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Two Practical Syntheses of an Anti-inflammatory Sesquiterpene Furoic Acid from *Sinularia* spp.

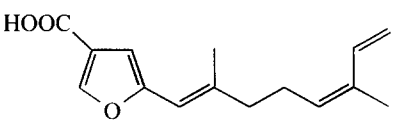
David H. Williams and D. John Faulkner*

Scripps Institution of Oceanography, University of California at San Diego, La Jolla, California 92093-0212, USA

Abstract: The sesquiterpene (1′*E*,5′*E*)-2-(2′,6′-dimethylocta-1′,5′,7′-trienyl)-4-furoic acid (**2**), which is an anti-inflammatory metabolite of the soft coral *Sinularia* spp. has been synthesized by two routes, both of which employ a Claisen rearrangement.

The inflammatory response is mediated by the biosynthesis of eicosanoids, such as prostaglandins and leukotrienes, from arachidonic acid.[1,2] The pathways that result in the biosynthesis of eicosanoids are collectively known as the "arachidonic acid cascade" and the inflammatory response can be modified by inhibiting these pathways. Arachidonic acid release from the *sn*-2 position of membrane phospholipids is controlled by the enzyme phospholipase A_2 (PLA_2). Therefore, inhibition of PLA_2 has become a target for the development of therapeutic agents to treat inflammation.

In 1977, the sesquiterpene (1′*E*,5′*Z*)-2-(2′,6′-dimethylocta-1′,5′,7′-trienyl)-4-furoic acid (**1**) was isolated from the Australian soft coral *Sinularia gonatodes*.[3] This was later followed by the discovery that several species of *Sinularia* contained related sesquiterpene furans, including a geometrical isomer (1′*E*,5′*E*)-2-(2′,6′-dimethylocta-1′,5′,7′-trienyl)-4-furoic acid (**2**) from *S. capillosa*.[4] In 1994, the furoic acid **1**, which had been isolated from an Indian specimen of *Sinularia* sp., was shown to inactivate bee venom PLA_2 *in vitro*.[5] Intrigued by the idea that such a simple compound might be a useful anti-inflammatory agent, we synthesized several simple alkylated furan 3-carboxylic acids[6] but the resulting structure/activity study did not give useful information about the pharmacophore required for PLA_2 activity. In order to determine the relative importance of the furan and diene portions of the molecule, we have investigated two routes to synthesize furoic acid **2**, which was not readily available from the natural source.



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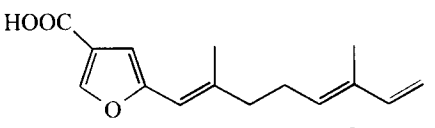

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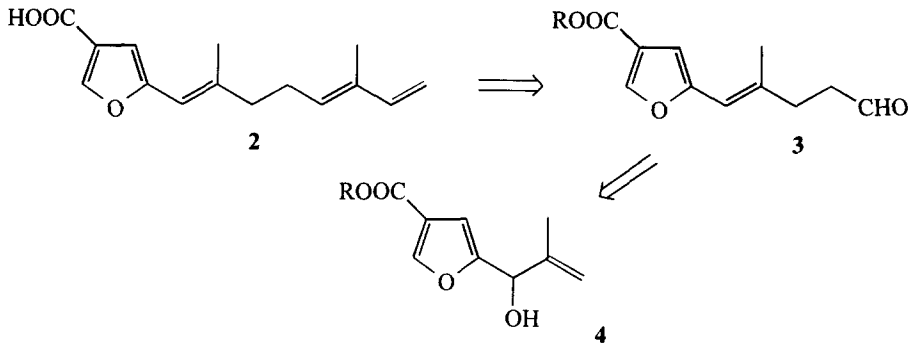
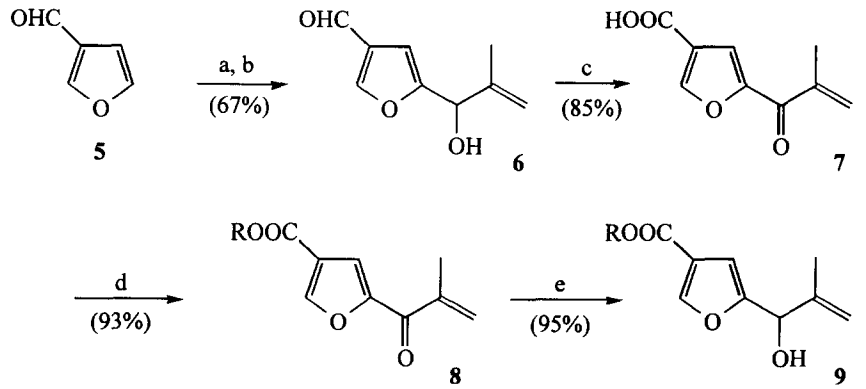
The retro-synthetic plan is outlined in Scheme 1. The terminal diene of furoic acid **2** was envisaged to arise from the stereocontrolled Horner-Wadsworth-Emmons homologation of aldehyde **3** which would be formed from the allylic carbinol **4** using a Claisen rearrangement, which was expected to give a product having predominantly the (1′*E*)-geometry. For the synthesis of an allylic carbinol **4** we proposed to take advantage of the methods developed by Garst and co-workers for the regioselective synthesis of 2,4-disubstituted furans.[7]



Scheme 1.

