The synthesis of the isomeric components of San Jose scale pheromone — an illustration of a stereospecific synthesis of trisubstituted alkenes

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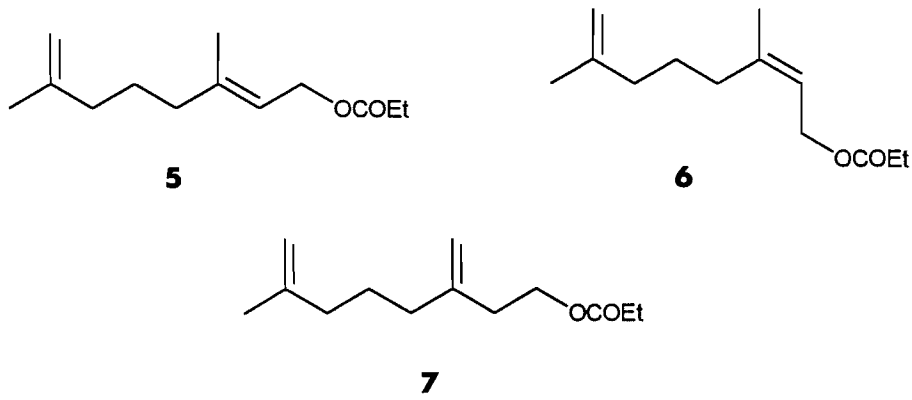
The three isomeric components of the San Jose scale pheromone, **5**–**7**, have been synthesized from a common β-keto ester intermediate. A study of the alkylation of the dianion of methyl acetoacetate with a series of alkylating agents with the same carbon skeleton has been carried out. The trisubstituted alkenes in **5** and **6** have been synthesized stereospecifically via a copper-catalyzed coupling of a methyl Grignard reagent with the *E* or *Z* enol phosphate from the alkylated β-keto ester. In the case of the *Z* enol derivative, the coupling reaction was carried out on the diethyl- and diphenylphosphates, and the enol triflate. The diethyl enol phosphate gave the highest stereoselectivity. The synthetic pheromones were attractive to San Jose scale in the field.



5 **6** **7**

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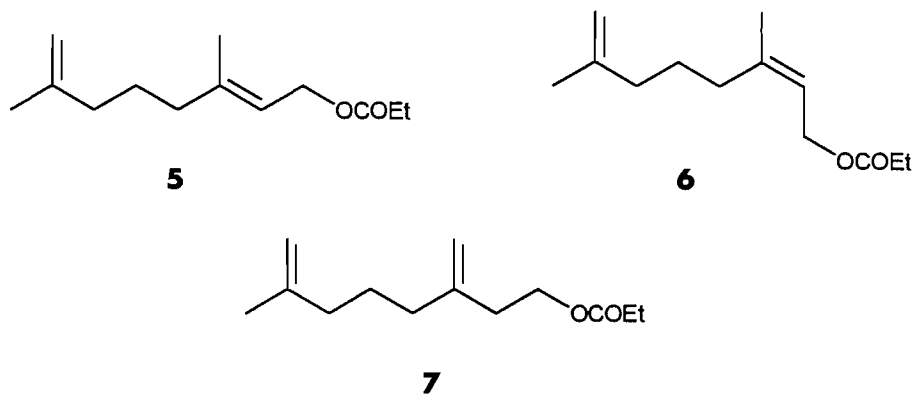
Utilisant un β-céto ester commun comme intermédiaire, on a synthétisé les trois isomères **5**–**7** de la phéromone du pou de San José. On a réalisé une étude de l'alkylation du dianion de l'acétoacétate de méthyle par une série d'agents d'alcoylation ayant le même squelette carboné. On a synthétisé les alcènes trisubstitués **5** et **6** d'une manière stéréospécifique en faisant appel à un couplage catalysé par le cuivre d'un méthyl magnésien avec le phosphate d'énol *E* ou *Z* obtenu à partir du β-céto ester alcoylé. Dans le cas du dérivé énolique *Z*, on a réalisé la réaction de couplage sur les phosphates énoliques diéthylé et de diphénylé et sur le triflate énolique. Le phosphate énolique diéthylique donne la meilleure stéréosélectivité. Dans les champs, les phéromones de synthèse attirent le pou de San José.



5 **6** **7**

[Traduit par la rédaction]

Introduction

The ability to introduce alkenes with control of the position and geometry of the double bond has led to significant advances in the synthesis of natural and unnatural products for several decades (1). Those methods which allow one to control the regio- and stereochemistry of the double bond often have the most widespread utility. The synthesis of tri- and tetrasubstituted alkenes is usually more challenging than that of disubstituted alkenes.

3,3-Dimethylacrylate esters undergo regioselective deprotonation (2), and subsequent alkylation of the derived lithium carbanions usually occurs at the α-carbon, although the copper enolate of the dianion from the corresponding acid was found to react with allylic halides at the γ-carbon (3).

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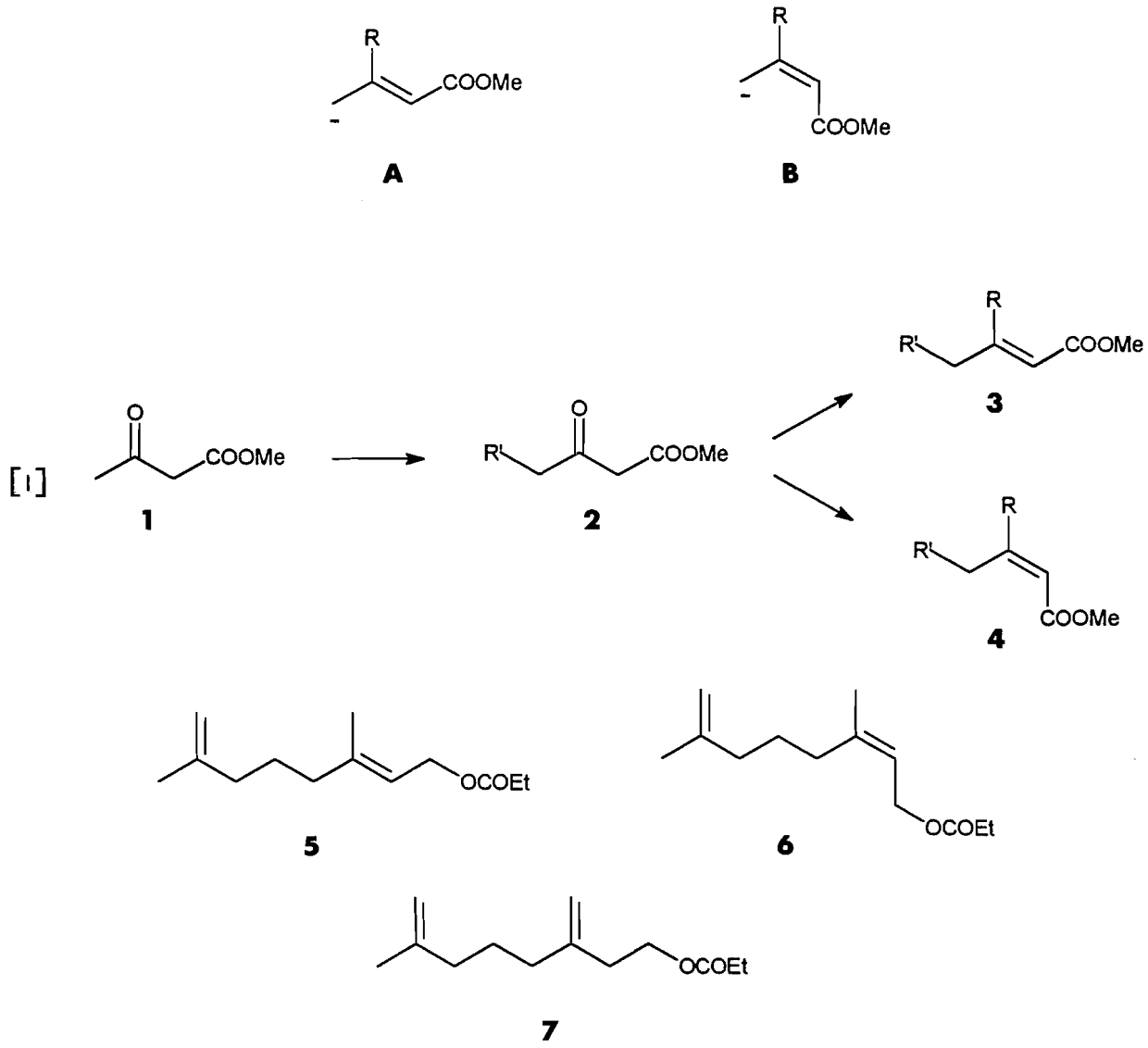


