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A consecutive approach towards the stereoselective synthesis of trisubstituted THF domains☆

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Abstract—A highly efficient, consecutive approach for the construction of synthetically valued, enantiomerically pure, trisubstituted THF domains **3**–**10** in a stereoselective manner starting from glycal derived allylic alcohols **1a**–**1d** under Sharpless asymmetric epoxidation (SAE) conditions is reported. The reaction involves the intramolecular asymmetric ring opening (ARO) of in situ formed enantiopure 2,3-epoxy alcohols followed by protection of the diol.

1. Introduction

In recent years consecutive reactions[1] have received much attention by the chemical community, because they address fundamental principles of synthetic efficiency and reaction design. They are more efficient and cost effective than conventional stepwise transformations, as they yield complex molecules from simple starting materials with a high chemo-, regio- and stereoselectivity. Ideally, these reactions occur in a consecutive fashion, by the successive addition of reagents, without the isolation of intermediates in the sense of a 'one-pot synthesis'.[2]

Tetrahydrofurans (THFs), found in many naturally occurring compounds,[3,4] are of paramount importance since these heterocycles, both naturally produced and synthetically derived, often display diverse biological activity.[5] Their stereoselective synthesis with required protections is a desired goal despite it being an elusive and challenging objective.

Sharpless asymmetric epoxidation (SAE) of allylic alcohols is one of the most significant developments in the history of asymmetric catalysis.[6–8] The products of this process, enantio- or diastereomerically enriched epoxy alcohols, are amongst the most valuable and versatile intermediates in organic synthesis,[9] because they readily undergo regioselective ring-opening reactions.[10] As a result, the Sharpless asymmetric epoxidation has found extensive utility in the synthesis of natural products.[11] In our research on the synthetic applications of glycals derived acyclic α,β-unsaturated sugar aldehydes,[12] commonly known as Perlin aldehydes,[13] while carrying out epoxidation studies on these Perlin aldehyde derived allylic alcohols, it was found that **1c**, among the allylic alcohols studied was transformed into a THF derivative, an increasingly significant motif in natural products[14] during its SAE (Fig. 1) by using super-stoichiometric amount of catalysts [2.0 equiv Ti(*O*-*i*-Pr)$_4$, 2.5 equiv diethyl tartrate (DET) and 3.0 equiv *t*-BuOOH].

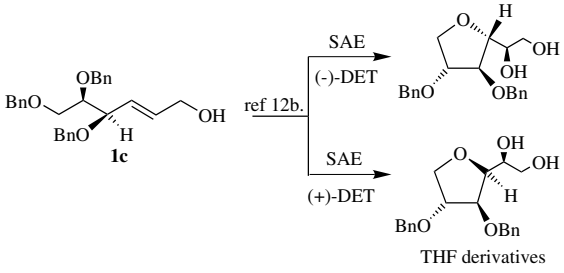

Figure 1.

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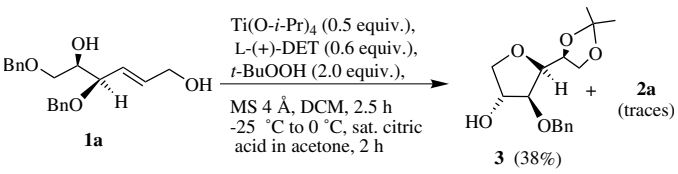
In association with one of the projects for achieving the synthesis of biologically important compounds, large quantities of stereochemically pure 2,3,4-trisubstituted THF derivatives are required. Very recently we have disclosed a novel and very efficient methodology for their preparation, starting from enantiomerically pure 2,3-epoxy alcohols in good to very good yields.[12a] Here we presumed that the increase in the yield of the 2,3-epoxy alcohols may help in obtaining THF derivatives in a more commanding yield. Over the course of our study towards the improvement of yields of 2,3-epoxy alcohols, we found a new and efficient method for the stereoselective synthesis of enantiopure trisubstituted THF domains whose results are discussed below.

2. Results and discussion

In order to increase the yield of the epoxy alcohols, SAE of allylic alcohols **1a**–**1d** (Scheme 1) was repeated using different permutations and combination of factors such as varying the ratios of the Sharpless reagents, performing the reaction in inert atmosphere. However, neither of our attempts was able to achieve any increment in the yields of the 2,3-epoxy alcohols **2a**–**2d**, except a slight change in the time of reaction.

