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THALLIUM IN ORGANIC SYNTHESIS. 55. OXIDATIVE DIMERIZATION OF 4-ALKOXYCINNAMIC ACIDS TO 2,6-DIARYL-3,7-DIOXABICYCLO[3.3.0]-OCTANE-4,8-DIONES WITH THALLIUM(III) TRIFLUOROACETATE (TTFA)[1,2]

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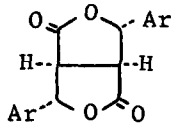
Cinnamic acid-derived fused bis-lactones of type 1 (2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane-4,8-diones), several of which have been isolated from a cultured mushroom, Inonotus sp. K-1410, have recently been reported to inhibit catechol-O-methyltransferase, DOPA decarboxylase, and cyclic AMP phosphodiesterase.[4,5] These fused bis-lactones have been converted by acid-catalyzed rearrangement[6,7] into 1-aryl-1,2-dihydronaphthalene-2,3-dicarboxylic acids (2) which, in addition to being naturally-occurring lignans,[8,9] are attractive synthetic intermediates for the closely related semisynthetic antineoplastic 4'-demethylepipodophyllotoxin-β-D-glucosides.[10] Furthermore, the fused bis-lactones 1 should be capable of facile conversion (by reduction followed by acid-catalyzed cyclization) to the fused ethers 3 and 4. Compounds of type 3 have recently been shown to be germination inhibitors,[11,12] while the naturally-occurring bis-ethers 4[13] are constituents both of the Chinese drug 'shin-i' (used for treatment of nasal empyema and headache)[14] and of a Nigerian bark extract (used for toothache, colds and coughs, and as a vermifuge).[15]

The only known method for the synthesis of the fused bis-lactones 1 involves prolonged phenol oxidative coupling of a 4-hydroxycinnamic acid derivative with ferric chloride and oxygen.[16,17] We now report that a variety of 4-alkoxycinnamic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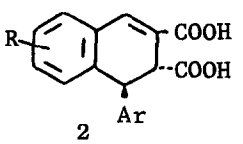
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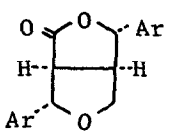
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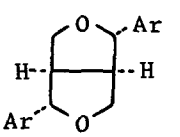
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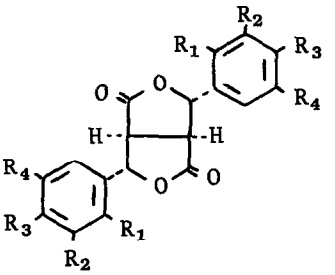
acids may be instantaneously converted to the corresponding fused bis-lactones 1 by non-phenolic coupling with thallium(III) trifluoroacetate (TTFA) in trifluoroacetic acid/methylene chloride at room temperature in the presence of boron trifluoride etherate. A typical conversion is as follows: A solution of 3,4-dimethoxycinnamic acid (0.83 g, 4 mmol) in a mixture of 10 mL of TFA and 40 mL of methylene chloride, was added all at once to a vigorously stirred solution of 2.4 g (4.4 mmol) of TTFA in 1.5 mL of TFA and 5 ml of methylene chloride containing 1 mL of boron trifluoride etherate at room temperature. The reaction mixture was quenched immediately with 30 mL of tert-butanol and extracted with 3 x 50 ml of chloroform. The extracts were washed with water (4 x 75 ml) followed by aqueous 5% sodium bicarbonate (3 x 50 ml), and the chloroform extracts were dried over anhydrous sodium sulfate. Evaporation of the solvent followed by filtration through neutral alumina (chloroform/pentane, 1:1) gave 290 mg (47%)[18] of analytically pure 2,6-(3',4'-dimethoxyphenyl)-3,7-dioxobicyclo[3.3.0]octane-4,8-dione (1c), mp 204-206° (lit mp 204-205°,[5] 207°[16]). Data for some representative oxidative dimerizations of cinnamic acid derivatives are summarized in Table 1.

