A general convergent strategy for the synthesis of tetra-substituted furan fatty acids (FuFAs)

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Abstract: Using a palladium catalysed - acid mediated isomerisation sequence, tetrasubstituted furans suitable for furan fatty acid (FuFA) total synthesis can be effectively constructed in high yield. This convergent approach installs the essential carbon side chains at the α_1- and α_2 -positions, the β_1-methyl group, and importantly, an electron withdrawing group at the β_2-position *tempering* the reactivity of the electron rich furan in the FuFAs. When this EWG is an ester, it was conveniently transformed into the required β_1-methyl group in three high yielding synthetic steps. Using this approach, the total synthesis of 11D5 and 11D3 was accomplished in 7-steps from commercially available starting materials in overall yields of 52% and 48%, respectively. Furthermore, this methodology also provided an efficient synthetic route to the decarboxy analogues of both 11D5 and 11D3.

Introduction

The furan fatty acids (FuFAs) (figure 1, **1**) afford significant nutritional health benefits to humans by providing an important defence against the development of chronic inflammatory disease, and over the past 30 years nutritional studies have established the advantages of diets that contain FuFAs.[1]

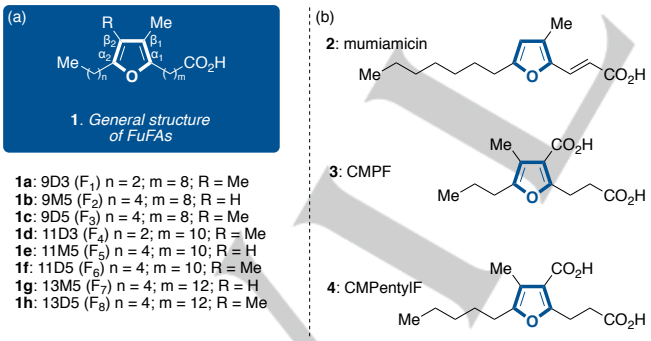
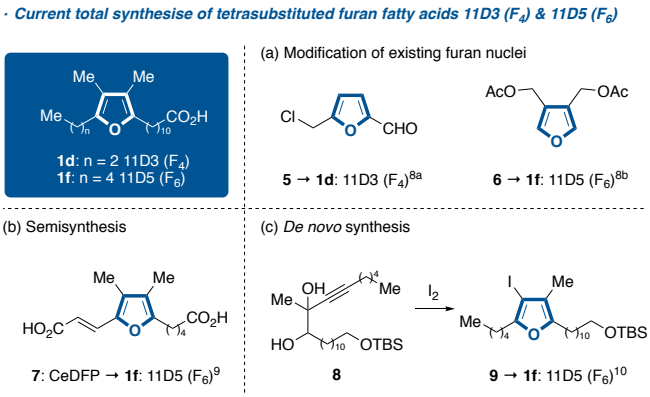


Figure 1. (a) General structure of the FuFAs; (b) The antibiotic mumiamicin, and related urofuran acids CMPF and CMPentylF.

More recently, it has been demonstrated that the electron rich furan within the FuFAs can readily scavenge radicals, including reactive oxygen species, potentially providing protection to the bilayer of membranes from oxidative damage.[1b,2] Furthermore, members of the FuFAs have been shown to be potent antibiotics (e.g. mumiamicin **2**),[3] and their oxidative catabolites CMPF (**3**) and CMPentyl (**4**) have been implicated in renal failure and type 2 diabetes; however, their precise role has yet to be fully explained.[1a,4] Consequently, the importance of the FuFAs in human diets cannot be overstated.

Over 25 FuFAs have been discovered to date, with the eight principal FuFAs (figure 1, **1a-h**) being characterized by an electron rich furan core, a fatty acid side chain at the α_1 -position, a propyl or pentyl carbon chain at α_2 -position, a methyl group at the β_1-position, and either a hydrogen or methyl group at the β_2-position. The origin of dietary FuFAs is primarily from plant, algae and marine bacteria, where they subsequently accumulate in higher-order fish and mammals.[1a,5] A significant limiting factor in FuFA studies has been an adequate supply of material. Trisubstituted FFAs can be readily isolated from natural sources such as latex, whereas their tetrasubstituted counterparts can prove elusive. This is due, in part, to their capacity to readily undergo oxidation leading to ring-opened products, and their very low natural abundance (e.g. approx. 1% or less in fish fatty acid samples).[2a,6] Recently, Vetter and co-workers reported a countercurrent chromatography (CCC) methodology for the isolation of 100mg amounts of 11D5 from 4,7,10,13,16,19-docosahexaenoic acid ethyl ester (DHA-EE),[7] but this approach has yet to be reported for the isolation of other tetrasubstituted, less abundant FuFAs.

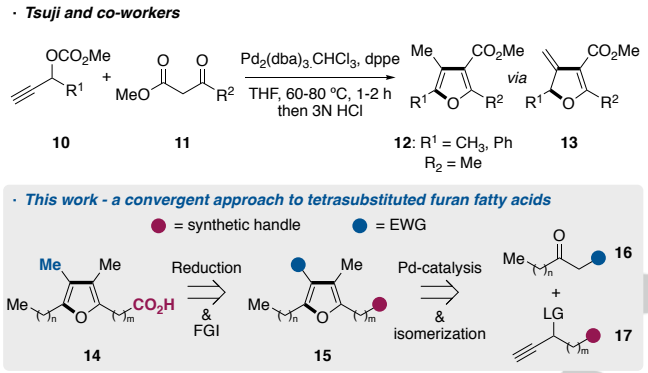
Synthetic studies leading to the total synthesis of tetrasubstituted furan fatty acids are scarce in the literature (scheme 1).



Scheme 1. Strategies employed in the total synthesis of 11D3 (F_4) and 11D5 (F_6).

To date, only three strategies have been reported (a) synthetic modification of existing furan nuclei;[8] (b) semi-synthesis from a furan fatty acid oxidation product;[9] and (c) a *de novo* synthetic approach using an electrophilic cyclisation of a propargylic diol.[10] While each strategy is significant in its own right, providing a synthesis of *either* 11D3 or 11D5, there still remains a need to develop a more general approach or methodology. Therefore, with these studies in mind, together with our own efforts on FuFA synthesis,[11] we sought a flexible convergent synthetic method that could be employed to synthesize *any* tetrasubstituted furan fatty acid or analogue thereof.

Central to our approach is the palladium mediated formation of furans from propargyl carbonates and 1,3-dicarbonucleophiles, first reported by Tsuji in 1985 (scheme 2).[12] This methodology has been exploited to great effect to form several important heterocycles such as pyrroles, dihydropyrroles, chromanes, tetrahydrobenzofurans and dihydrofurans;[13] yet its application in the target synthesis of furan natural products has been limited.[14]



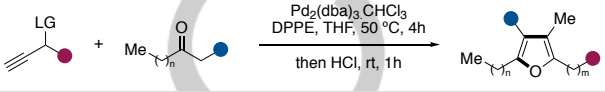
Scheme 2. Convergent approach to tetrasubstituted FuFAs.

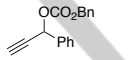
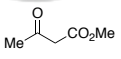
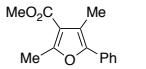
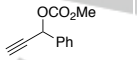
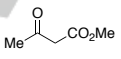
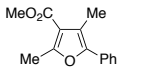
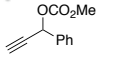
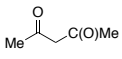
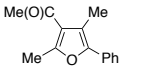
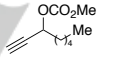
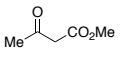
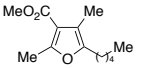
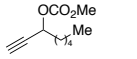
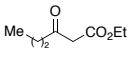
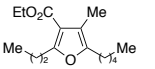
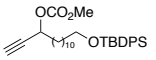
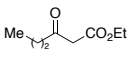
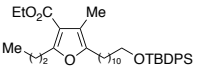
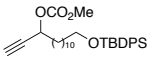
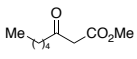
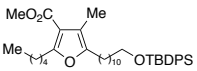
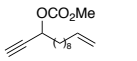
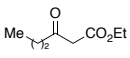
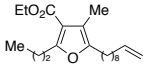
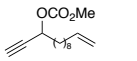
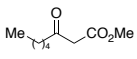
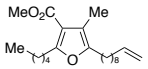
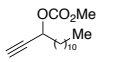
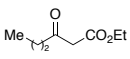
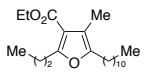
This highly convergent methodology utilizes palladium catalysis to give a methylidene dihydrofuran **13** that can be subsequently aromatized to its furan (**12**) through acid mediated isomerization. Tsuji's original reports[12] established this methodology to give tri- and tetrasubstituted methylene dihydrofurans furans; importantly, the acid catalyzed isomerization of the methylene dihydrofurans to tetrasubstituted furans was demonstrated for a limited number of examples. Additionally, Yoshida and co-workers employed this Pd-methodology to deliver a synthesis of tetrasubstituted pyrroles.[13d] Accordingly, through the judicious selection of a 1,3-dicarbonyl (**16**) and propargylate (**17**) this would provide a furan **15** after Pd-mediated catalysis and acid catalyzed isomerization. Importantly, this furan would contain a methyl group at the 3-position, have the desired carbon chains fully intact at the 2- and 5-positions, and an EWG at the 4-position tempering the reactivity of the furan. Additionally, this convergent approach, together with a synthetic handle on **17** and an EWG on **16**, would ensure flexibility in the synthesis. Conversion of the furan **15** to the FuFA **14** would then be accomplished through reduction of EWG at the 4-position and subsequent functional group manipulation, where the EWG is acting as a masked methyl group.

