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Regio- and Stereocontrolled Selective Debenzylation and Substitution Reactions of C-2 Formyl Glycals. Application in the Synthesis of Constrained β-Sugar Amino Acids

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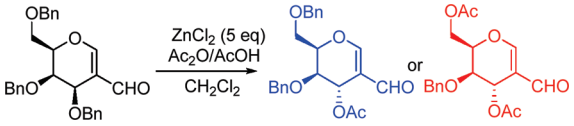

O-Benzyl-protected C-2 formyl glycals are regioselectively deprotected and acetylated first at C-3 and then at C-6 upon treatment with a $ZnCl_2-Ac_2O-AcOH$ reagent combination. Treatment of the thus-obtained C-3 acetate with various nucleophiles leads to substitution at C-3 with retention of stereochemistry in the galactal series, whereas mixed results were obtained with glucal-derived compounds. Two of the azido-substituted products were converted into the corresponding β-sugar amino acids.

Introduction

Selective protection/deprotection strategies are often a prerequisite[1] for the synthesis of various therapeutically useful molecules such as modified oligosaccharides, nucleosides, glycopeptides, etc. Among the plethora of protecting groups known in the literature, the benzyl group[2,3] is one of the most commonly used protecting groups in synthetic organic chemistry as it can be easily installed and is stable toward many reagents that are used in various synthetic operations. Further, it can be easily cleaved at the end of the synthetic endeavors under mild conditions.[2,3] Benzyl-protected sugar derivatives have great significance in the synthesis of oligosaccharides and natural products.[1] Although the hydroxyl groups present in a carbohydrate-derived molecule can be fully benzylated very easily,[3] the regioselective partial benzylation is still a problem and has been a subject of numerous studies.[4] Regioselective ring-opening of 4,6- or 1,2-*O*-benzylidene groups[5] and metal (e.g., copper and tin)-mediated selective benzylation[6] are some of the commonly employed methods. Indirect methods include the regioselective introduction of other protecting groups, followed by benzyl protection of the remaining hydroxyl groups[7] to obtain the partially benzylated sugar derivatives. An interesting alternative option to obtain such compounds is

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selective debenzylation of easily made polybenzylated compounds.[8] Debenzylation methods such as $ZnCl_2-Ac_2O-$AcOH-mediated debenzylation−acetolysis,[9b−9d] catalytic hydrogenolysis,[1] and employment of Lewis acids such as $SnCl_4$, $TiCl_4$, BCl_3, or $CrCl_2$/LiI have been studied for the preparation of partially benzylated monosaccharides.[9] The selective debenzylation has also been reported with TIBAL/DIBAL-H,[10] TMSI,[9a] NIS, or a combination of diacetoxyiodobenzene/iodine.[11]

Molecular recognition by the cell-surfaced carbohydrate linked proteins (glycoproteins) plays an important role in various biological functions such as trafficking of proteins, bacterial and viral infection, and metastasis.[12,13] Introduction of an amino and a carboxylic acid function onto a carbohydrate skeleton leads to sugar−amino acids (SAAs) which are of great interest as they can be easily converted to oligomers and saccharide−peptide hybrids and are ideal building blocks for combinatorial synthesis.[14] Sugar amino acids (SAA) exist in nature as cell wall components in the form of neuraminic and muramic acids.[15] They are also important structural moieties present in many natural products such as gougerotin[16] and aspiculamycin,[17] in which the basic structural framework is a pyranoside sugar β-amino acid. Because of the enormous potential and its applications, a number of research groups,[18−21] including ours,[22] have designed and synthesized many unnatural sugar amino acids and used them to create novel structural entities.

Result and Discussion

In continuation of our work on the functionalization of glycals,[23] we have made some interesting observations using C-2 formyl glycals which we wish to report here. In connection with another project,[23h] we were interested in debenzylating the 6-*O*-benzyl group of 3,4,6-tri-*O*-benzyl-C-2 formyl glycals. For this purpose, we wished to use the $ZnCl_2-Ac_2O-$AcOH reagent system[9b−9d] which is known to selectively debenzylate the 6-*O*-Bn group and yield the corresponding acetate from substrates that are devoid of C-2 formyl groups. However, use of the reported reagent system with 3,4,6-tri-*O*-benzyl-C-2-formyl glycals **1** and **4** (Scheme 1) led to a complex mixture of products as gauged by thin-layer chromatographic analysis of the reaction mixture. Optimization of the reaction conditions led us to use only 5 equiv of $ZnCl_2$ (instead of 10 equiv as reported[9b−9d]) and Ac_2O-AcOH in a 2:1 ratio, and dichloromethane (DCM) as cosolvents (instead of using only Ac_2O-AcOH as solvent) at 10−25 °C led to a clean reaction. Thus, interestingly, tri-*O*-benzyl-C-2-formyl galactal **1** produced 3-*O*-acetyl derivative **2** (Scheme 1) as a major product along with the minor diacetoxy compound **3** in a 10:1 ratio and in 78% combined yield in 1 h. Further, on careful monitoring of the progress of the reaction, it was found that depending upon time we could control the removal of either only 3-*O*-Bn or both 3-*O*-Bn and 6-*O*-Bn groups (Scheme 1). Thus, reaction of **1** with $ZnCl_2-Ac_2O-$AcOH for 5 h gave the diacetate **3** (having acetate groups at the C-3 and C-6 positions) as the major product along with monoacetate **2** as the minor product in 10:1 ratio in 70% combined yield. Likewise, the glucal derivative **4** gave monoacetate **5** as the major product (**5**:**6** = 10:2 ratio) in 72% yield in 45 min, whereas **6** became the major product after 4 h. This indicates that in these reactions initially compounds **2** and **5** are

