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"One-pot" Access to α-D-Mannopyranosides from Glycals Employing Ruthenium Catalysis

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Abstract

Ru-catalyzed synthesis of α-D-mannopyranosides from glucal is described *via* one-pot glycosylation-dihydroxylation reaction. This method is amenable to a variety of acceptors, including carbohydrate-derived and amino-acid containing alcohols to obtain mannosylated peptides and disaccharides.

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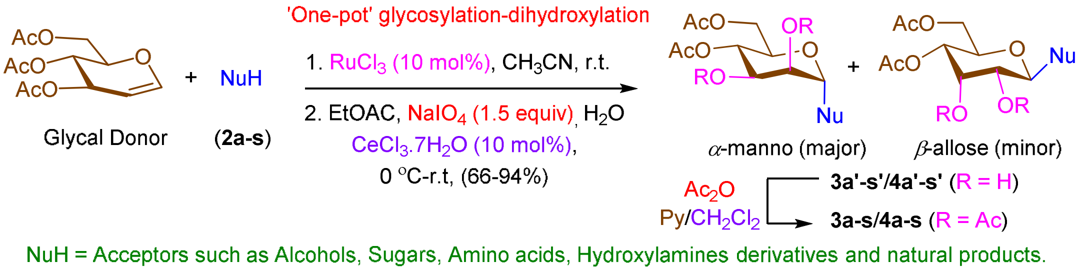
An efficient and convenient one-pot method for the preparation of α-D-mannopyranosides from glycal is described.



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ARTICLE TYPE

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Ru-catalyzed synthesis of α-D-mannopyranosides from glycal is described *via* one-pot glycosylation-dihydroxylation reaction. This method is amenable to a variety of acceptors, including carbohydrate derived and amino-acid containing alcohols to obtain mannosylated peptides and disaccharides.

In view of critical role played by carbohydrates in diverse set of biological processes,[1] development of stereoselective and efficient methods for assembling potent sugar molecules continues to serve as important chemical tools in glyco-science as well as in chemical biology. However, our understanding of these dynamic biosynthetic processes remains incomplete as the Nature seldom provides sufficient amount of pure and well defined saccharides for biological studies, hence, access to significant quantities of target homogeneous glycoconjugates often relies on chemical synthesis.[2] Unlike polypeptides and polynucleotide syntheses, incorporating glycosidic linkages with regio and stereocontrolled manner is notoriously difficult and remains challenging forefronts in the area of complex oligosaccharides syntheses.[3]

Owing to the unique importance of β-mannans[4a] and α-linked oligomannosides[4b] in biological system and synthetic challenges associated with mannosylation, designing of new glycosylation strategies for constructing selective glycosidic linkages in mannopyranosides remains a venerable task for carbohydrate researchers. As evident, a plethora of glycosylation reagent systems have been investigated for the activation of glycosyl donor, functionalized with a leaving group at anomeric carbon such as anomeric halides, anomeric oxygen or sulphur-derived latent moiety (Figure 1).[5] Despite the significant advances in the chemical glycosylation, extensive studies of functional group manipulation and anomeric activation in diverse reaction conditions such as temperature, solvents, etc., have remained quite elusive. In parallel, the transition-metal mediated glycosylation as an alternative equivalents approach has become increasingly popular in recent years.[6]

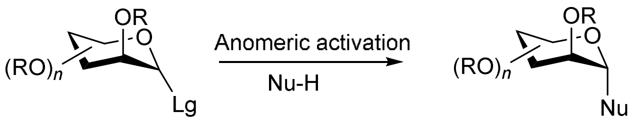


Figure 1 Mannosylation by using glycosyl donor.

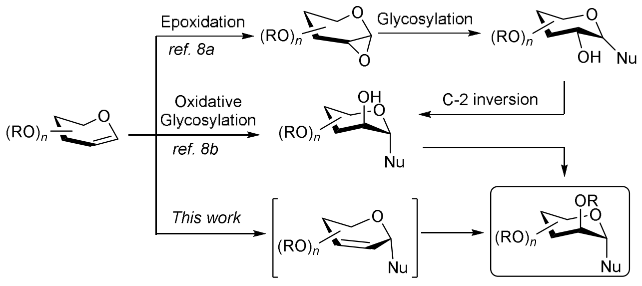


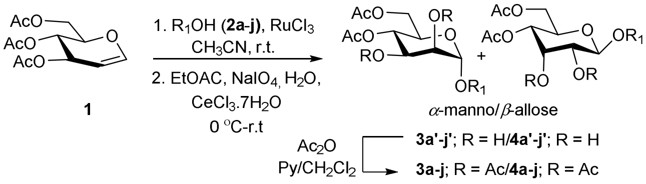
Figure 2 Synthesis of mannopyranosides from glycal.

