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Optimised total syntheses of the F-furan fatty acids F_5 and F_6 and some deuterated derivatives

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Dedicated, with the greatest respect, to the memory of Professor Alan R. Katritzky

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ABSTRACT

Optimised syntheses of F_5- and F_6-furan fatty acids **2** and **3** are described in full. Key steps include furan formation from a single 3-alkyne-1,2-diol **6** using 5-*endo*-dig cyclisations triggered by silver(I) nitrate or iodine. Introduction of the final carboxylic acid function and one-carbon homologation were achieved by cross metathesis with benzyl acrylate and hydrogenation. Iodine-methyl exchange of intermediate iodofurans was achieved by direct treatment with methyl lithium, which gave trideuterated derivatives **16** of the F_6 acid by using CD_3Li. The two acids **2** and **3** proved very unstable; thus, if samples are to be stored for extended periods, this should be as an ester and not as the free acids. This instability does raise questions regarding previously determined levels of these free acids (and perhaps some of their structurally close relatives) in various natural sources.

1. Introduction

Concerns with the perceived deleterious effects of modern dietary habits in general on Public Health in the Developed World have led to many ideas for change, one of the most prominent being to increase the consumption of fish and related food sources, due to the likely benefits imparted by the relatively high concentrations of omega-3 fatty acids, which these contain. Indeed, this is now official advice from the UK Government,[1] as well as a general view amongst the medical profession.[2] Typically, eating fish twice a week is advocated; this arguably relatively low amount is, ironically, seemingly due to largely human-generated levels of pollution in rivers and the oceans.[2] A significant component of such fish oils are the furan fatty acids **1**[3] although, despite the foregoing advice, nothing like so much is known about the possible roles of these metabolites and the potential benefits to human health (Fig. 1). The compounds were first discovered in 1961[3] and have been detected in just about all organisms that have been investigated for their presence since this discovery.[4] Despite such a remarkable ubiquity in Nature, their precise role currently remains uncertain but is believed to be associated with potent radical scavenging and hence *anti*-oxidant activity, which may even help protect against atherosclerosis and cardiovascular disease amongst others.[3]

The most common furan fatty acids (F-acids) are tri- or tetra-substituted derivatives [**1**; R=H or Me]. Typical values for m and n are 2 or 4 and 8, 10 or 12, respectively. In common with other fatty acid series, various abbreviated nomenclature systems have been developed, the first being suggested by Glass et al. and based on GC retention times of the corresponding methyl esters.[5] This system is the origin of the terms 'F_5' and 'F_6' associated with the furan fatty acids **2** and **3**, respectively, which are the topics of this present paper and which will be used throughout this report, although more descriptive alternatives have been proposed recently.[6,7] Their common occurrence is illustrated by an initial isolation from the Northern pike, *Esox Lucius*,[5,8] which was soon followed by their detection in other freshwater[9,10] and marine fish species[10–16] various mammals,[17] crustaceans,[18–20] amphibians and reptiles;[19] of course, the presence of the acids in many animal species probably reflects the nature of their diet. Exceptional F-acids with extremely lengthy unsaturated side chains have been identified in some species of marine sponges, along with more common examples.[21] In addition, members of the F-acid group have also been found in marine bacteria,[22–24] algae,[25,26] terrestrial plants[27,28] and various types of yeast and fungi.[29] Given such a diverse range of sources, it is hardly surprising that the F-acids occur in many foodstuffs; recently identified examples include a surprisingly high concentration in

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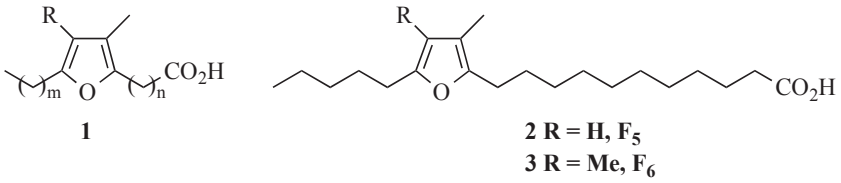


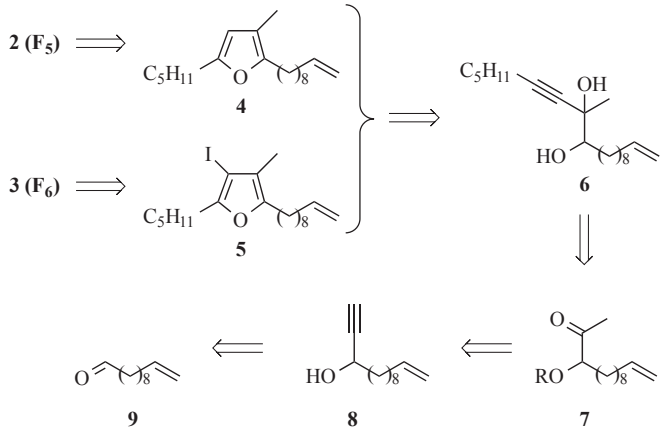
Fig. 1. The common furan fatty acids and the F_5 and F_6 furan fatty acids.

butter on sale in Germany[30] and in virgin olive oil.[28] No doubt, many other processed foods also contain variable amounts of the F-acids, which biosynthetically, generally seem to arise by the oxidation of polyunsaturated fatty acids;[3,31] remarkably, despite their instability (see below), levels of furan fatty acids have been recently been reported to *increase* during the deep-fat frying of fish.[32]

Previous total chemical syntheses of the F_5 and F_6 fatty acids **2** and **3** have been few. The first approach by the Glass group resulted in overall yields of 2 and 8%, respectively, but was notable for proving their structures.[33] A major problem in these schemes was introduction of the longer side chain, which was addressed by an alternative strategy reported by Schödel and Spiteller,[34] which featured sequential Friedel–Crafts acylation and Wolff-Kishner reduction to arrive at the required saturated long chain carboxylic acid substituent in F-acid F_6 **3**. Glass followed this with a neat synthesis of a ^{14}C-labelled F_6 derivative using sequential Vilsmeier formylation, Wittig homologation and hydrogenation to arrive at the longer side chain.[6] The more recent synthesis of F-acid F_5 by Bach and Krüger is even more appealing and well illustrates the synthetic power of modern catalysed coupling technology.[35] Starting with 4,5-dibromofuran-2-carboxaldehyde, sequential regiospecific Sonogashia and Negishi-type couplings serve to introduce the lengthier side chain and a β-methyl group; later Wittig homologation and hydrogenation completes this highly practical synthesis. Our own first foray into this area[36] will be mentioned later, as a contrast to the successful and optimised synthesis, aimed in particular at producing useable amounts of a labelled derivative, which is described in full below.[37]

2. Results and discussion

Both targets **2** and **3** appeared to be accessible from a common yne-diol **6** using methodology developed by us: firstly, a silver-catalysed 5-*endo*-dig cyclisation[38] of this diol **6** was expected to deliver the advanced intermediate furan **4** while a similar cyclisation but induced by molecular iodine[39] would result in formation of the related iodofuran **5**, which should then allow incorporation of the final methyl group on the way to F-acid F_6 **3** (Scheme 1). The

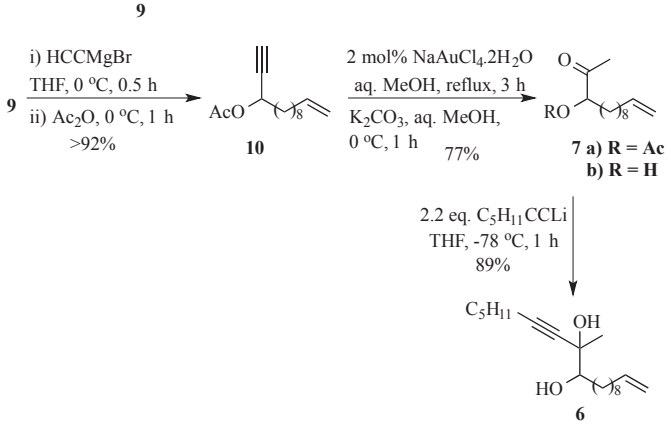


Scheme 1. The overall retrosynthetic plan to F-acids F_5 and F_6.

reasons for choosing a terminal alkene function as the precursor to the final carboxylic acid function were threefold: firstly, we anticipated that the alkene should survive unmolested during the preceding steps, secondly that the necessary acid function and the additional carbon could readily be introduced using a cross metathesis reaction (and, if not that there were many plausible alternatives); finally, and crucially, the starting material **9** is cheap and readily available, being derived from the corresponding carboxylic acid, itself an important antifungal compound, which is obtained by pyrolysis of castor oil.[40]

The steps from this initial compound **9** seemed likely to be relatively straightforward: addition of ethyne, hydration of the resulting alkynol **8** to give the hydroxyl-ketone **7** and finally addition of 1-heptyne, to arrive at the common intermediate **6**.

