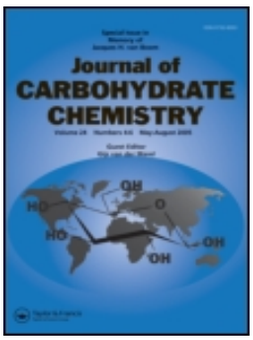

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On the Origin of the Facial Selectivity of the Sharpless Asymmetric Dihydroxylation of Styrene Derivatives

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ABSTRACT

Xylose/styrene-based substrates were reacted with Sharpless asymmetric dihydroxylation reagents AD-mix α and AD-mix β. Unlike the previously reported xylose allyl ether, the saccharide unit did not affect the stereochemical outcome of the reaction. Asymmetric dihydroxylation using AD-mix α or AD-mix β of the chiral olefin gave mainly one diastereoisomer (de: 98%) with S and R configuration respectively. A modelling study directed at a rationalisation of the asymmetric dihydroxylation data is described and applied to diversely derivatised styrenes.

Key Words: Asymmetric dihydroxylation; Chiral olefin; Modelling study.

INTRODUCTION

The Sharpless asymmetric dihydroxylation (AD) methodology[1] has evolved into one of the most powerful tools for enantioselective functionalisation of olefins and found wide applications in total synthesis and medicinal chemistry. For instance, AD of **2** successfully afforded intermediates en route to novel nucleoside analogues such as **1** as inhibitors of reverse transcriptase in the treatment of HIV infection.[2–4] AD

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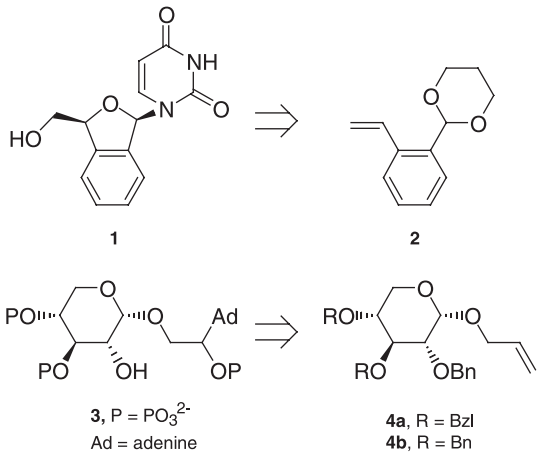


Figure 1. Biological relevant compounds prepared using Sharpless AD as a key step.

of **4a** was also a key reaction in the preparation of Adenophostin A analogues (Figure 1).[5,6]

While optimising the catalysts, Sharpless and Corey have proposed models based on X-ray crystallographic data and NOE experiments, respectively, to rationalise the enantiofacial selectivity of the reaction with styrene (Figure 2).[7–9]

A survey of Sharpless AD of achiral styrene derivatives[2,7,10–13] showed that different substitutions in *ortho*, *meta* or *para* positions of the aromatic ring usually slightly affect the enantiomeric excess (ee).

