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Total Synthesis of Aculeatin A via Double Intramolecular Oxa-Michael Addition of Secondary/Tertiary Alcohols

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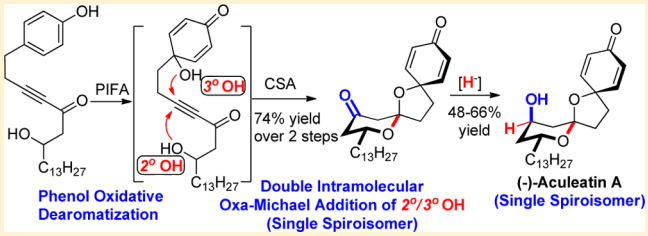
Supporting Information

ABSTRACT: A new synthetic strategy was developed for a concise total synthesis of aculeatin A as a single spiroisomer in both racemic and enantioselective fashions in 8−10 steps with ∼10% overall yield from the known alkyne **11**, featuring phenol oxidative dearomatization, double intramolecular oxa-Michael addition of secondary/tertiary alcohols, and chemo- and stereoselective reduction of ketone. The new synthetic strategy greatly expedites the access to the potent antiprotozoal aculeatin A, 6-*epi*-aculeatin D, and their analogues.



Aculeatins A−C (Figure 1) were reported in 2000 by Heilmann and co-workers from the petroleum extracts of

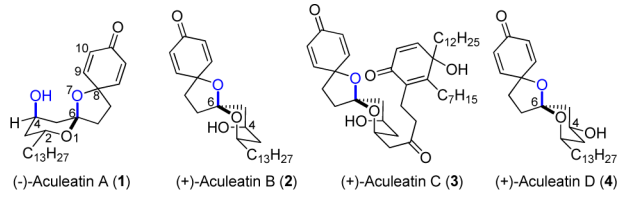
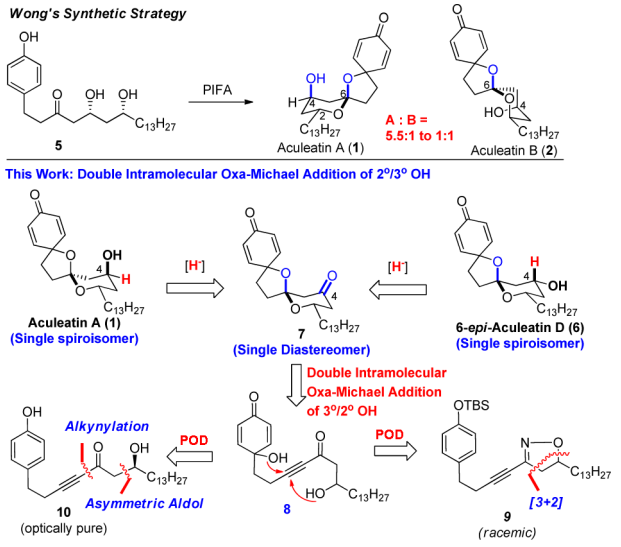


Figure 1. Aculeatins A−D.

rhizomes of the plant *Amomum aculeatum* Roxb,[1] which has been widely used in Papua New Guinea as a traditional medicine against fever and malaria. Aculeatin D, the fourth member of the aculeatin family, was identified 1 year later as a new minor compound from the same petroleum extract.[2] Aculeatins A−D have shown potent *in vitro* antiprotozoal activity (IC_{50} 0.18−3.0 μM) against *Plasmodium falciparum* and *Trypanosoma brucei rhodesiense* and *cruzi* and moderate cytotoxicity (IC_{50} 0.38−2.0 μM) against the KB cell lines.[1,2] Structurally, aculeatins A−D represent a novel type of natural products with a fascinating and unprecedented 1,7-dioxadispiro[5.1.5.2]pentadecane skeleton (cf., dispiroketal cyclohexadienone). Interestingly, aculeatin B is a spiroepimer (C6) of aculeatin A and a C4 epimer of aculeatin D. These stereochemical differences were found to affect their biological potency: aculeatin A was three times more potent than aculeatin B with similar cytotoxicity against KB cell lines; aculeatin D exhibited a doubled cytotoxicity but weaker antiprotozoal activity as compared to aculeatin B. Due to the structural novelty and potent biological activities, aculeatins A−D have received intensive attention from synthetic communities, culminating in many total syntheses.[3]

The first, racemic total synthesis of aculeatins A and B (3:1 mixture) was elegantly achieved in 2002 by Wong,[3a] who developed a highly efficient biomimetic cascade strategy involving phenyliodine bis(trifluoroacetate)[4] (PIFA)-mediated phenol oxidation[5]/spiroketalization (Scheme 1). This biomimetic

Scheme 1. Synthetic Strategy and Previous Approach for Aculeatins



approach was fully exploited in all subsequent syntheses of aculeatins and their analogues.[3] It is therefore not surprising that all previous total syntheses would yield a similar spiroisomeric mixture of aculeatins (A/B or D/6-*epi*-D). It would be highly desirable to achieve a stereoselective synthesis of the single spiroisomer aculeatin A because it is more potent (IC_{50} 0.18 μM)

