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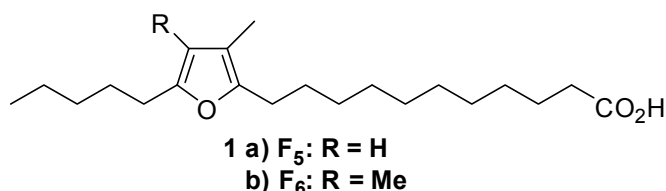
OPTIMIZED SYNTHESSES OF THE FURAN FATTY ACIDS F₅ AND F₆ FEATURING CONVERSION OF A β-IODOFURAN INTO A β-METHYLFURAN IN A SINGLE OPERATION

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Abstract – Optimized syntheses of the furan fatty acids F₅ **1a** and F₆ **1b** are described, which give >60% overall yields over 7 or 8 steps respectively starting from 10-undecenal **6**. The F₆ approach also features a conversion of a β-iodofuran into the corresponding β-methyl derivative in a single operation.

Furan fatty acids are widely distributed in Nature and have been detected in various foods such as olive oil and butter, in a number of plant species and in some yeasts, marine bacteria and algae. However, it is their occurrence in often considerable quantities in a great variety of fish oils which has caused the greatest interest, as this may be associated with the well-established dietary benefits of consuming fish rather than meat products. This is perhaps best illustrated by the finding that Greenlanders suffer much less from cardiovascular diseases than those on a ‘Western’ diet, despite that the former group eat foods which are very rich in fats and cholesterol, thereby rather contradicting current thinking regarding the origins of atherosclerosis. All of these ideas are summarized in an excellent review by Spiteller.¹



While whole series of furan-containing fatty acids have been identified from natural sources,² two members which often predominate and which are associated with the Omega-3 fatty acids, are furan fatty acid F₅ **1a** and especially F₆ **1b**;¹ both compounds are likely biosynthesised from linoleic acid.³

Dedicated to Professor Albert Padwa in recognition of his outstanding contributions to synthetic chemistry.

One problem which has bedeviled this area in general is the extreme sensitivity of the acids **1** and relatives, especially to autoxidation, meaning that many isolates may well be artefacts of the actual natural structures.⁴ Intriguingly, while this represents a real challenge in terms of manipulating these compounds, it may offer an explanation as to how such metabolites express their bioactivity, that is by rapidly reacting with peroxy radicals thereby acting as protective components in such fats.¹ In addition, the well known sensitivity to acids displayed by furans in general may also play a part in this instability.

Clearly, in order to further progress research in this area, the availability of decent samples of both acids is highly desirable, especially labelled material. Existing syntheses, while certainly validating the structures of the acids **1**, are in general not always efficient enough for this purpose. More important is the goal of arriving at a late intermediate with much greater stability than the target acids **1** which can be readily, efficiently and rapidly converted into these very sensitive targets. Previous approaches have featured the classical furan preparations employed by the Glass group,⁵ subsequently improved by Schödel and Spittler,⁶ which can be used to obtain both acids **1**, a synthesis of F₅ **1a** by building the furan ring onto 1-acetyl-1-cyclododecene,⁷ and a conceptually different method wherein modern Pd(0)-catalyzed methods are some of the key steps used to homologate the starting material, 4,5-dibromofuran-2-carboxaldehyde.⁸

Certainly, the last method at least can be used to secure useable quantities of the acids **1**. The earlier Glass route has also been used to generate ¹³C-labelled material.⁹ Of relevance both to the probable source of these acids and to their possible mode of action, the acids **1** have been made using a biomimetic approach from linoleic acid¹⁰ and also from enediones generated by autoxidation of the original acids.⁴

Our own approaches to the two acids **1** are based on new syntheses of furans developed in Cardiff, both of which feature 5-*endo*-dig cyclisations of 3-alkyne-1,2-diols **2** (Figure 1).

