Intramolecular [2 + 2] Ketene Cycloadditions. Synthesis of Isoflavones and 3-Aroylbenzofurans

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The conversion of 2-(carboxyalkoxy)benzils to the corresponding phenoxyketenes leads to an intramolecular [2 + 2] ketene cycloaddition to ultimately yield isoflavones and/or 3-aroylbenzofurans. The ketenes may be generated by the classical dehydrochlorination of the acid chloride or by using Perkin reaction conditions, sodium acetate in refluxing acetic anhydride. The initial cycloaddition products are the corresponding β-lactones, which may decarboxylate to the isolated isoflavones and/or 2-aroylbenzofurans. The product distributions are dependent upon the substitution pattern in the original benzil acids.

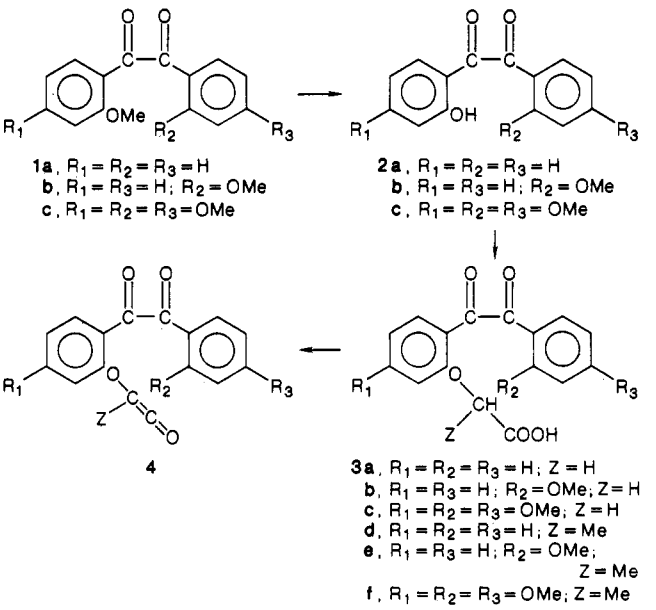
Intramolecular ketene [2 + 2] cycloaddition reactions have recently proved to be an excellent route to the synthesis of polycyclic compounds.[1] We have had some success in developing a new synthesis of benzofurans and polycyclic cyclobutanones using this methodology.[1c-f] This report describes the synthesis of isoflavones and 3-aroylbenzofurans using as a key step in the synthesis an intramolecular [2 + 2] ketene cycloaddition reaction to a carbonyl group.

The isoflavones are common constituents of plants of the Leguminosae family. These compounds show a variety of biological activities, such as antimicrobial activity[2] and estrogenic activity,[3] and the benzofurans or coumarones have long been known to be widely used in many areas but principally in pharmacology. These biological properties have stimulated a lot of interest in the synthesis of isoflavones[4] and 3-aroylbenzofurans.[5] In an effort to further explore the potential applications of intramolecular [2 + 2] ketene cycloadditions, we targeted the basic isoflavone structure.

