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New Glycosylation Reaction Based on Alkyne-$Co_2(CO)_6$ Complex

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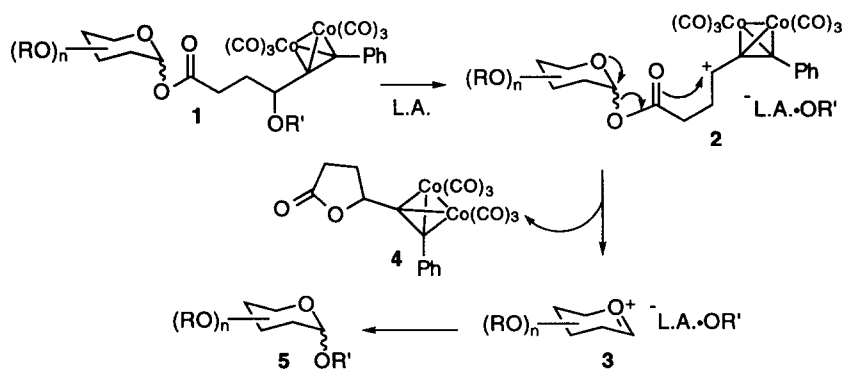
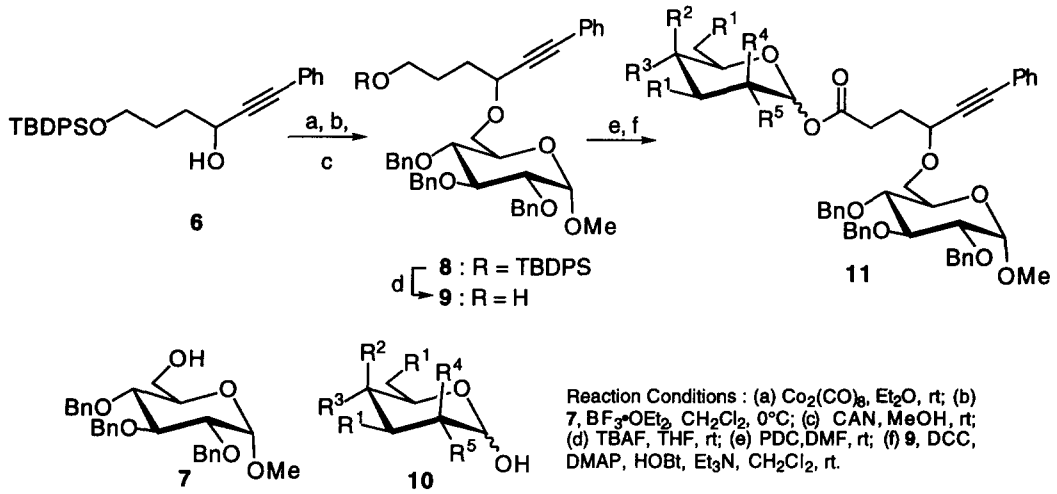
Abstract: *O*-Protected glycopyranoside possessing 4-(*O*-protected-glucosyl)-6-phenyl-5-hexynoate residue at anomeric position was converted into the corresponding cobalt complex, which on exposure to trimethylsilyl trifluoromethanesulfonate afforded glucosylglucoside derivative in a good yield *via* internal delivery of glycosyl acceptor. Similar *O*-protected galactopyranoside and mannopyranoside derivatives provided the corresponding galactosylglucoside and mannosylglucoside derivative, respectively. © 1997 Elsevier Science Ltd.

Dicobalthexacarbonyl-complexed propynyl ether derivatives produce, on acid treatment, the corresponding propynyl cation species with cobalt complexation. This cationic intermediate has been well known to be stabilized by vicinal cobalt complex moiety and be captured by various kinds of external as well as internal nucleophiles resulting in, after decomplexation, an efficient propynylation (Nicholas reaction).[1] Like the *n*-pentenyl glycoside chemistry developed by Fraser-Reid[2,3] we envisaged that *O*-protected glucopyranoside derivative **1** possessing the cobalt-complexed 4-alkoxy-6-phenyl-5-hexynoate residue at anomeric position would furnish the corresponding propynyl cation **2** under Lewis acid condition. This cationic intermediate **2** would spontaneously collapse to form the oxocarbenium cation **3** with liberation of the cobalt-complexed γ-lactone **4**. Oxocarbenium cation **3** would be then intramolecularly captured by its counter alkoxy anion species leading to generate **5**. Described herein are preliminary results of successful application of the Nicholas cationic intermediate to novel internal type[4] of glycosylation reaction where migration of the alkoxy group at propynyl position to anomeric position is the most crucial point.



