Gram-Scale Quaternarization of the Anomeric Position of Carbohydrates: Dramatic Effects of Molecular Sieves on Rhodium(II)-Mediated Decomposition of Diazo Sugars

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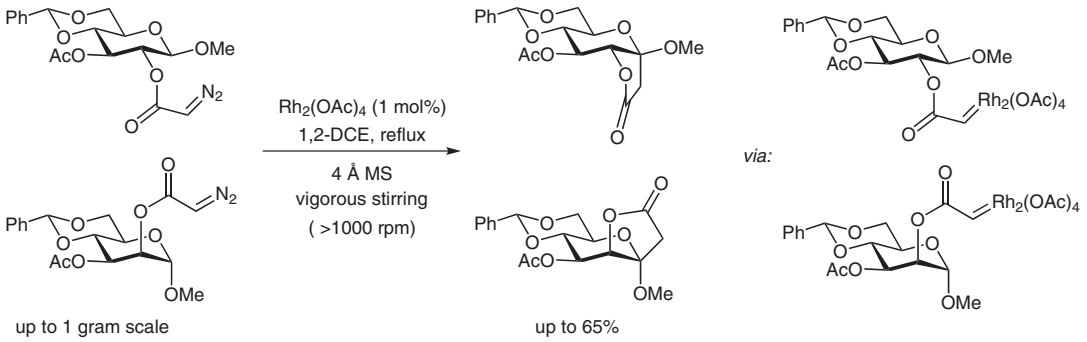
Received: 21.05.2012; Accepted after revision: 10.07.2012

PSP No 239

Abstract: The optimization of rhodium(II) carbene mediated quaternarization of the anomeric position of carbohydrates is reported. Preparation of ketopyranosides in good and reliable yields requires reverse addition of the substrate to a highly diluted suspension of the catalyst in refluxing 1,2-dichloroethane, as well as addition of a carefully controlled amount of molecular sieves, and vigorous stirring. Following these optimized reaction conditions, functionalization of the anomeric position of carbohydrates can finally be performed on a preparative scale.

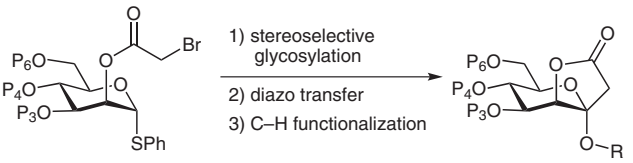
Key words: rhodium, carbenes, molecular sieves, insertion, carbohydrates



Scheme 1 Carbene-mediated functionalization of the anomeric C–H bond of carbohydrates

Introduction

Since the pioneering work of Teyssié and co-workers in early 1970s,[1] rhodium(II) carboxylates and carboxamidates have been widely used to catalyze carbene-mediated transformations.[2] Thus, smooth decomposition of diazo compounds by rhodium(II) salts delivers metal carbenes with finely tuned chemical properties arising from the unique structure and coordinating properties of the catalyst.[3,4] Among carbene-mediated transformations, stereospecific formation of a new C–C bond from an unreactive C–H bond is of particular interest because it opens new ways for planning the synthesis of complex molecules.[5] In this context, we recently reported that insertion of Rh(II) carbenes into the anomeric C–H bond of carbohydrates provides an efficient access toward both α- and β-ketopyranosides.[6] Thus, after stereoselective formation of a glycosidic linkage by anchimeric assistance, a key bromoacetate at position 2 was converted into a diazo acetate. This carbene precursor then induced quaternarization of the anomeric position in a late stage of the synthetic process (Scheme 2). This preliminary study revealed that slow addition of the substrate to a highly diluted suspension of the catalyst in refluxing 1,2-dichloroethane was critical to prevent carbene dimerization.



Scheme 2 Preparation of ketopyranosides by functionalization of the anomeric C–H bond

However, adaptation of this procedure to the large-scale preparation of ketopyranosides might be tricky, and we therefore undertook studies on new model compounds in order to identify reaction conditions enabling quater-

SYNTHESIS 2012, 44, 3731–3734
Advanced online publication: 29.08.2012
DOI: 10.1055/s-0032-1317013; Art ID: SS-2012-T0456-PSP

narization of carbohydrates on a preparative scale (Scheme 1).

