Total Synthesis of Chelerythrine, a Benzo[*c*]phenanthridine Alkaloid[1)]

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By taking advantage of our novel synthetic methods involving CsF-mediated Claisen rearrangement of an aryl propargyl ether to a 2-methylbenzolfuran and oxidative cleavage of the furan ring to a salicylaldehyde, total synthesis of chelerythrine, a benzo[*c*]phenanthridine alkaloid, was accomplished *via* the common intermediate (5) prepared through the two routes shown in Chart 3.

Keywords cesium fluoride; Claisen rearrangement; aryl propargyl ether; 2-methylbenzofuran; masked salicylaldehyde; chelerythrine; basic acylation; Claisen–Schmidt reaction

In previous papers,[2)] we reported a general synthetic method for the preparation of the fully aromatized, phenolic and non-phenolic nitidine (**1**) type of benzo[*c*]-phenanthridine alkaloids showing antileukemic properties.[3)] However, our synthetic method lacks general applicability to the synthesis of the 7,8-dioxygenated alkaloids such as chelerythrine (**2**), because the Bischler–Napieralski[2a)] reaction of the aromatic amide (**3**), one of the key steps in the method, produces exclusively nitidine (**1**) through the expected cyclization of the formyl group to the *para* position with respect to the C_3-methoxy group as shown in Chart 1. In connection with the development of a widely applicable synthetic method for chelerythrine-type alkaloids, which contain a benzene ring with four successive substitutions, we recently reported novel methods for the preparation of a suitably substituted benzene ring involving CsF-mediated Claisen rearrangement of an aryl propargyl ether (A) to a 2-methylbenzolfuran (B) and oxidative cleavage of the benzofuran (B) with osmium tetroxide (OsO_4) and periodate followed by alkaline hydrolysis to a salicylaldehyde (C)[4)] (see Chart 2). Then, we applied the new methods to synthesis of **2** and briefly described a successful result.[5)] The details of that work are the subject of this paper.

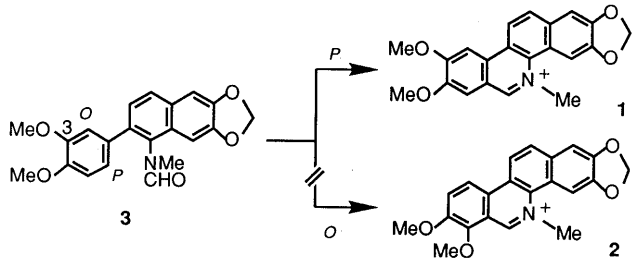

Chart 1

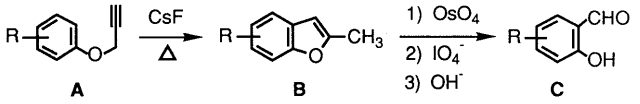

Chart 2

Our synthetic strategy for chelerythrine by taking advantage of our novel methods mentioned above is shown in Chart 3, and consists of two routes, in which compound **5** is the common key intermediate.

