Studies toward Total Synthesis of Non-aromatic *Erythrina* Alkaloids. (4).[1] Oxidation of Furan Ring of D-Furanoerythrinans with *N*-Bromoacetamide

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Oxidation of the furan ring in the D-furanoerythrinan 1 with *N*-bromoacetamide in protic solvents gave the dioxygenated dihydrofurans 4 or 6. Acidic treatment of 4 or 6 caused two kind of reactions depending on the conditions: one is regeneration of a furan with concomitant introduction of an OR group or a double bond in the adjacent ring to give the ring C-functionalized D-furanoerythrinans 5, 8, and 9, and the other is the formation of the γ-lactones 7, 10, and 11.

Keywords *Erythrina* alkaloid; synthesis; β-erythroidine; furan; oxidation; *N*-bromoacetamide; γ-lactone

In a preceding paper[2] we have developed two routes for the synthesis of the β-erythroidine skeleton through oxidative degradation of the aromatic ring (ring A) in erythrinans as a key step. One method is the oxidative transformation of a furan ring to γ-lactone and the other is the ozonolytic cleavage of a trimethoxybenzene ring. In the furan route the D-furanoerythrinan **1** was converted into the key intermediate keto-acid **3** by oxidation with *N*-bromosuccinimide (NBS), followed by catalytic reduction of the resulting 12-hydroxy-α,β-unsaturated γ-lactone **2**. Although this synthetic route is attractive, several problems had to be solved for the total synthesis of β-erythroidine, since β-erythroidine contains a dienol moiety that is vulnerable to oxidation and catalytic reduction. In order to transform **1** and **3** or its equivalent without using catalytic reduction, we deal in detail, in this paper, with the oxidation of the D-furanoerythrinan **1** and the reaction of the oxidation products under acidic conditions as a model experiment of β-erythroidine synthesis.

Oxidative ring fission of furans is well known to be caused by various oxidants,[3] and the nature of the products depends on the oxidants, the substrates, and the reaction conditions. The conversion of furans to γ-lactones has been achieved by oxidation with *m*-chloroperbenzoic acid,[4] 2,3-dichloro-5,6-dicyano-1,4-benzoquinone,[5] and singlet oxygen.[6] In these oxidations, the substrates consume four equivalents of oxidants to give a hydroxy-α,β-unsaturated γ-lactone (A). Recently, oxidation of furans with *N*-bromoacetamide (NBA)[7] to an α,β-unsaturated γ-lactone (B) was also reported. Another interesting example is the oxidation of a benzofuran with thallium trinitrate (TTN)[8] to yield a 1,2-dimethoxyfuran (C). The latter two products have the same oxidation state as a β,γ-unsaturated γ-lactone (D), one of the target products in this study. Thus, we chose NBA and TTN as oxidizing agents.