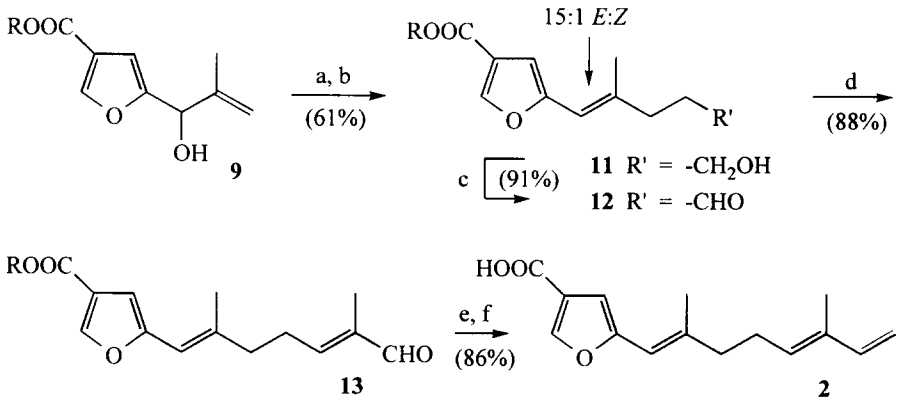
The synthesis of 2,4-disubstituted furans frequently requires many steps that usually include multiple protection and deprotection reactions. Using the method of Lee *et al.*,[7] 3-furaldehyde (**5**) was converted into carbinol **6** in 68% yield. A small quantity of the corresponding 2,3-disubstituted furan was formed but this was easily removed by chromatography. Jones' oxidation[8] of the carbinol **6** gave the keto-acid **7** that was esterified with trimethylsilylethanol using DCC/DMAP to obtain the keto-ester **8** in 78%



Scheme 2. (R = $-CH_2CH_2SiMe_3$) a. *n*-BuLi, morpholine, -78 °C. b. *s*-BuLi, methacrolein, -78 → 0 °C. c. Jones' reagent. d. $Me_3SiCH_2CH_2OH$, DCC, DMAP. e. $NaBH_4/CeCl_3$, 0 °C.

overall yield. Reduction of the keto-ester **8** with Luche's reagent[9] provided the required carbinol **9** in 95% yield (50 % overall yield from 3-furaldehyde).

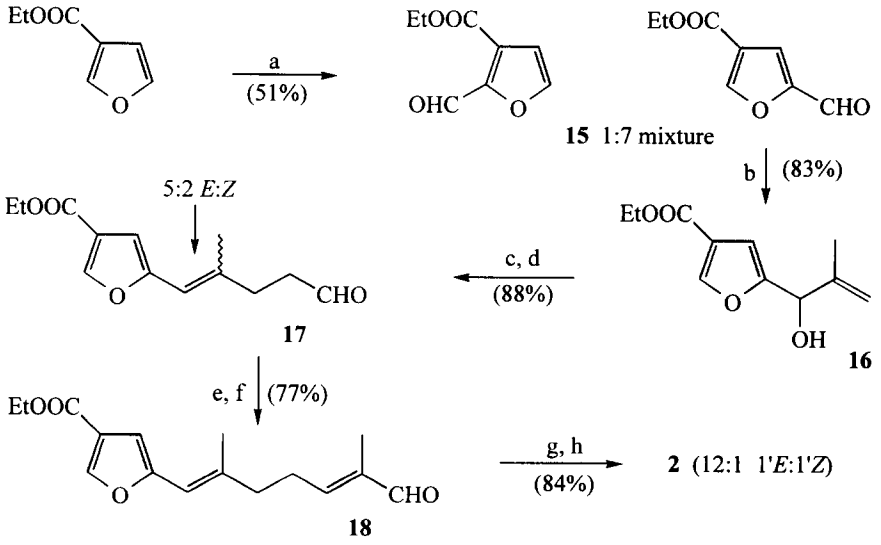
The key step in the synthesis involved the use of Johnson's orthoester modification of the Claisen rearrangement.[10,11] Treatment of the carbinol **9** with trimethyl orthoformate in refluxing toluene containing trimethylacetic acid produced the diester **10** in 77% yield with the expected 93:7 ratio of *E/Z* isomers at the newly formed olefinic bond. The presence of two isomers was readily detected by the presence of two allylic methyl signals in the ^{1}H NMR spectrum. Selective reduction of the saturated ester group to obtain the primary alcohol **11** was achieved in 87% yield by using lithium borohydride in ether containing 4 equivalents of methanol.[12] At this stage the two geometrical isomers could be separated with difficulty by flash chromatography. Oxidation of the carbinol **11** with PCC[13] proceeded smoothly to obtain aldehyde **12**. Homologation of aldehyde **12** with 2-(triphenylphosporanylidene)-propionaldehyde in refluxing toluene gave the trisubstituted α,β-unsaturated aldehyde **13** in 88% yield with >95% *E*-configuration at the newly formed olefinic bond (the *Z*-isomer was not in fact observed by ^{1}H NMR spectroscopy). A Wittig reaction using methyltriphenylphosphonium bromide and potassium hexamethyldisilazane at -40 °C in THF-toluene converted the aldehyde **13** into the *E,E*-diene **14**, which was treated with tetra-*n*-butylammonium fluoride to obtain furoic acid **2** in 23% overall yield from 3-furaldehyde.



Scheme 3. (R = -$CH_2CH_2SiMe_3$) a. $(MeO)_3CMe$, *t*-BuCOOH, toluene, rf. b. $LiBH_4$, MeOH (4 eq.), Et_2O. c. PCC. d. $CH_3C(=PPh_3)CHO$, toluene, rf. e. $CH_2=PPh_3$, THF/toluene. f. TBAF.