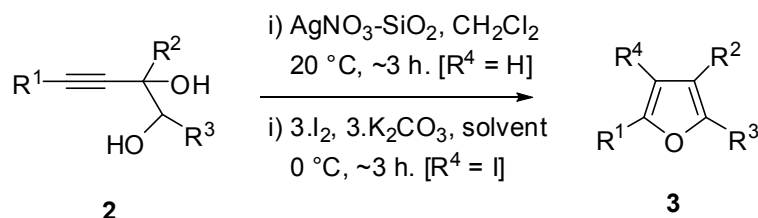
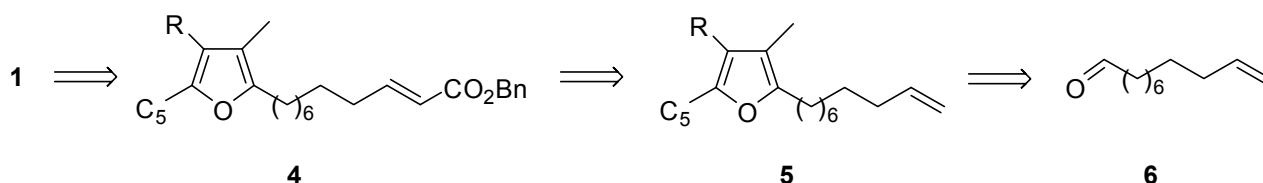


Figure 1. Syntheses of highly substituted furans from 3-alkyne-1,2-diols

In the catalysed method, the cyclisations are induced by silver(I) and generally give the furans [**3**; R⁴ = H] in quantitative yields,¹¹ while an earlier method employs iodocyclisations which deliver the iodofurans [**3**;

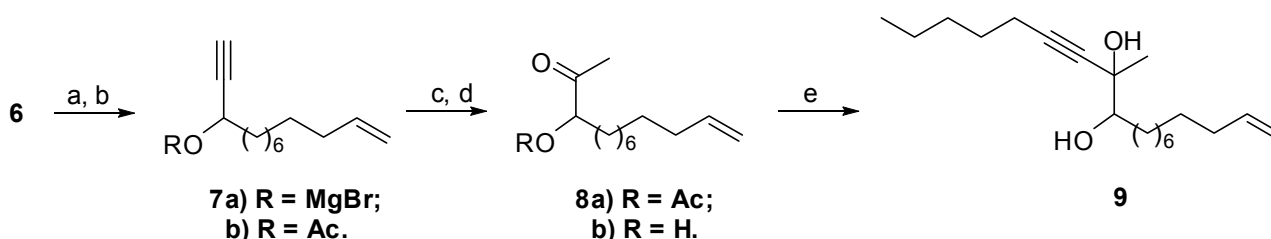
$R^4 = I]$ usually in good yields,¹² which are set up for additional homologation to fully substituted derivatives. We have previously reported the use of these cyclisations in approaches to both furan acids **1**, although neither was realistically capable of delivering gram quantities of product, due to inefficient steps in the early stages and a later oxidation step in which the acid group was generated.¹³ Herein, we report solutions to these limitations using a modified and much more efficient strategy, which also provides late intermediates which are more stable and which are easily converted into the final product **1**.

The key to this modified approach is the very late introduction of the carboxylic acid function using a cross metathesis with benzyl acrylate, which allows generation of the acids **1** by simultaneous alkene hydrogenation and ester hydrogenolysis of the late intermediates **4**. (Scheme 1). The metathesis precursors **5** could then be derived using the chemistry outlined in Figure 1 and, very fortunately, the cheap, commercially available aldehyde **6**, thereby obviating many of the tedious early stage problems.



Scheme 1. Retrosynthetic analysis of furan acids **1**

After some optimization, the present early steps are now very efficient: addition of commercial ethynylmagnesium bromide to the aldehyde **6** gave the expected propargylic alcohol salt **7a**, direct acetylation of which without aqueous work-up, gave the acetate **7b** (Scheme 2).

