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Synthesis of potential allosteric modulators of Hsp90 by chemical glycosylation of *Eupomatenoid-6*

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Abstract

Hsp90 (Heat shock protein-90) is a chaperone protein and an established anti-apoptotic target in cancer therapy. Most of the known small-molecule inhibitors that have shown potent antitumor activity target the Hsp90 N-terminal domain and directly inhibit its ATP-ase activity. Many of these molecules display important secondary effects. A different approach to Hsp90 inhibition consists of targeting the protein C-terminal domain (CTD) and modulating its chaperone activity through allosteric effects. Using an original computational approach, allosteric hot-spots in the CTD have been recently identified that control interdomain communication. A combination of virtual and experimental screening enabled identification of a rhamnosylated benzofuran (*Eupomatenoid-2*) as a lead for further development. In this paper we describe glycodiversification of *Eupomatenoid-2* using chemical glycosylation of the 2-(4'-hydroxyphenyl)benzofuran aglycon (a.k.a. *Eupomatenoid-6*). Glycosylation of the phenol by glycosyl bromides under basic conditions afforded the desired products in the *gluco*-, *galacto*- and *fuco*- series. This approach failed in the *manno*- and *rhamno*- series. However, mannosylation and rhamnosylation of *Eupomatenoid-6* could be obtained under carefully controlled acidic conditions, using *O*-benzoxazolyl imidate (OBox) donors. The glycosides obtained are currently under investigation as modulators of Hsp90 chaperone activity.

Keywords : Eupomatenoid, phenol glycosylation, Hsp90, *O*-benzoxazolyl imidate (OBox), Glycodiversification, Phase Transfer Catalysis

1. Introduction

Heat Shock Proteins (HSPs) are a class of functionally related chaperone proteins, which are overexpressed as a protective mechanism in cells exposed to a variety of stressful events. They have been shown to possess a pivotal role in cell cycle progression and cell death (apoptosis) and to be involved in many diseases. In particular, Hsp90 is established as an anti-apoptotic target in cancer therapy.^{1,2} Hsp90 consists of four domains, an N-terminal ATP binding site domain, a middle domain that regulates ATP hydrolysis, a charged region, and a C-terminal homodimerization domain.³ These domains are involved in complex internal dynamics processes that control the chaperone activity of the

protein and, with it, the signaling pathways regulated by Hsp90, which controls a number of client proteins.^{1,4}

Numerous small-molecule inhibitors of Hsp90 have been identified and have shown potent antitumor activity in a wide-range of malignancies.⁵ Most of these molecules, such as Geldanamycin or Radicicol,⁶ target the Hsp90 N-terminal domain and directly inhibit its ATP-ase activity. The aminocoumarin Novobiocin and its analogues^{7,8} have been shown to bind the C-terminal domain (CTD) of Hsp90 and to cause proteosomal degradation of the clients by inhibiting correct folding. A recent study has shown that the activity and selectivity of Novobiocin can be tuned by glycosylation at the 4' position.⁹

Using an original computational approach,^{10,11} allosteric hot-spots in Hsp90 CTD that control interdomain communication have been recently identified by Colombo and co-workers. Virtual screening enabled the identification of a group of 14 molecules targeted to these hot spots, six of which were experimentally shown to bind the CTD and to control Hsp90 function in cellular studies.¹¹ Allosteric modulation of Hsp90 may allow adjustments to the internal dynamics of the protein, leading to fine tuning of the signalling pathways it regulates. Thus, allosteric inhibitors or activators of Hsp90 activity may become useful tools for system biology studies.

Among the hits identified,¹¹ we focused our attention on the rhamnosylated 2-(4'-hydroxyphenyl)-5-propenyl-benzofuran scaffold **1** (*Eupomatenoid-2*,¹² Figure 1). The aglyconic part is also known as *Eupomatenoid-6* (**2**, Figure 1), a natural product extracted from the leaves of *Piper fulvescens* that has been the subject of several syntheses.¹³⁻¹⁶ Glycodiversification¹⁷⁻¹⁹ of **1** has the potential to generate a set of diverse modulators of Hsp90 activity.^{9,20,21}

In this paper, we report our studies on the chemical glycosylation of *Eupomatenoid-6* (**2**).

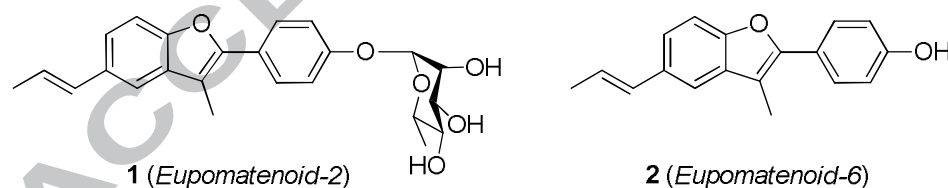
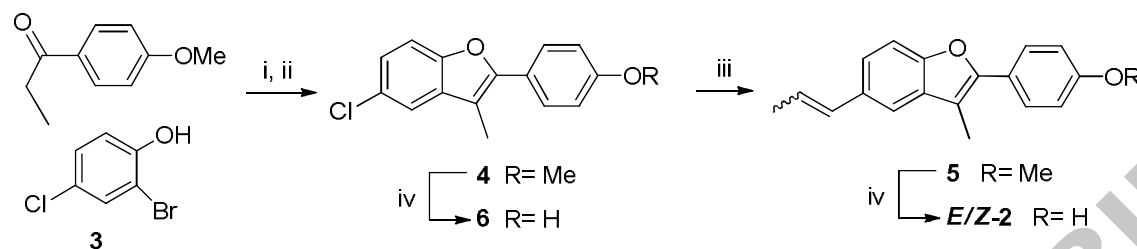


Figure 1. The rhamnosylated 2-phenyl-5-propenyl-benzofuran scaffold **1** and its aglycon **2**.

2. Results and discussion

Eupomatenoid-6 (**2**) was prepared according to a reported procedure¹³ shown in Scheme 1, that starts from 2-bromo-4-chlorophenol **3** and leads to the intermediate 5-chlorobenzofuran **4**, which is

transformed in **2** using a Stille coupling. Due to the diastereomeric purity of the Stille reagent used, the target **2** was obtained as a 3:1 *E:Z* mixture.

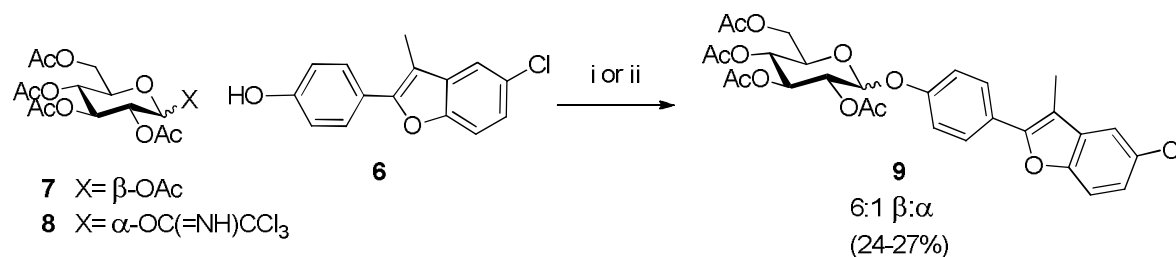


Scheme 1: Synthesis of *Eupomatenoid-6* (**2**) and the glycosylation model aglycon **6**. i. Pd(OAc)₂, *rac*-2-(di-*tert*-butylphosphino)-1,1'-binaphthyl (*rac*-DTBPB), NaOtBu, toluene, MW 100°C, 1h; ii. TFA/DCM, r.t., 45% over two steps; iii. Tri-*N*-butyl(1-propenyl)tin, [HPTBu₃][BF₄]Pd₂dba₃, CsF, 85%, *E:Z* 3:1; iv. NaSEt, DMF, 145°C, >95%.

For the exploration of different glycosylation strategies the 5-chlorobenzofuran **6** (Scheme 1) was chosen as a model aglycon, because it is synthetically more accessible than **2** and avoids the analysis of *E:Z* mixtures. Compound **6** was obtained in good yield by demethylation of **4** using sodium ethanethiolate.¹³

Glycosylation of phenols is associated with several specific problems.^{22,23} First, under acidic conditions, phenols are weaker nucleophiles compared to alcohols, because the aromatic ring is electron withdrawing. Moreover, under classical Lewis acid catalyzed glycosylation conditions, *C*-glycosylation competes with, or often prevails over, *O*-glycosylation. Nonetheless, acceptable yields can usually be obtained even with not very active glycosyl donors (such as *O*-acetates) using phenols carrying electron-donating groups (e.g., *p*-methoxyphenol).²⁴

We initially tested the glycosylation of **6** with β-D-glucose penta-*O*-acetate **7** in the presence of boron trifluoride etherate²⁴ and with α-D-glucose tetra-*O*-acetyl-trichloroacetimidate **8**²⁵ in the presence of TMSOTf at -20°C (Scheme 2). In both cases, **9** was isolated in low yields (24% and 27%) as a 6:1 (β:α) anomeric mixture and extensive decomposition of the aglycon was observed. Upon suggestion by a referee, the glycosylation reaction was also performed in the presence of boron trifluoride and TEA.²⁶ A slight improvement in the diastereoselectivity was indeed observed (β:α, 10:1) but yields remained disappointingly low (30% ca.).