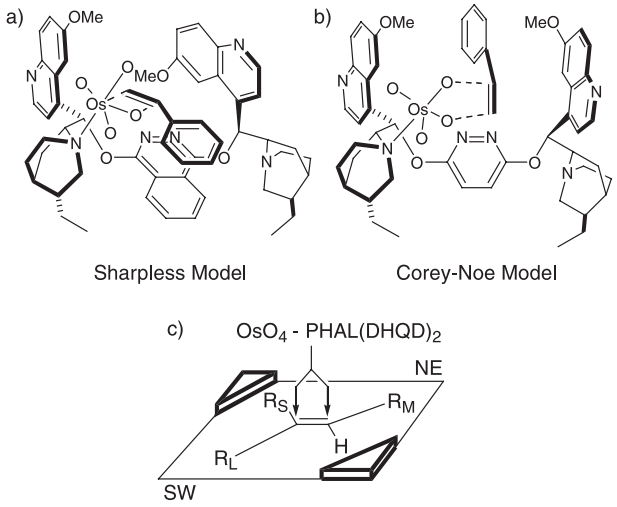
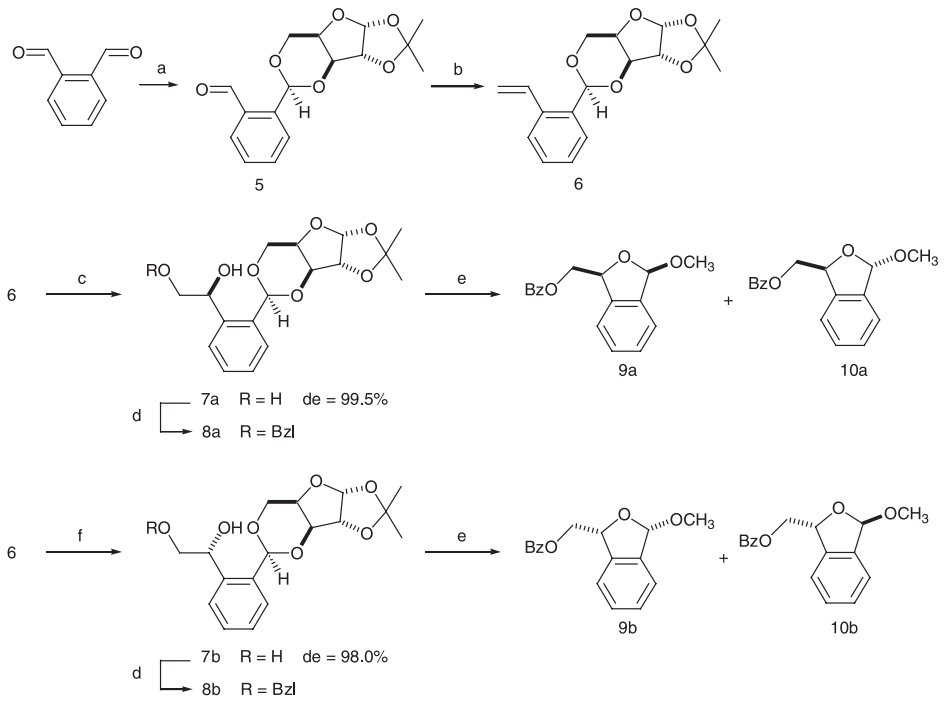


Figure 2. (a) L-shaped model with $(DHQD)_2PHAL$.[8] (b) U-shaped model with $(DHQD)_2PYDZ$.[9] (c) Mnemonic device. (From Ref. [8].)

In contrast, AD of chiral alkenes is harder to rationalize since a substrate intrinsic enantiocontrol may be operative.[14] For instance, asymmetric dihydroxylation of allyl α-D-xylosides such as **4a** and **4b** highlighted a great double diastereoselection effect.[5,6,15] Eventfully, the xylose moiety, which can be seen as a chiral auxiliary, inverted the sense of attack according to the Sharpless mnemonic. We attempted to account for these observations using molecular dynamics methods and proposed a model that agreed with the experimental data. We report herein our studies on asymmetric dihydroxylation of a different xylose derivative featuring a styrene moiety and the rationalisation of the data.

RESULTS AND DISCUSSION

In previous work,[2–4] we reacted the dioxane derivative **2** to synthesize the nucleoside **1** via asymmetric dihydroxylation (Figure 1). Although the dihydroxylation proceeded uneventfully, the separation of enantiomers remained tricky.[2–4] We opted for the use of a chiral auxiliary such as a monosaccharide to obtain diastereoisomers and hence to facilitate the separation.[17] For that purpose, the use of a partially protected xylofuranoside was envisaged, and the suitable dialdehyde was converted



Scheme 1. (a) 1,2-*O*-isopropylidene-α-D-xylofuranose, *p*-TSA, THF; (b) $BrMePh_3P$, BuLi, THF; (c) AD-mix α, *tert*-BuOH/H_2O; (d) BzCl, $N(C_2H_5)_3$, toluene; (e) AcOH, H_2O then MeOH HCl 1%; (f) AD-mix β, *tert*-BuOH/H_2O.

