Studies toward Total Synthesis of Non-aromatic *Erythrina* Alkaloids. (2).[1] A General Method for Synthesis of Perhydro-6*H*-pyrido[2,1-*i*]indole Derivatives: Synthesis of Isoerythroidine Skeleton

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A general method for synthesis of a physiologically important skeleton, perhydro-6*H*-pyrido[2,1-*i*]indole, through cyclization of an active methylene group to an *N*-acyliminium, was developed. Treatment of the ketoester 5 with $BF_3 \cdot Et_2O$ in methylene chloride resulted in deacetalization of the ethylene acetal group accompanied with the expected double cyclization to give the tricyclic product 8 in 83% yield, and 8 was smoothly decarbomethoxylated to give decahydro-6*H*-pyrido[2,1-*i*]indole-2,6-dione (9). The former compound 8 was converted into derivatives of the isoerythroidine skeleton, 14 and 16.

Keywords 6*H*-pyrido[2,1-*i*]indole; intramolecular cyclization; tandem cyclization; active methylene; *N*-acyliminium; *Erythrina* alkaloid; erythroidine; isoerythroidine; unsaturated δ-lactone

6*H*-Pyrido[2,1-*i*]indole, particularly its perhydro derivative, is the common skeleton for both aromatic and non-aromatic *Erythrina* alkaloids, which are remarkable for curare-like action following oral administration.[2] Known venoms such as histrionicotoxin, pumiliotoxin B, and gephyrotoxin also possess a part of this skeleton. Therefore, the physiological activity of perhydro-6*H*-pyrido[2,1-*i*]-indole derivatives is of interest. However, little synthetic work has been done except for aromatic erythrinan derivatives.[3] Recently we described, in connection with studies directed toward total synthesis of non-aromatic *Erythrina* alkaloids, a method of preparing perhydro-pyridoindoles through oxidative cleavage of a trimethoxy-benzene or a furan ring of aromatic erythrinan derivatives.[4] However, the method has limitations in synthesizing compounds which have substituents vulnerable to oxidation. Therefore, a new general method based on a different strategy leading to a perhydro-pyridoindole skeleton is required.

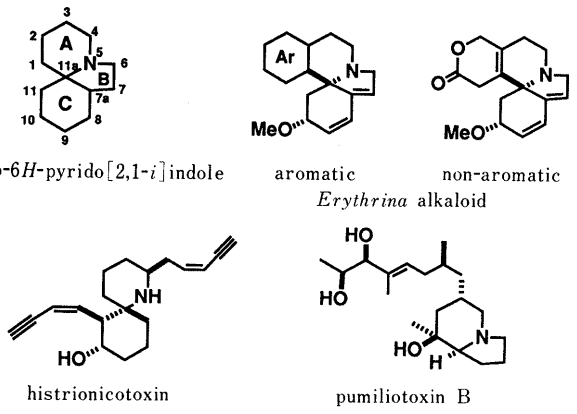

Chart 1

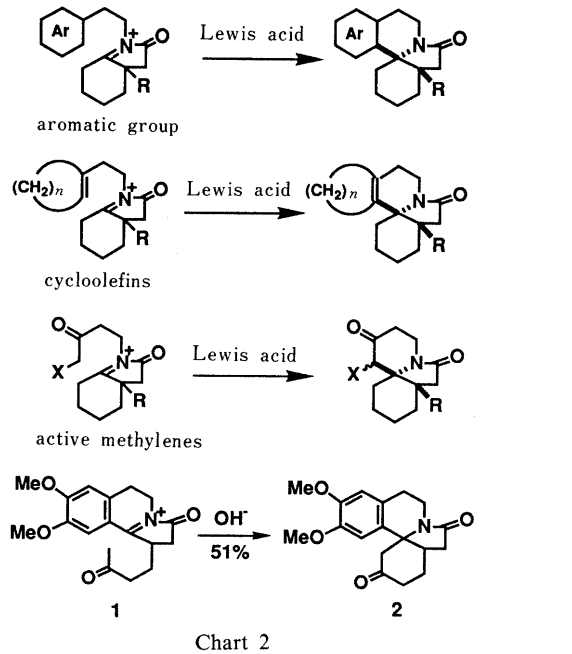

Chart 2

Aromatic erythrinan derivatives are readily available by intramolecular cyclization of the aromatic group of *N*-arylethylhydroindole derivatives to an *N*-acyliminium, catalyzed by Lewis acids (method A).[3] Analogous cyclization of *N*-cycloalkenylethylhydroindole derivatives proceeds as well (method B).[5] We supposed that an active methylene might undergo similar cyclization to an *N*-acyliminium (method C), though there is no example of this sort of cyclization except for the base-catalyzed cyclization of **1** to **2**.[6]

This paper deals with the synthesis of perhydro-pyrido-indole derivatives according to this strategy, and describes the transformation of the product into derivatives of the isoerythroidine skeleton.

Results and Discussion

Lewis Acid Catalyzed Cyclization of Active Methylene Group to *N*-Acyliminium As a simple model of the cyclization, we chose compound **6** which would be formed by deacetalization of the ethylene acetal **5**. When this deacetalization is done under Lewis acid catalysis, the cyclization of the resulting carbonyl to the amide group and the subsequent cyclization of **6** to **8** under the same reaction condition are expected to occur.

