Total Synthesis of Dihydroreynosin and Dihydrosantamarine *via* Tandem Cope-Claisen Rearrangement

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The total synthesis of dihydroreynosin (**1**) and dihydrosantamarine (**2**) *via* tandem Cope-Claisen rearrangement has been accomplished starting from (S)-carvone (**4**).

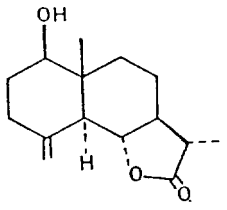
Introduction

Reports dealing with isolation, structual elucidation and chemistry of sesquiterpene lactones have increased dramatically during the last two decades. The increasing attention in this group of natural products has been drawn mainly due to their various biological activities.[1]

Eudesmanolide, one of the important skeletal types of naturally occurring bicyclic sesquiterpene lactones, has been particularly inspiring with regard to its total synthesis.[2] We now wish to report a total synthesis of two eudesmanolides, dihydroreynosin (**1**) and dihydrosantamarine (**2**) by using the strategy of tandem Cope-Claisen rearrangement.[3]

Results and Discussion

Since epoxidation of cyclodecadienolides followed by acid catalyzed transformation of the resulting oxides has been believed to be the most likely biogenic route[4] to bicyclic sesquiterpene lactones, the epoxide **3** was selected as a target precursor for the synthesis of **1** and **2**.



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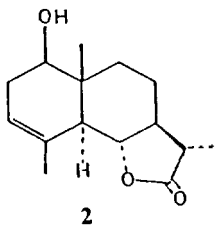

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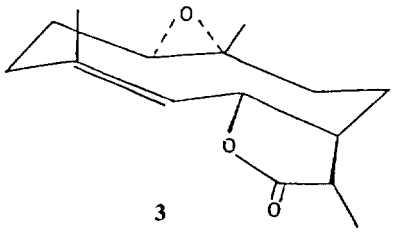
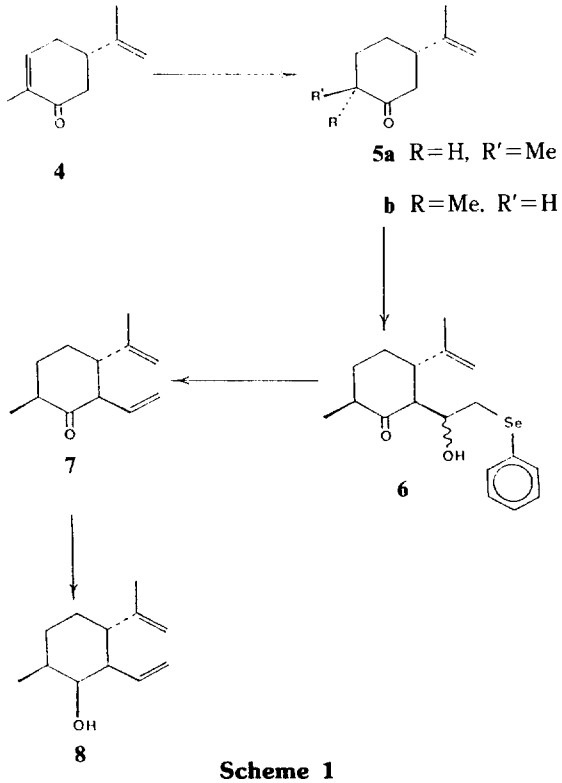


3

The total synthesis of **1** and **2** started from (S)-carvone (**4**), which affords the same stereochemistry as the naturally occurring enantiomers, santamarine[5] and reynosin[6] have (Scheme 1).

Treatment of **4** with K-Selectride followed by an oxidative work-up gave a 83:17 mixture of **5a** and **5b**. The crude mixture was purified by flash chromatography to provide **5a** in 70% yield. Alternatively, reduction of (S)-carvone with lithium-bronze[7] produced a 85:15 mixture of **5a** and **5b** and purification of the crude mixture gave **5a** in 62% yield. Treatment of **5a** with LDA followed by condensation with (phenylseleno) acetaldehyde[8] furnished the β-hydroxyselenide **6**.

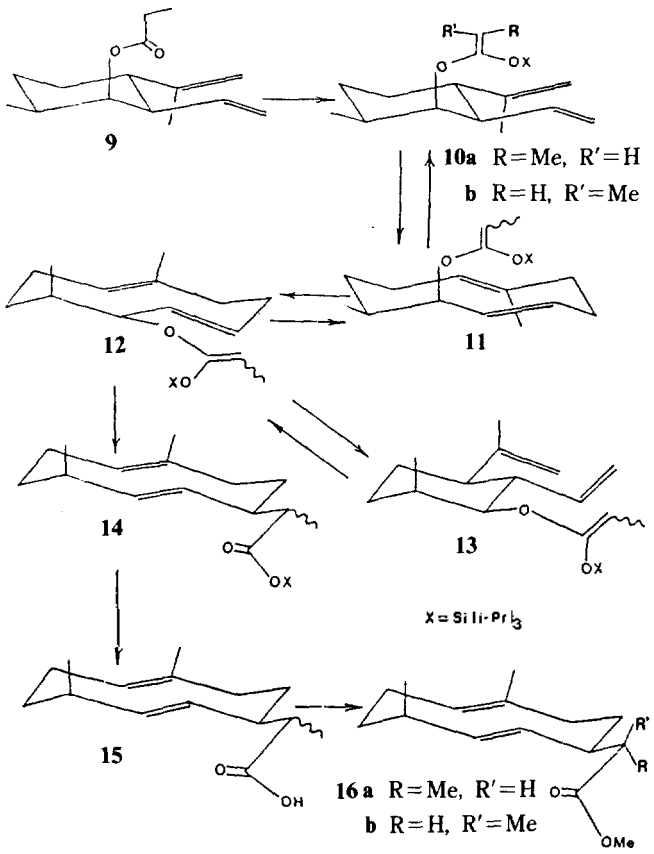


4 **5a** R=H, R'=Me; **b** R=Me, R'=H; **6**, **7**, **8**

Scheme 1

Reaction of the crude selenide **6** with mesyl chloride in the presence of triethylamine provided **7**. After a brief purification of the crude **7** by flash chromatography, treatment of **7** with L-Selectride followed by an oxidative work-up gave the divinyl axial alcohol **8** in 44% overall yield from **5a**.

