Decoupling experiments demonstrate that ring A is now 1,2,4-trisubstituted, and H-4 is shifted to 8.68 ppm with a very small coupling constant. The changed polarity, the molecular formula (by HRFABMS) that includes one more oxygen, and the changes in the ^{1}H NMR spectrum make it clear that this compound is 3,11-dihydroxystaurosporine (**3**). This substance was also very active against KB cells, but no good quantitative data could be obtained.

Experimental Section

General Procedures. All solvents were distilled in glass prior to use. Melting points are uncorrected.

Isolation of 11-Hydroxystaurosporine (2). Freeze-dried tunicate (53.3 g) was extracted with 550 mL of MeOH/H_2O (4.5:1) to give 11.0 g of crude material. The residual tunicate was reextracted with 350 mL of MeOH, which afforded 3.6 g of dark green waxy solid. Extraction of this with 60 mL of CH_2Cl_2/EtOH (1:1) and then evaporation of half of this solution yielded 0.459 g of dark foamy gum. As much as possible was dissolved in hexane/EtOAc (1:1), and the solution was subjected to flash vacuum chromatography on silica. Elution with hexane/EtOAc (7:3) afforded 47.4 mg of a mixture of sterols; elution with MeOH gave 349 mg of a dark yellow solid. Flash vacuum chromatography of this material on RP-18 in two stages gave several fractions, totaling 27 mg, which were eluted with MeOH/H_2O (75:25). Preparative HPLC (Rainin Amino column, $CHCl_3$/MeOH (20:1)) of these fractions afforded 3.4 mg (.013%) of 11-hydroxystaurosporine, which exhibited a distinctive long-wavelength active spot on TLC, as a pale yellow amorphous solid, $[\alpha]_D$ +10.3 (c = 0.3, MeOH): see Table I for NMR data; UV (MeOH) 212 (29 200), 246 (25 600), 256 (24 500), 292 (50 500), 300 (46 400), 334 (sh) (10 500), 356 (9800), 374 (11 100) nm; IR (KBr) 3400 (br), 1660, 1572, 1453, 1340, and 745 cm^{-1}; HRFABMS 483.2045 calcd for $C_{28}H_{27}N_4O_4$ (MH^+) 483.2032 (Δmmu −2.3); CD 372 nm (Δε, −5.97), 355 (−4.33), 339 (−3.48), 300 (+8.12), 277 (−13.67), 247 (−6.05), 232 (+1.39), 223 (−9.09).

Acetylation of 1.0 mg of **2** with 10 μL of Ac_2O in 0.1 mL of pyridine (overnight) gave a 90% yield of the diacetate after removal of the solvent under a stream of nitrogen, followed by extraction with chloroform and workup under the usual conditions. The diacetate had two new methyl peaks at 2.3 and 2.4 ppm in the ^{1}H NMR spectrum.

3,11-Dihydroxystaurosporine. Preparative HPLC (Amino column, $CHCl_3$/MeOH, 10:1) of the MeOH/H_2O (60:40) fraction from the RP-18 flash chromatography above afforded 0.7 mg (0.0002%) of 3,11-dihydroxystaurosporine as an off-white amorphous solid: ^{1}H NMR (MeOH-d_4) δ 8.69 (1 H, d, J = 2.7), 7.53 (1 H, dd, J = 7.7, 1.3), 7.25 (1 H, d, J = 8.5), 7.21 (1 H, t, J = 7.7), 7.01 (1 H, dd, J = 8.5, 2.4), 6.95 (1 H, dd, J = 7.7, 0.8), 6.54 (1 H, dd, J = 9.1, 4.0), 5.01 and ~4.93 (2 H, AB q, the fourth signal is obscured by the solvent), 4.54 (1 H, br s), 3.62 (1 H, br multiplet), 3.15 (1 H, multiplet, partially obscured by solvent), 3.04 (3 H, s), 2.71 (3 H, br s), 2.46 (1 H, dt, J = 12.5, 4.5), 2.41 (3 H, s); HRFABMS 499.1973 (MH^+) calcd for $C_{28}H_{27}N_4O_5$ 499.1981 (Δmmu = −0.8).

