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3-Aryltetronic Acids: Efficient Preparation and Use as Precursors for Vulpinic Acids

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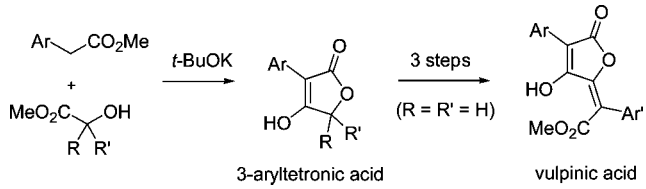

3-Aryltetronic acids were prepared in one step by treatment of a mixture of methyl arylacetates and methyl hydroxyacetates with potassium *tert*-butoxide, via tandem transesterification/Dieckmann condensation. Several mushroom or lichen pigments, vulpinic acids, were synthesized from 3-(4-methoxyphenyl)tetronic acid in three steps involving the reaction of the corresponding dianion with an α-ketoester and the dehydration of the tertiary alcohols obtained into mixtures of (*E*)- and (*Z*)-alkenes, which were converted under UV irradiation at 254 nm to natural (*E*)-isomers. Syntheses of pinastric acid, 4,4′-dimethoxyvulpinic acid, and the first synthesis of recently isolated methyl 3′,5′-dichloro-4,4′-di-*O*-methylatromentate were hence achieved in an efficient manner.

Introduction

The tetronic acid (4-hydroxybutenolide) moiety occurs in the structure of many natural products having important biological activities.[1] This is the case of ascorbic acid (vitamin C). Various terpenes, alkaloids, antibiotics, and the mushroom pigments pulvinic acids also contain a tetronic acid-derived fragment.[1] Several non-natural 3-aryltetronic acids have been reported as insecticides and acaricides[2] and as antioxidant and anti-inflammatory compounds.[3] We became interested in developing an efficient synthetic approach to these compounds, which could also serve as building blocks in the synthesis of pulvinic acid derivatives[4−6] (Figure 1).

Several synthetic routes to variously substituted tetronic acids have been reported.[1] Recent methodologies developed make use of the reaction of active methylene compounds with activated derivatives of α-hydroxyacids,[7] the oxidative expansion of 4-hydroxy-2-cyclobutenone,[8] the base-catalyzed reaction of alkyl propiolates with aldehydes,[9a] the acid-catalyzed hydrolysis-

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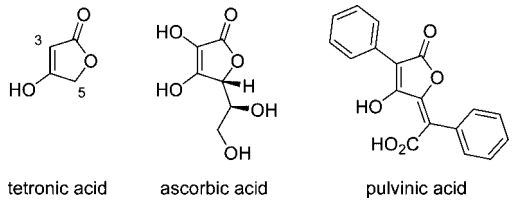
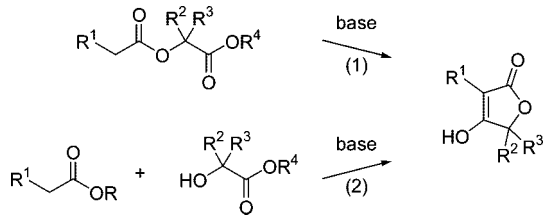


FIGURE 1. Tetronic acid and natural products, containing a tetronic acid moiety.

SCHEME 1. Synthesis of Tetronic Acids via Dieckmann Condensation

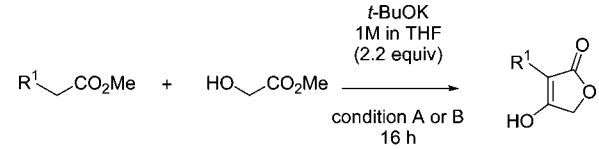


lactonization of enamines obtained from γ-hydroxy-α,β-alkynyl esters,[9b] and the tandem Wittig−Claisen reaction of α-hydroxyesters with (triphenylphosphoranylidene)ketene.[10] Methyl 3-aryltetronates have been prepared from 3-bromo-4-methoxy-2(5*H*)-furanone via Suzuki−Miyaura cross-coupling.[11]

The Dieckmann condensation,[12] which was first reported by Lacey in the preparation of 3-acetyltetronic acids,[13] has been used for the synthesis of 3-aryltetronic acids[14] and is still widely employed.[1,15] It is based on the treatment of an ester of α-hydroxyester with an appropriate base (Scheme 1, eq 1). We reasoned that direct access to 3-aryltetronic acids could be possible by simply mixing an alkyl arylacetate and an α-hydroxyester in the presence of a base (Scheme 1, eq 2). Such a process would thus involve a transesterification step, followed by the Dieckmann condensation. It is worth noting that recently reported cross-coupling methods allow efficient preparation of various alkyl arylacetates.[16]

We recently reported preliminary results concerning the one-pot synthesis of 3-aryltetronic acids.[17] Herein we report these results in full detail as well as the synthesis of three natural methyl pulvinates (vulpinic acids). Pinastric acid, methyl 4,4′-di-*O*-methylatromentate (4,4′-dimethoxyvulpinic acid), and recently isolated methyl 3′,5′-dichloro-4,4′-di-*O*-methylatromentate[18] were thus synthesized from 3-(4-methoxyphenyl)tetronic acid in a straightforward manner, involving as the key step the reaction of the corresponding dianion with α-ketoesters.

