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Microwave-accelerated Claisen rearrangements of allyl tetronates and tetramates

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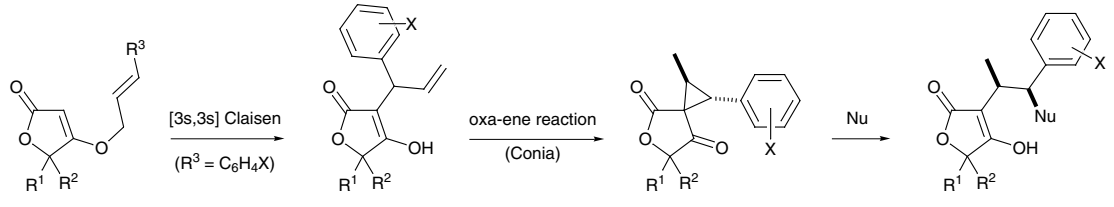
Abstract—[3,3]-Sigmatropic rearrangements of allyl tetronates and allyl tetramates to give 3-allyltetronic or -tetramic acids, respectively, proceed within 20–60 min under microwave irradiation (300 W, 130–190 °C). Consecutive (homo)sigmatropic [1,5] H-shifts such as oxa-ene reactions are promoted less effectively, which allows the isolation of Claisen intermediates of sigmatropic domino sequences, in contrast to conventional heating.

Functionalized 3-alkyltetronic acids **4**, which are of medical interest as potential antibiotic, antiviral and antineoplastic agents,[1] have been recently obtained from a thermal domino Claisen/Conia/ring-opening reaction of the corresponding allyl tetronates **1**.[2] These, in turn, were readily available from a domino addition/intramolecular Wittig alkenation between the corresponding α-hydroxy allyl esters and the phosphorus ylide $Ph_3P{=}C{=}C{=}O$.[3] By proper choice of conditions either the Claisen products **2** or the oxa-ene (Conia) rearranged products, the 3-(spirocyclopropyl)dihydrofuran-2,4-diones **3**, were formed as main products in cases where the allyl tetronates **1** bore an alkyl or a phenyl residue R^3 (Scheme 1). Herein we report on the dramatically shortened reaction times required for the formation of **2** under microwave irradiation[4] conditions and on the synthesis of analogous Claisen products from allyl tetronates bearing chloroaryl residues R^3, which is impossible under classical thermal conditions.

The conventional thermal synthesis of **2** (alongside some follow-up Conia product **3**) from the tetronates **1** in refluxing acetonitrile normally requires long reaction times, typically 24–48 h. A selective synthesis of **3** could



	X	R^1	R^2
1-3 a	2-Cl	$-(CH_2)_5-$	
b	3-Cl	$-(CH_2)_5-$	
c	4-Cl	$-(CH_2)_5-$	
d	3-NO_2	$-(CH_2)_5-$	
e	4-NO_2	$-(CH_2)_5-$	
f	H	H	Ph

Scheme 1. Domino [3s,3s] Claisen/Conia/ring-opening reaction of allyl tetronates **1**.

Keywords: Tetronic acid; Claisen rearrangement; Microwave; Tetramates.
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Table 1. Thermal versus microwave syntheses[5] of tetronic acids **2** and spirocyclopropyl furandiones **3**

Starting compound	Yields **2**:**3** (%) from the thermal reaction in CH_3CN	Yields **2**:**3** (%) from the microwave reaction in CH_3CN	Yields **2**:**3** (%) from the thermal reaction in toluene/sealed tube
1a	0:0[a]	42:58[b]	0:64[c]
1b	0:0[a]	55:45[b]	0:63[c]
1c	0:0[a]	43:52[b]	0:89[c]
1d	56:8[d]	44:16[b]	0:68[e]
1e	32:0[d]	26:37[b]	0:42[f]
1f	42:12[d]	61:16[g]	0:70[e]

[a] CH_3CN, reflux, 84 h.
[b] CH_3CN, 300 W microwave, 150 °C, 1 h.
[c] Toluene, 160 °C, 48 h, sealed tube.
[d] CH_3CN, reflux, 48 h.
[e] Toluene, 170 °C, 35 h, sealed tube.
[f] Toluene, 180 °C, 48 h, sealed tube.
[g] CH_3CN, 300 W microwave, 130 °C, 1 h.

