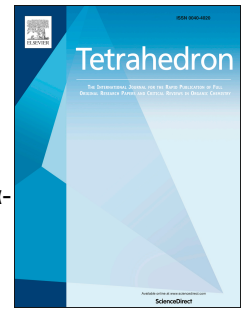
Accepted Manuscript



Allylic Strain as a Stereocontrol Element in the Hydrogenation of 3-Hydroxymethyl-cyclohex-3-en-1,2,5-triol Derivatives. Synthesis of the Carbasugar Pseudo-2-deoxy-α-D-glucopyranose

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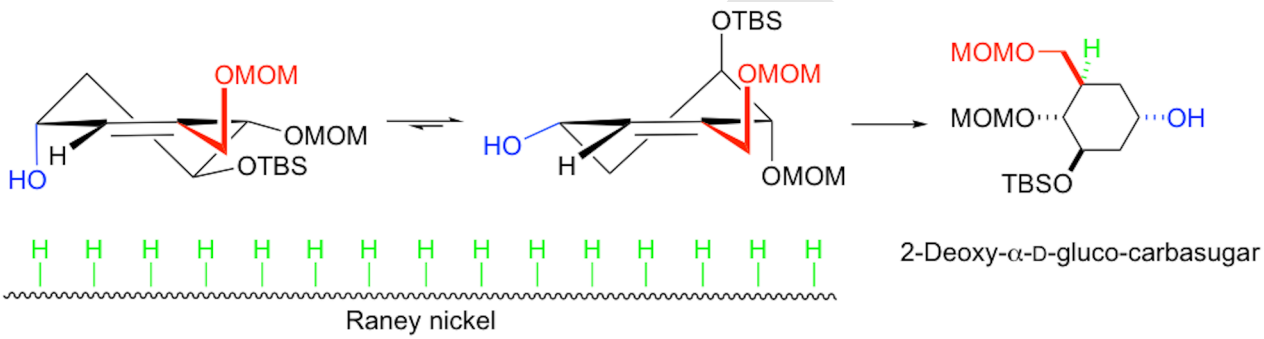

Allylic Strain as a Stereocontrol Element in the Hydrogenation of 3-Hydroxymethyl-cyclohex-3-en-1,2,5-triol Derivatives. Synthesis of the Carbasugar Pseudo-2-deoxy-α-D-glucopyranose.

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Abstract

By adaptation of a literature method developed in the glucose series and standard protecting group manipulations a 2-deoxy-D-glucose derivative is converted to a series of 1*R*,2*R*,5*R*-3-hydroxymethyl-cyclohexen-1,2,5-triol derivatives whose reduction to the corresponding diastereomeric D-gluco and L-ido-2-deoxy carbasugars is studied. When the hydroxymethyl group is tied up in a cyclic isopropylidene acetal with the adjacent 6-hydroxy group the *cis*-fused products with the ido-configuration are formed preferentially whereas protection of the hydroxymethyl group as a methoxymethyl ether results in the formation of the D-gluco isomer on hydrogenation over Raney nickel. This result is rationalized in terms of the minimization of allylic strain in the course of the reduction, enables the preparation of the carbasugar pseudo-2-deoxy-α-D-glucopyranose, and suggests that the conformation of the side chain is an important control element in the chemistry of the pseudosugars as it is in the sugars themselves.

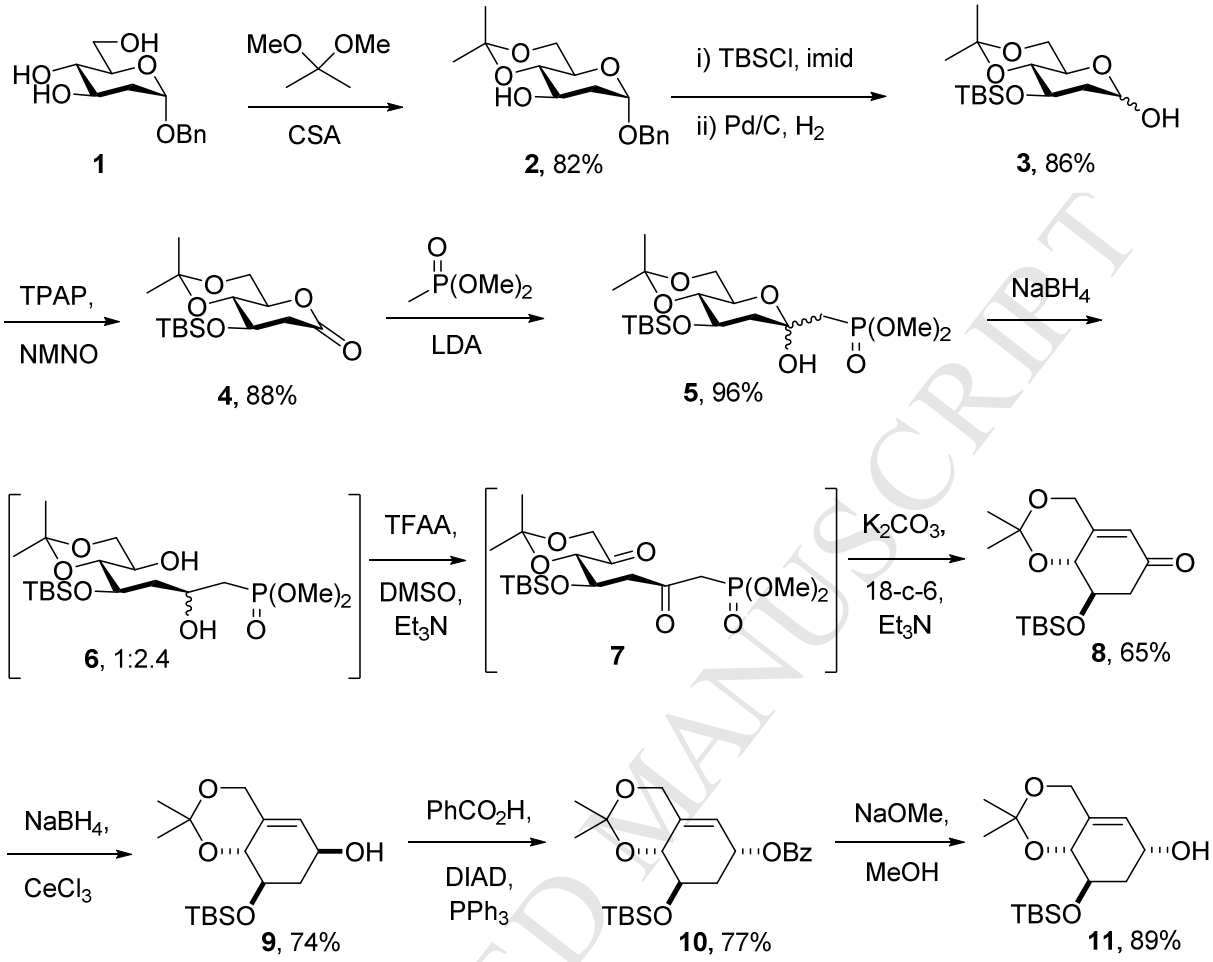
Introduction

In the course of an ongoing investigation into the synthesis of a series of carbacyclic sugar analogs[1-2] and their conjugates, we had occasion to prepare and study the catalytic hydrogenation of derivatives of 1*R*,2*R*,5*R*-3-hydroxymethyl-cyclohexen-1,2,5-triol. We report on the manner in which the facial selectivity of the hydrogenation reaction, affording diastereomeric carbasugars with either the D-gluco or L-ido configurations, varies as a function of the manner in which the hydroxymethyl group is

protected. We demonstrate that selectivity for the gluco isomer is optimal in a monocyclic system with the hydroxymethyl protected as a MOM ether, which we attribute to the minimization of allylic strain in the transition state for hydrogenation. This reduction enables the completion of the first synthesis of the carbasugar, pseudo-2-deoxy-α-D-glucose.

