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The Chemistry of Thujone

I. Synthesis of Insect Juvenile Hormone Analogs Via Wittig Coupling[1]

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Syntheses of the C_8 and C_{10} olefinic units *cis*- and *trans*-5-ethyl-1-iodo-hex-4-enes and *cis*- and *trans*-7-ethyl-3-iodo-oct-6-enes are described. The Wittig coupling of such units with derivatives of α- and β-thujaketonic acids to give analogs of insect juvenile hormones is discussed.

The presently marketable products from the forestry industry, one of the largest and economically most important in Canada, are derived from specific segments of the tree. Disposal of other materials, e.g., bark, leaves, and branches, generally termed "slash," often leads to a variety of environmental problems. This report describes our initial investigations in the development of a program designed to (a) stimulate utilization of some of the waste products, in particular the "leaf oils" obtained from the steam distillation of "slash", and (b) provide products which could in turn be used by various industries.

The monoterpene thujone **1** (*1*) is the major component (ca. 88%) of the western red cedar "leaf oils." In view of the attractive functionality and known chemistry of thujone, studies were undertaken to evaluate its utility as a building unit in the syntheses of insect control agents.

Since the structure elucidation (*2*) of the juvenile hormone from *Hyalophora cecropia* as methyl-*trans*, *trans*, *cis*-10,11-epoxy-7-ethyl-3,11-dimethyl-2,6-tridecadienoate **2**, a great deal of effort has been expended on the identification and synthesis of natural juvenates and closely related analogs (*3*). Indeed, activity was found to be retained by many analogs with considerable structural variations (*4*, *5*). With this background knowledge in hand, investigations toward the synthesis of juvenile hormone analogs were initiated.

Permanganate cleavage of thujone had provided α-thujaketonic acid **3** (*1*) and subsequent methylation (*6*) made available the ester **4**. The acid **3** on treatment with aqueous acid or simply by thermolysis gave *cis*-β-thujaketonic acid **5**. Alternatively, reaction of **4** with sodium methoxide promoted stereospecific ring opening to provide *trans*-β-thuja-

[1] This article is dedicated to Professor W. S. Johnson on the occasion of his 65th birthday. Included among the numerous elegant contributions which Johnson has made to organic chemistry are his recent synthetic achievements in the insect area.

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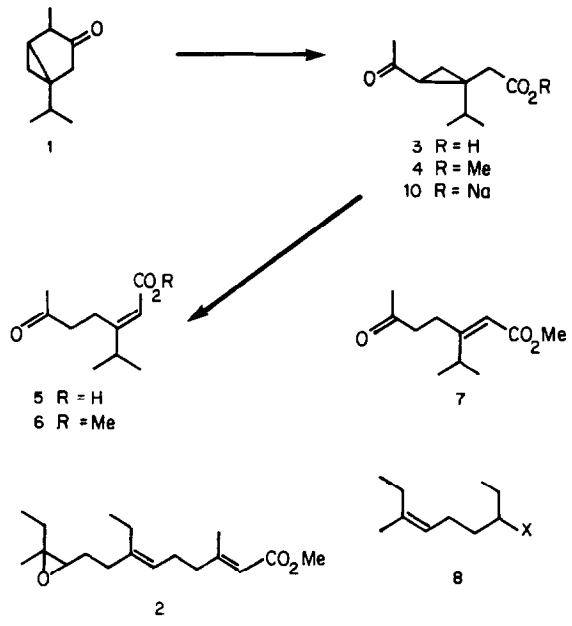


FIGURE 1

ketonic acid methyl ester **7**. These readily available, isomeric thujaketonic acids (and esters) were considered potential units for coupling with a suitable 10-carbon unit such as **8** to provide analogs of the known juvenile hormone **2**.

In the first instance, the Wittig reaction was considered as a means of elaborating the thujone-derived acids and esters. Thus preliminary investigations, to determine the suitability of these carbonyl compounds to Wittig olefination, were carried out. The results of the model studies are summarized in Table 1. Limited success was obtained by reaction of **4** with methyltriphenylphosphorane, generated in 1,2-dimethoxyethane (DME) with sodium hydride, to give the terminal olefin **9** in 21% yield. Similar reaction with isopropyltriphenylphosphorane, however, failed to yield any olefination product. It was presumed that the acidity of the methylene group α- to the ester function had promoted competing side reactions, and thus the sodium salt **10** was subjected to the Wittig reaction.

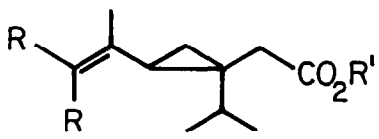
TABLE 1

MODEL WITTIG REACTIONS WITH DERIVATIVES OF α-THUJAKETONIC ACID

Substrate	Phosphonium salt	Product (%)[a]	Method[b]
4	$(Ph)_3P^+CH_3\,Br^-$	**9** (21)	A
4	$(Ph)_3P^+CH(CH_3)_2\,I^-$	No reaction	A
10	$(Ph)_3P^+CH_3\,Br^-$	**11** (90)	B
10	$(Ph)_3P^+CH(CH_3)_2\,I^-$	**12** (83)	B

[a] Yields of isolated materials.

[b] Method A: sodium hydride and 1,2-dimethoxyethane; method B: sodium hydride and dimethylsulfoxide.



9 R = H, R' = Me
11 R = R' = H
12 R = Me, R' = H

Indeed, reaction of **10** in dimethylsulfoxide (DMSO) with the methyl and isopropyl ylids gave the expected olefins **11** and **12** in 90 and 83% yields, respectively. Therefore the first objective had been realized, and more importantly, the high yield production of a tetrasubstituted double bond has been demonstrated.