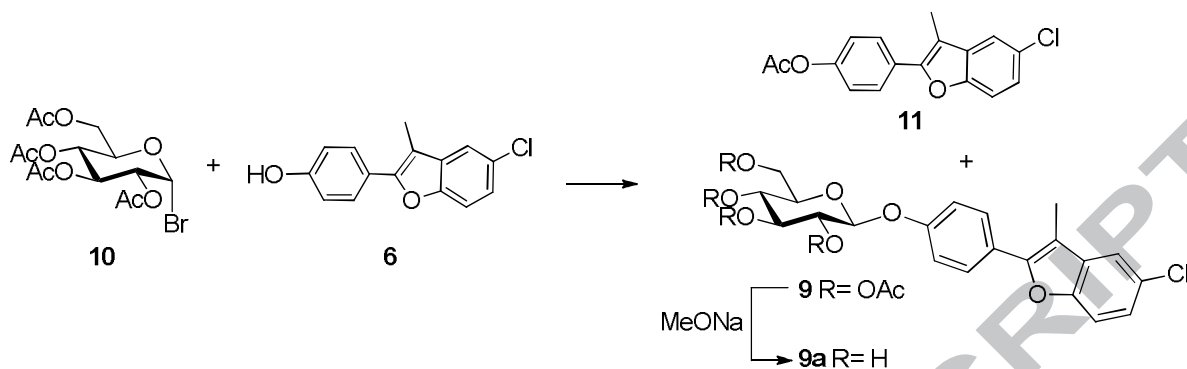


Scheme 2: Glycosylation of **6** under acidic conditions. i. **7** (1.5 eq), BF₃·Et₂O (3 eq), r.t. ii. **8** (1.2 eq), TMSOTf (0.1 eq), -20 °C.

The aglycon instability and the scarce reactivity under acidic conditions associated with poor stereoselectivity prompted us to examine glycosylation by glycosyl halide donors under basic conditions, where phenols are easily deprotonated.²³

Glycosylation of model acceptor **6** with α -D-glucosyl bromide tetra-*O*-acetate donor **10** was screened under different experimental conditions (Table 1). Reaction of **10** with **6** in the presence of excess silver carbonate afforded only traces of the expected product **9** (β anomer) and the acetylated acceptor **11** was recovered as the major product (Table 1, entry 1). Reaction of the Cs salt of **6** with excess **10** in DMF at 60°C led to recovery of unreacted starting material (Table 1, entry 2). Phase Transfer Catalysis (PTC) conditions were explored under various experimental setups. Tetrabutylammonium iodide (TBAI) was initially examined, using an excess (3 eq) of donor in CHCl₃ as a solvent and aq. K₂CO₃ as the base, following a reported procedure²⁷ (Table 1, entry 3). Under these conditions the β -glycosylation product **9** was formed in good yields (60%), but the conversion was incomplete. Similar results were obtained using the more efficient catalyst tetrabutylammonium hydrogensulfate (TBAHSO₄) (entry 4, 65% yield). Lowering the amount of donor (0.66 eq, entry 5) was beneficial for the chromatographic isolation of **9**, but worsened considerably the yields of the reaction. Indeed, it was more convenient to isolate the glycosylation product after deprotection (MeONa) to yield **9a** (Table 1, entry 6, 60% yield over the two steps).

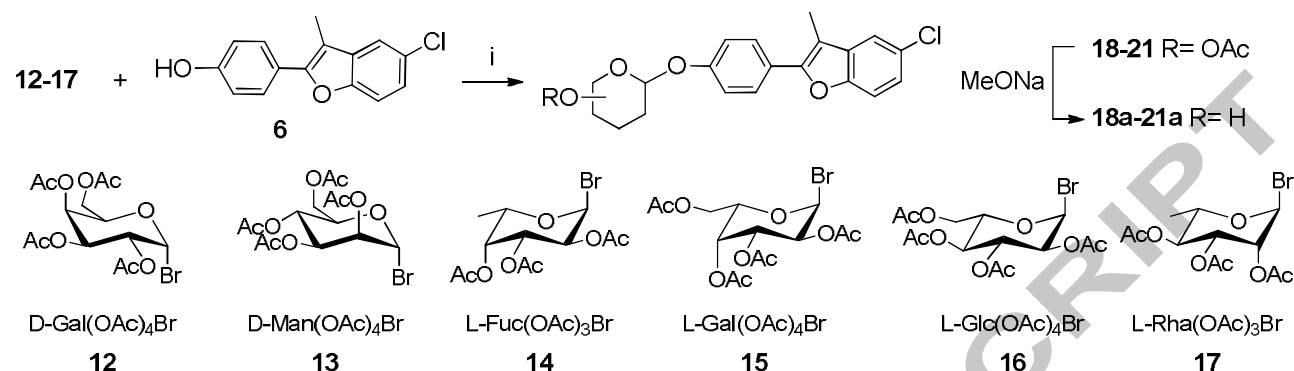
The anomeric configuration of **9** was assigned as β after deacetylation to **9a**, which showed a J_{1,2} coupling constant of 7.3 Hz (DMSO-d₆, Supplementary Figure 3).

Table 1: Initial screening for optimal glycosylation conditions of acceptor **6** with donor **10**

Entry	Eq. donor	Reagents	Solvent	T	Time	9 Yield	Other products
1	3	Ag ₂ CO ₃ (3.65 eq)	Pyridine	r.t.	24 h	Traces	11 (50%)
2	3	6 Cs salt ^a	DMF	60°C	24 h	-	starting materials traces of 11
3	3	TBAI (0.2 eq) K ₂ CO ₃ (6 eq)	CHCl ₃ -H ₂ O ^b	r.t.	24 h	60%	starting materials traces of 11
4	3	TBAHSO ₄ (0.5 eq) K ₂ CO ₃ (6 eq)	CHCl ₃ -H ₂ O ^c	r.t.	8 h	65%	starting materials traces of 11
5	0.66	TBAHSO ₄ (0.5 eq) K ₂ CO ₃ (6 eq)	CHCl ₃ -H ₂ O ^c	r.t.	24 h	30%	starting materials 11 (20 %)
6	3	TBAHSO ₄ (0.5 eq) K ₂ CO ₃ (6 eq)	CHCl ₃ -H ₂ O ^c	r.t.	24 h	60% ^d	starting materials 11 (10 %)

^a Generated with Cs₂CO₃ ^b 0.04M, H₂O: 5% w/w_{K₂CO₃}; ^c 0.1M, H₂O: 5% w/w_{K₂CO₃}; ^d Yield calculated over 2 steps after deprotection to afford **9a**.

The reaction of different glycosyl bromide donors (L-Glc, D- and L-Gal and L-Fuc configuration) with **6** under the optimized conditions led to the desired products in modest to excellent yields (Table 2). An excess of donor or acceptor was used depending on the availability of the bromide. The fucosylated product was obtained in almost quantitative yield using an excess of donor (Table 2, entry 4). The anomeric configuration of all glycosylated products was confirmed to be β only (**18a-21a**, Table 2) by experimental NMR $J_{H1,H2}$ coupling constants of the deacetylated products.

Table 2: Glycosylation of acceptor **6** with different donors.

Entry	Donor	Eq donor	Product	Isolated yield ^a	By-products
1	16	0.83	18a	36% (43%) ^b	11 (30%)
2	12	3	19a	41% ^b	-
3	15	0.83	20	62% (77%)	traces of 11
4	14	3	21a	>95% ^b	-
5	13	0.66	-	^c	-
6	17	0.66	-	^c	-

i. CHCl₃ (0.1-0.2M)/ water (5% w/w_{K₂CO₃}), TBAHSO₄ (0.5 eq), K₂CO₃ (6 eq) at room temperature for 24h. ^a Yields in brackets are calculated based on the limiting agent. ^b Yield calculated over 2 steps after deprotection. ^c No reaction occurred.

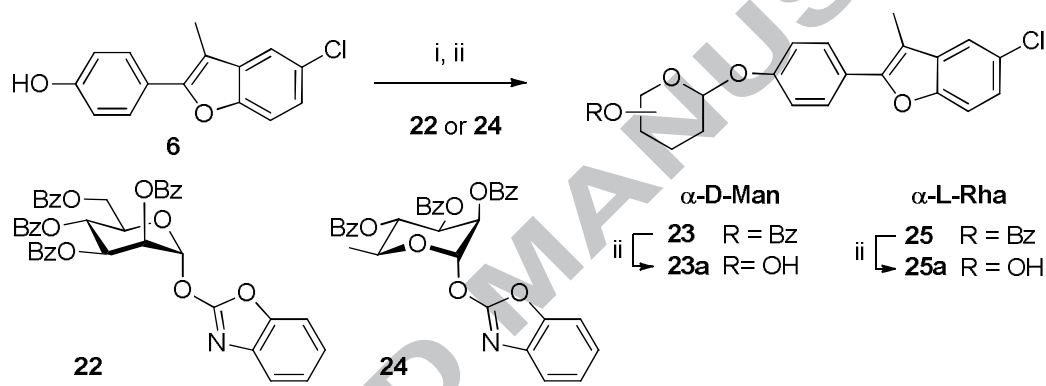
Disappointingly, under these conditions glycosides of *manno*- configuration (D-Man and L-Rha) were not accessible; attempted reaction gave only complete recovery of starting material (Table 2, entries 5-6).

Mitsunobu conditions were explored whereby **6** was treated with tetra-*O*-benzoyl-rhamnose and Ph₃P,²⁸ but again only unreacted starting material was recovered.

Attempts to glycosylate **6** with rhamnose penta-*O*-acetate in the presence of boron trifluoride etherate²⁴ or with mannose tetra-*O*-benzoyl-trichloroacetimidate in the presence of TMSOTf were not successful. No reaction was observed in the first case, while *C*-glycosylation and aglycon decomposition were detected in the second case. Demchenko and co-workers recently reported a new class of glycosyl donors, the *O*-benzoxazolyl (OBox) imidates,²⁹ that possess intermediate reactivity properties relative to *O*-trichloroacetimidates and thioglycosides. In particular OBox glycosides react with nucleophiles under Lewis acid activation at very low temperature, which may prevent degradation of our acid-sensitive

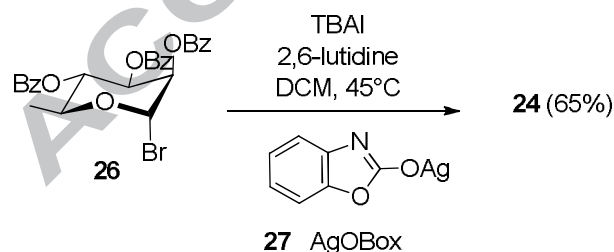
acceptor. Following Demchenko procedure, a mixture of acceptor (**6**) and the known donor α -D-Man(OBz)₄-OBox **22**²⁹ (1.2eq) was dissolved in 1,2-dichloroethane (1,2-DCE) and cooled to -78°C, with the solvent solidifying at -35°C. After addition of a 0.1M TMSOTf solution in 1,2-DCE (0.1 eq) the reaction mixture was slowly warmed to -30°C and quenched by water addition after 2 min stirring. Work-up and chromatographic purification afforded product **23** as a single (α) isomer in 33% yield (Table 3, entry 1). Similarly, the unprecedented rhamnosyl donor **24** was prepared in 65% yield from tri-*O*-benzoyl- α -L-rhamnosyl bromide **26** and AgOBox **27** (Scheme 3) and reacted with **6**, providing product **25** in high yield (87%, Table 3, entry 2). Zemplén deprotection of the *O*-benzoyl glycosides followed by reverse phase automated chromatography afforded the corresponding glycosides **23a** and **25a**.