Here, we anticipated that by modifying the work-up procedure of the SAE of allylic alcohol would be helpful for achieving the goal. A literature survey for the preparation of sensitive epoxy alcohols revealed that the saturated citric acid solution in ether: acetone (9:1) is recommended for the removal of Ti(*O*-*i*-Pr)$_4$ from the reaction mixture instead of using 10% aqueous solution of tartaric acid.[15] Since the solubility of citric acid is better in acetone, we opted for saturated citric acid in acetone instead of an ether/ether–acetone solution of citric acid as a quenching agent.

Our modified work-up procedure entails additional stirring of the reaction mixture containing **2a** (TLC) obtained by SAE of **1a** using sub-stoichiometric amount of reagents [Ti(*O*-*i*-Pr)$_4$ (0.5 equiv) and (+)-DET (0.6 equiv)], with saturated citric acid solution in acetone for 2 h, resulting in the formation of an insoluble titanium citrate complex.[15] The filtrate obtained after filtration was evaporated, dissolved in dichloromethane (DCM) and washed with the minimum amount of water to remove the excess of citric acid. The extracted organic layer was then evaporated. The residue thus obtained was taken in ether. To it 10 mL of 4% NaOH solution in brine was added and then stirred for 45 min at 0 °C to hydrolyze the tartrate ester. The resulting solution was extracted with ether. The combined organic layer was dried over anhydrous sodium sulfate and concentrated to yield an oily product. Surprisingly, purification of the oily product furnished a highly substituted THF domain **3** (3,6-anhydro galactitol derivative) as the major product (38% yield) instead of the epoxy derivative **2a** which was isolated in trace amounts only (Scheme 2).



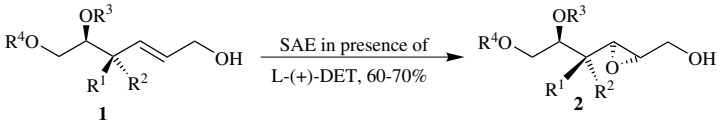
Scheme 2. Consecutive approach towards the synthesis of THF domain.

Encouraged by these results, attempts towards optimization to obtain the highly substituted THF domain **3** in a better yield by replacing the quenching reagent, a saturated solution of citric acid in acetone with a solution of citric acid in 2,2-dimethoxypropane, yielded **3** in only 24% yield along with 2,3-epoxy alcohol **2a** (51%) in 4 h. While quenching the reaction mixture with saturated citric acid solution in 10% aqueous acetone, only **2a** was obtained in a 63% yield. However, an appreciable increase in the yield of **3** (48%) was observed (Table 1, entry 1) when this reaction was carried out using stoichiometric amounts of the Sharpless reagents (Scheme 3, Path A).

To understand the importance of this consecutive one-pot process, we synthesized the same THF **3** step-wise via **2a** (Scheme 3, Path B). In this case the overall yield of THF **3** obtained was 42%, whereas the above mentioned consecutive approach afforded the same THF domain in a 48% yield.

Having optimized the reaction conditions and ensured the literature precedent[16] on the importance of 2,3,4-trisubstituted THF domains, a series of enantiopure allylic alcohols **1a**–**1d** were successfully transformed into their corresponding trisubstituted THF domains (Table 1) under similar reaction conditions as described above, in acceptable yields with >99% stereoselectivity in all cases.

However, in the case of **1d** where the reaction was carried out by using (−)-DET, the corresponding 2,3-epoxy alco-

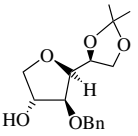
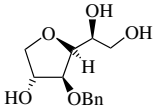
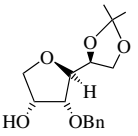
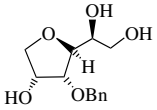
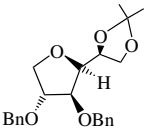
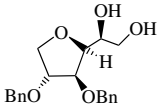
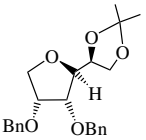
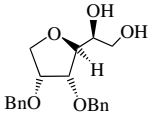
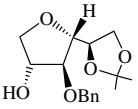
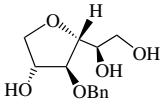
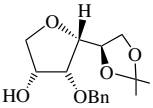
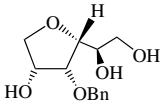
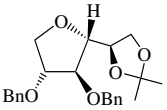
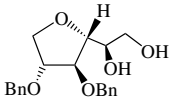


