Research article Available online www.ijsrr.org ISSN: 2279–0543

International Journal of Scientific Research and Reviews

Metal Catalyzed Stereo Selective Synthesis of Chiral Sugar-Based Glycosides

Samiran Halder

Department of Chemistry, Charuchandra College, Kolkata-700029, India
email: samiran14cd@gmail.com

ABSTRACT

Glycal- the C_1-C_2 double bonded aldose is one of the most convenient chiral synthons in synthetic chemistry. Simple sugars Glucose, Galactose can be easily converted into a variety of glycals which are valuable starting materials for highly stereo controlled synthesis of optically pure compounds. 2-*C*-Formyl glycals is a special class of carbohydrate compounds possessing conjugated enyloxy carbonyl functional groups react with allyloxysilane in presence of metal Lewis acids catalyst like Indium(III) chloride can install allyl alcohol at C_3 to achieve *C*-3-*O*-allyloxy glycosides products with excellent chemo- regio- and stereo selectivity. $InCl_3$ reveals outstanding catalytic efficiency for this glycosylation reaction to afford only the C-3-*O*-allylated anomers in excellent yield (90%).All the target compounds were characterized byFT-IR, NMR spectral and HR-MS data.

KEYWORDS: Glycal, glycosylation, allyloxysilane, anomers, chiral synthons, NMR Spectroscopy

***Corresponding author:**

Samiran Halder

Department of Chemistry,

Charuchandra College,

Kolkata-700029, India

email: samiran14cd@gmail.com

INTRODUCTION

Carbohydrates are the most abundant organic compounds occurring in the Nature. They play vital role in the biological processes[1,2] among which the cell recognition or cell-antigen interactions are particularly important. Ease availability, their multichiral architecture and well-defined stereochemistry have made them attractive precursors in organic synthesis. Carbohydrate derivatives are used during the last few decades as 'chiral pool' constituents in the enantioselective synthesis of biologically active compounds. In chiron approach the sugar skeleton is incorporated into the target molecule.[3,4]

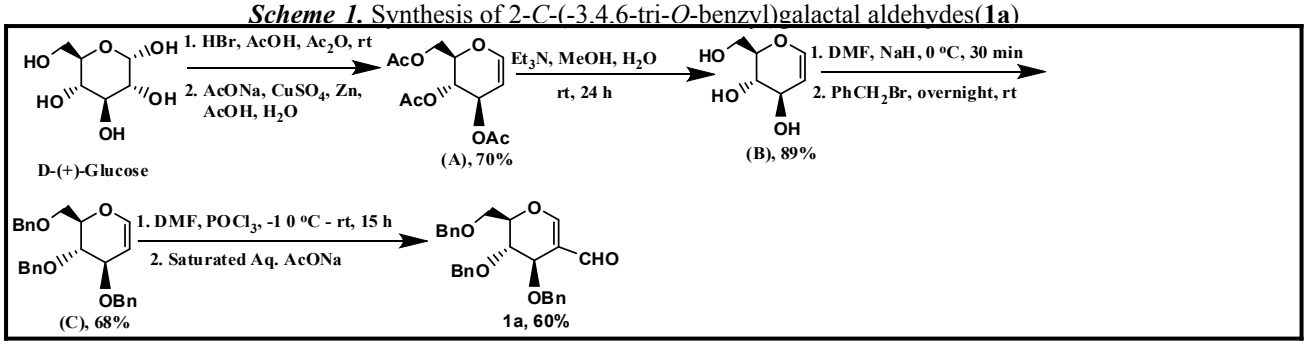
These compounds are of major significance in synthesis because of the wide range of biologically important compounds that can be obtained from them by addition and other chemical processes.[5,6]The presence of an α,β-unsaturated carbonyl moiety has extended the versatility of 2-*C*-formyl glycals as potential synthons. Synthesis of *C*-3-*O*-allyl-2-*C*-formyl glycals are under taken toward synthesis of sugar-based new chiral heterocycles involving metal catalyzed π-bond activation and cyclization process.[7]2-*C*-Formyl glycals bearing an α,β-unsaturated system are ideally suitable for Michael reaction, but they do not undergo either acid- or base-catalyzed Michael addition reactions with alcohols or phenols under standard reaction conditions. Interestingly, Lewis acid catalyzed glycosylation of the formyl glycals is known in the literature.[8]More than stoichiometric amount of BF_3 and $ZnCl_2$ (5 equivalent) are used to afford only the *C*-3-*O*-glycosides involving displacement of the C_3-substituent. I am also looking for a chemoselective catalytic system under mild and acid free reaction conditions toward the new chiral *C*-3-*O*-glycosides as there are some weaknesses in the current glycals system.[9-12]Indium(III) chloride, which is a relatively strong Lewis acid, has been used as a catalyst for a wide variety of organic reactions.

