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New syntheses of D-tagatose and of 1,5-anhydro-D-tagatose from D-galactose derivatives ☆

Pier Luigi Barili, Giancarlo Berti, Giorgio Catelani *, Felicia D'Andrea, Lucia Miarelli

Dipartimento di Chimica Bioorganica, Universitá di Pisa, Via Bonanno 33, I-56126, Pisa, Italy

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Abstract

3,4-*O*-Isopropylidene-D-*lyxo*-hexopyranosid-2-ulose derivatives, obtained by oxidation of 3,4,6-protected D-galactopyranosides, can be alkylated in their anionic 2,6-pyranose forms to produce bis-glycosides containing the 2,5-dioxabicyclo[2.2.2]octane ring system. The 1-benzyl-2-methyl bis-glycoside **4b**, when subjected to catalytic hydrogenolysis, produces the methyl D-*lyxo*-hexopyranos-2-uloside **10**, existing as an 8:2 mixture of 1,5-pyranose anomers **9**. Computational and NMR evidence is presented in favour of the hypothesis that the major anomer has the α configuration. Reduction of **9/10** with $NaBH_4$ gives methyl 3,4-*O*-isopropylidene-β-D-tagatopyranoside, that can be hydrolyzed to D-tagatose. A simple synthesis of 1,5-anhydro-D-tagatose, starting from 1,5-anhydro-D-galactitol, is also presented. All new compounds were fully characterized by elemental analysis and by ^1H and ^{13}C NMR spectroscopy.

Keywords: D-Tagatose; β-D-Tagatopyranoside; 1,5-Anhydro-D-tagatose; 2,5-Dioxabicyclo[2.2.2]octane

1. Introduction

D-Tagatose, long known as an isomerization product of D-galactose [2], is not available as such from any practical natural source, since it has so far been found only as

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* Corresponding author.

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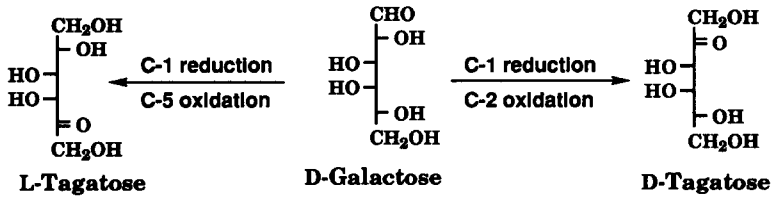


Scheme 1.

a hydrolysis product of the exudate of the tropical plant *Sterculia setigera* [3]. Only recently a biological role of its 1-phosphate and 1,6-bisphosphate has been recognized in biotransformations of D-galactose and lactose in several microorganisms [4] and D-tagatose has been found to activate glyconeogenesis and glycogenolysis [5]. It has also been proposed as a low-caloric sweetener [6]. The renewed interest in D-tagatose may make desirable new synthetic approaches to this ketose, since the much simpler methods based on the isomerization of D-galactose involve extensive purification problems and do not give direct access to selectively protected derivatives.

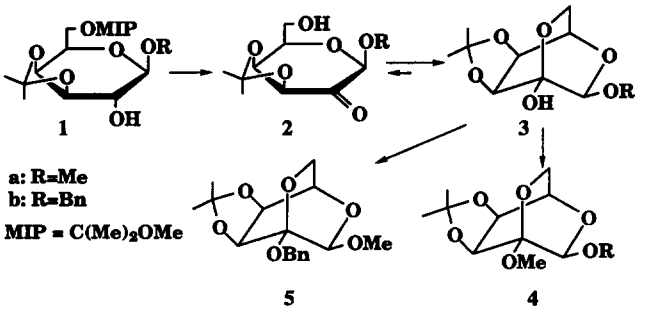
The relative configuration of the chiral part of D-galactose can give access to either D- or L-tagatose through oxidation, respectively, at C-2 or at C-5, preceded or followed by the reduction at C-1 (Scheme 1). We have recently described a synthesis of L-tagatose from 1,5-anhydro-D-galactitol [1d] and report now on a preparation of D-tagatose, based on this approach.

2. Results and discussion

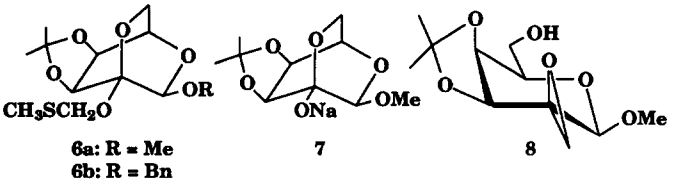
Bis-acetals of type **1**, easily prepared from D-galactopyranosides in high yield [7], are ideally suited for the oxidation at position 2, which can be carried out under a range of conditions, including the use of several Me_2SO-based reagents, provided that the very acid-labile mixed acetal protection on 6-OH is not lost before completion of the oxidation. This oxidative step will be discussed in greater detail in a forthcoming paper on the conversion of D-galactose into D-talosamine derivatives. For our purpose, the Moffatt conditions (Me_2SO, dicyclohexylcarbodiimide, H_3PO_4, pyridine) turned out to be well suited for the conversion of **1** into **2** in over 80% yield (Scheme 2).

