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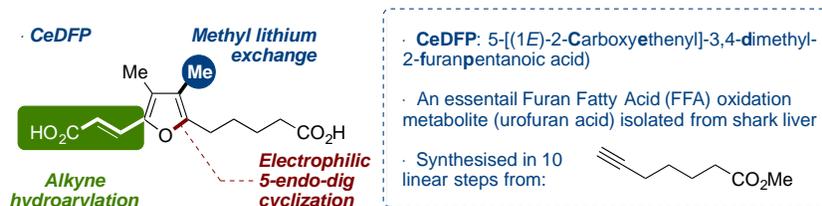
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Total synthesis of the *tetra*-substituted furan fatty acid metabolite CeDFP *via* Au-catalyzed intermolecular alkyne hydroarylation

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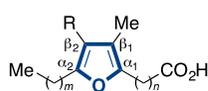
Supporting Information Placeholder



ABSTRACT: The first total synthesis of the *tetra*-substituted furan fatty acid (FFA) metabolite 5-[(1*E*)-2-carboxyethenyl]-3,4-dimethyl-2-furanpentanoic acid (CeDFP), is reported. CeDFP is a FFA metabolite isolated from shark livers and is related to the known FFA metabolites CMPF and CMPentylF. Key elements of the synthetic route to CeDFP include an iodine promoted 5-*endo*-*dig* cyclization of an 1,2-alkyne diol, a methyl lithium mediated insertion of the C₃-methyl group, and an Au(I)-catalyzed *intermolecular* hydroarylation to introduce the unsaturated ester.

The Furan Fatty Acids (**1**: FFAs) are an important class of natural products and metabolites due to their observed nutritional health benefits and impact on inflammatory and cardiovascular diseases.¹ To date, over 25 members have been discovered, and they are structurally characterized by a furan ring with a fatty acid side chain at the α_1 -position, a short alkyl side chain at the α_2 -position, a methyl group at the β_1 -position, and a hydrogen or methyl group at the β_2 -position (figure 1a). The FFAs are understood to originate from plant, algae and marine bacteria, and as a result they then accrue in higher order fish and mammals; therefore, the furan fatty acids are not produced *de novo* within humans and animals, but are accumulated through ingestion.^{1a,2}

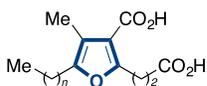
(a) Furan fatty acids



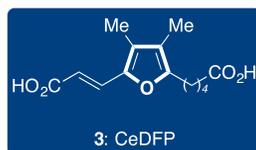
1: General structure

9D3 (F₁) $m = 2; n = 8; R = \text{Me}$
9M5 (F₂) $m = 4; n = 8; R = \text{H}$
9D5 (F₃) $m = 4; n = 8; R = \text{Me}$
11D3 (F₄) $m = 2; n = 10; R = \text{Me}$
11M5 (F₅) $m = 4; n = 10; R = \text{H}$
11D5 (F₆) $m = 4; n = 10; R = \text{Me}$
13M5 (F₇) $m = 4; n = 12; R = \text{H}$
13D5 (F₈) $m = 4; n = 12; R = \text{Me}$

(b) Urofuran acids



2a: ($n = 2$) CMPF
2b: ($n = 4$) CMPentylF



3: CeDFP

Figure 1. (a) The general structure of the 8 predominant furan fatty acids; (b) three significant urofuran acid metabolites of the FFAs.

