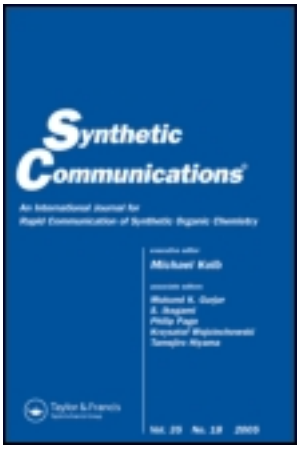


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# Synthesis of a Dimethylfuran-Containing Macrolide Insect Pheromone

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# Synthesis of a Dimethylfuran-Containing Macrolide Insect Pheromone

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**Abstract:** The synthetic pathway to the furan-containing macrolide pheromone (**1**) of *Galerucella* beetles was shortened from 13 steps in the original synthesis to 10 steps, and the overall yield was increased greater than six-fold. A concise Reformatsky-based sequence of reactions was utilized to construct the key precursor, 2,3-dimethyl-2-butenolide. Reduction of the butenolide with diisobutylaluminum hydride afforded 3,4-dimethylfuran. A one-pot sequence of lithiation, alkylation by a tetrahydropyranyl (THP)-containing iodide, a second lithiation, and, finally, formylation gave the required tetrasubstituted furan intermediate, 3,4-dimethyl-5-[5-(tetrahydrofuran-2-yloxy)pentyl]-2-furaldehyde. To continue construction of the three-carbon acyl side chain, the aldehyde was converted to an unsaturated ester by a Horner–Wadsworth–Emmons (HWE) condensation with triethyl phosphonoacetate. After reduction of the double bond in the ester side chain and removal of protective groups, the lactone ring was closed using the Mitsunobu method, which is milder, is simpler, and could be accomplished with less solvent than the previous (Yamaguchi) method.

**Keywords:** 2,3-Dimethyl-2-butenolide, 12,13-dimethyl-5,14-dioxabicyclo[9.2.1]-tetradeca-1(13),11-dien-4-one, 3,4-dimethylfuran, *Galerucella*, macrolide, pheromone, purple loosestrife, Reformatsky

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## INTRODUCTION

Insect pheromones can have unusual chemical structures. Previously, a furan-containing macrolide, 12,13-dimethyl-5,14-dioxabicyclo[9.2.1]-tetradeca-1(13),11-dien-4-one, structure **1** in Fig. 1, was identified from the beetle species *Galerucella calmariensis* and *G. pusilla*.[1] These species were introduced into North America from Europe as biological control agents for the invasive wetland weed purple loosestrife (*Lythrum salicaria*) and have had significant success in suppressing this noxious plant. A practical need is for scientists and land managers to be able to monitor beetle populations, and the pheromone is useful for this purpose.[1,2] An improved synthetic method for lactone **1** was developed to help meet that need.

The original approach was to prepare 3,4-dimthylfuran (**7** in Fig. 1) by a Diels–Alder route, attach or elaborate appropriate functionalized side chains at the 2-and 5-positions, and finally to join the ends of the side chains to form the lactone ring.[1] This strategy was generally preserved in the present work, but a simpler and less expensive (Reformatsky-based) approach to 3,4-dimethylfuran was developed, a milder and simpler lactonization reaction was employed, and the conditions for running several other reactions were improved.

## RESULTS AND DISCUSSION

To prepare dimethylbutenolide (**6**), hydroxyacetone (**2**) was acetylated to acetyloxyacetone (**3**) with acetyl chloride in pyridine[3,4] in 77% yield (Fig. 1). Reformatsky reaction[5] of **3** with ethyl 2-bromopropionate and granulated zinc in ether afforded a mixture of ethyl 4-acetyloxy-3-hydroxy-2,3-dimethylbutyrate (**4**) and 4-hydroxy-3,4-dimethyl-dihydrofuran-2-one (**5**). When this mixture was refluxed in toluene with *p*-toluenesulfonic acid and anhydrous $MgSO_4$ as a drying agent,[6] **4** quickly cyclized to **5**, and **5** slowly dehydrated to 2,3-dimethyl-2-butenolide (**6**). The yield of **6** from **3** was 72%.

Reduction of **6** to make 3,4-dimethylfuran (**7**) was done with diisobutylaluminum hydride (DiBAL) and proceeded in 40% yield.[7] The entire synthetic pathway to **7** was shortened from six steps [1] to just four by changing from the previously used Diels–Alder route[1] to that based on Reformatsky chemistry via intermediate **6**. The new method was efficient, used cheaper reagents, and was simpler to perform.

A minor difficulty was removal of toluene from **6,** and residual toluene was the major impurity after distillation (23%, by gas chromatography, GC). The small amount of this solvent did not interfere with