As reported in a preliminary communication [8], the hexos-2-ulose derivatives **2a** and **2b** exist at equilibrium almost exclusively as their tautomeric 2,5-dioxabicyclo[2.2.2]octane hemiacetal forms **3a** and **3b**. The sole by-products observed in the oxidation of **1** were the *O*-methylthiomethyl derivatives **6** of the bicyclooctanes **3**, isolated in less than 10% yield. Compounds of this type are often formed as side-products in oxidations involving Me_2SO [9].

We have now found that the hemiacetal hydroxyl groups of compounds **3a** and **3b** can be easily alkylated in their anionic forms to produce the bis-acetal derivatives **4a** and **4b**. Methylations can be carried out with Me_2SO_4 and 1 M NaOH in tetrahydrofuran–water, but yields are better if sodium hydride is used as a base and methyl iodide as alkylating agent in DMF (Table 1). The benzylation of **3a** with sodium hydride and



Scheme 2.



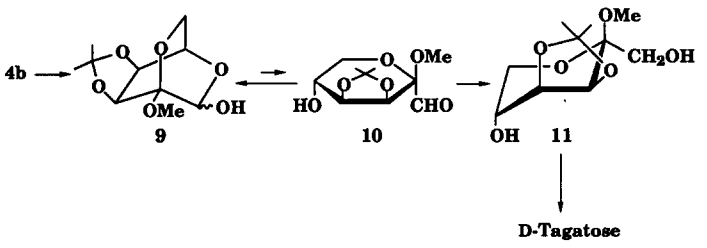
benzyl bromide gave a lower yield of **5** (50%), possibly because of a slower reactivity of the alkylating reagent causing a competition by degradative processes of **2a** in the alkaline medium. A rough estimation of the stability of the sodium salt **7** was obtained by NMR spectroscopy: the spectra of freshly prepared solutions of the salt showed only the expected signal pattern (Tables 2–4), but extensive degradation, revealed by the appearance of many new unassigned signals, was observed in spectra taken after 30 min.

As an alternative approach to the methylation of **3a**, it was treated with diazomethane in ethyl ether, but in this case the compound reacted in its ketonic form **2a**, and the spiro-epoxide **8** was formed stereospecifically.

Table 1
Alkylation of 2,5-dioxabicyclo[2.2.2]octane type tautomers

Compound	Method [a]	Reaction time (h)	Product	Yield (%)
3a	A	24	**4a**	34
3a	B	4	**4a**	62
3a	C	0.5	**4a**	81
3b	C	1	**4b**	93
3a	C	3	**5**	48
14	B	1	**15**	12
14	C	1	**15**	30
14	D	0.3	**15**	64

[a] See Experimental.

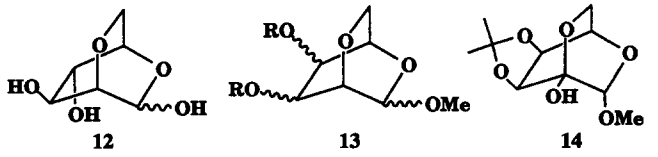


Scheme 3.

The benzyl glycoside **4b** was particularly useful for our purpose of the selective reduction at C-1 necessary for obtaining D-tagatose, the acetal function at C-2 offering a simple intramolecular protection for the ketonic group. It was therefore subjected to hydrogenolysis over Pd–C to liberate the aldehyde group. The product (quantitative yield) was entirely in the hemiacetal form, as a mixture of the anomers of **9** in ratios ranging in different solvents from 71/29 ($CDCl_3$) to 87/13 (CD_3CN). No evidence for the presence at equilibrium of the aldehydic form **10** was obtained from IR or NMR spectra.

Compound **9** is, as far as we could ascertain, the first reported example of a hexos-2-ulo-2,6-pyranoside, and the fact that it exists entirely in its 1,5-pyranose forms, confirms the particular stability of the 2,5-dioxabicyclo[2.2.2]octane ring structure, in spite of the fact that it contains three six-membered rings in a boat conformation (Scheme 3). In the only documented case of a 2,6-anhydrohexose [10], 2,6-anhydro-D-mannose (**12**), a 3-demethoxy unprotected analogue of **9**/**10**, the high prevalence of the hemiacetal forms **12** was inferred from the presence of only a very weak CHO absorption in the IR spectrum, but no confirmatory NMR data were given [1].

