Studies on the Oxidation of Methyl 2,3-*O*-Isopropylidene-β-D-ribofuranoside with Pyridinium Dichromate. Identification of Unexpected By-Products

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Oxidation of methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (**1a**) with pyridinium dichromate yields, in addtition to the expected methyl 2,3-*O*-isopropylidene-β-D-*ribo*-1,4-pentodialdofuranoside (**1b**), methyl 2,3-*O*-isopropopylidene-β-D-erythrosi-durono-1,4-lactone (**3**) and the dimeric ester **1e**. The structures of the latter compounds were determined by spectroscopic methods. A mechanistic scheme is proposed for their formation.

In connection with our studies on the synthesis of D-ribose derivatives bearing lipophilic chains, we wanted to synthesize methyl 2,3-*O*-isopropylidene-β-D-*ribo*-1,4-pentodialdofuranoside (**1b**). Structures of this and other compounds are shown in Fig. 1. The sugar aldehyde **1b** has already been successfully employed in a wide variety of chain-extension reactions (for representative examples see Refs. 1–6) and is usually prepared by oxidation of the title alcohol **1a**. Although a number of other oxidation systems have provided **1b** in low to good yields,[7–11] we decided to employ the inexpensive oxidant pyridinium dichromate (PDC) in CH_2Cl_2, which allows for preparatively simple, mild, safe and effective oxidation of alcohols to carbonyl compounds.[12]

Treatment of **1a** with PDC at room temperature led to incomplete oxidation even after prolonged reaction times (Table 1, entry 1). Entry numbers given in the paper refer to Table 1. This result agrees with the observation of others[13,14] concerning the difficulty of oxidising sugar alcohols. In addition to the expected product **1b**, a less polar by-product was formed in significant amounts as evidenced by TLC analysis of the reaction mixture. However, flash chromatography, followed by GLC analysis, revealed that this by-product was actually a mixture of two compounds which were separated by fractional distillation. Spectroscopic investigation of both products (Tables 2 and 3) allowed assignment of their structures. Thus the low-boiling component was actually the lactone **3**, and the structure assigned to the high-boiling one was **1e**. Conclusive evidence in favour of structure **3** was obtained by means of a crystal structure determination[15] (Fig. 2) when the compound was finally obtained in suitable crystalline form.

The assignment of the ^{1}H NMR spectrum of **3** (Table 2) is readily understood and is in accordance with the crystal structure analysis. The latter shows that the furanose ring adopts an almost planar conformation and that the 1,3-dioxolane ring has an envelope conformation. The dihedral angles H(3)–C(3)–C(2)–H(2) and H(1)–C(1)–C(2)–H(2) are 7.5 and 107.0°, respectively. The NMR coupling constants calculated[16] on this basis are 8.1 and 0.5 Hz, respectively. Taking into account that these calculated values are based on solid-phase data and that oxygen substituents are involved in the molecular framework, they may be considered as being in good agreement with the measured values of 5.5 and 0 Hz, respectively (Table 2) for the same compound.

The assignment (Table 2) of each individual proton in the ^{1}H NMR spectrum of the dimer **1e** was not as straightforward as in the case of **3**, and required the use of double resonance experiments. Thus, irradiation of the dd (H-4) at 5.192 ppm converted both the dd (H-3) at 4.524 ppm and the t (H-2) at 4.620 into broad singlets. Irradiation of the td (H-4′) at 4.372 ppm converted the d (H-5′) at 4.180 ppm into a distorted singlet and the dd (H-3′) at 4.633 ppm into a doublet. Furthermore, irradiation of the d (H-2′) at 4.577 ppm converted the dd (H-3′) at 4.633 ppm into a distorted singlet, the small coupling to H-4′ being reduced as observed in all protons coupled to others with small coupling constants, i.e., less than 0.7 Hz. Finally, irradiation of one of the methyl groups, i.e., the unresolved q at 1.310 ppm, converted the corresponding q at 1.464 into a singlet. The coupling constants for the pairs H-2/H-3 and H-2′/H-3′ are quite different, 0.7 Hz for the former and 5.9 Hz for the latter. Thus different conformations must be adopted in

