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Furan-2,3-diones as masked dipoles: synthesis of isotetronic acids and mechanistic considerations

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ABSTRACT

The formal dipolar behaviour of furan-2,3-diones is illustrated by their reaction with ethyl glyoxylate under Lewis basic activation uniquely, giving access to isotetronic derivatives. The Janus-type nature of the activated species, both nucleophilic and electrophilic is revealed by ring-opening of the starting ketolactone. An unexpected reversible side-reaction was identified by in situ monitoring.

1. Introduction

The isotetronic moiety is well represented in the realm of secondary metabolites;[1] a few examples are displayed on Fig. 1. Additionally, medicinal chemistry studies identified more than 70 compounds that exhibited interesting biological activities, mainly as HIV-integrase inhibitors.[2] It is therefore not surprising to find a fair number of reports dealing with the synthesis of such molecules.

Most synthetic routes to these compounds rely on aldolisation reactions,[3] and several asymmetric versions have been developed.[4] Less conventional methods were also explored.[5]

We recently initiated a series of studies directed towards the use of particular substrates that could reveal a dipolar nature after appropriate activation by a Lewis base (see Scheme 1), On this topic, our group recently described the activation of β-lactams **7** by highly nucleophilic pyridines, and their subsequent reaction with ethyl glyoxylate to form oxazinanones **8**.[6] We next examined the feasibility of a similar reaction employing a furanone **9** as a masked dipole. Isotetronic derivatives seemed perfect examples to showcase the potentialities of these particular substrates possessing an ambivalent nature with masked nucleophilic and electrophilic sites on the same compound. The present investigation reports the reaction of furandiones with a highly activated aldehyde (ethyl glyoxylate) forming functionalised isotetronic derivatives through Lewis base catalysis.

A very nice example of such a reaction was reported by the group of Yanagisawa,[7] moreover in an enantioselective manner, by using a chiral tin Lewis acid **13** in conjunction with a strong nucleophile, here sodium methoxide (see Scheme 2). Our goal was to explore this

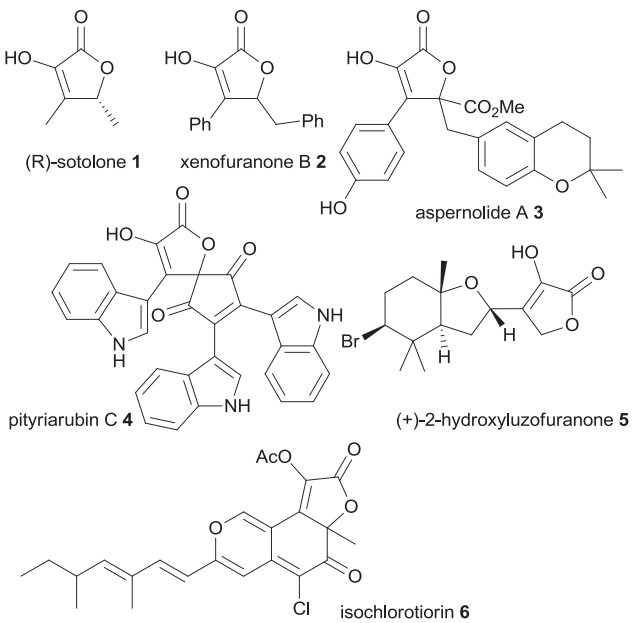

Fig. 1. Natural compounds with an embedded isotetronic moiety.

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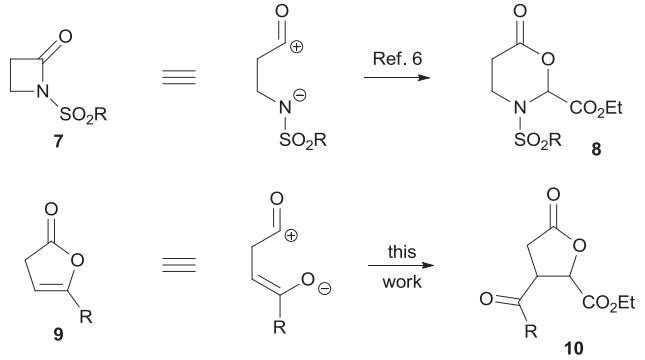
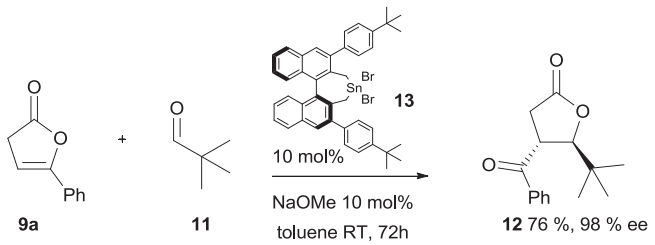


Scheme 1. Formal dipoles.