MATERIALS AND METHODS

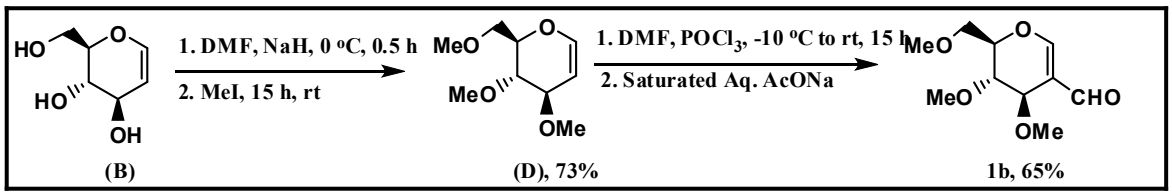
Material Synthesis:

Synthesis of 2-C-formyl-3,4,6-tri-*O*-benzyl-/methyl glycals (1a-d): 2-*C*-Formyl-glycal aldehydes (glucal and galactal) were synthesized as depicted in Scheme 1–Scheme 4. Glucose and galactose were converted into the corresponding glycal acetates upon treatment of dry HBr-AcOH and Zn-Cu couple. These glycal acetates were hydrolyzed and protected through alkylation (benzyl and methyl) after formation of alkoxide using NaH in DMF. They were subsequently converted into the corresponding 2-*C*-formyl glycals (**1a**, **1b**, **1c** and **1d**) by Vilsmeier-Haak reaction.[9,13]

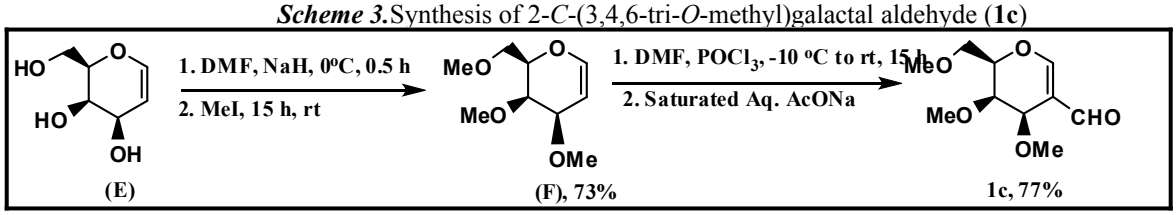
Scheme 1. Synthesis of 2-*C*-(-3,4,6-tri-*O*-benzyl)galactal aldehydes(**1a**)



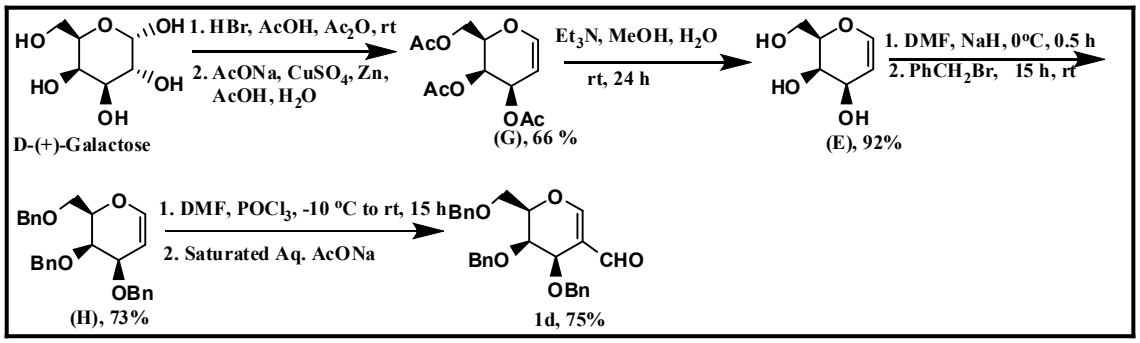
Scheme 2. Synthesis of 2-C-(3,4,6-tri-O-methyl)glucal aldehyde (**1b**)



