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Synthesis of the Insecticide Prothrin and Its Analogues from Biomass-Derived 5-(Chloromethyl)furfural

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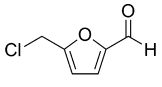
Supporting Information

ABSTRACT: Prothrin, a synthetic pyrethroid insecticide, was synthesized from the biomass-derived platform chemical 5-(chloromethyl)furfural in six steps and overall 65% yield. Two structural analogues of prothrin were also prepared following the same synthetic approach. Preliminary testing of these furan-based pyrethroids against the yellow fever mosquito *Aedes aegypti* indicates promising insecticidal activities.

KEYWORDS: *biomass, furans, pyrethroids, synthesis, 5-(chloromethyl)furfural*

INTRODUCTION

Previously, we have described the synthesis of the natural herbicide δ-aminolevulinic acid (**2**)[1] and the anti-ulcer drug ranitidine (Zantac) (**3**)[2] from the renewable platform chemical 5-(chloromethyl)furfural (CMF) (**1**), which can be derived in a single step from either sugars, cellulose, or raw biomass in isolated yields between 80 and 90%.[3] In a continuing effort to expand the derivative markets of CMF (**1**), we now report a simple, six-step approach to the furan-based pyrethroid insecticide prothrin (**4**) alongside five-step routes to analogues **5** and **6**.



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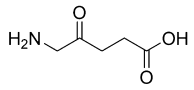

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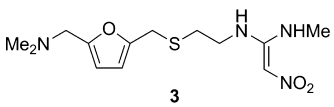

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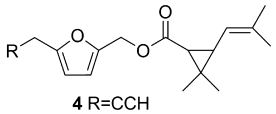
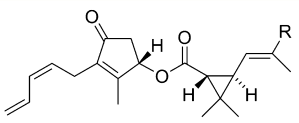
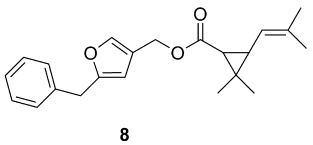


4 R=CCH
5 R=CN
6 R=OPh

The naturally occurring insecticide pyrethrum, isolated from flowers of *Chrysanthemum* sp., has been in commercial use for over 100 years.[4] Elucidation of the chemical structure of its active constituents [i.e., pyrethrins (**7**)] in 1924 ultimately led to the production of several synthetic pyrethroids.[5] As a result of extensive structure−activity studies, the insecticidal and toxicological properties of these compounds typically surpass those of the natural products. Prothrin (**4**) is a member of the synthetic furan-based pyrethroids,[6] which class also includes resmethrin (**8**), a high-volume commercial insecticide.[7]



7a R= Me
7b R= CO_2Me



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Pyrethroids are generally well-suited for agricultural and household uses because of their biodegradability and low mammalian toxicity, and demand for these products has increased in the past decade with the declining use of organophosphates. However, all United States Environmental Protection Agency (U.S. EPA)-registered pesticides are regularly submitted to a process by which they are systematically reviewed to establish that they can still perform their intended function without unreasonable adverse effects on human health or the environment, and this process applies constant pressure on the development of new generations of products that are even more selective in their mode of action.

The synthesis of prothrin (**4**) was first reported in 1969 and is always completed by esterification of 5-propargylfurfuryl alcohol (**10**) with chrysanthemic acid chloride.[6] Because chrysanthemic acid is commercially available as a synthetic version of the natural product,[8] the actual target of prothrin syntheses becomes compound **10**, and most approaches to this molecule have centered around either the reaction of a metalated derivative of furfuryl alcohol (**9**) with a propargyl electrophile[9] or a metalated acetylene with a 5-methyl-substituted furfuryl alcohol derivative incorporating a leaving group (**11**) (Scheme 1).[10,11] Looking to the structures of both compound **10** and CMF (**1**), it becomes apparent that a concise route connecting them should be achievable, and we

