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Article

Iron(III) Chloride Catalyzed Glycosylation of Peracylated Sugars with Allyl/Alkynyl Alcohols

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Neste trabalho, o emprego de cloreto férrico como um eficiente catalisador em reações de glicosilação de açúcares na presença de álcoois alílicos e propargílicos é descrito. Os glicosídios correspondentes foram obtidos com rendimentos de moderados a bons. Este novo procedimento apresenta maior seletividade quando comparado a métodos clássicos encontrados na literatura. As principais características desse método simples incluem condições de reação não perigosas, quantidade de catalisador baixa, bom rendimento e seletividade anomérico elevada.

In this work, the use of ferric chloride as an efficient catalyst in glycosylation reactions of sugars in the presence of allyl and alkynyl alcohols is described. The corresponding glycosides were obtained with moderate to good yields. This new procedure presented greater selectivity when compared to classic methods found in the literature. Principal features of this simple method include non-hazardous reaction conditions, low-catalyst loading, good yields and high anomeric selectivity.

Keywords: glycosylation, iron(III) chloride, stereoselective, carbohydrate, green chemistry

Introduction

Many carbohydrate-containing complex natural compounds are found in nature as important biological substances. Recent biological studies on these glycosides, such as proteoglycans, glycoproteins, glycolipid and antibiotics at the molecular level have shed light on the biological significance of their carbohydrate parts (glycons) in molecular recognition for the transmission of biological information.[1]

With the stimulant biological background, the synthesis of carbohydrate-containing compounds is becoming more and more important in the field of organic chemistry and chemical biology.[2] On the other hand, glycosylation is a key reaction for the introduction of a carbon chain into the anomeric position of a glycal or a sugar derivative bearing a leaving group at C-1. Due to the importance of glycosylic compounds, the present subject has received considerable attention in recent years.[3]

Substantial number of reports has appeared in the literature on glycosylation reaction employing common reagents such as $BF_3.OEt_2$,[4] indium metal,[5] $HClO_4$-SiO_2,[6] $InCl_3$/IBX (iodoxybenzoic acid),[7] $InBr_3$[8] and $SnCl_4$.[9] Glycosides have been also synthesized via Ferrier rearrangement starting from the corresponding unsaturated glycosides with alcohols in presence of $InCl_3$,[10] $Bi(OTf)_3/SiO_2$-$Bi(OTf)_3$[11] and other acid catalysts.[12]

In an environmentally benign chemistry on carbohydrates, i.e., green carbohydrate chemistry requires for clean, efficient and selective processes have increased the demand for such metal-based reaction promoters, especially in catalytic amounts. However, many catalysts are derived from heavy or rare metals and their toxicity and prohibitive prices constitute severe drawbacks for large-scale applications. In contrast, iron is one of the most abundant metals on earth, and consequently one of the most inexpensive and environmentally friendly ones. Moreover, many iron salts and complexes are commercially available, or their applications are well described in the literature.[13] Despite its advantages, it is surprising that, until recently, iron was relatively underrepresented in the field of catalysis including nucleophilic additions/substitutions, reductions, oxidations, hydrogenations, cycloadditions, isomerizations, rearrangements, as well as polymerizations.[14] However, iron(III) chloride has been extensively utilized for glycosylation reactions with different sugar moieties like

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2-acylamido-2-deoxy-β-D-glucopyranose-1-acetates, etc., with the use of a quantitative amount of iron(III) chloride.[15] In addition, iron chloride was successfully employed for the Ferrier rearrangement.[16]

Whilst there are several published procedures[4-12] for the glycosylation reactions, many of these methods require the use of expensive reagents and have limitations in terms of yields, stereoselectivities, reaction temperature, the catalyst/reagents used and their quantitative amounts. Therefore, our aim was to find a method that utilized mild, relatively cheap reagents and flexible enough to allow the synthesis of glycosides.

