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An Effective One-Pot Synthesis of 5-Substituted Tetronic Acids

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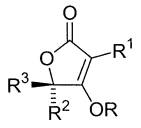
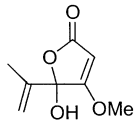
Abstract: An expeditious one-pot synthesis of 5-substituted tetronic acids from aldehydes and terminal conjugated alkyne as starting materials is described. The entire process embodies two consecutive chemical events: a catalytic domino reaction to build the 1,3-dioxolane scaffolds **5** and a two-step acid-catalyzed trans-acetalization−lactonization reaction to furnish the tetronic acid derivatives **6**.

Tetronic acids (4-hydroxy-5*H*-furan-2-one) form a subclass of β-hydroxybutenolides with the generic structure **1**.[1] The best known members of this family are vitamin C (ascorbic acid) **2** and pennicillic acid **3**. A great number of these compounds and their metabolites are found in many natural products, which exhibit a wide array of biological properties.[1,2]



1 R = R^1 = R^2 = R^3 = H

2 R = R^2 = H; R^1 = OH; R^3 = $CH(OH)CH_2OH$



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Several strategies have been used for the preparation of 5-substituted tetronic acids. Most of them utilize either a Dieckmann reaction[2a,3] or a cyclization of a suitable β-ketoester derivative bearing a γ-halogen atom[4] or a γ-oxygenated function.[5−7] Other methods utilize ketenes to generate the γ-lactonic ring.[8] Also, 1,3-dioxolan-4-ones,[9] 2-dioxolanones,[10] and substituted 3-furanones[11] have been used as templates in the synthesis of these molecules. To the best of our knowledge, a one-pot synthesis of tetronic acid derivatives using cheap, commercially available, and nonelaborated starting materials has not been described.[12] We report here on a simple, general, and effective one-pot method to obtain 5-substituted tetronic acids. The method comprises two consecutive processes: a catalytic domino reaction to build the 1,3-dioxolane intermediates **5**[13] and a two-step acid-catalyzed trans-acetalization−lactonization reaction to furnish the tetronic acid derivatives **6** (Scheme 1).

Domino processes,[14] when they are performed in a catalytic manner, constitute a powerful and economical synthetic way to introduce chemical and structural complexity. The search for and development of this kind of chemical processes is a great challenge in organic and medicinal chemistry.[15] Recently, we described[13] a domino process based on the catalytic generation of a reactive

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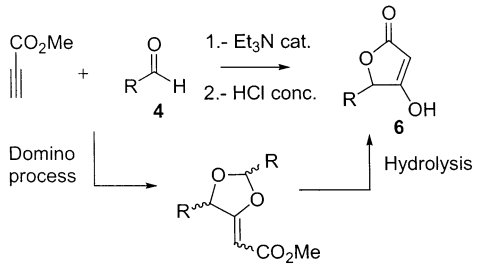
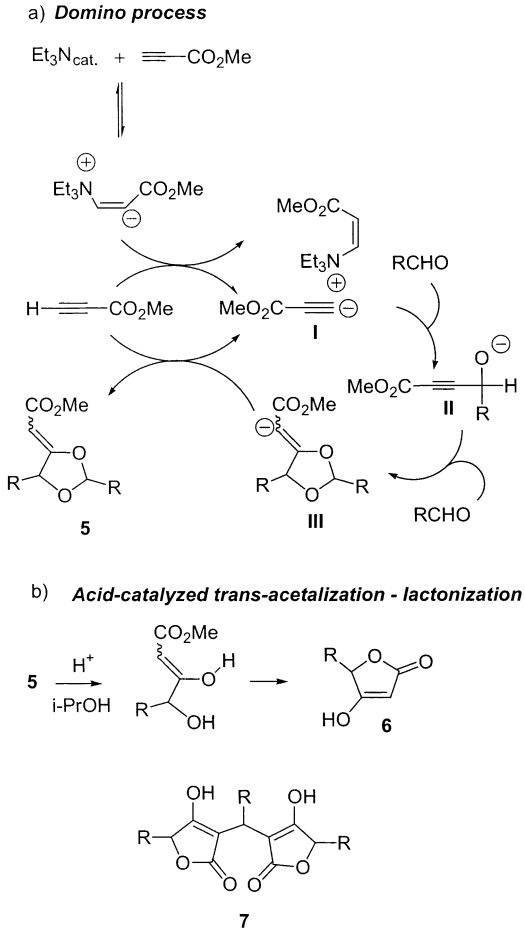
SCHEME 1. One-Pot Synthesis of 5-Substituted Tetronic Acids

