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PAPER

Aluminium triflate catalysed *O*-glycosidation: temperature-switched selective Ferrier rearrangement or direct addition with alcohols†

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A temperature-controlled mechanism switch between the $Al(OTf)_3$-catalysed direct addition of alcohols or the Ferrier rearrangement reactions in some glycals is presented. The scope and limitations are investigated as are the influence of the stereochemistry and nature of the protecting groups on the glycal substrate.

Introduction

The rapid assembly of complex materials requires powerful approaches to bond-forming reactions. An ability to form carbon and oxygen bonds to carbohydrate derivatives is a key feature in the synthesis of many natural and physiologically active substances, and glycals are frequently-used starting materials for the synthesis of important chiral compounds.[1] The alkene function in these substrates lends itself to a variety of transformations, including addition reactions,[2] Ferrier rearrangement reactions,[3] *etc.* Glycals have accordingly been utilised in a variety of partial and total syntheses of chiral natural products, many of which are *O*-glycosides.[1,4]

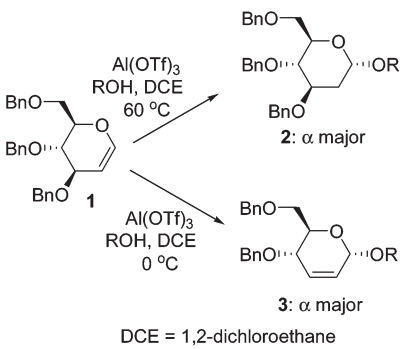
O-Glycosides can be generated from glycals by the catalysed addition of alcohols of various descriptions to the alkene.[4,5] In this way, a range of *O*-glycosides has been prepared making use of, for example, $BF_3{\cdot}Et_2O$, BCl_3, Ph_3P-HBr, *p*-TsOH, CSA and $Pd(OAc)_2$ as catalysts.[5] Otherwise, the Ferrier rearrangement is a powerful approach to the synthesis of pseudoglycals and their derivatives, starting from glycals.[3,6] This rearrangement reaction is usually performed by reacting the glycal with a Lewis acid catalyst or with redox reagents, such as $InCl_3$, ceric ammonium nitrate, $HClO_4$–SiO_2, $SnCl_4$, $Sc(OTf)_3$ and $Fe_2(SO_4)_3{\cdot}xH_2O$.[7]

We herein disclose a simple temperature-controlled selection between the direct addition of alcohols to the alkene of tri-*O*-benzyl-D-glucal to generate 2-deoxy-*O*-glycoside sugars or the Ferrier rearrangement reaction to produce the corresponding pseudoglycals, both reactions being mediated by $Al(OTf)_3$. We expand the protocol to other substrates, discussing the application of the technology to systems with better leaving groups and, ultimately, to the facile synthesis of disaccharide sugars and highly desirable bolaform-type structures.[8]

Results and discussion

We recently detailed the efficient tetrahydropyranylation and tetrahydrofuranylation reactions of various alcohols making use of $Al(OTf)_3$ as catalyst.[9] As an extension of that study, $Al(OTf)_3$-catalysed reactions of tri-*O*-benzyl-D-glucal **1** with various alcohols were investigated.

To our delight, substrate **1** readily generated the 2-deoxyglycosides **2** in acceptable to good yields within one hour when the substrate was allowed to react with 1.5 equivalents of the alcohol reagent in the presence of 5 mol% $Al(OTf)_3$ as catalyst in 1,2-dichloroethane as solvent at 60 °C (Scheme 1, Table 1, entries 1–5). The *O*-glycoside formation favoured the α-anomer, as expected for systems absent of protecting groups at the C-2



Scheme 1 Temperature-controlled selective addition or Ferrier rearrangement reactions.

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Table 1 $Al(OTf)_3$-catalysed addition of alcohols to glucal **1**[a]

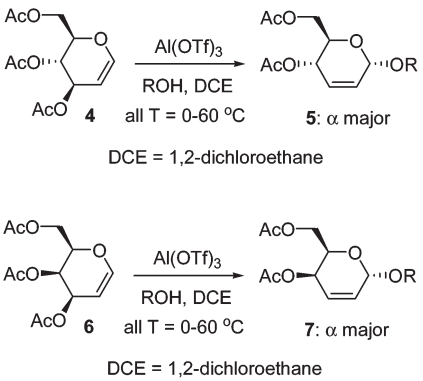
Entry	Alcohol R =	*T* (°C)	Product	α : β ratio[b]	Yield[c] (%)
1	CH_3	60	**2a**	1 : 1	56
2	Benzyl	60	**2b**	3 : 2	69
3	Propargyl	60	**2c**	7 : 3	74
4	Allyl	60	**2d**	2 : 3	72
5	4-C_6H_4Br	60	**2e**	4 : 1	67
6	CH_3	0	**3a**	7 : 1	74
7	Benzyl	0	**3b**	7 : 1	69
8	Propargyl	0	**3c**	8 : 1	74
9	Allyl	0	**3d**	3 : 1	83
10	4-C_6H_4Br	0	**3e**	4 : 1	63
11	4-$C_6H_4OCH_3$	0	**3f**	9 : 1	76
12	Cyclohexyl	0	**3g**	8 : 1	86
13	—	0	**3b**	4 : 1	67

[a] 5 mol% $Al(OTf)_3$, 0.48 mmol substrate, 0.72 mmol alcohol (1.5 eq.), 2.0 mL DCE. [b] Determined using ^1H NMR spectroscopy. [c] Isolated yield.

position of the sugar capable of participating in anchimeric assistance.[10]

