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1,2-DIDEOXY-3,4:5,7-BIS-O-(1-METHYLETHYLIDENE)-D-gluco- and D-galacto-HEPT-1-YNITOLS: SYNTHESIS AND CONFORMATIONAL STUDIES.

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Abstract - 1,2-Dideoxy-3,4:5,7-bis-O-(1-methylethylidene)-D-gluco- and D-galacto-hept-1-ynitols were synthesized starting respectively from benzyl α,β-D-glucopyranoside and from benzyl α,β-D-galactopyranoside by bis-acetonidation, hydrogenolysis, Wittig reaction with chloromethylenetriphenylphosphorane, and dehydrohalogenation. The structures of the obtained compounds were confirmed by the NMR spectrocopic data which also allowed to determine the conformations of the molecules.

The construction of complex carbohydrates containing more than six or seven carbon atoms is a present-day challenge to organic chemists due to the wide spreading of structures related to branched-chain or chain-elongated carbohydrates in natural products or in biologically significant synthetic C-analogues of sugars.

As ethynyl group is a versatile functional group useful in the chain-elongation, compounds like glyco-1-ynitols may be suitable intermediates for the synthesis of poly-hydroxylated linear or branched carbohydrate-like compounds. In fact, when transformed into the corresponding acetylides, these ynitols can be coupled with a variety of electrophyles such as epoxides,[1] carbonyl compounds,[2] halides,[3] etc.

The known syntheses[4] of glyco-1-ynitols involve the addition of acetylene to a sugar aldehyde in the hemiacetalic form, *i.e.* a $C_n + C_2$ process (scheme 1, via a). This approach, however, presents the drawback that the C_{n+2} 1-ynitols are obtained as diastereoisomeric mixtures, of various compositions, at the newly formed C-3 stereogenic centre. Our approach, a $C_n + C_1$ process (scheme 1, via b) in which a C_1 fragment is added to a C_n sugar, overcomes such disvantage as all the stereocentres are pre-existing in the starting sugar. This procedure is therefore of choice; in fact only one stereoisomer is obtained and the often difficult problem of separating a diastereoisomeric mixture is avoided. According to this approach this paper describes the synthesis of 1,2-dideoxy-3,4:5,7-bis-O-(1-methylethylidene)-D-gluco- and -D-galacto-hept-1-ynitols 1a and 1b. The scheme 2 reports the synthetic pathways.

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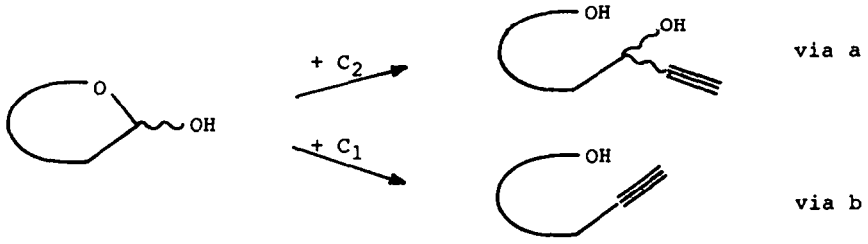


