Chem. Pharm. Bull. **46**(12) 1872—1877 (1998) Vol. 46, No. 12

Studies toward Total Synthesis of Non-Aromatic Erythrinan Alkaloids. 7.[1] Synthesis of Cocculolidine Skeleton

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Received August 10, 1998; accepted September 25, 1998

The skeletal structure of cocculolidine (1), a D-nor-erythrinan alkaloid, was synthesized as the 8-oxo derivative 2 by several routes *via* the diester 4 as a key intermediate. One route was an ozonolysis of 14,15,17-trimethoxy-8-oxo-erythrinan (3) to directly yield 4 in 63%. The other was the Ce(IV) methanesulfonate oxidation of 16,17-dimethoxy-8-oxo-erythrinan (6) to yield the *p*-quinone 7 (94%), which was converted to the same diester 4 by ozonolysis and peroxide oxidation (70%). The diester 4 was transformed to the corresponding anhydride 5, which was regioselectively reduced with a bulky borohydride (K-selectride®) to give the desired lactone 2.

Key words cocculolidine; regioselective reduction; cerium(IV) oxidation; D-nor-erythrinan alkaloid; ozonolysis; aromatic ring cleavage

In a previous communication[2] we reported the synthesis of the skeletal structure **2** of cocculolidine (**1**), which is a D-nor-erythrinan alkaloid occurring in *Cocculus trilobus* DC.[3] (Menispermaceae). This synthesis was achieved by a regioselective reduction of the anhydride **5** which, in turn, was prepared, through the diester **4**, by an ozonolytic cleavage of the trimethoxyerythrinan derivative **3**.[4]

Although the transformation of **3** to **2** can be achieved in a straightforward manner, preparation of **3** from an appropriate starting material requires a number of steps and the overall yield was unsatisfactory (for example, the yield of **3** by the cyclization of the corresponding trimethoxyphenethylamine was 51%).[4] We therefore sought a new route to the diester **4** from more easily available dimethoxyerythrinans, and succeeded in finding several routes to efficiently synthesize **4** from 16,17-dimethoxyerythrinan **6** through an oxidation to *p*-quinone **7**. This paper discusses details of synthesis of the cocculolidine skeleton **2** with these new routes included.

Results and Discussion

Preparation of the Diester (4) from Trimethoxyerythrinan Derivatives (3, 10) As reported previously,[4] the ozonolysis of 14,15,17-trimethoxy-8-oxo-*cis*-erythrinan (**3**) in CH_2Cl_2 gave the diester **4** in 63% yield along with the epoxide **8** as a by-product (12%). The ozonolysis of **3** in the presence of the regulator (BF_3–Et_2O) gave **4** (48%) and the enol-ether **9** (22%) with recovery of the starting material (3%).

The isomeric 14,16,17-trimethoxy-8-oxo-*cis*-erythrinan (**10**) yielded an enol-ether **11** (76%) by the ozonization in the presence of BF_3–Et_2O. Ozonization without regulator reduced the yield of **11** to 47%. The enol-ether **11** was converted to **4** by ruthenium tetroxide oxidation[5] in poor yield.

Oxidation of **10** with cerium(IV) ammonium nitrate (CAN) gave *p*-quinone derivative **7** in 40% yield. Ozonolysis of **7** followed by peroxide oxidation afforded **4** in 70% yield after treatment with diazomethane.

Preparation of the Diester (4) from Dimethoxyerythrinan Derivative (6) 16,17-Dimethoxy-8-oxo-*cis*-erythrinan (**6**) is readily available from 2,3-dimethoxyphenethylamine in 67% yield.[4]

In order to transform **6** into the diester **4**, it was first converted to the *p*-quinone **7** by Ce(IV) oxidation, then degraded to **4** through ozonolysis. The oxidation of **6** with CAN in AcOH–MeCN gave the *p*-quinone **7** in only 36% yield with major formation of the nitro compound **12** (60%). Com-

