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Unusual α-glycosylation with galactosyl donors with a C2 ester capable of neighboring group participation

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Abstract—Glycosylation of 4-methoxyphenyl 2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (**2**) with isopropyl 3-*O*-allyl-2,4,6-tri-*O*-benzoyl- (**9**) or 6-*O*-allyl-2,3,4-tri-*O*-benzoyl-1-thio-β-D-galactopyranoside (**7**) as the donor, afforded an α- and β-linked mixture, whereas with isopropyl 3-*O*-chloroacetyl-2-*O*-benzoyl-4,6-*O*-benzylidene- (**13**) and isopropyl 3-*O*-allyl-2-*O*-benzoyl-4,6-*O*-benzylidene-1-thio-β-D-galactopyranoside (**15**) as the donor, glycosylation of **2** gave α-linked products only, indicating that 4,6-*O*-benzylidenation led to α-stereoselectivity in spite of the C2 ester capable of neighboring group participation. Using **15** as the donor, glycosylation of mannose derivatives with 2- or 3-OH's, glucose with 2- or 3-OH's, galactose with 2-, or 3-, or 4-OH's, glucosamine and glucuronic acid with a 4-OH, and a lactose derivative with a 4-OH, also furnished α-linked products. However, when using **15** as the donor, glycosylation of aglycon alcohol or sugars with 6-OH's yielded normal β-linked products.

Oligosaccharides play key roles in many biological processes. When conjugated to proteins to form glycoproteins, they alter protein structure and function. When combined with lipids, they can play pivotal functions in cell–cell recognition and signal transduction.[1] Oligosaccharides have also been found to control the development and defence mechanisms of plants.[2] The increased appreciation of the role of carbohydrates in biological and pharmaceutical science has resulted in a revival of interest in carbohydrate chemistry.[3]

A central problem in carbohydrate chemistry is how to control the stereo outcome of glycosylation. Generally, it is believed that glycosyl donors possessing an acyloxyl group as a participating function at C-2 gives exclusively the corresponding 1,2-*trans* glycoside with high stereoselectivity in any glycosylation reaction. Therefore, the most widely used approach for achieving stereochemical control in the formation of β-glucosidic linkages involves the use of a C2 ester capable of neighboring group participation.[4] Some reports disclosed unusual 1,2-*cis*-glycosylation owing to 'double stereodifferentiation'.[5] Our previous report[6] explored very unusual α-(1→3)-glycosylations with glucosyl donors having a C2 ester capable of neighboring group participation. This communication discusses unusual 1,2-*cis*-galactosylations with galactosyl donors having C2 ester groups.

As shown in Scheme 1, 4-methoxyphenyl 2,3,6-tri-*O*-benzoyl-β-D-galactopyranoside (**2**) was chosen as the glycosyl acceptor, and partially *O*-alkylated galactosyl derivatives were chosen as the donors to investigate the effect of alkyl substitution in the donors on the stereo outcome of glycosylation. It was found (entry i) that coupling of perbenzoylated galactosyl trichloroacetimidate **1** with the acceptor **2** gave the β-linked disaccharide **3** completely, showing the normal 1,2-*trans*-glycosylation controlled by C2 neighboring group participation. However, when isopropyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (**4**, entry ii) or 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl trichloroacetimidate (**6**, entry iii) as the donors were coupled with **2**, α- and β-linked mixtures (α:β = 1:4) were obtained, indicating that the presence of the electron-withdrawing benzoyl groups in donor **1** tended to give more β-linkage compared to the acetyl groups in **4** and **6**. The results of entries ii and iii also reveal that the leaving group, isopropylthio and trichloroacetimidate, did not make a significant difference in the stereoselectivity of glycosylation although the promoters used were quite different.

