Simple and Efficient Method for the Synthesis of Galactofuranosides

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An efficient and improved one-pot method for the synthesis of galactofuranosides via iodine-promoted cyclization of galactose diethyl dithioacetal in the presence of alcohol, acting both as solvent and nucleophile, is described. The reaction is carried out at room temperature. Alcohols, such as methanol, cyclohexanol and tert-butanol, were used as nucleophiles for the reaction using 2%, 3% and 5% iodine promoter, respectively. A key finding in this study was that the iodine-promoted cyclization of galactose diethyl dithioacetal with alcohol led to selective formation of β -galactofuranoside allowing the efficient preparation of derivatives of this monosaccharide.

Keywords: *carbohydrate; galactofuranose; iodine; cyclization; β -galactofuranosides*

INTRODUCTION

Monosaccharides found in mammalian cells are in the six-membered pyranose conformation. In lower organisms, such as bacteria, parasites, and fungi, several monosaccharides are observed to be in their furanose form, wherein the linear six carbon sugar is cyclized into a five membered ring. The most common furanoses are the arabinofuranose, galactofuranose, and fructo-

furanose (Lowary, 2003). Hexopyranosides are thermodynamically more stable than their furanoside counterparts due to steric, and electronic factors (Plavec *et al.*, 1996). Among the common furanosides, D-galactofuranose (D-Galf) is the only one that occurs naturally. Both the alpha (α) and beta (β) anomers of galactofuranose are produced by various lower organisms, with the beta anomer being more prevalent (Lowary, 2003). Several pathogenic

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organisms are thought to produce this thermodynamically less stable and more sterically-hindered conformation of sugar as an important element for their survival. These include *Mycobacterium*, *Trypanosoma*, *Leishmania* and *Aspergillus* which are responsible for certain species-associated diseases that are difficult to treat (Tefsen *et al.*, 2012).

Galf is one of the components of complex cell wall of pathogenic fungi such as *Aspergillus fumigatus* that helps prevent lysis (Latge, 2007; Tefsen *et al.*, 2012). Parasitic protozoa such as *Trypanosoma* and *Leishmania*, which cause sleeping sickness and Chagas disease, and leishmaniasis respectively, have galactofuranose residues in glycoproteins and glycolipids that account for their virulence (Tefsen *et al.*, 2012). Other applications of galactofuranoses include further study on the prevention of biofilm formation to counteract fungal infections. This is similar to yeast and bacteria biofilms which is mainly composed of galactofuranose containing galactomannans and alpha-glucans (Peltier, 2008; Loussert *et al.*, 2010). Thiodisaccharide Galf-S-(1→6)-Galf-OMe was synthesized and showed a moderate competitive inhibition with the β -galactofuranoside of *Penicillium fellatatum* (Repetto, Marino, and Varela, 2013). Another study showed that a 9-heptadecyl galactofuranose thioglycoside and its sulfone displayed a significant inhibitory potency of less than 5 $\mu\text{g/mL}$ against *M. smegmatis* (Davis *et al.*, 2007).

Thus, Galf-containing cellular components are viewed as putative targets in drug discovery and

development of methods to synthesize Galf derivatives is continuously being sought. Methods such as kinetically-controlled Fischer glycosylation (Lubineau and Fischer, 1991; Arasappan and Fraser-Reid, 1995; Velty *et al.*, 1997), high temperature acylation (D'Accorso *et al.*, 1983), cyclization of dithioacetals (Green and Pacsu, 1938), or open-chain *S,O*-acetals (McAuliffe and Hindsgaul, 1997), ring opening of 1,4-anhydrogalactopyranose derivatives (Kovensky and Sinay, 2000), and formation of 1,2:5:6-di-*O*-isopropylidene derivatives (Morgenlie, 1973; Wang *et al.*, 2003; Rauter *et al.*, 1995) have been reported.

