GENERAL METHOD FOR SYNTHESIS OF ERYTHRINAN AND HOMOERYTHRINAN ALKALOIDS (2): APPLICATION OF PUMMERER-TYPE REACTION TO THE SYNTHESIS OF HOMOERYTHRINAN RING SYSTEM[1]

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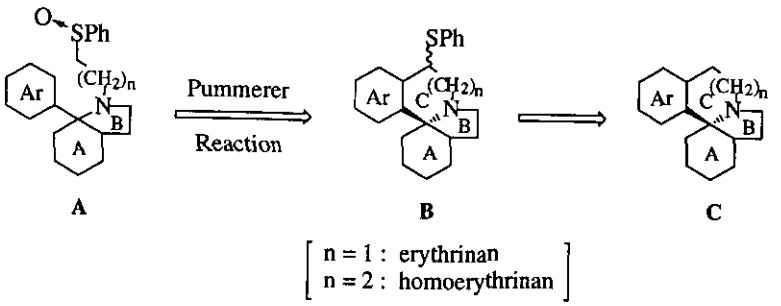
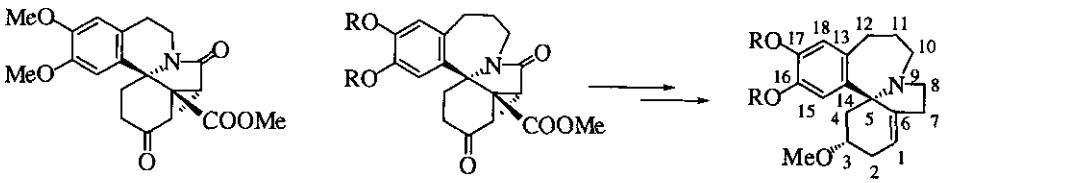
Abstract – The synthesis of cyclohomoerythrinan (**2a**), a potential intermediate to homoerythrinan alkaloids, was achieved by a Pummerer-Type cyclization of the hydroindole sulfoxide (**11**), which was prepared from the dioxopyrroline (**6**) in five steps *via* a [2+2] photocycloaddition reaction followed by an anionic 1,3-shift.

Recently, we developed a new method for constructing erythrinan ring system by a Pummerer-type cyclization.[2] A typical example is the synthesis of the cycloerythrinan (**1**),[3] which is one of the key intermediates to various erythrinan alkaloids. In this paper, we show that the same strategy is also safely applicable for constructing seven-membered C-ring analog, homoerythrinan ring system. The target molecule in this investigation, the cyclohomoerythrinan (**2a**), is a potential intermediate to homoerythrinan alkaloids, since its methylenedioxy analog (**2b**) has already been converted to the alkaloids, schelhammericine and 3-epischelhammericine.[4]

The substrate for the Pummerer reaction, the hydroindole *N*-propyl sulfoxide (**11**), was prepared as follows. Condensation of methyl 3,4-dimethoxybenzoylacetate (**4**) with 3-phenylsulfanylpropylamine[5] gave the enamine (**5**), which on acylation with oxalyl chloride gave the *N*-phenylsulfanylpropyl dioxopyrroline (**6**) in a good yield. [2+2] Photocycloaddition of **6** to 2-trimethylsilyloxybutadiene smoothly occurred in a regio- and stereo-specific manner to give the silyloxy-vinylcyclobutane (**7**) as a sole adduct in 83% yield. The stereochemistry of **7** at the three newly created chiral carbons was deduced from the spectral similarity with the compounds resulted in a similar reaction.[2,6] Reduction of **7** with $NaBH_4$ gave the alcohol **8** with α-

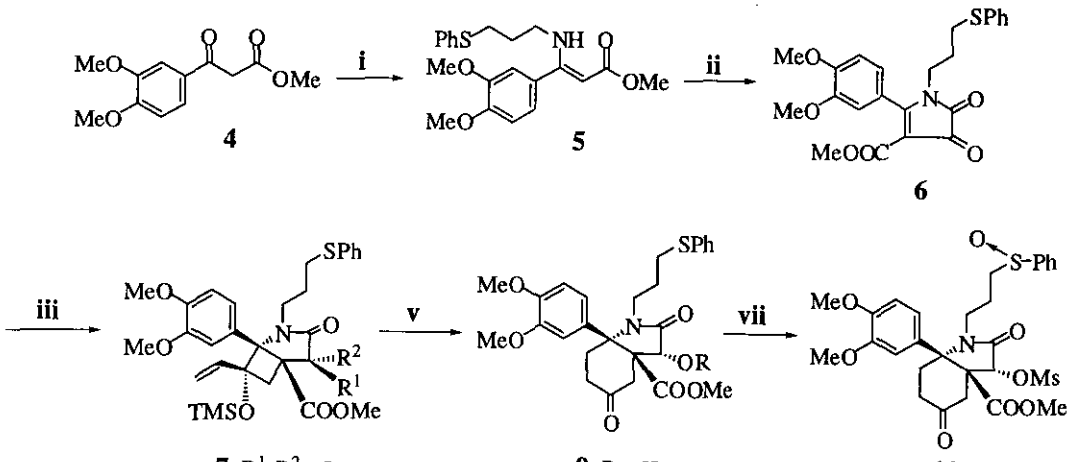
Scheme 1.





configuration[7] in 84% yield. Treatment of **8** with tetrabutylammonium fluoride (TBAF) caused anionic 1,3-rearrangement[8] of the silyloxy-vinylcyclobutane moiety to give the cyclohexanone derivative (**9**) in 86% yield. Mesylation of **9** and oxidation of the resulting mesylate (**10**) with $NaIO_4$ gave the hydroindole sulfoxide (**11**) in an overall yield of 51% from **6**.