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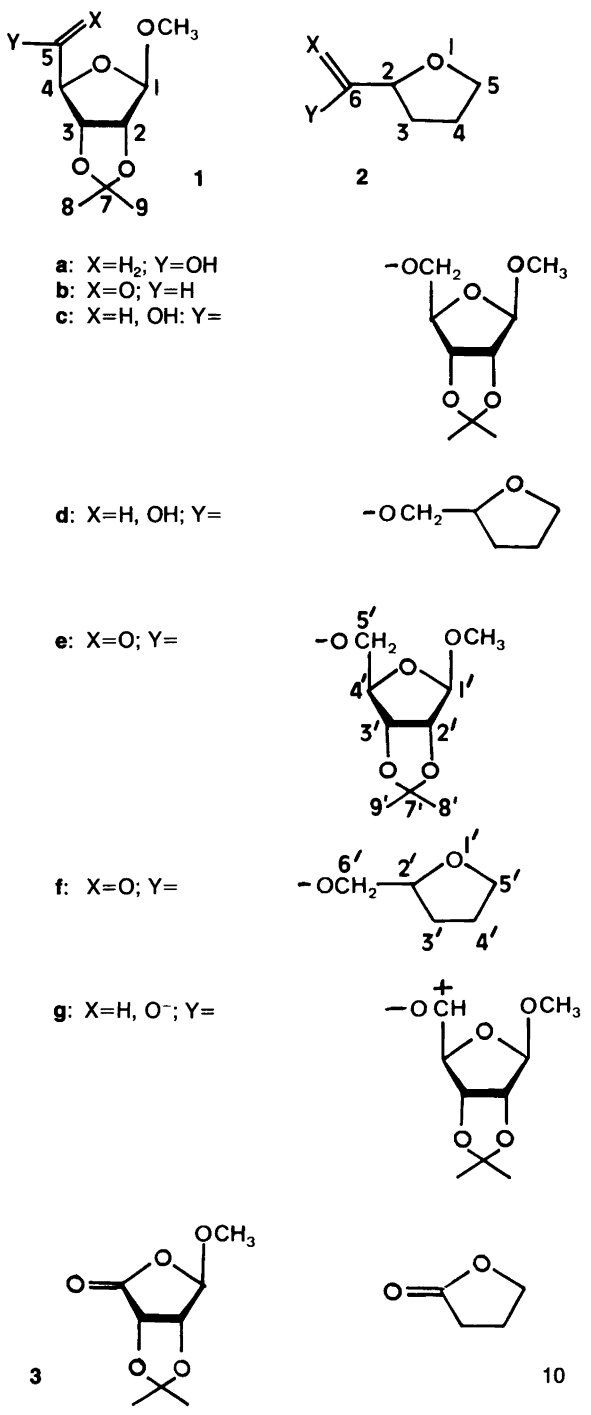


Fig. 1. Structures of compounds encountered in this study.

solution by the two furanose rings. In fact, the data indicate that the alcohol moiety adopts a flattened envelope conformation while the acid moiety of the dimer adopts a twist conformation.[16] It is plausible to suggest that adoption of the twist form by the latter may be attributed to unfavourable non-bonded interactions between the carbonyl function in position 4 of the ring and the anomeric oxygen atom at position 1.

To confirm the assignment of the spectrum the 400 MHz ^{1}H NMR spectra of both aldehyde **1b** and the alcohol **1a** (Table 2) were recorded. The splitting pattern for protons H-2, H-3 and H-4 of the aldehyde **1b** was found to be quite similar to that for the corresponding protons of the dimer. It must be pointed out that complete assignment of the protons of **1b** was also the result of a double resonance experiment where irradiation of the resonance at 4.491 ppm caused those at 5.043 and 4.468 ppm to collapse to broad singlets. A previously reported 100 MHz ^{1}H NMR spectrum of **1b** represents[7] protons H-2, H-3 and H-4 as an unresolved multiplet. Furthermore, the splitting pattern of protons H-2 and H-3 (two doublets with coupling constant of 5.9 Hz) in alcohol **1a** agrees well with that of the corresponding protons of the alcohol part of the dimeric ester **1e**.