1a. R^1=OBn, R^2=R^3=H, R^4=Bn
1b. R^1=R^3=H, R^2=OBn, R^4=Bn
1c. R^1=OBn, R^2=H, R^3=R^4=Bn
1d. R^1=H, R^2=OBn, R^3=R^4=Bn

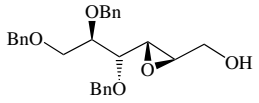
2a. R^1=OBn, R^2=R^3=H, R^4=Bn
2b. R^1=R^3=H, R^2=OBn, R^4=Bn
2c. R^1=OBn, R^2=H, R^3=R^4=Bn
2d. R^1=H, R^2=OBn, R^3=R^4=Bn

Scheme 1. Sharpless asymmetric epoxidation.

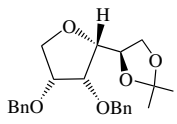
Table 1. Results of synthesis of THF domains from glycal derived allylic alcohols

Entry	Reactant	Reagent/time (h)	Major product	Minor product
1	**1a**	(+)-DET/4.5	 **3** (48%)	 **3a** (4%)
2	**1b**	(+)-DET/4.5	 **4** (51%)	 **4a** (5%)
3	**1c**	(+)-DET/14	 **5** (55%)	 **5a** (10%)
4	**1d**	(+)-DET/11	 **6** (40%)	 **6a** (10%)
5	**1a**	(−)-DET/4.5	 **7** (48%)	 **7a** (5%)
6	**1b**	(−)-DET/4.5	 **8** (46%)	 **8a** (5%)
7	**1c**	(−)-DET/14	 **9** (52%)	 **9a** (10%)

hol **2e** was isolated as the major product in a 76% yield along with traces of **10**.

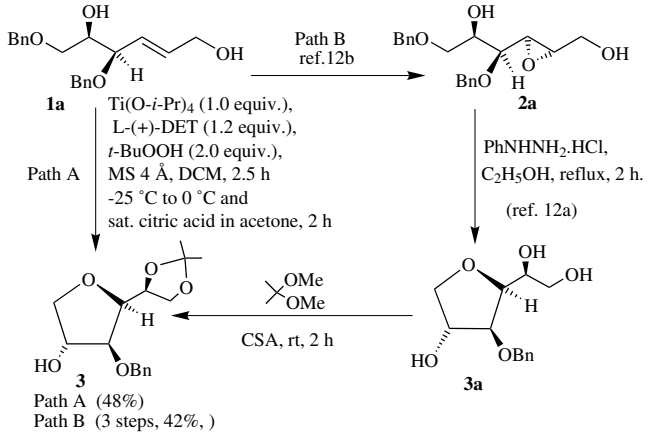


2e



10

Thus, the above results led us to argue that the insoluble titanium citrate complex formed during work-up, probably induces the C3 selectivity leading to intramolecular nucleophilic asymmetric ring opening (ARO) of the epoxide at C3 involving the participation of the C-(6)-benzyloxy oxygen atom followed by protection of the terminal vicinal diol by acetone to afford **3**.



Scheme 3. Consecutive and stepwise synthesis of THF domain **3**.

3. Conclusion

In summary, this report describes a facile and mild protocol for stereoselective synthesis of highly substituted enantiomerically pure THF domains directly from allylic alcohols derived from their respective glycals under SAE condition. Moreover, this consecutive approach circumvent the need to isolate the intermediate 2,3-epoxy alcohol and thereby shows significant 'cost/time benefits' by reducing the amount of solvents, reagents, adsorbents and energy.