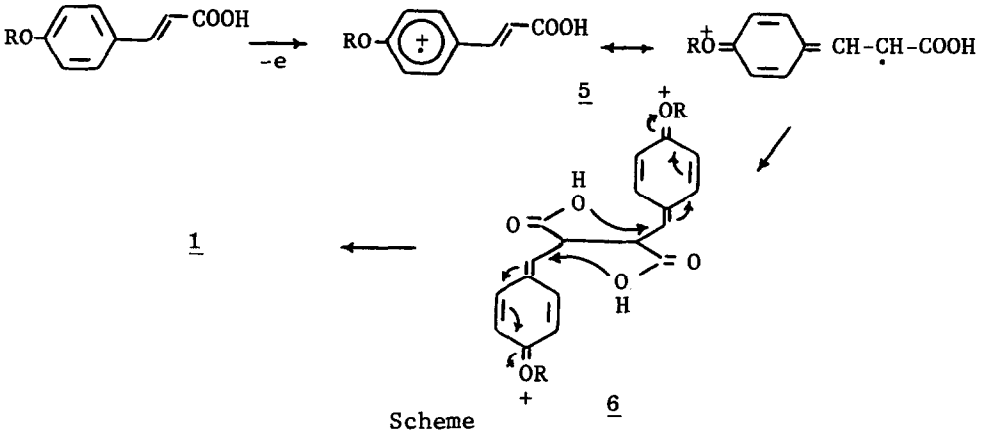
Table 1. Oxidative Dimerization of Cinnamic Acids with TTFA



Cmpd.	R	Yield, %	mp °C
1a	$R_1 = R_2 = R_3 = OCH_3$, $R_4 = H$	39	190-194d (ref. 5)
1b	$R_2 = R_3 = R_4 = OCH_3$, $R_1 = H$	54	133-135
1c	$R_1 = R_4 = H$, $R_2 = R_3 = OCH_3$	47	204-206
1d	$R_1 = R_4 = H$, $R_2 + R_3 = OCH_2O$	31	189-191
1e	$R_1 = R_2 = R_4 = H$, $R_3 = OCH_3$	12	128-130

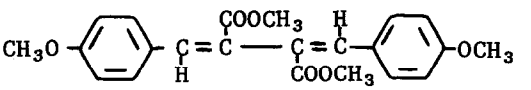
We suggest that the conversion of p-alkoxycinnamic acids to the fused bis-lactones 1 with TTFA is best explained on the basis of the mechanism outlined in

the Scheme; that is, initial one-electron oxidation of the cinnamic acid to the



Scheme

radical cation 5, dimerization of the latter to 6, and final intramolecular conjugate addition. Fully consistent with this interpretation are our observations that (a) cinnamic acid itself is recovered unchanged under the above reaction conditions, and (b) oxidation of the methyl ester of p-methoxycinnamic acid proceeds smoothly (2 min) to give the dehydro dimer 7 in 78% yield by deprotonation of the initially formed product of radical dimerization.[19]



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References and Notes

1. For the previous paper in this series, see E. C. Taylor, I. J. Turchi, and A. McKillop, Heterocycles, submitted for publication.

2. We are indebted to the National Science Foundation (Grant # CHE76-16506) and to Eli Lilly & Co. for financial support of this work.

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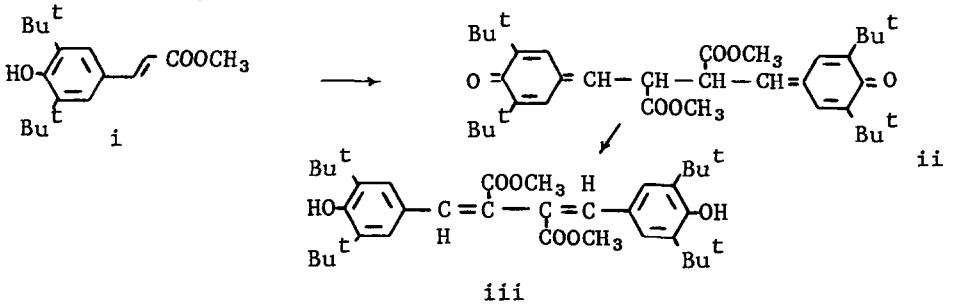
18. Conversion yield based upon recovery of 100 mg of starting material.

19. A precedent for this conversion is the transformation of methyl (E)-4-hydroxy-3,5-di-tert-butylcinnamate (i) to the bis-phenol (iii), via prototropic re-



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arrangement of the initially formed bis-quinone methide (ii), by oxidative dimerization with potassium ferricyanide (K. V. Sarkanen and A. F. A. Wallis, J. Chem. Soc. Perkin I, 1878 (1973).

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