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A Practical Enantioselective Synthesis of the Cigarette Beetle Sex Pheromone Serricornin

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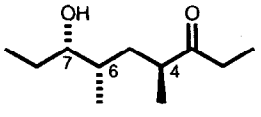
Abstract: (4*RS*,6*S*,7*S*)-7-hydroxy-4,6-dimethyl-3-nonanone (serricornin and its C4-epimer) may be prepared from oxazolidinone **5** in 8 steps with an overall yield of 33%.

INTRODUCTION

The sex attractant secreted by the female cigarette beetle (*Lasioderma serricorne* F), a commercially important pest, was identified as serricornin (**1**, 7-hydroxy-4,6-dimethyl-3-nonanone) by Chuman in 1979.[1] It was later shown by Mori and Chuman that the absolute configuration of the natural pheromone is (4*S*,6*S*,7*S*).[2] There is considerable interest in the development of a viable commercial synthesis of serricornin. Stereochemistry seems to play an important role in the attractiveness of synthetic material to male cigarette beetles.[3] Of particular importance is the finding that the (4*S*,6*S*,7*R*) isomer has inhibitory properties.[3b,4] Furthermore, it has been shown that there is rapid epimerization at C4 under even slightly acidic conditions (*e.g.* in $CDCl_3$) and that the (4*R*,6*S*,7*S*) and (4*S*,6*S*,7*S*) isomers are readily separable by chromatography.[5] Thus it seems clear that a synthesis of serricornin intended for use in commercial insect lures should be designed to provided material of (4*RS*, 6*S*, 7*S*) stereochemistry. In other words, only the stereocenters at C6 and C7 need to be considered in the synthetic design.



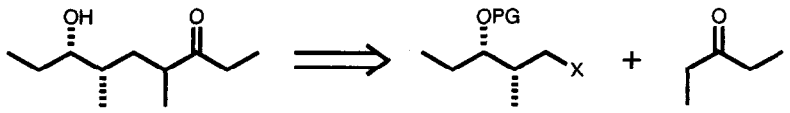
(4*S*,6*S*,7*S*)-**1**

There have been numerous stereoselective syntheses of serricornin reported.[2, 5-13] The only route shorter than ten steps from readily available starting materials was reported by Shimizu;[11] the key step involved

the palladium-catalyzed hydrogenolysis of an alkenyloxirane and provides serricornin in five steps from (*E*)-2-methyl-2-pentenol. However, the material produced is of only 88-96% ee (at C6 and C7) and thus may not be as attractive in pheromone-based lures as a preparation of higher stereochemical purity. Other more lengthy syntheses of serricornin did not appear to be suitable for the preparation of gram-quantities of material.

We decided that a viable synthesis of serricornin could be based on a synthesis of an enantiomerically pure alkylating agent **2** (Scheme 1). A TBS-protected iodide (**2**: PG = TBS, X = I) was previously employed by Mori; this compound was prepared from methyl (*R*)-3-hydroxypentanoate in 11 steps and 22% overall yield.[5] For possible multi-gram applications, a shorter route was desired. In addition, we wanted an early crystalline intermediate to facilitate the purification of relatively large quantities of material and to allow improvement of stereopurity by recrystallization (if required).

Scheme 1



1 **2** **3**

The coupling of the subunits **2** and **3** has been reported to take place smoothly (80% yield) using LDA in THF/HMPA.[5] However, others have had difficulty in reproducing this result, and have noted isolated yields of ca. 35% along with elimination products.[6,7] Hence, we recognized that a less capricious coupling method would need to be developed in order to reliably prepare commercial quantities of serricornin.

We now report the development of a synthesis of serricornin suitable for the preparation of gram-quantities of material.