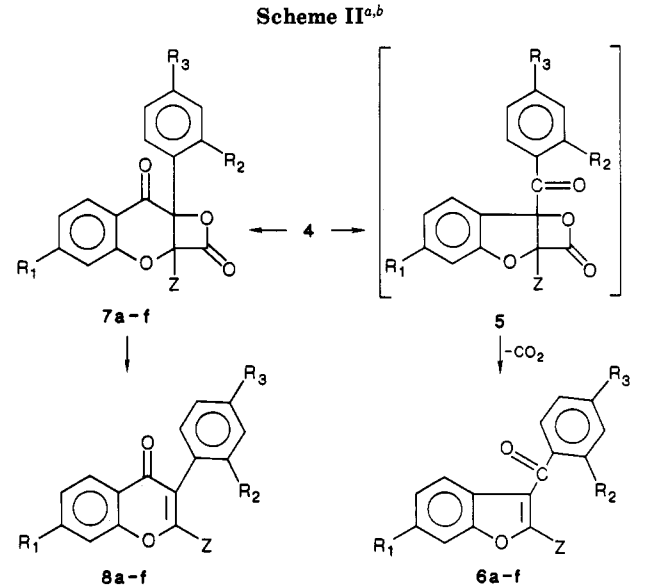
The starting compounds for our synthesis are 2-methoxybenzils **1a–c**, which were readily prepared by the oxidation of the corresponding benzoins by standard literature procedures. Demethylation of the benzils as shown in Scheme I resulted in the 2-hydroxybenzil compounds **2a–c**. Conversion of **2a–c** to 2-(carboxyalkoxy)benzils **3a–f** was accomplished by reaction with ethyl α-bromo carboxylates and subsequent hydrolysis. The acids were converted to the corresponding acid chlorides with a large excess of oxalyl chloride. The acid chlorides upon treatment with triethylamine were expected to undergo dehydrochlorination to the corresponding phenoxyketenes **4**.

The slow addition of a benzene solution of the acid chloride of **3a–f** to a benzene solution containing a large excess of triethylamine resulted in the formation of 3-aroylbenzofurans **6** and isoflavones **8**. The products are the result of the triethylamine dehydrochlorination of the acid chlorides to phenoxyketenes **4**, which undergo an intramolecular [2 + 2] cycloaddition with one or the other

Scheme I



Scheme II[a,b]



[b] Compounds **7a–c** were not isolable because of decarboxylation to the corresponding isoflavones. Compounds **7d,e** were isolable but could be decarboxylated to the corresponding isoflavones by heating at 150 °C for 5 h.

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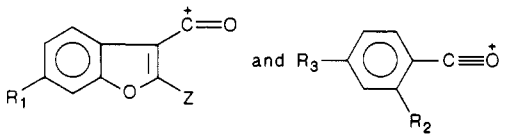
Table I. Distributions of Isoflavone or Isoflavone β-Lactones and 3-Aroylbenzofurans

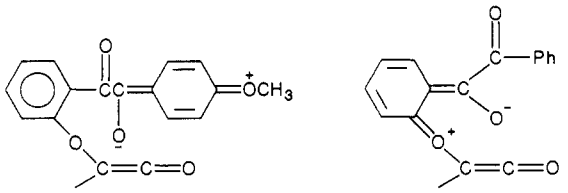
acid	products	yields[a] (%)	acid	products	yields[a] (%)
3a	**6a**	50	**3d**	**6d**	63
	8a	23		**7d**	trace
3b	**6b**	15	**3e**	**6e**	24
	8b	55		**7e**	49
3c	**8c**	59	**3f**	**7f**	57
	6c			**6f**	

[a] The yields are based on the carboxylic acids and represent separated and purified yields.

Scheme III



Scheme IV

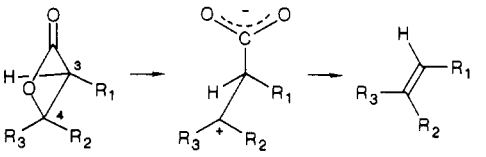


of the two carbonyl groups present to yield the expected β-lactones. As revealed in Scheme II, cycloaddition of the ketene function with the carbonyl group bonded to the same ring results in the β-lactone **5**, which readily decarboxylates to the 3-aroylbenzofurans **6**. Conversely, cycloaddition of the ketene function to the other carbonyl group results in the isoflavone β-lactone **7**, which in some instances, **7a–c**, readily decarboxylate to the isoflavones **8** and in other instances, **7d–e**, require heating at 150 °C for decarboxylation to occur. The product distributions of isoflavone or isoflavone β-lactone and 3-aroylbenzofurans are shown in Table I. In those preparations where a mixture of isoflavone or isoflavone β-lactone and 3-aroylbenzofuran were obtained, separation was accomplished by silica gel column chromatography. The isoflavones or isoflavone β-lactones and 3-aroylbenzofurans were easily differentiated by GC/MS. The 3-aroylbenzofurans consistently reveal the major mass fragments as shown in Scheme III, while the isoflavones and isoflavone β-lactones do not.