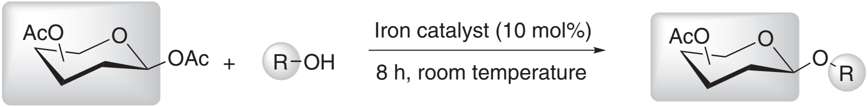
Results and Discussion

Considering all these aspects, herein, it is reported an efficient, mild, cost-effective procedure for glycosylation of peracetylated-β-D-sugar catalyzed by $FeCl_3$ (Scheme 1).

To gain some preliminary information of this synthetically useful reaction, screening experiments were performed. It was carried out the reaction employing 1.0 equivalent of β-D-glucose pentaacetate (**1**), 1.2 equivalent of allyl alcohol (**2**), 20 mol% of catalyst in dry dichloromethane at room temperature under different conditions to get the glycoside (Table 1). Firstly, it was tested different catalysts, among these, $FeCl_3$ showed a positive result in terms of yield as compared with other catalysts (Table 1, entries 1-6). Henceforth, it was focused our attention towards the use of iron salts for this transformation.

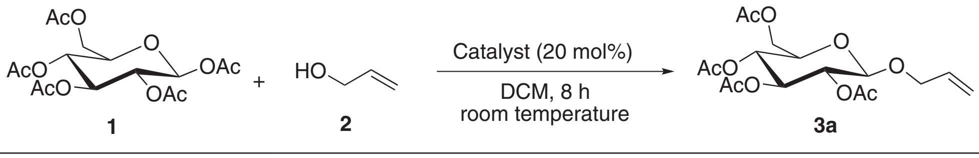
The influence of different iron salts was further studied to check the reaction course. All these catalysts provide the corresponding glycoside **3** in traces, whereas $FeCl_3$ was the only one to provide isolable yields of product (Table 2, entries 1-6). It was observed the formation of **3a** as a pure isomer (assigned by nuclear magnetic resonance, NMR) in 26% yield.

In continuation of our optimization, it was next studied other factors including catalyst loading, reaction temperature and solvent. Analyzing Table 3, it was possible to verify that the amount of catalyst loading (from 5 to 20 mol%) has the influence of the glycosylation reaction. When the amount of catalyst loading was decreased from 20 to 10 mol%, the yield got increased to 64% (Table 3, entries 1-3). This is due to the catalyst concentration which plays a fundamental role in this glycosylation reaction.[17] Also, catalyst loadings 7 and 5 mol% gave the corresponding product in low yield as compared with the use of 10 mol% (Table 3, entries 3-5). In all cases, the uncharacterizad polymerization products or side products were also observed, whereas using 10 mol% $FeCl_3$, comparative low amounts of byproduct formation was observed. Finally, to further optimize the protocol, it was necessary to examine the effect of the solvent in promoting the reaction efficiency.



Scheme 1. Synthesis of glycosides catalyzed by $FeCl_3$.

Table 1. Screening of catalyst[a]



entry	Catalyst	Yield[b] / %
1	ZnO	traces
2	$ZnCl_2$	traces
3	$CuBr_2$	traces
4	InI	–
5	$SnCl_2$	traces
6	$FeCl_3$	26

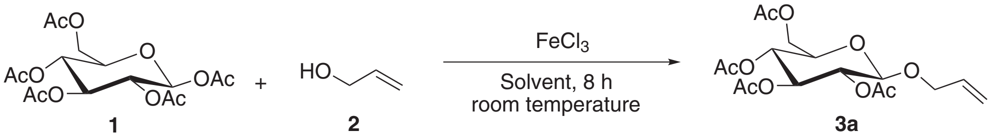
[a]Unless otherwise mentioned, reactions were performed using: alcohol (1.2 equivalent) to a stirred suspension of peracetylated sugar (1 equivalent) and $FeCl_3$ (20 mol%) in ultra-dry conditions; [b]isolated yield.