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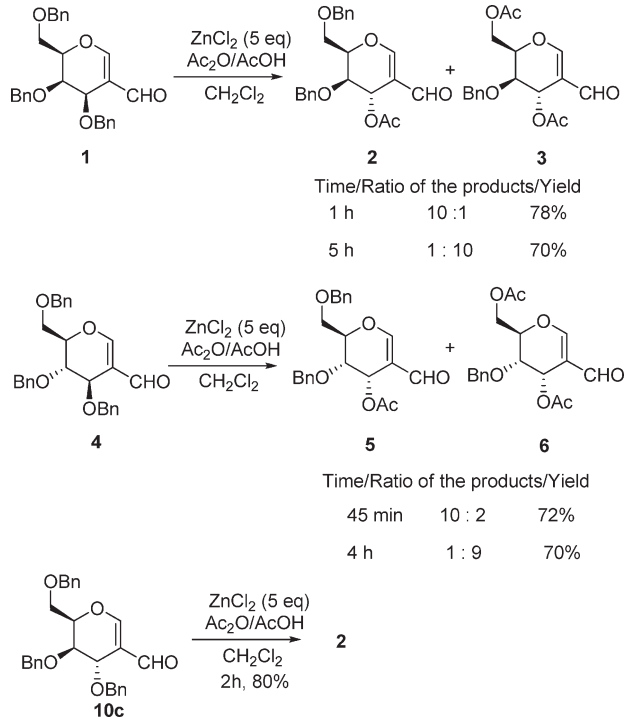
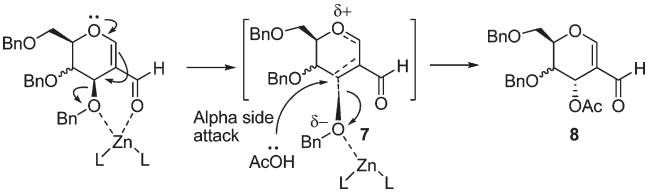
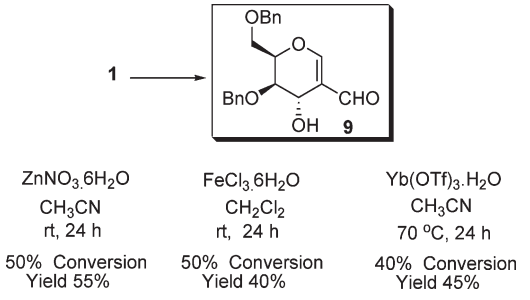
SCHEME 1. Selective Acetolysis of Benzyloxy Group



SCHEME 2. Proposed Mechanism for C-3 Debenzyloxylation



SCHEME 3. Attempts for Debenzylation with Different Lewis Acids



formed which get converted into the diacetates **3** and **6** respectively on prolonged reaction under the reaction conditions. It is evident from these observations that 3-*O*-Bn group in C-2-formyl glycals gets debenzylated at a faster rate as compared to the 6-*O*-Bn group.

In a separate experiment,[24] compound **10c**, vide infra, a stereoisomer of compound **1**, was treated under the present reaction conditions with the $ZnCl_2-Ac_2O-AcOH$ reagent system in CH_2Cl_2. The reaction took 2 h to reach completion, and compound **2** was the sole product obtained in 80% yield. This probably suggests that the C-5 substitution is controlling the stereochemical outcome of this and related reactions.

It is quite likely that the Lewis acid ($ZnCl_2$) coordinates with the nearby C-2 formyl group (Scheme 2), thus facilitating the preferential removal of the 3-*O*-Bn group with the help of the ring oxygen, as shown, to form an intermediate **7** followed by the attack of acetic acid opposite to the leaving group to form **8**. It appears that the Lewis acid coordinated −*O*-Bn group blocks the β-face and hence acetic acid preferentially attacks from the α-face irrespective of the orientation of the substitutent at C-4. This is also due to the fact that the extended conjugation of ring oxygen, with the double bond and the aldehyde group, will be maintained if the incoming nucleophile attacks at C-3 forming a thermodynamically controlled product.

The same debenzylation was attempted by using hydrated Lewis acids, such as $ZnNO_3 \cdot 6H_2O$, $FeCl_3 \cdot 6H_2O$, and $Yb(OTf)_3 \cdot H_2O$, but without acetic anhydride and acetic acid in order to check if the water of hydration affects the reaction. Indeed, the 3-*O*-Bn group was debenzylated to give compound **9** (Scheme 3) having a free hydroxyl group at C-3, but the reactions were extremely sluggish and were not completed even on prolonged reaction time giving only low yields of the product. Interestingly, the X-ray crystallographic data for compound **9** revealed that the hydroxyl group at the C-3 position is *trans* substituted with respect to the C-4 and C-5 stereocenters. In other words, inversion of stereochemistry at the C-3 position had taken place during this reaction. The products obtained from these Lewis acid mediated reactions in all the cases were same as confirmed by comparison of their NMR spectral data.[25]

Acetylation of C-3 hydroxy derivative **9** produced the corresponding acetate (Scheme 4) whose spectral data were found to be exactly similar to that of the monoacetoxy derivative viz. **2** obtained from C-2-formyl-tri-*O*-benzyl galactal **1**. This confirmed the stereochemistry of acetoxy derivative **2** at C-3. Further, in the case of diacetate **3**, the stereochemistry was confirmed through NOE correlations[25] where irradiation of H-5 led to an enhancement of the signal for H-4, as expected, but not for H-3. Similarly, irradiation of H-3 did not lead to the enhancement of signal for H-4, confirming that H-3 is trans to both H-4 and H-5. This also proves that compound **3** is formed from compound **2** upon prolonged reaction time and both have the same stereochemistry at C-3.

