Reaction of Phenylselenenyl Chloride with Δ^2-Erythrinans in Methanol: Conformational Fluctuation and Stereochemical Pathway[1)]

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Reaction of Δ^2-erythrinan derivatives with PhSeCl in methanol gave the following results. The PhSe group was introduced from the β-face (convex face) for 6β-ethoxycarbonyl-7-oxo and Δ^6-7-mesyloxy derivatives (1 and 12), and from the α-face (concave face) for 7α- and 7β-mesyloxy derivatives (16 and 24), while the C–Se bond was always formed at C-3. The structure and stereochemistry of the products were proved by X-ray analyses of the derived 7-*O*-mesylates (5 and 17). The reasons for the above stereochemical difference and the regiochemical identity were explained by considering the conformational fluctuations in the ground and transition states of the model compounds a, b, and c based on Chem 3D calculations. These results show that small conformational fluctuations can produce great changes in the stereochemical outcome, particularly in ionic addition reactions.

Keywords phenylselenenylation; ionic addition reaction; stereochemistry; Δ^2-erythrinan; Δ^3-erythrinan; conformation; conformational fluctuation; X-ray analysis; *Erythrina* alkaloid

The Sharpless method for constructing allyl ethers and esters from olefinic compounds by the action of phenylselenenyl chloride (PhSeCl) in appropriate solvents is potentially useful for natural product synthesis.[2)] Although the stereochemistry of this reaction may be predicted by assuming that the PhSe cation firstly attacks from the less hindered face and the subsequent introduction of the anion (from solvent) occurs from the back side so as to leave the substituents in diaxial orientation, as in usual ionic addition reactions, such assignment sometimes leads to an incorrect conclusion. Compounds with very similar structures and stereochemical relationships sometimes give products of opposite stereochemistry, implying that the stereochemical pathway of the reaction is not readily predictable, unless detailed analysis of the reaction is carried out. This paper treats such problems for Δ^2-erythrinan derivatives, all of which have very similar structures and stereochemistries.

For convenience of exposition, this paper will be divided into three sections: 1) reaction of various Δ^2-erythrinans with PhSeCl in MeOH and elucidation of the structures of the products (regiochemistry) by nuclear magnetic resonance (NMR) spectroscopy, 2) verification of the stereostructures by X-ray crystallographic analysis, and 3) discussion of the stereochemical pathways which can account for all aspects of the phenylselenenylation and the subsequent reactions.

Results and Discussion

Reaction of Δ^2-*cis*-Erythrinans with PhSeCl in MeOH

Reaction of the 6β-ethoxycarbonyl-7,8-dioxo-Δ^2-*cis*-erythrinan (**1**) with PhSeCl in MeOH followed by oxidation gave the allyl methyl ether **2** as a single product, which was decarbethoxylated to **3** on heating with $MgCl_2$[3)] in

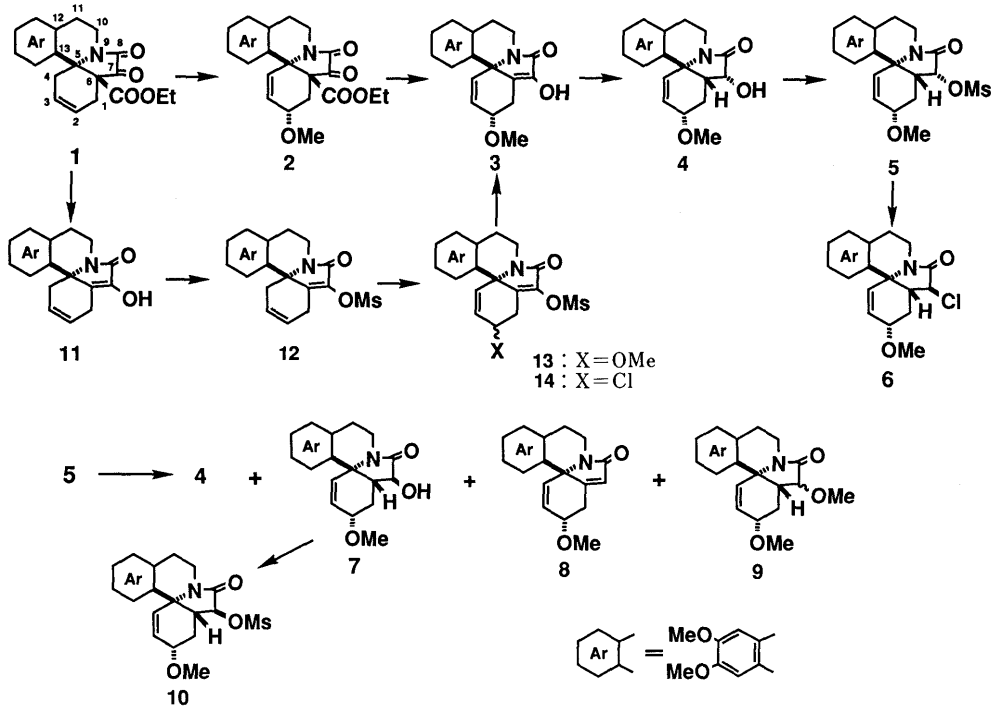

Chart 1

hexamethylphosphoric triamide (HMPA). The ultraviolet (UV) spectrum of **3** (λ_{max} 239 and 283 nm) is unchanged from that of **2** (λ_{max} 239 and 282 nm), suggesting that the position of the newly formed double bond is at 3–4, and not at 1–2. Reduction of **3** with either $NaBH_4$ in ethanol–tetrahydrofuran (THF) or Bu_4NBH_4 in MeOH gave a single product **4**, which was supposed to be the 7α-isomer. As discussed in section 3, the 2α-methoxy group prevents the approach of hydride reagent from the α-face. Compound **4** gave the *O*-mesylate **5** (isomer I) on usual methanesulfonylation (mesylation). The *O*-mesylate **5** resisted dehydromesylation with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU), but yielded a chloro derivative **6** on heating with LiCl in dimethylformamide (DMF). Compound **6** was unchanged on further treatment with LiCl in DMF or on heating with DBU.

Regiochemistry of the allyl methyl ether group in these compounds was clarified by means of a proton decoupling experiment for **6**: the proton geminal to OMe at δ 4.04 was coupled to one of the olefinic proton at δ 6.11, while the proton geminal to Cl appeared at δ 5.16 (d), being coupled with H-6 at δ 2.46 with $J=10$ Hz. Irradiation of H-6 did not produce any change of the olefinic protons, thus proving that the double bond is at 3–4 and not at 1–2.

Alkaline hydrolysis of the *O*-mesylate **5** with 10% KOH–MeOH gave, as discussed previously,[4] the epimerized alcohol **7** as a major product together with the alcohol **4**, the olefin **8**, and a mixture of the methoxy derivatives **9**. The alcohol **7** gave the *O*-mesylate **10**, which was supposed to be the 2α-OMe, 7β-OMs isomer (isomer II).

A similar phenylselenenylation (in MeOH) of the enol *O*-mesylate **12**, which in turn was prepared by decarbethoxylation[3] of **1** followed by mesylation, gave a mixture of **13** and **14**. The mixture was treated, without separation, with $AgNO_3$ in MeOH to give a single product **13**. Hydrolysis of **13** with KOH–MeOH yielded a product identical with **3**, indicating that phenylselenenylation of **12** had taken place with the same regio- and stereochemistry as in the case of **1**.

Reaction of the 7α-mesyloxy-8-oxo-Δ^2-*cis*-erythrinan **16**, which was prepared by hydride reduction of **11**[4] followed by mesylation, with PhSeCl in MeOH took place with the same regiochemistry but with different stereochemistry from that of **1**. The product (after oxidation) was the 2β-OMe isomer **17** (isomer III), which was not identical with **5** or **10**. In contrast to **5**, the *O*-mesylate **17** was smoothly dehydromesylated with DBU to give an olefin **18**, which was different from the olefin **8** obtained from **5**.

