement of **19**, we believe that the latter is more plausible for the formation of 1,2-*trans*-glycosides.[19,20] Further synthetic and mechanistic elaborations of this new stereodirecting protecting group are currently underway.

Experimental Section

Typical glycosylation procedure (synthesis of **5**): A solution of a glycosyl donor **1a** (69.1 mg, 0.10 mmol), BSP (23.0 mg, 0.11 mmol), DTBMP (41.1 mg, 0.20 mmol), and molecular sieves 4 Å (ca. 100 mg) in CH_2Cl_2 (1.0 mL) was treated with Tf_2O (38.4 mg, 0.14 mmol) at −60 °C. After 10 min, glycosyl acceptor **4e** (112 mg, 0.15 mmol) was added at this temperature. The reaction mixture was at this temperature for 15 min, then quenched by addition of Et_3N (0.1 mL), and warmed to room temperature. To this solution was added saturated aqueous $NaHCO_3$ solution, and organic phase was separated. The aqueous phase was extracted three times with ethyl acetate, and the combined organic extracts were washed with saturated aqueous NaCl solution, dried with $MgSO_4$, filtered, and concentrated under reduced pressure by rotary evaporator to give the crude product. Purification by flash column chromatography (silica gel 10 g; elution with 30% ethyl acetate in hexane) afforded **5** in 98% (92.1 mg, α:β = < 1:99) as a white amorphous substance. $[\alpha]_D^{20} = +59.8$ (*c* 0.4, $CHCl_3$); IR (KBr): $\tilde{\nu} = 1732$(s), 1389, 1354, 1301, 1271, 1068, 1010, 740, 711; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.81$ (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 3.44 (dt, $J = 9.7$, 3.1 Hz, 1H, H-5′), 3.58–3.68 (m, 3H, H-4′, H-6′) 3.83 (t, $J = 9.0$ Hz, 1H, H-3′), 3.89–4.18 (m, 6H, H-6, P(O){OCH_2C-(CH_3)$_2$CH_2O}), 4.24–4.36 (m, 2H, H-2′, H-5), 4.41 (d, $J = 12.4$ Hz, 1H, CH_2Ph), 4.50 (d, $J = 12.4$ Hz, 1H, CH_2Ph), 4.81 (d, $J = 10.8$ Hz, 1H, CH_2Ph), 4.56 (t, $J = 10.4$ Hz, 1H, H-2), 4.71 (d, $J = 8.0$ Hz, 1H, H-1′), 4.77 (d, $J = 10.8$ Hz, 1H, CH_2Ph), 4.78 (d, $J = 10.4$ Hz, 1H, CH_2Ph), 4.96 (d, $J = 10.4$ Hz, 1H, CH_2Ph), 5.46 (t, $J = 9.8$ Hz, 1H, H-4), 5.88 (d, $J = 10.4$ Hz, 1H, H-1), 6.17 (dd, $J = 9.8$, 9.4 Hz, 1H, H-3), 7.09–7.53 (m, 26H, Ar), 7.69–7.74 (m, 2H, Ar), 7.85–7.91 ppm (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.41$ (CH_3), 21.49 (CH_3), 32.05 (C, $J_{CP} = 5.3$ Hz), 54.49 (CH, C2), 67.53 (CH_2, C-6), 68.37 (CH_2, C6′), 69.54 (CH, C4), 72.11 (CH, C3), 73.42 (CH_2, *C*H_2Ph), 74.85 (CH_2, *C*H_2Ph), 75.02 (CH, C5′), 75.28 (CH_2, *C*H_2Ph), 77.60 (CH, C4), 77.59–77.70 (CH_2, 2C, P(O){O*C*H_2C(CH_3)$_2$*C*H_2O}), 78.60 (CH, C5), 79.27 (CH, $J_{CP} = 6.9$ Hz, C2′), 82.04 (CH, C1), 83.04 (CH, $J_{CP} = 3.0$ Hz, C3′), 100.71 (CH, $J_{CP} = 3.1$ Hz, C1′), 126.75 (C), 127.05 (C), 127.54 (CH), 127.61 (CH), 127.72 (CH, 2C), 127.81 (CH, 2C), 128.16 (CH, 2C), 128.16 (C), 128.27 (CH, 2C), 128.30 (CH, 4C), 128.32 (CH, 4C), 128.38 (CH, 2C), 128.59 (C), 129.25 (CH, 2C), 129.72 (CH, 2C), 129.80 (CH, 2C), 129.91 (C), 130.02 (C), 130.90 (C), 132.30 (CH, 2C), 133.46 (CH), 133.49 (CH), 137.90 (C), 137.98 (C), 138.11 (C), 140.37 (C), 140.61 (C), 162.05 (C=O), 163.20 (C=O), 165.31 (C=O), 165.90 (C=O); HRMS (FAB) *m*/*z*: calcd for $C_{66}H_{61}Cl_4NO_{16}PS$: 1326.2203 $[M+H]^+$; found: 1326.2195.

Received: July 7, 2006
Revised: August 15, 2006
Published online: October 20, 2006

Keywords: carbohydrates · glycosylation · oligosaccharides · protecting groups · stereoselective synthesis

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[19] It is unlikely that the excellent selectivity is attributed to the steric effect because the use of steric hindered alcohols showed lower selectivity than one of less hinder alcohols (Table 1, entries 1–3).

[20] Thiomannoside **14k** gave the corresponding α-triflate intermediate upon activation by BSP and Tf_2O as judged by the low temperature ^{1}H NMR study, and the intermediate selectively afforded α-glycoside upon treatment of alcohol. The result absolutely denies the path A and is consistent with the path B.

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