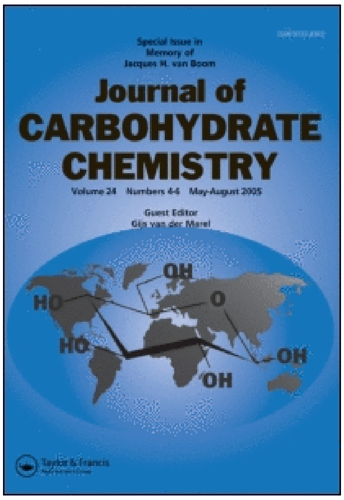

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Chain-Extension of Carbohydrates.I. Cyano-amination of 1, 2:3, 4-Di-O-Isopropylidene-α-D-galacto- hexodialdo-1, 5-pyranose

S. Czernecki[a]; A. Dieulesaint[a]; J-M. Valery[a]
[a] Laboratoire de Chimie des Glucides., Université P.M. Curie. Tour, Paris, FRANCE

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CHAIN-EXTENSION OF CARBOHYDRATES.I.

CYANO-AMINATION OF 1,2:3,4-DI-*O*-ISOPROPYLIDENE-α-*D*-*GALACTO*- HEXODIALDO-1,5-PYRANOSE.

S.Czernecki*, A.Dieulesaint and J-M.Valery.

Laboratoire de Chimie des Glucides.
Université P.M. Curie. Tour 54-55.
4 Pl. Jussieu; 75005 Paris. FRANCE.

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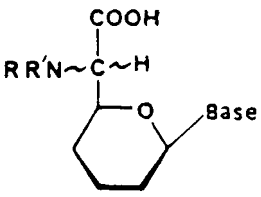
ABSTRACT.

Cyano-amination of the title compound was shown to occur with high yield and high diastereofacial selectivity.

The *C*-glycopyranosylated[1] and *C*-glycofuranosylated[2] -α-amino-acids, substructures **1** and **2** , are found in many natural products.



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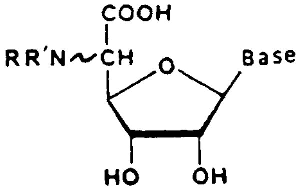

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As a part of an ongoing program on chain-extension of carbohydrate derivatives directed toward the synthesis of biologically important compounds, we decided to examine the possibilities of cyano-amination of dialdosugar derivatives using the

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Strecker reaction.[3] Hydrolysis[4] followed by deprotection of amino-group[5] would transform the resulting α-amino-nitrile into the parent α-amino-acid.

This old reaction and its modifications[6] are often employed on simple molecules but scarcely in case of polyfunctional molecules, especially enolisable aldehydes. We describe herein our preliminary results.

The 1,2:3,4-di-O-isopropylidene-α-D-galacto-hexodialdo-1,5-pyranose 3 was chosen as model compound. This dialdopyranose was already prepared in two steps from D-galactose[7] however we preferred to use the Swern oxidation[8] which afforded a purer compound.

The use of the standard conditions initially described by Strecker (NH_4Cl, NaCN, H_2O) did not afford the desired α-amino-nitriles but a mixture of the two epimeric cyanohydrins.

Finally, the best results of cyano-amination were obtained with the Knoevenagel modification[9] using sodium hydrogenosulfite, a non-tertiary amine and sodium cyanide. The reaction is conducted around room temperature and leads to a mixture of α-amino-nitriles in excellent yield (see table).

The ratio of the two epimers 4n and 5n was determined from the integration of the H-1 signals in the ^1H 250 MHz NMR spectra. Several primary and secondary amines were employed with the same success,the lower yield obtained with methylamine could be due to its volatility. Except for the mixtures 4a-5a,4b-5b and 4e-5e, the α-amino-nitriles were separated either by column chromatography or crystallization.[10] The L-glycero- configuration at C-6 was determined by X-ray spectroscopy* for compound 4c and attributed by analogy to the major α-amino-nitriles 4.