Similarly, reaction of the 7α-*O*-acetate **19** with PhSeCl in MeOH took place mainly with the same regio- and stereochemistry as that of **17**. It gave **20a**, **20b**, and **21**[5] in yields of 47, 18, and 35% on overnight reaction at room temperature, and **20a** and **21** in 60 and 20% yields on reflux for 4 h. Acetylation of **20a** gave **20b**, which, on oxidation with $NaIO_4$, yielded **22**. Hydrolysis of **22** followed by mesylation of the resulting alcohol gave a product identical with **17**.

The regiochemistry of these compounds was revealed by a proton decoupling experiment with **22**: on irradiation of H-6 at δ 3.3 (found by irradiation of the proton geminal to the acetoxy group at δ 5.42), neither of the olefinic protons was affected.

In order to obtain the fourth isomer, the 2β-OMe, 7β-OMs derivative **25**, reaction of the 7β-OMs derivative **24** with PhSeCl in MeOH was undertaken. The product was a mixture of **25** and **26**, which were separated by chromatography. The methoxy derivative **25** was not identical with the above three isomers, and so was supposed to be the 2β-OMe, 7β-OMs isomer (isomer IV). The chloro derivative **26** was treated with $AgNO_3$ in

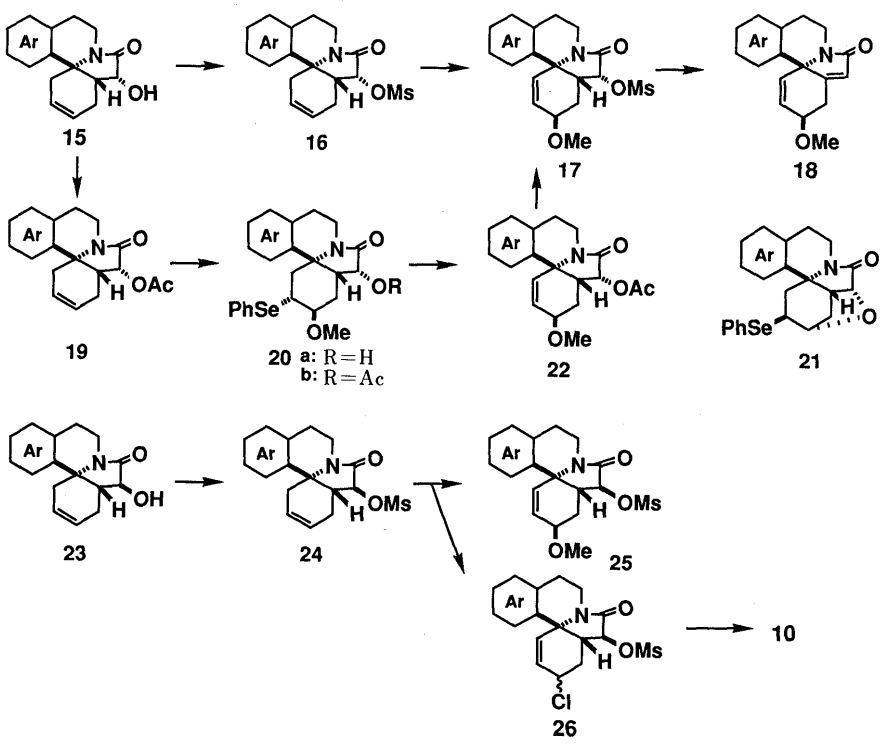

Chart 2

MeOH to give a methoxy derivative which was identical with the isomer II (**10**) described above.

X-Ray Crystallographic Analyses of 5 (Isomer I) and 17 (Isomer III) In order to confirm definitively the stereostructures of all products and to gain further insight into their conformations, two *O*-mesylates, **5** and **17**, were subjected to X-ray crystallographic analyses.

As is clear from the data (Figs. 1 and 2), the 2-OMe group is α and β oriented in **5** and **17**, respectively, and the 7-OMs group of both compounds is in α orientation. The ring A conformation of compound **5** is a half-chair of ${}_1H^6$ and that of compound **17** is an inverted form (${}^1H_6$). The dihedral angles between H-6 and 7α-OMs are 90° in **5** and 155° in **17**; the data account well for the facts that **17** is easily dehydromesylated, while **5** resisted the reaction on treatment with DBU. The dihedral angles between H-6 and H-7 in **5** and **17** are 32° and 36°, respectively.

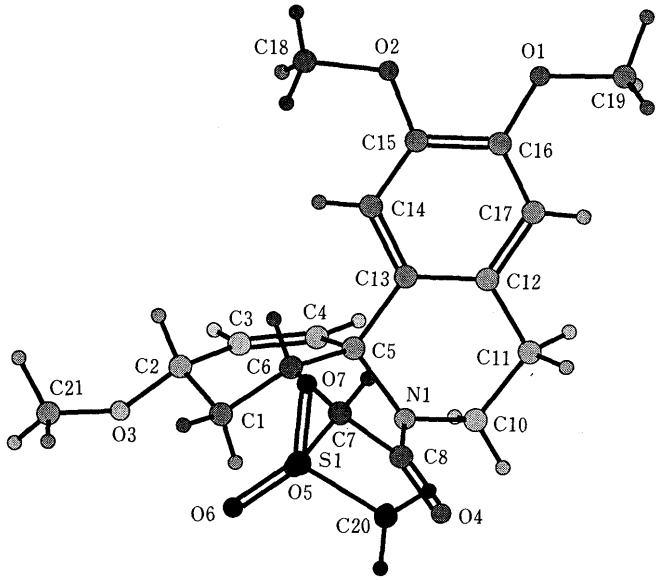

Fig. 1. Chem 3D Model of Compound **5** (Isomer I) Based on X-Ray Coordinates

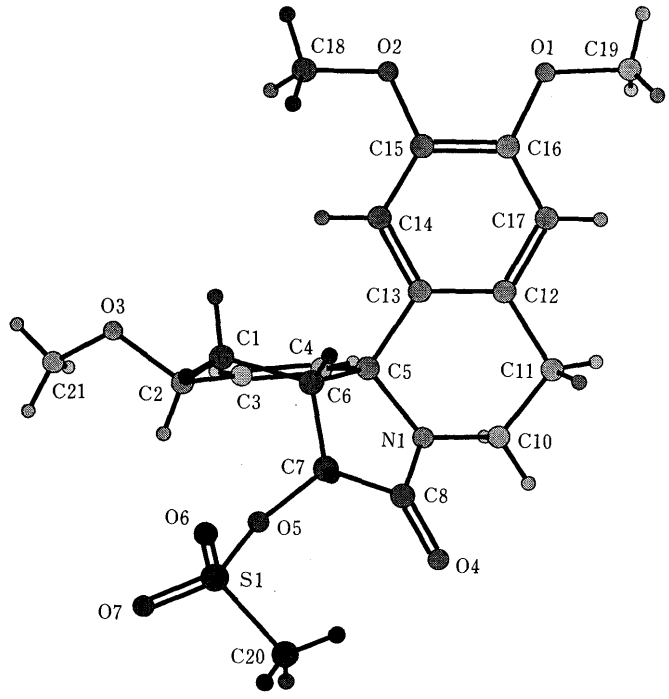

Fig. 2. Chem 3D Model of Compound **17** (Isomer III) Based on X-Ray Coordinates

The isomers II (**10**) and IV (**25**) are therefore proved to be the 2α-OMe, 7β-OMs and 2β-OMe, 7β-OMs derivatives, respectively.

Regio- and Stereochemical Pathways As revealed in the above sections, introduction of the PhSe group at the 2–3 double bond in the erythrinans occurred from the β-face (convex face) for **1** and **12**, and from the α-face (concave face) for **16** and **24**, and the C–Se bond was always formed at C-3, not at C-2. In this section, we discuss why the above stereochemical difference arose and why the regioselectivity was the same.

