Synthesis of four possible stereoisomers of 1,2-epoxy-3-hydroxyerythrinans: total synthesis of an alkenoid-type erythrinan alkaloid, (±)-erythratidine [1]

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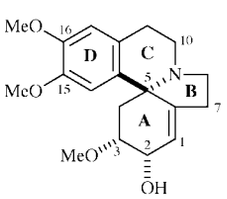
Four stereoisomers of 1,2-epoxy-3-hydroxyerythrinans are synthesized and their stereochemistries determined unambiguously. Of these, the 1,2α-epoxy-3α-alcohol **4** is converted to the alkenoid-type alkaloid, (±)-erythratidine **1**, utilizing reductive migration of an α,β-unsaturated γ,δ-epoxyamide with samarium diiodide as a key step.

Introduction

Erythrinan alkaloids possessing an aromatic D-ring are classified into two sub-groups, dienoid and alkenoid types, according to the structure of the A/B-rings.[2] More than thirty members of the latter alkaloid type are now known. Most of them bear an additional chiral center at C-2 (for example, erythratidine **1**),[3] whose stereochemistry has been elucidated principally based on the coupling constant between H-2 and H-3 in the ^{1}H NMR spectrum.[3b] Although total synthesis of dienoid-type alkaloids (for example, erysotrine **2**) has been achieved by several routes,[4] synthesis of alkenoid-type alkaloids is still elusive except that of the simplest one, 3-demethoxyerythratidinone **3**.[5] In this paper, we present the first total synthesis of an alkaloid of this type, (±)-erythratidine **1**, from the stereochemically well established precursor, the 1,2α-epoxy-3α-hydroxyerythrinan **4**.



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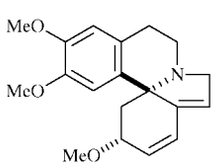

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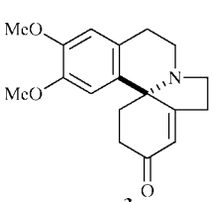

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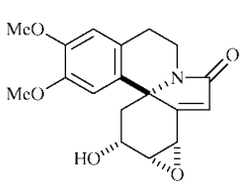

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Results and discussion

Synthetic plan and improved synthesis of (±)-erysotrine 2

We planned to synthesize all the four possible stereoisomers **4**, **13**–**15** of 1,2-epoxy-3-hydroxyerythrinans with unequivocal determination of their stereochemistries from the dienone **7**, which has been reported previously as a synthetic intermediate to erysotrine **2**.[4a] In the present synthesis, several steps which had previously given unsatisfactory yield were modified. First, conversion of homoveratrylamine to the dioxopyrroline **5** was achieved in 73% yield (53% in ref. 4*a*) (Scheme 1). The dioxopyrroline **5** was converted to **6** using the following modified procedure: the Diels–Alder reaction adduct of **5** with 1-methoxy-3-(trimethylsilyloxy)buta-1,3-diene [instead of 1,3-bis(trimethylsilyloxy)butadiene in ref. 4*a*] was reduced with $LiBH_4$ without isolation, followed by hydrolysis with HCl which afforded **6** in 78% yield (53% in ref. 4*a*). Mesylation and demethoxycarbonylation of the resulting mesyl derivative with $CaCl_2$ in DMSO gave **7** in 81% yield (76.5% in ref. 4*a*). Reduction of **7** in methanol with $NaBH_4$–$CeCl_3$ gave the 3α-alcohol **8** and 3β-alcohol **9** in 88% and 9% yield, respectively.[6] The α-alcohol **8** was converted to (±)-erysotrine **2** in 79% yield (67% in ref. 4*a*), improving the overall yield of **2** from homoveratrylamine to 32%, in contrast to the previously reported yield of 10%.

Synthesis of four stereoisomers 4, 13–15 of an 1,2-epoxy-3-hydroxyerythrinan

Oxidation of the α-alcohol **8** with *m*-chloroperbenzoic acid (MCPBA) in CH_2Cl_2 gave an epoxide **4** as a single product in 70% yield (Scheme 2).[7] It had the molecular formula $C_{18}H_{19}NO_5$, and showed only one singlet olefinic proton signal, at δ 6.48, with disappearance of the olefinic protons attributable to H-1 and H-2, indicating it to be a 1,2-epoxide. On the other hand, similar oxidation of the β-alcohol **9** did not produce an epoxide but instead regenerated the dienone **7** in 22% yield. The methyl ether, erysotramidine **10**, was inert to MCPBA.[8] The oxidation of **8** proceeded through a hydrogen-bonded transition state as reported by Henbest and Wilson.[9] For the β-alcohol **9**, a hydrogen-bonded transition structure would hardly be generated on the β-face of the molecule due to the severe steric hindrance by the aromatic ring, instead causing allylic oxidation at C-3. Thus, α-configuration of the epoxide ring in **4** was suggested.

Oxidation of the dienone **7** with H_2O_2–NaOH in methanol–1,4-dioxane proceeded readily at 0 °C to afford two epoxy ketones, **11** and **12**, in 70% yield in the ratio 11 : 3 (Scheme 3). Both of them were 1,2-epoxides, because they showed only one singlet olefinic proton signal, at δ 6.56 and 6.41 in the ^{1}H NMR spectrum, respectively. They also exhibited similar patterns of

