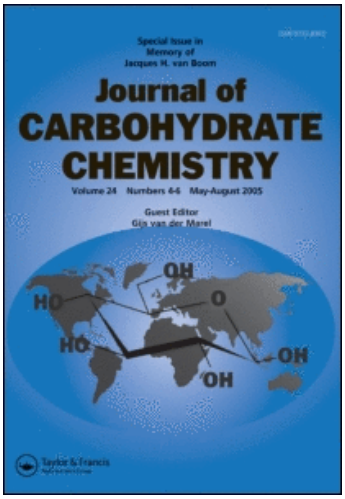

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Chain-Extension of Carbohydrates. II[1] Stereospecific Ethynylation of Protected Pyrano- and Furano- Dialdoses

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

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CHAIN-EXTENSION OF CARBOHYDRATES. II.[1] STEREOSPECIFIC ETHYNYLATION OF PROTECTED *PYRANO*- AND *FURANO*- DIALDOSES.

S.Czernecki* and J-M.Valéry.

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

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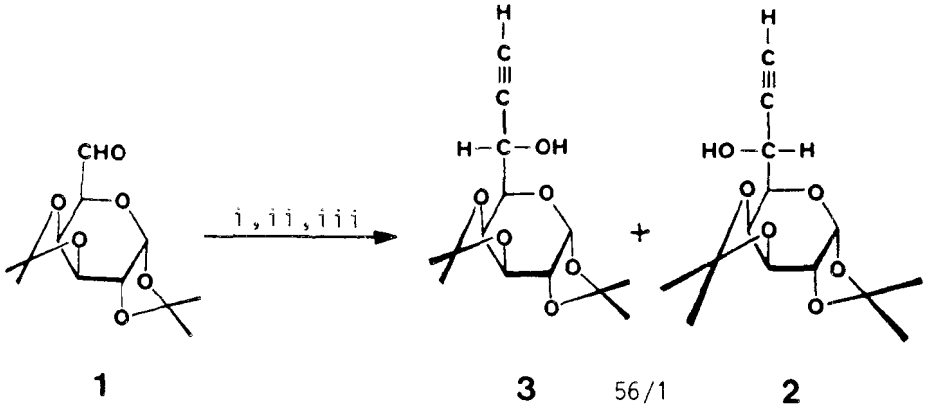
ABSTRACT.

Stereospecific high-yielding ethynylation of protected dialdoses is described.

Recently, the synthesis of higher-carbon carbohydrates has received increasing attention from organic chemists.[2] In that area, the versatility of the ethynyl group has already been demonstrated,[3,4] especially for the synthesis of seven or eight carbon compounds, but the diastereoselection generally obtained in the ethynylation step was not very high. We report herein our results on the stereospecific ethynylation of some protected aldehydo-dialdoses. The readily available[1] 1,2:3,4-di-O-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose 1 was chosen as a model compound.

It was known from previous studies that the reaction of Grignard reagents with 1 gives higher diastereoselectivity in ether[5] than in THF.[6,7] To further enhance the diastereoselection, we decided to fix the conformation of the dialdosugar side-chain by chelation of magnesium with the aldehyde function and the ring oxygen atom using magnesium bromide in ether. Since the mono-Grignard reagent of acetylene cannot be

prepared in this solvent,[8] trimethylsilylacetylene was employed as a source of the ethynyl group. The Grignard reagent was prepared by successive exchanges with methyl-lithium and with magnesium bromide in ether. The cleavage of the trimethylsilyl group[9] was carried out on the crude ethynylated mixture (Scheme 1) and the ratio of the two epimers ascertained by ^{1}H NMR spectroscopy (250 MHz) and GC analysis. Our results are summarized in Table 1.



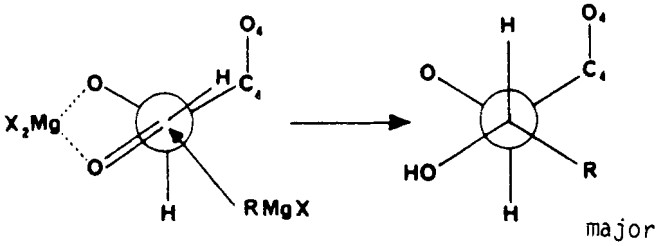
Scheme 1: Reagents; i, $MgBr_2$-Et_2O; ii, Me_3Si—C≡C-MgBr, Et_2O, -30°C; iii, $AgNO_3$, EtOH-H_2O, KCN/H_2O.

Table 1: Diastereoselection in ethynylation of 1 .

Entry	Organometallic reagent	Solvent	t °C	Yield %	Ratio of 2 : 3
1	H-C≡C-MgBr[a]	THF	20	73	1.5:1
2	Me_3Si-C≡C-Li	Et_2O	-15	92	1:2
3	Me_3Si-C≡C-MgBr[b]	Et_2O	0	91	1:26
4	-dito-	Et_2O	-20	95	1:49
5	-dito-	Et_2O	-30	94	1:56[c]

a. Ref. 8; b. Previous complexation of 1 with 8 equiv. of anhyd. $MgBr_2$ in Et_2O; c. Pure 3 was isolated in 73% yield.

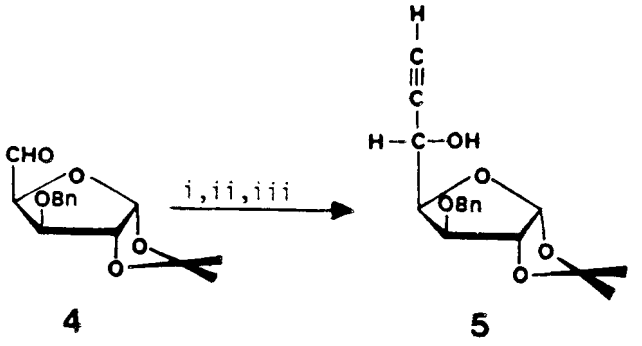
The L-*glycero*- configuration of the new chiral center at C-6 of the major product is in agreement with preferred nucleophilic attack on the *si* face of the chelated aldehyde 1 as predicted by Cram's chelate rule[10] (Scheme 2).



