Stereodivergent Synthesis of Diastereoisomeric Carba Analogs of Glycal-Derived Vinyl Epoxides: A New Access to Carbasugars

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ABSTRACT A convenient method for the stereoselective synthesis of diasteroisomeric vinyl epoxides (−)-**2**α and (−)-**2**β, the carba analogs of D-galactal and D-allal-derived vinyl epoxides **1**αand **1**β, has been elaborated starting from tri-*O*-acetyl-D-glucal. The key step of this synthesis is an application of the known Claisen thermal rearrangement of a glucal derivative, the vinyl allyl ether (+)-**3b**, which allows to switch the glycal structure into the corresponding carba analog scaffold. Epoxides (−)-**2**α and (−)-**2**β derive from the same synthetic intermediate, the *trans* diol (+)-**5**. *Chirality 23:820–826, 2011.* © 2011 Wiley-Liss, Inc.

KEY WORDS: carbasugars; stereoselective synthesis; Claisen thermal rearrangement

INTRODUCTION

Carbasugars are carbocyclic analogs of carbohydrates that play a crucial role within the broad field of carbohydrate mimetics.[1] Natural carbasugars as well as synthetic carbasugars have shown to possess interesting biological activities.[2,3] They are particularly attractive, because their structural resemblance to the parent sugars would facilitate their recognition by biological systems in place of the related natural sugars. Moreover, the structural substitution of the endocyclic oxygen atom with a methylene group leads to compounds that are more stable toward endogenous degradative enzymes.

The synthetic strategies adopted to obtain carbapyranoses can be broadly classified as: (*i*) synthetic methods that use non carbohydrates as starting materials[4–6] and (*ii*) protocols that utilize carbohydrates as the precursors.[7,8] In this framework, the use of carbohydrates provides important advantages, over the other methods, in the preparation of their carbocyclic analogs mostly because the enantiomeric purity of the target carbasugars is generally guaranteed.

Recently, we have developed a new uncatalyzed, substrate-dependent, stereospecific glycosylation process using the diastereoisomeric D-allal and D-galactal-derived vinyl epoxides **1**α and **1**β, as unprecedented glycosyl donors (Scheme 1).[9,10]

On this basis, we herein focus our attention on the synthesis of enantiopure carba analogs of glycosyl donors **1**α and **1**β, the diastereoisomeric vinyl epoxides **2**α and **2**β, to check their suitability as pseudoglycosyl donors, with the aim to realize a new approach to the stereoselective synthesis of carbasugars.

The most significant features of our stereoselective synthetic strategy are (*i*) the construction of the carbocyclic system **4** by way of an application of the known Claisen rearrangement developed by Sudha and Nagarajan[11] to the glycal substrate **3b** and (*ii*) the synthesis of an efficient carba-type precursor, the *trans* diol **5**, which is easily transformed into diastereoisomeric vinyl epoxides **2**α and **2**β (Scheme 2).

MATERIALS AND METHODS

All reactions were performed in flame-dried modified Schlenk (Kjeldahl shape) flasks fitted with a glass stopper or rubber septa under a positive pressure of argon. Air- and moisture-sensitive liquids and solutions were transferred via a syringe. Organic solutions were dried on Na_2SO_4 and concentrated by a rotary evaporator below 40°C at ca. 25 Torr. Flash column chromatography was performed using 230–400 mesh silica gel. Analytical thin layer chromatography (TLC) was performed on Alugram SIL G/UV_{254} silica gel sheets with detection by 0.5% phosphomolybdic acid solution in 95% ethanol (EtOH). Preparative TLC was performed using glass plates precoated to a depth of 0.25 or 0.50 mm with 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Et_3N, Ac_2O, and CH_2Cl_2 were distilled from CaH_2, tetrahydrofuran (THF) was distilled from Na/benzophenone. Anhydrous *N*,*N*-dimethylformamide (DMF), CH_3CN, and Pyridine were purchased from Aldrich. PMBCl, $Ph_3PMe^+I^-$, potassium hexamethyldisilazide (KHMDS), $NaBH_4$, BnBr, NaH, 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ), MsCl, Ms_2O, *t*-BuOK, 1,2;3,4-di-*O*-isopropyliden galactopyranose, and 3-cyclohexene-1-methanol were purchased from Aldrich and used without purification. 2-Iodoxybezoic acid (IBX) was synthesized according to the literature methods,[12] glucal diol (+)-**6** was prepared as previously described.[13]

Proton and carbon-13 nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were recorded on a Bruker AC 250 NMR spectrometer (300 and 62.5 MHz for ^{1}H and ^{13}C, respectively); chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and refer to residual protium in the NMR solvent ($CHCl_3$: δ 7.26). Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, and/or multiple resonances), integration, and coupling constant in Hertz (Hz). Optical rotations were acquired on a Perkin Elmer-341 Digital Polarimeter. Melting points were recorded with a Kofler melting point apparatus and were uncorrected. High-performance liquid chromatography with Daicel Chiracel OD-H chiral column was used for the measurements (97:3 hexane/*i*-Pr_2O).

EXPERIMENTAL

3,4-Di-O-(p-Methoxybenzyl)-6-O-(2-Tetrahydropyranyl)-D-Glucal (−)-(7)

A solution of *trans* diol (+)-**6**[13] (1.18 g, 5.13 mmol) in anhydrous DMF (15 mL) was added dropwise at 0°C to a suspension of 60% NaH in

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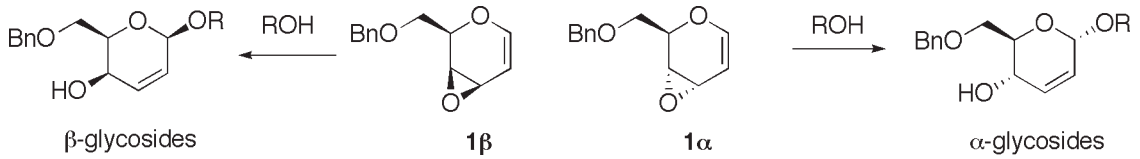


Scheme 1. Stereospecific glycosylation of alcohols by vinyl epoxides **1**α and **1**β.

