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A SYNTHESIS OF β-ALLYL SUBSTITUTED ISOTETRONIC ACID DERIVATIVES VIA THERMAL CLAISEN REARRANGEMENT

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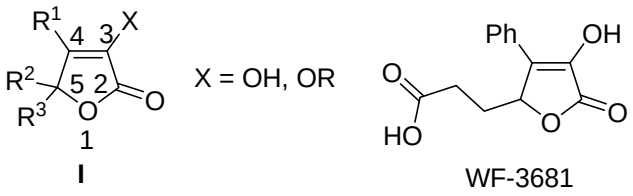
Abstract – Isotetronic acids are of great interest in agricultural and pharmacological research and occur in a number of natural products. This paper describes the first Claisen rearrangement of the *O*-allyl substituted isotetronic acids **2** under thermal conditions furnishing the β-allyl substituted isotetronic acid derivatives **3** in high yields.

Isotetronic acid derivatives posses as a common feature the central 2-(5*H*)-furanone unit I substituted with hydroxy or alkoxy groups at position 3 (Figure 1). They have frequently been isolated from a variety of natural sources and recognized as a kind of important butenolides.[1,2] A wide spectrum of biological activities has been reported. For example, WF-3681 produced by *Chaetomella raphigera* has been reported to be an effective aldose reductase inhibitor.[3] Many other isotetronic acids are found to be useful as anti-oxidants and anti-inflammatory agents,[4] inhibitors of CDKs,[5] anti-depressants and perfumes.[1] Isotetronic acid derivatives have also been used as synthetic building blocks during the synthesis of tetrodotoxin,[6] 6-thiosialic and neuraminic acid.[7] Although a number of synthetic approaches to this class of compounds have been reported,[1,5,8] the development of new and practical methods that can create structural diversity is of considerable interests. During the course of our study, we recently have shown that *O*-protected isotetronic acid derivatives can be achieved via an expedient DBU/Et_3N-mediated sequential homoaldol-lactonization-alkylation reactions of ethyl pyruvate with various electrophiles.[9] The protocol carries several notable advantages such as the wide substrates, simple operation, exceedingly mild condition and no use of any expensive reagents.

The aliphatic Claisen rearrangement is a [3,3]-sigmatropic rearrangement in which an allyl vinyl ether is converted thermally to an γ,δ-unsaturated carbonyl compound.[10] Depending on the type of allyl vinyl ethers, a great number of carbonyl compounds can be produced. Consequently, many chemists aspired to

employ a Claisen rearrangenment in a key carbon-carbon bond-forming step, attesting to the synthetic power of this kind of reaction.[11] In continuation of our work in the synthesis of novel isotetronic acid compounds, we wish to report herein that the 3-OH allyl-protected isotetronic acids **2** can readily be elaborated to β-allyl substituted isotetronic acids via the thermal aliphatic Claisen rearrangement.

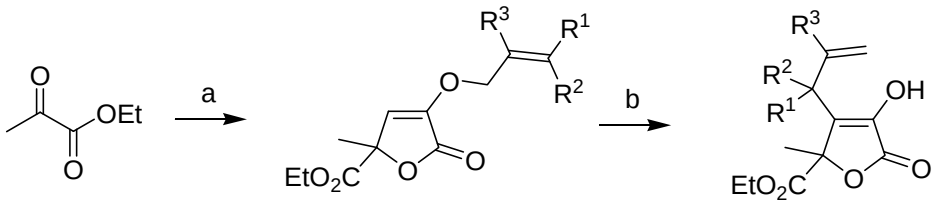


I

Figure 1. General structure of isotetronic acids **I** and a representative WF-3681

The synthetic strategy is outlined in Scheme 1. First, the 3-*O*-protected isotetronic acids **2** required as our key starting material were synthesized using our recently established method.[9] Thus, ethyl pyruvate **1** was allowed to react with different allyl halides by employment DBU along with Et_3N as the base (equivalent ratio 0.20:0.85). The base-couple-mediated sequential homoaldol-lactonization-allylation reactions provided the *O*-protected isotetronic acid derivatives **2** in 80-85% yield.

With the 3-*O*-protected isotetronic acids **2** on hand, the Claisen rearrangement reactions were attempted. We chose 4-allyloxy-2,5-dihydro-2-methyl-5-oxo-2-furancarboxylic acid ethyl ester **2a** as a model substrate to test the reactivity. After careful optimization of the reaction conditions, **2a** was successfully rearranged to the β-allyl substituted isoletronic acid **3a**. In a typical protocol, 0.5 mmol **2a** in toluene was heated in a sealed tube at 170 °C for 22 h. Usual work-up on the resultant mixture afforded **3a** in 86% yield. The effect of solvent on the reaction was also briefly examined. We found that toluene is the best choice for the reaction whereas other solvents such as benzene xylene, and *N*,*N*-dimethylaniline were inappropriate for the reaction or caused a severe deterioration in yield.



