3-Hydroxy-4,5-dimethyl-2(5*H*)-furanone (1; R_1, R_2 = Me):[17] short-path distillation (0.1 mm, 25–150 °C) gave a clear light amber liquid (0.985 g, 63% yield): ^{1}H NMR (acetone-d_6) δ 1.34 (d, J = 6.0, 3 H, $-CH_3$), 1.89 (s, 3 H, $-CH_3$), 4.83 (q, J = 6.0, 1 H, $-OCH-$), 8.13 (s, 1 H, $-OH$).

5-(2-Chloro-1-hydroxy-1-phenylethyl)-2,4-oxazolidinedione (5) and 5-(2-Phenyloxiranyl)-2,4-oxazolidinedione (6). Reaction of **2** (9.90 mmol) and 2-chloroacetophenone (1.61 g, 10.4 mmol) was carried out as described above except that 1 h after warming to 25 °C aqueous HCl (60 mL, 0.5 M) was added. Chromatography (silica gel washed with 2% H_3PO_4/MeOH, $CHCl_3/CH_3CN$) gave **5** as an inseparable 1.6:1 mixture of diastereomers (1.01 g, 40% yield): ^{1}H NMR (acetone-d_6) δ 4.21 (AB q, J = 12, $-CH_2-$), 4.28 (s, $-CH_2-$), 5.47 (s, 0.38 H, $-CH-$), 5.52 (s, 0.62 H, $-CH-$), 7.24–7.70 (m, 5 H, Ar*H*). The epoxide **6** was obtained as a single diastereomer (0.49 g, 23% yield). Recrystallization (hexane/ether): mp 98–99 °C. ^{1}H NMR (acetone-d_6) δ 2.90 (d, J = 5, 1 H, $-CH_2-$), 3.39 (d, J = 5, 1 H, $-CH_2-$), 5.33 (s, 1 H, $-CH-$), 7.25–7.53 (m, 5 H, Ar*H*). Allylic alcohol **4a** (R_1 = Ph) was also isolated (0.085 g, 4% yield).

(2,4-Dioxooxazolidin-5-ylidene)phenylacetaldehyde (7). A solution of **4a** (R_1 = Ph) (2.01 g, 11.4 mmol) in acetone (100 mL) was treated with MnO_2 (3 × 5 g, t = 0, 25 min, 4 h). After 6 h, filtration through Celite, concentration, and chromatography (CH_2Cl_2/CH_3CN/HOAc) gave **7** as a solid (1.56 g, 79%): recrystallization (Et_2O/hexane); mp 170–172 °C (effervescence); ^{1}H NMR (acetone-d_6) δ 7.42 (bd s, 5 H, Ar*H*), 10.9 (s, 1 H, $-CHO$).

3,5-Dihydroxy-4-phenyl-2(5*H*)-furanone (8). Aldehyde **7** (0.197 g, 0.907 mmol) and 1:1 HOAc–12 N HCl (1 mL) were heated at 100 °C for 20 min and then immediately cooled in an ice bath. Water was added, and the mixture was extracted repeatedly with Et_2O, dried ($MgSO_4$), and concentrated. Chromatography (CH_2Cl_2/MeOH/HOAc) gave **8** as a solid (0.089 g, 51% yield): mp 202–203 °C (effervescence); ^{1}H NMR (acetone-d_6) δ 6.52 (bd s, 1 H, $-OCH-$), 6.8 (bd s, 1 H, $-OH$), 7.3–7.5 (m, 3 H, Ar*H*), 7.90 (d, J = 7, 1 H, Ar*H*), 9.55 (bd s, 1 H, $-OH$).

Addition of Methyllithium to 7. MeLi (0.90 mL, 1.25 mmol, 1.4 M in Et_2O) was added dropwise to a solution of **7** (0.109 g, 0.502 mmol) in THF (10 mL) at −78 °C. After 30 min methanolic HCl was added and the solution allowed to warm to 25 °C, concentrated, and chromatographed ($CHCl_3/CH_3CN$/HOAc) to give **4a** (R_1 = Ph, R_2 = Me) as a solid (0.102 g, 87% yield).