Results and Discussion

We began our study by taking Cbz protected propargyl alcohol **18**[15] with methyl acetoacetate **19** under the palladium catalyzed conditions reported by Yoshida and co-workers,[13d] followed by treatment of the crude reaction product with 1M HCl, and gratifyingly, this provided the furan **20** in 72% isolated yield (Table 1, entry 1). An increase in isolated yield to 85% was observed when benzyl carbonate **18** was replaced with the methyl carbonate **21**;[16] and consequently, all subsequent reactions were undertaken with this activating group (entry 2).

Table 1. Palladium mediated, acid catalysed formation of tetrasubstituted furans.



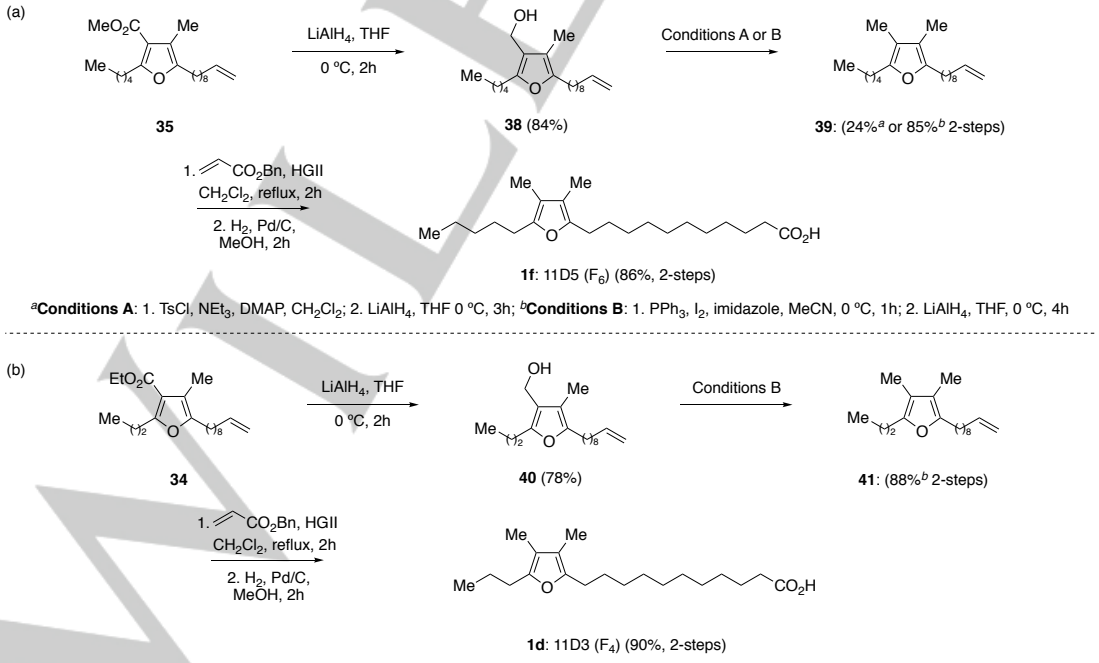
entry[a]	propargylate	1,3-dicarbonyl	furan (%)[b]
1	 **18**	 **19**	 **20** (72%)
2	 **21**	 **19**	 **20** (85%)
3	 **21**	 **22**	 **23** (81%)
4	 **24**	 **19**	 **25** (81%)
5	 **24**	 **26**	 **27** (87%)
6	 **28**	 **26**	 **30** (93%)
7	 **28**	 **31**	 **32** (87%)
8	 **33**	 **26**	 **34** (82%)
9	 **33**	 **31**	 **35** (89%)
10	 **36**	 **26**	 **37** (89%)

[a] All reactions were performed using the 1,3-dicarbophile (1 equiv.), the carbonate (1 equiv.), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol%), DPPE (10 mol%) for 3 h at 50°C under argon atmosphere; after which 1M HCl (2 mL) was added and stirring continued for 2 h at room temperature. [b] Isolated chemical yields.

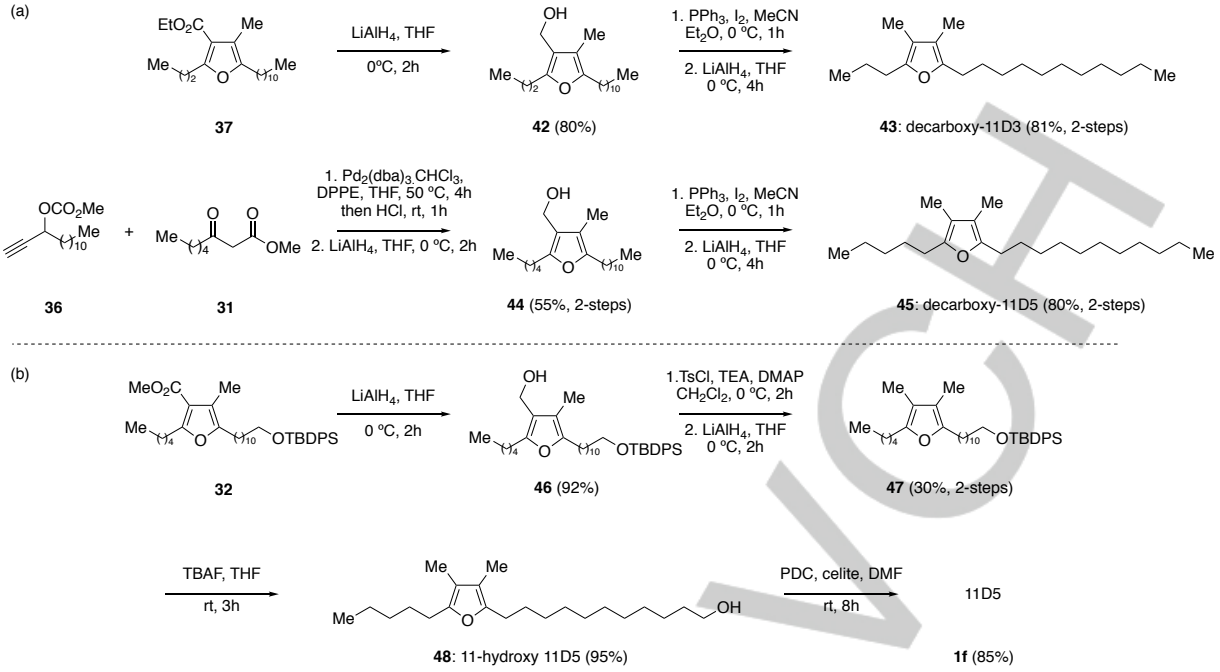
This reaction could also be undertaken with acetylacetone (**22**) to give furan **23**, with a methylketone at the 4-position in a comparable yield of 81% (entry 3). A propargyl acetate with a pentyl side chain (**24**) when reacted with methyl acetoacetate **19** provided furan **25** in 81% yield (entry 4); and importantly this propargyl acetate (**24**) delivered furan **27** in 87% yield (entry 5) when reacted with ethyl 3-oxohexanoate (**26**), therefore delivering potential urofuran analogues. Key tetrasubstituted FuFAs 11D3 (F_4) **1d** and 11D5 (F_6) **1f** have a 11-carbon acid side chain, and accordingly treatment of TBDPS protected propargyl acetate **28** with ethyl 3-oxohexanoate (**26**) or methyl 3-oxooctanoate (**31**),[17] afforded furans **30** and **32** in 93 and 87% isolated yield, respectively (entries 6 and 7). These two furans, **30** and **32**, now contain an appropriate functional group that can be transformed into the desired acid within 11D3 (F_4) and 11D5 (F_6). Similarly, propargylate **33** containing a terminal alkene could be reacted with ethyl 3-oxohexanoate (**26**) or ethyl 3-oxooctanoate (**31**), delivering furans **34** and **35** in 82 and 89% isolated yield, respectively (entries 8 and 9). Again, each of these furans could be effectively transformed into the acid within 11D3 (F_4) and 11D5 (F_6) through cross metathesis.[10a,b] Finally, propargyl acetate **36** could be reacted again with ethyl 3-oxohexanoate (**26**) potentially delivering a decarboxy analogue of 11D3 (F_4) **37** (entry 10).