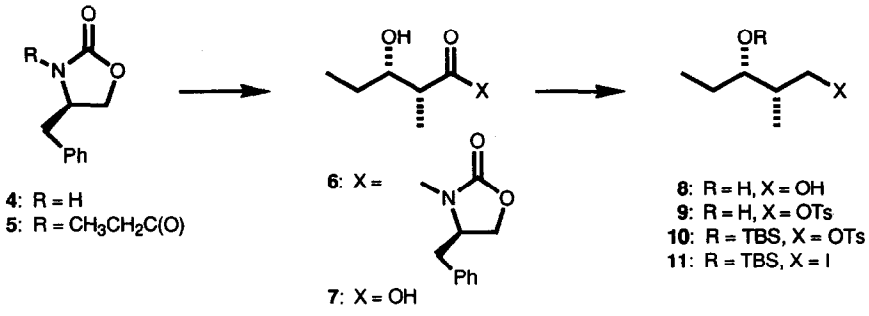
RESULTS AND DISCUSSIONS

To install the key C6 and C7 stereocenters in **2** we turned to the elegant aldol methodology developed by Evans[14,15] since (a) it is well-known to provide syn aldol products in high stereochemical purity, (b) many oxazolidinone derivatives are crystalline, and (c) the chiral auxiliary may be easily removed and recycled. The route shown in Scheme 2 proved to work well. Thus the boron enolate of oxazolidinone **5** was condensed

with propanal to provide the crystalline aldol adduct **6** with excellent diastereoselectivity (ratio of diastereomers = 98.5 : 0.9 : 0.3 : 0.3). After a single recrystallization, only a single diastereomer (of the derived TMS ethers) was detectable by GC. The advantages of using phenylalanine-derived oxazolidinones which tend to produce highly crystalline intermediates have been espoused previously,[15] and, in fact, the required aldol adduct arising from a norephedrine-derived oxazolidinone[14] was not crystalline.

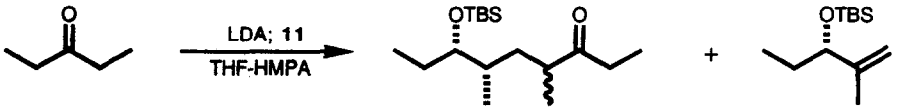
Hydrolysis of **6** to acid **7** with LiOOH proceeded in good yield (76%)[16] and allowed for the easy recovery of oxazolidinone **4** (84% after recrystallization) by simple acid-base extraction. The acid was reduced to diol **8** ($LiAlH_4$, 88%) which, in turn, was easily manipulated (p-TsCl, Et_3N, cat. DMAP; TBSCl, imidazole; NaI) into the desired alkylating agent **11** (78% overall yield from **8**). The 6-step sequence to convert oxazolidinone **5** into iodide **11** is straight-forward and has been used to produce 100 g lots of **11** routinely with overall yields of ca. 40%.

Scheme 2



The optical rotation of iodide **11** prepared by this route was 15.7° (c 3.5, $CHCl_3$) which compared favourably with the value of 15.6° (c 4.0, $CHCl_3$) previously reported by Mori for material known to be enantiomerically pure.[5] However, β-hydroxy acids (such as **7**) have been known to undergo unexpected racemization (*via* reversible dehydration/hydration),[17] and optical rotation is notoriously unreliable as an accurate measure of enantiomeric purity.[18] Hence, we also determined the enantiomeric purity of intermediate **9** by ^{19}F NMR analysis of its MTPA ester.[19] Only a single diastereomer was observed. Since the transformations from **9** to **11** should not affect the stereocenters, it is reasonable to infer that our iodide **11** is enantiomerically pure. It then follows that serricornin produced from this iodide will be stereochemically pure at C6 and C7 and thereby free of inhibitory isomers.

