Synthesis of *Erythrina* and Related Alkaloids. XXIV.[1] Total Synthesis of Erysotrine from 1,7-Cycloerythrinan Derivatives by the Use of a New 1,2-Carbonyl Transposition Method

Yoshisuke TSUDA,*[,a] Shinzo HOSOI,[a] Akira NAKAI,[a] Yuki SAKAI,[a] Tomoko ABE,[a] Yukari ISHI,[a] Fumiyuki KIUCHI,[a] and Takehiro SANO[b]

Faculty of Pharmaceutical Sciences Kanazawa University,[a] 13-1 Takara-machi, Kanazawa 920, Japan and Showa College of Pharmaceutical Sciences,[b] Higashi-tamagawagakuen 3-chome, Machida-shi, Tokyo 194, Japan. *Received October 15, 1990*

Treatment of 2,8-dioxo-1,7-cycloerythrinans with phenylselenenyl chloride in the presence of $BF_3 \cdot Et_2O$ as a catalyst gave 3-chloro-3-phenylselenenyl derivatives through the 3-phenylselenenyl derivative, which changed into the Δ^3-3-phenylselenenyl derivative on further reaction. Both the 3-phenylselenenyl and 3-chloro-3-phenylselenenyl derivatives gave the 3,3-dimethoxy derivative on treatment with mercury(II) perchlorate (MPC) in methanol, thus providing a new method for introduction of a masked carbonyl group at the α-position to the original carbonyl group. Thus, the reaction of 1 with phenylselenenyl chloride under acidic conditions followed by MPC treatment in methanol and borohydride reduction gave the 2α-hydroxy-3,3-dimethoxy derivative in 57% yield. This was converted to the conjugated ketone in four steps (72%). The carbomethoxy group of this compound was removed by the $CaCl_2$–dimethyl sulfoxide–3-ethylpentane-3-thiol method to give the enone 4 (70—80%) which isomerized to the conjugated ketone 25c (100%). This was converted to a natural *Erythrina* alkaloid, (±)-erysotramidine (5), in four steps (31%), and thence to (±)-erysotrine (6).

Keywords *Erythrina* alkaloid; erysotrine; total synthesis; 1,7-cycloerythrinan; phenylselenenylation; mercury(II) perchlorate; α,α-dimethoxylation; 1,2-carbonyl transposition; decarbomethoxylation; calcium chloride–dimethyl sulfoxide

The 6β-ethoxycarbonyl-2,8-dioxo-1,7-cyclo-*cis*-erythrinan (**1**) is a potential synthetic intermediate of natural erythrinan alkaloids, since it is easily preparable from homoveratrylamine and ethyl 5,5-ethylenedioxy-2-oxocyclohexanecarboxylate (seven steps with 40% overall yield) through intramolecular cyclization of an *N*-acyliminium compound of *N*-arylethylhydroindole type.[1,2] and it is appropriately protected at C-1 for further manipulation of rings A and B to synthesize the natural alkaloids.[1] most of which possess an oxygenated function at C-3. This paper describes transformation of **1** to natural erythrinan alkaloids of alkenoid and dienoid type, presenting a total synthesis of (±)-erysotrine (**6**).[3]

The procedure is schematically shown in Chart 1. This transformation requires the following three steps: 1) transposition of the oxygenated function from C-2 to C-3, 2) removal of the extra COOEt group, and 3) requisite alignment of the functional groups at rings A and B. These are treated in the above order.

Results and Discussion

Firstly, we attempted to introduce a methoxy group at C-3 by the action of mercury(II) ion in methanol on the 3-phenylselenenyl derivative **7**, because a soft–soft interaction of Hg and Se atoms might assist the expected substitution. However, the reaction of **7** with mercury(II) perchlorate (MPC) in methanol unexpectedly resulted in the introduction of two methoxy groups; this result instead opened up a new 1,2-carbonyl transposition method.

Introduction of a Carbonyl Function at C-3 *via* Phenylselenenylation (1→2) Treatment of **1a** with phenylselenyl chloride (PhSeCl) in tetrahydrofuran (THF) in the presence of $BF_3 \cdot Et_2O$ as a catalyst gave four products A—D, depending on the amount of reagent and the reaction conditions (Fig. 1). Compound A was formed initially and obtained as a major product by a short reaction (30 min) with 1 mol of PhSeCl. With an excess of the reagent under reflux for a longer time, compound D was obtained as a major product. Compound B and C were proved to be intermediary products. Isolation of each compound and

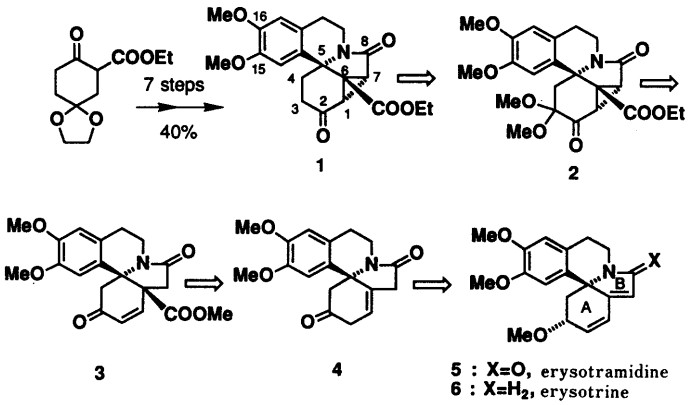

Chart 1. Synthetic Strategy for Erysotrine (**6**)

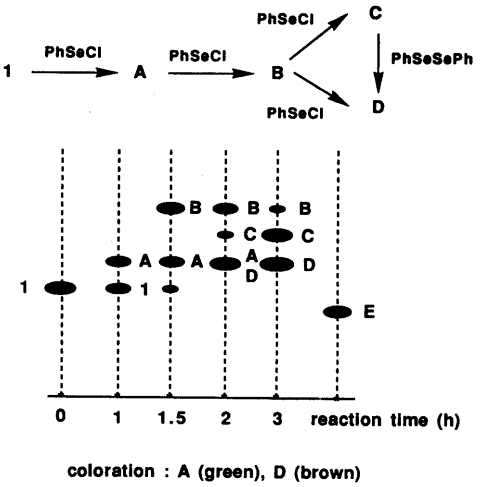

Fig. 1. TLC of the Reaction Mixture of **1** and PhSeCl

Reaction conditions, see text. Solvent, benzene : acetone = 4 : 1.

treatment of them with PhSeCl clarified that the reaction proceeds in the sequence A→B→C, and that the path C→D is catalyzed by $(PhSe)_2$ (see also below).

Chromatographic separation of the product over silica gel often gave a fifth compound E, which was not present in the reaction mixture, suggesting that some of the above four compounds changed into E on chromatography.

Compound A is the monophenylselenenyl derivative **7a**, which can also be prepared on treatment of **1a** with *n*-BuLi and diphenyl diselenide, though the yield was lower. The structure was proved by the desorption chemical ionization mass spectrum (DCI-MS), by other spectral data, and by conversion to the unsaturated ketone **8a** on treatment with hydrogen peroxide. On treatment with MPC in methanol, **7a** gave in high yield the α,α-dimethoxyketone **9a** (=**2**), whose structure was proved by analysis of the ^{1}H- and ^{13}C-nuclear magnetic resonance (^{1}H- and ^{13}C-NMR) spectra (for details of this new oxidative methoxylation reaction, see also below).

When compound A was adsorbed on silica gel and exposed to air, it gradually changed into the diketone **10a** which was identical with compound E, indicating that compound E was produced from compound A presumably by air oxidation as shown in Chart 3. On treatment with sodium sulfide, compound A regenerated compound **1a**, which was clearly the product due to the substitution reaction on the Se atom by sulfide anion.

Compound B had the formula $C_{27}H_{26}ClNO_6Se$ as evidenced from DCI-MS, and gave the chloro olefin **12a** and the dimethoxyketone **9a** on treatment with hydrogen peroxide in methanol. When dissolved in methanol, compound B rapidly changed into the methoxy derivative **13a** which gradually afforded the dimethoxyketone **9a** on prolonged standing in the same solvent. The dimethoxyketone **9a** was also obtained directly from compound B on treatment with MPC in methanol. These findings suggested the structure of compound B as the 3-chloro-3-phenylselenenyl derivative **11a** (for the stereochemistry, see below). On treatment with PhSeCl in THF, compound B gave compounds C and D.

Compound C had the same molecular formula as that of compound B (by DCI-MS), and gave the chloro olefin **12a** on treatment with hydrogen peroxide suggesting that it is a stereoisomer of compound B. In contrast to B, compound C was stable to methanol at room temperature, but changed into the dimethoxyketone **9a** and the diketone **10a** on heating in methanol or on treatment with a catalytic amount of TsOH in methanol at room temperature. The dimethoxyketone **9a** was obtained quantitatively on treatment of compound C with MPC in methanol. Compound C gave compound D and the chloro olefin **12a** on treatment with $(PhSe)_2$.