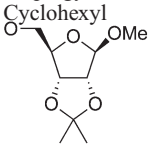
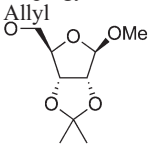
Most surprisingly, when the reaction temperature was lowered to 0 °C, the mechanism of the reaction changed altogether to produce, instead of the 2-deoxy-1-*O*-glycoside, the Ferrier rearranged pseudoglycal products **3** (Scheme 1, Table 1, entries 6–12). This outcome was obtained without fail for each of the alcohols employed in the first round of experiments. Here too, the products were obtained predominantly as the α-anomers, in good yields. While the yields overall remain modest to good, the switch between the mechanisms in simple consequence of temperature changes is attractive. The use of THF or acetonitrile as solvent failed to show this switch in mechanism which was observed only with DCM and 1,2-dichloroethane. In both instances (*i.e.* for THF or acetonitrile as solvent), only the Ferrier rearranged products were obtained for reactions that mimicked Table 1, entries 6–12, regardless of the reaction temperature. Treatment of the substrate **1** in 1,2-dichloroethane with $Al(OTf)_3$ without any added alcohol (Table 1, entry 13) led to the generation of the pseudoglycal **3b** in 67% yield, indicating that the glycal substrate may be directly activated toward Ferrier rearrangement chemistry without an added nucleophile. Some measure of competition was noted in all of these reactions where the C-3 benzyloxy leaving group also acted as nucleophile to yield **3b** as an unwanted by-product (≤5% in all cases). A possible rationalisation for this mechanistic outcome may lie in the ability of $Al(OTf)_3$ to behave as a Lewis acid[11] or, by virtue of its ability to bind to and polarise ROH compounds, as a Lewis-assisted Brønsted acid.[12] We propose that $Al(OTf)_3$ interacts with the OBn group as a Lewis acid, at low temperature, activating it as a leaving group in a mechanism akin to an assisted S_N2' (borderline, or S_N1') nucleophilic displacement. At higher temperature, the enol ether is rather protonated by the Lewis-assisted Brønsted acid, leading to the 2-deoxy product *via* the oxocarbenium intermediate so common in sugar chemistry. The latter would not be dissimilar to the supported HBr catalyst applied previously in the synthesis of 2-deoxy sugars.[13]

When moving to the tri-*O*-*acetyl*-D-glucal and -galactal substrates (Scheme 2, Table 2), which should produce the less competitive acetate nucleophile from the C-3 leaving group, the



Scheme 2 Ferrier-exclusive products from acetate-protected glycals.

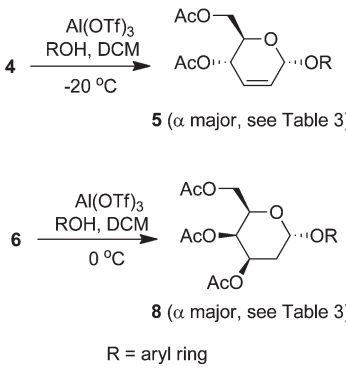
Table 2 $Al(OTf)_3$-catalysed Ferrier rearrangement addition products[a]

Entry	R =	Product	α : β ratio[b]	Yield[c] (%)
1	CH_3	**5a**	5 : 1	81
2	Benzyl	**5b**	7 : 1	84
3	Propargyl	**5c**	8 : 1	78
4	Cyclohexyl	**5d**	8 : 1	86
5		**5e**	9 : 1	68
6	Propargyl	**7a**	>19 : 1	75
7	Allyl	**7b**	>19 : 1	71
8		**7c**	9 : 1	63

[a] 5 mol% $Al(OTf)_3$, 0.74 mmol substrate, 1.10 mmol alcohol (1.5 eq.), 3.0 mL DCE. [b] Determined using ^1H NMR spectroscopy. [c] Isolated yield.

competition reaction was altogether suppressed. The Ferrier-rearranged *O*-glycoside could be obtained in excellent yields for a variety of alcohol nucleophiles, including a D-ribose derivative which led to disaccharide formation in good yield. In contrast to the benzyl-protected substrate, no manipulation of the reaction temperature could induce direct addition of the alcohol to generate the 2-deoxy sugars, presumably due to strong activation of the acetate leaving group by its complexation to the $Al(OTf)_3$ catalyst.

When making use of phenols as nucleophiles a different picture emerged. The tri-*O*-*acetyl*-D-glucal and -galactal substrates shuttled between the two mechanisms (Scheme 3, Table 3) as a function of their stereochemistry. Accordingly, reactions performed at temperatures as low as −20 °C allowed the preparation of the Ferrier rearrangement *O*-glycosides as dominant products from tri-*O*-*acetyl*-D-glucal while reactions performed at 0 °C gave *C*-arylation products, an aspect we are currently investigating in more detail. This observation is likely an O–C rearrangement to the thermodynamically more stable product, a process that has been used to prepare natural and physiologically active compounds.[14] Reaction of tri-*O*-*acetyl*-D-



Scheme 3 Temperature switching mechanism with phenolic nucleophiles.

Table 3 $Al(OTf)_3$-catalysed reactions with phenolic nucleophiles[a]

Entry	Ar =	Product	α : β ratio[b]	Yield[c] (%)
1	C_6H_5	**5f**	>19 : 1	73
2	4-C_6H_4Br	**5g**	>19 : 1	86
3	4-C_6H_4I	**5h**	9 : 1	81
4	2-C_6H_4I	**5i**	9 : 1	76
5	4-$C_6H_4OCH_3$	**5j**	>19 : 1	88
6	4-$C_6H_4CH_3$	**5k**	>19 : 1	91
7	2-Naphthyl	**5l**	9 : 1	68
8	C_6H_5	**8a**	>19 : 1	68
9	4-C_6H_4Br	**8b**	18 : 1	76
10	4-C_6H_4I	**8c**	11 : 1	73
11	2-C_6H_4I	**8d**	>19 : 1	66
12	4-$C_6H_4OCH_3$	**8e**	>19 : 1	64
13	4-$C_6H_4CH_3$	**8f**	>19 : 1	71
14	2-Naphthyl	**8g**	>19 : 1	53

