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Abnormal Claisen rearrangements of tetronates and stereoselective ring opening of intermediate spirocyclopropanes

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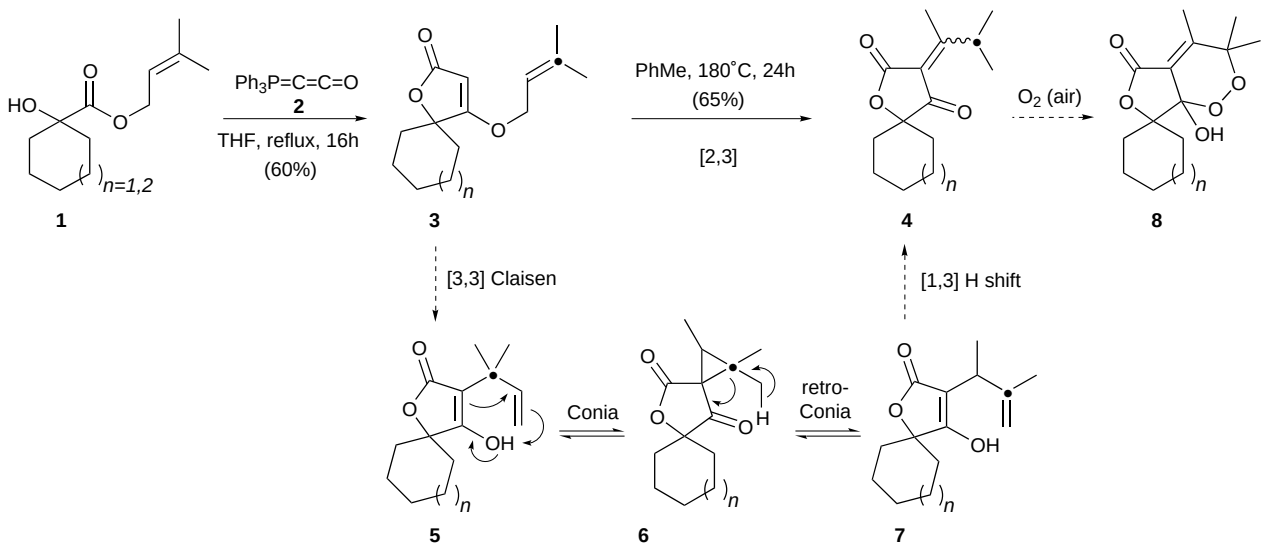
Abstract—Thermal [2,3]-sigmatropic rearrangements of allyltetronates proceed via 3-(spirocyclopropyl)dihydrofuran-2,4-diones; in some cases these could be isolated and their cyclopropane rings stereoselectively opened with alcohols or water to give 3-(β-*syn*-alkoxy)tetronic acids. Treatment of a 5,5-disubstituted benzyltetronate with LDA also produced a 3-substituted tetronic acid by an anionic [1,3]-rearrangement.

The Claisen rearrangement of allyl vinyl ethers is arguably one of the most important sigmatropic reactions. It has found widespread synthetic application due to the simplicity of the protocol and the high degree of stereoselectivity and functional group reorganisation it proceeds with.[1] Thorough mechanistic investigations have been carried out both into the nature of intermediates and the influence of solvents and catalysts.[2] Every so often since the early days of this reaction, rearrangements of certain allyl vinyl ethers have been observed which clearly deviate from the normal [3,3]-sigmatropic pattern and which are customarily referred to as 'abnormal' Claisen reactions. The conversions of allyloxybenzenes into either *p*-allyl-phenols ([3,5]-rearrangement)[3] or *o*-allyl-phenols ([1,3]-rearrangement),[4] and the [2,3]-rearrangement of 4-allyloxytetrahydroazepin-2-ones[5] are typical examples. We have now found that abnormal rearrangements are also possible with allyl and benzyltetronates (i.e. 4-allyloxy- or 4-benzyloxy-2,5-dihydrofuran-2-ones). They can be harnessed for the construction of various types of 3,5-disubstituted tetronic acids.



Scheme 1. [2,3]-Sigmatropic rearrangement of 4-(3′-methylbut-2′-enyl)-5-spirotetronates **3**.

