# A new synthesis of the $F_5$ furan fatty acid and a first synthesis of the $F_6$ furan fatty acid

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**Dedicated to Dr Nouria A. Al-Awadi, in recognition of her notable contributions to science in Kuwait**

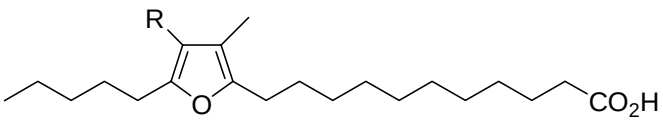
**Abstract**

Total syntheses have been achieved of the two furan fatty acids $F_5$ and $F_6$ **1**, in which the central step features generation of the furan ring using either iodine or silver-induced 5-*endo*-dig cyclisations of suitably functionalized 3-alkyne-1,2-diols.

**Keywords:** Furan, fatty acid, iodocyclisation, 5-*endo*-dig, silver(I)-catalysed, synthesis

## Introduction

The furan fatty acids $F_5$ and $F_6$, **1**a and **1**b, are unusual in that they contain respectively a tri- and a tetra-substituted furan core; most furanoid fatty acids are 2,5-disubstituted compounds.[1] First identified in *Exocarpus cupressiformis* seed oil,[2] they occur in fish oils where they may be associated with reproductive cycles,[3] and are also found in marine sponges,[4] and in many plant species, which inevitably means they are present in many foods.[5] While their precise role remains unclear, urofuran acids [structure **1**, but $CO_2H$ in place of the 3-methyl group], which occur in human urine are likely metabolites of these natural products.[6]

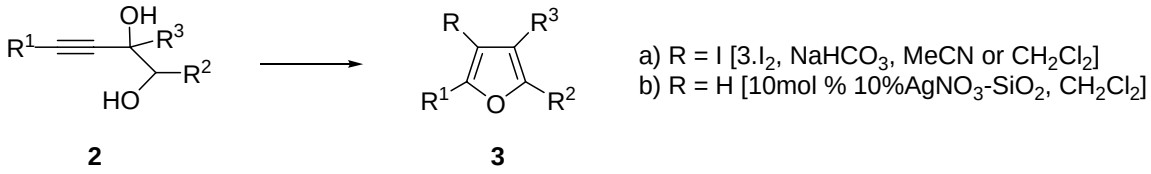



**1** a) R = H: Furan acid $F_5$
b) R = Me: Furan acid $F_6$.

There have been three previous syntheses of $F_5$ furan fatty acid **1a**, the first starting from methyl 3-methyl-2-furoate delivered the methyl ester and served to confirm the proposed structure but, while brief, was rather inefficent.[7] Subsequently, two rather different approaches were reported much later, in 1998. In Marson and Harper's route,[8] 1-acetyl-1-cyclododecene is homologated by the sequential addition of heptynyl lithium and alkene epoxidation. Furan formation was then achieved using catalytic acid and mercury(II) to provide an excellent yield of the aldehyde corresponding to furan $F_5$ **1a**. In a conceptually very different approach, Bach and Krüger set out with 4,5-dibromofuran-2-carboxaldehyde and employed the greater reactivity of the α-bromide to attach the necessary methoxycarbonyldecyl chain using a regiospecific Sonogashira coupling, followed by Wittig homologation to establish the pentyl chain. The β-methyl was then introduced by a second Pd(0)-catalysed coupling with tetramethyltin acting as the carbon source and the synthesis was completed by hydrogenation of the two unsaturated linkages and finally ester hydrolysis.[9] As far as we are aware, there has been no report of a synthesis of furan fatty acid $F_6$ **1b**

As a result of our studies of the 5-*endo* cyclisation mode,[10] we have recently defined two novel approaches to poly-substituted furans **3** using "Baldwin-favoured" 5-*endo*-dig cyclisations[11] of 3-alkyne-1,2-diols **2** (Scheme 1). In the first method, exposure of the precursors **2** to excess iodine in the presence of a mild base led to 70~85% yields of the iodofurans **3a**.[12] In a much more environmentally friendly process, isomerisation and dehydration of the alkyne-diols **2** to the trisubstituted furans **3b** has been achieved using catalytic quantities of silver nitrate on silica gel; yields using this heterogeneous and easily recycled and reused catalyst are essentially quantitative.[13] It occurred to us that both furan fatty acids **1** would provide significant tests of these two methodologies, both of which, in principle, should be suitable for the synthesis of both acids **1**.




