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Selective Cleavage of Aromatic Rings by Ozonolysis. I. Application to *o*-Dimethoxybenzene Derivatives

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Ozonolytic cleavage of *o*-dimethoxybenzene derivatives to dimethyl *Z,Z*-muconates is satisfactorily controlled by the addition of boron trifluoride etherate as a regulator. By this oxidation, 3,4-dimethoxybenzyl alcohol gave an α-pyrone derivative (**6**) and erythrinan derivatives gave D-seco-erythrinans in appreciable yields.

Keywords——ozonolysis; ozone; boron trifluoride etherate; *o*-dimethoxybenzene derivative; aromatic ring cleavage; dimethyl *Z,Z*-muconate; α-pyrone; erythrinan; D-seco-erythrinan

Oxidative cleavage of phenolic compounds, particularly catechols, by enzymes is widely observed in nature, and represents an important pathway in the biosynthesis of non-aromatic compounds from aromatic compounds. The reaction is classified into two types[1]; an intradiol type (I) and an extradiol type (II). Pyrocatechase oxidizes catechols by route I giving rise to muconic acid derivatives and *meta*-pyrocatechase cleaves the same substrate by route II to give compounds which possess three different oxygenated functional groups.

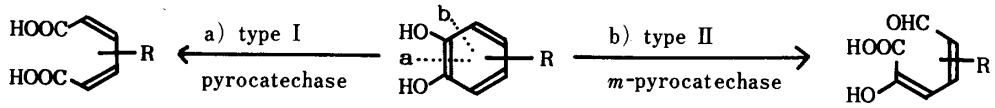

Chart 1

Oxidation of catechol to monomethyl muconate with molecular oxygen in methanol with presence of cuprous chloride and pyridine is a non-enzymatic model of pyrocatechase.[2] An analogous entry can be achieved by using peracids.[3]

Ozone is the reagent that makes the above reaction chemically feasible. It decomposes phenolic compounds extensively, so that the reaction is seldom used for synthetic purposes except for complete degradation of the phenolic moiety, such as for structure determinations. However, for *o*-dialkoxybenzene derivatives it cleaves the aromatic ring first at the position between two alkoxy groups as in the intradiol-type reaction (I) giving rise to muconate derivatives. Examples can be seen in the ozonolysis of dihydrocodeine (**1**) to the lactone (**2**)[4] and in the elegant total synthesis of strychnine [**3**→**4**] by Woodward's group.[5] This reaction, as suggested by Woodward, if well applied to various aromatic compounds, may provide an attractive synthetic method for terminally functionalized conjugated *Z,Z*-dienes which are otherwise hardly accessible. However, it is generally difficult to control the reaction at the stage of muconate, because the muconate is susceptible to further ozonolysis. In fact, the yield of the muconate from *o*-dimethoxybenzene derivatives is low.

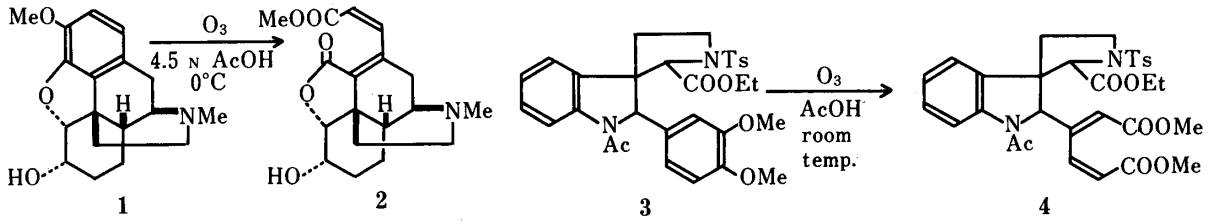

Chart 2

Some work on the control of ozonolysis of non-aromatic double bonds has been reported. Slomp, Jr. and Johnson[6] cleaved an isolated double bond while leaving a conjugated ketone intact by ozonization in the presence of pyridine, showing that the reactivity of ozone is reduced by pyridine or pyridine oxide. Veysoglu *et al.*[7] used appropriate ozonizable dyes as internal indicators for selective cleavage of dienoic acid derivatives. However, to our knowledge, no report on the control of ozonolysis of aromatic compounds has appeared.

In this paper we wish to report that the ozonolytic cleavage of *o*-dimethoxybenzenes to muconates is well regulated by addition of boron trifluoride etherate as a regulator. This is shown by the following example.

Ozonolysis of 3,4-dimethoxybenzyl alcohol (**5**) in CH_2Cl_2 at $-78\,^{\circ}C$ without the regulator gave the pyrone (**6**) in 20% yield. The structure of **6** was determined from the spectral data (see Experimental). The yield of **6** increased on addition of a Lewis acid to the medium, the best result being obtained when the ozonolysis was carried out in the presence of 1—3 mol eq of BF_3–Et_2O. Then the yield reached to 54%. A protonic acid such as *p*-toluenesulfonic acid had no effect. In acetic acid (in this case the reaction temperature could not be lowered because of solidification) under Woodward's conditions[5a] the result was again unsatisfactory.

