Synthesis of Nitidulid Beetle Pheromones: Alkyl-Branched Tetraene Hydrocarbons

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Synthetic procedures are presented for four tetraene hydrocarbons that had been identified as pheromone components for the driedfruit beetle, *Carpophilus hemipterus* (L.), or the dusky sap beetle, *C. lugubris* Murray (Coleoptera: Nitidulidae). These compounds are (2E,4E,6E,8E)-3,5,7-trimethyl-2,4,6,8-decatetraene, (2E,4E,6E,8E)-3,5,7-trimethyl-2,4,6,8-undecatetraene, (2E,4E,6E,8E)-7-ethyl-3,5-dimethyl-2,4,6,8-decatetraene, and (2E,4E,6E,8E)-7-ethyl-3,5-dimethyl-2,4,6,8-undecatetraene. The general synthetic scheme starts with tiglic aldehyde, (E)-2-methyl-2-butenal, extends the carbon chain with two Wittig–Horner olefinations, and completes the chain with a Wittig reaction. Lithium aluminum hydride reductions and manganese dioxide partial oxidations are used to prepare the intermediates for the subsequent chain extensions. The incorporation of methyl or ethyl side chains is controlled by the choice of the Wittig–Horner reagent, triethyl 2-phosphonopropionate or triethyl 2-phosphonobutyrate, respectively. After distillation of the final products, the all-E 3,5,7-trimethyl tetraenes were produced in 83–84% purity and 40–42% overall yield and the all-E 7-ethyl-3,5-dimethyl tetraenes in 71–73% purity and 20–25% overall yield from tiglic aldehyde.

Insect pheromones have become important and highly specific tools for monitoring and controlling pest species. It is important for synthetic pheromones to be available for practical applications because only minute amounts of the natural compounds are present in insects, and these chemicals would be prohibitively expensive to obtain from them on a large scale. A new class of compounds was recently discovered in two economically important species of beetles in the family Nitidulidae. The aggregation pheromone of the driedfruit beetle, *Carpophilus hemipterus* (L.), was found to include two novel tetraene hydrocarbons (Scheme I, structures 1 and 2) (Bartelt et al., 1990a), and the dusky sap beetle, *C. lugubris* Murray, was found to use the related tetraene 4 as its pheromone (Bartelt et al., 1990b). Further work with *C. hemipterus* revealed that tetraene 3 is also present and is biologically active (Bartelt et al., unpublished results). As outlined briefly by Bartelt et al. (1990a), analytical samples of tetraenes 1 and 2 had been synthesized previously by two different approaches to aid in proving these structures. The present paper gives details for the more successful and general of these approaches, which also allows incorporation of ethyl side chains to make 3 and 4. The scheme is suitable for gram-scale synthesis and makes these potent attractants available for field evaluation.

EXPERIMENTAL PROCEDURES

Spectra. For NMR spectroscopy, all samples were dissolved in C_6D_6. (The tetraenes, especially, showed a tendency to polymerize or degrade in $CDCl_3$, probably because acid was present.) All spectra were recorded on a Bruker WM 300-MHz WB spectrometer. Chemical shifts are reported in parts per million from tetramethylsilane with the residual proton resonance of C_6D_6 as an internal reference for protons (7.20 ppm) and the center ^{13}C resonance of C_6D_6 as an internal reference for ^{13}C (128.0 ppm). The same 5-mm $^1H/^{13}C$ dual probe was used for both proton and carbon observation. The DEPT experiment (Doddrell et al., 1982) was used to obtain the proton multiplicities of each carbon. The proton spectra reported in the literature for 6a–c (Jones et al., 1977), 7a (Venkataraman and Cha, 1987), and 7c (Patel and Pattenden, 1985) differ some-

