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DIRECT AND STEREOSELECTIVE SYNTHESIS OF 2-AZIDO-2-DEOXY-β-D-MANNOSIDES USING THE PHOSPHATE METHOD†

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Abstract – TMSOTf-promoted glycosidation of 2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α-D-mannosyl diphenyl phosphate with a variety of acceptor alcohols in CH_2Cl_2 at –30 °C in the presence of pulverized 4-Å molecular sieves (MS) afforded 2-azido-2-deoxy-β-mannosides in high yields and with good to high β-selectivities.

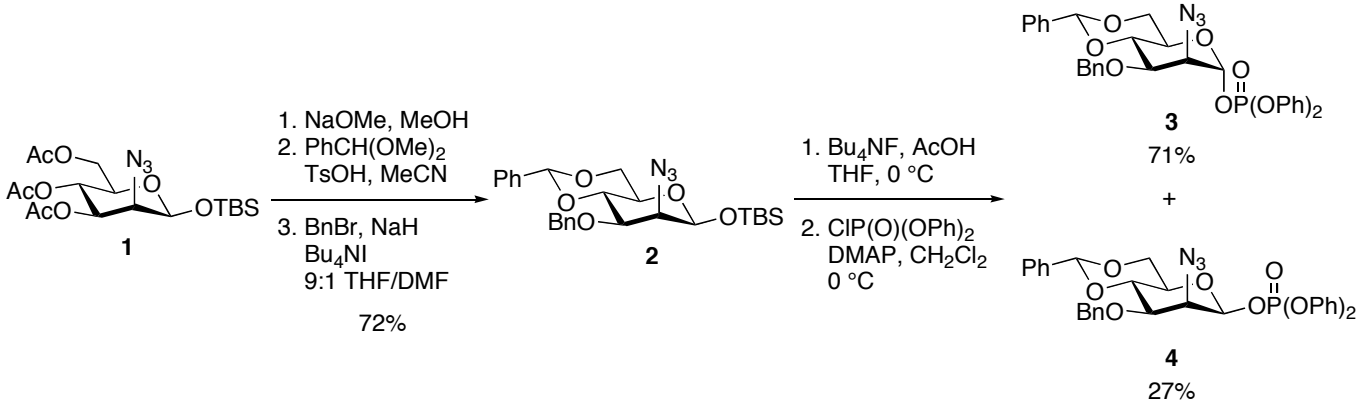
The β-linked 2-acetamido-2-deoxy-D-mannosides are present in a number of bacterial capsular polysaccharides and lipopolysaccharides (LPS). Due to the potential utilization of capsular polysaccharides as immunogens in providing protection against bacterial infection[1] and due to the overwhelming spectrum of biological activities of LPS, efforts have been devoted to the stereocontrolled construction of 2-acetamido-2-deoxy-β-D-mannosidic linkages.[2] Although the first example reported by Paulsen and co-workers involved the use of 2-azido-2-deoxy-α-D-mannosyl bromide as a donor,[3] most approaches to this type of glycoside rely on indirect methods. The 2-oximinoglycosyl donor approach[4,5] and the S_N2 inversion of readily available β-glucosides at C-2 with an azide nucleophile[6] have been developed for this purpose, and these methods provide reliable access to pure 2-acetamido-2-deoxy-β-mannosides. However, it is clear that a direct β-glycosidation would constitute an ideal procedure in terms of efficiency and practicality. In this context, extension of the Crich's β-selective mannosylation methodology[7] to the synthesis of 2-azido-2-deoxy-β-mannosides was recently reported by van der Marel and co-workers.[8] They demonstrated that the activator systems 1-(phenylsulfinyl)-piperidine/Tf_2O and diphenyl sulfoxide/Tf_2O are effective for the glycosidation of 4,6-*O*-benzylidene-protected 2-azido-2-deoxy-1-thiomannoside, producing 2-azido-2-deoxymannosides in good yields with

† Dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

good β-selectivities: however, the operational inconvenience[8c]—acceptor alcohols must be added after activation of the donor—as well as the formation of the leaving group-derived by-products seems to be less favorable from a practical standpoint.

As part of a program to extend the glycosidation method that capitalizes on phosphorus-containing leaving groups,[9,10] we have reported that TMSOTf-promoted reaction of 2,3-di-*O*-benzyl-4,6-*O*-benzylidene- D-mannosyl diethyl phosphite with a broad variety of acceptor alcohols in CH_2Cl_2 at –45 °C offers a facile and high-yielding route to β-mannosides.[11] As an extension of the mannosylation reaction, we addressed the direct construction of 2-azido-2-deoxy-β-mannosidic linkages. In our previous mannosylation studies, the use of diethyl phosphite as a leaving group proved to be optimal in terms of reactivity and product yield.[11] However, the difficulty in preparation of 2-azido-2-deoxyglycosyl donors carrying a phosphite as a leaving group[9i,12] prompted us to investigate the reaction of 2-azido-3-*O*-benzyl-4,6-*O*- benzylidene-2-deoxy-D-mannosyl diphenyl phosphates.

