X-ray Structure of Compound 5. Working in a drybox, under a stream of cold (ca. -20 °C) nitrogen gas to prevent melting, a single crystal of compound **5** was loaded into a capillary and sealed with wax. It was quickly transferred to the diffractometer and cooled to -100 °C in a N_2 stream. Space group, unit cell, and data collection information are provided in Table IV. The solution and refinement were uneventful, except for the hydrido hydrogen atom, which tended to refine to an unacceptably short Ir-H separation. This atom was held fixed at its Fourier difference map position. Remaining hydrogen atoms were placed in idealized locations. Consistent with the low melting point of the material, there is considerable apparent thermal motion of several of the atoms, most notably C5 and C6 of the indium ethyl group. As a result of this thermal anisotropy, the calculated C5-C6 bond distance is unrealistically short (1.29 (2) Å). Being suspicious that this might indicate a vinyl group, formed by metal-catalyzed dehydrogenation, we analyzed the remaining crystals from this batch (^{1}H NMR, C_6D_6) but found absolutely no evidence for a vinyl group nor for any compound other than **5**. Final refinement data is included in Table IV. Largest residual density in the final difference Fourier map is 1.42 e/Å^3 near the indium atom. Bond distances and angles are listed in Tables I and II. Nonhydrogen atom positions are listed in Table V. Anisotropic thermal parameters, hydrogen atom positions, a listing of F_{obs} vs F_{calc} (Tables 6-8), and a stereodrawing of the unit cell (Figure 2) are available as supplementary material.

Acknowledgment. The crystal of compound **5** was skillfully mounted by L. Lardear. We also thank L. Ayers for technical assistance and P. Fagan and R. T. Baker for communicating results prior to publication.

Supplementary Material Available: Tables of anisotropic thermal parameters (Table 6) and hydrogen atom parameters (Table 7) and a stereodrawing of the unit cell (Figure 2) (3 pages); listing of F_{obs} vs F_{calc} (Table 8) (3 pages). Ordering information is given on any current masthead page.

A Short, Enantioselective Synthesis of (-)-Swainsonine[1]

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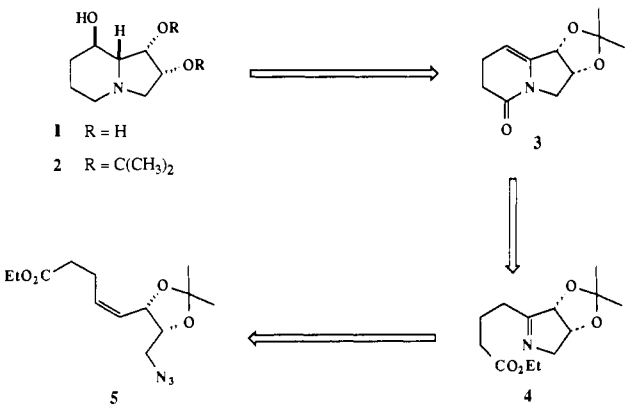
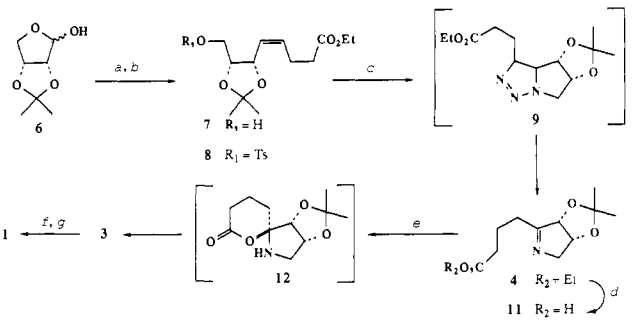
Abstract: A practical, enantioselective synthesis of (-)-swainsonine (**1**) has been achieved in seven steps from 2,3-*O*-isopropylidene-D-erythrose (**6**). The key step involves the construction of the bicyclic imine **4** by an intramolecular 1,3 dipolar cycloaddition of azide **5**. This study highlights the synthetic utility of the intramolecular 1,3 dipolar cycloaddition of the unactivated olefinic azides in natural product synthesis.

