# Lignin model glycosides: preparation and optical resolution

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**Synthetic protocols for the preparation of the 3-hydroxy-3-(4-hydroxy-3-methoxyphenyl)-2-(2-methoxyphenoxy)propyl β-D-glucopyranosides and corresponding xylopyranosides have been developed. Glycosylation of racemic 1-(4-benzyloxy-3-methoxyphenyl)-3-hydroxy-2-(2-methoxyphenoxy)propanone with the per-benzoylated pyranosyl bromides of D-glucose and D-xylose affords diastereomeric mixtures of the β-glycosides in up to 92% yield. Stereoselective reduction of the benzoyl ketone with $Zn(BH_4)_2$ gives the protected *erythro* diastereomers (2*R*,3*S* and 2*S*,3*R*) of 3-hydroxy-3-(4-hydroxy-3-methoxyphenyl)-2-(2-methoxyphenoxy)propyl β-D-gluco- and -xylo-pyranosides. Reduction with (+)- or (−)-DIP chloride affords the protected *threo* diastereomers (2*S*,3*S* and 2*R*,3*R*) without any significant enantioselectivity. Deprotection then gives the desired lignin dimer glycosides. The use of the pyranoside to provide diastereomers leads to the enrichment (> 90%) of several individual enantiomers using silica gel chromatography, and also allows the rapid assessment of enantiomeric purity by $^1H$ NMR spectroscopy.**

## Introduction

The level to which the matrix polymers of the woody cell wall interact with one another is poorly understood. At present, it is impossible to isolate lignin free of carbohydrates and hemicelluloses free of lignin. This phenomenon is the basis upon which the general hypothesis has developed that cellulose is hydrogen-bonded to hemicelluloses, and the hemicelluloses are covalently attached to lignin.[1] It is through these interactions that woody cell walls are thought to obtain their high mechanical strength and resistance to rapid biodegradation.[2]

It has been further suggested that the predominant mode of covalent attachment of hemicelluloses to lignin is through the benzylic position of guaiacylglycerol β-guaiacyl ethers.[3,4] This is thought to be brought about by random nucleophilic attack of the intermediate quinone methide formed during lignin biosynthesis. As the lignin metabolic pathway is energetically expensive, and the linkage of hemicelluloses to lignin is thought to be essential for the chemical and physical behaviour of the cell wall, an argument could be put forward that the formation of this bond may be accomplished with a higher level of control than random attack.[5] In support of this claim, the recent work on forage cell walls has highlighted the biological control associated with the incorporation of phenolic acids into the lignin macromolecule in corn.[6] If there is some level of biological control exerted on the formation of lignin–hemicellulose covalent bonds, then it follows that there are sites for attachment other than the benzylic position.

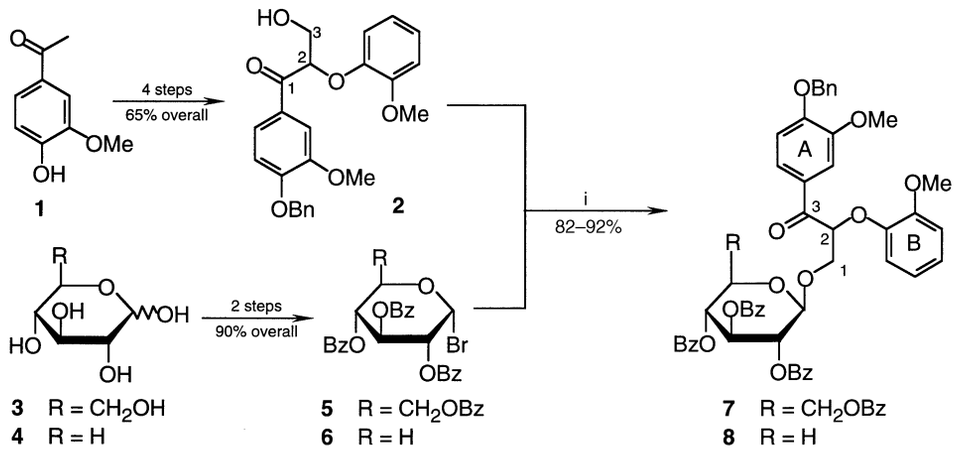
One such possibility is the glycosidic linkage of hemicelluloses through the reducing end to the primary position of the arylpropane side chain. Indeed, *cis*-isoconiferin has been detected in the bark of European beech (*Fagus sylvatica*).[7] It is also important to note that there are several unassigned correlations in 2D heteronuclear multiple quantum-filtered coherence (HMQC) and 2D heteronuclear multiple bond coherence (HMBC) spectra of native lignins and lignin–carbohydrate complexes.[8] Unambiguous assignment of these correlations can only come about through the preparation and NMR characterization of accurate model compounds. The recent identification of a new lignin structure through the use of model compounds and NMR spectroscopy[9] highlights the importance of this approach in ascertaining cell wall structural aspects, and makes this foray into the synthesis and characterization of lignin glycosides worthwhile.

