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NEW SYNTHESIS OF THE CALIFORNIA RED SCALE SEX PHEROMONE

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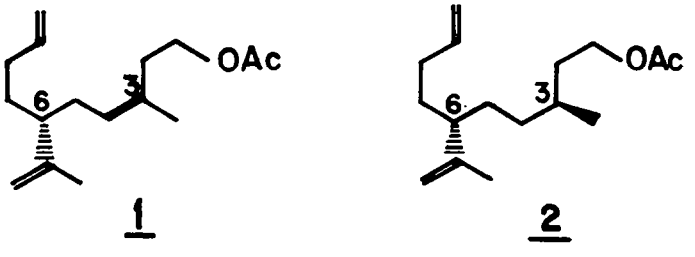
Abstract.- The target molecules 1 and 2 were synthesized from a common intermediate 6 prepared from (R)-Limonene. The first enantioselective synthesis of 2 is described.

California red scale (CRS) is one of the main citrus pests in California, South Africa, Australia and the Mediterranean countries; and it is known to cause losses to other crops as well[1,2]. Components 1 and 2 of the sex pheromone of CRS (Scheme I) have been identified and synthesized by Roelofs[3] and Anderson[4]. During the last ten years several alternative syntheses have been developed for 1 and 2[5-8]. The chiral centers in these compounds were constracted either using chiral intermediates derived from natural products or by addition of organocuprates to optically active unsaturated esters[9]. The synthesis of the Z trisubstituted double bond in 1 has been accomplished either by using negatively charged Wittig reagents[10] or via [2,3]-sigmatropic Wittig rearrangement[11]. These methods have one main drawback; the expense of the starting material and/or of the reagents used. In order to supply the pheromone components in gram quantities for field tests an alternative approach is now described. In our method, a common chiral intermediate for the synthesis of both 1 and 2, has been prepared from (R)-Limonene, a cheap starting material readily available in over 98% e.e., specifically as a building unit for chiral center C6.