In all studied cases, a strong diastereoselection was observed (#9/1) and was not significantly affected by the nature of the

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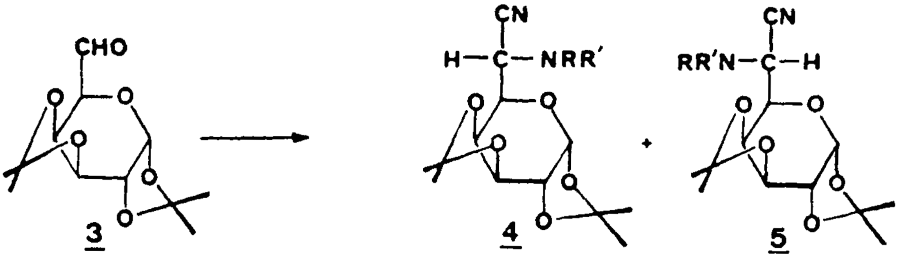
*Professor H. Gillier-Pandraud (Laboratoire de Chimie Structurale Biomoléculaire,Université Paris-Nord) is gratefully aknowledged for the structure determination of 4c.

TABLE.



	R	R'	Yield[a] (%)	Ratio(%)-(yield%[b])	
				4	5
a	CH_3	H	60	86	14
b	CH_3	CH_3	86	91	9
c	$PhCH_2$	H	94	91 (71)	9
d	$PhCH_2$	$PhCH_2$	100	80 (43)	20 (3)
e	S(−)$PhCH_2(CH_3)$	H	92	82	18
f	R(+)$PhCH_2(CH_3)$	H	100	85 (49)	15

a) Crude yield of the mixture.
b) Isolated yield of pure isomer.

amine. We did check that the reaction was not under thermodynamic control by verifying that the minor α-amino-nitrile 5c was recovered unchanged after being replaced under the conditions of its formation.

The rationalization of the results dealing with the exocyclic functionalization of carbohydrate derivatives is generally difficult owing to the need of clarifying two uncertainties (the conformation of reacting species and the direction of attack) with only one observation (overall diastereofacial induction). This aspect of the problem will be published in due course.

As far as synthetic utility is concerned, this method compares favorably with previously described procedures[11] in terms of yield and diastereoselection. Moreover, the mild conditions employed make it suitable for sensitive aldehydes and the use of toxic reagent such as cyanhydric acid is obviated.[12]

EXPERIMENTAL

General procedures are the same as indicated before.[13]

1,2:3,4-di-O-isopropylidene-α-D-galacto-hexodialdo-1,5-pyranose 3. Dimethyl-sulfoxide (9.4mL, 121mmol) dissolved in CH_2Cl_2 (25mL) was added dropwise to a cooled (-55°C) solution of oxalyl chloride (8.3mL, 95mmol) in CH_2Cl_2 (125mL) under Argon. After 2 min. of gentle stirring, a solution of 1,2:3,4-di-O-isopropylidene-α-D-galacto-pyranose[14] (14.4g, 55.4mmol) in CH_2Cl_2 (50mL) was carefully added. After 15 min. at -55°C a white precipitate was observed and the reaction mixture was slowly warmed up to -30°C. At this temperature, triethylamine (39mL, 279mmol) was added dropwise. The mixture first clarified, then a yellow precipitate was formed and the whole was allowed to warm up to room temperature. Water (100mL) was added and the mixture transferred in a separatory funnel. After two extractions (CH_2Cl_2, 100mL) the organic layers were successively washed with 20% aqueous HCl, water, 5% aqueous $NaHCO_3$, brine, dried ($MgSO_4$) and evaporated to dryness to give a colorless, chromatographically homogeneous syrup pure enough for further cyano-amination (13.57g, 95%); b.p. 145-150°C/0.5 mm Hg; TLC R_F= 0.46 (pet. ether/ether 35:70) and 0.55 (pet. ether/ethyl acetate 70:35); $[\alpha]_D^{20}$ -116 (c 1.0, $CHCl_3$), reported[7] -113 (c 3.4, $CHCl_3$); IR (neat) 2740, 1740, 1385 and 1375 cm^{-1}.