into the corresponding cyclic diacetal **5** using standard conditions (Scheme 1). **5** was next homologated into the styrene derivative **6** by treatment with methyltriphenylphosphonium bromide and butyl lithium in THF. The Wittig adduct **6** was the substrate for the subsequent Sharpless asymmetric dihydroxylation (AD). Thus, **6** was alternatively reacted with AD-mix α and AD-mix β in a mixture of *tert*-butyl alcohol/water to afford the expected diols **7a** (78%) and **7b** (81%), respectively, as single isomers as shown by ^{1}H and ^{13}C NMR. Further HPLC and GC-MS analysis confirmed this high selectivity (de: 99.5% for **7a**, de: 98% for **7b**). Fortunately, the separation of the isomers became easy, as well as did the preparation of optically pure analogues. Selective protection of the diols **7a** and **7b** was accomplished by treatment with benzoyl chloride in toluene–triethylamine mixture at −20°C to give the esters **8a** and **8b**, respectively. The benzoate **8a** was treated with HCl 1% in methanol to afford the benzo[*c*]furan derivatives **9a** and **10a** in a 1:1 ratio. Under similar conditions, the hydroxyester **8b** gave the heterocycles **9b** and **10b** as an equimolar mixture.

The enantiofacial selectivity in the asymmetric dihydroxylation reaction was determined by X-ray crystallography of diol **7a** (Figure 3). The absolute configuration at the carbon atom created during the oxidation was *S* with AD-mix α in agreement with the mnemonic rule.[9]

These high diastereoselections with both AD-mix α and β were striking for several reasons. First, this data contrasted with the previous observations where the effect of the sugar moiety was strong and led to the unexpected diol according to Sharpless mnemonic.[15] Secondly, the corresponding dioxane **2**[2–4] was earlier reacted with AD-mix α and β with similar selectivities, indicating no substrate control of the reaction. Finally, the asymmetric dihydroxylation of monosaccharides does not usually provides diols with so high excesses.[19–22]

This high enantiofacial discrimination together with the absence of substrate induction at the asymmetric dihydroxylation step deserved further investigations. Earlier, we reported a pure molecular mechanics method based on a simulated annealing to rationalize the unusual behaviour of **4b**.[15] In the present work, an enhanced version of the protocol based on a genetic algorithm was exploited and included the computation of the solvation free energy contribution. The full protocol and its testing on a variety of substrates will be reported in due course.

For the comparison purpose, we thought to apply this enhanced protocol to styrene. The computation led to two energetically accessible models within 1 kcal.mol^{-1}, which

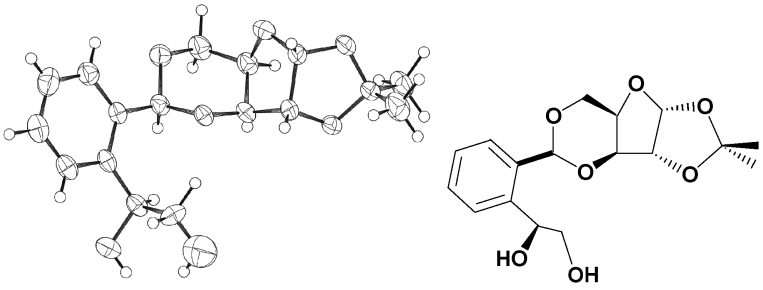


Figure 3. Ortep diagram of diol **7a**. (From Ref. [18].)

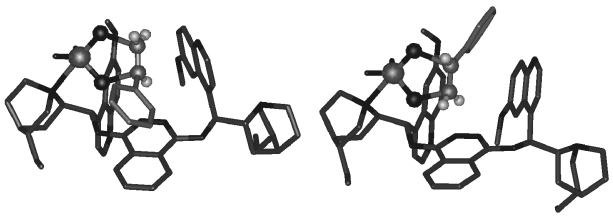


Figure 4. Computed transition states for the AD with AD-mix β of styrene. Only olefin hydrogens are shown for clarity.

predicted the observed enantiofacial selectivity (Figure 4). Interestingly, these two models resemble those alternatively proposed by Sharpless and Corey.[7–9] A closer look reveals that the assembly conformations differed mainly for the olefin positioning, the catalyst conformation being roughly similar. Indeed, the catalyst conformation corroborated that proposed by Sharpless on NMR basis.[9]

The high convergence of the experimentally pictured (Figure 2) and computational models (Figure 5) was encouraging. We next investigated the AD transition states of **2** and **6**. Again, the proposed models were in accordance with the experimental observations (Figures 5 and 6).

