Carbohydrate Research, 26 (1973) 163–167
© Elsevier Scientific Publishing Company, Amsterdam – Printed in Belgium

BRANCHED-CHAIN AMINO SUGARS. STEREOSPECIFIC SYNTHESIS OF 3-*C*-(2-ACETAMIDOETHYL)-3-DEOXY-1,2-*O*-ISOPROPYLIDENE-β-L-LYXOFURANOSE

ALEX ROSENTHAL AND D. A. BAKER

Department of Chemistry, The University of British Columbia, Vancouver 8, B.C., (Canada)

(Received July 11th, 1972, accepted September 6, 1972)

ABSTRACT

Condensation of 1,2:5,6-di-*O*-isopropylidene-α-D-*xylo*-hexofuranos-3-ulose (**1**) with diethyl cyanomethylphosphonate afforded a mixture of the *cis*- and *trans*-3-cyanomethylene-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*xylo*-hexofuranoses (**2**) in 80% yield. Catalytic reduction of **2** yielded 3-*C*-cyanomethyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose (**4**) exclusively. Palladium and hydrogen was found to rearrange the exocyclic double bond of **2** to give the 3,4-ene (**3**). Catalytic reduction of **3** also proceeded stereospecifically to yield **4**. Selective hydrolysis of **4** yielded the diol **5**, which was cleaved with periodate and the product reduced with sodium borohydride to afford crystalline 3-*C*-cyanomethyl-3-deoxy-1,2-*O*-isopropylidene-β-L-lyxofuranose (**6**) in 87% yield. Catalytic reduction of the latter with hydrogen and platinum in the presence of acetic anhydride and ethanol gave the crystalline L-amino sugar, 3-*C*-(2-acetamidoethyl)-3-deoxy-1,2-*O*-isopropylidene-β-L-lyxofuranose (**7**) in 92% yield.

DISCUSSION

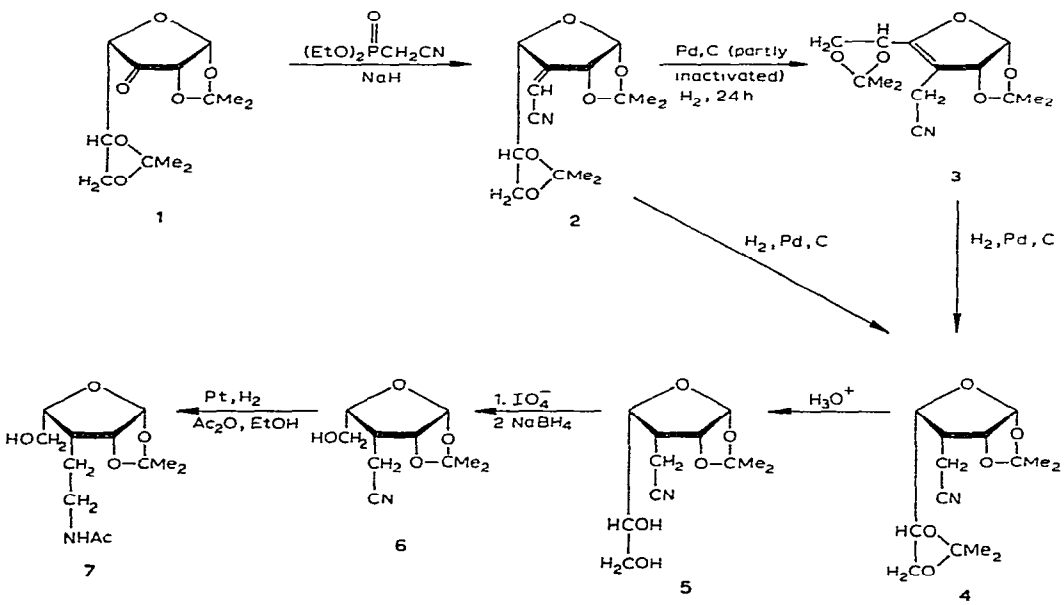
Two previous communications[1,2] from this laboratory have dealt with the application of the Wittig reaction to 5-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranos-3-ulose and to 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose to afford unsaturated, branched-chain, 3-cyanomethylene sugars. Reduction of the cyanomethylene sugars proceeded stereospecifically to give novel branched-chain 3-cyanomethyl-3-deoxy-D-sugars. Subsequently, Tronchet and co-workers[3] also showed that 5-deoxy-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranos-3-ulose reacted with cyanomethylene-triphenylphosphorane to provide a mixture of the expected *cis*- and *trans*-cyanomethylene sugars, which underwent stereospecific dihydroxylation to give branched-chain sugars. The synthetic utility of the endo 1,2-*O*-isopropylidene group and an exo group at position 5 (or 5, 6) in leading to stereospecific products has also been noted by other authors[3–7].