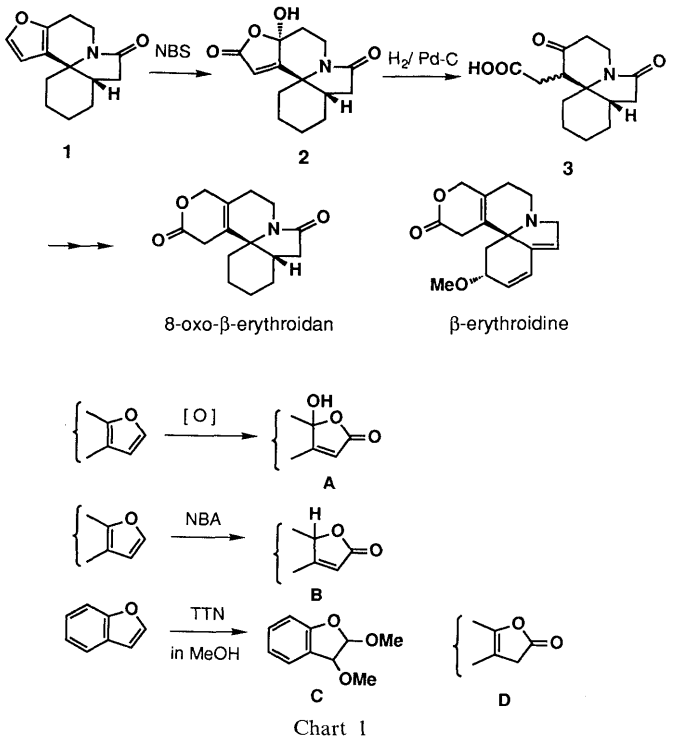


Chart 1

Results and Discussion

Treatment of **1** with NBA in methanol at room temperature for 5 min caused oxidation of the furan ring to give two dimethoxydihydrofuran derivatives **4a** and **4b** in 53% and 26% yields. Although no confirmatory evidence concerning the stereochemistry of the introduced OMe groups was available, the products are assumed to be stereoisomers with respect to the configuration of C_{15}-OMe. The configuration of the C_{12}-OMe group in both products was assigned as α by considering that the reaction produced the thermodynamically more stable isomer (the formation of **4** from **6** supports this consideration, see below). Inspection of stereostructures produced by the Chem 3D program revealed that the 12α-OMe isomer has a chair-form ring C, while the corresponding 12β-OMe isomer has a boat or twisted boat conformation due to the presence of severe steric interactions between the C_{12}-OMe group and the lactam carbonyl of ring B and between the C14-methine and C4-methylene groups.

Oxidation of **1** with TTN in methanol occurred under drastic conditions (60 °C, 30 min) and gave the above mentioned dimethoxydihydrofurans **4** as a stereoisomeric mixture in 47% yield with 50% recovery of the starting material. Prolonged oxidation (18 h) of **1** under the same conditions gave the 11-methoxyfuran **5** as a single product in 62% yield. These facts demonstrate that **5** is formed through the dimethoxydihydrofurans **4**.

Similar oxidation of **1** with NBA in aqueous acetone was completed at room temperature in a few minutes, though no characterizable product was isolated by chromatography on silica gel. However, when the reaction mixture was

allowed to stand at room temperature for 96 h after the oxidation had been completed, two products **7** and **8** were isolated in the yield of 38% each by chromatography on silica gel. These two products were not detected in the initial oxidation mixture. Their structures were assigned as an α,β-unsaturated γ-lactone **7** and 11-hydroxyfuran **8** from their spectral data. The γ-lactone **7** was identical with the compound obtained by reduction of the 12-hydroxy-γ-lactone **2** with sodium borohydride.[2b]

The above result indicates that the products **7** and **8** were formed from an unstable oxidation product by a rearrangement. The direct oxidation product is presumed to be the dihydroxydihydrofuran **6**, since the dimethoxyfuran **4** was obtained in the yield of 72% as a 1 : 1 stereoisomeric mixture of **4a** and **4b** when the crude product was treated with methanol in the presence of *p*-toluenesulfonic acid (*p*-TsOH). This indicates that **4** is the thermodynamically more stable isomer with respect to the configuration of C_{12}.