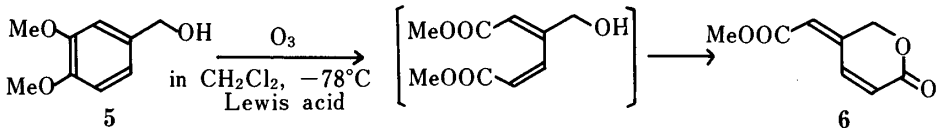

Chart 3

The other examples are collected in Table II. Most of them, in ozonolysis in the presence of BF_3–Et_2O, gave satisfactory yields of muconate derivatives.

It should be noted that 3,4-dimethoxytoluene (**7**) gave the dimethyl muconate (**8**) of (2*Z*,4*Z*)-configuration. The structure was proved as follows. Elvidge *et al.*[8a] obtained (2*Z*,4*E*)-3-methyl muconic acid (**9**) in minute amount together with the γ-lactone (**14**) by a

TABLE I. Ozonolysis of 3,4-Dimethoxybenzyl Alcohol (**5**)[a]

Entry	Regulator	Yield of **6** (%)	Entry	Regulator	Yield of **6** (%)
1	None	20	7	$TiCl_4$ (1 eq mol)	Trace
2	BF_3–Et_2O (1 eq mol)	54	8	$ZnCl_2$ (1 eq mol)	Trace
3	BF_3–Et_2O (3 eq mol)	54	9	TsOH (1 eq mol)	Trace
4	BF_3–Et_2O (10 eq mol)	Trace	10	98% AcOH[b]	Trace
5	$SnCl_4$ (1 eq mol)	40	11	4.5 N AcOH[c]	27
6	$FeCl_3$ (1 eq mol)	29			

a) Reaction conditions: in CH_2Cl_2 at $-78\,^{\circ}C$ for 20 min, except for entries 10 and 11. *b*) At 15 °C, 20 min.[5a] *c*) At 0 °C, for 80 min.[4a]

peracid oxidation of 3,4-dihydroxytoluene (**13**). Treatment of **8** with 10% NaOH at room temperature gave the (2*Z*,4*E*)-acid (**9**), identical with Elvidge's sample. Methylation of this with CH_2N_2 gave the (2*Z*,4*E*)-dimethyl ester (**10**) which was apparently different from **8**. Treatment of **8** with 20% NaOH under reflux gave the (2*E*,4*E*)-acid (**11**) (mp 230 °C) as expected. Methylation of **11** with CH_2N_2 gave the (2*E*,4*E*)-dimethyl ester **12** (mp 53—55 °C).[8a] In the nuclear magnetic resonance (NMR) spectra, the dimethyl ester (**8**) showed the coupling constant between H_b and H_c as $J=12.1$ Hz, while the corresponding coupling constants in the (2*Z*,4*E*)- and (2*E*,4*E*)-dimethyl esters were 16.0 and 15.7 Hz, respectively. This confirms that our dimethyl ester (**8**) is of (2*Z*,4*Z*)-configuration. Elvidge *et al.*[8b] reported

