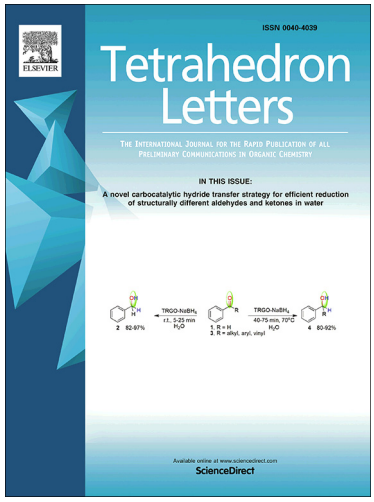


Simple and Mild Stereoselective *O*-Glycosidation using 1,2-Anhydrosugars Under Neutral Conditions

Devaraj Somasundaram, Kalpattu K. Balasubramanain, Bhagavathy Shanmugasundaram

PII: S0040-4039(19)30085-1
DOI: https://doi.org/10.1016/j.tetlet.2019.01.049
Reference: TETL 50582

To appear in: *Tetrahedron Letters*

Received Date: 25 November 2018
Revised Date: 19 January 2019
Accepted Date: 23 January 2019

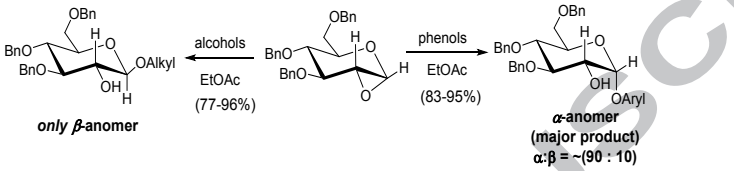
Please cite this article as: Somasundaram, D., Balasubramanain, K.K., Shanmugasundaram, B., Simple and Mild Stereoselective *O*-Glycosidation using 1,2-Anhydrosugars Under Neutral Conditions, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.01.049

Graphical Abstract

Simple and Mild Stereoselective *O*-Glycosidation using 1,2-Anhydrosugars Under Neutral Conditions

Leave this area blank for abstract info.

Devaraj Somasundaram,[a] Kalpattu K Balasubramanian,[b] and Shanmugasundaram Bhagavathy*[a]



ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

Simple and Mild Stereoselective *O*-Glycosidation using 1,2-Anhydrosugars Under Neutral Conditions

Devaraj Somasundaram[a] , Kalpattu K Balasubramanain[b], and Bhagavathy Shanmugasundaram[a]*

[a]*Department of Chemistry, B. S. Abdur Rahman Crescent Institute of Science and Technology, Vandalur, Chennai 600015, India*
[b]*Department of Biotechnology, Indian Institute of Technology Madras, Guindy, Chennai 600048, India*

* Corresponding author. Tel.: +91-044-2275-1347; fax: +91-044-2275-1349; e-mail: bhagavathy@crescent.education

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
1,2-Anhydrosugars
Glycal epoxide
Aromatic glycosylation
Aryl glycosides
Alkyl glycosides

ABSTRACT

The ring opening of *α*-D-1,2-anhydrohexapyranoses with phenols proceeded smoothly in ethyl acetate (neutral conditions) in the absence of metal ion catalysts or additives to stereoselectively furnish 1,2-*cis*-*α*-aryl glycosides as the major product and 1,2-*trans*-*β*-aryl glycosides as the minor product in good yields. Under similar conditions, this ring opening reaction with alcohols afforded exclusively *β*-alkyl glycosides in excellent yields.