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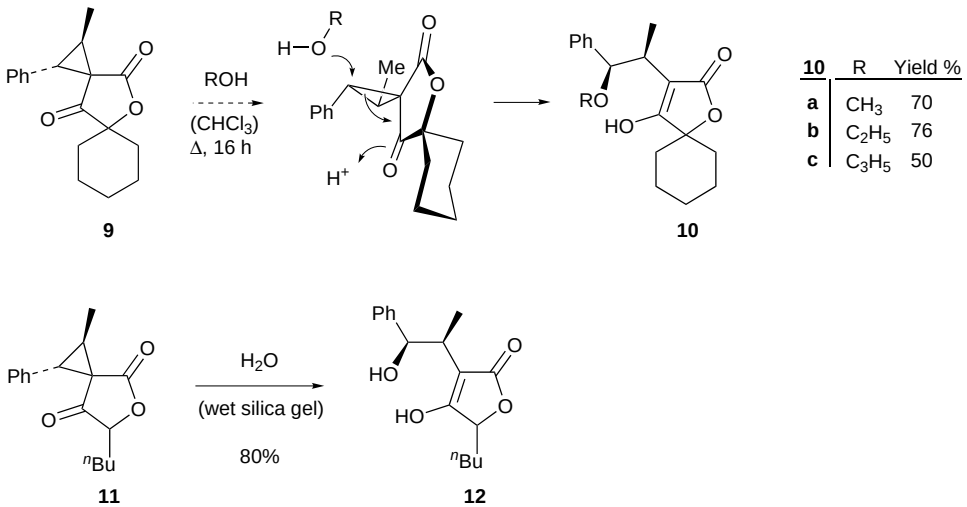
4-(3′-Methylbut-2′-enyl)-5-spirotetronates **3** were thermally converted to unassigned 2:1 mixtures of *Z*- and *E*-isomers of 3-(1′,2′-dimethylpropylidene)-5-spirodihydrofuran-2,4-diones **4** by heating solutions in toluene to 180°C in a sealed glass tube. Compounds **3**, in turn, were readily available from a domino addition–intramolecular Wittig olefination between α-hydroxy allyl esters **1** and the cumulated phosphorus ylide $Ph_3P{=}C{=}C{=}O$ **2**.[6] A plausible mechanism for this formal [2,3]-rearrangement is outlined in Scheme 1. An initial [3,3]-Claisen process produces the 3-allyltetronic acids **5** which are not isolable but undergo a consecutive Conia-type oxa-ene reaction to give the spirocyclopropanes **6**. These can then open the three-membered ring using H-atoms from any of the three surrounding methyl groups, leading either back to the 'normal' Claisen products **5** or to the 'abnormal' product **7**. The latter evade the back (Conia) reaction via a [1,3]-H shift followed by an enol–keto tautomerisation to eventually yield *E*/*Z*-isomeric mixtures of **4**.[7] These are stable only under a protective gas atmosphere and prone to autoxidation to bicyclic hemiketal endoperoxides **8**.[8] The synthesis of **4** from **1** and **2** may be carried out as a 'one-pot' multi-step reaction in toluene solution in a sealed bomb tube in an overall yield of 25%.

Elusive spirocyclopropyl intermediates similar to **6** were proposed by Prager and Rhoads for the abnormal rearrangement of allyloxytetrahydroazepinones.[5] Perfectly stable 3-(spirocyclopropyl)dihydrofuran-2,4-diones were recently isolated as products of the thermal rearrangement of allyl and cinnamyltetronates.[9] Lack-



Scheme 2. β-*syn*-Selective solvolyses of 3-(spirocyclopropyl)dihydrofuran-2,4-diones **9**/**11**.