The propionate **9** was prepared by treatment of **8** with propionyl chloride in 91% yield (Scheme 2). Treatment of **9** with LDA in the presence of HMPA (23% HMPA/THF) followed by quenching with triisopropylsilyl chloride afforded the silyl ketene acetal **10A** as a 90:10 mixture of **10a** and **10b** in 100% GC yield. In contrast, treatment of **9** with LDA followed by quenching with a triisopropylsilyl chloride solution in HMPA provided the silyl ketene acetal **10B** as a 9:91 mixture of **10a** and **10b** in 96% GC yield. The observed stereoselectivity results from the kinetic enolate formation of **9**, and this enolization takes a different course as a func-



Scheme 2

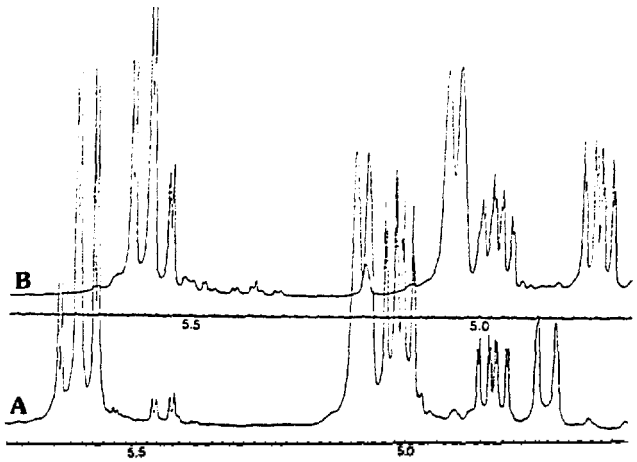
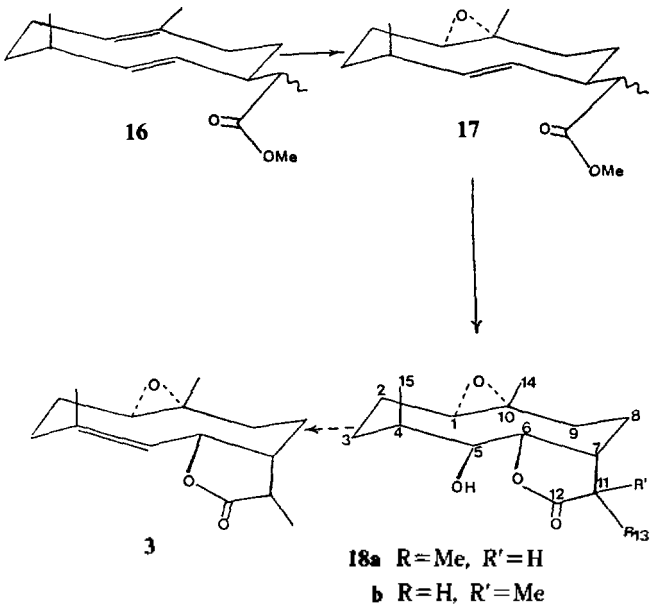


Figure 1. The 500 MHz NMR spectra of **16A** and **16B**.



Scheme 3.

tion of the solvent employed.[9]

A dodecane solution of the silyl ketene acetal **10A** was heated at 200℃ for 140 minutes, and then dodecane was removed under vacuum to give **14** in 69% GC yield with no indication of O- to C-silyl migration. Hydrolysis of the crude **14** with KF · $2H_2O$ in HMPA for 90 minutes followed by an acid-base extraction povided the (1*E*, 6*E*)-cyclodecadienoic acid **15** in 34% overall yield from the ester **9**.

Methylation of the acid **15** with diazomethane gave the (1*E*, 6*E*)-cyclodecadienoic ester **16A** as a 75:25 mixture of **16a** and **16b** in 87% yield. The structure of **16A** was fully characterized by 500 MHz NMR, IR, GC/MS and HREIMS analysis. The ^{1}H-NMR spectrum of **16A** showed the characteristic vinyl protons of C-5 and C-6 at 5.55 (dd, J=15.9, 3.7 Hz) and 4.97 ppm (ddd, J=15.9, 9.8, 1.8 Hz), respectively. Irradiation of the C-14 methyl group of **16A** gave a 0.7% N. O. E. enhancement[10] of the C-6 hydrogen, and irradiation of the C-5 hydrogen of **16A** gave a 3.0% enhancement of the C-1 hydrogen. The result of N. O. E experiment confirmed the structural assignment of **16A**, and the IR absorption of **16A** at 985 cm^{-1} (C-H OOP stretching) also demonstrated the presence of *trans*-disubstituted double bond.[11] The HREIMS spectrum of **16A** showed the parent ion at m/e 250.1948 (calcd. for $C_{16}H_{26}O_2$ 250.1933).

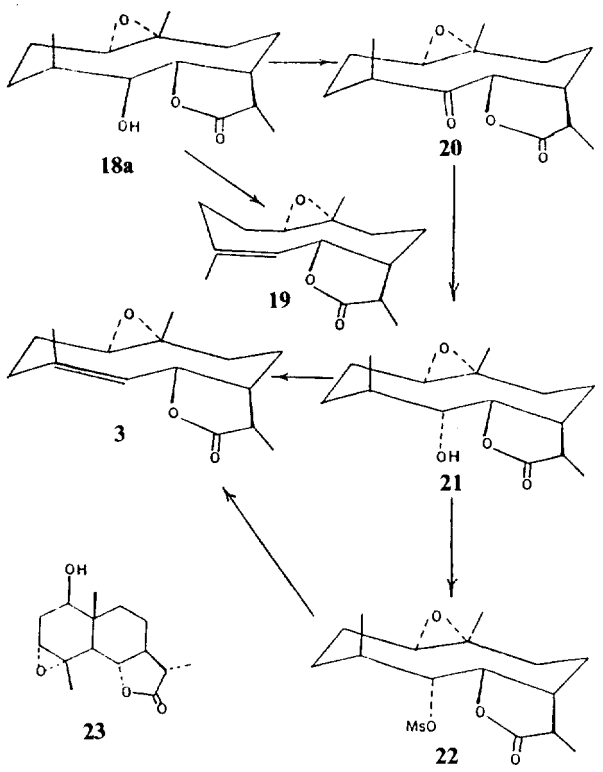
However, thermolysis of **10B** under the same conditions followed by subsequent transformation afforded the ester **16B** as a 33:67 mixture of **16b** and **16a** in overall 29% yield from **9**. The vinyl protons of **16A** and **16B** in 500 MHz ^{1}H-NMR spectra are shown in Figure 1.