Preparation of 9. A solution of **10** (1.5 g, 5.2 mmol) in THF (10 mL) at −78 °C was added all at once, via cannula, to **2** (4.95 mmol) in THF (50 mL) at −78 °C. After 1.5 h the mixture was allowed to warm to 25 °C. After 1.5 h, aqueous HCl (40 mL, 0.5 N) was added. Extraction (Et_2O), drying ($MgSO_4$), concentration, and chromatography ($CHCl_3$/HOAc) gave 3-[3-(2,4-dioxo-oxazolidin-5-yl)-3-phenyloxiranyl]propionic acid methyl ester (**11**) as a 3:2 mixture of diastereomers (oil, 1.30 g, 86% yield): ^{1}H NMR (acetone-d_6) δ 1.28–1.42 (m, 1 H, $-CH_2-$), 1.52–1.66 (m, 1 H, $-CH_2-$), 2.37–2.46 (m, 2 H, $-CH_2CO_2Me$), 3.58 (s, 3 H, $-OCH_3$), 3.62 (dd, J = 5.1, 7.1, 0.6 H, $-CH-$), 3.76 (dd, J = 5.0, 7.2, 0.4 H, $-CH-$), 5.29 (s, 0.6 H, $-CH-$), 5.49 (s, 0.4 H, $-CH-$), 7.34–7.51 (m, 5 H, Ar*H*). The epoxides (0.303 g, 0.992 mmol) were heated in aqueous HCl (6 N, 10 mL) at 100 °C for 61 h. Concentration gave a solid which was extracted repeatedly with acetone. Concentration gave a brown solid (0.289 g) which was filtered through silica gel (Et_2O) to give **9** as an off-white solid (0.202 g, 82% yield): recrystallization (EtOAc/hexane); mp 179–181 °C (lit.[12c] mp 177–179 °C); ^{1}H NMR, IR, and MS were identical to those reported in the literature.[12c]

Methyl 4-Bromo-5-oxo-5-phenylpentanoate (10). Methyl 5-oxo-5-phenylpentanoate was brominated according to the method of King and Ostrum.[18] Filtration through silica gel ($CHCl_3$–CH_3CN) gave **10** as a pale orange oil (98% yield): ^{1}H NMR (acetone-d_6) δ 2.2–2.7 (m, 2 H, $-(CH_2)_2-$), 3.66 (s, 3 H, $-OCH_3$), 5.65 (dd, J = 5.0, 7.5, 1 H, $-CHBr-$), 7.5–7.7 (m, 3 H, Ar*H*), 8.07 (d, J = 6, 2 H, Ar*H*).

5-Methyl-2,4-oxazolidinedione. Iodomethane (0.26 mL, 4.16 mmol) was added all at once to **2** (3.96 mmol) in THF (40 mL) at −78 °C. After 15 min the mixture was allowed to warm to 25 °C. After 1 h the pale yellow solution was treated with HCl in dioxane (2.1 mL, 4 N). The solution was concentrated, and the resulting solid was triturated with ether. The ether washings were filtered through silica gel. Concentration gave a clear colorless oil (0.57 g). Chromatography (silica gel, hexane/EtOAc) gave 5-methyl-2,4-oxazolidinedione (0.37 g, 82%): ^{1}H NMR (acetone-d_6) δ 1.5 (d, J = 6, 3 H, $-CH_3$), 5.0 (q, J = 6, 1 H, $-CHCH_3$).

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Supplementary Material Available: Spectral data and analytical results for **1**, **4a**, **6**, **7**, **8**, and **11** (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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A δ-Keto Aldehyde Synthesis: Application to the Preparation of the Sex Pheromone of the Douglas-Fir Tussock Moth

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δ-Keto aldehydes are useful intermediates in many syntheses. They have been prepared by a variety of methods, most of which involve adding three carbons at the site α to the keto group. These methods include conjugate addition of an enamine to acrolein followed by hydrolysis,[1] alkylation of enolates with 1,3-dichloropropene or 2-(2-bromoethyl)-1,3-dioxolane followed by hydrolysis,[2] or alkylation with allyl bromide followed by hydroboration and oxidation.[3] Cycloaddition of a ketone enol ether with acrolein followed by hydrolysis does likewise.[4] Oxidative opening of 1-alkylcyclopentenones is another alternative.[5] Some methods afford δ-keto aldehydes under acidic or basic conditions where they become cyclohexenones in situ.[6]

We are interested in preparing δ-keto aldehydes from acid chlorides using Grignard reagents derived from the now readily available[7] 2-(3-halopropyl)-1,3-dioxolanes or dioxanes.[8] Simple Grignard reagents afford good yields of ketones upon reaction with acid chlorides at −78 °C in tetrahydrofuran,[9] and there was no evidence to suggest that our proposed Grignard reagents might not be successful also.

