Studies toward Total Synthesis of Non-aromatic *Erythrina* Alkaloids. (1).¹⁾ Synthesis and Isomerization of Unsaturated Bicyclic δ -Lactones

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As a model of the C/D ring system of erythroidines, bicyclic unsaturated δ -lactones were synthesized in a regio-selective manner, and their isomerization reactions in the presence of acid, base (DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene), and NaOH were studied. In the lactone form, the 6-ene (**3**) was the most unstable and isomerized to the 5-ene (**1**) then to the 1⁽⁶⁾-ene (**2**). The latter two lactones equilibrate to give *ca.* 3:2 mixture of **1** and **2** in the presence of DBU. On the contrary, in the opened form (NaOH), the lactone **1** was the most unstable and isomerized to **2** and **3**. The 1⁽¹⁰⁾-ene (**4**) was inert under all of the conditions examined.

Keywords *Erythrina* alkaloid; erythroidine; intramolecular Horner–Emmons reaction; decarbomethoxylation; unsaturated δ -lactone; 3-oxabicyclo[4.4.0]dec-5-en-4-one; 3-oxabicyclo[4.4.0]dec-1⁽⁶⁾-en-4-one; 3-oxabicyclo[4.4.0]dec-6-en-4-one; 3-oxabicyclo[4.4.0]dec-1⁽¹⁰⁾-en-4-one; isomerization

Erythrina alkaloids are remarkable for their strong curare-like action on oral administration. There are more than 60 alkaloids of this group. Total syntheses of those which have an aromatic group at ring D (aromatic *Erythrina* alkaloids) have been accomplished,²⁾ but synthesis of so-called non-aromatic *Erythrina* alkaloids, all of which have an unsaturated lactone ring at ring D instead of an aromatic group, is still elusive.

In 1958, Boekelheide and Morrison³⁾ reported that, on treatment with 10% NaOH solution, α -erythroidine exclusively isomerized into β -erythroidine. The reaction includes an interesting migration of a conjugated double bond to an unconjugated position.

In the connection with synthetic studies of erythroidines, we are interested in the above migration and wondered whether it is due to an inherent property of the erythroidine skeleton or not. Therefore, as a model experiment, we have examined isomerization reactions of a simple bicyclic system corresponding to rings C and D of erythroidines, because the results obtained should provide useful information for the synthesis of these alkaloids. For this purpose, we have synthesized the four unsaturated lactones **1**–**4** in a selective manner and examined their isomerization reactions under various conditions.

Synthesis of the Unsaturated Lactones **1**–**4** A. The

Lactones **1 and **2**** The syntheses of lactones **1** and **2** were previously reported by Lythgoe's group.⁴⁾ They obtained **1** in 48% yield from 2-acetoxymethylcyclohexanone by Reformatsky reaction with methyl bromoacetate followed by dehydration with acetic anhydride. They also prepared **2** in 44% yield from the enol benzoate **5** (prepared from 2-hydroxymethylcyclohexanone in two steps) by acid hydrolysis, hydride reduction, and Jones oxidation. Our synthesis of these lactones is more straightforward and selective.

2-Hydroxymethylcyclohexanone **6** was phosphonoacetylated with diethylphosphonoacetyl chloride⁵⁾ to give **7** (70%). Intramolecular Horner–Emmons reaction of **7** in dimethoxyethane (DME) on treatment with KH gave the lactone **1**, mp 59–60 °C, in 76% yield.

Treatment of 2-methoxycarbonylcyclohexanone **8a** with 35% formaldehyde and a catalytic amount of triethylamine in methanol gave the 2-hydroxymethyl derivative **9a** in almost quantitative yield.⁶⁾ This was phosphonoacetylated as above and the resulting **10a** was subjected to an intramolecular Horner–Emmons reaction with NaH to yield the lactone **11a**. The corresponding ethyl ester **11b** was similarly synthesized from **8b** via the phosphonoacetate **10b**. When the cyclization of **10b** was performed with EtONa–EtOH, **11b** was obtained in low yield accompanied with a solvolytic ring opening product **12**.

The methoxycarbonyl group of **11a** was removed by application of Tsuda's kinetically controlled decarbomethoxylation method of vinylogous β -keto methyl esters.⁷⁾ Thus, heating of **11a** with $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ in dimethyl sulfoxide (DMSO) containing *tert*-heptylmercaptan at 145 °C for 2 h gave the lactone **2** in 68% yield as a kinetically controlled product. Prolonged heating of the reaction mixture promoted the isomerization of the double bond, thus decreasing the amount of the lactone **2**. The ethyl ester **11b** resisted decarbomethoxylation as expected.

