Discriminative Glycosylation of 3-(Aryloxy)propane-1,2-diols by Choice of a Glycosyl Donor

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Abstract: Regioselective glycosylation of *rac*-guaifenesin (**1A**) with various glycosyl donors viz., β-D-glucosepentaacetate (**2**), pyridyl 2,3,4,6-*O*-tetra-*O*-benzyl-1-thio-β-D-galactopyranoside (**9**), 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-α/β-D-ribo- (**13**) and xylofuranoside (**17**) is reported. Glycosyl donors **2**, **13** and **17** bearing ester protecting groups is reported to exhibit high regioselectivity to form the corresponding diastereomeric mixture of 1-*O*-glycosylated guaifenesin derivatives **3A**, **14A** and **18A**, respectively; formation of diglycosylated derivatives **5A**, **15A** and **19A** is not observed. While no such selectivity is observed when the donor **9** bearing ether protecting groups is used in the coupling reaction with **1A**, resulting in the formation of digalactosylated derivatives **10A**. That the regioselectivity is not dependent upon substituents present on the aromatic ring is shown by coupling **1B** with **2** to isolate 1-*O*-glycosylated derivative **3B**; formation of diglycosylated derivative **5B** was not observed. Applicability of this finding is shown by preparation of enantiopure guaifenesin [(*R*)-**1** (98% ee) and (*S*)-**1** (98% ee)] by separation of their corresponding diastereomers (*R*)-**3** and (*S*)-**3**, respectively.

Key words: regioselective glycosylations, 3-(aryloxy)propane-1,2-diols, glycosyl donors, guaifenesin, resolution

The *O*-glycosylation method to attach a sugar to other than sugar molecules[1] (aglycons) such as macrolides,[2] inositols,[3] amino acids[4]/peptides,[5] phenols,[6] and others[7] has been routinely practiced to synthesize natural products of biological and pharmaceutical importance.[8] From a synthetic standpoint, the efficacy of the *O*-glycosylation reaction generally involves achieving high chemical yield, regioselectivity,[9] and stereoselectivity.[10] Among them, high regioselectivity was realized by the selective protection of the hydroxyl group of the aglycon bearing more than one hydroxyl group to avoid greater number of possibilities though it increases the number of unit operations in a multistep total synthesis. While the practical stereoselective *O*-glycosylations (1,2-*cis*[10j] and 1,2-*trans*) has been very well demonstrated and reviewed,[10] there is a need to study regioselective glycosylations of aglycons.

We report here our studies in this direction on the regioselective glycosylation of 3-(aryloxy)propane-1,2-diols that are components of pharmaceutically important products such as guaifenesin (1),[11] chlorfenesin,[12] and mephanesin[13] (Figure 1).

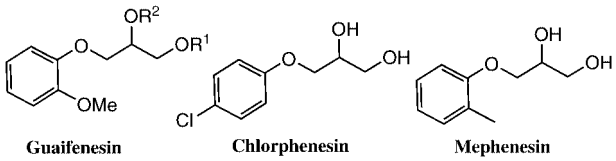

Figure 1 Structures of guaifensin, chlorphenesin and mephenesin

The benefits of the study include synthesis of single isomer drugs[14] and prodrugs[15] by separation of diastereomers formed due to glycosylation.

Regioselective glycosylation of *rac*-**1A** was evaluated by reacting with two mole equivalents of β-D-glucosepentaacetate (**2**) in $CH_2Cl_2/BF_3{\cdot}OEt_2$[15] at room temperature (Scheme 1). It resulted in the isolation of monoglycosylated guaifenesin diastereomers (*R*)-**3** (42%), (*S*)-**3** (44%) along with the transesterification product 1-*O*-acetylguaifenesin derivative *rac*-**4A** (8%) after separation by column chromatography. Formation of the 1,2-di-*O*-glycosylated derivatives **5A** was not observed even when the same reaction was performed using a large excess of the donor **2** (3 mole equiv). Products (*R*)-**3** and (*S*)-**3** were designated as β-glycosides due to C-2 neighboring group participation of the glycosyl donor **2** and from the appearance of corresponding H-1 at δ = 4.84 and 4.96, respectively, as doublets with a coupling constant of J = 8.4 Hz in their ^{1}H NMR spectra. (*R*)-**3** and (*S*)-**3** were characterized as monoglycosylated derivatives of **1A** from their ^{1}H NMR spectra by integration of the protons, however, regiochemistry in the glycosylation could not be assigned due to overlap of signals between δ = 3.60–4.30. In order to establish the regiochemistry in glycosylation reaction, (*R*)-**3** and (*S*)-**3** were converted to their corresponding acetates (*R*)-**6** and (*S*)-**6**, respectively. (*R*)-**6** and (*S*)-**6** were characterized by ^{1}H NMR spectra as 1-*O*-glycosyl derivatives from the appearance of the corresponding H-2 protons at δ = 5.10–5.30 respectively shifted downfield due to acetylation. *Rac*-**4** was characterized as 1-*O*-acetylguaifenesin by comparison of ^{1}H NMR spectrum with that of an authentic sample. Thus, acetylation of **1A** with Ac_2O/pyridine resulted in the isolation of mono- and 1,2-di-*O*-acetylguaifenesin (*rac*-**4** and *rac*-**7**), formation of 2-*O*-acetylguaifensin (*rac*-**8**) was not observed. In the ^{1}H NMR spectra of *rac*-**4**, H-1 appeared at δ = 4.35 (2 H) and H-2 of *rac*-**7** appeared at δ = 5.32 (1 H).

