Efficient Synthesis of the *Aonidiella aurantii* (Mask.) Sex Pheromone Component: (3*S*,6*RS*)-3-Methyl-6-(1-Methylethenyl)-9-decenyl Acetate

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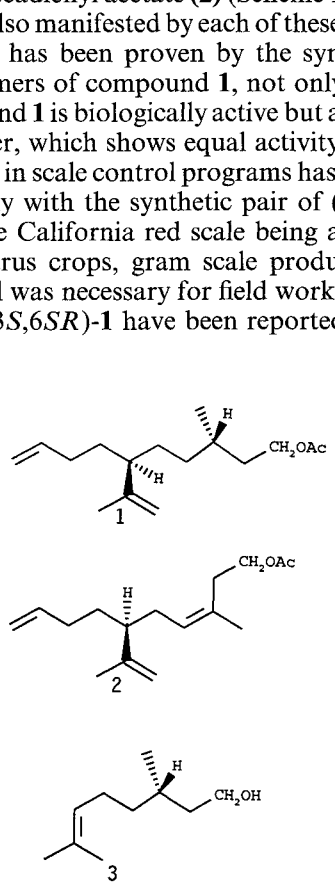
The title compound, active component of the sex pheromone of *Aonidiella aurantii* (California Red Scale), was synthesized in three steps starting from *S*-citronellyl acetate with a 30% overall yield. The key feature of the synthesis is a copper salt assisted, highly regioselective attack of the 4-butenyl bromide Grignard reagent on the γ-site of the chloroallylic system of (*S*)-8-chloro-3,7-dimethyl-6-octenyl acetate **(8a)**.

California red scale, *Aonidiella aurantii* (Mask.), is a significant citrus pest in California, Australia and the Mediterranean region. The sex pheromone of the insect, isolated in 1980 by Roelofs,[1] was found to be a mixture of two components, (*S*,*S*)-3-methyl-6-(1-methylethenyl)-9-decenyl acetate **(1)** and (*Z*,*S*)-3-methyl-6-(1-methylethenyl)-3,9-decadienyl acetate **(2)** (Scheme 1). Pheromonal activity is also manifested by each of these compounds separately. As has been proven by the synthesis of all four stereoisomers of compound **1**, not only the natural 3*S*,6*S* compound **1** is biologically active but also its 3*S*,6*R* diastereoisomer, which shows equal activity.[2] Considerable field work in scale control programs has been carried out successfully with the synthetic pair of (3*S*,6*S*)- and (3*S*,6*R*)-**1**. The California red scale being an important parasite of citrus crops, gram scale production of the active material was necessary for field works and several syntheses of (3*S*,6*SR*)-**1** have been reported.[2-4]



Scheme 1

Some of the cited syntheses use as starting material (*S*)-citronellol **(3)** which provides the appropriate stereochemistry at C-3 of **1**. The most attractive approach to the synthesis of compound **1** is the preparation of an ω-functionalized derivative of citronellol and the subsequent S_N2' carbon alkylation by suitable organocopper reagent. This approach has already been explored, but the reported synthesis[4] of the ω-functionalized citronellol with an allylthiobenzothiazole moiety is complicated, and the final product requires laborious purification in order to eliminate the sulfur-containing byproducts and to display its biological activity.

As part of our continuing interest in the development of simple and efficient syntheses of active pheromone substances, we prepared the 3*S*, 6*SR* pair of **1** on a multigram scale for the needs of an extended scale control program in Greece. We report herein a direct ω-functionalization of (*S*)-citronellol **(3)** and the preparation of easily accessible derivatives suitable for a *C*-alkylation γ to the functionalized end by organocopper reagents.

(*S*)-Citronellol is commercially available in high optical purity. In the present work, the citronellol used had an optical purity (ee) > 95% {$[\alpha]_D^{20} = -3.4$ (neat)}. Allylic hydroxylation of the cintronellol esters **4** by *tert*-butyl hydroperoxide, catalyzed by selenium dioxide, according to a well established procedure[5] gave the terminal hydroxycitronellols **5** in 51.5% yield (Scheme 2).

