× 10^4), ^{1}H NMR (CD_3COCD_3) δ 12.19 (1 H, s, exchanges with D_2O), 8.76 (1 H, s, exchanges with D_2O), 7.62–6.70 (4 H, m), 5.79 (1 H, dd, J = 6, 10), 3.76 (3 H, s), 3.35–2.71 (2 H, AB of ABX), 2.04 (6 H, s); ^{13}C NMR, see Table I; mass spectrum, m/e 314 (M^+, 79%), 194 (M^+ – 120, 13). Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.34, H, 5.82.

The monomethyl ether (**10**) could also be prepared by methylation of **6** (100 mg) using CH_3I (5 mL) and K_2CO_3 (100 mg) in Me_2CO (10 mL). After 5 h at room temperature, the suspension was concentrated in vacuo, diluted with H_2O (15 mL), and extracted with EtOAc (4 × 15 mL). The combined dried (Na_2SO_4) EtOAc layer was concentrated to give a yellow oil from which 58 mg of **10** was obtained from *n*-hexane, mp 184–187 °C, identical with the sample prepared from CH_2N_2 (mixture melting point, TLC, IR).

Degradation of Emorydone (8). Emorydone (8, 50 mg) was dissolved in 6 mL of glacial HOAc, 6 mL of hydrobromic acid was added, and the solution was refluxed for 3 h (yellow color disappeared), cooled, diluted with H_2O (25 mL), and extracted with Et_2O (4 × 30 mL). The combined ether layers (dried over Na_2SO_4) were evaporated, and the residue was chromatographed over silica gel 60 (20 g). Elution with 20% Me_2CO–hexane yielded a fraction from which 20 mg of **3**, mp 65–68 °C (*n*-hexane), was obtained. This was identical with an authentic sample of **3** (melting point, mixture melting point, TLC, superimposable IR).

Elution with 60% Me_2CO–hexane (200 mL) yielded a crystalline residue from which 10 mg of **4**, mp 186–188 °C ($CHCl_3$) was obtained. This sample was identical with the isolated sample of **4** (melting point, mixture melting point, TLC, superimposable IR).

Transformation of Vafzelin (1). A 20-mg sample of vafzelin (**1**) was dissolved in MeOH (5 mL) and refluxed for 6 h. The yellow solution was evaporated to dryness and the yellow oil chromatographed over silica gel 60 (30 g). Elution with 200 mL of $CHCl_3$ gave 12 mg of emorydone (**8**), which was identical with the previously isolated sample [TLC, co-TLC, superimposable IR spectra ($CHCl_3$)]. Elution with an additional 100 mL of $CHCl_3$ gave 3 mg of **7** (TLC, co-TLC, HPLC).

To 20 mg of vafzelin (**1**) in 10 mL of MeOH was added 40 mg of K_2CO_3. The suspension was stirred for 0.5 h and then 3 mL of CH_3I was added. The suspension (yellow) was stirred for 24 h, filtered, concentrated, and then partitioned between Et_2O (4 × 20 mL) and H_2O (20 mL). The combined dried (Na_2SO_4) ether layers were evaporated and 14 mg of **14** was obtained from *n*-hexane, mp 133–135 °C, identical with the previously prepared sample [mixture melting point, TLC, co-TLC, superimposable IR (KBr)].

Stability Studies of Vafzelin (1), 2-Hydroxy-7,8-dehydrograndiflorone (7), and Emorydone (8) by HPLC. Kinetic studies on the interconversions of **1**, **7**, and **8** were accomplished by using high-performance liquid chromatographic analysis of the reaction mixtures. A 3.9 mm × 30 cm C_{18} reversed-phase column (μ-Bondapak C_{18}, Waters Assoc. Inc.) with a 10-μm particle size was used for the study. The mobile phase was prepared by using 6.6 g of K_2HPO_4, 9.4 g of KH_2PO_4, 2.0 L of H_2O, and 2.0 L of CH_3OH, and a flow-rate of 1.0 mL/min was used. Two ultraviolet detectors (254 and 280 nm) were used in series for the quantitation of the products and for the verification of their identities, using A_{254}/A_{280} ratios.[13] The retention times that were observed for **7**, **8**, and **1** were 4.5, 18.2, and 27.4 min and the A_{254}/A_{280} observed values were 0.38, 0.98, and 0.61, respectively.

