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Highly diastereoselective 1,2-dichlorination of glycals using NCS/PPh_3: study of substituent and solvent effects

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ABSTRACT

Highly diastereoselective 1,2-dichlorination of glycals has been achieved at room temperature conditions in good to excellent yields using a milder, more convenient, less hazardous reagent combination NCS/PPh_3 giving only one major product out of four possible diastereomers [either α-*gluco* (**2**) or α-*manno* (**4**)] depending upon the substituents. The diastereoselectivity is maximum (100% α/β-selectivity as well as *cis*/*trans* selectivity) for D-galactal and L-rhamnal derivatives. Detailed studies showed that solvent and substituent effects play a significant role in determining the product distribution.

1. Introduction

Halogeno sugars are valuable starting materials for the synthesis of amino-sugars, deoxy sugars, and deoxy nucleosides, which are not easily obtainable. Due to the polar nature of C–X bonds, halogeno sugars are easily attacked by a wide range of nucleophiles giving biologically significant molecules. Halogeno sugars specially 1- or/and 2-halogenated ones are of particular interest because 1-halogeno sugars have become the most frequently used glycosyl donor in O-glycosylation of both sugar and non-sugar compounds (aglycones),[1] whereas 2-halogeno sugars can be used for the generation of 2-deoxy glycosides. Further, the anomeric carbon of sugar shows electrophilic reactivity in most of the reactions but halogeno sugars have been successfully exploited in the generation of the corresponding anomeric carbanions[2] and radicals.[3]

First report on 1,2-dichlorination of glycals dates back to 1920 when Fischer et al. investigated the addition of molecular chlorine to D-glucal triacetate in carbon tetrachloride at 0–2 °C and obtained a mixture of diastereomers because 1,2-dichlorination of glycals may generate four possible diastereomers (**2**–**5** in Fig. 1).[4] Lemieux and Fraser-Reid studied the addition of halogens to glycals and proposed a mechanism, which leads to products of thermodynamic control.[5,6] Later, Igarashi et al.[7] in 1970, Boullanger et al.[8] in 1976, and Horton et al.[9] in 1986 established that product formation is under kinetic, not thermodynamic control; the product distribution is dependent on the polarity of the solvent and even on the electron-withdrawing or -donating effect of the substituent at C-6 as well as stereochemistry of substituent at C-4 of sugar moiety. Kent et al.[10] and Hall et al.[11] reported the reaction of glycals with NCS/HCl system instead of molecular chlorine to obtain the products **2**, **3**, **4**, and **5** in 15.7, 4.4, 1.4, and 10.7% yields, respectively. Thus, the NCS/HCl method lacked the stereoselectivity achieved even with molecular chlorine. A detailed description of product distributions achieved under different reaction conditions is given in Table 1. The above methods suffer from either or both of the following drawbacks: (i) handling of gaseous molecular chlorine is hazardous (Hathaway et al. 1991), (ii) lack of stereoselectivity as an inseparable mixture of diastereomers results (Fig. 1). Although

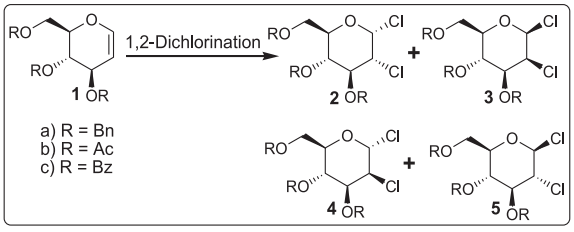

Fig. 1. Possible diastereomers in the 1,2-dichlorination of glycals **2** (α-*gluco*), **3** (β-*manno*), **4** (α-*manno*), **5** (β-*gluco*).

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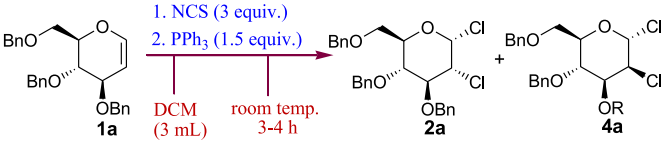
Table 1
Literature methods on 1,2-dichlorination of glycals using different reaction conditions

Entry	Reaction conditions	Nature of solvent	Product distribution (%)			
			α-*gluco* (**2**)	β-*manno* (**3**)	α-*manno* (**4**)	β-*gluco* (**5**)
1	Cl_2, 0 °C	Non-polar	76%	3%	4%	17%
	(Horton et al.)[9]	Polar	35%	23%	24%	18%
2	Cl_2, 0 °C	Non-polar	85.3%	3.8%	4.5%	1.6%
	(Igarashi et al.)[7]	Polar	9.4%	6.4%	45.1%	39.1%
3	NCS/HCl	Non-polar	15.7%	4.4%	1.4%	10.7%
	(Kent, et al.)[10]	Polar	—	—	—	—
4	Cl_2, 0 °C	Non-polar	80%	Traces	Traces	Traces
	(Lemieux et al.)[5,6]	Polar	—	—	—	—
5	Cl_2, 0–2 °C	Non-polar only	A mixture of isomers, which were not separated			
	(Fischer et al.)[4]					

Colovic et al.[12] in 2008 achieved considerably higher selectivity under milder conditions for the bromination of glycals using quaternary ammonium bromide, there is no such stereoselective method for the chlorination of glycals. Keeping in mind the above mentioned facts a milder, less hazardous, and more selective method is highly needed for the 1,2-dichlorination of glycals. Recently, Yoshimitsu et al. successfully exploited the NCS/PPh_3 system for the dichlorination of olefins giving products of anti-addition.[13] This prompted us to examine whether the NCS/PPh_3 system was suitable to perform the chlorination of glycals. With our interest in halogeno-sugars and glycals,[14,15] herein we report a convenient method for the chlorination of glycals using NCS/PPh_3 system with better diastereoselectivity than the existing methods. The stereochemical outcome is interestingly quite different in glycals from that of simple olefins. The superiority of the present methodology over already existing methods (Table 1) lies in the use of lesser hazardous reagents and higher diastereoselectivity.