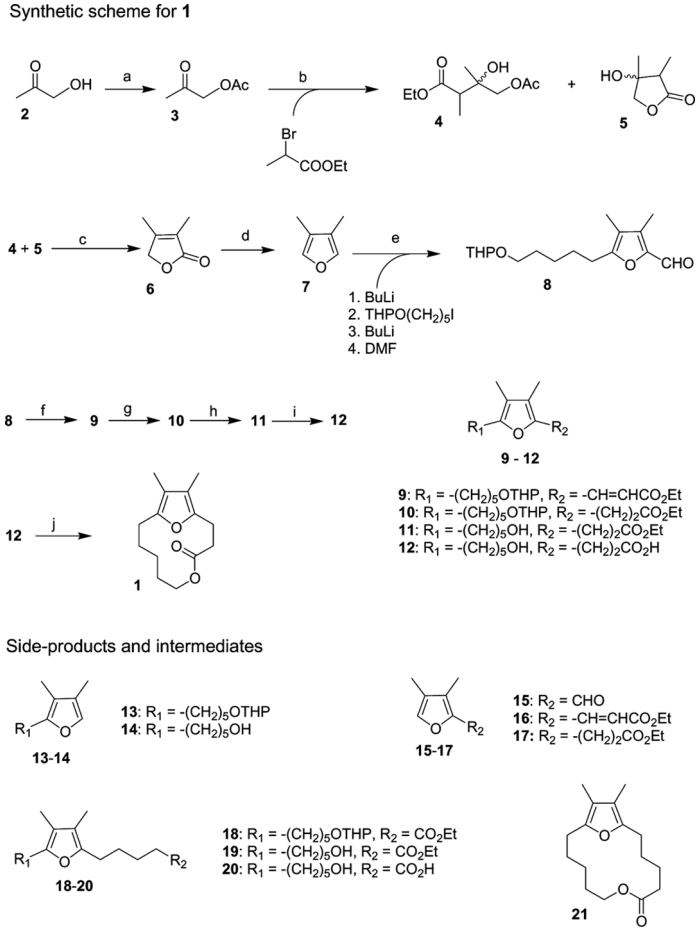


***Figure 1.*** Synthesis of *Galerucella* macrolide pheromone (**1**) and various side products of reaction steps (see text). Reaction conditions: (a) pyridine, 0°C, acetyl chloride addition over 45 min then reflux 3 h; 77% from **2**; (b) granular zinc, ether, iodine catalyst, reflux 4 h; (c) *p*-toluenesulfonic acid, powdered $MgSO_4$, toluene, reflux 6 h; 70% from **3**; (d) diisobutylaluminum hydride, ether, −20°C, 1 h; 40%; (e, in one pot) (1) addition of BuLi to **7**, THF, −15°C, 2 h, (2) addition of 2-[(5-iodopentyl)oxy]tetrahydropyran, −15°C, 1 h, then rt, 1 h, (3) addition of BuLi, 0°C, 2 h, (4) addition of dimethylformamide, 0°C, 15 min, then rt, 1 h; 56% overall; (f) triethyl 2-phosphonoacetate, Li*Ot*Bu, hexane, 25°C 30 min, then addition of **8**, 2 h; 87%; (g) 10% *p*d on carbon, hexane, $h_2$ (1 atm), rt, 4 h; 95%; (h) pyridinium *p*-toluenesulfonate, EtOH, 55°C, 3.5 h; quant.; (i) KOH, 1:1 MeOH/$H_2O$, 45°C, 4 h, quant.; (j) diethyl azodicarboxylate, triphenylphosphine, toluene, rt, 15 min, then addition of **12** over 3.25 h; 60%.

subsequent reactions and was readily removed later, from higher molecular-weight products, but it made yield measurement for **6** (and **7**) more difficult. An additional washing/extraction step is described in the experimental section for removal of toluene, if this is desired.

As shown previously,[1] furan **7** could be lithiated at the 2-position[8] and then alkylated with 2-[(5-iodopentyl)oxy]tetrahydropyran to give the trisubstituted furan **13** (62% yield of **13** from **7**). In the subsequent reaction, **13** could be formylated[1,9] to **8** by lithiation of the 5-position, followed by reaction with dry *N*,*N*-dimethylformamide (DMF). Furan-containing compounds are often labile,[9] and in initial attempts to synthesize **1**, there was substantial loss of many furan intermediates during chromatographic purification on silica gel (for example, up to 50% for trisubstituted furan **13**). Here we found it was possible and convenient to do both addition reactions sequentially in one pot, allowing tetrasubstituted furan **8** to be prepared directly without having to isolate the rather labile **13**. Incomplete reactions in the one-pot approach gave **13** and aldehyde **15** as by-products. These were carried along in the reaction scheme until their derivatives (**14** and **17**) were removed during later steps, without chromatography.

To continue construction of the three-carbon acyl side chain, the aldehyde **8** was converted to unsaturated ester **9** by a Horner–Wadsworth–Emmons (HWE) condensation with triethylphosphonoacetate in hexane, using lithium *tert*-butoxide as the base.[10] This method is milder and consistently gives higher yields than the commonly used *n*-butyllithium base.[11] The yield of this reaction was improved from 40%[1] to 87%. Dry tetrahydrofuran (THF) is also an acceptable solvent for this reaction. The side-chain double bond of **9** was selectively reduced by hydrogenation over 10% Pd on carbon in hexane to give **10**.[1,12] Impurity **17** (Fig. 1), was removed from this relatively stable and nonvolatile product by Kugelrohr distillation, which was done to avoid possible interference with the final lactonization reaction. Deprotection of the tetrahydropyranyl (THP) ether of **10** with pyridinium *p*-toluenesulfonate in EtOH[13] afforded hydroxy ester **11**. Saponification of **11** with potassium hydroxide (KOH) in aqueous MeOH[1] yielded the hydroxy acid **12**. Intermediates **8**–**12** were not purified by chromatography, but the nonacidic impurities were easily removed when an aqueous solution of the potassium salt of hydroxy acid **12** was extracted with hexane.

The final reaction was to close the lactone ring. Previously,[1] lactone formation was accomplished by converting hydroxy acid **12** to a mixed anhydride with 2,4,6-trichlorobenzoyl chloride, followed by cyclization under high-dilution conditions in refluxing toluene using 4-(*N*,*N*-dimethylamino)pyridine as the catalyst.[14] Here we employed an alternative method that utilizes triphenylphosphine and diethyl azodicarboxylate to activate the hydroxyl function.[15] Some previously reported lactonizations were

done under high-dilution reaction conditions to prevent dimerization,[15,16] but this was less of a problem with **1**, and lactonization ran successfully at concentrations of up to 10 g per liter. This method proceeds at room temperature and proved very satisfactory.

In the original synthesis of **1**, formation of lactone dimer was noted [R. J. B. unpublished data] and was 10.5–13.5% the amount of **1** in three runs, verified by MS [$m/z$ (%) 472 ($M^+$, 100), 235 (17), 177 (48), 135 (75)] and proton NMR (much like that of **1**). Dimer formation results when the concentration of reactants during lactonization is too high. In the present study, the dimer was barely detectable (<1% the amount of **1**). Having to use the high-dilution technique is a substantial inconvenience when large batches of lactone are to be prepared because of the great volumes of solvents involved. Because of the low degree of dimerization observed here, the present lactonization reaction can be run with far less solvent.