One approach to **5** started with a phenol (**6**) which had

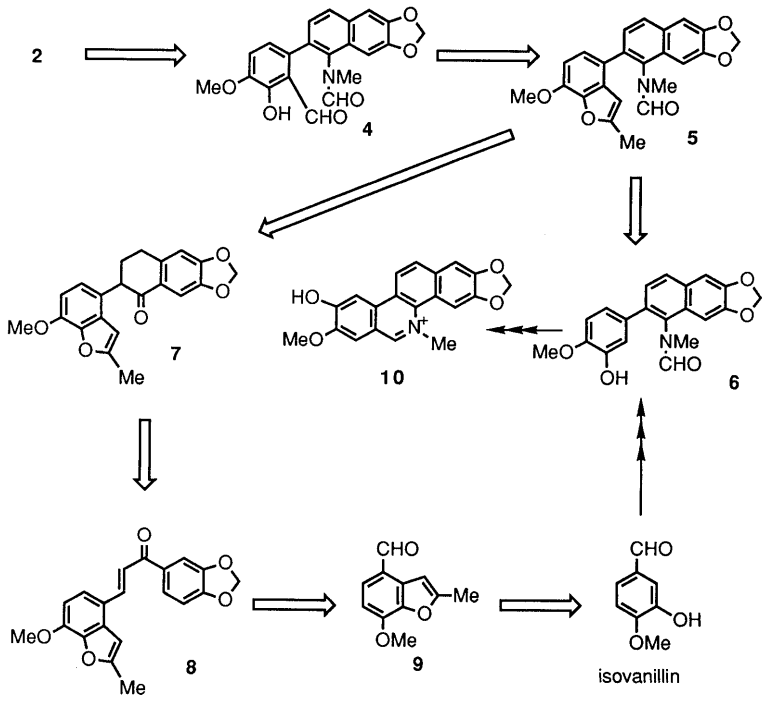

Chart 3

already been prepared as the intermediate for synthesis of isoterihanine (**10**).[6] In a previous paper,[4] we reported that the CsF-mediated Claisen rearrangement of the propargyl ether (**11**) in diphenyl ether provided the 2-methylbenzofuran derivative (**5**). Precise re-examination of the Claisen rearrangement of **11** in the presence of CsF revealed that the reaction in *N*,*N*-diethylaniline gave an expected benzofuran (**5**)[4] in 58% yield along with the demethoxy compound (**12**) in 2% yield. The molecular formula of the by-product (**12**) was $C_{22}H_{17}NO_4$. Its infrared (IR) spectrum showed an absorption band due to the *N*-formyl group at 1668 cm^{-1} and its ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectrum showed the signals due to the 2-methylfuran ring at δ 2.47 (3H, d, J=1.1 Hz) and 6.40 (1H, q, J=1.1 Hz), and no signal due to a methoxy group. The structure of the by-product (**12**) can, therefore, be represented by formula **12**. This result suggests that the propargyl group cyclized to the *ipso* position to the methoxy group and then the methoxy group was eliminated according to the mechanism for the Claisen rearrangement reported by Schmid *et al.*[7] Since each product showed, on thin layer chromatography (TLC), two spots attributable to rotational isomers due to the *N*-methylformamide group, the TLC of the products showed a complex pattern. Separation of the products, therefore, was very difficult and repeated chromatography was necessary to isolate each product.

So another approach to **5** shown in Chart 3, which started from the CsF-mediated Claisen rearrangement of isovanillin propargyl ether (**13**), was investigated. Thus, reaction of isovanillin with propargyl bromide and potassium carbonate in *N*,*N*-dimethylformamide (DMF) afforded **13** in 95% yield. Compound **13** was next subjected to the CsF-mediated Claisen rearrangement in *N*,*N*-diethylaniline at 215 °C to provide a benzofuran (**9**) in only 22% yield. The structure of **9** was elucidated on the basis of the elemental analysis data ($C_{11}H_{10}O_3$) and the ^{1}H-NMR spectrum [δ 2.50 (3H, d, J=1.0 Hz, C_2-Me); 7.10 (1H, q, J=1.0 Hz, C_3-H); 9.97 (1H, s, CHO)]. We supposed that the low yield could be attributed to the presence of the aldehyde group in the basic medium at high temperature. In order to improve the yield of Claisen rearrangement reaction, we examined a CsF-mediated Claisen rearrangement reaction after protecting the aldehyde group in **13** as a diethylacetal. Acetalization of **13** with ethyl orthoformate in the presence of ammonium chloride (NH_4Cl) in absolute ethanol gave an acetal (**14**) in 91% yield. The Claisen rearrangement of **14** in the presence of CsF in *N*,*N*-diethylaniline at 215 °C followed by treatment with 5% hydrochloric acid gave the expected **9** in 70% yield.[8]

Subsequently, attempts were made to prepare the key intermediate (**15**) from **9** by utilizing our methods which were developed during synthetic studies on nitidine-type benzo[*c*]phenanthridine alkaloids.[2,6,8-10] The Claisen–Schmidt reaction of **9** with acetopiperone in the presence of sodium hydroxide in aqueous ethanol[9] gave a chalcone (**8**) in 94% yield, and this was converted to a cyano-ketone (**15**) by hydrocyanation with potassium cyanide in acetic acid and ethyl cellosolve[9] in 87% yield. Hydrolysis of **15** with sodium hydroxide in aqueous ethanol[10] afforded a keto-acid (**16**) in 91% yield. Hydrogenolysis of **16** with palladium chloride and Norit in an acidic medium[10] gave an acid (**17**) in 94% yield. Basic acylation[2c] of **17** with phosphorus oxychloride in acetonitrile in the presence of potassium carbonate provided the desired tetralone (**7**) in 86% yield. Treatment of **7** with methylamine gas in the presence of titanium tetrachloride followed by reduction with soidum borohydride afforded a tetrahydronaphthylamine derivative (**18**) in 87% yield. In its ^{1}H-NMR spectrum **18** showed signals assignable to a proton geminal to a methylamino group at δ 3.65 (1H, d, J=3.3 Hz). The coupling constant[11] suggests that the resulting amine (**18**) has *cis*-configuration, as shown in Chart 4. A solution of **18** in dry chloroform was treated with freshly prepared chloral[2b,6] to give a formamide (**19**) in 91.2% yield. Dehydrogenation of **19** with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) in benzene provided in 89% yield the common key intermediate (**5**), which was identical with the sample (**5**) synthesized from **11** by the other route mentioned above. Successive treatment of **5**

