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Chiral Synthesis of *Erythrina* Alkaloids. (2).[1] Synthesis of *enantio*-Type Erythrinan Alkaloids Utilizing Asymmetric Acylation and Kinetic Resolution of Diastereomers[2]

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Oxalylation of the enamino-ester 13 derived from the L-dopa derivative 12 gave the dioxopyrroline of (6*S*)-configuration (15A) diastereoselectively (50—60% diastereomer excess). This was converted to a mixture of erythrinans of (5*S*,6*R*,7*R*,10*S*) and (5*R*,6*S*,7*S*,10*S*) configuration by cyclization with $BF_3 \cdot Et_2O$. The de of the major diastereomer (A) was elevated to 82% by application of a kinetic resolution of diastereomers (partial hydrolysis of the ethylene acetal group), where the minor diastereomer (B) was hydrolyzed more rapidly. The acetal 17A which remained unchanged was converted, in several steps, to the *enantio*-type erythrinan alkaloid, (−)-3-demethoxyerythratidinone (−)-7, and also to the 1,7-cycloerythrinan (−)-9, a key intermediate to *Erythrina* alkaloids. The more easily hydrolyzable diastereomer (B) was similarly converted to the enantiomer (+)-9. The mechanism of partial racemization, sometimes observed in the product, is discussed.

Keywords *enantio*-erythrinan alkaloid; chiral synthesis; asymmetric acylation; kinetic resolution; 3-demethoxyerythratidinone; 1,7-cycloerythrinan

Erythrinan alkaloids have been successfully synthesized in racemic forms by three routes[3]: (1) Diels–Alder route,[4] (2) intramolecular cyclization route,[5] and (3) photochemical route.[6] Recently a chiral synthesis of the natural alkaloid, (+)-erysotrine, by route (1) was achieved under super high pressure.[7] In this paper, we describe the chiral synthesis of erythrinan alkaloids by route (2) starting from the same amine as in route (1), which preferentially gave the alkaloids of *enantio*-type.[2]

Results and Discussion

Synthesis of Chiral Erythrinans by Asymmetric Intramolecular Acylation Followed by Kinetic Resolution of Diastereomers Synthesis of the erythrinan skeleton in a racemic form was accomplished starting from an arylethylamine (**1**) by condensation with the β-ketoester (**2**) and oxalylation of the resulting enamino-ester (**3**), followed by borohydride reduction, and cyclization with $BF_3 \cdot Et_2O$ (Chart 1).[5a] Thus, from a chiral arylethylamine (such as **12**), a similar sequence of reactions would give the chiral dioxopyroline (**15**) and then the erythrinan (**17**) diastereoselectively.

Enantiomerically pure 3,4-dimethoxyphenylalanine derivative (**12a**) was prepared from L-dopa (**11**) by the method of Shrecker and Hartwell.[8] Condensation of **12a** with ethyl 5,5-ethylenedioxy-2-oxocyclohexanecarboxylate (**2**) gave a chiral enamino-ester (**13a**) in 98% yield. Oxalylation of **13a** gave a mixture of two diastereomers (**15a**), where the major product (**A**) was the (6*S*,10*S*)-isomer and the minor product (**B**) was the (6*R*,10*S*)-isomer, based on the evidence described in the next section. Chemical yield and diastereomer excess (de) in this intramolecular acylation depended on the reaction conditions (solvent and temperature), the results being shown in Tables I, II, and III. In tetrahydrofuran (THF), dimethoxyethane (DME), CH_2Cl_2, and toluene, both the

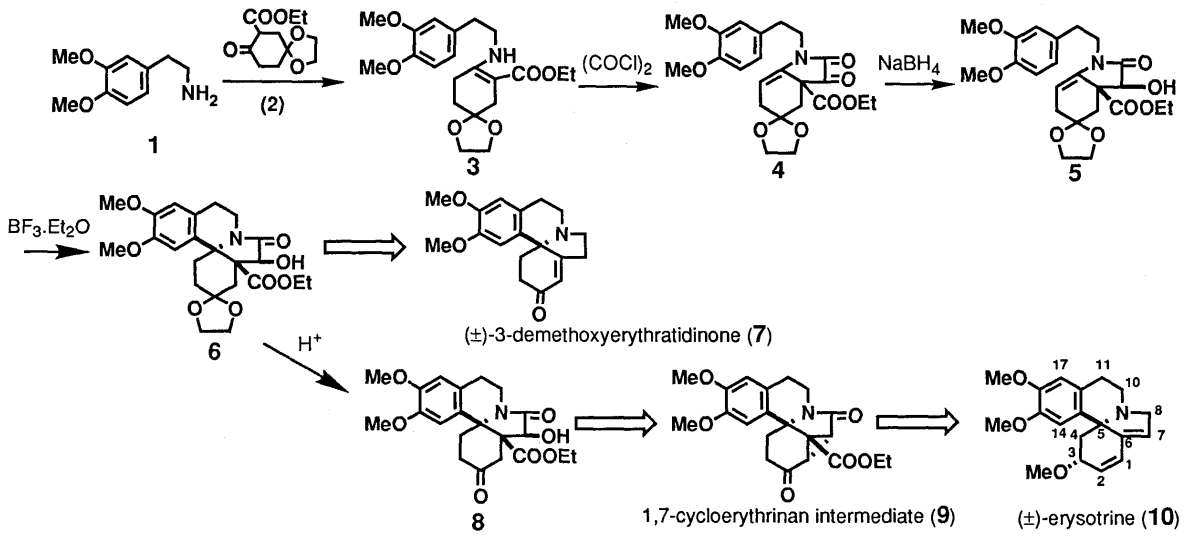


Chart 1. Reported Synthetic Route to Erythrinan Alkaloids (Racemic) by Cyclization Method[5]

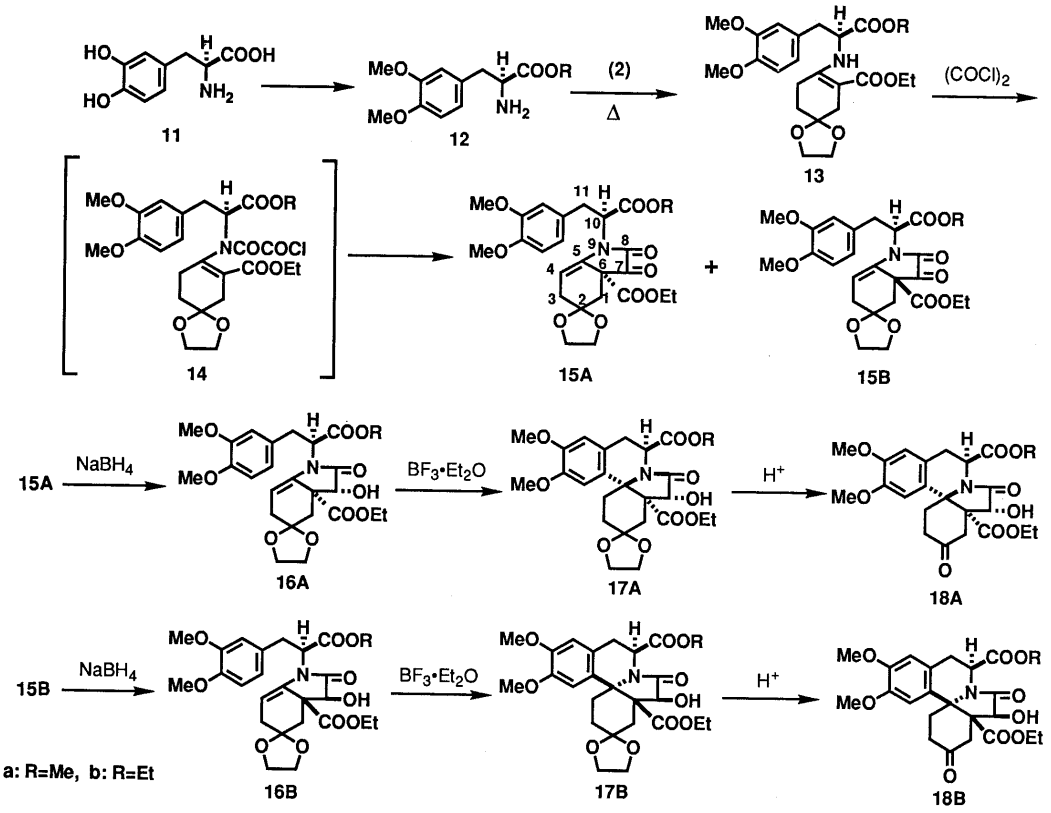


Chart 2. Synthesis of Chiral Erythrinans by Asymmetric Intramolecular Acylation

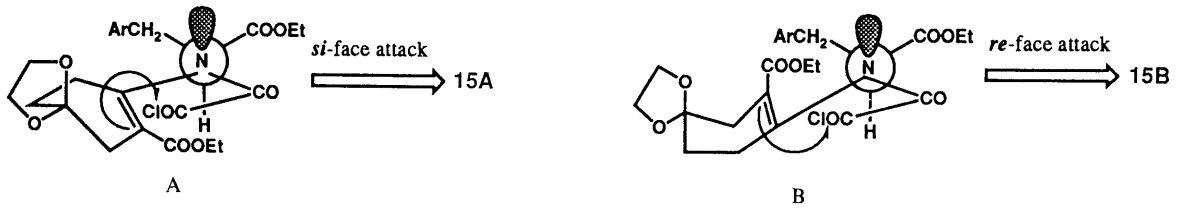


Fig. 1. Two Transition States in Dioxopyrroline Formation

TABLE I. Influence of Solvent on the Reaction **13a→15a**[a]

Solvent	Yield (%)	% de[b]	$[\alpha]_D$ ($CHCl_3$)
Et_2O	96	52	−112° (c=0.966)
THF	19	44	−104° (c=0.42)
DME	10	47	−108° (c=0.55)
CH_2Cl_2	42	38	−97° (c=0.92)
Toluene	29	40	−100° (c=0.64)

a) Sample: 100 mg. Conditions: −15 °C, 50 min. *b*) Determined from the 400 MHz ^{1}H-NMR spectra.

TABLE II. Influence of Temperature on the Reaction **13a→15a**[a]

Temp. (°C)	Yield (%)	% de[b]	$[\alpha]_D$ ($CHCl_3$)
0	72	37	−95° (c=0.692)
−15	96	52	−112° (c=0.966)
−18	80	62	−126° (c=0.45)
−20	45	55	−114° (c=0.62)
−40	No reaction		

a) Sample: 100 mg. Solvent: Et_2O. *b*) Determined from the 400 MHz ^{1}H-NMR spectra.

