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# First Total Synthesis of Louisianin A

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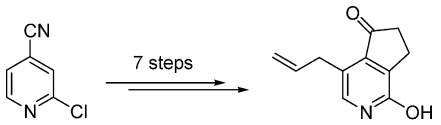
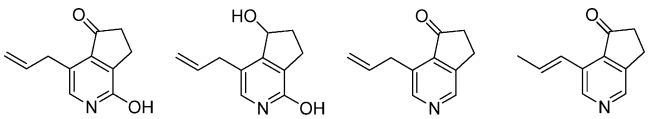



**5** **1**

**Louisianin A**

The first total synthesis of louisianin A, 4-allyl-6,7-dihydro-1-hydroxycyclopenta[*c*]pyridin-5-one, is achieved from 2-chloro-4-cyanopyridine **5** via seven steps in an overall 24% yield. The key step is a cyclization−decarboxylation sequence toward the formation of a cyclopentenone ring.

Louisianins A−D (**1**−**4**) were produced in the cultured broth



**1** **2** **3** **4**

of *Streptomyces* sp. WK-4028, which has been isolated from a soil sample collected in Louisiana (U.S.A.).[1] Louisianin A showed highly potent inhibition of the growth of testosterone-responsive Shionogi carcinoma SC 115 cells with an $IC_{50}$ value of 0.6 $\mu$g/mL in the presence of $10^{-7}$ M testosterone.[2] Louisianin A has been converted to louisianin C, which was then isomerized to louisianin D. Louisianins C and D exhibited potent suppression for the formation of cultured vascular endothelial cells in vitro.[3] To date, the only report concerning the synthesis of louisianins, which detailed the preparation of louisianin C in 11% overall yield (Kelly et al.),[4] started from 3,5-dibromopyridine. Syntheses of other members in the family have not appeared in the literature. In this report we describe the first total synthesis of louisianin A from a readily available starting material 2-chloro-4-cyanopyridine (**5**).

The main structural feature of louisianins is a pyridine ring fused with cyclopentenone. In the earlier synthetic design for louisianin C (**3**), a symmetrical 3,5-diallyl-substituted pyridine was used as a key intermediate.[4] Ring closure at C(4) by either of the two allyl groups resulted in an identical product. Such a strategy, however, cannot be utilized successfully for the synthesis of louisianins A (**1**) and B (**2**), in which the presence of a hydroxyl group at C(2) breaks the symmetry of pyridine ring. In the present design the two alkyl substituents at C(3) and C(5) were introduced sequentially, so that the direction of cyclopentenone ring closure could be effectively controlled.

The complete synthetic sequence is outlined in Scheme 1, starting from the unsymmetrical 2-chloro-4-cyanopyridine (**5**). Deprotonation of **5** at C(3) by lithium diisopropylamide (LDA) at −78 °C,[5] followed by iodination afforded 2-chloro-4-cyano-3-iodopyridine (**6**) in 42% yield. The yield of **6** can be improved to 68% by performing the reaction at −95 °C employing kinetic control over site selectivity of deprotonation.[6] A small coupling constant (ca. 5 Hz) between the C(5) and C(6) of aromatic protons verified their relative ortho-position, thus confirming that iodination had occurred at C(3).

The chlorine atom at C(2) of **6** was transformed to a methoxy group of **7** in 92% yield.[7] The three-carbon side chain at C(3) was added to yield **8** in good yield (95%) by coupling with methyl acrylate under standard palladium(0)-catalyzed Heck conditions.[8] A large coupling constant (16 Hz) for the olefinic protons, which appeared at $\delta$ 7.1 and 7.9, suggested a transoid geometry of the double bond. Hydrogenation of **8** with 5% Pd/C afforded **9** in 91% yield. The ester group was unaffected as indicated by the persistence of a strong absorption at 1739 $cm^{-1}$.

The substituent at C(5) was introduced by bromination in acetic acid to afford compound **10** regioselectively in 85%.[9] The position of bromine was determined by the disappearance of proton signal at $\delta$ 7.1 in **9**, while maintaining the signal at $\delta$ 8.2 (H(6)) as a singlet. The bromine substituent was transformed to an allyl group via Pd(0)-catalyzed Stille coupling to allyltri-