To simplify the problem, we chose compounds **a**—**c** as models of **1**, **12**, and **16** (and **24**), and calculated the steric energies of their ground state conformations and the steric energy changes during the reaction by the use of Chem 3D.[6]

The energy difference between two conformations for **a**, the ${}^1B^4$ (A) and the ${}_1B_4$ (B), is 3 kcal/mol, showing that the former is more stable than the latter. Thus, the attack of the cation is considered to occur from the β-face (convex face) of the former conformation. Accepting the concept that the subsequent addition of an anion takes place from the back side so that both substituents adopt antiparallel orientations, the initially formed non-classical cation (illustrated by classical forms, C and D, where the PhSe group is simplified to an Me group) should be deformed to chair conformation, E or F. The energy difference of these cations was calculated as 4.4 kcal/mol, indicating that the cation formed at C-2 is preferred to

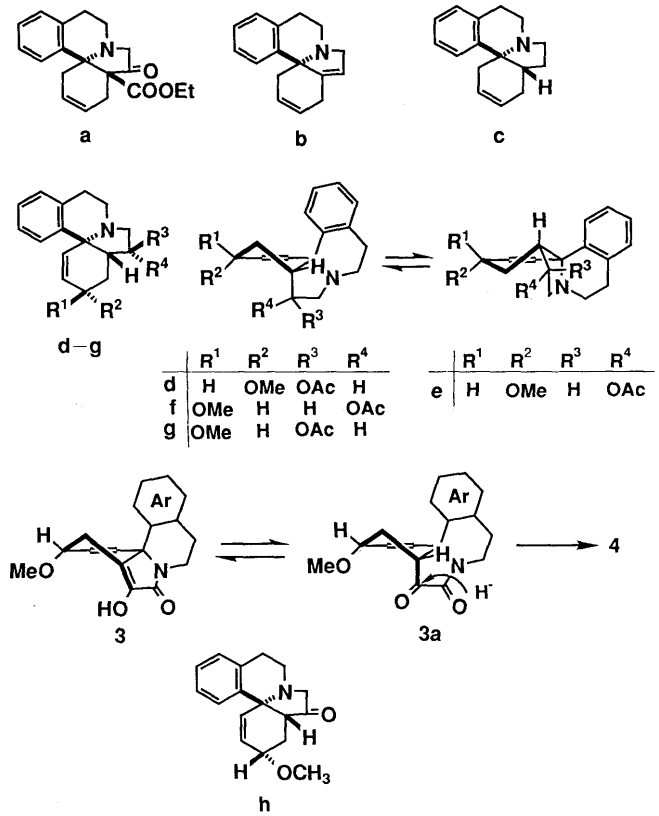

Chart 3

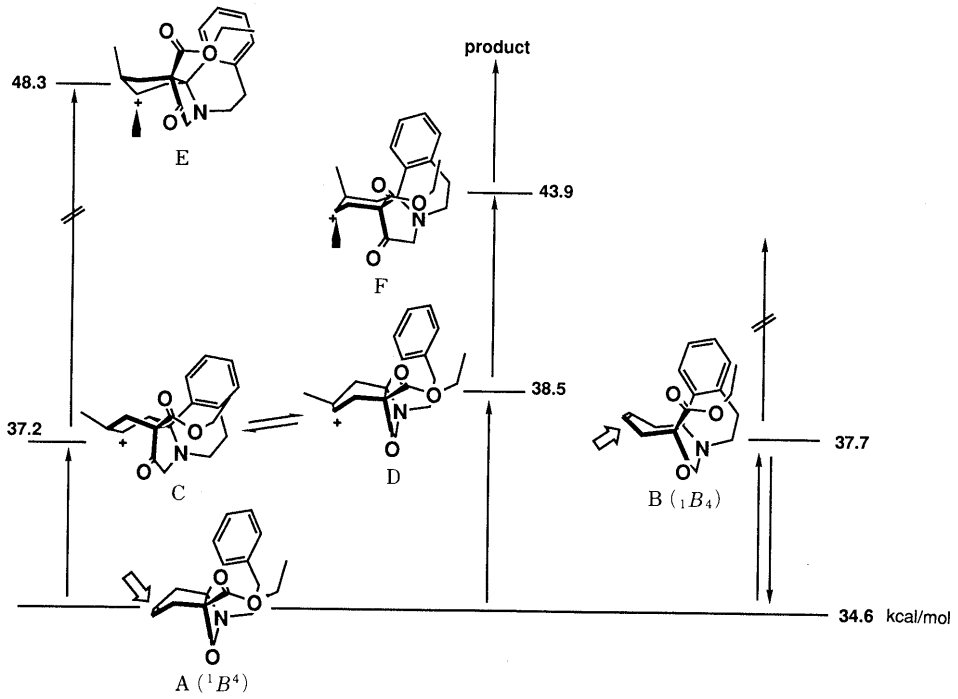

Fig. 3. Chem 3D Calculated Steric Energy Difference of Ground and Transition States for Model Compound **a**

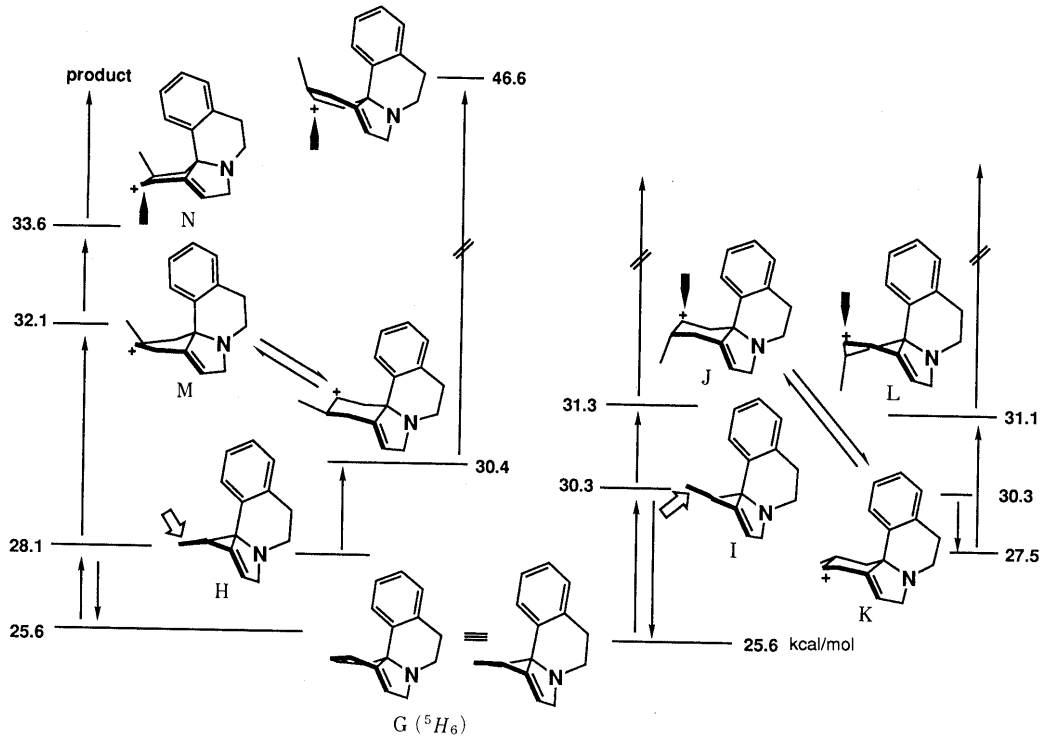

Fig. 4. Chem 3D Calculated Steric Energy Difference of Ground and Transition States for Model Compound **b**

that formed at C-3. The result leads to the product of 3β-SePh and 2α-OMe configuration, thus explaining the regio- and stereoselective introduction of the OMe group at the C-2 position for **a** (hence for **1**).

The enol mesylate **12** gave the 2α-OMe product **13**. Calculations for the model compound **b** showed that its most stable conformation at the ground state is the $^5H_6$ (G). We consider, however, that when a cation approaches G, it will be deformed to H or I for steric reasons. The energy difference between them is 2 kcal/mol, suggesting that the β-face attack on H is preferable. Even if α-face cation attack occurrs on I, the intermediate cations (J and K), though they have low energy levels, will experience severe steric interaction in the subsequent diaxial introduction of an anion, and thus should collapse to the ground state. On the other hand, the intermediate non-classical cation formed by the β-face attack of the reagent on H is deformed to the one suitable chair conformation (N) for subsequent diaxial introduction of the anion, because of the presence of the 6–7 double bond.