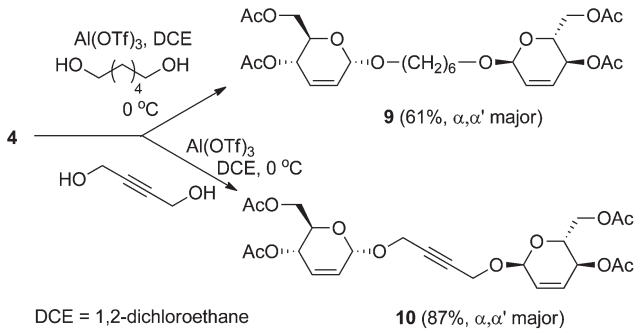
[a] 5 mol% $Al(OTf)_3$, 0.74 mmol substrate, 1.10 mmol alcohol (1.5 eq.), 3.0 mL DCE. [b] Determined using ^1H NMR spectroscopy. [c] Isolated yield.

galactal at 0 °C provided the corresponding direct addition 2-deoxy derivatives but was unreactive at lower temperatures thereby preventing the possibility of Ferrier rearrangement under our conditions. In all cases the α-*O*-glycoside dominated.

Quite usefully, the employment of alkyl terminal diols allowed symmetrical dimer formation of the pseudoglycals **9** or **10** from **4** (Scheme 4). This was achieved when reacting the glucal with 1,4-butynediol or 1,6-hexanediol at low temperature, to produce so-called bolaform-type compounds.[8] In both cases, the α,α′ ratio to α,β′ product was 8 : 1 (determined from the respective ^1H NMR spectra). Such materials show rather remarkable physical characteristics and allow self-assembly of supramolecular structures.[15]

Conclusions

We have shown an ability to switch between $Al(OTf)_3$-catalysed direct addition of alcohols to the alkene functional group of glycals and Ferrier rearrangement reactions by simply manipulating the temperature under which the reaction is performed, when tri-*O*-benzyl-D-glucal is used as substrate with alkyl alcohols as nucleophiles. This allows the ready synthesis either of the



Scheme 4 Formation of symmetrical bolaform-type compounds.

corresponding 2-deoxy-D-glucoside derivatives or their pseudoglycal counterparts at will, from common starting materials. With the tri-*O*-acetyl substrates, the reaction was limited to the Ferrier rearrangement when making use of aliphatic alcohols. However, with phenols the situation was different, once again allowing access to both mechanisms. This methodology allowed symmetrical dimer formation when making use of diols. We are currently investigating this chemistry with the view to its application to other materials with interesting characteristics, such as bolaforms.[8,11] In this context, the work holds promise, based on the successes with the diols already shown here, to allow the ready synthesis of unsymmetrical bolaform-type structures, which are highly sought after compounds.

General methods

All reactions were performed under an atmosphere of either nitrogen or argon. Reagents were used as received from commercial sources without further purification. Unless otherwise stated, dry solvents[16] were used in oven dried, flamed out glass apparatus. Qualitative thin layer chromatography (TLC) was conducted on "Merck GF254 precoated silica plates" (0.25 mm layer). The chromatograms were eluted using an appropriate solvent system as indicated for column chromatography. Compounds were visualised by their fluorescence under UV light (254 nm), as well as by spraying the plate with anisaldehyde spray followed by heating with a heat gun or over a Bunsen burner. "Flash chromatography" refers to column chromatography under nitrogen pressure using "Merck Kieselgel 60 (230–400 mesh), with eluents mixed in a volume per volume ratio. Room temperature refers to *ca.* 20–23 °C. NMR spectra were recorded by means of a Varian Gemini 2000, 300 MHz and a Bruker Ultrashield 400 MHz spectrometer in $CDCl_3$ unless otherwise indicated. *J* values are given in Hz. Fractional numbers of protons given in the ^1H NMR data, below, reflect the relative ratio of the isomers. Mass spectrometry was performed on Thermo Double Focusing Sector high resolution mass spectrometer. Ionisation techniques include EIMS and CIMS. A Tensor 27 spectrophotometer was used to record IR spectra using an ATR fitting. The data are listed with the characteristic peaks indicated in wavenumber (cm^{-1}). Melting points were determined using a Gallencamp oil immersion apparatus and are uncorrected.

Experimental section

General procedure for glycosylation reactions

To a solution of the specific glycal in DCE or DCM (2 mL), were added a glycosyl acceptor alcohol (1.5 eq) and 5 mol% Al $(OTf)_3$ and the resulting mixture was stirred at the temperature indicated (0 °C, room temperature or heated at 60 °C) until TLC analysis showed completion of the reaction. Thereafter, the reaction was quenched by addition of a saturated aqueous $NaHCO_3$ solution (0.5 mL). The reaction mixture was extracted twice with DCM (5 mL) and the organic layer washed with H_2O (2 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by column chromatography on silica gel using a mixture of ethyl acetate and hexane as eluent.

Many of the compounds reported here have been previously prepared and fully characterised. In all cases, the analytical data produced for the products here compared favourably with literature data. A list of the known compounds follows in the References, which are listed by product number.[17–27,29–32] The data for only new or incompletely characterised compounds are given here.

***O*-Glycoside 2b.**[18] This product has been previously reported[18] but no data are presented. Glycosidation of 3,4,6-tri-*O*-benzyl-D-glucal (200 mg, 0.48 mmol) with benzyl alcohol (78 mg, 0.72 mmol, 1.5 eq.) at 60 °C for 1 hour afforded glucoside **2b** as an inseparable α/β (3 : 2) mixture in a combined yield of 174 mg (69%) as a light yellow oil. Found C, 77.9; H, 6.7%. $C_{34}H_{36}O_5$ requires C, 77.8; H, 6.9%; R_f = 0.43 (7 : 1, Hexane–EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.05 (m, 20H), 4.97 (s, 0.7H), 4.89 (d, 0.3H, *J* 8.0 Hz), 4.85 (s, 0.3H), 4.81 (d, 0.7H, *J* 8.0 Hz), 4.65–4.30 (m, 8H), 4.09–3.85 (m, 1H), 3.80–3.49 (m, 3H), 2.25 (dd, 0.7H, *J* 16.0, 4.0 Hz), 2.12 (d, 0.3H, *J* 12.0 Hz), 1.67 (t, 0.7H, *J* 12.0 Hz), 1.58 (t, 0.3H, *J* 10.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6, 138.5, 138.4, 138.1, 137.9, 137.6, 128.8, 128.5, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 126.9, 97.6, 96.7, 78.2, 77.7, 77.3, 75.4, 75.0, 73.4, 73.0, 71.8, 71.5, 71.4, 71.3, 70.9, 70.5, 69.8, 68.8, 35.4, 35.0; IR ν_{max} 1698, 1492, 1454, 1070, 1011, 732, 694 cm^{-1}; HR-CIMS calc for $C_{27}H_{30}O_5$ 434.2093 $[M–C_7H_6]^+$, found 434.2063.