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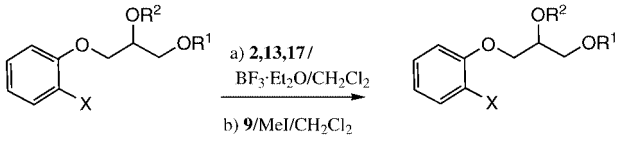
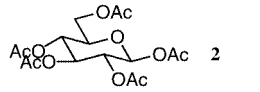


racemic A) X = OMe B) X = H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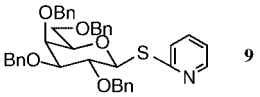
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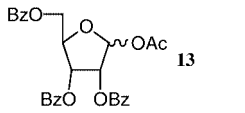
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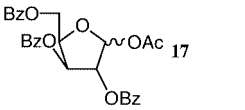
17

1 R^1=R^2=H
3 R^1=2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-, R^2=H
4 R^1=Ac, R^2=H
5 R^1=R^2=2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-
6 R^1=2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-, R^2=Ac
7 R^1=R^2=Ac
8 R^1=H, R^2=Ac
10 R^1=R^2=2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl-
11 R^1=2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl-, R^2=H
12 R^1=2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl-, R^2=Ac
14 R^1=2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl-, R^2=H
15 R^1=R^2=2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl-
16 R^1=2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl, R^2=Ac
18 R^1=2,3,5-tri-*O*-benzoyl-β-D-xylofuranosyl, R^2=H
19 R^1=R^2=2,3,5-tri-*O*-benzoyl-β-D-xylofuranosyl-
20 R^1=2,3,5-tri-*O*-benzoyl-β-D-xylofuranosyl, R^2=Ac
22 R^1=-β-D-ribofuranosyl, R^2=H
23 R^1=-β-D-xylofuranosyl, R^2=H

Scheme 1

The high regioselectivity observed in these reactions was surprising while working in the area of glycosylations of inositols, saccharides (pyrano and furano forms) and 2-deoxysaccharides for the last two decades. It has been reported that 3-(aryloxy)propane-1,2-diols with a substituent in the *para* position show a much higher enantioselectivity (92–94% ee, *S*) than the corresponding derivatives with *ortho*-substituents (34–88% ee, *S*) in lipase-catalyzed sequential *trans* esterification route.[16] A similar observation was made in Sharpless asymmetric dihydroxylation of aryl allyl ethers, the *ortho*-substituted derivatives have been shown to give low enantiopurity (28–63% ee, *S*).[17]

In order to check the regioselectivity versus the role of substituent, we decided to study the glycosylation of unsubstituted aryloxy derivatives. Thus, regioselective glycosylation of 3-(phenoxy)propane-1,2-diol (*rac*-**1B**) with **2** (one, two, and three mole equivalents separately) under similar reaction conditions was performed to observe once again high regioselectivity leading to the isolation of the mono 1-*O*-glycosylated derivative **3B** (82%, diastereomeric mixture) and the monoacetylated derivative *rac*-**4B** (7%) similar to the reactivity observed for *rac*-**1A**. Formation of the corresponding 1,2-di-*O*-glycosylated derivative **5B** was not observed. Compounds **3B**, its corresponding acetyl derivative **6B** and *rac*-**4B** were characterized analogous to (*R*)-**3**, (*R*)-**6** and *rac*-**4A** by ^{1}H NMR spectra. Thus, it was evident that substituents on the aromatic ring did not play any decisive role in directing regioselective glycosylations.

In order to evaluate, if the observed regioselectivity is also common to other glycosyl donors, we chose pyridyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-galactopyranoside (**9**)[18] as a glycosyl donor and iodomethane activation procedure that was proven in our laboratory to be mild and highly stereoselective for performing this experiment. Thus, coupling of *rac*-**1A** and *rac*-**1B** separately with one and two mole equivalents of the donor **9** for 48–72 hours in dichloromethane and 5% iodomethane at 50 °C resulted in the isolation of di-*O*-galactosylated derivatives **10A** and **10B** and the corresponding mono-*O*-galactosylated derivatives **11A** and **11B** respectively. Thus, no regioselectivity was observed in these reactions. Compounds **10A** and **10B** were characterized as di-*O*-galactosylated derivatives from the ^{1}H NMR spectrum by the integration of the protons. Compounds **11A** and **11B** were characterized as 1-*O*-galactosylated derivatives by converting them to the corresponding 2-*O*-acetyl derivatives **12A** and **12B**, respectively and from the appearance of the H-2 proton at δ = 5.20–5.30 shifted downfield due to acetylation.

In order to ascertain whether the observed regioselectivity is related to the glycosyl donor bearing electron-withdrawing ester group or electron-donating ether protecting group, glycosylation of *rac*-**1A** was carried out with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-α/β-D-ribofuranoside (**13**)[19] (CH_2Cl_2/BF_3·OEt_2). It resulted in the isolation of a diastereomeric mixture of 1-*O*-β-D-ribofuranosyl guaifenesin derivative *rac*-**14A** in good yield (82%); formation of di-*O*-ribosylated derivative **15A** and *trans* esterification products were not observed. Compound **14A** was characterized by ^{1}H NMR spectrum, analogous to (*R*)-**3**, as its 1-*O*-ribofuranosyl derivative by preparation of its corresponding acetylated derivative *rac*-**16A**.

