Synthesis of Erythrina and Related Alkaloids. XXII.[1] Intramolecular Cyclization Approach. (1): New Synthetic Route to Erythrinan and Related Heterocycles and Synthesis of (±)-3-Demethoxyerythratidinone

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Heating of cycloalkanone-2-carboxylate with β-arylethylamine, and oxalylation of the resulting enamino-ester followed by Lewis acid-catalyzed intramolecular cyclization afforded various erythrinan-type heterocycles in excellent yields. This method is widely applicable not only to the synthesis of erythrinans but also to that of A-nor and A-homo analogs and ring-D variants of erythrinan. The alkoxycarbonyl group on the products was readily removed by a new decarbalkoxylation method (heating with magnesium chloride–dimethyl sulfoxide combination). Thus, starting from 2-ethoxycarbonyl-4,4-ethylenedioxy-cyclohexanone, the 2,8-dioxo-erythrinan derivative (35) was synthesized in several steps in high yield, and was readily converted to the natural *Erythrina* alkaloid, 3-demethoxyerythratidinone.

Keywords *Erythrina* alkaloid; new synthesis; 3-demethoxyerythratidinone; decarbalkoxylation; β-ketoester; magnesium chloride–dimethyl sulfoxide; *N*-acylimminium; 2-oxoerythrinan; intramolecular cyclization; dioxopyrroline

Alkaloids having a 1*H*-indolo[7*a*,1-*a*]isoquinoline ring system occurring in the plants of *Erythrina* spp. (Leguminosae) are of considerable interest because of their strong curare-like muscle relaxant action which appears after oral administration.[2] Because of their unique spiro amine structure and physiological activities, these alkaloids have been targets of synthesis for a long time. Over sixty erythrinan alkaloids are now known and they can be conveniently divided into aromatic (*e.g.* **1**—**3**) and non-aromatic (*e.g.* **4**) types based on the structure of ring D.[3] Although total synthesis of the non-aromatic alkaloids still has to be achieved, that of the aromatic alkaloids has been reported by several groups, including ours, in the past ten years.[4]

Our approach to the total synthesis of aromatic erythrinan alkaloids has involved examination of three different routes: 1) a Diels–Alder approach, 2) an intramolecular cyclization approach, and 3) a photochemical approach. All of them have successfully led to the erythrinan skeleton and thus to the natural alkaloids.[4] Details of our Diels–Alder approach have been described already.[5] In the following several papers we will present details of the intramolecular cyclization approach.

Results and Discussion

New Route to Erythrinan and Related Spiro-Type Heterocycles[6] Since the first successful synthesis of 15,16-dimethoxyerythrinan by Belleau,[7] the intramolecular cyclization of an aromatic group to an *N*-acylimminium compound derived from an acylenamine on an *N*-arylethylhydroindole structure has been widely investigated by many workers, leading to various modifications.[8,9] One of the important results of this approach is that of Mondon,[10] who demonstrated that cyclization occurs even more readily when the lactam carbonyl is placed in the potential five-membered ring instead of six-membered ring. He succeeded in preparing the methoxy compound **5**[11] which provided the key intermediate for the total synthesis of erysotrine **1**.[12]

Including this, all of the previous approaches[8] have utilized the acylenamine of the *endo* (5–6) double bond (**B**) which forms the reactive *N*-acylimminium derivative (**A**) by the action of acids (such as phosphoric acid). We considered that protonation at the double bond of acylenamines to form *N*-acylimminiums should occur more easily in the case of an *exo* double bond than an *endo* double bond for stereo-electronic reasons, and thus cyclization of the former acylenamines (**C**) to erythrinans (**D**) should proceed far more readily than that of the latter acylenamines (**B**).

Fixation of the double bond at an *exo* position would be achieved by an angular substitution, and the resulting 3,3-disubstituted dihydro-oxopyrrole should have high electrophilicity at C_2, as already shown in dioxopyrroline chemistry.[13]

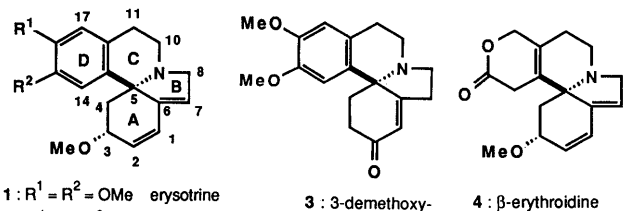


Chart 1

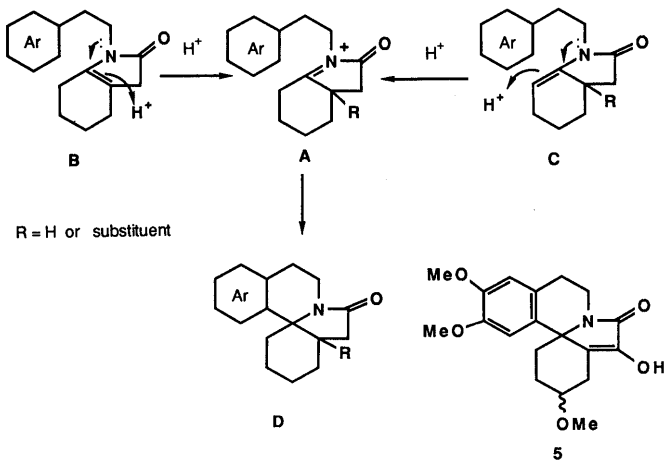


Chart 2

Based on the above considerations, we developed the following convenient route to erythrinan, which constitutes a simple and high-yield conversion of cycloalkanone-2-carboxylates (**E**) into 6-alkoxycarbonyl-erythrinan or its analogs (**H**) *via* intramolecular electrophilic cyclization of 3,3-disubstituted dioxopyrrolines (**G**). The general scheme of this transformation is given in Chart 3.

Table I. Cyclization of **8a** to **9a**

Reagent	Reaction conditions	Yield (%)
Anhyd. H_3PO_4[a]	r.t., 1.5 h	90 (86)[b]
PPE	90 °C, 1.5 h	100
$BF_3 \cdot Et_2O$, CH_2Cl_2	r.t., 3 h	100
$AgClO_4$, benzene	80 °C, 0.5 h	100
$POCl_3$, toluene	100 °C, 2.5 h	61
H_3PO_4–MeOH–H_2O[c]	Reflux, 7.5 h	35
$AgBF_4$, benzene	Reflux, 11 h	40
$AlCl_3$, Me_2S	r.t., 20 min	41
10% HCl–MeOH	Reflux, 2.5 h	0

a) Prepared by using 85% H_3PO_4 (15 g) and P_2O_5 (5 g). *b*) Overall yield from **6**. *c*) Mondon's conditions (ref. 14). r.t. = room temperature.

Heating of homoveratrylamine and ethyl cyclohexanone-2-carboxylate **6** and oxalylation of the resulting enamino-ester **7a** with oxalyl chloride at 0—5 °C afforded the dioxohydroindole derivative, or 3,3-disubstituted dioxopyrroline, **8a** in high yield. In this compound the double bond is fixed at the *exo* position to the five-membered ring due to the presence of a COOEt group at the angular position. This reactive acylenamine easily cyclizes under mild conditions, *e.g.*, on treatment with a Lewis acid such as $BF_3 \cdot Et_2O$ in CH_2Cl_2, to furnish the erythrinan **9a** in quantitative yield.

Other β-arylethylamines ($ArCH_2CH_2NH_2$ for Ar = **b**—**h**) similarly gave the erythrinans (**9b**—**9h**) as expected. Although the intermediate enamino-ester (**F**) and the dioxopyrroline (**G**) can be isolated and characterized spectroscopically, it is not necessary to isolate them. A general one-pot reaction procedure is described in the experimental section.

As the cyclizing agent, polyphosphoric acid (PPA) or

Table II. Cyclization of **G** to **H**

G	Reagent	Conditions	Product	Yield (%)	mp (°C)	IR (cm^{-1})	NMR (δ in $CDCl_3$)
8a	H_3PO_4[a]	r.t, 1.5 h	**9a**	90 (86)[c]	177—179	1770, 1740, 1700	0.70
8b	PPA[b]	80 °C, 0.5 h	**9b**	96 (93)[c]	184—185	1765, 1730, 1700	0.63
8c	PPA	80 °C, 3 h	**9c**	82 (78)[c]	171—173	1765, 1745, 1705	0.67
8d	H_3PO_4	50 °C, 0.5 h	**9d**	60	238—240	1765, 1740, 1710	0.77
8e	H_3PO_4	80 °C, 1.5 h	**9e**	31 (30)[c]	292—295	1765, 1725, 1685	0.58[e]
8f	$BF_3 \cdot Et_2O$	Reflux, 2 h	**9f**	56 (28)[c]	229—233	1765, 1740, 1705	0.65[e] (0.73)[f]
8g	PPE	50 °C, 2 h	**9g**	85	145—146	1766, 1739, 1717	0.85
8h	—[d]	—[d]	**9h**	(20)[c]	300—303	1700, 1740, 1700	0.48[e]
G ($n=5$)	H_3PO_4	r.t., 50 min	**12**	(62)[c]	153—156	1765, 1732, 1717	0.62
G ($n=7$)	H_3PO_4	50 °C, 2 h	**13**	(63)[c]	222—224	1765, 1740, 1705	0.70

a) Anhydrous H_3PO_4 (see Table I and Experimental). *b*) Prepared from 85% H_3PO_4 (33 g) and P_2O_5 (25 g), 110 °C, 6 h. *c*) Overall yield from **E**(**6**). *d*) Cyclization upon oxalylation (yield from **7h**). *e*) Solvent: DMSO-d_6. *f*) Diacetate (mp 207—208 °C) in $CDCl_3$.

