

A Concise Total Synthesis of ($\pm$)-3-Demethoxyerythratidinone Based on an Acid-Promoted Double Cyclization of α -Sulfinylacetamides

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The total synthesis of the *Erythrina* alkaloid ($\pm$)-3-demethoxyerythratidinone (**20**) has been accomplished in 39% overall yield from homoveratrylamine (**1**) by 8 chemical operations, using a tandem cationic cyclization of the Pummerer rearrangement intermediate derived from the sulfoxide **5** as the key step. Of particular interest is the observation that heating of **5** with *p*-toluenesulfonic acid provides the erythrinan **6** (and the deprotected derivative **7**) as a single stereoisomer, whereas similar treatment of **5** in the presence of ethylene glycol gives initially the bicyclic lactam **8**, which then cyclizes under the reaction conditions used to afford a mixture of two diastereomeric erythrinans **6** and **9**. A possible explanation of these contrasting results is presented.

Keywords acylenamide; *N*-acyliminium ion; α -chlorosulfide; ($\pm$)-3-demethoxyerythratidinone; *Erythrina* alkaloid; olefin cyclization; sulfoxide; thionium ion

The *Erythrina* family of alkaloids constitutes an important class of naturally occurring bases, which continues to elicit the interest of synthetic organic chemists. Previous reports from our laboratory¹⁾ have described a direct access to the erythrinan skeleton by an acid-promoted double cyclization of *N*-arylethyl-*N*-(cyclohex-1-enyl)- α -sulfinylacetamides. In this paper,²⁾ we wish to report an application of this method to the facile total synthesis of ($\pm$)-3-demethoxyerythratidinone (**20**), an alkaloid isolated from *Erythrina lithosperma*.^{3,4)}

The synthesis of the key sulfoxide **5** was begun by condensation of homoveratrylamine (**1**) and cyclohexane-1,4-dione monoethylene acetal (**2**) to give the imine **3**. *N*-Acylation of **3** with (methylthio)acetic anhydride followed

by oxidation of the acylenamide **4** with sodium metaperiodate (NaIO_4) gave **5** in 75% overall yield from **1**.

The sulfoxide **5** was heated in benzene in the presence of 2 molar eq of *p*-toluenesulfonic acid (PTSA) with azeotropic removal of water for 10 min to give the erythrinan **6**⁵⁾ and its deprotected derivative **7** in 19 and 53% yields, respectively. Compound **7** was readily reprotected by a standard method to give **6**.

Our attention was then focused on direct access to the erythrinan **6** from **5**. Thus, a benzene solution of **5** containing 2 molar eq of ethylene glycol was heated with PTSA (2 eq) for the same period of reflux (10 min). Unexpectedly, the major product was the bicyclic lactam **8** (89% yield) and the desired erythrinan **6** was obtained in only a minute amount.