An analog of **1**, with two additional carbons in the lactone ring, was also found in the final crude product. This artifact of synthesis was identified as 14,15-dimethyl-7,16-dioxabicyclo[11.2.1]hexadeca-1(15),13-dien-6-one (**21** in Fig. 1) by gas chromatographic/mass spectrometric (GC/MS) analysis (at 264, molecular weight was 28 mass units higher than **1**) and by NMR (two additional methylene carbons in ester portion of lactone ring). This same impurity **21** was found in the original synthesis[1] of **1** [R. J. B. unpublished data]. Formation of precursor**18** to this macrolide impurity occurred when **9** was converted to **10**, if triethyl phosphonoacetate (TEPA) was present in the hydrogenation reaction mixture. Homologation of esters to α,β-unsaturated esters with TEPA has been reported.[17] Formation of this macrolide impurity can be easily prevented by washing the HWE reaction mixture with 0.1 N NaOH during the workup and verifying removal of TEPA by GC.

In summary, improvements to the synthetic pathway include a concise Refomatsky-based route from commercially available **2** to **6** and subsequently **7**, an expeditious, one-pot route to aldehyde **8**, a more efficient HWE olefination, and the use of Mitsunobu lactonization chemistry. Overall yield, from starting materials, was increased from 1%[1] to 6%, and the total number of steps was reduced from 13 to 10. These improvements should aid the practical availability of this pheromone.

## EXPERIMENTAL

### Chemicals and General Methods

Dry THF was prepared by distillation from sodium benzophenone ketyl. Commercially available organic reagents were obtained from Aldrich and

were used without further purification. Reactions were generally performed under an atmosphere of dry argon in oven-dried glassware. Removal of solvent during workups was accomplished by rotary evaporation at water aspirator vacuum.



## Analysis of Reaction Products

Progress of synthetic reactions was monitored by GC or GC/MS. All structures were additionally verified by NMR. The $^{1}H$ and $^{13}C$ chemical shifts for compounds **8**–**13** and **1** are given in Tables 1 and 2, respectively; numbered structures are given in Fig. 2.

The Hewlett-Packard (HP) 5890 Series II gas chromatograph was equipped with flame ionization detector and split/splitless inlet and was interfaced to an HP ChemStation data system. The column was a DB-5 capillary (30 m × 0.25 mm, 0.25-μm thick film, J&W Scientific, Folsom, CA). Carrier gas was He. The oven temperature was

**Table 1.** Proton shifts ($CDCL_3$)

| | Compound | | | | | | |
|---|---|---|---|---|---|---|---|
| Position | **13** | **8** | **9** | **10** | **11** | **12** | **1** |
| 1 | 3.74, 3.39 | 3.73, 3.38 | 3.74, 3.40 | 3.74, 3.39 | 3.64 | 3.67 | 4.21 |
| 2 | 1.62, 1.62 | 1.61, 1.61 | 1.64, 1.64 | 1.62, 1.62 | 1.58 | 1.57 | 1.72 |
| 3 | 1.40, 1.40 | 1.40, 1.40 | 1.41, 1.41 | 1.37, 1.37 | 1.37 | 1.37 | 1.21 |
| 4 | 1.62, 1.62 | 1.69, 1.69 | 1.66, 1.66 | 1.59, 1.59 | 1.59 | 1.59 | 1.62 |
| 5 | 2.55, 2.55 | 2.64, 2.64 | 2.58, 2.58 | 2.51, 2.51 | 2.51 | 2.53 | 2.60 |
| 6 | — | — | — | — | — | — | — |
| 7 | — | — | — | — | — | — | — |
| 7A | 1.87 | 1.91 | 1.88 | 1.83 | 1.83 | 1.83 | 1.83 |
| 8 | — | — | — | — | — | — | — |
| 8A | 1.92 | 2.26 | 2.05 | 1.85 | 1.85 | 1.86 | 1.86 |
| 9 | 7.04 | — | — | — | — | — | — |
| 10 | | 9.64 | 7.43 | 2.84 | 2.85 | 2.87 | 2.90 |
| 11 | | | 6.18 | 2.58 | 2.58 | 2.62 | 2.42 |
| 12 | | | — | — | — | — | — |
| 1′ | 4.58 | 4.56 | 4.59 | 4.58 | | | |
| 2′ | 1.71, 1.58 | 1.70, 1.56 | 1.72, 1.58 | 1.71, 1.58 | | | |
| 3′ | 1.83, 1.52 | 1.81, 1.52 | 1.84, 1.54 | 1.83, 1.53 | | | |
| 4′ | 1.58, 1.53 | 1.55, 1.52 | 1.56, 1.53 | 1.57, 1.53 | | | |
| 5′ | 3.87, 3.50 | 3.85, 3.49 | 3.86, 3.51 | 3.87, 3.50 | | | |
| 1″ | | | 4.23 | 4.13 | 4.14 | | |
| 2″ | | | 1.32 | 1.26 | 1.26 | | |

