Carbohydrate Research, 63 (1978) 307–311

Note

Synthesis of methyl 4-amino-4,6-dideoxy-α-D-galactopyranoside from a glycosulose precursor

CALVIN L. STEVENS* AND STANISLAS H. CZERNECKI†

**Department of Chemistry, Wayne State University, Detroit, Michigan 48202 (U.S.A.)*
†*Laboratoire de Cinétique et Mécanismes de Réactions Organiques, CNRS, E.R. 84, Université Pierre et Marie Curie, 4 Place Jussieu, 75230 Paris, cédex 05 (France)*

(Received April 22nd, 1977; accepted for publication in revised form, August 18th, 1977)

Several syntheses of 4-amino-4,6-dideoxyhexoses have been realized in our laboratory[1–3], generally via nucleophilic displacement of a methylsulfonyloxy group by azide anion. The present synthesis involves oxidation at C-4 to a ketone followed by oximation and reduction. This procedure has been previously reported[1,4–7], and is of greatest value when the reduction step is stereospecific[1]. In the present example, methyl 2,3-di-*O*-benzyl-6-deoxy-α-D-galactopyranoside (**1**) was transformed into methyl 4-amino-2,3-di-*O*-benzyl-4,6-dideoxy-α-D-galactopyranoside (**3**) in 60% overall yield; removal of the protecting groups gave thomosamine.

DISCUSSION

The starting D-galactose derivative[8] **1** was oxidized at 60° by dimethyl sulfoxide–phosphorus pentaoxide[10] in the presence of pyridine to give the glycosulose derivative **6** as an oil, in 95% yield. It is noteworthy that oxidation of the *gluco* isomer **2** is very

TABLE I

CHEMICAL SHIFTS OF RING PROTONS AND FIRST-ORDER COUPLING-CONSTANTS

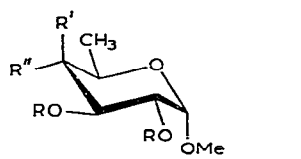
N.m.r. parameter	*Compound*	*H-1*	*H-2*	*H-3*	*H-5*	*H-6*
δ (p.p.m.) and multiplicity[a]	6[b]	4.57(d)	3.56(d of d)	4.27(d)	3.96(q)	1.30(d)
	7[c]	4.75(d)	3.70(t)	3.95(d)	4.9(q)	1.53(d)
J (Hz)	6	$J_{1,2}$ 2.5	$J_{2,3}$ 8.4		$J_{5,6}$ 5.5	
	7	$J_{1,2}$ 3.5	$J_{2,3}$ 3.5		$J_{5,6}$ 6.5	

[a]Peak multiplicities: d, doublet, t, triplet, q, quartet. [b]Measured at 60 MHz in C_6D_6. [c]Measured at 60 MHz in CD_3COCD_3.

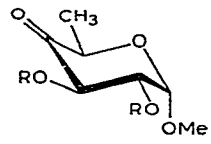
slow under these conditions (1% of reaction after 4 days). Oxidation of **1** with ruthenium tetraoxide[11,12] did not give good results in our hands, probably because of oxidation of the benzyl groups.

The ^{1}H-n.m.r. spectrum of the ketone **6** shows that the $^4C_1$(D) conformation is favored. Signals were attributed by double-irradiation techniques (Table I) and the coupling constants of H-2 with H-1 and H-3 indicate that H-2 and H-3 are axial, and that H-1 is equatorial.

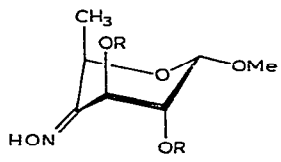
Treatment of the ketone **6** with hydroxylamine hydrochloride in pyridine–ethanol[4] gave the oxime **7** as a mixture of *syn* and *anti* isomers. Column chromatography afforded a pure, crystalline oxime in high yield (80%). Reduction of **7**, either as the pure isomer or as a mixture, by lithium aluminum hydride in anhydrous ether, gave only one amino sugar derivative (**3**), that having the D-*galacto* configuration.