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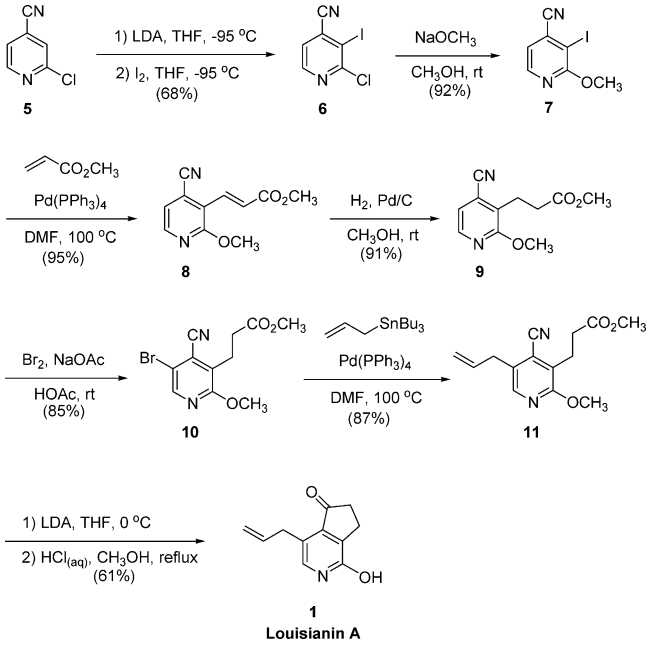
**SCHEME 1**




*n*-butyltin.[4,10] When compound **10** was treated with allyltri-*n*-butyltin and $Pd(PPh_3)_4$ in DMF at 100 °C for 20 h, the products were found to be a 8:1 mixture of **11** and a double bond migrated isomer.[10b] The degree of isomerization can be depressed by reducing the reacting time. An optimal yield of 87% without double bond migration was achieved by completing the reaction in 6.5 h.

The final step was a cyclization−decarboxylation sequence for the generation of a fused cyclopenteone ring of louisianin A. It was accomplished by deprotonation of **11** with LDA at 0 °C, followed by a nucleophilic attack on the cyano group to close the ring. Hydrolysis under acidic conditions induced decarboxylation to **1**. In this process the methoxy group at C(2) was also transformed to the desired hydroxy group. The yield of this final step was remarkably good (61%). The spectral features of louisianin A thus prepared were consistent with those reported in the literature.[1]

The total synthesis of louisianin A has been achieved starting from 2-chloro-4-cyanopyridine **5** in seven steps with high yield. The geometry of the final product was confirmed by spectral comparison with authentic samples. We are actively pursuing the synthesis of other members of the louisianin family, progress toward which will be reported in due course.

## Experimental Section

**2-Chloro-4-cyano-3-iodopyridine (6).** To a solution of 2-chloro-4-cyanopyridine (**5**) (1.39 g, 10 mmol) in dry THF (50 mL) was added a LDA solution (12 mmol) at −95 °C under nitrogen over a period of 2 min. A solution of iodine (3.8 g, 15 mmol, 1.5 equiv) in THF (10 mL) was added at −95 °C over another 2 min. The mixture was stirred overnight, then was quenched by the addition of a saturated sodium sulfite solution (30 mL) at 0 °C. The resulting mixture was extracted with ethyl acetate (3 × 50 mL). The extracts were combined and washed with saturated sodium sulfite (15 mL) and brine (15 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford a brownish solid (2.82 g). The crude product was purified by flash column chromatography eluting with hexane/EtOAc (10:1). Compound **6** (1.80 g, 68%) was collected as a white solid. Mp 149−150 °C; IR (KBr) 3071, 2233, 1582, 1557, 1429, 1339 1174 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.52 (d, $J$ = 4.8 Hz, 1H), 7.40 (d, $J$ = 4.8 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 157.0, 149.1, 131.9, 125.3, 117.1, 99.3; MS (EI): *m*/*z* 264 ($M^+$); HRMS (EI) *m*/*z* calcd for $C_6H_2N_2ClI$ 263.8951, found 263.8954. Anal. Calcd for $C_6H_2N_2ClI$: C, 27.24; H, 0.76; N, 10.59. Found: C, 27.46; H, 0.67; N, 10.70.

**4-Cyano-3-iodo-2-methoxypyridine (7).** A solution of sodium methoxide was freshly prepared by adding sodium (0.46 g, 20 mmol, 2 equiv) to methanol (30 mL) under nitrogen at 0 °C. To this solution was added 2-chloro-4-cyano-3-iodopyridine (**6**) (2.645 g, 10 mmol), and the solution was stirred at room temperature for 16 h, while the reaction was monitored by thin-layer chromatography (TLC). Upon completion the solvent was evaporated, and distilled water (20 mL) was added. The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The combined extract was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to yield a yellowish solid (2.84 g). The product was purified by flash column chromatography eluting with hexane/EtOAc (30:1) to afford **7** (2.39 g, 92%) as a white solid. Mp 163−164 °C; IR (KBr) 2952, 2231, 1570, 1529, 1464, 1373, 1049 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.23 (d, $J$ = 5.2 Hz, 1H), 7.05 (d, $J$ = 5.2 Hz, 1H), 4.03 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 163.1, 147.3, 130.9, 119.8, 117.5, 85.0, 55.5; MS (EI): *m*/*z* 260 ($M^+$); HRMS (EI) *m*/*z* calcd for $C_7H_5N_2OI$ 259.9447, found 259.9445. Anal. Calcd for $C_7H_5N_2OI$: C, 32.32; H, 1.92; N, 10.77. Found: C, 32.59; H, 1.95; N, 10.70.