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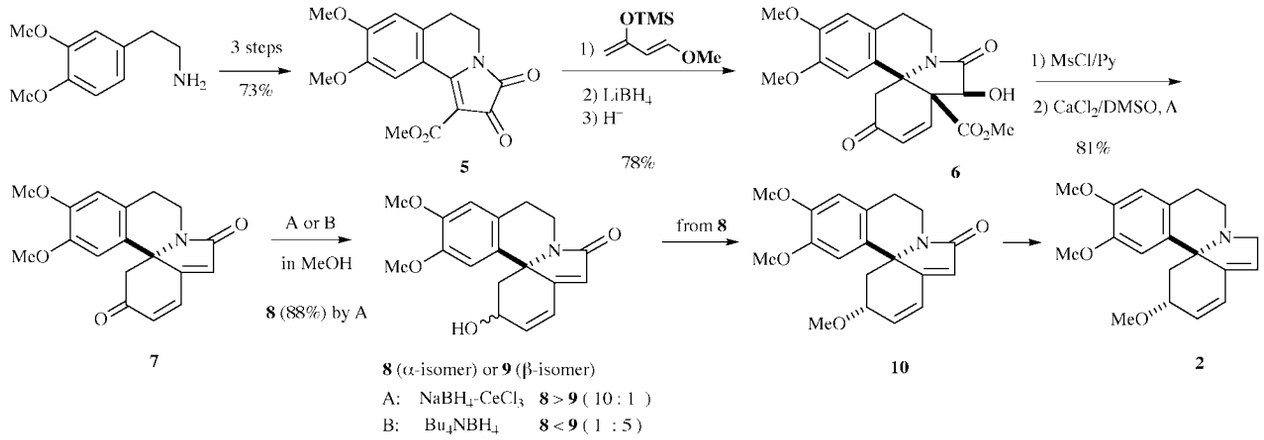
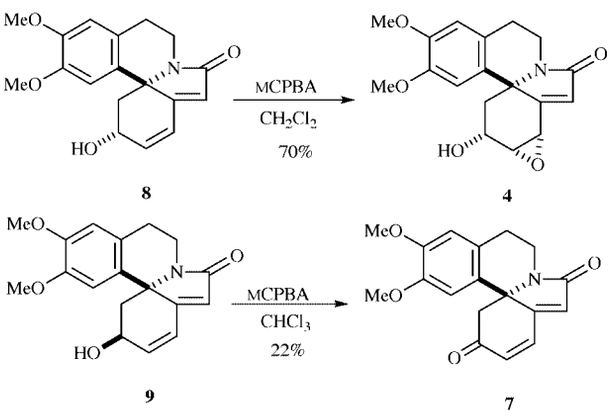
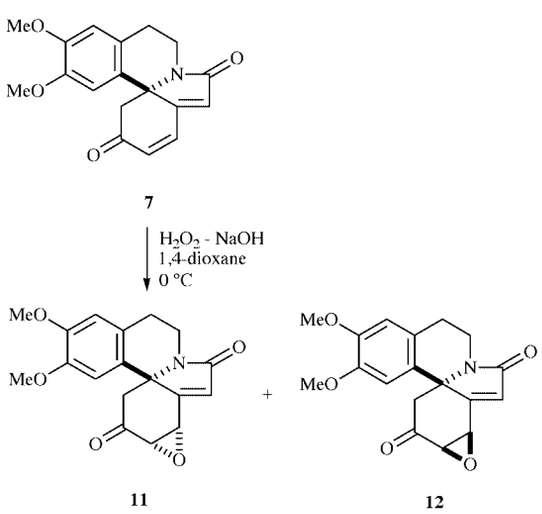


Scheme 1



Scheme 2



Scheme 3

fragmentation in the mass spectra. The major product was suggested to be the α-epoxide **11** and the minor product to be the β-epoxide **12**, because the β-face of **7** is shielded by the aromatic ring, and thereby the approach of the reagent from the α-face would be favoured (Fig. 1).[10,11]

Reduction of the α-epoxy ketone **11** with $NaBH_4$–$CeCl_3$ afforded two epoxy alcohols in 71% and 13% yield. The minor product was identical with the α-epoxy-α-alcohol **4** described above; thus the major one was assigned to be the α-epoxy-β-alcohol **13** (Scheme 4). Reduction of **11** with Bu_4NBH_4 gave the β-alcohol **13** as a single product. Reduction of the β-epoxy ketone **12** with $NaBH_4$–$CeCl_3$ gave two alcohols, **14** and **15**, in the ratio 5:2, and that with Bu_4NBH_4 afforded the same alcohols with a slightly different selectivity (3:1). The major

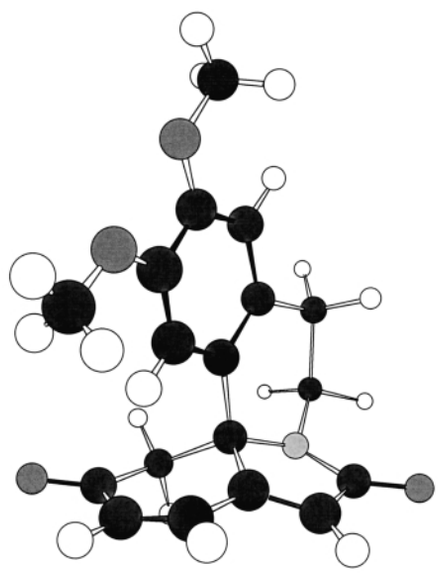


Fig. 1 Optimized structure of compound **7** (by AM1).

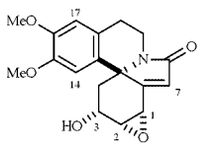
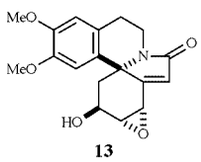
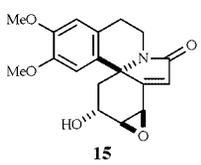
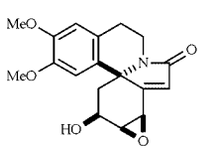
product **14** was assigned as the β-alcohol and the minor product **15** as the α-alcohol, because a nuclear Overhauser effect (NOE) (0.9%) was observed between H-3 and H-14 in **15**, while no NOE between them was observed in **14**.[12]

The assigned stereochemistries of these four epoxy alcohols were supported by the following spectral evidence. As seen from Table 1, the H-14s of β-epoxides **14** and **15** resonate at significantly lower fields (0.7–0.8 ppm) than those of α-epoxides **4** and **13**, indicating that the H-14s of the β-epoxides are spatially close to the 3-OH oxygen atoms.[12] Configurations of the hydroxy group at C-3 are clarified by the presence (α-alcohol) or absence (β-alcohol) of an NOE between H-3 and H-14.

