Carbohydrate Research, 246 (1993) 371–376
Elsevier Science Publishers B.V., Amsterdam

Note

Stereoselective synthesis of deoxyhexopyranosides and deoxyhexopyranosid-2-uloses from 2-hydroxyglycal-derived precursors

Oscar Varela, Griselda M. De Fina and Rosa M. de Lederkremer

Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Pabellón II, Ciudad Universitaria, 1428-Buenos Aires (Argentina)

(Received November 19th, 1992; accepted March 12th, 1993)

Previous work from our laboratory has shown that 2-hydroxyglycal esters, readily available from the corresponding glycosyl bromides[1], react with alcohols in the presence of *N*-iodosuccinimide[1] or tin(IV) chloride[2] to give diastereoselectively the α anomers of alkyl 3-deoxyhex-2-enopyranosides[1] (for example **1**) and alkyl 3,4-dideoxy-3-enopyranosid-2-uloses[1,2] (**3** and **4**) with high yields. We now report the conversion, by simple and highly stereoselective reactions, of these derivatives into 3-deoxy, 3,4-dideoxy, and 3,4-unsaturated hexopyranosides, and 3,4-dideoxyhex-2-uloses.

Catalytic hydrogenation (10% Pd–C) of 2-propyl 2,4,6-tri-*O*-acetyl-3-deoxy-α-D-*erythro*-hex-2-enopyranoside (**1**) proceeded with excellent diastereofacial selectivity to give 85% of the 3-deoxyhexoside **2** having the *ribo* configuration. The structure of **2** was deduced from the ^{1}H NMR coupling constants ($J_{1,2}$ 3.6, $J_{2,3}$ 5.5, and $J_{2,3'}$, 11.2 Hz; Table I) which agreed with the J values calculated by applying the additivity rules[3] for an ideal $^4C_1$ conformation of the 3-deoxy-α-D-*ribo*-hexopyranoside ($J_{1,2}$ 3.6, $J_{2,3}$ 4.9 and $J_{2,3}$, 11.5 Hz). Assignment of the ^{13}C NMR spectrum of **2** (Table II) was made by comparison with that reported[4] for methyl 3-deoxy-α-D-*ribo*-hexopyranoside, by taking into account the effect of acylation on the individual chemical shifts[5].

The high diastereofacial selectivity observed for the saturation of the double bond of **1** may be explained by accepting that this compound reacts in the favored $^0H_5$(D) conformation[1,6], which satisfies two stereolectronic requirements: the anomeric and the allylic effects. The quasiaxially oriented anomeric isopropyl group would induce the addition of hydrogen from the opposite β face, resulting in the *R* configuration at C-2. Lichtenthaler and co-workers[7] have also observed anomeric stereocontrol in addition reactions occurring on a vicinal carbonyl group. In contrast, Ferrier et al.[8] reported that hydrogenation of 1,2,4,6-tetra-*O*-acetyl-3-

TABLE I

^{1}H NMR data (δ in ppm, J in Hz) for compounds **2** and **5–11**

Compound	H-1	H-2	H-3	H-3′	H-4, H-4′	H-5	H-6, H-6′	$J_{1,2}$	$J_{2,3}$	$J_{2,3'}$	$J_{3,4}$	$J_{3',4}$
2	5.05	4.80	2.20	1.95	4.80	4.00	← 4.20 →	3.6	5.5	11.2	5.5	11.0
5	4.70		2.70	2.34	← 1.96 →	4.58	← 4.10 →				11.0	3.0
6	5.38	5.26	5.86		5.72	4.46	← 4.17 →	4.1			11.0	
7	5.08	4.76	← 2.10–0.66 [a] →				← 4.15–4.00 →	3.0	5.0	11.0		
8	4.88	3.80	← 2.10–1.40 →				← 3.80–3.60 →	3.6				
9	5.00	4.70	← 2.10–1.50 →				← 4.08–3.90 →	3.5	5.8	10.6		
10	6.22	4.93	← 2.12–1.60 →				← 4.15–4.00 →	3.3	6.5	10.0		
11	5.68	4.76	← 2.17–1.40 →			3.86	← 4.07 →	8.0	6.3	10.2		

[a] Overlapped with the H-cholestanyl.