## Results and discussion

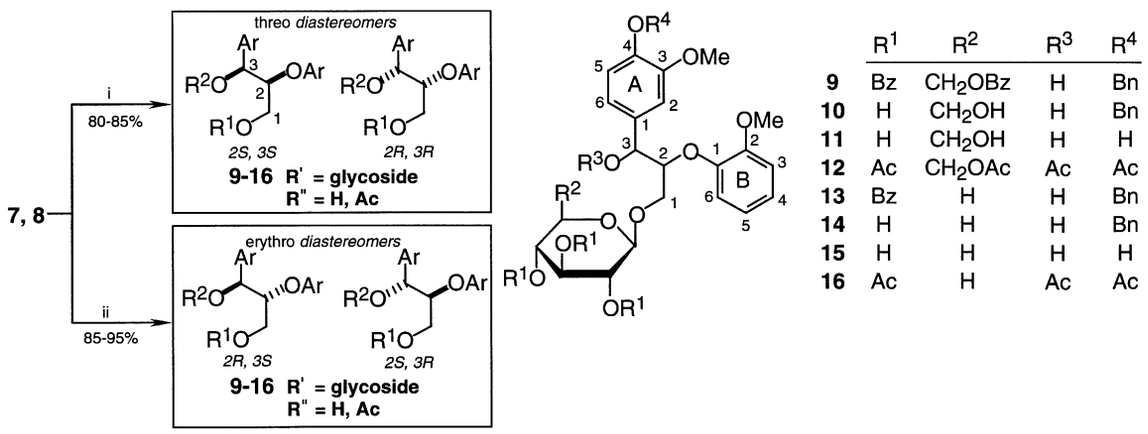
The lignin precursor was prepared by a standard route,[10] namely benzylation of acetovanillone **1**, bromination, and coupling with guaiacol. Subsequent hydroxymethylation leads to a racemic mixture of 1-(4-benzyloxy-3-methoxyphenyl)-3-hydroxy-2-(2-methoxyphenoxy)propanone (**2**, 65% overall). The glycosyl bromides **5** and **6** were prepared by per-benzoylation of the glycose, followed by treatment with HBr (90% overall).[11] The crystalline bromides **5** and **6** were stable as long as they were stored desiccated in the freezer.

Several modifications of the silver triflate-based (AgOTf) glycosylation strategy were performed to optimize the reaction of the alcohol **2** with bromides **5** and **6**. This strategy, when utilized with an acylated glycosyl bromide, favours β-glycosidation. A standard AgOTf glycosylation with 2,4,6-trimethylpyridine (collidine), molecular sieves and the per-acetylated glucosyl bromide was not highly successful. Modification of the reaction system by use of the per-benzoylated glucosyl bromide increased yields significantly. Subsequently it was determined that performing the glycosylation with the benzoylated glucosyl bromide but without the acid scavenger (collidine) afforded the glycosides (**7** and **8**) in up to 92% yield (Scheme 1).

NMR spectra of products **7** and **8** indicate a mixture of epimers, both of which contained a β-glycosidic linkage. The presence of epimers is due to the placement of the optically active carbohydrate on alcohol **2**, a molecule with a chiral centre at the 2-position of the propyl side chain. Brief attempts were made at resolution of this mixture by flash chromatography, but without success. Stereoselective reduction was then performed to produce the enriched *threo* and *erythro* diastereomers. It has recently been shown that molecules such as these can be reduced to afford high *erythro*-selectivity with $Zn(BH_4)_2$.[12] This methodology was used to produce the *erythro* diastereomers (92:8 *erythro*:*threo*) of




**Scheme 1** Protocol for the preparation of the protected glycosides of racemic 1-(4-benzyloxy-3-methoxyphenyl)-3-hydroxy-2-(2-methoxyphenoxy)-propanone **2**. *Reagent:* i, AgOTf, 4 Å molecular sieves.




| | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|
| **9** | Bz | $CH_2OBz$ | H | Bn |
| **10** | H | $CH_2OH$ | H | Bn |
| **11** | H | $CH_2OH$ | H | H |
| **12** | Ac | $CH_2OAc$ | Ac | Ac |
| **13** | Bz | H | H | Bn |
| **14** | H | H | H | Bn |
| **15** | H | H | H | H |
| **16** | Ac | H | Ac | Ac |

**Scheme 2** Reduction and deprotection of the lignin glycoside model compounds. *Reagents:* i, DIP-Cl; ii, $Zn(BH_4)_2$.

compounds **9** and **13** in 90% yield (Scheme 2). Removal of the benzoate groups with sodium methoxide in MeOH gave the *erythro* diastereomers of compounds **10** and **14**, which upon debenzylation gave the desired *erythro* models **11** and **15**. Cleavage of the glucopyranosyl substituent of compound **11** with β-glucosidase gave the known *erythro* lignin model dimer, and acetylation of compounds **11** and **15** gave the per-acetates **12** and **16**, respectively.