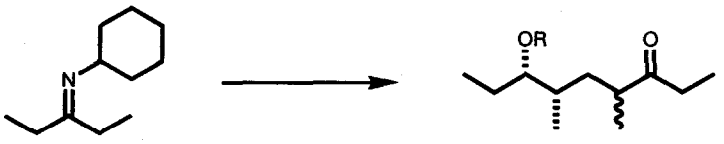
When we treated the lithium enolate of 3-pentanone with iodide **11** under typical alkylation conditions (THF/HMPA),[5] we could isolate the desired product **12** in only 30-35% yields. There was also isolated a volatile by-product which was identified as the allylic ether **13**, a product of competing E_2 elimination.[6] No improvements in yields of **12** were observed with numerous changes in reaction conditions (e.g. stoichiometry of reagents, temperature, quantity of HMPA).



12 **13**

The alkylation of metalloimines has been shown to be an effective method for the preparation of branched ketones.[20,21] Initial experiments using the cyclohexylimine of 3-pentanone[21] (**14**) in place of the parent ketone were encouraging in that only trace amounts of elimination product **13** were detected but yields of **12** were still low (ca. 50%). Fortunately, we found that the low yields were due to incomplete deprotonation of imine at the low temperatures (LDA, THF, -50 °C to -23 °C) used, and when deprotonations were carried out at higher temperatures (0 °C), much better results were obtained.[22] The solution of metalloimine produced at 0 °C was bright yellow and consistently afforded excellent (85-94% after acid hydrolysis and purification) yields of **12**. Thus the use of a metalloimine instead of a ketone enolate overcame the problem of competing E_2 elimination and also offered an extra bonus in that the suspected carcinogen HMPA was no longer required.

Scheme 3



14

12: R = TBS
1: R = H (4*R**,6*S*,7*S*)

The crude alkylation product could be directly hydrolyzed to serricornin and its C4 epimer using the conditions (HOAc-THF-H_2O, 80% yield from **11**) previously described by Mori with the slight modification that it was necessary to add acid during the course of the reaction to neutralize cyclohexylamine formed (from

imines present in the crude product). The overall yield of **(4*RS*,6*S*,7*S*)-1** from oxazolidinone **5** was 33%; from commercially available[23] **4** (which is recycled), the sequence is 9 steps with an overall yield of 30%.

In summary, we have described an enantioselective synthesis of serricornin and its C4 epimer that allows for the preparation of multi-gram quantities of material. The synthetic pheromone thus produced has been shown to be very effective in attracting male cigarette beetles.[24]

EXPERIMENTAL

General All reactions were performed in oven or flame-dried glassware under an atmosphere of dry N_2 unless otherwise specified. ^1H and ^{13}C NMR spectra were recorded on Bruker AC-200 or AM-250 spectrometers in $CDCl_3$ solution unless otherwise noted; signal positions are reported relative to an internal Me_4Si (^1H NMR, δ 0.0) or $CDCl_3$ (^{13}C NMR, δ 77.0) standard. IR spectra were obtained on a BOMEM MB-100 FT-IR spectrometer while mass spectra were recorded on a Varian VG7070 mass spectrometer using EI (70 eV) ionization. Rotations were measured on a JASCO DIP-360 digital polarimeter. Gas chromatographic analyses were performed on a Hewlett-Packard 5890 instrument fitted with a 30 m x 0.25 mm DB-1701 column; a temperature program with an initial temperature of 150 °C for 5 min followed by a 20 °C/min ramp to 250 °C was used. Elemental analyses were performed by M-H-W laboratories, Phoenix, AZ.

D-Phenylalanine was obtained from United States Biochemical Corp. Tributylborane was purchased from Callery Chemical Company while trifluoromethanesulfonic acid was obtained from Lancaster. Methylene chloride, Et_3N, iPr_2NH, and cyclohexylamine were distilled from CaH_2 before use; Et_2O and THF were dried over $Na/Ph_2C{=}O$ ketyl and distilled under N_2. Other reagents were purchased from Aldrich Chemical Company and were used without further purification. (*R*)-Phenylalaninol was prepared by conversion of phenylalanine to its methyl ester followed by reduction with $NaBH_4$ as described by Yamada.[25,26] It was converted to (*R*)-4-(phenylmethyl)oxazolidinone (**4**) and the *N*-propanoyl derivative **5** {$[\alpha]_D$ -99.6° (c 1.04, EtOH); lit (*S*)[15]: $[\alpha]_D$ +99.5° (c 1.01, EtOH)} essentially as described by Evans for the corresponding (*S*) compounds.[15] Imine **14** was prepared from 3-pentanone and $C_6H_{11}NH_2$ according to the method of Silverstein (cat TsOH, PhH, reflux).[21]