The generality of high regioselectivty was further confirmed by coupling *rac*-**1A** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-α/β-D-xylofuranose (**17**).[20] Reaction of *rac*-**1A** with **17** (CH_2Cl_2/BF_3·OEt_2) resulted in the isolation of diastereomeric mixture of 1-*O*-xylofuranosyl guaifenesin derivative **18A** (80%), once again exhibiting high regioselectivity. Formation of di-*O*-xylofuranosyl derivative **19A** was not observed. Compound **18A** and its acetyl derivative **20A** were characterized by ^{1}H NMR spectra analogous to **12A** and **16A**.

The observed regioselectivity was benefited by the isolation of enantiopure (*R*)- and (*S*)-guaifenesin (**1**). The compounds (*R*)-**3** and (*S*)-**3** were deacetylated in 10% methanolic ammonia solution to (*R*)-**21** and (*S*)-**21**, respectively, in quantitative yield and were individually subjected to acid-catalyzed hydrolysis in 10% aq H_2SO_4 at 90 °C for 3 hours to isolate by extraction into ethyl acetate enantiomerically enriched guaifenesin (*S*)-**1** (93.0% ee)

and (*R*)-**1** (91.0% ee), respectively (Figure 2). Further recrystallization from hot ethanol improved the enantiopurity to 98.0%ee.[17,21]

(*R*)-**3** R^1=2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-, R^2=H
(*S*)-**3** R^1=2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-, R^2=H
(*R*)-**6** R^1=2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-, R^2=Ac
(*S*)-**6** R^1=2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-, R^2=Ac
(*R*)-**21** R^1=-β-D-glucopyranosyl-, R^2=H
(*S*)-**21** R^1=-β-D-glucopyranosyl-, R^2=H
(*S*)-**1** R^1=R^2=H
(*R*)-**1** R^1=R^2=H

Figure 2 Structures of compounds (*S*)- and (*R*)-**1**, **3**, **6**, and **21**

The compounds **14A** and **18A** were deacetylated ($NaHCO_3$/MeOH) to obtain diastereomeric mixture of 1-*O*-β-D-ribofuranosylguaifenesin (**22A**) and 1-*O*-β-D-xylofuranosylguaifenesin (**23A**), attempts were not made to separate the diastereomers.

In conclusion, high regioselective glycosylation of *rac*-guaifenesin (**1**) was achieved by choice of a glycosyl donor. Glycosyl donor bearing electron-withdrawing (ester) protecting groups exhibited high regioselectivity. No regioselectivity was observed when glycosyl donor possessing benzyl ether protecting group was used. The stereoselectivty was controlled by use of well-established protocols in the coupling reactions. The high regioselectivty observed is not related to the substituent present on the aromatic group was also demonstrated. The utility of these results was benefited by preparation of enantiopure (*R*)- and (*S*)-guaifenesin (**1**) in 98% ee.

^{1}H NMR spectra were recorded using the following instruments: at 200 MHz on a Varian Gemini; at 300 MHz on a Bruker Avance; at 400 MHz on a Varian Unity, with TMS as an internal standard for solutions in $CDCl_3$. The *J* values are reported in Hz. Optical rotations were measured with a Jasco DIP-370 instrument. Organic solutions were dried over anhyd Na_2SO_4.

(2*R*)-3-(2-Methoxyphenoxy)-1-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)propane-1,2-diol [(*R*)-3] and (2*S*)-3-(2-Methoxyphenoxy)-1-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)propane-1,2-diol [(*S*)-3]; Typical Procedure

To a solution of β-D-glucosepentaacetate **2** (10 g, 25.6 mmol) in anhyd CH_2Cl_2 (100 mL) was added **1A** (2.54 g, 12.8 mmol) and $BF_3{\cdot}OEt_2$ (1.93 ml, 15.38 mmol) at 0 °C. The reaction mixture was stirred for 8 h at r.t. Progress of the reaction was monitored by TLC. After completion of the reaction, anhyd K_2CO_3 (1.93 g) was added, stirred for 30 min, filtered, and the residue was washed with CH_2Cl_2 (150 mL). The filtrate was transferred to a separating funnel, washed with H_2O (2 × 50 mL), brine (50 mL), the organic phase was separated, dried (Na_2SO_4), and concentrated to obtain a residue containing a diastereomeric mixture of (*R*)-**3,** (*S*)-**3**, and *rac*-**4A**. They were separated by column chromatography (silica gel, 60–120 mesh, eluent: hexane–EtOAc, 4:1) to isolate (2*R*/*S*)-1-*O*-acetyl-3-(2-methoxyphenoxy)propane-1,2-diol (*rac*-**4A**), followed by (*R*)-**3** and (*S*)-**3**.

***rac*-4A**

Yield: 0.24 g (8%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.10 (s, 3 H, $OCOCH_3$), 3.82 (s, 3 H, OCH_3), 3.90–4.10 (m, 2 H, H-1), 4.20 (m, 3 H, H-2, 3), 6.90 (m, 4 H, ArH).

MS (EI, 70 eV): *m*/*z* (%) = 240 (1, [M^+]).