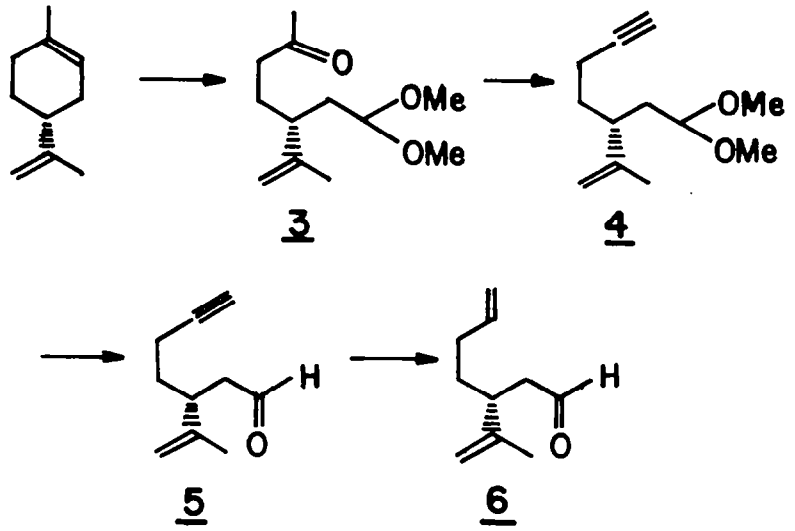


Scheme I

RESULTS AND DISCUSSION

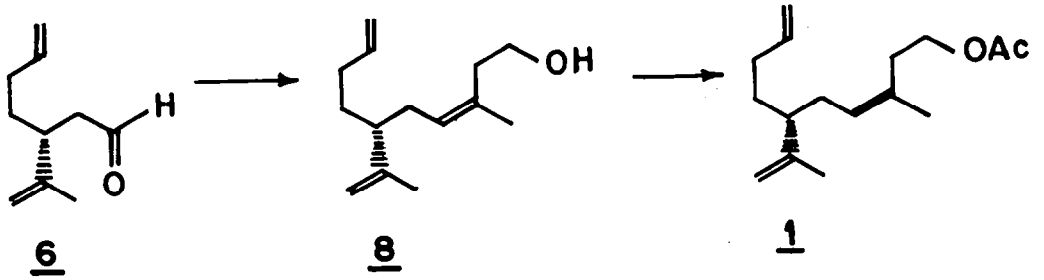
Selective cleavage of the six membered ring by ozonolysis is a well known procedure in terpene chemistry. Keto-acetal 3 has been prepared in 100 g. scale by ozonolysis of (R)-Limonene in methanol at -70°C[12], and the methyl ketone unit was converted to terminal

acetylene 4 via its enol phosphate using lithium tetramethylpiperidide as base giving a product in which the ratio of terminal to internal acetylene was found to be 15:1. When lithium diisopropylamide was used as a base this ratio reversed to 1:5.7 respectively. These results are in full agreement with the work of Negishi[13]. The synthesis of 6 was completed by two further steps: mild cleavage of 4 to give the aldehydo-acetylene 5, followed by Lindlar reduction (Scheme II).



