Total Synthesis of Lemaireocereine

Hisashi ISHII,* Tsutomu ISHIKAWA, Shuji OHTA, Masahiro SUZUKI, and Takashi HARAYAMA

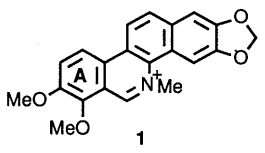
Faculty of Pharmaceutical Sciences, Chiba University, 1–33, Yayoi-cho, Inage-ku, Chiba 263, Japan. *Received January 11, 1992*

By utilizing newly developed synthetic methods *i.e.* 2-methylbenzofuran formation by CsF-mediated Claisen rearrangement of an aryl propargyl ether and its transformation to a salicylaldehyde by oxidative cleavage of the furan ring, total synthesis of a coctus alkaloid, lemaireocereine (2), was accomplished *via* ten steps from the aldehyde (4) in 22% yield.

Keywords lemaireocereine; successive substitution; benzofuran ring fission; synthesis; hydrogenolysis; simple isoquinoline; Boc; Cbz

Among simple isoquinoline alkaloids, which were defined as isoquinolines having no additional cyclic structures except a methylenedioxy group in their molecules,[1] there are few simple tetrahydroisoquinolines containing a benzene ring with four successive substitutions, such as 7,8-dioxygenated isoquinoline alkaloids. Recently, we reported the total synthesis of chelerythrine (**1**) having such a substitution pattern on its ring A.[2] In the course of our synthetic study on **1**, we succeeded in developing two new synthetic methods, *i.e.*, preparation of 2-methylbenzofuran by the CsF-mediated Claisen rearrangement of an aryl propargyl ether and transformation of the 2-methylbenzofuran to a salicylaldehyde by oxidative cleavage of the fused furan ring[3] (see Chart 2). These methods should be suitable for preparing aromatic compounds with four successive substituents involving alkoxy group(s). Then, by taking advantage of these methods, we planned to synthesize simple 7,8-dioxygenated isoquinoline alkaloids such as lemaireocereine (**2**)[4] and arizonine (**3**).[5] In this paper we present the details of a total synthesis of **2**.

We designed the synthetic plan shown in Chart 3, starting from the aldehyde (**4**),[6] which was one of the key intermediates for the synthesis of **1**.[2] Thus, aldol condensation of **4** with nitromethane in acetic acid in the presence of ammonium acetate under reflux gave the β-nitrostyrene (**5**) in 61% yield.[7] Successive treatment of **5** with lithium aluminum hydride in ether–tetrahydrofuran (THF) and carbobenzoxy chloride (Cbz Cl) in a two-phase medium (10% sodium hydroxide solution–methylene chloride) afforded the desired mono-Cbz derivative (**6**) in 76% yield along with a small amount of a di-Cbz derivative (**7**).[9] The molecular formula of **7** was $C_{28}H_{27}NO_7$. Moreover, compound **7** showed an absorption band due to a carbonate at 1785 cm^{-1} other than that due to the expected carbamate at 1725 cm^{-1} in the infrared (IR) spectrum and the signals due to two benzoxy groups at δ 5.09 (2H, s), 5.26 (2H, s), 7.25 (5H, s), and 7.37 (5H, s) in the ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectrum. Therefore, the structure of this by-product can be represented by formula (**7**).



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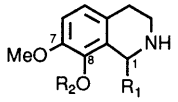
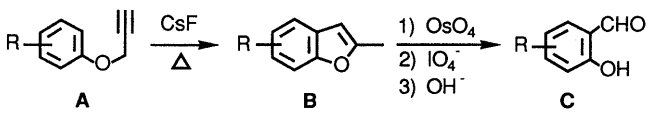