In an effort to make the synthesis more efficient, we embarked on a second route that would reduce the number of steps and be more convenient on a larger scale. In a recent synthesis of methanofuran, Rinehart and co-workers[14] employed methyl 2-formyl-4-furoate, obtained by Vilsmeier formylation of methyl 3-furoate, as a starting material.[15] In our hands, Vilsmeier formylation of ethyl 3-furoate gave a 7:1 mixture of ethyl 2-formyl-4-furoate (**15**) and ethyl 2-formyl-3-furoate in 51% yield based on starting material consumed. The mixture of aldehydes was treated with 2-propenyl magnesium bromide in THF[16,17]

to obtain, after chromatography, an 83% yield of the allylic alcohol **16**. In order to form the aldehyde **17** directly from the allylic alcohol, we investigated the Claisen rearrangement of an allyl vinyl ether.[11,18] The mercury(II) trifluoroacetate catalyzed transetherification of ethyl vinyl ether with the allylic alcohol gave the ethyl vinyl ether, which was heated in refluxing toluene for 40 min. to obtain the aldehyde **17** in 79% overall yield (88% based on starting material consumed). Unfortunately, the [3,3]-sigmatropic rearrangement gave a disappointing 5:2 ratio of *E*:*Z* geometrical isomers.[19] However, treatment of this 5:2 mixture of isomers with a catalytic amount of *p*-toluenesulfonic acid in refluxing dichloromethane caused a partial isomerization of the mixture toward the thermodynamically more stable isomer, resulting in an 85% yield of a 12:1 mixture of *E* and *Z* isomers of aldehyde **17**. Since the isomerization could be accomplished with such ease, we decided to reserve this reaction for use at a later stage in the synthesis. The 5:2 mixture of *E* and *Z* isomers of aldehyde **17** was reacted with 2-(triphenylphosporanylidene)-propionaldehyde in refluxing toluene to obtain the trisubstituted α,β-unsaturated aldehyde **18**, which was subjected to acid catalyzed equilibration to obtain a 12:1 mixture of 1′*E* and 1′*Z* isomers, with complete retention of the 5′*E* stereochemistry in 77% overall yield. The synthesis was completed by treatment of the α,β-unsaturated aldehyde **18** with methyltriphenylphosphonium bromide and potassium hexamethyldisilazane at -40 °C in THF-toluene followed by hydrolysis of the ethyl ester to obtain the furoic acid **2** in 84% overall yield but as a 12:1 mixture of geometric isomers at the 1′ position. Thus, the



Scheme 4. a. $POCl_3$, DMF, 128-133 °C. b. CH_2=C(Me)MgBr, THF, -45 → 25 °C. c. EtOCH=CH_2, $Hg(TFA)_2$, rf. d. Toluene, rf. e. $CH_3C(=PPh_3)CHO$, toluene, rf. f. *p*-TsOH, CH_2Cl_2 g. $CH_2=PPh_3$, THF/toluene. h. NaOH, MeOH.

second synthesis is shorter, requiring six steps from a commercially available starting material, is more convenient for large scale preparation, and gives a slightly higher 24% overall yield but is less stereoselective.

The furoic acid **2** inhibited bee venom PLA_2 (46% at 0.8 μg/mL) but is about an order of magnitude less active than furoic acid **1**, suggesting that the correct geometry of the 5′-olefin is important though not vital for activity. By way of comparison, 5-(1′-geranyl)-3-furoic acid, synthesized earlier by Dr. K. A. Albizati,[6] was almost two orders of magnitude less active than furoic acid **1**.

EXPERIMENTAL SECTION

General Methods: All solvents were redistilled prior to use and all other chemicals and reagents were used as supplied, unless specifically stated otherwise. Ultraviolet and infrared spectra were recorded on Perkin-Elmer Lambda 3B and 1600 series spectrometers, respectively. ^1H NMR were recorded at 200 MHz and ^{13}C NMR spectra were recorded at 50 MHz on a Bruker WP-200 SY spectrometer. Low resolution mass spectra were recorded on a Hewlett Packard 5988A spectrometer. High resolution mass spectra were measured on a VG ZAB mass spectrometer at the Regional Mass Spectrometry Facility, UC Riverside.

2-(1′-Hydroxy-2′-methylprop-2′-enyl)-4-furaldehyde (6): *n*-Butyl lithium (0.528 mL, 2.3 M, 1.22 mM, 1.05 eq) in cyclohexane was added to a stirred solution of morpholine (0.106 mL, 1.22 mM, 1.05 eq) in THF (5 mL) under argon at -78 °C over 10 min. After 20 min. a solution of freshly distilled 3-furaldehyde (**5**, 0.1 mL, 1.16 mM) in THF (2.5 mL) was added dropwise and stirring continued for a further 30 min. at -78 °C. *s*-Butyl lithium (1.012 mL, 1.2 M, 1.22 mM, 1.05 eq) in cyclohexane was added to the solution over 10 min and vigorous stirring was maintained for a further 2.5 hr. at -78 °C. Methacrolein (0.105 mL, 1.27 mM, 1.1 eq) in THF (2 mL) was added to the cream slurry and the mixture was stirred for 2 hr. at - 78 °C and allowed to warm to 0 °C over 2 hr. The reaction mixture was diluted with diethyl ether (100 mL) and washed with cold aqueous hydrochloric acid (20 mL, 5%), saturated aqueous sodium bicarbonate (20 mL), and brine (25 mL). The organic phase was dried, evaporated, purified by flash chromatography on silica using ethyl acetate-hexane (1:3 → 1:2) as eluant, and recrystallised from ether-hexane to give 2-(1′-hydroxy-2′-methylprop-2′-enyl)-3-furaldehyde (15 mg, 8%) and 2-(1′-hydroxy-2′-methylprop-2′-enyl)-4-furaldehyde (**6**, 0.131 g, 68%) as a white solid: mp 45-46 °C; IR (CH_2Cl_2) 1685, 1540 cm^{-1}; UV (CH_3OH) 257 nm; ^1H NMR ($CDCl_3$) δ 1.72 (3H, br s), 2.47 (1H, br d, J = 4 Hz), 5.04 (1H, br s), 5.16 (1H, br s), 5.18 (1H, br s), 6.65 (1H, s), 8.01 (1H, s), 9.86 (1H, s); ^{13}C NMR ($CDCl_3$) δ 18.5, 71.4, 104.2, 113.3, 129.4, 143.6, 151.2, 157.9, 184.7; CIMS (CH_4) *m/z* (int.) 167 ($M+H^+$, 100), 149 (64), 125 (9); HRCIMS (CH_4) obsd. *m/z* = 167.0715, $C_9H_{11}O_3$ ($M+H^+$) requires *m/z* = 167.0708.

