Studies toward Total Synthesis of Non-aromatic *Erythrina* Alkaloids. (3).[1] Synthesis of β-Erythroidine Skeleton (β-Erythroidan)

Kimiaki ISOBE,*[,a] Kunihiko MOHRI,[a] Yuji ITOH,[a] Yuki TOYOKAWA,[a] Naoko TAKEDA,[a] Jun-ichi TAGA (deceased),[a] Shinzo HOSOI,[b] and Yoshisuke TSUDA*[,b]

Showa College of Pharmaceutical Sciences,[a] 3-3165 Higashi-tamagawagakuen, Machida, Tokyo 194, Japan and Faculty of Pharmaceutical Sciences,[b] Kanazawa University, 13-1 Takara-machi, Kanazawa 920, Japan. *Received March 26, 1992*

The β-erythroidine skeleton (β-erythroidan) was synthesized as the 8-oxo derivative by two different routes. One is a four-step synthesis starting from 15,16,17-trimethoxy-8-oxo-*cis*-erythrinan (2) *via* ozonolytic cleavage of the aromatic ring. The other is a five-step synthesis starting from D-furano-8-oxo-*cis*-erythrinan (13) *via* oxidative cleavage of the furan ring. The two routes gave the same 14,17-dihydro-16(15*H*)-oxaerythrinan-8,15-dione (1) (8-oxo-β-erythroidan). 8-Oxo-β-erythroidan (1) was not identical with the compound previously reported by Kitahara and Matsui, suggesting that their synthesis is questionable.

Keywords *Erythrina* alkaloid; non-aromatic *Erythrina* alkaloid; β-erythroidine; β-erythroidan; 15,16,17-trimethoxyerythrinan; D-furanoerythrinan; oxidative cleavage; allylic rearrangement; selenium dioxide oxidation

Non-aromatic *Erythrina* alkaloids (such as erythroidines) characteristically have a δ-lactone at ring D instead of the aromatic ring in aromatic *Erythrina* alkaloids. They are considered to be biosynthesized from aromatic precursors through an oxidative cleavage of the aromatic ring (Chart 1).[2] Although total synthesis of aromatic *Erythrina* alkaloids has been achieved by several methods in the last ten years,[3] the non-aromatic alkaloids (such as α- and β-erythroidines) and the skeletal compounds are still elusive in spite of the efforts of many workers.[4]

Here we describe the first synthesis of the β-erythroidine skeleton, 14,17-dihydro-16(15*H*)-oxaerythrinan-15-one, (we call this β-erythroidan, hereafter) as its 8-oxo derivative (**1**) by two different routes.[5] The first route is based on the ozonolytic cleavage of a trimethoxybenzene ring of an aromatic erythrinan derivative (resembling a proposed biosynthetic pathway) and the second route is based on the oxidative cleavage of a furan ring of a D-furanoerythrinan.

Results and Discussion

β-Erythroidan from Trimethoxyerythrinan Previously we reported[6] that ozonolysis of 15,16,17-trimethoxy-8-oxo-*cis*-erythrinan (**2**) at −78 °C in the presence of potassium carbonate gave two products, **3** and **4**, in 43 and 12% yields; these are the products of C_{15}–C_{16} and C_{16}–C_{17} fissions, respectively. Of these, **3** was transformed as follows into the lactone-acid **7**, the proposed intermediate[2] in the biosynthesis. This transformation established, at the same time, the structures of the ozonolysis products.

When **3** was heated with 70% acetic acid at 130 °C, a pyrone derivative **5** was produced in 57% yield. Hydrolysis of **5** with 10% sodium hydroxide (NaOH) followed by reduction with sodium borohydride ($NaBH_4$) gave, after acidification, a mixture of lactone-acids, **7a** and **7b**. These were separated by chromatography, after methylation with diazomethane to **8a** and **8b**. In the ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectra, **8a** and **8b** exhibited the signal of the proton geminal to the lactonic oxygen (H-17) at δ 5.07 and 5.04, respectively, both as broad singlets, proving that they are stereoisomers derived from **3**. The lactone-acid **9** expected from the ozonolysis product **4** by this transformation would give a triplet or double doublet signal for the corresponding proton.

The carboxyl group in **7** was removed photochemically, because it is at an allylic position.[7] On irradiation of an alkaline solution of **7** (mixture of **7a** and **7b**) with a 100 W high-pressure mercury lamp (without a filter), the expected decarboxylation product **1** was produced, though the yield was not satisfactory (18%). In the ^{1}H-NMR spectrum, the coupling pattern of ring D protons in **1** was in good