The α/β equilibrium ratio of **9** could not immediately be deduced from the NMR spectra of the mixture, since the absence of a proton at C-2 precluded the use of $J_{1,2}$ for the assignment of the anomeric configurations. Furthermore, if an undistorted boat conformation is assumed for the rings of **9**, one cannot invoke the anomeric effect to

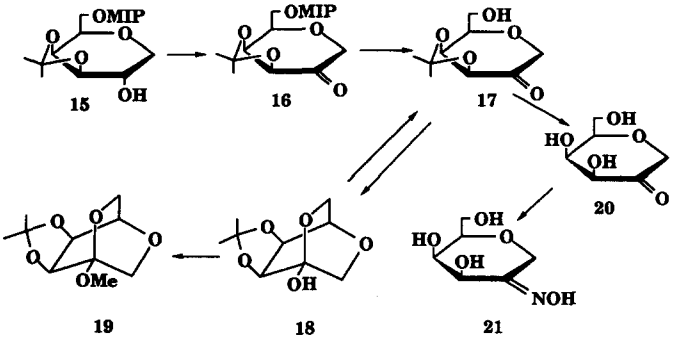


[1] Another compound, supposedly an analogue of **12** in the *ido* series [H. Paulsen, H. Höhne, and P.L. Durette, *Chem. Ber.*, 109 (1976) 597–604] and for which ^1H NMR data were presented, showing a 30/70 α/β anomeric ratio, was later shown [12b] to have a different structure.

explain the preference for one of the two anomers, since the orientation of the (C-1)–OH bond with respect to one of the O-5 lone-pair orbitals, which appears to be the main determining factor of the anomeric effect, would be the same in the α and β anomers of **9**. It may be mentioned that X-ray diffraction [11] and ^{1}H NMR data [12] on many methyl α- and β-glycosides of the general formula **13** show significant deviations towards twist-boat forms. They involve pseudorotations occurring in opposite directions in α- (anticlockwise) and β-forms (clockwise), leading, however, in both cases to an approach to conformations more favourable for the operation of the anomeric effect, which therefore cannot explain the significant preference observed for one of the anomers. Although in the case of **9** the non-availability of the pure anomers did not allow direct structural investigations, molecular mechanics computations (Pcmodel program [13]) confirmed that deviations of this type are present in the anomers of **9**. For instance (C-5–O-5–C-1–C-2) dihedral angles of $-7.5°$ for α-**9** and $+10.9°$ for β-**9**, and a ΔE of -0.98 kcal/mol in favour of the α anomer, corresponding to an α/β ratio of 80:20, resulted from these computations. A comparison of the latter data with the experimentally found anomeric ratios (see above) is in favour of the hypothesis that the α anomer of **9** is preponderant at equilibrium. Further evidence in favour of this hypothesis came from a comparison of the ^{1}H NMR spectrum of **9** with those of **3a** and its α anomer **14** [8], and with the published data on methyl 2,6-anhydrohexopyranosides of the general formula **13** [12], for which, in all four stereochemical possibilities (*manno, talo, ido*, and *altro*), the $\delta_{H\text{-}1}$ value is higher in the α than in the β anomer, as found in the major anomer of **9**. Furthermore, the $\delta_\alpha - \delta_\beta$ value of -2.7 ppm found for C-3 in the ^{13}C NMR spectrum of α,β-**9** is compatible with a γ effect of a gauche or anti OH group on the γ-carbon [14]. One can therefore conclude with reasonable confidence that **9** exists at equilibrium mainly in the α form, even if a direct proof, or a theoretical explanation on the basis of the anomeric effect, cannot be presented. Other effects, such as H-bonding, steric, or dipole–dipole interactive factors may have a significant influence.

Compound **9 / 10** was quantitatively reduced with sodium borohydride in methanol to methyl 3,4-*O*-isopropylidene-β-D-tagatopyranoside (**11**), which exists entirely in the $^2C_5$ conformation. Hydrolysis of **11** with aqueous acetic acid gave quantitatively D-tagatose.

Oxidation of the 1,5-anhydro-D-galactitol derivative **15** with tetrapropylammonium



Scheme 4.

perruthenate (TPAP) and 4-methylmorpholine *N*-oxide [15] in CH_2Cl_2 gave, in 97% yield, the 1,5-anhydro-D-tagatose derivative **16**, which was deprotected in position 6 with dilute aqueous acetic acid to produce **17** (Scheme 4). In this case the preference for the 2,5-dioxabicyclo[2.2.2]octane hemiacetal form **18** is less pronounced, the ratio of tautomers **17**/**18** being 6:4 at equilibrium in CD_3CN [8]. This may explain the fact that methylation with sodium hydride and methyl iodide in DMF gave the glycoside **19** in only 30% yield. However, when a more reactive methylating reagent, methyl triflate in tetrahydrofuran, was used, the yield rose to 64%. This confirmed the hypothesis presented above that a rapid alkylation is necessary in order to avoid unwanted side-reactions affecting the ketonic form, labile under basic conditions.