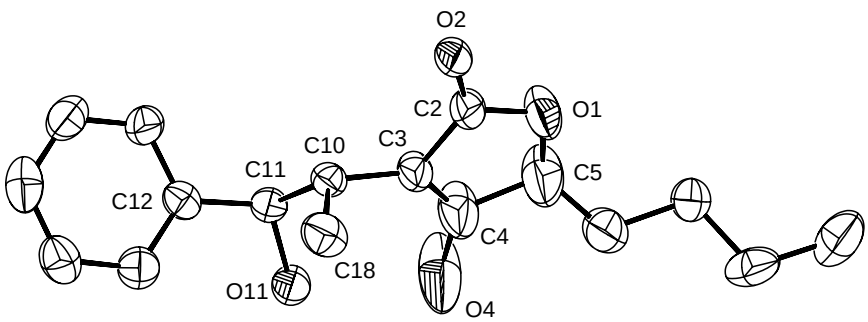
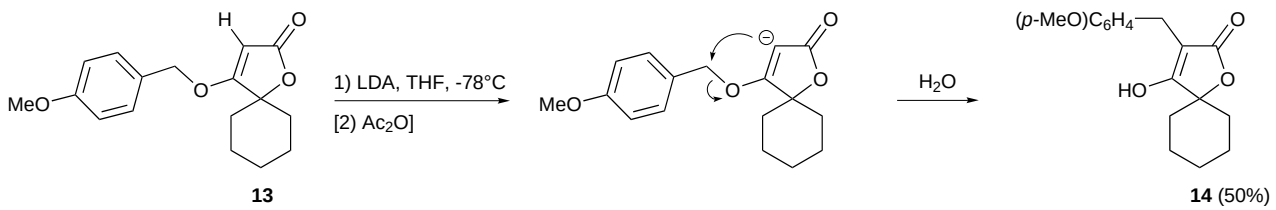


Figure 1. Molecular structure of **12** (ORTEP representation, 50% probability ellipsoids). Selected bond lengths (Å) and angles (°): O1–C2 1.360, C2–O2 1.202, C2–C3 1.446, C3–C4 1.318, C4–O4 1.336, C2–C3–C4 105.40, C4–C5–O1 101.66, C3–C10–C18 111.94, C3–C10–C11 112.24, C10–C11–O11 107.47, C10–C11–C12 112.32, O11–C11–C10–C18 62.14, C3–C10–C11–C12 170.93.



Scheme 3. Anionic [1,3]-rearrangement of benzyltetronate **13**.

ing α-H-bearing substituents other than the methyl group, their cyclopropane rings cannot be cleaved thermally in two different ways like **6**. However, owing to the electron-withdrawing effect of the two geminal carbonyl groups at C-3, the three-membered ring in 3-(spirocyclopropyl)dihydrofuran-2,4-diones is amenable to nucleophilic cleavage. This offers an attractive synthetic route to 3-(β-alkoxy)alkyltetronic acids, many of which show herbicidal activity. Refluxing **9** in methanol or in mixtures of chloroform and an excess of either ethanol or allylalcohol for 16 h furnished the respective 3-(α-methyl,β-alkoxy,β-phenyl)ethyltetronic acids **10**[10] in good yields (Scheme 2). The regioselectivity of this reaction originates from the fact that cleavage of the cyclopropane ring occurs so as to generate the more stable benzyl cation intermediate. The exclusive formation of the *syn*-isomer results from the phenyl and the methyl residues being *trans* to each other in the starting spirolactone **9**. Hydrolysis was found to be an even quicker process, indicating that protonation of the ketone oxygen atom might be the initial step. For instance, cinnamyl 5-butyltetronate **11** was hydrolysed on a silica gel column during the work-up to yield the 3-(β-hydroxy)alkyltetronic acid **12**.[11] Its molecular structure is shown in Fig. 1.

An anionic [1,3]-sigmatropic rearrangement of a 5,5-disubstituted benzyltetronate was found serendipitously when attempting to acylate the corresponding lithium enolate with acetic anhydride at C-3.[12] Deprotonation of *p*-methoxybenzyl-5-spirocyclohexyltetronate **13** with LDA at −78°C almost instantaneously produced the rearranged lithium 3-(*p*-methoxy)benzyltetronate (Scheme 3). Only a little of the 3-acetyltetronate was found (10%), even when the acetic anhydride was added immediately (1 min) after the LDA solution. Aqueous work-up eventually yielded the tetronic acid **14**.[13]