It seemed of interest to extend the Wittig reaction to an appropriately blocked 3-ketose having endo 1,2- and 5,6-*O*-isopropylidene groups in order to determine the conformational effects of these groups on the stereochemistry of the products.

Periodate oxidation of the 5,6-glycol group of the product followed by sodium borohydride reduction[7] of the resulting aldehydo sugar might be expected to give a branched-chain L-sugar.

Condensation of 1,2:5,6-di-*O*-isopropylidene-α-D-*xylo*-hexofuranos-3-ulose[6] (**1**) with diethyl cyanomethylphosphonate in the presence of sodium hydride afforded a mixture of the *cis*- and *trans*-3-cyanomethylene-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*xylo*-hexofuranoses (**2**) in 80% yield. Reduction of the mixture of unsaturated cyanomethylene sugars proceeded stereospecifically to give crystalline **4** in almost quantitative yield. The configuration of **4** at C-3 was readily ascertained from its n.m.r. spectrum. The H-2 signal of **4** appeared as a triplet at τ 5.27 having $J_{1,2} = 4$ Hz and $J_{2,3} = 5.0$ Hz. The large $J_{2,3}$ value indicates that H-2 and H-3 of **4** are *cis*[6,7], and **4** must, therefore, be 3-*C*-cyanomethyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose. The stereospecificity of the reduction of **2** is in complete accord with the fact that hydride reduction of **1** also proceeds stereospecifically to yield 1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose[4].

An unusual and unexpected migration of the exocyclic double bond in the cyanomethylene sugars (**2**) was obtained during the attempted reduction of these unsaturated sugars with hydrogen and an old sample of palladium on charcoal. Although a minor amount of **2** was reduced to the saturated, branched-chain, cyano sugar **4**, the major proportion of **2** was converted into a new unsaturated cyano sugar **3**. A similar allylic rearrangement together with reduction has previously been reported[6] when a 3,4-unsaturated sugar derivative was treated with hydrogen in the presence of palladium of platinum dioxide. The structure of **3** was tentatively assigned



on the basis of its n.m.r. spectrum (see Experimental section). Narrow couplings (< 1 Hz) in signals of three of the protons (at τ 4.73, 5.28, and ~5.8) indicated long-range coupling of hydrogen atoms with an allylic hydrogen. The n.m.r. data thus support the assignment of structure **3** as it possesses three allylic protons, namely, H-2, H-5, and the methylene groups attached to C-3. Stereospecific hydrogenation of **3** to afford **4** is again in accord with the finding that catalytic or hydride reduction of 3-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enofuranose gave 3-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose exclusively[6].

Selective hydrolysis of the 5,6-*O*-isopropylidene group of **4** was achieved with methanolic aqueous sulfuric acid to afford the diol **5** in 88% yield. Periodate oxidation of **5**, followed by immediate reduction of the resulting aldehydo sugar with sodium borohydride, gave crystalline 3-*C*-cyanomethyl-3-deoxy-1,2-*O*-isopropylidene-β-L-lyxofuranose (**6**) in 87% yield. Both n.m.r. and i.r. data were in complete accord with the assignment of structure **6**.

Catalytic reduction of the cyano group was accomplished by reducing **6** in acetic anhydride and ethanol with hydrogen in the presence of platinum dioxide to give crystalline 3-*C*-(2-acetamidoethyl)-3-deoxy-1,2-*O*-isopropylidene-β-L-lyxofuranose (**7**) in 92% yield. The assignment of structure was in complete agreement with the n.m.r. and i.r. spectra, and elemental analysis for **7**. The ease of preparation and high yield of **7** makes this synthesis an attractive route for the synthesis of branched-chain analogues of the L-sugars present in antibiotics[8,9].

EXPERIMENTAL

General considerations. — These have been described previously[7].