From the fungus *Rhizoctonia leguminicola* there was isolated a toxic indolizidine alkaloid, swainsonine (**1**).[3] Swainsonine has also been shown to be present in locoweed (*Astragalus lentiginosus*[4a]) and *Swainsona canescens*,[4b] as well as in the fungus *Metarhizium anisopliae*.[5] The pronounced α-mannosidase inhibitory[6] and immunoregulative[5,7] properties of swainsonine have stimulated considerable interest in biosynthetic[8] and pharmacological[9] studies, and its total synthesis has been achieved by several groups.[10] As demand for swainsonine in cancer research remains

Scheme I



Scheme II[a]



[a] Reagents and conditions: (a) $Br^-Ph_3P^+CH_2CH_2CH_2CO_2Et$, KN(TMS)$_2$, THF, -78 °C; (b) *p*-TsCl, Et_3N, CH_2Cl_2; (c) NaN_3, DMF, 70 → 100 °C; (d) K_2CO_3, aqueous MeOH, room temperature; (e) toluene, reflux; (f) BH_3, THF/H_2O_2-NaOH; (g) 6 N HCl, THF.

(1) A preliminary account of this work was presented in part at the 16th International Symposium on the Chemistry of Natural Products, Kyoto, Japan, May 29-June 3, 1988 and at the 3rd Chemical Congress of North America, Toronto, Canada, June 1988.

(2) Undergraduate Research Participant.

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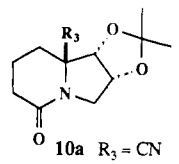
high, its chemical preparation as a practical alternative to natural sources is highly desirable. Herein we wish to report a practical and enantioselective synthesis of (-)-swainsonine (**1**), which is amenable to large-scale preparation.

According to our retrosynthetic analysis (Scheme I), swainsonine should be readily available from enamide **3**, which in turn might be derived from imine **4**. The stereospecific hydroboration[11] of enamide **3** can be expected to take place on the least hindered, convex face of the molecule. We envisioned the construction of the bicyclic imine **4** by an intramolecular 1,3 dipolar cycloaddition of the olefinic azide **5**.[12]

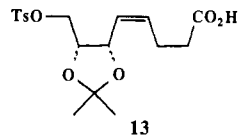
In fact, this conceptually appealing cycloaddition approach was readily reduced to practice. The requisite starting material was found in alcohol **7**, which was readily prepared, in 50–65% yield, by coupling the known 2,3-*O*-isopropylidene-D-erythrose (**6**)[13] with (3-carbethoxypropyl)triphenylphosphonium bromide[14] [KN-$(SiMe_3)_2$, THF, -78 → 0 °C] (Scheme II).[15] Treatment of alcohol **7** with *p*-toluenesulfonyl chloride, followed by the displacement of the *p*-tosyl group with NaN_3 (DMF, 70 → 100 °C) and the concomitant 1,3 dipolar cycloaddition gave the imino ester **4** in 81% overall yield.[16] Triazoline **9** was assumed to be an intermediate that readily undergoes decomposition to give imine **4**. Interestingly, none of the corresponding aziridine was found in the reaction mixture.

Despite many attempts under various conditions, not surprisingly, the imino ester **4** failed to cyclize to enamide **3**. In sharp contrast, treatment of **4** with aluminum reagents (Et_2AlCN or Me_2AlSPh)[17] at room temperature yielded amides **10a** and **10b**



10a R_3 = CN

10b R_3 = SPh



13

in good yield. Unfortunately, their conversion to **3** could not be accomplished in reasonable yield. At this juncture it appeared to us that acid **11** would undergo the internal cyclization to provide lactone **12**, which would then suffer acyl group migration and subsequent dehydration. Some credence for this approach was found in an exploratory experiment in which treatment of acid **13** with NaN_3 (DMF, 70 → 100 °C) gave directly, albeit in poor (6%) yield, the desired enamide **3**, in addition to several unidentified products. Consequently, the crystalline acid **11** (mp 108–110 °C) was prepared (74% yield) by mild hydrolysis (K_2CO_3, aqueous MeOH) of the imino ester **4**. When the former was heated at reflux in toluene, the desired transformation to **3** was achieved in 87% yield.