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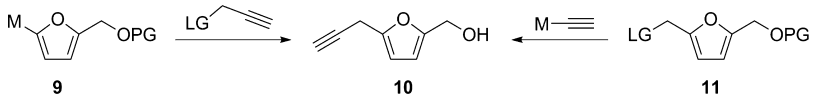
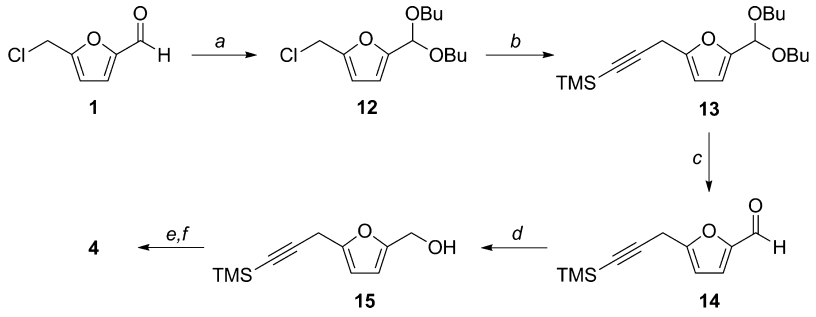
Scheme 1. Approaches to the Synthesis of 5-Propargylfurfuryl Alcohol (10)[a]



[a]LG, leaving group; PG, protecting group.

Scheme 2. [a]



[a]Reagents: *a*, 1-butanol, concentrated HCl (catalyst), 98%; *b*, TMS−acetylene, CuI, K_2CO_3, CH_3CN, 55 °C, 88%; *c*, 1 M aqueous HCl, 97%; *d*, $NaBH_4$, MeOH, 0 °C, 98%; *e*, chrysanthemic acid chloride, benzene, reflux, 95%; and *f*, Bu_4NF, THF, −20 °C, 84%.

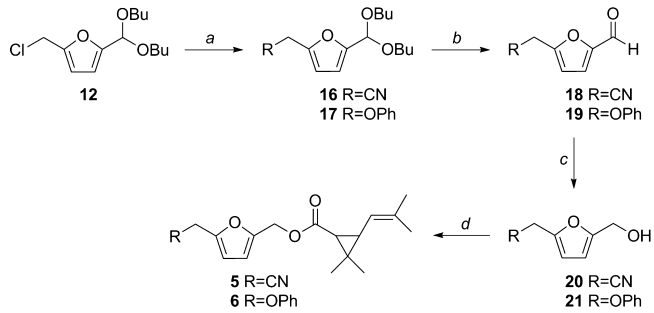
were naturally attracted to published methods that involved CMF (**1**) as a precursor to structure **11**[10] but considered the use of organometallics a serious drawback to any industrial application of this synthetic approach. We proposed that the installation of the propargyl group could instead be achieved by copper(I)-mediated coupling of the chloromethyl functionality to an acetylene derivative.[12] The synthesis is shown in Scheme 2.

Attempts to couple compound **1** and trimethylsilyl (TMS) acetylene in the presence of the aldehyde group were unsuccessful; thus, CMF (**1**) was protected as the dibutyl acetal (**12**). Coupling of the alkyne to compound **12** proceeded to give compound **13** in good yield, which was hydrolyzed to the furfural derivative (**14**). Reduction of compound **14** with sodium borohydride gave alcohol **15**. Compound **15** is essentially a protected form of compound **10**, but to complete the synthesis of prothrin (**4**), we esterified compound **15** with chrysanthemic acid chloride and, finally, desilylated with tetrabutylammonium fluoride. It was necessary to retain the TMS protecting group until the end of the synthesis, because any attempt to remove it at an earlier stage resulted in gradual isomerization of the triple bond to the allene.

The above-described route to prothrin (**4**) does not necessitate the synthesis of a 5-methylfurfuryl precursor to compound **10** but rather derives it directly from biomass. It also involves no organometallic reagents, requires no chromatographic separations until the final step, and proceeds in an overall 65% yield. The efficiency of this approach and the ready availability of CMF (**1**) presented an attractive opportunity to carry out analoging studies on the prothrin framework.