1. Introduction

In recent years, aromatic *O*-glycosidation has received considerable attention from both synthetic and medicinal chemists because of their diverse biological activities[1] and pharmaceutical potentials.[2] The recent review by Jacobsen and co-workers has extensively discussed the various methods for the synthesis of aryl glycosides.[3] Glycosyl acetates, phosphates, halides, trichloroacetimidates and sulphoxides are commonly used as glycosyl donors.[4] Free glycals as well as their derivatives with good leaving groups at the allylic position have also been used as glycosyl donors.[5] Although a plethora of methods are available in the literature for *O*-glycosidation, they suffer from limitations such as low yields, poor stereoselectivity and the requirement of catalysts, additives or promoters. Some of these methods are not amenable for large scale production due to cost of the reagents, poor atom economy, long reaction times, high temperature conditions, difficulty in accessing the glycosyl donor or tedious workup procedures.

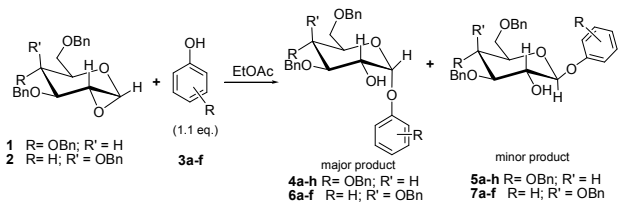
In the case of aryl glycosides it is not easy to obtain good yields because of dimerisation,[6] use of hazardous metal salts[7] and the formation of *C*-glycosides in the case of activated aromatic compounds.[8] The use of 1,2-anhydrosugars as glycosyl donor is well known for the synthesis of alkyl and aryl glycosides.[9] However, most of these cases require either metal salts of the phenol[10] or expensive catalysts/promoters.[11] Few cases lead to a mixture of products resulting in low yields with the requirement of harsh reaction conditions and tedious work up.[12]

In the case of phenols as nucleophiles, the stereochemical course of the ring opening reaction of 1,2-anhydrosugars is largely influenced by an external additive or bases and the electronic nature of the substitutents.[13] Higher selectivity in favour of the *a*-anomer has been reported when the glycosidation was conducted using $ZnCl_2$.[13b] Regio- and stereoselective glycosylation of sugar 1,2-diols and 1,3-diols using catalytic amounts of cyclic boronate esters derived from these diols is also known.[14] To date there have been no reports on the metal ion free, catalyst free and additive/activator free stereoselective synthesis of aryl glycosides at ambient temperature. Herein, we describe a simple and mild stereoselective *O*-glycosidation method using 1,2-anhdyrosugars under neutral conditions.

2. Results and Discussion

The substrates, 1,2-*α*-D-anhydroglucose **1** and 1,2-*α*-D-anhydrogalactose **2** were obtained by the stereoselective epoxidation of 3,4,6-tri-*O*-benzyl-D-glucal and 3,4,6-tri-*O*-benzyl-D-galactal, respectively, *via in situ* generation of dimethyldioxirane using oxone/acetone in a biphasic system as described in the literature.[15] The crude 1,2-anhydrosugars were directly used for further reactions.

Our initial reaction of 1,2-anhydro-3,4,6-tri-*O*-benzyl-*α*-D-glucopyranose **1** with *p*-cresol **3a** in acetonitrile at ambient temperature for 3 h proceeded smoothly to yield *α*-*p*-cresyl 3,4,6-tri-*O*-benzyl-D-glucopyranoside **4a** (1,2-*trans*-adduct) as the major product and *β*-*p*-cresyl 3,4,6-tri-*O*-benzyl-D-glucopyranoside **5a** (1,2-*cis*-adduct) as the minor product (Scheme 1).



1 R= OBn; R' = H
2 R= H; R' = OBn
3a-f
4a-h R= OBn; R' = H
6a-f R= H; R' = OBn
5a-h R= OBn; R' = H
7a-f R= H; R' = OBn

Scheme 1. Ring opening of α-D-1,2-anhydrosugars **1** and **2** with phenols

As the solvent polarity is known to influence the stereoselectivity in glycosidation reactions,[16] we screened various solvents (free of moisture) with different dielectric constants such as CH_2Cl_2, acetonitrile, ethyl acetate (free of acetic acid), acetone, toluene, DMF and DMSO. The ring opening of **1** with *p*-cresol in the above solvents led predominantly to *α*-anomer **6a** as the major product and *β*-anomer **7a** as the minor product (Table 1). Anomeric ratios were determined by HPLC analysis of the crude product.

