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Synthesis of Louisianin C

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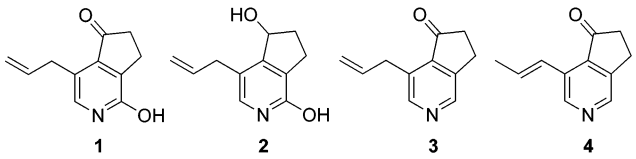
Received February 5, 2003

Abstract: The synthesis of louisianin C (**3**), a member of a small family of 3,4,5-trisubstituted pyridyl natural products, is achieved in six steps and 11% overall yield starting from commercially available 3,5-dibromopyridine. The key step is a fluoride-induced desilylation−cyclization to afford carbinol **12**.

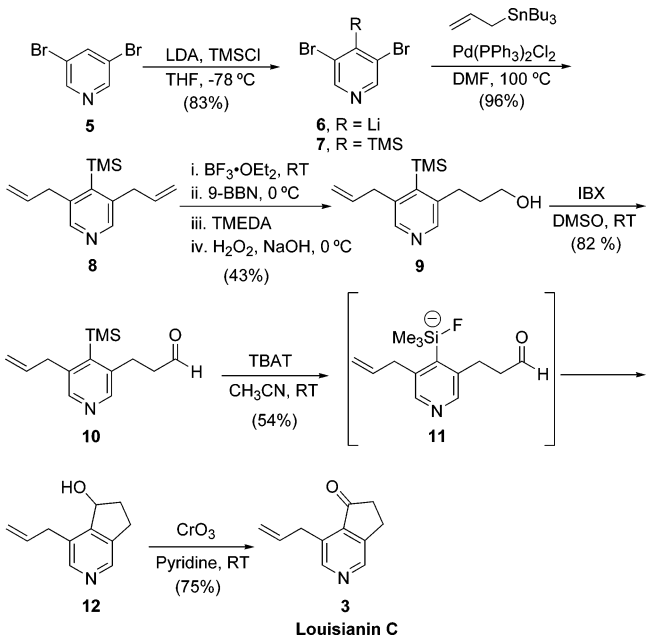
Louisianins A−D (**1**−**4**) are a small family of alkaloids produced by a species of *Streptomyces* isolated from a soil sample collected in the state of Louisiana (USA).[1,2] Louisianin A (**1**) has been converted into louisianin C (**3**) and the latter has been isomerized to louisianin D (**4**), but no louisianin species has yet been secured by total synthesis.[3] We now report the first total synthesis of a member of this family, louisianin C (**3**).



The louisianins lack any evident element of symmetry, but the synthesis of louisianin C begins with the symmetrical, commercially available dibromide **5**, which was ortho-lithiated to **6** according to the method of Gu.[4] Reaction of **6** with trimethylsilyl chloride afforded **7** in 83% overall yield from **5**. Palladium-catalyzed double allylation of **7** then delivered **8** in 96% yield.[5]

Monohydroboration of **8** was achieved with 9-BBN. Prior complexation of the pyridine nitrogen in **8** with BF_3•OEt_2 (to prevent the nitrogen from complexing with the 9-BBN)[6] increased the yield significantly (TMEDA cleaves the BF_3−pyridine complex). After oxidation of the borane with alkaline hydrogen peroxide, primary alcohol **9** was

SCHEME 1



obtained in 43% yield along with 45% recovery of **8** (the yield of **9** is 77% based on unrecovered starting material; higher conversions were eschewed to minimize the amount of diol produced). Alcohol **9** was oxidized to aldehyde **10** with *o*-iodoxybenzoic acid (IBX).[7]

The key transformation, the cyclization of **10** to **12**, was then achieved with tetrabutylammonium triphenylsilyldifluoride (TBAT), presumably via a species akin to **11**.[8,9] Use of $Bu_4N^+ F^-$ (TBAF) instead of TBAT gave inferior yields. The merits of TBAT over TBAF are that it is anhydrous and does not contain naked (and basic) fluoride ion.[10] The spectra of **12** are in agreement with those reported[3] by Omura et al. (**12** was an intermediate in the conversion of **1** to **3**). Oxidation of **12** following the procedure of Ōmura et al. provided louisianin C (**3**).[3] Insufficient natural louisianin C (**3**) was available for direct comparison, but a copy of the ^{1}H NMR spectrum of the natural material was in excellent agreement with our spectrum. The other spectra of synthetic louisianin C (**3**) agree with those reported for the natural material.[1]

In conclusion, this work provides the first total synthesis of any member of the louisianin family, confirms the structure of louisianin C (**3**), and indirectly affirms the structures of other members of the louisianin family.