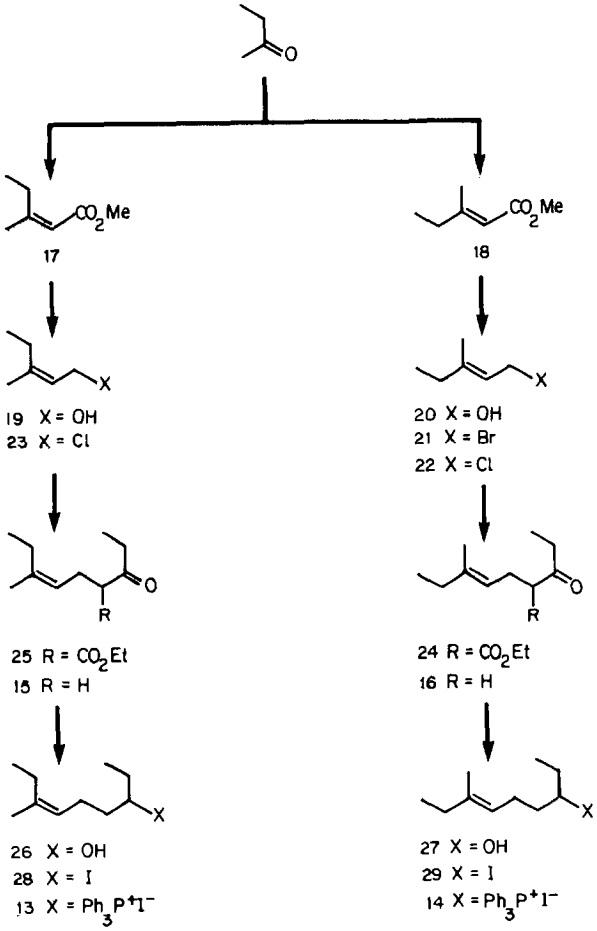


FIGURE 2

TABLE 2

PREPARATION OF ALLYLIC HALIDES FROM **20**

Product	Yield[a]	Percentage *trans*[b]	Method[c]	Ref.
21	86	92	A	(*9*)
21	50	86	B	(*10*)
21	65[d]	94	C	(*11*)
21	66[d]	94	D	—
22	74[e], 13[f]	100	E	(*12*)
22	36[g]	100	F	(*13*)
22	85	100	G	(*8*)

[a] Isolated yields.

[b] Ratio determined by the relative peak areas for the vinylic methyl absorbances in the ^{1}H-nmr spectra (270 MHz).

[c] Method A: PBr_3, Et_2O; B: PBr_3, CaH_2, Et_2O; C: CBr_4, Ph_3P, CH_3CN; D: inverse addition Ph_3P, CBr_4, $CaCO_3$, CH_3CN; E: CCl_4; Ph_3P; F: $(CCl_3)_2CO$, Ph_3P; G: NCS, DMS, CH_2Cl_2.

[d] Contaminated with small amounts of $CHBr_3$.

[e] Contaminated with small amounts of Ph_3PO and CCl_4.

[f] Yield after purification from contaminants.

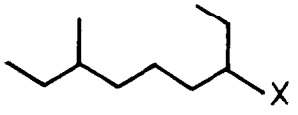
[g] Low yield partly due to the difficulty in separation from chloroacetones.

Attention was then focused on the preparation of C_{10} units such as **13** and **14**. Trost *et al.* (*7*) had prepared the ketone **15** which, together with the isomer **16**, seemed a likely progenitor of the phosphonium salt **13** (and **14**). The proposed routes to **13** and **14** are shown in Fig. 2.

The *cis*- and *trans*-esters were prepared as described in the literature (*7*) and separated by spinning band distillation. Reduction with lithium aluminum hydride gave the pure, isomeric, allylic alcohols **19** and **20**. Since isomeric purity of the intermediates was a prerequisite for the formation of specific hormone analogs, conversions to the allylic halides were studied in some detail. The results of various preparations of the halides **21** and **22** are given in Table 2. Notably, each of the routes to the bromide **21** was eliminated due to concomitant *trans,cis* isomerization. Although each of the routes to the chloride **22** proceeded without any detectable bound bond isomerization, only that using *N*-chlorosuccinimide/dimethylsulfide (*8*) gave **22** readily isolable in high yield. Similar results had been reported by Normant *et al.* (*8*) on the preparation of the *cis*-chloride **23**.

Condensation of **22** with the anion of ethyl-3-oxopentanoate gave the *trans*-ketoester **24** which on treatment with barium hydroxide (*9*) gave the pure *trans*-ketone **16**. The integrity of the geometry of the olefin was determined by 270-MHz ^{1}H-nmr spectroscopy. The ketoester **24** was also available directly from the alcohol **20**, by reaction with *n*-butyllithium, methanesulfonyl chloride, and lithium chloride, as described by Stork *et al.* (*14*), followed by *in situ* treatment with the sodium salt of ethyl-3-oxopentanoate. Lower yields (ca. 45%) and small but detectable amounts of olefin isomerization (*cis/trans*) precluded the use of this method. Similar (Fig. 2) manipulations of the *cis*-alcohol **19** provided the isomeric ketone **15**.

Reduction with sodium borohydride provided the alcohols **26** and **27**. The *trans*-iodide **29** was prepared by reaction of **27** with triphenylphosphite diiodide (*15*); however, on reaction with triphenylphosphine, **29** failed to produce the required salt **14**. The saturated iodide **31**, obtained by hydrogenation, and subsequent iodination, of **27**, also failed to produce a Wittig salt on reaction with triphenylphosphine.



30 X = OH
31 X = I

The relative ease of phosphonium salt formation from primary halides (*16*) allowed the modification depicted in Figs. 3 and 4. Here, condensation of the chloride **23** with the anion of diethylmalonate gave the diester **32**, which on saponification provided the diacid **33**. Decarboxylation of **33** gave the acid **34** but in poor yield, apparently due to formation of a cyclic product such as the lactone **35**. Decarboethoxylation of **32** with sodium chloride in moist DMSO (*17*) afforded the ester **36** in good yield. Direct alkylation of the anion of ethyl acetate (*18*) also gave **36**. Lithium aluminum hydride reduction of either **34** or **36** provided the primary alcohol **37**. Iodination and subsequent