With this tandem double cyclization in mind, we synthesized the precursor **5** as follows. Firstly, the ethylene acetal of 2-oxocyclohexaneacetic acid (**3**) was condensed with β-alanine to give an amide **4**. Activation of the carboxyl group of **4** as an imidazolide followed by reaction with methyl potassium malonate in the presence of magnesium

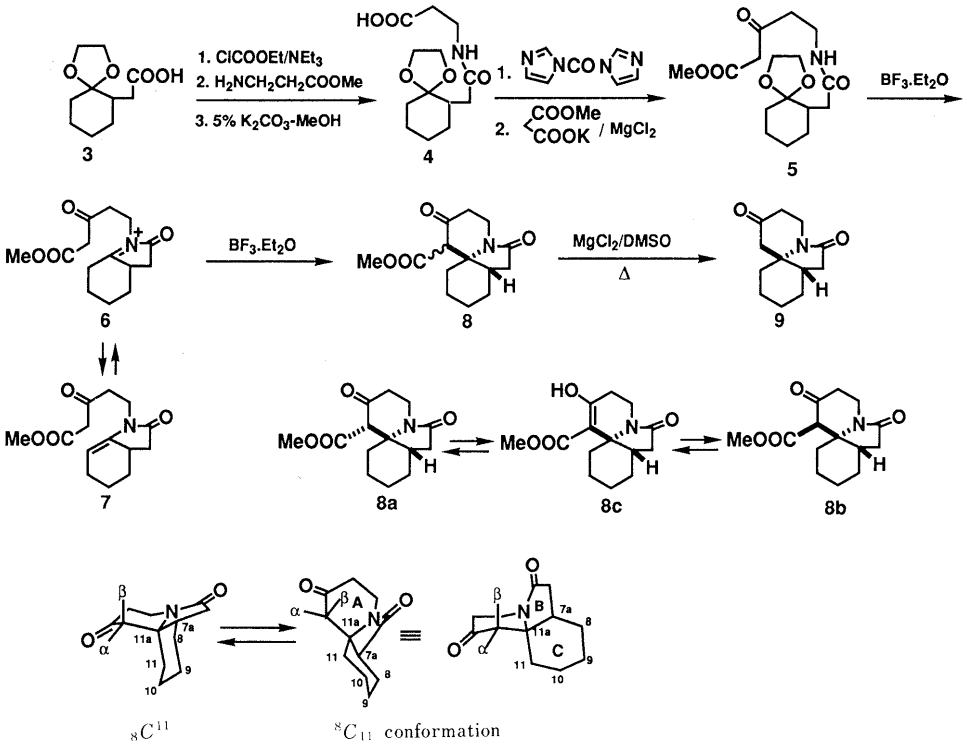

Chart 3

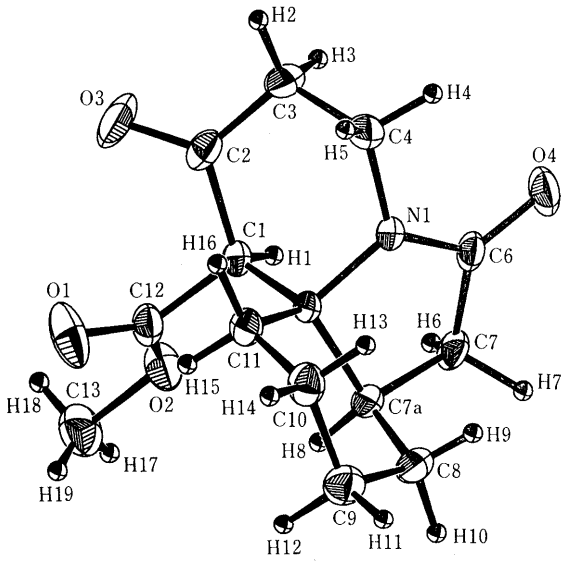

Fig. 1. ORTEP Drawing of **8a** (The Enantiomeric Form Is Indicated)

chloride gave the ketoester **5**.

Treatment of **5** with $BF_3 \cdot Et_2O$ in methylene chloride resulted in deacetalization to afford the expected double cyclization product **8**, together with the enamide **7**, which was considered to be derived by isomerization of the intermediate **6**. Further treatment of **7** with $BF_3 \cdot Et_2O$ gave **8**, as expected.

Compound **8** was obtained as a mixture of stereoisomers, one of which (**8a**) crystallized from ether as prisms of mp 124—125 °C. The X-ray analysis of a single crystal of **8a** revealed the stereostructure of this compound to be as shown in Fig. 1: the B/C rings are *cis*-junctured, the methoxycarbonyl group is *trans* to H-7a and equatorially oriented to ring A (chair form), and ring C has an $^8C_{11}$ conformation.

On standing in $CDCl_3$, **8a** gradually changed into a mixture, which was identical with that obtained by the cyclization reaction. Analogous epimerization was also observed on a thin layer chromatography (TLC) plate: each spot corresponding to **8a** or **8b** gave two spots (of **8a** and **8b**), when two dimensional TLC was performed. Thus, **8a** and **8b** are stereoisomers concerning the configuration of the methoxycarbonyl group. In fact, MM2 calculations showed that **8a** is not the most stable isomer; the 1β-COOMe isomer with ring A in $_8C^{11}$ conformation has the lowest steric energy (35.2 kcal/mol) and the energy difference between α and β isomers is *ca.* 1 kcal/mol.

Heating a mixture of **8** with magnesium chloride in dimethyl sulfoxide (DMSO) resulted in decarbomethoxylation[7] to give decahydro-6*H*-pyrido[2,1-*i*]indole-2,6-dione (**9**) in good yield. Both **8** and **9** are appropriately functionalized for introduction of a further substituent into this skeleton.

Synthesis of Compounds with the Isoerythroidine Skeleton Since all attempts at direct introduction of a C_1-unit at C-1 of **8** were unsuccessful,[8] probably due to the sterically hindered nature of C-1 in this compound, we turned our attention to reduction of the methoxycarbonyl group to a hydroxymethyl group. Thus, a mixture of **8** was treated with ethylene glycol and $BF_3 \cdot Et_2O$ in methylene chloride to give an ethylene acetal **10** as a 6:1 mixture of the stereoisomers. We consider that the major constituent in this product is the isomer of axial orientation (**10b**), which was formed from the more stable β isomer in **8**. The following transformations supported this assignment.