Experimental Section[11]

3,5-Dibromo-4-(trimethylsilyl)pyridine (7). A solution of 3,5-dibromopyridine (**5**) (2.00 g, 8.44 mmol) in dry tetrahydrofuran (67 mL) was added by cannula over 30 min to a stirring

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(2) Another alkaloid, ulupyrinone, with the same carbon skeleton as the louisianins has been isolated from a source from Uluday, Turkey: Henne, P.; Grabley, S.; Thiericke, R.; Zeeck, A. *Ann.* **1997**, *5*, 937−939.

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10.1021/jo0341618 CCC: $25.00
Published on Web 05/10/2003

solution of lithium diisopropylamide [prepared by adding at −78 °C 2.5 M *n*-butyllithium in hexanes (3.4 mL, 8.6 mmol, 1.0 equiv) to diisopropylamine (1.21 mL, 8.61 mmol, 1.02 equiv) in THF (50 mL) and stirring for 5 min] under nitrogen at −78 °C. After 5 min, trimethylsilyl chloride (1.50 mL, 11.8 mmol, 1.40 equiv) was added in one portion. The reaction was monitored by TLC (silica, 49:1 hexanes:ethyl acetate) and, after a period of 25 min, the solution was quenched with a satd aqueous solution of ammonium chloride (10 mL) and was allowed to reach room temperature. The resulting mixture was extracted twice with diethyl ether. The combined organic extracts were washed once with water and once with brine. The organic phase was dried over anhyd magnesium sulfate, filtered, and concentrated in vacuo to afford the crude product as yellow crystals (2.40 g). Flash column chromatography on silica gel (5 × 18 cm) with 49:1 hexanes:ethyl acetate as eluent gave the purified product (2.17 g, 83% yield): white flakes, mp 55−56 °C; IR (KBr) 2985, 2949, 2897, 1476, 1245, 1164 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.56 (s, 2H), 0.57 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 149.6, 128.1, 2.9; HRMS (ESI) calcd for $C_8H_{12}Br_2NSi$ [M + H] 307.9106, found 307.9092. Anal. Calcd for $C_8H_{11}Br_2NSi$: C, 31.09; H, 3.59; N, 4.53. Found: C, 30.97; H, 3.31; N, 4.36.

3,5-Diallyl-4-(trimethylsilyl)pyridine (8). A solution of 3,5-dibromo-4-(trimethylsilyl)pyridine (**7**) (8.22 g, 26.6 mmol) and allyltributyltin (17.6 mL, 79.8 mmol, 3.00 equiv) in dimethylformamide (132 mL) was degassed by bubbling nitrogen through it for 30 min. Dichlorobis(triphenylphosphine)palladium(II) (1.87 g, 2.66 mmol, 10 mol %) was then added, and the reaction flask was heated at 100 °C. When the reaction was complete [ca. 20 h, TLC monitoring (silica, 20:1 hexanes:ethyl acetate)] the vessel was cooled to room temperature and the mixture was filtered through a pad (4 cm diameter, 4 cm height) of activated basic alumina (Brockmann I) in a fine porosity sintered glass funnel to remove the palladium and tin residues. The basic alumina was washed with 400 mL of hexanes. The combined filtrate and washes were extracted three times with 1 M ammonium hydroxide to further remove tin residues, and the organic layer was washed 3 times with water and once with brine, dried over anhyd $MgSO_4$, and concentrated in vacuo. The pale yellow oil was purified by flash column chromatography on silica gel (6 × 22 cm) with 9:1 hexanes:ethyl acetate as eluent to yield a slightly yellow oil (6.15 g, 96% yield); IR (neat, NaCl) 3081, 3006, 2979, 2954, 2901, 1638, 1409, 1253 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (s, 2H), 6.04−5.90 (m, 2H), 5.11 (dd, 2H, J = 10.2, 1.8 Hz), 4.86 (dd, 2H, J = 17.1, 1.8 Hz), 3.54−3.51 (m, 4H), 0.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 146.4, 139.2, 137.6, 116.2, 37.5, 3.0; HRMS (ESI) calcd for $C_{14}H_{22}NSi$ [M + H] 232.1522, found 232.1524. Anal. Calcd for $C_{14}H_{21}NSi$: C, 72.66; H, 9.15; N, 6.05. Found: C, 72.76; H, 8.85; N, 5.89.