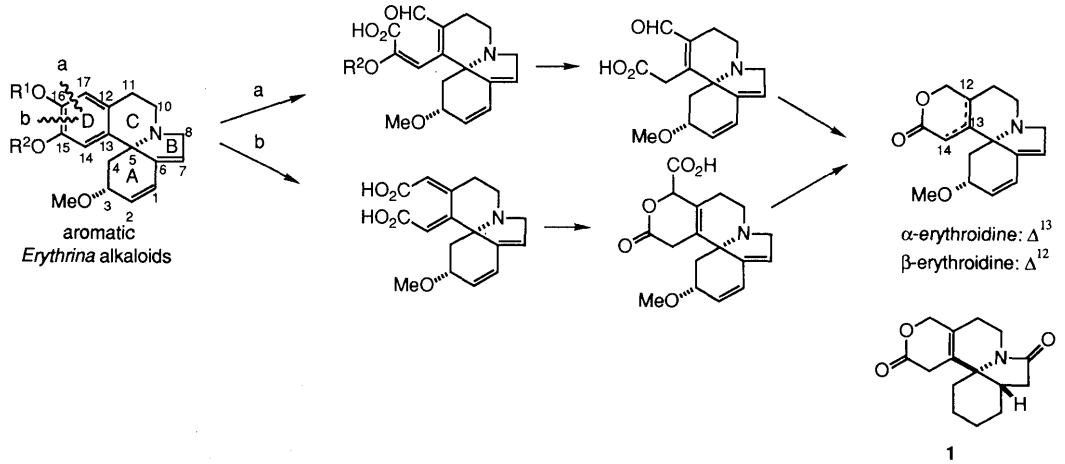

Chart 1

© 1992 Pharmaceutical Society of Japan

NII-Electronic Library Service

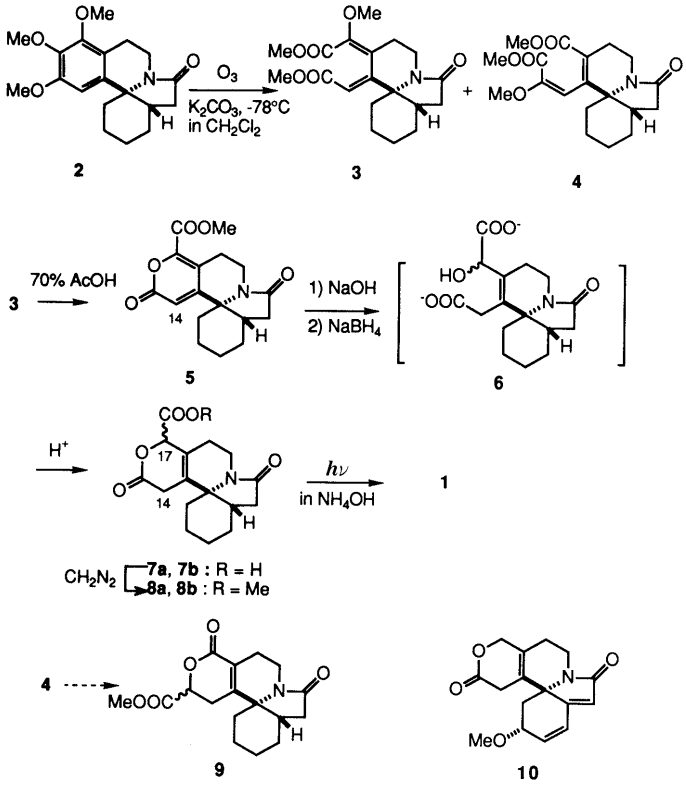

Chart 2

agreement with that of natural 8-oxo-β-erythroidine **10**[8] (Table I), supporting the correctness of the structure.

β-Erythroidans from D-Furanoerythrinan D-Furanoerythrinans are also attractive precursors for synthesis of erythroidines, since oxidative cleavage of the furan ring followed by introduction of a C_1-unit will lead to an unsaturated δ-lactone. Conversion of furans into γ-lactones by oxidation has been achieved by various reagents such as singlet oxygen,[9] anodic oxidation,[10] 2,3-dichloro-5,6-dicyano-1,4-benzoquinone,[11] and *m*-chloroperbenzoic acid.[12] We found that an excess of *N*-bromosuccinimide (NBS) is a good reagent to obtain the hydroxy unsaturated γ-lactone **15** from D-furano-8-oxo-*cis*-erythrinan **13**. Thus, treatment of **13**, which was prepared from **11**, with 3 mol eq of NBS in dioxane–water gave **15** in 72% yield. When 1 mol eq of NBS was used, the product was a complex mixture. Compound **15** exhibited hydroxyl (3250 cm^{-1}), γ-lactone (1770 cm^{-1}), and lactam (1680 cm^{-1}) absorptions in the infrared (IR) spectrum, and the signal of an olefinic proton at δ 5.95 as a singlet in the ^{1}H-NMR spectrum, proving the structure. We consider that **15** was produced by a four-electron oxidation from the furan **13** through a dihydroxy intermediate **14**.[13]

When **15** was treated with diazomethane, two stereoisomeric adducts, **16a** and **16b**, were produced. Reduction of **15** with $NaBH_4$ gave an unsaturated γ-lactone **17**, in which the configuration of H-12 (δ 5.09, ddd, J=11.7, 5.9, 1.7 Hz) was assigned as α, because, if it were of β orientation, ring C would take a boat conformation, which would have severe steric interactions.

On the other hand, hydrogenation of **15** over 10% Pd–C in ethanol afforded a mixture of keto-acids, **18a** and **18b**. Although these were not separated at this stage, separation was satisfactorily effected by chromatography of the

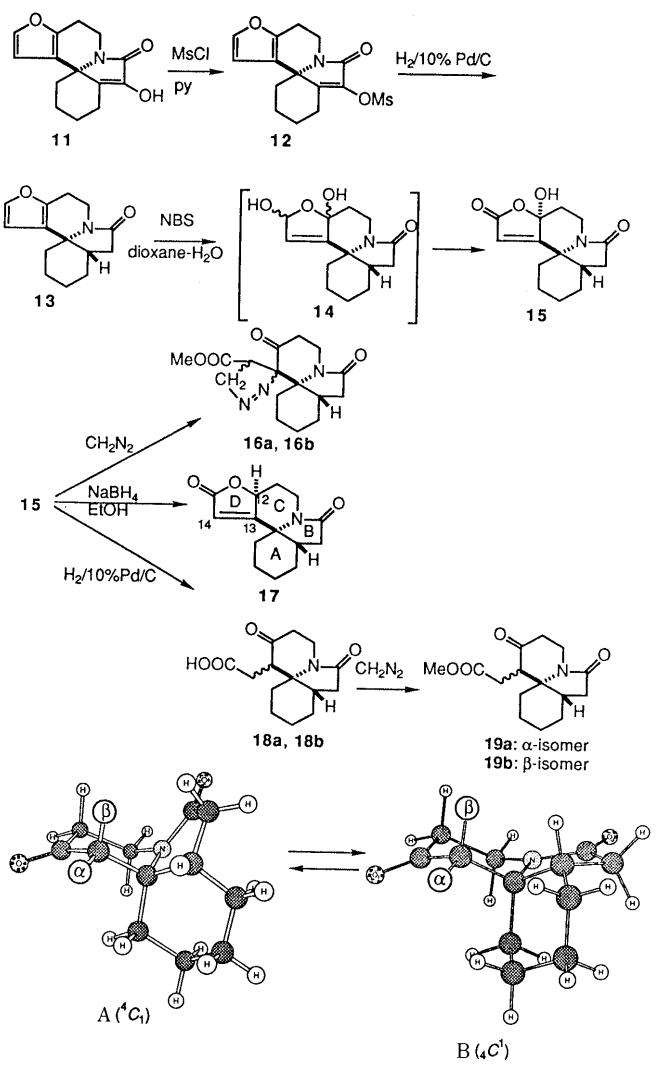

Chart 3

corresponding methyl esters. The less polar ester **19a** (mp 93—96 °C, 61% yield from **15**) was stable to 5% sodium methoxide in methanol, while the more polar ester **19b** (mp 83—85 °C, 30% yield from **15**) was changed into **19a** on treatment with the same reagent at room temperature, thus proving that they are the stereoisomers, and **19a** is more stable than **19b**. MM2 calculations for each isomer revealed that, though two conformations (A and B) are possible, the α-CH_2COOMe epimer always has smaller steric energy than the β-CH_2COOMe epimer has: the difference of ths steric energies for the most stable conformations between α and β epimers is *ca.* 1.5 kcal/mol. We therefore conclude that **19a** and **19b** are the α- and β-epimers concerning the stereochemistry of the side chain, respectively.

