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Facile TMSOTf-catalyzed preparation of 2-deoxy α-*O*-aryl-D-glycosides from glycosyl acetates

Guofang Yang · Qingbing Wang · Xiaosheng Luo · Jianbo Zhang · Jie Tang

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Abstract 2-Deoxy α-*O*-aryl glycosides were conveniently obtained by reaction of 2-deoxy-glycosyl acetates with phenols in the presence of TMSOTf as the promoter. The current method provides the *O*-aryl glycosides with good to excellent yields, and sole alpha selectivity.

Keywords Stereoselective · 2-deoxy sugars · Aryl glycoside · Glycosyl acetates · TMSOTf

Aromatic deoxygenated glycosides are common structural unites in many natural products possessing important biological properties, which include antibiotics such as Landomycin, antitumor agents such as Chromomycin and Olivomycin and so on [1–3]. However, the efficient construction of *O*-aryl glycosides can be difficult to achieve due to the electron-withdrawing properties of aromatic rings [4] and the facile rearrangement of the resulting *O*-aryl glycosides to their corresponding *C*-aryl glycosides [5–9]. Additionally, stereoselective synthesis of 2-deoxy-glycosidic linkage [10,11] has been found to be one of the most challenging tasks in the synthesis of these natural products owing to the absence of stereoelectronic influences of substitutions at *C*-2 carbon [12]. To circumvent these problems for 2-deoxy glycoside synthesis, glycosyl donors with 2-substituents such as halides [13–15] and aryl selenyl and sulfenyl derivatives [16–18] of 1, 2-anhydropyranoses [19] acting as a neighboring group are widely applied in this kind of glycosylation, followed by reductive removal of the 2-substituents (Scheme 1). The drawback of this approach is that the introduction and removal of the participating functionality often requires toxic reagents; moreover, extra steps often lead to time-consuming synthetic procedures.

Several methods are available for direct β-selective glycosylation in which α-glycosyl halides, glycosyl phosphites, glycosyl acetates, and trichloroacetimidates are employed as glycosyl donors in combination with a mild promoter [20–25]. In contrast, only a few procedures for preparation of α-glycosides have been reported in moderate yields by acid-catalyzed activation of glycals, silyl ethers [26–31]. For example, Flack *et al*. have successfully employed triphenylphosphinehydrogenbromide (TPHB) to promote direct addition of various alcohols and carboxylic acids to glycals [32]. The approach directly introduces hydrogen at *C*-2, and α-glycosides often predominate due to the kinetic anomeric effect [33].

Clearly, the application of direct methods for the efficient and stereoselective construction of 2-deoxy *O*-aryl glycosides is highly desirable [34–37]. In order to develop more convenient synthetic route, we therefore set out to use the 2-deoxy glycosyl acetates as a convenient glycosyl donor. In this note, we report the direct glycosylation of phenols with 2-deoxy glycosyl acetates [22] with exclusive α-selectivity.

We initially employed Lewis acid in the presence of 1.0 equiv 2-deoxy-tetra-*O*-acetyl- α-D-glucopyranoside **1** and 1.0 equiv phenol **2a** in CH_2Cl_2. As we anticipated, treatment of 2-deoxy glucosyl acetate with $BF_3{\cdot}Et_2O$ in dichloromethane

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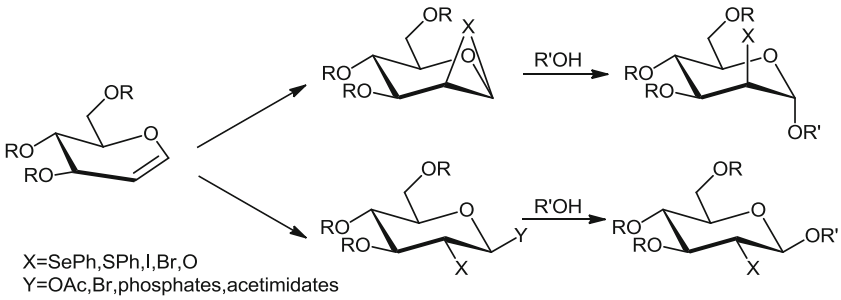
G. Yang · Q. Wang · X. Luo · J. Zhang (✉) · J. Tang
Department of Chemistry, East China Normal University, Shanghai 200062, China
e-mail: jbzhang@chem.ecnu.edu.cn

Q. Wang
State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Science, 354 Fenglin Road, Shanghai 200032, China

Scheme 1 Known synthetic strategies towards 2-deoxy O-glycosides



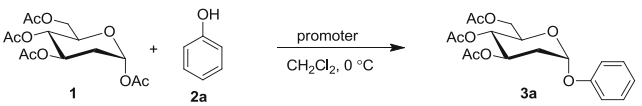
within 3.2 h afforded phenyl 2-deoxy-α-D-glucopyranoside **3a** with 40 % yield, while no β-anomer was detected (Table 1, entry 1). The conversion to the α-phenolic glycoside was evidenced by ^{1}H NMR data showing a dramatic upfield shift of the anomeric proton (δ 5.68 ppm) when compared with the anomeric acetate (δ 6.26 ppm), and the chemical shifts are identical to the data reported [32].