Deprotection of **17**/**18** under mild acidic conditions gave 1,5-anhydro-D-tagatose (**20**), a diastereomer of 1,5-anhydro-D-fructose, a natural product isolated from the mushroom *Morchella vulgaris* [16]. NMR and IR spectra of **20** revealed, as reported also for the *fructo* analogue [16,17], the absence of carbonyl signals and a very complex situation arising from the equilibria between monomeric tautomers and dimeric forms. The oximation of crude **20** with hydroxylamine hydrochloride in dry pyridine gave a crystalline oxime **21**, fully characterized by NMR spectral analysis.

3. Experimental

General methods are those reported in Ref. [1d]. Previously described procedures were used for the preparation of the starting compounds, **1a** [7,18], **1b** [7], and **14** [1c]. NMR spectral data for all compounds are collected in Tables 2–4.

Oxidation of **1a**.—A solution of **1a** (5.9 g, 19.2 mmol), pyridine (1.5 mL), and phosphoric acid (0.6 mL) in dry 2:1 Me_2SO–benzene (30 mL) was cooled at 0°C and treated, under magnetic stirring, with dicyclohexylcarbodiimide (12.2 g, 59.1 mmol). The mixture was slowly allowed to attain room temperature and stirred until the starting material had completely disappeared (48 h, TLC monitoring, 95:5 CH_2Cl_2–Me_2CO), then cooled to 0°C, treated with a methanolic solution of oxalic acid (9.8 g in 24 mL), and further stirred for 1 h. The precipitated *N,N'*-dicyclohexylurea was filtered off and washed with benzene and EtOAc; the combined organic solutions were washed with satd aq $NaHCO_3$, dried, and evaporated in vacuo to give a syrupy residue, from which a further crop of *N,N'*-dicyclohexylurea was precipitated by treatment with acetone (30 mL). Filtration and evaporation of the solution gave a crude residue (4.2 g) that, submitted to silica gel flash-chromatography (95:5 CH_2Cl_2–Me_2CO + 0.1% Et_3N), led to the following products.

Methylthiomethyl (methyl 3,4-*O*-isopropylidene-β-D-*lyxo*-hexopyranosid)-2-ulo-2,6-pyranoside (**6a**, 393 mg, 7% yield); syrup; R_f 0.23 (8:2 hexane–EtOAc); $[\alpha]_D$ −79.4° (*c* 1.9, $CHCl_3$). Anal. Calcd for $C_{12}H_{20}O_6S$: C, 49.3; H, 6.9. Found: C, 49.5; H, 6.8.

Methyl 3,4-*O*-isopropylidene-β-D-*lyxo*-hexopyranosid-2-ulo-2,6-pyranose (**3a**, 3.24 g, 73% yield); R_f 0.50 (3:7 hexane–EtOAc); mp 88–89°C (from hexane); $[\alpha]_D$ − 45.7° (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{10}H_{16}O_6$: C, 51.7; H, 6.9. Found: C, 51.8; H, 7.3.

Oxidation of **1b**.—The oxidation of **1b** (1.8 g, 4.71 mmol) by the procedure

Table 2
Chemical shifts (δ, CD_3CN)

Compound	H-1	H-1′	H-3	H-4	H-5	H-6a	H-6b	Dioxolanic Me		OMe-1	Benzylic	CH_2 [a]	Others
3a	4.47		4.14	4.45	3.91	4.09	3.97	1.48	1.34	3.47			
3b	4.69		4.14	4.46	3.96	4.14	4.07	1.51	1.35		4.89	4.62	
4a	4.49		4.16	4.43	3.92	4.15	4.06	1.48	1.33	3.45			3.41
4b	4.73		4.17	4.46	3.98	4.19	4.18	1.51	1.35		4.89	4.61	3.45
5	4.58		4.26	4.50	3.98	4.24	4.16	1.56	1.39	3.45	4.88		
6a	4.55		4.19	4.45	3.94	4.16	4.08	1.48	1.33	3.45			4.90,4.80,2.12
6b	4.80		4.21	4.47	4.00	4.20	4.19	1.50	1.35		4.90	4.62	4.92,4.84,2.11
7 [b]	4.42		4.06	4.46	3.90	4.04	3.95	1.51	1.36	3.46			
8	4.47		4.17	4.36	3.83	3.85	3.57	1.39	1.27	3.40			2.98,2.91
9α [c]	5.09		4.65	4.41	3.59	4.15	3.68	1.38	1.01				3.49
9β [c]	4.76		3.72	3.91	3.41	4.01	3.73	1.38	1.01				3.51
11	3.54	3.45	4.34	4.14	3.90	3.77	3.42	1.41	1.29				3.17
14	4.62		4.36	4.37	3.92	4.15	3.80	1.49	1.32	3.38			
16	4.12	4.02	4.43	4.54	3.96	3.59	3.54	1.35	1.33				3.16,1.31
17	4.02	4.14	4.43	4.55	3.87	3.67	3.67	1.34	1.34				
18	3.78	3.56	4.18	4.41	3.78	4.20	4.03	1.49	1.33				
19	3.99	3.51	4.22	4.41	3.76	4.23	4.05	1.49	1.33				3.33
21 [d]	5.17	3.78	4.35	4.01	3.61	3.76	3.68						