When hexoses are treated with alcohols under Fischer glycosylation conditions (acid in an alcoholic solvent), furanosides are formed initially, which are then converted to their pyranoside forms (Capon, 1969). Furanosides are considered the kinetic products of this reaction and are often formed in excellent yields as a mixture of anomers, if proper conditions are chosen. D-Galactose was converted to a mixture of anomeric methyl furanosides via a ferric chloride-catalyzed Fischer glycosylation (Lubineau and Fischer, 1991). Fraser-Reid and coworkers also reported a Fischer glycosidation of D-galactose under kinetic conditions using *n*-pentenyl alcohol and camphorsulfonic acid (CSA) at 90–100 °C for six hours to afford *n*-pentenyl galactofuranoside (**5**) as a mixture of anomers (Figure 1, Arasappan and Fraser-Reid, 1995). The reaction also gave the corresponding anomeric mixture of pyranosides (**6**), albeit in poor yield.

Figure 1. Fischer glycosidation of D-galactose (Arasappan and Fraser-Reid, 1995).

A modified method for glycosylation of 4-penten-1-ol with D-galactose was done in tetrahydrofuran using ferric chloride as the promoter and calcium chloride as an additive. The reaction afforded, after 54 hours at room temperature and *in situ* acetylation, a mixture of furanosides and the corresponding pyranosides

with a net preference for β -furanoside and α -pyranoside derivatives (Velty *et al.*, 1997). The favorable formation of the furanoside products over the thermodynamically more stable pyranosides was attributed to the complexation of the furanoside forms by Ca^{+2} ion (Angyal, 1980).

The first synthesis of perbenzoylated β -D-galactofuranoside (**7**) and α -D-galactofuranoside (**8**) was discovered serendipitously in an attempt to prepare 1,2,3,4,5-penta-O-benzoyl- β -D-galactopyranose

Figure 2. High temperature benzylation of D-galactose (D'Accorso *et al.*, 1983).

An unconventional approach to the synthesis of galactofuranosides from galactopyranose involves the reaction of protected 1,4-anhydrogalactopyranose derivatives with alcohols in the presence of camphorsulfonic acid for 3–4 days via regioselective ring opening of the bicyclic system to yield the desired galactofuranosides (Kovensky and Sinay, 2000). Another method used acyclic glycosyl dithioacetals as precursors in the synthesis of glycosyl furanosides (Fischer, 1894; Green,

D'Accorso *et al.*, 1983). Treatment of D-galactose with benzoyl chloride and pyridine at 100 °C resulted in the formation of **7** and **8** instead of the target galactopyranoside product (Figure 2).

1966; Pacsu and Green, 1936). One example involved the preparation of 1-chloro-1-(ethylthio) derivatives (**10**) of D-glucose and D-galactose from the corresponding dithioacetal pentaacetates (Figure 3, Wolfrom *et al.*, 1944). The *S,O* acetals (**11**) formed were found to undergo regio- and stereoselective cyclization following deacetylation and treatment with a mixture of HgO and HgCl₂ in either methanol or ethanol to give the corresponding β -D-furanosides (**12**).

Figure 3. Cyclization of *S,O* acetals to give ethyl β -D-galactofuranoside (Wolfrom *et al.*, 1944).

An elegant extension of this method was demonstrated by McAuliffe and Hindsgaul (1997) by treatment of a peracetylated diethyl dithioacetal of D-galactose with acetyl chloride and boron trifluoride diethyl etherate to give the acyclic 1-chloro-(ethylthio) derivative **10**. Glycosidation of acceptor **13** with donor **10** in the presence of AgOTf and Ag₂CO₃, provided *S,O*-acetal **14**. Deacetylation of **14** under Zémlén conditions (Zemplén *et al.*, 1953) followed by addition of HgO and HgCl₂ to the methanolic solution and subsequent acetylation gave β -galactofuranoside **16** (Figure 4, McAuliffe and Hindsgaul, 1997).

Relevant to these methods is a report

involving the 1,3-dibromo-5,5-dimethylhydantoin (DBDH)-mediated activation of glycosyl dithioacetals leading to the formation of glycofuranosides (Madhusudan and Misra, 2005). However, a major disadvantage of these methods is the use of toxic heavy metal salts and expensive reagents. A related methodology that circumvents this limitation is the treatment of glucosyl, mannosyl and arabinosyl dithioacetals with a dilute solution of iodine (I₂) in methanol to give the corresponding glycosyl furanosides (Szarek *et al.*, 1986).