Formation of the *threo* diastereomers was accomplished by reduction of the benzoyl ketone with (+)- or (−)-diisopinocampheylchloroborane (DIP chloride™, Scheme 2).[13,14] These reagents have been reported to provide enantioselective reductions for numerous ketones. However, in the cases of compounds **7** and **8**, both *threo* epimers were formed in equal amounts. Assuming the stereoselectivity of the reduction is controlled by the 2-aryloxy substituent, an enantioselective reduction of epimeric compound **7** or **8** would provide one *threo* and one *erythro* isomer, depending on which chiral reductant was used. However, the reduction must be somewhat more complicated than this scenario, as either reductant afforded both *threo* isomers. The same deprotection steps used for the *erythro* isomers gave the *threo* isomers of compounds **10**–**12** and **14**–**16**.

The glycosides formed by the attachment to the racemic lignin model provided a convenient method for ascertaining enantiomeric ratios using the most inexpensive and abundant chiral reagents available in nature—carbohydrates.[15] Signal separation in the $^1$H NMR spectra of several protons allowed for rapid assessment of enantiomeric purity (Fig. 1), and in some cases signal separation in the $^{13}$C spectra was on the order of 1 ppm. The use of carbohydrates also allowed for attempted separations of these models using conventional chromatography

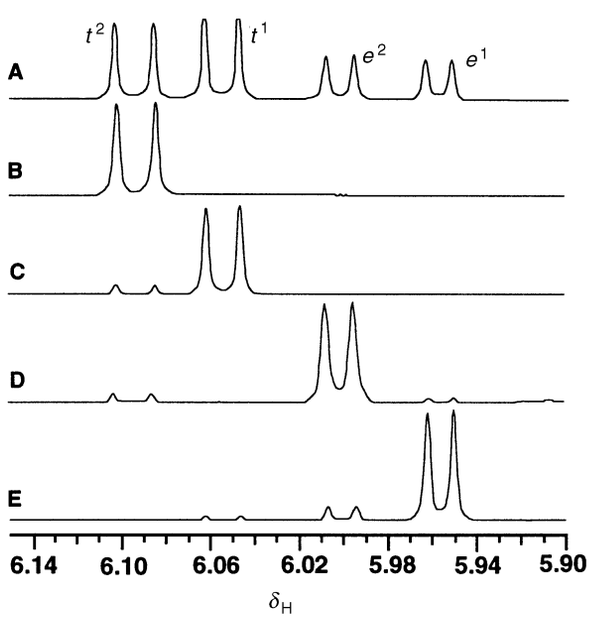



**Fig. 1** $^1$H NMR spectra of the benzylic proton region of the diastereomers of compound **12** initially enriched by different reduction methods. A, $NaBH_4$; B and C: (+)-DIP-Cl and preparative TLC (PLC) of the per-acetates; D and E, $Zn(BH_4)_2$ and PLC of the per-acetates.

systems, *i.e.*, reversed-phase HPLC and silica gel chromatography. As exemplified in Fig. 1, we have been able to separate the lignin–glycoside per-acetates **12** using conventional preparative TLC (silica gel). A relatively non-selective reduction of compound **7** with $NaBH_4$ with subsequent deprotection and

per-acetylation afforded a mixture of the 4 diastereomers (spectrum A). Applying the same sequence with different reductants afforded enriched mixtures of the *threo* and *erythro* diastereomeric per-acetates which were further purified by preparative TLC (spectra B–E).

In summary, the preparation and characterization of lignin model enantiomers and their glycosides may eventually help to unravel the complex issues surrounding the biosynthesis and biodegradation[16] of lignin, lignans and neolignans. Carbohydrates may also, in some cases, provide a simple method for generating diastereomers from mixtures of optical isomers. These diastereomers can be separated by conventional means, with later use of β-glucosidase to selectively remove the glycoside. Carbohydrates can also simply be used for assessing enantiomeric excess.

## Experimental

### General

NMR spectra were recorded in [$^2H_6$]acetone with the central solvent peak serving as the internal reference ($\delta_H$ 2.04, $\delta_C$ 29.8), with 200, 400 or 500 MHz instruments; *J*-values are given in Hz. Mass spectra were run on a JEOL JMS-SX102 instrument. Optical rotations were recorded at ambient temperature on a Perkin-Elmer Model 141 polarimeter; $[\alpha]_D$-values are given in units of $10^{-1}$ deg cm$^2$ g$^{-1}$. All reactions were performed under an atmosphere of dry nitrogen. Crystalline hydroxy ketone **2** was prepared by established procedures,[10,17] and the benzoylated pyranosyl bromides (**5** and **6**) were prepared essentially by the method of Fletcher.[11] Reactions were performed separately subsequent to the stereoselective reductions (*i.e.*, $Zn(BH_4)_2$ *vs.* DIP-Cl) for the *threo* and *erythro* isomers, and yields were independent of starting isomer.