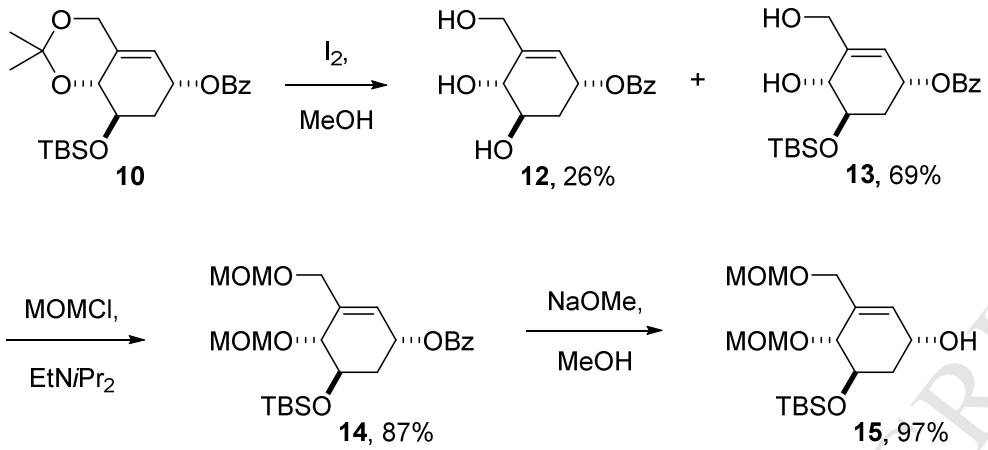
Results

Adapting a protocol described by Shing and coworkers for the synthesis of the gabosines and related compounds from gluconolactone,[3-5] benzyl 2-deoxy-α-D-gluopyranoside **1**[6] was treated with 2,2-dimethoxypropane in DMF at room temperature in the presence of camphor-10-sulfonic acid, resulting in the formation of the isopropylidene derivative **2** in 82% yield. Silylation with *tert*-butyldimethylsilyl chloride and imidazole in DMF was followed by hydrogenolysis of the benzyl glycoside to give 86% of the lactol **3** in the form of a mixture of anomers. Oxidation with catalytic tetrapropylammonium perruthenate and *N*-methyl-morpholine *N*-oxide[7] then afforded 88% of the lactone **4**, which on treatment with dimethyl methylphosphonate and LDA in THF at -78 ^{o}C provided the ketose **5** in 96% yield in the form of a single unassigned anomer, presumably with the equatorial phosphonate group. Reduction with sodium borohydride in THF have a diol **6** as an unassigned 1:2.4 mixture of anomers that was immediately oxidized by the Swern protocol to give a dione **7** that, on stirring with potassium carbonate and 18-crown-6 in toluene, was transformed to the enone **8** in 65% overall yield from **5**. The reduction of **5** to **6**, followed by reoxidation was necessary as attempted direct conversion of **5** to the enone **8** by the Swern protocol resulted only in the formation of elimination products. Luche reduction[8] of **8** gave 74% of allylic alcohol **9**, which was converted to the ester **10** in 77% yield by Mitsunobu inversion,[9] and finally to the epimeric alcohol **11** in 89% yield on exposure to sodium methoxide in methanol (Scheme 1).



Scheme 1. Synthesis of Enone **8** and Allylic Alcohol **11**

Exposure of **10** to iodine in methanol at room temperature afforded the triol **12** in 26% yield along with the desired monosilyl ether **13** in 69% yield. The same transformation could also be effected by stirring a methanolic solution of **10** with Amberlyst 15 acidic resin when **12** and **13** were isolated in 25 and 64% yield, respectively. Reaction of **13** with methoxymethyl chloride in the presence of Hünig's base then afforded 87% of the bis(methoxymethyl) ether **14**, from which the ester was removed with sodium methoxide to give the allylic alcohol **15** in 97% yield (Scheme 2).

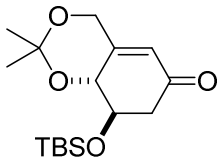
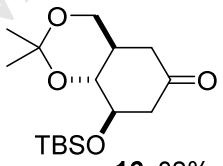
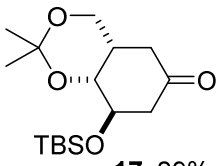
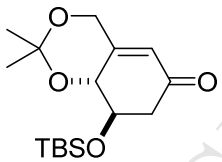
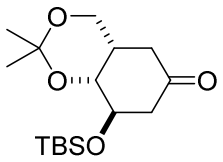
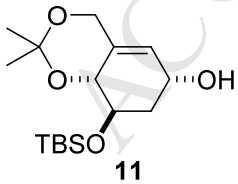
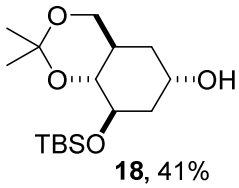
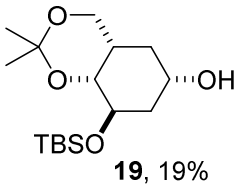


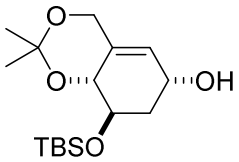
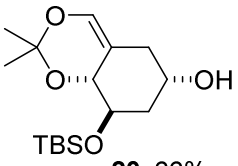
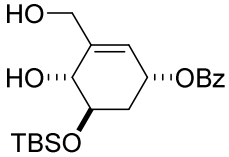
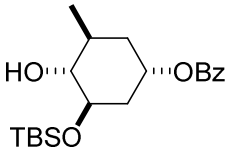
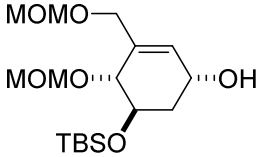
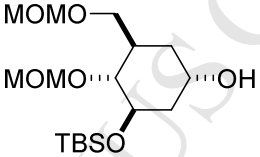
Scheme 2. Preparation of Allylic Alcohol **15**

Exposure of enone **8** to 1 atmosphere of hydrogen in THF at room temperature resulted in the formation of an approximately 1.1:1 mixture of the *trans*- and *cis*-fused ketones **16** and **17** as judged by NMR spectroscopy of the crude reaction mixture, from which the individual compounds were isolated in 32 and 29% yield, respectively (Table 1, entry 1). Reduction of **8** by stirring with phenylsilane in the presence catalytic hexakis(triphenylphosphino)copper hydride[10-11] in toluene at room temperature for 3 days gave 30% of the *cis*-fused product **17** and 47% of the recovered substrate, with no indication of the formation of the *trans*-fused isomer **16** from the NMR spectra of the crude reaction mixture (Table 2, entry 2). Hydrogenation of the allylic alcohol **11** was attempted under multiple conditions, mostly resulting in relatively complex reaction mixtures contained products derived from saturation of the alkene, deoxygenation, loss of the acetonide, and combinations of these transformations as judged by mass spectrometry. The only relatively clean reaction mixture arose from stirring of **11** in aqueous ethanol under one atmosphere of hydrogen pressure in the presence of Raney nickel, resulting in the isolation of the *trans*- and *cis*-fused saturated alcohols **18** and **19** in 41 and 29% yield, respectively (Table 1, entry 3). Attempted hydrogenation of **11** over Crabtree's catalyst[12] in dichloromethane resulted not in reduction but migration of the alkene into the heterocyclic ring giving **20** in 66% isolated yield (Table

1, entry 4). No conversion was observed on attempted hydrogenation of **11** in the presence of Wilkinson's catalyst[13] at atmospheric pressure, just as no reaction was found on stirring **11** with potassium azodicarboxyate and acetic acid in methanol at room temperature. Hydrogenation of the allylic ester **13** over palladium on charcoal in ethanol at room temperature was accompanied by hydrogenolysis of the primary allylic alcohol resulting in the formation of **21** in 56% yield along with 9% of a second, uncharacterized isomer (Table 1, entry 5). Finally, reduction of the MOM-protected allylic alcohol **15** over Raney nickel in aqueous ethanol gave the desired selectivity, resulting in the isolation of **22** in 92% yield with no indication of the formation of a minor isomer in the NMR spectra of the crude reaction mixture (Table 1, entry 6).