Treatment of **3** with diborane in THF produced the crystalline swainsonine acetonide (**2**) [mp 101–103 °C (lit.[3a] mp 105–107 °C)] as a single diastereomer, in 79% yield. The synthesis was then completed by acid hydrolysis (6 N HCl, THF)[10a,f] of **2** to yield swainsonine (**1**) in 85% yield as a colorless solid, identical with an authentic sample by melting point and mixed melting point [mp 140–142 °C (lit.[3a] mp 144–145 °C)], ^1H and ^{13}C NMR, IR, TLC behavior in several solvent systems, and mass spectral comparison.

In summary, a short and enantioselective synthesis of swainsonine (**1**) has been achieved in seven steps from the known and readily available 2,3-*O*-isopropylidene-D-erythrose (**6**). This study highlights the synthetic utility of the intramolecular 1,3 dipolar cycloaddition of unactivated olefinic azides in natural product synthesis. Further efforts to extend our basic strategy to other alkaloids as well as structural analogues of swainsonine (**1**) are in progress.[18]

Experimental Section

General Procedures. Tetrahydrofuran was distilled from sodium benzophenone ketyl under nitrogen. Methylene chloride and triethylamine were distilled from CaH_2. All reactions were carried out under nitrogen atmosphere and were monitored by analytical thin-layer chromatographic methods (TLC) using E. Merck silica gel 60F-254 glass plates (0.25 mm). Flash column chromatography was carried out by using E. Merck silica gel 60 (0.063–0.200 mm).

(+)-(4*R*,*cis*)(*Z*)-2,2-Dimethyl-5-(4-carbethoxy-1-butenyl)-1,3-dioxolane-4-methanol (7). To a solution of (3-carbethoxypropyl)triphenylphosphonium bromide (19.52 g, 42.7 mmol) in anhydrous THF (50 mL) was added dropwise potassium bis(trimethylsilyl)amide [KN-$(SiMe_3)_2$] (82 mL, 41.0 mmol) at 0 °C over 10 min. The resulting red solution was stirred for an additional 30 min at 0 °C and then cooled to -78 °C. A solution of 2,3-*O*-isopropylidene-D-erythrose[13] (2.74 g, 17.09 mmol) in THF (15 mL) was added dropwise. The reaction mixture was brought to room temperature overnight and then quenched with saturated aqueous NH_4Cl. The product was extracted with ether, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by SiO_2 column chromatography yielded 2.55 g (58%) of **7**, as a pale, yellow oil: $[\alpha]^{25}_D$ = +29.25° (*c* 3.33, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, 3 H, *J* = 7.1 Hz), 1.40 (s, 3 H), 1.50 (s, 3 H), 1.95 (t, 1 H, *J* = 5.8 Hz), 2.33–2.50 (m, 4 H), 3.57 (t, 2 H, *J* = 5.8 Hz), 4.13 (q, 2 H, *J* = 7.1 Hz), 4.27 (m, 1 H), 5.05 (t, 1 H, *J* = 7.4 Hz), 5.53 (dd, 1 H, *J* = 7.4 and 11.0 Hz), 5.61 (m, 1 H); HRMS (M - CH_3) 243.1233 calcd for $C_{13}H_{22}O_5(-CH_3)$, found 243.1226.