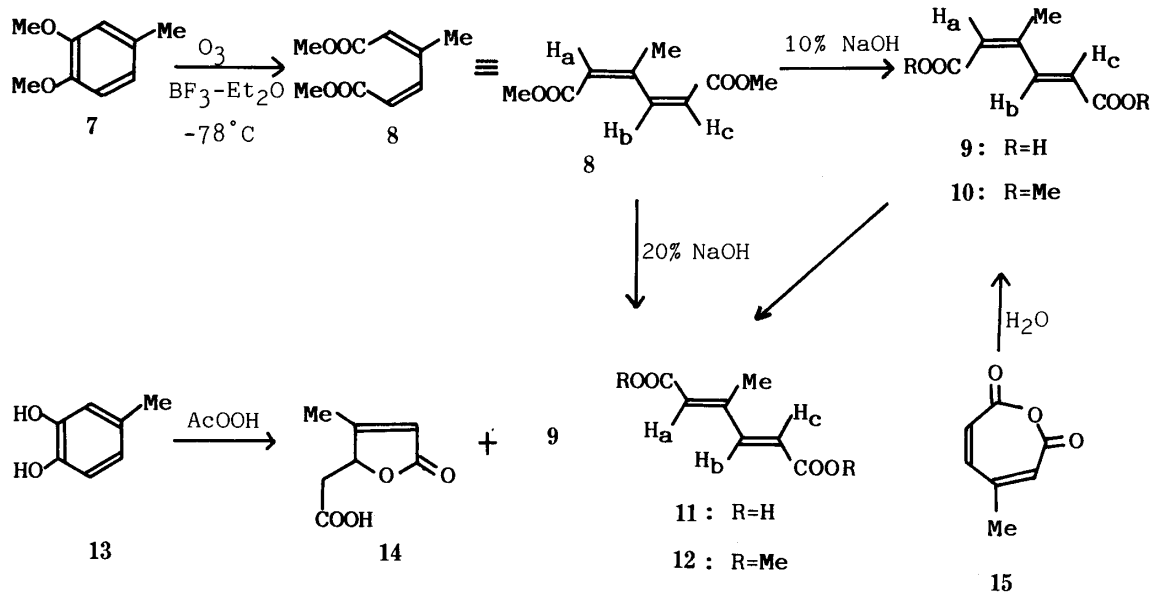

Chart 4

TABLE II. Ozonolysis of *o*-Dimethoxybenzene Derivatives

Entry	Starting material	Reaction conditions		Yield of products (%)			
		Regulator[a]	Time (min)[b]				
1	**5**	A	20	**6**	20		
2	**5**	B	20	**6**	54		
3	**7**	B	20	**8**	49		
4	**16**	B	240	—	—		
5	**17**	B	20	**18**	66		
6	**19**	A	20	**20**	45		
7	**19**	B	20	**20**	78		
8	**21**	A	20	**22**	8		
9	**21**	B	20	**22**	66		
10	**23**	A	20	**24**	47		
11	**23**	B	20	**24**	76		
12	**25**	A	90	**27**	63		
13	**25**	B	90	**26**	22	**27**	48
14	**28**	A	40	**29**	33	**30**	15
15	**28**	B	80	**29**	23	**30**	14
16	**32**	A	240	**33**	34	**34**	7
17	**32**	B	240	**33**	39	**34**	8

a) A: without regulator. B: with BF_3–Et_2O (1 eq mol) as a regulator. *b*) Reaction time for 1 mmol of a starting material.

an attempted preparation of the (2*Z*,4*Z*)-acid. However, when the anhydride (**15**) obtained by a peracid oxidation of 4-methyl-1,2-benzoquinone was treated with water, it immediately isomerized into the (2*Z*,4*Z*)-acid (**9**). Therefore, our preparation seems to be the first example of a stable derivative of the (2*Z*,4*Z*)-isomer.

Introduction of an electron-withdrawing group on the aromatic ring retards the ozonolytic cleavage. In the case of dihydroisocarbostyril (**16**), the starting material was recovered unchanged after 60 min of oxidation. Further ozonization produced profound decomposition of the compound as indicated by the complex spots on thin layer chromatography (TLC). In contrast to this, the seven-membered lactam (**17**) gave the desired diester (**18**) in 66% yield after 20 min of oxidation. Apparently the skewed conformation of this molecule reduces the degree of conjugation of the lactam carbonyl to the aromatic ring. Therefore the electron density on the aromatic ring of this compound is not so much lowered as that of **16**.[9]

More complex molecules such as erythrinans (**19** and **21**) also gave the expected D-seco-erythrinans (**20** and **22**, respectively), in appreciable yields by this modified method.

For trimethoxybenzene derivatives, ozonolytic cleavage again took place at the position between two adjacent methoxy groups and gave the muconate carrying a methoxy group. Thus 14,16,17-trimethoxy-8-oxoerythrinan (**23**) gave the diester (**24**) in 76% yield. In the reaction without the regulator the yield was decreased to 47%. The 14,15,17-trimethoxy derivative (**25**) gave the expected diester (**26**) in 22% yield together with a further degradation