In the event, (Scheme 2), an optimum method featured the addition of commercial ethynylmagnesium bromide to the aldehyde **9** in ice-cold tetrahydrofuran, which delivered an essentially quantitative yield of the desired alcohol. However, as the anticipated optimum method for the subsequent alkyne hydration step required the alcohol to be protected as the corresponding acetate, the reaction was instead quenched using acetic anhydride at the same temperature. After 1 h, yields of the acetoxy derivative **10** were routinely at least 92%. Using the alternative alkyne nucleophile, lithium acetylide–ethylene diamine complex (LAEDA), was considerably less effective, with yields typically not much above 60% overall, following an aqueous work-up to give the intermediate alkynol and separate acetylation (Ac_2O, DMAP, CH_2Cl_2, 0–20 °C, 3 h).



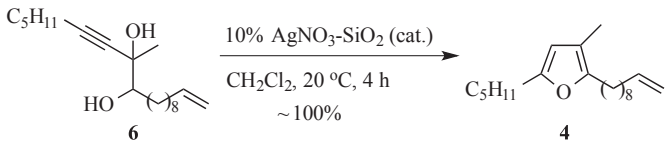
Scheme 2. The initial steps leading to common intermediate **6**.

Hydration of the alkyne group was accomplished using Utimoto's excellent gold-catalysed method[41] employing ca. 2 mol% of sodium gold(III) chloride as the catalyst, in refluxing aqueous methanol, for, which use of freshly distilled water was essential if high yields of the acetoxy-ketone **7a** were to be obtained. We then found that it was also essential to carry out an aqueous work-up of this reaction, rather than to directly basify it, in order to hydrolyse the acetoxy group. Given that the latter reaction was carried out separately with ice cooling rather than at ambient temperature,

when yields fell away dramatically, then just below 80% combined yields of the hydroxyl-ketone **7b** were routinely obtained for these two steps.

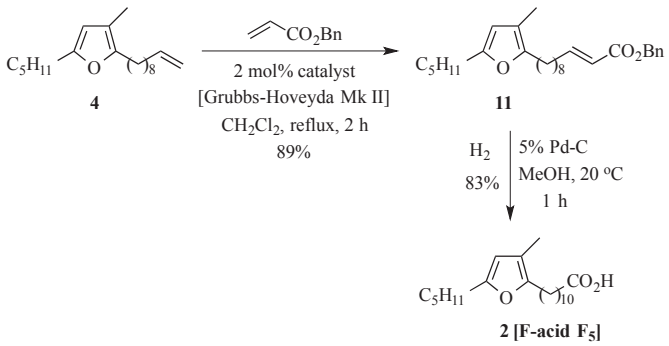
Addition of the second acetylide, 1-lithioheptyne, was then carried out in the simplest way by adding 2.2 equiv of the latter to the hydroxyl-ketone **7b** without using any protection of the alcohol group; this delivered typically a 90% yield of pure common intermediate alkyne-diol **6**, as a 4:1 mixture of diastereoisomers.[42] While this might seem wasteful in terms of 1-heptyne and butyllithium, overall it is more atom efficient than, say, protection of the alcohol in the hydroxyl-ketone **7** using a TBDMS group. This would not only add two steps, which while no doubt efficient, would not give quantitative yields, it would also produce waste, which would be difficult to recycle, whereas, in principle, the excess 1-heptyne could be recovered. The cost overall is also lower.

We first pursued a synthesis of F-acid F_5 **2** and so exposed the alkyne-diol 6–10 mol % silver(I) nitrate on silica gel in dichloromethane, conditions which were successful in our initial studies[38] and were very pleased to isolated the desired furan **4** in essentially quantitative yield after 4 h reaction time at ambient temperature followed by a simple filtration through Celite (Scheme 3). The product was completely pure according to the quality of all its NMR data.



Scheme 3. Formation of the furan precursor **4** to F-acid F_5 **2**.

We then addressed the final steps, using 1-octene as a model alkene. The key idea was to carry out a cross metathesis using benzyl acrylate, which was expected to introduce both the required carboxylate group and the additional carbon atom and give an intermediate unsaturated benzyl ester, hydrogenation of which would lead directly to the desired saturated acid. Initial studies using Grubbs second generation catalyst[43] failed to give more than traces of the desired model product, (*E*)-benzyl 2-nonenoate, despite some literature precedent.[44] Two key changes led to success: firstly, we turned to the alternative Grubbs–Hoveyda catalyst[45] and used only freshly distilled benzyl acrylate;[46] these changes were spectacular in effect, typically affording around 90% yields of the 2-nonenoate, and continued to work in the real example of alkene **4** (Scheme 4). Initially, 3 equiv of benzyl acrylate were used to ensure complete reaction of the more precious furan alkene **4**, but this inevitably resulted in contamination of the desired product **11** by the excess acrylate and also by variable amounts of the cross metathesis homodimer, dibenzyl fumarate. Fortunately, we were able



Scheme 4. The final steps leading to F-acid F_5 **2**.

to reduce the amount of acrylate to only 1.3 equiv without reducing the yield of ester **11**, which resulted in negligible fumarate formation and hence product contamination by only a small amount of acrylate. Optimised conditions for both the model and actual cross metatheses were to heat the reactants and catalyst at reflux in dry dichloromethane for 2 h and consistently delivered around 90% isolated yields, after chromatographic separation of the excess acrylate.

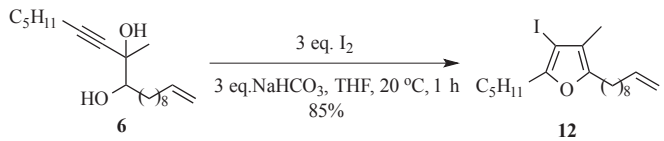
However, this separation was not necessary, once the penultimate intermediate **11** had been fully characterised: the anticipated final combined alkene hydrogenation–ester hydrogenolysis worked extremely well and in the process converted any excess acrylate into propanoic acid, which was easily removed by a water wash (Scheme 4). Unfortunately, attempts to combine the two steps, that is, to replace the metathesis reaction nitrogen atmosphere with hydrogen and utilise the ruthenium present as a hydrogenation catalyst, were unsuccessful, despite some precedent.[44]

A final purification using a short silica gel column typically provided an 83% yield of pure furan fatty acid F_5 **2**, which displayed spectroscopic and analytical data identical to those previously recorded.[33–35] We were surprised to find that the F-acid F_5 **2** is rather unstable; significant decomposition set in even when it was stored for a day at −20 °C in the dark under nitrogen. If left in the open laboratory without any special protection, very noticeable disintegration had occurred within 3 h; much the same was true of solutions in deuteriochloroform used to record NMR spectra. Fortunately, the penultimate precursor, the unsaturated benzyl ester **11** and the foregoing alkene **4**, are much more stable, but still require care if they are to be preserved, which is typical of many aliphatic furan derivatives. If pure samples are stored at −20 °C in the dark under nitrogen, these compounds survive well for many months. This has two implications. Firstly, when samples of the F-acid F_5 **2** are required for analytical work, especially when this is of a quantitative nature, then reference samples must be prepared immediately prior to the work and preferably stored at as low a temperature as possible. Of course, one of the wonders of the metathesis chemistry is that despite its mechanistic sophistication, it is a very easy reaction to perform, given due attention to the cleanliness of all the components.[48] We therefore have no hesitation in recommending this approach for the regular synthesis of pure analytical samples to the 'synthetically inexperienced,' because the last or last two steps are so relatively simple to carry out and to work-up. A second key point, which might be addressed by the foregoing recommendation, is to question the accuracy of previous determinations of the levels of F-acids in their various sources, in view of the obvious variations in the unstable F-acid standards as well as the isolated F-acids themselves, which could influence such results. Obviously, this is a moot point and is made with no intent to criticise previous research in this area but merely to sound a note of caution. It is also clear that rapid derivatisation of the free F-acids from whatever source, preferably as simple esters, is a firm recommendation to improve the accuracy and reproducibility in such analytical results.[7] The very recent report[32] of an *increase* in F-acid concentrations when fish is deep-fried does, however, provide an interesting contrast to these conclusions and suggestions!