Table 2. Screening of iron catalyst[a]

entry	Iron catalyst	Catalyst loading / mol%	Yield[b] / %
1	$FeCl_3$	20	26
2[c]	Fe_2O_3 (nano)	20	traces
3	$Fe(NO_3)_3.9H_2O$	20	traces
4[d]	Aerosil 200-$FeCl_3$	25% (m/m)	traces
5	Fe(III) acetate	20	traces
6	$Fe(acac)_3$	20	traces

[a]Unless otherwise mentioned, reactions were performed using: alcohol (1.2 equivalent) to a stirred suspension of peracetylated sugar (1 equivalent) and $FeCl_3$ (20 mol%) in ultra-dry conditions; [b]isolated yield; [c]nanoparticles; [d]silica crafted with $FeCl_3$.

Table 3. Screening of the catalyst loading, solvent and temperature[a]



entry	$FeCl_3$ / mmol%	Solvent	Temperature	Yield[b] / %
1	20	CH_2Cl_2	rt	26
2	15	CH_2Cl_2	rt	22
3	10	CH_2Cl_2	rt	64
4	7	CH_2Cl_2	rt	28
5	5	CH_2Cl_2	rt	18
6[c]	10	CH_3CN	rt	bp[c]
7[d]	10	Et_2O	rt	–[d]
8	10	CH_2Cl_2:Et_2O	rt	26
9[c]	10	CH_2Cl_2	reflux	bp

[a]Unless otherwise mentioned, reactions were performed using: alcohol (1.2 equivalent) to a stirred suspension of peracetylated sugar (1 equivalent) and $FeCl_3$ (20 mol%) in an ultra-dry conditions; [b]isolated yield; [c]byproducts were observed; [d]no reaction; rt: room temperature.

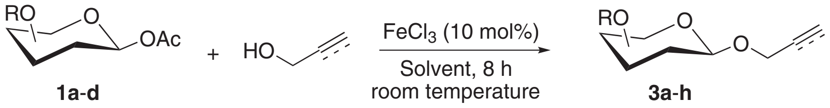
The use of dichloromethane gave the higher yields as compared with other solvents (Table 3, entries 6-8). Also, elevated temperature exhibited negative effect, which affords the byproduct formation as compared with room temperature (Table 3, entries 9 and 3).

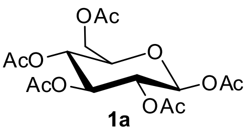
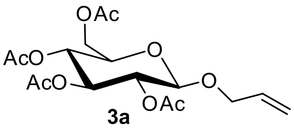
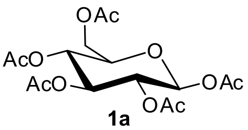
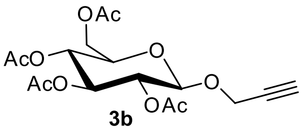
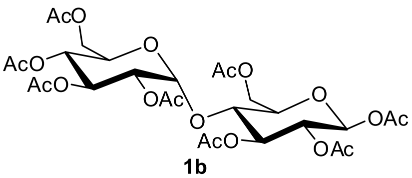
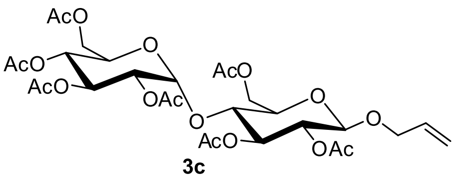
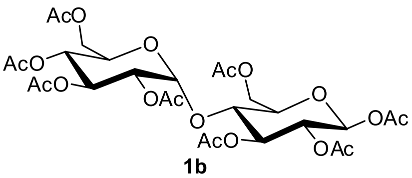
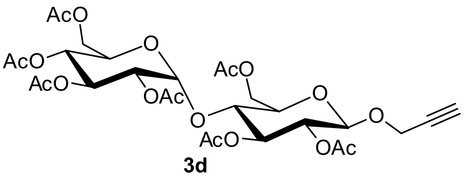
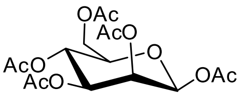
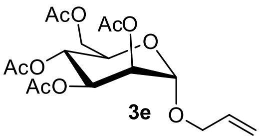
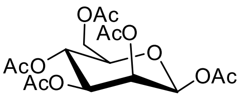
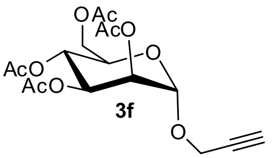
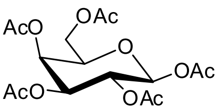
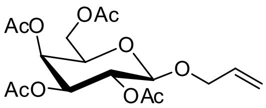
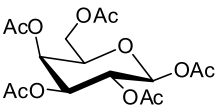
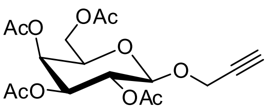
With the optimized conditions in hands, it was subsequently used this approach to synthesize different glycosides derived from β-D-glucose, β-D-mannose, β-D-maltose, β-D-galactose using $FeCl_3$ catalyst. The results were summarized in Table 4. Our general reaction conditions involve the addition of alcohol (1.2 equivalent) to a stirred suspension of peracetylated sugar (1 equivalent) and $FeCl_3$ (10 mol%) in dry dichloromethane at room temperature. In all cases, the product formation was observed as a single isomer in moderate to good yield (Table 4, entries 1-9).

