A MILD AND RAPID 1,2-TRANS-GLYCOSIDATION METHOD VIA BENZOYL-PROTECTED GLYCOPYRANOSYL P,P-DIPHENYL-N-(p-TOLUENESULFONYL)PHOSPHINIMIDATES†

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Abstract —— A highly efficient 1,2-trans-glycosidation reaction with a range of acid-labile alcohols has been developed by employing benzoyl-protected glycopyranosyl P,P-diphenyl-N-(p-toluenesulfonyl)phosphinimidates as glycosyl donors.

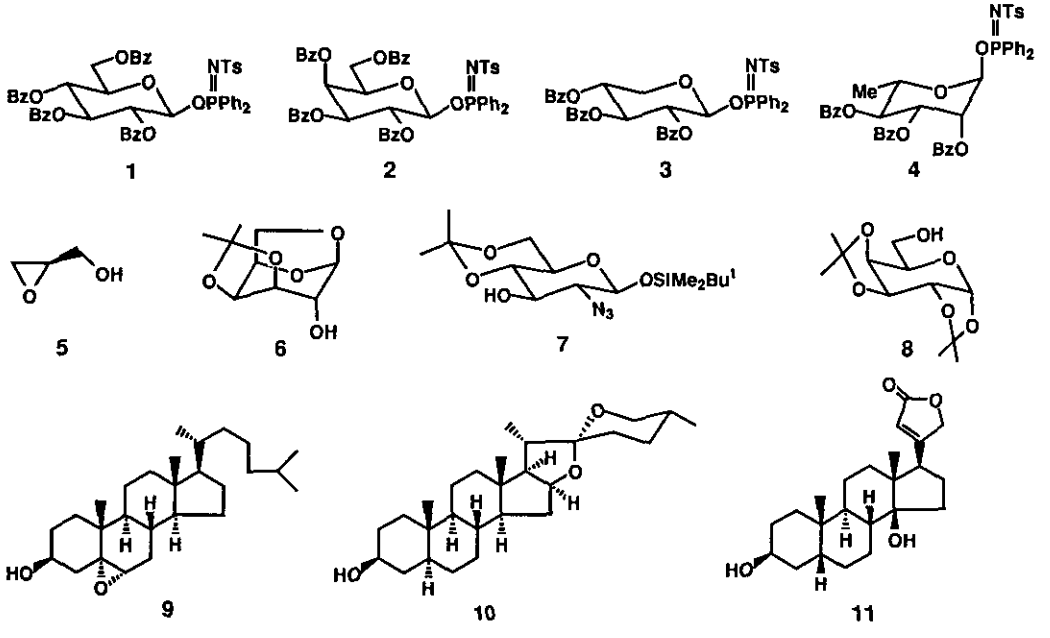
The development of efficient and stereocontrolled glycosidation reactions is becoming of crucial importance owing to the increasingly recognized significance of saccharide components of biomolecules containing the glycosidic linkage in the biological processes. Despite the many advances in this area,[1,2] however, there still remains a need for appreciable developments in terms of efficacy, generality, and stereocontrol. Considering that the leaving group of glycosyl donors is one of the most critical factors responsible for the selectivity and yield of glycosidation reaction, we became interested in the prospects of devising novel glycosyl donors with excellent shelf-life which could be coupled with equimolar proportions of glycosyl acceptors in the presence of promoters other than heavy-metal salts to give saccharides with desired anomeric configuration. We recently developed a *rapid and efficient method for the stereocontrolled* construction of 1,2-trans-β-glycosidic linkage using benzyl- or benzoyl-protected glycopyranosyl diphenyl phosphates as glycosyl donors.[3] Along this line, we report herein a mild and rapid glycosidation method via benzoyl-protected glycopyranosyl P,P-diphenyl-N-(p-toluenesulfonyl)phosphinimidates, which has advantages of allowing a facile entry to 1,2-trans-glycosides of acid-labile alcohols as well as operational simplicity.

†Dedicated to the memory of the late Professor Tetsuji Kametani.

Table 1. 1,2-trans-Glycosidation reaction of benzoyl-protected glycopyranosyl P,P-diphenyl-N-(p-toluenesulfonyl)phosphinimidates (1-4).[a]

entry	donor	acceptor	conditions: temp °C	conditions: time min	1,2-trans-glycoside: yield,[b]%	nmr data[c]: $\delta^{1}H$[d]	nmr data[c]: $\delta^{13}C$[e]	$[\alpha]^{22}_{D}$,deg(c,$CHCl_3$)
1	1	5	-30	15	81	5.04	100.7	+37.3(1.22)
2	1	6	-10	20	77	5.02	100.2	+1.8(1.34)
3	1	7	-10	10	78	5.12	101.1	+8.7(0.70)
4	1	9	-20	10	74	4.89	100.9	+5.1(2.45)
5	1	10	-10	20	70	4.93	100.0	-7.5(1.03)
6[f]	1	11	-15	20	51	4.80	99.0	+23.5(1.32)
7	2	8	-30	15	79	5.01	101.8	+42.8(0.99)[g]
8	2	9	-20	10	72	4.87	101.4	+65.6(1.58)
9	3	10	-10	20	73	4.95	98.4	-42.1(1.28)
10[h]	4[i]	11	-10	60	76	5.10	95.8	+79.8(1.00)