[a] Aromatic protons resonate between δ 7.3 and 7.4.
[b] In D_2O/NaOD.
[c] In C_6D_6.
[d] In CD_3OD/D_2O.

described above led, after silica gel flash-chromatography (6:4 hexane–EtOAc), to the following products.

Methylthiomethyl (benzyl 3,4-*O*-isopropylidene-β-D-*lyxo*-hexopyranosid)-2-ulo-2,6-pyranoside (**6b**, 128 mg, 7.4% yield); syrup; R_f 0.27 (8:2 hexane–EtOAc); $[\alpha]_D$ −76.2° (*c* 0.7, $CHCl_3$). Anal. Calcd for $C_{18}H_{24}O_6S$: C, 58.7; H, 6.6. Found: C, 59.0; H, 6.6.

Benzyl 3,4-*O*-isopropylidene-β-D-*lyxo*-hexopyranosid-2-ulo-2,6-pyranose (**3b**, 1.13 g, 78% yield); R_f 0.33 (1:1 hexane–EtOAc); mp 125–127°C (from hexane); $[\alpha]_D$ −71.0° (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.3; H, 6.5. Found: C, 62.3; H, 6.8.

1,5-Anhydro-3,4-O-isopropylidene-6-O-(1-methoxy-1-methylethyl)-D-tagatose (**16**).—A solution of **15** (1.99 g, 7.2 mmol) and pre-dried [15] 4-methylmorpholine-*N*-oxide (1.45 g, 12.4 mmol) in dry CH_2Cl_2 (60 mL), to which freshly activated crushed 4 Å molecular sieves (7 g) had been added, was stirred for 30 min. The mixture was then treated with TPAP (0.126 g, 0.36 mmol, 0.05 equiv) and stirred until the starting material had disappeared (TLC, 9:1 CH_2Cl_2–Me_2CO; 15 min). The mixture was filtered through a short layer of Celite, and the solution washed with brine (2 × 50 mL), dried, and evaporated; the crude residue was subjected to silica gel flash-chromatography (3:7 hexane–EtOAc + 0.1% Et_3N) to give **16** as a white solid (1.92 g, 97% yield); R_f 0.56 (3:7 hexane–EtOAc); mp 70–72°C (from hexane–EtOAc); $[\alpha]_D$ − 30.8° (*c* 0.7, $CHCl_3$). Anal. Calcd for $C_{13}H_{22}O_6$: C, 56.9; H, 8.1. Found: C, 56.8; H, 7.7.

Table 3
J-Couplings (Hz) [a]

Compound	$J_{1,1'}$	$J_{1',3}$	$J_{1,6}$	$J_{3,4}$	$J_{4,5}$	$J_{4,6b}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$	Others
3a			0.72	8.18	4.43	1.31	1.47	1.82	9.55	
3b			0.6	8.17	4.47	1.15	1.56	1.74	9.64	J_{CH_2Ph} 11.72
4a			0.64	8.15	4.48	1.23	1.55	1.80	9.73	
4b			0.5	8.15	4.51	0.70	1.65	1.65		J_{CH_2Ph} 11.73
5			0.56	8.14	4.51	1.18	1.56	1.74	9.72	
6a			0.59	8.14	4.54	1.16	1.59	1.71	9.73	J_{CH_2S} 11.22
6b			0.6	8.14	4.59	0.49	1.53	1.70		J_{CH_2Ph} 11.62, J_{CH_2S} 11.21
8				6.53	1.94		6.00	6.04	11.23	
9α [b]				7.88	3.56	1.73	0.3	3.18	9.14	$J_{3,5}$ 0.4
9β [b]			0.4	8.16	4.21	1.54	0.95	2.40	9.64	
11	11.78			6.66	3.72		3.25	4.75	11.74	
14				8.10	4.45	1.80	0.54	3.00	9.37	
16	15.82	0.51		6.12	1.64		5.24	7.04	10.08	$J_{1,3}$ 0.6
17	15.91	0.58		6.16	1.60		6.30	5.93		$J_{1,3}$ 0.53
18	9.10			8.18	4.18	1.42	1.29	2.13	9.82	
19	9.37	0.51		8.14	4.09	1.53	1.23	2.29	9.84	$J_{3,5}$ 0.34, $J_{3,6}$ 0.36, $J_{1,5}$ 0.36
21 [c]	14.28	0.79		3.47	1.14		7.08	4.61	11.08	$J_{1,3}$ 0.3