For the stability studies, 1.0 mg/mL solutions of each of the three test compounds were prepared by using CH_3OH, 0.1 N HCl in CH_3OH, K_2CO_3-saturated CH_3OH, and ethyl acetate. The 12 solutions were stored at room temperature, and the reactions products were quantitated by using peak heights of the HPLC analysis.

Acknowledgment. This investigation was supported in part by a grant from the National Cancer Institute (CA 15590) and the Research Institute of Pharmaceutical Sciences, The University of Mississippi. We are grateful to Dr. B. S. Joshi, Ciba-Geigy Research Center, Bombay, India, for an authentic sample of demethoxymatteucinol, to Dr. J. N. Roitman, USDA, Berkeley, CA, for a sample of emorydone, and to Dr James McCloskey, College of Pharmacy, University of Utah, for high-resolution mass spectra. We thank Mr. Gbile (FRIN) for identification of plant material and B.O.O. acknowledges a fellowship from the Federal Government of Nigeria.

Registry No. 1, 77744-51-5; 2, 75724-88-8; 3, 91-64-5; 4, 77744-52-6; 4 *C*-acetyl derivative, 7073-22-5; 4 *O*-methyl derivative, 1719-22-8; 5, 56297-79-1; 6, 77744-53-7; 7, 77744-54-8; 8, 65653-67-0; 9, 77744-55-9; 10, 77744-56-0; 11, 77744-57-1; 12, 77744-58-2; 14, 77744-59-3.

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Thallium in Organic Synthesis. 60. 2,6-Diaryl-3,7-dioxabicyclo[3.3.0]octane-4,8-dione Lignans by Oxidative Dimerization of 4-Alkoxycinnamic Acids with Thallium(III) Trifluoroacetate or Cobalt(III) Trifluoride[1,2]

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Oxidation of *p*-alkoxycinnamic acids either with thallium(III) trifluoroacetate in TFA/CH_2Cl_2 or with cobalt(III) trifluoride in CH_3CN, in the presence of a small amount of BF_3·Et_2O, results in instantaneous oxidative dimerization to give the bislactone lignans **1**. A mechanism for this transformation is discussed.

The fused bislactones **1** belong to a naturally occurring family of compounds, some of which have been found in a cultured mushroom, *Inonotus* sp. K-1410, and which exhibit inhibitory activity against catechol-*O*-methyl-

(1) For the preceding paper in this series, see: Taylor, E. C.; Andrade, J. G.; Rall, G. J. H.; McKillop, A. *J. Am. Chem. Soc.* **1980**, *102*, 6513–6519.

(2) We are indebted to the National Science Foundation (Grant CHE76 16506 to Princeton University) for financial support for this work.

(3) John Simon Guggenheim Memorial Fellow, 1979–1980.