1 **2** **3**

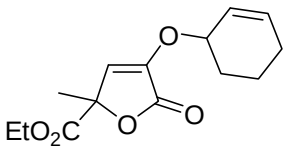
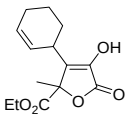
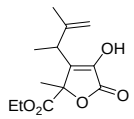
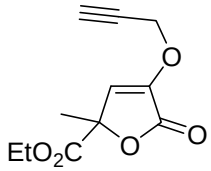
Reagents and conditions: (a) ethyl pyruvate **1** (2.33 g, 20.0 mmol), DBU (0.30 g, 2.0 mmol), Et_3N (0.86 g, 8.5 mmol), CH_2Cl_2 (50 mL), rt, 0.5 h; then an allyl halide $R^1R^2C{=}CR^3{-}CH_2X$ (10.5 mmol) in CH_2Cl_2 (20 mL), rt, 15 h. (b) in a sealed tube: **2** (0.5 mmol), toluene (8 mL), 170 °C, 22 h.

Scheme 1. Synthetic pathway to the β-allyl substituted isotetronic acid derivatives **3**

It has been reported that the Claisen rearrangement can be performed under milder conditions with aid of the use of a transition metal salt like $Pd(OAc)_2$.[12] Based on this view, we also investigated the reaction of **2a** under the catalysis of $Pd(OAc)_2$. A set of different condition combinations were attempted, but all failed to facilitate the reaction. Thus, for example, treatment of **1a** in CH_2Cl_2 at room temperature for overnight, no reaction occurred in the presence of 2% or 5% mmol $Pd(OAc)_2$. Increasing the dosage of $Pd(OAc)_2$ to 10% mmol didn't show any beneficial effect on promoting the rearrangement. Switching the solvent to CH_3CN, toluene, xylene and THF the reaction were still unsuccessful at ambient conditions. Thus, the thermal condition was determined to be our choice.

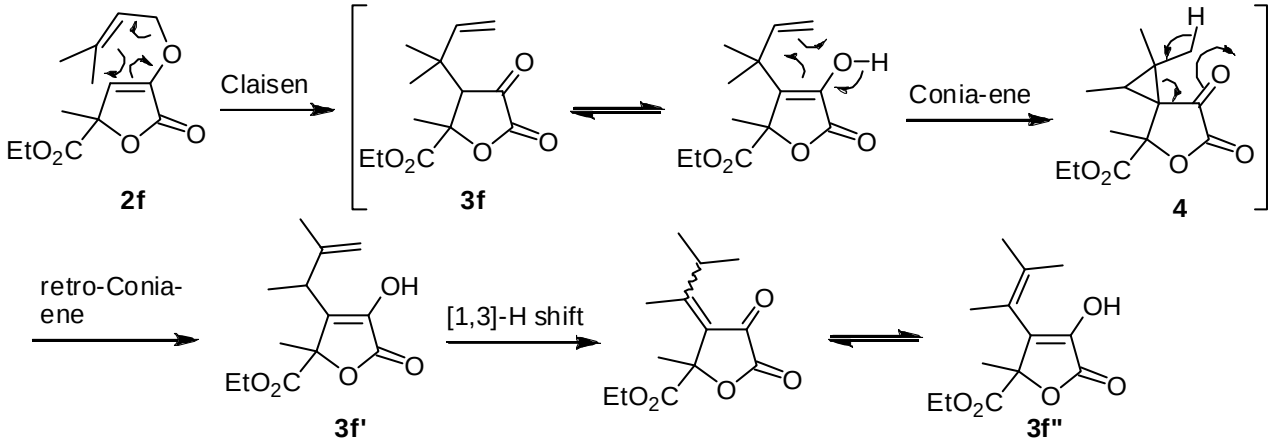
The preparative scope of our methodology was investigated under the above optimal thermal conditions: heating 0.5 mmol **2** in toluene as solvent in a sealed tube for a specific time. As exhibited in Table 1, the reaction proceeded smoothly under comparable conditions and seems to tolerate a wide range of substrates with different substitution pattern on the allyl moiety. The pure products **3a-e** could be obtained by column chromatography (eluent: EtOAc/PE) in 70–86% yields (Table 1, entries 1-5). It is worthy to note that the protocol is equally applicable to the cyclohex-2-enyloxy substituted isotetronic acid **2e**, which delivered the corresponding rearranged product **3e** in a moderate yield (Table 1, entry 5).