With a general synthetic method in-hand, focus then moved to delivering a total synthesis of 11D5 (F_6) and 11D3 (F_4), respectively (scheme 3). Treatment of ethyl ester **35** with $LiAlH_4$ at 0°C gave the primary alcohol **38** in 78% isolated yield. Initial attempts at reducing the primary alcohol **38** to the methyl group was by way of conversion to its tosylate, followed by treatment with excess $LiAlH_4$; however, this provided the tetrasubstituted furan **39** in a very modest 24% isolated yield. Fortunately, this poor yield could be overcome by adopting the method of MaGee and co-workers,[18] developed in their synthesis of calicogorgins A and C. This involved conversion of the primary alcohol to its corresponding iodide; with the desired methyl groups being generated after reduction with a metal hydride. Accordingly, addition of iodine to **38** in the presence of PPh_3 and imidazole, gave the crude iodide after work-up, which was subsequently reduced with $LiAlH_4$ giving furan **39** in an excellent 85% yield over 2-steps. With alkene **39** in hand, the final step in the synthesis of 11D5 (F_6) was to introduce the carboxylic acid group. This was achieved using the method of Knight and co-workers,[10a,b] through cross metathesis of **39** with benzyl acrylate in the presence of Hoveyda-Grubbs 2nd generation catalyst, followed by immediate hydrogenation of the crude product to reveal the reduced free acid, and was achieved in 86% yield over 2-steps. The ^1H and ^{13}C NMR of the product **1f** was identical with that previously reported for 11D5 (F_6),[10a,b] confirming its total synthesis in 7-linear steps (5 purifications) from commercially available starting material in 52% overall yield. The total synthesis of 11D3 (F_4) was carried out under the same conditions from ethyl ester **34** (scheme 3(b)). Each reaction proceeded smoothly providing product **1d** in 7-linear steps and 48% overall yield from commercially available 10-undecenal, whose spectroscopic data were in full agreement with that of 11D3 (F_4).[8a]

Having completed the total synthesize of 11D3 and 11D5, our attention then turned to synthesizing analogues of the FuFAs lacking the terminal carboxy group (scheme 4). The synthesis of decarboxy-11D3 was accomplished through $LiAlH_4$ mediated reduction of ethyl ester **37** providing primary alcohol **42** in 80% yield. The alcohol **42** was then efficiently converted to its primary iodide, using the PPh_3 / I_2 / imidazole protocol, and subsequently reduced with $LiAlH_4$ giving the tetra-alkylfuran **43** in an 81% isolated yield over 2-steps. Decarboxy-11D5 (**45**) was prepared in an analogous manner, but without isolation of the ethyl ester from the initial palladium mediated cyclisation. Hence, treatment of the methyl propargylate **36** with 1,3-dicarbophile **31** using the



Scheme 3. Completion of the total synthesis of (a) 11D5 (F_6); (b) 11D3 (F_4).



Scheme 4. Total synthesis of (a) decarboxy-11D5 (F6) and decarboxy-11D3 (F_4); and (b) 11-hydroxy 11D5 (F_6).

conditions described in scheme 3 gave the crude methyl ester, that was subsequently reduced with $LiAlH_4$ to the primary alcohol **44** in 55% over 2-steps. This alcohol (**44**) was then fully reduced to the C-3 methyl, using the PPh_3 / I_2 / imidazole / $LiAlH_4$ protocol, providing decarboxy-11D5 **45** in 80% overall yield over 2-steps. Finally, a 11-hydroxy analogue of FuFA 11D5 could be conveniently prepared from the tetrasubstituted OTBDPS ethyl ester **32**, *via* reduction with $LiAlH_4$ to provide the primary alcohol **46** in 92% yield. The conversion of the primary alcohol (**46**) to its methyl was performed using Conditions A from scheme 4, instead of the MaGee[18] protocol, as it was anticipated that competing halogenation of the OTBDPS may occur.[11b]Consequently, primary alcohol **46** was converted to its tosylate, followed by treatment of the unstable crude product with excess $LiAlH_4$ giving the tetrasubstituted furan **47** in a very modest 30% isolated yield over these 2-steps; deprotection with TBAF then gave the 11-hydroxy 11D5 (**47**) analogue in near quantitative yield. This analogue can be converted to 11D5 (**1f**) *via* standard PDC oxidation, but the approach described in scheme 3(a) is far superior in terms of step efficiency and over chemical yield.

Conclusion

In conclusion, we have developed a convergent approach to tetrasubstituted furans using a palladium catalyzed - acid mediated isomerization sequence as a key step. These furans are appropriately substituted and stable, enabling them to act as suitable precursors in the synthesis of the chemically labile tetrasubstituted FuFAs. Using this approach, the total synthesis of two important FuFAs, 11D3 (F_4) **1d** and 11D5 (F_6) **1f**, has been completed in 7-linear steps each, from commercially available starting materials, and in 52% and 48% overall yield, respectively. The generality of this synthetic approach to tetrasubstituted furans was further exemplified by the total synthesis of 3 further tetrasubstituted FuFAs analogues; decarboxy-11D5 (**45**), decarboxy-11D3 (**43**) and 11-hydroxy-11D5 (**48**).

Experimental Section

General: Commercially available reagents and solvents were used throughout without further purification, except tetrahydrofuran (benzophenone/Na still). Diethyl ether were purchased dry from commercial suppliers. Light petroleum refers to the fraction with bp 40-60 ºC. Thin layer chromatography was carried out on Merck Kieselgel 60 GF254 aluminium foil backed plates. The plates were visualized under UV light and/or anisaldehyde stain. Flash chromatography was carried out using Merck Kieselgel 60 H silica or Matrix silica 60, with the eluent specified. IR spectra were recorded using Perkin Elmer FTIR Spectrometer (Paragon 100) as solutions using chloroform as solvent. ^1H and ^{13}C NMR spectra were recorded using Bruker 400 MHz NMR machine (^1H 400 MHz, ^{13}C frequencies 100 MHz respectively); chemical shifts are quoted in ppm and coupling constants, *J*, are quoted in Hz; d-Chloroform was used throughout unless otherwise stated. Spectra were calibrated to residual solvent peaks. High resolution mass spectra were carried out on a Thermofisher exactive (orbi) resolution mass spectrometer. (±)-Oct-1-yn-3-ol,[19a] (±)-tridec-12-en-1-yn-3-ol,[19b] (±)-tetradic-1-yn-3-ol[19c] and (±)-12-((tert-butyldiphenylsilyl)oxy)dodecanal[19d] and methyl 3-oxooctanoate (**31**)[19e] were prepared using literature methods.

General method for the preparation of carbonates

To a stirred solution of propargyl alcohol (1 equiv.) and pyridine (10 equiv.) in dichloromethane (50 mL) was added dropwise chloroformate (4 equiv.) at 0°C and the stirring was continued for 2.5 h at the same temperature. The reaction mixture was diluted with saturated aq. NH_4Cl (30 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organics were washed with brine (100 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The title compound was isolated by column chromatography.

(±)-Benzyl (1-phenylprop-2-yn-1-yl) carbonate (18).[20a] To a stirred solution of 1-phenyl-2-propyn-1-ol (0.520 g, 3.95 mmol) and pyridine (2.5 mL, 32 mmol) in dichloromethane (50 mL) was added dropwise benzyl chloroformate (2.0 g, 12 mmol) at 0°C and the stirring was continued for 2.5 h at the same temperature. The reaction mixture was diluted with saturated aq. NH_4Cl (30 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organics were washed with brine (100 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The title compound was isolated by column chromatography (19:1, light petroleum: ethyl acetate) yielding the title compound **18** a colourless liquid (0.841 g, 3.16 mmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57 - 7.24 (10H, m), 6.31 (1H, d, *J* = 2.0 Hz), 5.21 (1H, d, *J* = 11.6 Hz), 5.18 (1H, d, *J* = 11.6 Hz), 2.73 (1H, d, *J* = 2.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.2, 135.8, 134.9, 129.4, 128.8, 128.7, 128.4, 128.4, 127.8, 79.6, 76.6, 70.2, 69.5 ppm; IR (neat) 3289, 3090, 3066, 3035, 2127, 1748, 1650 cm^{-1}; HRMS (ESI-pos) *m/z* [M + Na$^+$] calcd for $C_{17}H_{14}O_3$, 289.0835; found 289.0829.

(±)-Methyl (1-phenylprop-2-yn-1-yl) carbonate (21).[20b] Using the general procedure with 1-phenyl-2-propyn-1-ol (0.270 g, 2.05 mmol), and methyl chloroformate the title compound was isolated by column chromatography (25:1, hexane: ethyl acetate) yielding the title compound **21** a colourless liquid (0.331 g, 1.74 mmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55 - 7.53 (2H, m), 7.40-7.36 (3H, m), 6.28 (1H, d, *J* = 2.0 Hz), 3.80 (3H, s), 2.71 (1H, d, *J* = 2.4 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.9, 135.8, 129.4, 128.8, 127.7, 79.6, 76.7, 76.5, 55.2 ppm; IR (neat) 3303, 3036, 2255, 1747, 1322, 1257 cm^{-1}; HRMS (ESI-pos) *m/z* [M + H$^+$] calcd for $C_{11}H_{10}O_3$, 191.0703; found 191.0701.

(±)-Methyl oct-1-yn-3-yl carbonate (24). Using the general procedure with (±)-oct-1-yn-3-ol[19a] (0.352 g, 2.79 mmol) and methyl chloroformate, the title compound **23** was isolated by column chromatography (25:1, hexane: ethyl acetate) (0.418 g, 2.46 mmol, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.18 (1H, td, *J* = 4.8 Hz and 2.4 Hz), 3.79 (3H, s), 2.50 (1H, d, *J* = 2.4 Hz), 1.83 - 1.77 (2H, m), 1.55 - 1.27 (6H, m), 0.88 (3H, t, *J* = 6.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.5, 80.6, 77.4, 76.2, 55.05, 34.6, 31.2, 24.5, 22.5, 14.0 ppm; IR (neat) 3295, 2957, 2937, 2862, 2124, 1752, 1443 cm^{-1}; HRMS (ESI-pos) *m/z* [M + H$^+$] calcd for $C_{10}H_{16}O_3$, 185.1172; found 185.1171.