TABLE III. Influence of Base and Solvent on the Reaction **13b→15b**[a]

Base (eq)	Solvent	Temp. (°C)	$(COCl)_2$ (eq)	Yield (%)	% de[b]	**15b** (**A**:**B**)
None	Et_2O	−15	3	90	50	3.0:1
n-BuLi (1)	THF	−78→0	3	41	29	1.8:1
n-BuLi (1)+HMPA	Et_2O	−78→0	3	36	26	1.7:1
NaH (1.2)	Et_2O	0	3	60	51	3.1:1
Et_3N (1.2)	Et_2O	0	3	73	50	3.0:1
Et_3N (3)	Et_2O	r.t.	1.2	43	23	1.6:1
Et_3N (3)	CH_2Cl_2	r.t.	1.8	66	23	1.6:1
Et_3N (3)	Toluene	r.t.	1.8	58	52	3.2:1

a) Sample: 100 mg. *b*) Determined from the 500 MHz ^{1}H-NMR spectra. r.t. = room temperature.

yield and diastereoselectivity were poor, but the best result was obtained in the reaction in ether at −15 °C to −18 °C, where chemical yield and diastereomer excess were 80—90% and 50—60%, respectively. Oxalylation at room temperature in the presence of a base (Et_3N) in CH_2Cl_2 resulted in a poor diastereomer ratio (**A**:**B**=1.6:1, 23% de), and that in toluene gave a result similar to the reaction

in ether at −15 °C without the base (52% de).

The reaction proceeds in two steps: *N*-acylation followed by *C*-acylation. Asymmetric induction occurs at the second step. Although the energy difference between the two transition states, A and B, was not *a priori* evaluated, the above result shows that the *si*-face attack is preferred to the *re*-face attack (Fig. 1).

The dioxopyrroline (**15a**) of 55% de was reduced with $NaBH_4$, and cyclized with $BF_3 \cdot Et_2O$ in CH_2Cl_2 to yield the erythrinan (**17a**) as a diastereoisomeric mixture of **A** and **B**. This mixture was hydrolyzed with 5% HCl to a mixture of **18a** (**A** and **B**) in an overall chemical yield of 91% with the same diastereomer excess (55% de, **A** : **B** = 3.4 : 1) as in **15a**. Since previous studies[5a] on compounds which lack the C_{10}-COOR group had revealed that $NaBH_4$ reduction of the C_7-ketone gave the alcohol *cis* to the C_6-COOEt group and the following Lewis acid-catalyzed cyclization always gave *cis*-fused erythrinans, the stereochemistries of the products are (5*S*,6*R*,7*R*,10*S*) and (5*R*,6*S*,7*S*,10*S*) for **A** and **B**, respectively.

The chiral erythrinan (**17a**) was thus obtained from the methyl ester (**12a**). However, the diastereomer excess in the product was still unsatisfactory (50—60%) and the two diastereomers could not be separated chromatographically. Moreover, a partial randomization of the ester group in the product due to an ester exchange reaction, that prevented purification of the diastereomers, was sometimes observed (the compounds have different kinds of ester groups in the molecule). These disadvantages were avoided by using the corresponding ethyl ester.

The ethyl ester (**12b**), prepared from L-dopa (**11**), was converted to the erythrinan (**17b**) as in the case of corresponding methyl ester in an overall chemical yield of 64% and diastereomer excess of 51%. The derived ketone (**18b**) was easily separable from **17b** by silica gel chromatography. Importantly, it was also found that, when the acetal was partially hydrolyzed, the resulting ketone (**18b**) and the unchanged acetal (**17b**) had a remarkable difference in diastereomer ratios, suggesting an appreciable difference in the hydrolysis rate between the two diastereomers. This means that the kinetic resolution of two diastereomers is possible, when an appropriate hydrolytic condition is adopted. Thus, the acetal (**17b**) of 51% de was hydrolyzed with 5% HCl–acetone (1 : 1) for 3 h at 27 °C to give the acetal (**17b**) of 83% de (**A** : **B** = 11 : 1) and the ketone (**18b**) of −5% de (**A** : **B** = 1 : 1.1), thus elevating the diastereomer excess of the major (5*S*,6*R*,7*R*,10*S*)-isomer to 83% from the original 51% by kinetically controlled acid hydrolysis of the acetal mixture.

This large difference in hydrolysis rates between the two diastereomers may be attributed to the conformational difference of the diastereomers. Assuming that the C_{10}-COOR groups in both isomers are equatorially oriented,[9] the (5*R*,6*S*,7*S*,10*S*)-isomer (**B**) would have a severe steric interaction between the ethylene acetal and C_6-COOEt groups, thus destabilizing the compound and accelerating the hydrolytic cleavage of the ethylene acetal group.

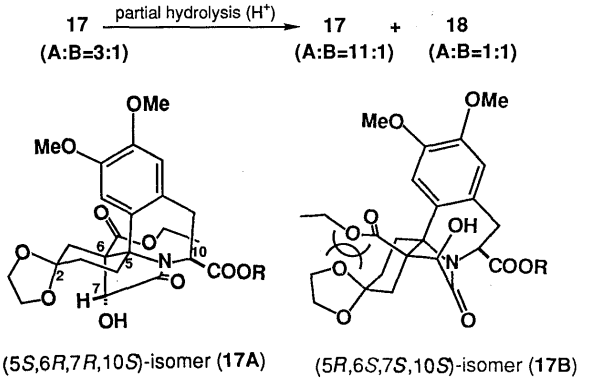
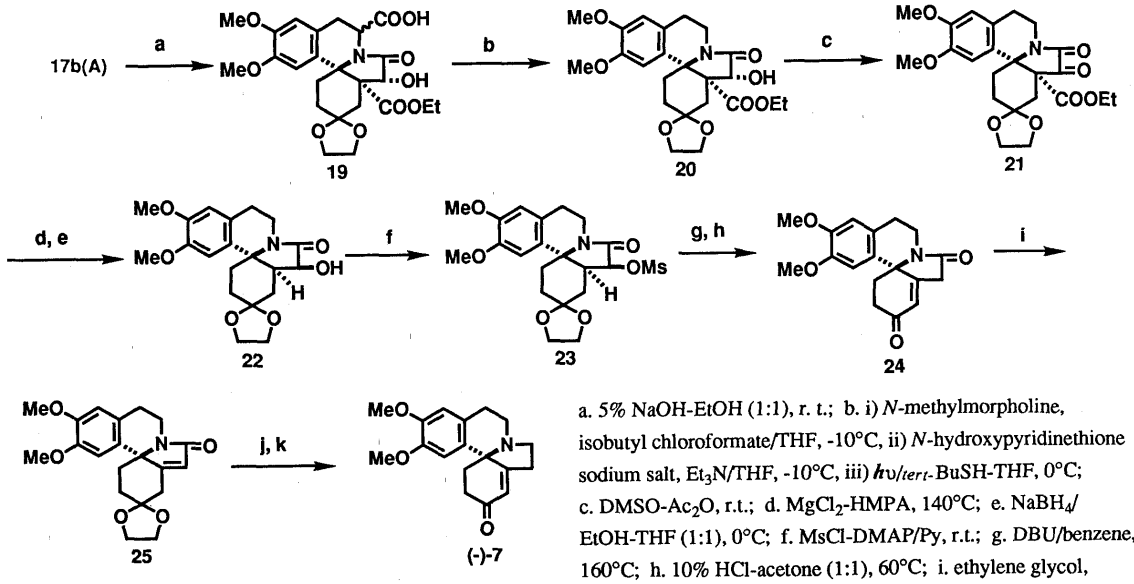


Fig. 2. Conformational Difference between Two Diastereomers in Partial Hydrolysis of the Acetal Group



a. 5% NaOH-EtOH (1:1), r. t.; b. i) *N*-methylmorpholine, isobutyl chloroformate/THF, -10°C, ii) *N*-hydroxypyridinethione sodium salt, Et_3N/THF, -10°C, iii) *hν*/*tert*-BuSH-THF, 0°C; c. DMSO-Ac_2O, r.t.; d. $MgCl_2$-HMPA, 140°C; e. $NaBH_4$/EtOH-THF (1:1), 0°C; f. MsCl-DMAP/Py, r.t.; g. DBU/benzene, 160°C; h. 10% HCl-acetone (1:1), 60°C; i. ethylene glycol, *p*-TsOH/benzene, reflux; j. $LiAlH_4$-$AlCl_3$ (3:1)/ Et_2O-THF, 0°C; k. 5% HCl-acetone (3:5), 80°C.

Chart 3. Synthesis of (−)-3-Demethoxyerythratidinone (−)-7

Synthesis of (−)-3-Demethoxyerythratidinone, an Enantiomer of the Natural Alkaloid The acetal (**17b-A**) of 83% de was converted to (−)-demethoxyerythratidinone [(−)-**7**], an enantiomer of the natural alkaloid, as follows, thus proving its absolute configuration.

Alkaline hydrolysis of **17b-A** followed by decarboxylation of the resulting acid (**19**) by Barton's method[10] gave the decarboxylated product (**20**), which was identical with the corresponding racemic compound[5a] in terms of ^{1}H-NMR spectrum and TLC behavior.

This was converted into (−)-**7** in the same manner as reported for the racemic compound,[5a] as being shown in Chart 3 (see also Experimental). The final product, obtained in the overall yield of 15% from **17b**, was identical with the alkaloid 3-demethoxyerythratidinone ($[\alpha]_D$ +325°),[11] in terms of spectral data and TLC behavior except that it had an opposite sign of the optical rotation ($[\alpha]_D$ −236°), thus indicating that the present synthesis gave the erythrinan of *enantio*-type. The $[\alpha]_D$ value revealed that it has 73% enantiomer excess (ee).[12]

Synthesis of the (−)-1,7-Cycloerythrinan [(−)-9], a Key Intermediate to *enantio*-Erythrinan Alkaloids Next, we converted **17b** to the 1,7-cycloerythrinan derivative [(−)-**9**], a key intermediate to dienoid type erythrinan alkaloids.

Acid deacetalization of another lot of **17b** (**A**) (83% de) followed by alkaline hydrolysis and decarboxylation by Barton's method[10] gave the ketone [(+)-**8**] in 49% yield from **17b**. The optical rotation of this product ($[\alpha]_D$ +75°) indicated its optical purity to be 64% ee by comparison with the optically pure isomer ($[\alpha]_D$ +117.1°) (see below), implying 19% loss of optical purity expected from the diastereomer excess of the original compound.[12] Recrystallizations of this product from MeOH–Et_2O resulted in the compound of 85% ee ($[\alpha]_D$ +100°) as prisms of mp 264—267 °C.

The compound (+)-**8** of 70% ee was mesylated and then demesylated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give the 1,7-cycloerythrinan derivative [(−)-**9**] (mp 184—186 °C, $[\alpha]_D$ −28.4°) in 92% yield from (+)-**8**. It was identical with the corresponding racemic compound[5b] in terms of ^{1}H-NMR spectrum and TLC behavior. This should be the (1*R*,5*S*,6*S*,7*S*)-isomer. Since (±)-**9** has already been converted to (±)-erysotrine (**10**), a similar sequence of reactions would give the alkaloid of *enantio*-type.

