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Carbohydrate Research 318 (1999) 167–170

CARBOHYDRATE RESEARCH

Note

# D-Tagatose derivatives from D-fructose by a facile epimerisation procedure☆

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Received 9 March 1999; revised 8 April 1999; accepted 9 April 1999

**Abstract**

1,2-*O*-Isopropylidene-β-D-fructopyranose was directly converted into 5-*O*-cyclohexylcarbamoyl-1,2-*O*-isopropylidene-3,4-*O*-(2,2,2-trichloroethylidene)-β-D-tagatopyranose by treatment with chloral/*N*,*N*′-dicyclohexylcarbodiimide. Subsequent acid-catalysed cleavage of the isopropylidene protecting group followed by acetylation afforded, exclusively, 1,2-di-*O*-acetyl-5-*O*-cyclohexylcarbamoyl-3,4-*O*-(2,2,2-trichloroethylidene)-α-D-tagatopyranose. This product was simultaneously dehydrochlorinated and decarbamoylated to 1,2-di-*O*-acetyl-3,4-*O*-ethylidene-α-D-tagatopyranose using $Bu_3SnH$/AIBN. 

*Keywords:* Carbohydrates; D-Fructose; D-Tagatose; Epimerisation; Chloral acetals

The convenient one-pot methodology developed for the epimerisation of aldopyranoses using chloral [2] also turned out to be valuable for epimerisations of cyclitols [1,3]. Generally, highly carbonyl-active aldehydes like chloral react in the presence of the co-reagent *N*,*N*′-dicyclohexylcarbodiimide (DCC) with polyols having a cis–trans sequence of three contiguous hydroxyl groups. Thus, cyclic acetals are formed with simultaneous inversion of the configuration at the middle chiral C-atom. The mechanism of this non-conventional acetalation/epimerisation procedure was described in previous reports [1,2]. In this paper, we show that the rare monosaccharide D-tagatose can be easily prepared from D-fructose. Moreover, it is demonstrated how some useful tagatopyranose derivatives are accessible by variation of the protecting groups.

1,2-*O*-Isopropylidene-β-D-fructopyranose (**1**) is a suitable starting material for the reaction with chloral/DCC. The compound has the required cis–trans sequence of three OH groups and it can be prepared in relatively large amounts from D-fructose in only two steps via the corresponding 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose [4]; for the preparation of **1** see also Ref. [5].

In order to convert the D-fructose derivative **1** into a D-tagatose derivative by inversion of the configuration at C-4, compound **1** was heated for 4–5 h with chloral/DCC in 1,2-dichloroethane. The 5-*O*-cyclohexylcarbamoyl-1,2-*O*-isopropylidene-3,4-*O*-(2,2,2-trichloroethylidene)-β-D-tagatopyranose (**2**) was isolated in a yield of 59% after column chro-

☆ Epimerisation of carbohydrates and cyclitols, Part 16. For Part 15, see Ref. [1].

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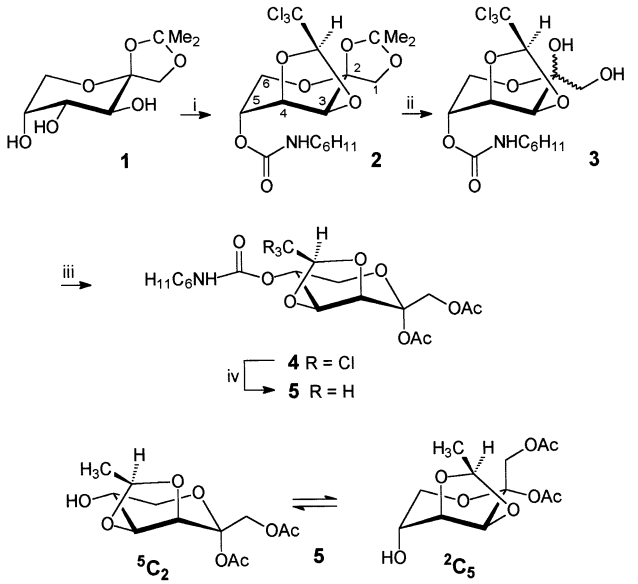
0008-6215/99/$ - see front matter 
PII: S0008-6215(99)00090-7

matography (Scheme 1). Because of the new stereogenic centre of the trichloroethylidene moiety, a diastereomeric mixture (endo-H/exo-H form 30:1) was formed; the pure endo-H diastereomer was obtained by recrystallisation of the diastereomeric mixture from ethyl acetate or by HPLC fractionation.