(*R*)-3

Yield: 2.85 g (42%); $[\alpha]_D^{24}$ +6.3 (*c* = 2.0, $CHCl_3$); mp 82–84 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.90, 1.98, 2.02, 2.10 (4 s, 12 H, 4 × $OCOCH_3$), 3.60–3.80 (m, 3 H, H-1, 6′), 3.90 (s, 3 H, OCH_3) 3.96–4.30 (m, 5 H, H-2, 3, 5′, 6′′), 4.84 (d, 1 H, $J_{1,2}$ = 8.4 Hz, H-1′), 4.90–5.22 (m, 3 H, H-2′, 3′, 4′), 6.90 (m, 4 H, ArH).

MS (FAB): *m*/*z* = 529 [M^+ + H].

Anal. Calcd for $C_{24}H_{32}O_{13}$: C, 54.52; H, 6.10. Found: C, 54.39; H, 6.01.

(*S*)-3

Yield: 2.98 g (44%); $[\alpha]_D^{24}$ –11.10 (*c* = 2.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.96, 2.00, 2.02, 2.04 (4 s, 12 H, 4 × $OCOCH_3$), 3.60–3.75 (m, 2 H, H-6′, 6′′), 3.85 (s, 3 H, OCH_3), 3.96–4.34 (m, 6 H, H-1, 2, 3, 5′), 4.96 (d, 1 H, $J_{1,2}$ = 8.3 Hz, H-1′), 5.00–5.30 (m, 3 H, H-2′, 3′, 4′), 6.94 (m, 4 H, ArH).

MS (FAB): *m*/*z* = 529 [M^+ + H].

Anal. Calcd for $C_{24}H_{32}O_{13}$: C, 54.52; H, 6.10. Found: C, 54.37; H, 6.02.

3-Phenoxy-1-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)propane-1,2-diol (3B)

A reaction of **2** (6.0 g, 15.4 mmol) in CH_2Cl_2 (60 mL) with *rac*-**1B** (1.3 g, 7.7 mmol) and $BF_3{\cdot}OEt_2$ (1.17 mL, 9.2 mmol) for 6 h performed as described for (*R*)-**3** resulted in the isolation of **4B**, followed by **3B**.

4B

Yield: 0.11 g (7%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.08 (s, 3 H, $OCOCH_3$), 3.98 (d, 2 H, $J_{2,3}$ = 6.8 Hz, H-3), 4.04–4.30 (m, 3 H, H-1, 2), 6.80–7.00 (m, 3 H, ArH), 7.18–7.32 (m, 2 H, ArH).

MS (EI, 70 eV): *m*/*z* = 210 (1, [M^+]).

3B

Yield: 3.16 g (82%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.96, 2.02, 2.04, 2.08 (4 s, 12 H, 4 × $OCOCH_3$), 3.60–4.30 (m, 9 H, H-1, 2, 3, OH, 5′, 6′, 6′′), 4.80–5.20 (m, 4 H, H-1′, 2′, 3′, 4′), 6.80–6.92 (m, 3 H, ArH), 7.30 (m, 2 H, ArH).

MS (FAB): *m*/*z* = 499 [M^+ + H].

Anal. Cacld for $C_{23}H_{30}O_{12}$: C, 55.41; H, 6.06. Found: C, 54.81; H, 6.16.

(2*R*/*S*)-1-*O*-Acetyl-3-(2-methoxyphenoxy)propane-1,2-diol (*rac*-4A) and (2*R*/*S*)-1,2-Di-*O*-acetyl-3-(2-methoxyphenoxy)propane-1,2-diol (*rac*-7A); Typical Procedure

To a solution of *rac*-**1A** (1.98 g, 10 mmol) in CH_2Cl_2 (40 mL) was added Ac_2O (2.5 mL, 25 mmol) and pyridine (2 mL) and the mixture was stirred for 3 h at r.t. The product *rac*-**7A** was isolated by standard work-up procedure and chromatography (silica gel, 60–120 mesh, eluent: hexane–EtOAc, 4:1) as a syrup, followed by monoacetyl derivative *rac*-**4A**.

***rac*-7A**
Yield: 0.28 g (10%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.14, 2.16 (2 s, 6 H, 2 × $OCOCH_3$), 3.82 (s, 3 H, OCH_3), 4.16 (m, 2 H, H-3), 4.28 (m, 1 H, H-1), 4.50 (m, 1 H, H-1), 5.36 (m, 1 H, H-2), 6.90 (m, 4 H, ArH).

MS (EI, 70 eV): *m*/*z* = 282 [M^+].

Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.56; H, 6.42. Found: C, 60.06; H, 6.36.

***rac*-4A**
Yield: 1.85 g (78%).

1-*O*-Acetyl-3-(phenoxy)propane-1,2-diol (4B) and 1,2-Di-*O*-acetyl-3-(phenoxy)propane-1,2-diol (7B)
A reaction of **1B** (1.0 g, 5.95 mmol) in CH_2Cl_2 (20 mL) with Ac_2O (1.2 mL) and pyridine (2.4 mL) was performed as described for **4A** to isolate **7B** as a syrup, followed by the monoacetyl derivative **4B**.