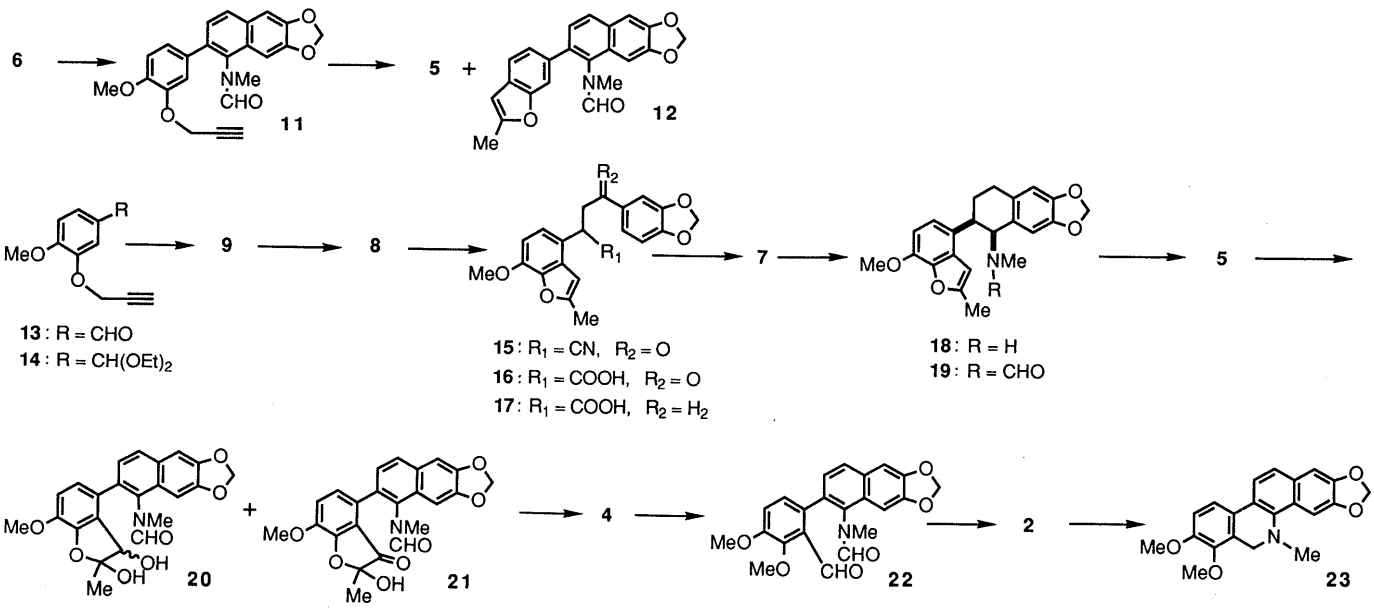

Chart 4

with a stoichiometric amount of OsO_4 in pyridine and sodium hydrogen sulfite ($NaHSO_3$) afforded the diol (**20**) and the ketol (**21**) in 77.0% and 3% yields, respectively. The structure of the major product (**20**) was elucidated on the basis of the results of chemical ionization mass spectrometry (CIMS) [*m/z* 424 (MH^+)] and the IR spectrum (3440 and 1665 cm^{-1}),[12] and that of the minor product on the basis of the results of MS [*m/z* 421 (M^+)] and the IR spectrum (3200, 1721, and 1661 cm^{-1}).[12] The diol (**20**) was subsequently treated with periodic acid (HIO_4) in aqueous dioxane and aqueous 5% sodium hydroxide to give a salicylaldehyde (**4**)[12] in 70% yield.[14] Methylation of **4** with dimethyl sulfate in DMF in the presence of potassium carbonate afforded a methyl ether (**22**)[12] in 92% yield.

Finally, an attempt was made to convert **22** to **2** *via* hydrolysis of the *N*-formyl group and simultaneous condensation of the resulting amino group with an aldehyde group. Treatment of **22** with *p*-toluenesulfonic acid in xylene under reflux gave in a 49% yield of **2**,[15,16] which was subsequently converted to dihydrochelerythrine (**23**) in 76% yield.[15] These synthetic samples (**2** and **23**) were identical with corresponding authentic samples by IR and ^{1}H-NMR comparisons.

Experimental

Melting points were measured on a micro melting point hot-stage apparatus (Yanagimoto) and are uncorrected. IR sepctra 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) and JEOL GSX-400 (400 MHz) and/or −500 (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. MS were taken on a Hitachi M-60 spectrometer (direct inlet) at 70 eV. Column chromatography was carried out on aluminum oxide (Woelm, W200, neutral), silica gel (Merck, Silica gel 60, No. 7734) or silica gel (Nacalai Tesque Inc., Silica gel 60, 230—400 mesh). In general, an 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. CsF was heated and powdered under argon before use. Compounds for which no melting point is given are oily.