Dibutylboron triflate was prepared as described by Evans,[27] taking special care to wait until the reaction is initiated before the bulk of the CF_3SO_3H is added. To a well-stirred solution of Bu_3B (neat, 711 mL, 531 g, 2.92 mol) in a 2 L 3-neck round-bottomed flask was added 15 mL of CF_3SO_3H. The reaction mixture was warmed to 40 °C and stirred until gas evolution (butane) commenced (usually <10 min). The remainder of the CF_3SO_3H (258 mL total, 439 g, 2.92 mol) was then added dropwise via a dropping funnel such that the internal temperature remained at 40-45 °C. At the end of the addition, the temperature was raised to 50 °C and the flask was placed under vacuum (20 torr) to remove dissolved butane. Subsequent distillation (bp 64-65 °C/ 2.5 torr; lit.[27] 60 °C/2.0 torr) provided 682 g (85 %) of Bu_2BOTf as a yellow liquid.

(R)-3-[(2R,3S)-3-hydroxy-2-methyl-1-oxopentyl]-4-phenylmethyl-1,3-oxazolidin-2-one (6). A 10 L flask equipped with a mechanical stirrer was charged with 460 g (1.97 mol) of propionyloxazolidinone **5** and 2.5 L of dry CH_2Cl_2, and the mixture was cooled to 0 °C. Bu_2BOTf (650 g, 2.37 mol) and Et_3N (463 mL, 334 g, 3.3 mol) were then added sequentially; both reagents were added dropwise such that the internal temperature did not exceed 3 °C. The resulting light yellow solution was stirred at 0 °C for 30 min then cooled to -70 °C. Freshly distilled propanal (127 g, 2.19 mol) was then added over 30 min. After being stirred at -70 °C for a further 30 min and at 0 °C for 1 h, the reaction mixture was quenched by the addition of 2000 mL of 1 M aqueous pH 7 phosphate buffer and 3000 mL of MeOH, taking care not to allow the temperature to warm above 15 °C. A mixture of MeOH/30% H_2O_2 (2:1 v/v, 1800 mL) was then added at such a rate as to keep the temperature below 10 °C. The mixture was stirred at 10 °C for 1 h. The organic phase was separated, the solvent was removed in vacuo, and the resulting semi-solid was taken up in 800 mL of Et_2O. The aqueous phase was extracted with 3 x 500 mL of Et_2O and all the ether layers were combined. The combined organic phase was washed with 10% $NaHCO_3$ (500 mL) and brine (500 mL), dried ($MgSO_4$), and concentrated to afford a light yellow solid. Recrystallization from hexane-EtOAc (2:1, 1500 mL, reflux then cooled to 4 °C for 2 days) provided 540 g (80%) of the aldol product **6** as white crystals. $[\alpha]_D$ -38.9 (c 1.07, $CHCl_3$), -93.7 (c 1.06, EtOH); mp 78-79 °C; IR (KBr) 3523, 1761, 1700, 1377, 1217, 701 cm^{-1}; ^1H NMR (200 MHz) δ 7.38 (5 H, m), 4.70 (1 H, m), 4.26-4.13 (2 H, m), 3.90-3.70 (2 H, m), 3.24 (1 H, dd, J = 3.3, 13.4 Hz), 3.02 (1 H, s), 2.79 (1 H, dd, J = 9.3, 13.4 Hz), 1.70-1.35 (2 H, m), 1.25 (3 H, d, J = 6.9 Hz), 0.98 (3 H, t, J = 7.4 Hz); ^{13}C NMR (50 MHz) δ 177.3, 152.9, 134.9, 129.3, 127.3, 72.9, 66.0, 55.0, 41.7, 37.6, 26.7, 10.3, 10.2; MS m/e (rel intensity) 291 (M^+, 12), 244 (33), 133 (34), 178 (34), 158

(30), 115 (46), 91 (47), 86 (88), 57 (100). Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.26; N, 4.81. Found: C, 66.15; H, 7.00; N, 5.11.