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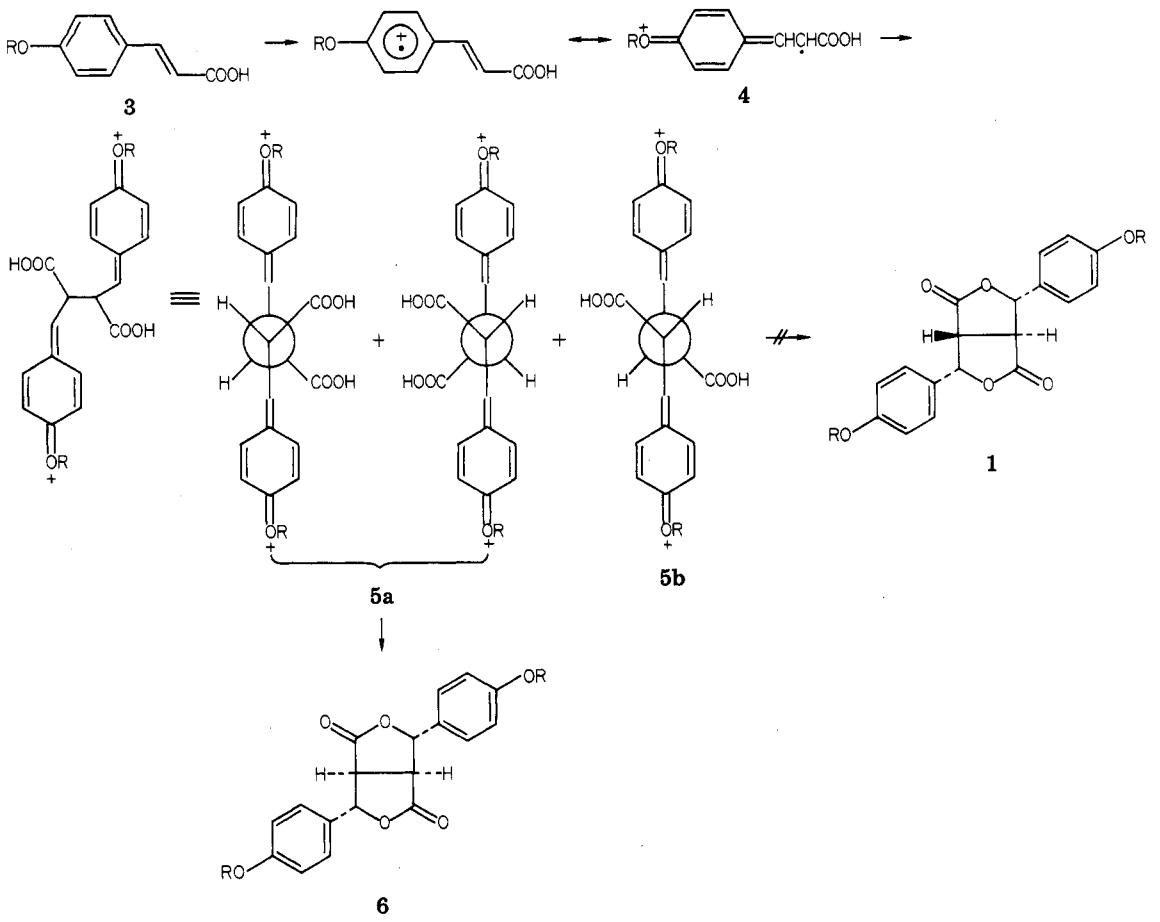
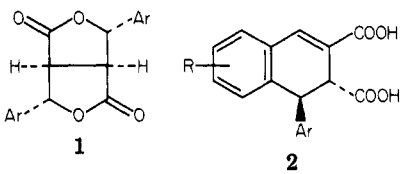
0022-3263/81/1946-3078$01.25/0

Scheme I



transferase, DOPA decarboxylase, and cyclic AMP phosphodiesterase.[4,5] These bislactones undergo an acid-catalyzed rearrangement to 1-aryl-1,2-dihydronaphthalene-2,3-dicarboxylic acids (2),[6,7] which are themselves naturally



occurring lignans.[8,9] Fused bislactones of type 1 with 4-hydroxyphenyl substituents have been prepared by prolonged bimolecular phenolic oxidative coupling of 4-hydroxycinnamic acids with ferric chloride and oxygen.[10,11] A more recent general method for the preparation of 1 involves the titanium tetrachloride catalyzed condensation of 2,5-bis(trimethylsiloxy)furan with carbonyl compounds.[12] We describe in this paper the preparation of some 2,6-bis(4-alkoxyphenyl) bislactones of type 1 by oxidative dimerization of *p*-alkoxycinnamic acids (3) with thallium(III) trifluoroacetate (TTFA) or cobalt(III) trifluoride (CoF_3).

The reaction of a number of *p*-alkoxycinnamic acids with 1 equiv of TTFA[13] in trifluoroacetic acid/methylene chloride containing $BF_3{\cdot}Et_2O$ resulted in the instantaneous formation of 1 in moderate yields, with 80–100% consumption of starting material (see Table I). The reactions were immediately quenched[14] with *tert*-butyl alcohol in order to avoid total decomposition of the desired bislactones, presumably by further oxidation with excess TTFA or by acid-catalyzed decomposition by $BF_3{\cdot}Et_2O$. Filtration of a chloroform solution of the crude product through a small amount of silica gel and alumina, as described in the Experimental Section, generally afforded a pure, white, voluminous product after trituration with ethanol/pentane.