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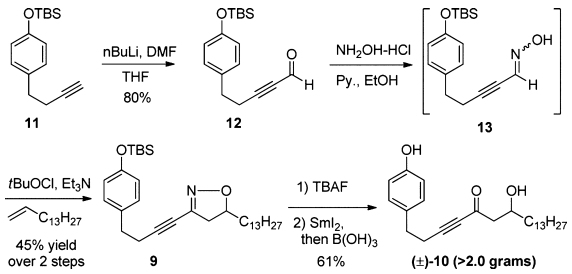
than its spiroepimer aculeatin B. We herein report a new synthetic strategy that would lead to the single spiroisomer aculeatin A, featuring (i) phenol oxidative dearomatization/double intramolecular oxa-Michael addition[6] (POD/DIOMA) and (ii) chemo- and stereoselective reduction of the C4 carbonyl group as the final step (Scheme 1). In addition, this late-stage reduction strategy permitted us to access the 6-*epi*-aculeatin D, which was also more potent than its natural counterpart and equipotent to that of aculeatin A.[7]

Our synthetic strategy (Scheme 1) was primarily inspired by Forsyth's pioneering work on double intramolecular oxa-Michael addition (DIOMA),[8] which provided a single diastereomeric 6,6-spiroketal[9] due to the double stabilization by the anomeric effect.[10] We envisioned that the 5,6-spiroketal moiety of aculeatin A could be constructed as a single spiroisomer by a similar DIOMA (**8** → **7**). The employment of the tertiary alcohol for DIOMA, however, is unprecedented in the literature, possibly due to being prone to dehydration under the acidic conditions. Nonetheless, an appropriate acid might be found to promote the oxa-Michael addition in a favorable 5-*exo*-*dig* mode.[11] The resulting carbonyl group at C4 of **7** could be utilized for chemo- and stereoselective reduction to deliver the required secondary alcohol at C4, furnishing aculeatin A (**1**) and/or 6-*epi*-aculeatin D (**6**). The required tertiary alcohol **8** could be derived from phenol oxidative dearomatization (POD) of **10**, which could be easily prepared in racemic and enantioselective fashions via reductive ring opening of [3 + 2]-dipolar cycloaddition[12] adduct **9** or asymmetric acetate aldol[13] and alkynylation reaction, respectively.

A large-scale synthesis of racemic **10** was first undertaken to verify our new synthetic strategy (Scheme 2). Formylation of

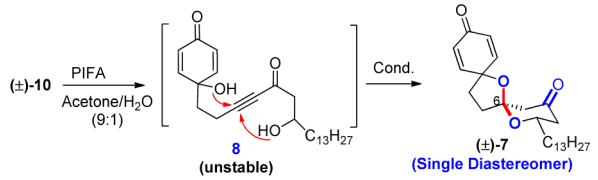
Scheme 2. Synthesis of (±)-β-Hydroxyalkynone (10) via 1,3-Dipolar Cycloaddition



the known alkyne **11**[14] with *n*BuLi/DMF and condensation of the resulting aldehyde **12** with hydroxylamine gave a *cis*/*trans* mixture of alkynyl-subsituted hydroxylimine **13**, which upon treatment of *t*BuOCl underwent 1,3-dipolar cycloaddition with 1-pentadecene to provide isoxazoline **9** as the single regioisomer. After removal of the TBS protecting group, the α,β-unsaturated isoxazoline was chemoselectively reduced by SmI_2 using Carreira's protocol,[15] providing the racemic **10** with 22% overall yield for the five steps.

With over 2 g of (±)-**10** in hand, we set out to explore the phenol oxidative dearomatization (POD) and the subsequent key DIOMA (Table 1). After preliminary screening of oxidants (oxone, phenyliodine bis(trifluoroacetate), (diacetoxyiodo)-benzene) for POD,[5] we chose PIFA for the oxidative dearomatization of (±)-**10**, which cleanly provided the unstable **8** as the only isolable product. A variety of conditions were then screened for the DIOMA of the freshly prepared **8** and are summarized in Table 1. In contrast to Forsyth's condition,[8]

Table 1. Phenol Oxidative Dearomatization and Double Intramolecular Oxa-Michael Addition; Reaction Progress Monitored by TLC



entry	acid/base[a] (equiv)	solvents	temp (°C)	yield (7, %)[b]
1	TsOH (2.0)	PhMe or PhH	rt	0
2	AgOTf (2.0)	CH_2Cl_2	rt	13
3	AuCl (2.0)	THF	rt	9
4	A-15 (4.0)	CH_2Cl_2	rt	45
5	**CSA (2.0)**	**CH_2Cl_2**	**rt**	**74**
6	CSA (2.0)	THF	rt	NR
7	KO^{t}Bu (0.1)	THF	0 → rt	0[c]

[a]A-15 = amberlyst 15. CSA = (*R*)-(−)-10-camphorsulfonic acid. [b]Isolated yields from **10**. NR = no reaction. [c]Decomposition observed.

TsOH did not effectively promote the bicyclization of **8** (entry 1), although partial cyclization (mono-oxa-Michael addition) was observed by TLC. Lewis acids including AgOTf[16] and AuCl[17] sluggishly promoted the DIOMA to give **7** in low isolated yield (9% and 13% yield over two steps, entries 2 and 3), while extension of the reaction time (>48 h) resulted in a complex mixture. Basic condition (entry 7) led to decomposition of **8** (other attempted bases including NaH and DBU). Further surveys of various protic acids proved that amberlyst 15[18] (A-15, entry 4) and (*R*)-(−)-10-camphorsulfonic acid (CSA, entry 5) in CH_2Cl_2 were superior for the DIOMA of **8**, cleanly providing the 5,6-spiroketal **7**[19] as a single diastereomer in 45% and 74% yields over two steps, respectively. The exclusive diastereoselectivity may be attributed to the double stabilization by the anomeric effect when both C−O bonds (C6) were in axial orientations.[9] Noteworthy is that the Michael addition of the two OH groups to the conjugated triple bond led to only the thermodynamically more stable isomer of the spiroketal, which was similar to the exclusive formation of 6-*epi*-aculeatin D under strongly acidic conditions.[3i] Apparently, exclusive access to the thermodynamically less stable isomer(s) of the spiroketal(s) still remains to be developed. Most importantly, this unprecedented combination of POD and DIOMA allowed us to readily access the single diastereomeric 5,6-spiroketal framework present in aculeatin A, which could not be achieved by previous synthetic strategies for aculeatins.[3]