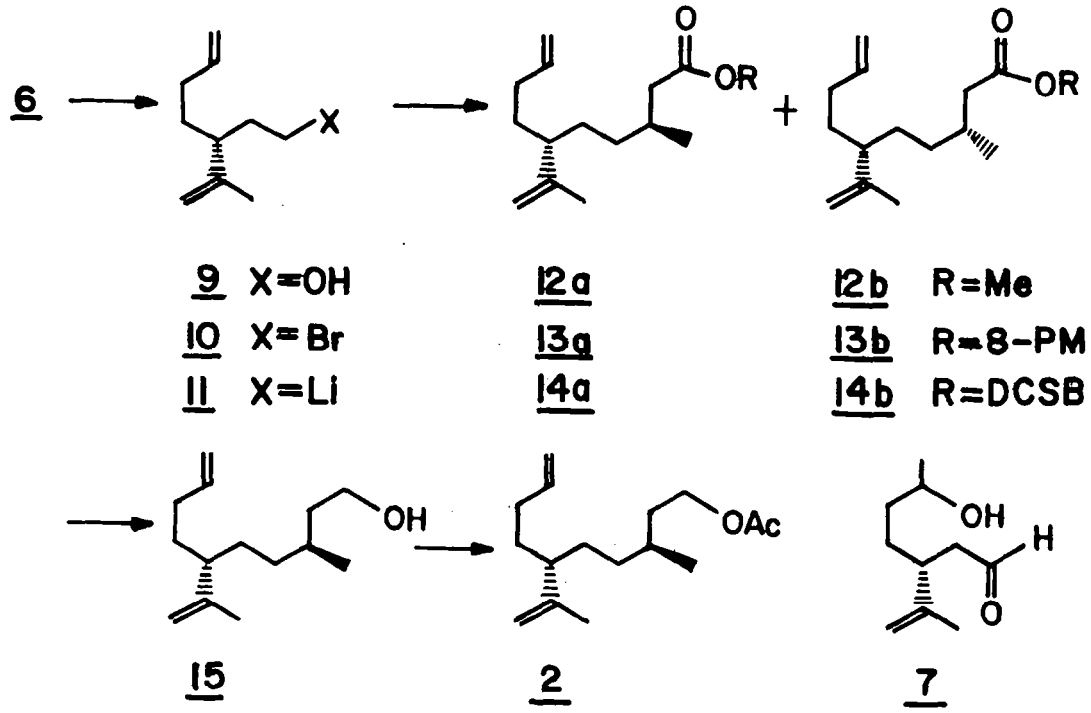
Scheme II

Conponent 1 was prepared in two steps from 6 by a Wittig reaction, using a reagent prepared from ethylene oxide and ethylenetriphenylphosphorane; and acetylation, following a procedure which was originally developed for the synthesis of the White Peach scale sex pheromone[12] (Scheme III). The main drawback of this approach is poor stereoselectivity in the Wittig condensation, resulting in the formation of the Z and E isomer in a 63:37 ratio. Although it has been found in field tests that the E isomer does not inhibit male trapping, we have tried to improve the relative yield of the active isomer. It was found that changing the base from n-butyl lithium to sodium bis(trimethylsilyl)amide had little effect on the Z:E ratio which was changed to 67:33, but in view of the high chemical yield achieved this was the method of choice. According to results published by Caine(10), a negative charge on the chain of the aldehyde can direct the steric course of the Wittig condensation to give the Z isomer exclusively, but unfortunately applying this approach to aldehydo-alcohol 7 and aldehydo-acetylene 5, did not lead to the hoped-for increase in the Z to E ratio, and moreover the yields were low. Acetylation of the crude alcohol 8 gave 1 whose synthesis was thus accomplished in overall 37% yield from (R)-Limonene, giving a product which was > 98% ee at C6, and contained 67% of the active isomer 1.



Scheme III

The strategy for the synthesis of 2 was based on Yamamoto's finding[14] that a reagent of type $RCuBF_3$ can react in good yield with unsaturated esters by 1,4 addition. Intermediate 6 was the starting material for the bromide 10 via alcohol 9 in 67% yield. The corresponding organocuprate was made from bromide 10 via alkyl lithium 11 prepared in ether and CuI, and reacted with E-methyl crotonate in the presence of BF_3 to form in good yield the corresponding diastereomeric esters 12a and 12b in a 45:55 ratio[15] (Scheme IV). The disadvantage of having to use at least two equivalents of alkylcuprate, in our case the expensive component, was overcome by using a high order organocuprates of the type $R^*Me(CN)CuLi_2$[16], which consumes only one equivalent of 10. Here the ratio of 12a to 12b was found to be 48:52[15]. It is worth mentioning that $R^*Me(CN)CuLi_2$ transfers the chiral intermediate and the methyl as well in a 12:1 ratio, and the side product methyl 3-methylbutanoate was easily removed by distillation. The synthesis of the second component of the CRS sex pheromone 2 was completed by two additionaal steps, reduction with lithium aluminum hydrid to give 15 followed by acetylation. The production contained 48% of the active component 2 and 52% of its diastereoisomer.



Scheme IV

In view of this low stereoselectivity, we tried to improve the enantioselectivity by the use of chiral crotonates. This methodology has made great strides during the last five years[17-19]. Chiral esters can be prepared easily since variety of optically active alcohols are now commercially available. Based on Oppolzer's[18] results according to which, 1,4-addition of an alkylcuprate BF_3 complex to (-)-8-phenylmenthyl (8-PM) E-crotonate occurs with high enantioselectivity from the Re face of the enoate, addition of an intermediate of the type $RCuBF_3$ prepared from 6 should lead to the 13a 3S,6R diastereomer. Our experimental result fully confirm Oppolzer's model since ester 13a 3S,6R was the major diastereomer and 13b 3R,6R (Scheme IV) was the minor product in 9:1 ratio, >80% d.e.[15].

However, as corollary, 1,4-addition of the $RCuBF_3$ reagent to (+)-8-phenylmentyl (8+PM) Z-crotonate should give as major compound 13a 3S,6R and in lower selectivity[18] if a similar intermediate is operating. This assumption was fully conformed experimentally, esters 13a and

13b being formed in a 7:3 ratio[15]. Because the stereoselectivity of 1,4 addition to the E-8-phenylmenthyl ester was not satisfactory we prepared 10-dicyclohexyl-sulfamoyl-D-isobornyl (DCSB) E-crotonate[19] following Oppolzer's procedure. Addition of our organocuprate BF_3 complex in the presence of tributylphosphine gave as expected product 14a 3S,6R but the diastereoselectivity was not higher than 80% d.e.[15]. Ester 14a was reduced by lithium aluminium hydride to alcohol 15 which was acetylated to give 2. The first enantioselective synthesis of the active component 2 of the sex pheromone of the California red scale has thus been accomplished in an overall 70% yield from 10. Compounds 1 and 2 have identical I.R., N.M.R. and M.S. with the authentic pheromone components and were found to be active in field tests.

