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Controlled Garegg Conditions for Selective Iodination on Pyranose Templates

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Regio- and stereoselective iodinations under controlled Garegg conditions were performed on vicinal diols and contiguous triols located on pyranose templates. β-D-Fructo- or psicopyranose-based diols were selectively iodinated at C-5 or C-4, respectively, to afford the L-*sorbo* or D-tagato iodohydrins. In contrast, the related triols only underwent selective iodination at C-5. Application of the process to D-gluco- and D-galactopyranosides resulted in selective iodination at C-3 or C-4, respectively, to afford the D-*allo* or D-*gluco* iodohydrins.

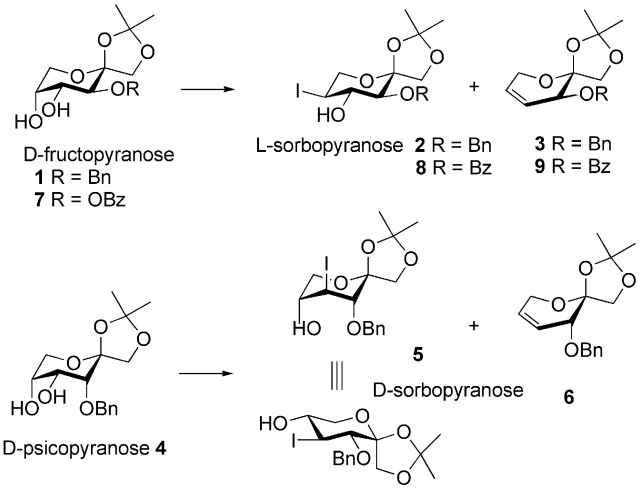
Introduction

Direct stereoselective nucleophilic displacement of a hydroxy group through Mitsunobu-related processes is an invaluable tool in organic synthesis and more specifically in glycochemistry, Selective iodo-functionalisation on polyhydroxylated templates has received a lot of attention over the years because iodo derivatives can easily be converted into a number of functions and have shown a broad range of reactivities based either on radical or on ionic transformations.[1]

Introduction of iodine by direct replacement of a hydroxy group is one of the major approaches, making use of a large number of reagents, many of them phosphorus-based.[2] The most popular iodination systems are indisputably those developed over the past decades by Garegg and Samuelsson.[3] The main drawback of those methods in glycochemistry is the generation of side-products, namely alkenes, so deoxy-iodo sugars are frequently prepared through standard nucleophilic displacement of sulfonates,[4] but also by more unusual methods.[5]

For the introduction of an iodine atom onto an unprotected carbohydrate skeleton, selective substitution of primary hydroxy groups over secondary ones is in principle readily achievable. In contrast, any attempt to achieve reaction of one specific secondary alcohol in the presence of others often requires the development of a protection/deprotection sequence, which can be a demanding task.[6] Direct application of Garegg's reagent system to vicinal diols is a key elimination method for one-step conversions into olefins.[7a] Here we disclose our studies on the use of a modified Garegg's reagent system to perform selective iodination of carbohydrate-based vicinal secondary diols[8] and its extension to triol systems.

A couple of D-ketopyranose derivatives were used for preliminary evaluation of the reaction. When the standard elimination procedure previously described by Lichtenthaler[7b] was first applied to **1** (Scheme 1), the olefin **3** was exclusively formed in 63% yield. With a slight change in the conditions, it could be observed after 1 h (Table 1, Entry 1) that the olefin **3** was formed in 53% yield together with the L-*sorbo*-configured 5-deoxy-5-iodopyranose **2** (40% yield) resulting from stereoselective introduction of iodine at C-5. The above result reveals not only the high efficiency of the reaction (over 93% conversion yield) but also the potential for selective iodination of a diol system. With that in mind, we carried out an optimisation study both on the D-*fructo* diol **1** and on its D-*psico* epimer **4**.



Scheme 1.[8] Selective iodination of ketopyrano diols.

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Table 1.[8] Conditions applied to promote selective iodination of vicinal diols in the D-*fructo* and the D-*psico* series.

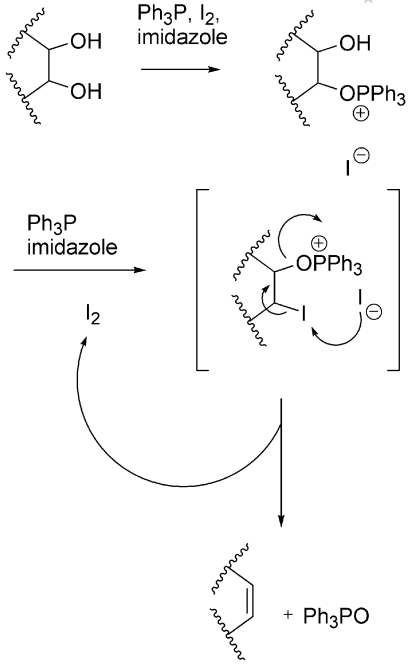
Entry	Starting ketose	Solvent	I_2 (equiv.)[a]	Temp.	Time (h)	Iodide (%)	Olefin (%)
1	**1**	toluene	1.4	110 °C	1	**2** (40)	**3** (53)
2	**4**	toluene	1.4	110 °C	1	**5** (8)	**6** (67)
3	**1**	toluene	1.4	r.t.	24	–[b]	–
4	**4**	toluene	1.4	r.t.	24	–[b]	–
5	**1**	THF	1.4	r.t.	15	**2** (7)	–
6	**4**	THF	1.4	r.t.	15	–[b]	–
7	**1**	THF	1.0	reflux	4	**2** (94)	–
8	**4**	THF	1.0	reflux	4	**5** (56)	–
9	**1**	1,4-dioxane	1.0	65 °C	72	**2** (67)	–
10	**4**	1,4-dioxane	1.0	65 °C	72	**5** (43)	–
11	**7**	THF	1.0	reflux	4	**8** (70)	
12	**7**	THF	1.4	reflux	20	**8** (–)	**9** (87)

[a] Together with triphenylphosphane (1.5 equiv.) and imidazole (3.0 equiv.). [b] No reaction detected by tlc.