When a mixture of the keto-acids **18** was treated with dimethyloxosulfonium methylide prepared from trimethyloxosulfonium tetrafluoroborate, a single oxido-acid **20** was produced, which gave a methyl ester **21** (83% from **18**) on methylation with diazomethane. We thought that under this methylenation condition the less stable isomer **18b** might firstly be epimerized into the more stable isomer **18a** then methylenated. The same oxido-ester **21** was directly obtained from a mixture of **19a** and **19b** under a similar methylenation condition, though the yield was lower (52%). Since a model experiment[14] has shown

NII-Electronic Library Service

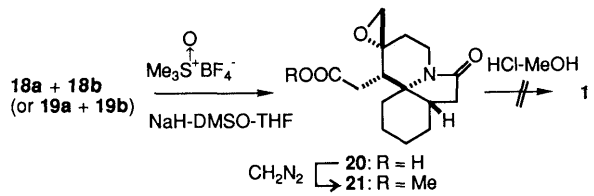

Chart 4

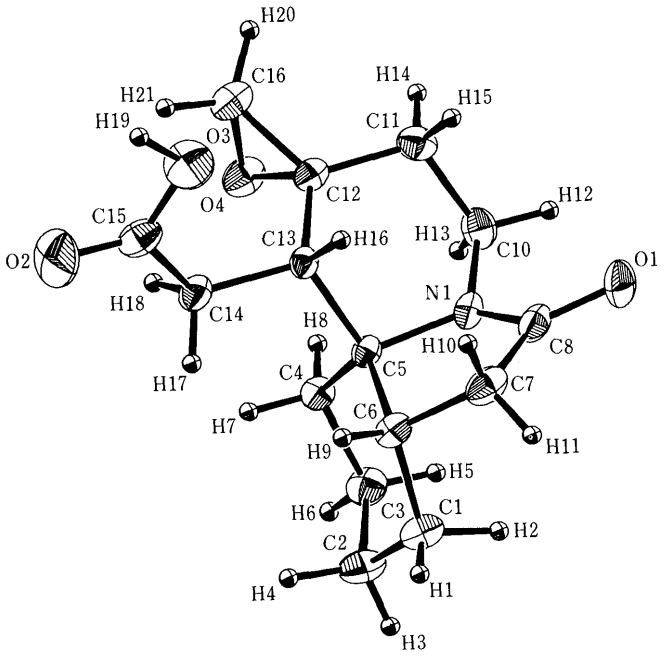

Fig. 1. ORTEP Drawing of Compound **20**

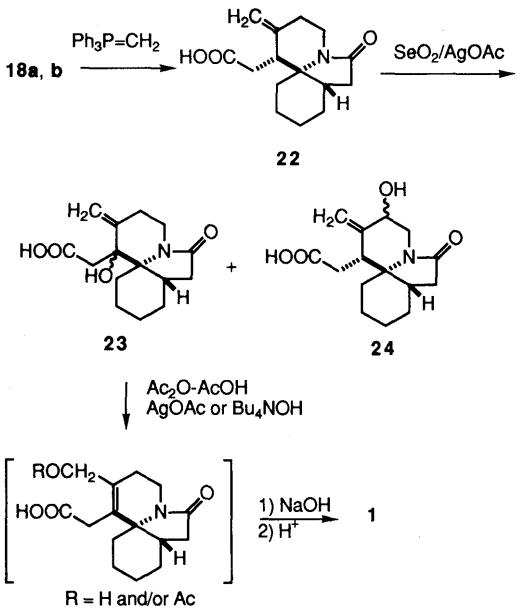

Chart 5

that this methylenation occurs from the opposite side of the side chain, the product should have the stereochemistry depicted. This assignment was verified by an X-ray crystallographic analysis of **20**. The result (Fig. 1) showed that the compound had the $^4C_1$ conformation for ring A.

Since the acid catalyzed cyclization of compound **20** was unsuccessful (details will be reported separately), we turned our attention to a different route: conversion of the carbonyl group into a methylene group and allylic oxidation followed by an allylic rearrangement.

Wittig reaction for a mixture of the keto-acids **18** with an excess of methylenetriphenylphosphorane in toluene gave the *exo*-methylene derivative **22** as a single product (93%). We again thought that the product should have the more stable equatorial configuration of the side chain, for the same reason as discussed for **20**. Treatment of **22** with selenium dioxide in ethanol–water (5 : 1) in the presence of silver acetate[15] resulted in two hydroxylated compounds, **23** and **24**, in nearly equal amounts (total yield of 99%), both of which showed the presence of a hydroxy group (3350 and 3360 cm^{-1}, respectively. The structures of these compounds were elucidated from the ^{1}H-NMR spectra: compound **23** showed the *exo*-methylene signals at δ 4.86 and 5.00 (each as a broad singlet), while **24** showed the corresponding signals at δ 4.89 and 5.15 (each as a broad singlet) together with a signal of a proton geminal to the hydroxyl at δ 4.20 as a broad singlet.

The allylic rearrangement of the alcohol **23** was achieved, when **23** was heated in acetic acid–acetic anhydride (Ac_2O) with silver acetate (or tetrabutylammonium hydroxide) at 100 °C. The reaction mixture showed the presence of an acetate group (in ^{1}H-NMR) together with the expected δ-lactone **1**. Thus, it was hydrolyzed with NaOH. Acidification of the resulting mixture gave the expected lactone **1** in 21% yield. Attempted rearrangement without silver acetate or tetrabutylammonium acetate (*e.g.*, AcOH, AcOH–Ac_2O or AcOH–Ac_2O–AcONa) did not give the unsaturated δ-lactone **1** upon similar treatment. The lactone **1** was identical with the compound obtained in the above section, supporting the correctness of the assigned structure.

Ambiguity in Kitahara's Synthesis of 8-Oxo-β-erythroidan

In 1974, Kitahara and Matsui[16] reported the synthesis of 8-oxo-β-erythroidan (compound **d**) by the route shown in Chart 6. However, compound **d** was not identical with the above 8-oxo-β-erythroidan **1** in comparisons of the spectral data (Table I). It was also not identical with the structural isomer **29**,[1] which could be derived if the benzylidene derivative had the isomeric structure (**a'**).

As found in a model experiment[14] and in the previous section, the oxido-ester **20** did not give the unsaturated δ-lactone **1** on treatment with methanolic hydrochloride (HCl–MeOH), while the previous authors obtained compound **d** by cyclization of compound **c** with HCl–MeOH.[16] We have also found that neither the methyl ester **19a** nor **19b** is identical with their intermediary methyl ester **b**, since the ^{1}H-NMR data for **19a** and **19b** were different from those reported for compound **b**, indicating that the reported structure for compound **b** is incorrect.

Therefore, we have re-investigated their synthetic route starting from 16-methoxy-8-oxo-*cis*-erythrinan **25**. Birch reduction followed by acid treatment of the resulting dihydro derivative **26** gave two ketones, **27** and **28**, as reported previously.[16] On treatment with benzaldehyde under an alkaline condition, **27** and **28** gave different benzylidene derivatives, **30** (mp 198—200 °C) and **31** (mp 184—186 °C), respectively, though the yield was low in each case.