B. The Lactone **3** The lactone **3** was synthesized by a modification of Belleau's procedure.⁸⁾ Prins reaction of the homoallylic acid **13** with trioxane in trifluoroacetic acid at 10 °C for 18 h gave a mixture of **1**, **2**, and **3** in a ratio of *ca.* 2:1:7 in 45% yield. From this mixture, the lactone **3** was purified by preparative high performance liquid chromatography (HPLC) on an octadecyl silica (ODS)

Chart 2

column (see Experimental).

C. The Lactone 4 The lactone **4** is not known, and was synthesized as follows. Methylenation of ethyl 2-oxocyclohexanecarboxylate **14** with dimethyl oxosulfonium methylide gave a single oxirane derivative **15a** in 30% yield. Dimethylsulfonium methylide gave the same oxirane **15a** in 13% yield.

The stereochemistry of the oxirane ring in **15a** was clarified by the following experiments. Compound **14** was transformed to ethyl 2-methylenecyclohexanecarboxylate **16** by Nozaki's methylenation.⁹⁾ Epoxidation of **16** with *m*-chloroperbenzoic acid (*m*CPBA) gave a mixture of two stereoisomeric oxiranes, **15a** and **15b**, in a ratio of 2:1 (determined by HPLC on an ODS column). On the other hand, iodolactonization of the acid **17** derived from **16** gave a single iodolactone **18** quantitatively. The stereochemistry of **18** is clear from a mechanistic consideration of the iodolactonization: the I^+ should attack from the opposite face of the side chain and the carboxylate anion should attack from the back side of the intermediary iodonium ion. Treatment of **18** with EtONa in EtOH gave a single oxirane which was identical with **15a**. Thus, **15a** and **15b** have *syn* and *anti* configurations for O to CH_2COOR , respectively. Predominant formation of **15a** over **15b** in *m*CPBA oxidation may be explained by the Henbest effect.¹⁰⁾

Treatment of **15a** with 2% methanolic hydrochloric acid¹¹⁾ did not give any unsaturated lactones, but instead gave four products, **19**–**22**. Compounds **19** and **20** were γ -lactones (1772 and 1767 cm^{-1} , respectively). The former had the formula $C_9H_{13}O_2Cl$ and contained Cl (MS: M^+ at m/z 190 and 188 were 1:3), and the latter ($C_9H_{14}O_3$) contained a hydroxy group (3440 cm^{-1}) instead of Cl, thus indicating the structures. Compounds **21** and **22** were δ -lactones (1733 and 1725 cm^{-1} , respectively). Compound **21** was isomeric to **19** and contained a Cl atom, and compound **22** contained an OMe group (δ 3.26) instead of

Chart 3

Cl. These and the other spectral data supported the assigned structures. The stereochemistries were assigned from mechanistic considerations, as shown in Chart 4.

On the other hand, heating of **15a** in benzene with pyridinium *p*-toluenesulfonate (PPTS) afforded the lactones **2** and **4** together with a mixture of the aldehyde **23** and a tosylate **24** (**2**:**4**:**23**+**24**=4:6:17). A similar treatment of **15b** gave **2**, **4**, and the hydroxy-lactone **20** in a ratio of 4:9:21. The aldehyde **23** and the lactone **20** are the stereospecific products from the oxiranes **15a** and **15b**, respectively, and the tosylate **24** is also a specific product from **15a** (see Chart 5). The formation of the same unsaturated lactones **2** and **4** from both isomers **15a** and **15b** suggests that these lactones were produced mainly through the carbocation **25**. However, a contribution of the concerted mechanism can not be ruled out, because the ratios of 4/2 from **15a** and **15b** were different (6/4 vs. 9/4).

D. Characterization of the Lactones 1–4 Each of the above unsaturated lactones **1**–**4** was readily purified by

preparative HPLC on an ODS column and characterized spectroscopically as shown in Tables I and II.

Isomerization of Unsaturated Lactones A. Acid-Catalyzed Isomerization Each of the lactones **1**–**4** was heated with 2% PPTS in benzene at 120 °C in a sealed tube for 5 h and the products were analyzed by HPLC. The results are shown in Table III.

The lactone **3** isomerized to **1**, giving rise to a 9:1 mixture of **1** and **3**, while the other lactones were unchanged under these conditions.

B. Base-Catalyzed Isomerization The lactones were heated with 2% 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene at 120 °C in a sealed tube and the products were analyzed by HPLC. The results are shown in Table IV.

The lactone **3** was very labile: it irreversibly isomerized to **1** giving rise to an 8:2 mixture of **1** and **2** after 0.5 h.

The lactones **1** and **2** slowly isomerized to give an equilibrium mixture of **1** and **2** (*ca.* 3:2) from either compound. The lactone **4** was stable under these conditions.

Lithgoe's group⁴⁾ isolated the lactone **1** in 30% yield on isomerization of **2** with piperidine in ethanol (reflux, 17 h). This agrees with our observation.

C. Isomerization with NaOH The lactones were heated with 10% NaOH at 120 °C for 5 h and the product was analyzed by HPLC after acidification and extraction. The results are shown in Table V.