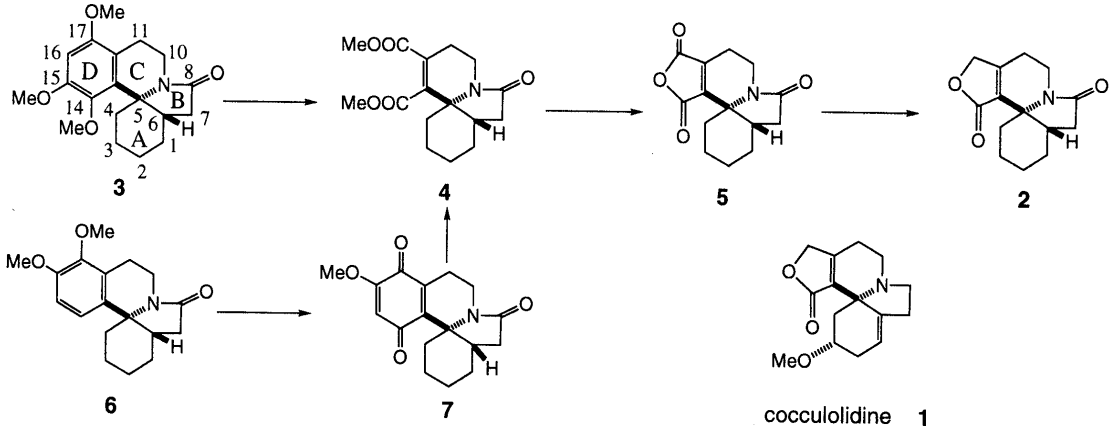

Chart 1

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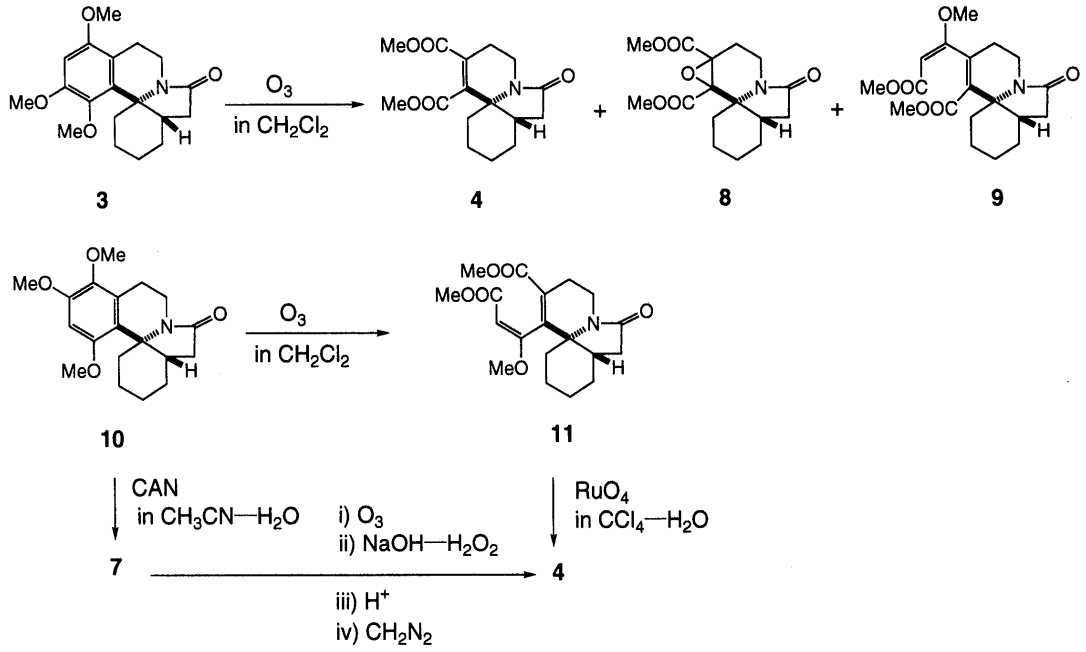


Chart 2

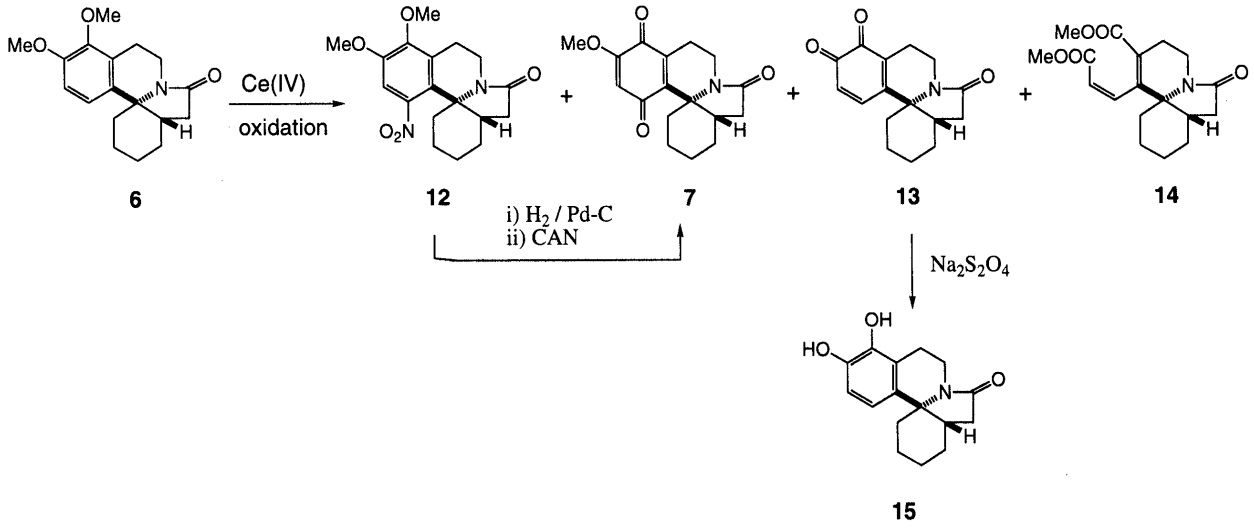


Chart 3

Table 1. Ce(IV) Oxidations of 16,17-Dimethoxy-8-oxo-*cis*-erythrinan (**6**)