In both cases (with or without the chiral auxiliary), the styrene part of the substrate fitted in the same zone as did the styrene. However, although the fully protected xylofuranoside ring did not have any influence on the stereofacial selection, it was found to be involved in hydrophobic interactions with a methoxyquinoline moiety (Figure 5). Consequently, a new spatial arrangement of the catalyst occurred. This additional interaction might explain the gain in selectivity observed between styrene (97% ee with both AD-mix α and AD-mix β) and **6** (de: 99.5% with AD-mix α, de: 98% with AD-mix β). In terms of excess, this difference may be viewed as low. However, in terms of free energy of activation, the gain is large. For instance a de of 97% requires a difference in energy between the transition states leading to the minor and major isomers of 2.3 kcal.mol^{-1} while a de of 99.5% is equivalent to $\Delta G = 3.2$ kcal.mol^{-1}.

In contrast, **2** fitted in the ''binding site'' with roughly identical arrangements to styrene (Figure 5). Regarding the observed ee's and the proposed models, we could conclude about a negligible effect of any small *ortho* group. Indeed, although this latter is

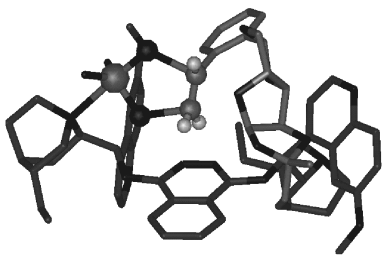


Figure 5. Computed transition states for the AD-mix β of **6**.

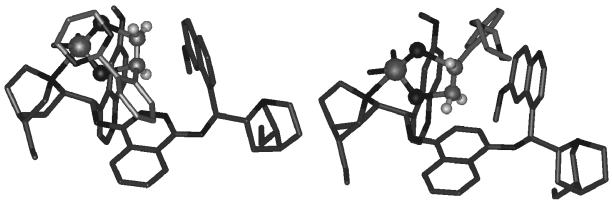


Figure 6. Computed transition states for the AD with AD-mix β of **2**.

facing the solvent increasing unfavourable contacts with the polar medium (*tert*-BuOH/H_2O), it did not sterically clash with the catalyst nor favorably interact with it.

In conclusion, we successfully used the Sharpless asymmetric dihydroxylation as a key step in the preparation of saccharide analogues **9** and **10**. The introduction of a chiral auxiliary allowed an easier identification and purification of both isomers produced. Interestingly, unlike the previously reported xylose-based substrate **4a**, **6** was dihydroxylated with high stereoselectivity. These results prompted us to look back to our initial modelling work on AD. We exploited an enhanced version of this protocol to account for these last observations. This modelling study highlighted two energetically accessible models previously proposed by Corey and Sharpless. These two models were also proposed for AD of styrene derivatives **2** and **6** and shed light on aromatic stacking, hydrophobic and steric interactions that can explain the experimental data. Further optimisation of the procedure, test of its versatility and rationalisation of Sharpless mnemonic device will be presented in due course.

EXPERIMENTAL

Melting points were determined on a digital melting-point apparatus (Electrothermal) and are uncorrected. Optical rotations were recorded at 22°C in $CHCl_3$ or MeOH solutions with a digital polarimeter DIP-370 (JASCO) using a 1dm cell and rotations are given in 10^{-1} deg cm^2 g^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or Me_2SO-d_6 (internal Me_4Si) respectively at 300.13. MHz and at 75.47 MHz (Bruker AM WB-300). Coupling constants (*J*) are given in Hz. TLC was performed on Silica F254 (Merck) with detection by UV light at 254 nm or by charring with phosphomolybdic–H_2SO_4 reagent. Column chromatography was effected on Silica Gel 60 (Merck, 230 mesh). Commercial reagents were supplied by Lancaster or Acros.

Computational simulations were performed with the Insight II® 2000 package using a modified CFF91 force field and a protocol reported elsewhere.[23] Graphical displays were printed out from the Insight II® molecular modeling system.