1 R = $PhCH_2$, R' = OH, R" = H
2 R = $PhCH_2$, R' = H, R" = OH
3 R = $PhCH_2$, R' = NH_2, R" = H
4 R = $PhCH_2$, R' = H, R" = NH_2
5 R = H, R' = NHAc, R" = H



6 R = $PhCH_2$



7 R = $PhCH_2$

Its structure was established by comparison in vapor-phase chromatography (v.p.c.) with the authentic product as well as with the *gluco* isomer **4** previously prepared in our laboratory[8,9]. The v.p.c. retention-times were sufficiently different (19 and 22 min) for differentiation of two isomers. A large injection of the crude product showed a small shoulder (<0.5%) corresponding to the *gluco* isomer. The amino sugar glycoside **3** was further characterized by the physical constants of its hydrochloride.

In order to confirm that there was no configurational isomerization at C-3 and/or C-5, all of the transformations leading from **6** to **5** were also performed without any intermediate purification. The final, crude product was trimethylsilylated and analyzed by v.p.c.; the chromatogram showed only one peak. Comparisons with authentic[8] **5** and with the *gluco* isomer[9] confirmed the *galacto* configuration of the product.

Previously, the *O*-isopropylidene group has been used effectively for directing stereospecific reduction of carbohydrate oximes[1]. The excellent stereospecificity of the reduction of the oxime **7** as compared with the reduction of the ketone **6** in this work may be related to differences in conformation. The n.m.r. spectrum of the oxime showed that it does not adopt the same conformation as the ketone. The n.m.r. data

are compatible with the $^1C_4$(D) conformation (shown in formula **7**), although the small coupling-constants might be attributed to a distorted chair-form. In this situation, the H-2 signal is observed as a triplet and the low value of $J_{2,3}$ indicates that H-2 and H-3 cannot be diaxial. The preference for the $^1C_4$(D) conformation may be attributed to large interactions between the oximido group and the two vicinal substituents (CH_3 and OCH_2-Ph) in the $^4C_1$(D) conformation, although that conformation has a 1,3-diaxial interaction as well as an unfavorable anomeric effect.

In the $^1C_4$(D) conformation, steric hindrance allows only the axial attack of the hydride, giving the *galacto* isomer. By comparison, reduction of the ketone **6** under the same conditions is not stereospecific, and gives 75% of methyl 2,3-di-*O*-benzyl-6-deoxy-α-D-galactopyranoside (**1**) and 25% of methyl 2,3-di-*O*-benzyl-6-deoxy-α-D-glucopyranoside (**2**).

EXPERIMENTAL

General methods. — Melting points were taken on a Thomas–Hoover apparatus and are uncorrected. T.l.c. was effected on silica gel H from Brinkmann Instruments on 5 × 20-cm glass plates. I.r. spectra were recorded on a Perkin–Elmer Infracord instrument. Specific rotations were measured with a Perkin–Elmer 141 polarimeter. The n.m.r. spectra were recorded with a Varian T-60 spectrometer with tetramethylsilane as the internal standard. V.p.c. analyses were performed on an F & M Scientific Corp. instrument (Model 810) fitted with a flame-ionization detector. The following columns were used: (*a*) 3% of phenyl diaminosuccinate on Chromosorb W, 61 × 0.65 cm; (*b*) 5% of SE52 on Chromosorb W, 183 × 0.65 cm.