Experimental Section

The instruments used were as follows: ^1H NMR, Variane T-60, Bruker WP-400; IR, Perkin-Elmer 257; GLC, Hewlett-Packard 5890, carrier gas helium, capillary column carbowax 20M 50 m.; MS, Varian MAT-711. THF was dried over potassium, ether was dried over LAH; Silica gel Merck (230-400 mesh) Kieselgel 60.

(R)-1,1-Dimethoxy-3-(1-methylethenyl)-6-heptyne 4.

(R)-(+)-7,7-Dimethoxy-5-(1-methylethenyl)-2-heptanone 3 (21.4 g. 0.1 mol)[12] was converted to 4 according to Negishi[13] in 90% crude yield. IR ($CHCl_3$) 3310, 1650, cm^{-1}; NMR (CCl_4) δ 4.7 (s, 2H), 3.17 (s, 6H), 2.2 (t, 1H), 1.65 (s, 3H).

(R)-3-(1-methylethenyl)-6-heptynal 5. Crude (R)-1,1-Dimethoxy-3-(1-methylethenyl)-6-heptyne 4 (17.6 g, 0.09 mol) was added to 170 ml of acetone and 170 ml of 10% Hydrochloric acid solution. The reaction was stirred for 2 hours at room temperature, then the acid was quenched with 10% $NaHCO_3$ and the acetone was removed at reduced pressure, the product was extracted with CH_2Cl_2 (150 mL X 4), the organic layers were washed with brine and dried over Na_2SO_4, to give 9.4 g. (70%) of 5 after chromatography over silica gel column (hexane:methylene chloride 8:1). IR ($CHCl_3$) 3310, 1730, 1650, cm^{-1}; NMR (CCl_4) δ 9.64 (t, 1H), 4.78 (s, 2H) 2.58 (t, 1H), 1.85-2.3 (m, 5H), 1.61 (s, 3H), 1.35 (m, 2H).

(R)-3-(1-methylethenyl)-6-heptenal 6. (R)-3-(1-methylethenyl)-6-heptynal 5 (9.5 g. 63 mmol) were dissolved in 65 mL of hexane and reduced over Lindlar catalyst at atmospheric pressure for 2 hours. The catalyst was filtered off and the solvent was evaporated to give 9.3 g. of 6 in 97% yield. IR ($CHCl_3$) 1730, 1650, cm^{-1}; NMR (CCl_4) δ 9.35 (t, 3H), 5.8-5.3 (m, 1H), 5.05 (d, 2H), 4.75 (s, 2H), 1.82-2.55 (m, 5H), 1.65 (s, 3H), 1.35 (m, 2H); MS, found for $C_{10}H_{16}O$ m/e 152.1192 (Calcld m/e 152.1200).

(3Z,6R)-3-methyl-6-(1-methyletthenyl)-3,9-decadien-1-ol 8. Solution of sodium bis(trimethylsilyl)amide (1M solution in hexane 65.8 mL, 66 mmol) was added to ethyltriphenylphosphonium bromide (24.5 g, 66 mmol) in 130 mL THF at room temperature. The mixture was stirred for 2 hours and then cooled down to -5°C. Ethylene oxide (3.3 mL, 66 mmol) was added by a precooled syringe, keeping the temperature at -5°C. The reaction was warmed up to 25°C and sodium bis(trimethylsilyl)amide solution (65.8 mL, 66 mmole) was added. The mixture was stirred for 3 hours and then cooled down to -70°C. The aldehyde 6 (5.0 g, 33 mmol) dissolved in 10 mL of THF was added dropwise, the reaction was stirred for 15 min. at -70°C and for 45 min. at room temperature. 150 mL of water was added and the solvents were removed under reduced pressure. The aqueous phase was extracted with hexane (30 mL x 3), the combined organic extracts were dried over $MgSO_4$ and concentrated. The resultant mixture was chromatographed over silica gel (hexane-methylene chlorine 2:1 as eluent) to give 5.1 g of alcohols in 74.5% yield, Z:E ratio 67:33. IR ($CHCl_3$) 3620, 1650, cm^{-1}; NMR ($CDCl_3$) 400 MHz δ 5.72-5.88 (m, 1H), 5.13 (t, 1H), 4.93 (d, 1H), 4.88 (d, 1H), 4.76 (s, 1H), 4.68 (s, 1H), 3.5 (t, 2H), 2.21 (t, 2H), 1.85-2.15 (m, 5H), 1.7 (s, 3H), 1.61 (s, 3H), 1.37 (m, 2H).

