Available online at www.sciencedirect.com
SCIENCE DIRECT
Carbohydrate Research 341 (2006) 1737–1742
Carbohydrate RESEARCH

Note

Synthesis of 1,4-anhydro-D-fructose and 1,4-anhydro-D-tagatose

Gyula Dekany,[a] Inge Lundt,[b,*] Andreas J. Steiner[c] and Arnold E. Stütz[c]

[a]*Glycom ApS, Department of Chemistry, Technical University of Denmark (DTU), Building 201, DK-2800 Kgs. Lyngby, Denmark*
[b]*Department of Chemistry, Technical University of Denmark (DTU), Building 201, DK-2800 Kgs. Lyngby, Denmark*
[c]*Glycogroup, Institut für Organische Chemie der Technischen Universität Graz, Stremayrgasse 16, A-8010 Graz, Austria*

Received 6 February 2006; received in revised form 27 February 2006; accepted 1 March 2006
Available online 5 April 2006

Abstract—1,4-Anhydro-D-fructose and 1,4-anhydro-D-tagatose were prepared from 1,2-*O*-isopropylidene-D-glucofuranose via the common intermediate 3,5,6-tri-*O*-benzyl-D-glucitol. The title compounds may be interesting anti-oxidants and feature activities akin to their natural pyranoid counterpart, 1,5-anhydro-D-fructose.

Keywords: 1,4-Anhydroketose; Anti-oxidant; Synthesis

1,5-Anhydro-D-fructose, **1** (AF),[1] is a natural product liberated from starch as a metabolite of microbial glucan lyases.[2] Not unexpectedly, similar to ascorbic acid, it was found to be a potent anti-oxidant agent.[3] Aqueous solutions of compound **1** are stable under neutral conditions and, unlike ascorbic acid, are not oxidised by molecular oxygen.[4] Synthetic approaches have been pioneered by Lichtenthaler[5] in 1980, and classical chemical[6] and enzymatic[7] routes from 1,5-anhydro-D-glucitol have been made available since. Due to its interesting properties, 1,5-anhydrofructose properties are heavily patented, for example, as a possible ascorbic acid replacement in cosmetics and food industry.[8]

Interestingly, apart from 1,5-anhydro-D-tagatose[9] related anhydrohexoses differing in ring size or configuration have not been reported thus far. Such compounds may bear similarly exciting properties as 1,5-anhydrofructose (**1**) and could be a first step towards the 'missing links' between AF and L-ascorbic acid (**2**) (Fig. 1).

We have now prepared the furanoid AF-isomers 1,4-anhydro-D-fructose (**3**) as well as its epimer at C-4, 1,4-anhydro-D-tagatose (**4**) via a simple route from 1,2-*O*-isopropylidene-D-glucofuranose (**5**). The key intermediate, an open-chain glucitol derivative, was available following work by Mulzer and co-workers:[10] Compound **5** was conventionally per-*O*-benzylated employing benzyl bromide in tetrahydrofurane/*N*,*N*-dimethylformamide (4:1) in the presence of NaH giving per-*O*-protected-D-glucofuranose **6**. 1,2-*O*-Deprotection with *p*-toluenesulfonic acid occurred smoothly in CH_3CN/H_2O furnishing aldose **7**. Reduction of free glucofuranose **7** with $NaBH_4$ in methanol gave 3,5,6-tri-*O*-benzyl-D-glucitol **8** in excellent overall yield (73% from compound **5**) (Scheme 1).

Selective 1-*O*-tosylation was achieved by slow addition of 2.9 equiv of tosyl chloride to a solution of **8** in dichloromethane/pyridine (30:1). Due to spontaneous ring closure under these conditions, the labile tosylate **9** could not be detected by TLC and the exclusively isolated product turned out to be the desired 1,4-anhydro-3,5,6-tri-*O*-benzyl-D-glucitol (**10**). Standard Dess–Martin oxidation in dichloromethane employing 1.4 equiv of reagent resulted in smooth formation of the fully protected 1,4-anhydro-D-fructose derivative **11**. This was converted into the corresponding diethyl acetal **12** by reaction with ethanol in the presence of *p*-toluenesulfonic acid at ambient temperature.