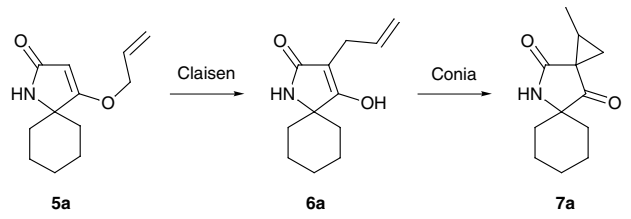
be achieved by heating solutions of **1** in toluene in a sealed glass tube at 160–190 °C for 24–48 h.[2c]

While tetronates **1a**–**c** with an *o*-, *m*-, or *p*-chlorophenyl substituent R^3 could be converted into the corresponding 1-(chlorophenyl)-2-methyl-11-oxadispiro[2.1.5.2]dodeca-4,12-diones **3** under these conditions, the corresponding tetronic acids **2** were not accessible by refluxing in acetonitrile. Even prolonged reaction times (up to 84 h) still resulted in 100% of the starting tetronate being recovered from the reaction mixture. However, heating of acetonitrile solutions of these tetronates in a sealed vessel placed in a 300 W focused single-mode microwave reactor (CEM) at 150 °C for 1 h gave easily separable mixtures of compounds **2** and **3** in almost quantitative yields (Table 1). Although allyl tetronates containing a nitrophenyl group can be rearranged to tetronic acids **2** by conventional heating in acetonitrile, we found that microwave irradiation gave similar yields in much shorter time with less solvent being required. Only for the preparation of pure tetronic acid **2e** was the thermal process superior to the microwave protocol. Difficulties were encountered with the *o*-nitrophenyl derivative both under conventional thermal and microwave conditions, which led to complicated mixtures of inseparable products. In general, microwave irradiation represents a highly efficient means for the Claisen rearrangement of differently substituted allyl tetronates. It reduces reaction times from days to a single hour while at the same time increasing the overall yields considerably.

3-Substituted tetramic acids, possessing an even greater biological potential[6] than tetronic acids, were obtained accordingly by microwave-accelerated Claisen rearrangement of the corresponding allyl tetramates. For instance, the simple derivative **5a**, synthesized from ketenylidenetriphenylphosphorane and allyl α-aminocyclohexylcarboxylate,[3] furnished the tetramic acid **6a** in 90% yield and virtually devoid of by-products and of spirolactam **7a**, when irradiated at 110 °C for only 25 min (Scheme 2). Shorter exposure to microwaves at higher temperatures gave rise to mixtures of **6a** and **7a**, whereas conventional heating in acetonitrile gave poor yields of **6a** (at reflux) or again mixtures of Claisen and Conia products (in the bomb tube).[7]

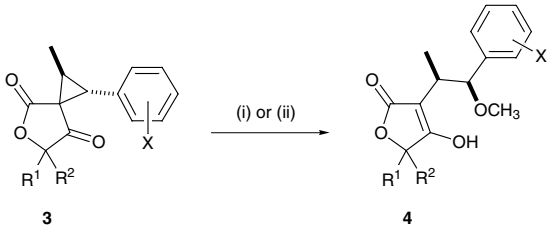
Tetronic acids **4** (with $R^3 = H$, alkyl, Ph) have been synthesized earlier by nucleophilic cleavage of the cyclopropane ring of 3-(spirocyclopropyl)-dihydrofuran-2,4-diones **3** with alcohols, amines, thiols and carbon nucleophiles, in some cases as the final step of an extended one-pot domino reaction starting with tetronates **1**.[2a] Derivatives of **3** bearing strongly electron-withdrawing aryl substituents X are markedly less reactive. For instance, the nitrophenyl-substituted 3-(spirocyclopropyl)dihydrofuran-2,4-diones **3d**–**e** proved inert to refluxing methanol/chloroform and could only be converted to tetronic acids **4** by initial treatment with 1 equiv of $HBF_4 \cdot Et_2O$ to increase the electrophilicity of the cyclopropyl ring by protonation of the keto oxygen and finally with methanol (Scheme 3).[8]

Allyl tetronates with a trisalkylsubstituted alkene moiety such as **8** undergo a formal [2,3]-sigmatropic rearrangement under thermal conditions[2a] leading to 3-alkylidenefurandiones such as **10** as the end products of a Claisen/Conia/retro-Conia cascade inevitably termi-