(±)-Methyl tridec-12-en-1-yn-3-yl carbonate (33). Using the general procedure with (±)-tridec-12-en-1-yn-3-ol[19b] (0.676 g, 3.50 mmol) and methyl chloroformate, the title compound **33** was isolated by column chromatography (19:1, light petroleum: ethyl acetate) as a pale-yellow liquid (0.634 g, 2.76 mmol, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.83 (1H, ddt, *J* = 17.6, 8.0 and 6.8 Hz), 5.21 (1H, td, *J* = 6.4 and 2.0 Hz), 5.04 - 4.93 (2H, m), 3.83 (3H, s), 2.53 (1H, s), 2.08 - 2.03 (2H, m), 1.89 - 1.77 (2H, m), 1.48 - 1.41 (2H, m), 1.41 - 1.24 (10H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.0, 139.2, 114.1, 80.1, 74.9, 67.9, 54.9, 34.5, 33.8, 29.3, 29.07, 29.03, 28.9, 24.7 ppm; IR (neat) 3295, 3077, 2927, 2855, 1753, 1640, 1442, 1265, 910 cm^{-1}; HRMS (ESI-pos) *m/z* [M + Na$^+$] calcd for $C_{15}H_{24}O_3$, 275.1618; found 275.1617.

(±)-Methyl tetradec-1-yn-3-yl carbonate (36). Using the general procedure with (±)-tetradic-1-yn-3-ol[19c] (1.796 g, 8.323 mmol) and methyl chloroformate, the title compound **33** was isolated by column chromatography (19:1, light petroleum: ethyl acetate) as colourless liquid (1.851 g, 6.906 mmol, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.18 (1H, td, *J* = 6.4 and 2.0 Hz), 3.79 (3H, s), 2.49 (1H, d, *J* = 2.0 Hz), 1.81 - 1.78 (2H, m), 1.50 - 1.40 (2H, m), 1.28 - 1.24 (16H, m), 0.86 (3H, t, *J* = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.0, 80.6, 74.4, 68.0, 55.0, 34.6, 31.9, 29.6, 29.6, 29.5, 29.5, 29.4, 29.1, 24.8, 22.7, 14.2 ppm; IR (neat) 3309, 3155, 2924, 2854, 1751, 1273 cm^{-1}; HRMS (ESI-pos) *m/z* [M + H$^+$] calcd for $C_{16}H_{27}O_3$, 269.2111; found 269.2110.

(±)-14-((tert-Butyldiphenylsilyl)oxy)tetradec-1-yn-3-yl methyl carbonate (28). Ethynylmagnesium bromide (3.6 mL, 1.8 mmol, 0.5 M in THF) was added to a solution of 12-((tert-butyldiphenylsilyl)oxy)dodecanal[19d] (0.610 g, 1.39 mmol) in THF (3 mL) at 0°C. The reaction was allowed to warm to room temperature and stirred for 3 h. After addition of saturated aq. NH_4Cl (10 mL), the organic phrase is separated, and the aqueous phrase was washed with diethyl ether (3 x 10 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The residue was then purified via column chromatography (15:1, light petroleum: ethyl acetate) yielding the propargyl alcohol as a colourless oil (0.561 g, 1.15 mmol, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68 - 7.67 (4H, m), 7.46 - 7.37 (6H, m), 4.39 (1H, td, *J* = 2.0 Hz and 6.4 Hz), 3.67 (2H, t, *J* = 6.4 Hz), 2.48 (1H, s), 1.77 - 1.70 (2H, m), 1.61 - 1.54 (4H, m), 1.36 - 1.27 (14H, m), 1.06 (9H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 135.6, 134.2, 129.4, 127.5, 85.0, 72.8, 64.0, 62.3, 37.6, 32.6, 29.6, 29.6, 29.5, 29.5, 29.3, 29.2, 26.8, 25.7, 25.0, 19.2 ppm; IR (neat) 3402, 3302, 3155, 2931, 2252, 1103 cm^{-1}; HRMS (ESI-pos) *m/z* [M + H$^+$] calcd for $C_{30}H_{44}O_2Si$, 465.3183; found 465.3177. Methyl chloroformate (0.305 g, 3.23 mmol) was added to a cooled (0°C) solution of propargylic alcohol (0.500 g, 1.08 mmol) and pyridine (0.8 mL, 8 mmol) in dichloromethane (13 mL). The reaction was allowed to stir at the same temperature for 3 h. The reaction mixture was diluted with saturated aq. NH_4Cl (10 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organics were washed with brine (50 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The title compound **28** was isolated by column chromatography (19:1, light petroleum: ethyl acetate) yielding a colourless liquid (0.464 g, 0.889 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.71 - 7.68 (4H, m), 7.46 - 7.37 (6H, m), 5.22 (1H, td, *J* = 2.0 Hz and 6.8 Hz), 3.83 (3H, s), 3.67 (2H, t, *J* = 6.4 Hz), 2.53 (1H, s), 1.87 - 1.81 (2H, m), 1.61 - 1.47 (4H, m), 1.36 - 1.27 (14H, m), 1.07 (9H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.0, 135.6, 134.2, 129.4, 127.5, 80.6, 74.4, 67.9, 64.0, 55.0, 34.6, 32.6, 29.6, 29.6, 29.5, 29.4, 29.3, 29.0, 26.8, 25.7, 24.7, 19.2 ppm; IR (neat) 2931, 2854, 2252, 1751, 1273 cm^{-1}; HRMS (ESI-pos) *m/z* [M + H$^+$] calcd for $C_{32}H_{46}O_2Si$, 523.3238; found 523.3232.

General method for furan formation. To a stirred solution of the methyl carbonate (1 equiv.) in THF was added the 1,3-dicarbophile (1 equiv.), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol%) and DPPE (10 mol%) at RT and stirring was continued for 3 h at 50°C under argon atmosphere. To the reaction mixture was then added 1M HCl (2 mL), and further stirring was continued for 2 h at room temperature. After filtration of the reaction mixture using small amount of silica gel followed by concentration, the residue was chromatographed on silica gel to give the title compounds.

Methyl 2,4-dimethyl-5-phenylfuran-3-carboxylate (20).[14b] To a stirred solution of methyl (1-phenylprop-2-yn-1-yl) carbonate **21** (0.474 g, 1.78 mmol) in THF (10 mL) were added methyl acetoacetate **19** (0.196 g, 1.69 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.087 g, 0.084 mmol) and DPPE (0.067 g, 0.17 mmol) at room temperature, and stirring was continued for 3 h at 50°C under argon atmosphere. The reaction mixture was then added 1M HCl (2 mL), and further stirring was continued for 2 h at room temperature. After filtration of the reaction mixture using small amount of silica gel followed by concentration, the residue was chromatographed on silica gel (9:1, light petroleum: ethyl acetate) to give the title compound **20** a yellow oil (0.341 g, 1.44 mmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 - 7.56 (2H, m), 7.42 - 7.24 (3H, m), 3.84 (3H, s), 2.59 (3H, s), 2.38 (3H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 158.3, 147.8, 131.0, 128.5, 128.4, 127.2, 126.1, 116.9, 115.2, 51.1, 14.5, 10.9 ppm; IR (neat) 2955, 1740, 1441 cm^{-1}; HRMS (ESI-pos) *m/z*: [M + H$^+$] calcd for $C_{14}H_{14}O_3$, 231.1016; found 231.1014.

1-(2,4-Dimethyl-5-phenylfuran-3-yl)ethan-1-one (23). Starting from propargylic carbonate **21** (0.074 g, 0.28 mmol) and acetylacetone **22** (0.028 g, 0.28 mmol) in THF (2 mL), the above general procedure gave the title compound **23** as a yellow oil (0.049 g, 0.23 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 - 7.54 (2H, m), 7.43 - 7.27 (3H, m), 2.61 (3H, s), 2.47 (3H, s), 2.38 (3H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.2, 157.3, 148.0, 130.7, 129.0, 128.6, 127.4, 124.5, 116.2, 31.1, 15.4, 11.5 ppm; IR (neat) 3058, 2962,1955, 1666, 1072, 765 cm^{-1}; HRMS (ESI-pos) *m/z*: [M + H$^+$] calcd for $C_{14}H_{14}O_2$, 215.1067; found, 215.1063.

Methyl 2,4-dimethyl-5-pentylfuran-3-carboxylate (25). Following general procedure using methyl oct-1-yn-3-yl carbonate **24** (0.10 g, 0.54 mmol) and methyl acetoacetate **19** (0.063 g, 0.54 mmol), the title compound **25** was isolated by column chromatography (19:1, hexane: ethyl acetate) yielding a pale yellow oil (0.098 g, 0.44 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.78 (3H, s), 2.48 (2H, t, *J* = 8.0 Hz), 2.04 (3H, s), 1.56 - 1.52 (2H, m), 1.29 - 1.23 (4H, m), 0.86 (3H, t, *J* = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 157.5, 150.1, 114.4, 113.8, 51.0, 31.3, 28.2, 25.5, 22.4, 14.3, 14.1, 9.9 ppm; IR (neat) 2954, 2859, 1749, 1583, 1090 cm^{-1}; HRMS (ESI-pos) *m/z*: [M + H$^+$] calcd for $C_{13}H_{20}O_3$, 225.1485; found, 225.1484.