2. Results and discussion

In order to test our hypothesis, we chose tri-*O*-benzyl-D-glucal (**1a**) for 1,2-dichlorination using NCS/PPh_3 system (Scheme 1). Initially, we carried out the reaction of **1a** in DCM using different ratios of NCS and PPh_3 at room temperature. The results are summarized in Table 2 and it has been found that the reaction does not occur at all when NCS/PPh_3 system was used in the ratios of 1:1, 1:2, and 1:3 (entries 1, 4, and 5, Table 2). The reaction occurred best when the NCS/PPh_3 reagent combination was used in the ratios of 2:1 and 3:1 (entries 2 and 3, Table 2). Thus, 2:1 (NCS:PPh_3) was the ratio of choice for 1,2-dichlorination reaction.



Scheme 1. 1,2-Dichlorination of glycals (**1a**–**c**) using NCS/PPh_3 reagent combination as chlorinating agent.

Table 2
Standardization of reaction conditions for 1,2-dichlorination of tri-*O*-benzyl-D-glucal

Entry	NCS/PPh_3 (mmol)	Yield%	Product distribution **2a**:**4a** (%)
1	1:1	05%	—
2	2:1	90%	1:0.23 (81:19%)
3	3:1	90%	1:0.23 (81:19%)
4	1:2	No reaction	—
5	1:3	No reaction	—

Reagents & conditions: substrate **1a** (100 mg, 0.24 mmol), NCS (3 equiv, 96 mg), PPh_3 (1.5 equiv, 94 mg), dichloromethane (4 mL), room temperature, 3–4 h.

Under the optimized conditions the reaction was found to be diastereoselective (α/β-selectivity as well as *cis*/*trans* selectivity) because only two of the four possible diastereomers were obtained, i.e., only **2a** (α-*gluco*) and **4a** (α-*manno*) were obtained in the ratio of 1:0.23 with excellent yield (entry 2, Table 2). On carrying out the 1,2-dichlorination reaction at 1.0 gram scale showed similar results. Further, in order to see the effect of temperature on the stereochemical outcome and rate of reaction, 1,2-dichlorination was carried out at lower (upto 0 °C) or higher (upto 60 °C) temperatures. Decreasing the temperature had no effect on the stereochemical outcome of the reaction except that the reaction proceeded at a slower rate. At higher temperatures the reaction mixture got charred giving only small amount of the products. The structure and stereochemistry of products **2a** (α-*gluco* as major product) and **4a** (α-*manno* as minor product) were determined by ^{1}H NMR by comparing the chemical shifts (δ value) and coupling constants ($J_{1,2}$ value) of products obtained using the present methodology with spectroscopic data available in literature (Table 3). In the ^{1}H NMR spectrum, appearance of two distinct doublet signals for anomeric protons, one at δ=6.14 ppm ($J_{1,2}$=3.5 Hz) and the other at δ=6.23 ppm ($J_{1,2}$=1.3 Hz), corresponding to diastereoisomers **2a** (α-*gluco* diastereomer) and **4a** (α-*manno* diastereomer) respectively, are consistent with NMR data available in the literature (entries 1 and 3, Table 3). When tri-*O*-acetyl-D-glucal (**1b**) was subjected to similar reaction conditions, the results showed a contrasting feature. Here **4b** [α-*manno* diastereomer, δ=6.17 ppm ($J_{1,2}$=1.3 Hz)] was the major product and **2b** [(α-*gluco* diastereomer, δ=6.15 ppm ($J_{1,2}$=3.5 Hz)] was the minor product (entry 2, Table 4). Gratifyingly, we obtained 100% selectivity (α/β-selectivity as well as *cis*/*trans* selectivity) when tri-*O*-benzoyl-D-glucal (**1c**) was subjected to 1,2-dichlorination reaction under similar conditions, i.e., only α-*manno* diastereomer was formed in this case (entry 3, Table 4).

Table 3
Chemical shifts of H-1 and coupling constants ($J_{1,2}$) of diastereomers expected from dichlorination of glycals reported in literature

Entry	Compound	$\delta_{H\text{-}1}$[a]	$J_{1,2}$ (Hz)[a]
1	**2**	6.16	3.5–3.7
2	**3**	5.60	1.2
3	**4**	6.17	1.0–1.5
4	**5**	5.31	9.3

[a] For chemical shifts ($\delta_{H\text{-}1}$) and coupling constants ($J_{1,2}$ value) of 1,2-dichlorination products of protected glucal see Ref. 7.

After getting promising results using the NCS/PPh_3 reagent combination in case of different glucals (**1a**–**c**), we applied this reagent system to different galactals. All the galactals (**1e**–**g**) showed 100% selectivity (α/β-selectivity as well as *cis*/*trans* selectivity), i.e., only α-*galacto* diastereomer was formed out of the four possible diastereomers (entries 5,6, and 7, Table 4). This method was next extended to 2,3,4,6-tetra-*O*-acetyl-D-glucal (**1d**), which was prepared from the easily available starting material glucose penta-acetate.[16] Compound **1d** was subjected to NCS/PPh_3 conditions leading to the formation of **2d** and **4d** in the ratio of 1:0.32 in 3–4 h (Scheme 2). The ^{1}H NMR spectrum of the purified product showed two sharp singlets for H-1 at δ=6.20 and 6.33 ppm in the ratio of 1:0.32 (76:24%). From the chemical shift values it can be concluded[17] that1,2-*cis*-dichloro diastereomer (**2d**) is the major product (76%) and 1,2-*trans*-dichloro diastereomer (**4d**) is the minor product (24%) as shown in Scheme 2. Our next target was to carry out 1,2-dichlorination of silyl protected glycals. Unfortunately,