4. Experimental

4.1. General

Organic solvents were dried by standard methods. Ti(*O*-*i*-Pr)$_4$, (+)-diethyl L-tartrate, (−)-diethyl D-tartrate and 6.0 M solution of *t*-BuOOH in nonane were purchased from Aldrich chemical co. Allylic alcohols **1a**–**1d** were synthesized in the laboratory. All the products were characterized by ^{1}H, ^{13}C, IR, ESI-MS and EI-HRMS (C, H, O). Analytical TLC was performed using 2.5 × 5 cm plates coated with a 0.25 mm thickness of silica gel (60F-254), and visualization was accomplished with $CeSO_4$ and subsequent charring over a hot plate. Column chromatography was performed using silica gel (60–120 and 100–200 mesh). NMR spectra were recorded on Bruker Avance DPX 200 FT, Bruker Robotics and Bruker DRX 300 Spectrometers at 200, 300 MHz (^{1}H) and 50, 75 MHz (^{13}C). Experiments were recorded in $CDCl_3$ at 25 °C. Chemical shifts are given on the δ scale and are referenced to the TMS at 0.00 ppm for proton and 0.00 ppm for carbon. For ^{13}C NMR reference, $CDCl_3$ appeared at 77.4 ppm, unless otherwise stated. IR spectra were recorded on Perkin–Elmer 881 and FTIR-8210 PC Shimadzu Spectrophotometers. Mass spectra were recorded on a JEOL JMS-600H high-resolution spectrometer using EI mode at 70 eV. Optical rotations were determined on an Autopol III polarimeter using a 1 dm cell at 28 °C in chloroform as the solvent; concentrations mentioned are in g/100 mL.

4.2. General procedure for the preparation of THF domains

A solution of Ti(*O*-*i*-Pr)$_4$ (0.30 mL, 1.0 mmol) and L-(+)-diethyl tartrate (0.20 mL, 1.2 mmol) in DCM (5 mL) was stirred at −25 °C for 0.5 h in the presence of MS 4 Å. To this mixture, a solution of compound **1a** (328 mg, 1.0 mmol) in DCM (5 mL) was added and the mixture stirred at the same temperature. After 0.5 h of stirring a 6.0 M solution of *t*-BuOOH in nonane (0.34 mL, 2.0 mmol) was added and the temperature of the reaction raised to 0 °C and left to stir until the disappearance of the starting material (TLC). A saturated citric acid solution in acetone (15 mL) was added to quench the reaction at 0 °C and stirred for another 2 h. The titanium-citrate complex formed was filtered through a Celite pad. The filtrate obtained was concentrated to dryness under reduced pressure. This residue was dissolved in DCM and washed with the minimal amount (1 × 5 mL) of water to remove excesses of citric acid in the mixture. The combined organic layer collected was concentrated. The residue obtained was dissolved in Et_2O (20 mL) and stirred with 4% NaOH in brine solution (10 mL) at 0 °C for 0.75 h to hydrolyze and remove excess diethyl tartrate. Afterwards, the ether layer was separated, washed with brine, dried over Na_2SO_4 and concentrated to afford the crude product. This was purified by column chromatography to furnish pure THF **3** (141 mg, 48%) and **3a** (10 mg, 4%). A similar reaction protocol was adopted for compounds **1b**, **1c** and **1d** using (+)- and (−)-DET.

4.2.1. (2*S*,3*S*,4*S*,5*R*)-1,2-*O*-Isopropylidine-3,6-anhydro-4-*O*-benzyl-D-galactitol 3. Sticky solid, eluent for column chromatography: EtOAc/hexane (1/4, v/v), $[\alpha]_D = +14.0$ (*c* 0.100, $CHCl_3$); R_f 0.35 (3/7 EtOAc/hexane); IR (neat, cm^{-1}): 3320 (O–H str), 3069, 3031 (=C–H str), 2987, 2931, 2876 (–C–H str), 1603, 1498, 1458 (C=C str), 1373 (C–H def. of CH_3), 1210, 1050 (C–O str); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.27 (m, 5H, Ar*H*), 4.65 (br s, 2H, CH_2Ph), 4.39–4.32 (m, 2H) 4.13–4.07 (m, 3H), 3.99–3.94 (m, 2H), 3.72 (d, $J = 9.9$ Hz, 1H), 1.43 (s, 3H, CH_3), 1.37 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.1 (Ar q*C*), 128.6, 127.9, 127.7 (Ar*C*), 108.9 (q*C*), 84.1 (CH), 81.3 (CH), 75.0 (CH), 74.3 (CH_2), 73.6 (CH), 72.6 (CH_2), 67.1 (CH_2), 26.8 and 25.6 (2 × CH_3); mass (ESI-MS) *m*/*z* 294; found 295 $[M+1]^{+\cdot}$, 255, 237 $[M-C_3H_7O]^{+\cdot}$, 207, 181; EI-HRMS: (M+H) calcd for $C_{16}H_{22}O_5$+H, 295.1545; found 295.1546.