Entry	Conditions					Yield (%)			
	Oxidant (eq)	Additive	Solvent	Temp.	Time	**12**	**7**	**13**	**14**
1	CAN (2.2)		AcOH–MeCN	r.t.	16 h	60	36	—	—
2	CAN (3.8)	PDCNO	MeCN–H_2O	0 °C	20 min	9	19	61	11
3	$Ce(OSO_3H)_4$ (4.4)	1 M $HClO_4$	MeCN–H_2O	r.t.	45 min	—	15	83	—
4	$Ce(OSO_2CF_3)_4$ (6.0)		AcOH	r.t.	12 h	—	89	—	—
5	$Ce(OSO_2CH_3)_4$ (6.0)		AcOH	r.t.	2 h	—	94	—	—

pound **12** was also obtained in 82% yield by nitration of **6** in AcOH and it was convertible into the *p*-quinone **7** by CAN oxidation after reduction of the nitro group to the amine. The CAN oxidation of **6** with pyridine-2,6-dicarboxylic acid *N*-oxide (PDCNO) as an additive[6] gave *o*-quinone **13** as a major product, along with the *p*-quinone **7**, the nitro compound **12**, and the seco-ester **14**[4] in the yields shown in Table 1.

Formation of the nitro compound **12** was avoided by changing the Ce(IV) ion to what does not have a nitro-ligand and has a high oxidation potential. Thus, the oxidation of **6** with cerium(IV) sulfate[7] in a 1 M perchloric acid solution gave the *p*-quinone **7** and the *o*-quinone **13** in the total yield of 98% with predominant formation of **13**. Cerium(IV) triflu-

oromethanesulfonate[8] increased the yield of *p*-quinone **7** to 89%. The best yield (94%) of *p*-quinone **7** was obtained when cerium(IV) methanesulfonate in AcOH was used as an oxidant.

Thus, the best route to **4** from **6** is the oxidation with cerium(IV) methanesulfonate to yield the *p*-quinone **7** first, which is convertible to the diester **4** in 70% yield by ozonolysis followed by peroxide oxidation.

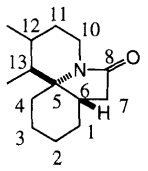
Structure Determination of Oxidation Products The structures of the above oxidation products were elucidated from their formulae and spectral data as follows. The diester **4** was described earlier.[4] The epoxide **8** had a formula $C_{16}H_{21}NO_6$, suggesting one more oxygen than **4**, and showed two methyl ester signals (δ 3.80, 3.77). In the ^{13}C-NMR spectrum, the signals of C_{12} and C_{13} were observed at δ 67.0 and 59.4, respectively, locating the epoxide ring at this position. The *p*-quinone **7** showed only one methoxy signal (at δ_H 3.81 and at δ_C 56.2). In the IR spectrum it showed the quinone carbonyls at 1680 and 1640 cm^{-1} in addition to the γ-lactam carbonyl at 1705 cm^{-1}, all of which corresponded to the carbon signals at δ 186.2, 181.3, and 176.5. The *o*-quinone **13** was a red gum and showed, in the ^{13}C-NMR spectrum, the carbonyl signals at δ 179.4 and 178.6, along with the lactam carbonyl at δ 174.2, and the ^{1}H-signal at δ 7.17 and 6.36 (each d, J=10.3 Hz). Since it was unstable and decomposed on standing in air, rigid characterization was done by converting it to the catechol derivative **15** (mp 236—238°C), which showed a ^{1}H-NMR signal corresponding to two aromatic protons at δ 6.70 (s). The seco-ester **11** was identical with the specimen previously obtained by ozonolysis.[4]

Formation of the Cocculolidine Skeleton (2) from the Diester (4) Hydrolysis of **4** with 10% HCl in 70% AcOH at 100 °C and cyclization of the resulting dicarboxylic acid **16** by heating with acetic anhydride gave the anhydride **5** almost quantitatively.

Treatment of **5** with zinc borohydride in tetrahydrofuran (THF) at room temperature gave two isomeric γ-lactones, **2** and **17**, in 31% and 11% yields, respectively. On the other hand, reduction of **5** with potassium tri-*sec*-butylborohydride (K-selectride®) gave the γ-lactone **2** as a sole product in 70% yield. The structures of **2** and **17** were firmly established on the basis of their nuclear Overhauser effect (NOE) correlation spectroscopy (NOESY) and NOE difference spectra. First, all proton signals of **2** and **17** were assigned by their H–H 2D correlated spectroscopy (COSY). Then, irradiation of a singlet at δ 4.66 (–COOC$\underline{H}_2$–) in **2** resulted in a clear NOE enhancement of the C_{11}-protons (δ 2.52, 2.28), proving that it is the compound of structure **2** (cocculolidine type). On the other hand, the NOESY spectra of **17** showed a clear correlation between the protons at δ 4.98 (dt) and δ 1.20, which are attributable to H-14α and H-3β, respectively, thus indicating the conformation **17a**,[9] but showed no correlation beween the protons at C_{14} [δ 4.98 (dt) and 4.91 (ddd)] and those at C_{11} (*ca.* δ 2.41, 2.32).