The diphenyl phosphate was prepared starting with the known compound **1**[13] (Scheme 1). Deacetylation of triacetate **1** with NaOMe in MeOH was followed by reprotection of the C4 and C6 hydroxyl groups as their benzylidene acetal and that of the C3 hydroxyl group as its benzyl ether to give 1-*O*-TBS glycoside **2** in 72% yield in three steps. After desilylation of **2** with Bu_4NF in the presence of AcOH, the resultant hemiacetal was phosphorylated under Sabesan conditions[14] to give diphenyl phosphates **3** and **4** in 71% and 27% yields, respectively.

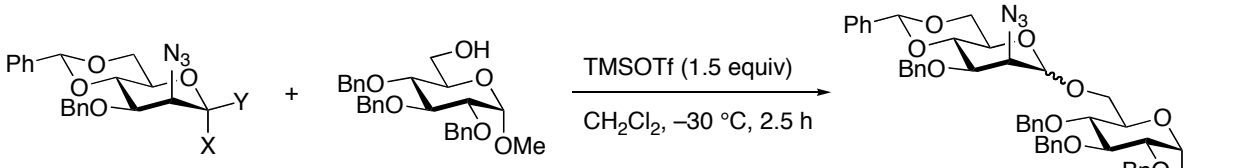


Scheme 1. Preparation of 2-azido-2-deoxymannosyl diphenyl phosphates **3** and **4**

With donors **3** and **4** in hand, we then explored TMSOTf-promoted glycosidation with 6-*O*-unprotected glucoside **5**. Addition of 1.5 equiv of TMSOTf to a mixture of the donor (**3** or **4**) and 1.1 equiv of acceptor **5** in CH_2Cl_2 afforded disaccharide **6**, the α:β ratio of which was assayed by HPLC (Zorbax® Sil

column).[15,16] An initial experiment revealed that the reaction of α-phosphate **3** proceeded to completion within 2.5 h at –30 °C, providing disaccharide **6** in 65% yield with good β-selectivity (α:β = 18:82) (Table 1, entry 1). Since the modest product yield was attributed to the partial hydrolysis of the benzylidene acetal under acidic conditions, we expected that the side reaction could be suppressed by an additive that buffers the Lewis acidity of TMSOTf. Gratifyingly, pulverized 4-Å MS[17] turned out to be suitable for this purpose, improving the chemical yield to 80% without affecting the β-selectivity (entry 2). It was anticipated that the same β-selectivity could be obtained by the use of β-phosphate **4** as a donor if the reaction proceeded through the intermediacy of the corresponding glycosyl triflate as demonstrated by Crich and co-workers for their β-selective mannosylation method.[7c] However, a slight erosion in β-selectivity (α:β = 18:82 → 24:76) was observed in the reaction of β-phosphate **4** with alcohol **5** (entry 3). This result suggests that the use of α-phosphate **3** is essential for obtaining higher β-selectivity, although the reason is not clear at present.

Table 1. Glycosidation of 2-Azido-2-deoxymannosyl Diphenyl Phosphates with Alcohol **5**[a]



3: X = $OP(O)(OPh)_2$, Y = H
4: X = H, Y = $OP(O)(OPh)_2$

5

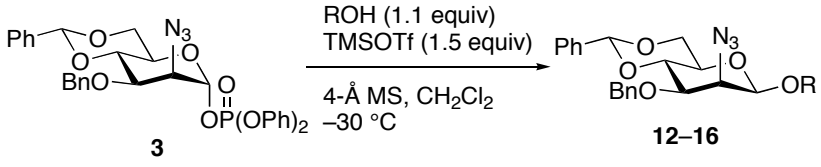
6

entry	donor	additive	yield, %	α:β[b]
1	**3**	none	65	18:82
2	**3**	4-Å MS	80	18:82
3	**4**	4-Å MS	84	24:76

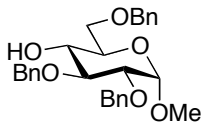
[a] A 1 M solution of TMSOTf in CH_2Cl_2 was added to a mixture of the donor and alcohol **5** in CH_2Cl_2 at –30 °C. [b] The ratio was determined by HPLC [column, Zorbax® Sil, 4.6 × 250 mm; eluent, 4:1 *n*-hexane/AcOEt; flow rate, 1.0 mL/min; t_R (α-anomer **6**α) = 16.7 min, t_R (β-anomer **6**β) = 31.3 min].