One explanation for the partial loss of the stereospecificity of tandem Cope-Claisen rearrangement could be the geometrical isomerism[12] of the silyl ketene acetals **10** during thermolysis.

Since the C-13 methyl group on **16** would be transformed to an exocyclic methylene funtionality, its stereochemistry is not important. Nevertheless, the silyl ketene acetal **10A** was utilized as a precursor for tandem Cope-Claisen rearrangement because **10A** gave **16** more sterespecifically than **10B**.

Conversion of **16A** to the epoxide **3** requires the formation of the γ-butyrolactone, the selective transposition of the disubstituted double bond and the epoxidation.

Since it was not possible to selectively funtionalize the disubstituted double bond of **16A**, the trisubstituted double bond was protected by epoxidation. Treatment of **16A** with one equivalent of MCPBA provided the epoxide **17** in 70% yiele (Scheme 3). Treatment of **17** with OsO_4 effected syn-hydroxylation, and spontaneous lactonization of the resulting diol provided the hydroxylactone **18**. The crude **18** was purified by flash chromatography to give a 10:1 mixture of **18a** and **18b** as white flakes in 97% yield. Crystallization of the



Scheme 4.

product mixture from ether gave pure **18a** as white needles. The ^{1}H-NMR spectrum of **18a** showed the characteristic resonances at 2.98 (dd, J=9.2, 5.5 Hz, 1H on C-1), 3.97 (ddd, J=9.8, 3.7, 1.8 Hz, 1H on C-5) and 4.39 ppm (dd, J=4.9, 1.8 Hz, 1H on C-6). The formation of a *trans*-lactone could not be confirmed solely by the coupling constants ($J_{4,5}$=3.7, $J_{5,6}$=1.8, $J_{6,7}$=4.9 Hz), since the values can vary with the rest of configuration of the ten-membered ring.[1] However, irradiation of the C-6 hydrogen of **18a** gave a 4.2% N. O. E enhancement of the C-14 methyl signal and irradiation of the C-5 hydrogen gave a 11.5% enhancement of the C-1 hydrogen. The result of N. O. E experiment were in accord only with the *trans*-lactone structure of **18a**. The IR spectrum of **18a** displayed the characteristic carbonyl absorption of γ-butyrolactone at 1775 cm^{-1} and the HREIMS spectrum of **18a** showed the parent ion at m/e 268.1654 (cald. for $C_{15}H_{24}O_4$ 268.1675).

Although the dehydration of secondary alcohol with Martin sulfurane agent [**MSA**][13] is known to proceed *via* anti-elimination for acyclic systems, the unusually mild reaction conditions prompted us to examine the use of this reagent for the dehydration of **18a**. Reaction of the alcohol **18a** at room temperature with **MSA** for 16 hours followed by flash chromatography provided **19** as a white solid in 60% yield. The ^{1}H-NMR spectrum of **19** showed the characteristic resonances at 5.01 (d, J=11 Hz, 1H on C-6) and 5.42 ppm (d, J=11 Hz, 1H on C-5). Irradiation of the C-15 methyl hydrogens of **19** gave a 1.4% N. O. E enhancement of the C-5 hydrogen. The coupling constants[14] and the result of N. O. E experiment were well in accord with the assigned structure of **19**. The Z-double bond formation of **19** is expected from the configuration of the alcohol **18a** and the proposed anti-elimination mechanism for the dehydration of various alcohols with **MSA**.

Since syn-elimination of derivatives of **18a** could not be effected and since anti-elimination of **18a** produced a Z-double bond, the alcohol **18a** was converted to the epimeric alcohol **21** by oxidation and subsequent reduction. Oxidation of **18a** at 0℃ with pyridinium dichromate[15] in DMF provided the ketone **20** in 87% yield (Scheme 4). The IR spectrum of **20** showed the characteristic carbonyl absorptions at 1717 and 1780 cm^{-1}. The proton on C-6 showed a doublet (J=7.9 Hz) at 4.76 ppm in ^{1}H-NMR spectrum, and the parent ion at m/e 266 was detected by GC/MS analysis.

Reduction of the ketone **20** at 0℃ with $NaBH_4$ produced the epimeric alcohol **21** in 82% yield. The reduction occurs selectively by attack from the outside face of the carbonyl in the predicted and preferred conformation. The ^{1}H-NMR spectrum of **21** showed the characteristic resonances at 2.93 (dd, J=10.1, 3.1 Hz, 1H on C-1), 3.62 (dd, J=8.5, 5.1, 1 Hz, 1H on C-5) and 4.45 ppm (dd, J=5.4, 1 Hz, 1H on C-6). Irradiation of the C-6 hydrogen of **21** gave a 6.8% N. O. E enhancement of the C-14 methyl signal and a 2.9% enhancement of the C-5 hydrogen. The HREIMS spectrum of **21** showed the parent ion at m/e 268.1688 (calcd. for $C_{15}H_{24}O_4$ 268.1675). The alcohol **21** was protected by a conversion to the sulfonate **22**. Treatment of **21** with mesyl chloride provided **22** in 92% yield. The structure of **22** was confirmed by ^{1}H-NMR. IR was MS analysis and the ^{1}H-NMR spectrum of **22** displayed the characteristic resonances at 3.11 (s, CH_3SO_3-), 4.48 (dd, J=9.2, 1.8 Hz, 1H on C-6) and 4.91 ppm (br.s, 1H on C-5).

Elimination of the sulfonate **22** in acetone at reflux with tetra-*n*-butylammonium oxalate[16] for 5 days followed by purification with flash chromatography over deactivated silica gel gave **3** in 40% yield. The ^{1}H-NMR spectrum of **3** showed the typical resonances at 2.68 (dd, J=12.2, 2.4 Hz, 1H on C-1), 4.59 (t, J=9.8 Hz, 1H on C-6) and 5.20 ppm (d, J=9.8 Hz, 1H on C-5). The results of IR and GC/MS analysis were in accord with the assigned structure of **3**. Dehydration of **21** was also effected by the sulfurane agent to give a poor yield of **3**. The synthesis of **1** and **2** was completed by isomerization[4] of the epoxide **3**.