Acknowledgements

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7. **3-(1′,2′-Dimethylpropylidene)-1-oxa-spiro[4.5]decane-2,4-dione [(*Z*)+(*E*)]-4a**: White crystals, mp 141°C; ν_{max} (KBr): 1759, 1711, 1607 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.11/1.14 (6 H, d each, ^3J=6.80 Hz, C*Me*$_2$), 1.37–1.75 (10 H, m, CH_2), 2.47/2.51 (3 H, s each, CH_3), 4.43/4.47 (1 H, sept. each, ^3J=6.80 Hz, C*H*Me$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 15.9/16.0, 20.0/20.1, 21.2, 21.4, 24.3, 24.4, 26.6 (*C*Me$_2$), 31.1, 32.3, 86.6/86.7 (C-5), 115.1/115.4 (C-3), 166.8/167.8 (=*C*Me), 191.3/191.8 (C-2), 200.2/201.4 (C-4); *m*/*z* (EI): 236 (M$^+$, 41%), 218 (M$^+$–H_2O, 30%), 203 (*218*–Me$^+$, 40%), 190 (11%), 175 (19%), 110 (30%), 95 (100%). Anal. calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.09; H, 8.61%.
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10. **3-(2′-Methoxy-1′-methyl-2′-phenyl)ethyl-4-hydroxy-1-oxa-spiro[4.5]dec-3-en-2-one** (±)-**10a**: Off-white crystals, mp 154°C; ν_{max} (KBr): 3430, 1702, 1659, 1601 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (3 H, d, ^3J=7.32 Hz, C*Me*), 1.55–1.85 (10 H, m, CH_2), 2.82 (1 H, dq, ^3J=7.32, ^3J=2.13 Hz, C*H*Me), 3.42 (3 H, s, OMe), 4.60 (1 H, d, ^3J=2.13 Hz, PhC*H*), 7.26–7.41 (5 H, m, ar. H), 10.48 (1 H, s, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 11.4 (C*C*H$_3$), 21.8/21.9, 24.6, 32.8/33.3 (CH_2), 35.8 (*C*CH$_3$), 57.2 (OCH_3), 81.5 (C-5), 87.5 (OCH), 102.8 (C-3), 126.7, 128.0, 128.4 (ar. CH), 137.8 (C-*ipso*), 173.3 (C-4), 179.6 (C-2); *m*/*z* (EI): 316 (M$^+$, 1%), 301 (M$^+$–CH_3, 9%), 149 (15%), 122 (35%), 121 (100%). Anal. calcd for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65. Found: C, 72.19; H, 7.66%.

3-(2′-Ethoxy-1′-methyl-2′-phenyl)ethyl-4-hydroxy-1-oxa-spiro[4.5]dec-3-en-2-one (±)-**10b**: White crystals, mp 145°C; ν_{max} (KBr): 3434, 1704, 1659, 1603 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (3 H, d, ^3J=7.36 Hz, CC*Me*), 1.32 (3 H, t, ^3J=7.07 Hz, OC*Me*), 1.56–1.86 (10 H, m, CH_2), 2.82 (1 H, dq, ^3J=7.36, ^3J=2.13 Hz, C*H*Me), 3.48 (1 H, dq, ^3J=7.07, ^2J=9.60 Hz, CH*H*O), 3.67 (1 H, dq, ^3J=7.07, ^2J=9.60 Hz, C*H*HO), 4.69 (1 H, d, ^3J=2.13 Hz, PhC*H*), 7.12–7.40 (5 H, m, ar. H), 10.65 (1 H, s, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 10.4 (CC*C*H$_3$), 13.6 (OC*C*H$_3$), 20.0/20.7, 23.5, 31.4/32.3 (CH_2), 34.7 (C*C*CH$_3$), 64.2 (OCH_2), 80.8 (C-5), 84.4 (OCH), 101.9 (C-3), 125.6, 126.8, 127.3 (ar. CH), 137.5 (C-*ipso*), 172.3 (C-4), 178.7 (C-2); *m*/*z* (EI): 330 (M$^+$, 8%), 301 (M$^+$–C_2H_5, 24%), 284 (12%), 136 (36%), 135 (100%). Anal. calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.86; H, 7.96%.