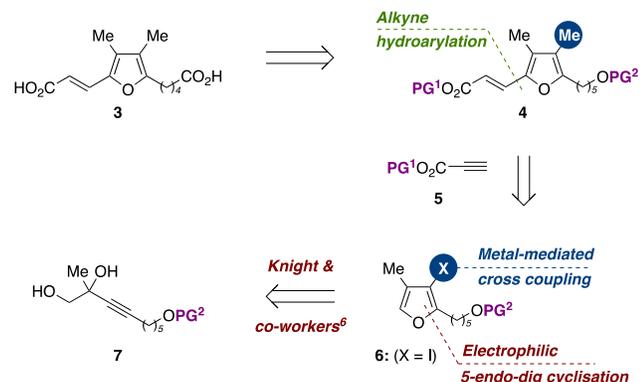
Once accumulated it is probable that the FFAs are further catabolized within animals *via* oxidation within the liver. This process gives rise to urofuran acids, whose structures can vary considerably depending on the species. Significantly, in humans, two principal urofuran acids 3-carboxy-4-methyl-5-propyl-2-furanpropionic acid (CMPF, **2a**) and 3-carboxy-4-methyl-5-pentyl-2-furanpropionic acid (CMPentylF, **2b**) (figure 1b) have been detected, with the levels of **2a** being elevated in patients suffering from renal failure.^{1c,3} However, the exact role and mode-of-action of CMPF (**2a**) in renal failure and particularly type-2 diabetes has been intensely debated, and as yet to be fully elucidated.^{1a}

Another important catabolite is the tetra-substituted furan, 5-[(1*E*)-2-carboxyethenyl]-3,4-dimethyl-2-furanpentanoic acid (CeDFP, **3**). This urofuran acid has been detected in the urine of cattle^{4a} and more significantly, can be found in appreciable amounts within the bile of sharks, making up almost 10% dry weight of the liver.^{4b} Metabolite **3** differs significantly from CMPF (**2a**) and CMPentylF (**2b**) as the β_1 methyl group remains intact, and both the α_1 and α_2 side chains have undergone incomplete β -oxidation. To date this metabolite can only be obtained through isolation from shark livers, and consequently this method is unsustainable. Therefore, given this and the recent attention that the FFAs have garnered due to their potent antioxidant potential, we deemed that a first chemical synthesis of **3** was warranted.^{1,4b,5}

Our approach to the total synthesis of **3** is outlined in the retrosynthetic analysis shown in scheme 1. Judicious selection of the protecting group (PG¹) on the carboxyl group, and masking of the terminal acid of the **5** as the protected (PG²) primary alcohol, will give tetra-substituted furan **4**. We envisaged using two key transformations to deliver this key

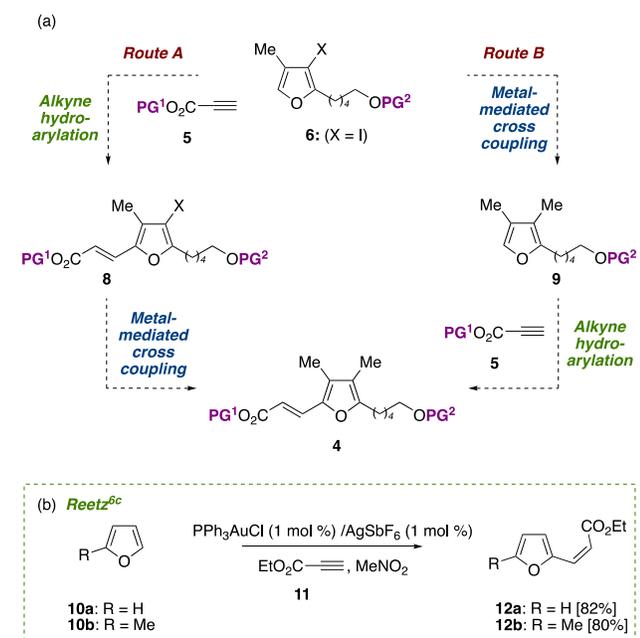
tetra-substituted furan **4**; (i) a Au-catalyzed *intermolecular* alkyne hydroarylation between a furan and a propiolate (**5**); and (ii) a metal-mediated cross coupling to introduce the methyl group of the furan. This approach reveals a tri-substituted furan **6** as a suitable precursor, that can be obtained via an electrophilic 5-*endo-dig* cyclization⁶ of propargyl 1,2-diol **7**.

Scheme 1. Retrosynthetic analysis of furan fatty acid metabolite 3.