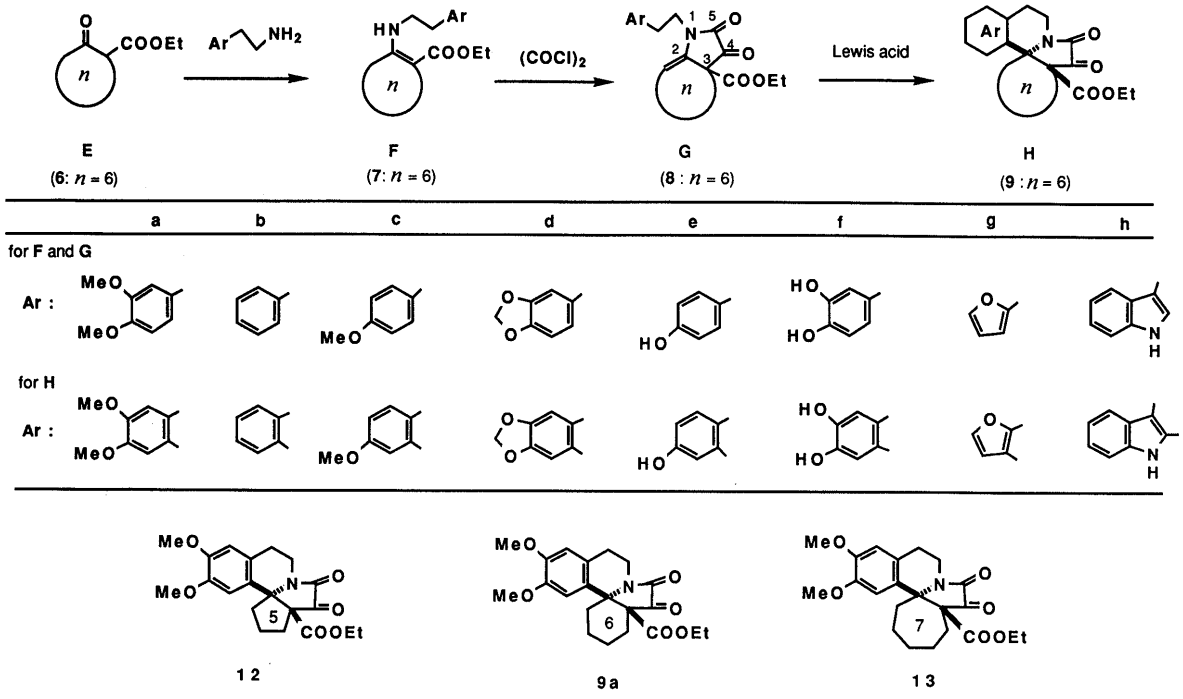


Chart 3

anhydrous phosphoric acid is most widely applicable, and cyclizes not only compounds possessing a *p*-activating substituent in the aromatic nucleus (*e.g.*, **8a** or **8d**), but also compounds which do not carry activating group at the *p*- or *o*-position (*e.g.*, **8b** or **8c**). Products from the latter group are particularly important in the synthesis of "abnormal type" erythrinan alkaloids such as **2**. Polyphosphate ester (PPE), $BF_3 \cdot Et_2O$ in methylene chloride, and $AgClO_4$ in benzene were effective only with compounds which carry a *p*-activating group (*e.g.*, **8a**, **8d**, **8f**), but were often superior to PPA or phosphoric acid as regards the yield and easiness of work-up. $BF_3 \cdot Et_2O$ in CH_2Cl_2 is recommended for the preparation of phenolic erythrinans (*e.g.* **9f**), because they are fairly soluble in water and difficult to extract with organic solvents from the reaction mixture. Evaporation of the solvent from the reaction mixture followed by chromatography of the residue made possible the separation of the phenolic products in pure form. $POCl_3$, H_3PO_4–MeOH–H_2O,[14] $AgBF_4$ in benzene, and $AlCl_3$ in Me_2S were moderately effective for cyclization of **8a** to give **9a** in 61, 35, 40, and 41% yields, respectively. Protonic acids such as 10% HCl in MeOH were not effective, and did not give any characterizable product.

The infrared (IR) spectra of the products exhibited three well separated carbonyl absorptions at 1680—1770 cm^{-1}. In the ^1H-nuclear magnetic resonance (NMR) spectra the methyl proton signal of the ethyl ester group appeared at unusually high field (δ 0.6—0.8). Compared to the signal in the compound before cyclization, it was shifted up-field by 0.4—0.5 ppm indicating that the methyl group in the products is placed in the shielding region of the aromatic nucleus (ring D), which implies the A/B-*cis* configuration of the products.

This assignment of the stereochemistry was confirmed by an alternative synthesis of **9a**. Hydrogenation of the Diels-Alder product **11**[5] of butadiene and the isoquinolino-pyrrolinedione **10** gave a compound identical with **9a**.

A-Nor- and A-homo-erythrinans, **12** and **13**, are also readily prepared by this method starting from cyclopentanone- and cycloheptanone-2-carboxylate, respectively (Chart 3). For those, an interesting relationship between ring size and cyclization speed was observed. As shown in Table III, the cyclization requires more forcing conditions when the ring size is increased from 5 to 7, thus indicating that the cyclization rate is in the order of 5 > 6 > 7 for ring A.

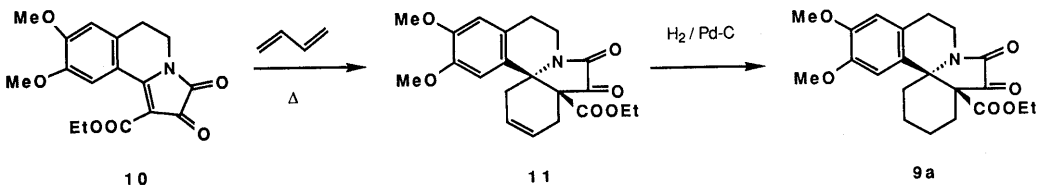
Another generalization of this method is the synthesis of erythrinan variants of ring D heterocycles. Thus, starting from 2-furylethylamine, the D-furano analog **9g** was prepared in 85% yield. From tryptamine, the D-indolo analog **9h** was directly obtained on oxalylation of the enamino-ester **7h** with oxalyl chloride. Although the overall yield of the latter transformation is 20%, it could presumably be increased by optimization of the reaction conditions.

Since the 6-ethoxycarbonyl group in the products is easily removed by our new decarbalkoxylation method (see below), the above method provides a new practical synthetic route to erythrinan type heterocycles. It has the following particular advantages: 1) the procedure involves few stepa and has a high yield, starting from easily available β-ketoesters, 2) the method is widely applicable for synthesizing all types of erythrinans, not only ring A-activated but also non-activated ones, and variants of rings A and D, and 3) phenolic erythrinans can be

TABLE III. Cyclization of **G** by Anhydrous H_3PO_4

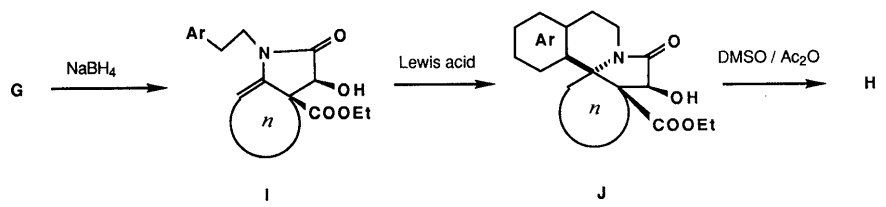
G(n)	Product	Reaction conditions	Isolated yield[a]
5	**12**	r.t., 50 min	62
6	**9a**	r.t., 1.5 h	86
7	**13**	50 °C, 2 h	63

a) Overall yield from the corresponding cycloalkanone-2-carboxylate.

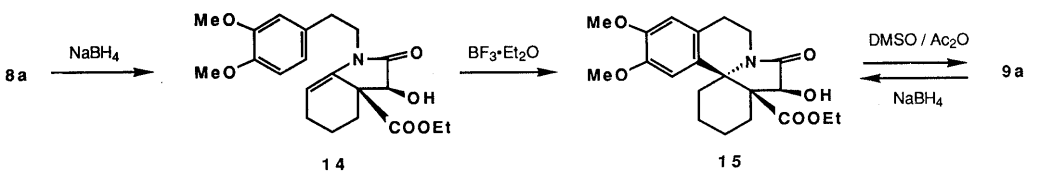


10 11 9a

Chart 4



I J

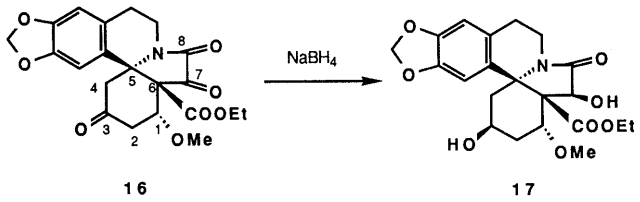


14 15

Chart 5

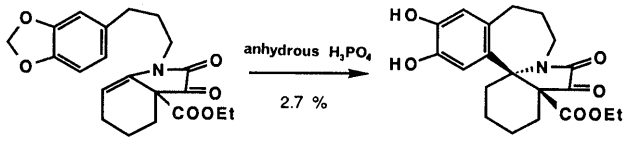
synthesized without protecting the phenolic hydroxyl groups.

An important modification of this new cyclization method applicable to compounds carrying acid sensitive functional groups was also developed as follows (Chart 5). Reduction of **G** (*e.g.* **8a**) with sodium borohydride gave the alcohol (**I**) (*e.g.* **14**) as a sole product, which cyclized far more rapidly than the corresponding ketone (**G**) to give the 7-hydroxyerythrinan (**J**) (*e.g.* **15**). This was convertible to **H** by dimethyl sulfoxide (DMSO)/Ac_2O oxidation, in high yield. Although either the ketone **G** or the alcohol **I** gave the erythrinan **H** or **J** quantitatively, the latter compound cyclized under milder conditions (for example, cyclization of **14** to **15** is completed within 30 min at room temperature in the presence of $BF_3 \cdot Et_2O$, while the cyclization of **8a** to **9a** required 3 h under the same conditions), suggesting that the conformational change of the five-membered ring on reduction greatly assists the cyclization. A successful example of this new modification is described in the next section.