2 : R_1 = H, R_2 = Me

3 : R_1 = Me, R_2 = H

Chart 1



A **B** **C**

Chart 2

Next, an attempt was made to transform **6** into a salicylaldehyde derivative (**9**).[3] Treatment of **6** with a stoichiometric amount of osmium tetroxide (OsO_4) in pyridine provided an osmate, which was decomposed by sodium hydrogen sulfite treatment to afford a diol (**8**)[11] in 96% yield. Oxidation of the diol (**8**) with sodium metaperiodate ($NaIO_4$) in aqueous methanol gave an aldehyde-acetate (**9**) in 79% yield.[3] Hydrolysis of **9** with 1% sodium hydrogen carbonate solution and 5% sodium hydroxide solution gave rise to a mixture of products showing many spots on thin layer chromatography (TLC). On the other hand, hydrogenolysis of **9** using a hydrochloric acid solution of palladium chloride and Norit[12] caused deprotection of the Cbz group and subsequent tetrahydroisoquinoline formation to provide the expected isoquinoline-acetate hydrochloride (**10**) in 84% yield. The molecular formula of **10** was $C_{12}H_{15}NO_3 \cdot HCl$ and its ^{1}H-NMR spectrum showed the signal due to two hydrogens on C_1 as a singlet at δ 4.20. These results suggest that the product can be represented by formula (**10**). Hydrolysis of **10** with 1% sodium hydroxide aqueous methanolic solution afforded a phenol amine (**11**) in 72% yield. Methylation of **11** with diazomethane or dimethyl sulfate was unsuccessful. Therefore, an alternative attempt was made to synthesize **2** *via* an imidodicarbonate (**12**) with a diprotected amino group.

Treatment of **6** with di-*tert*-butyl dicarbonate (Boc_2O) in acetonitrile gave **12** in 98% yield.[13] Dihydroxylation of **12** with a stoichiometric amount of OsO_4 afforded a diol (**13**)[11] in 93% yield, which was oxidized with $NaIO_4$ and subsequently hydrolyzed with 1% sodium hydrogen carbonate solution to provide a salicylaldehyde derivative (**14**) in 76% yield. Methylation of **14** with dimethyl sulfate and potassium carbonate in dimethylformamide (DMF) gave quantitatively a methylated aldehyde (**15**). Unfortunately, reaction of **15** with 10% palladium on carbon (Pd–C) under a hydrogen atmosphere did not produce the

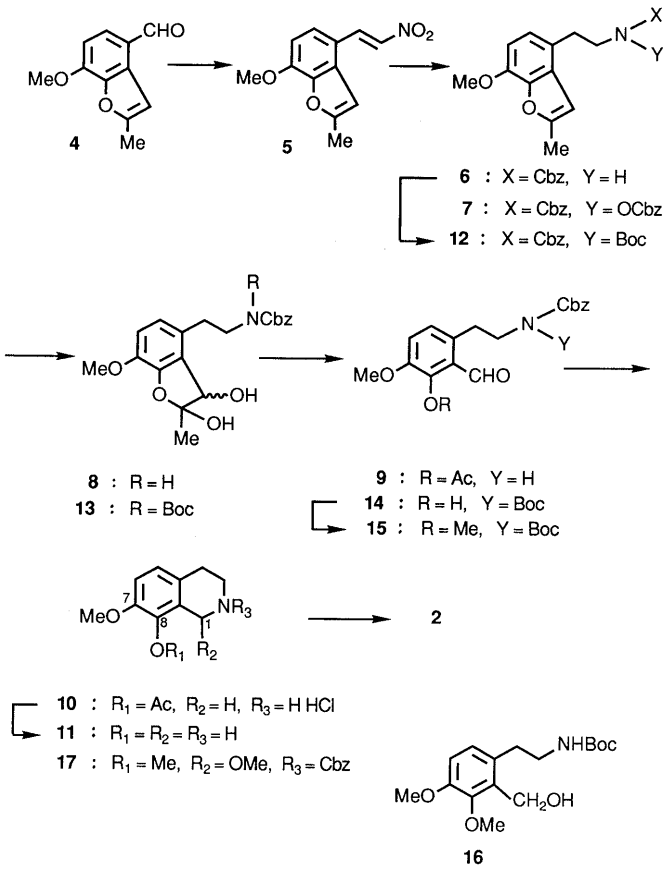


Chart 3

expected tetrahydroisoquinoline derivative but produced a benzyl aldohol (**16**) in 78% yield, in contrast to the result with **9** mentioned above. Next, deprotection of the Boc group in **15** was examined. Treatment of **15** with trifluoroacetic acid (TFA) gave an isoquinoline derivative (**17**)[14] in 86% yield. Successive treatment of **17** with 10% Pd–C under a hydrogen atmosphere and with methanol saturated with hydrogen chloride gave the desired **2** as the hydrochloride,[15] which was identical with a sample alternatively synthesized by the method of J. E. Knapp *et al.*[16a] on the basis of IR (KBr) and ^{1}H-NMR spectral comparisons.