Compound D had the formula $C_{27}H_{25}NO_6Se$ and exhibited an olefinic proton signal (δ 6.36, s) in the ^{1}H-NMR spectrum. It was a conjugated ketone as evidenced from the infrared (IR) absorption band at 1689 cm^{-1}. It also showed the absorptions of a five-membered lactam (1710

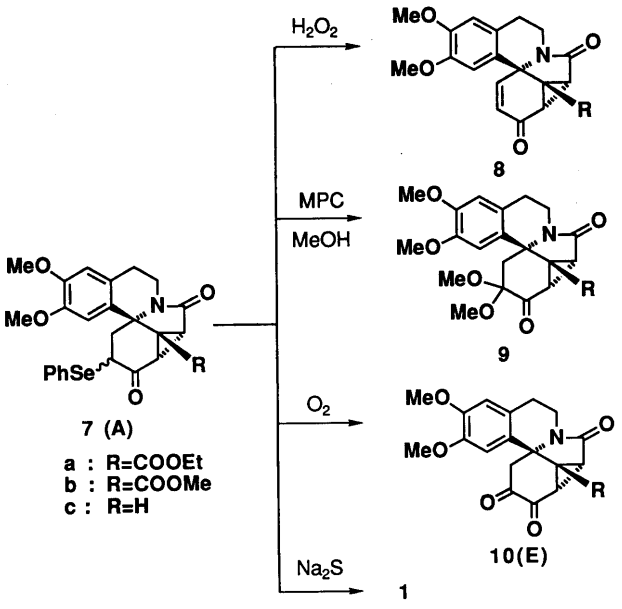

Chart 2

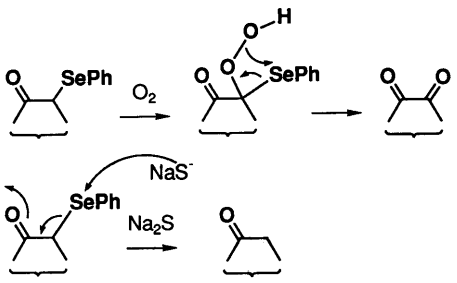

Chart 3

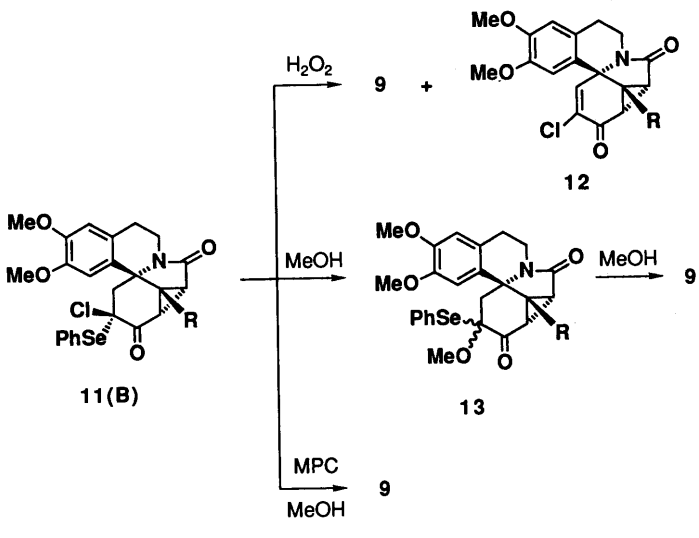

Chart 4

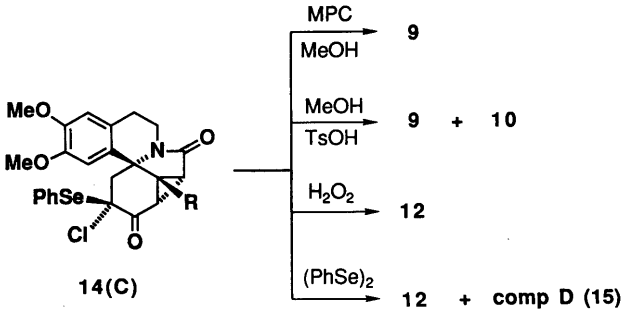

Chart 5

cm^{-1}) and an ester (1730 cm^{-1}) group. All of those data and the ^{13}C-NMR spectrum indicated the structure **15a** for compound D.

When compound D was treated with sodium sulfide in methanol, it changed into the methoxyketone **17a** which, on heating with 2.5% HCl, gave the conjugated ketone **8a**, identical with the compound obtained from compound A, together with the hydroxyketone **18a**, thus supporting the structure **15a**. The formation of **17a** from **15a** can be rationalized in terms of Michael addition of methanol followed by the substitution reaction of NaS^- anion on the Se atom in the resulting **16a** (see Chart 3). Attempts at chromatographic isolation of **16a** after the reaction of **15a** with NaOMe in methanol failed, the isolated product being a methoxy-diketone **19**, which is apparently the product of air oxidation of **16**, as discussed above, thus proving the intermediary formation of **16**. In contrast to A, B, and C, compound D was inert to MPC in methanol: it only formed an insoluble complex which regenerated compound D on decomposition with sodium sulfide.

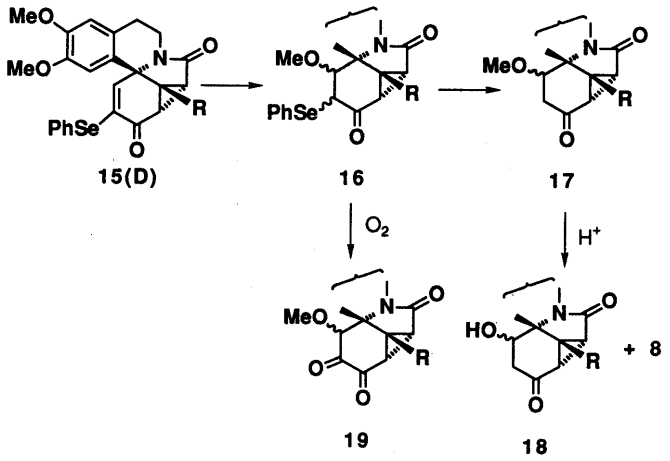

Chart 6

The above reaction with PhSeCl is explained as shown in Chart 7. The initially formed phenylselenenyl derivative **7** (A) is converted to compound B by one of the three possible paths (i—iii in Chart 8) where the second molecule of PhSeCl is reduced to $PhSe^-$. The kinetically formed compound B equilibrates with the thermodynamically more stable isomer C, probably through a Pummerer type intermediate **20**, which may isomerize to **15** (D) by deprotonation. Based on the above argument, we consider the stereochemistries of compounds B and C as the PhSe-inside (**11**) and PhSe-outside (**14**) configurations, respectively, since introduction of Cl^- (or Cl^+) from the β-face of the cycloerythrinan is favorable due to steric hindrance. Thus, in the kinetically produced compound (B), the PhSe group is at the more compressed position (PhSe-inside) and Cl is at the less hindered position (outside), *i.e.*, the structure **11**. On the contrary, the bulkier PhSe group is at the less compressed position (PhSe-outside) in the thermodynamically produced compound C, *i.e.*, the structure **14**. The reactions A→B→C are mediated by PhSeCl as suggested above, but compound C was stable to PhSeCl, implying that the reverse reaction **14→20** under catalysis of PhSeCl is too slow to be observed. Both compounds B and C changed, though slowly, into compound D on reaction with $(PhSe)_2$. The presence of $(PhSe)_2$ (or its equivalent) in the reaction mixture is conceivable, if we accept one of the three paths in Chart 8 for formation of compound B from compound A, producing $PhSe^-$, which will couple with PhSeCl to give $(PhSe)_2$.

TABLE I. ^{13}C-NMR Data for 1,7-Cycloerythrinan Derivatives (in Chloroform-*d*)

Carbon	1a	1c	7a	11a	14a	15a	15b	9a	9b	9c
1	35.1	30.3	34.0	32.5	30.0	39.1	38.9	32.2	31.9	30.1
2	200.7	203.0	198.1	190.7	186.8	186.1	185.9	195.3	195.2	197.2
3	34.9	34.7	44.7	69.3	70.9	140.4	140.4	97.2	97.2	97.2
4	28.7	27.5	28.4	28.3	28.2	147.5	147.5	28.3	28.3	27.4
5	61.9	59.1	62.8	61.8	62.1	61.3	61.3	61.9	61.5	59.0
6	46.5	28.8	45.4	43.1	41.2	48.0	47.7	42.7	42.3	26.2
7	33.6	33.6	32.9	30.3	27.9	34.1	33.9	31.7	31.4	27.2
8	167.1	168.8	167.5	168.3	168.8	166.6	167.0	167.6	167.6	169.1
10	36.9	36.2	44.1	53.5	52.9	28.5	28.6	45.4	45.4	45.4
11	35.2	33.6	34.4	35.7	35.6	36.3	36.2	34.9	34.9	33.8
12	127.5	129.8	127.5	127.4	127.3	127.0	126.8	127.4	127.4	130.0
13	126.5	125.3	126.5	126.6	126.3	126.5	126.6	127.3	127.3	126.2
14	108.9	107.3	108.9	109.6	109.7	108.7	108.6	109.8	109.6	107.7
15	147.6	148.0	147.6	147.5	147.4	148.1	148.1	147.5	147.6	146.7
16	148.5	148.2	148.5	148.8	148.8	148.6	148.6	148.6	148.7	148.2
17	112.3	112.0	112.1	112.1	112.3	111.7	111.8	112.1	112.2	112.1
OMe	55.9	55.7	55.8	56.0	55.9	55.9	55.8	56.1	56.1	56.0
	56.0	56.0	56.0	55.8	56.2	56.0	56.1	55.9	55.8	56.3
								49.9	49.9	49.7
								49.8	49.8	49.8
COOEt	167.1		166.8	166.8	167.0	165.3		167.1		
	61.9		62.0	62.1	62.1	62.0		61.9		
	13.6		13.7	13.7	13.9	13.5		13.7		
COOMe							167.0		167.6	
							52.8		61.9	
SePh s			126.6	125.9	127.8	126.0	126.0			
SePh d			128.6	129.1	129.2	129.3	129.8			
SePh d			135.3	137.8	137.5	136.2	136.2			
SePh d			131.5	130.0	130.7	129.9	129.9			