7B
Yield: 0.27 g (18%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.04, 2.08 (2 s, 6 H, 2 × $OCOCH_3$), 4.04 (d, 2 H, $J_{2,3}$ = 6.7 Hz, H-3, 3′), 4.12 (dd, 1 H, $J_{1,2}$ = 6.6 Hz, $J_{1,1'}$ = 12.2 Hz, H-1), 4.20 (dd, 1 H, $J_{1',2}$ = 3.48 Hz, H-1′), 5.30 (m, 1 H, H-2), 6.80–7.00 (m, 3 H, ArH), 7.18–7.34 (m, 2 H, ArH).

MS (EI, 70 eV): *m*/*z* = 252 (1, [M^+]).

Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 62.15; H, 6.51.

4B
Yield: 0.89 g (71%).

(2*R*)-2-*O*-Acetyl-3-(2-methoxyphenoxy)-1-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)propane-1,2-diol [(*R*)-6]; Typical Procedure
To a solution of (*R*)-**3** (0.2 g) in CH_2Cl_2 (6 mL) was added pyridine (0.4 mL), Ac_2O (0.28 mL), and a catalytic amount of *N*,*N*-dimethylaminopyridine (2 mg). The reaction mixture was stirred at r.t. for 6 h, diluted with H_2O (10 mL), and stirred for 5 min. CH_2Cl_2 (50 mL) was added and the organic layer was washed with 5% aq $CuSO_4$ (2 × 35 mL), H_2O (50 mL), dried (Na_2SO_4), and concentrated. The residue obtained was chromatographed (silica gel; hexane–EtOAc, 9:1) to isolate the title compound as a solid; yield: 0.09 g (92%); mp 109–111 °C; $[\alpha]_D^{24}$ –6.0 (*c* = 1.0, $CHCl_3$) .

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.90, 1.96, 2.00, 2.02, 2.06, 2.08 (5 s, 15 H, 5 × $OCOCH_3$), 3.70 (m, 1 H, H-6′), 3.90 (s, 3 H, OCH_3), 3.98–4.40 (m, 6 H, H-1, 3, 5′, 6″), 4.98 (d, 1 H, $J_{1,2}$ = 8.2 Hz, H-1′), 5.02–5.16 (m, 4 H, H-2, 2′, 3′, 4′), 6.90 (m, 4 H, ArH).

MS (FAB): *m*/*z* = 571 [M^+ + H].

Anal. Calcd for $C_{26}H_{34}O_{14}$: C, 54.93; H, 5.67. Found: C, 54.63; H, 5.43.

(2*S*)-2-*O*-Acetyl-3-(2-methoxyphenoxy)-1-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)propane-1,2-diol [(*S*)-6]
A reaction of (*S*)-**3** (0.1 g, 0.19 mmol) in CH_2Cl_2 (2 mL) with pyridine (0.1 mL), Ac_2O (0.2 mL), and a catalytic amount of *N*,*N*-dimethylaminopyridine (1 mg) was carried out as described for (*R*)-**6** to isolate the title compound as a syrup; yield: 0.085 g (89%); $[\alpha]_D^{24}$ –3.1 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.90, 1.98, 2.00, 2.02, 2.04 (5 s, 15 H, 5 × $OCOCH_3$), 3.85 (m, 1 H, H-6′), 3.92 (s, 3 H, OCH_3), 3.98–4.40 (m, 6 H, H-1, 3, 5′, 6″), 4.94 (d, 1 H, $J_{1,2}$ = 8.0 Hz, H-1′), 5.00–5.30 (m, 4 H, H-2, 2′, 3′, 4′), 6.90 (m, 4 H, ArH).

MS (FAB): *m*/*z* = 571 [M^+ + H].

Anal. Calcd for $C_{26}H_{34}O_{14}$: C, 54.93; H, 5.67. Found: C, 54.77; H, 5.63.

3-(2-Methoxyphenoxy)-1,2-di-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)propane-1,2-diol (10A) and 3-(2-Methoxyphenoxy)-1-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)propane-1,2-diol (11A); Typical Procedure
A mixture of **9** (1.8 g, 2.99 mmol), *rac*-**1A** (0.29 g, 1.49 mmol) and powdered 4 Å molecular sieves (50 mg) in anhyd CH_2Cl_2 (50 mL) containing 5% MeI was heated to 50 °C for 48–72 h. Reaction was monitored by TLC, when complete it was filtered on a Celite pad, and the residue was washed with EtOAc (100 mL). The combined filtrates were concentrated, and the residue was chromatographed (silica gel, 60–120 mesh, hexane–EtOAc, 9:1) to obtain the title compound as a syrup followed by **11a**.

11a
Yield: 0.58 g (31%); $[\alpha]_D$ +30.00 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.38–3.60 (m, 4 H, H-1, 6′, 6″), 3.50 (s, 3 H, OCH_3), 3.60 (s, 3 H, OCH_3), 3.80–4.04 (m, 4 H, H-1, 3), 4.18–5.00 (m, 24 H, H-2′, 2″, 3, 3″, 4′, 4″, 5′, 5″, 8 × C$H_2$$C_6H_5$), 5.20 (d, 1 H, $J_{1,2}$ = 2.5 Hz, H-1′), 5.20 (d, 1 H, $J_{1,2}$ = 3.10 Hz, H-1″), 6.80 (m, 4 H, ArH), 7.10–7.40 (m, 40 H, ArH).

Anal. Calcd for $C_{78}H_{82}O_{14}$: C, 75.34; H, 6.64. Found: C, 75.55; H, 6.35.

