Synthesis of Homoerythrinan Alkaloids of 1(2)-Alkene and 1,6-Diene Types: Total Synthesis of Comosine, Dihydroschelhammeridine, Schelhammeridine, and 3-Epischelhammeridine[1,2]

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Total syntheses of homoerythrinan alkaloids of 1(2)-alkene type, dihydroschelhammeridine and comosine, and those of 1,6-dienoid type, schelhammeridine and 3-epischelhammeridine, were achieved. Total synthesis of the former alkaloids provided definite proof of their A/B-*cis* stereochemistry. In relation to the stereochemistry, the conformations of erythrinan and homoerythrinan alkaloids are discussed.

Key words homoerythrinan alkaloid; total synthesis; dihydroschelhammeridine; comosine; schelhammeridine; 3-epischelhammeridine

In a preceding paper,[3] we reported the first total synthesis of homoerythrinan alkaloids of 1(6)-alkene type, schelhammericine and 3-epischelhammericine. In this paper we describe the synthesis of alkaloids with 1(2)-alkenoid and 1,6-dienoid type structures: the former is represented by comosine and dihydroschelhammeridine and the latter by schelhammeridine and 3-epischelhammeridine.

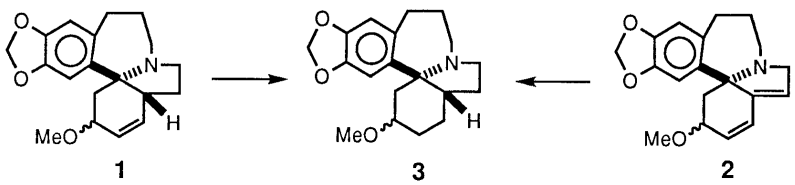
Stereochemistry of 1(2)-Alkene Type Homoerythrinan Alkaloids Dihydroschelhammeridine (alkaloid A)[4] and comosine (alkaloid 1)[5] are homoerythrinan alkaloids isomeric to schelhammericine and 3-epischelhammericine, respectively, bearing the double bond at the 1(2) position. Although the stereochemistry of their A/B ring juncture was assumed as *trans* for the reasons given below, this is not established yet.[6] Hydrogenation of alkaloid A gave a saturated compound which was identical with tetrahydroschelhammeridine, a hydrogenation product of schelhammeridine **2b**,[4] in which the hydrogen was assumed to be introduced from the less hindered α face of the molecule. However, Mondon and Seidel[7] found that the analogous hydrogenation of the corresponding erythrinan alkaloid of dienoid type (*e.g.*, erysotrine) always gives the *cis*-fused tetrahydro derivative, and suggested that the above compounds might have A/B-*cis*-configuration (*e.g.*, **1a**, **1b**). To resolve this problem, we set out to synthesize the corresponding alkaloids of A/B-*cis* stereochemistry in an unequivocal manner.

Synthesis of a Key Intermediate, the Conjugated Ketone 5a The preferred intermediate to the alkaloids under consideration would be the conjugated ketone **5a**, which was supposed to be preparable by isomerization of the enone **4** as in the case of erythrinan alkaloids. However, in sharp contrast to the erythrinan series, in which the 1(6)-ene-3-one quantitatively isomerized into the conjugated enone on treatment with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU),[8] **5a** was not available by base-catalyzed isomerization of **4**. The unconjugated enone **4**,[3] on contact with base, spontaneously gave an oxo-dibenzazecine **6**, suggesting that the conjugated enone **5a** of the seven-membered C-ring is very labile to bases.[9] Therefore a different approach, direct preparation of **5a** under a non-basic condition, had to be explored.

This may be accomplished by a reductive ring opening of the cyclohomoerythrinan **8a** with the use of tributyltin radical, since an analogous preparation of the 6-methoxycarbonyl derivative **5b** from **7b** proceeded in high overall yield.[3] The corresponding de-methoxycarbonyl compound **7a** should directly give **5a** *via* the same sequence of reactions.

The requisite cyclohomoerythrinan **7a** can be prepared from the known trioxo compound **12** (R = Me)[3] as shown in Chart 3 with the use of a dealkoxycarbonylation procedure of β-ketoesters previously reported by Tsuda *et al.*[8,10]

For large-scale synthesis, the ethyl ester **13a** (prepared in a similar way to the methyl ester,[3] see Chart 4) was used for reasons of solubility. The ethyl ester was *ca.* 4 times more soluble in acetonitrile (12 mg/ml) than the methyl ester[3] (2.8 mg/ml), and the yield of photocycloaddition of **13a** to 1-methoxy-3-trimethylsilyloxybutadiene was comparable to that of the methyl ester (80%). The photo-adduct **17** was converted into the keto-alcohol **20a**[11] by similar procedures to those described



a: α-OMe, b: β-OMe

Chart 1

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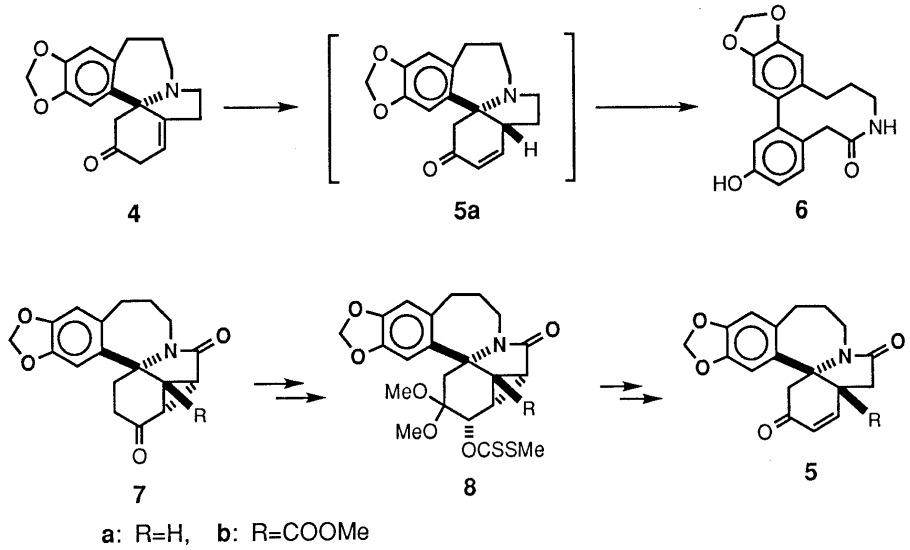

Chart 2

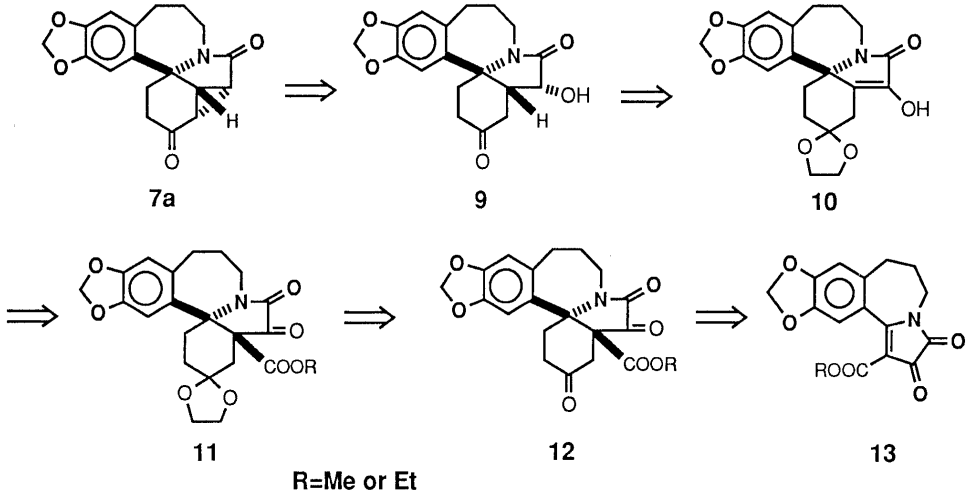

Chart 3

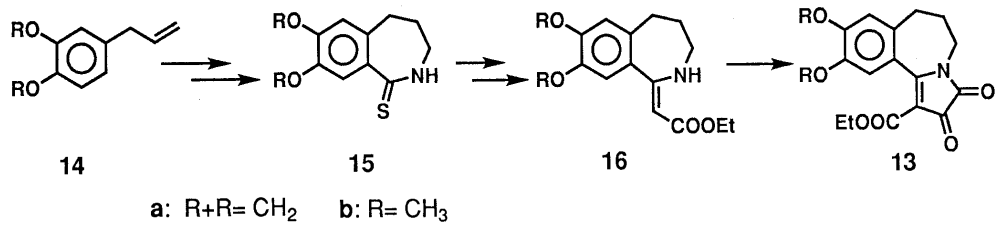

Chart 4

in a previous paper.[3] The overall yield of **20a** from safrole **14a** was 22% with 8 steps.

The alcohol **20a** was converted by dimethyl sulfoxide (DMSO)–Ac_2O oxidation to the trioxo derivative **21**, which on ethylene-acetalization with ethylene glycol and *p*-TsOH gave the mono-ethyleneacetal **22** (Chart 5). The structure of **22** was proved as follows (Chart 5). Acetylation of **20a** followed by ethylene-acetalization and hydrolysis of the resulting **20b** with K_2CO_3–MeOH gave the 7α-hydroxy-ethylene acetal **24a**, which, on oxidation with DMSO–Ac_2O, gave **22**. The stereochemistry of **20a** was also clarified by the transformations depicted in Chart 5.

Deethoxycarbonylation of **22** with $MgCl_2$ in DMSO containing *tert*-heptylmercaptan[10] gave **10**, which was reduced with $NaBH_4$, and the resulting alcohol **25** was treated with 5% HCl to give the ketone **9**, whose stereochemistry was proved to be as depicted by conversion of **9** to the intramolecular methyl-acetal **26** on treatment with MeOH and *p*-TsOH. The keto-alcohol **9** was converted to the cyclohomoerythrinan **7a** on mesylation followed by intramolecular alkylation with methanolic K_2CO_3. The overall yield of **7a** from **20a** was 62%.