TABLE 1. One-Pot Synthesis of Tetronic Acids 3a−k from Methyl Arylacetates and Methyl Glycolate



1 (1 equiv) **2a** (1.2 equiv) **3**

entry	1	3	R^1	condition[a]	yield (%)
1	**1a**	**3a**	C_6H_5	A	97
2	**1b**	**3b**	2-(MeO)C_6H_4	A	95
3	**1c**	**3c**	3-(MeO)C_6H_4	A	80
4	**1d**	**3d**	4-(MeO)C_6H_4	A	85
5	**1d**	**3d**	4-(MeO)C_6H_4	B	90
6	**1e**	**3e**	3,4-$(MeO)_2C_6H_3$	A	81
7	**1f**	**3f**	4-(HO)C_6H_4	A[b]	80
8	**1g**	**3g**	4-ClC_6H_4	A	82
9	**1h**	**3h**	4-BrC_6H_4	A	61
10	**1h**	**3h**	4-BrC_6H_4	B	59
11	**1i**	**3i**	4-FC_6H_4	A	98
12	**1j**	**3j**	4-$(O_2N)C_6H_4$	A	0
13	**1k**	**3k**	2-thienyl	B	70

[a] Condition A: THF, reflux. Condition B: DMF, rt. [b] Three equivalents of *t*-BuOK was employed.

Results and Discussion

Among the bases that have been employed to carry out the Dieckmann condensation, we selected potassium *tert*-butoxide, which is available in anhydrous form as a solution in THF. In the reaction involving methyl 4-methoxyphenylacetate **1d** and methyl glycolate **2a**, optimal yields of the corresponding tetronic acid were obtained by performing it overnight (16 h), either in THF at reflux or in DMF at room temperature.[17] Although 1 equiv *t*-BuOK should theoretically be sufficient, 2.2 equiv of base was required for better results.

Several 3-aryl- and 3-heteroaryltetronic acids were prepared from methyl glycolate **2a** and various substituted acetates, which were either commercially available or readily prepared from the corresponding carboxylic acids.[19] The results are summarized in Table 1. In a few cases, both condition A (THF, reflux) and condition B (DMF, rt) were applied from the same esters, leading to equally good results (Table 1, entries 3, 4, 9, and 10). Performing the reaction in THF facilitated the workup, and thus condition A was applied in most cases. The yields were usually good to excellent. Among the other characteristic features of the tetronic acids isolated is the chemical shift of the singlet corresponding to the methylene protons [δ varying from 4.73 to 4.83 in $(CD_3)_2CO$]. Several methyl methoxyphenylacetates were used as substrates (Table 1, entries 2−5). The position of the methoxy group on the aromatic ring had little influence on the yield. Compound **3d** had been formerly prepared on a larger scale by the usual Dieckmann condensation in 67% yield,[14] while it was obtained in 90% yield following our one-pot process.

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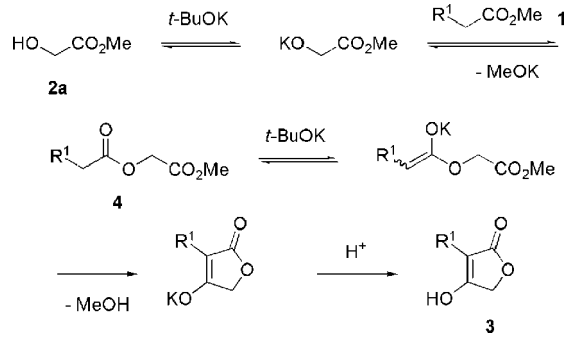
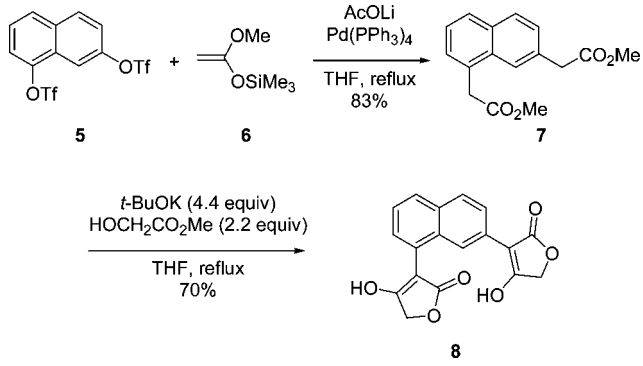
SCHEME 2. Mechanism of the One-Step Synthesis of Tetronic Acids



SCHEME 3. Synthesis of Bis(tetronic acid) 8



Tetronic acids substituted by 4-halo and 4-hydroxyphenyl groups were also efficiently obtained (Table 1, entries 7−11). However, the reaction of methyl 4-nitrophenylacetate **1j** did not afford the expected adduct (Table 1, entry 12). The ester was recovered unchanged after the workup. It may be assumed that under the reaction conditions ester **1j**, in which the methylene protons are very acidic, is readily converted to the corresponding stable potassium enolate and then cannot lead to the transesterification intermediate. A tetronic acid substituted by a 2-thienyl group was obtained in 70% yield (Table 1, entry 13).