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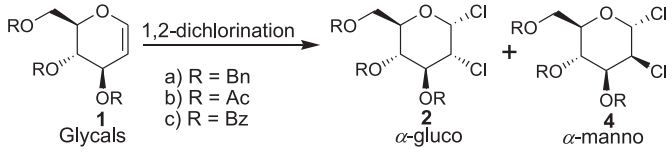
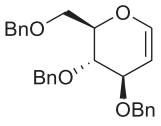
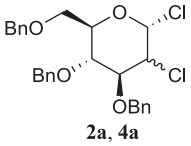
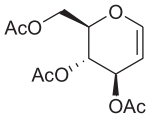
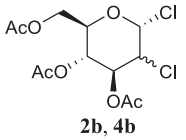
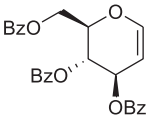
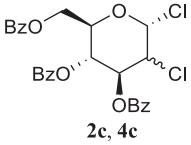
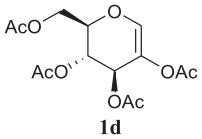
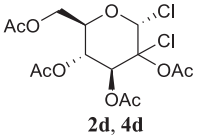
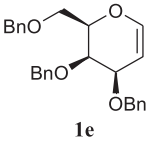
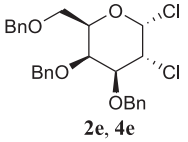
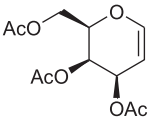
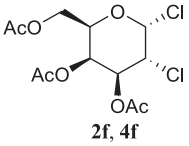
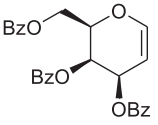
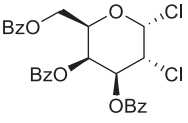
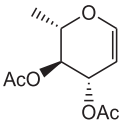
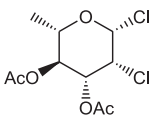
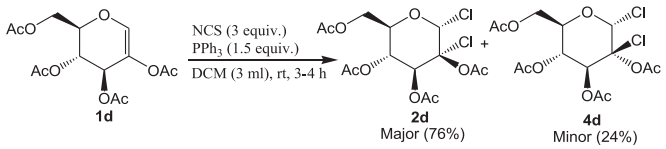
Table 4
Diastereoselective 1,2-dichlorination of glycals using NCS/PPh_3 reagent combination as chlorinating agent



Entry	Substrate[a]	Product	*cis*/*trans* Selectivity **2**:**4** (%)	α/β Selectivity	Yield(%)[b]
1	 **1a**	 **2a**, **4a**	1:0.23 (81:19%)	100%	90
2	 **1b**	 **2b**, **4b**	1:1.46 (41:59%)	100%	88
3	 **1c**	 **2c**, **4c**	0:1 (100% *trans*)	100%	88
4	 **1d**	 **2d**, **4d**	1:0.32 (76:24%)	100%	90
5	 **1e**	 **2e**, **4e**	1:0 (100% *cis*)	100%	89
6	 **1f**	 **2f**, **4f**	1:0 (100% *cis*)	100%	88
7	 **1g**	 **2g**, **4g**	1:0 (100% *cis*)	100%	88
8	 **1h**	 **2h**	1:0 (100% *cis*)	100%	90

[a] Reagents & conditions: substrate (100 mg), NCS (3 equiv), PPh_3 (1.5 equiv), DCM (3 mL), room temperature, 3–4 h, stir.
[b] For entries 1, 2, and 4 overall yields of inseparable mixtures (*α-gluco*/*α-manno*) whereas for entries 3, 5, 6, and 7 isolated yields after column chromatography are mention.



Scheme 2. 1,2-Dichlorination of 2,3,4,6-tetra-*O*-acetyl-D-glucal (**1d**).

silyl protecting groups (−OTMS, −OTBDMS and −OTBDPS groups) do not survive the NCS/PPh_3 reagent system and get decomposed within 1 h under the standardized conditions.

Finally, the deoxy sugar 3,4-di-*O*-acetyl-L-rhamnal (**1h**) was subjected to NCS/PPh_3 reagent conditions to see what happens to product distribution. Rhamnal acetate (**1h**) was synthesized from easily available starting material L-rhamnal (**A**) in three steps

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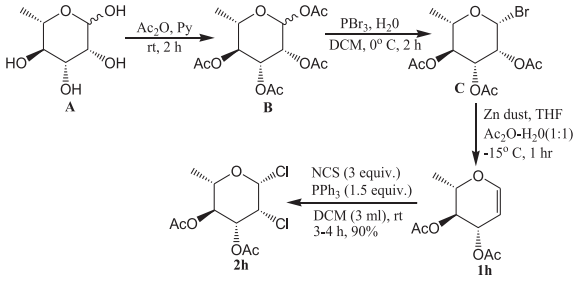
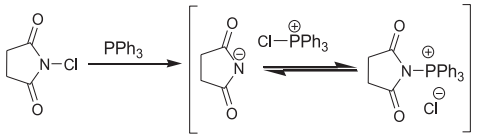
namely (1) acetylation, (2) bromination, and (3) elimination (Scheme 3). On carrying out 1,2-dichlorination of **1h** it was found that the reaction proceeds with 100% diastereoselectivity (Scheme 3, entry 8, Table 4). The appearance of a doublet for H-1 at δ=6.09 ppm with $J_{1,2}$ value of 3.7 Hz in ^{1}H NMR spectrum confirms the formation of *syn* addition product **2h**. The ^{1}H NMR data exactly matches with the literature data (Horton et al., reported H-1 at δ=6.08 ppm with $J_{1,2}$=3.7, see Ref. 9).