Synthesis of the (+)-1,7-Cycloerythrinan [(+)-9], a Key Intermediate to Natural Erythrinan Alkaloids Erythrinan derivatives with the natural type configuration were also available from the dioxopyrroline mixture of poor diastereomer ratio by utilizing kinetic resolution. The dioxopyrroline (**15b**) of 29% de (**A** : **B** = 1.8 : 1) was reduced with $NaBH_4$, and then cyclized to **17b**. Partial hydrolysis of **17b** with 5% HCl–acetone (1 : 1) at 27 °C for 3 h gave the ketone (**18b**) and the acetal (**17b**) in 50% and 47% yield, with de of 13% (**A** < **B**) and 83% (**A** > **B**), respectively. The ketone (**18b**) was reconverted to the acetal, which was against subjected to the partial hydrolysis to yield the ketone (**18b-B**) of 66% de and the acetal of 26% de in 40% and 53% yields, respectively. Recrystallizations of the ketone (**18b-B**) furnished colorless needles, mp 189—193 °C, 90% de.

This ketone was hydrolyzed to the acid and then decarboxylated to yield (−)-**8**, whose $[\alpha]_D$ was −71.3°, thus indicating 61% ee. The enantiomer excess was raised to 81% ee (mp 265—267 °C, $[\alpha]_D$ −94.1°) by several recrystallizations. This was converted to the (+)-1,7-cycloerythrinan (+)-**9** (mp 187—188 °C, $[\alpha]_D$ +33.9°) as described for the (−)-isomer. The product belongs to the (1*S*,5*R*,6*R*,7*R*) stereochemical series, as do the natural alkaloids.

Partial Racemization in the Cyclization Product If both diastereomers used in the above synthesis were enantiomerically homogeneous, the enantiomer excesses of the resulting products should reflect the diastereomer excess of the starting materials, respectively. However, in each case, a partial loss of enantiomer excess (compared to the diastereomer excesses of the starting materials) in the cyclization products were observed (Table IV). This implies that the starting diastereomers were not enantiomerically pure but already partially contained enantiomers. In this section, we discuss how and at what stage this racemization took place.

When the ketone (**18**) of 55% de was hydrolyzed with 5% NaOH–EtOH, two carboxylic acids, colorless needles (mp 249 °C) and a gum, were obtained in the total yield of 97%. The crystalline acid gave a methyl ester (colorless prisms, mp 237—239 °C) and proved to be a racemate,[13] since it showed no CD absorption at 250—600 nm and gave the racemic (±)-**8** (mp 215—217 °C) on alkaline hydrolysis followed by decarboxylation. Chromatography on a chiral column confirmed this conclusion: it gave two

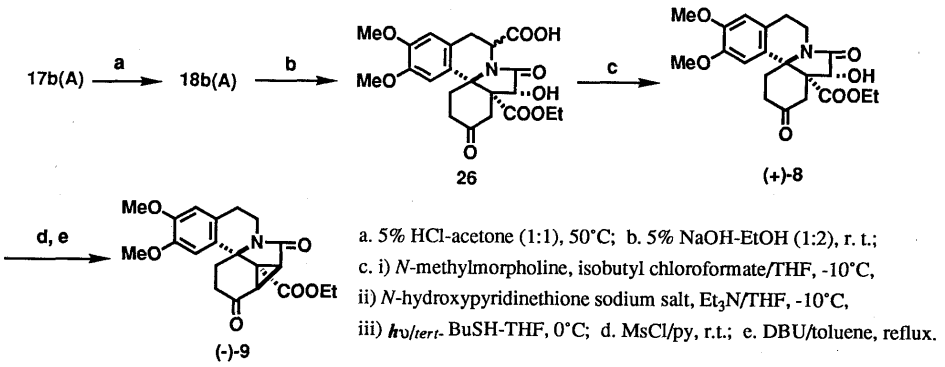
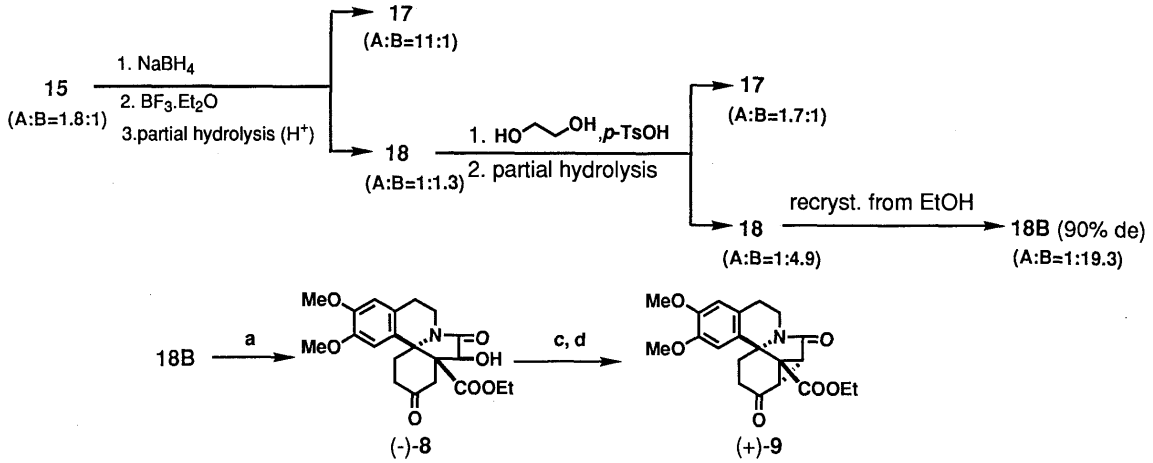


Chart 4. Synthesis of the (−)-1,7-Cycloerythrinan (−)-**9**



a. 5% NaOH-EtOH (1:1), r.t.; b. i) *N*-methylmorpholine, isobutyl chloroformate/THF, -15°C, ii) *N*-hydroxypyridinethione sodium salt, Et_3N/THF, -15°C, iii) *hν*/*tert*-BuSH-THF, 0°C; c. MsCl/py, r.t.; d. DBU/toluene, reflux.

Chart 5. Synthesis of the (+)-1,7-Cycloerythrinan (+)-**9**

TABLE IV. Enantiomer Content in Erythrinans Obtained by BF_3 Treatment

Erythrinan Diastereomer de		Prepared by BF_3 reflux	Enantiomer content calcd from		Product ee
			MTPA ester	ee of product	
18A	83%[b]	15 min	Trace	—[c]	
18A (17A)	83%[b]	1 h	5%	(5%)[d]	(−)-7 73%
18A	83%[b]	2 h	—	9.5%	(+)-**8** 64%
18A	55%[a]	3.5 h	14%	—	
18B	90%[b]	1.5 h	—	14.5%	(−)-**8** 61%

a) From the methyl ester **18a**. *b*) From the ethyl ester **18b**. *c*) Not determined. *d*) Data from **17b-A**.

peaks in a ratio of 1 : 1. An X-ray analysis of this methyl ester revealed its structure as (±)-**18a-A** (Fig. 3).

On the other hand, the gummy acid ($[\alpha]_D$ +4.5°) gave the methyl ester of mp 102—103 °C ($[\alpha]_D$ +10.8°) (on chromatography and several crystallizations after methylation with diazomethane), whose ^{1}H-NMR spectrum was superimposable on that of the above racemic methyl ester. This product was proved to be enantiomerically homogeneous by chiral column chromatography, and was converted, on alkaline hydrolysis followed by decarboxylation, to optically active (+)-**8** (mp 263—266 °C, $[\alpha]_D$ +117.1°).

The ratio of the above racemic and chiral acids was *ca.* 1 : 1. These results can be explained in terms of stereochemical inversion of C_{10}-COOR: epimerization of this group in either of the diastereomers **A** and **B** produces the enantiomers of their counterparts, *i.e.*, (−)-**A** from (+)-**B** and (−)-**B** from (+)-**A**, thus resulting in a partial racemization of the product, when two diastereomers coexist. The above result also shows that the diastereomer **A** is thermodynamically more stable than the diastereomer **B**, since (+)-**B** epimerized into (−)-**A** on alkaline hydrolysis, but not *vice versa*.

For **17** and **18**, at what stage does the partial racemization occur? Since the alcohol (**14**) regenerated the ketone (**15**) on oxidation without noticeable loss of the original optical activity, and since the acetal (**17**) was hydrolyzed to the ketone (**18**) without significant change of its diastereomer excess, steps in hydride reduction and acid hydrolysis were excluded. If the latter step participated in the epimerization [such as **B** to (−)-**A**], the diastereomer excess (in the ^{1}H-NMR spectrum) of the product should be changed. Thus, the most probable step is the BF_3-catalyzed cyclization of dioxopyrroline (**16**) to the erythrinan (**17**). Supporting this consideration, the ketone (**18a**) of 55% de, obtained by cyclization with $BF_3 \cdot Et_2O$ for 3.5 h at refluxing temperature followed by complete acid hydrolysis, was proved to contain *ca.* 14% of an enantiomer in the major isomer (**A**), because the derived α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) ester showed peaks ascribable to the enantiomer in a ratio of 6 : 1, together with the peaks derived from the isomer (**B**).

As is apparent from Table IV, the content of the enantiomer ratio increased with increase of refluxing time with BF_3. It was negligibly small for erythrinans obtained by reflux for 15 min, but was 5% at 1 h. (−)-3-Demethoxyerythratidinone [(−)-**7**] derived from this specimen showed 73% ee, in agreement with the decrease (10%) calculated from the enantiomer content (5%, obtained from the ^{1}H-NMR spectrum of the MTPA-ester of the derived ketone **18b-A**).

The enantiomer excess of erythrinan (−)-**8** derived from **18b-B** of 90% de (natural configuration) was 61%, suggesting the presence of 14.5% enantiomer in **18b-B**. This indicates that epimerization from **A** to (−)-**B** is also possible under BF_3 catalysis. Thus, we conclude that partial epimerization of the C_{10}-COOR group, under these conditions, is reversible and probably occurs at the stage of the iminium salt, which may be accelerating the epimerization.