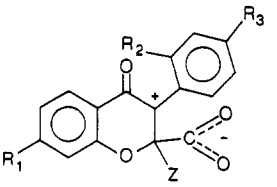
It is apparent from the data in Table I that the presence of a methoxy group(s) in an ortho and/or para position influences the carbonyl group that undergoes cycloaddition with the ketene functionality. If there is no substituent on the benzene ring as in **3a**, the total yield is 73% with a ratio of 3-aroylbenzofuran to isoflavone of 2. Alternatively, if there is a methoxy substituent in the ortho position as in **3b**, the ratio of isoflavone to benzofuran is 3.6 and if there are two methoxy groups ortho and para as in **3c**, no benzofuran is obtained, only isoflavone. These results are quite consistent with an intramolecular ketene cycloaddition process when the two resonance structures as shown in Scheme IV are considered for the two different processes.

The decarboxyation of the intramolecular [2 + 2] ketene cycloaddition products **5** and **7** is interesting. The β-lactones derived from cycloaddition to the carbonyl group bonded to the same benzene ring **5** are not isolable and decarboxylate during the cycloaddition process to yield the 3-aroylbenzofurans **6**. The formation of the resonance-stabilized benzofuran and the ring strain associated with

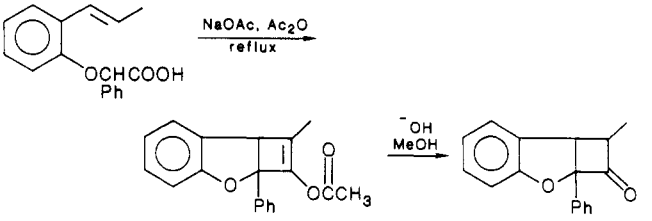
Scheme V



Scheme VI



Scheme VII



9 **10**

a four-membered ring fused to a five-membered ring that is fused to a benzene ring must be responsible for this facile decarboxylation. Conversely, the isoflavone β-lactones were isolable and quite stable in some instances and unstable in other cases. It is pertinent to note that the isoflavone β-lactones could not be isolated when Z = H in **7** although a weak β-lactone band (1850 cm^{-1}) in the infrared spectrum was observable from an aliquot of the reaction mixture. These results are quite consistent with a recent report on the thermal decarboxylation of β-lactones.[7] This report provides evidence of a zwitterionic intermediate for this decarboxylation. The stabilization of the unsaturated center at C-4 tremendously affects the rate of decarboxylation (Scheme V). The better stabilized C-4, the greater the rate of decarboxylation. In our isoflavone β-lactones **7**, if Z = H, the 3-phenyl group can rotate in the plane of the resulting sp^2-hybridized carbon atom and C-3 is stabilized by phenyl (when $R_2 = R_3 = H$) or more significantly (Scheme VI) by anisyl resonance stabilization (when $R_2 = R_3 = OMe$). Consequently, decarboxylation occurs very readily. However, if Z = Me, the zwitterions are forced to a twisted conformation and C-3 does not obtain the stabilizing influence of the phenyl and/or anisyl substituents and thus decarboxylation occurs only upon heating.