paraffin (1.03 g, 25.6 mmol, 5.0 equiv) in anhydrous DMF (15 mL). After stirring at r.t. for 30 min, the suspension was cooled at 0°C and *p*-methoxybenzylchloride PMBCl (1.7 mL, 12.8 mmol, 2.5 equiv.) was added dropwise. The reaction mixture was allowed to warm to r.t. and stirred for 12 h. Dilution with Et_2O and evaporation of the washed (saturated aqueous NaCl) and dried ($MgSO_4$) organic solution afforded 3,4-di-*O*-*para*-methoxybenzyl (PMB)-derivative (−)-**7** (2.02 g, 84% yield), practically pure as a yellow oil, which was used in the next step without any further purification: R_f = 0.20 (8:2 hexane/ethyl acetate (AcOEt)); $[\alpha]_D^{20}$ −0.3 ($CHCl_3$, *c* 1.5). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.17–7.36 (m, 4H), 6.78–6.97 (m, 4H), 6.40 (ddd, 1H, *J* = 6.2, 3.1, and 1.3 Hz), 4.84 (ddd, 1H, *J* = 6.2, 2.7, 0.9 Hz), 4.55–4.82 (m, 2H), 4.77 (d, 1H, *J* = 10.8 Hz), 4.68 (d, 1H, *J* = 10.8 Hz), 4.49 (dd, 1H, *J* = 11.3 and 1.9 Hz), 4.13–4.22 (m, 1H), 3.95–4.12 (m, 2H), 3.65–3.93 (m, 3H), 3.80 (s, 6H), 3.42–3.55 (m, 1H), 1.41–1.92 (m, 6H). ^{13}C NMR (62.5 MHz, $CDCl_3$) (2 diastereoisomers) δ 159.4, 144.8, 130.6, 129.7, 129.6, 113.9, 100.2, 100.0, 99.4, 99.2, 75.8, 75.6, 74.3, 73.6, 73.5, 70.4, 62.5, 62.2, 55.5, 30.7, 25.6, 19.7, 19.5. Anal. Calcd for $C_{27}H_{34}O_7$: C, 68.92; H, 7.29. Found: C, 69.24; H, 7.55.

3,4-Di-O-(p-Methoxybenzyl)-D-Glucal (−)-(8)

3,4-Di-*O*-PMB-derivative (−)-**7** (2.0 g, 4.26 mmol) was dissolved in a (1.5:2:1) AcOH/THF/H_2O mixture (70 mL), and the reaction solution was stirred for 12 h at 50°C. After dilution with Et_2O and neutralization with solid $NaHCO_3$, evaporation of the washed (saturated aqueous $NaHCO_3$ and saturated aqueous NaCl) and dried organic solution afforded a crude solid product (2.35 g) consisting of primary alcohol (−)-**8**, which was purified by recrystallization from hexane/AcOEt (1.28 g, 78% yield), m.p. 67–69°C: R_f = 0.14 (7:3 hexane/AcOEt); $[\alpha]_D^{20}$ −21.7 ($CHCl_3$, *c* 0.6). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.21–7.32 (m, 4H), 6.84–6.92 (m, 4H), 6.39 (dd, 1H, *J* = 6.2, 1.2 Hz), 4.87 (dd, 1H, *J* = 6.2, 2.7 Hz), 4.78 (d, 1H, *J* = 11.1 Hz), 4.64 (d, 1H, *J* = 11.1), 4.60 (d, 1H, *J* = 11.1 Hz), 4.50 (d, 1H, *J* = 11.1 Hz), 4.16–4.22 (m, 1H), 3.87–3.96 (m, 1H), 3.82–3.86 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.76 (dd, 1H, *J* = 8.4, 6.5 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 159.5, 159.4, 144.6, 130.3, 130.2, 129.9, 129.6, 114.0, 100.4, 77.4, 75.3, 74.3, 73.5, 70.5, 62.0, 55.4. Anal. Calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.82; H, 6.53.

2-Formyl-3,4-Di-(p-Methoxybenzyloxy)-3,4-Dihydro-2H-Pyrane (9)

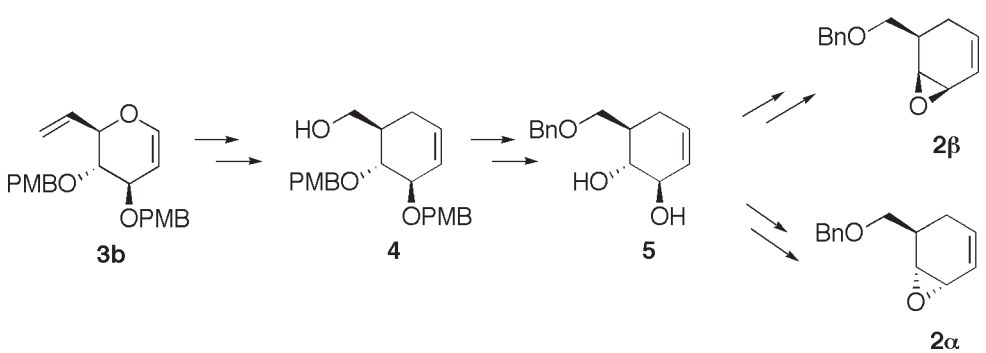
IBX (2.18 g, 7.77 mmol, 3.0 equiv)[12] was added to a solution of primary alcohol (−)-**8** (1.0 g, 2.59 mmol) in anhydrous CH_3CN (60 mL), and the reaction mixture was stirred at 45°C for 5 h. After cooling, the reaction mixture was filtered on a pad of Celite® that was further eluted with AcOEt. Evaporation of the solvent afforded aldehyde **9** (0.93 g, 94% yield), pure as an oil, which was used in the next step without any further purification: R_f = 0.22 (7:3 hexane/AcOEt); ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.53 (d, 1H, *J* = 0.6 Hz), 7.20–7.34 (m, 2H), 7.09–7.17 (m, 2H), 6.79–6.93 (m, 4H), 6.65 (d, 1H, *J* = 6.2 Hz), 5.00–5.09 (m, 1H), 4.62 (d, 1H, *J* = 11.7 Hz), 4.55 (d, 1H, *J* = 11.7 Hz), 4.51–4.59 (m, 1H), 4.29 (s, 2H), 4.01–4.06 (m, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.72–3.78 (m, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 198.9, 159.6, 159.5, 145.0, 129.7, 129.6, 129.4, 114.2, 114.0, 100.5, 79.4, 72.2, 71.6, 69.4, 66.9, 55.5. Anal. Calcd for $C_{22}H_{24}O_6$: C, 68.74; H, 6.29. Found: C, 69.02; H, 6.11.

1,5-Anhydro-Di-O-(p-Methoxybenzyl)-2,6,7-Trideoxy-D-arabino-Hept-1,6-Dienitol (+)-(3b)