Scope and Limitations

Carbene precursor **1** was first prepared after adaptation of a bromoacetylation/diazo transfer sequence recently reported by Fukuyama.[7,8] Decomposition of **1** under $Rh_2(OAc)_4$ catalysis was then performed on a 0.1 mmol scale. Thus, at a sub-millimolar concentration (Table 1, entry 1) the targeted γ-lactone **2** was obtained only in low yield together with large amounts of dimer **3**. As expected, decreasing catalyst loading and concentration diminished this intermolecular side reaction (entry 2). Nevertheless, further dilution delivered **2** in poor yield because of competitive formation of **4** (Figure 1) by insertion of the reactive moiety into water (entry 3).

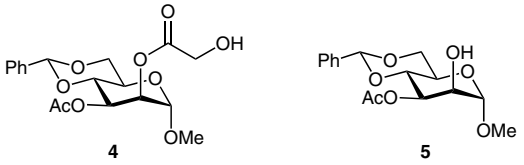
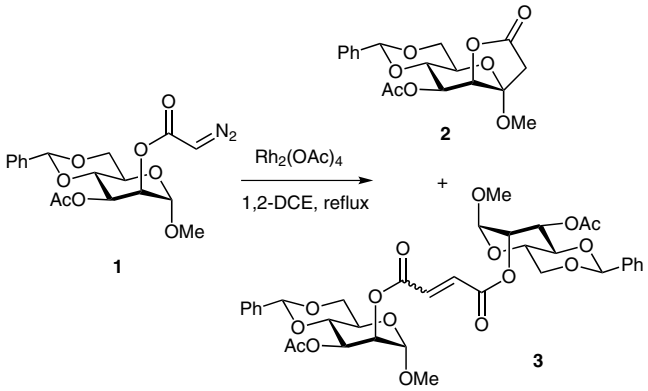


Figure 1 By-products arising from the decomposition of **1**

Table 1 Catalytic Decomposition of α-Mannoside **1**



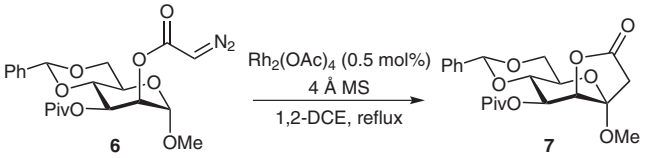
Entry	$Rh_2(OAc)_4$ (mol%, concn)	Rate (μmol/h)	4 Å MS	Yield (%) of **2**	Yield (%) of **3**
1[a]	5, 0.8 mM	40	no	43[b]	42[b]
2[a]	2, 0.16 mM	40	no	64[b]	11[b]
3[c]	2, 0.08 mM	12	no	30[b]	0
4[d]	2, 0.08 mM	12	no	45[b]	0
5[e]	2, 0.08 mM	12	yes	90[f]	0

[a] 1,2-Dichloroethane freshly distilled over P_2O_5.
[b] Evaluated by ^1H NMR of the crude product.
[c] Additional 55% of **4** from insertion into water.
[d] 1,2-dichloroethane freshly distilled twice over P_2O_5.
[e] Commercially available anhydrous 1,2-dichloroethane.
[f] After purification by chromatography.

More careful distillation of the solvent (twice over P_2O_5) did not improve the yield of γ-lactone **2** (entry 4), but addition of 4 Å molecular sieves[9] finally fully prevented this side reaction, even when simply using commercially available anhydrous 1,2-dichloroethane (entry 5). However, while increasing the scale to one mmol under these newly optimized conditions, **2** could only be obtained in moderate yield. Careful analysis of the crude product showed some recovered starting material,[10] together with alcohol **5** (Figure 1) that might result from degradation of a transient oxonium ylide.[11]