TABLE II

^{13}C NMR chemical shift values (δ in ppm) for compounds **2** and **5–11**

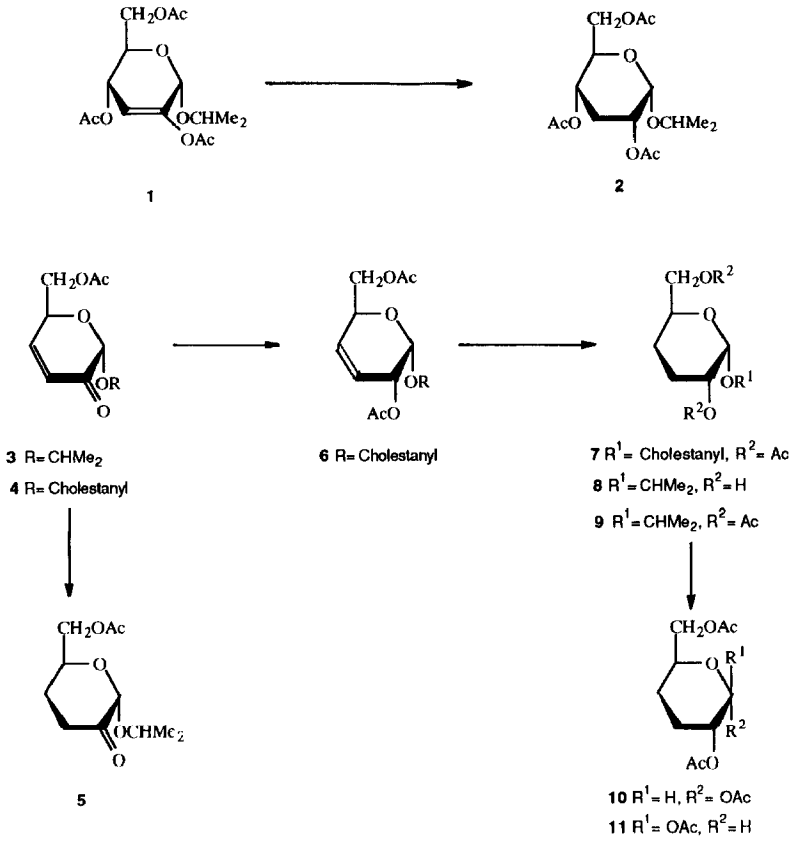
Compound	C-1	C-2	C-3	C-4	C-5	C-6
2	93.2	67.8 *	28.7	65.9	67.6 *	62.3
5	98.0	201.9	34.7 *	29.2 *	66.2	65.7
6	93.5	66.6	128.0 *	124.2 *	66.6	65.4
7	94.4	70.1	[a]	[a]	66.2 *	66.0 *
8	96.3	68.7	26.0 *	27.0 *	67.7	65.3
9	94.3	70.1	23.2 *	26.6 *	66.3 *	66.0 *
10	89.4	68.3	22.7 *	26.0 *	68.3	65.9
11	93.4	68.3	25.6 *	27.0 *	74.0	65.4

[a] Overlapped with C-cholestanyl. * Signals are interchangeable.

deoxy-α-D-*erythro*-hex-2-enopyranose with 5% Pd–$BaSO_4$ afforded a 1.7 : 1 mixture of 3-deoxyhexoses having the *ribo* and *arabino* configurations. The highly selective hydrogenation of **1** may be attributed to the steric hindrance at the α face, caused by the anomeric isopropyl substituent, which is bulkier than an acetyl group.

In order to prepare the corresponding 3,4-dideoxyglycos-2-ulose derivatives, the hydrogenation of alkyl hex-3-enopyranosid-2-uloses was also investigated. Thus, hydrogenation of compound[1] **3** over 10% Pd–C afforded 2-propyl 6-*O*-acetyl-3,4-dideoxy-α-D-*glycero*-hexopyranosid-2-ulose (**5**) in 87% yield. The ^{13}C NMR spectrum of **5** showed signals for the C-2 carbonyl group (201.9 ppm), the anomeric carbon (98.0 ppm), and for the C-3 and C-4 methylene groups (34.7 and 29.2 ppm).

Reduction of the α,β-unsaturated carbonyl system of the sugar enones, such as **3** and **4**, should lead to the corresponding glycosides of 3,4-dideoxyhexopyranoses. Thus, compound **4** was reduced with an excess of sodium borohydride, and the product was acetylated to furnish cholestanyl 2,6-di-*O*-acetyl-3,4-dideoxy-α-D-*erythro*-hex-3-enopyranoside (**6**) in 77% yield. The configuration of C-2 was assigned on the basis of the value (4.1 Hz) of $J_{1,2}$, which is characteristic of an axial–equatorial disposition of vicinal protons. Further confirmation of the stereochemistry of C-2 was obtained by hydrogenation of **6**, which gave crystalline cholestanyl 2,6-di-*O*-acetyl-3,4-dideoxy-α-D-*erythro*-hexopyranoside (**7**). The signal for H-2 in the ^1H NMR spectrum of **7** appeared in a clear region, and thus $J_{2,3}$ (5.0 Hz) and $J_{2,3}$, (11.0 Hz) could be accurately measured and indicated the *R* configuration at C-2. The high diastereoselectivity observed for the reduction of the carbonyl group in **4** is most probably due to the stereocontrol exerted by the anomeric center on the hydride-addition on the vicinal carbonyl group[7]. The reduction of the glyculose derivative **3** was also highly stereoselective, and the crude product obtained by borohydride reduction of **3**, was immediately hydrogenated to furnish 2-propyl 3,4-dideoxy-α-D-*erythro*-hexopyranoside (**8**) in 94% overall yield. As the ^1H NMR spectrum of **8** was rather complex, this compound was converted into the diacetate **9**, whose spectrum showed coupling constants corresponding to the *erythro* relationship of the asymmetric centers.