Next, partial alkylation of the donor was examined to observe the effect of electron-donating groups on the stereoselectivity of the glycosylation. It was found that coupling isopropyl 6-*O*-allyl-2,3,4-tri-*O*-benzoyl-1-thio- (**7**, entry iv) and 3-*O*-allyl-2,4,6-tri-*O*-benzoyl-1-thio-β-D-galactopyranoside (**9**, entry v) with the acceptor **2**

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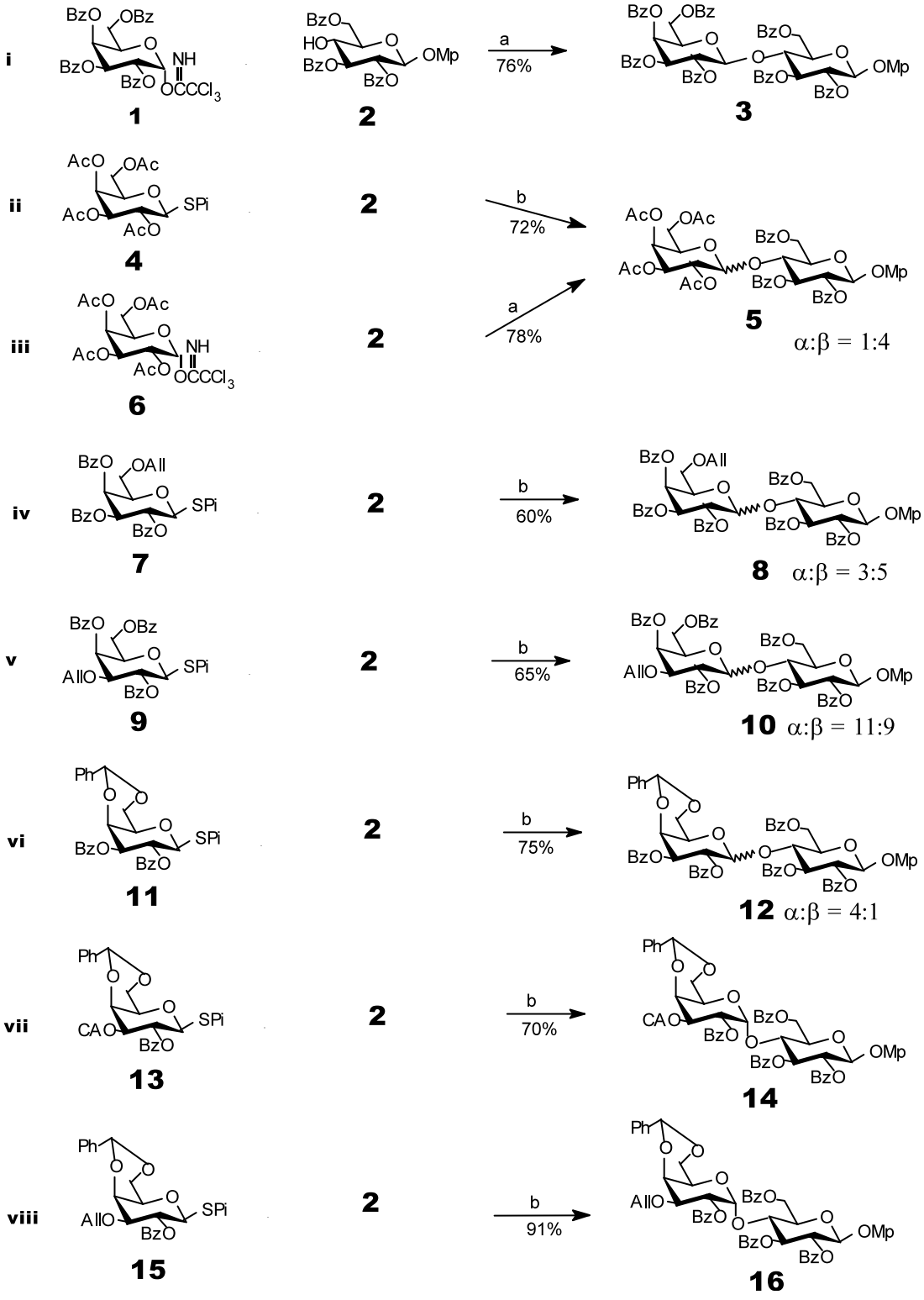
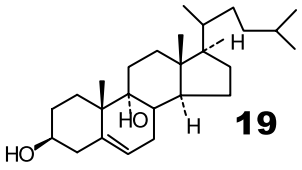
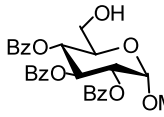
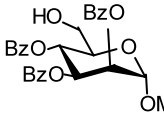
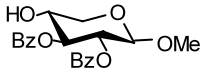
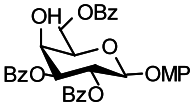
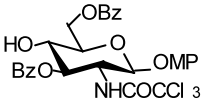
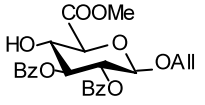
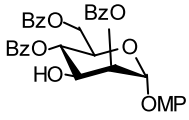
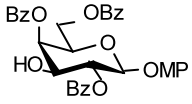
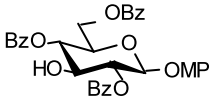
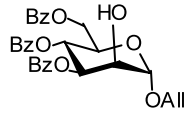
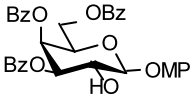
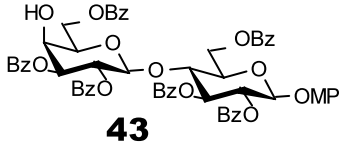