Experimental

Melting points were measured on a micro melting point hot-stage apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded in Nujol on a Hitachi 215 spectrometer and ^{1}H-NMR spectra in deuteriochloroform on Hitachi R-24B (60 MHz), JEOL FX-270 (270 MHz), JEOL GSX-400 (400 MHz) and/or -500A (500 MHz) spectrometers, unless otherwise noted. The ^{1}H-NMR data are reported in parts per million downfield from tetramethylsilane as an internal standard (δ 0.0) and coupling constants in hertz. Electron impact mass spectra (EIMS) were taken on a Hitachi M-60 instrument (direct inlet) at 70 eV and fast atom bombardment mass spectrum (FABMS) was run on a JEOL JMS-HX110A using *m*-nitrobenzyl alcohol as the matrix. Column chromatography was carried out on aluminum oxide (Woelm, W200, neutral), silica gel (Merck, Silica gel 60, No. 7734 or No. 9385) or Florisil (Nacalai Tesque Inc., 100—200 mesh). In general, the extract was washed with brine, dried over anhydrous K_2CO_3, then filtered, and the filtrate was evaporated to dryness under reduced pressure, unless otherwise noted. Compounds for which no melting point is given are oily.

7-Methoxy-2-methyl-4-(2-nitrovinyl)benzo[*b*]furan (5) A solution of aldehyde (**4**) (1 g, 5.26 mmol), nitromethane (1.65 g, 27.04 mmol), and ammonium acetate (0.588 g, 7.63 mmol) in acetic acid (2.7 ml) was heated under reflux for 1.5 h. The reaction mixture was poured into ice-water. The precipitate was filtered off and washed well with water. The dried precipitate was dissolved in benzene and subjected to column chromatography on aluminum oxide (11 g) with benzene to afford **5** (0.747 g, 61%), mp 121—123 °C (yellow prisms from MeOH). IR: 1620, 1330 cm^{-1}. ^{1}H-NMR (60 MHz): 2.50 (3H, s, CH_3), 4.02 (3H, s, OCH_3), 6.59 (1H, s, C_3-H), 6.76 (1H, d, J=8.8 Hz, C_6-H), 7.37 (1H, d, J=8.8 Hz, C_5-H), 7.56 (1H, d, J=14.0 Hz, $C_{2'}$-H), 8.17 (1H, d, J=14.0 Hz, $C_{1'}$-H). *Anal.* Calcd for $C_{12}H_{11}NO_4$: C, 61.80: H, 4.75; N, 6.01. Found: C, 61.65; H, 4.80; N, 5.97.

4-(2-*N*-Carbobenzoxyaminoethyl)-7-methoxy-2-methylbenzo[*b*]furan (6) and 4-(2-*N*,*O*-Dicarbobenzoxyhydroxyaminoethyl)-7-methoxy-2-methylbenzo[*b*]furan (7) A solution of **5** (2.0 g, 8.58 mmol) in THF (10 ml) was added dropwise to a suspension of $LiAlH_4$ (1.3 g, 34.3 mmol) in dry Et_2O (174 ml) under ice-cooling with stirring, and then the reaction mixture was heated under reflux. After 30 min, $LiAlH_4$ (0.329 g, 8.59 mmol) was added portionwise and the mixture was heated under reflux for a further 20 min. Excess hydride was decomposed with wet ether and water. The supernatant was decanted and the precipitates were washed with Et_2O. The combined organic layer was dried and evaporated under reduced pressure. The residue was dissolved in ether and extracted with 5% HCl solution. The acidic solution was made alkaline with 5% NaOH solution and extracted with CH_2Cl_2. A small amount of the crude amine was characterized as the picrate, mp 218—221 °C (yellow plates from acetone–MeOH). *Anal.* Calcd for $C_{18}H_{18}N_4O_9$: C, 49.77; H, 4.18; N, 12.90. Found: C, 49.79; H, 4.25; N, 12.77. A mixture of 10% NaOH solution (5.5 ml) and Cbz Cl (1.472 g, 8.63 mmol) was added to a solution of the crude amine (1.61 g) in CH_2Cl_2 (5.5 ml). The reaction mixture was stirred at room temperature for 30 min, then diluted with water and extracted with Et_2O. The residue was subjected to flash chromatography on silica gel (No. 9385) (190 g). Elution with benzene–AcOEt (50 : 1) gave **7** (0.105 g, 3%), mp 65—67 °C (colorless prisms from hexane–AcOEt). IR ($CHCl_3$): 1785, 1725 cm^{-1}. ^{1}H-NMR (270 MHz): 2.41 (3H, d, J=1.0 Hz, CH_3), 3.03 (2H, t, J=7.8 Hz, $C_{1'}$-H_2), 3.89 (2H, t, J=7.8 Hz, $C_{2'}$-H_2), 3.95 (3H, s, OCH_3), 5.09 (2H, s, CH_2O), 5.26 (2H, s, CH_2O), 6.29 (1H, br d, J=1.0 Hz, C_3-H), 6.62 (1H, d, J=8.0 Hz, C_6-H), 6.89 (1H, d, J=8.0 Hz, C_5-H), 7.25 (5H, s, aromatic protons), 7.37 (5H, s, aromatic protons). *Anal.* Calcd for $C_{28}H_{27}NO_7$: C, 68.70; H, 5.56; N, 2.86. Found: C, 68.41; H, 5.59; N, 2.81. Successive elution with the same solvent gave **6** (2.224 g, 76%), mp 86—87.5 °C (colorless needles from hexane–AcOEt). IR: 3300, 1680 cm^{-1}. ^{1}H-NMR (60 MHz): 2.45 (3H, d, J=0.8 Hz, CH_3), 2.92 (2H, t, J=6.0 Hz, $C_{1'}$-H_2), 3.41 (2H, t, J=6.0 Hz, $C_{2'}$-H_2), 3.96 (3H, s, OCH_3), 4.70 (1H, m, NHCO), 5.10 (2H, s, CH_2O), 6.38 (1H, br s, C_3-H), 6.62 (1H, d, J=8.3 Hz, C_6-H), 6.86 (1H, d, J=8.3 Hz, C_5-H), 7.31 (5H, s, aromatic protons). *Anal.* Calcd for $C_{20}H_{21}NO_4$: C, 70.70; H, 6.24; N, 4.13. Found: C, 70.63; H, 6.24; N, 4.09.