### Glycosylations

Racemic compound **2** (537 mg, 1.31 mmol) was dissolved in methylene dichloride (20 cm$^3$, distilled from $CaH_2$). Powdered molecular sieves (4 Å, 2 g) were added and the solution was cooled to 0 °C. Crystalline bromide **3** (1.18 g, 1.79 mmol) was then added followed by silver triflate (584 mg, 2.27 mmol). The mixture was kept at 0 °C in the dark and well stirred for 90 min, when TLC ($CHCl_3$–EtOAc, 9:1) indicated the complete disappearance of substrate **2**. The mixture was filtered through Celite and subsequently washed with aq. $Na_2S_2O_3$ (1×) followed by aq. $NH_4Cl$ (2×). Drying ($Na_2SO_4$) and filtration gave a foamy solid, which was purified by silica gel chromatography ($CHCl_3$–EtOAc, 12:1) to afford 2-(4-benzyloxy-3-methoxybenzoyl)-2-(2-methoxyphenoxy)ethyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside **7** as a powder (1.205 g, 92.8%) composed of two diastereomers; $\delta_H$(400 MHz) 4.24 (1 H, dd, *J* 6.8 and 11.6, H-1), 4.35 (1 H, dd, *J* 4.9 and 11.3, H-1), 4.39 (1 H, dd, *J* 4.9 and 11.3, H-1), 4.40 (1 H, dd, *J* 3.3 and 11.6, H-1) and 5.43–5.55 (4 H, m, Glc-1 and Glc-2); $\delta_C$(100 MHz) 69.6 and 70.6 (C-1), 80.1 and 82.2 (C-2), 101.3 and 101.9 (Glc-1), 194.4 and 194.8 (C-3). Compound **8**, 2-(4-benzyloxy-3-methoxybenzoyl)-2-(2-methoxyphenoxy)ethyl 2,3,4-tri-*O*-benzoyl-β-D-xylopyranoside, was prepared in the same manner and was isolated as a powder: $\delta_H$(200 MHz) 4.20–4.28 (2 H, m, H-1), 4.31–4.40 (2 H, m, H-1), 5.20–5.28 (2 H, m, Xyl-1) and 5.58–5.76 (2 H, m, H-2); $\delta_C$(50 MHz) 69.1 and 69.6 (C-1), 80.4 and 81.8 (C-2), 100.5 and 101.3 (Xyl-1) and 194.8 (C-3).

### Zinc borohydride reductions

Epimeric ketones **7** and **8** were reduced with $Zn(BH_4)_2$ in EtOAc as described previously[12] to form products **9**-*erythro* and **13**-*erythro*, respectively. The diastereomers of **9**-*erythro*-3-benzyloxy-3-(4-benzyloxy-3-methoxyphenyl)-2-(2-methoxyphenoxy)propyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside were isolated quantitatively as a syrup and the bulk of the material (*threo*:*erythro*, 8:92) was submitted directly to deacylation. An analytical sample was reserved and purified by preparative TLC (PLC) ($CHCl_3$–EtOAc, 4:1), which provided enrichment of the individual diastereomers of **9**-*erythro* as glasses; Isomer I (faster by TLC): $\delta_H$(400 MHz) 3.86 (1 H, dd, *J* 4.0 and 11.3, H-1), 4.21 (1 H, dd, *J* 4.9 and 11.3, H-1), 4.47 (1 H, br d, *J* 4.6 and 9.4, H-2), 4.81 (1 H, br t, *J* 5.3, H-3) and 5.20 (1 H, d, *J* 7.9, Glc-1); $\delta_C$(100 MHz) 68.7 (C-1), 72.9 (C-3), 84.0 (C-2) and 101.8 (Glc-1); Isomer II (90% purity): $\delta_H$(400 MHz) 3.98 (1 H, d, *J* 6.9 and 11.4, H-1), 4.07 (1 H, dd, *J* 3.0 and 11.4, H-1), 4.49 (2 H, m, H-2 and Glc-5), 4.87 (1 H, br t, *J* 4.6, H-3) and 5.32 (1 H, d, *J* 8.1, Glc-1); $\delta_C$(100 MHz) 69.5 (C-1), 73.0 (C-3), 85.2 (C-2) and 102.1 (Glc-1). Diastereomers *erythro*-3-benzyloxy-3-(4-benzyloxy-3-methoxyphenyl)-2-(2-methoxyphenoxy)propyl 2,3,4-tri-*O*-benzoyl-β-D-xylopyranoside **13**-*erythro*: $\delta_H$(200 MHz) 3.93 (1 H, dd, *J* 6.5 and 11.2, H-1), 4.21 (1 H, dd, *J* 5.0 and 10.6, H-1), 4.56 (1 H, d, *J* 4.5, H-2), 4.92 (1 H, m, H-3) and 5.13 (1 H, d, *J* 6.1, Xyl-1); $\delta_C$(50 MHz) 68.2 and 68.7 (C-1), 72.8 and 72.9 (C-3), 83.9 and 84.9 (C-2) and 101.1 and 101.3 (Xyl-1).