Whalley and co-workers have described the cyclization of some benziloxyacetic acids similar to **3** to yield the isoflavone, the isomeric 3-aroylcoumarone, or a mixture of both.[6] The cyclizations were accomplished by refluxing the acid and sodium acetate in acetic anhydride for several hours; i.e., Perkin reaction conditions. It became apparent to us that these described cyclizations could in fact be intramolecular [2 + 2] ketene cycloaddition reactions with subsequent decarboxylation in refluxing acetic anhydride. To determine if the phenoxyketenes are formed under these Perkin reaction conditions, we treated [(*o*-

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propenylphenoxy)phenyl]acetic acid with sodium acetate in acetic anhydride and refluxed for 4 h. The cyclobutanone enol ester **9** was formed in 90% yield and was easily hydrolyzed in basic methanol to the expected cyclobutanone **10**, thus establishing that the phenoxyketenes are formed under these conditions (Scheme VII). Furthermore, we have refluxed acid **3d** with sodium acetate and acetic anhydride in benzene and obtained both the 3-aroylbenzofuran **6d** and the β-lactone isoflavone **7d**. Also, these reaction conditions on **3e** resulted in the formation of the 3-aroylbenzofuran **6e** and the β-lactone isoflavone **7e**. This further substantiates that treatment of the acid with sodium acetate and acetic anhydride in refluxing benzene does generate the phenoxyketene which undergoes a [2 + 2] cycloaddition to form the β-lactone. Hence, the use of Perkin reaction conditions does not necessitate the normal Perkin reaction mechanism but instead may involve a ketene intermediate as these experiments demonstrate.

Experimental Section

NMR spectra were recorded on a VXR-300 spectrometer, employing deuteriochloroform as the solvent with TMS as the internal standard. The IR spectra were obtained on a Perkin-Elmer 1330 spectrometer. The GC/MS spectra were recorded on a Hewlett-Packard 5790A Series GC/mass spectrometer. All melting points are uncorrected. Column chromatography was performed on EM Laboratories silica gel 60 PF-254. Rotary preparative chromatography was performed with silica gel 7GF from Baker Chemical Co. (precoated TLC plates, 2.5-mm thick, 50 g of silica gel on glass).

The starting 2-methoxybenzils **1a** and **1b** were prepared by a literature procedure[8] in 61% and 41% yields, respectively, and **1c** was prepared by a different literature procedure in 41% yield.[9]

Preparation of 2-Hydroxybenzils 2a–c. Compound **1a** was demethylated by using concentrated HCl and pyridine to give **2a** in 71% yield: IR 1720, 1670, 1630 cm^{-1}; GC/MS (70 eV), m/e (relative intensity) 226 (M^+, 5), 121 (100), 105 (38).

Compound **2b** was obtained by refluxing **1b** with 48% HBr and AcOH for 1.5 h: IR 3420, 1630, 1595 cm^{-1}; GC/MS (70 eV), *m/e* (relative intensity) 256 (M^+, 5), 135 (100), 121 (19).

Compound **1c** was heated on the steam bath with 3 equiv of $AlCl_3$ in ethylene chloride for 2.5 h and workup with acid followed by base yielded 2,2′-dihydroxy-4,4′-dimethoxybenzil, mp 135–137 °C (lit.[9] mp 136–139 °C). This benzil was methylated with 1 equiv of dimethyl sulfate in the presence of potassium carbonate to give **2c**, which was crystallized from MeOH and hexane to give a 26% yield, mp 110 °C (lit.[6a] mp 110 °C).

General Procedure for 2-Acetoxybenzil Preparations 3a–f. A solution of the 2-hydroxybenzil in acetone containing 1.1 equiv of ethyl α-bromoacetate or ethyl α-bromopropionate and 1.5–2 equiv of anhydrous potassium carbonate was gently refluxed. Refluxing is continued until the starting compounds are consumed as evidenced by TLC. About 7–9 h are required for completion of the reaction as the yellowish reaction solution becomes colorless. The reaction solution is filtered and the acetone removed under reduced pressure. The concentrated filtrate was hydrolyzed with 2 equiv of KOH in 90% alcohol. Some of the alcohol was removed under reduced pressure, water was added, and then the solution was acidified with dilute HCl. The acid solution was extracted with ether and the ether extracts were dried over anhydrous magnesium sulfate. Evaporation of the ether resulted in the 2-acetoxybenzils. Infrared revealed that the ester carbonyl absorptions at 1750 cm^{-1} had disappeared and the acid carbonyl absorption at 1720 cm^{-1} was present.