The lactones **2**–**4** were unchanged under these conditions. However, the lactone **1** was unstable and gave a mixture of **1**, **2**, and **3** in a ratio of 1:8:6. The result corresponds to the exclusive isomerization of α -erythroidine to β -erythroidine.³⁾

The above results indicate that for the hydroxy-acid

TABLE I. Characterization of the δ -Lactones 1–4

	1	2	3	4
State	mp 59–60 °C	Oil	Oil	Oil
IR (cm ⁻¹) ^{a)}	1721, 1700	1730	1736	1731
¹ H-NMR ^{b)} δ , (J)				
Olefin H	5.69 br s	—	5.58 br s	5.75 br s
OCH ₂	4.37 dd (11, 6) 3.93 t (11)	4.68 br s	4.33 dd (11, 5) 3.89 t (11)	4.80 dd (13, 1.5) 4.66 dd (13, 1.2)
COCH ₂	—	2.93 br s	3.30 s	2.78 dd (16.5, 6) 2.27 dd (16.5, 11)
HPLC <i>t_R</i> (min) ^{c)}	12.3	16.8	15.4	14.4

a) CHCl₃ solution. b) CDCl₃ solution. c) Column, TSK gel 120T (ODS, 4.6 × 250 mm); mobile phase: 50% MeOH (0.6 ml/min).

TABLE II. ¹³C-NMR Data (100 MHz) for Unsaturated δ -Lactones (in CDCl₃)

Carbon	5-Ene 1	1 ⁽⁶⁾ -Ene 2	6-Ene 3	1 ⁽¹⁰⁾ -Ene 4
1	35.2 d	124.3 s	34.6 d	131.4 s
2	70.6 t	71.7 t	72.6 t	72.0 t
4	164.6 s	169.7 s	170.7 s	171.7 s
5	114.0 d	34.4 t	36.9 t	37.2 t
6	163.3 s	124.3 s	129.0 s	31.5 d
7	33.1 t	24.7 ^{a)} t	123.6 d	24.8 ^{a)} t
8	28.8 ^{a)} t	22.1 t	24.7 t	20.8 ^{a)} t
9	25.9 ^{a)} t	22.1 t	24.4 ^{a)} t	29.3 t
10	24.3 ^{a)} t	28.3 ^{a)} t	21.1 ^{a)} t	124.3 d

a) Assignments may be interchanged in each column.

Fig. 1. HPLC of δ -Lactones 1–4 and Oxiranes 15a and 15b

Mobile phase: 50% MeOH (0.6 ml/min). Column: TSK gel 120T (ODS, 4.6 × 250 mm). Detector: refractive index.

forms, in contrast to the lactone forms, the *exo*-cyclic unsaturated structure **26** is unstable and rapidly isomerizes to the *endo*-cyclic unsaturated structures **27** and **28**. Such a migration of the double bond from an *exo*-cyclic (conjugated) to an *endo*-cyclic (unconjugated) position was supported by the isomerization reaction of the conjugated acid **29** with KOH. On treatment with 10 N KOH at 140 °C for 10 h, **29** gave a 8 : 1 mixture of **13** and **29** with preference for the unconjugated *endo*-cyclic isomer **13**.¹²⁾ The stability

TABLE III. Isomerization of Unsaturated δ -Lactones under Acidic Conditions (PPTS)^{a)}

Compound	Product (%) ^{b)}			
	1	2	3	4
1	100	—	—	—
2	—	100	—	—
3	90	—	10	—
4	—	—	—	100

a) Reaction conditions: 2% PPTS in benzene at 120 °C for 5 h. b) Products were analyzed by HPLC on an ODS column.

TABLE IV. Isomerization of Unsaturated δ -Lactones under Basic Conditions (DBU)^{a)}

Compound	Product (%) ^{b)}			
	1	2	3	4
1	60	40	—	—
2	58	42	—	—
3 ^{c)}	77	22	1	—
4	—	—	—	100

a) Reaction conditions: 2% DBU in benzene at 120 °C for 5 h. b) Products were analyzed by HPLC on an ODS column. c) Reaction time 0.5 h.

TABLE V. Isomerization of Unsaturated δ -Lactones under Basic Conditions (NaOH)^{a)}

Compound	Product (%) ^{b)}			
	1	2	3	4
1	7	53	40	—
2	—	100	—	—
3	2	—	98	—
4	—	—	—	100

a) Reaction conditions: 10% NaOH at 120 °C for 5 h. b) Products were analyzed by HPLC on an ODS column.

Chart 6

and isomerization of these lactones and the corresponding hydroxy acid are summarized in Chart 6.

Lythgoe's group⁴⁾ isolated only the lactone **2** (98%) after treatment of the lactone **1** with 10 N KOH at 130 °C for

18 h. Reinvestigation of their isomerization reaction (at 140 °C) revealed that the products were a mixture of **2** and **3** in a ratio of 1 : 1 after 15 h and in a ratio of 2 : 1 after 30 h.