Scheme 1

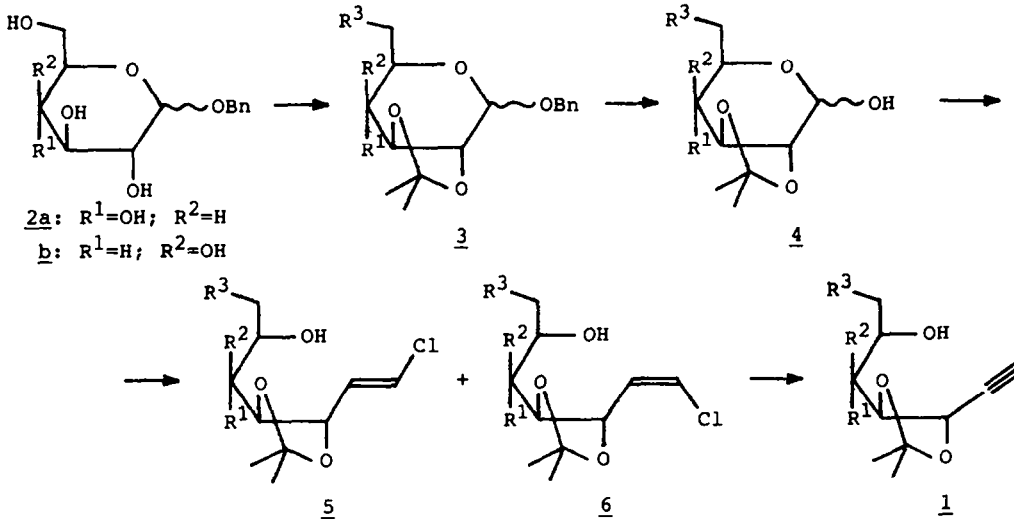
Acetonidation of benzyl α,β-D-glucopyranoside[5] 2a and benzyl α,β-D-galacto-pyranoside[6] 2b was effected in the kinetic conditions of Debost et al.[7] yielding respectively the bis-acetonides 3a and 3b in high yields as mixtures of α- and β-anomers. As the stereochemistry of the anomeric centre had to be destroyed in the following step we utilized the obtained anomeric mixtures of the benzyl glycosides without separation.

The deblocking of the anomeric position was achieved by hydrogenolysis in ethyl alcohol carried out in the presence of triethylamine to avoid solvolysis of the isopropylidene protections with consequent full deprotection of the sugars. The reaction time was different in the two cases: in fact, while benzyl glucoside 3a could be de-benzylated to 4a in few hours monitoring carefully the reaction in order to prevent further reduction to a glucitol, de-benzylation of 3b to 4b needed about 48 hours to be completed.

The Wittig reaction of 4 with chloromethylenetriphenylphosphorane yielded in both cases a 1:1 mixture of the E/Z chlorovinyl derivatives 5 and 6.

Dehydrohalogenation of these ethylenic compounds with n-butyl-lithium at -78°C eventually furnished the desired heptynitols 1a and 1b in good yields.

The structures of the compounds 1 were fully confirmed by the spectroscopic



a: R^1, R^3=O-C$(CH_3)_2$-O; R^2=H b: R^1=H; R^2, R^3=O-C$(CH_3)_2$-O

Scheme 2

Table 1. ^{1}H- and ^{13}C-NMR data of compounds 1a and 1b.

compd	H-1	H-3	H-4	H-5	H-6	H-7a	H-7b	OH	dioxolane methyls		dioxane methyls	
	^{1}H chemical shifts (ppm)											
1a¶	2.52	4.74	4.36	3.75	3.83	3.63	3.91	2.3	1.50	1.42	1.46	1.38
1b	2.51	4.59	4.34	3.70	3.60	3.84	4.05	2.64	1.54	1.41	1.44	1.42

compd	$J_{1,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{6,7a}$	$J_{6,7b}$	$J_{7a,7b}$	$J_{6,OH}$
	^{1}H coupling constants (Hz)							
1a¶	2.0	7.5	3.5	9.5	9.0	5.5	12.0	-
1b	2.5	4.5	8.5	1.5	2.5	2.0	12.5	11.0

compd	C-1	C-2	C-3	C-4	C-5	C-6	C-7	dioxolane			dioxane		
								C	Me	Me	C	Me	Me
	^{13}C chemical shifts (ppm)												
1a	74.6	81.2	65.7	80.8	71.8	63.6	64.3	110.9	26.1	26.3	99.1	19.5	27.9
1b	74.0	82.5	68.5	79.6	73.6	62.9	65.5	111.4	26.1	27.4	99.1	18.5	29.3

¶A second order multiplet was present in the ^{1}H-NMR spectrum of 1a for the resonances of 5, 6, 7a, and 7b hydrogen atoms; a spin system simulation using the PANIC program of Brüker allowed the determination of the chemical shifts and the coupling constants of all these nuclei.