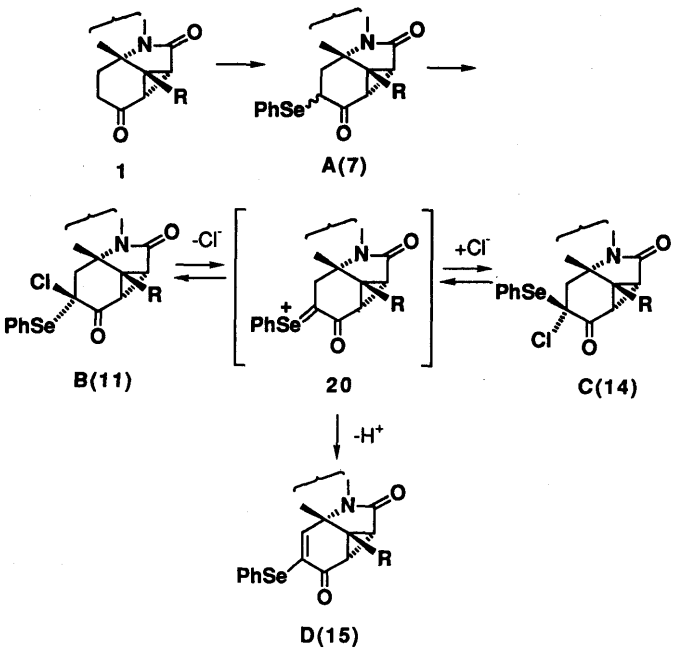

Chart 7

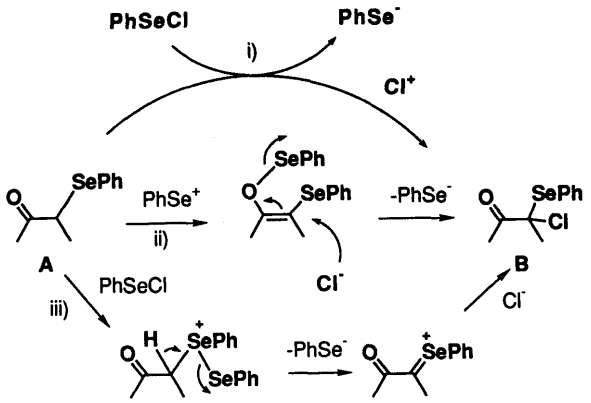

Chart 8

The 6-methoxycarbonyl derivative **1b** gave similar results, the products being **7b** and **11b** when a restricted amount of reagent was used, and **15b** with an excess of the reagent.

Phenylselenenylation of cycloalkanones under acidic conditions has so far been reported to give only the monophenylselenenyl derivatives.[4] Our present investigation has shown, for the first time, that the reaction gives not only the monophenylselenenyl derivative but also α-chloro-α-phenylselenenyl derivatives,[5] and sometimes the unsaturated phenylselenenyl derivative when an excess of the reagent is used. The similar phenylselenenylation of *O*-methylestrone[6] supports these findings.

As indicated above, all phenylselenenylated products (except compound D) gave the α,α-dimethoxyketone **9** when treated with MPC in methanol. Conversion of compound B or C to **9** by this reaction seems reasonable. However, the reaction of an α-phenylselenenyl ketone (A) to give the dimethoxyketone **9** by the action of MPC in methanol needs to be explained, because the reaction is accompanied with oxidation of the substrate. We consider that the reaction proceeds as shown in Chart 9, where Hg^{2+} mediates the methoxylation. This oxidative methoxylation is also

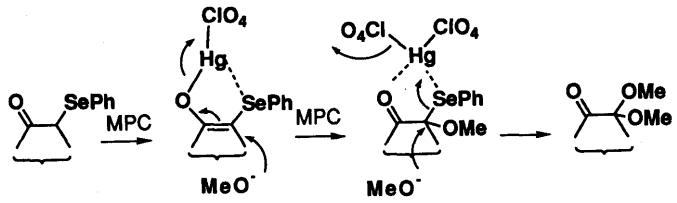

Chart 9. Oxidative Methoxylation of α-Phenylselenenyl Ketones with MPC

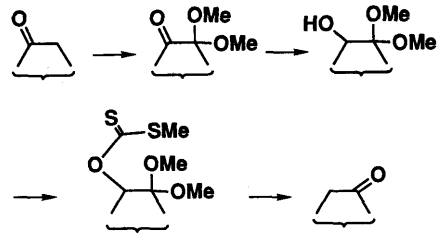

Chart 10. 1,2-Carbonyl Transposition

mediated by other metal cations such as Tl^{3+}. Thus, the reaction of either **7** or **11** (or **14**) with thallium(III) trinitrate (TTN) in MeOH gave the same α,α-dimethoxyketone **9**.[7] Interestingly, the reaction of **7** to **9** was more rapidly mediated by TTN, while that of **11** (or **14**) to **9** was more rapidly mediated by MPC. This metal effect will be discussed in a future communication.

The cycloerythrinan derivative **1a** was thus converted to the α,α-dimethoxyketone **9a** by one-pot reaction in a yield of *ca.* 60%: phenylselenenylation with PhSeCl in THF catalyzed by $BF_3 \cdot Et_2O$ and treatment of the resulting phenylselenenylated mixture with MPC in MeOH. The methyl ester **1b** also gave the dimethoxyketone **9b** in good yield. The 1,7-cycloerythrinan **1c** similarly gave the dimethoxylated product **9c** in 68% yield by one-pot treatment.

Removal of the C-2 Oxygenated Function (2→3) In the above section, we presented an efficient method of dimethoxylation at the α-position to a carbonyl group. Removal of the original carbonyl function from the resulting α,α-dimethoxyketone (followed by acid hydrolysis) completes a 1,2-carbonyl transposition procedure.[8] This can be done by reduction of the ketone to the alcohol followed by radical cleavage of its dithiocarbonate with tributyltin hydride (Chart 10). An example of the overall procedure of this 1,2-carbonyl transposition method is a successful conversion of estrone to isoestrone.[6] Here we deal with compounds **9a** (=**2**), **9b**, and **9c**.

Sodium borohydride reduction of **9a** gave the 2α-alcohol **21a** as a single product,[1] which was converted to the dithiocarbonate **22a**. Compound **22a** was smoothly reduced by tributyltin hydride, with concomitant ring opening of the conjugated cyclopropane ring, to give **23a**, which on acid treatment furnished the conjugated ketone **25a**.

For removal of the COOEt group at the next stage of the synthesis (see below), it was necessary to exchange the COOEt to COOMe. This transformation should be done at the stage of the 1,7-cyclo derivatives, since an alkoxycarbonyl group on the cyclopropane ring is easily hydrolyzable, or otherwise, it is highly resistant to hydrolysis or transesterification.[1] Thus, treatment of **21a** with NaOMe

in methanol resulted in the requisite transesterification in high yield to give **21b**.

This was converted to the dithiocarbonate **22b**, then treated with tributyltin hydride to yield **23b**, which, on mild acid hydrolysis, gave the required conjugated ketone **25b** (=**3**). Similarly the 6βH-derivative **9c**, by the above four successive reactions, gave the conjugated ketone **25c** in 66% yield.

Decarbomethoxylation from Vinylogous β-Keto Methyl Esters (3→4) Previously we presented a useful decarbalkoxylation method of β-keto esters ($MgCl_2$–dimethyl sulfoxide (DMSO) combination).[2,9] This method was also applicable to vinylogous β-keto esters, particularly for methyl esters.

The ethyl ester **25a** resisted decarbethoxylation even at 170 °C, but the methyl ester **25b** was smoothly decarbomethoxylated on heating with $MgCl_2$ in DMSO (containing

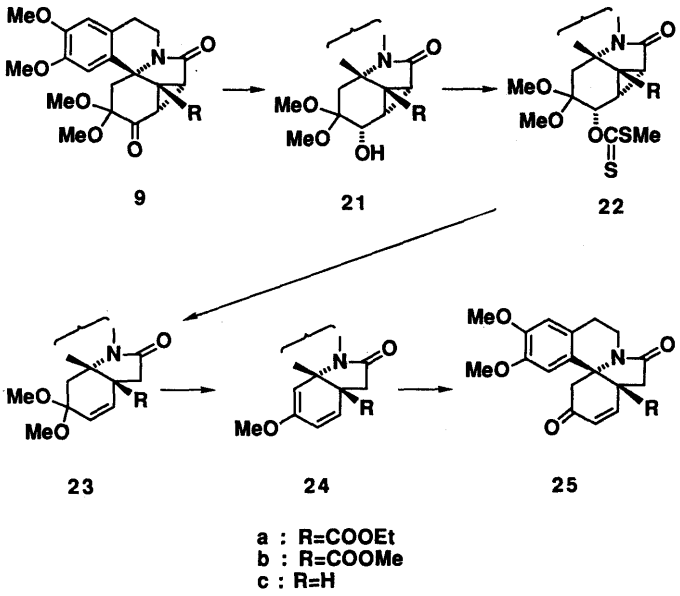

Chart 11

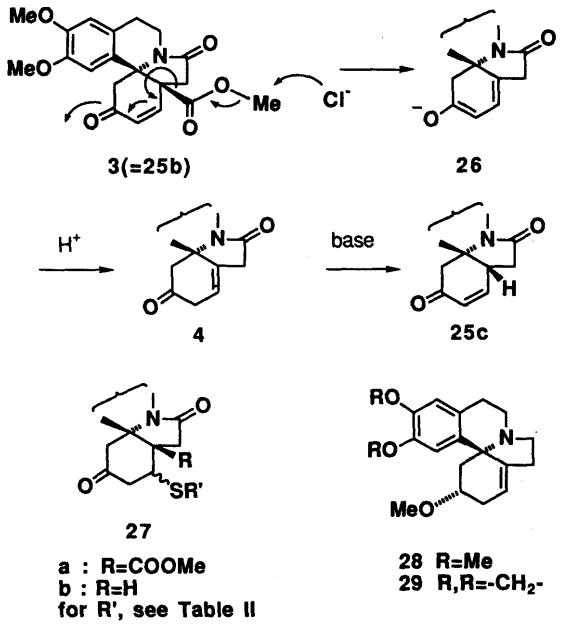

Chart 12

EtSH) at 140 °C to give, in 55% yield, the enones **4** and **25c** in a 1 : 1 ratio. The difference of reactivity of ethyl *vs.* methyl ester is obviously due to the steric hindrance at the position where Cl^- attacks.