The findings revealed in this investigation will be very useful for the synthesis not only of natural products but also of unnatural compounds containing an unsaturated lactone ring.

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 chloroform solutions and the data are given in cm^{-1} . Proton nuclear magnetic resonance (^1H -NMR) spectra were taken with a JEOL FX-100 (100 MHz) or a JEOL GX-400 (400 MHz) spectrometer and carbon-13 NMR (^{13}C -NMR) spectra on a JEOL GX-400 (100 MHz), both in chloroform-*d* solutions with tetramethylsilane as an internal standard, and the chemical shifts are given in δ values. Mass spectra (MS) and high-resolution mass spectra (HRMS) were taken with a Hitachi M-80 machine and M^+ and/or major peaks are indicated as m/z (%). Column chromatography was performed on silica gel (Fuji-Devison BW-820MH). For thin layer chromatography (TLC), Merck precoated plates GF₂₅₄ were used and spots were monitored under ultraviolet (UV) (254 nm), then developed by spraying 10% phosphomolybdic acid in EtOH 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 comparison of TLC behavior and ^1H -NMR and IR spectra.

HPLC Conditions Analytical HPLC was performed on a Tosco TSK-gel 120T column (ODS, 4.6×250 mm). Mobile phase: 50% MeOH. Flow rate: 0.6 ml/min. Detection: refractive index. Preparative HPLC was carried out on an ODS column (20×250 mm) with a flow rate of 5 ml/min.

3-Oxabicyclo[4.4.0]dec-5-en-4-one (1) Triethylamine (2.0 g) was added to a mixture of 2-hydroxymethylcyclohexanone (**6**) (1.28 g) and diethylphosphonoacetyl chloride (3.2 g) in CH_2Cl_2 (25 ml) at -78°C under an Ar atmosphere. After being stirred for 30 min at the same temperature, the mixture was poured into ice-water and extracted with CH_2Cl_2 . Concentration of the extract *in vacuo* below 30°C and chromatography of the residue with AcOEt gave the phosphonate **7** (2.14 g, 70%) as a colorless oil. IR (neat): 1739, 1710, 1260, 1010. ^1H -NMR: 4.6–3.9 (6H, m, $\text{OCH}_2\text{CH}_3 \times 2$ and OCH_2), 2.96 (2H, d, $J = 22$ Hz, CH_2PO), 1.35 (6H, t, $J = 7$ Hz, $\text{OCH}_2\text{CH}_3 \times 2$).

Potassium hydride (23.6% in oil, 221 mg) was added to a stirred solution of the phosphonoacetate **7** (400 mg) in DME (10 ml) at 0°C and the mixture was stirred at room temperature for 30 min. The reaction was quenched with aqueous NH_4Cl , then the solution was acidified with 5% HCl and extracted with ether. Chromatography of the product gave, from the AcOEt–hexane (1 : 3) eluate, the lactone **1** (150 mg, 76%), mp 59 – 60°C (lit. 59 – 60°C).⁸⁾ Anal. Calcd for $\text{C}_9\text{H}_{12}\text{O}_2$: C, 71.03; H, 7.95. Found: C, 70.81; H, 8.25.

Methyl 1-Hydroxymethyl-2-oxocyclohexanecarboxylate (9a) Triethylamine (0.5 ml) was added to a mixture of methyl 2-oxocyclohexanecarboxylate (**8a**) (456 mg) and 35% formaldehyde (2 ml) in MeOH (10 ml) at room temperature. After being stirred for 2 h at the same temperature, the mixture was poured into saturated aqueous NaHCO_3 solution and extracted with CH_2Cl_2 . Concentration of the extract and chromatography of the residue gave, from the hexane–AcOEt (2 : 1) eluate, **9a** (538 mg, 98%) as a colorless oil. IR: 3400, 1724, 1696. ^1H -NMR: 3.80 (3H, s, OMe), 3.96–3.58 (3H, m, CH_2OH). MS: 168 ($\text{M}^+ - 18$, 3), 167 (7), 156 (58), 128 (31), 124 (100).

Ethyl 1-Hydroxymethyl-2-oxocyclohexanecarboxylate (9b) The ethyl ester **8b** (8.5 g) in MeOH (10 ml) was similarly reacted with 35% formaldehyde (13 ml) under triethylamine (0.5 ml) catalysis to give the corresponding ethyl ester **9b**⁶⁾ (9.1 g, 91%) as a colorless liquid, bp $104^\circ\text{C}/3$ mmHg. IR: 3570, 1730, 1705. ^1H -NMR (CDCl_3 + a drop of D_2O): 4.27 (2H, q, $J = 7$ Hz, OCH_2CH_3), 3.78 (2H, brs, CH_2O), 1.30 (3H, t, $J = 7$ Hz, OCH_2CH_3).

