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Facile synthesis of 6a-carba-β-D-fructopyranose through an RCM approach

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Abstract

A new synthetic approach toward 6a-carba-β-D-fructopyranose, a non-nutritive sweetener related to topiramate, is described. This scheme uses 2-*C*-hydroxymethyl-L-erythrose acetonide as starting material and efficiently delivers the target compound applying an RCM protocol for the construction of the carbocycle ring.

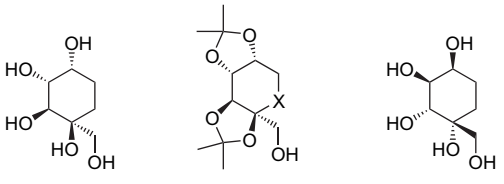
1. Introduction

Carbocyclic analogs of monosaccharides, in which a methylene group has replaced the endocyclic oxygen, were initially coined as pseudo-sugars,[1] whereas later the term carbasugars[2] prevailed. Carbasugars and some of their derivatives display a wide range of biological properties owing to their close structural resemblance to carbohydrates.[3–5] Carbahexopyranoses have been thoroughly studied during the past three decades, after their derivatives were found to occur naturally,[6–8] as components, for example, of antibiotics[9] and α-glycosidase inhibitors.[3,10] Consequently, extensive research work has been devoted to the preparation of a variety of carbasugars and related analogs.[11,12] These compounds were evaluated in depth for their biological action as enzyme inhibitors and regulators,[12,13] and for their potential use as artificial non-nutritive sweeteners.[8,14]

6a-Carba-β-D-fructopyranose (**1**, Fig. 1) could be used as a non-nutritive sweetener since it has a sweet taste.[14b] In addition, **1** can easily provide access to compound **2**, which is an active carba-isostere of topiramate (**3**), a useful antiepileptic drug.[15]

Enantiomerically pure **1** has been synthesized previously from a chemically resolved Diels–Alder adduct of furan and acrylic acid,[16] from (−)-quinic acid,[17] and from an enzymatically resolved homochiral building block derived from cyclohexene.[18] Additionally, the enantiomer of **1**, 6a-carba-β-L-fructopyranose (**4**), has been targeted by two different groups.[16,19]

Carbasugar **1** and a plethora of natural products and compounds with pharmaceutical and biological interest contain a chiral tertiary alcohol moiety. Stereoselective construction of this quaternary carbon center usually represents a major challenge in the planned synthetic route.[20] A part of our recent research work focuses on the synthesis of such compounds starting from inexpensive commercially available asymmetric materials like carbohydrates.[21] Among the different general approaches[22] for the construction of carbocycles from carbohydrates, RCM represents a very attractive synthetic tool.[23] In continuation of our previous work, we wish to report here a new and very efficient approach for the synthesis of enantiopure **1** through an RCM approach.



1 **2** X = CH_2, **3** X = O **4**

Figure 1.

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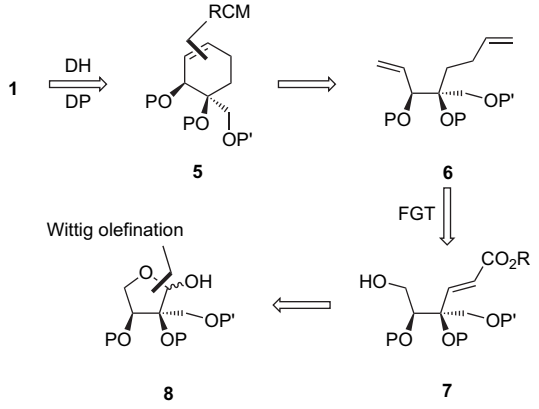
2. Results and discussion

For the synthesis of **1**, we envisaged the retrosynthesis depicted in Scheme 1. According to this plan the desired target could be derived from deprotection (DP) of the cis-dihydroxylation (DH) product of cyclohexene derivative **5**, which in turn is disconnected to diene **6** via an RCM reaction. The latter leads back to the unsaturated hydroxy-ester **7** through standard functional group transformations (FGT), and **7** could be reached from **8** employing a Wittig olefination.