The difference in the regioselectivity depending on reducing agents in the reduction of **5** deserves some comment. Particularly, formation of the product **17** due to the reduction at the more hindered carbonyl by the zinc borohydride reduction, though to a minor extent, cannot be overlooked. Kayser *et al.*[10] reported that unsymmetrically substituted succinic anhydride **18** was reduced regioselectively at the more hindered carbonyl CO(a), when treated with sterically small hydrides such as $NaBH_4$. This was explained by an intrinsic higher reactivity of CO(a) than CO(b), as suggested by larger LUMO coefficients at CO(a) than those at CO(b). However, when the reducing agent became bulky as that of K-selectride®, the selectivity was reversed because the steric effect between the substituent and the reagent overcame the intrinsic higher reactivity of CO(a). This intrinsic higher reactivity of the carbonyl adjacent to a substituent also held for the reduction of the substituted maleic anhydride **21**, which gave **22** exclusively on reduction with $NaBH_4$. The selectivity was lower to some extent, but was not reversed for the reduction with K-selectride®, because the system is so planar that the steric effect on the reagent approach is only marginally affected by the presence or absence of neighboring methyl substituents. However, our anhydride **5** is a completely different

Table 2. ^{13}C-NMR Data for 8-Oxococculolidine Skeleton **2** and Related Compounds (in $CDCl_3$)[a]



Carbon No.	4	8	9	11	7	12	13	14	15	2	17
1	24.4[b]	24.5[b]	27.4[b]	26.0[b]	27.1[b]	29.8[b]	26.3[b]	32.0[b]	25.4[b]	25.2[b]	25.6[b]
2	23.4[b]	24.0[b]	26.8[b]	24.7[b]	21.5[b]	21.7[b]	20.9[b]	26.1[b]	19.6[b]	23.0[b]	21.7[b]
3	20.7[b]	19.8[b]	20.9[b]	20.4[b]	19.4[b]	20.9[b]	19.4[b]	24.9[b]	19.2[b]	20.0[b]	20.7[b]
4	19.5[b]	19.8[b]	19.7[b]	19.2[b]	18.4[b]	20.6[b]	18.2[b]	19.9[b]	18.4[b]	19.2[b]	19.5[b]
5	62.1	63.3	62.3	63.8	62.9	63.5	61.9	63.2	60.4	60.2	60.7
6	34.7	34.4	34.5	35.0	34.0	33.5	33.3	34.8	35.6	34.5	34.9
7	36.7[c]	34.1[c]	37.1[c]	36.0[c]	37.1[c]	38.3[c]	36.4[c]	36.3[c]	34.7[c]	36.1[c]	37.2[c]
8	174.9	171.4	175.9	174.2	176.3	176.1	174.2	173.9	171.9	170.9	171.5
10	32.1[c]	30.1[c]	33.3[c]	32.8[c]	33.0[c]	32.4[c]	32.7[c]	33.0[c]	34.0[c]	32.6[c]	32.9[c]
11	31.6[c]	30.0[c]	31.1[c]	31.1[c]	30.8[c]	31.9[c]	30.3[c]	33.0[c]	32.2[c]	32.1[c]	32.8[c]
12	146.3	67.0	139.1	143.9	146.7	131.0	150.2	145.2	132.5	159.6	162.6
13	128.5	59.4	135.7	130.7	140.2	128.2	134.0	126.4	119.3	131.6	124.2

a) Data for the other carbons are shown in the experimental section. *b*, *c*) Assignments may be interchanged in each column.