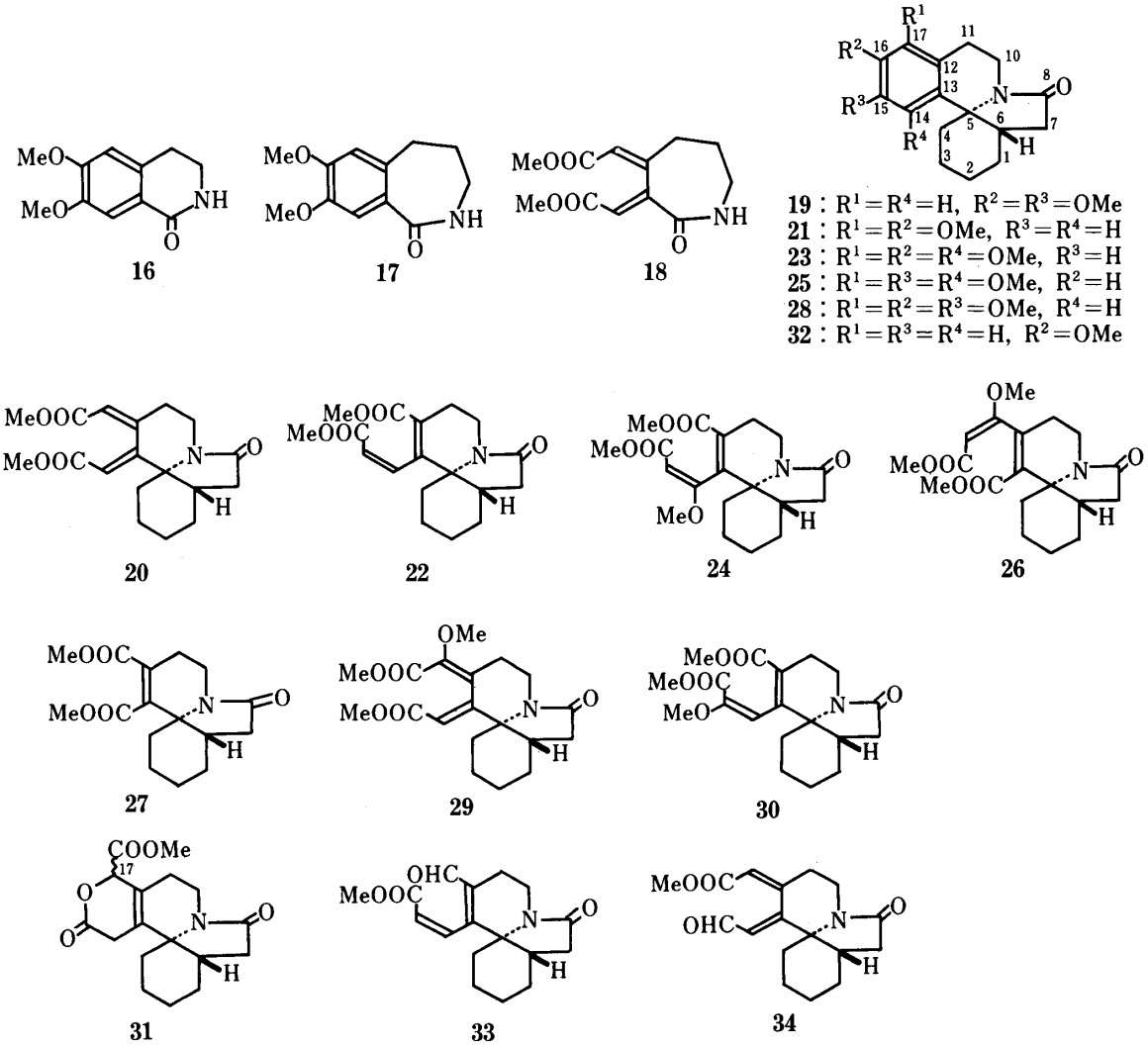

Chart 5

product (**27**) (48%) and the starting material (3%). This compound, when ozonized without BF_3–Et_2O, afforded only **27** in 63% yield. The 15,16,17-trimethoxyerythrinan (**28**) was an exception, giving two muconate derivatives (**29** and **30**) in 33% and 15% yields with ozone only. Addition of BF_3–Et_2O retarded consumption of the starting material and reduced the yields of **29** and **30** to 23% and 14%, respectively. A better result was obtained in ozonization in the presence of K_2CO_3, wherein the yields of **29** and **30** were 43% and 12%, respectively.

The structures of **29** and **30** were elucidated by transformation of the major product **29** into the δ-lactone **31** in four steps (acid hydrolysis, hydride reduction, acid cyclization, and esterification); the C_{17}-proton signal of **31** appeared as a broad singlet.[10]

For ozonolysis of monomethoxyerythrinan derivative, a longer reaction time was required (until all the starting material was consumed as determined by TLC). Thus, 16-methoxy-8-oxoerythrinan (**32**) gave, after 4 h of oxidation, two aldehyde esters **33** and **34** in 34% and 7% yields with ozone alone. The yields were not improved by addition of BF_3–Et_2O (39% for **33** and 8% for **34**). The structures of **33** and **34** are based on their ^{1}H-NMR spectra, in which **33** exhibited the aldehyde proton as a singlet at δ 9.74 and **34** showed it at δ 9.68 as a doublet (J = 7.8 Hz).

We consider that the mechanism of regulation of the oxidation by BF_3–Et_2O may be as follows. BF_3–Et_2O may coodinate to the double bond of the muconate, thus reducing the electron density of the double bond and suppressing further attack by ozone. Wibaut *et al.*[11] reported that ozone and gaseous boron trifluoride form a complex which enhances the electrophilicity of ozone, thus producing profound oxidation of aromatic rings. However, their reagent and the experimental conditions are apparently different from ours. In our case, the already coordinated BF_3, *i.e.* BF_3–Et_2O may have little ability to coordinate to ozone.

The present paper indicates that ozonolytic cleavage of *o*-dimethoxybenzene derivatives can be satisfactorily controlled by the addition of boron trifluoride etherate, giving the product at the stage of dimethyl muconate. This modified ozonolytic cleavage of aromatic rings will be extremely useful in the synthesis of complex molecules such as natural products. Applications to simple trimethoxybenzene derivatives will be reported in a separate paper.

Experimental

Melting points were determined on a Yanagimoto model MP apparatus and are uncorrected. Infrared (IR) spectra were taken with a Jasco IR-810 spectrophotometer and are given in cm^{-1}. Ultraviolet (UV) spectra were obtained in methanol with a Hitachi U-3200 spectrophotometer. Absorption maxima are given in nm and ε values are given in parenthesis. ^{1}H- and ^{13}C-NMR spectra were recorded on a Hitachi R-600 spectrometer and/or a JEOL FX-100 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard and are given in δ. High-resolution mass spectra (HRMS) were determined with a JEOL JMS D-300 spectrometer. The termination of the ozonolytic reaction was determined as the time at which the starting material was no longer detectable on a thin layer chromatoplate. For preparative high-performance liquid chromatography (HPLC), a Kusano CPS-HS-221-1 column (silica gel, 22 mm i.d. × 100 mm) was used.