16 17

Chart 6

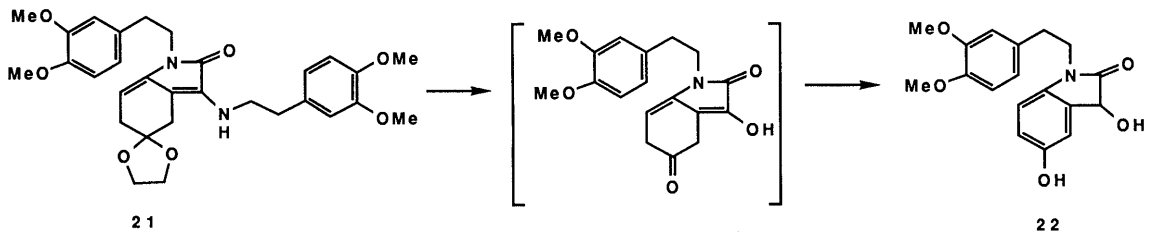


19 20

Chart 7

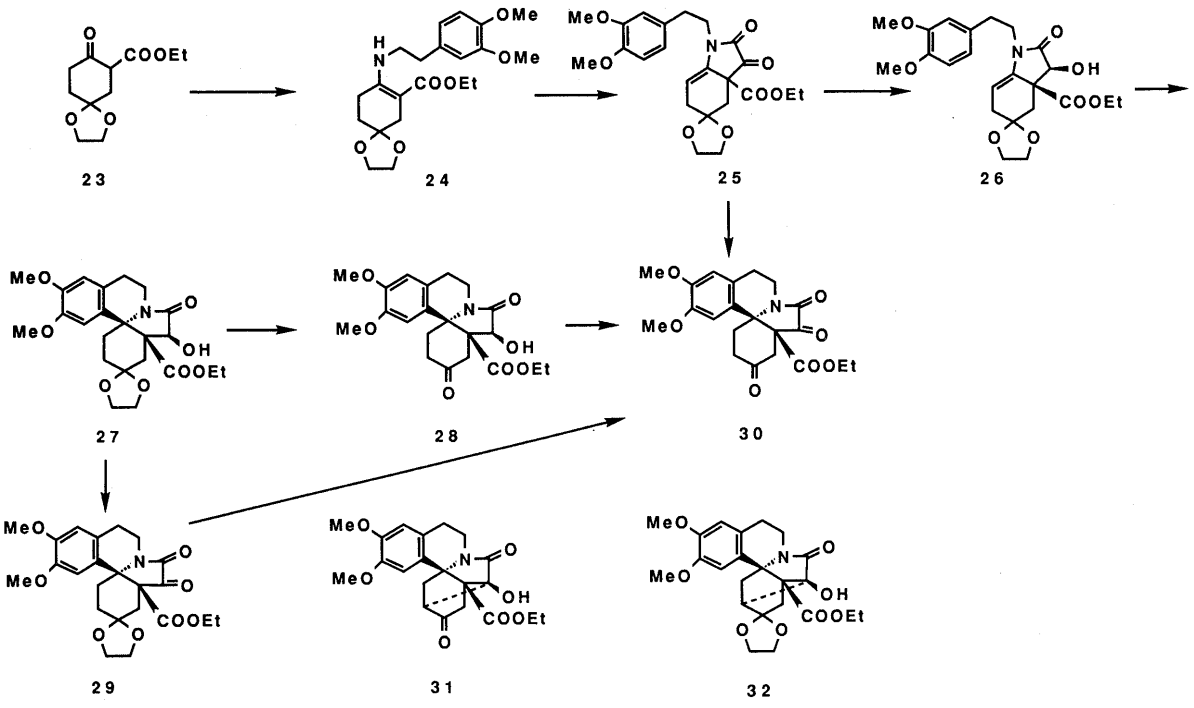
The configuration of the newly produced alcoholic group was determined as follows. Reduction of the 7,8-dione **9a** with sodium borohydride gave a single alcohol **15**, which was identical with the alcohol obtained by the cyclization of **14**. We have previously shown that sodium borohydride reduction of **16** gave the diol **17** as a sole product whose configuration was established by X-ray analysis.[15] This indicates that the hydride reduction of the 7-oxo group in 6-ethoxycarbonyl-7,8-dioxoerythrinan takes place from the opposite side of the 6-COOEt group, even when there is a 1α-methoxy group to hinder the approach of a hydride anion. This argument should also be applicable to the reduction of **9a** to **15**, which therefore must give the hydroxyl group *cis* to COOEt. This conclusion clarifies the stereochemistry of the non-cyclized compound **14**.

The above cyclization methods, however, did not give



21 22

Chart 8



23 24 25 26 27 28 30 29 31 32

Chart 9

good results when applied to *N*-arylpropylhydroindole derivatives in the hope of preparing the homoerythrinan skeleton. The only successful example which gave a homoerythrinan was the cyclization of **19** by anhydrous phosphoric acid, though the yield of **20** was poor (2.7%) and partial hydrolytic cleavage of the methylenedioxy group occurred.

Synthesis of 2-Oxoerythrinan Derivatives[16] In order to achieve total synthesis of the natural erythrinan alkaloids, it is necessary to introduce oxygenated functions at ring A. The carbonyl group is considered to be the most versatile for this purpose. Mondon *et al.*[17] reported the attempted cyclization of the ethyleneacetal **21** by using phosphoric acid. However, they obtained the aromatization product **22** only. The presence of a COOEt group at the angular position in our cyclization should prevent this undesirable aromatization and lead to the expected erythrinan.

The hydroindole **25** was prepared analogously by condensation of ethyl 4,4-ethylenedioxycyclohexanone-2-carboxylate **23** and homoveratrylamine, followed by oxalylation. Although the cyclization of **25** gave the expected 2-oxo-erythrinan derivative **30**, the yield was unsatisfactory and side reactions occurred. For example, the cyclization of the ketone **25** with $BF_3 \cdot Et_2O$ in CH_2Cl_2 took 19 h and gave a mixture of four compounds, **29** (35%), **30** (25%), **31** (4%), and **32** (3%)[18] (details will be described in a separate paper). Based on the evidence described in the above section, this side reaction was avoided by taking an alcohol **26** as the substrate.

The ketone **25** was reduced with sodium borohydride to the alcohol **26** (90%). This was cyclized by using $BF_3 \cdot Et_2O$ in CH_2Cl_2, with retention of the ethyleneacetal group, to give the expected erythrinan **27** in almost quantitative yield within 2 h at room temperature. The product **27** was oxidized with DMSO/acetic anhydride to the 7,8-dione **29** in 90% yield.[19] These products were converted to **28** and **30** on hydrolysis with 80% AcOH or 10% HCl, respectively.

Removal of the 6-COOEt Group: New Decarbalkoxylation Method ($MgCl_2$/DMSO Combination) from β-Ketoesters[20] In this section we discuss the removal of the angular COOEt group from the above synthesized erythrinans. The problem we are treating here, *i.e.* preparing ketones from β-ketoesters, is one of the basic procedures in organic synthesis.[21] If a new, efficient method is developed, it would have great synthetic value.

The 7,8-dioxoerythrinan **9a** is resistant to both acid and base hydrolysis, indicating that the ester carbonyl in this molecule is strongly hindered. On treatment with *tert*-butoxide, the ring B is opened to give an acid **33**. Treatment with $AlCl_3/Me_2S$ (HSAB combination)[22] resulted only in cleavage of the aromatic methoxy groups, giving rise to **9f**. Heating of **9a** with NaCl/DMSO (Krapcho's method)[23] afforded the desired ketone **34a** but in only 30% yield even under optimum conditions (170 °C 24 h), degradation of the product being severe under such drastic conditions.

Among the known reagents including those mentioned above, metal halides in dipolar aprotic solvents[23,24] are particularly interesting, since the reaction is carried out under neutral conditions and is thus applicable to compounds which are sensitive to acids and bases. The reaction proceeds through S_N2 attack of a halide anion at the alkyl carbon of the ester group α to the oxygen. However, the hitherto known method [use of alkali metal halides in DMSO or hexamethylphosphoric triamide (HMPA)] usually requires a high temperature thus reducing the yield owing to thermal degradation of the product, particularly for thermally unstable compounds. We thought that an appropriate bivalent cation would chelate to the two carbonyl groups of the β-ketoester moiety, thus facilitating an S_N2 attack of the halide anion at the alkyl carbon by reducing the electron density of this portion and by increasing the softness of the anion.

On examination of various metal halides in DMSO we found that halides of group IIa metals such as magnesium or calcium are excellent for this purpose; decarbalkoxylation occurs at lower temperatures and is completed within a shorter time than with the NaCl/DMSO combination. For example, heating of **9a** with excess magnesium chloride in DMSO (containing 10% EtSH) at 155—160 °C produced **34a** in 63% yield (net yield 80%). The product was identical with the compounds prepared by Mondon's procedure.[10]

Since application of this new modification of decarbalkoxylation to the various β-ketoesters and the details of experimental procedure were first reported,[20] several comments must be added here on the practice of this method. 1) For the halide, either the hydrate or the

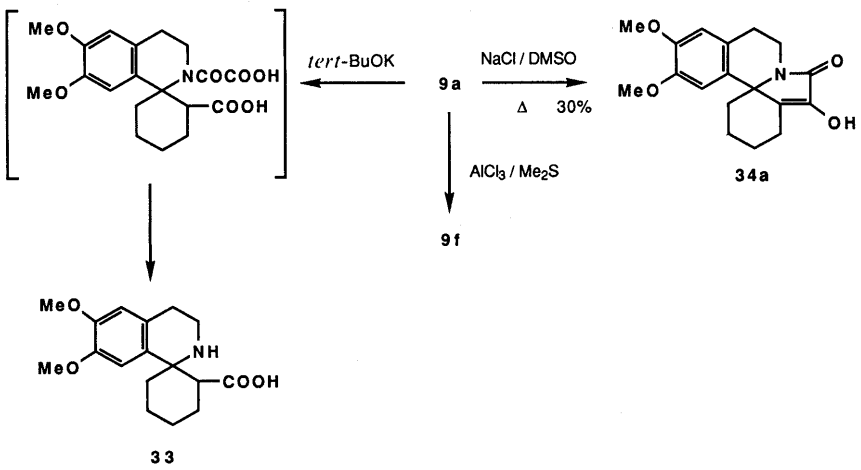


Chart 10

anhydrous salt can be used, the yields being comparable in both cases. 2) Use of HMPA, instead of DMSO, as a solvent will reduce the reaction temperature by *ca.* 10°C. However, it is often difficult to remove HMPA from the reaction mixture without distillation. DMSO allows easier work-up after the reaction, the product being extractable with $CHCl_3$ after addition of water. 3) Coloring of the reaction mixture during the reaction, which is due to aerial oxidation of the intermediary metal enolate, can hardly be avoided even by carrying out the reaction under an argon or a nitrogen atmosphere, but can be conveniently avoided by addition of *ca.* 1/10 volume of thiol (such as EtSH) to the reaction mixture.[25] 4) Alkylation of the intermediary enolate by the formed ethyl or methyl chloride was observed, though rarely, as a side reaction, when the reaction was performed in a sealed tube. This can also be avoided by addition of EtSH.