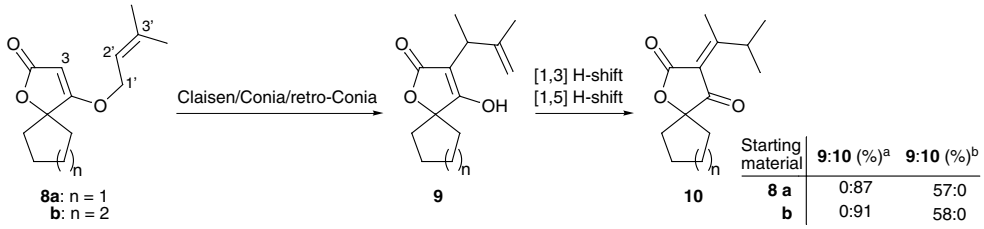
Conditions	Yields **6a**:**7a** (%)
CH_3CN, reflux, 16 h	16:0
CH_3CN, sealed tube, 130 °C, 38 h	69:26
toluene, sealed tube, 180 °C, 48 h	23:75
CH_3CN, 110 °C, 25 min 300 W microwave	90:3
toluene, 150 °C, 15 min 300 W microwave	41:47

Scheme 2. [3s,3s]-Claisen and Claisen–Conia reactions of allyl tetramate **5a**.



	Starting material	Conditions	Yield (%)
4 a	3a	(i)	63
b	3b	(i)	56
c	3c	(i)	89
d	3d	(ii)	92
e	3e	(ii)	80
f	3f	(i)	64

Scheme 3. Reagents and conditions: (i) **3** (1.0 mmol), CH_3OH (5 mL), $CHCl_3$ (20 mL), reflux, 24 h; (ii) **3** (1.0 mmol), $CHCl_3$ (20 mL), $HBF_4{\cdot}Et_2O$ (7.5 M, 0.15 mL), rt, 1 h, then CH_3OH (8 mL), reflux, 16 h.



	Starting material	9:10 (%)[a]	9:10 (%)[b]
	8 a	0:87	57:0
	b	0:91	58:0

Scheme 4. (a) Thermal conditions: toluene, 200 °C, 42 h, sealed tube; (b) microwave conditions: toluene, 190 °C, 20 min, 300 W.

nated by two H-shift steps. Carrying out the reaction under microwave irradiation not only cut down the required reaction times from 42 h to 20 min but also gave rise exclusively to the [2,3]-rearranged 3-allyltetronic acids **9** (Scheme 4).[9]

In conclusion, we have demonstrated that microwave irradiation is a valuable tool for speeding up the Claisen rearrangement of allyl tetramates and tetronates, with a lesser effect on other consecutive sigmatropic processes such as oxa-ene and H-shift reactions. Contrary to conventional thermal processing, this allows for the isolation of Claisen intermediates from cascade sequences in most cases.

Acknowledgements

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5. Typical procedure for the generation of compounds **2** and **3** from **1** using microwave heating: Tetronate **1a** (550 mg, 1.73 mmol) was placed in a glass vial with a magnetic stirrer and acetonitrile (5 mL). The vial was sealed and placed inside a CEM Discover™ single-mode microwave synthesizer where it was exposed to microwaves at 150 °C for 1 h. The cap was then removed and the solvent evaporated in vacuo. The residue was purified by column chromatography (silica gel 60; diethyl ether/hexane, 1:1, v/v) to give 1-(2′-chlorophenyl)-2-methyl-11-oxadispiro[2.1.5.2]dodecane-4, 12-dione **3a** (320 mg, 58%) mp 175 °C (found: C, 67.91; H, 5.98. $C_{18}H_{19}ClO_3$ requires C, 67.82; H, 6.01%) and 3-[1′-(2″-chlorophenyl)prop-2′-enyl]-4-hydroxy-1-oxaspiro-[4.5]dec-3-en-2-one **2a** (230 mg, 42%) mp 158–159 °C (found: C, 67.77; H, 5.92). **2a**: ν_{max} (KBr)/cm^{-1} 3415, 1750, 1625; ^1H NMR (300 MHz, $CDCl_3$): δ 1.60–1.77 (10H, m), 4.65 (1H, dd, ^3J 6.1, ^4J 1.5 Hz, 1′-H), 5.00 (1H, dt, ^3J 17.3, ^4J 1.5 Hz, $=CH_{trans}$), 5.27 (1H, dt, ^3J 10.2, ^4J 1.5 Hz, $=CH_{cis}$), 6.14–6.26 (1H, m, =CH), 7.02–7.49 (4H, m, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.7, 24.4, 32.8, 32.9, 40.1, 82.5, 99.1, 117.8, 128.5, 129.6, 129.9, 130.1, 134.1, 136.3, 137.3, 179.0, 185.0; *m/z* (EI) 321 (M^++1, 0.4%), 320 (0.8), 319 (0.7), 318 (1.6), 302 (0.1), 301 (0.2), 300 (0.3), 283 (78), 194 (4), 193 (3), 192 (8), 191 (6), 153 (44), 151 (100). **3a**: ν_{max} (KBr)/cm^{-1} 2939, 1773, 1732, 1309, 1120; ^1H NMR (270 MHz, $CDCl_3$): δ 1.16–1.89 (m, 10H), 1.50 (3H, d, ^3J 6.2 Hz, CH_3), 2.90 (1H, dq, ^3J 6.2, 9.2 Hz, 1-H) 3.27 (1H, d, ^3J 9.2 Hz, 2-H),

