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The synthesis of 2-deoxy-α-D-glycosides from D-glycals catalyzed by TMSI and PPh_3

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ABSTRACT

2-Deoxyglycosides were synthesized in high α-selectivity by the direct addition of alcohols to D-glucal and D-galactal catalyzed by TMSI and PPh_3. The acid labile isopropylidene group is tolerated under this condition.

1. Introduction

2-Deoxy-sugars are an important class of carbohydrates that are present in natural products.[1–3] Many biologically active compounds, especially antitumor antibiotics such as anthracyclines, aureolic acids, orthosamycins, angucyclins, and enediynes, contain one or more 2-deoxyglycoside in their scaffolds.[4] In order to study the roles of 2-deoxyglycosides, a variety of approaches for the synthesis of 2-deoxyglycosides have been developed,[1,5] such as they can be prepared by use of thioglycoside donors, activated oxygen derivatives, glycosyl halides, and glycals.[6] Of these developed methods, acid-catalyzed addition to glycals is the most direct method. For example, triphenylphosphine hydrobromide (TPHB), the most widely used catalytic system, promotes the addition of alcohols to glycals and the products were obtained in good to excellent yields and high α-selectivity.[7] In addition, many other acid-catalyzed systems such as BCl_3 or BBr_3,[8] $CeCl_3{\cdot}7H_2O/NaI$[4], $GaCl_3$,[9] ceric ammonium nitrate,[10] and Rhenium(V) [$ReOCl_3(SMe_2)(OPPh_3)$][11] have been developed. Recently, Lin's group found that $AlCl_3$ could also promote the addition under microwave irradiation.[12] However, several limitations of these catalysts including high toxicity and high cost hamper their wider use. There is still a need to find a low toxicity and low cost catalyst. It is well known that TMSI can catalyze the tetrahydropyranylation of unbulky alcohols.[13] Furthermore, Cha et al. found that TMSI–PPh_3 was a convenient and highly effective catalyst for the tetrahydropyranylation of aliphatic and aromatic alcohols with dihydropyran at ambient temperature.[14] TMSI was also a good reagent for preparing glycosyl iodide, which was used as a good glycosyl donor.[15] As glycals are liable to acidic conditions and led to 2,3-unsaturated glycosides,[16] to the best of our knowledge, there is no report on the TMSI-catalyzed direct addition of alcohols to D-glucal and D-galactal to form 2-deoxyglycosides. Herein we used TMSI and PPh_3 as mild catalyst to activate the glycals in the presence of a variety of hydroxylic nucleophiles and the corresponding 2-deoxyglycosides were prepared in high α-selectivity. Moreover, the acid labile protecting group was tolerated under this condition.

2. Results and discussion

2.1. Promoter selection

To find an alternative to the most widely used catalyst TPHB, we replaced HBr with other Lewis acids or Brönsted acids to find out which one could catalyze the reaction of glycals with alcohols to form α-2-deoxyglycosides, and effectively prevent the undesirable Ferrier rearrangement. 3,4,6-tri-*O*-benzyl-D-galactal (**1a**), prepared from 3,4,6-tri-*O*-acetyl-D-galactal via a classic method,[17] first reacted with methanol in anhydrous dichloromethane at 40 °C in the presence of PPh_3. Several Lewis or Bronsted acids such as $BF_3{\cdot}OEt_2$, TMSOTf, TMSI, $FeCl_3$, and TfOH were added as catalyst (Table 1). Among them, $BF_3{\cdot}OEt_2$ and TMSI activated the reaction and the products were obtained in high yields and excellent α-selectivity without any Ferrier rearrangement. Similarly, TMSI catalyzed addition to 3,4,6-tri-*O*-benzyl-D-glucal (**1b**) produced the corresponding methyl 2-deoxy glycoside (**2b**) in both high yield and α-selectivity. However, methanol addition to 3,4,6-tri-*O*-benzyl-D-glucal (**1b**)

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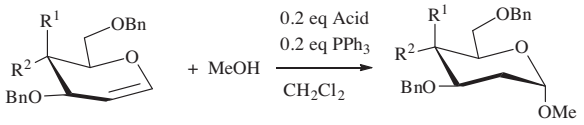
Table 1
Effect of promoters on the formation of methyl 2-deoxyglycosides[a]



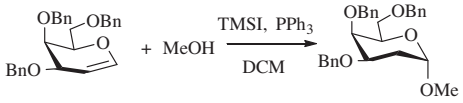
Galactal (**1a**): R^1=OBn, R^2=H
Glucal (**1b**): R^1=H, R^2=OBn

