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Biomimetic Total Synthesis of (±)-8-Oxoerymelanthine

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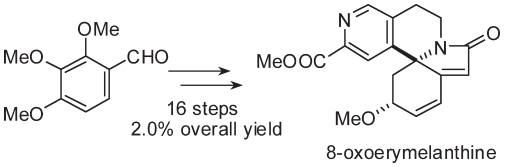

Erymelanthine **1** and 8-oxoerymelanthine **2** are unique erythrina alkaloids containing a pyridine ring. We synthesized (±)-8-oxoerymelanthine **2** in 2.0% overall yield using the following key reactions. The characteristic 6-5-6-6-membered ring system was constructed by the stereoselective intermolecular Diels−Alder reaction. Oxidative cleavage of the aromatic D-ring was conducted chemo- and regioselectively by ozonolysis in the presence of BF_3-etherate. This cleavage site is identical to the site cleaved during the biosynthesis of erymelanthine **1**. Nitrogen incorporation was achieved by aminolysis. Conversion of the D-ring pyridone to the corresponding pyridine was efficiently accomplished by palladium-catalyzed reduction of aryl triflate **21**. This is not only the first total synthesis of (±)-8-oxoerymelanthine **2** (where the D-ring is pyridine) but also, more importantly, a biomimetic total synthesis of an erythrinan D-aza alkaloid.

Introduction

Erythrina alkaloids have attracted much attention, because in addition to their characteristic polycondensed structures, they exhibit curare-like and hypnotic activity as well as pharmacological effects, such as sedation, hypotension, neuromuscular inhibition, and CNS effects.[1,2] This family of alkaloids is conveniently categorized into aromatic and non-aromatic alkaloids according to whether the D-ring is aromatic or non-aromatic.[1] The majority of erythrinan alkaloids belong to the aromatic subclass, and most of the alkaloids in this subclass have two oxygenated functions, one at C-15 and one at C-16. These alkaloids are termed "normal", since their biosynthesis is believed to use 3,4-dihydroxyphenethylamine as the starting material. Non-aromatic alkaloids consist of ring D-oxa and ring D-aza compounds,[1] such as the erythroidines[3] and erymelanthine.[4] These non-aromatic alkaloids are known to be biologically synthesized from aromatic alkaloids through oxidative cleavage of the D-ring, followed by recyclization.[1,4]

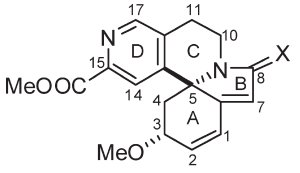

FIGURE 1. Structures of erymelanthine **1** and 8-oxoerymelanthine **2**.

Many methods have been reported for the total synthesis of erythrina alkaloids having an aromatic D-ring,[5] whereas only a few papers have reported the total synthesis of alkaloids with a non-aromatic D-ring. The latter reports include the synthesis of cocculolidine by Kitahara's group[6a] and β-erythroidine by the laboratories of Hatakeyama[6b] and Funk.[6c] Cocculolidine[7] and β-erythroidine[3] are ring D-oxa compounds, with D-rings that are five-membered and six-membered lactones, respectively. The present paper focuses on the D-aza alkaloids, erymelanthine **1** and 8-oxoerymelanthine (melanacanthine)

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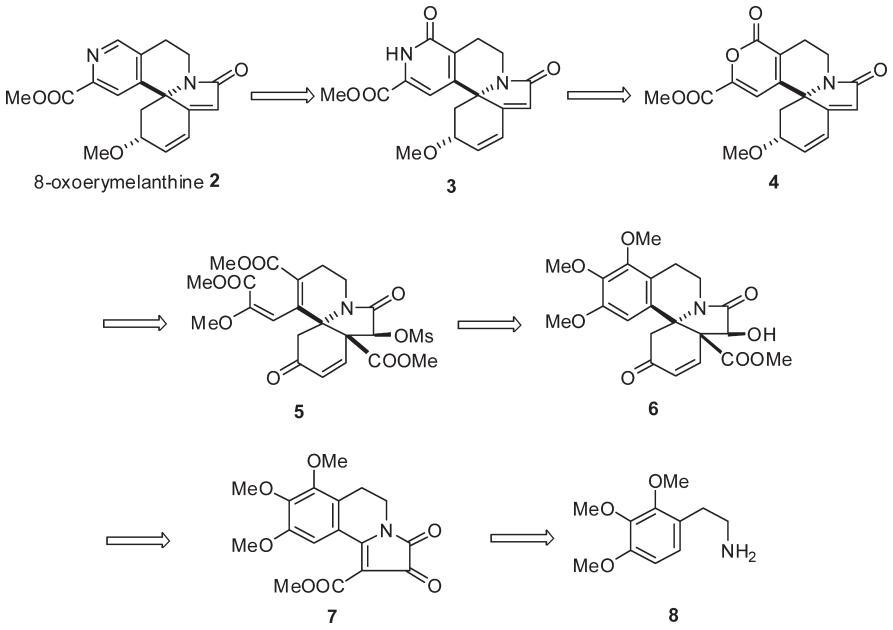
SCHEME 1