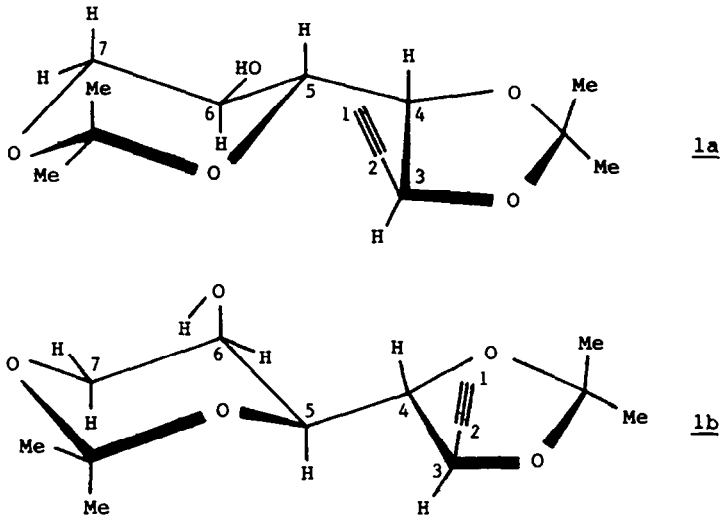
^{1}H- and ^{13}C-NMR data.

Compounds 1a and 1b contain a dioxane ring and a dioxolane ring joined by the C(4)-C(5) bond; the presence and the size of the two rings was confirmed by the ^{13}C chemical shifts of the two acetal carbons (99.1 and 110.9 ppm in 1a; 99.1 and 111.4 ppm in 1b) which are inside the intervals given in the literature[8] for an acetal carbon in a six-membered ring in the chair form (97.1-99.9 ppm) and in a five membered ring (108.1-111.4 ppm).

Each of the four isopropylidene methyl resonances could also be unequivocally assigned either to one of the methyl groups of the dioxolane ring or to one of the methyl groups of the dioxane ring (see table 1), as in the ^{13}C-NMR spectra distinct intervals are given in the literature[8] for an equatorial, for an axial methyl in an isopropylidene six membered ring and for the methyls in a dioxolane five membered ring.

Recently El Ashry described[9] a shift rule for the assignment in the ^{1}H-NMR spectra of the methyl groups of isopropylidenes to α-terminal, α-threo, or α-erythro rings based on the difference in the chemical shifts between the proton resonances of the two methyl groups of the isopropylidenes. Our compounds 1a and 1b, in which an α-threo isopropylidene dioxolane ring is present, show that in the application of this rule care should be payed when substituents with strong magnetic effect, e.g. the ethynyl group, are present.

In fact when 2D-heteronuclear shift correlated spectroscopy experiments were carried out to allow the assignments of the methyl signals also in the ^{1}H-NMR spectra the resonance values of the dioxolane isopropylidene methyl groups were



1a

1b

Figure 1

found at 1.42 and 1.50 ppm for 1a and 1.41 and 1.54 ppm for 1b which corresponded to $\Delta\delta$ values of 0.08 and 0.13 ppm. El Ashry's paper[8] reports that for α-threo isopropylidene derivatives $\Delta\delta$ is 0.05 ppm. Our $\Delta\delta$s fall above the limit of 0.05 ppm, so that El Ashry's rule doesn't apply to this case, probably owing to the strong deshielding effect of the ethynyl substituent on the cis-oriented methyl group.

The analysis of the ^{1}H-NMR spectra allows also to determine some of the conformational features of the compounds 1a and 1b. The coupling constants for the vicinal hydrogen atoms (see table 1) indicate that the molecules 1a and 1b respectively assume the conformation depicted in the figure 1 in which all the interactions between the two rings are at a minimum. In both cases a chair conformation is assumed by the dioxane ring but, in order to let the bulky C-5 substituent be equatorially oriented, the dioxane ring is in the ^5C_O conformation in 1a while the same ring is in the $^OC_5$ conformation in 1b. It follows that the free hydroxyl group is equatorial in 1a and axial in 1b. In the latter compound the hydroxyl hydrogen atom is strongly hydrogen bonded to the 1,3-diaxial lone pairs of the oxygen atoms of the dioxane ring as indicated by its ^{1}H-NMR signal (d, $J_{6,OH}$=11 Hz).