Another challenge in our synthetic plan arose from the final-stage functionalization: chemo- and stereoselective reduction of (±)-**7** to (±)-aculeatin A (**1**). Our initial strategy for this final functionalization involved two steps (Table 2): (i) stereoselective reduction of both carbonyl groups at C4 and C11 and (ii) chemoselective oxidation of allylic alcohol at C11 to a ketone. Pleasingly, such strategy proved quite successful: K-selectride at −78 °C could stereoselectively reduce both carbonyl groups (C11 and C4), and subsequent chemoselective oxidation of allylic alcohol (C11) with MnO_2[20] furnished (±)-aculeatin A in 48% yield over two steps as a single diastereomer[21] (entry 1). Other reducing agents including DIBALH, $NaBH_4$−$CeCl_3$, and LiAlH(O^{t}Bu)$_3$ generated a diastereomeric mixture of **1** and **6** after MnO_2 oxidation in good to excellent combined yield (entries 2−4). Interestingly, LiAlH(O^{t}Bu)$_3$ was later found to chemoselectively reduce the

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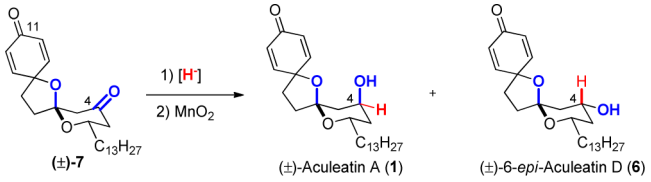
Table 2. Reduction of Ketone (±)-7 to (±)-Aculeatin A (1) and (±)-6-*epi*-Aculeatin D (6); Reaction Run with 20 mg of (±)-7



entry	$[H^-]^a$	solvent	temp	yield (%, **1**:**6**)^b
1	**K-Selectride**	**THF**	**-78**	**48 (>20:1)**
2	DIBALH	DCM	−78	51 (10:1)
3	$NaBH_4/CeCl_3$	MeOH/DCM	−78	83 (1.1:1)
4	$LiAlH(O^tBu)_3$	THF	0	69 (1:3)^c
5	(*R*)-CBS (cat.) catecholborane	THF	−20	<10
6	(*R*)-CBS (cat.) BH_3-SMe_2	THF	−20	44 (3:1)^d
7	(*R*)-alpine-borane	THF	rt	0
8	**Ru*/HCO_2H-Et_3N**	**DCM**	**rt**	**83 (3.8:1)**^{c,d}

^{a}(*R*)-CBS = (*R*)-(+)-2-methyl-CBS-oxazaborolidine. Ru* = RuCl(*p*-cymene)[(*S*,*S*)-Ts-DPEN]. ^{b}Isolated yield over 2 steps, diastereomeric ratio based on isolated yield. ^{c}Combined yield of **1** and **6** without MnO_2 oxidation. ^{d}Enantiomeric excess of **1** was determined by chiral HPLC to be 1−10% ee.

ketone on C4 to afford a 1:3 diastereomeric mixture of **1** and **6** in 69% combined yields without MnO_2 oxidation (entry 4). The diastereoselectivity favoring **6** was particularly noteworthy since all other conditions (except entry 3) examined gave **1** as the major or only product. Although attempts to perform reductive kinetic resolution[22] of the racemic ketone **7** were not successful (entries 5−8) due to the low conversion and/or enantioselectivity (<10% ee), we unexpectedly observed that Noyori reduction[23] of the ketone (±)-**7** (entry 8) was chemo- and stereoselective to provide aculeatin A without additional MnO_2 oxidation in 66% yield (along with 17% yield of **6**). The tolerance of the labile cyclohexadienone[24] that readily underwent rearomatization was worthy of notice. To the best of our knowledge, this was the first example that C4 secondary alcohol was installed chemo- and stereoselectively in the final step of total synthesis of aculeatins.

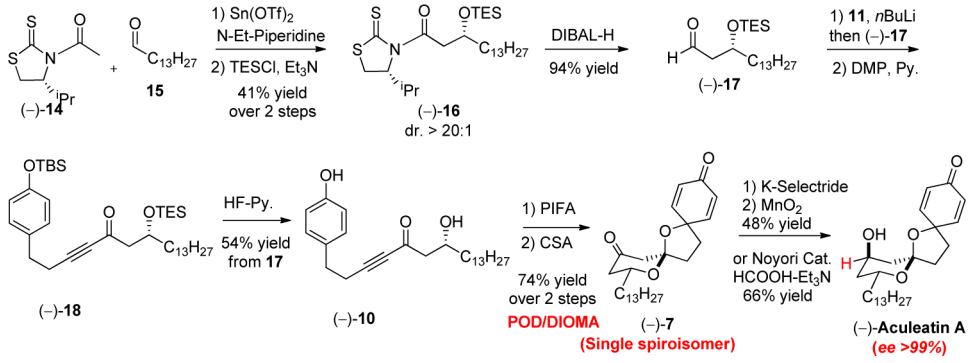
After considerable efforts on reductive kinetic resolution of the racemic ketone (±)-**7** (Table 2) and lipase-catalyzed kinetic resolution[25] of the racemic aculeatin A proved fruitless, we developed an alternative route to prepare the optically active (−)-**10**[26] for an enantioselective total synthesis of aculeatin A as the single spiroisomer using the new POD/DIOMA strategy (Scheme 3). Asymmetric acetate aldol of (−)-**14** and aldehyde **15** using the Nagao-Fujita[27] protocol followed by silylation gave (−)-**16** in 41% overall yield with excellent diastereoselectivity. Removal of the chiral auxiliary with DIBALH, alkynylation of the resulting aldehyde with **11**, oxidation with Dess−Martin periodinane (DMP), and desilylation with HF-pyridine provided the enantiomerically pure (−)-**10** in 51% yield over four steps. The alkynyl alcohol (−)-**10** was subjected to the same three-step (or four-step) sequence: POD, DIOMA, and reduction (and MnO_2 oxidation), furnishing the (−)-aculeatin A with optical purity of >99% ee as the single spiroisomer. All spectrascopic data of the synthetic aculeatin A were identical to those reported for the authentic sample (−)-aculeatin A in the literature.[1,3]

