Kinetic Products Under Thermal Conditions: Rapid Entry into α/β-D-Galactofuranosides Using Microwave Irradiation and Selective Lewis Acids

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A modified Fischer-Lubineau reaction, employing microwave irradiation and selected Lewis acids such as $Mn(ClO_4)_2$, $Mn(C_2H_3O_2)_3$, $FeCl_3$, $CoCl_2$, and AgF as independent additives, induces rapid entry into α/β-D-galactofuranosides in very good yield and purity.

Keywords D-Galactofuranosides; Lewis acid coordination; Zwitterionic polysaccharide PS A1; Microwave irradiation; M,P arrangement; Fisher-Lubineau reaction

INTRODUCTION

D-Galactofuranosides (D-Gal*f*) have been identified and well characterized in oligosaccharides and glycoconjugates existing within many infectious organisms including *Mycobacterium tuberculosis*, *Mycobacterium leprae, Escherichia coli, Trypanosoma cruzi, Leishmania, Paracoccidioides brasiliensis,* and *Bacteroides fragilis,* to name a few.[1] Considerable attention to the constituents of these pathogens has revealed that their survival and virulence is directly reliant on D-galactofuranoside moieties. These sugars have mostly been found as terminal, nonreducing units such as in the CD4+ T-cell immunostimulatory capsular zwitterionic polysaccharide PS A1 (**1**) (Fig. 1).[2]

Ironically, D-galactofuranoside is nonexistent in mammalian tissue and has been shown to be an antigenic determinant representing a valuable

Figure 1: Immunostimulatory zwitterionic polysaccharide PS A1 (**1**) from *Bacteroides fragilis* NCTC 9343 containing a terminal D-Gal*f* unit.

target for new drug agents and therapies.[3–6] Although of immense impor-
tance, our current biological understanding of many aspects of D-Gal*f,* such as
its metabolic processes, have proven difficult to elucidate due to complications
in obtaining derivatives.[7]

One drawback is that unlike their thermodynamically favorable pyra-
noside counterparts, hexofuranosides are not commercially available. Equi-
libration and anomeric control of both hexo-pyranoside and hexo-furanoside
syntheses must be considered in addition to the competing donor/acceptor reac-
tions for its construction. To this extent, pioneering work by H.E. Fischer from
1893 to 1895[8–11] demonstrated that furanosides could be obtained from cor-
responding unprotected pyranoses using simple alcohols and Brønsted-Lowry
acids.

Further studies by J.C. Fischer and A. Lubineau[12] established that when
unprotected monosaccharides were subjected to thermal heating in the pres-
ence of anhydrous Lewis acid $FeCl_3$ and methanol, the reaction yielded kineti-
cally favored methyl furanoside (**3**) as the major product in a mixture of α- and
β-anomers (Sch. 1). The reaction took approximately 28 h and in addition the
purification proved to be challenging and cumbersome.
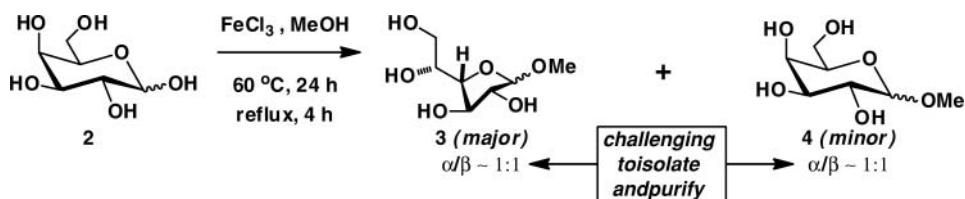
Scheme 1: Fischer-Lubineau D-Gal*f* synthesis.

Ferrières and Plusquellec have also utilized $FeCl_3$ as a promoter but with $CaCl_2$ as an additive in THF to obtain D-Gal$f$.[13–16] Although other methods have been reported, including base-mediated furanoside formation,[17,18] reduction of lactones,[19] acid-catalyzed ring opening of 1,4-anhydrosugars,[20] high-temperature benzoylation,[21] cyclization with mercuric salts,[22,23] and the utilization of dithioacetal derivatives of galactose,[24–26] the chemical synthesis of D-Gal$f$ remains to be an important yet challenging endeavor.