Scheme I[a]

a: R = COOEt
b: R = CH_2OH
c: R = CHO
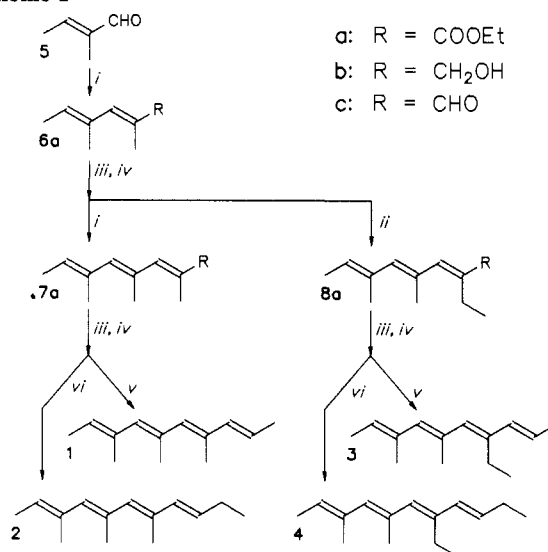
[a] Key: (i) TEPP, BuLi, THF, RT; (ii) TEPB, BuLi, THF, 65 °C; (iii) LiAlH₄, ether, 0 °C to RT; (iv) MnO₂, CH₂Cl₂, RT; (v) (ethylidene)triphenylphosphorane, THF, RT; (vi) (propylidene)triphenylphosphorane, THF, RT. Functional group conversions: iii produces the alcohols 6b, 7b, and 8b; iv produces the aldehydes 6c, 7c, and 8c.

what in chemical shift from those included here because of solvent differences.

All carbon and proton resonances were assigned for tetraenes 1–4 (Table I). The proton assignments for 3 were made by analogy to 1, 2, and 4, which had been assigned previously (Bartelt et al., 1990a,b). The heteronuclear correlation experiment (Bax and Morris, 1981) was used to assign the shifts for those carbons with attached hydrogens. Assignments of the remaining quaternary carbons (3, 5, and 7) were based on the additivity rules for shifts of alkene carbons (Pretsch et al., 1983, p C90). Proton spectra of tetraene samples were usually obtained with approximately 2 mg of solute dissolved in 0.35 mL of solvent, but samples for carbon analysis contained approximately 100 mg of solute dissolved in 0.35 mL of solvent. Proton shifts for the more concentrated solutions differed from those of the dilute samples by as much as 0.05 ppm, but no

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Table I. Assignments of Carbon-13 and Proton Shifts in Tetraenes 1-4

	^{13}C shift, ppm				^1H shift, ppm			
	1	2	3	4	1[a]	2[a]	3	4[b]
carbon no. in chain								
1	13.9	13.9	13.9	13.9	1.64	1.64	1.64	1.64
2	124.8	124.8	124.9	124.9	5.52	5.53	5.54	5.53
3	132.4	132.4	132.6	132.5				
4	134.9	134.9	134.0	134.0	6.03	6.04	6.11	6.09
5	133.7[c]	133.7[c]	133.9	133.9				
6	134.9	135.2	134.2	134.5	6.03	6.06	6.00	6.02
7	133.9[c]	133.9[c]	140.0	140.0				
8	137.7	135.6	136.2	134.0	6.25	6.27	6.11	6.11
9	123.4	130.5	123.0	130.2	5.63	5.71	5.68	5.76
10	18.5	26.5	18.6	26.6	1.73	2.12	1.73	2.11
11		14.3		14.2		1.03		1.02
methyl branches								
3-methyl	16.9	16.9	16.9	16.9	1.74	1.75	1.74	1.75
5-methyl	19.3	19.3	19.0	19.0	1.98	1.99	2.00	2.00
7-methyl	14.4	14.5			2.00	2.00		
7-ethyl branch								
methylene			21.3	21.3			2.57	2.58
methyl			14.9	14.9			1.19	1.20

[a] Data from Bartelt et al. (1990a). [b] Data from Bartelt et al. (1990b). [c] These assignments may be reversed.

changes in the ^{13}C spectra were observed due to concentration. The proton data reported in Table I are for dilute solutions.