7.24–7.40 (4H, m, Ph); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 11.4, 21.0, 21.1, 32.2, 32.4, 37.8, 38.0, 47.3, 89.2, 126.8, 129.3, 129.6, 130.6, 131.4, 135.4, 171.3, 208.4; m/z (EI) 321 (M^++1, 4%), 320 (38), 319 (14), 318 (91), 305 (6), 303 (32), 302 (6), 300 (19), 287 (6), 285 (18), 283 (66), 265 (23), 219 (18), 178 (17), 152 (85), 129 (100).

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7. **6a**: mp 166 °C; ν_{max} (KBr)/cm^{-1} 3191, 3081, 1745, 1686; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37–1.67 (10H, m), 2.52 (2H, dd, ^3J 6.9, 5.5 Hz, 1′-H), 2.94 (1H, t, ^3J 5.5 Hz, 3-H), 4.94–4.98 (1H, m, $=CH_{cis}$), 5.03 (1H, ddt, ^3J 17.1, $^2J = {}^4J$ 1.5 Hz, $=CH_{trans}$), 5.57–5.71 (1H, m, 2′-H), 8.78 (1H, s, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.2, 21.3, 24.8, 30.3, 32.7, 49.0 (C-3), 66.8, 118.6, 133.0, 173.4, 212.2. **7a**: mp 156 °C, $R_f = 0.75$ (ethyl acetate); ν_{max} (KBr)/cm^{-1} 3185, 1748, 1683; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23–1.67 (10H, m), 1.34 (3H, d, ^3J 6.2 Hz, CH_3), 1.45 (1H, dd, ^3J 8.3, ^2J 3.4 Hz, 1-H) 1.73 (1H, dd, ^3J 8.8, ^2J 3.4 Hz, 1-H′), 1.85–1.95 (1H, m, 2-H), 8.45 (1H, s, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 12.0, 21.4, 21.5, 24.8, 26.3, 32.7, 33.2, 34.1, 34.7, 65.9, 173.5, 212.4. **7a′** (diastereomer): mp 156 °C, $R_f = 0.66$ (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 (3H, d, ^3J 6.2 Hz, CH_3), 1.23–1.67 (10H, m), 1.37 (1H, dd, ^3J 8.3, ^2J 3.5 Hz, 1-H) 1.77 (1H, dd, ^3J 8.6, ^2J 3.5 Hz, 1-H′), 2.00–2.08 (1H, m, 2-H), 8.61 (1H, s, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.2, 21.2, 21.3, 24.7, 25.9, 31.5, 33.0, 33.7, 34.5, 66.0, 174.5, 211.0.
8. Typical procedure (i) for the methanolysis of **3**: **3a** (400 mg, 1.26 mmol) was dissolved in dry chloroform (20 mL) and methanol (5 mL). The solution was heated to reflux for 24 h after which the solvent was removed in vacuo. The residue was purified by column chromatography (silica gel 60; diethyl ether/hexane: 1:1, v/v) to give 3-[*syn*-2′-(*o*-chlorophenyl)-2′-methoxy-1′-methylethyl]-4-hydroxy-1-oxaspiro[4.5]dec-3-en-2-one **4a** as a white solid (278 mg, 63%) mp 180 °C; (found: C, 64.91; H, 6.56. $C_{19}H_{23}ClO_4$ requires C, 65.05; H, 6.61%); ν_{max} (KBr)/cm^{-1} 3416, 2936, 1705, 1632; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (3H, d, ^3J 7.3 Hz, 1′-CH_3), 1.16–1.84 (10H, m), 2.98 (1H, dq, ^3J 7.3, 1.9 Hz, 1′-H), 3.39 (3H, s, OCH_3), 4.93 (1H, d, ^3J 1.9 Hz, 2′-H), 7.23–7.40 (4H, m, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.6, 21.8, 22.0, 24.6, 32.7, 32.9, 33.3, 57.4, 81.9, 84.3, 102.8, 126.6, 127.8, 129.2, 130.2, 133.3, 135.1, 173.0, 179.3; m/z (EI) 352 (M^+, 0.2%), 351 (0.1), 350 (0.9), 320 (0.1), 318 (0.7), 302 (0.1), 300 (0.3), 265 (0.7), 157 (39), 155 (100).