A highly apparent analogue to prothrin (**4**) is the cyanomethylfuran derivative (**5**), and this was targeted for synthesis along with the known resmethrin-like aryloxymethyl analogue (**6**).[13] Thus, in the approach to analogues **5** and **6**, the acetylene nucleophile is exchanged for cyanide and phenoxide, respectively. We had initially supposed that conversion of CMF (**1**) into acetal **12** would not be necessary in these cases, because compound **1** is known to be effectively substituted with nucleophiles, such as alcohols[3a] and azide anion.[1] However, attempts to directly substitute the chloromethyl group in compound **1** with either phenol or cyanide were unsuccessful. From substituted acetals **16** and **17**, the syntheses proceeded as for compound **4** but are one step shorter, because no deprotection is required at the end (Scheme 3). The overall yields of analogues **5** and **6** from CMF (**1**) were 51 and 70%, respectively.

Scheme 3. [a]



[a]Reagents: *a*, for compound **16**, NaCN, DMSO, 85 °C, 78%; for compound **17**, phenol, K_2CO_3, DMSO, 50 °C, 87%; *b*, 1 M aqueous HCl; *c*, $NaBH_4$, $MeOH/CH_2Cl_2$, 0 °C; and *d*, chrysanthemic acid chloride, benzene, reflux.

MATERIALS AND METHODS

2-(Chloromethyl)-5-(dibutoxymethyl)furan (12).[14] CMF (**1**) (2.00 g, 13.8 mmol) was dissolved in 1-butanol (40 mL), and concentrated HCl (0.1 mL) was added. The solvent was then removed using a rotary evaporator under high vacuum (0.1 mmHg) while cooling the evaporating flask in an ice−water bath. The product **12** was obtained as a yellow oil (3.721 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.32 (s, 1H), 6.29 (s, 1H), 5.47 (s, 1H), 4.53 (s, 2H), 3.51 (m, 4H), 1.52 (m, 4H), 1.35 (m, 4H), 0.88 (t, 7.3 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.1, 150.1, 110.4, 109.4, 96.5, 65.7, 37.7, 31.9, 19.5, 14.0. HRMS: $(M - OBu)^+$, $C_{10}H_{14}O_2Cl$ calculated, 201.0682; found, 201.0678.

2-(Dibutoxymethyl)-5-[3-(trimethylsilyl)prop-2-yn-1-yl]furan (13). Copper(I) iodide (0.269 g, 1.41 mmol), potassium carbonate (0.328 g, 2.37 mmol), and (trimethylsilyl)acetylene (0.21 mL, 0.15 g, 1.5 mmol) were added to a solution of compound **12** (0.328 g, 1.19

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mmol) in anhydrous acetonitrile (10 mL) under argon. The suspension was heated to 55 °C and stirred overnight. Saturated aqueous $NaHCO_3$ (50 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane, the organic layers were combined and dried over sodium sulfate, and the solvent was evaporated to give compound **13** as a yellow oil (0.353 g, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.31 (d, 3.1 Hz, 1H), 6.17 (d, 3.1 Hz, 1H), 5.45 (s, 1H), 3.61 (s, 2H), 3.56−3.44 (m, 4H), 1.59−1.52 (m, 4H), 1.40−1.32 (m, 4H), 0.90 (t, 7.5 Hz, 6H), 0.16 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.0, 150.1, 109.0, 106.7, 101.0, 96.5, 86.5, 65.4, 31.8, 20.1, 19.4, 13.9, 0.0. HRMS: $(M - OBu)^+$, $C_{15}H_{23}O_2Si$ calculated, 263.1462; found, 263.1469.

5-[3-(Trimethylsilyl)prop-2-yn-1-yl]furfural (14). A mixture of compound **13** (0.210 g, 0.624 mmol) and 1 M HCl (10 mL) was stirred for 2 h and then extracted with dichloromethane. The combined organic layers were dried over sodium sulfate and the solvent was evaporated to give compound **14** as a yellow solid (0.125 g, 97%) with a melting point (mp) of 46 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.55 (s, 1H), 7.19 (d, 3.6 Hz, 1H), 6.49 (d, 3.6 Hz, 1H), 3.72 (s, 2H), 0.18 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 177.2, 157.5, 152.5, 123.1, 109.9, 98.9, 88.1, 20.5, −0.1. HRMS: $(M + H)^+$, $C_{11}H_{15}O_2Si$ calculated, 207.0835; found, 207.0833.