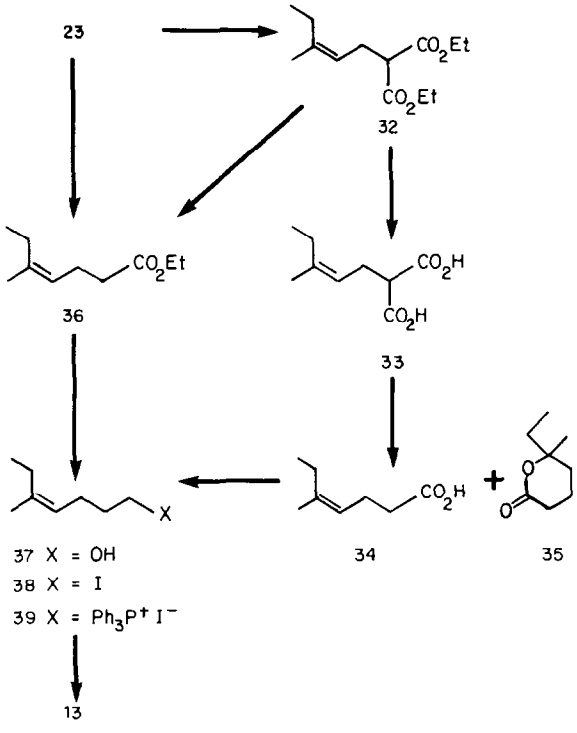


FIGURE 3

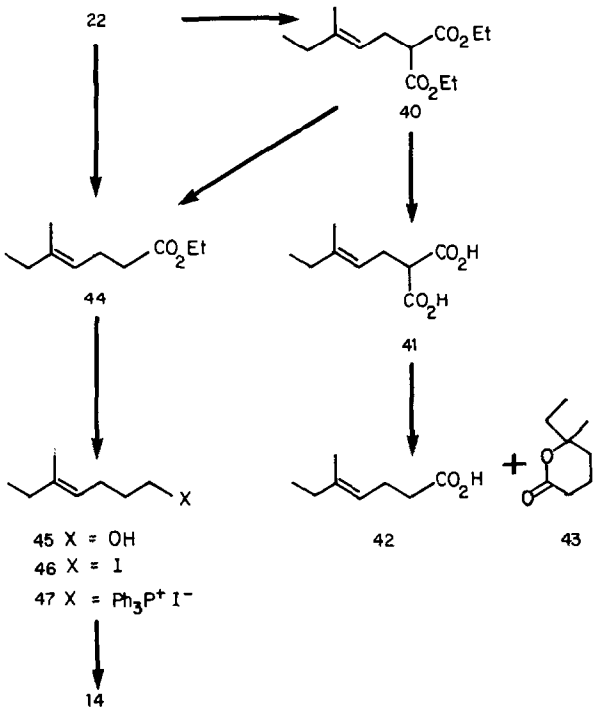


FIGURE 4

reaction with triphenylphosphine gave the primary phosphonium salt **39**. Treatment of **39** with *n*-butyllithium produced the bright orange ylid which, when quenched with ethyl iodide, gave the required Wittig reagent **13** in 90% yield.

A similar series of transformations (Fig. 4) from the *trans*-chloride **22** provided the salt **14**.

TABLE 3

WITTIG REACTIONS WITH THE PHOSPHONIUM SALTS **39** AND **13**

Salt	Substrate	Product	Yield (%)[a]	Method[b]
39	PhCHO	**48**	72	A
39	$PhCOCH_3$	**49**	63	A
39	**4**	**50**	33	A
39	**6**	**51**	70	A
39	**7**	**52**	72	A
39	**10**	—	—	B
13	PhCHO	**53**	80	A
13	$PhCOCH_3$	—	—	A
13	**4**	—	—	A
13	**6**	—	—	A
13	**7**	—	—	A
13	**10**	—	—	B

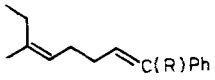
[a] Isolated yields.

[b] Method A: *n*-BuLi, THF, −78 → − 20°C; B: NaH, DMSO.

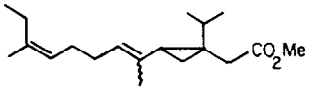
With the required Wittig reagents now in hand, their coupling, first with simple carbonyl systems and then with the thujone-derived ketones, was investigated. The results are summarized in Table 3.

The phosphorane derived from **39** reacted with benzaldehyde and with acetophenone to provide **48** and **49**, respectively, in good yields. Reaction with the esters derived from thujone proceeded in satisfactory yields to give the expected analogs as mixtures of geometrical isomers about the newly formed olefinic linkage. Surprisingly, the reaction with the sodium salt of α-thujaketonic acid **10**, as described in the model series (Table 1), was unsuccessful.

Only the trisubstituted olefin **53** could be prepared from the Wittig agent **13**. Notably, here the substrate does not provide a labile hydrogen, thus the absence of olefination products from the reactions of the ketones **4**, **6**, **7**, and **10** may be due, in part, to the increased basicity of the phosphorane derived from **13**. In addition, the increased steric bulk of this phosphorane presumably retards addition to the carbonyl unsaturation thus favoring acid–base-type reactions leading to enolate formation and halting normal Wittig coupling.



48 R=H
49 R=Me



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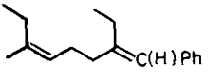

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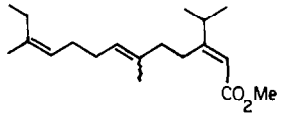

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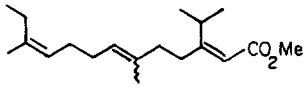

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Thus, *via* the primary phosphonium salt **39**, C_{18}-ester analogs of the natural juvenate **2** were available. Compounds bearing the C_7-vinylic ether group could not be obtained by Wittig coupling with the phosphorane derived from **13**.

In view of these limitations, an alternative approach, which would not only provide the required tetrasubstituted olefins but also allow generation of specific geometry about the 6,7-unsaturation, was considered. The results of this investigation and the biological evaluations of products reported here will be reported later.

EXPERIMENTAL

Uncorrected melting points were determined on a Reichert micro hot stage. Boiling points are uncorrected. Infrared spectra were recorded on either a Perkin–Elmer 710 or

457 spectrophotometer. ^{1}H-nmr spectra were recorded on a Varian T-60, HA-100, or XL-100 or a 270-MHz spectrometer, with Me_4Si as internal standard. Mass spectra were recorded on an Atlas CH-4B or AEI MS-902 instrument. Microanalyses were carried out by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia.