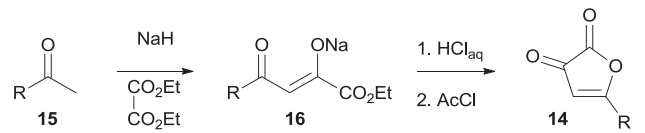


Scheme 2. Enantioselective synthesis of lactone **12**.

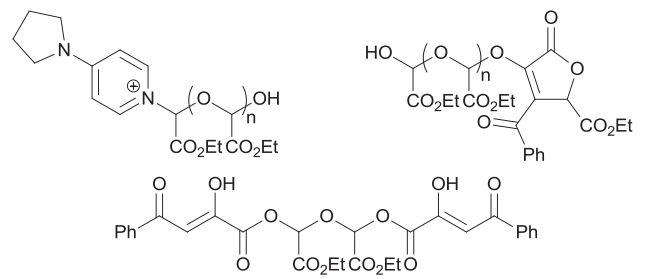
transformation solely using Lewis bases as promoters, in a simplified setting, and to explore the mechanistic details of such a process.

2. Results and discussion

We started by attempting to reproduce the Yanagisawa transformation using only highly nucleophilic and basic pyridines (DMAP, super-DMAP.)[8] It became rapidly apparent that furanones of type **9** were not ring-opened even under forcing conditions. We therefore turned our attention towards furandiones **14** as much more electrophilic substrates, with success. The syntheses of the starting materials[9] are straightforward and high yielding, as presented in Scheme 3 (see Schemes 4 and 5).

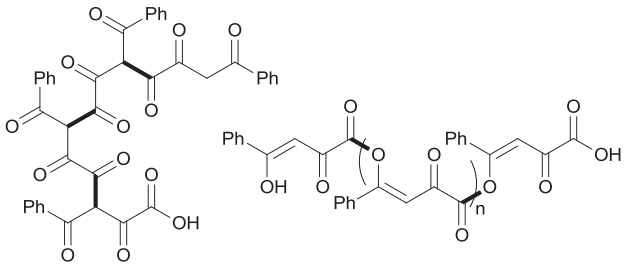


Scheme 3. Syntheses of furan-2,3-diones **14a**–**h**.



Scheme 4. Oligomeric structures putatively formed under reaction conditions.

Optimisation studies were undertaken next, a 10% molar catalytic charge of 4-pyrrolidinopyridine indeed triggered the



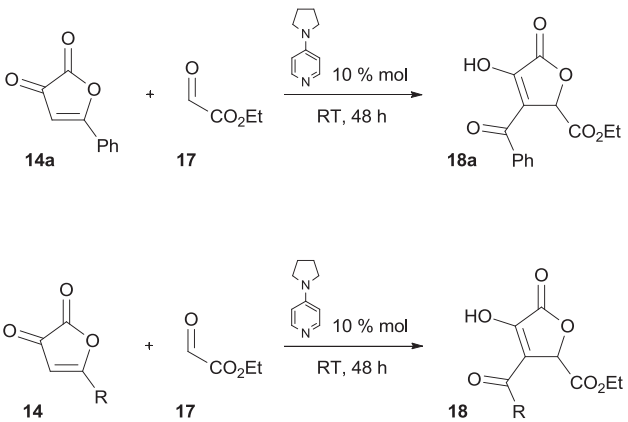
Scheme 5. Oligomeric structures putatively formed from furandione **14** alone.

transformation of furandione **14a** (used as model compound) with ethyl glyoxylate **17** that showed its exceptional reactivity in previous investigations.[10] Four solvents were tested to define the best reaction medium, see Table 1. After 48 h the reaction reached

Table 1
Optimisation of the reaction medium

Solvent	Toluene-d^8	$CDCl_3$	THF-d^8	CD_3CN
Yield	55%	70%	47%	28%

completion in all cases at room temperature, the slowest conversion being observed in toluene. From this it was clear that chloroform was the solvent of choice. Attempts to accelerate the conversion by increasing the temperature resulted in decreased yields with extensive side-reactions. Lower catalyst loadings were tested, resulting in impractically long reaction times. Optimal conditions were defined as follows: 10 mol % of PPY at room-temperature in chloroform at a concentration of 0.3 mol L^{-1}, which were employed in the next step for scope testing, see Table 2.



