JOC Notes

Neighboring Group Participation of 9-Anthracenylmethyl Group in Glycosylation: Preparation of Unusual *C*-Glycosides

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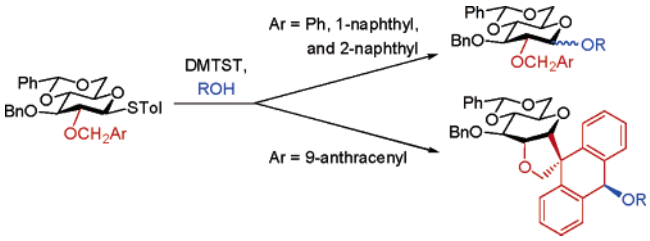

A coupling of 2-*O*-arylmethylated D-glucose-derived thioglycosides with various alcohols in the presence of DMTST as an activator is described. The requisite glycosyl donors are efficiently prepared by one-pot procedures. When the aryl groups are phenyl, *p*-methoxyphenyl, 1-naphthyl, and 2-naphthyl groups, a mixture of α- and *β*-anomeric *O*-glycosides is obtained under the conditions, whereas when the aryl group is the 9-anthracenyl group, a highly stereoselective formation of the unusual *C*-glycosides in good yields via neighboring group participation of the 9-anthracenylmethyl group followed by coupling with a variety of alcohols is observed. Three new chiral centers including a quaternary carbon are created in one single step.

Stereoselective formation of a glycosidic bond is a central challenge in the synthesis of oligosaccharides as well as glycoconjugates.[1] D-Glucose, the most abundant sugar from natural sources, is a typical component of numerous biologically potent molecules. The stereocontrol of α- or *β*-coupling at its anomeric center is influenced by various factors.[2] Among these, the protecting group used to mask its C2-hydroxyl plays a crucial role. Benzyl ethers at the C2 position make the donor more reactive (armed)[3] and are generally known to act as silent bystanders in the glycosylation event that usually leads to the formation of an α-glycoside by the virtue of anomeric effect.[4] While, *β*-selectivity is typically achieved via anchimeric assistance of an ester protecting group at C2[5] or through participation of solvent such as acetonitrile,[6] competing side reactions of ortho ester formation in the former and imidate generation in the latter are some of the major drawbacks of these methods.[2] Although *π*−*π* interactions are well established in organic synthesis and are often used to get a particular diastereoisomer in excess,[7] such interactions have not been studied in sugar coupling at all. We postulated that the placement of various arylmethyl groups at the O2 position of D-glucose should influence the stereoselective outcome of glycosylation, and the 1,2-*trans*-selectivity could be achieved either via a favorable *π*−*π* interaction between the *p*-orbitals of the stabilized oxonium ion intermediate and that of the aromatic ring or via steric hindrance when the size of aryl ring is increased.

To evaluate this hypothesis, we selected different thioglycosides **2** and **4**−**7** for model studies. The synthesis of these donors using consecutive one-pot reactions is schematically summarized in Table 1. The tetraol **1**, obtained from D-glucose in two steps via a one-pot per-*O*-acetylation−anomeric substitution of thiocresol[8] followed by deacetylation, underwent 4,6-*O*-benzylidenation (91%) and subsequent 2,3-*O*-benzylation (90%) to provide the ether derivative **2**. Regioselective discrimination of 2,3-diequatorial dihydroxyls in a hexopyranoside is a challenging task. For this purpose, a highly regioselective Et_3SiH-reductive O3-etherification of the trimethylsilyl ether with benzaldehyde in the presence of TMSOTf[9] or $Cu(OTf)_2$ [10] as the catalyst was recently developed by us. One-pot preparation of the bis-OTMS compound **3** from the tetraol **1** in 72% yield was carried out through a combination of 4,6-*O*-benzylidenation and 2,3-di-*O*-silylation. Sequential benzylation of **3** at O3 followed by O2-arylmethylation (NaH, $ArCH_2X$) in a one-pot manner afforded the corresponding ethers **4**−**7** in 73%, 78%, 81%, and 82% yields, respectively.