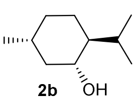
In addition to the well appreciated role played by glycals as versatile and chiral synthons in the synthesis of several complex oligosaccharides and glycoconjugates,[7] the exceptional synthetic potential of enol-ether functionality in glycals has been also highlighted for the preparation α-D-mannopyranosides.[8] Since the traditional glycal assembly approach represents the most efficient and reliable method for this conversion otherwise time consuming and involves multi-steps wherein the epoxidation of glycal substrate to generate 1,2-anhydropyranosides following epoxide ring-opening and subsequent inversion of C-2 stereocenter led to desired mannoside.[8a] Alternatively, the oxidative mannosylation in one-pot *via* epoxidation-glycosylation from glucal utilizing stiochiometric amount of sulfoxide reagent and triflic anhydride has encountered several drawbacks.[8b] Regardless of the stereochemical outcome, use of unconventional and toxic reagent system, excessive loading of nucleophiles and complicated reaction operation, low yield and limited substrate scope have long been recognized as unsolved issues.

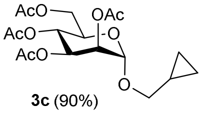
In this context, search of new protocol for the synthesis of structurally diverse sugar molecules from readily available starting materials by using mild reagent system is always appreciated. To pursue our interest in glycoconjugate syntheses and developing new glycosylation methods,[9] herein, we present an alternative process applicable for efficient and convenient synthesis of α-D-mannopyranosides *via* one pot glycosylation-dihydroxylation of glycals exploiting ruthenium catalysis. Recent demonstration on the efficiency of ruthenium(III) chloride as Lewis acid in glycosylation[9g] and its ability to generate ruthenium(VIII) oxide, a well known oxidant for stereoselective *cis*-dihydroxylation of olefins,[10] encouraged us to relate this strategy to readily prepare mannopyranoside from glycals in one-pot. We anticipated that *in situ* generation of RuO_4 from a combination of reagent system $RuCl_3$/$NaIO_4$ would promote oxidative dihydroxylation of C(2)-C(3) olefin, which in turn could be obtained by $RuCl_3$-catalyzed glycosylation of corresponding glycal in preceding step.

To test this hypothesis, the glycosylation reaction of 3,4,6-tri-*O*-acetyl glucal (**1**) with benzyl alcohol (**2a**) was performed in the presence of 5 mol% $RuCl_3$ in acetonitrile at room temperature. To our delight, the reaction proceeded smoothly and complete conversion was realized within 10 min to afford corresponding 2,3-unsaturated glucoside with high stereoselectivity in favour of α-anomer. Subsequently, the crucial *in situ* dihydroxylation of resultant C(2)-C(3) olefin in pyran ring was achieved by introducing aqueous solution of $NaIO_4$ as secondary oxidant in the presence of catalytic amount of $CeCl_3.7H_2O$ at 0°C. Although, complete conversion of glycal (**1**) to 2,3-*syn*-diol (**3a'**) was observed in 10 min,[11] the *in situ* dihydroxylation of anomeric mixture of 2,3-unsaturated glucosides afforded α-D-mannopyranosides (**3a'**) as major product in 92% yield along with trace amount of epimeric β-allopyranoside (**4a'**) as another product (Table 1, entry1).

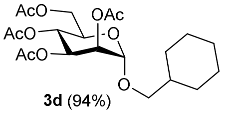
Table 1 Screening of ruthenium-catalyzed glycosylation/dihydroxylation in one-pot[a]



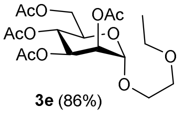
Entry	R₁OH	Time (1,2)[b]	Yield (%)[c]	α-manno/β-allose[d]
1	BnOH **2a**	10,10 min	92	>89:11
2	 **2b**	30, 10 min	88	>96



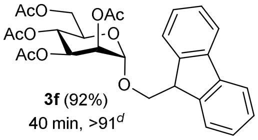
3c (90%)
30 min, >96[d]



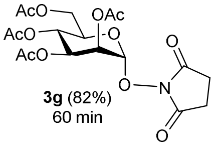
3d (94%)
35 min, >96[d]