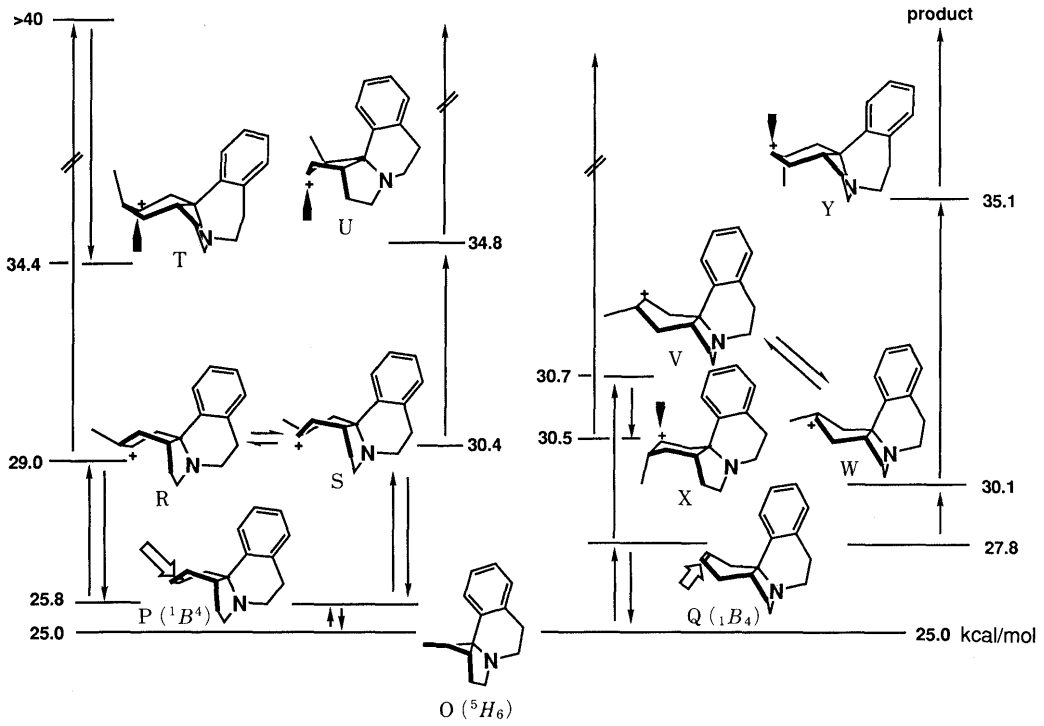

Fig. 5. Chem 3D Calculated Steric Energy Difference of Ground and Transition States for Model Compound **c**

Although the energy level of this 3β-substituted cation (N) is relatively high, only a slight energy increase is necessary to take this conformation from M (least motion principle). The reaction thus proceeds through this species, giving rise to the 3β-SePh and 2α-OMe product.

As a model of **16** and **24**, calculations were done for **c**,[7] for which three stable conformations are possible at the ground state. Although the most stable one is the $^5H_6$ conformation (O), we assume that the cation attack proceeds through the $^1B^4$ (P) or the $_1B_4$ (Q) conformation as discussed above. The energy difference between these conformations is 2 kcal/mol. If we assume that the cation attacks from the β-face of the former, the initially formed boat form cation (shown as classical forms, R and S) must be deformed to chair form (T or U) for diaxial introduction of an anion. In this process, the cation R will pass through a high energy transition state, since rings B and C have to be inverted at the same time (violation of least motion principle); thus, this process is expected to be difficult. Although the other cation S will take the chair conformation U without such difficulty, the following diaxial introduction of an anion is sterically hindered because of the sp^3 character of the C-7 position. Those cations would therefore collapse to the ground state. On the other hand, the cation formed by the α-face attack to the $_1B_4$ conformation (Q) will take chair forms (X and Y) without great difficulty. Of them, X is seriously hindered as regards diaxial introduction of an anion, while the other (Y) is free from such a 1,3-diaxial interaction for subsequent β-face introduction of an anion. The outcome of the above processes is exclusive formation of the 3α-SePh, 2β-OMe product.

The above results suggest that the stereochemistry of some ionic addition reactions is not necessarily determined by the step of cation introduction but may also be affected by the subsequent anion introduction step. In such cases, the cationic transition state should be, at least partially, in equilibrium with the ground state.

Of the four 2-OMe, 7-OMs isomers, three (**10**, **17**, **25**) should have the $^1H_6$ conformation for ring A, because the coupling constants between H-6 and H-7 of these compounds are 8—10 Hz. If compound **10** had the $_1H^6$ conformation as in **5**, the coupling constant between H-6 and H-7 would be nearly 0, since the dihedral angle between these protons in the $_1H^6$ conformation is estimated as *ca.* 90° (see the above section). Only the isomer **5** has the $_1H^6$ conformation for ring A, apparently due to the steric interaction between the 2α-OMe and 7α-OMs groups. Again, Chem 3D calculations for the model compounds, **d**—**g**, revealed that the $^1H_6$ conformations are more stable for **d**, **f**, and **g** by 1.2—1.5 kcal/mol than the corresponding $_1H^6$ conformations, while the latter conformation is more stable (1.1 kcal/mol) than the former for **e**.

The exclusive formation of the 7α-OH product **4** in the hydride reduction of **3** is well explained by the mechanism already discussed.[4] The reduction of **3** proceeds through the diketo form, which should have the conformation **3a** for the above reasons.[8] The α-face of this isomer is hindered by the presence of the 2α-OMe group, so the reduction occurs from the β-face, irrespective of the nature of the reducing agent.

The findings presented in this investigation illustrate that small structural fluctuations can produce great changes in the stereochemical outcome of the reaction, particularly for ionic addition reactions.

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 KBr disks and data are given in cm^{-1}. UV spectra were measured in EtOH and data are given in λ_{max} nm (ε). ^{1}H-Nuclear

magnetic resonance (^{1}H-NMR) spectra were taken with a JEOL FX-100 (100 MHz) spectrometer in chloroform-*d* 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). For thin layer chromatography (TLC), Merck precoated plates GF_{254} were used and spots were monitored by exposure to UV radiation (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.

Reaction of the 6β-Ethoxycarbonyl-7,8-dioxo-Δ^2-*cis*-erythrinan (1) with PhSeCl in MeOH A mixture of compound **1**[3] (950 mg) and PhSeCl (480 mg) in MeOH (150 ml) was stirred overnight at room temperature. Addition of water to the mixture and extraction with EtOAc, followed by chromatography of the extract, gave the adduct as a yellow gum from the $CHCl_3$ and $CHCl_3$–EtOAc (2:1) eluates. This was dissolved in MeOH (50 ml), then $NaIO_4$ (2 g) in water (30 ml) was added, and the whole was stirred at 0 °C for 1 h. Addition of water followed by extraction of the mixture with $CHCl_3$ and concentration gave a gum, which was chromatographed. Elution of the column with benzene–$CHCl_3$ (1:1) gave recovered olefin **1** (75 mg), then further elution with $CHCl_3$ and $CHCl_3$–EtOAc (2:1) gave the allyl methyl ether **2** (800 mg, 70%), as colorless prisms (from benzene), melting first at 110—120 °C, then solidifying and melting again at 172—174 °C. UV: 239, 282. IR: 1770, 1740, 1707. ^{1}H-NMR: 7.27 (2H, s, 1/3C_6H_6), 6.52, 6.35 (each 1H, s, ArH), 5.8—6.3 (2H, m, CH=CH), 3.80, 3.76, 3.18 (each 3H, s, OMe), 3.57 (2H, q, J=7 Hz, $COOCH_2CH_3$), 1.05 (3H, t, J=7 Hz, $COOCH_2CH_3$). *Anal.* Calcd for $C_{22}H_{25}NO_7 \cdot 1/3C_6H_6$: C, 65.28; H, 6.17; N, 3.17. Found: C, 65.34; H, 6.28; N, 3.08.