4-(2-*N*-Carbobenzoxyaminoethyl)-2,3-dihydroxy-7-methoxy-2-methyl-2,3-dihydrobenzo[*b*]furan (8) OsO_4 (1 g, 3.93 mmol) was added to a solution of **6** (1.113 g, 3.28 mmol) in dry pyridine (13 ml). The mixture was stirred at room temperature for 5.5 h, then a solution of sodium hydrogen sulfite (1.5 g, 14.42 mmol) in water (23 ml) and pyridine (15.7 ml) was added. The reaction mixture was stirred at room temperature for a further 1.5 h, poured into water and then extracted with AcOEt. The extract was washed with saturated aqueous $CuSO_4$ solution and brine, and dried over $MgSO_4$. The residue was subjected to flash chromatography on silica gel (No. 9385) (125 g) with $CHCl_3$–AcOEt (3 : 2) to afford an oily diol (**8**) (1.172 g, 96%). IR ($CHCl_3$): 3350, 1710 cm^{-1}. ^{1}H-NMR (60 MHz): 1.60 and 2.08 (total 3H, each s, C-CH_3 and $COCH_3$), 2.80 (2H, m, $C_{1'}$-H_2), 3.38 (2H, m, $C_{2'}$-H_2), 3.80 and 3.82 (total 3H, each s, OCH_3), 4.81 (1H, br s, C_3-H), 5.01 and 5.07 (total 2H, each s, CH_2O), 6.69 (2H, m, C_5-H and C_6-H), 7.30 (5H, s, aromatic protons). MS *m/z*: 373 (M^+).

2-Acetoxy-6-(2-*N*-carbobenzoxyaminoethyl)-3-methoxybenzaldehyde (9) $NaIO_4$ (430 mg, 2.01 mmol) was added to a solution of **8** (0.5 g, 1.34 mmol) in MeOH (8.5 ml) and water (2.9 ml). After being stirred at room temperature for 10 min, the reaction mixtue was poured into water, and extracted with Et_2O, and then the extract was dried over $MgSO_4$. The residue was recrystallized from ether to give **9** (393 mg, 79%), mp 118—120.5 °C (colorless needles). IR: 1765, 1685 cm^{-1}. ^{1}H-NMR (60 MHz): 2.35 (3H, s, $COCH_3$), 3.16 (2H, m, $C_{1'}$-H_2), 3.33 (2H, m, $C_{2'}$-H_2), 3.81 (3H, s, OCH_3), 5.09 (2H, s, CH_2O), 7.08 (2H, s, C_5-H and C_6-H), 7.32 (5H, s, aromatic protons), 10.22 (1H, s, CHO). *Anal.* Calcd for $C_{20}H_{21}NO_5$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.71; H, 5.72; N, 3.59.