For reduction of the methoxycarbonyl group in **10**, we found that the $LiBH_4$–methanol combination is the best reagent. Thus, reduction of **10** with this reagent in ether afforded the alcohol **11** in 85% yield. Although the product

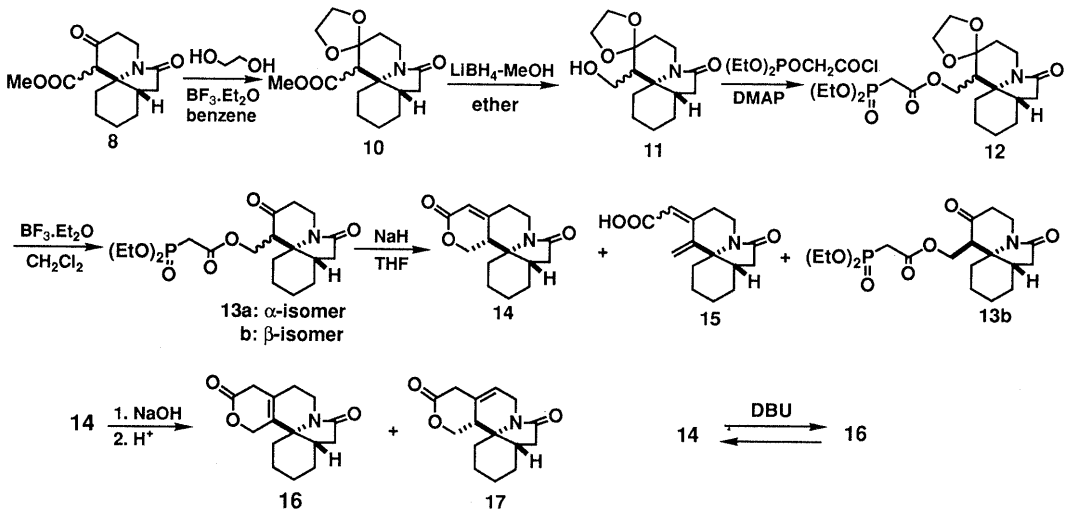

Chart 4

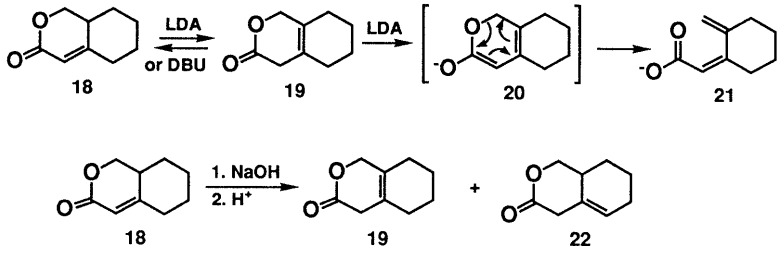

Chart 5

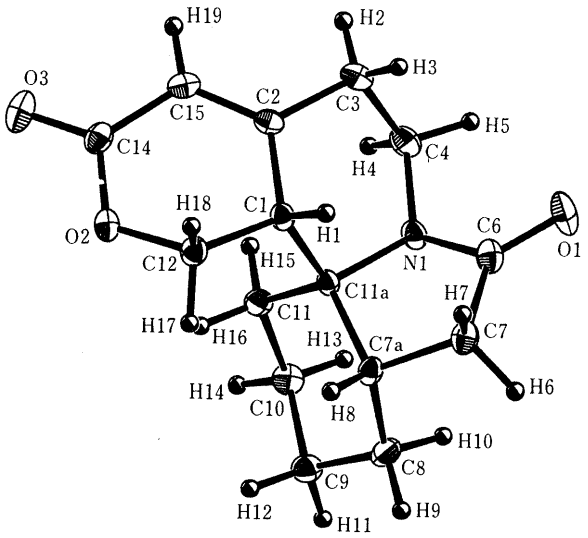

Fig. 2. ORTEP Drawing of **14**

was obtained as a mixture of stereoisomers, the reduction at the early stage indicated that the major isomer in **10** is more rapidly reduced, as expected, since the methoxycarbonyl group of equatorial orientation is hindered by the ethylene acetal ring and ring C, and thus should resist approach of a hydride reagent. The alcohol **11** (mixture) was converted to the phosphonate **12** by the action of diethylphosphonoacetyl chloride. Deacetalization of **12** with $BF_3 \cdot Et_2O$ in wet methylene chloride gave 89% yield of the ketophosphonate **13**, which was again a mixture of two stereoisomers, as evidenced by the peaks at 11.9 and 17.4 min in high-performance liquid chromatography (HPLC), in a ratio of 1 : 2.5. In this deacetalization, it was found that the minor isomer was initially produced, then the major isomer increased with time. This suggests that the initial deacetalization product is the axial isomer (**13b**), which epimerizes under the influence of $BF_3 \cdot Et_2O$ to give an equatorial isomer (**13a**). In agreement with this consideration, treatment of this mixture with NaH in ether effected the cyclization of only the major isomer (**13a**) giving rise to an unsaturated lactone **14**, together with a seco-acid **15**, the minor isomer (**13b**) remaining unaffected. The seco-acid **15** should be formed from **14** (or its isomerized product **16**) as discussed already by Forsch *et al.*[9] for the model compound **19**. The stereostructure of the lactone **14** was definitively established by an X-ray analysis (Fig. 2), which indicated that the C1–C12 bond is *trans* to H-7a and equatorially oriented to ring A, and ring C is in $^8C_{11}$ conformation, coinciding with the stereostructure of the crystalline ketoester **8a**.