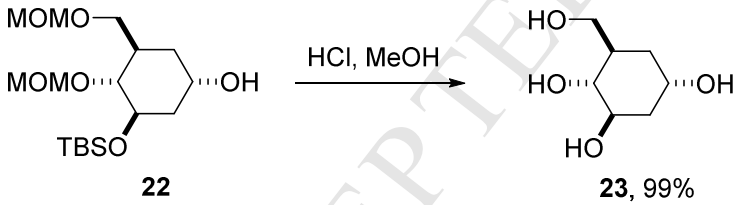
Table 1. Reductions of Ketone **8** and Allylic Alcohols **11** and **15**

Entry	**Substrate**	**Conditions**[a]	**Products**, yield
1	 **8**	H_2 (1 atm), Pd/C, THF	 **16**, 32% +  **17**, 29%
2	 **8**	$PhSiH_3$, $[(Ph_3P)CuH]_6$	 **17**, 30%
3	 **11**	H_2, Raney Ni, EtOH, H_2O	 **18**, 41% +  **19**, 19%

4	 **11**	Ir[(cod)(Cy_3P)(py)]PF_6, H_2, CH_2Cl_2	 **20**, 66%
5	 **13**	H_2, Pd/C, EtOH	 **21**, 56%
6	 **15**	H_2, Raney Ni, EtOH, H_2O	 **22**, 92%

a) All catalytic hydrogenations were conducted under 1 atm of hydrogen at room temperature.

Finally, gentle warming of **22** with HCl in methanol gave pseudo-α-D-glucopyranose **23** uneventfully in 99% yield (Scheme 3).



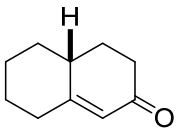
22 **23**, 99%

Scheme 3. Deprotection of **22** to Give Pseudo-2-deoxy-α-D-glucopyranose **23**

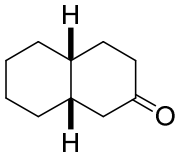
Discussion

The unselective formation of the *cis*,*trans*-mixture of **16** and **17** from **8** (Table 1, entry 1) is consistent with the selectivity observed on hydrogenation of $\Delta^{1,9}$-2-octalone **24**, a carbocyclic model for the bicyclic enone **8**, over palladium and platinum catalysts.[14-16] As hydrogenation of the model **24** could be optimized for formation of the *cis*-fused product *cis*-2-decalinone **25** under acidic conditions but not for

the *trans*-fused isomer **26** under any conditions reported,[14-16] the *trans*-selective hydrogenation of **8** to **16** was not pursued further. As cuprates and other nucleophiles are known to add to the carbocyclic model **24** in a highly *cis*-selective manner,[17-19] with *trans*-selectivity only obtained under thermodynamic conditions,[20] the preferential formation of **17** from **8** with Stryker's reagent (Table 1, entry 2) is unsurprising. Following the report of Shing and coworkers on the highly selective conversion of **27** to **28**,[4] hydrogenation of **11** over Raney Nickel in ethanol was attempted. While the desired *trans*-fused product **18** did predominate over its *cis*-fused isomer **19** under these conditions (Table 1, entry 3) the degree of selectivity was inadequate for our purposes. Switching to homogeneous catalysis, attempts to direct hydrogenation to formation of the *trans*-fused product with Crabtree's catalyst[21-24] resulted only in the migration of the allylic alkene into conjugation with the ethereal oxygen (Table 1, entry 4), a well-known process with this catalyst.[25]



24



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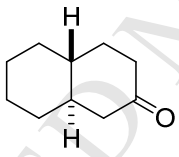

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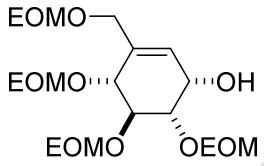

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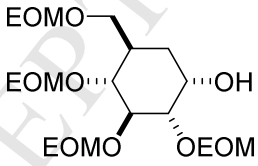


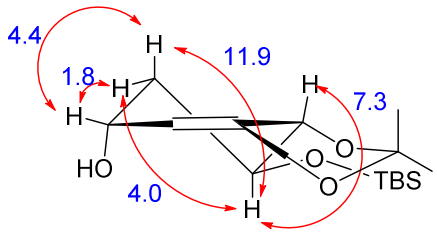
28

Thwarted in our attempts to achieve the desired selectivity with the bicyclic substrates, and encouraged by Shing's clean and high yielding reductions of **27** and related compounds into both stereoisomers as a function of catalyst and conditions,[4,26] we turned to monocyclic substrates. Stirring of the allylic diol **13** in ethanol over palladium on carbon and under one atmosphere of hydrogen resulted in a rare example of hydrogenolysis of an allylic C-O bond,[27-28] coupled with reduction of the alkene. The product **21** was

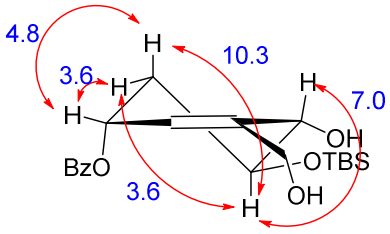
obtained as a single diastereomer in 56% isolated yield (Table 1, entry 5), albeit a minor diastereomer was observed in the reaction mixture, and can be considered as a protected version of pseudo-2,6-dideoxy-α-D-glucopyranose. Finally, taking note of Shing's successful selective reduction of **27** to **28**,[4] the allylic alcohol **15** was stirred in ethanol over Raney nickel under one atmosphere of hydrogen when the desired product **22** was obtained as a single diastereomer in 92% isolated yield (Table 1, entry 6).

The highly stereoselective reduction of **15** to **22** is consistent with Shing's reduction of **27** to **28** and is to be contrasted with the far less selective reduction of the bicyclic analog **11** (Table 1, entry 3) when a mixture of *trans*- and *cis* products **18** and **19** were obtained in an approximately 2:1 ratio. The contrasting selectivity between **15** and **27** on the one hand and **11** on the other hand argues against a hydroxyl directed mechanism as the sole stereochemical driving force. Rather, we suggest that the change in selectivity arises from a change in conformation on replacement of the cyclic acetal by two methoxymethyl ethers coupled with the freely rotating side chain in **15** (and **27**) adopting a perpendicular conformation to alkene. Thus, the unsaturated ring of octalin **11** adopts an approximate half-chair conformation **A** in which the hydroxyl group takes up a pseudoaxial position and the siloxy group a pseudoequatorial one (Figure 1). This conformation is largely conserved in the diol **13** after cleavage of the isopropylidene group, but on installation of the methoxymethylethers is replaced by a predominantly inverted half chair **B** in both the benzoate **14** and the alcohol **15** (Figure 1). Presumably, conformation **B** is favored in **14** and **15** due to the minimization of ^{1,2}A strain between the allylic MOM ether on the ring and the methoxymethoxymethyl substituent and of ^{1,3}A strain between the latter and the olefinic hydrogen. Conformation **B** also minimizes dipolar repulsions between the two MOM ethers and places the MOM and TBS ethers in pseudoaxial positions as is commonly found in cyclohexyl and pyranosyl systems containing multiple *trans*-vicinal siloxy and other bulky groups.[29-38]

