Synthesis of Homoerythrinan Alkaloids of 1(2)-Alkene and 1,6-Diene Types: Total Synthesis of Comosine, Dihydroschelhammeridine, Schelhammeridine, and 3-Epischelhammeridine1,2)

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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.

Sterechemistry of 1(2)-Alkene Type Homoerythrinan Alkaloids Dihydroschelhammeridine (alkaloid A)4) and comosine (alkaloid 1)3) 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.5) Hydrogenation of alkaloid A gave a saturated compound which was identical with tetrahydrodihydroschelhammeridine, a hydrogenation product of schelhammeridine 2h,4) in which the hydrogen was assumed to be introduced from the less hindered z face of the molecule. However, Mondon and Seidel2) 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),5) 5a was not available by base-catalyzed isomerization of 4. The unconjugated enone 4,3) on contact with base, spontaneously gave an oxo-dibenazacene 6, suggesting that the conjugated enone 5a of the seven-membered C-ring is very liable 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 cyclohydroerythrinan 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 cyclohydroerythrinan 7a can be prepared from the known trioxo compound 12 (R = Me)31 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 ester31 (2.8 mg/ml), and the yield of photo-cycloaddition of 13a to 1-methoxy-3-trimethylsilyloxybutadiene was comparable to that of the methyl ester (80%). The photo-adduct 17 was converted into the ketoalcohol 20a31 by similar procedures to those described

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Chart 1

a: ω-OMe, b: β-OMe
in a previous paper. The overall yield of 20a from safrole 14a was 22% with 8 steps.

The alcohol 20a was converted by dimethyl sulfoxide (DMSO)-Ac₂O oxidation to the trioxo derivative 21, which on ethylene-acetalization with ethylene glycol and p-TsOH gave the mono-ethylenacetal 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 K₂CO₃-MeOH gave the 7α-hydroxy-ethylene acetal 24a, which, on oxidation with DMSO–Ac₂O, gave 22. The stereochemistry of 20a was also clarified by the transformations depicted in Chart 5.

Deethoxycarbonylation of 22 with MgCl₂ in DMSO containing tert-heptylmercaptan gave 10, which was reduced with NaBH₄, 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 K₂CO₃. The overall yield of 7a from 20a was 62%.

By the same sequence of procedures as described in a previous paper, the 1,7-cyclo-ctis-homoerythrinan 7a was
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.  

**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-
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 Bu₄NBH₄ took place mainly from one direction.

On the other hand, reduction of 5a with NaBH₄–CeCl₃ 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-
enation of 31b gave the saturated compound 32b, epi-
meric to 32a.

The detailed $^1$H-NMR analysis of 31a and 31b revealed that they have a $^4$H$_2$ 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.

Reduction of the lactam carbonyl of 31a, 31b, 32a, and 32b with LiAlH$_4$.AlCl$_3$ in tetrahydrofuran (THF) gave, in excellent yields, the corresponding amines, 1a, 1b, 3a, and 3b, respectively. They were identical with comosine, dihydrocselinheridine, dihydrocomosine, and tetra-
dihydrocselhammeridine, respectively, based on comparisons of the $^1$H-NMR spectra with charts provided by Dr. N. Langlois.

**Total Synthesis of Schelhammeridine and 3-Epischelham-
meridine** Syntheses of these dienoid alkaloids were ac-
complished from the 8-oxo derivatives, 31a and 31b, in a
similar manner to that reported for erythrose from the
'corresponding 6,7-dihydro derivative. Lithiation of 31a and 31b followed by treatment with diphenylsileneide, gave phenylselenenyl derivatives, 33a and 33b, respectively. Oxidative elimination of the PhSe group from them by treatment with NaOCl afforded 34a and 34b, respectively. The latter was identical with 8-oxoschelhammeridine (alkaloid K). Reduction of 34a and 34b with LiAlH$_4$.AlCl$_3$ gave the corresponding amines, 2a and 2b, which were identical with 3-epischelhammeridine and schelham-
meridine based on a comparison of their $^1$H-NMR spectra with reported values.