The process leading to the formation of tetronic acids **3** very likely involves a transesterification and a Dieckmann condensation as the two main steps (Scheme 2). The transesterification of methyl ester **1** by the alkoxide derived from methyl glycolate yields ester **4**, which is then converted to the tetronic acid by the usual Dieckmann condensation.

It was also possible to achieve a double cyclization, starting from diester **7** (Scheme 3). This diester was prepared from ditriflate **5**[20] by a palladium-mediated double cross-coupling reaction involving (1-methoxyvinyloxy)trimethylsilane (**6**)[21] in the presence of lithium acetate.[22] Bis(tetronic acid) **8** was obtained in 70% yield by treatment of **7** with methyl glycolate (2.2 equiv) and *t*-BuOK (4.4 equiv) in refluxing THF. The two singlets corresponding to the methylene protons appeared at $\delta = 4.80$ and 4.90 in $(CD_3)_2SO$.

We also showed that thiotetronic acid can be prepared using the one-pot process (Scheme 4). Using methyl thioglycolate (**9**) instead of methyl glycolate, the reaction with ester **1d** led to expected adduct **10** in a 53% yield. The chemical shift of the methylene proton singlet is 4.10 ppm in $(CD_3)_2CO$.

SCHEME 4. Synthesis of Thiotetronic Acid 10

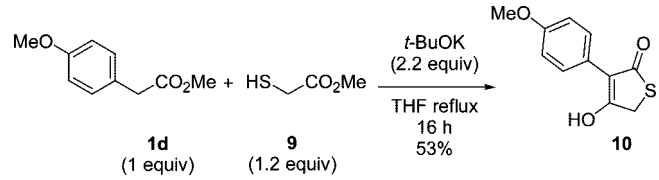
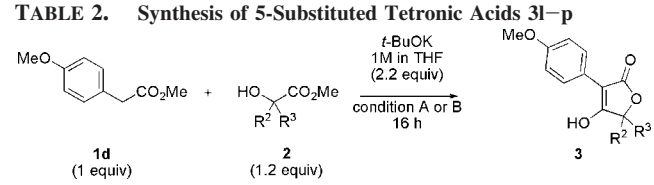


TABLE 2. Synthesis of 5-Substituted Tetronic Acids 3l−p



entry	2	3	R^2	R^3	condition[a]	yield (%)
1	**2b**	**3l**	Me	H	A	97
2	**2b**	**3l**	Me	H	B	96
3	**2c**	**3m**	$CH_3(CH_2)_3$	H	B[b]	60
4	**2d**	**3n**	C_6H_5	H	B	39
5	**2e**	**3o**	Me	Me	A	72
6	**2e**	**3o**	Me	Me	B	64
7	**2f**	**3p**	$-(CH_2)_5-$		A	70

[a] Condition A: THF, reflux. Condition B: DMF, rt. [b] The ethyl ester of 2-hydroxyhexanoic acid was employed.

By applying the one-pot conditions to the reaction of methyl 4-methoxyphenylacetate (**1d**) with various 2-substituted hydroxyacetates, we prepared several 5-substituted tetronic acids (Table 2). Both conditions A and B were found to be efficient for the preparation of tetronic acids **3l**, substituted at C5 by one methyl group (97 and 96% yield, Table 2, entries 1and 2, respectively), and **3o**, substituted at C5 by two methyl groups (72 and 64% yield, Table 2, entries 5 and 6, respectively). Under both conditions, compound **3l**, obtained from methyl (-)-lactate, was almost completely racemized. The reaction of **1d** with ethyl 2-hydroxyhexanoate in DMF afforded adduct **3m** in a 60% yield (Table 2, entry 3). The reaction involving methyl mandelate (**2d**) yielded C5-phenyl-substituted tetronic acid **3n** in only a 39% yield (Table 2, entry 4). In the intermediate arising from the transesterification of **2d**, the proton located in the phenyl α-position should be as acidic as that of the methylene protons, which may account for the lower efficiency of the cyclization in that case. Spirotetronic acid **3p** was obtained uneventfully, using the method from methyl 1-hydroxycyclohexanecarboxylate, prepared by esterification[19] of the corresponding hydroxyacid[23] (Table 2, entry 7). It is worth noting that several 3-arylspirotetronic acid derivatives, for example, the patented compounds spirodiclofen (Endivor) and spiromesifen (Oberon), have been reported to be efficient insecticides or acaricides.[2]