The starting substrates **11** required for this investigation were prepared as follows. Cobalt complexation of **6** with $Co_2(CO)_8$ was followed by treatment with methyl 2,3,4-tri-*O*-benzyl-α-D-glucoside (**7**) in the presence of BF_3•OEt_2 in CH_2Cl_2 at 0°C to afford, after decomplexation with CAN, **8** in 74% overall yield. The protecting group on a primary alcohol of **8** was removed by TBAF to give the alcohol **9** in 92% yield. Oxidation of **9** with PDC in DMF afforded the corresponding acid derivative, which was subsequently exposed to ester condensation condition with glycosyl donors **10** producing **11** in a range of 48 to 79% yield.

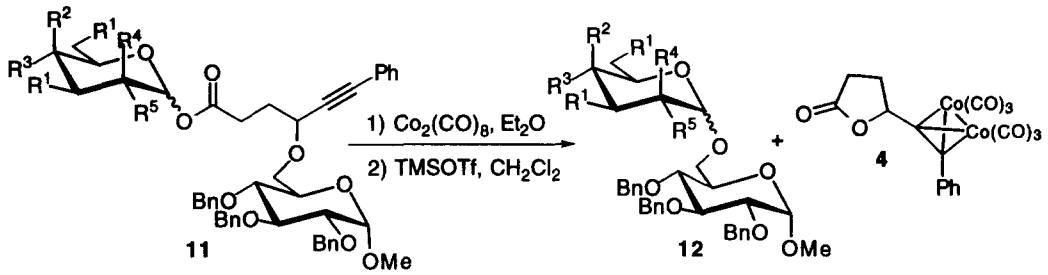


Reaction Conditions : (a) $Co_2(CO)_8$, Et_2O, rt; (b) **7**, BF_3•OEt_2, CH_2Cl_2, 0°C; (c) CAN, MeOH, rt; (d) TBAF, THF, rt; (e) PDC,DMF, rt; (f) **9**, DCC, DMAP, HOBt, Et_3N, CH_2Cl_2, rt.

With desired **11** in hand, we examined internal migration procedure for glycosylation reaction. Treatment of **11a** (α : β = 42 : 58)[5] with $Co_2(CO)_8$ gave the corresponding cobalt complexed **11a**, which was subsequently exposed to trimethylsilyl trifluoromethanesulfonate (TMSOTf)[6] in CH_2Cl_2 at -65°C to afford the desired *O*-benzyl-glucosylglucoside derivative **12a**[2a,7] (α : β = 46 : 54)[8] in 60% yield. The γ-lactone **4** with cobalt complexation was also isolated in a high yield (Table 1, entry 1).[9,10] Changing solvent from CH_2Cl_2 to propionitrile at -65°C brought about high β selectivity (entry 2). This observation is in line with the literature precedent.[11,12] Other results obtained under standard conditions were summarized in Table 1. Glycosylation reaction of **11b** (α : β = 65 : 35)[5] produced *O*-benzyl-galactosylglucoside **12b**[8,12] (entries 3,4). In contrast to cases of **11a** and **11b**, *O*-benzyl-mannosylglucoside **12c**[13] was obtained from **11c** in CH_2Cl_2 in a highly α selective fashion (entry 5), while no characteristic β selectivity in propionitrile could be detected (entry 6). These results could be interpreted in terms of steric hindrance of the axial benzyloxy functionality at C-2 position of **11c**. It should be mentioned that no glycosylation reaction took place and the starting material was recovered in 97% yield when **11a** was directly submitted to the above reaction condition except cobalt complex formation for 24 h. Therefore, cobalt complexation of the starting alkyne derivatives is mandatory for this type of glycosylation reaction.

