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Glycosyl Transfer by Isopropenyl Glycosides: Trisaccharide Synthesis in One Pot by Selective Coupling of Isopropenyl and *n*-Pentenyl Glycopyranosides[1]

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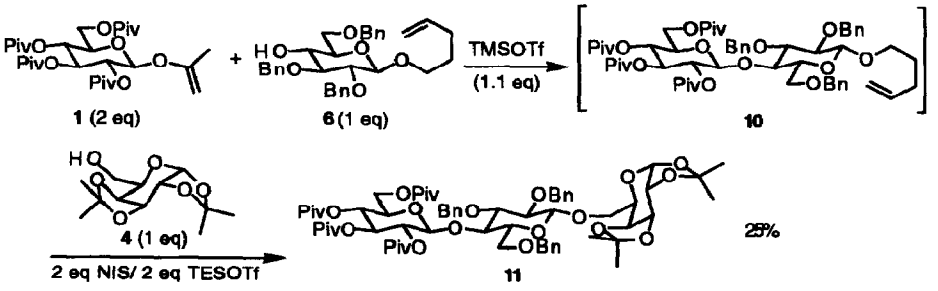
Abstract: *O*-Isopropenyl glycosides bearing ester protecting groups are activated as glycosyl donors by a variety of electrophiles. Diastereomerically pure β-glycoside products are formed in good yields. Selective activation of *O*-isopropenyl 2,3,4,6-tetra-*O*-pivaloyl-β-glucopyranoside in the presence of *O*-pent-4-enyl 2,3,4,6-tetra-*O*-benzyl-β-glucopyranoside allows two successive glycosyl couplings to be performed in a single pot to give trisaccharide in 25% yield.

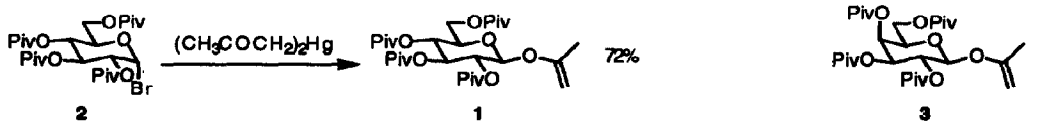
The importance of oligosaccharides and glycoconjugates as mediators of biological processes involving recognition and binding of cell surfaces[2-7] has stimulated the development of a variety of new methods for glycosyl transfer.[8] The goal of these synthetic efforts has been ultimately to elevate oligosaccharide synthesis to the level of efficiency currently enjoyed by oligonucleotide and oligopeptide synthesis.[9] We report here on the use of *O*-isopropenyl glycosides[10-12] bearing ester protecting groups for the completely stereoselective formation of β-glycosides. Selective activation of an isopropenyl glycoside in the presence of an *O*-pent-4-enyl glycoside[13] allows two successive glycosyl couplings to be performed in one pot to give trisaccharide as the product (Scheme I).

Scheme I



O-Isopropenyl 2,3,4,6-tetra-*O*-pivaloyl-β-glucopyranoside (**1**)[14] was prepared by the reaction of 2,3,4,6-tetra-*O*-pivaloyl-α-glucopyranosyl bromide[15] (**2**) with diacetonylmercury[16] (Scheme II). The

Scheme II



corresponding galactopyranoside (**3**)[14] was prepared similarly. Compounds **1** and **3** are activated as glycosyl donors by a variety of electrophiles, including triflic anhydride,[17] silver triflate,[18] and dimethyl-(methylthio)sulfonium triflate (DMTST).[19] However, activation by trimethylsilyl triflate (TMSOTf)[20] or *N*-iodosuccinimide/triflic acid (NIS/TfOH)[21] gives the highest yields of β-glycoside in the shortest reaction times. With these latter reagents, glycosyl couplings are complete within 2-5 min, at 0 °C.