Tetronic acids **3** that are not C5-substituted can be viewed as precursors for the synthesis of vulpinic and pulvinic acids. An alkylidenation at this position that would introduce the double bond substituted by an aryl group and a carboxyl function is required.[24] The preparation of three permethylated pulvinic acids from methyl 3-aryltetronates, via the reaction of the

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SCHEME 5. Synthesis of Vulpinic Acids 13a−c

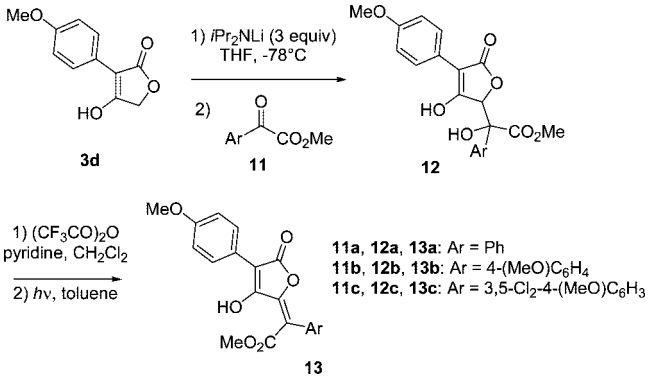

TABLE 3. Synthesis of Alcohols 12 and Vulpinic Acids 13

entry	12	13	Ar	12[a] yield (%)	12[b] isomer ratio	13[c] yield (%)
1	**12a**	**13a**	Ph	86	61/39	95
2	**12b**	**13b**	4-(MeO)C_6H_4	75	74/26	71
3	**12c**	**13c**	3,5-Cl_2-4-(MeO)C_6H_3	60	100/0	95

[a] Yield and isomer ratio in the isolated compound. [b] Ratio of less polar isomer/more polar isomer. [c] Overall yield over two steps.

corresponding anion with methyl 2-aryl-2-oxoacetates, was reported by Pattenden.[5j] Recently, we developed an access to various pulvinic derivatives, starting from tetronic acid protected as its benzyl ether and making use of a Suzuki−Miyaura cross-coupling.[6d,e]

Having efficient access to 3-aryltetronic acids **3**, we could envisage a straightforward synthesis of pulvinic derivatives from these compounds, especially if any protection step could be avoided. Three natural products that could be obtained starting from tetronic acid **3d** were chosen as targets (Scheme 5, Table 3). Pinastric acid (**13a**) has been isolated from lichens, and its antiviral, antimicrobial, and antitumor activities were recently reported.[25] 4,4′-Dimethoxyvulpinic acid (**13b**) has been isolated from *Pulveroboletus ravanelii*.[26] Several syntheses of **13a**[5o,q,6e] and **13b**[5f,h,6b] have been described. Methyl 3′,5′-dichloro-4,4′-di-*O*-methylatromentate (**13c**),[18] which was recently isolated from the fruiting body of *Scleroderma* sp. collected in Malaysia, has not yet been synthesized.

The preparation of alcohol **12a** by addition of the dianion generated from 3-(4-methoxyphenyl)tetronic acid **3d** to methyl benzoylformate (**11a**) was first studied. The amount of lithium diisopropylamide (LDA) employed to prepare the dianion was found to be an important parameter. Several attempts using 2.2 equiv of LDA resulted in the formation of **12a**, albeit in modest uncertain yields. On the contrary, reproducible good yields of **12a** were obtained using 3 equiv of LDA. Thus, the dianion was prepared in THF at −78 °C, and ketoester **11a** was added at this temperature. The reaction mixture was allowed to warm to room temperature overnight. This afforded alcohol **12a** as a mixture of two diastereomers in an 86% yield. The ratio of the less polar isomer to the more polar isomer was 61/39. In the ^{1}H NMR spectrum (CD_3OD), the methine proton appears as a singlet at $\delta = 5.62$ (less polar isomer) and at $\delta = 5.57$ (more polar isomer). Hence, it was shown that protection of the enol function of the tetronic derivative was not necessary for performing this key step.

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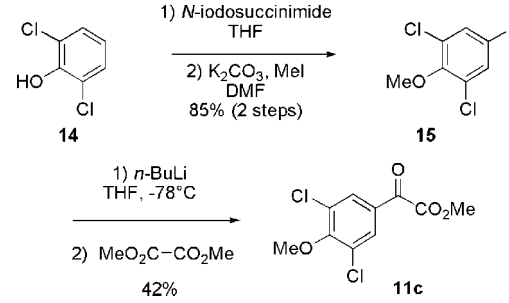
SCHEME 6. Synthesis of Ketoester 11c



Two other ketoesters were then used as substrates. Methyl 2-(4-methoxyphenyl)-2-oxoacetate **11b** was prepared by reaction of 4-methoxyphenyllithium generated from 4-iodoanisole with dimethyl oxalate.[27] Methyl 2-(3,5-dichloro-4-methoxyphenyl)-2-oxoacetate **11c** was synthesized in three steps from 2,6-dichlorophenol (Scheme 6). This compound was iodinated,[28] and then the phenol was converted to methyl ether **15**. Metalation of **15** with butyllithium, followed by treatment with 2 equiv of dimethyl oxalate, led to ketoester **11c**.