Since the reaction is specific to β-ketoesters and also to geminal esters (β-hydroxy and β-mesyloxy-esters being remained unreacted), the present method ($MgCl_2$/DMSO

Table IV. Decarbalkoxylation of β-Ketoesters by the $MgCl_2$ Method

Substrate	Solvent	Temperature (°C)	Time (h)	Product	Yield (%)
9a	HMPA	150—155	2	**34a**	73
9b	HMPA	160	3	**34b**	63
9c	DMSO	165	5	**34c**	62
9g	DMSO	160	3	**34g**	83
29	HMPA	145	2	**35**	98
11	HMPA	140—150	2	**36**	93
8a	HMPA	150—155	2	**37a**	54
8b	HMPA	150	1	**37b**	51

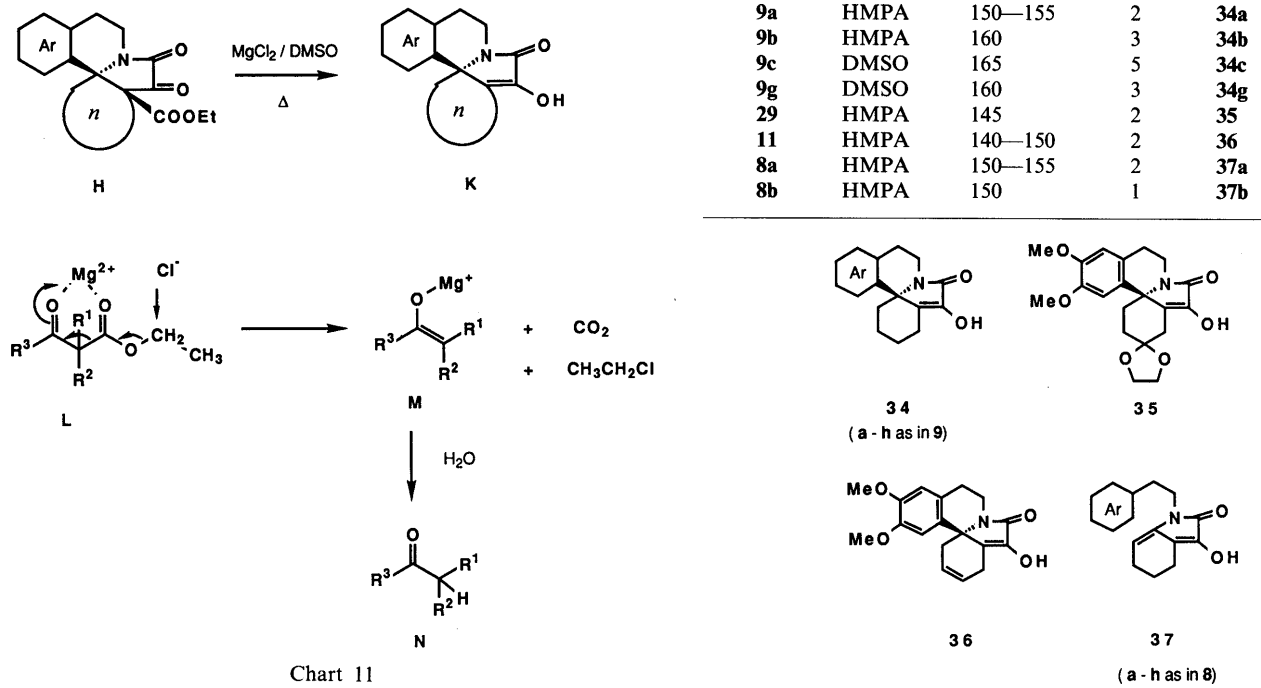


Chart 11

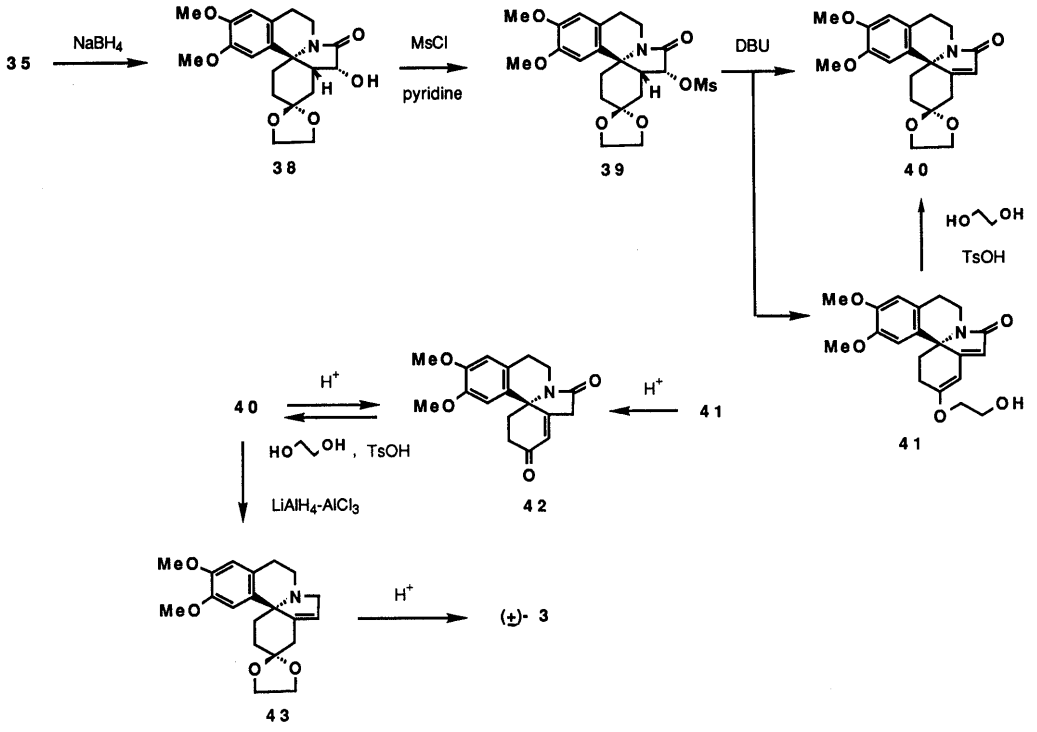


Chart 12

combination) is particularly useful for the removal of the ester group from hindered β-ketoesters in complex molecules, for which Krapcho's method (NaCl/DMSO combination) does not give satisfactory results.

The results for erythrinan derivatives are summarized in Table IV. It should be noted that deethoxycarbonylations of **29** and **11** each proceed in more than 90% yield.

Synthesis of (±)-3-Demethoxyerythratidinone[26] The decarbethoxylated compound **35** was converted as follows to (±)-3-demethoxyerythratidinone **3**, the simplest erythrinan alkaloid found in *Erythrina lithosperma* BLUME.[27]

Reduction of **35** with $NaBH_4$ gave the 6βH-7αOH derivative **38** as a single product.[28] In support of this stereochemical assignment, the derived mesylate **39** was smoothly dehydromesylated, on treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene at 160°C in a sealed tube, to give the expected olefin **40** and a dienoid lactam **41**. The structure of **40** was confirmed by the IR absorption of a five membered conjugated lactam at 1680 cm^{-1} and an olefinic proton signal (δ 5.87, 1H, br s) in the ^{1}H-NMR spectrum. Compound **41** had the same formula as **40** and showed ultraviolet (UV) absorption maxima at 233 and 285 nm and two olefinic proton signals at δ 5.87 (1H, s) and 5.63 (1H, s) in the ^{1}H-NMR spectrum. The IR spectrum showed the presence of a hydroxyl group and a conjugated lactam group at 3350 and 1650 cm^{-1}, respectively, confirming the structure **41** which was formed by the further action of the base on **40**. The assigned structure was confirmed by the quantitative conversion of **41** into **40** on treatment with *p*-TsOH and ethylene glycol. Thus, the overall yield of **40** from **39** is 89% after two reaction steps (DBU at 160°C then ethylene glycol/*p*-TsOH in benzene).

Compounds **40** and **41** gave the same conjugated ketone **42** on mild acid treatment. Migration of the double bond in this hydrolysis is indicated by the IR absorption at 1670 cm^{-1} (conjugated ketone) and NMR olefinic proton signal at δ 6.11, which appears as a triplet of $J=2$ Hz in the product **42**. Acetalization of **42** with ethylene glycol and *p*-TsOH regenerated **40**, accompanied by migration of the double bond.

The lactam carbonyl of **40** was selectively removed by reduction with $LiAlH_4$–$AlCl_3$[29] to yield the olefin **43**, in which the olefinic proton signal was shifted up-field and appeared as a multiplet. Deacetalization of **43**, again accompanied by migration of the double bond to the conjugated position, gave the amine (±)-**3** in 77% yield. The IR (in $CHCl_3$) and NMR spectra of this compound were identical with those of natural (+)-**3**-demethoxyerythratidinone kindly provided by Professor D. H. R. Barton. Thus, the total synthesis of this simplest erythrinan alkaloid in a racemic form was accomplished. The overall yield of (±)-**3** from **35** in five steps is 69%.

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, recorded on a Jasco IR-G spectrometer, and the data are given in cm^{-1}. ^{1}H-NMR spectra were taken with a JNM-PMX-60 (60 MHz) or 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; dif, diffused). 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*. 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 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 water 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.

Anhydrous H_3PO_4 was prepared from 80% H_3PO_4 (15 g) and P_2O_5 (5 g) on heating the mixture at 110 °C for 6 h. PPA was prepared from 80% H_3PO_4 (33 g) and P_2O_5 (25 g) on heating the mixture at 110 °C for 6 h. PPE was prepared as follows: a mixture of P_2O_5 (3 g), ether (3 ml), and chloroform (6 ml) was heated under reflux until the solution became clear (6 h) (filtered through a glass wool, if necessary), the solvent was evaporated off under reduced pressure, and the residual liquid was used directly.

Synthesis of Erythrinans (General Method) 2-Ethoxycarbonylcycloalkanone (1.0 g) and β-arylethylamine (1 mol eq) in EtOH (5 ml) were heated at 90—100 °C in a sealed tube for 2 h. Evaporation of the solvent left the enamino-ester (**F**), which may be purified by crystallizations from an appropriate solvent, but can be used for the next step without further purification. To a stirred benzene solution of the enamino-ester, oxalyl chloride (1.1 mol eq) in benzene was added dropwise at 0°C and stirring was continued for a further 0.5 h. Evaporation of the solvent *in vacuo* left the dioxopyrroline (**G**), which can be purified by crystallizations or by column chromatography, but can be used for the cyclization without further purification. The dioxopyrroline (**G**) was subjected to cyclization reaction by one of the following procedures to give the erythrinan (**H**) in the yield indicated in Tables I and II.

i) With PPA or anhydrous H_3PO_4: The dioxopyrroline **G** (0.5—1.5 g) was stirred with a large excess of PPA or anhydrous H_3PO_4 at an appropriate temperature (room temperature—50 °C) for 1—2 h. The mixture was poured into ice-water and extracted with $CHCl_3$. The organic layer was washed with water, dried, and concentrated to give the erythrinan (**H**) which was purified by chromatography or by crystallizations.

ii) With $BF_3 \cdot Et_2O$: Compounds **8a**, **8d**, and **8g** in CH_2Cl_2 were treated with $BF_3 \cdot Et_2O$ (2—3 mol eq) at an appropriate temperature (room temperature—50 °C) for 1—2 h. The mixture was washed with saturated aqueous $NaHCO_3$ and water, dried, and concentrated to give **9a**, **9d**, and **9g**, respectively. Compound **8f** in CH_2Cl_2 was treated with the same reagent under reflux for 2 h and the reaction mixture was poured onto the silica gel column. The column was washed with CH_2Cl_2 and eluted with AcOEt to yield **9f** (56%). Compounds **8b**, **8c**, and **8e** were recovered unchanged on treatment (reflux, 5—6 h) with this reagent.

iii) With other reagents: PPE was used in large excess as a solvent for cyclization of **8g** to **9g** (50 °C, 2 h). $AlCl_3$ was used at 1 mol eq, and $POCl_3$, $AgClO_4$, and $AgBF_4$ were used in excess, in the solvent indicated in Table I. In every case, excess reagent was decomposed by addition of water, then the reaction mixture was extracted with an appropriate organic solvent, and the extract was worked up as above to give the results indicated in Tables I and II.