It was speculated that $FeCl_3$ would function as Lewis acid and thus promote the glycosylation. By using the standard reaction conditions, it was then tested α-D-glucose pentaacetate as the sugar partner with allyl alcohol in presence of $FeCl_3$ catalyst. Unfortunately, however, our methodology fails.

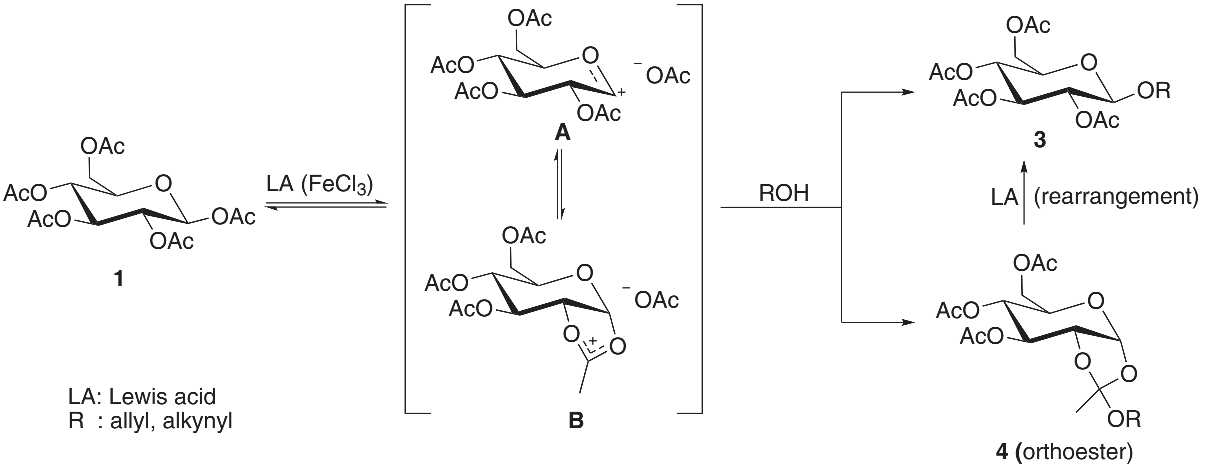
The mechanism of $FeCl_3$ mediated glycosylation is still an intriguing subject of study. Based on the literature report,[18] it was proposed the plausible reaction pathways of the glycosylation (Scheme 2). $FeCl_3$ would behave as Lewis acid and the initial step of the reaction is a Lewis acid promoted of β-D-glucose pentaacetate (**1**), involving

Table 4. Glycosylation of sugars with alcohols catalyzed by iron(III) chloride[a]