By the same sequence of procedures as described in a previous paper,[3] the 1,7-cyclo-*cis*-homoerythrinan **7a** was

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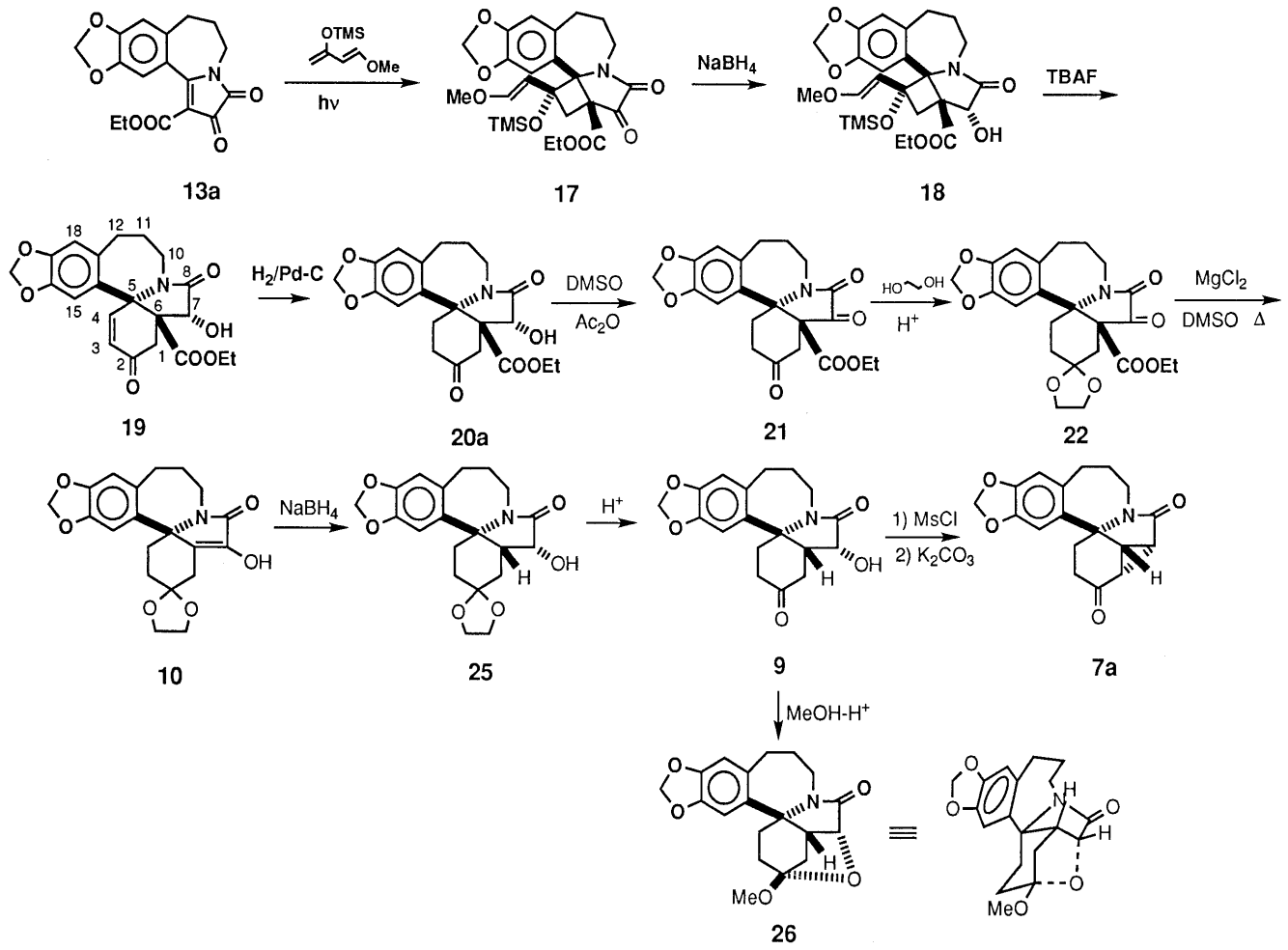

Chart 5

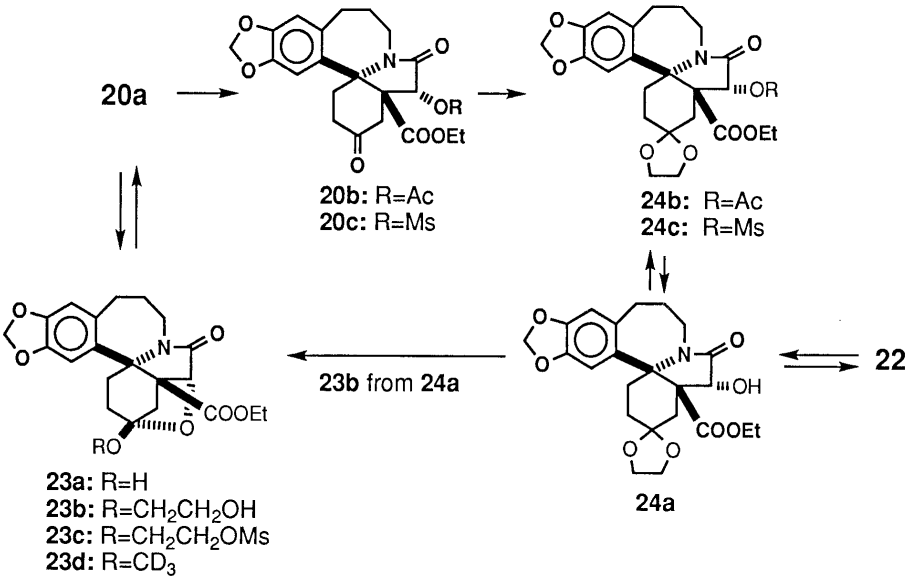

Chart 6

converted to the expected conjugated ketone **5a** in an overall yield of 49% (Chart 7). The product should have A/B-*cis*-configuration, because no stereochemical disturbance is expected during the above transformation. The ketone **5a** was stable under weakly acidic or neutral conditions, but on contact with base, immediately isomerized, with spontaneous ring opening, to give the dibenzazecine **6**, as predicted.[9]

Total Synthesis of Comosine and Dihydroschelhammeridine Reduction of the ketone **5a** with *n*-tetrabutylammonium borohydride in methanol gave two products (**29a** and **30a**). Since they were hardly separable by chromatog-

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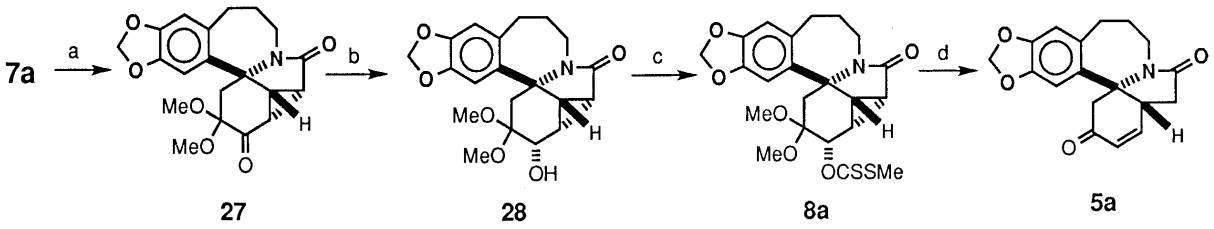
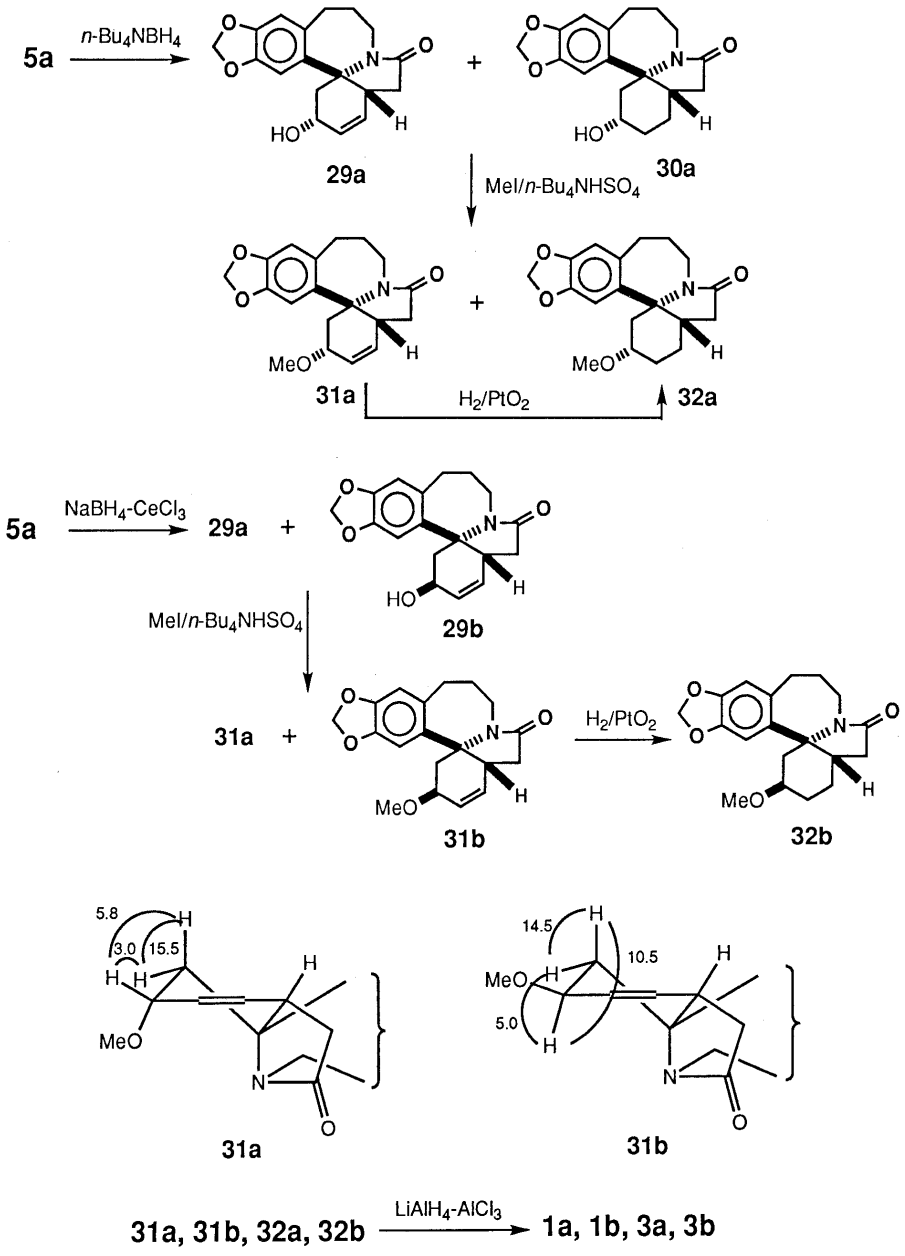