IR spectra of neat samples on KBr plates were taken with a Mattson Galaxy 6020 FTIR at 1-cm⁻¹ resolution. UV spectra were taken in ethanol by using a Perkin-Elmer Lambda 4B UV-vis spectrophotometer; concentrations were about 10^{-4} M, and the scanning range was 200–350 nm. Positive ion electron impact mass spectra were taken at 70 eV; sample introduction was always through a 15 m × 0.25 mm DB-1 capillary column. Mass spectra were run either on a Finnigan 4535 quadrupole mass spectrometer or on a Hewlett-Packard 5970 mass spectrometer. Except where otherwise indicated, the IR and mass spectra for 6a–c reported by Jones et al. (1977) agree well with the spectra reported here.

Gas Chromatography. All reactions were monitored by gas chromatography; a Varian 3700 GC, equipped with a 15 m × 0.25 mm DB-1 capillary column (1.0-μm film thickness) and a splitless injector, was interfaced to a Hewlett-Packard 3396A integrator. The temperature program was 100–200 °C at 10 °C/min or 50 °C for 2 min and then 10 °C per min to 180 °C. Retention indices were calculated for all compounds relative to n-alkanes as described by Poole and Schuette (1984, pp 24–25).

Reagents. Unless otherwise indicated, reagents were obtained from Aldrich Chemical Co. (Milwaukee, WI) and were used without purification. Methylene chloride (Baker, HPLC grade) was dried over molecular sieves (4A). Ether was dried over sodium metal. Tetrahydrofuran (THF) was tested to ensure that peroxides were absent, and then it was used without purification; traces of water were removed by excess base in reactions. Triethyl 2-phosphonopropionate (TEPP) was either purchased commercially or prepared by the Arbuzov reaction from ethyl 2-bromopropionate and triethyl phosphite as described by Gallagher and Webb (1974) (98% purity, by GC). Triethyl 2-phosphonobutyrate (TEPB) was prepared analogously. Propyltriphenylphosphonium iodide was prepared in the usual way by refluxing propyl iodide and triphenylphosphine in acetonitrile.

Ethyl (2E,4E)-2,4-Dimethyl-2,4-hexadienoate (6a). TEPP (24 g, 0.10 mol) was added to 100 mL of THF and a few milligrams of ethyltriphenylphosphonium bromide (used as a base indicator), and the mixture was cooled over ice. A nitrogen atmosphere was introduced. Butyllithium (2.5 M in hexane) was added slowly (keeping the temperature below 10 °C) until a permanent color change occurred (43 mL required; 40 mL expected). Tiglic aldehyde (5) (7.5 g, 0.09 mol) was added slowly, keeping the temperature below 10 °C, and then the mixture was allowed to warm to room temperature and was stirred for 2 h. Hexane and water (100 mL each) were added and the layers separated. The aqueous layer was washed with 50 mL of hexane (3×), and then the combined organic layers were washed with 100 mL of water (3×) and dried over Na₂SO₄. After rotary evap-

oration of solvent, the product was distilled (Kugelrohr, 0.5 Torr, 80 °C oven temperature) to afford 13.4 g of colorless liquid. By GC, purity was 89% (79% overall yield of the desired isomer): ¹H NMR δ 1.13 (3 H, t, J = 7.1), 1.59 (3 H, d, J = 7.0), 1.69 (3 H, dd, J = 1.1, 1.1), 1.94 (3 H, d, J = 1.2), 4.07 (2 H, q, J = 7.1), 5.56 (1 H, q, J = 7.0), 7.12 (1 H, br s); ¹³C NMR δ 13.9, 14.1, 14.5, 15.9 (CH₃), 60.4 (CH₂O), 130.6, 142.7 (CH=), 125.5, 133.5 (>C=), 168.2 (COO); IR 2981, 2933, 2862, 1707 (C=O), 1627, 1446, 1366, 1255, 1119, 1038, 748 cm⁻¹; UV λmax 270.5 nm; MS, m/z (% base) 168 (M⁺, 39), 153 (55), 140 (2), 139 (5), 125 (100), 123 (25), 111 (10), 95 (50), 93 (17), 79 (31), 77 (19), 67 (25), 55 (20), 53 (13), 43 (28), 41 (18) [Both of our instruments gave this mass spectrum, but it differed from that of Jones et al. (1977), especially in the intensities at m/z 153, 140, and 125. By tandem MS/MS, the unexpected base peak at m/z 125 (M − 43) was formed in two stages: first by loss of 15 mass units (CH₃) from the parent ion to produce the m/z 153 ion and then by loss of 28 mass units (C₂H₄) to form m/z 125. In the spectrum of Jones et al. (1977), loss of C₂H₄ directly from the parent ion was more prominent; m/z 140 had an intensity of 32%.]; GC retention index 12.31, minor isomers 11.40 (4%), 11.59 (3%).