### DIP chloride reductions

Reductions were essentially as described previously.[13,14] Purification by silica gel chromatography ($CHCl_3$–EtOAc, 7:1) afforded the *threo*-isomers of compounds **9** and **13** in yields which ranged from 82–88%. Individual isomers could not be readily separated. Diastereomers **9**-*threo*: $\delta_H$(400 MHz) 3.59 (1 H, dd, *J* 6.0 and 11.1, H-1), 3.80 (1 H, dd, *J* 4.6 and 11.6, H-1), 3.98 (1 H, dd, *J* 3.9 and 11.5, H-1), 4.2 (1 H, dd, *J* 3.1 and 11.1, H-1), 4.31–4.48 (4 H, m, H-2 and Glc-5), 4.84–4.90 (2 H, m, H-3), 5.23 (1 H, d, *J* 7.9, Glc-1) and 5.32 (1 H, d, *J* 7.9, Glc-1); $\delta_C$(100 MHz) 69.4 and 68.6 (C-1), 72.9 and 73.2 (C-3), 85.7 and 85.8 (C-2) and 101.7 and 101.9 (Glc-1); Diastereomers **13**-*threo* (separation into individual isomers was not attempted): $\delta_H$(200 MHz) 3.51 (1 H, dd, *J* 5.8 and 11.0, H-1), 4.17 (1 H, dd, *J* 3.1 and 11.0, H-1), 4.32–4.46 (1 H, m, H-2), 4.87–4.98 (1 H, m, H-3) and 5.11 (1 H, d, *J* 6.6, Xyl-1); $\delta_C$(50 MHz) 68.4 and 68.7 (C-1), 72.5 and 73.1 (C-3), 85.6 and 85.7 (C-2) and 100.9 and 101.6 (Xyl-1).

### Deprotection

A standard Zemplen deacetylation was performed with a catalytic amount of NaOMe in MeOH. Mixtures were typically left overnight and subsequently quenched with ion-exchange resin (Amberlite 120A, $H^+$ form). Processing and silica gel chromatography afforded the deacylated materials, which were submitted directly to debenzylation *via* catalytic hydrogenation.[10] Purification by silica gel chromatography ($CHCl_3$–MeOH, 6:1) afforded diastereomeric mixtures of compounds **11** and **15** (overall yields 80–90%). The materials were not readily separable by flash chromatography and were characterized as mixtures. NMR spectroscopic assignment to individual isomers was not attempted. Diastereomers *erythro*-3-(4-benzyloxy-3-methoxyphenyl)-3-hydroxy-2-(2-methoxyphenoxy)propyl β-D-glucopyranoside **11**: $\delta_H$(400 MHz) 3.69 (1 H, dd, *J* 5.0 and 11.0, H-1), 3.83 (1 H, dd, *J* 3.4 and 11.2, H-1), 4.04 (1 H, dd, *J* 3.4 and 11.2, H-1), 4.10 (1 H, dd, *J* 5.0 and 11.0, H-1), 4.30 (1 H, d, *J* 7.8, Glc-1), 4.34 (1 H, d, *J* 7.6, Glc-1), 4.51–4.55 (2 H, m, 2-H), 4.92 (1 H, d, *J* 5.0, 3-H) and 4.95 (1 H, d, *J* 5.0, H-3); $\delta_C$(100 MHz) 68.8 and 69.6 (C-1), 73.28 and 73.30 (C-3), 83.8 and 84.6 (C-2) and 104.3 and 104.7 (Glc-1); Diastereomers **11**-*threo*: $\delta_H$(100 MHz) 3.48 (1 H, dd, *J* 5.6 and 11.1, H-1), 3.75–3.86 (11 H, m, H-1 and $OCH_3$), 4.10 (1 H, dd, *J* 3.0 and 11.1, H-1), 4.27 (1 H, d, *J* 8.0, Glc-1), 4.35 (1 H, d, *J* 8.0, Glc-1), 4.34–4.46 (2 H, m, H-2) and 4.94 (2 H, m, H-3); $\delta_C$ 68.8 and 69.1 (C-1), 73.24 and 73.28 (C-3), 85.2 and 85.6 (C-2) and 104.3 and 104.5 (Glc-1). Diastereomers *erythro*-3-(4-benzyloxy-3-methoxyphenyl)-3-hydroxy-2-(2-methoxyphenoxy)propyl β-D-xylopyranoside **15**: $\delta_H$(200 MHz) 3.64 (1 H, dd, *J* 4.3 and 10.9, H-1), 4.06 (1 H, dd, *J* 5.2 and 10.9, H-1), 4.26 (1 H, dd, *J* 7.0 and 10.1, Xyl-1), 4.46–4.56 (1 H, m, H-2) and 4.92 (1 H, d,