To favour selective hydroxy substitution in the vicinal diol, the numbers of equivalents both of triphenylphosphane (1.5 equiv.) and of iodine (1.4 equiv.) were reduced. By severely limiting the amounts of both reagents relative to the original procedure (over 4 and 3 equiv., respectively),[3b] we hoped to attain a better selectivity. Both in the D-*fructo* and in the D-*psico* series (Table 1, Entries 1 and 2), however, we observed that olefination was predominating over iodination even after only 1 h under such conditions. Lowering the temperature (Entries 3 and 4) resulted in no reaction even after 24 h. However, replacement of toluene by THF (Entries 5 to 8) enhanced both solubilities and reactivities, and substitutive iodination could be optimised both in the D-*fructo* and in the D-*psico* series in THF at reflux over 4 h.

The above protocol, involving a moderate excess of iodine (1.4 equiv.), led us to reconsider the mechanism initially postulated by Garegg (Scheme 2).[3a] The elimination process appears to take place during the terminal phase with concomitant regeneration of iodine. In this last step, iodine could be seen to act as a catalyst, so a reduction in the amount of iodine to strictly one equivalent should favour selective monosubstitution.

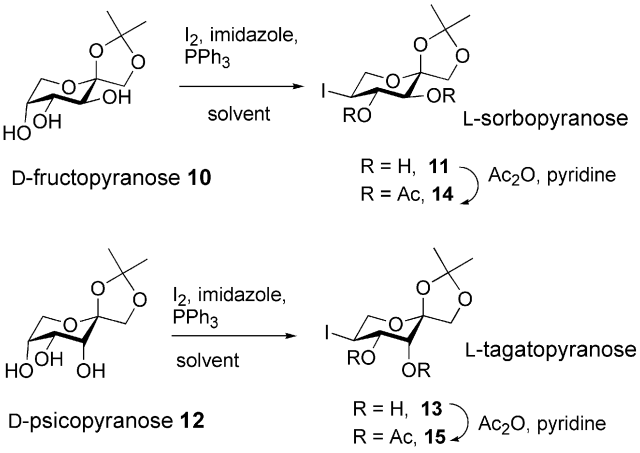
The best result was obtained by treatment of **1** with I_2 (1.0 equiv.), triphenylphosphane (1.5 equiv.) and imidazole (3.0 equiv.) for 4 h in THF at reflux, which provided selective iodination at C-5 in an excellent 94% yield (Entry 7). Application of the same conditions to the D-*psico* epimer **4** (Entry 8) resulted in selective iodination at C-4 and afforded a moderate 56% yield of the D-sorbo derivative **5**. Attempts to improve the conversion yields further by replacing THF by 1,4-dioxane at the same temperature still afforded the iodo compounds **2** and **5**, albeit with inferior yields (Entries 9 and 10). In the D-*fructo* series, iodination took place regio- and stereoselectively at C-5, whereas in the D-*psico* series iodination occurred regio- and stereoselectively at C-4. In both cases substitution with inversion of configuration was ascertained by NMR spectrometric assignments.



Scheme 2. The elimination mechanism under Garegg's conditions.[3a]

A comparative experiment was performed with the 3-*O*-benzoyl analogue **7** (Scheme 1), in which regio- and stereoselective iodo-inversion at C-5, affording the L-sorbo derivative **8** in 70% yield, was also observed (Entry 11). When the reaction was forced with iodine (1.4 equiv.) over 20 h (Entry 12), a clean, high-yielding conversion into the olefin **9** took place, through the transient iodo derivative **8** (easily detected by tlc monitoring).

With a protocol for selective iodination of *cis*-vicinal diols to hand, we became interested in exploring the possibilities of selective iodination on triol systems. The trials were thus extended to 1,2-*O*-isopropylidene-β-D-fructopyranose (**10**, Scheme 3) and 1,2-*O*-isopropylidene-β-D-psicopyranose (**12**): application of the previously established conditions also led to regio- and stereoselective iodinations. The C-5 regioselectivity observed for the D-fructopyrano triol **10**



Scheme 3. Selective iodination of ketopyrano triols.

was as expected, with inversion of configuration, thus yielding the L-sorbopyrano iodinated diol **11**. In contrast, the D-psicopyrano epimer **12** surprisingly underwent regioselective substitution not at C-4, but again at C-5, to yield the L-tagatopyrano iodinated diol **13**. The two diols **11** and **13** were quantitatively converted into the di-*O*-acetates **14** and **15** in order to facilitate the NMR structural analysis and ascertain the regio- and stereoselectivities of the reactions.

We attempted optimisation of the experimental conditions with the two triols **10** and **12**, starting from the procedure developed for diols (THF, reflux, 1.0 equiv. of iodine): in this case (Table 2, Entries 1 and 2), however, the observed yields did not exceed ca. 20% and even extension of the reaction time to 3 days (Entries 3 and 4) did not bring improvement. Replacement of THF with 1,4-dioxane and running the reaction under reflux for 4 h (Entries 5 and 6) resulted in increases in the yields of **11** and **13** to ca. 38%. No positive change was noted on increasing the reaction time to several days (Entries 7–10). However, on performing the reaction on a one-gram scale at reflux in 1,4-dioxane for 4 h (Entries 11 and 12), a more efficient conversion was achieved, producing the iodinated diols **11** and **13** in 65% and 63% yields, respectively.