Among the solvents screened, acetone and ethyl acetate gave the best results in terms of reaction time and yield. Since 1,2-anhydrosugars are prone to slowly open by reacting with trace amounts of moisture,[17] we chose ethyl acetate[18] over acetone to generalize this glycosidation reaction. Although the reaction required a much shorter reaction time in toluene, it was not preferred over ethyl acetate as some of the solid phenols were not easily soluble in toluene and required heating to higher temperatures to obtain a homogenous solution.

Table 1. Reaction of 1,2-anhydrosugar **1** with *p*-cresol

Entry	Solvent	Time (h)	Yield (%)[a]	*α*:*β*[b]
1	CH_2Cl_2	6.5	83	86:14
2	Acetonitrile	12	76	86:14
3	Acetone	6	85	88:12
4	Ethyl acetate	6	94	84:16
5	Toluene	2.15	87	85:15
6	DMF	24	no rxn	-[c]
7	DMSO	24	no rxn	-[c]

[a]Isolated yield after column chromatography; [b]Anomeric ratio determined by HPLC; [c]Incomplete reaction with only decomposed products.

This *cis*-*α*-selective aromatic glycosidation of 1,2-anhydrosugar **1** was generalized with phenols **3a-f** in ethyl acetate (Scheme 1, Table 2).[19] In all cases, the *α*-aryl glycoside **4a-h** was formed as the major product and the *β*-anomer **5a-h** as the minor product. Phenols bearing electron donating substituents as well as electron withdrawing substituents underwent this glycosidation in good yields.

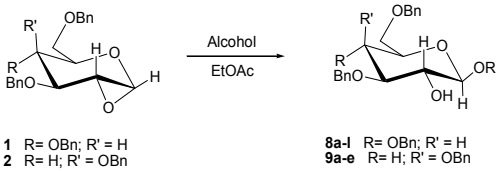
The glycosidation with galacto-epoxide **2** also yielded *α*-aryl galactoside **6a-f** as the major product and *β*-aryl galactoside **7a-f** as the minor product. In the case of phenols **3d**, **3e** and **3g**, trace amounts (<5%) of the hydrolyzed product[17] (1,2-diol) due to moisture was also observed. The workup of this reaction requires only evaporation of the solvent. All the aryl glycosides are known compounds and the spectral data are in accordance with those reported in the literature.[20]

Table 2. Ring opening reaction of **1** and **2** with phenols in ethyl acetate[a]

Entry	Substrate	Phenol	R	Time (h)	Product *α*:*β*	Yield[b] (%)	*Ratio α*:*β*[c]
1	**1**	**3a**	4-Me	6	**4a:5a**	94	84:16
2	**1**	**3b**	H	6	**4b:5b**	95	89:11
3	**1**	**3c**	2-Me	6	**4c:5c**	91	88:11
4	**1**	**3d**	4-F	6	**4d:5d**	83	85:15
5	**1**	**3e**	4-CN	6	**4e:5e**	87	88:12
6	**1**	**3f**	4-OMe	6	**4f:5f**	90	87:13
7	**1**	**3g**	4-NO_2	6	**4g:5g**	86	91:09
8	**1**	**3h**	2-Naphthol	6	**4h:5h**	93	91:09
9	**2**	**3a**	4-Me	6	**6a:7a**	90	93:06
10	**2**	**3b**	H	6	**6b:7b**	91	85:14
11	**2**	**3c**	2-Me	6	**6c:7c**	95	93:07
12	**2**	**3d**	4-F	6	**6d:7d**	88	95:05
13	**2**	**3e**	4-CN	6	**6e:7e**	85	87:13
14	**2**	**3f**	4-OMe	6	**6f:7f**	93	81:19

[a]Reagents and conditions: **1** or **2** (1.0 eq.), phenol (1.1 eq.), EtOAc (1mL), RT; [b]Isolated yield after short wash column chromatography; [c]Anomeric ratio determined by HPLC analysis of the crude product.