2a: R^1=OBn, R^2=H
2b: R^1=H, R^2=OBn

Entry	Glycal	Promoter	Product	Yield[b] %	α/β[c] ratio
1	**1a**	$BF_3{\cdot}OEt_2$	**2a**	88	>19:1
2	**1b**	$BF_3{\cdot}OEt_2$	Mixture[d]	—	
3	**1a**	TMSI	**2a**	91	>19:1
4	**1b**	TMSI	**2b**	92	6:1
5	**1a**	TfOH	Mixture[e]	—	
6	**1b**	TfOH	Mixture[e]	—	
7	**1a**	TMSOTf	Mixture[e]	—	
8	**1b**	TMSOTf	Mixture[e]	—	
9	**1a**	$FeCl_3$	Mixture[e]	—	
10	**1b**	$FeCl_3$	Mixture[e]	—	

[a] All reactions were carried out in anhydrous dichloromethane at 40 °C.
[b] Isolated yield.
[c] α/β ratio is determined by ^{1}H NMR.
[d] Mixture means 2,3-unsaturated glucoside and some other products.
[e] Mixture means 2-deoxyglycoside remained, a trace amount of 2,3-unsaturated glycoside and several unidentified byproducts.

Table 2
Optimization of the loading of TMSI–PPh_3 using **1a** and methanol[a]



Entry	Equivalent	Time (h)	Yield[b] (%)	α/β[c] ratio
1	0.05	2.0	91	>19:1
2	0.10	1.0	89	>19:1
3	0.20	1.0	85	>19:1

[a] All reactions were carried out in anhydrous dichloromethane at 40 °C.
[b] Isolated yield.
[c] α/β ratio is determined by ^{1}H NMR.

catalyzed by $BF_3{\cdot}OEt_2$ was slow under the same condition. Based on these results, TMSI was chosen as the activator to catalyze the addition reaction of the glycals and alcohols.

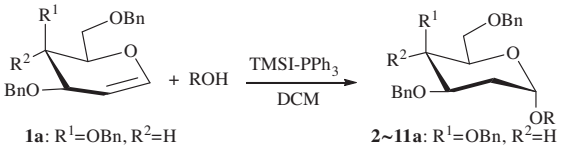
2.2. Optimization of the amount of TMSI–PPh_3

We investigated the effect of catalyst loading (5%, 10%, 20% eq TMSI–PPh_3) on the reaction (Table 2). With the increase of the amount of catalyst used, the reaction time decreased significantly but the yield also decreased slightly. To achieve the highest yield and selectivity, 5% TMSI was selected as the optimal amount of catalyst, although it took 2 h for the reaction to go to completion.

2.3. The scope of glycosyl acceptors

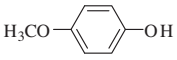
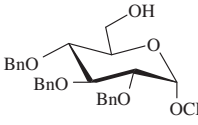
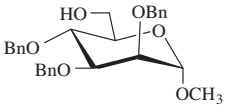
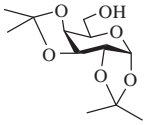
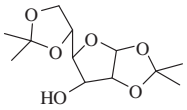
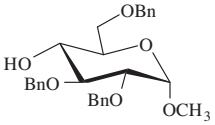
Under the optimized conditions, a variety of hydroxylic nucleophiles were used as the acceptor to react with **1a** and **1b** (Table 3). Simple alcohols including methanol, isopropanol, and benzyl alcohol produced good yield and high stereoselectivity, while the bulky *tert*-butanol produced moderate yield. This protocol also effectively promoted the phenol addition to glycal and yielded the corresponding products **6a** and **6b** (entry 5). The reactions were carried out in the presence of 5% TMSI–PPh_3 in anhydrous dichloromethane. However, when steric bulky glycosyl acceptors (Table 3, entries 6–10) were used, the reaction did not go to completion in 4 h because of the hindrance. It is needed to increase the amount of TMSI and PPh_3 from 5% to 20% in order to drive the reaction to completion. The desired disaccharide products **7–11** were isolated in 70–87% yield. Isopropylidene, the most commonly used protecting group in carbohydrate chemistry, is easily removed under acidic condition. It is notable that the isopropylidene group was well tolerated even with 20% TMSI treatment. Therefore, this TMSI–PPh_3 catalytic system should be useful for formation of various α-glycosides.