The epoxide **3** readily underwent isomerization to a mixture of dihydrosantamarine (**2**) and dihydroreynosin (**1**) by contact with untreated silica gel.

Flash chromatography with the crude products of elimination of **22** over untreated silica gel furinshed no epoxide **3**, but instead the isomerized products, **1** and **2**, were obtained. The formation of **1** and **2** was confirmed by ^{1}H-NMR, IR and GC/MS analysis. The ^{1}H-NMR spectrum of **2** showed the characteristic resonances at 3.65 (m, 1H on C-1), 3.95 (t, J=10.5 Hz, 1H on C-6) and 5.33 ppm (br.s, 1H on C-3). The ^{1}H-NMR of **1** showed peaks at 3.50 (m, 1H on C-1), 4.04 (t, J=10.4 Hz, 1H on C-6), 4.83 (d, J=1.2 Hz, 1H on C-15) and 4.97 ppm (d, J=1.2 Hz, 1H on C-15) in ^{1}H-NMR analysis.[17] To verify the structure of **2**, the known epoxide **23** was prepared by oxidation of **2** with MCPBA and characterized.[6] The conversion of **2** to santamarine has been reported.[18]

In summary, the total synthesis of eudesmanolides, dihydroreynosin (**1**) and dihydrosantamarine (**2**) has been accomplished starting from (S)-carvone (**4**). The pivotal precursor **3** was prepared *via* tandem Cope-Claisen rearrangement.

This synthesis demonstrates the usefulness of tandem Cope-Claisen rearrangement for the synthesis of various sesquiterpene lactones.

Experimental

Nuclear magnetic resonance (NMR) spectra were recorded at 500 MHz (Bruker WM500), 300 MHz (Varian VXR-300) or 60 MHz (Varian EM360L) as indicated. Spectra were recorded in $CDCl_3$ (treated with basic alumina), and the chemical shifts are reported in ppm(δ) relative to Me_4Si (δ 0.00) as an internal standard. Coupling constants are reported in Hz. Infrared (IR) spectra were recorded on a Perkin-Elmer 283 or Beckman Acculab 4 infrared spectrometer. Melting points were determined on a Mel-Temp melting point apparatus. All melting points are uncorrected. High resolution mass spectra were recorded on a VG Micromass 7070H spectrometer, and HP 5985 GC/MS was used for low resolution mass spectra.

Reactions were followed by thin-layer chromatography (TLC) and/or gas chromatography (GC). Thin-layer chromatography was performed on Merck silica gel glass plate precoated with silica gel 60. Gas chromatography was conducted with a 12 m DB-5 fused-quartz capillary column using a Hewlett-Packard 5880A GC. Hexadecane was used as an internal standard for the calculation of GC yields. Flash chromatography was performed with Merck 40-63 μm silica gel. Deactivated silica gel with Et_3N means that the column with silica gel was equilibrated with approximately 3% Et_3N solution prior to the application of crude product into the column. Flasks were silanized for silyl ketene acetal rearrangements by soaking into 5% bis (trimethylsilyl) acetamide in toluene at room temperature overnight. Reactions were run under an atmosphere of argon.

Preparation of (2*S*, 5*S*)-2-Methyl-5-(1-methylethenyl)-1-cyclohexanone (5a) by Lithium-bronze Reduction A 250 m*l* three-neck flask fitted with a glass-coated magnetic strirrer, a dry-ice condenser with an Ar inlet, and a 50 m*l* additional funnel. The apparatus was flame-dried and maintained under positive Ar pressure. Sliced lithium (2.22 g, 320 mmol) was added, and ammonia (50 m*l*) was distilled from sodium into the reaction vessel. Gradually the lithium became coated with bronze globules and eventually a bronze-colored liquid with a smooth mirror finish was formed. When bronze formation was complete, dry ether (30 m*l*) was added and the rate of stirring was increased to disperse the reagent as well as possible. A solution of (S)-carvone (4) (24.12 g, 160.5 mmol) and tert-butyl alcohol (15.14 m*l*, 160.6 mmol) was added dropwise over 100 min. After the addition was complete, the reaction mixture was stirred for another 20 min. Excess lithium was destroyed by the dropwise addition of an ether solution equimolar in acetone and ethanol. Enough water (60 m*l*) to dissolve the lithium salts was then added, and the reaction mixture was extracted with hexanes (1×100, 2×50 m*l*). The combined organic extracts were dried ($MgSO_4$) and the solvents were removed in vacuo. The residue (25.53 g, **5a**:**5b** = 85:15) was purified by flash chromatography (5% EtOAc-hexanes) to provide **5a** (15.06 g, 99.1 mmol) in 62% yield a clear liquid. ^{1}H-NMR ($CDCl_3$, 500 MHz); δ 1.04 (d, J=6.1, 3H), 1.74 (s, 3H), 4.73 (s, 1H), 4.76 (s, 1H); IR (neat): 2940, 1725, 1660, 1470, 1390, 900 cm^{-1}; GC/MS (EI); 152 (M^+), 137, 109, 95 (100), 82, 81 amu.

Preparation of (2*S*, 5*S*)-2-Methyl-5-(1-methylethenyl)-1-cyclohexanone (5a) by K-Selectride Reduction. To a solution of (S)-carvone (12.01 g, 80.0 mmol) in THF (150 m*l*) at −78℃ was added dropwise 1.0 M K-Selectride (84.0 m*l*, 84.0 mmol, Aldrich) in THF over 20 min. After 1 hr, the reaction mixture was warmed to 0℃, and quenched by the addition of 3N NaOH (60 m*l*, 180 mmol). The resulting solution was treated at 0℃ with 35% H_2O_2 (20 m*l*, 200 mmol), and stirred overnight. The reaction mixture was concentrated under reduced pressure, and extracted with hexanes (3×50 m*l*). The combined extracts were washed with 20% $NaHSO_3$ (2×20 m*l*), brine (20 m*l*), and dried ($MgSO_4$). The solvents were removed in vacuo, and the residue (15.38 g, **5a**:**5b** = 83:17) was purified by flash chromatography (5% EtOAc-hexanes) to give **5a** (8.53 g, 56.1 mmol) in 70% yield as a clear liquid.