2-(Hydroxymethyl)-5-[3-(trimethylsilyl)prop-2-yn-1-yl]furan (15). Sodium borohydride (0.0720 g, 1.90 mmol) was added to a solution of compound **14** (0.391 g, 1.90 mmol) in methanol (10 mL) at 0 °C. The mixture was allowed to come to room temperature over 2 h with stirring. The solvent was evaporated and the residue was taken up in dichloromethane (25 mL), which was washed with saturated aqueous NH_4Cl solution. The aqueous layer was back-extracted with dichloromethane, the organic layers were combined and dried over sodium sulfate, and the solvent was evaporated to give compound **15** as a pale yellow oil (0.388 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.21 (d, 3.0 Hz, 1H), 6.16 (d, 3.0 Hz, 1H), 4.56 (s, 2H), 3.62 (s, 2H), 1.73 (s, 1H), 0.17 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.4, 150.2, 108.8, 107.1, 101.1, 86.6, 57.3, 20.0, 0.0. HRMS: $(M + H)^+$, $C_{11}H_{17}O_2Si$ calculated, 209.0992; found, 209.0987.

Mixture of (±)-*cis*- and (±)-*trans*-{5-[3-(Trimethylsilyl)prop-2-yn-1-yl]furan-2-yl}methyl-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane-1-carboxylate. Compound **15** (0.157 g, 0.754 mmol) was dissolved in dry benzene (25 mL) under argon. A mixture of (±)-*cis*- and (±)-*trans*-chrysanthemic acid chloride (0.156 g, 0.836 mmol) was added and the solution was heated at reflux for 5 h. The reaction was allowed to cool to room temperature and the solvent was evaporated. Excess chrysanthemic acid chloride was removed under high vacuum (0.1 mmHg) to give the product as a brown oil (0.257 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.32 (m, 1H, H_d and $H_{d'}$), 6.19 (m, 1H, H_c and $H_{c'}$), 5.38 (d, 8.5 Hz, 0.4H, H_j), 5.09−4.90 (m, 2H, H_e and $H_{e'}$), 4.88 (d, 7.7 Hz, 0.6H, $H_{j'}$), 3.62 (s, 2H, H_b and $H_{b'}$), 2.06 (dd, 7.7 Hz, 5.5 Hz, 0.6H, $H_{i'}$), 1.88 (t, 8.5 Hz, 0.4H, H_i), 1.75−1.65 (m, 6H, H_k, $H_{k'}$, H_l, and $H_{l'}$), 1.41 (d, 5.5 Hz, 0.6 H, $H_{f'}$), 1.25−1.11 (m, 6H, H_g, $H_{g'}$, H_h, and $H_{h'}$), 0.18 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.2, 170.7, 151.1, 151.0, 149.2, 149.1, 135.6, 134.9, 121.2, 118.1, 111.6, 111.4, 107.4, 100.8, 86.7, 58.1, 57.7, 34.7, 33.1, 32.6, 31.1, 29.0, 28.9, 26.8, 26.0, 25.7, 22.2, 20.5, 20.1, 18.6, 18.4, 14.8, 0.1. HRMS: $(M + H)^+$, $C_{21}H_{31}O_3Si$ calculated, 359.2037; found, 359.1999.