(3Z,6R)-3-methyl-6-(1-methylethenyl)-3,9-decadien-1-yl Acetate 1. Acetyl chloride (2.7 g, 34.3 mmol) was added to solution of alcohol 8 (5.1 g, 24.5 mmol) and triethylamine (4.8 mL, 34.3

mmol) in 60 mL of dry ether at 0°C. The mixture was stirred for 2 hours at room temperature and then 50 mL of water were added. The product was extracted with ether (30 mL x 3) and the ether phase was washed with cold 1N HCl, brine and dried over Na_2SO_4. The solvent was removed to give 5.8 g of 1 and it's (3E,6R) isomer in 95% yield (Z:E ratio 67:33). IR ($CHCl_3$) 1740, 1650, cm^{-1}; NMR ($CDCl_3$) 400 MHz δ 5.73-5.88 (m, 1H) 5.15 (t, 1H), 4.95 (d, 1H), 4.89 (d, 1H), 4.77 (s, 1H), 4.68 (s, 1H), 4.07 (t, 2H), 2.35 (t, 2H), 1.88, 2.16 (m, 5H), 2.05 (s, 3H), 1.7 (s, 3H), 1.61 (s, 3H), 1.35 (m, 2H).

(R)-3-(1-methylethenyl)-6-hepten-1-ol 9. 9 g of 6 (59 mmol) were dissolved in dry ether and added dropwise to suspension of lithium aluminium hydride (11.15 g 30 mmol) in dry ether (50 mL) at 0°C. The cooling bath was removed and the reaction was stirred for 1 hour at room temperature. The reaction was cooled down to 0°C and 1.1 mL of water were added carefully, followed by 1.1 mL of 15% sodium hydroxide and 3.3 mL of water. The organic layer was decantated, dried over Na_2SO_4 and the solvent was removed to give 8.7 g of alcohol 9 in 95% yield. IR ($CHCl_3$) 3640, 1650, cm^{-1}; NMR (CCl_4) δ 5.86-5.32 (m, 1H), 4.84 (d, 2H), 4.6 (s, 2H), 3.4 (t, 2H), 1.82-2.25 (m, 3H) 1.58 (s, 3H), 1.32-1.55 (m, 4H); MS, found for $C_{10}H_{18}O$ m/e 154.1344 (calcd m/e 154.1358).