Half-chair A

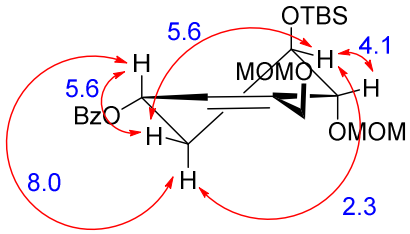


11

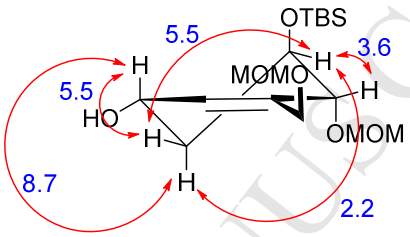


13

Half-chair B



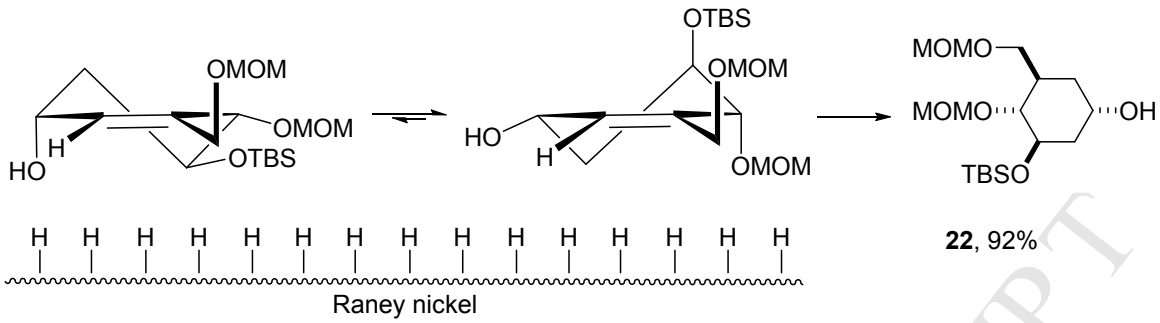
14



15

Figure 1. Predominant Conformations of **11**, **13**, **14**, and **15**, with Diagnostic ^{3}J H,H-Coupling Constants in Hz

On this basis the facial selecivity in the reduction of **15** is readily understood in terms steric shielding of the top face by the combination of pseudoaxial siloxy group and the methoxymethoxymethyl group in the major conformation **B**. In the minor conformation **A** the methoxymethoxymethyl group also adopts a perpendicular conformation so as to minimize allylic strain and in doing so shields the same face of the alkene (Scheme 4), consistent with other well-known models for the control of stereoselectivity in concerted additions to allylic alcohols and ethers.[39-40]



Scheme 4. Allylic Strain Minimization-Based Model for the Selective Reduction of **15**

Conclusion

We have adapted the Shing synthesis of carbasugars to the 2-deoxyglucose series and have completed a synthesis of the previously unknown pseudo-2-deoxy-α-D-glucopyranose **23** and of a protected version of its 2,6-dideoxyanalog **21**. In the course of this synthesis we studied the hydrogenation of several derivatives of 1,2,5-trihydroxy-3-hydroxymethylcyclohexene and found the selectivity to depend critically on the protection of the hydroxymethyl group. When it is tied up an isopropylidene acetal with the 6-hydroxy group reductions are either selective for the formation of the *cis*-fused bicyclic derivative with the pseudo-idose configuration or are little selective, whereas protection in the form of a MOM ether results in the clean formation of the desired gluco-isomer. We rationalize this selectivity as arising from minimization of allylic strain in the transition state for reduction and suggest that the conformation of the side chain is an important control element in the chemistry of the pseudopyranoses just as it is in that of the pyranoses themselves.[41-44]

Experimental Section

General information: Except for hydrogenation reactions, all reactions were performed using oven-dried glassware under an argon atmosphere. Reagents and solvents were purchased from commercial suppliers and were used without further purification unless otherwise specified. Reaction progress was

monitored by analytical thin-layer chromatography (TLC) on pre-coated glass backed plates and visualized by UV irradiation (254 nm) or by staining with basic potassium permanganate or ceric ammonium molybdate (CAM) solutions. Chromatographic purifications were performed on silica gel (230-400 mesh) columns. Specific rotations were measured on an automatic polarimeter with a path length of 100 mm in the solvent specified; concentrations are given in g/100 mL. NMR solvents were used without purification. Chemical shifts are given in ppm (δ) and coupling constants (*J*) are given in Hz. Multiplicities are given as singlet (s), broad singlet (br s), doublet (d), triplet (t), doublet of doublets (dd), triplet of doublets (td), multiplet (m), apparent quartet (app q), apparent pentet (app p), etc. High resolution mass spectra (HRMS) were recorded on a mass spectrometer with an electrospray ionization (ESI) source coupled to a time-of-flight (TOF) mass analyzer.

Benzyl 2-deoxy-4,6-*O*-isopropylidene-α-D-glucopyranoside (2). A mixture of 2-deoxy-D-glucose (800 mg, 4.87 mmol), benzyl alcohol (8 mL) and acetyl chloride (0.35 mL, 4.87 mmol) was heated to 50 °C for 10 min. The reaction was quenched by adding triethylamine and the excess benzyl alcohol was removed by concentration under reduced pressure. Chromatographic purification (9% methanol/dichloromethane) afforded benzyl 2-deoxy-α-D-glucopyranoside **1** as a white solid (1.16 g, 94%), with spectral data consistent with the literature.[6] To a stirred solution of this glycoside (1.16 g, 4.56 mmol) and (1*S*)-(+)-10-camphorsulfonic acid (211.9 mg, 0.9 mmol) in DMF (12 mL) at room temperature was added 2,2-dimethoxypropane (5.6 mL, 45.6 mmol). The reaction mixture was stirred for 5 h before it was diluted with ethyl acetate, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Chromatographic purification (30% ethyl acetate/hexanes) afforded the title compound as a colorless oil (1.10 g, 82%): $[\alpha]_D^{21}$ 80.9 (*c* 1.08, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 4.97 (dd, *J* = 3.9, 1.1 Hz, 1H), 4.67 (d, *J* = 11.9 Hz, 1H), 4.44 (d, *J* = 11.9 Hz, 1H), 4.08 (ddd, *J* = 11.2, 9.0, 5.2 Hz, 1H), 3.83 (dd, *J* = 10.0, 5.2 Hz, 1H), 3.76 (t, *J* = 10.0 Hz, 1H), 3.69 (ddd, *J* = 10.0, 9.0, 5.2 Hz, 1H), 3.52 (t, *J* = 9.0 Hz, 1H), 2.23 (ddd, *J* = 13.3, 5.2, 1.1 Hz, 1H), 1.76 (ddd, *J* = 13.3, 11.2, 3.9 Hz, 1H),

1.52 (s, 3H), 1.42 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.4, 128.4 (2 Cs), 127.84 (2 Cs), 127.78, 99.9, 97.2, 76.4, 69.0, 66.3, 63.7, 62.4, 37.4, 29.2, 19.2. HRMS (ESI-TOF) m/z: Calcd. for $C_{16}H_{22}O_5Na$ ([M + Na]$^+$): 317.1365; found: 317.1376.

3-*tert*-Butyldimethylsilyl-2-deoxy-4,6-*O*-isopropylidene-D-glucono-1,5-lactone (4). A solution of benzyl 2-deoxyglucoside **2** (1.10 g, 3.73 mmol), *tert*-butyldimethylsilyl chloride (1.69 g, 11.2 mmol) and imidazole (761 mg, 11.2 mmol) in DMF (15 mL) was stirred at room temperature for 8 h before it was diluted with ethyl acetate, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude silylated product (1.57 g) was dissolved in ethyl acetate (11 mL), treated with Pd/C (274 mg) and stirred at room temperature under a hydrogen atmosphere (1 atm) for 4 h. The solution was filtered through Celite and the filtrate was concentrated under reduced pressure to dryness. Chromatographic purification (20% ethyl acetate/hexanes) afforded the hemiacetal **3** as a mixture of anomers (1.02 g, 86%, α:β = 1.8:1). A mixture of the this product (2.18 g, 6.84 mmol), 4-methylmorpholine *N*-oxide (1.20 g, 10.3 mmol) and activated 3 Å molecular siveves (829 mg) in dichloromethane (13 mL) was stirred at room temperature for 1 h before it was cooled to 0 °C. Tetra-*n*-propylammonium perruthenate (120 mg, 5 mol %) was added and the reaction mixture was stirred for a further 2 h at room temperature before it was concentrated under reduced pressure. Ethyl acetate was added to the residue and the mixture was then filtered through Celite. The filtrate was washed successively with 5% aqueous Na_2SO_3, saturated aqueous $CuSO_4$, and brine, dried over Na_2SO_4 and concentrated under reduced pressure. Chromatographic purification (10% ethyl acetate/hexanes) afforded the title lactone as a white solid (1.90 g, 88%): $[\alpha]_D^{21}$ 7.7 (*c* 0.93, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04 (td, *J* = 7.8, 5.8 Hz, 1H), 4.02 (dd, *J* = 10.4, 5.1 Hz, 1H), 3.90 (td, *J* = 9.9, 5.1 Hz, 1H), 3.81 (t, *J* = 10.4 Hz, 1H), 3.70 (dd, *J* = 9.9, 7.8 Hz, 1H), 3.07 (dd, *J* = 18.0, 7.8 Hz, 1H), 2.58 (dd, *J* = 18.0, 5.8 Hz, 1H), 1.50 (s, 3H), 1.42 (s, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 99.9,

74.1, 69.0, 68.0, 61.6, 39.3, 28.8, 25.6 (3 Cs), 18.8, 18.0, -4.5, -5.1. HRMS (ESI-TOF) m/z: Calcd. for $C_{15}H_{28}O_5SiNa$ ($[M + Na]^+$): 339.1604; found: 339.1620.