In a previous paper,[10] we showed that, for bicyclic unsaturated δ-lactones, the conjugated structure **18** is the most stable in the lactone form, while, when treated with NaOH, it exclusively isomerized (after acid treatment) into the unconjugated lactones, **19** and **22**, suggesting that the unconjugated forms are more stable in the hydroxy-acid form. Thus, treatment of **14** with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) in benzene at 120 °C gave a 3 : 1 mixture of **14** and **16**, and treatment with 10% NaOH (followed by acidification) gave a 3 : 2 mixture of **16** and **17**. These isomeric lactones were separated by recycling preparative HPLC.

These lactones are skeletal isomers of non-aromatic *Erythrina* alkaloids, α- and β-erythroidine, for which we

propose the name "isoerythroidines".

Experimental

General Unless otherwise stated, the following procedures were adopted. Melting points were determined on a Yanaco micro hot stage melting point apparatus and are uncorrected. Infrared (IR) spectra were taken in $CHCl_3$ solutions and are given in cm^{-1}. Proton-nuclear magnetic resonance (^{1}H-NMR) spectra were taken with a JEOL FX-100 (100 MHz) spectrometer in $CDCl_3$ solution with tetramethylsilane as an internal standard, and the chemical shifts are given in δ values. Mass spectra (MS) and high-resolution MS (HRMS) were taken with a Hitachi M-80 machine and M^+ and/or major peaks are indicated as m/z. Column chromatography was performed on Wakogel C-200 (silica gel), gas chromatography (GC) on a 1.5% OV-1 (on Shimalite W, 1 m × 4 mm) column, and HPLC on an octadodecyl silica column (Toso TSK-gel 120T, 4.6 × 250 mm, for analytical and 20 × 250 mm for preparative purposes). For TLC, Merck precoated plates GF_{254} were used and spots were monitored under ultraviolet (UV) (254 nm), then developed by spraying 1% $Ce(SO_4)_2$ in 10% H_2SO_4 and heating the plates at 100 °C until coloration took place. All organic extracts were washed with brine and dried over anhydrous sodium sulfate before concentration. Identities were confirmed by mixed melting point determination (for crystalline compounds) and also by comparisons of TLC behavior and ^{1}H-NMR and IR spectra.

The Acid 4 Ethyl chloroformate (0.95 ml) was added to an ice-cooled mixture of 2-oxocyclohexaneacetic acid ethylene acetal (**3**, 1.81 g) and triethylamine (1.83 g) in CH_2Cl_2 (30 ml), and the mixture was stirred for 30 min. A solution of β-alanine methylester hydrochloride (2.47 g) and triethylamine (1.83 g) in CH_2Cl_2 (15 ml) was added to the mixture, and stirring was continued for a further 1 h at 0 °C. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with AcOEt to yield the amide-ester (2.2 g, 85%). ^{1}H-NMR: 6.22 (1H, br s, NH), 3.87 (4H, br s, OCH_2CH_2O), 3.63 (3H, s, OMe), 3.44 (2H, q, J=6 Hz, $NHC\underline{H}_2$), 2.47 (2H, t, J=6 Hz, $C\underline{H}_2COOMe$), 2.43 (1H, br dd, J=13.2, 4.4 Hz, CH).

The amide-ester (2.2 g) in 5% K_2CO_3–MeOH (60 ml) was heated at 50 °C for 1.5 h. After evaporation of MeOH, the mixture was diluted with water and washed with ether. The aqueous layer was acidified with HCl and extracted with AcOEt to give the acid **4** (2.03 g, 97%), as a colorless powder from acetone–ether, mp 125—127 °C. IR (KBr): 3380, 2500, 1720, 1696, 1632, 1609. ^{1}H-NMR (CD_3OD): 3.92 (4H, s, OCH_2CH_2O), 3.36 (2H, q, J=6.5 Hz, $NHC\underline{H}_2$), 2.49 (2H, t, J=6.5 Hz, $C\underline{H}_2COOH$). MS: 271 (M^+, 7), 199 (7), 155 (34), 99 (100). *Anal.* Calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.28; H, 7.91; N, 5.23.

The Ketoester 5 A mixture of **4** (1.03 g) and 1,1′-carbonyldiimidazole (0.78 g) in tetrahydrofuran (THF, 30 ml) was stirred overnight at room temperature under an Ar atmosphere. Anhydrous $MgCl_2$ (440 mg) and methyl potassium malonate (655 mg) were added to this mixture, and the whole was heated under reflux for 20 min, then at 45 °C for 6 h with stirring. The solvent was evaporated off and the residue was extracted with AcOEt. The organic layer was washed with 5% citric acid solution, saturated aqueous $NaHCO_3$ and water, dried, and concentrated. Chromatography of the residue gave, from the benzene–acetone (2 : 1) eluate, the ketoester **5** (1.07 g, 86%), as colorless needles from ether, mp 92—93 °C. IR: 1746, 1716, 1662. ^{1}H-NMR: 6.21 (1H, br s, NH), 3.93 (4H, br s, OCH_2CH_2O), 3.74 (3H, s, OMe), 3.49 (2H, q, J=5.5 Hz, $NHC\underline{H}_2$), 3.46 (2H, s, $COC\underline{H}_2COOMe$), 2.79 (2H, t, J=5.5 Hz, CH_2CO), 2.46 (1H, br dd, J=13.5, 4.4 Hz, CH). ^{13}C-NMR: 202.4 s, 173.0 s, 167.3 s, 110.1 s, 64.6 t, 64.5 t, 52.4 q, 49.0 t, 42.6 t, 41.7 d, 36.5 t, 34.3 t, 33.9 t, 30.1 t, 24.5 t, 23.7 t. MS: 327 (M^+, 26), 282 (14), 255 (17), 182 (17), 155 (86), 99 (100). *Anal.* Calcd for $C_{16}H_{25}NO_6$: C, 58.70; H, 7.70; N, 4.28. Found: C, 58.48; H, 7.92; N, 4.28.