*J* 5.5, H-3); $\delta_C$(50 MHz) 68.3 and 69.0 (C-1), 73.2 and 73.3 (C-3), 83.9 and 84.4 (C-2), 104.3 and 104.8 (Xyl-1). Diastereomers **15**-*threo*: $\delta_H$(200 MHz) 3.36–3.60 (2 H, m, H-1, Xyl-4), 4.04 (1 H, dd, *J* 4.0 and 10.9, H-1), 4.22 (1 H, dd, *J* 7.1 and 14.6, Xyl-1), 4.38–4.50 (1 H, m, H-2), 4.96 (d, *J* 5.6, H-3) and 4.98 (1 H, d, *J* 4.8, H-3); $\delta_C$ 68.4 and 68.6 (C-1), 73.2 and 73.4 (C-3), 85.2 and 85.6 (C-2) and 104.5 and 104.6 (Xyl-1).

**Per-acetates**

Acetylations were performed with acetic anhydride and 4-(dimethylamino)pyridine in methylene dichloride. After work-up the samples were purified by PLC using $CHCl_3$–EtOAc (3 : 1) as the solvent. Yields after TLC were 90–94%. The individual isomers of 3-acetoxy-3-(4-benzyloxy-3-methoxy)-2-(2-methoxyphenoxy)propyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside **12** were obtained in relatively high purity (contaminated only with the other diastereomer) based on NMR spectroscopy. **12t$_1$** (> 97%); $[\alpha]_D$ −10.9 (*c* 1.44, acetone); $\delta_H$(400 MHz) 1.92, 1.96, 1.97, 1.98, 2.11 and 2.21 ($COCH_3$), 3.66 (1 H, dd, *J* 3.4 and 12.0, H-1), 3.83 and 3.84 ($OCH_3$), 3.88 (1 H, ddd, *J* 2.4, 5.2 and 10.1, Glc-5), 3.92 (1 H, dd, *J* 3.8 and 12.0, H-1), 4.01 (1 H, dd, *J* 2.4 and 12.3, Glc-6), 4.20 (1 H, dd, *J* 5.2 and 12.3, Glc-6), 4.66 (1 H, dt, *J* 3.6 and 7.1, H-2), 4.95 (1 H, d, *J* 7.5, Glc-1), 4.99 (1 H, t, *J* 8.5, Glc-2), 5.01 (1 H, t, *J* 9.8, Glc-4), 5.28 (1 H, t, *J* 9.3, Glc-3), 6.09 (1 H, d, *J* 7.0, H-3), 6.87 (1 H, ddd, *J* 2.0, 7.1 and 7.9), 6.96 (1 H, dt, *J* 1.5 and 7.7), 7.00 (1 H, dt, *J* 2.0 and 8.1), 7.01–7.05 (3 H, m) and 7.20 (1 H, br s); $\delta_C$(100 MHz) 20.4, 20.5, 20.5, 20.6, 20.7 and 21.0 ($COCH_3$), 56.3 and 56.3 ($OCH_3$), 62.7 (Glc-6), 68.1 (C-1), 69.4 (Glc-4), 72.1 (Glc-2), 72.4 (Glc-5), 73.2 (Glc-3), 75.4 (C-3), 82.6 (C-2), 101.7 (Glc-1), 113.0, 113.8, 119.1, 120.1, 121.7, 123.4, 123.6, 137.0, 140.7, 149.0, 151.7 and 152.0 (Ar) and 168.9, 169.9, 170.0, 170.2 and 170.6 ($COCH_3$).