RESULTS AND DISCUSSION

We elected to revisit the Fischer-Lubineau D-Gal$f$ synthesis and rationalize the use of microwave irradiation as a thermal source for kinetic product formation. As our current research program focuses on chemical modifications of D-Gal$f$ in ZPS PS A1 (**1**) for immunogen development,[27] having a reliable means to obtain D-galactofuranoside in very good yield and high purity is of great importance.

Since the spectroscopic data of methyl α/β-D-galacto-furanoside and -pyranoside (D-Gal$p$) was known,[12,16,28,29] methanol was chosen as the initial acceptor for direct comparison. Therefore, when unprotected D-galactose (**2**) was dissolved in anhydrous methanol and subjected to microwave irradiation in the presence of 1 mole equivalent anhydrous $FeCl_3$ for 5 min at stage 1 (microwave was equilibrated to 300 W, 60°C, 4 bar) and then for 5 min at stage 2 (microwave was equilibrated to 300 W, 70°C, 5 bar), the overall conversion was 35% to 45% (Table 1, entries 1 and 2). In realizing that an extended incubation

Table 1: Optimization of methyl D-galactofuranoside synthesis using microwave irradiation and anhydrous $FeCl_3{}^a$
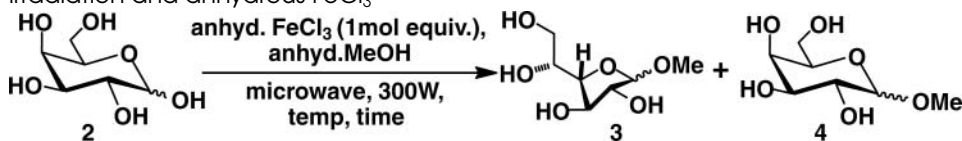
	Stage 1		Stage 2		% Yield[b]/α:β[c]		
Entry	Temp (°C)	Time (min)	Temp (°C)	Time (min)	D-Gal$f$ (**3**)	D-Gal$p$ (**4**)	Overall % yield
1	60	5	70	5	25 / 1:2	5 / 2:1	35
2	60	10	70	5	35 / 1:3	10 / 2:1	45
3	60	20	70	15	60 / 1:5	15 / 3:1	75
4	60	30	70	25	70 / 1:7	17 / 5:1	87
5	60	30	70	35	75 / 1:8	20 / 6:1	95

[a]CEM Discover Microwave; microwave power was set to 300 W.
[b]Isolated.
[c]Determined from ^{1}H NMR sample of unpurified reaction mixture; chemical shifts of anomers compared to literature precedent.

period would have a bearing on the overall conversion (Table 1, entries 3 and 4), further optimization of the dual-stage time course provided 75% yield of the desired D-Gal*f* with an α/β selectivity of 1:8 (Table 1, entry 5). It is important to note that allowing the reaction to run in excess of 70 min or increasing the temperature in stage 2 led to decreased yields of methyl D-Gal*f* and in some cases decomposition. The microwave-assisted efforts yielded an improvement in reaction rate, from the reported 240 min to 65 min, and we noted an improvement in yield and α/β selectivity of methyl D-galactofuranoside.

With the described protocol in hand, we next turned our attention to examining the Lewis acid/additive scope. A literature search revealed that carbohydrates and derivatives thereof are known to form complexes with metal cations.[30,31] Furthermore, experimental evidence has shown that the outcomes in acid-mediated glycosylation may influence the α/β and D-Gal*f*/D-Gal*p* selectivities.[31,32]

