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2-Allyloxyphenyl glycoside as a new and stable type of glycosyl donors

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Abstract—A high-yielding coupling of a new and stable type of glycosyl donors, namely 2-allyloxyphenyl glycoside, with a variety of alcohols via NIS/TfOH reagent combination as effective activators at room temperature is described here.

Complex carbohydrates, which are ubiquitously distributed in numerous biological systems, play significant roles in a diverse set of processes, including viral and bacterial infection, tumor metastasis, angiogenesis, inflammation, immunological response, signal transduction, and cell–cell communication.[1] For the synthesis of these potent sugars, the development of novel and efficient methodologies to construct the glycosidic bond has gained an immense attention in carbohydrate chemistry.[2] Most of the efforts have focused on the invention of new glycosyl donors, the discovery of reagent combinations for their activation, and the investigation of automated one-pot synthesis in solution[3] or solid phase.[4] Glycosyl trichloroacetimidates,[5] thioglycosides,[6] glycosyl halides,[7] 4-*n*-penten-1-yl glycosides,[8] glycosyl sulfoxides,[9] glycals,[10] selenoglycosides,[11] glycosyl phosphates[12] and phosphites,[13] 2-(hydroxycarbonyl)benzyl glycosides,[14] and in situ generated anomeric oxosulfonium species[15] are most widely used as donors for the assembly of oligosaccharides and glycoconjugates. Among these common protocols, the stable thioglycosides and 4-*n*-penten-1-yl glycosides serve not only as anomeric-protected sugars for manipulation of functional groups at various positions, but also as glycosyl donors for further coupling with various alcohols in the presence of activators. Herein, we introduce two new and stable types of donors, 2-allyloxyethyl glycoside **1** and 2-allyloxyphenyl glycoside **2**, and report the utility of **2** in the construction of various glycosidic linkages.

Fraser-Reid and co-workers in their elegant explorations on 4-*n*-penten-1-yl glycoside donors have established the mechanistic rationale for electrophilic activation of a remote double bond.[8] It has been invoked that such a process proceeds via a five-membered ring transition state involving both oxygen atoms that finally leads to the liberation of anomeric center and a halomethylfuran side product.[8d] We postulated that the terminal double bonds of glycosides **1** and **2** (Scheme 1), upon exposure to electrophiles, may in principle be activated to trigger a concerted reaction via intramolecular cyclization involving two oxygen atoms to form the six-membered ring chair and skew-boat transition states **3** and **4**, respectively. Through the participation of the lone pair electrons on the oxygen atom of sugar ring, both intermediates could lead to a reactive oxonium ion **5**, which would furnish the expected O-glycoside **6** upon quenching with an alcohol.

To test this hypothesis, D-mannose was selected for the model study. The corresponding 2-allyloxyethyl (**8**) and 2-allyloxyphenyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside (**11**) were prepared in a straightforward manner, as outlined in Scheme 2. Treatment of compound **7** with commercially available 2-allyloxyethanol in the presence of Dowex 50WX4-200 ion-exchange resin at reflux temperature followed by per-*O*-benzylation provided the desired product **8** and its β-anomeric isomer in