The structures of the products were proved spectroscopically and by chemical correlations. Treatment of **4** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene quantitatively isomerized it to a conjugated enone which was identical with **25c** obtained from 6βH-1,7-cycloerythrinan (see above), thus proving the stereochemistry at C-6. Those facts suggested that the enone **4** had been initially produced from the intermediary diene-enolate **26** by kinetic trapping of proton, which then migrated under the decarbomethoxylation conditions to give **25c**.

We found that $CaCl_2$ instead of $MgCl_2$ is more effective to remove the ester group from vinylogous β-keto methyl esters, in terms of both the yield and selectivity.[10] It must be emphasized that the reaction with the $CaCl_2$–DMSO combination always gives the kinetic product, the nonconjugated enone, predominantly. Thus, heating of **25b** (=**3**) with $CaCl_3$–DMSO (EtSH) at 140 °C gave the enones **4** and **25c**, in 74—83% yield, in a ratio of 5 : 1—4 : 3.

Several other points should be mentioned: the decarbomethoxylation of vinylogous β-keto esters is often accompanied with a side reaction, Michael addition of the thiol

Table II. Decarbomethoxylation of **25b** by the $CaCl_2$–DMSO Method[a]

Additive R'SH	**25b** (recovery)	Product (yield, %)				
		4	**25c**	Adduct	**27a**	**27b**
$PhCH_2SH$	48	34	5		12	1 (R'=$PhCH_2$)
PhSH	16	34	18		15	18 (R'=Ph)
EtSH	13	43	31		7	6 (R'=Et)
tert-BuSH	12	63	24		0	0
tert-HepSH	9	80	11		0	0

a) Reaction conditions: see Experimental.

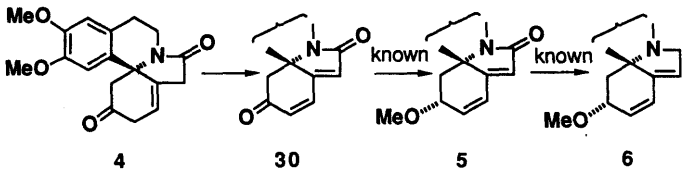

Chart 13

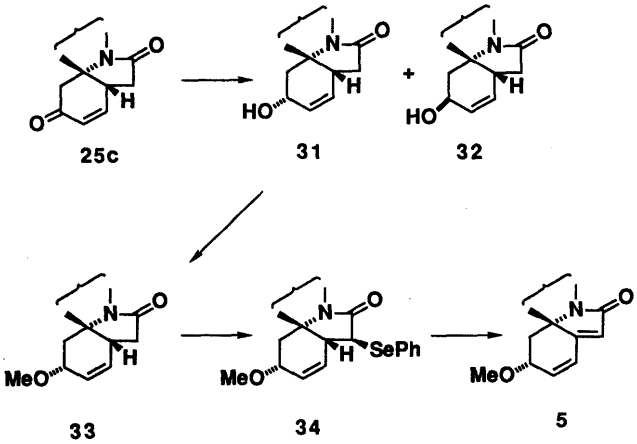

Chart 14

group to the conjugated ketone, forming **27**. The formation of **27a** prevents further decarbomethoxylation. This side reaction is particularly evident when EtSH or PhSH is used as an antioxidant[2] and can not readily be avoided by regulation of the amount of thiol. However, it was well avoided by the use of a bulky thiol such as 2-methylpropane-2-thiol or 3-ethylpentane-3-thiol, which are weak Michael addends. Thus, $CaCl_2$–DMSO (3-ethylpentane-3-thiol) was the best combination to prepare the nonconjugated ketones by decarbomethoxylation of vinylogous β-keto methyl esters. By this modified method, the methyl ester **25b** was converted into the enone **4** in an average yield of 70—80%. Enones of the structure **4** are potential intermediates in the preparation of alkenol type erythrinan alkaloids such as dihydroerysotrine **28** and erythramine (**29**).

Other applications of this decarbomethoxylation method to various vinylogous β-keto esters will be reported in a separate paper.

Total Synthesis of Erysotrine (4→5→6) Oxidation of the nonconjugated ketone **4** with dichlorodicyanobenzoquinone (DDQ) in benzene gave the dienone **30**, though in low yield (29%).[11] The yield of **30** was improved to 39% on treatment of **4** with pyridinium hydrobromide perbromide in chloroform followed by dehydrobromination with DBU.

Since the dienone **30** has already been converted into the dienoid type natural alkaloids erysotramidine (**5**) and erysotrine (**6**) by stereoselective reduction, methylation, and reductive removal of the lactam group,[12] the synthesis of the dienone **30** constitutes a total synthesis of (±)-erysotrine (**6**) in a formal sense.

A more efficient total synthesis of **5** and **6** was achieved from the conjugated enone **25c** as follows. The enone **25c** was reduced stereoselectively to the 3α-alcohol **31** with $NaBH_4$–$CeCl_3$ in methanol (**31**/**32** ratio was 3/1).[13] The alcohol **31** was methylated with iodomethane in the presence of a phase-transfer catalyst to give **33**. Phenylselenenylation of **33** with $(PhSe)_2$ and lithium diisopropylamide (LDA) followed by oxidative elimination of the phenylselenenyl group gave, in 95% yield, the dienoid lactam **5**, (±)-erysotramidine. Reduction of **5** with $LiAlH_4$ and $AlCl_3$[12] gave (±)-erysotrine (**6**). The identities of these products were confirmed by direct comparisons with the samples reported previously.[12] Thus, the total synthesis of erysotrine was accomplished.

Several new synthetic methods developed in the course of this work (presented in this and preceding several papers) are general ones and applicable not only to the synthesis of erythrinan alkaloids but also to the synthesis of other natural products and to their transformations.

Experimental

General Unless otherwise stated, the following procedures were adopted. Melting points were determined on a Yanaco micro hot stage melting point apparatus and are uncorrected. IR spectra were taken in KBr disks on a Jasco IR-G spectrometer, and the data are given in cm^{-1}. ^{1}H-NMR spectra were taken with a JEOL FX-100 (100 MHz) spectrometer in chloroform-*d* solution with tetramethylsilane as an internal standard, and the chemical shifts are given in δ values (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad). Mass spectra (MS) and high resolution mass spectra (HRMS) were taken with a Hitachi M-80 machine and M^+ and/or major peaks are indicated as *m/z*. DCI-MS were taken on a Shimadzu LKB-9000A spectrometer with ammonia or isobutane as a carrier gas. Column chromatography was performed on Wakogel C-200 (silica gel). For thin layer chromatography (TLC), Merck precoated plates GF_{254} were used and spots were monitored by ultraviolet (UV) (254 nm), then developed by spraying 1% $Ce(SO_4)_2$ in 10% H_2SO_4 and heating the plates at 100 °C until coloration took place. All organic extracts were washed with brine and dried over anhydrous sodium sulfate before concentration. Identities were confirmed by mixed melting point determination (for crystalline compounds) and also comparisons of TLC behavior and ^{1}H-NMR and IR spectra. MPC used was a trihydrate, $Hg(ClO_4)_2 \cdot 3H_2O$.

Phenylselenenylation of the 6β-Ethoxycarbonyl-2,8-dioxo-1,7-cycloerythrinan (1a) (1) Formation of Compound A: A mixture of **1a** (1.02 g), PhSeCl (504 mg, 1.0 eq), and $BF_3 \cdot Et_2O$ (10 drops) in THF (40 ml) was refluxed under an Ar atmosphere for 30 min. The cooled mixture was poured into $CHCl_3$ and the combined organic layer was washed with aqueous $NaHCO_3$ and concentrated. Chromatography of the residue gave compound A (**7a**, 412 mg, 28%), the starting material (**1a**, 560 mg), and the diketone E (**10a**, 260 mg, 25%).

7a (Compound A): Pale yellow oil. ^{1}H-NMR: 7.52 (2H, m, SePh), 7.24 (3H, m, SePh), 6.75, 6.45 (each 1H, s, ArH), 3.80 (6H, s, 2×OMe), 1.00 (3H, t, J=7 Hz, $COOCH_2C\underline{H}_3$). DCI-MS (ammonia): 559 $[(M+NH_4)^+$ for $C_{27}H_{27}NO_6{}^{80}Se]$.

10a (Compound E): Yellow crystals (from CH_2Cl_2–$CHCl_3$), mp 252—253 °C. IR: 1725, 1715, 1690. ^{1}H-NMR: 7.04, 6.58 (each 1H, s, ArH), 3.86 (6H, s, 2×OMe), 1.13 (3H, t, J=7 Hz, $COOCH_2C\underline{H}_3$). MS: 399 (M^+). *Anal.* Calcd for $C_{21}H_{21}NO_7$: C, 63.15; H, 5.30; N, 3.51. Found: C, 62.97; H, 5.35; N, 3.46.

(2) Formation of Compound B: A mixture of **1a** (1.005 g), PhSeCl (591 mg, 1.2 eq), and $BF_3 \cdot Et_2O$ (8 drops) in THF (50 ml) was treated as above for 2 h, then PhSeCl (200 mg, 0.4 eq) was added, and the reaction was continued for a further 1.5 h. Work-up of the mixture and chromatography of the product gave compound B (**11a**, 310 mg, 21%) from the benzene–acetone (6:1) eluate, and a mixture of compounds A (**7a**) and D (**15a**) (592 mg), and compound E (**10a**, 239 mg, 23%) from the benzene–acetone (2:1) eluate.

11a (Compound B): Pale yellow prisms (from benzene–hexane), mp 159—161 °C. IR: 1740, 1710, 1695. ^{1}H-NMR: 7.66 (2H, m, SePh), 7.32 (3H, m, SePh), 6.97, 6.56 (each 1H, s, ArH), 3.84, 3.83 (each 3H, s, OMe), 1.04 (3H, t, J=7 Hz, $COOCH_2C\underline{H}_3$). DCI-MS (ammonia): 593 $[(M+NH_4)^+$ for $C_{27}H_{26}{}^{35}ClNO_6{}^{80}Se]$.