Treatment of **11** with trifluoroacetic anhydride (TFAA) in CH_2Cl_2 at room temperature for 6 h gave the ex-

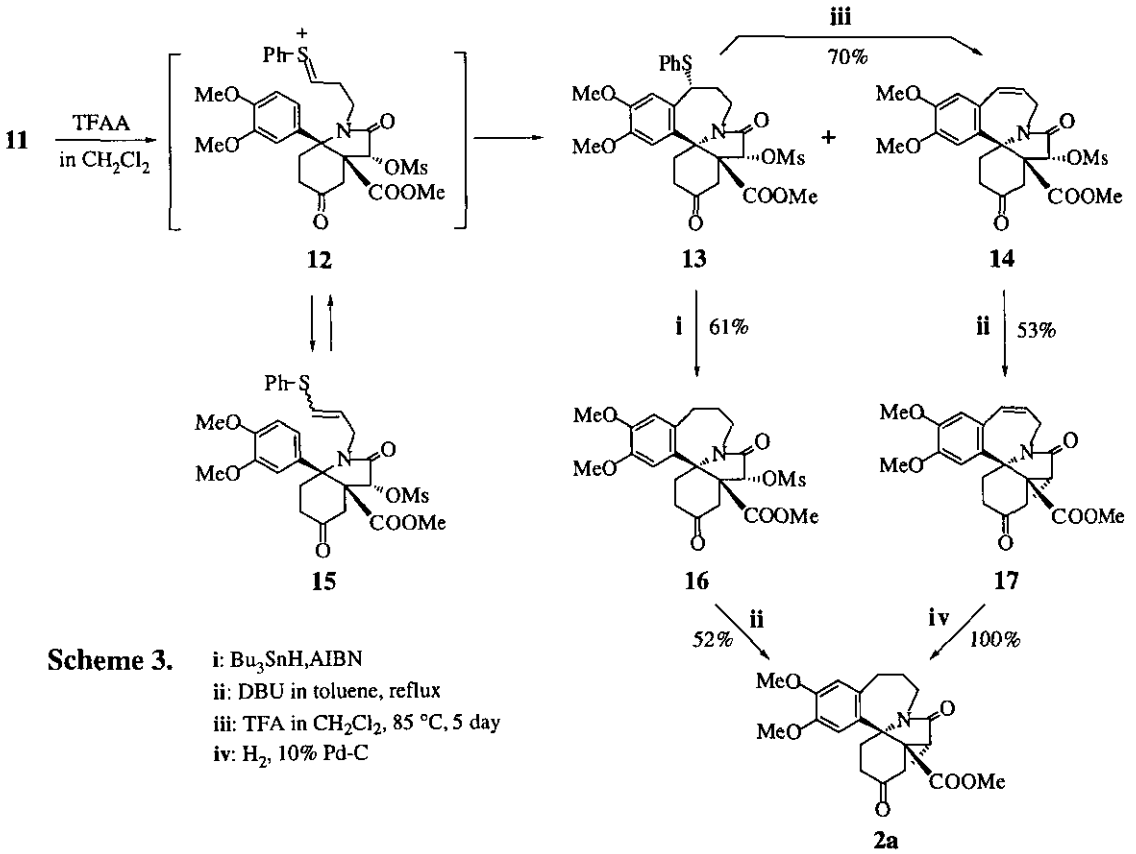


i: $PhS(CH_2)_3NH_2$, AcOH in EtOH (82%), **ii**: $(COCl)_2$ in Et_2O (96%), **iii**: 2-TMSO-butadiene, hv in DME (83%)
iv: $NaBH_4$ (89%), **v**: TBAF in THF (86%), **vi**: MsCl in pyridine (89%), **vii**: $NaIO_4$ in H_2O-MeOH (91%)

pected Pummerer cyclization product, the 12-phenylthiohomoerythrinan (**13**), in 16% yield together with the uncyclized vinyl sulfide (**15**) (41%). The yield of **13** was improved to 51%, when the reaction was

carried out in a sealed tube at 80℃ for 48 h, but with contamination of a small amount of the 11,12-dehydro derivative (**14**). Further elongation of the reaction time (120 h) resulted in exclusive formation (67%) of **14**. Thus, heating of **13** with trifluoroacetic acid in CH_2Cl_2 produced **14** in 70% yield.