From our data we observed that Lewis acids, in which the central atom is in +I, +III, or +IV oxidation state (Table 2, entries 1, 2, 6, 8, 11, and 13–16), provided excellent overall yield of the glycoside. However, when Zn(II), Cu(I), and Cu(II) (Table 2, entries 3–5) were used, there was no observed product. Use of Amberlyst 15 as an additive gave the methyl α-D-galactopyranoside (**4**) in very good yield and high α-selectivity while TMSOTf did not lead to product formation (or at best a trace amount) (Table 2, entries 17 and 18). Remarkably, only FeCl$_3$ and AgF (Table 2, entries 8 and 12) gave the best overall yields and α/β selectivities of methyl D-Gal*f*. Interestingly, the α/β ratio of D-Gal*f* was compromised when MnCl$_2$, and Mn(ClO$_4$)$_2$ was used, whereas Mn(C$_2$H$_3$O$_2$)$_3$ provided only methyl α-D-Gal*f* in a mixture with α/β-D-Gal*p* (Table 2, entries 9–11). On the other hand, CoCl$_2$ (Table 2, entry 7) was selective for α-D-Gal*f*. It is worth noting that all the manganese and cobalt salts used (Table 2, entries 7, and 9–11) provided D-Gal*f* as the major product, albeit with an overall decrease in yield as compared to entries 8 and 12. Our data suggest that the oxidation state of the central atom in the Lewis acid does not control α/β selectivities but rather other properties have a direct affect on product outcome.

One likely explanation is that in general, metal cations are known to coordinate with ligands via *O*-atoms.[33] A noted steric arrangement in which three *O*-atoms found on three consecutive *C*-atoms in such a conformation that the first and second are *gauche*$^+$ and the second and third *gauche*$^-$ or (*threo-threo*) has a profound bearing on metal cation coordination due to no unfavorable interactions.[34] This has been commonly referred to as the "M,P arrangement."[35] Findings suggest that the most common occurrence is a sequence of axial (ax), equatorial (eq), and axial OH groups on chair-formed 6-membered rings (**5**, **6a–b**) or envelope-formed 5-membered rings (**6c–d**) (Fig. 2).[30] The "M,P arrangement," in subsequent flipped orientations of the pyranoside or furanoside, can also be noted as an equatorial (eq), axial (ax), and equatorial (eq) convention.

Table 2: Effect of Lewis acids/additives on microwave-assisted methyl D-Gal*f* synthesis[a]
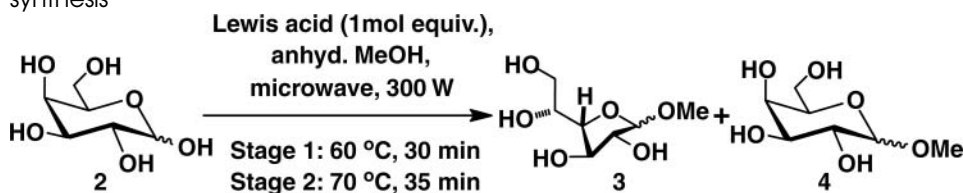
Entry	Lewis acid/ additive[b]	Central metal atom oxidation state	Ionic radii (Å)[c]	% Yield[d]/α:β[e]		Overall % yield
				3	**4**	
1	BF$_3$.OEt$_2$	III	0.87	25/1:5	63/5:1	88
2	AlCl$_3$	III	1.18	15/1:7	80/5:1	95
3	ZnCl$_2$	II	1.42	0/—	0/—	0
4	CuI	I	1.45	0/—	0/—	0
5	CuSO$_4$	II	1.45	0/—	0/—	0
6	InCl$_3$	III	1.46	23/1:7	74/5:1	97
7	**CoCl$_2$**	II	**1.52**	48/2:1	30/5:1	78
8	**FeCl$_3$**	III	**1.56**	75/1:8	20/6:1	95
9	**MnCl$_2$**	II	**1.61**	49/1:3	28/2:1	77
10	**Mn(ClO$_4$)$_2$**	II	**1.61**	59/1:1	20/10:1	79
11	**Mn(C$_2$H$_3$O$_2$)$_3$**	III	**1.61**	55/100:1	24/3:1	79
12	**AgF**	I	**1.65**	75/1:6	21/6:1	96
13	TiCl$_4$	IV	1.76	15/1:4	75/5:1	90
14	Ti(O*i*-Pr)$_4$	IV	1.76	16/1:4	73/5:1	89
15	Sc(OTf)$_3$	III	1.84	25/1:7	70/5:1	95
16	Yb(OTf)$_3$	III	2.22	20/1:7	72/5:1	92
17	Amberlyst 15	—	—	15/1:5	75/9:1	90
18	TMSOTf	—	—	0/—	0/—	0

[a] CEM Discover Microwave; microwave power was set to 300 W.
[b] Anhydrous.
[c] See reference 36.
[d] Isolated.
[e] Determined from ^{1}H NMR of unpurified reaction mixture; chemical shift of anomers compared to literature precedent.