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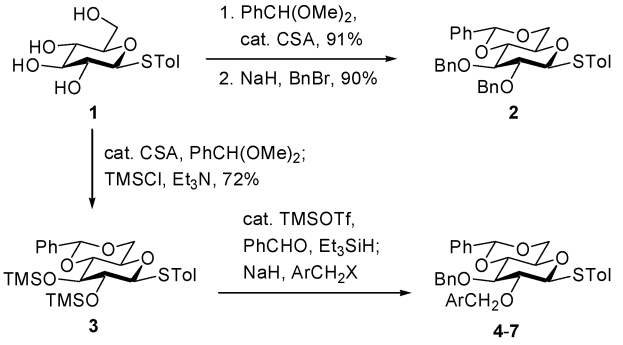
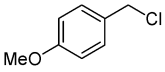
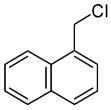
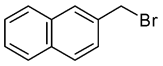
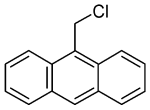
TABLE 1. Preparation of Various 3-*O*-Benzyl-4,6-*O*-benzylidene-2-*O*-arylmethylated Thioglycosides

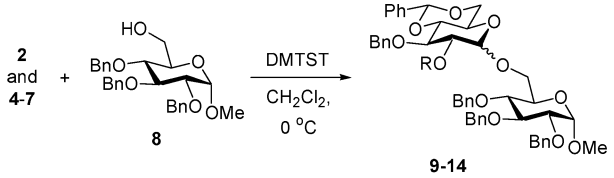


entry	$ArCH_2X$	product	yield(%)
1		**4**	73
2		**5**	78
3		**6**	81
4		**7**	82

With this set of donors **2** and **4**−**7** in hand, we further examined their coupling with the D-glucopyranosyl 6-alcohol **8**[11] in CH_2Cl_2 at 0 °C employing $CF_3SO_3^-S^+Me_2SMe$ (DMTST)[12] as a promoter (Table 2). As expected, the 2-OBn donor **2** furnished the disaccharide **9**[13] (entry 1, 83%) as an anomeric mixture with the predominance of the α-isomer (α/β = 2/1). In entry 2, the *p*-methoxybenzyl (PMB) group in compound **4** was found to be unstable under the glycosylation conditions that led to a mixture of four *O*-glycosides after overnight stirring: the expected products **10** (11%, α/β = 1/1) and the corresponding PMB-deprotected compounds **11** (43%, α/β = 1/1). The succeeding glycosylations with donors bearing 1-naphthylmethyl (1-NAP) and 2-NAP groups at O2 gave the *O*-disaccharides **12** and **13**, respectively, as anomeric mixtures with marginal variations in α/β ratios (entries 3 and 4). With the hope that a bulkier and more electron-rich anthracenylmethyl group would show some steric effect or π−π interaction, compound **7** (entry 5), which also exhibits a strong fluorescence at both wavelengths of UV light, was subjected to glycosylation under similar conditions. Two products were obtained from this reaction. However to our surprise, none of them showed any fluorescence upon TLC analysis.

The ^1H NMR spectrum of the major product revealed some prominent features (see the Supporting Information). (1) The downfield signals corresponding to the anthracene ring protons and the corresponding benzylic protons were missing. (2) There were two singlets in the δ 5−6 ppm region in place of anticipated one singlet for the acetal proton of 4,6-*O*-benzylidene ring. From the analyses of its ^{13}C, DEPT, and $^1H-^{13}C$ COSY NMR spectra, the peaks of C1′ acetal and C9 and C10 carbons of anthracenyl ring were not seen; instead, three extra signals, two tertiary carbons (δ 80.0 and 81.5) and a quaternary carbon (δ 58.0), were observed. The $^1H-^1H$ COSY spectrum indicated one more interesting facet, the correlation between H2′ and H3′ was weak, and there was no coupling between these two protons, clearly suggesting a dihedral angle of 90° and that the donor-derived sugar ring is no longer present in the usual $^4C_1$ conformation but rather a half chair or skew boat conformation. The NOESY spectrum exhibited a correlation of two H6 protons with a tertiary proton (δ 5.20) at the tertiary carbon (δ 80.0) and not with the H1′. The above evidence clearly confirmed that the major compound is not the expected *O*-glycoside **14** but a unique *C*-glycoside **15** (Table 3, entry 1), formed by neighboring group participation of 9-anthracenemethyl group.[14] The minor adduct also displayed similar spectral properties and HRMS data as that of **15**. No *O*-glycoside **14** was detected.