Column chromatography utilized Merck silica gel 60 (70–230 mesh) or Merck aluminum oxide 90 (neutral). Preparative and thin-layer chromatography utilized Merck silica gel GF 254.

As a matter of routine, all reagents and solvents were recrystallized or distilled prior to use.

α-Thujaketonic acid **3**. The acid was prepared by the method of Werner and Bogert (*1*). Thus treatment of cedar leaf oil (ca. 88% thujone) (70 g) with potassium permanganate (100 g) in water (1.2 liters) gave **3** (53.4 g, 67%); mp (hexane/benzene) 71–74°C [lit. (*1*) mp 75–76°C].

α-Thujaketonic acid methyl ester **4**. A solution of sodium hydroxide (9.5 g) in water (28 ml) was added (during 45 min) to the acid **3** (39.6 g) and dimethyl sulfate (29.9 g) in dioxane (400 ml). The mixture was heated to reflux for 30 min, cooled, poured into 5% sodium bicarbonate solution, and extracted with dichloromethane. The extract was dried (Na_2SO_4) and concentrated *in vacuo*. Distillation of the residue gave the ester **4** (26 g, 61%); bp 58°C (0.3 Torr); ir (film) 1738, 1697, and 1172 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 3.57 (3H, s, $-OCH_3$), 2.46 (2H, ABq, J = 16.5 Hz, $-CH_2CO_2CH_3$), 2.26 (3H, s, $-COCH_3$), 1.94 (1H, dd, J = 8, 6 Hz, cyclopropyl-H), 0.91 (3H, d, J = 6 Hz, $-CHCH_3$), 0.89 (3H, d, J = 6 Hz, $-CHCH_3$); *m/e* 198 (M^+), 166, 124 (100%), 109, 96.

cis-β-Thujaketonic acid **5**. A suspension of the acid **3** (5 g) in water (400 ml) was heated at reflux for 48 hr. The mixture was cooled and extracted with ether. The extract was dried (Na_2SO_4) and concentrated *in vacuo* to give **5** (3.3 g, 66%); mp (hexane/benzene) 74–77°C [lit. (*1*) mp 78–79°C].

trans-β-Thujaketonic acid methyl ester **7**. A solution of the ester **4** (1.3 g) in methanol (10 ml) was added to sodium methoxide (from 0.4 g of sodium) in methanol (40 ml). The mixture was stirred at ambient temperature for 20 hr and quenched with glacial acetic acid (2 ml). The solvents were removed *in vacuo*, and the residue was partitioned between water and ether. The ether extract was washed with 5% sodium hydroxide solution and brine, dried (Na_2SO_4), and concentrated. The residue was dissolved in saturated sodium bisulfite solution (3 ml) and stirred vigorously for 2 hr. The solution was washed with ether, and evaporation of the dried (Na_2SO_4) ether extract gave a 3:1 mixture of starting materials **4** and **7** (820 mg). The aqueous phase was diluted with 5 *M* sodium hydroxide solution (15 ml) and extracted with ether. The extract was dried (Na_2SO_4) and concentrated to give **7** (138 mg, 10%) as a colorless liquid; ir (film) 1714, 1640, and 1170 cm^{-1}; uv (EtOH) 217 nm (log ε, 4.09); ^{1}H-nmr ($CDCl_3$) δ 5.37 (1H, s, C_2–H), 4.01 (1H, septet, J = 6.5 Hz, $-CH(CH_3)_2$), 3.56 (3H, s, $-OCH_3$), 2.43 (4H, m, C_4–H_2 and C_5–H_2), 2.07 (3H, s, $-COCH_3$), 1.03 (6H, d, J = 6.5 Hz, $-CH(CH_3)_2$); *m/e* 198 (M^+), 166, 123 (100%), 95. *Anal.* Calcd for $C_{11}H_{18}O_3$: C, 66.67; H, 9.09. Found: C, 66.40; H, 9.08.

The olefin **9**. Methyltriphenylphosphonium bromide (3.8 g) was added to a suspension of sodium hydride (255 mg) in dry 1,2-dimethoxyethane (20 ml) at ambient temperature under a nitrogen atmosphere. The mixture was heated at reflux for 3 hr and

cooled to ca. 25°C. A solution of **4** (2.0 g) in DME (10 ml) was added, and the solution stirred at ambient temperature for 1.5 hr, poured into water (35 ml), and extracted with ether. The extract was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Chromatography on silica gel gave **9** (416 mg, 21%) as a colorless liquid; bp 231°C; ir (film) 1741 and 1645 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 4.78 (1H, bs, vinyl-H), 4.62 (1H, bs, vinyl-H), 3.63 (3H, s, $-OCH_3$), 1.84 (3H, bs, vinyl-CH_3), 0.98 (6H, d, J = 6 Hz, $-CH(CH_3)_2$); *m/e* 196 (M^+), 107, 69 (100%). *Anal.* Calcd for $C_{12}H_{20}O_2$: C, 73.47; H, 10.20. Found: C, 73.28; H, 10.20.

The olefin **11**. A solution of methyltriphenylphosphonium bromide (10.5 g) in DMSO (50 ml) was added to dimsyl sodium (from 0.8 g of sodium hydride) in DMSO (60 ml) at ambient temperature under a nitrogen atmosphere. The mixture was stirred for 15 min, cooled to ca. 10°C, and treated with the salt **10** (5.9 g). The mixture was stirred at ambient temperature for 20 hr, diluted with water (200 ml), and washed with dichloromethane. The aqueous layer was acidified with 3 *M* sulfuric acid and extracted with light petroleum ether. The organic extract was washed with water, dried (Na_2SO_4), and concentrated *in vacuo* to give **11** (4.75 g, 90%); bp 250°C; ir (film) 1736, 1712, and 1613 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 4.81 (1H, bs, vinyl-H), 4.54 (1H, bs, vinyl-H), 1.73 (3H, s, vinyl-CH_3), 0.97 (3H, d, J = 6 Hz, $-CHCH_3$), 0.91 (3H, d, J = 6 Hz, $-CHCH_3$); *m/e* 182 (M^+), 139, 93, 69 (100%). *Anal.* Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.20; H, 9.91.