   Acid-catalyzed methanolysis (ii) of **3d**: **3d** (520 mg, 1.46 mmol) was placed in a round-bottomed flask with a side arm. Under a constant stream of nitrogen dry chloroform (20 mL) was added followed by the slow addition of HBF_4 in diethyl ether (7.5 M, 0.2 mL). The solution was stirred for 1 h, then methanol (10 mL) was added and the solution was refluxed for 16 h. The solvent was removed in vacuo and the residue was purified by column chromatography (silica gel 60; diethyl ether/hexane, 1:1, v/v) to give 4-hydroxy-3-[*syn*-2′-methoxy-1′-methyl-2′-(*m*-nitrophenyl)ethyl]-1-oxaspiro[4.5]dec-3-en-2-one **4d** (485 mg, 92%) as a white solid of mp 163 °C; (found: C, 63.11; H, 6.46. $C_{19}H_{23}NO_6$ requires C, 63.15; H, 6.41%); ν_{max} (KBr)/cm^{-1} 3433, 2937, 1701, 1660, 1602, 1536, 1353; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (3H, d, ^3J 7.3 Hz, 1′-CH_3), 1.13–1.84 (10H, m), 2.83 (1H, dq, ^3J 7.3, 2.8 Hz, 1′-H), 3.41 (3H, s, OCH_3), 4.66 (1H, d, ^3J 2.8 Hz, 2′-H), 7.43–7.61 and 8.10–8.17 (4H, m, Ph), 10.00 (1H, s, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.6, 21.6, 21.8, 24.4, 32.6, 33.1, 35.5, 57.6, 82.1, 86.4, 102.0, 121.4, 123.0, 129.6, 132.9, 140.6, 148.4, 173.0, 179.7; m/z (EI) 361 (M^+, 0.5%), 344 (1), 331 (2), 329 (17), 311 (3), 299 (8), 167 (47), 166 (100).
9. Typical procedure for the [2,3]-sigmatropic rearrangement of allyl tetronates **8**: a tightly sealed vial charged with a solution of **8b** (500 mg, 2.12 mmol) in dry toluene (6 mL) was placed in a CEM Discover™ single-mode microwave synthesizer and irradiated at 190 °C and 3.5 bar for 20 min. The resulting mixture was left overnight in a refrigerator for crystallization of product **9b**. Colorless crystals (290 mg, 58%) were obtained after washing the crude three times with toluene; mp 132 °C; ν_{max} (KBr)/cm^{-1} 3413, 3072, 2937, 1702, 1643, 1384; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20–1.81 (10H, m), 1.27 (3H, d, ^3J 7.0 Hz, 1′-CH_3), 1.76 (3H, s, 2′-CH_3), 3.12 (1H, q, ^3J 7.0 Hz, 1′-H), 5.05 (2H, d, ^2J 2.7 Hz, $=CH_2$), 7.64 (1H, br, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 16.9, 21.6, 21.7, 22.3, 24.3, 32.6, 32.7, 34.5, 82.4, 101.6, 110.9, 148.4, 173.8, 178.2; Accurate mass m/z (EI): calculated 236.14123; found 236.14156.