Treatment of 5 with $BF_3 \cdot Et_2O$ A mixture of the ketoester **5** (127 mg) and $BF_3 \cdot Et_2O$ (0.24 ml) in CH_2Cl_2 (2.5 ml) was heated in a sealed tube at 50 °C for 2 h. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. Chromatography of the product gave the enamide **7** (15 mg, 14.5%) and the tricyclic compound **8** (85 mg, 82.5%). Compound **8** showed two spots (**8a** and **8b**) on TLC. Crystallizations of **8** from ether gave **8a** (upper spot) as colorless prisms, mp 126—128 °C. IR (KBr): 1758, 1697, 1681. ^{1}H-NMR (400 MHz): 4.45 (1H, ddd, J=13.7, 8.3, 1.5 Hz, one of H-4), 3.76 (3H, s, OMe), 3.46 (1H, s, H-1). ^{13}C-NMR: 201.4 (s, CO), 175.1 (s, CO_2Me), 167.3 (s, CONH), 66.2 (s, C-11a), 64.7 (d, C-1), 52.2 (q, Me), 39.5 (t, C-3), 37.2 (t, C-7), 35.0 (t, C-4), 34.5 (d, C-7a), 29.2 (t, C-8), 25.6 (t, C-11), 21.6 (t, C-10), 19.5 (t, C-9). *Anal.* Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.21; N, 5.28. Found: C, 63.43; H, 7.35; N, 5.26.

The Enamide **7**: Gum. ^{1}H-NMR: 5.63 (1H, t-like, =CH), 3.65 (3H, s, OMe), 3.40 (2H, s, $COC\underline{H}_2COOMe$), 2.86 (2H, t, J=6.3 Hz, $COCH_2$). MS: 265 (M^+, 18), 233 (45), 191 (19), 164 (67), 150 (100), 122 (23). HRMS: Calcd for $C_{14}H_{19}NO_4$: 265.1311. Found: 265.1319.

Treatment of 7 with $BF_3 \cdot Et_2O$ A mixture of **7** (43 mg) and $BF_3 \cdot Et_2O$ (*ca.* 0.15 ml) in CH_2Cl_2 (2.5 ml) was heated in a sealed tube at 50 °C for 1.5 h with stirring and worked up as described above to give **8** (25 mg, 58%).

Epimerization of 8 (1) In $CDCl_3$: A solution of **8a** in $CDCl_3$ was kept standing at room temperature. After 24 h, the solution showed ^{1}H-NMR peaks corresponding to **8c** (COOMe at δ 3.85, s; one of H-4 at δ 4.16, dd, J=14, 8 Hz; OH at δ 12.8, s) and **8b** (COOMe at δ 3.74, s; H-1 at δ 3.59, d, J=1.5 Hz; and one of H-4 at δ 4.39, ddd, J=13.2, 8.3, 1.5 Hz); these peaks gradually increased with a corresponding decrease in those of **8a**. The ratio of **8a** : **8b** : **8c** in the mixture obtained by the above cyclization was 2.5 : 3 : 2 as calculated from the COOMe peak intensities.

(2) On a TLC Plate: A mixture of **8** was developed on a 5 × 5 cm silica gel plate (Macherey-Nagel, SIL G-25 UV_{254}) with benzene–acetone (3 : 1). The plate was dried with a drier and kept for 30 min at room temperature, then developed at right angles to the first development. Each spot gave two spots corresponding to **8a** and **8b**.

MM2 Calculations for 8 The minimum steric energies were calculated for the most stable conformations of each isomer of **8** by Chem 3D plus software (v. 3.0). For $^8C_{11}$ conformation: α-isomer, 37.3; β-isomer, 36.7 kcal/mol. For $_8C^{11}$ conformation: α-isomer (ring A, boat), 36.2; β-isomer, 35.2 kcal/mol.

Decahydro-6*H*-pyrido[2,1-*i*]indole-2,6-dione (9) A mixture of **8** (52.5 mg), anhydrous $MgCl_2$ (93 mg), and *tert*-heptylmercaptan (*ca.* 0.1 ml) in DMSO (1 ml) was heated at 130 °C for 3.5 h. The mixture was poured into 1 N HCl and extracted with $CHCl_3$. Chromatography of the product gave the starting material **8** (10 mg, 19%) from the benzene–acetone (3 : 1) eluate and **9** (31 mg, 76%) from the benzene–acetone (2 : 1) eluate, as colorless prisms from ether, mp 112—114 °C. IR: 1712, 1682. ^{1}H-NMR: 4.36 (1H, ddd, J=13, 7, 2.5 Hz, one of H-4), 3.05 (1H, m, one of H-4). MS: 207 (M^+, 88), 164 (100), 151 (61), 122 (44). *Anal.* Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.48; H, 8.43; N, 6.71.

The Alcohol 11 A mixture of the ketoester **8** (453 mg), ethylene glycol (5.2 ml), and $BF_3 \cdot Et_2O$ (0.8 ml) in benzene (15 ml) was heated under reflux for 5 h. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with benzene. Chromatography of the product gave the ethylene acetal **10** (511 mg, 93%) as a colorless oil, which was a mixture of **10a** and **10b**. GC: 12.9, 13.7 min (6 : 1). IR: 1736, 1673. ^{1}H-NMR: 4.18—3.66 (4H, m, OCH_2CH_2O), 3.65, 3.64 (total 3H, s, OMe). MS: 309 (M^+, 25), 266 (23), 150 (11), 99 (100). HRMS: Calcd for $C_{16}H_{23}NO_5$: 309.1575. Found: 309.1610.