We prepared the Grignard reagents from 2-(3-bromopropyl)-4,4,6-trimethyl-1,3-dioxane and from 2-(3-bromopropyl)-4,4,5,5-tetramethyl-1,3-dioxolane with magnesium turnings[7] in THF at reflux or at 25–30 °C; however, adding

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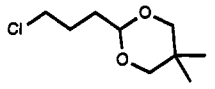
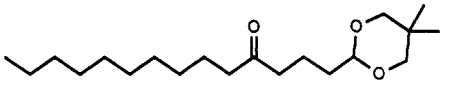
either of these to undecanoyl chloride in THF at −78 °C gave no ketone. Likewise, adding undecanoyl chloride to the cooled Grignard reagent gave none. The major product was instead the ester from the cleavage of the THF. This was identified as 4-bromobutyl undecanoate (with about 5% of the corresponding chloro compound) by comparison with a sample prepared from the acid chloride, THF, and an equimolar amount of magnesium bromide prepared in situ from magnesium and 1,2-dibromoethane. In another attempt, the cooled Grignard reagent was treated with HMPA and then the acid chloride was added. This again gave the ester with no ketone. Quenching a Grignard solution with water afforded the expected propyldioxane with no recovered bromoacetal, confirming the formation of the Grignard reagent. Similar bromo-Grignard reagents have been used in conjugate addition reactions without difficulty,[10] but they are apparently less reactive than simple Grignard reagents and cannot compete with the magnesium bromide catalyzed reaction of THF with acid chlorides. This contrasts with the reagents from the shorter chain 2-(2-bromoethyl)dioxanes, which lead to γ-keto aldehydes with no competing attack on THF.[11] Perhaps the lower reactivity here is caused by more effective intramolecular coordination of the magnesium by one or two of the acetal oxygens. In earlier work,[12] we found the same problem with the Grignard reagent from the protected ketone, 2-(3-bromopropyl)-2,5,5-trimethyl-1,3-dioxane.

The cleavage of ethers with carboxylic acid chlorides has been carried out using a wide variety of anhydrous metal halides as catalysts, but magnesium chloride was found to be ineffective.[13] Therefore, to avoid the reaction with THF, we turned to the corresponding chloro Grignard reagents. Forbes and co-workers showed that the chloro acetals at 1–2 molar concentration do not react with magnesium in THF without heat, and with prolonged heating they give low yields;[14] however, at 5 molar concentration below 30 °C, Grignard reagents did form. We attempted these Grignard preparations with 1 and mag-



