# Efficient Chemical Conversion of Louisianin A to C and D, The Inhibitor of Angiogenesis

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Louisianins A to D were isolated from the fermentation broth of *Streptomyces* sp. WK-4028. Among the components, louisianin A (**1**) remarkably inhibited the growth of testosterone-responsive Shionogi carcinoma SC 115 cells in the presence of $10^{-7}$ M testosterone with an $IC_{50}$ value of 0.6 $\mu$g/ml [1,2]. On the other hand, louisianin C (**5**) and D (**6**) showed only a slight inhibitory activity on the growth of testosterone-responsive SC 115 cells.

Recently, in the course of a screening program aimed at antiangiogenic activity, we found that louisianin C (**5**) and D (**6**) potently suppressed the tube formation of cultured vascular endothelical cells *in vitro*.

However, only a small quantities of louisianin C (**5**) and D (**6**) were isolated from the fermentation broth of *Streptomyces* sp. WK-4028, whereas there is a large production of louisianin A (**1**).

Therefore, to obtain more louisianin C and D, we attempted an efficient chemical conversion from louisianin A (**1**).

Louisianin A (**1**) was treated with phosphoryl chloride ($POCl_3$) at 120~125°C[3] to obtain chloro derivative (**2**) in 86% yield. **2** was reduced by Zn-AcOH at 50°C[4] to afford **3** (52% yield) and **4** (35% yield). Furthermore, under the same condition, **3** was dechlorinated to give **4** in 48% yield. Moreover, **4** was oxidized in the treatment of $CrO_3$-pyridine[5] to obtain louisianin C (**5**) in 75% yield. Finally, **5** was treated with 1,8-diazabicyclo-[5,4,0]-undec-7-ene (DBU) in benzene at 85°C[6] to obtain louisianin D (**6**) in 84% yield. (Scheme 1)

In summary, the efficient conversion of louisianin A (**1**) to C (**5**) (51% overall yield, based on **3** recovered), and D (**6**) (43% overall yield, based on **3** recovered) enables us to prepare additional quantities of louisianin C (**5**), and D (**6**) to clarify their biological activity.

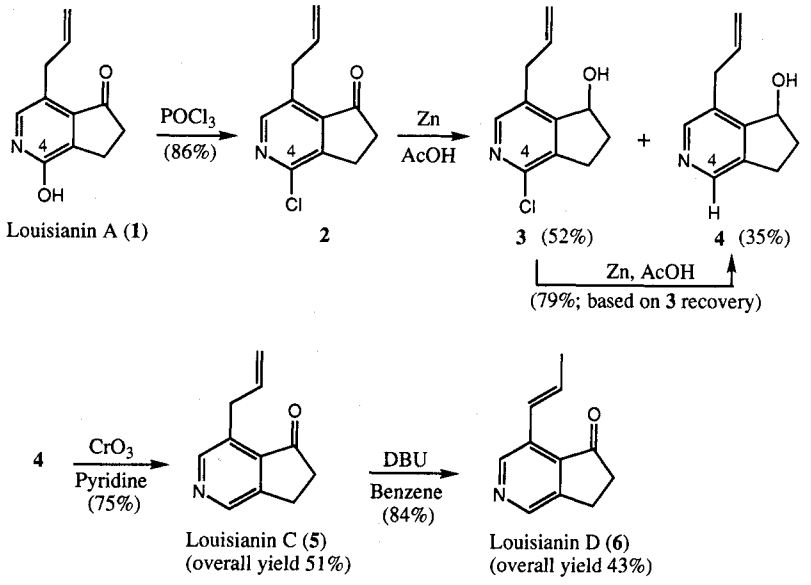
## Experimental

Melting points were determined with a Yanaco micro melting point apparatus and are uncorrected. $^1H$ NMR spectra and $^{13}C$ NMR spectra were measured with a JEOL EX-270 or a Varian VEX-300 spectrometer. Mass spectra were recorded on a JEOL JMS-DX 300 or a JEOL JMS-AX 505 HA. IR spectra were recorded on a HORIBA FT-210 spectrophotometer. Precoated TLC Merck silica gel 60 $F_{254}$ plates (0.25 or 0.5 mm thick, 20 × 20 cm) were used for preparative TLC (PTLC). All reactions were performed under Argon atmosphere.

7-Allyl-5-aza-4-chloro-indan-1-one (**2**)

The solution of **1** (48.7 mg, 0.26 mmol) in $POCl_3$ (3 ml) was stirred at 120~125°C for 4 hours. The reaction mixture was cooled with an ice bath and saturated aqueous $NaHCO_3$ (30 ml) was added slowly. The mixture was extracted with $CHCl_3$ (10 ml × 1, 5 ml × 2). The extract was washed with water then with saturated aqueous NaCl, and dried over $Na_2SO_4$. It was filtered and the filtrate was concentrated on a rotary evaporator. The

Scheme 1. Efficient synthetic conversion from louisianin A (**1**) to D (**6**).



residue was subjected by PTLC ($CH_2Cl_2$ : $CH_3OH$ 15 : 1) to give **2** (41.7 mg, 86.0%): yellow oil; IR (film) $cm^{-1}$ 3431 (m), 3080 (m), 2980 (m), 2925 (s), 2852 (w), 2357 (w), 1973 (w), 1720 (s), 1639 (m), 1573 (m), 1448 (s), 1402 (m), 1375 (m), 1296 (m), 1270 (m), 1253 (m), 1211 (m), 1192 (m), 1165 (m), 1095 (w), 1058 (m), 985 (m), 977 (m), 918 (m), 854 (m), 831 (w); $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 8.18 (1H, s), 5.96~5.81 (1H, m), 5.05~4.97 (2H, m), 3.71 (2H, d, $J$=6.6 Hz), 3.08~3.03 (2H, m), 2.72~2.67 (2H, m). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 205.87, 149.22, 148.98, 147.41, 142.50, 134.93, 132.54, 117.14. 36.35, 32.05, 24.05; MS (EI) *m/z* 207 ($M^+$), 192 ($M^+-15$); HR EI-MS (*m/z*:) found: 207.0453 ($M^+$), calcd for $C_{11}H_{10}ClNO$: 207.0451.