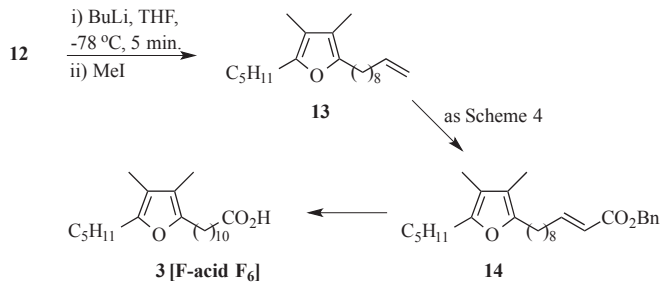
We then turned to using the common intermediate **6** as a precursor to the F-acid F_6 **3**. In our initial model studies of the iodocyclisation approach to β-iodofurans,[39] we had found that either dichloromethane or acetonitrile were highly suitable solvents, the use of which routinely resulted in ca. 90% yields of the desired iodofurans. It therefore came as an unpleasant surprise when such cyclisations of much more 'fatty' precursors such as yne-diol **6** were found to give very poor yields of iodofurans. Fortunately, a brief solvent screen revealed that ethyl acetate restored the high level of iodofuran formation.[36] However, when this was used in the case of yne-diol **6**, only around 60% conversion to the corresponding

iodofuran **12** occurred, with the remainder being unidentified decomposition or other products. Happily, by changing the solvent to tetrahydrofuran, the high return was restored in this case, with pure iodofuran **12** being isolated in 85% yield after the simplest of work-ups (Scheme 5).

The additional β-methyl group in F-acid F_6 **3** was then introduced by the standard method of halogen-metal exchange using butyllithium followed by quenching with iodomethane. Clean samples of the fully substituted furan **13** were isolated in around 75% yields but these were always contaminated with significant amounts (up to 5–15%) of the corresponding demethyl derivative, the precursor **4** of F-acid F_5, presumably because of the difficulties of completely removing all water from the iodomethane used as the electrophile, as well as from other sources (Scheme 6).



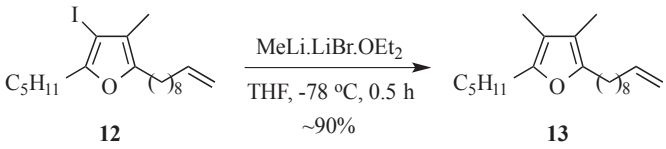
Scheme 5. The key iodocyclisation step.



Scheme 6. Completion of the first approach to F-acid F_6 **3**.

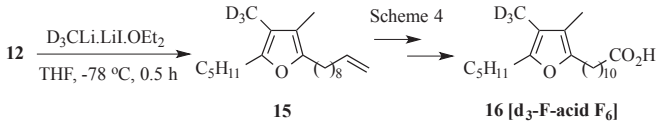
Not surprisingly, the synthesis of F-acid F_6 **3** was readily completed using exactly the same methodology shown in Scheme 4, via the homologated benzyl ester **14** in essentially the same excellent yields (Scheme 6). The acid **3** proved to be just as unstable and sensitive as F_5 **2** and hence exactly the same comments made above apply to this more substituted derivative.

There remained the irritation that the samples of F-acid F_6 **3** were always contaminated with small amounts of F-acid F_5 **2**, which could not be separated by HPLC on a preparative scale in our hands. We also had to address the problem of how to incorporate a useful and safe label into F_6. These two features led one of us (AWTS) to suggest that the halogen-metal exchange be carried out using *methyl*lithium rather than the conventional butyllithium, thereby generating iodomethane in situ, which would then trap the intermediate furyl β-carbanion without the need to add any additional reactant. There seems to be no precedent for this and so we were delighted to find that the idea worked very well and routinely produced the F-acid F_6 precursor **13** in around 90% isolated yields from the iodofuran **12**, which was contained by <3% of the corresponding demethyl compound **4** (Scheme 7).



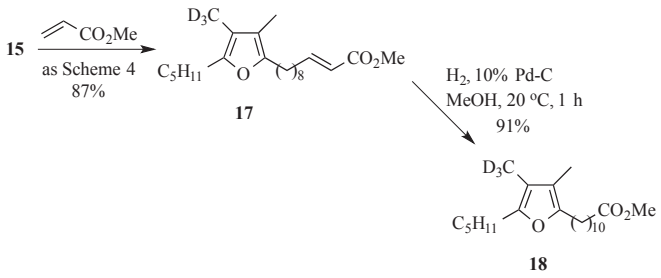
Scheme 7. Iodine-methyl exchange using methyllithium.

As well as greatly diminishing the amount of non-methylated product formed in the halogen-methyl exchange step, this idea had its origins in the commercial availability of d_3-methyllithium because, if successful, it would allow the easy introduction of a fully deuterated methyl group into the F-acid F_6 **3**. As expected in the light of the chemistry shown in Scheme 7, this did indeed work well and delivered the first deuterated intermediate **15**, which was then smoothly converted in similarly excellent yields into the trideuterio-F-acid F_6 **16** with no interference from or loss of the new deuterium atoms (Scheme 8).



Scheme 8. Synthesis of d_3-F-acid F_6 **16** using $D_3CLi{\cdot}LiI$ complex.

In similar fashion, cross metathesis of the deuterated furan **15** with methyl acrylate worked equally well; subsequent hydrogenation of the resulting unsaturated methyl ester **17** now delivered the methyl ester **18** (Scheme 9). This is a particularly useful standard for F-acid analysis, as these are best derivatised as their methyl esters[7] and being an ester, compound **18** doers not suffer from the instability of the free F-acids and hence will survive for lengthy periods if stored carefully. It can also readily be converted into the corresponding acid **16** by base-induced hydrolysis if required.

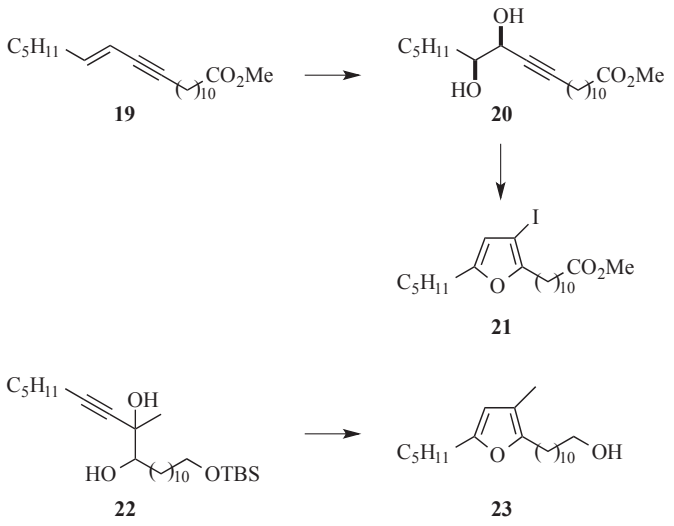


Scheme 9. Synthesis of the saturated, trideuterated methyl ester **18** of F-acid F_6.

3. Conclusions

This present approach is capable of providing at least hundreds of milligrams of both F-acids **2** and **3**. This is in contrast to our two previous approaches, which while achieving the final goals of F-acids total syntheses, are, as they stand, not suitable for producing the final products on this scale (Scheme 10).[36] In the first, the Sonogashira product **19** was regiospecifically bis-hydroxylated at the alkene group; subsequent iodocyclisation of the resulting alkyne-diol **20** gave the iodofuran **21**.

We were never able to optimise introduction of the required methyl group at this stage, using Stille-type couplings and the synthesis also no doubt suffered from the small scale we were working on, without the knowledge of the extreme sensitivity of the final F-acid F_5 **2**. This potentially briefer approach, which could have been adapted to a synthesis of F-acid F_6 **3**, was modified to a relative of the present approach but incorporating an intact side chain carrying a distal protected alcohol group; a key step was the highly efficient Ag(I)-catalysed cyclisation of yne-diol **22** into the furan **23**. An unsolved problem in this case, along with a number of unoptimised earlier steps, was the final oxidation, which was never especially efficient despite trying a range of typical reagents, possibly at least partly due once again to product decomposition.



Scheme 10. Our previous approaches to the F-acids.

In summary, the present optimised procedure can provide useful quantities of both F-acids **2** and **3** and, more importantly for analytical purposes, esterified derivatives with much greater stability, which can be used as accurate standards for the quantification and hence reasoned exploration of the relevance or otherwise of these and homologous F-acids to human health.

4. Experimental

4.1. General

Reagents were obtained from Aldrich, Alfa Aesar, Lancaster, Fluka and Strem chemical suppliers and used as received unless otherwise specified. Solvents and reagents were purified according to the procedures of Perrin, Armarego and Perrin.[49]

All non-aqueous reactions, unless otherwise stated, were conducted in oven- or flame-dried glassware under an atmosphere of dry nitrogen with magnetic stirring. Solid carbon dioxide and an acetone bath (−78 °C) or an ice-water bath (0 °C) were used to obtain low temperature.