Scheme 3.Synthesis of 2-*C*-(3,4,6-tri-*O*-methyl)galactal aldehyde (**1c**)



Scheme 4.Synthesis of 2-*C*-(-3,4,6-tri-*O*-benzyl)galactalaldehyde (**1d**)



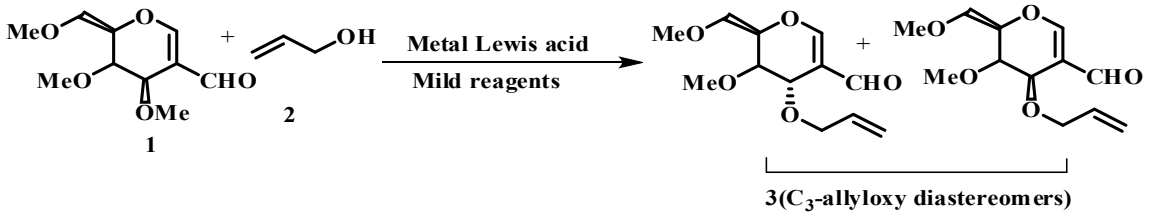
RESULTS AND DISCUSSIONS

Installation of Allyloxy Group to 2-C-Formyl Glycals:

From the beginning, glycosylation reaction of 2-*C*-formyl glycal (**1**) is investigated using metal Lewis acid catalysts which can install allyl alcohol (**2**) at C_3 to achieve *C*-3-*O*-allyloxy products (**3**) with excellent chemo- regio- and stereoselectivity. Stereoselective synthesis of the two possible isomeric chiralsugar-based synthons of C-3-*O*-allyl-2-*C*-formyl glycals is under taken (Scheme 5). It is expected that choice of proper metal catalyst can chelate preferentially either sugar-

ring oxygen or aldehyde oxygen to incorporate allyloxy group to direct displacement of the OR group at the C_3 position. Herein, role of the Lewis acid is to guide the position as well as orientation of the incoming nucleophile to afford chiral synthons with high selectivities.

Scheme 5.Strategy for the synthesis of C-3-*O*-allyl-2-*C*-formyl glycals

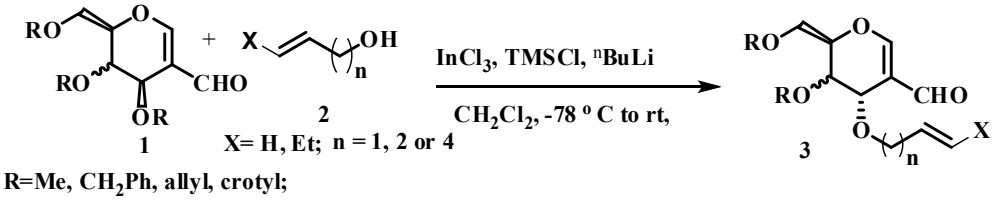


Development and Optimization of the Reaction:

The glycosylation reaction of (-)-3,4,6-tri-*O*-methyl-2-*C*-formyl-D-glucal (**1b**) with allyloxysilane is chosen as model reaction (Scheme 5). However, allyloxysilane is prepared *in situ* using ^{n}BuLi at -78 °C and TMSCl in dichloromethane. After used various metal catalysts I have foundIndium(III) chloridean excellent catalyst to maximize the yields as well as to enhance the chemo-, regio- and stereoselectivity of this glycosylation reaction . It has also afforded the most desired regioisomer **3.** $InCl_3$ reveals outstanding catalytic efficiency for this glycosylation reaction to afford only the C-3-*O*-allylated anomers (**3**) in excellent yield (90%). Besides anomeric selectivity; the yield is also very high. After extensive studies polar aprotic solvent dichloromethane is found as ideal reaction medium for the chemical process.In the case of2-*C*-formyl galactal I have found only *C*-3-*O*-glycosides with exclusive formation of α-diastereomer.