8-Acetoxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (10)

An aqueous solution of $PdCl_2$[17] (4 ml) and Norit (0.45 g) were added to a solution of **9** (0.4 g, 1.08 mmol) in EtOH (180 ml). The mixture was hydrogenated at room temperature under atmospheric pressure until absorption of hydrogen ceased. The catalyst was filtered off on a Celite bed and the filtrate was evaporated under reduced pressure. The residue was recrystallized from EtOH to afford **10** (0.232 g, 84%), mp 242—247 °C (colorless needles). IR (KBr): 1760 cm^{-1}. ^{1}H-NMR (270 MHz in MeOH-d_4): 2.31 (3H, s, $COCH_3$), 3.07 (2H, t, J=6.3 Hz, C_4-H_2), 3.45 (2H, t, J=6.3 Hz, C_3-H_2), 3.81 (3H, s, OCH_3), 4.20 (2H, s, C_1-H_2), 7.07 (1H, d, J=8.6 Hz, C_5-H or C_6-H), 7.15 (1H, d, J=8.6 Hz, C_5-H or C_6-H). *Anal.* Calcd for $C_{12}H_{15}NO_3 \cdot HCl$: C, 55.93; H, 6.27; N, 5.43. Found: C, 55.68; H, 6.09; N, 5.26.

8-Hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (11) A solution of **10** (100 mg, 0.39 mmol) in MeOH (6 ml) was treated with a 1% NaOH solution (4 ml) under ice-cooling. The mixture was stirred at room temperature for 1 h, diluted with water, and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and the filtrate was evaporated to dryness under reduced pressure to afford a labile phenol amine (**11**) (50 mg, 72%), mp 173—176.5 °C (Colorless needles). IR (KBr): 3290, 1585, 1500 cm^{-1}. ^{1}H-NMR (500 MHz): 2.72 (2H, t, J=5.9 Hz, C_4-H_2), 3.08 (2H, t, J=5.9 Hz, C_3-H_2), 3.86 (3H, s, OCH_3), 4.01 (2H, s, C_1-H_2), 6.60 (1H, d, J=8.2 Hz, C_5-H or C_6-H), 6.70 (1H, d, J=8.2 Hz, C_5-H or C_6-H). MS *m/z*: 179 (M^+).

4-(2-*N*-Carbobenzoxy-*N*-carbo-*tert*-butoxyaminoethyl)-7-methoxy-2-methylbenzo[*b*]furan (12) A solution of di-*tert*-butyl dicarbonate (3.55 g, 16.3 mmol) in CH_3CN (10 ml) was added to a solution of **6** (5 g, 14.73 mmol) and 4-dimethylaminopyridine (0.18 g, 1.47 mmol) in CH_3CN (30 ml) and then the reaction mixture was stirred at room temperature for 18.5 h. After further addition of a solution of di-*tert*-butyl dicarbonate (6.1 g, 27.9 mmol) and 4-dimethylaminopyridine (0.54 g, 4.42 mmol) in CH_3CN (8 ml), the reaction mixture was stirred for a further 48.5 h. The solvent was evaporated to dryness under reduced pressure, and the residue was diluted with 1 M $KHSO_4$ solution and then extracted with Et_2O. The extract was washed with 1 M $KHSO_4$ and 1 M $NaHCO_3$ solutions, and dried over $MgSO_4$. The residue was chromatographed on silica gel (330 g) with hexane–AcOEt (4:1) to afford **12** (6.339 g, 98%). IR (neat): 1790, 1750, 1695 cm^{-1}. ^{1}H-NMR (400 MHz): 1.46 (9H, s, *tert*-Bu), 2.41 (3H, d, J=1.1 Hz, CH_3), 2.98 (2H, m, $C_{1'}$-H_2), 3.84 (2H, m, $C_{2'}$-H_2), 3.96 (3H, s, OCH_3), 5.21 (2H, s, CH_2-O), 6.33 (1H, d, J=1.1 Hz, C_3-H), 6.62 (1H, d, J=8.1 Hz, C_6-H), 6.85 (1H, d, J=8.1 Hz, C_5-H), 7.79 (5H, m, aromatic proton). MS *m/z*: 439 (M^+).