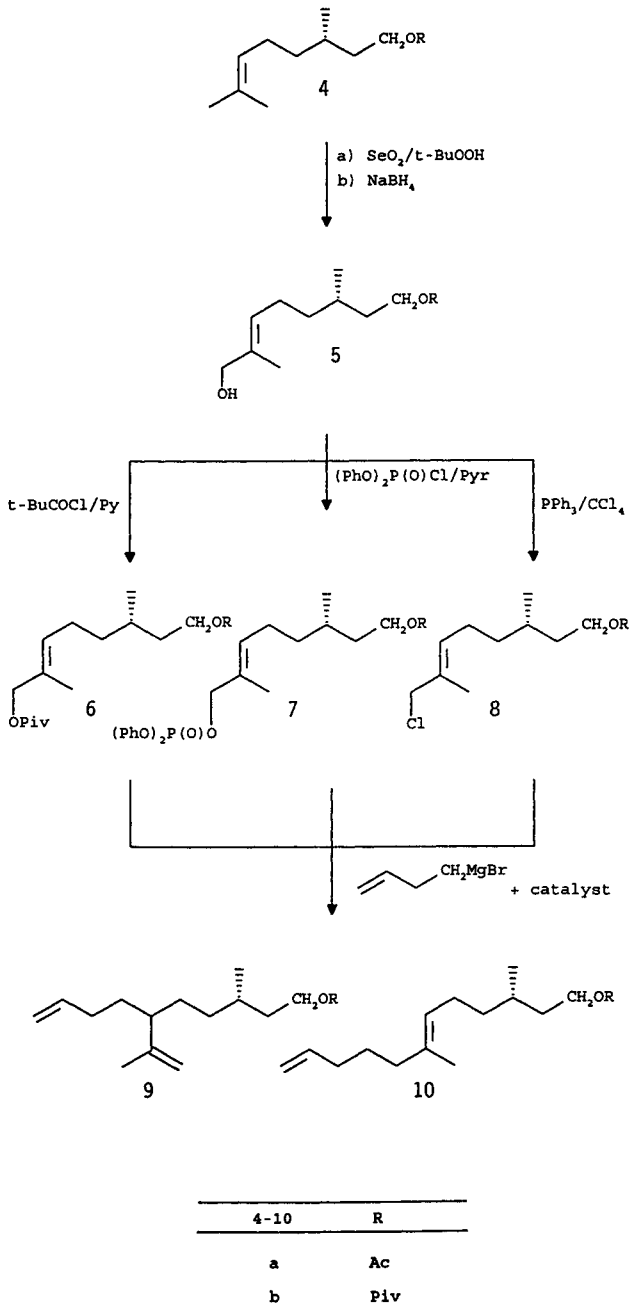
Among the various allylic derivatives that have been reported to give *C*-alkylation γ to the functional end by copper salt assisted Grignard reagents, we selected those which can be prepared easily by simple and common reagents, e.g. pivalic acid esters,[6] phosphate esters[7] and allylic chlorides[8] (Scheme 2).

The pivalic acid esters **6** and the phosphate esters **7** are prepared in excellent yield by the addition of pivaloyl chloride and diphenylphosphorochloride, respectively, to a pyridine solution of the hydroxycitronellols **5**. The allylic chloride **8** is prepared, also in excellent yield, by the

Table 1.

Compound[a]	bp (°C/mmHg)	IR ν (cm^{-1})	MS *m/z* (%)
5a	135–140/0.5	3620, 3440, 1742	214 (M^+, 1), 172 (2), 121 (32), 93 (14), 81 (15), 43 (100)
5b	140–145/0.5	3620, 3440, 1728	172 (1), 153 (1), 136 (8), 121 (47), 107 (10), 93 (20), 69 (15), 57 (100)
6b	130–135/0.2	1728	256 (2), 169 (1), 136 (6), 121 (31), 81 (12), 57 (100)
7b		1728, 1160	239 (1), 153 (2), 136 (16), 121 (92), 81 (37), 57 (100)
8a	90–95/0.5	1742, 682	198 (1), 196 (3), 153 (3), 136 (11), 121 (58), 93 (18), 81 (42), 67 (42), 43 (100)
8b	95–100/0.3	1728, 682	174 (1), 172 (3), 136 (6), 121 (66), 107 (13), 93 (24), 81 (37), 57 (100)

[a] All compounds gave satisfactory analytical data, C, H, ± 0.20%.



4-10	R
a	Ac
b	Piv

Scheme 2

reaction of hydroxycitronellols **5** with a solution of triphenylphosphine in carbon tetrachloride.[9] Properties of all the derivatives are given in Table 1.

C-Alkylation at the γ-position to the functional end of citronellol was realized by reaction of 4-butenylmagnesium bromide with the appropriate derivative in the presence of copper salts. The results are summarized in Table 2. With the exception of entry 3, all experiments were performed by addition of the derivative to the Grignard solution containing the copper complex.

As shown, the best selectivity was obtained with the chloro derivatives **8a** and **8b**, using stoichiometric quantities of the Grignard reagent and copper salt (Scheme 2). No nucleophilic attack was observed on the acetate group of **8a**, although three equivalents of organometallic reagent were used. Thus the laborious and inefficient sequence of protections (as the pivalate) and deprotections of the hydroxy group at C-1 of citronellol is avoided, and the synthesis of the target molecule is reduced to three steps starting from (*S*)-citronellyl acetate.