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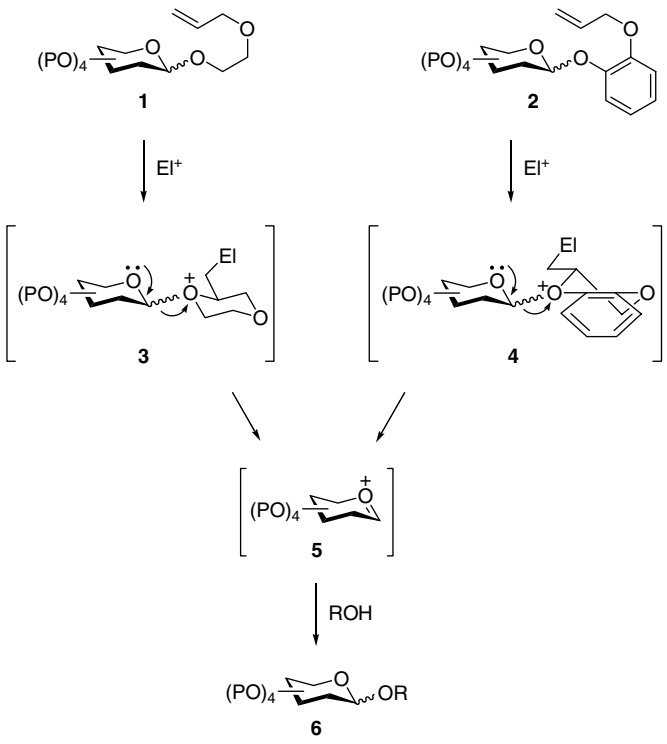
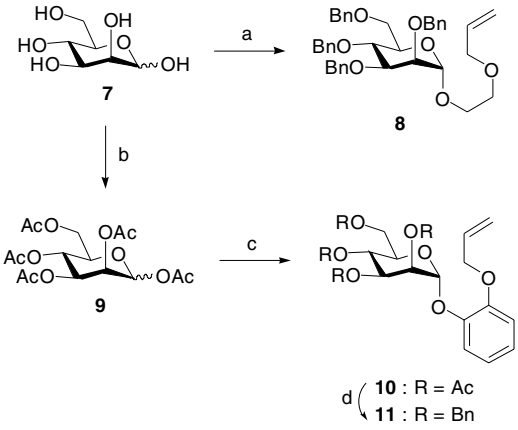


Scheme 1.

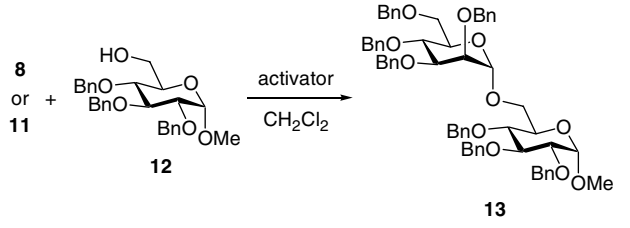


Scheme 2. Reagents and conditions: (a) (i) 2-allyloxyethanol, Dowex-50WX4-200 resin, 100 °C; (ii) NaH, BnBr (**8**: 42%, β-isomer: 6%, in two steps); (b) 0.03% $Cu(OTf)_2$, 5.1 equiv Ac_2O, 0 °C to rt, neat, 99%; (c) 2-allyloxyphenol, TMSOTf, CH_2Cl_2, 3 Å MS, 0 °C, 63%, recovered **9**: 30%; (d) (i) NaOMe, MeOH; (ii) NaH, BnBr (89% in two steps).

42% and 6% isolated yields, respectively. Reaction of **7** with 2-allyloxyphenol[16] under identical conditions, however, gave unsatisfactory results. Alternatively, TMSOTf-catalyzed coupling of easily accessible D-mannopyranosyl pentaacetate **9**[17] and 2-allyloxyphenol led to the 2-allyloxyphenyl-α-glycoside **10** in 63% yield; substantial amount (30%) of the starting material **7** was recovered that was recycled in the next batch. Functional group transformation of tetraacetate **10** through a two-stepped deacetylation (NaOMe, MeOH) and per-*O*-benzylation (NaH, BnBr) yielded the corresponding ether **11** (89%). The allyloxyethyl and allyloxyphenyl glycosides can be purified by column chromatography on silica gel and are stable compounds, which can be stored at room temperature for a few months without any change.

Initial optimization for coupling of donors **8** and **11** with the known D-glucopyranosyl 6-OH **12**[18] employing a variety of reagent combinations and temperature conditions in dichloromethane is summarized in Table 1. In entry 1, reaction of **8** and **12** using NIS/TfOH combination at 0 °C furnished the desired α-mannoside **13**,[19] albeit in a low yield. Nevertheless, conducting the addition of NIS and TfOH or TESOTf at 0 °C and warming up the reaction to room temperature resulted in the

Table 1. Coupling of the glycosyl donors **8** or **11** with the 6-alcohol **12** to the α-linked disaccharide **13** in the presence of various activators