Addition of the dianion of **3d** to ketoesters **11b** and **11c** afforded alcohols **12b** and **12c**, respectively (Scheme 5, Table 3). In both cases, mixtures of diastereomers were also obtained. However, in **12c**, the less polar isomer was largely predominant in the crude product, and only this isomer was eventually isolated after chromatography. Alcohols **12a−c** were then treated with trifluoroacetic anhydride and pyridine in dichloromethane, leading to the corresponding alkenes **13a−c**. In the case of alcohols **12b** and **12c**, the single less polar isomers were used as substrates, while **12a** was used as a mixture of isomers. In any case, mixtures of (*E*)- and (*Z*)-stereomers were obtained (47/53 to 58/42 ratio). It has been shown that mixtures of alkyl pulvinate stereomers could be converted selectively to the nature-relevant (*E*)-isomers when exposed to UV irradiation or even to daylight.[5k,m] Indeed, irradiation of a toluene solution of the mixtures of alkenes **13** at 254 nm for 8 h cleanly led to the pure (*E*)-isomers. This isomerization allowed the completion of the synthesis of three natural products **13a−c** and in particular the completion of the first synthesis of methyl 3′,5′-dichloro-4,4′-di-*O*-methylatromentate (**13c**). The physical and spectroscopic data for the synthetic compounds were in good agreement with those reported in the literature (Experimental Section). This strategy was thus found to be very straightforward and especially efficient for the preparation of unsymmetrical vulpinic acids, in which the two aryl groups are different and are not as readily accessible as symmetrical ones.

Conclusion

In conclusion, we have reported the one-pot synthesis of a variety of 3-aryltetronic acids, unsubstituted, monosubstituted, or disubstituted at C5, from the corresponding alkyl hydroxyacetates and methyl arylacetates. This tandem process combines a transesterification and a subsequent Dieckmann condensation. The method was also used to prepare a bis(tetronic acid) from the corresponding diester and a thiotetronic acid from methyl

(27) For the preparation of ethyl 2-(4-methoxyphenyl)-2-oxoacetate by reaction of 4-methoxyphenylmagnesium bromide with diethyl oxalate, see: Creary, X.; Mehrsheikh-Mohammadi, M. E. *J. Org. Chem.* **1986**, *51*, 2664–2668.
(28) Deng, H.; Jung, J.-K.; Liu, T.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 9032–9034.

thioglycolate. The preparation of other heterocycles by a similar one-pot method is underway. Finally, we described the straightforward three-step syntheses of three natural vulpinic acids **13a**−**c** from readily available tetronic acid **3d**. This is the first total synthesis of recently isolated methyl 3′,5′-dichloro-4,4′-di-*O*-methylatromentate **13c**. It should be noted that the synthesis of compounds **13a** and **13c** (obtained in 70 and 48% yield, respectively, from ester **3d**) certainly represents one of the most efficient routes to unsymmetrical vulpinic acids. This result was obtained because of the one-step 3-aryltetronic acid preparation and also the avoidance of any protection/deprotection step in the course of the synthetic sequence.

Experimental Section

General Procedure A for the Synthesis of Tetronic Acids (in THF). To a solution of ester **1** (1 equiv) and hydroxyester **2** (1.2 equiv) in anhydrous THF was added a 1 M solution of potassium *tert*-butoxide (2.2 equiv) in THF. The suspension obtained was then refluxed under argon overnight. After cooling to rt, the reaction mixture was poured into cooled 1 N HCl. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were then washed with water and dried over Na_2SO_4. After filtration and concentration under vacuum, the residue was purified by column chromatography (silica gel, 200:1 and then 95:5 containing 0.2% acetic acid CH_2Cl_2/methanol) to give the corresponding tetronic acid **3**.

General Procedure B for the Synthesis of Tetronic Acids (in DMF). To a solution of ester **1** (1 equiv) and hydroxyester **2** (1.2 equiv) in DMF was added a 1 M solution of potassium *tert*-butoxide (2.2 equiv) in THF. The solution was stirred under argon at rt overnight. The reaction mixture was then poured into cooled 1 N HCl. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were then washed several times with water and dried over Na_2SO_4. After filtration and concentration under vacuum, the residue was purified by column chromatography (silica gel, 200:1 and then 95:5 containing 0.2% acetic acid CH_2Cl_2/methanol) to give the corresponding tetronic acid **3**.