2, which were isolated from *Erythrina melanacantha*.[4] Erymelanthine (**1**) and 8-oxoerymelanthine (**2**) are unique compounds because they are the only two erythrina alkaloids possessing a pyridine ring. During biosynthesis, the D-aza alkaloid is believed to be produced by aromatic ring cleavage followed by ammonia incorporation. This biosynthetic pathway is consistent with the co-isolation of erymelanthine and aromatic alkaloids such as erysovine and erysodine.[4] We report herein the first total synthesis of 8-oxoerymelanthine **2**, a non-aromatic erythrinan D-aza alkaloid. Many 8-oxo alkaloids have been reported,[1,8] and oxidation at C-8, leading to the 8-oxo-alkaloids, is known to be one step in their biosynthesis.[1,4]

A retrosynthetic analysis is illustrated in Scheme 1. The target compound, 8-oxoerymelantine **2**, can be derived from D-aza compound **3** by appropriate reduction. Pyrone **4** would permit nitrogen incorporation by ammonolysis or aminolysis to give **3**. D-oxa compound **4** would be obtained from muconate **5** by acid treatment, followed by modification of the A- and B-rings. D-ring cleavage compound **5** would be obtained from trimethoxybenzene derivative **6** by chemo- and regioselective ozonolysis in the presence of BF_3-etherate, as previously reported.[9a,9b] Aromatic erythrinan compound **6** would be constructed via dioxopyrroline **7** from aryl ethylamine **8** by the method previously reported by our group, in which a stereoselective intermolecular Diels−Alder reaction was used.[10] Aryl ethylamine **8** is available from trimethoxybenzaldehyde.[11] It should be noted that this synthetic strategy is in accord with the biosynthetic pathway: (1) construction of the 6-5-6-6-membered ring system using a dopamine derivative as the starting material, (2) oxidative cleavage of the aromatic D-ring,[4a] and (3) nitrogen incorporation into the D-ring.

Results and Discussion

Construction of the Tetracyclic Ring System. The characteristic 6-5-6-6-membered ring system of the important synthetic intermediate **6** was constructed using a method previously developed for the synthesis of aromatic erythrinan alkaloids (Scheme 2).[10] Arylethylamine **8**, synthesized from 2,3,4-trimethoxybenzaldehyde using the procedure of Kubota et al.,[11] was condensed with methyl malonyl chloride by the Schotten−Baumann reaction to yield amide **9**. Bischler−Napieralski reaction of **9** using a polyphosphate ester (PPE)[12] produced the C-ring closure product **10**, which was