A plausible mechanism which accounts for the formation of both by-products, and of course of the aldehyde **1b**, from the alcohol **1a** is outlined in Scheme 1. Thus, all reaction products can initially be envisaged as being formed from a common intermediate, namely the chromate ester **4**. The latter can either collapse in the usual way to the aldehyde **1b** or degrade, by formaldehyde expulsion, to the resonance stabilised cation **5**. The latter can be further elaborated, via the chromite ester **6** to the lactone **3**. An alternative mechanistic scheme might involve an initial hydrogen atom transfer, followed by an electron transfer,[17] to give the resonance stabilised cation **7**. The latter can be cyclised to the intermediate **8** which can also provide the lactone **3** through a glycol-type cleavage. The possibilities for the interception of **5** by a water molecule and subsequent oxidation of the resulting lactol to the lactone **3** should, however, not be underestimated. Since the aldehyde **1b** is known to add water readily,[7] it might also combine easily with unchanged alcohol **1a** to give the hemiacetal **1c** which may be further oxidised to the ester **1e**. This mechanism is in accordance with that proposed for the CrO_3-oxidation of 1,4-diols to lactones.[18]

It has been shown that PDC oxidations of secondary carbohydrate alcohols can be accelerated by molecular sieves.[13] Accordingly, when oxidation of **1a** was conducted in the presence of 4 Å molecular-sieve beads (entry 2), the reaction was complete within 24 h while an increase in the ratio of aldehyde to by-products was observed. Since the formation of **1e** is the result of a bimolecular reaction, the oxidation was repeated in dilute solution (entry 3). The expected further increase of the ratio of aldehyde to by-products was indeed observed. At that time we became aware of a recent report[14] claiming dramatic acceleration in the PDC oxidation of secondary carbohydrate alcohols when molecular-sieve-activated powder and glacial AcOH are used in combination. Thus, when the oxidation of **1a** was conducted in dilute solution and under the above-mentioned conditions (entry 4), not only was a dramatic acceleration of the reaction observed (complete within ca. 20 min) but also the ratio of aldehyde to by-products was substantially improved. It must be noted that significant quantities of **1e** and **3** were also formed when **1a** was

Table 1. Oxidations with PDC.

Run	Substrate	PDC[a]	MS[b]	Reaction time/h[c]	Products[d] (t_R/min)		
					1b (10.8)	**1e** (28.8)	**3** (14.8)
1	**1a**	4.5	0	48[e]	1.0	5.6	2.6
2	**1a**	4.5	1.5	20	1.0	4.7	1.6
3[f]	**1a**	4.5	1.5	25	4.2	1.2	1.0
4[g]	**1a**	5.0	3.0	0.33	6.5	1.2	1.0
5[h]	**1a**	10.5	1.5	6	–	2.2	1.0
					2b (8.2)	**2f** (20.6)	**10** (14.2)
6	**2a**	4.5	1.5	20	7.7	11.1	1.0
					1f (22.4)	**2f** **1e**	**3**
7	**2a**+**1b**[i]	4.5	1.5	24	32.0	20.0 1.0	1.4
					1b (10.8)	**1e** (28.8)	**3** (14.8)
8[j]	**1b**	4.5	1.5	12	1.0	8.0	5.3
9[j]	**1b**	0	1.5	12	1.0	0	0
10[j]	**1b**	0	0	12	1.0	0	0

[a]mmol per 3 mmol substrate in 10 ml CH_2Cl_2 unless otherwise stated. [b]4 Å molecular-sieve beads (g) per 3 mmol substrate. [c]At room temperature. [d]Relative quantities of products in the reaction mixture, are expressed as a ratio, retention time (t_R/min). [e]Incomplete reaction; reaction went to completion after a further 6 h only after addition of a further 2 mmol PDC and molecular-sieve beads (0.8 g). [f]40 ml solvent. [g]30 ml solvent, activated 4 Å molecular sieve powder, pulverised PDC and 100 % AcOH (0.6 ml). [h]DMF as solvent. [i]3.5 mmol **1b**; aldehyde components and possibly **10** were removed on aqueous work-up which included washing with sat. $NaHSO_3$ prior to silica gel filtration. [j]Work-up after the indicated reaction time.

oxidised under conditions (DMF as the solvent, entry 5) known to convert primary alcohols into carboxylic acids.[12] A re-examination of the TLC results for the reactions described in entries 1–4 revealed that, with the exception of entry 4 where only a minute amount of acid was detected, significant amounts of the corresponding carboxylic acid were formed, thus explaining the low mass recovery (ca. 50 %) of non-polar products.