The structure of **2** (endo-H form) is supported by characteristic $^{1}H$ and $^{13}C$ NMR signals for the carbamoyl and chloral acetal function. The chemical shifts of H-3 ($\delta$ 4.40 ppm) and H-4 ($\delta$ 4.55 ppm) show the presence of an acetal at these positions. Furthermore, the coupling constants between H-3/H-4 and H-4/H-5 are in agreement with the configuration shown. The singlets of the trichloroethylidene acetal protons were used to determine the ratio of the endo-H/exo-H diastereomers. As already reported in previous papers (e.g., Refs. [1–3]) the acetal proton of the endo-H form ($\delta$ 5.54 ppm) is always downfield shifted compared with that of the exo-H form ($\delta$ 5.31 ppm).

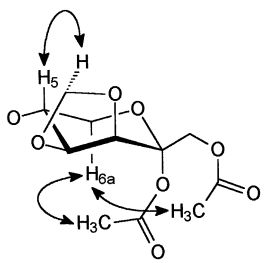
The D-tagatose derivative **2** was deprotected stepwise: at first the carbamoyl group by heating in methanolic sodium methoxide and then the acid-stable trichloroethylidene function by dehydrochlorination to an ethylidene acetal followed by acid-catalysed deacetalation. In order to avoid any generation of furanose derivatives, the sequence described in Scheme 1 was realised. An anomeric mixture of **3** was generated by treatment of **2** with aqueous trifluoroacetic acid (TFA). Further conventional acetylation of **3** afforded 1,2-di-*O*-acetyl-5-*O*-cyclohexylcarbamoyl-3,4-*O*-(2,2,2-trichloroethylidene)-α-D-tagatopyranose (**4**) in a yield of 93%. No traces of the β anomer were detected after a reaction time of 48 h under standard conditions [6]. It is noticeable that two intermediates, probably monoacetyl derivatives, could be detected by TLC before completion. Comparison of the $^{1}H$ NMR spectra of **2** and **4** shows that several coupling constants are significantly different. Thus, the coupling constants of compound **2** ($J_{4,5}$ 5.5, $J_{5,6a}$ 1.5, and $J_{5,6b}$ 2.1 Hz) indicate a trans-diequatorial arrangement of H-4 and H-5, whereas the corresponding data of compound **4** ($J_{4,5}$ 7.3, $J_{5,6ax}$ 10.4, $J_{5,6eq}$ 5.8 Hz) indicate a trans-diaxial arrangement of these protons,




Scheme 1. (i) Chloral/DCC ($ClCH_2CH_2Cl$); (ii) TFA/$H_2O$; (iii) $Ac_2O$/pyridine; (iv) $Bu_3SnH$/AIBN (toluene).

i.e., a conformational interconversion from $^{2}C_5$ (**2**) to $^{5}C_2$ (**4**) has occurred. The $^{5}C_2$ conformation should be thermodynamically favoured, since the anomeric effect works effectively together with the favourable equatorial orientation of the C-1 acetoxymethyl group. In compound **2** ($^{2}C_5$) this argument is likewise fulfilled.

In order to confirm the α configuration of compound **4**, a NOE measurement was carried out, which showed the correlation of the axially arranged H-6 to both $CH_3$ groups of the acetyl functions (Scheme 2). This result fits only with the α anomer. As an additional indication, no interaction was found between H-4 and the two exocyclic H-1 and H-1′. Furthermore, only a very weak correlation was observed between H-3 and H-1/H-1′. Finally, the correlation between the acetal-H




Scheme 2. NOE experiment: correlation illustrated in a molecule fragment of 1,2-di-*O*-acetyl-5-*O*-cyclohexylcarbamoyl-3,4-*O*-(2,2,2-trichloroethylidene)-α-D-tagatopyranose (**4**).

and H-5 confirms the endo-H arrangement of the cyclic acetal function in **4** (Scheme 2).