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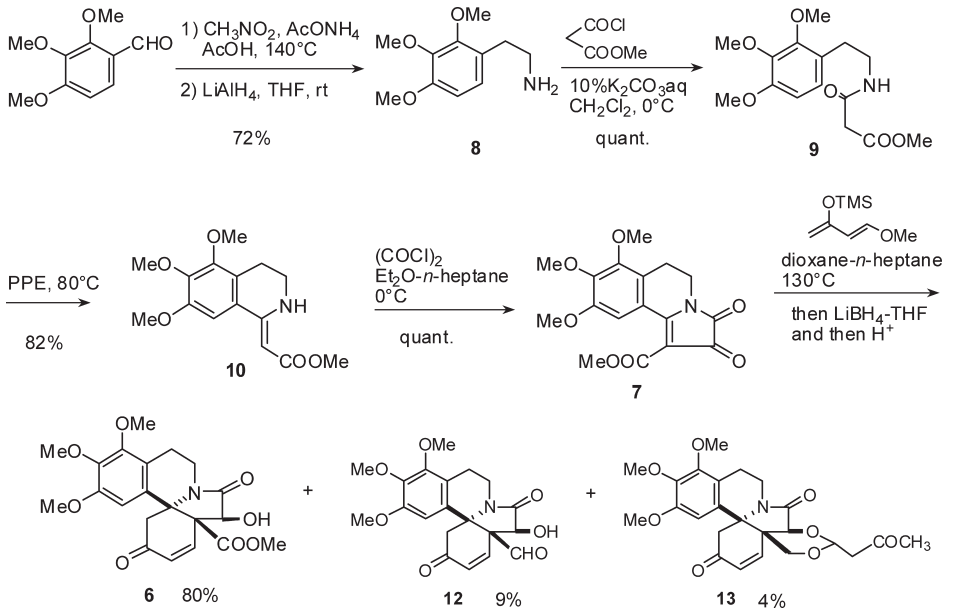
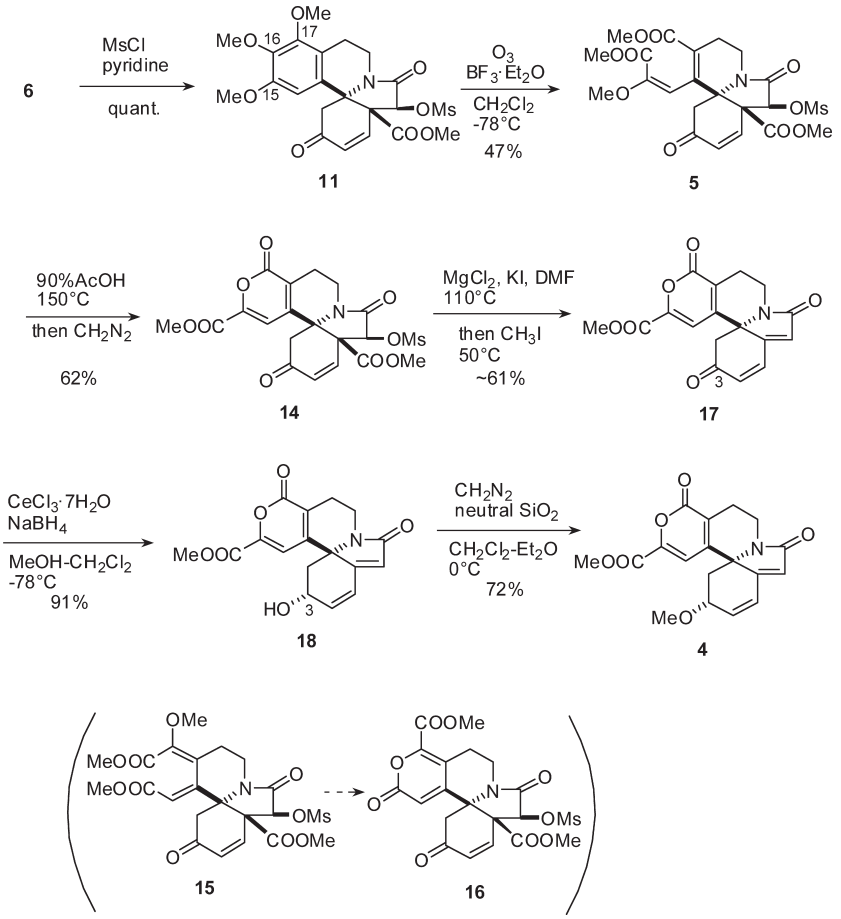
SCHEME 2



SCHEME 3



then treated with oxalyl chloride to give the desired dioxopyrroline **7** in excellent yield.

