[26] G. A. Jeffrey in *Landolt-Börnstein Series, Vol. VII:1b* (Ed.: W. Saenger), Springer, Berlin, **1989**, pp. 277–348.
[27] F. Takusagawa, A. Shimada, *Acta Crystallogr. Sect. B* **1976**, *32*, 1925–1927.
[28] G. R. Desiraju, *Acc. Chem. Res.* **1996**, *29*, 441.
[29] This is believed to be the reason for the closer proximity of C–H ⋯ O with the β-pyridyl H-atom instead of the α-pyridyl H-atom, which could be expected for an unrestricted arrangement on an ideally flat surface. Calculations are currently being performed to elucidate the nature of the molecular interactions in more detail.
[30] J. V. Barth, H. Brune, R. J. Behm, G. Ertl, *Phys. Rev. B* **1990**, *42*, 9307–9318.
[31] K. Kern, H. Niehus, A. Schatz, P. Zeppenfeld, J. George, G. Comsa, *Phys. Rev. Lett.* **1991**, *67*, 855–858.
[32] D. Vanderbilt, *Surf. Sci.* **1992**, *268*, L300–L304.
[33] A. de Vita, J. Weckesser, J. V. Barth, K. Kern, unpublished results.

Ring-Closing Alkyne Metathesis: Application to the Stereoselective Total Synthesis of Prostaglandin E_2-1,15-Lactone[**]

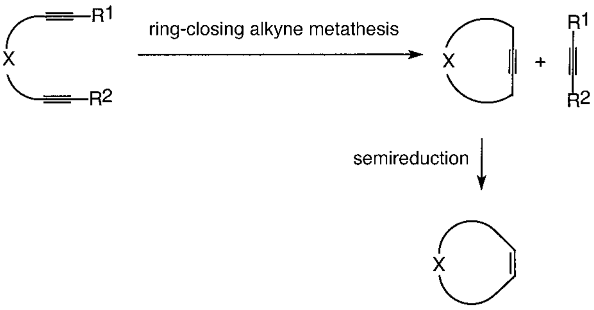
Alois Fürstner[*] and Karol Grela

Dedicated to Professor Günther Wilke on the occasion of his 75th birthday

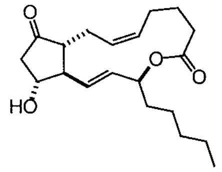
Among the few limitations that infringe upon the superb overall application profile of ring-closing olefin metathesis (RCM), the lack of control over the configuration of the newly formed double bond constitutes a significant handicap when applied to the macrocyclic series.[1] The cycloalkenes formed are usually obtained as mixtures of the *E* and *Z* isomers, with the *E* isomers dominating in most of the recorded examples.[1, 2] This constitutes a significant drawback in many natural product syntheses as can be clearly seen, for example, from the epothilone case.[3]

To circumvent this inherent problem, we have recently proposed an indirect but stereoselective approach to macrocyclic *Z* alkenes which comprises a ring-closing metathesis reaction of diyne substrates followed by semireduction of the resulting cycloalkyne products (Scheme 1).[4] Schrock-type tungsten alkylidyne complexes such as $[W(\equiv CCMe_3)(OtBu)_3]$[5] as well as a newly discovered molybdenum chloride species formed in situ from $[Mo\{N(tBu)(Ar)\}_3]$ and CH_2Cl_2[6, 7] were found to be efficient precatalysts for this unprecedented type of ring-forming reaction.[8] In terms of functional group compatibility, these initiator systems exhibit complementary behavior.

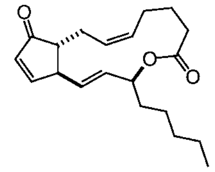
To gain a better understanding of the relevance and scope of this conceptually new approach, we were prompted to extend our studies beyond model compounds and to venture into the total synthesis of biologically significant and structurally more demanding targets. We felt that prostaglandin lactones such as **1**–**3**, a rather unique class of natural products isolated from the nudibranch *Tethys fimbria*,[9, 10] would provide an ideal testing ground in this respect.