Ethyl 4-methyl-5-pentyl-2-propylfuran-3-carboxylate (27). Following general procedure using methyl oct-1-yn-3-yl carbonate **24** (0.092 g, 0.50 mmol) and ethyl 3-oxohexanoate **26** (0.079 g, 0.50 mmol), the title compound **27** was isolated by column chromatography (19:1, hexane: ethyl acetate) yielding a pale yellow oil (0.116 g, 0.435 mmol, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.24 (2H, q, *J* = 7.2 Hz), 2.86 (2H, t, *J* = 7.6 Hz), 2.48 (2H, t, *J* = 7.6 Hz), 2.04 (3H, s), 1.65 - 1.63 (2H, m), 1.60 - 1.54 (2H, m), 1.31 (3H, t, *J* = 7.2 Hz),1.30 - 1.25 (4H, m), 0.92 (3H, t, *J* = 7.2 Hz), 0.85 (3H, t, *J* = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 161.2, 150.0, 114.3, 113.3, 59.6, 31.2, 30.6, 28.2, 25.5, 22.4, 21.7, 14.3, 14.0, 13.8, 9.9 ppm; IR (neat) 2960, 2862, 1712, 1576, 1080 cm^{-1}; HRMS *m/z*, HRMS (ESI-pos) *m/z*: [M + H$^+$] calcd for $C_{16}H_{26}O_3$, 267.1955; found 267.1952.

Ethyl 5-(11-((tert-butyldiphenylsilyl)oxy)undecyl)-4-methyl-2-propylfuran-3-carboxylate (30). Following general procedure using ethyl 3-oxohexanoate **26** (0.041 g, 0.26 mmol) and propargylic carbonate **28** (0.133 g, 0.254 mmol), the title compound **30** was obtained by column chromatography (19:1, light petroleum: ethyl acetate) as a yellow oil (0.142 g, 0.236 mmol, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 - 7.64 (4H, m), 7.43 - 7.35 (6H, m), 4.26 (2H, q, *J* = 7.2 Hz), 3.65 (2H, t, *J* = 6.4 Hz), 2.88 (2H, t, *J* = 8.0 Hz), 2.50 (2H, t, *J* = 7.2 Hz), 2.07 (3H, s), 1.70 - 1.60 (2H, m), 1.57 - 1.53 (4H, m), 1.33 (3H, t, *J* = 7.2 Hz), 1.38 - 1.27 (14H, m), 1.05 (9H, s), 0.93 (3H, t, *J* = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 161.3, 150.1, 135.6, 134.2, 129.5, 127.6, 114.3, 113.4, 64.1, 59.6, 32.6, 30.1, 29.7, 29.6, 29.4, 29.1, 28.5, 26.9, 25.8, 25.5, 21.7, 19.3, 14.2, 13.9, 10.0 ppm; IR (neat) 3050, 2958, 2855, 1712, 1576 cm^{-1}; HRMS (ESI-pos) *m/z*: [M + H$^+$] calcd for $C_{38}H_{56}O_4Si$, 605.4021; found 605.4016.

Methyl 5-(11-((tert-butyldiphenylsilyl)oxy)undecyl)-4-methyl-2-pentylfuran-3-carboxylate (32). Following general procedure using β-keto **31**[19e] (0.080 g, 0.47 mmol) and propargylic carbonate **28** (0.238 g, 0.455 mmol) the title compound **32** was obtained by column chromatography (20:1, light petroleum: ethyl acetate) as a yellow oil (0.217 g, 0.350 mmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 - 7.68 (4H, m), 7.46 - 7.35 (6H, m), 3.89 (3H, s), 3.66 (2H, t, *J* = 6.4 Hz), 2.91 (2H, t, *J* = 6.4 Hz), 2.52 (2H, t, *J* = 7.6 Hz), 2.07 (3H, s), 1.66 - 1.53 (6H, m), 1.40 - 1.27 (18H, m), 1.06 (9H, s), 0.95 (3H, t, *J* = 6.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.6, 150.0, 135.5, 134.1, 129.4, 127.5, 114.2, 64.0, 50.8, 32.6, 31.4, 29.6, 29.6, 29.3, 29.0, 28.5, 27.99, 27.90, 26.8, 25.7, 25.5, 22.3, 19.2, 14.0, 9.9 ppm; IR (neat) 3071, 3049, 2924, 2854, 1715, 1576 cm^{-1}; HRMS (ESI-pos) *m/z*: [M + Na$^+$] calcd for $C_{39}H_{58}O_4Si$, 641.3997; found 641.3985.

Ethyl 5-(dec-9-en-1-yl)-4-methyl-2-propylfuran-3-carboxylate (34). Following general procedure using ethyl 3-oxohexanoate **26** (0.252 g, 1.43 mmol) and propargylic carbonate **33** (0.360 g, 1.43 mmol) the title compound **34** was obtained by column chromatography (19:1, light petroleum: ethyl acetate) as a yellow oil (0.383 g, 1.15 mmol, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.83 (1H, ddt, *J* = 17.6, 8.0 and 4.4 Hz), 4.99 - 4.90 (2H, m), 4.25 (2H, t, J = 7.2 Hz), 2.86 (2H, t, *J* = 7.2 Hz), 2.48 (2H, t, *J* = 7.2 Hz), 2.48 (2H, t, *J* = 7.2 Hz), 2.04 (3H, s), 2.04 - 2.01 (2H, m), 1.67 - 1.52 (2H, m), 1.40 - 1.22 (13H, m), 0.91 (3H, t, *J* = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 161.3, 150.0, 139.3, 114.3, 114.1, 59.6, 33.8, 30.8, 29.4, 29.3, 29.1, 29.0, 28.9, 28.5, 25.5, 21.7, 14.4, 13.8, 9.9 ppm; HRMS (ESI-pos) *m/z*: [M + H$^+$] calcd for $C_{21}H_{34}O_3$, 335.2581; found, 335.2587.

Methyl 5-(dec-9-en-1-yl)-4-methyl-2-pentylfuran-3-carboxylate (35). Following general procedure using β-keto **31**[19e] (0.265 g, 1.54 mmol) and propargylic carbonate **33** (0.581 g, 2.32 mmol) the title compound **35** was obtained by column chromatography (19:1, light petroleum: ethyl acetate) as a yellow oil (0.480 g, 1.38 mmol, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.83 (1H, ddt, *J* = 17.6, 8.0 and 4.4 Hz), 5.32 - 4.93 (2H, m), 3.82 (3H, s), 2.91 (2H, t, *J* = 7.2 Hz), 2.52 (2H, t, *J* = 7.2 Hz), 2.07 (3H, s), 2.06 - 2.02 (2H, m), 1.68 - 1.55 (4H, m), 1.49 - 1.20 (14H, m), 0.89 (3H, t, *J* = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 161.6, 150.1, 139.3, 114.2, 114.1, 113.0, 50.9, 33.8, 31.4, 29.4, 29.3, 29.1, 29.0, 28.9, 28.5, 28.0, 27.9, 25.5, 22.4, 14.0, 8.9 ppm; HRMS (ESI-pos) *m/z*: [M + H$^+$] calcd for $C_{22}H_{36}O_3$, 349.2737; found, 349.2738.

Ethyl 4-methyl-2-propyl-5-undecylfuran-3-carboxylate (37). Following general procedure using ethyl 3-oxohexanoate **26** (0.749 g, 4.74 mmol) and propargylic carbonate **36** (0.847 g, 3.16 mmol) the title compound **37** was obtained by column chromatography (20:1, light petroleum: ethyl acetate) as yellow oil (0.940 g, 2.69 mmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.25 (2H, q, *J* = 7.2 Hz), 2.86 (2H, t, *J* = 7.6 Hz), 2.48 (2H, t, *J* = 7.6 Hz), 2.04 (3H, s), 1.69 - 1.59 (2H, m), 1.56 - 1.51 (2H, m), 1.32 (3H, t, *J* = 7.2 Hz), 1.30 - 1.23 (16H, m), 0.91 (3H, t, *J* = 7.6 Hz), 0.86 (3H, t, *J* = 7.6 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 161.3, 150.1, 114.3, 113.3, 59.6, 31.9, 30.0, 29.7, 29.6, 29.4, 29.1, 28.5, 25.5, 22.7, 21.7, 14.4, 14.2, 13.8, 9.9 ppm; IR (neat) 3055, 2854, 2685, 1705, 1265 cm^{-1}; HRMS (ESI-pos) *m/z*: [M + H$^+$] calcd for $C_{22}H_{27}O_3$, 351.2894; found, 351.2893.

General method for ester reduction. To a cooled solution of ester (2 equiv.) at 0°C in THF was added $LiAlH_4$ (2 equiv. of 1 M in THF). After being stirring at the same temperature for 2h, the reaction was quenched by the carefully addition of methanol (0.5 mL) and water (0.5 mL). After 30 min. at room temperature, the reaction mixture was then poured into diethyl ether (10 mL), dried over $MgSO_4$ and filtered. The unfiltered residue was extracted with diethyl ether (4 x 5 mL) and all extracts were combined and evaporated under reduced pressure. The title compounds were then isolated by column chromatography.