2-(1′-Oxo-2′-methylprop-2′-enyl)-4-furoic acid (7): Jones' reagent[8] (0.6 mL, 8 M, 4.8 mM, 8 eq) was added dropwise over 5 min. to a stirred solution of carbinol **6** (100 mg, 0.6 mM) in acetone (5 mL) at 0 °C. The solution was allowed to warm to room temperature and was stirred for 45 min. The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic extract was washed with brine (2 x 25 mL), dried over Na_2SO_4, and the solvent evaporated. The residue was recrystallised from ethyl acetate-hexane to obtain 2-(1′-oxo-2′-methylprop-2′-enyl)-4-furoic acid (**7**, 0.091 g, 84%) as colourless cubes: mp 133-134 °C; IR (CH_2Cl_2) 3000 (br), 1745, 1695, 1655, 1580 cm^{-1}; UV (CH_3OH) 280, 235 nm; ^1H NMR ($CDCl_3$) δ 2.05 (3H, br s), 5.90 (1H, d, J = 1.5 Hz), 6.03 (1H, br s), 7.43 (1H, s), 8.26 (1H, s); ^{13}C NMR ($CDCl_3$) δ 18.5, 118.2, 120.1, 126.1, 143.1, 151.8, 152.4, 167.2, 183.6; CIMS (NH_3) *m/z* (int.) 198 ($M+NH_4^+$, 37), 181 ($M+H^+$, 100), 139 (42); HRCIMS (NH_3) obsd. *m/z* = 198.0767, $C_9H_{12}NO_4$ $(M+NH_4)^+$ requires *m/z* = 198.0766.

2-Trimethylsilylethyl 2-(1′-oxo-2′-methylprop-2′-enyl)-4-furoate (8): A solution of DCC (515 mg, 2.5 mM, 1.5 eq) in dichloromethane (3 mL) was added dropwise, over 5 min., to a stirred chilled solution of the furoic acid **7** (300 mg, 1.66 mM) in dichloromethane (5 mL) containing DMAP (51 mg, 0.41 mM, 0.25 eq) and 2-trimethylsilylethanol (0.36 mL, 2.5 mM, 1.5 eq) at 0 °C. The solution was allowed to warm to room temperature and was stirred for 1 hr. The reaction mixture was filtered through celite and the filtrate evaporated. The residue was purified by flash chromatography on silica using ethyl acetate-hexane (1:9) as eluant and recrystallised from ethyl acetate-hexane to obtain 2-trimethylsilylethyl 2-(1′-oxo-2′-methylprop-2′-enyl)-4-furoate (**8**, 433 mg, 93%) as white needles: mp 46-47 °C; IR (CH_2Cl_2) 1720, 1655, 1580 cm^{-1}; UV (CH_3OH) 273, 239 nm; ^1H NMR ($CDCl_3$) δ 0.06 (9H, s), 1.08 (2H, m), 2.04 (3H, br s), 4.36 (2H, m), 5.86 (1H, br s), 6.00 (1H, br s), 7.39 (1H, s), 8.15 (1H, s); ^{13}C NMR ($CDCl_3$) δ -1.5, 17.4, 18.5, 63.4, 118.4, 121.3, 125.8, 143.1, 150.4, 152.0, 162.2, 183.8; CIMS (CH_4) *m/z* (int.) 281 ($M+H^+$, 100) 253 (29), 237 (22); HRCIMS (CH_4) obsd. *m/z* = 281.1213, $C_{14}H_{21}SiO_4$ ($M+H^+$) requires *m/z* = 281.1209.

2-Trimethylsilylethyl 2-(1′-hydroxy-2′-methylprop-2′-enyl)-4-furoate (9): Sodium borohydride (44 mg, 1.15 mM, 1 eq) was added to a stirred solution of keto-ester **8** (322 mg, 1.15 mM) in methanol (10 mL) containing cerium(III) chloride heptahydrate (471 mg, 1.26 mM, 1.1 eq). After 30 min. at 0 °C, aqueous ammonium chloride (20 mL, 10%) was added and the mixture was extracted with ethyl acetate (2 x 60 mL). The combined organic extracts were washed with brine (2 x 25 mL), dried over Na_2SO_4, evaporated, and purified by flash chromatography on silica using ethyl acetate-hexane (1:3) as eluant to give 2-trimethylsilylethyl 2-(1′-hydroxy-2′-methylprop-2′-enyl)-4-furoate (**9**, 310 mg, 96%) as a colourless oil: IR (CH_2Cl_2) 1710, 1545 cm^{-1}; UV (CH_3OH) 240 nm; ^1H NMR ($CDCl_3$) δ 0.05 (9H, s), 1.05 (2H, m), 1.72 (3H, br s), 2.07 (1H, d, J = 4 Hz), 4.31 (2H, m), 5.04 (1H, br s), 5.13 (1H, br d, J = 4 Hz), 5.18 (1H, br s), 6.60 (1H, s), 7.92 (1H, s); ^{13}C NMR ($CDCl_3$) δ -1.5, 17.3, 18.5, 62.8, 71.3, 107.0, 112.8, 120.3, 143.6, 147.1, 156.0, 163.2; CIMS (CH_4) *m/z* (int.) 283 ($M+H^+$, 24), 281 ($M-H^+$, 27), 265 (100), 255 (66), 239

(72), 237 (25), 165 (25); HRCIMS (CH_4) obsd. *m/z* = 283.1352, $C_{14}H_{23}SiO_4$ ($M+H^+$) requires *m/z* = 283.1366.