[a] COSY experiment revealed several small long-range *J* couplings: here are reported only the surely measurable values.
[b] In C_6D_6.
[c] In CD_3OD/D_2O.

1,5-Anhydro-3,4-O-isopropylidene-D-tagatose (**17**) *and 1,5-anhydro-3,4-O-isopropylidene-D-tagatopyranose* (**18**).—Compound **16** (1.46 g, 5.3 mmol) was dissolved in MeOH (150 mL) containing 0.5 mL of aq 60% AcOH; after 1 h stirring at 50°C, the solution was evaporated in vacuo and coevaporated with toluene (3 × 30 mL) to give a crude residue (1.36 g) that was submitted to silica gel flash-chromatography (3:7 hexane–EtOAc). After an unidentified by-product (R_f 0.53 in 3:7 hexane–EtOAc, 154 mg), a tautomeric mixture of **17** and **18** was obtained (0.96 g, 89% yield); R_f 0.30 (3:7 hexane–EtOAc); crystallization from hexane gave the bicyclo tautomer **18**; mp 119–122°C; $[\alpha]_D$(initial) + 17.4° (*c* 0.9, $CHCl_3$). Anal. Calcd for $C_9H_{14}O_5$: C, 53.5; H, 7.0. Found: C, 53.7; H, 7.2.

Alkylation of 2,5-dioxabicyclo[2.2.2]octan-1-ol derivatives.—The following general procedures were used.

Method A. The 2,5-dioxabicyclo[2.2.2]octan-1-ol derivative (1.0 mmol) was dissolved in 1 M NaOH (2.3 mL, 2.3 equiv) and immediately treated under stirring at room temperature with Me_2SO_4 (0.115 mL, 1.2 mmol); the solution was stirred until the starting material disappeared (TLC monitoring), then extracted with CH_2Cl_2 (5 × 50 mL). The combined extracts were dried and evaporated to give crude products, directly analyzed by NMR spectroscopy, and, if necessary, subjected to flash chromatography, leading to pure products.

Method B. The 2,5-dioxabicyclo[2.2.2]octan-1-ol derivative (1.0 mmol) was dissolved in THF (6 mL) and treated at room temperature with 1 M NaOH (2.3 equiv) and

Table 4
^{13}C (δ, ppm CD_3CN)

Compound	C-1	C-2	C-3	C-4	C-5	C-6	Dioxolanic C			OMe-1	OMe	Others					
3a	101.71	93.03	76.74	74.16	67.61	64.41	113.36	26.25	25.17	56.42							
3b	99.68	93.15	76.69	74.10	67.74	64.47	113.37	26.27	25.21			70.69	138.82	129.26	129.02	128.65	
4a	101.62	95.38	77.34	74.24	67.48	64.65	113.15	26.29	25.12	55.71	52.44						
4b	99.66	95.50	77.29	74.19	67.63	64.72	113.15	26.33	25.17		52.59	70.28	138.87	129.32	128.96	128.65	
5	101.78	95.63	77.53	74.26	67.50	64.85	113.26	26.40	25.26	55.87		66.60	140.38	129.04	128.23	128.06	
6a	101.44	95.51	77.18	74.02	67.41	64.80	113.23	26.32	25.27	55.84		69.81	14.47				
6b	99.65	95.79	77.23	74.07	67.66	64.97	113.35	26.29	25.21			70.40	138.77	129.27	128.89	128.63	69.82	14.42
7 [a]	104.22	96.62	79.09	73.84	67.08	63.47	113.20	26.21	24.93	57.66							
8	101.93	58.57	75.89	74.69	74.03	62.11	110.86	26.68	25.82	56.91		47.95					
9α	93.20	96.41	74.34	72.47	68.36	65.16	111.55	26.22	24.62		51.30						
9β	94.17	95.30	76.99	74.10	66.97	64.53	113.16	26.22	24.91		52.58						
11	62.25	98.16	72.65	76.96	66.94	62.29	110.54	26.21	25.70		48.83						
14	103.25	93.39	74.80	72.41	68.59	65.04	111.45	26.27	24.68	56.14							
16	73.90	205.30	77.21	77.58	76.58	61.04	111.39	27.29	25.99			100.93	44.80	24.70	24.70		
17	73.92	205.46	78.05	78.05	77.17	62.11	111.68	27.22	25.92								
18	69.97	93.12	77.65	73.66	67.17	65.61	111.68	25.21	25.01								
19	67.86	95.69	73.87	73.87	66.97	65.78	111.16	26.24	24.89		51.49						
21 [b]	61.40	154.66	71.61	71.44	79.79	62.40											