TABLE 2. Coupling of O2-Arylmethylated Thioglycosides 2 and 4−7 with the 6-Alcohol 8 To Form the Corresponding Disaccharides 9−14, Respectively



9 : R = Bn
10 : R = PMB
11 : R = H
12 : R = 1-Naphthylmethyl
13 : R = 2-Naphthylmethyl
14 : R = 9-Anthracenylmethyl

entry	thioglycoside	*t* (h)	product	yield (%)	α/β
1	**2**	6	**9**	83	2.0/1
2	**4**	20	**10**	11	1/1
			+	+	
			11	43	1/1
3	**5**	7	**12**	77	1.6/1
4	**6**	7	**13**	81	1.8/1
5	**7**	8	**14**	0	

This was an interesting result, and efforts were made to examine this novel reaction in detail. A series of experiments was conducted using donor **7** and various alcohols as acceptors under similar reaction conditions, and the results are outlined in Table 3. In all of the cases studied so far, we observed clean reactions giving *C*-

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(12) Fugedi, P.; Garegg, P. J. *Carbohydr. Res.* **1986**, *149*, C9−C12.
(13) Tanaka, H.; Sakamoto, H.; Sano, A.; Nakamura, S.; Nakajima, M.; Hashimoto, S. *Chem. Commun.* **1999**, 1259−1260.
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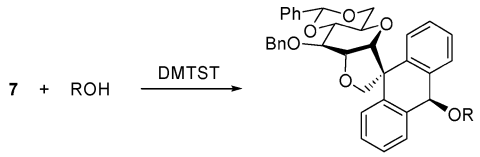
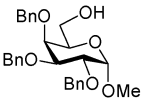
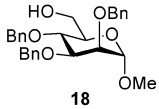
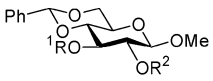
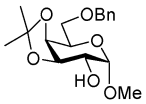
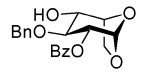
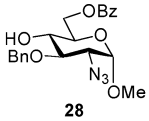
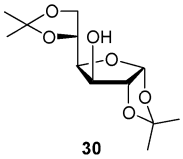
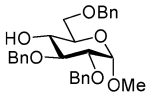
TABLE 3. Coupling of Compound 7 with Various Alcohols to the *C*-Glycosides via Intramolecular Participation of the Anthracenyl Group



entry	ROH	t(h)	product	yield(%)	*endo*/*exo*
1	**8**	8	**15**	82	1/7.2
2	 **16**	8	**17**	83	1/7.2
3	 **18**	10	**19**	92	1/5
4	 **20** : R^1 = OBn, R^2 = H	22	**21**	78	*exo* only
5	**22** : R^1 = H, R^2 = OBn	20	**23**	80	1/10
6	 **24**	18	**25**	80	*exo* only
7	 **26**	18	**27**	87	*exo* only
8	 **28**	20	**29**	67	*exo* only
9	 **30**	16	**31**	76	1/12
10	 **32**	23	**33**	50	*exo* only

glycosides as sole products with the time scale ranging from 4 to 8 h for primary alcohols and from 16 to 23 h for secondary alcohols. Most of the secondary alcohols furnished a single diastereoisomer. No *O*-glycoside was ever encountered. In entry 2, the D-galactose-derived 6-OH **16**[15] cleanly afforded the *C*-glycoside **17** in 72% yields along with the other isomer in minor proportion (10%). A similarly protected D-mannopyranoside **18**[16] (entry 3) gave the adduct **19** and its corresponding minor epimer in 77% and 15% yields, respectively. In cases of secondary alcohols, the D-glucopyranosyl 2-OH **20**[17] (entry 4) and 3-OH **22**[17] (entry 5), the D-galactose-derived 2-OH **24**[9] (entry 6), the 1,6-anhydro-β-L-idose-derived 4-OH **26**[18] (entry 7), the D-glucosamine derived 4-OH **28**[19] (entry 8), and diacetone α-D-glucose **30** (entry 9) each underwent a facile reaction, and the unusual *C*-glycoside products **21** (78%, *exo* only), **23** (80%, *endo*/*exo* = 1/10), **25** (80%, *exo* only), **27** (87%, *exo* only), **29** (67%, *exo* only), and **31** (76%, *endo*/*exo* = 1/12) were obtained in good yields, respectively. Finally, the D-glucose-derived 4-OH **32**[20] (entry 10), however sluggish to react under the conditions, did furnish the expected *C*-glycoside **33** (50%) along with the recovery of the acceptor **32** to the extent of 47%.