With amount of boron trifluoride diethyl etherate ranged from 0.3 to 2.0 equivalents, the yields were still low and the reactions were incomplete (entries 1–3). Similarly, changing the catalyst to tin tetrachloride, the reaction was incomplete even after 3.0 h (entries 4–5), and the formation of by-products was increased when 1.0 equiv of the promoter was used (entry 6). We found that 0.1 or 0.2 equiv TMSOTf (entries 7 and 8) was better to promote the glycosylation of 2-deoxy glucosyl acetates **1** with phenol. With 0.3 equiv TMSOTf, the reaction proceeded well and the product was obtained in acceptable yield (entry 9). However, the yield of the glucoside **3a** could be dropped to 61 % when 0.4 equiv of TMSOTf was used (entry 10); however, the use of H_2SO_4-SiO_2 reagent [38–40] (entry 11 and 12), which is a solid acid catalyst as a novel promoter for glycosylation, made the reactions sluggish.

During the transformation performed by 1.0 equiv of the phenol and 0.3 equiv of the TMSOTf, trace amount of the unreacted 2-deoxy glycosyl acetates was observed. In order to improve the yield, then we investigated the other factors on the reaction (Table 2). Apparently, the best result was achieved when the reaction was processed with 1.5 equiv phenol (entry 3). Treatment of both 2-deoxy glucose acetate donor **1** and phenol **2a** (1.5 equiv) with 0.3 equiv TMSOTf at −15 °C, provided the desired *O*-aryl glycoside **3a**. However, it took 3 h for the reaction to go to completion. Raising the temperature shortened the reaction time (Table 2, entry7), however, the yield decreased to 80 % at 20 °C. Additionally, we also found that the addition of 4 Å molecular sieves powder was helpful to the progress of the reaction and reduce the decomposition of our donor (entry 5–7).

With TMSOTf (0.3 equiv) as promoter and CH_2Cl_2 as solvent at 0 °C, we then examined the generality of this α-selective glycosylation of 2-deoxyglucosyl acetates **1** with a

Table 1 Optimization of promoters in the glycosylation

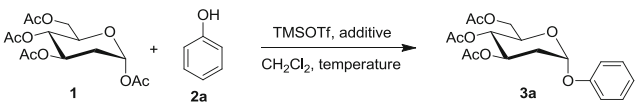


Entry	Promoter	Equivalent	Time(h)	Yield(%)[a]
1	$BF_3.Et_2O$	0.3	3.2	40
2		0.5	3.0	43
3		2.0	1.0	35
4	$SnCl_4$	0.2	3.0	38
5		0.3	3.0	40
6		1.0	1.0	10
7	TMSOTf	0.1	3.0	51
8		0.2	1.8	60
9		0.3	1.2	66
10		0.4	1.0	61
11	H_2SO_4-SiO_2	0.3	4.0	NR[b]
12		1.0	3.0	NR

[a] Isolated yield

[b] No product was detected

Table 2 Optimization of the direct glycosylation



Entry	Phenol (equiv)	Temp, (°C)	Time (h)	Additive	Yield(%)[a]
1	1.0	0	1.2	none	66
2	1.2	0	1.2	none	71
3	1.5	0	1.2	none	80
4	2.0	0	1.2	none	78
5	1.5	0	1.2	4Å MS	89
6	1.5	−15	3.0	4Å MS	56
7	1.5	20	1.0	4Å MS	80

[a] Isolated yield

Fig. 1 Phenols in the coupling reaction

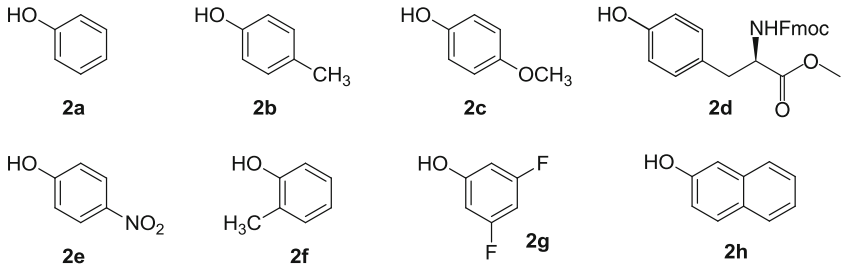
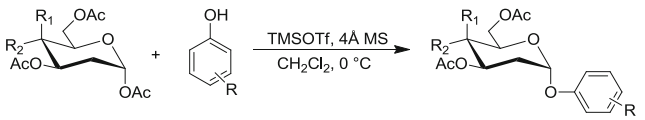