The above results indicate that the sulfenium cation (**12**) generated from the sulfoxide (**11**) by elimination of CF_3COOH caused two reactions: the migration of $C{=}S^+$ bond to **15** and the cyclization of the aromatic ring to **13**. The vinyl sulfide (**15**) equilibrates to the sulfenium cation (**12**) by the acid-catalyzed double bond migration, thus giving rise to the cyclization product (**13**) and its PhSH elimination product (**14**) irreversibly.



Scheme 3. i: Bu_3SnH,AIBN
ii: DBU in toluene, reflux
iii: TFA in CH_2Cl_2, 85 °C, 5 day
iv: H_2, 10% Pd-C

The compounds (**13**) and (**14**) were converted to the cyclohomoerythrinan (**2a**) as follows. Radical reduction of **13** with Bu_3SnH-AIBN gave the homoerythrinan (**16**) in 61% yield, which on treatment with DBU in refluxing toluene yielded **2a** in 52% yield. Treatment of the other Pummerer product (**14**) with DBU followed by catalytic hydrogenation of the resulting 11,12-dehydrocyclohomoerythrinan (**17**) on 10%Pd-C also gave **2a** in an overall yield of 53%. The ^{1}H-NMR data of **2a** were consistent with those of the methylenedioxy analog (**2b**)[4b] except the signals due to the dimethoxy group instead of the methylenedioxy

moiety, thus confirming the structure.

Since the methylenedioxy analog (**2b**) has been converted to the natural homoerythrinan alkaloids *via* a 1,2-carbonyl-transposition reaction,[4] the same sequence of reactions for **2a** would give the alkaloid such as 2,7-dihydrohomoerysotrine (**3a**).[9] In summary, the cyclization using Pummerer reaction of hydroindole sulfoxides was proved to be safely applicable to the synthesis of not only erythrinan but also homoerythrinan ring systems.

EXPERIMENTAL

General Remarks Unless otherwise stated, following procedures were adopted. All melting points were determined with YANACO MP-S1 hot-stage melting point apparatus and are uncorrected. IR spectra were measured with JASCO FT/IR-5000 Fourier transform infrared spectrophotometer using KBr and are given in ν_{max} cm^{-1}. UV spectra were recorded on Hitachi U-3200 spectrophotometer in dioxane and given in λ_{max} nm (ε). NMR spectra were obtained with a JEOL JNM-EX90 (^1H; 90 MHz, ^{13}C; 22.5 MHz) or JNM-α500 (^1H; 500 MHz, ^{13}C; 125 MHz) in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. The chemical shifts were given in δ values. Low- and High-resolution MS spectra (LRMS and HRMS) were obtained by JEOL JMS-D300 or JMS-HX110A spectrometer at 30 or 70 eV and M^+ and the base peak were indicated by *m/z* (%). All organic extracts were washed with water or brine, and dried over Na_2SO_4 or $MgSO_4$ before concentration. Preparative thin layer chromatography (PTLC) was performed with 20 x 20 cm precoated silica gel 60 F_{254} glass plates (0.5 mm thickness / Merck). Column chromatography and flash chromatography was carried out with SiO_2 (Wakogel C-200 / Wako pure chemical industry Ltd.). Identities were confirmed by comparisons of mp (for crystalline compounds), spectral data, and TLC behaviors.

3-Phenylsulfanylpropylamine Thiophenol (25.3 g, 230 mmol) was added to a solution of 85% KOH (34.1 g, 518 mmol) in EtOH (200 mL) at rt under Ar atmosphere. The mixture was stirred for an additional 10 min to afford potassium thiophenolate. A solution of 3-bromopropylamine hydrobromide (50.0 g, 230 mmol) in EtOH (200 mL) was added dropwise to the above mixture over a period of 5 min, then the whole was heated under reflux for 2.5 h under stirring. After removal of precipitates by filtration, the filtrate was concentrated to dryness. The residue was dissolved in benzene, then washed with water, and concentrated. The residue was chromatographed in CH_2Cl_2 to give 3-phenylsulfanylpropylamine (36.8 g, 97%), as a colorless oil (lit.,[5b] bp 125-126℃ / 4 mmHg). IR: 3314, 1636, 1574. ^1H-NMR: 1.78 (2H, quintet, *J*=7 Hz, -$SCH_2\underline{CH_2}CH_2N$-), 2.8-3.1 (4H, m, -$S\underline{CH_2}CH_2\underline{CH_2}N$-), 7.1-7.4 (5H, m, PhH). LRMS: 167 (M^+, 100).

Enamine (5) A mixture of methyl 3,4-dimethoxybenzoylacetate (**4**) (7.062 g, 30 mmol), 3-phenylsulfanyl-propylamine (14.865 g, 90 mmol), and acetic acid (5.341 g, 90 mmol) in MeOH (100 mL) was heated under reflux for 30 h with stirring. After concentration of the mixture *in vacuo*, the residue was