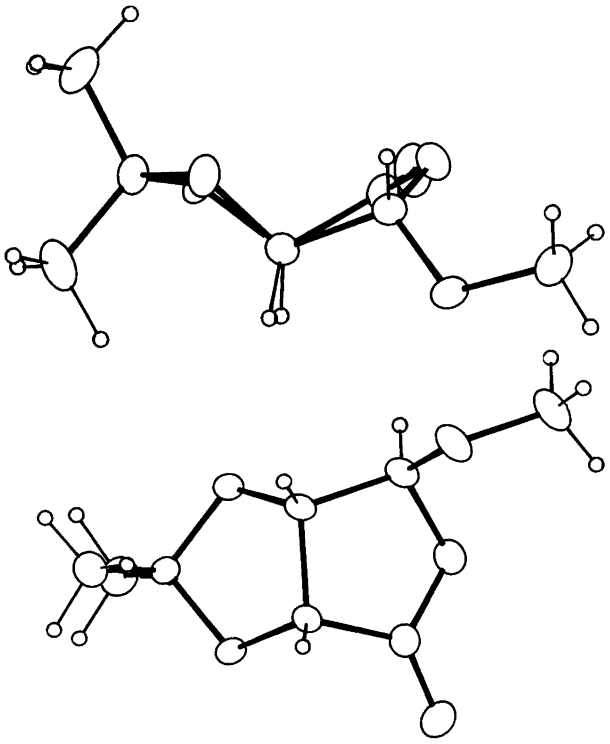


Fig. 2. Stereo drawings of methyl 2,3-*O*-isopropylidene-β-D-erythrosidurono-1,4-lactone (**3**).

At this point it was of interest to examine whether **1e** and **3** could result from further reactions of the aldehyde **1b**. Thus, when purified **1b** was treated with PDC (entry 8) and the reaction mixture worked-up after 12 h, formation of by-products was already evident from TLC. Subsequent gas chromatography revealed that **1b** had already been almost completely converted into the lactone **3** and the dimer **1e**. Moreover, blank experiments, either with (entry 9) or without (entry 10) molecular-sieve beads, failed to show any formation of by-products. These experiments led us to add to the already proposed mechanistic scheme the formation of **3** and **1e** from **1b**. Thus, **3** can conceivably be formed by the addition of water to **1b** followed by PDC to give **9**, which undergoes further degradation, with the expulsion of HCO_2H, to the cation **5**. The latter can be elaborated to **3** as has already been indicated. On the other hand, **1e** can be formed by a Tischtschenko reaction[19] of **1b** through the intermediacy of **1g**, which is either stabilised by or catalytically formed in the presence of chromium species.