4.2.2. (2*S*,3*S*,4*R*,5*R*)-1,2-*O*-Isopropylidine-3,6-anhydro-4-*O*-benzyl-D-glucitol 4.[†] Solid, mp 56–58 °C, eluent for column chromatography: EtOAc/hexane (9/41, v/v), $[\alpha]_D = -12.0$ (*c* 0.100, $CHCl_3$); R_f 0.44 (3/7 EtOAc/hexane); IR (KBr, cm^{-1}): 3431 (O–H str), 3030 (=C–H str), 2925, 2861 (–CH str), 1660, 1590, 1454 (C=C str), 1367 (C–H def. of CH_3), 1093 (C–O str); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39–7.33 (m, 5H, Ar*H*), 4.73 (d, $J = 11.4$ Hz, 1H, CH_2Ph), 4.62 (d, $J = 11.4$ Hz, 1H, CH_2Ph), 4.23 (dd, $J = 10.6$ Hz and $J = 5.3$ Hz, 1H), 4.14–3.97 (m, 4H), 3.92–3.87 (m, 2H), 3.74 (dd, $J = 9.4$ Hz and $J = 5.0$ Hz, 1H), 2.76 (br d, $J = 5.9$ Hz, 1H, OH), 1.46 (s, 3H, CH_3), 1.38 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.5 (Ar q*C*), 128.9, 128.6, 128.5 (Ar*C*), 110.0 (q*C*), 82.6 (CH), 80.1 (CH), 76.1 (CH), 73.1 (CH_2), 72.8 (CH_2), 70.6 (CH), 66.9 (CH_2), 26.9 and 25.4 (2 × CH_3); mass (ESI-MS) *m*/*z* 294; found 295 $[M+1]^{+\cdot}$, 269, 237 $[M-C_3H_7O]^{+\cdot}$, 207, 181; EI-HRMS: (M+H) calcd for $C_{16}H_{22}O_5$+H, 295.1545; found 295.1533.

4.2.3. (2*S*,3*S*,4*S*,5*R*)-1,2-*O*-Isopropylidine-3,6-anhydro-4,5-di-*O*-benzyl-D-galactitol 5. Oil, eluent for column chromatography: EtOAc/hexane (1/9, v/v), $[\alpha]_D = +5.95$ (*c* 0.235, $CHCl_3$); R_f 0.58 (1/4 EtOAc/hexane); IR (neat, cm^{-1}): 3064, 3032 (=C–H str), 2925, 2854 (–CH str), 1600, 1495, 1456 (C=C str), 1371 (C–H def. of CH_3), 1068 (C–O str); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.27 (m, 10H, Ar*H*), 4.60–4.47 (m, 4H, 2 × CH_2Ph), 4.36 (dd,

[†] The appearance of the –OH signal in the ^{1}H NMR spectra may be due to some non-covalent type of interaction(s) between the *syn* related –OH and –OBn groups.

$J = 12.9$ Hz and $J = 6.4$ Hz, 1H), 4.12–3.94 (m, 6H), 3.82 (d, $J = 9.1$ Hz, 1H), 1.42 (s, 3H, CH_3), 1.37 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.3, 138.0 (Ar q*C*), 128.9, 128.8, 128.7, 128.1, 128.0, 127.9 (Ar*C*), 109.1 (qC), 82.5 (CH), 82.0 ($2\times$CH), 73.5 (CH), 72.6 (CH_2), 72.3 (CH_2), 71.7 (CH_2), 67.6 (CH_2), 27.0 and 25.7 ($2\times CH_3$); mass (ESI-MS) *m*/*z* 384; found 385 $[M+1]^{+\cdot}$, 353 $[M-CH_2O-1]^{+\cdot}$, 294 $[M-CH_2Ph+1]^{+\cdot}$, 243, 181; EI-HRMS: (M+H) calcd for $C_{23}H_{28}O_5$+H, 385.2015; found 385.2048.