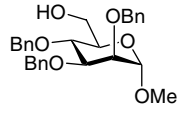
Entry	Donor	Activator	*T* (°C)	Yield (%)
1	**8**	NIS/TfOH	0	12
2	**8**	NIS/TfOH	0→rt	31
3	**8**	NIS/TESOTf	0→rt	26
4	**8**	ICl/AgOTf	0	0
5	**8**	IDCP	0→rt	0
6	**11**	ICl/AgOTf	0	53
7	**11**	NIS/TfOH	rt	81

formation of **13** in 31% (entry 2) and 26% (entry 3) yields, respectively. Other promoters like ICl/AgOTf and IDCP were found to be ineffective for the activation of **8**; no coupling product was obtained in both cases (entries 4 and 5). In contrast, glycosidation reactions of the 2-allyloxyphenyl glycoside **11** exhibited promising results. While, coupling of compounds **11** and **12** to disaccharide **13** could be promoted by ICl/AgOTf (entry 6, 53%), NIS/TfOH system worked the best for their activation. The reaction cleanly and rapidly afforded **13** in 81% yield, at ambient temperature (entry 7).

These results guided us to explore the inherent potential of 2-allyloxyphenyl glycosides. A variety of acceptors (Table 2) were then tested to examine the glycosidation scope of the donor **11**, including the linear alcohols **14**–**16**, D-mannopyranosyl 6-OH **17** and 1-OH **18**, D-galactopyranosyl 6-OH **19**, 1,6-anhydro-β-L-idopyranosyl 4-OH **20**,[20] and D-glucosamine-derived 4-OH **21**.[21] In general, the reactions were carried out in 4 h, and the α-mannopyranosylated adducts **22**–**29** (entries 1–8) were obtained in good yields, respectively. As anticipated, a clear preference for the formation of α-isomer was observed in glycosylations with various acceptors except in the case of acceptor **19**, which generated the corresponding β-isomer in minor proportions (entry 6, $\alpha/\beta = 2.4{:}1$). Highly stereoselective formation of the 1,1′-α,α′-linked mannoside **26** is noteworthy (entry 5, 71%). Of particular interest is the installation of α-1→6 and α-1→4-linked disaccharides **25** and **29**, which are the vital components of biologically important GPI anchors. The configurations of compounds **22**–**29** were unambiguously determined either through data comparison with the literature reports or via analyses of ^{1}H, ^{13}C, and 2D NMR spectra.[22]

Table 2. NIS/TfOH-activated coupling of the glycosyl donor **11** with various alcohols **14**–**21** at rt to the α-mannopyranosylated products **22**–**29**, respectively

14 : CH_3OH
15 : $PhCH_2OH$
16 : $n\text{-}C_8H_{17}OH$



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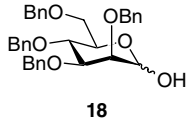

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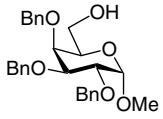

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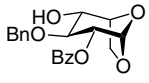

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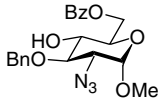

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Entry	Acceptor	Product	Yield (%)
1	**14**	**22**	82
2	**15**	**23**	85
3	**16**	**24**	73
4	**17**	**25**	65
5	**18**	**26**[a]	71
6	**19**	**27**[b]	71
7	**20**	**28**	82
8	**21**	**29**	72

[a] 1,1′-α,α′-Linked disaccharide.
[b] $\alpha/\beta = 2.4{:}1$.

In conclusion, we have successfully developed a new and stable type of glycosyl donors, namely 2-allyloxyphenyl glycoside, from easily accessible 2-allyloxyphenol and investigated its assembly with a variety of alcohols in good yields via NIS/TfOH reagent combination as effective activator at room temperature. The ease of preparation, handling and storage together with simple reaction set-up, and clean glycosylations make these glycosides attractive donors for the synthesis of oligosaccharides and glycoconjugates.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.12.127.