Ozonolysis of *o*-Dimethoxybenzene Derivatives. General Procedure——Ozone was generated with an ozone generator ("0-1-2", 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. Ozonized oxygen was passed into a solution of the dimethoxybenzene derivatives (1.0 mmol) and BF_3–Et_2O (148 mg, 1.0 mmol) in CH_2Cl_2 (30 ml) at −78 °C until the starting material disappeared on TLC. The excess ozone was removed by suction with a water aspirator. The reaction mixture was washed with water, dried over anhydrous Na_2SO_4 or $MgSO_4$, and concentrated to dryness. The residue was purified by chromatography and/or by crystallization.

Ozonolysis of 3,4-Dimethoxybenzyl Alcohol (5)——i) With BF_3–Et_2O: Ozonized oxygen was passed into a CH_2Cl_2 (30 ml) solution of **5** (168 mg, 1.0 mmol) and BF_3–Et_2O (142 mg, 1.0 mmol) with stirring at −78 °C for 20 min. The product was purified by passing it through a short column of silica gel with hexane–AcOEt (2:1). Evaporation of the solvent and crystallization of the residue from ethyl acetate gave 5,6-dihydro-5*E*-(methoxycarbonylmethylene)-2-pyrone (**6**) (91 mg, 54%), mp 85—87 °C. IR (Nujol): 1720, 1590. ^{1}H-NMR: 8.33 (1H, dd, J = 10.2 and 0.6 Hz, olefinic H), 6.18 (1H, d, J = 10.2 Hz, olefinic H), 5.93 (1H, m, olefinic H), 5.20 (2H, d, J = 1.8 Hz), 3.79 (3H, s, OCH_3). ^{13}C-NMR: 51.8 (q, OCH_3), 70.3 (t, O–CH_2), 118.8 (d, =CH), 123.6 (d, =CH), 138.1 (s,

=C<), 140.9 (d, =CH), 162.1 (s, C=O), 164.8 (s, C=O). *Anal.* Calcd for $C_8H_8O_4$: C, 57.14; H, 4.80. Found: C, 56.94; H, 4.67. HRMS *m/z*: Calcd for $C_8H_8O_4$: 168.0420. Found 168.0385.

ii) Without a Regulator: Compound **5** (168 mg, 1.0 mmol) in CH_2Cl_2 (30 ml) was ozonized for 20 min as above without addition of BF_3–Et_2O. Work-up of the reaction mixture as described above gave **6** (34 mg, 20%).

iii) In 4.5 N AcOH Solution: A solution of **5** (166 mg, 1.0 mmol) in 4.5 N AcOH (10 ml) was ozonized at 0 °C with a stream of ozonized oxygen. After 80 min, the reaction mixture was brought to pH 6 by addition of solid $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was washed with water, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by passing it through a short silica gel column with hexane–AcOEt (2 : 1) to give **6** (45 mg, 27%).

Ozonolysis of 3,4-Dimethoxytoluene (7)——3,4-Dimethoxytoluene was ozonized as described in the general procedure to give dimethyl (2*Z*,4*Z*)-3-methyl-2,4-hexadienedioate (**8**) in 49% yield, as an oil. IR ($CHCl_3$): 1720, 1610. ^{1}H-NMR: 7.13 (1H, d, J=12.1 Hz, olefinic H_b), 5.88 (1H, d, J=12.1 Hz, olefinic H_c), 5.79 (1H, br s, olefinic H_a), 3.70 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 2.08 (3H, d, J=1.2 Hz, CH_3). ^{13}C-NMR: 23.5 (q, CH_3), 51.1 (q, OCH_3), 51.4 (q, OCH_3), 117.7 (d, =CH), 119.6 (d, 2× =CH), 145.1 (d, =CH), 153.2 (s, =C<), 165.8 (s, C=O), 166.1 (s, C=O). MS *m/z*: 184 (M^+).

Isomerization of 8 with NaOH——Treatment of **8** with 10% NaOH: A solution of **8** (55 mg) in 10% NaOH (5 ml) was stirred at room temperature for 1 h and acidified (Congo-red) with concentrated hydrochloric acid. The precipitated (2*Z*,4*E*)-3-methyl-2,4-hexadienedioic acid (25 mg, 50%) was crystallized from ethanol as needles. mp 170—172 °C (lit. mp *ca.* 170 °C or 178—179 °C).[8a] The acid (**9**) was treated with ethereal diazomethane to give dimethyl (2*Z*,4*E*)-3-methyl-2,4-hexadienedioate (**10**) as an oil. IR ($CHCl_3$): 1720, 1635, 1605. ^{1}H-NMR: 8.62 (1H, d, J=16.0 Hz, olefinic H_b), 6.17 (1H, d, J=16.0 Hz, olefinic H_c), 5.94 (1H, br s, olefinic H_a), 3.79 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 2.04 (3H, d, J=1.2 Hz).

