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), pyriddyliodine, 2,3,4,6-O-tetra-O-benzyl-1-thio-β-D-galactopyranoside (9), 1-O-acetyl-2,3,5-tri-O-benzoyl-α-D-thio-ribose (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, glycopyranoses) such as macrocles,2 inositol,3 amino acids/peptides,4 phenols,5 and others7 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,3 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-cis10 and 1,2-trans) has been very well demonstrated and reviewed,10 there is a need to study regioselective glycosylation 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 chlorphenenesin,12 and mephenesin13 (Figure 1).

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Figure 1 Structures of guaifenesin, chlorphenenesin and mephenesin

The benefits of the study include synthesis of single isomer drugs and prodrugs 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 CH2Cl2/BrF3·OEt2 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-acytylguaifenesin 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 1H NMR spectra. (R)-3 and (S)-3 were characterized as monoglycosylated derivatives of 1A from their 1H 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 1H 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 1H NMR spectrum with that of an authentic sample. Thus, acetylation of 1A with Ac2O/pyridine resulted in the isolation of mono- and 1,2-di-O-acytylguaifenesin (rac-4 and rac-7), formation of 2-O-acytylguaifenesin (rac-8) was not observed. In the 1H 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).
The high regioselectivity observed in these reactions was remarkable while working in the area of glycosylations of inositol, saccharides (pyrano and furano forms) and 2-deoxy saccharides 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. 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, \( S \)).

In order to check the regioselectivity versus the role of substituent, we decided to study the glycosylation of unsubstituted arylxy 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 \( ^1H \) 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-\( \beta \)-D-galactopyranoside \((9)^{13}\) 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 \( ^1H \) 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 \( \delta = 5.20–5.30 \) 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-\( \alpha \)/\( \beta \)-D-ribofuranosyl \((13)^{19}\) \((\text{CH}_2\text{Cl}_2/\text{BF}_3\cdot\text{OEt}_2)\). It resulted in the isolation of a diastereomeric mixture of 1-\( O \)-\( \beta \)/\( \alpha \)-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 \( ^1H \) 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 regioselectivity was further confirmed by coupling rac-1A with 1-\( O \)-acetyl-2,3,5,tri-\( O \)-benzoyl-\( \alpha \)/\( \beta \)-D-xylofuranose \((17)^{20}\). Reaction of rac-1A with 17 \((\text{CH}_2\text{Cl}_2/\text{BF}_3\cdot\text{OEt}_2)\) 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 \( ^1H \) 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 \( \text{H}_2\text{SO}_4 \) 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.\textsuperscript{17,21}

![Figure 2 structures of compounds (S)- and (R)-1, 3, 6, and 21](image)

The compounds 14A and 18A were deacetylated (NaHCO\textsubscript{3}/MeOH) to obtain diastereomeric mixture of 1-\(\text{O}-\beta\text{-D-ribofuranosylguaiifenesin}\) (22A) and 1-\(\text{O}-\beta\text{-D-xylofuranosylguaiifenesin}\) (23A), attempts were not made to separate the diastereomers.

In conclusion, high regioselective glycosylation of rac-guaiifenesin (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 stereoselectivity was controlled by use of well-established protocols in the coupling reactions. The high regioselectivity 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)-guaiifenesin (1) in 98% ee.

\textsuperscript{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\textsubscript{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\textsubscript{2}SO\textsubscript{4}.

(2R)-3-(2-Methoxyphenoxy)-1-O-(2,3,4,6-tetra-O-acetyl-\(\beta\text{-D-}
\text{glucopyranosyl})propane-1,2-diol ([R]-3) and (2S)-3-(2-Methoxyphenoxy)-1-O-(2,3,4,6-tetra-O-acetyl-\(\beta\text{-D-}
\text{glucopyranosyl})propane-1,2-diol ([S]-3); Typical Procedure

To a solution of \(\beta\text{-D-glucosepentacetate}\) (2.0 g, 25.6 mmol) in anhyd CH\textsubscript{2}Cl\textsubscript{2} (100 mL) was added 1A (2.54 g, 12.8 mmol) and BF\textsubscript{3}-Et\textsubscript{2}O (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\textsubscript{2}CO\textsubscript{3} (1.93 g) was added, stirred for 30 min, filtered, and the residue was washed with CH\textsubscript{2}Cl\textsubscript{2} (150 mL). The filtrate was transferred to a separating funnel, washed with H\textsubscript{2}O (2 \times 50 mL), brine (50 mL), the organic phase was separated, dried (Na\textsubscript{2}SO\textsubscript{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 (2R/S)-1-O-acetyl-3-(2-methoxyphenoxy)propane-1,2-diol (rac-4A), followed by (R)-3 and (S)-3.