4-(2-*N*-Carbobenzoxy-*N*-carbo-*tert*-butoxyaminoethyl)-2,3-dihydroxy-7-methoxy-2-methyl-2,3-dihydrobenzo[*b*]furan (13) OsO_4 (1 g, 3.93 mmol) was added to a solution of **12** (1.45 g, 3.3 mmol) in dry pyridine (13 ml). The mixture was stirred at room temperature for 3.5 h, then a solution of sodium hydrogen sulfite (1.51 g, 14.51 mmol) in water (23 ml) and pyridine (15.8 ml) was added. The reaction mixture was stirred at room temperature for a further 2.5 h, poured into water and then extracted with AcOEt. The extract was washed with saturated aqueous $CuSO_4$ and brine, and dried over $MgSO_4$. The residue was subjected to flash chromatography on silica gel (No. 9385) (180 g) with $CHCl_3$–AcOEt (2:1) to give **13** (5.823 g, 93%). IR ($CHCl_3$): 1785, 1730, 1685 cm^{-1}. ^{1}H-NMR (400 MHz): 1.41 (2/3×9H, s, *tert*-Bu), 1.49 (1/3×9H, s, *tert*-Bu), 1.60 (2/3×3H, s, CCH_3), 2.05 (1/3×3H, s, $COCH_3$), 2.85 (2/3×2H, m, $C_{1'}$-H_2), 2.96 (1/3×3H, m, $C_{1'}$-H_2), 3.79 (2/3×2H, m, $C_{2'}$-H_2), 3.97 (1/3×2H, m, $C_{2'}$-H_2), 3.82 (2/3×3H, s, OCH_3), 3.85 (1/3×3H, s, OCH_3), 5.17 (2/3×2H, s, CH_2O), 5.23 (1/3×2H, m, CH_2O), 6.53 (1/3×2H, m, C_5-H and C_6-H), 6.74 (2/3×2H, m, C_5-H and C_6-H), 7.38 (5H, m, aromatic protons). High-resolution MS Calcd for $C_{25}H_{31}NO_8$: 473.2050. Found: 473.2027.

6-(2-*N*-Carbobenzoxy-*N*-carbo-*tert*-butoxyaminoethyl)-2-hydroxy-3-methoxybenzaldehyde (14) $NaIO_4$ (3.94 g, 18.42 mmol) was added to a solution of **13** (5.82 g, 12.29 mmol) in MeOH (77.4 ml) and water (26.8 ml). The reaction mixture was stirred at room temperature for 5 min, poured into water, and extracted with Et_2O. A solution of the crude product (5.39 g) in EtOH (353 ml) and 1% $NaHCO_3$ solution (143 ml) was refluxed for 45 min. After cooling, the reaction mixture was poured into ice-water, made acidic with 5% HCl solution and then extracted with Et_2O. The extract was dried over $MgSO_4$. The residue was sujected to column chromatography on silica gel (100 g) with hexane–AcOEt (1:1) to give **14** (4.00 g, 76%), mp 68.5—70 °C (pale yellow pillars from AcOEt–hexane). IR: 1725, 1685, 1645 cm^{-1}. ^{1}H-NMR (500 MHz): 1.46 (9H, s, *tert*-Bu), 3.11 (2H, m, $C_{1'}$-H_2), 3.82 (2H, m, $C_{2'}$-H_2), 3.88 (3H, s, OCH_3), 5.22 (2H, s, CH_2-O), 6.64 (1H, d, J=8.1 Hz, C_4-H), 6.97 (1H, d, J=8.1 Hz, C_5-H), 7.39 (5H, m, aromatic protons), 10.30 (1H, s, CHO), 12.22 (1H, s, OH). *Anal.* Calcd for $C_{23}H_{27}NO_7$: C, 64.32; H, 6.34; N, 3.26. Found: C, 64.46; H, 6.38; N, 3.12.