Formule 1

In a parallel experiment, 2-propyl 3,4-dideoxy-α-D-*erythro*-hexopyranoside (**8**) was acetolyzed, giving rise to an anomeric mixture of 1,2,6-tri-*O*-acetyl-3,4-dideoxy-D-*erythro*-hexopyranosides, separable by HPLC, and affording the α anomer **10** as the main product. The ^{1}H and ^{13}C NMR spectral data of **10** and **11**, together with the measured optical rotation values, confirmed the anomeric configurations of both compounds.

EXPERIMENTAL

General methods–Melting points were determined with a Thomas–Hoover apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 141 polarimeter for solutions in $CHCl_3$. Column chromatography was performed on Silica Gel 60 (230–400 mesh, Merck). TLC was performed on aluminium sheets precoated with Silica Gel 60F (Merck), with the solvent systems: (*A*) 2:1 hexane–EtOAc, (*B*) 19:1 PhMe–EtOAc, and (*C*) EtOAc. Detection was effected by charring with 10% H_2SO_4–EtOH. HPLC was performed with a Micromeritics

liquid chromatograph, equipped with a refractive-index detector, and using an Altech R-Sil C_{18} (50 × 1 cm) column and 1:1 acetone–water as the solvent at 1.2 ml min^{-1}. The NMR spectra were recorded in $CDCl_3$ with a Varian XL-100 (^1H, 100.1 MHz; ^{13}C, 25.2 MHz) or with a Bruker AC 200 (^1H, 200 MHz) spectrometer.

2-Propyl 2,4,6-tri-O-acetyl-3-deoxy-α-D-ribo-hexopyranoside (**2**).—Compound[1] **1** (0.33 g, 1 mmol) dissolved in dry MeOH (10 mL) was hydrogenated with 10% Pd–C (50 mg). When the consumption of H_2 ceased (16 h), TLC showed a single spot (R_f 0.37, *A*). The catalyst was filtered off and the filtrate concentrated affording syrupy **2** (0.28 g, 85%); $[\alpha]_D$ +132° (*c* 1). Anal. Calcd for $C_{15}H_{22}O_8$: C, 54.22; H, 7.23. Found: C, 54.48; H, 7.39.

2-Propyl 6-O-acetyl,3,4-dideoxy-α-D-glycero-hexopyranosid-2-ulose (**5**).—Hydrogenation of compound[1] **3** (0.16 g, 0.7 mmol) in MeOH (10 mL) under the conditions described for the hydrogenation of **1**, gave the glycosidulose **5** (0.14 g, 87%); $[\alpha]_D$ +103° (*c* 1). Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.33; H, 7.70.

Cholestanyl 2,6-di-O-acetyl-3,4-dideoxy-α-D-erythro-hex-3-enopyranoside (**6**).—To a solution of compound[2] **4** (0.16 g, 0.28 mmol) in dry MeOH (10 mL) $NaBH_4$ (60 mg, 1.6 mmol) was added. After stirring for 4 h at room temperature, the mixture was made neutral with Dowex 50W (H^+); the resin was filtered off, and the filtrate concentrated. The resulting syrup was dissolved in 1:1 Ac_2O–pyridine (2 mL) at 0°C, and the solution was kept overnight at 0°C. Methanol (2 mL) was added and toluene (3 × 15 mL) was evaporated from the mixture to remove pyridine. The residue showed a main product on TLC (R_f 0.27, *B*), which was isolated by column chromatography (8:1 hexane–EtOAc) and identified as **6** (0.13 g, 77%); $[\alpha]_D$ +63° (*c* 0.4). Anal. Calcd for $C_{37}H_{60}O_6$: C, 73.96; H, 10.16. Found: C, 73.70; H, 10.13.

Cholestanyl 2,6-di-O-acetyl-3,4-dideoxy-α-D-erythro-hexopyranoside (**7**).—A solution of **6** (60 mg, 0.1 mmol) in EtOAc (10 mL) was hydrogenated over 10% Pd–C (30 mg) for 24 h. The catalyst was filtered off and the solvent evaporated affording pure **7** (R_f 0.24, *B*), which crystallized from MeOH (55 mg, 87%); mp 91–92.5 °C; $[\alpha]_D$ + 94° (*c* 0.7). Anal. Calcd for $C_{37}H_{62}O_6$: C, 73.71; H, 10.37. Found: C, 73.37; H, 10.12.