O-Acylated materials were also found to be suitable substrate for this new glycosylation reaction (entries 7,8). 2,3,4,6-Tetra-*O*-benzoyl-glucoside derivative **11d** (α : β = 45 : 55)[5] was successively treated with $Co_2(CO)_8$ and TMSOTf to furnish the glucosylglucoside derivative **12d**[14] in a highly β selective manner[8] in

rather lower yield (37%, entry 7) along with **4** (86%). 2,3,4,6-Tetra-*O*-benzoyl-mannoside derivative **11e** (α : β = 29 : 71)[5] gave the mannosylglucoside derivative **12e**[15] exclusively[8] in 43% yield (entry 8). High stereoselectivity observed in the above reactions (entries 7,8) can be rationalized by consideration of neighboring group participation[14a,15,16] of the C-2 benzoyloxy group.



a : $R^1 = R^3 = R^5$ = OBn, $R^2 = R^4$ = H, **b** : $R^1 = R^2 = R^5$ = OBn, $R^3 = R^4$ = H
c : $R^1 = R^3 = R^4$ = OBn, $R^2 = R^5$ = H, **d** : $R^1 = R^3 = R^5$ = OBz, $R^2 = R^4$ = H
e : $R^1 = R^3 = R^4$ = OBz, $R^2 = R^5$ = H

Table 1. Glycosylation Reaction of 11 *via* Internal Delivery Pathway

entry	substrate	(α : β)[a]	solvent[b]	temp.(°C)	time[c]	product (%)	(α : β)[d]	**4** (%)
1	**11a**	(42 : 58)	CH_2Cl_2	-65	10 min	**12a** (60)	(46 : 54)	88
2	**11a**	(42 : 58)	EtCN[e]	-65	2 h	**12a** (74)	(9 : 91)	82
3	**11b**	(65 : 35)	CH_2Cl_2	-65	20 min	**12b** (77)	(42 : 58)	98
4	**11b**	(65 : 35)	EtCN	-65	1.5 h	**12b** (76)	(20 : 80)	87
5	**11c**	(26 : 74)	CH_2Cl_2	-65	10 min	**12c** (65)	(94 : 4)	70
6	**11c**	(26 : 74)	EtCN	-65	3 h	**12c** (59)	(51 : 49)	74
7	**11d**	(45 : 55)	CH_2Cl_2	-65	1 h	**12d** (37)	(1 : 99)	86
8	**11e**	(29 : 71)	CH_2Cl_2	-65	10 min	**12e** (43)	(99 : 1)	65

[a] Determined by 500 MHz ^{1}H NMR. [b] TMSOTf (1.1 equiv.) was employed as an activator in CH_2Cl_2, while 2.0 equiv. of TMSOTf was necessary in EtCN. [c] Reaction was monitored by TLC and quenched when the starting material was consumed. [d]Determined by HPLC. [e] In this case, 4.0 equiv. of TMSOTf was required for consumption of **11a**.

Thus we developed novel type of glycosylation reaction by taking advantage of the inherent useful property of alkyne-$Co_2(CO)_6$ complex, namely easy generation and stabilization of propynyl cation by cobalt complex moiety. Improvement of chemical yields as well as stereoselectivity is now in progress.

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(5) Each isomer (α and β) consists of two stereoisomers due to propynyl stereogenic center. Ratio of these isomers was not estimated by spectroscopic means. However, ratio of α to β could be determined by ^{1}H NMR spectroscopy.

(6) After searching for several Lewis acids such as $TiCl_4$, $SnCl_4$, and BF_3•OEt_2, TMSOTf was found to be a suitable one for this reaction. In addition, it was shown that more than an equivalent of TMSOTf is necessary for consumption of the starting material.

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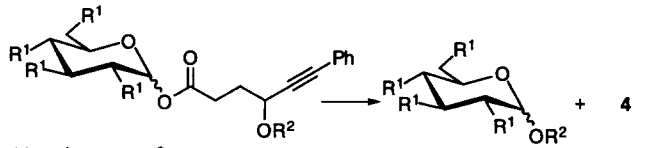
(8) Ratio of α to β was determined by HPLC.

(9) When **11a** (α : β = 28 : 72 or α : β = 99 : 1) was exposed to TMSOTf independently, **12a** (α : β = 44 - 45 : 56 - 54) was again obtained nonselectively regardless of composition of α and β isomers in the starting **11a**. This observation strongly suggests that this reaction must proceed *via* the oxocarbenium cation species such as **3**.

(10) Crossover experiment with a mixture of **13** and **14** (1 : 1) under the standard condition described in the text afforded **15** and **16** in 47 and 50% yield, respectively. No crossover products **17** and **18** could be detected in the reaction mixture. Details of this result will be published in somewhere else.



13 : R^1 = OBn, R^2 = Bz
14 : R^1 = OMe, R^2 = Piv
15 : R^1 = OBn, R^2 = Bz **17** : R^1 = OBn, R^2 = Piv
16 : R^1 = OMe, R^2 = Piv **18** : R^1 = OMe, R^2 = Bz

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