The mechanism originally proposed[15] for this oxidative dimerization is summarized in Scheme I. The radical cation resonance contributor 4 initially couples to yield a mixture of **5a** (a *d,l* pair) and **5b** (meso). Intermediate **5a** is capable of cyclization to the cis-fused product 1, with aromatic substituents in the thermodynamically most stable configuration, but intermediate **5b** (if formed) must suffer a different ultimate fate, since cyclization to the highly strained trans-fused bislactone 6 was never observed. Support for this mechanism was based[15] upon the known side-chain coupling of methyl 3,5-di-*tert*-butyl-4-hydroxycinnamate with potassium ferricyanide[16] and the

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(13) The stoichiometry of this coupling reaction requires only 0.5 equiv of TTFA, but higher yields were obtained when a full equivalent was employed.
(14) The role of *tert*-butyl alcohol in halting further oxidation by residual TTFA is probably due both to its Lewis base properties and to conversion of TTFA into the much weaker oxidizing agent (*t*-BuO)Tl(OCOCF$_3$)$_2$ [analogous to the well-known conversion of Tl(OCOCH$_3$)$_3$ to CH$_3$OTl(OCOCH$_3$)$_2$ with methanol: Criegee, R.; Kraft, L.; Rank, B. *Justus Liebigs Ann. Chem.* **1933**, *507*, 159–197].
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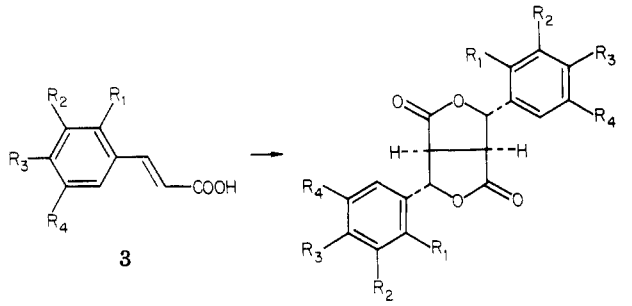
Table I. Synthesis of 2,6-Diaryl-3,7-dioxabicyclo[3.3.0]octane-4,8-diones by Oxidative Dimerization of Cinnamic Acids

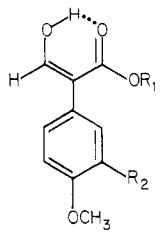


3 1

compd	R_1	R_2	R_3	R_4	oxidant[a] TTFA, % yield[b]	oxidant[a] CoF_3, % yield	oxidant[a] CoF_3, % consumed
a	CH_3O	CH_3O	CH_3O	H	39	5	41
b	H	CH_3O	CH_3O	CH_3O	54	15	56
c	H	CH_3O	CH_3O	H	47	33	40
d	H	OCH_2O		H	31	28	50
e	H	H	CH_3O	H	12	23	27
f	H	CH_3O	HO	H		20	86

[a] All oxidations were carried out in the presence of $BF_3 \cdot Et_2O$. [b] 80–100% of starting material was routinely consumed.

purported analogous transformation of methyl 4-methoxycinnamate to dimethyl 1,4-bis(4-methoxyphenyl)-1,3-butadiene-2,3-dicarboxylate with TTFA. We have now found that the latter oxidation product is, in fact, methyl 4-methoxyphenylmalonaldehydate (**7**). The formation of



7, $R_1 = CH_3$; $R_2 = H$
9, $R_1 = H$; $R_2 = OCH_3$

this compound suggests an alternative mechanism for the oxidative dimerization of cinnamic acids which is detailed in Scheme II. In this pathway, the initial step is oxythallation of the carbon–carbon double bond to give intermediate **8**, rather than electron transfer to give a radical cation (e.g., **4**). The bislactone **1** then arises by oxidative displacement of Tl(III) by participation of the cinnamate moiety, followed by intramolecular Michael addition as shown.

A side product (6% yield) from the reaction of 3,4-dimethoxycinnamic acid (**3c**) with $TTFA/BF_3 \cdot Et_2O$ is 3,4-dimethoxyphenylmalonaldehydic acid (**9**), which is presumably formed from an intermediate analogous to **8** (see Scheme II) by aryl migration. The isolation of **9** supports the mechanism suggested in Scheme II but does not prove, of course, that this pathway is followed to the exclusion of the alternative side-chain coupling route.

Dimerization of cinnamic acids to fused bislactones (**1**) was also accomplished with CoF_3 as oxidant in the presence of $BF_3 \cdot Et_2O$. Starting materials were consumed much more slowly by this reagent than by $TTFA/BF_3 \cdot Et_2O$, and the reaction was always incomplete after 90 min, despite the use of a 2.5-fold excess of CoF_3 (see Table I). Reaction of methyl 4-methoxycinnamate with CoF_3 gave only tars; neither the side-chain coupling product nor the arylmalonaldehydate (**7**) was formed. Since Co(III) salts are known to be one-electron oxidants,[17] we assume that the observed dimerization of cinnamic acids to **1** by CoF_3 probably proceeds via coupling of an intermediate radical cation (Scheme I).