4-Hydroxy-3-phenylfuran-2(5*H*)-one (3a). According to general procedure A, from methyl phenylacetate (0.29 mL, 2.0 mmol), methyl glycolate (0.19 mL, 2.4 mmol), and potassium *tert*-butoxide (4.4 mL, 4.4 mmol, 1 M in THF) in THF (10 mL), tetronic acid **3a** was obtained as a beige solid (0.34 g, 97%): mp 253 °C (lit.[14] 254 °C); TLC R_f 0.10 (9:1 CH_2Cl_2/MeOH); IR (KBr pellet) ν_{max} 680, 782, 1019, 1061, 1163, 1316, 1351, 1397, 1433, 1462, 1499, 1599, 1695, 2621, 2935 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 4.79 (s, 2H), 7.22−7.27 (m, 1H), 7.35−7.40 (m, 2H), 7.98−8.15 (m, 2H); ^{13}C NMR (100 MHz, acetone-d_6) δ 66.7, 100.2, 127.5, 127.8 (2C), 128.8 (2C), 131.5, 173.3, 173.9; MS (ESI-TOF) *m*/*z* 177 [M + H]$^+$, 199 [M + Na]$^+$.

4-Hydroxy-3-(4-methoxyphenyl)-5-methylfuran-2(5*H*)-one (3l). According to general procedure A, from methyl 4-methoxyphenylacetate (0.32 mL, 2.0 mmol), (−)-methyl L-lactate (0.23 mL, 2.4 mmol), and potassium *tert*-butoxide (4.4 mL, 4.4 mmol, 1 M in THF) in THF (10 mL), tetronic acid **3l** was obtained as a yellow solid (0.43 g, 97%): mp 202 °C; TLC R_f 0.20 (9:1 CH_2Cl_2/MeOH); IR (KBr pellet) ν_{max} 830, 999, 1082, 1171, 1249, 1390, 1516, 1611, 1695, 2658, 2932 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 1.53 (d, 3H, J = 6.6 Hz), 3.80 (s, 3H), 4.94 (q, 1H, J = 6.6 Hz), 6.94 (d, 2H, J = 9.1 Hz), 7.89 (d, 2H, J = 9.1 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 18.5, 55.4, 73.7, 100.1, 114.2 (2C), 123.7, 129.4 (2C), 159.5, 172.4, 175.3; MS (ESI-TOF) *m*/*z* 221 [M + H]$^+$, 243 [M + Na]$^+$. Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.28; H, 5.45.

4-Hydroxy-3-(4-methoxyphenyl)-1-oxaspiro[4.5]dec-3-en-2-one (3p). According to general procedure A, from methyl 4-methoxyphenylacetate (0.32 mL, 2.0 mmol), anhydrous methyl 1-hydroxycyclohexanecarboxylate **2f** (0.35 mg, 2.2 mmol), and potassium *tert*-butoxide (4.4 mL, 4.4 mmol, 1 M in THF) in THF (10 mL), tetronic acid **3p** was obtained as a white solid (0.38 g, 70%): mp 245 °C; TLC R_f 0.20 (95:5 CH_2Cl_2/MeOH); IR (KBr pellet) ν_{max} 832, 1247, 1275, 1389, 1516, 1612, 1644, 1686, 2635, 2941 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 1.26−1.37 (m, 1H), 1.60−1.80 (m, 7H), 2.00−2.08 (m, 2H), 3.80 (s, 3H), 6.93 (d, 2H, J = 9.1 Hz), 7.39 (d, 2H, J = 9.1 Hz), 10.46 (bs, 1H, OH); ^{13}C NMR (100 MHz, acetone-d_6) δ 22.8 (2C), 25.1, 33.5 (2C), 55.5, 81.6, 99.8, 114.3 (2C), 123.7, 129.8 (2C), 159.5, 171.6, 177.6; MS (ESI-TOF) *m*/*z* 275 [M + H]$^+$; HRMS (ESI-TOF) calcd for $C_{16}H_{18}NaO_4$ [M + Na]$^+$ 297.1103, found 297.1112.

Dimethyl 2,2′-(Naphthalene-1,7-diyl)diacetate (7). To lithium acetate (0.93 g, 14 mmol, 4 equiv) and tetrakistriphenylphosphine palladium (0.61 g, 0.53 mmol, 0.15 equiv) were successively added a solution of ditriflate **5** (1.5 g, 3.5 mmol, 1 equiv) in degassed THF (22 mL) and ketene silyl acetal **6** (2.0 g, 11 mmol, 3 equiv), which was previously prepared from methyl acetate[21] and contained about 20% methyl (trimethylsilyl)acetate. The reaction mixture was refluxed for 3 h. After it had cooled to rt, water was added, and then the layers were separated. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by column chromatography (silica gel, 9:1 to 8:2 pentane/EtOAc) to give diester **7** as a colorless oil (3.2 g, 83%): TLC R_f 0.40 (8:2 pentane/EtOAc); IR (NaCl, film) ν_{max} 831, 1013, 1164, 1206, 1264, 1435, 1510, 2953, 3055 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 3.69 (s, 3H), 3.72 (s, 3H), 3.83 (s, 2H), 4.07 (s, 2H), 7.40−7.43 (m, 2H), 7.45 (dd, 1H, J = 8.3, 1.6 Hz), 7.75−7.80 (m, 1H), 7.84 (d, 1H, J = 8.3 Hz), 7.87 (bs, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 39.0, 41.8, 52.2 (2C), 124.1, 125.6, 127.4, 127.9, 128.4, 129.2, 130.4, 132.1, 132.2, 132.9, 172.0, 172.1; MS (ESI-TOF) *m*/*z* 295 [M + Na]$^+$; HRMS (ESI-TOF) calcd for $C_{16}H_{16}NaO_4$ [M + Na]$^+$ 295.0946, found 295.0945.