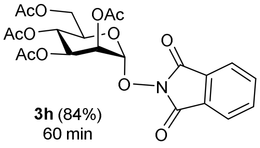
3e (86%)
30 min, >93[d]



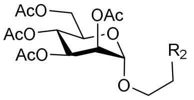
3f (92%)
40 min, >91[d]



3g (82%)
60 min



3h (84%)
60 min



3i; R_2 = Cl, (80%), 20 min, >91[d]
3j; R_2 = NHCbz, (84%), 30 min, >92[d]

[a] Reaction conditions:**1** (1.0 equiv), R_1OH (1.2 equiv.), $RuCl_3$ (5.0 mol%), CH_3CN (2 mL), EtOAc (2 mL), $NaIO_4$ (1.5 equiv.), H_2O (1 mL), $CeCl_3.7H_2O$ (5.0 mol%). [b]Time required for glycosylation(1)-dihydroxylation (2). [c]Isolated and un-optimized yields over 2 steps. [d]The ratios were analyzed by ^1H NMR spectrum.

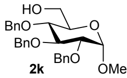
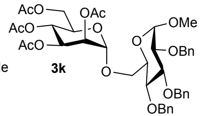
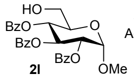
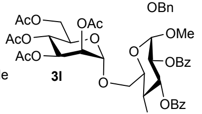
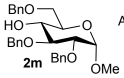
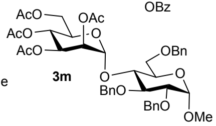
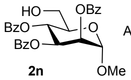
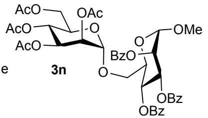
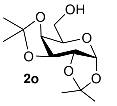
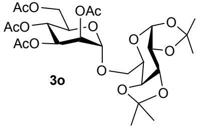
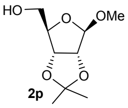
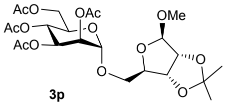
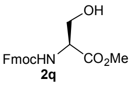
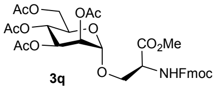
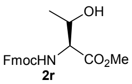
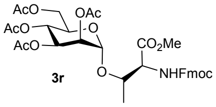
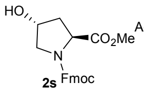
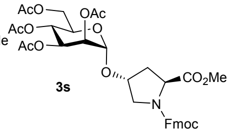
Noteworthy, anomeric activation of glycal donor in glycosylation step would have a significant influence on the stereochemical outcome in the dihydroxylation reaction. For instance, the glycosylation reaction of **1** with a secondary alcohol such as L-menthol (**2b**) and subsequent *in situ* dihydroxylation resulted menthyl-α-D-mannopyranoside (**3b'**) as a major product (dr, >96) in 88% yields over 2 steps. (Table 1, entry 2). The ^1H NMR spectrum of **3a'** reveals the presence of characteristic resonance due to anomeric proton of α-D-mannopyranoside at δ 4.98 (s, 1H), whilst resonance of benzylic protons of were observed at δ 4.72 and 4.54 (each d, J = 11.8 Hz, each 1 H, -CH_2Ph), however, corresponding chemical shifts for minor epimer **4a'** were identified at 4.78 and 4.62 (each d, J = 7.8 and 11.8 Hz, each 0.12H, -CH_2Ph).[12] Furthermore, the ^{13}C spectrum ambiguously proved the presence of anomeric carbon at δ 98.8 whereas minor peak at δ 99.4 further confirmed the product with high selectivity in favour of α-mannopyranoside. On the other hand, the dihydroxylation of 2,3-unsaturated benzyl α-glucoside with catalytic OsO_4,[10f,g,13a] isoelectronic to RuO_4 and relatively more toxic, usually takes 2 days to afford corresponding *cis*-diol (**3a'**) in moderate yield.[14] Acetylation of 2,3-*syn*-diols with acetic anhydride in the presence of pyridine and catalytic amount of DMAP in dichloromethane as the solvent afforded the corresponding per-acetylated glycosides (**3a-3j**) in quantitative yields. The spectroscopic analyses indicate that dihydroxylation occurred in highly stereocontrolled manner depending on anomeric configuration of the Ferrier product.