In summary, we have developed a new cascade strategy for a concise total synthesis of aculeatin A as a single spiroisomer in both racemic and enantioselective fashions in eight steps with 10.7% overall yield and in nine steps with 10.2% overall yield from known alkyne **11** and the known **14**, respectively. This constituted the first example that did not employ the final phenol oxidation/spiroketalization in total syntheses of aculeatins and that yielded the single spiroisomeric, more potent aculeatin A. Total synthesis of the racemic 6-*epi*-aculeatin D was also accomplished by taking advantage of the final stereoselective reduction of DIOMA adducts. The key features of our synthesis include (i) construction of the single diastereomeric 5,6-spiroketal framework of aculeatins via phenol oxidative dearomatization (POD) and double intramolecular oxa-Michael addition (DIOMA) and (ii) chemo- and/or stereoselective reduction of a ketone to install the required secondary alcohol at C4 as the final step. This new POD/DIOMA synthetic strategy coupled with chemo- and stereoselective reduction of the ketone may be exploited in synthesis of other aculeatins and their analogues for biological activity evaluation.

EXPERIMENTAL SECTION

NMR spectra were recorded on a 400 MHz spectrometer (400 MHz for ^1H, 100 MHz for ^{13}C). Chemical shifts are reported in parts per million (ppm) as values relative to the internal chloroform (7.26 ppm for ^1H and 77.16 ppm for ^{13}C). Infrared (IR) spectra were recorded as neat samples (liquid films on KBr plates). HRMS spectra were recorded with a TOF detector. Normal phase HPLC was used to determine enantiomeric excess of chiral compounds with eluents of hexane/*i*-PrOH. Reactions were carried out in oven or flame-dried glassware under a nitrogen atmosphere, unless otherwise noted. Tetrahydrofuran (THF) was freshly distilled before use from sodium using benzophenone as indicator. Dichloromethane (CH_2Cl_2) was freshly distilled before use from calcium hydride (CaH_2). All other anhydrous solvents were dried over 3 or 4 Å molecular sieves.

Scheme 3. Enantioselective Total Synthesis of (−)-Aculeatin A



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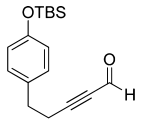
Compounds **11**[28] and **14**[27] have been reported and were prepared according to the literatures.



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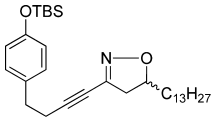
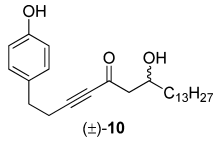
To a solution of alkyne **11** (9.88 g, 38.0 mmol) in THF (100 mL) at −78 °C was added *n*BuLi (24.7 mL, 2.0 M in hexanes,49.4 mmol) dropwise. After 1 h of stirring, dry DMF (4.4 mL, 57.0 mmol) was added at −78 °C. The reaction mixture was stirred at −78 °C for 1 h and then quenched with saturated aqueous NH_4Cl solution. The organic layer was collected, and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 10:1) to afford the desired aldehyde **12** (8.75 g, 80% yield) as a yellow oil. IR (neat, cm^{-1}): 3037, 2954, 2931, 2890, 2857, 2361, 2337, 2198, 1667, 1608, 1510, 1467, 1254, 1132. ^1H NMR (400 MHz, $CDCl_3$) δ: 9.16 (s, 1H), 7.06 (d, J = 8.0 Hz, 2H), 6.78 (d, J = 8.0 Hz, 2H), 2.84 (t, J = 7.2 Hz, 2H), 2.67 (t, J = 7.2 Hz, 2H), 0.98 (s, 9H), 0.19 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.3, 154.6, 132.3, 129.4 (2C), 120.3 (2C), 98.4, 82.2, 33.2, 25.8 (3C), 21.7, 18.3, −4.3 (2C). HRMS (CI-TOF) m/z calcd for $C_{17}H_{25}O_2Si$ $[M + H]^+$ 289.1624, found 289.1624.