*Methyl 2,3-di-*O*-benzyl-6-deoxy-α-*D*-xylo-hexopyranosid-4-ulose* (**6**). — A solution of methyl 2,3-di-*O*-benzyl-6-deoxy-α-D-galactopyranoside (**1**, 7.6 g) in anhydrous dimethyl sulfoxide (80 ml) containing dry pyridine (7.5 ml) was stirred under nitrogen. Phosphorus pentaoxide (11 g) was introduced in three portions and the mixture was heated at 60° until v.p.c. analysis on column *a* (180°) showed no starting material. The mixture was cooled to room temperature, water (1 liter) was added, and the product was extracted with diethyl ether (3 × 75 ml). The extracts were dried with sodium sulfate and evaporated *in vacuo* to give 5.4 g (90%) of crude **6** (99% pure by v.p.c. analysis). Flash distillation (0.1 mmHg) gave an analytical sample (4.8 g), $[\alpha]_D^{20}$ +90.8° (*c* 5.59, chloroform). The o.r.d. curve of **6** exhibited a positive Cotton effect with a peak at 323 nm; ν_{max} 1730 cm^{-1} (C=O); n.m.r. data (C_6D_6): δ 3.30 (3 H, s, OCH_3), 7.20 (10 H, s, C_6H_5), 4.54 (2 H, s, CH_2Ph), 4.43 and 4.86 (2 H, AB, *J* 11 Hz) CH_2Ph.

Anal. Calc. for $C_{21}H_{24}O_5$: C, 70.79; H, 6.79. Found: C, 71.02; H, 6.91.

*Methyl 2,3-di-*O*-benzyl-6-deoxy-α-*D*-xylo-hexopyranosid-4-ulose oxime* (**7**). — The crude glycosulose **6** (5.4 g) was treated with an excess of hydroxylamine hydrochloride (5 g) in 1:1 pyridine–ethanol (25 ml). The mixture was heated for 5 h under reflux, cooled, diluted with water (30 ml) and, after evaporation of the ethanol *in vacuo*, extracted with diethyl ether (3 × 10 ml). The extracts were dried with sodium

sulfate and evaporated to give the crude oxime **7** (5.34 g). The n.m.r. spectrum of the crude mixture showed two peaks for the OH proton (δ 9.05 and 9.25 in chloroform-*d*) corresponding to the *syn* and *anti* isomers (~17:3). The mixture was dissolved in the minimum of diethyl ether and passed through a column of Florisil (elution with 1:4 ether–pentane). The oxime crystallized to give 4.9 g (81%) of solid, m.p. 75–76°. One more recrystallization from isopropyl ether–pentane afforded an analytical sample; m.p. 77–78°, $[\alpha]_D^{31}$ +74.6° (*c* 2.0, chloroform); ν_{max} 1650 (weak, C=N), 3360 cm^{-1} (OH); n.m.r. data ($CDCl_3$): δ 3.32 (3 H, s, OCH_3), 4.50 (4 H, multiplet, CH_2Ph), 7.16 (10 H, s, C_6H_5), 9.05 (1 H, s, OH).

Anal. Calc. for $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N, 3.77. Found: C, 68.14; H, 6.72; N, 3.76.

*Methyl 4-amino-2,3-di-*O*-benzyl-4,6-dideoxy-α-*D*-galactopyranoside* (**3**) *and its hydrochloride.* — A solution of the oxime **7** (871 mg) in anhydrous ether (2 ml) was added dropwise to a suspension of lithium aluminum hydride (0.5 g) in ether (10 ml). The reaction was complete (t.l.c.) after 6 h at room temperature. The mixture was treated successively with water (0.5 ml), 15% sodium hydroxide (0.5 ml), and water (1.5 ml). The white precipitate was filtered off and washed with ethyl ether. Evaporation of the solvent gave **3** as a pale-yellow oil; yield 757 mg (90%). V.p.c. analysis with column *a* (185°) showed one peak (retention time 21.5 min) corresponding to the *galacto* isomer **3**. The retention time of the *gluco* isomer[9] under the same conditions was 19 min and mixed injection of the latter with the crude product showed two peaks (19 and 21.5 min). The proportion of the *gluco* isomer in the mixture was estimated to be <0.5%. Flash distillation (0.1 mmHg) gave an analytical sample.

Anal. Calc. for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.44; H, 7.72; N, 4.04.