*Wittig reaction of 1,2:5,6-di-*O*-isopropylidene-α-D-*xylo*-hexofuranos-3-ulose* (**1**) *to yield 3-*C*-cyanomethyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose* (**4**). — To a suspension of sodium hydride (30 mg) in anhydrous 1,2-dimethoxyethane (20 ml) was carefully added a solution of diethyl cyanomethylphosphonate (0.220 g) in 1,2-dimethoxyethane (15 ml). When the evolution of gas had ceased the mixture was filtered (all operations were performed in a dry box under a nitrogen atmosphere) and the solution was then cooled to 0°. To the cold solution of the carbanion a solution of the ketose[1] **1**, 0.290 g) in 1,2-dimethoxyethane (2 ml) was added, with stirring and external cooling. The mixture was then allowed to warm to room temperature, left for 4 h, and then diluted with ice–water (20 ml) and extracted with ether (3 × 15 ml). The combined ether extracts were washed with water and dried over magnesium sulfate. After removal of the ether by evaporation, the product was crystallized from ether–petroleum ether (b.p. 30–60°) to yield 0.260 g (80%) of a crystalline mixture, inseparable by chromatography, of *cis*- and *trans*-3-cyanomethylene-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*xylo*-hexofuranose (**2**); m.p. 95–98°; ν_{max}^{Nujol} 2260 cm^{-1} (C≡N); τ^{CDCl_3} 4.1 (d, $J_{1,2}$ 4 Hz, H-1), 4.20 (q, H-1′), 4.33 (t, H-1′), 4.8 (pair d, $J_{1,2}$ 1.5 Hz, $J_{1,2}$ 4 Hz, H-2), 5.04 (pair d, H-2), 5.2–6.2 (m) 4H, 8.4, 8.58, 8.62 (s, Me).

Hydrogenation of the mixture of *cis* and *trans*-unsaturated sugars **2** (0.260 g) in ethanol (10 ml) in the presence of 5% palladium on charcoal (0.100 g) at room temperature and 1 atm pressure gave, after conventional processing, solid 3-*C*-cyanomethyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose (**4**); yield 0.260 g. Compound **4** was recrystallized from ether–petroleum ether (b.p. 30–60°); m.p. 112°, $[\alpha]_D^{25}$ −29 (*c* 2.3, chloroform); ν_{max}^{Nujol} 2280 cm^{-1} (C≡N); τ^{CDCl_3} 4.20 (d, $J_{1,2}$ 4 Hz, H-1). 5.27 (t, 1H, $J_{2,3}$ 5.0 Hz, H-2), 5.48–6.52 (m), 7.0–7.7 (m, 3H, H-3, H-1'), 8.46–8.68 (4s, Me). Irradiation at τ 4.20 collapsed the triplet at τ 5.27 to a doublet.

Anal. Calc. for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.33; H, 7.63; N, 4.69.

Conversion of unsaturated sugars **2** *into 3-C-cyanomethyl-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-erythro-hex-2-enofuranose* (**3**) *and reduction of* **3** *to yield* **4**. — The cyanomethylene sugars **2** (1 g) were added to a mixture of ethanol (25 ml) and partially inactive (old sample) 5% palladium on charcoal (0.500 g) and the resulting mixture was hydrogenated for 24 h at room temperature and 1 atm pressure. About 15 ml of hydrogen was absorbed. The reaction was monitored by t.l.c. on silica gel with 9:1 benzene–methanol as developer (R_F 0.55, 0.48, and 0.33 for compounds **3**, **2**, and **4**, respectively). The mixture of products was separated by column chromatography on silica gel, with 4:1 benzene–ethyl acetate as developer to afford 0.370 g of compound **3**, 0.170 g of a mixture of *cis*- and *trans*-unsaturated sugars **2**, and 0.140 g of the reduced cyanomethyl sugar **4**.

Compound **3** had τ^{CDCl_3} 4.0 (d, $J_{1,2}$ 4.2 Hz, H-1), 4.73 (2 pairs of d, *J* 1 Hz, H-2), 5.28 (3 narrow doublets, each pair separated by 7 Hz, *J* 0.6 Hz, 1H), 5.62– 6.18 (2H, 5 peaks each separated by about 7 Hz, peaks at τ 5.75 and 6.02 had shoulder, separation about 0.3 Hz), 6.5 (d, 2H, *J* 4.8 Hz), 8.56, 8.62 (2s, 12H).

Hydrogenation of **3** in the presence of active palladium on charcoal gave compound **4**, identical by n.m.r. and i.r. spectra with that obtained by hydrogenation of **2**.

3-C-Cyanomethyl-3-deoxy-1,2-O-isopropylidene-β-L-lyxofuranose (**6**). — To a solution of 3-*C*-cyanomethyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose (**4**) (0.160 g in 9 ml of methanol) was added 0.7M sulfuric acid (1.5 ml) and the mixture was kept for 7 h. The mixture was then neutralized by adding solid sodium hydrogen carbonate and was extracted with chloroform (4 × 15 ml). The combined chloroform extracts were dried over sodium sulfate and evaporated to give 3-*C*-cyanomethyl-3-deoxy-1,2-*O*-isopropylidene-α-D-gulofuranose (**5**), yield 0.121 g (88%) as a syrup; τ^{CDCl_3} 4.07 (d, 1H, H-1), 5.23 (broad t, 1H, H-2), 7.0–7.5 (m, 5H, $CH_2C{\equiv}N$, H-3, C-6 OH, C-6 OH), 8.40, 8.64 (2s, 6H). Upon addition of D_2O, the two peaks in the region τ 7.0–7.5 disappeared.