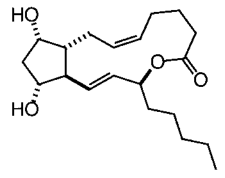
Scheme 1. Stereoselective synthesis of macrocyclic *Z* alkenes by ring-closing alkyne metathesis and subsequent semireduction.



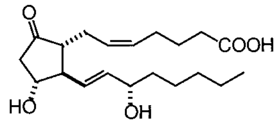
PGE$_2$-1,15-lactone (**1**)



PGA$_2$-1,15-lactone (**2**)



PGF$_2$-1,15-lactone (**3**)



PGE$_2$ (**4**)

PGE$_2$-1,15-lactone **1** as a prototype member of this family exerts strong biological effects in vitro and in vivo, including a significant decrease of gastric secretion when administered intravenously in dogs (90 % at a dose of 100 $\mu g\,kg^{-1}$)[10c] as well as ichthyotoxic properties at 1–10 $\mu g\,mL^{-1}$ concentrations.[9] Furthermore, **1** is readily hydrolyzed into parent prostaglandin E$_2$ **4** by various esterases and therefore constitutes an attractive prodrug for this physiologically highly active metabolite.[10c, 11] In view of differing enzyme activity distribution in tissue, one may even envisage its sustained and localized release. From the chemical point of view, the instrinsically labile β-hydroxy ketone substructure of all members of the PGE series towards acid as well as base renders lactone **1** a formidable probe for the applicability of the alkyne metathesis/Lindlar reduction strategy to sensitive compounds in general.

The results of our investigations are summarized in Scheme 2. Three-component coupling[12] as the most elegant method for the construction of prostaglandin skeletons accounts for a straighforward formation of the required cyclization precursor **13**. Thus, commercially available prop-

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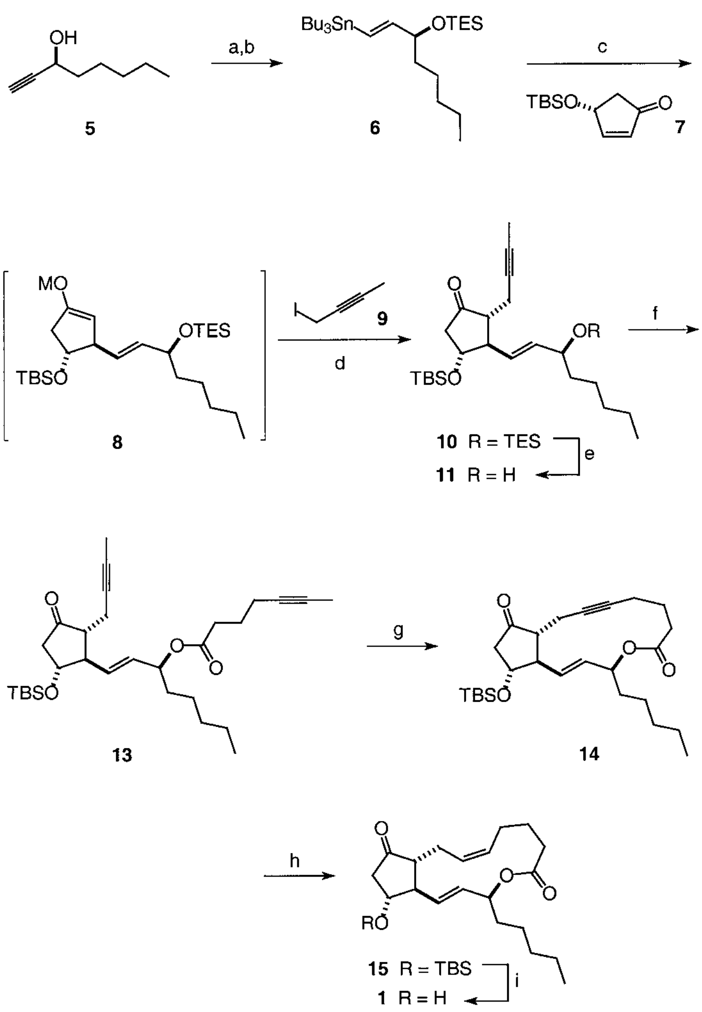