The Enamino-esters **7a**: Colorless needles from EtOH, mp 60—61 °C. IR: 1640, 1585, 1515. ^{1}H-NMR: 8.92 (1H, br s, NH), 6.72 (3H, s, ArH), 4.07 (2H, q, $J=7.8$ Hz, $COOC\underline{H}_2CH_3$), 3.81 (6H, s, 2 × OMe), 3.29 (2H, br t, $J=6.8$ Hz, CH_2NH), 2.73 (2H, t, $J=6.8$ Hz, CH_2Ar), 1.22 (3H, t, $J=7.8$ Hz, $COOCH_2C\underline{H}_3$). MS: 333 (M^+).

7e: Colorless prisms from EtOH, mp 260—261 °C. IR: 3250, 1618, 1570, 1515. ^{1}H-NMR: 8.80 (1H, br s, NH), 6.93 (2H, d, $J=8.4$ Hz, ArH), 6.65 (2H, d, $J=8.4$ Hz, ArH), 4.04 (2H, q, $J=7$ Hz, $COOC\underline{H}_2CH_3$), 3.30 (2H, q, $J=6.5$ Hz, CH_2NH), 2.67 (2H, t, $J=6.5$ Hz, CH_2Ar), 1.21 (3H, t, $J=7$ Hz, $COOCH_2C\underline{H}_3$). MS: 289 (M^+).

The Dioxopyrrolines **8a**: Yield 97%. Yellow prisms from benzene–ether, mp 113—116 °C. IR: 1770, 1715, 1678. ^{1}H-NMR: 6.73 (3H, s, ArH), 5.23 (1H, dif t, $J=3.8$ Hz, =CH), 4.07 (2H, q, $J=7.1$ Hz, $COOC\underline{H}_2CH_3$), 3.83, 3.81 (each 3H, s, OMe), 1.18 (3H, t, $J=7.1$ Hz, $COOCH_2C\underline{H}_3$). *Anal.* Calcd for $C_{21}H_{25}NO_6$: C, 65.10; H, 6.50; N, 3.62. Found: C, 65.02; H, 6.41; N, 3.71.

8b: Yield 96.8%. Yellow needles from ether, mp 102—104 °C. IR: 1780, 1730, 1690. ^{1}H-NMR: 7.22 (5H, s, ArH), 5.22 (1H, t, $J=4$ Hz, =CH), 4.10 (2H, q, $J=7$ Hz, $COOC\underline{H}_2CH_3$), 1.18 (3H, t, $J=7$ Hz, $COOCH_2C\underline{H}_3$). *Anal.* Calcd for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.80; H, 6.41; N, 4.00.

8c: Yield 100%. Yellow needles from benzene–ether, mp 93—94 °C. IR: 1775, 1735, 1690. ^{1}H-NMR: 7.11 (2H, d, J=8.5 Hz, ArH), 6.78 (2H, d, J=8.5 Hz, ArH), 5.26 (1H, t, J=4 Hz, =CH), 4.10 (2H, q, J=7 Hz, $COOC\underline{H}_2CH_3$), 3.73 (3H, s, OMe), 1.18 (3H, t, J=7 Hz, $COOCH_2C\underline{H}_3$). *Anal.* Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 66.95; H, 6.22; N, 3.77.

8d: Yield 66%. Yellow gum. ^{1}H-NMR: 6.68 (3H, s, ArH), 5.87 (2H, s, OCH_2O), 5.23 (1H, dif t, J=4 Hz, =CH), 4.12 (2H, q, J=7 Hz, $COOC\underline{H}_2CH_3$), 1.20 (3H, t, J=7 Hz, $COOCH_2C\underline{H}_3$). MS: 371 (M^+).

8e: Yield 98.3%. Yellow gum. IR (film): 3450, 1775, 1740—1670, 1610. ^{1}H-NMR: 6.97 (2H, d, J=7.5 Hz, ArH), 6.70 (2H, d, J=7.5 Hz, ArH), 5.24 (1H, dif t, J=4 Hz, =CH), 4.07 (2H, q, J=7 Hz, $COOC\underline{H}_2CH_3$), 1.14 (3H, t, J=7 Hz, $COOCH_2C\underline{H}_3$). MS: 343 (M^+)

8f: Yield 49.2%. Yellow gum. IR ($CHCl_3$): 3400, 1773, 1735, 1713—1615. MS: 359 (M^+).

8g: Yield 80%. Yellow prisms from ether, mp 96—97 °C. IR: 1770, 1720, 1685. ^{1}H-NMR: 7.2—7.3, 6.2—6.3, 6.0—6.1 (each 1H, furan), 5.22 (1H, dif t, J=4 Hz, =CH), 4.10 (2H, q, J=7 Hz, $COOC\underline{H}_2CH_3$), 1.20 (3H, t, J=7 Hz, $COOCH_2C\underline{H}_3$). *Anal.* Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.04; N, 4.41. Found: C, 64.05; H, 5.92; N, 4.11.

The Erythrinans 9a: Colorless needles from MeOH, mp 177—179 °C. ^{1}H-NMR: 6.70, 6.60 (each 1H, s, ArH), 4.5—4.7 (1H, m, NCH), 3.87, 3.86 (each 3H, s, OMe), 3.61 (2H, q, J=7.3 Hz, $COOC\underline{H}_2CH_3$), and Table II. ^{13}C-NMR: 196.2 s, 167.1 s, 158.0 s, 148.6 s, 147.7 s, 128.8 s, 126.1 s, 111.5 d, 108.9 d, 63.5 s, 61.7 t, 60.4 s, 56.1 q, 56.0 q, 35.9 t, 35.4 t, 28.3 t, 23.8 t, 16.8 t, 16.5 t, 13.3 q. *Anal.* Calcd for $C_{21}H_{25}NO_6$: C, 65.10; H, 6.50; N, 3.62. Found: 64.99; H, 6.41; N, 3.44.

9b: Colorless needles from ether, mp 184—185 °C. ^{1}H-NMR: 7.13 (4H, br s, ArH), 4.4—4.8 (1H, m, NCH), 3.57 (2H, q, J=7 Hz, $COOC\underline{H}_2CH_3$), and Table II. *Anal.* Calcd for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.66; H, 6.33; N, 4.05.

9c: Colorless needles from MeOH, mp 171—173 °C. ^{1}H-NMR: 7.0—6.65 (3H, m, ArH), 4.3—4.7 (1H, m, NCH), 3.74 (3H, s, OMe), 3.55 (2H, q, J=7 Hz, $COOC\underline{H}_2CH_3$), and Table II. *Anal.* Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 66.93; H, 6.28; N, 3.69.

9d: Colorless needles from MeOH, mp 238—240 °C. ^{1}H-NMR: 6.71, 6.58 (each 1H, s, ArH), 5.94 (2H, s, OCH_2O), 4.4—4.65 (1H, m, NCH), 3.67 (2H, q, J=7.1 Hz, $COOC\underline{H}_2CH_3$), and Table II. ^{13}C-NMR: 195.9 s, 166.9 s, 158.0 s, 147.2 s, 146.5 s, 129.7 s, 127.5 s, 108.6 d, 105.7 d, 101.3 t, 63.7 s, 61.8 t, 60.5 s, 36.3 t, 35.4 t, 28.9 t, 23.3 t, 17.0 t, 16.6 t, 13.4 q. *Anal.* Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.55; H, 5.69; N, 4.04.

9e: Colorless prisms from MeOH, mp 292—295 °C. ^{1}H-NMR (DMSO-d_6): 6.97 (1H, d, J=8.2 Hz, ArH), 6.68 (1H, d, J=2.4 Hz, ArH), 6.65 (1H, dd, J=8.2, 2.4 Hz, ArH), 4.30 (1H, m, NCH), 3.46—3.61 (2H, $COOC\underline{H}_2CH_3$) and Table II. HRMS: Calcd for $C_{19}H_{21}NO_5$: 343.1418. Found: 343.1425.

9f: Colorless prisms from ether, mp 229—233 °C. ^{1}H-NMR (DMSO-d_6): 6.64, 6.49 (each 1H, s, ArH), 3.56 (2H, q, J=7 Hz, $COOC\underline{H}_2CH_3$), and Table II. HRMS: Calcd for $C_{19}H_{21}NO_6$: 359.1368. Found: 359.1365. On actylation with Ac_2O–pyridine, it gave the diacetate as colorless prisms from MeOH, mp 207—208 °C. IR: 1765, 1725, 1717. ^{1}H-NMR: 7.00, 6.95 (each 1H, s, ArH), 3.65 (2H, q, J=7 Hz, $COOC\underline{H}_2CH_3$), 2.26 (6H, s, 2×OAc), and Table II. *Anal.* Calcd for $C_{23}H_{25}NO_8$: C, 62.29; H, 5.68; N, 3.16. Found: C, 61.95; H, 5.71; N, 3.05.

9g: Colorless needles from MeOH, mp 145—147 °C. ^{1}H-NMR: 7.27, 6.30 (each 1H, d, J=2 Hz, furan), 3.6—4.0 (2H, $COOC\underline{H}_2CH_3$), and Table II. *Anal.* Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.04; N, 4.41. Found: C, 64.51; H, 6.21; N, 4.16.

9h: Colorless prisms from $CHCl_3$–MeOH, mp 300—303 °C. ^{1}H-NMR (DMSO-d_6): 6.8—7.5 (4H, ArH), 3.6—4.0 (2H, $COOC\underline{H}_2CH_3$), and Table II. *Anal.* Calcd for $C_{21}H_{22}N_2O_4 \cdot 1/2H_2O$: C, 67.18; H, 6.18; N, 7.46. Found: C, 67.02; H, 5.91; N, 7.41.