General Procedure for Intramolecular Ketene Cycloadditions. The 2-acetoxybenzils were stirred with 5–8 equiv of oxalyl chloride in dry benzene for 8–12 h. When IR revealed that the carbonyl group of the acid at 1720 cm^{-1} had disappeared and the acid chloride carbonyl absorption at 1800 cm^{-1} had appeared, the excess oxalyl chloride and benzene were removed under vacuum. The oily acid chlorides were dissolved in dry benzene and added slowly using a syringe to 3–4 equiv of triethylamine in benzene. (These cycloadditions were run under a nitrogen atmosphere and in flame-dried glassware by using a magnetic stirrer). The solutions were stirred for 8–12 h at about 50 °C. The amine salt was removed by filtration and the filtrate concentrated under reduced pressure. The isoflavone or isoflavone β-lactone and 3-aroylbenzofurans were separated by silica gel chromatography using an eluting solvent of ethyl acetate/hexane (1:9 to 1:7).

3-Benzoylbenzofuran (6a) and Isoflavone (8a). From 1.42 g of **3a**, a mixture of **6a** and **8a** was obtained. Silica gel chromatography resulted in 0.55 g (50%) of **6a** and 0.25 g (23%) of **8a**.

6a: mp 63–65 °C (lit.[11] mp 60 °C); IR 1650 cm^{-1}; GC/MS (70 eV), *m/e* (relative intensity) 222 (M^+, 73), 194 (13), 145 (100), 105 (13), 77 (33); ^1H NMR ($CDCl_3$) δ 8.05 (s, 1 H), 7.4–7.9 (m, 8 H), 8.2 (m, 1 H).

8a: mp 133–135 °C (lit.[12] mp 132 °C); IR 1630 cm^{-1}; GC/MS (70 eV), *m/e* (relative intensity) 222 (M^+, 77), 120 (26), 92 (27); ^1H NMR ($CDCl_3$) δ 7.4–7.85 (m, 8 H), 8.0 (s, 1 H), 8.3 (m, 1 H).

3-(2-Methoxybenzoyl)benzofuran (6b) and 2′-Methoxyisoflavone (8b). From 0.46 g of acid **3b**, a mixture of **6b** and **8b** was obtained. Separation and purification by silica gel chromatography resulted in 55 mg (15%) of **6b** as an oil and 200 mg (55%) of **8b**.

6b: IR 1645, 1595, 1550 cm^{-1}; GC/MS (70 eV), *m/e* (relative intensity) 252 (M^+, 100), 235 (23), 207 (10), 145 (40), 135 (14); ^1H NMR ($CDCl_3$) δ 3.8 (s, 3 H), 7.0 (m, 2 H), 7.7–8.1 (m, 5 H), 7.9 (s, 1 H), 8.6 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 190.1, 156.9, 155.7, 153.7, 131.9, 129.7, 129.1, 125.6, 124.6, 124.5, 122.8, 122.9, 120.4, 111.6, 111.4, 55.7.

8b: mp 180–181 °C (lit.[13] mp 174–178 °C, lit.[6a] mp 184 °C); IR 1640, 1600, 1575 cm^{-1}; GC/MS (70 eV), *m/e* (relative intensity) 252 (M^+, 100), 221 (78), 131 (42), 121 (34); ^1H NMR ($CDCl_3$) δ 3.8 (s, 3 H), 7.0 (m, 2 H), 7.3–7.5 (m, 4 H), 7.7 (m, 1 H), 8.0 (s, 1 H), 8.3 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 178.0, 157.5, 156.3, 154.2, 133.4, 131.7, 129.8, 126.4, 125.0, 124.6, 122.7, 120.8, 120.6, 118.0, 111.2, 55.7.