Anal. Calcd for $C_{12}H_{18}O_6$ (258.27): C, 55.80; H, 7.03.
Found : C, 55.32; H, 7.32.

An oxime of the syrupy aldehyde was prepared by treatment with hydroxylamine hydrochloride in 95% ethanol in the presence of $NaHCO_3$. The product was recrystallized from hexane:

m.p. 112-113°C $[\alpha]_D^{20}$ -135.7 (c 3.2, $CHCl_3$)
Lit.[7] m.p. 113-114°C $[\alpha]_D^{20}$ -132 (c 2.3, $CHCl_3$)

6-L-glycero-N-benzyl-amino-6-deoxy-1,2:3,4-di-O-isopropylidene-α-D-galacto-heptopyranuronitrile 4c.

The following procedure is representative. Aqueous sodium bisulphite (4M, 0.25mL, 1mmol) and 3 (258mg, 1mmol) were allowed to react 20 min. at 35°C under vigourous stirring. Then benzylamine (118mg, 0.120mL, 1.1mmol) diluted with ethanol (0.2mL) was added and the mixture stirred 20 min. at 35°C before addition of sodium cyanide (75mg, 1.53mmol). After 4 hours at room temperature, the mixture was taken up in chloroform (15mL)- water (15mL) and extracted with chloroform (3x15mL). The organic layers were washed with brine (2x10mL), water (10mL) and dried over $MgSO_4$. Evaporation of the solvent gave the epimeric mixture of 4c and 5c (351mg, 94%) in a 91:9 ratio. Recrystallization from hexane afforded pure 4c (265mg, 71%); m.p. 90-91°C; TLC R_F= 0.72 (pet. ether/ether 25:75); $[\alpha]_D^{20}$ -41.1 (c 2.4, $CHCl_3$); IR 3310, 3060, 3030, 1605, 1585, 1385, 1375, 740 and 695 cm^{-1}; ^1H NMR 250 MHz ($CDCl_3$) δ 7.37-7.25 (m, 5H, C_6H_5), 5.56 (d, 1H, $J_{1,2}$= 5Hz, H-1), 4.68 (dd, 1H, $J_{2,3}$= 2.5Hz, $J_{3,4}$= 7.75Hz, H-3), 4.44 (dd, 1H, $J_{4,5}$= 1.5Hz, H-4), 4.38 (dd, 1H, H-2), 4.06 and 3.83 (m, 2H, N-CH_2), 3.95 (m, 2H, $J_{5,6}$= 8Hz, H-5 and H-6), 1.87 (1H, NH), 1.54 (s, 3H, CH_3) and 1.34 (2s, 6H, $2CH_3$).

Anal. Calcd for $C_{20}H_{26}O_5N_2$ (374.42): C, 64.15;H, 7.01;N, 7.48
Found : C, 64.05; H, 7.35;N, 7.76

Flash chromatography of the mother liquors afforded an analytical sample of the minor isomer 5c; m.p. 113-115°C; TLC R_F= 0.68 (pet. ether/ether 25:75); $[\alpha]_D^{20}$ -151 (c 0.8, $CHCl_3$); ^1H NMR 250 MHz ($CDCl_3$) δ 7.4-7.26 (m, 5H, C_6H_5), 5.58 (d, 1H, $J_{1,2}$= 4.75Hz, H-1), 4.63 (dd, 1H, $J_{2,3}$= 2.5Hz, $J_{3,4}$= 7.75Hz, H-3), 4.35 (m, 2H, $J_{4,5}$= 2.5Hz, H-2 and H-4), 4.10 and 3.90 (m, 2H, N-CH_2), 3.93 (m, 1H, $J_{5,6}$= 6.5Hz, H-5), 3.83 (m, 1H, H-6), 2.07 (1H, NH), 1.53 (s, 3H, CH_3), 1.46 (s, 3H, CH_3) and 1.35 (2s, 6H, $2CH_3$).

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