A general method to directly alkylate the carbanion corresponding to synthons **A** or **B** has not been reported to date. The Horner-Wadsworth-Emmons reaction has proven useful in the synthesis of molecules of structure **3** in which the group R is "smaller" than the $R'CH_2$ (4) group. The conjugate addition of cuprates to alkynes (5) has provided a highly stereoselective route to compounds of the type **3** (6). A recent very promising method utilizes the stereospecific conjugate addition of a stannyl cuprate to propargyl esters to give either the (*E*)- or (*Z*)-3-stannyl-2-alkenoate depending on the reaction conditions (7). Subsequent coupling of the vinyl stannane or halogenation followed by coupling gives the (*E*)- or (*Z*)-trisubstituted alkene (8).

A few years ago we developed a method for the stereospecific synthesis of the trisubstituted alkenes **3** or **4** (9). This, in combination with the dianion alkylation of β-keto esters such as **1** (10), led to a method to introduce the units **A** or **B** into a synthetic intermediate via the pathway outlined in eq. [1]. In this paper we report the application of this methodology to the synthesis of the three components of the San Jose scale pheromone.

The San Jose scale, *Quadraspidiotus pernicious*, is a widespread insect pest that attacks fruit and ornamental trees. San Jose scale is a particularly serious pest in the apple orchards of the southern Okanagan Valley of British Columbia. The insect is controlled by heavy pruning, and extensive spraying of dormant oil and organophosphates. By optimizing the timing of the organophosphate sprays, which are targeted at the mature male stage of the insect (11), the amount of spray required for control can be reduced significantly. The female scale produces a mixture of three compounds that are highly attractive to the male species. The structures of the three compounds, **5**–**7**, were solved by spectroscopic methods (12) and confirmed by synthesis (13).

Following the preliminary communication of our work (14), two other syntheses of these compounds were reported (15). The first of these syntheses involved a regioselective allylic chlorination of the propionate esters of geraniol or nerol followed by reduction of the allylic halide to give **5** or **6** as shown in eq. [2] (15*a*). The second method relied on the photochemical isomerization of the conjugated ester shown in eq. [3] to a mixture of the β,γ-unsaturated esters in which the desired disubstituted alkene was the major component and it was converted into **7** (15*b*).

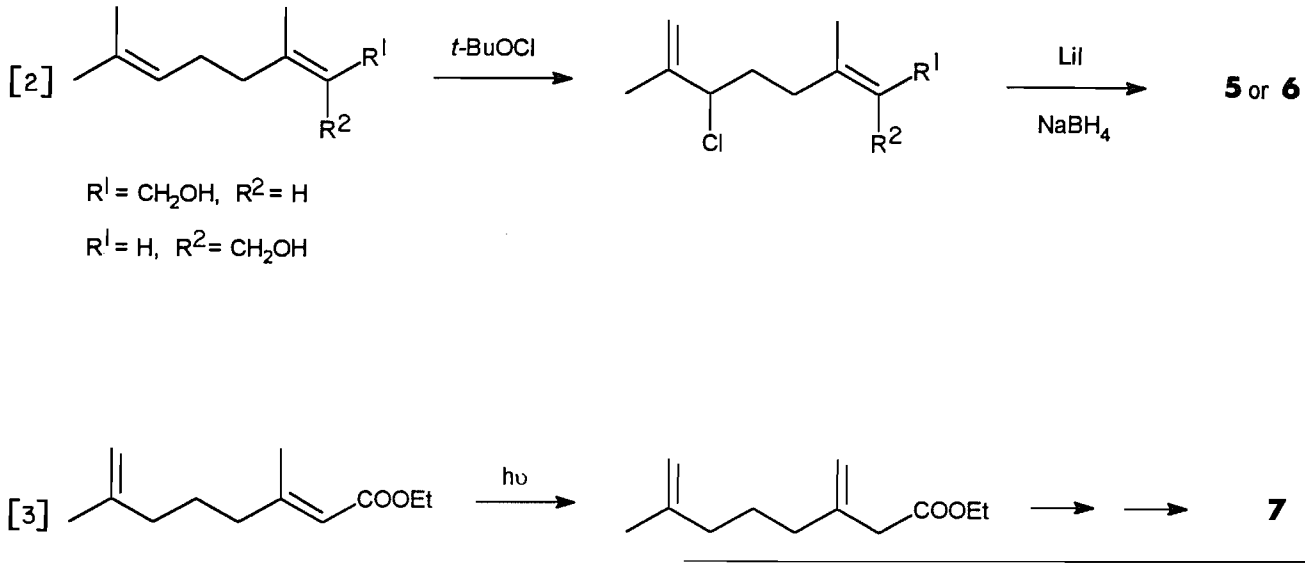


TABLE 1. Alkylation of the dianion from methyl acetoacetate (**8**) with alkylating agents **9**[a]

Entry	**9**, X =	Yield of **10**[b] (%)
1	Br	70
2	I	65
3	$PhSO_3$	62
4	TsO	56
5	TfO	45
6	$MeSO_3$	40

[a]All alkylations were carried out by adding **9** to the solution of the dianion in THF at 0°C.
[b]Yield of distilled product **10**.

TABLE 2. Copper-catalyzed Grignard coupling with enol derivatives **11**[a]

Entry	**11**, R =	Yield of **12**[b]	*E*:*Z*
a	$PO(OPh)_2$	78%	90:10
b	$PO(OEt)_2$	70%	98:2
c	OTf	82%	88:12

[a]Coupling reactions were carried out by adding the enol derivative **11** to a solution of MeCu and MeMgCl in THF at −25°C.
[b]Yield of distilled or chromatographed product **12**.