NII-Electronic Library Service

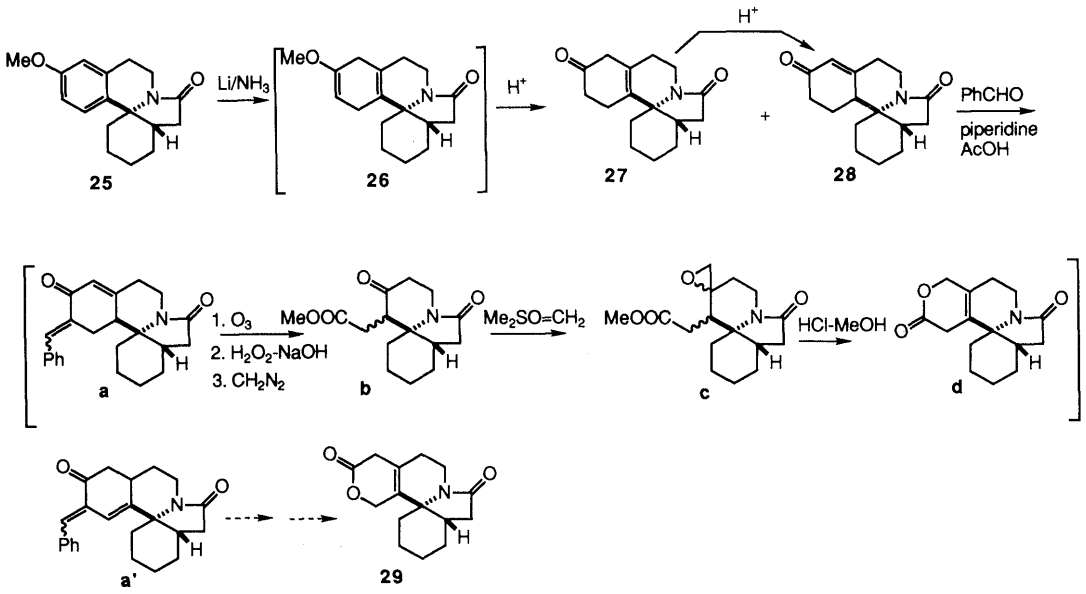

Chart 6

Reported synthesis of 8-oxo-β-erythroidan (Compound **d**) by Kitahara and Matsui.[16]

TABLE I. Comparison of the Spectral Data of 8-Oxo-β-erythroidine **10**, 8-Oxo-β-erythroidan **1**, the Isomer **29**, and Compound **d**

	8-Oxo-β-erythroidine **10**[8]	8-Oxo-β-erythroidan **1**	Isomer **29**[1]	Compound **d**[16]
State	mp 183 °C	mp 190 °C (dec.)	Oil	mp 155—156 °C
IR	1750, 1700	1755, 1725	1745, 1677	1725, 1685
^{1}H-NMR δ(*J*)	(400 MHz)	(500 MHz)	(400 MHz)	(60 MHz)
C_{10}–H_2	3.22 ddd	2.96 ddd	3.00 m	
	(14, 8, 6)	(13.5, 11.5, 5.5)		
	4.34 ddd	4.22 dd (13.5, 7.5)	4.18 dd	
	(14, 8, 2)		(13.5, 7.5)	
–$COCH_2$–	3.10 d	3.13 dquin	3.00 br s	
		(20, 2.5)		
		3.20 br d (20)		
–OCH_2–	4.59 d (16)	4.65 d (15)	4.92 t (2)	4.65 s
	4.73 d (16)	4.71 d (15)	4.91 t (2)	

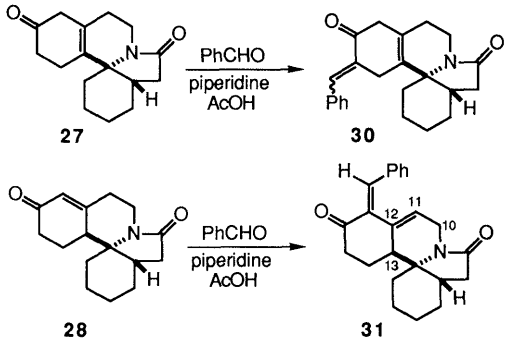

Chart 7

Both **30** and **31** had the same formulae $C_{22}H_{25}NO_2$. In the ^{13}C-NMR spectra, besides expected absorptions of olefinic, phenyl, and carbonyl carbons, compound **30** exhibited nine CH_2 and one CH (δ 34.3) signals, while compound **31** showed eight CH_2, and two CH (δ 42.5 and 34.8) signals, suggesting that the double bond in **30** is tetra-substituted (at C_{12}–C_{13}) and that in **31** is tri-substituted. Thus, the proton at δ 6.65 (s) in **30** is assigned as that of the benzylidene group. The olefinic proton in **31** appeared at δ 5.82 as a quartet of J=3 Hz. The proton of the benzylidene group appeared at δ 7.45 (s) overlapping with the phenyl protons at δ 7.2—7.6. In the H–H correlation spectroscopy (COSY) spectrum of **31**, the olefinic proton (δ 5.82) showed correlation peaks with the protons at C_{10} and the proton at C_{13}, revealing that the double bond is at C_{11}–C_{12}. A decoupling experiment revealed that the coupling constants between the olefinic proton and the protons at C_{10} and C_{13} are all 3 Hz. These data lead to the structures **30** and **31** as depicted, respectively.

The stereochemistry of the benzylidene group in **31** was elucidated by a nuclear Overhauser effect (NOE) experiment. On irradiation of the olefinic proton at δ 5.82, the intensity of the phenyl proton at δ 7.49 (d) was enhanced (0.6%), but that of the proton at δ 7.45 (s) was not changed in the NOE difference spectrum.

Although the physical and spectral data for **31** seemed to agree with those of compound **a** [lit.[16] mp 185.5—186.5 °C, IR: 1680, 1675 (sh), 1650, 1638, 1595, 1585 cm^{-1}, ^{1}H-NMR: δ 5.84 (br s)], the structure was different from that reported. Neither **30** nor **31** would give the methyl ester **19** on ozonolysis followed by methylation. Further structural evidence of compounds **b**, **c**, and **d** was not available.

Experimental

Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were taken in KBr disks, recorded on a JASCO IR-810 spectrophotometer, and are given in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra were recorded on a Hitachi R-600 or a JEOL FX-100 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard and are given in δ. High-resolution mass spectra (HRMS) were determined with a JEOL JMS D-300 spectrometer. Thin layer chromatography (TLC) was performed on precoated Kieselgel 60 F_{254} plates and spots were monitored by UV (254 nm), then developed by spraying 0.5% $Ce(SO_4)_2$–0.5% $(NH_4)_6Mo_7O_{24}$ in 5% H_2SO_4 and heating the plates at 100 °C until coloration took place. Column chromatography was performed on Wakogel C-200 (silica gel). For preparative high-performance liquid chromatography (HPLC), a Kusano CPS-HS-

NII-Electronic Library Service

221-1 with a silica gel column (22 mm i.d. × 100 mm) was used. MM2 calculations were run on Macintosh IIcx with Chem 3D *plus* (ver 3.0). All organic extracts were washed with brine and dried over anhydrous $MgSO_4$ before concentration. Identities were confirmed by comparison of melting point (for crystalline compounds), TLC behavior, and IR and ^{1}H-NMR spectra.