Claisen Rearrangement of the *N*-Formyl Propargyl Ether (11) in *N,N*-Diethylaniline in the Presence of CsF: 2-[6-(2-Methylbenzo[*b*]furanyl)]-6,7-methylenedioxy-1-(*N*-methylformamido)naphthalene (12) and 2-[4-(7-Methoxy-2-methylbenzo[*b*]furanyl)]-6,7-methylenedioxy-1-(*N*-methylformamido)naphthalene (5) A suspension of **11** (5.37 g, 13.8 mmol) and CsF (2.95 g, 19.4 mmol) in *N,N*-diethylaniline (103 ml) was heated at 215 °C with stirring for 26.5 h under argon, and, after cooling, was diluted with benzene. After removal of the insoluble material by filtration, the filtrate was washed with 5% HCl and brine. The residue was chromatographed on silica gel with hexane–AcOEt (2 : 1) to afford **12** (0.09 g, 2% yield), mp 203—206 °C (colorless plates from $CHCl_3$–MeOH). *Anal.* Calcd for $C_{22}H_{17}NO_4$: C, 73.53; H, 4.77; N, 3.90. Found: C, 73.31; H, 4.79; N, 3.87. IR: 1668 cm^{-1}. ^{1}H-NMR (400 MHz) δ: 2.47 (3H, d, J= 1.1 Hz, C–Me), 2.88 (1/22 × 3H, s, NMe), 3.03 (21/22H × 3H, s, NMe), 6.10 (2H, s, OCH_2O), 6.40 (1H, q, J=1.1 Hz, $C_{3'}$-H), 7.09 (1H, s, C_8-H), 7.10 (1H, dd, J=8.1, 1.5 Hz, $C_{5'}$-H), 7.21 (1H, s, C_5-H), 7.33 (1H, d, J=1.5 Hz, $C_{7'}$-H), 7.40 (1H, d, J=8.4 Hz, C_3-H), 7.49 (1H, d, J=8.1 Hz, $C_{4'}$-H), 7.74 (1H, d, J=8.4 Hz, C_4-H), 8.14 (21/22H × 1H, s, NCHO), 8.36 (1/22 × 1H, s, NCHO). Successive elution with the same solvent afforded **5** (3.13 g, 58.3% yield), mp 233—236 °C (lit.[4] mp 233—235 °C).

4-Methoxy-3-(2-propynyloxy)benzaldehyde (13) A mixture of isovanillin (140 g, 0.92 mol), propargyl bromide (150 g, 1.26 mol), and K_2CO_3 (173 g, 1.25 mol) in DMF (350 ml) was stirred at room temperature for 4 h. The reaction mixture was diluted with water and extracted with ether. The extract was washed with 5% NaOH solution and brine. The residue was recrystallized from MeOH to afford **13** (168 g, 95% yield), mp 73—74 °C (colorless needles). *Anal.* Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.43; H, 5.30. IR: 3230, 1675 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 2.53 (1H, t, J=2.5 Hz, acetylenic proton), 3.95 (3H, s, OMe), 4.81 (2H, d, J=2.5 Hz, OCH_2), 6.98 (1H, d, J=9.0 Hz, C_5-H), 7.51 (1H, dd, J=9.0, 2.0 Hz, C_6-H), 7.54 (1H, d, J=2.0 Hz, C_2-H), 9.85 (1H, s, CHO).

4-Formyl-7-methoxy-2-methylbenzo[*b*]furan (9): a) Claisen Rearrangement of the Propargyl Ether (13) in *N,N*-Diethylaniline in the Presence of CsF A suspension of **13** (0.338 g, 2.04 mmol) and CsF (3.11 g, 20.05 mmol) in *N,N*-diethylaniline (3.7 ml) was refluxed for 2 h under argon. The mixture was diluted with ether. After removal of the insoluble material by filtration, the filtrate was washed with 5% HCl and brine. The residue was chromatographed on silica gel (8 g, Merck). Elution with hexane–AcOEt (8 : 1) gave **9** (0.084 g, 22% yield), mp 68.5—69 °C (colorless plates from EtOH). *Anal.* Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.26; H, 5.33. IR: 1668 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 2.50 (3H, d, J=1.0 Hz, C_2-Me), 4.05 (3H, s, OMe), 6.78 (1H, d, J=7.2 Hz, C_6-H), 7.10 (1H, q, J=1.0 Hz, C_3-H), 7.56 (1H, d, J=7.2 Hz, C_5-H), 9.97 (1H, s, CHO).

b) Claisen Rearrangement of the Diethylacetal (14) in *N,N*-Diethylaniline in the Presence of CsF A suspension of below-mentioned **14** (7.65 g, 28.94 mmol) and CsF (9.54 g, 62.80 mmol) in *N,N*-diethylaniline (48 ml) was refluxed for 3 h under argon. The reaction mixture was worked up in the same way as described for the Claisen reaction of **13** and the filtrate was washed with 5% HCl and brine. The residue was subjected to chromatography on Florisil (120 g) with hexane–AcOEt (4 : 1) to afford **9** (3.82 g, 70% yield), mp 68.5—70 °C (colorless plates from EtOH).