4-*tert*-Butyldimethylsilyl-1,3-dideoxy-1-dimethoxyphosphinyl-5,7-*O*-isopropylidene-D-*gluco*-2-heptulo-2,6-pyranose (5). To a stirred solution of diisopropylamine (1.68 mL, 12.01 mmol) in THF (5.8 mL) at -78 °C was added *n*-butyllithium solution (2.5 M in hexanes, 4.8 mL, 12.01 mmol) dropwise. After stirring at the same temperature for 0.5 h, dimethyl methylphosphonate (1.30 mL, 12.0 mmol) was added dropwise. The reaction mixture was stirred for 0.5 h at -78 °C before a solution of the above lactone **4** (1.90 g, 6.00 mmol) in THF (10 mL) was added dropwise. After completion (2 h), saturated aqueous NH_4Cl was added and the reaction mixture was allowed to warm to room temperature, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Chromatographic purification (50% ethyl acetate/hexanes) afforded the title compound as a white solid (2.54 g, 96%): $[\alpha]_D^{21}$ 9.1 (*c* 0.47, $CHCl_3$). ^{1}H NMR (499 MHz, $CDCl_3$) δ 4.04 (ddd, *J* = 10.8, 9.0, 5.2 Hz, 1H), 3.88 (ddd, *J* = 10.6, 9.0, 5.2 Hz, 1H), 3.81 (dd, *J* = 10.3, 5.2 Hz, 1H), 3.78 – 3.67 (m, 7H), 3.41 (t, *J* = 9.2 Hz, 1H), 2.24 – 2.08 (m, 3H), 1.54 (dd, *J* = 13.0, 10.8 Hz, 1H), 1.48 (s, 3H), 1.40 (s, 3H), 0.87 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 99.4, 96.5 (d, *J* = 8.4 Hz), 76.1, 67.4 (d, *J* = 5.4 Hz), 64.9, 62.5, 53.5 (d, *J* = 5.7 Hz), 51.7 (d, *J* = 6.7 Hz), 45.4 (d, *J* = 15.1 Hz), 36.8 (d, *J* = 135.2 Hz), 29.2, 25.8 (3 Cs), 19.1, 18.2, -4.4, -4.9. ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.51. HRMS (ESI-TOF) m/z: Calcd. for $C_{18}H_{37}O_8PSiNa$ ($[M + Na]^+$): 463.1893; found: 463.1875.

(4*R*,10*R*)-4-((*tert*-Butyldimethylsilyl)oxy-6,6-dimethyl-5,7-dioxa-Δ^{1,9}-octalin-2-one (8). To a stirred solution of the above phosphonate **5** (2.54 g, 5.77 mmol) in THF (15 mL) at room temperature was added sodium borohydride (654 mg, 17.3 mmol). The reaction mixture was stirred at room temperature for 4 h before it was concentrated to dryness, diluted with ethyl acetate and washed with water, and brine, dried over Na_2SO_4 and concentrated under reduced pressure to give a crude diol **6** (2.55 g) which

was directly used for next step without purification. A solution of dimethyl sulfoxide (2.46 mL, 34.6 mmol) in dichloromethane (12 mL) at -78 °C was treated dropwise with a solution of trifluoroacetic anhydride (3.20 mL, 23.1 mmol) in dichloromethane (12 mL) and stirred at -78 °C for 2 h, before a solution of the above diol (2.55 g) in dichloromethane (24 mL) was added dropwise. After stirring for 2 h at the same temperature triethylamine (6.43 mL, 46.1 mmol) was added dropwise and stirring continued at -78 °C for another 1 h, before the reaction mixture was allowed to warm to room temperature and diluted with dichloromethane. The mixture was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give a crude diketone **7** (2.79 g), which was taken up in toluene (20 mL), treated with 18-crown-6 (76.2 mg, 0.29 mmol) and potassium carbonate (2.39 g, 17.30 mmol), and stirred at room temperature for 18 h before it was concentrated under reduced pressure. Chromatographic purification (7% ethyl acetate/hexanes) of the residue afforded the title compound as a light yellow oil (1.17 g, 65%): $[\alpha]_D^{21}$ -128.6 (*c* 1.09, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (m, 1H), 4.48 – 4.39 (m, 3H), 4.05 (ddd, *J* = 12.2, 8.1, 5.1 Hz, 1H), 2.68 (ddd, *J* = 16.4, 5.1, 1.2 Hz, 1H), 2.47 (dd, *J* = 16.4, 12.2 Hz, 1H), 1.49 (s, 3H), 1.41 (s, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.6, 159.0, 122.1, 100.4, 72.8, 71.3, 61.5, 46.2, 25.7 (4 Cs), 22.2, 18.1, -4.5, -5.0. HRMS (ESI-TOF) m/z: Calcd. for $C_{16}H_{28}O_4SiNa$ ($[M + Na]^+$): 335.1655; found: 335.1663.

(2*S*,4*R*,10*R*)-4-((*tert*-Butyldimethylsilyl)oxy-6,6-dimethyl-5,7-dioxa-Δ^{1,9}-octalin-2-ol (9). To a stirred solution of enone **8** (1.21 g, 3.87 mmol) and cerium (III) chloride heptahydrate (1.73 g, 4.65 mmol) in MeOH (20 mL) at -20 °C was added sodium borohydride (220 mg, 5.81 mmol). After stirring at -20 °C for 1 h, the reaction was quenched by addition of saturated aqueous NH_4Cl. The reaction mixture was allowed to warm to room temperature, a mixture of water and ethyl acetate was added and the resulting mixture was filtered through Celite. The filtrate was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Chromatographic purification (25% ethyl acetate/hexanes) afforded the title compound as a

colorless oil (901.1 mg, 74%): $[\alpha]_D^{21}$ -63.5 (*c* 0.48, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.50 (br s, 1H), 4.43 (dd, *J* = 13.8, 1.7 Hz, 1H), 4.39 (br s, 1H), 4.25 (d, *J* = 7.0 Hz, 1H), 4.09 (d, *J* = 13.8 Hz, 1H), 3.75 (ddd, *J* = 12.0, 7.0, 3.6 Hz, 1H), 2.20 (dddd, *J* = 12.3, 5.3, 3.6, 1.4 Hz, 1H), 1.64 – 1.56 (m, 1H), 1.49 (s, 3H), 1.37 (s, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 133.1, 124.9, 99.2, 73.3, 70.8, 66.6, 63.0, 40.4, 28.3, 25.8 (3 Cs), 20.0, 18.2, -4.5, -5.0. HRMS (ESI-TOF) m/z: Calcd. for $C_{16}H_{30}O_4SiNa$ ($[M + Na]^+$): 337.1811; found: 337.1816.