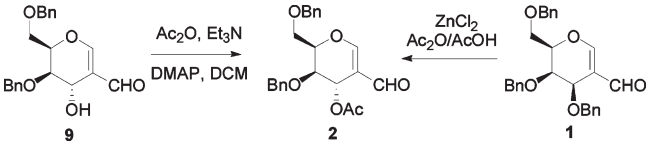
The stereochemistry at the C-3 position in compounds **5** and **6** (obtained from glucal derivative **4**) was also confirmed on the basis of the single-crystal X-ray data for the diacetoxy derivative **6** (Figure 2, Supporting Information) which showed that the acetoxy group at the C-3 position is *cis* with respect to the C-4 substituent and *trans* with respect to the C-5 substituent.

Interestingly, when the monoacetoxy derivative **2** was subjected to hydrolysis using NaOMe in MeOH (Scheme 5) to obtain the corresponding C-3 hydroxy derivative **9**, it was observed, by thin-layer chromatographic analysis, that a nonpolar product, as compared to the starting material **9**, was formed. The ^1H NMR spectral analysis of this

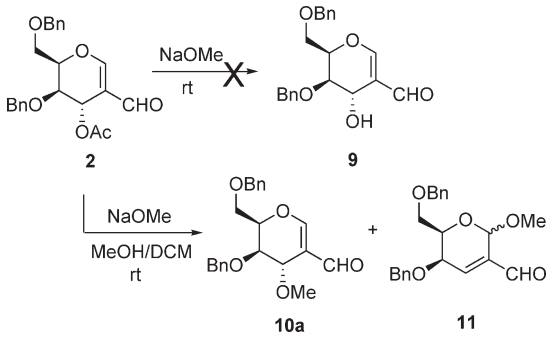
(24) (a) We thank one of the reviewers for suggesting this possible reaction pathway. (b) We thank one of the reviewers for suggesting that we perform these experiments.

(25) See the Supporting Information for spectral data.

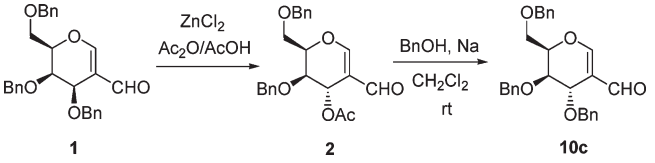
SCHEME 4. Acetylation of Compound 9



SCHEME 5. Deacetylation of Compound 2 Leading to Substitution

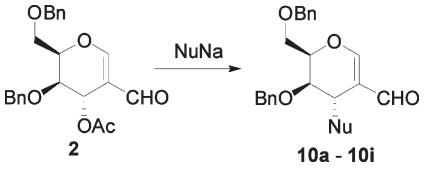


SCHEME 6. Nucleophilic Displacement Using Benzyloxy Nuclophile



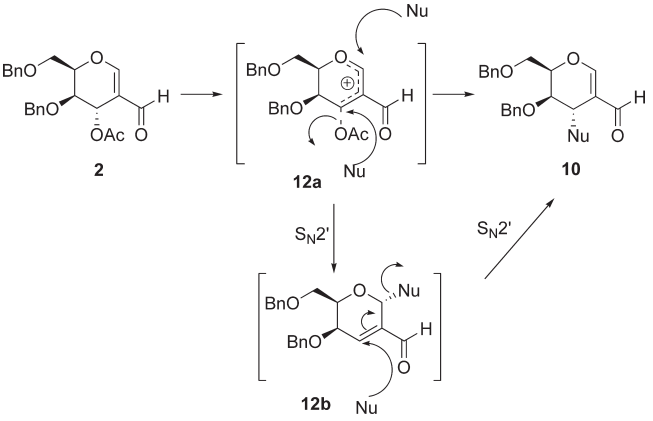
compound showed the presence of a singlet at δ 0.37 corresponding to the methoxy protons. Since the starting material **2** is an allyl acetate system, we surmised that the −OMe nucleophile could have replaced the acetoxy group before the hydrolysis took place. Further, it is possible that the −OMe group was present either at the C-3 position (compound **10a**, Scheme 5) or at the C-1 position (compound **11,** Scheme 5). But the ^{1}H NMR and COSY spectra of the product revealed[25] that the OMe group was at the C-3 position having structure **10a**. Thus, its ^{1}H NMR spectrum showed a singlet at δ 0.43 for the olefinic proton (H-1), and H-3 appeared as a doublet at δ 0.20 with $J = 2.4$ Hz. At this stage, however, the stereochemistry of the −OMe substitutent could not be ascertained. In order to find out the stereochemistry at the C-3 position in the nucleophilic substitution reactions we used another nucleophile (OBn). Thus, treatment of C-3 acetoxy derivative **2** with benzyl alcohol, as a source of nucleophile, in the presence of metallic sodium in CH_2Cl_2 as solvent at room temperature afforded compound **10c** (Scheme 6). The ^{1}H NMR spectrum of compound **10c** revealed that the product obtained is a C-2 formyl-tri-*O*-benzyl sugar derivative but appeared to be different from C-2 formyl-tri-*O*-benzyl galactal **1**, suggesting that the stereochemistry at the C-3 center must be different. As can be seen in the ^{1}H NMR spectrum[25] of both of these compounds, viz. **10c** and **1**, the H-1 proton appeared as a singlet at δ 7.46 and 7.24, respectively, confirming that both of these compounds are substituted at the C-3 position and not at C-1. But the difference in the pattern of other peaks was clearly evident.