Yield: 0.24 g (8%).

\textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}); \(\delta = 2.10\) (s, 3 H, OCH\textsubscript{3}), 3.82 (s, 3 H, OCH\textsubscript{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 (EL, 70 eV); m/z (%): 240 (1, [M\(^+\)]).

(\(\text{R}\))-3

Yield: 2.85 g (42%); \(\left[\alpha\right]_D\textsubscript{22} = 6.3 (c = 2.0, CHCl\textsubscript{3}) ; mp 82–84 °C.

\textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}); \(\delta = 1.90, 1.98, 2.02, 2.10\) (4 s, 12 H, 4 \(\times\) OCH\textsubscript{3}), 3.60–3.80 (m, 3 H, H-1, 6'), 3.90 (s, 3 H, OCH\textsubscript{3}), 3.96–4.30 (m, 5 H, H-2, 3, 5'), 4.84 (d, 1 H, \(J_{\text{2,1}} = 8.4\) 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\textsubscript{23}H\textsubscript{30}O\textsubscript{12}: C, 54.52; H, 6.10. Found: C, 54.39; H, 6.01.

(\(\text{S}\))-3

Yield: 2.98 g (44%); \(\left[\alpha\right]_D\textsubscript{22} = -11.10 (c = 2.0, CHCl\textsubscript{3}) ;

\textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}); \(\delta = 1.96, 2.00, 2.02, 2.04\) (4 s, 12 H, 4 \(\times\) OCH\textsubscript{3}), 3.60–3.75 (m, 2 H, H-6, 6''), 3.85 (s, 3 H, OCH\textsubscript{3}), 3.96–4.34 (m, 6 H, H-1, 2, 3, 5'), 4.96 (d, 1 H, \(J_{\text{1,2}} = 8.3\) 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\textsubscript{23}H\textsubscript{30}O\textsubscript{12}: C, 54.52; H, 6.10. Found: C, 54.37; H, 6.02.

3-Phenoxy-1-O-(2,3,4,6-tetra-O-acetyl-\(\beta\text{-D-glucopyranosyl})propane-1,2-diol (3B)

A reaction of 2 (6.0 g, 15.4 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (60 mL) with rac-1B (1.3 g, 7.7 mmol) and BF\textsubscript{3}-Et\textsubscript{2}O (1.17 mL, 9.2 mmol) for 6 h performed as described for (\(\text{R}\))-3 resulted in the isolation of 4B, followed by 3B.

4B

Yield: 3.16 g (82%).

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}); \(\delta = 2.08\) (s, 3 H, OCH\textsubscript{3}), 3.98 (d, 2 H, \(J_{\text{2,3}} = 6.8\) 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 (EL, 70 eV); m/z = 210 (1, [M\(^+\)]).

3B

Yield: 3.16 g (7%).

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}); \(\delta = 1.96, 2.02, 2.04, 2.08\) (4 s, 12 H, 4 \(\times\) OCH\textsubscript{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. Calcd for C\textsubscript{23}H\textsubscript{30}O\textsubscript{12}: C, 55.41; H, 6.06. Found: C, 54.81; H, 6.16.

(2R/S)-1-O-Acetyl-3-(2-methoxyphenoxy)propane-1,2-diol (rac-4A) and (2R/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\textsubscript{2}Cl\textsubscript{2} (40 mL) was added Ac\textsubscript{2}O (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.

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

1H NMR (200 MHz, CDCl3): δ = 2.14–2.16 (2 s, 6 H, 2 × OCOCCH3), 3.82 (s, 3 H, OCH3), 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+].

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

1-O-Acetyl-3-(phenox y)propane-1,2-diol (4B) and 1,2-Di-O-acetyl-3-(phenox y)propane-1,2-diol (7B)
A reaction of 1B (1.0 g, 5.95 mmol) in CH2Cl2 (20 mL) with Ac2O (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%).