Conclusion

Starting from the same chiral precursor (*S*)-(+)-**12**, the

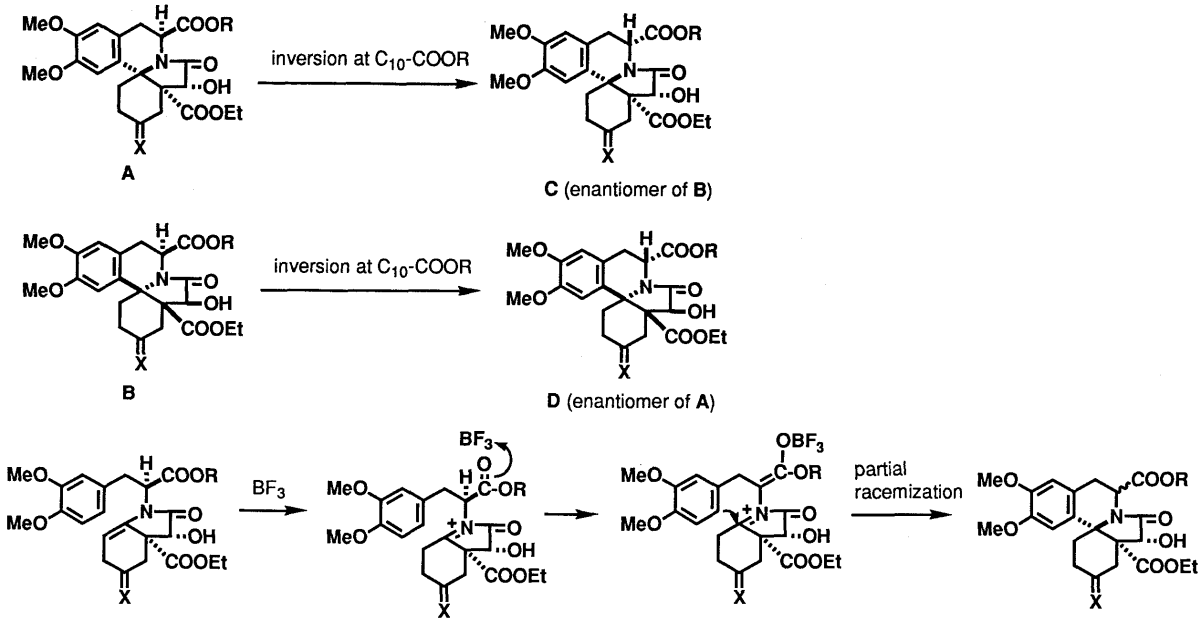


Chart 6. Mechanism of Partial Racemization in Erythrinan Synthesis

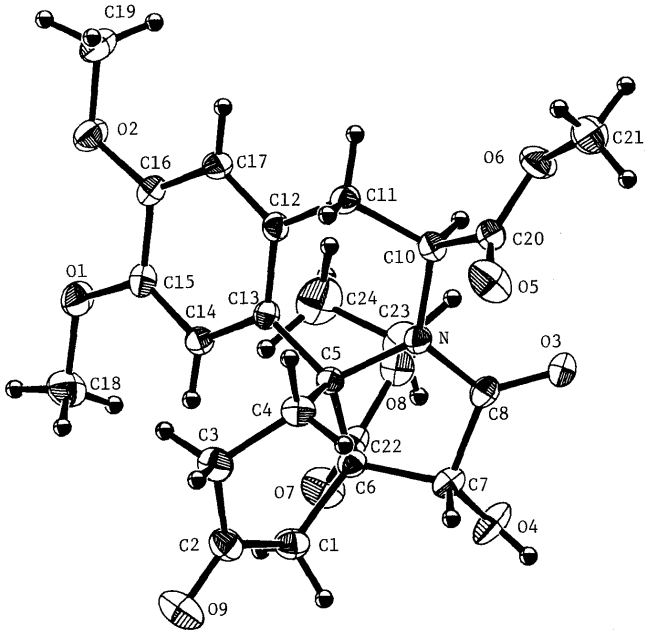


Fig. 3. ORTEP Drawing of the Racemic Methyl Ester (±)-**18a-A**

present results indicate that it is possible to synthesize both enantiomers of aromatic type *Erythrina* alkaloids in chiral forms: the Diels–Alder method gives the alkaloids of the (+)-series and the intramolecular cyclization method gives those of the (−)-series.

Experimental

Unless otherwise noted, the following procedures were adopted. Melting points were determined on a Yanaco micro hot stage melting point apparatus and are uncorrected. Infrared (IR) spectra were taken in $CHCl_3$ solutions and are given in cm^{-1}. ^{1}H-NMR spectra were taken on a JEOL-GX 500 (500 MHz) spectrometer in $CDCl_3$ solutions with tetramethylsilane as an internal standard, and the chemical shifts are given in δ values. Diastereomer ratio was calculated by comparisons of the signal intensities of the two diastereomers. Mass spectra (MS) and high-resolution MS (HRMS) were taken with a Hitachi M-80 machine and are indicated at *m/z*. $[\alpha]_D$'s were measured on a Nihon Bunko DIP-181 polarimeter. Preparative thin-layer chromatography (PTLC) was performed with precoated silica gel plates, Merck 60 F_{254} (1 mm thick). Column chromatography was carried out with silica gel (Wakogel C-200) and flash chromatography with Merck Kieselgel 60. For TLC, Merck precoated plates GF_{254} were used and spots were monitored under ultraviolet light (UV, 254 nm), then developed by spraying 1% $Ce(SO_4)_2$ in 10% H_2SO_4 and heating the plate at 100 °C until coloration took place. MTPA esters were prepared by a usual method: treatment of the substrate (10—20 mg) in pyridine (5—10 drops) and CCl_4 (5—10 drops) with (*S*)-(−)-MTPA chloride (20—40 mg) and 4,4-dimethylaminopyridine (DMAP) (2—3 mg) at room temperature for 20—50 h under an Ar atmosphere, followed by purification of the product by flash chromatography. 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 by comparisons of TLC behavior and IR and NMR spectra.

(*S*)-(+)-3,4-Dimethoxyphenylalanine Methyl Ester (12a) The hydrochloride of **12a** was prepared according to the reported method,[8] as colorless fine needles from EtOH–Et_2O, mp 157—159 °C. $[\alpha]_D^{20}$ +6.6° (c=1.0, MeOH. [lit. mp 158—159 °C, $[\alpha]_D^{20}$ +6.8° (c=2.0, MeOH)].[8] The free base (**12a**) was obtained from the hydrochloride by basification with K_2CO_3 and extraction with CH_2Cl_2, as colorless needles from hexane, mp 58—59 °C, $[\alpha]_D^{20}$ +23.4° (c=1.0, MeOH), and was used without further purification. Enantiomeric purity of **12a** was confirmed by converting it (21 mg) into the MTPA-amide (34 mg, 89%), a colorless gum. ^{1}H-NMR: 7.22—7.33 (5H, m, PhH), 6.96 (1H, d, J=8 Hz, NH), 6.60 (1H, d, J=8 Hz, ArH), 6.40 (1H, dd, J=8, 2 Hz, ArH), 6.39 (1H, d, J=2 Hz, ArH), 4.93 (1H, ddd, J=8, 7.5, 5 Hz, NHC<u>H</u>), 3.77, 3.69, 3.56, 3.38 (each 3H, s, OMe), 3.03 (1H, dd, J=14, 5 Hz, one of $ArCH_2$), 2.90 (1H, dd, J=14, 7.5 Hz, one of $ArCH_2$).

(*S*)-(+)-3,4-Dimethoxyphenylalanine Ethyl Ester (12b) This was prepared as described for the methyl ester with some modification of the reported procedure.[8] A mixture of L-dopa **11** (20 g), 100% formic acid (180 ml) and Ac_2O (60 ml) was stirred at room temperature for 3 h, and then concentrated. The residue was dissolved in water (100 ml) and again concentrated *in vacuo*. This operation was repeated six times. To the residue in water (30 ml), 10 N NaOH (30 ml) and dimethyl sulfate (19 ml) were added at 0 °C, and the mixture was stirred at room temperature for 30 min. Dimethyl sulfate (19 ml) was added three times (total 76 ml) at 30 min intervals, while the temperature was kept below 40 °C and the pH at 5—9 [by addition of 10 N NaOH (58 ml)]. After addition of dimethyl sulfate, the mixture was made alkaline by addition of 10 N NaOH (10 ml), stirred for 30 min, then acidified with 8 N H_2SO_4 (21 ml) at pH 2, and extracted with AcOEt. The residue obtained by evaporation of AcOEt was dissolved in EtOH (260 ml) containing acetyl chloride (56 ml), and the mixture was stirred at room temperature for 3 h, then

concentrated *in vacuo*. Crystallizations of the product from EtOH–Et_2O gave **12b**-HCl (19.5 g, 66% from **11**), as colorless needles, mp 176—178 °C. $[\alpha]_D^{22}$ +18.4° (c=1.0, EtOH). ^{1}H-NMR: 8.71 (3H, br s, NH_3^+), 6.91 (1H, d, J=1.5 Hz, ArH), 6.82 (1H, dd, J=7.8, 1.5 Hz, ArH), 6.77 (1H, d, J=7.8 Hz, ArH), 4.37 (1H, dd, J=6.9, 5.5 Hz, NHC$\underline{H}$), 4.12 (2H, q, J=7.1 Hz, COOC$\underline{H}_2$CH$_3$), 3.86, 3.81 (each 3H, s, OMe), 3.39 (1H, dd, J=14.2, 5.5 Hz, one of ArCH_2), 3.30 (1H, dd, J=14.2, 6.9 Hz, one of ArCH_2), 1.17 (3H, t, J=7.1 Hz, COOCH$_2$C$\underline{H}_3$). *Anal.* Calcd for $C_{13}H_{20}ClNO_4$: C, 53.89; H, 6.96; N, 4.83. Found: C, 53.67; H, 7.00; N, 4.77.

The free base (**12b**): Colorless gum. $[\alpha]_D^{22}$ +14.5° (c=1.0, EtOH). ^{1}H-NMR: 6.81 (1H, d, J=8.3 Hz, ArH), 6.74 (1H, dd, J=8.3, 2.0 Hz, ArH), 6.73 (1H, br s, ArH), 4.18 (2H, q, J=7.1 Hz, COOC$\underline{H}_2$CH$_3$), 3.87, 3.86 (each 3H, s, OMe), 3.70 (1H, dd, J=7.8, 5.4 Hz, NHC$\underline{H}$), 3.04 (1H, dd, J=13.7, 5.4 Hz, one of ArCH_2), 2.83 (1H, dd, J=13.7, 7.8 Hz, one of ArCH_2), 1.75 (2H, br s, NH_2), 1.27 (3H, t, J=7.1 Hz, COOCH$_2$C$\underline{H}_3$). HRMS: Calcd for $C_{13}H_{19}NO_4$ (M^+): 253.1313. Found: 253.1307.

The MTPA-amide: Colorless gum. It was enantiomerically pure. ^{1}H-NMR: 7.30—7.39 (5H, m, ArH), 7.06 (1H, d, J=8.8 Hz, NH), 6.67 (1H, d, J=7.8 Hz, ArH), 6.50 (1H, d, J=2.4 Hz, ArH), 6.48 (1H, s, ArH), 4.98 (1H, ddd, J=8.8, 7.3, 5.4 Hz, NHC$\underline{H}$), 3.84, 3.64 (each 3H, s, OMe), 3.45 (1H, d, J=1.5 Hz, OMe), 3.11 (1H, dd, J=14.2, 5.4 Hz, one of ArCH_2), 2.98 (1H, dd, J=14.2, 7.3 Hz, one of ArCH_2), 1.28 (3H, t, J=7.1 Hz, COOCH$_2$C$\underline{H}_3$).