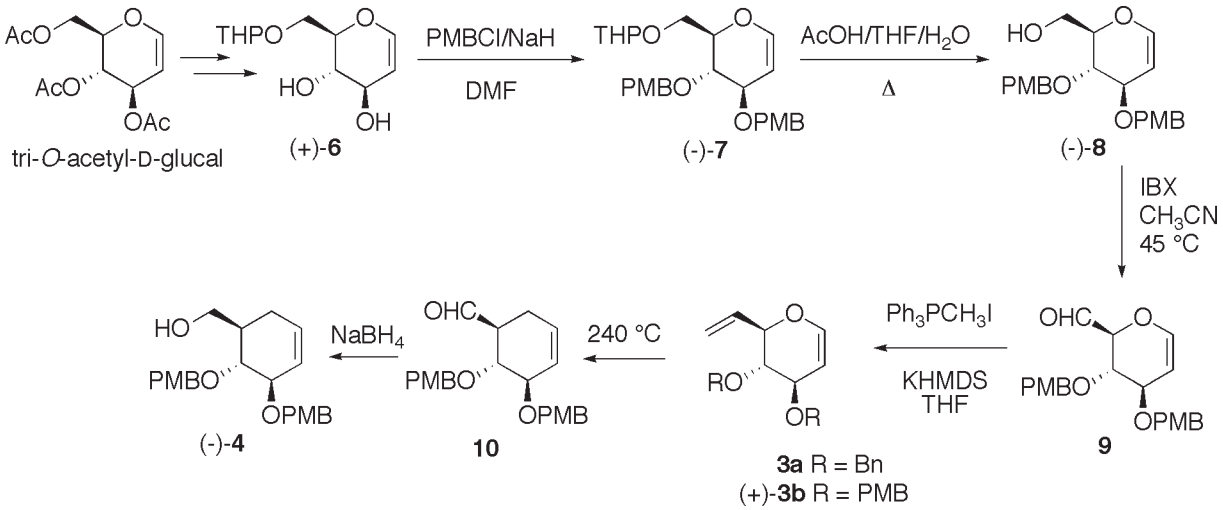
A solution 0.5*M* of KHMDS in THF (6.8 mL, 3.40 mmol, 1.4 equiv) was added dropwise to a solution of $Ph_3PMe^+I^-$ (1.47 g, 3.65 mmol, 1.5 equiv) in anhydrous THF (15 mL) at −78°C, and the mixture was stirred at the same temperature for 30 min and at 0°C for 1 h. After cooling at −78°C, a solution of aldehyde **9** (0.93 g, 2.43 mmol) in anhydrous THF (15 mL) was added dropwise, and the reaction mixture was stirred at r.t. for 5 h. Dilution with Et_2O and filtration on Fluorisil®-silica gel pad afforded an organic solution, which was washed (saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl) and dried. Evaporation of the organic solution afforded a crude product consisting of olefin (+)-**3b**, practically pure as a solid, m.p. 35–37°C (0.845 g, 91% yield): R_f = 0.43 (7:3 hexane/AcOEt); $[\alpha]_D^{20}$ +1.1 ($CHCl_3$, *c* 0.10). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.17–7.37 (m, 4H), 6.79–6.97 (m, 4H), 6.41 (d, 1H, *J* = 6.2 Hz), 6.03 (ddd, 1H, *J* = 17.2, 10.5 and 6.5 Hz), 5.41 (d, 1H, *J* = 17.2 Hz), 5.30 (d, 1H, *J* = 10.5 Hz), 4.85 (dd,1H, *J* = 6.2 and 2.7 Hz), 4.70 (d, 1H, *J* = 10.7 Hz), 4.60 (d, 1H, *J* = 10.7), 4.57 (d, 1H, *J* = 11.3 Hz), 4.51 (d, 1H, *J* = 11.3 Hz), 4.29 (t, 1H, *J* = 7.7 Hz), 4.12–4.20 (m, 1H), 3.80 (s, 6H), 3.56 (dd, 1H, *J* = 8.5 and 6.2 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 159.5, 159.4, 144.6, 134.6, 130.7, 130.4, 129.8, 129.5, 118.4, 113.9, 100.7, 78.2, 78.1, 75.3, 73.6, 70.6, 55.4. Anal. Calcd for $C_{23}H_{26}O_5$: C, 72.23; H, 6.85. Found: C, 72.82; H, 6.73.

3,4-Di-O-(p-Methoxybenzyl)-5a-Carba-D-Glucal (−)-(4)

Olefin (+)-**3** (0.50 g, 1.31 mmol) was dissolved in 1,3-dichlorobenzene (5 mL), and the mixture was stirred at 240°C for 20 min in AP 100 Silicone oil (Aldrich) warming bath. After cooling, the reaction mixture was added to a solution of $NaBH_4$ (0.075 g, 1.96 mmol, 6 equiv) in anhydrous 2:1 THF/EtOH (5 mL) and stirred at r.t. for 20 min. After dilution with CH_2Cl_2, evaporation of the washed (saturated aqueous NaCl) and dried



Scheme 2. Carba *trans* diol **5** as common synthetic intermediate of carba vinyl epoxide **2**α and **2**β.



Scheme 3. Synthesis of primary alcohol (−)-**4**.

organic solution, afforded primary alcohol (−)-**4** (0.483 g, 96% yield), pure as a solid, m.p. 46–48°C: R_f = 0.28 (1:1 hexane/AcOEt); $[\alpha]_D^{20}$ −14.6 ($CHCl_3$, *c* 0.52). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.19–7.39 (m, 4H), 6.80–6.95 (m, 4H), 5.62–5.81 (m, 2H), 4.91 (d, 1H, *J* = 11.0 Hz), 4.67 (d, 1H, *J* = 11.0 Hz), 4.66 (d, 1H, *J* = 11.2 Hz), 4.58 (d, 1H, *J* = 11.2 Hz), 4.15–4.25 (m, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.49–3.67 (m, 3H), 1.57–2.22 (m, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 159.5, 159.4, 130.6, 130.1, 129.7, 128.9, 128.2, 127.0, 126.2, 114.1, 114.0, 82.1, 81.1, 74.1, 71.2, 66.0, 55.4, 40.7, 28.2. Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 72.02; H, 7.43.

6-O-Benzyl-3,4-Di-O-(p-Methoxybenzyl)-5a-Carba-D-Glucal (+)-(11)

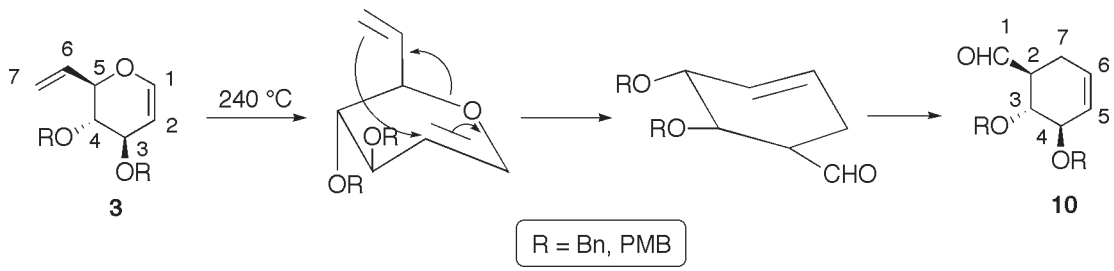
Primary alcohol (−)-**4** (0.483 g, 1.26 mmol) in anhydrous DMF (4 mL) was added dropwise at 0°C to a suspension of 60% NaH in mineral oil (0.15 g, 3.78 mmol, 3.0 equiv) in anhydrous DMF (4 mL), and the resulting reaction mixture was stirred at r.t. for 40 min. After cooling at 0°C, BnBr (0.37 mL, 3.15 mmol, 2.5 equiv) was added dropwise, and the mixture was stirred at r.t. for 2 h. Evaporation of the washed (saturated aqueous NaCl) and dried organic layer, afforded a crude mixture (0.631 g), which was subjected to flash chromatography. Elution with an 8:2 hexane/AcOEt mixture afforded monobenzyl-derivative **(+)-11**, pure as a liquid (0.567 g, 95% yield): R_f = 0.36 (8:2 hexane/AcOEt); $[\alpha]_D^{20}$ +2.9 ($CHCl_3$, *c* 0.83). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.15–7.40 (m, 9H), 6.80–6.92 (m, 4H), 5.61–5.81 (m, 2H), 4.81 (d, 1H, *J* = 10.5 Hz), 4.62 (s, 2H); 4.55 (d, 1H, *J* = 10.5 Hz), 4.50 (s, 2H), 4.10–4.21 (m, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.53–3.71 (m, 3H), 2.20–2.31 (m, 2H), 1.99–2.15 (m, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 159.3, 138.8, 138.4, 132.4, 132.2, 129.8, 129.6, 129.2, 128.9, 128.6, 127.9, 127.8, 127.6, 113.9, 81.0, 79.4, 74.2, 73.2, 71.3, 70.7, 55.5, 39.5, 29.0. Anal. Calcd for $C_{30}H_{34}O_5$: C, 75.92; H, 7.22. Found: C, 76.04; H, 7.53.