As shown in Figure 5, stirring dithioacetal **17** in 1% I₂ in methanol for 32 hours afforded glucofuranoside **18** in 74% yield.

This reaction was only applied to arabinose, glucose and mannose-derived dithioacetals, but not to those derived from galactose. We previously reported adapting this method for the iodine-induced dithioacetal cyclization in octanol towards the synthesis of octyl galactofuranosides (Completo and Lowary,

2008). This was the first reported synthesis of β -octyl galactofuranoside using galactose-derived dithioacetal. We now report here an extension of the utility of our method by using other simple and sterically-hindered alcohols, acting as both solvent and nucleophile, in the synthesis of corresponding galactofuranosides (Figure 6).

Figure 4. Synthesis of galactofuranosides via cyclization of open-chain *S,O*-acetals (McAuliffe and Hindsgaul, 1997).

Figure 5. Reaction of *D*-glucose diethyl dithioacetal with I_2 and methanol (Szarek et al., 1986).

Figure 6. Use of cyclization of diethyl dithioacetal 2 to prepare alkyl galactofuranosides.

EXPERIMENTAL METHODS

General Methods. Reactions were carried out in oven-dried glassware. All reagents were purchased from commercial sources and were used without further purification unless noted. Unless stated otherwise, all reactions were carried out at room temperature under a positive pressure of nitrogen and were monitored by TLC on Silica Gel 60 F₂₅₄ (0.25 mm, E. Merck). TLC spots were detected under UV light or by charring with acidified *p*-anisaldehyde solution in ethanol. All organic solutions were dried with anhydrous MgSO₄. Unless otherwise indicated, all column chromatography was performed on Silica Gel (40–60 μ m). The ratio between silica gel and crude product ranged from 100 to 50:1 (w/w). Optical rotations were measured at 22 $\pm$ 2 °C using Perkin Elmer 241 Polarimeter at the Department of Chemistry, University of Alberta, Edmonton, Canada. ¹H NMR spectra were recorded using 500 MHz Agilent or 400 MHz JEOL Lambda NMR spectrometers and chemical shifts were referenced to either trimethylsilane (TMS) (0.0 ppm, CDCl₃), CD₃OD (3.30 ppm, CD₃OD) or HOD (4.78 ppm, D₂O). ¹H data were reported as though they were first order. ¹³C NMR spectra were recorded at 125 MHz or 100 MHz using Agilent or JEOL Lambda NMR spectrometers, respectively. ¹³C NMR chemical shifts were referenced to internal CDCl₃ (77.23 ppm, CDCl₃), or CD₃OD (48.9 ppm, CD₃OD) or external acetone (31.07, D₂O). Assignments of resonances in NMR spectra were made using ¹H–¹H COSY and HMQC experiments. Organic solutions were concentrated under vacuum at <40 °C. All electrospray ionization (ESI-MS) mass spectral data were obtained using Bruker micrOTOF-Q II mass spectrometer. Mass spectra were recorded on samples suspended in mixtures of THF with MeOH and added NaCl.

Synthesis of Compounds. *D*-galactose diethyl dithioacetal (**2**). *D*-galactose (50.00 g, 0.278 mol) was dissolved at room temperature (rt) in concentrated HCl (75 mL). Ethanethiol (50

mL) was then added, and the reaction mixture was shaken vigorously, releasing the pressure occasionally. After 3–5 minutes, a definite temperature increase was noted; a little amount of ice and ice water was then added. More ice water was added and the crystalline product formed was filtered and washed with small amount of ice water. Recrystallization from absolute ethanol afforded a pure white crystalline **2** (37.00 g, 47% yield). ¹H NMR (500 MHz, CDCl₃, δ_{H}) 4.13 (dd, 1 H, *J* = 9.0, 1.5 Hz, H-5), 4.07 (d, 1 H, *J* = 10.0 Hz, H-1), 3.91 (dd, 1 H, *J* = 9.0, 1.5 Hz, H-3), 3.88 (dd, 1 H, 1 H, *J* = 10.0, 1.5 Hz, H-2), 3.64 (d, 1 H, *J* = 9.0 Hz, H-4), 3.62 (d, 2 H, *J* = 7.0 Hz, H-6_a, H-6_b), 2.77–2.65 (m, 4 H, 2 x SCH₂), 1.27–1.23 (m, 6 H, 2 x CH₃); ¹³C NMR (125 MHz, CDCl₃, δ_{C}) 72.8, 71.9, 71.8, 71.1 (C-2, C-3, C-4, C-5), 65.1 (C-6), 56.4 (C-1), 25.4, 25.4 (2 x ethyl CH₂), 14.9, 14.8 (2 x ethyl CH₃). ESI-MS *m/z* calcd. for (M + Na) C₁₀H₂₂O₅S₂Na: 309.0806. Found: 309.0897.