**(*E*)-Methyl 3-(4′-Cyano-2′-methoxypyridin-3′-yl)acrylate (8).** To a pressure-resistant glass tube containing 4-cyano-3-iodo-2-methoxypyridine (**7**) (0.52 g, 2 mmol) in DMF (3 mL) were added methyl acrylate (0.9 mL, 10 mmol, 5 equiv), triethylamine (0.34 mL, 2.4 mmol, 1.2 equiv), and tetrakis(triphenylphosphine)-palladium (0.116 g, 5 mol %). The solution was frozen at 77 K, and was degassed by pumping under vacuum. The tube was then sealed and heated to 100 °C for 36 h. The reaction was cooled to room temperature and was filtered through silica gel, which was washed with ethyl acetate (3 × 30 mL). The combined solution was concentrated in vacuo to obtain a yellowish solid (0.54 g). The product was purified by flash column chromatography eluted with hexane/EtOAc (10:1) to afford **8** (0.41 g, 95%) as a white solid. Mp 113−114 °C; IR (KBr) 2958, 2235, 1724, 1574, 1553, 1394, 1313, 1051 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.26 (d, $J$ = 5.2 Hz, 1H), 7.89 (d, $J$ = 16 Hz, 1H), 7.18 (d, $J$ = 5.2 Hz, 1H), 7.07 (d, $J$ = 16 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 166.8, 162.2, 147.8, 134.6, 126.2, 122.0, 119.8, 119.3, 115.4, 54.5, 52.0; MS (EI) *m*/*z* 218 ($M^+$); HRMS (EI) *m*/*z* calcd for $C_{11}H_{10}N_2O_3$ 218.0692, found 218.0699. Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.59; N, 12.84. Found: C, 60.77; H, 4.81; N, 12.82.

**Methyl 3-(4′-Cyano-2′-methoxypyridin-3′-yl)propanoate (9).** A round-bottom flask containing **8** (0.79 g, 3.62 mmol) and Pd/C (5%, 0.08 g) in methanol (20 mL) was flushed with hydrogen gas three times. The mixture was stirred with a magnetic bar under hydrogen at atmospheric pressure for 3 h. The solution was filtered and concentrated in vacuo to obtain a viscous liquid (0.84 g). The crude product was purified by flash column chromatography eluting with hexane/EtOAc (5:1) to afford **9** (0.72 g, 91%) as a colorless liquid. IR (neat, KBr) 2953, 2235, 1739, 1588, 1562, 1455, 1393, 1094 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.15 (d, $J$ = 5.2 Hz, 1H), 7.05 (d, $J$ = 5.2 Hz, 1H), 3.99 (s, 3H), 3.70 (s, 3H), 3.14 (t, $J$ = 7.8 Hz, 2H), 2.66 (t, $J$ = 7.8 Hz, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 172.2, 162.2, 145.6, 126.3, 122.0, 118.0, 115.6, 54.0, 51.6, 32.2, 24.3; MS (EI) *m*/*z* 220 ($M^+$); HRMS (EI) *m*/*z* calcd for $C_{11}H_{12}N_2O_3$ 220.0848, found 220.0845. Anal. Calcd for

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$C_{11}H_{12}N_2O_3$: C, 60.00; H, 5.45; N, 12.72. Found: C, 60.15; H, 5.55; N, 12.67.

**Methyl 3-(5′-Bromo-4′-cyano-2′-methoxypyridin-3′-yl)propanoate (10).** To a solution of methyl 3-(4′-cyano-2′-methoxypyridin-3′-yl)propanoate (**9**) (1.25 g, 5.68 mmol) and sodium acetate (0.49 g, 5.98 mmol, 1.05 equiv) in glacial acetic acid (5 mL) was added dropwise bromine (1.46 mL, 28.38 mmol, 5 equiv) at 10 °C. The solution was stirred at room temperature for 24 h. The reaction was quenched by the addition of saturated sodium sulfite solution (15 mL) at 0 °C. The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The combined extract was washed once with saturated sodium sulfite solution (10 mL) and once with brine (10 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford a white solid (1.82 g). The product was purified by flash column chromatography eluted with hexane/EtOAc (15:1) to give **10** (1.44 g, 85%) as a white solid. Mp 99−100 °C; IR (KBr) 2952, 2240, 1739, 1560, 1202, 1171, 1036 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.27 (s, 1H), 3.97 (s, 3H), 3.70 (s, 3H), 3.15 (t, $J$ = 7.6 Hz, 2H), 2.66 (t, $J$ = 7.6 Hz, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 172.0, 161.0, 146.9, 129.0, 124.8, 114.1, 112.0, 54.4, 51.8, 32.1, 25.0; MS (EI) $m/z$ 298 ($M^+$); HRMS (EI) $m/z$ calcd for $C_{11}H_{11}N_2O_3Br$ 297.9953, found 297.9955. Anal. Calcd for $C_{11}H_{11}N_2O_3Br$: C, 44.16; H, 3.68; N, 9.37. Found: C, 44.17; H, 3.82; N, 9.30.