2-Trimethylsilylethyl (1′*E*)-2-(4′-methoxycarbonyl-2′-methylbut-1′-enyl)-4-furoate (10): Trimethyl acetic acid in toluene (0.5 mL, 0.25 M, 0.067 eq) was added every 30 min for 15 hr. to a refluxing solution of carbinol **9** (530 mg, 1.88 mM) in toluene (40 mL) containing trimethylorthoformate (5 mL, 39 mM, 21 eq). The solution was allowed to cool, diluted with ethyl acetate (150 mL), washed with saturated aqueous sodium bicarbonate (2 x 30 mL) then brine (30 mL), dried over Na_2SO_4, and the solvent evaporated. The residue was purified by flash chromatography on silica using ethyl acetate-hexane (3:17 → 1:3) as eluant to give 2-trimethylsilylethyl (1′*E*)-2-(4′-methoxycarbonyl-2′-methylbut- 1′-enyl)-4-furoate (**10**, 420 mg, 66%; 70% based on starting material consumed) as a colourless oil: IR (CH_2Cl_2) 1735, 1720 cm^{-1}; UV (CH_3CN) 278 (sh), 260, 256 nm; ^1H NMR ($CDCl_3$) δ 0.05 (9H, s), 1.06 (2H, m), 1.96 (3H, br s), 2.49 (4H, br s), 3.66 (3H, s), 4.32 (2H, m), 6.05 (1H, br s), 6.50 (1H, s), 7.87 (1H, s); ^{13}C NMR ($CDCl_3$) δ -1.5, 17.3, 18.5, 32.6, 35.5, 51.7, 62.6, 107.2, 114.0, 120.8, 138.7, 145.5, 154.2, 163.4, 173.3; CIMS (CH_4) *m/z* (int.) 339 ($M+H^+$, 16) 311 (89) 295 (43), 221 (100); HRCIMS (CH_4) obsd. *m/z* = 339.1633, $C_{17}H_{27}SiO_5$ ($M+H^+$) requires *m/z* = 339.1628.

2-Trimethylsilylethyl (1′*E*)-2-(5′-hydroxy-2′-methylpent-1′-enyl)-4-furoate (11): Lithium borohydride (5 mg, 5 eq) was added to a chilled solution of the diester **10** (15 mg, 0.044 mM) in ether (2 mL) containing methanol (7 μL, 4 Eq) at 0 °C and the solution was stirred for 1 hr. The solution was diluted with ether (30 mL) and quenched with aqueous ammonium chloride (5 mL, 10%). The organic layer was washed with brine (10 mL), dried over Na_2SO_4, and the solvent evaporated. The residue was purified by flash chromatography on silica using ethyl acetate-hexane (35:65) as eluent to obtain, together with the *Z*-isomer (0.5 mg, 4%), 2-trimethylsilylethyl (1′*E*)-2-(5′-hydroxy-2′-methylpent-1′-enyl)-4-furoate (**11**, 12 mg, 87%) as an oil: IR (CH_2Cl_2) 2955, 1715 cm^{-1}; UV (MeOH) 275 (sh), 260, 257 nm; ^1H NMR ($CDCl_3$) δ 0.06 (9H, s), 1.07 (2H, m), 1.76 (2H, m), 1.98 (3H, br s), 2.26 (2H, br t, *J* = 8 Hz), 3.68 (2H, t, *J* = 6 Hz), 4.33 (2H, m), 6.08 (1H, br s), 6.50 (1H, s), 7.87 (1H, s); ^{13}C NMR ($CDCl_3$) δ -1.5, 17.3, 18.6, 30.7, 36.9, 62.4, 62.6, 106.8, 113.6, 120.8, 140.4, 145.4, 154.4, 163.5; CIMS (NH_3) *m/z* (int.) 328 ($M+NH_4^+$, 8), 311 ($M+H^+$, 19), 283 (57), 90 (100); HRCIMS (NH_3) obsd. *m/z* = 311.1683, $C_{16}H_{27}SiO_4$ ($M+H^+$) requires *m/z* = 311.1678.

2-Trimethylsilylethyl (1′*Z*)-2-(5′-hydroxy-2′-methylpent-1′-enyl)-4-furoate: ^1H NMR ($CDCl_3$) δ 0.06 (9H, s), 1.07 (2H, m), 1.76 (2H, m), 1.90 (3H, br s), 2.47 (2H, br t, *J* = 8 Hz), 3.70 (2H, t, *J* = 6 Hz), 4.33 (2H, m) 6.03 (1H, br s), 6.50 (1H, s), 7.86 (1H, s).

2-Trimethylsilylethyl (1′*E*)-2-(5′-oxo-2′-methylpent-1′-enyl)-4-furoate (12): The carbinol **11** (30 mg, 0.097 mM) in dichloromethane (2 mL) was added to a stirred mixture of PCC (42 mg, 0.19 mM, 2 eq), fused sodium acetate (2 mg, 25%), and powdered 3Å molecular sieves (100 mg) in dichloromethane at 0 °C. After 5 min., the reaction mixture was allowed to warm to room temperature and was stirred for a

further 40 min. The reaction mixture was diluted with ether (20 mL), filtered through celite, further diluted with ether (80 mL) and washed with saturated aqueous sodium bicarbonate solution (10 mL). The organic phase was dried over Na_2SO_4, the solvent evaporated, and the product purified by flash chromatography on silica using ethyl acetate-hexane (15:85) as eluent to give 2-trimethylsilylethyl (1′*E*)-2-(5′-oxo-2′-methylpent-1′-enyl)-4-furoate (**12**, 27.5 mg, 91%) as an oil: IR (CH_2Cl_2) 1720 cm^{-1}; UV (MeOH) 275 (sh), 261, 256 nm; ^1H NMR ($CDCl_3$) δ 0.05 (9H, s), 1.06 (2H, m), 1.97 (3H, br s), 2.50 (2H, m), 2.64 (2H, m), 4.33 (2H, m), 6.06 (1H, br s), 6.50 (1H, s), 7.87 (1H, s), 9.80 (1H, s); ^{13}C NMR ($CDCl_3$) δ -1.5, 17.3, 18.7, 32.7, 42.0, 62.7, 107.3, 114.2, 120.8, 138.4, 145.6, 154.0, 163.4, 201.4; CIMS (CH_4) *m/z* (int.) 309 ($M+H^+$, 20), 281 (79), 265 (100), 191 (79); HRCIMS (CH_4) obsd. *m/z* = 309.1525, $C_{16}H_{25}SiO_4$ ($M+H^+$) requires *m/z* = 309.1522.