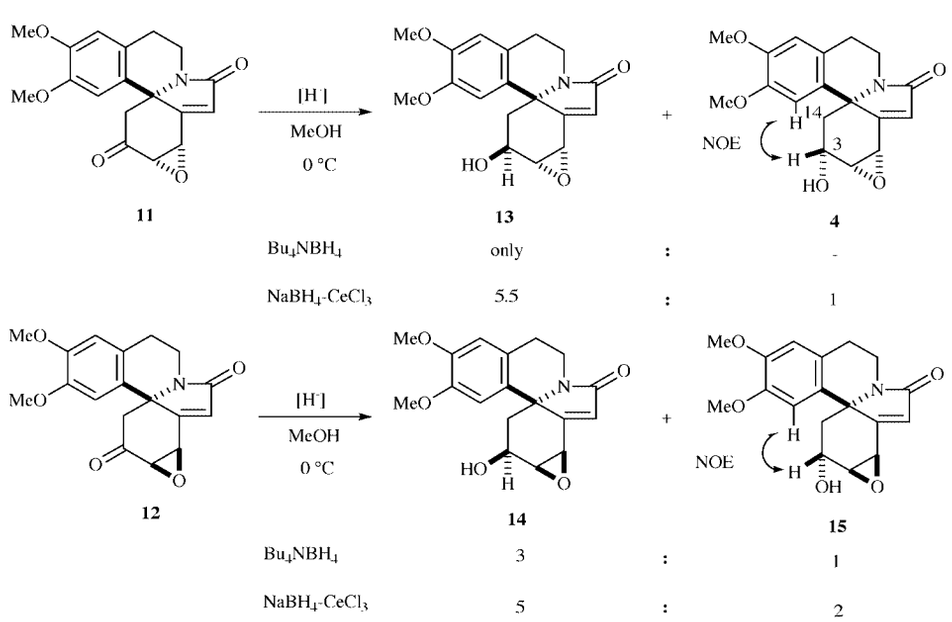
Stereochemistry in hydride reduction of the dienone and epoxy ketones

The intriguing stereochemical outcome of hydride reductions of 3-ketones **7**, **11**, **12** with two reagents, $NaBH_4$–$CeCl_3$ (reagent A)[13] and Bu_4NBH_4 (reagent B) are discussed in this section. Reduction of dienone **7** resulted in the formation of 3α-alcohol **8** and 3β-alcohol **9** the ratio 10:1 (97%) with reagent A, whereas 3β-alcohol **9** was formed stereoselectively with reagent B (**8**:**9** = 1:5, 62% yield).[6] This reversal of stereoselectivity depending on the reducing agent is explained as follows: reagent B attacks the ketone from the less hindered α-face, and with reagent A the dienone **7** formed a complex with the cerium salts and sterically hindered the α-face of the molecule, forcing attack of the hydride from the β-side (Fig. 2). A similar explanation was given for the stereochemical outcome on hydride reduction of

Table 1 Selected chemical shifts of epoxy alcohols (^{1}H NMR)[a]

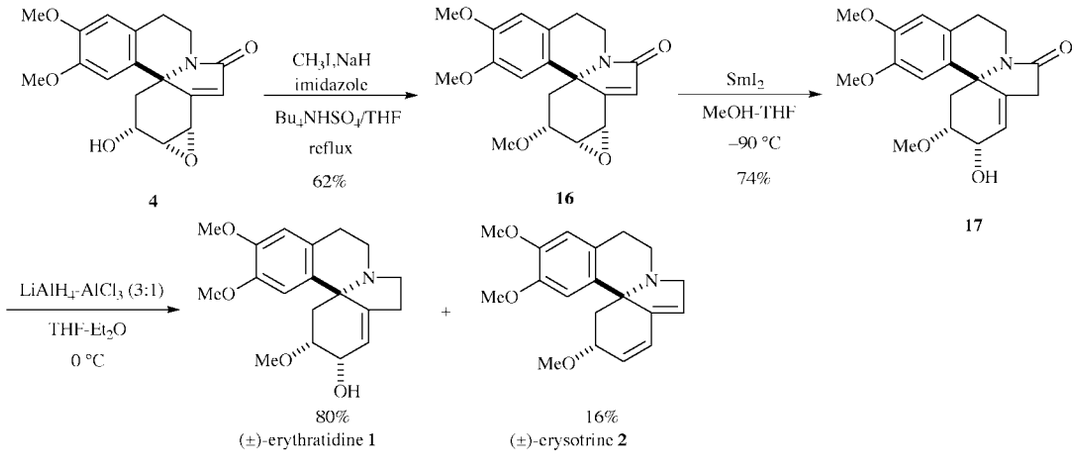
Epoxy ketones	H-1	H-2	H-3	H-7	H-14	H-17	NOE (H3 · · · H14)
 **4**	4.30	3.77	4.06	6.48	**6.75**	6.60	+
 **13**	4.27	3.64	4.39	6.45	**6.91**	6.73	−
 **15**	4.17	3.68	4.08	6.47	**7.48**	6.66	+
 **14**	4.27	3.81	4.05	6.25	**7.72**	6.58	−

[a] In $CDCl_3$–CD_3OD (3 : 1).



Scheme 4

bicyclo[3.1.0]hexanones with reagent A, in which attack of the hydride from the concave face of the molecules is favored.[14] Reductions of the 1,2-epoxy ketones **11** and **12** by the above two reagents (A and B) occurred selectively from the same α-face, with some difference in the selectivity. The results for reduction of **11** and **12** with Bu_4NBH_4 indicate that this bulky reagent attacked from the less hindered α-face of the molecule (Fig. 2). Reduction of the epoxy ketones with $NaBH_4$–MCl_x (M = metal) generally proceeds by inducing intramolecular chelation of the metal ion between the carbonyl and epoxy oxygen atoms, producing *erythro*-selectivity in the products as a consequence of the less-hindered-face attack (the same face as the epoxy group).[15] In a rigid system like 2,3-epoxycyclohexanone, lanthanoid metal chlorides such as $CeCl_3$ or YCl_3 which have a marked affinity for an oxygen atom are particularly effective for gaining high selectivity.[15b,16] Stereoselective fomation of the β-alcohol **13** from the α-epoxy ketone **11** was thus conceivable. However, preferential formation of the β-alcohol **14** from the β-epoxy ketone **12** does not follow the above chelation mechanism, indicating that such an intramolecular chelation on the β-face of **12** is difficult for steric reasons. In this case, the result might be explained in a way similar to that for the reduction of dienone **7** with reagent A.