The A-ring possessing the desired stereochemistry was constructed using the Diels−Alder reaction with the required activated diene. Thus, a solution of pyrroline **7** and 1-methoxy-3-trimethylsilyloxy-butadiene in dioxane/*n*-heptane was heated in a sealed tube at 130 °C for 1 h to afford tetracyclic ring products. The crude products, without

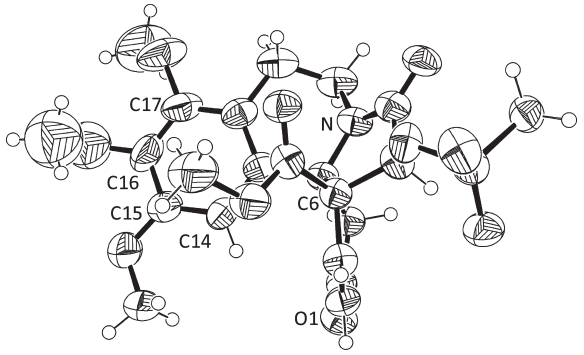
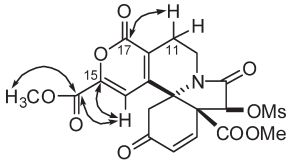


FIGURE 2. Ortep drawing of the mesylate **11**.

purification, were reduced with $LiBH_4$ and then treated with HCl to afford three enones, **6** (80%), **12** (9%), and **13** (4%), whose structures were assigned on the basis of their spectral data. The Diels−Alder reaction proceeded by endotype addition as reported previously.[10] In the ^1H NMR spectrum of enone **6**, the methyl protons of the angular ester at C-6 were observed at δ 3.29, indicating that the methyl group is considerably shielded. This shielding effect is presumably caused by anisotropy of the aromatic D-ring, because the angular methyl ester at C-6 is fixed in the region just above the aromatic D-ring. X-ray crystallographic analysis of mesylate **11** described below agreed well with this theory.

Oxidative Cleavage of the Aromatic D-Ring. Oxidative cleavage of aromatic rings is widespread in nature but is limited in the laboratory because of the difficulty in controlling the reaction. Our group reported that ozonolytic cleavage of *o*-dimethoxybenzenes to muconates was satisfactorily controlled by addition of BF_3-etherate as a regulator.[9] This oxidation reaction was applied to the aromatic erythrinan compound **11**, which was derived from alcohol **6** by treatment with methanesulfonyl chloride (Scheme 3). The reaction proceeded chemo- and regioselectively to afford muconate **5** in 47% yield, and the starting material **11** was recovered in 15% yield. The enone functionality in the A-ring remained intact, suggesting that BF_3 coordinates to the carbonyl oxygen of the enone and decreases the electron density of the double bond. The regioselective C−C bond cleavage of the D-ring is explained as follows. Following X-ray crystallographic analysis of compound **11**, the ORTEP drawing of **11** showed that the angular methoxycarbonyl group at C-6 is fixed above the aromatic D-ring (Figure 2), thus inhibiting the approach of ozone species from the upper face. The ^1H NMR spectrum also indicated that mesylate **11** adopts a similar conformation in solution. Thus, the methyl protons of the angular ester at C-6 were observed at δ 3.37, indicating that the methyl group is shielded and that the methyl ester is fixed in the region above the aromatic D-ring; therefore, the ozone species is assumed to approach from the lower face.

On the lower face, the C-17 side is less crowded than the C-15 side when BF_3 coordinates to the A-ring enone. The ^1H NMR spectrum of **11**, determined in CD_2Cl_2 in the presence of BF_3-etherate (1.2 equiv), which were the reaction conditions of ozonolysis, was compared with that in the absence of BF_3-etherate (Supporting Information). The results demonstrated that the A-ring enone protons at C-1 and C-2 and the B-ring proton at C-7 were deshielded in the presence of



14

FIGURE 3. Significant HMBC correlation of pyron **14**.

BF_3-etherate, indicating that BF_3 coordinates to the A-ring enone as well as to the B-ring amide. It is reasonable that regioselective ozonolysis occurred between C-16 and C-17 since the bond between C-16 and C-17 is less crowded than that between C-15 and C-16, which lies close to the A-ring enone that is coordinated by BF_3. It is noteworthy that the oxidative cleavage site is the same as that of biosynthetic oxidation.[4] In the absence of BF_3-etherate, ozonolysis of **11** gave a complex mixture containing a trace of muconate **5**.