All solutions of crude products were dried by brief exposure to dried magnesium sulfate ($MgSO_4$). Column chromatography refers to flash column chromatography using Merck Kieselgel 60H silica or Matrix silica 60 as the stationary phase.

Infra-red spectra were recorded in the range 4000–600 cm^{-1} using a Perkin–Elmer 1600 series Fourier Transform Infrared Spectrometer, as liquid films between sodium chloride plates [film], unless otherwise stated. All absorptions are quoted in wave numbers (cm^{-1}). Proton (^1H) NMR spectra were recorded using an Avance Bruker DPX 400 instrument (400 MHz); the same instrument operating at 100.6 MHz was used to obtain ^{13}C spectra. Spectra were obtained as dilute solutions in deuteriochloroform, unless otherwise stated. The chemical shifts were recorded relative to residual chloroform (7.27 or 77.0 ppm) as an internal standard. Deuterium NMR spectra were recorded using a Jeol Eclipse (+) (300 MHz) instrument for dilute solutions in chloroform containing a trace of deuteriochloroform. The chemical shifts were recorded relative to deuteriochloroform (7.27 ppm). All coupling constants (J) are recorded in Hertz (Hz). Assignments were made on the basis of chemical shift and coupling constant data using DEPT-90, DEPT-135, COSY, NOESY, HSQC and HMBC experiments where required. Mass spectrometric data were determined using a Waters GCT Premier instrument and electron impact ionisation (EI) unless otherwise stated, in which case such data were obtained using a Waters LCT Premier XE instrument (LRMS) or Agilent 5975C Series GC/MSD (GC–MS) and atmospheric pressure chemical ionisation (APCI) or electrospray ionisation (ES). High resolution mass spectrometric (HRMS) data were determined with the molecular formula corresponding to the observed signal using the most abundant isotopes of each element.

*4.1.1. 3-Acetoxytridec-12-en-2-one **10**.* To an oven-dried 250 ml three neck round-bottomed flask fitted with a gas bubbler and under an atmosphere of dry nitrogen were added ethynylmagnesium bromide (50.0 ml of a 0.5 M solution in tetrahydrofuran, 25.0 mmol) and dry tetrahydrofuran (160 ml). The solution was stirred and cooled in an ice-water bath for 10 minutes then undecylenic aldehyde **9** (4.55 ml, 20.83 mmol) was added dropwise via syringe. After 0.5 h (TLC monitoring), acetic anhydride (2.75 ml, 29.16 mmol) was added dropwise. After 1 h, the reaction mixture was quenched by the addition of ice-cold saturated aqueous ammonium chloride (30 ml) and concentrated under reduced pressure. The residue was extracted with ether (3×25 ml) and the combined extracts washed with water (50 ml) and brine (50 ml) then dried, filtered though a plug of silica gel with dichloromethane (100 ml) and the solvents evaporated to yield the *acetate* **10** as a colourless oil (4.87 g, 99%), which was pure according to the following data: R_f 0.28 (5:95 EtOAc–hexanes); ν_{max}/cm^{-1} (film) 3308, 3077, 2927, 2856, 2333, 1744, 1641, 1372, 1234, 1022, 910, 630; δ_H (400 MHz, $CDCl_3$) 5.81 (1H, ddt, J=17.0, 10.2 and 6.8, 12-H), 5.34 (1H, td, J=6.7 and 2.1, 3-H), 5.00 (1H, app. ddd, J=17.0, 3.5 and 1.4, 13-H_a), 4.93 (1H, ddt, J=10.2, 2.2 and 1.4, 13-H_b), 2.45 (1H, d, J=2.1, 1-H), 2.09 (3H, s, Me), 2.07–2.00 (2H, m, CH_2), 1.80–1.70 (2H, m, CH_2), 1.48–1.32 (2H, m, CH_2), 1.26 (10H, br s, 5× CH_2); δ_C (100 MHz, $CDCl_3$) 169.9 (C=O), 139.1 (12-CH), 114.1 (13-CH_2), 81.4 (2-C), 77.4 (3-CH), 73.4 (1-CH), 34.6 (CH_2), 33.8 (CH_2), 29.47 (CH_2), 29.44 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 24.9 (CH_2), 21.0 (Me); m/z (EI) 236 $[M]^+$ (15%), 59 (100); HRMS: m/z (EI) calcd for $C_{15}H_{24}O_2$ [M], 236.1776, found, $[M]^+$, 236.1770.

*4.1.2. 3-Hydroxytridec-12-en-2-one **7b**.*

i) 3-Acetoxytridec-12-en-2-one **7a**

Sodium gold chloride (0.131 g, 0.33 mmol) was added to a stirred solution of acetate **10** (3.89 g, 16.46 mmol) in aqueous methanol (40 ml, 9:1 methanol/distilled water) and the resulting mixture heated at reflux for 3 h. The cooled solution was then concentrated and the residue diluted with ether (50 ml) and washed with brine/2 M aqueous ammonia (1:1, 2×50 ml), water (50 ml) and brine (50 ml) then dried, filtered and evaporated to yield the *acetoxy-ketone* **7a** as a pale yellow oil (3.56 g, 85%), which showed ν_{max}/cm^{-1} (film) 3076, 2927, 1745, 1734, 1641, 1435, 1372, 1240, 1044, 994, 909; δ_H (400 MHz, $CDCl_3$) 5.82 (1H, ddt, J=16.9, 10.2 and 6.7, 12-H), 5.03–4.97 (2H, m, 13-H_a and 3-H), 4.94 (1H, ddt, J=10.2, 2.1 and 1.0, 13-H_b), 2.17 (3H, s, Me), 2.16 (3H, s, Me), 2.08–2.00 (2H, m, CH_2), 1.80–1.70 (2H, m, 4-CH_2), 1.42–1.32 (2H, m, CH_2), 1.28 (10H, br s, 5× CH_2); δ_C (100 MHz, $CDCl_3$) 205.5 (2-C=O), 170.8 (C=O), 139.3 (12-CH), 114.3 (13-CH_2), 78.9 (3-CH), 33.9 (CH_2), 30.4 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 26.2 (Me), 25.3 (CH_2), 20.8 (Me).

The sample was used immediately in the next step.

ii) 3-Hydroxytridec-12-en-2-one **7b**

Potassium carbonate (4.55 g, 32.92 mmol) was added to a stirred solution of foregoing acetoxy-ketone **7a** (3.56 g, 14.00 mmol) in aqueous methanol (40 ml, 9:1 methanol/water) cooled in an ice-water bath. After 0.5 h, the solution was concentrated and the

residue extracted with ether (3×25 ml). The combined organic extracts were washed with water (50 ml) and brine (50 ml) then dried, filtered and evaporated. The residue was purified by column chromatography (15:85 EtOAc–petroleum ether) to yield the *hydroxyl-ketone* **7b** (2.68 g, 90%) as a colourless oil: R_f 0.65 (15:85 EtOAc–hexane); ν_{max}/cm^{-1} (film) 3477, 3076, 2925, 2854, 1714, 1640, 1464, 1438, 1358, 1247, 1130, 1087, 994, 909, 722; δ_H (400 MHz, $CDCl_3$) 5.82 (1H, ddt, *J*=17.0, 10.2 and 6.7, 12-H), 5.00 (1H, app. ddd, *J*=17.0, 3.7 and 1.6, 13-H_a), 4.94 (1H, ddt, *J*=10.2, 2.2 and 1.2, 13-H_b), 4.19 (1H, dd, *J*=7.3 and 3.7, 3-H), 2.21 (3H, s, 1-Me), 2.09–1.99 (2H, m, CH_2), 1.90–1.80 (1H, m, 4-H_a), 1.65–1.52 (2H, m, CH_2), 1.51–1.43 (1H, m, 4-H_b), 1.40–1.36 (4H, m, 2× CH_2), 1.30 (6H, br s, 3× CH_2); δ_C (100 MHz, $CDCl_3$) 209.9 (C=O), 139.1 (12-CH), 114.1 (13-CH_2), 76.9 (3-CH), 33.7 (CH_2), 33.6 (CH_2), 29.46 (CH_2), 29.42 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 25.1 (1-Me), 24.8 (CH_2); *m/z* (EI) 212 $[M]^+$ 10%, 149 (40), 109 (50), 84 (100); HRMS: *m/z* (EI) calcd for $C_{13}H_{24}O_2$, [*M*], 212.1776, found, $[M]^+$, 212.1781.