The olefin **12**. Similar treatment of **10** (1.9 g) with isopropyltriphenylphosphonium iodide gave **12** (1.5 g, 83%) as a pale yellow liquid: ir (film) 1703 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 1.71 (3H, s, $-CH_3$), 1.64 (3H, s, $-CH_3$), 1.57 (3H, s, $-CH_3$), 0.96 (6H, d, J = 7 Hz, $-CH(CH_3)_2$); *m/e* 210 (M^+), 167, 121 (100%), 107. *Anal.* Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.04; H, 10.29.

cis- and trans-Methyl 3-methyl-2-pentenoates **17** *and* **18**. Trimethylphosphonoacetate (109.3 g) was added to a slurry of sodium hydride (29.4 g of 50% oil dispersion) in dry 1,2-dimethoxyethane (1.2 liters) at 0–5°C, and the resultant mixture was stirred at ambient temperature for 1 hr. Butan-2-one (43.6 g) in 1,2-dimethoxyethane (100 ml) was added (ca. 20 min), and the mixture was stirred for 20 hr, diluted with water (300 ml), and extracted with ether. The extract was washed with brine, dried (Na_2SO_4), and concentrated. The crude esters were purified by vacuum distillation (15 Torr) and separated by spinning band distillation at atmospheric pressure to give: the *cis*-ester **17** (11.6 g); bp 148°C; ir (film) 1718 and 1642 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 5.64 (1H, m, C_2–H), 3.67 (3H, s, $-OCH_3$), 2.64 (2H, q, J = 7.5 Hz, C_4–H_2), 1.87 (3H, d, J = 1.4 Hz, C_3–CH_3), 1.07 (3H, t, J = 7.5 Hz, C_5–H_3); *m/e* 128 (M^+), 97, 28. *Anal.* Calcd for $C_7H_{12}O_2$: C, 65.58; H, 9.44. Found: C, 65.38; H, 9.37; and the *trans*-ester **18** (21.0 g); bp 155°C; ir (film) 1719 and 1646 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 5.68 (1H, q, J = 1.3 Hz, C_2–H), 3.68 (3H, s, $-OCH_3$), 2.18 (2H, q, J = 7.5 Hz, C_4–H_2), 2.16 (3H, d, J = 1.3 Hz, C_3–CH_3), 1.07 (3H, t, J = 7.5 Hz, C_5–H_3); *m/e* 128 (M^+), 97, 43. Found: C, 65.61; H, 9.41.

cis-3-Methyl-2-penten-1-ol **19**. A solution of the *cis*-ester **17** (36.0 g) in dry ether (50 ml) was added to a slurry of lithium aluminum hydride (16.7 g) in dry ether (300 ml) at 0–5°C. The mixture was stirred at ambient temperature for 5 hr, diluted with water (15 ml), then with 10% sodium hydroxide solution (20 ml) and a further amount (50 ml) of water. The mixture was filtered, and the filtrate was dried (Na_2SO_4) and concentrated.

The residue was distilled under vacuum (ca. 15 Torr) to give the alcohol **19** (24.3 g, 89%); bp 153°C; ir (film) 3370 and 1667 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 5.31 (1H, t, $J = 7$ Hz, C_2–H), 4.01 (2H, d, $J = 7$ Hz, C_1–H_2), 2.05 (2H, q, $J = 7.5$ Hz, C_4–H_2), 1.70 (3H, bs, C_3–CH_3), 1.02 (3H, t, $J = 7.5$ Hz, C_5–H_3); *m/e* 100 (M^+), 71, 31. *Anal.* Calcd for $C_6H_{12}O$: C, 71.95; H, 12.08. Found: C, 72.15; H, 11.94.

trans-3-Methyl-2-penten-1-ol **20**. Similarly, treatment of the ester **18** with lithium aluminum hydride gave the alcohol **20** (90%); bp 160°C; ir (film) 3356 and 1666 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 5.37 (1H, tq, $J = 7$, 1.4 Hz, C_2–H), 4.16 (2H, d, $J = 7$ Hz, C_1–H_2), 2.04 (2H, q, $J = 7.5$ Hz, C_4–H_2), 1.68 (3H, bs, C_3–CH_3), 1.02 (3H, t, $J = 7.5$ Hz, C_5–H_3); *m/e* 100 (M^+), 71. *Anal.* Calcd for $C_6H_{12}O$: C, 71.95; H, 12.08. Found: C, 72.20; H, 12.20.

The chloride **22**. Dimethyl sulfide (0.15 ml) in dry dichloromethane (0.25 ml) was added to *N*-chlorosuccinimide (0.22 g) in dichloromethane (1.25 ml) at 0°C under an atmosphere of dry nitrogen. The solution was stirred at 0°C for 1 hr, cooled to −25°C, and treated with a solution of the alcohol **20** (0.15 g) in dichloromethane (0.25 ml). The mixture was stirred at 0°C for 30 min then at ambient temperature for 1.5 hr. Saturated sodium bicarbonate solution was added, and the mixture was extracted with dichloromethane. The extract was washed with brine and dried ($MgSO_4$). The solvents were distilled off, and the residue was fractionated at 76 Torr to give **22** (0.15 g, 85%); bp_{76} 87°C; ir (film) 1665 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 5.47 (1H, bt, $J = 8.6$ Hz, vinyl-H), 4.14 (2H, d, $J = 8.6$ Hz, $-CH_2Cl$), 2.08 (2H, 1, $J = 7$ Hz, $-CH_2CH_3$), 1.74 (3H, s, vinyl-CH_3), 1.02 (3H, dt, $J = 7$, 0.8 Hz, $-CH_2CH_3$); *m/e* 118 and 120 (M^+).