Scheme 1. Glycosylation of 4-methoxyphenyl 2,3,6-tri-*O*-benzoyl-D-glucopyranoside (**2**) with a variety of donors.

gave mixtures containing substantial α-linkage (α:β= 3:5 and 11:9, respectively) compared to the entries i. The results of entries iv and v also showed that the effect of 3-*O*-alkylation on α-linkage formation dominated the effect of 6-*O*-alkylation. Moreover, the effect of 4,6-*O*-benzylidenation of the galactosyl donors was investigated (entries vi, vii, viii). Overall, with 4,6-*O*-benzylidenated galactosyl derivatives as the donors and **2** as the acceptor, the couplings gave disaccharides with exclusive or predominantly α-linkages. Among the entries, the use of isopropyl 2,3-*O*-benzoyl-4,6-*O*-benzylidene-1-thio-β-D-galactopyranoside (**11**, entry vi) as the donor afforded a disaccharide mixture with α:β= 4:1, while 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-chloro-

Table 1. Glycosylation of isopropyl 3-*O*-allyl-2-*O*-benzoyl-4,6-*O*-benzylidene-1-thio-β-D-galactopyranoside (**15**) with a variety acceptors

variety	Acceptor	Product	Yield	Configuration
n-lauryl alcohol	**17**	**18**	85%	β
	**19**	**20**	85%	β
	**21**	**22**	95%	β
	**23**	**24**	95%	β
	**25**	**26**	90%	α:β = 7:2
	**27**	**28**	90%	α
	**29**	**30**	60%	α
	**31**	**32**	90%	α
	**33**	**34**	65%	α
	**35**	**36**	90%	α
	**37**	**38**	90%	α
	**39**	**40**	90%	α
	**41**	**42**	70%	α
 **43**		**44**	45%	α

acetyl- (**13**, entry vii), and 3-*O*-allyl-2-*O*-benzoyl-4,6-*O*-benzylidene-1-thio-β-D-galactopyranoside (**15**, entry viii) as the donors, afforded exclusively α-linked disaccharides. This is not difficult to understand since the 3-*O*-chloroacetyl group in **13**, and the 3-*O*-allyl group in **15** are electron-donating compared to the 3-*O*-benzoyl group in **11**, and they possess a synergistic effect with the 4,6-*O*-benzylidene group in these compounds.