4.2.4. (2*S*,3*S*,4*R*,5*R*)-1,2-*O*-Isopropylidine-3,6-anhydro-4,5-di-*O*-benzyl-D-glucitol 6. Oil, eluent for column chromatography: EtOAc/hexane (2/23, v/v), $[\alpha]_D = -23.6$ (*c* 0.165, $CHCl_3$); R_f 0.61 (1/4 EtOAc/hexane); IR (neat, cm^{-1}): 3064 (=CH str), 2925, 2857 (–CH str), 1495, 1456 (C=C str), 1373 (C–H def. of CH_3), 1148, 1066 (C–O str); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.26 (m, 10H, Ar*H*), 4.68–4.57 (m, 4H, $2\times CH_2$Ph), 4.10 (dd, $J = 11.1$ Hz and $J = 5.7$ Hz, 1H), 4.03–3.98 (m, 4H), 3.94–3.84 (m, 3H), 1.40 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.2 (Ar q*C*), 128.8, 128.7, 128.5, 128.2, 128.1 (Ar*C*), 109.9 (qC), 82.8 (CH), 78.2 (CH), 77.3 (CH), 76.1 (CH), 72.3 and 72.2 ($2\times CH_2$), 70.2 (CH_2), 66.5 (CH_2), 26.7 and 25.3 ($2\times CH_3$); mass (ESI-MS) *m*/*z* 384; found 385 $[M+1]^{+\cdot}$; 345, 181; EI-HRMS: (M+H) calcd for $C_{23}H_{28}O_5$+H, 385.2015; found 385.1974.

4.2.5. (2*R*,3*R*,4*S*,5*R*)-1,2-*O*-Isopropylidine-3,6-anhydro-4-*O*-benzyl-D-galactitol 7. Oil, eluent for column chromatography: EtOAc/hexane (1/4, v/v), $[\alpha]_D = +47.29$ (*c* 0.148, $CHCl_3$); R_f 0.34 (3/7 EtOAc/hexane); IR (neat, cm^{-1}): 3436 (O–H str), 3032 (=CH str), 2985, 2926 (–CH str), 1655, 1456 (C=C str), 1376 (C–H def. of CH_3), 1256, 1214 and 1069 (C–O str); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.29 (m, 5H, Ar*H*), 4.67 (d, $J = 11.7$ Hz, 1H, CH_2Ph), 4.57 (d, $J = 11.7$ Hz, 1H, CH_2Ph), 4.37 (dt, $J = 6.8$ Hz and $J = 3.3$ Hz, 1H), 4.23 (br s, 1H), 4.10 (dd, $J = 8.5$ Hz and $J = 7.4$ Hz, 1H), 3.93 (br s, 4H), 3.61 (dd, $J = 8.6$ Hz and $J = 6.3$ Hz, 1H), 1.45 (s, 3H, CH_3), 1.36 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 137.9 (Ar q*C*), 128.9, 128.4, 128.3 (Ar*C*), 110.3 (qC), 85.5 (CH), 85.1 (CH), 75.8 (CH), 75.0 (CH and CH_2), 72.2 (CH_2), 66.6 (CH_2), 26.4 and 25.0 ($2\times CH_3$); mass (ESI-MS) *m*/*z* 294; found 295 $[M+1]^{+\cdot}$, 237 $[M-C_3H_7O]^{+\cdot}$, 202 $[M-CH_2Ph-1]^{+\cdot}$, 181; EI-HRMS: (M+H) calcd for $C_{16}H_{22}O_5$+H, 295.1545; found 295.1553.