3,3′-(Naphthalene-1,7-diyl)bis(4-hydroxyfuran-2(5*H*)-one) (8). To a solution of dimethyl 2,2′-(naphthalene-1,7-diyl)diacetate **7** (0.10 g, 0.37 mmol, 1 equiv) and anhydrous methyl glycolate (0.062 mL, 0.81 mmol, 2.2 equiv) in anhydrous THF (2 mL) was added a 1 M solution of potassium *tert*-butoxide (1.6 mL, 1.6 mmol, 4.4 equiv) in THF. The suspension obtained was then refluxed under argon overnight. After cooling to rt, the reaction mixture was poured into cooled 1 N HCl (5 mL). The aqueous layer was extracted with ethyl acetate, and the combined organic layers were then washed with brine and dried over Na_2SO_4. After filtration and concentration under vacuum, the residue was purified by precipitation in acetone to give the corresponding bis(tetronic acid) **8** (84 mg, 70%): mp >280 °C dec; IR (KBr pellet) ν_{max} 837, 1024, 1043, 1161, 1315, 1346, 1421, 1569, 1617, 1663, 1703, 2620, 2932 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 4.80 (s, 2H), 4.90 (s, 2H), 7.37 (d, 1H, J = 7.2 Hz), 7.50 (dd, 1H, J = 8.0, 7.2 Hz), 7.87 (d, 1H, J = 8.0 Hz), 7.93 (d, 1H, J = 8.8 Hz), 8.11 (dd, 1H, J = 8.8, 1.5 Hz), 8.39 (bs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 66.2, 66.9, 97.4, 99.1, 123.0, 124.6, 125.1, 127.5, 127.6, 127.7, 128.3, 128.5, 131.4, 131.8, 173.0, 173.4, 175.1, 175.7; MS (ESI-TOF) *m*/*z* 347 [M + Na]$^+$, 671 [2M + Na]$^+$; HRMS (ESI-TOF, negative-ion mode) calcd for $C_{18}H_{11}NaO_6$ [M − H]$^-$ 323.0556, found 323.0565.

1,3-Dichloro-5-iodo-2-methoxybenzene (15). To a solution of 2,6-dichlorophenol (10 g, 61 mmol, 1 equiv) in THF (110 mL) was added *N*-iodosuccinimide (20 g, 92 mmol, 1.5 equiv). The resulting mixture was stirred for 2 h, and then a 10% aqueous solution of $Na_2S_2O_3$ and Et_2O were added. The aqueous layer was extracted with Et_2O. The combined organic layers were then washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The resulting white solid was dissolved in DMF (110 mL), and then K_2CO_3 (39 g, 282 mmol, 4.6 equiv) and methyl iodide (8.0 mL, 129 mmol, 2.1 equiv) were added. After 48 h, water was added, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with 1% HCl and brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue obtained was purified by column chromatography using a combi-

flash system (silica gel, cyclohexane) to give compound **15** (16 g, 85% over two steps) as a white solid: mp 83 °C (lit.[29] 82−83 °C); TLC R_f 0.65 (pentane); IR (KBr pellet) ν_{max} 803, 858, 984, 1256, 1416, 1464, 1543, 1731, 2925, 3064 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 7.62 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 60.9, 86.3, 130.6 (2C), 137.4 (2C), 152.7.

Methyl 2-(3,5-Dichloro-4-methoxyphenyl)-2-oxoacetate (11c). A solution of *n*-butyllithium (1.0 mL, 1.55 M in hexanes, 1.6 mmol, 1.2 equiv) was added dropwise to a solution of 1,3-dichloro-5-iodo-2-methoxybenzene **15** (0.40 g, 1.3 mmol, 1 equiv) in THF (9 mL), at −78 °C. The reaction mixture was stirred for 30 min at −78 °C and was then transferred via cannula to a solution of dimethyl oxalate (0.31 g, 2.6 mmol, 2.0 equiv) in THF (10 mL) at −78 °C. The yellow solution obtained was stirred for 2 h at −78 °C and then allowed to warm to rt. A saturated aqueous NH_4Cl solution was added. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. Silica gel chromatography (98:2 cyclohexane/EtOAc) afforded ketoester **11c** (0.13 g, 42%): mp 79−80 °C; TLC R_f 0.25 (95:5 cyclohexane/EtOAc); IR (KBr pellet) ν_{max} 986, 1208, 1223, 1265, 1691, 1732, 2961 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 3.99 (s, 3H), 3.99 (s, 3H), 8.08 (s, 2H); ^{13}C NMR (100 MHz, acetone-d_6) δ 53.3, 61.2, 129.5, 130.4 (2C), 131.0 (2C), 157.9, 162.8, 182.5; MS (ESI-TOF) *m/z* 285, 287, 289 $[M + Na]^+$; HRMS (ESI-TOF) calcd for $C_{10}H_8{}^{35}Cl_2NaO_4$ $[M + Na]^+$ 284.9697, found 284.9714.