Methyl α/β -D-galactofuranoside (3). Dithioacetal **2** (5.90 g, 0.14 mol) was dissolved in 2% I₂ in MeOH (w/v, 295 mL) at rt and stirred for 7 h. Excess I₂ was quenched by incremental addition of solid sodium thiosulfate (Na₂S₂O₃) until the I₂ color diminished. This was followed by the addition of solid sodium bicarbonate (NaHCO₃) to neutralize the reaction mixture. Evaporation of the solvent gave **35** (β/α = 9:1) as a yellow solid (21.20 g, 78%). *R_f* 0.34 (6:1 CH₂Cl₂–MeOH); β -isomer (isolated pure after column chromatography): [α]_D –20.6 (*c* 1.1, CH₃OH); ¹H NMR (400 MHz, D₂O, δ_{H}) 4.83 (s, 1 H, H-1), 3.98–3.92 (m, 2 H, H-4, H-5), 3.88 (dd, 1 H, *J* = 4.3, 4.3 Hz, H-3), 3.77–3.73 (m, 1 H, H-2), 3.66–3.64 (m, 2 H, H-6_a, H-6_b), 3.45 (s, 3 H, OCH₃); ¹³C NMR (100 MHz, D₂O, δ_{C}) 108.6 (C-1), 83.3 (C-2), 81.6 (C-4), 71.3 (C-3), 71.1 (C-5), 63.2 (C-6), 55.4 (OCH₃). ESI-MS *m/z* calcd. for (M + Na) C₇H₁₄O₆Na: 217.0688. Found: 217.0758.

Methyl 2,3,5,6-tetra-O-benzoyl- β -D-galactofuranoside (20). Dithioacetal **3** (5.90 g, 14.0 mmol) was dissolved in 295 mL of 2% (w/v) iodine in methanol in a round bottom flask at room

temperature for 7 hours. Increments of sodium thiosulfate were added in the solution to remove excess I_2 . A small amount of sodium bicarbonate was added to neutralize the solution. Evaporation of the solvent gave a yellow solid **methyl α/β -D-galactofuranoside (3)**. R_f 0.31 (4:1 CH_2Cl_2 :MeOH). ESI-MS m/z calcd. for $(M+Na)$ $C_7H_{14}O_6Na$: 217.0682. Found: 217.1001.

This solid product was carried over to the next step of benzylation by dissolving **3** with 70.0 mL of pyridine at 0°C. Benzoyl chloride (12.0 mL, 0.103 mmol) was added dropwise while maintaining the temperature. The mixture was allowed to stir overnight after the addition while warming to room temperature. The mixture was quenched by adding ice-water to remove the excess benzoyl chloride, and diluted with approximately 150 mL of dichloromethane. The organic layer was washed successively with water, two portions of 1M HCl, and saturated aqueous solution of sodium bicarbonate. The organic solution was dried with the addition of sodium sulfate and the solvent was evaporated. The crude product was purified using column chromatography (3:1 Hexane:EtOAc) to yield **20** (8.98 g, 14.71 mmol, 71% over two steps). R_f 0.25 (3:1 Hexane:EtOAc); $[\alpha]_D -20.6$ (c 1.1, $CHCl_3$); 1H NMR (500 MHz, $CDCl_3$, δ_H) 8.20-7.95 (m, 8 H, Ar), 7.58-7.35 (m, 12 H, Ar), 6.15 (m, 1 H, H-5), 5.71 (d, 1 H, $J = 5.3$ Hz, H-3), 5.55 (s, 1 H, H-2), 5.27 (s, 1 H, H-1), 4.85 (m, 2 H, H-6_a, H-6_b), 4.74 (dd, 1 H, $J = 5.0, 3.9$ Hz, H-4), 3.52 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C): 166-165 (C=O), 134-133 (Ar), 130-128 (Ar), 106.9 (C-1), 82.2 (C-2), 81.3 (C-4), 77.7 (C-3), 70.4 (C-5), 63.6 (C-6), 55.1 (OCH_3). ESI-MS m/z calcd. for $(M+Na)$ $C_{35}H_{30}O_{10}Na$: 633.1731. Found: 633.2075.