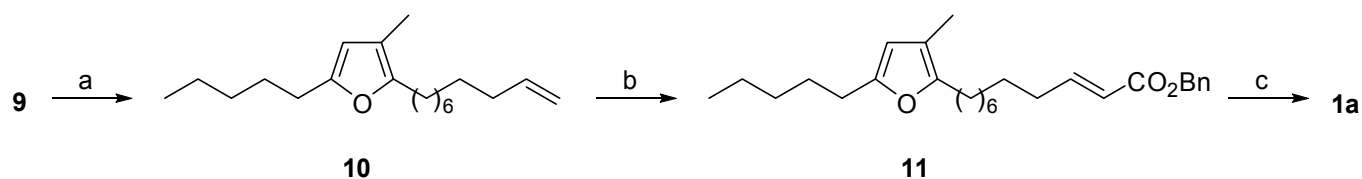


Scheme 2. Reagents and conditions: a) HCCMgBr, THF, 0 °C, 0.5 h; b) Ac₂O, 0 °C, ~1 h (92%, 2 steps); c) NaAuCl₄·2H₂O, aq. MeOH, ~90 °C, 3 h (ref. 14); d) 2 equiv. K₂CO₃, MeOH, H₂O, 0 °C, 1 h (85%, 2 steps); e) 2.2 equiv. C₅H₁₁CClLi, THF, 0 °C, 1 h (95%).

Subsequent hydration of the alkyne function using the excellent gold(III)-catalysed method developed by Fukuda and Utimoto¹⁴ followed by an aqueous work-up and finally hydrolysis of the intermediate acetoxy-ketone **8a** delivered excellent overall yields of the acyloin **8b**. It was important to stop the

gold-catalysed hydration after 3 h and also essential to hydrolyze the acetate group at 0 °C rather than at ambient temperature to secure high yields. Addition of just over two equivalents of heptynyl lithium then gave the common intermediate **9** in excellent yield in a diastereoisomeric ratio of *ca.* 5:1; the exact identities of which were not determined.¹⁵ We find this direct method to be more efficient in all respects, relative to alcohol protection (for example using TBDMS), condensation and finally deprotection. By taking all reagents and solvents into account, the direct approach is also more atom efficient and in any case gave better yields, largely due to the fewer steps and hence a lesser amount of compound handling and reaction work-ups; on a large scale, the excess 1-heptyne could also be recovered.

The synthesis of furan fatty acid F₅ was then completed (Scheme 3). Silver(I)-catalysed cyclisation as expected¹¹ delivered a quantitative yield of the furan **10**. We were then surprised to find that cross metathesis with benzyl acrylate using Grubbs Mark II catalyst¹⁶ was quite ineffective, at least in refluxing dichloromethane. Fortunately, substitution by the Grubbs-Hoveyda Mark II catalyst¹⁷ did work rapidly and very well to give an excellent return of the desired ester **11**.¹⁸

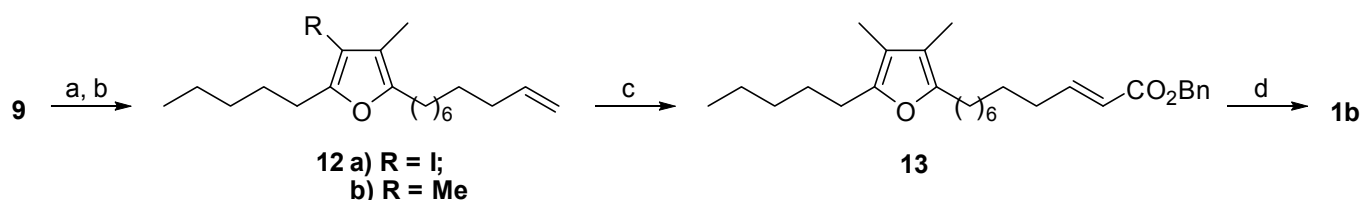


Scheme 3. Reagents and conditions: a) 10 mol % of 10% AgNO₃-SiO₂, CH₂Cl₂, 20 °C, 4 h (100%); b) 1.4 equiv. CH₂=CHCO₂Bn, Grubbs-Hoveyda Mark II catalyst, 40 °C, 2 h; c) 1 atmos. H₂, 5% Pd-C, MeOH, 20 °C, 1 h, aqueous work-up (85% for two steps).