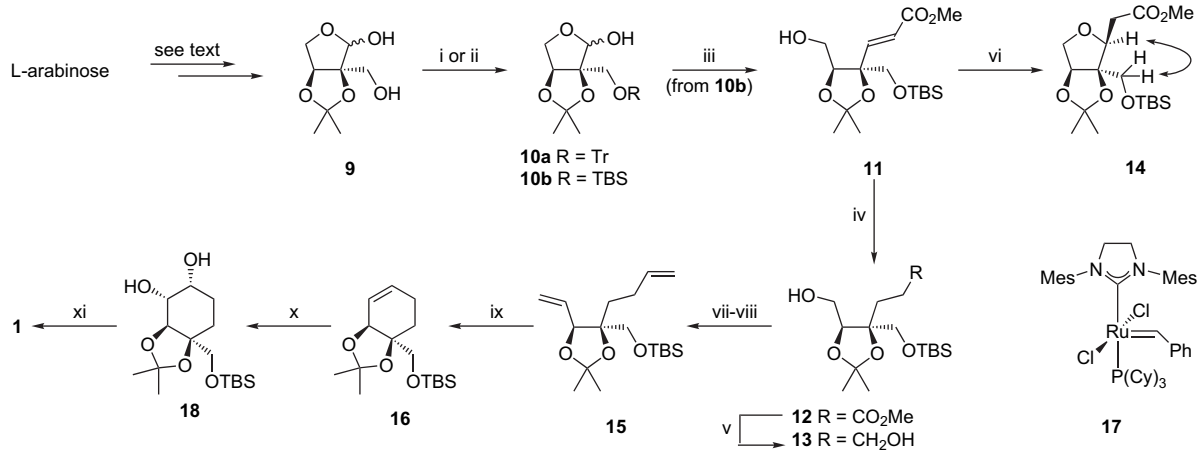
Scheme 1. Retrosynthetic analysis (P, P′=protecting groups).

Practically, hydroxymethyl erythrose **9** (Scheme 2) is easily accessible in high yields and multigram quantities from L-arabinose.[21c,24] In addition, it was clear that by choosing **9** (an equivalent of **8**) as the starting material, two key points in our planned synthesis were going to be resolved in a straightforward manner: unambiguous establishment of the correct stereochemistry at the quartenary center and protection of the *cis* diol system. Bearing in mind the inevitable masking of the primary hydroxyl group, we realized that a substantially bulky protecting group would be required in order to exclude a concurrent etherification of the hemiacetal functionality and, preferentially, a group belonging to the same acetonide orthogonal set. To address this issue, **9** reacted initially with trityl chloride[21c] to produce trityl-ether **10a**. However, subsequent Wittig olefination of **10a** proved troublesome. None of the desired ester was observed even upon prolonged application of forceful conditions.[25] This result can be solely attributed to the steric hindrance induced by the bulky trityl group. Therefore, we decided to turn our attention to the corresponding silyl-ether, **10b**. After some experimentation, we managed to prepare **10b** in good yield. The best results were obtained using pyridine as base and adding gradually the silyl chloride to prevent formation of the corresponding bis-silylated derivative. To our delight Wittig olefination worked uneventfully for **10b** avoiding the formation of tetrahydrofuran by-products by the addition of a catalytic amount of acid. Moreover, it is worthy mentioning that only the *E*-unsaturated ester **11** was formed, in contrast to the previously described results regarding reactions of stabilized ylides with γ-lactols of the same configuration.[26] Substitution at C-2 seems to play a crucial role in this stereochemical outcome.

Nevertheless, the stereochemistry of the newly formed double bond in **11** was of no importance since we intended to reduce it in the next step. A one-step procedure involving conjugate reduction of both double bond and ester moieties in **11** could be considered as an attractive option to directly prepare **13**. Indeed, this was tested using $NaBH_4$ but, instead of diol **13**, the unwanted furan derivative **14** was formed. Obviously, this could be accredited to the tendency of **11** to undergo an intramolecular 1,4-conjugate addition of the free hydroxyl group[27] in a slightly basic medium. Structural assignment of **14**, which was obtained as the sole product, was based on NOE studies (see Scheme 2).

An indirect route was then adopted involving initially the selective reduction of the double bond under mild conditions (Ra-Ni) to reach hydroxy-ester **12**. A second reduction, using $LiBH_4$, followed in order to obtain the desired diol, **13**.