When applied to furandiones **14**, these conditions allowed complete conversion in less than 24 h, see Table 2. All reactions were also run in THF since, without a clear rationale, certain substrates performed better in this solvent. Yields are between 42 and 73% when the right medium was chosen. In all cases the product was isolated by simple evaporation of the solvent. Attempts of purification by chromatography means on silica or alumina gels led to ca. 10% decrease in yields and gave still impure compounds contaminated with degradation products. The crude reaction products could be engagement in further reactions without problem following procedures of silylation,[4b,4f] triflation,[3e] Williamson

Table 2
Formation of isotetronic acids **18**

Substrate, R	Yield in $CDCl_3$	Yield in THF-d^8
14a: Ph	70%	47%
14b: 2-C_6H_4OMe	65%	73%
14c: 4-C_6H_4OMe	51%	38%
14d: 4-C_6H_4Me	33%	42%
14e: 4-C_6H_4Cl	31%	44%
14f: 4-C_6H_4F	43%	39%
14g: 4-$C_6H_4NO_2$	45%	30%
14h: *tert*-Bu	47%	46%

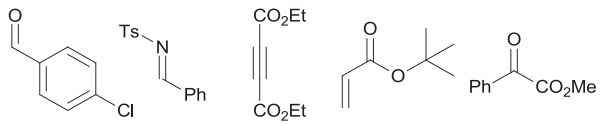


Fig. 2. Other substrates tested.

alkylation,[3h,11] or acylation.[11] We next varied the electrophile opposed to the furandione, however, much as in our preceding studies with β-lactams,[6] this met only with disappointment as none of the substrates presented in Fig. 2 gave rise to the expected ring-opening. Despite introduction of additives known to activate aldehydes (LiCl, Schreiner's thiourea), screening of other Lewis bases (DABCO, tributylphosphine, azide anion) no trace of the corresponding condensation products could be observed. Intrigued by these results, we gathered as much information as possible about this transformation in order to gain some insight into this peculiar reaction. Firstly, as only fair yields were observed, we were intrigued by the absence of observable side-products in the crude reaction mixture that could explain the loss of material. After 24 h of incubation, all starting furandione **14** was consumed and the desired product **18** was the sole compound visible in the proton NMR spectrum. We monitored the reaction against time by running it in an NMR tube. Results are displayed in Fig. 3. The characteristic H4 proton of the starting furandione **14a** resonates at 6.5 ppm as a singlet, while the product shows a new singlet at 5.9 ppm denoting the resonance of H5 in the isotetronic structure **18a**. The

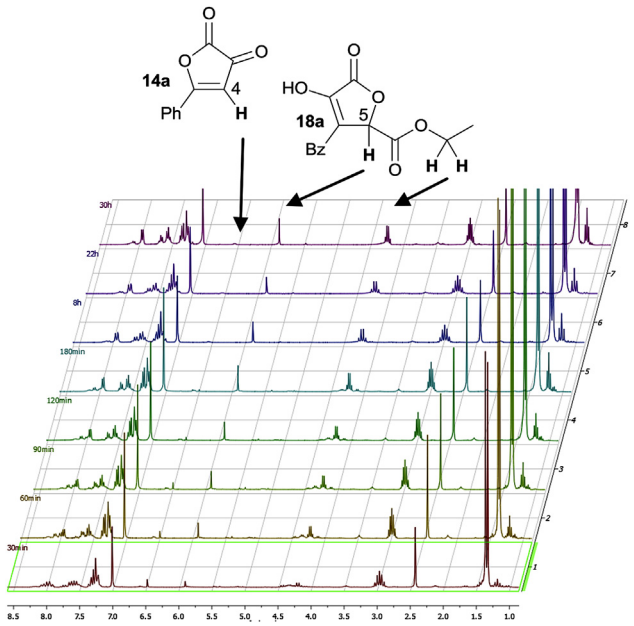


Fig. 3. Proton NMR monitoring of the reaction, disappearance of **14a** and formation of **18a**.

ester quadruplet at 4.2 ppm also proves the incorporation of the glyoxylate moiety into the isotetronic skeleton.

If at first glance this accumulation of spectra simply shows the smooth conversion of **14a** into **18a**, a more informative phenomenon was revealed after careful examination of the quantitative data extracted from it.

By using 1,3,5-tris(isopropyl)benzene as an internal standard the exact quantity of each compound could be measured at all times. Inspection of these figures allowed two conclusions to be drawn. First, the reaction is initially a fast process, since after half an hour, two-thirds of the starting material was consumed, and, after 3 h it had nearly disappeared.

Secondly, and most interestingly, when adding residual reactant and product formed, one realises that a substantial amount of matter is missing, which is not clearly visible in the proton NMR spectra. Even more intriguing, this 'missing material' actually increases from the onset of the reaction and for 2 h, then steeply decreases to finally stabilise at around 30% of the mixture, as can be seen in Fig. 4.