Enthused by these findings, we explored this glycosidation methodology for the synthesis of alkyl glycosides. Treatment of 1,2-anhydrosugar **1** with isopropanol in ethyl acetate at ambient temperature for 3 h proceeded smoothly to yield exclusively *β*-isopropylglucoside **8a** (1,2-*trans*-adduct) in 80% yield. The scope was demonstrated by extending it to a number of primary and secondary alcohols. Treatment of 1,2-anhydrosugar **1** with various alcohols (Table 3) in ethyl acetate at ambient temperature proceeded smoothly to afford the corresponding *β*-alkyl glucosides **8a-l** in very good yields (Scheme 2, Table 3);[19] no traces of *α*-alkyl glycosides were observed in these reactions.



1 R= OBn; R' = H
2 R= H; R' = OBn

8a-l R= OBn; R' = H
9a-e R= H; R' = OBn

Scheme 2. Reaction of *α*-D-1,2-anhydrosugars **1** and **2** with alcohols

This reaction was also facile in the case of menthol (Table 3, Entry 11). Even cholesterol was found to undergo glycosidation but required slightly elevated conditions *viz.,* reflux in toluene for 2 h (Table 3, entry 12), which compared favourably to the harsh conditions and low yield reported in the literature.[21] Allylic alcohols and propargyl alcohol (Table 3, entries 6-8) were also suitable substrates. Furthermore, this glycosidation was equally facile in the case of 1,2-anhydro-*α*-D-galactopyranose **2**. The reaction of **2** with alcohols in ethyl acetate gave the corresponding *β*-alkyl galactosides **9a-e** in good yields. All *β*-*O*-alkyl glycosides are known compounds and the spectral data are in accordance with those reported in the literature.[20,22]

Table 3. Reaction of **1** and **2** with alcohols in ethyl acetate[a]

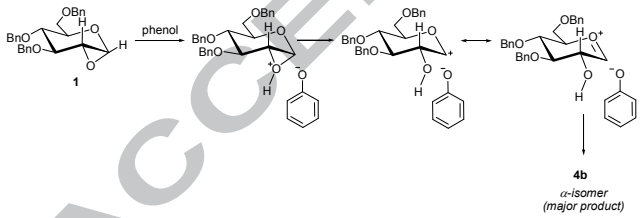
Entry	R-OH	Substrate	Time (h)	Product	Yield[b] (%)	*α*:*β*[c]
1	Isopropanol	**1**	6	**8a**	96	Only *β*
2	Methanol	**1**	6	**8b**	96	Only *β*
3	Ethanol	**1**	6	**8c**	95	Only *β*
4	*n*-Butanol	**1**	9	**8d**	86	Only *β*
5	*t*-Butanol	**1**	6	**8e**	82	Only *β*
6	Allylic alcohol	**1**	8	**8f**	88	Only *β*
7	Cinnamyl alcohol	**1**	6	**8g**	88	Only *β*
8	Propargyl alcohol	**1**	8	**8h**	77	Only *β*

9	Cyclohexanol	**1**	6	**8i**	82	Only β
10	Benzylalcohol	**1**	6	**8j**	95	Only β
11	Menthol	**1**	8	**8k**	88	Only β
12	Cholesterol	**1**	2[d]	**8l**	77	Only β
13	Methanol	**2**	5	**9a**	88	Only β
14	Isopropanol	**2**	6	**9b**	92	Only β
15	Ethanol	**2**	6	**9c**	95	Only β
16	Allylic alcohol	**2**	6	**9d**	85	Only β
17	Benzyl alcohol	**2**	5	**9e**	88	Only β

[a]Reagents and conditions: **1** or **2** (1.0eq.), alcohol (1.1eq.), EtOAc (1 mL), RT; [b]Isolated yield after short column chromatography; [c]Determined by NMR; [d]Reaction was facile only when heated at reflux in toluene at 110 °C for 2 h.