$LiBH_4$ (380 mg) and MeOH (1.05 ml) were added to a solution of the ethylene acetal **10** (511 mg) in ether (35 ml), and the mixture was heated under reflux with monitoring of the progress of the reaction by TLC. After 6 h, the mixture was poured into ice-water and extracted with $CHCl_3$. Chromatography of the product gave the alcohol **11** (410 mg, 85% from **8**) from the benzene–acetone (2 : 1) eluate, as a gum. HPLC: 14.3, 15.0 min (1 : 5). IR: 3540, 1670. ^{1}H-NMR: 4.14—3.36 (7H, m, OCH_2CH_2O, $C\underline{H}_2OH$, one of H-4). MS: 281 (M^+, 29), 238 (54), 151 (28), 117 (21), 99 (100). HRMS: Calcd for $C_{15}H_{23}NO_4$: 281.1625. Found: 281.1640.

The Phosphonate 12 A solution of diethylphosphonoacetyl chloride, prepared from diethylphosphonoacetic acid (1.28 g), in CH_2Cl_2 (5 ml) was added to a mixture of the alcohol **11** (624 mg) and 4-dimethylaminopyridine (761 mg) in CH_2Cl_2 (35 ml), and the mixture was stirred for 40 min under ice-cooling, and then poured into ice-water and extracted with CH_2Cl_2. Purification of the product by flash chromatography gave the phosphonate **12** (877 mg, 86%) as a colorless oil. HPLC: 33.1, 41.4 min (1 : 3.5). IR: 1728, 1666. ^{1}H-NMR: 4.14 (4H, dq, J=8.3, 7 Hz, $P(O)OCH_2$), 3.96 (4H, br s, OCH_2CH_2O), 3.34, 2.96 (total 2H, each d, J=22.7, 21.5 Hz, $P(O)CH_2$), 1.35 (6H, t, J=7 Hz, $OCH_2C\underline{H}_3$). MS: 459 (M^+, 23), 264 (100), 263 (63), 250 (35), 150 (48), 149 (55), 99 (73). HRMS: Calcd for $C_{21}H_{34}NO_7P$: 459.2019. Found: 459.1992.

Cyclization of the Ketophosphonate 13 A mixture of the phosphonate **12** (295 mg) and $BF_3 \cdot Et_2O$ (2.25 ml) in CH_2Cl_2 (45 ml) was stirred at room temperature for 30 h. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 to yield the deacetalization product **13** (239 mg). HPLC: 11.9, 17.4 min (1 : 2.5).

A solution of **13** (239 mg) in THF (8 ml) was added to NaH (60% oil dispersion, 31 mg) suspended in THF (7 ml) and the mixture was stirred at 0 °C for 4 h. The mixture was poured into 1 N HCl and extracted with CH_2Cl_2. The organic layer was washed with aqueous $NaHCO_3$ and water, dried, and concentrated. Chromatography of the residue gave the lactone **14** (51 mg, 30%) from the benzene–acetone (1 : 1) eluate and the

TABLE I. Positional Parameters and B_{eq} for **8a**

Atom	x	y	z	B_{eq}
O(1)	0.6828 (6)	0.0355 (4)	0.4415 (6)	7.9 (3)
O(2)	0.7802 (5)	0.2028 (3)	0.5174 (4)	5.0 (2)
O(3)	0.7139 (5)	0.0475 (3)	0.0894 (6)	7.5 (2)
O(4)	0.2893 (5)	0.5511 (3)	−0.0669 (5)	5.2 (2)
N(1)	0.3078 (4)	0.3530 (3)	0.0419 (4)	3.3 (2)
C(1)	0.5805 (6)	0.2199 (3)	0.2350 (5)	3.1 (2)
C(2)	0.6035 (6)	0.1482 (4)	0.0721 (7)	4.1 (2)
C(3)	0.5000 (7)	0.2119 (5)	−0.1051 (7)	4.6 (3)
C(4)	0.3119 (7)	0.2894 (5)	−0.1193 (6)	4.3 (3)
C(6)	0.3216 (6)	0.4749 (3)	0.0613 (6)	3.7 (2)
C(7)	0.3773 (7)	0.4943 (4)	0.2545 (7)	4.0 (2)
C(7a)	0.3483 (6)	0.3816 (4)	0.3432 (6)	3.4 (2)
C(8)	0.1607 (7)	0.4157 (4)	0.3586 (8)	4.3 (3)
C(9)	0.0925 (8)	0.3043 (5)	0.3754 (8)	4.8 (3)
C(10)	0.1033 (7)	0.2242 (5)	0.2205 (7)	4.2 (3)
C(11)	0.2911 (6)	0.1742 (4)	0.2201 (7)	3.6 (2)
C(11a)	0.3801 (5)	0.2780 (3)	0.2131 (5)	2.9 (2)
C(12)	0.6837 (6)	0.1427 (4)	0.4088 (7)	4.1 (2)
C(13)	0.891 (1)	0.1367 (7)	0.688 (1)	6.6 (4)
H(1)	0.651 (5)	0.289 (4)	0.254 (5)	2.8 (8)
H(2)	0.476 (7)	0.151 (5)	−0.212 (7)	6 (1)
H(3)	0.571 (6)	0.272 (4)	−0.117 (6)	5 (1)
H(4)	0.258 (5)	0.357 (4)	−0.220 (6)	3.5 (9)
H(5)	0.228 (6)	0.237 (4)	−0.156 (6)	5 (1)
H(6)	0.513 (6)	0.499 (4)	0.307 (6)	4 (1)
H(7)	0.297 (8)	0.583 (6)	0.272 (8)	7 (1)
H(8)	0.432 (5)	0.349 (4)	0.459 (6)	2.8 (8)
H(9)	0.093 (5)	0.469 (4)	0.263 (5)	2.6 (9)
H(10)	0.165 (8)	0.468 (5)	0.469 (8)	7 (1)
H(11)	−0.039 (9)	0.334 (5)	0.367 (8)	8 (2)
H(12)	0.181 (6)	0.255 (4)	0.492 (6)	4 (1)
H(13)	0.022 (6)	0.273 (4)	0.108 (6)	4 (1)
H(14)	0.045 (7)	0.160 (5)	0.221 (7)	6 (1)
H(15)	0.360 (5)	0.121 (4)	0.324 (5)	2.5 (8)
H(16)	0.305 (5)	0.119 (4)	0.127 (6)	4 (1)
H(17)	0.96 (1)	0.203 (7)	0.75 (1)	11 (2)
H(18)	0.981 (7)	0.089 (5)	0.657 (6)	4 (1)
H(19)	0.81 (1)	0.094 (7)	0.73 (1)	9 (2)