There are several advantages associated with the use of this reagent rather than $TTFA/BF_3 \cdot Et_2O$. The crude bislactones are purer and require filtration only through Florisil; thus, there is less risk of losing the desired products on the filtration support. This oxidation procedure is also applicable to the dimerization of 4-hydroxycinnamic acids (e.g., **3f**): $TTFA/BF_3 \cdot Et_2O$ generally destroys such substrates. Although poor yields of bislactones are obtained from trialkoxycinnamic acids, and only 27–56% of substrate alkoxy-substituted cinnamic acids are consumed (compared with 80–100% consumption by $TTFA/BF_3 \cdot Et_2O$), cinnamic acids recovered from $CoF_3/BF_3 \cdot Et_2O$-mediated oxidations are easily recycled after filtration through Florisil.

Several cinnamic acid analogues failed to dimerize on treatment with $TTFA/BF_3 \cdot Et_2O$. 3,4-Dimethoxycinnamyl alcohol (**10a**) yielded a tarry product mixture containing a small amount of 3,4-dimethoxycinnamaldehyde (**10b**) rather than the anticipated fused bisether. 3,4-Dimethoxycinnamaldehyde oxime (**10c**) also gave only the aldehyde **10b**, but this result is perhaps unsurprising since thallium(III) trinitrate (TTN) is known to convert oximes to the corresponding aldehydes.[18] *N*-Ethyl-3,4-dimethoxycinnamylamine (**10d**), 3-(2-thienyl)acrylic acid (**11a**), and 3-(2-furyl)acrylic acid (**11b**) each failed to give an isolable product on treatment with either TTFA or CoF_3 in the presence or absence of $BF_3 \cdot Et_2O$.

Experimental Section

General Procedure for Oxidative Coupling of Cinnamic Acids with Thallium(III) Trifluoroacetate (TTFA). The cinnamic acid (20 mmol) in methylene chloride/trifluoroacetic

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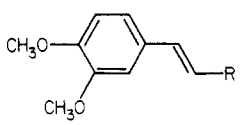
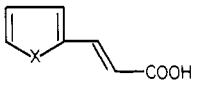


10a, R = CH_2OH
b, R = CHO
c, R = CH=NOH
d, R = $CH_2NHC_2H_5$



11a, X = S
b, X = O

acid (4:1, 30–35 mL) is added all at once to a rapidly stirred solution of TTFA (10.6 g, 20 mmol) in methylene chloride/TFA (4:1, 500 mL) and BF_3·Et_2O (4–5 mL) at room temperature. The deep red reaction mixture is quenched *immediately* with *tert*-butyl alcohol (100 mL). It is of utmost importance that the rapid addition of *tert*-butyl alcohol take place less than 1 s after addition of the substrate. Water (200 mL) is added and the methylene chloride layer is separated. The remaining aqueous solution is extracted with chloroform, and the combined organic layers are washed with water (4 × 200 mL) and saturated aqueous sodium bicarbonate (3 × 100 mL), dried over Na_2SO_4, and evaporated. The oily residue is then filtered through a short column packed with alumina (*maximum* 6–7 g) covered with silica gel (*maximum* 12–14 g), with chloroform as eluent. The crude product is triturated with a few milliliters of warm ethanol, and the resultant mixture treated dropwise with pentane until precipitation ceases. The solid thus obtained is collected by filtration and washed with cold ether to give the pure (TLC) 2,6-diaryl-3,7-dioxabicyclo-[3.3.0]octane-4,8-diones cited below. Yields are based on recovered starting material.

2,6-Bis(2,3,4-trimethoxyphenyl)-3,7-dioxabicyclo[3.3.0]-octane-4,8-dione (1a): from 2,3,4-trimethoxycinnamic acid; R_f (5% acetone/chloroform) 0.60; mp 133–135 °C;[19] 39% yield; IR ($CHCl_3$) 2935, 1774, 1602 cm^{-1}; NMR ($CDCl_3$) δ 7.05 (d, 2 H, J = 8.5 Hz), 6.66 (d, 2 H, J = 8.5 Hz), 5.75 (br s, 2 H), 3.94 (s, 6 H), 3.87 (s, 12 H), 3.71 (br s, 2 H).

Anal. Calcd for $C_{24}H_{26}O_{10}$: C, 60.75; H, 5.52. Found: C, 60.95; H, 5.85.