The Enamino-ester (13a) A mixture of the methyl ester **12a** (1.456 g, 6.1 mmol) and ethyl 5,5-ethylenedioxy-2-oxocyclohexanecarboxylate (**2**, 1.389 g, 6.1 mmol) in MeOH (20 ml) was heated in a sealed tube at 150 °C for 6 h and concentrated. Flash chromatography of the product (benzene : AcOEt = 5 : 1) gave **13a** (2.679 g, 98%) as a colorless gum. $[\alpha]_D^{25}$ −106° (c=1.01, $CHCl_3$). IR: 1731, 1639, 1594. ^{1}H-NMR: 6.75 (3H, br s, ArH), 4.12 (2H, q, J=7 Hz, COOC$\underline{H}_2$CH$_3$), 3.95 (4H, m, OC$\underline{H}_2$C$\underline{H}_2$O), 3.86 (6H), 3.71 (3H) (each s, OMe), 3.00 (2H, m, ArCH_2), 2.47 (2H, br s, H-1), 2.21 (2H, br t, J=7 Hz, H-4), 1.74 (2H, br t, J=7 Hz, H-3), 1.25 (3H, t, J=7 Hz, COOCH$_2$C$\underline{H}_3$). HRMS: Calcd for $C_{23}H_{31}NO_8$ (M^+): 449.2050. Found: 449.2061.

The Enamino-ester (13b) This was prepared from the ethyl ester **12b** (3.029 g, 12 mmol) and **2** (2.7 g, 11.8 mmol) in EtOH (20 ml) as in the case of methyl ester. Chromatography of the product (hexane : AcOEt = 1 : 1) gave **13b** (5.16 g, 94%) as a colorless gum. $[\alpha]_D^{24}$ −92° (c=0.98, $CHCl_3$). IR: 1727, 1639, 1591. ^{1}H-NMR: 9.36 (1H, d, J=8.8 Hz, NH), 6.77 (3H, m, ArH), 4.25 (1H, dt, J=8.8, 5.4 Hz, NHC$\underline{H}$), 4.11, 4.17 (each 2H, q, J=7.1 Hz, COOC$\underline{H}_2$CH$_3$), 3.95 (4H, m, OC$\underline{H}_2$C$\underline{H}_2$O), 3.86, 3.85 (each 3H, s, OMe), 3.06 (1H, dd, J=13.7, 4.9 Hz, one of ArCH_2), 2.94 (1H, dd, J=13.7, 8.3 Hz, one of ArCH_2), 2.47 (2H, br s, H-1), 2.33, 2.17 (each 1H, dt, J=17.1, 6.8 Hz, H-4), 1.68 (2H, m, H-3), 1.25, 1.23 (each 3H, t, J=7.1 Hz, COOCH$_2$C$\underline{H}_3$). HRMS: Calcd for $C_{24}H_{33}NO_8$ (M^+): 463.2204. Found: 463.2214.

Oxalylation of the Enamino-ester (13a) (1) A solution of oxalyl chloride (3 eq) in an appropriate dried solvent was added to a solution of **13a** (100 mg) in the same solvent (5 ml) at 0°, −15°, −18°, −20°, −40°, or −70 °C, and the mixture was stirred for 50 min at the same temperature under an Ar atmosphere. It was poured into ice-water, and extracted with Et_2O, and the product was purified by PTLC (AcOEt : benzene = 2 : 1) to give **15a**. See Tables I and II.

(2) A solution of oxalyl chloride (4.04 g, 31.8 mmol) in Et_2O (100 ml) was added to a solution of **13a** (4.769 g, 10.6 mmol) in Et_2O (350 ml) at −15 °C to −18 °C over a period of 1.5 h under an Ar atmosphere. After 10 min, the mixture was poured into ice-water and extracted with Et_2O. The extract was washed with saturated $NaHCO_3$ solution and brine, dried, and concentrated *in vacuo*. Purification of the residue by flash chromatography (AcOEt : benzene = 1 : 1) gave **15a** (4.325 g, 83%) as a yellow gum (**A** : **B** = 3.4 : 1). $[\alpha]_D^{25}$ −123° (c=0.902, $CHCl_3$). IR: 1777, 1736, 1684. HRMS: Calcd for $C_{25}H_{29}NO_{10}$ (M^+): 503.1792. Found: 503.1796. ^{1}H-NMR: for **A**: 5.20 (1H, dd, J=7, 6 Hz, H-10), 5.08 (1H, t, J=5 Hz, H-4), 3.84 (6H), 3.75 (3H) (each s, OMe), 3.60 (1H, dd, J=14, 6 Hz, one of H-11), 3.29 (1H, dd, J=14, 7 Hz, one of H-11), 2.91, 1.75 (each 1H, d, J=13 Hz, H-1), 2.50, 2.41 (each 1H, dd, J=16, 5 Hz, H-3), 1.20 (3H, t, J=7 Hz, COOCH$_2$C$\underline{H}_3$); for **B**: 5.30 (1H, t, J=5 Hz, H-4), 4.93 (1H, t, J=7 Hz, H-10), 3.84 (6H), 3.78 (3H), (each s, OMe), 3.58, 3.38 (each 1H, dd, J=15, 7 Hz, H-11), 2.92, 1.81 (each 1H, d, J=13 Hz, H-1), 2.53 (2H, m, H-3), 1.20 (3H, t, J=7 Hz, COOCH$_2$C$\underline{H}_3$).

Oxalylation of the Enamino-ester (13b) (1) The ethyl ester **13b** (5.16 g, 11.14 mmol) in Et_2O (260 ml) was oxalylated with oxalyl chloride (2.85 ml, 33.4 mmol) in Et_2O (90 ml) at −10 °C for 1.5 h as described above to give **15b** as a gum (**A** : **B** = 3 : 1). IR: 1777, 1734, 1693. HRMS: Calcd for $C_{26}H_{31}NO_{10}$ (M^+): 517.1946. Found: 517.1926. ^{1}H-NMR: for **A**: 5.20 (1H, dd, J=8.3, 6.4 Hz, H-10), 5.10 (1H, t, J=4.2 Hz, H-4), 3.84 (6H, s, OMe), 3.60 (1H, dd, J=14.7, 6.4 Hz, H-11), 3.29 (1H, dd, J=14.7, 8.3 Hz, H-11), 2.91, 1.75 (each 1H, d, J=13.2 Hz, H-1), 2.50, 2.41 (each 1H, dd, J=18.1, 4.1 Hz, H-3), 1.21, 1.19 (each 3H, t, J=7.1 Hz, COOCH$_2$C$\underline{H}_3$); for **B**: 5.29 (1H, t, J=4.2 Hz, H-4), 4.90 (1H, t, J=7.1 Hz, H-10), 3.84 (6H, s, OMe), 3.57 (1H, dd, J=14.2, 7.1 Hz, H-11), 3.41 (1H, dd, J=14.2, 8.3 Hz, H-11), 2.92, 1.80 (each 1H, d, J=13.2 Hz, H-1), 2.53 (2H, m, H-3), 1.26, 1.17 (each 3H, t, J=7.1 Hz, COOCH$_2$C$\underline{H}_3$). This was used without further purification.

(2) Oxalyl chloride (0.85 ml, 7.72 mmol) in CH_2Cl_2 (30 ml) was added to a mixture of Et_3N (2.7 ml, 19.44 mmol) and **13b** (3.0 g, 6.48 mmol) in CH_2Cl_2 (30 ml) at room temperature over a period of 10 min and the mixture was stirred for 20 min under an Ar atmosphere. Chromatography of the product (hexane : AcOEt = 1 : 2) gave **15b** (2.524 g, 75%) of 29% de. See also Table III.

$NaBH_4$ Reduction of the Dioxopyrroline (15a) A mixture of **15a** (3.613 g, 7.18 mmol) of 55% de and $NaBH_4$ (274 mg, 7.21 mmol) in EtOH (174 ml) was stirred at 0 °C for 15 min. Chromatography of the product (AcOEt) gave **16a** (3.62 g, 100%) of 55% de as a colorless gum (**A** : **B** = 3.4 : 1). $[\alpha]_D^{25}$ +16° (c=1.17, $CHCl_3$). IR: 1736, 1683, 1510. HRMS: Calcd for $C_{25}H_{31}NO_{10}$ (M^+): 505.1948. Found: 505.1945. ^{1}H-NMR: for **A**: 5.12 (1H, dd, J=7, 6 Hz, H-10), 5.09 (1H, t, J=3.5 Hz, H-4), 3.87, 3.85, 3.70 (each 3H, s, OMe), 3.50 (1H, dd, J=14, 7 Hz, one of H-11), 3.14 (1H, dd, J=14, 6 Hz, one of H-11), 2.98, 1.75 (each 1H, d, J=13 Hz, H-1), 2.50, 2.45 (each 1H, dd, J=18, 3.5 Hz, H-3), 1.18 (3H, t, J=7 Hz, COOCH$_2$C$\underline{H}_3$); for **B**: 5.15 (1H, t, J=3.5 Hz, H-4), 4.74 (1H, t, J=7 Hz, H-10), 3.86, 3.84, 3.74 (each 3H, s, OMe), 3.48, 3.28 (each 1H, q, J=7 Hz, H-11), 2.98, 1.74 (each 1H, d, J=13 Hz, H-1), 2.57, 2.42 (each 1H, dd, J=18, 3.5 Hz, H-3), 1.18 (3H, t, J=7 Hz, COOCH$_2$C$\underline{H}_3$).

Oxidation of **16a** with DMSO–Ac_2O for 17 h at room temperature regenerated the dioxopyrroline (**15a**) with the original optical rotation, $[\alpha]_D^{20}$ −118° (c=0.84, $CHCl_3$), in 94% yield.

$NaBH_4$ Reduction of the Dioxopyrroline (15b) The ethyl ester **15b** of 51% de (see above) in EtOH (200 ml) was reduced with $NaBH_4$ (0.3 g, 7.93 mmol) to give **16b** (4.49 g, 78% from **13b**) of 50% de (**A** : **B** = 3 : 1). IR: 1734, 1683. HRMS: Calcd for $C_{26}H_{33}NO_{10}$ (M^+): 519.2102. Found: 519.2116. ^{1}H-NMR: for **A**: 5.10 (1H, t, J=3.9 Hz, H-4), 3.86, 3.84 (each 3H, s, OMe), 3.49 (1H, dd, J=14.7, 7.8 Hz, one of H-11), 3.12 (1H, dd, J=14.7, 6.8 Hz, one of H-11), 2.98, 1.73 (each 1H, d, J=12.9 Hz, H-1), 2.49, 2.41 (each 1H, dd, J=17.8, 3.9 Hz, H-3), 1.17, 1.16 (each 3H, t, J=7.1 Hz, COOCH$_2$C$\underline{H}_3$); for **B**: 4.67 (1H, t, J=14.2, 7.8 Hz, H-11), 2.54 (1H, dd, J=14.2, 3.9 Hz, H-3), 1.22, 1.16 (each 3H, t, J=7.1 Hz, COOCH$_2$C$\underline{H}_3$).