TABLE II. Positional Parameters and B_{eq} for **14**

Atom	x	y	z	B_{eq}
O(1)	0.4471 (2)	0.8122 (3)	0.7980 (2)	4.7 (1)
O(2)	0.5825 (2)	0.0888 (2)	0.6059 (1)	3.23 (8)
O(3)	0.7176 (2)	0.1036 (3)	0.5472 (2)	4.4 (1)
N(1)	0.5644 (2)	0.5730 (3)	0.8012 (1)	2.51 (8)
C(1)	0.5102 (2)	0.3656 (3)	0.6616 (2)	2.17 (9)
C(2)	0.5926 (2)	0.4664 (3)	0.6292 (2)	2.5 (1)
C(3)	0.6086 (3)	0.6614 (4)	0.6583 (2)	3.3 (1)
C(4)	0.6426 (3)	0.6781 (4)	0.7705 (2)	3.2 (1)
C(6)	0.4653 (2)	0.6495 (4)	0.7991 (2)	3.1 (1)
C(7)	0.3826 (2)	0.5007 (4)	0.7950 (2)	3.1 (1)
C(7a)	0.4530 (2)	0.3271 (4)	0.8125 (2)	2.4 (1)
C(8)	0.4953 (2)	0.2756 (4)	0.9222 (2)	3.2 (1)
C(9)	0.5983 (2)	0.1541 (4)	0.9581 (2)	3.0 (1)
C(10)	0.6950 (2)	0.2424 (4)	0.9375 (2)	2.9 (1)
C(11)	0.6598 (2)	0.2691 (4)	0.8266 (2)	2.5 (1)
C(11a)	0.5497 (2)	0.3776 (3)	0.7766 (2)	2.01 (8)
C(12)	0.4850 (2)	0.1784 (4)	0.6157 (2)	2.8 (1)
C(14)	0.6523 (2)	0.1863 (4)	0.5747 (2)	2.9 (1)
C(15)	0.6518 (2)	0.3817 (4)	0.5840 (2)	2.9 (1)
H(1)	0.441 (2)	0.424 (3)	0.638 (2)	2.2 (5)
H(2)	0.663 (2)	0.713 (4)	0.640 (2)	4.2 (7)
H(3)	0.539 (2)	0.724 (4)	0.628 (2)	4.0 (7)
H(4)	0.721 (2)	0.632 (3)	0.806 (2)	3.1 (6)
H(5)	0.639 (2)	0.805 (4)	0.793 (2)	3.8 (6)
H(6)	0.347 (2)	0.517 (3)	0.850 (2)	3.7 (6)
H(7)	0.329 (2)	0.510 (3)	0.736 (2)	2.8 (6)
H(8)	0.411 (2)	0.231 (3)	0.775 (2)	2.0 (5)
H(9)	0.432 (2)	0.222 (4)	0.938 (2)	3.5 (6)
H(10)	0.515 (2)	0.391 (4)	0.959 (2)	3.5 (6)
H(11)	0.618 (2)	0.130 (4)	1.027 (2)	3.3 (6)
H(12)	0.581 (2)	0.035 (4)	0.926 (2)	3.0 (6)
H(13)	0.714 (2)	0.359 (4)	0.970 (2)	3.5 (6)
H(14)	0.769 (2)	0.170 (4)	0.961 (2)	3.3 (6)
H(15)	0.720 (2)	0.331 (3)	0.814 (2)	2.0 (5)
H(16)	0.649 (2)	0.147 (4)	0.801 (2)	3.6 (6)
H(17)	0.464 (2)	0.088 (4)	0.661 (2)	3.4 (6)
H(18)	0.427 (2)	0.187 (3)	0.552 (2)	2.5 (5)
H(19)	0.703 (2)	0.441 (4)	0.562 (2)	3.6 (6)

ketophosphonate **13b** (85.5 mg, 32%, HPLC: 11.9 min) from the acetone eluate. Acidification of the $NaHCO_3$ washing and extraction with CH_2Cl_2 gave the seco-acid **15** (34 mg, 20%).

The Lactone **14**: Colorless prisms from ether, mp 214—215 °C. IR: 1728, 1682. ^{1}H-NMR (400 MHz): 6.01 (1H, d, J=0.9 Hz, =CH), 4.56 (1H, dd, J=12.8, 5.5 Hz), 4.52 (1H, dd, J=12.8, 2.7 Hz) (OCH_2), 4.31 (1H, ddd, J=13.1, 4.9, 3.3 Hz), 2.80 (1H, dt, J=13.1, 7.9 Hz) (H-4). ^{13}C-NMR: 173.9 s, 163.0 s, 157.1 s, 117.0 d, 65.6 s, 65.4 t, 46.1 d, 37.3 t, 36.3 t, 34.9 d, 33.6 t, 28.2 t, 25.6 t, 20.7 t, 19.4 t. MS: 261 (M^+, 85), 218 (18), 174 (40), 150 (100), 149 (85), 138 (37). *Anal.* Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.97; H, 7.39; N, 5.35.

The Seco-Acid **15**: Colorless prisms from acetone, mp 158—161 °C. ^{1}H-NMR: 5.78 (1H, s, =CH), 5.16 (2H, s, $=CH_2$), 4.16 (1H, ddd, J=13, 5, 2.8 Hz, one of H-4). MS: 261 (M^+, 100), 246 (21), 218 (86), 202 (32), 150 (33). *Anal.* Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.12; H, 7.22; N, 5.38.