The stereochemistry of newly formed stereocenters in compound **3a** was precisely correlated by spectroscopic analysis and compared with literature data.[13b] In the ^1H NMR spectrum of **3a**, presence of resonance due to anomeric proton at δ 4.89 (d, J_{1-2} = 1.2 Hz) and chemical shifts of other sugar protons at δ 5.38 (dd, J_{3-4} = 10.1 Hz, H-3), 5.30 (dd, J_{4-5} = 10.2 Hz, H-4), 5.29 (dd, J_{2-3} = 3.5 Hz, H-2) with distinctive coupling constant verified the *trans*-diaxial, *trans*-diequatorial or *cis*-(e,a) relationship between adjacent protons. In the proton-decoupled carbon spectrum of **3a**, the anomeric carbon was observed at 96.7 ppm whilst resolved signals for C(2)-C(6) were identified in between 60 and 70 ppm. In addition, compound **3a** gave satisfactory MS/HRMS analysis [HRMS (ESI) *m/z* [M + $NH_4]^+$ calcd. for $C_{21}H_{20}O_{10}N^+$: 456.18842; found: 456.18803]. The overall spectroscopic data of benzyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (**3a**) consistent and with conformity that of observed in later experiment.[14]

To probe the scope of above-mentioned method, a range of acceptors comprising alicyclic (**2c**,**2d**), 2-ethoxyethanol (**2e**), and 9-fluorenemethanol (9FM, **2f**), were successfully coupled with glycal in one-pot method to obtain various functionalized mannopyranosides in good yields (Table 1). In contrast, hydroxylamine derivatives such as *N*-hydroxysuccinimide (**2g**) and *N*-hydroxyphthalimide (**2h**), underwent glycosylation in highly stereoselective manner to generate corresponding α-O-mannosylhydroxylamine derivatives (**3g**,**3h**) in high yields with exclusive α-selectivity. A facile deprotection of phthalimide group would generate *O*-aminoxy-mannosyl, wherein the presence of aminoxy moiety at sugar anomeric center offers further synthetic value in constructing neoglycoconjugates of biological significance.[15]

Additionally, the glycosylation-dihydroxylation reaction of **1** with 2-chloroethanol (**2i**) and 2-amino-alcohol (**2j**) proceeded smoothly to produce corresponding mannosides comprising 2-chloro/amino-ethyl linkers at anomeric center (**3i**,**3j**). Notably, the glycosides containing spacers or linkers are often utilized in the chemical ligation of sugars to various biomolecules and serves as valuable building blocks of *N*-linked glycan core.[16] Therefore, this approach seems to be advantageous to obtain modified-carbohydrate scaffolds, generally known as glycomimetics.[17] Next, we focused on glycosylation of sugar-derived acceptors to access disaccharide containing mannose. Thus, various acceptors comprising glucose, mannose, galactose, ribose sugar (**2k-p**) were successfully glycosylated under present reagent system at ambient temperature to generate variety of α-(1→6, 1→5, 1→4)-linked disaccharides containing mannose (**3k-p**) in stereoselective manner (Table 2, entries 1-6).

Table 2 Direct access to α-D-mannopyranosides from glucal[a]

Entry	Acceptor	Product	Time[b]	Yield (%)[c] α-manno/β-allose[d]
1	 2k	 3k	60 min	70% >90
2	 2l	 3l	45 min	74% >89
3	 2m	 3m	80 min	66%
4	 2n	 3n	40 min	76% >88
5	 2o	 3o	30 min	72% >88
6	 2p	 3p	40 min	68% >88
7	 2q	 3q	30 min	86% >87
8	 2r	 3r	40 min	76% >90
9	 2s	 3s	60 min	70%

[a]Reaction conditions: see general experimental procedure. [b]Time required for glycosylation (1)-dihydroxylation (2). [c]Isolated and un-optimized yields over 2 steps. [d] The ratios were based on relative integration of separable protons in ^{1}H NMR spectrum.

The gaining impetus of mannosylated peptides constructs[18] in Nature has motivated us to investigate glycosylation of serine and threonine to incorporate mannose into peptide. Therefore, coupling of Fmoc-Ser-OMe (**2q**) and Fmoc-The-OMe (**2r**) with glucal **1** was accomplished under ruthenium promoted tandem glycosylation-dihydroxylation to obtain mannosylated peptides (**3q**,**3r**) in good yields (Table 2, entry 7,8). Encouraged by these results, we envisioned a robust and straightforward synthetic route for Hyp-functionalized mannose. Thus, ruthenium mediated glycosylation/dihydroxylation of glycal with N-α-fluorenylmethoxycarbonyl-*trans*-4-hydroxy-L-proline methyl ester (Fmoc-Hyp-OMe) as glycosyl acceptor resulted venerable α-linked mannoside (**3s**) in satisfactory yield as a mixture of rotamers.[19] Nevertheless, the use of present reagent system highlights the stereoselective transformations of glucal to α-D-mannopyranosides with high yield in one-pot procedure[20] and likely to find applicability in oligosaccharide and glycoconjugate syntheses.