Mixture of (±)-*cis*- and (±)-*trans*-Prothrin (4). A mixture of (±)-*cis*- and (±)-*trans*-{5-[3-(trimethylsilyl)prop-2-yn-1-yl]furan-2-yl}methyl-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane-1-carboxylate (0.143 g, 0.399 mmol) was dissolved in tetrahydrofuran (THF) (10 mL) and the solution was cooled to −20 °C in a dry-ice/ethylene glycol bath. A solution of tetrabutylammonium fluoride in THF (1.0 M, 0.44 mL, 0.44 mmol) was added dropwise with stirring. After 15 min at −20 °C, saturated ammonium chloride (50 mL) was added and the aqueous layer was separated and extracted with ethyl acetate. The organic layers were combined and dried over sodium sulfate, and the solvent was evaporated. The residue was purified by flash column chromatography on silica gel (20:1 hexanes/ethyl acetate) to give compound **4** as a pale yellow oil (0.095 g, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.30 (t, 3.0 Hz, 1H, H_d and $H_{d'}$), 6.18 (d, 3.0 Hz, 1H, H_c and $H_{c'}$), 5.35 (d, 8.4 Hz, 0.4H, H_j), 5.04−4.90 (m, 2H, H_e and $H_{e'}$), 4.85 (d, 7.9 Hz, 0.6H, $H_{j'}$), 3.56 (d, 2.4 Hz, 2H, H_b and $H_{b'}$), 2.13 (t, 2.4 Hz, 1H, H_a and $H_{a'}$), 2.05 (dd, 7.9 Hz, 5.4 Hz, 0.6H, $H_{i'}$), 1.87 (t, 8.4 Hz, 0.4H, H_i), 1.72−1.65 (m, 6H, H_k, $H_{k'}$, H_l, and $H_{l'}$), 1.40 (d, 5.4 Hz, 0.6H, $H_{f'}$), 1.24−1.09 (m, 6H, H_g, $H_{g'}$, H_h, and $H_{h'}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.9, 170.5, 150.5, 150.4, 149.2, 149.1, 135.4, 134.6, 121.1, 118.1, 111.4, 111.3, 107.3, 78.6, 70.3, 57.9, 57.5, 34.5, 32.9, 32.4, 30.9, 28.8, 28.7, 26.6, 25.9, 25.5, 22.1, 20.3, 18.5, 18.4, 18.2, 14.7. HRMS: $(M + H)^+$, $C_{18}H_{23}O_3$ calculated, 287.1642; found, 287.1639.

2-(Cyanomethyl)-5-(dibutoxymethyl)furan (16). Sodium cyanide (0.174 g, 3.55 mmol) was added to a solution of compound **12** (0.811 g, 2.95 mmol) in dimethyl sulfoxide (DMSO) (6 mL) and the mixture was stirred at 90 °C under argon for 3 h. Saturated aqueous $NaHCO_3$ (50 mL) was added and the mixture was extracted with hexanes. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over sodium sulfate, and decolorized with charcoal. The solvent was evaporated to give compound **16** as a light yellow oil (0.608 g, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.34 (s, 1H), 6.28 (s, 1H), 5.44 (s, 2H), 3.60−3.42 (m, 4H), 1.65−1.47 (m, 4H), 1.45−1.27 (m, 4H), 0.90 (t, 7.5 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.8, 143.1, 115.6, 109.4, 109.2, 96.5, 65.9, 31.9, 19.5, 17.8, 14.1. HRMS: $(M - OBu)^+$, $C_{11}H_{14}NO_2$ calculated, 192.1019; found, 192.1019.

5-(Cyanomethyl)furfural (18). A mixture of compound **16** (0.224 g, 0.844 mmol) and 1 M HCl (10 mL) was stirred for 2 h and then extracted with dichloromethane. The organic layers were combined and dried over sodium sulfate, and the solvent was evaporated to give compound **18** as a brown oil (0.109 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.55 (s, 1H), 7.20 (d, 3.0 Hz, 1H), 6.56 (d, 3.0 Hz, 1H), 3.88 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 177.6, 153.2, 149.9, 122.7, 114.6, 111.7, 18.2. HRMS: $(M + H)^+$, $C_7H_6NO_2$ calculated, 136.0393; found, 136.0389.