***O*-Glycoside 2c.** Glycosidation of 3,4,6-tri-*O*-benzyl-D-glucal (200 mg, 0.48 mmol) with propargyl alcohol (40 mg, 0.72 mmol, 1.5 eq.) at 60 °C for 1 hour afforded glucoside **2c** as an inseparable α/β (7 : 3) mixture in a combined yield of 167 mg (74%) as a light yellow oil. R_f = 0.39 (7 : 1, hexane–EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.06 (m, 15H), 5.05 (s, 0.7H), 4.95 (s, 0.3H), 4.80 (t, 1H, *J* 10.2 Hz), 4.61–4.35 (m, 6H), 4.18 (s, 0.6H, OCH_2), 4.09 (1.4H, OCH_2), 3.95–3.86 (m, 1H), 3.69 (d, 1H, *J* 10.8 Hz), 3.62–3.49 (m, 2H), 2.33 (s, 0.3H), 2.31 (s, 0.7H), 2.26–2.19 (m, 1H), 1.71–1.56 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 138.3, 138.0), 137.5, 128.4, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 96.6, 96.1, 80.2, 79.2, 78.0, 77.9, 77.4, 74.9, 74.3, 74.1, 73.4, 71.7, 71.1, 70.8, 68.8, 68.6, 57.2, 53.9, 35.3, 35.0; IR ν_{max}/cm^{-1} 2860, 1501, 1456, 1301, 1070, 736, 698; MS: No useful peaks were identified from the CIMS spectrum.

***O*-Glucoside 2e.** Glycosidation of 3,4,6-tri-*O*-benzyl-D-glucal (200 mg, 0.48 mmol) with *p*-bromobenzyl alcohol (134 mg, 0.72 mmol, 1.5 eq.) at 60 °C for 1 hour afforded glucoside **2e** as an inseparable α/β (4 : 1) mixture in a combined yield of 194 mg (67%) as a light yellow oil. Found C, 67.7; H, 5.7%. $C_{34}H_{35}BrO_5$ requires C, 67.7; H, 5.9%; R_f = 0.53 (4 : 1, hexane–EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.08 (m, 19H), 4.95 (s, 1H), 4.74 (d, 1H, *J* 10.5 Hz), 4.61–4.40 (m, 6H), 4.31 (d, 1H, *J* 12.0 Hz), 3.94–3.85 (m, 1H), 3.69 (d, 2H, *J* 9.0 Hz), 3.58–3.50 (m, 2H), 2.20 (dd, 1H, *J* 13.1, 4.3 Hz), 1.67 (dd, 1H, *J* 16.6, 7.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.3, 138.0, 137.6, 136.6, 131.5, 131.4, 129.5, 129.2, 128.5, 128.4, 128.0, 127.9, 127.8, 127.8, 127.7, 127.7, 127.6, 127.5, 126.9, 121.6, 121.3, 96.7, 78.2, 77.6, 75.0, 73.5, 71.0, 70.9, 68.9, 68.1, 35.3; IR ν_{max}/cm^{-1} 3088, 3030, 2864, 1493, 1362, 1096, 803, 734, 696; MS: No useful peaks were identified from the CIMS spectrum apart from those arising from the bromobenzyl fragment.

***O*-Glucoside 3e.** Glycosidation of 3,4,6-tri-*O*-benzyl-D-glucal (200 mg, 0.48 mmol) with *p*-bromobenzyl alcohol (134 mg, 0.72 mmol, 1.5 eq.) at 0 °C for 7 hours afforded **3e** as an inseparable α/β (4 : 1) mixture in a combined yield of 150 mg (63%) as a light yellow oil. Found C, 65.7; H, 5.9%. $C_{27}H_{27}BrO_4$ requires C, 65.5; H, 5.5%; R_f = 0.49 (5 : 1, hexane–EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.09 (m, 14H), 6.00 (d, 1H, *J* 10.2 Hz), 5.69 (dt, 1H, *J* 10.3, 2.3 Hz), 5.10 (d, 0.2H, *J* 1.2 Hz), 5.01 (d, 0.8H, *J* 2.1 Hz), 4.73–4.33 (m, 6H), 4.09 (dt, 1H, *J* 9.3, 1.5 Hz), 3.91–3.89 (m, 1H), 3.60–3.58 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.0, 137.9, 137.1, 131.4, 130.9, 129.6, 128.3, 127.9, 127.8, 127.7, 127.6, 126.2, 121.4, 94.0, 73.3, 71.0, 70.2, 69.3, 69.2, 68.6; IR ν_{max}/cm^{-1} 3063, 2865, 1453, 1362, 1096, 803, 734, 696; MS: No useful peaks were identified from the CIMS spectrum.