6-O-Benzyl-5a-Carba-D-Glucal (+)-(5)

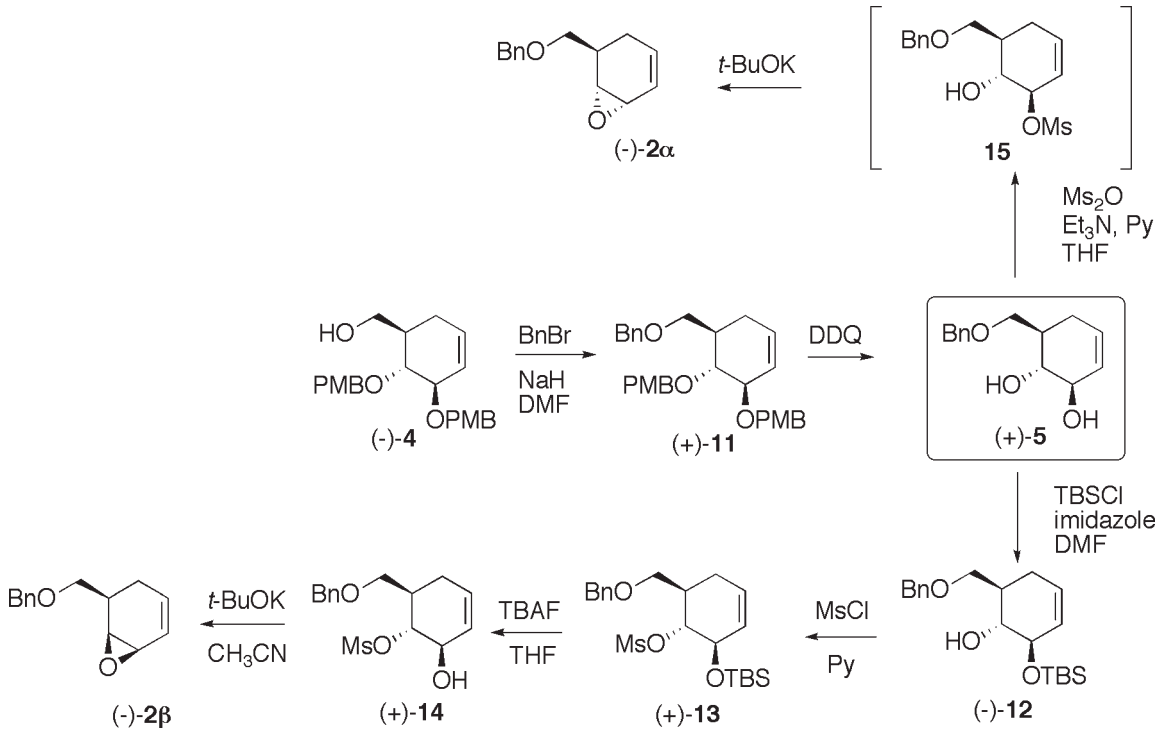
2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (0.405 g, 1.79 mmol, 1.5 equiv) was added at r.t. to a solution of benzyl derivative (+)-**11** (0.567 g, 1.19 mmol) in 18:1 CH_2Cl_2/H_2O mixture (34 mL) and the reaction solution was stirred at the same temperature for 3 h. After dilution with CH_2Cl_2, evaporation of the washed (saturated aqueous $NaHCO_3$ and saturated aqueous NaCl) and dried organic layer, afforded a crude product (0.35 g), which was subjected to flash chromatography. Elution with 1:1 hexane/AcOEt mixture afforded *trans* diol (+)-**5**, pure as a liquid (0.22 g, 79% yield): R_f = 0.18 (1:1 hexane/AcOEt); $[\alpha]_D^{20}$ +40.8 ($CHCl_3$, *c* 0.13). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.19–7.49 (m, 5H), 5.42–5.71 (m, 2H), 4.55 (s, 2H), 4.12–4.24 (m, 1H), 3.49–3.76 (m, 3H), 1.85–2.24 (m, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 137.8, 128.7, 128.5, 128.1, 127.9, 127.0, 77.4, 74.0, 73.7, 73.5, 38.4, 28.4. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 72.02; H, 7.43.

6-O-Benzyl-3-O-(t-Butyldimethylsilyl)-5a-Carba-D-Glucal (−)-(12)

A solution of *trans* diol (+)-**5** (3.35 g, 14.4 mmol) in anhydrous DMF (38 mL) containing imidazole (1.97 g, 28.88 mmol, 2.0 equiv) was treated at 0°C with TBSCl (2.60 g, 17.33 mmol, 1.2 equiv), and the reaction mixture was stirred at r.t. for 48 h. Dilution with Et_2O and evaporation of the washed (saturated aqueous NaCl) and dried organic solution afforded a crude product (4.93 g, 98% yield) consisting of *O-tert*-butyl-dimethylsilyl (TBS)-derivative (−)-**12**, practically pure as a liquid, which was used in the next step without any further purification: R_f = 0.69 (1:1 hexane/AcOEt); $[\alpha]_D^{20}$ −8.6 ($CHCl_3$, *c* 0.43). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.23–7.40 (m, 5H), 5.58–5.68 (m, 1H), 5.43–5.51 (m, 1H), 4.57 (d, 1H, *J* = 12.3 Hz) 4.51 (d, 1H, *J* = 12.3 Hz), 4.12–4.20 (m, 1H), 3.50–3.68 (m, 3H), 1.88–2.35 (m, 3H), 0.92 (s, 9H), 0.12 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 138.4, 129.7, 128.5, 127.7, 126.9, 75.6, 75.1, 73.5,



Scheme 4. Claisen rearrangement of glucal (+)-**3** into carba system **10**.



Scheme 5. Stereodivergent synthesis of vinyl epoxides (−)-**2**α and (−)-**2**β from *trans* diol (+)-**5**.