Treatment of **8** with 20% NaOH: A solution of **8** (125 mg, 0.7 mmol) in 20% NaOH was heated at 120 °C in a sealed tube for 5 h. On acidification of the solution with concentrated hydrochloric acid, (2*E*,4*E*)-3-methyl-2,4-hexadienedioic acid (**11**) was obtained as needles, mp 220—225 °C (lit. mp 223—227 °C),[8a] which on esterification with diazomethane gave dimethyl (2*E*,4*E*)-3-methyl-2,4-hexadienedioate (**12**), as fine needles from aqueous methanol, mp 55—56 °C (lit. mp 55—56 °C).[8a] IR (KBr): 1720, 1615. ^{1}H-NMR: 7.29 (1H, d, J=15.7 Hz, olefinic H_b), 6.21 (1H, d, J=15.7 Hz, olefinic H_c), 6.04 (1H, br s, olefinic H_a), 3.79 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 2.30 (3H, d, J=1.2 Hz).

Attempted Ozonolysis of 6,7-Dimethoxy-3,4-dihydroisocarbostyril (16)——Treatment of **16** (207 mg, 1.0 mmol) and BF_3–Et_2O (142 mg, 1.0 mmol) in CH_2Cl_2 (30 ml) with O_3 for 60 min at −78 °C was recovered the starting material quantitatively. The product after 4 h of ozonization showed complex spots on TLC.

Ozonolysis of 7,8-Dimethoxy-2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one (17)——Compound **17** (221 mg, 1.0 mmol) was ozonized in the presence of BF_3–Et_2O (1.0 mmol) in CH_2Cl_2 (30 ml) at −78 °C and worked up as described in the general procedure to give 2,3-bis(methoxycarbonylmethylene)caprolactam (**18**) (66%), mp 150—152 °C (AcOEt). IR (Nujol): 1730, 1660, 1625. ^{1}H-NMR: 6.45 (1H, s, olefinic H), 5.87 (1H, br s, olefinic H), 3.71 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 3.26 (2H, m), 2.68 (2H, t-like), 1.98 (2H, m). ^{13}C-NMR: 27.7 (t), 37.8 (t), 42.3 (t), 51.4 (q), 51.7 (q), 118.5 (d), 122.2 (d), 151.0 (s), 152.6 (s), 165.2 (s, 2C), 168.9 (s). *Anal.* Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.70; H, 6.07; N, 5.38. HRMS *m/z*: Calcd for $C_{12}H_{15}NO_5$: 253.0950. Found: 253.0977.

15,16-Dimethoxy-8-oxo-*cis*-erythrinan (19)——A solution of 3,4-dimethoxyphenylethylamine (9.05 g, 50 mmol) and ethyl 2-oxo-1-cyclohexaneacetate (9.25 g, 50 mmol) in toluene (100 ml) was refluxed for 8 h. To the cooled mixture, 57% HI (24 ml) was added. The mixture was stirred for 30 min at room temperature, diluted with AcOEt, washed with aqueous $NaHSO_3$ and water, and dried over Na_2SO_4. After removal of the solvent, the residue was crystallized from ether–hexane to give **19** (12.80 g, 85%) as colorless prisms, mp 110—112 °C (lit. 117—118 °C).[12]

16,17-Dimethoxy-8-oxo-*cis*-erythrinan (21)——2,3-Dimethoxyphenylethylamine (9.05 g, 50 mmol) and ethyl 2-oxo-1-cyclohexaneacetate (9.25 g, 50 mmol) in toluene (100 ml) were condensed and cyclized with 57% HI as described above to give **21** (10.09 g, 67%), mp 154—158 °C (ether–hexane). IR (KBr): 1680, 1600. ^{1}H-NMR: 7.11 (1H, d, J=8.5 Hz, ArH), 6.79 (1H, d, J=8.5 Hz, ArH), 3.85 (3H, s, OCH_3), 3.79 (3H, s, OCH_3). *Anal.* Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.34; H, 7.80; N, 4.53. HRMS *m/z*: Calcd for $C_{18}H_{23}NO_3$: 301.1678. Found: 301.1686.

14,16,17-Trimethoxy-8-oxo-*cis*-erythrinan (23)——2,3,5-Trimethoxyphenylethylamine (10.55 g, 50 mmol) and ethyl 2-oxo-1-cyclohexaneacetate (9.25 g, 50 mmol) were condensed and cyclized with 57% HI as described above to give **23** (9.43 g, 57%) as colorless prisms, mp 124—126 °C (AcOEt). IR (KBr): 1690, 1600. ^{1}H-NMR: 6.39 (1H, s, ArH), 3.86 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.70 (3H, s, OCH_3). *Anal.* Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.60; H, 7.72; N, 4.18. HRMS *m/z*: Calcd for $C_{19}H_{25}NO_4$: 331.1782. Found: 331.1771.