However, coordination of metal cations via a *C*-1, *C*-2, *C*-3 eq-eq-ax conformation, such as in D-glucose (**7**), is highly unfavorable. Importantly, documented studies of complex formation with cations have been carried out using acyclic polyols and they can adapt the "M,P arrangement."[34]

In addition, it has also been observed that the radii of metal ions affecting the extent of coordination can shift the equilibrium in favor of α-anomers,[31] although based on our findings, in conjunction with microwave irradiation, one can expect favorable β-D-Gal*f* outcomes except in cases where CoCl$_2$ and Mn(C$_2$H$_3$O$_2$)$_3$ are employed. Importantly, we argue that the ionic radii of Ag, Mn, Fe, and Co (1.65 Å, 1.61 Å, 1.56 Å, and 1.52 Å, respectively)[36] allow for
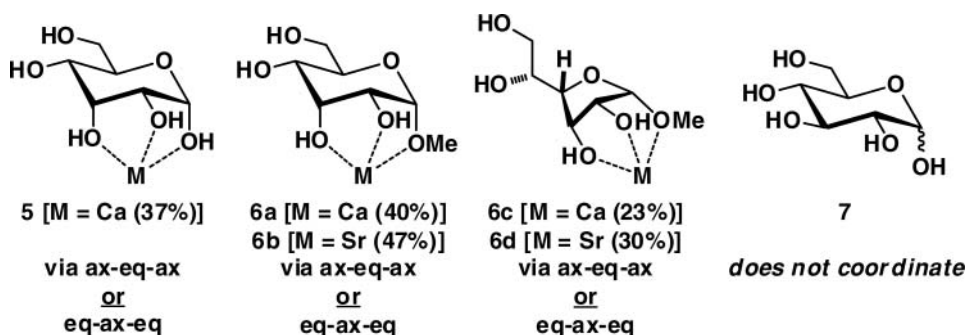
Figure 2: Coordination of alkaline-earth metal ions with D-allopyranosides (**5**, **6a**,**b**) and 3-*O*-methyl *α*-D-allofuranose (**6c**,**d**).[31]

the best eq-ax-eq coordination at the *C*-3, *C*-4, and *C*-5 hydroxyls. We also believe that the coordination number and outer orbital electron configuration of the central atom are responsible for our observed product yields and conformational forms.

A plausible mechanism for the formation of alkyl D-galacto-furanoside and -pyranoside is shown in Scheme 2. It is well known that D-galactose (**2**) exists in equilibrium with the open-chain form, which can readily undergo isomerization through the *C*-5 or *C*-4 hydroxyls. However, in the instances where Lewis acids are used, two metal coordinating paths are highly plausible. In pathway a (when M = Mn, Fe, Co, or Ag), and for formation of **9**, the oxygen atom of the pyranose ring can coordinate to the Lewis acid, which leads to the acyclic aldose sugar in the highly stable eq-ax-eq (3,4,5-erythro-threo or "MP arrangement") configuration.[37] The *C*-4 axial hydroxyl group can then attack the carbonyl aldehyde and lead to the cyclization forming a five-membered furanose ring, which can then undergo dehydration to form the oxocarbenium intermediate **10**. Glycosylation can then occur to render the furanoside as the major kinetic product, which, dependent upon the Lewis acid used, can give rise to either *α*- or *β*-anomers (Table 2; entries 8 versus 11 for example) in very good yields.[38,39]

In pathway b (when M ≠ Mn, Fe, Co, or Ag), and for the formation of **12**, metal coordination at the anomeric hydroxyl can lead to the oxocarbenium ion intermediate through the loss of M-OH. Once this intermediate is formed, the anomeric effect is attributed in controlling the orientation of the acceptor as predominantly *α*. In fact, in all cases we observed the *α*-anomer dominated, with only a minor amount of *β*-anomer being characterized.