A systematic study on glycosylation of **15** with a variety of acceptors was carried out as indicated in Table 1. With sugar acceptors with 4-OH's such as **27**, **29**, **31**, and **43**, glycosylation using **15** gave α-linked products only. Meanwhile, condensation of **15** with methyl 2,3-di-*O*-benzoyl-β-D-xylopyranoside (**25**) afforded predominantly the α-linked disaccharide **26** (α:β = 7:2). With sugar acceptors with a 3-OH such as **33**, **35**, and **37**, glycosylation using **15** also furnished α-linked products only. Glycosylation of **15** with acceptors with 2-OH's such as **39** and **41** similarly yielded α-linked products, exclusively. However, it was noted that the stereo outcome of glycosylation using **15** of aglycon acceptors such as lauryl alcohol (**17**) and cholesterol (**19**), and with acceptors with 6-OH's such as **21** and **23** was still controlled by neighboring group participation giving β-linked products only. All of the products were fully characterized by ^{1}H and ^{13}C NMR spectrometry.[7]

From the studies described above, we summarize our findings as follows: (1) alkyl substitution of the acylated galactosyl donor tends to give some α-linkage formation; (2) 4,6-*O*-benzylidenation of the galactosyl donor leads strongly to α-linkage formation in spite of the C2 ester capable of neighboring group participation. The effect of 4,6-*O*-benzylidenation of the galactosyl donor with a C2 ester was just opposite to that of the corresponding 4,6-*O*-benzylidenation of the glucosyl donor which always gave β-linkages in (1→3)-glucosylation;[8] (3) glycosylation of a 4,6-*O*-benzylidenated galactosyl donor with acceptors such as sugars with 2-, or 3-, or 4-OH's gave exclusively or predominantly α-linked products.

We hypothesize that electron-donating groups in the donor stabilize galactosyloxocarbonium ion intermediates leading to more α products. However, this may not account for the dramatic impact on stereoselectivity of galactosylation. The detailed mechanism for the 1,2-*cis*-glycosylation with galactosyl donors having a C2 ester group capable of neighboring group participation will depend on studies on further coupling reactions using structurally different donors and acceptors, and on calculations of the transition states of the couplings, and these will be a focus for further work.

Acknowledgements

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7. General reaction conditions: (a) The trichloroacetimidate donor (2.0 mmol) and the acceptor (2.0 mmol) were dried together under high vacuum for 2 h, then dissolved in anhyd CH_2Cl_2 (30 mL). TMSOTf (30 μL, 0.08 equiv.) was added dropwise at −25°C with N_2 protection. The reaction mixture was stirred for 3 h, during which time the temperature was gradually warmed to ambient temperature. Then the mixture was neutralized with triethylamine, concentrated and purified by column chromatography (2:1 ~ 1:1 petroleum ether–EtOAc) to afford the products. (b) The thioalkyl donor (2.0 mmol) and the acceptor (2.0 mmol) were dried together under high vacuum for 2 h, then dissolved in anhydrous CH_2Cl_2 (30 mL). NIS (2.0 mmol) and TMSOTf (120 μL, 0.20 equiv.) were added at −25°C with N_2 protection. The reaction mixture was stirred for 3 h, during which time the temperature was gradually warmed to ambient temperature. Then the mixture was worked up as described above to afford the products.
Selected physical data of some products: **10β**: $[\alpha]_D$ = +23.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.11 (d, 1H, $J_{1,2}$ 7.8 Hz, H-1′), 4.71 (d, 1H, $J_{1,2}$ 8.0 Hz, H-1), 3.69 (s, 3H, CH_3O). ^{13}C NMR ($CDCl_3$): δ 101.07 (J_{C1-H1} = 157.8 Hz, C-1′), 100.59 (J_{C1-H1} = 160.1 Hz, C-1), 55.44 (CH_3O). **10α**: $[\alpha]_D$ = +84.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 5.70 (d, 1H, $J_{1,2}$ 3.7 Hz, H-1′), 5.16 (d, 1H, $J_{1,2}$ 7.6 Hz, H-1), 3.69 (s, 3H, CH_3O). ^{13}C NMR ($CDCl_3$): δ 100.11 (J_{C1-H1} = 164.4 Hz, C-1), 97.40 (J_{C1-H1} = 173.0 Hz, C-1′), 55.44 (CH_3O). **12β**: $[\alpha]_D$ = +0.7 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 5.12 (d, 1H, $J_{1,2}$ 7.7 Hz, H-1′), 4.87 (d, 1H, $J_{1,2}$ 7.8 Hz, H-1), 3.66 (s, 3H, CH_3O). ^{13}C NMR ($CDCl_3$): δ 101.50 (J_{C1-H1} = 159.6 Hz, C-1), 100.52 (J_{C1-H1} = 158.3 Hz, C-1′), 100.19 (J_{PhC-H} = 166.6 Hz, Ph*C*H=). **12α**: $[\alpha]_D$ = +104.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 5.80 (d, 1H, $J_{1,2}$ 3.1 Hz, H-1′), 5.24 (d, 1H, $J_{1,2}$ 7.4 Hz, H-1). ^{13}C NMR ($CDCl_3$): δ 100.44 (J_{C1-H1} = 159.2 Hz, C-1), 100.15 (J_{PhC-H} = 160.3 Hz, PhCH=), 97.91 (J_{C1-H1} = 175.2 Hz, C-1′). **16**: $[\alpha]_D$ = +101.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 5.72 (dd, 1H, $J_{1,2}$ 3.8 Hz, H-1′), 5.20 (d, 1H, $J_{1,2}$ 7.5 Hz, H-1), 3.71 (s, 1H, CH_3O). ^{13}C NMR ($CDCl_3$): δ 100.87 (J_{C1-H1} = 157.8 Hz, C-1), 100.18 (J_{PhC-H} = 162.7 Hz, Ph*C*H=), 97.96 (J_{C1-H1} = 174.2 Hz, C-1′), 55.46 (CH_3O). **22**: $[\alpha]_D$ = +4.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 4.81 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.69 (d, 1H, $J_{1,2}$ = 8.1 Hz, H-1′). ^{13}C NMR ($CDCl_3$): δ 101.98 (C-1), 100.25 (Ph*C*H=), 96.16 (C-1′), 54.85 (CH_3O). **32**: $[\alpha]_D$ = +8.2 (*c*