5β-Ethoxycarbonyl-14,15-dimethoxy-6,7-dioxo-A-norerythrinan 12 2-Ethoxycarbonylcyclopentanone (1 g) and homoveratrylamine (1.28 g) in EtOH (5 ml) were heated in a sealed tube at 100°C for 80 min to give the enamino-ester as a yellow gum (2.34 g, 100%). IR (film): 1730, 1655, 1600, 1515. ^{1}H-NMR: 7.41 (1H, br s, NH), 6.73—6.76 (3H, ArH), 4.11 (2H, q, J=7.3 Hz, $COOC\underline{H}_2CH_3$), 3.83 (6H, s, 2×OMe), 3.1—3.6 (2H, CH_2NH), 2.77 (2H, t, J=6.6 Hz, $ArCH_2$), 1.23 (3H, t, J=7.3, $COOCH_2C\underline{H}_3$). MS: 319 (M^+).

The enamino-ester (2.29 g) and oxalyl chloride (1.18 g) in benzene were reacted at 0 °C for 90 min, and the resulting product was treated with anhydrous H_3PO_4 (10 ml) at room temperature for 50 min to give the A-norerythrinan **12** (1.60 g, 62.2%) as colorless prisms from ether, mp 153—156 °C. ^{1}H-NMR: 6.52, 6.41 (each 1H, s, ArH), 4.5—4.8 (1H, NCH), 3.80 (3H, s, 2×OMe), 3.61 (2H, q, J=7 Hz, $COOC\underline{H}_2CH_3$), and Table II. *Anal.* Calcd for $C_{20}H_{23}NO_6$: C, 67.18; H, 6.18; N, 7.46. Found: C, 67.02; H, 5.91; N, 7.41.

7β-Ethoxycarbonyl-16,17-dimethoxy-8,9-dioxo-A-homoerythrinan 13 2-Ethoxycarbonylcycloheptanone (1g) and homoveratrylamine (1.08 g) were reacted as above to give the enamino-ester (1.84 g, 100%), as colorless needles from EtOH, mp 60—61 °C. IR: 1635, 1590, 1515, ^{1}H-NMR: 6.67 (3H, br s, ArH), 4.07 (2H, q, J=7 Hz, $COOC\underline{H}_2CH_3$), 3.80 (6H, s, 2×OMe), 3.2—3.7 (2H, CH_2NH), 2.73 (2H, br t, J=7 Hz, $ArCH_2$), 1.23 (3H, t, J=7 Hz, $COOCH_2C\underline{H}_3$). MS: 347 (M^+).

The enamino-ester (0.5 g) was converted, by the action of oxalyl chloride (0.24 g) at 0 °C for 40 min, to the dioxopyrroline (0.58 g, 100%), as yellow prisms from benzene–hexane, mp 107—109°C. IR: 1770, 1725, 1670. ^{1}H-NMR: 6.70 (3H, s, ArH), 5.3—5.6 (1H, =CH), 4.10 (2H, q, J=7 Hz, $COOC\underline{H}_2CH_3$), 3.83, 3.80 (each 3H, s, OMe), 1.20 (3H, t, J=7 Hz, $COOCH_2C\underline{H}_3$). MS: 401 (M^+).

This product (0.35 g) was treated with a large excess of anhydrous H_3PO_4 at 50°C for 2 h to give the A-homoerythrinan **13** (0.22 g, 62.9%), as colorless needles from CH_2Cl_2–MeOH, mp 222—224 °C. ^{1}H-NMR: 6.53, 6.48 (each 1H, s, ArH), 3.81, 3.78 (each 3H, s, OMe), 3.43 (2H, q, J=7 Hz, $COOC\underline{H}_2CH_3$), and Talbe II. *Anal.* Calcd for $C_{22}H_{27}NO_6$: C, 65.82; H, 6.78; N, 3.49. Found: C, 65.52; H, 6.71; N, 3.91.

Hydrogenation of 11 Compound **11**[5] (20 mg) was hydrogenated in EtOH over 5% Pd–C for 3 h and worked up in a usual manner to give **9a** (20 mg).

Synthesis of Erythrinans *via* Hydride Reduction of Dioxopyrrolines The dioxopyrroline **8a** (0.7 g) and $NaBH_4$ (70 mg) in EtOH (10 ml) were stirred at 0 °C for 20 min. The mixture was poured into water and extracted with $CHCl_3$. Concentration of the extract gave **14** as a colorless gum. IR ($CHCl_3$): 1730, 1715, 1670. ^{1}H-NMR: 6.71 (3H, s, ArH), 4.95—5.1 (1H, =CH), 4.10 (2H, q, J=7 Hz, $COOC\underline{H}_2CH_3$), 3.83, 3.81 (each 3H, s, OMe), 1.19 (3H, t, J=7 Hz, $COOCH_2C\underline{H}_3$). MS: 389 (M^+).

This product was dissolved in CH_2Cl_2 (20 ml) and treated with $BF_3 \cdot Et_2O$ (2 mol eq) at room temperature for 20 min. The mixture was washed with water and the organic layer was concentrated to give the erythrinan **15** (100%) as colorless needles from ether, mp 216—218 °C. IR: 1725, 1675. ^{1}H-NMR: 6.78, 6.50 (each 1H, s, ArH), 4.62 (1H, d, J=5 Hz, CHOH, changed to a singlet on addition of D_2O), 3.80 (6H, s, 2×OMe), 3.67 (2H, q, J=7 Hz, $COOC\underline{H}_2CH_3$), 0.78 (3H, t, J=7 Hz, $COOCH_2C\underline{H}_3$). *Anal.* Calcd for $C_{21}H_{27}NO_6$: C, 64.76; H, 6.99; N, 3.60. Found: C, 64.77; H, 6.70; N, 3.52. Treatment of **14** with PPE at 85°C for 35 min gave **15** quantitatively.

Oxidation of 15 to 9a Compound **15** (0.1 g) was stirred with DMSO (1 ml) and Ac_2O (0.5 ml) overnight at room temperature. The mixture was poured into water and extracted with $CHCl_3$. Concentration of the extract gave **9a** (94 mg).

Hydride Reduction of 9a Compound **9a** (1.87 g) in tetrahydrofuran (THF)–EtOH (1 : 1, 160 ml) was reduced with $NaBH_4$ (1 g) for 1 h at 0 °C. Dilution of the mixture with water and extraction with $CHCl_3$ gave **15** (1.84 g, 98%). The TLC behavior and ^{1}H-NMR spectrum indicated that this is a single isomer.

The *O*-mesylate was prepared by mesylation with methanesulfonyl chloride and pyridine (room temperature, 1.5 h), as colorless needles from MeOH, mp 195—197 °C (87%). IR: 1720, 1705. ^{1}H-NMR: 6.77, 6.52 (each 1H, s, ArH), 5.46 (1H, s, CHOMs), 3.81 (6H, s, 2×OMe), 3.75 (2H, q, J=7 Hz, $COOC\underline{H}_2CH_3$), 3.32 (3H, s, Ms), 0.82 (3H, t, J=7 Hz, $COOCH_2C\underline{H}_3$). *Anal.* Calcd for $C_{22}H_{29}NO_8S$: C, 56.52; H, 6.25; N, 3.00. Found: C, 56.29; H, 6.13; N, 2.89.

Attempted Synthesis of C-Homoerythrinan 2-Ethoxycarbonylcyclohexanone (0.6 g) and 3-[3,4-methylenedioxyphenyl]propylamine (0.65 g) were condensed, then oxalylated according to the general procedure to yield the dioxopyrroline **19** (0.81 g, 60%) as a yellow gum. IR (film): 1770, 1735—1710, 1685, 1675. ^{1}H-NMR: 6.62 (3H, s, ArH), 5.82 (2H, s, OCH_2O), 5.13 (1H, dif t, =CH), 4.13 (2H, q, J=7 Hz, $COOC\underline{H}_2CH_3$), 1.18 (3H, t, J=7 Hz, $COOCH_2C\underline{H}_3$). MS: 373 (M^+).

This product (0.57 g) was treated with anhydrous H_3PO_4 (5 ml) for 2.5 h at room temperature and worked up as described in the general procedure. Chromatography of the $CHCl_3$ extract (0.37 g) gave **20** (15 mg, 2.7%), mp 214—217 °C, as colorless needles from MeOH. IR: 1765, 1733, 1715. ^{1}H-NMR (DMSO-d_6): 6.25, 6.15 (each 1H, s, ArH), 4.13 (1H, m, NCH), 3.93 (2H, q, J=7Hz, $COOC\underline{H}_2CH_3$), 1.07 (3H, t, J=7 Hz, $COOCH_2C\underline{H}_3$). HRMS: Calcd for $C_{20}H_{23}NO_6$: 373.1524. Found: 373.1519.

Condensation of 2-Ethoxycarbonyl-4,4-ethylenedioxycyclohexanone and Homoveratrylamine The enamino-ester **24** was prepared in either of the

following ways in 80—97% yield. It can be used without further purification.

i) The carboxylate **23** (12 g) and homoveratrylamine (10.5 g) in EtOH (100 ml) were heated under reflux for 5 h. The solvent was evaporated off and the residual solid was washed with ether to remove the unchanged starting materials to leave **24** (15 g).

ii) Equimolar amounts of **23** and homoveratrylamine were heated neat at 110 °C for 2 h. The product was dissolved in benzene and the separated water was removed by drying over sodium sulfate. Concentration of the dried benzene solution gave **24**, as colorless prisms from MeOH–ether, mp 67—69.5 °C. IR: 1635, 1585, 1510. ^{1}H-NMR: 8.90 (1H, dif t, NH), 6.66 (3H, s, ArH), 4.04 (2H, q, J=7 Hz, $COOC\underline{H}_2CH_3$), 3.92 (4H, s, OCH_2CH_2O), 3.82, 3.79 (each 3H, s, OMe), 3.35 (2H, br q, J=7 Hz, NCH_2), 2.75 (2H, t, J=7 Hz, $ArCH_2$), 1.23 (3H, t, J=7 Hz, $COOCH_2C\underline{H}_3$). *Anal.* Calcd for $C_{21}H_{29}NO_6$: C, 64.43; H, 7.47; N, 3.58. Found: C, 64.51; H, 7.30; N. 3.31.

The Dioxopyrroline 25 The enamino-ester **24** (0.5 g) was oxalylated (0 °C, 30 min) and worked up as described in the general procedure to give **25** (0.57 g, 100%) as yellow prisms from ether, mp 106—107 °C, which can be used without further purification. IR: 1770, 1720, 1690. ^{1}H-NMR : 6.08 (3H, s, ArH), 5.20 (1H, t, J=4 Hz, =CH), 3.95 (4H, s, OCH_2CH_2O), 4.09 (2H, q, J=7 Hz, $COOC\underline{H}_2CH_3$), 3.82, 3.80 (each 3H, s, OMe), 1.24 (3H, t, J=7 Hz, $COOCH_2C\underline{H}_3$). *Anal.* Calcd for $C_{23}H_{27}NO_8$: C, 60.96; H, 6.28; N, 3.23. Found: C, 61.02; H, 6.11; N, 3.01.