Decarbethoxylation of 2 A mixture of **2** (515 mg) and $MgCl_2$ (593 mg) in HMPA (12 ml) containing *tert*-heptylmercaptan (1 ml) was heated at 145 °C for 1.5 h. The cooled mixture was diluted with EtOAc, washed with 1 N HCl, then extracted with 2 N NaOH. The alkaline extract was acidified with HCl and extracted with EtOAc. Chromatography of the product gave, from the $CHCl_3$–EtOAc (4:1 and 1:1) eluates, the decarbethoxy derivative **3** (288 mg, 68%), as colorless prisms (from MeOH), mp 205—207 °C. UV (EtOH): 239, 283. UV (EtOH–NaOH): 286. IR: 3400, 1755, 1700. ^{1}H-NMR: 6.55, 6.48 (each 1H, s, ArH), 5.8—6.35 (2H, m, CH=CH), 3.82, 3.80, 3.20 (each 3H, s, OMe). *Anal.* Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.21; H, 6.22; N, 4.32.

Hydride Reduction of 3 1) A mixture of **3** (320 mg) and $NaBH_4$ (14 mg) in THF–EtOH (1:1, 35 ml) was stirred at 0 °C for 40 min. Usual work-up of the mixture gave the 7α-alcohol **4** (298 mg, 93%), as colorless prisms (from acetone–ether), mp 129—132 °C. IR ($CHCl_3$): 3320, 1694. ^{1}H-NMR (400 MHz): 6.54, 6.51 (each 1H, s, ArH), 5.99, 5.87 (each 1H, d, J=9.2 Hz, CH=CH), 3.84 (6H), 3.46 (3H) (each s, OMe). *Anal.* Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 65.79; H, 7.01; N, 4.18.

2) A mixture of **3** (47 mg) and Bu_4NBH_4 (100 mg) in MeOH (20 ml) was stirred at room temperature for 30 min. Work-up of the product gave **4** (45 mg, 95%), which was identical with the compound obtained above in terms of TLC behavior and ^{1}H-NMR spectra.

The *O*-Mesylate 5 (Isomer I) Compound **4** (286 mg) was mesylated with pyridine (24 ml) and MsCl (176 mg) for 1 h at room temperature. Usual work-up of the mixture gave the *O*-mesylate **5** (304 mg, 87%). It crystallized as colorless prisms from MeOH–benzene, mp 184 °C, and as colorless needles from CH_2Cl_2–MeOH, mp 189—191 °C. IR: 1700. ^{1}H-NMR (400 MHz): 6.54, 6.45 (each 1H, s, ArH), 5.99 (1H, d, J=10 Hz), 5.80 (1H, dt, J=10, 1.8 Hz) (CH=CH), 5.12 (1H, d, J=8.2 Hz, CHOMs), 3.85 (6H), 3.46 (3H) (each s, OMe), 3.30 (3H, s, Ms). *Anal.* Calcd for $C_{20}H_{25}NO_7S$: C, 56.72; H, 5.95; N, 3.31. Found: C, 56.55; H, 6.12; N, 3.52. A single crystal in the prism form (mp 184 °C) was subjected to an X-ray analysis.

Attempted Dehydromesylation of 5 with DBU A mixture of **5** (50 mg) and DBU (0.5 g) in toluene (5 ml) was heated at 100—120 °C for 1 h, or **5** was heated with neat DBU at 110—120 °C for 3 h. The spot of **5** on TLC was unchanged afterwards.

Reaction of 5 with LiCl A mixture of **5** (110 mg) and LiCl (480 mg) in DMF (15 ml) was heated at 135—140°C for 1 h under an Ar atmosphere. After addition of water, the mixture was extracted with $CHCl_3$. Chromatography of the product gave the chloro derivative **6** (70 mg, 70%), as colorless prisms (from ether), mp 141—143 °C. IR: 1698. ^{1}H-NMR: 6.62, 6.58 (each 1H, s, ArH), 6.11 (1H, dd, J=10, 4 Hz), 5.89 (1H, d, J=10 Hz) (CH=CH), 5.16 (1H, d, J=10 Hz, CHCl), 4.04 (1H, m, CHOMe), 3.86, 3.82, 3.45 (each 3H, s, OMe). *Anal.* Calcd for $C_{19}H_{22}ClNO_4$: C, 62.72; H, 6.09; N, 3.85. Found: C, 62.51; H, 5.88; N, 3.68. Compound **6** was recovered unchanged on further treatment with LiCl in DMF at 150—160 °C for 8 h, or on heating with 10% DBU in toluene at 145 °C for 5 h.

Alkaline Hydrolysis of the *O*-Mesylate (5) The *O*-mesylate **5** (260 mg) was hydrolyzed with 10% KOH–MeOH (25 ml) under reflux for 1.5 h. The mixture was diluted with water and extracted with $CHCl_3$. The product was first separated by medium-pressure liquid chromatography (MPLC) [solvent: $CHCl_3$–MeOH (15:1)] to yield **9** (20 mg, 9%), a mixture of **8**, **4**, and **7** (34 mg), and a mixture of **4** and **7** (153 mg). The mixture of **8**, **4**, and **7** was separated by preparative TLC (PTLC) to yield **8** (14 mg, 7%) and a mixture of **4** and **7** (20 mg). The mixture of **4** and **7** was separated by MPLC [solvent: benzene–acetone (1:1)] to give **4** (55 mg, 26%) and **7** (102 mg, 48%).

The Olefin **8**: Colorless prisms from acetone–ether, mp 184—187 °C. IR ($CHCl_3$): 1668. ^{1}H-NMR (400 MHz): 7.06, 6.73 (each 1H, s, ArH), 6.88 (1H, dd, J=9.8, 3 Hz), 6.13 (1H, m) (CH=CH), 6.03 (1H, s, H-7), 3.87, 3.77, 3.43 (each 3H, s, OMe). MS: 327 (M^+, 15), 294 (14), 85 (60), 83 (100). HRMS: Calcd for $C_{19}H_{21}NO_4$: 327.1649. Found: 327.1652.

The 7β-Alcohol **7**: Colorless prisms from acetone–ether, mp 197—199 °C. IR ($CHCl_3$): 3380, 1689. ^{1}H-NMR (400 MHz): 6.59 (2H, s, ArH), 6.09 (1H, dd, J=10, 4.6 Hz), 5.89 (1H, d, J=10 Hz) (CH=CH), 4.85 (1H, d, J=9.8 Hz, CHOH), 3.86, 3.82, 3.45 (each 3H, s, OMe). *Anal.* Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 65.83; H, 6.92; N, 4.03.

The Compound **9**: Pale yellow oil. This was supposed to be a mixture of 7α and 7β isomers on the basis of the IR (1684 cm^{-1}), MS [*m/z* 359 (M^+, 100)], and ^{1}H-NMR (five OMe peaks at δ 3.85, 3.84, 3.73, 3.68, and 3.50) spectra.

The *O*-Mesylate (10) (Isomer II) The 7β-alcohol **7** (83 mg) in pyridine (7 ml) was mesylated with MsCl (110 mg) for 2.5 h at room temperature to give, on usual work-up, the *O*-mesylate **10** (87 mg, 85%), as colorless prisms (from MeOH–ether), mp 163—164 °C. IR ($CHCl_3$): 1702, 1358, 1171. ^{1}H-NMR (400 MHz): 6.61, 6.57 (each 1H, s, ArH), 6.11 (1H, dd, J=10.2, 4.8 Hz), 5.92 (1H, d, J=10.2 Hz) (CH=CH), 5.91 (1H, d, J=9.5 Hz, CHOMs), 3.86, 3.82, 3.47 (each 3H, s, OMe), 3.33 (3H, s, Ms). ^{1}H-NMR (C_6D_6): 6.43, 6.17 (each 1H, s, ArH), 6.16 (1H, d, J=8.5 Hz, CHOMs), 5.73 (1H, dd, J=10, 5 Hz), 5.46 (1H, d, J=10 Hz) (CH=CH), 3.44, 3.35, 3.29 (each 3H, s, OMe), 2.98 (3H, s, Ms). *Anal.* Calcd for $C_{20}H_{25}NO_7S$: C, 56.42; H, 5.95; N, 3.31. Found: C, 56.57; H, 6.11; N, 3.33.