Treatment of muconate **5** in acetic acid at 150 °C for 7 h in a sealed tube provided a ring-closure product, which was then treated with diazomethane. HMBC correlation of the product (Figure 3) indicated that the product was pyrone **14** and not its isomer **16** that would be derived from the C15−C16 cleavage product **15**. Upon treatment of pyrone **14** with $MgCl_2$ and KI at 110 °C, decarboxylation of the vinylogous β-keto ester, followed by elimination of mesylate, took place to produce dienone **17**. Dienone **17** was reduced regio- and stereoselectively by $NaBH_4$ in the presence of $CeCl_3$ to afford the alcohol **18** as a single isomer in 91% yield. The stereochemistry at C-3 was determined as a 3α-alcohol by comparison with the NMR spectra of natural erysotramidine, which is an alkaloid related to erymelantine.[10,13] Allylic alcohol **18** was converted to the corresponding methyl ether **4** by treatment with diazomethane in the presence of neutral silica gel.[14]

Nitrogen Incorporation. All attempts at ammonolysis to directly convert pyrone **4** to the corresponding pyridone **3** failed. In contrast, aminolysis was achieved using *p*-methoxybenzylamine. Upon treatment of **4** with *p*-methoxybenzylamine in methanol, both the pyrone and the methyl ester were transformed to the corresponding pyridone and *p*-methoxybenzyl (PMB) amide, respectively, to afford PMB amide **19** (Scheme 4). Diamide **19** in TFA was heated at 100 °C for 4 h in a sealed tube to give the deprotected product **20**. The amide group at C15 was converted to the corresponding methyl ester by refluxing in methanol in the presence of TMSCl[15] to give ester **3** in excellent yield.

To complete the total synthesis of 8-oxoerymelanthine **2**, reduction of pyridone to the corresponding pyridine was required. After many attempts, this conversion was achieved via trifluoromethanesulfonate (triflate) **21**, which was obtained from pyridone **3** by treatment with trifluoromethanesulfonic anhydride. Appropriate conditions were found to reduce triflate **21** to provide target compound **2** in quantitative yield. The present method is a modification of the strategy reported by Ortar's group[16] and used 1,

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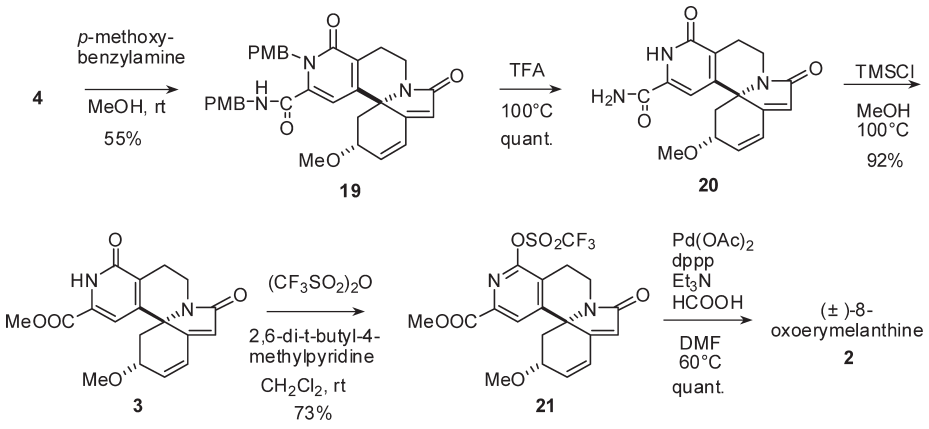
SCHEME 4



3-bis(diphenylphosphino)propane (dppp)[17] instead of the reported phosphine ligands.[16] A mixture of triflate **21**, $Pd(OAc)_2$, dppp, triethylamine, and formic acid in DMF was heated at 60 °C for 1 h in a sealed tube to give (±)-8-oxoerymelanthine **2** in quantitative yield. Thus, palladium-catalyzed reduction was achieved to provide only the desired product. The spectral properties of synthetic (±)-**2** were identical to those previously reported for the natural product.[4b]

Conclusions

Total synthesis of (±)-8-oxoerymelanthine **2** was accomplished in 2.0% overall yield using the regioselective Diels–Alder reaction, ozonolysis of the aromatic ring, and aminolysis as the key reactions. This is the first total synthesis of an erythrinan alkaloid belonging to the D-aza compound category. The synthetic route is in accord with the biosynthetic pathway in terms of the construction of the 6-5-6-6-membered ring system from a dopamine derivative as a starting material,[1,18] oxidative cleavage of the aromatic D-ring and nitrogen incorporation into the D-ring. The present work opens a new avenue for the synthesis of non-aromatic erythrinan D-heteroatom containing alkaloids.