**2** **3**

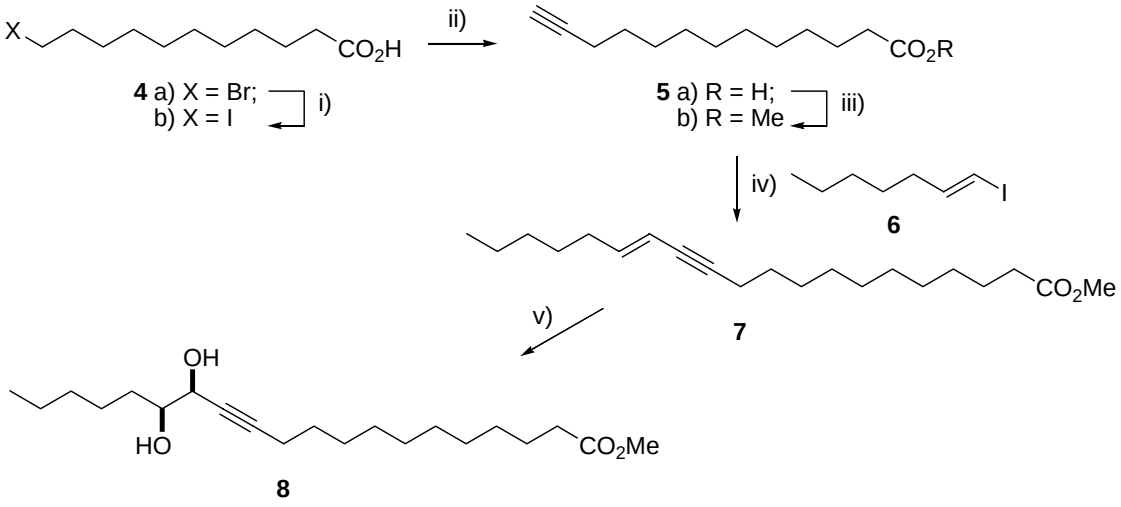
**Scheme 1**

Herein, we report in preliminary form on the successful applications of these two approaches, which have nevertheless revealed a few surprises along the way.

## Results and Discussion

Our first approach was aimed at the $F_5$ furan fatty acid methyl ester using our iodocyclisation methodology[12] and featuring generation of the required alkyne-diol by selective *bis*-

hydroxylation of the corresponding enyne. We began by converting commercially available 11-bromoundecanoic acid **4a** into the corresponding iodide **4b**[14] using a Finkelstein reaction and then coupling this with lithium acetylide-ethylenediamine complex [LAEDA] using HMPA as solvent, which gave the alkynoic acid **5a** routinely in ca. 85% yields (Scheme 2).[15] This was then smoothly esterified using acidic methanol to give the methyl ester **5b**. Although many alkynes have been prepared successfully from both chlorides and bromides using LAEDA,[16] in the case of the bromo-acid **4a**, in our hands, the reaction proved difficult to drive to completion and the use of more forcing conditions and/or greater amounts of LAEDA resulted in significant amounts of isomerisation of the initial alkynoic acid **5a** to the corresponding 11-ynoic acid. The (*E*)-iodoalkene **6** was prepared in excellent yield from 1-heptyne by sequential hydroalumination using Dibal-H and halogenation by *N*-iodosuccinimide[17]; a subsequent Sonogashira coupling[18] with iodo-ester **5b** then gave the (*E*)-enyne **7**. As we clearly did not require homochiral material, this was then *bis*-hydroxylated regioselectively at the alkene function, as originally reported by the Sharpless group,[19] but using the simpler achiral Warren procedure,[20] which delivered an excellent 86% yield of the required alkyne-diol **8**.