Results and discussion

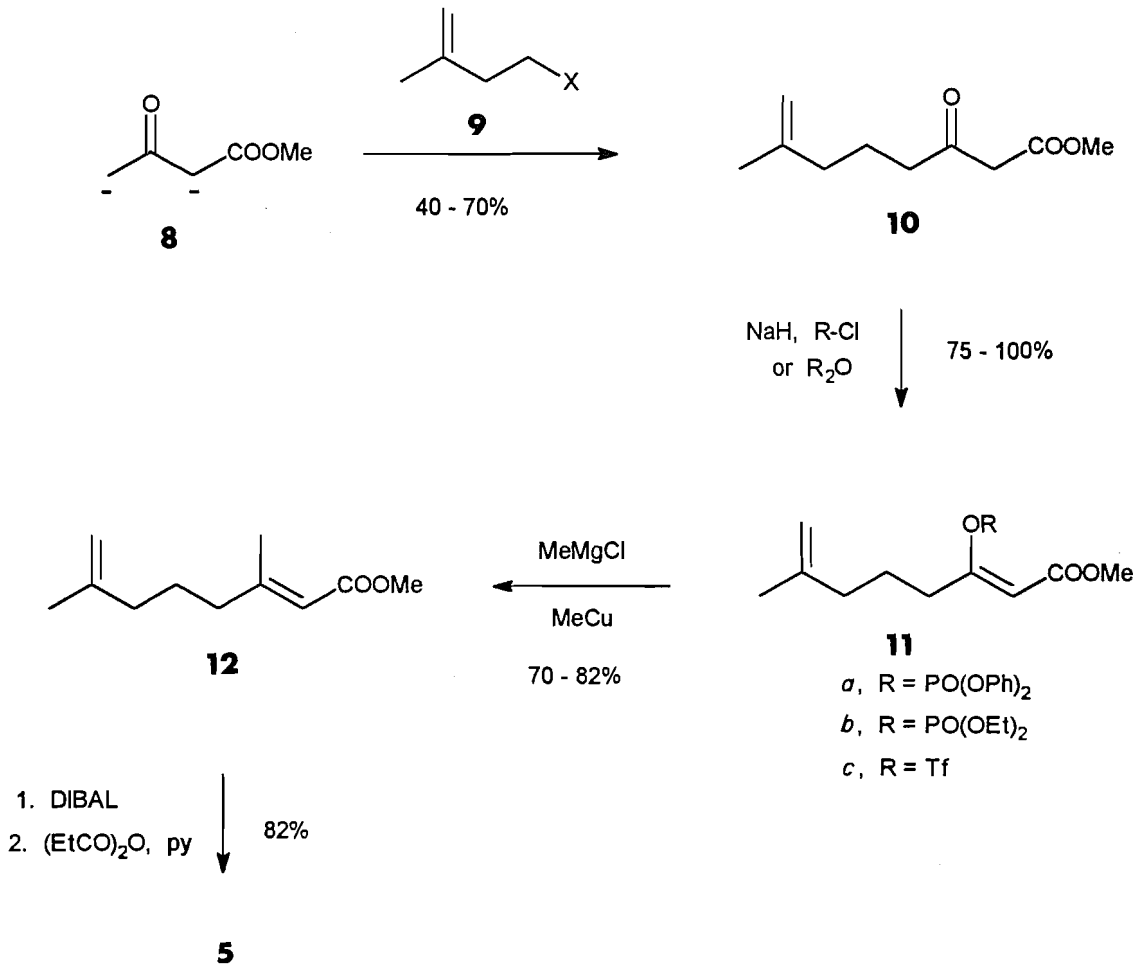
We sought a method to prepare all three of the San Jose scale pheromone components from a common intermediate. An obvious choice for this intermediate is the β-keto ester **10**, which would be readily available from the dianion **8** of methyl acetoacetate and an alkylating agent derived from 3-methyl-3-buten-1-ol (**9**, X = OH). This provided an opportunity to evaluate the utility of various alkylating agents in the reaction with the dianion of methyl acetoacetate. Table 1 contains the results of a study of leaving groups in this alkylation. The highest yields are obtained with halides, although the aryl sulfonates are usually easier to prepare and purify. Thus, we found the benzenesulfonate to be best for the large scale preparation of **10**. In the case of hindered alkylating agents we have found that the triflate is the best leaving group (16).

The β-keto ester **10** was converted into the *Z*-enol phosphates and enol triflate **11**. These reactions were very stereoselective. The enol derivative **11***b* was obtained in excellent yield and the greater than 99% *Z* as determined by GC. The stereochemistry of the olefin was proven by ^1H NMR. Next we undertook a study of the coupling reaction of these enol derivatives with the methyl Grignard reagent in the presence of a copper catalyst (17). The diphenyl phosphate and triflate gave a higher yield of **12**, but with a lower stereoselectivity (Table 2). Because of the difficulty in separating the geometric isomers of **12**, experimentally we found the diethyl phosphate coupling to be the most satisfactory to carry out in this case.

The *E*-alkene **12** was then converted into the *E* pheromone **5** by reduction and esterification in greater than 80% yield for the two steps. This compound had identical spectroscopic properties and biological activity to the natural pheromone.

By altering the reaction conditions, we are able to cleanly prepare the *E*-enol phosphate **13**. This stereoselectivity takes advantage of the fact that in ether solvents the metal cation enolates are tight ion pairs and in these solvents exist as the coordinated complex **15**, whereas in more polar solvents, such as HMPA and organic cationic counterions, the enolate is free and exists in the W-conformation **16** in which the negatively charged oxygens are distant from each other (18). In each case the O-alkylating agent traps the enolate before any conformational isomerization. Thus **16** gives **13** in good yield with no trace of any *Z*-enol phosphate **11***b* in the crude reaction mixture as determined by GC. The copper-catalyzed Grignard coupling of **13** then gives **14** in good yield and excellent stereoselectivity. Ester **14** was reduced and esterified to give the pheromone **6**, which was identical to the naturally occurring compound.

The synthesis of the third component of the pheromone mixture, alkene **7**, presented a different problem if we were to use the β-keto ester **10** as starting material. Due to the acidity of the α-methylene protons, Wittig reactions and their variations proceed in low yield on enolizable β-keto esters. We had shown that trimethylsilylmethylmagnesium chlo-



ride in the presence of nickel(II) added cleanly to enol phosphates of β-keto esters (19). Indeed the addition of these reagents to **11***b* or **13** gave the corresponding allyl silanes **17** and **18**, respectively. Treatment of these allyl silanes with a variety of protic and Lewis acids gave the cyclized compound **19** as the only isolable product. If the reaction was allowed to continue for longer periods of time **19** did slowly isomerize to the endocyclic isomers. Thus electrophilic attack on the terminal disubstituted alkene is faster than attack on the conjugated alkene, and the deactivating effect of the ester must be greater than the activating effect of the allylic trimethylsilyl group (20).

This problem was eventually solved by reducing the ester and then carrying out an olefination reaction. Ester reduction was achieved in two ways. The first involved formation of the monoanion of the β-keto ester **10** and reduction of this monoanion with DIBAL (21) to **20**. In the second method, the ketone carbonyl was converted into its silyl enol ether. The ester was then reduced and the enol ether hydrolyzed during work-up to give **20**. In our hands the latter route, although longer, consistently gave better yields of **20**. The keto alcohol **20** was then esterified and treated with the modified Tebbe reagent (22) to give **7**, which was identical in spectroscopic properties and biological activity to the third component of the San Jose scale pheromone.

Thus we have illustrated the utility of the methodology to stereoselectively introduce the units **A**, **B**, or **C** into a molecule using the alkylation of the dianion of a β-keto ester. The three synthetic components **5**–**7** were used to monitor San Jose scale in the Okanagan Valley. All three isomers were active in the field and the *E* isomer **5** was the most attractive of the three at the same release rates (23).