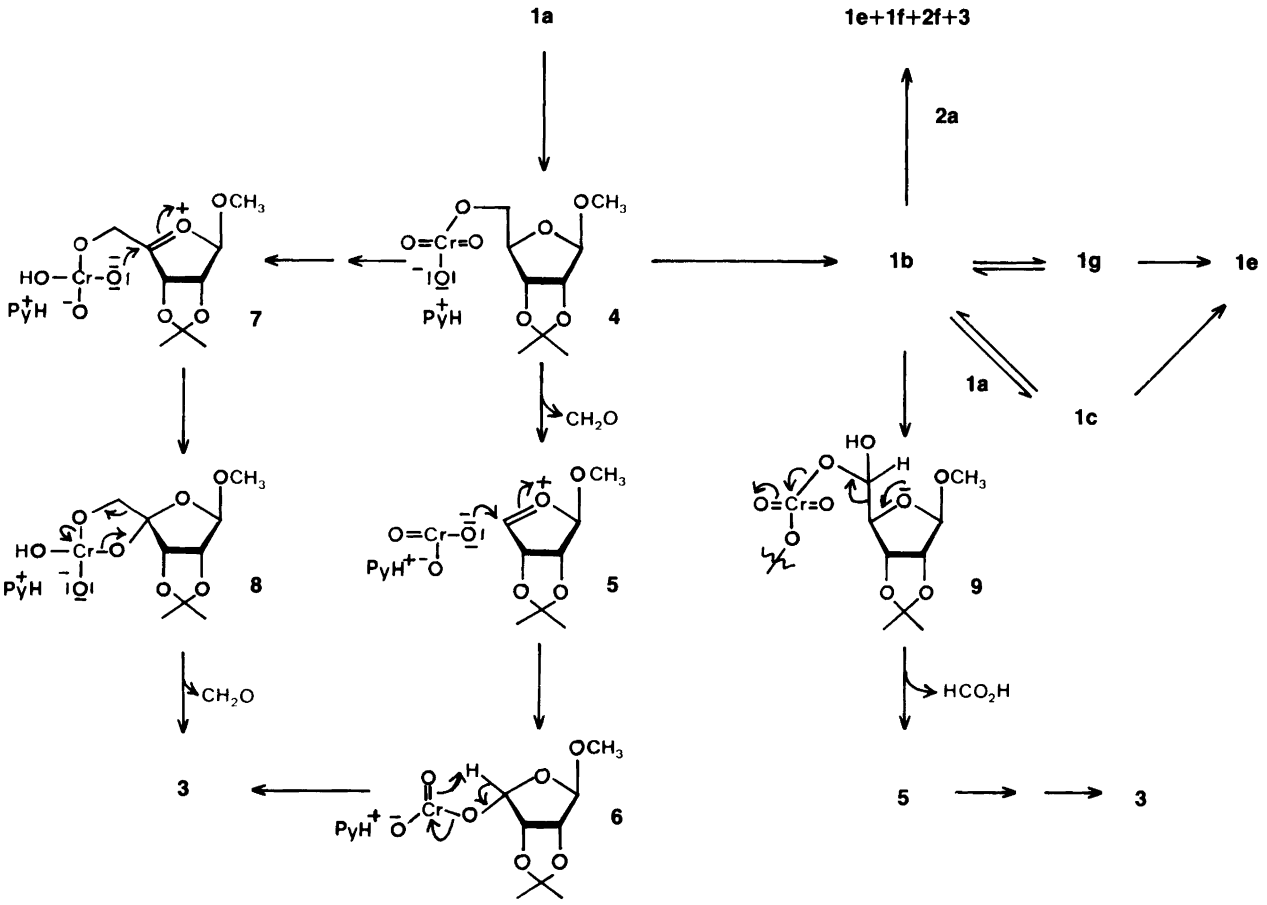
It must be noted that oxidation of the aldehyde **1b** in the presence of tetrahydrofurfuryl alcohol (**2a**), a simpler analogue of **1a**, produced a mixture of four non-polar components (entry 7), after an aqueous $NaHSO_3$ work-up. Based solely on mass spectrometric evidence (Table 3) we as-

Table 2. NMR data for the by-products of the PDC oxidation of **1a** and **2a**. The 400 MHz ^{1}H NMR spectra of **1a** and **1b** are given for comparison.[a]