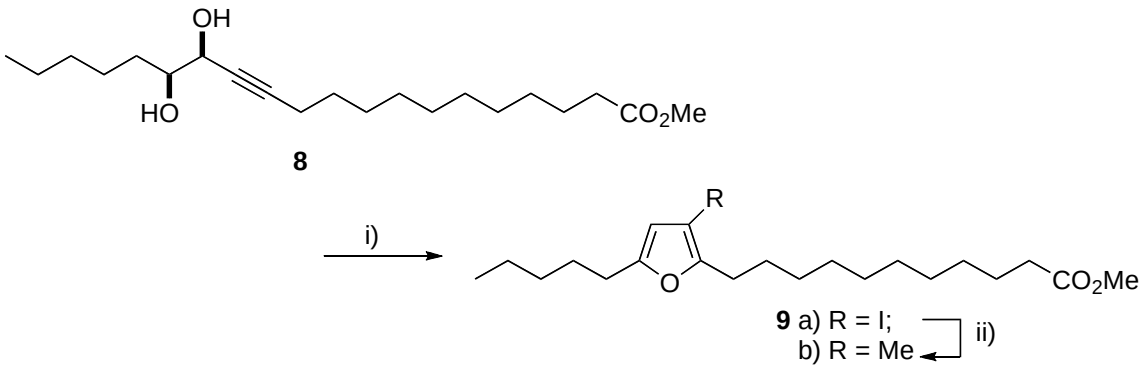



**Scheme 2.** *Reagents:* i) 4. Nal, dry acetone, reflux, 12h (83%); ii) 4.HCCLi$H_2N$ $(CH_2)_2NH_2$[LADEA], HMPA, 0 °C, 0.5h (93%); iii)AcCl (cat.), dry MeOH, 20 °C, 16h (84%); iv) Cul (cat.), $(Ph_3P)_4Pd$ (cat.), (*E*)-$C_5H_{11}$CH=CHI, dry $Et_2NH$, 20°C, 16h (74%); v) $K_3Fe(CN)_6$, $K_2CO_3$, $MeSO_2NH_2$, quinuclidine (cat.), $K_2OsO_4$**.**$2H_20$ (cat.), 1:1 *t*-BuOH-$H_2O$, 20 °C, 24h (86%).

We were dismayed to find that our initial attempts to carry out a 5-*endo*-dig iodo-cyclisation[12] using the alkene-diol **8** met with almost complete failure. Using the 'standard' conditions consisting of three equivalents each of iodine and sodium hydrogen carbonate in either dry acetonitrile or dichloromethane gave at most 10% yields of the desired and indeed

expected iodofuran **9a** (Scheme 3). Alterations to the base (potassium carbonate, triethylamine), the electrophile (bis(*sym*-collidine)iodine(I) hexafluoro-phosphate, phenylselanyl chloride) and working at lower temperatures were equally ineffective. Some NMR and mass spectrometric evidence pointed towards formation of the di-iodide by direct addition of iodine to the alkyne group.