6-(2-*N*-Carbobenzoxy-*N*-carbo-*tert*-butoxyaminoethyl)-2,3-dimethoxybenzaldehyde (15) A mixture of **14** (2.50 g, 5.82 mmol), K_2CO_3 (1.93 g, 13.99 mmol), and Me_2SO_4 (0.81 g, 6.42 mmol) in DMF (36.5 ml) was stirred at 40 °C for 2 h. The reaction mixture was diluted with water, stirred for a further 1 h, and then extracted with AcOEt. The extract was washed with 5% aqueous NaOH and brine. The residue was subjected to column chromatography on silica gel (27 g) with $CHCl_3$–AcOEt (10:1) to afford **15** (2.59 g, quant.). IR: 1790, 1745, 1695 cm^{-1}. ^{1}H-NMR (500 MHz): 1.39 (9H, s, *tert*-Bu), 3.15 (2H, t, J=6.6 Hz, $C_{1'}$-H_2), 3.86 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.92 (2H, t, J=6.6 Hz, $C_{2'}$-H_2), 5.16 (2H, s, CH_2O), 6.77 (1H, d, J=8.2 Hz, C_6-H), 6.96 (1H, d, J=8.2 Hz, C_5-H), 7.37 (5H, m, aromatic protons), 10.51 (1H, s, CHO). High resolution MS (FAB) Calcd for $C_{24}H_{30}NO_7$ (MH^+): 444.2023. Found: 444.2014.

6-(2-*N*-Carbo-*tert*-butoxyaminoethyl)-2,3-dimethoxybenzyl Alcohol (16) A solution of **15** (0.3 g, 0.67 mmol) in MeOH (19 ml) containing 10% Pd–C (0.21 g) was hydrogenated at room temperature and atmospheric pressure until absorption of hydrogen ceased. The catalyst was filtered off on a Celite bed and the filtrate was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel (5 g) with AcOEt to give **16** (0.17 g, 78%), mp 93—95 °C (colorless plates). IR ($CHCl_3$): 3450, 1700 cm^{-1}. ^{1}H-NMR (270 MHz in DMSO-d_6): 1.37 (9H, s, *tert*-Bu), 2.73 (2H, t, J=7.6 Hz, $C_{1'}$-H_2), 3.06 (2H, t, J=7.6 Hz, $C_{2'}$-H_2), 3.71 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.49 (2H, d, J=4.9 Hz, CH_2O. Collapsed to a singlet on adding D_2O), 4.75 (1H, t, J=4.9 Hz, O<u>H</u>. Disappeared on adding D_2O), 6.86 (1H, d, J=8.2 Hz, C_4-H or C_5-H), 6.91 (1H, d, J=8.2 Hz, C_4-H or C_5-H). *Anal.* Calcd for $C_{16}H_{25}NO_5$: C, 61.71; H, 8.09; N, 4.50. Found: C, 61.56; H, 8.23; H, 4.50.

2-Carbobenzoxy-1,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline (17) TFA (6.2 ml) was added dropwise to a solution of **15** (0.3 g, 0.68 mmol) in CH_2Cl_2 (25 ml) at 0 °C and the mixture was stirred at room temperature for 10 min, then poured into water and extracted with Et_2O. The extract was dried over $MgSO_4$. The residue was subjected to column chromatography on silica gel (10 g) with CH_2Cl_2–acetone (10:1) to give **17** (0.208 g, 86%). IR ($CHCl_3$): 1695 cm^{-1}. High resolution MS Calcd for $C_{20}H_{23}NO_5$: 357.1577. Found: 357.1566.

Lemaireocereine (2) A mixture of **17** (0.344 g, 0.96 mmol) and 10% Pd–C (0.317 g) in AcOH (28.9 ml) was hydrogenated at room temperature and atmospheric pressure until absorption of hydrogen ceased. The catalyst was filtered off on a Celite bed. The filtrate was diluted with water, made alkaline with 28% NH_4OH solution and then extracted with CH_2Cl_2. The extract was dried over $MgSO_4$. The residue was dissolved in MeOH saturated with HCl gas and the solvent was evaporated off under reduced pressure. The residue was recrystallized from CH_2Cl_2–AcOEt to afford **2** hydrochloride (0.17 g, 77%), mp 198—200 °C (colorless needles) (lit. mp 189—190 °C[16a]; mp 194—195 °C[16b]). IR (KBr): 3035, 1580, 1495, 1280, 1225, 1095 cm^{-1}. ^{1}H-NMR (500 MHz): 3.10 (2H, t, J=6.1 Hz, C_4-H_2), 3.42 (2H, t, J=6.1 Hz, C_3-H_2), 3.84 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.35 (2H, s, C_1-H_2), 6.85 (2H, s, C_5-H and C_6-H). *Anal.* Calcd for $C_{11}H_{15}NO_2 \cdot HCl$: C, 57.51; H, 7.02; N, 6.10. Found: C, 57.18; H, 7.10; N, 6.13. **2**: ^{1}H-NMR (60 MHz): 2.71 (2H, t, J=6.0 Hz, C_4-H_2), 3.08 (2H, t, J=6.0 Hz, C_3-H_2), 3.80 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 4.02 (2H, s, C_1-H_2), 6.76 (2H, s, C_5-H and C_6-H). MS *m/z*: 193 (M^+).