Boron,[23a] aluminium,[23a] zirconium[23b] and zinc[23c-e] are known to bring about *cis*-stereoselective ring opening of α-1,2-anhydrosugars by phenols and *C*-nucleophiles. Mechanistically, intramolecular ligand transfer from the metal to the anomeric carbocation has been proposed to account for the observed stereochemistry. In contrast, metal phenoxides give β-aryl glycosides *via* an S_N2 pathway.[13]

The contrasting stereochemical preference exhibited by alcohols and phenols under neutral conditions in the absence of any catalysts, additives or promoters in our ring opening reaction indicates that the pKa of the aglycone hydroxyl group may have a role in directing the stereochemical course of the reaction. Alcohols, which are weak acids compared to phenols, probably react *via* an S_N2 mechanism to provide β-alkyl glycosides; while in the case of phenols, which are relatively stronger acids than alcohols, the mechanism (Scheme 3) could proceed by an S_N1 pathway *via* the formation of an oxocarbenium ion that would lead to mixtures of α- and β-aryl glycosides with 1,2-*trans*-α-aryl glycosides as the major product. The anomeric stabilisation in the case of α-aryl glycosides may be a reason for the formation of α-isomers as the major product. The *trans* stereoselectivity observed in the case of benzoic acid[24] is difficult to account for with the present data. We have also observed only the formation of β-glycosyl benzoate when **1** was treated with benzoic acid (Scheme 3) under our conditions.



Scheme 1. Plausible mechanism for the ring opening reaction of **1**

The driving force is presumably protonation of the epoxide with the phenolic hydrogen that leads to weakening of the anomeric C-O epoxide bond of the anhydrosugar further assisted by mesomeric interaction of the ring oxygen. This is supported by the fact under identical conditions no reaction was observed in the case of cyclohexene epoxide with either isopropanol or phenol. Our studies reveal that the pka of the aglycone alone cannot be the deciding factor to account for the contrasting stereoselectivity observed in the case of alcohols, phenols and carboxylic acids. Further investigation is needed to understand the mechanistic aspects dictating the stereochemical course of this ring opening reaction.

In summary, we have developed a mild and stereoselective method for the glycosidation of phenols and alcohols under neutral conditions by the ring opening of 1,2-anhydrosugars which are readily available from the epoxidation of glycals. This approach directly provides easy access to aryl glycosides with a free hydroxyl group at the C-2 position of the sugar moiety that can be exploited for the synthesis of carbohydrates containing a 1,2-linkage, as found in many natural glycoconjugates, such as saponins.[25]

Acknowledgments Dr. K. K. Balasubramanian thanks INSA for the award of INSA Senior Scientist and financial support.