Cyclohexyl α/β -D-galactofuranoside (4). Dithioacetal **2** (302.6 mg, 1.06 mmol) was dissolved in 3% I_2 in cyclohexanol (w/v, 10 mL) at rt and stirred for 24 h. Excess I_2 was quenched by incremental addition of solid $Na_2S_2O_3$ until the I_2 color diminished. This was followed by the addition of $NaHCO_3$ to neutralize the reaction mixture. Evaporation

of the solvent gave **4** ($\beta/\alpha = 5.4:1$) as a yellow solid (152.60 mg, 55%). R_f 0.45 (α), 0.41 (β) (7:1 DCM-MeOH); $[\alpha]_D -10.5$ (c 1.2, MeOH); 1H NMR (400 MHz, D_2O): δ_H 5.17 (1 H, d), 5.12 (1 H, d), 4.06 (1 H, dd), 3.99 (1 H, dd), 3.95 (1 H, dd), 3.82 (1 H, dt), 3.65-3.60 (3 H, m), 1.72 (s, 4H), 1.27 (6 H, m); ^{13}C NMR (100 MHz, D_2O): δ_C 106.24, 100.16, 82.86, 82.03, 78.52, 76.99, 71.65, 63.81, 34.19, 26.10, 24.98. ESI-MS: m/z $(M+Na)^+$: 285.1

Tert-butyl α/β -D-galactofuranoside (5). ($C_{10}H_{20}O_6$). Dithioacetal **2** (300.0 mg, 1.05 mmol) was dissolved in 5% I_2 in *t*-butyl alcohol (w/v, 10.17 mL) at rt and stirred for 24 h. Excess I_2 was quenched by incremental addition of solid $Na_2S_2O_3$ until the I_2 color diminished. This was followed by the addition of $NaHCO_3$ to neutralize the reaction mixture. Evaporation of the solvent gave **5** ($\beta/\alpha = 1:1$) as a yellow solid (135.10 mg, 54.42%). R_f 0.32 (α), 0.38 (β) (7:1 DCM-MeOH); 1H NMR (400 MHz, CD_3OD): δ_H 5.50 (1 H, s), 5.15 (1 H, d), 4.00 (1 H, dd), 3.94 (1 H, dd), 3.88 (1 H, dd), 3.77 (1 H, m), 3.64 (3 H, m), 1.26 (9 H, s); ^{13}C NMR (100 MHz, CD_3OD): δ_C 104.30, 97.53, 84.02, 83.56, 78.22, 76.06, 72.43, 64.67, 29.20. ESI-MS: m/z $(M+Na)^+$: 259.1.

RESULTS AND DISCUSSION

Several methods for the conversion of acyclic sugar dithioacetals to β -D-furanosides have been reported but the use of toxic heavy metals and expensive reagents preclude its general utility (McAuliffe and Hindsgaul, 1997; Madhusudan and Misra, 2005).

A modified method circumventing this limitation is the iodine-promoted cyclization of glucosyl, mannosyl and arabinosyl-derived dithioacetals in methanol to give the corresponding glycosyl furanosides (Szarek *et al*, 1986). Likewise, we were the first to report the use of galactose-derived dithioacetal in a similar reaction (Completo and Lowary, 2008). The major advantage of this dithioacetal cyclization reaction in preparing galactofuranosides is its simplicity. Not only does this technique avoid the use of toxic heavy metals, it is also inexpensive, simple

and, most importantly, provides high yield of galactofuranosides without or minimal formation of galactopyranosides. We applied this method in the synthesis of methyl and octyl galactofuranosides as intermediates for the preparation of molecular probes of a mycobacterial cell wall enzyme galactofuranosyltransferase (Rose *et al.*, 2006; Belánová *et al.*, 2008).