**Table 2.** Carbon shifts ($CDCL_3$)

| | Compound | | | | | | |
|---|---|---|---|---|---|---|---|
| Position | **13** | **8** | **9** | **10** | **11** | **12** | **1** |
| 1 | 67.5 | 67.3 | 67.4 | 67.5 | 62.9 | 62.9 | 63.0 |
| 2 | 29.5 | 29.4 | 29.4 | 29.5 | 32.6 | 32.4 | 25.3 |
| 3 | 25.6 | 25.9 | 25.9 | 25.8 | 25.2 | 25.2 | 22.3 |
| 4 | 28.3 | 27.7 | 28.0 | 28.5 | 28.4 | 28.3 | 25.0 |
| 5 | 26.0 | 26.5 | 26.3 | 26.0 | 25.9 | 25.7 | 23.2 |
| 6 | 151.2 | 158.7 | 154.3 | 148.8 | 148.7 | 148.8 | 148.3 |
| 7 | 114.4 | 118.8 | 117.6 | 114.6 | 114.7 | 115.0 | 115.2 |
| 7A | 7.9 | 7.6 | 8.0 | 8.3 | 8.3 | 8.3 | 8.0 |
| 8 | 120.9 | 135.5 | 127.5 | 115.4 | 115.4 | 115.5 | 115.2 |
| 8A | 8.3 | 8.8 | 8.9 | 8.3 | 8.3 | 8.3 | 8.3 |
| 9 | 136.2 | 147.0 | 144.6 | 145.9 | 146.0 | 145.7 | 146.2 |
| 10 | | 176.7 | 129.3 | 21.7 | 21.7 | 21.6 | 22.8 |
| 11 | | | 111.6 | 33.3 | 33.3 | 32.9 | 34.9 |
| 12 | | | 167.9 | 172.9 | 173.0 | 177.0 | 173.8 |
| 1′ | 98.8 | 98.9 | 98.8 | 98.8 | | | |
| 2′ | 30.8 | 30.8 | 30.7 | 30.8 | | | |
| 3′ | 19.6 | 19.7 | 19.6 | 19.7 | | | |
| 4′ | 25.5 | 25.5 | 25.4 | 25.5 | | | |
| 5′ | 62.2 | 62.4 | 62.3 | 62.3 | | | |
| 1″ | | | 60.1 | 60.3 | 60.4 | | |
| 2″ | | | 14.4 | 14.1 | 14.2 | | |

programmed from 50 to 280°C at 10°C/min, and the detector temperature was 280°C. The inlet temperature was 220°C, and 1.0-μL sample injections were made in splitless mode.

Electron impact mass spectra (70 eV) were obtained with an HP 5973 MSD instrument, interfaced to an HP 6890 GC, equipped with a splitless inlet. Several columns were used but gave comparable results to that used for GC. The oven temperature was typically programmed from 50 to 250°C at 10°C/min, the inlet temperature was 220°C, and the transfer line temperature was 250°C. A thin-film column (DB-1, 15 m × 0.25 mm, mm, 0.10-μm-thick film) was used to analyze for the dimer of **1** (oven temperature programmed from 50 to 300°C at 10°C/min, inlet temperature 280°C, and transfer line temperature 300°C).

$^1$H NMR, $^{13}$CNMR, and 2D NMR spectra were acquired on a Bruker (Bellerica, MA) Avance 500 spectrometer using a 5-mm inverse broadband probe. Samples were dissolved in $CDCl_3$, and all spectra were acquired at 300 K. $^1$H and 2-D homonuclear one-bond *J* coupling correlation spectroscopy (COSY) spectra were acquired at 500 MHz, whereas $^{13}$C and

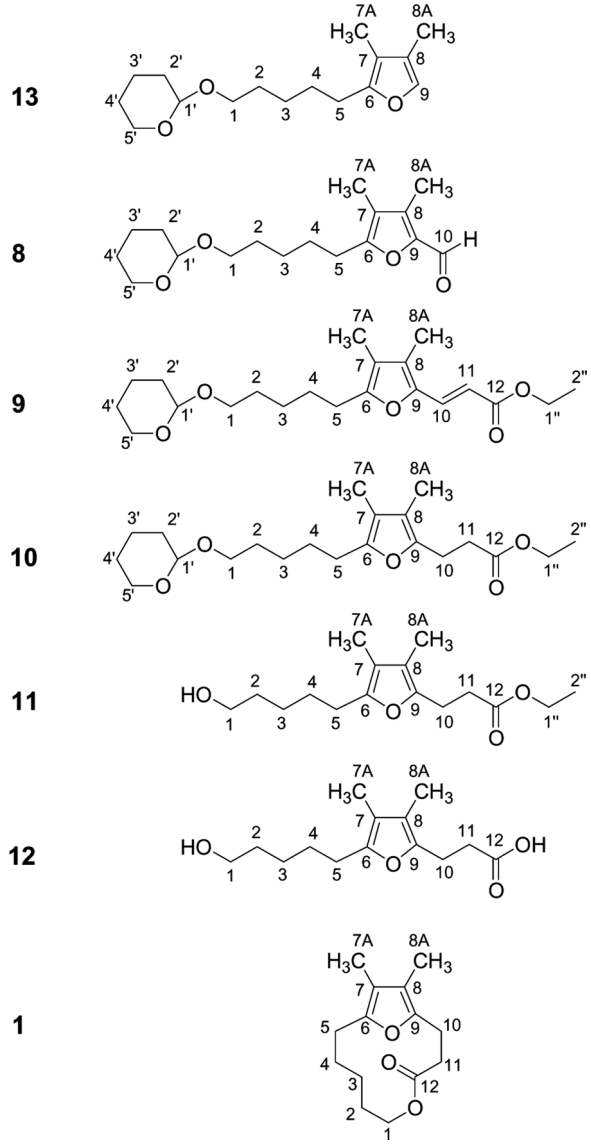


*Figure 2.* Structures for the $^{1}H$ and $^{13}C$ chemical shifts for compounds **8**–**13** and **1**, given in Tables 1 and 2.

distortionless enhancement by polarization transfer (DEPT) spectra were acquired at 125 MHz. Heteronuclear single quantum coherence (HSQC) and heteronuclear multiple bond correlation (HMBC) experiments were

conducted to aid in the assignment of chemical shifts. $^{1}$H- and $^{13}$C-Predictive software[18] and analogy to known compounds also aided shift assignment. Chemical shifts are reported as parts per million (PPM) relative to tetramethylsilane (TMS).