chromatographed with hexane-AcOEt (7:1) to give methyl (*Z*)-3-(3-phenylsulfanylpropyl)amino-3',4'-dimethoxycinnamate (**5**) (9.388 g, 82%) as a pale yellow oil. IR: 3275, 1655, 1611. UV: 257 (15200), 297 (17600). ^{1}H-NMR: 1.78 (2H, quintet, *J*=7 Hz, -$SCH_2C\underline{H}_2CH_2N$-), 2.91 (2H, t, *J*=7 Hz, -$SC\underline{H}_2CH_2CH_2$-N-), 3.23 (2H, sextet, *J*=7 Hz, -$SCH_2CH_2C\underline{H}_2$-N-), 3.66, 3.86, 3.91, (each 3H, s, OMe), 4.64 (1H, s, olefinic H), 6.8-6.9 (3H, m, ArH), 7.2-7.3 (5H, m, PhH), 8.50 (1H, br t, *J*=7 Hz, NH). ^{13}C-NMR: 30.7 (t), 30.8 (t), 43.5 (t), 50.4 (q), 56.1 (qx2), 85.6 (d), 111.1 (d), 111.3 (d), 120.8 (d), 126.2 (d), 128.7 (s), 129.1 (dx2), 129.5 (dx2), 136.1 (s), 149.0 (s), 150.1 (s), 165.2 (s), 170.9 (s). LRMS *m/z*: 387 (M^+, 93), 165 (100). HRMS Calcd for $C_{21}H_{25}NO_4S$ (M^+): 387.1503. Found: 387.1503.

Dioxopyrroline (6) A solution of oxalyl chloride (3.772 g, 30 mmol) in dry ether (50 mL) was added dropwise to a solution of **5** (9.578 g, 25 mmol) in dry ether (200 mL) at 0℃ over a period of 30 min with stirring. After 20 min, dioxane (100 mL) was added to the mixture, then the whole was heated at 70℃ to remove ether. After heating for 20 min, the reaction mixture was cooled to rt and crystallization was induced by addition of dry benzene, ether, and CH_2Cl_2. Recrystallizations from the same solvent gave 2-(3,4-dimethoxyphenyl)-1-(3-phenylsulfanylpropyl)-3-methoxycarbonylpyrroline-4,5-dione (**6**) (10.496 g, 96%) as orange plates, mp 137-140° C. IR: 1686, 1748, 1760. UV: 255 (16100), 358 (5700), 398 (4300, sh). ^{1}H-NMR: 1.5-1.9 (2H, m, -$SCH_2C\underline{H}_2CH_2N$-), 2.7-2.9 (2H, m, -$SC\underline{H}_2CH_2CH_2N$-), 3.6-4.0 (2H, m, -$SCH_2CH_2C\underline{H}_2N$-), 3.70, 3.85, 4.00 (each 3H, s, OMe), 6.9-7.0 (3H, m, ArH), 7.1-7.3 (5H, m, PhH). ^{13}C-NMR: 27.7 (t), 30.7 (t), 40.7 (t), 51.3 (q), 55.9 (q), 56.0 (q), 103.4 (s), 110.8 (d), 111.0 (d), 119.0 (s), 121.6 (d), 126.2 (d), 128.8 (dx2), 129.3 (dx2), 135.0 (s), 148.9 (s), 152.1 (s), 158.2 (s), 161.3 (s), 177.8 (s), 178.0 (s). *Anal.* Calcd for $C_{23}H_{23}NO_6S$: C, 62.57; H, 5.25; N, 3.17. Found: C, 62.29; H, 5.31; N, 2.88. LRMS: 441 (M^+, 45), 332 (100).

Photocycloaddition of 6 to 2-Trimethylsilyloxy-1,3-butadiene A mixture of **6** (3.0 g, 7 mmol) and 2-trimethylsilyloxy-1,3-butadiene (1.932 g, 14 mmol) in DME (400 mL) was irradiated with 300 W high pressure mercury lamp with Pyrex filter (>300 nm) at 0℃ for 3 h under stirring. After removal of the solvent, the residue was chromatographed with hexane-AcOEt (1:2) to afford *dl*-(1*R**,5*S**,7*S**)-1-(3,4-dimethoxyphenyl)-5-methoxycarbonyl-3,4-dioxo-2-(3-phenylsulfanylpropyl)-7-trimethylsilyloxy-7-vinyl-2-azabicyclo[3.2.0]heptane (**7**) (3.311 g, 83%) as a pale yellow gum. IR: 1771, 1738, 1721. UV: 243 (12900). ^{1}H-NMR: 0.10 (9H, s, OTMS), 1.1-2.1 (2H, m, -$SCH_2C\underline{H}_2CH_2N$-), 2.7-2.9 (2H, m, -$SC\underline{H}_2CH_2CH_2N$-), 2.33, 3.21 (each 1H, d, *J*=13 Hz, -CH_2-), 3.5-3.9 (2H, m, -SCH_2CH_2-$C\underline{H}_2N$-), 3.50, 3.74, 3.86 (each 3H, s, OMe), 5.41 (1H, dd, *J*=2, 10 Hz, vinyl), 5.49 (1H, dd, *J*=2, 17 Hz, vinyl), 6.13 (1H, dd, *J*=10, 17 Hz, vinyl), 6.7-7.2 (8H, m, ArH, PhH). ^{13}C-NMR: 1.7 (qx3), 26.4 (t), 31.4 (t), 36.8 (t), 43.9 (t), 52.7 (q), 55.4 (s), 55.7 (q), 55.8 (q), 75.5 (s), 81.1 (s), 110.5 (d), 111.7 (d), 116.1 (t), 121.5 (d), 124.7 (s), 126.0 (d), 128.8 (dx2), 129.4 (dx2), 135.6 (s), 139.9 (s), 148.5 (s), 149.2 (s), 161.8 (s), 166.6 (s), 193.8 (s). LRMS: 583 (M^+), 332 (100). HRMS Calcd for $C_{30}H_{37}NO_7SSi$ (M^+): 583.2057. Found: 583.2042.