(2*R*,4*R*,10*R*)-4-((*tert*-Butyldimethylsilyl)oxy-6,6-dimethyl-5,7-dioxa-Δ^{1,9}-octalin-2-yl Benzoate (10). To a stirred solution of **9** (125.8 mg, 0.40 mmol), triphenyl phosphine (125.9 mg, 0.48 mmol) and benzoic acid (58.6 mg, 0.48 mmol) in THF (2 mL) at 0 ^{o}C was added a solution of diisopropyl azodicarboxylate (97.1 mg, 0.48 mmol) in THF (0.7 mL) dropwise. The reaction mixture was stirred at room temperature for 10 h before it was concentrated to dryness under reduced pressure. Chromatographic purification (5% ethyl acetate/hexanes) afforded the title compound as a colorless oil (128.6 mg, 77%): $[\alpha]_D^{21}$ 137.5 (*c* 1.14, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.7 Hz, 2H), 7.57 (t, *J* = 7.7 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 5.69 – 5.62 (m, 1H), 5.53 (br s, 1H), 4.42 (dd, *J* = 14.3, 1.7 Hz, 1H), 4.23 (d, *J* = 7.6 Hz, 1H), 4.19 (d, *J* = 14.3 Hz, 1H), 4.12 (ddd, *J* = 11.8, 7.6, 3.9 Hz, 1H), 2.11 (ddt, *J* = 14.4, 3.9, 1.8 Hz, 1H), 1.95 (ddd, *J* = 14.4, 11.8, 4.4 Hz, 1H), 1.51 (s, 3H), 1.41 (s, 3H), 0.90 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 138.2, 133.0, 130.2, 129.6 (2 Cs), 128.4 (2 Cs), 117.8, 99.3, 73.2, 68.4, 68.3, 62.5, 36.0, 27.8, 25.8 (3 Cs), 20.3, 18.3, -4.5, -4.8. HRMS (ESI-TOF) m/z: Calcd. for $C_{23}H_{34}O_5SiNa$ ($[M + Na]^+$): 441.2073; found: 441.2056.

(2*R*,4*R*,10*R*)-4-((*tert*-Butyldimethylsilyl)oxy-6,6-dimethyl-5,7-dioxa-Δ^{1,9}-octalin-2-ol (11). To a stirred solution of ester **10** (500 mg, 1.19 mmol) in MeOH (2 mL) at room temperature was added sodium methoxide (96.8 mg, 1.79 mmol). After stirring at room temperature for 12 h, the reaction mixture was neutralized with Amberlyst 15 hydrogen form and then filtered. The filtrate was concentrated under

reduced pressure to give a residue, chromatographic purification (25% ethyl acetate/hexanes) of which afforded the title compound as a colorless oil (335.8 mg, 89%): $[\alpha]_D^{21}$ 25.8 (*c* 0.55, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 – 5.52 (m, 1H), 4.39 (dd, *J* = 14.2, 1.7 Hz, 1H), 4.29 (br s, 1H), 4.18 – 4.11 (m, 2H), 3.99 (ddd, *J* = 11.9, 7.3, 4.0 Hz, 1H), 1.98 (ddt, *J* = 13.9, 4.0, 1.8 Hz, 1H), 1.77 (ddd, *J* = 13.9, 11.9, 4.4 Hz, 1H), 1.48 (s, 3H), 1.39 (s, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7, 121.5, 99.2, 73.5, 67.8, 65.2, 62.6, 38.8, 28.0, 25.8 (3 Cs), 20.2, 18.2, -4.4, -4.8. HRMS (ESI-TOF) m/z: Calcd. for $C_{16}H_{30}O_4SiNa$ ($[M + Na]^+$): 337.1811; found: 337.1822.

(1*R*,2*R*,5*R*)-1,2-Dihydroxy-3-(hydroxymethyl)cyclohex-3-en-5-yl Benzoate (12) and (1*R*,2*R*,5*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-2-hydroxy-3-(hydroxymethyl)cyclohex-3-en-5-yl Benzoate (13). To a solution of **10** (1.14 g, 2.72 mmol) in MeOH (2 mL) was added a solution of iodine in MeOH (1%, 20 mL). After stirring at room temperature for 3 h, the reaction was quenched by addition of saturated aqueous $Na_2S_2O_3$ (50 mL) and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduce pressure. Chromatographic purification (33% ethyl acetate/hexanes) afforded the silyl ether **13** as a colorless oil (708.7 mg, 69%) and then the triol **12** as a colorless solid (185 mg, 26%).

Silyl ether **13**: $[\alpha]_D^{21}$ 176.7 (*c* 0.09, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.6 Hz, 2H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 5.92 – 5.86 (m, 1H), 5.61 (m, 1H), 4.34 – 4.22 (m, 2H), 4.17 (d, *J* = 7.0 Hz, 1H), 4.09 (ddd, *J* = 10.3, 7.0, 3.6 Hz, 1H), 2.13 (dtd, *J* = 13.9, 3.6, 1.0 Hz, 1H), 1.98 (ddd, *J* = 13.9, 10.3, 4.8 Hz, 1H), 0.91 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9, 142.3, 133.0, 130.2, 129.6 (2 Cs), 128.4 (2 Cs), 122.6, 74.1, 71.0, 68.1, 64.7, 34.6, 25.8 (3 Cs), 18.1, -4.5, -4.7. HRMS (ESI-TOF) m/z: Calcd. for $C_{20}H_{30}O_5SiNa$ ($[M + Na]^+$): 401.1760; found: 401.1778.

Triol **12**: $[\alpha]_D^{21}$ 114.6 (*c* 0.24, MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ 8.00 (d, *J* = 7.6 Hz, 2H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 5.97 – 5.90 (m, 1H), 5.63 (m, 1H), 4.26 – 4.15 (m, 2H), 4.03 – 3.95 (m,

2H), 2.19 – 2.11 (m, 1H), 2.08 – 1.98 (m, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 166.0, 144.2, 132.8, 130.2, 129.0 (2 Cs), 128.1 (2 Cs), 120.2, 71.2, 69.5, 68.2, 61.8, 33.1. HRMS (ESI-TOF) m/z: Calcd. for $C_{14}H_{16}O_5Na$ ($[M + Na]^+$): 287.0895; found: 287.0896.

(1*R*,2*R*,5*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-2-(methoxymethoxy)-3-((methoxymethoxy)methyl)cyclohex-3-en-5-yl Benzoate (14). A stirred solution of diol **13** (441.8 mg, 1.17 mmol) in *N,N*-diisopropylethylamine (5 mL) at 0 °C was treated with chloromethyl methyl ether (1.77 mL, 23.34 mmol), and stirred at room temperature for 24 h before it was diluted with ethyl acetate, and washed with 1 *N* HCl, and brine, dried over Na_2SO_4 and concentrated under reduced pressure. Chromatographic purification (10% ethyl acetate/hexanes) afforded the title compound as a colorless oil (473.8 mg, 87%): $[\alpha]_D^{21}$ 67.6 (*c* 0.46, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.4 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.4 Hz, 2H), 6.03 (br s, 1H), 5.73 (m, 1H), 4.82 (d, *J* = 6.8 Hz, 1H), 4.73 (d, *J* = 6.8 Hz, 1H), 4.67 (d, *J* = 6.5 Hz, 1H), 4.61 (d, *J* = 6.5 Hz, 1H), 4.22 (ddd, *J* = 5.6, 4.1, 2.3 Hz, 1H), 4.20 – 4.08 (m, 2H), 3.87 (d, *J* = 4.1 Hz, 1H), 3.43 (s, 3H), 3.37 (s, 3H), 2.20 (dt, *J* = 12.8, 5.6 Hz, 1H), 2.02 (ddd, *J* = 12.8, 8.0, 2.3 Hz, 1H), 0.90 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 136.5, 132.9, 130.4, 129.6 (2 Cs), 128.3 (2 Cs), 126.5, 97.8, 95.3, 75.6, 69.3, 68.1, 67.4, 56.0, 55.4, 32.3, 25.7 (3 Cs), 18.0, -4.9 (2 Cs). HRMS (ESI-TOF) m/z: Calcd. for $C_{24}H_{38}O_7SiNa$ ($[M + Na]^+$): 489.2284; found: 489.2292.