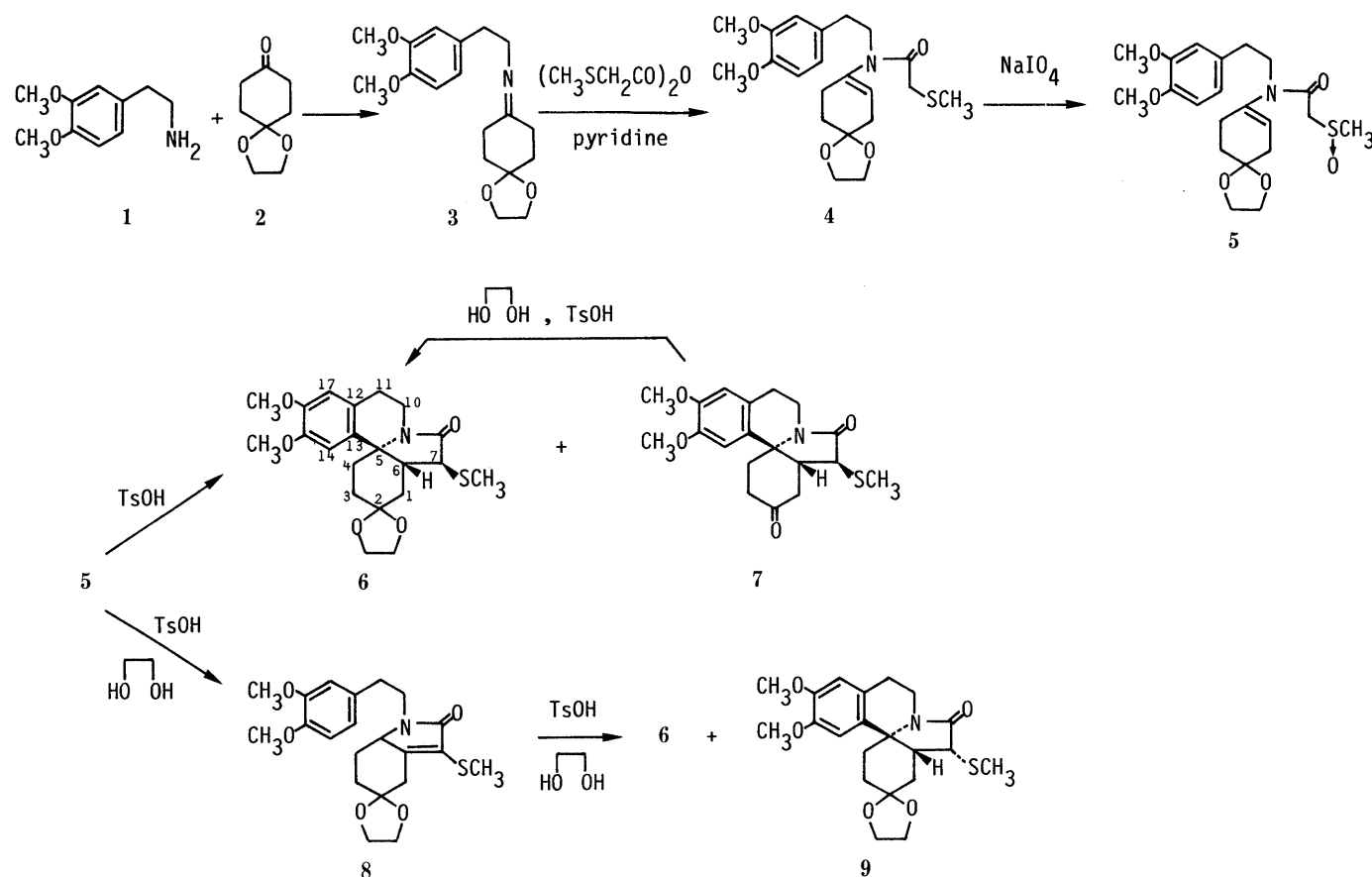


Chart 1

The structure of **8** was deduced from the proton nuclear magnetic resonance ($^1\text{H-NMR}$) spectral data, which showed the down-field shift (δ 2.41) of the SMe protons, clearly indicative of the vinyl-sulfide structure. The absence of a singlet due to the methine proton adjacent to the SMe excludes the possibility of the structure **17**. The lactam **8** was found to cyclize to erythrinan derivatives when heated for a long time. After a 5 h period of reflux, compound **8** was completely transformed into two diastereomeric erythrinans **6** and **9** in 40 and 29% yields, respectively. Practically, it is not necessary to isolate the lactam **8**: on heating of the sulfoxide **5** in the presence of ethylene glycol and PTSA for 5 h, the erythrinans **6** and **9** were obtained in 73 and 22% yields, respectively. Desulfurization of **6** and **9** with Raney nickel in boiling ethanol afforded the same

erythrinan **10**,⁶⁾ which was then deprotected to give the ketone **11**.^{1a,7)}

The stereochemistry of the methylthio group of **6** and **9** was established on the basis of the following chemical evidence. Oxidation of **6** with NaIO_4 followed by thermolysis of the resultant sulfoxide **12** in boiling toluene for 7 h gave the unsaturated lactam **13**^{4a)} in 84% yield. By contrast, similar treatment of the sulfoxide **14** derived from **9** gave only a small quantity of the lactam **13** even after heating for 12 h; the starting material **14** was recovered in 80% yield. Since the thermal elimination of sulfenic acid from sulfoxides is known to proceed *via* a *syn*-mechanism,⁸⁾ we were prompted to assign the stereochemistry between the methylthio group at C(7) and H-6 in **6** as *cis* and that in **9** as *trans*.