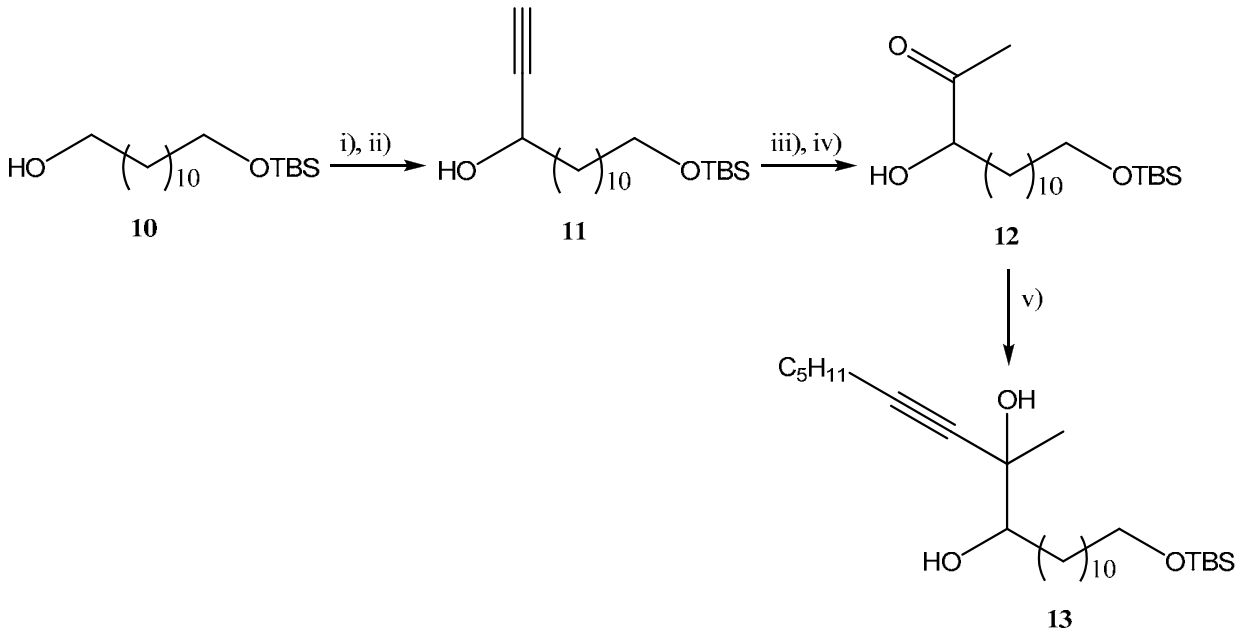
Reasoning that the lengthy carbon chain was perhaps coiling in solution and preventing cyclisation in the expected manner, we carried out a solvent study to try and rescue the situation. Tetrahydrofuran proved completely ineffective and the use of very non-polar petrol ether was precluded because the precursor **8** was not appreciably soluble. In an effort to pursue the theme of using a non-polar solvent system, a small percentage of acetonitrile was added to increase the substrate solubility but this also proved ineffective. Remarkably, when a small amount of ethyl acetate was used to increase the solubility, NMR analysis of the crude product showed an appreciable amount of iodofuran to have formed. Even better, when neat ethyl acetate was used as the solvent, the conversion after 24h at 40 $^{o}$C was even better, but the product **9a** was always accompanied by a second, as yet unidentified by-product. A final optimization showed that the reaction in ethyl acetate was unexpectedly both very rapid and clean: work-up after one hour at ambient temperature secured a 93% yield of the iodofuran **9a** (Scheme 3), uncontaminated by the by-product, which is evidently formed from the initial product **9a**. Although we could not gain firm evidence to support the suggestion, we speculate that this might have been the 3,4-di-iodide derived from the iodofuran **9a**.




**Scheme 3.** Reagents: i) 3$NaHCO_3$, alkyne-diol 8, dry EtOAc, 20°C, add 3$I_2$, 20°C, 1 h (93%); ii) $Me_4Sn$, $(Ph_3P)_4Pd$ (cat.), CuI (cat.), *N*-methylpyrrolidine, 65°C, 16 h (sealed tube) (57%).

In similar fashion to some related attempts to introduce the final methyl group using Stille-type methodology,[9] we found it difficult to complete this transformation without the formation of the desmethyl derivative [**9**; R = H]. The conditions shown in Scheme 3 were amongst the best we found and the poor yield was more associated with losses during the difficult chromatographic separation of the target **9b** than with substrate decomposition. Unfortunately, the presence of the ester group rather precluded using what would probably be the most efficient

way to effect this transformation, that of halogen-metal exchange at low temperature and reaction with iodomethane. We therefore modified the approach to incorporate both the opportunity to use the latter chemistry for incorporation of the necessary β-methyl group and also to exploit our newer silver(I)-catalysed cyclisation methodology (Scheme 1). The initial steps are shown in Scheme 4. Beginning with the mono-TBS derivative **10** of 1,12-dodecanediol,[21] PCC oxidation followed by condensation delivered the alkynol **11**.