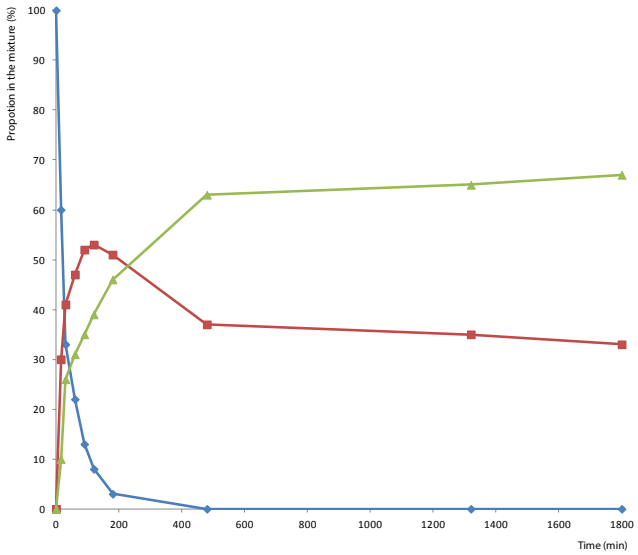


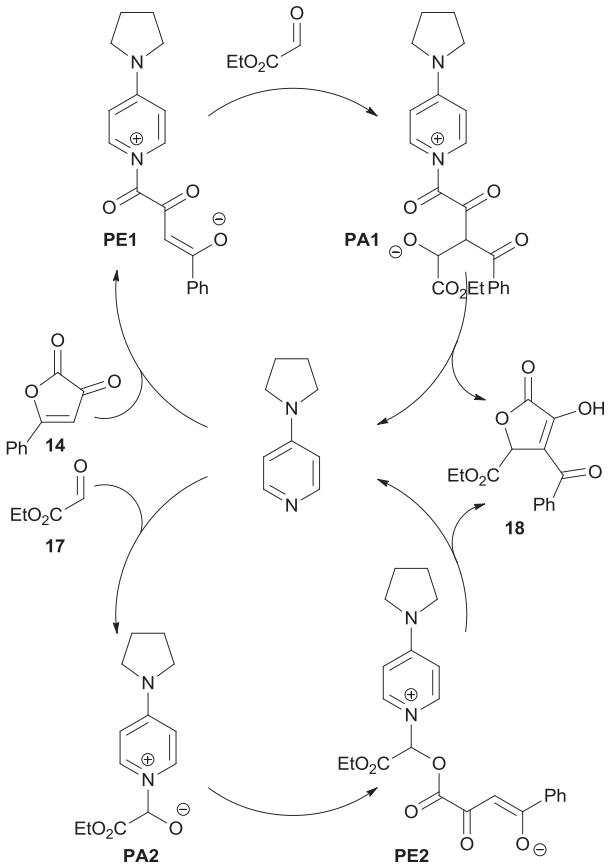
Fig. 4. Proportions in % of ◆) starting **14a**, ▲) product **18a**, and ■) 'missing material' plotted against reaction time.

In fact, upon more careful examination of the proton NMR spectra at intermediate times, one can see tiny signals that fade into the background noise at longer reaction times.

Attempts to isolate this portion of the reaction mixture were in vain, only product **18a** could be recovered after chromatographic separations. This experimental detail brought us to the trail of polymeric materials. Mass spectrometry performed on reaction mixtures showed several signals with high molecular masses (m/e>300 Da, up to 899 Da!) suggesting the presence of oligomeric compounds. From this we can hypothesize the occurrence of a fast oligomerisation process resulting in a quick consumption of the starting furandione. Partial depolymerisation then slowly takes place, accounting for the final decrease in the amount of 'missing material.' Additionally, the structure of **14a** suggests a strong propensity to polymerise alone. To verify this, the evolution of a solution of **14a** in the presence of 10 mol % of PPY was followed by proton NMR, showing the rapid disappearance of the starting compound. After 18 h, only unresolved signals, barely visible against the background noise were observed. Mass-spectrometry again showed a series of peaks with high molecular masses.