References and notes

1. (a) Pratt, M. R.; Bertozzi, C. R. *Chem. Soc. Rev.*, **2005**, *34*, 58; (b) Boeckler, G. A.; Gershenzon, J.; Unsicker, S. B. *Phytochemistry*, **2011**, *72*, 1497; (c) Wu, X-C.; Chen, W-F.; Qian, C-D.; Li, O.; Li P.; Wen, Y-P. *The Journal of Microbiology*, **2007**, *45*, 499; (d) Buskas, T.; Ingale S.; Boons, G. J. *Glycobiology*, **2006**, *16*, 113; (e) Herzner, H.; Reipen, T.; Schultz, M.; Kunz, H. *Chem. Rev*., **2000**, *100*, 4495. (f) Bertozzi C. R.; Kiessling, L. L. *Science*, **2001**, *291*, 2357; (g) Yang, Y.; Zhang, X.; Yu, B. *Nat. Prod. Rep.*, **2015**, *32*, 1331.
2. (a) Yamanoi, T.; Midorikawa, M.; Oda, Y. *Heterocycles*, **2014**, *88*, 201; (b) Kleeb, L.; Pang, L.; Mayer, K.; Eris, D.; Sigl, A.; Preston, R. C.; Zihlmann, P.; Sharpe, T.; Jakob, R. P.; Abgottspon, D.; Hutter, A. S.; Scharenberg, M.; Jiang, X.; Navarra, G.; Rabbani, S.; Smiesko, M.; Lüdin, N.; Bezençon, J.; Schwardt, O.; Maier, T.; Ernst, B. *J. Med. Chem.*, **2015**, *58*, 2221; (c) Hesser, A. R.; Brandsen, B. M.; Walsh, S. M.; Wang, P.; Silverman, S. K. *Chem. Commun.*, **2016**, ***52***, 9259.
3. Jacobsen, M.; Malmberg, J.; Ellervik, U. *Carbohydr. Res.*, **2006**, *341*, 1266.
4. Danishefsky, S. J.; Gervay, J.; Peterson, J. M.; McDonald, F. E.; Doseki, K.; Griffith, D. A.; Oriyama, T.; Marsden, S. P. *J. Am. Chem. Soc.*, **1995**, *117*, 1940.
5. (a) Gomez, A. M.; Lobo, F.; Uriel, C.; Lopez, J. C. *Eur. J. Org. Chem.*, **2013**, ***32***, 7221; (b) Taillefumler, C.; Chapleur, Y. *Chem. Rev.*, **2004**, *104*, 263.
6. (a) Tanaka, M.; Takahashi, D.; Toshima, K. *Org. Lett.*, **2016**, *18*, 5030; (b) Tanaka, M.; Nashida, J.; Takahashi, D.; Toshima, K. *Org. Lett.,* **2016**, *18*, 2288.
7. Nakagava, A.; Tanaka, M.; Hanamura, S.; Takahashi, D.; Toshima, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 10935.
8. (a) Levy, D. E.; Tang, C. *The chemistry of C-glycosides*, Pergamon press, Oxford, **1995**; (b) Sugai, T.; Okazaki, H.; Kuboki, A.; Ohta, H. *Bull. Chem. Soc. Jpn.,* **1997**, *70,* 2535.
9. (a) Kubota, Y.; Haraguchi, K.; Kunikata, M.; Hayashi, M.; Ohkawa, M.; Tanaka, H. *J. Org. Chem.*, **2006**, *71*, 1099; (b) Matsushita, Y-I.; Sugamoto, K.; Kita, Y.; Matsui, T. *Tetrahedron Lett.,* **1997**, *38***,** 8709; (c) Du, Y.; Kong, F. *J. Carbohydr. Chem.*, **1995**, *14*, 341; (d) Gervay, J.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 5448; (e) Seeberger, P. H.; Eckhardt, M.; Gutteridge, C. E.; Danishefsky, S. J. *J. Am. Chem. Soc.*, **1997**, *119*, 10064.
10. Liu, C. F.; Xiong, D-C.; Ye, X-S. *Tetrahedron Lett.*, **2016**, *57*, 1372.
11. Li, Y.; Tang, P.; Chen, Y.; Yu, B. *J. Org. Chem.* **2008**, *73*, 4323.
12. (a) Hickinbottom, W. J. *J. Chem. Soc.,* **1928**, 3140; (b) Brigl, P. *Z. physiol. Chem.* **1922**, *122*, 245.
13. (a) Dushin, R. G.; Danishefsky, S. J. *J. Am. Chem. Soc.*, **1992**, *114*, 3471; (b) Chiappe, C. G.; Moro, L.; Munforte, P. *Tetrahedron*, **1997**, *53*, 10471; (c) Santiago, C. C.; Lafuente, L.; Bravo, R.; Díaz, G.; Ponzinibbio, A. *Tetrahedron Lett.*, **2017**, *58*, 3739.
14. Nakagava, A.; Tanaka, M.; Hanamura, S.; Takahashi, D.; Toshima, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 10935.
15. Cheshev, P.; Marra, A.; Dondoni, A. *Carbohydr. Res*., **2006**, *341*, 2714.
16. (a) Nigudkar, S. S.; Demchenko, A. V. *Chem. Sci.*, **2015**, *6*,