**Conformational Difference between Erythrinan and Homoerythrinan Alkaloids** The result of hydride reduc-
tion of the homoerythrinan enone 5a is remarkably dif-
ferent from that of the corresponding erythrinan enone 36; the latter predominantly gave the $\alpha$-alcohol with NaBH$_4$.CeCl$_3$ and the $\beta$-alcohol with Bu$_3$NBH$_4$, 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-reduc-
tion of a conjugated ketone, preferentially producing an equatorial alcohol, and $n$-Bu$_3$NBH$_4$ (reagent B) is a bulky reducing agent that attacks the ketone from the less hindered face of the molecule.

Erythrinan and homoerythrinan $^{1,2,3,}$-ones, 35 and 4, gave parallel results for both reagents with relatively high selectivity: an $\alpha$-alcohol with reagent A and a $\beta$-alcohol with reagent B. This result is readily understandable, since either compound can take only one conformation, $^3$H$_4$, in which the $\beta$-face of the molecule is apparently hindered by the aromatic ring.

Reduction of $^4$H$_3$-3-ones, 36 and 5a, with reagent A proceeds in different conformers: $^4$H$_3$ for erythrinan and
$^4$H$_3$ for homoerythrinan, thus giving stereochemically different products. Conformational analyses of products by $^1$H-NMR indicated that 3z-OR was quasi-equatorial in the $^1$-erythrinan series and quasi-axial in the $^1$-homoerythrinan series (see above). MM2 calculations indicated that $^3$H$_4$ is more stable by 3.3 kcal/mol in a $^1$-erythrinan-3-one and less stable by 0.9 kcal/mol in a $^1$-homoerythrinan-3-one than the corresponding $^4$H$_3$ con-
formers. Thus, the $\alpha$-alcohol predominates in the former and the $\beta$-alcohol in the latter. Accordingly, in reduction with reagent B, the $\beta$-alcohol predominated for erythrinan and $\alpha$-alcohol did so for homoerythrinan in the 1,4-reduc-
tion 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 reagen-
t B gave results parallel to those for $^1$-3-ones, again
suggesting conformational difference between erythrinan and homoerythrinan-3-ones: $^3$C$_4$ for the former and $^4$C$_4$ for the latter. These are in fact the most stable con-
formations; 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 $\alpha$-alcohol. In the erythrinan, the reduction might proceed through $T_3$, be-
cause this is the second most favoured conformation (AE from $^1$C$_4$ is 3.0 kcal/mol) and both the $\alpha$- and $\beta$-faces of the $^3$C$_4$ 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 $^4$C$_1$ or form $T_3$; the energy difference between these confor-
mations is 1.2 kcal/mol. An X-ray analysis of the 8-

oxo-homoerythrinan-3-one 38 revealed that ring A of this compound has a twist ($T_2$) conformation in the solid state.

Difference of conformational energies between $^4$H$_4$ and $^5$H$_4$ 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-$^4$-erythrinans adopt $^5$H$_4$ or $^4$H$_4$ con-
formation depending on whether the 3-OR configuration is $\alpha$ or $\beta$. On the other hand, 8-oxo-$^1$-homoerythrinans
Table 1. Hydride Reduction of Erythrinan- and Homoeorythrinan-3-ones (in MeOH, 0°C)

<table>
<thead>
<tr>
<th>3-Ketones</th>
<th>n</th>
<th>NaBH₄–CoCl₂ 1,2-Reduction α : β</th>
<th>n-Bu₃NBH₄ 1,2-Reduction α : β</th>
<th>n-Bu₃NBH₄ 1,4-Reduction α : β</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Diagram]</td>
<td></td>
<td>1.2-Reduction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Diagram]</td>
<td></td>
<td>1.4-Reduction</td>
<td></td>
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</tr>
</tbody>
</table>

R = OMe for n = 2 (erythrinan), R = -CH₂- for n = 3 (homoeorythrinan). The ratio was determined by HPLC on TSK-Gel Si60 (CHCl₃:MeOH=19:1). a) See reference 3.