(3) Formation of Compound C: Compound **1a** (503 mg), PhSeCl (517 mg, 2.1 eq), and $BF_3 \cdot Et_2O$ (5 drops) in THF (20 ml) were heated as above. Portions of PhSeCl (259 mg, 1 eq, and 510 mg, 2 eq) were added to the mixture after 1 h and after a further 2 h, and the reflux was continued for a total of 11 h. Work-up as above and chromatography of the product gave compound C (**14a**, 436 mg, 58%) and compound D (**15a**, 276 mg, 39%) from the benzene–EtOAc (4:1) eluate.

14a (Compound C): Pale yellow prisms (from benzene–ether), mp 121—122 °C. IR: 1725, 1720, 1710. ^{1}H-NMR: 7.60 (2H, m, SePh), 7.38 (3H, m, SePh), 7.18, 6.56 (each 1H, s, ArH), 3.88, 3.86 (each 3H, s, OMe), 1.20 (3H, t, J=7 Hz, $COOCH_2C\underline{H}_3$). DCI-MS (ammonia): 593 $[(M+NH_4)^+$ for $C_{27}H_{26}{}^{35}ClNO_6{}^{80}Se]$.

(4) Formation of Compound D: The reaction of **1a** (1.0 g) in THF (40 ml) in the presence of $BF_3 \cdot Et_2O$ (11 drops) as a catalyst for 11 h with occasional additions of PheSeCl (1.02, 0.85, and 0.571 g, total 4.8 eq) gave compound C (**14a**, 375 mg, 25%) and compound D (**15a**, 866 mg, 62%).

15a (Compound D): Yellow prisms (from EtOAc–ether), mp 224—225 °C. IR: 1725, 1705, 1695. ^{1}H-NMR: 7.52 (2H, m, SePh), 7.28 (3H, m, SePh), 6.54, 6.44 (each 1H, s, ArH), 6.36 (1H, s, H-4), 3.84, 3.76 (each 3H, s, OMe), 0.90 (3H, t, J=7 Hz, $COOCH_2C\underline{H}_3$). DCI-MS (ammonia): 557 $[(M+NH_4)^+$ for $C_{27}H_{25}NO_6{}^{80}Se]$.

Treatment of Compound A (7a) with PhSeCl Compound A (**7a**, 92 mg) in THF (7 ml) containing $BF_3 \cdot Et_2O$ (3 drops) was treated with PhSeCl as follows under an Ar atmosphere with monitoring by TLC: i) 33 mg (1 eq) of PhSeCl and reflux for 2 h, and ii) further addition of 66 mg of PhSeCl (2 eq) and reflux for 8 h, iii) then for a further 5 h, and iv) the resulting mixture was heated with $(PhSe)_2$ (20 mg) for 2 h. The following compounds were formed: i) compound B, ii) compounds B and C, and iii) compounds B, C, and D. The major product in iv) was compound D.

Treatment of Compound B (11a) with PhSeCl Compound B (**11a**, 10 mg) was heated with PhSeCl (10 mg, 3 eq) and $BF_3 \cdot Et_2O$ (1 drop) in THF (2 ml) at 80 °C. After 1 h (i), $BF_3 \cdot Et_2O$ (1 drop) was added, and the reaction was monitored at 1 h (ii), 3 h (iii), and 5 h (iv), then 15 mg of PhSeCl was added and the mixture was heated for a further 3 h (v). The results were as follows: (i) compound B (unchanged), (ii) compound B and compound C, (iii) compounds B, C, and D, (iv) compounds B and C < compound D, and (v) compounds B and C ≪ compound D.

Treatment of Compound C (14a) with PhSeCl or $(PhSe)_2$ (1) Compound **14a** (5 mg) was heated with PhSeCl (10 mg, 6 eq) and $BF_3 \cdot Et_2O$ (1 drop) in THF (1.5 ml) at 80 °C for 5.5 h (the TLC pattern was unchanged). $(PhSe)_2$ (15 mg, 5.4 eq) was added to this mixture and the whole was heated for 3.5 h (i), then 15 mg (5.4 eq) of $(PhSe)_2$ was added and the mixture was heated for a further 1 h (ii). The TLC of (i) showed compounds C and D, and that of (ii) almost entirely D. The ^{1}H-NMR spectrum of the products in (ii) indicated the formation of compound D with a small amount of the chloro olefin **12a** and compound C.

(2) Compound **14a** (5 mg) and $(PhSe)_2$ (15 mg) in THF (2 ml) were heated in a sealed tube at 80 °C for 1 h. The TLC pattern and ^{1}H-NMR spectrum of the product (3 mg, isolated by chromatography) showed that it was a mixture of compound D **15a**, the chloro olefin **12a**, and the starting material **14a**.

15,16-Dimethoxy-6β-methoxycarbonyl-2,8-dioxo-1,7-cycloerythrinan (1b) Compound **1a** (300 mg) in dry MeOH was treated with 1% NaOMe–MeOH (15 ml) for 2 h at room temperature. The mixture was neutralized with Amberlite IRC-50 (H^+) and concentrated to give the methyl ester **1b** (280 mg, 97%), as colorless prisms (from MeOH), mp 225—227 °C (previously reported as a gum).[1] The spectral data were identical with those reported.[1]

Phenylselenenylation of Compound 1b (1) A mixture of **1b** (505 mg), PhSeCl (310, 324, 156 mg, total 3.0 eq), and $BF_3 \cdot Et_2O$ (15 drops) in THF (35 ml) was heated under reflux for a total of 9 h. Work-up of the mixture as described above gave compound **7b** (370 mg, 52%) and the starting material **1b** (150 mg, 30%).

7b: Gum. ^{1}H-NMR: 7.58 (2H, m, PhSe), 7.32 (3H, m, PhSe), 6.82, 6.54 (each 1H, s, ArH), 3.84 (6H, s, 2 × OMe), 3.52 (3H, s, COOMe). DCI-MS (isobutane): 528 (MH^+ for $C_{26}H_{25}NO_6{}^{80}Se$).

(2) A mixture of **1b** (502 mg), PhSeCl (543, 397, and 270 mg, total 4.5 eq), and $BF_3 \cdot Et_2O$ (5 drops) in THF (35 ml) was heated under reflux for total 5.5 h. Work-up of the mixture gave **11b** (318 mg, 42%) and **15b** (295 mg, 42%).

11b: Pale yellow prisms (from MeOH), mp 158—161 °C. ^{1}H-NMR: 7.67 (2H, m, PhSe), 7.35 (3H, m, PhSe), 6.96, 6.56 (each 1H, s, ArH), 3.86, 3.85, 3.59 (each 3H, s, OMe). DCI-MS (isobutane): 562 (MH^+ for $C_{26}H_{24}{}^{35}ClNO_6{}^{80}Se$).

15b: Yellow prisms (from AcOEt–ether), mp 106—107 °C. ^{1}H-NMR: 7.50 (2H, m, PhSe), 7.26 (3H, m, PhSe), 6.52, 6.44 (each 1H, s, ArH), 6.36 (1H, s, H-4), 3.84, 3.78, 3.42 (each 3H, s, OMe). DCI-MS (isobutane): 526 (MH^+ for $C_{26}H_{23}NO_6{}^{80}Se$).

Air Oxidation of Compound A (7a) Compound A (**7a**) in benzene was adsorbed on SiO_2 and kept at room temperature. After 1 d, TLC showed the formation of compound E, and after 10 d, elution of the column with benzene–acetone gave compound E (**10a**) exclusively.

Reaction of Compound A (7a) with MPC (1) A solution of **7a** (100 mg) and MPC (380 mg) in MeOH (10 ml) was stirred for 3 h at room temperature. The mixture was treated with dilute Na_2S solution until the solution became faintly alkaline, and then it was filtered. The filtrate was extracted with $CHCl_3$. The product obtained from the extract was purified by chromatography to give the dimethoxyketone **9a** (69 mg, 84%) as a colorless gum.

(2) A solution of **1a** (100 mg) and PhSeCl (100 mg) in THF (15 ml) was stirred for 22 h at room temperature, then refluxed for 5 h to give a mixture of **7a** and **11a** (on TLC). After evaporation of the solvent, the residue was dissolved in MeOH (10 ml) and treated with MPC (490 mg, 4 eq) for 17 h at room temperature. The mixture was diluted with water and extracted with $CHCl_3$. Concentration of the dried extract and chromatography of the residue gave **9a** (66 mg, 57%) as an oil from the benzene–AcOEt (4 : 1) eluate. IR: 1730, 1715, 1700. ^{1}H-NMR: 7.00, 6.50 (each 1H, s, ArH), 3.98 (2H, q, J = 7 Hz, $COOCH_2CH_3$), 3.82, 3.22 (each 6H, s, OMe), 1.07 (3H, t, J = 7 Hz, $COOCH_2CH_3$). MS: 445 (M^+). HRMS: Calcd for $C_{23}H_{27}NO_8$: 445.2171. Found: 445.2156.

Reaction of Compound A (7a) with Na_2S Compound **7a** (50 mg) in MeOH (5 ml) was stirred with an excess of Na_2S solution for 2 h at room temperature. Extraction of the mixture with $CHCl_3$ and chromatography of the product gave compound **1a** (20 mg) and compound **7a** (5 mg).

Reaction of Compound A (7a) with H_2O_2 A solution of **7a** (40 mg) and 30% H_2O_2 (5 drops) in MeOH (15 ml) was stirred for 15 min at room temperature. Chromatography of the product gave the conjugated ketone **8a** (28 mg, 100%) as colorless prisms (from MeOH), mp 189—192 °C. IR: 1730, 1720, 1700. ^{1}H-NMR: 7.08 (1H, d, J = 10 Hz, H-4), 6.65, 6.59 (each 1H, s, ArH), 6.24 (1H, dd, J = 10, 1 Hz, H-3), 3.90, 3.83 (each 3H, s, OMe), 0.91 (3H, t, J = 7 Hz, $COOCH_2CH_3$). *Anal.* Calcd for $C_{21}H_{21}NO_6 \cdot H_2O$: C, 62.84; H, 5.73; N, 3.49. Found: C, 63.23; H, 5.52; N, 3.42.