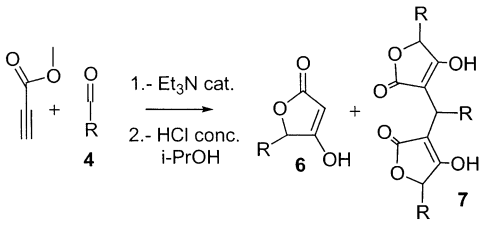


SCHEME 2. One-Pot Synthesis of the Tetronic Acid Derivatives 6



conjugated acetylide by the Michael addition of triethylamine to the terminal conjugated alkynoate in the presence of an aldehyde. The key to this system is the low pK_a value of these terminal conjugated alkynoates (pK_a < 18.8).[16] The whole process is outlined in Scheme 2a. The generated ammonium acetylide **I** reacts with one molecule of aldehyde to give the ammonium alkoxide **II** which, in turn, reacts with another molecule of aldehyde to furnish the intermediate vinylammonium **III**. This anion deprotonates to the starting alkynoate generating the 1,3-dioxolane **5** and acetylide **I** which reinitiates the cycle. This domino process builds up the 1,3-dioxolane

TABLE 1



				% yield[a,b]		
entry		R		A	B	C
1	**4a**	Me	**6a**[3f]	**69**		
			7a	**5**		
2	**4b**	n-Pr	**6b**	**65**		
			7b	**5**		
3	**4c**	i-Pr	**6c**		58	**65**
4	**4d**	t-Bu	**6d**	47	56	**62**
5	**4e**	CH_2=$CH(CH_2)_2$	**6e**	**58**		
6	**4f**	$BnOCH_2$	**6f**	**48**[c]		

intermediates **5** in excellent yields and high efficiency. The synthesis of **5** involves the creation of two C−O bonds and one C−C bond with both atom economy and structure economy. These 1,3-dioxolanes **5** are suitable scaffolds to generate the 3-oxo-γ-lactone ring core of the tetronic acids with different patterns of substitution at C-5. Thus, simple trans-acetalization liberates the required γ-hydroxy β-ketoester intermediates, which lactonize to furnish the tetronic acid derivatives **6** (Scheme 2b). Tetronic acid derivatives are quite reactive toward aldehydes to give dilactone compounds **7**.[17] Because the trans-acetalization reaction liberates 1 equiv of aldehyde, formation of dilactones **7** can involve a serious loss of product. Fortunately, under controlled conditions, 1,3-dioxolanes **5** selectively furnish tetronic acid derivatives **6**. When both processes are carried out in the same flask, without the isolation of intermediates, in a one-pot fashion, the resulting chemical system constitutes a very appealing reaction manifold for the synthesis of substituted tetronic acid derivatives (see Table 1). The scope and effectiveness of the method is demonstrated by the results given in Table 1. 5-Alkyl-substituted tetronic acid derivatives are quite accessible regardless off the ramification grade of the alkyl chain (entries 1−4). Aldehydes **4a** and **4b** require 24 h of acid-catalyzed alcoholysis to yield the expected tetronic derivatives **6a** and **6b** in good yields. After 24 h, a remaining amount of dioxolanes **5** (6%) is still present in the reaction medium and dilactone **7** (5%) begins to appear. Longer reaction times lower the tetramate yield favoring the dilactone production. In the case of the more sterically demanding aldehydes **4c** and **4d**, an excess of aldehyde (4 equiv) and longer reaction time for the acid-catalyzed trans-acetalization of the dioxolane intermediates are required to improve the yield from a modest 45−50% to a better 60−65% (entries 3, 4). In the reaction with isobutanal, the amount of unreacted dioxolane **5c** obtained decreases from 18% at 24 h to 10% at 72 h. Similarly, unreacted **5d** decreases from 13% to 5%. In both cases, there is no significant formation of the corresponding dilactones due to the steric volume of the R group in these aldehydes. Tetra-

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mates featuring a functionalized alkyl chain in the form of a terminal double bond can be synthesized in good yields from the appropriate aldehyde (entry 5). This functionality can be further used to elaborate more complex molecules or to join this molecule to other biologically active structures.[18] The biologically relevant 5-hydroxymethyl derivatives[19] are obtained in good yields with partial recovery of the starting aldehyde in the form of its dialkyl acetal (entry 6). Aromatic aldehydes are not reactive enough to be used as starting materials in these processes. 2,5-Diaryl-substituted dioxolane intermediates **5**, if formed, do not give a clean and synthetically useful acid-catalyzed trans-acetalization−lactonization reaction.