Methyl 4-Oxo-3-oxabicyclo[4.4.0]dec-5-ene-1-carboxylate (11a) Diethylphosphonoacetyl chloride (prepared from 3.2 g of the acid)⁵⁾ in CH_2Cl_2 (20 ml) was added to a mixture of **9a** (1.2 g) and triethylamine (3.3 g) in CH_2Cl_2 (40 ml). After being stirred for 30 min at room temperature, the mixture was washed with saturated aqueous NaHCO_3 solution and

concentrated. Flash chromatography of the residue with benzene–acetone (4 : 1) gave crude **10a** (0.78 g) as an oil. ^1H -NMR: 4.44 (2H, ABq, $\Delta\delta = 0.22$ ppm, $J = 11$ Hz, OCH_2), 4.16 (4H, dq, $J = 8.3$, 7 Hz, $\text{POOCH}_2\text{CH}_3 \times 2$), 3.77 (3H, s, OMe), 2.95 (2H, d, $J = 21.5$ Hz, CH_2PO), 1.35 (6H, t, $J = 7$ Hz, $\text{OCH}_2\text{CH}_3 \times 2$).

Crude **10a** (780 mg) in DME (10 ml) was added slowly to a stirred solution of NaH (130 mg) in DME (20 ml) at 0°C , and the mixture was stirred for 30 min at 0°C and 30 min at room temperature. After decomposition of the reagent with AcOH, the mixture was poured into 1 N HCl and extracted with ether. Chromatography of the product gave, from the benzene–acetone (10 : 1) eluate, **11a** (346 mg, 26% from **9a**) as colorless plates from ether, mp 83 – 84°C . IR (KBr): 1727, 1701. ^1H -NMR: 5.89 (1H, brs, =CH), 4.59, 4.04 (each 1H, d, $J = 11.2$ Hz, OCH_2), 3.77 (3H, s, OMe). MS: 210 (M^+ , 48), 178 (22), 150 (100). Anal. Calcd for $\text{C}_{11}\text{H}_{14}\text{O}_4$: C, 62.85; H, 6.71. Found: C, 62.60; H, 6.97.

Ethyl 4-Oxo-3-oxabicyclo[4.4.0]dec-5-ene-1-carboxylate (11b) The ethyl ester **9b** (2.4 g) in CH_2Cl_2 (50 ml) was phosphonoacetylated with diethylphosphonoacetyl chloride (3.88 g) and triethylamine (2.4 g) at 0°C for 30 min to give the phosphonoacetate **10b** (3.9 g, 97%) as a colorless liquid. IR (neat): 1742, 1739, 1719. ^1H -NMR: 4.5–3.9 (8H, m, OCH_2 and $\text{OCH}_2\text{CH}_3 \times 3$), 2.94 (2H, d, $J = 22$ Hz, CH_2PO), 1.36 (9H, t, $J = 7$ Hz, $\text{OCH}_2\text{CH}_3 \times 3$).

Compound **10b** (1 g) in DME (30 ml) was treated with KH (23.6% in oil, 120 mg) at 0°C for 30 min and at room temperature for 30 min. Chromatography of the product gave, from the AcOEt–hexane (1 : 5) eluate, **11b** (550 mg, 82%) as colorless prisms, mp 58 – 60°C . IR (Nujol): 1725. ^1H -NMR: 5.87 (1H, brs, =CH), 4.58, 4.06 (each 1H, d, $J = 11$ Hz, OCH_2), 4.22 (2H, q, $J = 7$ Hz, OCH_2CH_3), 1.27 (3H, t, $J = 7$ Hz, OCH_2CH_3). Anal. Calcd for $\text{C}_{12}\text{H}_{16}\text{O}_4$: C, 64.24; H, 7.19. Found: C, 64.18; H, 7.23.

Treatment of 10b with EtONa–EtOH The phosphonoacetate **10b** (800 mg) in 2.5% EtONa–EtOH (10 ml) was stirred for 1.5 h at room temperature. The mixture was brought to pH 5 with 10% HCl and extracted with CH_2Cl_2 . Chromatography of the product gave, from the AcOEt–hexane (1 : 4) eluate, **11b** (52 mg, 11%) and **12** (127 mg, 21%). Compound **12** was an oil. IR (neat): 1735, 1720, 1660, 1630. ^1H -NMR: 6.16, 5.54 (each 1H, brs, =CH₂), 4.22, 4.14 (each 2H, q, $J = 7.2$ Hz, $\text{OCH}_2\text{CH}_3 \times 2$), 1.31, 1.26 (each 3H, t, $J = 7.2$ Hz, $\text{OCH}_2\text{CH}_3 \times 2$). HRMS: Calcd for $\text{C}_{12}\text{H}_{20}\text{O}_4$: 228.1361. Found: 228.1385.