Scheme 2. a) Et_3SiCl, imidazole, DMF, room temperature, 24 h; b) $n\mathrm{Bu_3SnH}$, azoisobutyronitrile (AIBN; cat.), 130 °C, 2 h, 73 % (over both steps); c) 1.) nBuLi, THF, −78 °C, 1 h; 2.) Me_2Zn, −78 °C → 0 °C, 15 min; 3.) compound **7**, −78 °C, 1 h; d) THF/HMPA, then compound **9**, −78 °C → −40 °C, 19 h; e) HOAc, THF/H_2O, room temperature, 3 h, 74 % (over steps c–e); f) 5-heptynoic acid (**12**), diisopropyl carbodiimide, DMAP cat., CH_2Cl_2, room temperature, 3 h, 94 %; g) [Mo{N(tBu)(Ar)}$_3$] (Ar = 3,5-dimethylphenyl) (7.5 mol %), CH_2Cl_2/toluene, 80 °C, 16 h, 68–73 %; h) H_2 (1 atm), Lindlar catalyst, quinoline cat., hexane, room temperature, 2 h, 86 %; i) aq. HF, MeCN, room temperature, 1 h, 88 %.

argyl alcohol **5** (*ee* = 98 %) is protected as a triethylsilyl (TES) ether prior to conversion into vinylstannane **6** under free-radical conditions.[13] Tin for lithium exchange on exposure of substrate **6** to nBuLi at low temperature followed by addition of Me_2Zn affords a zincate intermediate which undergoes smooth conjugate addition to the known Michael acceptor **7** (*ee* = 94 %).[14] Enolate **8** thus formed is quenched with propargyl iodide **9**[15] to afford adduct **10**.[16] Selective deprotection of the TES group of the crude material with dilute HOAc in aqueous THF delivers compound **11** in diastereomerically and enantiomerically pure form in 74 % yield over both steps (*ee* ≥ 99 %).[17a] This excellent result reflects the high reactivity of **9** as the electrophile in this three-component assembly. Subsequent esterification of the free OH group of **11** with 5-heptynoic acid (**12**)[15b] in the presence of diisopropyl carbodiimide and catalytic amounts of 4-dimethylaminopyridine (DMAP) readily provides diyne **13** and sets the stage for the crucial macrocyclization by ring-closing alkyne metathesis.

Gratifyingly, this key transformation proceeds very well using the catalyst formed in situ from [Mo{N(tBu)(Ar)}$_3$] (Ar = 3,5-dimethylphenyl) and CH_2Cl_2 in toluene at 80 °C,[6] affording the desired cycloalkyne **14** in 68–73 % yield (four runs).[18] Several aspects are noteworthy: The [Mo{N(tBu)(Ar)}$_3$]-derived catalyst was previously shown to tolerate esters, ethers, silyl ethers, *tert*-amides, thioethers, and pyridine groups,[6] but its reactivity towards ketones was unknown. Since the rather labile aldol substructure of substrate **13** is fully preserved in the product, this example not only extends this list by an additional electrophilic group, but clearly attests to the mildness of the method in general terms. Careful chromatographic inspection of the reaction mixture reveals that no racemization takes place before or after ring closure and the *ee* of the substrate (*ee* = 99 %)[17a] and of the product (*ee* = 98 %)[17b] are also virtually identical. Finally, this example nicely demonstrates that the catalyst rigorously distinguishes between the triple bonds (reactive) and a preexisting double bond (inert) of the substrate.

Standard Lindlar hydrogenation of cycloalkyne **14** followed by deprotection of the residual TBS ether with aqueous HF in acetonitrile[19] completes this total synthesis of the marine natural product prostaglandin E_2-1,15-lactone **1** which is obtained in 28 % yield over the entire eight-step sequence.[20] Its 600 MHz NMR spectra are in full agreement with the data reported in the literature.[9, 21] By virtue of the known enzymatic hydrolysis of this compound into prostaglandin E_2 **4** as well as by the known transformation of **1** into PGA_2-1,15-lactone **2**,[10c] formal total syntheses of these interesting natural products have also been accomplished.