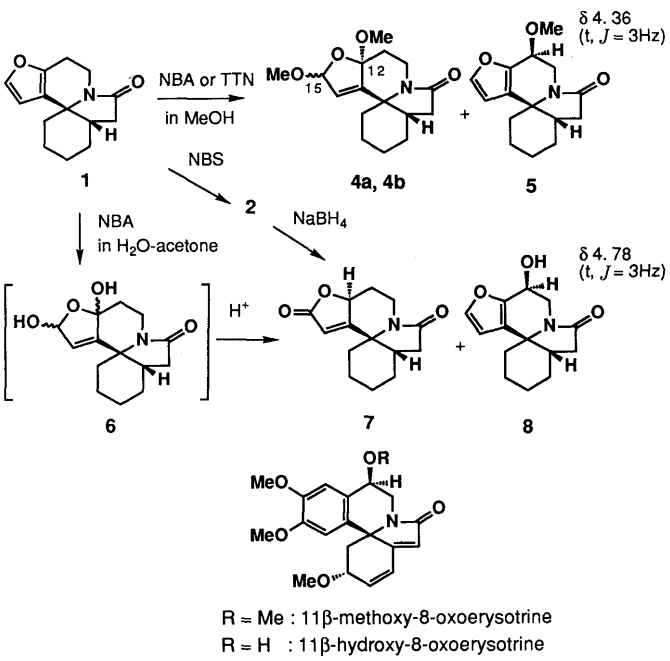


Chart 2

The configuration of the newly introduced OMe or OH group at C_{11} in the furan derivative **5** or **8** was deduced as β on the basis of the ^{1}H-nuclear magnetic resonance (NMR) spectra, in which the C_{11}-proton appeared as a triplet with a small coupling constant (δ 4.36, $J=3$ Hz for **5** and δ 4.78, $J=3$ Hz for **8**), suggesting that the configuration of the C_{11}-proton is equatorial. This assignment is consistent with the corresponding coupling constant of 11β-methoxy-8-oxoerysotrine[9] and 11β-hydroxy-8-oxoerysotrine.[10]

When **6** was treated with acid, dehydration readily took place under mild conditions. The major reaction was the formation of the ring C functionalized furan derivative **8** (Table I). Treatment of **6** with silica gel in methanol also gave **4** (25%) and **8** (24%). Dehydration of **6** with perfluorinated cation-exchange powder (Nafion-H) in tetrahydrofuran (THF) gave the 11β-hydroxyfuran **8** exclusively (92%). Unexpectedly, the 11β-hydroxyfuran **8** was formed in 95% yield, when **6** was treated with Nafion-H even in MeOH, the 11-methoxyfuran **5** not being detected.

Cleavage of methanol from the dimethoxydihydrofurans **4** was also carried out under several acidic conditions. Treatment of **4** with *p*-TsOH in benzene under reflux for 2.5 h gave two major products, the Δ^{10}-furan **9** (50%) and the unsaturated γ-lactone **7** (23%), along with two minor products, the 12-methoxy-γ-lactone **10** (4%), and the 11-methoxyfuran **5** (2%). Treatment of **4** with 10% hydrochloric acid in aqueous acetone at room temperature gave three products, the enol lactone **11** (38%), the unsaturated γ-lactone **7** (30%), and the 11-hydroxyfuran **8** (32%). In contrast to **6**, treatment of **4** with Nafion-H in THF or MeOH did not cause any reaction at room temperature, but gave the 11-methoxyfuran **5** as a single product on heating in benzene, though the yield was not satisfactory (45%).

The structures of the rearrangement products **9**, **10**, and **11**, were deduced from their spectral data (see Experi-

TABLE I. Acid Rearrangement of Dioxygenated Dihydrofurans **4** and **6**

Conditions					Products (yield %)						
					Furans			γ-Lactones			Others
Sub.	Acid	Solvent	Temp. (°C)	Time (h)	**5**	**8**	**9**	**7**	**10**	**11**	**4**
6	*p*-TsOH	MeOH	r.t.	5	—	—	—	—	—	—	72
6	SiO_2	MeOH	r.t.	1	—	24	—	—	—	—	25
6	Naf-H	THF	r.t.	0.5	—	92	—	—	—	—	—
6	Naf-H	MeOH	r.t.	0.5	—	95	—	—	—	—	—
4	*p*-TsOH	Benz	80	2.5	3	—	50	23	4	—	—
4	HCl	H_2O	r.t.	16.5	—	32	—	30	—	38	—
4	Naf-H	Benz	80	0.5	45	—	—	—	—	—	—

Naf-H: Nafion-H; Benz: benzene. r.t.: room temperature.

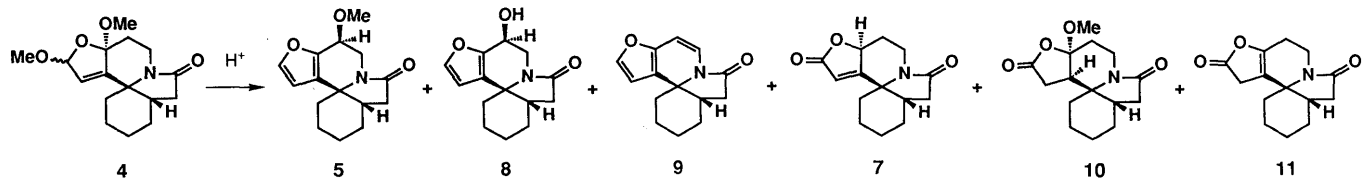


Chart 3

mental). It is worthwhile to note that the methoxylactone **10** and the enol lactone **11** are structurally equivalent to the keto-acid **3**, which was the key intermediate to construct the δ-lactone ring required for the synthesis of the erythroidine skeleton.