## Synthetic Details

The synthetic precursor, 2-[(5-iodoopentyl)oxy]tetrahydropyran, was prepared from 1,5-pentanediol by monohalogenation with aqueous HI (supplementary materials for Ref. 1), followed by protection of the free hydroxyl group as a THP ether.[13] 5-Iodoopentan-1-ol MS (EI) $m/z$ (%) 214 ($M^+$, 0.3), 155 (5), 141 (2), 127 (3), 87 (35), 69 (100), 55 (8), 41 (73); 2-[(5-iodoopentyl)oxy]tetrahydropyran MS (EI) $m/z$ (%) 298 ($M^+$, 0.6), 297 (5), 197 (17), 183 (3), 171 (12), 155 (7), 85 (100), 69 (50), 56 (12), 41 (34).

### Acetoxyacetone (**3**)

Hydroxyacetone (**2**, 50 g, 0.68 mol) and pyridine (58.2 mL, 57 g, 0.72 mol) were added to a 250-mL three-neck flask equipped with a mechanical stirrer, thermometer, and dropping funnel. The mixture was stirred at 0°C (ice bath) while acetyl chloride (53.2 mL, 59 g, 0.75 mol) was added dropwise (reaction exothermic) over the course of 45 min, keeping the temperature less than 30°C. Upon completion of the addition, the dropping funnel was replaced with a reflux condenser. When the reaction approached completion, as evidenced by a steady or dropping temperature, the mixture was heated to 60°C for 3 h. After cooling, ether (100 mL) was added to precipitate by-product pyridinium hydrochloride, which was removed by filtration. The precipitate was rinsed with additional ether ($3 \times 100$ mL). The ether filtrates were combined and washed successively with brine ($2 \times 40$ mL), saturated aqueous $Na_2CO_3$ (20 mL), and water (20 mL). The resulting pale yellow solution was dried ($MgSO_4$). After filtration and removal of solvent, oil remained (67.8 g). Kugelrohr distillation (oven temperature 40°C, 0.04 torr) afforded 64.5 g of a colorless oil, which was 94% **3** (yield of **3** from **2** was 77%). MS (EI) $m/z$ (%) 116 ($M^+$, 12), 86 (14), 73 (5), 43 (100).

### Ethyl 4-Acetyloxy-3-hydroxy-2,3-dimethylbutyrate (4) and 4-Hydroxy-3,4-dimethyl-dihydro-furan-2-one (**5**)

Granular zinc (30 g, 0.46 mol) was added to a 500-mL, round-bottomed flask, and the metal was covered with ether (120 mL). Ethyl 2-bromopropionate (31 mL, 43.2 g, 0.23 mol), ester **3** (25 g, 0.22 mol), and a

crystal of iodine were added. The reaction mixture was heated at gentle reflux until **3** was fully consumed (4 h, reaction monitored by GC/MS). Onset of reaction was characterized by disappearance of iodine color, followed by development of cloudiness and yellow color in solution.

The reaction mixture was cooled to 0°C, and 2 N HCl (120 mL) was added. The phases were separated, and the aqueous phase was extracted with ether ($3 \times 50$ mL). The organic phases were combined, washed with brine (50 mL) and saturated aqueous $NaHCO_3$ (20 mL), and then dried ($Na_2SO_4$). Filtration and removal of solvent afforded 29.2 g of a mixture containing **4** and **5** (two GC-separable diastereomers of each). Mass spectrum of major diastereomer for **4**: MS (EI) $m/z$ (%) 203 (M-15, 0.05), 173 (M-45, 1), 145 (40), 131 (23), 117 (9), 102 (23), 99 (42), 74 (26), 57 (17), 43 (100); and for **5**: MS (EI) $m/z$ (%) 130 ($M^+$, 14), 112 (28), 99 (7), 84 (9), 72 (13), 56 (20), 43 (100). Mass spectra of diastereomers were nearly identical.

## 2,3-Dimethyl-2-butenolide (**6**)

Toluene (200 mL), powdered anhydrous $MgSO_4$ (10 g), *p*-toluenesulfonic acid (10 g), **4** + **5** (30.6 g), and several boiling stones were added to a 500-mL, three-neck flask equipped with a mechanical stirrer and reflux condenser. The vigorously stirred mixture was heated to reflux. The solution darkened rapidly. Reaction progress was monitored periodically by GC-MS. Cyclization of **4** to **5** occurred quickly, but after 3 h, dehydration of **5** to **6** was still incomplete. Additional $MgSO_4$ (5 g) and *p*-toluenesulfonic acid (2 g) were added, and the reaction was complete after refluxing for another 4 h. The mixture was cooled and filtered. The filtrate was washed successively with brine (100 mL), 5% $NaHCO_3$ solution (100 mL), and brine (100 mL) again. The combined aqueous layers were neutralized with solid $NaHCO_3$ and extracted with ether ($3 \times 100$ ML). The orange-colored organic phases were combined and dried ($MgSO_4$). Solvent was removed by rotary evaporation. Kugelrohr distillation (oven temperature 60–100°C, 0.10 torr) afforded 17.9 g of a very pale yellow oil, which was 59% **6** (yield from compound **3** was 72%). The major impurities were toluene (23%), and **5** (9%) by GC analysis; other impurities were not greater than 3%. Removal of toluene from **6** by rotary evaporation without losing product was difficult. MS (EI) $m/z$ (%) 112 ($M^+$, 73), 83 (70), 55 (100), 41 (8). $^1$H NMR δ 1.82 (3H, s, C**H**$_3$), 2.02 (3H, s, C**H**$_3$), 4.62 (2H, s, -C**H**$_2$-O). $^{13}$C NMR δ 8.3 and 12.2 (-**C**H$_3$), 72.5 (-**C**H$_2$-O), 123.2 and 156.2 (olefinic **C**), and 175.4 (carbonyl **C**).