(+)-(4*R*,*cis*)(*Z*)-2,2-Dimethyl-5-(4-carbethoxy-1-butenyl)-1,3-dioxolane-4-methanol *p*-Toluenesulfonate (8). To a solution of alcohol **7** (1.958 g, 7.57 mmol) and triethylamine (1.6 ml, 11.47 mmol) in dry $CHCl_2$ (28 mL) at 0 °C were added *p*-toluenesulfonyl chloride (1.64 g, 8.60 mmol) and *N*,*N*-dimethyl-4-aminopyridine (89 mg, 0.73 mmol). The mixture was stirred at room temperature for 20 h and was then diluted with ethyl acetate (200 mL). The reaction mixture was washed with H_2O (2 × 40 mL), saturated aqueous $NaHCO_3$ (2 × 40 mL), and brine solution (1 × 40 mL), dried over Na_2SO_4, and concentrated in vacuo to a yellow oil. Purification by SiO_2 column chromatography yielded 2.64 g (85%) of tosylate **8**, as a pale, yellow oil: $[\alpha]^{25}_D$ = +25.48° (*c* 2.41, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, 3 H, *J* = 7.2 Hz), 1.33 (s, 3 H), 1.36 (s, 3 H), 2.35–2.39 (m, 4 H), 2.44 (s, 3 H), 3.88 (dd, 1 H, *J* = 6.8 and 10.2 Hz), 4.01 (dd, 1 H, *J* = 4.6 and 10.2 Hz), 4.12 (q, 2 H, *J* = 7.2 Hz), 4.32 (m, 1 H), 5.00 (dd, 1 H, *J* = 6.6 and 8.7 Hz), 5.35 (dd, 1 H, *J* = 8.7 and 10.4 Hz), 5.58 (m, 1 H), 7.34 (d, 2 H, *J* = 8.2 Hz), 7.79 (d, 2 H, *J* = 8.2 Hz).

(-)-(1*S*,5*R*)-3,3-Dimethyl-8-(3-carbethoxy-1-propyl)-7-aza-2,4-dioxabicyclo[3.3.0]oct-7-ene (4). To a solution of tosylate **8** (122.4 mg, 0.30

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(18) The synthesis of stereoisomers and structural analogues of swainsonine is of current interest in the attempt to elucidate the correlation of structure and biological activity.

mmol) in DMF (3 mL) was added sodium azide (98.7 mg, 1.52 mmol). The mixture was heated at 80 °C for approximately 48 h under N_2 atmosphere. The mixture was then diluted with ethyl acetate (40 mL), washed with H_2O (3 × 5 mL) and brine solution (2 × 5 mL), dried over Na_2SO_4, and concentrated in vacuo. The product was purified by SiO_2 column chromatography (eluted with 1:1 hexane/ethyl acetate, R_f = 0.21) to afford 72 mg (95%) of the imino ester **4**, as a viscous, yellow oil: $[\alpha]^{25}_D = -34.25°$ (*c* 2.73, $CHCl_3$); IR ($CHCl_3$) 1635 (s), 1720 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20 (t, 3 H, *J* = 7.1 Hz), 1.30 (s, 3 H), 1.31 (s, 3 H), 1.91–2.02 (m, 2 H), 2.31–2.52 (m, 4 H), 3.81 (br d, 1 H, A of AB q), 3.94 (d, 1 H, B or AB q, *J* = 16.9 Hz), 4.07 (q, 2 H, *J* = 7.1 Hz), 4.67 (m, 1 H), 4.86 (d, 1 H, J = 5.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.13, 20.88, 25.60, 26.80, 29.91, 33.66, 60.20, 64.63, 77.64, 86.52, 111.77, 173.13, 175.84; HRMS ($M^+ - C_2H_5OH$) 209.1052 calcd for $C_{13}H_{21}NO_4(-C_2H_5OH)$, found 209.1049.