Table 3: TMSOTf-promoted glycosylation reaction of acceptors **6** with D-Man-OBox (**22**) and L-Rha-OBox (**24**).



Entry	Acceptor	Donor	Product	Isolated yield
1	6	22	23	33%
2	6	24	25	87%

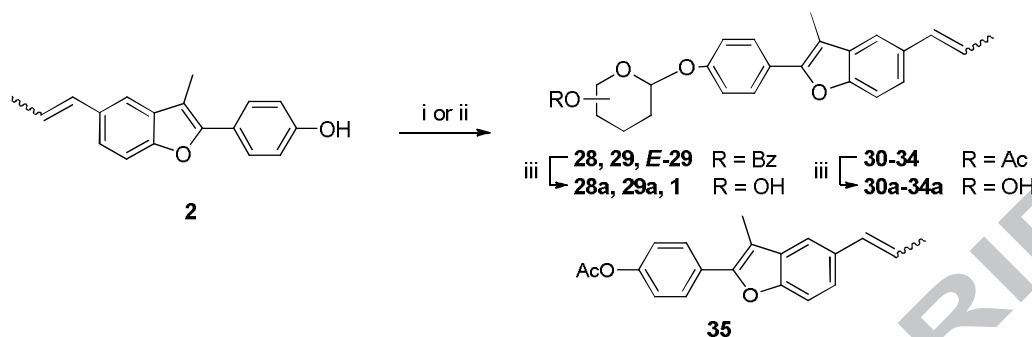
i. **6** (1 eq, 0.2M in 1,2-DCE), **22** or **24** (1.2 eq), TMSOTf (0.1 eq), -78°C to m.p., 5 min; ii. MeONa, MeOH, r.t.



Scheme 3: Preparation of α -L-Rha(OBz)₃-OBox **24** by reaction of tri-*O*-benzoyl- α -L-rhamnosyl bromide **26** with AgOBox **27**.

Thus, with these two strategies in hands, scaffold **2** was glycosylated with different glycosyl donors. The OBox strategy was successfully applied for the preparation of the D-Man and L-Rha derivatives (**28** and **29**, respectively), which were obtained in moderate to good yields (Table 4, entries 1-2).

When performing the reaction on the pure *E* isomer of **2** (**E-2**, *Eupomatenoid-6*), product **E-29** was obtained in 70% yield (Table 4, entry 3). Benzoate hydrolysis of **E-29** under Zemplén conditions afforded α -L-rhamnosyl 2-(4'-hydroxy-phenyl)-5-prop-1-E-enyl-benzofuran **1** (*Eupomatenoid-2*) which was found to be identical to an authentic sample obtained from the National Cancer Institute Collection (NCI). The α configuration of *Eupomatenoid-2*, previously assigned to the natural product without unequivocal experimental evidence,¹² was confirmed by analysis of ^1H coupling constants and of the ^1H NOESY spectrum. The signal of H_4 of **1** appears as a t with $J_{3,4} = J_{4,5} = 9.5$ Hz, which is consistent with a chair ($^1\text{C}_4$) conformation. The anomeric coupling constant ($J_{1,2}$) of 1.8 Hz is typical of α -*rhamno* glycosides and strong nOe contacts for H_1 are observed only with H_2 and H_{ortho} of the phenol moiety, as expected for an α rhamnoside (see Supplementary Figure 13). Glycosylation of **2** under PTC conditions afforded the D-/L-Glc, D-/L-Gal and L-Fuc β glycosides in moderate yields (Table 4). As shown in the model system, higher yields of the desired products were obtained using an excess of donor (Table 4, compare entries 4 and 5). Nonetheless, in some cases, an excess of acceptor was employed to simplify the purification procedure, since the glycosylation products often co-elute with the donor. For the same reason in some cases products were purified after deacetylation and yields are given over the two steps (Table 4, entries 6-8 and 10).

Table 4: Glycosylation of acceptor **2** with different glycosyl donors.

Entry	Donor	Eq donor	Product	Isolated yield ^a
1	22	1.2	28	54%
2	24	1.2	29	55%
3	24	1.2	E-29	70%
4	10	0.66	30	25% (39%)
5	10	3	30^b	50%
6	16	0.83	31a^c	32% ^d (38%)
7	12	0.66	32a	47% ^d (70%)
8	12	3	32a	50% ^d
9	15	0.83	33	61% (71%)
10	14	0.66	34a	49% ^d (73%)

i. TMSOTf (0.1 eq), 1,2-DCE (0.2M), -78°C to m.p., 5 min; ii. CHCl₃ (0.1-0.2M)/water (5% w/w_{K₂CO₃}), TBAHSO₄ (0.5 eq), K₂CO₃ (6 eq) r.t., 24h; iii. MeONa, MeOH, r.t. ^aYields in brackets are calculated based on the limiting agent; ^b **35** (20%); ^c **35** (30%); ^dYield calculated over 2 steps after deacetylation.

3. Conclusions

Chemical glycosylation of the phenol functionality of *Eupomatenoid-6* (**2**) and of its synthetic precursor **6** was achieved using glycosyl halides under basic phase transfer conditions for the D- and L-*gluco*-, D- and L-*galacto*- and L-*fuco*- glycosides. Products of *manno*- configuration (L-Rha and D-Man) were obtained using the corresponding OBox-imidate donor under Lewis acid catalysis at low temperature. In all cases 6-deoxy sugars (L-Rha and L-Fuc) afforded the corresponding glycosides in considerably higher yields; this is in accord with previous reports for chemical glycosylation of phenols.²³ The anomeric configuration of the products was determined by NMR J_{H1-H2} coupling constants or, when this was not

distinctive, by analysis of the nOe contacts. β -Glycosides were obtained in the *gluco*-, *galacto*- and *fuco*-series, α -glycosides in the *manno*- and *rhamno*- series.

The compounds synthesized have undergone preliminary testing for binding to the Hsp90 C-terminal domain.³⁰ Several have been found to bind as well as *Eupomatenoid-2*. These molecules are currently being analyzed for allosteric modulation of Hsp90 function in cellular models.

4. Experimental

4.1 General Methods

All chemical reagents were of analytical grade, and used as supplied. Organic solvents were dried according to common literature protocols. All non-hydrolytic reactions were conducted under a positive pressure of nitrogen. Analytical thin layer chromatography (TLC) was performed on silica gel 60-F254 (Merck). Plates were visualized by ultraviolet (UV) light, or treatment with molybdc reagent solution, followed by heating. Compounds were purified by flash chromatography using Silica gel 60 (0.040-0.063 mm, 230-400 mesh particle size) by Merck. Automated flash chromatography by Biotage instrument (Biotage Isolera™ Prime) was used to purify final compounds. KP-Sil™ (40–65 μ m, average 50 micron) Biotage SNAP cartridges were used for direct-phase purifications (for reverse-phase: KP-C18-HS™, average 25 micron); solvents were of reagent grade and were used as supplied. ¹H-NMR spectra were recorded at 400 MHz and ¹³C-NMR spectra were recorded at 100 MHz, using a Bruker Avance 400 instrument. Chemical shifts (δ) are reported in ppm using residual solvent signals from deuterated solvents as references.³¹ Signals in ¹H and ¹³C NMR spectra were assigned with the aid of two dimensional COSY and HSQC spectra. For some signals in ¹H NMR spectra, the coupling patterns were reported as multiplets due to high order coupling or signal overlap. Mass spectrometry was performed under positive/negative-mode electrospray ionization (ESI) on a ThermoFinnigan LCQ™ Classic or Waters® Micromass® Q-ToF micro™ Mass (ESI-HRMS) and for high resolution on Bruker Daltonics APEX II (FT-ICR). Optical rotations were measured in a 10 cm cell with a Perkin-Elmer 241 polarimeter at 25°C. Compounds **3**, **7**, **10** and **12** are commercially available (Sigma-Aldrich). Compounds **1**,¹² **2**, **4** and **5**,¹³ **13**,³² **14**,³³ **15**,³⁴ **16**,³⁵ **17**³⁶ and **18**²⁹ are known. The characterization of protected glycosides **9**, **18-21**, **23**, **25**, **28-34** is detailed in the supplementary information.

4.2 General procedures

4.2.1 Glycosylation under phase transfer catalysis

Peracetylated glycosyl bromide (3 eq) and 2-(4'-hydroxyphenyl)benzofuran (**2** or **6**, 1 eq) were dissolved in chloroform (10 mL/mmol). Tetrabutylammonium hydrogen sulfate (0.5 eq), potassium carbonate (6

eq) and water (5% w/w of potassium carbonate) were added to the solution. The reaction mixture was stirred for 24h at room temperature. The reaction mixture was diluted with chloroform, the organic layer was washed with 0.1M HCl, sat. NaHCO₃ and brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by automated flash chromatography (hexane/ethyl acetate gradient elution).

4.2.2 TMSOTf-promoted glycosylation with *O*-Benzoxazolyl imidates

A mixture of glycosyl donor (1.2 eq) and aglycon (1 eq) in dry 1,2-dichloroethane (5 mL/mmol) was stirred under nitrogen atmosphere at room temperature for 5 min and then cooled to -78 °C. A 0.1M solution of TMSOTf (0.1 eq) in dry 1,2-dichloroethane was added to the frozen mixture. Since 1,2-dichloroethane melts at -35°C, the reaction mixture was let warm to -30/-20°C and stirred for 2 min at this temperature. After the reaction was finished (TLC), the reaction mixture was diluted with CH₂Cl₂ and washed with 1% aq. NaOH and water. The organic phase was dried over anhydrous Na₂SO₄, and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate gradient elution).