The proposed mechanism for the iodine-promoted cyclization reaction is shown in Figure 7. The initial step involves the nucleophilic attack of one of the sulfur atoms of **2** on the electrophilic iodine to form

sulfonium ion **19**. Iodine is a soft acid (Pearson, 1987) and it easily complexes with the sulfur atom of one of the thiol groups to form a sulfonium ion. The sulfonium ion, being a good leaving group, can then be easily cleaved to form thiocarbenium **20**. Subsequent cyclization of **20** gives thioglycoside **21**, which then reacts with another molecule of iodine to generate intermediate **22**. Loss of ethyl sulfenium iodide leads to oxacarbenium intermediate **23**, which can be attacked by an alcohol such as methanol, acting as both solvent and nucleophile, to give methyl glycoside **3**.

Figure 7. Proposed mechanism of iodine-induced dithioacetal cyclization in methanol.

Synthesis of Methyl galactofuranoside 3 and Perbenzoylated methyl galactofuranoside 24. Further extension of this method was applied in the synthesis of a perbenzoylated methyl galactofuranoside **24**. To implement this approach, D-galactose **1** was treated with ethanethiol and HCl to give diethyl dithioacetal **2** in 47% yield using an established method (Wolfrom, 1940). This was followed by the iodine-promoted

cyclization of intermediate **2** to methyl galactofuranoside **3** (Figure 8). Table 1 shows the different iodine concentrations used to obtain the optimal conditions in the synthesis of methyl galactofuranoside **3**. We observed that the reaction rate was dependent on iodine concentration. Although the use of higher concentrations of iodine (3–5%) resulted in shorter reaction times, this, however, resulted in the formation of significant amount of salt

that hindered purification of the product. It was only during reactions beyond 24 h that we start to observe (via thin layer chromatography) the increase in the formation of the α anomer product. Thus, it was necessary to use lower iodine concentration (2%) without significant effect in the ratio (average α : β ratio of 8-9:1) and yield (74-78%) obtained for the product. Thus, cyclization of intermediate **2** was effected by treatment with 2% I_2 (by weight, 0.08 M) in methanol to give intermediate **3** (Figure 8). The reaction was quenched by adding solid $Na_2S_2O_3$ until the solution turned colorless. The solution was

then neutralized with solid $NaHCO_3$ and the solvent was evaporated under reduced pressure. However, the formation of solid salts during work-up and the polar nature of the product (intermediate **3**) made purification difficult. This prompted us to perform the benzylation reaction without purification of crude intermediate **3**. Therefore, pyridine was added to the crude methyl galactofuranoside **3**, followed by dropwise addition of benzoyl chloride. The resulting perbenzoylated product, **24**, was obtained in 71 % yield over two steps after purification by column chromatography.

Figure 8. Preparation of Methyl galactofuranoside **24** via Cyclization of Dithioacetal.

Table 1. Synthesis of **3** as a Function of Iodine Concentration.

Concentration (w/v)	Time (h)	Yield	Product Ratio (β : α)
1%	24	74%	(8.2:1)
2%	8	78%	(9:1)
3%	3	77%	(9.2:1)
4%	2	78%	(9.2:1)
5%	<1	76%	(9.3:1)

Using 1H and ^{13}C NMR spectroscopy, we were able to discriminate between the formation of the α and β -configuration of the product. The singlet signal of the anomeric hydrogen ($\delta_H = 5.80$ ppm) established the *trans* relationship between H-1 and H-2. A *cis* relationship between H-1 and H-2 would have shown a larger coupling constant ($J_{1,2} = 3-5$ Hz) (Cyr and Perlin, 1979). Also, the chemical shift of the anomeric carbon of **24** was shifted downfield ($\delta_C = 106.9$ ppm) compared to the more upfield shift ($\delta_C \sim 103$ ppm) of the anomeric carbon of an α -product (Cyr and Perlin, 1979). In addition to this, the C-2 and C-4 signals resonated at 82.2 and 81.2 ppm, respectively. These signals are significantly more downfield than the carbons in pyranosides and, thus, conclusively establish the furanose ring form of **24**. The observed 1H

NMR and ^{13}C NMR data were consistent with the previously reported characteristic signal pattern for β -D-galactofuranosides (Cyr and Perlin, 1979) and with our results (Completo and Lowary, 2008).