4.1.3. (RS, RS)- and (RS, SR)-8-Methylnonadec-18-en-6-yne-8,9-diol ***6***. Butyllithium (11.63 ml of a 2.5 M solution in tetrahydrofuran, 29.08 mmol) was added dropwise to a stirred solution of 1-heptyne (3.84 ml, 29.08 mmol) in tetrahydrofuran (50 ml) cooled in an ice-water bath. After stirring for 0.5 h, the contents were transferred to an oven-dried pressure-equalising dropping funnel attached to a second flask containing a stirred solution of hydroxy-ketone **7b** (2.058 g, 9.69 mmol) in tetrahydrofuran (50 ml) maintained at −78 °C. The lithiated 1-heptyne was carefully added dropwise and the resulting solution stirred at the same temperature for 1 h and then quenched by the addition of saturated aqueous ammonium chloride (20 ml). The bulk of the organic solvents were then evaporated and the residue extracted with ethyl acetate (3×25 ml). The combined extracts were washed with water (50 ml) and brine (50 ml) then dried, filtered and evaporated. Separation of the residue by column chromatography yielded the *diol* **6** (2.68 g, 89%) as a pale yellow oil consisting of a mixture of diastereomers in a 4:1 ratio, which were not separated. The major diastereomer had R_f 0.21 and the minor diastereomer R_f 0.29 in 1:4 EtOAc–hexanes. The mixture showed υ_{max}/cm^{-1} (film) 3407, 3077, 2927, 2856, 2245, 1641, 1466, 1378, 1329, 1207, 1078, 993, 909, 734; δ_H (400 MHz, $CDCl_3$) 5.82 (1H, ddt, *J*=17.0, 10.2 and 6.7, 18-H), 5.00 (1H, app. ddd, *J*=17.0, 3.6 and 1.6, 19-H_a), 4.94 (1H, ddt, *J*=10.2, 2.1 and 1.1, 19-H_b), 3.54 (0.80H, dd, *J*=7.8 and 2.0, 9-H), 3.36 (0.20H, dd, *J*=10.0 and 1.8, 9-H), 2.24–2.17 (2H, m), 2.08–2.03 (2H, m), 1.69–1.57 (2H, m), 1.55–1.46 (2H, m), 1.40 (3H, s, 8-Me), 1.38–1.33 (8H, m, 4× CH_2), 1.29 (8H, br s, 4× CH_2); δ_C (100 MHz, $CDCl_3$) *major diastereomer:* 139.2 (18-CH), 119.1 (19-CH_2), 85.6 (C), 77.9 (9-CH), 73.5 (C), 71.2 (C), 33.8 (CH_2), 31.0 (CH_2), 31.0 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 28.3 (CH_2), 26.6 (CH_2), 23.6 (8-Me), 22.1 (CH_2), 18.6 (CH_2), 14.0 (1-Me); *minor diastereomer:* 139.2 (18-CH), 119.1 (19-CH_2), 82.4 (C), 78.5 (9-CH), 74.5 (C), 71.9 (C), 38.2 (CH_2), 36.2 (CH_2), 32.4 (CH_2), 31.1 (CH_2), 29.97 (CH_2), 29.93 (CH_2), 29.8 (CH_2), 29.48 (CH_2), 29.42 (CH_2), 28.3 (CH_2), 26.2 (CH_2), 26.0 (8-Me), 18.6 (CH_2), 16.0 (1-Me). The whole sample showed *m/z* (EI) 291 $[M-H_2O$, 5%], 169 (100); HRMS: *m/z* (EI) calcd for $C_{20}H_{34}O$ [$M-H_2O$], 290.2610, found $[M-H_2O]^+$, 290.2607.

4.1.4. 2-(Dec-9-en-1-yl)-3-methyl-5-pentylfuran ***4***. 10% Silver nitrate on silica gel (0.253 g, 0.148 mmol) was added to a stirred solution of the foregoing mixture of diastereomeric diols **6** (0.459 g, 1.488 mmol) in dichloromethane (5 ml), contained in a foil-wrapped flask to prevent exposure to light. After 3 h, the mixture was filtered through a pad of Celite, which was then washed with fresh dichloromethane. The combined filtrates were evaporated to leave the *furan* **4** (0.430 g, 100%) as a colourless oil: ν_{max}/cm^{-1} (film) 3077, 2926, 2855, 1641, 1597, 1463, 1379, 1261, 1157, 1105, 993, 956, 910; δ_H (400 MHz, $CDCl_3$) 5.82 (1H, ddt, *J*=17.0, 10.2 and 6.7, 9′-H), 5.75 (1H, s, 4-H), 5.01 (1H, app. ddd, *J*=17.0, 3.5 and 1.6, 10′-H_a), 4.94 (1H, ddt, *J*=10.2, 2.1 and 1.1, 10′-H_b), 2.53 (2H, t, *J*=6.2, furyl-CH_2), 2.51 (2H, t, *J*=6.1, furyl-CH_2), 2.10–2.01 (2H, m, CH_2), 1.91 (3H, s, 3-Me), 1.66–1.54 (4H, m, 2× CH_2), 1.43–1.33 (4H, m, 2× CH_2), 1.31 (10H, br app. s, 5× CH_2), 0.91 (3H, t, *J*=7.0, 5″-Me); δ_C (100 MHz, $CDCl_3$) 153.5 (C), 149.4 (C), 139.2 (9′-CH), 114.1 (10′-CH_2), 113.8 (3-C). 107.6 (4-CH), 33.8 (CH_2), 31.5 (CH_2), 29.46 (CH_2), 29.41 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 28.0 (CH_2), 27.9 (CH_2), 25.9 (CH_2), 22.5 (CH_2), 14.0 (5″-Me), 9.9 (3-Me); *m/z* (APCI) 291 [M+H, 100%], 115 (40); HRMS: *m/z* (APCI) calcd for $C_{20}H_{35}O$, [*M*+*H*], 291.2688, found [M+H], 291.2699.

4.1.5. (E)-Benzyl 11-(3-methyl-5-pentylfuran-2-yl)undec-2-enoate ***11***. Grubbs–Hovayda Mk II catalyst (42 mg, 0.067 mmol) was added to a stirred solution of the foregoing furan **4** (0.391 g, 1.35 mmol) in dry dichloromethane (12 ml). Freshly distilled benzyl acrylate (0.26 ml, 1.76 mmol) was added and the solution gently heated to reflux under an atmosphere of dry nitrogen for 2 h. The solution was then cooled and filtered through a plug of silica gel and the solvent evaporated to yield the *benzyl ester* **11** (0.510 g, 89%) as a colourless oil: ν_{max}/cm^{-1} (film) 3065, 3033, 2928, 2856, 1724, 1654, 1597, 1497, 1456, 1406, 1377, 1264, 1172, 1046, 1017, 981, 809, 735, 697; δ_H (400 MHz, $CDCl_3$) 7.41–7.34 (5H, m, 5× Ar–H), 7.03 (1H, dt, *J*=14.3 and 7.0, 9′-CH), 5.87 (1H, d, *J*=14.3, 10′-CH), 5.74 (1H, s, 4-H), 5.18 (2H, s, OCH_2), 2.52 (2H, t, *J*=7.5, furyl-CH_2), 2.50 (2H, t, *J*=7.5, furyl-CH_2), 2.20 (2H, app. q, *J*=7.0, 8′-CH_2), 1.90 (3H, s, furyl-3-Me), 1.65–1.53 (2H, m, CH_2), 1.50–1.40 (2H, m, CH_2), 1.36–1.31 (4H, m, 2× CH_2), 1.29 (10H, app. br s, 5× CH_2), 0.90 (3H, t, *J*=6.8, 5″-Me); δ_C (100 MHz, $CDCl_3$) 166.6 (C=O), 153.5 (C), 150.2 (3-CH), 149.4 (C), 136.2 (C), 128.6 (2× Ar–CH), 128.3 (Ar–CH), 128.2 (2× Ar–CH), 120.9 (2-CH), 107.6 (4-CH), 66.0 (OCH_2), 32.3 (CH_2), 31.4 (CH_2), 30.4 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.7 (CH_2), 28.0 (CH_2), 28.0 (CH_2), 27.9 (CH_2), 25.9 (CH_2), 22.5 (CH_2), 14.0 (5″-Me), 9.9 (3-Me); *m/z* 425 $[M^+$, 15%], 317 (5), 165 (100); HRMS *m/z* (EI) calcd for $C_{28}H_{40}O_3$ [*M*], 422.2977, found $[M]^+$, 424.2975.