Moreover the two H(4)-H(5) ^{1}H-NMR coupling constants (respectively 3.5 and 8.5 Hz) are justified by a prevalently gauche, for 1a, and anti-periplanar, for 1b, arrangement of these two vicinal hydrogen atoms.

Acknowledgements.

We thank Prof. G. Russo for the helpful discussions and Mr. M. Lovati for the 2D-heterocorrelated NMR experiments.

EXPERIMENTAL

Benzyl 2,3:4,6-bis-O-(1-methylethylidene)-D-glucopyranoside 3a.

An α,β anomeric mixture of benzyl glucopyranoside 2a (2.71 g, 10 mmol) was dissolved in dry N,N-dimethylformamide (DMF) (25 ml) at 0°C and Sikkon (5 g), 2-methoxypropene (3.8 ml, 40 mmol) in dry DMF (10 ml), and p-toluenesulfonic acid (20 mg) were added. The mixture was stirred at 0° for 5 h, then sodium carbonate (1 g) was added. After stirring for 30' at room temperature, the solid was filtered off and the solvent evaporated, the crude product was chromatographed on a silica gel column eluted with hexane-ethyl acetate-triethylamine 80:20:0.1 yielding 3.11 g (89%) of the compound 3a as an oil. $|\alpha|_D^{20}$ +35° (c=1.0, $CHCl_3$). ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 1.40-1.55 (cluster of singlets, 12 H, Me_2C), 3.0-4.2 (m, 6 H, H-2, H-3, H-4, H-5, and H_2-6), 4.63 and 4.75 (ABq, 1.3 H, J 12 Hz, CH_2Ph in the α anomer), 4.69 and 4.89 (ABq, 0.7 H, J 12 Hz, CH_2Ph in the β anomer), 4.76 (d, 0.35 H, J 7.5 Hz, H-1 in the β anomer), 5.22 (d, 0.65 H, J 3 Hz, H-1 in the α anomer), and 7.30 (s, 5 H, Ph). Anal. Calc. for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48. Found: C, 65.02; H, 7.61.

Benzyl 2,3:4,6-bis-O-(1-methylethylidene)-D-galactopyranoside 3b.

Compound 2b (2.17 g, 8.0 mmol) was treated as 2a to give an anomeric mixture of 3b (2.62 g, 93%) as an oil. $|\alpha|_D^{20}$ +33° (c=1.2, $CHCl_3$). ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 1.25-1.50 (cluster of singlets, 12 H, Me_2C), 3.0-4.5 (m, 6 H, H-2, H-3, H-4, H-5, and H_2-6), 4.65 (d, 0.5 H, J 7.5 Hz, H-1 in the β anomer), 4.67 and 4.95 (ABq, 1 H, J 12 Hz, CH_2Ph in the β anomer), 4.70 (s, 1 H, CH_2Ph in the α anomer), 5.37 (d, 0.5 H, J 2.5 Hz, H-1 in the α anomer), and 7.30 (s, 5 H, Ph). Anal. Calc. for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48. Found: C, 64.98; H, 7.32.

2,3:4,6-Bis-O-(1-methylethylidene)-D-glucopyranose 4a.

Compound 3a (2.45 g, 7.0 mmol) was added to a suspension of 140 mg of 10% Pd/C in 100 ml of ethanol plus 1 ml of triethylamine and stirred under hydrogen atmosphere until 1 mol equivalent of H_2 was absorbed (about 6 hours). The catalyst was filtered off and the filtrate was evaporated under reduced pressure to yield compound 4a (1.51 g, 83%) as a glass. $|\alpha|_D^{20}$ -34° (c=1.6, $CHCl_3$). ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 1.3-1.5 (cluster of singlets, 12 H, Me_2C), 3.4-5.0 (m, 7 H), and 9.77 (d, 0.10 H, J 1.5 Hz, CHO). Anal. Calc. for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74. Found: C, 55.21; H, 7.54.