a: i. PhSeCl/cat. $BF_3.Et_2O$, ii. MPC/MeOH, b: $NaBH_4$, c: NaH/CS_2-MeI, d: Bu_3SnH.

Chart 7



31a, 31b, 32a, 32b $\xrightarrow{LiAlH_4\text{-}AlCl_3}$ **1a, 1b, 3a, 3b**

Chart 8

raphy, the mixture was converted to the *O*-methyl ethers with iodomethane in the presence of a phase-transfer catalyst, then separated by medium pressure liquid chromatography (MPLC) to give an allyl-ether **31a** and a saturated ether **32a** in a ratio of 1 : 2. Catalytic hydrogenation of **31a** gave **32a**, indicating that they have the same stereochemistry with respect to the alcohol group; the former was a 1,2-reduction product and the latter was a 1,4-reduction product. The result implies that the reduction with Bu_4NBH_4 took place mainly from one direction.

On the other hand, reduction of **5a** with $NaBH_4$–$CeCl_3$ in methanol gave two epimeric allyl alcohols, **29a** and **29b**, in a ratio of 1 : 2, which were separated by MPLC after conversion to the *O*-methyl ethers, **31a** and **31b**. Hydrog-

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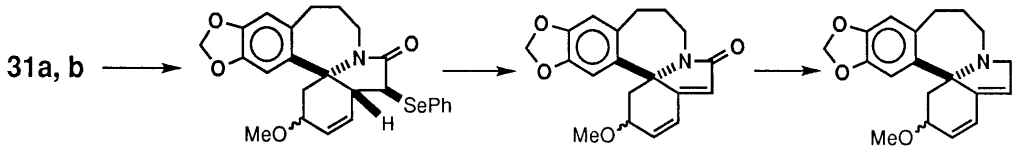

Chart 9

enation of **31b** gave the saturated compound **32b**, epimeric to **32a**.

The detailed ^{1}H-NMR analysis of **31a** and **31b** revealed that they have a $^4H_5$ conformation and the configurations of the OMe group are quasi-axial and quasi-equatorial, respectively. Their structures were proved by converting them to the natural alkaloids, in which the stereochemistry of the methoxyl group had already been established.[6]

Reduction of the lactam carbonyl of **31a**, **31b**, **32a**, and **32b** with $LiAlH_4$-$AlCl_3$ in tetrahydrofuran (THF)[12] gave, in excellent yields, the corresponding amines, **1a**, **1b**, **3a**, and **3b**, respectively. They were indentical with comosine, dihydroschelhammeridine, dihydrocomosine, and tetrahydroschelhammeridine, respectively, based on comparisons of the ^{1}H-NMR spectra with charts provided by Dr. N. Langlois.

Total Synthesis of Schelhammeridine and 3-Epischelhammeridine Syntheses of these dienoid alkaloids were accomplished from the 8-oxo derivatives, **31a** and **31b**, in a similar manner to that reported for erysotrine from the corresponding 6,7-dihydro derivative.[8] Lithiation of **31a** and **31b** followed by treatment with diphenyldiselenide, gave phenylselenenyl derivatives, **33a** and **33b**, respectively. Oxidative elimination of the PhSe group from them by treatment with $NaIO_4$ afforded **34a** and **34b**, respectively. The latter was identical with 8-oxoschelhammeridine (alkaloid K).[4] Reduction of **34a** and **34b** with $LiAlH_4$–$AlCl_3$ gave the corresponding amines, **2a** and **2b**, which were identical with 3-epischelhammeridine[13] and schelhammeridine[14] based on a comparison of their ^{1}H-NMR spectra with reported values.

Conformational Difference between Erythrinan and Homoerythrinan Alkaloids The result of hydride reduction of the homoerythrinan enone **5a** is remarkably different from that of the corresponding erythrinan enone **36**[8]; the latter predominantly gave the α-alcohol with $NaBH_4$–$CeCl_3$ and the β-alcohol with Bu_4NBH_4, while **5a** gave the opposite results, suggesting that 1(2)-ene-3-ones are reduced through different conformations in the erythrinan and homoerythrinan series. Table 1 shows the results of hydride reduction of various erythrinan and homoerythrinan 3-ones by the above reagents.

$NaBH_4$–$CeCl_3$ (reagent A) is known to favor 1,2-reduction of a conjugated ketone, preferentially producing an equatorial alcohol,[15] and *n*-Bu_4NBH_4 (reagent B) is a bulky reducing agent that attacks the ketone from the less hindered face of the molecule.

Erythrinan and homoerythrinan $\Delta^{1(6)}$-3-ones, **35** and **4**, gave parallel results for both reagents with relatively high selectivity: an α-alcohol with reagent A and a β-alcohol with reagent B. This result is readily understandable, since either compound can take only one conformation, $^3H_4$, in which the β-face of the molecule is apparently hindered by the aromatic ring.

Reduction of $\Delta^{1(2)}$-3-ones, **36** and **5a**, with reagent A proceeds in different conformers: $^5H_4$ for erythrinan and $^4H_5$ for homoerythrinan, thus giving stereochemically different products. Conformational analyses of products by ^{1}H-NMR indicated that 3α-OR was quasi-equatorial in the Δ^1-erythrinan series and quasi-axial in the Δ^1-homoerythrinan series (see above). MM2 calculations indicated that $^5H_4$ is more stable by 3.3 kcal/mol in a Δ^1-erythrinan-3-one and less stable by 0.9 kcal/mol in a Δ^1-homoerythrinan-3-one than the corresponding $^4H_5$ conformers. Thus, the α-alcohol predominates in the former and the β-alcohol in the latter. Accordingly, in reduction with reagent B, the β-alcohol predominated for erythrinan and α-alcohol did so for homoerythrinan in the 1,2-reduction products, although 1,4-reduction always predominated in this case. Further reduction of the 1,4-reduction products would follow the same path as that of the saturated ketone described below.

Reduction of the saturated ketones, **37** and **38**, with reagent A gave results parallel to those for Δ^1-3-ones, again suggesting conformational difference between erythrinan and homoerythrinan-3-ones: $^1C_4$ for the former and $^4C_1$ for the latter. These are in fact the most stable conformations; energy differences between them are 5.5 kcal/mol for erythrinan-3-one in favor of the former and 3.8 kcal/mol for homoerythrinan-3-one in favor of the latter. However, reduction with reagent B gave unexpected results: both erythrinan and homoerythrinan-3-ones were reduced with this reagent in favor of an α-alcohol. In the erythrinan, the reduction might proceed through T_3, because this is the second most favoured conformation (ΔE from $^1C_4$ is 3.0 kcal/mol) and both the α- and β-faces of the $^1C_4$ conformer are hindered by the presence of the aromatic ring and ring B. In homoerythrinan-3-one, the reduction should have occurred from the most stable $^4C_1$ or form T_3: the energy difference between these conformations is 1.2 kcal/mol. An X-ray analysis of the 8-oxohomoerythrinan-3-one **38** revealed that ring A of this compound has a twist (T_3) conformation in the solid state.

Difference of conformational energies between $^4H_5$ and $^5H_4$ in these alkaloids must be so small as to allow easy interconversion through structural changes at rings B and C. Conformational analysis data given in Table 2 indicate that 8-oxo-Δ^1-erythrinans adopt $^5H_4$ or $^4H_5$ conformation depending on whether the 3-OR configuration is α or β. On the other hand, 8-oxo-Δ^1-homoerythrinans

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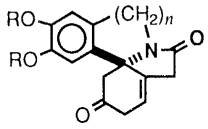
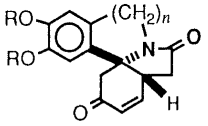
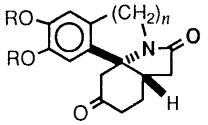
Table 1. Hydride Reduction of Erythrinan- and Homoerythrinan-3-ones (in MeOH, 0 °C)

3-Ketones		n	$NaBH_4$–$CeCl_3$	n-Bu_4NBH_4	
			1,2-Reduction α : β	1,2-Reduction α : β	1,4-Reduction α : β
	**35**	2	4.5 : 2	1 : >10	
	4	3	5 : 1[a]	1 : 6[a]	
	**36**	2	2.1 : 1	1 : 2.2 :	5.3 : 2.1
	5a	3	1 : 2	1 : — :	2 : 0.5
	**37**	2	3 : 1	2.5 : 1	
	38	3	1 : 1.5	3 : 1	

R=OMe for n=2 (erythrinan), R=–CH_2– for n=3 (homoerythrinan). The ratio was determined by HPLC on TSK-Gel Si60 ($CHCl_3$: MeOH = 19 : 1). *a*) See reference 3.