4-Methoxy-3-(2-propynyloxy)benzaldehyde Diethyl Acetal (14) A mixture of **13** (50 g, 0.263 mol), ethyl orthoformate (44.55 g, 0.30 mol), and NH_4Cl[17] (1.25 g, 23 mmol) in absolute EtOH (50 ml) was heated under reflux for 3 h. The solvent and the resulting ethyl formate were removed by distillation. The residue was dissolved in ether and washed with brine. The residue was distilled under reduced pressure to give **14** (62.88 g, 91% yield), bp 149—151 °C/3 mmHg. *Anal.* Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.94; H, 7.53. IR ($CHCl_3$): 3295 cm^{-1}. ^{1}H-NMR (60 MHz): 1.20 (6H, t, J=7.0 Hz, 2 × Me), 2.45 (1H, t, J=2.3 Hz, acetylenic proton), 3.55 (4H, d, J=7.0 Hz, 2 × OCH_2Me), 3.82 (3H, s, OMe), 4.73 (2H, d, J=2.3 Hz, OCH_2), 5.41 (1H, s, O–CH–O), 6.81 (1H, d, J= 8.3 Hz, C_5-H), 7.09 (1H, dd, J=8.3, 0.2 Hz, C_6-H), 7.13 (1H, d, J= 0.2 Hz, C_2-H).

3-[4-(7-Methoxy-2-methyl)benzo[*b*]furanyl]-1-(3,4-methylenedioxyphenyl)-2-propen-1-one (8) A solution of **9** (9.99 g, 52 mmol) and acetopiperone (9.6 g, 58.5 mmol) in EtOH (150 ml) was treated with 10% NaOH solution (25.3 ml, 63.2 mmol). The mixture was stirred at room temperature overnight and poured into a large amount of cold water. The resulting solid mass was filtered off and washed with ice-water until the washings showed neutral. Recrystallization of the crude material from $CHCl_3$–MeOH afforded **8** (16.57 g, 94% yield), mp 134.5—136 °C (yellow fine needles). *Anal.* Calcd for $C_{20}H_{16}O_5$: C, 71.42; H, 4.80. Found: C, 71.24; H, 4.80. IR: 1647 cm^{-1}. ^{1}H-NMR (60 MHz): 2.51 (3H, d, J=1.0 Hz, CMe), 4.03 (3H, s, OMe), 6.04 (2H, s, OCH_2O), 6.69 (1H, d, J=1.0 Hz, $C_{3'}$-H), 6.74 (1H, d, J=8.0 Hz, $C_{6''}$-H), 6.89 (1H, d, J= 8.0 Hz, $C_{5''}$-H), 7.32 (1H, d, J=8.0 Hz, $C_{5'}$-H), 7.41 (1H, d, J=15.0 Hz, C_2-H), 7.53 (1H, d, J=2.0 Hz, $C_{2''}$-H), 7.64 (1H, dd, J=8.0, 2.0 Hz, $C_{6''}$-H), 8.01 (1H, d, J=15.0 Hz, C_3-H).

2-[4-(7-Methoxy-2-methylbenzo[*b*]furanyl)]-4-(3,4-methylenedioxyphenyl)-4-oxobutyronitrile (15) A solution of **8** (15 g, 44.6 mmol) in ethyl cellosolve (2-ethoxyethanol) (120 ml) was treated with acetic acid (3 ml, 52.4 mmol) at 120 °C. An aqueous solution of potassium cyanide (6.8 g, 102 mmol) in water (30 ml) was added dropwise to the solution while the temperature was held at 110—120 °C. The mixture was stirred at the same temperature for 5 min and then poured into ice-water. The resulting solid mass was filtered off and washed with cold water until the washings showed neutral. Recrystallization of the crude product from $CHCl_3$–MeOH afforded **15** (14.1 g, 87% yield), mp 119—122 °C (colorless fine needles). *Anal.* Calcd for $C_{21}H_{17}NO_3$: C, 69.41; H, 4.72; N, 3.86. Found: C, 69.59; H, 4.74; N, 3.86. IR: 2236, 1679 cm^{-1}. ^{1}H-NMR (60 MHz): 2.47 (3H, d, J=0.8 Hz, CMe), 3.37 (1H, dd, J=18.0, 6.5 Hz, C_3-H_a), 3.74 (1H, dd, J=18.0, 7.2 Hz, C_3-H_b), 3.97 (3H, s, OMe), 4.69 (1H, dd, J=7.2, 6.5 Hz, C_2-H), 6.02 (2H, s, OCH_2O), 6.54 (1H, d, J=0.8 Hz, $C_{3'}$-H), 6.68 (1H, d, J= 8.5 Hz, $C_{5'}$- or $C_{6'}$-H), 6.81 (1H, d, J=8.0 Hz, $C_{5''}$-H), 7.16 (1H, d, J=8.5 Hz, $C_{5'}$- or $C_{6'}$-H), 7.39 (1H, d, J=2.0 Hz, $C_{2''}$-H), 7.45 (1H, dd, J=8.0, 2.0 Hz, $C_{6''}$-H).