Suspecting that partial conversion of the substrate and formation of **5** might have been induced by the additive, we then moved back to 3-*O*-pivalate compound **6**, a substrate that was already quaternarized in good yield on a 0.5 mmol scale in the absence of molecular sieves (Table 2, entry 1).[6] The influence of the amount of additive was evaluated first, a parameter that we did not carefully control until then, on the outcome of the transformation. Thus, decomposition of **6** with 0.5 mol% of catalyst was complete with up to 10 grams of molecular sieves per milligram of catalyst, but dramatically decreased at higher ratio (Table 2, entries 2–6). Moreover, additional stirring of the substrate over molecular sieves before its reverse addition to a suspension of the catalyst and drying agent resulted in moderate to low conversion (entries 7 and 8), whereas using powder instead of mesh (entries 9 and 10) had no visible effect.

Table 2 Influence of Molecular Sieves on the Decomposition of **6**

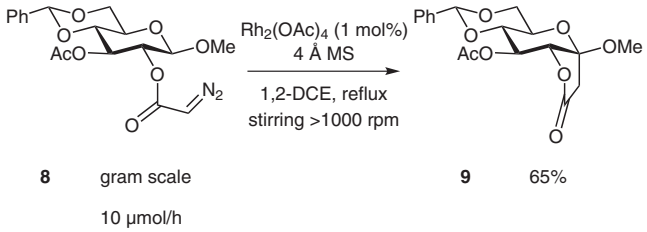


Entry	4 Å MS	MS/$Rh_2(OAc)_4$	Conv. (%)[a]	Yield (%)
1[6]	no	–	100	77[b]
2	8–12 mesh	1 g/mg	100	15–70[a]
3	8–12 mesh	3	100	62[a]
4	8–12 mesh	10	100	45[a]
5	8–12 mesh	20	70	53[a]
6	8–12 mesh	40	50	21[a]
7[c]	8–12 mesh	3	80	63[a]
8[c]	8–12 mesh	20	40	15[a]
9	powder	1	100	65[a]
10	powder	3	100	59[a]

[a] Evaluated by ^1H NMR of the crude product.
[b] After purification by chromatography.
[c] Substrate dried over 4 Å MS before the reaction.

However, even if full conversion of diazo sugar **6** could always be ensured at low molecular sieves/catalyst ratio, the yield of γ-lactone **7** was dramatically nonreproducible (Table 2, entry 2) because of the erratic formation of a by-product related to **5**. Suspecting that this side reaction might be due to the high heterogeneity of the reaction mixture, we became very careful at controlling the stirring, and were very pleased to see that **7** could be obtained in reproducible yield when the reaction mixture was placed under vigorous stirring (>1000 rpm).

Having a better understanding of the effects of molecular sieves on this quaternarization process, the decomposition of diazo sugar **1** was finally conducted on a one mmol scale in 52% yield. Moreover, the carbene precursor **8** in the β-gluco series was also prepared and functionalization of its axial anomeric C–H bond on a gram-scale in 65% yield was performed (Scheme 3).



Scheme 3 Gram-scale decomposition of **8**

Conclusion

In summary, we have shown that molecular sieves have a dramatic effect on carbene-mediated functionalization of the anomeric C–H bond of carbohydrates. Thus, the amount of additive must be carefully controlled, and the reaction mixture must be placed under vigorous stirring in order to prevent partial conversion of the substrate and loss of the reactive moiety. After optimization of the reaction conditions, decomposition of diazo sugars was finally performed on a gram-scale in the presence of 1 mol% of catalyst using commercially available anhydrous solvent. Functionalization of the anomeric C–H bond of carbohydrates on preparative scale now opens the way to the design and preparation of new chemical tools for glycobiology.[12]