Hydrogenolytic deprotection of **11** and the acetal **12**, respectively, gave free 1,4-anhydro-D-fructose (**3**) (48% from compound **5**) and its free diethylacetal **13** (36% from **5**), respectively, in excellent overall yields. Akin

* Corresponding author. Tel.: +45 4525 2133; fax: +45 4593 3968; e-mail: il@kemi.dtu.dk

0008-6215/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2006.03.001

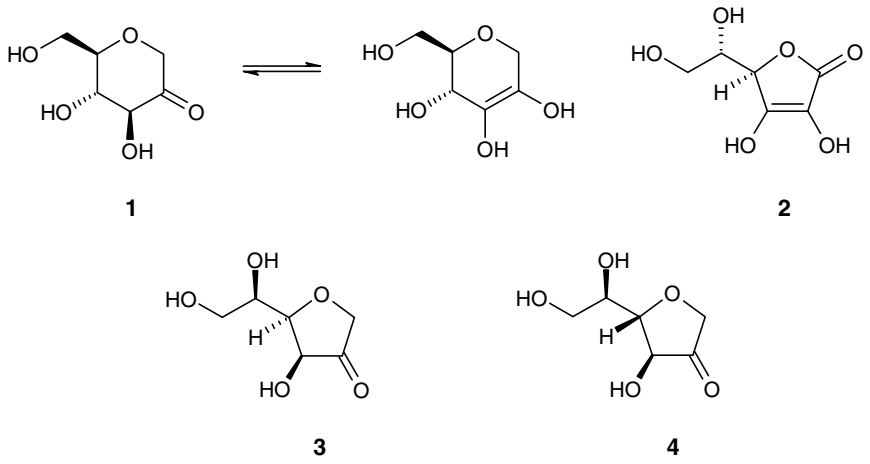
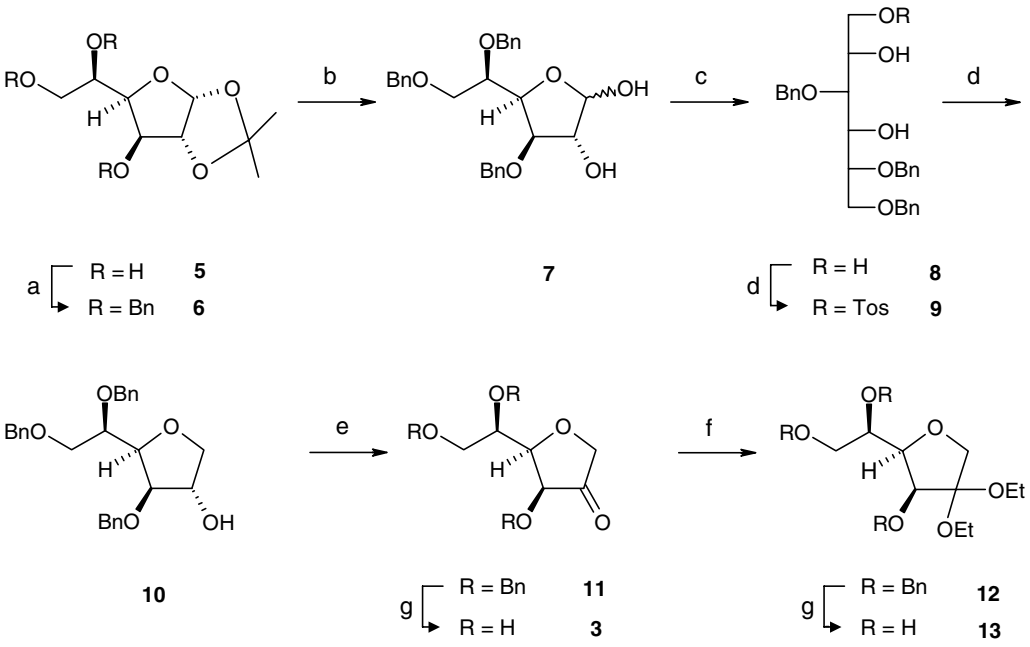


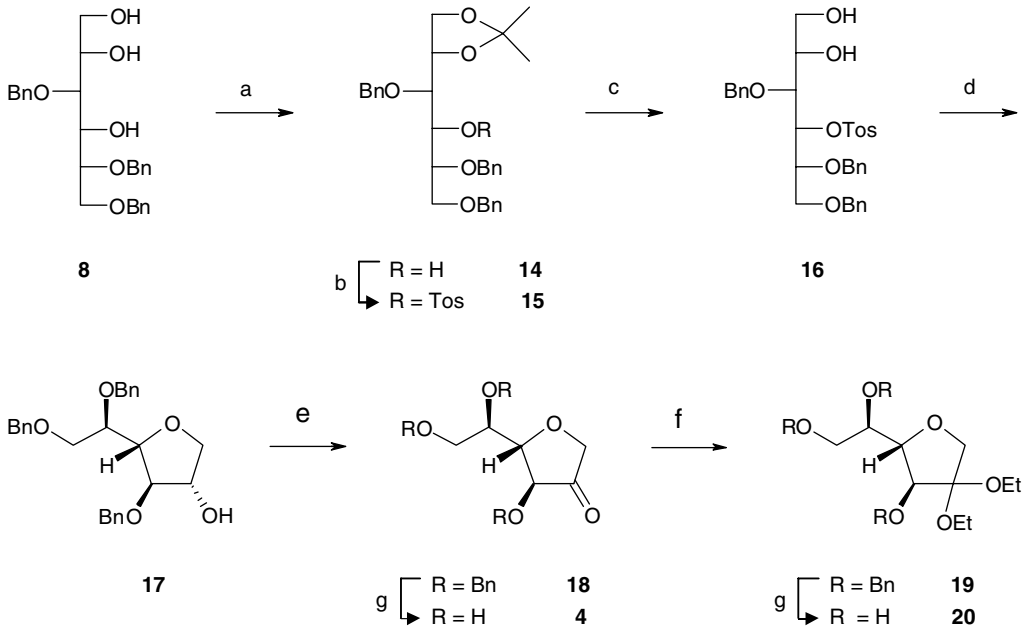
Figure 1.