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References and Notes

1) J. Lundstöm, "The Alkaloids," Vol. 21, ed. by A. Brossi, Academic Press, Inc., New York, 1983, p. 254.
2) H. Ishii, T. Ishikawa, S. Takeda, S. Ueki, M. Suzuki, and T. Harayama, *Chem. Pharm. Bull.*, **38**, 1775 (1990).
3) H. Ishii, T. Ishikawa, S. Takeda, S. Ueki, and M. Suzuki, *Chem. Pharm. Bull.*, **40**, 1148 (1992).
4) R. Mata and J. L. McLaughlin, *Phytochemistry*, **19**, 673 (1980); S. Pummangura and J. L. McLaughlin, *J. Nat. Prod.*, **44**, 498 (1981).
5) J. G. Bruhn, *Lloydia*, **39**, 197 (1976); J. Strömbom and J. G. Bruhn, *Acta Pharm. Suec.*, **15**, 127 (1978) [*Chem. Abstr.*, **89**, 126107*w* (1978)].

6) Compound **4** was prepared from isovanillin by means of the following sequence of reactions in 60% overall yield: *a*) etherification with propargyl bromide–K_2CO_3 in DMF for 4 h at room temperature; *b*) acetalization with ethyl orthoformate–NH_4Cl in absolute EtOH under reflux for 2.5 h; *c*) i) heating at 210 °C in *N*,*N*-diethylaniline with CsF for 3 h, ii) deacetalization with 5% HCl. H. Ishii, T. Ishikawa, S. Takeda, M. Suzuki, and T. Harayama, *Chem. Pharm. Bull.*, **40**, 2002 (1992).
7) In this connection, an aldol condensation of **4** with nitromethane in AcOH in the presence of AcONa under reflux gave **5** in 31% yield while a condensation in MeOH in the presence of CH_3NH_2[8] at room temperature gave **5** in 49% yield, along with 44% recovery of **4**.
8) F. A. Ramirez and A. Burger, *J. Am. Chem. Soc.*, **72**, 2781 (1950); G. Hahn and K. Stiehl, *Chem. Ber.*, **71**, 2154 (1938).
9) Reduction of **5** with Zn(Hg)–HCl or catalytic reduction of **5** on 5% Pd–C in HCl–EtOH,[10] followed by reaction with Cbz Cl, gave **6** in only 12% and 10% yields, respectively.
10) M. Kohno, S. Sasao, and S.-I. Murahashi, *Bull. Chem. Soc. Jpn.*, **63**, 1252 (1990).
11) The ^{1}H-NMR spectrum showed that the product existed as an euilibrium mixture of cyclic acetal forms and an open ketone form in solution.[3]
12) H. Ishii, E. Kawanabe, K.-I. Harada, T. Deushi, T. Watanabe, Y.-I. Ichikawa, M. Sakamoto, T. Ishida, T. Takahashi, K. Nakajima, and T. Ishikawa, *Chem. Pharm. Bull.*, **31**, 3039 (1983).
13) L. Grehn, K. Gunnarsson, and U. Ragnasson, *Acta Chem. Scand., Ser. B*, **40**, 745 (1986).
14) The spectral data for **17** indicated that the compound (**17**) has a methoxy group at C_1 even though methanol was not used. The methoxy group presumably arose from MeOH contaminating the CH_2Cl_2.
15) The aldehyde (**15**) was directly converted to lemaireocereine (**2**) hydrochloride in 69% yield without isolation of intermediates *via* three steps, *i.e.*, deprotection with TFA, hydrogenolysis and hydrochloride salt formation.
16) *a*) D. Dwuma-Badu, J. S. K. Ayim, T. T. Dabra, M. M. El-Azizi, P. L. Schiff, Jr., D. J. Slatkin, and J. E. Knapp, *J. Nat. Prod.*, **46**, 342 (1983); *b*) G. Grethe, H. L. Lee, M. Uskokovic, and A. Brossi, *J. Org. Chem.*, **33**, 494 (1968).
17) Palladium chloride (1 g) was dissolved in concentrated HCl solution (2.5 ml) and water (6 ml). Then, the total volume of the resulting solution was made up to 60 ml by addition of water.