TABLE 1. Nucleophilic Substitution Reactions with Compound 2



compd no.	nucleophiles (Nu)	time (min)	*T* (°C)/solvent	yield (%)
10a	OMe	30	rt/DCM	90
10b	*O*-allyl	60	rt/DCM	90
10c	OBn	120	rt/DCM	88
10d	OPh	60	rt/DCM	90
10e	SPh	60	rt/DCM	90
10f	*S*-tolyl	60	rt/DCM	92
10g	*O*-cyclohexyl	120	rt/DCM	85
10h	dimethyl malonate	120	rt/DCM	86
10i	N_3	240	70/DMF	88

SCHEME 7. Proposed Mechanism for Nucleophilic Attack on Compound 2

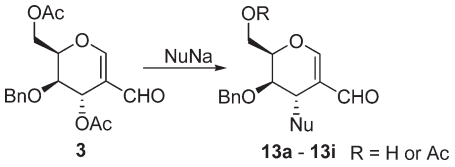


Thus, in compound **10c** the H-6, H-4, and H-6′ protons were well separated at δ 3.82, 3.69, and 3.60 as dd, brs, and dd, respectively, whereas the protons H-6 and H-4 were found to merge at δ 3.98 in compound **1**. The substantial difference of the appearance of the benzylic protons was also observed in their ^{1}H NMR spectra. The stereochemistry at C-3 in **10c** was also confirmed from the NOE experiments,[25] where irradiation of H-4 led to the enhancement of signal for proton H-5, as expected, while there was no enhancement for H-3 proton, indicating that H-3 and H-4 were *trans* disposed. Therefore, it was now clear that in the nucleophilic reactions of 3-acetoxy derivatives, the nucleophiles attack at the C-3 position from the α-side, i.e., *trans* to the C-4 substituent.[26] Thus, the stereochemistry at C-3 of **10a** was also concluded to be α, as shown, in the structure.

The regio- and stereoselectivity obsereved in these nucleophilic substitutions could be explained as follows: Removal

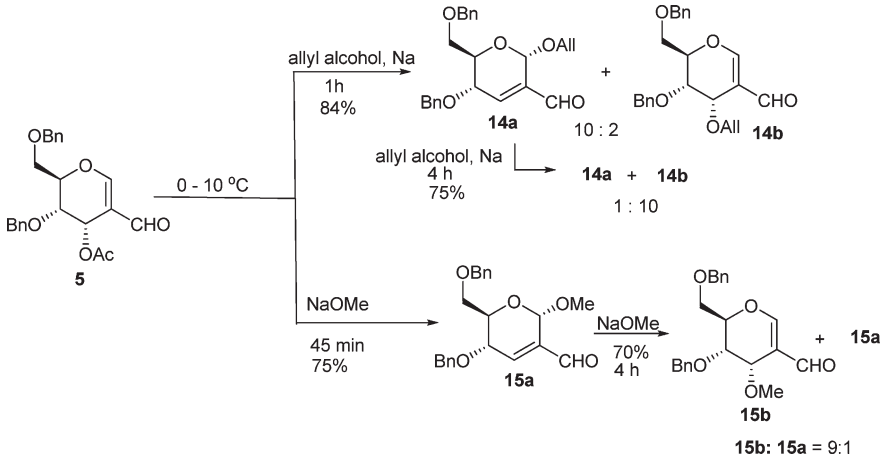
(26) For a somewhat similar kind of chemistry with tri-*O*-methyl-*C*-2-formyl galactal/glucal, see: (a) Booma, A.; Balasubramanian, K. K. *Tetrahedron Lett*. **1992**, *33*, 3049. (b) Booma, C.; Balasubramanian, K. K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 393However, these reports are confined only to the replacement of the C-3 methoxy group with a few nucleophiles in presence of 1.2 equiv of $BF_3 \cdot OEt_2$ to obtain only C-3-substituted product in both glucal and galactal cases.

TABLE 2. Nucleophilic Substitution Reaction with Compound 3



compd no.	nucleophiles (Nu)	R (H or Ac)	time (min)	*T* (°C)/solvent	yield (%)
13a	OMe	H	30	rt/DCM	87
13b	OEt	H	30	rt/DCM	85
13c	*O*-allyl	H	60	rt/DCM	90
13d	OPh	OAc	60	rt/DCM	88
13e	SPh	OAc	60	rt/DCM	90
13f	*S*-toluyl	OAc	60	rt/DCM	90
13g	*O*-naphthyl	OAc	60	rt/DCM	85
13h	dimethyl malonate	OAc	120	rt/DCM	88
13i	N_3	OAc	240	70/DMF	82