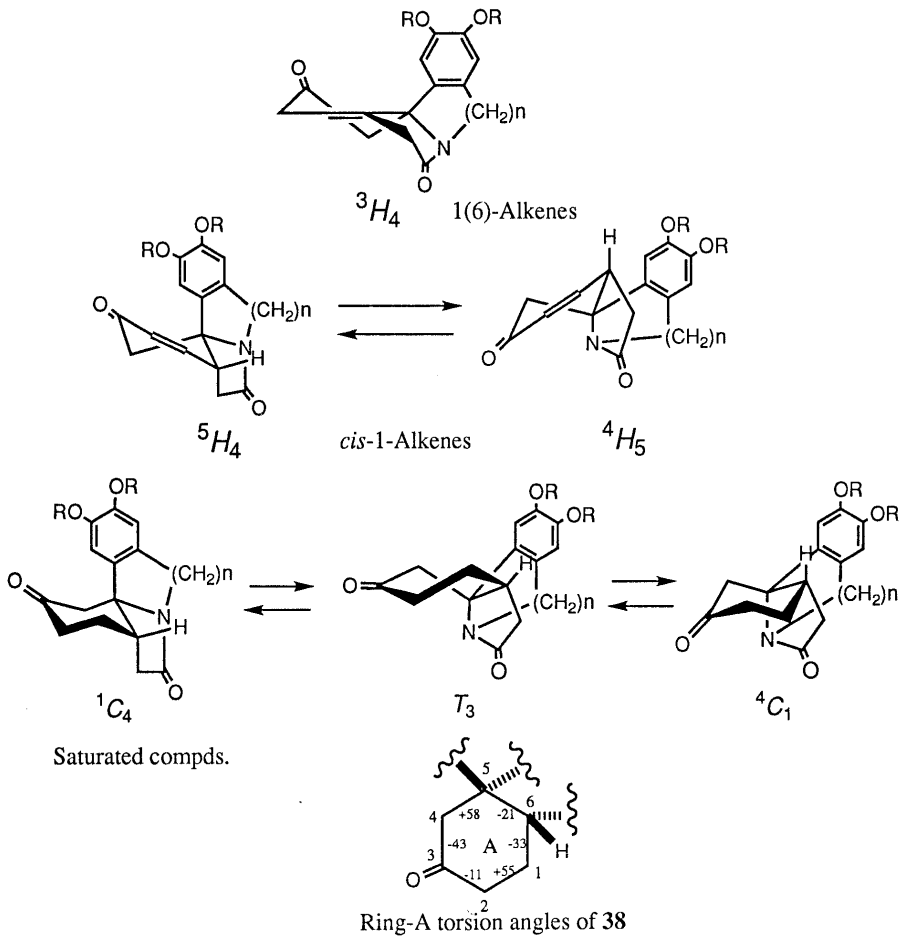


Fig. 1. Plausible Conformations of Erythrinan and Homoerythrinan-3,8-diones

adopt only $^4H_5$ conformation. However, the corresponding amines, **1a** (comosine) and **1b** (dihydroschelhammeridine), take conformations of $^5H_4$ for 3α-OMe and $^4H_5$ for 3β-OMe, respectively, as evidenced from the ^{1}H-NMR spectra.

Experimental

Unless otherwise noted, the following procedures were adopted. Melting points were determined on a Yanaco micro hot stage melting point apparatus and are uncorrected. IR spectra were taken as KBr disks on a Jasco IR-G spectrometer and data are given in cm^{-1}. ^{1}H-NMR spectra were taken with a JNM-PMX-60 (60 MHz), JEOL FX 100 (100 MHz), or JEOL GX 400 (400 MHz) spectrometer in $CDCl_3$ solu-

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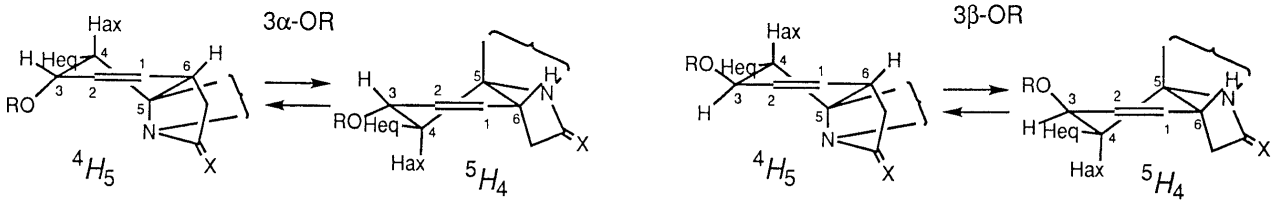
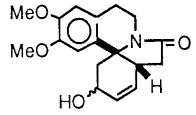
Table 2. Ring-A Conformations of Δ^1-Erythrinans and Δ^1-Homoerythrinans



Series	3α-OR				3β-OR			
	Compd.	$J(H)_{3,4eq}$	$J(H)_{3,4ax}$	Assigned conformation	Compd.	$J(H)_{3,4eq}$	$J(H)_{3,4ax}$	Assigned conformation
8-Oxoerythrinan (X=O)	**39a**	5	10	$^5H_4$	**39b**	5	9.5	$^4H_5$
8-Oxohomoerythrinan (X=O)	**31a**	3	5.8	$^4H_5$	**31b**	5	10.5	$^4H_5$
Homoerythrinan ($X=H_2$)	**1a**	5	11.5	$^5H_4$	**1b**	5.4	9.8	$^4H_5$



39a: R=α-OH
39b: R=β-OH

tions 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 carried out with silica gel (Wacogel C-200). MPLC was performed on a Merck Lobar column. For thin-layer chromatography (TLC), Merck precoated plates GF_{254} were used and spots were monitored under UV light (254 nm), then developed by spraying 1% $Ce(SO_4)_2$ in 10% H_2SO_4 and heating the plate at 100 °C until coloration took place. Preparative TLC (PTLC) was performed with precoated silica gel plates, Merck 60 F_{254} (0.5 mm thick). 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 IR and NMR spectra.

Ethyl 2-(2,3,4,5-Tetrahydro-7,8-methylenedioxy-1*H*-2-benzazepin-1-ylidene)acetate (16a) A solution of the thiolactam **15a** (5.0 g) and ethyl bromoacetate (4.53 g, 1.2 eq) in CH_3CN (180 ml) was stirred at room temperature for 17 h. After removal of the solvent, the residue was dissolved in CH_2Cl_2. This solution was washed three times with saturated $KHCO_3$ solution, dried, and concentrated to give a residue, which was dissolved in *N*,*N*-dimethylformamide (DMF, 180 ml). The solution thus obtained was heated with triphenylphosphine (15 g), and potassium *tert*-butoxide (100 mg) under reflux for 8 h under an Ar atmosphere. The mixture was concentrated *in vacuo*, the residue was dissolved in benzene, and the solution was extracted with 10% HCl (80 ml × 3). The acidic extract was basified with K_2CO_3 and extracted with CH_2Cl_2. Chromatography of the product gave **16a** (5.6 g, 96%) from the $CHCl_3$–AcOEt (9:1) eluate. It gave colorless needles from ether–hexane, mp 118—119 °C. IR: 1650. ^{1}H-NMR (60 MHz): 6.78, 6.57 (each 1H, s, ArH), 5.90 (2H, s, OCH_2O), 4.50 (1H, s, =CH–), 4.05 (2H, q, J=7 Hz, $COOCH_2CH_3$), 3.05 (2H, q, J=6 Hz, $NHCH_2$), 2.63 (2H, t, J=6 Hz, $ArCH_2$), 1.96 (2H, m, CH_2), 1.25 (3H, t, J=7 Hz, $COOCH_2CH_3$). *Anal.* Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 4.89. Found: C, 65.22; H, 6.20; N, 4.89.

Ethyl 2-(2,3,4,5-Tetrahydro-7,8-dimethoxy-1*H*-2-benzazepin-1-ylidene)-acetate (16b) Treatment of **15b** (2 g) as above gave **16b** (1.67 g, 69%). Colorless needles from hexane, mp 76—78 °C. IR: 1640. ^{1}H-NMR (60 MHz): 6.81, 6.60 (each 1H, s, ArH), 4.54 (1H, s, =CH–), 4.15 (2H, q, J=7 Hz, $COOCH_2CH_3$), 3.87 (6H, s, 2 × OMe), 3.10 (2H, t, J=6 Hz, $NHCH_2$–), 2.70 (2H, t, J=7 Hz, $ArCH_2$), 2.03 (2H, m, CH_2), 1.27 (3H, t, J=7 Hz), $COOCH_2CH_3$). MS: 291 (M^+). *Anal.* Calcd for $C_{16}H_{21}NO_4$: C, 65.95; H, 7.27; N, 4.81. Found: C, 66.01; H, 7.23; N, 4.77.

Dioxopyrrolobenzazepine 13a Oxalyl chloride (3.6 g) was added dropwise to a cooled solution of **16a** (6 g) in dry ether (270 ml) and the mixture was stirred for 2 h at 0 °C. The precipitated crystals were collected by filtration and recrystallized from CH_2Cl_2–AcOEt to give **13a** (6.65 g, 93%) as orange needles, mp 248—250 °C. IR: 1755, 1730, 1670. ^{1}H-NMR (60 MHz): 6.98, 6.62 (each 1H, s, ArH), 5.91 (2H, s, OCH_2O), 4.12 (2H, q, J=7 Hz, $CO_2CH_2CH_3$), 3.52 (2H, t, J=6 Hz, $>NCH_2$–), 2.72 (2H, t, J=6 Hz, $ArCH_2$), 1.25 (3H, t, J=7 Hz, $CO_2CH_2CH_3$). *Anal.* Calcd for $C_{17}H_{15}NO_6$: C, 62.00; H, 4.59; N, 4.25. Found: C, 61.74; H, 4.43; N, 4.06.