A notable feature of this microwave-assisted method for furanose formation is that solvent polarity apparently does not influence anomeric ratios as other solvents were tested and yielded similar stereochemical outcomes, albeit at significant loss in overall product yields. In our experiments we believe that
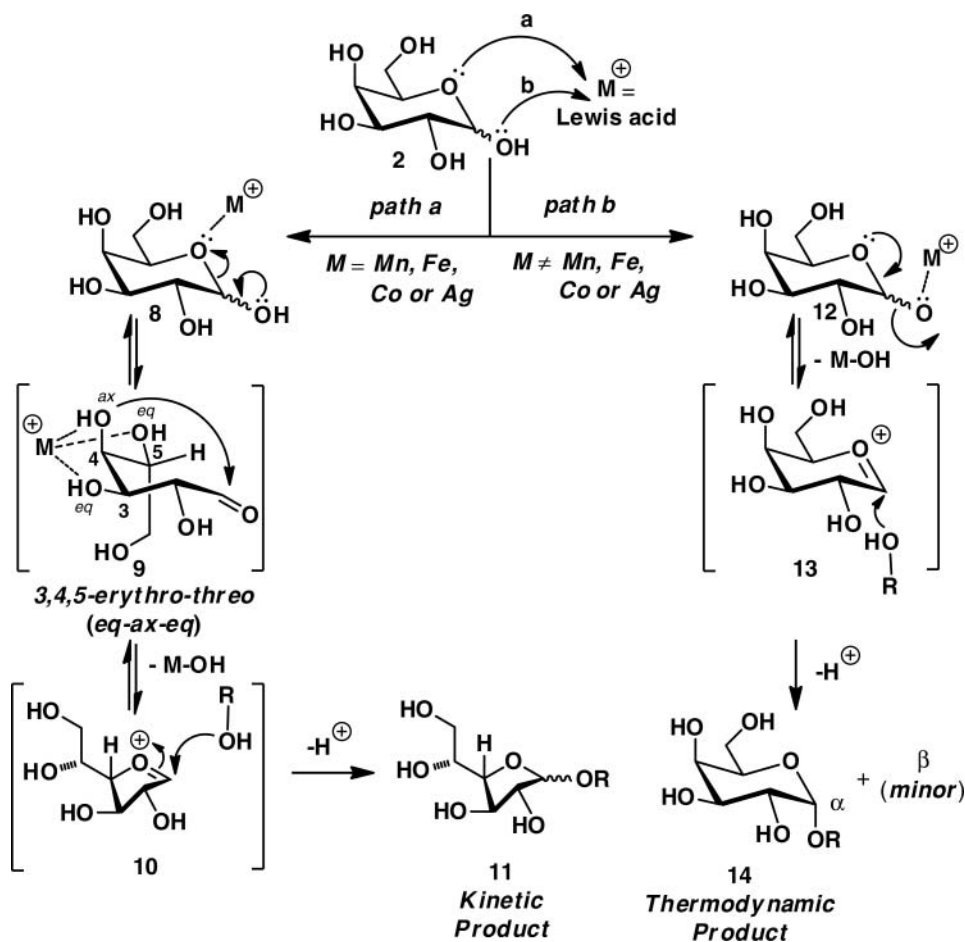
Scheme 2: Proposed mechanism for the Lewis acid-mediated D-galacto-furnoside and -pyranoside formation.

initially methanol will coordinate to the Lewis acid in a monodentate fashion but then be displaced by a more entropically favored tridentate coordination complex such as in **9** due to the chelate effect. Lewis acid coordination to the final D-galactofuranoside is also possible, but the 3,4,5-erythro-threo (eq-ax-eq) coordination prevails such as in **9**. It is important to consider that in a recent report, it was shown that stereoselective glycosylations of 1-thioimidoyl hexofuranosides could be achieved by adjusting the concentration of promoter Cu(OTf)$_2$.[37b] In that report, ^{13}C NMR spectrum was used to illustrate that copper(II) ions could assist in five-membered ring preservation through the complexation of the *O*-5 of the furanosidic derivative. Although another report describing how ultrasound affects bond rotation in the Diels-Alder reaction

exists,[40] we do not believe, at this point, that microwave irradiation affects bond rotation for selective β-formation in our examples.