14,15,17-Trimethoxy-8-oxo-*cis*-erythrinan (25)——A solution of 2,4,5-trimethoxyphenylethylamine (10.55 g, 50 mmol) and ethyl 2-oxo-1-cyclohexaneacetate (9.25 g, 50 mmol) in toluene (100 ml) was heated under reflux for 8 h and evaporated to dryness under reduced pressure. The residue was heated in polyphosphoric acid (prepared by heating a mixture of 240 g of P_2O_5 and 160 ml of phosphoric acid at 100 °C for 3 h) at 80 °C for 8 h. Water was added to the cooled mixture and the whole was extracted with $CHCl_3$. The extract was washed with water, dried over

anhydrous $MgSO_4$ and concentrated. The residue was purified by chromatography over silica gel (AcOEt–hexane, 2:1) followed by crystallization from ether–hexane to give **25** (8.44 g, 51%) as colorless prisms, mp 120—124 °C. IR (KBr): 1690, 1600. ^{1}H-NMR: 6.42 (3H, br s, ArH), 3.89 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.77 (3H, s, OCH_3). *Anal.* Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.62; H, 7.69; N, 4.21. HRMS *m/z*: Calcd for $C_{19}H_{25}NO_4$: 331.1782. Found: 331.1760.

15,16,17-Trimethoxy-8-oxo-*cis*-erythrinan (28)——2,3,4-Trimethoxyphenylethylamine (10.55 g, 50 mmol) and ethyl 2-oxo-1-cyclohexaneacetate (9.25 g, 50 mmol) were condensed and cyclized with 57% HI to give **28** (13.2 g, 80%) as colorless prisms, mp 91—92 °C (ether–hexane). IR (KBr): 1685, 1600. ^{1}H-NMR: 6.69 (1H, s, ArH), 3.86 (9H, s, 3 × OCH_3). *Anal.* Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.69; H, 7.70; N, 4.18. HRMS *m/z*: Calcd for $C_{19}H_{25}NO_4$: 331.1784. Found: 331.1786.

16-Methoxy-8-oxo-*cis*-erythrinan (32)——3-Methoxyphenylethylamine (7.55 g, 50 mmol) and ethyl 2-oxo-1-cyclohexaneacetate (9.25 g, 50 mmol) were condensed and cyclized with 57% HI as described above to give **32** (9.76 g, 72%) as colorless prisms, mp 109—110.5 °C (ether–hexane). IR (KBr): 1685, 1610. ^{1}H-NMR: 7.31 (1H, d, J=8.5 Hz, ArH), 6.72 (1H, dd, J=8.5 and 2.7 Hz, ArH), 6.66 (1H, d, J=2.7 Hz, ArH), 3.78 (3H, s, OCH_3). *Anal.* Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.01; H, 7.98; N, 5.14. HRMS *m/z*: Calcd for $C_{17}H_{21}NO_2$: 271.5720. Found: 271.5600.

Ozonolysis of 19——Compound **19** (301 mg, 1.0 mmol) was ozonized in the presence of BF_3–Et_2O (1 mmol) in CH_2Cl_2 (30 ml) at −78 °C according to the general procedure. The product was purified by column chromatography on silica gel (AcOEt–hexane, 2:1) to give 1,2-bis(methoxycarbonylmethylene)-decahydro-6*H*-pyrido[2,1-*i*]indol-6-one (**20**), mp 92 °C. IR (KBr): 1730, 1690. ^{1}H-NMR: 6.03 (1H, br s, olefinic H), 5.94 (1H, br s, olefnic H), 3.65 (6H, s, OCH_3). *Anal.* Calcd for $C_{18}H_{23}NO_5 \cdot 1/2H_2O$: C, 63.19; H, 7.06; N, 4.10. Found: C, 62.99; H, 6.95; N, 3.95. HRMS *m/z*: Calcd for $C_{18}H_{23}NO_5$: 333.1577. Found: 333.1599.

Ozonolysis of 21——Compound **21** (301 mg, 1.0 mmol) was ozonized in the presence of BF_3–Et_2O (1.0 mmol) in CH_2Cl_2 (30 ml) at −78 °C to give 2-methoxycarbonyl-1-(2-methoxycarbonylvinyl)-3,4,7,7a,8,9,10,11-octahydro-6*H*-pyrido[2,1-*i*]indol-6-one (**22**) (78%) as an oil. IR ($CHCl_3$): 1730, 1680. ^{1}H-NMR: 6.77 (1H, d, J=12.0 Hz, olefinic H), 5.98 (1H, d, J=12.0 Hz, olefinic H), 3.67 (3H, s, OCH_3), 3.64 (3H, s, OCH_3). HRMS *m/z*: Calcd for $C_{18}H_{23}NO_5$: 333.1577. Found: 333.1560.

Ozonolysis of 23——Compound **23** (331 mg, 1.0 mmol) was ozonized in the presence of BF_3–Et_2O (1.0 mmol) in CH_2Cl_2 (30 ml) at −78 °C to give **24**, mp 121—123 °C (AcOEt–hexane). IR (KBr): 1728, 1680, 1642, 1600. ^{1}H-NMR: 5.19 (1H, s, olefinic H), 3.77 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 3.64 (3H, s, OCH_3). *Anal.* Calcd for $C_{19}H_{25}NO_6$: C, 62.79; H, 6.93; N, 3.85. Found: C, 62.59; H, 6.99; N, 3.88. HRMS *m/z*: Calcd for $C_{19}H_{25}NO_6$: 363.1682. Found: 363.1702.