To rationalize the stereochemical outcome in sequential glycosylation-dihydroxylation method, a plausible pathway could be proposed based on literature precedent on glycosylation[9g] and *cis*-dihdroxylation[10] (Figure 3). The predominant formation of axial anomer in first step attributed to dominant anomeric effect and equilibrium between kinetic and thermodynamic oxocarbenium intermediate. Subsequent oxidation of Ru(III) to Ru(VIII) in the presence of IO_4^- followed by [3+2]-*syn*-cycloaddition of RuO_4 to the C(2)-C(3) olefin from the less sterically hindered face, then oxidation following hydrolytic dissociation of Ru-complex will provide desired α-D-mannose epimeric *cis*-diol as major product.

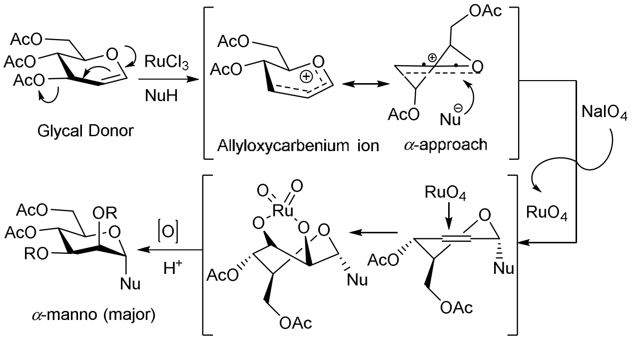


Figure 3 Mechanistic representation of ruthenium-catalyzed glycosylation/dihydroxylation.

In summary, we demonstrated an efficient and convenient ruthenium-catalyzed highly α-selective glycosylation and *syn*-dihydroxylation to obtain α-D-mannopyranosides in one-pot. Usefulness of this method has been highlighted in the glycosylation of diverse range acceptors comprising sugar and amino-acid derived alcohols to incorporate mannose in disaccharides and peptides. Considering the ready availability of starting materials and the exceptional versatility of glycals, this economical and eco-friendly ruthenium reagent system should contribute significantly in glyco-chemistry. The insights outcome of present protocol to access N-/C-linked glycosides constitutes exploiting Ru-catalysis is currently under investigation.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [General synthesis information and ^{1}H NMR, ^{13}C NMR spectra, IR spectra and MS/HRMS data of all the products are provided]. See DOI: 10.1039/b000000x/

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12 See supporting information.

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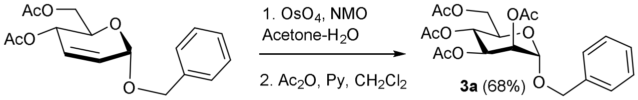

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20 **General experimental procedure for Ru-catalyzed one-pot glycosylation/dihydroxylation method:** (1) To a stirred solution of 3,4,6-tri-*O*-acetyl-D-glucal **1** (1 equiv) and acceptor (1.2 equiv) in anhydrous acetonitrile (2 mL/mmol) under an atmosphere of argon was added $RuCl_3$ (10 mol%) at room temperature. The reaction mixture was stirred until the complete consumption of the starting material (glycal), adjudged by TLC. (2) The reaction mixture was cooled at 0 °C and diluted with EtOAc (2 mL). An aqueous solution of $NaIO_4$ (1.5 equiv) and $CeCl_3.7H_2O$ (5 mol%) in 1 mL H_2O was added to above mention reaction and stirred vigrously. The reaction deemed complete by TLC in utmost 10 min to obtain corresponding diols. The reaction was quenched with saturated $NaHCO_3$ (10 mL), diluted with EtOAc (10 mL), and extracted with EtOAC (3 X 30 mL). The combined organic layes were washed with brine solution, dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by silica gel coloumn chromatography (Hexanes-EtOAc 2:1). Following acetylation of diol in CH_2Cl_2 (5 mL), pyridine (0.5 mL), and acetic anhydride (5 equiv) in the presence of catalytic amount of DMAP gave corresponding per-acetylated glycoside. Following usual work-up and purification by chromatography (silica gel, hexanes-EtOAc) afforded desired α-D-mannopyranosides (**3a-s**) as major product in good yields. All the compounds were confirmed by ^{1}H NMR, ^{13}C NMR and MS/HRMS spectroscopy and overall data were in complete agreement with the assigned structure.