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Highly Efficient Stereoselective Glycosylation of β-Citronellol

Ram Naresh Yadav[1,2], Saima Sardar[1] and Bimal Krishna Banik[1,3,✉]

ABSTRACT

Stereoselective synthesis of terpene alcohol, β-citronellol is achieved in excellent yield by molecular iodine- and indium salts-catalyzed reactions with protected glycal and protected bromo sugar derivatives.

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KEYWORDS

Glycosylation, Alcohol, Terpene, Catalysis

INTRODUCTION

Glycosylation of alcohols with glycal and bromo sugar is a fascinating area of research. In general, this reaction requires catalyst to activate the alkene bond in glycal and the bromo group present in sugar derivatives. Our research on glycosylation of alcohols is proved to be highly important in diverse areas. Specifically, molecular iodine-catalyzed reaction of racemic and optically active 3-hydroxy β-lactams with glycal is described [1-7]. In addition, indium metal is found to be an excellent promoter in the stereospecific glycosylation of bromo sugar with different alcohols [8-12]. It is important to mention that molecular iodine-catalyzed reactions afford α-glycosides as the only products. In contrast, indium-induced reactions produce β-glycosides as the only products. Therefore, we have access of several medicinally important α-and β-glycosides through simple but mechanistically unique methods. In this communication, efficient stereoselective glycosylation β-citronellol by molecular iodine- and indium salts-catalyzed reactions is described [13-36]. The possible mechanistic routes of these methods are also advanced.

RESULTS AND DISCUSSION

Following our research on β-lactams and to connect glycosylation on our current research, this study described herein was undertaken [37-43]. Reaction of glycal **1a** with β-citronellol **2** in the presence of molecular iodine produced α-glycoside **3a** as the major isomer in 70-80 % yield (**Scheme-I** and Table-1). The presence of the other isomer **3b** was detected. An identical reaction between **1b** and **2** failed to produce any glycosides **4a** or **4b**. The only differences between **1a** and **1b** were the nature of the protective groups present in these two molecules.

Author affiliations:

[1]Department of Chemistry, The University of Texas-Pan American, 1201 West University Drive, Edinburg, TX 78539, USA
[2]Department of Chemistry, Faculty of Engineering & Technology, Veer Bahadur Singh Purvanchal University, Jaunpur-222 003, India
[3]Current Address: Vice President, Community Health Systems of South Texas, Edinburg, Texas 78539, USA

✉To whom correspondence to be addressed:

E-mail: bimalbanik10@gmail.com; bimal.banik@chsst.org

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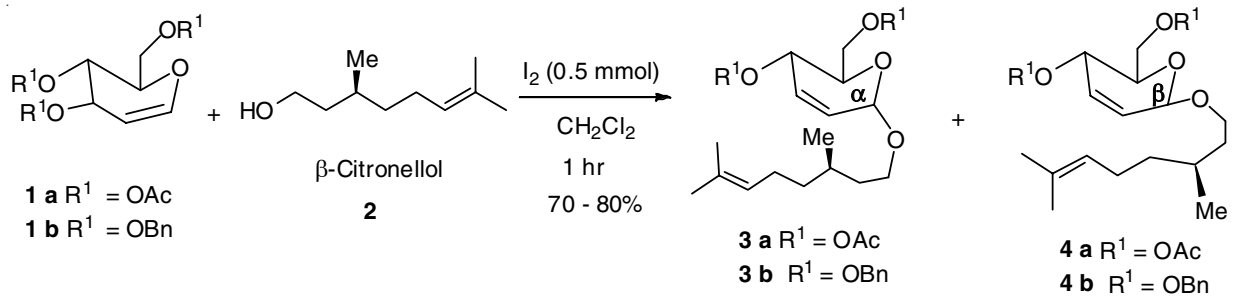


Scheme-I: Iodine catalyzed O-glycosylation of D-glucal derivatives with terpene alcohol