Dioxopyrrolobenzazepine 13b Treatment of **16b** (2.7 g) as described above gave **13b** (2.36 g, 73.5%) as orange-red prisms from CH_2Cl_2–AcOEt, mp 231—234 °C. IR: 1750, 1725, 1680. ^{1}H-NMR: 7.18, 6.70 (each 1H, s, ArH), 4.17 (2H, q, J=7 Hz, $COOCH_2CH_3$), 3.92, 3.83 (each 3H, s, OMe), 1.24 (3H, t, J=7 Hz, $COOCH_2CH_3$). MS: 345 (M^+). *Anal.* Calcd for $C_{18}H_{19}NO_6$: C, 62.60; H, 5.55; N, 4.06. Found: C, 62.55; H, 5.55; N, 3.96.

Photocycloaddition of Dioxopyrrolobenzazepine 13a to 1-Methoxy-3-trimethylsilyloxybutadiene A solution of **13a** (3 g) and 1-methoxy-3-trimethylsilyloxybutadiene (2.58 g) in CH_3CN (300 ml) was irradiated with a 300 W high-pressure mercury lamp equipped with a Pyrex filter at 0 °C for 20 min under an N_2 atmosphere. After removal of the solvent below 40 °C, the residue was purified by chromatography to give, from the benzene–AcOEt (9:1) eluate, the photo-adduct **17** (3.67 g, 80%) as colorless prisms from acetone–ether, mp 168—170 °C. IR: 1770, 1740, 1715. ^{1}H-NMR (60 MHz): 6.73, 6.47 (each 1H, s, ArH), 6.43 (1H, d, J=13 Hz, –CH=CHOMe), 5.80 (2H, s, OCH_2O), 4.58 (1H, d, J=13 Hz, –CH=CHOMe), 3.70 (2H, q, J=7 Hz, $CO_2CH_2CH_3$), 3.47 (3H, s, OMe), 3.25 and 2.22 (each 1H, d, J=13 Hz, $H_2C<$ on cyclobutane), 0.77 (3H, t, J=7 Hz, $CO_2CH_2CH_3$), 0.03 (9H, s, TMS). *Anal.* Calcd for $C_{25}H_{31}NO_8Si$: C, 59.86; H, 6.23; N, 2.79. Found: C, 59.73; H, 6.29; N, 2.69.

Reduction of Photo-Adduct 17 The photo-adduct **17** (4 g) in MeOH (180 ml) was reduced with $NaBH_4$ (302 mg) under stirring at 0 °C for 20 min. The product was extracted with $CHCl_3$ to give **18** (4 g, 100%) as colorless needles from CH_2Cl_2–MeOH, mp 171—173 °C. IR: 1730, 1690. ^{1}H-NMR (60 MHz): 6.78, 6.40 (each 1H, s, ArH), 5.93 (1H, d, J=13 Hz, –CH=CHOMe), 5.75 (2H, s, OCH_2O), 4.81 (1H, s, >CHOH), 4.73 (1H, d, J=13 Hz, –CH=CHOMe), 3.75 (2H, q, J=7 Hz, $CO_2CH_2CH_3$), 3.48 (3H, s, OMe), 3.04 and 2.52 (each 1H, d, J=13 Hz, $H_2C<$ on cyclobutane), 0.86 (3H, t, J=7 Hz, $CO_2CH_2CH_3$), 0.12 (9H, s, TMS). MS: 489 (M^+).

6β-Ethoxycarbonyl-7α-hydroxy-16,17-methylenedioxy-2,8-dioxo-Δ^3-*cis*-homoerythrinan (19) A solution of 0.1 M *tetra-n*-butylammonium fluoride (TBAF) in THF (56 ml) was added dropwise into an argon-purged solution of **18** (2.0 g) in dry THF (30 ml) at −30 °C for 30 min and the mixture was stirred for a further 45 min at the same temperature, then gradually brought to room temperature, and stirred for 1 h. The mixture was diluted with CH_2Cl_2, washed with water, and concentrated to give **19** (1.45 g, 89%), which was purified by crystallizations from MeOH to afford colorless prisms, mp >300 °C. IR: 1720, 1680, 1670. ^{1}H-NMR (60 MHz): 6.57, 6.53 (each 1H, s, ArH), 6.48, 6.18 (each 1H, d, J=9 Hz, –CH=CHCO–), 5.87 (2H, s, OCH_2O), 4.50 (1H, s, >CHOH),

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3.70 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 0.93 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$). *Anal.* Calcd for $C_{21}H_{21}NO_7$: C, 63.15; H, 5.30; N, 3.51. Found: C, 63.25; H, 5.23; N, 3.44.

6β-Ethoxycarbonyl-7α-hydroxy-16,17-methylenedioxy-2,8-dioxo-*cis*-homoerythrinan (20a) The enone **19** (1.0 g) in THF (260 ml)–acetone (40 ml) was hydrogenated over 10% Pd–C (2 g) for 3 h at room temperature under an H_2 pressure of 4 kg/cm^2. Removal of the solvent and catalyst gave **20a** (1.01 g, 100%). This product gave colorless prisms, mp 263—266 °C from CH_2Cl_2–MeOH. IR: 7120, 1680, MS: 401 (M^+). *Anal.* Calcd for $C_{21}H_{23}NO_7 \cdot 1/3H_2O$: C, 61.89; H, 5.85; N, 3.45. Found: C, 62.26; H, 5.71; N, 3.59.

The compound is in an equilibrium between a keto-alcohol form **20a** and a hemiacetal form **23a** in solution. ^{1}H-NMR (100 MHz in DMSO-d_6): **23a**: 7.14, 6.64 (each s, ArH), 6.84 (s, OH), 5.94 (s, OCH_2O), 4.26 (s, >C$\underline{H}$–OH), 0.78 (t, J=7 Hz, $CO_2CH_2C\underline{H}_3$); **21a**: 7.14, 6.66 (each s, ArH), 6.37 (s, OH), 5.96 (s, OCH_2O), 4.52 (s, >C$\underline{H}$–OH), 0.88 (t, J=7 Hz, $CO_2CH_2C\underline{H}_3$). ^{1}H-NMR (100 MHz in $CDCl_3/CD_3OD$=4/1) also showed the presence of two compounds **20a** and **23a** or **23d**. **20a**: 6.78, 6.56 (each s, ArH), 5.93 (s, OCH_2O), 4.82 (s, >C$\underline{H}$–OH), 1.01 (t, J=7 Hz, $CO_2CH_2C\underline{H}_3$); **23a** or **23d**: 6.80, 6.54 (each s, ArH), 5.93 (s, OCH_2O), 4.54 (s, >C$\underline{H}$–O), 0.93 (t, J=7 Hz, $CO_2CH_2C\underline{H}_3$). When this solution was allowed to stand for 6 d at room temperature, the spectrum converged to that of **23a** or **23d**.

6β-Ethoxycarbonyl-16,17-methylenedioxy-2,7,8-trioxo-*cis*-homoerythrinan (21) A solution of the keto-alcohol **20a** (2.77 g) in Ac_2O (15 ml) and DMSO (30 ml) was stirred for 17 h at room temperature. Water was added to the reaction mixture and the precipitate that appeared was collected by filtration. The filtrate was extracted with $CHCl_3$ and the extract was combined with the above precipitate and concentrated. Crystallization of the residue from MeOH gave **21** (2.62 g, 95%) as colorless prisms, mp 185—189 °C. IR: 1770, 1740, 1730, 1710. ^{1}H-NMR (60 MHz): 6.67, 6.48 (each 1H, s, ArH), 5.87 (2H, s, OCH_2O), 3.56 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 1.93 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$). MS: 399 (M^+). *Anal.* Calcd for $C_{21}H_{21}NO_7$: C, 63.15; H, 5.30; N, 3.51. Found: C, 62.79; H, 5.38; N, 3.47.

6β-Ethoxycarbonyl-2,2-ethylenedioxy-16,17-methylenedioxy-7,8-dioxo-*cis*-homoerythrinan (22) Compound **21** (2.62 g), ethylene glycol (15 ml), and *p*-TsOH (1.5 g) in benzene (170 ml) was heated under reflux for 4 h with the use of a Dean–Stark water separator. The cooled mixture was washed with saturated $NaHCO_3$. The water layer was re-extracted with $CHCl_3$. The combined benzene and $CHCl_3$ layers were concentrated to give **22** (2.88 g, 99%), as colorless needles from CH_2Cl_2–MeOH, mp 255—260 °C. IR: 1765, 1725, 1715. ^{1}H-NMR (60 MHz): 6.63, 6.47 (each 1H, s, ArH), 5.85 (2H, s, OCH_2O), 3.83 (4H, m, $OC\underline{H}_2C\underline{H}_2O$), 0.85 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$). MS: 443 (M^+). *Anal.* Calcd for $C_{23}H_{25}NO_8$: C, 62.29; H, 5.68; N, 3.16. Found: C, 62.04; H, 5.66; N, 2.97.

Reaction of 20a with Ethylene Glycol Attempted ethylene-acetalization of **20a** (300 mg) as described above gave the intramolecular hemiacetal **23b** (350 mg, 100%), as colorless needles from AcOEt, mp 196—198 °C. IR: 1725, 1690. ^{1}H-NMR (100 MHz): 6.76, 6.52 (each 1H, s, ArH), 5.92 (2H, s, OCH_2O), 4.56 (1H, s, >CH–O), 3.96 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 3.80 (4H, m, $OC\underline{H}_2C\underline{H}_2O$), 0.92 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), MS: 445 (M^+). *Anal.* Calcd for $C_{23}H_{27}NO_8$: C, 62.01; H, 6.11; N, 3.14. Found: C, 61.86; H, 6.12; N, 2.89.