3,4-Dimethylfuran (**7**)

Dry ether (200 mL, distilled from benzophenone ketyl) and **6** (8.0 g, 71 mmol) were added to a 500-mL, three-neck flask equipped with a mechanical stirrer, thermometer, and dropping funnel. The mixture was stirred and cooled to −20°C. Diisobutylaluminum hydride (1 M solution in hexane, 80 mmol) was added slowly, avoiding temperature increase. After addition was complete, the mixture was allowed to stir at −20°C for 1 h before quenching the reaction with 10% aqueous $H_2SO_4$ (50 mL). After warming to ambient temperature, the organic and aqueous phases were separated. The aqueous phase was extracted with ether (3 × 40 mL), and the ether extracts were combined with the organic phase, then washed with brine (50 mL) and 5% $NaHCO_3$ solution (50 mL), and dried ($MgSO_4$). Filtration and removal of solvent by distillation through a Vigreux column at atmospheric pressure, followed by Kugelrohr distillation (oven temperature 40°C, 16–20 mm Hg) afforded 11.2 g of a clear colorless oil. The distillate contained primarily **7** and residual solvents (hexane, methylcyclopentane, and toluene). By NMR (calculations based on integrals of methyl signals), the product was 25% **7** by weight; yield corrected for purity was 40%. Product **7** is relatively volatile, and some was lost in the workup, reducing the yield. Removal of residual solvents from **7** was difficult, but these did not interfere with the next reaction. MS (EI) *m/z* (%) 96 ($M^+$, 100), 95 (43), 81 (12), 67 (69), 65 (18), 53 (24), 41, (28), 39 (26). $^1$H NMR δ 1.97 (6H, s, C**H**$_3$), 7.17 (2H, s, **H**C=).

The following procedure can be used to remove toluene from compound **6** (and therefore, from **7**): Distilled **6** (3.38 g) was dissolved in water (60 mL), and nonpolar organic impurities, such as toluene, were washed away with hexane (60 mL). The hexane phase was extracted with water (2 × 15 mL). The aqueous phases, now containing **6**, were combined, and NaCl (30 g) was added. The brine-containing solution turned cloudy (salting out of **6**) and was extracted with ether (4 × 50 mL). After drying ($Na_2SO_4$) and removing the solvent, oil remained (2.76 g, purity of 98% by GC analysis). Reduction of **6** (2.73 g of purified product, 24 mmol) to **7** with diisobutylaluminum hydride (1 M solution in hexane, 28 mmol), conducted as before with removal of solvent at atmospheric pressure followed by Kugelrohr distillation, afforded a colorless oil (1.24 g). By NMR, this product contained 90% **7** by weight, and yield from **6** was 49%.

3,4-Dimethyl-5-[5-(tetrahydrofuran-2-yloxy)pentyl]-2-furaldehyde (**8**)

A stirred solution of furan **7**(1.18 g, 12.3 mmol) in dry THF (40 mL) was cooled to −20°C. Butyllithium (2.5 M solution in hexane, 13 mmol, slight excess) was added dropwise, and the solution was stirred at −20°C for 2 h.

Aliquots were periodically taken by syringe, quenched with $D_2O$, and analyzed by GC/MS to follow the progress of lithiation. (Molecular weight of **7** increased from 96 to 97 if lithiation had occurred before $D_2O$ was added; $D_2O$ had no effect on the mass spectrum when added to **7** before butyllithium.) Upon warming again to room temperature, GC/MS analysis revealed lithiation was >80% complete. (Observed percent lithiation is typically less than actual percent lithiation because of traces of water picked up during the handling of samples). Then 2-[(5-iodopentyl)oxy]tetrahydropyran (3.91 g, 13 mmol) was added dropwise. Stirring was continued for 1 h at −20°C and then for 1 h at room temperature. After alkylation of **7** to **13** was verified by GC/MS analysis, the solution was cooled to −5°C. Butyllithium solution (2.5 M in hexane, 13 mmol) was added. Stirring was continued for 1.5 h at room temperature. Aliquots were periodically taken by syringe, quenched with $D_2O$, and analyzed by GC/MS to follow the progress of lithiation. (Molecular weight of **13** increased from 266 to 267 if lithiation had occurred before $D_2O$ was added; $D_2O$ had no effect on the mass spectrum when added to **13** before butyllithium.) GC/MS analysis revealed lithiation was >80% complete. After cooling once more in an ice bath, dry dimethylformamide (DMF, distilled from $CaH_2$, 1.5 mL, 19.4 mmol) was added to the solution via syringe. The mixture was stirred at 0°C for 30 min and then 3 h at room temperature. After quenching with water (10 ml), the phases were separated, the organic phase became bright orange, and the aqueous phase became ruby red in color. The aqueous phase was extracted with 1:1 ether/hexane (4 × 40 ml). The combined organic layers were successively washed with 1 *N* HCl (10 mL), water (10 mL), 5% sodium bicarbonate (10 mL), and brine (10 mL). A minor amount of additional product was recovered from these aqueous washes by neutralizing with solid $NaHCO_3$ and extracting with 1:1 ether/hexane (3 × 40 ml), then washing with brine (5 mL). All organic extracts were combined and dried (MgSO4). Filtration and removal of solvent resulted in 3.46 g of product, which contained (GC analysis) 56% product **8** (yield from **7** was 56%), 13% 3,4-dimethyl-furanaldehyde (**15**), and 10% intermediate **13**. MS (EI) $m/z$ (%) 294 ($M^+$, 0.5), 210 (100), 194 (5), 180 (7), 163 (8), 151 (59), 137 (41), 125 (34), 109 (10), 85 (78), 67 (15). The NMR spectral data are given in Table 1. This compound was used in the subsequent reaction without further purification. Mass spectrum of impurity **15**: MS (EI) $m/z$ (%) 124 ($M^+$, 100), 95 (14), 81 (5), 67 (21).

### Ethyl 3-{3,4-Dimethyl-5-[5-(tetrahydrofuran-2-yloxy)pentyl]-2-furyl}acrylate (**9**)

Triethyl 2-phosphonoacetate (TEPA, 2.84 g, 12.6 mmol) was added to dry hexane (5 ml, dried over Na metal), and the mixture was stirred at 25°C.