Scheme 5

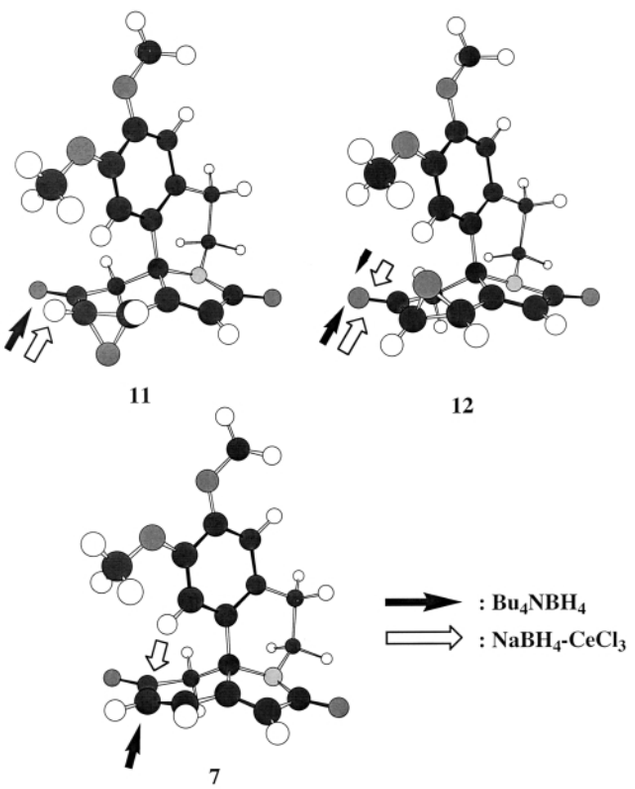


Fig. 2 Hydride reduction of the dienone **7** and epoxy ketones **11** and **12** (the structures were optimized by AM1).

Conversion of the 1,2α-epoxy-3α-alcohol 4 to (±)-erythratidine

From the results obtained above, the most effective route to **4**, which has the correct stereochemistry for the synthesis of (±)-erythratidine **1**, is the $NaBH_4$–$CeCl_3$ reduction of the dienone **7** followed by oxidation of the resulting alcohol **8** with MCPBA (yield: 62%, 2 steps). The 3α-hydroxy-1,2α-epoxide **4** thus obtained was methylated with iodomethane in the presence of a phase-transfer catalyst (Bu_4NHSO_4) to form the *O*-methyl derivative **16** in 62% yield (see Scheme 5).[17]

Molander *et al.*[18] reported that functionalized vinyloxiranes readily undergo reductive ring opening with samarium diiodide (SmI_2) in THF in the presence of a proton source to provide (*E*)-allylic alcohols. In their examples, exclusive kinetic protonation to the intermediate was observed.[18a] Reaction of **16** with samarium(II) iodide proceeded very rapidly to afford the expected allylic alcohol **17** in 74% yield. It exhibited one olefinic proton signal, at δ 6.06, as a doublet of doublets in the ^{1}H NMR spectrum and had the molecular formula $C_{19}H_{23}NO_5$, thus confirming the expected transformation. Finally, the lactam carbonyl group was removed by reduction with $LiAlH_4$–$AlCl_3$ combination[19] to yield (±)-erythratidine **1** in 79% yield, accomplishing its total synthesis. The base thus obtained was identical with (+)-erythratidine[3b] according to ^{1}H NMR and IR spectra.[20] (±)-Erysotrine **2** was a by-product in this reduction (17%).

Conclusions

In conclusion we were able to accomplish the total synthesis of an alkenoid-type erythrinan alkaloid, (±)-erythratidine, *via* reductive migration of α,β-unsaturated γ,δ-epoxy amide **16** with samarium diiodide as a key reaction.

Experimental

Unless otherwise noted, the following procedures were adopted. Non-aqueous reactions were carried out under argon in dried glassware. Anhydrous solvents were freshly distilled as follows: tetrahydrofuran (THF) and Et_2O were distilled under argon from sodium and benzophenone immediately prior to use. Pyridine was distilled under argon from CaH_2. Mps were determined on a Yanaco micro hot stage melting point apparatus and are uncorrected. IR spectra were taken as KBr disks on a JASCO IR-G spectrometer and data are given in cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were taken with a JEOL GX 500 (^{1}H: 500 MHz; ^{13}C: 125 MHz) spectrometer for solutions in $CDCl_3$ with tetramethylsilane as internal standard, and chemical shifts are given in δ-values with coupling constants (*J*) in Hz. Mass spectra (MS) and high-resolution MS (HRMS) were taken with a Hitachi M-80 machine and M^+ and/or major peaks are indicated as *m*/*z*. Column chromatography was carried out with silica gel (Wacogel C-200). Recycling high-performance liquid chromatography (RHPLC) was performed on JAI LC-908 with a JAIGEL H column using $CHCl_3$ as the mobile phase. Medium-pressure liquid chromatography (MPLC) was performed on a Merck Lobar column [LiChroprep Si 60 (40–63 μm)]. For TLC, Merck precoated plates GF_{254} were used and spots were monitored under UV light (254 nm), then developed by spraying with 10% H_2SO_4 and heating the plate at 100 °C until coloration took place. Preparative TLC (PTLC) was performed with precoated silica gel plates, Merck 60 F_{254} (1 mm thick). All organic extracts were washed with brine and dried over anhydrous sodium sulfate before concentration. Identities were confirmed by mixed mp determinations (for crystalline compounds) and by comparisons of TLC behavior and IR and ^{1}H NMR spectra.