3,5-*O*-(*S*)-(2-Ethenylbenzylidene)-1,2-*O*-isopropylidene-α-D-xylofuranose (6). A suspension of methyltriphenylphosphonium bromide (7.0 g, 19.59 mmol) in dry tetrahydrofuran (20 mL) at 0°C under N_2 was treated dropwise with *n*-butyl lithium (12.3 mL of 1.6 M in hexane, 19.59 mmol), warmed to room temperature for 1 h, and re-cooled to 0°C during the addition of compound **5**[14] (3.0 g, 9.79 mmol) in tetra-

hydrofuran (10 mL). After 1 h at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL) and extracted with diethyl ether (2 × 50 mL). The extract was worked up, and the crude product was purified by column chromatography (hexane–acetone, 95:5) to afford **6** (2.1 g, 69%) as a white solid, mp 85.3–87.6°C. $[\alpha]_{24}^{D}$ − 16.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (m, 2H, H-3 and H-6), 7.28 (m, 2H, H-4 and H-5), 7.07 (dd, 1H, *J* 1.0, *J* 11.0, C*H*CH_2), 6.05 (d, 1H, $J_{1,2}$ 3.6, H-1), 5.62 (m, 1H, *J* 17.5, CHC*H*$_2$), 5.57 (s, 1H, CH), 5.30 (m, 1H, CHC*H*$_2$), 4.60 (d, 1H, $J_{2,3}$ 0, H-2), 4.44 (d, 1H, $J_{5a,5b}$ 13.4, H-5a), 4.39 (bs, 1H, H-4), 4.12 (bs, 1H, H-3), 4.11 (d, 1H, H-5b), 1.49 (s, 3H, CH_3), 1.31 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.3 (C-1), 133.9 (2C, C-2, *C*HCH_2), 129.2, 127.6, 126.4 and 126.0 (4C, C-3, C-4, C-5 and C-6), 116.4 (CH*C*H_2), 111.8 (Ciso), 105.6 (C-1), 98.1 (CH), 83.8 (C-2), 78.9 (C-4), 72.1 (C-3), 66.8 (C-5), 26.7 (CH_3), 26.1 (CH_3).

Anal. Calcd for $C_{17}H_{20}O_5$ (304.34): C 67.09, H 6.62; Found: C 66.97 H 6.78.

3,5-*O*-(*S*)[2-((*S*)-1,2-Dihydroxyethyl)benzylidene]-1,2-*O*-isopropylidene-α-D-xylofuranose (7a). A mixture of AD-mix α (2.3 g) in *tert*-butyl alcohol (8.2 mL) and water (8.2 mL) was stirred at room temperature until both phases were clear. After the mixture was cooled to 0°C, compound **6** (0.5 g, 1.64 mmol) was added in one portion and the heterogeneous slurry was stirred vigorously at 0°C for 10 h. The reaction mixture was quenched by addition of sodium sulfite (2.5 g) at 0°C, warmed to room temperature and stirred for one hour. The product was extracted with dichloromethane (20 mL), the extract was concentrated and the crude product was purified by column chromatography (hexane–acetone, 50:50) to afford **7a** (0.45 g, 81%) as a white solid, mp 190.2–190.7°C. $[\alpha]_{20}^{D}$ + 29.7 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (m, 2H, H-3 and H-6), 7.30 (m, 2H, H-4 and H-5), 6.04 (d, 1H, $J_{1,2}$ 3.6, H-1), 5.59 (s, 1H, CH), 5.17 (dd, 1H, *J* 3.4, *J* 8.0, C*H*OH), 4.55 (d, 1H, $J_{2,3}$ 0, H-2), 4.39 (bd, 1H, H-5a), 4.38 (bs, 1H, H-4), 4.09 (d, 1H, $J_{3,4}$ 1,7, H-3), 4.08 (dd, 1H, $J_{4,5b}$ 1.7, $J_{5a,5b}$ 13.3, H-5b), 3.79 (dd, 1H, *J* 3.3, *J* 11.2, C*H*$_a$H$_b$OH), 3.64 (dd, 1H, *J* 8.0, CH$_a$*H*$_b$OH), 3.13, 2.00 (bs, 2H, OH), 1.48 (s, 3H, CH_3), 1.29 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0 (C-1), 134.4 (C-2), 129.6, 127.8, 127.0, 126.9 (4C, C-3, C-4, C-5 and C-6), 112.0 (Ciso), 105.6 (C-1), 98.8 (CH), 83.7 (C-2), 78.8 (C-4), 71.9 (C-3), 70.8 (CHOH), 67.5 (CH_2OH), 66.7 (C-5), 26.6 (CH_3), 26.1 (CH_3).