SCHEME 8. Substitution Reaction of Compound 5 with Alkoxy Nucleophiles

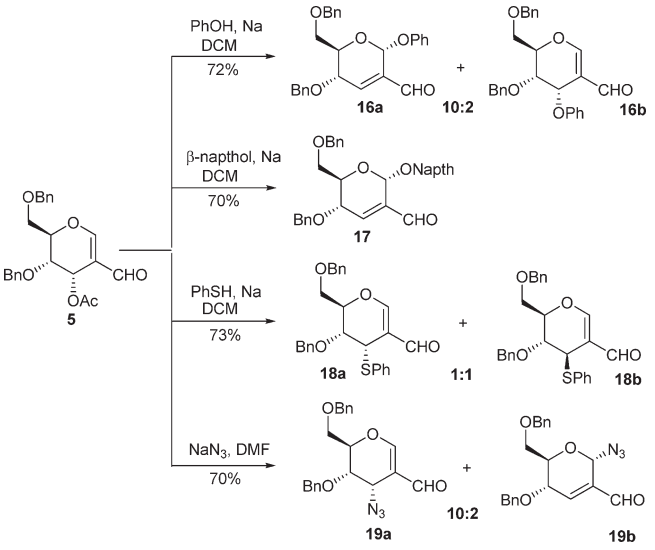


of the acetoxy group, possibly via solvolysis, may lead to the intermediate **12** (Scheme 7) in which the positive charge is delocalized on to ring oxygen and three carbons (C-1, C-2, and C-3). In this situation, the incoming nucleophile can attack either of the two centers C-1 or C-3. It appears that the preferable position for attack by the nucleophile is C-3 and not C-1 and that from the α-side, i.e., opposite to the *β*-oriented substitutents at C-4 and C-5 in compound **2**, a galactal derivative is obtained. This is again due to the fact that the extended conjugation of ring oxygen with the double bond and the aldehyde group will be maintained if the incoming nucleophile attacks at C-3 forming a thermodynamically controlled product. Alternatively, it is likely[24a] that two S_N2' reactions occur which are initiated by 1,4-conjugate additions on vinyl aldehydes. The first S_N2' reaction leads to products of type **12b** with retention of stereochemistry at C-1, followed by second S_N2' reaction on vinyl aldehyde **12b** to lead to the observed products, again with the retention of stereochemistry. When compound **10a**, in a separate experiment,[24b] was reacted with NaOMe/MeOH/DCM, no redistribution of product was observed and the compound **10a** was recovered.

After confirming the regio- and stereoselectivity in nucleophilic substitution reactions with this C-3-substituted derivative **2**, we reacted it with various other nucleophiles such as alcoholic (viz. -*O*-allyl, -*O*-cyclohexyl), phenolic (-OPh, -O-naphthyl), thio (-SPh, 4-methylthiophenyl), carbon (dimethyl malonate), and nitrogen nucleophiles (-N_3) to obtain very good yields (85−92%) of the corresponding C-3 substituted products (**10a**−**i**) as shown in Table 1. To further support our assumptions, we confirmed the stereochemistry of the C-3 setreocenter in the case of **10b** and **10f** through NOE experiments.[25]

Even diacetate **3**, a galactal derivative, on similar treatment with various nucleophiles gave only the the corresponding C-3-substituted products (**13a**−**i**, Table 2). In reactions with nucleophiles such as -OMe, -OEt, and -*O*-allyl we obtained the C-3-substituted products, but under these conditions, the C-6-acetoxy group was also found to become deacetylated to the corresponding free hydroxyl group. The stereochemistry at the C-3 center of these products **13a**−**i** formed from **3** was confirmed on the basis of the coupling constant of the H-3 proton which has a value around 2.7 Hz except for the thiophenyl nucleophile (J = 2.0 Hz)

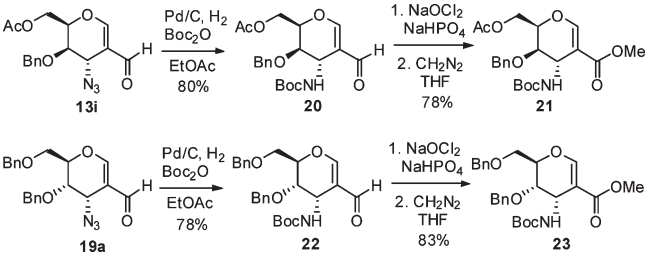
SCHEME 9. Substitution Reaction of Compound 5 with Phenolic, Thio, And Nitrogen Nucleophiles



indicating that a trans diequatorial relation exists between H-3 and H-4.

