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A preparation of protected 2-deoxy-2-hydroxymethyl-D-mannose and -D-glucose derivatives not involving organometallic reagents[1]

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Abstract

The branched chain protected sugar, 2-*C*-hydroxymethyl-2,3;5,6-di-*O*-isopropylidene-D-manno-furanose was specifically benzylated at the primary hydroxyl group position by the stannylene procedure (93%). Oxidation with pyridinium chlorochromate gave in 71% yield 2-*C*-benzyloxy-methyl-2,3;5,6-di-*O*-isopropylidene-D-mannonolactone which was reduced with 3 equiv of samarium diiodide in oxolane to a 56:44 mixture of the 2-deoxy derivatives, 2-*C*-benzyloxymethyl-2-deoxy-5,6-*O*-isopropylidene-D-mannono- (**5**) and -D-glucono-lactones in 83% combined yield. Reduction of lactone **5** with DIBAH in dichloromethane gave the protected branched chain sugar, 2-*C*-benzyloxy-2-deoxy-5,6-*O*-isopropylidene-D-mannose in 63% yield. In the reduction of 2-*C*-hydroxymethyl-2,3;5,6-di-*O*-isopropylidene-D-mannonolactone and 2-*C*-hydroxymethyl-D-mannonolactone in water solution, only lactones with the D-*manno* configuration, 2-deoxy-2-*C*-hydroxymethyl-5,6-*O*-isopropylidene-D-mannonolactone and 2-deoxy-2-*C*-hydroxymethyl-D-mannono-(1,5)-lactone, could be isolated or characterized among the products of the reaction.

Keywords: Branched-chain sugars; Stannylenes; Samarium diiodide

1. Introduction

We have recently reported a synthesis of the branched-chain hexose, 2-deoxy-2-hydroxymethyl-D-mannose [1]. Interest in this sugar stemmed from the fact that enzymatic aldol condensation with pyruvate yielded a precursor of sequence 12–20 of Amphothericin B. The key step for the branching was the copper-catalysed conjugate addition of vinylmagnesium bromide to an unsaturated ester, a product of a Wittig–Horner condensation. We now report a method for the preparation of derivatives of the same branched-chain hexose which does not involve organometallic reagents.

Most textbooks report the Fischer–Kiliani condensation of cyanide with ketoses as a route to

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[1] Dedicated to Professor Roger Jeanloz on the occasion of his 80th birthday.