2-Propyl 3,4-dideoxy-α-D-erythro-hexopyranoside (**8**).—To a solution of **3** (0.144 g, 0.63 mmol) in MeOH (10 mL), $NaBH_4$ (0.14 g, 3.7 mmol) was added. After stirring at room temperature for 24 h no starting material was detected on TLC, and the mixture was treated as described for the preparation of **6**. The homogeneous (R_f 0.55, *C*) syrup (0.12 g) obtained was dissolved in MeOH (10 mL) and hydrogenated over 10% Pd–C (30 mg) as described previously affording syrupy **8** (0.11 g, 94%); $[\alpha]_D$ +128° (*c* 0.8); R_f 0.50 (*C*). Anal. Calcd for $C_9H_{18}O_4$: C, 56.82; H, 9.54. Found: C, 56.68, H, 9.81.

2-Propyl 2,6-di-O-acetyl-3,4-dideoxy-α-D-erythro-hexopyranoside (**9**).—Compound **8** (0.09 g, 0.47 mmol) was treated with 1:1 Ac_2O–pyridine (4 mL) at 4°C for 20 h. Methanol (10 mL) was added and, after 30 min, the solvent was evaporated.

Pyridine was removed by repeated addition and evaporation of toluene. The product **9** (0.10 g, 80%) was isolated as a syrup; $[\alpha]_D$ +133° (*c* 1.6). Anal. Calcd for $C_{18}H_{22}O_5$; C, 60.45; H, 8.58. Found: C, 60.05; H, 8.86.

1,2,6-Tri-O-*acetyl-3,4-dideoxy-α*-D-erythro-*hexopyranose* (**10**) *and its β anomer* (**11**).—To a solution of crude **8**, obtained from **3** (68 mg, 0.3 mmol) as described previously, in AcOH (6.5 mL), a cold mixture of Ac_2O (6.5 mL) and H_2SO_4 (0.4 mL) was slowly added at 0°C. The solution was kept at 4°C for 72 h and NaOAc (1.5 g) was added. The mixture was stirred for additional 30 min at room temperature, and concentrated. The residue was extracted with CH_2Cl_2 (3 × 50 mL), and the extract washed with satd aq $NaHCO_3$ and satd aq NaCl, dried ($MgSO_4$), concentrated and chromatographed on a silica gel column with 5:1 hexane–EtOAc. Fractions containing a single spot (R_f 0.56, *A*) were combined and evaporated to a syrup, whose ^1H NMR spectrum revealed the presence of both **10** and **11**. This mixture was separated by HPLC using a reverse-phase column and acetone–water as solvent (see *General methods*).

The main product, t_R 14.4 min, was identified as the α anomer **10** (35 mg, 50.4%); $[\alpha]_D$ +72° (*c* 0.6). Anal. Calcd for $C_{12}H_{18}O_7$: C, 52.55; H, 6.61. Found: C, 52.87; H, 6.84.

The minor product, t_R 13.7 min, was the β anomer **11** (11 mg, 16%); $[\alpha]_D$ −13° (*c* 0.3).

ACKNOWLEDGMENTS

We thank CONICET (Consejo Nacional de Investigaciones Científicas y Técnicas de la República Argentina) and the University of Buenos Aires for financial support, and UMYMFOR (CONICET-FCEN) for the microanalyses.

REFERENCES

1 O. Varela, G.M. De Fina, and R.M. de Lederkremer, *Carbohydr. Res.*, 167 (1987) 187–196.
2 G.M. De Fina, O. Varela, and R.M. de Lederkremer, *Synthesis*, (1988) 891–893.
3 C. Altona and C.A.G. Haasnoot, *Org. Magn. Reson.*, 13 (1980) 417–429.
4 K. Bock and C. Pedersen, *Adv. Carbohydr. Chem. Biochem.*, 41 (1983) 27–66.
5 A.S. Perlin, *M.T.P. Int. Rev. Sci. Org. Chem., Ser. 2*, 7 (1976) 1–34.
6 A.F. Hadfield and A.C. Sartorelli, *Carbohydr. Res.*, 101 (1982) 197–208.
7 F.W. Lichtenthaler, S. Nishiyama, P. Köhler, and H.J. Linder, *Carbohydr. Res.*, 136 (1985) 13–26.
8 R.J. Ferrier, W.G. Overend, and G.H. Sankey, *J. Chem. Soc.*, (1965) 2830–2836.