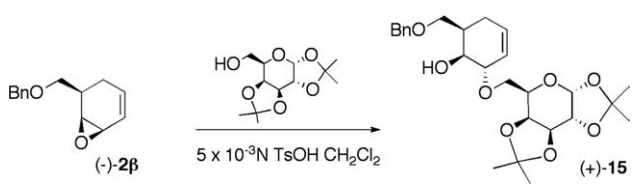
72.4, 38.8, 28.8, 26.0, 18.3, −4.2, −4.3. Anal. Calcd for $C_{20}H_{32}O_3Si$: C, 71.77; H, 7.74. Found: C, 72.02; H, 7.43.

6-O-Benzyl-3-O-(t-Butyldimethylsilyl)-4-O-Mesyl-5a-Carba-D-Glucal (+)-(13)

A solution of alcohol (−)-**12** (2.46 g, 7.08 mmol) in an 1:1 anhydrous pyridine/CH_2Cl_2 mixture (16 mL) was treated at 0°C with MsCl (1.1 mL, 14.16 mmol, 2 equiv), and the reaction mixture was stirred 12 h at the same temperature. Dilution with Et_2O and evaporation of the washed (10% aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl) and dried organic solution afforded a crude product (2.89 g, 96% yield) consisting of mesylate (+)-**13**, practically pure, as a solid, which was used in the next step without any further purification, m.p. 144–146°C: R_f = 0.14 (9:1 hexane/AcOEt); $[\alpha]_D^{20}$ +16.8 ($CHCl_3$, *c* 0.44). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.28–7.40 (m, 5H), 5.64–5.82 (m, 1H), 5.51 (dd, 1H, *J* = 10.0 and 1.7 Hz), 4.64 (dd, 1H, *J* = 8.7 and 6.5 Hz), 4.51 (s, 2H), 4.32–4.44 (m, 1H), 3.66 (dd, 1H, *J* = 9.4 and 3.7 Hz), 3.55 (dd, 1H, *J* = 9.4 and 6.4 Hz), 3.04 (s, 3H), 2.04–2.49 (m, 3H), 0.91 (s, 9H), 0.12 (s, 3H) 0.07 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 137.5, 129.7, 128.7, 127.9, 127.4, 126.0, 75.2, 73.6, 72.9, 72.0, 38.2, 33.6, 25.8, 24.0, 18.5, −5.1, −5.2. Anal. Calcd for $C_{21}H_{34}O_5SSi$: C, 59.12; H, 8.03. Found: C, 59.50; H, 7.81.

6-O-Benzyl-4-O-Mesyl-5a-Carba-D-Glucal (+)-(14)

A solution of mesylate (−)-**13** (4.20 g, 9.56 mmol) in anhydrous THF (315 mL) was treated at 0°C with 1*M* tetrabutylammonium fluoride (TBAF) in THF (9.56 mL, 9.56 mmol, 1.0 equiv). After 2 h stirring at the same temperature, dilution with Et_2O and evaporation of the washed (saturated aqueous NaCl) and dried organic solution afforded a crude product consisting of *trans* hydroxy mesylate (+)-**14** which was subjected to flash chromatography. Elution with a 6:4 hexane/AcOEt mixture afforded *trans* hydroxy mesylate (+)-**14** (2.12 g, 71% yield), pure as a liquid: R_f = 0.22 (6:4 hexane/AcOEt); $[\alpha]_D^{20}$ +19.3 ($CHCl_3$, *c* 0.53). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.27–7.40 (m, 5H), 5.67–5.78 (m, 1H), 5.52–5.60 (m, 1H), 4.70 (dd, 1H, *J* = 10.7 and 7.6 Hz), 4.54 (d, 1H, *J* = 11.8 Hz), 4.47 (d, 1H, *J* = 11.8 Hz), 4.37–4.45 (m, 1H), 3.63 (dd, 1H *J* = 9.5 and 4.7 Hz), 3.57 (dd, 1H *J* = 9.5 and 3.2 Hz), 3.11 (s, 3H), 2.14–2.38 (m, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 138.2, 128.5, 127.8, 127.7, 127.6, 127.4, 85.7, 73.4, 71.5, 69.8, 38.5, 38.1, 29.0. Anal. Calcd for $C_{15}H_{20}O_5S$: C, 57.67; H, 6.45. Found: C, 58.01; H, 6.09.



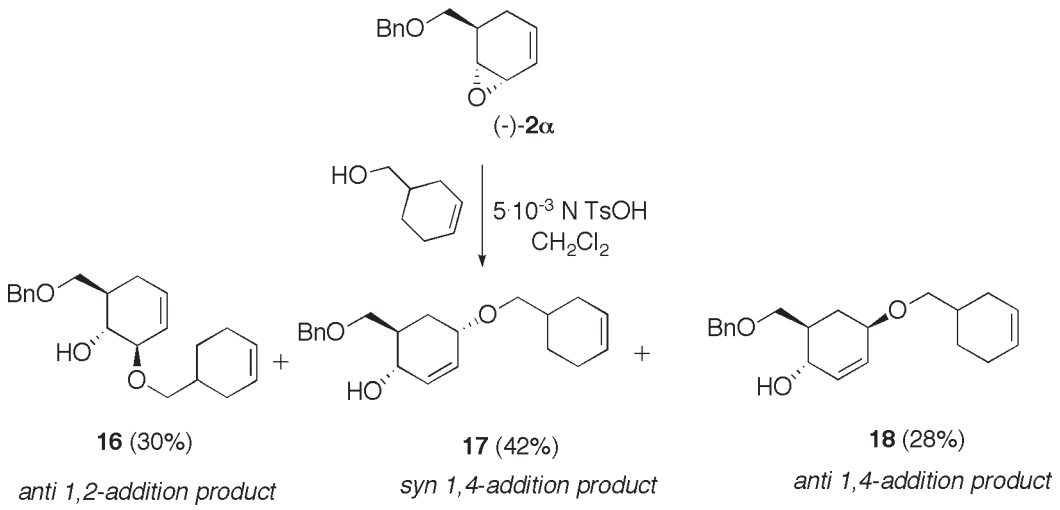
Scheme 6. Reaction of epoxide (−)-**2**β with1,2;3,4-di-*O*-isopropyliden-α-D-galoctopyranose.

6-O-Benzyl-3,4-Anhydro-5a-Carba-D-Galactal (−)-(2β)

A solution of *trans* hydroxy mesylate (+)-**14** (1.06 g, 3.40 mmol) in anhydrous benzene (65 mL) was treated with *t*-BuOK (0.381 g, 3.40 mmol, 1.0 equiv), and the resulting reaction mixture was stirred 4 h at room temperature. Dilution with Et_2O and evaporation of the filtered organic solution afforded a crude product consisting of epoxide (−)-**2**β (0.631 g, 99% yield) practically pure, as a liquid: R_f = 0.40 (8:2 hexane/AcOEt); $[\alpha]_D^{20}$ −3.9 ($CHCl_3$, *c* 0.13). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.28–7.41 (m, 5H), 5.87–6.02 (m, 2H), 4.62 (d, 1H, *J* = 12.0 Hz), 4.55 (d, 1H, *J* = 12.0 Hz), 3.52–3.70 (m, 3H), 3.28–3.33 (m, 1H), 2.02–2.27 (m, 2H), 1.70–1.84 (m, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 138.4, 132.7, 128.5, 127.7, 123.2, 73.4, 73.0, 56.5, 47.8, 33.7, 24.7. Enantiomeric excess (*ee*) >99%. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.86; H, 7.31.