Table 3
Synthesis of 2-deoxyglycosides from glycals and various alcohols[a]



1a: R^1=OBn, R^2=H
1b: R^1=H, R^2=OBn

2~11a: R^1=OBn, R^2=H
2~11b: R^1=H, R^2=OBn

Entry	Donor	Acceptor	hours	Yield[b]	α/β ratio[c]
1	**1a**	Methanol	2	**2a**: 85%	>19:1
	1b			**2b**: 92%	6:1
2	**1a**	Benzyl alcohol	2	**3a**: 84%	>19:1
	1b			**3b**: 94%	15:1
3	**1a**	2-Propanol	4	**4a**: 84%	>19:1
	1b			**4b**: 89%	3:1
4	**1a**	*t*-Butanol	4	**5a**: 57%	>19:1
	1b			**5b**: 56%	5:1
5	**1a**		10	**6a**: 67%	>19:1
	1b			**6b**: 75%	>19:1
6[d]	**1a**		10	**7a**: 80%	>19:1
	1b			**7b**: 86%	>19:1
7[d]	**1a**		10	**8a**: 73%	>19:1
	1b			**8b**: 74%	>19:1
8[d]	**1a**		10	**9a**: 84%	>19:1
	1b			**9b**: 79%	7:1
9[d]	**1a**		10	**10a**: 75%	>19:1
	1b			**10b**: 87%	>19:1
10[d]	**1a**		10	**11a**: 72%	>19:1
	1b			**11b**: 70%	>19:1

[a] All reactions were carried out in anhydrous dichloromethane at 40 °C.
[b] The yield is the isolated yield.
[c] α/β ratio is determined by ^{1}H NMR.
[d] 20% PPh_3 and TMSI were used.

The addition reactions to galactal displayed high α-stereoselectivity, which is consistent with the anomeric effect. In contrast, addition reactions to glucal generally gave a lower α/β ratio. This phenomenon probably can be explained by the steric hindrance of the axial benzyloxyl group at the C-4 position of galactal, which prevents the attack by acceptors from the top face of the sugar ring, thus promoting the formation of α-isomer.

2.4. The reaction mechanism

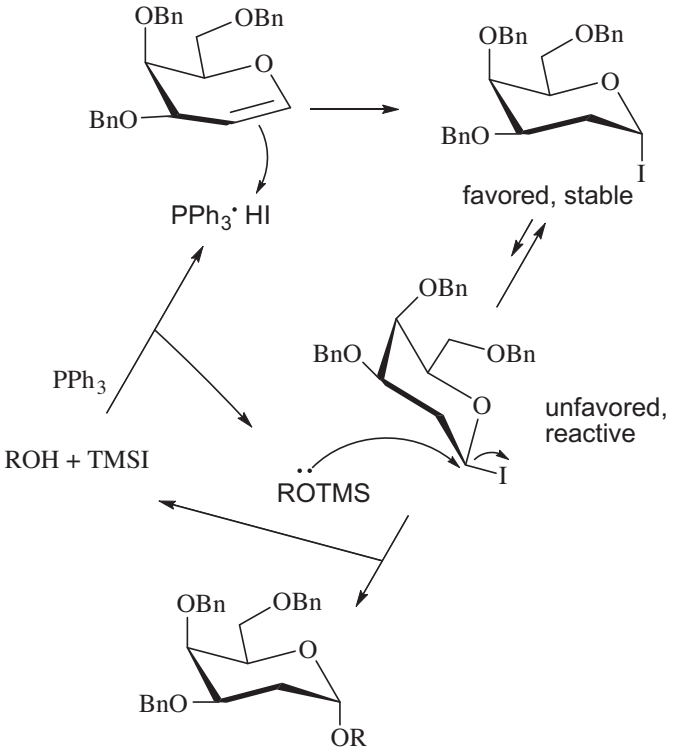
We demonstrated that TMSI–PPh_3 was an effective catalyst system for the direct 2-deoxy glycosidation from glycals. Here we propose a possible mechanism for the reaction. TMSI firstly reacts with ROH to form PPh_3·HI and TMSOR in the presence of Lewis base PPh_3. PPh_3·HI serves as a better catalyst than PPh_3·HBr to initiate the protonation of the glycal because of its stronger acidity. Moreover, TMSOR is a better nucleophile than ROH (Scheme 1). When the reaction is carried out in the absence of PPh_3 a complex mixture is observed. When TMSOTf is used, PPh_3·HOTf and TMSOR should be formed in a similar way, but the strong acidity of PPh_3·HOTf led to side reactions.

In summary, we have successfully synthesized α-2-deoxyglycosides in good yield and stereoselectivity by using TMSI–PPh_3 as the catalyst to promote the addition of hydroxylic nucleophiles to glycals. Nucleophiles include simple alcohols, partially protected monosaccharides, and a phenol. In addition, the acid labile isopropylidene group is tolerated under this condition.