The β-ketoester **24**. Ethyl-*β*-oxovalerate (0.61 g) was added to a stirred suspension of potassium hydride (0.186 g) in 1,2-dimethoxyethane (4 ml) at 0°C under a nitrogen atmosphere. After 15 min at 0°C, the chloride **22** (0.47 g) in 1,2-dimethoxyethane (4 ml) was added at 0°C. The mixture was stirred 15 min at 0°C and then 15 hr at ambient temperature. Water and cold 1 *N* hydrochloric acid were added, and the mixture was extracted with petroleum ether (30–60). The extract was dried ($MgSO_4$) and passed through a short column of silica gel. Elution with ether gave **24** (0.8 g, 89%); $bp_{0.4}$ 90°C; ir (film) 1736, 1716, and 1666 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 5.01 (1H, dt, $J = 7.5$, 1 Hz, vinyl-H), 4.20 (2H, q, $J = 7.2$ Hz, $-CO_2CH_2CH_3$), 3.49 (1H, t, $J = 7.7$ Hz, $-COCHCO_2Et$), 2.56 (4H, m, $-CH_2CHCO_2Et + -COCH_2CH_3$), 1.98 (2H, q, $J = 7.5$ Hz, vinyl-CH_2CH_3), 1.63 (3H, s, vinyl-CH_3), 1.25 (3H, t, $J = 7.2$ Hz, $-CO_2CH_2CH_3$), 1.06 (3H, t, $J = 7.3$ Hz, $-COCH_2CH_3$), 0.96 (3H, t, $J = 7.5$ Hz, vinyl $-CH_2CH_3$); *m/e* 226, 169, 123. *Anal.* Calcd for $C_{13}H_{22}O_3$; C, 68.99; H, 9.80. Found: C, 68.92; H, 9.82.

The ketone **16**. Barium hydroxide (0.16 g) was added to a solution of the keto-ester **24** (0.079 g) in ethanol (0.27 ml) and water (1.13 ml), and the mixture was heated under reflux in an atmosphere of nitrogen for 19 hr. The cooled mixture was diluted with water and extracted with petroleum ether (30–60). The extract was washed with brine, dried ($MgSO_4$), and concentrated to give **16** (0.041 g, 76%); $bp_{0.3}$ 30–45°C; bp 206°C; ir (film) 1712 and 1668 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 5.07 (1H, t, $J = 7.5$ Hz, vinyl-H), 2.42 (4H, m, $-CH_2CH_2$–COEt), 2.26 (2H, q, $J = 7.6$ Hz, $-COCH_2CH_3$), 1.98 (2H, q, $J = 7.5$ Hz, vinyl-CH_2CH_3), 1.60 (3H, s, vinyl-CH_3), 1.04 (3H, t, $J = 7.6$ Hz, $-COCH_2CH_3$), 0.96 (3H, t, $J = 7.5$ Hz, vinyl-CH_2CH_3); *m/e* 154 (M^+), 82, 55. *Anal.* Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.97. Found: C, 77.77; H, 11.60.

The β-ketoester **25**. The chloride **23** provided the β ketoester **25**; bp 258°C; ir (film) 1740 and 1708 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 4.89 (1H, t, $J = 7.1$ Hz, vinyl-H), 3.23 (1H, t, $J = 7.1$ Hz, $-CHCO_2Et$), 2.02 (2H, q, $J = 7.5$ Hz, $-CH_2CH_3$), 1.62 (3H, bs, vinyl-CH_3), 0.94 (3H, t, $J = 7.5$ Hz, $-CH_2CH_3$); *m/e* 226 (M^+), 169, 123. *Anal.* Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69,09; H, 9.80.

The ketone **15**. As described for the preparation of **16**, the ketoester **25** gave **15** (87%); bp 202°C; ir (film) 1709 and 1670 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 5.00 (1H, m, vinyl-H), 2.03 (2H, q, $J = 7.5$ Hz, $-CH_2CH_3$), 1.63 (3H, bs, vinyl-CH_3), 0.96 (3H, t, $J = 7.5$ Hz, $-CH_2CH_3$); *m/e* 154 (M^+), 82, 57. *Anal.* Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 78.12; H, 11.52.

The alcohol **26**. The *cis*-ketone **15** (4 g) in 95% ethanol (7 ml) was treated with a slurry of sodium borohydride (1 g) in 95% ethanol (90 ml), and the mixture was stirred at ambient temperature for 3 hr. The solvent was removed *in vacuo*, and the residue was partitioned between water and ether. The organic phase was washed with brine, dried over potassium hydroxide, and concentrated. The crude product was distilled *in vacuo* (ca. 20 Torr) to give the alcohol **26** (3.7 g, 92%); bp 210°C; ir (film) 3400 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 5.01 (1H, t, $J = 7$ Hz, vinyl-H), 3.44 (1H, m, $-CHOH$), 2.01 (2H, q, $J = 7.2$ Hz, $-CH_2CH_3$), 1.62 (3H, bs, vinyl-CH_3), 0.94 (3H, t, $J = 7.2$ Hz, $-CH_2CH_3$); *m/e* 156 (M^+), 138, 109. *Anal.* Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.56; H, 12.85.

The alcohol **27**. Similarly, the ketone **16** gave **27** (95%); bp_{23} 114°C; ir (film) 3360 and 1666 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 5.09 (1H, tq, $J = 7$, 1.3 Hz, vinyl-H), 3.43 (1H, m, $-CHOH$), 1.98 (2H, 1, $J = 7$ Hz, $-CH_2CH_3$), 1.60 (3H, bs, vinyl-CH_3), 0.97 (3H, t, $J =$ 7 Hz, $-CH_2CH_3$); *m/e* 156 (M^+), 138, 109. *Anal.* Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.60; H, 12.98.

The iodide **29**. Triphenylphosphite (15.5 g) in dry ether (50 ml) was added (ca. 30 min) to a solution of iodine (12.7 g) in dry ether (250 ml) at 0–5°C. The mixture was stirred at ambient temperature for 17 hr and treated with a solution of the alcohol **27** (7.5 g) in ether (25 ml). Stirring was continued for a further 1 hr, and the mixture was concentrated, *in vacuo*, to a volume of ca. 70 ml, passed through a short plug of neutral alumina, and eluted with petroleum ether (65–110). The eluate was concentrated *in vacuo* to give **29** (10.2 g, 79%); bp 230°C (d); ir (film) 1668 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 5.02 (1H, m, vinyl-H), 3.96 (1H, m, $-CHI$), 1.60 (3H, bs, vinyl-CH_3), 0.95 (3H, t, $J =$ 7 Hz, $-CH_2CH_3$); *m/e* 266 (M^+), 138, 55. *Anal.* Calcd for $C_{10}H_{19}I$: C, 45.13; H, 7.20. Found: C, 45.50; H, 7.20.