The acid-stable trichloroethylidene group of **4** was converted into an acid-labile ethylidene acetal by a radical dehydrohalogenation using $Bu_3SnH$/AIBN [7]. On heating compound **4** with this reagent in toluene, the carbamoyl group was removed as well (Scheme 1). However, for a complete decarbamoylation, an excess of the hydride is essential. The 1,2-di-*O*-acetyl-3,4-*O*-ethylidene-β-D-tagatopyranose (**5**) was isolated in a yield of 72%. The coupling constants $J_{3,4}$ 5.5 Hz and $J_{4,5}$ 4.0 Hz of compound **5** indicate an equilibrium between the two conformations $^2C_5$ and $^5C_2$ (Scheme 1).

## 1. Experimental

*General.*—Column chromatography: E. Merck Silica Gel 60 (63–200 μm); thin-layer chromatography (TLC): E. Merck Silica Gel 60 $F_{254}$ foils; HPLC: Knauer equipment, Vertex column B31-Y520 (Eurosher 100-15, 15 μm) 5:1 heptane–EtOAc, detection by refractive index. NMR: AC 250 and ARX 300; internal standard TMS. Melting points were measured using a Leitz polarising microscope (Laborlux 12 Pol) equipped with a hot stage (Mettler FP 90). 1,2-*O*-Isopropylidene-β-D-fructopyranose (**1**) [4] was prepared from the corresponding 1,2:4,5-di-*O*-isopropylidene derivative [5] by selective acid hydrolysis following the procedure reported by Lichtenthaler et al. [8] using a mixture of $H_2SO_4$ (1 M, 10 mL), MeOH (120 mL) and $H_2O$ (100 mL) at room temperature (rt).

(R)-*5*-O-*Cyclohexylcarbamoyl*-*1,2*-O-*isopropylidene*-*3,4*-O-*(2,2,2*-*trichloroethylidene)*-*β*-D-*tagatopyranose* (**2**).—To a solution of 1,2-*O*-isopropylidene-β-D-fructopyranose (**1**) [5] (1.0 g, 4.54 mmol) in dry 1,2-dichloroethane (15 mL), chloral (2.34 g, 15.89 mmol) and DCC (2.35 g, 11.35 mmol) were sequentially added. Subsequently, the mixture was refluxed under stirring for 4–5 h (TLC control). After cooling to rt and addition of $CH_2Cl_2$ (20 mL) and 10% aq AcOH (30 mL), the reaction mixture was shaken for about 30 min to destroy excess DCC. The precipitated *N*,*N*′-dicyclohexyl urea was removed by filtration, the organic phase was separated, and the aqueous phase was washed with $CH_2Cl_2$ (2 × 15 mL). The combined extracts were washed with water (2 × 20 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography ($R_f$ 0.35, 5:1 heptane–EtOAc) giving 1.27 g (59.1%) of the diastereomeric 30:1 endo-H/exo-H mixture of **2**. The pure endo-H form was obtained by recrystallisation from EtOAc or by HPLC: 1.10 g (51.2%) of **2** as colourless crystals; mp 198.5–201 °C; $[\alpha]_D^{25}$ −32.4° (*c* 0.98, $CHCl_3$); $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 5.54 (s, 1 H, acetal-H), 5.09 (ddd, 1 H, $J_{5,6a}$ 1.5 Hz, $J_{5,6b}$ 2.1 Hz, H-5), 4.70 (d, 1 H, $J_{NH,CH}$ 7.9 Hz, N–H), 4.55 (ddd, 1 H, $J_{4,5}$ 5.5 Hz, $^4J_{4,6}$ 1.8 Hz, H-4), 4.40 (d, 1 H, $J_{3,4}$ 5.2 Hz, H-3), 4.20 (dd, 1 H, $^2J_{6,6}$ 13.4 Hz, H-6a), 4.10 (d, 1 H, $^2J_{1a,1b}$ 10.4 Hz, H-1a), 4.05 (d, 1 H, H-1b), 3.68 (ddd, 1 H, H-6b), 3.53–3.36 (m, 1 H, cyclohexyl-CH), 1.97–1.83 (m, 2 H, cyclohexyl-$CH_2$), 1.74–1.57 (m, 3 H, cyclohexyl-$CH_2$), 1.38–1.05 (m, 5 H, cyclohexyl-$CH_2$), 1.51, 1.43 (2 s, 3 H, isopropyl-$CH_3$). $^{13}$C NMR (63 MHz, $CDCl_3$): $\delta$ 154.0 (NH–C=O), 113.4 ($C(CH_3)_2$), 107.8 (acetal-C), 102.5 (C-2), 99.2 ($CCl_3$), 74.9, 72.4, 67.3 (C-3, C-4, C-5), 73.2 (C-1), 59.3 (C-6), 50.1 (cyclohexyl-CH), 33.3, 25.4, 25.4, 24.7, 24.7 (5 cyclohexyl-$CH_2$), 27.3, 25.2 (2 $C(CH_3)_2$). Anal. Calcd for $C_{18}H_{26}Cl_3NO_7$ (474.76): C, 45.54; H, 5.52; N, 2.95. Found: C, 45.52; H, 5.46; N, 2.96.