2-[4-(7-Methoxy-2-methylbenzo[*b*]furanyl)]-4-(3,4-methylenedioxyphenyl)-4-oxobutanoic Acid (16) An aqueous solution of NaOH (58.5 g) in water (600 ml) was added to a solution of **15** (50 g, 0.138 mol) in EtOH

(220 ml). The mixture was refluxed for 4 h under argon, then cooled, diluted with water, washed with ether, and acidified with concentrated HCl. The precipitate was filtered off and was dissolved in $CHCl_3$. The $CHCl_3$ solution was dried over $MgSO_4$. The residue was recrystallized from $CHCl_3$–MeOH to afford **16** (47.85 g, 91% yield), mp 187—189 °C (colorless prisms). *Anal.* Calcd for $C_{21}H_{18}O_7$: C, 65.96; H, 4.75. Found: C, 65.76; H, 4.74. IR: 1698, 1665 cm^{-1}. ^{1}H-NMR (60 MHz, acetone-d_6): 2.44 (3H, s, CMe), 3.18 (1H, dd, J=17.1, 4.0 Hz, C_3-H_a), 3.88 (1H, dd, J=17.1, 9.6 Hz, C_3-H_b), 3.93 (3H, s, OMe), 4.44 (1H, dd, J=9.6, 4.0 Hz, C_2-H), 6.07 (2H, s, OCH_2O), 6.68 (1H, s, $C_{3'}$-H), 6.75 (1H, d, J=8.2 Hz, $C_{6'}$-H), 6.90 (1H, d, J=8.3 Hz, $C_{5'}$-H), 7.10 (1H, d, J=8.2 Hz, $C_{5'}$-H), 7.43 (1H, d, J=1.5 Hz, $C_{2'}$-H), 7.67 (1H, dd, J=8.3, 1.5 Hz, $C_{6'}$-H).

2-[4-(7-Methoxy-2-methylbenzo[*b*]furanyl)]-4-(3,4-methylenedioxyphenyl)butanoic Acid (17) A solution of **16** (25.0 g, 65.38 mmol) in acetic acid (1500 ml) containing 1% aqueous palladium chloride solution[18] (105 ml) and Norit (8.75 g) was hydrogenated at room temperature and atmospheric pressure until adsorption 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 ether–hexane to afford **17** (22.75 g, 94% yield), mp 108—110 °C (colorless prisms). *Anal.* Calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.49; H, 5.49. IR: 1696 cm^{-1}. ^{1}H-NMR (500 MHz): 2.15 (1H, m, C_3-H_a), 2.41 (1H, m, C_3-H_b), 2.45 (3H, d, J=0.8 Hz, CMe), 2.49 (2H, t, J=7.2 Hz, C_4-H), 3.73 (1H, t, J=7.2 Hz, C_2-H), 3.98 (3H, s, OMe), 5.90 (2H, s, OCH_2O), 6.41 (1H, d, J=0.8 Hz, $C_{3'}$-H), 6.55 (1H, dd, J=8.0, 1.7 Hz, $C_{6''}$-H), 6.61 (1H, d, J=1.7 Hz, $C_{2''}$-H), 6.69 (2H, d, J=8.0 Hz, $C_{5''}$-H and $C_{6''}$-H), 7.03 (1H, d, J=8.0 Hz, $C_{5'}$-H).

2-[4-(7-Methoxy-2-methylbenzo[*b*]furanyl)]-6,7-methylenedioxy-3,4-dihydronaphthalen-1(2*H*)-one (7) Phosphorus oxychloride (7.1 ml, 18 mmol) was added dropwise to an ice-cooled solution of **17** (5.57 g, 15.13 mmol) in acetonitrile (39 ml) containing potassium carbonate (4.65 g, 33.7 mmol). The mixture was heated at 55—60 °C for 2.5 h with stirring. The reaction mixture was poured into ice-water and extracted with $CHCl_3$. The extract was washed with 5% NaOH solution and brine. The residue was recrystallized from $CHCl_3$–MeOH to afford **7** (4.57 g, 86% yield), mp 119.5—202.5 °C (colorless needles). *Anal.* Calcd for $C_{21}H_{18}O_5$: C, 71.99; H, 5.18. Found: C, 72.01; H, 5.25. IR: 1664 cm^{-1}. ^{1}H-NMR (60 MHz): 2.20—2.60 (2H, m, C_3-H_2), 2.43 (3H, d, J=1.0 Hz, CMe), 2.80—3.15 (2H, m, C_4-H), 3.75—4.00 (1H, m, C_2-H), 3.97 (3H, s, OMe), 6.00 (2H, s, OCH_2O), 6.18 (1H, d, J=1.0 Hz, $C_{3'}$-H), 6.63 (1H, d, J=8.0 Hz, $C_{6'}$-H), 6.68 (1H, s, C_5-H), 6.85 (1H, d, J=8.0 Hz, $C_{5'}$-H), 7.53 (1H, s, C_8-H).