Scheme 1. Reagents and conditions: (a) THF/DMF (4:1, v/v), NaH, benzyl bromide; (b) CH_3CN/H_2O (10:1, v/v), *p*-toluenesulfonic acid; (c) CH_3OH, $NaBH_4$; (d) CH_2Cl_2, pyridine, tosyl chloride; (e) CH_2Cl_2, Dess–Martin periodinane; (f) EtOH, *p*-toluenesulfonic acid; (g) CH_3OH, $Pd(OH)_2/C$, H_2.

to its pyranoid counterpart **1**, free ketose **3** was found to be in equilibrium with hemiacetalic forms.

For the preparation of 1,4-anhydro-D-tagatose (**4**), intermediate glucitol **8** was treated with acetone dimethylacetal (2,2-dimethoxypropane) under acidic conditions to give the known[10] 1,2-*O*-isopropylidene derivative **14** in 70% yield. Its reaction with tosyl chloride provided stable 4-tosylate **15**. Conventional acidic removal of the isopropylidene group and basic treatment of the resulting diol **16** led smoothly to intramolecular displacement of the tosyloxy group with inversion of configuration at C-4 providing the desired intermediate 1,4-anhydro-D-galactitol **17**, which exhibited a poorly resolved ^1H NMR spectrum due to pronounced overlapping of six multiplet signals between 3.74 and 3.91 ppm. Dess–Martin oxidation gave 3,5,6-tri-*O*-benzyl-D-tagatose **18**, which could easily be converted into the corresponding diethyl acetal **19**. Conventional hydrogenolytic removal of benzyl groups provided free 1,4-anhydro-D-tagatose (**4**) (36% from **5**) and its diethyl acetal **20** (34% from **5**), respectively, in high overall yields (Scheme 2). Estimated from ^{13}C NMR spectra, compound **4** was found to form a 1:1 mixture of the free ketose (C-2: 215 ppm) and one predominating hemiace-



Scheme 2. Reagents and conditions: (a) acetone, 2,2-dimethoxypropane, *p*-toluenesulfonic acid; (b) CH_2Cl_2, pyridine, tosyl chloride; (c) CH_3CN/H_2O (9:1, v/v), *p*-toluenesulfonic acid; (d) CH_2Cl_2, NEt_3; (e) CH_2Cl_2, Dess–Martin periodinane; (f) EtOH, *p*-toluenesulfonic acid; (g) CH_3OH, $Pd(OH)_2/C$, H_2.

tal (C-2: 102.9 ppm) as the two strongly preponderating main products together with at least two minor, possibly dimeric, components as was suggested by four additional smaller signals in the anomeric region.

In conclusion, the route presented is based on simple chemistry and allows access to the title compounds in excellent overall yields on bench scale. Improvements and scaling potential as well as anti-oxidant properties of the new 1,4-anhydroketoses **3** and **4** are currently being investigated.

1. Experimental

1.1. General methods

Melting points were recorded on a Tottoli apparatus and are uncorrected. Optical rotations were measured on a JASCO Digital Polarimeter or with a Perkin Elmer 341 with a path length of 10 cm. NMR spectra were recorded at 500 MHz (^1H), and at 125 MHz (^{13}C). $CDCl_3$ was employed for protected compounds and CD_3OD for free sugars. Chemical shifts are listed in delta employing residual, not deuterated, solvent as the internal standard. The signals of the protecting groups were found in the expected regions and are not listed explicitly.

Electrospray mass spectra were recorded on an HP 1100 series MSD, Hewlett Packard. Samples were dissolved in acetonitrile/CH_3OH mixtures. The scan mode for negative ions (mass range 100–1000 D) was employed varying the fragmentation voltage from 30 to 130 V. TLC was performed on precoated aluminium sheets (E. Merck 5554). Compounds were detected by staining with concd H_2SO_4 containing 5% vanillin. For column chromatography Silica Gel 60 (E. Merck) was used.