Scheme 3. Preparation of L-rhamnal (**1h**) and its 1,2-dichlorination using NCS/PPh_3 reagent combination.

2.1. Mechanism

1,2-Dichlorination of glycals involves a two-step mechanism. First step is an electrophilic attack of the chlorophosphonium ion generated in situ from NCS/PPh_3 (as shown in Scheme 4) at C-2 of glycal double bond while the second step involves nucleophilic attack of Cl^- (present in the medium) at the anomeric center.[13]



Scheme 4. Generation of chlorophosphonium ion from NCS/PPh_3.

In the first step the electrophile (chlorophosphonium ion) attacks C-2 of the glycal double bond with assistance from the lone pair on the ring oxygen giving oxocarbenium ions **I** or **II** (step 1, Fig. 2) depending upon the substituents, e.g., in the case of tri-*O*-benzyl-D-glucal (**1a**) preferred attack takes place mainly from the α-face of conformer **B** ($^5H_4$) (Fig. 3a) giving the glucose-derived oxocarbenium ion (**I**) while in the case of tri-*O*-acetyl-D-glucal (**1b**) the preferred attack takes place mainly from the β-face of

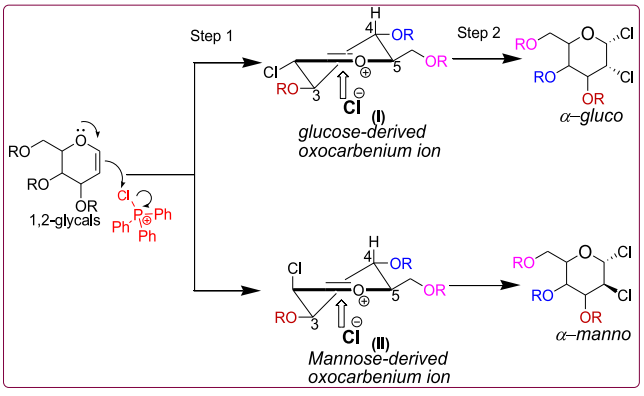


Fig. 2. Plausible mechanism for 1,2-dichlorination of glycals using NCS/PPh_3 as chlorinating agent.

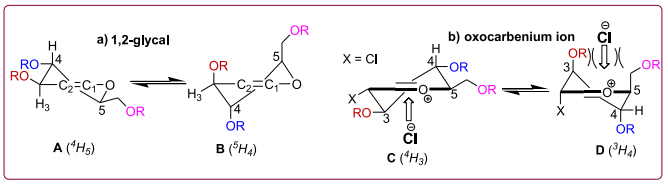


Fig. 3. a. Ground state conformations of 1,2-glycal **A** ($^4H_5$) and **B** ($^5H_4$). b. Conformations of oxocarbenium ion **C** ($^4H_3$) and **D** ($^3H_4$).

conformer **A** ($^5H_4$) (Fig. 3a) giving the mannose-derived oxocarbenium ion (**II**). Thus, the electrophilic attack in the step 1 is governed by the ground state conformations of 1,2-glycals **A** ($^4H_5$) or **B** ($^5H_4$) depending upon the substituents.[18] In the second step the nucleophilic attack onto the oxocarbenium ions (**I** and **II**, Fig. 2) occurs preferentially to a conformer in which the C-5 substituent is equatorial (conformer **C**, Fig. 3b) to avoid powerfully destabilizing interactions in the transition state when this substituent is axial (conformer **D**, Fig. 3b).[19] The stereoselectivity of the nucleophilic attack of Cl^- (step 2, Fig. 2) will depend on the relative energies of the transition states for nucleophilic attack.[20] Therefore, regardless of the position of the equilibrium of Fig. 3 the two conformers of the oxocarbenium ion (**C** & **D**, Fig. 3b) do not react with nucleophiles at the same rate. The α-selective reaction thus appears to be a result of an interconverting mixture of conformers, arguably favoring the $^3H_4$ conformer **D**, reacting through the lowest-energy transition state[20] (namely, via conformer **C**), in accord with the Curtin–Hammett kinetic scenario.[20] Thus, substituent effect plays a role in the electrophilic attack (step 1) while step 2 is α-selective irrespective of the substituents.

2.2. Solvent effects in the 1,2-dichlorination of glycals

In order to see the effect of solvent polarity on product distribution we have selected **1a** and **1b** as model substrates. We have carried out the chlorination in polar and non-polar solvents, such as CCl_4, CH_2Cl_2, CH_3CN or CH_3NO_2 using NCS/PPh_3 in the ratio of 2:1 under optimized conditions. 1,2-Dichlorination of **1a** and tri-*O*-acetyl-D-glucal (**1b**) showed opposite trends. In case of tri-*O*-benzyl-D-glucal (**1a**), increasing the polarity of solvent from CCl_4 to CH_3NO_2 decreased the percentage of the product **2a** (α-*gluco*) from 85% to 73% while that of **4a** (α-*manno*) increased from 15% to 27% though the major product was always the same, i.e., **2a** (α-*gluco*) as shown in Fig. 4a. On carrying out similar studies on **1b** we found that the percentage of **2b** (α-*gluco*, minor product) increased from 39% to 49% while that of **4b** (α-*manno*, major product) decreased from 61% to 51% as shown in Fig. 4b. The only common feature was that in both the cases (**1a** and **1b**), the percentage of major product always decreased with increase in solvent polarity from CCl_4 to CH_3NO_2 while that of the minor product increased though the major product was always the same in different solvents (α-*gluco* in case of **1a** and α-*manno* in case of **1b**).