Reaction of Compound B with MeOH (1) Compound **11a** (11 mg) in MeOH (10 ml) was stirred at room temperature. After 30 min, the mixture showed almost a single spot corresponding to the methoxy compound **13a**. However, after evaporation of the solvent the dimethoxyketone **9a** was obtained.

(2) Compound **11b** (100 mg) in MeOH was stirred for 1.4 h at room temperature. Careful evaporation of the solvent gave the methoxy compound **13b** as a gum. ^{1}H-NMR: 7.41 (2H, m, PhSe), 7.27 (3H, m, PhSe), 6.96, 6.52 (each 1H, s, ArH), 3.82, 3.80, 3.60, 3.50 (each 3H, s, OMe). DCI-MS (isobutane): 558 (MH^+ for $C_{27}H_{27}NO_7{}^{80}Se$).

On further stirring of **13b** in MeOH, it changed into the dimethoxyketone **9b** (gum). ^{1}H-NMR: 6.95, 6.47 (each 1H, s, ArH), 3.80 (6H), 3.55 (3H), 3.20 (6H) (each s, 5 × OMe). MS: 431 (M^+).

Reaction of Compound B (11a) with H_2O_2 Compound **11a** (50 mg) and 30% H_2O_2 (10 drops) in MeOH (15 ml) were stirred for 50 min at room temperature. The mixture was diluted with $CHCl_3$, washed with aqueous $NaHCO_3$, and concentrated. Chromatography of the residue gave the chloro olefin **12a** (5 mg, 17%) and the dimethoxyketone **9a** (21 mg, 55%).

12a: Colorless prisms (from AcOEt–MeOH), mp 209—210 °C. IR: 1725, 1710, 1700. ^{1}H-NMR: 7.23 (1H, s, H-4), 6.67, 6.60 (each 1H, s, ArH), 3.89, 3.84 (each 3H, s, OMe), 0.91 (3H, t, J = 7 Hz, $COOCH_2CH_3$). MS: 417, 419 (M^+, 3 : 1). HRMS: Calcd for $C_{21}H_{20}{}^{35}ClNO_6$: 417.0974. Found: 417.1008.

Reaction of Compound B (11a) with MPC A solution of **11a** (19 mg) and MPC (40 mg, 2.5 eq) in MeOH–$CHCl_3$ (3 : 1, 8 ml) was stirred for 40 min at room temperature, then diluted with $CHCl_3$, and washed with aqueous $NaHCO_3$. The organic layer was washed with brine, dried, and concentrated. Chromatography of the residue gave the dimethoxyketone **9a** (12 mg, 83%) from the benzene–acetone (4 : 1) eluate.

Reaction of Compound C (14a) with MeOH (1) Compound **14a** (10 mg) in MeOH (2 ml) was heated under reflux for 8 h under an Ar atmosphere. TLC of the mixture showed the presence of the dimethoxyketone **9a** and the diketone **10a**.

(2) Compound **14a** (100 mg) in MeOH (40 ml) was heated under reflux with a catalytic amount of *p*-TsOH for 30 min, then stirred for 4 h at room temperature. Evaporation of the solvent and usual work-up of the residue gave the dimethoxyketone **9a** (30 mg, 39%) and the diketone **10a** (40 mg, 58%).

Reaction of Compound C (14a) with H_2O_2 A solution of **14a** (5 mg), 30% H_2O_2 (1 drop) and pyridine (1 drop) in CH_2Cl_2 was stirred for 30 min at room temperature. Chromatography of the product gave the chloro olefin **12a** (2.4 mg, 80%).

Reaction of Compound C (14a) with MPC A solution of **14a** (10 mg) and MPC (20 mg, 2.0 eq) in MeOH (2 ml) was stirred for 20 min at room temperature and worked up as above. Chromatography of the product gave the dimethoxyketone **9a** (6 mg, 77%).

Reaction of Compound D (15a) with Na_2S and MeOH An excess of Na_2S was added to a stirred solution of compound **15a** (145 mg) in MeOH (36 ml) and the mixture was stirred for 5 min, then neutralized with 1 N HCl and extracted with $CHCl_3$. Purification of the extract by preparative TLC gave the methoxyketone **17a** (93 mg, 86%), as colorless plates (from MeOH), mp 215—219 °C. IR: 1720, 1710, 1690. ^{1}H-NMR: 7.26, 6.62 (each 1H, s, ArH), 3.89, 3.83, 3.36 (each 3H, s, OMe), 0.95 (3H, t, J = 7 Hz, $COOCH_2CH_3$). MS: 415 (M^+). *Anal.* Calcd for $C_{22}H_{25}NO_7$: C, 63.60; H, 6.07; N, 3.37. Found: C, 63.48; H, 5.99; N, 3.45.

Reaction of Compound D (15a) with NaOMe A 5% NaOMe–MeOH solution (10 drops) was added to a stirred solution of **15a** (50 mg) in MeOH (25 ml) and the mixture was stirred for 1 h at room temperature, then diluted with water, and extracted with $CHCl_3$. Chromatography of the extract gave **19a** (30 mg, 78%) as a yellow oil from the benzene–acetone (4 : 1) eluate. IR ($CHCl_3$): 1730, 1720, 1695. ^{1}H-NMR: 7.28, 6.62 (each 1H, s, ArH), 3.88, 3.85, 3.45 (each 3H, s, OMe), 1.02 (3H, t, J = 7 Hz, $COOCH_2CH_3$). MS: 429 (M^+).

Acid Treatment of 17a Compound **17a** (11 mg) in 5% HCl–THF (1 : 1, 1 ml) was heated at 80 °C for 1 h. Addition of water and extraction with $CHCl_3$ gave 9 mg of the product, which was judged to be a mixture of the conjugated ketone **8a**, the hydroxyketone **18a**, and the starting material **17a** on the basis of TLC behavior and the ^{1}H-NMR spectrum.

Phenylselenenylation of 15,16-Dimethoxy-2,8-dioxo-1,7-cycloerythrinan (1c) (1) The cycloerythrinan **1c** (130 mg) was treated with 0.1 M *n*-BuLi (0.4 ml) and $(PhSe)_2$ (194 mg) in benzene (10 ml) in the presence of 12-crown-4 (8 drops) to give the phenylselenenyl derivative **7c** (103 mg, 53%) as colorless needles (from MeOH), mp 211—213 °C. IR: 1690. ^{1}H-NMR: 7.55 (2H, m, PhSe), 7.30 (3H, m, PhSe), 6.64, 6.56 (each 1H,

s, ArH), 4.16 (2H, m, H-3 and one of H-10), 3.89, 3.85 (each 3H, s, OMe). MS: 469 (M^+ for $C_{24}H_{23}NO_4{}^{80}Se$), 312 (base peak).

(2) Compound **1c** in THF (or CH_2Cl_2) was treated with PhSeCl (2 eq-excess) under reflux for 4 h. The product showed two spots on TLC: one corresponded to **7c** and the other (upper one) was supposed to be **11c**. This material was used for the next step without separation (see below).

The Conjugated Ketone 8c Compound **7c** (25 mg) in CH_2Cl_2 (2.5 ml) was treated with 15% H_2O_2–MeOH (2 drops) at 0 °C for 15 min. Work-up of the mixture gave the conjugated ketone **8c** (12 mg, 72%) as colorless prisms (from MeOH), mp 169—172 °C. IR: 1690. ^{1}H-NMR: 7.90 (1H, d, J=10 Hz, H-4), 6.53 (2H, s, ArH), 6.08 (1H, d, J=10 Hz, H-3), 4.17 (1H, m, one of H-10), 3.82 (6H, s, 2×OMe). MS: 311 (M^+), 257 (M^+-54). *Anal.* Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.62; H, 5.44; N, 4.28.

The Dimethoxyketone 9c (1) By MPC: Compound **7c** (20 mg) in MeOH (5.5 ml) was treated with MPC (79 mg, 4.0 eq) to give **9c** (16 mg, 100%) as colorless needles (from MeOH), mp 209—212 °C. IR: 1720, 1695. ^{1}H-NMR: 6.63, 6.45 (each 1H, s, ArH), 3.85, 3.80, 3.20, 3.17 (each 3H, s, OMe), 2.35 (2H, s, H-4). MS: 373 (M^+). *Anal.* Calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.23; H, 6.19; N, 3.66.

(2) By TTN: Compound **7c** (22 mg) in MeOH (5 ml) was treated with TTN (82 mg, 4 eq) for 3 h at room temperature to give the dimethoxyketone **9c** (13 mg, 86%).

(3) One Pot Transformation of **1c** to **9c**: A solution of the cycloerythrinan **1c** (16 mg) and PhSeCl (19.5 mg, 2 eq) in THF (2 ml) was stirred at room temperature for 48 h. The solvent was evaporated off and the residue in MeOH (4 ml) was treated with MPC (150 mg, 6 eq) at room temperature for 1 h. Work-up of the mixture as described above gave the dimethoxyketone **9c** (13 mg, 68%).

The 2,3,8-Trioxo Derivative 10c The dimethoxyketone **9c** (19 mg) in acetone (3.5 ml) was heated with 5% HCl (3.0 ml) at 70 °C for 2 h. The product was taken up into $CHCl_3$ and worked up as usual to give the trioxo derivative **10c** (16 mg, 96%) as yellow crystals, mp 256—259 °C. IR: 1720, 1700. ^{1}H-NMR: 6.78, 6.63 (each 1H, s, ArH), 4.14 (1H, m, one of H-10), 3.93, 3.89 (each 3H, s, OMe). MS: 327 (M^+), 257 (M^+-70). *Anal.* Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.24; N, 4.28. Found: C, 66.12; H, 5.20; N, 4.43.