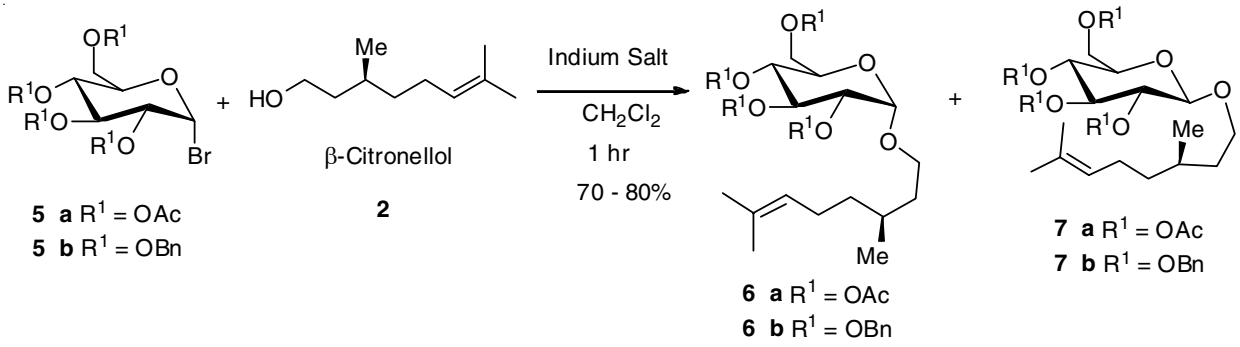
TABLE-1

Entry	Glycosyl donar	Glycosyl accepter	Activator/ promoters	Solvent(s)	Time (h)	Yield[a] (%)	a:b[b] ratio
1	**1a**	2	I_2	CH_2Cl_2	1.5	70-80	8:2
2	**1b**	2	I_2	CH_2Cl_2	5	Trace	–

[a]Isolated yield after column chromatography purification. [b]Anomeric ratio determined by the ^{1}H NMR spectroscopy of the crude reaction mixture.

Reaction of bromosugars **5a** and **5b** with **2** in the presence of indium bromide produced predominantly β-glycosides **7a** and **7b** regardless of the nature of the protective groups in the presence of in the sugar derivative (**Scheme-II** and Table-2). The yield of the product **7b** with **5b** was poor and this reaction was non-stereoselective: an identical ratio of α- and β-glycosides were formed.

The anomeric oxygen in the sugar unit was capable of expel bromine (halogen) of the bromo sugar derivative in the presence of activator (Lewis acid) (**Scheme-III**). Indium was

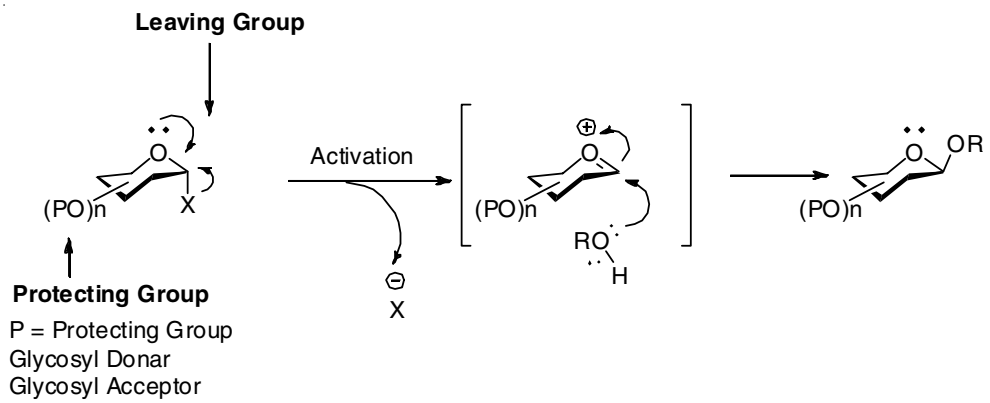


Scheme-II: Indium salt catalyzed O-glycosylation of bromo_D-glucose derivatives with terpene alcohol

TABLE-2

Entry	Glycosyl donar	Glycosyl accepter	Activator/ promoters	Solvent(s)	Time (h)	Yield[a] (%)	a:b[b] ratio
1	**5a**	2	$InBr_3$	CH_2Cl_2	1	80	1:9
2	**5b**	2	$InBr_3$	CH_2Cl_2	3	60	1:1

[a]Isolated yield after column chromatography purification; [b]Anomeric ratio determined by the ^{1}H NMR spectroscopy of the crude reaction mixture.



Scheme-III: General mechanism of glycosylation of β-halosugar

the activator in this reaction. This process resulted in the generation of highly reactive oxenium ion. A nucleophilic attack to this oxenium ion was possible to obtain a mixture of glycosides. Because of the higher stability of the β-glycoside, this isomer became the major product. This mechanism was further strengthened by the fact that the acetoxy protecting group produces the major compound as β-isomer compared to benzyl ether (**Scheme-IV**). A 3-acetoxy group was helpful to form cyclic carbocation species with the anomeric carbon through a neighboring group participation act mechanism. Such neighbouring group participation was not possible with the benzyl ether. At the end, a nucleophilic attack by the alcohol through route "a" produced the β-isomer which has the *trans* 1, 2 system. An attached through route "b" produced the *cis* α-isomer.