However, when C-3 acetoxy derivative **5**, obtained from the corresponding *C*-2-formyl glucal derivative **4**, was treated with different nucleophiles mixed results were obtained (Scheme 8). Thus, reaction of compound **5** with allyl alcohol in the presence of Na metal in DCM at 0−10 °C led to the formation of **14a** and **14b** as a 10:2 mixture in 70 and 12% yields, respectively, as confirmed by the ^{1}H NMR spectral analysis. Thus, in the ^{1}H NMR spectrum of **14a**, H-1 appeared as a singlet at δ 5.39 as a doublet and H-3 appeared at δ 6.86 with $J = 2.0$ Hz. The stereochemistry at C-1 was confirmed through NOE experiments.[25] Thus, irradiation of H-1 led to the enhancement of signals for proton H-6 and H-6′, confirming that $-CH_2OBn$ is cis to the H-1 proton. In the ^{1}H NMR spectrum of **14b**, while H-1 merged with the aromatic protons, the proton H-3, with $J = 1.9$ Hz which is estimated from the J value of H-4, merged with benzylic protons at δ 4.50−4.62. This value of coupling constant clearly suggests that H-3 is cis with respect to H-4. Likewise, reaction of **5** with sodium methoxide in MeOH solvent at 0−10 °C gave **15** as the only product having the methoxy substituent at C-1 as indicated by its ^{1}H NMR spectral data.[25] Thus, H-3 appeared as a doublet at δ 6.85 with $J =$ 1.7 Hz, whereas H-1 appeared as a singlet at δ 5.22. Reactions with other nucleophiles such as PhOH and β-naphthol similarly gave major products in which the nucleophiles had attacked at C-1 (Scheme 9). However, reaction of 3-acetoxy derivative **5** with thiophenol gave an inseparable 1:1 mixture of products **18a** and **18b**. Both of these compounds were C-3 substituted as confirmed from their ^{1}H NMR spectral data.[24] Thus, the aldehyde proton appeared as two singlets of equal intensity at δ 9.38 and 9.31. Further, while H-1 for one epimer appeared as a singlet at δ 7.43, for the other epimer the H-1 merged with the aromatic protons. Interestingly, however, reaction of **5** with sodium azide in DMF at 70 °C gave a C-3-substituted product **19a** as the major product,[25] along with a small amount of **19b** (Scheme 9). Thus, in **19a** proton H-1 appeared as a singlet at δ 7.37 and H-3 as a doublet at

SCHEME 10. Synthesis of Constrained β-Sugar Amino Acids



δ 4.76 with $J = 3.9$ Hz, confirming that H-3 and H-4 are *cis* oriented with respect to each other.

For the mechanistic considerations,[24a,24b] pure compounds **14a** and **15a** were separately treated with allyl alcohol/Na and NaOMe, respectively, to observe any redistribution of products. Indeed, the product **14a** led to the formation of a mixture of **14a** and **14b** in a 1:10 ratio. On the other hand, compound **15a** led to the formation of compounds **15b** and **15a** in 9:1 ratio. These experiments clearly suggest that substitution at C-3 leading to **14b** and **15b** as major products is due to their thermodynamic stability. Further, the retention of stereochemistry observed in these reactions is due to two S_N2' reactions, as mentioned above (cf. Scheme 7).

In continuation of our work[22] in the area of sugar amino acids, synthesis of constrained β-sugar amino acids has also been attempted. For this purpose, when C-3 azido-substituted compound **13i** (Scheme 10) was subjected to Pd/C-catalyzed hydrogenolysis in the presence of Boc_2O in EtOAc solvent[27] it gave a Boc-protected amine derivative **20**. The aldehyde was subjected to oxidation using $NaOCl_2$ under standard conditions,[28] and the crude acid thus obtained was subjected to esterification using diazomethane to obtain the orthogonally protected β-sugar amino acid **21** in 78% yield. The single-crystal X-ray data for **21** (Figure 3, Supporting Information) once again confirmed the stereochemistry at the C-3 position to be α-oriented and *trans* with respect to the C-4 and C-5 substituents. Similarly, the C-3 azido substituted compound **19a** derived from C-2-formyl glucal derived acetoxy derivative **5** was also converted into amine derivative **22**, which was then transformed into the corresponding β-sugar amino acid **23**.

Conclusion

We have developed a method for the regio- and stereoselective acetolysis of benzyloxy group in tri-*O*-benzyl-C-2-formyl glycals. The products so obtained underwent nucleophilic substitution reactions with a variety of nucleophiles. In the case of C-2 formyl galactal derived allylic acetate, substitution took place at the C-3 position with retention of stereochemistry, whereas in the case of C-2 formyl glucal derived allylic acetate substitution took place mainly at the C-1 position from the α-side. These reactions demonstrate the regio- and stereocontrol due to the possible anomeric or extended anomeric effect. The structures of the products obtained were confirmed by extensive spectroscopic studies and X-ray crystallographic data in some cases. We have also

(27) Pearson, C.; Rinehart, K. L.; Sugano, M. *Tetrahedron Lett*. **1999**, *40*, 411.
(28) Schwab, J. M.; Klassen, J. B. *J. Am. Chem. Soc*. **1984**, *106*, 7217.

utilized this method in the preparation of orthogonally protected β-sugar amino acids.

Experimental Section

General Procedure for Selective Acetolysis of Tri-*O*-benzyl-C-2-formyl Glycals. A mixture of freshly fused $ZnCl_2$ (1.53 g, 11.25 mmol) and Ac_2O/AcOH (2:1 ratio, 6 mL) in dry DCM (4 mL) was cooled to 10 °C using an ice−water bath. A solution of tri-*O*-benzyl-C-2-formyl glycal (1 g, 2.25 mmol) in DCM (4 mL) was quickly added. The reaction was stirred at 25 °C and monitored at regular intervals (TLC monitoring). At an appropriate time (see the main text), the reaction was quenched with saturated aqueous $NaHCO_3$ solution and was extracted with DCM (3×25 mL). The organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. Concentration of the organic phase on a rotary evaporator gave a crude mixture of products which was purified through column chromatography.