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

adopt only $^4H_4$ conformation. However, the corresponding amines, 1a (comosine) and 1b (dihydroeschelhammeridine), take conformations of $^5H_4$ for 3α-OMe and $^4H_5$ for 3β-OMe, respectively, as evidenced from the $^1H$-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-PX60 (60 MHz), JEOL FX 100 (100 MHz), or JEOL GX 400 (400 MHz) spectrometer in CDCl₃ solu-
Table 2. Ring-A Conformations of α-D-Erythrinans and α-D-Homoerythrinans

<table>
<thead>
<tr>
<th>Series</th>
<th>Compd.</th>
<th>J(H3, 4-ene)</th>
<th>J(H3, 4-ene)</th>
<th>Assigned conformation</th>
<th>Compd.</th>
<th>J(H3, 4-ene)</th>
<th>J(H3, 4-ene)</th>
<th>Assigned conformation</th>
</tr>
</thead>
</table>
| 8-Oxocinhydrin (X = O) | 39a | 5 | 10 | \(H_2\) | 39b | 5 | 9.5 | \(H_2\)
| 8-Oxohomoerythrin (X = O) | 31a | 3 | 5.8 | \(H_2\) | 31b | 5 | 10.5 | \(H_2\)
| Homoerythrin (X = H_2) | 1a | 5 | 11.5 | \(H_2\) | 1b | 5 | 9.8 | \(H_2\)

Ethyl 2-(2,3,4,5-Tetrahydro-7,8-methylenedioxy-1H-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 CHCl_3 (180 ml) was stirred at room temperature for 17 h. After removal of the solvent, the residue was dissolved in CHCl_3. This solution was washed three times with saturated KHC_2O_4 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 x 3). The acidic extract was basified with K_2CO_3 and extracted with CHCl_3. 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. 1H-NMR (60 MHz): 6.78, 6.57 (each 1H, s, ArH), 5.90 (2H, s, OCH_2O), 4.80 (2H, q, J = 7 Hz, COOC_2H_5), 3.05 (2H, q, J = 6 Hz, NHCH_2), 2.63 (2H, t, J = 6 Hz, ArCH), 1.96 (2H, m, CH_2), 1.25 (3H, t, J = 7 Hz, COOC_2H_5), Anal. Caled for C_15H_17NO_2 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-dimethoxycarbonyl-1H-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. 1H-NMR (60 MHz): 6.81, 6.60 (each 1H, s, ArH), 4.54 (1H, s, CH=), 4.15 (2H, q, J = 7 Hz, COOC_2H_5), 3.87 (6H, 2 x OMe), 3.10 (2H, t, J = 6 Hz, -NHCH_2-), 2.70 (2H, q, J = 7 Hz, ArCH), 2.03 (2H, m, CH_2), 1.27 (3H, t, J = 7 Hz), COOC_2H_5, MS: 291 (M^-). Anal. Caled for C_15H_17NO_2 C: 65.95; H: 7.27; N: 4.81. Found: C: 66.01; H: 7.23; N: 4.77.

Dioxypyrrolobenzazepine 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 CHCl_3-AcOEt to give 13a (6.65 g, 93%) as orange needles, mp 246—250°C. IR: 1755, 1730, 1670.

1H-NMR (60 MHz): 6.98, 6.62 (each 1H, s, ArH), 5.91 (2H, s, OCH_2O), 4.12 (2H, q, J = 7 Hz, COOC_2H_5), 3.52 (2H, t, J = 6 Hz, -NCH_2-), 2.72 (2H, t, J = 6 Hz, ArCH), 1.25 (3H, t, J = 7 Hz, COOC_2H_5), Anal. Caled for C_16H_18NO_2 C: 64.00; H: 5.92; N: 4.59. Found: C: 64.17; H: 5.93; N: 4.57.