Acknowledgment. We thank Jay Corgiat, Mark Hamann, and Toshio Ichiba for collecting the tunicate, Professor Claude Monniot for identifying the rather poorly preserved tunicate, Ryuichi Sakai and the University of Illinois for the mass spectra, Professor Gordon Gribble for useful discussions, and Wesley Yoshida for his interest and his knowledgeable capabilities with measuring NMR spectra. R.B.K. thanks Hamilton College for a generous sabbatical leave, and we are grateful for continuing support from the PharmaMar Co.

Supplementary Material Available: ^{1}H and ^{13}C NMR spectra, HMBC data, and a CD curve of **2** and a ^{1}H NMR spectrum of **3** (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Asymmetric Epoxidation of Allylic Alcohols Catalyzed by Titanium Alkoxide–Peptide and –α-Amino Acid Complexes Anchored by Phenolic Schiff Base

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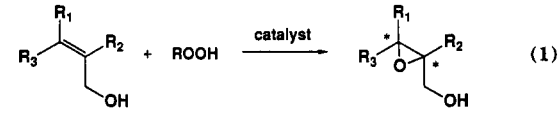
It has become important in synthetic organic chemistry to design enantioselective catalysts that yield optically active compounds with high asymmetric induction.[2] Our recent studies concerning the design of asymmetric catalyst have revealed that several metal complexes of peptide and α-amino acid derivatives anchored by phenolic Schiff bases are quite efficient catalysts for a variety of asymmetric synthetic reactions.[3] During our examination of the scope and limitations of this novel catalyst system, our interest became extended to the asymmetric epoxidation of allylic alcohols. This process has been demonstrated by Katsuki and Sharpless using titanium alkoxide–dialkyl tartrate based catalysts.[4] We wish to report the asymmetric epoxidation of allylic alcohols catalyzed by the peptide and the amino acid complexes of titanium(IV) alkoxides anchored by a phenolic Schiff base.[5]



(1)

The epoxidation of nerol (**1a**) by *tert*-butyl hydroperoxide (TBHP) was performed in methylene chloride at −20 °C in the presence of 10 mol % of a complex formed by mixing equimolar amounts of Ti(O^{i}Pr)$_4$ and Nap-*S*-Val-*S*-Phe-OMe (**2**), which has exhibited high enantioselectivity in the asymmetric syntheses of cyanohydrins,[3b] to afford the corresponding (2*S*,3*R*)-2,3-epoxynerol in 13% ee. The enantioselectivity could be increased to 48% ee by using a salicylal moiety of peptide (**3**) and cumene hydroperoxide (CHP) as the oxidant. It should be noted that the Schiff base of α-amino acid, Dbs-*S*-Val (**4**), also provided similar enantioselectivity (50% ee). This reaction using Dbs-*R*-Val inverted the facial selectivity to afford (2*R*,3*S*)-2,3-epoxynerol in 85% yield with an ee of 46%. In contrast, the use of Dbs-*S*-Valinol (**5**) and Dbs-*S*-Val-NHCy (**6**) lowered the enantioselectivity of the process. It was also observed that the use of a variety of organic hydroperoxides as oxidants influenced the stereoselectivity as well as the reactivity considerably.[6] Sterically hindered hydroperoxides such as 1,1,3,3-tetramethylbutyl hydroperoxide and

(1) Showa Denko awardee in Synthetic Organic Chemistry, Japan (1991–1993).

(2) For review: (a) *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol 5. (b) Noyori, R.; Kitamura, M. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer: Berlin, 1989; Vol. 5, pp 115–198.

(3) (a) Mori, A.; Ohno, H.; Nitta, H.; Tanaka, K.; Inoue, S. *Synlett* **1991**, 563. (b) Mori, A.; Nitta, H.; Kudo, M.; Inoue, S. *Tetrahedron Lett.* **1991**, *32*, 4333. Nitta, H.; Yu, D.; Kudo, M.; Mori, A.; Inoue, S. *J. Am. Chem. Soc.* In press. (c) Mori, A.; Yu, D.; Inoue, S. *Synlett* **1992**, 427.