4.2.3 General procedure for Zemplen hydrolysis of acetates/benzoates

A 1 M solution of sodium methoxide in dry methanol (0.5 eq / *O*-cleavage) was drop-wise added to a solution of the peracetylated (or a suspension of the perbenzoylated) product in methanol (0.1 M). The reaction mixture was stirred for 1 h (2 h for *O*-Bz) at room temperature and then neutralized with IR-120 H⁺ (Amberlite) resin. The resin was filtered off and the combined filtrate was concentrated in *vacuo*. The product was purified by reverse-phase automated flash chromatography (water/methanol gradient elution).

4.3 Synthesized compounds

4.3.1 4-(5-Chloro-3-methyl-2-benzofuranyl)-phenol (6) Compound **4**¹³ (710 mg, 2.6 mmol) was dissolved in dry DMF (13 mL). EtSNa (450 mg, 5.2 mmol) was added and the mixture was stirred at 145 °C for 4 h. The reaction was cooled to r.t. and sat. NH₄Cl was added (10 mL). The mixture was extracted with EtOAc and the combined organic layers were washed with H₂O and brine, dried over anhydrous Na₂SO₄, filtered off and concentrated in vacuum. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate gradient elution) to afford 662 mg (98 %) of the demethylated benzofuran **6**. *R*_f = 0.30 (85:15 Hex:EtOAc); ¹H NMR (400 MHz, CDCl₃) δ 7.74 – 7.64 (m, 2H, 2 x H-*m*-Phe-O), 7.47 (dd, *J* = 2.1, 0.5 Hz, 1H, H-4 Bf), 7.36 (dd, *J* = 8.6, 0.5 Hz, 1H, H-7 Bf), 7.21 (dd, *J* = 8.6, 2.1 Hz, 1H, H-6 Bf), 6.99 – 6.91 (m, 2H, 2 x H-*o*-Phe-O), 4.90 (s, 1H, OH), 2.40 (s, 3H, CH₃ Bf). ¹³C NMR (101 MHz, CDCl₃) δ 155.7 (C_{quat}-Phe-O), 152.3 (C-7a), 152.1 (C-2), 132.9 (C-5), 128.6 (2 x C-*o*-Phe-O), 128.0 (C_{quat}-

Phe, C-3a), 124.1 (C-6), 118.9 (C-4), 115.8 (2 x C-*m*-Phe-O), 111.9 (C-7), 109.5 (C-3), 9.4 (CH₃ Bf). HRMS (ESI) calcd for C₁₅H₁₀O₂Cl₁ [M-H]⁻ 257.03748, found 257.03747.

4.3.2 Benzoxazolyl 2,3,4-tri-*O*-benzoyl- α -L-rhamnopyranoside (24) AgOBox²⁹ (324 mg, 1.34 mmol), 2,6-lutidine (117 μ L, 1.00 mmol) and TBAI (14 mg, 0.04 mmol) were added to a solution of 2,3,4-*O*-benzoyl- α -L-rhamnopyranosyl bromide (363 mg, 0.67 mmol) in dry CH₂Cl₂ (4.5 mL) under nitrogen atmosphere. The reaction mixture was stirred for 4 h at 50°C and then diluted with CH₂Cl₂ and washed with 1% aq. NaOH (2 x 10 mL), water (2 x 10 mL) and brine (10 mL). The organic phase was dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate gradient elution) to afford **24** (257 mg, 65% yield) as a white solid. *R*_f = 0.44 (8:2 Hex:EtOAc); [α]_D²⁵ +40.3 (c 1.0, CHCl₃); ¹H NMR (CDCl₃): δ 8.11 (d, *J* = 7.6 Hz, 2H, 2 x *o*-CH-Bz), 7.99 (d, *J* = 7.8 Hz, 2H, 2 x *o*-CH-Bz), 7.84 (d, *J* = 7.9 Hz, 2H, 2 x *o*-CH-Bz), 7.65 (t, *J* = 7.3 Hz, 1H, *p*-CH-Bz), 7.60 – 7.50 (m, 4H, 1 x *p*-CH Bz, 2 x *m*-CH Bz, *H*-4_{Box}), 7.50 – 7.40 (m, 4H, 2 x *m*-CH-Bz, 1 x *p*-CH-Bz, *H*-7_{Box}), 7.34 – 7.25 (m, 4H, 2 x *m*-CH-Bz, *H*-5_{Box}, *H*-6_{Box}), 6.57 (d, 1H, *J*_{1,2} = 1.1 Hz, *H*-1), 6.04 – 5.90 (m, 2H, *H*-2, *H*-3), 5.79 (t, *J* = 9.6 Hz, 1H, *H*-4), 4.44 (dq, *J* = 12.3, 6.1 Hz, 1H, *H*-5), 1.42 (d, *J* = 6.2 Hz, 3H, CH₃-Rha). ¹³C NMR (CDCl₃): δ 165.8 (C=O Bz), 165.6 (C=O Bz), 165.4 (C=O Bz), 161.3 (C-2_{Box}), 148.7 (C-7a_{Box}), 140.7 (C-3a_{Box}), 133.9 (*p*-CH-Bz), 133.6 (*p*-CH-Bz), 133.4 (*p*-CH-Bz), 130.1 (2 x *o*-CH-Bz), 129.9 (4 x *o*-CH-Bz), 129.1 (C_{quat}. Bz), 129.0 (2 x C_{quat}. Bz), 128.8 (2 x *m*-CH-Bz), 128.6 (2 x *m*-CH-Bz), 128.5 (2 x *m*-CH-Bz), 124.7 (C-6_{Box}), 123.6 (C-5_{Box}), 118.9 (C-4_{Box}), 110.1 (C-7_{Box}), 97.9 (C-1), 71.1 (C-4), 69.7 (C-2), 69.4 (C-3), 69.3 (C-5), 17.8 (CH₃-Rha). HRMS calcd for C₃₄H₂₇N₁O₉Na₁ [M+Na]⁺ 616.15780, found 616.15736.

4.3.3 4-[3-methyl-5-(*E*-prop-1-enyl)benzofuran-2-yl]phenyl α -L-rhamnopyranoside (1, Eupomatenoid-2) Compound **1** (42mg, 0.06 mmol) was prepared following general procedures 4.2.2 (**E-29**, 70%) and 4.2.3 (quant.) and it was isolated after automated flash chromatography purification (chloroform/methanol gradient elution). *R*_f = 0.32 (9:1 CH₂Cl₂:CH₃OH); ¹H NMR (400 MHz, CD₃OD) δ 7.78 – 7.67 (m, 2H, 2 x *H*-*m*-Phe-O), 7.43 (bs, 1H, *H*-4 Bf), 7.32 (d, *J* = 8.5 Hz, 1H, *H*-7 Bf), 7.27 (dd, *J* = 8.5, 1.5 Hz, 1H, *H*-6 Bf), 7.23 – 7.10 (m, 2H, 2 x *H*-*o*-Phe-O), 6.50 (dd, *J* = 15.7, 1.5 Hz, 1H, =CH-Ar), 6.23 (dq, *J* = 15.7, 6.5 Hz, 1H, =CH-Me), 5.51 (bd, *J* = 1.5 Hz, 1H, *H*-1), 4.04 (dd, *J* = 3.3, 1.8 Hz, 1H, *H*-2), 3.88 (dd, *J* = 9.5, 3.4 Hz, 1H, *H*-3), 3.67 (tt, *J* = 6.2, 4.6 Hz, 1H, *H*-5), 3.49 (t, *J* = 9.5 Hz, 1H, *H*-4), 2.40 (s, 3H, CH₃ Bf), 1.88 (dd, *J* = 6.6, 1.5 Hz, 3H, Me-CH=), 1.26 (s, 3H, CH₃ Rha). ESI-MS calcd for C₂₄H₂₆O₆Na₁ [M+Na]⁺ 433.2, found 433.3; calcd for C₄₈H₅₁O₁₂ [2M-H]⁻ 819.3, found 819.6.

4.3.4 4-[5-Chloro-3-methylbenzofuran-2-yl]phenyl β -D-glucopyranoside (9a) Compound **9a** (24 mg, 0.057 mmol) was prepared following general procedures 4.2.1 and 4.2.3 (60% yield, over two steps). *R*_f = 0.23 (9:1 CH₂Cl₂:CH₃OH); [α]_D²⁵ -55.0 (c 0.1, Dioxane); ¹H NMR (400 MHz, MeOD) δ 7.80 – 7.69 (m, 2H, 2

x H-*m*-Phe-O), 7.54 (d, $J = 2.1$ Hz, 1H, H-4 Bf), 7.42 (d, $J = 8.6$ Hz, 1H, H-7 Bf), 7.27 – 7.20 (m, 3H, H-6 Bf, 2 x H-*o*-Phe-O), 5.00 (dd, $J = 5.4, 2.1$ Hz, 1H, H-1), 3.93 (dd, $J = 12.1, 2.0$ Hz, 1H, H-6b), 3.72 (dd, $J = 12.1, 5.6$ Hz, 1H, H-6a), 3.53 – 3.46 (m, 3H, H-5, H-3, H-2), 3.45 – 3.38 (m, 1H, H-4), 2.42 (s, 3H, CH₃ Bf). ¹³C NMR (101 MHz, MeOD) δ 159.2 (C_{quat}-Phe-O), 153.5 (C-7a Bf), 153.4 (C-2 Bf), 134.0 (C-5 Bf), 129.2 (2 x C-*m*-Phe-O), 126.3 (C-3a Bf, C_{quat}-Phe), 125.2 (C-6 Bf), 119.8 (C-4 Bf), 117.9 (2 x C-*o*-Phe-O), 112.8 (C-7 Bf), 110.9 (C-3 Bf), 102.1 (C-1), 78.2 (C-5), 78.0 (C-3), 74.9 (C-2), 71.3 (C-4), 62.5 (C-6), 9.3 (CH₃ Bf). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.78 – 7.71 (m, 3H, 2 x H-*m*-Phe-O, H-4 Bf), 7.59 (d, $J = 8.7$ Hz, 1H, H-7 Bf), 7.31 (dd, $J = 8.7, 2.2$ Hz, 1H, H-6 Bf), 7.20 (d, $J = 8.9$ Hz, 2H, 2 x H-*o*-Phe-O), 5.36 (d, $J = 4.5$ Hz, 1H, OH-2), 5.13 (d, $J = 4.3$ Hz, 1H, OH-3), 5.06 (d, $J = 5.2$ Hz, 1H, OH-4), 4.96 (d, $J = 7.3$ Hz, 1H, H-1), 4.58 (t, $J = 5.7$ Hz, 1H, OH-6), 3.76 – 3.65 (bddd, 1H, $J = 11.7, 5.7, 1.5$ Hz, 1H, H-6a), 3.48 (dt, $J = 11.7, 5.9$ Hz, 1H, H-6b), 3.42 – 3.34 (m, 1H, H-5), 3.33 – 3.11 (m, 6H, H-3, H-2, H-4), 2.41 (s, 3H, CH₃ Bf). HRMS (ESI) calcd for C₂₁H₂₁O₇Cl₁Na₁ [M+Na]⁺ 443.08683, found 443.08705.