**Methyl 3-(5′-Allyl-4′-cyano-2′-methoxypyridin-3′-yl)propanoate (11).** A solution of methyl 3-(5′-bromo-4′-cyano-2′-methoxypyridin-3′-yl)propanoate (**10**) (0.897 g, 3 mmol) and allyltri-*n*-butyltin (1.12 mL, 3.6 mmol, 1.2 equiv) in DMF (5 mL) was degassed by bubbling nitrogen through it for 30 min. Tetrakis(triphenylphosphine)-palladium (0.35 g, 10 mol %) and the mixture was heated to 100 °C for 6.5 h. The reaction was allowed to cool to ambient temperature and was then filtered through a silica gel pad to remove palladium. The pad was washed with ethyl acetate (3 × 30 mL). The combined solution was concentrated in vacuo to afford a yellowish liquid (1.12 g), which was further purified by flash column chromatography eluting with hexane/EtOAc (15:1) to afford **11** (0.678 g, 87%) as a colorless solid. Mp 51−52 °C; IR (KBr) 2953, 2230, 1740, 1587, 1561, 1472, 1393, 1079 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.01 (s, 1H), 5.98−5.88 (m, 1H), 5.17−5.08 (m, 2H), 3.97 (s, 3H), 3.69 (s, 3H), 3.49 (d, $J$ = 6.4 Hz, 2H), 3.13 (t, $J$ = 7.8 Hz, 2H), 2.65 (t, $J$ = 7.8 Hz, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 172.3, 160.7, 145.5, 134.6, 128.9, 126.1, 122.7, 117.4, 114.5, 53.9, 51.6, 35.1, 32.4, 24.6; MS (EI) $m/z$ 260 ($M^+$); HRMS (EI) $m/z$ calcd for $C_{14}H_{16}N_2O_3$ 260.1161, found 260.1163. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.62; H, 6.15; N, 10.77. Found: C, 64.37; H, 6.14; N, 10.68.

**Louisianin A (1).** To a solution of methyl 3-(5′-allyl-4′-cyano-2′-methoxypyridin- 3′-yl)propanoate (**11**) (0.26 g, 1 mmol) in dry THF (10 mL) was added a LDA solution (1.2 mmol) at 0 °C over a period of 2 min. The reaction solution was stirred at 0 °C for another 2 min, and then the reaction was quenched by the addition of saturated ammonium chloride (5 mL). The resulting mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford a yellow solid (0.28 g). The crude product was dissolved in methanol (10 mL), and the solution was treated with concentrated hydrochloric acid solution (5 mL) at 0 °C. The acidic solution was heated to reflux for 22 h. Methanol was removed by evaporation, and the brownish residue was extracted with ethyl acetate (5 × 20 mL). The combined extract was washed once with saturated sodium bicarbonate solution (10 mL) and once with brine (10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The yellowish crude product (0.16 g) was purified by flash chromatography eluting with hexane/EtOAc (1:3) to give **1** (0.116 g, 61%) as a white solid. Mp 187−188 °C; IR (KBr) 2929, 1716, 1665, 1614, 1448, 1427, 1199 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 12.60 (br, 1H), 7.18 (s, 1H), 5.97−5.87 (m, 1H), 5.10−5.05 (m, 2H), 3.54 (d, $J$ = 6.8 Hz, 2H), 3.02−2.99 (m, 2H), 2.72−2.70 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 207.3, 164.2, 149.2, 144.6, 135.6, 132.3, 116.8, 116.2, 36.2, 31.3, 22.7; MS (EI) $m/z$ 189 ($M^+$); HRMS (EI) $m/z$ calcd for $C_{11}H_{11}NO_2$ 189.0790, found 189.0786.

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**Supporting Information Available:** Experimental general information and $^1H$ and $^{13}C$ NMR spectra for compounds **6**−**11** and louisianin A. This material is available free of charge via the Internet at http://pubs.acs.org.

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