Isomerization of the Lactone 14 (1) With DBU: The lactone **14** (25 mg) in benzene containing 2% DBU (5 ml) was heated in a sealed tube at 110 °C for 5 h. The reaction mixture was diluted with benzene, washed with 1 N HCl, and concentrated. Purification of the residue by a recycling preparative HPLC gave the starting material **14** (8.5 mg) and the isomeric lactone **16** (3 mg).

(2) With NaOH: The lactone **14** (65 mg) was heated with 10% NaOH (5 ml) in a sealed tube at 110 °C for 5 h. The cooled reaction mixture was acidified with dilute H_2SO_4 and stirred for 30 min at room temperature, and then extracted with $CHCl_3$. The product (65 mg) was a mixture of isomeric lactones, **16** and **17**, (*ca.* 3:2) on the basis of the ^{1}H-NMR spectrum. This mixture was heated in a sealed tube with 2% pyridinium *p*-toluenesulfonate in benzene (5 ml) at 110 °C for 2 h.[10] The reaction mixture was diluted with $CHCl_3$, washed with saturated aqueous $NaHCO_3$ and water, dried, and concentrated. Purification of the residue by a recycling preparative HPLC gave **16** (26 mg) and a mixture of **14** and **17** (28 mg).

The Lactone **16**: Colorless oil. IR: 1745, 1677. ^{1}H-NMR (400 MHz): 4.92, 4.91 (each 1H, t, J=2 Hz, OCH_2), 4.18 (1H, dd, J=13.5, 7.5 Hz, H-4), 2.90 (2H, br s, $COCH_2$). ^{13}C-NMR: 174.3 s, 169.1 s, 131.8 s, 125.8 s, 67.5 t, 61.2 s, 36.4 t, 34.8 d, 34.5 t, 33.2 t, 31.9 t, 27.1 t, 26.5 t, 20.2 t, 19.9 t. MS: 261 (M^+, 60), 218 (100). HRMS: Calcd for $C_{15}H_{19}NO_3$: 261.1364. Found: 261.1382.

The Lactone **17**: This was obtained as a colorlss solid contaminated with lactone **14**. ^{1}H-NMR: 5.55 (1H, br s, =CH), 4.0—4.4 (4H, overlapped signals, OCH_2 and $CONCH_2$), 3.22 (2H, br s, $COCH_2$).

X-Ray Crystallographic Analyses 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[11] and refined by a full-matrix least-squares method taking account of anisotropic temperature factors for non-hydrogen atoms. All hydrogen atoms were located from the difference Fourier map and refined with isotropic temperature factors. Positional parameters are given in Tables I and II.

Crystal Data for **8a:** Triclinic, a=8.287(3) Å, b=10.990(2) Å, c=7.828(3) Å, α=90.66(2)°, β=106.90(3)°, γ=74.58(2)°. V=655.9(4) Å^3. Z=2, D_c=1.34 g/cm^3. Space group, $P\bar{1}$. Reflections, 1577. R=0.073.

Crystal Data for **14**: Monoclinic, a=12.665(2) Å, b=7.4040(8) Å, c=14.601(2) Å, β=112.28(1)°. V=1266.9(3) Å^3. Z=4. D_c=1.37 g/cm^3. Space group, $P2_1/a$. Reflections, 1644. R=0.042.

References and Notes

1) Part XXXII of Synthesis of *Erythrina* and Related Alkaloids. Part XXXI: Y. Tsuda, S. Hosoi, N. Katagori, C. Kaneko, and T. Sano,

Heterocycles, **33**(2), 497 (1992).
2) L. E. Craig, "The Alkaloids," Vol. 5, ed. by R. H. F. Manske, Academic Press, New York, 1955, p. 265.
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) *a*) K. Isobe, K. Mohri, M. Maeda, T. Takeda, and Y. Tsuda, *Chem. Pharm. Bull.*, **35**, 2602 (1987); *b*) K. Isobe, K. Mohri, Y. Itoh, Y. Toyokawa, N. Takeda, J. Tada, and Y. Tsuda, *ibid.*, **35**, 2618 (1987); *c*) K. Isobe, K. Mohri, K. Tokoro, C. Fukushima, F. Higuchi, J. Taga, and Y. Tsuda, *ibid.*, **36**, 1275 (1988).
5) *a*) V. Boekelheide, M. Muller, J. Jack, T. T. Grossnickle, and M. Chang, *J. Am. Chem. Soc.*, **81**, 3955 (1959); *b*) M. Muller, T. T. Grosnickle, and V. Boekelheide, *ibid.*, **81**, 3959 (1959); *c*) A. Mondon and B. Neffgen, *Chem. Ber.*, **103**, 3050 (1970); *d*) We have found that Lewis acids effectively catalyze this cyclization to give ring D non-aromatic derivatives under mild conditions. This will be reported separately.
6) V. Prelog, A. Langemann, O. Rogig, and M. Ternbah, *Helv. Chim. Acta*, **42**, 1301 (1959).
7) Y. Tsuda and Y. Sakai, *Synthesis*, **1981**, 118.
8) For example, treatment of **8** with HCHO–Et_3N gave a compound in which two hydroxymethyl groups were introduced at C-3, and reaction with $PhCH_2OCH_2Cl$ and base gave the *O*-alkylated product, exclusively.
9) J. V. Forsch, I. T. Harrison, B. Lythgoe, and A. K. Saksena, *J. Chem. Soc., Perkin Trans. 1*, **1974**, 118.
10) Y. Tsuda, A. Ishiura, S. Takamura, S. Hosoi, K. Isobe, and K. Mohri, *Chem. Pharm. Bull.*, **39**, 2797 (1991).
11) G. Gilmore, "Mithril: a Computer Program for the Automatic Solution of Crystal Structures from X-Ray Data," University of Glasgow, Scotland, 1983.