1H NMR (200 MHz, CDCl3): δ = 2.04–2.08 (2 s, 6 H, 2 × OCOCCH3), 4.04 (dd, 2 H, J1,2 = 12.2 Hz, H-1), 4.20 (dd, 1 H, J2,3 = 3.8 Hz, H-2), 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+]).

4B
Yield: 0.89 g (71%).

(2R)-2-O-Acetyl-3-(2-methoxyphenox y)-1-O-(2,3,4,6-tetra-O-acetyl-1,2-di-<p>glucopyranosyl)propane-1,2-diol ([R]-6); Typical Procedure
To a solution of (R)-3 (0.2 g) in CH2Cl2 (6 mL) was added pyridine (0.4 mL), Ac2O (0.28 mL), and a catalytic amount of methylaminopyridine (2 mg). The reaction mixture was stirred at r.t. for 6 h, diluted with H2O (10 mL), and stirred for 5 min. CH2Cl2 (50 mL) was added and the organic layer was washed with 5% aq CuSO4 (2 × 35 mL), H2O (50 mL), dried (Na2SO4), and concentrated. The residue obtained was chromatographed (silica gel; hexane–EtOAc, 9:1) to isolate the title compound as a syrup; yield: 0.09 g (92%); mp 109–111 °C; [α]D 24 = 6.80 (c = 1.0, CHCl3).

1H NMR (300 MHz, CDCl3): δ = 1.90, 1.96, 2.00, 2.02, 2.06, 2.08 (5 s, 15 H, 5 × OCOCCH3), 3.70 (m, 1 H, H-6’), 3.90 (s, 3 H, OCH3), 3.98–4.40 (m, 6 H, H-1, 3, 5’, 6’), 4.98 (d, 1 H, J1,2 = 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].

rac-1A
Yield: 0.58 g (31%); [α]D 24 +30.00 (c = 1.0, CHCl3).

1H NMR (400 MHz, CDCl3): δ = 3.38–3.60 (m, 4 H, H-1, 6’, 6”), 3.50 (s, 3 H, OCH3), 3.60 (s, 3 H, OCH3), 3.80–4.04 (m, 4 H, H-1, 3), 4.18–5.00 (m, 24 H, H-2, 2’, 3’, 4’, 4”, 5’, 5”, 8 × CH2CH2H3), 5.20 (d, 1 H, J1,2 = 2.5 Hz, H-1’), 5.20 (d, 1 H, J1,2 = 3.10 Hz, H-1”), 6.80 (m, 4 H, ArH), 7.10–7.40 (m, 40 H, ArH).

rac-1B
Yield: 0.324 g (55%); [α]D 24 +27.40 (c = 1.0, CHCl3).

1H NMR (300 MHz, CDCl3): δ = 3.42–3.78 (m, 4 H, H-1, 6’, 6”), 3.82 (s, 3 H, OCH3), 3.86–5.00 (m, 14 H, H-2, 2’, 3’, 4’, 4”, 5’, 5”, 8 × CH2CH2H3), 5.15 (d, 1 H, J1,2 = 2.5 Hz, H-1’), 6.85 (m, 4 H, ArH), 7.10–7.40 (m, 20 H, ArH).
Anal. Calcd for C32H40O18: C, 73.31; H, 6.64. Found: C, 72.96; H, 6.46.

2-O-Acetyl-3-(2-methoxyphenox y)-1-O-(2,3,4,6-tetra-O-benzyl-d-galactopyranosyl)propane-1,2-diol (12A)
A reaction of 11A (0.18 g, 0.25 mmol) in CH2Cl2 (4 mL) with Ac2O (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%).

1H NMR (300 MHz, CDCl3): δ = 3.42–3.80 (m, 4 H, H-1, 6’, 6”), 3.84 (s, 3 H, OCH3), 3.86–5.00 (m, 14 H, H-2, 2’, 3’, 4’, 4”, 5’, 5”, 8 × CH2CH2H3), 5.20 (d, 1 H, J1,2 = 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 C44H54O22: C, 72.42; H, 6.60. Found: C, 72.54; H, 6.76.