3-Oxabicyclo[4.4.0]dec-1⁶-en-4-one (2) Compound **11a** (100 mg) and $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ (559 mg) in DMSO (5 ml) containing *tert*-heptylmercaptan (0.4 ml) were heated in a sealed tube at 145°C for 2 h under an Ar atmosphere. The mixture was poured into 1 N HCl and extracted with ether. Concentration of the extract and chromatography of the residue gave, from the benzene–acetone (20 : 1) eluate, the lactone **2** (49 mg, 68%). MS: 152 (M^+ , 91), 124 (25), 108 (38), 95 (100). HRMS: Calcd for $\text{C}_9\text{H}_{12}\text{O}_2$: 152.0837. Found: 152.0812.

3-Oxabicyclo[4.4.0]dec-6-en-4-one (3) 1-Cyclohexene-1-acetic acid **13** (1.685 g) and trioxane (0.38 g) in trifluoroacetic acid (5 ml) were stirred at 10°C for 18 h. The mixture was diluted with CH_2Cl_2 , washed with 5% NaHCO_3 and brine, dried, and concentrated. Chromatography of the residue gave, from the hexane–AcOEt eluate, a mixture of the lactones (0.9 g, 58%) **3**, **2**, and **1** in a ratio of ca. 7 : 1 : 2. A portion of this mixture was separated by preparative HPLC to give the pure lactone **3** as a colorless oil. MS: 152 (M^+ , 15), 122 (12), 93 (73), 79 (100). HRMS: Calcd for $\text{C}_9\text{H}_{12}\text{O}_2$: 152.0837. Found: 152.0853.

Methylenation of Ethyl 2-Oxocyclohexanecarboxylate (14) with Sulfonium Ylides (1) Trimethyloxosulfonium iodide (616 mg) in DMSO (4 ml) was converted to the ylide on treatment with NaH (114 mg, 60% oil dispersion) for 30 min at room temperature under an Ar atmosphere. Compound **14** (500 mg) in DMSO (4 ml) was added to this solution, and the mixture was heated at 50°C for 2 h with stirring, then poured into ice-water and extracted with ether. Chromatography of the extract gave, from the benzene–hexane (9 : 1) eluate, the oxirane **15a** (162 mg, 30%) as a colorless oil. Its homogeneity was confirmed by HPLC. IR: 1715. ^1H -NMR: 4.12 (2H, q, $J = 7$ Hz, $\text{COOCH}_2\text{CH}_3$), 2.61 (2H, ABq, $\Delta\delta = 0.17$ ppm, $J = 4.4$ Hz, oxirane), 1.25 (3H, t, $J = 7$ Hz, $\text{COOCH}_2\text{CH}_3$). ^{13}C -NMR: 70.0, 60.3, 60.0, 53.2, 36.8, 34.1, 32.7, 30.2, 24.4, 23.4, 14.2. MS: 198 (M^+ , 5), 137 (100). HRMS: Calcd for $\text{C}_{11}\text{H}_{18}\text{O}_3$: 198.1255. Found: 198.1277.

(2) Trimethylsulfonium iodide (651 mg) was converted to the ylide with NaH (60% oil dispersion, 130 mg) in DMSO (4 ml) as described above. Compound **14** (500 mg) in tetrahydrofuran (THF) (5 ml) was added to this solution and the mixture was stirred at 0°C for 1 h. Work-up of the mixture gave **15a** (71 mg, 13%). Its homogeneity was confirmed by HPLC.

Ethyl 2-Methylenecyclohexanecarboxylate (16) $\text{Zn}-\text{CH}_2\text{Br}_2-\text{TiCl}_4$ re-

agent⁹⁾ was prepared by the method described in Organic Synthesis.¹³⁾ Compound **14** (200 mg) in CH₂Cl₂ (10 ml) was added dropwise to a stirred slurry of the above reagent (10 ml) at 0 °C and the mixture was stirred at room temperature. After 1.5 h, ether and saturated NaHCO₃ solution were added, and after further stirring for 1 h, the mixture was filtered. The separated organic layer was dried and concentrated. Chromatography of the residue in benzene gave **16**¹⁴⁾ (159 mg, 80%) as an oil. IR: 1720. ¹H-NMR: 4.66, 4.53 (each 1H, s, =CH₂), 4.12 (2H, q, *J*=7.3 Hz, COOCH₂CH₃), 1.25 (3H, t, *J*=7.3 Hz, COOCH₂CH₃). MS: 168 (M⁺ - 14, 52), 137 (M⁺ - OEt, 100).