3-Allyl-5-(3-hydroxypropyl)-4-(trimethylsilyl)pyridine (9). Boron trifluoride diethyl etherate (1.42 mL, 11.2 mmol, 1.00 equiv)[6] was added dropwise over 5 min to a stirred solution of 3,5-diallyl-4-(trimethylsilyl)pyridine (**8**) (2.60 g, 11.2 mmol) in THF (112 mL) under nitrogen at 0 °C. A 0.50 M solution of 9-borabicyclo[3.3.1]nonane in THF (27 mL, 14 mmol, 1.2 equiv) was added dropwise, over 15 min, at room temperature. The mixture was left to stir overnight (15 h) to ensure a completed reaction. The colorless solution was treated with *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (0.85 mL, 5.6 mmol, 0.5 equiv), and after ∼1 min of stirring a white precipitate formed. The reaction vessel was cooled to 0 °C, and a 2.5 M sodium hydroxide:35% hydrogen peroxide (1:1, v/v, 60.5 mL)[6] solution was added in one portion. The excess peroxide was quenched by addition of aliquots of a satd aqueous solution of sodium sulfite until (60 mL) peroxide indicator strips (EM Quant, Fisher cat. no. 10011-1) were negative. The aqueous mixture was then extracted three times with 20-mL portions of dichloromethane, and the combined organic extracts were washed with water and brine, dried over anhyd magnesium sulfate, filtered, and concentrated in vacuo to yield a yellow oil (2.66 g). The oil was purified by flash column chromatography on silica gel (4 × 18 cm) with 7:3 ethyl acetate:hexanes as eluent. Two purified compounds were isolated: the starting material 3,5-diallyl-4-(trimethylsilyl)pyridine (**8**) (1.16 g, 45% yield) and the desired product 3-allyl-5-(3-hydroxypropyl)-4-(trimethylsilyl)pyridine (**9**) (1.20 g, 43%, 77% based on unrecovered **8**): clear colorless oil; IR (neat, NaCl) 3342, 2979, 2949, 1680, 1413, 1254 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.18 (s, 1H), 6.02−5.91 (m, 1H), 5.10 (dd, 1H, J = 10.2, 1.7 Hz), 4.86 (dd, 1H, J = 17.1, 1.7 Hz), 3.72 (t, 2H, J = 6.3 Hz), 3.52−3.49 (m, 2H), 2.86−2.80 (m, 2H), 1.86−1.78 (m, 2H), 1.82 (br s, 1H), 0.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 147.9, 146.1, 142.4, 139.6, 137.5, 116.4, 61.9, 37.6, 36.2, 30.1, 3.1; HRMS (ESI) calcd for $C_{14}H_{23}NOSi$ [M + H] 250.1627, found 250.1623.

3-[5-Allyl-4-(trimethylsilyl)pyridin-3-yl]propanal (10). Caution! IBX is explosive under impact or upon heating to >200 °C.[12] *o*-Iodoxybenzoic acid (IBX, 1.16 g, 4.15 mmol, 1.2 equiv)[13] was added to a stirred solution of 3-allyl-5-(3-hydroxypropyl)-4-(trimethylsilyl)pyridine (**9**) (861 mg, 3.46 mmol) in dimethyl sulfoxide (8.3 mL) at room temperature, giving a homogeneous solution. Reaction progress was monitored by TLC (an aliquot of reaction mixture was partitioned between water and CH_2Cl_2 and the CH_2Cl_2 layer was spotted on the silica plate and eluted with ethyl acetate); after 1 h the starting material was consumed. Water (10 mL) was then added to the solution and a white precipitate formed, which was removed by filtration through a pad (2 cm diameter, 1 cm height) of Celite in a fine porosity sintered glass funnel. The Celite was rinsed with dichloromethane to ensure complete recovery of product. The resulting combined biphasic filtrate and rinse was separated and the aqueous phase was extracted with two 15-mL portions of additional dichloromethane. The combined organic layers were washed twice with 10-mL portions of water (to remove any excess DMSO) and brine and dried over anhyd magnesium sulfate. After concentration in vacuo, the oil was purified by flash column chromatography on silica gel (2 × 17 cm) with 95:5 dichloromethane:methanol as eluent to afford 3-[5-allyl-4-(trimethylsilyl)pyridin-3-yl]propanal (**10**) (700 mg, 82% yield) as a clear colorless oil. The product was stored under nitrogen at −24 °C; IR (neat, NaCl) 2978, 2953, 2899, 1724, 1412, 1255 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.84 (s, 1H), 8.24 (s, 1H), 8.22 (s, 1H), 6.02−5.92 (m, 1H), 5.11 (dd, 1H, J = 10.2, 1.7 Hz), 4.86 (dd, 1H, J = 17.1, 1.7 Hz), 3.51 (dd, 2H, J = 3.9, 1.7 Hz), 3.11−3.05 (m, 2H), 2.76 (t, 2H, J = 8.4 Hz), 0.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 148.8, 147.5, 146.2, 140.5, 139.6, 137.4, 116.5, 46.6, 37.5, 25.9, 3.0; HRMS (ESI) calcd for $C_{14}H_{22}NOSi$ [M + H] 248.1471, found 248.1472.