Lithium *tert*-butoxide (1.0 M solution in hexane, 13 mmol) was added in one portion via syringe. The solution became turbid and only slight heating of the mixture was observed. After stirring for one h, a solution of the aldehyde **8** (3.43 g of previous product, containing 6.53 mmol **8**, in 2 mL of ether) was added dropwise. The solution clarified as aldehyde was added but an oily paste appeared. Ether (20 mL) was added, and the oil slowly dissolved. The mixture was allowed to stir for a total of 5.5 h before water (10 mL) was added to quench the reaction. The hexane phase, containing the product, was washed with 0.1 *N* NaOH (10 mL) and water (10 mL). (The NaOH wash removes excess TEPA, which, if present, would lead to formation of homolog **18** during the subsequent hydrogenation reaction of **9** to **10**.) The aqueous phase was back-extracted with hexane (30 mL), and the hexane phases were combined, washed with a saturated brine solution (10 mL), and dried ($Na_2SO_4$). Removal of TEPA was verified by GC analysis. Filtration and removal of solvent resulted in 4.21 g of product, which contained 49% product **9** (yield from **8** was 87%), 23% ethyl 3-{3,4-dimethyl-2-furyl}-acrylate (**16**) from residual **15**, and 10% compound **13**. MS (EI) $m/z$ (%) 364 ($M^+$, 9), 280 (56), 234 (52), 207 (37), 179 (16), 133 (17), 85 (100), 67 (15). The NMR spectral data are given in Table 1. This compound was used in the next reaction without further purification. Mass spectrum of impurity **16**: MS (EI) $m/z$ (%) 194 ($M^+$, 80), 149 (100), 122 (60), 107 (30), 91 (47), 77 (37), 67 (15).

### Ethyl 3-{3,4-Dimethyl-5-[5-(tetrahydrofuran-2-yloxy)pentyl]-2-furyl}propanoate (**10**)

Hexane (125 ml), ester **9** (4.19 g of previous product, 5.63 mmol), and the 10% palladium on carbon catalyst (ca. 100 mg) were added to a 500-mL round-bottomed flask that was capped with a septum and equipped with a magnetic stirrer and a two syringe needles. Either hydrogen or argon could be delivered through one needle, and the second needle served as a vent. The mixture was stirred and hydrogen was bubbled in, vigorously at first, to saturate the system, and then more slowly, reducing to several bubbles per second. To monitor progress by GC, the solution was purged with argon, an aliquot was taken, and, if the reaction was incomplete, hydrogen was again introduced. After 7 h, additional solvent (125 mL) and 10% palladium on carbon catalyst (ca. 100 mg) were added. The reaction was complete after 24 h, and the mixture was purged with argon and filtered through a plug of powdered $MgSO_4$ to remove the catalyst. The amount of the crude product after solvent removal was 3.86 g, which contained 36% saturated ester **10**, 19% ethyl 3-{3,4-dimethyl-2-furyl}propanoate (**17**) from residual **16**, and 13% compound **13**. The ester impurity **17** was removed by Kugelrohr

distillation of this lower-boiling point compound (0.1 torr, 80°C) to afford an oily residue (2.82 g), which contained 12% compound **13** and 70% product **10**. The yield of the conversion of **9** to **10** was 96%. There was less than 3% overreduction (i.e., of the furan ring). MS (EI) $m/z$ (%) 366 ($M^+$, 25), 321 (10), 281 (100), 263 (13), 235 (10), 209 (26), 193 (83), 177 (22), 149 (12), 135 (80), 85 (75), 67 (10). The NMR spectral data are given in Table 1. The compound was used directly in the next reaction. Mass spectrum of ester impurity **17** (removed by Kugelrohr distillation): MS (EI) $m/z$ (%) 196 ($M^+$, 19), 167 (4), 122 (57), 109 (100), 79 (11). The mixture also contained a small amount (<2%) of ethyl 3-{3,4-dimethyl-5-[5-(tetrahydrofuran-2-yloxy)pentyl]-2-furyl}pentanoate (**18**): MS (EI) $m/z$ (%) 394 ($M^+$, 7), 349 (5), 309 (63), 263 (14), 237 (11), 177 (20), 149 (39), 135 (36), 85 (100). This ester could be as much as 19% of the hydrogenation product if the excess TEPA was not removed.

Ethyl 3-[5-(5-Hydroxypentyl)-3,4-dimethyl-2-furyl]propanoate (**11**)

The THP protecting group was removed from **10** (2.80 g of previous product, 5.36 mmol), using absolute ethanol (80 mL) and pyridinium *p*-toluenesulfonate (PPTS, 250 mg, 1.02 mmol) catalyst. The mixture was stirred and heated to 55°C for 4.5 h, when analysis by GC-MS indicated that the reaction was complete. The ethanol was removed by rotary evaporation. The product was taken up in ether (10 mL) and passed through a 1.0 cm × 5 cm column of silica gel to remove the catalyst. The silica was rinsed with 20 mL of ether to ensure complete recovery of the hydroxy ester **12**. Removal of solvent afforded 2.32 g of oil, which contained 67% **11** (yield from **10** was >99%) and 8% 3,4-dimethyl-2-(5-hydroxypentyl)-furan (**14**) from residual **13**. There was evidence for other impurities, but none of these exceeded 2% by GC. MS (EI) $m/z$ (%) 282 ($M^+$, 26), 237 (8), 209 (54), 195 (25), 149 (8), 135 (100), 123 (11), 91 (8), 55 (11). The NMR spectral data are given in Table 1. This compound was used directly in the next reaction. Mass spectrum of impurity, **14**: MS (EI) $m/z$ (%) 182 ($M^+$, 19), 149 (3), 135 (8), 123 (15), 109 (100), 79 (12). The mixture also contained a small amount (<2%) of ethyl 3-{3,4-dimethyl-5-[5-hydroxyoxy)pentyl]-2-furyl}pentanoate (**19**): MS (EI) $m/z$ (%) 310 ($M^+$, 33), 265 (19), 237 (58), 209 (9), 195 (89), 149 (100), 135 (68), 123 (25), 109 (15).