Scheme 2

This procedure allowed us to obtain pure L-*glycero*- isomer 3 in 73% yield by direct recrystallization.

Another example, but chosen from the *furano*- series, exemplifies the efficiency of this procedure. Reaction of pentodialdose 4[11] under the above conditions afforded compound 5 in 83% yield. No C-5 epimer was detected by GC analysis and ^{1}H NMR (250 MHz). Compound 5 was characterized as it's crystalline benzoate. (See Experimental).



4 5

The scope and synthetic application of this method of ethynylation is currently under investigation.

EXPERIMENTAL

General procedures are the same as indicated before.[12]

7,8-Dideoxy-1,2:3,4-di-O-isopropylidene-L-*glycero*-α-D-*galacto*-oct-7-ynopyranose 3. The reaction was carried out under argon. Two batches of anhydrous magnesium bromide (8 mmol each) were prepared from the reaction between magnesium (200 mg) and 1,2-dibromoethane (690 µL 8mmol) in ether (6 mL) at room temperature. In a separate flask, trimethylsilylacetylene (625 µL, 4.4 mmol) was added dropwise to a cooled (-5 °C) solution of methyl lithium 1.45 M in ether (2.75 mL, 4 mmol). After 30 min this mixture was added to one batch of freshly prepared anhydrous $MgBr_2$. The resulting white suspension was cooled to -30 °C. The dialdosugar 1 (263 mg, 1.02 mmol) dissolved in ether (3 mL) was added to the second batch of $MgBr_2$ (8 mmol) and the resulting mixture was added to the above suspension at -30 °C. The temperature of the reaction mixture was allowed to attain room temperature before careful hydrolysis by cold aqueous saturated ammonium chloride (30 mL). After decantation, the aqueous layer was extracted with ether (2 x 15 mL), the organic layers washed with water (15 mL) and dried over Na_2SO_4. Evaporation of the solvent afforded a crystalline mass which was directly submitted to the desilylation procedure described by Schmidt and Arens.[9] Evaporation of most of the solvent and trituration of the residue in water (5 mL) followed by extraction with ether (3 x 15 mL) and usual processing left a solid (273 mg, 94%): mp 130 °C; TLC R_F=0.49 (pet-ether/ether 1:2); GC analysis (phenyldiethanolamine succinate 3%, 0.60 m, 135 °C) showed ca. 1.75% of the D-*glycero*- epimer. Recrystallization (dichloromethane-petroleum ether) yielded pure 3, 213 mg (73%): mp 135-7 °C; $[\alpha]_D^{20}$ -56.3 (c 0.95, $CHCl_3$); Lit.[7] mp 136-7 °C; $[\alpha]_D^{20}$ - 57 (c 1.2, $CHCl_3$); IR (KBr) 3440, 3250, 2120, 1385, 1370 cm^{-1}; ^1H NMR 250 MHz ($CDCl_3$) δ 5.57 (d, 1H, J_{1-2} = 4.75 Hz, H-1), 4.65 and 4.61 (m, 2H, H-3 and H-6), 4.48 (dd, 1H, J_{3-4} = 8 Hz, J_{4-5} = 1.5 Hz, H-4), 4.35 (dd, 1H, J_{2-3} = 2.5 Hz, H-2), 3.79 (dd, 1H, J_{5-6} = 8.5 Hz, H-5), 2.68 (b.s, 1H, OH), 2.55 (d, 1H, J_{6-8} = 2 Hz, H-5), 1.58 - 1.48 - 1.38 and 1.27 (4s, 4x3H, 4 CH_3).

Anal. Calcd for $C_{14}H_{20}O_6$ (284.31): C, 59.14; H, 7.09.
Found : C, 59.05; H, 6.97.

3-O-Benzyl-6,7-dideoxy-1,2-O-isopropylidene-β-L-*ido*-hept-6-ynofuranose 5. When submitted to the same reaction sequence, the pentodialdose 4, (276 mg, 0.99 mmol) yielded the sirupy alcohol 5 (251 mg, 83%): homogenous on TLC R_F= 0.21 (pet. ether/ether 50/50) 0.50 (chloroform/ether 3/1); GC analysis (same column as above, 170 °C) showed less than 3% of the C-5 epimer; IR (neat) 3400, 3280, 2120, 1375, 1380 cm^{-1}; ^1H NMR 250 MHz ($CDCl_3$) δ 7.34 (m, 5H, C_6H_5), 5.97 (d, 1H, J_{1-2}= 3.7 Hz, H-1), 4.74 (dd, 1H, J_{4-5}= 8.15 Hz, J_{5-7}= 2.15 Hz, H-5), 4.66 and 4.43 (ABq, 2H, CH_2-Ph), 4.62 (d, 1H, J_{1-2}= 3.7 Hz, J_{2-3}= 0 Hz, H-2), 4.32 (dd, 1H, J_{3-4}= 3.4 Hz, H-3), 2.45 (d, 1H, H-7), 1.50 and 1.33 (2s, 2x3H, 2 CH_3). The acetylenic alcohol 5 was characterized as it's crystalline benzoate: mp 122-4 °C; $[\alpha]_D^{20}$ -29.3 (c 1, $CHCl_3$); Lit.[3] mp 124-5 °C; $[\alpha]_D^{20}$ -32 ±3 (c 1, $CHCl_3$).

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