With the optimal conditions identified, the scope of the reaction was explored (Table 2). The glycosidation of α-phosphate **3** with less reactive 4-*O*-unprotected glucoside **7** proceeded to completion within 4 h under these conditions, leading to the preferential formation of β-disaccharide **12**β, which corresponds to a constituent of the capsular polysaccharide of *Streptococcus pneumoniae* type 19F (entry 1). The best β-selectivity (α:β = 8:92) was achieved by the glycosidation of the 2-*O*-unprotected glucoside **8** (entry 2). The galactose, mannose and L-rhamnose derivatives **9**–**11** could be uneventfully glycosylated under these conditions with good β-selectivities (entries 3–5).

Table 2. Glycosidation of Diphenyl Phosphate **3** with Various Acceptor Alcohols[a]

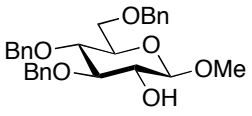


ROH =



7

			product		
entry	acceptor	time, h		yield, %	α:β[b]
1	**7**	4	**12**	76	19:81
2	**8**	3	**13**	87	8:92
3	**9**	4	**14**	79	19:81
4	**10**	4	**15**	75	15:85
5	**11**	3	**16**	85	16:84



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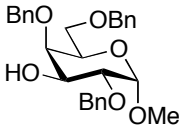

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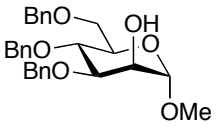

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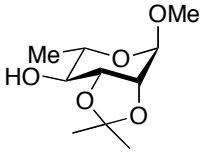

11

[a] A 1 M solution of TMSOTf in CH_2Cl_2 was added to a mixture of donor **3**, the acceptor alcohol and pulverized 4-Å MS in CH_2Cl_2 at –30 °C. [b] The ratio was determined by HPLC (column, Zorbax® Sil, 4.6 × 250 mm; eluent, 4:1 or 5:1 *n*-hexane/AcOEt; flow rate, 1.0 mL/min).

In conclusion, we have demonstrated that TMSOTf-promoted glycosidation of 2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α-D-mannosyl diphenyl phosphate (**3**) with a variety of acceptor alcohols in CH_2Cl_2 at –30 °C in the presence of pulverized 4-Å MS exhibits good to high β-selectivities. High product yields can be achieved with approximately equimolar proportions of the donor **3** and acceptor alcohols, and of particular note is a simple reaction protocol that does not need the pre-activation of the donor. Further investigation into the mechanism of this glycosidation is currently underway, and results will be reported in due course.

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13. W. Kinzy and R. R. Schmidt, *Liebigs Ann. Chem*., 1985, 1537. Schmidt and Kinzy illustrated in their article that 1-*O*-TBS glycoside with an α-configuration at C-1 was obtained by silylation of the corresponding hemiacetal. However, the ^{1}H NOE interactions of H-1 with H-2 (9.0%), H-3 (6.0%) and H-5 (13.1%) unambiguously established the β-configuration of 1-*O*-TBS glycoside **2**.
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15. A typical experimental procedure is illustrated as follows (Table 1, entry 2): TMSOTf in CH_2Cl_2 (1.0 M, 0.15 mL, 0.15 mmol) was added to a stirred mixture of diphenyl phosphate **3** (61.6 mg, 0.10 mmol), alcohol **5** (51.1 mg, 0.11 mmol) and pulverized 4-Å MS (80 mg) in CH_2Cl_2 (1 mL) at –30 °C. After stirring for 2.5 h, the reaction was quenched with Et_3N (0.1 mL). The mixture was poured into a two-layer mixture of AcOEt (2 mL) and saturated aqueous $NaHCO_3$ (3 mL), and the whole mixture was extracted with AcOEt (20 mL). The organic extract was successively washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (2 × 5 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (104.9 mg), which was purified by flash column chromatography (silica gel 5 g, 5:1 *n*-hexane/AcOEt) to give disaccharide **6** (66.0 mg, 80%, α:β = 18:82) as a white solid. The α- and β-glycosides were separated by flash column chromatography with 5:1 *n*-hexane/AcOEt for characterization purposes.
16. The stereochemical assignments were verified by ^{1}H NOE correlations between H-1′ and H-5′ of the β-anomers.
17. 4-Å MS pellets, purchased from Junsei Chemical Co., Ltd., were finely ground in mortar and activated by heating in vacuo at 220 °C for 12 h.