Hydride Reduction of 25 Compound **25** (1 g) and $NaBH_4$ (25 mg) in EtOH (20 ml) were stirred at 0 °C for 40 min, then the solvent was evaporated off under reduced pressure. The residue was taken up into $CHCl_3$, and the organic layer was washed with water, dried, and concentrated to give **26** (0.9 g), which can be used without further purification. **26** forms colorless prisms from ether, mp 135—136 °C. IR: 3400, 1735, 1700, 1685. ^{1}H-NMR: 6.73 (3H, s, ArH), 5.07 (1H, t, J=4 Hz, =CH), 4.13 (2H, q, J=7 Hz, $COOC\underline{H}_2CH_3$), 3.93 (4H, s, OCH_2CH_2O), 3.83 (6H, s, 2×OMe), 1.22 (3H, t, J=7 Hz, $COOCH_2CH_3$). *Anal.* Calcd for $C_{23}H_{29}NO_8$: C, 60.68; H, 6.71; N. 3.22. Found: C, 60.49; H. 6.55; N, 3.21.

Cyclization of 26 to the Erythrinan 27 Compound **26** (0.9 g) and $BF_3 \cdot Et_2O$ (1 g, 3 mol eq) in CH_2Cl_2 (10 ml) were stirred at room temperature for 2 h. The mixture was diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ and water, dried, and concentrated to give the erythrinan **27** (0.9 g, 100%), mp 173—174 °C, as colorless prisms from MeOH. IR: 3200, 1725, 1690. ^{1}H-NMR: 6.62, 6.48 (each 1H, s, ArH), 5.17 (1H, d, J=5 Hz, CHOH, changed to a singlet on addition of D_2O). 3.93 (4H, s, OCH_2CH_2O), 3.78 (6H, s, 2×OMe), 0.78 (3H, t, J=7 Hz, $COOCH_2C\underline{H}_3$). *Anal.* Calcd for $C_{23}H_{29}NO_8$: C, 60.68; H, 6.71; N, 3.22. Found: C, 60.62; H, 6.57; N, 3.16.

Oxidation of 27 Compound **27** (6.93 g) in DMSO (100 ml) and Ac_2O (35 g) was stirred at room temperature overnight. The mixture was poured into ice-water (250 ml) and the mixture was stirred for 1 h. The precipitated crystals were collected by filtration and crystallized from ether to give **29** (6.5 g, 92%) as colorless needles, mp 185—186 °C. IR: 1765, 1735, 1710. ^{1}H-NMR: 6.53 (2H, s, ArH), 3.86 (4H, s, OCH_2CH_2O), 3.80 (6H, s, 2×OMe), 3.57 (2H, q, J=7 Hz, $COOC\underline{H}_2CH_3$), 0.66 (3H, t, J=7 Hz, $COOCH_2C\underline{H}_3$). *Anal.* Calcd for $C_{23}H_{27}NO_8$: C, 60.96; H, 6.28; N, 3.23. Found: C, 60.69; H, 6.29; N, 3.17.

Acid Hydrolysis of 27 Compound **27** (0.9 g) in 80% AcOH (20 ml) was heated under reflux for 3 h. Evaporation of the solvent gave **28** (0.81 g, 100%) as colorless needles from MeOH, mp 217—218°C. IR: 3200, 1728, 1710, 1685. ^{1}H-NMR: 6.52 (2H, s, ArH), 4.2—4.6 (2H, CHOH, NCH), 3.84, 3.83 (each 3H, s, OMe), 0.80 (3H, t, J=7 Hz, $COOCH_2C\underline{H}_3$). *Anal.* Calcd for $C_{21}H_{25}NO_7$: C, 62.52; H, 6.25; N, 3.47. Found: C, 62.29; H. 6.39; N, 3.22.

The 2,7,8-Trioxo Compound 30 i) Compound **28** (50 mg) was oxidized with DMSO (2 ml) and Ac_2O (1 ml) at room temperature overnight to give **30** (45 mg), as colorless prisms from $CHCl_3$, mp 282—283 °C. IR: 1770, 1742, 1720, 1703. ^{1}H-NMR: 6.62, 6.56 (each 1H, s, ArH), 3.87, 3.86 (each 3H, s, OMe), 3.66 (qd, J=7, 1.5 Hz, $COOC\underline{H}_2CH_3$), 0.73 (3H, t, J=7 Hz, $COOCH_2C\underline{H}_3$). HRMS: Calcd for $C_{21}H_{23}NO_7$: 401.1473. Found: 401.1471.

ii) Compound **29** (20 mg) was hydrolyzed with 80% AcOH (5 ml) at 90 °C for 1 h to give **30** (17 mg).

Attempted Decarbethoxylation of 9a i) Acid or Base Treatment: Compound **9a** was recovered unchanged (73—90%) on treatment with 10% HCl—MeOH at 90—100°C for 2 h in a sealed tube or 15% KOH–MeOH under reflux for 7 h.

ii) Compound **9a** (97 mg) in 5% *tert*-BuOK/*tert*-BuOH (4 ml) was heated at 90—100 °C for 2.5 h. Neutralization of the mixture with HCl and extraction with AcOEt gave **33** as a gum (86 mg). IR ($CHCl_3$): 1690. It formed a methyl ester on methylation with diazomethane in MeOH–ether. IR ($CHCl_3$): 1735. ^{1}H-NMR: 6.62, 6.38 (each 1H, s, ArH), 3.81 (6H, s, 2×OMe), 3.78 (3H, s, COOMe). MS: 305 (M^+).

iii) $AlCl_3/Me_2S$ Method: Compound **9a** (106 mg) and $AlCl_3$ (110 mg) in Me_2S (1 ml) and CH_2Cl_2 (2 ml) were stirred at room temperature for 19 d. The reaction mixture was poured onto a silica gel column and the column was washed with $CHCl_3$ to recover the starting material (27 mg). Elution of the column with AcOEt gave **9f** (41 mg) which formed prisms from $CHCl_3$, mp 273—275°C (dec.). This product was dimorphic with the sample obtained by the direct cyclization of **8f**. The derived diacetate was identical with **9f**-diacetate described above.

iv) NaCl/DMSO method: Compound **9a** (100 mg) and NaCl (20 mg) in DMSO (3 ml) and water (7 drops) were heated at 170 °C for 24 h. The mixture was diluted with water and extracted with $CHCl_3$. Concentration of the extract gave a residue, which was chromatographed in $CHCl_3$ to give the starting material (10 mg) and the decarbethoxylated product **34a** (22 mg, 27%) (see below).

Decarbalkoxylation of β-Ketoesters by $MgCl_2$/DMSO (or HMPA) (General Method) β-Ketoesters and $MgCl_2$ (anhydrous or hydrate, 5 mol eq) in DMSO or HMPA containing 1/10 volume of EtSH were heated at 140—160 °C for 1—3 h. If EtSH is not added, the reaction should be done under an argon (or nitrogen) atmosphere. The reaction mixture was worked up by one of the following procedures.

Procedure A (DMSO Solvent): The mixture was acidified with 1 N HCl and extracted with $CHCl_3$. The organic layer, on concentration, gave the decarbalkoxylated product, which was purified by chromatography or crystallizations. If the product is a diosphenol such as **K**, the following modification is recommended. The $CHCl_3$ layer was re-extracted with 2 N NaOH. Concentration of the organic layer gave the starting material (if present). Acidification and extraction of the aqueous NaOH layer with $CHCl_3$ gave, on concentration of the extract, the decarbalkoxylated product.

Procedure B (HMPA Solvent): The solvent was removed by evaporation under reduced pressue and the residue was taken up in benzene. The organic layer was washed with 1N HCl and water, and concentrated to give the product, which was purified by chromatography or crystallizations.

Decarbethoxylation of 9a i) $MgCl_2$/DMSO Method: **9a** (100 mg) and $MgCl_2$ (160 mg) in DMSO (7 ml) were heated at 155 °C for 3h under an Ar atmosphere and worked up by procedure A to give **9a** (46 mg) and **34a** (44 mg, 54%).

ii) $MgCl_2 \cdot 6H_2O$/DMSO Method: **9a** (98 mg) and $MgCl_2 \cdot 6H_2O$ (266 mg, 5 mol eq) in DMSO (7 ml) and EtSH (0.7 ml) were heated in a sealed tube at 155—160 °C for 6 h and worked up by procedure A to give **9a** (18 mg) and **34a** (50 mg, 63%).

iii) $MgCl_2$/HMPA Method: **9a** (668 mg) and $MgCl_2$ (845 mg) in HMPA (10 ml) were heated at 150—155 °C for 2 h under an Ar atmosphere and worked up by procedure B to give **34a** (400 mg, 73%).

iv) $CaCl_2 \cdot 2H_2O$/DMSO Method: **9a** (100 mg) and $CaCl_2 \cdot 2H_2O$ (5 mol eq) in DMSO (4 ml) and EtSH (0.4 ml) were heated at 150 °C for 5 h and worked up by procedure A to give **9a** (52 mg) and **34a** (35 mg, 43%).

Decarbethoxylated Products 34 **34a**: Colorless prisms from AcOEt, mp 179—180 °C (lit. mp 180°C).[14] IR: 1765(w), 1660. ^{1}H-NMR: 7.03, 6.65 (each 1H, s, ArH), 6.36 (1H, s, OH, disappeared on addition of D_2O), 3.86, 3.84 (each 3H, s, OMe). MS: 315 (M^+).

The methyl ether was prepared, by treatment of the CH_2Cl_2 solution with ethereal diazomethane, as a gum (lit. mp 132 °C).[14] IR ($CHCl_3$): 1675. ^{1}H-NMR: 6.98, 6.33 (each 1H, s, ArH), 3.93, 3.83, 3.81 (each 3H, s, OMe). MS: 329 (M^+).

The acetate was prepared by acetylation with Ac_2O–pyridine as colorless prisms from ether, mp 146—148 °C (lit. mp 148 °C).[14] IR ($CHCl_3$): 1770, 1685. ^{1}H-NMR: 7.04, 6.71 (each 1H, s, ArH), 3.88, 3.86 (each 3H, s, OMe), 2.30 (3H, s, OAc). ^{13}C-NMR: 167.6s, 163.7s, 148.3 s, 146.8 s, 145.2 s (C=C–OAc), 138.0 s (C=C–OAc), 129.8 s, 126.9 s, 112.5d, 110.4 d, 62.5 s, 56.4 q, 55.9 q, 41.4 t, 36.6 t, 28.1 t, 26.8 t, 25.2 t, 21.4 t, 20.0 q. MS: 357 (M^+).