Next, diol **13** was oxidized under classic Swern reaction conditions. The 1,6-bisaldehyde intermediate, being highly



Scheme 2. Synthesis of **1**. Reagents and conditions: (i) see Ref. 21c; (ii) TBSCl, pyridine, 70 °C, 81%; (iii) $Ph_3P{=}CHCO_2Me$, $PhCO_2H$, toluene, 80 °C, 77%; (iv) H_2, Ra-Ni, MeOH, 25 °C, 93%; (v) $LiBH_4$, Et_2O, 25 °C, 94%; (vi) $NaBH_4$, MeOH, 25 °C, 70%; (vii) $(COCl)_2$, DMSO, CH_2Cl_2, −60 to −40 °C, then Et_3N, −78 to 25 °C; (viii) $Ph_3P^+CH_3Br^-$, 12-crown-4-ether, *n*-BuLi, THF, −78 to 25 °C, 50% overall from **13**; (ix) Grubbs' catalyst **17**, CH_2Cl_2, 25 °C, 82%; (x) OsO_4, NMO, Me_2CO, H_2O, 25 °C, 99%; (xi) TFA, H_2O, 25 °C, 95%.

unstable, was used directly in the next step after a short workup. Thus, double olefination was followed and the desired diene **15** was obtained in an overall good yield.

Having in place the two terminal alkene moieties in **15**, we then investigated conditions to reach cyclohexene derivative **16** through a ring closure olefin metathesis.[28] To the best of our knowledge, there is no precedent for an RCM reaction of a 3,4,4-trisubstituted diene but in fact, we were glad to realize that this metathesis worked smoothly at room temperature using the commercially available Grubbs' second generation catalyst **17**.[29]

Dihydroxylation of the RCM product **16** was best performed using OsO_4 in a mixture of acetone and water,[30] yielding almost quantitatively diol **18**, whereas reaction in MeOH was very sluggish. As expected this reaction occurred with exclusive facial selectivity, influenced by the stereochemistry of the neighboring C-2.[31] The trans disposition of C-2 and C-3 protons was clearly deduced based on their small coupling constant.

Finally, exposure of partially protected pentaol **18** to aqueous TFA caused the removal of both silyl and acetonide groups and furnished crystalline 6a-carba-β-D-fructopyranose (**1**), in one step and in an excellent yield.

3. Conclusions

In this article, a convenient alternative synthesis of enantiopure 6a-carba-β-D-fructopyranose (**1**) is described. Practically, it embodies facile functional group interconversions starting from 2-*C*-hydroxymethyl-L-erythrose acetonide (**9**), an easily accessible L-arabinose chiron, and relies on an RCM reaction for the construction of the carbocycle ring. It delivers **1** in nine steps and in an overall yield higher than 21%.[32] Moreover, it is important to note that the same synthetic sequence could be also applied for the preparation of enantiopure 6a-carba-β-L-fructopyranose (**4**) using the equally easy available enantiomer of **9**, 2-*C*-hydroxymethyl-D-erythrose acetonide (a D-arabinose derived chiron).[21e,24]

4. Experimental

4.1. General

All commercially available grade quality reagents were used without further purification. All solvents were purified by standard procedures before use. Dry solvents were obtained by literature methods and stored over molecular sieves. All reactions were conducted under nitrogen atmosphere. All reactions were monitored on commercially available pre-coated TLC plates (layer thickness 0.25 mm) of Kieselgel 60 F_{254}. Compounds were visualized by use of a UV lamp or/and *p*-anisaldehyde ethanolic solution and warming. Column chromatography was performed in the usual way using Merck 60 (40–60 μm) silica gel. NMR spectra were recorded on a 300 MHz spectrometer (^{1}H: 300 MHz, ^{13}C: 75 MHz) in $CDCl_3$, unless otherwise stated. Chemical shifts are given in parts per million and *J* in hertz using solvent or tetramethylsilane as an internal reference. IR spectra were recorded on an FTIR instrument as indicated. Mass spectra were obtained by electro spray technique, positive mode (ES-MS) or MALDI-FTMS.