Synthesis*C*-3-*O*-allyl-2-*C*-formyl glycal glycosides:

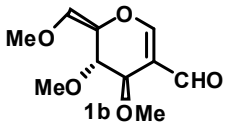
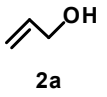
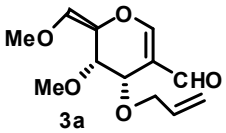
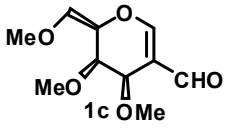
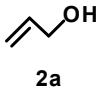
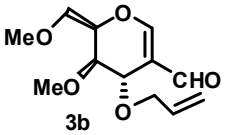
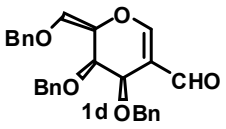
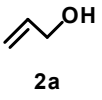
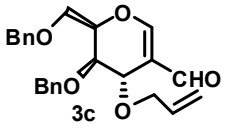
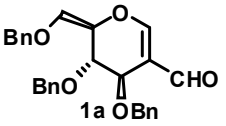
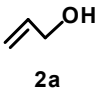
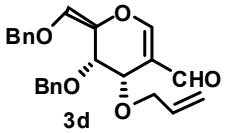
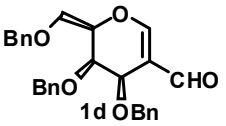
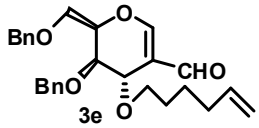
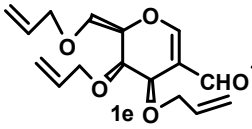
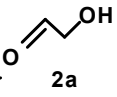
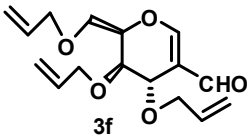
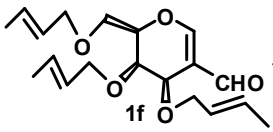
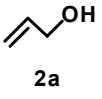
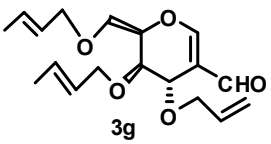
Scheme 6. Synthesis C-3-O-allyl-2-C-formyl glycals



With this initial success, the versatility of the benign synthetic approach is examined using various 2-*C*-formyl glycals and allyl alcohols (Scheme 6). The results are shown in Table 1. The metal catalyzed (3-5 mol%) glycosylation reaction is studied to furnish *C*-3-*O*-allylated products with good regio- and stereoselectivity. The reaction rates are usually fast (3.0-5.0 h) and high yielding (81-90%). Methyl (entries 1, 2 of Table 1), benzyl (entries 3, of Table 1), allyl (entry 5,

Table 1) and crotyl (entry 6, Table 1) protected 2-*C*-formyl glycals systems are tolerated in the synthetic protocol developed under the mild reaction conditions. $InCl_3$have smoothly transformed the precursors to the desired *C*-3 glycosylated products (Table 1) with comparable yield and stereoselectivity. $InCl_3$have produced only the *C*-3 substituted products (Table 1). Other alcohol with double bond is also installed exclusively at *C*-3 (entry 5, Table 1).

Table 1: Experimental data of*C*-3-*O*-alkyl-2-*C*-formyl glycosides

Entry	Aldehyde	Alcohol	Glycoside	ML_n	Time(h)	Yield(%)
1.	 1b	 2a	 3a	$InCl_3$	4.0	90
2.	 1c	 2a	 3b	$InCl_3$	3.5	86
3.	 1d	 2a	 3c	$InCl_3$	4.5	82
4.	 1a	 2a	 3d	$InCl_3$	4.0	81
5.	 1d	 2c	 3e	$InCl_3$	5.0	86
6.	 1e	 2a	 3f	$InCl_3$	5.0	84
7.	 1f	 2a	 3g	$InCl_3$	4.5	81