Preparation of (1*S*, 2*R*, 3*S*, 6*S*)-2-Ethenyl-6-methyl-3-(1-methylethenyl)-1-cyclohexanol (8). The reaction was carried out by the published procedure[19] using **5a** and phenylselenoacetaldehyde to give **8** in 44% overall yield from **5a** as a yellowish liquid. ^{1}H-NMR ($CDCl_3$, 500 MHz); δ 1.00 (d, J=6.7, 3H), 1.61 (s, 3H), 2.11 (m, 1H), 2.39 (dt, J=3.7, 11.9, 1H), 3.72 (br.s. 1H), 4.72 (m, 2H), 5.09 (m, 2H), 5.82 (m, 1H); IR (neat): 3600-3300, 2940, 1660, 1390 cm^{-1} GC/MS (EI): 180 (M^+), 165, 162, 147, 138, 122, 105, 93, 79 (100) amu.

Preparation of (1*S*, 2*R*, 3*S*, 6*S*)-2-Ethenyl-6-methyl-3-(1-methylethenyl)cyclohexyl Propionate (9). To a solution of **8** (2.14 g, 11.92 mmol) in CH_2Cl_2 (12 m*l*) and pyridine (1.60 m*l*, 19.66 mmol) at 0℃ was added DMAP (145 mg, 1.19 mmol) and propionyl chloride (1.55 m*l*, 17.88 mmol). The resulting solution was warmed to room temperature and stirred for 4 hr. The reaction mixture was diluted with water (15 m*l*), concentrated under reduced pressure, and then extracted with ether (3×30 m*l*). The combined extracts were washed with water (15 m*l*), brine (10 m*l*), and dried ($MgSO_4$). The solvents were evaporated in vacuo, and the residue was purified by flash chromatography (3% EtOAc-hexanes) to give **9** (2.56 g, 10.85 mmol) in 91% yield as a clear liquid. ^{1}H-NMR ($CDCl_3$, 500 MHz); δ 0.85 (d, J=6.7, 3H), 1.18 (t, J=7.3, 3H), 1.60 (s, 3H), 2.37 (q, J=7.3, 2H), 4.71 (br.s, 2H), 5.00 (m, 2H), 5.20 (br.s, 1H), 5.50 (m, 1H); IR (neat): 3080, 2940, 1750, 1200, 900 cm^{-1} GC/MS (EI): 236 (M^+), 221, 207, 195, 180, 162, 147 (100), 133, 121 amu.

Preparation of (1*Z*)-1-[(1*S*, 2*R*, 3*S*, 6*S*)-2-Ethenyl-6-methyl-3-(1-methylethenyl)cyclohexyloxy]-1-triisopropylsiloxy-1-propene (10a). To a solution of diisopropylamine (2.15 m*l*, 15.36 mmol) in THF (15 m*l*) at 0℃ was added a 2.32 M *n*-BuLi (6.02 m*l*, 13.96 mmol) in hexanes. The solution was cooled to −78℃ and HMPA (3.45 m*l*) was added. After 5 min, a solution of **9** (2.19 g, 9.31 mmol) in THF (3 m*l*) was added dropwise over 5 min at −78℃. The reaction mixture was stirred for another 20 min, then quenched at −78℃ with triisopropylsilyl chloride (3.00 m*l*, 14.00 mmol) neat. The solution was warmed to room temperature over 50 min, and diluted with cold saturated $NaHCO_3$ (15 m*l*). The reaction mixture was concentrated under reduced pressure, and extracted with pentane (3×30 m*l*). The combined extracts were washed with $NaHCO_3$ (2×15 m*l*), brine

(15 m*l*), and dried (Na_2SO_4). The solvents were removed in vacuo to give the crude silyl ketene acetals **10A** (4.65 g, *Z*:*E*=90: 10) in 100% GC yield as a pale yellow liquid.

Preparation of (1*E*)-1-[(1*S*, *R*, 3*S*, 6*S*)-2-Ethenyl-6-methyl-3-(1-methylethenyl)cyclohexyloxy]-1-triisopropylsiloxy-1-propene (10b). The addition of a solution of **9** in HMPA into a LDA solution at −78℃ followed by quenching with triisopropylsilyl chloride provided the crude silyl ketene acetals **10B** (*Z*:*E*=8:92) in 100% yield as a pale-yellow liquid.

Preparation of 2-[(1*R*, 2*E*, 4*S*, 7*E*)-4-8-Dimethyl-2, 7-cyclodecadien-1-yl]propionic Acid (15). A solution of **10A** (4.65 g, 9.31 mmol) in degassed dodecane (30 m*l*) was placed into silanized flask under Ar. The flask was immersed into an oil bath pre-equilibrated at 200℃ for 140 min. The solution was cooled, and dodecane was removed by vacuum distillation using Kugelrohr apparatus. The crude tandem Cope-Claisen rearrangement products **14** (69% GC yield) were dissolved into HMPA (5.0 m*l*), and treated with KF · $2H_2O$ (1.75 g, 18.6 mmol). The resulting heterogeneous mixture was stirred at room temperature for 90 min, and diluted with ether (50 m*l*). After HMPA was washed out with water (3×15 m*l*), the ethereal solution was extracted with 1 N NaOH (3×10 m*l*), and then the basic extracts were neutralized at 0℃ with 3 N HCl (10 m*l*). The insoluble acid **15** in aqueous phase were extracted with ether (3×30 m*l*), and the combined extracts were washed with water (15 m*l*), brine (15 m*l*), and dried ($MgSO_4$). The solvents were removed in vacuo to give **15** (757 mg, 3.21 mmol) in 34% overall yield from **9** as a viscous liquid. ^{1}H-NMR ($CDCl_3$, 60 MHz); δ 1.00 (br.s, 3H), 1.12 (br.s, 3H), 1.53 (s, 3H), 4.6-5.9 (m, 3H), 11.20 (br.s, 1H); IR (neat): 3400-2500, 1720, 1460, 1230, 1000 cm^{-1} GC/MS (EI): 236 (M^+), 218, 175, 163, 107, 81 (100) amu.