4.3.5 4-[5-Chloro-3-methylbenzofuran-2-yl]phenyl β -L-glucopyranoside (18a) Compound **18a** (40 mg, 0.094 mmol) was prepared following general procedures 4.2.1 and 4.2.3 (43% yield, over two steps). $R_f = 0.23$ (9:1 CH₂Cl₂:CH₃OH); [α]_D²⁵ +55 (c 0.1, Dioxane). ¹H NMR (400 MHz, CD₃OD) δ 7.80 – 7.69 (m, 2H, 2 x H-*m*-Phe-O), 7.56 (d, $J = 1.9$ Hz, 1H, H-4 Bf), 7.44 (d, $J = 8.6$ Hz, 1H, H-7 Bf), 7.27 – 7.20 (m, 3H, H-6 Bf, 2 x H-*o*-Phe-O), 5.02 (dd, $J = 5.4, 2.0$ Hz, 1H, H-1), 3.94 (dd, $J = 12.1, 2.0$ Hz, 1H, H-6b), 3.74 (dd, $J = 12.1, 5.6$ Hz, 1H, H-6a), 3.58 – 3.38 (m, 4H, H-5, H-3, H-2, H-4), 2.43 (s, 3H, CH₃ Bf). ESI-MS calcd for C₂₁H₂₁O₇Cl₁Na₁ [M+Na]⁺ 443.1, found 443.3; calcd for C₄₂H₄₂O₁₄Cl₂Na₁ [2M+Na]⁺ 863.2, found 863.1; calcd for C₄₂H₄₁O₁₄Cl₂ [2M-H]⁻ 839.2, found 839.3.

4.3.6 4-[5-Chloro-3-methylbenzofuran-2-yl]phenyl β -D-galactopyranoside (19a) Compound **19a** (29 mg, 0.07 mmol) was prepared following general procedures 4.2.1 and 4.2.3 (41% yield, over two steps). $R_f = 0.25$ (9:1 CH₂Cl₂:CH₃OH); [α]_D²⁵ -52 (c 0.15, Dioxane). ¹H NMR (400 MHz, CD₃OD) δ 7.78 – 7.71 (m, 2H, 2 x H-*m*-Phe-O), 7.54 (d, $J = 1.9$ Hz, 1H, H-4 Bf), 7.43 (d, $J = 8.9$ Hz, 1H, H-7 Bf), 7.29 – 7.22 (m, 3H, H-6 Bf, 2 x H-*o*-Phe-O), 4.96 (d, $J = 7.7$ Hz, 1H, H-1), 3.93 (d, $J = 3.2$ Hz, 1H, H-4), 3.87 – 3.70 (m, 4H, H-2, H-6a, H-6b, H-5), 3.61 (dd, $J = 9.7, 3.4$ Hz, 1H, H-3), 2.42 (s, 3H, CH₃ Bf). ¹³C NMR (101 MHz, CD₃OD) δ 159.3 (C_{quat}-Phe-O), 153.6 (C-7a Bf), 153.4 (C-2 Bf), 134.0 (C-5 Bf), 129.2 (2 x C-*m*-Phe-O), 126.2 (C-3a Bf, C_{quat}-Phe), 125.2 (C-6 Bf), 119.8 (C-4 Bf), 118.0 (2 x C-*o*-Phe-O), 112.8 (C-7 Bf), 110.9 (C-3 Bf), 102.7 (C-1), 77.1 (C-5), 74.9 (C-3), 72.2 (C-2), 70.2 (C-4), 62.5 (C-6), 9.3 (CH₃ Bf). HRMS (ESI) calcd for C₂₁H₂₁O₇Cl₁Na₁ [M+Na]⁺ 443.08680, found 443.08682.

4.3.7 4-[5-Chloro-3-methylbenzofuran-2-yl]phenyl β -L-galactopyranoside (20a) Compound **20a** (55 mg, 0.13 mmol) was prepared following general procedures 4.2.1 (**14**, 77%) and 4.2.3 (quant. yield). $R_f = 0.25$ (9:1 CH₂Cl₂:CH₃OH); [α]_D²⁵ +52.0 (c 0.1, Dioxane). ¹H NMR (400 MHz, CD₃OD) δ 7.78 – 7.71 (bd, 2H,

2 x H-*m*-Phe-O), 7.55 – 7.52 (bd, 1H, H-4 Bf), 7.45 – 7.40 (bd, 1H, H-7 Bf), 7.28 – 7.20 (bs, 3H, H-6 Bf, 2 x H-*o*-Phe-O), 4.96 (d, $J = 7.7$ Hz, 1H, H-1), 3.93 (d, $J = 3.4$ Hz, 1H, H-4), 3.88 – 3.70 (m, 4H, H-2, H-6a, H-6b, H-5), 3.66 – 3.57 (m, 1H, H-3), 2.42 (s, 1H, CH₃ Bf). ESI-MS calcd for C₂₁H₂₁O₇Cl₁Na₁ [M+Na]⁺ 443.1, found 443.3; calcd for C₄₂H₄₂O₁₄Cl₂Na₁ [2M+Na]⁺ 863.2, found 863.2; calcd for C₄₂H₄₁O₁₄Cl₂ [2M-H]⁻ 839.2, found 839.1.

4.3.8 4-[5-Chloro-3-methylbenzofuran-2-yl]phenyl β-L-fucopyranoside (21a) Compound **21a** (35 mg, 0.088 mmol) was prepared following general procedures 4.2.1 (**21**, >95%) and 4.2.3 (quant. yield). $R_f = 0.38$ (9:1 CH₂Cl₂:CH₃OH); $[\alpha]_D^{25} +52.0$ (c 0.1, Dioxane). ¹H NMR (400 MHz, CD₃OD) δ 7.79 – 7.70 (m, 2H, 2 x H-*m*-Phe-O), 7.54 (d, $J = 2.0$ Hz, 1H, H-4 Bf), 7.42 (d, $J = 8.6$ Hz, 1H, H-7 Bf), 7.29 – 7.13 (m, 3H, H-6 Bf, 2 x H-*o*-Phe-O), 4.94 (d, $J = 7.7$ Hz, 1H, H-1), 3.93 – 3.83 (m, 1H, H-5), 3.79 (dd, $J = 9.7, 7.7$ Hz, 1H, H-2), 3.69 (bd, $J = 2.9$ Hz, 1H, H-4), 3.61 (dd, $J = 9.7, 3.4$ Hz, 1H, H-3), 2.42 (s, 3H, CH₃ Bf), 1.33 (d, $J = 6.5$ Hz, 3H, CH₃ Fuc). ¹³C NMR (101 MHz, CD₃OD) δ 159.3 (C_{quat}-Phe-O), 153.6 (C-7a Bf), 153.4 (C-2 Bf), 134.0 (C-5 Bf), 129.1 (2 x C-*m*-Phe-O), 126.2 (C-3a Bf, C_{quat}-Phe), 125.2 (C-6 Bf), 119.8 (C-4 Bf), 117.9 (2 x C-*o*-Phe-O), 112.8 (C-7 Bf), 110.9 (C-3 Bf), 102.4 (C-1), 75.0 (C-3), 72.9 (C-4), 72.3 (C-5), 72.0 (C-2), 16.8 (CH₃ Fuc), 9.3 (CH₃ Bf). HRMS (ESI) calcd for C₂₁H₂₁Cl₁O₆Na₁ [M+Na]⁺ 427.09189, found 427.09228.

4.3.9 4-[5-Chloro-3-methylbenzofuran-2-yl]phenyl α-D-mannopyranoside (23a) Compound **23a** (9 mg, 0.02 mmol) was prepared following general procedures 4.2.2 (**23**, 33%) and 4.2.3 (52%) and it was isolated after automated flash purification (chloroform/methanol gradient elution). $R_f = 0.27$ (9:1 CH₂Cl₂:CH₃OH); $[\alpha]_D^{25} +85.0$ (c 0.1, Dioxane). ¹H NMR (400 MHz, CD₃OD) δ 7.78 – 7.71 (m, 2H, 2 x H-*m*-Phe-O), 7.54 – 7.52 (m, 1H, H-4 Bf), 7.44 – 7.39 (m, 1H, H-7 Bf), 7.29 – 7.21 (m, 3H, H-6 Bf, 2 x H-*o*-Phe-O), 5.57 (d, $J = 1.6$ Hz, 1H, H-1), 4.04 (bdd, $J = 3.3, 1.8$ Hz, 1H, H-2), 3.93 (dd, $J = 9.4, 3.4$ Hz, 1H, H-3), 3.85 – 3.68 (m, 3H, H-4, H-6a, H-6b), 3.66 – 3.55 (m, 1H, H-5), 2.41 (s, 3H, CH₃ Bf). ¹³C NMR (101 MHz, CD₃OD) δ 158.0 (C_{quat}-Phe-O), 153.5 (C-7a Bf), 153.4 (C-2 Bf), 134.0 (C-5 Bf), 129.2 (2 x C-*m*-Phe-O), 126.2 (C-3a Bf, C_{quat}-Phe), 125.2 (C-6 Bf), 119.8 (C-4 Bf), 118.0 (2 x C-*o*-Phe-O), 112.8 (C-7 Bf), 111.0 (C-3 Bf), 100.1 (C-1), 75.6 (C-5), 72.4 (C-3), 71.9 (C-2), 68.3 (C-4), 62.7 (C-6), 9.3 (CH₃ Bf). HRMS (ESI) calcd for C₂₁H₂₁O₇Cl₁Na₁ [M+Na]⁺ 443.08680, found 443.08718.