Isomer **12t$_2$**: 91% by NMR; $[\alpha]_D$ −37.6 (*c* 1.19, acetone); $\delta_H$(400 MHz) 1.74, 1.91, 1.97, 1.99, 2.00 and 2.22 ($COCH_3$), 3.58 (1 H, dd, *J* 6.7 and 11.29, H-1), 3.82 and 3.83 (3 H, s, $OCH_3$), 3.90 (1 H, ddd, *J* 2.4, 5.0 and 10.1, Glc-5), 4.03 (1 H, dd, *J* 3.2 and 11.3, H-1), 4.07 (1 H, dd, *J* 2.4 and 12.3, Glc-6), 4.23 (1 H, dd, *J* 5.0 and 12.3, Glc-6), 4.72 (1 H, dt, *J* 3.2, 6.6, H-2), 4.81 (1 H, d, *J* 8.1, Glc-1), 4.91 (1 H, dd, *J* 8.1 and 9.8, Glc-2), 5.01 (1 H, t, *J* 9.8, Glc-4), 5.20 (1 H, t, *J* 9.5, Glc-3), 6.05 (1 H, d, *J* 6.1, H-3), 6.83 (1 H, ddd, *J* 1.8, 7.3 and 7.9), 6.90–7.04 (5 H, m) and 7.22 (1 H, br s); $\delta_C$(100 MHz) 20.4, 20.5, 20.5, 20.5, 20.6 and 20.9 ($COCH_3$), 56.1 and 56.3 ($OCH_3$), 62.6 (Glc-6), 69.3 (C-1), 69.4 (Glc-4), 72.0 (Glc-2), 72.4 (Glc-5), 73.4 (Glc-3), 74.8 (C-3), 81.8 (C-2), 101.5 (Glc-1), 112.5, 113.4, 118.2, 120.1, 121.5, 123.1, 123.5, 136.8, 140.8, 149.5, 151.4 and 152.2 (Ar) and 168.9, 169.6, 169.9, 170.0, 170.2 and 170.7 ($COCH_3$) (HRMS: $C_{35}H_{42}O_{17}$ requires M, 734.2422. Found: $M^+$, 734.2416).

Isomer **12e$_1$**: 87% by $^1$H NMR spectroscopy; $[\alpha]_D$ −16.1 (*c* 1.28, acetone); $\delta_H$(400 MHz) 1.94, 1.98, 2.00, 2.04 and 2.22 ($COCH_3$), 3.67 (1 H, dd, *J* 5.9 and 11.1, H-1), 3.80 and 3.83 ($OCH_3$), 3.91 (1 H, ddd, *J* 2.5, 5.1 and 10.0, Glc-5), 4.06 (1 H, dd, *J* 4.7 and 11.1, H-1), 4.06 (1 H, dd, *J* 2.5 and 12.3, Glc-6), 4.20 (1 H, dd, *J* 5.1 and 12.3, Glc-6), 4.77 (1 H, dt, *J* 4.9 and 5.8, H-2), 4.88 (1 H, d, *J* 8.0, Glc-1), 4.96 (1 H, dd, *J* 8.0 and 9.6, Glc-2), 5.02 (1 H, dd, *J* 9.5 and 10.1, Glc-4), 5.26 (1 H, t, *J* 9.5, Glc-3), 6.00 (1 H, d, *J* 5.0, H-3), 6.85 (1 H, ddd, *J* 2.2, 6.8 and 7.9, B-5), 6.92–7.03 (3 H, m, B-3, -4 and -6), 7.03 (1 H, d, *J* 8.1, A-5), 7.09 (1 H, ddd, *J* 0.4, 1.8 and 8.1, A-6) and 7.29 (1 H, d, *J* 1.7, A-2); $\delta_C$(100 MHz) 20.4, 20.4, 20.5, 20.5, 20.7 and 20.9 ($COCH_3$), 56.2 and 56.2 ($OCH_3$), 62.6 (Glc-6), 68.1 (C-1), 69.3 (Glc-4), 72.1 (Glc-2), 72.4 (Glc-5), 73.4 (Glc-3), 74.7 (C-3), 80.7 (C-2), 101.4 (Glc-1), 113.4, 113.7, 118.9, 121.2, 121.7, 123.1, 123.6, 136.5, 140.7, 148.5, 151.7 and 151.9 (Ar) and 168.9, 169.7, 169.8, 169.9, 170.3 and 170.6 ($COCH_3$).

Isomer **12e$_2$**: 85.5% by $^1$H NMR spectroscopy; $[\alpha]_D$ −21.6 (*c* 1.16, acetone); $\delta_H$(400 MHz) 1.81, 1.92, 1.98, 1.99, 2.00 and 2.22 (s, $COCH_3$), 3.80 and 3.82 (s, $OCH_3$), 3.77–3.83 (H-1), 3.93 (1 H, ddd, *J* 2.4, 5.0 and 10.0, Glc-5), 3.97 (1 H, dd, *J* 4.3 and 11.3, H-3), 4.09 (1 H, dd, *J* 2.4 and 12.3, Glc-6), 4.25 (1 H, dd, *J* 5.0 and 12.3, Glc-6), 4.78 (1 H, dt, *J* 4.5 and 6.5, H-2), 4.85 (1 H, d, *J* 8.1, Glc-1), 4.93 (1 H, dd, *J* 8.1 and 9.6, Glc-2), 5.02 (1 H, t, *J* 9.7, Glc-4), 5.22 (1 H, t, *J* 9.5, Glc-3), 5.96 (1 H, d, *J* 4.7, H-3), 6.84 (1 H, ddd, *J* 2.4, 6.6 and 7.9), 6.92–7.08 (5 H, m) and 7.27 (1 H, d, *J* 1.8); $\delta_C$(100 MHz) 20.4, 20.4, 20.4, 20.5, 20.6 and 20.8 ($COCH_3$), 56.1 and 56.2 ($OCH_3$), 62.6 (Glc-6), 68.7 (C-1), 69.3 (Glc-4), 72.0 (Glc-2), 72.4 (Glc-5), 73.4 (Glc-3), 74.9 (C-3), 81.0 (C-2), 101.4 (Glc-1), 113.1, 113.5, 118.9, 120.8, 121.6, 123.2, 123.4, 136.3, 140.7, 148.9, 151.7 and 151.9 (Ar) and 168.9, 169.8, 169.9, 170.0, 170.2 and 170.7 ($COCH_3$) (HRMS: $C_{35}H_{42}O_{17}$ requires M, 734.2422. Found: $M^+$, 734.2433).