1.2. 1,4-Anhydro-3,5,6-tri-*O*-benzyl-D-glucitol (10)

To a stirred solution of **8**[10] (220 mg, 0.49 mmol) in dry CH_2Cl_2 (10 mL), pyridine (310 μL, 303 mg, 3.8 mmol) and tosyl chloride (260 mg, 1.4 mmol) were added in small portions over a period of 72 h at ambient temperature. The excess of reagent was quenched by the addition of water (2 mL), the organic layer was extracted consecutively with 5% aq HCl and satd aq $NaHCO_3$ and dried (Na_2SO_4). Filtration, removal of the solvent under reduced pressure and column chromatography on silica gel (4:1, cyclohexane/EtOAc) gave **10** (184 mg, 0.42 mmol, 86%) as a colourless syrup; $[\alpha]_D^{20}$ −46.1 (*c* 1.3, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 4.82–4.48 (6H, 3 × CH_2–Ph), 4.30 (n.r., 1H, H-2), 4.20 (dd, 1H, $J_{3,4} = 3.4$ Hz, $J_{4,5} = 9.3$ Hz, H-4), 4.14 (dd, 1H, $J_{1,1'} = 9.8$ Hz, $J_{1,2} = 3.9$ Hz, H-1), 4.04 (ddd, 1H, $J_{5,6} = 2.0$ Hz, $J_{5,6'} = 5.4$ Hz, H-5), 4.01 (m, 1H, H-3), 3.92 (dd, 1H, $J_{6,6'} = 10.8$ Hz, H-6), 3.73 (dd, 1H, H-6′), 3.72 (dd, 1H, $J_{1',2} < 1$ Hz, H-1′), 2.20 (br s, OH-2); ^{13}C NMR: δ 84.3 (C-4), 79.4 (C-3), 76.4 (C-5), 74.6, 74.4 (C-1, C-2), 73.7, 72.8, 72.4 (3 × CH_2–Ph), 71.5 (C-6). Anal. Calcd for $C_{27}H_{30}O_5$: C, 74.63; H, 6.96. Found: C, 74.60; H, 7.00.

1.3. 1,4-Anhydro-3,5,6-tri-*O*-benzyl-D-fructose (11)

To a solution of **10** (460 mg, 1.06 mmol) in dry CH_2Cl_2 (20 mL), Dess–Martin periodinane (640 mg, 1.51 mmol) was added and the reaction mixture was stirred for 4 h at ambient temperature. After extraction with satd aq $NaHCO_3$, the organic layer was separated, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The remaining residue was subjected to column chromatography on silica gel (10:1, cyclohexane/EtOAc) to furnish compound **11** (360 mg, 0.83 mmol, 79%) as a colourless syrup; $[\alpha]_D^{20}$ −54.6 (*c* 1.6, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 4.90–456 (6H, 3 × CH_2–Ph), 4.33 (dd, 1H, $J_{3,4} = 5.4$ Hz, $J_{4,5} = 7.3$ Hz, H-4), 4.24 (d, 1H, $J_{1,1'} = 17.6$ Hz, H-1), 4.17 (ddd, 1H, $J_{5,6} = 3.2$ Hz, $J_{5,6'} = 5.1$ Hz, H-5), 4.01 (d, 1H, H-3), 3.93 (d, 1H, H-1′), 3.86 (dd, 1H, $J_{6,6'} = 10.5$ Hz, H-6), 3.74 (dd, 1H, H-6′); ^{13}C NMR: δ 211.7 (C-2), 79.6, 77.0, 76.2 (C-3, C-4, C-5), 73.7, 73.0, 72.3 (3 × CH_2–Ph), 70.2, 69.7 (C-1, C-6). Anal. Calcd for $C_{27}H_{28}O_5$: C, 74.98; H, 6.53. Found: C, 74.92; H, 6.60.

1.4. 1,4-Anhydro-3,5,6-tri-*O*-benzyl-D-fructose diethyl acetal (12)

To a solution of **11** (330 mg, 0.76 mmol) in dry ethanol (20 mL), *p*-toluenesulfonic acid monohydrate (200 mg, 1.1 mmol) was added and the reaction mixture was stirred overnight at ambient temperature. After neutralisation with $NaHCO_3$ and filtration, the solvent was removed under reduced pressure. The remaining residue was purified by column chromatography on silica gel (13.1, cyclohexane/EtOAc), yielding compound **12** (340 mg, 0.67 mmol, 88%) as a colourless syrup; $[\alpha]_D^{20}$ −20.6 (*c* 2.7, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 5.00–4.50 (6H, 3 × CH_2–Ph), 4.31 (dd, 1H, $J_{3,4} = 3.4$ Hz, $J_{4,5} = 9.3$ Hz, H-4), 4.10 (ddd, 1H, $J_{5,6} = 2.0$ Hz, $J_{5,6'} = 5.4$ Hz, H-5), 4.06 (d, 1H, H-3), 4.04 (d, 1H, $J_{1,1'} = 8.5$ Hz, H-1), 3.96 (dd, 1H, $J_{6,6'} = 10.7$ Hz, H-6), 3.92 (d, 1H, H-1′), 3.75 (dd, 1H, H-6′), 3.72–3.50 (m, 4H, 2 × OCH_2Me), 1.30–1.24 (m, 6H, 2 × OCH_2Me); ^{13}C NMR: δ 109.8 (C-2), 80.3, 79.1, 76.8 (C-3, C-4, C-5), 73.9, 73.7, 72.4 (3 × CH_2–Ph), 71.4, 70.9 (C-1, C-6), 59.6, 57.3 (2 × OCH_2Me), 15.8, 15.7 (2 × OCH_2Me). Anal. Calcd for $C_{31}H_{38}O_6$: C, 73.49; H, 7.56. Found: C, 73.43; H, 7.61.