Experimental Section

Methyl 7,8,9-Trimethoxy-2,3-dioxo-2,3,5,6-tetrahydropyrrolo-[2,1-*a*]-isoquinoline-1-carboxylate (7). A solution of oxalyl chloride (1.69 g, 13.3 mmol) in dry ether (40 mL) was added dropwise to a stirred solution of **10** (3.25 g, 11.1 mmol) in dry ether (40 mL) and dry-*n*-heptane (40 mL) at 0 °C, and the mixture was stirred for 1 h. Orange yellow crystals were spontaneously precipitated and collected by filtration. Dioxopyrroline **7** (3.79 g, 99%) was obtained as orange yellow prisms by recrystallization from AcOEt/*n*-hexane. Mp 149–150 °C; IR (KBr) 1720, 1700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (1H, s), 4.06, 3.92, 3.877 and 3.875 (each 3H, s), 3.79 (2H, t, J = 7.2 Hz), 3.08 (2H, t, J = 7.2 Hz); LR-EIMS m/z 347 (M^+); HR-EIMS m/z calcd for $C_{17}H_{17}NO_7$ 347.1005, found 347.1004.

1,2-Didehydro-7-hydroxy-15,16,17-trimethoxy-6-methoxycarbonyl-3,8-dioxoerythrinan (6). A solution of dioxopyrroline **7** (3.82 g, 11 mmol) and 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (6.33 g, 27.5 mmol) in dry dioxane/dry *n*-heptane (42 mL/9.5 mL) was heated at 130 °C for 1 h in a sealed tube. The reaction mixture was concentrated in vacuo, and the residue was dissolved in dry THF (100 mL). To this solution at −78 °C was added a solution of $LiBH_4$ (120 mg, 5.5 mmol) in dry THF (20 mL), and the mixture was stirred for 1 h. The reaction was quenched with 5% HCl (76.4 mL) and THF (76.4 mL), and the resulting mixture was refluxed for 1 h. The mixture was extracted with $CHCl_3$, washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography with AcOEt to afford **6** (3.67 g, 80%), **12** (364 mg, 9%), and **13** (219 mg, 4%). **6**: colorless needles; mp 108–122 °C (AcOEt/*n*-hexane); IR (KBr) 3200, 1735, 1695, 1680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (1H, d, J = 10.6 Hz), 6.45 (1H, d, J = 10.6 Hz), 6.30 (1H, s), 4.75 (1H, s), 4.36 (1H, ddd, J = 13.2, 6.1, 1.8 Hz), 4.30 (1H, br s), 3.823, 3.817, and 3.65 (each 3H, s), 3.29 (3H, s), 3.19 (1H, d, J = 15.6 Hz), 3.05 (1H, dt, J = 12,1, 4.0 Hz), 2.91 (1H, ddd, J = 16.5, 4.0, 1.8 Hz), 2.79 (1H, d, J = 15.6 Hz), 2.61 (1H, ddd, J = 16.5, 12.1, 6.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.5, 169.6, 168.4, 152.2, 150.9, 147.2, 141.6, 131.6, 128.1, 119.9, 103.1, 77.2, 63.6, 60.7 (×2), 59.8, 55.7, 52.5, 50.4, 35.1, 21.3; HR-EIMS m/z calcd for $C_{21}H_{23}NO_8$ 417.1424, found 417.1401.