(−)-(1*S*,5*R*)-3,3-Dimethyl-8-(3-carboxy-1-propyl)-7-aza-2,4-dioxabicyclo[3.3.0]oct-7-ene (11). The imino ester **4** (884 mg, 3.46 mmol) was dissolved in 33 mL of methanol and 10 mL of water. Potassium carbonate (1.20 g, 8.75 mmol) was added. The mixture was stirred at room temperature for 12 h and was concentrated in vacuo to remove MeOH. The aqueous mixture was washed with ether (1 × 10 mL) and then cooled to 0 °C. After the pH of the solution was adjusted to 3 with 1 N HCl, the solution was saturated with solid sodium chloride. The aqueous layer was repeatedly extracted with ethyl acetate and methylene chloride. The organic extracts were combined, dried over Na_2SO_4, and concentrated in vacuo to give 579 mg (74% yield) of acid **11**, as a yellow solid: mp 105–110 °C $[\alpha]^{25}_D = -28.46°$ (*c* 0.98, $CHCl_3$); IR ($CHCl_3$) 3510 (br), 1720 (s), 1640 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.34 (s, 6 H), 1.91–2.04 (m, 2 H), 2.33–2.38 (m, 2 H), 2.45–2.64 (m, 2 H), 3.88 (br d, 1 H, A of AB q), 3.98 (d, 1 H, B of AB q, *J* = 16.8 Hz), 4.72 (m, 1 H), 4.95 (d, 1 H, *J* = 5.7 Hz), 9.47–9.82 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.81, 25.53, 26.83, 29.74, 33.54, 63.53, 77.24, 86.32, 112.09, 176.31, 177.76.

(−)-(7*S*,8*R*)-7,8-*O*-Isopropylidenedioxy-2-oxo-1-azabicyclo[4.3.0]non-5-ene (3). A solution of acid **11** (355 mg, 1.56 mmol) in toluene (35 mL) was refluxed with a Dean–Stark trap for 30 h. The solution was then cooled to room temperature, and the solvent was removed in vacuo. The residue was purified by SiO_2 column chromatography (eluted with 1:1 hexane/ethyl acetate, R_f = 0.5 in 10:1 CH_2Cl_2/MeOH) to provide 284 mg (87%) of enamide **3**: $[\alpha]^{25}_D = -86.70°$ (*c* 1.82, $CHCl_3$); IR ($CHCl_3$) 1650 (s), 1680 (sh) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.36 (s, 3 H), 1.45 (s, 3 H), 2.34–2.57 (m, 4 H), 3.70 (dd, 1 H, *J* = 5.5 and 13.1 Hz), 3.86 (d, 1 H, *J* = 13.1 Hz), 4.73 (br t, 1 H), 5.03 (d, 1 H, J = 5.9 Hz), 5.24 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.85, 25.69, 27.44, 30.44, 49.95, 75.88, 79.30, 101.59, 112.76, 139.95, 168.50; HRMS (M^+) 209.1052 calcd for $C_{11}H_{15}NO_3$, found 209.1047.

(−)-(1*S*,2*R*,8*R*,8a*R*)-1,2-*O*-Isopropylidenedioxy-8-hydroxyindolizidine (Swainsonine Acetonide; 2). To a cold (0 °C) solution of enamide 3 (261 mg, 1.29 mmol) in anhydrous THF (1.6 mL) was added 5.0 mL of 1.0 M BH_3·THF solution. The reaction was brought to room temperature overnight. The solvent was removed in vacuo, and ethanol (3 mL) was then added. To this solution were added sodium hydroxide (208 mg, 5.20 mmol) and 30% hydrogen peroxide (0.6 mL). An additional 2 mL of ethanol was added and the mixture refluxed for 2 h. The mixture was cooled, the ethanol removed in vacuo, and the residue dissolved in 3 mL of H_2O. The aqueous solution was saturated with solid NaCl and then extracted five times each with ethyl acetate and methylene chloride. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to give crude **2** as a colorless solid. Purification by SiO_2 column chromatography (eluted with 25:1 CH_2Cl_2/MeOH) afforded 209.1 mg (79%) of the pure product (visualized with I_2) as a white crystal: mp 100–103 °C; $[\alpha]^{25}_D = -72.76°$ (*c* 0.43, MeOH) [lit.[3a] $[\alpha]^{24}_D = -75.1°$ (*c* 1.54, MeOH)]; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.18–1.24 (m, 1 H), 1.33 (s, 3 H), 1.51 (s, 3 H), 1.61–1.70 (m, 4 H), 1.85 (m, 1 H), 2.05 (m, 1 H), 2.13 (dd, *J* = 4.2 and 10.7 Hz, 1 H), 2.98 (dt, *J* = 3.2 and 10.6 Hz, 1 H), 3.16 (d, *J* = 10.7 Hz, 1 H), 3.81–3.87 (m, 1 H), 4.61 (dd, *J* = 4.2 and 6.2 Hz, 1 H), 4.71 (dd, *J* = 4.6 and 6.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.08, 24.81, 25.96, 33.01, 51.60, 59.88, 67.53, 73.68, 78.26, 79.17, 111.37; HRMS (M^+) 213.1365 calcd for $C_{11}H_{19}NO_3$, found 213.1366.