1.5. 1,4-Anhydro-D-fructose diethyl acetal (13)

To a solution of **12** (320 mg, 0.63 mmol) in dry CH_3OH (20 mL), $Pd(OH)_2$/C (20%, 50 mg) was added and the resulting heterogeneous reaction mixture was stirred under an atmosphere of H_2 at ambient pressure and temperature for 16 h. Filtration of the catalyst, removal of the solvent under reduced pressure and column chromatography on silica gel (EtOAc) yielded the pure compound **13** (123 mg, 0.52 mmol, 82%) as colourless crystals; mp 92–93 °C; $[\alpha]_D^{20}$ −0.6 (*c* 2.1, CH_3OH); ^{1}H NMR (MeOH-d_4): δ 4.06 (d, 1H, $J_{3,4} = 2.9$ Hz, H-3), 3.93 (dd, 1H, $J_{4,5} = 8.3$ Hz, H-4), 3.87 (ddd, 1H, $J_{5,6} = 3.4$ Hz, $J_{5,6'} = 5.9$ Hz, H-5), 3.85 (d, 1H, $J_{1,1'} = 8.8$ Hz, H-1), 3.74 (d, 1H, H-1′), 3.73 (dd, 1H, $J_{6,6'} = 10.7$ Hz, H-6), 3.70–3.50 (m, 5H, H-6′, 2 × OCH_2Me), 1.21, 1.18 (2 × t, 2 × 3H, 2 × OCH_2Me); ^{13}C NMR: δ 109.1 (C-2), 81.6 (C-4), 72.4, 70.0, 69.4 (C-1, C-3, C-5), 63.8 (C-6), 58.6, 56.8 (2 × OCH_2Me), 14.6, 14.3 (2 × OCH_2Me). Anal. Calcd for $C_{10}H_{20}O_6$: C, 50.84; H, 8.53. Found: C, 50.80; H, 8.57.

1.6. 1,4-Anhydro-D-fructose (3)

To a solution of **11** (319 mg, 0.74 mmol) in dry CH_3OH (25 mL), $Pd(OH)_2$/C (20%, 50 mg) was added and the resulting heterogeneous reaction mixture was stirred under an atmosphere of H_2 at ambient pressure and temperature for 3 h. Filtration of the catalyst and removal of the solvent under reduced pressure yielded compound **3** (115 mg, 96%, colourless syrup) as a mixture of the free ketose and two hemiacetal forms. Main product: ^{13}C NMR (CD_3OD): δ 105.5 (C-2), 81.3 (C-4), 73.9, 71.6, 70.1 (C-1, C-3, C-5), 63.7 (C-6). Side products: ^{13}C NMR (CD_3OD): δ 214.1, 105.5 (C-2), 82.0, 79.8 (C-4), 73.4, 72.2, 71.7, 70.1, 70.0, 68.9 (C-1, C-3, C-5), 63.8, 63.0 (C-6); API-ES: Calcd for $C_6H_{10}O_5$ 162.1436 [M−H]. Found 161.130.

1.7. 3,5,6-Tri-*O*-benzyl-1,2-*O*-isopropylidene-D-glucitol (14)

To a solution of **8**[10] (2.38 g, 5.26 mmol) in dry acetone (25 mL), 2,2-dimethoxypropane (1.30 mL, 1.10 g, 10.6 mmol) and *p*-toluenesulfonic acid monohydrate (100 mg, 0.5 mmol) were added, and the resulting reaction mixture stirred at ambient temperature for 2 h until TLC showed complete conversion of the starting material. Neutralisation with Na_2CO_3, filtration, removal of the solvents under reduced pressure and chromatography of the remaining residue on silica gel (5:1, cyclohexane/EtOAc) yielded compound **14** (1.82 g, 3.69 mmol, 70%) as a colourless syrup. $[\alpha]_D^{20}$ −53.3 (*c* 1.4, CH_2Cl_2), $[\alpha]_D^{20}$ −54.4 (*c* 1.55, $CHCl_3$);[10] ^{1}H NMR ($CDCl_3$): δ 4.88–4.30 (6H, 3 × CH_2–Ph), 4.44 (ddd, 1H, $J_{1,2} = 6.3$ Hz, $J_{1',2} = 7.8$ Hz, $J_{2,3} = 7.3$ Hz, H-2), 4.07 (dd, 1H, $J_{1,1'} = 8.3$ Hz, H-1), 3.85 (dd, 1H, $J_{5,6} = 2.9$ Hz, $J_{6,6'} = 10.3$ Hz, H-6), 3.78 (m, 1H, H-3), 3.74 (dd, 1H, H-1′), 3.69 (dd, 1H, $J_{5,6'} = 4.9$ Hz, H-6′), 3.60 (m, 1H, H-5), 3.51 (ddd, 1H, $J_{3,4} < 1$ Hz, $J_{4,5} = 8.3$ Hz, H-4), 2.70 (d, 1H, $J = 8.8$ Hz, OH-4); ^{13}C NMR: δ 78.2, 77.9, 77.9 (C-2, C-3, C-5), 74.1, 73.8, 72.2, 71.4 (C-4, 3 × CH_2–Ph), 69.9, 66.4 (C-1, C-6). Anal. Calcd for $C_{30}H_{36}O_6$: C, 73.15; H, 7.37. Found: C, 73.10; H, 7.43.