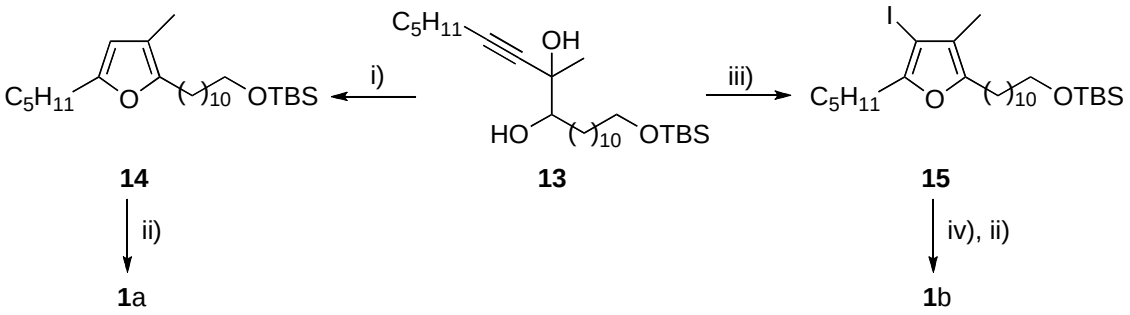



**10** **11** **12** **13**

**Scheme 4.** *Reagents:* i) PCC, Celite, $CH_2CI_2$, 20 °C, 2 h (87%); ii) HCCMgBr, THF, (93%); iii) $Ac_2O$, DMAP (cat.), pyridine, 20 °C, 16 h, (88%); iv) $NaAuCI_4.2H_2O$ (cat.), aq. MeOH, reflux 5 h, then cool, add sat. aq. $K_2CO_3$, 20 °C, 1 h (79%); v) 2.2 $C_5H_{11}CCLi$, THF, -78 °C ~ 0 °C (95%).

Temporary protection of the alcohol group as the corresponding acetate was followed by alkyne hydration using an excellent gold(III)-catalysed method[23] and a basic work-up with aqueous carbonate to arrive at the acyloin **12** in good overall yield. Reaction with two equivalents of lithio-heptyne then delivered the required alkyne-diol **13** in excellent yield. This direct approach was favoured over the more usual tactic of alcohol protection, alkyne addition and deprotection on the grounds of both expediency and atom efficiency: the equivalent of 1-heptyne present in the final product was easily removed by rotary evaporation and about the same number of atoms or less was wasted in this way, relative to using a protection-deprotection method, which in most cases would require additional reagents and solvents.

We were delighted to find that the silver(I)-catalysed method was effective in converting the alkyne-diol **13** into the $F_5$ furan fatty alcohol **14** in essentially quantitative yield (Scheme 5). Final deprotection and oxidation[8] then provided the target **1a** in good yield.




**Scheme 5.** *Reagents:* i) 10 mol% of 10 % $AgNO_3$-$SiO_2$, $CH_2CI_2$, 20 $^oC$, 5 h (97%); ii) TBAF, THF, 20 $^oC$, 1.5 h (90 %) then 5 PDC, Celite, DMF, 20 $^oC$, 8 h (85%); iii) as i), Scheme 3, (87%); iv) BuLi, THF, -78 $^oC$, 5 min then MeI (90%).

Using the crucial information gained during out first synthesis of furan $F_5$ **1a** (Scheme 3), the same precursor **13** was also treated with iodine in ethyl acetate, when the iodofuran **15** was formed in excellent yield. Once again, Stille and related Pd(0)-catalysed displacements of iodine by methyl proved difficult, mainly because of formation of variable amounts de-iodinated material which again was very difficult to separate from the desired product. However, working at this lower oxidation level allowed us to use the older method of halogen-metal exchange and alkylation, which proved to be much more reliable (Scheme 5). The crude product was then deprotected and oxidized in similar fashion to provide the first synthetic sample of $F_6$ furan fatty acid **1b**.[24] Hence, these last two approaches may be competitive with alternatives featuring Pd(0)-catalysed couplings, despite the necessity for including the additional oxidation steps.

## Acknowledgements

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21. Precursor **10** was prepared by first treating the diol with BuLi in tetrahydrofuran hopefully to form the mono-lithium salt, followed by reaction at 0 $^{o}$C with one equivalent of TBSCl. While reasonably efficient, we found it very difficult to separate this from the *bis*-silyl derivative. A longer alternative started with Baeyer-Villiger oxidation of cyclododecanol,[22] hydrolysis of the resulting lactone, silylation and $LiAlH_4$ reduction. While not especially efficient (60~65% overall yield), the product **10** was much more easily obtained in a pure state.
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24. Spectroscopic and analytical data consistent with the proposed structures and also where appropriate with reported literature data have been obtained for all compounds reported herein.