2-(Cyanomethyl)-5-(hydroxymethyl)furan (20). Sodium borohydride (0.0560 g, 1.47 mmol) was added to a solution of compound **18** (0.155 g, 1.15 mmol) in methanol (10 mL) at 0 °C. The reaction was allowed to stir for 2 h at 0 °C. Saturated aqueous NH_4Cl (25 mL) was added and the mixture was extracted with dichloromethane. The organic layers were combined and dried over sodium sulfate, and the solvent was evaporated to give compound **20** as a brown liquid (0.142 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.22 (d, 3.0 Hz, 1H), 6.20 (d, 3.0 Hz, 1H), 4.48 (s, 2H), 3.72 (s, 2H), 3.16 (br, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.9, 142.8, 115.7, 109.3, 108.9, 56.9, 17.5. HRMS: $(M - OH)^+$, C_7H_6NO calculated, 120.0444; found, 120.0435.

Mixture of (±)-*cis*- and (±)-*trans*-[5-(Cyanomethyl)furan-2-yl]methyl-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)-cyclopropane-1-carboxylate (5). Compound **20** (0.152 g, 1.11 mmol) was dissolved in dry benzene (25 mL) under argon. A mixture of (±)-*cis*- and (±)-*trans*-chrysanthemic acid chloride (0.247 g, 1.32 mmol) was added and the solution was heated at reflux for 2 h. The reaction was allowed to cool to room temperature and the solvent was evaporated. The residue was taken up in dichloromethane (20 mL), which was then washed with brine. The aqueous layer was back-extracted with dichloromethane. The organic layers were combined and dried over sodium sulfate, and the solvent was evaporated. The crude product was purified by flash column chromatography on silica gel (10:1 hexanes/ethyl acetate) to give compound **5** as a light yellow oil (0.244 g, 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.28 (s, 1H, H_d and $H_{d'}$), 6.22 (s, 1H, H_c and $H_{c'}$), 5.28 (d, 8.3 Hz, 0.4H, H_j), 5.01−4.84 (m, 2H, H_e and $H_{e'}$), 4.80 (d, 7.0 Hz, $H_{j'}$), 3.70 (s, 2H, H_b and $H_{b'}$), 1.99 (t, 7.0 Hz, 0.6H, $H_{i'}$), 1.83 (t, 8.3 Hz, 0.4H, H_i), 1.68−1.56 (m, 6H, H_k, $H_{k'}$, H_l, and $H_{l'}$), 1.33 (d, 5.4 Hz, 0.6H, $H_{f'}$), 1.20−1.00 (m, 6H, H_g, $H_{g'}$, H_h, and $H_{h'}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.0, 170.6, 150.9, 150.8, 144.0, 144.0, 135.7, 135.0, 121.1, 118.1, 115.6, 111.8, 111.7, 109.6, 57.8, 57.4, 34.6, 33.2, 32.7, 31.0, 29.1, 28.8, 26.9, 26.0, 25.7, 22.2, 20.5, 18.6, 18.5, 17.6, 14.9. HRMS: $(M + H)^+$, $C_{17}H_{22}NO_3$ calculated, 288.1600; found, 288.1612.

2-(Dibutoxymethyl)-5-(phenoxymethyl)furan (17). Phenol (0.232 g, 2.47 mmol) and potassium carbonate (0.360 g, 2.61

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mmol) were added to a solution of compound **12** (0.564 g, 2.05 mmol) in DMSO (5 mL), and the mixture was stirred at 50 °C under argon for 5 h. Saturated aqueous $NaHCO_3$ (50 mL) was added and the mixture was extracted with hexanes. The organic layers were combined, washed with saturated aqueous $NaHCO_3$, and dried over sodium sulfate. The solvent was evaporated to give compound **17** as a pale yellow oil (0.592 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34−7.25 (m, 2H), 7.02−6.93 (m, 3H), 6.42 (d, 3.3 Hz, 1H), 6.40 (d, 3.3 Hz, 1H), 5.55 (s, 1H), 4.99 (s, 2H), 3.65−3.49 (m, 4H), 1.70−1.55 (m, 4H), 1.51−1.35 (m, 4H), 0.95 (t, 7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.3, 152.4, 150.2, 129.4, 121.2, 114.9, 110.3, 109.0, 96.5, 65.5, 62.4, 31.8, 19.4, 13.9. HRMS: $(M - OBu)^+$, $C_{16}H_{19}O_3$ calculated, 259.1329; found, 259.1331.