In these experiments, two closely moving spots are appeared in the TLC (almost identical R_f) of the post reaction mixture which are due to the presence of corresponding*C*-3-*O*-allyl-2-*C*-formyl glycosides. The products is determined by NMR methods after purification by column chromatography. A number of new chiral synthons synthesized in this mild catalytic approach are the potential candidates for construction of valuable chiral heterocyclic scaffolds like chiral pyranopyran and others.[5]

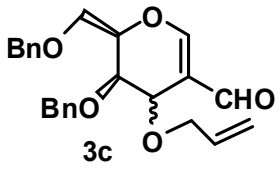
General experimental procedure for preparation of*C*-3-*O*-allyl-2-*C*-formyl glycoside:

Synthesis of (2R,3R,4S)-4-(allyloxy)-3-(benzyloxy)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyran-5-carbaldehyde (3c) :

Allyl- and other unsaturated alcohols (**2**,1.0 mmol) was taken in DCM (3.0 mL) under argon atmosphere and ^{n}BuLi (1.6M) was added dropwise at -78 ºC. After 20 min., TMSCl (1.5 mmol), 2-*C*-formyl glycal (**1**) and Lewis acid catalyst $InCl_3$(2-3 mmol) were added and the content of the reaction mixture was allowed to room temperature. Progress of the reaction was monitored by TLC and it was complete in 4.5h. The diastereoisomers were isolated after purification through MPLC (Eyela; Column: 50x2.5cm; flow rate: 3mL/min; silica gel: 230-400mesh; Eluent: 9-11% EtOAc/pet. ether). Thus, the reaction of 2-*C*-formyl-3,4,6-tri-*O*-benzylgalactal (**1d**, 444 mg, 1.0 mmol) with Prop-2-en-1-ol (**2a**,58 mg,1.0 mmol)afforded(2R,3R,4S)-4-(allyloxy)-3-(benzyloxy)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyran-5-carbaldehyde (**3c**) after processing in an isolated yield of 82% (323 mg, 0.82 mmol).

Characteristic data:

Compound **3c**



Yield:82% (323 mg, 0.82 mmol).

Characteristic: Colorless viscous liquid.

$[\alpha]_D^{25}$ +102.9º (*c* 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.65 (1H, dd, *J* = 6.0, 9.0 Hz), 3.74 (1H, s), 3.84 (1H, dd, *J* = 6.0, 3.0 Hz), 4.09 (2H, d, *J* = 6.0 Hz), 4.35-4.63 (6H, m), 5.14-5.29 (2H, m), 5.82-5.95 (1H, m), 7.21-7.46 (11H, m), 9.39 (1H, s).

^{13}C NMR (75 MHz, $CDCl_3$): δ 62.9, 68.3, 70.4, 70.6, 72.1, 73.5, 75.8, 117.1, 118.0, 127.8, 128.0, 128.1, 128.4, 128.5, 134.7, 137.1, 137.5, 166.0, 190.2.

FT-IR (neat, cm^{-1}): 921, 1072, 1220, 1455, 1624, 1672, 2734, 2858, 2921, 3030, 3439.

HR-MS (*m/z*) for $C_{24}H_{27}O_5$ (M+1): Calculated 395.1780, Found 395.1770.

CONCLUSIONS

2-*C*-formyl-glycal synthons are synthesized by glycosylation reaction of 2-*C*-formyl glycals in presence of commercially available metal catalysts $InCl_3$with low catalytic loading (3-5 mol%).

Allyl and functionalized alcohols are successfully converted into corresponding allyloxysilanes and the glycals are glycosylated *in situ* in highly chemo-, regio- and stereoselective fashion. The reaction is fast and high yielding. The regioselection is quite different from the normal glycosylation reaction in presence of Lewis acid. A number of new sugar-based chiral synthons are synthesized for the first time which are the potential candidates for construction of new chiral heterocycles like pyranopyran, fused-pyranopyran etc. The proposed model of the mechanistic pathway for the reaction is also outlined to explain the unusual stereoselectivity toward construction of the chiral building blocks.

ACKNOWLEDGEMENTS

I am grateful to Dr. Mominul Sinan& Dr. Parimal Routh (Charuchandra College) for helping me to prepare the manuscript and Professor.Dilip Kumar Maiti, Dept. of Chemistry, University of Calcutta for providing his laboratory facilityand financial support.

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