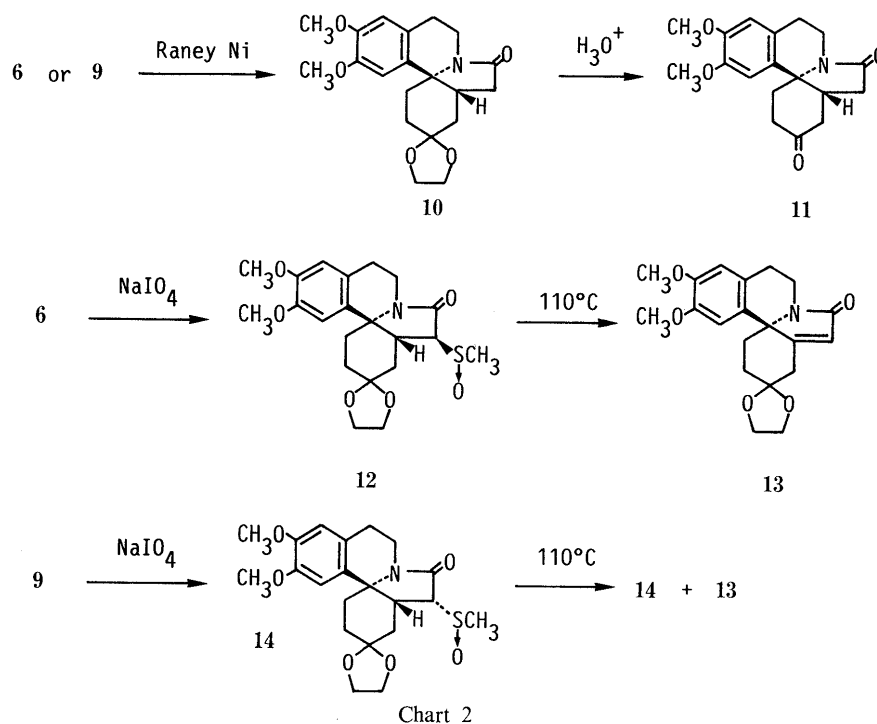


Chart 2

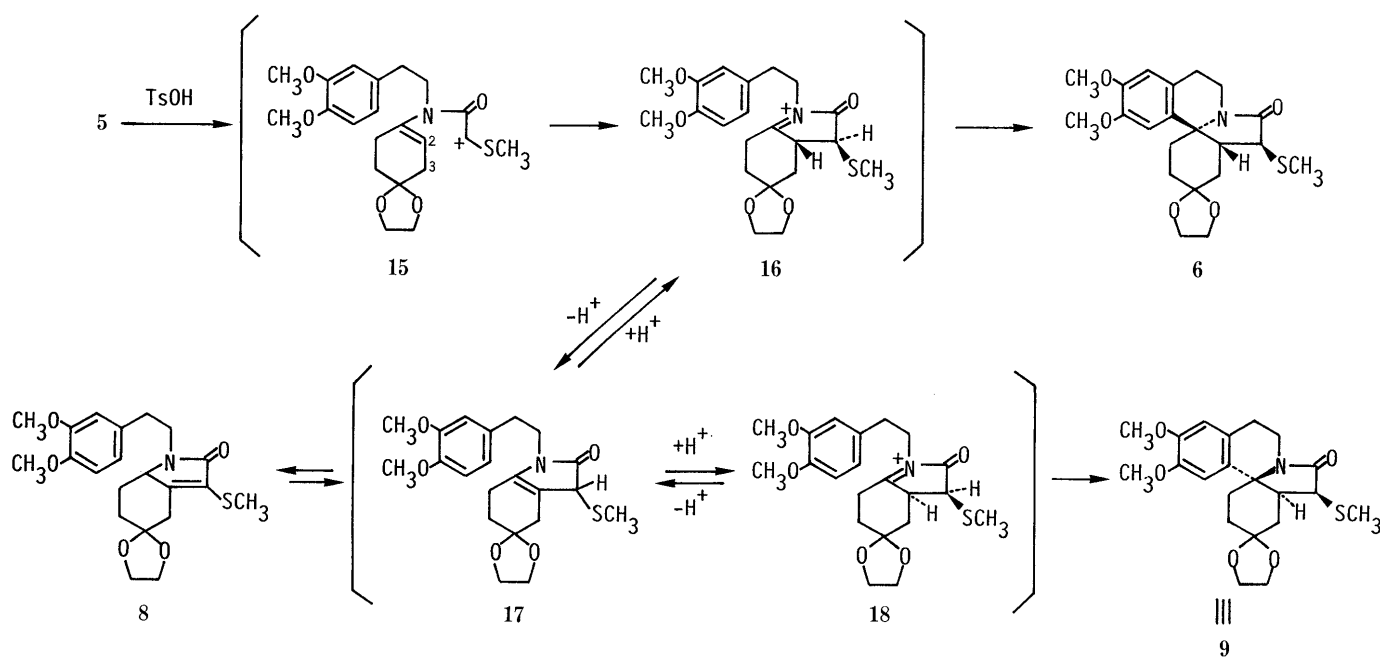


Chart 3

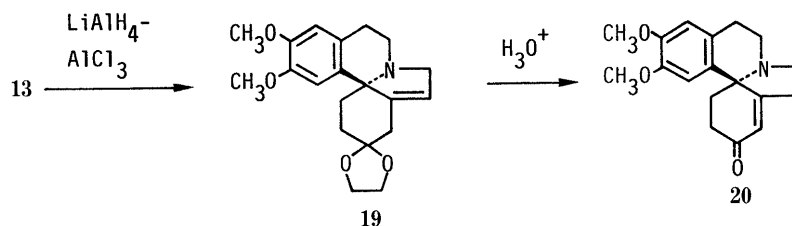


Chart 4

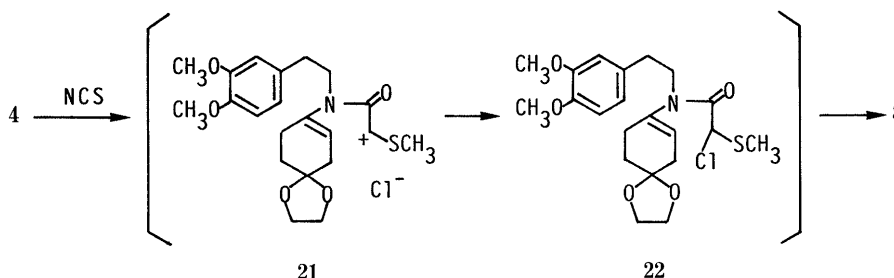


Chart 5

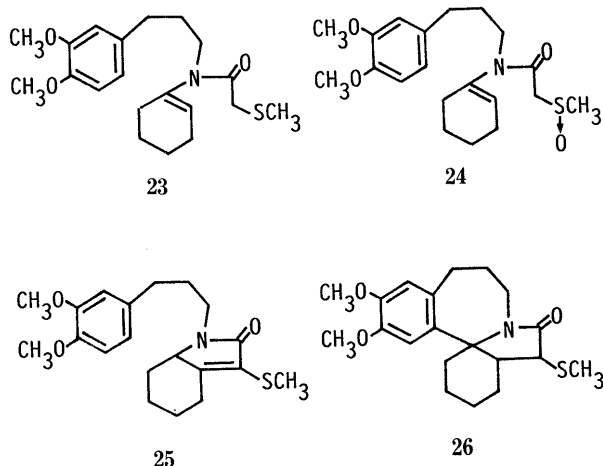


Chart 6

The above results show that the stereochemical outcome of the tandem cationic cyclization is strongly influenced by the presence of ethylene glycol. Ring closure of the initially formed thionium ion intermediate **15** may proceed *via* a transition state so as to avoid steric repulsion between the methylthio group and the C(2)–C(3) bond of the cyclohexene ring to afford, stereoselectively, the *N*-acyliminium ion **16**. In the absence of ethylene glycol, thus formed **16** undergoes rapid cyclization to give the erythrinan **6** (and its deprotected derivative **7**) as a single stereoisomer. On the other hand, in the presence of ethylene glycol, abstraction of the proton at C(3a) of **16** by the glycol, which acts as a base, is much faster than its cyclization, to afford the acylenamide **17**. Subsequent 1,3-proton shift produces the more stable unsaturated lactam **8**. Under acidic conditions, a reverse isomerization of **8** to **17** could be possible. The thermodynamically-controlled protonation of **17** results in the formation of both the *N*-acyliminium ions **16** and **18** in favor of the more stable **16**. These intermediates then cyclize to give the diastereomeric erythrinans **6** and **9**.

With **13** in hand, the remaining steps of the synthesis were carried out by the reported procedure.^{4a} Reduction of **13** with combined lithium aluminum hydride (LiAlH₄) and

aluminum chloride (AlCl₃) gave the amine **19** in 91% yield. Deprotection of **19** with 5% hydrochloric acid in acetone furnished, with concomitant migration of the double bond, (±)-3-demethoxyerythratidinone (**20**) in 94% yield. Thus, we succeeded in the synthesis of **20** in 39% overall yield from homoveratrylamine (**1**) by a sequence of 8 chemical operations.