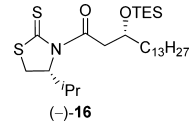
(±)-**9**

To a solution of α,β-unsaturated aldehyde **12** (6.19 g, 21.5 mmol) in EtOH (96%, 170 mL) at room temperature were added NH_2OH-HCl (2.24 g, 32.3 mmol) and pyridine (Py, 6.9 mL). The mixture was stirred at room temperature for 2 h and subsequently concentrated under reduced pressure. To the resulting residue were added EtOAc (50 mL) and water (10 mL), and the organic layer was collected. The organic fractions were washed with water (2 × 5 mL) and brine, dried over Na_2SO_4, and concentrated under reduced pressure. To a solution of the crude oximes, Et_3N (6 mL), and pentadecene (11.8 mL, 43 mmol) in Et_2O (250 mL) at −78 °C was added *t*BuOCl (5.0 mL, 43.0 mmol) dropwise under a nitrogen atmosphere. The resulting reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with water (20 mL). The organic layer was collected, and aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 5:1) to afford the desired isoxazoline (±)-**9** as a light yellow oil (4.85 g, 45% yield over two steps). IR (neat, cm^{-1}): 2927, 2855, 2360, 1609, 1510, 1349, 1257, 1130, 1100. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.06 (d, J = 8.4 Hz, 2H), 6.77 (d, J = 8.4 Hz, 2H), 4.66−4.58 (m, 1H), 3.03 (dd, J = 16.8, 10.4 Hz, 1H), 2.81 (t, J = 8.0 Hz, 2H), 2.63 (t, J = 8.0 Hz, 3H), 1.72−1.69 (m, 1H), 1.55−1.49 (m, 1H), 1.26 (m, 22H), 0.98 (s, 9H), 0.88 (t, J = 6.4 Hz, 3H), 0.19 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.3, 143.1, 132.9, 129.4 (2C), 120.1 (2C), 98.3, 82.0, 71.2, 43.2, 35.1, 33.7, 32.0, 29.8−29.5 (br, 8C), 25.8 (3C), 25.4, 22.8, 22.1, 18.3, 14.2, −4.4 (2C). HRMS (CI-TOF) m/z calcd for $C_{32}H_{54}NO_2Si$ $[M + H]^+$ 512.3924, found 512.3918.



(±)-**10**

To a solution of isoxazoline (±)-**9** (4.80 g, 9.40 mmol) in THF (90 mL) at 0 °C was added tetrabutylammonium fluoride (TBAF, 20.7 mL, 1.0 M in THF, 20.7 mmol). After 1 h, the reaction was quenched with saturated aqueous NH_4Cl solution. The organic layer was collected, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 5:1) to afford the desired product (3.20 g, 85% yield) as a light yellow oil. IR (neat, cm^{-1}): 3628, 3412, 2920, 2852, 2300, 1614, 1516, 1465, 1350, 1336, 1249, 1103. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.07 (d, J = 8.0 Hz, 2H), 6.78 (d, J = 8.0 Hz, 2H), 5.16 (s, 1H, OH), 4.66−4.59 (m, 1 H), 3.04 (dd, J = 16.4, 10.4 Hz, 1H), 2.81 (t, J = 8.0 Hz, 2H), 2.66−2.60 (m, 3H), 2.00 (br, OH) 1.72−1.68 (m, 1 H), 1.58−1.50 (m, 1H), 1.25 (m, 22H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.7, 143.4, 132.0, 129.6 (2C), 115.5 (2C), 98.8, 82.2, 71.0, 43.1, 35.0, 33.6, 32.0, 29.8−29.5 (br, 8C), 25.4, 22.8, 22.1, 14.2. HRMS (CI-TOF) m/z calcd for $C_{26}H_{40}NO_2$ $[M + H]^+$ 398.3059, found 398.3063. To a solution of desilylated isoxazoline (3.18 g, 8.01 mmol) obtained above in anhydrous and degassed THF (200 mL) at 0 °C was added SmI_2 (288 mL, 0.1 M in THF, 28.8 mmol) slowly, maintaining a dark blue color throughout the reaction. The reaction mixture was stirred for additional 30 min at 0 °C and then was quenched by bubbling a stream of oxygen to give a yellow solution, which was poured into $B(OH)_3$ (7.2 g) solution in H_2O (400 mL). The mixture was stirred for 30 min at room temperature and diluted with Et_2O (50 mL). The organic layer was collected, and the aqueous phase was extracted with Et_2O (3 × 400 mL). The combined organic fractions were washed with brine (2 × 50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 2:1) to afford the desired β-hydroxylalkynone (±)-**10** (2.31 g, 71.4% yield) as a light yellow oil. IR (neat, cm^{-1}): 3338, 2923, 2853, 2211, 1659, 1515, 1456, 1244, 1170, 826, 670. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.05 (d, J = 8.0 Hz, 2H), 6.78 (d, J = 8.0 Hz, 2H), 6.07 (s, 1H, OH), 4.11−4.06 (m, 1H), 2.80 (t, J = 7.2 Hz, 2H), 2.69−2.59 (m, 4H), 1.45−1.37 (m, 2H), 1.28−1.22 (m, 22H), 0.88 (t, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 188.1, 154.8, 131.5, 129.6 (2C), 115.6 (2C), 95.2, 81.6, 68.0, 52.3, 36.5, 33.1, 32.0, 29.8−29.5 (br, 8C), 25.5, 22.8, 21.6, 14.2. HRMS (CI-TOF) m/z calcd for $C_{26}H_{40}O_3$ $[M]^-$ 400.2977, found 400.2972.