From the conceptual point of view it should be emphasized that this novel entry into the prostaglandin series is inherently flexible and has therefore *strategic* advantages over more conventional approaches: esterification of compound **13** with alkynoic acids other than **12** followed by ring closure of the resulting diynes by alkyne metathesis opens a rather general way for the assembly of prostaglandin libraries differing in the α-chain which are difficult to prepare otherwise.[22]

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[1] Reviews: a) R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413–4450; b) A. Fürstner, *Top. Organomet. Chem.* **1998**, *1*, 37–72; c) S. K. Armstrong, *J. Chem. Soc. Perkin Trans. 1* **1998**, 371–388; d) M. Schuster, S. Blechert, *Angew. Chem.* **1997**, *109*, 2124–2144; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2036–2055; e) A. Fürstner, *Top. Catal.* **1997**, *4*, 285–299; f) K. J. Ivin, J. C. Mol, *Olefin Metathesis and Metathesis Polymerization*, Academic Press, New York, **1997**.

[2] For illustrative examples from our group see: a) A. Fürstner, K. Langemann, *J. Org. Chem.* **1996**, *61*, 3942–3943; b) A. Fürstner, K. Langemann, *Synthesis* **1997**, 792–803; c) A. Fürstner, T. Gastner, H. Weintritt, *J. Org. Chem.* **1999**, *64*, 2361–2366; d) A. Fürstner, G. Seidel, N. Kindler, *Tetrahedron* **1999**, *55*, 8215–8230; e) A. Fürstner, J. Grabowski, C. W. Lehmann, *J. Org. Chem.* **1999**, *64*, 8275–8280; f) A. Fürstner, T. Müller, *J. Am. Chem. Soc.* **1999**, *121*, 7814–7821; g) A. Fürstner, K. Langemann, *J. Am. Chem. Soc.* **1997**, *119*, 9130–9136.

[3] For an authoritative and comprehensive review on epothilone syntheses by RCM see: K. C. Nicolaou, N. P. King, Y. He, *Top. Organomet. Chem.* **1998**, *1*, 73–104.

[4] a) A. Fürstner, G. Seidel, *Angew. Chem.* **1998**, *110*, 1758–1760; *Angew. Chem. Int. Ed.* **1998**, *37*, 1734–1736. b) A. Fürstner, O. Guth, A. Rumbo, G. Seidel, *J. Am. Chem. Soc.* **1999**, *121*, 11108–11113.

[5] a) R. R. Schrock, D. N. Clark, J. Sancho, J. H. Wengrovius, S. M. Rocklage, S. F. Pedersen, *Organometallics* **1982**, *1*, 1645–1651; b) J. H. Freudenberger, R. R. Schrock, M. R. Churchill, A. L. Rheingold, J. W. Ziller, *Organometallics* **1984**, *3*, 1563–1573; c) R. R. Schrock, *Polyhedron* **1995**, *14*, 3177–3195.

[6] A. Fürstner, C. Mathes, C. W. Lehmann, *J. Am. Chem. Soc.* **1999**, *121*, 9453–9454.

[7] For a review on preparation and coordination chemistry of [Mo{N(*t*Bu)(Ar)}$_3$] see: C. C. Cummins, *Chem. Commun.* **1998**, 1777–1786.

[8] For a short review on alkyne metathesis see: U. H. F. Bunz, L. Kloppenburg, *Angew. Chem.* **1999**, *111*, 503–505; *Angew. Chem. Int. Ed.* **1999**, *38*, 478–481.

[9] a) C. Cimino, A. Crispino, V. Di Marzo, G. Sodano, A. Spinella, G. Villani, *Experientia* **1991**, *47*, 56–60; b) G. Cimino, A. Spinella, G. Sodano, *Tetrahedron Lett.* **1989**, *30*, 3589–3592; c) G. Cimino, A. Crispino, V. Di Marzo, A. Spinella, G. Sodano, *J. Org. Chem.* **1991**, *56*, 2907–2911.