α-Chlorosulfides have been used as initiating groups for olefin cyclization with the aid of Lewis acid.⁹⁾ We therefore turned our attention to the behavior of the α-chlorosulfide **22**. In an attempt to prepare **22**, the sulfide **4** was treated with *N*-chlorosuccinimide (NCS) in carbon tetrachloride at room temperature. However, no chlorinated product was detected in the crude reaction mixture and, instead, the bicyclic lactam **8** was directly obtained in 52% yield. The formation of **8** from **4** may involve either a direct cyclization of the intermediate thionium ion **21** or a thermal olefin cyclization of the α-chlorosulfide **22**.⁹⁾ The fact that the erythrinan derivative (e.g., **6**) was not formed under the conditions used suggests that such aromatic cyclization of the *N*-acyliminium ion as **16** to **6** requires more elevated temperatures.

Finally, we examined the cyclization of the *N*-arylpropyl-substituted sulfoxide **24** in the hope of obtaining the homoerythrinan **26**. Thus, when a benzene solution of **24** was heated in the presence of PTSA (3 eq) for 4 h, a mixture of several products was obtained. The only product isolated in a pure form was the bicyclic lactam **25** (13%).

Experimental

Melting points are uncorrected. Infrared (IR) spectra were recorded with a JASCO IRA-1 spectrophotometer. ¹H-NMR spectra were determined with a JEOL JNM-PMX 60 (60 MHz) or a Varian XL-300 (300 MHz) spectrometer using tetramethylsilane as an internal standard. High-resolution mass spectra (MS) were obtained with a Hitachi M-80 instrument at 20 eV. Column chromatography was performed on Silica gel 60 PF₂₅₄ (Merck) under pressure.