2,3:4,6-Bis-O-(1-methylethylidene)-D-galactopyranose 4b.

Compound 3b (2.24 g, 6.4 mmol) was hydrogenated as 3a for 48 h to yield compound 4b (1.24 g, 75%) as a glass. $|\alpha|_D^{20}$ -8° (c=2.0, $CHCl_3$). ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 1.3-1.5 (cluster of singlets, 12 H, Me_2C), 3.4-5.1 (m, 7 H), and 9.65 (bs, 0.15 H, CHO). Anal. Calc. for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74. Found: C, 54.98; H, 7.66.

E And Z 1,2-dideoxy-1-chloro-3,4:5,7-bis-O-(1-methylethylidene)-D-gluco-hept-1-enitols 5a and 6a.

To a suspension of chloromethylenetriphenylphosphonyl iodide (3.16 g, 7.2 mmol) in 8 ml of dry tetrahydrofuran (THF) under nitrogen atmosphere, 4.5 ml of 1.6 M n-butyl-lithium in hexane were dropwise added. To the obtained dark red solution 1.26 ml of hexamethylphosphoramide (7.2 mmol) were added, followed by a solution of compound 4a (470 mg, 1.8 mmol) in 8 ml of dry THF. The reaction was completed in 1.5 h; a saturated aqueous solution of NH_4Cl (100 ml) was then added and the mixture was extracted with methylene chloride. After drying and evaporation under reduced pressure a crude product was obtained which was chromatographed on a silica gel column eluted with hexane-ethyl acetate-triethylamine 70:30:0.1 to yield 132 mg of the higher R_f compound 5a and 130 mg of the lower R_f compound 6a (50% overall yield). Compound 5a: oil. $|\alpha|_D^{20}$ -55° (c=1.0, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.37, 1.42, 1.43, and 1.45 (12 H, 4 s, Me), 2.5 (1 H, m, OH), 3.61 (1 H, dd, $J_{7a,7b}$ 13 and $J_{6,7a}$ 10.5 Hz, H-7a), 3.77 (1 H, dd, $J_{4,5}$ 3.5 and $J_{5,6}$ 9 Hz, H-5), 3.8-4.0 (2 H, m, H-6 and H-7b), 4.04 (1 H, dd, $J_{3,4}$ 8 Hz, H-4), 4.57 (1 H, ddd, $J_{1,3}$ 1 and $J_{2,3}$ 6.5 Hz, H-3), 5.95 (1 H, dd, $J_{1,2}$ 13.5 Hz, H-2), and 6.30 (1 H, dd, H-1). Anal. Calc. for $C_{13}H_{21}O_5Cl$: C, 53.34; H, 7.23. Found: C, 53.19; H, 7.40. Compound 6a: m.p. 95°C (hexane). $|\alpha|_D^{20}$ -3° (c=3.0, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.40, 1.44, 1.44, and 1.46 (12 H, 4 s, Me), 2.0 (1 H, m, OH), 3.62 (1 H, dd, $J_{7a,7b}$ 13 and $J_{6,7a}$ 10.5 Hz, H-7a), 3.68 (1 H, dd, $J_{4,5}$ 2.5 and $J_{5,6}$ 8.5 Hz, H-5), 3.85-4.0 (2 H, m, H-6 and H-7b), 4.06 (1 H, dd,

$J_{3,4}$ 8.5 Hz, H-4), 5.17 (1 H, ddd, $J_{1,3}$ 0.5 and $J_{2,3}$ 8.5 Hz, H-3), 5.84 (1 H, dd, $J_{1,2}$ 7.5 Hz, H-2) and 6.24 (1 H, dd, H-1). Anal. Calc. for $C_{13}H_{21}O_5Cl$: C, 53.34; H, 7.23. Found: C, 53.48; H, 7.35.