A small sample of the crude solid was silylated (TMSCl, Et_3N) and the resulting TMS ethers were analyzed by GC. The ratio of the four diastereomers (in order of elution, retention time in min) was 0.9 (14.3): 0.3 (14.8) : 98.5 (15.5): 0.3 (15.6).

(2R, 3S)-3-hydroxy-2-methylpentanoic acid (7). A 10 L flask equipped with a mechanical stirrer was charged with 400 g (1.37 mol) of aldol adduct **6** and 4 L of THF/H_2O (4:1). The mixture was cooled to 0 °C and 563 mL of 30% H_2O_2 was added over 30 min followed by 60 g of LiOH in 1800 mL of H_2O. The mixture was stirred at 0 °C for 2 h. Na_2SO_3 (700 g in 3000 mL of H_2O) was then added to quench excess H_2O_2. An ice-bath was used to keep the temperature below 20 °C. The organic phase was separated and the solvent was evaporated (rotary evaporator, bath temperature 25 °C). The resulting creamy solid was taken up in H_2O (1000 mL) and CH_2Cl_2 (500 mL). The aqueous phase was added to the original one. The combined aqueous phases were extracted with 2 x 400 mL of CH_2Cl_2. It was then cooled to 0 °C, the pH was lowered to 1 by the addition of 6 M HCl (ca. 200 mL), and the mixture was extracted with 6 x 400 mL of EtOAc. The combined EtOAc extracts were concentrated by rotoevaporation with a water bath kept at 20-25 °C, and the crude β-hydroxyacid was dissolved in 1500 mL of 5% $NaHCO_3$ (Caution: vigorous CO_2 evolution). This aqueous solution was extracted with 2 x 400 mL of CH_2Cl_2 to remove the remainder of the chiral auxiliary (20 g after concentration). It was then cooled to 0 °C, acidified to pH 1 with 6 M HCl, and extracted with 6 x 200 mL of EtOAc. The EtOAc layers were combined, dried ($MgSO_4$), and concentrated (water bath at 20-25 °C) to afford 137 g (76%) of acid **7** as a colorless oil which was used without further purification: $[\alpha]_D$ -4.2° (c 1.01, $CHCl_3$), -14.1° (c 1.02, MeOH); lit[28]: $[\alpha]_D$ = -14.8° (c 4.3, MeOH); IR (neat) 2500-3500, 1709 cm^{-1}; ^1H NMR (200 MHz) δ 6.96 (2 H, br s), 3.88 (1 H, ddd, J = 3.6, 5.6, 7.6 Hz), 2.60 (1 H, dq, J = 3.6, 7.2 Hz), 1.60-1.40 (2 H, m), 1.20 (3 H, d, J = 7.2 Hz), 0.98 (3 H, t, J = 7.4 Hz);.^{13}C NMR (50 MHz) δ 179.6, 73.3, 43.8, 26.5, 10.4, 10.0.

Concentration of the initial CH_2Cl_2 extracts gave a solid which was recrystallized from EtOAc-hexanes (900 mL, 2:1) to afford 202 g (84% recovery) of oxazolidinone **4**. A small (8 g) second crop was obtained by re-working of the mother liquor.