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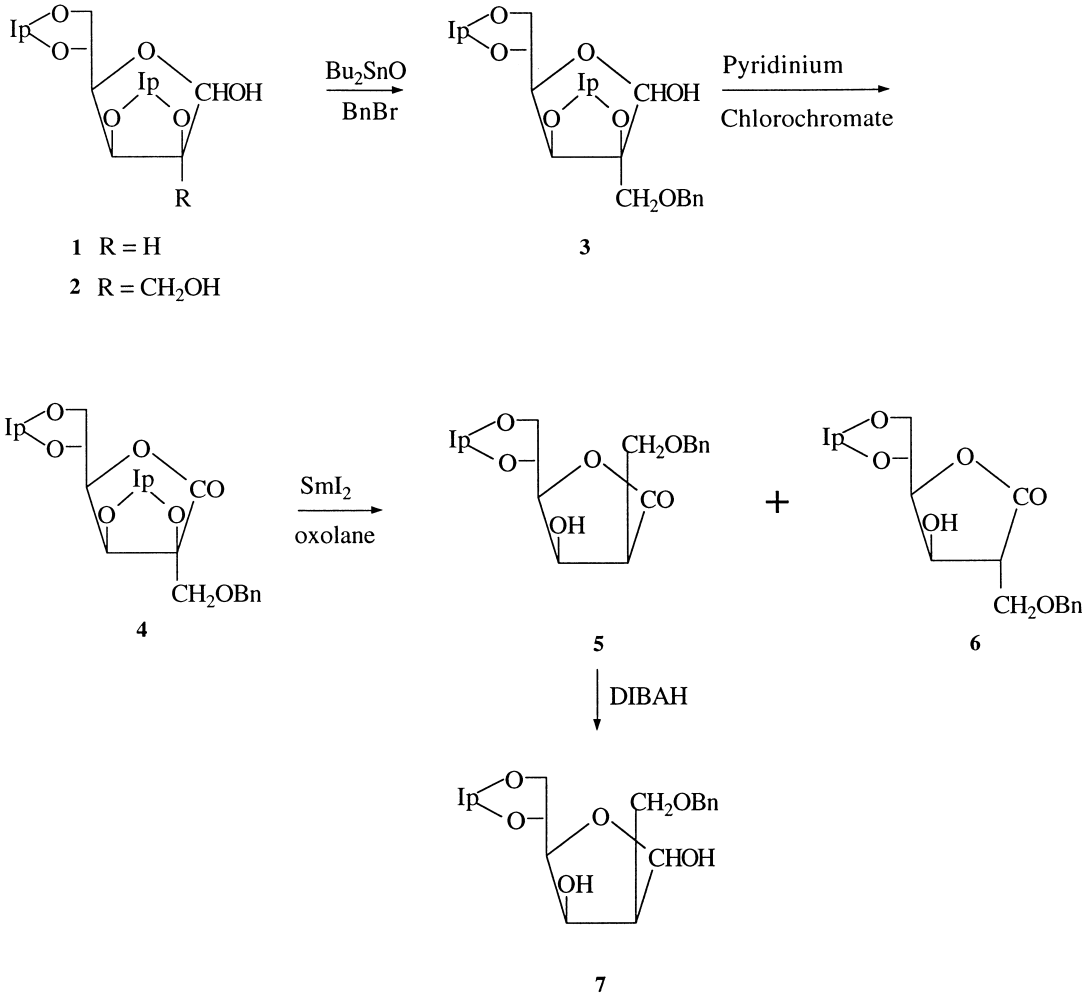
branched-chain sugars. We are aware of only two applications of this method which are closely related. Wood and Neish [2] prepared the cyanohydrin of D-fructose following the method of Zervas and Sessler [3] with pure liquid hydrogen cyanide in great excess. After acidic hydrolysis, and some purification steps, they isolated a crystalline lactone from which 2-*C*-hydroxymethyl-D-glucose was prepared on the mole scale by sodium amalgam reduction. Gorin and Perlin [4] achieved cyanohydration of 3-*O*-benzyl-D-fructose with sodium cyanide at pH 9.3. Partial crystallisation of the lactone occurred after several months to give 3-*O*-benzyl-2-*C*-hydroxymethyl-D-mannono-γ-lactone in 24% yield from the mixture.

2. Discussion

In view of all these practical difficulties, we considered that the most convenient starting material was 2-*C*-hydroxymethyl-2,3;5,6-di-*O*-isopropylidene-D-mannose (**2**) (Scheme 1). Compound **2** is readily available in 86% yield by aldol condensation of 2,3;5,6-di-*O*-isopropylidene-D-mannose **1** with formaldehyde [5]. Benzylation of **2** by the stannylene procedure gave the benzyl ether **3** (93% yield), rather than the benzyl mannoside. This is in agreement with the general observation that the primary position is preferred in similar reactions. Although the interpretation of the ^{1}H NMR spectrum was not straightforward, TLC (1:1 hexane–ethyl acetate) gave no evidence for the presence of a presumably more polar primary alcohol. Furthermore, lactone **4** was obtained in 71% yield by oxidation of **3** with pyridinium chlorochromate [6].