The Dimethoxy-alcohol 21a The dimethoxyketone **9a** (120 mg) in MeOH (10 ml) was reduced with $NaBH_4$ (15 mg) to give the alcohol **21a** (100 mg, 83%) as colorless needles (from CH_2Cl_2–hexane), mp 189—191 °C. IR: 3320, 1715, 1675. ^{1}H-NMR: 6.68, 6.45 (each 1H, s, ArH), 4.52 (1H, br s, CHOH), 3.63 (6H), 3.33 (3H), 3.20 (3H) (each s, OMe), 0.88 (3H, t, J=7 Hz, $COOCH_2C\underline{H}_3$). MS: 447 (M^+). *Anal.* Calcd for $C_{23}H_{29}NO_8$: C, 61.73; H, 6.53; N, 3.13. Found: C, 61.77; H, 6.41; N, 3.01.

On acetylation with pyridine–Ac_2O, **21a** gave the acetate as colorless needles (from MeOH), mp 230—232 °C. IR: 1745, 1730, 1690. ^{1}H-NMR: 6.83, 6.38 (each 1H, s, ArH), 5.35 (1H, m, CHOAc), 3.78 (6H), 3.35 (3H), 3.13 (3H) (each s, OMe), 0.97 (3H, t, J=7 Hz, $COOCH_2C\underline{H}_3$). MS: 489 (M^+).

One-Pot Transformation of 1a to the Dimethoxy-alcohol 21a Compound **1a** (500 mg), PhSeCl (375 mg, 1.5 eq), and $BF_3\cdot Et_2O$ (4 drops) in THF (25 ml) were heated under reflux for 3 h under an Ar atmosphere, then concentrated *in vacuo*. The residue was dissolved in MeOH (60 ml), MPC (1.8 g) was added at 0 °C, and the mixture was stirred for 1.5 h at room temperature. After further addition of MPC (0.6 g) and stirring overnight, the mixture was separated by filtration into the precipitate and the filtrate. The filtrate was treated with Na_2S until the solution became faintly alkaline and the resultant black precipitate was removed by filtration with the aid of Celite. The filtrate was diluted with water and extracted with $CHCl_3$. Chromatography of the product from the $CHCl_3$ extract gave crude **9a** (508 mg) from the benzene–acetone (4:1) eluate; this product was dissolved in MeOH (40 ml) and reduced with $NaBH_4$ (44 mg) for 1.5 h at 0 °C. The mixture was acidified with 1 N HCl to pH 4 and extracted with CH_2Cl_2. Concentration of the dried extract gave **21a**, which was crystallized from MeOH–Et_2O (281 mg, 48%). The first precipitate gave **17a** (46 mg, 9%) on decomposition by treatment with Na_2S in MeOH.

Transesterification of 21a to the Methyl Ester 21b Compound **21a** (305 mg) was dissolved in dry MeOH (15 ml) and treated with 10% NaOMe–MeOH (15 ml) for 3 h at room temperature. The separated crystals were collected by filtration to give **21b** (184 mg). The filtrate was neutralized with Amberlite IRC-50 (H^+) and concentrated to give a residue which was crystallized from MeOH to give a further crop of **21b** (89 mg). Total yield: 273 mg (92%).

21b: Colorless prisms (from MeOH), mp 211—213 °C. IR: 1725, 1670, ^{1}H-NMR: 6.78, 6.56 (each 1H, s, ArH), 4.56 (1H, br d, J=6 Hz, H-2), 3.86, 3.84, 3.40, 3.38, 3.24 (each 3H, s, OMe). MS: 433 (M^+). *Anal.* Calcd for $C_{22}H_{27}NO_8\cdot 1/2H_2O$: C, 59.73; H, 6.33; N, 3.17. Found: C, 59.99; H, 6.15; N, 3.13.

The Dimethoxy-alcohol 21c The dimethoxyketone **9c** (100 mg) in MeOH (5 ml) was reduced with $NaBH_4$ (30 mg) for 2 h at room temperature to give the alcohol **21c** (97 mg, 96%) as colorless needles (from benzene), mp 122—124 °C. IR: 3400, 1658. ^{1}H-NMR: 6.67, 6.55 (each 1H, s, ArH), 4.50 (1H, d, J=11 Hz, H-2), 3.90, 3.86, 3.33, 3.26 (each 3H, s, OMe). MS: 375 (M^+), 258 (base peak). *Anal.* Calcd for $C_{20}H_{25}NO_6$: C, 63.98; H, 6.71; N, 3.73. Found: C, 63.70; H, 6.81; N, 3.79.

The Dithiocarbonate 22b A mixture of the alcohol **21b** (500 mg), NaH (60% oil dispersion, 291 mg), and a catalytic amount of imidazole (20 mg) in THF (250 ml) was heated under reflux for 4 h under an Ar atmosphere. Carbon disulfide (3 ml) and iodomethane (3 ml) were added successively, and the mixture was heated for a further 40 min, then concentrated to *ca.* 1/3 volume. The mixture was brought to pH 8 by addition of AcOH and water, and extracted with $CHCl_3$. Concentration of the extract and chromatography of the residue gave, from the $CHCl_3$–AcOEt (5:1) eluate, **22b** (490 mg, 81%) as colorless needles (from MeOH), mp 205—206 °C. IR: 1730, 1690. ^{1}H-NMR: 7.00, 6.54 (each 1H, s, ArH), 6.18 (1H, d, J=6 Hz, H-2), 3.87, 3.86, 3.46, 3.44, 3.18 (each 3H, s, OMe), 2.54 (3H, s, SMe). MS: 523 (M^+). *Anal.* Calcd for $C_{24}H_{29}NO_8S_2$: C, 55.05; H, 5.58; N, 2.67. Found: C, 54.76; H, 5.59; N, 2.65.

This product was hydrolyzed by 3% HCl to the keto-dithiocarbonate (gum). IR ($CHCl_3$): 1733, 1725, 1715. ^{1}H-NMR: 6.87, 6.58 (each 1H, s, ArH), 6.70 (1H, d, J=7 Hz, H-2), 3.86 (6H), 3.60 (3H) (each s, OMe), 2.56 (3H, s, SMe). MS: 477 (M^+).

15,16-Dimethoxy-6β-methoxycarbonyl-3,8-dioxo-Δ^1-erythrinan (25b=3) The dithiocarbonate **22b** (203 mg) in toluene (200 ml) was added dropwise to a hot stirred solution of tributyltin hydride (Bu_3SnH, 0.5 ml, 5 eq) and azobisisobutyronitrile (AIBN) (catalytic amount) in toluene (50 ml) under an Ar atmosphere, and the mixture was refluxed for a further 4 h. The cooled mixture was poured onto a silica gel column and the column was washed with benzene to remove tin compounds. Elution of the column with $CHCl_3$ and $CHCl_3$–AcOEt (1:1) gave **23b** (204 mg) as a gum, which was used for the next step without further purification. An analytical sample was crystallized from ether as colorless prisms, mp 194—196 °C. IR: 1740, 1695. ^{1}H-NMR: 6.66, 6.20 (each 1H, s, ArH), 6.59, 6.01 (each 1H, d, J=10 Hz, H-1 and H-2), 3.50, 3.36, 2.96, 2.94, 2.80 (each 3H, s, OMe). *Anal.* Calcd for $C_{22}H_{27}NO_7$: C, 63.30; H, 6.52; N, 3.36. Found: C, 63.30; H, 6.70; N, 3.18.

Compound **23b** (204 mg) was hydrolyzed with 2% HCl (10 ml)–acetone (40 ml) at 50 °C for 1 h to give the conjugated ketone **25b** (=**3**) (139 mg, 97% from **22b**), as colorless prisms (from ether), mp 206—207 °C. IR: 1730, 1700, 1680. ^{1}H-NMR: 7.24, 6.38 (each 1H, d, J=12 Hz, H-1 and H-2), 6.54, 6.48 (each 1H, s, ArH), 3.82, 3.68, 3.26 (each 3H, s, OMe). MS: 371 (M^+). *Anal.* Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.57; H, 5.76; N, 3.90.

Transformation of 21a to 6β-Ethoxycarbonyl-15,16-Dimethoxy-3,8-dioxo-Δ^1-erythrinan (25a) The ethyl ester **21a** (39 mg) was similarly converted to the dithiocarbonate **22a** (36 mg, 77%), colorless needles (from MeOH), mp 217—218 °C. IR: 1735, 1690. ^{1}H-NMR: 7.00, 6.53 (each 1H, s, ArH), 6.18 (1H, m, H-2), 3.86 (6H), 3.44 (3H), 3.20 (3H) (each s, OMe), 1.00 (3H, t, J=7 Hz, $COOCH_2C\underline{H}_3$). MS: 537 (M^+). This was treated with Bu_3SnH to convert it into the olefin **23a** (18.6 mg, 96%), colorless prisms (from MeOH), mp 182—183 °C. IR: 1730, 1690. ^{1}H-NMR: 6.82, 6.48 (each 1H, s, ArH), 6.69, 6.13 (each 1H, d, J=10 Hz, H-1 and H-2), 3.82, 3.76, 3.48, 3.20 (each 3H, s, OMe), 0.86 (3H, t, J=8 Hz, $COOCH_2C\underline{H}_3$). MS: 431 (M^+). In the $CDCl_3$ solution, **23a** changed gradually into **24a**. ^{1}H-NMR: 6.82, 6.48 (each 1H, s, ArH), 6.33 (1H, d, J=10 Hz, H-1), 5.95 (1H, dd, J=10, 2 Hz, H-2), 4.72 (1H, d, J=2 Hz, H-4), 3.82, 3.76, 3.54 (each 3H, s, OMe), 0.86 (3H, t, J=8 Hz, $COOCH_2C\underline{H}_3$). This was hydrolyzed as above to the conjugated ketone **25a** (96% from **23a**), colorless prisms (from ether), mp 150—151 °C. ^{1}H-NMR: 7.26 (1H, d, J=12 Hz, H-1), 6.54, 6.50 (each 1H, s, ArH), 6.38 (1H, d, J=12 Hz, H-2), 3.82, 3.68 (each 3H, s, OMe), 0.84 (3H, t, J=8 Hz, $COOCH_2C\underline{H}_3$). MS: 385 (M^+). *Anal.* Calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.61; H, 5.89; N, 3.62.