1,2-Dihalo-pyranosides can easily be converted to 2-haloglycals using literature methods.[21] 2-Haloglycals contain vinylic halide moiety, which may find applications in organic synthesis especially Pd-catalyzed C–C coupling reactions. Although there are several examples of C–C bond formations using 2-iodo or 2-bromoglycals,[22] transition metal-catalyzed C–C bond formation reactions of 2-chloroglycals has not been reported to date. In order to demonstrate the application of 2-chloroglycals in C–C bond formation reactions, we carried out the reaction of 3,4,6-tri-*O*-benzyl-2-chloro-2-deoxy-α-glucopyranosyl chloride (**2a**/**4a** mixture) with potassium *tert*-butoxide in diethyl ether to give 2-chloroglycal (**6**),[21] which was subsequently subjected to modified Suzuki conditions to produce the coupled product **8** (Scheme 5) in

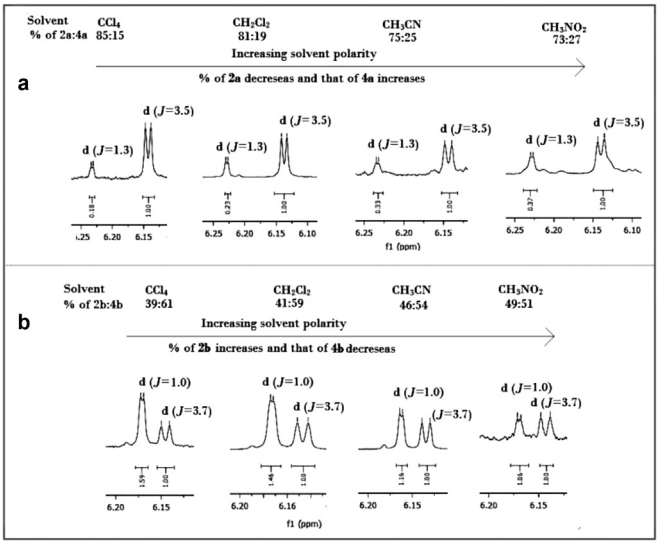
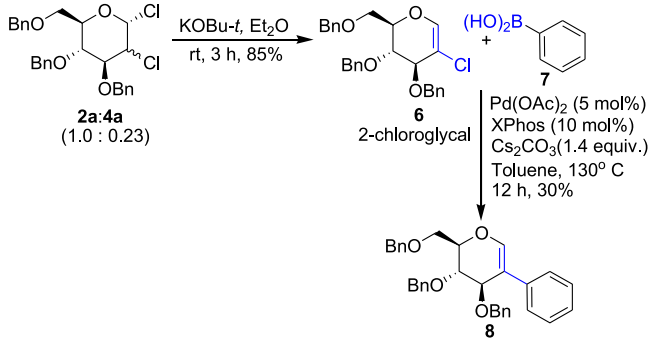


Fig. 4. a. 1,2-Dichlorination of tri-*O*-benzyl-D-glucal in different solvents; b. 1,2-dichlorination of tri-*O*-acetyl-D-glucal in different solvents.



Scheme 5. Conversion of 1,2-dichloropyranoside (**2a**/**4a**) into 2-chloroglycal (**6**) and subsequent Suzuki coupling.

somewhat low yield (30%) considering the low reactivity of vinylic chlorides.[23] The coupled product **8** was confirmed by comparing the NMR data with literature reports.[22]

3. Conclusions

In conclusion our investigation showed that diastereoselective 1,2-dichlorination of different protected glycals can be achieved by using NCS/PPh_3 reagent combination. Improved stereoselectivity, less hazardous reagent combination, and room temperature conditions are the advantages of the present method over the existing methods available in the literature. Finally, the downstream product, i.e., 2-chloroglycal has been utilized for Pd-catalyzed Suzuki coupling.

4. Experimental section

4.1. General information

^1H and ^{13}C NMR spectra were recorded on Bruker 200, 400 and 500 MHz spectrometers with TMS as the internal standard. Chemical shifts are expressed in parts per million (δ ppm). MS were recorded on Waters LC Mass spectrometer (Model No. Symapt MS). Silica gel coated aluminum plates were used for TLC. Elemental analyses were performed on Vario Elementar (Model No. EL-III, installed at CSIR-IIIM, Jammu, India-180001). Reagents and solvents used were mostly of LR grade. Optical rotation measurements were carried out on Perkin–Elmer 241 polarimeter.

4.2. General procedure for 1,2-dichlorination of glycals

To a solution of the glycal (100 mg) in CH_2Cl_2 (3 mL) was added PPh_3 (1.5 equiv) followed by NCS (3.0 equiv) over a period of 5 min. After stirring for 3–4 h at room temperature, the completion of reaction was checked by TLC. Then the mixture was treated with saturated $NaHCO_3$, poured into a separatory funnel, and extracted with DCM. The separated organic phase was washed with sodium thiosulphate to remove Cl_2, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by 60–120 silica gel column chromatography (EtOAc/hexane) to yield the chlorinated products (88–90%) as colorless syrups.

4.3. Preparation and spectral data of compounds 2a and 4a

Prepared by the general procedure for the dichlorination of glycals by using **1a** (100 mg, 0.24 mmol), NCS (96 mg, 3 equiv.), and PPh_3 (94 mg, 1.5 equiv) to yield α-*gluco*/α-*manno* mixture (**2a**/**4a** in the ratio of 1:0.23) as semisolid (90% yield).