***cis*-2-[4-(7-Methoxy-2-methylbenzo[*b*]furanyl)]-6,7-methylenedioxy-*N*-methyl-1,2,3,4-tetrahydro-1-naphthylamine (18)** A solution of **7** (3.47 g, 9.90 mmol) in dry $CHCl_3$ (34 ml) was added to an ice-cooled solution of $MeNH_2$ (9.42 g, 303.3 mmol) in dry $CHCl_3$ (33 ml). The mixture was then added dropwise to a solution of titanium tetrachloride (1.2 ml) in dry $CHCl_3$ (33 ml) at 0—5 °C over 20 min with stirring and then the reaction mixture was stirred at room temperature for 2.5 h and refluxed for a further 30 min. The resulting precipitates were filtered off and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in dry MeOH (100 ml). The solution was treated with sodium borohydride (0.75 g, 19.9 mmol) with stirring overnight at room temperature. The reaction mixture was diluted with water and extracted with ether. The residue was recrystallized from $CHCl_3$–MeOH to afford **18** (3.14 g, 87% yield), mp 139—142.5 °C (colorless prisms). *Anal.* Calcd for $C_{22}H_{23}NO_4$: C, 72.32; H, 6.32; N, 3.83. Found: C, 72.02; H, 6.33; N, 3.80. IR: 3334 cm^{-1}. ^{1}H-NMR (270 MHz): 1.08 (1H, br s, NH), 1.95 (1H, m, C_3-H_a), 2.11 (3H, s, NMe), 2.48 (3H, d, J=0.7 Hz, CMe), 2.57 (1H, m, C_3-H_b), 2.85 (1H, m, C_4-H_a), 2.99 (1H, m, C_4-H_b), 3.40 (1H, dt, J=11.9, 3.3 Hz, C_2-H), 3.65 (1H, d, J=3.3 Hz, C_1-H), 4.00 (3H, s, OMe), 5.92 (2H, s, OCH_2O), 6.44 (1H, d, J=0.7 Hz, $C_{3'}$-H), 6.65 (1H, s, C_5- or C_8-H), 6.72 (1H, d, J=7.9 Hz, $C_{5'}$-H), 6.75 (1H, s, C_5- or C_8-H), 7.00 (1H, d, J=7.9 Hz, $C_{5'}$- or $C_{6'}$-H).

***cis*-2-[4-(7-Methoxy-2-methylbenzo[*b*]furanyl)]-1-(*N*-methylformamido)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene (19)** A mixture of **18** (4.41 g, 12.1 mmol) and freshly prepared chloral[19] (2.4 ml, 24.5 mmol) in dry $CHCl_3$ (42 ml) was refluxed for 3 h. The mixture was poured into water and extracted with $CHCl_3$. The residue was recrystallized from $CHCl_3$–MeOH to give **19** (4.33 g, 91% yield), mp 202.5—204 °C (colorless prisms). *Anal.* Calcd for $C_{23}H_{23}NO_5$: C, 70.21; H, 5.89; N, 3.56. Found: C, 70.00; H, 5.88; N, 3.53. IR: 1664 cm^{-1}. ^{1}H-NMR (500 MHz): 2.07— 2.11 (1H, m, C_3-H_a), 2.23—2.32 (1H, m, C_3-H_b), 2.45 (10/11 × 3H, s, NMe), 2.49 (3H, d, J=1.0 Hz, CMe), 2.62 (1/11 × 3H, s, NMe), 2.93 (1H, m, C_4-H_a), 3.02 (1H, m, C_4-H_b), 3.43 (1H, m, C_2-H), 3.98 (3H, s, OMe), 4.73 (1H, d, J=4.9 Hz, C_1-H), 5.96 (2H, s, OCH_2O), 6.39 (1H, d, J= 1.0 Hz, $C_{3'}$-H), 6.54 (1H, s, C_5- or C_8-H), 6.67 (1H, s, C_5- or C_8-H), 6.71 (1H, d, J=8.3 Hz, $C_{5'}$- or $C_{6'}$-H), 6.83 (1H, d, J= 8.3 Hz, $C_{5'}$- or $C_{6'}$-H), 7.41 (10/11H × 1H, s, NCHO), 7.69 (1/11H × 1H, s, NCHO).

Dehydrogenation of the Formamide (19) with DDQ A solution of DDQ (10.11 g, 44.5 mmol) in dry benzene (240 ml) was added to a solution of **19** (5.66 g, 14.4 mmol) in dry benzene (40 ml). The mixture was refluxed for 2 h. The resulting precipitates were filtered off and the filtrate was evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ and washed with 5% aqueous NaOH and brine. The residue was chromatographed on silica gel (15 g). Elution with $CHCl_3$ gave **5** (4.97 g, 89% yield), mp 233—235 °C (colorless prisms from $CHCl_3$–MeOH), which was identical with a sample (**5**) prepared by the CsF-mediated Claisen rearrangement of **11**.