Treatment of 3 with Acetic Acid Compound **3**[6] (200 mg) in 70% AcOH (3 ml) was heated in a sealed tube at 130 °C for 8 h and the solvent was evaporated off. The residue in AcOEt was purified by passing it through a short silica gel column with AcOEt to give the pyrone **5** (100 mg, 57%), as colorless prisms from AcOEt, mp 156—158 °C. IR: 1715, 1700, 1670. ^{1}H-NMR: 6.57 (1H, s, H-14), 3.92 (3H, s, OMe). ^{13}C-NMR: 172.8 s, 160.3 s, 159.5 s, 159.0 s, 144.7 s, 119.3 s, 114.5 d, 61.7 s, 52.9 q, 37.2 d, 35.8 t, 35.0 t, 34.2 t, 26.7 t, 21.6 t, 20.4 t, 19.7 t. HRMS *m/z*: Calcd for $C_{17}H_{19}NO_5$: 317.1264. Found: 317.1264.

Transformation of 5 into the Lactone-acid (7) Compound **5** (317 mg) was heated with 10% NaOH (1 ml) at 80 °C for 1 h. After addition of $NaBH_4$ (42 mg), the mixture was stirred at room temperature for 1 h, then acidified with 10% HCl, and extracted with $CHCl_3$ to give the crude lactone-acid **7** (202 mg, 66%).

The crude **7** (100 mg) in MeOH (5 ml) was methylated with ethereal diazomethane for 5 min. Purification of the product by HPLC with AcOEt as an eluent gave **8a** (52 mg, 50%) and **8b** (47 mg, 45%). **8a**: Colorless prisms from AcOE–hexane, mp 117—119 °C. IR: 1765, 1740, 1700. ^{1}H-NMR: 5.07 (1H, br s, H-17), 3.78 (3H, s, OMe), 3.28 (2H, br s, H-14). ^{13}C-NMR: 174.3 s, 167.9 s × 2, 135.0 s, 123.3 s, 79.1 d, 61.7 s, 53.1 q, 36.4 t, 34.1 d, 33.1 t, 30.9 t, 30.6 t, 26.1 t, 25.1 t, 20.1 t, 19.8 t. HRMS *m/z*: Calcd for $C_{17}H_{21}NO_5$: 319.1420. Found: 319.1403. **8b**: Colorless gum. IR ($CHCl_3$): 1760, 1680. ^{1}H-NMR: 5.04 (1H, br s, H-17), 3.82 (3H, s, OMe), 3.27 (2H, br s, H-14). ^{13}C-NMR: 173.4 s, 167.9 s × 2, 134.6 s, 123.5 s, 78.3 d, 61.7 s, 53.1 q, 36.1 t, 34.4 d, 33.4 t, 31.6 t, 30.9 t, 26.3 t, 25.0 t, 19.4 t × 2. HRMS *m/z*: Calcd for $C_{17}H_{21}NO_5$: 319.1420. Found: 319.1428.

Photodecarboxylation of 7 Compound **7** (94 mg) was dissolved in 3 N NH_4OH (150 ml) and internally irradiated with a 100 W high-pressure mercury lamp (without a filter) at room temperature for 2 h. The mixture was concentrated under reduced pressure below 50 °C to one-third volume, acidified with 10% HCl, and extracted with $CHCl_3$. Chromatography of the product gave, from the AcOEt–EtOH (20 : 1) eluate, 8-oxo-β-erythroidan (**1**), (14 mg, 18%), as colorless prisms from AcOEt, mp 190 °C (dec.). HRMS *m/z*: Calcd for $C_{15}H_{19}NO_3$: 261.1362. Found: 261.1359. ^{13}C-NMR: 173.9 s, 168.8 s, 130.6 s, 124.2 s, 70.4 t, 61.4 s, 36.2 t, 34.3 d, 33.1 t, 31.1 t, 30.6 t, 26.2 t, 23.9 t, 19.7 t, 19.6 t. Other data see Table I.

D-Furano-8-oxo-*cis*-erythrinan (13) A solution of D-furano-7,8-dioxo-erythrinan (**11**)[17] (5.0 g) and methanesulfonyl chloride (14.1 g) in pyridine (100 ml) was stirred at room temperature for 80 min. The mixture was acidified with 10% HCl, and extracted with CH_2Cl_2 to give the enol-mesylate **12** (6.3 g, 95%), as colorless prisms from MeOH–CH_2Cl_2, mp 169—171 °C. IR: 1680. ^{1}H-NMR: 7.33, 6.54 (each 1H, d, J=2 Hz, furan-H), 3.42 (3H, s, mesyl). HRMS *m/z*: Calcd for $C_{15}H_{17}NO_5S$: 323.3664. Found: 323.3671.

Compound **12** (0.5 g) in EtOH (30 ml) containing 10% NaOH (0.5 ml) was hydrogenated over Raney Ni (7.5 g) at 2 kg/cm^2 at room temperature for 25 min. After removal of the catalyst and the solvent, the residue was taken up in $CHCl_3$, washed with water, and concentrated to give **13** (0.3 g, 92%), as colorless prisms from AcOEt, mp 118—119 °C. IR: 1680. ^{1}H-NMR: 7.29, 6.44 (each 1H, d, J=2 Hz, furan-H). HRMS *m/z*: Calcd for $C_{14}H_{17}NO_2$: 231.1260. Found: 231.1263.

Oxidation of 13 with NBS A mixture of **13** (1.3 g) and NBS (3.0 g) in dioxane–H_2O (5 : 1, 25 ml) was stirred at room temperature for 1.5 h. The mixture was quenched with 10% Na_2SO_3, acidified with 10% HCl, and extracted with CH_2Cl_2. The product from the organic extract was dissolved in 10% K_2CO_3 and washed with CH_2Cl_2. The aqueous layer was acidified with 10% HCl and extracted with $CHCl_3$. Concentration of the extract gave the hydroxy-lactone **15** as a solid mass, which was recrystallized from MeOH as colorless prisms (1.06 g, 72%), mp 228.5—230.5 °C. IR: 3275, 1770, 1675. ^{1}H-NMR: 5.91 (1H, s, H-14), ^{13}C-NMR: 171.8 s, 167.2 s, 169.3 s, 114.9 d, 104.5 s, 62.6 s, 37.5 d, 36.8 t, 34.4 t, 33.7 t, 29.3 t, 25.6 t, 20.7 t, 20.6 t. HRMS *m/z*: Calcd for $C_{14}H_{17}NO_4$: 263.1156. Found: 263.1145.

Treatment of the Hydroxy-lactone 15 with Diazomethane Ethereal diazomethane was added to a solution of **15** (100 mg) in Et_2O (5 ml) and CH_2Cl_2 (10 ml) until evolution of N_2 gas ceased, then the solvent was evaporated off. The product was chromatographed with AcOEt to give adducts **16a** (76 mg, 63%) and **16b** (23 mg, 19%). **16a**: Colorless prisms from Et_2O, mp 126—130 °C. IR: 1730, 1690. ^{1}H-NMR: 5.10 (2H, d, J=9 Hz, $=NCH_2-$), 3.77 (3H, s, OMe). MS *m/z*: 319 (M^+). **16b**: Colorless prisms from Et_2O, mp 158—160 °C. IR: 1730, 1695. ^{1}H-NMR: 4.84 (2H, d, J=8 Hz, $=NCH_2-$), 3.68 (3H, s, OMe). MS *m/z*: 319 (M^+).