Initially three equivalents of the acrylate were used, which meant that the product **11** was heavily contaminated not only with this excess acrylate but also by varying amounts of the homo-metathesis product, dibenzyl fumarate. The ester **11** could be separated using column chromatography, but we wished to avoid this for obvious reasons. Fortunately, we found the cross metathesis to be equally effective using only 1.3 equivalents of benzyl acrylate; the resulting ester **11** was now contaminated only with the slight excess of benzyl acrylate. This was not separated at this stage as it was converted into propanoic acid in the final hydrogenation-hydrogenolysis step and then easily removed by a water wash.¹⁹ The resulting furan F₅ **1a** showed spectroscopic and analytical data identical to those previously reported.^{5,7,8,18} It was also very unstable, with decomposition becoming noticeable after only a day or so even when stored at -20 °C. However, the penultimate precursor, the ester **11** proved much more stable, if still sensitive, and the alkene **10** even more so in cold, dark and oxygen-free conditions. Either of these intermediates are thus storable late stage precursors of furan F₅ **1a**. As the two final steps are both

triggered by catalysts and are reasonably simple to carry out and to work-up, these should be transformations that could be carried out by the relatively synthetically inexperienced and hence could provide a ready supply of the acid **1a** on a regular basis.

The synthesis of furan fatty acid F₆ **1b** began with an iodocyclisation to form the furan ring (Scheme 4).¹² In previous work, we had discovered that various precursors having lengthy fatty chains did not respond well to the use of the usual solvents for this cyclisation (MeCN, dichloromethane), but that ethyl acetate was eminently suitable.¹³ We were surprised to find that such cyclisations of alkyne-diol **9** in EtOAc only delivered around 60% yields of rather dirty products. Fortunately, simply changing to tetrahydrofuran resulted in excellent yields of the iodofuran **12a**.

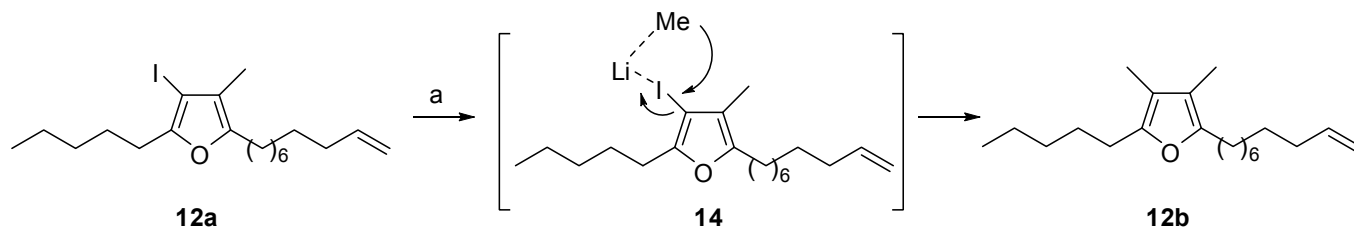


Scheme 4. Reagents and conditions: a) 3.I₂, 3.K₂CO₃, THF, 0 °C, 3 h (85%); b) 1.05 equiv. BuLi, -78 °C, THF, 5 min then 2 equiv. MeI (~90%); c) as step b, Scheme 3; d) as step c), Scheme 3.

Exchange of the iodine atom for a methyl group was then carried out using the well established procedure of halogen-metal exchange using a slight excess of butyl lithium at low temperature followed by rapid quenching of the resulting β-lithio furan with iodomethane. The resulting fully substituted furan **12b** could be isolated in excellent yields and when subjected to the same two reactions shown in Scheme 3 for the synthesis of furan F₅, *via* benzyl ester **13**,²⁰ which was again not separated from the slight excess of benzyl acrylate, led to the furan fatty acid F₆ **1b** again in excellent yields, which also showed identical spectroscopic data to those previously reported.^{5,9}