N-(1,4-Dioxaspiro[4,5]dec-7-en-8-yl)-N-[2-(3,4-dimethoxyphenyl)ethyl]-α-(methylthio)acetamide (4) A solution of homoveratrylamine (**1**) (2.3 g, 12.8 mmol) and cyclohexane-1,4-dione monoethylene acetal (**2**) (2.0 g, 12.8 mmol)¹⁰⁾ in benzene (30 ml) was heated under reflux, in a flask equipped with a Dean-Stark water separator, for 5 h. A solution of (methylthio)acetic anhydride¹¹⁾ (5.0 g, 25.6 mmol) in benzene (5 ml) and

pyridine (2.0 g, 25.6 mmol) was added to the above solution containing the imine **3** at 0 °C, and the mixture was stirred at room temperature overnight. The reaction mixture was washed successively with dilute HCl, saturated NaHCO₃ solution, and brine, then dried over MgSO₄. The solvent was evaporated off and the residue was chromatographed on silica gel (benzene–ethyl ether, 1 : 1) to give the amide **4** (3.98 g, 75%) as yellow needles, mp 89–90 °C (from hexane–benzene). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1645, 1515. ¹H-NMR (CDCl₃, 60 MHz) δ : 1.6–2.05 (2H, m), 2.05–2.5 (4H, m), 2.22 (3H, s, SMe), 2.6–3.0 (2H, m), 3.25 (2H, s), 3.4–3.8 (2H, m), 3.83 (3H, s, OMe), 3.87 (3H, s, OMe), 3.97 (4H, s, OCH₂CH₂O), 5.3–5.65 (1H, m, C=CH), 6.76 (3H, s, aromatic protons). *Anal.* Calcd for C₂₁H₂₉NO₅S: C, 61.89; H, 7.17; N, 3.44. Found: C, 61.76; H, 7.30; N, 3.63.

N-(1,4-Dioxaspiro[4,5]dec-7-en-8-yl)-N-[2-(3,4-dimethoxyphenyl)ethyl]- α -(methylsulfinyl)acetamide (5) A solution of NaIO₄ (196 mg, 0.92 mmol) in water (4 ml) was added dropwise to an ice-cooled solution of **4** (340 mg, 0.83 mmol) in methanol (10 ml) and the mixture was stirred at room temperature overnight. The precipitated inorganic material was removed by filtration and methanol was evaporated off. The aqueous layer was extracted with chloroform (5 ml $\times$ 6) and the extract was dried over MgSO₄. The solvent was evaporated off and the residue was chromatographed on silica gel (acetone) to give the sulfoxide **5** (353 mg, quantitative) as a pale yellow oil. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1640, 1515. ¹H-NMR (CDCl₃, 60 MHz) δ : 1.6–2.1 (2H, m), 2.1–2.55 (4H, m), 2.55–3.0 (2H, m), 2.73 (3H, s, SMe), 3.5–4.2 (4H, m), 3.82 (3H, s, OMe), 3.85 (3H, s, OMe), 3.96 (4H, s, OCH₂CH₂O), 5.35–5.65 (1H, m, C=CH), 6.73 (3H, s, aromatic protons). Exact MS m/z : Calcd for C₂₁H₂₉NO₆S: 423.1713. Found: 423.1685.

2,2-Ethylenedioxy-15,16-dimethoxy-7 β -methylthio-*cis*-erythrinan-8-one (6) and 15,16-Dimethoxy-7 β -methylthio-*cis*-erythrinan-2,8-dione (7) PTSA monohydrate (233 mg, 1.22 mmol) was added to benzene (20 ml) and the mixture was heated under reflux with azeotropic removal of water for 1 h, then cooled under a nitrogen atmosphere. A solution of the sulfoxide **5** (259 mg, 0.61 mmol) in benzene (10 ml) was added to the above solution containing anhydrous PTSA, and the mixture was heated again under reflux with azeotropic removal of water for 10 min. The reaction mixture was washed with saturated NaHCO₃ solution and brine, then dried over MgSO₄. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane–ethyl acetate, 1 : 1). The first eluate gave **6** (47 mg, 19%), mp 170–171 °C (hexane–ethyl acetate). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1680. ¹H-NMR (CDCl₃, 300 MHz) δ : 1.72 (1H, ddd, J =14.0, 7.0, 4.5 Hz), 1.88 (1H, ddd, J =14.0, 8.2, 5.8 Hz), 2.03–2.11 (2H, m), 2.09 (3H, s, SMe), 2.26–2.30 (2H, m), 2.48 (1H, ddd, J =9.5, 5.5, 3.8 Hz), 2.76 (1H, ddd, J =16.0, 6.0, 3.8 Hz), 2.94 (1H, ddd, J =16.5, 10.0, 7.0 Hz), 3.26 (1H, dddd, J =13.3, 10.0, 5.8, 1.0 Hz), 3.86 (3H, s, OMe), 3.88 (3H, s, OMe), 3.91–4.06 (4H, m, OCH₂CH₂O), 4.00 (1H, d J =5.0 Hz, H-7), 4.14 (1H, ddd, J =13.0, 6.8, 4.0 Hz), 6.62 (1H, s, aromatic proton), 6.83 (1H, s, aromatic proton). *Anal.* Calcd for C₂₁H₂₇NO₅S: C, 62.20; H, 6.71; N, 3.45. Found: C, 61.83; H, 6.64; N, 3.62. The second eluate gave **7** (117 mg, 53%), mp 112–113 °C (from hexane–ethyl acetate). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1725, 1695. ¹H-NMR (CDCl₃, 60 MHz) δ : 2.06 (3H, s, SMe), 2.34 (4H, brs), 2.5–4.1 (7H, m), 3.85 (3H, s, OMe), 3.89 (3H, s, OMe), 4.15–4.65 (1H, m, H-6), 6.58 (1H, s, aromatic proton), 6.68 (1H, s, aromatic proton). *Anal.* Calcd for C₁₉H₂₃NO₅S $\cdot$ 1/4H₂O: C, 62.36; H, 6.47; N, 3.83. Found: C, 62.35; H, 6.54; N, 3.81.