*4.3.1. 3,4,6-Tri-O-benzyl-2-chloro-2-deoxy-α-glucopyranosyl chloride (**2a**).* R_f (10% EtOAc/hexane) 0.5; IR ($CHCl_3$) 1635, 1219, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (m, 15H), 6.14 (d, J=3.5 Hz, 1H), 4.96 (d, J=10.4 Hz, 1H), 4.53 (m, 6H), 4.12 (dd, J=10.2, 3.5 Hz, 1H), 4.02 (dd, J=10.0, 8.9 Hz, 1H), 3.81–3.75 (m, 2H), 3.66 (dd, J=11.1, 1.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 137.9, 137.8, 137.7, 137.5, 137.3, 128.5, 128.5, 128.5, 128.4, 128.4, 128.2, 127.9, 127.9, 127.8, 127.8, 127.8, 127.6, 94.4, 81.5, 76.7, 76.3, 75.3, 73.9, 73.5, 67.5, 60.5, ESI MS (m/z): 486 $[M]^+$.

*4.3.2. 3,4,6-Tri-O-benzyl-2-chloro-2-deoxy-α-mannopyranosyl chloride (**4a**).* R_f (10% EtOAc/hexane) 0.6; IR ($CHCl_3$) 1635, 1219, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (m, 15H), 6.23 (d, J=1.3 Hz, 1H), 4.86 (d, J=10.6 Hz, 1H), 4.74–4.63 (m, 6H), 4.18 (d, J=2.4 Hz, 1H), 4.09 (d, J=1.2 Hz, 1H), 3.81–3.75 (m, 2H), 3.69 (d, J=0.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 129.4, 128.5, 128.5, 128.4, 128.4, 128.3, 128.1, 128.1, 128.1, 128.1, 128.0, 127.9, 127.9, 127.9, 127.8, 127.8, 127.7, 126.3, 92.5, 75.5, 74.9, 73.4, 73.1, 72.1, 71.9, 67.9, 60.9, ESI MS (m/z): 486 $[M]^+$.

4.4. Preparation and spectral data of compounds 2b and 4b

Prepared by the general procedure for dichlorination of glycals by using **1b** (100 mg, 0.37 mmol), NCS (147 mg, 3 equiv), and PPh_3 (145 mg, 1.5 equiv) to yield α-*gluco*/α-*manno* mixture (**2b**/**4b** in the ratio of 1:1.46) as semisolid (88% yield).

*4.4.1. 3,4,6-Tri-O-acetyl-2-chloro-2-deoxy-α-glucopyranosyl chloride (**2b**).* R_f (20% EtOAc/hexane) 0.6; $[\alpha]_D^{25}$ +227 (c 1.0, $CHCl_3$);[7] IR ($CHCl_3$) 1744, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.17 (d, J=0.9 Hz, 1H), 5.61 (dd, J=9.9, 3.7 Hz, 2H), 5.11 (dd, J=10.1, 9.5 Hz, 1H), 4.35–4.29 (m, 2H), 4.20 (m, 1H), 2.12 (s, 6H), 2.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 169.9, 169.3, 90.9, 71.9, 68.5, 64.6, 61.4, 59.8, 20.7, 20.7, 20.7; ESI MS (m/z): 342 $[M]^+$.

*4.4.2. 3,4,6-Tri-O-acetyl-2-chloro-2-deoxy-α-mannopyranosyl chloride (**4b**, major product).* R_f (30% EtOAc/hexane) 0.6; $[\alpha]_D^{25}$ −44 (c 1.0, $CHCl_3$);[7] IR ($CHCl_3$) 1744, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.15 (d, J=3.7 Hz, 1H), 5.49 (m, 2H), 4.65 (dd, J=3.7, 1.4 Hz, 1H), 4.28 (m, 2H), 4.13 (dd, J=12.6, 2.1 Hz, 1H), 2.09 (s, 6H), 2.06 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 169.7, 169.5, 92.5, 71.4, 70.8, 68.1,

61.1, 57.7, 20.6, 20.5, 20.5, ESI MS (m/z): 342 $[M]^+$. Anal. Calcd for $C_{12}H_{16}Cl_2O_7$: C, 42.00; H, 4.70. Found C, 41.87; H, 4.59.

4.5. Preparation and spectral data of 3,4,6-tri-*O*-benzoyl-2-chloro-2-deoxy-α-mannopyranosyl chloride (4c)

Prepared by the general procedure for dichlorination of glycals by using **1c** (100 mg, 0.22 mmol), NCS (88 mg, 3 equiv), and PPh_3 (86 mg, 1.5 equiv) to yield the desired product **4c** as semisolid (90% yield); R_f (10% EtOAc/hexane) 0.5; $[\alpha]_D^{25}$ +2.7 (c 1.0, $CHCl_3$); IR ($CHCl_3$) 1727, 1601, 771 cm^{-1}; ^1H NMR (125 MHz, $CDCl_3$) δ 8.10 (dd, J=16.3, 8.0 Hz, 3H), 7.99 (dd, J=9.6, 8.6 Hz, 4H), 7.58–7.51 (m, 2H), 7.44 (m, 3H), 7.41–7.37 (m, 4H), 6.30 (d, 1H), 6.15 (t, J=9.9 Hz, 1H), 6.06 (dd, J=10.1, 3.4 Hz, 1H), 4.89 (d, J=3.4 Hz, 1H), 4.70–4.64 (m, 2H), 4.48 (dd, J=12.1, 3.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 165.3, 164.9, 133.5, 133.5, 133.4, 132.9, 129.9, 129.7, 129.6, 129.5, 129.2, 129.1, 128.4, 128.4, 128.3, 128.3, 128.3, 128.2, 128.2, 128.2, 90.9, 71.8, 69.0, 65.1, 61.9, 59.9, ESI MS (m/z): 528 $[M]^+$. Anal. Calcd for $C_{27}H_{22}Cl_2O_7$: C, 61.26; H, 4.19. Found C, 61.22; H, 4.15.