Table I illustrates the results of glycosylations using **1** as the glycosyl donor and TMSOTf or NIS/TfOH as the promoter. Reactions using **3** as the glycosyl donor gave similar results. Yields of β-disaccharide or β-glycoside were good, except from the reaction of the sterically hindered glycosyl acceptor, **8** (Table I, reaction 5). No α-glycoside was detected in the crude products by ^{1}H NMR.

The glycosylation of *O*-pent-4-enyl 2,3,4,6-tetra-*O*-benzyl-β-glucopyranoside (**6**) by **1** (Table I, reaction 3) is a striking result, since no self-coupling of **6** was detected by TLC or ^{1}H NMR. Thus, **1** is activated as the glycosyl donor more readily than **6**, despite the fact that **1** bears electronically "disarming"[22] ester protecting groups and **6** bears electronically "arming" ethereal protecting groups.[23]

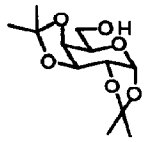
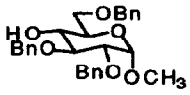
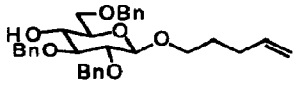
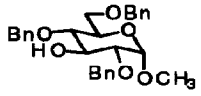
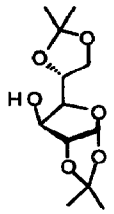
The selective activation of **1** in the presence of **6** was next utilized to perform two successive glycosyl couplings in a single pot, leading to the synthesis of trisaccharide **11** (Scheme I). Compounds **6** and **1** reacted in acetonitrile at 0 °C with TMSOTf as the promoter. After 5 minutes, **4** and NIS/triethylsilyl triflate[24] were added. After 5 more minutes at 0 °C, work-up and column chromatography gave **11**[14] in 25% overall yield. The second glycosyl coupling (that of intermediate *n*-pentenyl disaccharide **10**) proceeded with an β:α selectivity of 7.3:1.0.

When the one-pot synthesis of **11** was performed using NIS and silver triflate as the activators for the second coupling, **11** was obtained in the same yield and diastereomeric purity, but only after the reaction had stirred overnight at room temperature. When purified **10** (70 % yield, Table I, reaction 3) was coupled with one equivalent of **4**, **11** was produced in 43% yield. Thus, the yield of trisaccharide produced by the one-pot procedure is essentially the same as the overall yield of trisaccharide produced by two discrete reactions.

Our synthesis of **11** is one of only a few examples of multiple glycosylation reactions being conducted selectively in one pot, *without intervening chemical steps for manipulation of protecting or anomeric-activating groups*.[25,26] Our strategy for iterative glycosylations conducted in one pot depends not only on the selective activation of one anomeric activating/protecting group over another but also on the synthesis of the oligosaccharide from the nonreducing end toward the reducing end. The alternative, synthesis from the reducing end toward the nonreducing end, inherently requires that a minimum of one selective deprotection step be performed on the growing oligosaccharide chain between successive glycosyl couplings.

Our work on the chemistry of *O*-isopropenyl glycosides and on the selective activation of glycosyl donors as an efficient means to oligosaccharide synthesis continues.

Table I. β-Glycosylation of Various Glycosyl Acceptors by *O*-Isopropenyl 2,3,4,6-Tetra-*O*-Pivaloyl-β-Glucopyranoside (**1**).[a]

reaction	promoter	glycosyl acceptor	yield, %[b,c]
1	1 eq NIS/2.6 eq TfOH	 **4**	70
2	1.4 eq TMSOTf	 **5**	69
3	1.1 eq TMSOTf	 **6**	70
4	1.4 eq TMSOTf	 **7**	74
5	1.2 eq TMSOTf	 **8**	23
6	2 eq NIS/2 eq TfOH	 **9**	64

[a]Reactions were run with 0.077 mmol (1 equivalent) of glycosyl acceptor and 2 equivalents of **1** in 2 mL of dry acetonitrile, 0 °C, with activated powdered 4 Å molecular sieves, under argon. [b]Yields are for chromatographically purified β-glycosides. No α-glycoside product was detected by ^{1}H NMR. [c]See note 14.

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