Preparation of Methyl 2-[(1*R*, 2*E*, 4*S*, 7*E*)-4,8-Dimethyl-2,7-cyclodecadien-1-yl]propionate (16). To a solution of ether (10 m*l*) and 40% aqueous KOH (5 m*l*) at 0℃ was added N- nitrosomethylurea (75% pure, 882 mg, 6.42 mmol). The yellow diazomethane-ether layer was taken and added at 0℃ to a solution of **15** (757 mg, 3.21 mmol) in ether (5 m*l*). After 10 min, acetic acid was added dropwise until the remaining diazomethane was consumed as indicated by the disappearance of the yellow color. The aqueous phase was separated, and extracted with ether (3×20 m*l*). The combined extracts were washed with 5% $NaHCO_3$ (2×10 m*l*), brine (10 m*l*), and dried ($MgSO_4$). The solvents were removed in vacuo, and the residue was purified by flash chromatography (3% EtOAc-hexanes) to give **16A** (698 mg, 2.79 mmol) in 87% yield as a 75:25 mixture of **16a** and **16b**. ^{1}H-NMR ($CDCl_3$, 500 MHz); δ 1.07 (d, J=7, 3H), 1.08 (d, J=7, 3H), 1.52 (s, 3H), 3.61 (s, 2.3H), 3.66 (s, 0.7H), 4.80 (ddd, J=15.9, 9.8, 1.8, 0.3H), 4.97 (ddd, J=15.9, 9.8, 1.8, 0.7H), 5.04 (br.d, J=11.6, 1H), 5.55 (dd, J=15.9, 3.7, 0.7H), 5.58 (dd, J=15.9, 3.7, 0.7H); IR (neat): 2930, 1740, 1450, 1155, 985 cm^{-1} HREIMS: calcd. for $C_{16}H_{26}O_2$ 250.1933, Found 250. 1948, 218, 190, 175, 168, 163, 162 (100), 147, 133, 121, 95 amu.

Thermolysis of **10B**, and subsequent transformations under the same conditions provided **16B** in 29% overall yield from **9** as a 33:67 mixture of **16a** and **16b**.

Preparation of Methyl 2-[(1*R*, 2*E*, 4*S*, 7*R*, 8*R*)-7,8-Epoxy-4, 8-dimethyl-2-cyclodecen-1-yl]propionate (17). To a solution of **16A** (507 mg, 2.02 mmol) in CH_2Cl_2 (20 m*l*) was added freshly prepared 0.5 N $NaHCO_3$ (20 m*l*, 10 mmol). The resulting solution was vigorously stirred and cooled in an ice-bath. A solution of MCPBA (385 mg, 2.22 mmol) in CH_2Cl_2 (5 m*l*) was added dropwise at 0℃. After 25 min, the aqueous phase was separated, and extracted with CH_2Cl_2 (2×15 m*l*). The combined extracts were washed with 10% Na_2SO_3 (15 m*l*), 5% $NaHCO_3$ (10 m*l*), brine (10 m*l*), and dried (Na_2SO_4). The solvents were evaporated in vacuo, and the residue was purified by flash chromatography (5-10% EtOAc-hexanes, deactivated silica gel with Et_3N) to give **17** (376 mg, 1.41 mmol) in 70% yield as a colorless liquid. ^{1}H-NMR ($CDCl_3$, 500 MHz); δ 1.04 (d, J=6.7, 3H), 1.12 (d, J=6. 7, 3H), 1.26 (s, 3H), 3.63 (s, 3H), 5.25 (ddd, J=15.9, 10.4, 1, 1H), 5.72, (dd, J=15.9, 4.3, 1H); IR (neat): 2970, 1735, 1455, 1390, 1195, 1160, 985 cm^{-1} GC/MS (EI): 266 (M^+), 248, 234, 208, 195, 179, 161, 121, 93, 81 (100) amu.

Preparation of (1*S*, 2*S*, 3*S*, 6*R*, 7*R*, 10*S*, 11*S*)-6,7-Epoxy-2-hydroxy-3,7,11-trimethyl-12-oxo-13-oxabicyclo [8.3.0^{1,10}]tridecane (18a). To a solution of **17** (376 mg, 1.41 mmol) in ether (5 m*l*) at room temperature was added a solution of OsO_4 (358 mg, 1.41 mmol) in pyridine (1.2 m*l*, 14.8 mmol) and ether (4 m*l*). The resulting solution was stirred for 24 hr during which time the solution darkened. The reaction was quenched by the addition of a solution of $NaHSO_3$ (734 mg, 7.05 mmol) in pyridine (11.5 m*l*), and water (11.0 m*l*). The solution was stirred for 3 hr, and extracted with CH_2Cl_2 (3×25 m*l*). The combined extracts were washed with water (15 m*l*), brine (15 m*l*), and dried (Na_2SO_4). The solvents were removed in vacuo, and the resulting white solid was purified by flash chromatography (30-50% EtOAc-hexanes) to give a 10:1 mixture of **18a** and **18b** (368 mg, 1.37 mmol) in 97% yield as a white flakes. Crystallization from ether provided pure **18a** as white needles. m.p.: 159-161℃; ^{1}H-NMR ($CDCl_3$, 500 MHz); δ 1.00 (d, J=6.7, 3H), 1.34 (d, J=7.3, 3H), 1.40 (s. 3H), 2.98 (dd, J=9.2, 5.5, 1H), 3.97 (ddd, J=9.8, 3.7, 1.8, 1H), 4.39 (dd, J=4.9, 1.8, 1H); IR ($CHCl_3$): 3600-3300, 2940, 1775, 1460, 1175, 905 cm^{-1}; HREIMS: calcd. for $C_{15}H_{24}O_4$ 268.1675, Found 268.1654, 250, 207, 193, 181, 169, 137, 121, 93 (100) amu.

Preparation of (1*R*, 2*Z*, 6*R*, 7*R*, 10*S*, 11*S*)-6,7-Epoxy-3,7,11-trimethyl-12-oxo-13-oxabicyclo [8.3.0^{1,10}]tridec-2-ene (19). To a solution of **18a** (19.6 mg, 0.073 mmol) in CH_2Cl_2 (1 m*l*) at room temperature was added a solution of Martin sulfurane agent (73.7 mg, 0.11 mmol) in CH_2Cl_2 (1 m*l*). The reaction mixture was stirred at room temperature for 16 hr, and purified by flash chromatography (20-40% EtOAc-hexanes, deactivated silica gel with Et_3N) to give **19** (11.0 mg, 0.044 mol) in 60% yield as a white solid. Crystallization from ether-pentane afforded colorless needles. m.p.: 162-164℃; ^{1}H-NMR ($CDCl_3$, 500 MHz); δ 1.18 (d, J=7.3, 3H), 1.43 (s, 3H), 1.85 (s, 3H), 5.01 (d, J=11.0, 1H), 5.42 (d, J=11.0, 1H); IR ($CHCl_3$): 2980, 2910, 1785, 1675, 1470, 1190, 1120, 880 cm^{-1} GC/MS (CI): 251 (M^++1), 223 (100), 205, 187, 177, 159, 111, 81 amu.