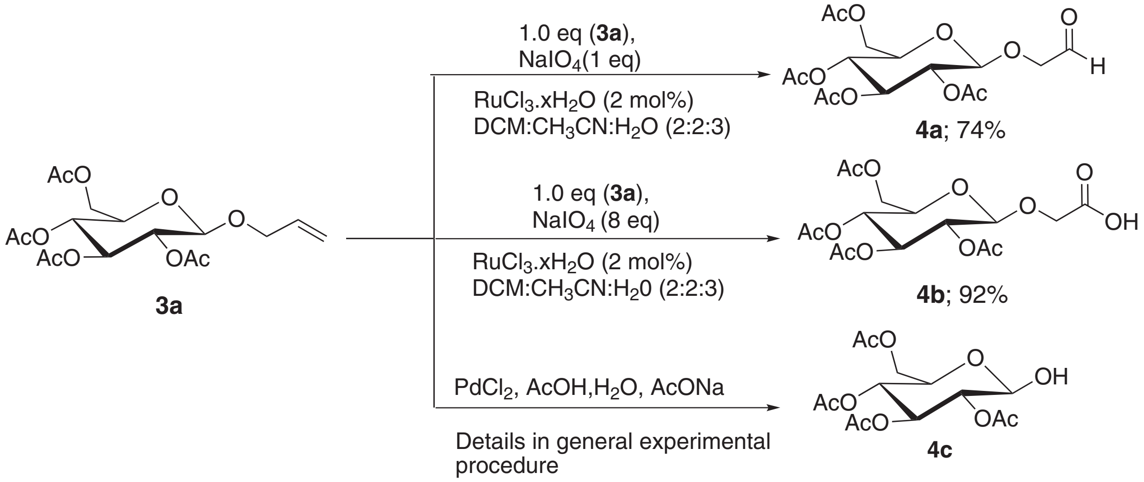


	Sugar	Product	Yield[b] / %
1	 **1a**	 **3a**	64
2	 **1a**	 **3b**	53
3	 **1b**	 **3c**	48
4	 **1b**	 **3d**	58
5	 **1c**	 **3e**	51
6	 **1c**	 **3f**	53
7[c]	 **1d**	 **3g**	64
8[c]	 **1d**	 **3h**	39

[a]Details in general experimental procedure; [b]isolated yield; [c]the starting material and desired product showed the same α/β relationship (1:10). The anomeric ratios were determined by comparison of the integral intensities of the corresponding signals in NMR spectra.



Scheme 2. Plausible reaction pathways.



Scheme 3. Functionalization of allyl glycoside.

the participation of the C-2 acetoxy group, to give an oxocarbenium acetate ion pair (**A**) or dioxolenium ion (**B**). The carbenium ion would react with the allyl/alkynyl alcohol to give the desired 1,2-*trans*-glucoside (**3**) and 1,2-orthoester (**4**). Furthermore, the orthoester (**4**) would rearrange[19] to give the glycosylated product (**3**).

A great deal of interest has been laid in the application of synthesized compounds. Especially allyl glycoside, **3a** is attractive due to the presence of the terminal double bond that is amenable to easy further functionalization leading to other molecules[20] or selective deprotection of allyl group from glycoside **3a** without affecting other functional groups on glycosides, which afford the anomeric alcohol **4c** and this would be used as building blocks on carbohydrate arrays (Scheme 3).[21] The synthesized compound **4a** and **4b** have to be used as starting material for the Ugi four component reactions which demonstrates the synthetic utility of this class of compounds.[22]

Experimental

^{1}H and ^{13}C NMR spectra were recorded at 400 MHz with tetramethylsilane as internal standard. Column chromatography was performed using Merck silica gel (230-400 mesh). Thin layer chromatography (TLC) was performed using Merck silica gel GF254, 0.25 mm thickness. For visualization, TLC plates were placed under acidic vanillin. All solvents were used in dry conditions.