4.6. Preparation and spectral data of compounds 2d and 4d

Prepared by the general procedure for dichlorination of glycals by using **1d** (100 mg, 0.30 mmol), NCS (121 mg, 3 equiv.), and PPh_3 (119 mg, 1.5 equiv) to yield the α-*gluco*/α-*manno* mixture (**2d**/**4d** in the ratio of 1:0.32) as semisolid (90% yield).

*4.6.1. 2,3,4,6-Tetra-O-acetyl-2-chloro-2-deoxy-α-glucopyranosyl chloride (**2d**).* R_f (30% EtOAc/hexane) 0.5; IR ($CHCl_3$) 1744, 771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.20 (s, 1H), 5.97 (d, J=8.8 Hz, 1H), 5.10–5.07 (m, 1H), 4.41 (dt, J=8.3, 5.4 Hz, 2H), 4.23 (dd, J=9.5, 4.7 Hz, 1H), 2.18 (s, 3H), 2.12 (s, 3H), 2.09 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 169.2, 169.1, 168.8, 108.7, 71.9, 71.9, 65.3, 61.6, 20.7, 20.7, 20.6, 20.5, ESI MS (m/z): 400 $[M]^+$.

*4.6.2. 2,3,4,6-Tetra-O-acetyl-2-chloro-2-deoxy-α-mannopyranosyl chloride (**4d**).* R_f (30% EtOAc/hexane) 0.5; IR ($CHCl_3$) 1744, 771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.33 (s, 1H), 5.74 (d, J=9.0 Hz, 1H), 5.12–5.10 (m, 1H), 4.41 (dt, J=8.3, 5.4 Hz, 2H), 4.23 (dd, J=9.5, 4.7 Hz, 1H), 2.18 (s, 3H), 2.16 (s, 3H), 2.11 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 169.3, 169.2, 168.8, 107.9, 72.7, 72.1, 65.0, 61.5, 20.7, 20.6, 20.5, 20.4, ESI MS (m/z): 400 $[M]^+$.

4.7. Preparation and spectral data of 3,4,6-tri-*O*-benzyl-2-chloro-2-deoxy-α-galactopyranosyl chloride (2e)

Prepared by the general procedure for dichlorination of glycals by using **1e** (100 mg, 0.24 mmol), NCS (96 mg, 3 equiv), and PPh_3 (94 mg, 1.5 equiv) to yield α-*gluco* isomer (**2e**) as semisolid (89% yield); R_f (10% EtOAc/hexane) 0.6; $[\alpha]_D^{25}$ +10 (c 1.0, $CHCl_3$); IR ($CHCl_3$) 1618, 1113, 771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43–7.25 (m, 15H), 6.18 (d, J=3.5 Hz, 1H), 4.91 (d, J=11.1 Hz, 1H), 4.80 (d, J=11.4 Hz, 1H), 4.73 (d, J=11.4 Hz, 1H), 4.64 (dd, J=10.5, 3.5 Hz, 1H), 4.54–4.41 (m, 3H), 4.32 (t, J=6.5 Hz, 1H), 4.01 (s, 1H), 3.94 (dd, J=10.5, 2.6 Hz, 1H), 3.61–3.52 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 137.6, 128.7, 128.7, 128.6, 128.5, 128.5, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 127.9, 127.9, 127.9, 127.9, 127.7, 95.6, 78.4, 75.3, 74.5, 73.6, 73.6, 72.9, 67.8, 58.8; ESI MS (m/z): 486 $[M]^+$. Anal. Calcd for $C_{27}H_{28}Cl_2O_4$: C, 66.53; H, 5.79. Found C, 66.45; H, 5.69.

4.8. Preparation and spectral data of 3,4,6-tri-*O*-acetyl-2-chloro-2-deoxy-α-glalactopyranosyl chloride (2f)

Prepared by the general procedure for dichlorination of glycals by using **1f** (100 mg, 0.37 mmol), NCS (147 mg, 3 equiv.), and PPh_3 (145 mg, 1.5 equiv) to yield the desired product **2f** as semisolid (89% yield); R_f (20% EtOAc/hexane) 0.6; $[\alpha]_D^{25}$ +154 (c 1.0, $CHCl_3$); IR ($CHCl_3$) 1744, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.21 (d, J=3.6 Hz, 1H), 5.50 (d, J=3.0 Hz, 1H), 5.38 (dd, J=11.1, 3.2 Hz, 1H), 4.61 (t, J=6.4 Hz, 1H), 4.44 (dd, J=11.0, 3.6 Hz, 1H), 4.18–4.06 (m, 2H), 2.15 (s, 3H), 2.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 169.8, 169.6, 93.6, 69.8, 69.2, 67.5, 60.9, 55.4, 20.7, 20.6, 20.5, ESI MS (m/z): 342 $[M]^+$. Anal. Calcd for $C_{12}H_{16}Cl_2O_7$: C, 42.00; H, 4.70. Found C, 41.92; H, 4.67.