(2E,4E)-2,4-Dimethyl-2,4-hexadien-1-ol (6b). LiAlH₄ (1.0 M solution in ether, 70 mL, 0.070 mol) was chilled over ice in a nitrogen atmosphere. Distilled product 6a [13.3 g, containing 11.8 g (0.070 mol) of the E,E isomer] was diluted with 10 mL of ether and was added over 25 min, keeping the temperature below 15 °C. The mixture was stirred for 4 h at room temperature and then chilled over ice. Excess reagent was decomposed by adding water, dropwise at first, keeping the temperature below 15 °C. A total of 30 mL of water and then 30 mL of 20% NaOH were added. The solution was decanted from the white pasty residue and the residue triturated with 15 mL of ether (3×). The combined organic layers were dried overnight over MgSO₄. After filtering and rotary evaporation, 10.4 g of colorless oil was recovered (88% purity, by GC): ¹H NMR δ 1.60 (3 H, d, J = 6.9), 1.71 (3 H, s), 1.80 (3 H, d, J = 0.9), 4.01 (2 H, br s), 4.60 (1 H, v br s), 5.42 (1 H, q, J = 6.9), 5.98 (1 H, br s); ¹³C NMR δ 13.7, 15.4, 16.6 (CH₃), 68.9 (CH₂O), 124.1, 129.3 (CH=), 133.6, 134.5 (>C=); IR 3327 (OH), 2979, 2916, 2860, 1442, 1379, 1068, 1009, 876, 515 cm⁻¹; UV λmax 231.3 nm; MS, m/z (% base) 126 (M⁺, 42), 111 (29), 108 (5), 97 (37), 93 (35), 91 (27), 84 (28), 83 (33), 77 (32), 69 (39), 55 (100), 43 (81), 41 (76); GC retention index 10.58, minor isomers 10.10 (3%), 10.28 (4%).

(2E,4E)-2,4-Dimethyl-2,4-hexadienal (6c). MnO₂ (activated, 50 g), product 6b (10.2 g from the previous reaction, containing 9.0 g of the E,E isomer), and methylene chloride (500 mL) were stirred at room temperature. The reaction was monitored by GC and was 90% complete after 3.5 h. However, no further change occurred. An additional 10 g of MnO₂ was added and within 0.5 h, the reaction was complete. The product was filtered and dried over MgSO₄, and the solvent was re-

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moved by rotary evaporation. The resulting yellow oil (9.4 g, 89% purity by GC) was used directly in the subsequent reactions: ^{1}H NMR δ 1.59 (3 H, d, J = 7.0), 1.74 (3 H, dd, J = 1.1, 1.1), 1.84 (3 H, br s), 5.75 (1 H, q, J = 7.0), 6.50 (1 H, br s), 9.29 (1 H, s); ^{13}C NMR δ 10.6, 14.2, 15.5 (CH$_3$), 135.1, 154.1 (CH=), 134.3, 134.3 (>C=), 195.0 (CHO); IR 2974, 2930, 2859, 2710 (CHO), 1686 (C=O), 1623, 1443, 1390, 1194, 1016, 693, 524 cm^{-1}; UV λ_{max} 280.6 nm; MS, m/z (% base) 124 (M$^+$, 9), 109 (100), 95 (2), 91 (3), 81 (17), 79 (21), 77 (7), 67 (10), 55 (9), 53 (12), 41 (17); GC retention index 10.68, minor isomers 9.77 (2%), 9.88 (1%), 10.02 (1%).