The results demonstrate that the acid-catalyzed reaction of the direct oxidation products **4** and **6** causes two types of rearrangement; one is the regeneration of a furan ring with introduction of an oxygen group at C_{11} or a double bond at ring C, and the other is the formation of a γ-lactone ring. These rearrangements probably proceed *via* the formation of the same oxonium ion **12** generated by acid-catalyzed demethoxylation of C_{12}-OMe or dehydroxylation of C_{12}-OH. Subsequent deprotonation of C_{11}-H and elimination of the C_{15}-oxygen function from the intermediate **13** lead to regeneration of a furan ring with concomitant introduction of an OR group into ring C (a or b).

On the other hand, deprotonation from C_{15} of **12** yields the acid labile 15-oxyfuran **14**, which leads to the γ-lactone derivatives. Ketonization of **14** by protonation at C_{12} or C_{14} produces the α,β-unsaturated γ-lactone **7** or the enol lactone **11**, respectively, though it is not excluded that acid catalyzed isomerization of the double bond between these lactones could have occurred during the reaction. Formation of the methoxylactone **10** may be rationalized in terms of addition of methanol to the enol lactone **11**.

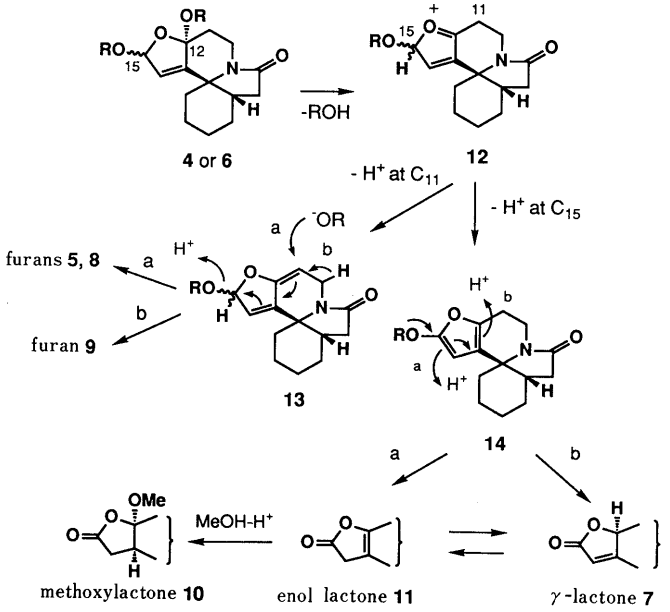


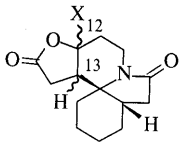
Chart 4

The configuration of 12-H in **7** was assigned as α for the same reason as in the case of **4**. The 12αH isomer adopts a ring C chair form, while the 12βH isomer should have a boat form at ring C with a steric interaction between the C4-methylene and C14-methine groups.

We consider that the methoxylactone **10** was produced through a thermodynamically controlled process, thus having the most stable configuration. The steric energies of the most stable configurations of the four possible stereoisomers **10a—d** were thus calculated by MM2 (Table II).[11] The result showed that all of the isomers have $_1C^4$ conformations, and the 12αOMe-13αH isomer (**10a**) is far more stable ($\Delta E < 3$ kcal/mol) than the other three isomers. However, the steric energy values obtained in these calculations are not highly reliable (quality = 1), because a torsional parameter of the methoxylactone moiety is missing. Therefore, the steric energies of the corresponding 12H-lactones (**16a—d**) were calculated by a similar procedure for comparison, and the resulting values were highly acceptable (quality = 3). The results again showed that 12αH-13αH isomer (**16a**) is the most stable among the four stereoisomers and the magnitudes of steric energy differences are of the same order for both series, suggesting that our energy evaluation for methoxylactones **10a—d** may be correct.