The next step was the replacement by hydrogen of the tertiary oxygen atom. It has been reported that the free radical deoxygenation of tertiary alcohols via dithiocarbonates involves large amounts of initiators [7]. Paracyanobenzoates of tertiary alcohols are reduced by tributylstannane



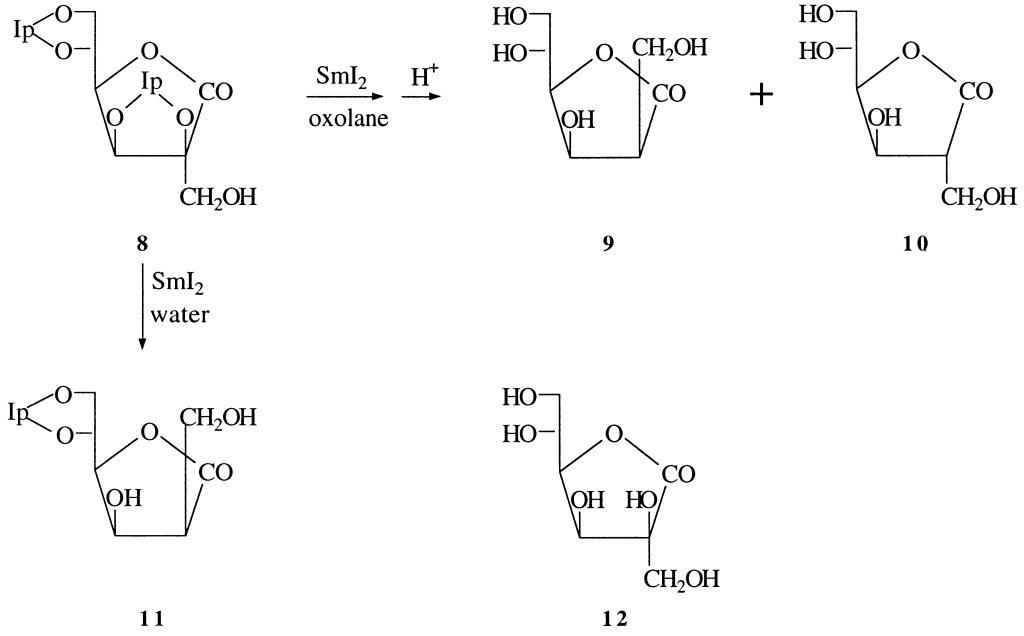
Scheme 1.

when geminal to a carbonyl [8] but the utilization of this method in the present case would have involved several additionnal steps. At this stage, our attention was turned to a paper describing the α-deoxygenation of aldonolactones [9] by samarium diiodide [10]. It was then of interest to test this approach for the deoxygenation of a tertiary alcohol. A solution of lactone **4** in oxolane–ethylene glycol was treated at room temperature by SmI_2 in the same solvent (3 equiv) to give a 56:44 mixture of the D-*manno* (**5**) and D-*gluco* (**6**) isomers. The reduction was instantaneous and the combined yield of reduced lactones (83%) was comparable to that reported in the reduction of secondary hydroxyl groups at the same position. The D-*manno* configuration was ascribed to the lactone with the larger $J_{2,3}$ coupling (5 Hz). The corresponding value for its isomer was 1.5 Hz. The chemical shifts of H-2 protons in deuterium oxide were 2.95 and 2.77 ppm, respectively, for lactones **5** and **6**.

Efforts were made towards minimal protection. Reduction, under the same conditions of lactone **8** (Scheme 2), readily prepared according to ref. [8], gave also a mixture of products with the D-*manno* and D-*gluco* configurations in very good combined yield (91%), but in this case the proportion of the D-*manno* derivative in the mixture was increased to 75%. Partial hydrolysis of the acetal function occurred during the work-up, thus for identification purpose the preparations were converted to the free lactones **9** and **10** by treatment with an acidic resin. The relevant NMR data for H-2 were δ 3.15 ppm ($J_{2,3}$ 5 Hz) for **9** and δ 2.83 ppm ($J_{2,3}$ 2 Hz) for **10**.