[a] In D_2O.
[b] In CD_3OD/D_2O.

Me_2SO_4 (1.2 mmol). The biphasic mixture was treated and worked up as reported in method A.

Method C. A suspension of 80% NaH in mineral oil (50 mg, 1.67 mmol) was washed with hexane and dry DMF (4 mL) was added. After cooling at 0°C, a solution of the pertinent 2,5-dioxabicyclo[2.2.2]octan-1-ol derivative (1.0 mmol) in dry DMF (2 mL) was added. The red solution was immediately treated with a solution of the alkylating reagent (2.4 mmol) in dry DMF (0.60 mL) and stirred until the starting material had completely disappeared (TLC monitoring). To the yellowish solution, cooled at 0°C, excess of MeOH was added in order to destroy unreacted NaH. After 15 min stirring the solution was evaporated in vacuo. The residue was poured into H_2O (3 mL) and extracted with CH_2Cl_2 (5 × 20 mL); the combined extracts were dried and evaporated to give the crude alkylation products, analyzed by NMR spectroscopy and, if necessary, subjected to silica gel flash-chromatography, leading to pure products.

Method D. A solution of 2,5-dioxabicyclo[2.2.2]octan-1-ol derivative (1.0 mmol) in dry THF (10 mL) was added to a suspension of NaH (1.05 mmol) in dry THF (5 mL) cooled at −10°C. The mixture was treated with methyl triflate (0.120 mL, 1.05 mmol) and stirred at −10°C, until the starting material had disappeared. The reaction was quenched by addition of excess of solid Na_2CO_3. Filtration, evaporation and flash chromatography gave the pure product.

The results of different runs of alkylation reactions are collected in Table 1. The following products were obtained.

Methyl (methyl 3,4-*O*-isopropylidene-β-D-*lyxo*-hexopyranosid)-2-ulo-2,6-pyranoside (**4a**); R_f 0.61 (9:1 CH_2Cl_2–Me_2CO); mp 57–59°C (from hexane); $[\alpha]_D$ − 43.5° (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{11}H_{18}O_6$: C, 53.6; H, 7.4. Found: C, 53.7; H, 7.9.

Methyl (benzyl 3,4-*O*-isopropylidene-β-D-*lyxo*-hexopyranosid)-2-ulo-2,6-pyranoside (**4b**); R_f 0.64 (3:7 hexane–EtOAc); syrup; $[\alpha]_D$ − 66.2° (*c* 1.3, $CHCl_3$). Anal. Calcd for $C_{17}H_{22}O_6$: C, 63.3; H, 6.9. Found: C, 63.2; H, 7.0.

Benzyl (methyl 3,4-*O*-isopropylidene-β-D-*lyxo*-hexopyranosid)-2-ulo-2,6-pyranoside (**5**); R_f 0.20 (8:2 hexane–EtOAc); mp 33–36°C (from EtOH); $[\alpha]_D$ − 14.7° (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{17}H_{22}O_6$: C, 63.3; H, 6.9. Found: C, 63.2; H, 6.5.

Methyl 1,5-anhydro-3,4-*O*-isopropylidene-β-D-tagatopyranoside (**19**); R_f 0.73 (3:7 hexane–EtOAc); syrup; $[\alpha]_D$ + 10.7° (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.5; H, 7.5. Found: C, 55.2; H, 7.2.

Methyl 2,2'-anhydro-2-C-hydroxymethyl-3,4-O-isopropylidene-β-D-talopyranoside (**8**).—A solution of **3a** (214 mg, 0.92 mmol) in Et_2O (10 mL) was treated at room temperature, with stirring, with an ethereal solution of CH_2N_2 until the solution had a persistent yellow colour (2 mL). After 5 h an additional volume (2 mL) of CH_2N_2 was added and the solution was stirred for a further 24 h. The reaction was stopped by dropwise addition of aq 60% AcOH until the yellowish colour completely disappeared. The solvents were removed under reduced pressure, giving a crude product (260 mg) consisting (TLC) mainly of **8** and some starting material. It was dissolved in CH_2Cl_2 (20 mL) and washed with 1 M NaOH (2 × 10 mL) in order to remove unreacted **3a**. The organic solution was dried, filtered, and evaporated, to give pure **8** as a white solid (160 mg, 71% yield); R_f 0.40 (9:1 CH_2Cl_2–Me_2CO); $[\alpha]_D$ − 19.1° (*c* 1.0, $CHCl_3$); mp

106–107°C (petroleum ether–EtOAc). Anal. Calcd for $C_{11}H_{18}O_6$: C, 53.6; H, 7.4. Found: C, 53.5; H, 7.2.