(R)-*5*-O-*Cyclohexylcarbamoyl*-*3,4*-O-*(2,2,*-*2*-*trichloroethylidene)*-*α,β*-D-*tagatopyranose*-(**3**).—A solution of **2** (250 mg, 0.53 mmol) in aq TFA (60% v/v, 10 mL) was stirred for 12 h at rt. After evaporation of the solvents under reduced pressure, the residue was twice co-distilled with toluene (2 × 10 mL) under reduced pressure and subsequently purified by column chromatography ($R_f$ 0.35, 1:1 toluene–EtOAc) yielding 215 mg (93.9%) of the syrupy anomeric mixture **3** (α/β = 45.3:54.7); $^1$H NMR (250 MHz, $CD_3OD$): $\delta$ 5.60 (s, 1 H, α acetal-H), 5.50 (s, 1.21 H, β acetal-H). $^{13}$C NMR (63 MHz, $CD_3OD$): $\delta$ 156.9, 156.5 (α/β NH–C=O), 109.1, 107.6 (α/β acetal-C), 100.9, 100.4 (α/β $CCl_3$), 96.7, 96.4 (C-2), 79.5, 78.2, 76.2, 73.9, 69.3, 69.1 (α/β C-3, C-4, C-5), 66.4, 65.9 (α/β C-1), 58.8 58.7 (α/β C-6), 51.3, 51.2

(α/β cyclohexyl-CH), 33.9, 33.8, 26.4, 25.9, 25.7, 25.2 (α/β cyclohexyl-$CH_2$). Anal. Calcd for $C_{15}H_{22}Cl_3NO_7$ (434.70): C, 41.45; H, 5.10; N, 3.22. Found: C, 41.11; H, 5.33; N, 3.06.

(R)-*1,2-Di*-O-*acetyl-5*-O-*cyclohexylcarbamoyl-3,4*-O-*(2,2,2-trichloroethylidene)*-α-D-*tagatopyranose* (**4**).—The α/β anomeric mixture of **3** (100 mg, 0.23 mmol) was treated with a mixture of $Ac_2O$ (5 mL) and pyridine (5 mL) under stirring at rt. First two monoacetylation products were detectable by TLC ($R_f$ 0.08 and 0.185, 5:1 toluene–EtOAc), the diacetylation reaction being completed after 48 h ($R_f$ of **4**: 0.30). After evaporation of the solvents under reduced pressure, the residue was co-distilled with toluene (2 × 10 mL) and purified by column chromatography with the above solvent mixture to give 102 mg (93.2%) of **4** as colourless crystals, mp 196–198 °C (EtOAc); $[\alpha]_D^{25}$ −20.80° (*c* 0.95, $CHCl_3$); $^1$H NMR (300 MHz, $C_6D_6$): δ 5.24 (d, 1 H, $^2J_{1a,1b}$ 11.7 Hz, H-1a), 5.16 (s, 1 H, acetal-H), 5.10 (m, 1 H, $J_{5,6ax}$ 10.4 Hz, $J_{5,6eq}$ 5.8 Hz, H-5), 4.90 (d, 1 H, $J_{3,4}$ 5.4 Hz, H-3), 4.85 (d, 1 H, H-1b), 4.74 (dd, 1 H, $J_{4,5}$ 7.4 Hz, H-4), 4.12 (d, 1 H, $J_{NH,CH}$ 7.9 Hz, N–H), 4.09 (dd, 1 H, $^2J_{6a,6b}$ 11.3 Hz, H-6e), 3.48 (dd, 1 H, H-6a), 3.46 (m, 1 H, cyclohexyl-CH), 1.80–1.65 (m, 2 H, cyclohexyl-$CH_2$), 1.70, 1.63 (2 s, 6 H, C(O)$CH_3$), 1.46–1.28 (m, 3 H, cyclohexyl-$CH_2$), 1.09–0.65 (m, 5 H, cyclohexyl-$CH_2$). $^{13}$C NMR (63 MHz, $CDCl_3$): δ 169.6, 168.1 (2 *C*(O)$CH_3$), 154.0 (NH–C=O), (106.4 (*C*-$CCl_3$), 101.1 (C-2), 98.8 ($CCl_3$), 77.6 (C-4), 75.2 (C-3), 67.2 (C-5), 62.5 (C-1), 60.2 (C-6), 50.1 (cyclohexyl-CH), 33.3, 25.4, 25.4, 24.7, 24.7 (5 cyclohexyl-$CH_2$), 21.7, 20.5 (2 C(O)*C*$H_3$). Anal. Calcd for $C_{19}H_{26}Cl_3NO_9$ (518.77): C, 43.99; H, 5.05; N, 2.70. Found: C, 44.09; H, 5.08; N, 2.77.