4.1.1. 2-C-(tert-Butyldimethylsilyloxy)-2,3-O-isopropylidene-L-erythrofuranose (*10b*)

Alcohol **9**[21c,24] (2 g, 10.5 mmol) was dissolved in dry pyridine (100 mL) and TBSCl (1.9 g, 12.6 mmol) was added in portions over a period of 30 min. The mixture was stirred for 20 h at 70 °C under an Ar atmosphere and then poured into a mixture of CH_2Cl_2 (100 mL) and H_2O (100 mL). The aqueous phase was extracted with CH_2Cl_2 (3×100 mL), and the combined organic phases were washed with saturated brine (3×100 mL) and dried (Na_2SO_4). After removal of the solvents under reduced pressure, the residual oil was purified by column chromatography on silica gel with a mixture of hexane/EtOAc (5:1 v/v) to give 2.59 g of lactols **10b** (81%) as a thick oil (mixture of α and β anomers in a ratio of ca. 1:1). R_f (hexane/EtOAc 4:1 v/v) 0.55; FTIR (neat film) 3445, 2977, 2932, 2858, 1472, 1372, 1252, 1107, 1006, 839, 779 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.31 (d, *J*=7.1 Hz, 1H), 4.95 (d, *J*=11.6 Hz, 1H), 4.66 (br d, *J*=3.2 Hz, 2H), 4.65 (s, 1H), 4.39 (d, *J*=7.1 Hz, 1H), 4.08–4.00 (m, 3H), 3.95 (d, *J*=10.9 Hz, 1H), 3.84 (d, *J*=10.9 Hz, 1H), 3.78 (d, *J*=11.6 Hz, 1H), 3.74 (s, 2H), 3.53 (dd, *J*=10.9, 3.2 Hz, 1H), 1.54 (s, 3H), 1.48 (s, 3H), 1.41 (s, 3H), 1.38 (s, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.13 (s, 6H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 113.5 (*C*Me$_2$), 104.7 (C-1$_\beta$), 97.7 (C-1$_\alpha$), 92.2 (C-2), 88.3 (C-2), 83.3 (C-4), 82.8 (C-4), 72.1 (C-5), 68.0 (C-5), 64.1 (C-2′), 63.1 (C-2′), 27.5 (2×C*Me*$_2$), 27.0 (C*Me*$_2$), 26.8 (C*Me*$_2$), 25.7 (C*Me*$_3$), 25.6 (C*Me*$_2$), 18.1 (*C*Me$_3$), 18.0 (*C*Me$_3$), −5.6 (SiMe$_2$), −5.7 (SiMe$_2$); HRMS *m/z* 327.1600 [$C_{14}H_{28}O_5SiNa$ (M+Na)$^+$ requires 327.1598].

4.1.2. (4S,5S,E)-Methyl 4-(tert-butyldimethylsilyloxymethyl)-4,5-O-isopropylidene-4,5,6-trihydroxyhex-2-enoate (*11*)

Lactol **10b** (2.44 g, 8 mmol) and benzoic acid (250 mg, 2 mmol) were dissolved in dry toluene (75 mL). Methyl (triphenylphosphoranylidene)acetate (3.2 g, 9.6 mmol) was added and the mixture was heated for 2 days at 70 °C under an Ar atmosphere. Then, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel with a mixture of hexane/EtOAc (8:1 v/v) to give 2.22 g of unsaturated ester **11** (77%) as a thick oil. R_f (hexane/EtOAc 4:1 v/v) 0.45; $[\alpha]_D^{25}$ −26.0 (*c* 2.7, $CHCl_3$); FTIR (neat film) 3480, 2980, 2932, 2853, 1733, 1653, 1472, 1436, 1383, 1298, 1159, 1090, 989, 839, 780 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (d, *J*=15.8 Hz, 1H, H-3), 6.21 (d, *J*=15.8 Hz, 1H, H-2), 4.35 (t, *J*=5.8 Hz, 1H, H-5), 3.75 (s, 3H, OMe), 3.74–3.68 (m, 2H, H-6), 3.67 (s, 2H, H-4′), 2.24 (br s, 1H, OH), 1.53 (s, 3H, CMe$_2$), 1.44 (s, 3H, CMe$_2$), 0.91 (s, 9H, CMe$_3$), 0.09 (s, 6H, SiMe$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4 (C-1), 146.2 (C-3), 122.0 (C-2), 109.3 (*C*Me$_2$), 83.6 (C-4), 81.8 (C-5), 67.8 (C-4′), 61.8 (C-6), 51.5 (OMe), 27.7 (C*Me*$_2$), 26.3 (C*Me*$_2$), 25.7 (C*Me*$_3$), 18.1 (*C*Me$_3$), −5.6 (SiMe$_2$), −5.8 (SiMe$_2$); HRMS *m/z* 383.1861 [$C_{17}H_{32}O_6SiNa$ (M+Na)$^+$ requires 383.1860].