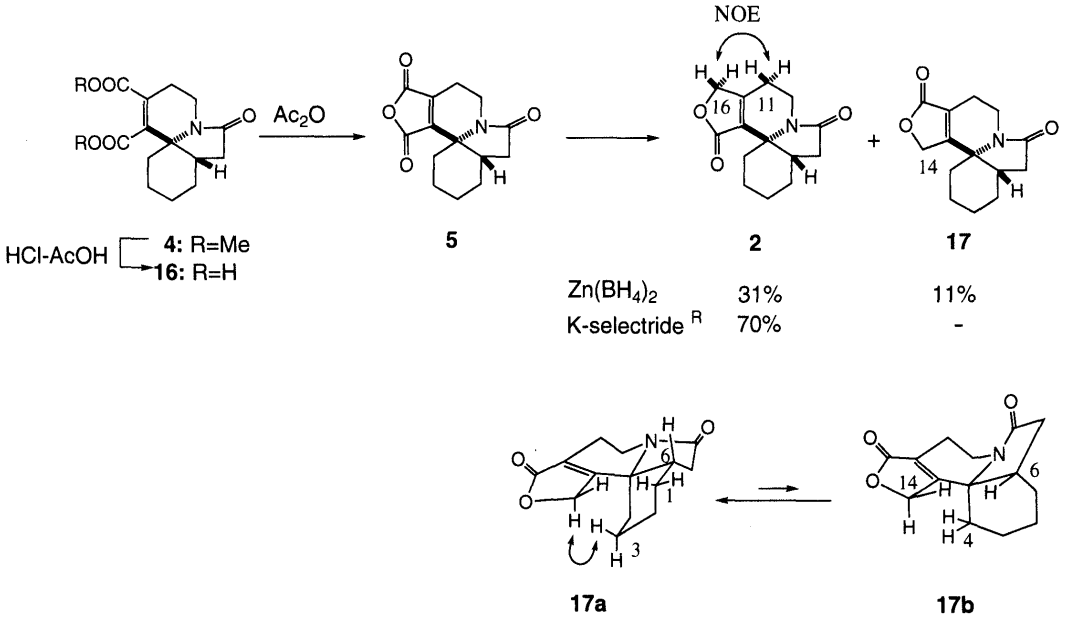


Chart 4

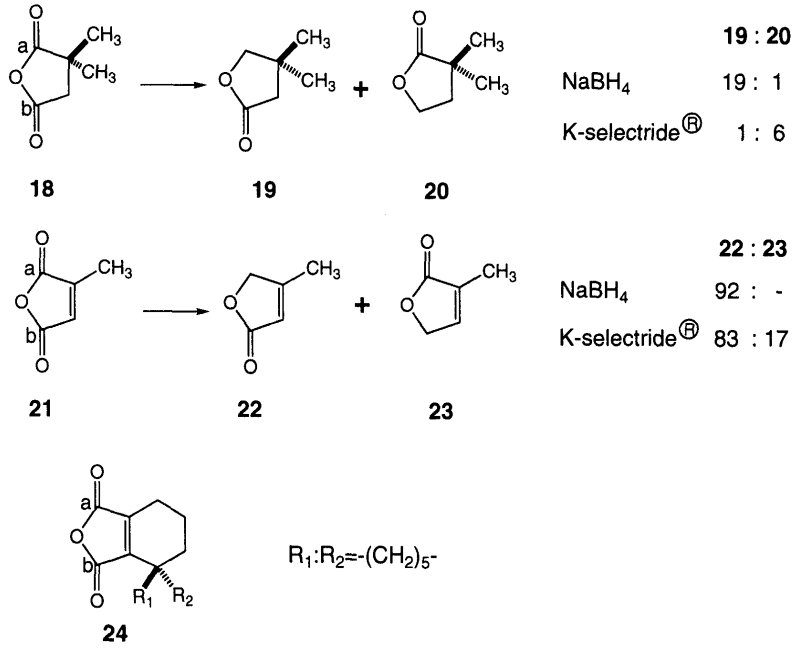


Chart 5. (by Kayser *et al.*[10])

situation: CO at C_{14} is severely hindered by the presence of two alkyl substituents (as R_1 and R_2 in **24**), while CO at C_{16} does not have such a factor. Formation of a single lactone **2** with K-selectride® indicates that this is a case where the steric effect overcomes all other factors. Formation of the lactone **17** in which the reduction occurred at the more hindered carbonyl, though to a lesser extent, by the sterically smaller reagent, zinc borohydride, suggested that CO at C_{14} is intrinsically more reactive than the CO at C_{16}, as Kayser reported,[10] since otherwise the product would be only **2**.

Experimental

Unless otherwise stated, the following procedures were adopted. Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were taken in KBr disks, recorded on a JASCO IR-810 spectrophotometer, and are given in cm^{-1}. ^1H- and ^{13}C-NMR spectra were recorded on a Hitachi R-600 (60 MHz), JOEL JNM-EX90 (90 MHz), JOEL JNM-GX270 (270 MHz) or JOEL JNM-α500 (500 MHz) spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard and are given in δ. Mass spectra (MS) and high-resolution MS (HR-MS) were determined with a JEOL JMS D-300 spectrometer and M^+ is given in *m/z*. UV spectra are given in λmax nm (log ε). Thin layer chromatography (TLC) was performed on precoated Kieselgel 60 F_{254} plates and spots were monitored by UV (254 nm), then developed by spraying 0.5% $Ce(SO_4)_2$–0.5% $(NH_4)_6Mo_7O_{24}$ in 5% H_2SO_4 and heating the plates until coloration took place. Column chromatography was performed on Wakogel C-200 (silica gel). For medium-pressure liquid chromatography (MPLC), a Kusano CPS-HS-221-1 column (silica gel, 22 mm i.d.×100 mm) was used. Ozone was generated with an ozone generator ("O-1-2", Nihon Ozone Co., Ltd.), using commercial-grade oxygen as a source. The flow rate of oxygen was 50 ml/min, and the voltage was adjusted to 80 V. All organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated to yield

the product(s).

The 8-oxoerythrinans **3**, **6**, and **10**, and their ozonolysis products **4**, **9**, **11**, and **14** were described previously.[4]

Ozonolysis of 14,15,17-Trimethoxy-8-oxo-*cis*-erythrinan (3) (1) Ozonolysis without BF_3–Et_2O:[4] The products were purified by MPLC using AcOEt–hexane (3 : 1) as an eluent to give **4** (63%) and **8** (12%). **4**: ^{13}C-NMR: 168.1, 165.9 (CO), 52.5, 52.3 (OMe). **8**: mp 119—121 °C (AcOEt–hexane). IR: 1750, 1740, 1690. ^{1}H-NMR: 3.80, 3.77 (each 3H, s, OMe), 2.66—2.46 (1H, m), 2.38—2.18 (4H, m), 2.05—1.92 (2H, m), 1.90—1.73. (2H, m), 1.70—1.45 (8H, m), 1.28—1.10 (3H, m). ^{13}C-NMR: 167.8, 166.5 (CO), 53.1, 52.8 (OMe). HR-MS: Calcd for $C_{16}H_{21}NO_6$: 323.1369. Found: 323.1399.