4.1.6. 11-(3-Methyl-5-pentylfuran-2-yl)undecanoic acid–F_5 furan fatty acid ***2***. A 250 ml round-bottomed flask was fitted with a three-way tap and charged with 10% w/w palladium on carbon (72 mg). Methanol (50 ml) was added carefully followed by the benzyl ester **11** (0.573 g, 1.35 mmol). The flask was evacuated, flushed with hydrogen (×3) and the mixture stirred for 1 h at ambient temperature and then filtered through a silica gel plug, which was washed with methanol. The combined filtrates were concentrated, the residue dissolved in ether (30 ml) and the resulting solution washed with water (3× 20 ml) then dried, filtered and evaporated. The residue was rapidly purified by column chromatography (pentane/diethyl ether, 95:5) to yield the *furan fatty acid* **2** (0.376 g, 83%) as a colourless oil, υ_{max}/cm^{-1} (film) 3095, 3037, 2927, 2855, 2673, 1710, 1576, 1466, 1432, 1413, 1284, 1235, 949, 795, 722; δ_H (400 MHz, $CDCl_3$) 12.0–10.5 (1H, br s, OH), 5.74 (1H, s, 4-H), 2.53 (2H, t, *J*=6.4, furyl-CH_2), 2.50 (2H, t, *J*=6.2, furyl-CH_2), 2.36 (2H, t, *J*=7.5, 10′-CH_2), 1.91 (3H, s, 3-Me), 1.69–1.54 (6H, m, 3× CH_2), 1.37–1.32 (6H, m, 3× CH_2), 1.29 (10H, br s, 5× CH_2), 0.90 (3H, t, *J*=6.9, 5″-Me); δ_C (100 MHz, $CDCl_3$) 180.1 (C=O), 153.5 (C), 149.4 (C), 113.8 (C), 107.6 (4-CH), 34.1 (CH_2), 31.4 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.26 (CH_2), 29.21 (CH_2), 29.1 (CH_2), 28.7 (CH_2), 28.0 (CH_2), 27.9 (CH_2), 25.9 (CH_2), 24.7 (CH_2), 22.4 (CH_2), 14.0 (5″-Me), 9.9 (3-Me); *m/z* (EI) 336 $[M^+$, 50%], 86 (100); HRMS *m/z* (EI) calcd for $C_{21}H_{36}O_3$ [*M*], 336.2664, found [M], 336.2669.

4.1.7. 2-(Dec-9-en-1-yl)-4-iodo-3-methyl-5-pentylfuran ***12***. Sodium hydrogen carbonate (0.464 g, 5.52 mmol) was added to a stirred solution of diol **6** (0.568 g, 1.84 mmol) in tetrahydrofuran (50 ml) cooled in an ice-water bath. After 0.25 h, iodine (1.402 g, 5.52 mmol) was added to the solution in one portion and stirring

continued without further cooling for 3 h. Sufficient saturated aqueous sodium sulphite was then added dropwise until the iodine colouration was dissipated before evaporation of the bulk of the tetrahydrofuran under reduced pressure. The residue was extracted with ether (3×25 ml) and the combined extracts washed with water (50 ml) and brine (50 ml) then dried and filtered through a silica plug using 99:1 pentane/ether as the eluent. Evaporation of the filtrate left the *iodofuran* **12** (0.649 g, 85%) as a colourless oil: ν_{max}/cm^{-1} (film) 3078, 2926, 2855, 1640, 1623, 1573, 1458, 1375, 1024, 989, 909, 720, 708; δ_H (400 MHz, $CDCl_3$) 5.82 (1H, ddt, *J*=17.1, 10.2 and 6.7, 9′-H), 5.00 (1H, app. ddd, *J*=17.1, 3.5 and 1.7, 10′-H_a), 4.94 (1H, ddt, *J*=10.2, 2.2 and 1.2, 10′-H_b), 2.62 (2H, t, *J*=7.5, furyl-CH_2), 2.56 (2H, t, *J*=7.4, furyl-CH_2), 2.08–2.01 (2H, m, CH_2), 1.87 (3H, s, 3-Me), 1.65–1.53 (4H, m, 2× CH_2), 1.42–1.31 (6H, m, 3× CH_2), 1.30 (8H, app. br s, 4× CH_2), 0.91 (3H, t, *J*=7.1, 5″-Me); δ_C (100 MHz, $CDCl_3$) 153.6 (C), 149.8 (C), 139.2 (9′-CH), 116.7 (3-C), 114.1 (10′-CH_2), 69.8 (4-C), 33.8 (CH_2), 31.2 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 28.5 (CH_2), 27.8 (CH_2), 27.7 (CH_2), 26.5 (CH_2), 22.4 (CH_2), 14.0 (5″-Me), 11.3 (3-Me)); *m*/*z* (EI) 416 [M, 50%]$^+$, 84 (100); HRMS *m*/*z* (EI) calcd for $C_{20}H_{33}IO$ [*M*], 416.1576, found [M]$^+$, 416.1577.

4.1.8. 2-(Dec-9-en-1-yl)-3,4-dimethyl-5-pentylfuran *13*

4.1.8.1. Method 1. Iodofuran **12** (0.456 g, 1.095 mmol) dissolved in dry tetrahydrofuran (10 ml) in a 50 ml three-necked round-bottomed flask was cooled to −78 °C and stirred for 10 min. Butyllithium (0.53 ml of a 2.5 M solution in hexanes, 1.31 mmol) was added dropwise and the resulting solution stirred for a further 3–5 min. Freshly distilled iodomethane (0.10 ml, 1.53 mmol) was added in one portion and the mixture stirred for a further 10 min before warming to ambient temperature and stirring for an additional 10 min. The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride solution (2 ml). The bulk of the tetrahydrofuran was removed under reduced pressure and the product extracted into ether (3×5 ml). The combined extracts were dried, filtered and evaporated and the product purified by column chromatography (pentane/ether, 99:1) to yield the *dimethylfuran* **13** (0.248 g, 75%) as a yellow oil: R_f 0.28 (pentane/ether, 99:1); ν_{max}/cm^{-1} (film) 3077, 2926, 2856, 1641, 1597, 1466, 1378, 1256, 1134, 1109, 1054, 993; δ_H (400 MHz, $CDCl_3$) 5.82 (1H, ddt, *J*=17.0, 10.2 and 6.7, 9′-H), 5.00 (1H, app. ddd, *J*=17.0, 3.6 and 1.5, 10′-H_a), 4.94 (1H, ddt, *J*=10.2, 2.3 and 1.2, 10′-H_b), 2.49 (4H, app. t, *J*=7.5, 2× furyl-CH_2), 2.05 (2H, app. q, *J*=7.0, 8′-CH_2), 1.84 (6H, app. s, 2× furyl-Me), 1.63–1.51 (4H, m, 2× CH_2), 1.42–1.33 (4H, m, 2× CH_2), 1.29 (10H, app. br s, 5× CH_2), 0.88 (3H, t, *J*=6.8, 5″-Me); δ_C (100 MHz, $CDCl_3$) 148.4 (2× C), 139.2 (9′-CH), 114.4 (2× C), 114.1 (10′-CH_2), 33.8 (CH_2), 31.5 (CH_2), 29.47 (CH_2), 29.40 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 28.4 (CH_2), 26.1 (CH_2), 26.1 (CH_2), 22.5 (4″-CH_2), 14.0 (5″-Me), 8.3 (2× Me); *m*/*z* (EI) 304 [M, 5%]$^+$, 247 (50), 179 (100); HRMS *m*/*z* (EI) calcd for $C_{21}H_{36}O$ [*M*], 304.2766, found [M]$^+$, 304.2766.

4.1.8.2. Method 2. Methyl lithium·lithium bromide complex (2.63 ml of a 1.5 M solution in ether, 3.94 mmol) was added dropwise to a stirred solution of iodofuran **12** (0.328 g, 0.787 mmol) in tetrahydrofuran (10 ml) maintained at −78 °C and the solution stirred for 0.5 h. After warming to ambient temperature and stirring for a further 0.5 h, the reaction mixture was quenched by the addition of saturated aqueous ammonium chloride (5 ml). The bulk of the tetrahydrofuran was evaporated and the product extracted into ether (3×10 ml). The combined extracts were washed with water (30 ml) and brine (30 ml) then dried, filtered and evaporated to yield the *furan* **13** (0.210 g, 88%) as a pale yellow oil. All spectroscopic and analytical data were identical to those recorded for the sample prepared by *Method 1.*