Table 3 Substrate scope for TMSOTf-catalyzed glycosylation[a]



Entry	R_1	R_2	R	Product	Yield(%)[b]
1	H	OAc	H	**3a**	89
2	H	OAc	*p*-CH_3	**3b**	85
3	H	OAc	*p*-OCH_3	**3c**	88
4	H	OAc	tyrosine[c]	**3d**	85
5	H	OAc	*p*-NO_2	**3e**	90
6	H	OAc	*o*-CH_3	**3f**	82
7	H	OAc	3,5-di-F	**3g**	79
8	H	OAc	phenyl[d]	**3h**	95
9	OAc	H	H	**5a**	81
10	OAc	H	*p*-CH_3	**5b**	75
11	OAc	H	*p*-OCH_3	**5c**	85
12	OAc	H	tyrosine[c]	**5d**	84
13	OAc	H	*p*-NO_2	**5e**	72
14	OAc	H	*o*-CH_3	**5f**	81
15	OAc	H	3,5-di-F	**5g**	80
16	OAc	H	phenyl[d]	**5h**	88

[a] Reaction condition: TMSOTf (0.3 equiv), glycosyl acetates (1.0 equiv) and phenols (1.5 equiv) were stirred in CH_2Cl_2 at 0 °C

[b] Isolated yield

[c] *N*-Fmoc-(*L*)-tyrosine methyl ester

[d] 2-Naphthol

panel of phenols (**2a**-**h** in Fig. 1) as acceptors[1]. From Table 3, we can conclude that not only the phenols with electron-donating substituents (entries 2, 3 and 4), but also those with electron-withdrawing (entry 5, 7 and 8) and hindered phenols (entry 6) could give excellent results. All the reactions provided the corresponding 2-deoxy α-aryl-*O*-glycosides **3a**-**h** as the only detectable glycosylation products in good to excellent yields (79–95 %). Additionally, the undesired *C*-aryl glycosides were not observed in the reaction. Compared to glycosylation of 2-deoxyglucosyl acetate **1**, the glycosylation of 2-deoxygalactosyl acetate **4** with acceptors (**2a**-**h**) proceeded smoothly, providing the expected corresponding α-*O*-aryl galactosides **5a-h** in good yields under the catalysis of TMSOTf (0.3 equiv) in CH_2Cl_2 at 0 °C. Notably, the efficiency of this methodology is demonstrated by the coupling of 2-deoxy galactose acetate donor with the relatively hindered 2-methylphenol (**2f**) to form α-*O*-aryl galactoside **5f** in 81 % yield (entry 14), though the reaction is a little slower compared to the corresponding glucosides counterpart (compared to entry 10)[2].

[1] **Experimental procedure**: The 2-deoxy glycosyl acetate **1** or **4** (30 mg, 0.09 mmol), 4 Å molecular sieves, and **2a-g** (1.5 equiv) were combined with 0.3 equvilent of TMSOTf in anhydrous dichloromethane (3 ml) at 0 °C. After 0.5–3.0 h, the molecular sieves was filtered off, followed the reaction mixture washed with iced saturated $NaHCO_3$ and iced brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuum*. The residue was purified by silica gel column chromatography to obtain products (petroleum ether/ethyl acetate =5/1, v/v).