4.3.10 4-[5-Chloro-3-methylbenzofuran-2-yl]phenyl α-L-rhamnopyranoside (25a) Compound **25a** (36 mg, 0.09 mmol) was prepared following procedures 4.2.2 (**25**, 87%) and 4.2.3 (quant.). $R_f = 0.35$ (9:1 CH₂Cl₂:CH₃OH); $[\alpha]_D^{25} -124.7$ (c 0.1, Dioxane). ¹H NMR (400 MHz, CD₃OD) δ 7.72 – 7.66 (m, 2H, 2 x H-*m*-Phe-O), 7.47 (d, $J = 2.1$ Hz, 1H, H-4 Bf), 7.37 (d, $J = 8.6$ Hz, 1H, H-7 Bf), 7.22 – 7.14 (m, 3H, H-6 Bf, 2 x H-*o*-Phe-O), 5.51 (d, $J = 1.6$ Hz, 1H, H-1), 4.04 (dd, $J = 3.4, 1.8$ Hz, 1H, H-2), 3.88 (dd, $J = 9.5, 3.5$ Hz, 1H, H-3), 3.66 (dq, $J = 9.9, 6.2$ Hz, 1H, H-5), 3.49 (t, $J = 9.5$ Hz, 1H, H-4), 2.35 (s, 3H, CH₃ Bf), 1.26 (d, $J = 6.2$ Hz, 4H, CH₃ Rha). ¹³C NMR (101 MHz, CD₃OD) δ 157.9 (C_{quat}-Phe-O), 153.4 (C-7a Bf), 153.3 (C-2 Bf), 134.0 (C-5

Bf), 129.2 (2 x C-*m*-Phe-O), 126.2 (C-3a Bf, C_{quat}-Phe), 125.1 (C-6 Bf), 119.7 (C-4 Bf), 117.7 (2 x C-*o*-Phe-O), 112.7 (C-7 Bf), 111.0 (C-3 Bf), 99.7 (C-1), 73.8 (C-4), 72.2 (C-3), 72.0 (C-2), 70.8 (C-5), 18.1 (CH₃ Rha), 9.3 (CH₃ Bf). HRMS (ESI) calcd for C₂₁H₂₁O₆ClNa₁ [M+Na]⁺ 427.09189, found 427.09208.

4.3.11 *E,Z*-4-[3-methyl-5-(prop-1-enyl)benzofuran-2-yl]phenyl α-D-mannopyranoside (28a) Compound **28a** (34 mg, 0.08 mmol) was prepared following general procedures 4.2.2 (**28**, 54%) and 4.2.3 (quant.) and it was isolated as 1:1 *E:Z* mixture after automated flash chromatography (chloroform/methanol gradient elution). *R_f* = 0.26 (9:1 CH₂Cl₂:CH₃OH). ¹H NMR (400 MHz, CD₃OD) δ 7.78 – 7.69 (m, 2H, 2 x H-*m*-Phe-O), 7.44 (s, 0.5H, H-4 Bf_E), 7.42 (s, 0.5H, H-4 Bf_Z), 7.39 (d, *J* = 8.5 Hz, 0.5H, H-7 Bf_Z), 7.33 (d, *J* = 8.5 Hz, 0.5H, H-7 Bf_E), 7.30 – 7.15 (m, 3H, H-6 Bf_E, H-6 Bf_Z, 2 x H-*o*-Phe-O), 6.61 – 6.44 (m, 1H, =CH-Ar_Z, =CH-Ar_E), 6.24 (dq, *J* = 15.6, 6.5 Hz, 0.5H, =CH-Me_E), 5.77 (dq, *J* = 11.6, 7.1 Hz, 0.5H, =CH-Me_Z), 5.56 (bs, 1H, H-1), 4.07 – 4.00 (m, 1H, H-2), 3.93 (dd, *J* = 9.4, 3.3 Hz, 1H, H-3), 3.84 – 3.69 (m, 3H, H-4, H-6a, H-6b), 3.62 (ddd, *J* = 9.7, 5.0, 2.5 Hz, 1H, H-5), 2.42 (s, 1.5H, CH₃ Bf_Z), 2.41 (s, 1.5H, CH₃ Bf_E), 1.92 (dd, *J* = 7.2, 1.8 Hz, 1.5H, CH₃-CH= _Z), 1.88 (dd, *J* = 6.6, 1.5 Hz, 1.5H, CH₃-CH= _E). ¹³C NMR (101 MHz, CD₃OD) δ 157.7 (C_{quat}-Phe-O), 157.7 (C_{quat}-Phe-O), 154.3 (C-7a Bf), 153.8 (C-7a Bf), 152.2 (C-2 Bf), 152.1 (C-2 Bf), 134.3 (C-5 Bf), 133.6 (C-5 Bf), 132.6 (C-3a Bf), 132.5 (=CH-Ar_E), 132.4 (C-3a Bf), 131.3 (=CH-Ar_Z), 129.0 (2 x C-*m*-Phe-O_Z), 129.0 (2 x C-*m*-Phe-O_E), 126.8 (2 x C_{quat}-Phe), 126.5 (C-6 Bf_Z), 126.3 (=CH-Me_Z), 124.9 (=CH-Me_E), 123.4 (C-6 Bf_E), 120.2 (C-4 Bf_Z), 117.9 (4 x C-*o*-Phe-O), 117.3 (C-4 Bf_E), 111.5 (C-7 Bf_E), 111.3 (C-3 Bf), 111.2 (C-3 Bf), 111.1 (C-7 Bf_Z), 100.1 (C-1), 75.5 (C-5), 72.4 (C-3), 71.9 (C-2), 68.3 (C-4), 62.7 (C-6), 18.6 (CH₃-CH= _E), 14.8 (CH₃-CH= _Z), 9.4 (2 x CH₃ Bf). HRMS (ESI) calcd for C₂₄H₂₆O₇Na₁ [M+Na]⁺ 449.15707, found 449.15713.

4.3.12 *E,Z*-4-[3-methyl-5-(prop-1-enyl)benzofuran-2-yl]phenyl α-L-rhamnopyranoside (29a)

Compound **29a** (29 mg, 0.07 mmol) was prepared following general procedures 4.2.2 (**29**, 55%) and 4.2.3 (quant.) and it was isolated as 1.5:1 *E:Z* mixture after automated flash chromatography (chloroform/methanol gradient elution). *R_f* = 0.33 (9:1 CH₂Cl₂:CH₃OH); ¹H NMR (400 MHz, CD₃OD) δ 7.77 – 7.67 (m, 4H, 2 x H-*m*-Phe-O), 7.43 (bs, 0.6H, H-4 Bf_E), 7.40 (bs, 0.4H, H-4 Bf_Z), 7.38 (bd, *J* = 8.4 Hz, 0.4H, H-7 Bf_Z), 7.32 (bd, *J* = 8.5 Hz, 0.6H, H-7 Bf_E), 7.27 (dd, *J* = 8.6, 1.4 Hz, 0.6H, H-6 Bf_E), 7.24 – 7.09 (m, 4.4H, H-6 Bf_Z, 2 x H-*o*-Phe-O), 6.62 – 6.40 (m, 2H, =CH-Ar_Z, =CH-Ar_E), 6.23 (dq, *J* = 15.5, 6.5 Hz, 0.6H, =CH-Me_E), 5.77 (dq, *J* = 11.6, 7.1 Hz, 0.4H, =CH-Me_Z), 5.51 (bs, 1H, H-1), 4.02 (dd, *J* = 15.9, 3.8 Hz, 1H, H-2), 3.88 (dd, *J* = 9.5, 3.3 Hz, 1H, H-3), 3.76 – 3.56 (m, 1H, H-5), 3.49 (t, *J* = 9.5 Hz, 1H, H-4), 2.40 (s, 1.2H, CH₃ Bf_Z), 2.39 (s, 1.8H, CH₃ Bf_E), 1.91 (dd, *J* = 7.2, 1.7 Hz, 1.2H, CH₃-CH= _Z), 1.88 (dd, *J* = 6.5, 1.3 Hz, 1.8H, CH₃-CH= _E), 1.26 (d, *J* = 6.1 Hz, 3H, CH₃ Rha). ¹³C NMR (101 MHz, CD₃OD) δ 157.6 (2 x C_{quat}-Phe-O), 154.3 (C-7a Bf), 153.8 (C-7a Bf), 152.1 (2 x C-2 Bf), 134.2 (C-5 Bf), 133.5 (C-5 Bf), 132.6 (=CH-Ar_E), 132.6 (C-3a Bf), 132.4 (C-3a Bf), 131.4 (=CH-Ar_Z), 129.0 (4 x C-*m*-Phe-O), 126.7 (2 x C_{quat}-Phe), 126.5 (C-6 Bf_Z), 126.3

(=CH-Me_z), 124.8 (=CH-Me_E), 123.4 (C-6 Bf_E), 120.2 (C-4 Bf_z), 117.7 (4 x C-*o*-Phe-O), 117.3 (C-4 Bf_E), 111.4 (C-7 Bf_E), 111.1 (C-7 Bf_z), 99.8 (C-1), 73.8 (C-4), 72.2 (C-3), 72.0 (C-2), 70.8 (C-5), 18.6 (CH₃-CH=_E), 14.8 (CH₃-CH=_z), 9.4 (2 x CH₃ Bf). ESI-MS calcd for C₂₄H₂₆O₆Na₁ [M+Na]⁺ 433.2, found 433.5; calcd for C₄₈H₅₁O₁₂ [2M-H]⁻ 819.3, found 819.9.