1.8. 3,5,6-Tri-*O*-benzyl-1,2-*O*-isopropylidene-4-*O*-tosyl-D-glucitol (15)

To a solution of **14** (1.25 g, 2.54 mmol) in dry CH_2Cl_2 (20 mL), pyridine (5.00 mL, 4.9 g, 62 mmol) and tosyl chloride (3.40 g, 17.8 mmol) were added and the resulting reaction mixture was stirred for 3 days at ambient temperature. The excess of reagent was quenched by the addition of water (10 mL), the organic layer was extracted consecutively with 5% aq HCl and satd aq $NaHCO_3$ and dried (Na_2SO_4). Filtration and removal of the solvent under reduced pressure gave pure **15** (1.61 g, 2.49 mmol, 98%) as a colourless syrup. $[\alpha]_D^{20}$ +6.2 (*c* 2.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 4.95 (dd, 1H, $J_{3,4} = 4.4$ Hz, $J_{4,5} = 3.9$ Hz, H-4), 4.68–4.36 (6H, $3 \times CH_2$–Ph), 4.30 (ddd, 1H, $J_{1,2} = 6.3$ Hz, $J_{1',2} = 6.8$ Hz, $J_{2,3} = 6.3$ Hz, H-2), 3.96 (dd, 1H, $J_{1,1'} = 8.3$ Hz, H-1), 3.93 (m, 1H, H-5), 3.73 (dd, 1H, H-1′), 3.72 (dd, 1H, H-3), 3.67 (dd, 1H, $J_{5,6} = 4.9$ Hz, $J_{6,6'} = 10.3$ Hz, H-6), 3.48 (dd, 1H, $J_{5,6'} = 5.9$ Hz, H-6′); ^{13}C NMR: δ 81.4, 78.4, 77.2, 76.7 (C-2, C-3, C-4, C-5), 74.5, 73.4, 72.8 ($3 \times CH_2$–Ph), 69.4, 66.1 (C-1, C-6). Anal. Calcd for $C_{37}H_{42}O_8S$: C, 68.71; H, 6.55. Found: C, 68.63; H, 6.60.

1.9. 3,5,6-Tri-*O*-benzyl-4-*O*-tosyl-D-glucitol (16)

To a solution of **15** (0.87 g, 1.35 mmol) in CH_3CN/H_2O (10 mL, 9:1 v/v), *p*-toluenesulfonic acid monohydrate (200 mg, 1.1 mmol) was added and the reaction mixture was stirred for 16 h at ambient temperature. CH_2Cl_2 (100 mL) was added to the reaction mixture, which was then extracted with satd aq $NaHCO_3$. The organic layer was separated, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Column chromatography on silica gel (2:1, cyclohexane/EtOAc) yielded compound **16** (0.79 g, 1.30 mmol, 97%) as a colourless syrup. $[\alpha]_D^{20}$ +21.3 (*c* 3.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 5.16 (dd, 1H, $J_{3,4} = 6.5$ Hz, $J_{4,5} = 2.4$ Hz, H-4), 4.74–4.38 (6H, $3 \times CH_2$–Ph), 3.97 (m, 1H, H-5*), 3.78 (m, 2H, H-2*, H-3), 3.68 (dd, 1H, $J_{5,6} = 6.4$ Hz, $J_{6,6'} = 10$ Hz, H-6), 3.55 (dd, 1H, $J_{5,6'} = 6.3$ Hz, H-6′), 3.53 (dd, 1H, $J_{1,1'} = 11$ Hz, $J_{1,2} = 6.3$ Hz, H-1), 3.37 (dd, 1H, $J_{1',2} = 4.4$ Hz, H-1′), 2.50 (br s, 2H, OH-1, OH-2); ^{13}C NMR: δ 81.3, 77.8, 77.7 (C-3, C-4, C-5), 74.7, 73.5, 73.3 ($3 \times CH_2$–Ph), 70.4 (C-2), 69.4 (C-6), 64.0 (C-1). *may be interchanged. Anal. Calcd for $C_{34}H_{38}O_8S$: C, 67.31; H, 6.31. Found: C, 67.27; H, 6.35.