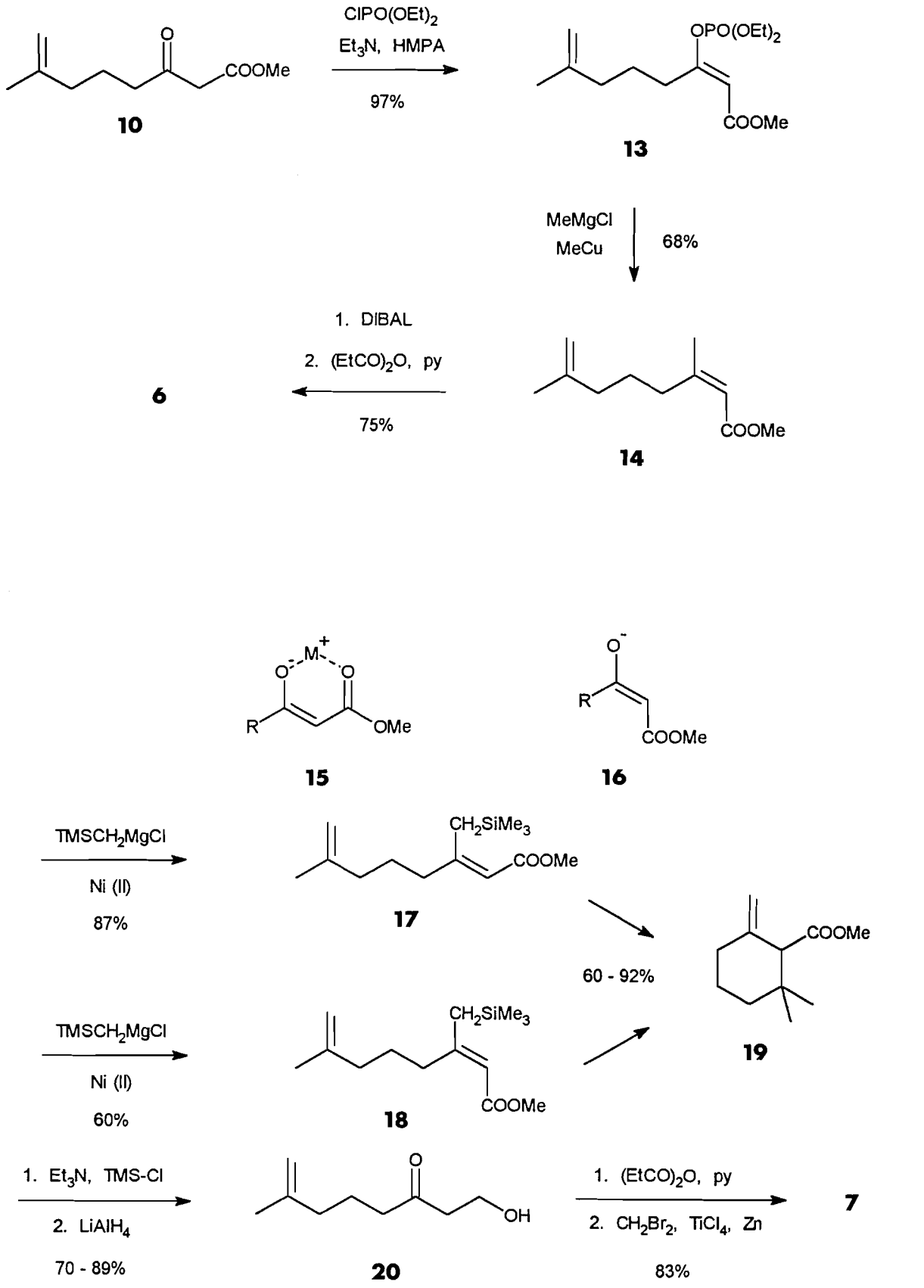
Experimental section

General procedures

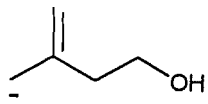
Kugelrohr distillations were performed with a Büchi Kugelrohr apparatus. Infrared spectra were recorded in chloroform solution on a Perkin–Elmer model 710 spectrophotometer, and were calibrated with the 1601 cm^{-1} band of polystyrene. Proton nuclear magnetic resonance spectra were recorded on a Varian T-60 (60 MHz) and a Bruker WP-80 (80 MHz). Chemical shifts are reported on the δ scale, with $CDCl_3$ as solvent and tetramethylsilane as internal standard. The multiplicity, coupling constants (if determined), and integrated peak areas are given in parentheses after each signal. Low-resolution mass spectra were recorded on a Kratos-AEI MS-50, and high-resolution mass measurements were determined on a Kratos-AEI MS-9 or MS-50. Both instruments were operated at an ionization potential of 70 eV. Elemental analyses were performed by Mr. Peter Borda, Microanalysis Laboratory, University of British Columbia.

Silica gel $PF_{254+366}$ (E. Merck) was used for both analytical and preparative thin-layer chromatography, while flash chromatography (24) was carried out using Silica Gel 60, 230–400 mesh ASTM (E. Merck). All mixed solvent systems are expressed in ratios by volume.

The petroleum ether used was of the boiling range 30–60°C. Dry solvents were prepared as follows: diethyl ether and tetrahydrofuran by distillation from lithium aluminium hydride or sodium–



benzophenone; dichloromethane by distillation from phosphorus pentoxide; and acetone by distillation from Drierite. *n*-Butyllithium and diisobutylaluminium hydride solutions were obtained from Aldrich. The *n*-BuLi solutions were standardized by titration against 0.1 M *tert*-butanol solution using 1,10-phenanthroline as indicator (25). Sodium hydride (Aldrich) was weighed as a 60% dispersion in mineral oil and washed with ether or petroleum ether to remove the oil prior to use. All reactions were run under a dry nitrogen at-



c

mosphere and organic extracts were dried with anhydrous magnesium sulfate.

*4-Bromo-2-methyl-1-butene (**9**a)*

This compound was prepared from 1.4 g (16 mmol) of 3-methyl-3-buten-1-ol in 42% distilled yield according to the procedure of Bhanot and Dutta (26) to give a colourless oil; bp 105°C/760 Torr (1 Torr = 133.3 Pa) (lit. (26) bp 105–107°C/760 Torr); ^{1}H NMR (60 MHz) δ: 1.76 (bs, 3H), 2.53 (t, J = 7 Hz, 2H), 3.43 (t, J = 7 Hz, 2H), and 4.7–5.0 (m, 2H).

*4-Iodo-2-methyl-1-butene (**9**b)*

A solution of 10.0 g (42 mmol) of the tosylate **9***d* (see below) was dissolved in 160 mL of a dry acetone-saturated solution of NaI. This solution was stirred at room temperature overnight. Then the solid salts were filtered off and the precipitate was washed several times with acetone. The acetone was evaporated under reduced pressure. The resulting oil was dissolved in 100 mL of ether and washed with 2 × 50 mL of 10% aqueous $Na_2S_2O_3$. The aqueous layers were extracted with 3 × 50 mL of ether. The ether layers were combined, dried, and the solvents were removed under reduced pressure to yield 5.9 g (72%) of a crude product, which was one spot by TLC and was suitable for the subsequent dianion alkylation. This material was a pale orange oil that gradually darkened on standing; ^{1}H NMR (60 MHz) δ: 1.70 (bs, 3H), 2.57 (t, J = 7 Hz, 2H), 3.23 (t, J = 7 Hz, 2H), and 4.77 (bd, J = 4 Hz, 2H); HRMS calcd. for C_5H_9I: 195.9749; found: 195.9753.

*3-Methyl-3-butenyl-1-benzenesulfonate (**9**c)*

A solution of 8.00 g (93 mmol) of 3-methyl-3-buten-1-ol in 100 mL of CH_2Cl_2 was flushed with N_2 and cooled in an ice bath. Pyridine (14.7 g, 15.0 mL, 0.186 mol) and benzenesulfonyl chloride (16.4 g, 11.8 mL, 0.093 mol) were added, and the resulting solution was stirred at 0°C for 4 h. The reaction mixture was then diluted with cold ether and acidified with cold 1 M HCl. The organic layer was separated, washed with cold saturated aqueous $NaHCO_3$ solution, cold brine, dried, filtered, and concentrated to give a quantitative yield (21.0 g) of the benzenesulphonate **9***c* as a yellow oil. The benzenesulfonate is relatively unstable and is best stored at 0°C or lower. The material darkens quickly at room temperature and should be used as soon as possible. ^{1}H NMR (60 MHz) δ: 1.60 (bs, 3H), 2.32 (t, J = 7 Hz, 2H), 4.13 (t, J = 7 Hz, 2H), 4.68 (bd, 2H), and 7.25–7.9 (m. 5H); HRMS calcd. for $C_{11}H_{14}O_3S$: 226.0664; found: 226.0671.

*3-Methyl-3-butenyl-1-p-toluenesulfonate (**9**d)*

This material was prepared from 2.0 g (23 mmol) of 3-methyl-3-buten-1-ol in 97% crude yield according to the procedure of Trost and Kunz (27) to give **9***d* as a yellow oil that was used directly in the dianion alkylation or to prepare the iodide **9***b* above.