Methyl 8,9-dimethoxy-2,3-dioxo-2,3,5,6-tetrahydropyrrolo-[2,1-*a*]isoquinoline-1-carboxylate 5

A solution of methyl 2-(chloroformyl)acetate (1.63 g, 11.9

mmol) in $CHCl_3$ (9 ml) was added dropwise to a stirred solution of 3,4-dimethoxyphenylethylamine (1.8 g, 9.93 mmol) in $CHCl_3$ (11 ml) containing 10% aq. K_2CO_3 (16.5 ml, 11.9 mmol) at 0 °C. Stirring was continued for a further 1 h, the organic layer was separated, and the aqueous layer was extracted with $CHCl_3$. The combined organic layer was dried and evaporated to give a residue, which was purified by SiO_2 chromatography (eluent: $CHCl_3$) to give the amide (2.70 g, 97%).

A solution of the amide (5.0 g, 17.8 mmol) and polyphosphoric ester (PPE) (50 g) in anhydrous $CHCl_3$ (50 ml) was heated under reflux for 3.5 h. After the reaction mixture had cooled to room temperature, ice was added carefully to decompose any excess of PPE. The mixture was basified with 10% aq. K_2CO_3, and then extracted with $CHCl_3$. The extract was washed with water, dried, and evaporated to dryness. The residue was chromatographed on Florisil, using benzene as eluent, to give an isoquinoline derivative as a syrup.

A 10% ethereal solution of oxalyl dichloride (1.1 mol equiv.) was added dropwise to a stirred solution of the above syrup in Et_2O (50 ml) at 0 °C, and the mixture was stirred for an additional 1 h. The precipitated crystals were collected by filtration. The filtrate was evaporated to give a solid, which was purified by SiO_2 chromatography with $CHCl_3$ to give the *dioxopyrroline* **5**[4a] (4.11 g, 73%).

1,2-Didehydro-7β-hydroxy-15,16-dimethoxy-6-methoxycarbonyl-3,8-dioxoerythrinan 6

A mixture of the dioxopyrroline **5** (1 g, 3.15 mmol) and 1-methoxy-3-(trimethylsilyloxy)buta-1,3-diene (1.35 g, 7.83 mmol) was heated in a sealed tube with stirring for 1 h at 130 °C. The mixture was diluted with THF (40 ml) and cooled to −75 °C. $LiBH_4$ (214 mg, 9.83 mmol) was added to the mixture at −75 °C and stirring was continued for 30 min at −20 to −30 °C. 5% HCl (30 ml) and THF (20 ml) were added to the mixture and the whole was heated at reflux for 30 min. The reaction mixture was extracted with $CHCl_3$. Concentration of the extract gave a residue, which was crystallized from benzene to give *title compound* **6**[4a] (944 mg, 78% from **5**).

1,2,6,7-Tetrahydro-15,16-dimethoxy-3,8-dioxoerythrinan 7

A mixture of **6** (4.1 g, 10.6 mmol) and methanesulfonyl chloride (2.5 ml, 31.8 mmol) in pyridine (62 ml) was stirred for 2 h at room temperature. The cooled mixture was basified with 5% aq. K_2CO_3. The precipitated crystals (the corresponding mesyl derivative, 3.8 g) were collected by filtration. The filtrate was extracted with EtOAc to give another 876 mg of the mesyl derivative (total yield 95%).

A mixture of the above mesyl derivative (2.58 g, 5.5 mmol) and anhydrous $CaCl_2$ (4.3 g, 38.5 mmol) in DMSO (60 ml) was heated at 140 °C for 3 h with stirring under an argon atmosphere. After dilution with water, the mixture was extracted with $CHCl_3$. Crystallization of the extract's residue from EtOAc gave the dienone **7**[4a] (1.1 g). The mother liquor was chromatographed in EtOAc to give another crop of 362 mg of **7** (total yield 85%).

$NaBH_4$–$CeCl_3$ Reduction of 7

$NaBH_4$ (50 mg, 1.28 mmol) was added to a solution of **7** (200 mg, 0.64 mmol) and $CeCl_3 \cdot 7H_2O$ (480 mg, 1.28 mmol) in MeOH (30 ml) at 0 °C. The mixture was stirred for 5 min at 0 °C. After decomposition of excess of hydride with ice, the mixture was extracted with $CHCl_3$. The product was purified by MPLC ($CHCl_3$–MeOH 14:1) to give the *α-alcohol* **8**[4a] (178 mg, 88%) and the *β-alcohol* **9**[4a] (18 mg, 9%).

(±)-Erysotramidine 10

Iodomethane (1.5 ml, 24.1 mmol) was added to a mixture of α-alcohol **8** (216 mg, 0.69 mmol), KOH (462 mg, 8.23 mmol) and Et_4NBr (463 mg, 2.20 mmol) in THF (20 ml) and the mixture was stirred for 48 h at room temperature. The reaction mixture was extracted with $CHCl_3$. Purification of the extract by flash chromatography ($CHCl_3$–MeOH 9:1) gave *title compound* **10**[4a] (246 mg, 100%).

(±)-Erysotrine 2

A solution of AlH_3 (18 ml) [prepared from $LiAlH_4$ (315 mg, 8.3 mmol) and $AlCl_3$ (360 mg, 2.7 mmol) in Et_2O (45 ml)] was added to a solution of **10** (246 mg, 0.75 mmol) in THF (22 ml) at 0 °C. The mixture was stirred for 1 h at 0 °C under a nitrogen atmosphere. The reaction was quenched with ice–water, and the mixture was basified (pH 12) by addition of 28% NH_4OH and extracted with diethyl ether. The extract was dried over K_2CO_3 and concentrated *in vacuo* to give *(±)-erysotrine* **2** (186 mg, 79%).[4a]