(2S,3S)-2-Methyl-1,3-pentanediol (8). To a solution of crude hydroxy acid **7** (195 g, 1.48 mol) in 2000 mL of dry Et_2O at 0 °C was added slowly a solution of $LiAlH_4$ (103.3 g, 2.7 mol) in 2000 mL of dry Et_2O via cannula. The resulting mixture was stirred at rt for 5 h. It was then cooled to 0 °C, and quenched by careful addition of $Na_2SO_4 \cdot 10H_2O$ (Glauber's salt). When gas evolution ceased, the mixture was allowed to stand at rt for 12 h then filtered through a short pad of Celite. The filter cake was washed well with warm EtOAc (4 x 400 mL). The combined filtrates were dried ($MgSO_4$) and concentrated to afford diol **8** (154 g, 88%) as a slightly yellow oil. $[\alpha]_D$ 1.1° (c 2.8, $CHCl_3$); lit.[8]: $[\alpha]_D^{23}$ 2.41° (c 1.08, $CHCl_3$);.IR (neat) 3339, 2924 cm^{-1}; ^1H NMR (250 MHz) δ 4.77 (2 H, s, exch D_2O), 3.71 (1 H, m), 3.65 (2 H, d, *J* = 5.6 Hz), 1.90-1.70 (1 H, m), 1.6-1.35 (2 H, m), 0.95 (3 H, t, *J* = 7.4 Hz), 0.88 (3 H, d, *J* = 7.1 Hz); ^{13}C NMR (63 MHz) δ 75.0, 66.2, 38.6, 26.6, 10.5 and 9.9; MS m/e (rel intensity) 119 (26), 101 (29), 83 (100), 71 (28), 59 (78). Anal. Calcd for $C_6H_{14}O_2$: C, 60.98; H, 11.94. Found: C, 61.24; H, 11.76.

(2S,3S)-2-Methyl-1-(4-methylbenzenesufonyloxy)-3-pentanol (9). To a solution of diol **8** (154 g, 1.30 mol) in 1500 mL of CH_2Cl_2 at rt was added *p*-TsCl (254 g, 1.33 mol), Et_3N (192 mL, 140 g, 1.38 mol), and a catalytic amount (1 g) of DMAP. The reaction mixture was stirred at rt for 18 h. The solvent was then removed by rotoevaporation and the residue was taken up in Et_2O (3000 mL) and H_2O (1000 mL). The organic layer was washed with water (2 x 1000 mL), brine (1000 mL), dried ($MgSO_4$) and concentrated to give monotosylate **9** (320 g, 90%) which was converted to its TBDMS ether without further purification. An analytically pure sample was obtained by flash chromatography (hexanes-EtOAc, 70:30) as a colorless oil. $[\alpha]_D$ -10.5° (c 1.0, $CHCl_3$); IR (neat) 3483, 1598, 1355, 1179, 957, 827 cm^{-1}; ^1H NMR (250 MHz) δ 7.78 (2 H, d, *J* = 8.2 Hz), 7.35 (2 H, d, *J* = 8.2 Hz), 4.08 (1 H, dd, *J* = 7.6, 9.6 Hz), 3.88 (1 H, dd, *J* = 6.1, 9.6 Hz), 3.50-3.65 (1 H, m), 2.44 (3 H, s), 1.85-1.95 (1 H, m), 1.35-1.55 (2 H, m), 0.91 (3 H, t, *J* = 7.3 Hz), 0.84 (3 H, d, *J* = 7.0 Hz); ^{13}C NMR (63 MHz) δ 144.7, 133.0, 129.8, 127.7, 72.8, 72.0, 37.3, 27.1, 21.5, 10.3, 9.4; MS m/e (rel intensity) 273 (13), 255 (8), 173 (72), 155 (29), 101 (37), 91 (83), 83 (100). Anal. Calcd for $C_{13}H_{20}O_4S$: C, 57.33; H, 7.40. Found: C, 57.33; 7.40.

A sample was converted to its MTPA ester (MTPA-Cl, Et_3N, cat. DMAP) for analysis by ^{19}F NMR spectroscopy. The ester derived from (R)-(+)-MTPA[19] exhibited a single resonance at δ 71.08 [upfield from $CFCl_3$ using CF_3COOH (δ 76.53) as an external standard] while the diastereomers formed from (±)-MTPA[29] showed a pair of signals at δ 71.04 and 71.08.