General experimental procedure (**3a**-**h**)

Allyl or propargyl alcohol (1.2 equivalent) was added to a stirred suspension of peracetylated sugar (1 equivalent) and $FeCl_3$ (10 mol%) in dry dichloromethane (1 mL) at room temperature in ultra-dry conditions under inert atmosphere. After completion of the reaction as monitored by thin-layer chromatography (TLC), the reaction was diluted with dichloromethane and washed with water, and worked up in the usual manner. The crude product was purified by chromatography on silica gel (ethyl acetate:hexane 1:1) to afford the corresponding glycoside in good yield and with high selectivity.

Conclusions

In conclusion, our methodology has several notable advantages such as mild reaction conditions that make use of a reagent of relatively low toxicity, low-catalyst loading, good yields and high anomeric selectivity. Efforts to construct a library of compounds with this method are still underway in our laboratory.

Supplementary Information

Experimental details and spectral data are available free of charge at http://jbcs.sbq.org.br as a PDF file.

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References

1. Ernst, B.; Hart, G.; Sinay, P. In *Carbohydrates in Chemistry and Biology*; Wiley-VCH: New York, NY, USA, 2000; Fraser-Reid, B. O.; Tatsuta, K.; Thiem, J. In *Glycoscience: Chemistry and Chemical Biology I-III*; Springer: Berlin, Germany, 2001.
2. Nicolaou, K. C.; Mitchell, H. J.; *Angew. Chem., Int. Ed.* **2001**, *40*, 1576; Lehnert, T.; Özüduru, G.; Grugel, H.; Albrecht, F.; Telligmann, S. M.; Boysen, M. M. K.; *Synthesis* **2011**, *17*, 2685 and references there in; Crich, D.; *J. Org. Chem.* **2011**, *76*, 9193.
3. Ayed, C.; Palmier, S.; Lubin-Germain, N.; Uziel, J.; Augé, J.; *Carbohydr. Res.* **2010**, *345*, 2566; Levy, D. E.; Fügedi, P. In *Organic Chemistry of Sugars*; CRC Press.: Boca Raton, FL, USA, 2006, p. 269.
4. Lin, Y. A.; Chalker, J. M.; Davis, B. G.; *J. Am. Chem. Soc*. **2010**, *132*, 16805 and references therein.
5. Lubin-Germain, N.; Baltaze, J. P.; Coste, A.; Hallonet, A.; Lauréano, H.; Legrave, G.; Uziel, J.; Augé, J.; *Org. Lett*. **2008**, *10*, 725.
6. Agarwal, A.; Rani, S.; Vankar, Y. D.; *J. Org. Chem.* **2004**, *69*, 6137.
7. Yadav, J. S.; Reddy, B. V. S.; Reddy, R. C.; *Tetrahedron Lett.* **2004**, *45*, 4583.
8. Yadav, J. S.; Reddy, B. V. S.; Raju, A. K.; Rao, C.V.; *Tetrahedron Lett.* **2002**, *43*, 5437.
9. Boryski, J.; Grynkiewicz, G.; *Synthesis* **2001**, *14*, 2170; Xue, J. L.; Cecioni, S.; He, L.; Vidal, S.; Praly, J. P.; *Carbohydr. Res.* **2009**, *344*, 1646 and references therein.
10. Nagaraj, P.; Ramesh, N. G.; *Tetrahedron Lett.* **2009**, *59*, 3970; Mukherjee, D.; Yousuf, S. K.; Taneja, S. C.; *Tetrahedron Lett.* **2008**, *49*, 4944; Das, S. K.; Reddy, K. A.; Abbineni, C.; Roy, J.; Rao, K. V. L. N.; Sachwani, R. H.; Iqbal, J.; *Tetrahedron Lett.* **2003**, *44*, 4507; Ghosh, R.; De, D.; Shown, B.; Maiti, S. B.; *Carbohydr. Res.* **1999**, *321*, 1.