*3-Methyl-3-butenyl-1-trifluoromethanesulfonate (**9**e)*

To a solution of 73 μL (0.91 mmol) of pyridine in 1 mL of CH_2Cl_2 at −40 to −50°C was added 140 μL (0.82 mmol) of freshly purified trifluoromethanesulfonic anhydride with stirring. A white precipitate formed immediately and after 5 min a solution of 71 mg (0.82 mmol) of 3-methyl-3-buten-1-ol was added to the mixture. The mixture was stirred at −40 to −50°C for 15 min, The precipitate was filtered off and washed with cold hexane. The filtrates were combined and the solvents removed under reduced pressure while maintaining the temperature below 0°C. The residue was dissolved in cold hexane (−20°C), and filtered. The solvent was removed from the filtrate while maintaining the temperature below 0°C to yield 165 mg (92%) of the triflate **9***e* as a pink oil that was used directly in the dianion step.

*3-Methyl-3-butenyl-1-methanesulfonate (**9**f)*

To a solution of 0.67 mL (4.8 mmol) of triethylamine in 10 mL of ether at 0°C was added a solution of 0.30 g (3.5 mmol) of 3-methyl-3-buten-1-ol in 10 mL of ether. After stirring at 0°C for 5 min, 0.27 mL (3.5 mmol) of methanesulfonyl chloride was added to the reaction, and the mixture was stirred at 0°C for 1 h and then warmed to room temperature. The reaction was quenched with 1 M HCl, and the organic phase was washed with 2 × 10 mL of 1 M HCl, 2 × 10 mL of saturated $NaHCO_3$, once with saturated brine, and dried. The solvent was removed under reduced pressure to yield 0.57 g (quantitative) of the mesylate **9***f* as a colourless oil that could be used directly in the dianion alkylation. A small amount was purified by chromatography using petroleum ether – ethyl acetate (6:1) to give pure **9***f* as a colourless oil; ^{1}H NMR (60 MHz) δ: 1.65 (bs, 3H), 2.45 (t, J = 7 Hz, 2H), 3.01 (s, 3H), 4.35 (t, J = 7 Hz, 2H), and 4.78 (bd, 2H); HRMS calcd. for $C_6H_{12}O_3S$: 164.0507; found: 164.0500.

*Methyl 7-methyl-3-oxo-7-octenoate (**10**)*

The dianion of methyl acetoacetate was prepared by using the following general procedure (10). Sodium hydride (60% by weight in oil, 1.12 equiv.) was weighed into a flask, washed under a N_2 atmosphere with ether, and resuspended in dry tetrahydrofuran. The flask was sealed, flushed with N_2, and cooled in an ice bath. Methyl acetoacetate (1.00 equiv.) was syringed dropwise into the NaH suspension, and the resulting monoanion was stirred at 0°C for 15 min, before the *n*-butyllithium (2.0 M in hexane, 1.12 equiv.) was syringed dropwise into the cooled reaction mixture. The resulting orange dianion solution was stirred at 0°C for 15 min. In the case of the triflate **9***e*, the dianion solution was cooled to −40°C for the addition of the alkylating agent. The alkylating agent (0.80 equiv.) dissolved in minimum dry THF was then syringed dropwise into the flask. No immediate change occurred, but within 5 min the reaction mixture became a lighter orange and was more difficult to stir due to the abundant formation of precipitate. The suspension was stirred for 1 h at 0°C, warmed to room temperature and stirred for a further 2 h.

The reaction mixture was diluted with ether and acidified with 1 M HCl. The organic layer was separated, washed with saturated aqueous $NaHCO_3$ solution, brine, dried, filtered, and concentrated to give the crude β-keto ester. This material was distilled at 0.3 Torr and the distillate boiling from 74–76°C was collected to give the desired product **10**. The yields of pure distilled product are given in Table 1. The β-keto ester **10** is a colourless oil; IR ν_{max}: 900, 1660, 1715, and 1745 cm^{-1}; ^{1}H NMR (80 MHz) δ: 1.70 (bs, 3H), 1.6–2.2 (m, 4H), 2.52 (t, J = 7 Hz, 2H), 3.45 (s, 2H), 3.73 (s, 3H), and 4.65 (m, 2H); MS m/z (relative intensity): 41 (57), 43 (87), 55 (77), 59 (42), 68 (56), 69 (58), 74 (100), 101 (37), 111 (35), 116 (75), 117 (34), 129 (37), 166 (18) and 184 (24). Anal. calcd. for $C_{10}H_{16}O_3$: C 65.19, H 8.75; found: C 65.16, H 8.80.

*Methyl (2Z)-3-(diethylphosphoryloxy)-7-methyl-2,7-octadienoate (**11**a)*

Sodium hydride (60% by weight in oil, 0.238 g, 5.97 mmol) was weighed into a flask, washed under a N_2 atmosphere with 15 mL of ether, and resuspended in 20 mL of fresh ether. The flask was flushed with N_2 and cooled in an ice bath. The β-keto ester **10** (1.00 g, 5.43 mmol) dissolved in 5 mL of ether was added dropwise to the NaH suspension. The resulting monoanion was stirred at 0°C for 15 min before diethyl chlorophosphate (0.984 g, 0.82 mL, 5.70 mmol) was syringed dropwise into the cooled reaction mixture. Within 30 min a thick white precipitate had formed (NaCl) and stirring was continued overnight at room temperature.

The reaction mixture was quenched with saturated aqueous NH_4Cl solution and then acidified with 1 M HCl. The organic layer was separated, washed with saturated aqueous $NaHCO_3$ solution, washed with brine, dried, filtered, and concentrated to give 1.74 g (100%) of the crude enol phosphate, which was suitable for the coupling reaction. The product was >99% *Z* by GC analysis. This material was purified by column chromatography using pe-

troleum ether – ethyl acetate (1:1) to give 1.30 g (75%) of the enol phosphate **11***a* as a pale yellow oil; IR ν_{max}: 990, 1020, 1270, 1420, 1670, and 1725 cm^{-1}; ^1H NMR (80 MHz) δ: 1.35 (dt, J = 1 and 7 Hz, 6H), 1.70 (bs, 3H), 1.6–2 (m, 2H), 2–2.3 (m, 2H), 2.43 (bt, J = 7 Hz, 2H), 3.67 (s, 3H), 4.25 (q, J = 7 Hz, 4H), 4.70 (bs, 2H), and 5.41 (s, 1H); MS m/z (relative intensity): 41 (22), 79 (29), 81 (22), 99 (80), 127 (55), 134 (42), 155 (100), 164 (10), 166 (30), 177 (9), 192 (21), 220 (25), 252 (12), 289 (6), 320 (2). Anal. calcd. for $C_{14}H_{25}O_6P$: C 52.50, H 7.87; found: C 52.57, H 7.90.

*Methyl (2Z)-3-(diphenylphosphoryloxy)-7-methyl-2,7-octadienoate (**11**b)*

This compound was prepared following the same method as for **11***a* using 0.24 g (6.0 mmol) of NaH (60% by weight), 1.0 g (5.4 mmol) of ester **10**, and 1.5 g (5.6 mmol) of diphenyl chlorophosphate to quantitatively yield the enol phosphate **11***b*, which was used in the coupling reaction. A small sample of this material was purified by column chromatography using petroleum ether – ethyl acetate (4:1) to give pure **11***b* as a colourless oil; IR ν_{max}: 1020, 1625, 1685, and 1725 cm^{-1}; ^1H NMR (60 MHz) δ: 1.65 (bs, 3H), 2 (m, 4H), 2.51 (bt, J = 7 Hz, 2H), 3.72 (s, 3H), 4.74 (bs, 2H), 5.64 (s, 1H), and 7.2–7.7 (m, 10H); HRMS calcd. for $C_{22}H_{25}O_6P$: 416.1389; found: 416.1395.