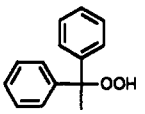
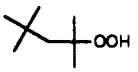
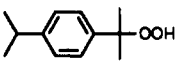
(4) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *Ibid.* **1987**, *109*, 5765. See also: Rossiter, B. E. ref 2a, pp 193–246.

(5) For the structure of the complex, see ref 3b.

(6) Effect of hydroperoxide (TBHP vs Ph_3COOH) in the asymmetric epoxidation catalyzed by titanium(IV)–pyridinediol complex was reported: Hawkins, J. M.; Sharpless, K. B. *Tetrahedron Lett.* **1987**, *28*, 2825.

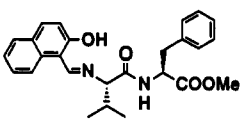
0022-3263/92/1957-6329$03.00/0

Table I. Asymmetric Epoxidation of Nerol (1a) with Various Hydroperoxides Catalyzed by Peptide (Amino Acid Derivative)-Ti(O^{i}Pr)$_4$ Complex[a]

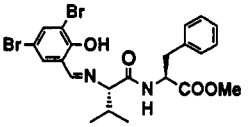
peptide (amino acid deriv)	peroxide	temp, °C	time, h	yield, %	% ee (2S,3R)
2	TBHP[b]	-20	17	40	13
3	TBHP	-20	27	33	34
3	CHP[c]	-20	32	61	48
4	CHP	-20	16	90	50
ent-4[d]	CHP	-20	20	86	46 (2R,3S)
5	CHP	-20	23	36	35
6	CHP	-20	26	43	7
4		-20	2	89	62
4		-40	5	90	66
4		-20	70	45	57
4		-20	5	85	46
4	Ph_3COOH			no reaction	

[a] In methylene chloride [peptide (amino acid derivative)]:[Ti(O^{i}Pr)$_4$]:[nerol]:[hydroperoxide] = 0.1:0.1:1.0:2.0. [b] TBHP/^{t}BuOOH. [c] CHP/PhC(CH$_3$)$_2$OOH. [d] Dbs-*R*-Val.

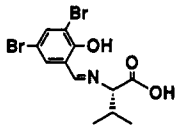
1,1-diphenylethyl hydroperoxide (DPEHP) increased the stereoselectivity. In addition, a benzylic hydroperoxide such as CHP, DPEHP, or diisopropylbenzene hydroperoxide enhanced the reactivity to afford the epoxide in good yield in a short reaction time. Among several hydroperoxides examined, DPEHP dramatically increased the enantioselectivity to yield the corresponding epoxide in up to 66% ee and the results are summarized in Table I.



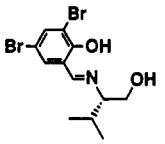
Nap-*S*-Val-*S*-Phe-OMe (2)



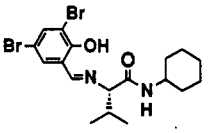
Dbs-*S*-Val-*S*-Phe-OMe (3)



Dbs-*S*-Val (4)



Dbs-*S*-Valinol (5)

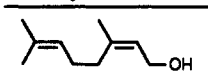
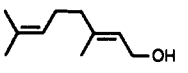
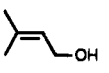
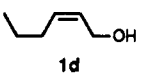
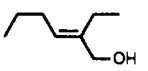


Dbs-*S*-Val-NHCy (6)

Asymmetric epoxidation of several allylic alcohols **1b–f** were similarly carried out as shown in Table II. The epoxidations of 3,3-disubstituted allylic alcohols generally proceeded in good yield with high enantioselectivity. In addition, cis-allylic alchols afforded product epoxy alcohols with higher enantioselectivity than the trans-isomer. Indeed, the reaction of *cis*-2-hexenol afforded the corresponding epoxy alcohol in 72% ee (entry **1d**), while *trans*-2-hexenol resulted in giving the epoxide with lower enantioselectivity (18% ee, entry **1e**).