In order to probe the reaction scope, we elected to use allyl alcohol and 2-phenylethanol as acceptors in the furanoside synthesis. Both allyl D-galactofuranosides (**15a,b**) and phenylethyl D-galactofuranosides (**16a,b**) were obtained in good yield and anomeric selectivity (Sch. 3).[41] The minor allyl α-D-galactofuranoside (**15a**) was unequivocally confirmed by x-ray crystal structure analysis.
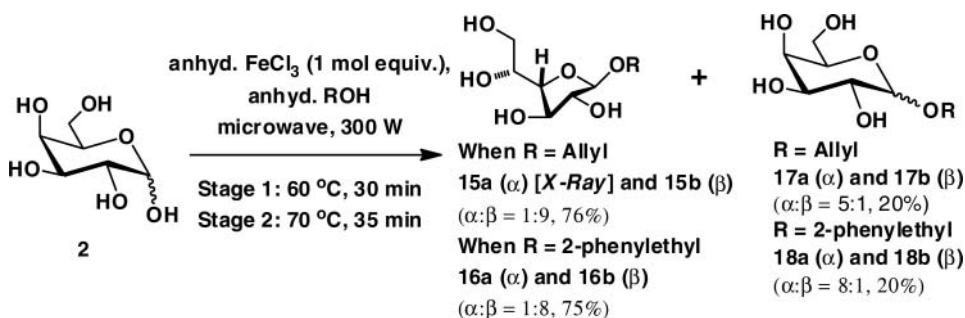
Scheme 3: Synthesis of allyl- and phenylethyl-D-galactosides.

CONCLUSION

In conclusion, we have successfully employed microwaves in a modified Fischer-Lubineau reaction for alkyl D-galactofuranoside synthesis, which led to an increase in reaction rate and product/anomeric ratios. The reaction scope was examined with acceptors such as allyl- and phenylethyl-alcohols, the aforementioned acceptor yielding an X-ray crystal. Our results also reveal a direct correlation between the properties of Lewis acids and furanoside synthesis. A *C*-3, *C*-4, *C*-5-*erythro-threo* eq-ax-eq Lewis acid complex, such as **9**, led to galactofuranoses as kinetic products under thermal conditions. One can expect further applicable work in this area as we utilize the constructed furanosides as acceptors/donors for oligomer synthesis. Importantly, the allyl β-D-galactofuranoside building block has been utilized to synthesize lipid-bearing β-1,6-linked D-Gal*f* disaccharide as a biological probe.[42] We also plan to probe oxidative protocols for vicinal diol interconversions leading to novel glycoconjugation methods.

EXPERIMENTAL

Supplementary information (SI) available: NMR spectra for all compounds and X-ray data for **15a**. Contact the corresponding author for this information.

Allyl β-D-galactofuranoside (**15b**) was also synthesized via a Schmidt gly-cosylation strategy as a reference sample for comparison purposes and for de-termining α/β ratios.

Materials and Methods

All reagents were purchased from Aldrich unless otherwise noted. Anhy-drous ferric chloride was purchased from Alfa Aesar. Anhydrous methanol was purchased from EMD Chemicals (DriSolv). Palladium chloride was purchased from STREM Chemicals. Indium chloride, copper iodide, and copper sulfate were purchased from Alfa Aesar. TMSOTf was purchased from Acros Organ-ics. Allyl alcohol was distilled prior to use. Celite was purchased from Aldrich (catalog no. 221791). Except as otherwise indicated, reactions were carried out under argon. Microwave reactions were conducted using a capped vial on a CEM Discover Microwave System. All reactions were monitored by thin layer chromatography using 0.25-mm Dynamic Adsorbents' precoated silica gel (par-ticle size 0.03–0.07 mm, catalog no. 84111). Column chromatography was per-formed using Whatman Purasil 60 Å (230–400 mesh ASTM) silica gel. Yields refer to chromatographically and spectroscopically pure compounds, except as otherwise noted. Diastereomeric ratios were determined from ^{1}H NMR spec-tra of nonpurified reaction mixtures. Proton and carbon-13 NMR spectra were recorded on Varian Mercury 400, Varian Unity 500, and Varian 500 Direct Drive System spectrometers. The residual CDCl$_3$ singlet at δ 7.26 ppm and δ 77 ppm was used as the standard for ^{1}H NMR and ^{13}C NMR spectra, respec-tively. Mass spectra were recorded on Micromass GCT at 70 eV.