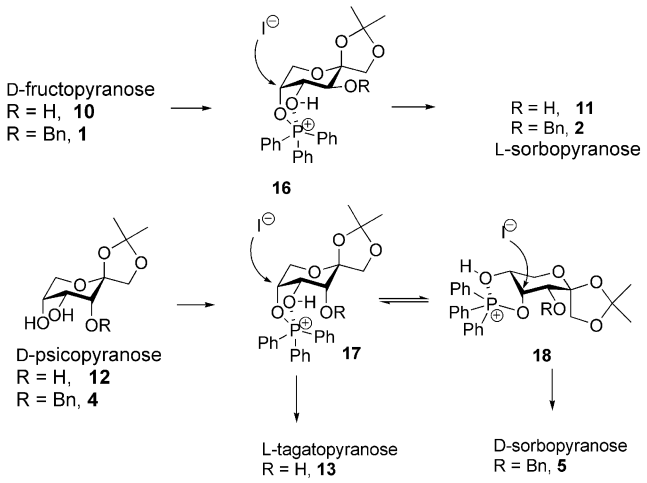
Table 2. Conditions applied to promote selective iodination of vicinal triols in the D-*fructo* and the D-*psico* series.

Entry	Starting ketose	Solvent	I_2 (equiv.)[a]	Temp.	Time (h)	Iodide (%)
1	**10**	THF	1.0	reflux	4	**11** (21)
2	**12**	THF	1.0	reflux	4	**13** (20)
3	**10**	THF	1.0	reflux	72	**11** (15)
4	**12**	THF	1.0	reflux	72	**13** (11)
5	**10**	dioxane	1.0	reflux	4	**11** (38)
6	**12**	dioxane	1.0	reflux	4	**13** (39)
7	**10**	dioxane	1.0	reflux	72	**11** (27)
8	**12**	dioxane	1.0	reflux	72	**13** (21)
9	**10**	dioxane	1.0	reflux	120	**11** (39)
10	**12**	dioxane	1.0	reflux	120	**13** (31)
11	**10**	dioxane	1.0	reflux	4	**11** (65)[b]
12	**12**	dioxane	1.0	reflux	4	**13** (63)[b]

[a] Together with triphenylphosphane (1.5 equiv.) and imidazole (3.0 equiv.). [b] Reactions performed on the gram scale.

Although satisfactory results had been obtained in terms of selective conversion of ketopyrano triols into iodinated diols, there was still a question about the C-5 regioselectivity on the D-psicopyranose template, which suggested reconsideration of the mechanistic pathway (Scheme 4).

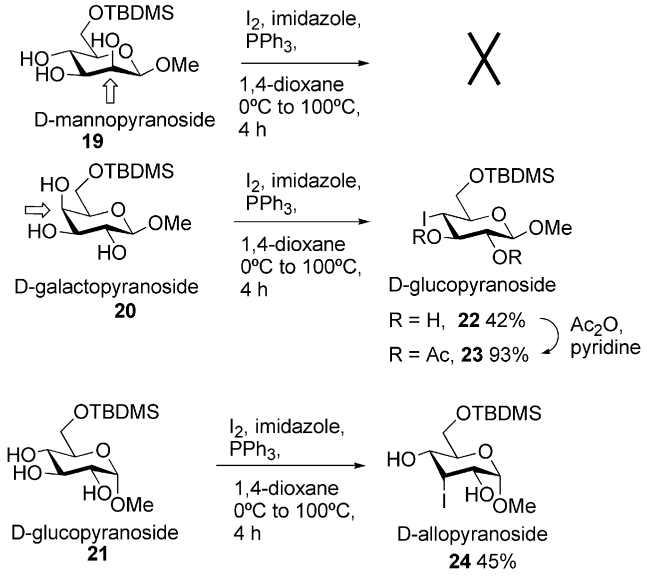
An initial postulate with regard to the selectivities in vicinal diols could be the driving force of the more thermodynamically stable isomer to be formed. In the D-fructopyranose case, the intermediate oxyphosphonium species **16** would fix the conformation and favour iodo-inversion at C-5 to produce an L-sorbopyranose framework, for which the $^2C_5$ conformer would have all substituents in equatorial positions. In the D-psicopyranose case, the similar intermediate **17** might enter into an equilibrium between two tautomers **17** and **18**, and the latter would preferably undergo



Scheme 4. Proposed mechanism for regioselective iodination in the D-*fructo* and the D-*psico* series.

inversion at C-4 to produce a D-sorbopyrano framework, in which the $^5C_2$ conformer would also have all substituents in equatorial positions. This proposed explanation would fit with the D-fructopyrano triol **10** but not with the D-psicopyrano triol **12**. The difference in reactivity of the latter system could be the result of the lower probability of tautomer **18** when R = H, together with contributing anchimeric assistance of the axial OH-3 group in tautomer **17** (Scheme 4): in such a case, the intermediate **17** would probably undergo "normal" iodo-inversion at C-5.

We then pushed our investigation further, into contiguous triols based on the aldopyranosides **19**, **20** and **21** (Scheme 5). The primary hydroxy groups of the starting β-pyranosides were first selectively protected in the form of *O*-silyl ethers. From the above results, we expected the iodo-inversion to occur at C-2 in the mannopyranoside **19** and at C-4 in the galactopyranoside **20**: in both cases these reac-



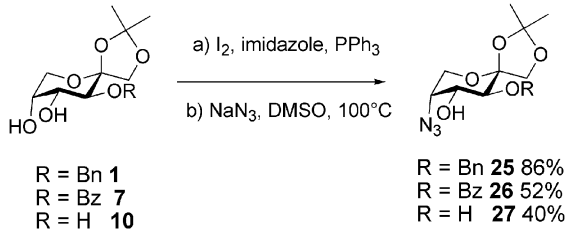
Scheme 5. Selective iodination of aldopyrano triols.

tions should afford fully equatorial products, whereas no prediction of selectivity could reasonably be put forward for the glucopyranoside **21**.