(5-(11-((tert-Butyldiphenylsilyl)oxy)undecyl)-4-methyl-2-pentylfuran-3-yl)methanol (46). To a cooled solution of ester **32** (0.544 g, 0.880 mmol) at 0°C in THF (3.5 mL) was added $LiAlH_4$ (1.76 mL, 1.76 mmol, 1 M in THF). After being stirring at the same temperature for 2h, the reaction was quenched by the carefully addition of methanol (0.5 mL) and water (0.5 mL). After 30 min at room temperature, the reaction mixture was then poured into diethyl ether (10 mL), dried over $MgSO_4$ and filtered. The unfiltered residue was extracted with diethyl ether (4 x 5 mL) and all extracts were combined and evaporated under reduced pressure. The title compound **46** was isolated by column chromatography (4:1, light petroleum: ethyl acetate) yielding a colourless oil (0.478 g, 0.810 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 - 7.71 (4H, m), 7.47 - 7.39 (6H, m), 4.45 (2H, s), 3.70 (2H, t, *J* = 6.4 Hz), 2.61 (2H, t, *J* = 7.2 Hz), 2.54 (2H, t, *J* = 7.2 Hz), 1.99 (3H, s), 1.67 - 1.55 (6H, m), 1.40 -1.27 (18H, m), 1.09 (9H, s), 0.93 (3H, t, *J* = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.2, 149.5, 135.6, 134.2, 129.5, 127.5, 119.1, 113.6, 64.0, 55.4, 32.6, 31.4, 29.7, 29.6, 29.5, 29.4, 29.2, 28.8, 28.7, 26.9, 26.0, 25.9, 25.8, 22.4, 19.2, 14.0, 8.1 ppm; HRMS (ESI-pos) *m/z*: [M + H$^+$] calcd for $C_{38}H_{58}O_3Si$, 591.4228; found, 591.4221.

(5-(Dec-9-en-1-yl)-4-methyl-2-propylfuran-3-yl)methanol (40). Following general procedure, furan ester **34** (0.740 g, 2.22 mmol) was reduced to give the title compound **40** after column chromatography (8:1, light petroleum: ethyl acetate) as a pale-yellow oil (0.584 g, 1.86 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.83 (1H, ddt, *J* = 17.6, 8.0 and 4.4 Hz), 5.04 - 4.93 (2H, m), 4.43 (2H, s), 2.57 (2H, t, *J* = 7.2 Hz), 2.51 (2H, t, *J* = 7.2 Hz), 2.06 (2H, t, *J* = 7.2 Hz), 1.97 (3H, s), 1.68 - 1.58 (4H, m), 1.37 - 1.26 (10H, m), 0.94 (3H, t, *J* = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.0, 149.6, 139.2, 119.3, 114.1, 113.5, 55.9, 33.8, 29.4, 29.3, 29.2,

29.1, 28.9, 28.6, 28.0, 25.9, 22.3, 13.7, 8.1 ppm; HRMS (ESI-pos) *m/z*: [M + H$^+$] calcd for $C_{19}H_{32}O_2$, 315.2295; found, 315.2289.

(5-(Dec-9-en-1-yl)-4-methyl-2-pentylfuran-3-yl)methanol (38). Following general procedure, furan ester **35** (0.452 g, 1.29 mmol) was reduced to give the title compound **38** after column chromatography (9:1, light petroleum: ethyl acetate) as a colourless oil (0.347 g, 1.08 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.83 (1H, ddt, *J* = 17.6, 8.0 and 4.4 Hz), 4.99 - 4.90 (2H, m), 4.33 (2H, s), 2.54 (2H, t, *J* = 7.2 Hz), 2.47 (2H, t, *J* = 7.2 Hz), 2.01 (2H, t, *J* = 7.2 Hz), 1.97 (3H, s), 1.57 - 1.55 (4H, m), 1.49 - 1.20 (14H, m), 0.87 (3H, t, *J* = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.3, 149.6, 139.3, 119.2, 114.1, 113.6, 55.5, 33.8, 31.4, 29.5, 29.4, 29.2, 29.1, 28.9, 28.8, 28.71, 26.1, 25.9, 22.4, 14.0, 8.2 ppm; IR (neat) 3325, 3073, 2925, 1641, 1465, 993 cm^{-1}; HRMS (ESI-pos) *m/z*: [M + Na$^+$] calcd for $C_{21}H_{36}O_2$, 343.2606; found, 343.2608.

(4-Methyl-2-propyl-5-undecylfuran-3-yl)methanol (42). Following general procedure, furan ester **37** (0.845 g, 2.414 mmol) was reduced to give the title compound **42** after column chromatography (10:1, light petroleum: ethyl acetate) as a colourless oil (0.595 g, 1.93 mmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.40 (2H, s), 2.53 (2H, t, *J* = 7.6 Hz), 2.47 (2H, t, *J* = 7.2Hz), 1.93 (3H, s), 1.62 - 1.52 (4H, m), 1.30 - 1.27 (16H, m), 0.89 (3H, t, *J* = 7.2 Hz), 0.84 (3H, t, *J* = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.1, 149.7, 119.4, 113.6, 55.5, 32.0, 29.7, 29.6, 29.4, 29.3, 28.7, 28.1, 25.9, 22.7, 22.3, 14.2, 13.8, 8.2 ppm; IR (neat) 3410, 3155, 2924, 2854, 1465 cm^{-1}; HRMS (ESI-pos) *m/z*: [M + H$^+$] calcd for $C_{20}H_{36}O_2$, 309.2788; found, 309.2786.

(4-Methyl-2-pentyl-5-undecylfuran-3-yl)methanol (44). Following general procedure, crude furan ester obtained from *β*-keto **31**[19e] (0.059 g, 0.341 mmol) and propargylic carbonate **36** (0.092 g, 0.342 mmol) was reduced to give the title compound **44** after column chromatography (15:1, light petroleum: ethyl acetate) as colourless oil (0.060 g, 0.19 mmol, 55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.43 (2H, s), 2.58 (2H, t, *J* = 7.2 Hz), 2.51 (2H, t, *J* = 7.2 Hz), 1.97 (3H, s), 1.62 - 1.56 (4H, m), 1.33 - 1.27 (20H, m), 0.92 - 0.76 (6H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.2, 149.5, 119.1, 113.5, 55.5, 31.9, 31.4, 29.68, 29.66, 29.63, 29.4, 29.3, 29.2, 28.7, 28.6, 26.0, 25.9, 22.7, 22.4, 14.1, 14.0, 8.1 ppm; IR (neat) 3417, 3387, 3305, 3155, 2924, 1465 cm^{-1}; HRMS (ESI-pos) *m/z*: [M + H$^+$] calcd for $C_{22}H_{40}O_2$, 321.3152; found, 321.3164

2-(Dec-9-en-1-yl)-3,4-dimethyl-5-propylfuran (41). To a stirred, cooled (0°C) solution of furan alcohol **40** (0.505 g, 1.73 mmol), recrystallized triphenylphosphine (0.590 g, 2.249 mmol), and imidazole (0.153 g, 2.246 mmol) in acetonitrile and diethyl ether (1:1.6, 3.6 mL) was slowly added iodine (0.609 g, 2.422 mmol) giving a yellow suspension. After stirring at the same temperature for 1 h, the reaction mixture was diluted with diethyl ether (5 mL) and sequentially washed with saturated aq. $Na_2S_2O_3$, sat. $CuSO_4$, and H_2O. The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford the crude product as a brown oil. The residue was taken up in THF (3.5 mL) and treated with $LiAlH_4$ (3.5 ml, 3.5 mmol, 1 M in THF) at 0°C for 4 h. The reaction was quenched by the carefully addition of methanol (1 mL) and water (1 mL). After 1 h at room temperature, the reaction mixture was then poured into diethyl ether (20 mL), dried over $MgSO_4$ and filtered. The unfiltered residue was extracted with diethyl ether (4 x 10 mL) and all extracts were combined and evaporated under reduced pressure. The title compound **41** was isolated by column chromatography (19:1, light petroleum: ethyl acetate) yielding a colourless liquid (0.406 g, 1.47 mmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.80 (1H, ddt, *J* = 17.6, 8.0 and 4.4 Hz), 5.00 - 4.89 (2H, m), 2.48 - 2.43 (4H, m), 2.04 - 1.99 (2H, m), 1.81 (6H, s), 1.61 - 1.51 (4H, m), 1.37 - 1.26 (10H, m), 0.89 (3H, t, *J* = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.5, 148.3, 139.3, 114.7, 114.5, 114.1, 33.8, 29.5, 29.4, 29.2, 29.1, 29.0, 28.8, 28.1, 26.1, 22.2, 13.8, 8.4 ppm; IR (neat) 3077, 2926, 2855, 1641, 1455, 1380 cm^{-1}; HRMS (ESI-pos) *m/z*: [M + H$^+$] calcd for $C_{19}H_{31}O$, 276.2448; found, 276.2403.