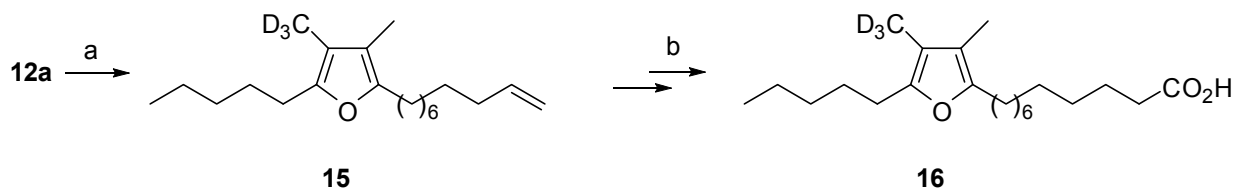
Despite the decent yields reported in Scheme 4, the iodine-methyl exchange step was particularly demanding and very prone to give products contaminated with corresponding protonated species [**12**; R = H] and hence final products containing furan F₅. The other product of the halogen-metal exchange step, iodobutane, is sufficiently unreactive to interfere with the alkylation step, at least at low temperature. However, we wondered if by using *methyl* lithium, it would be possible to generate much more reactive iodomethane *in situ* by a similar exchange and hence obviate the need to handle and purify this toxic material. We could find no literature precedent for this idea and therefore were somewhat pessimistic about the chances of success. We were therefore delighted to find that adding a slight excess of 1.6M

ethereal methyl lithium-lithium bromide complex to a cold solution of the iodofuran **12a** in tetrahydrofuran routinely gave 90~95% yields of the F₆ precursor **12b** (Scheme 5).



Scheme 5. Reagents and conditions: a) 1.3 equiv. 1.6M MeLi·LiBr in Et₂O, THF, -78 °C, 5 min (~ 95%).

Perhaps the transformation involves formation of a complex **14** between the lithium and iodine atoms prior to C-C bond formation, and hence the intermediate iodomethane is never really 'free' and hence is available to couple immediately. To emphasize the utility of this reaction, addition of deuteriomethyl lithium-lithium iodide complex (0.5M in ether) under otherwise identical conditions gave >90% yields of the trideuterated F₆ precursor **15**, and thence trideuterated furan F₆ **16**,²¹ typically contaminated with <3% of the corresponding F₅ precursor **10**, following cross metathesis and hydrogenation-hydrogenolysis (Scheme 6).



Scheme 6. Reagents and conditions: a) 1.3 equiv. 0.5M CD₃Li·LiI in Et₂O, THF, -78 °C, 5 min (~ 95%); b) as Scheme 4.

The schemes described above deliver >60% overall yields of both furan fatty acids F₅ and F₆ **1** over seven or eight reproducible and optimized steps, starting from the commercially available aldehyde **6** and should therefore be capable of delivering such compounds in gram quantities and in labeled forms if desired. All steps have been carried out on a gram scale in the yields quoted. More stable late precursors offer the prospect of storing material for long periods, which is very difficult in the case of the fatty acids themselves. Finally, the use of methyl lithium alone for the direct iodine-methyl exchange reaction simplifies this tricky transformation for the elaboration of β-methyl-furans and possibly related structures.