2-Trimethylsilylethyl (1′*E*,5′*E*)-2-(7′-oxo-2′,6′-dimethylhept-1′,5′-dienyl)-4-furoate (13): 2-(Triphenylphosphoranylidene)-propionaldehyde (173.5 mg, 0.54 mM, 1.5 eq) was added to a stirred solution of aldehyde **12** (112 mg, 0.36 mM) in toluene (10 mL) and the mixture was refluxed under nitrogen for 10 hr. The solution was allowed to cool to room temperature and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica using ethyl acetate-hexane (9:41) as eluant to afford 2-trimethylsilylethyl (1′*E*,5′*E*)-2-(7′-oxo-2′,6′-dimethylhept-1′,5′-dienyl)-4-furoate (**13**, 111 mg, 88%) as an oil: IR (CH_2Cl_2) 1715, 1685 cm^{-1}; UV (CH_3CN) 275 (sh), 261, 257, 228 nm; ^1H NMR ($CDCl_3$) δ 0.06 (9H, s), 1.07 (2H, m), 1.76 (3H, br s), 2.00 (3H, br s), 2.40 (2H, m), 2.55 (2H, m), 4.33 (2H, m), 6.07 (1H, br s), 6.47 (1H, br t, *J* = 8 Hz), 6.52 (1H, br s), 7.88 (1H, s), 9.39 (1H, s); ^{13}C NMR ($CDCl_3$) δ -1.4, 9.3, 17.3, 18.6, 27.3, 39.0, 62.7, 107.3, 114.4, 120.9, 138.8, 139.8, 145.6, 153.1, 154.1, 163.4, 195.1; CIMS (NH_3) *m/z* (int.) 366 ($M+NH_4^+$, 22), 349 ($M+H^+$, 6), 127 (37), 90 (100); HRCIMS (NH_3) obsd. *m/z* = 349.1830, $C_{19}H_{29}SiO_4$ ($M+H^+$) requires *m/z* = 349.1835.

2-Trimethylsilylethyl (1′*E*,5′*E*)-2-(2′,6′-dimethylocta-1′,5′,7′-trienyl)-4-furoate (14): A solution of potassium hexamethyldisilazane (3 mL, 1.49 mM, 2.7 eq, 0.5 M) in toluene was added dropwise to a stirred mixture of methyltriphenylphosphonium bromide (0.590 g, 1.65 mM, 3.0 eq) in THF (10 mL) at -40 °C. The mixture was stirred for 1 hr. at -40 °C to give a deep yellow colouration. A solution of the aldehyde **13** (192 mg, 0.55 mM) in THF (5 mL) was added dropwise to the ylid solution and stirring was maintained for 1 hr. at - 40 °C. The reaction mixture was quenched by dropwise addition of ammonium chloride solution, followed by warming to room temperature, at which point ether (200 mL) was added. The organic layer was washed with water (50 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography on silica using ethyl acetate-hexane (6:100) as eluant to obtain 2-trimethylsilylethyl (1′*E*,5′*E*)-2-(2′,6′-dimethylocta-1′,5′,7′-trienyl)-4-furoate (**14**, 177 mg, 93%) as an oil: IR (CH_2Cl_2) 1715 cm^{-1}; UV (MeOH) 276 (sh), 260, 255, 232, 227 nm; ^1H NMR ($CDCl_3$) δ 0.06 (9H, s), 1.07 (2H, m), 1.74 (3H, br s), 1.97 (3H, br s), 2.31 (4H, m), 4.33 (2H, m), 4.93 (1H, br d, *J* = 11 Hz), 5.08 (1H, br d, *J* = 17 Hz), 5.47 (1H, br t, *J* = 7 Hz), 6.05 (1H, br s), 6.35 (1H, dd, *J* = 17, 11 Hz), 6.49

(1H, s), 7.87 (1H, s); ^{13}C NMR ($CDCl_3$) δ -1.4, 11.7, 17.4, 18.7, 26.7, 40.3, 62.6, 106.8, 110.8, 113.7, 120.8, 131.7, 134.5, 140.4, 141.4, 145.3, 154.6, 163.5; CIMS (NH_3) *m/z* (int.) 347 ($M+H^+$, 17), 319 (52), 265 (6); HRCIMS (NH_3) obsd. *m/z* = 347.2050, $C_{20}H_{31}SiO_3$ ($M+H^+$) requires *m/z* = 347.2042.

(1′*E*,5′*E*)-2-(2′,6′-Dimethylocta-1′,5′,7′-trienyl)-4-furoic acid (2): A solution of TBAF in THF (0.12 mL, 1N, 2 eq) was added to a solution of the diene **14** (21 mg, 0.06 mM) in THF (2 mL) at room temperature. After 4 hr., the solution was diluted with ethyl acetate (50 mL) and washed with aqueous hydrochloric acid (10 mL, 0.1N) and water (2 x 10 mL). The organic layer was dried over Na_2SO_4 and the solvent evaporated to afford (1′*E*,5′*E*)-2-(2′,6′-dimethylocta-1′,5′,7′-trienyl)-4-furoic acid (**2**, 14 mg, 93%) as an amorphous solid: IR (CH_2Cl_2) 3300 (br), 1715, 1695 cm^{-1}; UV (MeOH) 276 (sh), 262, 257, 233, 227 nm; ^{1}H NMR ($CDCl_3$) δ 1.75 (3H, br s), 1.98 (3H, br s), 2.29 (4H, m), 4.94 (1H, br d, *J* = 11 Hz), 5.10 (1H, br d, *J* = 17 Hz), 5.47 (1H, br t, *J* = 7 Hz), 6.07 (1H, brs), 6.36 (1H, dd, *J* = 17, 11 Hz), 6.52 (1H, s), 7.99 (1H, s); ^{13}C NMR ($CDCl_3$) δ 11.7, 18.7, 26.7, 40.3, 106.6, 110.9, 113.5, 119.7, 131.7, 134.6, 141.1, 141.3, 146.9, 155.1, 168.5; CIMS (NH_3) *m/z* (int.) 264 ($M+NH_4^+$, 22), 247 ($M+H^+$, 82), 165 (100), 147 (66); HRCIMS (NH_3) obsd. *m/z* = 264.1604, $C_{15}H_{22}NO_3$ ($M+NH_4^+$) requires *m/z* = 264.1600.