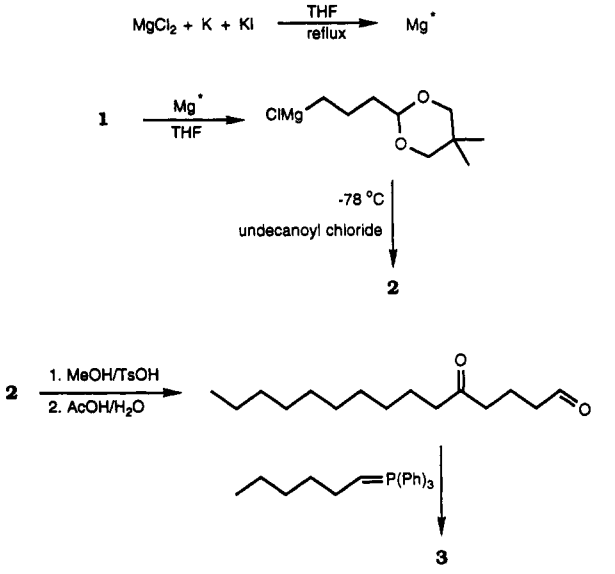
1

nesium turnings at various concentrations at room temperature and at reflux in ether or THF, including 5 molar as described by Forbes, all without any reaction. We attempted to initiate the reaction with ultrasonic irradiation and dibromoethane to no avail. Abbott and Spencer[15] chose to use freshly reduced magnesium powder with 2-(3-chloropropyl)-1,3-dioxolane, and we have found that this works swiftly with 1 as well. The resulting Grignard reagent was treated with an equimolar amount of undecanoyl chloride at −78 °C to afford the ketone, 2, in 94% yield.

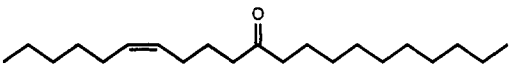


2

Scheme I



The Douglas-fir tussock moth, *Orgyia pseudosugata*, causes widespread damage to forests, and the sex pheromone offers the possibility of species-specific control of populations. The pheromone, (*Z*)-6-heneicosen-11-one, 3,



3

was first reported in 1975,[16] and since then it has been synthesized by a variety of routes.[17] We have prepared it by a new route, Scheme I, that offers high yields from readily available materials in few steps. The δ-keto acetal prepared from Grignard reagent 1 was transacetalized and hydrolyzed[18] and then treated with the Wittig reagent from 1-bromohexane to afford the pheromone, 3, in 73% overall yield from 1.

In the Wittig reaction, it is necessary to use an excess of the phosphonium salt over the base; otherwise, the solution remains basic enough to cause cyclization of the δ-keto aldehyde to the cyclohexenone. Using potassium *tert*-butoxide as base (not a lithium base[19]) led to the cis isomer selectively, no trans being detectable by ^{13}C NMR.

Experimental Section

All reagents were purchased from Aldrich. ^1H NMR and ^{13}C NMR spectra were recorded at 300.075 and 75.46 MHz, respectively, in $CDCl_3$. Tetrahydrofuran was distilled from sodium benzophenone ketyl.

2-(4-Oxotetradecyl)-5,5-dimethyl-1,3-dioxane. Anhydrous $MgCl_2$ (1.35g, 0.0142 mol), potassium metal (0.90 g, 0.023 mol), KI (0.85g, 0.0051 mol), and THF (25 mL) were mixed together under a nitrogen atmosphere, with magnetic stirring. The mixture was heated at reflux for 2.5 h, during which time it became black. The mixture was then allowed to cool to room temperature for 0.5 h. 2-(3-Chloropropyl)-5,5-dimethyl-1,3-dioxane[7] (1.00 g, 0.005 20 mol) was then added all at once to the black activated

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magnesium. The mixture became slightly warm and was then allowed to stir 0.5 h. The Grignard mixture was then chilled to −78 °C with an acetone/dry ice bath followed by the addition of undecanoyl chloride (1.06 g, 0.005 20 mol) all at once. The mixture was stirred at −78 °C for 1 h and then warmed to room temperature over 0.5 h. While still under nitrogen, water was added dropwise to the reaction mixture to decompose any unreacted potassium metal and the excess $MgCl_2$ and then extracted with hexane (3 × 20 mL). The extracts were combined, dried with $MgSO_4$, and filtered and the hexane removed by rotary evaporation to obtain 1.6 g of crude keto acetal (94%), which was then converted to the keto aldehyde without further purification. ^{13}C NMR: δ 14.23, 18.43, 21.89, 22.89, 23.02, 23.90, 29.62, 29.87, 30.13, 32.07, 34.21, 42.45, 42.83, 102.01, 210.94.