2,6-Bis(3,4,5-trimethoxyphenyl)-3,7-dioxabicyclo[3.3.0]-octane-4,8-dione (1b): from 3,4,5-trimethoxycinnamic acid; R_f (5% acetone/chloroform) 0.56; mp 195–198 °C (lit.[5] mp 195–196 °C);[19] 54% yield; IR ($CHCl_3$) 1780 cm^{-1}; NMR ($CDCl_3$) δ 6.51 (br s, 4 H), 5.87 (br s, 2 H), 3.85 (s, 12 H), 3.82 (s, 6 H), 3.57 (br s, 2 H).

2,6-Bis(3,4-dimethoxyphenyl)-3,7-dioxabicyclo[3.3.0]octane-4,8-dione (1c): from 3,4-dimethoxycinnamic acid; R_f (5% acetone/chloroform) 0.65; mp 204–206 °C (lit.[10] mp 207 °C); 47% yield; IR ($CHCl_3$) 1780 cm^{-1}; NMR ($CDCl_3$) δ 6.80–6.95 (m, 6 H), 5.88 (br s, 2 H), 3.88 (s, 12 H), 3.62 (br s, 2 H).

Anal. Calcd for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35. Found: C, 63.98; H, 5.42.

3,4-Dimethoxyphenylmalonaldehydic Acid (9). This compound was obtained from the bicarbonate washings of the above preparation of **1c**. Since compound **9** was chromatographically inseparable from the recovered starting material, the mixture was separated by successive recrystallizations of the starting material from benzene/pentane and/or ethanol. Acid **9**, recovered as an oil from the mother liquors, had R_f (8% acetone/chloroform) 0.30; 6% yield; IR (neat) 1680, 1605 cm^{-1}; NMR ($CDCl_3$) δ 11.08 (br s, 1 H), 7.16 (br s, 1 H), 7.07 (m, 2 H), 6.89 (br s, 1 H), 3.83 (s, 3 H), 3.80 (s, 3 H); exact mass calcd for $C_{11}H_{12}O_5$ m/e 224.068 47, found 224.067 94.

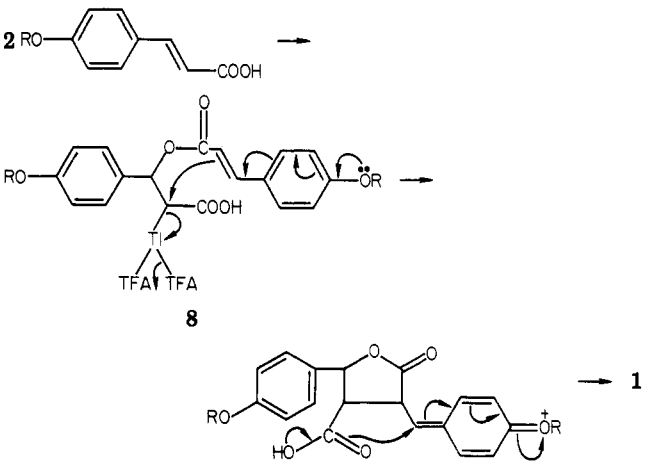
2,6-Bis[3,4-(methylenedioxy)phenyl]-3,7-dioxabicyclo-[3.3.0]octane-4,8-dione (1d): from 3,4-(methylenedioxy)cinnamic acid; R_f (5% acetone/chloroform) 0.52; mp 189–191 °C; 31% yield; IR ($CHCl_3$) 1775 cm^{-1}; NMR ($CDCl_3$) δ 6.70–6.85 (m, 6 H), 5.97 (s, 4 H), 5.93 (br s, 2 H), 3.72 (br s, 2 H).

Anal. Calcd for $C_{20}H_{14}O_8$: C, 62.83; H, 3.69. Found: C, 62.58; H, 3.68.

2,6-Bis(4-methoxyphenyl)-3,7-dioxabicyclo[3.3.0]octane-4,8-dione (1e): from 4-methoxycinnamic acid with silica gel TLC (5% acetone/chloroform); R_f (5% acetone/chloroform) 0.42; mp 128–130 °C (lit.[12] mp 153.5–154 °C);[20] 12% yield; IR ($CHCl_3$) 1775 cm^{-1}; NMR ($CDCl_3$) δ 6.75–7.35 (m, 8 H), 5.83 (br s, 2 H), 3.75 (s, 6 H), 3.60 (br s, 2 H).

Anal. Calcd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.59; H, 5.34.