^{1}H NMR (δ)	^{13}C NMR (δ)
Compound **3**	
1.364 (3 H, q,[c] *J* 0.4 Hz, C-Me)	25.736, 26.681 (C-7, C-8)
1.444 (3 H, q,[c] *J* 0.4 Hz, C-Me)	57.098 (C-5)
3.513 (3 H, s, H-5)	74.494 (C-2)
4.533 (1 H, d, *J* 5.5 Hz, H-2)	79.329 (C-3)
4.783 (1 H, d, *J* 5.5 Hz, H-3)	105.124 (C-1)
5.320 (1 H, s, H-1)	114.485 (C-6)
	173.437 (C-4)
Compound **1e**	
1.294, 1.310 (6 H, two q,[b] *J* 0.4 Hz, C-Me)	24.986, 25.107, 26.430, 26.444 (C-8, C-8′, C-9, C-9′)
1.457, 1.464 (6 H, two q,[b] *J* 0.4 Hz, C-Me)	55.022, 55.556 (C-6, C-6′)
3.295, 3.381 (6 H, two s, O-Me)	81.781, 82.202 (C-2, C-2′)
4.180 (2 H, d, *J* 6.9 Hz, H-5′)	83.738, 84.106, 84.415 (C-3, C-3′, C-4′)
4.372 (1 H, td, *J* 6.9 and 0.6 Hz, H-4′)	85.231 (C-4)
4.524 (1 H, dd, *J* 5.9 and 0.6 Hz, H-3)	109.539, 109.562 (C-1, C-1′)
4.577 (1 H, d, *J* 5.9 Hz, H-2′)	112.639, 112.817 (C-7, C-7′)
4.620 (1 H, t, *J* 0.7 Hz, H-2)	169.750 (C-5)
4.633 (1 H, dd, *J* 5.9 and 0.7 Hz, H-3′)	
4.952 (1 H, s, H-1′)	
5.013 (1 H, s, H-1)	
5.192 (1 H, dd, *J* 5.9 and 0.7 Hz, H-4)	
Compound **2f**	
1.838–2.088 (6 H, m, H-4, H-3′, H-4′)	25.224, 25.238, 25.659, 25.678 (C-3′, C-4′)
2.216–2.318 (2 H, m, H-3)	27.764, 28.002 (C-4)
3.738–4.040 (4 H, m, H-5, H-5′)	30.252, 30.268 (C-3)
4.040–4.151 (2 H, m, H-6′)	66.623, 66.636 (C-5′)
4.151–4.226 (1 H, m, H-2′)	68.403, 68.415 (C-5)
4.448–4.515 (1 H, m, H-2)	68.483, 69.326 (C-6′)
	76.376, 76.426, 76.622, 76.660 (C-2, C-2′)
	173.338 (C-6)[c]

[a]400 MHz ^{1}H NMR spectrum of **1a**: δ 1.317 (3 H, s, C-Me), 1.480 (3 H, s, C-Me), 3.338 (1 H, br, OH), 3.417 (3 H, s, O-Me), 3.617 and 3.660 (2 H, AB system [*J* −10.3 Hz] of d [*J* 3.3 Hz], H-5), 4.394 (1 H, t, *J* 3.3 Hz, H-4), 4.583 (1 H, d, *J* 5.9 Hz, H-3), 4.810 (1 H, d, *J* 5.9 Hz, H-2), 4.967 (1 H, s, H-1). 400 MHz ^{1}H NMR spectrum of **1b**: δ 1.321 (3 H, q,[b] *J* 0.6 Hz, C-Me), 1.484 (3 H, q,[b] *J* 0.6 Hz, C-Me), 3.444 (3 H, s, O-Me), 4.468 (1 H, t, *J* 0.7 Hz, H-2), 4.491 (1 H, dd, *J* 5.7 and 0.7 Hz, H-3), 5.043 (1 H, unresolved dd, *J* 5.7 Hz, H-4), 5.080 (1 H, s, H-1), 9.576 (1 H, s, CO-H). [b]Unresolved. [c]This low intensity signal indicates that the chemical shifts (C-6) of the stereoisomers resulting from use of the achiral alcohol **1a** are accidentally equal.

signed the structure **1f** to the major product. It was not possible to separate it from the other dimers, **1e** and **2f**, either by column chromatography or by fractional distillation. The ester **1f** is presumably formed by PDC oxidation of the hemiacetal **1d**, which in turn is produced by the interception of the aldehyde **1b** by the alcohol **2a**. This finding provides evidence in favour of formation of **1e** through the intermediacy of a hemiacetal. Formation of by-products such as **1e** and **3** has, to the best of our knowledge, not been reported so far for PDC oxidations of alcohols. This, together with the known slow oxidation of carbohydrate alcohols suggests that these findings might be attributed to the presence of oxygen atoms next to the hydroxy group to be oxidised, and in our case in particular to the presence of the ring oxygen atom. Complexation of this oxygen to the chromium atom of the intermediate **4** retards collapse to the aldehyde to an extent that allows other reactions to compete successfully. In order to test this hypothesis we subjected the simplest model, the alcohol **2a**, to PDC oxidation (entry 6) and analysed the products by GLC–MS. This revealed that the main products of the reaction were tetrahydrofurfural (**2b**), γ-butyrolactone (**10**), and the dimeric ester **2f**. Additional evidence in favour of these assignments accrued from their NMR spectra after fractional distillation of the crude reaction mixture. The dramatic acceleration of such oxidations when activated molecular-sieve powder and a proton donor such as AcOH are present, may thus be attributed, not merely to the role of molecular sieves as a water scavenger, but also to the suppression of the above-mentioned complexation. This in turn allows for the correct orientation, inside the molecular-sieve cavity, of the chromium–oxygen double bond with respect to the hydrogen to be transferred.[13]