Table 1. Synthesis of β-Allyl Substituted Isotetronic Acids **3** via Claisen Rearrangement[a]

Entry	**2**	R^1	R^2	R^3	Temperature (°C)	Time (h)	Products **3**	Yield (%)[b]
1	**2a**	H	H	H	170	22	**3a**	86
2	**2b**	H	H	Me	170	24	**3b**	85
3	**2c**	H	Me	H	170	25	**3c**	82
4	**2d**	H	Ph	H	180	25	**3d**	70
5	**2e**				180	24	 **3e**	72
6	**2f**	Me	Me	H	180	30	 **3f'**	78[c]
7	**2g**				180	30	**3g**	NR[d]

[a] Reagents and conditions: Reactions were conducted on 0.5 mmol scale and heated to 170 °C for 22 h in a sealed tube. [b] Isolated yield. [c] Containing unassigned amount of the isomer **3f''** (structure shown in Scheme 2). [d] Not determined.

Interestingly, the 3,3-dimethyl substituted allylic counterpart **2f** took a more complicated course, leading to the abnormal formation of the 3-methylbut-3-en-2-yl substituted analogue **3f'** and unassigned amount of the 3-methylbut-2-en-2-yl isomer **3f''** as evidenced by GC and NMR. Although the mechanistic detail is a blur at present stage, a plausible rationale accounting for the formation of **3f'** and **3f''** is depicted in Scheme 2.[13] Under the standard condition, **2f** underwent the normal Claisen rearrangement leading to product **3f**, which may be instable and cannot survive the condition. Instead, **3f** would undergo a consecutive *intra*molecular Conia-type oxa-ene reaction leading to the formation of the spiro intermediate **4**. Compound **4** experienced a further retro-Conia-ene type reaction to afford the isolated isotetronic acid **3f'** with concurrent cyclopropane ring opening and regeneration of an olefinic double bond. Formation of **3f''** is tentatively accounted for by a consecutive [1.3]-H shift followed by a keto-enol tautomerisation.[13]



Scheme 2. Plausible mechanism for Claisen rearrangement/Conia-type oxa-ene reaction of **2f**

A limitation was observed when we try to extend the reaction to the propargylic vinylic compound **2g**. Under our conditions, formation of the expected allenic product **3g** couldn't be detected (Table 1, entry 7). In summary, the Claisen rearrangement reaction of a series of the 3-OH allyl-protected isotetronic acids **2** was successfully performed under heating conditions. We believe that this protocol provide a reliable synthetic way to β-substituted isotetronic acid derivatives with high yields.

EXPERIMENTAL

NMR spectra were recorded on a JEOL ECA-400 spectrometer operating at 400 MHz for proton, and 100 MHz for carbon. ^{1}H chemical shifts (δ) are reported in ppm relative to TMS as internal standard. ^{13}C chemical shifts were internally referenced to the deuterated solvent signals in $CDCl_3$ (δ 77.00 ppm). Mass spectra were recorded on a HP 5989A mass spectrometer. High-resolution mass spectra data were measured with a Bruker micrOTOF II instrument.

General Procedure:

In a sealed tube was placed a solution of **2** (0.5 mmol) in dry toluene (8 mL), and the mixture was stirred under heating at 170 °C for 22 h. The resultant mixture was cooled to rt, and the solvent was removed at reduced pressure. The residue was dissolved in CH_2Cl_2 (5 mL), washed twice with water, dried over $MgSO_4$, filtered, and concentrated under high vacuum. The crude product was subjected to flash column chromatography on silica gel with a 1:3 mixture of EtOAc-PE, affording pure **3** as highly viscous yellow oil.

3-Allyl-4-hydroxy-2-methyl-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (3a): Pale yellow oil. IR (CH_2Cl_2): 3323, 1786, 1743, 1650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.83-5.79 (1 H, m, C=CH-), 5.16-5.12 (2 H, m, CH_2=C), 4.17 (2 H, q, ^3J = 7.32 Hz, OCH_2), 3.09 (2 H, d, ^3J = 6.88 Hz, C=C-CH_2), 1.69 (3 H, s, CH_3), 1.27 (3 H, t, ^3J = 7.32 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 168.5, 139.1, 134.6, 131.1, 118.2, 84.9, 62.6, 29.2, 21.2, 14.1; MS (EI): *m/z* 226 [M^+, 100%]. HRMS (ESI): calcd for $C_{11}H_{14}O_5$+Na 249.0739, found 249.0731.