4.3.13 *E,Z*-4-[3-methyl-5-(prop-1-enyl)benzofuran-2-yl]phenyl β-D-glucopyranoside (30a) Compound **30a** (12 mg, 0.02 mmol) was prepared following general procedures 4.2.1 (**30**, 39%, yield based on the limiting agent) and 4.2.3 (>95%) and it was isolated as 3:1 *E:Z* mixture by a flash chromatography (CHCl₃:MeOH) followed by a reverse-phase chromatography (water/methanol) that allowed to remove donor derived by-products. *R*_f = 0.25 (9:1 CH₂Cl₂:CH₃OH). ¹H NMR (400 MHz, CD₃OD) δ 7.80–7.68 (m, 2H, 2 x H-*m*-Phe-O), 7.48–7.44 (m, 0.75H, H-4 Bf_E), 7.44–7.42 (m, 0.25H, H-4 Bf_z), 7.40 (d, *J* = 8.5 Hz, 0.25H, H-7 Bf_z), 7.34 (d, *J* = 8.5 Hz, 0.75H, H-7 Bf_E), 7.29 (dd, *J* = 8.5, 1.5 Hz, 0.75H, H-6 Bf_E), 7.26–7.19 (m, 2.25H, H-6 Bf_z, 2 x H-*o*-Phe-O), 6.59–6.47 (m, 1H, =CH-Ar_z, =CH-Ar_E), 6.25 (dq, *J* = 15.7, 6.6 Hz, 0.75H, =CH-Me_E), 5.78 (dq, *J* = 11.5, 7.2 Hz, 0.25H, =CH-Me_z), 4.99 (dd, *J* = 5.4, 2.0 Hz, 1H, H-1), 3.93 (dd, *J* = 12.1, 1.9 Hz, 1H, H-6a), 3.73 (dd, *J* = 12.1, 5.6 Hz, 1H, H-6b), 3.54–3.45 (m, 3H, H-5, H-2, H-3), 3.45–3.38 (m, 1H, H-4), 2.43 (s, *J* = 4.3 Hz, 0.75H, CH₃ Bf_z), 2.42 (s, 2.25H, CH₃ Bf_E), 1.93 (dd, *J* = 7.2, 1.8 Hz, 0.75H, CH₃-CH=_z), 1.89 (dd, *J* = 6.6, 1.5 Hz, 2.25H, CH₃-CH=_E). ¹³C NMR (101 MHz, CD₃OD) δ 158.9 (C_{quat.}-Phe-O), 158.8 (C_{quat.}-Phe-O), 154.3 (C-7a Bf), 153.8 (C-7a Bf), 152.2 (2 x C-2 Bf), 134.3 (C-5 Bf), 133.6 (C-5 Bf), 132.6 (=CH-Ar_E), 131.3 (=CH-Ar_z), 129.0 (2 x C-*m*-Phe-O_z), 128.9 (2 x C-*m*-Phe-O_E), 126.8 (C-3a Bf), 126.5 (C-6 Bf_z), 126.3 (=CH-Me_z), 124.9 (=CH-Me_E), 123.4 (C-6 Bf_E), 120.2 (C-4 Bf_z), 117.9 (4 x C-*o*-Phe-O), 117.3 (C-4 Bf_E), 111.4 (C-7 Bf_E), 111.2 (C-3 Bf), 111.1 (C-7 Bf_z), 102.1 (C-1), 78.2 (C-5), 78.0 (C-3), 74.9 (C-2), 71.4 (C-4), 62.5 (C-6), 18.6 (CH₃-CH=_E), 14.8 (CH₃-CH=_z), 9.4 (2 x CH₃ Bf). HRMS (ESI) calcd for C₂₄H₂₆O₇Na₁ [M+Na]⁺ 449.15707, found 449.15714.

4.3.14 *E,Z*-4-[3-methyl-5-(prop-1-enyl)benzofuran-2-yl]phenyl β-L-glucopyranoside (31a) Compound **31a** (35 mg, 0.08 mmol) was prepared following general procedures 4.2.1 and 4.2.3 and it was isolated as 1.7:1 *E:Z* mixture in 38% yield (based on the limiting agent) over two steps. *R*_f = 0.25 (9:1 CH₂Cl₂:CH₃OH). ¹H NMR (400 MHz, CD₃OD) δ 7.79–7.67 (m, 2H, 2 x H-*m*-Phe-O), 7.45 (s, 0.63H, H-4 Bf_E), 7.43 (s, 0.37H, H-4 Bf_z), 7.39 (d, *J* = 8.4 Hz, 0.37H, H-7 Bf_z), 7.34 (d, *J* = 8.5 Hz, 0.63H, H-7 Bf_E), 7.28 (dd, *J* = 8.5, 1.6 Hz, 0.63H, H-6 Bf_E), 7.26–7.19 (m, 2.37H, H-6 Bf_z, 2 x H-*o*-Phe-O), 6.61–6.44 (m, 1H, =CH-Ar_z, =CH-Ar_E), 6.24 (dq, *J* = 15.6, 6.5 Hz, 0.63H, =CH-Me_E), 5.77 (dq, *J* = 11.6, 7.2 Hz, 0.37H, =CH-Me_z), 5.03–4.95 (m, 1H, H-1), 3.93 (dd, *J* = 11.9, 1.7 Hz, 1H, H-6a), 3.73 (dd, *J* = 12.1, 5.5 Hz, 1H, H-6b), 3.57–3.38 (m, 4H, H-5, H-2, H-3, H-4), 2.43 (d, *J* = 5.4 Hz, 1.1H, CH₃ Bf_z), 2.42 (s, 1.9H, CH₃ Bf_E), 1.92 (dd, *J* = 7.2, 1.8 Hz, 1.1H, CH₃-CH=_z), 1.89 (dd, *J* = 6.6, 1.5 Hz, 1.9H, CH₃-CH=_E). ESI-MS calcd for C₂₄H₂₆O₇Na₁ [M+Na]⁺ 449.2, found 449.4; calcd for C₄₈H₅₂O₁₄Na₁ [2M+Na]⁺ 875.3, found 875.2.

4.3.15 E,Z-4-[3-methyl-5-(prop-1-enyl)benzofuran-2-yl]phenyl β -D-galactopyranoside (32a)

Compound **32a** (21 mg, 0.049 mmol) was prepared following general procedures 4.2.1 and 4.2.3 and it was isolated as 1.7:1 *E:Z* mixture in 70% yield (based on the limiting agent) over two steps. $R_f = 0.25$ (9:1 $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH}$). ^1H NMR (400 MHz, CD_3OD) δ 7.78 – 7.66 (m, 2H, 2 x H-*m*-Phe-O), 7.44 (d, $J = 11.8$ Hz, 0.63H, H-4 Bf_E), 7.43 (bs, 0.37H, H-4 Bf_Z), 7.40 (d, $J = 8.4$ Hz, 0.37H, H-7 Bf_Z), 7.34 (d, $J = 8.5$ Hz, 0.63H, H-7 Bf_E), 7.29 (dd, $J = 8.5$, 1.5 Hz, 0.63H, H-6 Bf_E), 7.27 – 7.16 (m, 2.37H, H-6 Bf_Z, 2 x H-*o*-Phe-O), 6.62 – 6.43 (m, 1H, =CH-Ar_Z, =CH-Ar_E), 6.25 (dq, $J = 15.7$, 6.5 Hz, 0.63H, =CH-Me_E), 5.78 (dq, $J = 11.6$, 7.1 Hz, 0.37H, =CH-Me_Z), 4.95 (dd, $J = 7.7$, 1.7 Hz, 1H, H-1), 3.93 (d, $J = 3.3$ Hz, 1H, H-4), 3.90 – 3.69 (m, 4H, H-2, H-6a, H-6b, H-5), 3.61 (dd, $J = 9.7$, 3.3 Hz, 1H, H-3), 2.43 (s, 1.1H, CH_3 Bf_Z), 2.42 (s, 1.9H, CH_3 Bf_E), 1.92 (dd, $J = 7.2$, 1.8 Hz, 1.1H, $\text{CH}_3\text{-CH=}$ _Z), 1.89 (dd, $J = 6.5$, 1.5 Hz, 1.9H, $\text{CH}_3\text{-CH=}$ _E). ^{13}C NMR (101 MHz, CD_3OD) δ 159.0 (C_{quat.}-Phe-O), 154.3 (C-7a Bf), 152.2 (C-2 Bf), 134.3 (C-5 Bf), 132.7 (C-3a Bf), 132.6 (=CH-Ar_E), 131.3 (=CH-Ar_Z), 129.0 (2 x C-*m*-Phe-O_Z), 128.9 (2 x C-*m*-Phe-O_E), 126.8 (2 x C_{quat.}-Phe), 126.5 (C-6 Bf_Z), 126.3 (=CH-Me_Z), 124.9 (=CH-Me_E), 123.4 (C-6 Bf_E), 120.2 (C-4 Bf_Z), 118.0 (4 x C-*o*-Phe-O), 117.3 (C-4 Bf_E), 111.4 (C-7 Bf_E), 111.2 (2 x C-3 Bf), 111.1 (C-7 Bf_Z), 102.8 (C-1), 77.1 (C-5), 74.9 (C-3), 72.3 (C-2), 70.2 (C-4), 62.5 (C-6), 18.6 ($\text{CH}_3\text{-CH=}$ _E), 14.8, ($\text{CH}_3\text{-CH=}$ _Z), 9.4 (2 x CH_3 Bf). HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{26}\text{O}_7\text{Na}_1$ $[\text{M}+\text{Na}]^+$ 449.15707, found 449.15756.

4.3.16 E,Z-4-[3-methyl-5-(prop-1-enyl)benzofuran-2-yl]phenyl β -L-galactopyranoside (33a) Compound **33a** (36 mg, 0.08 mmol) was prepared following general procedures 4.2.1 (**33**, 71%, yield based on the limiting agent) and 4.2.3 (>95%) and it was isolated as 1.5:1 *E:Z* mixture. $R_f = 0.25$ (9:1 $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH}$).