(R)-*1,2-Di*-O-*acetyl-3,4*-O-*ethylidene*-α-D-*tagatopyranose* (**5**).—A solution of **4** (2.6 g, 5.01 mmol), $Bu_3SnH$ (5.25 g, 18.04 mmol) and AIBN (100 mg) in dry toluene (35 mL) was heated at 80 °C under stirring (Ar atmosphere). After 6 h, $Bu_3SnH$ (1.46 g, 5.01 mmol) and AIBN (30 mg) was added and heating was continued for further 6 h. An intermediate ($R_f$ 0.48, 2:1 toluene–EtOAc) detected during this period had now disappeared. After cooling down, the solution was shaken with a saturated aq KF (30 mL) for 30 min and the precipitated $Bu_3SnF$ was removed by filtration. Subsequently, the organic phase was separated, washed twice with water (15 mL), dried ($Na_2SO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography ($R_f$ 0.17, 2:1 toluene–EtOAc) giving 1.05 g (72.4%) of **5** as a colourless syrup, $[\alpha]_D^{22}$ +38.2° (*c* 1.34, $CHCl_3$); $^1$H NMR (250 MHz, $CDCl_3$): δ 5.08 (q, 1 H, $J_{acetal\text{-}H,acetal\text{-}CH_3}$ 4.8 Hz, acetal-H), 4.81 (dd, 1 H, $J_{4,5}$ 4.0 Hz, H-4), 4.41 (d, 1 H, $J_{3,4}$ 5.5 Hz, H-3), 4.41 (dd, 1 H, $^2J_{6a,6b}$ 11.1 Hz, H-6a), 4.35 (d, 1 H, $^2J_{1a,1b}$ 11.9 Hz, H-1a), 4.34 (ddd, 1 H, $J_{5,6a}$ 4.1 Hz, $J_{5,6b}$ 6.9 Hz, H-5), 4.23 (d, 1 H, H-1b), 4.16 (dd, 1 H, H-6b), 3.29 (br, 1 H, OH), 2.11, 2.07 (2 s, 6 H, C(O)$CH_3$), 1.31 (d, 3 H, acetal-$CH_3$). $^{13}$C NMR (63 MHz, $CDCl_3$): δ 171.0, 170.7 (2 *C*(O)$CH_3$), 103.7 (acetal-C), 103.6 (C-2), 84.2, 80.0, 78.1 (C-3, C-4, C-5), 64.7, 62.0 (C-1/C-6), 20.8, 20.8 (2 C(O)*C*$H_3$), 19.6 (acetal-$CH_3$). Anal. Calcd for $C_{12}H_{18}O_8$ (290.27): C, 49.65; H, 6.25. Found: C, 49.51; H, 6.39.

## Acknowledgements

We are grateful to the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for financial support.

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