After having identified a plausible explanation for the limitation in the yield of this reaction, we wanted to rationalise the limitation in scope. Why is ethyl glyoxylate the sole successful substrate in

this transformation? From a fundamental viewpoint, the envisioned mechanism at the base of this project is in concurrence with a second, less intuitive, scenario. In Scheme 6, both sequences of events are presented. The upper one, our working hypothesis, starts

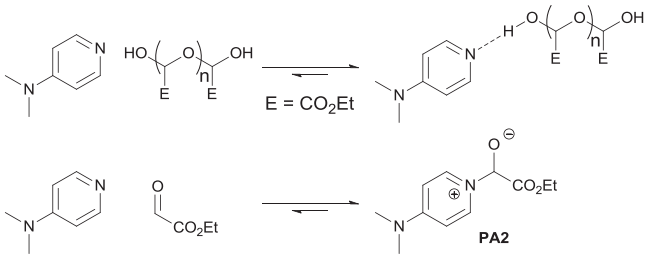


Scheme 6. Two plausible mechanisms for the formation of **18**.

with the ring-opening of furandione **14** by the catalyst to form a pyridinium-enolate PE1. The latter attacks, in an aldolisation step, aldehyde **17** to form a pyridinium-alcoholate **PA1**, finally ring-closing into product **18** with expulsion of PPY. An alternative route is conceivable, depicted in the lower part of Scheme 6. PPY starts by attacking aldehyde **17** giving pyridinium-alcoholate **PA2**, the oxygen anion then serves as a nucleophile to ring-open furandione **14** to lead to pyridinium-enolate **PE2**, which after an intramolecular S_N2 reaction gives **18**. Although peculiar, this last sequence of events could explain that only the extremely electrophilic aldehyde **17** is reactive in the transformation as it is the sole to give rise to a nucleophilic alcoholate of type **PA2**.

This scenario is furthermore substantiated by carbon-NMR experiments on mixtures of ethyl glyoxylate and DMAP. We therefore looked for putative interactions between the pyridine and ethyl glyoxylate, proposed in Scheme 7; these studies had to circumvent a practical difficulty.

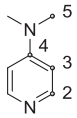
As shown in previous work,[6] ethyl glyoxylate exists as partially polymerized acetalic forms, which are in equilibrium with the monomeric aldehyde **17**. Oligomers have hydroxyl end-groups which could also interact with the pyridine nitrogen lone-pair. We therefore compared three solutions by ^{13}C NMR with a constant concentration of DMAP as model catalyst: 1. the catalyst alone, 2. in the presence of methanol, used as a model compound for the hemiacetalic end groups of ethyl glyoxylate oligomers, and 3. ethyl glyoxylate itself, which under these conditions contains ca. 30% of

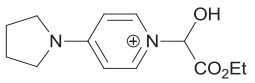


Scheme 7. Two modes of interaction between the pyridine catalyst and ethyl glyoxylate.

monomeric aldehyde **17**. The shifts in ppm are reported for the three solutions in Table 3. As can be seen, methanol exerts a notable but small influence on DMAP, while ethyl glyoxylate has a more pronounced effect on the chemical shifts, with large modifications of the C2 and C4 resonances. These shifts are in agreement with the formation of a pyridinium moiety as expected if **PA2** is present in notable amounts. Mass-spectrometry also indicated the formation of such an adduct, as solutions of PPY and ethyl glyoxylate indeed revealed the presence of the pyridinium-alcohol **19**, depicted in Fig. 5. Simply protonated PPY was not detected in these solutions.

Table 3
Chemical shifts in ^{13}C, δ, ppm

		DMAP	DMAP+MeOH	DMAP+EtG
	C5	38.15	38.22 (∼)	39.23 (+)
	C4	154.09	154.73 (+)	**156.89** (++)
	C3	106.56	106.74 (∼)	106.64 (∼)
	C2	149.64	148.68 (−)	**139.08** (− −)



19: $C_{13}H_{19}N_2O_3^+$
m/z_{theo} = 251,1390
m/z_{exp} = 251.1413

Fig. 5. Addition adduct **19**, observed by mass-spectrometry.

In a final part of our investigations, we wanted to determine the rate-order of ethyl glyoxylate in this reaction. Precise kinetic studies were hampered by the difficulty in following this fast reaction. UV−vis spectrometry was unable to detect the disappearance of the furandione or the formation of isotetronic product in a clear manner, and NMR spectroscopy gave only semi quantitative results as, over time of an acquisition, most of the conversion had occurred.

No clear acceleration of the reaction rate could be measured by increasing the number of equivalents of ethyl glyoxylate, but this caused an increase in the extent of parasitic side-reactions, resulting in lower formation of **18**.

3. Conclusions

A novel route to highly functionalised isotetronic compounds was optimised, exploiting the formal dipolar nature of the furandione substrates after nucleophilic attack. In the course of this study, the putative activation of ethyl glyoxylate by a highly nucleophilic pyridine was substantiated by various techniques. An interesting 'reservoir effect' was brought to light, with initial polymerisation of the substrate which then slowly converts into the expected product. We are currently exploiting the knowledge gained in this study to employ other 'masked dipoles' in organocatalysis.