General Method for Microwave-Assisted
D-Galactofuranoside Synthesis

A 10-mL CEM Discover microwave vial was oven dried, capped, and cooled under argon. To the vial D-galactose (0.05 g, 0.28 mmol) was added followed by FeCl$_3$ (Lewis acid) (0.045 g, 0.28 mmol). To the mixture, anhydrous methanol (alcohol) (2.5 mL) was added slowly. The vial was capped according to the man-ufacturer's instructions and placed in the single-mode microwave cavity. Then the microwave was run at two stages: (a) 30 min at 60°C, 10 bar, and 300 W, and (b) 35 min, 70°C, 10 bar, and 300 W. After allowing the vial to cool to rt, sat-urated NaHCO$_3$ (3 mL) was added and stirred for 5 min. The reaction mixture was then filtered through celite and the filtrate was dried on a rotor evapora-tor to afford a yellow slurry. The slurry was then extracted with a mixture of hot ethyl acetate/ethanol mixture (2:1). The extract was then filtered through celite and dried over a rotor evaporator. The extraction process was repeated again. The filtrate was concentrated under vacuum and purified by gradient

column chromatography using silica gel as the stationary phase and mixture of methanol and dichloromethane (1:15 to 1:5) as the mobile phase.

NMR Data

*1. Methyl α-*D-*Galactofuranoside (3α)[12,16a,28,29] (Main Data)*

^{1}H NMR (CD$_3$OD, 500 MHz): δ 4.73 (1 H, J = 1.5 Hz, H-1).

^{13}C NMR (CD$_3$OD, 125 MHz): δ 103.8 (C-1).

*2. Methyl β-*D-*Galactofuranoside (3β)[12,16a,28,29] (Main Data)*

^{1}H NMR (CD$_3$OD, 500 MHz): δ 4.71 (1 H, J = 4.6 Hz, H-1).

^{13}C NMR (CD$_3$OD, 125 MHz): δ 110.8 (C-1).

*3. Methyl α-*D-*Galactopyranoside (4α)*

^{1}H NMR (CD$_3$OD, 500 MHz): δ 4.62 (d, 1 H, J = 3.5 Hz, H-1), 3.79 (d, 1 H, J = 2.5 Hz), 3.57–3.72 (m, 5 H), 3.31 (s, 3 H, OMe).

^{13}C NMR (CD$_3$OD, 125 MHz): δ 101.5 (C-1), 72.3, 71.5, 71.0, 70.2, 62.8 (C-6), 55.6 (O$\underline{Me}$).

HRMS (EIMS, M$^+$): calcd for C$_7$H$_{14}$O$_6$ 194.0790, found 194.0798.

*4. Methyl β-*D-*Galactopyranoside (4β)*

^{1}H NMR (CD$_3$OD, 500 MHz): δ 4.02 (d, 1 H, J = Hz), 3.73 (d, 1 H, J = Hz), 3.64 (ddd, 2 H, J = Hz), 3.43 (s, 3 H, OMe), 3.33–3.42 (m, 3 H).

^{13}C NMR (CD$_3$OD, 125 MHz): δ 106.0 (C-1), 76.7, 74.9, 72.5, 70.3, 62.5 (C-6), 57.2 (OMe).

HRMS (EIMS, M$^+$): calcd for C$_7$H$_{14}$O$_6$ 194.0790, found 194.0788.