General Procedure for Nucleophilic Substitution Reactions. To a solution of acetylated derivative (0.5 mmol) in 5 mL of DCM were added a nucleophile (1.5 mmol) and sodium metal (1 mmol) at 0−10 °C. After completion of the reaction (TLC monitoring), the reaction mixture was poured onto crushed ice (20 g) and extracted with DCM (3×10 mL). The organic layer was washed with water and brine and dried over anhydrous sodium sulfate. Evaporation of the solvent on a rotary evaporator gave a crude product which was purified through column chromatography. (Note: In the case of azide nucleophile, sodium azide was taken in 5 mmol quantity, the solvent used was DMF, and the reaction mixture was heated at 70 °C for an appropriate time).

(3*S*,4*R*,5*R*)-4-(Benzyloxy)-5-(benzyloxymethyl)-2-formyl-3,4-dihydro-2*H*-pyran-3-yl acetate (2). Yield: 70%. R_f: 0.3 (hexane/ethyl acetate, 4:1). $[\alpha]_D = +64.0$ (*c* 1.0, DCM), liquid. IR (neat) ν_{max}/cm^{-1}: 3061, 3031, 2924, 2871, 1739, 1676, 1629, 1369, 1269, 1101, 1024, 739. ^1H NMR (400 MHz, $CDCl_3$): δ 9.38 (1H, s, −CHO); 7.54 (1H, s, H-1); 7.25−7.37 (10H, m, Ar-H); 5.76 (1H, d, *J* = 2.2 Hz, H-3); 4.76 (1H, d, *J* = 12.0 Hz, PhCH); 4.55 (1H, d, *J* = 12.0 Hz, PhCH); 4.50 (1H, d, *J* = 11.7 Hz, PhCH); 4.43 (1H, d, *J* = 11.7 Hz, PhCH); 4.20 (1H, merged dd, *J* = 5.9, 5.8 Hz, H-5); 3.80 (1H, dd, *J* = 10.0, 6.8 Hz, H-6); 3.71 (1H, brs, H-4); 3.51 (1H, dd, *J* = 10.0, 5.4 Hz, H-6′); 2.06 (3H, s, OAc). ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.97, 169.79, 165.82, 137.32, 136.97, 128.43, 128.39, 128.11, 127.92, 127.88, 127.61, 115.59, 76.14, 73.67, 71.89, 71.80, 69.96, 68.28, 58.83, 21.01. MSES: *m*/*z* 397 $[M + 1]^+$, 419 $[M + Na]^+$. Anal. Calcd for $C_{23}H_{24}O_6$: C, 69.68; H, 6.10. Found: C, 69.60; H, 6.17.

(3*S*,4*R*,5*R*)-3-Acetoxy-4-(benzyloxy)-2-formyl-3,4-dihydro-2*H*-pyran-5-yl)methyl Acetate (3). Yield: 60%. R_f: 0.25 (hexane/ethyl acetate, 4:1). $[\alpha]_D = +115.0$ (*c* 2.0, DCM), oil. IR (neat) ν_{max}/cm^{-1}: 3061, 2924, 2853, 1746, 1673, 1625, 1371, 1194, 1113, 1045, 738. ^1H NMR (400 MHz, $CDCl_3$): δ 9.39 (1H, s, −CHO); 7.55 (1H, s, H-1); 7.29−7.37 (5H, m, Ar-H); 5.79 (1H, d, *J* = 2.2 Hz, H-3); 4.76 (1H, d, *J* = 12.2 Hz, PhCH); 4.57 (1H, d, *J* = 12.0 Hz, PhCH); 4.35 (1H, dd, *J* = 11.5, 7.3 Hz, H-6); 4.22 (1H, merged dd, *J* = 6.6, 5.4 Hz, H-5); 4.13 (1H, dd, *J* = 11.4, 4.9 Hz, H-6′) 3.68 (1H, brs, H-4); 2.06 (3H, s, OAc); 1.99 (3H, s, OAc). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.92, 170.39, 169.84, 165.44, 136.56, 128.61, 128.52, 128.31, 115.58, 74.75, 71.67, 69.34, 62.56, 58.50, 21.04, 20.66. MSES: *m*/*z* 349 $[M+1]^+$, 371 $[M+Na]^+$. Anal. Calcd for $C_{18}H_{20}O_7$: C, 62.06; H, 5.79. Found: C, 62.00; H, 5.84.

(3*S*,4*R*,5*R*)-4-(Benzyloxy)-5-(benzyloxymethyl)-3-hydroxy-3,4-dihydro-2*H*-pyran-2-carbaldehyde (9). Yield: 55%. R_f: 0.3 (hexane/ethyl acetate, 7:3). $[\alpha]_D = +110.0$ (*c* 1.5, DCM), solid. Mp: 80 °C. IR (neat) ν_{max}/cm^{-1}: 3358, 3065, 3013, 1678, 1627. ^1H NMR (400 MHz, $CDCl_3$): δ 9.37 (1H, s, −CHO); 7.44 (1H, s, H-1); 7.22 − 7.37 (10H, m, Ar-H); 4.64 (1H, d, *J* = 11.7 Hz, PhCH); 4.64 (1H, d, *J* = 2.4 Hz, H-3); 4.57 (1H, d, *J* = 12.0, PhCH); 4.50 (1H, d, *J* = 12.0 Hz, PhCH); 4.45 (1H, d, *J* = 11.7 Hz, PhCH); 4.37 (1H, merged dd, *J* = 6.6, 5.6 Hz, H-5); 3.86 (1H, dd, *J* = 10.2, 7.1 Hz, H-6); 3.73 (1H, brs, H-4); 3.64 (1H, dd, *J* = 10.0, 5.4 Hz, H-6′); 2.75 (1H, brs, −OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.93, 165.32, 137.58, 137.26, 128.45, 127.98, 127.78, 120.07, 75.97, 75.89, 73.53, 72.71, 72.34, 68.32, 57.73. MSES: *m*/*z* 355 $[M + 1]^+$, 377 $[M + Na]^+$. Anal. Calcd for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26. Found: C, 71.13; H, 6.30.