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21. General procedure for coupling of the glycosyl donor **11** with various alcohols. Trifluoromethanesulfonic acid (0.3 equiv) was added to a solution of compound **11** (1.2 equiv), an alcohol (1.0 equiv, **14**–**21**), and *N*-iodosuccinimide (2.0 equiv) in dichloromethane (20 mL per gram of **11**) at room temperature under nitrogen. The reaction was monitored by TLC till the total consumption of starting material (~4 h). Triethylamine (5.0 equiv) was added to the solution, the mixture was filtered through paper, and the filtrate was sequentially washed by 5% $Na_2S_2O_{3(aq)}$, saturated $NaHCO_{3(aq)}$, and brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo to yield a residue, which was purified by flash column chromatography to provide the desired α-mannopyranosylated adducts (Table 2).
22. Spectral data of selected new compounds. Compound **11**: $[\alpha]_D^{25}$ +59.3 (*c* 1.6, $CHCl_3$); IR ($CHCl_3$) *v* 3064, 2856, 1643, 1592, 1498, 1451, 1358, 1254, 1213, 1112, 1026, 992, 751, 697, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.20 (m, 20H, Ph-H), 7.13 (dd, $J = 7.9$, 1.4 Hz, 1H, PhH), 7.02–6.97 (m, 1H, PhH), 6.91–6.85 (m, 2H, PhH), 6.04 (ddt, $J = 17.2$, 10.5, 5.2 Hz, 1H, C*H*=CH_2), 5.59 (d, $J = 1.7$ Hz, 1H, H-1), 5.39 (ddt, $J = 17.2$, 3.2, 1.6 Hz, 1H, CH=CH_2), 5.25 (ddt, $J = 10.5$, 2.9, 1.4 Hz, 1H, CH=CH_2), 4.94 (d, $J = 10.8$ Hz, 1H, CH_2Ph), 4.79 (s, 2H, CH_2Ph), 4.70 (s, 2H, CH_2Ph), 4.65 (d, $J = 12.0$ Hz, 1H, CH_2Ph), 4.57 (d, $J = 10.8$ Hz, 1H, CH_2Ph), 4.51–4.47 (m, 3H, CH_2CH=CH_2, CH_2Ph), 4.21–4.06 (m, 4H, H-2, H-3, H-4, H-5), 3.83 (dd, $J = 11.0$, 4.4 Hz, 1H, H-6a), 3.73 (dd, $J = 11.0$, 1.5 Hz, 1H, H-6b); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4 (C), 145.8 (C), 138.5 (C), 138.3 (C), 138.2 (C), 133.3 (CH), 128.3 (CH), 128.23 (CH), 128.20 (CH), 128.1 (CH_2), 127.8 (CH), 127.7 (CH), 127.62 (CH), 127.60 (CH), 127.49 (CH), 127.46 (CH), 127.3 (CH), 123.5 (CH), 121.3 (CH), 119.4 (CH), 117.3 (CH_2), 114.4 (CH), 97.8 (CH), 79.9 (CH), 75.0 (CH_2), 74.7 (CH × 2), 73.2 (CH_2), 72.7 (CH), 72.6 (CH_2), 72.2 (CH_2), 69.6 (CH_2), 69.1 (CH_2); HRMS (FAB, MNa^+) calcd for $C_{43}H_{44}O_7Na$ 695.2994, found 695.2985. Compound **28**: $[\alpha]_D^{28}$ +77.1 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) *v* 3031, 2913, 2867, 1719, 1651, 1637, 1451, 1360, 1270, 1102 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, $J = 7.4$, 0.7 Hz, 2H, Bz-H), 7.59 (t, $J = 7.4$ Hz, 1H, ArH), 7.45 (t, $J = 7.4$ Hz, 2H, ArH), 7.36–7.25 (m, 18H, ArH), 7.21–7.45 (m, 5H, ArH), 7.45–7.10 (m, 2H, ArH), 5.50 (d, $J = 1.8$ Hz, 1H, H-1′), 5.13 (d, $J = 1.9$ Hz, 1H, H-1), 5.03 (dd, $J = 8.2$, 1.8 Hz, 1H, H-2′), 4.86 (d, $J = 10.8$ Hz, 1H, $PhCH_2$), 4.83 (t, $J = 4.3$ Hz, 1H, H-3), 4.67–4.54 (m, 8H, $PhCH_2$), 4.50 (d, $J = 10.8$ Hz, 1H, $PhCH_2$), 4.04 (d, $J = 8.0$ Hz, 1H, H-5), 3.94 (dd, $J = 8.0$, 4.3 Hz, 1H, H-4), 3.91–3.84 (m, 2H, H-3′, H-6a′), 3.81 (dd, $J = 9.0$, 3.0 Hz, 1H, H-6b′), 3.74–3.64 (m, 5H, H-6a, H-6b, H-2, H-4′, H-5′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8 (C), 139.2 (C), 138.9 (C), 138.3 (C), 138.11 (C), 138.10 (C), 133.4 (CH), 130.0 (CH), 129.1 (C), 128.5 (CH), 128.3 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 100.8 (CH), 99.3 (CH), 80.7 (CH), 79.6 (CH), 78.8 (CH), 76.7 (CH), 75.37 (CH_2), 75.33 (CH), 75.1 (CH), 74.8 (CH_2), 74.4 (CH), 73.6 (CH_2), 72.9 (CH), 72.8 (CH_2), 72.4 (CH_2), 69.5 (CH_2), 65.9 (CH_2); HRMS (FAB, M^+) calcd for $C_{54}H_{54}O_{11}Na$ 901.3564, found 901.3578. Compound **29**: $[\alpha]_D^{23}$ −63.0 (*c* 2.1, $CHCl_3$); IR ($CHCl_3$) *v* 2908, 2867, 2102, 1721, 1453, 1276, 1106, 1052, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05–8.03 (m, 2H, ArH), 7.55–7.52 (m, 1H, ArH), 7.42–7.39 (m, 2H, ArH), 7.33–7.13 (m, 25H, ArH), 5.34 (d, $J = 2.6$ Hz, 1H, H-1′), 4.90 (d, $J = 11.0$ Hz, 1H, $PhCH_2$), 4.80 (d, $J = 3.4$ Hz, 1H, H-1), 4.76 (d, $J = 10.8$ Hz, 1H, $PhCH_2$), 4.73 (dd, $J = 12.0$, 2.2 Hz, 1H, H-6a), 4.67 (d, $J = 11.8$ Hz, 1H, $PhCH_2$), 4.64 (d, $J = 10.8$ Hz, 1H, $PhCH_2$), 4.59 (d, $J = 11.8$ Hz, 1H, $PhCH_2$), 4.53 (d, $J = 12.0$ Hz, 1H, $PhCH_2$), 4.47 (dd, $J = 12.0$, 5.2 Hz, 1H, H-6b), 4.46 (d, $J = 10.8$ Hz, 1H, $PhCH_2$), 4.39 (d, $J = 12.0$ Hz, 1H, $PhCH_2$), 4.31 (d, $J = 12.0$ Hz, 1H, $PhCH_2$), 4.23 (d, $J = 12.0$ Hz, 1H, $PhCH_2$), 4.04 (t, $J = 9.0$ Hz, 1H, H-4), 3.94–3.81 (m, 5H, H-5, H-3, H-5′, H-6a′, H-6b′), 3.72 (t, $J = 2.6$ Hz, 1H, H-2′), 3.70 (dd, $J = 11.0$, 4.2 Hz, 1H, H-4′), 3.60 (dd, $J = 11.0$, 2.6 Hz, 1H, H-3′), 3.43 (s, 3H, OMe), 3.41 (dd, $J = 10.0$, 3.4 Hz, 1H, H-2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1 (C), 138.5 (C), 138.4 (C), 138.36 (C), 138.3 (C), 137.6 (C), 133.0 (CH), 130.0 (C), 129.7 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.29 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 127.97 (CH), 127.8 (CH), 127.74 (CH), 127.71 (CH), 127.61 (CH), 127.59 (CH), 127.3 (CH), 127.2 (CH), 127.1 (CH), 101.7 (CH), 98.4 (CH), 80.4 (CH), 79.4(CH), 77.5 (CH), 76.7 (CH), 74.8 (CH_2), 74.77 (CH), 74.71 (CH_2), 73.5 (CH), 73.3 (CH_2), 72.5 (CH_2), 72.4 (CH_2), 68.9 (CH), 68.8 (CH_2), 63.6 (CH_2), 63.6 (CH), 55.3 (CH_3); HRMS (FAB, MNa^+) calcd for $C_{55}H_{57}O_{11}N_3Na$ 958.3891, found 958.3895.