Anal. Calcd for $C_{17}H_{22}O_7$ (338.35): C 60.35, H 6.55; Found: C 60.52, H 6.82.

3,5-*O*-(*S*)[2-((*R*)-1,2-Dihydroxyethyl)benzylidene]-1,2-*O*-isopropylidene-α-D-xylofuranose (7b). Using the same procedure as detailed for compound **6** but using AD-mix β, the isomer **7b** was obtained (0.43 g, 78%) as a white solid, mp 67.0–67.4°C. $[\alpha]_{21}^{D}$ − 18.9 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (m, 2H, H-6 and H-3), 7.28 (m, 2H, H-4 and H-5), 6.19 (d, 1H, $J_{1,2}$ 3.6, H-1), 5.56 (s, 1H, CH), 5.39 (dd, 1H, *J* 3.4, *J* 8.0, C*H*OH), 4.59 (d, 1H, $J_{2,3}$ 0, H-2), 4.39 (dd, 1H, $J_{4,5a}$ 1,7, $J_{5a,5b}$ 10.7, H-5a), 4.38 (bs, 1H, H-4), 4.12 (bs, 1H, H-3), 4.10 (dd, 1H, $J_{4,5b}$ 2.0, H-5b), 3.69 (dd, 1H, *J* 3.2, *J* 11.2, C*H*$_a$H$_b$OH), 3.63 (dd, 1H, *J* 8.5, CH$_a$*H*$_b$OH), 3.13, 2.00 (bs, 2H, OH), 1.51 (s, 3H, CH_3), 1.33 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9 (C-1), 134.2 (C-2), 129.7, 127.7, 127.5, 127.4 (4C, C-3, C-4, C-5 and C-6), 112.0 (Ciso), 105.7 (C-1), 100.2 (CH), 83.8 (C-2), 78.9 (C-4), 71.9 (C-3), 70.7 (CHOH), 67.8 (CH_2OH), 66.7 (C-5), 26.7 (CH_3), 26.2 (CH_3).

Anal. Calcd for $C_{17}H_{22}O_7$ (338.35): C 60.35, H 6.55; Found: C 60.48, H 6.52.

3,5-*O*-(*S*)[2-((*S*)-2-Benzoyloxy-1-hydroxyethyl)benzylidene]-1,2-*O*-isopropylidene-α-D-xylofuranose (8a). To a stirred solution of diol **7a** (1.0 g, 2.95 mmol) in anhydrous toluene (4.4 mL) and triethylamine (1.1 mL) at − 20°C benzoyl chloride (335 μg, 2.95 mmol) was added dropwise. The reaction mixture was stirred for 12 h, water (10 mL) was added, and the mixture was extracted with diethyl ether (2 × 10 mL). The extract was worked up, and the crude product was purified by column chromatography (hexane–acetone, 85:15) to afford **8a** (0.9 g, 69%) as a white solid, mp 127.9–128.3°C. $[\alpha]_{21}^{D}$ + 13.3 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (m, 2H, H-3 and H-6), 7.57–7.37 (m, 7H, H-4, H-5, COPh), 6.03 (d, 1H, $J_{1,2}$ 3.2, H-1), 5.71 (s, 1H, CH), 5.45 (bd, 1H, *J* 7.7, C*H*OH), 4.61 (m, 1H, CH_aH$_b$O), 4.55 (d, 1H, $J_{2,3}$ 0, H-2), 4.39 (m, 3H, H-4, H-5a and CH$_a$$H_b$O), 4.12 (bd, 1H, $J_{5a,5b}$ 11.7, H-5b), 4.10 (bs, 1H, H-3), 3.10 (bs, 1H, OH), 1.49 (s, 3H, CH_3), 1.28 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8 (COPh), 138.1 (C-1), 134.5 (C-2), 133.1 (C-para/OBz), 129.9 (C-i/OBz), 129.7, 129.5, 128.3, 128.1, 126.8, 126.7 (8C, C-ortho/OBz, C-meta/OBz, C-3, C-4, C-5 and C-6), 111.8 (Ciso), 105.6 (C-1), 98.0 (CH), 83.7 (C-2), 78.8 (C-4), 72.0 (C-3), 69.4 (CHOH), 68.7 (CH_2OH), 66.7 (C-5), 26.7 (CH_3), 26.1 (CH_3).