3-Phenox y-1,2-di-O-(2,3,4,6-tetra-O-benzyl-d-galactopyranosyl)propane-1,2-diol (10B) and 3-Phenox y-1-O-(2,3,4,6-tetra-O-benzyl-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 4 Å molecular sieves (50 mg) in anhyd CH2Cl2 (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 11B.

11A
Yield: 0.34 g (55%); [α]D 24 +27.40 (c = 1.0, CHCl3).

1H NMR (300 MHz, CDCl3): δ = 3.34–3.58 (m, 4 H, H-1, 6’, 6”), 3.78–4.02 (m, 2 H, H-1), 4.20–5.00 (m, 24 H, H-2, 2’, 3’, 4’, 4”, 5’, 5”, 8 × CH2CH2H3), 5.10 (d, 1 H, J1,2 = 3.3 Hz, H-1’), 5.22 (d, 1 H, J1,2 = 3.7 Hz, H-1”), 6.80–6.90 (m, 3 H, ArH), 7.04–7.40 (m, 42 H, ArH).

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11B
Yield: 0.25 g (44%); [\alpha]_{D}^{24} = +34.53 (c = 1.0, CHCl_{3}).

1H NMR (200 MHz, CDCl_{3}): \delta = 3.40–3.58 (m, 2 H, H-6', 6''), 3.72–4.10 (m, 4 H, H-1, 2, 3), 4.34–4.98 (m, 12 H, H-2', 3', 4', 5'), 4 \times CH_{2}CH_{2}H), 5.22 (d, 1 H, J_{1}=3.7 Hz, H-1'), 6.70–6.98 (m, 3 H, ArH). 7.04–7.40 (m, 22 H, ArH).


(2R/S)-2-(2-Methoxyphenoxy)-1-O-(2,3,5-tri-O-benzoyl-\beta-D-ribofuranosyl)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).

1H NMR (200 MHz, CDCl_{3}): \delta = 3.24–3.80 (m, 8 H, H-1, 3, 5', 6', 6''), 3.84 (s, 3 H, OCH_{3}), 4.20–4.40 (m, 4 H, H-2, 3', 4'), 4.70 (d, 1 H, J_{1}=7.0 Hz, H-1'), 7.04 (m, 4 H, ArH).

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


(2S)-2-(2-Methoxyphenoxy)-1-O-(\beta-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).

1H NMR (300 MHz, CDCl_{3}): \delta = 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, 3', 4'), 4.50 (d, 1 H, J_{1}=7.0 Hz, H-1'), 7.04 (m, 4 H, ArH).

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

Anal. Calcd for C_{38}H_{36}O_{12}: C, 53.33; H, 6.71. Found: C, 53.21; H, 6.58.

(2S)-2-(2-Methoxyphenoxy)-1-O-(\beta-D-glucopyranosyl)propane-1,2-diol ([S]-1); Typical Procedure
To a solution of (R)-21 (1.3 g, 3.45 mmol) in H_{2}O (13 mL) was added 10% aq H_{2}SO_{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_{2}O (10 mL). The filtrate was transferred to a separating funnel, extracted with EtOAc (2 × 25 mL), the combined organic phases were dried (Na_{2}SO_{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); [\lambda]_{D}^{24} +8.3 (c = 1.18, MeOH); [\lambda]_{D}^{24} +11.2 (c = 1.0, EtOH).
Acid-catalyzed hydrolysis of (5)-21 (1.1 g, 2.92 mmol) in H₂O (11 mL) and 10% aq HSO₄ (2 mL) for 3 h was carried out as described for (5)-21 to isolate the title compound; yield: 0.52 g (88%); [α]D = −11.0 (c = 1.0, EtOH); [α]D = +11.5 (c = 1.0, MeOH); [α]D = −1.2 (c = 1.0, EtOH).

R-(2S)-3-(2-Methoxyphenylopropane-1,2-diol (22A)
A reaction of 18A (1.2 g, 175 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%); [α]D = +12.4 (c = 1.0, MeOH).

H NMR (200 MHz, D₂O): δ = 3.40 – 3.85 (m, 3 H, H-1, 2), 3.90 (s, 3 H, OCH₃), 4.00 – 4.40 (m, 7 H, H-3, 2, 4), 7.10 (m, 4 H, ArH).

MS (FAB): m/z = 331 [M⁺ + H⁺].


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References