Ethyl 2-formyl-4-furoate (15): Phosphorus oxychloride (9 mL, 96.5 mmol, 1.3 eq) was added dropwise over 15 min. to stirred DMF (10 mL, 129 mmol, 1.7 eq) at 0 °C and the mixture was then allowed to warm to room temperature. Ethyl 3-furoate (10 mL, 74 mmol) was added and the solution was heated to 126 °C. The reaction rapidly becomes exothermic requiring removal of the oil bath, after which the temperature was maintained at 128-133 °C for 1 hr. The reaction mixture was allowed to cool and the brown tar was poured into stirred ice water. The solution was extracted with ether (350 mL), which was washed with water (100 mL), saturated aqueous sodium bicarbonate (100 mL) and brine (50 mL). The organic phase was dried over Na_2SO_4, the solvent evaporated, and the residue purified by Kugelrohr distillation (2 mm Hg; 40→70 °C) to obtain the starting ester (3.2 g, 32%) and an inseparable mixture of ethyl 2-formyl-4-furoate (**14**) and ethyl 2-formyl-3-furoate (4.41 g, 35%) in a ratio of 7:1 respectively: IR (CH_2Cl_2) 1725, 1690, 1585 cm^{-1}; UV (CH_3OH) 262 nm; ^{1}H NMR ($CDCl_3$) δ 1.34 (3H, t, *J* = 7 Hz), 4.32 (2H, q, *J* = 7 Hz), 7.52 (1H, s), 8.19 (1H, s), 9.66 (1H, s); ^{13}C NMR ($CDCl_3$) δ 14.2, 61.2, 119.7, 121.9, 151.4, 153.2, 161.6, 177.8; CIMS (CH_4) *m/z* (int.) 169 ($M+H^+$, 100), 141 (11); HRCIMS (CH_4) obsd. *m/z* = 169.0500, $C_8H_9O_4$ ($M+H^+$) requires *m/z* = 169.0501.

Ethyl 2-(1′-hydroxy-2′-methylprop-2′-enyl)-4-furoate (16): A solution of 2-propenyl magnesium bromide[16,17] in THF (4.2 mL, 0.25 N, 1.05 eq) was added dropwise to a stirred solution of the mixture of aldehydes from the reaction above (168 mg, 1 mM) in THF (6.25 mL) at -45 °C. The solution was allowed to warm to room temperature over 2 hr. The solution was poured into aqueous ammonium chloride (20 mL, 10%) and extracted with ethyl acetate (150 mL). The organic phase was dried over Na_2SO_4, the solvent evaporated, and the residue passed through a short silica gel plug using ethyl acetate-hexane (1:3) as eluant to obtain, after further purification by Kugelrohr distillation (2 mm Hg,

60 °C), ethyl 2-(1′-hydroxy-2′-methylprop-2′-enyl)-4-furoate (**16**, 175 mg, 83%) as an oil: IR ($CHCl_3$) 1715 cm^{-1}; UV (MeOH) 238 nm; ^1H NMR ($CDCl_3$) δ 1.33 (3H, t, J = 7 Hz), 1.73 (3H, br s), 4.28 (2H, q, J = 7 Hz), 5.04 (1H, br s), 5.14 (1H, br s), 5.19 (1H, br s), 6.61 (1H, s), 7.95 (1H, s); ^{13}C NMR ($CDCl_3$) δ 14.3, 18.4, 60.5, 71.3, 107.0, 112.8, 120.1, 143.7, 147.2, 156.1, 163.1; CIMS (CH_4) *m/z* (int.) 211 ($M+H^+$, 100), 193 (92), 169 (22); HRCIMS (CH_4) obsd. *m/z* = 211.0962, $C_{11}H_{15}O_4$ ($M+H^+$) requires *m/z* = 211.0970.

Ethyl 2-(5′-oxo-2′-methylpent-1′-enyl)-4-furoate (17): A catalytic amount of mercuric trifluroacetate (30 mg, 10%) was added to a stirred solution of carbinol **16** (173 mg, 0.82 mM) in ethyl vinyl ether (50 mL) and the reaction mixture was refluxed for 3 hr. The solution was diluted with diethyl ether (100 mL), washed with saturated aqueous sodium bicarbonate (2 x 30 mL) then water (50 mL), dried over Na_2SO_4, and the solvent evaporated. The residue was refluxed in toluene (30 mL) and after 40 min. the solution was allowed to cool to room temperature at which time the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica using ethyl acetate-hexane (1:4) as eluant to afford a mixture of geometric isomers (*E*:*Z* = 5:2) of ethyl 2-(5′-oxo-2′-methylpent-1′-enyl)-4-furoate (**17**, 154 mg, 79%; 88% based on unrecovered starting material) as an oil: IR (CH_2Cl_2) 1720 cm^{-1}; UV (MeOH) 275 (sh), 260, 255 nm; ^1H NMR ($CDCl_3$) δ 1.34 (3H, t, J = 7 Hz), 1.98 (3H, br s), 2.50 (2H, m), 2.64 (2H, m), 4.29 (2H, q, J = 7 Hz), 6.06 (1H, br s), 6.52 (1H, s), 7.89 (1H, s), 9.79 (1H, s); ^{13}C NMR ($CDCl_3$) δ 14.3, 18.6, 32.6, 41.9, 60.4, 107.2, 114.1, 120.6, 138.4, 145.6, 154.0, 163.2, 201.4; CIMS (CH_4) *m/z* (int.) 237 ($M+H^+$, 100), 193 (55), 191 (60); HRCIMS (CH_4) obsd. *m/z* = 237.1138, $C_{13}H_{17}O_4$ ($M+H^+$) requires *m/z* = 237.112684.