Ozonolysis of 25——i) With BF_3–Et_2O: A solution of **25** (331 mg, 1.0 mmol) and BF_3–Et_2O (142 mg, 1.0 mmol) in CH_2Cl_2 (30 ml) was ozonized for 90 min at −78 °C. The product was purified by HPLC using AcOEt–hexane (3:1) as an eluent to give **27** (48%), **26** (22%), and the starting material (**25**) (3%).

Compound **27**: An oil. IR ($CHCl_3$): 1730, 1698, 1648. ^{1}H-NMR: 3.82 (3H, s, OCH_3), 3.73 (3H, s, OCH_3). HRMS *m/z*: Calcd for $C_{16}H_{21}NO_5$: 307.1417. Found: 307.1410.

Compound **26**: An oil. IR ($CHCl_3$): 1720 (sh), 1689, 1605. ^{1}H-NMR: 5.00 (1H, s, olefinic H), 3.66 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 3.64 (3H, s, OCH_3). HRMS *m/z*: Calcd for $C_{19}H_{25}NO_6$: 363.1680. Found: 363.1653.

ii) Without a Regulator: A solution of **25** (331 mg, 1.0 mmol) in CH_2Cl_2 (30 ml) was ozonized for 90 min at −78 °C. HPLC of the product gave **27** (63%).

Ozonolysis of 28——i) Without a Regulator: A solution of **28** (331 mg, 1.0 mmol) in CH_2Cl_2 (30 ml) was ozonized for 40 min at −78 °C. The product was purified by HPLC using AcOEt as an eluent to give **29** (33%) and **30** (15%).

Compound **29**: Colorless prisms, mp 112—113 °C (AcOEt–hexane). IR (KBr): 1735, 1695, 1655. ^{1}H-NMR: 5.88 (1H, s, olefinic H), 3.72 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 3.67 (3H, s, OCH_3). *Anal.* Calcd for $C_{19}H_{25}NO_6$: C, 62.79; H, 6.93; N, 3.85. Found: C, 62.67; H, 7.02; N, 3.80. HRMS *m/z*: Calcd for $C_{19}H_{25}NO_6$: 363.1682. Found: 363.1710.

Compound **30**: An oil. IR ($CHCl_3$): 1730, 1670. ^{1}H-NMR: 5.66 (1H, s, olefinic H), 3.74 (6H, s, OCH_3), 3.64 (3H, s, OCH_3). HRMS *m/z*: Calcd for $C_{19}H_{25}NO_6$: 363.1682. Found: 363.1689.

ii) With BF_3–Et_2O: Ozonized oxygen was bubbled into a solution of **28** (331 mg, 1.0 mmol) and BF_3–Et_2O (142 mg, 1.0 mmol) in CH_2Cl_2 (30 ml) for 80 min at −78 °C, and worked up in a usual manner. HPLC of the product using AcOEt as an eluent gave **29** (23%) and **30** (14%).

iii) With K_2CO_3: Ozonized oxygen was bubbled into a solution of **28** (331 mg, 1.0 mmol) and powdered K_2CO_3 (500 mg) in CH_2Cl_2 (30 ml) for 40 min at −78 °C. HPLC of the product gave **29** (43%) and **30** (12%).

Ozonolysis of 32——i) With BF_3–Et_2O: Ozonized oxygen was bubbled into a solution of **32** (271 mg, 1.0 mmol) and BF_3–Et_2O (142 mg, 1.0 mmol) in CH_2Cl_2 (30 ml) for 4 h at −78 °C. HPLC of the product using AcOEt–hexane (3:1) as an eluent gave **33** (39%) and **34** (8%).

Compound **33**: An oil. IR ($CHCl_3$): 1730, 1690. ^{1}H-NMR: 9.74 (1H, s, CHO), 6.74 (1H, d, J=12.0 Hz, olefinic H), 6.29 (1H, d, J=12.0 Hz, olefinic H), 3.67 (3H, s, OCH_3). HRMS *m/z*: Calcd for $C_{17}H_{21}NO_4$: 303.1471. Found: 303.1501.

Compound **34**: An oil. IR ($CHCl_3$): 1735, 1680. ^{1}H-NMR: 9.68 (1H, d, J=7.8 Hz, CHO), 6.24 (1H, s, olefinic H),

6.10 (1H, d, $J=7.8$ Hz), 3.67 (3H, s, OCH_3). HRMS m/z: Calcd for $C_{17}H_{21}NO_4$: 303.1470. Found: 303.1480.

ii) Without BF_3–Et_2O: Compound **32** (271 mg, 1 mmol) in CH_2Cl_2 (30 ml) was ozonized for 4 h at −78 °C and worked up in a usual manner to give **33** (34%) and **34** (7%).

References and Notes

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