Reaction of the Enol *O*-Mesylate (12) with PhSeCl in MeOH Compound **11**[3] (100 mg) and MsCl (60 mg) in pyridine (5 ml) were stirred overnight at room temperature. Work-up of the product gave the *O*-mesylate **12** (97 mg, 78%), as colorless prisms (from MeOH–ether). ^{1}H-NMR: 7.01, 6.57 (each 1H, s, ArH), 5.6—6.2 (2H, m, CH=CH), 3.80, 3.76 (each 3H, s, OMe), 3.39 (3H, s, Ms).

TABLE I. Crystal Data for Compounds **5** and **17**

	5	**17**
Crystal system	Orthorhombic	Triclinic
Lattice parameters		
a (Å)	19.055 (5)	13.093 (4)
b (Å)	17.462 (2)	16.205 (1)
c (Å)	12.199 (4)	9.8128 (8)
α (°)		102.325 (6)
β (°)		93.73 (2)
γ (°)		88.74 (2)
V (Å^3)	4059 (3)	2029.7 (6)
Space group	*Pbca*	$P\bar{1}$
Z value	8	4
D_C value (g/cm^3)	1.39	1.39
Number of reflections		
Collected	5432	9707
Used for calculations ($>3\sigma$ (*I*))	1871	4760
R value	0.043	0.044

The *O*-mesylate **12** and PhSeCl (260 mg) in MeOH (40 ml) were stirred at room temperature for 2 d. After removal of the solvent, the product was taken up in $CHCl_3$ and washed with water. Chromatography of the product gave an adduct as a gum from the $CHCl_3$ eluate, and the gum was dissolved in dioxane (20 ml) and treated with $NaIO_4$ (0.5 g) in water (20 ml) at 0 °C for 1 h. Addition of water to the mixture and extraction with $CHCl_3$ gave, after concentration of the extract, **13** and **14** (two spots on TLC), which were dissolved in MeOH (50 ml), treated with $AgNO_3$ (excess) for 4.5 h under reflux, then diluted with water and extracted with $CHCl_3$. Chromatography of the product gave **12** (32 mg) and the methyl ether **13** (54 mg, 52%), as colorless needles (from MeOH), mp 185—185.5 °C. UV: 284. IR: 1695. ^{1}H-NMR: 6.61, 6.57 (each 1H, s, ArH), 5.7—6.25 (2H, m, CH=CH), 3.79 (6H), 3.41 (3H) (each s, OMe), 3.37 (3H, s, Ms). *Anal.* Calcd for $C_{20}H_{23}NO_7S$: C, 57.00; H, 5.50; N, 3.32. Found: C, 56.72; H, 5.44; N, 3.01.

Hydrolysis of 13 Compound **13** (20 mg) in 10% KOH–EtOH (10 ml) was heated under reflux for 30 min. The mixture was acidified with dilute HCl and extracted with $CHCl_3$. Crystallizations of the product from MeOH gave colorless prisms (13 mg, 80%), mp 205—206 °C. This product was identical with compound **3** described above.

The 7α- and 7β-*O*-Mesyl-8-oxo-Δ^2-*cis*-erythrinan (16 and 24) A mixture of **15** and **23** (265 mg obtained by hydride reduction of **11**)[4] in pyridine (12 ml) was treated with MsCl (0.34 ml) for 2.5 h at room temperature. The product obtained on usual work-up was separated by column chromatography on a silica gel column followed by recycling HPLC on an ODS column to give the 7α-*O*-mesylate **16** (113 mg) and 7β-*O*-mesylate **24** (96 mg).

The 7α-*O*-Mesylate **16**: Colorless prisms from MeOH, mp 168—169 °C. IR ($CHCl_3$): 1698, 1363, 1169. ^{1}H-NMR: 6.79, 6.59 (each 1H, s, ArH), 6.06, 5.08 (each 1H, br d, J=10 Hz, CH=CH), 5.01 (1H, d, J=6.6 Hz,

TABLE IIa. Positional Parameters and B_{eq} for **5**

Atom	x	y	z	B_{eq}
S(1)	0.11688 (6)	0.05952 (7)	0.5540 (1)	4.67 (6)
O(1)	−0.2097 (2)	0.3797 (1)	0.6393 (2)	4.3 (1)
O(2)	−0.2350 (1)	0.2491 (2)	0.5534 (2)	4.5 (1)
O(3)	−0.1108 (2)	−0.1226 (2)	0.8507 (3)	6.1 (2)
O(4)	0.1063 (2)	0.1505 (2)	0.8389 (3)	6.0 (2)
O(5)	0.0769 (1)	0.0430 (1)	0.6642 (2)	3.9 (1)
O(6)	0.1479 (2)	−0.0107 (2)	0.5251 (3)	5.9 (2)
O(7)	0.0703 (2)	0.0956 (2)	0.4806 (3)	9.0 (2)
N(1)	−0.0118 (2)	0.1389 (2)	0.8738 (3)	3.9 (2)
C(1)	−0.0406 (2)	−0.0210 (3)	0.7680 (4)	3.9 (2)
C(2)	−0.1131 (2)	−0.0493 (2)	0.7994 (4)	4.3 (2)
C(3)	−0.1453 (2)	0.0039 (3)	0.8801 (4)	4.8 (2)
C(4)	−0.1281 (2)	0.0769 (3)	0.8894 (3)	4.0 (2)
C(5)	−0.0758 (2)	0.1159 (2)	0.8144 (3)	3.4 (2)
C(6)	−0.0456 (2)	0.0610 (2)	0.7264 (3)	3.1 (2)
C(7)	0.0249 (2)	0.0965 (2)	0.7042 (3)	3.4 (2)
C(8)	0.0467 (2)	0.1310 (2)	0.8139 (3)	3.9 (2)
C(10)	−0.0191 (3)	0.1955 (3)	0.9606 (4)	5.2 (3)
C(11)	−0.0491 (3)	0.2686 (3)	0.9158 (4)	4.7 (3)
C(12)	−0.0970 (2)	0.2587 (2)	0.8171 (3)	3.2 (2)
C(13)	−0.1101 (2)	0.1882 (2)	0.7692 (3)	3.0 (2)
C(14)	−0.1575 (2)	0.1833 (2)	0.6811 (3)	3.3 (2)
C(15)	−0.1899 (2)	0.2476 (2)	0.6395 (3)	3.1 (2)
C(16)	−0.1755 (2)	0.3196 (2)	0.6860 (3)	3.2 (2)
C(17)	−0.1298 (2)	0.3237 (2)	0.7731 (3)	3.7 (2)
C(18)	−0.2562 (3)	0.1778 (3)	0.5076 (5)	4.5 (3)
C(19)	−0.1955 (4)	0.4544 (3)	0.6806 (5)	5.3 (3)
C(20)	0.1832 (4)	0.1223 (4)	0.5950 (9)	7.6 (4)
C(21)	−0.1057 (7)	−0.1828 (4)	0.7773 (7)	9.0 (5)
H(1)	−0.021 (2)	−0.053 (2)	0.711 (3)	4 (1)
H(2)	−0.012 (2)	−0.027 (2)	0.831 (3)	4 (1)
H(3)	−0.143 (2)	−0.049 (2)	0.729 (3)	3.7 (9)
H(4)	−0.185 (2)	−0.021 (2)	0.925 (4)	7 (1)
H(5)	−0.150 (2)	0.115 (2)	0.943 (3)	4 (1)
H(6)	−0.073 (2)	0.064 (2)	0.662 (2)	2.2 (7)
H(7)	0.021 (2)	0.137 (2)	0.652 (3)	2.9 (8)
H(8)	0.026 (2)	0.205 (2)	0.991 (3)	5 (1)
H(9)	−0.051 (3)	0.171 (3)	1.017 (4)	8 (1)
H(10)	−0.011 (2)	0.301 (2)	0.887 (3)	6 (1)
H(11)	−0.073 (2)	0.306 (2)	0.964 (3)	6 (1)
H(12)	−0.167 (2)	0.139 (2)	0.649 (3)	3.1 (9)
H(13)	−0.120 (2)	0.366 (2)	0.805 (3)	2.6 (8)
H(14)	−0.067 (4)	−0.188 (4)	0.747 (6)	13 (3)
H(15)	−0.111 (3)	−0.228 (3)	0.835 (5)	11 (2)
H(16)	−0.146 (3)	−0.189 (3)	0.715 (6)	12 (3)
H(17)	0.211 (4)	0.098 (4)	0.650 (6)	15 (3)
H(18)	0.202 (3)	0.131 (3)	0.534 (5)	8 (2)
H(19)	0.162 (4)	0.166 (4)	0.626 (7)	16 (3)
H(20)	−0.213 (2)	0.152 (2)	0.484 (3)	4 (1)
H(21)	−0.283 (2)	0.190 (2)	0.444 (4)	7 (1)
H(22)	−0.275 (2)	0.148 (2)	0.562 (4)	6 (1)
H(23)	−0.211 (2)	0.455 (2)	0.752 (3)	5 (1)
H(24)	−0.228 (2)	0.496 (3)	0.633 (4)	8 (1)
H(25)	−0.148 (2)	0.470 (2)	0.658 (4)	6 (1)