Ethyl (1′*E*,5′*E*)-2-(7′-oxo-2′,6′-dimethylhept-1′,5′-dienyl)-4-furoate (18):

2-(Triphenylphosphoranylidene)-propionaldehyde (310 mg, 1.5 eq) was added to a stirred solution of aldehyde **17** (153 mg, 0.65 mM) in toluene (10 mL) and the mixture was refluxed under nitrogen for 10 hr. The solution was allowed to cool to room temperature and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica using ethyl acetate-hexane (9:41) as eluant to obtain a mixture of geometric isomers (1′*E*:*Z* = 3:1) of aldehyde **18** (159 mg, 89%).

p-Toluenesulfonic acid (5 mg, 10%) was added to a stirred solution of the mixed aldehydes (72 mg, 0.26 mM) in dichloromethane (25 mL) and the mixture was refluxed for 2 hr. The solution was diluted with dichloromethane (40 mL), washed with aqueous sodium bicarbonate (10 mL, 20%) then water (10 mL), dried over Na_2SO_4, and the solvent evaporated. The residue was passed through a short silica plug with ethyl acetate-hexane (1:4) as eluant to obtain a mixture of geometric isomers (1′*E*:*Z* = 12:1) containing primarily ethyl (1′*E*,5′*E*)-2-(7′-oxo-2,′6′-dimethylhept-1′,5′-dienyl)-4-furoate (**18**, 65 mg, 87%) as an oil: IR (CH_2Cl_2) 1720, 1685 cm^{-1}; UV (MeOH) 275 (sh), 261, 257, 228 nm; ^1H NMR ($CDCl_3$) δ 1.33 (3H, t ,J = 7 Hz), 1.76 (3H, br s), 2.00 (3H, br s), 2.36 (2H, m), 2.54 (2H, m), 4.29 (2H, q, J = 7 Hz), 6.07 (1H, br s), 6.47 (1H, br t, J = 7 Hz), 6.52 (1H, s), 7.89 (1H, s), 9.39 (1H, s); ^{13}C NMR ($CDCl_3$) δ 9.2, 14.3, 18.5,

27.2, 38.9, 60.4, 107.2, 114.3, 120.6, 138.8, 139.7, 145.6, 153.0, 154.0, 163.2, 195.1; CIMS (NH_3) *m/z* (int.) 294 ($M+NH_4^+$, 100), 277 ($M+H^+$, 42), 193 (25); HRCIMS (NH_3) obsd. *m/z* = 277.1436, $C_{16}H_{21}O_4$ ($M+H^+$) requires *m/z* = 277.1440.

Ethyl (1′*E*,5′*E*)-2-(2′,6′-dimethylocta-1′,5′,7′-trienyl)-4-furoate (19): A solution of potassium hexamethyldisilazane (4.5 mL, 2.25 mM, 2.7 eq, 0.5 N) in toluene was added dropwise to a stirred mixture of methyltriphenylphosphonium bromide (0.893 g, 2.5 mM, 3 eq) in THF (10 mL) at -40 °C. The mixture was stirred for 1 hr. at -40 °C to give a deep yellow colouration. A solution of the aldehyde **18** (0.23 g, 0.833 mM) in THF (5 mL) was added dropwise to the ylid solution and stirring was maintained for 1 hr. at - 40 °C. The reaction mixture was quenched by dropwise addition of ammonium chloride solution followed by warming to room temperature, at which point the reaction mixture was diluted with ether (200 mL). The organic layer was washed with water (50 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography on silica using ethyl acetate-hexane (5:95) as eluant to obtain ethyl (1′*E*,5′*E*)-2-(2′,6′-dimethylocta-1′,5′,7′-trienyl)-4-furoate (**19**, 212 mg, 92%) as an oil: IR (CH_2Cl_2) 1715 cm^{-1}; UV (MeOH) 276 (sh), 260, 255, 232, 225 nm; ^1H NMR ($CDCl_3$) δ 1.34 (3H, t, *J* = 7 Hz), 1.74 (3H, br s), 2.00 (3H, br s), 2.26 (4H, m), 4.29 (2H, q, *J* = 7 Hz), 4.93 (1H, br d, *J* = 11 Hz), 5.08 (1H, br d, *J* = 17 Hz), 5.46 (1H, br t, *J* = 7 Hz), 6.05 (1H, br s), 6.35 (1H, dd, *J* = 17, 11 Hz), 6.50 (1H, s), 7.86 (1H, s); ^{13}C NMR ($CDCl_3$) δ 11.6, 14.3, 18.6, 26.7, 40.2, 60.3, 106.7, 110.8, 113.6, 120.6, 131.7, 134.5, 140.4, 141.3, 145.4, 154.6, 163.3; CIMS (NH_3): *m/z* = 275 ($M+H^+$, 100); HRCIMS (NH_3) obsd. *m/z* = 275.1635, $C_{16}H_{23}O_3$ ($M+H^+$) requires *m/z* = 275.1647.

(1′*E*,5′*E*)-2-(2′,6′-Dimethylocta-1′,5′,7′-trienyl)-4-furoic acid (2): Aqueous sodium hydroxide solution (2 mL, 0.5 N) was added to a solution of ester **19** (38 mg, 0.14 mM) in methanol (4 mL) and the mixture was stirred for 8 hr., after which time no starting material was observed by tlc. The solution was diluted with ethyl acetate (50 mL) and washed with aqueous hydrochloric acid (10 mL, 0.1N) and water (2x 10 mL). The organic layer was dried over Na_2SO_4, and the solvent evaporated to afford (1′*E*, 5′*E*)-2-(2′,6′-dimethylocta-1′,5′,7′-trienyl)-4-furoic acid (**2**, 31 mg, 91 %) as an amorphous solid.

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