(2S,3S)-3-t-Butyldimethylsilyloxy-2-methyl-1-(4-methylbenzenesufonyloxy)pentane (10). To a mixture of crude hydroxy tosylate **9** (162 g, 0.60 mol) in 100 mL of dry DMF was added TBSCl (109 g, 0.72 mol) and imidazole (103 g, 1.5 mol). The reaction mixture was stirred at ambient temperature for 24 h. It was then poured into 700 mL of ice-water and extracted with Et_2O (2 x 500 mL). The organic layer was washed with water (4 x 200 mL), dried ($MgSO_4$), and concentrated to give 214 g of a yellow oil which was used without further purification. A small amount of material was purified by flash chromatography (hexanes-EtOAc, 9:1) to give a colorless oil. $[\alpha]_D$ -3.01° (c 1.03, $CHCl_3$); IR (neat) 2920, 1599, 1364, 1181, 967, 837, 775, 667 cm^{-1}; ^1H NMR (200 MHz) δ 7.78 (2 H, d, J = 8.3), 7.33 (2 H, d, J = 8.3), 3.93 (2 H, AB of ABX, J_{AX} = 6.4, J_{BX} = 7.3, J_{AB} = 9.3 Hz, Δδ = 0.13), 3.58 (1 H, dt, J = 3.1, 6.6 Hz), 2.44 (3 H, s), 1.93 (1 H, dq, J = 3.1, 6.8 Hz), 1.40 (2 H, dq, J = 6.8, 7.2 Hz), 0.82 (3 H, d, J = 6.8 Hz), 0.81 (9 H, s), 0.79 (3 H, t, J = 7.2 Hz), 0.00 (3 H, s), -0.04 (3 H, s); ^{13}C NMR (50 MHz) δ 144.6, 133.1, 129.7, 127.8, 73.2, 73.0, 36.8, 28.6, 25.7, 21.5, 18.0, 10.4, 10.0, -4.3, -4.9. ^1H NMR data in CCl_4 have been reported for this compound.[5]

(2R,3S)-3-t-Butyldimethylsilyloxy-1-iodo-2-methylpentane (11). A mixture of tosylate **10** (186 g, 0.48 mol), NaI (109 g, 0.69 mol) and $NaHCO_3$ (269 g, 3.2 mol) in acetone (1500 mL) was heated at reflux for 24 h. It was then cooled to rt and acetone was removed *in vacuo*. The residue was diluted with water (400 mL) and extracted with Et_2O (2 x 400 mL). The organic layer was washed with H_2O (500 mL), saturated $NaHCO_3$ (500 mL), and brine (500 mL), then was dried ($MgSO_4$) and concentrated by rotoevaporation. Flash chromatography of the residue (1 kg silica) using hexanes as eluent provided iodide **11** (154 g, 87% from **9**) as a colorless oil. $[\alpha]_D^{23}$ 15.7° (c 3.52, $CHCl_3$); lit [5]: $[\alpha]_D^{23}$ 15.6° (c 4.02, $CHCl_3$); IR(neat) 2946, 2857, 1465, 1254, 1063, 1019, 843, 777 cm^{-1}; ^1H NMR (200 MHz) δ 3.71 (1 H, dt, J = 3.2, 6.5 Hz), 3.37 (1 H, dd, J = 6.2, 9.4 Hz), 3.10 (1 H, dd, J = 7.3, 9.4 Hz), 1.91 (1 H, app d of sextets, J = 3.2, 6.7 Hz), 1.53 (2 H, dq, J = 6.7, 7.4 Hz), 1.03 (3 H, d, J = 6.7 Hz), 0.95 (9 H, s), 0.91 (3 H, t, J = 7.4 Hz), 0.14 (3 H, s) and 0.13 (3 H, s); ^{13}C NMR (50 MHz) δ 73.6, 40.4, 26.8, 25.9, 18.1, 14.5, 12.8, 9.9, -4.2, -4.5.