Purification of the diastereomers of 3-acetoxy-3-(4-benzyloxy-3-methoxyphenyl)-2-(2-methoxyphenoxy)propyl 2,3,4-tri-*O*-acetyl-β-D-xylopyranoside **16** was not attempted. **16**-*erythro*: $\delta_H$(200 MHz) 1.98, 1.99, 2.02, 2.07 and 2.23 ($COCH_3$), 3.46 (1 H, dd, *J* 9.2 and 11.72, Xyl-5), 3.65 (1 H, dd, *J* 5.46 and 10.93, H-1), 3.78, 3.80, 3.82 and 3.83 (s, $OCH_3$), 3.95 (1 H, dd, *J* 4.27 and 11.10, H-1), 4.05 (1 H, dd, *J* 5.25 and 11.66, Xyl-5), 4.7–4.8 (2 H, m, Xyl-1, H-2), 4.8–4.95 (2 H, m, Xyl-2, Xyl-4), 5.17 (1 H, t, *J* 4.8, Xyl-3), 5.99 (1 H, dd, *J* 5.21 and 4.9, H-3), 6.86–6.94 (1 H, m), 6.96–7.16 (5 H, m) and 7.30 (1 H, d, *J* 1.47); $\delta_C$(50 MHz) 20.5, 20.6, 20.7, 20.8 and 20.9 ($COCH_3$), 56.2 and 56.2 ($OCH_3$), 62.5 and 62.6 (Xyl-5), 67.7 and 68.3 (C-1), 69.6 and 69.7 (Xyl-4), 71.6 (Xyl-2), 72.1 and 72.2 (Xyl-3), 74.7 and 74.8 (C-3), 80.78 and 81.0 (C-2), 101.5 and 101.6 (Xyl-1), 113.0, 113.0, 113.3, 113.5, 113.7, 118.9, 119.0, 120.8, 121.1, 121.6, 121.6, 123.15, 123.4, 123.6, 129.0, 129.7, 136.3, 136.6, 140.7, 148.5, 148.8, 151.7, 151.8 and 151.9 (Ar) and 168.9, 169.8, 169.9, 170.1 and 170.2 ($COCH_3$) (HRMS: $C_{35}H_{38}O_{15}$ requires M, 662.2211. Found: $M^+$, 662.2204).

**16**-*threo*: $\delta_H$(200 MHz) 1.98, 1.99, 2.00, 2.12 and 2.23 ($COCH_3$), 3.40–3.56 (1 H, m, Xyl-5), 3.62 (1 H, dd, *J* 3.6 and 11.8, H-1), 3.82 and 3.83 (6 H, s, $OCH_3$), 3.95–4.13 (2 H, m, H-1, Xyl-5), 4.60–4.78 (2 H, m, H-2, Xyl-1), 4.80–5.28 (3 H, m, Xyl-2, Xyl-3, Xyl-4), 6.08 (d, *J* 6.3, H-3), 6.11 (1 H, d, *J* 7.3, H-3) and 6.78–7.35 (7 H); $\delta_C$(50 MHz) 20.4, 20.6, 20.9 and 21.3 ($COCH_3$), 56.2 ($OCH_3$), 62.4 and 62.6 (Xyl-5), 67.8 and 68.8 (C-1), 69.5 and 69.7 (Xyl-4), 71.3 and 71.7 (Xyl-2), 72.0 and 72.2 (Xyl-3), 74.9 and 75.5 (C-3), 81.8 and 82.6 (C-2), 101.4 and 101.9 (Xyl-1), 112.5, 112.9, 113.4, 113.7, 118.3, 119.2, 120.1, 121.6, 123.1, 123.5, 136.8, 137.0, 140.7, 149.4 and 152.1 (Ar) and 168.8, 170.0 and 170.2 ($COCH_3$) (HRMS: $C_{35}H_{38}O_{15}$ requires M, 662.2211. Found: $M^+$, 662.2213).

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