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4. Experimental section

^{1}H NMR (300 MHz) and ^{13}C (75 MHz) spectra were recorded with Brüker Avance 300 MHz spectrometers using tetramethylsilane as an internal standard. Chemical shifts (δ) are given in parts per million and coupling constants are given as absolute values expressed in Hertz. Electrospray ionization (ESI) mass spectra were collected using a Q-TOF instrument supplied by WATERS. Samples (solubilized in CH_3CN at 1 mg mL^{-1} and then diluted by 1000) were introduced into the MS via an UPLC system whilst a Leucine Enkephalin solution was co-injected via a micro pump. Infrared spectra were recorded with a Nicolet iS10 Infrared FT ATR spectrometer. Thin-layer chromatography (TLC) was carried out on aluminium sheets precoated with silica gel 60 F254 (Merck). Column chromatography separations were performed using Merck Kieselgel 60 (0.040–0.060 mm). Tetrahydrofuran and dichloromethane were dried immediately before use by distillation from standard drying agents.

4.1. General procedure for β-ketolactones synthesis

To a solution of diethyl oxalate (1 equiv) in EtOH, NaH (1 equiv, 60% in oil) and the methylketone were successively added portionwise at 0 °C under inert atmosphere. After 16 h of stirring at room temperature, the reaction mixture was concentrated in vacuo. The resulting sodium salt was washed several times with diethylether. This sodium salt was dissolved and stirred 2 day at room temperature in a solution of HCl (40 equiv, 6M) and acetonitrile. The reaction mixture was concentrated in vacuo and dissolved in dichloromethane. The media was treated with an aqueous solution of $NaHCO_3$ (until basic pH) and extracted three times. Then aqueous phase was treated with HCl 6M (until acidic pH), filtered and dried to get the resulting β-ketoacid as a solid. The β-ketoacid was dissolved in acetyl chloride at room temperature for 16 h. The reaction mixture was concentrated under vacuum. The resulting power was washed with a small volume of cold ether to give β-ketolactones as a solid.

*4.1.1. 5-Phenylfuran-2,3-dione (**14a**).* Yellow solid, 0.24 g (78% yield) and perfectly fits analytic data described in Ref. 9. mp=133–135 °C; IR υ(cm^{-1}): 3062, 3026, 1785, 1712, 1592, 1492, 1450, 1411, 1366, 1310, 1291, 1277, 1165, 1129, 1109, 1087, 805, 758. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.65 (d, J=8.3 Hz, 2H), 7.48–7.03 (m, 7H), 5.56 (dd, J=5.7, 2.7 Hz, 1H), 3.38 (dd, J=16.6, 5.7 Hz, 1H), 2.95 (dd, J=16.6, 2.7 Hz, 1H), 2.43 (s, 3H).

*4.1.2. 5-(2-Methoxyphenyl)furan-2,3-dione (**14b**).* Orange solid, 784.3 mg (85% yield); mp=150–152 °C; IR υ(cm^{-1}): 3089, 1820, 1715, 1592, 1583, 1487, 1421, 1080, 982. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 (d, J=7.9 Hz, 1H), 7.75–7.59 (m, 1H), 7.12 (dd, J=16.9, 8.2 Hz, 2H), 6.72 (s, 1H), 4.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.76, 175.30, 161.47, 155.07, 136.70, 128.64, 121.11, 111.74, 106.85, 55.94. HRMS m/z (ESI, TOF) calcd. For $C_{11}H_8O_4Na$ (M+Na)$^+$ 227.0320, found 227.0324.

*4.1.3. 5-(4-Methoxyphenyl)furan-2,3-dione (**14c**).* Orange solid, 855 mg (93% yield); mp=140–142 °C IR υ(cm^{-1}): 3089, 1820, 1715, 1592, 1583, 1487, 1421, 1080, 982. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.91 (d, J=8.9 Hz, 1H), 7.07 (d, J=8.9 Hz, 1H), 6.30 (s, 1H), 3.95 (s, 3H).). ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.81, 177.77, 165.72, 155.78, 130.25, 118.16, 115.20, 99.92, 55.89. HRMS m/z (ESI, TOF) calcd. For $C_{11}H_9O_4$ (M+H)$^+$ 205.0501, found 205.0501.

*4.1.4. 5-(4-Methylphenyl)furan-2,3-dione (**14d**).* Yellow solid, 670.3 mg (74% yield); mp=139–141 °C; IR υ(cm^{-1}): 3092, 1825, 1710, 1593, 1584, 1485, 1418, 1320, 1268, 1005, 989. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.84 (d, J=8.3 Hz, 2H), 7.40 (d, J=8.0 Hz, 2H), 6.37 (s, 1H), 2.50 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.30, 178.25, 155.26, 147.16, 130.33, 127.80, 123.27, 100.91, 22.15. HRMS m/z (ESI, TOF) calcd. For $C_{11}H_9O_3$ (M+H)$^+$ 189.0552, found 189.0554.