The kinetic resolution[7] of a racemic secondary alcohol, 2-methyl-2-octen-4-ol (**7**), was carried out using 0.6 equiv of the hydroperoxide. When CHP was used as an oxidant, the yield of the recovered alcohol was 40% (66% ee) along with 54% of the corresponding epoxy alcohol (threo/erythro (93:7)) at -20 °C for 3 h. The k_{fast}/k_{slow} value for this process was estimated to be 4.9.[7] When TBHP was used, the allylic alcohol was recovered in 30% yield (49% ee) with 58% of the epoxy alcohol.

Table II. Asymmetric Epoxidation of Allylic Alcohols by 1,1-Diphenylethyl Hydroperoxide Catalyzed by 4-Ti(O^{i}Pr)$_4$ Complex[a]

allylic alcohol	time, h	yield, %	% ee (confign)
 **1a**	5	90	66 (2S,3R)
 **1b**	7	83	66 (2S,3S)
 **1c**	3	74	54[b]
 **1d**	70	54	72[b]
 **1e**	70	31	18[b]
 **1f**	46	56	25[b]

[a] The reactions were carried out in methylene chloride at -40 °C. [b] The absolute configuration was not identified.

Experimental Section

General. Unless noted, solvents and chemicals were purchased and used without further purification. Methylene chloride was distilled from CaH_2. 1,1-Diphenylethyl hydroperoxide was prepared in a manner as reported.[8] *N*-(2-Hydroxy-1-naphthylidene)-(*S*)-valyl-(*S*)-phenylalanine methyl ester (**2**) and *N*-(3,5-dibromosalicylidene)-(*S*)-valyl-(*S*)-phenylalanine methyl ester (**3**) were synthesized according to the reported method.[3b,9] (*E*)-2-Ethyl-2-hexenol (**1f**) was prepared from 2-ethyl-2-hexenal by reduction with sodium borohydride. 2-Methyl-2-octen-4-ol (**7**) was prepared from 3-methyl-2-butenal by alkylation with *n*-butyllithium.

(7) Martin, V. S., Woodard, S. S., Katsuki, T., Yamada, Y., Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

(8) Richardson, W. H.; Hodge, V. F. *J. Org. Chem.* **1970**, *35*, 4012.

(9) McIntire, F. C. *J. Am. Chem. Soc.* **1947**, *69*, 1377.

***N*-(3,5-Dibromosalicylidene)-(*S*)-valine (4, Dbs-*S*-Val)** was prepared in a similar manner as described previously[9] (90% yield): mp 178–180 °C, $[\alpha]^{25}_D$ −32.5° (*c* 0.20, CH_3OH); ^1H NMR (270 MHz, CD_3OD) δ 8.40 (s, 1 H), 7.77 (d, *J* = 2.4 Hz, 1 H), 7.53 (d, *J* = 2.5 Hz, 1 H), 4.09 (d, *J* = 4.9 Hz, 1 H), 2.34–2.45 (m, 1 H), 1.02 (d, *J* = 6.8 Hz, 3 H), 1.00 (d, *J* = 6.8 Hz, 3 H); IR (KBr) 3450 (br), 2970, 2900 (br), 2460 (br), 2350, 1880 (br), 1710, 1650, 1590, 1480, 1340, 1260, 1230, 1220, 1200, 1030, 1000, 860, 680, 580, 540, 420 cm^{-1}. Anal. Calcd for $C_{12}H_{13}NO_3Br_2$: C, 38.02; H, 3.46; N, 3.70. Found: C, 37.97; H, 3.44; N, 3.67.