Mesylation of **23b** (200 mg) with MsCl (102 mg) and pyridine (4 ml) for 1 h at 0 °C gave the mesylate **23c** (235 mg, 100%) as colorless needles from MeOH, mp 224—227 °C. This was different from the mesylate **24c**. IR: 1720, 1705. ^{1}H-NMR (100 MHz): 6.76, 6.52 (each 1H, s, ArH), 5.92 (2H, s, OCH_2O), 4.54 (1H, s, >CH–O), 4.36 (2H, t, J=4 Hz, $OCH_2C\underline{H}_2OMs$), 3.68 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 3.91 (2H, t, J=4 Hz, $OC\underline{H}_2CH_2OMs$), 3.06 (3H, s, Ms), 0.92 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$). MS: 523 (M^+).

6β-Ethoxycarbonyl-2,2-ethylenedioxy-7α-methanesulfonyloxy-16,17-methylenedioxy-8-oxo-*cis*-homoerythrinan (24c) Compound **20a** (30 mg) was mesylated with MsCl (0.2 ml) and pyridine (1 ml) for 1 h at 0 °C and the product **20c**, obtained by a usual work-up, was subjected to ethylene-acetalization as described above to give **24c** (39 mg, 100%), as colorless needles from MeOH, mp 205—207 °C. IR: 1720, 1690. ^{1}H-NMR (100 MHz): 6.68, 6.50 (each 1H, s, ArH), 5.94 (1H, s, >CH–OMs), 5.88 (2H, s, OCH_2O), 3.98 (4H, m, $OC\underline{H}_2C\underline{H}_2O$), 3.86 (2H, q, J=7.5 Hz, $CO_2C\underline{H}_2CH_3$), 3.36 (3H, s, Ms), 1.06 (3H, t, J=7.5 Hz, $CO_2CH_2C\underline{H}_3$). MS: 523 (M^+). *Anal.* Calcd for $C_{24}H_{29}NO_{10}S$: C, 55.06; H, 5.58; N, 2.68. Found: C, 54.88; H, 5.60; N, 2.70.

Acetylation of 20a The keto-alcohol **20a** (440 mg) was acetylated with Ac_2O (4 ml) and pyridine (8 ml) overnight at room temperature and worked up as usual to give the acetate **20b** (530 mg, 100%) as colorless needles from CH_2Cl_2–Et_2O, mp 234—236 °C. IR: 1750, 1730, 1720, 1690. ^{1}H-NMR (100 MHz): 6.76, 6.56 (each 1H, s, ArH), 6.00 (1H, s, >CH–OAc), 5.94 (2H, s, OCH_2O), 3.65 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 2.09 (3H, s, OAc), 1.00 (3H, t, J=7.5 Hz, $CO_2CH_2C\underline{H}_3$). MS: 443 (M^+). *Anal.* Calcd for $C_{23}H_{25}NO_8$: C, 62.29; H, 5.68; N, 3.16. Found: C, 62.29; H, 5.65; N, 3.16.

Ethylene-acetalization of 20b The acetate **20b** (107 mg), ethylene glycol (0.5 ml), and *p*-TsOH (40 mg) in benzene (20 ml) were heated with Dean–Stark water separator under reflux for 18 h. The cooled mixture was washed with saturated $NaHCO_3$ and the benzene layer was concentrated. Chromatography of the residue gave, from the benzene–EtOAc (3 : 2) eluate, **24b** (80 mg, 68%), as colorless needles from MeOH, mp 255—260 °C. IR: 1750, 1720, 1700. ^{1}H-NMR (100 MHz): 6.73, 6.50 (each 1H, s, ArH), 6.04 (1H, s, >CH–OAc), 5.88 (2H, s, OCH_2O), 3.94 (4H, m, $OC\underline{H}_2C\underline{H}_2O$), 3.72 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 2.16 (3H, s, OAc), 1.00 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$). MS: 487 (M^+). *Anal.* Calcd for $C_{25}H_{29}NO_9 \cdot 1/6C_6H_6$: C, 62.38; H, 6.04; N, 2.80. Found: C, 62.33; H, 6.12; N, 2.84.

Interconversion of 24 and 22 1) Compound **24b** (30 mg) was hydrolyzed with 5% K_2CO_3–MeOH (3 ml) at room temperature for 15 min to give **24a**, which was oxidized with DMSO (0.5 ml) and Ac_2O (0.25 ml) for 17 h at room temperature. Work-up of the product gave **22** (21 mg, 77%), identical with the specimen obtained above.

2) Reduction of **22** with $NaBH_4$ in MeOH gave **24a** (^{1}H-NMR identification), which converted into **23b** on crystallization from MeOH (^{1}H-NMR identification).

Deethoxycarbonylation of 22 A mixture of **22** (2.5 g), anhydrous $MgCl_2$ (4.25 g, 5 eq), and *tert*-heptylmercaptan (24 ml) in DMSO (216 ml) was heated at 160 °C for 3 h under an Ar atmosphere. DMSO was evaporated *in vacuo* and the residue was acidified with dilute HCl, adjusting to pH 6, and extracted with $CHCl_3$ to give **10** (1.9 g, 82%), as pale yellow prisms from CH_2Cl_2–MeOH, mp 278—280 °C. IR: 1660. ^{1}H-NMR ($CDCl_3$–CD_3OD, 60 MHz): 6.58, 6.50 (each 1H, s, ArH), 5.80 (2H, s, OCH_2O), 3.90 (4H, s, $OC\underline{H}_2C\underline{H}_2O$). MS: 371 ($M^+$). *Anal.* Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.67; H, 5.68; N, 3.77.

2,2-Ethylenedioxy-7α-hydroxy-16,17-methylenedioxy-8-oxo-*cis*-homoerythrinan (25) Compound **10** (1.9 g) in MeOH (160 ml) and THF (40 ml) was reduced with $NaBH_4$ (780 mg) at 0 °C for 1 h and then at room temperature for 3 h. The mixture was concentrated to a half volume and extracted with $CHCl_3$ to give **25** (1.8 g, 94%), as colorless needles from MeOH, mp 233—235 °C. IR: 1670. ^{1}H-NMR (60 MHz): 6.73, 6.33 (each 1H, s, ArH), 5.80 (2H, s, OCH_2O), 4.05 (1H, d, J=6 Hz, >C$\underline{H}$–OH), 3.93 (4H, s, $OC\underline{H}_2C\underline{H}_2O$). MS: 373 ($M^+$). *Anal.* Calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.27; H, 6.18; N, 3.70.

7α-Hydroxy-16,17-methylenedioxy-2,8-dioxo-*cis*-homoerythrinan (9) The ethylene-acetal **25** (1.8 g) was hydrolyzed in acetone–5% HCl (1 : 1, 200 ml) for 3 h at 70 °C with stirring. The mixture was concentrated to a half volume and extracted with $CHCl_3$. The product was crystallized from MeOH–CH_2Cl_2 to give **9** (1.67 g, 100%) as colorless needles, mp 241—243 °C. IR: 1680, 1715. ^{1}H-NMR (60 MHz): 6.65, 6.38 (each 1H, s, ArH), 5.80 (2H, s, OCH_2O). MS: 329 (M^+). *Anal.* Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.87; N, 4.06. Found: C, 65.44; H, 5.82; N, 4.25.

Intramolecular Acetal 26 A mixture of **9** (20 mg) and a catalytic amount of *p*-TsOH in MeOH (2 ml) was heated at 60 °C for 20 min with stirring. Neutralization of the mixture with saturated $NaHCO_3$ solution and extraction with $CHCl_3$ gave the methyl-acetal **26** (18 mg, 80%) as colorless needles from CH_2Cl_2–ether, mp 206—207 °C. IR: 1680. ^{1}H-NMR (60 MHz): 6.67, 6.33 (each 1H, s, ArH), 5.80 (2H, s, OCH_2O), 4.11 (1H, d, J=6 Hz, C_7-H), 3.23 (3H, s, OMe). *Anal.* Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.51; H, 6.14; N, 4.06.

16,17-Methylenedioxy-2,8-dioxo-1,7-cyclo-*cis*-homoerythrinan (7a) A mixture of **9** (1.67 g), 4-dimethylaminopyridine (60 mg) and methanesulfonyl chloride (0.87 g) in pyridine (40 ml) was stirred at 0 °C for 2 h. The reaction mixture was quenched with ice-water, and extracted with $CHCl_3$. Concentration of the extract gave a residue which was heated in 5% K_2CO_3–MeOH (120 ml) at 75 °C for 1 h. The mixture was extracted with $CHCl_3$. Chromatography of the extract, eluting with $CHCl_3$–AcOEt (1 : 1), gave **7a** (1.22 g, 77%) as colorless needles from MeOH,

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mp 255—257 °C. IR: 1670 (br). ^{1}H-NMR (100 MHz): 6.82, 6.52 (each 1H, s, ArH), 5.92 (2H, s, OCH_2O). ^{13}C-NMR: 203.0 s, 170.8 s, 146.7 s, 140.7 s, 134.1 s, 133.4 s, 111.1 s, 106.5 s, 101.4 s, 65.6 s, 36.7 t, 35.6 t, 31.8 t, 30.1 d, 29.0 d, 26.4 t. MS: 311 (M^+). *Anal.* Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.02; H, 5.49; N, 4.49.

3,3-Dimethoxy-16,17-methylenedioxy-2,8-dioxo-1,7-cyclo-*cis*-homoerythrinan (27) A mixture of **7a** (645 mg), PhSeCl (590 mg), and $BF_3 \cdot Et_2O$ (0.1 ml) in dry THF (70 ml) was heated under reflux for 1 h under an Ar atmosphere, then concentrated *in vacuo*. The residue was dissolved in dry MeOH (70 ml), mercury(II) perchlorate (MPC, 3.3 g) was added, and the mixture was stirred for 30 min at 65 °C. After removal of precipitates by filtration, the filtrate was treated with Na_2S until the solution became faintly alkaline. The resultant black precipitate was removed by filtration with the aid of Celite. The filtrate was diluted with water and extracted with $CHCl_3$. The product was purified by chromatography with benzene–AcOEt (1 : 1) to give **27** (485 mg, 63%) as colorless needles from MeOH–CH_2Cl_2, mp 200—202 °C. IR: 1730, 1690. ^{1}H-NMR (60 MHz): 6.75, 6.40 (each 1H, s, ArH), 5.83 (2H, s, OCH_2O), 3.20, 3.17 (each 3H, s, OMe). MS: 371 (M^+). *Anal.* Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.97; H, 5.72; N, 3.59.