*4.1.3. (4S,5S)-Methyl 4-(tert-butyldimethylsilyloxy-methyl)-4,5-O-isopropylidene-4,5,6-trihydroxyhexanoate (**12**)*

Unsaturated ester **11** (1.98 g, 5.5 mmol) was dissolved in MeOH (100 mL). A catalytic amount of Ra-Ni was added and the mixture was vigorously stirred under H_2 (1 atm) for 24 h at room temperature. Then, the reaction mixture was filtered through Celite®, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel with a mixture of hexane/EtOAc (8:1 v/v) to give 1.85 g of ester 12 (93%) as a thick oil: R_f (hexane/EtOAc 4:1 v/v) 0.31; $[\alpha]_D^{25}$ +9.3 (*c* 15.9, $CHCl_3$); FTIR (neat film) 3472, 2987, 2954, 2933, 2859, 1742, 1463, 1372, 1254, 1177, 1089, 839, 779 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.02 (t, J=6.4 Hz, 1H, H-5), 3.70–3.64 (m, 2H, H-6), 3.61 (d, J=9.8 Hz, 1H, H-4′a), 3.58 (s, 3H, OMe), 3.34 (d, J=9.0 Hz, 1H, H-4′b), 2.53 (br s, 1H, OH), 2.45–2.34 (m, 1H, H-2a), 2.25–2.15 (m, 1H, H-2b), 1.82–1.72 (m, 2H, H-3), 1.34 (s, 3H, CMe_2), 1.26 (s, 3H, CMe_2), 0.81 (s, 9H, CMe_3), 0.05 (s, 6H, $SiMe_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9 (C-1), 108.3 (*C*Me_2), 83.1 (C-4), 82.0 (C-5), 65.7 (C-4′), 60.6 (C-6), 51.4 (OMe), 28.0 (C-3), 27.9 (C*Me*$_2$), 26.5 (C*Me*$_2$), 25.6 (C*Me*$_3$), 25.5 (C-2), 18.0 (*C*Me_3), −5.8 ($SiMe_2$), −5.9 ($SiMe_2$); HRMS *m/z* 385.2020 [$C_{17}H_{34}O_6SiNa$ $(M+Na)^+$ requires 385.2017].

*4.1.4. (2S,3S)-3-(tert-Butyldimethylsilyloxymethyl)-2,3-O-isopropylidene-1,2,3,6-tetraol (**13**)*

A solution of ester **12** (1.6 g, 4.4 mmol) in dry diethylether (25 mL) was cooled to 0 °C under an Ar atmosphere. Then, $LiBH_4$ (210 mg, 9.7 mmol) was added in portions and the mixture was stirred vigorously for 2 h at the same temperature. The reaction was quenched by the addition of a few drops of EtOAc and left stirring until it reached room temperature. Saturated brine (70 mL) was added and the mixture was extracted with EtOAc (2×50 mL). The combined organic phases were dried (Na_2SO_4) and the solvents were removed under reduced pressure. Column chromatography of the obtained residue on silica gel with a mixture of hexane/EtOAc (3:1 v/v) gave 1.41 g of diol **13** (96%) as a thick oil. R_f (hexane/EtOAc 1:1 v/v) 0.37; $[\alpha]_D^{25}$ +21.8 (*c* 7.6, $CHCl_3$); FTIR (neat film) 3434, 2954, 2932, 2859, 1473, 1370, 1254, 1217, 1098, 1056, 839 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.13 (t, J=6.2 Hz, 1H, H-2), 3.75 (d, J=9.9 Hz, 1H, H-3′a), 3.74–3.70 (m, 2H, H-1), 3.62–3.58 (m, 2H, H-6), 3.46 (d, J=9.9 Hz, 1H, H-3′b), 3.36 (br s, 1H, OH), 3.15 (br s, 1H, OH), 1.76–1.52 (m, 4H, H-4 and H-5), 1.44 (s, 3H, CMe_2), 1.36 (s, 3H, CMe_2), 0.89 (s, 9H, CMe_3), 0.08 (s, 6H, $SiMe_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 107.9 (*C*Me_2), 82.8 (C-3), 82.6 (C-2), 65.5 (C-3′), 62.6 (C-6), 60.5 (C-1), 28.0 (C-4), 26.7 (C*Me*$_2$), 26.4 (C*Me*$_2$), 25.8 (C-5), 25.6 (C*Me*$_3$), 17.9 (*C*Me_3), −5.8 ($SiMe_2$), −5.9 (CMe_2); HRMS *m/z* 357.2070 [$C_{16}H_{34}O_5SiNa$ $(M+Na)^+$ requires 357.2068].