4.9. Preparation and spectral data of 3,4,6-tri-*O*-benzoyl-2-chloro-2-deoxy-α-galactopyranosyl chloride (2g)

Prepared by the general procedure for dichlorination of glycals by using **1g** (100 mg, 0.22 mmol), NCS (88 mg, 3 equiv.), and PPh_3 (86 mg, 1.5 equiv) to yield the desired product **2g** as semisolid (88% yield); R_f (10% EtOAc/hexane) 0.5; $[\alpha]_D^{25}$ +80.3 (c 1.0, $CHCl_3$); IR ($CHCl_3$) 1728, 1601, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02–7.98 (m, 4H), 7.90–7.86 (m, 2H), 7.56–7.39 (m, 7H), 7.32 (d, J=7.8 Hz, 2H), 6.39 (d, J=3.6 Hz, 1H), 6.05 (d, J=2.1 Hz, 1H), 5.82 (dd, J=11.0, 3.2 Hz, 1H), 4.97 (t, J=6.5 Hz, 1H), 4.76 (dd, J=11.0, 3.6 Hz, 1H), 4.61 (dd, J=11.5, 6.8 Hz, 1H), 4.40 (dd, J=11.5, 6.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 165.2, 165.2, 133.8, 133.4, 133.5, 130.3, 129.9, 129.9, 129.9, 129.8, 129.8, 129.2, 128.9, 128.8, 128.7, 128.6, 128.5, 128.5, 128.4, 127.8, 93.8, 70.4, 69.9, 68.5, 61.7, 56.1, ESI MS (m/z): 528 $[M]^+$. Anal. Calcd for $C_{27}H_{22}Cl_2O_7$: C, 61.26; H, 4.19. Found C, 61.19; H, 4.11.

4.10. 3,4-Di-*O*-acetyl-2-chloro-2,6-dideoxy-α-glucopyranosyl chloride (2h)

Prepared by the general procedure for dichlorination of glycals by using **1h** (100 mg, 0.47 mmol), NCS (187 mg, 3 equiv.), and PPh_3 (185 mg, 1.5 equiv) to yield the desired product **2h** as white solid (88% yield); mp135–136 °C, R_f (10% EtOAc/hexane) 0.6; $[\alpha]_D^{25}$ −214 (c 1.0, $CHCl_3$); IR ($CHCl_3$) 1728, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.09 (d, J=3.7 Hz, 1H), 5.47 (dd, J=10.4, 9.5 Hz, 1H), 4.83 (t, J=9.7 Hz, 1H), 4.31 (dq, J=10.1, 6.2 Hz, 1H), 4.14 (dd, J=10.5, 3.7 Hz, 1H), 2.07 (d, J=7.8 Hz, 6H), 1.25 (d, J=6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 169.78, 92.7, 73.6, 71.4, 68.9, 58.2, 20.7, 20.6, 17.1, ESI MS (m/z): 242 $[M]^+$. Anal. Calcd for $C_8H_{12}Cl_2O_4$: C, 39.53; H, 4.98. Found C, 39.49; H, 4.4.93.

4.11. 3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-5-chloro-3,4-dihydro-2*H*-pyran (6)

To a solution of 1,2-dichloropyranoside **2a**/**4a** mixture (200 mg, 0.41 mmol) in diethyl ether (3 mL) was added KO*t*-Bu (92 mg, 2 equiv). The reaction mixture was allowed to stir for 3 h. Completion of reaction was checked by TLC. The reaction mixture was extracted with ethyl acetate, dried over Na_2SO_4, and concentrated. The residue was purified by 60–120 silica gel column chromatography (EtOAc/hexane) to yield the product **6** (85%) as white solid. M.p 30–35 °C; R_f (20% EtOAc/hexane) 0.55; IR ($CHCl_3$) 3064, 3031, 2906, 2867, 1649, 1496, 1454, 1364, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.18 (m, 15H), 6.64 (s, 1H), 4.60 (m, 6H), 4.27 (dd, J=10.1, 5.2 Hz, 1H), 4.10 (d, J=4.3 Hz, 1H), 3.95 (dd, J=5.5, 4.4 Hz, 1H), 3.79 (dd, J=10.7, 6.1 Hz, 1H), 3.66 (dd, J=10.7, 4.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.5, 137.9, 137.8, 137.6, 128.6, 128.5, 128.0, 127.9, 127.8, 110.0, 76.5, 76.4, 73.8, 73.5, 72.8, 72.5, 67.8; ESI MS (m/z): 450 $[M]^+$. Anal. Calcd for $C_{27}H_{27}ClO_4$: C, 71.91; H, 6.03. Found C, 71.83; H, 6.00.

4.12. 3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-5-phenyl-2*H*-pyran (8)

The compound **6** (100 mg, 0.22 mmol) was dissolved in toluene (3 mL) phenylboronic acid **7** (27 mg, 1 equiv) was added to it followed by the addition of Cs_2CO_3 (101 mg, 1.4 equiv) and SPhos

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(10 mol %). The reaction mixture was allowed to stir at 130 °C for 12 h. After standard workup the crude was purified by column chromatography (EtOAc/petrol) to afford **8** (48%) as semisolid. R_f (20% EtOAc/petrol): 0.45; $[\alpha]_D^{25}$ −6.6 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3083, 3071, 3038, 2929, 2871, 1627, 1613, 1488, 1455, 1399, 1344, 1288, 849, 800, 735, 691, 681; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 19H), 6.83 (s, 1H), 4.71–4.56 (m, 4H), 4.51 (s, 2H), 4.27 (dd, *J*=10.0, 5.2 Hz, 1H), 4.08 (d, *J*=4.2 Hz, 1H), 3.93 (dd, *J*=5.4, 4.6 Hz, 1H), 3.77 (dd, *J*=10.6, 6.1 Hz, 1H), 3.67 (dd, *J*=10.6, 4.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 137.8, 137.7, 137.6, 137.5, 128.6, 128.5, 128.5, 128.6, 128.5, 128.4, 128.3, 128.3, 128.3, 128.3, 128.3, 128.2, 128.2, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 127.8, 112.9, 76.5, 76.5, 73.7, 73.5, 72.8, 72.4, 67.7; ESI MS (*m*/*z*): 492 $[M]^+$. Anal. Calcd for $C_{33}H_{32}O_4$: C, 80.46; H, 6.55. Found C, 80.40; H, 6.51.

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Supplementary data

Supplementary data contains the copies of ^{1}H NMR and ^{13}C NMR data of products. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.12.088.

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