11A
Syrup; yield: 0.34 g (55%); $[\alpha]_D$ +27.40 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.40–3.78 (m, 4 H, H-1, 6′, 6″), 3.82 (s, 3 H, OCH_3), 3.86–5.00 (m, H-2, 3, 2′, 3′, 4′, 5′, 4 × C$H_2$$C_6H_5$), 5.15 (d, 1 H, $J_{1,2}$ = 2.5 Hz, H-1′), 6.85 (m, 4 H, ArH), 7.10–7.40 (m, 20 H, ArH).

Anal. Calcd for $C_{44}H_{48}O_9$: C, 73.31; H, 6.71. Found: C, 72.96; H, 6.46.

2-*O*-Acetyl-3-(2-methoxyphenoxy)-1-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)propane-1,2-diol (12A)
A reaction of **11A** (0.18 g, 0.25 mmol) in CH_2Cl_2 (4 mL) with Ac_2O (0.15 mL), pyridine (0.30 mL) and a catalytic amount of *N*,*N*-dimethylaminopyridine (3 mg) was performed as described for (*R*)-**6** to isolate the title compound as a syrup; yield: 0.17 g (87%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.42–3.80 (m, 4 H, H-1, 6′, 6″), 3.84 (s, 3 H, OCH_3), 3.86–5.00 (m, 14 H, H-3, 2′, 3′, 4′, 5′, 4 × C$H_2$$C_6H_5$), 5.20 (d, 1 H, $J_{1,2}$ = 2.5 Hz, H-1′), 5.28 (m, 1 H, H-2), 6.88 (m, 4 H, ArH), 7.15–7.40 (m, 20 H, ArH).

Anal. Calcd for $C_{46}H_{50}O_{10}$: C, 72.42; H, 6.60. Found: C, 72.54; H, 6.76.

3-Phenoxy-1,2-di-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)propane-1,2-diol (10B) and 3-Phenoxy-1-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)propane-1,2-diol (11B)
A reaction of **9** (2.0 g, 3.23 mmol) with *rac*-**1B** (0.27 g, 1.66 mmol) and powdered 4Å molecular sieves (50 mg) in anhyd CH_2Cl_2 (50 mL) containing 5% MeI for 48–72 h was carried out as described for **10A** to isolate the title compound as a syrup, followed by **11B**.

10B
Yield: 0.80 g (41%); $[\alpha]_D$ +40.86 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.34–3.58 (m, 4 H, H-6′, 6″), 3.78–4.02 (m, 2 H, H-1), 4.20–5.00 (m, 24 H, H-2′, 2″, 3′, 3″, 4′, 4″, 5′, 5″, 8 × C$H_2$$C_6H_5$), 5.10 (d, 1 H, $J_{1,2}$ = 3.3 Hz, H-1″), 5.22 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1′), 6.80–6.90 (m, 3 H, ArH), 7.04–7.40 (m, 42 H, ArH).

Anal. Calcd for $C_{77}H_{80}O_{13}$: C, 76.24; H, 6.64. Found: C, 75.86; H, 6.51.

11B

Yield: 0.25 g (44%); $[\alpha]_D$ +34.53 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.40–3.58 (m, 2 H, H-6′, 6″), 3.72–4.10 (m, 5 H, H-1, 2, 3), 4.34–4.98 (m, 12 H, H-2′, 3′, 4′, 5′, 4 × C*H*$_2$C$_6$H$_5$), 5.22 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1′), 6.70–6.98 (m, 3 H, ArH), 7.04–7.40 (m, 22 H, ArH).

Anal. Calcd for $C_{43}H_{46}O_8$: C, 74.76; H, 18.52. Found: C, 75.81; H, 6.59.

2-*O*-Acetyl-3-phenoxy-1-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)propane-1,2-diol (12B)

A reaction of **11B** (0.2 g, 0.29 mmol) in CH_2Cl_2 (6 mL) with Ac_2O (0.2 mL), pyridine (0.4 mL) and a catalytic amount of *N*,*N*-dimethylaminopyridine (5 mg) was performed as described for (*R*)-**6** to isolate the title compound as a syrup; yield: 0.19 g (87%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.44–3.62 (m, 2 H, H-6′, 6″), 3.72–4.14 (m, 4 H, H-1, 3), 4.32–5.00 (m, 12 H, H-2′, 3′, 4′, 5′, 4 × C*H*$_2$C$_6$H$_5$), 5.24 (d, 1 H, $J_{1,2}$ = 3.5 Hz, H-1′), 5.28 (m, 1 H, H-2), 6.72–7.00 (m, 3 H, ArH), 7.10–7.40 (m, 22 H, H-ArH).

Anal. Calcd for $C_{45}H_{48}O_9$: C, 73.75; H, 6.60. Found: C, 72.94; H, 6.41.

(2*R*/*S*)-3-(2-Methoxyphenoxy)-1-*O*-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)propane-1,2-diol (14A)

A reaction of **13** (2.0 g, 3.96 mmol), *rac*-**1A** (0.78 g, 3.96 mmol) with $BF_3{\cdot}OEt_2$ (0.6 mL, 4.76 mmol) in anhyd CH_2Cl_2 (40 mL) for 4 h as described for (*R*)-**3** resulted in the isolation of the title compound; yield: 2.10 g (82%); $[\alpha]_D^{24}$ +28.10 (c = 1.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.70–4.20 (m, 8 H, H-1, 2, 3, OCH_3), 4.50–4.80 (m, 3 H, H-4′, 5′, 5″), 5.28 (s, 1 H, H-1′), 5.60–5.80 (m, 2 H, H-2′, 3′), 6.80 (m, 4 H, ArH), 7.20–8.20 (m, 15 H, ArH).