*4.1.5. Methyl 2-((2S,3R,4S)-3-(tert-butyldimethylsilyloxy-methyl)-3,4-isopropylidene-dihydroxytetrahydrofuran-2-yl)-acetate (**14**)*

$NaBH_4$ (38 mg, 1 mmol) was added to a solution of unsaturated ester **11** (73 mg, 0.2 mmol). The mixture was stirred for 48 h at room temperature. Then, glacial acetic acid was added dropwise until pH 7 was reached. EtOAc (10 mL) was added and the resulting solution was stirred for 30 min at room temperature. Then, it was washed with saturated aqueous sodium bicarbonate solution (25 mL) and saturated brine (25 mL). After drying (Na_2SO_4), the solvents were removed under reduced pressure and the obtained residue was purified by column chromatography on silica gel with a mixture of hexane/EtOAc (4:1 v/v) to give 51 mg of ester **14** (70%) as an oil. R_f (hexane/EtOAc 4:1 v/v) 0.64; $[\alpha]_D^{25}$ +11.6 (*c* 0.8, $CHCl_3$); FTIR (neat film) 2986, 2954, 2931, 2858, 1744, 1472, 1463, 1371, 1252, 1101, 839, 779 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.62 (d, J=3.2 Hz, 1H, H-4), 4.08 (dd, J=7.7, 5.1 Hz, 1H, H-2), 3.98 (d, J=10.9 Hz, 1H, H-5a), 3.74 (br d, J=1.3 Hz, 2H, H-3′), 3.71 (s, 3H, OMe), 3.55 (dd, J=10.9, 3.2 Hz, 1H, H-5b), 2.68–2.64 (m, 2H, C*H*$_2$CO), 1.49 (s, 3H, CMe_2), 1.39 (s, 3H, CMe_2), 0.90 (s, 9H, CMe_3), 0.09 (s, 6H, $SiMe_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9 (CO), 112.8 (*C*Me_2), 91.4 (C-3a), 84.5 (C-2), 78.5 (C-4), 72.4 (C-5), 64.4 (C-3′a), 51.7 (OMe), 34.8 (*C*H_2CO), 27.1 (C*Me*$_2$), 27.0 (C*Me*$_2$), 25.8 (C*Me*$_3$), 18.2 (*C*Me_3), −5.6 ($SiMe_2$); HRMS *m/z* 383.1859 [$C_{17}H_{32}O_6SiNa$ $(M+Na)^+$ requires 383.1860].

*4.1.6. (3S,4S)-4-(tert-Butyldimethylsilyloxymethyl)-3,4-O-isopropylidene-octa-1,7-diene-3,4-diol (**15**)*

Dry DMSO (1.4 mL, 20 mmol) was slowly added to a solution of $(COCl)_2$ (0.9 mL, 10.8 mmol) in dry CH_2Cl_2 (15 mL) at −60 °C under an Ar atmosphere. The mixture was stirred at this temperature for 10 min at which time a solution of diol **13** (1.2 g, 3.6 mmol) in dry CH_2Cl_2 (6 mL) was added dropwise. The resulting mixture was stirred for 15 min while the temperature was kept at −40 °C. Then, it was cooled at −78 °C and Et_3N (6 mL, 43 mmol) was added slowly. Stirring was continued for 30 min, the cooling bath was removed, and the mixture was left for an additional period of 2 h at room temperature. After the addition of CH_2Cl_2 (50 mL), the reaction mixture was washed with saturated brine (2×50 mL) and the combined organic phases were dried (Na_2SO_4). Removal of the solvents under reduced pressure (below 45 °C) gave crude dialdehyde as a yellow oil. This was used without any further purification in the next step. Thus, a solution of $Ph_3P^+CH_3Br^-$ (7.67 g, 21.5 mmol) and 12-crown-4-ether (0.7 mL, 4.3 mmol) in dry THF (20 mL) was cooled to −78 °C under an Ar atmosphere. A 1.6 M solution of *n*-BuLi in hexanes (13.1 mL, 30 mmol) was added dropwise and the mixture was stirred for 1 h at 0 °C. Then, it was re-cooled to −60 °C and a solution of the crude dialdehyde in dry THF (10 mL) was slowly added. The temperature was kept at −20 °C for 3 h and then the mixture was left at room temperature overnight. After quenching with a saturated aqueous ammonium chloride solution (20 mL) and the addition of H_2O (30 mL), the resulting slurry was extracted with CH_2Cl_2 (3×30 mL). The combined organic phases were dried (Na_2SO_4) and the solvents were removed under reduced pressure. The obtained residue was purified by column chromatography on silica gel with a mixture of hexane/EtOAc (20:1 v/v) to give 0.59 g of diene **15** (50% overall from **13**) as an oil. R_f (hexane/EtOAc 5:1 v/v) 0.48; $[\alpha]_D^{25}$ +4.0 (*c* 2.6, $CHCl_3$); FTIR