TABLE IIb. Positional Parameters and B_{eq} for **17**

Atom	x	y	z	B_{eq}
S(1)	0.3800 (1)	0.26215 (7)	0.6393 (1)	3.87 (5)
O(1)	0.4065 (2)	−0.0422 (2)	−0.3794 (3)	4.7 (1)
O(2)	0.5488 (2)	0.0522 (2)	−0.2352 (3)	4.4 (1)
O(3)	0.5351 (3)	0.3609 (2)	0.2401 (3)	5.1 (2)
O(4)	0.1889 (3)	0.0961 (2)	0.4120 (3)	5.9 (2)
O(5)	0.3424 (2)	0.2405 (2)	0.4794 (3)	3.7 (1)
O(6)	0.4718 (2)	0.2157 (2)	0.6579 (3)	5.3 (2)
O(7)	0.3814 (3)	0.3515 (2)	0.6740 (3)	5.9 (2)
N(1)	0.2352 (3)	0.1313 (2)	0.2105 (3)	3.8 (1)
C(1)	0.4922 (3)	0.2276 (3)	0.2798 (5)	3.5 (2)
C(2)	0.4524 (4)	0.3157 (3)	0.2775 (5)	4.1 (2)
C(3)	0.3605 (4)	0.3163 (3)	0.1770 (4)	4.0 (2)
C(4)	0.3040 (3)	0.2497 (3)	0.1249 (4)	3.6 (2)
C(5)	0.3230 (3)	0.1613 (2)	0.1495 (4)	3.1 (2)
C(6)	0.4109 (3)	0.1595 (3)	0.2641 (4)	3.0 (2)
C(7)	0.3574 (4)	0.1553 (3)	0.3937 (4)	3.5 (2)
C(8)	0.2511 (3)	0.1226 (3)	0.3435 (4)	4.0 (2)
C(10)	0.1425 (3)	0.1065 (3)	0.1218 (5)	4.3 (2)
C(11)	0.1676 (4)	0.0357 (3)	0.0012 (5)	4.1 (2)
C(12)	0.2670 (3)	0.0476 (2)	−0.0621 (4)	3.4 (2)
C(13)	0.3412 (3)	0.1021 (2)	0.0092 (4)	3.0 (2)
C(14)	0.4358 (3)	0.1060 (3)	−0.0499 (4)	3.4 (2)
C(15)	0.4573 (3)	0.0556 (2)	−0.1752 (4)	3.3 (2)
C(16)	0.3805 (3)	0.0025 (2)	−0.2515 (4)	3.6 (2)
C(17)	0.2881 (4)	−0.0009 (3)	−0.1949 (4)	3.7 (2)
C(18)	0.6282 (4)	0.1038 (4)	−0.1595 (6)	5.2 (3)
C(19)	0.3301 (5)	−0.0896 (4)	−0.4676 (6)	5.7 (3)
C(20)	0.2802 (5)	0.2237 (4)	0.7190 (6)	4.9 (3)
C(21)	0.5307 (8)	0.4497 (4)	0.2881 (9)	7.6 (4)
H(1)	0.541 (3)	0.212 (2)	0.198 (3)	2.5 (7)
H(2)	0.531 (3)	0.230 (2)	0.368 (4)	3.2 (8)
H(3)	0.431 (3)	0.343 (3)	0.378 (5)	5 (1)
H(4)	0.355 (2)	0.385 (2)	0.142 (3)	2.3 (7)
H(5)	0.250 (3)	0.256 (2)	0.065 (4)	3.0 (8)
H(6)	0.445 (2)	0.107 (2)	0.236 (3)	2.1 (7)
H(7)	0.398 (3)	0.124 (3)	0.447 (4)	4 (1)
H(8)	0.086 (4)	0.089 (3)	0.178 (5)	7 (1)
H(9)	0.120 (3)	0.156 (3)	0.079 (5)	6 (1)
H(10)	0.107 (3)	0.025 (2)	−0.064 (4)	5 (1)
H(11)	0.176 (3)	−0.017 (3)	0.035 (4)	5 (1)
H(12)	0.479 (3)	0.139 (2)	−0.004 (4)	3.1 (9)
H(13)	0.236 (3)	−0.034 (2)	−0.238 (4)	2.6 (8)
H(14)	0.581 (6)	0.474 (4)	0.253 (7)	11 (2)
H(15)	0.462 (5)	0.471 (4)	0.248 (7)	10 (2)
H(16)	0.512 (5)	0.460 (4)	0.394 (7)	12 (2)
H(17)	0.230 (3)	0.260 (2)	0.710 (4)	3 (1)
H(18)	0.274 (4)	0.161 (4)	0.672 (5)	8 (2)
H(19)	0.299 (4)	0.233 (3)	0.816 (6)	8 (2)
H(20)	0.638 (3)	0.090 (2)	−0.068 (4)	3.0 (8)
H(21)	0.691 (4)	0.090 (3)	−0.206 (5)	7 (1)
H(22)	0.608 (4)	0.161 (3)	−0.156 (5)	6 (1)
H(23)	0.300 (3)	−0.133 (3)	−0.421 (4)	5 (1)
H(24)	0.364 (4)	−0.115 (3)	−0.546 (5)	6 (1)
H(25)	0.270 (4)	−0.052 (3)	−0.484 (5)	8 (2)

CHOMs), 3.85, 3.80 (each 3H, s, OMe), 3.24 (3H, s, Ms). *Anal.* Calcd for $C_{19}H_{23}NO_6S$: C, 58.00; H, 5.89; N, 3.56. Found: C, 58.21; H, 5.96; N, 3.66.

The 7β-*O*-Mesylate **24**: Colorless prisms from ether, mp 128—130 °C. IR ($CHCl_3$): 1707, 1360, 1171. ^{1}H-NMR: 6.70, 6.59 (each 1H, s, ArH), 5.97 (2H, brs, CH=CH), 5.11 (1H, d, J=9.5 Hz, CHOMs), 3.86, 3.80 (each 3H, s, OMe), 3.35 (3H, s, Ms). *Anal.* Calcd for $C_{19}H_{23}NO_6S$: C, 58.00; H, 5.89; N, 3.56. Found: C, 57.77; H, 6.06; N, 3.71.