A more recent paper [11] reported on the reduction of sugar lactones in oxolane–water mixtures. We examined the behaviour in this solvent system of the same lactone **8** and also that of the free lactone **12** (Scheme 2). Lactone **12** was prepared by acidic hydrolysis of **8**. The product appeared homogeneous by ^1H NMR. The constitution of a γ-lactone and its configuration were indicated by the small value of the coupling constant, 3.5 Hz, between protons H-3 and H-4. These would exhibit a *trans* diaxial relationship in a δ-lactone. The carbonyl infrared frequency, 1772.7 cm^{-1} is of poor diagnostic value.

Reduction of lactone **8** occurred very rapidly in water–oxolane mixture as evidenced by the disappearance of the blue colour of SmI_2. However, the ethereal extract contained only the D-*manno* product **11**, isolated in 51% yield. In the experiments with lactone **12**, ether extraction of the reduced products is obviously not suitable. After the removal of cations over an ion-exchange column and partial chromatographic purification, a crude fraction was obtained in 81% yield. Its ^1H NMR spectrum characterized it as a mixture of the D-mannonolactone **9** (55%) and another, unidentified compound. It is remarkable that, in these two reductions in the presence of water, we have not observed, in the products, the NMR signal that



Scheme 2.

could possibly correspond to H-2 of the D-*gluco* isomer **10**.

For the conversion of the lactones to the hemiacetals, we first tried the classical method, sodium amalgam in water. In this way, 2-*C*-hydroxy-D-gluconolactone has previously been reduced to 2-*C*-hydroxymethyl-D-glucose on the mole scale in 65% yield [2]. The conditions of the reduction of D-gluconolactone to D-glucose have been carefully worked out [12], and these experiments were repeated without any problem. However, the same technique failed when applied to lactone **9** as checked by the triphenyltetrazolium test [13]. We also failed to obtain any reducing sugar with sodium borohydride in acidified water [14]. Finally, the protected lactone **5** was reduced in dichloromethane solution by diisobutylaluminium hydride [15] in hexane, to give the protected sugar, 2-*C*-benzyloxymethyl-2-deoxy-5,6-*O*-isopropylidene-D-mannose (**7**) (Scheme 1) in 63% yield.

3. Experimental

General methods.—Chromatographic separations have been performed on silica gel columns. In the descriptions of the NMR spectra, H_a and H_b refer to the proton of the branched group.

2-C-*Benzyloxymethyl-2,3;5,6-di*-O-*isopropylidene*-D-*mannose* (**3**).—A soln of the protected sugar **2** (3.1 g; 10.7 mmol) and Bu_2SnO (2.93 g; 1.1 equiv) in toluene (100 mL) was refluxed for 16 h (Dean-Stark), and then concentrated to about 50 mL and cooled to room temperature. Tetrabutylammonium bromide (1.7 g; 0.5 equiv) and benzyl bromide (1.53 mL; 1.2 equiv) were added and the soln was heated at 80 °C for 1 h. Evaporation of volatiles gave a residue, from which the benzyl ether **3** was separated by chromatography (3:1 hexane–EtOAc), as a syrup (3.54 g; 93%), $[\alpha]_D^{20}$ +5.5° (*c* 1.1, CH_2Cl_2). Anal. Calcd for $C_{20}H_{28}O_7$: C, 63.13; H, 7.42, O, 29.45. Found: C, 62.83; H, 7.31; O, 29.37.