^1H NMR (400 MHz, CD_3OD) δ 7.79 – 7.69 (m, 2H, 2 x H-*m*-Phe-O), 7.46 (bs, 0.6H, H-4 Bf_E), 7.43 (bs, 0.4H, H-4 Bf_Z), 7.40 (d, $J = 8.4$ Hz, 0.4H, H-7 Bf_Z), 7.34 (d, $J = 8.5$ Hz, 0.6H, H-7 Bf_E), 7.29 (dd, $J = 8.5$, 1.4 Hz, 0.6H, H-6 Bf_E), 7.27 – 7.15 (m, 2.4H, H-6 Bf_Z, 2 x H-*o*-Phe-O), 6.62 – 6.43 (m, 1H, =CH-Ar_Z, =CH-Ar_E), 6.25 (dq, $J = 13.2$, 6.5 Hz, 0.6H, =CH-Me_E), 5.78 (dq, $J = 11.6$, 7.1 Hz, 0.4H, =CH-Me_Z), 4.95 (dd, $J = 7.7$, 1.6 Hz, 1H, H-1), 3.93 (d, $J = 3.3$ Hz, 1H, H-4), 3.89 – 3.68 (m, 4H, H-2, H-6a, H-6b, H-5), 3.61 (dd, $J = 9.7$, 3.3 Hz, 1H, H-3), 2.43 (s, 1.2H, CH_3 Bf_Z), 2.42 (s, 1.8H, CH_3 Bf_E), 1.92 (dd, $J = 7.2$, 1.7 Hz, 1.2H, $\text{CH}_3\text{-CH=}$ _Z), 1.89 (dd, $J = 6.5$, 1.4 Hz, 1.8H, $\text{CH}_3\text{-CH=}$ _E). ESI-MS calcd for $\text{C}_{24}\text{H}_{26}\text{O}_7\text{Na}_1$ $[\text{M}+\text{Na}]^+$ 449.2, found 449.5; calcd for $\text{C}_{48}\text{H}_{52}\text{O}_{14}\text{Na}_1$ $[\text{2M}+\text{Na}]^+$ 875.3, found 875.3; calcd for $\text{C}_{48}\text{H}_{51}\text{O}_{14}$ $[\text{2M-H}]^-$ 851.3, found 851.3.

4.3.17 E,Z-4-[3-methyl-5-(prop-1-enyl)benzofuran-2-yl]phenyl β -L-fucopyranoside (34a) Compound **34a** (17 mg, 0.043mmol) was prepared following general procedures 4.2.1 and 4.2.3 and it was isolated as 3.5:1 *E:Z* mixture in 49% yield over two steps. $R_f = 0.37$ (9:1 $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH}$). ^1H NMR (400 MHz, CD_3OD) δ 7.76 – 7.67 (m, 2H, 2 x H-*m*-Phe-O), 7.44 (bs, 0.78H, H-4 Bf_E), 7.41 (bs, 0.22H, H-4 Bf_Z), 7.39 (d, $J = 8.4$ Hz, 0.22H, H-7 Bf_Z), 7.33 (d, $J = 8.5$ Hz, 0.78H, H-7 Bf_E), 7.30 – 7.25 (m, 0.78H, H-6 Bf_E), 7.22 – 7.11 (m, 2.22H, H-6 Bf_Z, 2 x H-*o*-Phe-O), 6.59 – 6.42 (m, 1H, =CH-Ar_Z, =CH-Ar_E), 6.24 (dq, $J = 15.6$, 6.5 Hz,

0.78H, =CH-Me_E), 5.77 (dq, *J* = 11.6, 7.2 Hz, 0.22H, =CH-Me_Z), 4.92 (dd, *J* = 7.7, 2.3 Hz, 1H, H-1), 3.89 – 3.74 (m, 2H, H-5, H-2), 3.68 (d, *J* = 3.1 Hz, 1H, H-4), 3.60 (dd, *J* = 9.7, 3.4 Hz, 1H, H-3), 2.41 (s, 0.66H, CH₃ Bf_Z), 2.40 (s, 2.34H, CH₃ Bf_E), 1.92 (dd, *J* = 7.2, 1.8 Hz, 0.66H, CH₃-CH= _Z), 1.88 (dd, *J* = 6.6, 1.5 Hz, 2.34H, CH₃-CH= _E), 1.32 (d, *J* = 6.5 Hz, 3H, CH₃ Fuc). ¹³C NMR (101 MHz, CD₃OD) δ 158.9 (C_{quat}-Phe-O), 158.8 (C_{quat}-Phe-O), 154.3 (C-7a Bf), 153.8 (C-7a Bf), 152.2 (C-2 Bf), 152.1 (C-2 Bf), 134.3 (C-5 Bf), 133.6 (C-5 Bf), 132.7 (C-3a Bf), , 132.6 (=CH-Ar _E), 132.4 (C-4a Bf), 131.3 (=CH-Ar _Z), 128.9 (2 x C-*m*-Phe-O _Z), 128.9 (2 x C-*m*-Phe-O _E), 126.7 (C_{quat}-Phe), 126.6 (C_{quat}-Phe), 126.5 (C-6 Bf _Z), 126.3 (=CH-Me _Z), 124.9 (=CH-Me _E), 123.4 (C-6 Bf _E), 120.2 (C-4 Bf _Z), 117.8 (4 x C-*o*-Phe-O), 117.3 (C-4 Bf _E), 111.4 (C-7 Bf _E), 111.2 (C-3 Bf), 111.1 (C-3 Bf), 111.1 (C-7 Bf _Z), 102.4 (C-1), 75.0 (C-3), 72.9 (C-4), 72.2 (C-5), 72.0 (C-2), 18.6 (CH₃-CH= _E), 16.8 (2 x CH₃ Fuc), 14.8 (CH₃-CH= _Z), 9.4 (2 x CH₃ Bf). HRMS (ESI) calcd for C₂₄H₂₆O₆Na₁ [M+Na]⁺ 433.16216, found 433.16227.

Acknowledgments

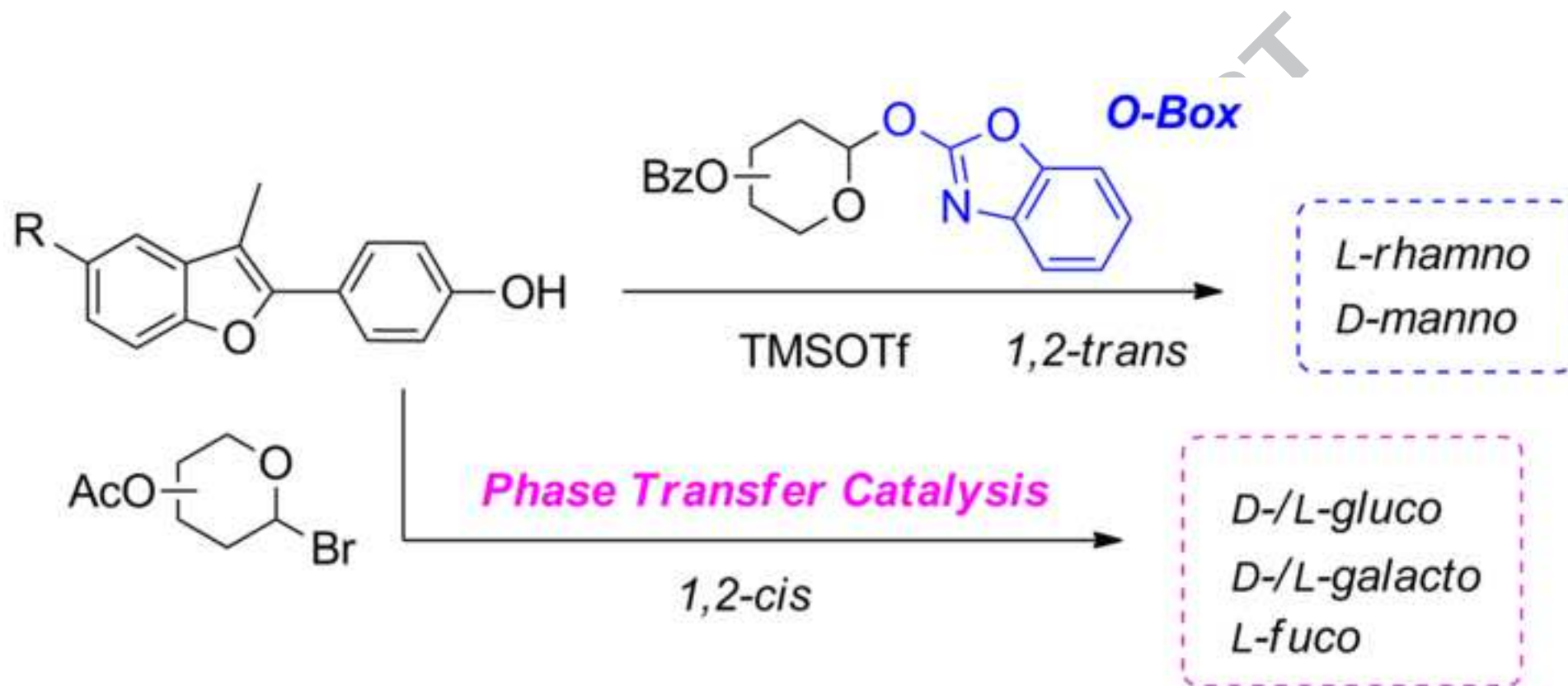
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Supplementary data

Supplementary data associated with this article (synthesis and characterization of all protected glycosides, ¹H-NMR and ¹³C-NMR spectra of all final compounds) can be found, in the online version, at <http://dx.doi.org/10.1016/>

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Highlights

- Chemical glycodiversification of a complex phenol aglycon was achieved
- *gluco*-, *galacto*- and *fuco*-sides were prepared using bromide donors and PTC
- α -*manno* and -*rhamno* derivatives were prepared using *O*-benzoxazolyl imidate donors
- A library of 14 glycosylated benzofuran derivatives was obtained