6-Ethoxycarbonyl-7-hydroxy-15,16-dimethoxy-10-methoxycarbonyl-2,8-dioxoerythrinan (18a) (A and B) (1) A mixture of **16a** (3.35 g, 6.63 mmol) of 55% de and $BF_3 \cdot Et_2O$ (6.63 mmol) in CH_2Cl_2 (100 ml) was heated under reflux for 3.5 h in an Ar atmosphere. The mixture was poured into ice-water and extracted with CH_2Cl_2 to yield the acetal (**17a**). IR: 1724, 1700. HRMS: Calcd for $C_{25}H_{31}NO_{10}$ (M^+): 505.1948. Found: 505.1944. ^{1}H-NMR: for **A**: 6.78, 6.70 (each 1H, s, ArH), 5.29 (1H, s, H-7), 4.42 (1H, dd, J=10, 6 Hz, H-10), 3.86, 3.83, 3.80 (each 3H, s, OMe), 0.75 (3H, t, J=7 Hz, COOCH$_2$C$\underline{H}_3$); for **B**: 5.16 (1H, s, H-7), 0.84 (3H, t, J=7 Hz, COOCH$_2$C$\underline{H}_3$).

(2) The product **17a** (3.26 g) was stirred with 5% HCl (25 ml) in acetone (25 ml) at 50 °C for 30 min. The mixture was concentrated to a half volume, poured into ice-water, and extracted with $CHCl_3$. Chromatography of the product (AcOEt) gave the ketone **18a** (2.811 g, 91%) of 55% de (**A** : **B** = 3.4 : 1) as a colorless gum. $[\alpha]_D^{25}$ −4.5° (c=0.986, $CHCl_3$). IR: 1732, 1712. HRMS: Calcd for $C_{23}H_{27}NO_9$ (M^+): 461.1687. Found: 461.1692. ^{1}H-NMR: for **A**: 6.67, 6.61 (each 1H, s, ArH), 4.96 (1H, t, J=7 Hz, H-10), 4.50 (1H, s, H-7), 3.87, 3.82, 3.77 (each 3H, s, OMe), 0.77 (3H, t, J=7 Hz, COOCH$_2$C$\underline{H}_3$); for **B**: 6.61, 6.53 (each 1H, s, ArH), 4.30 (1H, s, H-7), 4.00 (1H, dd, J=10, 4 Hz, H-10), 3.85, 3.83, 3.82 (each 3H, s, OMe), 0.84 (3H, t, J=7 Hz, COOCH$_2$C$\underline{H}_3$).

The MTPA-ester of **18a**: The above mixture (16 mg) was converted to the MTPA-ester (22.7 mg, 99%), where **A** : **B** = 3.4 : 1 and **A**: enantiomer of **A** = 6 : 1. ^{1}H-NMR: for **A**: 6.59, 6.47 (each 1H, s, ArH), 5.84 (1H, s, H-7), 4.89 (1H, t, J=6 Hz, H-10), 3.80, 3.73, 3.71, 3.44 (each 3H, s, OMe), 0.52 (3H, t, J=7 Hz, COOCH$_2$C$\underline{H}_3$); Enantiomer of **A**: 5.88 (1H, s, H-7); for **B**: 6.53, 6.38 (each 1H, s, ArH), 5.67 (1H, s, H-7), 3.78, 3.77, 3.72, 3.52 (each 3H, s, OMe), 0.56 (3H, t, J=7 Hz,

$COOCH_2C\underline{H}_3$).

6,10-Diethoxycarbonyl-2,2-ethylenedioxy-7-hydroxy-15,16-dimethoxy-8-oxoerythrinan (17b) (A and B) A mixture of **13b** (obtained above, 2.42 g, 4.66 mmol) and $BF_3 \cdot Et_2O$ (1.76 ml) in CH_2Cl_2 (170 ml) was heated under reflux for 1 h under an Ar atmosphere and worked up as above. Chromatography of the product (hexane : AcOEt = 1 : 9) gave the acetal **17b** (2.10 g, 87%) of 51% de as a colorless gum (**A** : **B** = 3.1 : 1). IR: 1728, 1700. HRMS: Calcd for $C_{26}H_{33}NO_{10}$ (M^+): 519.2102. Found: 519.2099. ^{1}H-NMR: for **A**: 6.78, 6.70 (each 1H, s, ArH), 5.28 (1H, s, H-7), 4.38 (1H, dd, J = 10.3, 5.9 Hz, H-10), 3.86, 3.84 (each 3H, s, OMe), 1.32 (3H, t, J = 7.1 Hz, C_{10}-$COOCH_2C\underline{H}_3$), 0.74 (3H, t, J = 7.1 Hz, C_6-$COOCH_2C\underline{H}_3$); for **B**: 6.77, 6.62 (each 1H, s, ArH), 5.14 (1H, s, H-7), 3.85, 3.84 (each 3H, s, OMe), 1.30 (3H, t, J = 7.1 Hz, C_{10}-$COOCH_2C\underline{H}_3$), 0.86 (3H, t, J = 7.1 Hz, C_6-$COOCH_2C\underline{H}_3$).

Partial Hydrolysis of the Acetal (17b) (Kinetic Resolution of Diastereomers) A 5% HCl solution (100 ml) was added to a solution of **17b** (2.10 g) of 51% de in acetone (100 ml) and the mixture was stirred at 27 °C for 3 h. Then solid $NaHCO_3$ was added until evolution of CO_2 ceased, and the mixture was extracted with $CHCl_3$. Chromatography of the product (hexane : AcOEt = 1 : 9) gave the acetal **17b-A** (1.305 g, 62%) of 83% de (**A** : **B** = 11 : 1) and the ketone **18b** (0.578 g, 30%) of −5% de (**A** : **B** = 1 : 1.1).

(5*S*,6*R*,7*R*,10*S*)-6,10-Diethoxycarbonyl-7-hydroxy-15,16-dimethoxy-2,8-dioxoerythrinan (18b-A) The acetal **17b** of 83% de (1.275 g, 2.46 mmol) was hydrolyzed with 5% HCl (60 ml) in acetone (60 ml) at 50 °C for 4 h. Chromatography of the product (hexane : AcOEt = 1 : 9) gave the ketone **18b** (1.07 g, 92%) of 83% de. ^{1}H-NMR: 6.67, 6.61 (each 1H, s, ArH), 4.51 (1H, s, H-7), 4.95 (1H, t, J = 6.6 Hz, H-10), 3.87, 3.82 (each 3H, s, OMe), 1.29 (3H, t, J = 7.1 Hz, C_{10}-$COOCH_2C\underline{H}_3$), 0.76 (3H, t, J = 7.1 Hz, C_6-$COOCH_2C\underline{H}_3$); HRMS: Calcd for $C_{24}H_{29}NO_9$ (M^+): 475.1840. Found: 475.1837.

The MTPA-ester: The above obtained ketone **18b** (90 mg) was converted to the MTPA-ester (128 mg, 98%), colorless gum, where **A** : **B** = 11 : 1 and **A**: enantiomer of **A** = 20 : 1. ^{1}H-NMR: for **A**: 6.66, 6.54 (each 1H, s, ArH), 5.91 (1H, s, H-7), 4.98 (1H, t, J = 6.6 Hz, H-10), 3.86, 3.80, 3.51 (each 3H, s, OMe), 1.30, 0.59 (each 3H, t, J = 7.1 Hz, $COOCH_2C\underline{H}_3$); Enantiomer of **A**: 5.94 (1H, s, H-7): for **B**: 6.60, 6.46 (each 1H, s, ArH), 5.71 (1H, s, H-7), 3.84, 3.79, 3.59 (each 3H, s, OMe), 1.33, 0.63 (each 3H, t, J = 7.1 Hz, $COOCH_2C\underline{H}_3$).

(5*R*,6*S*,7*S*,10*S*)-6,10-Diethoxycarbonyl-7-hydroxy-15,16-dimethoxy-2,8-dioxoerythrinan (18b-B) (1) The dioxopyrroline **15b** of 29% de (3.06 g) was reduced with $NaBH_4$ (112 mg) in EtOH (20 ml) at 0 °C for 20 min to give the alcohol **15b** (2.94 g, 96%) of 31% de, as colorless gum. This was heated with $BF_3 \cdot Et_2O$ (2.15 ml, 3 eq) in CH_2Cl_2 (120 ml) under reflux for 1.5 h in an Ar atmosphere and worked up as described above. Chromatography of the product (hexane : AcOEt = 1 : 9) gave the erythrinan **17b** (2.56 g, 87%) of 29% de, as a colorless gum.

(2) The acetal **17b** (2.56 g) in acetone (100 ml) was treated with 5% HCl (100 ml) at 27 °C for 3 h and worked up as described in the case of partial hydrolysis. Chromatography of the product (hexane : AcOEt = 1 : 9) gave the acetal **17b** (1.214 g, 47%) of 83% de (**A** : **B** = 11 : 1) and the ketone **18b** (1.188 g, 50%) of 13% de (**A** : **B** = 1 : 1.3).

A mixture of **18b** of 13% de (1.188 g), *p*-TsOH · H_2O (100 mg), and ethylene glycol (2.1 ml) in benzene (60 ml) was heated under reflux for 1h. The cooled mixture was washed with saturated $NaHCO_3$ solution and the water layer was extracted with $CHCl_3$. The combined organic layer, on concentration, gave the acetal **17b** (1.206 g) as a gum. This was again partially hydrolyzed with 5% HCl (50 ml) in acetone (50 ml) at 27 °C for 3 h, and the product was chromatographed to give the acetal **17b** (690 mg, 53%) of 26% de (**A** : **B** = 1.7 : 1) and the ketone **18b** (472 mg, 40%) of 66% de (**A** : **B** = 1 : 4.9). Crystallizations of this ketone from EtOH–Et_2O gave **18b-B** as colorless needles (263 mg), mp 189—193 °C, whose diastereomer excess was 90% (**A** : **B** = 1 : 19.3). IR: 1716. ^{1}H-NMR: 6.62, 6.54 (each 1H, s, ArH), 4.30 (1H, s, H-7), 3.97 (1H, dd, J = 11.9, 3.7 Hz, H-10), 3.86, 3.83 (each 3H, s, OMe), 1.32, 0.83 (each 3H, t, J = 7.1 Hz, $COOCH_2C\underline{H}_3$). MS: 475 (M^+). *Anal.* Calcd for $C_{24}H_{29}NO_9$: C, 60.62; H, 6.15; N, 2.95. Found: C, 60.76; H, 6.15; N, 2.93.