***N*-(3,5-Dibromosalicylidene)-(*S*)-valinol (5, Dbs-*S*-valinol).** To a solution of (*S*)-valinol (0.21 g, 2.0 mmol) in methanol (10 mL) was added 3,5-dibromosalicylaldehyde (0.62 g, 2.2 mmol) and anhydrous sodium sulfate (0.71 g, 10 mmol), and the mixture was stirred for 15 min at room temperature. After sodium sulfate was removed by filtration, the solvent was evaporated in vacuo to leave a yellow solid, which was washed with hexane and dried in vacuo (0.69 g, 95%). Recrystallization was carried out from methanol (10 g/L): mp 143–144 °C, $[\alpha]^{25}_D$ −6.57° (*c* 0.35, CH_3OH); ^1H NMR (270 MHz, $CDCl_3$) δ 14.71 (br, s, 1 H), 8.19 (s, 1 H), 7.66 (d, *J* = 2.6 Hz, 1 H), 7.31 (d, *J* = 2.1 Hz, 1 H), 3.89 ($^1/_2$ AB qd, *J* = 11.3, 3.2 Hz, 1 H), 3.74 ($^1/_2$ AB qd, *J* = 11.3, 8.8 Hz, 1 H), 3.17–3.23 (m, 1 H), 2.54 (br, s, 1 H), 1.92–2.04 (m, 1 H), 0.98 (d, *J* = 6.8 Hz, 6 H); IR (KBr) 3450 (br), 3270 (br), 2970, 2870, 2330, 1640, 1600, 1510, 1500, 1420, 1210, 1130, 1065, 1040, 1020, 900, 860, 750, 680, 650, 600, 530 cm^{-1}. Anal. Calcd for $C_{12}H_{15}NO_2Br_2$: C, 39.48; H, 4.14; N, 3.84. Found: C, 39.60; H, 4.19; N, 3.93.

***N*-(3,5-Dibromosalicylidene)-(*S*)-valylcyclohexylamide (6, Dbs-*S*-Val-NHCy)** was prepared in a similar manner as described previously[3b] (54% yield): mp 213.0–214.0 °C, $[\alpha]^{25}_D$ +45.0° (*c* 0.10, CH_3OH); ^1H NMR (270 MHz, $CDCl_3$) δ 16.32 (s, 1 H), 8.23 (s, 1 H), 7.77 (d, *J* = 2.6 Hz, 1 H), 7.44 (d, *J* = 2.1 Hz, 1 H), 5.69 (d, *J* = 8.6 Hz, 1 H), 3.75–3.89 (m, 1 H), 3.72 (d, *J* = 4.3 Hz, 1 H), 2.41–2.53 (m, 1 H), 1.05–1.98 (m, 10 H), 0.97 (d, *J* = 6.8 Hz, 3 H), 0.90 (d, *J* = 6.8 Hz, 3 H); IR (KBr) 3420 (br), 3280, 2920, 2840, 2340, 1630, 1540, 1440, 1360, 1340, 1210, 1160, 1080, 1040, 960, 880, 850, 670 cm^{-1}. Anal. Calcd for $C_{18}H_{24}N_2O_2Br_2$: C, 46.98; H, 5.26; N, 6.09. Found: C, 46.99; H, 5.06; N, 6.27.

General Procedure for Asymmetric Epoxidation of Allylic Alcohols. To 4 (19.0 mg, 0.05 mmol) and molecular sieves 4A (20 mg) in dry methylene chloride (2.0 mL) was added under nitrogen titanium(IV) isopropoxide (0.05 mmol) at room temperature, and the mixture was stirred for 30 min and then cooled to −40 °C. Nerol (1a, 77 mg, 0.5 mmol) and a hydroperoxide (1.0 mmol) were added successively, and the resulting mixture was stirred for the period stated in Tables I and II during which the consumption of starting allylic alcohol was monitored by TLC analysis (SiO_2, hexane/EtOAc (2:1)). The solution was poured over saturated aqueous ammonium chloride (20 mL), and the aqueous layer was extracted with ether (20 mL × 2). The combined organic layers were dried (Na_2SO_4) and concentrated to leave a crude oil. Purification of the crude product was performed by silica gel column chromatography (hexane/ethyl acetate (3:1)) to afford the corresponding epoxy alcohol which was identical with the authentic sample prepared as reported.[4] Optical purity of epoxynerol was determined by HPLC analysis (column, Sumitomo Chemical Co. Sumichiral OA-4700; eluent, 100:1 hexane/2-propanol, flow rate, 1.0 mL/min; detection, 215 nm; t_R, 18.6 min (2*R*,3*S*), 21.2 min (2*S*,3*R*)).