Epoxidation of 16 Compound **16** (470 mg) and *m*CPBA (555 mg) in CH₂Cl₂ (10 ml) were stirred for 3 h at 0 °C and for 2 h at room temperature. After addition of 10% Na₂SO₃ solution (5 ml), the mixture was poured into saturated aqueous NaHCO₃ and extracted with CH₂Cl₂ to give a mixture of **15a** and **15b** (496 mg, 98%). The ratio of **15a** to **15b** was 2:1 as evidenced from HPLC. These products were separated by preparative HPLC. Compound **15b** was a colorless oil. IR: 1720. ¹H-NMR: 2.57 (2H, ABq, $\Delta\delta$ =0.18 ppm, *J*=4.4 Hz, oxirane), 4.12 (2H, q, *J*=7 Hz, COOCH₂CH₃), 1.25 (3H, t, *J*=7 Hz, COOCH₂CH₃). ¹³C-NMR: 172.6, 60.4, 60.2, 50.7, 37.9, 34.7, 33.4, 31.2, 25.3, 23.7, 14.2. MS: 198 (M⁺). HRMS: Calcd for C₁₁H₁₈O₃: 198.1255. Found: 198.1253.

The Iodolactone 18 Compound **16** (165 mg) was hydrolyzed with 5% NaOH (3 ml) and EtOH (1 ml) on heating at 50 °C for 3 h to give the acid **17** (151 mg), after acidification and extraction with AcOEt. This was dissolved in 0.5 M NaHCO₃ (7 ml) and KI₃ solution [prepared from iodine (465 mg), KI (908 mg), and water (3 ml)] was added, then the mixture was stirred overnight at room temperature, and extracted with CH₂Cl₂. The organic layer was washed with aqueous Na₂S₂O₃ and brine, and concentrated to give the iodolactone **18** (255 mg, 100%) as colorless prisms from ether, mp 60–61.5 °C. IR: 1781, 1762. ¹H-NMR: 3.45 (2H, s, CH₂I), 2.32–2.82 (3H, m, COCH₂, CH). MS: 280 (M⁺, 5), 153 (26), 139 (100). Anal. Calcd for C₉H₁₃IO₂: C, 38.59; H, 4.86. Found: C, 38.45; H, 4.75.

Treatment of 18 with NaOEt A mixture of the iodolactone **18** (162 mg) and 1 M NaOEt–EtOH (3.6 ml) in EtOH (5 ml) was stirred for 4.5 h at room temperature and 30 min at 30 °C, then poured into ice-water and extracted with CH₂Cl₂ to give the oxirane **15a** (80 mg, 80%). Its homogeneity was confirmed by HPLC.

Treatment of the Oxirane 15a with 2% Methanolic Hydrochloric Acid The oxirane **15a** (50 mg) in MeOH (10 ml) containing concentrated hydrochloric acid (0.6 ml) was stirred for 40 h at room temperature. The mixture was diluted with water and extracted with CHCl₃. HPLC of the product gave **19** (8 mg, 17%), **20** (13 mg, 30%), **21** (3 mg, 6%), and **22** (6 mg, 13%).

Compound **19**: Colorless oil. IR: 1772. ¹H-NMR (400 MHz): 3.65 (2H, ABq, $\Delta\delta$ =0.06 ppm, *J*=12 Hz, CH₂Cl), 2.72–2.64 (2H, m, COCH₂), 2.42 (1H, m, CH). MS: 190 (M⁺ for ³⁷Cl, 0.2), 188 (M⁺ for ³⁵Cl, 0.6), 139 (100).

Compound **20**: Colorless oil. IR: 3440, 1767. ¹H-NMR (400 MHz): 3.68 (2H, ABq, $\Delta\delta$ =0.07 ppm, *J*=12.5 Hz, CH₂O), 2.7–2.6 (2H, m, COCH₂), 2.52–2.45 (1H, m, CH). MS: 170 (M⁺, 0.14), 139 (100). HRMS: Calcd for C₉H₁₄O₃: 170.0942. Found: 170.0958.

Compound **21**: Colorless oil. IR: 1733. ¹H-NMR (400 MHz): 4.66, 4.36 (each 1H, d, *J*=12.5 Hz, OCH₂), 3.05 (1H, dd, *J*=19.1, 7.3 Hz), 2.44 (1H, dd, *J*=19.1, 4.4 Hz) (COCH₂). MS: 190 (M⁺ for ³⁷Cl, 1.5), 188 (M⁺ for ³⁵Cl, 4.3), 116 (100).

Compound **22**: Colorless oil. IR: 1725. ¹H-NMR (400 MHz): 4.46 (1H, d, *J*=12.5 Hz), 4.29 (1H, dd, *J*=12.5, 1.8 Hz) (OCH₂), 3.26 (3H, s, OMe), 2.97 (1H, dd, *J*=18.3, 7.3 Hz), 2.21 (1H, dd, *J*=18.3, 2 Hz) (COCH₂). MS: 184 (M⁺, 26), 169 (28), 111 (100). HRMS: Calcd for C₁₀H₁₆O₃: 184.1099. Found: 184.1102.