*4.1.5. 5-(4-Chlorophenyl)furan-2,3-dione (**14e**).* Yellow solid, 384.2 mg (82% yield); mp=149–151 °C; IR υ(cm^{-1}): 3082, 1820, 1712, 1592, 1492, 1420, 1109, 1087, 805, 758. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (d, J=8.6 Hz, 2H), 7.58 (d, J=8.6 Hz, 2H), 6.42 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.20, 177.92, 154.56, 141.94, 130.04, 128.83, 124.49, 101.74. HRMS m/z (ESI, TOF) calcd. For $C_{10}H_5O_3NaCl$ (M+Na)$^+$ 230.9825, found 230.9834.

*4.1.6. 5-(4-Fluorophenyl)furan-2,3-dione (**14f**).* Yellow solid, 587.3 mg (64% yield); mp=137–139 °C; IR υ(cm^{-1}): 3100, 1820, 1715, 1590, 1485, 1418, 1105, 1084. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.94–7.85 (m, 1H), 7.21 (d, J=8.6 Hz, 1H), 6.31 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.15, 177.97, 165.21, 154.69, 130.38 (d, J=9.7 Hz), 122.36, 117.20 (d, J=22.5 Hz), 101.32 (d, J=1.6 Hz). HRMS m/z (ESI, TOF) calcd. For $C_{10}H_6O_3F$ (M+H)$^+$ 193.0301, found 193.0304.

*4.1.7. 5-(4-Nitrophenyl)furan-2,3-dione (**14g**).* Yellow solid, 632.7 mg (68% yield); mp=150–152 °C; IR υ(cm^{-1}): 3100, 1820, 1715, 1590, 1579, 1485, 1418, 1390, 1210, 1084. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.37 (d, J=8.9 Hz, 2H), 8.04 (d, J=8.8 Hz, 2H), 6.49 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.15, 177.97, 165.21, 154.69, 130.38 (d, J=9.7 Hz), 122.36, 117.20, 101.32. Note that the two carbonyl resonances could not be detected even after modification of the relaxation parameters. HRMS m/z (ESI, TOF) calcd. For $C_{10}H_5NO_5Na$ (M+Na)$^+$ 242.0065, found 242.0066.

*4.1.8. 5-tert-Butylfuran-2,3-dione (**14h**).* Prepared according to a reported procedure, see Ref. 9. ^{1}H NMR (300 MHz, $CDCl_3$): (62%) δ 6.44 (s, 1H), 1.33 (s, 18H). HRMS m/z (ESI, TOF) calcd. For $C_8H_{10}O_3Na$ (M+Na)$^+$ 177.0528, found 177.0529.

4.2. General procedure for isotetronic acid derivatives synthesis

To a stirred solution of β-ketolatone (1 equiv), ethyl glyoxalate, 50% in toluene (Alfa Aesar) (1 equiv) in $CDCl_3$ (1 mL), 1,3,5-tris(isopropyl)benzene as an internal reference (1 equiv), is added 10 mol % of 4-PPY. After 24 h at RT, NMR analysis was performed and yields were determined.

*4.2.1. Ethyl 3-benzoyl-4-hydroxy-5-oxo-2,5-dihydrofuran-2-carboxylate (**18a**).* 70 % in $CDCl_3$ and 47% in THF-d^8 ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (m, 2H), 7.55 (m, 3H), 5.87 (s, 1H), 4.24 (q, J=7.1 Hz, 2H), 1.23 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.82, 168.18, 166.66, 149.15, 137.92, 136.53, 129.14, 128.34, 120.38, 77.02, 62.74, 13.85. HRMS m/z (ESI, TOF) calcd. For $C_{14}H_{13}O_6$ (M+H)$^+$ 277.0712, found 277.0716.

*4.2.2. Ethyl 4-hydroxy-3-(2-methoxybenzoyl)-5-oxo-2,5-dihydrofuran-2-carboxylate (**18b**).* 65 % in $CDCl_3$ and 73% in THF-d^8 ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (t, J=7.9 Hz, 1H), 7.51 (d, J=6.6 Hz, 1H), 7.10 (t, J=7.5 Hz, 1H), 7.04 (d, J=8.5 Hz, 1H), 5.88 (s, 1H), 4.08–3.85 (m, 2H), 3.96 (s, 3H), 1.02 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 191.87, 166.23, 166.04, 157.37, 154.98, 134.36, 130.16, 127.09, 125.36, 121.21, 111.35, 76.28, 62.41, 55.63, 13.64. HRMS m/z (ESI, TOF) calcd. For $C_{15}H_{15}O_7$ (M+H)$^+$ 307.0818, found 307.0826.

