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An extremely mild and stereocontrolled construction of 1,2-*cis*-α-glycosidic linkages *via* benzyl-protected glycopyranosyl diethyl phosphites

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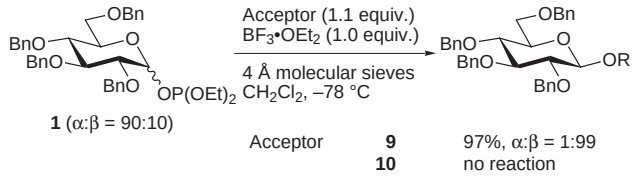
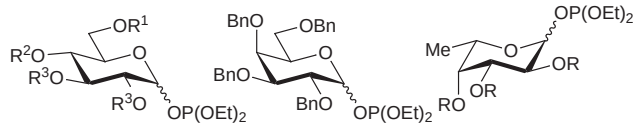
A highly stereocontrolled 1,2-*cis*-α-glycosidation reaction under conditions mild enough for acid-labile alcohols has been developed using benzyl-protected glycopyranosyl diethyl phosphites as glycosyl donors in the presence of 2,6-di-*tert*-butylpyridinium iodide and tetrabutylammonium iodide.

Due to the rapidly recognised biological significance of the saccharide residues of carbohydrate-containing biomolecules, the rational design and development of stereocontrolled glycosidation reactions[1] are of growing importance not only in carbohydrate chemistry but also in medicinal chemistry.[2] One of the current topics in this area is the emergence of glycosyl phosphites as a new family of glycosyl donors,[3–6] the effectiveness of which has been demonstrated well by high-yield and α-selective sialylation[3a,4a,b] using sialyl phosphite as a donor and TMSOTf as a promoter. As yet another advantage of glycosyl phosphites, we recently reported that glycosidations of benzyl-protected glycopyranosyl diethyl phosphites with a variety of acceptor alcohols could be effected with the aid of $BF_3{\cdot}OEt_2$ as a promoter at −78 °C to exhibit the highest 1,2-*trans*-β-selectivity known to date for glycosidations without neighboring group participation.[7] During the course of mechanistic investigations of the reaction, we found that the glucopyranosyl phosphite **1**† could not be directly activated by $BF_3{\cdot}OEt_2$ at −78 °C. This result, together with the finding that the trimethylsilyl ether **10** derived from *O*-6-unprotected glycoside **9** did not serve as a glycosyl donor (Scheme 1),



Scheme 1

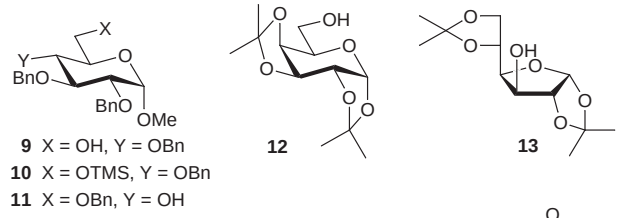
suggested that glycosidation should be effected with the aid of the BF_3–acceptor alcohol complex[8] which functioned as a proton donor to activate the phosphite group to give oxocarbenium ion and diethyl phosphite. Although TfOH is known to activate the phosphite **1** to give mainly 1,2-*trans*-β-glucosides,[4c] there has been no reported attempt to use promoters with much lower Brønsted acidity. At this stage, we envisaged that if the phosphite group could be activated using promoters such as pyridinium iodides, the glycosidation process *via* glycopyranosyl iodide coupled with Lemieux's *in situ* anomerisation method[9] might lead to the construction of 1,2-*cis*-α-glycosidic linkages under extremely mild reaction conditions.[10–12] Herein, we report a new aspect of glycosidations with benzyl-protected glycopyranosyl diethyl phosphites, wherein the combined use of 2,6-di-*tert*-butylpyridinium iodide (DTBPI)[13] as a promoter and tetrabutylammonium iodide as an additive proves to be the superior choice for allowing exceptionally high levels of 1,2-*cis*-α-selectivity, as well as glycosylations of even highly sensitive aglycones.