***O*-Glucoside 3f.** Glycosidation of 3,4,6-tri-*O*-benzyl-D-glucal (200 mg, 0.48 mmol) with *p*-methoxybenzyl alcohol (90 μL, 0.72 mmol, 1.5 eq.) at 0 °C for 7 hours afforded **3f** as an inseparable α/β (9 : 1) mixture in a combined yield of 146 mg (76%) as a light yellow oil. Found C, 75.3; H, 7.1%. $C_{28}H_{30}O_5$ requires C, 75.3; H, 6.8%; R_f = 0.46 (5 : 1, hexane–EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26–7.11 (m, 12H), 6.78–6.76 (m, 2H), 5.98 (d, 1H, *J* 10.2 Hz), 5.68 (d, 1H, *J* 10.2 Hz), 5.10 (s, 0.1H), 5.02 (s, 0.9H), 4.68–4.33 (m, 6H), 4.10 (d, 1H, *J* 9.3 Hz), 3.93 (m, 1H), 3.72–3.56 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 138.1, 138.0, 130.6, 130.0, 129.7, 129.8, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 126.6, 113.7, 93.6, 73.3, 70.9, 70.3, 69.6, 69.2, 68.8, 55.2; IR ν_{max}/cm^{-1} 3031, 2865, 1513, 1247, 1027, 820, 733, 697; MS: No useful peaks were identified from the CIMS spectrum.

Disaccharide 5e. Glycosidation of 3,4,6-tri-*O*-acetyl-D-glucal (200 mg, 0.735 mmol) with methyl 2,3-*O*-isopropylidine-β-D-ribofuranoside (224 mg, 1.1 mmol, 1.5 eq.) for 1 hour at room temperature afforded glycoside **5e** as an inseparable α/β (9 : 1) mixture in a combined yield of 208 mg (68%) as a clear oil. Found C, 55.0; H, 7.2%. $C_{19}H_{28}O_{10}$ requires C, 54.8; H, 6.8%; R_f = 0.31 (3 : 1, hexane–EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.87–5.71 (m, 2H), 5.21 (dd, 1H, *J* 9.9, 1.2 Hz), 5.07 (s, 0.1H), 4.95 (s, 0.9H), 4.9 (s, 1H), 4.61 (d, 1H, *J* 5.7 Hz), 4.48 (d, 1H, *J* 5.7 Hz), 4.29–4.26 (m, 1H), 4.19–4.07 (m, 2H),

4.02–3.97 (m, 1H), 3.71–3.68 (m, 1H), 3.46–3.43 (m, 1H), 3.21 (s, 3H), 2.00–1.98 (m, 6H), 1.38 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8, 170.2, 129.3, 127.4, 112.3, 109.3, 95.0, 85.1, 85.0, 82.0, 69.6, 67.0, 65.0, 62.7, 54.8, 26.4, 24.9, 20.9, 20.7; IR ν_{max}/cm^{-1} 2987, 2939, 2836, 1741, 1371, 1224, 1015, 869, 736; HR-CIMS calc for $C_{18}H_{25}O_{10}$ 401.1448 $[M–CH_3]^+$, found 401.1363.

***O*-Glucoside 5h.** Glycosidation of 3,4,6-tri-*O*-acetyl-D-glucal (200 mg, 0.735 mmol) with 4-iodophenol (194 mg, 1.2 equivalents, 0.882 mmol) and $Al(OTf)_3$ (20 mol%, 69 mg) in DCM (2.0 mL) at −20 °C for 3 hours afforded glycoside **5h** as an inseparable α/β (9 : 1) mixture in a combined yield of 257 mg (81%) as a cream solid. Found C, 44.6; H, 4.3%. $C_{16}H_{17}IO_6$ requires C, 44.5; H, 4.0%; Mp 56–58 °C; R_f = 0.55 (3 : 1, hexane–EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.55 (d, 2H, *J* 9.0 Hz), 6.85 (d, 2H, *J* 8.7 Hz), 6.01(d, 1H, *J* 10.2 Hz), 5.94 (dt, 1H, *J* 10.3, 2.3 Hz), 5.62 (s, 1H), 5.34 (dd, 1H, *J* 9.5, 1.4 Hz), 4.27–4.12 (m, 2H), 4.09 (dd, 1H, *J* 11.6, 1.6 Hz), 2.07 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 170.6, 170.2, 156.8, 138.2, 130.3, 126.6, 119.3, 92.8, 85.0, 67.8, 64.8, 62.5, 20.9, 20.6; IR ν_{max}/cm^{-1} 2952, 2360, 1735, 1483, 1368, 1219, 978, 816; HR-CIMS calc for $C_{14}H_{14}IO_6$ 372.9937 $[M–C_2H_3O_2]^+$, found 327.9980.

***O*-Glucoside 5i.** Glycosidation of 3,4,6-tri-*O*-acetyl-D-glucal (200 mg, 0.735 mmol) with 2-iodophenol (194 mg, 1.2 equivalents, 0.882 mmol) and $Al(OTf)_3$ (20 mol%, 69 mg) in DCM (2.0 mL) at −20 °C for 7 hours afforded glycoside **5i** as an inseparable α/β (9 : 1) mixture in a combined yield of 241 mg (76%) as a cream solid. Found C, 44.8; H, 3.9%. $C_{16}H_{17}IO_6$ requires C, 44.5; H, 4.0%; Mp 47–49 °C; R_f = 0.59 (3 : 1, hexane–EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.71 (dd, 1H, *J* 8.1, 1.5 Hz), 7.23 (ddd, 1H, *J* 8.4, 7.5, 1.5 Hz), 7.14 (dd, 1H, *J* 8.2, 1.6 Hz), 6.74 (ddd, 1H, *J* 9.0, 7.2 1.5 Hz), 6.02–5.89 (unresolved fine ABX system, 2H), 5.58 (d, 1H, *J* 1.8 Hz), 5.33 (dd, 1H, *J* 9.3, 1.2 Hz), 4.27–4.19 (m, 2H), 4.10 (d, 1H, *J* 9.9 Hz), 2.05 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 170.7, 170.2, 156.2, 139.3, 130.5, 129.5, 126.6, 124.6, 117.4, 94.4, 88.5, 68.0, 64.9, 62.5, 21.0, 20.7; IR ν_{max}/cm^{-1} 2931, 2360, 1739, 1438, 1367, 1225, 1042, 958, 750; HR-CIMS calc for $C_{14}H_{14}IO_4$ 372.9937 $[M–C_2H_3O_2]^+$, found 372.9983.