2-C-*Benzyloxymethyl-2,3;5,6-di*-O-*isopropylidene*-D-*mannonolactone* (**4**).—Pyridinium chlorochromate (2.04 g; 1.5 equiv) was added to a suspension of **3** (2.4 g; 6.3 mmol) and powdered 4 Å molecular sieves in CH_2Cl_2 (40 mL) under a N_2 atmosphere. The suspension was stirred for 2 h at room temperature, dry ether was added (200 mL) and stirring was continued until the black precipitate became granular. The precipitate was removed by filtration and washed with ether. Chromatography of the residue (85:5 and then 4:1 hexane–EtOAc) gave lactone **4** (1.69 g; 71%), mp 87–88 °C (ether–hexane); $[\alpha]_D^{20}$ +39.4° (*c* 1.27, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 7.43–7.2 (m, 5 H, Ph), 4.76 (d, 1 H, $J_{3,4}$ 3 Hz, H-3), 4.61 (d, 1 H, *J* 12 Hz, PhC*H*H), 4.52 (d, 1 H, PhCH*H*), 4.47–4.34 (m, 2 H, H-4, H-5), 4.15 (dd, 1 H, $J_{5,6}$ 5, $J_{6,6'}$ 10 Hz, H-6), 4.07 (dd, 1 H, $J_{5,6'}$ 4 Hz, H-6′), 3.94 (d, 1 H, J_{ab} 9 Hz, H_b), 3.72 (d, 1 H, H_a), 1.47 (s, 6 H, 2 Me), 1.38 (s, 6 H, 2 Me). Anal. Calcd for $C_{20}H_{26}0_7$: C, 63.46; H, 6.93; O, 29.61. Found: C, 63.37; H, 6.99; O, 29.82.

2-C-*Benzyloxymethyl-2-deoxy-5,6*-O-*isopropylidene*-D-*mannono*- (**5**) *and* -D-*glucono*- (**6**) *lactones*.—To a soln of lactone **4** (151 mg; 0.4 mol.) and ethylene glycol (297 mg; 12 equiv) in oxolane (4 mL), under an argon atmosphere, was added dropwise a soln of SmI_2 in oxolane (0.1 M; 18 mL). Filtration of the mixture over a layer of silica gel, removal of volatiles from the filtered soln and chromatography of the residue (1:1 light petroleum–EtOAc) separated first the mannonolactone **5** (58 mg; 56%), mp 98–99 °C (hexane–EtOAc); $[\alpha]_D^{20}$ +31.2° (*c* 1.025, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 7.4–7.2 (m, 5 H, Ph), 4.71 (ddd, 1 H, $J_{2,3}$ 5, $J_{3,4}$ 3, $J_{3,OH}$ 3 Hz, H-3), 4.57 (s, 2 H, $PhCH_2$), 4.45 (ddd, 1 H, $J_{4,5}$ 8, $J_{5,6}$ 6, $J_{5,6'}$ 4 Hz, H-5), 4.20 (dd, 1 H, H-4), 4.16 (dd, 1 H, $J_{6,6'}$ 9 Hz, H-6), 4.04 (dd, 1 H, H-6′), 3.95 (d, 1 H, $J_{2,b}$ 7 Hz, H_b), 3.94 (d,1 H, J_{2a} 5 Hz, H_a), 3.22 (d, 1 H, OH), 2.95 (ddd, 1 H, H-2), 1.45 (s, 3 H, Me), 1.37 (s, 3 H, Me). Anal. Calcd for $C_{17}H_{22}O_6$: C, 63.33; H, 6.88; O, 29.79. Found: C, 63.09; H, 6.92; O, 29.62.

Further elution gave the gluconolactone **6** (45 mg; 44%), mp 75–76 °C (2-isopropoxypropane); $[\alpha]_D^{20}$ +43.7° (*c* 0.48, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 7.45–7.15 (m, 5 H, Ph), 4.60 (m, 1 H, H-3), 4.56 (d, 1 H, *J* 12 Hz, PhCH*H*), 4.47 (d, 1 H, PhC*H*H), 4.37 (m, 2 H, H-4, H-5), 4.19 (m, 1 H, H-6′), 4.04 (dd, 1 H, $J_{6,6'}$ 9, $J_{5,6}$ 4 Hz, H-6), 3.84 (dd, 1 H, $J_{2,a}$ 3, $J_{a,b}$ 9 Hz, H_a), 3.77 (dd, 1 H, $J_{2,b}$ 4 Hz, H_b), 2.77 (ddd, 1 H, $J_{2,3}$ 1.5 Hz, H-2), 2.75 (s,1 H, OH), 1.46 (s, 3 H, Me), 1.37 (s, 3 H, Me). Anal. Calcd for $C_{17}H_{22}0_6$: C, 63.33; H, 6.88; O, 29.79. Found: C, 62.99; H, 6.91; O, 29.96.