2687; (b) Kafle, A.; Liu, J.; Cui, L. *Can. J. Chem.*, **2016**, *94*, 894.
17. Rani, S.; Vankar, Y. D. *Tetrahedron Lett*., **2003**, *44*, 907.
18. Ethyl acetate (LR grade) is known to contain acidic impurities and hence was initially distilled over anhydrous K_2CO_3 followed by distillation over CaH_2. However, HPLC grade ethyl acetate with zero moisture content can also be directly used for this reaction.
19. To a solution of phenol or alcohol (1.1 equiv.) in freshly distilled dry EtOAc (1 mL), 1,2-anhydrosugar **1** or **2** (100 mg, 1.0 equiv.) was added and stirred at ambient temperature under an inert atmosphere for the specified time. Upon reaction completion (TLC), the reaction was concentrated in *vacuo* and purified by a short wash column chromatography.
20. Somasundaram, D.; Balasubramanian, K. K.; Bhagavathy, S. *Carbohydr. Res*., **2017**, *449***,** 95.
21. Hardegger, E.; De Pascual, J. *Helvetica chima acta,* **1948**, *31*, 281.
22. (a) Santiago, C. C.; Lafuente, L.; Bravo, R.; Díaz, G.; Ponzinibbio, A. *Tetrahedron Lett.,* **2017**, *58*, 3739; (b) Mayato, C.; Dorta, R. L.; Vázquez, T. *Tet. Assymm.,* **2004**, *15*, 2385; (c) Bellucci, G.; Chiappe, C.; D'Andrea, F. *Tet. Assymm.,* **1995**, *6*, 221; (d) Charette, A. B.; Côté, B.; Marcoux, J. F. *J. Am. Chem. Soc*. **1991**, *113*, 8166.
23. (a) Rainer, J. D.; Cox, J. M. *Org. Lett.* **2000**, *2*, 2707; (b) Wipf, P.; Pierce, J. G.; Zhuang, N. *Org. Lett*. **2005**, *7*, 483; (c) Wagschal, S.; Guilbaud, J.; Rabet, P.; Farina, V.; Lemaire, S. J. *J Org. Chem*. **2015**, *80,* 9328; (d) Leeuwenburgh, M. A.; Timmers, C. M.; Marel, G. A. V.; Van Boom, J. H.; Mallet, J. M.; Sinaÿ, P. G. *Tetrahedron Lett*. **1997**, *38*, 6251; (e) Tatina, M. B.; Kusunuru, A. K.; Mukherjee, D. *Org. Lett*. **2015**, *17*, 4624.
24. Timmers, C. M.; Van Straten, N. C. R.; Van der Marel, G. A.; Van Boom, J. H. ***J.*** *Carbohydr. Chem.,* **1998**, *17*, 471.
25. (a) Gu, G.; Du, Y.; Linhardt, R. J. *J. Org. Chem.*, 2004, *69*, 5497; (b) David, G. Y.; Galonic, D. P. *Nature*, 2007, *446*, 1000.

HIGHLIGHTS

Title: Simple and Mild Stereoselective *O*-Glycosidation using 1,2-anhydrosugars Under Neutral Conditions

- Stereoselective aromatic glycosylation using 1,2-anhydrosugars.
- *O*-Glycosylation without the use of any additives/catalysts.
- Access to *O*-glycosides with free hydroxyl group at C-2 position.

Regards
Dr. S. Bhagavathy

26.