6-O-Benzyl-3,4-Anhydro-5a-Carba-D-Allal (−)-(2α)

Et_3N (70.0 μL, 0.553 mmol, 6.5 equiv), Py (1.0 μL, 0.01 mmol), and a solution of Ms_2O (0.015 g, 0.085 mmol, 1.0 equiv) in anhydrous THF (0.5 mL) were successively added to a solution of *trans* diol (+)-**5** (0.020 g, 0.085 mmol) in anhydrous THF (0.5 mL) at 0°C, and the reaction mixture was stirred at the same temperature for 30 min. The completeness of the mesylation was monitored by TLC analysis and after that, the mixture was treated in situ with *t*-BuOK (0.019 g, 0.170 mmol, 2.0 equiv) and stirred at r.t. for 2 h. Dilution with CH_2Cl_2 and evaporation of the fil-



Scheme 7. Reaction of epoxide (−)-**2**α with 3-cyclohexene-1-methanol.

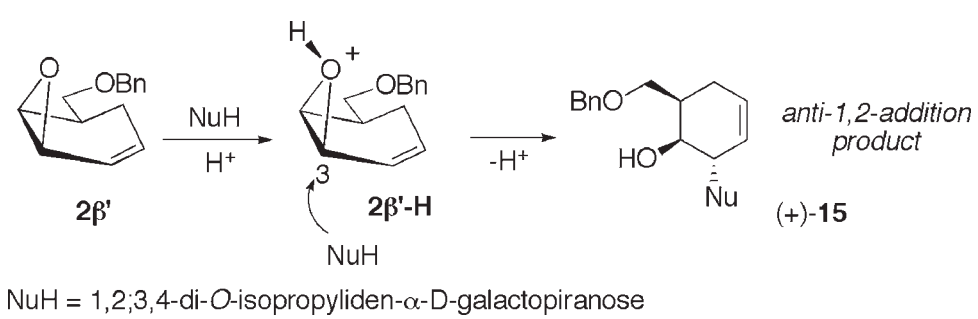
tered organic solution afforded a crude reaction product (0.020 g) consisting of epoxide (−)-**2**α together with a small amount (3%) of the di-*O*-mesyl derivative of the starting diol **5** (^{1}H NMR). The crude product was subjected to flash chromatography. Elution with an 8:2 hexane/AcOEt mixture afforded epoxide (−)-**2**α (0.15 g, 82% yield), pure as a liquid: R_f= 0.39 (8:2 hexane/AcOEt); $[\alpha]_D^{20}$ −1.5 ($CHCl_3$, *c* 0.11). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.28–7.40 (m, 5H), 5.84–5.97 (m, 1H), 5.71–5.82 (m, 1H), 4.52 (s, 2H), 3.42–3.51 (m, 1H), 3.45 (dd, 1H, *J* = 9.0 and 7.1 Hz), 3.35 (dd, 1H, *J* = 9.0 and 7.6 Hz), 3.19 (td, 1H, *J* = 4.0 and 1.7 Hz), 2.61–2.78 (m, 1H), 2.13–2.29 (m, 1H), 1.95–2.11 (m, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 138.3, 131.1, 128.5, 127.8, 127.7, 123.2, 73.3, 70.3, 56.3, 46.8, 31.9, 23.9. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.71; H, 7.23.

Reaction of Epoxide (−)-2β with 1,2;3,4-Di-O-(Isopropyliden)-D-Galactal Under 0.005 N TsOH·H_2O/CH_2Cl_2 Protocol

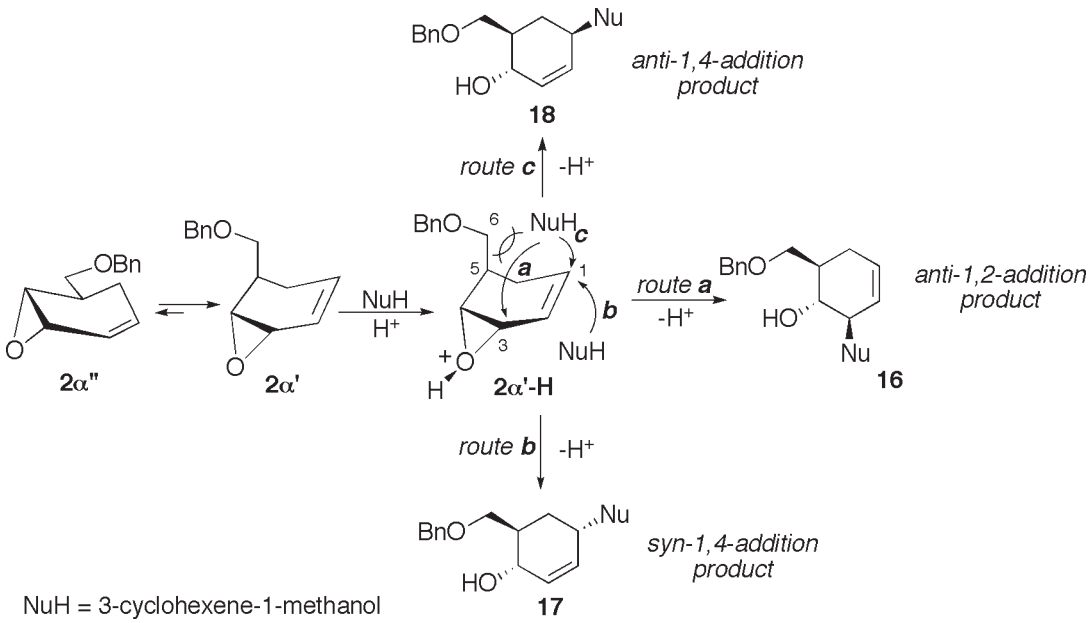
Epoxide (−)-**2**β (0.014 g, 0.065 mmol) was added to a solution of 1,2;3,4-di-*O*-(isopropyliden)-D-galactal (0.101 g, 0.39 mmol, 6.0 equiv), TsOH·H_2O (0.0012 g, 0.006 mmol, 0.1 equiv) in anhydrous CH_2Cl_2 (0.44 mL) [epoxide:1,2;3,4-di-(*O*-isopropyliden)-D-galactal:TsOH·H_2O = 1:6:0.05), and the reaction mixture was stirred at r.t. for 2 h. After dilution with CH_2Cl_2, solid $NaHCO_3$ was added and stirring was prolonged for 15 min. Evaporation of the washed (saturated aqueous NaCl) and filtered organic solution afforded a crude reaction product (0.069 g), consisting of corresponding *anti*-1,2-addition product **15** (Scheme 6) and the excess of 1,2;3,4-di-*O*-(isopropyliden)-D-galactal, which was subjected to preparative TLC (an 8:2 hexane/*i*-Pr_2O mixture was used as the eluant). Extraction of the more intense band afforded (+)-3-*O*-[6-(1,2:3,4-di-*O*-isopropyliden-α-D-galactopyranosyl)]-6-*O*-benzyl-5a-carba-D-gulal (**15**) (*anti*-1,2-addition product) (0.030 g, 87% yield), pure as a yellow oil: R_f= 0.16 (8:2 hexane/*i*-Pr_2O); $[\alpha]_D^{20}$ +4.4 ($CHCl_3$, *c* 0.52). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.27–7.40 (m, 5H), 5.89 (dt, 1H, *J* = 10.6, 3.9 Hz), 5.68–5.78 (m, 1H), 5.52 (d, 1H, *J* = 5.1 Hz), 4.62 (dd, 1H, *J* = 5.9, 2.4 Hz), 4.53 (s, 2H), 4.34 (dd, 1H, *J* = 5.4 and 2.4 Hz), 4.18–4.28 (m, 1H), 4.03–4.10 (m, 1H), 3.58–3.38 (m, 6H), 1.90–2.28 (m, 3H), 1.50 (s, 3H), 1.43 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 138.2, 130.5, 128.6, 127.9, 127.8, 124.6, 109.4, 108.8, 96.5, 73.6, 72.2, 71.8, 71.2, 70.9, 70.8, 68.2, 68.1, 66.1, 35.4, 29.9, 26.2, 26.0, 25.4, 24.7. Anal. Calcd for $C_{26}H_{36}O_8$: C, 65.53; H, 7.61. Found: C, 65.71; H, 7.25.