Iodination of the D-mannopyranoside **19** was not successful, the reaction leading to an intractable mixture of compounds. On the other hand, the D-galactopyranoside **20** underwent C-4 regio- and stereoselective substitution to afford a 42% yield of the 4-deoxy-4-iodo-D-glucopyranoside **22**, characterised as its 2,3-di-*O*-acetate **23** to facilitate NMR analysis. Finally, iodination of the D-glucopyranoside **22** occurred regio- and stereoselectively at C-3 to afford the 3-deoxy-3-iodo-D-allopyranoside **24** in 45% yield. This last case, of hardly predictable selectivity, could be closely correlated with previous results reported for Mitsunobu-type modifications of pyranosides.[9]

This study of selective iodination of vicinal diols and contiguous triols on pyranose templates under modified Garegg conditions has delivered interesting results in terms of regio- and stereoselectivity. From the above examples, we might propose some keys to elucidate the mechanism: one could assume that the first step of the conversion is the formation of a transient oxyphosphonium species through the reaction between the iodo-phosphonium reagent and the more nucleophilic hydroxy group. When a vicinal *cis* hydroxy group is present, a pentacoordinating phosphorus complex can arise, further inducing equilibration between tautomers (Scheme 4). The nucleophilic iodide ion finally attacks, in most cases, the better activated carbon site (**2**, **5**, **11**, **13**, **22**) and/or the better accessible position (**13**, **24**) to produce the more stable iodo derivative in a selective manner.

Over recent years D-fructose has been used as a starting material to prepare polyhydroxylated pyrrolidines, notably 2,5-dideoxy-2,5-imino-D-mannitol (DMDP).[6b,10] In previous approaches, multistep sequences were needed to reach the key intermediate in which an azido group is introduced at C-5. From the present study it has emerged that selective iodinations in D-fructopyrano systems should readily allow efficient introduction of azido moieties at C-5 in the D-*fructo* series (Scheme 6).



Scheme 6. Two-step formation of D-*fructo* azides from D-fructopyrano diols or triol.

Conversions through double inversions at C-5 in the D-*fructo* precursors **1** and **7** readily afforded the 3-*O*-benzyl-D-*fructo* azide **25** and the 3-*O*-benzoyl-D-*fructo* azide **26** in moderate to excellent overall yields. Even more attractive was the 40% yield two-step conversion of the readily available 1,2-*O*-isopropylidene-β-D-fructopyranose (**10**) into its 5-azido counterpart **27**: this intermediate can be regarded as a cornerstone in a six-step formal synthesis, involving our selective iodination protocol, of DMDP from D-fructose.

Conclusions

We have shown that regio- and stereoselective iodinations under controlled Garegg conditions can be efficiently performed on vicinal diols and contiguous triols on pyranose templates. β-D-Fructo- or psicopyranose-derived diols undergo selective iodo inversion at C-5 or C-4, respectively, to afford L-*sorbo* or D-*tagato* iodohydrins. In contrast, only selective iodination at C-5 occurs in the case of the related ketopyrano triols. Extension of the procedure to D-gluco- and D-galactopyranosides results in selective iodination at C-3 or C-4, respectively, to afford the D-*allo* or D-*gluco* iodohydrins. This method can be profitably applied in a regioselective two-step azidation of pyranose templates.

Experimental Section

General: Anhydrous reactions were performed under argon in predried flasks, with use of anhydrous solvents (distilled when necessary as described in ref.[20]) All chemicals obtained from commercial suppliers were used without further purification. TLC (precoated aluminium-backed plates, Merck Kieselgel 60F254) were visualised with UV light (254 nm) and by charring after spraying with H_2SO_4 solution in ethanol (10%). Column chromatography was carried out with silica gel 60N (spherical, neutral, 40–63 μm). Melting points were determined with a Büchi 510 apparatus and are uncorrected. Optical rotations were measured at 20 °C with a Perkin–Elmer 341 polarimeter with a 1 dm path length. IR spectra (absorption frequencies in cm^{-1}) were measured with a Thermo Scientific Nicolet iS10 FT-IR spectrophotometer. NMR spectra were recorded with a Bruker DPX 400 Avance 2 (400 MHz for ^1H; 100.6 MHz for ^{13}C) spectrometer with TMS as the internal standard. Chemical shifts are expressed in parts per million (ppm, δ units) downfield from TMS. Splitting patterns are designated as br. (broad), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and coupling constants are expressed in Hertz (Hz). Multiplicities were determined by use of the DEPT 135 sequence and peak assignments were established by NOESY, COSY, HSQC and HMBC experiments on all reported compounds. Mass spectra (MS) were recorded with an API300 Applied Biosystems instrument in electrospray (ES) mode and high-resolution mass spectra (HRMS) were recorded with a MicrOTOF-QII spectrometer in the electrospray ionisation (ESI) mode.

3-*O*-Benzyl-1,2-*O*-isopropylidene-β-D-fructopyranose (1): Preparation from D-fructose as described in ref.[11] [70551-32-5].

3-*O*-Benzoyl-1,2-*O*-isopropylidene-β-D-fructopyranose (7): Preparation in quantitative yield as described in ref.[12] [99648-49-4].

3-*O*-Benzyl-1,2-di-*O*-isopropylidene-β-D-psicopyranose (4): Preparation in five steps from D-fructose as described in ref.[13] [872345-40-9].

General Procedure for Regioselective Iodination of Diols: Triphenylphosphane (315 mg, 1.5 equiv.), imidazole (164 mg,

3.0 equiv.) and iodine (203 mg, 1.0 equiv.) were added to a solution of the diol (0.8 mmol) in THF (5 mL) and the mixture was stirred under reflux for 4 h. After concentration in vacuo and co-evaporations with toluene, the residue was purified by flash column chromatography (eluent PE/EtOAc 19:1 then 9:1).