[a] $BF_3 \cdot OEt_2$ (1.0 M in CH_2Cl_2, 0.23 mmol) was added at -30°C to a stirred mixture of glycopyranosyl phosphinimidate (0.21 mmol), glycosyl acceptor alcohol (0.2 mmol), and crushed molecular sieves 4A (ca. 100 mg) in CH_2Cl_2 (4 ml) under argon atmosphere. The mixture was allowed to react at the indicated temperature until no more progress of the reaction was observed by tlc analysis. [b] Based on the glycosyl acceptor alcohol (0.2 mmol) used, though recovery of the alcohols was always accompanied (recovery yields: 14% in entry 5, 26% in entry 6, 16% in entry 9, and 6-10% in the other entries). [c] Chemical shifts for the anomeric centers newly formed. [d] In $CDCl_3$ at 400 MHz. [e] In $CDCl_3$ at 100 MHz. [f] A 1:1 mixture of two isomeric anhydrodigitoxigenins (ca. 8%) was formed as by-products. [g] Ref. 9. [h] No trace of anhydrodigitoxigenins was detected. [i] Contaminated with 8% of its anomer.



Condensation of the 1-O-thallium (I) salts of benzoyl-protected D-glucopyranose, D-galactopyranose, D-xylopyranose, and L-rhamnopyranose with P,P-diphenyl-N-(p-toluenesulfonyl)phosphinimidic chloride[4] according to Perlin's method[5] (benzene, 23 ℃, 1 h) led to the predominant formation of the phosphinimidates (1-4), together with small proportions of their anomers. The anomeric ratios of the products were determined by ^{1}H nmr spectroscopy to be 90:10, 90:10, 92:8, and 92:8, respectively. The α- and β-anomers in all cases except in 4 and its anomer were readily separated by column chromatography on silica gel, and showed excellent shelf-stability.[6] In contrast, phosphinimidation of the 1-O-lithium salts under Shiba's conditions[7] (THF, -70 ℃, 0.5 h) altered the ratios of 1-3 to their anomers, leading to the diastereoselectivity of 22:78, 20:80, and 27:73, respectively.[8]

With convenient preparation of the phosphinimidates (1-4) and their anomers accomplished, we focused our attention on the survey of reaction conditions mild enough for acid-labile alcohols to be glycosylated efficiently. After considerable experimentation, the combined use of boron trifluoride etherate as a promoter and dichloromethane as a solvent proved to be eminently suitable. Thus, coupling of the phosphinimidates (1-4) (1.05 equiv.) with a range of alcohols (5 and 9-11) or suitably protected glycosides (6-8) (1.0 equiv.) in dichloromethane in the presence of $BF_3 \cdot OEt_2$ (1.15 equiv.) and crushed molecular sieves 4A at -30 to -10 ℃ proceeded rapidly to give exclusively the 1,2-trans-linked glycosides or disaccharides, as expected from the anchimeric assistance by the 2-benzoyl group (Table 1). No evidence of the formation of the products debenzoylated on O-2 or the orthoesters was detected. On the other hand, glycosidation reactions of their anomers under the above conditions did not occur, and much inferior yields were obtained under forcing conditions (0 ℃, 4-7 h).

It should be emphasized here that the acid-sensitive groups such as epoxy, acetal, or O-tert-butyldimethylsilyl groups are unaffected under the reaction conditions while such labile groups are incompatible with our previously reported method[3] via benzoyl-protected glycopyranosyl diphenyl phosphates. The survival of a wide variety of acid-labile groups suggests that the present procedure is much milder than that previously used, and is therefore likely to be of wider applicability. In this regard, of particular interest are the glycosylation reactions of tigogenin (10) and digitoxigenin (11) (entries 5, 6, 9, and 10), in which the superiority of our technique to the existing methods resorting to the Koenigs-Knorr or Helferich reactions is manifested by much shorter reaction times and better yields.[10]

In conclusion, we have demonstrated the effectiveness of the glycopyranosyl phosphinimidates as glycosyl donors in several sensitive situations. The application of this method to more complex systems including even highly sensitive aglycones as well as the possible use of benzyl-protected glycopyranosyl phosphinimidates is currently under investigation.

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