3-(2′-Allyloxy-1′-methyl-2′-phenyl)ethyl-4-hydroxy-1-oxa-spiro[4.5]dec-3-en-2-one (±)-**10c**: White crystals, mp 147°C; ν_{max} (KBr): 3432, 1775, 1736, 1659, 1602 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (3 H, d, $^3J=7.35$ Hz, Me), 1.19–1.78 (10 H, m, CH_2), 2.77 (1 H, dq, $^3J=7.35$, $^3J=2.04$ Hz, C*H*Me), 3.81 (1 H, dd, $^3J=6.83$, $^2J=12.36$ Hz, CH*H*O), 4.12 (1 H, dd, $^3J=4.99$, $^2J=12.36$ Hz, C*H*HO), 4.67 (1 H, d, $^3J=2.04$ Hz, PhC*H*), 5.24 (1 H, dd, $^3J=10.54$, $^2J=1.32$ Hz, *H*HC=), 5.28 (1 H, dd, $^3J=17.15$, $^2J=1.32$ Hz, H*H*C=), 5.87 (1 H, dddd, $^3J=17.15$, 10.54, 6.83, 4.99 Hz, *H*C=CH$_2$), 7.17–8.03 (5 H, m, ar. H), 10.24 (1 H, s, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 11.4 (CH_3), 21.7/21.9, 24.7, 32.8/33.3 (CH_2), 35.7 (*C*CH$_3$), 70.1 (OCH$_2$), 81.8 (C-5), 84.8 (OCH), 102.9 (C-3), 119.6 (=CH$_2$), 126.6, 127.9, 128.3 (ar. CH), 132.2 (H$_2$C*C*H=), 138.1 (C-*ipso*), 173.3 (C-4), 179.5 (C-2); m/z (EI): 343 (M$^+$, 13%), 284 (M$^+$–C$_3$H$_6$O, 9%), 245 (5%), 232 (8%), 118 (100%). Anal. calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.76; H, 7.66%.

11. **5-*n*-Butyl-3-(2′-hydroxy-1′-methyl-2′-phenyl)ethyl-4-hydroxydihydrofuran-2-one** (±)-**12**: Colourless crystals, mp 115°C; ν_{max} (KBr): 3443, 3078, 1759, 1669, 1611 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.71–0.85 (6 H, m, CH_3), 1.17–1.85 (4 H, m, CH_2), 1.27–1.34/1.49–1.54 (2×1 H, m each, H$_2$C-C-O), 2.67–2.72 (1 H, m, MeC*H*), 4.60–4.65 (1 H, m, C*H*OH), 5.01–5.04 (1 H, m, 5-H), 7.08–7.22 (5 H, m, Ph); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 10.0/10.1 (*C*H$_3$CH), 12.6/12.7/12.8/12.9 (*C*H$_3$CH$_2$), 21.0/21.2/21.3/21.4 (MeCH$_2$), 24.1/25.0/25.2/25.5 (*C*H$_2$Et), 30.0/30.1/30.6 (*C*H$_2$-C-O), 34.9/35.4 (MeCH), 75.5/75.7 (COH), 76.9/77.0/77.1/77.2 (C-5), 102.6/102.9/103.0 (C-3), 125.5/125.8, 126.6/126.8, 127.2/127.4 (ar. CH), 140.2/140.3 (C-*ipso*), 173.7/173.9 and 174.9/175.3 (C-2, C-4). Anal. calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.39; H, 7.67%. *Crystal data*: $C_{17}H_{22}O_4$, $M=290.35$, orthorhombic, space group *Pbcn*, $a=10.170(2)$, $b=20.203(5)$, $c=15.486(3)$ Å, $V=3181.8$ Å^3, $Z=8$, $F(000)=1248$, $T=153$ K, $\mu=0.1$ mm^{-1}; Siemens P4 diffractometer, 2081 unique reflections measured giving 1200 with $I>2\sigma(I)$; final $R_1=0.0695$, $wR_2=0.2076$. CCDC No. 162961.
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13. **4-Hydroxy-3-(*p*-methoxybenzyl)-1-oxa-spiro[4.5]dec-3-en-2-one 14**: Yellow, viscous oil; ν_{max} (Nujol mull): 3360, 1747, 1627, 1512 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05–1.83 (10 H, m, CH_2), 3.74 (3 H, s, CH_3), 4.52 (1 H, s, OH), 4.87 (2 H, s, Ar-CH$_2$), 6.84 (2 H, d, $^3J=8.5$ Hz, ar. CH), 7.20 (2 H, d, $^3J=8.5$ Hz, ar. CH); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 20.9, 23.4, 32.0 (CH_2), 54.3 (CH_3), 73.1 (Ar-CH$_2$), 82.5 (C-5), 86.8 (C-3), 113.1 (ar. CH), 125.2 (C-*ipso*), 128.7 (ar. CH), 158.1 (*C*-OMe), 171.2 (C-2), 184.0 (C-4); m/z (EI): 288 (M$^+$, 1%), 258 (3%), 210 (4%), 138 (100%). Anal. calcd for $C_{17}H_{20}O_4$: C, 70.82; H, 6.99. Found: C, 70.76; H, 7.06%.