7-Allyl-5-aza-4-chloro-1-hydroxy-indan (**3**) and 7-Allyl-5-aza-1-hydroxy-indan (**4**)

The mixture of **2** (41.7 mg, 0.20 mmol) and Zn powder (394 mg, 6.0 mmol) in AcOH (5 ml) were stirred at 50°C. After 18 hours, the reaction mixture was filtered. The filtrate was washed with $CHCl_3$, and the chloroform washings were concentrated *in vacuo*, and subjected by PTLC ($CH_2Cl_2$-$CH_3OH$ 15:1) to give **3** (21.9 mg, 52.0%) and **4** (12.3 mg, 35.0%). Under the same condition, **3** (21.9 mg, 0.10 mmol) was dechlorinated to give **4** (8.6 mg, 48.3%). **3**: colorless solid, mp 85~87 °C; IR (film) $cm^{-1}$ 3257 (s), 3072 (m), 2972 (m), 2942 (m), 2920 (m), 2860 (w), 2362 (w), 1635 (w), 1577 (m), 1450 (s), 1429 (m), 1394 (m), 1315 (m), 1292 (m), 1213 (w), 1184 (m), 1166 (m), 1078 (m), 1039 (w), 1005 (m), 975 (w), 910 (s), 864 (m); $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 7.98 (1H, s), 6.00~5.85 (1H, m), 5.31 (1H, dd, $J$=4.0, 6.9 Hz), 5.09~4.97 (2H, m), 3.52 (1H, dd, $J$=6.3, 15.8 Hz), 3.41 (1H, dd, $J$=6.3, 15.8 Hz), 3.06 (1H, ddd, $J$=6.3, 8.6, 17.2 Hz), 2.79 (1H, ddd, $J$=4.9, 8.9, 17.2 Hz), 2.46~2.32 (1H, m), 2.06~1.94 (1H, m), 1.89 (1H, br s); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 154.22, 148.56, 146.40, 137.78, 136.23, 131.35, 116.85, 75.35, 34.06, 33.60, 28.85; MS (EI) *m/z* 209 ($M^+$), 191 ($M^+-18$), 156 ($M^+-53$); HR EI-MS (*m/z*:) found: 209.0607 ($M^+$), calcd for $C_{11}H_{12}ClNO$: 209.0607; **4**: colorless oil; IR (film) $cm^{-1}$ 3210 (s), 3190 (s), 3080 (m), 2973 (m), 2931 (s), 2850 (m), 2717 (m), 1718 (m), 1637 (m), 1595 (m), 1423 (s), 1317 (m), 1288 (m), 1253 (m), 1172 (s), 1052 (s), 995 (m), 914 (s); $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 8.36 (1H, s), 8.21 (1H, s), 6.04~5.89 (1H, m), 5.29 (1H, dd, $J$=3.6, 6.9 Hz), 5.09~4.97 (2H, m), 3.55 (1H, dd, $J$=6.3, 15.5 Hz), 3.44 (1H, dd, $J$=6.3, 15.5 Hz), 3.08 (1H, dd, $J$=7.6, 16.2 Hz), 2.78 (1H, ddd, $J$=4.9, 8.6, 16.2 Hz), 2.42~2.28 (1H, m), 2.05~1.93 (1H, m), 1.76 (1H, br s); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 151.88, 148.16, 144.63, 139.19, 136.61, 132.07, 116.56, 74.57, 34.88, 34.15, 27.74; MS (EI) *m/z* 175 ($M^+$), 160 ($M^+-15$); MS (FAB, pos.) 176 ($M^++1$).

7-Allyl-5-aza-indan-1-one [louisianin C] (**5**)

To the solution of **4** (37.4 mg, 0.21 mmol) in pyridine (2 ml) $CrO_3$ (64.0 mg, 0.64 mmol) was added and the mixture was stirred at room temperature. After 2.5 hours, the reaction mixture was diluted with water (5 ml), extracted with AcOEt (10 ml × 2). The combined extracts were washed with saturated aqueous NaCl, dried over $Na_2SO_4$ and concentrated on a rotary evaporator. The residue was subjected by PTLC ($CH_2Cl_2$-$CH_3OH$ 15:1) to give **5** (27.7 mg, 74.9%): colorless oil. Spectral data (IR, $^1H$ and $^{13}C$ NMR and MS) of **5** were identical with louisianin C[2].

5-Aza-7-(*trans*-propeny)-indan-1-one [louisianin D] (**6**)

To the solution of **5** (11 mg, 0.064 mmol) in benzene (1 ml) DBU (19.5 mg, 0.13 mmol) was added and the mixture was stirred at 85°C. After 1 hour, the reaction mixture was cooled and benzene (10 ml) was added. The mixture was washed with saturated aqueous NaCl, dried over $Na_2SO_4$ and concentrated on a rotary evaporator. The residue was subjected by PTLC ($CH_2Cl_2$-$CH_3OH$ 20:1) to give **6** (9.2 mg, 83.6%) : colorless solid, mp 83~86°C. Spectral data (IR, $^1H$ and $^{13}C$ NMR and MS) of **6** were identical with louisianin D[2].

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