$NaBH_4$ Reduction of 15 A mixture of **15** (100 mg) and $NaBH_4$ (8 mg) in EtOH (10 ml) was stirred at 0 °C for 1 h. After evaporation of the solvent, the mixture was extracted with $CHCl_3$. The product **17** was crystallized from acetone as colorless prisms (73 mg, 78%), mp 132—134 °C. IR: 1763, 1690. UV (EtOH): 212 nm (ε=12700). ^{1}H-NMR: 5.96 (1H, d, J=1.7 Hz, H-14), 5.09 (1H, ddd, J=11.7, 5.9, 1.7 Hz, H-12). *Anal.* Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: 67.85; H, 6.76; N, 5.56. HRMS *m/z*: Calcd for $C_{14}H_{17}NO_3$: 247.1209. Found: 247.1210.

Hydrogenation of 15 and Subsequent Esterification Compound **15** (1.1 g) in EtOH (80 ml) was hydrogenated over 10% Pd–C (1.1 g) under 4 kg/cm^2 for 4 h at room temperature. After removal of the solvent and catalyst, the residue was dissolved in saturated $NaHCO_3$ solution, which was washed with CH_2Cl_2. The aqueous layer was acidified with 10% HCl and extracted with CH_2Cl_2 to give the keto-acid **18** as a crystalline mass. This was dissolved in ether–CH_2Cl_2 and methylated with ethereal diazomethane. The product was chromatographed in AcOEt–hexane (3 : 1) to give the methyl esters **19a** (0.72 g, 61% from **15**) and **19b** (0.35 g, 30% from **15**). **19a**: Colorless prisms from AcOEt, mp 93—96 °C. IR: 1740, 1712, 1685. ^{1}H-NMR: 3.69 (3H, s, OMe). ^{13}C-NMR: 206.3 s, 174.8 s, 172.2 s, 66.4 s, 55. 6 d, 52.0 q, 39.9 t, 37.1 t, 35.5 t, 33.9 d, 29.0 t × 2, 26.2 t, 21.6 t, 19.3 t. HRMS *m/z*: Calcd for $C_{15}H_{21}NO_4$: 279.1470. Found: 279.1482. **19b**: Colorless prisms from AcOEt, mp 83—85 °C. IR: 1745 (sh), 1735, 1700. ^{1}H-NMR: 3.69 (3H, s, OMe). ^{13}C-NMR: 208.3 s, 173.8 s, 171.1 s, 64.4 s, 52.1 d, 52.1 q, 35.7 t, 35.5 t, 34.5 t, 33.1 t, 32.8 t, 31.4 d, 24.3 t, 20.2 t, 19.3 t. HRMS *m/z*: Calcd for $C_{15}H_{21}NO_4$: 279.1470. Found: 279.1478.

Epimerization of 19 with Sodium Methoxide (1) A solution of **19b** (200 mg) in 5% MeONa–MeOH (5 ml) was stirred at room temperature for 2 h. The cooled solution was neutralized with 10% HCl, and concentrated to dryness, then the residue was extracted with $CHCl_3$. The product in AcOEt (3 : 1) was purified by passing it through a short silica gel column to give **19a** (164 mg, 82%).

(2) Compound **19a** (150 mg) was treated with 5% MeONa–MeOH (5 ml) and worked up as above. The starting material (**19a**, 128 mg) was recovered unchanged.

Methylenation of the Keto-acid 18 with Dimethyloxosulfonium Methylide (1) Trimethyloxosulfonium tetrafluoroborate: Silver tetrafluoroborate (12.0 g) in H_2O (50 ml) was added to a solution of trimethyloxosulfonium iodide (14.1 g) in H_2O (200 ml) and the mixture was stirred at room temperature for 1 h. The precipitate was removed by filtration and the filtrate was concentrated under reduced pressure. The crystalline residue was recrystallized from MeOH to give trimethyloxosulfonium tetrafluoroborate as colorless prisms. (7.0 g, 65%), mp 270—275 °C. *Anal.* Calcd for $C_3H_9OS \cdot BF_4$: C, 20.07; H, 5.04; S, 17.82. Found: C, 20.07; H, 5.05; S, 17.67.

(2) A mixture of NaH (50% oil dispersion, 144 mg) and dimethyl sulfoxide (DMSO, 15 ml) in tetrahydrofuran (THF, 20 ml) was stirred for 15 min under an argon atmosphere. Trimethyloxosulfonium tetrafluoroborate (0.54 g) and the keto-acid **18** (265 mg) were added to the above mixture and the whole was stirred at 0 °C for 15 min and then at room temperature overnight. The mixture was quenched with saturated NH_4Cl solution, acidified with 10% HCl, and extracted with $CHCl_3$. The organic layer was re-extracted with 5% K_2CO_3. The aqueous layer was acidified with 10% HCl and extracted with $CHCl_3$. A portion of the product was crystallized from AcOEt to give *rel*-[1*R*,2*S*,7a*R*,11a*R*]-1,2,3,4,7,7a,8,9,10,11-decahydro-2-epoxymethylene-6-oxo-6*H*-pyrido[2,1-*i*]indoleacetic acid **20** as colorless prisms, mp 167—169 °C. IR: 2600, 1720, 1630. ^{1}H-NMR: 2.42, 2.60 (each 1H, d, J=3.5 Hz, oxirane), see Fig. 1.

Compound **20** was methylated with ethereal diazomethane to give the methyl ester **21**, which was crystallized from AcOEt–hexane as colorless needles (243 mg, 83% from **18**), mp 105—106 °C. IR: 1740, 1685. ^{1}H-NMR: 2.33, 2.43 (each 1H, d, J=3.5 Hz, oxirane), 3.62 (3H, s, OMe). ^{13}C-NMR: 173.8 s, 172.8 s, 64.7 s, 56.0 s, 51.8 q, 48.4 t, 43.0 d, 36.7 t, 34.1 t, 33.6 d, 32.6 t, 28.4 t, 28.1 t, 24.5 t, 20.1 t, 18.3 t. HRMS *m/z*: Calcd for $C_{16}H_{23}NO_4$: 293.1625. Found: 293.1607.

Methylenation of the Keto-ester 19 with Dimethyloxosulfonium Methylide A mixture of keto-ester **19** (1.0 g) was methylenated with trimethyloxosulfonium tetrafluoroborate (1.9 g) and NaH (0.52 g) and worked up as described above to give **21** (0.55 g, 52%).