(3*S*,4*R*,5*R*)-4-(Benzyloxy)-5-(benzyloxymethyl)-34-methoxy-3,4-dihydro-2*H*-pyran-2-carbaldehyde (10a). Yield: 90%. R_f: 0.4 (hexane/ethyl acetate, 4:1). $[\alpha]_D = -210.0$ (*c* 1.0, DCM), liquid. ^1H NMR (400 MHz, $CDCl_3$): δ 9.41 (1H, s, −CHO); 7.43 (1H, s, H-1); 7.22−7.37 (10H, m, Ar-H); 4.60 (1H, d, *J* = 11.7 Hz, PhCH); 4.58 (1H, d, *J* = 12.0 Hz, PhCH); 4.50 (1H, d, *J* = 12.0 Hz, PhCH); 4.44 (1H, d, *J* = 11.7 Hz, PhCH); 4.38 (1H, brt, *J* = 6.4 Hz, H-5); 4.20 (1H, d, *J* = 2.4 Hz, H-3); 3.83 (1H, dd, *J* = 9.8, 7.1 Hz, H-6); 3.73 (1H, brs, H-4); 3.65 (1H, dd, *J* = 10.0, 5.8 Hz, H-6′); 3.37 (3H, s, OMe). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.38, 166.0, 137.54, 137.09, 128.52, 128.48, 128.18, 128.11, 127.90, 127.87, 117.74, 75.59, 73.55, 72.21, 69.92, 68.22, 64.94, 57.28. MSES: *m*/*z* 369 $[M+1]^+$, 391 $[M+Na]^+$. Anal. Calcd for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found: C, 71.66; H, 6.61.

(3*S*,4*R*,5*R*)-4-(Benzyloxy)-3-(*tert*-butoxycarbonylamino)-2-formyl-3,4-dihydro-2*H*-pyran-5-yl)methyl Acetate (20). Yield: 80%. R_f: 0.3 (hexane/ethyl acetate, 7:3). $[\alpha]_D = +53.2$ (*c* 1.0, DCM), oil. IR (neat) ν_{max}/cm^{-1}: 3256, 2926, 2840, 1745, 1690, 1632. ^1H NMR (400 MHz, $CDCl_3$): δ 9.36 (1H, s, −CHO); 7.48 (1H, s, H-1); 7.27−7.34 (5H, m, Ar-H); 4.79 (1H, d, *J* = 11.7 Hz, PhCH); 4.50−4.65 (3H, m, NH, H-3, PhCH); 4.39 (1H, dd, *J* = 11.4, 7.3 Hz, H-6); 4.16−4.23 (2H, m, H-5, H-6′); 3.85 (1H, brs, H-4); 2.03 (3H, s, OAc); 1.47 (9H, s, *t*-Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.30, 170.45, 165,31, 154.79, 137.04, 128.35, 127.97, 116.17, 80.23, 74.47, 71.58, 71.24, 60.07, 40.64, 28.25, 20.65. MSES: *m*/*z* 406 $[M+1]^+$, 428 $[M+Na]^+$. Anal. Calcd for $C_{21}H_{27}NO_7$: C, 62.21; H, 6.71; N, 3.45. Found: C, 62.14; H, 6.78; N, 3.42.

(3*S*,4*R*,5*R*)-4-(Benzyloxy)-3-(*tert*-butoxycarbonylamino)-2-formyl-3,4-dihydro-2*H*-pyran-5-yl)methyl Acetate (21). Yield: 78%. R_f: 0.4 (hexane/ethyl acetate, 7:3). $[\alpha]_D = +71.5$ (*c* 2.3, DCM), oil. IR (neat) ν_{max}/cm^{-1}: 3270, 2936, 1742, 1631. ^1H NMR (400 MHz, $CDCl_3$): δ 7.72 (1H, s, H-1); 7.26 − 7.34 (5H, m, Ar−H); 4.82 (1H, d, *J* = 11.7 Hz, NH); 4.52−4.63 (3H, m, 2×PhCH and H-6); 4.34 (1H, dd, *J* = 11.5, 7.8 Hz, H-6′); 3.96−4.12 (2H, m, H-5, H-3); 3.75 (4H, brs, H-4 and OMe); 2.02 (3H, s, OAc); 1.48 (9H, s, *t*-Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.51, 166.84, 157.26, 154.80, 137.30, 128.33, 127.90, 103.70, 80.20, 72.62, 71.78, 71.53, 63.20, 51.53, 42.77, 28.31, 20.67. MSES: *m*/*z* 436 $[M + 1]^+$, 458 $[M + Na]^+$. Anal. Calcd for $C_{22}H_{29}NO_8$: C, 60.68; H, 6.71; N, 3.22. Found: C, 60.73; H, 6.74; N, 3.19.

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Supporting Information Available: General experimental procedures and characterization data for all of the compounds, ^1H and ^{13}C NMR, COSY, and NOE spectra, and CIF files of compounds **6**, **9**, and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.