The iodide **28**. Similarly, the alcohol **26** gave (60%) the crude iodide **28**, which due to its instability was used directly without purification.

The alcohol **30**. A solution of the alcohol **27** (1.56 g) in absolute ethanol (130 ml) was hydrogenated under 1 atm of hydrogen in the presence of 10% palladium on carbon catalyst. The mixture was filtered through celite, and the filtrate was concentrated *in vacuo*. The residue was passed through neutral alumina with petroleum ether (65–110), and the eluate was concentrated to give the alcohol **30** (1.0 g, 64%); bp 206°C; ir (film) 3400 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 3.38 (1 H, m, $-CHOH$); *m/e* 158, 140, 129, 59. Calcd for $C_{10}H_{22}O$: C, 75.88; H, 14.01. Found: C, 75.60; H, 13.85.

The iodide **31**. Iodination of **30**, as described for the preparation of **29**, gave (79%) **31**; bp 224°C (d); ^{1}H-nmr ($CDCl_3$) δ 3.97 (1H, m, $-CHI$), 1.01 (3H, t, $J = 7$ Hz,

$-CH_2CH_3$); *m/e* 268 (M^+), 141. *Anal.* Calcd for $C_{10}H_{21}I$: C, 44.79; H, 7.89. Found: C, 44.88; H, 8.25.

The ester **36**. *n*-Butyllithium (6.1 ml of a 1M solution in hexane) was added to cyclohexyl isopropylamine (1.04 ml) in dry tetrahydrofuran (20 ml) at 0°C under a nitrogen atmosphere, and the solution was stirred 15 min at 0°C. The solution was then chilled to −78°C and ethyl acetate (530 mg) and HMPA (1 ml) were added. After 10 min, the chloride **23** (0.737 g) in dry tetrahydrofuran (2 ml) was added. Stirring was continued at −78°C for 10 min, and the mixture was warmed to 0°C over ca. 30 min. The mixture was diluted with 10% hydrochloric acid (25 ml) and dichloromethane (50 ml). The organic layer was concentrated, and the residue was dissolved in hexane. This solution was washed with water and brine, dried ($MgSO_4$), and concentrated to give **36** (0.83 g, 79%); bp_5 75–85°C; ir (film) 1735 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 5.1 (1H, m, vinyl-H), 4.15 (2H, q, $J = 7$ Hz), 2.2–2.8 (4H, m), 2.2 (2H, q, $J = 8$ Hz), 1.65 (3H, bs, vinyl-CH_3), 1.21 (3H, t $J = 7$ Hz, $-CH_2CH_3$), 0.98 (3H, t, $J = 8$ Hz, $-CH_2CH_3$).

The ester **44**. In a similar manner, **22** gave the ester **44** (76%); bp_{12} 83–85°C; ir (film) 1715 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 5.07 (1H, m, vinyl-H), 4.06 (2H, q, $J = 7.5$ Hz, $-OCH_2CH_3$), 2.27 and 2.05 (2H, q), 1.95 (2H, q, $J = 7$ Hz, vinyl-CH_2CH_3), 1.63 (3H, s, vinyl-CH_3), 1.23 (3H, t, $J = 7$ Hz, $-OCH_2CH_3$), 1.00 (3H, t, $J = 7$ Hz, vinyl-CH_2CH_3); *m/e* 170 (M^+), 125, 124, 96, 95, 88, 82. *Anal.* Calcd for $C_{10}H_{18}O_2$: C, 70.59; H, 10.59. Found: C, 70.83; H, 10.49.

The alcohol **37**. A solution of the ester **36** (0.4 g) in dry ether (5 ml) was added to a stirred suspension of lithium aluminum hydride (0.095 g) in ether (10 ml), and the mixture stirred at ambient temperature for 2 hr. Water was added, and the mixture was extracted with dichloromethane. The extract was washed with brine, dried ($MgSO_4$), and concentrated. Vacuum distillation of the residue gave **37** (0.23 g, 76%); bp_{12} 100°C; ir (film) 3400 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 5.03 (1H, m, vinyl-H), 3.51 (2H, t, $J =$ 7 Hz, $-CH_2OH$), 1.66 (3H, bs, vinyl-CH_3), 0.96 (3H, t, $J = 7.5$ Hz, vinyl-CH_2CH_3); *m/e* 128 (M^+), 81, 55. *Anal.* Calcd for $C_8H_{16}O$: C, 74.94; H, 12.58. Found: C, 74.93; H, 12.75.

The alcohol **45**. Similarly, **44** gave the alcohol **45**; bp_{12} 110–115°C; ir (film) 3226 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 5.08 (1H, t, $J = 7$ Hz, vinyl-H), 3.50 (2H, t, $J = 7$ Hz, $-CH_2OH$), 2.85 (1H, s, –OH), 1.61 (3H, bs, vinyl-CH_3), 0.97 (3H, t, $J = 7$ Hz, vinyl-CH_2CH_3); *m/e* 128 (M^+).

The iodide **38**. Treatment of the alcohol **37** with triphenylphosphite diiodide, as described for the preparation of **28**, gave **38** (61%); ^{1}H-nmr ($CDCl_3$) δ 5.00 (1H, m, vinyl-H), 3.16 (2H, t, $J = 6.5$ Hz, $-CH_2I$), 2.64 (3H, bs, vinyl-CH_3), 0.98 (3H, t, $J =$ 7.5 Hz, $-CH_2CH_3$).

The salt **39**. A solution of the crude iodide **38** (0.75 g) and triphenylphosphine (0.865 g) in ethyl acetate (5 ml) was heated at reflux for 17 hr. The mixture was cooled and diluted with ether (10 ml). The crystalline deposit was recrystallised from ethyl acetate to give **39** (0.94 g, 60%); mp 148–155°C; ^{1}H-nmr δ 7.85 (15H, m, $-P(C_6H_5)_3$), 5.09 (1H, m, vinyl-H), 3.62 (2H, m, $-CH_2P-$), 1.60 (3H, bs, vinyl-CH_3); *m/e* 373, 372, 262. *Anal.* Calcd for $C_{26}H_{30}PI$: C, 62.41; H, 6.04; I, 25.36. Found: C, 62.65; H, 6.12; I, 25.20.