3. Experimental

3.1. General procedures

All chemicals, reagents, and solvents were purchased from commercial sources where available. Dichloromethane was distilled over CaH_2. When dry conditions were required, the reactions were performed under an argon atmosphere. Thin-layer chromatography (TLC) plates were purchased from Liangchen Chemical Engineering Co. Ltd (Anhui Province). All compounds were visualized with 5% H_2SO_4 in EtOH, followed by heating. Flash column chromatography was performed on Silica Gel 60 (E. Merck, 0.063–0.200 mm). NMR spectra were recorded on a Bruker AMX-400 (400 MHz) instrument. Optical rotations were measured at 25 °C using an Optical Activity AA-10R automatic polarimeter.



Scheme 1. Possible catalytic cycle of TMSI–PPh_3 mediated 2-deoxyglycosidation.

3.2. Typical procedure for preparing 2-deoxyglycoside derivatives 2a, 2b, 3a, 3b, 4a, 4b, 5a, 5b, 6a, 6b

To a stirred solution of glycal (**1a** and **1b**, 1.0 equiv) in CH_2Cl_2 (2.0 mL) were added alcohol (2 equiv), PPh_3 (0.05 equiv), and TMSI (0.05 equiv). The mixture was stirred at 40 °C for 2–4 h, concentrated under reduced pressure, and purified by silica gel chromatography with EtOAc/PE (1:20) to give the products in 56–92% yields. The ^1H NMR and ^{13}C NMR data are listed in the Supplementary data.

3.3. Typical procedure for preparing 2-deoxyglycoside derivatives 7a, 7b, 8a, 8b, 9a, 9b, 10a, 10b, 11a, 11b

To a stirred solution of glycal (**1a** and **1b**, 1.0 equiv) in CH_2Cl_2 (2.0 mL) were added glycosyl acceptor (1.5 equiv), PPh_3 (0.20 equiv), and TMSI (0.20 equiv). The mixture was stirred at 40 °C for 10 h, concentrated under reduced pressure, and purified by silica gel chromatography with EtOAc/PE (1:8) to give the products in 67–86% yields. The ^1H NMR and ^{13}C NMR of the known compounds are listed in the Supplementary data.

3.3.1 Methyl 6-*O*-(2-deoxy-3,4,6-tri-*O*-benzyl-α-D-lyxo-hexopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (8a) and methyl 6-*O*-(2-deoxy-3,4,6-tri-*O*-benzyl-α-D-*arabino*-hexopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (8b)

Compound **8a**: $[\alpha]_D$ +47 (*c* 2.7, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.46–7.28 (m, 30H, Ph), 5.20 (s, 1H, H-1′), 4.99 (dd, 2H, *J* 11.6 Hz, PhCH_2), 4.83–4.43 (m, 11H, PhCH_2, H-1), 4.05–3.62 (m, 11H, H-2′, H-3′, H-4′, H-5′, H-6′, H-3, H-4, H-5, H-6), 3.32 (s, 3H, OCH_3), 2.33–2.27 (m, 1H, H-2a), 2.17–2.11 (m, 1H, H-2b); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.02, 138.61, 138.55, 138.51, 138.38, 138.20, 128.45–127.48, 98.79, 98.19, 80.26, 75.07, 74.91, 74.79, 74.34, 74.19, 73.39, 73.10, 72.67, 72.14, 71.37, 70.12, 69.93, 69.40, 66.32, 54.65, 31.07. HRMS: *m/z* Calcd for $C_{50}H_{60}O_{10}Na$ $[M+Na]^+$, 903.4084. Found 903.4062. Compound **8b**: $[\alpha]_D$ +53 (*c* 4.9, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.47–7.24 (m, 30H, Ph), 5.22 (s, 1H, H-1′), 5.01 (dd, 2H, *J* 10.8 Hz, PhCH_2), 4.85–4.51 (m, 11H, H-1, PhCH_2), 4.10–3.63 (m, 11H, H-2′, H-3′, H-4′, H-5′, H-6′, H-3, H-4, H-5, H-6), 3.36 (s, 3H, OCH_3), 2.46 (dd, 1H, H-2a), 1.82–1.75 (m, 1H, H-2b); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.82, 138.70, 138.67, 138.54, 138.42, 138.24, 128.44–127.53, 98.88, 97.76, 80.38, 78.26, 77.19, 75.04, 74.91, 74.80, 73.47, 72.74, 72.12, 71.53, 71.39, 70.83, 68.82, 65.96, 54.75, 35.31. HRMS: *m/z* Calcd for $C_{50}H_{60}O_{10}Na$ $[M+Na]^+$, 903.4084. Found 903.4090.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carres.2012.06.004.

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