Scheme 1. Reaction scheme for the pyridinium dichromate oxidation of methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (**1a**).

Table 3. Mass spectral data of products[a] from PDC oxidations.

Compound	*m/z* (% rel. int., identity)
3	*M* absent, 173 (33, *M*–Me), 129 (43, 173–CO_2), 100 (64, *M*–CH_2O–Me_2CO), 85 (100, 129–MeOCH), 71 (43, $C_3H_3O_2$).
1e	*M* absent, 389 (63, *M*–Me), 315 (28, *M*–MeO–Me_2CO), 271 (34, 389–$MeCO_2H$–Me_2CO), 186 (58, *M*–$MeOC_7H_{10}O_3CO_2H$) 173 (100, *M*–$MeOC_7H_{10}O_3CO_2CH_2$), 129 (58, 271–$MeOC_4H_3O_2CO$)
2f	200 (0.02, *M*), 172 (0.04, *M*–CO), 157 (0.04, *M*–CH_2CHO), 144 (23, *M*–CO–C_2H_4), 129 (11, *M*–C_4H_7O), 84 (45, *M*–$C_4H_7OCO_2H$), 71 (100, C_4H_7O).
1f	302 (0.003, *M*), 287 (100, *M*–Me), 272 (23, *M*–CH_2O), 213 (91, *M*–MeO–Me_2CO), 173 (70, *M*–$CO_2CH_2C_4H_7O$), 143 (42, 173–CH_2O), 115 (50, 173–Me_2CO), 85 (83, $MeC_3H_2O_2$), 71 (84, C_4H_7O).

[a]The lactone **3** and the esters **1e**, **2f** and **1f** had characteristic IR absorptions for their carbonyl functions at 1775 and 1730 cm^{-1}, respectively.

Experimental

IR spectra were recorded for 5% $CHCl_3$ solutions on a Perkin–Elmer model 399B spectrometer. ^1H and ^{13}C NMR spectra were obtained at 400.13 and 100.63 MHz on a Bruker AM400 spectrometer, using $CDCl_3$ as the solvent and tetramethylsilane (TMS) as an internal standard. Homonuclear proton decoupling was used when neccessary for chemical shift assignments. The broad-band decoupled ^{13}C spectra were obtained using standard one-pulse and spin-echo experiments. The latter technique was used in order to distinguish methyl and methine carbons from methylene and quaternary carbons.[20] Chemical shifts are reported in δ units, parts per million (ppm) downfield from TMS. GLC analyses were performed on a Hewlett-Packard HP 5710A gas chromatograph fitted with a 6′×1/8″ steel column having as stationary phase 10% SP-2330 on Supelcoport. Carrier gas flow-rate: 20 ml min^{-1} He; injection port temperature: 300 °C; program: 130–260 °C at 5 min^{-1}. Mass spectra were recorded at 70 eV on a JEOL JMS D-100 instrument. Optical rotations were determined using a Carl–Zeiss precision polarimeter.

Flash chromatography was performed on Merck Silica gel 60 (230–400 mesh). TLC was carried out on Polygram

(Macherey–Nagel) precoated plastic sheets (0.20 mm, Silica gel N-HR/UV_{254}) and the spots were visualised by spraying the chromatogram with a solution of naphthoresorcinol (200 mg), 95 % ethanol (100 ml), 85 % phosphoric acid (10 ml) and/or sulphuric acid (5 % in 95 % ethanol) and then heating it at 150 °C. TLC solvents were as follows: (A) ethyl acetate/petroleum ether b.p. 40–60 °C (PE): 2/3 (B) acetone/PE: 2/8, (C) ethyl acetate/diethyl ether: 3/1, and (D) ethyl acetate/PE: 1/3.