MS (FAB): *m*/*z* = 643 [M$^+$ + H].

Anal. Calcd for $C_{36}H_{34}O_{11}$: C, 67.28; H, 5.33. Found: C, 67.19; H, 5.24.4

(2*R*/*S*)-2-*O*-Acetyl-3-(2-methoxyphenoxy)-1-*O*-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)propane-1,2-diol (16A)

A reaction of **14A** (1.6 g, 2.49 mL) in CH_2Cl_2 (16 mL) with pyridine (0.4 mL, 4.98 mmol), Ac_2O (0.28 mL, 2.99 mmol) and a catalytic amount of *N*,*N*-dimethylaminopyridine (5 mg) was carried out as described for (*R*)-**6** to isolate the title compound as a syrup; yield: 1.58 g (92%); $[\alpha]_D^{24}$ +22.4 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.06 (s, 3 H, $OCOCH_3$), 3.68–4.20 (m, 7 H, H-1, 3, OCH_3), 4.40–4.80 (m, 3 H, H-4′, 5′, 5″), 5.20–5.30 (m, 2 H, H-1′, 2), 5.60–5.90 (m, 2 H, H-2′, 3′), 6.80 (m, 4 H, ArH), 7.20–8.20 (m, 15 H, ArH).

MS (FAB): *m*/*z* = 685 [M$^+$ + H].

Anal. Calcd for $C_{38}H_{36}O_{12}$: C, 66.66; H, 5.30. Found: C, 66.51; H, 5.19.

(2*R*/*S*)-3-(2-Methoxyphenoxy)-1-*O*-(2,3,5-tri-*O*-benzoyl-β-D-xylofuranosyl)propane-1,2-diol (18A)

A reaction of **17** (2.0 g, 3.96 mmol) in anhyd CH_2Cl_2 (40 mL), *rac*-**1A** (0.78 g, 3.96 mmol) and $BF_3{\cdot}Et_2O$ (0.6 mL, 4.76 mmol) for 5 h was performed as described for (*R*)-**3** to isolate the title compound as a syrup; yield: 2.05 g (80%); $[\alpha]_D^{24}$ +29.5 (*c* = 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.70–430 (m, 8 H, H-1, 2, 3, OCH_3), 4.50–4.80 (m, 3 H, H-4′, 5′, 5″), 5.30 (s, 1 H, H-1′), 5.70 (m, 1 H, H-2′), 5.80 (m, 1 H, H-3′), 6.80 (m, 4 H, ArH), 7.20–8.20 (m, 15 H, ArH).

MS (FAB): *m*/*z* = 643 [M$^+$ + H].

Anal. Calcd for $C_{36}H_{34}O_{11}$: C, 67.28; H, 5.33. Found: C, 67.12; H, 5.24.

(2*R*/*S*)-2-*O*-Acetyl-3-(2-methoxyphenoxy)-1-*O*-(2,3,5-tri-*O*-benzoyl-β-D-xylofuranosyl)propane-1,2-diol (20A)

A reaction of **18A** (1.5 g, 2.33 mmol) in CH_2Cl_2 (15 mL) with pyridine (0.38 mL, 4.67 mmol), Ac_2O (0.26 mL, 2.8 mmol) and a catalytic amount of *N*,*N*-dimethylaminopyridine (5 mg) was performed as described for (*R*)-**6** to isolate the title compound as a syrup; yield: 1.45 g (91%); $[\alpha]_D^{24}$ +24.5 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.04 (s, 3 H, $OCOCH_3$), 3.70–4.20 (m, 7 H, H-1, 3, OCH_3), 4.44–4.80 (m, 3 H, H-4′, 5′, 5″), 5.20–5.30 (m, 2 H, H-1′, 2), 5.60–5.90 (m, 2 H, H-2′, 3′), 6.84 (m, 4 H, ArH), 7.20–8.20 (m, 15 H, ArH).

MS (FAB): *m*/*z* = 685 [M$^+$ + H].

Anal. Calcd for $C_{38}H_{36}O_{12}$: C, 66.66; H, 5.30. Found: C, 66.59; H, 5.19.

(2*R*)-3-(2-Methoxyphenoxy)-1-*O*-(β-D-glucopyranosyl)propane-1,2-diol [(*R*)-21]

To a solution of **3** (2.0 g, 3.8 mmol) in MeOH (20 mL) was added 10% methanolic ammonia (10 mL). The mixture was stirred for 3 h at r.t.. After completion of the reaction, the solvent was removed to obtain the title compound as a syrup; yield: 1.36 g (99%); $[\alpha]_D^{24}$ –7.13 (*c* = 1.0, MeOH).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.24–3.80 (m, 7 H, H-1, 3, 5′, 6′, 6″), 3.84 (s, 3 H, OCH_3), 4.20–4.40 (m, 4 H, H-2, 2′, 3′, 4′), 4.70 (d, 1 H, $J_{1,2}$ = 7.0 Hz, H-1′), 7.04 (m, 4 H, ArH).