(2) Ozonolysis with BF_3–Et_2O:[4] MPLC of the product gave **4** (48%), **9** (22%) and the starting material **5** (3%). **9**: ^{13}C-NMR: 170.6 (=C–OMe), 166.7, 166.4 (CO), 92.1 (=C–H), 56.2, 51.5, 50.9 (OMe).

Ozonolysis of 14,16,17-Trimethoxy-8-oxo-*cis*-erythrinan (10)[4] MPLC of the product gave **11** (76% from ozonolysis with BF_3–Et_2O and 47% from ozonolysis without BF_3–Et_2O). **11**: ^{13}C-NMR: 173.8 (=C–OMe), 168.7, 166.4 (CO), 94.2 (=C–H), 56.2, 51.9, 51.0 (OMe).

RuO_4 Oxidation of 11 A ruthenium tetroxide solution was prepared from $NaIO_4$ (4.2 g) and RuO_2 (0.4 g) in CCl_4 (50 ml).[5] This solution was added to **11** (100 mg, 0.25 mmol) in CCl_4 (20 ml) and the mixture was stirred at room temperature for 14 h. The excess ruthenium tetroxide was destroyed by addition of 2-propanol. The mixture was then filtered and the CCl_4 layer separated. MPLC of the product gave **4** (14 mg, 17%) and the starting material **11** (29 mg, 29%).

CAN Oxidation of 14,16,17-Trimethoxy-8-oxo-*cis*-erythrinan (10) CAN (360 mg, 2.2 mol eq) was added to a solution of **10** (100 mg, 0.3 mmol) in MeCN (1.4 ml)–H_2O (0.5 ml) and the mixture was stirred at 0 °C for 10 min, then extracted with CH_2Cl_2. MPLC of the product with AcOEt gave the *p*-quinone **7** (36 mg, 40%) as pale yellow prisms from Et_2O, mp 158–160 °C. IR: 1705, 1680, 1640, 1600. UV (EtOH): 274 (4.43). ^{1}H-NMR: 5.82 (1H, s, olefinic H), 4.42—4.21 (1H, m), 3.81 (3H, s, OMe), 3.10—1.26 (14H, m). ^{13}C-NMR: 186.2, 181.3 (CO), 158.0 (=C-OMe), 108.0 (=C–H), 56.2 (OMe). *Anal.* Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.72, H, 6.45, N, 4.47. MS: 301 (M^+). HR-MS: Calcd for $C_{17}H_{19}NO_4$: 301.1315. Found: 301.1327.

Cerium(IV) Methanesulfonate A solution of CAN (71.24 g) in H_2O (208 ml) was added to a stirred solution of K_2CO_3 (45 g) in H_2O (248 ml). The yellow precipitates were collected and washed with H_2O. The wet precipitate was dissolved in methanesulfonic acid (50 g), and the mixture was concentrated *in vacuo* to give yellow crystals, which were dried at 70 °C for 10 h. This compound contained 3.8 mole of MsOH per one mole of Ce as indicated by titration with 0.1 M NaOH.

Ce(IV) Oxidation of 16,17-Dimethoxy-8-oxo-*cis*-erythrinan (6) (1) With CAN: A solution of CAN (603 mg, 2.2 mol eq) in MeCN (3 ml) was added to a solution of **6** (150 mg, 0.5 mmol) in AcOH (12 ml) and the mixture was stirred at room temperature for 16 h. The mixture was diluted with CH_2Cl_2 and the insoluble material was filtered off. The filtrate was washed with dilute NH_4OH and brine successively. MPLC of the product gave **12** (104 mg, 60%) and **7** (54 mg, 36%). **12**: Pale yellow prisms from AcOEt–hexane, mp 140—141°C. IR: 1715, 1520. ^{1}H-NMR: 7.01 (1H, s, Ar-H), 4.35—4.18 (1H, m), 3.87, 3.85 (each 3H, s, OMe), 3.38—1.33 (14H, m). ^{13}C-NMR: 150.7, 149.8, 144.5 (2x=C–OMe, =C–NO_2), 107.2 (=C–H), 60.1, 56.0 (OMe). MS: 346 (M^+). HR-MS: Calcd for $C_{18}H_{22}N_2O_5$: 346.1529. Found: 346.1547.