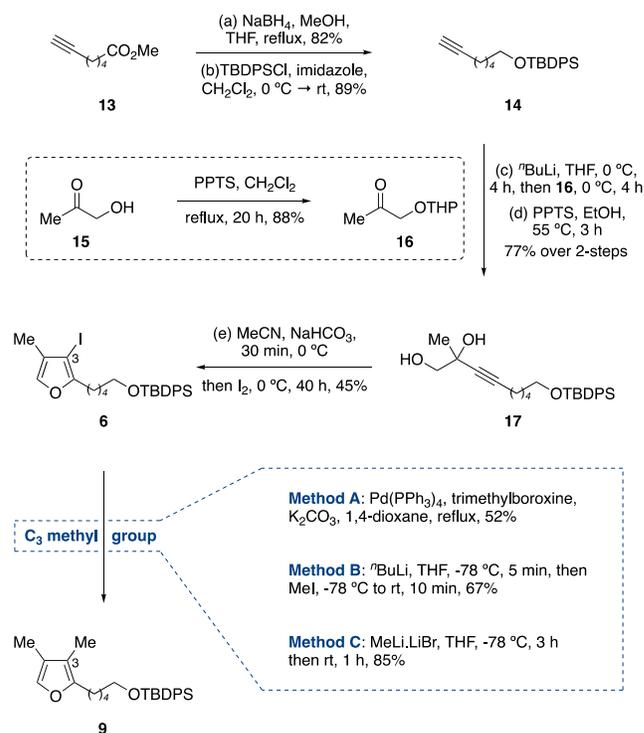
There are two plausible synthetic strategies to access tetra-substituted furan **4**; an intermolecular alkyne hydroarylation performed on **6**, followed by a metal mediated cross coupling to give **4** (scheme 2b, Route A); alternatively the sequence of these two reactions can be reversed, where the key Au(I)-hydroarylation transformation with **5** is performed with the trialkyl furan **9** (Route B). There are few examples of using an *intermolecular* hydroarylation transformation in target synthesis;⁷ however, an Au(I)-catalyzed *intermolecular* alkyne hydroarylation using furan and 2-methylfuran has been reported. Reetz and co-workers demonstrated that furan (**10a**) and 2-methylfuran (**10b**) undergo regioselective hydroarylation with ethyl propiolate (**11**), giving the *Z*-products (**12a** and **12b**, respectively) in high yield.^{7c}

Scheme 2. (a) Two plausible routes to tetra-substituted furan 4; (b) Au-catalyzed hydroarylation of ethyl propiolate with furan and 2-methylfuran.



Our approach began with the synthesis of the key tri-substituted furans **6** and **9**, respectively (scheme 3). Reduction of methyl 6-heptynoate **13** with NaBH₄ gave the alcohol in 82% isolated yield, which was subsequently protected as its TBDPS ether using standard conditions giving **14** in 89% yield. Deprotonation of **14** using ⁿBuLi followed by addition of the THP protected ketone **16**, and subsequent acid mediated deprotection of the THP-group, provided **17** in 77% yield over 2-steps.⁸ Propargyl-1,2-diol **17** could then be cyclized under modified conditions of Knight and co-workers⁶ to give the desired tri-substituted furan **6** in 45% isolated yield. The electrophilic 5-*endo-dig* cyclization of **6** using I₂ proved problematic on this substrate and was complicated by the further electrophilic iodination of the product; however, this over iodination could be suppressed by performing the reaction in acetonitrile and ensuring careful control of the reaction temperature.⁹ Conversion of the iodine at the C₃-position to the required methyl group in **9** could be achieved using three methods. Palladium cross-coupling with trimethylboroxine under Suzuki-conditions¹⁰ gave trialkylfuran **9** in a modest 52% yield. Alternatively, the action of ⁿBuLi on **6** at low temperature, followed by subsequent treatment of the lithiate with MeI^{8a} gave **9** in a more acceptable 67% yield. Finally, we found direct iodine-methyl exchange using a MeLi.LiBr complex in THF to be far superior, delivering **9** in 85% yield.

Scheme 3. Preparation of tri-substituted iodofuran 6 and trialkyl furan 9.