Optical rotations were measured at 20 °C with a Perkin-Elmer Model 341 polarimeter, in a 10 cm, 1 mL cell. IR spectra were recorded with a Nicolet 510 FT-IR spectrometer. Mass spectrometry spectra were recorded on a Waters ZQ 2000 spectrometer. High-resolution mass spectra were recorded on a Bruker MicrO-Tof-Q 2 spectrometer at CRMPO (Rennes, France). ^{1}H NMR spectra were recorded at 300 MHz with a Bruker Avance 300 spectrometer. ^{13}C NMR spectra were recorded at 75 MHz with a Bruker Avance 300 spectrometer with adoption of 77.00 ppm for the central line of $CDCl_3$. The relaxation delay (D1) was increased to 60 seconds for ^{13}C NMR spectra of diazo sugars. Reactions were monitored by TLC on a precoated silica gel 60 F_{254} plate (layer thickness 0.2 mm; E. Merck, Darmstadt, Germany) and detection by charring phosphomolybdic acid. Flash column chromatography was performed on silica gel 60 (230–400 mesh, E. Merck). Anhyd 1,2-dichloroethane and CH_2Cl_2 were purchased from Sigma-Aldrich. THF was distilled over sodium/benzophenone. All reactions were conducted under an argon atmosphere in flame-dried glassware. $Rh_2(OAc)_4$, was purchased from Sigma-Aldrich, and Deloxan® was purchased from Strem Chemicals.

Methyl 3-*O*-Acetyl-4,6-*O*-benzylidene-2-*O*-diazoacetyl-α-D-mannopyranoside (1)

To a solution of methyl 3-*O*-acetyl-4,6-*O*-benzylidene-α-D-mannopyranoside (1.06 g, 2.380 mmol) and pyridine (0.77 mL, 9.496 mmol) in anhyd CH_2Cl_2 (30 mL) at 0 °C was added bromoacetyl bromide (0.41 mL, 4.748 mmol). After stirring for 2 h at 0 °C, the reaction mixture was quenched with MeOH (3 mL), while TLC (cyclohexane–EtOAc, 1:1) showed complete consumption of the starting material, and aq 1 M HCl (20 mL) was added. After extractions with CH_2Cl_2 (3 × 20 mL), the combined organic layers were dried ($MgSO_4$), filtered, and concentrated under vacuum. To a solution of the residue and *N*,*N*′-ditosylhydrazine (1.62 g, 4.760 mmol) in distilled THF (35 mL) at 0 °C was added DBU (1.78 mL, 11.900 mmol). After TLC analysis (cyclohexane–EtOAc, 3:1) showed complete consumption of the starting material, sat. aq $NaHCO_3$ (30 mL) and EtOAc (30 mL) were added. The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (cyclohexane–EtOAc, 3:1) to give the diazo sugar **1** as a bright yellow foam (660 mg, 71%); $[\alpha]_D^{20}$ –25.2 (*c* = 1.0, $CHCl_3$).

IR (film): 2116, 1746, 1698, 1457, 1384, 1370, 1283, 1229, 1175, 1133, 1097, 1077, 1029 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.28 (m, 5 H_{arom}), 5.58 (s, 1 H, H-7), 5.46–5.31 (m, 2 H, H-2, H-3), 4.91 (br s, 1 H, H-8), 4.72 (s, 1 H, H-1), 4.30 (dd, *J* = 10.0, 4.0 Hz, 1 H, H-6$_{eq}$), 4.06–3.91 (m, 2 H, H-4, H-5), 3.90–3.79 (m, 1 H, H-6$_{ax}$), 3.42 (s, 3 H, OCH_3), 2.05 (s, 3 H, CH_3C=O).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9 (C=O), 165.9 (C=O), 137.0 (C_{arom}), 129.1 (CH_{arom}), 128.2 (CH_{arom}), 126.1 (CH_{arom}), 101.9 (C-7), 99.5 (C-1), 76.0 (C-4), 70.2 (C-2), 68.7 (C-6), 68.3 (C-3), 63.6 (C-5), 55.2 (OCH_3), 46.5 (C-8), 20.8 (CH_3C=O).

MS (ESI): *m*/*z* = 415 (MNa^+).

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{20}N_2O_8$ + Na: 415.1117; found: 415.1115.