MCPBA Oxidation of the 3α-alcohol 8

(1) In CH_2Cl_2. MCPBA (80%; 690 mg, 3.2 mmol) was added to a solution of **8** (200 mg, 0.64 mmol) in CH_2Cl_2 (40 ml). The mixture was stirred for 24 h at room temperature. The reaction mixture was washed successively with aq. $Na_2S_2O_3$, saturated aq. $NaHCO_3$, and brine. The organic layer was concentrated and the residue was crystallized from EtOAc to give the *1,2α-epoxy-3α-alcohol* **4** (97 mg). Chromatography of the mother liquor (acetone–hexane 4:1) gave another 51 mg of **4** (total yield 148 mg, 70%). Compound **4** gave colorless prisms from EtOAc, mp 258–261 °C; ν_{max} 1671 (C=O); δ_H ($CDCl_3$–CD_3OD 3:1) 6.75 (1H, s, H-14), 6.60 (1H, s, H-17), 6.48 (1H, s, H-7), 4.30 (1H, d, *J* 3.7, H-1), 4.06 (1H, ddd, *J* 11.2, 5.3, 1.9, H-3), 3.89 (1H, ddd, *J* 12.7, 8.5, 7.3, H^{β}-10), 3.87, 3.84 (each 3H, s, OMe), 3.77 (1H, dd, *J* 3.7, 1.9, H-2), 3.57 (1H, ddd, *J* 12.7, 7.3, 5.0, H^{α}-10), 3.10 (1H, ddd, *J* 16, 8.5, 7.3, H^{α}-11), 2.97 (1H, ddd, *J* 16, 7.3, 5.0, H^{β}-11), 2.37 (1H, dd, *J* 12.0, 5.3, H-4), 1.53 (1H, dd, *J* 12.0, 11.2, H-4); *m/z* (EI) 329 (M^+, 95%), 257 (100) (Found: M^+, 329.1261. $C_{18}H_{19}NO_5$ requires *M*, 329.1262).

(2) In $CHCl_3$. MCPBA (80%; 1.09 g, 5.05 mmol) was added to a solution of **8** (315 mg, 1.01 mmol) in $CHCl_3$ (20 ml). After stirring for 24 h at room temperature, the mixture was worked up as described above to afford **4** (160 mg, 49%).

MCPBA Oxidation of the 3β-alcohol 9

The reaction was carried out with **9** (50 mg, 0.16 mmol) and MCPBA (80%; 135 mg, 0.8 mmol) as described for **8**. The product was purified by PTLC, developing with $CHCl_3$–MeOH (14:1), to give the *dienone* **7** (8 mg, 22%) with recovery of **9** (12 mg, 24%).

H_2O_2–NaOH Oxidation of the dienone 7

4 M NaOH (2.5 ml) and 30% aq. H_2O_2 (2.3 ml) were added to a solution of **7** (550 mg, 1.77 mmol) in 1,4-dioxane (10 ml)–MeOH (20 ml) at 0 °C. The mixture was stirred for 90 min at 0 °C, diluted with water, and extracted with $CHCl_3$. Purification of the extract by chromatography (THF–$CHCl_3$ 1:1) gave the *α-epoxy ketone* **11** (315 mg, 55%) and the *β-epoxy ketone* **12** (89 mg, 15%).

The α-epoxy ketone **11**: colorless needles from EtOAc, mp 192–193 °C; ν_{max} 1715, 1693; δ_H 6.66, 6.65 (each 1H, s, ArH), 6.56 (1H, s, H-7), 4.52 (1H, d, *J* 3.5, H-2), 4.20 (1H, ddd, *J* 13.4, 7.0, 4.7, H^{β}-10), 3.84, 3.79 (each 3H, s, OMe), 3.81 (1H, br d, *J* 3.5, H-1), 3.32 (1H, ddd, *J* 13.4, 8.9, 5.8, H^{α}-10), 3.01 (1H, ddd, *J* 16.3, 8.9, 7.0, H^{β}-11), 2.93, 2.86 (each 1H, d *J* 13.5, H-4), 2.81 (1H, ddd, *J* 16.3, 5.8, 4.7, H^{α}-11); *m/z* (EI) 327 (M^+, 88%), 298 (100) (Found: C, 65.90; H, 5.26; N, 4.17. $C_{18}H_{17}NO_5$ requires C, 66.05; H, 5.24; N, 4.28%).

The β-epoxy ketone **12**: colorless prisms from EtOAc, mp 221–222 °C; ν_{max} 1715, 1692; δ_H 7.71 (1H, s, H-14), 6.60 (1H, s, H-17), 6.41 (1H, s, H-7), 4.53 (1H, d, *J* 4.3, H-2), 4.11 (1H, ddd, *J* 13.0, 6.3, 4.5, H^{β}-10), 3.78 (1H, d, *J* 4.3, H-1), 3.26 (1H, ddd, *J* 13.0, 9.1, 5.2, H^{α}-10), 3.20, 2.94 (each 1H, d, *J* 16.7, H-4), 3.04 (1H, ddd, *J* 16, 9.1, 6.3, H^{β}-11), 2.72 (1H, ddd, *J* 16.0, 5.2, 4.5, H^{α}-11); *m/z* (EI) 327 (M^+, 56%), 298 (100) (Found: C, 65.75; H, 5.24; N, 4.14%).

Reduction of the α-epoxy ketone 11

(1) With reagent A. $NaBH_4$ (33 mg, 1.22 mmol) was added to a mixture of **11** (200 mg, 0.61 mmol) and $CeCl_3 \cdot 7H_2O$ (330 mg, 1.22 mmol) in MeOH (20 ml) at 0 °C. The mixture was stirred for 10 min at 0 °C. After decomposition of excess of hydride with ice, the mixture was extracted with $CHCl_3$. The products were separated by MPLC ($CHCl_3$–MeOH 9 : 1) to give the *1,2α-epoxy-3β-alcohol* **13** (142 mg, 71%) and the *1,2α-epoxy-3α-alcohol* **4** (27 mg, 13%).