[10] Compound **1** and other prostaglandin lactones have previously been prepared by conventional macrolactonization of the parent prostaglandins, see: a) E. J. Corey, K. C. Nicolaou, L. S. Melvin, *J. Am. Chem. Soc.* **1975**, *97*, 653–654; b) K. Narasaka, K. Maruyama, T. Mukaiyama, *Chem. Lett.* **1978**, 885–888; c) G. C. Bundy, D. C. Peterson, J. C. Cornette, W. L. Miller, C. H. Spilman, J. W. Wilks, *J. Med. Chem.* **1983**, *26*, 1089–1099; d) G. D. Bundy, D. R. Morton, D. C. Peterson, E. E. Nishizawa, W. L. Miller, *J. Med. Chem.* **1983**, *26*, 790–799.

[11] For timely and comprehensive treatises see: a) *Prostaglandins, Leucotrienes and Other Eicosanoids. From Biogenesis to Clinical Applications* (Eds.: F. Marks, G. Fürstenberger), WILEY-VCH, Weinheim, **1999**; b) P. W. Collins, S. W. Djuric, *Chem. Rev.* **1993**, *93*, 1533–1564.

[12] For reviews on "three-component coupling" see: a) R. Noyori, M. Suzuki, *Angew. Chem.* **1984**, *96*, 854–882; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 847; b) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**, pp. 298–322.

[13] S-M. L. Chen, R. E. Schaub, C. V. Grundziskas, *J. Org. Chem.* **1978**, *43*, 3450–3454. This paper pretends that the hydrostannylation of the TES ether of alcohol **5** is regio- and diastereoselective according to ^{13}C NMR data. Careful analysis of the crude product by HPLC, however, shows that the purity is only about 90%. This material can be used directly in the next step, because the isomeric by-products do not undergo productive 1,4-addition, see: C. R. Johnson, T. D. Penning, *J. Am. Chem. Soc.* **1988**, *110*, 4726–4735.

[14] a) For the preparation of enone **7** see: R. Noyori, I. Tomino, M. Yamada, M. Nishizawa, *J. Am. Chem. Soc.* **1984**, *106*, 6717–6725; b) C. J. Forsyth, J. Clardy, *J. Am. Chem. Soc.* **1990**, *112*, 3497–3505.

[15] a) Iodide **9** was prepared by treatment of commercially available 2-butyn-1-ol with PPh$_3$, I$_2$, and imidazole according to a literature procedure: G. L. Lange, C. Gottardo, *Synth. Commun.* **1990**, *20*, 1473–1479; b) acid **12** was prepared from commercially available 3-pentyn-1-ol as described in: M. F. Ansell, J. C. Emmet, R. V. Coombs, *J. Chem. Soc. C* **1968**, 217–225.

[16] The three-component coupling was essentially carried out as described in: M. Suzuki, Y. Morita, H. Koyano, M. Koga, R. Noyori, *Tetrahedron* **1990**, *46*, 4809–4822.

[17] a) Determined by HPLC on a Chiracel OD-H column with *n*-heptane/2-propanol as mobile phase. b) Determined by HPLC on a Chiralpak AD column with *n*-heptane/2-propanol (95:5) as mobile phase.

[18] Compound **14**: colorless syrup; $[\alpha]_D^{20} = -189.7$ ($c = 0.23$, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 0.03$ (3H, s), 0.04 (3H, s), 0.87 (9H, s), 1.20–2.50 (21H, m), 2.69 (1H, dd, $J = 18.4, 7.8$ Hz), 2.98 (1H, d, $J = 15.4$ Hz), 4.0 (1H, m), 5.10 (1H, dt, $J = 8.0, 5.2$ Hz), 5.88 (2H, m); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = -4.8, -4.6$, 14.0, 17.5, 18.0, 19.0, 22.5, 22.6, 25.5, 25.7, 31.6, 34.1, 34.9, 46.6, 54.8, 56.1, 72.2, 73.0, 79.3, 79.6, 130.4, 132.3, 172.4, 211.8; IR (neat): $\tilde{\nu} = 2955$, 2930, 2857, 1746, 1252, 1154, 1115, 964, 839, 778 cm^{-1}; MS (EI): m/z: 446 ([M^+], 1), 431 (1), 389 (33), 317 (18), 297 (8), 225 (5), 155 (5), 129 (10), 91(12), 75 (100), 55 (21); HRMS (C$_{26}$H$_{42}$O$_4$Si): m/z: 446.2850 (calcd: 446.2852); elemental analysis (%) calcd for C$_{26}$H$_{42}$O$_4$Si (446.71): C 69.91, H 9.48; found: C 70.08, H 9.42.