If the methoxylactone **10** was formed by addition of a methoxide to the oxonium ion **15**, the product should be a mixture of **10b** and **10d**, since the preferred configuration

TABLE II. The Steric Energies of the Most Stable Conformations of Stereoisomers of the 12OMe-Lactone **10** and 12H-Lactone **16**



10: X = OMe
16: X = H

Compound	Stereochemistry	Steric energy (kcal/mol)	ΔE (kcal/mol)
10a	12αOMe-13αH(*cis*)	38.3	0
10b	12βOMe-13βH(*cis*)	42.6	4.3
10c	12βOMe-13αH(*trans*)	44.5	6.2
10d	12αOMe-13βH(*trans*)	42.2	3.9
16a	12αH-13αH(*cis*)	29.2	0
16b	12βH-13βH(*cis*)	34.4	5.2
16c	12βH-13αH(*trans*)	34.5	5.3
16d	12αH-13βH(*trans*)	32.4	3.2

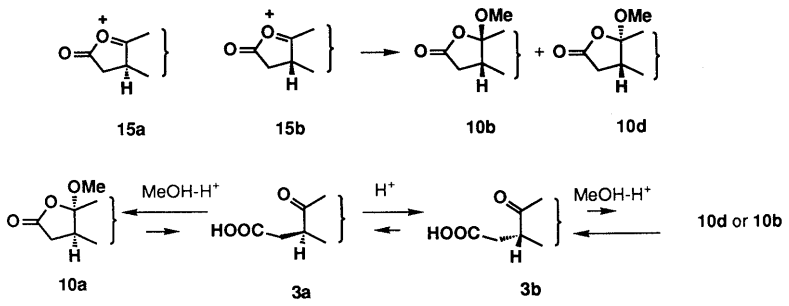


Chart 5

of the oxonium ion is 13βH (**15b**)[12] and the steric energy difference between the expected products, **10b** and **10d**, is only 0.4 kcal/mol. However, this mechanism is not consistent with the observed exclusive formation of a single stereoisomer.

Probably, the methoxylactone **10** was formed through the keto-acid **3**. Although the more stable configuration of **3** is the 13βH isomer (**3b**),[2b] the thermodynamically controlled condition (MeOH–H^+) would produce the most stable 12αOMe-13αH methoxylactone (**10a**) through the equilibrium shown in Chart 5.

Conclusion

Oxidation of the furanoerythrinan **1** with NBA in a protic solvent quantitatively gave 1,4-dioxygenated dihydrofuran derivatives which underwent two kinds of acid catalyzed rearrangement reactions. One is the regeneration of a furan with concomitant introduction of an OR group or a double bond in the adjacent ring to give ring C functionalized D-furanoerythrinans and the other is the formation of γ-lactones. Nafion-H exclusively produced a furan derivative (**8** from **6**, 95%) and hydrochloric acid mainly gave γ-lactones (**7** and **11** from **4**, 68%). These results suggest that the selection of the rearrangement route depends on the acidity of the reaction medium. Thus, if the reaction conditions leading to selective formation of the γ-lactones can be optimized, this oxidative method may be useful for the synthesis of erythroidines.

Experimental

Unless otherwise noted, the following procedures were adopted. All melting points are uncorrected. Infrared (IR) spectra were measured as Nujol mulls and are given in cm^{-1}. NMR spectra were taken on a JEOL JNM-FX 100 (^{1}H-NMR, 100 MHz; ^{13}C-NMR, 25 MHz) spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard and the chemical shifts are given in δ values. The following abbreviations are used; s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. High-resolution mass spectra (HRMS) were determined with a JEOL JMS-D 300 spectrometer at 30 eV using a direct inlet system. Ultraviolet (UV) spectra were measured in EtOH and are given in λ_{max} nm (ε). Preparative thin layer chromatography (PTLC) was performed with precoated silica gel plates, Merck 60 F_{254} (0.5 mm thick). Column chromatography was carried out with silica gel (Wakogel C-200). Medium pressure liquid chromatography (MPLC) was performed on a Kusano CIG prepacked silica gel column. All organic extracts were washed with brine and dried over $MgSO_4$ before concentration. Identities were confirmed by comparisons of TLC behavior and IR and NMR spectra.