The Dimethoxy-alcohol 28 Compound **27** (485 mg) in MeOH (70 ml) was reduced with $NaBH_4$ (88 mg) at 0 °C for 30 min. The mixture was extracted with CH_2Cl_2. Crystallization of the product from MeOH–CH_2Cl_2 gave **28** (488 mg, 100%) as colorless needles, mp 195—197 °C. IR: 1670. ^{1}H-NMR (60 MHz): 6.77, 6.45 (each 1H, s, ArH), 5.87 (2H, s, OCH_2O), 3.43, 3.40 (each 3H, s, OMe). MS: 373 (M^+). *Anal.* Calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.03; H, 6.26; N, 3.49.

16,17-Methylenedioxy-3,8-dioxo-Δ^1-*cis*-homoerythrinan (5a) A mixture of the alcohol **28** (520 mg), NaH (60% oil dispersion, 274 mg), and a catalytic amount of imidazole (15 mg) in dry THF (65 ml) was heated under reflux for 1 h under an Ar atmosphere. Carbon disulfide (3 ml) and iodomethane (3 ml) were added successively, and the mixture was heated for a further 30 min. The reaction mixture was poured into ice-water, acidified with AcOH, and extracted with $CHCl_3$. Concentration of the dried extract and chromatography of the residue gave, from the benzene–AcOEt (1 : 1) eluate, the dithiocarbonate **8a** (620 mg) as a gum. This was dissolved in toluene (70 ml) and heated with *n*-Bu_3SnH (3 ml) and α,α-azobisisobutyronitrile (AIBN, 22 mg) under reflux for 40 min under an Ar atmosphere. The cooled mixture was poured onto a silica gel column and the column was washed with benzene to remove tin compounds. Elution of the column with benzene–AcOEt (1 : 1) gave a gum, which was hydrolyzed with 2% HCl–acetone (1 : 1, 70 ml) for 5 min at room temperature. Extraction of the mixture gave the conjugated ketone **5a** (335 mg, 77% from **28**), as colorless prisms from CH_2Cl_2–MeOH, mp 212—214 °C. IR: 1690, 1680. ^{1}H-NMR (100 MHz): 6.73, 6.52 (each 1H, s, ArH), 6.64 (1H, dd, J = 10, 4 Hz, C_1-H), 6.14 (1H, dd, J = 10, 3 Hz, C_2-H). MS: 311 (M^+). *Anal.* Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.48; H, 5.48; N, 4.43.

***n*-Bu_4NBH_4 Reduction and Methylation of 5a** The enone **5a** (140 mg) in MeOH (30 ml) was reduced with *n*-Bu_4NBH_4 (661 mg) for 15 min at 0 °C. Extraction of the product with $CHCl_3$ gave a mixture of **29a** and **30a**. On repeated crystallizations from MeOH–CH_2Cl_2, **29a** gave colorless needles, mp 236—237 °C. ^{1}H-NMR (100 MHz): 6.69, 6.52 (each 1H, s, ArH), 6.02 (1H, dd, J = 10, 4 Hz, C_2-H), 5.94 (2H, s, OCH_2O), 5.72 (1H, ddd, J = 10, 3, 1 Hz, C_1-H). The above mixture of **29a** and **30a** was dissolved in dry THF (40 ml) and heated with NaH (64% oil dispersion, 300 mg) and a catalytic amount of imidazole under reflux for 30 min, then CH_3I (4 ml) and *n*-Bu_4NHSO_4 (150 mg) were added successively and the mixture was stirred at room temperature for 2 h and at 50 °C for 1 h. The reaction was quenched with 2% HCl, and the mixture was extracted with $CHCl_3$. Concentration of the extract and purification of the residue by MPLC (AcOEt–$CHCl_3$ = 1 : 1) gave **32a** (80 mg, 54%) and **31a** (37 mg, 25%).

31a: Colorless needles from MeOH–CH_2Cl_2, mp 236—237 °C. IR: 1690. ^{1}H-NMR (400 MHz): 6.60 (1H, s, C_{15}-H), 6.50 (1H, s, C_{18}-H), 6.00 (1H, ddd, J = 10.0, 4.5, 1.5 Hz, C_2-H), 5.91 (2H, s, OCH_2O), 5.71 (1H, ddd, J = 10.0, 3.0, 1.0 Hz, C_1-H), 3.71 (1H, dddd, J = 5.8, 4.5, 3.0, 1.0 Hz, C_3-H), 3.34 (3H, s, OMe), 2.37 (1H, dd, J = 15.5, 3.0 Hz, C_4-H_{eq}), 2.26 (1H, dd, J = 15.5, 5.8 Hz, C_4-H_{ax}). HRMS: Calcd for $C_{19}H_{21}NO_4$: 327.1469 (M^+). Found: 327.1475. *Anal.* Calcd for $C_{19}H_{21}NO_4 \cdot 1/3H_2O$: C, 68.50; H, 6.56; N, 4.20. Found: C, 68.14; H, 6.37; N, 4.14.

32a: Colorless prisms from benzene–ether, mp 176—178 °C. IR: 1680. ^{1}H-NMR (100 MHz): 6.76, 6.48 (each 1H, s, ArH), 5.91 (2H, s, OCH_2O), 3.56 (1H, m, >CHOMe), 3.26 (3H, s, OMe). HRMS: Calcd for $C_{19}H_{23}NO_4$: 329.1625 (M^+). Found: 329.1623. *Anal.* Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.27; H, 7.08; N, 4.14.

Hydrogenation of 31a The methyl ether **31a** (5 mg) was hydrogenated over PtO_2 (5 mg) in EtOH (7 ml) for 1 h at room temperature. Usual work-up gave **32a** (5 mg, 100%), which was identical with the compound obtained above.

$NaBH_4$–$CeCl_3$ Reduction and Methylation of 5a $CeCl_3 \cdot 6H_2O$ (341 mg, 2 eq) and $NaBH_4$ (20 mg, 1.1 eq) were added successively to a solution of **5a** (150 mg) in MeOH (40 ml) and the mixture was stirred at 0 °C for 20 min. The mixture was extracted with $CHCl_3$ and the extract was concentrated to yield a mixture of **29a** and **29b**. This was dissolved in THF (50 ml) and heated with NaH (64% oil dispersion, 340 mg) and a catalytic amount of imidazole under reflux for 40 min. CH_3I (2 ml) and *n*-Bu_4NHSO_4 (192 mg) were added successively and the mixture was stirred for a further 6 h at 50 °C. The reaction was quenched with 2% HCl, then the mixture was extracted with $CHCl_3$ to give, on purification of the product by MPLC with $CHCl_3$–AcOEt (1 : 1), **31b** (105 mg, 67%) and **31a** (45 mg, 29%).

31b: Colorless needles from MeOH–CH_2Cl_2, mp 175—176 °C. IR: 1690. ^{1}H-NMR (400 MHz): 6.75 (1H, s, C_{15}-H), 6.51 (1H, s, C_{18}-H), 5.95 (1H, ddd, J = 10.5, 3.0, 1.5 Hz, C_2-H), 5.92 (2H, s, OCH_2O), 5.57 (1H, ddd, J = 10.5, 3.0, 1.0 Hz, C_1-H), 3.79 (1H, dddd, J = 10.5, 5.0, 3.0, 1.0 Hz, C_3-H), 3.39 (3H, s, OMe), 2.61 (1H, dd, J = 14.5, 5.0 Hz, C_4-H_{eq}), 2.00 (1H, dd, J = 14.5, 10.5 Hz, C_4-H_{ax}). HRMS: Calcd for $C_{19}H_{21}NO_4$: 327.1469 (M^+). Found: 3227.1471. *Anal.* Calcd for $C_{19}H_{21}NO_4 \cdot 1/3H_2O$: C, 68.50; H, 6.56; N, 4.20. Found: C, 68.47; H, 6.40; N, 4.29.

Hydrogenation of 31b The methyl ether **31b** (20 mg) was hydrogenated over PtO_2 (20 mg) in EtOH (8 ml) for 1 h at room temperature to give **32b** (20 mg, 100%) as colorless needles from ether, mp 149—150 °C. IR: 1685. ^{1}H-NMR (100 MHz): 6.76, 6.46 (each 1H, s, ArH), 5.90 (2H, s, OCH_2O), 3.35 (3H, s, OMe), 3.10 (1H, m, >CHOMe). HRMS: Calcd for $C_{19}H_{23}NO_4$: 329.1625 (M^+). Found: 329.1623. *Anal.* Calcd for $C_{19}H_{23}NO_4 \cdot 1/3H_2O$: C, 68.04; H, 7.11; N, 4.18. Found: C, 68.10; H, 7.00; N, 4.11.