(−)-**16**

To a suspension of tin(II) triflate ($Sn(OTf)_2$, 4.51 g, 10.8 mmol) in CH_2Cl_2 (40 mL) was added *N*-ethylpiperidine (1.48 mL, 10.8 mmol) at −78 °C. (−)-**14** (1.82 g, 8.98 mmol) in CH_2Cl_2 (8 mL) was added to the cold reaction mixture via a cannula. The reaction mixture was allowed to warm to −40 °C and stirred for 4 h before cooling back to −78 °C. Aldehyde **15** (2.00 g, 9.85 mmol) in CH_2Cl_2 (8 mL) was added via a syringe pump to the enolate solution over 40 min. After being stirred for an additional 5 h at −78 °C, the reaction mixture was quenched with pH 7.0 phosphate buffer (50 mL). The organic layer was collected, and the

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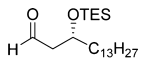
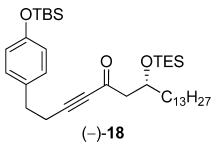
aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was used for the subsequent silylation reaction without purification. To a solution of the crude aldol product (3.73 g, 8.98 mmol) in dry CH_2Cl_2 (50 mL) were added triethylamine (Et_3N, 4.1 mL, 29.6 mmol) and 4-dimethylamino pyridine (DMAP, 0.24 g, 1.97 mmol). The resulting solution was cooled to 0 °C with an ice−water bath, and then triethylsilyl chloride (TESCl, 2.5 mL, 14.8 mmol) was added dropwise. After complete consumption of the starting material as indicated by TLC, the mixture was quenched by addition of saturated aqueous $NaHCO_3$ solution (15 mL). The organic layer was collected, and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 50:1) to afford (−)-**16** as a yellow oil (1.95 g, 41% yield over two steps). $[\alpha]_D$ = −217.0 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 2955, 2925, 2875, 2854, 1699, 1462, 1369, 1311, 1239, 1166, 1091, 1041, 1008. ^1H NMR (400 MHz, $CDCl_3$) δ: 5.05 (t, *J* = 7.2 Hz, 1H), 4.32−4.27 (m, 1H), 3.55−3.45 (m, 2H), 3.16 (dd, *J* = 16.8, 4.0 Hz, 1H), 3.02 (d, *J* = 11.2 Hz, 1H), 2.41−2.36 (m, 1H), 1.53−1.48 (m, 2H), 1.25 (m, 22H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.93 (t, *J* = 8.0 Hz, 9H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.59 (q, *J* = 8.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.0, 172.3, 71.8, 69.1, 45.8, 38.0, 32.1, 31.1, 31.0, 29.9−29.5 (br, 8C), 25.4, 22.8, 19.3, 18.0, 14.3, 7.1 (3C), 5.2 (3C). HRMS (CI-TOF) *m*/*z* calcd for $C_{28}H_{55}NO_2S_2Si$ $[M]^-$ 529.3443, found 529.3438.



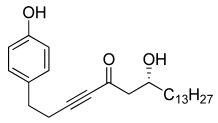
(−)-**17**

To a solution of (−)-**16** (1.54 g, 2.88 mmol) in CH_2Cl_2/hexane (28 mL, 1:1 v/v solution) was added DIBALH (5.76 mL, 1.0 M in hexanes, 5.76 mmol) at −78 °C, and the mixture was allowed to stir at the same temperature until no yellow color was observed. Then the reaction was quenched by addition of ethyl acetate (2 mL) at −78 °C and then saturated aqueous sodium potassium tartrate solution (20 mL). The mixture was allowed to warm to room temperature and stirred for 2 h. The organic layer was collected, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 50:1) to afford aldehyde (−)-**17** (1.01 g, 94% yield) as a colorless oil. $[\alpha]_D$ = −2.5 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 2956, 2925, 2876, 2855, 1728, 1465, 1415, 1377, 1239, 1104, 1009. ^1H NMR (400 MHz, $CDCl_3$) δ: 9.81 (t, *J* = 2.4 Hz, 1H), 4.21−4.15 (m, 1H), 2.52 (dd, *J* = 6.0, 2.4 Hz, 2H), 1.55−1.49 (m, 2H), 1.25−1.21 (m, 22H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.88 (t, *J* = 6.4 Hz, 3H), 0.59 (q, *J* = 8.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.6, 68.4, 51.1, 38.1, 32.1, 29.8−29.5 (br, 8C), 25.4, 22.8, 14.3, 7.0 (3C), 5.1 (3C). HRMS (CI-TOF) *m*/*z* calcd for $C_{22}H_{47}O_2Si$ $[M + H]^+$ 371.3345, found 371.3348.



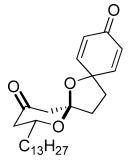
(−)-**18**

To a solution of alkyne **11** (0.898 g, 3.42 mmol) in THF (19 mL) at −78 °C was added *n*BuLi (1.56 mL, 2.0 M in hexanes, 3.12 mmol). The reaction mixture was stirred for 0.5 h. Aldehyde (−)-**17** (0.974 g, 2.63 mmol) in THF (15 mL) was added to the mixture at −78 °C, and then the reaction was stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and diluted with Et_2O (10 mL). The organic layer was collected, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic fractions were washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 50:1) to afford a mixture of diastereomers (1.17 g, 71% yield, dr 0.8:1) as a colorless oil. To a solution of diastereomers (0.855 g, 1.35 mmol) obtained above in dry CH_2Cl_2 (6.7 mL) at 0 °C were added pyridine (Py, 0.4 mL, 4.86 mmol) and Dess−Martin periodinane (DMP, 686 mg, 1.62 mmol). After vigorous stirring for 30 min at 0 °C, the cold bath was removed, and the reaction mixture was stirred at room temperature for 12 h until TLC indicated complete consumption of the starting material. The reaction mixture was diluted with Et_2O (10 mL) and poured into saturated aqueous $NaHCO_3$ solution containing excess $Na_2S_2O_3$. The mixture was stirred until the solid was completely dissolved. The organic phase was collected, washed sequentially with saturated aqueous $NaHCO_3$ solution, water, and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 20:1) to afford the ketone (−)-**18** (0.653 g, 77% yield) as a colorless oil. $[\alpha]_D$ = −3.8 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 2955, 2927, 2855, 2213, 1677, 1510, 1463, 1255, 1100, 1007, 915, 840. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.06 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 4.28−4.22 (m, 1H), 2.81 (t, *J* = 7.2 Hz, 2H), 2.72−2.56 (m, 4H), 1.48−1.45 (m, 2H), 1.33−1.27 (m, 22H), 0.99−0.94 (m, 18H), 0.89 (t, *J* = 7.2 Hz, 3H), 0.60 (q, *J* = 8.0 Hz, 6H), 0.19 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 186.2, 154.4, 132.4, 129.3 (2C), 120.1 (2C), 93.4, 82.0, 68.8, 53.4, 37.9, 33.3, 32.0, 29.8−29.4 (br, 8C), 25.7 (3C), 25.1, 22.8, 21.4, 18.2, 14.2, 6.9 (3C), 5.0 (3C), −4.4 (2C). HRMS (CI-TOF) *m*/*z* calcd for $C_{38}H_{68}O_3Si_2$ $[M]^-$ 628.4707, found 628.4712.