2-C-*Benzyloxymethyl-2-deoxy-5,6*-O-*isopropylidene*-D-*mannose* (**7**).—A soln of DIBAH in hexane (1 M, 0.28 mL) was added to a soln of **5** (82 mg; 0.25 mmol) in CH_2Cl_2 (2.5 mL), kept at −78 °C. The reaction was stopped after 30 min by the addition of a saturated soln of NH_4Cl, the mixture was diluted with CH_2Cl_2 and the organic layer

washed with water, dried and evaporated. Chromatography of the residue (3:1 light petroleum–EtOAc) gave **7** as a syrup (51 mg; 63%); $[\alpha]_D^{20}$ −11.3° (*c* 0.92 CH_2Cl_2). Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.93. H, 7.46; O, 29.61. Found: C, 62.89, H, 7.65; O, 29.71.

*2-Deoxy-2-hydroxymethyl-*D*-glucono-* (**10**) *and* -D-*mannono* (**9**) *-(1,4)-lactones*.—A soln of SmI_2 in oxolane (0.1 M; 39 mL) was added dropwise to a soln of lactone **8** (460 mg; 1.6 mmol) and ethylene glycol (1.07 mL; 12.2 mmol) in oxolane (10 mL) under an argon atmosphere. The mixture was filtered through a layer of silica gel and the solvent was removed by evaporation from the filtered soln. Chromatography of the residue (1:1 and 1:2 light petroleum–EtOAc) gave in succession the protected D-*gluco* derivative (46 mg), a mixed fraction (74 mg) and the protected D-*manno* derivative (217 mg). Deprotection of each of these fractions was achieved by brief treatment in water soln with Dowex-50 (H^+) resin.

Lactone **10** was obtained as a syrup, $[\alpha]_D^{20}$ +67° (*c* 0.6, H_2O); ^1H NMR (D_2O): δ 4.63 (dd, 1 H, $J_{2,3}$ 2, $J_{3,4}$ 4 Hz, H-3), 4.52 (dd, 1 H, $J_{4,5}$ 7 Hz, H-4), 4.03 (ddd, 1 H, $J_{5,6}$ 2.5, $J_{5,6'}$ 4.5 Hz, H-5), 3.90 (dd, 2 H, *J* 4 Hz, H_a, H_b), 3.80 (dd, 1H, $J_{6,6'}$ 10 Hz, H-6), 3.68 (dd, 1H, H-6′), 2.83 (ddd, 1H, H-2). Anal. Calcd for $C_7H_{12}O_6$, 0.5 H_2O: C, 41.79; H, 6.46. Found: C, 41.51; H, 6.28.

Lactone **9** was obtained as a syrup, $[\alpha]_D^{20}$ +70° (*c* 1 in H_2O); ^1H NMR (D_2O): δ 4.72 (dd, 1 H, $J_{2,3}$ 5, $J_{3,4}$ 3 Hz, H-3), 4.38 (dd, 1 H, $J_{4,5}$ 9 Hz, H-4) 3.96 (ddd, 1 H, $J_{5,6}$ 3, $J_{5,6'}$ 5.5 Hz, H-5), 3.895 (d, 1 H, $J_{2,a}$ 5.5 Hz, H_a), 3.890 (d, 1 H, $J_{2,b}$ 7.5 Hz, H_b), 3.80 (dd, 1 H, $J_{6,6'}$ 12 Hz, H-6), 3.66 (dd, 1 H, H-6′), 3.15 (ddd, 1 H, H-2). Anal. Calcd for $C_7H_{12}O_6$: C, 43.75; H, 6.25; O, 50.00. Found: C, 43.64; H, 6.11; O, 49.66.