(R)-3-(1-methylethenyl)-1-bromohept-6-ene 10. Methane sulfonyl chloride (5.6 mL, 72 mmol) was added dropwise during 20 min. to stirred solution of 9 (8.6 g, 56 mmol) and triethylamine (10.0 mL, 55 mmol) in dry CH_2Cl_2 under nitrogen atmosphere at 0°C. After 30 min. of stirring at 0°C the reaction was kept for additional two hours at room temperature, water (60 mL) were added and the layers were separated. The organic phase was washed with 1N HCl, brine, dried over Na_2SO_4 and the solvent was removed to give 12.3 g of crude mesylate ester in 95% yield. NMR (CCl_4) 5.85-5.38 (m, 1H), 4.95 (d, 2H), 4.73 (s, 2H), 4.00 (t, 3H), 1.80-2.32 (m, 5H), 2.86 (s, 3H), 1.62 (t, 3H), 1.28 (m, 2H). The crude mesylate ester was dissolved in dry THF (90 mL) and anhydrous lithium bromide (8.6 g, 98 mmol) were added to the stirred solution at 0°C and then for 2 hours at room temperature. Water (90 mL) were added, the solvent was removed and the organic layer was extracted with hexane (30 mL x 4). The organic extracts were combined, washed with water, brine and dried over Na_2SO_4. The solvent was removed to give 7.25 g of bromide 10 in 70% yield. NMR (CCl_4) δ 5.83-5.36 (m, 1H), 5.0 (d, 1H), 4.70 (s, 2H), 3.3 (t, 2H), 1.78-2.38 (m, 3H), 1.61 (s, 3H), 1.31-1.52 (m, 4H); MS, found for $C_{10}H_{17}Br^{(79)}$ m/e 216.0552 (calcd m/e 216.0513).

Methyl (3RS,6R)-3-methyl-6-(1-methylethenyl)-9-decenate 12. Methyl lithium (5.5 mL, 1.05 M in ether) was added dropwise to stirred cuprous cyanide (0.74 g, 8.25 mmol) in 2 mL of dry ether at -70°C. The suspension was warmed up to 0°C to give clear solution and cooled again to -70°C. Alkyl lithium 11 was prepared from alkyl bromide 10 (1.9 g, 8.8 mmol) and 2.5 eq. of lithium in dry ethyl ether (7.5 mL) stirred for one hour at 0°C to give solution of 11 (1.1 M) in ether (95%). Alkyl lithium 11 (7.5 mL, 8.25 mmol) was added to the methyl cuprate keeping the temperature below -65°C and the suspension was stirred for 10 min., then methyl E-crotonate (0.83 g, 1 eq.) was added dropwise at -70°C. The reaction was stirred for 40 min. at -70°C and 2 hours at -25°C before quenching with 20 mL of a 90% saturated NH_4Cl/10% concentrated NH_4OH solution. The layers were separated and the water was extracted with ether (15 mL x 4), washed with brine and dried over $MgSO_4$. The solvent was removed and the crude mixture was distilled bulb to bulb 100°C/0.5 mmHg to give 1.3g of 12 in 75% yield. IR ($CHCl_3$) 1740, 1650, cm^{-1}; NMR (CCl_4) δ 5.85-5.15 (m, 1H), 4.92 (d, 2H), 4.62 (s, 2H), 3.53 (s, 3H), 1.85-2.42 (m, 5H), 1.60 (s, 3H), 1.22 1.48 (m, 7H), 0.92 (d, 3H); MS, found for $C_{15}H_{26}O_2$ m/e 238.1939 (Calcd m/e 238.1933).

(3RS,6R)-3-Methyl-6-(methylethenyl)-9-decen-1-ol 15. Ester 12 (1.3 g, 5.5 mmol) was dissolved in 5 mL of dry ether and added dropwise to a stirred suspension of lithium aluminium hydride (0.11 g, 2.9 mmol) in dry ether (10 mL) at 0°C. The reaction was stirred for 2 hours at room temperature and worked up as described for 9 to give 1.1 g of alcohol 15 in 96% yield IR ($CHCl_3$) 3640, 1650, cm^{-1}; NMR (CCl_4) δ 5.8-5.3 (m, 1H), 3.56 (t, 2H), 1.85-2.12 (m, 3H), 1.63 (s, 3H), 1.1-1.6 (m, 9H), 0.95 (d, 3H).