Reaction of the 7α-*O*-Mesylate (16) with PhSeCl in MeOH: Formation of the Isomer III (17) A mixture of **16** (66 mg) and PhSeCl (64 mg) in MeOH (35 ml) was stirred overnight at room temperature. After concentration of the mixture to *ca.* 1/3 volume, water was added and the whole was extracted with $CHCl_3$. Chromatography of the product gave, from the $CHCl_3$–EtOAc (2:1) eluate, the adduct, which was dissolved in MeOH (8 ml) and treated with $NaIO_4$ (350 mg) in water (8 ml) for 1 h at 0 °C. The mixture was diluted with water and extracted with $CHCl_3$. Chromatography of the product gave the 2β-OMe derivative **17** (52 mg, 73%), as colorless prisms (from MeOH–ether), mp 173—175 °C. IR ($CHCl_3$): 1700, 1367, 1174. ^{1}H-NMR: 6.82, 6.56 (each 1H, s, ArH), 6.07 (1H, dd, J=10.5, 3 Hz), 5.89 (1H, d, J=10.5 Hz, CH=CH), 5.11 (1H, d, J=8.3 Hz, CHOMs), 3.85 (6H), 3.48 (3H) (each s, OMe), 3.27 (3H, s, Ms). *Anal.* Calcd for $C_{20}H_{25}NO_7S$: C, 56.72; H, 5.95; N, 3.31. Found: C, 56.85; H, 6.11; N, 3.36. A single crystal of this compound was subjected to an X-ray analysis.

Reaction of the 7α-*O*-Acetate (19) with PhSeCl in MeOH 1) A mixture of **19**[4] (80 mg) and PhSeCl (78 mg) in MeOH (10 ml) was stirred overnight at room temperature. After dilution with water, the mixture was extracted with $CHCl_3$, and the products were separated by PTLC to give **20b** (56 mg, 46.5%), **21** (37 mg, 35.4%), and **20a** (20 mg, 18%).

20a: Colorless gum. IR ($CHCl_3$): 3300, 1688. ^{1}H-NMR: 7.0—7.7 (5H, m, SePh), 6.74, 6.54 (each 1H, s, ArH), 3.82, 3.78, 3.36 (each 3H, s, OMe). MS: 503 (M^+ for ^{80}Se). On usual acetylation (pyridine–Ac_2O), it gave **20b**.

20b: Colorless gum. IR ($CHCl_3$): 1740, 1700. ^{1}H-NMR: 7.1—7.6 (5H, m, SePh), 6.71, 6.44 (each 1H, s, ArH), 5.12 (1H, d, J=7.5 Hz, CHOAc), 3.82, 3.78, 3.30 (each 3H, s, OMe), 2.10 (3H, s, Ac). MS: 545 (M^+ for ^{80}Se).

21: Colorless gum. IR ($CHCl_3$): 1685. ^{1}H-NMR: 7.05—7.65 (5H, m, SePh), 6.50 (2H, s, ArH), 3.82 (6H, s, OMe×2). MS: 471 (M^+ for ^{80}Se).

2) A mixture of **19** (90 mg) and PhSeCl (50 mg) in MeOH (10 ml) was heated at 50—55 °C for 4 h, and the mixture was worked up as above to give **21** (24 mg, 20%) and **20a** (80 mg, 64%).

Compound **20b** (56 mg) in MeOH (10 ml) was treated with $NaIO_4$ (0.5 g) in water (10 ml) at 0 °C for 50 min. Work-up of the mixture and purification of the product by PTLC gave **22** (27 mg, 68%) as a gum. IR ($CHCl_3$): 1740, 1700. ^{1}H-NMR: 6.83, 6.54 (each 1H, s, ArH), 6.09 (1H, dd, J=10, 4 Hz), 5.96 (1H, d, J=10 Hz) (CH=CH), 5.42 (1H, d, J=8.5 Hz, CHOAc), 3.85 (6H), 3.46 (3H) (each s, OMe), 2.18 (3H, s, Ac). HRMS: Calcd for $C_{21}H_{25}NO_6$: 387.1680. Found: 387.1671.

The 7α-*O*-Mesylate (17) (Isomer III) The *O*-acetate **22** (27 mg) in 10% KOH–MeOH (10 ml) was heated under reflux for 40 min. The mixture was diluted with water and extracted with $CHCl_3$. The product obtained from the $CHCl_3$ extract was mesylated with pyridine (20 ml) and MsCl (32 mg) at room temperature for 1 h to give the *O*-mesylate **17**, which was identical with the *O*-mesylate obtained from **16**.

The Olefin (18) The *O*-mesylate **17** (20 mg) in 5% DBU–toluene (10 ml) was heated under reflux for 3 h. The mixture was diluted with CH_2Cl_2 and washed with 1 N HCl. Concentration of the organic layer and purification of the residue by chromatography gave the olefin **18** (18 mg) as a colorless gum. IR ($CHCl_3$): 1650. ^{1}H-NMR: 7.01, 6.57 (each 1H, s, ArH), 5.8—6.0 (3H, m, =CH), 3.83 (6H), 3.50 (3H) (each s, OMe). HRMS: Calcd for $C_{19}H_{21}NO_4$: 327.1469. Found: 327.1455.

Reaction of the 7β-*O*-Mesylate (24) with PhSeCl in MeOH A mixture of the *O*-mesylate **24** (76 mg) and PhSeCl (74 mg) in MeOH (15 ml) was stirred overnight at room temperature, and worked up as described for **16**. The resulting product was dissolved in MeOH (8 ml) and treated with $NaIO_4$ (400 mg in water 8 ml) for 1 h at 0 °C. Chromatography of the product followed by PTLC [solvent, $CHCl_3$–EtOAc (4:1)] gave the starting material **24** (27 mg), the 2β-OMe derivative **25** (15 mg, 18%), and the 2-chloro derivative **26** (38 mg, 46%).

The 2β-OMe, 7β-OMs Derivative (Isomer IV) **25**: Colorless crystals from MeOH–ether, mp 118—121 °C. IR ($CHCl_3$): 1707, 1360, 1171. ^{1}H-NMR: 6.76, 6.56 (each 1H, s, ArH), 6.01 (1H, dd, J=11, 1.5 Hz), 5.76 (1H, J=11 Hz) (CH=CH), 5.06 (1H, d, J=10 Hz, CHOMs), 3.84 (6H), 3.40 (3H) (each s, OMe), 3.30 (3H, s, Ms). HRMS: Calcd for $C_{20}H_{25}NO_7S$: 423.1350. Found: 423.1375.

The 2-chloro derivative **26** solidified as prisms, mp 176—178 °C (dec.) and showed an OMe signal at δ 3.88 (6H). It was converted, without further purification, to the OMe derivative (isomer II) as follows. A mixture of **26** (17 mg) and $AgNO_3$ (165 mg) in MeOH (20 ml) was heated under reflux for 3 h, then concentrated to *ca.* 1/3 volume, diluted with water, and extracted with $CHCl_3$. Purification of the product by PTLC gave the isomer II (**10**) (9 mg, 53%).

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

References and Notes

1) Synthesis of *Erythrina* and Related Alkaloids. XXIX. Part XXVIII: Y. Tsuda, A. Ishiura, S. Takamura, S. Hosoi, K. Isobe, and K. Mohri, *Chem. Pharm. Bull.*, **39**, 2797 (1991).
2) Review: H. J. Reich, *Accounts Chem. Res.*, **12**, 22 (1979).
3) Y. Tsuda, Y. Sakai, A. Nakai, M. Kaneko, Y. Ishiguro, K. Isobe, J. Taga, and T. Sano, *Chem. Pharm. Bull.*, **38**, 1462 (1990).
4) Y. Tsuda, Y. Sakai, K. Akiyama, and K. Isobe, *Chem. Pharm. Bull.*, **39**, 2120 (1991).
5) This may be produced from **15** which might be formed by hydrolysis of the OAc group (through the action of PhSeCl) prior to phenylselenenylation of the double bond.
6) The authors thank Prof. K. Inomata, Faculty of Science, for allowing us to use the Chem 3D (V.2.0.1) program.
7) Chem 3D calculations for the 7α- or 7β-acetoxy derivatives gave essentially the same results.
8) Chem 3D calculations for the model compound **h** suggested that the energy difference between the $^1H_6$ and $_1H^6$ conformations is *ca.* 5 kcal/mol, showing a preference for the former.