With iodofuran **6** in-hand we elected to examine Route A (scheme 4 and table 1). Accordingly, using adapted conditions of Reetz^{6c} and a PPh₃AuCl/AgOTf catalysts system we were able to hydroarylate **6** using an excess of ethyl propiolate (**11**) in an encouraging 13% isolated yield (entry 1). As expected, the product isolated was predominantly of *Z*-configuration, with the ¹H NMR signals for the double bond appearing as doublets at δ 6.51 (*J* = 12.4 Hz) and δ 5.71 (*J* = 12.8 Hz) ppm, respectively. The Johnphos-Au(I) complex **19** has been shown

to be a superior Au(I)-complex in a diverse range of *inter*- and *intramolecular* processes,¹¹ and therefore this was selected as our preferred Au(I) complex for optimization over the PPh₃AuCl/AgOTf system.

Scheme 4 and Table 1. Au-catalyzed hydroarylation of iodofuran 6 to give 18.^a



entry	cat. (mol %)	11 [equiv]	time [h]	conc. [M]	Z/E ^b	18 [%] ^c
1	5 ^d	10	24	3	95/5	13
2	5	10	24	3	48/52	33
3	5	10	24	6	67/33	23
4	3	10	24	3	45/55	37
5	3	5	36	1	34/66	42
6	3	5	48	1	25/75	58

^aReactions performed in MeNO₂ at room temperature with Au(I)-complex **19**, unless otherwise stated. ^bDetermined by ¹H NMR. ^cIsolated yields. ^dPPh₃AuCl/AgOTf catalyst system.

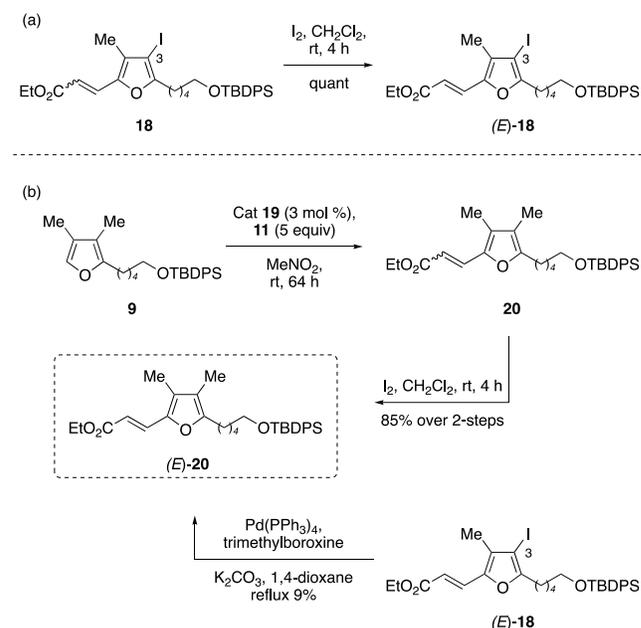
Replacing the PPh₃AuCl/AgOTf catalyst system with Au(I)-complex **19** had an immediate effect, giving the desired product **18** in 33% isolated yield (entry 2); whereas a doubling of concentration of the reaction mixture had a detrimental effect on yield (entry 3). A reduction of catalyst loading to 3 mol % was tolerated without any reduction in yield (entry 4). To improve purification, it was desirable to reduce the amount of ethyl propiolate (**11**), and accordingly, we observed that by decreasing the concentration, and increasing the reaction time, the equivalents of ethyl propiolate could be reduced significantly while maintaining overall chemical yield (entry 5). Finally, by extending the reaction time further to 48 h we achieved an acceptable yield of 58% for **18** (entry 6).

From table 1 it can be observed that the Johnphos Au(I)-complex **19**, gives significant Z/E mixtures in the product **18**, as compared to PPh₃Au(I)OTf. It transpires that extended reaction times lead to increased amounts of the *E*-stereoisomer, as highlighted in entries 5 and 6, respectively. However, the Z/E ratio from the Au(I)-catalyzed hydroarylation was inconsequential, as we were able to cleanly isomerize the Z/E mixtures obtained from the hydroarylation of **6** to its *E*-isomer upon treatment with I₂ (scheme 5a).¹² This was confirmed by the double bond signals of (*E*)-**18** now appearing in the ¹H NMR at δ 7.44 (*J* = 15.6 Hz) and δ 6.21 (*J* = 15.6 Hz) ppm, respectively.