Preparation of (1*S*, 3*S*, 6*R*, 7*R*, 10*S*, 11*S*)-6,7-Epoxy-3,7,11-trimethyl-2-oxo-12-oxo-13-oxabicyclo [8.3.0^{1,10}] tridecane (20). To a solution of **18a** (180 mg, 0.67 mmol) in DMF (5 m*l*) at 0℃ was added pyridinium dichromate (1.13 g, 3.01 mmol). The resulting solution was stirred at 0℃ for

12 hr, then diluted with water (20 ml). The reaction mixture was extracted with CH_2Cl_2 (3×25 ml), and the combined extracts were washed with water (15 ml), brine (15 ml), and dried (Na_2SO_4). The solvents were removed in vacuo, and the residue was purified by flash chromatography (20-30% EtOAc-hexanes) to give **20** (155 mg, 0.58 mmol) in 87% yield as a colorless liquid which solidified on standing. Crystallization from ether-pentane provided colorless prisms. m.p.: 95-96℃; ^{1}H-NMR ($CDCl_3$, 500 NMz); δ 1.28 (d, J=7.3, 3H), 1.32 (s, 3H), 1.33 (d, J=7.3, 3H), 2.53 (dd, J=10.4, 3.7, 1H), 2.87 (m, 1H), 4.76 (d, J=7.9, 1H); IR (neat): 2940, 1780, 1715, 1460, 1170 cm^{-1}; GC/MS (EI): 266 (M^+). 222, 208, 195, 169, 151, 125, 111, 81, 55 (100) amu.

Preparation of (1*S*, 2*R*, 3*S*, 6*R*, 7*R*, 10*S*, 11*S*)-6,7-Epoxy-2-hydroxy-3,7,11-trimethyl-12-oxo-13-oxabicyclo [8.3.0^{1,10}]tridecane (21). To a solution of **20** (140 mg, 0.52 mmol) in methanol (5 ml) at 0℃ was added $NaBH_4$ (20.0 mg, 0.52 mmol) in several portions. The resulting solution was stirred at 0℃ for 10 min, and then cautiously quenched with water (10 ml). The reaction mixture was concentrated under reduced pressure, and extracted with CH_2Cl_2 (3×20 ml). The combined extracts were washed with water (10 ml), brine (10 ml), and dried (Na_2SO_4). The solvents were evaporated in vacuo, and the residue was purified by flash chromatography (40-50% EtOAc-hexanes) to give **21** (114 mg, 0.43 mmol) in 82% yield as a white solid. Crystallization from ether provided colorless prisms. m.p.: 179-181℃; ^{1}H-NMR ($CDCl_3$, 500 MHz); δ 1.08 (d, J=6.7, 3H), 1.32 (d, J=7.9, 3H), 1.33 (s, 3H), 2.93 (dd, J=10.1, 3.1, 1H), 3.62 (ddd, J=8.5, 5.1, 1, 1H), 4.45 (dd, J=5.4, 1, 1H); IR ($CHCl_3$): 3600-3300, 2940, 1770, 1460, 1180, 1000 cm^{-1}; GC/MS (EI): 268 (M^+), 250, 207, 197, 181, 151, 121, 99 (100) amu.

Preparation of (1*S*, 2*R*, 3*S*, 6*R*, 7*R*, 10*S*, 11*S*)-6,7-Epoxy-2-methanesulfonatoxy-3,7,11-trimethyl-12-oxo-13-oxabicyclo [8.3.0^{1,10}]tridecane (22). To a solution of **21** (110 mg, 0.41 mmol) in CH_2Cl_2 (4 ml) and pyridine (0.17 ml, 2.10 ml) at 0℃ was added methanesulfonyl chloride (0.063 ml, 0.82 mmol). The resulting solution was warmed to room temperature and stirred for 10 hr. The reaction mixture was diluted with water (10 ml), and extracted with CH_2Cl_2 (3×20 ml). The combined extracts were washed with water (10 ml), brine (10 ml), and dried (Na_2SO_4). The solvents were removed in vacuo, and the residue was purified by flash chromatography (30-40% EtOAc-hexanes) to give **22** (131 mg, 0.38 mmol) in 92% yield as a white solid. Crystallization from ether-EtOAc afforded colorless prisms. m.p.: 139-140℃; ^{1}H-NMR ($CDCl_3$, 500 MMz); δ 1.11 (d, J=6.1, 3H), 1.27 (d, J=7.3, 3H), 1.42 (s, 3H), 2.83 (d, J=9.2, 1H), 3.11 (s, 3H), 4.48 (dd, J=9.2, 1.8, 1H), 4.91 (br. s, 1H); IR ($CHCl_3$): 2940, 1780, 1460, 1335, 1175, 920 cm^{-1}; MS (DIP): 346 (M^+), 267, 249, 231, 193, 169, 111, 55 (100) amu.

Preparation of (1*R*, 2*E*, 6*R*, 7*R*, 10*S*, 11*S*)-6,7-Epoxy-3,7,11-trimethyl-12-oxo-13-oxabicyclo [8.3.0^{1,10}]tridec-2-ene (3). To a solutin of **22** (24.5 mg, 0.070 mmol) in acetone (3 ml) was added tetrabutylammonium oxalate (81 mg, 0.14 mmol). The resulting solution was heated at reflux for 5 days, during which time more tetrabutylammonium oxalate (30 mg) was added every 48 hr. The reaction was diluted with water (10 ml), and extracted with EtOAc (3×20 ml). The combined extracts were washed with water (10 ml), brine (10 ml), and dried (Na_2SO_4). The solvents were removed in vacuo, and the residue was purified by flash chromatography (20-30% EtOAc-hexanes, deactivated silica gel with Et_3N) to give **3** (7.0 mg, 0.028 mmol) in 40% yield as a crystalline solid. Crystallization from ehter-pentane produced colorless prisms. m.p.: 105-107℃; ^{1}H-NMR ($CDCl_3$, 500 MHz); δ 1.13 (s, 3H), 1.24 (d, J=7.3, 3H), 1.82 (d, J=1.2, 3H), 2.68 (dd, J=12.2, 2.4, 1H), 4.59 (t, J=9.8, 1H), 5.20 (d, J=9.8, 1H); IR ($CHCl_3$): 2960, 1765, 1458 cm^{-1}; GC/MS (EI): 250 (M^+), 235, 222, 193, 177, 165, 137, 107, 81 (100) amu.