(2) With reagent B. Bu_4NBH_4 (24 mg, 0.36 mmol) was added to a solution of **11** (30 mg, 0.09 mmol) in MeOH (6 ml) at 0 °C. The mixture was stirred for 15 h at 0 °C and worked up as described above to afford the *1,2α-epoxy-3β-alcohol* **13** (32 mg, 100%) as colorless prisms, mp 244–246 °C (from EtOAc); ν_{max} 3430, 1715, 1693; δ_H ($CDCl_3$–CD_3OD 3 : 1) 6.91 (1H, s, H-14), 6.73 (1H, s, H-17), 6.45 (1H, s, H-7), 4.39 (1H, m, H-3), 4.27 (1H, d, *J* 3.2, H-1), 3.87 (1H, ddd, *J* 13.0, 8.6, 7.2, H^{β}-10), 3.86 (6H, s, 2 × OCH_3), 3.64 (1H, br d, *J* 3.2, H-2), 3.54 (1H, ddd, *J* 13.0, 6.9, 4.8, H^{α}-10), 3.08 (1H, ddd, *J* 16.2, 8.6, 6.9, H^{β}-11), 2.98 (1H, ddd, *J* 16.2, 7.2, 4.8, H^{α}-11), 2.47 (1H, d, *J* 14.1, H^{β}-4), 1.80 (1H, dd, *J* 14.1, 4.9, H^{α}-4); *m/z* (EI) 329 (M^+, 93%), 257 (100) (Found: C, 65.65; H, 5.85; N, 4.14. $C_{18}H_{19}NO_5$ requires C, 65.64; H, 5.82; N, 4.25%).

Reduction of the β-epoxy ketone 12

(1) With reagent A. The reduction of **12** (20 mg, 0.06 mmol) with $NaBH_4$ (3.3 mg, 0.12 mmol) and $CeCl_3 \cdot 7H_2O$ (33 mg, 0.12 mmol) in MeOH (6 ml) was carried out and worked up as described for **11** to give a mixture (14 mg, 70%) of the *3β-alcohol* **14** and the *3α-alcohol* **15** (**14**:**15** = 5:2, determined by ^{1}H NMR), which were separated by RHPLC ($CHCl_3$).

(2) With reagent B. The reduction of **12** (33 mg, 0.101 mmol) with Bu_4NBH_4 (26 mg, 0.404 mmol) in MeOH (10 ml) as described for **11** gave a mixture (32.5 mg, 98%) of **14** and **15** (**14**:**15** 3 : 1, determined by ^{1}H NMR).

The 1,2β-epoxy-3β-alcohol **14**: Colorless needles, mp 236–237 °C (from EtOAc); ν_{max} 3405, 1657; δ_H ($CDCl_3$–CD_3OD 3 : 1) 7.72 (1H, s, H-14), 6.58 (1H, s, H-17), 6.25 (1H, s, H-7), 4.27 (1H, d, *J* 4.7, H-1), 4.05 (1H, m, H-3), 4.03 (1H, ddd, *J* 13.1, 6.8, 4.5, H^{β}-10), 3.91, 3.84 (each 3H, s, 2 × OMe), 3.81 (1H, br d, *J* 4.7, H-2), 3.34 (1H, ddd, *J* 13.1, 8.9, 5.4, H^{α}-10), 3.01 (1H, ddd, *J* 16.2, 8.9, 6.8, H^{β}-11), 2.77 (1H, ddd, *J* 16.2, 5.4, 4.5, H^{α}-11), 2.35 (1H, dd, *J* 14.2, 9.2, H^{α}-4), 2.26 (1H, dd, *J* 14.2, 5.6, H^{β}-4); *m/z* (EI) 329 (M^+, 98%), 257 (100) (Found: C, 65.43; H, 5.85; N, 4.01%).

The 1,2β-epoxy-3α-alcohol **15**: Colorless prisms, mp 227–230 °C (from EtOAc); ν_{max} 3405, 1657; δ_H ($CDCl_3$–CD_3OD 3 : 1) 7.48 (1H, s, H-14), 6.66 (1H, s, H-17), 6.47 (1H, s, H-7), 4.17 (1H, d, *J* 3.9, H-1), 4.08 (1H, dd, *J* 9.8, 5, H-3), 3.87, 3.85 (each 3H, s, 2 × OCH_3), 3.86 (1H, ddd, *J* 12.3, 8.4, 6.8, H^{β}-10), 3.68 (1H, br d, *J* 3.9, H-2), 3.55 (1H, ddd, *J* 12.3, 6.7, 5.8, H^{α}-10), 3.04 (1H, ddd, *J* 15.8, 8.4, 6.7, H^{β}-11), 2.98 (1H, ddd, *J* 15.8, 6.8, 5.8, H^{α}-11), 2.60 (1H, dd, *J* 12.7, 5.0, H^{β}-4), 1.77 (1H, dd, *J* 12.7, 9.8, H^{α}-4); *m/z* (EI) 329 (M^+, 96%), 257 (100) (Found: M^+, 329.1267. $C_{18}H_{19}NO_5$ requires *M*, 329.1262).

6,7-Didehydro-1,2α-epoxy-3α,15,16-trimethoxy-8-oxoerythrinan 16

A mixture of **4** (156 mg, 0.47 mmol), NaH (60% oil dispersion; 100 mg, 2.35 mmol) and imidazole (3 mg, 0.04 mmol) in THF (20 ml) was heated at reflux for 1 h under a nitrogen atmosphere. CH_3I (95%; 6 ml, 40 mmol) and Bu_4NHSO_4 (50 mg, 0.15 mmol) were added to the cooled mixture and the mixture heated at reflux for a further 2 h. After removal of the precipitates by filtration, the filtrate was acidified with 1% aq. HCl and extracted with $CHCl_3$. The product was chromatographed (EtOAc) to give **16** (31 mg). The precipitate (sodium salt of **4**) was remethylated as described above to give a further crop of **16** (69 mg) (total yield: 100 mg, 62%). The *3α-methoxy-1,2α-epoxide* **16** crystallized in colorless needles from EtOAc, mp 169–170 °C; ν_{max} 1685; δ_H 6.74 (1H, s, H-14), 6.59 (1H, s, H-17), 6.49 (1H, s, H-7), 4.27 (1H, d, *J* 3.9, H-1), 3.93 (1H, ddd, *J* 12.7, 8.5, 7.3, H^{β}-10), 3.87, 3.84 (each 3H, s, 2 × OMe), 3.83 (1H, dd, *J* 3.9, 1.9, H-2), 3.73 (1H, ddd, *J* 11.1, 5.3, 1.9, H-3), 3.56 (1H, ddd, *J* 12.7, 7.3, 5.0, H^{α}-10), 3.40 (3H, s, OMe), 3.08 (1H, ddd, *J* 16.0, 8.5, 7.3, H^{α}-11), 2.97 (1H, ddd, *J* 16.0, 7.3, 5.0, H^{β}-11), 2.38 (1H, dd, *J* 12.0, 5.3, H^{β}-4), 1.58 (1H, dd, *J* 12, 11.1, H^{α}-4); *m/z* (EI) 343 (M^+, 98%), 257 (100) (Found: M^+, 343.1427; C, 66.16; H, 6.18; N, 3.97. $C_{19}H_{21}NO_5$ requires *M*, 343.1418; C, 66.46; H, 6.16; N, 4.08%).