(−)-**10**

To a solution of (−)-**18** (0.315 g, 0.502 mmol) in CH_3CN/THF (5 mL, 10:1 v/v solution) at 0 °C were added pyridine (Py, 0.75 mL) and HF-pyridine complex (0.75 mL). After 3 h, the reaction was quenched with saturated aqueous $NaHCO_3$ solution. The organic layer was collected, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic fractions were washed with saturated aqueous $CuSO_4$ solution and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 2:1) to afford the desired phenol (−)-**10** (0.200 g, 99% yield) as a light yellow oil. $[\alpha]_D$ = −7.4 (*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3369, 2924, 2853, 2212, 1663, 1515, 1461, 1246, 1171, 826. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.05 (d, *J* = 8.0 Hz, 2H), 6.78 (d, *J* = 8.0 Hz, 2H), 5.60 (br, OH), 4.10−4.06 (m, 1H), 2.81 (t, *J* = 7.2 Hz, 2H), 2.70 (br, OH), 2.69−2.60 (m, 4H), 1.42−1.33 (m, 2H), 1.28−1.25 (m, 22H), 0.88 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 188.0, 154.8, 131.6, 129.6 (2C), 115.6 (2C), 95.1, 81.7, 67.9, 52.3, 36.5, 33.1, 32.0, 29.8−29.5 (br, 8C), 25.5, 22.8, 21.6, 14.2. HRMS (CI-TOF) *m*/*z* calcd for $C_{26}H_{40}O_3$ $[M]^-$ 400.2977, found 400.2982.



7

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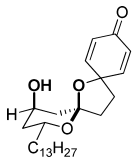
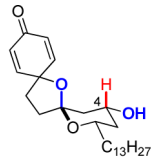
To a solution of phenol (±)-**10** (100 mg, 0.250 mmol) in acetone/water (7.5 mL, 5:1 v/v solution) at 0 °C was added phenyliodine bis(trifluoroacetate) (PIFA, 160 mg, 0.400 mmol) in one portion. After the mixture protected from light was stirred for 30 min, Na_2SO_4 and $NaHCO_3$ were added, and the mixture was stirred for another 10 min before filtration through a short pad of Celite. The filtrate was concentrated under reduced pressure to afford the crude product (±)-**8**, which was used without purification for the double intramolecular oxa-Michael addition. To a solution of the crude alkynone (±)-**8** in CH_2Cl_2 (5 mL), (1*R*)-(−)-10-camphorsulfonic acid (CSA, 115 mg, 0.500 mmol) was added in one portion. After complete consumption of the starting material (±)-**8** as indicated by TLC, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (5 mL). The organic layer was collected, and the aqueous layer was extracted with Et_2O (5 × 5 mL). The combined organic fractions were washed with brine (2 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 5:1) to afford the desired diketone (±)-7 (76.6 mg) as a light yellow oil in 74% yield over two steps. These procedures were repeated five times to obtain 383 mg of (±)-7 for subsequent reduction studies. The identical procedure was used to prepare the enantiomerically pure (−)-7 with the 74.5% overall yield from (−)-**10**. Spectroscopic data for the synthetic **7** was in good agreement with those reported in ref 19. Data for **8**: IR (neat, cm^{-1}): 3409, 2925, 2854, 2214, 1670, 1626, 1463, 1380, 1171. ^1H NMR (400 MHz, $CDCl_3$) δ: 6.85 (d, J = 10.0 Hz, 2H), 6.19 (d, J = 10.0 Hz, 2H), 4.10−4.06 (m, 1H), 3.24 (br, 2H, OH), 2.71−2.58 (m, 2H), 2.43 (t, J = 8.0 Hz, 2H), 2.02 (t, J = 8.0 Hz, 2H), 1.39−1.23 (m, 24H), 0.86 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 187.6, 185.5, 150.4, 128.8, 93.6, 81.5, 68.9, 67.8, 52.3, 37.8, 36.5, 32.0, 29.8−29.4 (br, 8C), 25.5, 22.8, 14.2, 14.0. HRMS (CI-TOF) m/z calcd for $C_{26}H_{40}O_4$ $[M]^-$ 416.2927, found 416.2928. Data for (−)-7: $[\alpha]_D$ = −5.4 (c 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 6.75 (ddd, J = 20.8, 9.6, 2.8 Hz, 2H), 6.13−6.07 (m, 2H), 4.14−4.09 (m, 1H), 2.75 (d, J = 14.4 Hz, 1H), 2.53 (d, J = 14.4 Hz, 1H), 2.41−2.38 (m, 3H), 2.25−2.18 (m, 1H), 2.09−2.04 (m, 2H), 1.67−1.62 (m, 1H), 1.53−1.47 (m, 1H), 1.40−1.16 (m, 22H), 0.86 (t, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 204.7, 185.4, 150.5, 148.7, 127.7, 127.3, 109.7, 79.8, 69.8, 49.9, 46.9, 38.8, 36.2, 34.9, 32.0, 29.8−29.5 (br, 8C), 25.6, 22.8, 14.2.