Ethyl (2E,4E,6E)-2,4,6-Trimethyl-2,4,6-octatrienoate (7a). The procedure was as described for ester **6a**; 5.0 g of product **6c** [containing 4.5 g (0.037 mol) of the *E,E* aldehyde] and 0.042 mol of TEPP were used. After distillation (Kugelrohr, 0.09 Torr, 75 °C oven temperature), 6.5 g of crude **7a** was recovered as a colorless oil. The purity of **7a** was 83% by GC. From the *E,E* isomer in distilled product **6a**, the calculated yield of ester **7a** was 70%: ^{1}H NMR δ 1.11 (3 H, t, J = 7.1), 1.59 (3 H, d, J = 7.0), 1.65 (3 H, br s), 1.87 (3 H, d, J = 1.0), 2.05 (3 H, d, J = 1.4), 4.11 (2 H, q, J = 7.1), 5.43 (1 H, q, J = 7.0), 5.98 (1 H, br s), 7.32 (1 H, br s); ^{13}C NMR δ 13.8, 14.4, 14.5, 14.5, 16.5, 18.3 (CH$_3$), 60.5 (CH$_2$), 126.9, 139.3, 143.9 (CH=), 126.2, 131.4, 133.5 (>C=), 168.4 (COO); IR 2981, 2931, 2860, 1705 (C=O), 1613, 1446, 1366, 1252, 1114, 1033, 749, 521 cm^{-1}; UV λ_{max} 295.4 nm [lit. 298 nm, (Venkataraman and Cha, 1987)]; MS, m/z (% base) 208 (M$^+$, 5), 179 (8), 161 (9), 135 (100), 119 (51), 105 (23), 91 (27), 79 (13), 77 (15), 65 (7), 55 (8), 43 (14), 41 (19); GC retention index 15.34, minor isomer 14.79 (2%).

(2E,4E,6E)-2,4,6-Trimethyl-2,4,6-octatrien-1-ol (7b). The procedure was as described for **6b**. Distilled product **7a** (6.0 g, containing 5.0 g of the *E,E,E* ester) yielded 5.0 g of colorless alcohol **7b** after removal of solvent (87% purity by GC). The product was used directly in the next reaction: ^{1}H NMR δ 1.63 (3 H, d, J = 6.9), 1.72 (3 H, br s), 1.86 (3 H, d, J = 1.1), 1.94 (3 H, br s), 3.80 (1 H, v br s), 4.04 (2 H, br s), 5.46 (1 H, q, J = 6.9), 5.93 (1 H, br s), 6.08 (1 H, br s); ^{13}C NMR δ 13.8, 15.6, 16.9, 19.0 (CH$_3$), 69.0 (CH$_2$OH), 124.5, 130.1, 134.2 (CH=), 132.1, 133.9, 135.4 (>C=); IR 3328 (OH), 2977, 2915, 2858, 1442, 1379, 1069, 1010, 895, 520 cm^{-1}; UV λ_{max} 261.9 nm; MS, m/z (% base) 166 (M$^+$, 6), 151 (2), 148 (2), 135 (100), 119 (40), 105 (28), 93 (35), 91 (42), 79 (22), 77 (26), 67 (19), 65 (15), 55 (20), 53 (18), 43 (30), 41 (43); GC retention index 13.64, minor isomer 13.25 (2%).