MS (FAB): *m*/*z* = 377 [M$^+$ + H].

Anal. Calcd for $C_{16}H_{24}O_9$: C, 53.33; H, 6.71. Found: C, 53.21; H, 6.58.

(2*S*)-3-(2-Methoxyphenoxy)-1-*O*-(β-D-glucopyranosyl)propane-1,2-diol [(*S*)-21]

A reaction of **3** (1.8 g, 3.40 mmol) in MeOH (20 mL) with 10% methanolic ammonia (10 mL) for 4 h was performed as described for (*R*)-**21** to obtain the title compound as a syrup; yield: 1.2 g (97%); $[\alpha]_D^{24}$ –25.5 (*c* = 1.0, MeOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.20–3.80 (m, 7 H, H-1, 3, 5′, 6′, 6″), 3.90 (s, 3 H, OCH_3), 4.00–4.30 (m, 4 H, H-2, 2′, 3′, 4′), 4.50 (d, 1 H, $J_{1,2}$ = 7.1 Hz, H-1′), 7.04 (m, 4 H, ArH).

MS (FAB): *m*/*z* = 377 [M$^+$ + H].

Anal. Calcd for $C_{16}H_{24}O_9$: C, 53.33; H, 6.71. Found: C, 53.19; H, 6.59.

(2*S*)-3-(2-Methoxyphenoxy)propane-1,2-diol [(*S*)-1]; Typical Procedure

To a solution of (*R*)-**21** (1.3 g, 3.45 mmol) in H_2O (13 mL) was added 10% aq H_2SO_4 (2 mL) at r.t. The reaction mixture was heated to 90 °C for 3 h. After completion of the reaction, the mixture was neutralized with aq $Ba(OH)_2$ solution, filtered through a Celite pad and washed with H_2O (10 mL). The filtrate was transferred to a separating funnel, extracted with EtOAc (2 × 25 mL), the combined organic phases were dried (Na_2SO_4), and evaporated. The residue was recrystallized twice from EtOH (4 mL) to obtain the title compound; yield: 0.61 g (90%) [98% ee determined by chiral HPLC method on a Chiracel OD column); $[\alpha]_D^{24}$ +11.1 (*c* = 1.0, EtOH); [Lit.[3] $[\alpha]_D^{24}$ +8.3 (*c* = 1.18, MeOH); Lit.[13] $[\alpha]_D^{24}$ +11.2 (*c* = 1.0, EtOH)].

(2*R*)-3-(2-Methoxyphenoxy)propane-1,2-diol [(*R*)-1]

Acid-catalyzed hydrolysis of (*S*)-**21** (1.1 g, 2.92 mmol) in H_2O (11 mL) and 10% aq H_2SO_4 (2 mL) for 3 h was carried out as described for (*S*)-**1** to isolate the title compound; yield: 0.52 g (88%) [98% ee determined by chiral HPLC method on a Chiracel OD column]; $[\alpha]_D^{24}$ –11.0 (c = 1.0, EtOH); [Lit.[3] $[\alpha]_D$ –8.3 (*c* = 1.18, MeOH); Lit.[13] $[\alpha]_D$ –1.2 (*c* = 1.0, EtOH)].

(2*R*/*S*)-3-(2-Methoxyphenoxy)-1-*O*-(β-D-ribofuranosyl)propane-1,2-diol (22A)

A reaction of **14A** (1.4 g, 2.04 mmol) in MeOH (14 mL) with 10% methanolic ammonia (6 mL) at r.t. for 5 h was performed as described for (*R*)-**21** to isolate the title compound **22A** as a syrup; yield: 0.53 g (79%); $[\alpha]_D^{24}$ +11.5 (c = 1.0, MeOH).

^{1}H NMR (200 MHz, D_2O): δ = 3.40–3.82 (m, 3 H, H-1, 2), 3.90 (s, 3 H, OCH_3), 4.10–4.40 (m, 7 H, H- 3, 2′, 3′, 4′, 5′, 5″), 5.00 (s, 1 H, H-1′), 7.15 (m, 4 H, ArH).

MS (FAB): *m*/*z* = 331 [M^+ + H].

Anal. Calcd for $C_{15}H_{22}O_8$: C, 54.54; H, 6.70. Found: C, 54.41; H, 6.58.

(2*R*/*S*)-3-(2-Methoxyphenoxy)-1-*O*-(β-D-xylofuranosyl)propane-1,2-diol (23A)

A reaction of **18A** (1.2 g, 1.75 mmol) in MeOH (10 mL), 10% methanolic ammonia (5 mL) for 14 h was performed as described for (*R*)-**21** to obtain the title compound **23A** as a syrup; yield: 0.51 g (88%); $[\alpha]_D^{24}$ +12.4 (*c* = 1.0, MeOH).

^{1}H NMR (200 MHz, D_2O): δ = 3.40–3.85 (m, 3 H, H-1, 2), 3.90 (s, 3 H, OCH_3), 4.00–4.40 (m, 7 H, H-3, 2′, 3′, 4′, 5′, 5″), 5.04 (s, 1 H, H-1′), 7.10 (m, 4 H, ArH).

MS (FAB): *m*/*z* = 331 [M^+ + H].

Anal. Cacld for $C_{15}H_{22}O_8$: C, 54.44; H, 6.7. Found: C, 54.32; H, 6.58.

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