(1*R*,2*R*,5*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-2-(methoxymethoxy)-3-((methoxymethoxy)methyl)cyclohex-3-en-5-ol (15). A stirred solution of benzoate **14** (269.2 mg, 0.58 mmol) in MeOH (3 mL) at room temperature was treated with sodium methoxide (46.7 mg, 0.87 mmol) and stirred at room temperature for 12 h. The reaction mixture was neutralized with Amberlyst 15 hydrogen form, filtered, and concentrated under reduced pressure. Chromatographic purification (33% ethyl acetate/hexanes) afforded the title compound as a colorless oil (202.5 mg, 97%): $[\alpha]_D^{21}$ 3.7 (*c* 0.62,

$CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 – 5.94 (m, 1H), 4.76 (d, *J* = 6.8 Hz, 1H), 4.70 (d, *J* = 6.8 Hz, 1H), 4.66 (d, *J* = 6.5 Hz, 1H), 4.59 (d, *J* = 6.5 Hz, 1H), 4.42 (m, 1H), 4.17 – 4.10 (m, 2H), 4.06 (d, *J* = 12.8 Hz, 1H), 3.78 (d, *J* = 3.6 Hz, 1H), 3.41 (s, 3H), 3.37 (s, 3H), 2.08 (dtt, *J* = 12.6, 5.5, 1.1 Hz, 1H), 1.74 (ddd, *J* = 12.6, 8.7, 2.2 Hz, 1H), 0.86 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.9, 131.5, 97.6, 95.0, 75.2, 69.1, 67.5, 64.4, 55.9, 55.3, 35.6, 25.7 (3 Cs), 17.9, -4.9 (2 Cs). HRMS (ESI-TOF) m/z: Calcd. for $C_{17}H_{34}O_6SiNa$ ($[M + Na]^+$): 385.2022; found: 385.2034.

(4*R*,9*R*,10*R*)-4-((*tert*-Butyldimethylsilyl)oxy-6,6-dimethyl-5,7-dioxadecalin-2-one (16) and (4*R*,9*S*,10*R*)-4-((*tert*-Butyldimethylsilyl)oxy-6,6-dimethyl-5,7-dioxadecalin-2-one (17) by Catalytic Hydrogenation of Enone 8. A solution of enone **8** (11.7 mg, 0.04 mmol) in THF (0.5 mL) was treated with Pd/C (4.0 mg), and stirred at room temperature under a hydrogen atmosphere (1 atm) for 8 h, then filtered through Celite. The filtrate was concentrated under reduced pressure to dryness to give a residue (11.6 mg) that was judged by integration of its ^{1}H NMR spectrum to be a 1.1:1 mixture of **16** and **17**. Chromatographic purification (8% ethyl acetate/hexanes) afforded **17** (3.4 mg, 29%) as a colorless oil. Further elution (12% ethyl acetate/hexanes) gave **16** (3.8 mg, 32%) as a colorless oil.

trans-Fused ketone **16**: $[\alpha]_D^{21}$ -5.0 (*c* 0.10, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.80 (ddd, *J* = 10.8, 8.9, 5.7 Hz, 1H), 3.76 (dd, *J* = 11.4, 4.7 Hz, 1H), 3.71 (dd, *J* = 10.6, 8.9 Hz, 1H), 3.67 (t, *J* = 11.4 Hz, 1H), 2.67 (ddd, *J* = 14.7, 5.7, 2.5 Hz, 1H), 2.45 (dd, *J* = 14.7, 10.8 Hz, 1H), 2.15 (ddd, *J* = 14.3, 4.0, 2.5 Hz, 1H), 2.03 (t, *J* = 14.3 Hz, 1H), 1.80 – 1.69 (m, 1H), 1.48 (s, 3H), 1.41 (s, 3H), 0.85 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 205.6, 99.2, 76.4, 72.0, 64.4, 49.5, 40.5, 33.9, 29.6, 25.7 (3 Cs), 19.0, 18.2, -4.4, -5.1. HRMS (ESI-TOF) m/z: Calcd. for $C_{16}H_{34}O_4NSi$ ($[M + NH_4]^+$): 332.2257; found: 332.2268.

cis-Fused ketone **17**: $[\alpha]_D^{21}$ 4.7 (*c* 0.17, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22 – 4.14 (m, 2H), 3.97 (t, *J* = 2.2 Hz, 1H), 3.54 (dd, *J* = 11.9, 1.3 Hz, 1H), 2.97 (dd, *J* = 14.1, 12.0 Hz, 1H), 2.75 (dd, *J* = 14.0, 2.8 Hz, 1H), 2.24 (dt, *J* = 14.0, 2.4 Hz, 1H), 2.21 – 2.06 (m, 2H), 1.52 (s, 3H), 1.44 (s, 3H), 0.85 (s, 9H), 0.07 (s, 3H), 0.05

(s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.1, 98.8, 72.2, 69.2, 63.9, 44.2, 39.6, 32.4, 29.8, 25.6 (3 Cs), 19.0, 17.9, -4.9, -5.0. HRMS (ESI-TOF) m/z: Calcd. for $C_{16}H_{34}O_4NSi$ ($[M + NH_4]^+$): 332.2257; found: 332.2268.

Preparation of Ketone 17 by Reduction of Enone 8 with Stryker's Reagent: To a stirred solution of triphenylphosphinecopper (I) hydride hexamer (6.3 mg, 5 mol %) in toluene (0.25 mL) at room temperature was added phenylsilane (11.8 μL, 0.10 mmol), followed by a solution of **8** (20.0 mg, 0.06 mmol) in toluene (0.2 mL). After stirring at room temperature for 48 h, the reaction mixture was diluted with ethyl acetate, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Chromatographic purification (8% ethyl acetate/hexanes) afforded **17** (6.0 mg, 30%) as a colorless oil with spectral data identical to the above sample. Further elution (11% ethyl acetate/hexanes) gave the recovered starting material (9.4 mg, 47%).

(2*S*,4*R*,9*R*,10*R*)-4-((*tert*-Butyldimethylsilyl)oxy-6,6-dimethyl-5,7-dioxadecalin-2-ol (18) and (2*S*,4*R*,9*S*,10*R*)-4-((*tert*-Butyldimethylsilyl)oxy-6,6-dimethyl-5,7-dioxadecalin-2-ol (19). To a stirred solution of **11** (112.7 mg, 0.36 mmol) in EtOH (0.5 mL) at room temperature was added a suspension of Raney nickel (20.0 mg, slurry in H_2O) in EtOH (1 mL). The reaction mixture was stirred at room temperature under a hydrogen atmosphere (1 atm) for 10 h before it was filtered through Celite and the filtrate concentrated under reduced pressure to dryness (113.3 mg). Examination of the crude reaction mixture by ^{1}H NMR spectroscopy revealed a 2:1 ratio of **18** and **19**. Chromatographic purification eluting with 17% ethyl acetate in hexanes, afforded **19** (21.7 mg, 19%) as a white solid. Further elution with 20% ethyl acetate in hexanes gave **18** (46.7 mg, 41%) as a colorless oil.

trans-Fused alcohol **18**: $[\alpha]_D^{21}$ -9.0 (*c* 1.35, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (app p, *J* = 2.9 Hz, 1H), 3.90 (ddd, *J* = 11.2, 8.6, 5.0 Hz, 1H), 3.67 (dd, *J* = 11.2, 4.9 Hz, 1H), 3.58 (t, *J* = 11.2 Hz, 1H), 3.35 (dd, *J* = 10.5, 8.6 Hz, 1H), 2.12 – 1.98 (m, 2H), 1.58 – 1.46 (m, 2H), 1.44 (s, 3H), 1.38 (s, 3H), 1.17 (td, *J* = 13.5, 2.9 Hz, 1H), 0.86 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 98.9, 78.1, 68.9, 66.5, 64.6,

41.2, 32.6, 32.5, 29.8, 25.8 (3 Cs), 19.2, 18.3, -4.3, -4.9. HRMS (ESI-TOF) m/z: Calcd. for $C_{16}H_{33}O_4Si$ ([M + H]$^+$): 317.2148; found: 317.2159.

cis-Fused alcohol **19**: $[\alpha]_D^{21}$ 21.7 (*c* 0.65, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (dd, *J* = 11.7, 2.6 Hz, 1H), 4.00 (tt, *J* = 11.3, 4.2 Hz, 1H), 3.88 (app q, *J* = 3.0 Hz, 1H), 3.75 (t, *J* = 3.0 Hz, 1H), 3.56 (dd, *J* = 11.7, 1.0 Hz, 1H), 1.98 (dd, *J* = 11.7, 11.3 Hz, 1H), 1.90 – 1.80 (m, 1H), 1.75 – 1.52 (m, 3H), 1.45 (s, 3H), 1.39 (s, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 98.5, 70.6, 69.4, 65.9, 64.7, 37.5, 33.4, 30.3, 29.8, 25.7 (3 Cs), 18.9, 17.9, -4.9, -5.1. HRMS (ESI-TOF) m/z: Calcd. for $C_{16}H_{32}O_4SiNa$ ([M + Na]$^+$): 339.1968; found: 339.1975.