Having established conditions for the hydroarylation and synthesis of **18**, we then applied these reaction conditions to the trialkylfuran **9** (scheme 5b). Pleasingly, we observed full conversion to the desired tetra-substituted furan **20** after a reaction time of 64h; and upon exposure to I₂, we subsequently converted this to (*E*)-**20** in 85% yield over these 2-steps. Alternatively, (*E*)-**20** could be synthesized upon exposure of iodo-furan (*E*)-**18** to palladium cross-coupling conditions with trimethylboroxine, albeit in a very poor yield of 9%. Attempts at introducing the C₃-methyl group using the transmetalation protocols outlined in scheme 3 were unsuccessful due to the presence of the *sensitive* unsaturated ester at C₅. This result

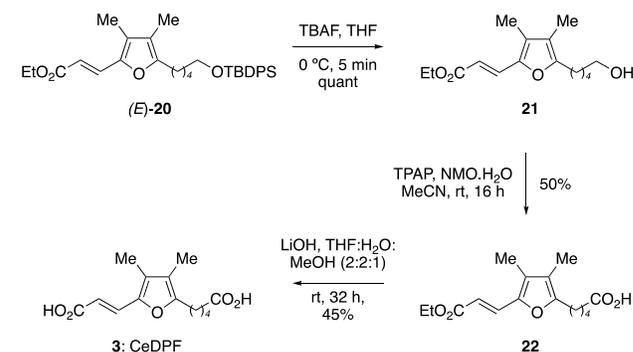
confirms that Route B (scheme 2) is the most efficient method to access (*E*)-**20**. Firstly, the cross-coupling of the C₃-iodo is superior when performed on the furan **6**, and secondly, the resultant trialkylfuran **9** is better suited to the subsequent Au(I)-catalyzed alkynyl hydroarylation transformation, likely due to its increased nucleophilicity compared to furan **6**.

Scheme 5. (a) I₂ mediated isomerization giving (*E*)-18**; (b) Synthesis of tetra-substituted furan (*E*)-**20**.**



The completion of the synthesis of **3** is shown in scheme 6. Silyl deprotection of (*E*)-**20** was achieved using TBAF in a quantitative yield, giving primary alcohol **21**. Oxidation to the 2-furanpentanoic acid proved capricious, with standard PDC conditions under several solvent conditions proving unproductive; however, the use of TPAP, with an NMO co-oxidant, finally gave the desired acid **22** in 50% isolated yield. The ethyl ester of **22** was then saponified using LiOH giving the **3** in 45% isolated yield.

Scheme 6. Completion of the synthesis of CeDFP (3).



In summary, a first total synthesis of the furan fatty acid metabolite 5-[(1*E*)-2-carboxyethenyl]-3,4-dimethyl-2-furan pentanoic acid (CeDFP, **3**) has been accomplished in 10-steps (4.1% overall yield) from commercially available methyl 6-heptynoate (**12**). The spectroscopic data for the synthesized material was in agreement with that reported^{4b} for the isolated natural product. Features of this synthesis include (a) an iodine promoted 5-*endo-dig* cyclization of an 1,2-alkyne diol under the adapted condition of Knight;⁶ (b) a methyl-lithium

mediated insertion of the C₃-methyl group; and notably (c) an Au(I)-catalyzed *intermolecular* hydroarylation to introduce the unsaturated ester. Importantly, in the approach described, the sequence in which steps (b) and (c) were implemented was found to be crucial. Given the importance of the furan fatty acids, and their oxidation metabolites (the urofuran acids), this first total synthesis can provide an effective model for synthesizing analogues of CeDFP. Furthermore, this approach highlights the use of Au(I) *intermolecular* hydroarylation as a suitable tactic in synthesizing these valuable natural products and metabolites.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

General experimental procedures, characterization data, and ¹H and ¹³C NMR spectra of new compounds. (PDF)

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Notes

The authors declare no competing financial interest.

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