Oxidation of 1 with NBA in Methanol NBA (27 mg, 1.5 mol eq) was added to a solution of **1** (30 mg) in MeOH (15 ml) at 0 °C and the mixture was stirred at room temperature for 5 min, and then diluted with CH_2Cl_2. The organic extract was washed with 10% Na_2SO_3 and brine, dried, and concentrated to dryness *in vacuo*. The residue was purified by PTLC (elution with EtOAc) to give **4a** (20 mg, 53%) and **4b** (10 mg, 26%).

Compound **4a**: Colorless prisms from Et_2O, mp 145—146 °C. IR ($CHCl_3$): 1680. UV: 210 (4600). ^{1}H-NMR: 3.18, 3.53 (each 3H, s, OMe), 5.39 (1H, d, J = 1 Hz, H-15), 5.91 (1H, d, J = 1 Hz, H-14). *Anal.* Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.72. Found: C, 65.70; H, 7.82; N, 4.66. HRMS *m/z* Calcd for M^+: 293.1625. Found: 293.1612.

Compound **4b**: Colorless prisms from Et_2O, mp 128—131 °C. IR ($CHCl_3$): 1680. UV: 210 (4500). ^{1}H-NMR: 3.10, 3.39 (each 3H, s, OMe), 5.87 (1H, s, H-15), 5.91 (1H, s, H-14). *Anal.* Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.72. Found: C, 65.42; H, 7.78; N, 4.56. HRMS *m/z* Calcd for M^+: 293.1625. Found: 293.1634.

Oxidation of 1 with TTN in Methanol 1) A solution of **1** (10 mg) in MeOH (15 ml) was treated with TTN (20 mg, 1 mol eq) at 60 °C for 30 min under stirring, then cooled. A small amount of NaCl was added and the mixture was stirred for a further 30 min. The resulting precipitate was removed by filtration and the filtrate was concentrated *in vacuo* and extracted with CH_2Cl_2. The organic extract was washed with brine, dried, and concentrated to dryness *in vacuo*. The residue was purified by PTLC (with EtOAc) to give a mixture of **4a** and **4b** (6 mg, 47%, net yield, 95%) and the starting material **1** (5 mg, 50%).

2) A solution of **1** (10 mg) in MeOH (15 ml) was treated with TTN (40 mg, 2 mol eq) at 60 °C for 18 h under stirring. After work-up as described above, the residue was purified by PTLC (elution with AcOEt) to give **5** (7 mg, 62%, net yield 89%) and the starting material **1** (3 mg, 30%).

Compound **5**: Colorless prisms from Et_2O–hexane, mp 128—131 °C. IR: 1680. UV: 213 (11000). ^{1}H-NMR: 3.30 (1H, dd, J = 3, 14 Hz, H-10), 3.42 (3H, s, OMe), 4.36 (1H, t, J = 3 Hz, H-11), 4.55 (1H, dd, J = 3, 14 Hz, H-10), 6.50 (1H, d, J = 2 Hz, H-14), 7.39 (1H, d, J = 2 Hz, H-15). HRMS *m/z* Calcd for $C_{15}H_{19}NO_3$ (M^+): 261.1345. Found: 261.1343.

Oxidation of 1 with NBA in Aqueous Acetone NBA (45 mg, 1.5 mol eq) was added to a solution of **1** (50 mg) in aqueous acetone (25 ml) at 0 °C and the mixture was stirred at room temperature for 5 min to give **6**. The reaction mixture was allowed to stand at room temperature for 4 d and then extracted with CH_2Cl_2. The organic extract was washed with 10% Na_2SO_3 and brine, dried, and concentrated to dryness *in vacuo*. The residue was purified by PTLC (with AcOEt) to give **7** (25 mg, 38%) and **8** (25 mg, 38%).

Compound **7**: Colorless prisms from CH_2Cl_2–Et_2O, mp 132—133 °C (lit. 132—134 °C).[2b]

Compound **8**: Colorless needles from CH_2Cl_2–Et_2O, mp 200—201 °C. IR: 3450, 1640. UV: 214 (11100). ^{1}H-NMR: 3.17 (1H, dd, J = 3, 14 Hz, H-10), 4.78 (1H, J = 3 Hz, H-11), 6.46 (1H, d, J = 2 Hz, H-14), 7.38 (1H, d, J = 2 Hz, H-15). *Anal.* Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 67.79; H, 6.75; N, 5.76. HRMS *m/z* Calcd for M^+: 247.1209. Found: 247.1185.