The hydrochloride was prepared[8]; it had m.p. 199–200°, $[\alpha]_D^{25}$ +90.7° (*c* 0.6, chloroform) [lit.[8] m.p. 199–200°, $[\alpha]_D^{25}$ +88.5° (*c* 0.89, chloroform)].

Anal. Calc. for $C_{21}H_{28}ClNO_4$: C, 64.08; H, 7.16; Cl, 9.00. Found: C, 63.99; H, 7.16, Cl, 8.97.

A second characterization of the amino sugar was made. From the pure glycosulose **6**, oximation and reduction were performed without purification of the oxime, and the crude mixture was treated as follows: acetylation with acetic anhydride in dry pyridine, debenzylation by hydrogenolysis in the presence of 10% palladium-on-charcoal and hydrogen chloride in methanol, and finally trimethylsilylation of the crude product (hexamethyldisilazane and chlorotrimethylsilane in dry pyridine) and v.p.c. analysis with column *b* (160°). The retention time of the observed peak was 8.4 min, identical with the retention time of the authentic product[8]. Mixed injection gave only one peak. Mixed injection with the corresponding *gluco* isomer[9] gave two peaks having retention times of 8.4 and 6.6 min, respectively.

*Reduction of methyl 2,3-di-*O*-benzyl-6-deoxy-α-*D*-xylo-hexopyranosid-4-ulose* (**6**). — Lithium aluminum hydride (100 mg) was added to a solution of **6** (370 mg) in ethyl ether (4 ml). After 6 h of boiling at reflux, the reaction was complete, as shown by t.l.c. (1:1 ether–pentane). After treatment as for the oxime, 296 mg (80%) of an

oil was obtained. Analytical t.l.c. (1:1 ether–pentane) showed two spots: R_F 0.3 (**1**) and R_F 0.4 (**2**). Preparative t.l.c. (20 × 20 cm × 1 mm) gave 75% of the *galacto* isomer **1**, m.p. 80–82° (lit.[9] 82–83°) and 25% of the *gluco* isomer **2**, characterized by chromatography and spectroscopy.

REFERENCES

1 C. L. Stevens, K. K. Balasubramanian, C. P. Bryant, J. B. Filippi, and P. M. Pillai, *J. Org. Chem.*, 38 (1973) 4311–4318, and references cited therein.
2 C. L. Stevens, J. P. Dickerson, K. G. Taylor, P. Blumbergs, and P. M. Pillai, *J. Org. Chem.*, 40 (1975) 2468–2470.
3 C. L. Stevens, D. Chitharanjan, K. G. Taylor, and P. M. Pillai, *J. Org. Chem.*, 40 (1975) 2471–2474.
4 C. L. Stevens, R. P. Glinski, and K. G. Taylor, *J. Org. Chem.*, 33 (1968) 1586–1592.
5 E. L. Albano and D. Horton, *Carbohydr. Res.*, 11 (1969) 485–495.
6 S. W. Gunner, W. G. Overend, and N. R. Williams, *Carbohydr. Res.*, 4 (1967) 498–504.
7 D. Horton in R. W. Jeanloz (Ed.), *The Amino Sugars*, Vol. IA, Academic Press, New York, 1969, p. 39.
8 C. L. Stevens, P. Blumbergs, and D. H. Otterbach, *J. Org. Chem.*, 31 (1966) 2817–2822.
9 C. L. Stevens, P. Blumbergs, F. A. Daniher, D. H. Otterbach, and K. G. Taylor, *J. Org. Chem.*, 31 (1966) 2822–2829.
10 K. Onodera, S. Hirano, and N. Kashimura, *J. Am. Chem. Soc.*, 87 (1965) 4651–4652.
11 P. J. Beynon, P. M. Collins, P. T. Doganges, and W. G. Overend, *J. Chem. Soc., C*, (1966) 1131–1136.
12 C. L. Stevens and C. P. Bryant, *Methods Carbohydr. Chem.*, 6 (1972) 337–341.