Acetalization of 7 to 6 Ethylene glycol (18 mg, 0.29 mmol) and PTSA monohydrate (3 mg) were added to a solution of **7** (117 mg, 0.29 mmol) in benzene (10 ml), and the mixture was heated under reflux with azeotropic removal of water for 3 h. The reaction mixture was washed with water and dried over MgSO₄. The solvent was evaporated off and the residue was chromatographed on silica gel (ethyl acetate) to give, quantitatively, the acetal **6**.

6,6-Ethylenedioxy-1,4,5,6,7,7a-hexahydro-1-[2-(3,4-dimethoxyphenyl)ethyl]-3-methylthio-2H-indol-2-one (8) Ethylene glycol (44 mg, 0.71 mmol) and a solution of the sulfoxide **5** (150 mg, 0.35 mmol) in benzene (5 ml) were successively added to a solution of anhydrous PTSA [prepared from 149 mg (0.71 mmol) of PTSA monohydrate] in benzene (20 ml), and the mixture was heated under reflux for 10 min, then cooled to room temperature. The reaction mixture was washed successively with saturated NaHCO₃ solution and brine, then dried over MgSO₄. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane–ethyl acetate, 1 : 1). The first eluate gave **8** (129 mg, 89%) as an oil. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1690. ¹H-NMR (CDCl₃, 60 MHz) δ : 0.95–4.2 (15H, m), 2.41 (3H, s, SMe), 3.82 (6H, s, OMe $\times$ 2), 6.71 (3H, s, aromatic proton). Exact MS m/z : Calcd for C₂₁H₂₇NO₅S: 405.1609. Found: 405.1618. The second eluate gave **6** (9 mg, 6%).

Formation of 6 and 2,2-Ethylenedioxy-15,16-dimethoxy-7 α -methylthio-*cis*-erythrinan-8-one (9) from 8 Ethylene glycol (37 mg, 0.59 mmol) and a solution of **8** (120 mg, 0.3 mmol) in benzene (5 ml) were successively added to a solution of anhydrous PTSA [prepared from 124 mg (0.6 mmol) of PTSA monohydrate] in benzene (20 ml) and the mixture was heated under reflux with azeotropic removal of water for 5 h. After usual work-up, the crude products were purified by chromatography on silica gel (hexane–ethyl acetate, 1 : 1). The first eluate gave **9** (35 mg, 29%), mp 171–172 °C (from hexane–ethyl acetate). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1710. ¹H-NMR (CDCl₃, 300 MHz) δ : 1.59–1.73 (3H, m), 1.93–2.22 (3H, m), 2.21 (3H, s, SMe), 2.52 (1H, dd, J =16.0, 4.8 Hz), 3.01–3.31 (3H, m), 3.25 (1H, d, J =6.6 Hz, H-7), 3.84 (3H, s, OMe), 3.91 (3H, s, OMe), 3.96–4.07 (4H, m, OCH₂CH₂O), 4.21–4.29 (1H, m), 6.52 (1H, s, aromatic proton), 6.73 (1H, s, aromatic proton). Exact MS m/z : Calcd for C₂₁H₂₇NO₅S: 405.1607. Found: 405.1586. The second eluate gave **6** (48 mg, 40%).

Formation of 6 and 9 from 5 Ethylene glycol (46 mg, 0.74 mmol) and a solution of **5** (156 mg, 0.37 mmol) in benzene (5 ml) were successively added to a solution of anhydrous PTSA [prepared from 155 mg (0.74 mmol) of PTSA monohydrate] in benzene (20 ml) and the mixture was heated under reflux with azeotropic removal of water for 5 h. After usual work-up, the crude products were purified by chromatography on silica gel (hexane–ethyl acetate, 1 : 1). The first eluate gave **9** (33 mg, 22%) and the second eluate gave **6** (110 mg, 73%).

2,2-Ethylenedioxy-15,16-dimethoxy-*cis*-erythrinan-8-one (10) a) From **6** Raney nickel (W-2) (*ca.* 4 g) was added to a solution of **6** (70 mg, 0.17 mmol) in ethanol (5 ml) and the mixture was heated under reflux for 1 h. The Raney nickel was filtered off and the filtrate was concentrated *in vacuo* to give **10**⁶⁾ (64 mg, quantitative) as an oil. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1675. ¹H-NMR (CDCl₃, 60 MHz) δ : 1.55–4.5 (13H, m), 3.83 (3H, s, OMe), 3.86 (3H, s, OMe), 3.97 (4H, s, OCH₂CH₂O), 6.56 (1H, s, aromatic proton), 6.80 (1H, s, aromatic proton).

b) From **9** Using a similar method to that above, compound **9** (40 mg, 0.1 mmol) was treated with Raney nickel to give **10** (38 mg, quantitative).