Enantiomeric excess values of other epoxy alcohols were determined by ^1H NMR analysis after transformation to the corresponding diastereomeric esters of (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA). ^1H NMR signals due to the proton(s) on the epoxy ring (270 MHz, C_6D_6): for the epoxide of 1b, δ 2.72 (major), 2.82 (minor); for the epoxide of 1c, δ 2.59 (major), 2.71 (minor); for the epoxide of 1d, δ 2.73 (major), 2.81 (minor); for the epoxide of 1e, δ 2.45 (major), 2.52 (minor) and 2.33 (major), 2.41 (minor); for the epoxide of 1f, δ 2.64 (major), 2.52 (minor).

Kinetic Resolution of Racemic 2-Methyl-2-octen-4-ol (7). To the 1:1 complex of 4 and $Ti(O^iPr)_4$ (0.05 mmol) as prepared above in the presence of molecular sieves 4A (20 mg) in methylene chloride (2.0 mL) was added 7 (0.5 mmol) and CHP (0.3 mmol) at −20 °C under a nitrogen atmosphere. The resulting mixture was stirred for 3 h and poured over saturated aqueous ammonium chloride (20 mL) to quench the reaction. After workup as above, chromatographic separation of the crude oil (SiO_2, hexane/EtOAc (6:1)) afforded optically active 2-methyl-2-octen-4-ol along with the corresponding epoxy alcohol with the diastereomeric ratio of 93:7. Optical purity of the allylic alcohol was determined by HPLC analysis of the derived benzoate ester (column, Sumitomo Chemical Co. Sumichiral OA-2000; eluent, 200:1 hexane/1,1-dichloroethane; flow rate, 1.0 mL/min; detection, 230 nm; t_R, 19.2 min and 20.7 min).[10] The diastereomeric ratio of the epoxy alcohol was determined by ^1H NMR (270 MHz, C_6D_6) analysis: signals due to the proton on the epoxy ring, δ 2.58 (threo), 2.50 (erythro).[11]

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Registry No. 1a, 106-25-2; 1a (2*S*,3*R*)-epoxide, 76985-26-7; 1a (2*R*,3*S*)-epoxide, 62777-72-4; 1b, 106-24-1; 1b (2*S*,3*S*)-epoxide, 82188-73-6; 1c, 556-82-1; 1c epoxide, 18511-56-3; 1c aldehyde, 107-86-8; 1d, 928-94-9; 1d epoxide, 90528-63-5; 1e, 928-95-0; 1e epoxide, 90528-62-4; 1f, 38384-38-2; 1f epoxide, 143508-88-7; 1f aldehyde, 645-62-5; 2, 143614-93-1; 3, 143508-83-2; 4, 143508-84-3; *ent*-4, 143508-87-6; 5, 143508-85-4; 6, 143508-86-5; (±)-7, 119204-52-3; 7 *threo*-epoxide, 142952-65-6; 7 *erythro*-epoxide, 142940-78-1; TBHP, 75-91-2; CHP, 80-15-9; $Ph_2C(CH_3)OOH$, 2186-29-0; $(CH_3)_3CCH_2C(CH_3)_2OOH$, 5809-08-5; 4-$(CH_3)_2CHC_6H_4C(CH_3)_2OOH$, 98-49-7; Ph_3COOH, 4198-93-0; (*S*)-valinol, 2026-48-4; 3,5-dibromosalicaldehyde, 90-59-5.

(10) Absolute configuration of 7 was not identified.

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The Synthesis of Phosphonate Esters, an Extension of the Mitsunobu Reaction

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Introduction

In this paper a general and efficient synthesis of phosphonate esters utilizing the Mitsunobu reaction is described.[1] Phosphonate esters are recognized as effective transition-state analogue inhibitors for a variety of enzymes including a number of proteases and esterases.[2] They have been used as nonhydrolyzable analogues of phosphates to inhibit dinucleoside triphosphate hydrolase,[3] phosphatidyltransferase,[4] and squalene synthetase.[5] In addition, phosphonate esters have been used as haptens for the production of catalytic antibodies possessing esterase activity.[6] Our interests span a number of these fields, and

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