Dichloromethane was distilled from CaH_2 and stored over 4 Å molecular sieve beads. Activated 4 Å molecular-sieve powder was prepared by grinding molecular-sieve beads (Merck, ca. 2 mm), heating the powder at 150 °C for 24 h and then over a Bunsen burner (ca. 340 °C) for 2 h. Acetic acid (100 %) was used as purchased (Merck). All experiments were carried out under a nitrogen atmosphere in dried glassware (overnight at 150 °C). Tetrahydrofurfuryl alcohol (**2a**) was distilled from 4 Å molecular-sieve beads under reduced pressure, whereas the alcohol **1a** was prepared according to a literature procedure.[21] All reactions were routinely followed by TLC and when found to be complete were immediately diluted with a threefold volume of diethyl ether, filtered and the resulting coloured solutions were concentrated under reduced pressure at room temperature. The filtrates were then passed through a short plug of silica gel 60 and concentrated and the residue was analysed by GLC–MS.

General procedures for PDC oxidation of alcohols **1a** *and* **2a**, *and for isolation of the products (see also Table 1).* PDC was added to a suspension of molecular sieves in a 0.3 M solution of alcohol in CH_2Cl_2 (entry 2) and the resulting mixture was stirred vigorously for 20 h at room temperature (reactions were best followed by TLC using system A for **1a** and system C for **2a**). Work-up as described above and flash column chromatography (50 g silica gel 60, solvent system D) gave in the case of **1a** (entry 2) two fractions. The less polar fraction contained a mixture of **1e** and **3** (260 mg, R_f of both in system D = 0.58) and the other the pure aldehyde **1b** (40 mg, R_f in system D = 0.41). The corresponding carboxylic acid (R_f = 0.04) was not eluted. The mixture of **1e** and **3** was fractionated at 0.6 mmHg to give **3** (70 mg, b.p. 60–65 °C) and the dimer **1e** (190 mg, b.p. 190–195 °C). Lactone **3** crystallised on refrigeration, and was recrystallised from diethyl ether/PE, m.p. 79–80 °C, $[\alpha]_D^{25}$ −53.3° (*c* 1, $CHCl_3$), R_f in system B = 0.27. Anal. $C_8H_{12}O_5$: C, H. Dimer **1e** (thick oil) had $[\alpha]_D^{25}$ −64.2° (*c* 1.93, $CHCl_3$), R_f in system B = 0.32. Anal. $C_{18}H_{28}O_{10}$: C, H. Since, in the case of **2a** (entry 6), the products of the reaction could not be separated by chromatography, giving a diffuse spot of R_f 0.38 in system C, oxidation was repeated on a 50 mmol scale and the crude reaction mixture was distilled to yield four fractions which were then examined by GLC–MS and ^1H and ^{13}C NMR spectroscopy. A forerun (14 mmHg, room temperature) was shown to be pyridine. A second fraction (0.2 g, 14 mmHg, 60–65 °C) was shown to be mainly tetrahydrofurfural (**2b**). The third fraction (0.3 g, 4 mmHg, 68–80 °C) contained mainly γ-butyrolactone (**10**). The dimer **2f** made up the fourth fraction (1.25 g, 4 mmHg, 140–144 °C). Anal. $C_{10}H_{16}O_4$: C, H.

*Methyl 2,3-O-Isopropylidene-β-D-*ribo*-1,4-pentodialdofuranoside* (**1b**). To a solution of **1a** in CH_2Cl_2 were added sequentially molecular sieves and acetic acid (entry 4) and the resulting mixture was stirred at room temperature for 5 min prior to the addition of PDC. The resulting suspension was vigorously stirred for 20 min and processed as described above (entry 2) to give pure **1b** (0.4 g, 67 %) which crystallised in the freezer with time. Aldehyde **1b** had physical properties identical with those previously reported.[9]

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