3-[5-(5-Hydroxypentyl)-3,4-dimethyl-2-furyl]propanoic Acid (**12**)

A 1:1 mixture of water and MeOH (80 mL) was placed in a flask with solid KOH (2.25 g). Ester **11** (2.30 g of previous product, 5.36 mmol)

was added, and the mixture was heated to 45°C and stirred for 4 h. A small amount of fine precipitate became visible upon cooling. The solution was concentrated to about 40 mL (most of the MeOH was removed), water (20 mL) was added, and the resulting solution was extracted with hexane ($3 \times 40$ mL) to remove nonacidic organic impurities, such as compound **14**. The combined hexane washes were back-extracted with water (10 mL), which had been made alkaline with a few mg of KOH. The combined aqueous solution was acidified ($pH < 2$) with 25% HCl, and the solution was extracted with ether ($5 \times 40$ mL) to recover free acid **12**. The combined extracts were washed with water (10 mL) and brine (10 mL) and dried ($MgSO_4$). Filtration and concentration of solvent at water aspirator pressure to about 5 mL, followed by removal of the remaining solvent under a stream of argon, afforded 2.17 g of product which contained 78% compound **12** (>99% yield from **11**), about 1% 3-[5-(5-hydroxypentyl)-3,4-dimethyl-2-furyl]pentanoic acid (**20**), and minor unidentified impurities. MS (EI) $m/z$ (%) 254 ($M^+$, 25), 195 (18), 181 (100), 149 (5), 135 (49), 91 (6), 55 (8). The NMR spectral data are given in Table 1. This compound was stored as a solution in ether at −70°C and used directly in the final reaction. The solvent was removed under a stream of argon just before use.

12,13-Dimethyl-5,14-dioxabicyclo[9.2.1]tetradeca-1(13),11-dien-4-one (**1**)

Anhydrous deoxygenated toluene (24 mL, dried by distillation from the sodium ketyl of benzophenone) was added to triphenylphosphine (2.11 g, 8.05 mmol). Diethyl azodicarboxylate (DEAD, 3.7 mL of a 40% solution in toluene, 8.22 mmol) was added at 25°C, and the mixture was stirred for 15 min. Hydroxy acid **12** (409 mg of previous product, 1.61 mmol, in 16 mL dry toluene) was added at a rate of 5 mL/h via syringe pump. The mixture was stirred for a further 2.5 h and stored overnight at −20°C. After warming to ambient temperature, the solvent was removed.

A large portion of the impurities (related to DEAD and by-product triphenylphosphine oxide) were removed from the product oil by adding 20% ether in hexane (120 mL), followed by silica gel (10 g), and stirring the mixture for 15 min. After filtration through a sintered glass funnel, the filtrate containing **1** was saved. The dried filter cake was transferred to a column, and additional **1** was eluted with 20% ether in hexane (80 mL). The solutions, containing **1**, were stored at −20°C overnight, decanted from precipitated triphenylphosphine oxide, then combined, reduced in volume from 320 mL to 75 mL, and again cooled to −20°C overnight to remove additional precipitated triphenylphosphine oxide.

After solvent removal, the oil contained partially purified **1**. Alternatively, the product oil (dissolved in toluene) can be purified by direct application to a larger silica column as described later for the partially purified material.

The product was purified on an open column of silica gel (20 g, column dimensions 2.8 cm × 9.5 cm), eluting with hexane (25 mL, 1 fraction), 5% ether in hexane (40 mL, 1 fraction), and 10% ether in hexane (10 mL, 15 fractions). Compound **1** was present, in high purity, in the sixth through tenth fractions, eluted with 10% ether in hexane. The fifth fraction eluted with 10% ether also contained **1** but with a significant amount of a side product (**21**, 13% of total by GC analysis). When chromatography was complete, 220 mg of **1** had a final purity of 95%, and 22 mg had a purity of 79%; overall yield of **1** from **12** was 60%. MS (EI) $m/z$ (%) 236 ($M^+$, 82), 208 (19), 193 (33), 180 (8), 149 (22), 135 (100), 123 (28), 91 (18), 77 (20). The NMR spectral data are given in Table 1. The MS and NMR spectral data were consistent with previous work.[1]

A different synthetic batch, from which TEPA had not been removed during the earlier synthetic step, contained a higher (19%) amount of side product **21**. This was chromatographed to afford 20 mg of the compound for analysis by GC/MS and NMR. MS (EI) $m/z$ (%) 264 ($M^+$, 100), 249 (8), 235 (8), 221 (16), 208 (26), 195 (15), 193 (12), 191 (15), 177 (79), 149 (37), 135 (97), 123 (22), 109 (8), 91 (12), 77 (11). $^1$H NMR δ1.24 (2H, m, H-3), 1.44 (2H, m, H-12), 1.64 (2H, m, H-2), 1.69 (2H, m, H-11), 1.84 (6H, s, H-7a and H-8a), 2.32 (2H, t, $J_{12\text{-}13} = 6.2$, H-13), 2.54 (2H, t, $J_{10\text{-}11} = 5.8$, H-10), 2.58 (2H, t, $J_{4\text{-}5} = 6.1$, H-5), 4.09 (2H, t, $J_{1\text{-}2} = 5.4$, H-1). $^{13}$C NMR δ 8.20 and 8.2.2 (7a and 7b, -**C**H$_3$), 23.19 (C-3), 24.05 (C-12), 24.75 (C-5), 25.12 (C-10), 26.22 (C-4), 26.73 (C-11), 27.62 (C-2), 35.24 (C-13), 62.62 (C-1, -**C**H$_2$-O), 115.15 (C-7), 115.77 (C-8), 146.69 (C-9), 147.74 (C-6), 173.35 (C-14, carbonyl **C**).

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