Dioxopyrrolobenzazepine 13b Treatment of 16b (2.7 g) as described above gave 13b (2.36 g, 73.5%) as orange-red crystals from CHCl_3-AcOEt, mp 213—234°C. IR: 1750, 1725, 1680. 1H-NMR (60 MHz): 7.20 (each 1H, s, ArH), 4.17 (2H, q, J = 7 Hz, COOC_2H_5), 3.92, 3.83 (each 3H, s, OMe), 1.24 (3H, t, J = 7 Hz, COOC_2H_5), MS: 345 (M^+). Anal. Caled for C_16H_18NO_2 C: 62.60; H: 5.55; N: 4.06. Found: C: 62.55; H: 5.55; N: 3.96.

Photocyclodition of Dioxopyrrolobenzazepine 13a to 1-Methoxy-3-trimethylsilylbutyloxybutadiene A solution of 13a (3 g) and 1-methoxy-3-trimethylsilylbutyloxybutadiene (2.58 g) in CHCl_3 (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. 1H-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, COOC_2H_5), 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, COOC_2H_5), 0.03 (9H, s, TMS). Anal. Caled for C_18H_24O_6Si 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 (4.6 g, 100%) as colorless needles from CHCl_3-MeOH, mp 171—173°C. IR: 1730, 1690. 1H-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, >CH=O), 4.73 (1H, d, J = 13 Hz, -CH=CHOME), 3.75 (2H, q, J = 7 Hz, COOC_2H_5), 3.48 (3H, s, OMe), 3.04 and 2.52 (each 1H, d, J = 13 Hz, H_2C=C on cyclobutane), 0.86 (3H, t, J = 7 Hz, COOC_2H_5), 0.12 (9H, s, TMS). MS: 469 (M^+)
Acetylation of 20a The keto-alcohol 20a (440 mg) was acetylated with Ac₂O (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 CH₂Cl₂-CH₂Cl, mp 234–236 °C. IR: 1750, 1735, 1670, 1690. 1H-NMR (100 MHz): 6.76, 6.56 (each 1H, s, ArH), 6.00 (1H, s, >CH-OAc), 5.94 (2H, s, OCH₂), 3.65 (2H, q, J = 7.5 Hz, CO₂CH₂CH₃), 2.09 (3H, s, OAc), 1.00 (3H, t, J = 7.5 Hz, CO₂CH₂CH₃). MS: 443 (M⁺). Anal. Calcd. for C₁₄H₂₁NO₄C₁₂: 62.29, H: 5.86, N: 3.16. Found: C: 62.29; H: 5.65; N: 3.16.

Ethylesterification 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 NaHCO₃ 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: 1790, 1720, 1700. 1H-NMR (100 MHz): 6.73, 6.50 (each 1H, s, ArH), 6.04 (1H, s, >CH-OAc), 5.88 (2H, s, OCH₂), 3.94 (4H, m, OCH₂CH₂), 3.72 (2H, q, J = 7.7 Hz, CO₂CH₂CH₃), 2.16 (3H, s, OAc), 1.00 (3H, t, J = 7.7 Hz, CO₂CH₂CH₃). MS: 487 (M⁺). Anal. Calcd. for C₁₄H₂₃NO₄: 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% K₂CO₃-MeOH (3 mL) at room temperature for 15 min to give 24a, which was oxidized with DMSO (0.5 mL) and Ac₂O (0.25 mL) for 2 h at room temperature. Work-up of the product gave 24b (21 mg, 77%), identical with the specimen obtained above.

2) Reduction of 22 with NaBH₄ in MeOH gave 24a (1H-NMR identification), which converted into 23b through the 1H-NMR identification.

Deethoxybenzoylation of 22 A mixture of 22 (2.5 g, anhydrous MgCl₂ (4.25 g, 2 eq), and 1-tert-butylmethacrylat (24 mg) in DMSO (216 mL) was heated at 160 °C for 3 h, then cooled. The mixture was evaporated in vacuo and the residue was acidified with dilute HCl, adjusting to pH 6, and extracted with CHCl₃ to give 10 (1.9 g, 82%), as pale yellow prisms from CHCl₃-MeOH, mp 278–280 °C. IR: 1660. 1H-NMR (CDCl₃-CD₂OD, 60 MHz): 6.58, 6.50 (each 1H, s, ArH), 5.80 (2H, s, OCH₂), 3.90 (4H, s, OCH₂CH₂). MS: 371 (M⁺). Anal. Calcd. for C₁₄H₂₃NO₄C: 64.68; H: 7.50; N: 3.77. Found: C: 64.67; H: 7.56; N: 3.77.