(5*R*,7*S*,10*R*)-5-((*tert*-Butyldimethylsilyl)oxy-3,3-dimethyl-2,4-dioxa-Δ^{1,9}-octalin-7-ol (20). A solution of **11** (14.6 mg, 0.05 mmol) and Crabtree's catalyst (0.8 mg, 2 mmol %) in dichloromethane (0.3 mL) was stirred at 0 ^{o}C under a hydrogen atmosphere (1 atm) for 3 h before it was concentrated under reduced pressure. Chromatographic purification (12% ethyl acetate/hexanes) afforded the title compound as a colorless oil (9.7 mg, 66%): $[\alpha]_D^{21}$ 9.6 (*c* 0.49, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 – 6.27 (m, 1H), 4.07 (m, 1H), 3.94 – 3.82 (m, 2H), 2.23 (d, *J* = 14.7 Hz, 1H), 2.13 – 2.01 (m, 2H), 1.56 (ddd, *J* = 13.2, 10.7, 2.0 Hz, 1H), 1.45 (s, 3H), 1.43 (s, 3H), 0.88 (s, 9H), 0.08 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.7, 107.0, 99.2, 74.1, 70.7, 66.3, 40.0, 34.9, 27.8, 25.8 (3 Cs), 21.3, 18.3, -4.4, -4.9. HRMS (ESI-TOF) m/z: Calcd. for $C_{16}H_{30}O_4SiNa$ ([M + Na]$^+$): 337.1811; found: 337.1816.

(1*R*,2*R*,3*S*,5*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-2-hydroxy-3-methylcyclohexan-5-yl Benzoate (21). To a solution of **13** (8.5 mg, 0.02 mmol) in EtOH (0.4 mL) was treated with $Pd(OH)_2$/C (3.0 mg, 20 wt %) and stirred at room temperature under a hydrogen atmosphere (1 atm) for 0.5 h before it was filtered through Celite. The filtrate was concentrated under reduced pressure and chromatographic purification of the residue (3% ethyl acetate/hexanes) afforded the title compound as a colorless oil (4.6 mg, 56%): $[\alpha]_D^{21}$ 19.1 (*c* 0.23, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.4 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.45

(t, *J* = 7.4 Hz, 2H), 5.34 (app p, *J* = 2.9 Hz, 1H), 3.88 (ddd, *J* = 11.6, 9.0, 6.0 Hz, 1H), 3.11 (t, *J* = 9.0 Hz, 1H), 2.22 (ddd, *J* = 14.1, 6.0, 2.9 Hz, 1H), 2.05 – 1.89 (m, 2H), 1.64 (ddd, *J* = 14.1, 11.6, 2.9 Hz, 1H), 1.38 (ddd, *J* = 14.3, 12.2, 2.9 Hz, 1H), 1.08 (d, *J* = 6.3 Hz, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 133.0, 130.5, 129.5 (2 Cs), 128.4 (2 Cs), 80.4, 72.8, 70.3, 37.6, 36.9, 31.9, 25.8 (3 Cs), 18. 0, 17.9, -4.2, -4.7. HRMS (ESI-TOF) m/z: Calcd. for $C_{20}H_{32}O_4SiNa$ ($[M + Na]^+$): 387.1968; found: 387.1966.

(1*R*,2*R*,3*R*,5*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-2-(methoxymethyloxy)-3-((methoxymethoxy)methyl)cyclohexan-5-ol (22). A solution of **15** (371.7 mg, 1.03 mmol) in EtOH (2 mL) was treated with a suspension of Raney nickel (40.0 mg, slurry in H_2O) in EtOH (2.5 mL), and stirred at room temperature under a hydrogen atmosphere (1 atm) for 2 h before it was filtered through Celite. The filtrate was concentrated under reduced pressure to dryness, and chromatographic purification (33% ethyl acetate/hexanes) of the residue afforded the title compound as a colorless oil (343.9 mg, 92%): $[\alpha]_D^{21}$ 44.0 (*c* 1.48, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89 (d, *J* = 6.7 Hz, 1H), 4.66 (d, *J* = 6.7 Hz, 1H), 4.62 (s, 2H), 4.14 (m, 1H), 3.99 (ddd, *J* = 10.1, 7.8, 4.4 Hz, 1H), 3.69 (dd, *J* = 9.5, 3.6 Hz, 1H), 3.61 (dd, *J* = 9.5, 6.6 Hz, 1H), 3.40 (s, 3H), 3.35 (s, 3H), 3.28 (dd, *J* = 9.3, 7.8 Hz, 1H), 2.18 – 2.07 (m, 1H), 1.95 (dtd, *J* = 13.5, 4.4, 2.4 Hz, 1H), 1.86 (dtd, *J* = 14.1, 4.4, 2.4 Hz, 1H), 1.61 (ddd, *J* = 14.1, 11.2, 3.0 Hz, 1H), 1.55 (ddd, *J* = 13.5, 10.1, 2.9 Hz, 1H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 98.4, 96.7, 81.2, 71.9, 68.5, 65.7, 56.1, 55.1, 40.6, 37.1, 34.8, 25.8 (3 Cs), 17.9, -4.7 (2 Cs). HRMS (ESI-TOF) m/z: Calcd. for $C_{17}H_{36}O_6SiNa$ ($[M + Na]^+$): 387.2179; found: 387.2180.

(1*R*,2*R*,3*R*,5*S*)-3-(Hydroxymethyl)cyclohexan-1,2,5-triol (Pseudo-2-deoxy-α-D-glucopyranose (23). A solution of **22** (10.0 mg, 0.03 mmol) in MeOH (0.5 mL) at room temperature was treated with concentrated HCl (5 μL) and stirred stirred at 60 °C for 5 h before it was concentrated under reduced pressure. Chromatographic purification (25% methanol/dichloromethane) afforded the title compound

as a colorless oil (4.4 mg, 99%): $[\alpha]_D^{21}$ 19.1 (*c* 0.22, MeOH ^{1}H NMR (600 MHz, CD_3OD) δ 4.09 (app p, *J* = 3.0 Hz, 1H), 3.75 (ddd, *J* = 11.7, 8.9, 4.9 Hz, 1H), 3.69 – 3.62 (m, 2H), 3.16 (dd, *J* = 10.4, 8.9 Hz, 1H), 2.03 (ddt, *J* = 13.5, 4.9, 3.0 Hz, 1H), 1.93 – 1.86 (m, 1H), 1.79 (dq, *J* = 14.1, 3.0 Hz, 1H), 1.43 – 1.34 (m, 2H). ^{13}C NMR (151 MHz, CD_3OD) δ 76.4, 70.3, 65.5, 63.3, 38.92, 38.85, 33.7. HRMS (ESI-TOF) m/z: Calcd. for $C_{14}H_{28}O_8Na$ ($[2M + Na]^+$): 347.1682; found: 347.1689.

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