Dihydroxylation of the 2-Methylbenzofuran (5) with OsO_4: The Diol (20) and the Ketol (21) OsO_4 (500 mg, 1.99 mmol) was added to a solution of **5** (640 mg, 1.65 mmol) in dry pyridine (13 ml). The mixture was stirred at room temperature for 2 h, then a solution of $NaHSO_3$ (760 mg, 7.22 mmol) in water (11 ml) and pyridine (13 ml) was added. The reaction mixture was stirred at room temperature for 2 h and poured into water. The solution was acidified with 5% aqueous HCl and extracted with AcOEt. The extract was washed with saturated aqueous $CuSO_4$ solution and brine, and then dried over $MgSO_4$. The residue in benzene–AcOEt (2 : 1) was chromatographed on silica gel (23 g). Elution with the same solvent afforded **21**[12] (20.2 mg, 3% yield), mp 290—298 °C (dec.) (colorless prisms from $CHCl_3$–MeOH–EtOH). *Anal.* Calcd for $C_{23}H_{19}NO_7$: C, 65.55; H, 4.54; N, 3.32. Found: C, 65.34; H, 4.59; N, 3.20. MS *m/z*: 421 (M^+). IR: 3200, 1721, 1661 cm^{-1}. Successive elution with the same solvent afforded **20**[12] (537 mg, 77% yield), mp 200—212 °C (dec.)(colorless plates from $CHCl_3$–EtOH). *Anal.* Calcd for $C_{23}H_{21}NO_7$: C, 65.24; H, 5.00; N, 3.31. Found: C, 64.65; H, 5.06; N, 3.20. CIMS (*iso*-C_4H_{10}) *m/z*: 424 (MH^+). IR: 3440, 1665 cm^{-1}.

2-(2-Formyl-3-hydroxy-4-methoxyphenyl)-1-(*N*-methylformamido)-6,7-methylenedioxynaphthalene (4) A solution of $HIO_4 \cdot 2H_2O$ (0.434 g, 1.9 mmol) in water (2.7 ml) and dioxane (7.5 ml) was added to a solution of **20** (0.518 g, 1.23 mmol) in dioxane (15 ml). The mixture was stirred at room temperature for 2 h under argon, then poured into water and extracted with benzene. A 5% NaOH solution (5 ml) was added to a solution of the residue in dioxane (17 ml). The mixture was stirred at room temperature overnight and poured into water. The solution was acidified with aqueous 5% HCl and extracted with benzene. The extract was dried over $MgSO_4$. The residue was recrystallized from $CHCl_3$–EtOH to provide **4**[12] (0.327 g, 70% yield), mp 245—246 °C (pale yellow prisms). *Anal.* Calcd for $C_{21}H_{17}NO_6$: C, 66.48; H, 4.52; N, 3.69. Found: C, 66.36; H, 4.56; N, 3.63. IR: 1680, 1645 cm^{-1}.

2-(2-Formyl-3,4-dimethoxyphenyl)-1-(*N*-methylformamido)-6,7-methylenedioxynaphthalene (22) A mixture of **4** (59.4 mg, 0.16 mmol), dimethyl sulfate (0.0164 ml, 0.17 mmol) and K_2CO_3 (52.4 ml, 0.38 mmol) in DMF (1 ml) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with benzene. The extract was washed with 5% NaOH solution and brine. The residue was recrystallized from $CHCl_3$–MeOH to give **22**[12] (56.5 mg, 92% yield), mp 217—220 °C (colorless prisms). *Anal.* Calcd for $C_{22}H_{19}NO_6$: C, 67.17; H, 4.87; N, 3.56. Found: C, 67.17; H, 4.87; N, 3.53. IR: 1666 cm^{-1}.

Chelerythrine (2) Chloride A solution of **22** (150 mg, 0.38 mmol) and *p*-toluenesulfonic acid (72.6 mg, 0.38 mmol) in xylene (10 ml) was refluxed for 7.5 h. The supernatant was decanted and the precipitate was dissolved in water. The aqueous solution was made alkaline with 28% NH_4OH solution and extracted with $CHCl_3$. A small amount of aqueous 10% HCl was added to an ice-cooled solution of the residue in $CHCl_3$ (5 ml). The precipitates were collected by filtration and recrystallized from ether–EtOH to afford chelerythrine (**2**) chloride (71.9 mg, 49% yield), mp 194—198 °C (yellow prisms). This compound was identical with a sample of chelerythrine (**2**) chloride[15] which was isolated from a natural source.

Dihydrochelerythrine (23) A solution of chelerythrine (**2**) chloride (26.6 mg, 0.07 mmol) and sodium borohydride (19.0 mg, 0.5 mmol) in MeOH (2.5 ml) was stirred at room temperature for 30 min. The mixture was diluted with water and extracted with $CHCl_3$. The residue was subjected to chromatography on aluminum oxide (1 g) with benzene to afford **23** (18.5 mg, 76% yield), mp 158—160 °C (colorless prisms from benzene–MeOH). This material was identical with an authentic sample of **23**.[15]

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References and Notes

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