Reaction of Epoxide (−)-2α with 3-Cyclohexene-1-Methanol Under 0.005 N TsOH·H_2O/CH_2Cl_2 Protocol

Epoxide (−)-**2**α (0.030 g, 0.139 mmol) was added to a solution of 3-cyclohexene-1-methanol (0.050 mL, 0.417 mmol, 3.0 equiv) in CH_2Cl_2 (1.4 mL) containing TsOH·H_2O (1.3 mg, 0.007 mmol, 0.05 equiv) (epoxide:3-cyclohexene-1-methanol:TsOH·H_2O = 1:3:0.05), and the reaction mixture was stirred at r.t. for 20 h. After dilution with CH_2Cl_2, solid $NaHCO_3$ was added, and stirring was prolonged for 15 min. Evaporation of the washed (saturated aqueous NaCl) and filtered organic solution afforded a crude reaction product (0.069 g) consisting of a 30:28:42 mixture of corresponding *anti*-1,2-addition product **16**, *anti*-1,4-addition product **18**, and *syn*-1,4-addition product **17** (Scheme 7) in the presence of an excess of 3-cyclohexene-1-methanol. The reaction mixture was dissolved in anhydrous pyridine (1.5 mL) and treated at 0°C with Ac_2O (0.5 mL), and the resulting reaction mixture was stirred at r.t. for 16 h. Dilution with toluene and evaporation of the organic solvent afforded a crude reaction product (0.086 g), which was subjected to preparative TLC (an 8:2 hexane/*i*-Pr_2O mixture was used as the eluant). Extraction of the two more intense bands (the slower moving band contained **17-Ac**) afforded an unseparable mixture of *anti*-1,2-addition product **16-Ac** and *anti*-1,4-addition product **18-Ac** (0.011 g) and 3-cyclohexenemethyl 6-*O*-benzyl-4-*O*-acetyl-5a-carba-α-D-*threo*-hex-2-enopyranoside (**17-Ac**; *syn*-1,4-addition product; 0.010 g, 19% yield), as a liquid: R_f = 0.17 (8:2 hexane/*i*-Pr_2O); ^{1}H NMR (250 MHz, $CDCl_3$) δ



Scheme 8. Rationalization of 1,2-regioselectivity observed with epoxide (−)-**2**β.



Scheme 9. Rationalization of regioselective result in nucleophilic addition reaction with epoxide (−)-**2**α.

7.35–7.27 (m, 5H), 5.99–5.88 (m, 1H), 5.76 (dd, 1H, J = 9.8, 2.0 Hz), 5.66 (br s, 2H), 5.30–5.20 (m, 1H), 4.53 (d, 1H, J = 12.0 Hz), 4.44 (d, 1H, J = 12.0 Hz), 3.83–3.73 (m, 1H), 3.52–3.25 (m, 4H), 2.36–2.19 (m, 1H), 2.10–2.00 (m, 4H), 1.99 (s, 3H), 1.53–1.92 (m, 3H), 1.11–1.36 (m, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.1, 138.6, 130.1, 128.5, 127.9, 127.8, 127.3, 126.2, 74.3, 74.2, 73.5, 73.2, 70.8, 70.7, 70.5, 35.2, 34.3, 29.1, 28.7, 25.9, 24.8, 21.4. Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.94; H, 7.89.

RESULTS AND DISCUSSION

The first part of the synthesis of epoxides **2**α and **2**β is centered on the previously described Claisen rearrangement of a suitable allyl-vinyl ether to transform a glycal system into a corresponding carbaglycal system.[11] The 3,4-di-*O*-benzyl-protected glycal **3a**, originally used by Sudha and Nagarajan to effect this transformation,[11] was not appropriate to our synthetic approach which needed the presence of a 3,4-di-*O*-protection easily removable without affecting the double bond. Our choice fell on the *p*-methoxybenzyl protective group, whose removal (DDQ/CH_2Cl_2/H_2O) is notoriously compatible with the presence of an unsaturation. As a consequence, the new allyl-vinyl ether (+)-**3b** was synthesized starting from tri-*O*-acetyl-D-glucal (Scheme 3). Following a previously described procedure,[13] tri-*O*-acetyl-D-glucal was transformed into *O*-tetrahydropyran (THP)-protected *trans* diol (+)-**6**, which was subsequently alkylated (PMBCl/NaH/DMF, room temperature protocol) to the corresponding 3,4-di-*O*-(*p*-methoxybenzyl)-glucal (−)-**7**.

Deprotection of acetal (−)-**7** with 1.5:2:1 AcOH/THF/H_2O mixture at 50°C afforded the 3,4-di-*O*-(PMB)-protected primary alcohol (−)-**8** in good yield (78%) after recrystallization from hexane/AcOEt. Attempts made to prepare alcohol (−)-**8** by (*i*) regioselective monosilylation of the primary hydroxy group of D-glucal, followed by *O*-PMB alkylation of the residual secondary hydroxy functionalities and C(6) deprotection[14] or (*ii*) a regioselective C(6)-*O*-PMB deprotection (trimethylsilyl iodide (TMSI)/Et_3N)[15] of the fully *O*-PMB protected D-glucal were unfortunately unsuccessful.