5-Oxopentadecanal. The keto acetal (1.6 g) prepared above was converted to the dimethyl acetal by treatment with methanol (30 mL) and *p*-toluenesulfonic acid (0.015 g) for 3 h at reflux temperature. The solution was then neutralized with K_2CO_3 and the methanol removed by rotary evaporation. Water was then added and the mixture extracted with one portion of hexane (25 mL). The organic layer was separated, washed with water, dried with $MgSO_4$, and filtered and the solvent removed by rotary evaporation. A ^{13}C NMR spectrum showed that the conversion to the dimethyl acetal was essentially complete. Glacial acetic acid (20 mL) and water (5 mL) were then added to the flask. The mixture was stirred for 4 h, at which time the solution was neutralized with cold saturated aqueous $NaHCO_3$ and extracted with hexane (3 × 15 mL), the extracts were dried with $MgSO_4$ and filtered, and the solvent was removed by rotary evaporation. Purification by column chromatography (silica gel, hexane eluent) afforded the keto aldehyde in 88% yield (1.1 g) from the chloroacetal, mp 40–42 °C (lit.[20] mp 43 °C). ^{13}C NMR: δ 14.11, 16.11, 22.69, 23.89, 29.32, 29.49, 29.58, 31.91, 41.32, 42.93, 43.04, 201.76, 210.31.

(*Z*)-6-Heneicosen-11-one. Hexyltriphenylphosphonium bromide (239 mg, 0.560 mmol), potassium *tert*-butoxide (57 mg, 0.51 mmol), and dry THF (5 mL) were combined at room temperature, with magnetic stirring, under a nitrogen atmosphere. The resulting orange solution was stirred for 1 h at room temperature, and then a solution of 5-oxopentadecanal (122 mg, 0.509 mmol) in THF (2 mL) was added via syringe. The orange color disappeared, and the reaction mixture was allowed to stir for 4 h. The resulting mixture was poured into water (50 mL) and extracted with one portion of hexane (20 mL). The extract was dried with $MgSO_4$ and filtered and the solvent removed by rotary evaporation. The remaining dark yellow liquid was then purified by column chromatography (alumina/hexane eluent) to yield 130 mg (83%) of (*Z*)-6-heneicosen-11-one. ^{13}C NMR: δ 14.11, 22.62, 22.72, 23.81, 23.95, 26.63, 27.26, 29.35, 29.47, 29.61, 31.57, 31.94, 42.11, 42.90, 128.72, 131.01, 211.32 (the NMR data compare favorably with literature[21] values).

4-Bromobutyl undecanoate. THF (20 mL), Mg (0.12 g, 4.9 mmol), and 1,2-dibromoethane (0.92 g, 4.9 mmol) were combined under nitrogen, with magnetic stirring. Slight warming initiated the reaction between the halide and magnesium turnings. After all of the magnesium was consumed, undecanoyl chloride (1.0 g. 4.9 mmol) was added all at once via syringe. The solution was allowed to stir for 6 h at room temperature. The THF was removed by rotary evaporation, the residue washed with water (50 mL) and then taken up in hexane (20 mL), dried with $MgSO_4$, and filtered, and the solvent removed by rotary evaporation. The resulting yellow liquid was then passed through a column (alumina/hexane eluent) to afford 1.4 g of 4-halobutyl undecanoate (95% bromo, 5% chloro) in 89% yield. IR (neat): 2925, 2854, 1737, 1466, 1252, 1170 cm^{-1}. ^1H NMR: δ 0.88 (t, 3 H, *J* = 7.0 Hz), 1.26 (broad, 14 H), 1.61 (m, 2 H), 1.79 (m, 2 H), 1.93 (m, 2 H), 2.30 (t, 2 H, *J* = 7.6 Hz), 3.44 (t, 2 H, *J* = 6.6 Hz, CH_2Br), 3.57 (t, *J* = 6.6 Hz, CH_2Cl, 5% of 2 H), 4.10 (t, 2 H, *J* = 6.2 Hz). ^{13}C NMR: δ 14.06, 22.69, 25.00, 27.38, 29.18, 29.29, 29.48, 29.57, 31.90, 33.01, 34.33, 63.20, 173.83.

Registry No. 1, 65984-84-1; 2, 142066-38-4; 3, 54844-65-4; $H_3C(CH_2)_9COCl$, 17746-05-3; $H_3C(CH_2)_9CO(CH_2)_3CHO$, 86648-94-4; $H_3C(CH_2)_4CHP^+(Ph)_3Br^-$, 4762-26-9; $H_3C(CH_2)_9CO_2(CH_2)_4Br$, 142066-39-5; $Br(CH_2)_2Br$, 106-93-4.

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