Aculeatin A (**1**)

Method A. To a solution of ketone (±)-7 (20 mg, 0.050 mmol) in THF (1 mL) was added a solution of K-Selectride (0.12 mL, 1.0 M in THF, 0.120 mmol) at −78 °C. After 20 min of stirring at −78 °C, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution (1 mL), EtOAc (2 mL), and water (0.5 mL). The organic layer was collected, and the aqueous layer was extracted with EtOAc (2 × 1 mL). The combined organic fractions were washed with water (0.5 mL) and brine (2 × 0.2 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was used for the subsequent oxidation without further purification. To the crude diol in CH_2Cl_2 (1.0 mL) was added MnO_2 (activated powder, 88 mg, 1.0 mmol). After 1 h the mixture was filtered through a short pad of Celite and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 2:1) to afford (±)-aculeatin A as a colorless oil (9.6 mg, 48% yield over two steps). The identical procedure was also used to prepare the enantiomerically pure (−)-aculeatin A with 48.5% yield from ketone (−)-7.

Method B. To a solution of ketone (±)-7 (20 mg, 0.050 mmol) in CH_2Cl_2 (0.5 mL) were added RuCl(*p*-cymene)[(*S*,*S*)-Ts-DPEN] (0.10 mg, 0.5 mol %), HCO_2H (19 μL, 0.50 mmol), and Et_3N (28 μL, 0.20 mmol). The reaction mixture was stirred for 20 h at room temperature. After being diluted with water (1 mL), the organic layer was collected, and the aqueous layer was extracted with EtOAc (3 × 1 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ solution (0.5 mL) and brine (0.2 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 5:1 to 2:1) to afford (±)-aculeatin A as a colorless oil (13.2 mg, 66% yield, 10% ee) and (±)-6-*epi*-aculeatin D as a colorless oil (3.4 mg, 17% yield) in 83% total yield with diastereomeric ratio of 3.8:1. The identical procedure was used to prepare the enantiomerically pure (−)-aculeatin A with the 66% yield from ketone (−)-7. (−)-Aculeatin A: 99% ee (HPLC analysis conditions for aculeatin A: Daicel CHIRALPAK AD-H column; 5% *i*-PrOH in hexanes; 1.0 mL/min; t_R: 6.25 and 7.19 min). Aculeatin A: $[\alpha]_D$ = −6.2 (c 0.2, $CHCl_3$), lit. $[\alpha]_D$ = −5.3 (c 0.9, $CHCl_3$).[1] IR (neat, cm^{-1}): 3558, 2925, 2854, 1673, 1462, 1099. ^1H NMR (400 MHz, $CDCl_3$) δ: 6.85 (dd, J = 10.0, 2.8 Hz, 1H), 6.75 (dd, J = 10.0, 2.8 Hz, 1H), 6.15−6.09 (m, 2H), 4.13−4.10 (m, 2H), 3.35 (br 1H, OH), 2.40−2.32 (m, 1H), 2.25−2.20 (m, 1H), 2.05−2.00 (m, 3H), 1.92 (br d, J = 14.0 Hz, 1H), 1.79 (br d, J = 12.0 Hz, 1H), 1.58−1.39 (m, 5H), 1.39−1.19 (m, 20H), 0.87 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 185.3, 150.9, 148.7, 127.4, 127.1, 109.1, 79.7, 65.3, 64.8, 39.1 (2C), 37.9, 35.9, 34.1, 31.9, 29.7−29.5 (br, 8C), 25.6, 22.6, 14.1. HRMS (CI-TOF) m/z calcd for $C_{26}H_{42}O_4$ $[M]^-$ 418.3083, found 418.3085.



(±)-6-*epi*-Aculeatin D (**6**)

(±)-6-*epi*-Aculeatin D. IR (neat, cm^{-1}): 3432, 2925, 2854, 1672, 1462, 1127. ^1H NMR (400 MHz, C_6D_6) δ: 6.68 (dd, J = 10.0, 3.2 Hz, 1H), 6.15−6.10 (m, 2H), 6.02 (dd, J = 10.0, 2.0 Hz, 1H), 3.92−3.89 (m, 1H), 3.73−3.67 (m, 1H), 2.06−1.98 (m, 1H), 1.90−1.83 (m, 2H), 1.66−1.62 (m, 1H), 1.55−1.20 (m, 27H), 1.07 (q, J = 12.0 Hz, 1H), 0.92 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ: 185.2, 151.4, 149.4, 128.1, 127.7, 109.6, 79.8, 69.8, 65.8, 44.1, 41.8, 39.4, 37.0, 35.5, 32.9, 30.8−30.5 (br, 8C), 26.7, 23.7, 15.0. HRMS (CI-TOF) m/z calcd for $C_{26}H_{42}O_4$ $[M]^-$ 418.3083, found 418.3077.

■ ASSOCIATED CONTENT

Supporting Information

Tables of comparison of NMR data of our synthetic aculeatin A and 6-*epi*-aculeatin D with those reported and copies of ^1H and ^{13}C NMR of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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