Alcohol (−)-**8** was oxidized to aldehyde **9** by a very clean reaction with freshly prepared IBX[12] in CH_3CN at 45°C. It is worth noting that performing the oxidation reaction at a temperature higher than 45°C, the easy oxidation of the benzylic carbon of the *p*-methoxybenzyl group determined the formation of consisting amounts (more than 30%) of the corresponding *p*-methoxybenzaldehyde. Application of the previously described Wittig C_1-extension protocol ($Ph_3P^+CH_3I^-$/KHMDS/THF) to aldehyde **9**[11] afforded glycal-derived olefin (+)-**3b** in a high yield (91%).

Glycal (+)-**3b**, differing from **3a** only for the type of protecting groups, was subjected with success to the known thermal Claisen rearrangement (250°C)[11] to give γ,δ-unsaturated aldehyde **10**. In accordance with the seminal paper,[11] in this process, depicted in Scheme 4, the aldehydic C(1)-carbon of compound **10** derives from vinyl C(1)-carbon of the endocyclic double bond of glycal **3**. Aldehyde **10** turned out to be unstable, and therefore, it was immediately subjected to $NaBH_4$ reduction to alcohol (−)-**4** without any further purification (Scheme 3).

Alcohol (−)-**4** was easily benzylated by BnBr/NaH protocol to give the completely protected carbaglucal derivative (+)-**11** (Scheme 5). Due to the presence of orthogonal *O*-Bn and *O*-PMB protecting groups on the primary and secondary hydroxy groups, respectively, compound (+)-**11** appears to be a very useful substrate for further selective functionalization of the carba glucal skeleton.

As expected, the removal of the C(3)- and C(4)-*O*-PMB groups of (+)-**11** with DDQ did not affect the double bond of the carba glycal system and afforded C(6)-*O*-Bn protected *trans* diol (+)-**5**, a useful precursor of both chiral vinyl epoxides (−)-**2**α and (−)-**2**β (Scheme 5).

The elaboration of *trans* diol (+)-**5** into enantiopure epoxide (−)-**2**β was carried out by a stereoselective application of our recently described racemic protocol.[16] Following this procedure, *trans* diol (+)-**5** was selectively protected at the secondary allyl hydroxy group by TBSCl (1 equiv) with formation of the corresponding *O*-TBS derivative (−)-**12**, subsequently mesylated (MsCl/Py) at the residual secondary

hydroxyl group with the formation of mesylate (+)-**13**. Deprotection of (+)-**13** with TBAF/THF provided *trans* hydroxy mesylate (+)-**14** that, under basic conditions (*t*-BuOK), gave the desired epoxide (−)-**2**β [62% overall yield from *trans* diol (+)-**5**, four steps]. On the other hand, due to the known high reactivity and instability of the secondary aliphatic allylic mesylates,[17] *trans* diol (+)-**5** was transformed into allylic mesylate **15** with 1 equiv of Ms_2O at 0°C, and then, directly cyclized in situ, upon addition of *t*-BuOK, to give enantiopure epoxide (−)-**2**α, accompained by only a small amount (3%) of the di-*O*-mesylate of the starting *trans* diol (+)-**5**. Easy separation by flash chromatography (hexane/EtOAc 8:2 as the eluant) afforded epoxide (−)-**2**α as a pure enantiomer [82% yield from *trans* diol (+)-**5**].

Enantiopure vinyl epoxides (−)-**2**α and (−)-**2**β were then tested as pseudoglycosyl donors in nucleophilic addition reactions with two nucleophiles such as 1,2;3,4-di-*O*-isopropyliden-α-D-galoctopyranose and 3-cyclohexene-1-methanol, which were used as *O*-nucleophile models for the possible synthesis of mixed or homogenous carba disaccharides.

In accordance with the results obtained with racemic epoxides **2**α and **2**β, [16] the reaction of enantiopure epoxide (−)-**2**β with 1,2;3,4-di-*O*-isopropyliden-α-D-galoctopyranose (6 equiv) in 5×10^{-3} N TsOH in CH_2Cl_2, afforded, through a complete 1,2-regio- and *anti*-stereoselective process, the 3-*O*-(6-galactopyranosyl)-carba gulal (+)-**15** (*anti*-1,2-addition product), as the only reaction product (Scheme 6).

Conversely, the reaction of diastereoisomeric enantiopure vinyl epoxide (−)-**2**α with 3-cyclohexene-1-methanol (3 equiv) under acidic conditions (5×10^{-3} N TsOH in CH_2Cl_2), was not regio- and stereoselective affording a crude reaction mixture constituted by the *anti*-1,2-addition product **16**, together with the regioisomeric *syn*-**17** and *anti*-1,4-addition product **18** in a 30:42:28 ratio (Scheme 7). Separation of this mixture by preparative TLC afforded pure *syn*-1,4-addition products **17**, whereas the remaining *anti*-1,2-addition product **16** and *anti*-1,4-addition product **18** were still obtained as a mixture. It is worth noting that the structure of the purified addition product **17** corresponds to that of an homogenous simplified α-*O*-linked-1,6-carba-disaccharide (Scheme 7). Efforts will be made to have separated pure addition products **16** and **18**, the regio- and diastereoisomer of **17**, respectively.

The different regioselectivity observed in the reaction of chiral epoxide (−)-**2**α and (−)-**2**β with the selected *O*-nucleophile models, can be due to different conformational and streoelectronic effects involved in the ring opening reactions of these oxirane systems under acidic conditions. In epoxide (−)-**2**β, reacting through the only existing conformer **2**β′,[16] the nucleophilic attack on C(3) corresponds to a *trans* diaxial ring opening that is not hindered by any unfavorable steric effect and then allows to obtain (+)-**15** as the only reaction product (Scheme 8).

In diastereoisomeric epoxide (−)-**2**α a corresponding *trans* diaxial opening, possible only through the more stable conformer **2**α′, is not particularly favored due to the presence of a 1,3-*syn* diaxial interaction between the attacking nucleophile and the C(5)—C(6) bond of the side chain. In these conditions, regioisomeric nucleophilic attack on vinyl C(1) carbon, from α and β face, to give the addition products **17** and **18**, respectively (1,4-addition), can be competitive to the point of becoming the main addition process (Scheme 9).

In summary, we have developed a stereodivergent synthesis of vinyl epoxides (−)-**2**α and (−)-**2**β using tri-*O*-acetyl-D-glucal as the starting material and *trans* diol (+)-**5** as the pivotal synthetic intermediate. The key step of the synthesis is constituted by the well-known Claisen thermal rearrangement of a sugar to a pseudosugars[11] applied, in the present case, to 3,4-di-*O*-PMB-D-glucal derivative (+)-**3b**, the allyl vinyl ether which turned out to be appropriate for this transformation and the prosecution of the synthetic protocol. The reaction of epoxide (−)-**2**α with a model *O*-nucleophile, under acidic conditions, gives consistent amounts of the corresponding *syn*- and *anti*-1,4-addition products, having an α- and β-*O*-linked-1,6-carba disaccharide structure. This result makes epoxide (−)-**2**α a useful candidate for the construction of *O*-linked carba oligosaccharides and represents a potentially new synthetic tool to carbasugars synthesis.

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