15,16-Dimethoxy-*cis*-erythrinan-2,8-dione (11) A solution of **10** (99 mg, 0.275 mmol) in acetic acid (1.5 ml) and water (0.3 ml) was heated under reflux for 1 h, then cooled to room temperature. Dichloromethane (5 ml) was added to the reaction mixture and the whole was washed with saturated NaHCO₃ solution, then dried over MgSO₄. The solvent was removed by evaporation and the residue was chromatographed on silica gel (ethyl acetate) to give **11** (85 mg, 98%), mp 162–163 °C, lit.⁷⁾ mp 163.5–164 °C. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1720, 1680. ¹H-NMR (CDCl₃, 60 MHz) δ : 1.85–3.45 (12H, m), 3.82 (3H, s, OMe), 3.85 (3H, s, OMe), 4.0–4.6 (1H, m), 6.56 (1H, s, aromatic proton), 6.69 (1H, s, aromatic proton).

6,7-Didehydro-2,2-ethylenedioxy-15,16-dimethoxy-*cis*-erythrinan-8-one (13) A solution of NaIO₄ (99 mg, 0.46 mmol) in water (2 ml) was added in portions to a solution of **6** (170 mg, 0.42 mmol) in acetone (5 ml) at 0 °C and the mixture was stirred at room temperature for 15 h. The precipitated inorganic material was removed by filtration, acetone was evaporated off, and the aqueous layer was extracted with chloroform (4 ml $\times$ 5), then the extract was dried over MgSO₄. The solvent was evaporated off and the residue was chromatographed on silica gel (ethyl acetate) to give the sulfoxide **12** (167 mg, 95%) as an oil. This compound was dissolved in toluene (10 ml) containing NaHCO₃ (83 mg, 0.99 mmol) and the mixture was heated under reflux for 7 h, then cooled to room temperature. Inorganic material was removed by filtration, the solvent was evaporated off, and the residue was chromatographed on silica gel (hexane–ethyl acetate, 1 : 1) to give **13** (119 mg, 84%), mp 132–133 °C (from ethyl ether), lit.^{4a)} mp 133–135 °C. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1670. ¹H-NMR (CDCl₃, 60 MHz) δ : 1.1–4.5 (10H, m), 3.86 (3H, s, OMe), 3.88 (3H, s, OMe), 4.02 (4H, s, OCH₂CH₂O), 5.97 (1H, brs, C=CH), 6.72 (1H, s, aromatic proton), 7.02 (1H, s, aromatic proton).

2,2-Ethylenedioxy-15,16-dimethoxy-7 α -methylsulfinyl-*cis*-erythrinan-8-one (14) By using a similar procedure to that described above for the preparation of **12**, compound **9** (90 mg, 0.22 mmol) was oxidized with NaIO₄ (52 mg, 0.24 mmol) to give **14** (95 mg, quantitative), mp 222–223 °C (from hexane–ethyl acetate). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1690, 1075. ¹H-NMR (CDCl₃, 60 MHz) δ : 1.4–4.6 (12H, m), 2.88 (3H, s, SMe), 3.81 (3H, s, OMe), 3.88 (3H, s, OMe), 4.01 (4H, s, OCH₂CH₂O), 6.51 (1H, s, aromatic proton), 6.72 (1H, s, aromatic proton). *Anal.* Calcd for C₂₁H₂₇NO₆S: C, 59.84; H, 6.46; N, 3.32. Found: C, 59.65; H, 6.42; N, 3.39.

Thermolysis of 13 A mixture of **14** (91 mg, 0.22 mmol) and NaHCO₃ (45 mg, 0.54 mmol) in toluene (10 ml) was heated under reflux for 12 h. Inorganic material was removed by filtration, the solvent was evaporated off, and the residue was chromatographed on silica gel (ethyl acetate). The first eluate gave **13** (12 mg, 16%). The second eluate gave the recovered **14**

(73 mg, 80%).

6,7-Didehydro-2,2-ethylenedioxy-15,16-dimethoxy-*cis*-erythrinan (19) A solution of freshly sublimed AlCl_3 (660 mg, 4.95 mmol) in dry ethyl ether (4 ml) was added to a suspension of LiAlH_4 (198 mg, 5.21 mmol) in dry tetrahydrofuran (THF) (6 ml) at -15°C and the mixture was stirred at the same temperature for 30 min. A half volume (5 ml) of the resultant mixture was added to a solution of **13** (115 mg, 0.32 mmol) in THF (4 ml) at room temperature, and the mixture was stirred at the same temperature for 1 h. Ethyl ether (20 ml) was added to the reaction mixture and the whole was made alkaline by adding a 5% aqueous NH_4OH solution, then the organic layer was separated. The aqueous layer was further extracted with ethyl ether (5 ml $\times$ 4) and the combined organic layers were dried over K_2CO_3 . The solvent was evaporated off to give the amine **19** (100 mg, 91%)^{4a)} as an oil. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1510, 1250, 1100. $^1\text{H-NMR}$ (CDCl_3 , 60 MHz) δ : 1.5—4.2 (12H, m), 3.85 (6H, s, OMe $\times$ 2), 3.99 (4H, s, $\text{OCH}_2\text{CH}_2\text{O}$), 5.55—5.75 (1H, m, C=CH), 6.64 (1H, s, aromatic proton), 7.00 (1H, s, aromatic proton).