4.2.6. (2*R*,3*R*,4*R*,5*R*)-1,2-*O*-Isopropylidine-3,6-anhydro-4-*O*-benzyl-D-glucitol 8.[†] Solid mp 90–92 °C, eluent for column chromatography: EtOAc/hexane (9/41, v/v), $[\alpha]_D = +4.95$ (*c* 0.101, $CHCl_3$); R_f 0.43 (3/7 EtOAc/hexane); IR (KBr, cm^{-1}): 3441 (O–H str), 2925 (–CH str), 1597, 1454 (C=C str), 1366 (C–H def. of CH_3), 1067 (C–O str); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.33 (m, 5H, Ar*H*), 4.87 (d, $J = 11.1$ Hz, 1H, CH_2Ph), 4.67 (d, $J = 11.2$ Hz, 1H, CH_2Ph), 4.42–4.31 (m, 2H), 4.14–4.09 (m, 2H), 3.97 (dd, $J = 8.4$ Hz and $J = 6.1$ Hz, 1H), 3.88–3.81 (m, 2H), 3.70 (dd, $J = 9.2$ Hz and $J = 5.5$ Hz, 1H), 2.81 (br d, $J = 8.4$ Hz, 1H, OH), 1.45 (s, 3H, CH_3), 1.39 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.8 (Ar q*C*), 128.9, 128.5, 128.4 (Ar*C*), 109.4 (q*C*), 81.8 (CH), 79.4 (CH), 74.7 (CH_2), 74.0 (CH), 73.1 (CH_2), 71.8 (CH), 67.5 (CH_2), 27.1 and 25.8 ($2\times CH_3$); mass (ESI-MS) *m*/*z* 294; found 295 $[M+1]^{+\cdot}$, 288, 237 $[M-C_3H_7O]^{+\cdot}$, 202 $[M-CH_2Ph-1]^{+\cdot}$, 181; EI-HRMS: (M+H) calcd for $C_{16}H_{22}O_5$+H, 295.1545; found 295.1555.

4.2.7. (2*R*,3*R*,4*S*,5*R*)-1,2-*O*-Isopropylidine-3,6-anhydro-4,5-di-*O*-benzyl-D-galactitol 9. Oil, eluent for column chromatography: EtOAc/hexane (1/9, v/v), $[\alpha]_D = -7.7$ (*c* 0.220, $CHCl_3$); R_f 0.58 (3/7 EtOAc/hexane); IR (neat, cm^{-1}): 3065, 3032 (=C–H str), 2925, 2860 (–C–H str), 1597, 1456 (C=C str), 1372 (C–H def. of CH_3), 1213 and 1069 (C–O str); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.27 (m, 10H, Ar*H*), 4.64–4.46 (m, 4H, $2\times CH_2$Ph), 4.18–3.89 (m, 7H), 3.86 (dd, $J = 8.0$ Hz and $J = 2.3$ Hz, 1H), 1.46 (s, 3H, CH_3), 1.35 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.2, 138.0 (Ar q*C*), 128.8, 128.1, 128.0, 127.3 (Ar*C*), 109.7 (q*C*), 85.4 (CH), 84.5 (CH), 83.4 (CH), 75.8 (CH), 72.1 and 71.8 ($2\times CH_2$), 71.4 (CH_2), 67.7 (CH_2), 27.2 and 25.6 ($2\times CH_3$); mass (ESI-MS) *m*/*z* 384; found 385 $[M+1]^{+\cdot}$, 353 $[M-CH_2O-1]^{+\cdot}$, 295 $[M-CH_2Ph+2]^{+\cdot}$, 278 $[M-OCH_2Ph+1]^{+\cdot}$, 243, 207, 181; EI-HRMS: (M+H) calcd for $C_{23}H_{28}O_5$+H, 385.2015; found 385.1991.