E And Z 1,2-dideoxy-1-chloro-3,4:5,7-bis-O-(1-methylethylidene)-D-galacto-hept-1-enitols 5b and 6b.

Compound 4b (416 mg, 1.6 mmol) was submitted to chlorovinylation with the same procedure as 4a. The crude product was chromatographed with a silica gel column eluted with benzene-ethyl acetate-triethylamine 80:20:0.1 to yield 161 mg of the higher R_f compound 5b and 165 mg of the lower R_f compound 6b (70 % overall yield). Compound 5b: oil. $|\alpha|_D^{20}$ -14° (c=1.2, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.40, 1.40, 1.40, and 1.45 (12 H, 4 s, Me), 2.61 (1 H, d, $J_{6,OH}$ 11 Hz, OH), 3.59 (1 H, dddd, $J_{5,6}$ 1.5, $J_{6,7a}$ 2, and $J_{6,7b}$ 1.5 Hz, H-6), 3.80 (1 H, dd, $J_{4,5}$ 8 Hz, H-5), 3.84 (1 H, dd, $J_{7a,7b}$ 12.5 Hz, H-7a), 3.96 (1 H, dd, $J_{3,4}$ 7.5 Hz, H-4), 4.07 (1 H, dd, H-7b), 4.31 (1 H, ddd, $J_{1,3}$ 1 and $J_{2,3}$ 5.5 Hz, H-3), 5.98 (1 H, dd, $J_{1,2}$ 13.5 Hz, H-2), and 6.27 (1 H, dd, H-1). Anal. Calc. for $C_{13}H_{21}O_5Cl$: C, 53.34; H, 7.23. Found: C, 53.40; H, 7.30. Compound 6b: oil. $|\alpha|_D^{20}$ +38° (c=1.8, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.36, 1.42, 1.42, and 1.46 (12 H, 4 s, Me), 2.67 (1 H, d, $J_{6,OH}$ 11 Hz, OH), 3.62 (1 H, dddd, $J_{5,6}$ 1.5, $J_{6,7a}$ 2, and $J_{6,7b}$ 1.5 Hz, H-6), 3.86 (1 H, dd, $J_{4,5}$ 8.5 Hz, H-5), 3.84 (1 H, dd, $J_{7a,7b}$ 12.5 Hz, H-7a), 3.96 (1 H, dd, $J_{3,4}$ 7.5 Hz, H-4), 4.07 (1 H, dd, H-7b), 4.85 (1 H, ddd, $J_{1,3}$ 1, and $J_{2,3}$ 9 Hz, H-3), 5.81 (1 H, dd, $J_{1,2}$ 7.5 Hz, H-2), and 6.20 (1 H, dd, H-1). Anal. Calc. for $C_{13}H_{21}O_5Cl$: C, 53.34; H, 7.23. Found: C, 53.01; H, 7.08.

1,2-Dideoxy-3,4:5,7-bis-O-(1-methylethylidene)-D-gluco-hept-1-ynitol 1a.

Both compound 5a and compound 6a can be dehydrohalogenated by treatment of a THF solution (2 ml/1 mmol) at -78°C under nitrogen atmosphere with 4 mol eq of 1.6 M n-butyl-lithium in hexane for 1 h followed by quenching with saturated aqueous NH_4Cl and extraction with methylene chloride, drying, and evaporation. The yield of compound 1a was about 90%. Compound 1a: oil. $|\alpha|_D^{20}$ -49° (c=1.6, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$) and ^{13}C-NMR (50.3 MHz, $CDCl_3$): see table 1. Anal. Calc. for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.70; H, 7.98.

1,2-Dideoxy-3,4:5,7-bis-O-(1-methylethylidene)-D-galacto-hept-1-ynitol 1b.

Compounds 5b and 6b gave 1b with the above procedure (90 %). Compound 1b: m.p. 112°C (hexane). $|\alpha|_D^{20}$ -46° (c=1.6, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$) and ^{13}C-NMR (50.3 MHz, $CDCl_3$): see table 1. Anal. Calc. for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.62; H, 7.73.

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