(4RS,6S,7S)-7-t-Butyldimethylsilyloxy-4,6-dimethyl-3-nonanone (12, Serricornin TBDMS ether). To a solution of *i*-Pr_2NH (67.4 g, 0.67 mol) in 500 mL of dry THF at -78 °C was added *n*-BuLi (245

mL of a 2.5 M solution in hexanes, 0.61 mol). The light yellow solution was stirred at -78 °C for 30 min. Then imine **14** (100.8 g, 0.60 mol) was added slowly and the reaction mixture was warmed to 0 °C. The color of the solution changed to a bright yellow. After 30 min, the mixture was cooled to -50 °C and a solution of iodide **11** (120 g, 0.35 mol) in 100 mL of dry THF was added. The mixture was stirred at -50 °C for 10 min, warmed to 0 °C, and stirred at that temperature for 45 min. It was then poured into ice-brine (500 mL) and extracted with Et_2O (2 x 500 mL). The combined organic phase was washed sequentially with 400 mL aliquots of 2 M HCl , water, saturated $NaHCO_3$, and brine then dried ($MgSO_4$) and concentrated by rotoevaporation to give a yellow oil (147 g, >100% yield, contains some imine) which could be used without further processing. Purification of 30.0 g of this mixture by flash chromatography (hex-Et_2O, 20:1) gave 20.2 g (94% based on mass balance) of ketone **13** as a 1:1 mixture of diastereomers. $[\alpha]_D$ -10.9° (c 1.07, $CHCl_3$); lit.[5] $[\alpha]_D$ -8.7 (c 2.29, $CHCl_3$); IR(neat) 2920, 1713, 1463, 1253, 1055, 843, 774 cm^{-1}; ^1H NMR (250 MHz) δ 3.38 (1 H, dq, *J* = 3.4, 6.5 Hz), 2.70-2.30 (3 H, m), 1.78 (1 H, ddd, *J* = 4.6, 8.9, 13.6 Hz), 1.60-1.30 (4 H, m), 1.17-0.90 (6 H, m), 0.85 (9 H, s), 0.88-0.70 (6 H, m), 0.00 (3 H, s), -0.01 (3 H, s); ^{13}C NMR (63 MHz) : δ 215.1, 77.2, 77.1, 43.9, 36.8, 35.7, 34.8, 34.0, 33.7, 26.4, 26.2, 25.9, 18.1, 17.7, 15.9, 14.2, 13.9, 10.2, 10.1, 7.7, -4.2, -4.4, -4.5.

(4RS,6S,7S)-7-Hydroxy-4,6-dimethyl-3-nonanone [Serricornin 1 and its (4R,6S,7S)-epimer]. A solution of the crude product from the previous alkylation (100 g) in 1100 mL of AcOH-THF-H_2O (3:1:1, v/v) was stirred at 50-55 °C for 48 h. During this time, the pH was monitored every few hours and adjusted to ca. 1.4 with 1 M HCl. The mixture was then cooled in an ice bath and 6 M NaOH (1400 mL) was slowly added. The mixture was extracted with Et_2O (4 x 400 mL), and the combined organic layers were washed with H_2O (1000 mL), satd $NaHCO_3$ (2 x 500 mL - caution: foaming), and brine (300 mL). Drying ($MgSO_4$) followed by concentration gave the crude product as a yellow oil (110 g). This material was purified by flash chromatography (1500 g silica; hexanes-ether, 5:1) to afford serricornin and its (4*R*,6*S*,7*S*)-epimer as a 1:1 mixture of isomers (combined yield: 35.8 g, 80% from iodide **11**). The ^1H NMR spectra of the product were complicated due to the mixture of stereoisomers and open- and closed chain (hemiacetal) tautomers present but were consistent with data previously reported.[5] No attempt was made to separate the isomers, and the mixture has been used directly in insect lures with good success.[24]

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