4.1.9. (E)-Benzyl 11-(3,4-dimethyl-5-pentylfuran-2-yl)undec-2-enoate *14*

Grubbs–Hovayda Mk II catalyst (42 mg, 0.066 mmol) was added to a stirred solution of furan **13** (0.405 g, 1.33 mmol) in dry dichloromethane (12 ml). Freshly distilled benzyl acrylate (0.60 ml, 4.00 mmol) was added and the solution gently heated to reflux under an atmosphere of nitrogen for 2 h. The cooled solution was then filtered through a plug of silica gel and the solid washed with fresh dichloromethane. The combined filtrates were evaporated to yield the *benzyl ester* **14** (0.519 g, 89%) as a colourless oil: ν_{max}/cm^{-1} (film) 3065, 3033, 2928, 2856, 1724, 1654, 1497, 1377, 1264, 1173, 1046, 1017, 982, 808, 736, 698; δ_H (400 MHz, $CDCl_3$) 7.42–7.32 (5H, m, 5× Ar–H), 7.04 (1H, dt, *J*=13.0 and 7.0, 9′-H), 5.87 (1H, d, *J*=13.0, 10′-H), 5.18 (2H, s, OCH_2), 2.49 (4H, app. t, *J*=7.5, 2× furyl-CH_2), 2.20 (2H, app. q, *J*=7.0, 8′-CH_2), 1.90 (6H, app. s, 2× furyl-Me), 1.65–1.53 (2H, m, CH_2), 1.50–1.40 (2H, m, CH_2), 1.36–1.31 (4H, m, 2× CH_2), 1.29 (10H, m, 5× CH_2), 0.89 (3H, t, *J*=6.8, 5″-Me); δ_C (100 MHz, $CDCl_3$) 166.6 (C=O), 150.2 (9′-CH), 148.4 (2× C), 136.2 (C), 128.6 (2× Ar–CH), 128.3 (Ar–CH), 128.2 (2× Ar–CH), 120.9 (10′-CH), 114.4 (2× C), 66.0 (13-CH_2), 33.8 (CH_2), 31.4 (CH_2), 30.4 (CH_2), 29.35 (CH_2), 29.31 (CH_2), 29.1 (CH_2), 28.7 (CH_2), 28.05 (CH_2), 28.01 (CH_2), 27.9 (CH_2), 25.9 (CH_2), 22.5 (CH_2), 14.0 (5″-Me), 8.4. (Me), 8.3 (Me); *m*/*z* (EI) 439 [M, 15%]$^+$, 332 (5), 179 (100); HRMS *m*/*z* (EI) calcd for $C_{29}H_{42}O_3$ [*M*], 438.3134, found [M]$^+$, 438.3133.

4.1.10. (3,4-Dimethyl-5-pentylfuran-2-yl)undecanoic acid–F_6 furan fatty acid *3*

A 250 ml round-bottomed flask was fitted with a three-way tap and charged with 10% w/w palladium on carbon (71 mg). Methanol (50 ml) was added carefully followed by the foregoing benzyl ester **14** (0.583 g, 1.33 mmol). The flask was evacuated, flushed with hydrogen (×3) and then the mixture stirred for 1 h, filtered through a silica gel plug, which was then washed with methanol. The combined filtrates were evaporated and the residue dissolved in ether (30 ml). The resulting solution was washed with water (3×20 ml) then dried, filtered and evaporated. Immediate purification of the residue by column chromatography, eluting with pentane/diethyl ether (95:5), then gave the *F_6 furan fatty acid* **3** (0.424 g, 90%) as a colourless oil: υ_{max}/cm^{-1} (film) 3375, 2926, 2856, 2672, 1710, 1597, 1457, 1413, 1379, 1282, 1260, 1105, 910, 796, 734; δ_H (400 MHz, $CDCl_3$) 2.50 (4H, app. t, *J*=7.5, 2× furyl-CH_2), 2.36 (2H, t, *J*=7.5, 10′-CH_2), 1.85 (6H, app. s, 2× furyl-Me), 1.70–1.60 (4H, m, 2× CH_2), 1.59–1.52 (4H, m, 2× CH_2), 1.38–1.30 (4H, m, 2× CH_2), 1.29 (10H, app. br s, 5× CH_2), 0.90 (3H, t, *J*=7.0, 5″-Me); δ_C (100 MHz, $CDCl_3$) 179.9 (C=O), 148.4 (2× C), 114.4 (2× C), 34.1 (CH_2), 31.4 (CH_2), 29.54 (CH_2), 29.50 (CH_2), 29.45 (CH_2), 29.40 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.8 (CH_2), 28.4 (CH_2), 26.14 (CH_2), 26.10 (CH_2), 24.7 (CH_2), 22.4 (CH_2), 14.0 (5″-Me), 8.3 (2× Me); *m*/*z* (EI) 350 [M, 58%]$^+$, 86 (100); HRMS *m*/*z* (EI) calcd for $C_{22}H_{38}O_3$ [*M*], 350.2821, found [M], 350.2819.

4.1.11. 2-(Dec-9-en-1-yl)-3-methyl-4-trideuteriomethyl-5-pentylfuran *15*

4.1.11.1. Method 1. Iodofuran **12** (0.558 g, 1.34 mmol) dissolved in tetrahydrofuran (15 ml) in a 50 ml three-necked round-bottomed flask was cooled to −78 °C and stirred for 10 min. Butyllithium (0.64 ml of a 2.5 M solution in hexanes, 1.61 mmol) was then added dropwise. After 3 min, freshly distilled d_3-iodomethane (0.12 ml, 1.88 mmol) was added in one portion. Subsequent reaction and work-up as described above for the synthesis of furan **13** then gave the *4-d_3-furan* **15** (0.381 g, 92%) as a yellow oil: R_f 0.28 (pentane/diethyl ether, 99:1); ν_{max}/cm^{-1} (film) 3077, 2926, 2855, 1641, 1597, 1463, 1379, 1261, 1156, 1102, 993, 956, 909; δ_H (400 MHz, $CDCl_3$) 5.82 (1H, ddt, *J*=17.0, 10.2 and 6.7, 9′-H), 5.00 (1H, app. ddd, *J*=17.0, 3.7 and 1.6, 10′-H_a), 4.94 (1H, ddt, *J*=10.2, 2.2 and 1.2, 10′-H_b), 2.49 (4H, app. t, *J*=7.5, 2× furyl-CH_2), 2.05 (2H, app. q, *J*=7.0, 8′-CH_2), 1.84 (3H, s, 3-Me), 1.63–1.51 (4H, m, 2× CH_2), 1.42–1.33 (4H,

m, 2× CH_2), 1.29 (10H, br s, 5× CH_2), 0.91 (3H, t, J=7.0, 5″-Me); δ_D (46 MHz, $CHCl_3$) 1.83 (s, 4-CD_3); δ_C (100 MHz, $CDCl_3$) 148.4 (2× C), 139.2 (9′-CH), 114.4 (C), 114.3 (C), 114.1 (10′-CH_2), 33.8 (CH_2), 31.4 (CH_2), 29.4 (2× CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 28.0 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 22.4 (4″-CH_2), 14.0 (5″-Me), 8.3 (Me); HRMS m/z (EI) calcd for $C_{21}H_{33}D_3O$ [M], 307.2954, found $[M]^+$, 307.2959.

[No ^{13}C data is given for the CD_3 group, because the signal was so highly split that a complete set of resonances was not visible. This also applies to the other deuterated compounds described below].

4.1.11.2. Method 2. Methyl-$d_3$lithium (20.0 ml of a 0.5 M solution in diethyl ether complexed with LiI, 10.0 mmol) was added dropwise to a stirred solution of iodofuran **12** (1.23 g, 2.96 mmol) in tetrahydrofuran (10 ml) maintained at −78 °C and stirred for 0.5 h. After warming to ambient temperature and stirring for a further 0.5 h the reaction was quenched by the addition of aqueous ammonium chloride (5 ml). Tetrahydrofuran was evaporated and the residue diluted with diethyl ether (10 ml). The product was extracted into diethyl ether (2×10 ml) and the combined organic extracts washed with water (30 ml) and brine (30 ml) before the solvent was dried, filtered and evaporated to yield the *d_3-furan* **15** (0.783 g, 86%) as a pale yellow oil. All data obtained were in accord with those previously obtained from the conventional approach.