1.10. 1,4-Anhydro-3,5,6-tri-*O*-benzyl-D-galactitol (17)

A solution of **16** (0.73 g, 1.20 mmol) in dry CH_2Cl_2 (15 mL) containing Et_3N (5 mL) was stirred at 40 °C for 48 h, until TLC indicated complete conversion of the starting material. The reaction mixture was washed consecutively with 5% aq HCl and satd aq $NaHCO_3$, the organic layer was separated, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The remaining residue was purified by chromatography on silica gel (4:1, cyclohexane/EtOAc) to give compound **17** (0.45 g, 1.04 mmol, 86%) as a colourless syrup. $[\alpha]_D^{20}$ −70.4 (*c* 1.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 4.84–4.44 (6H, $3 \times CH_2$–Ph), 4.11 (dd, 1H, $J = 11.2$ Hz, $J = 2.4$ Hz), 4.05 (dd, 1H, $J = 2.0$ Hz, $J = 2.0$ Hz), 3.91–3.82 (m, 3H), 3.79–3.74 (m, 3H), 1.70 (br s, 1H, OH-2); ^{13}C NMR: δ 86.9, 84.6 (C-3, C-4), 77.4 (C-5), 75.1, 74.6 (C-1, C-2), 73.9, 73.7, 72.1 ($3 \times CH_2$–Ph), 70.9 (C-6). Anal. Calcd for $C_{27}H_{30}O_5$: C, 74.63; H, 6.96. Found: C, 74.60; H, 7.00.

1.11. 1,4-Anhydro-3,5,6-tri-*O*-benzyl-D-tagatose (18)

To a solution of **17** (360 mg, 0.83 mmol) in dry CH_2Cl_2 (20 mL), Dess–Martin periodinane (530 mg, 1.25 mmol) was added and the reaction mixture was stirred for 4 h at ambient temperature. After extraction with satd aq $NaHCO_3$, the organic layer was separated, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The remaining residue was subjected to column chromatography on silica gel (10:1, cyclohexane/EtOAc) to furnish compound **18** (319 mg, 0.74 mmol, 89%) as a colourless syrup. $[\alpha]_D^{20}$ −83.9 (*c* 2.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 4.90–4.40 (6H, $3 \times CH_2$–Ph) 4.18 (dd, 1H, $J_{3,4} = 6.8$ Hz, $J_{4,5} = 2.0$ Hz, H-4), 4.18 (d, 1H, $J_{1,1'} = 17.6$ Hz, H-1), 4.02 (d, 1H, H-1′), 3.98 (d, 1H, H-3), 3.78 (m, 3H, H-5, H-6, H-6′); ^{13}C NMR: δ 213.6 (C-2), 81.4, 77.0, 76.7 (C-3, C-4, C-5), 73.8, 73.4, 72.5 ($3 \times CH_2$–Ph), 70.9, 69.8 (C-1, C-6). Anal. Calcd for $C_{27}H_{28}O_5$: C, 74.98; H, 6.53. Found: C, 75.00; H, 6.59.

1.12. 1,4-Anhydro-3,5,6-tri-*O*-benzyl-D-tagatose diethyl acetal (19)

To a solution of **18** (240 mg, 0.56 mmol) in dry ethanol (20 mL), *p*-toluenesulfonic acid monohydrate (200 mg, 1.1 mmol) was added, and the reaction mixture was stirred overnight at ambient temperature. After neutralisation with $NaHCO_3$ and filtration, the solvent was removed under reduced pressure. The remaining residue was purified by column chromatography on silica gel (13:1, cyclohexane/EtOAc), yielding compound **19** (260 mg, 0.51 mmol, 92%) as a colourless syrup. $[\alpha]_D^{20}$ −7.7 (*c* 1.3, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 4.80–4.40 (6H, $3 \times CH_2$–Ph), 4.06 (dd, 1H, $J_{3,4} = 4.4$ Hz, $J_{4,5} = 4.4$ Hz, H-4), 3.98 (d, 1H, $J_{1,1'} = 9.3$ Hz, H-1), 3.79 (m, 2H, H-3, H-5), 3.73 (dd, 1H, $J_{5,6} = 3.9$ Hz, $J_{6,6'} = 10.7$ Hz, H-6), 3.70 (m, 1H, H-6′), 3.69 (d, 1H, H-1′), 3.66–3.42 (m, 4H, $2 \times OCH_2Me$), 1.22, 1.15 ($2 \times$ t, 2×3H, $2 \times OCH_2Me$); ^{13}C NMR: δ 107.3 (C-2), 85.1, 79.6, 77.7 (C-3, C-4, C-5), 73.6, 73.5, 71.9 ($3 \times CH_2$–Ph), 71.6, 71.3 (C-1, C-6), 58.9, 57.1 ($2 \times$

OCH_2Me), 15.7, 15.5 ($2 \times OCH_2Me$). Anal. Calcd for $C_{31}H_{38}O_6$: C, 73.49; H, 7.56. Found: C, 73.45; H, 7.61.