(2) With CAN+PDCNO: A solution of CAN (1.205 g, 4.4 mol eq) in MeCN–H_2O (1 : 1, 5 ml) was added dropwise to the suspended mixture of **6** (150 mg, 0.5 mmol) and PDCNO (229 mg, 2.5 mmol) in MeCN–H_2O (2 : 1, 10 ml) at 0 °C. The mixture was stirred at the same temperature for 20 min, then diluted with H_2O, and extracted with CH_2Cl_2. MPLC of the product gave **12** (14 mg, 9%), **7** (29 mg, 19%), **13** (82 mg, 61%), and **14** (19 mg, 11%). **13**: Red gum. ^{1}H-NMR: 7.17, 6.36 (each 1H, d, J=10.3 Hz, olefinic H), 4.39—4.15 (1H, m, H-10), 3.12—2.79 (1H, m, H-10), 2.56—1.25 (13H, m). ^{13}C-NMR: 179.4, 178.6 (CO), 138.5, 128.1 (=C–H). **14**:[4] ^{13}C-NMR: 168.0, 165.5 (CO), 141.5, 122.5 (=CH), 51.7, 51.5 (OMe).

(3) With $Ce(OSO_3H)_4$: A solution of $Ce(OSO_3H)_4$ (1.548 g, 4.4 mol eq) in 1 M $HClO_4$ (30 ml) was added to **6** (200 mg, 0.67 mmol) in MeCN (20 ml), and the mixture was stirred at room temperature for 45 min. The mixture was diluted with CH_2Cl_2 and the insoluble material was filtered off. The filtrate was washed with brine and H_2O successively. MPLC of the product gave **7** (30 mg, 15%) and **13** (150 mg, 83%).

(4) With $Ce(OSO_2CF_3)_4$: $Ce(OSO_2CF_3)_4$ (2.208 g, 6.0 mol eq) was added to a solution of **6** (150 mg, 0.5 mmol) in AcOH (12 ml) and the mixture was stirred at room temperature for 14 h. The mixture was diluted with CH_2Cl_2 and the insoluble material was filtered off. The filtrate was washed with brine and H_2O successively. MPLC of the product gave **7** (133 mg, 89%).

(5) With $Ce(OSO_2CH_3)_4$: $Ce(OSO_2CH_3)_4$ (1.56 g, 6.0 mol eq) was added to a solution of **6** (150 mg, 0.5 mmol) in AcOH (12 ml) and the mixture was stirred at room temperature for 20 min, then worked up as in (4). MPLC of the product gave **7** (141 mg, 94%).

Nitration of 16,17-Dimethoxy-8-oxo-*cis*-erythrinan (6) 17 N Nitric acid (8 ml) was added to a solution of **6** (1.013 g, 3.4 mmol) in AcOH (16 ml) and the mixture was stirred at room temperature for 15 min. The mixture was diluted with CH_2Cl_2, washed with saturated Na_2CO_3 solution, and concentrated. The product was purified by column chromatography and crystallizations to give **12** (958 mg, 82%).

Transformation of the Nitro Compound (12) to the *p*-Quinone (7) Compound **12** (2.0 g, 5.78 mmol) in EtOH (100 ml) was hydrogenated over 10% Pd–C (1 g) at room temperature for 8 h. Removal of the catalyst and solvent left 14-amino-16,17-dimethoxy-8-oxo-*cis*-erythrinan (1.794 g, 98%) as a colorless oil. This compound (60 mg, 0.19 mmol) was oxidized with CAN (312 mg, 3 mol eq) in THF (30 ml)–H_2O (5 ml) for 20 min. The mixture was concentrated and extracted with CH_2Cl_2. MPLC of the product with AcOEt gave **7** (36 mg, 63%).

The Catechol (15) from the *o*-Quinone (13) Sodium hydrosulfite (1.93 g, 20 mol eq) in water (10 ml) was added to a solution of crude *o*-quinone (150 mg, 0.55 mmol) in dioxane (9 ml) and the mixture was stirred at room temperature for 5 min, then poured into water (50 ml) and extracted with $CHCl_3$. Removal of the solvent gave a crystalline residue, which was recrystallized from AcOEt to give 16,17-dihydroxy-8-oxo-*cis*-erythrinan **15** (112 mg, 74%) as colorless prisms, mp 236—238 °C. IR: 3370, 1735. ^{1}H-NMR: 6.70 (2H, s, Ar-H), 4.49—4.34 (1H, m, H-10), 3.40—3.07 (1H, m, H-10), 2.93—1.58 (13H, m). ^{13}C-NMR: 141.3, 140.7 (CO), 113.3, 111.2 (=C–H). MS: 273 (M^+). HR-MS: Calcd for $C_{16}H_{19}NO_3$: 273.1364. Found: 273.1344.

Transformation of *p*-Quinone Derivative (7) to the Diester (4) A solution of **7** (98 mg, 0.33 mmol) in CH_2Cl_2 (30 ml) was ozonized at −78 °C for 10 min. After removing the excess ozone by suction with a water aspirator, MeOH (8.5 ml), 10% NaOH (1.8 ml), and 30% H_2O_2 (1.8 ml) were added to the solution, and the mixture was stirred for 10 min, then carefully acidified with 10% HCl and extracted with $CHCl_3$ to give the oily product. It was treated with ethereal diazomethane and the product was purified by MPLC with AcOEt–hexane (2 : 1) to give **4** (70 mg, 70%) as a colorless oil.