Anal. Calcd for $C_{24}H_{26}O_8$ (442.46): C 65.15, H 5.92; Found: C 64.97, H 6.19.

3,5-*O*-(*S*)[2-((*R*)-2-benzoyloxy-1-hydroxyethyl)benzylidene]-1,2-*O*-isopropylidene-α-D-xylofuranose (8b). Using the procedure described **8b** (0.94, 72%) was obtained as a white solid, mp 71.5–71.9°C, $[\alpha]_{22}^{D}$ − 10.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (m, 2H, H-6 and H-3), 7.57–7.36 (m, 9H, H-4, H-5, COPh), 5.97 (d, 1H, $J_{1,2}$ 3.3, H-1), 5.60 (s, 1H, CH), 5.59 (bd, 1H, *J* 7.5, C*H*OH), 4.55 (m, 1H, CH_aH$_b$O), 4.50 (d, 1H, $J_{2,3}$ 0, H-2), 4.32 (m, 3H, H-4, H-5a and CH$_a$$H_b$O), 4.10 (bd, 1H, $J_{5a,5b}$ 11.7, H-5b), 4.06 (bs, 1H, H-3), 3.05 (bs, 1H, OH), 1.44 (s, 3H, CH_3), 1.16 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) d 166.7 (COPh), 138.7 (C-1), 134.2 (C-2), 133.1 (C-para/OBz), 129.7 (C-i/OBz), 129.6, 127.9, 127.4, 127.2, (8C, C-ortho/OBz, C-meta/OBz, C-3, C-4, C-5 and C-6), 111.7 (Ciso), 105.5 (C-1), 99.6 (CH), 83.7 (C-2), 78.9 (C-4), 72.0 (C-3), 69.5 (CHOH), 68.3 (CH_2OH), 66.6 (C-5), 26.6 (CH_3), 25.8 (CH_3).

Anal. Calcd for $C_{24}H_{26}O_8$ (442.46): C 65.15, H 5.92; Found: C 65.04, H 6.17.

(1*R*,3*S*)-3-Benzoyloxymethyl-1,3-dihydro-1-methoxybenzo[*c*]furan (9a) and (1*S*,3*S*)-3-Benzoyloxymethyl-1,3-dihydro-1-methoxybenzo[*c*]furan (10a). The saccharide derivative **8a** (300 mg, 0.678 mmol) was taken up in 16.8 mL of 80% acetic acid and heated at 60°C for 2 hours. After solvent evaporation and co-evaporation with toluene, the residue was dissolved in methanolic HCl (1%, 3.5 mL), and the mixture was stirred for 2 h at room temperature. Water (20 mL) was added, and the mixture was extracted with diethyl ether (2 × 10 mL). The extract was worked up and purified by silica gel column chromatography (hexane–acetone, 95:5) to afford **9a** and **10a** (130 mg, 67%) obtained as a pair of diastereoisomers with a *cis*/*trans* ratio of 1:1. Both diastereoisomers **9a** *cis* and **10a** *trans* had physical data and NMR data identical to those previously described.[2]

(1*S*,3*R*)-Benzoyloxymethyl-1,3-dihydro-1-methoxybenzo[*c*]furan (9b) and (1*R*,3*R*)-Benzoyloxymethyl-1,3-dihydro-1-methoxybenzo[*c*]furan (10b). Using the above procedure **8b** (300 mg, 0.678 mmol) was converted to a mixture of **9b** and **10b** (128 mg, 66%) obtained as a pair of diastereoisomers with a *cis*/*trans* ratio of 1:1. Both

diastereoisomers **9b** and **10b** had physical data and NMR data identical to those previously described.[2]

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