*Methyl 3,4-O-isopropylidene-α,β-*D*-lyxo-hexopyranos-2-ulo-2,6-pyranoside (α,β-**9**).*—To a solution of **4b** (1.03 g, 3.2 mmol) in MeOH (100 mL) was added 10% Pd-on-charcoal (300 mg) and the mixture was stirred under H_2 at room temperature for 1 h. The mixture was filtered through Celite and the solution evaporated in vacuo to give a crude residue. Silica gel chromatography led to pure **9** (640 mg, 86% yield); R_f 0.41 (3:7 hexane–EtOAc); syrup, $[\alpha]_D$ (equilibrium) +21.5° (*c* 1.1, $CHCl_3$). ^1H NMR analysis in different solvents revealed the following α/β equilibrium ratios: 71:29 ($CDCl_3$), 72:28 (C_6D_6), 86:14 (Me_2SO-d_6), 87:13 (C_5D_5N), 82:18 (CD_3OD), 82:18 (CD_3CN). Anal. Calcd for $C_{10}H_{16}O_6$: C, 51.7; H, 6.9. Found: C, 51.2; H, 7.2.

*Methyl 3,4-O-isopropylidene-β-*D*-tagatopyranoside* (**11**).—A solution of **9** (810 mg, 3.5 mmol) in MeOH (70 mL) was treated with $NaBH_4$ (140 mg, 3.5 mmol) and stirred at room temperature for 15 min. The reaction was stopped by addition of Amberlist 15(H^+) resin (7 mL), and the solution immediately filtered; evaporation of the solvent in vacuo left pure **11** (800 mg, quantitative yield); R_f 0.30 (EtOAc); syrup; $[\alpha]_D$ −57.0° (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{10}H_{18}O_6$: C, 51.3; H, 7.7. Found: C, 51.0; H, 7.4.

D-*Tagatose.*—A solution of **11** (650 mg, 2.8 mmol) in aq 80% AcOH (10 mL) was warmed at 80°C under stirring for 10 min. After evaporation in vacuo, the dry residue was subjected five times to treatment with toluene (100 mL) and evaporation. The residue (quantitative yield) had mp 130–132°C; $[\alpha]_D$ (equilibrium) −2.9° (*c* 0.9, MeOH); lit. [19] mp 134–135°C, $[\alpha]_D^{20}$ −2.3° (*c* 2.2, H_2O); mp 133–134°C, $[\alpha]_D^{25}$ −5° (*c* 1.0, H_2O). The NMR data were identical to those reported for a pure sample of L-tagatose [1d].

*1,5-Anhydro-*D*-tagatose* (**20**).—A solution of **17**/**18** (130 mg, 0.64 mmol) in aq 60% AcOH (15 mL) was warmed at 60°C and stirred for 2 h. The solvents were removed in vacuo and the residue coevaporated with toluene (3 × 15 mL), leaving a semisolid, very hygroscopic, crude residue (100 mg); homogeneous by TLC analysis, R_f 0.14 (95:5 EtOAc–MeOH); $[\alpha]_D$ −6.8° (*c* 1.1, MeOH). IR analysis of the crude product gave no evidence of carbonyl absorption. The NMR spectra showed a very complex situation due to tautomeric equilibria, that precluded any interpretation.

*1,5-Anhydro-*D*-tagatose oxime* (**21**).—To a solution of crude **20** (100 mg, 0.62 mmol) in dry pyridine (4 mL) was added hydroxylamine hydrochloride (53 mg, 0.76 mmol), and the mixture was stirred at room temperature for 60 h. The solvent was removed under reduced pressure to give a crude solid residue consisting (NMR) of an *E*/*Z* mixture of oximes. A single crystallization from MeOH yielded pure **21** (probably the *Z* form) (30 mg, 27%); mp 176–179°C; R_f 0.59 (7:3 $CHCl_3$–MeOH); $[\alpha]_D$ −9.2° (*c* 0.5, MeOH). Anal. Calcd for $C_6H_{11}NO_5$: C, 40.7; H, 6.3; N, 7.9. Found: C, 40.5; H, 6.1; N, 7.8.

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