*4.2.3. Ethyl 4-hydroxy-3-(4-methoxybenzoyl)-5-oxo-2,5-dihydrofuran-2-carboxylate (**18c**).* 51 % in $CDCl_3$ and 38% in THF-d^8 ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (d, J=8.7 Hz, 1H), 7.02 (d, J=8.7 Hz, 1H), 5.87 (s, 1H), 4.22 (q, J=7.2 Hz, 1H), 1.21 (t, J=7.1 Hz, 2H). ^{13}C NMR

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(75 MHz, $CDCl_3$): 187.90, 167.72, 166.49, 164.42, 149.67, 137.90, 131.71, 120.48, 114.07, 77.04, 62.68, 55.62, 13.84. HRMS m/z (ESI, TOF) calcd. For $C_{15}H_{15}O_7$ $(M+H)^+$ 307.0818, found 307.0824.

*4.2.4. Ethyl 4-hydroxy-3-(4-methylbenzoyl)-5-oxo-2,5-dihydrofuran-2-carboxylate (**18d**).* 33 % in $CDCl_3$ and 42% in THF-d^8 ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (d, J=8.1 Hz, 2H), 7.35 (d, J=8.1 Hz, 2H), 5.89 (s, 1H), 4.21 (q, J=7.2 Hz, 2H), 1.20 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 189.45, 167.29, 166.29, 145.16, 137.90, 133.67, 129.51, 120.25, 76.94, 62.71, 21.69, 13.79. HRMS m/z (ESI, TOF) calcd. For $C_{15}H_{15}O_6$ $(M+H)^+$ 291.0869, found 291.0872.

*4.2.5. Ethyl 4-hydroxy-3-(4-chlorobenzoyl)-5-oxo-2,5-dihydrofuran-2-carboxylate (**18e**).* 31 % in $CDCl_3$ and 44% in THF-d^8 ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, J=8.6 Hz, 2H), 7.89 (d, J=8.5 Hz, 2H), 5.84 (s, 1H), 4.33–4.21 (m, 2H), 1.26 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 188.26, 167.88, 166.42, 140.30, 137.90, 134.72, 130.52, 129.53, 120.18, 76.79, 62.76, 13.67. HRMS m/z (ESI, TOF) calcd. For $C_{14}H_{12}O_6Cl$ $(M+H)^+$ 311.0322, found 311.0328.

*4.2.6. Ethyl 4-hydroxy-3-(4-fluorobenzoyl)-5-oxo-2,5-dihydrofuran-2-carboxylate (**18f**).* 43 % in $CDCl_3$ and 39% in THF-d^8 ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (d, J=8.7 Hz, 2H), 7.25 (d, J=8.7 Hz, 2H), 5.96 (s, 1H), 4.32–4.24 (m, 2H), 1.21 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 188.30, 168.36 (d, J=6.8 Hz), 166.63, 164.90, 147.49, 137.93, 132.09 (d, J=8.5 Hz), 121.26, 116.24 (d, J=22.3 Hz), 77.31, 63.69, 13.63. HRMS m/z (ESI, TOF) calcd. For $C_{14}H_{12}O_6F$ $(M+H)^+$ 295.0618, found 295.0625.

*4.2.7. Ethyl 4-hydroxy-3-(4-nitrobenzoyl)-5-oxo-2,5-dihydrofuran-2-carboxylate (**18g**).* 45 % in $CDCl_3$ and 30% in THF-d^8 ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (d, J=8.7 Hz, 1H), 7.02 (d, J=8.7 Hz, 1H), 5.87 (s, 1H), 4.31 (q, J=7.2 Hz, 2H), 1.31 (t, J=7.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 187.71, 168.27, 166.52, 150.39, 148.39, 141.40, 137.91, 130.13, 123.72, 76.91, 63.06, 13.93. HRMS m/z (ESI, TOF) calcd. For $C_{14}H_{11}NO_8Na$ $(M+Na)^+$ 344.0382, found 344.0378.

*4.2.8. Ethyl 4-hydroxy-5-oxo-3-pivaloyl-2,5-dihydrofuran-2-carboxylate (**18h**).* 47 % in $CDCl_3$ and 46% in THF-d^8 ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.58 (s, 1H), 4.42–4.25 (m, 2H), 1.35 (m, 3H) 1.25 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 202.57, 169.39, 166.90, 144.99, 120.56, 77.99, 62.56, 43.58, 24.92, 13.97. HRMS m/z (ESI, TOF) calcd. For $C_{12}H_{17}O_6$ $(M+H)^+$ 257.1025, found 257.1032. Experimental details.

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