*5. Allyl α-*D-*galactofuranoside (15α)[17]*

^{1}H NMR (400 MHz, CD$_3$OD): δ 5.86 (dddd, 1 H, J = 17.4, 10.4, 6.2, 5.2 Hz, H^b), 5.19–5.28 (m, 1 H, H^a), 5.04–5.12 (m, 1 H, H^a), 4.81 (d, 1 H, J = 4.9 Hz, H-1), 4.15–4.25 (m, 1 H, H-3), 3.95–4.05 (m, 2 H, H-4 and H^c overlap), 3.84–3.90 (m, 1 H, H-2), 3.60–3.66 (m, 1 H, H^c), 3.50–3.58 (m, 2 H, H-6 and H-5 overlap), 3.41–3.50 (m, 1 H, H-6).

^{13}C NMR (100 MHz, CD$_3$OD): δ 135.7, 117.5, 101.8, 83.5, 78.8, 76.2, 74.5, 69.7, 64.0.

HRMS (EIMS, M$^+$ + Na): calcd for C$_9$H$_{16}$NaO$_6$ 243.0845, observed 243.0847.

*6. Allyl β-D-galactofuranoside (**15β**)[17]*

^{1}H NMR (400 MHz, CD$_3$OD): δ 5.88 (dddd, 1 H, $J = 17.4, 10.4, 6.2, 5.2$ Hz, H[b]), 5.28 (qd, 1 H, $J = 17.0, 1.6$ Hz, H[a]), 5.11–5.14 (qd, 1 H, $J = 10.5, 1.6$ Hz, H[a]), 4.89 (d, 1 H, $J = 2.0$ Hz, H-1), 4.16–4.23 (m, 1 H, H-3), 3.98–4.03 (m, 1 H, H-6), 3.95–3.98 (m, 3 H, H-2 and H[c] overlap), 3.93 (dd, 1 H, $J = 6.5, 3.2$ Hz, H-6), 3.68–3.74 (m, 1 H, H-5), 3.62 (br s, -O<u>H</u>), 3.60 (d, 1 H, $J = 1.3$ Hz, H-4).

^{13}C NMR (100 MHz, CD$_3$OD): δ 135.9 (C[b]), 117.1 (C[a]), 108.7 (H-1), 84.3 (C-6), 83.4 (C-2), 78.8 (C[c]), 72.4 (C-5), 69.4 (C-3), 64.5 (C-4).

HRMS (EIMS, M[+] + Na): calcd for C$_9$H$_{16}$NaO$_6$ 243.0845, observed 243.0848.

*Crystallographic Data for **15β***

CCDC 795662 http://www.ccdc.cam.ac.uk/

Formula: C$_9$ H$_{16}$ O$_6$

Unit cell parameters: a 9.2341(2) b 9.4269(2) c 12.2070(3) space group P212121

*7. Phenylethyl α-D-galactofuranoside (**16α**)*

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.23–7.29 (m, 2 H, Ph), 7.15–7.21 (m, 3 H, Ph), 4.90 (d, 1 H, $J = 3.4$ Hz, H-1), 3.66–4.6 (m, 7 H, H-2, H-3, H-4, H-5, H-6 and -OC<u>H</u>$_2$CH$_2$Ph overlap), 3.40–3.46 (m, 1 H, -OC<u>H</u>$_2$CH$_2$Ph), 2.88 (t, 2 H, $J = 6.7$ Hz, -OCH$_2$C<u>H</u>$_2$Ph).

^{13}C NMR (125 MHz, acetone-D6): δ 140.1, 129.8, 129.0, 126.9, 99.9, 85.6, 83.8, 78.9, 76.1, 71.4, 62.5. 36.7.

^{13}C NMR (125 MHz, CD$_3$OD): δ 140.3, 130.1, 129.3, 127.2, 100.2, 84.2, 83.3, 78.7, 76.6, 72.2, 71.5, 62.8. 36.9.

HRMS (EIMS, M[+] + Na): calcd for C$_{14}$H$_{20}$NaO$_6$ 307.1158, observed 307.1163.

ACKNOWLEDGMENTS

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