Anal. Calcd for $C_{16}H_{12}O_3$: C, 76.19; H, 4.76. Found: C, 76.18; H, 4.92.

2′,4′,7-Trimethoxyisoflavone (8c). From 0.5 g of **3c** was obtained 230 mg (59%) of **8c**: mp 148–149 °C (lit.[14] mp 148 °C); IR 1630, 1600 cm^{-1}; GC/MS (70 eV), *m/e* (relative intensity) 312 (M^+, 100), 295 (14), 283 (10), 281 (50), 266 (10), 161 (19), 151 (25); ^1H NMR ($CDCl_3$) δ 3.75 (s, 3 H), 3.85 (s, 3 H), 3.9 (s, 3 H), 6.5–7.3 (m, 5 H), 7.9 (s, 1 H), 8.2 (d, 1 H); ^{13}C NMR ($CDCl_3$) δ 176.0, 163.8, 161.1, 158.5, 157.9, 153.7, 132.3, 127.8, 122.2, 114.3, 113.5, 104.4, 100.1, 99.1, 55.8, 55.8, 55.7, 55.4.

3-Benzoyl-2-methylbenzofuran (6d) and β-Lactone of 2-Carboxy-3-hydroxy-2-methyl-2,3-dihydroisoflavone (7d). From 0.5 g of acid **3d**, a mixture of **6d** and **7d** was obtained. Separation by silica gel chromatography resulted in 240 mg (63%) of **6d** and a trace of **7d**.

6d: obtained as an oil by initially column chromatography and then rotary chromatography; IR 1640, 1570 cm^{-1}; GC/MS (70 eV), *m/e* (relative intensity) 236 (M^+, 79), 207 (10), 159 (35), 105 (15); ^1H NMR ($CDCl_3$) δ 2.5 (s, 3 H) 7.25–7.7 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 191.9, 161.9, 153.6, 139.3, 132.6, 129.0, 128.5, 126.8, 124.3, 123.5, 121.3, 116.9, 110.8, 14.7.

7d: mp 91–93 °C; IR 1850, 1685, 1605 cm^{-1}; GC/MS (70 eV), *m/e* (relative intensity) 236 ($M^+ - CO_2$, 61), 235 (100), 115 (17), 92 (11); ^1H NMR ($CDCl_3$) δ 1.45 (s, 3 H), 7.1–8.0 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 186.1, 168.3, 157.9, 137.2, 131.6, 130.1, 128.9, 128.7, 125.5, 123.9, 119.4, 118.5, 90.9, 83.9, 18.8.

3-(2-Methoxybenzoyl)-2-methylbenzofuran (6e) and β-Lactone of 2-Carboxy-3-hydroxy-2-methyl-2′-methoxy-2,3-

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dihydroisoflavone (7e). From 0.5 g of acid **3e**, a mixture of **6e** and **7e** was obtained. Separation by silica gel chromatography resulted in 90 mg (24%) of **6e** and 210 mg (49%) of **7e**.

6e: mp 90–92 °C; IR 1630, 1600, 1570 cm^{-1}; GC/MS (70 eV), *m/e* (relative intensity) 266 (M^+, 100), 235 (38), 234 (10), 159 (32), 135 (44); ^1H NMR ($CDCl_3$) δ 2.4 (s, 3 H), 3.8 (s, 3 H), 7.0–7.6 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 191.1, 163.2, 156.6, 153.28 131.7, 130.6, 128.5, 126.2, 123.9, 123.5, 121.1, 120.6, 117.7, 111.2, 110.4, 55.4, 14.3.

Anal. Calcd for $C_{13}H_{14}O_3$: C, 76.69; H, 5.26. Found: C, 76.67; H, 5.32.