(±)-Dihydroschelhammeridine (Alkaloid A) (1b) A solution of AlH_3 (1 ml) [prepared from $LiAlH_4$ (76 mg) and $AlCl_3$ (248 mg) in dry THF (6 ml)–ether (4 ml)] was added to a solution of **31b** (20 mg) in dry THF (4 ml) and the mixture was stirred for 1 h at room temperature. It was diluted with ether, adjusted to pH 8 by adding 28% NH_4OH, and extracted with ether. The organic layer was extracted with 1 N HCl. The acidic layer was basified with 28% NH_4OH and extracted with $CHCl_3$ to give the amine **1b** (16.3 mg, 85%), which was purified by chromatography with $CHCl_3$–MeOH (15 : 1) to afford a colorless oil. ^{1}H-NMR (100 MHz, $CDCl_3$): 6.74 (1H, s, C_{15}-H), 6.54 (1H, s, C_{18}-H), 5.88 (2H, br s, OCH_2O), 3.83 (1H, m, C_3-H), 3.28 (3H, s, OMe), 2.46 (1H, dd, J = 14, 5 Hz, C_4-H_{eq}), 1.98 (1H, dd, J = 14, 10 Hz, C_4-H_{ax}). ^{1}H-NMR (400 MHz, C_6D_6): 6.73 (1H, s, C_{15}-H), 6.52 (1H, s, C_{18}-H), 5.95 (1H, br d, J = 10.0 Hz, C_1-H), 5.44 (1H, ddd, J = 10.0, 4.0, 2.0 Hz, C_2-H), 5.37 (2H, br s, OCH_2O), 3.82 (1H, ddd, J = 9.8, 5.4, 2.0 Hz, C_3-H), 3.16 (3H, s, OMe), 2.52 (1H, dd, J = 13.6, 5.4 Hz, C_4-H_{eq}), 1.96 (1H, dd, J = 13.6, 9.8 Hz, C_4-H_{ax}). HRMS: Calcd for $C_{19}H_{23}NO_3$: 313.1676. Found: 313.1676. Picrate: yellow needles from MeOH, mp 194—196 °C.

(±)-Comosine (Alkaloid 1) (1a) The methyl ether **31a** (22 mg) was reduced as described above to give **1a** (21 mg, 100%) as a colorless oil. ^{1}H-NMR (100 MHz, $CDCl_3$): 6.70 (1H, s, C_{15}-H), 6.58 (1H, s, C_{18}-H), 6.01 (1H, m, C_1-H), 5.77 (1H, dd, J = 10, 1 Hz, C_2-H), 5.87 (2H, br s, OCH_2O), 3.28 (3H, s, OMe), 2.58 (1H, dd, J = 12, 5 Hz, C_4-H_{eq}), 1.56 (1H, dd, J = 12, 11 Hz, C_4-H_{ax}). ^{1}H-NMR (400 MHz, C_6D_6): 6.91 (1H, s, C_{15}-H), 6.56 (1H, s, C_{18}-H), 5.78 (1H, ddd, J = 10.5, 2.0, 1.0 Hz, C_2-H), 5.61 (1H, ddd, J = 10.5, 4.5, 1.0 Hz, C_1-H), 5.38 (2H, br s, OCH_2O), 3.40 (1H, dddd, J = 11.5, 5.0, 2.0, 1.0 Hz, C_3-H), 3.03 (3H, s, OMe), 2.54 (1H, dd, J = 12.0, 5.0 Hz, C_4-H_{eq}), 1.70 (1H, dd, J = 12.0, 11.5 Hz, C_4-H_{ax}). HRMS: Calcd for $C_{19}H_{23}NO_3$: 313.1676. Found: 313.1686. The HCl salt: colorless needles from acetone, mp 199—202 °C.

(±)-Tetrahydroschelhammeridine (3b) The saturated methyl ether **32b** (20 mg) was reduced as described above to give **3b** (19 mg, 100%) as colorless needles from acetone, mp 135—137 °C. ^{1}H-NMR (100 MHz): 6.86 (1H, s, C_{15}-H), 6.55 (1H, s, C_{18}-H), 5.87 (2H, br s, OCH_2O), 3.32 (3H, s, OMe). HRMS: Calcd for $C_{19}H_{25}NO_3$: 315.1832. Found: 315.1837.

(±)-Dihydrocomosine (3a) The saturated methyl ether **32a** (20 mg) was reduced as described above to give **3a** (19 mg) as colorless needles

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from acetone, mp 159—161 °C. ^{1}H-NMR (100 MHz): 6.93 (1H, s, C_{15}-H), 6.60 (1H, s, C_{18}-H), 5.90 (2H, br s, OCH_2O), 3.23 (3H, s, OMe). HRMS: Calcd for $C_{19}H_{25}NO_3$: 315.1832. Found: 315.1829.

(±)-8-Oxoschelhammeridine (34b) (Alkaloid K) The 8-oxo derivative **31b** (20 mg) in THF (1 ml) was treated with lithium diisopropylamide (2 eq) in THF (2 ml) and with *n*-BuLi in hexane (1 ml) at −78 °C for 30 min under an Ar atmosphere, then $(PhSe)_2$ (38 mg) was added and the mixture was stirred for 1 h. It was acidified with 1 N HCl and extracted with $CHCl_3$. Concentration of the extract gave **33b** as a gum, which was dissolved in MeOH–water. This solution was treated with $NaIO_4$ (50 mg) for 30 min at room temperature, then extracted with $CHCl_3$. Purification of the product by chromatography gave **34b** (15 mg) as colorless needles from MeOH, mp 212—213 °C. UV: 285 (5100), 243 (14700). IR (CCl_4): 1690. ^{1}H-NMR (100 MHz): 6.83 (1H, d, J=10 Hz, C_1-H), 6.58 (1H, s, C_{15}-H), 6.47 (1H, s, C_{18}-H), 6.14 (1H, dd, J=10, 5 Hz, C_2-H), 6.02 (1H, s, C_7-H), 5.88 (2H, m, OCH_2O), 3.07 (3H, s, OMe). MS: 325 (M^+, base peak). HRMS: Calcd for $C_{19}H_{19}NO_4$: 325.1313. Found: 325.1304.

(±)-Schelhammeridine (2b) The 8-oxo derivative **34b** (11 mg) in dry THF (2 ml) was reduced with AlH_3 for 40 min at 0 °C and worked up as described for **1b**. The product was purified by chromatography with $CHCl_3$–MeOH (15 : 1) to give **2b** (9 mg), as a solid. UV: 290 (4030), 237 (11300). ^{1}H-NMR (100 MHz, C_6D_6): 6.68 (1H, s, C_{15}-H), 6.52 (1H, s, C_{18}-H), 6.19 (1H, d, J=10 Hz, C_2-H), 6.16 (1H, s, C_7-H), 5.68 (1H, dd, J=10, 5 Hz, C_1-H), 5.32, 5.20 (each 1H, ABq, J=2 Hz, OCH_2O), 2.78 (3H, s, OMe). MS: 311 (M^+), 84 (base peak). HRMS: Calcd for $C_{19}H_{21}NO_3$: 311.1520. Found: 311.1517.

(±)-Epischelhammeridine (2a) The α-isomer **31a** was similarly converted to **34a** and then to **2a**.

8-Oxo-3-epischelhammeridine **34a**: ^{1}H-NMR (100 MHz): 6.80 (1H, dd, J=10, 2 Hz, C_1-H), 6.64 (1H, s, C_{15}-H), 6.48 (1H, s, C_{18}-H), 6.18 (1H, br d, J=10 Hz, C_2-H), 6.06 (1H, s, C_7-H), 5.88 (2H, m, OCH_2O), 3.35 (3H, s, OMe).

3-Epischelhammeridine **2a**: UV: 289 (4150), 238 (9200). ^{1}H-NMR (100 MHz): 6.62 (1H, s, C_{15}-H), 6.46 (1H, s, C_{18}-H), 6.42 (1H, dd, J=10, 2 Hz, C_1-H), 5.90 (2H, s, OCH_2O), 5.86 (1H, br d, J=10 Hz, C_2-H), 3.28 (3H, s, OMe). MS: 311 (M^+), 84 (base peak). HRMS: Calcd for $C_{19}H_{21}NO_3$: 311.1520. Found: 311.1538.

Saturated Ketones 37 and 38 The enones **36** and **5a** were hydrogenated over 10% Pd–C in acetone for 2.5 h at room temperature under atmospheric pressure, and worked up as usual to give **37** and **38**, respectively.

37: Gum. IR: 1720, 1680. ^{1}H-NMR (100 MHz): 6.58, 6.54 (each 1H, s, ArH), 3.87, 3.85 (each 3H, s, OMe). MS 315 (M^+), 258 (base peak).

38: Gum. IR: 1720, 1680. ^{1}H-NMR (100 MHz): 6.66, 6.52 (each 1H, s, ArH), 5.94 (2H, s, OCH_2O). MS: 313 (M^+), 256 (base peak).

Hydride Reduction of Ketones (Analytical Procedure) Ketones **4**, **5a**, **35**—**38** (3—10 mg) in MeOH (1—2 ml) were reduced 1) with successive addition of $CeCl_3 \cdot 6H_2O$ (2.5 mol eq) and $NaBH_4$ (5.0 eq) and stirring for 20 min at 0 °C, or 2) with *n*-Bu_4NBH_4 (2 eq) for 10 min at 0 °C. The product obtained by a usual work-up was analyzed by HPLC and the product ratios were determined from the peak areas observed by UV at 254 nm. HPLC conditions: temperature 30 °C; flow rate 0.7 ml/min; column pressure: 35 kgf/cm^2.

X-Ray Crystallographic Analysis of the Saturated Ketone 38 Reflection data were collected on a Rigaku AFC-5R four-circle diffractometer controlled by the MSC/AFC program package, using Mo K_α radiation monochromated by a graphite monochromator, in the 2θ–ω scan mode. Reflections with intensity above the $3\sigma(I)$ level were used for the structure determination. The structures were solved by Mithril and refined by a full-matrix least-squares method using anisotropic temperature factors for nonhydrogen atoms. Hydrogen atoms were located at calculated positions. Crystal data: monoclinic, a=10.863 (4) Å, b=12.664 (5) Å, c=10.747 (6) Å. V=1478 (1) Å^3. Z=4. D_c=1.41 g/cm^3. Space group, $P2_1$. Reflections used for calculation, 1790. R=0.005. The compound was analyzed as a set of two molecules, both of which had the same conformation. Positional parameters are available on request to the authors.

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