[19] R. F. Newton, D. P. Reynolds, C. F. Webb, S. M. Roberts, *J. Chem. Soc. Perkin Trans. 1* **1981**, 2055–2058.

[20] We consider the "economy of steps" as a strategic goal for target oriented syntheses in general, see: A. Fürstner, *Synlett* **1999**, 1523–1533.

[21] Compound **1**: colorless needles; mp 76.5–77.5 °C (Et$_2$O/pentane) [ref [10c] 73–76° (Et$_2$O/hexane)]; $[\alpha]_D^{20} = -185.0$ (0.15, CHCl$_3$); ^{1}H NMR (600 MHz, CDCl$_3$): $\delta = 0.89$ (3H, t, $J = 6.8$ Hz), 1.20–2.18 (16H, m), 2.20 (1H, ddd, $J = 13.2, 9.4, 3.3$ Hz), 2.21 (1H, dd, $J = 18.9, 9.3$ Hz), 2.29 (1H, dt, $J = 13.2, 8.8$ Hz), 2.40 (1H, ddd, $J = 13.3, 8.7, 3.2$ Hz), 2.80 (1H, ddd, $J = 18.8, 7.8, 1.2$ Hz), 4.14 (1H, dt, $J = 7.9, 9.2$ Hz), 5.20 (1H, dt, $J = 8.5, 6.0$ Hz), 5.35 (1H, ddd, $J = 10.4, 9.6, 5.5$ Hz), 5.60 (1H, dt, $J = 10.5, 5.9$ Hz), 5.81 (1H, dd, $J = 15.9, 8.7$ Hz), 6.11 (1H, dd, $J = 15.8, 6.6$ Hz); ^{13}C NMR (150 MHz, CDCl$_3$): $\delta = 14.0$, 22.5, 23.9, 25.3, 25.5, 25.6, 31.5, 34.0, 34.2, 45.5, 55.0, 57.9, 71.7, 71.8, 128.9, 129.3, 131.9, 134.7, 173.2, 213.1. IR (Kbr): $\tilde{\nu} = 3431$, 3002, 2938, 2857, 1726, 1377, 1243, 1160, 1041, 728 cm^{-1}. MS (EI): m/z: 334 ([M^+], 24), 316 (38), 298 (13), 262 (39), 208 (63), 163 (64), 151 (22), 145 (15),133 (25), 121 (28), 107 (42), 91 (78), 79 (100), 67 (83), 55 (93).

[22] For a study on the solid phase synthesis of prostaglandin derivatives and of small prostaglandin libraries see: a) L. A. Thompson, F. L. Moore, Y. C. Moon, J. A. Ellman, *J. Org. Chem.* **1998**, *63*, 2066–2067; b) D. R. Dragoli, L. A. Thompson, J. O'Brien, J. A. Ellman, *J. Comb. Chem.* **1999**, *1*, 534–539; c) K. J. Lee, A. Angulo, P. Ghazal, K. D. Janda, *Org. Lett.* **1999**, *1*, 1859–1862.

IR-Thermographic Screening of Thermoneutral or Endothermic Transformations: The Ring-Closing Olefin Metathesis Reaction

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Whereas combinatorial chemistry in the area of pharmaceutical research has reached maturity,[1] the use of appropriate systems in catalysis still poses challenges.[2] Recently we reported the first cases of IR-thermographic detection and parallel screening of enantioselectivity in transition metal catalyzed and biocatalyzed organic transformations.[3] The test reactions chosen were all exothermic processes, enantioselectivity showing up as "hot spots" in the respective IR-thermographic images. IR-thermography had previously been used as a detection and/or screening system in achiral exothermic reactions mediated by heterogeneous catalysts.[4] Indeed, it was quietly assumed that only exothermic processes can be assayed by this method.[2, 4, 5] We now report that exothermicity is not a requirement in IR-thermographic screening of catalysts. Specifically, we demonstrate for the first time that in appropriate systems endothermic or even thermoneutral reactions can be successfully screened by time-

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