$NaBH_4$ Reduction of 7 $NaBH_4$ (702 mg, 18 mmol) was added to a solution of **7** (3.606 g, 6 mmol) in MeOH (60 mL) at -20℃ under stirring. The mixture was stirred at the same temperature for 10

min. After decomposition of an excess hydride by addition of H_2O, the resulting mixture was extracted with CH_2Cl_2. After removal of the solvent, the residue was chromatographed with hexane-AcOEt (1:1) and the eluate was crystallized from ether-hexane-CH_2Cl_2 to afford the alcohol (**8**) (3.219 g, 89%) as colorless prisms, mp 158-159℃. IR: 3264, 1723, 1676. UV: 240 (13600), 255 (10900). ^{1}H-NMR: 0.20 (9H, s, OTMS), 2.4-4.0 (8H, m, -CH_2-), 3.68, 3.76, 3.80 (each 3H, s, OMe), 5.18 (1H, dd, *J*=2, 10 Hz, vinyl), 5.31 (1H, s, C<u>H</u>OH), 5.39 (1H, dd, *J*=2, 17 Hz, vinyl), 6.62 (1H, dd, *J*=10, 17 Hz, vinyl), 6.5-6.8 (3H, m, ArH), 7.1-7.2 (5H, m, PhH). ^{13}C-NMR: 1.8 (qx3), 26.8 (t), 31.2 (t), 35.8 (t), 42.9 (t), 50.6 (s), 52.8 (q), 55.7 (q), 55.8 (q), 73.1 (d), 76.7 (s), 80.3 (s), 110.5 (d), 112.0 (t), 112.1 (d), 121.3 (d), 125.7 (d), 128.6 (dx2), 128.7 (dx2, s), 136.5 (s), 142.3 (s), 148.4 (s), 148.8 (s), 171.8 (s), 171.9 (s). LRMS: 585 (M^+, 9), 404 (100). HRMS Calcd for $C_{30}H_{39}NO_7SSi$ (M^+): 585.2271. Found: 585.2244.

Anionic [1,3] Rearrangement of 8 with TBAF A 1.0 M THF solution of TBAF (1026 μL, 1.02 mmol) in THF was injected at -30℃ into a solution of **8** (500 mg, 0.85 mmol) in THF (20 mL) under Ar atmosphere with stirring. The mixture was stirred for 20 min, and then heated under reflux for an additional 30 min. After cooling, the mixture was diluted with CH_2Cl_2 and the whole was washed with brine. Removal of the solvent from the organic layer gave the residue which was chromatographed with hexane-AcOEt (1:2) to afford *dl*-(3*R**,3a*S**,7a*R**)-7a-(3,4-dimethoxyphenyl)-3-hydroxy-3a-methoxycarbonyl-2,5-dioxo-1-(3-phenylsulfanylpropyl)-2,3,3a,4,5,6,7,7a-octahydroindole (**9**) (378 mg, 86%) as colorless prisms from hexane-CH_2Cl_2, mp 171-174℃. IR: 3410, 3140, 1721, 1667. UV: 237 (9900), 255 (7300). ^{1}H-NMR: 2.2-3.4 (12H, m, -CH_2-), 3.35, 3.81, 3.87 (each 3H, s, OMe), 5.05 (1H, s, C<u>H</u>OH), 6.6-6.8 (3 H, m, ArH), 7.23 (5H, s, PhH). ^{13}C-NMR: 27.6 (t), 30.1 (t), 31.9 (t), 35.7 (t), 39.6 (t), 41.5 (t), 52.6 (q), 55.9 (q), 56.0 (q), 59.9 (s), 67.6 (s), 71.4 (d), 110.2 (d), 110.9 (d), 119.4 (d), 126.5 (d), 129.0 (dx2), 130.0 (dx2), 130.4 (s), 135.3 (s), 148.9 (s), 149.3 (s), 171.0 (s), 174.6 (s), 206.9 (s). *Anal.* Calcd for $C_{27}H_{31}NO_7S$: C; 63.15, H; 6.08, N; 2.73. Found: C; 63.28, H; 6.13, N; 2.85. LRMS: 513 (M^+, 15), 404 (100).