5-(Phenoxymethyl)furfural (19).[15] A mixture of compound **17** (0.322 g, 0.970 mmol) and 1 M HCl (10 mL) was stirred for 2 h and then extracted with dichloromethane (20 mL). The organic layers were combined and dried over sodium sulfate, and the solvent was evaporated to give compound **19** as a yellow solid (0.194 g, 99%), with a mp of 84 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.64 (s, 1H), 7.36−7.20 (m, 3H), 7.05−6.91 (m, 3H), 6.61 (d, 3.3 Hz, 1H), 5.10 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 178.0, 158.1, 157.0, 152.9, 129.9, 122.4, 122.0, 115.0, 111.9, 62.7. HRMS: $(M + H)^+$, $C_{12}H_{11}O_3$ calculated, 203.0703; found, 203.0706.

2-(Hydoxymethyl)-5-(phenoxymethyl)furan (21).[13] Sodium borohydride (0.269 g, 7.08 mmol) was added to a solution of compound **19** (1.196 g, 5.915 mmol) in a 1:1 mixture of methanol and dichloromethane (20 mL) at 0 °C. The reaction was allowed to come to room temperature over 2 h with stirring. The solvent was evaporated, and the residue was taken up in dichloromethane (20 mL) and washed with brine. The aqueous layer was back-extracted with dichloromethane. The organic layers were combined, dried over sodium sulfate, and evaporated to give compound **21** as a pale yellow liquid (1.156 g, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36−7.25 (m, 2H), 7.04−6.94 (m, 3H), 6.37 (d, 2.7 Hz, 1H), 6.26 (d, 2.7 Hz, 1H), 4.96 (s, 2H), 4.56 (s, 2H), 2.91 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.5, 155.0, 150.3, 129.8, 121.6, 115.1, 111.1, 108.9, 62.6, 57.6. HRMS: $(M + H)^+$, $C_{12}H_{13}O_3$ calculated, 205.0859; found, 205.0861.

Mixture of (±)-*cis*- and (±)-*trans*-[5-(Phenoxymethyl)furan-2-yl]methyl-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)-cyclopropane-1-carboxylate (6).[13] Compound **21** (0.331 g, 1.62 mmol) was dissolved in dry benzene (25 mL) under argon. A mixture of (±)-*cis*- and (±)-*trans*-chrysanthemic acid chloride (0.364 g, 1.95 mmol) was added and the solution was heated at reflux for 3 h. The reaction was allowed to cool to room temperature and the solvent was evaporated. The residue was taken up in dichloromethane (25 mL), which was then washed with brine. The aqueous layer was back-extracted with dichloromethane. The organic layers were combined and dried over sodium sulfate, and the solvent was evaporated. The crude product was purified by flash column chromatography on silica gel (15:1 hexanes/ethyl acetate) to give compound **6** as a colorless oil (0.484 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35−7.24 (m, 2H), 7.03−6.93 (m, 3H), 6.39 (s, 2H, H_c, $H_{c'}$, H_d, and $H_{d'}$), 5.37 (d, 8.3 Hz, 0.15H, H_j), 5.13−4.95 (m, 4H, H_b, $H_{b'}$, H_e, and $H_{e'}$), 4.88 (d, 7.5 Hz, 0.85H, $H_{j'}$), 2.08 (t, 7.5 Hz, 0.85H, $H_{i'}$), 1.90 (t, 8.3 Hz, 0.15H, H_i), 1.81−1.65 (m, 6H, H_k, $H_{k'}$, H_l, and $H_{l'}$), 1.43 (d, 5.1 Hz, 0.85H, H_f), 1.30−1.08 (m, 6H, H_g, $H_{g'}$, H_h, and $H_{h'}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.3, 170.9, 158.5, 151.1, 151.1, 150.8, 150.6, 135.8, 135.1, 129.7, 121.5, 121.3, 118.3, 115.1, 111.6, 111.5, 111.1, 62.6, 58.2, 57.9, 34.8, 33.3, 32.8, 31.3, 29.2, 29.0, 27.0, 26.2, 25.8, 22.4, 20.6, 18.8, 18.6, 15.0. HRMS: $(M + H)^+$, $C_{22}H_{27}O_4$ calculated, 355.1909; found, 355.1925.