(±)-8-Oxoerythratidine 17

A 0.1 M solution of SmI_2 in THF (2 ml, 0.2 mmol) was added to a solution of **16** (35 mg, 0.10 mmol) in THF (2 ml)–MeOH (1 ml) at −90 °C and the mixture was stirred for 5 min at the same temperature. The reaction was quenched by addition of pH 8 phosphate buffer, and the mixture was extracted with $CHCl_3$. Purification of the product by PTLC ($CHCl_3$–MeOH 14 : 1) gave *(±)-8-oxoerythratidine* **17** (26 mg, 74%) as colorless prisms, mp 183–185 °C (from EtOAc); ν_{max} 3375, 1703, 1681; δ_H 6.68 (1H, s, H-17), 6.48 (1H, s, H-14), 6.06 (1H, dd, *J* 3.6, 2.4, H-1), 4.53 (1H, ddd, *J* 4.3, 3.6, 2.4, H-2), 4.24 (1H, ddd, *J* 13.1, 8.7, 5.7, H^{β}-10), 3.86, 3.82 (each 3H, s, 2 × OMe), 3.55 (1H, ddd, *J* 12.8, 4.3, 3.6, H-3), 3.42 (1H, ddd, *J* 13.1, 8.6, 6.5, H^{α}-10), 3.35 (3H, s, OMe), 3.04 (1H, ddd, *J* 16.3, 8.7, 6.5, H^{α}-11), 3.01 (1H, d, *J* 19.4, H^{α}-7), 2.97 (1H, ddd, *J* 16.3, 8.6, 5.7, H^{β}-11), 2.91 (1H, dt, *J* 19.4, 2.4, H^{β}-7), 2.21 (1H, dd, *J* 11.5, 3.6, H^{β}-4), 1.99 (1H, dd, *J* 12.8, 11.5, H^{α}-4); *m/z* (EI) 345 (M^+, 30%), 287 (100) (Found: C, 65.77; H, 6.71; N, 3.98. $C_{19}H_{23}NO_5$ requires C, 66.07; H, 6.71; N, 4.06%).

AlH_3 Reduction of 17

A solution of AlH_3 (2.5 ml) [prepared from $LiAlH_4$ (42 mg, 1.11 mmol) and $AlCl_3$ (48 mg, 0.36 mmol) in Et_2O (6 ml)] was added to a solution of **17** (33 mg, 0.10 mmol) in THF (3 ml) at 0 °C. The mixture was stirred for 3.5 h at 0 °C under a nitrogen atmosphere. Reaction was quenched with ice–water, and the mixture was basified (pH 12) by addition of 28% NH_4OH and extracted with diethyl ether. The extract was dried over K_2CO_3 and concentrated *in vacuo* to give a mixture of *(±)-erythratidine* **1** and *(±)-erysotrine* **2** (10 mg, **1**:**2** = 1:1, determined by ^{1}H NMR). The aqueous layer was extracted with $CHCl_3$ and concentated to dryness to give another crop of **1** (20.4 mg). Yield of **1** was 25.5 mg (80%) and that of **2** was 4.9 mg (16%).

(±)-Erythratidine **1**: a pale yellow gum, δ_H 6.62 (1H, s, H-17), 6.49 (1H, s, H-14), 5.85 (1H, m, H-1), 4.48 (1H, m, H-2), 3.86, 3.80 (each 3H, s, 2 × OMe), 3.69 (1H, ddd, *J* 12.8, 4.3, 3.7, H-3), 3.51 (1H, ddd, *J* 14.3, 11.0, 7.2, H^{β}-10), 3.36 (3H, s, OMe), 3.15 (1H, dd, *J* 14.3, 8.0, 1.4, H^{α}-10), 3.00 (1H, ddd, *J* 17.1, 11.0, 8.0, H^{α}-11), 2.95 (1H, td, *J* 9.0, 2.8, H^{β}-8), 2.67 (1H, td, *J* 9.0, 7.0, H^{α}-8), 2.58 (1H, ddd, *J* 17.1, 7.2, 1.4, H^{β}-11), 2.48 (1H, dtd, *J* 16.0, 9.0, 1.5, H^{α}-7), 2.24 (1H, m, H^{β}-7), 2.06 (1H, dd, *J* 11.3, 3.7, H^{β}-4), 1.82 (1H, dd, *J* 12.8, 11.3, H^{α}-4); *m/z* (EI) 331 (M^+, 6%), 300 (14), 274 (18), 273 (100), 272 (20), 258 (24), 257 (95), 256 (31), 244 (47), 242 (14), 149 (11), 83 (11) (Found: M^+, 331.1787. Calc. for $C_{19}H_{25}NO_4$: *M*, 331.1782). The picrate crystallized in yellow prisms, mp 217–219 °C (from acetone)

[*cf*. picrate of (+)-erythratidine,[3b] mp 220–222 °C] (Found: C, 53.36; H, 5.06; N, 9.82. $C_{19}N_{25}NO_4 \cdot C_6H_3N_3O_7$ requires C, 53.60; H, 5.00; N, 10.0%).

(±)-Erysotrine **2**:[4] δ_H 6.83 (1H, s, H-14), 6.62 (1H, s, H-17), 6.58 (1H, dd, *J* 10, 2, H-2), 6.00 (1H, br d, *J* 10, H-1), 5.73 (1H, br s, H-7), 3.85, 3.76, 3.33 (each 3H, s, 3 × OMe).

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