The diol **5** (0.121 g) in ethanol (4 ml) containing a saturated solution (0.2 ml) of sodium hydrogen carbonate was oxidized with sodium metaperiodate solution (0.106 g in 7 ml water). After stirring for 3 h, the excess sodium metaperiodate was decomposed by the addition of a drop of ethylene glycol. The resulting aldehydo sugar was immediately reduced with sodium borohydride (10 mg). The reaction mixture was kept for 4 h, acetone (1 drop) was added, and the mixture was stirred for

an additional 0.5 h. After the residue had been removed by filtration, the filtrate was extracted with dichloromethane (4 × 10 ml). The combined extracts were dried over sodium sulfate, filtered, and evaporated under diminished pressure to yield 0.105 g (87%) of the cyanomethyl-L-sugar **6**, which was recrystallized from ether; m.p. 81°, $[\alpha]_D^{24}$ +10° (*c* 1.6, chloroform); ν_{max}^{Nujol} 3500 (OH), 2245 cm^{-1} (C≡N); τ^{DCCl_3} (4.10 (d, 1H, $J_{1,2}$ 4 Hz, H-1), 5.23 (*t*, 1H, $J_{2,3}$ 4.5 Hz, H-2), 8.43, 8.67 (2s, 6H, CMe_2).

Anal. Calc. for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.22; H, 7.05; N, 6.50.

3-C-(2-Acetamidoethyl)-3-deoxy-1,2-O-isopropylidene-β-L-lyxofuranose (**7**). — A solution of 3-*C*-cyanomethyl-3-deoxy-1,2-*O*-isopropylidene-β-L-lyxofuranose (**6**) (0.018 g) in acetic anhydride (2 ml) and ethanol (2 ml) was hydrogenated, in the presence of platinum oxide (0.019 g), for 4.5 h at room temperature and 60 $lb.in^{-2}$. T.l.c. examination at this time indicated that the reaction was complete; the R_F value of **7** was 0.05 with 5:5:1 dichloromethane–ethyl acetate–ethanol as developer. The catalyst was then filtered off and the solvent evaporated to afford 0.020 g (92%) of crystalline **7**. Recrystallization from alcohol gave pure **7**; m.p. 133°, $[\alpha]_D^{25}$ +1.5° (*c* 1.6, chloroform); ν_{max}^{KBr} 1630 cm^{-1} (amide); τ^{CDCl_3} 3.8–4.3 (b, 1H, N-H) 4.17 (d, 1H, $J_{1,2}$ 4 Hz, H-1), 5.40 (*t*, 1H, $J_{2,3}$ 5 Hz, H-2), 5.5–6.8 (overlapping m, 4H), 7.4–8.4 (m, 5H, H-3 and CH_2CH_2), 8.06 (s, 3H, N-Ac), 8.50 and 8.22 (CMe_2).

Anal. Calc. for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.72; H, 8.27; N, 5.10.

ACKNOWLEDGMENT

This work was supported by the National Research Council of Canada.

REFERENCES

1 A. ROSENTHAL AND D. BAKER, *Tetrahedron Lett.*, (1969) 397.
2 A. ROSENTHAL, M. SPRINZL, AND D. A. BAKER, *Tetrahedron Lett.*, (1970) 4233.
3 J. M. J. TRONCHET, R. GRAF, AND R. GURNY, *Helv. Chim. Acta.*, 55 (1972) 613.
4 A. N. DE BELDER, *Advan. Carbohyd. Chem.*, 20 (1965) 220.
5 S. A. BARKER AND E. J. BOURNE, *Advan. Carbohyd. Chem.*, 7 (1952) 137.
6 K. N. SLESSOR AND A. S. TRACEY, *Can. J. Chem.*, 47 (1969) 3989; 48 (1970) 2900.
7 (a) A. ROSENTHAL AND M. SPRINZL, *Can. J. Chem.*, 47 (1969) 4477; (b) A. ROSENTHAL AND L. NGUYEN, *J. Org. Chem.*, 34 (1969) 1029 and references therein.
8 H. GRISEBACH AND R. SCHMID, *Angew. Chem. Internat. Edit.*, 11 (1972) 159.
9 S. HANESSIAN AND T. H. HASKELL, in W. PIGMAN AND D. HORTON, *The Carbohydrates*, 2nd Ed., Academic Press, New York, 1970, vol. IIA, p. 139.