2.2-Ethylenoxy-7-hydroxy-16,17-methenyldioxy-8-oxo-8-cis-homoerythrin (25) Compound 10 (1.9 g) in MeOH (160 mL) and THF (40 mL) was reduced with NaBH₄ (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 CHCl₃ to give 25 (1.8 g, 94%), as colorless needles from MeOH, mp 233–235 °C. IR: 1670. 1H-NMR (60 MHz): 6.73, 6.33 (each 1H, s, ArH), 5.80 (2H, s, OCH₂), 3.93 (4H, s, OCH₂CH₂). MS: 375 (M⁺). Anal. Calcd. for C₁₄H₂₁NO₄C: 64.73; H: 6.21; N: 3.75. Found: C: 64.27; H: 6.18; N: 3.70.

7a-Ethylenoxy-16,17-methenyldioxy-2,8-dioxo-8-cis-homoerythrin (9a) The ethylene-acetate 25 (1.8 g) was hydrolyzed in aqueous 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 CHCl₃. The product was crystallized from MeOH–CH₂Cl₂ to give 9 (1.67 g, 100%) as colorless needles, mp 241–243 °C. IR: 1680, 1715. 1H-NMR (60 MHz): 6.65, 6.38 (each 1H, s, ArH), 5.80 (2H, s, OCH₂), 4.11 (1H, d, J = 6.6 Hz, C₃-H), 3.23 (3H, s, OMe). Anal. Calcd. for C₁₄H₂₁NO₄C: 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 NaHCO₃ solution and extraction with CHCl₃ gave the methyl-acetal 26 (18 mg, 80%) as colorless needles from CH₂Cl₂–ether, mp 266–207 °C. IR: 1680. 1H-NMR (60 MHz): 6.67, 6.53 (each 1H, s, ArH), 5.80 (2H, s, OCH₂), 4.11 (1H, d, J = 6.6 Hz, C₃-H), 3.23 (3H, s, OMe). Anal. Calcd. for C₁₄H₂₁NO₄C: 65.64; H: 6.16; N: 4.08. Found: C: 66.51; H: 6.14; N: 4.06.

16,17-Methenyldioxy-2,8-dioxo-1,7-cyclo-cis-homoerythrin (7a) A mixture of 9 (1.67 g), 4-dimethylaminopyridine (46 mg) and methanesulfonic 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 CHCl₃. Concentration of the extract gave a residue which was heated in 5% K₂CO₃-MeOH (120 mL) at 75 °C for 1 h. The mixture was extracted with CHCl₃. Chromatography of the extract, eluting with CHCl₃–AcOEt (1:1), gave 7a (1.22 g, 77%) as colorless needles from MeOH.
mp 255—257°C. IR: 1670 (br). 1H-NMR (100 MHz): 6.82, 6.52 (each 1H, s, ArH). 5.92 (2H, s, OCH3). 13C-NMR: 203.0, 170.8, 146.7, 140.7, 134.1, 133.4, 11.1, 106.5, 101.4, 66.5, 36.7, 35.6, 31.8, 30.1, 29.0d, 26.4t.

Quinoline (31a) 1H-NMR (100 MHz): 6.76, 6.48 (each 1H, s, ArH), 5.91 (2H, s, OCH3), 3.56 (1H, m, >CHOME), 3.26 (3H, s, OMe). HRMS: Calculated for C19H20NO5: 329.1625 (M+). Found: 329.1623.

Hydrogenation of 31a The methyl ether 31a (5 mg) was hydrogenated over PdO (5 mg) in EtOH (7 ml) for 1 h at room temperature. 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 CHCl3, to give, on purification of the product by MPLC with CHCl3-AcOEt (1:1), 31b (105 mg, 67%), and 31a (45 mg, 29%).