2-(Dec-9-en-1-yl)-3,4-dimethyl-5-pentylfuran (39).[10a,b] Using the above procedure, furan alcohol **38** (0.452 g, 1.292 mmol) was reduced to give title compound **39** after column chromatography (19:1, light petroleum: ethyl acetate) as a colourless oil (0.328 g, 1.08 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.82 (1H, ddt, *J* = 17.6, 8.0 and 4.4 Hz), 4.99 - 4.89 (2H, m), 2.48 - 2.44 (4H, m), 2.01 (2H, q, *J* = 7.2 Hz), 1.97 (3H, s), 1.57 - 1.55 (4H, m), 1.49 - 1.20 (14H, m), 0.87 (3H, t, *J* = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.5, 148.5, 139.3, 114.5, 114.1, 33.8, 31.5, 29.5, 29.4, 29.4, 29.3, 29.2, 29.0, 28.8, 28.5, 26.1, 22.5, 14.1, 8.4 ppm; IR (neat) 3033, 2928, 2856, 1654, 1428 cm^{-1}; HRMS (ESI-pos) *m/z*: [M + H$^+$] calcd for $C_{21}H_{36}O$, 305.2839; found, 305.2836

3,4-Dimethyl-2-propyl-5-undecylfuran (43). Using the above procedure, furan alcohol **42** (0.38 g, 1.225 mmol) was reduced to give title compound **43** after column chromatography (0.380 g, 1.225 mmol) was obtained the title compound by column chromatography (20:1, light petroleum: ethyl acetate) as a colourless oil (0.314 g, 0.992 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.54 - 2.47 (4H, m), 1.85 (6H, s), 1.69 - 1.55 (4H, m), 1.30-1.27 (16H, m), 0.94 (3H, t, *J* = 7.2 Hz), 0.85 (3H, t, *J* = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.4, 148.2, 114.6, 114.4, 31.9, 29.7, 29.7, 29.6, 29.6, 29.4, 29.3, 28.8, 28.0, 26.1, 22.9, 22.1, 14.1, 13.8, 8.3 ppm; IR (neat) 3309, 3155, 2924, 1465 cm^{-1}; HRMS (ESI-pos) *m/z*: [M + H$^+$] calcd for $C_{20}H_{36}O$, 293.2839; found, 293.2853

3,4-Dimethyl-2-pentyl-5-undecylfuran (45). Using the above procedure, furan alcohol **44** (60 mg, 0.19 mmol) was reduced to give title compound **45** after column chromatography (25:1, light petroleum: ethyl acetate) as a colourless oil (48 mg, 0.152 mmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.50 (4H, t, *J* = 7.6 Hz), 1.85 (6H, s), 1.62 - 1.54 (4H, m), 1.33 - 1.27 (20H, m), 0.92 - 0.88 (6H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.5, 148.4, 114.4, 31.9, 31.4, 29.7, 29.7, 29.6, 29.4, 29.3, 29.2, 28.8, 28.5, 26.1, 26.0, 22.7, 22.5, 14.2, 14.1, 8.4 ppm; IR (neat) 3055, 2931, 2854, 1427 cm^{-1}; HRMS (ESI-pos) *m/z*: [M + Na$^+$] calcd for $C_{22}H_{40}O$, 407.3132; found, 407.3143.

11D3 (F_4) 11-(3,4-dimethyl-5-propylfuran-2-yl)undecanoic acid (1d).[8a] Hoveyda-Grubbs Catalyst 2nd (0.04 g, 0.05 mmol) was added to a stirred solution of furan **41** (0.260 g, 0.942 mmol) in dichloromethane (15 mL). Benzyl acrylate (0.210 g, 1.30 mmol) was added and the solution refluxed under argon for 3 h. The solution was filtered through a plug of silica and the solvent evaporated to yield a brown oil. The residue was taken up in methanol (10 mL) and treated with 10% palladium on carbon (0.150 g). The reaction was stirred under an atmosphere of hydrogen for 2 h then the catalyst removed by filtration. The solvent was removed under reduced pressure. The title compound **1d** was isolated by column chromatography (8:1, 4:1, 2:1, 1:1, light petroleum: ethyl acetate) yielding a colourless oil (0.272 g, 0.848 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.52 - 2.47 (4H, m), 2.37 (2H, t, *J* = 7.6 Hz), 1.85 (6H, s), 1.69 - 1.55 (6H, m), 1.41 - 1.23 (12H, m), 0.98 (3H, t, *J* = 6.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.9, 148.4, 148.2, 114.6, 114.4, 34.0, 30.3, 29.5, 29.4, 29.3, 29.25, 29.24, 29.0, 28.8, 28.1, 26.0, 24.6, 22.1, 13.8, 8.3 ppm; IR (neat) 3583, 3400, 2927, 2855, 2087, 1709, 1651 cm^{-1}; HRMS (ESI-pos) *m/z*: [M + H$^+$] calcd for $C_{20}H_{35}O_3$, 323.2581; found, 323.2582.

11D5 (F_6) 11-(3,4-dimethyl-5-pentylfuran-2-yl)undecanoic acid (1f).[10a,b] Using the above procedure and furan **39**, the title compound **1f** was isolated by column chromatography (8:1, 4:1, 2:1, 1:1, light petroleum: ethyl acetate) as a colourless oil (0.105 g, 0.300 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.52 - 2.47 (4H, m), 2.37 (2H, t, *J* = 7.6 Hz), 1.85 (6H, s), 1.69 - 1.63 (2H, m), 1.58 - 1.56 (4H, m), 1.36 - 1.29 (18H, m), 0.90 (3H, t, *J* = 6.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.7, 148.4, 148.4, 114.4, 34.2, 31.4, 30.3, 29.5, 29.4, 29.4, 29.3, 29.2, 29.0, 28.8, 28.5, 26.1, 26.0, 24.7, 22.4, 14.0, 8.4, 8.3 ppm; IR (neat) 3584, 3400, 2926, 2855, 1710, 1456, 1329 cm^{-1}; HRMS (ESI-pos) *m m/z*: [M + H$^+$] calcd for $C_{22}H_{38}O_3$, 351.2894; found, 351.2896

tert-Butyl((11-(3,4-dimethyl-5-pentylfuran-2-yl)undecyl)oxy)diphenylsilane (47). To a stirred, cooled (0°C) solution of alcohol **46** (0.04 g, 0.07 mmol), TEA (0.021 g, 0.21 mmol) and DMAP (0.002 g, 0.02 mmol) in dichloromethane (2 mL) was added 4-

toluenesulfonyl chloride (0.027 g, 0.14 mmol). The reaction mixture was stirred at 0°C for 24 h. Water (4 mL) was added, and then the organic phrase was washed with saturated aq. $NaHCO_3$ (4 mL) followed by brine. The organic phrase was collected and dried over $MgSO_4$, filtered, and the solvent evaporated under reduced pressure. The residue was dissolved in THF (3.5 mL), and then a solution of $LiAlH_4$ (0.2 mL, 0.2 mmol, 1 M in THF) was added dropwise at 0°C. After being stirring at the same temperature for 2 h, the reaction was quenched by the careful addition of methanol (0.5 mL) and water (0.5 mL). After 30 min at room temperature, the reaction mixture was then poured into diethyl ether (5 mL), dried over $MgSO_4$ and filtered. The solid residue was extracted with diethyl ether (4 x 5 mL) and all extracts were combined and evaporated under reduced pressure. The title compound **47** was isolated by column chromatography (90:1, light petroleum: ethyl acetate) yielding a colourless oil (0.012 g, 0.021 mmol, 30%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 - 7.68 (4H, m), 7.44 - 7.28 (6H, m), 3.67 (2H, t, *J* = 6.4 Hz), 2.51 (4H, t, *J* = 7.2 Hz), 1.86 (6H, s), 1.62 - 1.54 (6H, m), 1.40 - 1.27 (18H, m), 1.07 (9H, s), 0.91 (3H, t, *J* = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.5, 148.4, 135.7, 134.2, 129.4, 127.8, 114.4, 64.0, 32.6, 31.9, 29.6, 29.5, 29.5, 29.4, 29.2, 28.9, 28.8, 26.8, 26.8, 26.1, 26.0, 25.7, 22.4, 19.2, 14.1, 8.3, 8.3 ppm; HRMS (ESI-pos) *m/z*: [M + H$^+$] calcd for $C_{38}H_{58}O_2Si$, 575.4284; found, 575.4286.

11-(3,4-Dimethyl-5-pentylfuran-2-yl)undecan-1-ol (48). To a stirred, cooled (0°C) solution of the furan **47** (0.030 g, 0.058 mmol) in THF (1.2 mL) was added TBAF (0.12 mL, 0.12 mmol, 1 M in THF). After stirring at room temperature for 3 h, the solvent was evaporated and the residue was taken up in diethyl ether and H_2O (1:1, 5 mL). The organic layer was separated, and the aqueous layer was washed with diethyl ether (3 x 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The title compound **48** was isolated by column chromatography (4:1, light petroleum: ethyl acetate) yielding a colourless oil (0.019 g, 0.055 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.66 (2H, t, *J* = 6.8 Hz), 2.50 (4H, t, *J* = 7.2 Hz), 1.80 (6H, s), 1.61 - 1.54 (6H, m), 1.39 - 1.28 (18H, m), 0.90 (3H, t, *J* = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.4, 114.4, 63.1, 32.8, 31.4, 29.7, 29.5, 29.4, 29.2, 28.8, 28.5, 26.1, 26.1, 25.7, 22.4, 14.1, 8.4, 8.3 ppm; HRMS (ESI-pos) *m/z*: [M + H$^+$] calcd for $C_{22}H_{40}O_2$, 337.3101; found, 337.3107.