Entomological Studies. *Mosquitoes.* The Orlando strain of *Aedes aegypti* (established 1952) was reared in the insectary of the Mosquito and Fly Research Unit at the Center for Medical, Agricultural, and Veterinary Entomology (CMAVE), Agricultural Research Service (ARS), United States Department of Agriculture (USDA), according to the procedures described by Pridgeon et al.[16] Briefly, eggs were hatched in a flask with deionized water, left overnight, and transferred to a plastic tray containing distilled water. A powdered diet (2:1 pot belly pig chow/brewer's yeast) was added to each tray. Mosquitoes were reared in an environmental chamber at 28 °C, 80% relative humidity, and a photoperiod of 14 h/10 h (light/dark). Adults were held in a screened cage and provided 10% sucrose *ad libitum*. Female adults were used for all bioassays.

Adult Topical Bioassays. To determine the toxicity of each compound against female *A. aegypti*, samples were initially diluted to a 10% solution in DMSO. This solution was then serially diluted 1:10 in acetone and then topically applied to individual mosquitoes. Each addition of diluent and stock solution was weighed to allow for accurate concentration calculations and to account for pipetting variability because of the volatility of acetone. Prior to application, 5−7-day-old females were cold-anaesthetized and placed on a 4 °C chill table (BioQuip Products, Rancho Dominguez, CA). A 0.5 μL droplet of chemical solution was applied to the thorax using a 700 series gastight syringe and a PB 600 repeating dispenser (Hamilton, Reno, NV). Control treatments with 0.5 μL of acetone alone gave control mortality of less than 10%. After treatment, mosquitoes were kept in plastic cups and supplied with 10% sucrose solution for 24 h before mortality was recorded. Temperature and relative humidity were maintained at 26−27 °C and 80%, respectively. Cohorts of 20−30 mosquitoes were treated at each dose. Bioassays were replicated 3 times. Technical-grade permethrin (Chemservice, West Chester, PA), a combination of 46.1% *cis* and 53.2% *trans* isomers, was used as the positive control in all assays and diluted in the same manner as the test compounds. This system reliably results in a LD_{50} for permethrin of around 0.1 ng per mosquito.

RESULTS AND DISCUSSION

Preliminary entomological testing of pyrethroids **5** and **6** was conducted against prothrin (**4**) and the commercial insecticide permethrin as standards using the "Orlando" strain of the pesticide-susceptible mosquito *A. aegypti*, as described above. Mortality was recorded at 24 h post-application, and three replicates were performed. Averaged mortality counts are included in Table S1 of the Supporting Information, and the estimated LD_{50} values are given in Table 1. The activities of analogues **5** and **6** are thus within about a log of that of prothrin (**4**), which itself is more active than the natural pyrethrins.[17] Further testing will determine whether these derivatives show any useful selectivity in their action.

Table 1. Estimated LD_{50} Values (ng/Mosquito) of Analogues 5 and 6 with Prothrin (4) and Permethin Standards against *A. aegypti* "Orlando" Strain Mosquitos

toxicant	LD_{50}
permethrin	0.07
prothrin (**4**)	0.50
5	7.0
6	3.3

In conclusion, CMF (**1**), a biomass-derived platform chemical, is an attractive starting material for the high-yield synthesis of prothrin (**4**) and analogues **5** and **6**. This scalable synthetic approach could be generalized toward the renewable-sourced production of a variety of furan-based pyrethroids, which will enable further structure−activity studies and potential commercial development of this important family of insecticides.

ASSOCIATED CONTENT

Supporting Information

Details of entomological data and ^{1}H and ^{13}C NMR data for all compounds prepared in this work. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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