7e: mp 110–111 °C; IR 1850, 1690, 1605 cm^{-1}; GC/MS (70 eV), *m/e* (relative intensity) 310 (M^+, 3), 266 (25), 251 (43), 235 (100); ^1H NMR ($CDCl_3$) δ 1.4 (s, 3 H), 3.7 (s, 3 H), 6.9–8.0 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 186.0, 169.2, 158.0, 155.4, 136.8, 130.6, 128.8, 126.9, 126.6, 122.0, 121.4, 118.9, 118.5, 110.6, 91.0, 84.0, 55.6 18.0.

β-Lactone of 2-Carboxy-3-hydroxy-2-methyl-2′,4′,7-trimethoxy-2,3-dihydroisoflavone (7f). A 0.48-g (57%) portion of **7f** was obtained from 1 g of **3f**: mp >135 °C dec; IR 1850, 1685, 1610 cm^{-1}; GC/MS (70 eV), *m/e* (relative intensity) 326 ($M^+ - CO_2$, 39), 312 (8), 311 (41), 295 (100); ^1H NMR ($CDCl_3$) δ 1.5 (s, 3 H), 3.6 (s, 3 H), 3.8 (s, 3 H), 3.9 (s, 3 H), 6.45–6.75 (m, 4 H), 7.4 (d, 1 H), 7.9 (d, 1 H); ^{13}C NMR ($CDCl_3$) δ 184.5, 169.5 166.6, 161.8, 160.1, 156.3, 130.6, 127.6, 114.7, 112.3, 112.2, 104.8, 101.3, 98.9, 90.9, 83.6, 55.8, 55.6, 55.4, 18.1.

Anal. Calcd for $C_{20}H_{18}O_7$: C, 64.86; H, 4.86. Found: C, 65.35; H, 5.20.

6-Methyl-1-phenyl-2-oxa-3,4-benzobicyclo[3.2.0]heptan-7-one (10). A 0.5-g (1.87 mmol) portion of [(*o*-propenylphenoxy)phenyl]acetic acid was refluxed with 2.0 g (24 mmol) of sodium acetate and 15 mL (159 mmol) of acetic anhydride for 4 h. The reaction mixture was poured into a cold dilute aqueous sodium of hydroxide solution and extracted with ether. The ether extract was dried over anhydrous magnesium sulfate and then evaporated to 0.5 g (90%) of **9**: IR, 1760, 1680, 1605, 1590, cm^{-1}; GC/MS (70 eV), *m/e* (relative intensity) 292 (M^+, 13), 250 ($M^+ - 42$, 78), 235 (11), 222 (27), 221 (47), 205 (59), 194 (29), 178 (22), 165 (40), 42 (100); ^1H NMR ($CDCl_3$) δ 1.9 (s, 3 H), 2.15 (s, 3 H), 3.8 (s, 1 H), 6.8–7.6 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 166.8, 162.1, 137.5, 136.2, 134.1, 128.7, 128.5, 128.2, 127.9, 125.6, 124.4, 120.6, 111.7, 93.7, 55.3, 20.6, 12.3.

Compound **9** was treated with a 50% aqueous potassium hydroxide solution containing methanol. The methanol was removed under reduced pressure and the aqueous residue extracted with ether. Upon drying the ether over anhydrous magnesium sulfate, and the ether was evaporated to yield 0.3 g (64%) of **10**. The mp and IR and ^1H and ^{13}C NMR spectra were identical with those previously reported.[1f]

Cyclization of 3d and 3e Using Perkin Reaction Conditions. A 0.5-g portion of **3d** was refluxed with 1.5 equiv of acetic anhydride and 2.0 equiv of sodium acetate in 30 mL of benzene for 24 h. The reaction mixture was cooled and filtered and an IR spectrum of the concentrated filtrate revealed a strong β-lactone peak at 1850 cm^{-1}. Rotary chromatography of the filtrate resulted in 0.1 g of **6d** (25%) and 0.08 g of **7d** (17%).