Methanesulfonylation of 9 A mixture of **9** (200 mg, 0.39 mmol) and methanesulfonyl chloride (357 mg, 3.12 mmol) in pyridine (7 mL) was stirred at rt for 1.5 h. The reaction mixture was diluted with CH_2Cl_2, then the resulting solution was washed with H_2O, 5%HCl, and brine. After removal of the solvent from the organic layer, the residue was chromatographed with hexane-AcOEt (1:1) to afford the mesylate (**10**) (205 mg, 89%), as a colorless gum. IR: 1736, 1719. UV: 239 (11200). ^{1}H-NMR: 1.9-3.4 (12H, m, -CH_2-), 3.34, 3.35, 3.83, 3.89 (each 3H, s, OMe, OMs), 5.95 (1H, s, C<u>H</u>OMs), 6.6-6.9 (3H, m, ArH), 7.2-7.3 (5H, m, PhH). ^{13}C-NMR: 27.7 (t), 30.1 (t), 32.1 (t), 35.7 (t), 40.3 (q), 40.4 (t), 42.1 (t), 53.2 (q), 56.1 (q), 56.3 (q), 58.9 (s), 68.0 (s), 78.2 (d), 110.2 (d), 111.3 (d), 119.4 (t), 126.8 (d), 129.2 (dx2), 129.9 (s), 130.2 (dx2), 135.4 (s), 149.4 (s), 149.8 (s), 169.7 (s), 169.8 (s), 205.2 (s). LRMS: 591 (M^+, 23), 482 (100). HRMS Calcd for $C_{28}H_{33}NO_9S_2$ (M^+): 591.1593. Found: 591.1583.

Sulfoxide (11) An aqueous solution (7 mL) of $NaIO_4$ (688 mg, 3.2 mmol) was added in one portion to a solution of **10** (950 mg, 1.6 mmol) in MeOH (30 mL)-CH_2Cl_2 (3 mL) with stirring. After heating of the mixture under reflux for 50 min, it was extracted with CH_2Cl_2. Concentration of the organic layer to

dryness gave the residue which was chromatographed with hexane-AcOEt (1:1) to afford the sulfoxide (**11**) (887 mg, 91%) as a colorless gum. IR: 1727, 1149. UV: 239 (11700), 279 (3600). ^{1}H-NMR: 2.0-3.4 (total 12H, m, -CH_2-), 3.31, 3.32 (total 3H, each s, OMe), 3.36, 3.36 (total 3H, each s, OMe), 3.82, 3.85 (total 3H, each s, OMe), 3.89 (3H, s, OMe), 5.95, 5.98 (total 1H, each s, C<u>H</u>OMs), 6.6-6.8 (total 3H, m, ArH), 7.49, 7.52 (total 5H, each s, PhH). ^{13}C-NMR: 21.2, 21.6 (each t), 29.9 (t), 35.5 (t), 40.0 (q), 40.1 (t), 41.7, 41.8 (each t), 53.1 (q), 53.7, 54.0 (each t), 55.9 (qx2), 58.7 (s), 67.8, 67.9 (each s), 77.9 (d), 110.0 (d), 111.1, 111.2 (each d), 119.2 (t), 123.8, 123.9 (each dx2), 129.3, 129.3 (each dx2), 129.6 (s), 131.1, 131.2 (each d), 143.1, 143.2 (each s), 149.2, 149.3 (each s), 149.7 (s), 169.2, 169.5 (each s), 169.6, 169.8 (each s), 204.9, 205.0 (each s). LRMS: 592 (M^+-15, 100). HRMS Calcd for $C_{27}H_{30}NO_{10}S_2$ (M^+-15): 592.1308. Found: 592.1302.

Pummerer-Type Cyclizations of 11 (1) A mixture of **11** (100 mg, 0.16 mmol) and TFAA (1 mL, 7.08 mmol) in CH_2Cl_2 (2 mL) was stirred at rt for 6 h. After removal of the solvent and excess reagent *in vacuo*, the residue was chromatographed with benzene-acetone (3:1) to afford *dl*-(3*R**,3a*S**,7a*R**)-7a-(3,4-dimethoxyphenyl)-3-methanesulfonyloxy-3a-methoxycarbonyl-2,5-dioxo-1-(3-phenylsulfanyl-2-propenyl)-2,3,3a,4,5,6,7,7a-octahydroindole (**15**) (40 mg, 41%) and *dl*-(5*R**,6*S**,7*R**,12*S**)-7-methanesulfonyloxy-16,17-dimethoxy-6-methoxycarbonyl-2,8-dioxo-12-phenyl-sulfanylhomoerythrinan (**13**) (16 mg, 16%).

(2) A stirred mixture of **11** (200 mg, 0.33 mmol) and TFAA (2 mL, 14.2 mmol) in CH_2Cl_2 (20 mL) was heated in a sealed tube at 85℃ for 48 h. After removal of the solvent and reagent, the residue was chromatographed with hexane-AcOEt (1:1), and each product was purified by PTLC (AcOEt) and crystallizations from ether-hexane-CH_2Cl_2 to afford **13** (97 mg, 50%) and the Δ^{11}-homoerythrinan (**14**) (1 mg, 1%).

(3) A stirred mixture of **11** (1.0 g, 1.6 mmol) and TFAA (1.5 mL, 10.6 mmol) in CH_2Cl_2 (1 mL) was heated in a sealed tube at 85℃ for 8 days. After removal of the solvent and reagent, the residue was chromatographed with hexane-AcOEt (1:1), and the eluate was crystallized from ether-hexane-CH_2Cl_2 to afford **14** (530 mg, 67%).