1.13. 1,4-Anhydro-D-tagatose diethyl acetal (20)

To a solution of **19** (238 mg, 0.470 mmol) in dry CH_3OH (20 mL), $Pd(OH)_2/C$ (20%, 50 mg) was added and the resulting heterogeneous reaction mixture was stirred under an atmosphere of H_2 at ambient pressure and temperature for 16 h. Filtration of the catalyst and removal of the solvent under reduced pressure yielded the pure compound **20** (110 mg, 0.466 mmol, 99%) as a colourless syrup. $[\alpha]_D^{20}$ −10.6 (*c* 2.1, MeOH); ^1H NMR (CD_3OD): δ 4.02 (d, 1H, $J_{3,4} = 5.9$ Hz, H-3), 3.85 (d, 1H, $J_{1,1'} = 9.8$ Hz, H-1), 3.76 (d, 1H, H-1′), 3.70–3.55 (m, 8H, H-4, H-5, H-6, H-6′, $2 \times OCH_2Me$), 1.23, 1.18 ($2 \times$ t, 2×3H, $2 \times OCH_2Me$); ^{13}C NMR: δ 105.8 (C-2), 85.1 (C-4), 74.2, 71.6, 71.1 (C-1, C-3, C-5), 63.2 (C-6), 57.8, 57.5 ($2 \times OCH_2Me$), 14.5, 14.4 ($2 \times OCH_2Me$). Anal. Calcd for $C_{10}H_{20}O_6$: C, 50.84; H, 8.53. Found: C, 50.79; H, 8.55.

1.14. 1,4-Anhydro-D-tagatose (4)

To a solution of **18** (79 mg, 0.18 mmol) in dry CH_3OH (15 mL), $Pd(OH)_2/C$ (20%, 50 mg) was added and the resulting heterogeneous reaction mixture was stirred under an atmosphere of H_2 at ambient pressure and temperature for 2 h. Filtration of the catalyst and removal of the solvent under reduced pressure yielded compound **4** (29 mg, approximately 98% based on free ketose and hemiacetals, respectively) as a colourless syrup. ^{13}C NMR (CD_3OD): δ 215.0 (C-2, ketose), 102.9 (C-2, main hemiacetal), 83.4, 81.7 (C-4), 74.3, 74.3, 72.1, 71.4, 70.9, 69.9 (C-1, C-3, C-5), 63.3, 62.6 (C-6). API-ES: Calcd for $C_6H_{10}O_5$ 162.1436 [M−H]. Found 161.140.

Acknowledgements

A.E.S. thanks the Danish Technical University for a guest professorship (March–June 2002).

References

1. For a review see: Andersen, S. M.; Lundt, I.; Marcussen, J.; Yu, S. *Carbohydr. Res.* **2002**, *337*, 873–890.
2. Baute, M.-A.; Baute, R.; Deffieux, G. *Phytochemistry* **1988**, *27*, 3401–3403.
3. Elsser, D.; Morgan, J. A.; Thomas, L. V.; Yu. S. PCT Int. Appl. WO 02/26060, 2002; Elsser, D.; Morgan, J. A.; Thomas, L. V.; Yu. S. PCT Int. Appl. WO 02/26061, 2002.
4. Kurata, T.; Miyake, N.; Otsuka, Y. *Biosci., Biotechnol., Biochem.* **1996**, *60*, 1212–1214.
5. Lichtenthaler, F. W.; El Ashry, E. S. H.; Göckel, V. H. *Tetrahedron Lett.* **1980**, *21*, 1429–1432.
6. Nakamura, T.; Takahashi, A.; Kato, K. Jpn. Patent JP 63072696, 1988.
7. Taguchi, T.; Haruna, M.; Okuda, J. *Biotechnol. Appl. Biochem.* **1993**, *18*, 275–283; Freimund, S.; Huwig, A.; Giffhorn, F.; Köpper, S. *Chem. Eur. J.* **1998**, *4*, 2442–2455.
8. Hizukuri, S.; Abe, J.; Junichi, Y.; Muroya, K.; Yoshinaga, K. Jpn. Patent JP 2002058477, 2002; Ahren, B.; Yu, S. PCT Int. Appl. WO 2001051058, 2001.
9. Barili, P. L.; Berti, G.; Catelani, G.; D'Andrea, F.; Miarelli, L. *Carbohydr. Res.* **1995**, *274*, 197–208.
10. Mulzer, J.; Seilz, C.; Reutter, W. *Liebigs Ann. Chem.* **1991**, 957–960.