Conversion of the Diester (4) to the Anhydride (5) The diester **4** (0.45 g, 1.47 mmol) was heated with 70% AcOH (30 ml) and 10% HCl (10 ml) at 100 °C for 18 h. The mixture was concentrated under reduced pressure. The residual oil was dissolved in CH_2Cl_2 and extracted with 10% NaOH. The aqueous layer was acidified with 10% HCl and extracted with $CHCl_3$. Removal of the solvent gave a crystalline residue, which was recrystallized from AcOEt–Et_2O to give the diacid **16** (0.33 g, 81%) as colorless prisms, mp 107—109 °C. IR: 1718, 1690.

The diacid **16** (0.33 g, 1.18 mmol) in acetic anhydride (20 ml) was heated at 110 °C for 14 h. Removal of the solvent gave **5** as an oil. IR ($CHCl_3$): 1850, 1775, 1688.

Reduction of the Anhydride (5) (1) With $Zn(BH_4)_2$: A solution of zinc borohydride (631 mg, 6.67 mmol) in THF (6 ml) was added dropwise to a solution of compound **5** (330 mg, 1.27 mmol) in THF (2 ml) and the mixture was stirred at room temperature for 14 h. The reaction was quenched with 18% HCl. After stirring the mixture at room temperature for 2 h, it was acidified with 18% HCl and extracted with $CHCl_3$. The product was separated by MPLC using AcOEt–1% MeOH as an eluent to give **2** (31% from **4**) and **17** (11% from **4**).

2: Amorphous. mp 92—95 °C (AcOEt–MeOH) (oil in ref. 2). IR ($CHCl_3$): 1759, 1680. UV (MeOH): 213 (3.99). ^{1}H-NMR: 4.66 (2H, s, H-16), 4.25 (1H, dd, J=13.5, 7.5 Hz, H-10), 2.93 (1H, ddd, J=13.5, 11.0, 5.0 Hz, H-10), 2.52 (1H, ddd, J=18.5, 11.0, 7.5 Hz, H-11), 2.50 (1H, m, H-6), 2.31 (1H, dd, J=12.0, 8.0 Hz, H-7), 2.28 (1H, dd, J=18.5, 5.0 Hz, H-11), 2.26 (1H, dd, J=12.0, 9.0 Hz, H-7), 2.17 (1H, m, H-1), 1.93 (1H, m, H-3), 1.91 (1H, ddd, J=13.5, 9.0, 3.5 Hz, H-4), 1.68 (1H, m, H-3), 1.57 (1H, m, H-4), 1.52 (2H, m, H-2), 1.44 (1H, m, H-1). ^{13}C-NMR: 174.6 (CO), 71.0 (CH_2). *Anal.* Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 67.83, H, 6.91, N, 5.54. HR-MS: Calcd for $C_{14}H_{17}NO_3$: 247.1201. Found: 247.1207.

17: mp 207—209 °C (AcOEt–MeOH). IR: 1750, 1690. UV (MeOH): 206 (4.19). ^{1}H-NMR: 4.98 (1H, dt, J=17.1, 2.8 Hz, H-14), 4.91 (1H, ddd, J=17.1, 3.4, 1.7 Hz, H-14), 4.36 (1H, dd, J=13.5, 6.5 Hz, H-10), 2.88 (1H, m, H-10), 2.56 (1H, dd, J=18.6, 14.3 Hz, H-7), *ca.* 2.41 (1H, m, H-11), *ca.* 2.37 (2H, m, H-6, 7), *ca.* 2.32 (1H, m, H-11), 2.14 (1H, dt, J=14.0, 3.5 Hz,

H-4), 1.92 (1H, d, J=14.3 Hz, H-1), 1.82 (1H, dt, J=15.0, 4.0 Hz, H-3), 1.69 (1H, m, H-2), 1.67 (1H, m, H-4), 1.59 (1H, m, H-1), 1.50 (1H, m, H-2), 1.20 (1H, m, H-3). ^{13}C-NMR: 172.2 (CO), 69.9 (CH_2). *Anal.* Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 67.85, H, 7.05, N, 5.45. HR-MS: Calcd for $C_{14}H_{17}NO_3$: 247.1201. Found: 247.1203.

(2) With K-selectride®: 0.5 M Solution of K-selectride® in THF (27 ml) was added dropwise to a solution of the anhydride **5** (105 mg, 0.4 mmol) in THF (13 ml) at −78 °C under N_2 atmosphere and the mixture was stirred at the same temperature for 2 h. The reaction was quenched with 4 N NaOH (0.3 ml) and 30% H_2O_2 (0.4 ml). After stirring the mixture for 14 h at room temperature, it was acidified with 18% HCl and extracted with $CHCl_3$ to give an oily product, which was purified by MPLC using AcOEt–1% MeOH as an eluent to yield the lactone **2** (85 mg, 70% from **4**).

Acknowlegdgements We thank Prof. Emeritus T. Kikuchi and Prof. S. Kadota, Toyama Medical and Pharmaceutical University, for the measurement of the COSY and NOE difference spectra.

References and Notes

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