Conversion of 17b-A to (−)-Demethoxyerythratidinone [(−)-7] (1) (5*S*,6*R*,7*R*)-6-Ethoxycarbonyl-2,2-ethylenedioxy-7-hydroxy-15,16-dimethoxy-8-oxoerythrinan (**20**): The acetal **17b-A** of 83% de (950 mg) in EtOH (20 ml) was hydrolyzed with 5% NaOH (20 ml) at room temperature for 30 min. The mixture was poured into ice-water, acidified to pH 1 with 10% HCl, and extracted with AcOEt. The gummy product was dissolved in THF (15 ml), and *N*-methylmorpholine (240 μl) then isobutyl chloroformate (290 μl) were added at −10 °C under an Ar atmosphere. The mixture was stirred for 15 min at the same temperature. To this solution, *N*-hydroxypyridinethione sodium salt (300 mg) and triethylamine (280 μl) in THF (15 ml) were added at −10 °C can then the mixture was stirred for 50 min. After rapid removal of precipitates, *tert*-butylmercaptan (2.3 ml) was added to the filtrate and the mixture was irradiated with a 100 W Hg lamp for 20 min under an Ar atmosphere. The product was taken up in $CHCl_3$, washed with 1 N HCl, saturated $NaHCO_3$ solution and brine, dried, and concentrated. Flash chromatography of the residue (AcOEt) gave **20** (1.09 g) as a gum, whose ^{1}H-NMR spectrum was identical with that of the racemic specimen.[5a]

(2) (5*S*,6*R*,7*S*)-2,2-Ethylenedioxy-7-hydroxy-15,16-dimethoxy-8-oxoerythrinan (**22**): The above product was oxidized with dimethyl sulfoxide (DMSO) (9 ml) and Ac_2O (4.5 ml) at room temperature for 12 h. The product (**21**) obtained on usual work-up was dissolved in hexamethylphosphoric triamide (HMPA) (13.5 ml) and heated with anhydrous $MgCl_2$ (448 mg) at 140 °C for 2 h under an Ar atmosphere. The product obtained by usual work-up was reduced with $NaBH_4$ (33 mg) in EtOH–THF (1 : 1, 40 ml) at 0 °C for 30 min. Purification of the product by flash chromatography gave (+)-**22** (204 mg, 30%) as a colorless gum, $[\alpha]_D^{23}$ +82° (c = 0.408, $CHCl_3$). IR: 3370, 1690. ^{1}H-NMR (100 MHz): 6.69, 6.46 (each 1H, s, ArH), 4.4—3.9 (4H, $OC\underline{H}_2C\underline{H}_2O$), 3.86, 3.80 (each 3H, s, OMe). MS: 375 (M^+). This was identical with the reported racemic specimen[5a] in terms of IR and ^{1}H-NMR spectrum and TLC behavior.

(3) (5*S*)-15,16-Dimethoxy-$\Delta^{1(6)}$-erythrinan-2,8-dione (**24**): A mixture of (+)-**22** (204 mg), methanesulfonyl chloride (MsCl) (200 mg), and DMAP (20 mg) in pyridine (2 ml) was stirred at room temperature for 12 h, and worked up as usual. A mixture of the product and DBU (1.3 g) in benzene (4 ml) was heated at 160 °C for 10 h. The product was taken up in CH_2Cl_2, washed with 10% HCl, brine, dried, and concentrated. The residue was hydrolyzed with 10% HCl–acetone (1 : 1, 24 ml) at 60 °C for 1 h. Chromatography of the product (AcOEt : $CHCl_3$ = 2 : 1) gave (−)-**24** (89 mg, 87% from **22**), as a colorless gum. $[\alpha]_D^{23}$ −43° (c = 0.89, $CHCl_3$). IR: 1685, 1670. ^{1}H-NMR (100 MHz): 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).

(4) (−)-3-Demethoxyerythratidinone [(−)-7]: A mixture of (−)-**24** (89 mg), *p*-TsOH · H_2O (catalytic amount), and ethylene glycol (2.5 ml) in benzene (30 ml) was heated under reflux for 10 h. The mixture was washed with saturated $NaHCO_3$ solution and brine, dried, and concentrated. The product (83 mg) in THF (5 ml) was reduced with $LiAlH_4$ (50 mg) and $AlCl_3$ (58 mg) in Et_2O (3 ml) at 0 °C for 40 min. The excess reagent was decomposed by addition of 5% NH_4OH and the mixture was extracted with Et_2O and then CH_2Cl_2. The combined organic extract was dried over K_2CO_3 and concentrated. The residue was heated with 5% HCl (3 ml) in acetone (5 ml) at 80 °C for 2 h. The cooled mixture was basified with 28% NH_4OH to pH 11 and extracted with CH_2Cl_2 to give (−)-**7** (50 mg, 59% from **24**), as a pale yellow solid. $[\alpha]_D^{20}$ −236° (c = 0.8, $CHCl_3$). ^{1}H-NMR: 6.64, 6.53 (each 1H, s, ArH), 6.07 (1H, br s, H-1), 3.83, 3.72 (each 3H, s, OMe). HRMS: Calcd for $C_{18}H_{21}NO_3$ (M^+): 229.1520. Found: 299.1506. This was identical with an authentic sample of (+)-3-demethoxyerythratidinone (+)-**7** [lit. $[\alpha]_D^{20}$ +325° (c = 0.249, $CHCl_3$)][11] in terms of ^{1}H-NMR spectra and TLC behavior.

Alkaline Hydrolysis of the Ketone (18) (1) The methyl ester **18a** (1 g, **A** : **B** = 3.3 : 1) was hydrolyzed with 5% NaOH–EtOH (30 ml) at 0 °C for 30 min. The mixture was acidified with 10% HCl to pH 2 and extracted with AcOEt. The resulting carboxylic acid **26** (941 mg, 97%) was crystallized from $CHCl_3$ to give (±)-**26A** (280 mg) as colorless needles, mp 249—250 °C, $[\alpha]_D^{20}$ ±0° (c = 0.6, MeOH). ^{1}H-NMR (CD_3OD): 6.81, 6.70 (each 1H, s, ArH), 4.73 (1H, t, J = 6 Hz, H-10), 4.50 (1H, s, H-7), 3.82, 3.77 (each 3H, s, OMe), 3.50 (1H, d, J = 17 Hz, H-1), 3.22 (1H, dd, J = 16, 6 Hz, H-11), 3.08 (1H, dd, J = 16, 7 Hz, H-11), 3.01 (1H, d, J = 17 Hz, H-1), 0.72 (3H, t, J = 7 Hz, $COOCH_2C\underline{H}_3$). HRMS: Calcd for $C_{22}H_{25}NO_9$ (M^+): 447.1530. Found: 447.1530. CD at 250—600 nm: no peak.

Treatment of the crystalline acid (60 mg) with ethereal diazomethane gave (±)-**18a** (54 mg), as colorless prisms from MeOH, mp 208—211 °C, $[\alpha]_D^{24}$ ±0° (c = 1.33, $CHCl_3$). X-Ray analysis: see Fig. 3. Decarboxylation of this acid as described for **20** gave (±)-**8**, mp 237—239 °C, $[\alpha]_D^{25}$ ±0° (c = 0.74, $CHCl_3$). This was dimorphic to the reported racemate,[5a] mp 217—218 °C.

The mother liquor from the crystalline acid in MeOH was methylated

with ethereal diazomethane. Chromatography of the product (AcOEt) followed by repeated crystallizations gave a further crop of (±)-**18a** (182 mg) and a methyl ester (450 mg) of $[\alpha]_D^{24}$ +10.2° (c=1.25, $CHCl_3$). Further recrystallizations of the latter afforded (+)-**18a** (200 mg), as colorless prisms from MeOH, mp 102—103 °C, $[\alpha]_D^{24}$ +10.8° (c=1.1, $CHCl_3$). HPLC analysis on a Chiralpack AD column revealed that (+)-**18a** gave a single peak, while (±)-**18a** gave two peaks, one of which was identical with that of the former.

(2) The ethyl ester **18b** (2.7 g) of 50% de (**A** : **B** = 3 : 1) was hydrolyzed with 5% NaOH (30 ml) in EtOH (60 ml) at room temperature for 1 h. Acidification and extraction of the mixture with AcOEt gave the crystalline racemic acid (±)-**26A** (1.345 g), mp 249—250 °C, $[\alpha]_D^{25}$ ±0° (c=1.0, MeOH), and the gummy optically active acid (+)-**26A** (1.06 g), $[\alpha]_D^{25}$ +4.5° (c=0.54, $CHCl_3$).

(5*S*,6*R*,7*R*)-6-Ethoxycarbonyl-7-hydroxy-15,16-dimethoxy-2,8-dioxoerythrinan [(+)-8] (1) Optically pure compound from (+)-**18a-A**: The above-obtained methyl ester (+)-**18a-A** (53 mg) was hydrolyzed with alkali, and then decarboxylated as described in the case of **20** to give (+)-**8** (28 mg, 60%), as colorless needles from MeOH–Et_2O, mp 263—265 °C. $[\alpha]_D^{25}$ +117.1° (c=0.18, $CHCl_3$). ^{1}H-NMR: 6.56, 6.54 (each 1H, s, ArH), 4.33 (1H, s, H-7), 3.85, 3.83 (each 3H, s, OMe), 3.72, 3.53 (each 1H, dq, J=10.8, 7.1 Hz, $COOCH_2CH_3$), 3.26, 3.20 (each 1H, d, J=18.1 Hz, H-1), 0.81 (3H, t, J=7.1 Hz, $COOCH_2CH_3$). MS: 403 (M^+). *Anal.* Calcd for $C_{21}H_{25}NO_7$: C, 62.52; H, 6.25; N, 3.47. Found: C, 62.36; H, 6.37; N, 3.39.

(2) From **18b** of 83% de: The ketone **18b** (1.05 g) of 83% de (obtained by cyclization for 2 h with BF_3) was hydrolyzed with 5% NaOH (20 ml) in EtOH (40 ml) at room temperature for 1 h. The mixture was acidified to pH 2 and extracted with AcOEt. The product was dissolved in THF (20 ml) and decarboxylated as described in the case of **20**. Flash chromatography of the product (AcOEt) gave (+)-**8** (474 mg, 53% from **18b**) of 64% ee. $[\alpha]_D^{24}$ +75° (c=0.5, $CHCl_3$). Crystallization of this from MeOH–Et_2O gave a small amount of needles of mp 239—241 °C (53 mg, 6%); this product was mainly the racemic compound [$[\alpha]_D^{25}$ +5.5° (c=0.25, $CHCl_3$)]. Recrystallizations of the mother liquor from MeOH gave (+)-**8** (88 mg, 10%) of 85% ee, as colorless needles, mp 264—267 °C. $[\alpha]_D^{26}$ +100° (c=0.25, $CHCl_3$).

The MTPA-ester: The above-obtained (+)-**8** (50 mg) was converted into the MTPA-ester (72 mg, 94%), colorless gum. The ^{1}H-NMR spectrum showed that it is a 12 : 1 mixture of (+)-**8**-MTPA and (−)-**8**-MTPA. ^{1}H-NMR: for (+)-**8**-MTPA: 6.55, 6.50 (each 1H, s, ArH), 5.73 (1H, s, H-7), 3.84, 3.81, 3.49 (each 3H, s, OMe), 3.30, 3.00 (each 1H, d, J=18 Hz, H-1), 0.59 (3H, t, J=7.1 Hz, $COOCH_2CH_3$); for (−)-**8**-MTPA: 6.48 (1H, s, one of ArH), 5.76 (1H, s, H-7), 3.83, 3.79, 3.60 (each 3H, s, OMe).