(neat film) 3074, 2986, 2954, 2931, 2858, 1642, 1472, 1370, 1251, 1096, 839, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.91–5.72 (m, 2H, H-2 and H-7), 5.37 (d, J=17.0 Hz, 1H, H-1_t), 5.23 (d, J=10.3 Hz, 1H, H-1_c), 5.01 (d, J=17.0 Hz, 1H, H-8_t), 4.92 (d, J=10.3 Hz, 1H, H-8_c), 4.59 (d, J=6.4 Hz, 1H, H-3), 3.61 and 3.57 (ABq, J=10.9 Hz, 2H, H-4′), 2.27–2.15 (m, 1H, H-6a), 2.08–1.95 (m, 1H, H-6b), 1.54–1.49 (m, 2H, H-5), 1.46 (s, 3H, CMe_2), 1.38 (s, 3H, CMe_2), 0.88 (s, 9H, CMe_3), 0.06 (s, 6H, $SiMe_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0 (C-7), 137.3 (C-2), 117.5 (C-1), 114.1 (C-8), 107.9 (*C*Me_2), 83.8 (C-4), 82.1 (C-3), 65.2 (C-4′), 31.4 (C-5), 28.3 (C-6), 27.5 (C*Me*$_2$), 26.9 (C*Me*$_2$), 25.9 (C*Me*$_3$), 18.0 (*C*Me_3), −5.4 ($SiMe_2$), −5.7 ($SiMe_2$); HRMS *m/z* 349.2171 [$C_{18}H_{34}O_3SiNa$ $(M+Na)^+$ requires 349.2169].

4.1.7. (1S,2S)-1-(tert-Butyldimethylsilyloxymethyl)-1,2-O-isopropylidene-cyclohex-3-ene-1,2-diol (*16*)

Grubbs' second generation catalyst {benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro-(tricyclohexylphosphine)ruthenium (**17**), a total of 68 mg, 0.08 mmol} was periodically added to a stirring solution of diene **15** (555 mg, 1.7 mmol) in dry CH_2Cl_2 (80 mL) at room temperature and under an Ar atmosphere. After 2 days, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel with a mixture of hexane/EtOAc (20:1 v/v) to give 415 mg of cyclohexene derivative **16** (82%) as an oil. R_f (hexane/EtOAc 5:1 v/v) 0.59; $[\alpha]_D^{25}$ +16.1 (*c* 0.3, $CHCl_3$); FTIR (neat film) 3031, 2985, 2954, 2930, 2858, 1472, 1367, 1252, 1214, 1099, 1084, 1042, 839, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (dt, J=9.6, 3.6 Hz, 1H, H-3), 5.83–5.78 (m, 1H, H-4), 4.39 (d, J=3.6 Hz, 1H, H-2), 3.63 and 3.47 (ABq, J=10.2 Hz, 2H, H-1′), 2.20–2.13 (m, 1H, H-5a), 2.00–1.92 (m, 1H, H-5b), 1.85 (dt, J=12.9, 5.8 Hz, 1H, H-6a); 1.68 (ddd, J=13.5, 7.7, 5.8 Hz, 1H, H-6b), 1.42 (s, 3H, CMe_2), 1.39 (s, 3H CMe_2), 0.86 (s, 9H, CMe_3), 0.04 (s, 6H, $SiMe_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.9 (C-4), 125.4 (C-3), 108.6 (*C*Me_2), 81.3 (C-1), 72.2 (C-2), 67.8 (C-1′), 28.5 (C-6), 28.1 (C*Me*$_2$), 28.0 (C*Me*$_3$), 25.9 (C*Me*$_2$), 22.7 (C-5), 18.3 (*C*Me_3), −5.4 ($SiMe_2$), −5.5 ($SiMe_2$); HRMS *m/z* 321.1855 [$C_{16}H_{30}O_3SiNa$ $(M+Na)^+$ requires 321.1856].