4.1.12. 11-(3-Methyl-4-trideuteriomethyl-5-pentylfuran-2-yl)undecanoic acid—d_3-F_6 furan fatty acid ***16***.

i) Grubbs–Hovayda Mk II catalyst (9 mg, 0.015 mmol) was added to a stirred solution of the d_3-furan **15** (0.090 g, 0.290 mmol) in dichloromethane (5 ml). Freshly distilled benzyl acrylate (0.05 ml, 0.38 mmol) was added and the solution heated to reflux under an atmosphere of nitrogen for 2 h, then filtered through a plug of silica gel. The combined filtrate and washings were evaporated to leave (*E*)-*benzyl 11-(3-methyl-4-trideuteriomethyl-5-pentylfuran-2-yl)undec-2-enoate* (0.111 g, 86%) as a colourless oil: ν_{max}/cm^{-1} (film) 3033, 2928, 2856, 1724, 1654, 1497, 1455, 1405, 1377, 1294, 1266, 1174, 1047, 982, 809, 736, 697; δ_H (400 MHz, $CDCl_3$) 7.42–7.32 (5H, m, 5× Ar–H), 7.04 (1H, dt, J=13.0 and 7.0, 9′-CH), 5.87 (1H, d, J=13.0, 10′-CH), 5.18 (2H, s, OCH_2), 2.49 (4H, app. t, J=7.5, 2× furyl-CH_2), 2.20 (2H, app. q, J=7.0, 8′-CH_2), 1.83 (3H, s, 3- Me), 1.60–1.50 (2H, m, CH_2), 1.50–1.40 (2H, m, CH_2), 1.36–1.31 (4H, m, 2× CH_2), 1.29 (10H, app. br s, 5× CH_2), 0.89 (3H, t, J=7.0, 5″-Me); δ_D (46 MHz, $CHCl_3$) 1.82 (s, 4-CD_3); δ_C 166.6 (C=O), 150.1 (9′-CH), 148.44 (C), 148.40 (C), 136.2 (C), 128.6 (2× Ar–CH), 128.3 (Ar–CH), 128.2 (2× Ar–CH), 120.9 (10′-CH), 114.44 (C), 114.40 (C), 66.0 (13-CH_2), 32.4 (CH_2), 31.4 (CH_2), 30.4 (CH_2), 29.35 (CH_2), 29.31 (CH_2), 29.1 (CH_2), 28.7 (CH_2), 28.04 (CH_2), 28.01 (CH_2), 27.9 (CH_2), 26.1 (CH_2), 22.4 (CH_2), 14.0 (5″-Me), 8.3 (3-Me); m/z (EI) 442 [M, 15%]$^+$, 335 (5), 182 (100); HRMS m/z (EI) calcd for $C_{29}H_{39}D_3O_3$ [M], 441.3322, found $[M]^+$, 441.3321.

ii) In the same manner as for the synthesis of unlabelled F_6-furan fatty acid **3**, hydrogenation of the foregoing deuterated benzyl ester (0.426 g, 0.965 mmol) in the presence of 10% w/w palladium on carbon (50 mg) in methanol (40 ml) gave, after column chromatography (pentane/diethyl ether, 95:5), the *d_3-F_6-furan fatty acid* **16** (0.314 g, 92%) as a colourless oil: υ_{max}/cm^{-1} (film) 3375, 2926, 2856, 2672, 1710, 1597, 1457, 1413, 1379, 1282, 1260, 1105, 910, 796, 734; δ_H (400 MHz, $CDCl_3$) 2.50 (4H, app. t, J=7.5, 2× furyl-CH_2), 2.36 (2H, t, J=7.5, 10′-CH_2), 1.85 (3H, s, 3-Me), 1.70–1.60 (4H, m, 2× CH_2), 1.59–1.52 (4H, m, 2× CH_2), 1.38–1.30 (4H, m, 2× CH_2), 1.29 (10H, app. br s, 5× CH_2), 0.90 (3H, t, J=7.0, 5″-Me); δ_D (46 MHz, $CHCl_3$) 1.84 (s, 4-CD_3); δ_C (100 MHz, $CDCl_3$) 179.9 (C=O), 148.40 (C), 148.40 (C), 114.41 (C), 114.41 (C), 34.1 (CH_2), 31.4 (CH_2), 29.52 (CH_2), 29.50 (CH_2), 29.42 (CH_2), 29.41 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.8 (CH_2), 28.4 (CH_2), 26.14 (CH_2), 26.12 (CH_2), 24.7 (CH_2), 22.4 (CH_2), 14.0 (5″-Me), 8.3 (Me); m/z (EI) 350 [M, 58%]$^+$, 86 (100); HRMS m/z calcd for $C_{22}H_{35}D_3O_3$ [M], 353.3009, found [M], 353.3011.

4.1.13. (E)-Methyl 11-(3-methyl-4-trideuteriomethyl-5-pentylfuran-2-yl)undec-2-enoate ***17***. Grubbs–Hovayda Mk II catalyst (37 mg, 0.060 mmol) was added to a stirred solution of d_3-furan **15** (0.366 g, 1.190 mmol) in dichloromethane (20 ml). Freshly distilled methyl acrylate (0.16 ml, 1.785 mmol) was added and the solution heated to reflux under an atmosphere of dry nitrogen for 2 h then cooled and filtered through a plug of silica gel. The combined filtrate and washings were evaporated to give the *unsaturated methyl ester* **17** (0.378 g, 87%) as a colourless oil: ν_{max}/cm^{-1} (film) 3030, 2928, 2856, 1728, 1658, 1457, 1435, 1317, 1269, 1196, 1175, 1042, 979, 920, 851, 799, 703; δ_H (400 MHz, $CDCl_3$) 6.98 (1H, dt, J=15.6 and 7.0, 9′-CH), 5.82 (1H, dt, J=15.6 and 1.5, 10′-CH), 3.73 (3H, s, 13′-Me), 2.49 (4H, app. t, J=7.5, 2× furyl-CH_2), 2.19 (2H, app. qd, J=7.0 and 1.5, 8′-CH_2), 1.84 (3H, s, 3-Me), 1.63–1.52 (4H, m, 2× CH_2), 1.49–1.41 (2H, m, CH_2), 1.37–1.31 (4H, m, 2× CH_2), 1.29 (8H, br s, 4× CH_2), 0.89 (3H, t, J 7.1, 5″-Me); δ_D (46 MHz, $CHCl_3$) 1.82 (s, 4-CD_3); δ_C (100 MHz, $CDCl_3$) 167.1 (C=O), 149.7 (9′- CH), 148.4 (C), 148.3 (C), 120.8 (10′-CH), 114.5 (C), 114.3 (C), 51.3 (13-Me), 32.1 (CH_2), 31.4 (CH_2), 29.34 (CH_2), 29.31 (CH_2), 29.3 (CH_2), 29.22 (CH_2), 29.22 (CH_2), 29.1 (CH_2), 28.7 (CH_2), 28.5 (CH_2), 26.1 (CH_2), 22.4 (CH_2), 14.0 (5″-Me), 8.3 (3-Me); m/z 442 (EI) [M, 15%]$^+$, 365 (10), 105 (100); HRMS m/z (EI) calcd for $C_{23}H_{35}D_3O_3$ [M], 365.3009, found $[M]^+$, 365.3008.

4.1.14. Methyl 11-(3-methyl-4-trideuteriomethyl-5-pentylfuran-2-yl) undecanoate ***18***. A 100 ml round-bottomed flask fitted with a three way tap was charged with 10% w/w palladium on carbon (15 mg). Methanol (10 ml) was added carefully followed by the foregoing unsaturated methyl ester **17** (0.104 g, 0.285 mmol). The flask was evacuated, flushed with hydrogen (×3) and the mixture stirred for 1 h. The mixture was then filtered through a silica plug and the solvent and washings evaporated. The residue was diluted with diethyl ether (10 ml) and the solution washed with water (3×10 ml) then dried, filtered and evaporated and the product purified by column chromatography (pentane/diethyl ether, 95:5) to yield the *d_3-furan fatty acid methyl ester* **18** (0.095 g, 91%) as a colourless oil: υ_{max}/cm^{-1} (film) 2926, 2855, 2672, 1741, 1642, 1434, 1170; δ_H (400 MHz, $CDCl_3$) 3.67 (3H, s, 13′-Me), 2.49 (4H, app. t, J=7.5, 2× furyl-CH_2), 2.31 (2H, t, J 7.6, 10′-CH_2), 1.84 (3H, s, 3-Me), 1.67–1.59 (4H, m, 2× CH_2), 1.59–1.52 (4H, m, 2× CH_2), 1.36–1.24 (14H, m, 7× CH_2), 0.89 (3H, t, J=7.1, 5″-Me); δ_D (46 MHz, $CHCl_3$) 1.81 (s, 4-CD_3) δ_C (100 MHz, $CDCl_3$) 174.3 (C=O), 148.40 (C), 148.40 (C), 114.42 (C), 114.41 (C), 51.4 (13′-Me) 34.1 (CH_2), 31.4 (CH_2), 29.5 (CH_2), 29.42 (CH_2), 29.42 (CH_2), 29.21 (CH_2), 29.21 (CH_2), 29.20 (CH_2), 29.20 (CH_2), 28.8 (CH_2), 28.5 (CH_2), 26.1 (CH_2), 25.0 (CH_2), 22.4 (CH_2), 14.0 (5″-Me), 8.3 (3-Me); m/z (EI) 367 [M, 10%]$^+$, 105 (100); HRMS m/z (EI) calcd for $C_{23}H_{37}D_3O_3$ [M], 367.3166, found [M], 367.3165.

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