11. Babu, J. L.; Khare, A.; Vankar, Y. D.; *Molecules* **2005**, *10*, 884.
12. Tilve, R. D.; Alexander, M. V.; Khandekar, A. C.; Samant, S. D.; Kanetkar, V. R.; *J. Mol. Catal. A: Chem.* **2004**, *223*, 237; Churchill, D. G.; Rojas, C. M.; *Tetrahedron Lett.* **2002**, *43*, 7225.
13. Zettler, M. W. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., ed.; Wiley: New York, NY, USA, 1995; White, A. D. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., ed.; Wiley: New York, NY, USA, 1995; King, B. R.; *Encyclopedia of Inorganic Chemistry*; Wiley: New York, NY, USA, 1994.
14. Beller, M.; Bolm, C.; *Transition Metals for Organic Synthesis*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2004; Thomas, S. E. G.; *Transition Metals in Organic Synthesis, a Practical Approach*; Oxford University Press: Oxford, USA, 1997; Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev*. **2004**, *104*, 6217; Addis, D.; Shaikh, N.; Zhou, S.; Das, S.; Junge, K.; Beller, M.; *Asian. J. Chem.* **2010**, *5*, 1687; Driller, K. M.; Prateeptongkum, S.; Jackstell, R.; Beller, M.; *Angew. Chem., Int. Ed.* **2011**, *50*, 537.
15. Kiso, M.; Anderson, L.; *Carbohydr. Res.* **1979**, *72*, C12; Kiso, M.; Anderson, L.; *Carbohydr. Res.* **1979**, *72*, C15; Hasegawa, A.; Kiso, M.; *Carbohydr. Res.* **1979**, *74*, 341; Kiso, M.; Nishiguchi, H., Hasegawa, A.; *Carbohydr. Res.*, **1980**, *81*, C13; Kiso, M., Anderson, L.; *Carbohydr. Res.* **1985**, *136*, 309; Dasgupta, F.; Anderson, L.; *Carbohydr. Res.* **1990**, *202*, 239; Charbonnier, F.; Penades, S.; *Eur. J. Org. Chem*. **2004**, 3650; Seibel, J.; Hillringhaus, L.; Moraru, R.; *Carbohydr. Res.* **2005**, *340*, 507.
16. Masson, C.; Soto, J.; Bessodes, M.; *Synlett* **2000**, *9*, 1281; Churchill, D. G.; Rojas, C. M.; *Tetrahedron Lett.* **2002**, *43*,7225; Tilvea, R. D.; Alexander, M. V.; Khandekar, A. C.; Samant, S. D.; Kanetkar, V. R.; *J. Mol. Catal. A: Chem.* **2004**, *223*, 237.
17. Rulli, G.; Duangdee, N.; Baer, K.; Hummel, W.; Berkessel, A.; Gröger, H.; *Angew. Chem., Int. Ed*. **2011**, *50*, 7944.
18. Banoub, J.; Bundle, D. R.; *Can. J. Chem.* **1979**, *57*, 2091; Aich, U.; Loganathan, D.; *Carbohydr. Res.* **2006**, *341*, 19; Murakami, T.; Hirono, R.; Sato, Y.; Furusawa, K.; *Carbohydr.*

Res. **2007**, *342*, 1009; Xue, L. J.; Cecioni, S.; Vidal, S.; Praly, J. P.; *Carbohydr. Res.* **2009**, *344*, 1646.

19. Ogawa, T.; Beppu, K.; Nakabayashi, S.; *Carbohydr. Res.* **1981**, *93*, C6; Kong, F. *Carbohydr. Res.* **2007**, *342*, 345.
20. Synthetic procedure for aldehyde and acid derivative of **4a**-**b**: Buskas, T.; Söderberg, T.; Konradsson, P.; Reid, B. F.; *J. Org. Chem.* **2000**, *65*, 958; Virta, P.; Karskela, M.; Lönnberg, H.; *J. Org. Chem.* **2006**, *71*, 1989.
21. Ban, L.; Mrksich, M.; *Angew. Chem., Int. Ed.* **2008**, *47*, 3396.
22. Westermann, B.; Dörner, S.; *Chem. Commun.* **2005**, 2116.

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