Wittig Reaction of the Keto-acid 18 with Methylenetriphenylphosphorane A mixture of powdered methyltriphenylphosphonium bromide (6.71 g) and

NII-Electronic Library Service

potassium *tert*-amyloxide (11 ml of 1.66 mol/l solution) was refluxed for 30 min. Compound **18** (200 mg) was added to the above mixture and the whole was heated under reflux for 6 h. The mixture was acidified with 10% HCl and extracted with CH_2Cl_2. On concentration of the extract to one-fifth volume, crystalline material appeared in the solvent, and this was filtered off. The filtrate was passed through a short silica gel column with CH_2Cl_2. The eluate was extracted with 5% NaOH. The aqueous layer was acidified with 10% HCl and re-extracted with CH_2Cl_2 to give the *exo*-methylene derivative **22** (461 mg, 93%), as colorless prisms from AcOEt, mp 180—183 °C. IR: 1710, 1630. ^{1}H-NMR: 5.02, 4.81 (each 1H, s, $=CH_2$). ^{13}C-NMR: 176.0 s, 174.4 s, 144.1 s, 110.6 t, 64.9 s, 48.7 d, 37.6 t, 36.6 t, 35.3 t, 34.4 d, 32.5 t, 27.8 t, 24.3 t, 19.9 t, 18.8 t. HRMS *m/z*: Calcd for $C_{15}H_{21}NO_3$: 263.1520. Found: 263.1520.

Selenium Dioxide Oxidation of the *exo*-Methylene Derivative 22 A mixture of the *exo*-methylene derivative **22** (75 mg), SeO_2 (125 mg), and silver acetate (302 mg) in EtOH–H_2O (5 : 1, 9.6 ml) was heated in a sealed tube at 100 °C for 5 h, then the mixture was filtered and the filtrate was concentrated. The residue was chromatographed on silica gel with 3% MeOH–AcOEt to give **23** (40 mg, 50%) and **24** (39 mg, 49%). **23**: Colorless prisms from AcOEt, mp 195—208 °C (dec.). IR: 3350, 1700, 1620. ^{1}H-NMR: 5.00, 4.86 (each 1H, s, $=CH_2$). HRMS *m/z*: Calcd for $C_{15}H_{21}NO_4$: 279.1470. Found: 279.1448. **22**: Colorless prisms from AcOEt, mp 183 °C. IR: 3360, 1700, 1630. ^{1}H-NMR: 5.15, 4.89 (each 1H, s, $=CH_2$), 4.20 (1H, br s, –CHOH). ^{13}C-NMR: 174.8 s, 173.6 s, 146.8 s, 111.6 t, 71.4 d, 64.7 s, 44.2 t, 42.9 d, 36.6 t, 34.1 d, 32.2 t, 27.7 t, 23.3 t, 19.7 t, 18.7 t. HRMS *m/z*: Calcd for $C_{15}H_{21}NO_4$: 279.1470. Found: 279.1482.

Transformation of the Allylic Alcohol (23) into 8-Oxo-β-erythroidan (1) (1) A mixture of **23** (40 mg) and silver acetate (72 mg) in AcOH (4 ml)–Ac_2O (2 ml) was heated in a sealed tube at 100 °C for 5 h. Dilute HCl was added to the cooled mixture and the precipitate was removed by filtration. The filtrate was extracted with $CHCl_3$. The product showed signals due to Ac at δ 2.18 and 2.21 in the ^{1}H-NMR spectrum. This was heated with 10% NaOH (5 ml) at 100 °C for 5 h. The mixture was acidified with 10% HCl, then extracted with $CHCl_3$, and the product was purified by chromatography (AcOEt : MeOH = 99 : 1) to give **1** (8 mg, 21%).

(2) A mixture of **23** (50 mg) and tetra-*n*-butylammonium hydroxide (160 mg) in AcOH (5 ml)–Ac_2O (2.5 ml) was heated at 145 °C for 10 h. The mixture was diluted with $CHCl_3$, washed with water, dried over anhydrous Na_2SO_4, and concentrated. The residue was treated with 10% NaOH (5 ml) at 100 °C for 5 h and worked up as described above to give **1** (9 mg, 19%).

Benzylidenation of the Enone 27 Benzylidenation was done by Kitahara and Matsui's procedure.[16] Benzaldehyde (88 mg) in benzene (2 ml) was added at once to a stirred mixture of the enone **27** (200 mg), piperidine (40 mg), and acetic acid (26 mg) in benzene (8 ml), and the mixture was refluxed with stirring for 7 h under an argon atmosphere. The reaction mixture was poured into water and extracted with $CHCl_3$. The product was chromatographed to give, from the $CHCl_3$–Et_2O (15 : 1) eluate, a benzylidene derivative **30** (92 mg, 34%), as yellow crystals from *n*-PrOH, mp 198—200 °C. IR: 1710, 1670, 1595. ^{1}H-NMR: 7.2—7.6 (5H, m, ArH), 6.65 (1H, s, =CHPh), 4.27 (1H, dd, J=13, 8 Hz, H-10), 3.03 (1H, dt, J=13, 6 Hz, H-10). ^{13}C-NMR: 201.0 s, 174.6 s, 140.2 s, 136.1 s, 135.3 s, 132.0 d, 129.2 s, 129.2 d, 128.1 × 2 d, 128.1 d, 63.3 s, 40.1 t, 36.7 t, 34.3 d, 33.6 t, 30.6 t, 26.8 t, 26.7 t, 24.3 t, 20.2 t, 19.4 t. MS *m/z*: 347 (M^+). *Anal.* Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 79.01; H, 7.42; N, 4.08.

Benzylidenation of the Enone 28 The enone **28** (200 mg) was treated with benzaldehyde (88 mg) and piperidine (40 mg) and worked up as described above. The product was chromatographed to give **31** (100 mg, 37%), as yellow crystals from *n*-PrOH, mp 184—186 °C. IR 1690, 1680, 1640, 1590, 1585. ^{1}H-NMR: 7.2—7.6 (5H, m, ArH), 7.45 (1H, s, =CHPh), 5.82 (1H, q, J=3 Hz, =CH–), 4.37, 3.32 (each 1H, dt, J=20, 3 Hz, H-10), 2.78 (1H, m, H-13). ^{13}C-NMR: 199.8 s, 174.1 s, 137.1 d, 136.1 s, 134.9 s, 130.2 s, 129.5 × 2 d, 129.0 d, 128.7 × 2 d, 125.1 d, 62.4 s, 42.5 d, 38.6 t, 38.2 t, 37.2 t, 34.8 d, 28.4 t, 24.2 t, 21.0 t, 20.9 t, 19.5 t. MS *m/z*: 347 (M^+). *Anal.* Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 78.89; H, 7.39; N, 4.20.

X-Ray Crystallographic Analysis of 20 Reflection data were collected on a Rigaku AFC-5R four-circle diffractometer controlled by the MSC/AFC program package, using MoK_α radiation monochromated by a graphite monochromator, in the 2θ–ω scan mode. Reflections with intensity above the $3\sigma(I)$ level were used for the structure determination. The structures were solved by Mithril and refined by a full-matrix least-squares method using anisotropic temperature factors for non-hydrogen atoms. All hydrogen atoms were located from the Fourier map and refined with isotropic temperature factors. Positional parameters are listed in Table II.