In summary, we have developed an effective one-pot synthesis of 5-substituted tetronic acid derivatives using methyl propiolate and aldehydes as starting materials. The method embodies two consecutive chemical events: a quite efficient and atom-economy domino process followed by an effective and controlled acid-catalyzed trans-acetalization.

Experimental Section

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra of $CDCl_3$ solutions were recorded either at 200 and 50 MHz or at 500 and 125 MHz, respectively. FT-IR spectra were measured in chloroform solutions. Flash column chromatography was carried out with silica gel (particle size less than 0.020 mm) using appropriate mixtures of ethyl acetate and hexanes as eluent. Dichloromethane was distilled from CaH_2. Triethylamine was distilled from potassium hydroxide pellets. All other materials were obtained from commercial suppliers and used as received.

Products **6a**−**f** exist in solution as an equilibrium of the keto and enol tautomers. The solutions used to obtain the NMR spectra of products **6a**−**e** contain predominantly the enol form; therefore, the spectral data correspond to this tautomer. On the other hand, the solution used to obtain the NMR spectra of product **6f** contains predominantly the other tautomers; therefore, the spectral data correspond to the keto form.

General Procedure. Method A. Triethylamine (0.6 mmol) was added to a cooled (−78 °C) solution of methyl propiolate (3 mmol) and aldehyde (6.3 mmol) in dry CH_2Cl_2 (3 mL). The reaction mixture was stirred for 2 h at this temperature. Concentrated HCl (0.2 mL, ∼2.5 mmol of H^+) and 2-propanol (57 mL) were added, and the resulting solution was heated at 60 °C for 24 h. Evaporation of the solvent at reduced pressure followed by flash chromatography (eluent gradiant: ethyl acetate/hexane from 2:8 to 6:4) yielded tetronic acid derivatives **6a**−**g** as crystalline compounds. The amount of concentrated acid and 2-propanol was carefully studied so that the maximum yield of tetronic acids was obtained with respect to the formation of dilactones.

Method B. Same as method A but using a larger excess of aldehyde (12 mmol).

Method C. Same as method A, but using a longer trans-acetalization time (72 h) under more concentrated conditions (25 mL of *i*-PrOH).

4-Hydroxy-5-methyl-5*H*-furan-2-one (6a): mp 113−114 °C (lit.[3f] mp 112−115 °C). **Dilactone 7a:** mixture of diastereomers; mp 176.5−180.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35 (d, 3H, J = 7.3 Hz), 1.50 (d, 6H, J = 6.9 Hz), 4.12−4.16 (m, 1H), 3.20 (broad s, 1H), 4.78−4.85 (m, 2H), 12.80 (broad s, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz, major isomer) δ 178.7, 178.7, 102.0, 76.2, 20.7, 18.2, 17.3; IR ($CHCl_3$) ν 3018, 1701, 1651, 1629, 1450, 1348 cm^{-1}; MS *m*/*z* (rel intensity) 254 (M^+, 11), 239 (31), 141 (15), 146 (16), 69 (32), 68 (100), 53 (21). Anal. Calcd for $C_8H_{10}O_3$: C, 56.69; H, 5.55. Found: C, 56.70; H, 5.26.

4-Hydroxy-5-propyl-5*H*-furan-2-one (6b): mp 74.5−76.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.95 (t, 3H, J = 7.4 Hz), 1.42−1.51 (m, 2H), 1.61−1.68 (m, 1H), 1.91−1.98 (m, 1H), 4.84 (dd, 1H, J = 7.7, 3.7 Hz), 5.06 (s, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 184.1, 178.3, 88.7, 80.7, 33.3, 17.5, 13.5; IR ($CHCl_3$) ν 3030, 2966, 1807, 1759, 1633 cm^{-1}; MS *m*/*z* (rel intensity) 142 (M^+, 4.1), 100 (100), 99 (22), 72 (35), 71 (67), 57 (10). Anal. Calcd for $C_7H_{10}O_3$: C, 59.15; H, 7.09. Found: C, 59.21; H, 7.08.