(−)-(1*S*,2*R*,8*R*,8a*R*)-1,2,8-Trihydroxyoctahydroindolizine (Swainsonine; 1). To a solution of acetonide **2** (104 mg, 0.49 mmol) in THF (6.5 mL) was added 6.0 mL of 6 N HCl. The colorless solution was stirred overnight at room temperature. The solvent was removed in vacuo, leaving a colorless, viscous oil. The oil was then purified by ion-exchange chromatography (Dowex-1X8). Fractions (visualized with iodine or ninhydrin) were collected and concentrated in vacuo to furnish 72 mg (85% yield) of **1** as a white solid: mp and mixed mp 140–142 °C [lit.[3a] mp 144–145 °C]; $[\alpha]^{25}_D = -75.71°$ (*c* 2.33, MeOH) [lit.[3a] $[\alpha]^{25}_D = -87.2°$ (*c* 2.1, MeOH); lit.[4b] $[\alpha]^{25}_D = -78.9°$ (*c* 1.14, MeOH)]; R_f = 0.36 in 1-butanol/chloroform/methanol/concentrated ammonium hydroxide (4:4:4:1); ^1H NMR (D_2O, ref DSS, 300 MHz) δ 4.34 (m, 1 H, H-2), 4.24 (dd, $J_{1,8a}$ = 3.7 Hz, $J_{1,2}$ = 6.1 Hz, 1 H, H-1), 3.78 (ddd, *J* = 3.9, 9.3, and 10.7 Hz, 1 H, H-8), 2.89 (m, 1 H), 2.86 (dd, *J* = 2.6 and 11.0 Hz, 1 H, H-3), 2.53 (dd, *J* = 7.8 and 11.0 Hz, 1 H, H-3′), 2.04 (m, 1 H), 1.96 (m, 1 H), 1.89 (dd, $J_{8a,8}$ = 9.3 Hz, $J_{8a,1}$ = 3.7 Hz, H-8a), 1.70 (m, 1 H), 1.49 (m, 1 H), 1.22 (m, 1 H); ^{13}C NMR (D_2O, ref CH_3CN, 100 MHz) δ 23.21, 32.51, 51.72, 60.65, 66.37, 69.08, 69.72, 72.87; HRMS (M^+) 173.1052 calcd for $C_8H_{15}NO_3$, found 173.1041.

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Theonellamide F. A Novel Antifungal Bicyclic Peptide from a Marine Sponge *Theonella* Sp.[1]

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Abstract: A novel antifungal peptide, theonellamide F, was isolated from a marine sponge, genus *Theonella*. It is a dodecapeptide composed of L-Asn, L-*a*Thr, two residues of L-Ser, L-Phe, β-Ala, (2*S*,3*R*)-3-hydroxyasparagine, (2*S*,4*R*)-2-amino-4-hydroxyadipic acid, τ-L-histidino-D-alanine, L-*p*-bromophenylalanine, and (3*S*,4*S*,5*E*,7*E*)-3-amino-4-hydroxy-6-methyl-8-(*p*-bromophenyl)-5,7-octadienoic acid. Its bicyclic structure including absolute stereochemistry was unequivocally determined as **1**, which contains an unprecedented histidinoalanine bridge.

Marine sponges of the family Theonellidae, which includes the genera *Theonella* and *Discodermia*, have proved to be a source of metabolites with interesting biological activities as well as chemical structures. Compounds derived from this family are roughly divided into two classes:[2] (a) peptides, discodermins from

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