The salt **13**. A solution of *n*-butyllithium (2 ml of a 1 *M* solution) was added to a solution of the salt **39** (1 g) in dry tetrahydrofuran (25 ml) at ambient temperature

under an atmosphere of dry nitrogen. The resultant orange solution was stirred at ambient temperature for 10 min, then treated with ethyl iodide (0.5 ml). The mixture was stirred for 18 hr and concentrated *in vacuo*, and the residue was chromatographed on alumina (I). Elution with dichloromethane gave the salt **13** (0.98 g, 93%); mp 108–112°C; ^{1}H-nmr δ 5.00 (1H, m, vinyl-H), 4.58 (1H, m, –C*H*P–), 1.53 (3H, bs, vinyl-CH_3), 1.22 (3H, t, $J = 7$ Hz, $-CH_2CH_3$), 0.94 (3H, *t*, $J = 7.5$ Hz, $-CH_2CH_3$); *m/e* 401, 400, 262.

The olefin **48**. A solution of *n*-butyllithium (0.12 ml of a 1.3 *M* solution in hexane) was added to the salt **39** (80 mg) in dry tetrahydrofuran (3 ml) at 0°C under a nitrogen atmosphere. The mixture was stirred at 0°C for 15 min, treated with benzaldehyde (30 μl), and stirred at ambient temperature for 17 hr. The mixture was poured into water (10 ml) and extracted with dichloromethane. The extract was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Chromatography on silica gel gave **48** (23 mg, 72%) as a colorless oil; ir (film) 1600, 760, and 690 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 7.35 (5H, s, aromatic -H), 6.50 (1H, d, $J = 11$ Hz, Ph C*H* =), 5.70 (1H, dt, $J = 11$, 7 Hz, $-CH_2CH = CHPh$), 5.20 (1H, m, vinyl-H), 1.60 (3H, bs, vinyl-CH_3), 0.99 (3H, t, $J = 7$ Hz, $-CH_2CH_3$); *m/e* 200 (M^+), 130 (100%), 117, 55. High resolution molecular weight determination. *Anal.* Calcd for $C_{15}H_{20}$: 200.157. Found: 200.158.

The olefin **49**. As described for the preparation of **48**, the salt **39** (100 mg) reacted with *n*-butyllithium at 0°C and then with acepophenone at −78 to 60°C for 2 hr. The usual work-up provided the olefin **49** (25 mg, 63%) as a colorless oil; ir (film) 1595, 760, and 695 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 7.30 (5H, m, aromatic-H), 5.48 (1H, t, $J = 7$ Hz, vinyl-H), 5.08 (1H, m, vinyl-H), 0.95 (3H, t, $J = 7$ Hz, $-CH_2CH_3$); *m/e* 214 (M^+), 144, 131 (100%), 129. High resolution molecular weight determination. *Anal.* Calcd for $C_{16}H_{22}$: 214.172. Found: 214.171.

The ester **50**. As described for the preparation of **49**, the salt **39** reacted with **4** to give **50**, in 33% yield; ir (film) 1740, 1690, and 1170 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 5.15 (2H, m, vinyl-H), 3.65 (3H, s, $-OCH_3$), 1.65 (6H, bs, 2 × vinyl-CH_3), 0.95 (6H, d, $J = 6$ Hz, $-CH(CH_3)_2$; *m/e* 292 (M^+), 277, 249, 209, 135 (100%). High resolution molecular weight determination. *Anal.* Calcd for $C_{19}H_{32}O_2$: 292.240. Found: 292.242.

The ester **51**. As described for the preparation of **49**, the salt **39** and the ester **6** gave **51**, in 70% yield, as a colorless oil; ir (film) 1720, 1640, and 1170 cm^{-1}; $^{-}$H-nmr ($CDCl_3$) δ 5.58 (1H, s, C = $CHCO_2CH_3$), 5.10 (2H, m, 2 × vinyl-H), 3.65 (3H, s, $-OCH_3$), 1.86 (3H, bs, –vinyl-CH_3), 1.80 (3H, bs, vinyl-CH_3), 1.13 (6H, d, $J = 6$ Hz, $-CH(CH_3)_2$), 0.99 (3H, t, $J = 7$ Hz, $-CH_2CH_3$); *m/e* (M^+), 277, 261, 249, 222, 149 (100%). High resolution molecular weight determination. *Anal.* Calcd for $C_{19}H_{32}O$: 292.240. Found: 292.240.

The ester **52**. Similarly, the salt **39** and the ester **7** gave a 72% yield of **52** as a colorless oil; ir (film) 1720, 1640, 1168 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 5.50 (1H, bs, C = $CHCO_2CH_3$), 5.09 (2H, m, 2 × vinyl-H), 4.02 (1H, septet, $J = 6$ Hz, $-CH(CH_3)_2$), 3.56 (3H, s, $-OCH_3$), 2.10 (3H, s, vinyl-CH_3), 1.55 (3H, s, vinyl-CH_3), 1.02 (6H, d, $J = 6$ Hz, $-CH(CH_3)_2$); *m/e* 292 (M^+), 261, 235, 222, 149 (100%), 142. High resolution molecular weight determination. *Anal.* Calcd for $C_{19}H_{32}O$: 292.240. Found: 292.239.

The olefin **53**. As described above for the preparation of **48**, the salt **13** (100 mg) reacted with *n*-butyllithium and benzaldehyde (30 μl) to give **53** (35 mg, 80%) as a colorless oil; ir (film) 1640, 1600, 740, and 690 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 7.25 (5H, bs,

aromatic-H), 6.25 (1H, bs, C = C*H*Ph), 5.15 (1H, m, vinyl-H), 1.10 (3H, t, $J = 7.5$ Hz, $-CH_2CH_3$), 1.02 (3H, t, $J = 7$ Hz, $-CH_2CH_3$); *m/e* 228 (M^+), 158, 145, 129 (100%). High resolution molecular weight determination. *Anal.* Calcd for $C_{17}H_{24}$: 228.188. Found: 228.188.

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