1-(2,3-Dimethoxy-3-oxo-1-propenyl)-3,4,6,7,7a,10,11-heptahydro-7-methanesulfonyloxy-2,7a-dimethoxycarbonyl-6,10-dioxo-6*H*-pyrido[2,1-*i*]indole (5). Ozone was generated with an ozone generator (ON-1-2 Type, Nihon Ozone Co., Ltd.), using commercial-grade oxygen as a source. The flow rate of oxygen was 50 mL/min, and the voltage was adjusted to 80 V. Ozonized oxygen was passed into a solution of aromatic erythrinan compound **11** (935 mg, 1.89 mmol) and $BF_3 \cdot Et_2O$ (322 mg, 2.27 mmol) in CH_2Cl_2 (113 mL) at −78 °C for 17 min. After the excess ozone was removed by suction with an aspirator, 5% Pd/C (10 mg) was added to the solution, and the mixture was allowed to gradually warm to rt. The reaction mixture was filtrated, and the filtrate was diluted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, and evaporated. The residue was passed through short SiO_2 column chromatography and then purified by MPLC (AcOEt/*n*-hexane, 2:1) to afford **5** (467 mg, 47%) and starting material **11** (140 mg, 15%). **5**: IR ($CHCl_3$) 1740, 1725, 1625 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (1H, d, J = 10.7 Hz), 6.32 (1H, d, J = 10.7 Hz), 5.47 (1H, s), 5.21 (1H, d, J = 3.3 Hz), 4.27 (1H, dd, J = 5.3, 3.2 Hz), 3.78 (6H, s), 3.78 (1H, d, J = 16.4 Hz), 3.63 and 3.53 (each 3H, s), 3.37 (3H, s), 3.04 (1H, dt, J = 12.5, 4.0 Hz), 2.57 (1H, dd, J = 17.6, 4.0 Hz), 2.53 (1H, d, J = 16.4 Hz), 2.39–2.22 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.9, 167.6, 167.4, 164.1,

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162.3, 149.7, 142.3, 134.7, 131.9, 130.2, 102.6, 81.6, 64.8, 56.9, 55.8, 53.2, 52.5, 52.1, 45.9, 40.0, 34.1, 25.7; HR-EIMS m/z calcd for $C_{22}H_{25}NO_{12}S$ 527.1062, found 527.1079.

1,2,6,7-Tetradehydro-15-methoxycarbonyl-16(17*H*)-oxa-3,8,17-trioxoerythrinan (17). A solution of pyrone **14** (100 mg, 0.2 mmol), KI (106 mg, 0.62 mmol), and anhydrous $MgCl_2$ (100 mg, 1.04 mmol) in DMSO (8.0 mL) was heated at 110 °C in a sealed tube for 1 h. After the mixture was cooled to room temperature, CH_3I (5.90 g, 41.58 mmol) was added, and the mixture was stirred at 50 °C for 17 h. The mixture was diluted with $CHCl_3$, washed with brine, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel (AcOEt/*n*-hexane, 5:1) to afford **17** (41.5 mg, 61%) and starting material **14** (35.5 mg, 36%). **17**: colorless prisms; mp 248−251 °C (AcOEt); IR (KBr) 1700, 1690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (1H, dd, J = 10.2, 0.6 Hz), 7.19 (1H, s), 6.50 (1H, d, J = 10.2 Hz), 6.43 (1H, s), 4.49 (1H, ddd, J = 13.8, 5.1, 3.9 Hz), 3.90 (3H, s), 3.24 (1H, d, J = 15.7 Hz), 3.20 (1H, dd, J = 13.8, 8.1 Hz), 2.87 (1H, d, J = 15.7 Hz), 2.77 (2H, dd, J = 8.1, 4.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.9, 168.5, 159.7, 159.4, 151.5, 147.2, 146.5, 138.0, 132.5, 126.9, 126.8, 106.2, 65.8, 53.3, 49.9, 34.2, 23.6; HR-EIMS m/z calcd for $C_{17}H_{13}NO_6$ 327.0742, found 327.0757.