In conclusion, we propose a simple and efficient synthesis of one of the components of the California red scale sex pheromone, as a 1:1 mixture of (*S*,*S*)-3-methyl-6-(1-methylethenyl)-9-decenyl acetate and (3*S*,6*R*)-3-methyl-6-(1-methylethenyl)-9-decenyl acetate **(9a)** starting from (*S*)-citronellol with an overall yield of 30%. The synthetic compound gave satisfactory field tests for biological activity.

All reagents and solvents are commercially available and used as received. IR spectra were run on a Perkin-Elmer 7200 FT-IR spectrophotometer in 5% CCl_4 solutions. ^1H NMR spectra were recorded on a Bruker AC-300 (300 MHz). MS were measured on a GC-MS Hewlett-Packard 5890–5970 system with MS Chem station. Optical rotations were measured on a Perkin-Elmer 141 polarimeter.

(*S*)-3,7-Dimethyl-8-chloro-6-octenyl Acetate (8a):
A solution of **5a** (6.0 g, 0.028 mol) and triphenylphosphine (9.7 g, 0.037 mol) in CCl_4 (35.0 mL) was refluxed for 2 h. The reaction mixture was then cooled to r.t. and hexane (100 mL) was added. The precipitated phosphine oxide was filtered off, the solvent was evaporated under water-pump vacuum and the crude product was purified by distillation to afford pure **8a**: 4.9 g (75% yield). Bp 124–126°C/3.5 Torr; $[\alpha]_D^{20} = -4.1$ ($c = 1.12$, EtOH).

^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.89$ (3H, d, $J = 6.3$ Hz), 1.14–1.76 (6H, m), 1.63 (3H, s), 1.97–2.13 (1H, m), 2.01 (3H, s), 3.96 (2H, s), 4.06 (2H, t, $J = 6.9$ Hz), 5.36 (1H, t, $J = 7.2$ Hz).

Table 2.

Entry	Compound	Solvent	Copper salt	RMgX (equiv)	Catalyst (equiv)	Temp. (°C)	Yield (%)	Ratio **9/10**
1	**6b**	THF	CuCN·LiCl	2	0.03	−10	93	1.0:23
2	**6b**	Et_2O	CuCN·LiCl	2	0.10	−20	82	3.2:1
3	**6b**	THF	CuCN·LiCl	2	0.10	−40	92	1.0:25
4	**6b**	Et_2O	CuCN	2	0.10	−40	82	4.4:1
5	**7b**	Et_2O	CuCN	2	0.40	−78	83	7.3:1
6	**8a**	THF	CuCN·2LiCl	3	3.00	−78	78	21.0:1
7	**8b**	THF	CuCN·2LiCl	3	3.00	−78	87	13.0:1

(3*S*,6*RS*)-3-Methyl-6-(1-methylethenyl)-9-decenyl Acetate (9a):
To a Grignard solution prepared from 4-butenyl bromide (7.0 g, 0.052 mol) and magnesium turnings (1.4 g, 0.057 mol) in THF (30 mL) was added dropwise at 0 °C a solution of CuCN (4.8 g, 0.052 mol) and LiCl (4.6 g, 0.104 mol) in THF (60 mL) under nitrogen, and the resulting dark solution was stirred for 30 min at this temperature. The reaction mixture was then cooled to −78 °C and **8a** (4.0 g, 0.017 mol) was added dropwise over 1 h. The mixture was stirred at this temperature for a further 2 h and then poured into ice-cold aq NH_4Cl (10%; 50 mL) and extracted with petroleum ether (3 × 50 mL). The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated under vacuum. The resulting crude product was purified by distillation to afford pure **9a**: 3.3 g (78% yield). Bp 99–101 °C/0.4 Torr; $[\alpha]_D^{20} = -5.9$ ($c = 1.13$, EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.86$ (3 H, d, $J = 6.3$ Hz) and 0.87 (3 H, d, $J = 6.3$ Hz) (2 isomers), 1.09–1.48 (9 H, m), 1.56 (3 H, s), 1.87–1.97 (3 H, m). 2.01 (3 H, s), 4.05 (2 H, t, $J = 6.9$ Hz), 4.64 (1 H, d, $J = 2$ Hz), 4.73 (1 H, d, $J = 2$ Hz), 4.91 (1 H, dd, $J = 10.3$, 1.6 Hz), 4.96 (1 H, dd, $J = 17.0$, 1.6 Hz), 5.77 (1 H, ddt, $J = 17.0$, 10.3, 6.5 Hz).

MS: m/z (%) = 209 ($M^+ - 43$, 1), 192 (2), 177 (2), 163 (3), 149 (10), 135 (8), 123 (10), 109 (19), 95 (23), 81 (52), 69 (37), 67 (42), 55 (40), 43 (100).

IR (CCl_4): $\nu = 3075$, 1741, 1642, 912, 893 cm^{-1}.

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