4-Hydroxy-2-methyl-3-(2-methylallyl)-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (3b): Pale yellow oil. IR (CH_2Cl_2): 3321, 1786, 1745, 1655, 1379 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.85 (1 H, s, *H*CH=C), 4.77 (1 H, s, *H*CH=C), 4.15 (2 H, q, ^3J = 7.32 Hz, OCH_2), 3.06-3.01 (2 H, m, C=C-CH_2), 1.75 (3 H, s, CH_3), 1.70 (3 H, s, CH_3), 1.26 (3 H, t, ^3J = 7.32 Hz, CH_2CH_3); ^{13}C NMR (100 Hz, $CDCl_3$): δ 169.1, 168.5, 140.2, 139.1, 131.1, 113.4, 84.9, 62.6, 32.3, 29.7, 21.2, 14.0; MS (EI): *m/z* 240 [M^+, 100%]. HRMS (ESI): calcd for $C_{12}H_{16}O_5$+Na 263.0895, found 263.0896.

3-(But-3-en-2-yl)-4-hydroxy-2-methyl-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (3c): Pale yellow oil. IR (CH_2Cl_2): 3323, 1786, 1742, 1655, 1380 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.78-5.74 (1 H, m, C=CH), 5.06-5.01 (2 H, m, C=CH_2), 4.22 (2 H, q, ^3J = 7.32 Hz, OCH_2), 3.20 (1 H, m, -CH), 1.75 (3 H, s, CH_3), 1.28-1.25 (6 H, m, 2 CH_3); ^{13}C NMR(100 Hz, $CDCl_3$): δ 170.2, 168.5, 139.1, 137.5, 131.1, 114.1, 84.9, 62.6, 18.1, 22.1, 21.2, 14.0; MS (EI): *m/z* 240 [M^+, 95%]. HRMS (ESI): calcd for $C_{12}H_{16}O_5$+Na 263.0895, found 263.0893.

4-Hydroxy-2-methyl-5-oxo-3-(1-phenylallyl)-2,5-dihydrofuran-2-carboxylic acdi ethyl ester (3d): Yellow oil. IR (CH_2Cl_2): 3323, 1786, 1743, 1655, 1600, 1380 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.31-7.24 (5 H, m, Ph), 6.31-6.27 (1 H, m, C=CH), 5.21-5.11 (2 H, m, C=CH_2), 4.20 (2 H, q, ^3J = 7.32 Hz, OCH_2), 3.77-3.73 (1 H, m, C*H*Ph), 1.76 (3 H, s, CH_3), 1.28 (3 H, t, ^3J = 7.32 Hz, CH_3); ^{13}C NMR (100 Hz, $CDCl_3$): δ 169.1, 168.5, 143.2, 139.1, 140.6, 131.4, 130.6, 128.7, 123.2, 117.1, 84.9, 62.6, 43.1, 21.4, 14.0; MS (EI): m/z 302 [M^+, 90%]. HRMS (ESI): calcd for $C_{17}H_{18}O_5$+Na 325.1052, found 325.1048.

3-(Cyclohex-2-enyl)-4-hydroxy-2-methyl-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (3e): Yellow oil. IR (CH_2Cl_2): 3320, 2875, 1786, 1745, 1655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.91 (1 H, t, ^3J = 6.88 Hz, CH_2CH=), 5.54 (1 H, dd, $^3J_1$ = 6.8 Hz, $^3J_2$ = 6.9 Hz, CH=C), 4.21 (2 H, q, ^3J = 7.32 Hz,

OCH_2), 3.12-3.10 (1 H, m, C=C-C*H*), 1.78-1.70 (9 H, m, 3 CH_2 & CH_3), 1.27 (3 H, t, ^3J = 7.32 Hz, CH_3); ^{13}C NMR (100 Hz, $CDCl_3$): δ 174.2, 169.1, 138.2, 136.6, 130.1, 129.8, 126.2, 84.6, 62.6, 32.9, 26.9, 24.5, 21.5, 14.1; MS (EI): *m/z* 266 [M^+, 93.8%]. HRMS (ESI): calcd for $C_{14}H_{18}O_5$+Na 289.1052, found 289.1054.

4-Hydroxy-2-methyl-3-(3-methylbut-3-en-2-yl)-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (3f'): This compound was only obtained as yellow oil in unpurified form that contains unassigned amount of the isomer **3f''**. IR (CH_2Cl_2): 3320, 1786, 1742, 1655, 1379 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.97 (1 H, OH), 4.89 (1 H, s, *H*CH=C), 4.79 (1 H, s, *H*CH=C), 4.21 (2 H, q, ^3J = 7.32 Hz, OCH_2), 3.07-3.03 (1 H, m, -CH), 1.78 (3 H, s, CH_3), 1.70 (3 H, s, CH_3), 1.28-1.24 (6 H, m, 2 CH_3); ^{13}C NMR (100 Hz, $CDCl_3$): δ 169.1, 168.5, 141.1, 139.1, 131.2, 112.2, 84.9, 62.6, 32.3, 21.5, 21.2, 18.6, 14.1; MS (EI): *m/z* 254 [M^+, 70%]. HRMS (ESI): calcd for $C_{13}H_{18}O_5$+Na 277.1052, found 277.1046.

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