13: Colorless powder, mp 125-127° C. IR: 1725, 1704. UV: 244 (12300), 280 (4100). ^{1}H-NMR (500 MHz): 1.87 (1H, dt, *J*=7, 13 Hz, -CH_2-), 2.2-3.1 (6H, m, -CH_2-), 2.82, 3.31 (each 1H, d, *J*=17 Hz, -CH_2-), 3.04, 3.26, 3.78, 3.86 (each 3H, s, OMe, OMs), 4.06 (1H, dd, *J*=8, 14 Hz, -CH_2-), 4.70 (1H, dd, *J*=5, 13 Hz, C<u>H</u>SPh), 5.91, (1H, S, C<u>H</u>OMs), 6.77, 7.64 (each 1H, s, ArH), 7.1-7.3 (5H, m, PhH). ^{13}C-NMR (125 MHz): 31.5 (t), 32.2 (t), 34.0 (t), 37.3 (t), 39.1 (q), 40.6 (t), 46.2 (d), 53.0 (q), 55.7 (q), 55.9 (s), 56.4 (q), 71.8 (s), 78.3 (d), 112.2 (d), 113.4 (d), 126.7 (d), 128.3 (s), 128.9 (dx2), 139.8 (dx2), 130.5 (s), 134.9 (s), 147.1 (s), 148.6 (s), 167.0 (s), 170.5 (s), 205.9 (s). *Anal.* Calcd for $C_{28}H_{31}NO_9S_2$: C; 57.04, H; 5.30, N; 2.38. Found: C; 57.29, H; 5.43, N; 2.31. LRMS: 589 (M^+), 480 (100).

14: Colorless plates, mp 251-253° C. IR: 1727, 1705. UV: 231 (21100), 278 (9200). ^{1}H-NMR: 2.3-4.1 (7H, m, -CH_2-), 3.26, 3.41 (each 3H, s, OMe, OMs), 3.38 (6H, s, OMe), 4.49 (1H, dd, *J*=6, 16 Hz, vinyl), 5.55 (1H, s, C<u>H</u>OMs), 6.0-6.5 (2H, m, vinylic H), 6.65, 6.79 (each 1H, s, ArH). ^{13}C-NMR: 34.1 (t), 34.4 (t), 39.7 (t, q), 41.3 (t), 52.9 (q), 55.9 (q), 56.1 (q), 58.1 (s), 70.7 (s), 78.5 (d), 111.3 (d),

116.4 (d), 127.9 (d), 128.3 (s), 132.4 (s), 132.9 (d), 147.8 (s), 148.4 (s), 167.4 (s), 170.5 (s), 205.1 (s). *Anal.* Calcd for $C_{22}H_{25}NO_9S$: C; 55.11, H; 5.26, N; 2.92. Found: C; 55.03, H; 5.47, N; 2.85. LRMS: 479 (M^+, 33), 324 (100).

15: Colorless gum. IR: 1727. UV: 242 (14800), 268 (10200). ^{1}H-NMR: 2.0-4.4 (8H, m, -CH_2-), 3.34, 3.38, 3.85, 3.88 (each 3H, s, OMe, OMs), 5.5-6.0 (1H, m, vinyl), 5.95 (1H, s, C<u>H</u>OMs), 6.39 (1H, d, J=15 Hz, vinyl), 6.5-6.9 (3H, m, ArH), 7.2-7.4 (5H, m, PhH). ^{13}C-NMR: 30.1 (t), 35.7 (t), 40.3 (q), 40.4 (t), 44.3 (t), 53.2 (q), 56.1 (q), 56.3 (q), 59.0 (s), 68.0 (s), 78.1 (d), 110.3 (d), 111.4 (d), 119.5 (d), 123.8 (d), 127.8 (d), 129.5 (dx2, s), 130.5 (d), 131.0 (dx2), 133.5 (s), 149.4 (s), 149.9 (s), 169.3 (s), 169.8 (s), 205.3 (s). LRMS: 589 (M^+, 10), 480 (100). HRMS Calcd for $C_{28}H_{31}NO_9S_2$ (M^+): 589.1441. Found: 589.1448.

Treatment of 13 with TFA A stirred mixture of **13** (30 mg, 0.05 mmol) and TFA (1 mL, 13.0 mmol) in CH_2Cl_2 (3 mL) was heated in a sealed tube at 85℃ for 5 days. After concentration of the reaction mixture *in vacuo*, the residue was chromatographed with CH_2Cl_2, and the eluate was crystallized from ether-hexane-CH_2Cl_2 to give **14** (17 mg, 70%).