Dihydrosantamarine (**2**) and dihydroreynosin (**1**) were isolated instead of **3** by using untreated silica gel for flash chromatography. Dihydrosantamarine (**2**) ^{1}H-NMR ($CDCl_3$, 500 MMz); δ 0.89 (s, 3H), 1.23 (d, J=6.7, 3H), 1.82 (s, 3H), 3.65, (m, 1H), 3.95 (t, J=10.5, 1H), 5.33 (br. s, 1H); IR ($CHCl_3$): 3600-3200, 2940, 1780, 1470, 1140, 1000 cm^{-1} GC/MC (EI): 250 (M^+), 235, 232, 222, 193, 165, 153, 137, 107, 81 (100) amu. Dihydroreynosin (**1**) ^{1}H-NMR ($CDCl_3$, 500 MHz); δ 0.83 (s, 3H), 1.23 (d, J=7.3, 3H), 3.50 (m, 1H), 4.04 (t, J=10.4, 1H), 4.83 (d, J=1.2, 1H), 4.97 (d, J=1.2, 1H); IR ($CHCl_3$): 3600-3200, 1780, 1460, 1140 cm^{-1}; GC/MS (EI): 250 (M^+), 235, 232, 217, 206 (100), 193, 165 amu. Epoxydihydrosantamarine (**23**) ^{1}H-NMR ($CDCl_3$, 500 MHz); δ 0.93 (s, 3H), 1.23 (d, J=7.3, 3H), 1.47 (s, 3H), 3.00 (d, J=3.0, 1H), 3.42 (m, 1H), 3.92 (dd, J=11.6, 9.8, 1H); GC/MS (EI): 266 (M^+), 251, 248, 209, 193 (100), 163, 149, 135, 121 amu.

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The Mechanism of the Photocyclization of N-(2-Haloarylmethyl) pyridinium and N-(arylmethyl)-2-Halopyridinium Salts

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The photochemical and photophysical properties of N-(2-haloarylmethyl)pyridinium, N-(arylmethyl)-2-halopyridinium, N-(2-haloarylmethyl)-2-halopyridinium salts and N-(2-halobenzyl)-isoquinolinium salt are studied. The pyridinium salts phototocyclize to afford isoindolium salts, while the isoquinolium salts do not. In the photocyclization of N-(2-chlorobenzyl)-2-chloropyridinium salts, pyrido[2,1-a]-4-chloroisoindolium salt is formed by the cleavage of chlorine of pyridinium ring. This indicates that the excited moiety is not the phenyl ring, but the pyridinium ring. The triplet states of the pyridinium salts are believed to be largely involved in the photocyclization, since oxygen retards most of the reaction. Some assistance of a π-complex between the excited chlorine moiety of the salt and phenyl plane of the same molecule is required to explain the reactivity of the salts. N-(Benzyl)-2-chloro-pyridinium salt is two times more reactive than N-(2-chloro-benzyl)pyridinium salt. N-(Benzyl)-2-chloropyridinium salt can form π-complex effectively because of the electron-rich phenyl group. The π-complex affords an intermediate, phenyl radical by cleaving the chlorine atom. The photocyclized product, isoindolium salt is obtained by losing the hydrogen atom from the phenyl radical. The reactive pyridinium salts **1a**, **2a** and **3a** have a low fluorescence quantum yield (Φ_F<0.01) and a higher triplet energy (E_T>68 kcal/mole) than the unreactive quinolinium salt. The unreactivity of isoquinolinium salt can be understood in relation to its high fluorescence quantum yield and its low triplet energy (E_T= 61 kcal/mole).

Introduction

Photocyclization of 1-styrylpyridinium salts,[1] N-benzyl-(2-halobenzyl)amines,[2] and 2-chlorobenzanilides[3,4] are useful and convenient method for syntheses of N-heterocyclic compounds. We have been interested in the intramolecular photocyclization of N-arylmethyl-2-chloropyridinium salts[5] and N-(2-haloarylmethyl)-2-halopyridinium salts because the reaction can be used for heterocyclic compound syntheses. Only a little work has been done in this field.

Forzard and Bradsher[6] reported that an aqueous solution of 2-bromo-N-benzylpyridinium salt and N-(2-bromobenzyl) pyridinium salt, on irradiation with ultraviolet, cyclize intramolecularly to afford pyrido [2,1-a]isoindolium salt. Lyle and his collaborators[7] reported that an aqueous solution of N-(2-halobenzyl)-pyridinium salt could be photocyclized, while 1-(2-halogeno-3-quinolylmethyl)pyridinium salt which is electron-deficient in both aromatic rings could not. However, no mechanistic study of these salts has been done.

Here we report the photocyclizations of N-(2-halobenzyl)-2-halopyridinium salts, their reaction mechanisms, and the photophysical properties of the salts.

Results and Discussion

Preparative Photocyclization. When an aqueous solution of N-(2-chlorobenzyl) pyridinium bromide (0.013 M, **2a**) was irradiated with a high pressure Hg lamp, the intramolecular photocyclized product, isoindolium salt (**1b**) was obtained. The reaction was followed by the increasing absorption peak at 312 nm (see Figure 1, 2). It seems that the photocyclization is only reaction because of being observed the isosbestic point in UV absorption change of **2a** in water by monochromatic light (260± 5 nm). In methanol or ethanol, photocyclization of the salt fails. The aqueous solution of salt, **1a**, affords **1b** using the above condition.[5]

In order to study the relative reactivity of halogen atoms on both aromatic rings of the pyridinium salts, N-(2-chlorobenzyl)-2-chloropyridinium salt (**3a**) and N-(2-bromobenzyl)-2-bromopyridinium salt (**4a**) were prepared. In the photochemical reaction of the salt **3a** or **4a**, two possible products, **3b** and **3c** or **4b** and **4c** could be formed depending on which halogen atom is eliminated. Only pyrido [2,1-a]-4-chloroisoindolium bromide (**3b**), which chlorine atom of pyridinium ring is cleaved, was formed when the aqueous solution of