ACKNOWLEDGEMENTS

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- [Found: $M^+ - OH$, 291.2700. $C_{20}H_{35}O$ requires M , 291.2688]. The minor diastereoisomer could be identified and quantified by δ_H ($CDCl_3$, 400 MHz) 1.43 (s, 8-Me) and 3.36 (dd, J 8.0, 2.0 Hz); δ_C ($CDCl_3$, 100 MHz) 26.0 (q), 26.2 (t), 32.4 (t), 71.7 (s) and 77.9 (d).
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18. Intermediate **11**, a colourless oil, showed δ_H ($CDCl_3$, 400 MHz) 0.87 (3H, br. t, J ca. 7 Hz), 1.24-1.39 (16H, m), 1.40-1.47 (2H, m), 1.52-1.62 (4H, m), 1.90 (3H, s, 3-Me), 2.21 (2H, br. q, J ca. 6.8 Hz), 2.44-2.59 (4H, m), 5.20 (2H, s), 5.73 (1H, app. s, 4-H), 5.90 (1H, d, J 17.2 Hz), 7.04 (1H, dt, J 17.2, 7.1 Hz), 7.31-7.42 (5H, m). The final sample of F_5 -acid **1a** showed δ_H ($CDCl_3$, 400 MHz) 0.90 (3H, br. t, J 6.9 Hz), 1.25-1.37 (16H, m), 1.53-1.67 (6H, m), 1.90 (3H, s), 2.35 (2H, t, J 7.5 Hz), 2.50 (2H, t, J 7.4 Hz), 2.52 (2H, t, J 7.6 Hz), 5.73 (1H, s), 10.5-11.5 (1H, br., OH); δ_C ($CDCl_3$, 100 MHz) 9.9 (q), 14.0 (q), 22.4 (t), 24.7 (t), 25.9 (t), 27.9 (t), 28.0 (t), 28.7 (t), 29.1 (t), 29.2 (t), 29.3 (t), 29.4 (t), 29.5 (t), 29.6 (t), 31.4 (t), 107.6 (d), 113.8 (s), 149.4 (s), 153.5 (s), 180.1 (s); ν_{max} (film) 2926, 2855, 1710, and broad absorbance ~ 3200 -2400 cm^{-1} ; m/z (TOF EI) 336 (55%, M^+), 279 (25), 165 (100). [Found: M^+ , 336.2669. $C_{21}H_{36}O_3$ requires M , 336.2664].
19. Attempts to combine these two steps were not productive. See, for example, J. Cossy, F. C. Bargiggia, and S. BouzBouz, *Tetrahedron Lett.*, 2002, **43**, 6715.
20. Benzyl ester **13**, a colourless oil, showed δ_H ($CDCl_3$, 400 MHz) 0.87 (3H, t, J 7.0 Hz), 1.24-1.39 (16H, m), 1.40-1.47 (2H, m), 1.48-1.62 (4H, m), 1.90 (6H, s, 2 x Me), 2.21 (2H, q, J 6.8 Hz), 2.47 (4H, app. t, J 7.5 Hz), 5.17 (2H, s), 5.87 (1H, d, J 17.2 Hz), 7.00 (1H, dt, J 17.2, 7.1 Hz), 7.31-7.42 (5H, m). F_6 -acid **1b** showed δ_H ($CDCl_3$, 400 MHz) 0.87 (3H, t, J 7.0 Hz), 1.22-1.37 (16H, m), 1.47-1.67 (6H, m), 1.84 (6H, s), 2.32 (2H, t, J 7.6 Hz), 2.48 (6H, t, J 7.6 Hz); δ_C ($CDCl_3$, 100 MHz) 8.3 (q), 14.0 (2 x q), 22.4 (t), 24.7 (t), 26.1 (t), 28.4 (t), 28.6 (t), 28.7 (t), 28.8 (t), 29.1 (t), 29.2 (t), 29.3 (t), 29.4 (t), 29.5 (t), 31.4 (t), 31.5 (t), 114.4 (s), 148.4 (s), 179.9 (s); ν_{max} (film) 2926, 2855, 1710, and broad absorbance ~ 3300 -2700 cm^{-1} ; m/z (TOF EI) 350 (58%, M^+), 293 (53), 179 (85), 86 (100). [Found: M^+ , 350.2819. $C_{22}H_{38}O_3$ requires M , 350.2821].
21. d_3 - F_6 -acid **16**, an sensitive colourless oil, showed δ_H ($CDCl_3$, 400 MHz) essentially as for non-deuterated- F_6 -acid **1b** (ref. 20) except that the resonance at δ_H 1.84 integrated for 3H. Similarly, the ^{13}C spectrum was essentially identical to non-deuterated material; the CD_3 resonances were too small to be measured meaningfully. The presence of the CD_3 group was confirmed by δ_D ($CHCl_3 -$

1% CDCl₃, 360 MHz) 1.79, the only resonance observed in addition to CDCl₃, at δ_D 7.24; ν_{\max} (film) 2196 cm⁻¹, in addition to the absorbances reported above for acid **1b** (ref. 20); m/z (TOF EI) 353 (81%, M⁺), 296 (92), 182 (95), 86 (100); an ion at m/z 350 was absent (*cf.* ref. 20). [Found: M⁺, 353.3008. C₂₂H₃₅D₃O₃ requires *M*, 353.3009].