A 0.1-g portion of **3e** was treated as described above. An IR spectrum of an aliquot of the reaction mixture revealed a strong β-lactone peak at 1850 cm^{-1}. Thin layer chromatography revealed two spots with the same R_f values as characterized above for **6e** and **7e**. Preparative thin layer chromatography gave a trace of **6e** and **7e**, which were identified by IR and GC/MS.

General Procedure for Decarboxylation of β-Lactones 7d–f. A sample of the β-lactone was placed in a melting point capillary tube and heated in a melting point apparatus. When the temperature reached 135–140 °C, small bubbles began to appear. The temperature was kept at 150 °C for 5 h. The tube was broken and the contents were recovered for analysis.

2-Methylisoflavone (8d). This isoflavone was recovered as an oil: IR 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30 (s, 3), 7.25–8.25 (m, 9 H).

2-Methyl-2′-methoxyisoflavone (8e). This isoflavone was also recovered as an oil: IR 1645, 1600, 1575 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.2 (s, 3 H), 3.8 (s, 3 H), 7.0–8.2 (m, 8 H).

2-Methyl-2′,4′,7-trimethoxyisoflavone (8f). This isoflavone was recovered as a crystalline solid: mp 185–187 °C; IR 1625, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.2 (s, 3 H), 3.75 (s, 3 H), 3.85 (s, 3 H), 3.90 (s, 3 H), 6.6 (m, 2 H), 6.9 (m, 2 H), 7.1 (m, 1 H), 8.1 (d, 1 H); ^{13}C NMR ($CDCl_3$) δ 176.2, 163.7, 163.5, 160.9, 158.3, 157.6, 132.4, 127.7, 119.4, 117.2, 114.7, 113.8, 104.7, 99.9, 99.0, 55.7, 55.6, 55.4, 19.2.

Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.94; H, 5.52. Found: C, 69.86; H, 5.63.

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Registry No. **1a**, 34082-43-4; **1b**, 6706-92-9; **1c**, 82362-01-4; **2a**, 34589-99-6; **2b**, 107943-61-3; **2c**, 95281-05-3; **3a**, 113180-51-1; **3b**, 103031-10-3; **3c**, 103206-86-6; **3d**, 113180-52-2; **3e**, 113180-53-3; **3f**, 113180-54-4; **6a**, 6454-01-9; **6b**, 113180-55-5; **6d**, 18703-72-5; **6e**, 93321-78-9; **7d**, 113180-56-6; **7e**, 113180-57-7; **7f**, 113180-58-8; **8a**, 574-12-9; **8b**, 7622-32-4; **8c**, 7678-84-4; **8d**, 24258-66-0; **8e**, 113180-59-9; **8f**, 70387-01-8; **9**, 113218-61-4; **10**, 99477-35-7; 2-$HO_2CCH(Ph)OC_6H_4CH{=}CHCH_3$, 99477-28-8; $MeCHBrCO_2CH_2Me$, 535-11-5; 2,2′-dihydroxy-4,4′-dimethoxybenzil, 6706-94-1; ethyl α-bromoacetate, 105-36-2.

A General Method for the Synthesis of Tetramic Acid Derivatives

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Fragmentation of 2,5-disubstituted isoxazolium salts resulted in the formation of highly functionalized β-keto amide derivatives. Subsequent base-catalyzed cyclization afforded 3-acyltetramic acid derivatives similar to the tetramic acid moieties found in tirandamycin A/B and streptolydigin. The scope and limitations of this methodology for the total synthesis of naturally occurring tetramic acid antibiotics is discussed.

The dienoyl tetramic acids tirandamycin A (**1**) and B (**2**)[1] streptolydigin (**3**)[2] and ikarugamycin (**4**)[3] are representative examples of the structurally diverse family of tetramic acid antibiotics. The common feature of these natural products is the 2,4-pyrrolidinedione or tetramic

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