***O*-Glucoside 5l.** Glycosidation of 3,4,6-tri-*O*-acetyl-D-glucal (200 mg, 0.735 mmol) with 2-naphthol (127 mg, 1.2 equivalents, 0.882 mmol) and $Al(OTf)_3$ (20 mol%, 69 mg) in DCM (2.0 mL) at −20 °C for 7 hours afforded glycoside **5l** as an inseparable α/β (9 : 1) mixture in a combined yield of 178 mg (68%) as a cream solid. This compound has been previously reported,[26] but the structure apparently incorrectly assigned. We are able to obtain both the *O*- and *C*-glycosides, depending on the reaction conditions and we report the analytical data for the *O*-glycoside here. The reported data[26] concur with the *C*-glycoside in our hands, not the *O*-glycoside. (See main text discussing Scheme 3, relating to *C*-glycoside formation. We also obtained a single crystal X-ray structure of the *C*-glycoside.[29] For this compound, H-1 resonates as a doublet of doublets at 6.29 ppm (*J* 4.2 and 2.7 Hz) while in the *O*-glycoside H-1 resonates as a fine doublet at 5.79 ppm with *J* 1.5 Hz.)

Mp 72–74 °C; R_f = 0.58 (3 : 1, hexane–EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H δ 7.73–7.69 (m, 3H), 7.46 (d, 1H, *J* 2.4 Hz), 7.39 (ddd, 1H, *J* 9.3, 7.2, 1.2 Hz), 7.30 (ddd, 1H, *J* 9.3, 6.9, 1.2 Hz), 7.18 (dd, 1H, *J* 9.9, 3.9 Hz), 6.00 (unresolved fine ABXY system, 2H), 5.79 (d, 1H, *J* 1.5 Hz), 5.37 (d, 1H, *J* 9.6 Hz), 4.32–4.20 (m, 2H), 4.06 (d, 1H, *J* 10.5 Hz), 2.05 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 170.8, 170.3, 154.7, 134.4, 130.1, 129.7, 129.3, 127.6, 127.1, 127.0, 126.4, 124.3, 119.1, 111.2, 92.9, 67.9, 65.0, 62.6, 20.9, 20.6; IR ν_{max}/cm^{-1} 3296, 1631, 1602, 1513, 1468, 1218, 843; HR-CIMS calc for $C_{18}H_{17}O_4$ 297.1127 $[M–C_2H_3O_2]^+$, found 297.1098.

Disaccharide 7c. Glycosidation of 3,4,6-tri-*O*-acetyl-D-galactal (200 mg, 0.735 mmol) with methyl 2,3-*O*-isopropylidine-β-D-ribofuranoside (224 mg, 1.1 mmol, 1.5 eq.) for 3 hours at room temperature afforded **7c** as an inseparable α/β (9 : 1) mixture a combined yield of 193 mg (63%). Found C, 54.7; H, 6.8%. $C_{19}H_{28}O_{10}$ requires C, 54.8; H, 6.8%; R_f = 0.33 (2 : 1, hexane–EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.08 (dd, 1H, *J* 10.0, 5.1 Hz), 6.00 (dd, 1H, *J* 10.0, 2.6 Hz), 5.12 (s, 0.1H), 5.04 (s, 0.9H), 4.98–4.96 (m, 1H), 4.92 (s, 1H), 4.63 (d, 1H, *J* 6.0 Hz), 4.54 (d, 1H, *J* 3.9 Hz), 4.39–4.18 (m, 1H), 4.19 (d, 2H, *J* 6.0 Hz), 3.77 (dd, 1H, *J* 10.0, 5.6 Hz), 3.49 (t, 1H, *J* 9.6 Hz), 2.05 (s, 3H), 2.04 (s, 3H), 1.44 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 170.6, 170.3, 130.2, 125.2, 112.3, 109.3, 94.5, 85.1, 84.9, 82.0, 69.2, 66.9, 63.9, 62.6, 54.9, 26.4, 24.9, 20.8, 20.7; IR ν_{max}/cm^{-1} 2941, 2834, 2364, 1742, 1371, 1224, 1036, 869, 733; HR-CIMS $C_{18}H_{25}O_{10}$ 401.1448 $[M–CH_3]^+$, found 401.1358.

General procedure for *O*-glycosylation of tri-*O*-acetyl-D-galactal with phenolic nucleophiles

Tri-*O*-acetyl-D-galactal (200 mg, 0.735 mmol) was stirred in DCM (2 mL) with the phenol (1.2 equivalents, 0.882 mmol) and $Al(OTf)_3$ (5 mol%, 17 mg) at 0 °C. After completion of the reaction as traced by TLC, the reaction was quenched at 0 °C by adding concentrated sodium bicarbonate (2 mL) solution and the mixture extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried over anhydrous magnesium sulfate. The volatile component was removed under vacuum leaving the crude product that was subjected to column chromatography on flash silica for purification, and a solution of hexane and ethyl acetate (hexane–EtOAc, 3 : 1) was used as eluent.