Transformation of 21c to 15,16-Dimethoxy-3,8-dioxo-Δ^1-6βH-erythrinan (25c) The alcohol **21c** (390 mg) was converted to the dithiocarbonate **22c** as described above. This was heated with AIBN (15 mg) and Bu_3SnH (2.5 ml) in toluene (50 ml) at 90 °C for 1 h under an Ar atmosphere.

Chromatography of the product gave **23c** as an oil, which was dissolved in acetone (25 ml) and treated with 2% HCl (25 ml) for 10 min at room temperature to give **25c** (220 mg, 68% from **21c**) as colorless needles (from CH_2Cl_2–MeOH), mp 176—178 °C. IR: 1690, 1675. ^{1}H-NMR: 7.00 (1H, dd, J=10.5, 4.5 Hz, H-1), 6.61, 6.55 (each 1H, s, ArH), 6.26 (1H, dd, J=10.5, 1.5 Hz, H-2), 3.82, 3.72 (each 3H, s, OMe). MS: 313 (M^+). *Anal.* Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 69.18; H, 6.29; N, 4.52.

Decarbomethoxylation of the Vinylogous β-Keto Ester (25b) (1) Effect of Additives (RSH): A mixture of **25b** (10 mg), $CaCl_2$ (24 mg, 8 eq) and RSH (1 drop) in DMSO (1 ml) was heated in a sealed tube at 140 °C for 1—3 h. The mixture was diluted with water, acidified with HCl, and extracted with $CHCl_3$. The product was separated by preparative TLC ($CHCl_3$–acetone = 10 : 1) to give the results summarized in Table II.

(2) $CaCl_2$–DMSO–*tert*-HepSH Method: A mixture of **25b** (238 mg), $CaCl_2$ (572 mg, 8 eq), and 3-ethylpentane-3-thiol (1.15 ml) in DMSO (23 ml) was heated at 140 °C for 3.3 h. After work-up as above, the product was chromatographed to give, from the benzene–acetone (5 : 1) eluate, the enone **4** (136 mg, 68%) as colorless needles (from MeOH), mp 180—184 °C. IR: 1710, 1680. ^{1}H-NMR: 6.56, 6.30 (each 1H, s, ArH), 6.06 (1H, br s, H-1), 3.82, 3.74 (each 3H, s, OMe). MS: 313 (M^+). *Anal.* Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.86; H, 6.18; N, 4.51.

(3) $MgCl_2$–DMSO–EtSH Method: A mixture of **25b** (100 mg), $MgCl_2$ (210 mg, 8 eq) and EtSH (1 ml) in DMSO (10 ml) was heated at 140 °C for 2 h and worked up as above to give **4** (24 mg, 29%) and the isomeric enone **25c** (22 mg, 26%).

The EtSH Adducts Two EtSH adducts, **27a** and **27b**, were obtained in the reaction of **25b** (160 mg) with $CaCl_2$–DMSO–EtSH at 140 °C for 2 h together with **4** (44 mg, 32%) and the starting material **25b** (53 mg). **27a** (R = Et): yield, 33 mg (17%). Colorless gum. ^{1}H-NMR: 6.52, 6.47 (each 1H, s, ArH), 3.84 (6H), 3.24 (3H) (each s, OMe), 2.72 (2H, q, J=7.5 Hz, $SC\underline{H}_2CH_3$), 1.28 (3H, t, J=7.5 Hz, $SCH_2C\underline{H}_3$). MS: 433 (M^+). **27b** (R = Et): yield, 1 mg (0.5%). Colorless gum. IR ($CHCl_3$): 1720, 1690. ^{1}H-NMR: 6.60, 6.54 (each 1H, s, ArH), 3.86, 3.85 (each 3H, s, OMe), 2.67 (2H, q, J=7.5 Hz, $SC\underline{H}_2CH_3$), 1.34 (3H, t, J=7.5 Hz, $SCH_2C\underline{H}_3$). MS: 375 (M^+).

Isomerization of the Enone 4 to the Conjugated Ketone 25c A mixture of the enone **4** (10 mg) and DBU (5 drops) in benzene (1 ml) was heated in a sealed tube at 100 °C for 1.5 h. The mixture was washed with 2% HCl and concentrated to give the conjugated ketone **25c** (10 mg, 100%).

The Dienone 30 (1) A mixture of the enone **4** (57 mg) and DDQ (288 mg, 7 eq) in dioxane (4 ml) was heated in a sealed tube at 110 °C for 5 h. The mixture was taken up into $CHCl_3$, washed with 1 N NaOH and concentrated. Chromatography of the residue gave, from the $CHCl_3$–acetone (5 : 1) eluate, the dienone **30** (16 mg, 29%) and a trienone (8 mg, 15%).[11]

(2) A mixture of the enone **4** (21 mg) and pyridinium hydrobromide perbromide (32 mg, 1.5 eq) in $CHCl_3$ (2.5 ml) was stirred for 1.5 h at room temperature. Addition of water, acidification with HCl, and extraction with $CHCl_3$ of the mixture gave, after concentration, a gummy residue, which was heated with DBU (60 mg) in benzene (4 ml) under reflux for 1 h under an Ar atmosphere. The cooled mixture was washed with HCl and concentrated. Chromatography of the product gave the dienone **30** (8 mg, 39%) as colorless prisms (from MeOH–ether), mp 192—194 °C. This product was identical with the authentic specimen described in a previous paper.[12]

Reduction of 25c The conjugated ketone **25c** (220 mg) and $CeCl_3 \cdot 7H_2O$ (1.4 g, 5.4 eq) in MeOH (10 ml) were stirred at 0 °C for 10 min, then $NaBH_4$ (378 mg) was added and the mixture was stirred for a further 1.5 h at 0 °C. The precipitated crystals (**31**, 135 mg) was collected by filtration and the filtrate, after addition of water, was extracted with $CHCl_3$. Medium pressure liquid chromatography (MPLC) of the residue from the $CHCl_3$ extract gave **32** (46 mg) and **31** (9.5 mg). Total yield: **32** (46 mg, 21%), **31** (144.5 mg, 65%).

31 (The 3α-Alcohol): Colorless needles (from MeOH), mp 285.5—287 °C. IR: 3246, 1658. ^{1}H-NMR (400 MHz, $CDCl_3$–CD_3OD): 6.66 (2H, s, ArH), 6.05 (2H, s, H-1, 2), 4.17 (1H, ddd, J=10, 5, 1 Hz, H-3), 3.99 (1H, ddd, J=13, 7, 6 Hz, H-10), 3.87, 3.78 (each 3H, s, OMe), 2.72 (1H, dd, J=16.5, 9.5 Hz, H-7), 2.40 (2H, m, H-4, 7), 1.69 (1H, dd, J=12, 10 Hz, H-4). MS: 315 (M^+), 284 (base peak). *Anal.* Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.39; H, 6.58; N, 4.28.

32 (The 3β-Alcohol): Colorless gum. IR ($CHCl_3$): 3420, 1680. ^{1}H-NMR (400 MHz): 6.69, 6.56 (each 1H, s, ArH), 5.95 (1H, dd, J=10, 1 Hz, H-2), 5.76 (1H, ddd, J=10, 4, 2 Hz, H-1), 4.29 (1H, m, H-3), 4.20 (1H, ddd, J=13.5, 7.5, 2 Hz, H-10), 3.86, 3.85 (each 3H, s, OMe), 3.26 (1H, ddd, J=13.5, 11.5, 5.5 Hz, H-10), 3.18 (1H, ddd, J=9.5, 4, 3 Hz, H-6), 3.07 (1H, ddd, J=16.5, 11.5, 5.5 Hz, H-11), 2.61 (1H, ddd, J=16.5, 5.5, 2 Hz, H-11), 2.55 (1H, dd, J=17, 9.5 Hz, H-7), 2.47 (1H, ddd, J=14, 9.5, 5 Hz, H-4e), 2.17 (1H, dd, J=17, 3 Hz, H-7), 1.89 (1H, dd, J=14, 9.5 Hz, H-4a). MS: 315 (M^+), 284 (base peak). *Anal.* Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.53; H, 6.80; N, 4.59.

3α,15,16-Trimethoxy-8-oxo-Δ^1-*cis*-erythrinan (33) A mixture of **31** (200 mg), NaH (60% oil dispersion, 508 mg), and a catalytic amount of imidazole in dioxane (50 ml) was heated under reflux for 1 h, then n-Bu_4NHSO_4 (215 mg) and iodomethane (3 ml) were added and the mixture was stirred for 3 h at 70 °C. The cooled mixture was acidified with 2% HCl, and extracted with $CHCl_3$. Concentration of the extract and chromatography of the residue gave **33** (190 mg, 91%) as colorless prisms (from MeOH–ether), mp 149—151 °C. IR: 1675. ^{1}H-NMR: 6.66 (2H, s, ArH), 6.09 (2H, s, H-1 and H-2), 3.87, 3.79, 3.33 (each 3H, s, OMe). MS: 329 (M^+). *Anal.* Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.02; H, 6.95; N, 4.32.

(±)-Erysotramidine (8-Oxoerysotrine, 5) Compound **33** (86 mg) in THF (6 ml) was treated with LDA (2.4 eq) in THF (2 ml) at −78 °C for 30 min under an Ar atmosphere, then $(PhSe)_2$ (180 mg) was added and the mixture was stirred for 20 min. The mixture was acidified with 1 N HCl and extracted with CH_2Cl_2. Concentration of the extract gave a gum, which was dissolved in MeOH–water and treated with $NaIO_4$ (560 mg) for 30 min at room temperature. Purification of the product by chromatography gave the dienoid lactam **5** (81 mg, 95%) as a gum, which was identical with (±)-erysotramidine.[12]

(±)-Erysotrine (6) Reduction of **5** in a manner previously reported[12] gave (±)-erysotrine (**6**).

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