The products formation through molecular iodine-catalyzed reaction was explained in **Scheme-V**. The glycal in the presence of iodine as promoter formed the oxo-carbenium species through a displacement of the substituent present in C-3-position. An attack by the alcohol following route "a" produced α-isomer as the main product because this is the most stable isomer. An attack following route "b" was also possible to obtain β-glycoside. However, this route was less favourable because of the serious interaction of the non-bonded electrons that are present in the anomaric oxygen and the nucleophile. Moreover, because of the weak leaving group properties of the benzyl group present at C-3-position in glycal, it was obvious that the reaction becomes slow (or impossible to occur) with **1b**.

Conclusion

A facile and excellent method is developed for the stereoselective synthesis of oxygen glycosides of β-citronellol. The resulting products are highly functionalized and therefore, numerous useful chemical transformations can be performed for the preparation of complex organic molecules with complete stereochemistry control. Further, this method can be applied to several other natural products that have diverse functionalities in their structures.

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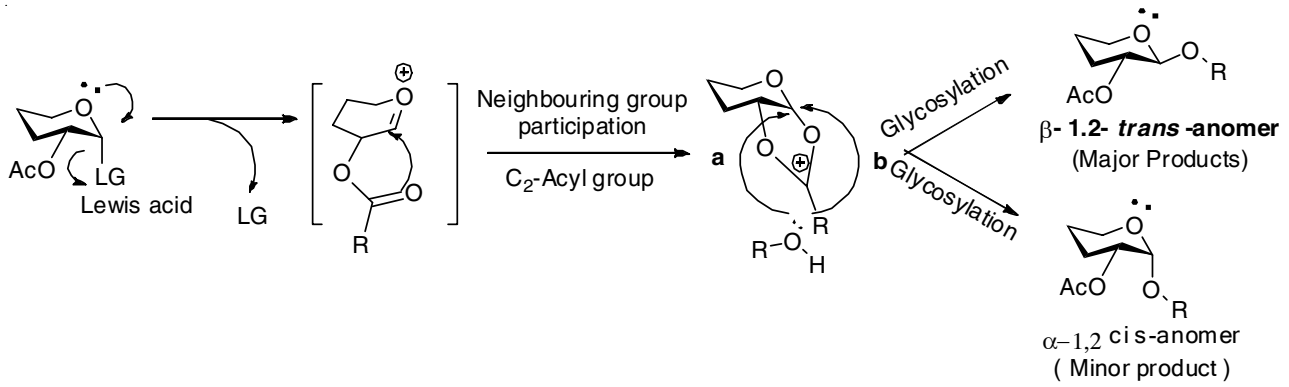
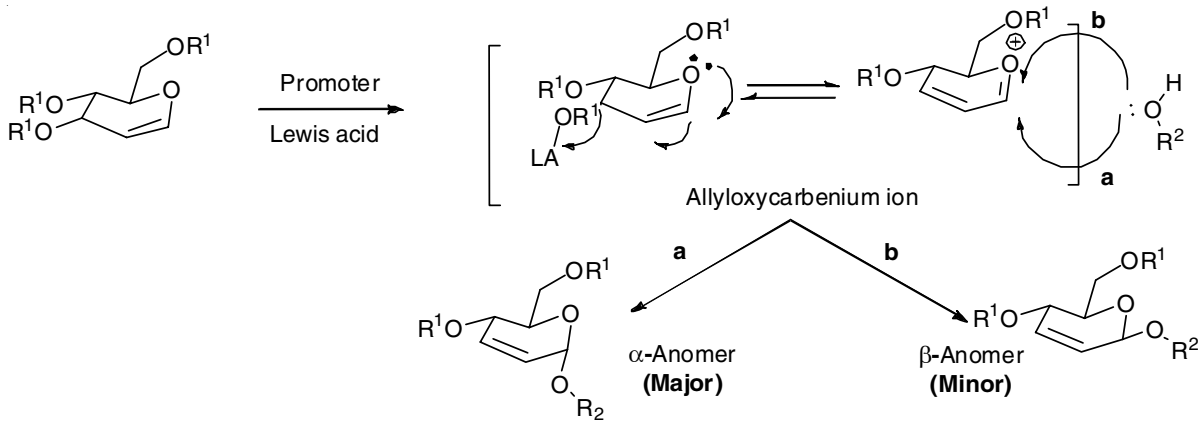


Scheme-IV: Mechanism of neighbouring participation. A route for the synthesis of 1,2-*cis* (α) and 1,2-*trans*(β) anomer



Scheme-V: Mechanism of ferrier type of O-glycosylation of tri-O-acetyl-D-Glucal. An α-anomeric selectivity

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