1,6-Didehydro-15,16-dimethoxy-*cis*-erythrinan-2-one [(+)-3-Demethoxyerythratinone (20)] A 5% HCl solution (4 ml) was added to a solution of the acetal **19** (100 mg, 0.29 mmol) in acetone (6 ml) and the mixture was heated under reflux for 1 h, then cooled to room temperature. Water (10 ml) was added to the reaction mixture and the whole was made alkaline by adding a 25% aqueous NH_4OH solution at 0°C , then extracted with chloroform (5 ml $\times$ 4). The extract was dried over K_2CO_3 , the solvent was evaporated off, and the residue was chromatographed on silica gel (ethyl acetate) to give **20** (82 mg, 94%), mp $103\text{--}104^\circ\text{C}$ (from benzene—light petroleum), lit.^{4a)} $101\text{--}102^\circ\text{C}$. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1665, 1610, 1505, 1250, 1110. $^1\text{H-NMR}$ (CDCl_3 , 60 MHz) δ : 2.0—3.7 (12H, m), 3.74 (3H, s, OMe), 3.85 (3H, s, OMe), 6.09 (1H, m, C=CH), 6.57 (1H, s, aromatic proton), 6.66 (1H, s, aromatic proton).

Formation of 8 from 4 *N*-Chlorosuccinimide (47 mg, 0.36 mmol) was added in portions to a solution of **4** (132 mg, 0.32 mmol) in carbon tetrachloride (20 ml) at 0°C and the mixture was stirred at room temperature overnight. The precipitated succinimide was filtered off, the solvent was evaporated off, and the residue was chromatographed on silica gel (benzene—ethyl acetate, 4:1) to give **8** (68 mg, 52%), which was identical with that obtained from the sulfoxide **5**.

***N*-(Cyclohex-1-enyl)-*N*-[3-(3,4-dimethoxyphenyl)propyl]- α -(methylthio)acetamide (23)** using a procedure similar to that described for the preparation of **4**, compound **23** (731 mg, 39%) was obtained from 3-(3,4-dimethoxyphenyl)propylamine (1 g, 5.1 mmol), cyclohexanone (5 g, 51 mmol), and (methylthio)acetic anhydride (1.67 g, 10.2 mmol) as an oil. IR $\nu_{\text{max}}^{\text{CCl}_4}$ cm^{-1} : 1640. $^1\text{H-NMR}$ (CDCl_3 , 60 MHz) δ : 1.3—2.3 (10H, m), 2.20 (3H, s, SMe), 2.4—2.9 (2H, m), 3.21 (2H, s, SCH_2), 3.3—3.6 (2H, m), 3.82 (6H, s, OMe $\times$ 2), 5.64 (1H, m, C=CH), 6.70 (3H, brs, aromatic protons). Exact MS m/z : Calcd for $\text{C}_{20}\text{H}_{29}\text{NO}_3\text{S}$: 363.1866. Found: 363.1854.

***N*-(Cyclohex-1-enyl)-*N*-[3-(3,4-dimethoxyphenyl)propyl]- α -(methylsul-**

finyl)acetamide (24) Using a procedure similar to that described for the preparation of **5**, the amide **23** (500 mg, 1.37 mmol) was oxidized with NaIO_4 (381 mg, 1.78 mmol) to give the sulfoxide **24** (320 mg, 62%) as an oil, which was used immediately to the next stage.

1,4,5,6,7,7a-Hexahydro-1-[3-(3,4-dimethoxyphenyl)propyl]-3-methylthio-2*H*-indol-2-one (25) A solution of **24** (684 mg, 1.7 mmol) in benzene (5 ml) was added to a solution of anhydrous PTSA [prepared from 648 mg (3.4 mmol) of PTSA monohydrate] in benzene (20 ml), and the mixture was heated under reflux with azeotropic removal of water for 4 h. After usual work-up, the crude products were purified by chromatography on silica gel (hexane—ethyl acetate, 4:1) to give **25** (78.3 mg, 13%) as an oil. IR $\nu_{\text{max}}^{\text{CCl}_4}$ cm^{-1} : 1685. $^1\text{H-NMR}$ (CDCl_3 , 60 MHz) δ : 1.2—4.0 (15H, m), 2.43 (3H, s, SMe), 3.82 (3H, s, OMe), 3.85 (3H, s, OMe), 6.76 (3H, s, aromatic protons). Exact MS m/z : Calcd for $\text{C}_{20}\text{H}_{27}\text{NO}_3\text{S}$: 361.1710. Found: 361.1723.

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References and Notes

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