All the new compounds are thoroughly characterized by spectral means. The spectral features discussed earlier were found to be representative. The absolute configuration of compound **21-*exo*** was unambiguously determined through its X-ray single-crystal analysis. In Figure 1 (see Supporting Information), the ORTEP drawing of compound **21-*exo*** indicates that the C1−C22 and O7−C29 bonds are on the same face of the tricyclic framework. As predicted from the ^{1}H NMR spectral analyses of these *C*-glycosides, the 4,6-*O*-benzylidenated hexopyranoside ring appears to assume a half chair structure with the HC2−C3H dihedral angle of ∼90°.

Apparently, a cascade of events is taking place under glycosylation conditions. Owing to the close proximity, the C9 double bond of the anthracene ring attacks the C1 position of the transient oxonium ion, to form a *cis*-fused tetrahydrofuran ring with a newly formed spiro carbon. This is followed by migration of the C10 double bond, to restore the aromaticity of one of the phenyl rings that in turn generates a carbocation at C10. The anthracene tricycle no longer remains in planar form and offers a facial bias to the incoming nucleophile, which approaches the C10 from the *exo*-face in a stereoselective manner to give the major *exo*-diastereoisomer. The overall process can be looked upon as a tandem intramolecular *C*-glycosylation followed by diastereoselective addition. Intramolecular *C*-arylations of 2-*O*-benzylated furanosides[21] and pyranosides[21e,22] in the absence of glycosyl acceptors have been documented in the literatures. In the previous reports,[22a,b] the O2-benzyl group undergoes a Friedel−Craft-type substitution reaction to

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(16) Srivastava, V. K.; Schuerch, C. *J. Org. Chem*. **1981**, *46*, 1121−1126.

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(18) Hung, S.-C.; Thopate, S. R.; Chi, F.-C.; Chang, S.-W.; Lee, J.-C.; Wang, C.-C.; Wen, Y.-S. *J. Am. Chem. Soc*. **2001**, *123*, 3153−3154.

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(21) (a) Martin, O. R. *Tetrahedron Lett*. **1985**, *26*, 2055−2058. (b) Martin, O. R. *Carbohydr. Res*. **1987**, *171*, 211−222. (c) Martin, O. R.; Mahnken, R. E. *J. Chem. Soc., Chem. Commun.* **1986**, 497−498. (d) Araki, Y.; Mokubo, E.; Kobayashi, N.; Nagasawa, J.; Ishido, Y. *Tetrahedron Lett*. **1989**, *30*, 1115−1118. (e) Martin, O. R.; Hendricks, C. A. V.; Deshpande, P. P.; Culter, A. B.; Kane, S. A.; Rao, S. P. *Carbohydr. Res*. **1990**, *196*, 41−58. (f) Martin, O. R.; Rao, S. P.; Hendricks, C. A. V.; Mahnken, R. E. *Carbohydr. Res*. **1990**, *202*, 49−66. (g) Anastasia, M.; Allevi, P.; Ciuffreda, P.; Fiecchi, A.; Scala, A. *Carbohydr. Res*. **1990**, *208*, 264−266.

(22) (a) Verlhac, P.; Leteux, C.; Toupet, L.; Veyrières, A. *Carbohydr. Res*. **1996**, *291*, 11−20. (b) Rousseau, C.; Martin, O. R. *Tetrahedron: Asymmetry* **2000**, *11*, 409−412. (c) Garard, N.; Rousseau, C.; Martin, O. R. *Tetrahedron Lett*. **2003**, *44*, 8971−8974.

generate a six-membered pyranosyl ring. Whereas, the O2-anthracenyl group in our case traverses an electrophilic addition to form a five-memebred furanosyl ring. Consequently, the aromaticity is lost thereby inviting a concomitant nucleophilic attack of the acceptor in a stereoselective manner to complete the process.

In conclusion, we have discovered that the O2-anthracenylmethyl group on a glucopyranosyl donor exhibits direct neighboring group participation under glycosylation conditions and leads to the formation of *C*-glycosides with unusual structures, in good yields and diastereoselectivity. The thioglycoside donors utilized in this study are all new compounds, which are also efficiently prepared by novel one-pot procedure. A unique feature of this reaction is that three new chiral centers are created in one single step, in a highly stereoselective manner. Such facile access to complex polycyclic cores may have broader implications in the context of synthesis of biologically relevant compounds.

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Supporting Information Available: Experimental procedures, characterization data, ^{1}H and ^{13}C spectra of all new compounds, and X-ray structural information for compound **21-*exo*** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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