1.1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.55 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1′), 4.80 (d, 1H, $J_{1,2}$ 7.3 Hz, H-1), 3.87 (s, 3H, CH_3O). ^{13}C NMR ($CDCl_3$): 100.92 (J_{C1-H1} = 159.1 Hz, C-1), 99.56 (J_{PhC-H} = 161.3 Hz, Ph*C*H=), 98.31 (J_{C1-H1} = 170.0 Hz, C-1′), 52.77 (CH_3O). **36**: $[\alpha]_D$ = +13.1 (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.64 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1′), 5.12 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 3.70 (s, 3H, CH_3O). ^{13}C NMR ($CDCl_3$): δ 101.12 (J_{C1-H1} = 159.9 Hz, C-1), 100.83 (J_{PhC-H} = 164.7 Hz, Ph*C*H=), 95.15 (J_{C1-H1} = 173.1 Hz, C-1′), 55.46 (CH_3O). **40**: $[\alpha]_D$ = +19.6 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.35 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1′), 5.21 (d, 1H, $J_{1,2}$ = 1.4 Hz, H-1). ^{13}C NMR ($CDCl_3$): δ 100.87 (Ph*C*H=), 98.85 (C-1′), 97.43 (C-1). **44**: $[\alpha]_D$ = +61.7 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.33 (d, 1H, $J_{1,2}$ 3.2 Hz, H-1″), 5.10 (d, 1H, $J_{1,2}$ 7.7 Hz, H-1′), 4.96 (d, 1H, $J_{1,2}$ 7.7 Hz, H-1), 3.68 (s, 3H, CH_3O). ^{13}C NMR ($CDCl_3$): δ 100.84 (J_{C1-H1} = 160.7 Hz, C-1), 100.76 (J_{C1-H1} = 160.7 Hz, C-1′), 100.25 (J_{PhC-H} = 162.4 Hz, Ph*C*H=), 99.98 (J_{C1-H1} = 170.0 Hz, C-1″), 55.43 (CH_3O).

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