*Methyl (2Z)-3-(trifluoromethylsulfonyloxy)-7-methyl-2,7-octadienoate (**11**c)*

The β-keto ester **10** (1.00 g, 5.43 mmol) in 50 mL of dry THF was added to 0.24 g (6.0 mmol) of NaH (60% by weight) and cooled to −78°C. Then 1.55 g (5.50 mmol) of Tf_2O was slowly added and the reaction mixture was allowed to warm to room temperature over several hours. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and then acidified with 1 M HCl. The organic layer was separated, washed with saturated aqueous $NaHCO_3$ solution, washed with brine, dried, filtered, and concentrated to give 1.7 g (ca. 100%) of the crude enol triflate **11***c*, which was suitable for the coupling reaction. A small amount of this material was purified by thin-layer chromatography using petroleum ether – ethyl acetate (9:1) to give pure **11***c* as a colourless oil; IR ν_{max}: 1630, 1665, and 1735 cm^{-1}; ^1H NMR (60 MHz) δ: 1.68 (bs, 3H), 2 (m, 4H), 2.51 (bt, J = 7 Hz, 2H), 3.70 (s, 3H), 4.65 (bs, 2H), and 5.52 (s, 1H); HRMS calcd. for $C_{11}H_{15}O_5F_3S$: 316.0592; found: 316.0587.

Preparation of the stock methylmagnesium chloride solution

Magnesium turnings (9.37 g, 0.385 mol) were weighed into a 500-mL, three-necked, round-bottom flask, equipped with a Dry Ice condenser and gas bubbling frit. The apparatus was sealed, flushed with N_2, and dried with a hot air gun. Dry THF (250 mL) was syringed into the flask, the condenser was cooled, and methyl chloride was bubbled into the stirred suspension. The Grignard reaction commenced immediately and was so vigorous that an ice bath was required to keep the reaction under control. As the reaction slowed, more methyl chloride was bubbled into solution. This procedure was repeated until all the magnesium had reacted (about 2 h). The resulting solution (with a fine black suspension) was cannulated into a stoppered, N_2 flushed bottle, and then titrated.

The titration was carried out as a back-titration. A 1 mL aliquot of the Grignard reagent was quenched with 50 mL of 0.05 M HCl. The resulting solution was titrated to a phenolphthalein endpoint using 0.1 M NaOH to give the total base concentration.

*Methyl (2E)-3,7-dimethyl-2,7-octadienoate (**12**)*

*(a) From the enol phosphate **11**a*

Purified cuprous iodide (28) (3.57 g, 0.019 mol) and 100 mL of THF were added to a 250-mL flask, which was equipped with an internal thermometer. The flask was flushed with N_2 and cooled to 0°C. Methyllithium (1.25 M in ether, 15 mL, 0.019 mol) was syringed dropwise into the stirred white suspension while keeping the internal temperature below 10°C. The resulting yellow MeCu suspension was stirred at 0°C for 10 min and then cooled to −30°C. Methylmagnesium chloride (1.3 M in THF, 24 mL, 0.031 mol) was syringed dropwise into the flask while maintaining the internal temperature below −25°C. The resulting clear, tan-coloured solution was stirred at −30°C for 15 min before a THF solution of the enol phosphate **11***a* (2.0 g, 6.2 mmol) was syringed into the flask. The resulting deep maroon solution was stirred for 3 h at −25°C.

The reaction mixture was quenched by pouring it quickly into a stirred, ice-cold mixture of NH_4Cl in aqueous NH_4OH. The organic layer was diluted with ether and washed with NH_4Cl in aqueous NH_4OH until these washes were no longer blue. The ethereal layer was washed with brine, dried, and the solvents removed under reduced pressure to give 1.05 g (92%) of the crude product as yellow oil that was purified by flash column chromatography using petroleum ether – ethyl acetate (19:1) to give 0.795 g (70%) of the ester **12**. The ratio of E:Z was determined by GC to be 98:2. The ester is a colourless oil, bp (Kugelrohr distillation) 65°C/0.1 Torr; IR ν_{max}: 1150, 1445, 1655, and 1715 cm^{-1}; ^1H NMR (80 MHz) δ: 1.70 (bs, 3H), 1.5–1.8 (m, 2H), 1.9–2.3 (m, 4H), 2.16 (d, J = 1 Hz, 3H), 3.68 (s, 3H), 4.70 (bs, 2H), and 5.65 (m, 1H); MS m/z (relative intensity): 41 (100), 55 (35), 59 (25), 67 (67), 68 (75), 69 (50), 81 (25), 82 (23), 83 (35), 95 (55), 108 (40), 114 (38), 122 (20), 123 (24), 124 (24), 125 (20), 135 (15), 139 (40), 150 (8), 167 (12), 182 (7). Anal. calcd. for $C_{11}H_{18}O_2$: C 72.49, H 9.95; found: C 72.56, H 9.90.

*(b) From the enol phosphate **11**b*

In the same manner as above, using 1.5 g (3.6 mmol) of the diphenyl phosphate **11***b*, 0.51 g (78%) of chromatographed ester **12** was obtained. The ratio of E:Z was 90:10 as determined by GC.

*(c) From the enol triflate **11**c*

In the same manner as above, using 1.2 g (3.8 mmol) of the triflate **11***c*, 0.57 g (82%) of chromatographed ester **12** was obtained. The ratio of E:Z was 88:12 as determined by GC.

(2E)-3,7-Dimethyl-2,7-octadien-1-ol

The α,β-unsaturated ester **12** (1.364 g, 7.48 mmol) was dissolved in 30 mL of ether, flushed with N_2, and cooled to 0°C. As diisobutylaluminium hydride (1 M in hexane, 18.7 mL, 1.87 mmol) was syringed into the flask, the reaction mixture became yellow, but the colour faded as all the DIBAL was added. Stirring was continued for 2 h at 0°C. The reaction was quenched at 0°C with saturated aqueous NH_4Cl solution and allowed to stir at this temperature for 1 h. The aluminum salts solidified into a sticky solid top layer, which was broken up and poured into a separatory funnel along with the aqueous and organic layers. This mixture was acidified with 1 M HCl and was shaken until the solid had dissolved. The ethereal layer was separated, washed several times with brine, dried, and the solvents were removed under reduced pressure to give 1.13 g (98%) of the alcohol as a yellow oil. The crude material was purified by column chromatography using petroleum ether – ethyl acetate (4:1) to give 0.96 g (84%) of the alcohol, which was shown to be 96% pure by GC. IR$_{\nu_{max}}$: 900, 995, 1660, 1680, 3475, and 3625 cm^{-1}; ^1H NMR (80 MHz) δ: 1.2–1.7 (m, 2H), 1.67 (bs, 3H), 1.70 (bs, 3H), 1.8–2.2 (m, 4H), 4.14 (d, J = 7 Hz, 2H), 4.67 (bs, 2H), and 5.65 (t, J = 7 Hz, 1H); MS m/z (relative intensity): 41 (100), 43 (37), 53 (27), 55 (46), 67 (36), 68 (65), 69 (75), 71 (40), 81 (40), 83 (34), 93 (17), 95 (35), 107 (10), 109 (14), 121 (18), 123 (11), 136 (14), 139 (2), 154 (1). Anal. calcd. for $C_{10}H_{18}O$: C 77.87, H 11.76; found: C 77.76, H 11.64.

E *Pheromone **5***

The above E alcohol (1.43 g, 9.27 mmol) and a catalytic amount of 4-dimethylaminopyridine (10 mg) were dissolved in 50 mL of ether under N_2. Propionic anhydride (1.33 g, 1.31 mL, 0.010 mol) and pyridine (1.46 g, 1.49 mL, 0.019 mol) were syringed into the reaction mixture, which was stirred at room temperature for 24 h. The reaction mixture was washed with 1 M HCl to remove pyridine. The organic layer was separated, washed with saturated aqueous $NaHCO_3$ solution and brine, dried, and the solvents were removed under reduced pressure to give 1.94 g (100%) of product

as a light yellow liquid. The crude material was Kugelrohr distilled at 85–90°C/0.05 Torr to give 1.87 g (96%) of the desired propionate **5** as a colourless oil; $IR_{\nu_{max}}$: 1195, 1660, 1680, and 1730 cm^{-1}; ^1H NMR (80 MHz) δ: 1.12 (t, J = 7 Hz, 3H), 1.2–1.7 (m, 2H), 1.70 (bs, 6H), 1.8–2.2 (m, 4H), 2.32 (q, J = 7 Hz, 2H), 4.6–4.8 (m, 4H), and 5.33 (t, J = 7 Hz, 1H); MS m/z (relative intensity): 53 (40), 55 (60), 57 (100), 68 (100), 69 (60), 79 (56), 80 (56), 81 (90), 93 (64), 94 (25), 95 (30), 96 (56), 97 (24), 107 (50), 108 (25), 109 (25), 121 (80), 136 (71), 139 (5), 154 (20), 195 (0.5), 210 (0.5). Anal. calcd. for $C_{13}H_{22}O_2$: C 74.24, H 10.54; found: C 74.00, H 10.65.