6,7-Dihydro-4-(2-propenyl)-5*H*-cyclopenta[*c*]pyridin-5-ol (12). A solution of 3-[5-allyl-4-(trimethylsilyl)pyridin-3-yl]-propanal (**10**) (172 mg, 0.696 mmol) in dry acetonitrile (11 mL) was transferred over 10 min by cannula under nitrogen to a flame-dried flask containing tetrabutylammonium triphenylsilyldifluoride (TBAT, 756 mg, 1.39 mmol, 2.0 equiv)[10] at room temperature. The reaction was refluxed at 85 °C and was monitored by TLC (silica, ethyl acetate). After 1 h the starting material was consumed. The reaction was cooled, 10 mL of 1 M sulfuric acid was added, and the solution was washed two times with dichloromethane to remove impurities. The aqueous layer was then made basic (pH ∼10) by addition of 2.5 M sodium hydroxide. The milky aqueous layer was extracted three times with 10-mL portions of dichloromethane; the combined organic extracts were washed once each with water and brine, dried over anhyd magnesium sulfate, and concentrated in vacuo to give a yellow oil (97 mg). The oil was purified by preparative thin-layer chromatography (silica, 95:5 dichloromethane:methanol) to afford **12** as a clear colorless oil (66 mg, 54% yield). The spectra are in agreement with those reported for **12**.[3] The HCl salt of **12** was prepared by bubbling HCl gas (generated by adding concentrated sulfuric acid to ammonium chloride) into a solution of **12** in ether. The ether was decanted, leaving behind a clear colorless oil that was placed under high vacuum, which caused the HCl salt to crystallize: **12**·HCl; white needles, mp 134−135 °C; IR (KBr) (**12**·HCl) 3300, 3039, 2972, 2912, 2692 cm^{-1};

(12) Plumb, J. B.; Harper, D. J. *Chem. Eng. News* **1990**, *July 16*, 3.
(13) The IBX was prepared according to the following reference: Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537−4538.

^{1}H NMR (**12**·HCl) (300 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.28 (s, 1H), 6.02−5.83 (m, 1H), 5.52 (dd, 1H, J = 6.6, 5.5 Hz), 5.29−5.23 (m, 1H), 5.17 (s, 1H), 3.78 (dd, 2H, J = 7.2, 5.5 Hz), 3.41−3.25 (m, 1H), 3.11−2.95 (m, 1H), 2.71−2.58 (m, 1H), 2.36−2.29 (m, 1H), 2.34 (br s, 1H); ^{13}C NMR (**12**·HCl) (100 MHz, $CDCl_3$) δ 163.1, 143.1, 138.3, 137.7, 134.4, 133.0, 119.1, 74.0, 34.8, 33.6, 28.3; HRMS (ESI) (**12**·HCl) calcd for $C_{11}H_{13}NO$ 176.1075, found 176.1072.

6,7-Dihydro-4-(2-propenyl)-5*H*-cyclopenta[*c*]pyridin-5-one, Louisianin C (3). Following the procedure in ref 3, chromium trioxide (100 mg, 1.00 mmol, 3.0 equiv) was added in one portion to a stirred solution of 6,7-dihydro-4-(2-propenyl)-5*H*-cyclopenta[*c*]pyridin-5-ol (**12**) (59.1 mg, 0.337 mmol) in pyridine (3.2 mL) at room temperature. The reaction was monitored by TLC (silica, ethyl acetate). After consumption of the starting material (2 h) the reaction mixture was diluted with water (10 mL). The mixture was extracted twice with 10-mL portions of dichloromethane and the combined organic extracts were washed with water and brine and dried over anhyd magnesium sulfate. The solvent was evaporated in vacuo to give a clear colorless oil. The oil was purified by using preparative thin-layer chromatography (silica, ethyl acetate) to afford **3** (42 mg, 72% yield) as a clear colorless oil: IR (neat, NaCl) 2976, 2925, 1718 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.47 (s, 1H), 6.02−5.92 (m, 1H), 5.09 (dd, 1H, J = 6.8, 1.6 Hz), 5.06 (m, 1H), 3.80 (d, 2H, J = 6.8 Hz), 3.16 (apparent t, 2H, J = 6.0 Hz), 2.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.9, 148.9, 147.9, 147.6, 139.5, 135.2, 132.8, 116.7, 36.6, 32.7, 23.3; HRMS (ESI) calcd for $C_{11}H_{12}NO$ [M + H] 174.0919, found 174.0913. The spectra are in agreement with those reported for **3**.[1]

Acknowledgment. We thank Dr. Satoshi Ōmura for a ^{1}H NMR spectrum of louisianin C and Mr. Stephen Chamberland for some preliminary studies.

Supporting Information Available: ^{13}C NMR spectra for **3**, **9**, **10**, and **12**·HCl. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0341618