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[1] (a) L. Xu, A. J. Sinclair, M. Faiza, D. Li, X. Han, H. Yin, Y. Wang, *Prog. Lipid Res.* **2017**, 68, 119; (b) G. Spiteller, *Mol. Biotechnol.* **2007**, 37, 5; (c) G. Spiteller, *Lipids* **2005**, *40*, 755.

[2] (a) Y. Okado, M. Kaneko, H. Okajima, *Biol. Pharm. Bull.* **1996**, *19*, 1607; (b) Y. Okada, H. Okajima, H. Konishi, M. Terauchi, K. Ishii, T. -M. Liu, H. Watanabe, *J. Am. Oil Chem. Soc.* **1990**, *67*, 858; (c) R. A. S. Lemke, A. C. Peterson, E. C. Ziegelhoffer, M. S. Westphall, H. Tjellström, J. J. Coon, T. J. Donohue, *Proc. Natl. Acad. Sci.* **2014**, *111*, E3450.

[3] T. Kimura, A. Tajima, Y. Inahashi, M. Iwatsuki, H. Kasai, T. Mokudai, Y. Niwano, K. Shiomi, Y. Takahashi, S. Ōmura, T. Nakashima, *J. Gen. Appl. Microbiol.* **2018**, *64*, 62.

[4] H. M. Liebich, A. Pickert, B. Tetschner, *J. Chromatogr. A* **1984**, *289*, 259.

[5] (a) K. Hannemann, V. Puchta, E. Simon, H. Ziegler, HG.Ziegler, G. Spiteller, *Lipids* **1989**, *24*, 296; (b) A. Batna, J. Scheinkönig, G. Spiteller, *Biochim. Biophys. Acta - Lipids Lipid Metab.* **1993**, *1166*, 171; (c) N. Shirasaka, K. Nishi, S. Shimizu, *Biochim. Biophys. Acta - Lipids Lipid Metab.* **1997**, *1346*, 253.

[6] (a) V. Gottstein, M. Müller, J. Günther, T. Kuballa, W. Vetter, *J. Agric. Food Chem.* **2019**, *67*, 11788; (b) M. Müller, M. Hogg, K. Ulms, W. Vetter, *J. Agric. Food Chem.* **2017**, *65*, 7919; (c) M. Englert, K. Ulms, C. Wendlinger, W. Vetter, *J. Sep. Sci.* **2016**, *39*, 490; (d) W. Vetter, S. Laure, C. Wendlinger, A. Mattes, A. W. T. Smith, D. W. Knight, *J. Am. Oil Chem. Soc.* **2012**, 89, 1501.

[7] M. Müller, K. Wasmer, W. Vetter, *J. Chromatogr. A* **2018**, *1556*, 88.

[8] (a) F. Chang, W. -H. Hsu, M. Mascal, *Sustain. Chem. Pharm.* **2015**, *1*, 14; (b) C. H. Rahn, D. M. Sand, Y. Wedmid, H. Schlenk, T. P. Krick, R. L. Glass, *J. Org. Chem.* **1979**, *44*, 3420.

[9] T. Wakimoto, H. Kondo, H. Nii, K. Kimura, Y. Egami, Y. Oka, M. Yoshida, E. Kida, Y. Ye, S. Akahoshi, T. Asakawa, K. Matsumura, H. Ishida, H. Nukaya, K. Tsuji, T. Kan, I. Abe, *Proc. Natl. Acad. Sci.* **2011**, *108*, 17533.

[10] (a) D. W. Knight, A. W. T. Smith, *Tetrahedron* **2015**, *71*, 7436; (b) D. W. Knight, A.W. T. Smith, *Heterocycles* **2012**, *84*, 361; (c) A. B. Evans, S. S.; Jones, D. W. Knight, W. -F. Tan, *Arkivoc* **2008**, *x*, 95; (d) S. P. Bew, G. M. M. El-Taeb, S. Jones, D. W. Knight, W. -F. Tan, *Eur. J. Org. Chem.* **2007**, 5759.

[11] (a) An initial version of this work was deposited in ChemRxiv on 29th November 2019, https://doi.org/10.26434/chemrxiv.11298398.v1; (b) Y. Wang, G. J. Pritchard, M. C. Kimber, *Org. Lett.* **2019**, *21*, 4892; (c) R. J. Lee, M. R. Lindley, G. J. Pritchard, M. C. Kimber, *Chem. Commun.* **2017**, *53*, 6327.

[12] (a) J. Tsuji, H. Watanabe, I. Minami, I. Shimizu, *J. Am. Chem. Soc.* **1985**, *107*, 2196; (b) I. Minami, M. Yuhara, H. Watanabe, J. A. Tsuji, *J. Organomet. Chem.* **1987**, *334*, 225.

[13] (a) Y. Zhou, F. -L. Zhu, Z. -T. Liu, X. -M. Zhou, X. -P. Hu, *Org. Lett.* **2016**, *18*, 2734; (b) M. Yoshida, S. Ohno, S. Eguchi, T. Mizuguchi, K. Matsumoto, K. Namba, *Tetrahedron* **2016**, *72*, 5633; (c) M. Yoshida, K. Kinoshita, K. Namba, *Org. Biomol. Chem.* **2014**, *12*, 2394; (d) M. Yoshida, C. Sugimura, *Tetrahedron Lett.* **2013**, *54*, 2082; (e) M. Yoshida, T. Nakagawa, K. Kinoshita, K. Shishido, *J. Org. Chem.* **2013**, *78*, 1687; (f) M. Yoshida, Y. Maeyama, K. Shishido, *Tetrahedron* **2012**, *68*, 9962; (g) M. Yoshida, C. Sugimura, K. Shishido, *Org. Lett.* **2011**, *13*, 3482; (h) M. Yoshida, M. Higuchi, K. Shishido, *Tetrahedron* **2010**, *66*, 2675; (i) M. Yoshida, M. Higuchi, K. Shishido, *Org. Lett.* **2009**, *11*, 4752.

[14] (a) M. Yoshida, S. Ohno, K. Shishido, *Chem. Eur. J.* **2012**, *18*, 1604; (b) X. -H. Duan, X. -Y. Liu, L. -N. Guo, M. -C. Liao, W. -M. Liu, Y. -M. Liang, *J. Org. Chem.* **2005**, *70*, 6980; (c) N. Monteiro, G. Balme, *J. Org. Chem.* **2000**, *65*, 3223.

[15] R. Shen, J. Yang, S. Zhu, C. Chen, L. Wu, *Adv. Synth. Catal.* **2015**, *357*, 1259.

[16] J. Tsuji, T. Sugiura, I. Minami, *Synthesis* **1987**, *1987*, 603.

[17] S. C. Case-Green, S. G. Davies, P. M. Roberts, A. J. Russell, J. E. Thomson, *Tetrahedron: Asymmetry* **2008**, *19*, 2620.

[18] D. I. MaGee, J. D. Leach, T. C. Mallais, *Tetrahedron Lett.* **1997**, *38*, 1289.

[19] (a) M. Hussein, A. Nasr El Dine, F. Farès, V. Dorcet, A. Hachem, R. A. Grée, *Tetrahedron Lett.* **2016**, *57*, 1990; (b) D. Zhang, J. M. Ready, *J. Am. Chem. Soc.* **2007**, *129*, 12088; (c) J. -D. Hamel, M. Beaudoin, M. Cloutier, J. -F. Paquin, *Synlett* **2017**, *28*, 2823; (d) C. Harcken, R. Brückner, *New J. Chem.* **2001**, *25*, 40; (e) S. C. Case-Green, S. G. Davies, P. M. Roberts, A. J. Russell, J. E. Thomson, *Tetrahedron: Asymmetry* **2008**, *19*, 2620.

[20] (a) R. Shen, J. Yang, S. Zhu, C. Chen, L. Wu, *Adv. Synth. Catal.* **2015**, *357*, 1259; (b) J. Tsuji, T. Sugiura, I. Minami, *Synthesis* **1987**, 603.

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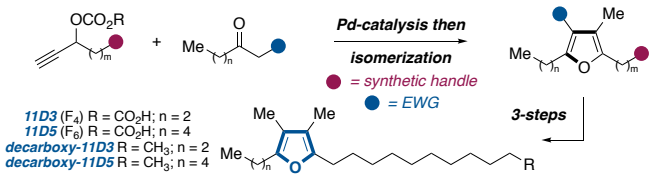

Tetrasubstituted Furan Fatty acids (FuFAs) are a vital and ubiquitous class of natural products, that upon ingestion afford significant health benefits. Herein, a general and modular approach to their total synthesis is presented, delivering short yet efficient syntheses of two key FuFAs, 11D3 (F_4) and 11D5 (F_6), in 52% and 48% overall yield, respectively. Significantly, this method offers an effective route to key analogues, such as decarboxy-11D3 and decarboxy-11D5.

Keywords: Furan • Fatty acid • palladium catalysis • convergent • natural products

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