Methyl (Dichloro-4-methoxyphenyl)-2-hydroxy-2-(3-hydroxy-4-(4-methoxyphenyl)-5-oxo-2,5-dihydrofuran-2-yl)acetate (12c). A solution of *n*-butyllithium (3.0 mL, 1.6 M in hexanes, 4.8 mmol, 3.3 equiv) was added dropwise to a solution of diisopropylamine (0.71 mL, 5.1 mmol, 3.5 equiv) in THF (7.5 mL) at −30 °C. After 30 min at −30 °C, the reaction mixture was cooled to −78 °C, and then a solution of tetronic acid **3d** (0.30 g, 1.5 mmol, 1 equiv) in THF (13.5 mL) was added dropwise. The yellow solution obtained was stirred at −78 °C for 1 h, and then ketoester **11c** (0.497 g, 1.9 mmol, 1.3 equiv) in solution in THF (6 mL) was added dropwise. The reaction mixture was allowed to warm slowly to rt. After being stirred overnight, the orange solution was poured into cooled 1 N HCl. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. Silica gel chromatography using a combiflash system (8:2 to 0:1 cyclohexane/acetone) afforded alcohol **12c** (0.41 g, 60%) as a single diastereoisomer: mp 60−61 °C; TLC R_f 0.30 (6:4 cyclohexane/acetone); IR (KBr pellet) ν_{max} 803, 994, 1143, 1179, 1252, 1516, 1659, 1744, 2957, 3446 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 3.79 (s, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 5.70 (s, 1H), 6.92 (d, 2H, J = 9.0 Hz), 7.57 (d, 2H, J = 9.0 Hz), 7.85 (s, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 54.0, 55.5, 61.1, 78.7, 81.2, 104.6, 114.4 (2C), 122.5, 128.2 (2C), 129.6 (2C), 130.3 (2C), 135.9, 153.0, 159.9, 170.1, 172.0, 172.1; HRMS (ESI-TOF) calcd for $C_{21}H_{18}NaO_8{}^{35}Cl_2$ $[M + Na]^+$ 491.0276, found 491.0268.

(*E*)-Methyl 2-(3,5-Dichloro-4-methoxyphenyl)-2-(3-hydroxy-4-(4-methoxyphenyl)-5-oxofuran-2(5*H*)-ylidene)acetate (13c). To a solution of alcohol **12c** (64 mg, 0.14 mmol, 1 equiv) in anhydrous CH_2Cl_2 (1.5 mL) at 0 °C was added trifluoroacetic anhydride (39 μL, 0.27 mmol, 2 equiv). After 10 min, anhydrous pyridine (77 μL, 0.95 mmol, 7 equiv) was added dropwise. The reaction mixture was allowed to slowly warm to rt under stirring overnight. Then 1 N HCl was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under vacuum. A solution of the mixture of (*E*)- and (*Z*)-alkenes obtained in toluene (15 mL) was then irradiated under UV at 254 nm in a Rayonet photochemical reactor for 8 h. After concentration under vacuum, (*E*)-isomer **13c** was obtained in pure form (60 mg, 95% over two steps): mp 172−173 °C (lit.[18] 170−171 °C); TLC R_f 0.45 (6:4 cyclohexane/EtOAc); IR (KBr pellet) ν_{max} 836, 1080, 1183, 1258, 1277, 1312, 1478, 1603, 1675, 1775, 2520, 2940 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 3.90 (s, 3H), 3.96 (s, 3H), 6.97 (d, 2H, J = 9.1 Hz), 7.19 (s, 2H), 8.12 (d, 2H, J = 9.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.7, 55.4, 61.0, 106.0, 112.3, 114.1 (2C), 121.4, 129.27 (2C), 129.33, 129.6 (2C), 130.6 (2C), 152.6, 156.0, 158.2, 159.9, 165.8, 170.9; HRMS (ESI-TOF) calcd for $C_{21}H_{16}NaO_7{}^{35}Cl_2$ $[M + Na]^+$ 473.0171, found 473.0168.

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Supporting Information Available: Experimental procedures and characterization for compounds **3b−i**, **3k**, **3m−o**, **11b**, **12a**, **12b**, **13a**, and **13b**. Copies of NMR spectra for all compounds. Comparison of spectroscopic data of natural and synthetic **13c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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