1 $R^1 = R^2 = R^3$ = Bn
2 $R^1 = R^2 = R^3$ = *p*-$ClC_6H_4CH_2$
3 R^1 = Tr, $R^2 = R^3$ = Bn
4 R^1 = TBDPS, $R^2 = R^3$ = Bn
5 R^1, R^2 = PhCH, R^3 = Bn

6

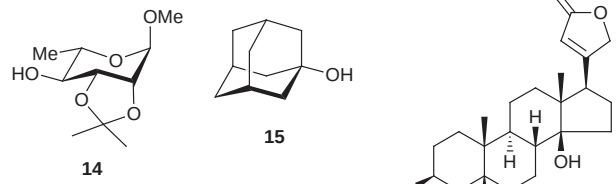
7 R = Bn
8 R = *p*-$ClC_6H_4CH_2$



9 X = OH, Y = OBn
10 X = OTMS, Y = OBn
11 X = OBn, Y = OH

12

13



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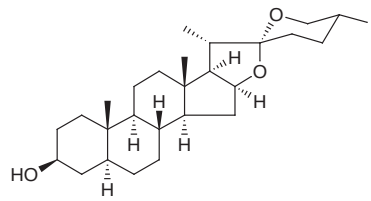

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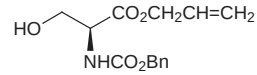

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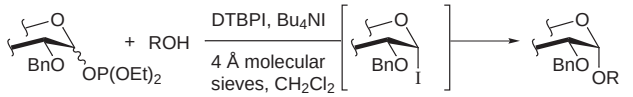
Since it is well-documented that glycosylations of less nucleophilic alcohols favor 1,2-*cis*-α-glycosides, we first examined glycosidation of **1** with **9** with a high reactivity in order to make an assessment as accurately as possible. After considerable experimentation, it was found that coupling of **1** (α:β = 90:10 or 75:25, 1.1 equiv.) with **9** (1.0 equiv.) in CH_2Cl_2 in the presence of DTBPI (1.2 equiv.) and pulverised 4 Å molecular sieves proceeded at room temperature for 48 h to afford the corresponding 1,2-*cis*-disaccharide in 85% yield with an α:β ratio of 92:8 (Table 1, entry 1). Since TLC and ^1H NMR analyses showed that *in situ* conversion of **1** into the α-glucopyranosyl iodide[14] proceeded to completion within 30 min irrespective of the anomeric composition of the donor, the glycosidation of the iodide *via in situ* anomerisation was presumed to be the rate-determining step. As expected, the addition of Bu_4NI (1.2 equiv.) to the above mixture facilitated the anomerisation process and shortened the reaction time to 24 h, providing the disaccharide in 84% yield with the same α-selectivity as above (entry 2).‡§

In order to clarify the scope and limitations of the present method, we then explored the glycosidation of glycosyl phosphites **1**–**8**† with a range of acceptor alcohols. The

Table 1 1,2-*cis*-Glycosidation reaction with glycopyranosyl diethyl phosphites[a]



Entry	Donor[b]	Acceptor	*t*/h	Yield[c] (%)	α : β[d]
1[e]	**1**	**9**	48	85	92 : 8
2	**1**	**9**	24	84	92 : 8
3	**1**	**11**	48	59	95 : 5
4	**1**	**12**	24	91	94 : 6
5	**1**	**13**	48	81	92 : 8
6	**1**	**15**	48	88	91 : 9[f]
7	**1**	**16**	48	89	90 : 10
8	**1**	**17**	36	92	92 : 8
9	**2**	**9**	24	88	95 : 5[g]
10	**3**	**9**	48	88	96 : 4[g]
11	**4**	**9**	48	91	96 : 4[g]
12	**5**	**9**	48	80	90 : 10[g]
13	**6**	**9**	48	85	95 : 5[g]
14	**6**	**14**	24	94	93 : 7[g]
15	**6**	**18**	48	87	93 : 7
16	**7**	**9**	3	82	88:12
17	**7**	**12**	4	95	89 : 11[g]
18	**8**	**9**	4	87	95 : 5
19	**8**	**12**	4	95	93 : 7[g]