3-*O*-Benzyl-5-deoxy-5-iodo-1,2-*O*-isopropylidene-α-L-sorbopyranose (2): Obtained from **1** (1.27 g, 94%) as a white solid, m.p. 123–125 °C, $[\alpha]_D$ = +51 (*c* = 0.14, $CHCl_3$), see ref.[8]

3-*O*-Benzyl-4,5-dideoxy-1,2-*O*-isopropylidene-α-L-*glycero*-hex-4-en-2-ulopyranose (3): Detection in trace amounts, see ref.[14] [132369-48-3].

3-*O*-Benzoyl-5-deoxy-5-iodo-1,2-*O*-isopropylidene-α-L-sorbopyranose (8): Obtained from **7** (0.97 g, 70%) as a white solid, m.p. 148–151 °C (PE/AcOEt), $[\alpha]_D$ = –136 (*c* = 0.75, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.43, 1.51 (2 × s, 6 H, CH_3), 2.69 (d, J_{vic} = 4.4 Hz, 1 H, OH-4), 3.92 and 3.97 (2 × d, J_{gem} = 9.2 Hz, 2 H, AB system, 1b-H, 1a-H), 3.93 (dd, J_{vic} = 5.0 Hz, 1 H, 6b-H), 4.03 (m, 1 H, 5-H), 4.14 (d, J_{gem} = 11.2 Hz, 1 H, 6a-H), 4.18 (dt, J_{vic} = 10.0 Hz, 1 H, 4-H), 5.16 (d, $J_{3,4}$ = 9.6 Hz, 1 H, 3-H), 7.43 (t, J_{vic} = 7.5 Hz, 2 H, *meta*-H-Ar), 7.58 (t, J_{vic} = 7.6 Hz, 1 H, *para*-H-Ar), 8.07 (d, J_{vic} = 7.5 Hz, 2 H, *ortho*-H-Ar) ppm. ^{13}C NMR: δ = 26.3, 26.8 (CH_3), 29.3 (C-5), 65.5 (C-6), 71.9 (C-1), 72.3 (C-3), 74.5 (C-4), 104.8 (C-2), 112.7 (Me_2C), 128.7 (*CH*-Ar *meta*), 129.2 (C_{IV}–Ar), 130.1 (*CH*-Ar *ortho*), 133.8 (*CH*-Ar *para*), 166.4 (C=O) ppm. IR (film): $\tilde{\nu}$ = 3540 (OH), 1708 (C=O). ESI-HRMS: calcd. for $C_{16}H_{19}INaO_6$: 457.0124; found 457.0133.

3-*O*-Benzoyl-4,5-dideoxy-1,2-*O*-isopropylidene-α-L-*glycero*-hex-4-en-2-ulopyranose (9): See ref.[7b] [99648-50-7].

3-*O*-Benzyl-4-deoxy-4-iodo-1,2-*O*-isopropylidene-β-D-sorbopyranose (5): This compound was obtained from **4** (0.76 g, 56%) in 56% yield as a pale yellow solid, m.p. 98–101 °C (PE/AcOEt), $[\alpha]_D$ = +21 (*c* = 0.54, $CHCl_3$), see ref.[8]

3-*O*-Benzyl-4,5-dideoxy-1,2-*O*-isopropylidene-β-D-*glycero*-hex-4-en-2-ulopyranose (6): Preparation in trace amounts [99685-19-5]. Orange oil, $[\alpha]_D$ = –240 (*c* = 5.53, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.37, 1.52 (2 × s, 6 H, CH_3), 3.78 (dd, J_{vic} = 4.3, $J_{3,5}$ = 1.8 Hz, 1 H, 3-H), 4.13 (s, 2 H, 1-H), 4.26 (br. d, J_{gem} = 17.1 Hz, 1 H, 6b-H), 4.39 (ddd, $J_{5,6a}$ = $J_{4,6a}$ = 2.0 Hz, 1 H, 6a-H), 4.56 and 4.66 (2 × d, J_{gem} = 11.8 Hz, 2 H, AB system, PhCH_2), 5.98 (br. d, $J_{4,5}$ = 10.3 Hz, 1 H, 5-H), 6.09 (br. d, 1 H, 4-H), 7.24–7.38 (m, 5 H, Ar-H) ppm. ^{13}C NMR: δ = 26.3, 27.1 (CH_3), 61.7 (C-6), 70.3 (PhCH_2), 71.9 (C-1), 72.9 (C-3), 103.9 (C-2), 111.9 (Me_2C), 122.2 (C-5), 127.8, 127.9, 128.9 (*CH*-Ar), 131.0 (C-4), 138.3 (C_{IV}–Ar) ppm. MS (ES$^+$): *m*/*z* = 299.0 [M + Na]$^+$.

1,2-*O*-Isopropylidene-β-D-fructopyranose (10): Preparation in two steps from D-fructose as described in refs.[14,15] [66900–93–4]. Colourless solid, m.p. 98–103 °C (AcOEt), $[\alpha]_D$ = –145 (*c* = 0.43, MeOH). ^{1}H NMR ([D$_6$]DMSO): δ = 1.31, 1.37 (2 × s, 6 H, CH_3), 3.46–3.50 (m, 3 H, 3-H, 4-H, 6b-H), 3.68 (br. s, 1 H, 5-H), 3.71 (d, J_{gem} = 10.8 Hz, 1 H, 6a-H), 3.73 (d, J_{gem} = 8.4 Hz, 1 H, 1b-H), 4.01 (d, 1 H, 1a-H), 4.56 (d, J_{vic} = 3.6 Hz, 1 H, OH-5), 4.64 and 4.76 (2 × d, J_{vic} = 5.2 and 6.8 Hz, 2 H, OH-3, OH-4) ppm. ^{13}C NMR: δ = 26.2, 27.0 (CH_3), 64.5 (C-6), 67.4 (C-4), 68.9 (C-5), 70.3 (C-1), 71.1 (C-3), 106.4 (C-2), 110.6 (Me_2C) ppm.