***O*-Galactoside 8a.**[29] This compound has been previously prepared but no data are given.[13] Glycosidation of 3,4,6-tri-*O*-acetyl-D-galactal (200 mg, 0.735 mmol) with phenol (83 mg, 1.2 equivalents, 0.882 mmol) and $Al(OTf)_3$ (20 mol%, 69 mg) in DCM (2.0 mL) at 0 °C for 4 hours afforded glycoside **8a** as an inseparable α/β (>19 : 1) mixture in a combined yield of 183 mg (68%) as a cream solid. Found C, 59.1; H, 5.8%. $C_{18}H_{22}O_8$ requires C, 59.0; H, 6.1%; Mp 120–122 °C; R_f = 0.41 (3 : 1, hexane–EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.21 (t, 2H, *J* 7.4 Hz), 6.66–6.92 (m, 3H), 5.67 (br s, 1H), 5.43 (dd, 1H, *J* 9.2, 2.6 Hz), 5.33 (br s, 1H), 4.19 (t, 1H, *J* 6.4 Hz), 4.02–3.98 (m, 2H), 2.18 (br t, 1H, *J* 12.6 Hz), 2.09 (s, 3H), 2.03 (dd, 1H, *J* 9.6 and 5.2 Hz), 1.95 (s, 3H), 1.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 170.3, 170.2, 170.0, 156.2, 129.4, 122.3,

116.4, 95.7, 67.4, 66.4, 65.9, 62.0, 30.1, 20.8, 20.6, 20.5; IR ν_{max}/cm^{-1} 2962, 1740, 1490, 1226, 1016, 798; HR-CIMS calc for $C_{18}H_{23}O_8$ 367.1393 $[M + H]^+$, found 367.1374, calc for $C_{16}H_{20}O_6$ $[M–C_2H_3O_2]^+$ 307.1182, found 307.1129.

***O*-Galactoside 8b.** Glycosidation of 3,4,6-tri-*O*-acetyl-D-galactal (200 mg, 0.735 mmol) with 4-bromophenol (152 mg, 1.2 equivalents, 0.882 mmol) and $Al(OTf)_3$ (20 mol%, 69 mg) in DCM (2.0 mL) at 0 °C for 6 hours afforded glycoside **8b** as an inseparable α/β (18 : 1) mixture in a combined yield of 249 mg (76%) as a cream solid. Found C, 48.2; H, 5.0%. $C_{18}H_{21}BrO_8$ requires C, 48.6; H, 4.8%; R_f = 0.44 (3 : 1, hexane–EtOAc); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.35 (d, 2H, *J* 8.4 Hz), 6.92 (d, 2H, *J* 8.4 Hz), 5.66 (br s, 1H), 5.43 (d, 1H, *J* 12.0 Hz), 5.35 (br s, 1H), 4.17 (t, 1H, *J* 6.4 Hz), 4.04–4.00 (m, 2H), 2.22 (br t, 1H, *J* 12.4 Hz), 2.12 (s, 3H), 2.06 (dd, 1H, *J* 12.8, 5.2 Hz), 1.98 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 170.3, 170.1, 170.0, 155.3, 132.3, 118.2, 114.7, 95.9, 67.6, 66.3, 65.8, 62.0, 30.0, 20.8, 20.6, 20.5; IR ν_{max}/cm^{-1} 2960, 1743, 1487, 1367, 1221, 1198, 1115, 1018, 823; HR-CIMS calc for $C_{18}H_{21}BrO_8$ 444.0420, 446.0399 $[M]^+$, found 444.0418, 446.0292, calc for $C_{16}H_{18}BrO_6$ $[M–C_2H_3O_2]^+$ 385.0287, 387.0266, found 385.0284, 387, 0269.

***O*-Galactoside 8c.** Glycosidation of 3,4,6-tri-*O*-acetyl-D-galactal (200 mg, 0.735 mmol) with 4-iodophenol (194 mg, 1.2 equivalents, 0.882 mmol) and $Al(OTf)_3$ (20 mol%, 69 mg) in DCM (2.0 mL) at 0 °C for 6 hours afforded glycoside **8c** as an inseparable α/β (11 : 1) mixture in a combined yield of 264 mg (73%) as a cream solid. Found C, 43.7; H, 4.1%. $C_{18}H_{21}IO_8$ requires C, 43.9; H, 4.3%; Mp 62–64 °C; R_f = 0.45 (3 : 1, hexane–EtOAc); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.52 (d, 2H, *J* 7.6 Hz), 6.80 (d, 2H, *J* 8.0 Hz), 5.66 (br s, 1H), 5.42 (d, 1H, *J* 12.4 Hz), 5.34 (s, 1H), 4.16 (t, 1H, *J* 6.4 Hz), 4.06–3.96 (m, 2H), 2.21 (br t, 1H, *J* 12.0 Hz), 2.11 (s, 3H), 2.05 (dd, 1H, *J* 9.8, 5.0 Hz), 1.98 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 170.2, 170.1, 169.9, 156.0, 138.2, 118.7, 95.8, 84.9, 67.6, 66.2, 65.7, 61.9, 30.0, 20.8, 20.6, 20.5; IR ν_{max}/cm^{-1} 2955, 1744, 1483, 1369, 1221, 1114, 1021, 820, 731; HR-CIMS calc for $C_{16}H_{18}IO_6$ $[M–C_2H_3O_2]^+$ 433.0148, found 433.0251.

***O*-Galactoside 8d.** Glycosidation of 3,4,6-tri-*O*-acetyl-D-galactal (200 mg, 0.735 mmol) with 2-iodophenol (194 mg, 1.2 equivalents, 0.882 mmol) and $Al(OTf)_3$ (20 mol%, 69 mg) in DCM (2.0 mL) at 0 °C for 7 hours afforded glycoside **8d** as an inseparable α/β (>19 : 1) mixture in a combined yield of 239 mg (66%) as a cream solid. Found C, 43.9; H, 4.4%. $C_{18}H_{21}IO_8$ requires C, 43.9; H, 4.3%; Mp 80–82 °C; R_f = 0.44 (3 : 1, hexane–EtOAc); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.70 (d, 1H, *J* 8.0 Hz), 7.20 (t, 1H, *J* 7.6 Hz), 7.03 (d, 1H, *J* 8.4 Hz), 6.71 (t, 1H, *J* 7.6 Hz), 5.70 (br s, 1H), 5.55–5.50 (m, 1H), 5.37 (br s, 1H), 4.18 (t, 1H, *J* 6.6 Hz), 3.99 (d, 2H, *J* 6.6 Hz), 2.24–2.14 (m, 2H), 2.08 (s, 3H), 1.95 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 170.2, 170.0, 169.8, 154.8, 139.3, 129.2, 124.1, 115.3, 96.4, 87.5, 68.0, 66.3, 65.9, 61.9, 30.0, 20.7, 20.6, 20.5; IR ν_{max}/cm^{-1} 2963, 1730, 1472, 1224, 1197, 1018, 799; HR-CIMS calc for $C_{16}H_{18}IO_6$ $[M–C_2H_3O_2]^+$ 433.0148, found 433.0060.