Hydrogenation of 31b The mixture was stirred for a further 30 min with 2% HCl. The reaction was quenched with 2% HCl, then the mixture was extracted with CHCl3, to give, on purification of the product by MPLC with CHCl3-AcOEt (1:1), 31b (203 mg, 67%) and 31a (20 mg, 10%).

(±)-Dihydroxydimer stick (10 mg) was dissolved in 1 ml of MeOH (30 ml) and heated with NaBH4 (10 mg) for 2 h at room temperature.

(±)-Dihydroxyderhaminocycline (31b) The saturated methyl ether 32a (20 mg) was reduced as described above to give 32a (19 mg, 100%) as colorless needles from acetonitrile, mp 200—202°C. 1H-NMR (100 MHz, CDCl3): 6.66 (1H, s, C1-H), 5.94 (2H, s, OCH3), 3.56 (1H, m, >CHOME), 3.26 (3H, s, OMe). HRMS: Calculated for C19H20NO5: 329.1625 (M+). Found: 329.1623.

Hydrogenation of 31a The methyl ether 31a (5 mg) was hydrogenated over PdO (5 mg) in EtOH (7 ml) for 1 h at room temperature. 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 CHCl3, to give, on purification of the product by MPLC with CHCl3-AcOEt (1:1), 31b (105 mg, 67%), and 31a (45 mg, 29%).

Hydrogenation of 31b The mixture was stirred for a further 30 min with 2% HCl. The reaction was quenched with 2% HCl, then the mixture was extracted with CHCl3, to give, on purification of the product by MPLC with CHCl3-AcOEt (1:1), 31b (203 mg, 67%) and 31a (20 mg, 10%).

(±)-Dihydroxydimer stick (10 mg) was dissolved in 1 ml of MeOH (30 ml) and heated with NaBH4 (10 mg) for 2 h at room temperature. The reaction was quenched with 2% HCl, then the mixture was extracted with CHCl3, to give, on purification of the product by MPLC with CHCl3-AcOEt (1:1), 31b (203 mg, 67%) and 31a (20 mg, 10%).

(±)-Dihydroxydimer stick (10 mg) was dissolved in 1 ml of MeOH (30 ml) and heated with NaBH4 (10 mg) for 2 h at room temperature.

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(±)-Dihydroxydimer stick (10 mg) was dissolved in 1 ml of MeOH (30 ml) and heated with NaBH4 (10 mg) for 2 h at room temperature. The reaction was quenched with 2% HCl, then the mixture was extracted with CHCl3, to give, on purification of the product by MPLC with CHCl3-AcOEt (1:1), 31b (203 mg, 67%) and 31a (20 mg, 10%).

(±)-Dihydroxydimer stick (10 mg) was dissolved in 1 ml of MeOH (30 ml) and heated with NaBH4 (10 mg) for 2 h at room temperature. The reaction was quenched with 2% HCl, then the mixture was extracted with CHCl3, to give, on purification of the product by MPLC with CHCl3-AcOEt (1:1), 31b (203 mg, 67%) and 31a (20 mg, 10%).
from acetone, mp 159—161 °C. 1H-NMR (100 MHz): 6.93 (1H, s, C15H-6), 6.60 (1H, s, C14H), 5.90 (2H, brs, OCH3), 3.23 (3H, s, OMe). HRMS: Calcd for C14H11NO2: 251.1383. Found: 251.1829.