(2*R*,4*aR*,5*aS*,8*aS*,9*S*,9*aR*)-5a-Methoxy-7-oxo-2-phenyloctahydrofuro[2′,3′:5,6]pyrano[3,2-*d*][1,3]dioxin-9-yl Acetate (2)

A suspension of $Rh_2(OAc)_4$ (5.7 mg, 12.970 μmol) in commercially available anhyd 1,2-dichloroethane (200 mL) was stirred for 1 h at r.t. with activated 4 Å molecular sieves (8 to 12 mesh, 6 g). A solution of **1** (510 mg, 1.297 mmol) in the same solvent (10 mL) was then added dropwise via a syringe pump (10 μmol/h) to the refluxing reaction mixture under vigorous stirring (>1000 rpm). After the end of the addition, the reaction mixture was stirred for 3 h in the presence of Deloxan®, filtered over Celite, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (cyclohexane–EtOAc, 3:1) to give the γ-lactone **2** (245 mg, 52%) as a colorless oil; $[\alpha]_D^{20}$ –78.4 (*c* = 1.0, $CHCl_3$).

IR (film): 1801, 1741, 1457, 1372, 1306, 1285, 1221, 1183, 1159, 1127, 1096, 1075, 1034, 1004 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53–7.29 (m, 5 H_{arom}), 5.55 (s, 1 H, H-7), 5.33 (dd, *J* = 9.9, 3.8 Hz, 1 H, H-3), 4.78 (d, *J* = 3.8 Hz, 1 H, H-2), 4.30 (dd, *J* = 10.0, 4.6 Hz, 1 H, H-6$_{eq}$), 4.02 (t, *J* = 9.9 Hz, 1 H, H-4), 3.95–3.74 (m, 2 H, H-5, H-6$_{ax}$), 3.38 (s, 3 H, OCH_3), 2.82 (d, *J* = 16.4 Hz, 1 H, H-8), 2.70 (d, *J* = 16.4 Hz, 1 H, H-8′), 2.13 (s, 3 H, CH_3C=O).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.3 (C=O), 170.3 (C=O), 136.7 (C_{arom}), 129.2 (CH_{arom}), 128.2 (CH_{arom}), 126.1 (CH_{arom}), 103.5 (C-1), 101.8 (C-7), 78.6 (C-2), 74.5 (C-4), 68.4 (C-3), 68.1 (C-6), 64.4 (C-5), 51.8 (OCH_3), 40.1 (C-8), 20.8 (CH_3C=O).

MS (ESI): m/z = 387 (MNa^+).

HRMS (ESI): m/z calcd for $C_{18}H_{20}O_8$ + Na: 387.1056; found: 387.1058.

Methyl 3-*O*-Acetyl-4,6-*O*-benzylidene-2-*O*-diazoacetyl-β-D-glucopyranoside (8)

To a solution of methyl 3-*O*-acetyl-4,6-*O*-benzylidene-β-D-glucopyranoside (4.09 g, 12.611 mmol) and pyridine (2.56 mL, 31.528 mmol) in anhyd CH_2Cl_2 (150 mL) at 0 °C was added bromoacetyl bromide (2.2 mL, 25.222 mmol). After stirring for 2 h at 0 °C, the reaction mixture was quenched with MeOH (1 mL), while TLC (cyclohexane–EtOAc, 1:1) showed complete consumption of the starting material, and a solution of aq 1 M HCl (50 mL) was added. After extractions with CH_2Cl_2 (3 × 70 mL), the combined organic layers were dried ($MgSO_4$), filtered, and concentrated under vacuum. To a solution of the residue and *N*,*N*′-ditosylhydrazine (8.6 g, 25.200 mmol) in distilled THF (350 mL) at 0 °C was added DBU (9.43 mL, 63.0 mmol). After TLC analysis (cyclohexane–EtOAc, 3:1) showed complete consumption of the starting material, sat. aq $NaHCO_3$ (50 mL) and EtOAc (50 mL) were added. The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (cyclohexane–EtOAc, 3:1) to give the diazo sugar **8** as a bright yellow foam (4.43 g, 90%); $[\alpha]_D^{20}$ –53.3 (c = 1.0, $CHCl_3$).