Desulfurization of 13 with Bu_3SnH A mixture of Bu_3SnH (137 μL, 0.51 mmol) and AIBN (6 mg, 0.04 mmol) in toluene (10 mL) was injected into a solution of **13** (100 mg, 0.17 mmol) in toluene (3 mL) over a period of 30 min at 90℃ under Ar atmosphere. The mixture was stirred for an additional 1 h at the same temperature. After removal of the solvent *in vacuo*, the residue was chromatographed with hexane-AcOEt (1:1) and the eluate was crystallized from hexane-CH_2Cl_2 to give *dl*-(5*R**,6*S**,7*R**)-7-methanesulfonyloxy-16,17-dimethoxy-6-methoxycarbonyl-2,8-dioxohomoerythrinan (**16**) (50 mg, 61%), as colorless prisms, mp 267-271℃. IR: 1721, 1705. UV: 235 (10300), 281 (3800). ^{1}H-NMR: 2.2-4.4 (12H, m, -CH_2-), 3.27, 3.28, 3.86, 3.87 (each 3H, s, OMe, OMs), 5.83 (1H, s, C<u>H</u>OMs), 6.58,6.75 (each 1H, s, ArH). ^{13}C-NMR: 24.7 (t), 31.1 (t), 31.3 (t), 34.3 (t), 37.2 (t), 39.3 (q), 40.7 (t), 52.9 (q), 55.8 (q), 56.3 (q), 57.1 (s), 71.3 (s), 78.4 (d), 111.9 (d), 114.9 (d), 128.6 (s), 132.5 (s), 147.3 (s), 148.8 (s), 167.7 (s), 170.2 (s), 205.9 (s). *Anal.* Calcd for $C_{22}H_{27}NO_9S$: C; 54.88, H; 5.65, N; 2.91. Found: C; 54.69, H; 5.78, N; 2.94. LRMS: 481 (M^+, 90), 330 (100).

***dl*-(1*R**,5*S**,6*S**,7*S**)-16,17-Dimethoxy-6-methoxycarbonyl-2,8-dioxo-1,7-cyclohomoerythrinan (2a)** A mixture of **16** (100 mg, 0.21 mmol) and DBU (158 mg, 1.04 mmol) in toluene (20 mL) was heated under reflux in Ar atmosphere for 6 h. After cooling, the mixture was diluted with CH_2Cl_2-benzene and the whole was washed with 5% HCl. Removal of the solvent from the organic layer *in vacuo* gave **2a** (42 mg, 52%) as a colorless gum. IR: 1694, 1705, 1738. UV: 234 (11400), 283 (3700). ^{1}H-NMR: 2.2-4.0 (10H, m, -CH_2-), 2.36 (1H, br d, *J*=10 Hz, >CH-), 2.92 (1H, d, *J*=10 Hz, >CH-), 3.40 (3H, s OMe), 3.89 (6H, s, 2xOMe), 6.61, 6.94 (each 1H, s, ArH). ^{13}C-NMR: 25.2 (t), 31.2 (t), 33.7 (d), 34.2 (d), 34.9 (t), 35.2 (t), 36.2 (t), 46.4 (s), 52.5 (q), 55.8 (q), 56.3 (q), 67.0 (s), 112.3 (d), 114.1 (d), 127.9 (s), 132.5 (s), 147.2 (s), 148.8 (s), 166.8 (s), 168.6 (s), 200.7 (s). LRMS: 385 (M^+, 14), 298 (100). HRMS Calcd for $C_{21}H_{23}NO_6$ (M^+): 385.1523. Found: 385.1500.

Treatment of 14 with DBU A mixture of **14** (200 mg, 0.42 mmol) and DBU (318 mg, 2.1 mmol) in toluene (50 mL) was heated under reflux in Ar atmosphere for 3.5 h. After cooling, the mixture was diluted with CH_2Cl_2 and the whole was washed with 5% HCl. After removal of the solvent, the residue was chromatographed with CH_2Cl_2 to give 1,7-cyclo-Δ^{11}-homoerythrinan **17** (84 mg, 53%), as a colorless gum. IR: 1731, 1705, 1684. UV: 228 (28000), 277 (11300). ^{1}H-NMR: 1.9-3.5 (5H, m, -CH_2-), 2.43 (1H, br d, *J*=10 Hz, >CH-), 2.74 (1H, d, *J*=10 Hz, >CH-), 3.32 (3H, s, OMe), 3.90 (6H, S, 2xOMe), 4.2-4.5 (1H, m, H-10), 6.2-6.5 (2H, m, vinyl), 6.70, 6.90 (each 1H, s, ArH). ^{13}C-NMR: 33.5 (d), 34.2 (t), 34.4 (d), 37.0 (t), 37.5 (t), 47.8 (s), 52.8 (q), 55.9 (q), 56.0 (q), 68.1 (s), 110.6 (d), 115.9 (d), 128.3 (s), 128.4 (d), 132.5 (s), 133.4 (d), 148.0 (s), 148.1 (s), 167.1 (s), 167.6 (s), 200.3 (s). LRMS: 383 (M^+, 36), 324 (100). HRMS Calcd for $C_{21}H_{21}NO_6$ (M^+): 383.1401. Found: 383.1385.

Catalytic Hydrogenation of 17 A mixture of **17** (50 mg, 0.13 mmol) and 10% Pd-C (5 mg) in THF (100 mL) was vigorously stirred under hydrogen atmosphere at rt for 4 h. Removal of the catalyst and solvent left a gum, which was purified by chromatography with AcOEt-CH_2Cl_2 to give **2a** (50 mg, 100%).

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