***O*-Galactoside 8e.**[30] This compound has been previously reported[30] but no analytical data were given. Glycosidation of 3,4,6-tri-*O*-acetyl-D-galactal (200 mg, 0.735 mmol) with 4-methoxyphenol (109 mg, 1.2 equivalents, 0.882 mmol) and $Al(OTf)_3$ (20 mol%, 69 mg) in DCM (2.0 mL) at 0 °C for 4 hours afforded glycoside **8e** as an inseparable α/β (>19 : 1) mixture in a combined yield of 186 mg (64%) as a cream solid. Found C, 57.9; H, 6.3%. $C_{19}H_{24}O_9$ requires C, 57.6; H, 6.1%; Mp 60–62 °C; R_f = 0.40 (3 : 1, hexane–EtOAc); ^1H NMR (400 MHz, $CDCl_3$): δ_H 6.96 (d, 2H, *J* 9.2 Hz), 6.78 (d, 2H, *J* 8.8 Hz), 5.59 (d, 1H, *J* 2.8 Hz), 5.48–5.43 (m, 1H), 5.36 (d, 1H, *J* 2.8 Hz), 4.26 (t, 1H, *J* 6.6 Hz), 4.07–4.03 (m, 2H), 3.73 (s, 3H), 2.20 (td, 1H, *J* 9.5, 2.7 Hz), 2.12 (s, 3H), 2.06 (dd, 1H, *J* 9.6, 5.2 Hz), 1.98 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 170.4, 170.2, 170.0, 154.9, 150.2, 117.7, 114.4, 96.5, 67.3, 66.4, 66.0, 62.1, 55.5, 30.2, 20.8, 20.7, 20.6; IR ν_{max}/cm^{-1} 2944, 1730, 1497, 1245, 1204, 1011, 975; HR-CIMS calc for $C_{19}H_{24}O_9$ $[M–C_2H_3O_2]^+$ 337, 1287, found 337.1315.

***O*-Galactoside 8f.**[30] This compound has been previously reported[30] but no analytical data were given. Glycosidation of 3,4,6-tri-*O*-acetyl-D-galactal (200 mg, 0.735 mmol) with *p*-cresol (95 mg, 1.2 equivalents, 0.882 mmol) and $Al(OTf)_3$ (20 mol%, 69 mg) in DCM (2.0 mL) at 0 °C for 4 hours afforded glycoside **8f** as an inseparable α/β (>19 : 1) mixture in a combined yield of 198 mg (71%) as a light yellow oil. Found C, 59.8; H, 6.2%. $C_{19}H_{24}O_8$ requires C, 60.0; H, 6.4%; R_f = 0.46 (3 : 1, hexane–EtOAc); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.05 (d, 2H, *J* 8.0 Hz), 6.92 (d, 2H, *J* 7.6 Hz), 5.65 (s, 1H), 5.46 (m, 1H), 5.36 (s, 1H), 4.24 (t, 1H, *J* 6.6 Hz), 4.08–4.01 (m, 2H), 2.26 (s, 3H), 2.19 (d, 1H, *J* 12.4 Hz), 2.12 (s, 3H), 2.06 (dd, 1H, *J* 9.4, 4.6 Hz), 1.99 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 170.3, 170.2, 170.0, 154.1, 131.6, 129.8, 116.4, 96.0, 67.3, 66.4, 66.0, 62.0, 30.2, 20.8, 20.6, 20.5, 20.4; IR ν_{max}/cm^{-1} 2961, 1742, 1509, 1220, 1037, 1018, 785; HR-CIMS calc for $C_{17}H_{21}O_6$ $[M–C_2H_3O_2]^+$ 321.1338, found 321.1271.

Synthesis of symmetrical glucoside bolaform 10

Tri-*O*-acetyl-D-glucal (400 mg, 1.470 mmol) was stirred in DCM (5 mL) with the diol (0.5 equivalents, 0.735 mmol) and $Al(OTf)_3$ (5 mol%, 17 mg) at room temperature. After completion of the reaction as traced by TLC (2 h), the reaction was quenched by adding concentrated sodium bicarbonate (4 mL) solution and the mixture extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried over anhydrous magnesium sulfate. The volatile component was removed under vacuum leaving the crude product that was subjected to column chromatography on flash silica for purification, using neat ethyl acetate as eluent. The pure product was obtained in a yield of 87% (444 mg).

Found C, 56.2; H, 6.2%. $C_{24}H_{30}O_{12}$ requires C, 56.5; H, 5.9%; Mp: 90–92 °C; R_f = 0.67 (ethyl acetate); ^1H NMR (300 MHz, $CDCl_3$): δ_H 5.83 (d, 2H, *J* 10.4 Hz), 5.77 (dt, 2H, *J* 10.2, 2.4 Hz), 5.29–5.22 (m, 2H), 5.14 (s, 2H), 4.36–3.96 (m, 10H), 2.03 (d, 12H, *J* 4.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 170.6, 170.1, 129.6, 127.1, 92.5, 81.9, 67.0, 65.0, 62.6, 55.1, 20.8, 20.6; IR ν_{max}/cm^{-1} 2923, 1727, 1374, 1230, 1187, 1031, 957; MS: No useful peaks were identified from the CIMS

spectrum. However, a carbohydrate-derived fragment was observed at HR-CIMS calc for $C_{10}H_{13}O_5$ 213.0763, found 213.0750.

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