TABLE II. Positional Parameters and B_{eq} for Compound **20**

Atom	*x*	*y*	*z*	B_{eq}
O(1)	0.7770 (3)	1.0974 (2)	0.2808 (1)	5.6 (2)
O(2)	1.0838 (4)	0.5833 (2)	0.3447 (2)	8.7 (2)
O(3)	1.1311 (4)	0.7163 (3)	0.2909 (2)	6.8 (2)
O(4)	1.1188 (2)	0.8942 (2)	0.4499 (1)	4.5 (1)
N(1)	0.8291 (3)	0.9977 (2)	0.3645 (1)	3.2 (1)
C(1)	0.5745 (4)	0.8619 (4)	0.3762 (2)	4.5 (2)
C(2)	0.5721 (5)	0.8418 (4)	0.4465 (2)	5.0 (2)
C(3)	0.6751 (4)	0.9074 (4)	0.4790 (2)	4.2 (2)
C(4)	0.8121 (4)	0.8791 (3)	0.4548 (2)	3.2 (2)
C(5)	0.8293 (3)	0.8899 (2)	0.3828 (1)	2.7 (1)
C(6)	0.7097 (3)	0.8513 (3)	0.3436 (2)	3.4 (2)
C(7)	0.7115 (4)	0.9194 (4)	0.2850 (2)	4.5 (2)
C(8)	0.7721 (3)	1.0151 (3)	0.3083 (2)	3.9 (2)
C(10)	0.9321 (4)	1.0637 (3)	0.3891 (2)	4.1 (2)
C(11)	1.0655 (4)	1.0219 (3)	0.3695 (2)	4.1 (2)
C(12)	1.0782 (3)	0.9122 (3)	0.3851 (1)	3.2 (2)
C(13)	0.9656 (3)	0.8467 (2)	0.3604 (2)	2.7 (1)
C(14)	0.9811 (4)	0.7352 (3)	0.3760 (2)	3.6 (2)
C(15)	1.0693 (4)	0.6707 (4)	0.3361 (2)	4.5 (2)
C(16)	1.2115 (4)	0.8744 (4)	0.3988 (2)	4.7 (2)
H(1)	0.519 (4)	0.822 (3)	0.352 (2)	5 (1)
H(2)	0.539 (3)	0.937 (3)	0.372 (2)	4.5 (9)
H(3)	0.486 (4)	0.856 (3)	0.461 (2)	6 (1)
H(4)	0.593 (4)	0.764 (4)	0.450 (2)	8 (1)
H(5)	0.659 (3)	0.976 (3)	0.469 (2)	5 (1)
H(6)	0.671 (4)	0.896 (3)	0.527 (2)	6 (1)
H(7)	0.823 (3)	0.808 (3)	0.465 (1)	3.6 (8)
H(8)	0.879 (3)	0.918 (2)	0.476 (1)	3.4 (8)
H(9)	0.722 (3)	0.788 (2)	0.333 (1)	1.8 (6)
H(10)	0.768 (4)	0.892 (3)	0.252 (2)	5 (1)
H(11)	0.624 (4)	0.932 (3)	0.269 (2)	6 (1)
H(12)	0.919 (3)	1.129 (3)	0.371 (2)	4.0 (8)
H(13)	0.922 (3)	1.069 (3)	0.434 (2)	4.7 (9)
H(14)	1.133 (4)	1.059 (3)	0.388 (2)	5 (1)
H(15)	1.074 (3)	1.032 (3)	0.324 (2)	5 (1)
H(16)	0.968 (3)	0.854 (2)	0.310 (1)	2.1 (6)
H(17)	0.894 (3)	0.701 (3)	0.376 (2)	4.4 (9)
H(18)	1.021 (3)	0.729 (2)	0.416 (2)	3.6 (8)
H(19)	1.186 (5)	0.662 (4)	0.271 (3)	11 (2)
H(20)	1.292 (5)	0.923 (4)	0.398 (2)	9 (1)
H(21)	1.232 (4)	0.798 (3)	0.392 (2)	5 (1)

Crystal Data: Orthorhombic, a=10.074 (1) Å, b=13.312 (1) Å, c=21.102 (6) Å. V=2830 (2) Å^3. Z=8. D_c=1.31 g/cm^3. Space group, *Pbcn*. Reflections used for calculation, 1444. R=0.052.

References and Notes

1) Synthesis of *Erythrina* and Related Alkaloids. XXXIII. Part XXXII: Y. Tsuda, A. Ishiura, S. Hosoi, and K. Isobe, *Chem. Pharm. Bull.*, **40**, 1697 (1992).
2) D. H. R. Barton, R. D. Bracho, C. J. Potter, and D. A. Widdowson, *J. Chem. Soc., Perkin Trans. 1*, **1974**, 2278.
3) Review: Y. Tsuda and T. Sano, "Studies in Natural Product Chemistry, Vol. 3 (Stereoselective Synthesis, Part B)" ed. by Atta-ur-Rahman, Elsevier, Amsterdam 1989, p. 455.
4) The synthesis of β-erythroidan as its 8-oxo derivative was reported (ref. 16). However, that synthesis is now revealed to be ambiguous (see also the last section).
5) Preliminary communication: K. Isobe, K. Mohri, Y. Itoh, Y. Toyokawa, N. Takeda, J. Taga, and Y. Tsuda, *Chem. Pharm. Bull.*, **35**, 2618 (1987).
6) K. Isobe, K. Mohri, K. Tokoro, C. Fukushima, F. Higuchi, J. Taga, and Y. Tsuda, *Chem. Pharm Bull.*, **36**, 1275 (1988).
7) K. Isobe, K. Mohri, J. Taga, Y. Sasaki, and Y. Tsuda, *Chem. Pharm. Bull.*, **40**, 2188 (1992).
8) A. S. Chawla, A. H. Jackson, and P. Ludgate, *J. Chem. Soc., Perkin*

NII-Electronic Library Service

Trans. 1, **1982**, 2903.
9) *a*) R. W. Denny and A. Nickon, *Organic Reactions*, **20**, 185, 282 (1973); *b*) H. Hikino, Y. Hikino, and I. Yoshioka, *Chem. Pharm. Bull.*, **12**, 755 (1964).
10) N. Clauson-Kaas and F. Limborg, *Acta Chem. Scand.*, **6**, 551 (1952).
11) K. Takeda, M. Ikuta, M. Miyawaki, and K. Tori, *Tetrahedron*, **22**, 1159 (1966).
12) K. Wiesner, T. Y. R. Tsai, R. Kumar, and H. Sivaramakrishnan, *Helv. Chim. Acta*, **67**, 1128 (1984).
13) The presence of this intermediate will be discussed in detail in a forthcoming communication.
14) Y. Tsuda, A. Ishiura, S. Takamura, S. Hosoi, K. Isobe, and K. Mohri, *Chem. Pharm. Bull.*, **39**, 2797 (1991).
15) The reaction without silver acetate gave a reddish crystalline mass, which could not readily be purified.
16) T. Kitahara and M. Matsui, *Agric. Biol. Chem.*, **38**, 171 (1974).
17) Y. Tsuda, Y. Sakai, A. Nakai, M. Kaneko, Y. Ishiguro, K. Isobe, J. Taga, and T. Sano, *Chem. Pharm. Bull.*, **38**, 1462 (1990).

NII-Electronic Library Service