Scheme II



8

General Procedure for Oxidative Coupling of Cinnamic Acids with Cobalt(III) Trifluoride. CoF_3 (0.58 g, 5 mmol) is suspended in 12 mL of dry acetonitrile containing 1 mL of BF_3·Et_2O, the suspension purged with N_2, and the cinnamic acid (2 mmol) added. The mixture is then stirred under N_2 at room temperature for 1.5 h, diluted to 150 mL with methylene chloride, and washed with two 100-mL portions of water. Unreacted cinnamic acid is recovered by extraction of the organic solution with two 50-mL portions of saturated aqueous sodium bicarbonate. The organic layer is dried (Na_2SO_4) and evaporated to dryness under reduced pressure, the residual oily liquid filtered through a short Florisil column, and the product worked up as before. Yields for the oxidative coupling of cinnamic acids to 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane-4,8-diones by CoF_3 are given in Table I.

2,6-Bis(4-hydroxy-3-methoxyphenyl)-3,7-dioxabicyclo-[3.3.0]octane-4,8-dione (1f): from 4-hydroxy-3-methoxycinnamic acid using CoF_3/BF_3·Et_2O as oxidant and trituration with acetone/pentane; R_f (5% acetone/chloroform) 0.20; mp 205–206 °C dec (lit.[10] mp 208–209 °C dec); 20% yield; IR (KBr) 3300–3550, 1780, 1605 (weak) cm^{-1}; NMR (Me_2SO-d_6) δ 6.85–7.10 (m, 6 H), 5.77 (br s, 2 H), 4.21 (br s, 2 H), 3.83 (s, 6 H).

Methyl 4-Methoxyphenylmalonaldehydate (7). Methyl 4-methoxycinnamate was oxidized with TTFA by the procedure described above for the oxidative dimerization of cinnamic acids, except that the addition of *tert*-butyl alcohol was delayed for 2 min. The crude product was purified by column chromatography (silica gel, chloroform as eluent) to give **7** as an oil: R_f (chloroform) 0.40; 91% yield; IR (neat) 2945, 1735, 1660, 1605, 1515 cm^{-1}; NMR ($CDCl_3$) δ 12.00 (br s, 1 H), 7.22 (br s, 1 H), 7.15 (d, 2 H, J = 8.5 Hz), 6.85 (d, 2 H, J = 8.5 Hz), 3.80 (s, 6 H); exact mass calcd for $C_{11}H_{12}O_4$ m/e 208.073 60, found 208.073 13.

The 2,4-dinitrophenylhydrazone of **7** had the following: R_f (5% acetone/chloroform) 0.50; mp (ethanol) 140–141 °C; IR (KBr) 3280, 1740, 1615, 1515 cm^{-1}; NMR ($CDCl_3$) δ 11.12 (br s, 1 H), 9.08 (d, 1 H, J = 2.5 Hz), 8.30 (dd, 1 H, J = 9.5, 2.5 Hz), 7.90 (d, 1 H, J = 9.5 Hz), 7.81 (d, 1 H, J = 7.5 Hz), 3.80 (s, 6 H).

Anal. Calcd for $C_{17}H_{16}N_4O_7$: C, 52.58; H, 4.15; N, 14.43. Found: C, 52.87; H, 4.30; 14.51.

Registry No. **1a**, 69813-30-5; **1b**, 69854-18-8; **1c**, 69854-19-9; **1d**, 69813-31-6; **1e**, 69813-32-7; **1f**, 77550-11-9; **3a**, 33130-03-9; **3b**, 90-50-6; **3c**, 2316-26-9; **3d**, 2373-80-0; **3e**, 830-09-1; **3f**, 1135-24-6; **7**, 63857-14-7; **7** DNP, 77508-30-6; **9**, 77508-31-7; **10a**, 18523-76-7; **10b**, 4497-40-9; **10c**, 77508-32-8; **10d**, 77508-33-9; **11a**, 1124-65-8; **11b**, 539-47-9; methyl 4-methoxycinnamate, 832-01-9; TTFA, 23586-53-0; CoF_3, 10026-18-3.

(19) In our preliminary communication (ref 15), the melting points of compounds **1a** and **1b** in Table I, p 3624, were inadvertently interchanged.

(20) A comparison of our NMR data with those given for the previous preparation of compound **1e** indicates that our lower melting compound may not have completely epimerized to the cis (with reference to the aromatic rings) isomer.