1,2-*O*-Isopropylidene-β-D-psicopyranose (12): Preparation from 1,2;4,5-di-*O*-isopropylidene-β-D-psicopyranose in quantitative yield as described in ref.[16] [20789–58–6]. Colourless solid, m.p. 159–162 °C (AcOEt). $[\alpha]_D$ = –124 (*c* = 0.53, MeOH). ^{1}H NMR ([D$_6$]-DMSO): δ = 1.29, 1.38 (2 × s, 6 H, CH_3), 3.46 (dd, $J_{3,4}$ = 2.4 Hz, 1 H, 3-H), 3.60–3.72 (m, 4 H, 4-H, 5-H, 6a-H, 6b-H), 3.88 (d, J_{gem} = 9.1 Hz, 1 H, 1b-H), 3.96 (d, 1 H, 1a-H), 4.89 and 5.12 (2 × d, J_{vic} = 5.8 and 5.3 Hz, 2 H, OH-4, OH-5), 5.01 (d, J_{vic} = 8.0 Hz, 1 H, OH-3) ppm. ^{13}C NMR: δ = 26.3, 26.9 (CH_3), 64.8 (C-6), 66.4 (C-4), 68.5 (C-5), 72.0 (C-1), 72.9 (C-3), 105.8 (C-2), 110.6 (Me_2C) ppm. IR (film): $\tilde{\nu}$ = 3390, 3290 (OH) cm^{-1}. MS (ES$^+$): *m*/*z* = 243.0 [M + Na]$^+$.

Methyl 6-*O*-*tert*-Butyldimethylsilyl-α-D-mannopyranoside (19): Preparation as described in ref.[18] [74247-81-7].

Methyl 6-*O*-*tert*-Butyldimethylsilyl-α-D-galactopyranoside (20): Preparation in 90% yield as described in ref.[17b,19] [181480-80-8].

Methyl 6-*O*-*tert*-Butyldimethylsilyl-β-D-glucopyranoside (21): Preparation in 92% yield as described in ref.[17] [74264-88-3].

General Procedure for Regioselective Iodination of Triols: Triphenylphosphane (315 mg, 1.5 equiv.), imidazole (164 mg, 3.0 equiv.) and iodine (203 mg, 1.0 equiv.) were added to a solution of the triol (0.8 mmol) in 1,4-dioxane (5 mL) and the mixture was stirred under reflux for 4 h. After concentration in vacuo and co-evaporations with toluene, the residue was purified by flash column chromatography (eluent PE/EtOAc 19:1 then 9:1).

5-Deoxy-5-iodo-1,2-*O*-isopropylidene-β-L-sorbopyranose (11): Preparation from **10** (0.97g, 65%) as a yellowish solid, m.p. 82–85 °C (PE/AcOEt), $[\alpha]_D$ = –11 (*c* = 0.51, MeOH). ^{1}H NMR ($CDCl_3$): δ = 1.46 and 1.51 (2 × s, 6 H, CH_3), 2.10 (d, J_{vic} = 9.6 Hz, 1 H, OH-3), 2.80 (d, J_{vic} = 1.6 Hz, 1 H, OH-4), 3.44 (t, J_{vic} = 9.2 Hz, 1 H, 3-H), 3.81 (dt, J_{vic} = 8.8 Hz, 1 H, 4-H), 3.87 (dd, 1 H, 6b-H), 3.93–3.97 (m, 1 H, 5-H), 3.97 (d, 1 H, 1b-H), 4.04 (d, J_{gem} = 10.8 Hz, 1 H, 6a-H), 4.18 (d, J_{gem} = 8.8 Hz, 1 H, 1a-H) ppm. ^{13}C NMR: δ = 26.4, 26.7 (CH_3), 28.2 (C-5), 66.0 (C-6), 72.1 (C-1), 72.9 (C-3), 77.0 (C-4), 105.7 (C-2), 112.6 (Me_2C) ppm. IR (film): $\tilde{\nu}$ = 3555 (OH) cm^{-1}. MS (ES$^+$): *m*/*z* = 413.0 [M + AcOH + Na]$^+$.

3,4-Di-*O*-acetyl-5-deoxy-5-iodo-1,2-*O*-isopropylidene-β-L-sorbopyranose (14): Preparation from **11** in quantitative yield by standard acetylation; yellowish solid, m.p. 95–98 °C (PE/AcOEt), $[\alpha]_D$ = +6 (*c* = 0.18, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.43, 1.49 (2 × s, 6 H, CH_3), 2.06, 2.08 (2 × s, 6 H, CH_3CO), 3.84 (d, J_{gem} = 9.3 Hz, 1 H, 1b-H), 3.89–4.04 (m, 3 H, 1a-H, 5-H, 6b-H), 4.12 (d, J_{gem} = 10.3 Hz, 1 H, 6a-H), 4.97 (d, J_{vic} = 9.7 Hz, 1 H, 3-H), 5.48 (t, J_{vic} = 9.7 Hz, 1 H, 4-H) ppm. ^{13}C NMR: δ = 20.8, 21.0 (2 × CH_3CO), 22.3 (C-5), 26.1, 26.2 (CH_3), 65.8 (C-6), 70.7 (C-3), 71.9 (C-1), 74.0 (C-4), 104.4 (C-2), 112.9 (Me_2C), 169.5, 170.3 (C=O) ppm. IR (film): $\tilde{\nu}$ = 1740 (C=O). ESI-HRMS: calcd. for $C_{13}H_{19}INaO_7$: 437.0073; found 437.0063.