(3RS,6R)-3-Methyl-6-(1-methylethenyl)-9-decen-1-yl Acetate 2. Acetyl chloride (0.58 g, 7.34 mmol) was added to a solution of alcohol 15 (1.1 g, 5.25 mmol) and triethylamine (0.75 g, 7.34 mmol) in 12 mL of dry ether at 0°C. The mixture was stirred for 2 hours at room temperature and worked up as described for 1 to give 1.2 g of 2 in 90% yield after bulb to bulb distillation at 110° C/0.3 mmHg. IR ($CHCl_3$) 1740, 1650, cm^{-1}; NMR (CCl_4) δ 5.85-5.35 (m, 1H), 4.92 (d, 2H), 4.6 (s, 2H), 3.92 (t, 2H), 1.85-2.15 (m, 3H), 1.63 (s, 3H), 1.1-1.6 (m, 9H) 0.88 (d, 3H).
(3S,6R)-3-Methyl-6-(1-methylethenyl)-9-decen-1-ol 15. Method a) Alkyl lithium 11 (3 mmol prepared as described for 12) was added to CuI (572 mg, 3 mmol) in 3 mL of dry ether at -70°C. BF_3OEt_2 (0.4 mL, 3 mmol) was added slowly and the mixture was stirred for 10 min. followed by addition of 8-PM E-crotonate (or 8+PM Z-coronate) (450 mg 1.5 mmol) dissolved in 2 mL of dry ether at -70°C. The reaction was stirred for 30 min. at -70°C, warmed up to room temperature and worked up as described in method b.
Method b) The alkyl lithium 11 (4.5 mmol prepared as described in preparation of 12) was added to CuI.PBu_3 complex (1.77 g, 4.5 mmol) in 3 mL of dry ether at -70°C. The mixture was warmed up to -30°C during 30 min. and then cooled down again to -70°C. $BF_3.OEt_2$ (0.6 mL, 4.5 mmol) was added and the mixture was stirred for 10 min. DCSB E-crotonate (690 mg, 1.5 mmol) dissolved in 2 mL of ether-tetrahedrofurane 4:1 was added at -70°C. The reaction was stirred for 1 hour at -70°C, then kept at -40°C for 8 hours, and 10 mL of 90% saturated NH_4Cl/10% concentrated NH_4OH were added. The ether phase was separated and the aqueous phase was extracted with ether (10 mL x 3), the combined ether extracts were stirred with MCPBA (770 mg, 4.5 mmol) for 10 min., washed with 10% $NaHCO_3$ and dried over $MgSO_4$. The solvent was removed under reduced pressure to give 725 mg of crude ester 14 (85%). The crude ester 14 (725 mg), dissolved in 3 mL ether was added to lithium aluminum hydride (90 mg, 2.4 mmol) suspension in 5 mL ether at 0°C. The reaction was stirred for 30 min. at room temperature and worked up as usual. The solvent was removed under reduced pressure to give 700 mg of 15 and the auxiliary DCSB alcohol. The alcohols were chromatographed over silica gel (eluted with hexane methylene chloride 4:1-2:1) to yield DCSB alcohol 430 mg and 15 230 mg (90%). IR ($CHCl_3$) 3620, 1650, cm^{-1}; NMR ($CDCl_3$) 400 MHz δ 5.72-5.85 (m, 1H), 4.98 (d, 1H), 4.93 (d, 1H); 4.72 (s, 1H), 4.63 (s, 1H) 3.63 (t, 2H), 2.06-1.85 (m, 3H), 1.58 (s, 3H), 1.0-1.5 (m, 9H), 0.88 (d, 3H).
(3S,6R)-3-methyl-6-(1-methylethenyl)-9-decen-1-yl Acetate 2. Acetylation of (3S,6R) alcohol was carried out as described for 1 in 90% yield. The ratio of (3S,6R) to (3R,6R) was determined by GLC to be 9:1. IR ($CHCl_3$) 1740, 1650, cm^{-1}; NMR (C_6D_6) 400 MHz δ 5.84-5.73 (m, 1H), 5.07 (d, 1H), 5.02 (d, 1H), 4.82 (s, 1H), 4.75 (s, 1H), 4.08 (t, 2H), 1.87-2.11 (m, 3H), 1.7 (s, 3H), 1.49 (s, 3H), 1.1-1.6 (m, 9H), 0.77 (d, 3H).

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