*Methyl (2E)-3-(diethylphosphoryloxy)-7-methyl-2,7-octadienoate (**13**)*

4-Dimethylaminopyridine (0.146 g, 1.2 mmol), triethylamine (1.21 g, 1.67 mL, 12.0 mmol), HMPA (2.15 g, 2.09 mL, 12.0 mmol), and the β-keto ester **10** (2.00 g, 10.9 mmol) were added to a flask. The resulting yellow solution was stirred for 30 min at 0°C and then cooled to −20°C. Diethyl chlorophosphate (2.07 g, 12.0 mmol) was added dropwise to the cooled solution and a heavy precipitate began to form immediately. The yellow-orange paste was warmed to room temperature and stirred at this temperature for 4 h. The reaction mixture was diluted with ether and acidified with 1 M HCl. The ethereal extracts were washed with saturated aqueous $CuSO_4$ to remove HMPA, dried and concentrated to give 3.39 g (97%) of product as an orange oil that was suitable for the Grignard coupling step. This material was >99% *E* by GC analysis and a small sample was purified by column chromatography using petroleum ether – ethyl acetate (1:1) to give a pure sample of enol phosphate **13** as a colourless oil; $IR_{\nu_{max}}$: 960, 1030, 1285, 1440, 1650, and 1720 cm^{-1}; ^1H NMR (80 MHz) δ: 1.35 (dt, J = 1 and 7 Hz, 6H), 1.73 (bs, 3H), 1.6–2 (m, 2H), 2–2.3 (m, 2H), 2.79 (bt, J = 7 Hz, 2H), 3.70 (s, 3H), 4.2 (m, J = 7 Hz, 4H), 4.70 (bs, 2H), and 5.85 (d, J = 1 Hz, 1H); MS m/z (relative intensity): 55 (15), 79 (20), 91 (26), 99 (72), 107 (20), 127 (51), 134 (42), 152 (10), 155 (100), 164 (15), 166 (30), 177 (5), 192 (16), 205 (4), 220 (23), 234 (9), 252 (12), 260 (5), 288 (4), 289 (3), 320 (3). Anal. calcd. for $C_{14}H_{25}O_6P$: C 52.50, H 7.87; found: C 52.38, H 7.90.

*Methyl (2Z)-3,7-dimethyl-2,7-octadienoate (**14**)*

This reaction was carried out following the same procedure as in the synthesis of **12** from **11***a* using cuprous iodide (8.91 g, 0.047 mol), methyllithium (1.7 M in ether, 27.5 mL, 0.047 mol), methylmagnesium chloride (1.5 M in THF, 52 mL, 0.078 mol), and the *E* enol phosphate **13** (5.0 g, 0.016 mol). The reaction was worked up to give 2.69 g (95%) of crude ester, which was purified by column chromatography to yield 1.94 g (68%) of a faint yellow oil in which the ratio of *E*:*Z* was determined by GC to be 97:3; bp (Kugelrohr distillation) 60°C/0.2 Torr; $IR_{\nu_{max}}$: 1180, 1440, 1650, and 1710 cm^{-1}; ^1H NMR (80 MHz) δ: 1.73 (bs, 3H), 1.5–1.8 (m, 2H), 1.89 (d, J = 1 Hz, 3H), 1.9–2.3 (m, 4H), 3.65 (s, 3H), 4.68 (bs, 2H), and 5.62 (bs, 1H); MS m/z (relative intensity): 41 (80), 53 (21), 55 (30), 59 (16), 67 (46), 68 (75), 82 (27), 83 (73), 95 (50), 108 (22), 109 (25), 114 (100), 122 (20), 123 (33), 135 (8), 139 (30), 150 (13), 167 (7), 182 (9). Anal. calcd. $C_{11}H_{18}O_2$: C 72.49, H 9.95; found: C 72.70, H 10.10.

(2Z)-3,7-Dimethyl-2,7-octadien-1-ol

This alcohol was produced by reduction of the α,β-unsaturated ester **14** (2.00 g, 0.011 mol) with diisobutylaluminium hydride (1 M in hexane, 27.5 mL, 0.0275 mol) according to the same procedure as for the ester **12** above. The reaction, on work-up, yielded 1.74 g (>100%) of crude alcohol, which was purified by chromatography using petroleum ether – ethyl acetate (4:1) to yield 1.40 g (82%) of the desired *Z* alcohol, which was greater than 90% *Z* by GC and was distilled (Kugelrohr) at 64°C/0.2 Torr; $IR_{\nu_{max}}$: 895, 985, 1650, 1670, 3450, and 3625 cm^{-1}; ^1H NMR (80 MHz) δ: 1.2–1.7 (m, 2H), 1.75 (bs, 6H), 1.8–2.2 (m, 4H), 4.12 (d, J = 6 Hz, 2H), 4.68 (bs, 2H), and 5.40 (t, J = 6 Hz, 1H); MS m/z (relative intensity): 41 (100), 43 (30), 53 (27), 55 (50), 56 (25), 67 (32), 68 (40), 69 (50), 71 (30), 81 (34), 83 (27), 93 (14), 95 (17), 107 (7), 109 (9), 121 (13), 123 (8), 136 (9), 139 (3), 154 (2). Anal. calcd. for $C_{10}H_{18}O$: C 77.87, H 11.76; found: C 77.57, H 11.89.

*Z Pheromone **6***

The above *Z* alcohol (0.90 g, 5.8 mmol) was esterified with a catalytic amount of 4-dimethylaminopyridine (10 mg), propionic anhydride (0.83 g, 0.82 mL, 6.4 mmol), and pyridine (0.93 g, 0.95 mL, 0.012 mol) as above for **5** to yield, after chromatography, 1.13 g (92%) of a colourless oil that distilled (Kugelrohr) at 60°C/0.02 Torr; $IR_{\nu_{max}}$: 1105, 1665, 1687, and 1725 cm^{-1}; ^1H NMR (80 MHz) δ: 1.12 (t, J = 7 Hz, 3H), 1.2–1.7 (m, 2H), 1.72 (bs, 3H), 1.74 (bs, 3H), 2.1 (bq, J = 7 Hz, 4H), 2.25 (q, J = 7 Hz, 2H), 4.5–4.7 (m, 4H), and 5.35 (bt, J = 7 Hz, 1H); MS m/z (relative intensity): 41 (98), 43 (20), 53 (38), 55 (70), 57 (100), 67 (62), 68 (91), 69 (78), 79 (49), 80 (52), 81 (99), 93 (66), 94 (25), 95 (42), 96 (54), 97 (23), 98 (41), 107 (47), 108 (23), 109 (28), 121 (74), 136 (76), 154 (20), 196 (1), 210 (1). Anal. calcd. for $C_{13}H_{22}O_2$: C 74.24, H 10.54; found: C 74.45, H 10.61.