Treatment of the Oxiranes 15 with PPTS (1) A mixture of the oxirane **15a** (50 mg), PPTS (12.7 mg), and molecular sieves 4A (excess) in benzene (10 ml) was heated under reflux for 5 h under an Ar atmosphere. The cooled mixture was washed with aqueous NaHCO₃ and concentrated. Chromatography of the residue gave, from the hexane–AcOEt (3:1) eluate, a mixture of **2** and **4** (19 mg, 50%). The ratio was 1:2 (HPLC). These products were separated by preparative HPLC.

The Lactone **4**: Colorless oil. MS: 152 (M⁺, 12), 108 (50), 94 (39), 93 (67), 79 (100). HRMS: Calcd for C₉H₁₂O₂: 152.0837. Found: 152.0809.

(2) Each of the oxiranes **15a** and **15b** (7.1 mg and 9.5 mg) and PPTS (20 mg) in benzene (1.0 ml) were heated in a sealed tube at 110 °C for 5 h. Each mixture was washed with saturated NaHCO₃ and concentrated, and the residue (5 mg from **15a** and 3 mg from **15b**) was analyzed by HPLC. A mixture of **2**, **4**, and **23** + **24** (**23** and **24** gave an inseparable peak) in a ratio of 4:6:17 was obtained from **15a**, and a mixture of **2**, **4**, and **20** in

a ratio of 4:9:21 from **15b**.

(3) A mixture of oxiranes **15a** and **15b** (2:1, 478 mg) and PPTS (100 mg) in benzene (5 ml) was heated in a sealed tube at 120 °C for 3 h and worked up as described above. Chromatography of the product eluting with benzene–acetone gave **23** (54 mg, 11%) from the 40:1 eluate, a mixture of **2**, **4**, and **24** (174 mg) from the 20:1 eluate, and **20** (74 mg, 18%) from the 2:1 eluate. The mixture of **2**, **4**, and **24** was separated by preparative HPLC to give **2** (30 mg, 8%), **4** (37 mg, 10%) and **24** (68 mg, 9%).

The Aldehyde **23**: Colorless oil, which was a mixture of **23a** and **23b** on the basis of the ¹H- and ¹³C-NMR spectra. IR: 1724. ¹H-NMR (400 MHz): 9.75 (brs), 9.56 (d, *J*=3 Hz) (CHO), 4.15–4.09 (2H, seven peaks, COOCH₂CH₃), 1.25 (3H, brt, *J*=7.3 Hz, COOCH₂CH₃). ¹³C-NMR: 204.1, 172.3, 60.3, 54.8, 39.3, 33.3, 31.0, 25.9, 25.0, 24.5, 14.2 and 204.5, 172.8, 60.3, 51.2, 36.4, 33.7, 29.8, 25.2, 23.8, 23.3, 14.2. MS: 198 (M⁺, 19), 197 (100), 169 (M–CHO, 35), 168 (28), 153 (30), 152 (18), 151 (37), 139 (95), 123 (30), 95 (40), 88 (40).

The *p*-Toluenesulfonate **24**: Colorless oil. IR: 1784. ¹H-NMR: 7.75, 7.33 (each 2H, d, *J*=8 Hz, ArH), 4.00 (2H, s, CH₂O), 2.8–2.1 (3H, m, COCH₂, CH), 2.46 (3H, s, Me). MS: 324 (M⁺, 3), 153 (48), 140 (51), 139 (100). HRMS: Calcd for C₁₆H₂₀O₅S: 324.1030. Found: 324.1039.

Isomerization of Lactones (1) With PPTS: The lactone (each 2–10 mg) was heated in a sealed tube with 2% PPTS in benzene (1 ml) at 120 °C for 5 h. The mixture was diluted with benzene, washed with saturated aqueous NaHCO₃, and concentrated. The residue was dissolved in 50% MeOH or MeOH and analyzed by HPLC (see Table III).

(2) With DBU: The lactone (each 2–10 mg) was heated in a sealed tube with 2% DBU in benzene (1 ml) at 120 °C for 5 h (for **1**, **2**, and **4**) or for 0.5 h (for **3**). The cooled mixture was diluted with ether, washed with 1 N HCl, and concentrated. The residue was analyzed by HPLC as described above (see Table IV).

(3) With NaOH: The lactone (each 2–10 mg) was heated in a sealed tube with 10% NaOH (1 ml) at 120 °C for 5 h. The cooled mixture was acidified with dilute H₂SO₄, stirred for 30 min at room temperature, then extracted with ether. The residue obtained from the ether extract was analyzed by HPLC as described above (see Table V).

Isomerization of the Conjugated Acid 29 The acid **29** (100 mg) was heated in a sealed tube with 10 N KOH at 140 °C for 10 h. The cooled mixture was acidified with HCl and extracted with CH₂Cl₂. The product was a mixture of **29** and **13** (1:8) on the basis of HPLC analysis.

References and Notes

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