IR (film): 2114, 1744, 1699, 1453, 1380, 1227, 1174, 1155, 1089, 1062, 1041, 1030, 1010 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.29 (m, 5 H_{arom}), 5.52 (s, 1 H, H-7), 5.34 (t, J = 9.4 Hz, 1 H, H-3), 5.06 (t, J = 9.4 Hz, 1 H, H-2), 4.80 (br s, 1 H, H-8), 4.51 (d, J = 9.4 Hz, 1 H, H-1), 4.39 (dd, J = 10.4, 4.8 Hz, 1 H, H-6_{eq}), 3.82 (t, J = 10.4 Hz, 1 H, H-6_{ax}), 3.71 (t, J = 9.4 Hz, 1 H, H-4), 3.59–3.47 (m, 4 H, OCH_3, H-5), 2.08 (s, 3 H, CH_3C=O).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1 (C=O), 136.7 (C_{arom}), 129.1 (CH_{arom}), 128.2 (CH_{arom}), 126.1 (CH_{arom}), 102.3 (C-1), 101.4 (C-7), 78.3 (C-4), 72.4 (C-2), 71.6 (C-3), 68.5 (C-6), 66.3 (C-5), 57.3 (OCH_3), 46.4 (C-8), 20.8 (CH_3C=O).

MS (ESI): m/z = 415 (MNa^+).

HRMS (ESI): m/z calcd for $C_{18}H_{20}N_2O_8$ + Na: 415.1117; found: 415.1112.

(2*R*,4*aR*,5*aR*,8*aR*,9*S*,9*aR*)-5a-Methoxy-7-oxo-2-phenyloctahydrofuro[2′,3′:5,6]pyrano[3,2-*d*][1,3]dioxin-9-yl Acetate (9)

A suspension of $Rh_2(OAc)_4$ (11 mg, 25 μmol) in commercially available anhyd 1,2-dichloroethane (300 mL) was stirred for 1 h at r.t. with activated 4 Å molecular sieves (8 to 12 mesh, 11 g). A solution of **8** (1.010 g, 2.58 mmol) in the same solvent (20 mL) was then added dropwise via a syringe pump (10 μmol/h) to the refluxing reaction mixture under vigorous stirring (>1000 rpm). After the end of the addition, the reaction mixture was stirred for 3 h in the presence of Deloxan®, filtered over Celite, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give the γ-lactone **9** (615 mg, 65%) as a colorless oil; $[\alpha]_D^{20}$ +6.1 (c = 1.0, $CHCl_3$).

IR (film): 1797, 1755, 1371, 1226, 1178, 1081, 1036 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.33 (m, 5 H_{arom}), 5.54 (s, 1 H, H-7), 5.30 (dd, J = 10.2, 5.8 Hz, 1 H, H-3), 4.45 (d, J = 5.8 Hz, 1 H, H-2), 4.37 (d, J = 5.8 Hz, 1 H, H-6), 3.95 (td, J = 10.2, 1.7 Hz, 1 H, H-4), 3.83–3.71 (m, 2 H, H-5, H-6), 3.41 (s, 3 H, OCH_3), 2.91 (d, J = 17.1 Hz, 1 H, H-8), 2.69 (d, J = 17.1 Hz, 1 H, H-8′), 2.13 (s, 3 H, CH_3C=O).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.8 (C=O), 169.5 (C=O), 136.5 (C_{arom}), 129.3 (CH_{arom}), 128.3 (CH_{arom}), 126.1 (CH_{arom}), 103.7 (C-1), 101.7 (C-7), 81.9 (C-2), 75.8 (C-4), 72.0 (C-3), 68.8 (C-6), 66.3 (C-5), 50.7 (OCH_3), 36.6 (C-8), 20.8 (CH_3C=O).

MS (ESI): m/z = 387 (MNa^+).

HRMS (ESI): m/z calcd for $C_{18}H_{20}O_8$ + Na: 387.1056; found: 387.1057.

Acknowledgment

Financial support of this work by CNRS (Research Fellowship to T.L.) and University Paris Descartes (MESR grant to M.B.A.) is gratefully acknowledged.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are ^1H and ^{13}C NMR spectra for compounds **1**, **2**, **4**, **8**, and **9**.

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