1,2,6,7-Tetradehydro-3α-methoxy-16-[(4-methoxyphenyl)methyl]-15-*N*-[(4-methoxyphenyl)methyl]-16(17*H*)-aza-8,17-dioxoerythrinan-15-Carboxamide (19). To a solution of **4** (40 mg, 0.12 mmol) in MeOH (2 mL) was added 40% 4-methoxybenzylamine (480 mg, 3.5 mmol) in MeOH (910 μL), and the mixture was stirred at rt for 2 h. Furthermore, 40% 4-methoxybenzylamine (320 mg, 2.3 mmol) in MeOH (607 μL) was added, and the mixture was stirred at rt for 70 h. AcOH (800 μL) was added, the mixture was refluxed for 3 h, and the residue was diluted with $CHCl_3$, washed with 5% HCl, dried over Na_2SO_4, and evaporated. The residue was passed through short SiO_2 column chromatography ($CHCl_3$/MeOH, 30:1) and then purified with MPLC ($CHCl_3$/MeOH, 80:1) to afford **19** (36 mg, 55%) and **4** (26 mg, 39%). **19**: colorless powder; mp 181−183 °C (AcOEt/*n*-hexane); IR (KBr) 3427, 1682, 1639 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$ + CD_3OD) δ 7.11 (2H, d, J = 8.2 Hz), 7.03 (2H, d, J = 8.2 Hz), 6.83 (2H, d, J = 8.2 Hz), 6.77 (1H, dd, J = 10.4, 2.4 Hz), 6.73 (2H, d, J = 8.2 Hz), 6.28 (1H, br d, J = 10.4 Hz), 6.27 (1H, s), 5.92 (1H, s), 5.58 (1H, d, J = 14.7 Hz), 5.27 (1H, d, J = 14.7 Hz), 4.32 (2H, dd, J = 19.5, 14.7 Hz), 4.30−4.19 (1H, m), 4.02−3.96 (1H, m), 3.80 (3H, s), 3.75 (3H, s), 3.47−3.34 (1H, m), 3.38 (3H, s), 3.00 (1H, dt, J = 18.5, 8.4 Hz), 2.83 (1H, dd, J = 11.9, 5.5 Hz), 2.79 (1H, ddd, J = 18.5, 7.0, 4.0 Hz), 1.71 (1H, dd, J = 11.9, 10.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$ + CD_3OD) δ 170.1, 163.4, 161.9, 159.3, 159.1, 155.6, 145.0, 140.3, 137.2, 129.7 (×2), 129.3 (×2), 128.9 (×2), 127.4, 124.1, 120.6, 114.2 (×2), 114.0 (×2), 103.3, 73.8, 65.1, 56.6, 55.4, 55.3, 46.7, 43.4, 41.1, 34.7, 22.6; HR-FAB-MS (positive-ion mode) m/z 568.2469 $[M + H]^+$ (calcd for $C_{33}H_{34}N_3O_6$ 568.2447).

8-Oxoerymelanthine (2). To a solution of **21** (7.3 mg, 0.0154 mmol), palladium acetate (0.6 mg, 0.0025 mmol, 16 mol %), 1,3-bis(diphenylphosphino)propane (dppp) (1.0 mg, 0.0025 mmol, 16 mol %), and Et_3N (10 μL, 0.0708 mmol) in dry DMF (60 μL) was added 99% formic acid (2 μL, 0.0508 mmol). The mixture was heated at 60 °C for 1 h in a sealed tube. The mixture was poured into brine and extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4 and evaporated. The residue was passed through short Al_2O_3 column chromatography (AcOEt/MeOH, 10:1) to afford 8-oxoerymelanthine **2** (4.9 mg, 98%). **2**: pale yellow prisms; mp 164−167 °C (AcOEt/*n*-hexane); IR (neat) 1720, 1686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.61 (1H, s), 7.99 (1H, s), 6.95 (1H, dd, J = 10.3, 1.8 Hz), 6.44 (1H, br d, J = 10.3 Hz), 6.06 (1H, s), 4.20 (1H, dt, J = 13.2, 7.3 Hz), 3.99 (3H, s), 3.85−3.76 (1H, m), 3.64 (1H, quintet), 3.36 (3H, s), 3.21−3.13 (2H, m), 2.79 (1H, dd, J = 12.1, 4.8 Hz), 1.82 (1H, dd, J = 12.1, 10.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 165.5, 155.6, 150.7, 146.2 (×2), 136.8, 133.7, 123.8, 120.6, 119.9, 74.1, 65.5, 56.6, 53.0, 40.5, 35.9, 24.6; LR-EIMS m/z 326 (M^+, 100%), 311 (45%), 294 (75%); HR-FAB-MS (positive-ion mode) m/z 327.1359 $[M+H]^+$ (calcd for $C_{18}H_{19}N_2O_4$ 327.1345). Anal. Calcd for $C_{18}H_{18}N_2O_4 - H_2O$: C, 62.78.; H, 5.85; N, 8.13. Found: C, 62.63; H, 5.68 ; N, 7.91.

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Supporting Information Available: Additional procedures and spectral data for all new compounds; copies of NMR spectra of compounds **2**−**14** and **17**−**21** and ^1H NMR spectra of compound **11** in CD_2Cl_2; CIF file for X-ray data of compound **11**. This material is available free of charge via the Internet at http://pubs.acs.org.