4.1.8. (1S,2S,3R,4R)-1-(tert-Butyldimethylsilyloxymethyl-1,2-O-isopropylidene-cyclohexane-1,2,3,4-tetraol (*18*)

A 2.5% w/v solution of OsO_4 in *tert*-BuOH (0.6 mL, 0.06 mmol) was added to a solution of cyclohexene derivative **16** (388 mg, 1.3 mmol) and NMO monohydrate (205 mg, 1.5 mmol) in a mixture of acetone/H_2O (1:1, 30 mL). The reaction mixture was stirred for 24 h at room temperature and then, with vigorous stirring, saturated aqueous solution of sodium thiosulfate was added dropwise until a starch/KI indicator gave a positive result. The resulting slurry was extracted with EtOAc (3×30 mL). The combined organic phases were dried (Na_2SO_4) and the solvents were removed under reduced pressure. The obtained residue was purified by column chromatography on silica gel with a mixture of hexane/EtOAc (2:1 v/v) to give 428 mg of diol **18** (99%) as a thick oil. R_f (hexane/EtOAc 1:1 v/v) 0.53; $[\alpha]_D^{25}$ +26.1 (*c* 0.5, $CHCl_3$); FTIR (neat film) 3428, 2949, 2928, 2855, 1462, 1368, 1248, 1089, 837, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.17 (d, J=2.4 Hz, 1H, H-2), 4.11–4.07 (m, 1H, H-4), 3.91–3.85 (m, 1H, H-3), 3.75 (d, J=9.8 Hz, 1H, H-1′a), 3.68 (br d, J=8.0 Hz, 1H, OH), 3.62 (d, J=9.8 Hz, 1H H-1′b), 2.48 (br s, 1H, OH), 1.89–1.67 (m, 4H, H-5 and H-6), 1.46 (s, 3H, CMe_2), 1.33 (s, 3H, CMe_2), 0.92 (s, 9H, CMe_3), 0.12 (s, 6H, $SiMe_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.4 (*C*Me_2), 81.0 (C-2), 79.3 (C-1), 69.7 (C-3), 69.2 (C-4), 67.8 (C-6′), 31.7 (C-6), 28.1 (C*Me*$_2$), 26.5 (C-5), 26.3 (C*Me*$_2$), 25.9 (C*Me*$_3$), 18.4 (*C*Me_3), −5.6 ($SiMe_2$); HRMS *m/z* 355.1909 [$C_{16}H_{32}O_5SiNa$ $(M+Na)^+$ requires 355.1911].

4.1.9. 6a-Carba-β-D-fructopyranose (*1*)

A cold mixture of TFA and H_2O (1:1, 40 mL) was added in a flask containing diol **17** (400 mg, 1.2 mmol). The mixture was stirred for 3 h at room temperature. Then, the volatiles were removed under reduced pressure and the mixture was co-evaporated with EtOH (3×20 mL). The obtained residue was re-dissolved in H_2O (20 mL) and this solution was washed with CH_2Cl_2 (3×20 mL). The aqueous phase was co-evaporated with EtOH (3×15 mL) to give 203 mg of 6a-carba-β-D-fructopyranose (**1**) (95%) as a white amorphous solid. Mp 96–98 °C (lit.[17b] mp 96–97 °C); $[\alpha]_D^{25}$ −53.5 (*c* 0.5, MeOH) [lit.[17b] $[\alpha]_D^{25}$ −53.0 (*c* 0.46, MeOH)]; ^1H and ^{13}C NMR were identical with those reported in the literature;[18] HRMS *m/z* 201.0734 [$C_7H_{14}O_5Na$ $(M+Na)^+$ requires 201.0733].

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