*Methyl (2Z)-3-(trimethylsilylmethyl)-7-methyl-2,7-octadienoate (**17**)*

The Grignard reagent was prepared from magnesium turnings (0.304 g, 0.0124 mol) and trimethylsilylmethyl chloride (1.66 g, 0.014 mol) in 20 mL of dry ether. This solution was cannulated into a clean flask under N_2 to remove any unreacted magnesium and then treated with 0.08 g (0.31 mmol) of nickel(II) acetylacetonate. Then 2.00 g (6.2 mmol) of the enol phosphate **11***b* was slowly added to the Grignard solution. After 0.5 h and 1.5 h, additional portions of the $Ni(acac)_2$ catalyst were added (0.08 g each time). The reaction was stirred overnight and quenched with 20 mL of dilute HCl. The aqueous phase was extracted with 3 × 20 mL of ether. The extracts were combined, washed with brine, dried, and the solvents removed under reduced pressure to yield 1.6 g of a crude product that was purified by column chromatography using petroleum ether – ethyl acetate (40:1) to give 1.37 g (87%) of a pale yellow oil; $IR_{\nu_{max}}$: 1620 and 1710 cm^{-1}; ^1H NMR (60 MHz) δ: 0.05 (s, 9H), 1.2–1.7 (m, 2H), 1.75 (bs, 3H), 1.8–2.2 (m, 4H), 2.45 (s, 2H), 3.65 (s, 3H), 4.7 (bs, 2H), and 5.65 (bs, 1H).

*Methyl (2E)-3-(trimethylsilylmethyl)-7-methyl-2,7-octadienoate (**18**)*

This compound was prepared in the same way as **17** using magnesium turnings (0.10 g, 4.0 mmol), trimethylsilylmethyl chloride (0.55 g, 5.0 mmol), 0.08 g (0.31 mmol) of nickel(II) acetylacetonate (0.03 g × 3), and the enol phosphate **13** (0.68 g, 2.1 mmol) to yield, after chromatography, 0.32 g (60%) of the *E* ester **18**; $IR_{\nu_{max}}$: 1635 and 1715 cm^{-1}; ^1H NMR (60 MHz) δ: 0.08 (s, 9H), 1.2–1.7 (m, 2H), 1.75 (bs, 3H), 1.8–2.2 (m, 2H), 2.15 (s, 2H), 2.6 (m, 2H), 3.62 (s, 3H), 4.65 (bs, 2H), and 5.6 (bs, 1H).

*Methyl 2,2 dimethyl-6-methylenecyclohexanecarboxylate (**19**)*

This compound was prepared with a variety of Lewis acid and acid catalysts on **17** or **18** using procedures established earlier in our laboratory (19). The product **19** was isolated in 64–92% yield and had spectroscopic and chromatographic properties identical to the compound prepared earlier (19).

*3-Oxo-7-methyl-7-octen-1-ol (**20**)*

*(a) Directly from the β-keto ester **10***

A solution 0.160 g (0.87 mmol) of the ester **10** in 20 mL of dry ether was added to 42 mg of NaH (60% oil, 1.0 mmol), which had been washed with dry petroleum ether at 0°C. The monoanion was stirred at 0°C for 10 min and then treated with 2.6 mL of a 1 M DIBAL solution in hexane. This reaction was allowed to warm to room temperature with stirring for 1 h. The reaction was quenched with saturated aqueous NH_4Cl and filtered through Celite. The aqueous phase was extracted with 3 × 30 mL of ether. The extracts were combined washed with brine, dried, and the solvents evaporated to give 167 mg of a crude product that was purified by column chromatography using petroleum ether – ethyl acetate (3:2) to give 94 mg (70%) of **20** as a colourless oil; $IR_{\nu_{max}}$: 895, 1060, 1650, 1705, and 3575 cm^{-1}; ^1H NMR (80 MHz) δ: 1.5–2.2 (m,

4H), 1.75 (bs, 3H), 2.47 (t, J = 7 Hz, 2H), 2.70 (t, J = 6 Hz, 2H), 3.87 (t, J = 6Hz, 2H), and 4.7 (bs, 2H); HRMS m/z calcd. for $C_9H_{16}O_2$: 156.1150; found: 156.1143.

(b) Via the enol silyl ether

The β-keto ester **10** (0.250 g, 1.36 mmol) was dissolved in 25 mL of dry ether and then 0.20 mL (1.4 mmol) of triethylamine was added and the solution was stirred for 10 min before 0.17 mL (1.36 mmol) of trimethylsilyl chloride was added. A thick, white precipitate formed immediately and the reaction was stirred overnight. The reaction mixture was filtered through Florisil and the column was washed with 25 mL of dry ether. The solvents were removed under reduced pressure to give 0.34 g (97%) of the silyl enol ether, which was used directly in the next step; ^{1}H NMR (60 MHz) δ: 0.4 (s, 9H), 1.8 (bs, 3H), 1.4–2.3 (m, 4H), 2.8 (t, J = 7 Hz, 2H), 3.75 (s, 3H), 4.7 (bs, 2H), and 5.15 (bs, 1H). This enol ether (0.163 g, 0.64 mmol) was dissolved in 1 mL of dry ether and added to a solution of 25 mg (0.64 mmol) of $LiAlH_4$ in 2 mL of dry ether at 0°C. The reaction was stirred at 0°C for 0.5 h and allowed to warm to room temperature for 0.5 h. The reaction was quenched with 1 M HCl and extracted with 3 × 10 mL of ether. The extracts were combined, washed with brine, dried, and the solvents removed to yield 101 mg of a pale yellow oil that was purified as above to yield 89 mg (89%) of the alcohol **20**.

Pheromone 7

A solution of the alcohol **20** (1.20 g, 7.68 mmol), 1.10 g (8.45 mmol) of propionic anhydride, 1.22 g (15.4 mmol) of pyridine, and a catalytic amount of DMAP were dissolved in 75 mL of ether and stirred overnight. The reaction mixture was washed with 1 M HCl, saturated aqueous $NaHCO_3$, and brine, then dried and the solvents removed under reduced pressure to yield 1.62 g (99%) of crude propionate ester. The crude ester was purified by column chromatography using petroleum ether – ethyl acetate (9:1) to give 1.46 g (90%) of pure keto ester; $IR_{\nu_{max}}$: 900, 1190, 1650, 1725, and 1740 cm^{-1}; ^{1}H NMR (80 MHz) δ: 1.14 (t, J = 7 Hz, 3H), 1.4–2.05 (m, 4H), 1.70 (bs, 3H), 2.38 (five-line pattern, 4H), 2.75 (t, J = 7 Hz, 2H), 4.35 (t, J = 7 Hz, 2H), and 4.7 (m, 2H); HRMS m/z calcd. for $C_{12}H_{20}O_3$: 212.1412; found: 212.1422.

To a stirred slurry of zinc dust (11.5 g, 0.176 mol) and dibromomethane (4.04 mL, 0.056 mol) in 100 mL of THF at −40°C was added 4.6 mL (0.042 mol) of $TiCl_4$ over 0.5 h in a well-vented fume-hood. The reaction was vigorous and copious amounts of a green gas evolved. After the addition of the $TiCl_4$, the reaction mixture was a gray slurry and was stirred at −40°C for 2 h and then at 0°C for at least 24 h before use. This solution of the active methylene complex could be stored in the freezer for up to 2 weeks.

A solution of 101 mg (0.48 mmol) of the above keto propionate in 3 mL of dry CH_2Cl_2 was treated with 3 × 3 mL of the above active methylene complex. The reaction was followed by TLC after each addition; the solution turned black immediately after each addition and then slowly cleared until after the final addition when the solution remained black. The reaction mixture was poured into a mixture of saturated aqueous $NaHCO_3$ and ether, and stirred until the ether layer became clear. The ether layer was removed, washed with brine, dried, and the solvents removed under reduced pressure to yield 90 mg of crude product, which was purified by column chromatography on Florisil using petroleum ether – ethyl acetate (19:1) to give 77 mg (83%) of **7** as a colourless oil; $IR_{\nu_{max}}$: 890, 1190, 1645, and 1730 cm^{-1}; ^{1}H NMR (80 MHz) δ: 1.12 (t, J = 7 Hz, 3H), 1.5–1.8 (m, 2H), 1.72 (bs, 3H), 1.85–2.5 (m, 8H), 4.20 (t, J = 7 Hz, 2H), 4.70 (bs, 2H), and 4.83 (bs, 2H); HRMS m/z calcd. for $C_{13}H_{22}O_2$: 210.1620; found: 210.1622.

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