[2] Selected spectral data for new compounds: **Compound 3d:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.98 (1 H, dd, J=3.2, 12.2 Hz), 2.02 (3 H, s), 2.04 (3 H, s), 2.05 (3 H, s), 2.45 (1 H, td, J=5.2, 13.0 Hz), 3.06 (2 H, dd, J=5.5, 13.0 Hz), 3.73 (3 H, s), 3.96 (1 H, d, J=12.5 Hz), 4.03 (1 H, d, J=8.6 Hz), 4.20 (1 H, t, J=6.5 Hz), 4.29 (1 H, dd, J=4.0, 12.2 Hz), 4.36 (1 H, dd, J=6.8, 10.5 Hz), 4.46 (1 H, dd, J=7.2, 10.5 Hz), 4.63 (1 H, d, J=7.5 Hz), 5.09 (1 H, t, J=9.9 Hz), 5.25 (1 H, d, J=8.0 Hz), 5.51 (1 H, ddd, J=3.9, 5.5, 11.1 Hz), 5.62 (1 H, br s), 6.99 (4 H, s), 7.30–7.38 (8 H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 20.6, 20.7, 20.9, 22.6, 29.3, 29.6, 31.9, 35.0, 37.3, 47.1, 52.3, 54.8, 61.9, 66.8, 68.5, 68.8, 69.0, 95.3, 116.4, 120.0, 124.9, 125.0, 127.0, 127.7, 129.6, 130.3, 141.3, 143.6, 143.7, 155.3, 155.5, 169.8, 170.2, 170.6, 171.8. ESI-HRMS: Calcd for $C_{37}H_{39}NO_{12}Na$ (M+Na) 712.2370,, found 712.2365. **Compound 5d:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.91 (3 H, s), 2.03 (3 H, s), 2.07 (1 H, dd, J=4.6, 12.8 Hz), 2.16 (3 H, s), 2.23 (1 H, td, J=3.2, 12.4 Hz), 3.06 (2 H, dd, J=6.0, 14.0 Hz), 3.74 (3 H, s), 4.04 (2 H, d, J=6.4 Hz), 4.18 (2 H, d, J=6.4 Hz), 4.35 (1 H, dd, J=7.5, 10.5 Hz), 4.45 (1 H, dd, J=7.5, 10.5 Hz), 4.64 (1 H, d, J=7.5 Hz), 5.22 (1 H, d, J=8.2 Hz), 5.37 (1 H, s), 5.47 (1 H, ddd, J=3.7, 4.4, 8.0 Hz), 5.67 (1 H, br s), 6.98 (4 H, s), 7.30–7.38 (8 H, m). ^{13}C (125 MHz, $CDCl_3$) δ 14.1, 20.5, 20.7, 20.8, 29.6, 30.2, 37.3, 47.1, 52.3, 54.8, 61.9, 65.9, 66.3, 66.8, 67.4, 95.9, 166.5, 120.0, 124.9, 125.0, 127.0, 127.7, 129.5, 130.3, 141.3, 143.7, 143.8, 155.5, 170.1, 170.2, 170.3, 171.8. ESI-HRMS: Calcd for $C_{37}H_{39}NO_{12}Na$ (M+Na) 712.2370,, found 712.2365. **Compound 3g:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.98–2.14 (10 H, m), 2.47 (1 H, dd, J=5.0, 13.0 Hz), 4.01 (2 H, t, J=6.0 Hz), 4.31 (1 H, dd, J=6.0, 13.0 Hz), 5.08 (1 H, t, J=10.0 Hz), 5.44–5.48 (1 H, m), 5.62 (1 H, d, J=3.0 Hz), 6.49–6.68(3 H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.5, 20.6, 20.8, 34.6, 61.9, 68.4, 68.8, 68.9, 95.6, 97.8, 98.0, 98.2, 100.1, 100.2, 100.3, 100.4, 157.7, 162.3, 162.4, 164.3, 164.4, 169.7, 170.1, 170.4. ESI-MS: Calcd for $C_{18}H_{20}F_2O_8Na$ (M+Na) 425.10, found 425.01. Anal. Calcd for $C_{18}H_{20}F_2O_8$: C, 53.73; H, 5.01. Found: C, 53.93; H, 5.11. **Compound 5g**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.95 (3 H, s), 2.03 (3 H, s), 2.11 (1 H, dd, J=5.0, 10.0 Hz), 2.15 (3 H, s), 2.24 (1 H, dd, J=5.0, 10.0 Hz), 4.04–4.12 (2 H, m), 4.19 (1 H, t, J=5.0 Hz), 5.38 (1 H, s), 5.41–5.44 (1 H, m), 5.67 (1 H, d, J=3.0 Hz), 6.47–6.64 (3 H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.4, 20.6, 20.8, 29.9, 62.0, 65.6, 67.2, 67.9, 96.4, 87.7, 97.9, 98.1, 100.2, 100.3, 100.4, 100.5, 158.0, 162.4, 162.5, 164.3, 164.5, 169.9, 170.1, 170.4. ESI-MS: Calcd for $C_{18}H_{20}F_2O_8Na$ (M+Na) 425.10, found 425.04. Anal. Calcd for $C_{18}H_{20}F_2O_8$: C, 53.73; H, 5.01. Found: C, 53.93; H, 5.11.

In conclusion, we have developed an efficient method for the stereoselective synthesis of 2-deoxy α-*O*-aryl glycosides from glycosyl acetates under the catalysis of TMSOTf in CH_2Cl_2 at 0 °C. It has advantages including short reaction steps, the applicability to a variety of phenol nucleophiles, and the sole α-selectivity. In all cases, the facile rearrangement of the resulting α-*O*-aryl glycosides to the corresponding *C*-aryl glycosides is not observed in the reaction. These features make this method an attractive alternative to existing methodologies for the preparation of 2-deoxy aromatic glycosides.

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