4.2.8. (2*R*,3*R*,4*R*,5*R*)-1,2-*O*-Isopropylidine-3,6-anhydro-4,5-di-*O*-benzyl-D-glucitol 10. Oil, eluent for column chromatography: EtOAc/hexane (2/23, v/v), $[\alpha]_D = +14.0$ (*c* 0.121, $CHCl_3$); R_f 0.62 (1/4 EtOAc/hexane); IR (neat, cm^{-1}): 3043 (=CH str), 2933 (–CH str), 1625, 1463 (C=C str), 1367 (C–H def. of CH_3), 1072 (C–O str); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42–7.28 (m, 10H, Ar*H*), 4.85 (d, $J = 11.6$ Hz, 1H, CH_2Ph), 4.73 (d, $J = 11.6$ Hz, 1H, CH_2Ph), 4.61 (d, $J = 11.9$ Hz, 1H, CH_2Ph), 4.53 (d, $J = 11.9$ Hz, 1H, CH_2Ph), 4.41 (dd, $J = 13.0$ Hz and $J = 6.4$ Hz, 1H), 4.19–4.06 (m, 3H), 3.98–3.88 (m, 4H), 1.43 (s, 3H, CH_3), 1.38 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.8 (Ar q*C*), 128.8, 128.6, 128.3, 128.2, 127.9 (Ar*C*), 110.1 (qC), 81.7 (CH), 79.7 (CH), 77.4 (CH), 74.2 (CH), 73.9 and 72.8 ($2\times CH_2$), 69.4 (CH_2), 67.1 (CH_2), 27.0 and 25.7 ($2\times CH_3$); mass (ESI-MS) *m*/*z* 384; found 385 $[M+1]^{+\cdot}$, 345, 221, 181; EI-HRMS: (M+H) calcd for $C_{23}H_{28}O_5$+H, 385.2015; found 385.1989.

4.2.9. (2*R*,3*S*)-4,5,6-Tri-*O*-benzyl-2,3-epoxy-D-glucitol 2e. Oil, eluent for column chromatography: EtOAc/hexane (3/22, v/v), $[\alpha]_D = -6.5$ (*c* 0.108, $CHCl_3$), R_f 0.50 (3/7 EtOAc/hexane); IR (neat, cm^{-1}): 3426 (O–H str), 3062, 3030 (=CH str), 2925, 2869 (–CH str), 1604, 1495, 1455 (C=C str), 1211 (C–O str of epoxides), 1097 (C–O str); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.25 (m, 15H, Ar*H*), 4.74–4.53 (m, 6H, $3\times CH_2$Ph), 3.79–3.64 (m, 5H), 3.52–3.47 (m, 1H), 3.21 (dd, $J = 4.0$ Hz and $J = 2.2$ Hz, 1H, H-3), 3.14 (ddd (o), $J = 4.6$ Hz and $J = 2.5$ Hz, 1H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6, 138.5 (Ar q*C*), 128.7, 128.2, 128.0 (Ar*C*), 79.4 (CH), 76.9 (CH), 73.9, 73.8, 73.0 ($3\times CH_2$), 69.7 (CH_2), 61.9 (CH_2), 56.0 (C-3), 55.5 (C-2); mass (ESI-MS) *m*/*z* 434; found 435 $[M+1]^{+\cdot}$, 343 $[M-CH_2Ph]^{+\cdot}$, 181; elemental analysis calcd for $C_{27}H_{30}O_5{\cdot}0.5H_2O$ (443.55) C, 73.11; H, 7.04. Found: C, 72.80; H, 6.56.

4.3. Procedure for the synthesis of 3a from 2a

To a solution of epoxy alcohol **2a** (500 mg, 1.45 mmol) in absolute alcohol (10 mL), a catalytic amount of phenyl hydrazine hydrochloride (14.46 mg, 0.10 mmol) was added and the mixture was stirred at reflux temperature for 2 h. After completion of the reaction (TLC), the reaction mixture was cooled to room temperature and neutralized with an excess of saturated K_2CO_3 solution. The organic layer was evaporated under reduced pressure and aqueous layer was extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and evaporated to yield the crude product, which was purified by silica gel column chromatography (silica gel, 3/97 MeOH/$CHCl_3$) to afford the pure tetrahydrofuran derivative **3a** (299 mg, 81%) as a white shiny solid.

4.4. Procedure for the synthesis of 3 from 3a

To a solution of **3a** (299 mg, 1.18 mmol) in acetone (5 mL), 2,2-dimethoxy propane (0.17 mL, 1.42 mmol) and a catalytic amount of (1*S*)-(+)-10-camphorsulfonic acid (27 mg, 0.01 mmol) were added. The mixture was stirred at room temperature for 2 h. Sodium bicarbonate was added and stirring was continued until the solution reached pH 6. The mixture was filtered through celite, the filter was washed with acetone and the solvent was removed in vacuo. The residue was partitioned between DCM and water. The aqueous layer was extracted with DCM (3×10 mL). The organic extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a residue, which was subjected to column chromatography to afford THF **3** (258 mg, 75%).

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