Synthesis of Cyclohexyl- α/β -galactofuranoside 4. Encouraged by these observations, we explored the general applicability of this method using more sterically hindered alcohols such as a secondary alcohol cyclohexanol. We anticipated that the hindered nature of cyclohexanol will require higher iodine concentration, thus, 3% iodine was used for the reaction. Indeed, it took 24 hours of continuous stirring to guarantee completion of the reaction. The cyclohexyl galactofuranoside **4** was obtained in 55% yield with 1:5.4 α/β product ratio. The ^1H NMR spectral data showed the alpha anomeric proton as a doublet at 5.17 ppm, while the beta anomeric proton gave a doublet at 5.12 ppm. This was confirmed by their $^3J_{1,2}$ values of 4.6 and 2.8 Hz, respectively, that is consistent with the characteristics of alkyl furanosides (Cyr and Perlin, 1979). The ^{13}C NMR spectra showed the α and β anomeric carbons resonating at 100.16 and 106.24 ppm, respectively. These data were consistent with the expected chemical shifts for hexofuranosides (Bock and Pedersen, 1983).

Synthesis of *tert*-Butyl- α/β -galactofuranoside 5. The use of tertiary alcohol, such as *tert*-butyl alcohol, was also explored. Due to the more hindered nature of *tert*-butyl alcohol and its weaker nucleophilicity, higher iodine concentration (5% w/v) was used to form the *tert*-butyl- α/β -galactofuranoside. The ^1H NMR signal for the β and α -protons were observed at 5.5 ppm and 5.15 ppm having $^3J_{1,2}$ values of 0 and 2.5 Hz, respectively, in a 1:1 ratio. A *cis* relationship between H-1 and H-2 of furanosides is expected to give a $^3J_{1,2}$ coupling constant of greater than 3, while a *trans* relationship should have a coupling constant between 0 to 3 (Cyr and Perlin, 1979). The experimental $^3J_{1,2}$ values obtained were consistent with the expected literature values indicative of α and

β Galf anomeric hydrogens. From the ^{13}C NMR spectrum, the chemical shift of the β -anomeric carbon was observed at 104.30 ppm, consistent with the signal of the expected anomeric carbon position for galactofuranosides (Bock and Pedersen, 1983). The ^{13}C chemical shifts for C-2 and C-4 were observed at 83.56 and 84.02 ppm, respectively. These are consistent with characteristic ^{13}C signals for furanose ring carbons resonating more downfield than pyranose ring carbons, thus further establishing that *tert*-butyl- β -galactofuranoside was formed.

The use of varying concentration of iodine is dependent on the steric bulkiness of the alkyl component of the alcohol used and which greatly affects the reaction time. The use of more sterically-hindered alcohol required higher iodine concentration as the promoter for the reaction to proceed to completion, else more than 24 h is needed to complete the reaction. Further method optimization is ongoing in our laboratory to improve the yield of the reaction using more hindered alcohols. To date, this is the first time that an iodine-promoted dithioacetal cyclization was used in preparing more sterically hindered alkyl furanosides. The application of this method in the synthesis of disaccharides is also being pursued in our laboratory.

CONCLUSION

In summary, we have demonstrated that a simple and efficient iodine-promoted cyclization of galactose-derived dithioacetal towards the synthesis of galactofuranoside derivatives can be effected using, not just primary alcohols, but also more sterically-hindered alcohols acting as both solvent and nucleophile. The results showed that alcohols with varying steric bulk such as methanol, cyclohexanol and *tert*-butanol acting as nucleophiles using 2%, 3% and 5% iodine as promoter, respectively, led to the selective formation of β -galactofuranoside derivatives in moderate to good yields. Further method optimization is underway in our laboratory to improve the yield of the reaction.

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