[a] Donor : acceptor : DTBPI : Bu_4NI molar ratio = 1.1 : 1.0 : 1.2 : 1.2. [b] The anomeric ratio of the phosphites: **1**, 90 : 10; **2**, 61 : 39; **3**, 50 : 50; **4**, 83 : 17; **5**, 66:34; **6**, 52 : 48; **7**, 49 : 51; **8**, 57 : 43. [c] Isolated total yield based on the acceptor alcohol used. [d] Determined by HPLC (column, Zorbax® Sil, 4.6 × 250 mm; eluent, 9–30% EtOAc in hexane or 14–22% THF in hexane; flow rate, 1.5 ml min^{-1}). [e] In the absence of Bu_4NI. [f] Determined by 125 MHz ^{13}C NMR. [g] Determined by 500 MHz ^1H NMR.

examples highlighted in Table 1 deserve some comment. In all cases except for the exceedingly sterically hindered, unreactive *O*-4-unprotected glycoside **11** (entry 3), the present glycosidations were found to offer a high-yielding entry to 1,2-*cis*-linked glycosides and disaccharides, utilising conditions under which highly acid-sensitive alcohols such as digitoxigenin **16** and tigogenin **17** were safely glycosylated (entries 7 and 8). While glycosidations of the D-gluco- and D-galactopyranosyl donors **1** and **6** displayed high levels of α-selectivity with various alcohols of different reactivities (entries 1–8 and 13–15), that of L-fucopyranosyl donor **7** was found to exhibit less satisfactory selectivity (entries 16 and 17). However, the α-selectivity was greatly improved by switching the protective group from a benzyl group to a *p*-chlorobenzyl group (entries 18 and 19),[15] although only a small enhancement was observed with the D-glucopyranosyl donor (entry 9). According to a general trend,[10,16] protection of the *O*-6 hydroxy group as a bulky triphenylmethyl or *tert*-butyldiphenylsilyl ether gave further enhanced α-selectivities of up to 96 : 4 (entries 10 and 11). In this regard, it is also of interest that the present protocol could be advantageously extended to glycosidation with 4,6-*O*-benzylidene-protected glucopyranosyl donor **5** (entry 12).[11]

In conclusion, the present method constitutes an exceptionally mild and general procedure for the highly stereocontrolled construction of 1,2-*cis*-α-glycosidic linkages. Thus, we have now developed a stereoselective entry to either 1,2-*cis*-α-glycosides or 1,2-*trans*-β-glycosides using glycosyl phosphites as common glycosyl donors by proper choice of the reaction conditions.

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Notes and references

† Glycopyranosyl diethyl phosphites **1**–**8** were readily prepared from the corresponding glycopyranoses according to the reported procedure (ref. 7), the anomeric ratios of which were determined by 109 MHz ^{31}P NMR using 85% H_3PO_4 as an external standard.

‡ Typical experimental procedure: A solution of **1** (72.6 mg, 0.11 mmol) in CH_2Cl_2 (1 ml) was added to a mixture of **9** (46.4 mg, 0.1 mmol), DTBPI (38.3 mg, 0.12 mmol), Bu_4NI (44.3 mg, 0.12 mmol) and pulverised 4 Å molecular sieves (50 mg). The whole mixture was stirred at room temperature for 24 h. Standard workup followed by column chromatography (silica gel, 6 : 1 hexane–AcOEt) furnished the corresponding disaccharide (82.9 mg, 84%) as a 92:8 mixture of α- and β-anomers.

§ The combined use of 2,6-di-*tert*-butylpyridinium bromide and Bu_4NBr under otherwise identical conditions (reaction time; 48 h) provided the disaccharide with the α : β ratio of 87 : 13 in 80% yield.

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