34b: Procedure B. Colorless prisms from AcOEt, mp 213—214.5 °C. IR: 1760 (w), 1685 (sh), 1650. ^{1}H-NMR: 7.0—7.6 (4H, ArH). *Anal.* Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 74.67; H, 6.81; N, 5.74.

34c: Procedure A. Colorless prisms from AcOEt, mp 199—200 °C. IR: 3110, 1655. ^{1}H-NMR: 6.55—7.3 (3H, ArH), 3.74 (3H, s OMe). MS: 285 (M^+).

34g: Procedure A. Colorless prisms from ether, mp 234—236 °C. IR: 3300—3500, 1640. ^{1}H-NMR: 7.35, 6.60 (each 1H, d, J=2.4 Hz, furan-H),

3.30 (1H, br s, OH). *Anal.* Calcd for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.44; H, 6.21; N, 5.66.

Decarbethoxylation of 29 Compound **29** (0.52 g) in HMPA (20 ml) was heated with $MgCl_2$ (0.67 g) at 145°C for 2 h, and worked up by procedure B to give **35** (0.43 g, 98%) as colorless prisms from MeOH, mp 213—215 °C. IR: 3200, 1770, 1710. ^{1}H-NMR: 6.92 (1/3H, s, ArH), 6.88 (2/3H, s, ArH), 6.63 (1/3H, s, ArH), 6.55 (2/3H, s, ArH), 3.84 (6H, s, OMe), 4.4—3.9 (4H, OCH_2CH_2O). HRMS: Calcd for $C_{20}H_{23}NO_6$: 373.1524. Found: 373.1531. The ^{1}H-NMR spectrum indicates that this is a mixture of diketo and diosphenol forms, and the spectrum was identical with that of the corresponding compound (gum) reported by Haruna and Ito.[28]

Decarbethoxylation of the Olefinic Compound 11 Compound **11**[5,18] (930 mg) in HMPA (20 ml) was heated with $MgCl_2$ (1.1 g) at 130—140 °C for 2 h and worked up by procedure B to yield **36** (710 mg, 93%), as colorless prisms from EtOH, mp 233—235 °C. IR: 3200, 1650. ^{1}H-NMR: 6.98, 6.50 (each 1H, s, ArH), 5.6—6.15 (2H, CH=CH), 3.78, 3.73 (each 3H, s, OMe). *Anal.* Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.72; H, 6.01; N, 4.35.

Decarbethoxylation of Dioxopyrrolines 8 The dioxopyrrolines **8a** and **8b** (100—200 mg) in DMSO (7 ml) were heated with $MgCl_2$ (5 mol eq) at 150—155 °C for 1—2 h and worked up by procedure A to give **37a** and **37b**, respectively, in the yeilds indicated in Table IV. **37a**: Pale red gum (lit. unstable crystals, mp 143 °C).[14] IR: 3200, 1668. ^{1}H-NMR: 6.6—6.7 (3H, ArH), 5.38 (1H, t, J=4 Hz, =CH), 3.85 (6H, s, OMe). MS: 315 (M^+). Cyclization of this product (150 mg) with H_3PO_4–MeOH–H_2O (3:2:3, 16 ml)[14] at 100 °C for 2 h gave **34a** (85 mg), which was identical with the compound obtained by decarbethoxylation of **9a**.

37b: Pale red gum. IR ($CHCl_3$): 1680—1720. ^{1}H-NMR: 7.18 (5H, s, ArH), 5.38 (1H, t, J=4 Hz, =CH). MS: 255 (M^+).

Hydride Reduction of 35 Compound **35** (50 mg) in THF–EtOH (1:1, 10 ml) was reduced with $NaBH_4$ (8 mg) at 0 °C for 1 h. The mixture was concentrated and the residue was taken up into $CHCl_3$. The organic extract gave, on concentration, the 7α-alcohol **38** as a colorless gum (52 mg, 100%). IR ($CHCl_3$): 3370, 1690. ^{1}H-NMR: 6.69, 6.46 (each 1H, s, ArH), 4.4—3.9 (4H, OCH_2CH_2O), 3.86, 3.80 (each 3H, s, OMe). MS: 375 (M^+).

The *O*-Mesylate 39 The alcohol **38** (4.2 g) and methanesulfonyl chloride (3.86 g) in pyridine (20 ml) were stirred at room temperature for 1 h. The mixture was poured into water and extracted with $CHCl_3$. The organic layer was washed with saturated aqueous $NaHCO_3$, 5% HCl and brine, dried, and concentrated to give **39** (4.93 g, 97%), as colorless needles from MeOH, mp 118—120 °C. IR: 1710. ^{1}H-NMR: 6.55, 6.37 (each 1H, s, ArH), 4.80 (1H, d, J=7 Hz, CHOMs), 3.90 (4H, s, OCH_2CH_2O), 3.80, 3.73 (each 3H, s, OMe), 2.93 (3H, s, OMs). MS: 453 (M^+). *Anal.* Calcd for $C_{21}H_{27}NO_8S$: C, 55.62; H, 6.00; N, 3.09. Found: C, 55.74; H, 5.95; N, 2.98.

Demethanesulfonylation of 39 The *O*-mesylate **39** (0.5 g) and DBU (3.44 g) in benzene (8 ml) were heated in a sealed tube at 160 °C for 8 h. The mixture was diluted with benzene, washed with 1 N HCl and water, dried, and concentrated. The HCl and water layers were combined and again extracted with $CHCl_3$. Chromatographies of the organic extracts gave **40** (76 mg from the benzene extract, 75 mg from the $CHCl_3$ extract) from the benzene eluates and **41** (21 mg from the benzene extract, 180 mg from the $CHCl_3$ extract) from the $CHCl_3$–MeOH (10:1) eluates.

40: Total yield, 151 mg (38%). Colorless needles from Et_2O, mp 133—135.5 °C. IR: 1680. ^{1}H-NMR: 6.88, 6.58 (each 1H, s, ArH), 5.87 (1H, br s, =CH), 3.93 (4H, s, OCH_2CH_2O), 3.80 (6H, s, 2×OMe). *Anal.* Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 66.93; H, 6.53; N, 3.92.

41: Total yield, 201 mg (51%). Yellow needles from benzene, mp 200—202 °C. IR: 3350, 1650, 1610. ^{1}H-NMR: 6.90, 6.60 (each 1H, s, ArH), 5.87 (1H, s, H-7), 5.63 (1H, s, H-1), 3.95 (4H, br s, OCH_2CH_2O), 3.78, 3.70 (each 3H, s, OMe). ^{13}C-NMR: 172.4s (C-8), 164.0s (C-2), 159.7s (C-6), 148.4s (C-15), 146.9s (C-16), 128.9s (C-13), 126.7s (C-12), 115.0d (C-14), 112.2d (C-17), 100.7d (C-7), 95.5d (C-1), 69.7t, 60.7t (OCH_2CH_2OH), 64.6s (C-5), 56.9q, 56.0q (OMe), 37.2t (C-10), 33.5t (C-11), 27.0t (C-3), 27.4t (C-4). UV:233 (14900), 385 (13700). *Anal.* Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.38; H, 6.45; N, 4.20.

Acid Hydrolysis of 40 and 41 i) Compound **40** (75 mg) in 5% HCl (12 ml) and acetone (12 ml) was heated at 60 °C for 30 min. After addition of water, the mixture was extracted with $CHCl_3$. The extract gave **42** as an oil (66 mg). IR ($CHCl_3$): 1685, 1670. ^{1}H-NMR: 6.57, 6.41 (each 1H, s, ArH), 6.11 (1H, t, J=2 Hz, =CH), 3.78, 3.70 (each 3H, s, OMe). MS: 313 (M^+), 254 (base peak).

ii) **41** (89 mg) gave, on similar hydrolysis, **42** (76 mg, 97%).

Acetalization of 41 and 42 i) Compound **41** (102 mg), ethylene glycol (2.5 ml), and *p*-TsOH (catalytic amount) in benzene (25 ml) were heated under reflux for 8 h. The cooled mixture was washed with water, dried, and concentrated to give the residue which was chromatographed to afford the acetal **40** (70 mg, 69%) and the starting material **41** (30 mg).

ii) Acetalization of **42** (25 mg) in a similar manner gave **40** (18 mg, 63%).

$LiAlH_4$–$AlCl_3$ Reduction of 40 $AlCl_3$ (sublimed, 1.8 g) in ether (10 ml) was added in a solution of $LiAlH_4$ (540 mg) in THF (15 ml) at −15°C and the mixture was stirred for 30 min. The resulting solution (10 ml) was added to a stirred solution of **40** (313 mg) in THF (10 ml). Stirring was continued for 1 h at room temperature, then the mixture was diluted with ether and the excess reagent was decomposed by addition of 5% aqueous NH_4OH. The ethereal layer was washed with water, dried over anhydrous K_2CO_3, and concentrated to give the amine **43** as an oil (260 mg, 87%). IR: no CO absorption. ^{1}H-NMR: 6.83, 6.48 (each 1H, s, ArH), 5.53 (1H, m, =CH), 3.90 (4H, s, OCH_2CH_2O), 3.77 (6H, s, 2×OMe). MS: 343 (M^+), 242 (base peak).

(±)-3-Demethoxyerythratidinone 3 The amine **43** (260 mg) in 5% HCl (10 ml) and acetone (15 ml) was heated under reflux for 1 h. The cooled mixture was basified with 28% ammonia and extracted with $CHCl_3$. The organic layer was washed with water, dried over anhydrous K_2CO_3, and concentrated to give **3** (201 mg, 77%). It formed colorless needles from benzene–light petroleum, mp 101—102 °C. IR ($CHCl_3$): 1665. ^{1}H-NMR: 6.65, 6.57 (1H, s, ArH), 6.11 (1H, t, J=1.8 Hz, =CH), 3.86, 3.75 (each 3H, s, OMe). HRMS: Calcd for $C_{18}H_{21}NO_3$: 299.1520. Found: 299.1526. The ^{1}H-NMR spectrum of this compound was superimposable on that of (+)-demethoxyerythratidinone provided by Prof. D. H. R. Barton.

The picrate formed yellow needles from acetone–MeOH, mp 250—252 °C. ^{1}H-NMR: 8.88 (2H, s, ArH of picric acid), 6.78 6.57 (each 1H, s, ArH), 6.37 (1H, t, J=1.8 Hz, =CH), 3.91, 3.78 (each 3H, s, OMe). *Anal.* Calcd for $C_{18}H_{21}NO_3 \cdot C_6H_3N_3O_7$: C, 54.54; H, 4.58; N, 10.60. Found: C, 54.36; H, 4.49; N, 10.33.

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