5-Deoxy-5-iodo-1,2-*O*-isopropylidene-α-L-tagatopyranose (13): Preparation from **12** (0.94g, 63%) as a yellowish solid, m.p. 155–158 °C (PE/AcOEt), $[\alpha]_D$ = –13 (*c* = 0.45, MeOH). ^{1}H NMR ($CDCl_3$): δ = 1.40, 1.50 (2 × s, 6 H, CH_3), 2.44 (d, J_{vic} = 3.6 Hz, 1 H, OH-3), 2.54 (d, J_{vic} = 4.4 Hz, 1 H, OH-4), 3.83 (t, J_{vic} = 3.0 Hz, 1 H, 3-H), 3.94 (dd, J_{vic} = 5.2, J_{gem} = 11.2 Hz, 1 H, 6b-H), 4.01–4.05 (m, 1 H, 4-H), 4.04 (d, J_{gem} = 9.4 Hz, 1 H, 1b-H), 4.09 (d, 1 H, 6a-H), 4.12 (d, 1 H, 1a-H), 4.22 (m, 1 H, 5-H) ppm. ^{13}C NMR: δ = 26.5, 26.8 (CH_3), 29.7 (C-5), 65.9 (C-6), 68.3 (C-1), 73.4, 73.6 (C-3, C-4), 96.0 (C-2), 112.6 (Me_2C) ppm. IR (film): $\tilde{\nu}$ = 3555 (OH) cm^{-1}. MS (ES$^+$): *m*/*z* = 413.0 [M + AcOH + Na]$^+$.

3,4-Di-*O*-acetyl-5-deoxy-5-iodo-1,2-*O*-isopropylidene-α-L-tagatopyranose (15): Preparation from **13** in quantitative yield by standard acetylation; yellowish solid, m.p. 106–109 °C (PE/AcOEt), $[\alpha]_D$ = –26 (*c* = 0.17, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.41, 1.49 (2 × s, 6 H, CH_3), 2.04, 2.12 (2 × s, 6 H, CH_3CO), 3.78 (d, J_{gem} = 9.2 Hz, 1 H, 1b-H), 3.93 (d, 1 H, 1a-H), 4.08 (dd, J_{gem} = 10.4, J_{vic} = 3.6 Hz, 1 H, 6b-H), 4.14–4.23 (m, 2 H, 5-H, 6a-H), 5.17 (d, $J_{3,4}$

= 3.2 Hz, 1 H, 3-H), 5.35 (dd, $J_{4,5}$ = 10.8 Hz, 1 H, 4-H) ppm. ^{13}C NMR: δ = 20.8 (2 × *C*H$_3$CO), 21.2 (C-5), 26.4, 26.9 (*C*H$_3$), 66.6 (C-6), 72.2 (C-3), 72.7 (C-4), 73.4 (C-1), 103.9 (C-2), 113.6 (Me$_2$*C*), 169.5, 169.9 (C=O) ppm. IR (film): $\tilde{\nu}$ = 1750 (C=O). ESI-HRMS: calcd. for $C_{13}H_{19}INaO_7$: 437.0073; found 437.0090.

Methyl 2,3-Di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl-4-deoxy-4-iodo-α-D-glucopyranoside (23): The crude iodination mixture obtained from the D-galactopyranoside **20** was concentrated in vacuo and the residue was subjected to a standard acetylation procedure. Purification by flash column chromatography (eluent PE/EtOAc 19:1) afforded **23** (0.22 g, 40% overall yield from **20**) as a yellowish solid, m.p. 93–96 °C (PE/AcOEt), $[\alpha]_D$ = +58 (*c* = 0.23, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.09, 0.10 (2 × s, 6 H, *Me*$_2$Si), 0.92 (s, 9 H, *t*BuSi), 2.06, 2.10 (2 × s, 3 H, *CH*$_3$CO), 3.39 (s, 3 H, OMe), 3.95–4.09 (m, 4 H, 4-H, 5-H, 6a-H, 6b-H), 4.78 (dd, $J_{2,1}$ = 3.6, $J_{2,3}$ = 10.0 Hz, 1 H, 2-H), 4.95 (d, 1 H, 1-H), 5.61 (t, $J_{3,4}$ = 10.0 Hz, 1 H, 3-H) ppm. ^{13}C NMR: δ = –5.0, –5.2 (*Me*$_2$Si), 18.5 (C$_{IV}$–*t*BuSi), 20.9, 21.1 (*CH*$_3$CO), 25.6 (C-4), 26.1 (*Me*$_3$CSi), 55.5 (OMe), 64.3 (C-6), 71.9 (C-2), 72.6 (C-3), 72.9 (C-5), 97.3 (C-1), 169.6, 170.3 (C=O) ppm. IR (film): $\tilde{\nu}$ = 1755 (C=O) cm^{-1}. MS (ES$^+$): *m*/*z* = 503.0 [M + H]$^+$. ESI-HRMS: calcd. for $C_{17}H_{32}IO_7Si$: 503.0956; found 503.0952.