(5*R*,6*S*,7*S*)-6-Ethoxycarbonyl-7-hydroxy-15,16-dimethoxy-2,8-dioxoerythrinan [(−)-8] The ketone **18b-B** of 90% de (263 mg, see above) was hydrolyzed with 5% NaOH (10 ml) in EtOH (10 ml) and the resulting acid was decarboxylated as described above. Chromatography of the product (AcOEt) gave (−)-**8** (158 mg, 71% from **18b**) of $[\alpha]_D^{23}$ −71.3° (c=0.8, $CHCl_3$). The enantiomer excess of this product was calculated as 61% by comparison with the pure (+)-enantiomer (see above). Recrystallizations of this from MeOH gave (−)-**8** (63 mg, 28%) of 81% ee, $[\alpha]_D^{22}$ −94.4° (c=0.5, $CHCl_3$), as colorless needles, mp 265—267 °C. IR (KBr): 1729, 1717, 1689. The ^{1}H-NMR spectrum was superimposable on that of (+)-**8**.

(1*R*,5*S*,6*S*,7*S*)-15,16-Dimethoxy-2,8-dioxo-1,7-cycloerythrinan [(−)-9] A mixture of (+)-**8** (83 mg) of 70% ee and MsCl (24 μl) in pyridine (2 ml) was stirred at room temperature for 6 h. The mixture was poured into ice-water and extracted with $CHCl_3$. A mixture of the product (99 mg) and DBU (250 μl) in toluene (5 ml) was heated under reflux for 4.5 h. The mixture was diluted with benzene, and washed with 1 N HCl, then the water layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried, and concentrated. Chromatography of the residue (benzene : AcOEt = 1 : 1) gave (−)-**9** (73 mg, 92%), which crystallized as colorless prisms from MeOH (42 mg, 53%), mp 184—186 °C. $[\alpha]_D^{28}$ −28.4° (c=0.75, $CHCl_3$). IR (KBr): 1723, 1698. ^{1}H-NMR: 6.83, 6.62 (each 1H, s, ArH), 4.34 (1H, ddd, J=13.2, 6.3, 1.4 Hz, one of H-10), 3.98, 3.89 (each 1H, dq, J=10.7, 7.1 Hz, $COOCH_2CH_3$), 3.88, 3.85 (each 3H, s, OMe), 0.98 (3H, t, J=7.1 Hz, $COOCH_2CH_3$). MS: 385 (M^+). *Anal.* Calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.52. Found: C, 65.46; H, 6.05; N, 3.56. This was identical with (±)-**9**[5b] in terms of ^{1}H-NMR spectrum and TLC behavior.

(1*S*,5*R*,6*R*,7*R*)-15,16-Dimethoxy-2,8-dioxo-1,7-cycloerythrinan [(+)-9] The (−)-enantiomer (−)-**8** (40 mg) of 81% ee was mesylated with MsCl in pyridine (1 ml), and the resulting mesylate was heated with DBU (250 μl) in toluene (5 ml). Work-up of the product as described above gave (+)-**9** (32 mg, 84%). Crystallizations of this from MeOH afforded colorless prisms (24 mg, 63%), mp 187—188 °C. $[\alpha]_D^{20}$ +33.9° (c=1.0, $CHCl_3$). IR (KBr): 1723, 1698. The ^{1}H-NMR spectrum was superimposable on that of (−)-**9**.

TABLE V. Positional Parameters and B_{eq} for (±)-**18a-A**

Atom	x	y	z	B_{eq}
O(1)	0.2593 (3)	0.16905 (9)	1.1029 (2)	3.9 (1)
O(2)	0.1129 (3)	0.25964 (8)	1.0115 (2)	3.9 (1)
O(3)	0.3389 (3)	0.07755 (9)	0.4620 (2)	3.8 (1)
O(4)	0.5193 (3)	0.0030 (1)	0.6470 (2)	4.6 (1)
O(5)	−0.0817 (3)	0.1014 (1)	0.3837 (2)	5.1 (1)
O(6)	0.0263 (3)	0.18441 (9)	0.3511 (2)	4.6 (1)
O(7)	0.5682 (3)	0.0495 (1)	0.9013 (2)	4.7 (1)
O(8)	0.5007 (2)	0.11325 (9)	0.7601 (2)	3.5 (1)
O(9)	0.0707 (3)	−0.0643 (1)	0.9047 (2)	5.5 (1)
N(1)	0.1772 (3)	0.0971 (1)	0.5958 (2)	2.6 (1)
C(1)	0.2726 (4)	−0.0131 (1)	0.8278 (3)	3.4 (1)
C(2)	0.0937 (4)	0.0244 (1)	0.8466 (3)	3.4 (1)
C(3)	−0.0499 (4)	0.0149 (2)	0.7967 (3)	3.6 (1)
C(4)	−0.0224 (4)	0.0434 (1)	0.6868 (3)	3.1 (1)
C(5)	0.1486 (3)	0.0768 (1)	0.7102 (2)	2.4 (1)
C(6)	0.3058 (3)	0.0362 (1)	0.7510 (2)	2.5 (1)
C(7)	0.3444 (4)	0.0169 (1)	0.6326 (3)	3.0 (1)
C(8)	0.2902 (3)	0.0667 (1)	0.5526 (2)	2.7 (1)
C(10)	0.1123 (4)	0.1496 (1)	0.5414 (2)	2.7 (1)
C(11)	−0.0067 (4)	0.1779 (1)	0.6111 (3)	2.9 (1)
C(12)	0.0675 (3)	0.1750 (1)	0.7414 (2)	2.5 (1)
C(13)	0.1415 (3)	0.1261 (1)	0.7908 (2)	2.4 (1)
C(14)	0.2033 (4)	0.1227 (1)	0.9129 (3)	2.7 (1)
C(15)	0.1953 (4)	0.1677 (1)	0.9840 (2)	2.9 (1)
C(16)	0.1198 (4)	0.2174 (1)	0.9339 (2)	2.8 (1)
C(17)	0.0564 (4)	0.2204 (1)	0.8137 (3)	2.9 (1)
C(18)	0.3363 (6)	0.1190 (2)	1.1569 (3)	4.7 (2)
C(19)	0.0378 (6)	0.3104 (2)	0.9631 (4)	4.3 (2)
C(20)	0.0086 (4)	0.1405 (1)	0.4161 (3)	3.1 (1)
C(21)	−0.0811 (8)	0.1858 (2)	0.2319 (4)	5.8 (2)
C(22)	0.4718 (4)	0.0666 (1)	0.8143 (3)	2.9 (1)
C(23)	0.6556 (5)	0.1446 (2)	0.8150 (4)	4.5 (2)
C(24)	0.6307 (7)	0.1784 (2)	0.9174 (5)	6.4 (2)
H(1)	0.340 (4)	−0.007 (1)	0.900 (3)	4.6 (8)
H(2)	0.312 (4)	−0.048 (1)	0.803 (3)	4.8 (8)
H(3)	−0.156 (4)	−0.004 (1)	0.780 (3)	5.1 (8)
H(4)	−0.052 (4)	0.042 (1)	0.864 (3)	5.5 (9)
H(5)	−0.121 (4)	0.069 (1)	0.654 (2)	3.4 (6)
H(6)	−0.020 (4)	0.016 (1)	0.627 (2)	3.4 (7)
H(7)	0.273 (3)	−0.014 (1)	0.603 (2)	2.8 (6)
H(8)	0.530 (4)	−0.021 (1)	0.603 (3)	4.1 (9)
H(9)	0.208 (3)	0.174 (1)	0.540 (2)	2.9 (6)
H(10)	−0.126 (4)	0.158 (1)	0.589 (2)	3.0 (6)
H(11)	−0.023 (4)	0.218 (1)	0.585 (2)	3.7 (7)
H(12)	0.247 (3)	0.089 (1)	0.947 (2)	3.0 (6)
H(13)	0.005 (3)	0.253 (1)	0.780 (2)	2.1 (5)
H(14)	0.256 (5)	0.086 (2)	1.133 (3)	6 (1)
H(15)	0.445 (6)	0.114 (2)	1.137 (4)	8 (1)
H(16)	0.361 (4)	0.127 (1)	1.240 (3)	5.4 (9)
H(17)	0.033 (4)	0.333 (1)	1.035 (3)	5.3 (8)
H(18)	0.100 (4)	0.326 (1)	0.908 (3)	4.3 (8)
H(19)	−0.085 (5)	0.304 (2)	0.921 (3)	7 (1)
H(20)	0.751 (5)	0.117 (2)	0.835 (3)	7 (1)
H(21)	0.674 (5)	0.170 (2)	0.749 (4)	9 (1)
H(22)	0.723 (5)	0.203 (2)	0.944 (4)	8 (1)
H(23)	0.541 (7)	0.204 (2)	0.862 (5)	12 (2)
H(24)	0.612 (7)	0.151 (2)	0.988 (5)	14 (2)
H(25)	−0.029 (7)	0.219 (2)	0.198 (5)	12 (2)
H(26)	−0.070 (5)	0.154 (2)	0.187 (4)	8 (1)
H(27)	−0.185 (6)	0.196 (2)	0.230 (4)	10 (2)

X-Ray Crystallographic Analysis of (±)-18a-A The reflection data

were collected on a Rigaku AFC-5R four circle diffractometer using graphite-monochromated MoK_α radiation as described in a previous paper[7b] and the structure was solved by the direct method using MITHRIL[14] and refined by the full-matrix least-squares procedure with anisotropic thermal factors for the non-hydrogen atoms and with isotropic ones for hydrogen atoms. Crystal data are as follows: monoclinic, $a=7.9181(9)$ Å, $b=24.053(3)$ Å, $c=11.6724(8)$ Å, $\beta=103.046(8)°$, $V=2165.7(4)$ Å^3, $D_c=1.42$ g/cm^3, $Z=4$. Space group, $P2_1/n$. Reflections: collected, 5562; used for calculation, 2370. $R=0.041$. Positional parameters are listed in Table V.

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9) The major diastereomer (**17b-A**) exhibited the C_{10}-H signal at δ 4.38 as dd ($J=10.3$, 5.9 Hz) indicating that the C_{10}-COOEt group is in an equatorial orientation. The corresponding couplings in the minor diastereomer (**17b-B**) could not be observed because of overlapped signals.
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11) D. H. R. Barton, A. A. L. Gunatilaka, R. M. Letcher, A. M. F. T. Lobo, D. A. Widdowson, *J. Chem. Soc., Perkin Trans. 1*, **1973**, 874.
12) The reason for the discrepancies between the observed and expected enantiomer excesses is discussed in the last section.
13) Attempted resolution of this racemic acid with burcine was unsuccessful. It gave a readily crystallizable burcine salt, mp 262—264 °C, $[\alpha]_D^{23}$ −10.7° ($c=1.05$, $CHCl_3$–MeOH, 1:1), as colorless needles from $CHCl_3$–EtOH. However, on acidification and extraction with AcOEt, it regenerated the racemic acid (±)-**26A**, suggesting that it was a double salt such as [burcine, (+)-**A**; burcine, (−)-**A**].
14) C. J. Gilmore, *J. Appl. Cryst.*, **17**, 42 (1984).