Dilactone 7b: mixture of diastereomers; mp 132.5−135.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, 3H, J = 7.3 Hz), 0.96 (t, 6H, J = 7.3 Hz), 1.21−1.26 (m, 2H), 1.36−1.60 (m, 4H), 1.60−1.69 (m, 2H), 1.69−1.75 (m, 2H), 1.91−1.99 (m, 2H), 4.04−4.10 (m, 1H), 2.80 (broad s, 1H), 4.75−4.78 (m, 2H), 12.17 (broad s, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz, major isomer) δ 178.3, 178.2, 101.4, 79.6, 33.9, 33.4, 25.7, 20.8, 17.7, 13.7, 13.5; IR ($CHCl_3$) ν 2963, 1698, 1648, 1629, 1466, 1652 cm^{-1}; MS, *m*/*z* (rel intensity) 338 (M^+, 1.0), 295 (15), 154 (34), 100 (20), 81 (17), 71 (17), 68 (100). Anal. Calcd for $C_8H_{10}O_3$: C, 63.89; H, 7.74. Found: C, 63.84; H, 7.74.

4-Hydroxy-5-isopropyl-5*H*-furan-2-one (6c): mp 96.5−98.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (d, 3H, J = 6.9 Hz), 1.08 (d, 3H, J = 7.0 Hz), 2.17−2.27 (m, 1H), 4.72 (d, 1H, J = 3.1 Hz), 5.09 (s, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 183.3, 178.5, 89.6, 84.8, 29.5, 18.6, 14.7; IR ($CHCl_3$) ν 3018, 2971, 1803, 1759, 1709, 1623 cm^{-1}; MS *m*/*z* (rel intensity) 142 (M^+, 20), 114 (80), 100 (100), 72 (79), 71 (67), 69 (30). Anal. Calcd for $C_7H_{10}O_3$: C, 59.15; H, 7.09. Found: C, 59.46; H, 7.25.

5-*tert*-Butyl-4-hydroxy-5*H*-furan-2-one (6d): mp 131.5−133.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.06 (s, 9H), 4.53 (s, 1H), 5.04 (s, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 183.9, 178.2, 90.4, 87.9, 25.6, 25.5; IR ($CHCl_3$) ν 3018, 2971, 1803, 1759, 1709, 1623 cm^{-1}; MS *m*/*z* (rel intensity) 156 (M^+, 11), 100 (100), 99 (57), 72 (63), 71 (80). Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.37; H, 7.73.

5-But-3-enyl-4-hydroxy-5*H*-furan-2-one (6e): mp 53.5−55.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.67−1.88 (m, 2H), 2.12−2.21 (m, 2H), 4.77−4.81 (m, 1H), 5.00 (s, 1H), 4.95−5.06 (m, 2H), 5.65−5.78 (m, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 184.5, 178.5, 137.2, 116.8, 89.7, 80.7, 31.4, 29.2; IR ($CHCl_3$) ν 3018, 2930, 1807, 1760, 1644, 1222 cm^{-1}; MS *m*/*z* (rel intensity) 154 (M^+, 0.8), 110 (100), 83 (12), 72 (18), 55 (54). Anal. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.46; H, 6.61.

5-Benzyloxymethyl-4-hydroxy-5*H*-furan-2-one (6f): mp 65.0−67.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.06 (d, 1H, J = 22.5 Hz), 3.17 (d, 1H, J = 22.5 Hz), 3.79−3.88 (m, 2H), 4.47 (d, 1H, J = 12.2 Hz), 4.54 (d, 1H, J = 12.2 Hz), 4.74−4.76 (m, 1H), 7.26−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 204.2, 170.3, 136.7, 128.5, 128.0, 127.5, 85.3, 73.7, 68.4, 38.2; IR ($CHCl_3$) ν 3018, 2930, 2866, 1807, 1760, 1672, 1225 cm^{-1}; MS *m*/*z* (rel intensity) 220 (M^+, 12), 107 (13), 91 (100), 65 (7.8). Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.69; H, 5.42.

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