Methyl 6-*O*-*tert*-Butyldimethylsilyl-3-deoxy-3-iodo-β-D-allopyranoside (24): Obtained from **21** (0.31g, 45%) as a yellowish solid, m.p. 152–155 °C (PE/AcOEt), $[\alpha]_D$ = +9 (*c* = 0.87, MeOH). ^{1}H NMR ($CDCl_3$): δ = 0.09 (s, 6 H, *Me*$_2$Si), 0.89 (s, 9 H, *tBu*Si), 2.85 (d, $J_{OH,2}$ = 2.8 Hz, 1 H, OH-2), 3.36 (ddd, $J_{5,4}$ = 4.8, $J_{5,6a}$ = 6.3, $J_{5,6b}$ = 8.8 Hz, 1 H, 5-H), 3.54 (s, 3 H, OMe), 3.59 (dd, $J_{2,3}$ = 2.6, $J_{2,1}$ = 7.4 Hz, 1 H, 2-H), 3.65 (d, $J_{OH,4}$ = 1.6 Hz, 1 H, OH-4), 3.79–3.85 (m, 1 H, 4-H), 3.82 (d, J_{gem} = 10.2 Hz, 1 H, 6b-H), 3.90 (d, 1 H, 6a-H), 3.93 (m, 1 H, 3-H), 4.18 (d, 1 H, 1-H) ppm. ^{13}C NMR: δ = –5.3 (*Me*$_2$Si), 18.3 (C$_{IV}$–*t*BuSi), 25.9 (*Me*$_3$CSi), 38.9 (C-3), 57.2 (OMe), 64.8 (C-6), 74.8 (C-2, C-4), 76.6 (C-5), 103.8 (C-1) ppm. IR (film): $\tilde{\nu}$ = 3250 (OH) cm^{-1}. MS (ES$^+$): *m*/*z* = 419.0 [M + H]$^+$. ESI-HRMS: calcd. for $C_{13}H_{27}INaO_5Si$: 441.0565; found 441.0561.

5-Azido-3-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-β-D-fructopyranose (25): Sodium azide (464 mg, 3.0 equiv.) was added to a solution of the iodo derivative **1** (1.0 g, 2.38 mmol) in DMSO (8 mL) and the mixture was then stirred at 90 °C for 3 days. After the mixture had cooled, ethyl acetate (200 mL) was added and the solution was washed with water (3 × 40 mL) and then brine (40 mL). After drying over $MgSO_4$ and concentration in vacuo, the crude residue was purified by column chromatography (eluent PE/EtOAc 9:1) to afford the azide **25** (734 mg, 92% yield) as a colourless solid, m.p. 107–109 °C (PE/AcOEt), $[\alpha]_D$ = –117 (*c* = 0.25, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = , 1.42, 1.48 (2 × s, 6 H, *CH*$_3$), 2.31 (d, $J_{OH,4}$ = 5.2 Hz, 1 H, OH), 3.67 (d, $J_{3,4}$ = 9.6 Hz, 1 H, 3-H), 3.74 (dd, J_{gem} = 12.4, $J_{6b,5}$ = 1.6 Hz, 1 H, 6b-H), 3.94 (m, 1 H, 5-H), 3.96 (d, J_{gem} = 8.6 Hz, 1 H, 1b-H), 3.99 (dd, $J_{6a,5}$ = 1.6 Hz, 1 H, 6a-H), 4.03 (d, 1 H, 1a-H), 4.19 (ddd, $J_{4,3}$ = 4.4, $J_{4,OH}$ = 5.2, $J_{4,5}$ = 9.6 Hz, 1 H, 4-H), 4.75 and 4.84 (2 × d, J_{gem} = 11.6 Hz, 2 H, AB system, Ph*CH*$_2$), 7.32–7.38 (m, 5 H, Ph) ppm. ^{13}C NMR: δ = 26.2, 27.0 (*CH*$_3$), 61.9 (C-6), 62.4 (C-5), 71.7 (C-4), 72.0 (C-1), 73.0 (C-3), 75.8 (Ph*CH*$_2$), 105.7 (C-2), 112.3 (Me$_2$*C*), 128.1, 128.3, 128.8 (*CH*-Ar), 137.8 (C$_{IV}$–Ar) ppm. IR (film): $\tilde{\nu}$ = 3541 (OH), 2119 (N$_3$) cm^{-1}. MS (ES$^+$): *m*/*z* = 374.5 [M + K]$^+$. ESI-HRMS: calcd. for $C_{16}H_{21}N_3NaO_5$: 358.1379; found 358.1377.

5-Azido-3-*O*-benzoyl-5-deoxy-1,2-*O*-isopropylidene-β-D-fructopyranose (26): Sodium azide (450 mg, 3.0 equiv.) was added to a solution of the iodo derivative **7** (1.0 g, 2.3 mmol) in DMSO (8 mL) and the mixture was then stirred at 90 °C for 3 days. After similar workup as for **25**, column chromatography (eluent PE/EtOAc 9:1) afforded the azide **26** (595 mg, 74% yield) as a colourless oil, $[\alpha]_D$ = –63 (*c* = 0.86, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.42, 1.49 (2 × s, 6 H, *CH*$_3$), 3.72–3.80 (m 1 H, 6-H), 3.93–4.08 (m, 4 H, 1a-H, 4-H, 5-H, 6b-H), 4.20 (d, J_{gem} = 8.8 Hz, 1 H, 1b-H), 5.43 (d, $J_{3,4}$ = 10.0 Hz, 1 H, 3-H), 7.43 (t, J_{vic} = 7.5 Hz, 2 H, *meta*-H-Ar), 7.58 (t, J_{vic} = 7.6 Hz, 1 H, *para*-H-Ar), 8.07 (d, J_{vic} = 7.5 Hz, 2 H, *ortho*-H-Ar) ppm. ^{13}C NMR: δ = 26.4, 26.6 (*CH*$_3$); 60.7 (C-4), 62.3 (C-6), 67.5 (C-5), 72.1 (C-1), 74.1 (C-3), 106.2 (C-2), 112.6 (Me$_2$*C*), 128.6, 128.7, 130.1 (*CH*-Ar); 133.8 (C$_{IV}$–Ar), 166.7 (C=O) ppm. IR (film): $\tilde{\nu}$ = 3459 (OH), 2104 (N$_3$), 1717 (C=O). ESI-HRMS: calcd. for $C_{16}H_{19}N_3NaO_6$: 372.1172; found 372.1177.

5-Azido-5-deoxy-1,2-*O*-isopropylidene-β-D-fructopyranose (27): Obtained from **10** in 62% yield as a colourless solid, m.p. 113–114 °C, see ref.[6a] [94801-01-1].

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