(2)-8-Oxoschelhammeridine (3b) (Alkaloid K) The 8-oxo derivative 3b (20 mg) in THF (1 ml) was treated with lithium disopropylamide (2 eq) in THF (20 ml) and with n-butyl lithium in hexane (1 ml) at −78 °C for 30 min under an Ar atmosphere, then (PhSeCl2) (38 mg) was added with the mixture was stirred for 1 h. It was acidified with 1 N HCl and extracted with CHCl3. Concentration of the extract gave 3b as a gum, which was dissolved in MeOH—water. This solution was treated with NaN3O (50 mg) for 30 min at room temperature, then extracted with CHCl3. Purification of the product by chromatography gave 3b (15 mg) as colorless needles from MeOH—CHCl3 (1:2) 213°C. UV: 285 (5100), 243 (14700), IR (CCl4): 1690. 1H-NMR (100 MHz): 6.83 (1H, d, J = 10 Hz, C13H-6), 6.58 (1H, s, C15H-6), 6.47 (1H, s, C14H), 6.14 (1H, dd, J = 10, 5 Hz, C12H-6), 6.02 (1H, s, C7H-3), 5.88 (2H, m, OCH3O), 3.07 (3H, s, OMe). MS: 325 (M+*, base peak). HRMS: Calcd for C14H13NO3: 325.1313. Found: 325.1304.

(2)-Schelhammeridine (2b) The 8-oxo derivative 3b (11 mg) in dry THF (2 ml) was treated with AlH3 for 40 min at 0 °C and worked up as described for 1b. The product was purified by chromatography with CHCl3−MeOH (15:1) to give 2b (9 mg), as a solid. UV: 290 (4030), 237 (11300). 1H-NMR (100 MHz, CD3OD): 6.68 (1H, s, C15H-6), 6.52 (1H, s, C18H-6), 6.19 (1H, d, J = 10 Hz, C12H-6), 6.16 (1H, s, C7H-3), 5.68 (1H, dd, J = 10, 5 Hz, C12H-6), 5.31, 5.20 (each 1H, ABq, J = 2 Hz, OCH3), 2.78 (3H, s, OMe). MS: 311 (M+*), 84 (base peak). HRMS: Calcd for C14H12NO3: 311.1520. Found: 311.1517.

(2)-Epichelhammeridine (2a) The α-isomer 3a was similarly converted to 3a and then to 2a.

8-Oxo-3-epichelhammeridine 34a: 1H-NMR (100 MHz): 6.80 (1H, dd, J = 10, 2 Hz, C12H-6), 6.64 (1H, s, C15H-6), 6.48 (1H, s, C14H-6), 6.26 (1H, brd, J = 10 Hz, C12H-6), 6.06 (1H, s, C13H-6), 5.82 (2H, m, OCH3O), 3.35 (3H, s, OMe).

3-Epichelhammeridine 2a: UV: 289 (4150), 238 (2900). 1H-NMR (100 MHz): 6.62 (1H, s, C15H-6), 6.46 (1H, s, C14H-6), 6.42 (1H, dd, J = 10, 2 Hz, C12H-6), 6.35 (1H, brd, J = 10 Hz, C12H-6), 6.26 (3H, s, OMe). MS: 311 (M+*), 84 (base peak). HRMS: Calcd for C14H12NO3: 311.1520. Found: 311.1538.

Saturated Ketones 37 and 38 The enones 36 and 5a were hydroxylated 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. 1H-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. 1H-NMR (100 MHz): 6.62, 6.52 (each 1H, s, ArH), 5.94 (2H, s, OCH3O). 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 with 1 with successive addition of CeCl3 (0.6, CH3OH (2.5 mol eq) and NaBH4 (5.0 eq) and stirring for 20 min at 0°C, or 2 with n-Bu4NBH (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 kg/cm2.

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/AF software package, using Mo Kα radiation monochromated by a graphite monochromator, in the 2θ = 0 scan mode. Reflections with intensity above the 3σ(I) level were used for the structure determination. The structures were solved by direct methods 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) Å3. Z = 4. D = 1.41 g/cm3. Space group, P21. Reflections used for calculation, 1790. R = 0.05. 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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References and Notes
3) See Part XLI.
11) The compound exists in solution as an equilibrium mixture with the intramolecular hemiacetal 23a, as evidenced from the 1H-NMR spectrum. The correlation reactions shown in Chart 6 (for details, see Experimental) supported the indicated stereochemistry. The same phenomenon was also observed for the corresponding methyl ester.