Acid Rearrangement of NBA Oxidation Product 6 1) A solution of crude **6** (prepared from 12 mg of **1**) and *p*-TsOH (2 mg) in MeOH (20 ml) was stirred at room temperature for 5 h. The product isolated from the reaction mixture in a usual way was chromatographed to give, from the CH_2Cl_2 eluate, a mixture of **4a** and **4b** (11 mg, 72%).

2) The crude **6** (prepared from 50 mg of **1**) was treated with SiO_2 (10 mg) in MeOH (30 ml) at room temperature for 1 h. After removal of SiO_2 by filtration, the filtrate was concentrated to dryness *in vacuo* and the residue was purified by PTLC (with AcOEt) to give a mixture of **4a** and **4b** (16 mg, 25%) and **7** (13 mg, 24%).

3) The crude **6** (prepared from 100 mg of **1**) was stirred with Nafion-H (50 mg) in THF (20 ml) at room temperature for 30 min. After removal of Nafion-H by filtration, the filtrate was concentrated to dryness *in vacuo*. Crystallizations of the residue from acetone–Et_2O gave **8** (98 mg, 92%).

4) The crude **6** (obtained from 100 mg of **1**) was similarly treated with Nafion-H (50 mg) in MeOH (20 ml) at room temperature for 30 min to give **8** (102 mg, 95%).

Acid Rearrangement of Dimethoxydihydrofuran 4 1) A solution of **4** (120 mg) and *p*-TsOH (5 mg) in benzene (100 ml) was heated under reflux for 2.5 h. The reaction mixture was diluted with benzene, washed with water, dried, and concentrated to dryness *in vacuo*. The residue was chromatographed over Florisil. Elution with benzene gave **9** (47 mg, 50%). Further elution with CH_2Cl_2 gave an oil, which was further purified by PTLC (with AcOEt–hexane 2 : 1) to give **7** (23 mg, 23%), **5** (3 mg, 3%), and **10** (5 mg, 4%).

Compound **9**: Colorless oil. IR (film): 1700, 1620. UV: 210 (4700), 215 sh (4600), 318 (4900). ^{1}H-NMR: 5.91 (1H, d, J = 8 Hz, H-11), 6.46 (1H, d, J = 1 Hz, H-14). 6.81 (1H, d, J = 8 Hz, H-10), 7.32 (1H, d, J = 1 Hz, H-15). HRMS *m/z* Calcd for $C_{14}H_{14}NO_2$ (M^+): 229.1103. Found: 229.1109.

Compound **10**: Colorless prisms from CH_2Cl_2, mp 87—90 °C. IR ($CHCl_3$): 1740, 1680. UV: 212 (4600). ^{1}H-NMR: 3.69 (3H, s, OMe). HRMS *m/z* Calcd for $C_{15}H_{21}NO_4$ (M^+): 270.1461. Found: 279.1468.

2) A solution of **4** (47 mg) in aqueous acetone (20 ml) was acidified with concentrated HCl (*ca.* 0.2 ml), and the mixture was stirred at room temperature for 16.5 h. The product obtained by a usual work-up was purified by PTLC (with AcOEt) to give **7** (13 mg, 30%), **8** (14 mg, 32%), and **11** (15 mg, 38%). Compound **11** formed colorless prisms from Et_2O–hexane, mp 152—154 °C. IR ($CHCl_3$): 1810, 1680. UV: 212 (4700). *Anal.* Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 67.75; H, 6.85; N, 5.42. HRMS *m/z* Calcd for M^+: 247.1206. Found: 247.1191.

3) A mixture of **4** (70 mg) and Nafion-H (70 mg) in benzene (20 ml) was heated under reflux for 30 min. After removal of Nafion-H by filtration, the filtrate was concentrated to dryness *in vacuo* and the residue was purified by MPLC (acetone : benzene = 1 : 1) to give **5** (35 mg, 45%).

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12) Ring C of the 13αH isomer (**15a**) should take a boat form.