*2-Deoxy-2-*C*-hydroxymethyl-5,6-*O*-isopropylidene-*D*-mannonolactone* (**11**).—A soln of SmI_2 in oxolane (0.1 M; 45 mL) was added dropwise to a soln of **8** (432 mg; 1.5 mmol) in degassed water (10 mL) kept at 0 °C under argon. After the addition of a satd soln of NH_4Cl (1 mL), filtration and evaporation of the organic solvent, the aqueous phase was extracted with ether. Chromatography of the extract (1:2 hexane–EtOAc) separated lactone **11** (178 mg; 51%), mp 87 °C (2-isopropoxypropane); $[\alpha]_D^{20}$ +85,2° (*c* 1.02, H_2O); ^1H NMR (D_2O): δ 4.69 (dd, 1 H, $J_{2,3}$ 5, $J_{3,4}$ 3 Hz, H-3), 4.56 (dd, 1 H, $J_{4,5}$ 6 Hz, H-4), 4.49 (ddd,1 H, $J_{5,6}$ 6, $J_{5,6'}$ 5 Hz, H-5), 4.18 (dd, 1 H, $J_{6,6'}$ 9 Hz H-6), 4.01 (dd, 1 H, H-6′), 3.92 (dd, 1 H, $J_{2,a}$ 5.5, $J_{a,b}$ 12 Hz, H_a), 3.84 (dd, 1 H, $J_{2,b}$ 7.5 Hz, H_b), 3.14 (ddd, 1 H, H-2), 1.45 (s, 3 H, Me), 1.37 (s, 3 H, Me). Anal. Calcd for $C_{10}H_{16}O_6$: C, 51.70, H, 6.95, O, 41.35. Found: C, 51.55; H, 6.95; O, 41.62.

*2-*C*-Hydroxymethyl-*D*-mannonolactone* (**12**).—A soln of lactone **8** (1.49 g; 5.13 mmol) in water (20 mL) was heated at 70 °C for 5 h in the presence of Dowex-50 (H^+) resin, (wet, 2 g). After filtration, the soln was evaporated to dryness. Chromatography of the residue (9:1 1-propanol–water) allowed separation of lactone **12** as a syrup (912 mg; 92%); IR (KBr): ν_{max} 1772.7 cm^{-1} (CO), 3422.8 cm^{-1} (OH); ^1H NMR (D_2O): δ 4.56 (dd,1 H, $J_{3,4}$ 3.5 Hz, $J_{4,5}$ 9 Hz, H-4), 4.40 (d, 1 H, H-3), 4.02 (ddd, 1 H, $J_{5,6}$ 3.5, $J_{5,6'}$ 5 Hz, H-5), 3.82 (dd, 1 H, $J_{6,6'}$ 12 Hz, H-6), 3.77 (s, 2 H, H_aH_b), 3.68 (dd, 1 H, H-6′).

Reduction of lactone **12** *by* SmI_2 *in water*.—A soln of SmI_2 in oxolane (0.1 M; 52 mL) was added dropwise to a soln of lactone **12** (360 mg; 1.73 mmol) in degassed water (17 mL) kept at 0 °C under argon. After removal of oxolane by evaporation, the soln was passed through a 1.5×15 cm column of Dowex-50 (H^+) resin. Acidic fractions were collected and evaporated to dryness, then kept for 16 h at room temperature to allow lactonisation. Chromatography (95:5 then 9:1 CH_2Cl_2–MeOH) allowed the separation of the reduced products (271 mg). The ^1H NMR spectrum (D_2O) was consistent with the presence of 55% of lactone **9** in this mixture.

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