(2E,4E,6E)-2,4,6-Trimethyl-2,4,6-octatrienal (7c). The procedure was as described for **6c**. Product **7b** (2.5 g, containing 2.2 g of the *E,E,E* alcohol) was stirred with 15 g of MnO$_2$ and yielded 2.5 g of aldehyde **7c** as a yellow oil after 3.3 h. By GC, purity was 93%: ^{1}H NMR δ 1.59 (3 H, d, J = 6.9), 1.66 (3 H, br s), 1.89 (3 H, br s), 1.92 (3 H, br s), 5.49 (1 H, q, J = 6.9), 6.07 (1 H, br s), 6.47 (1 H, br s), 9.37 (1 H, s); ^{13}C NMR δ 10.9, 13.9, 16.4, 17.8 (CH$_3$), 128.6, 142.5, 155.0 (CH=), 131.9, 133.5, 136.2 (>C=), 194.7 (CHO); IR 2966, 2923, 2858, 2710, 1678 (C=O), 1603, 1440, 1387, 1193, 1023, 913, 699, 528 cm^{-1}; UV λ_{max} 313.4 nm [markedly different from literature value, 282 nm (Patel and Pattenden, 1985)]; MS, m/z (% base) 164 (M$^+$, 28), 149 (28), 135 (100), 121 (47), 119 (44), 109 (36), 105 (69), 91 (74), 79 (48), 77 (46), 65 (24), 53 (31), 41 (66); GC retention index 13.77, minor isomer 13.17 (2%).

Ethyl (2E,4E,6E)-2-Ethyl-4,6-dimethyl-2,4,6-octatrienoate (8a). The Wittig–Horner reagent was prepared in THF (40 mL) as for **6a** except that TEPB (8.4 g, 0.033 mol) was used instead of TEPP. Upon permanent color change of the indicator with the addition of butyllithium, aldehyde **6c** [4.1 g, containing 3.7 g (0.030 mol) of the *E,E* isomer] was added in one portion and the mixture heated to reflux. The reaction was monitored by GC, and aldehyde **6c** was consumed within 1.8 h. Workup was as before. After distillation (Kugelrohr, 0.08 Torr, 75 °C oven temperature) 7.3 g of colorless product was obtained, and the purity was 64% by GC. From the *E,E* isomer in distilled product **6a**, the calculated yield of **8a** was 56%: ^{1}H NMR δ 1.11 (6 H, t, J = 7.2), 1.58 (3 H, d, J = 6.9), 1.65 (3 H, br s), 1.88 (3 H, d, J = 0.8), 2.57 (2 H, q, J = 7.4), 4.10 (2 H, q, J = 7.1), 5.42 (1 H, q, J = 6.9), 6.02 (1 H, br s), 7.29 (1 H, br s); ^{13}C NMR δ 13.8, 14.4, 15.0, 16.5, 17.9 (CH$_3$), 21.4 (CH$_2$), 60.3 (CH$_2$O), 126.9, 138.6, 143.5 (CH=), 131.4, 132.6, 133.5 (>C=), 168.0 (COO); IR 2978, 2935, 2876, 1706 (C=O), 1608, 1446, 1379, 1235, 1127, 1027, 762

cm^{-1}; UV λ_{max} 291.3 nm; MS, m/z (% base) 222 (M$^+$, 5), 207 (2), 193 (15), 175 (9), 161 (6), 149 (75), 133 (33), 121 (100), 105 (34), 91 (25), 79 (11), 77 (13), 65 (5), 55 (6), 41 (10); GC retention index 15.68, minor isomer 14.93 (15%). TEPB was also present after distillation (7%).

(2E,4E,6E)-2-Ethyl-4,6-dimethyl-2,4,6-octatrien-1-ol (8b). The reaction was carried out as described for **6b**. Distilled ester **8a** (5.5 g, containing 3.5 g of the *E,E,E* isomer) afforded alcohol **8b** (4.0 g) as a colorless oil after removal of solvent (purity 72% by GC): ^{1}H NMR δ 1.07 (3 H, t, J = 7.5), 1.62 (3 H, d, J = 6.9), 1.72, (3 H, br s), 1.94 (3 H, d, J = 0.9), 2.37 (2 H, q, J = 7.5), 3.87 (1 H, v br s), 4.12 (2 H, d, J = 1.2), 5.46 (1 H, q, J = 6.9), 5.96 (1 H, br s), 6.08 (1 H, br s); ^{13}C NMR δ 13.8, 13.9, 16.9, 18.8 (CH$_3$), 22.4 (CH$_2$), 66.6 (CH$_2$OH), 124.6, 130.1, 133.5 (CH=), 132.1, 133.8, 141.2 (>C=); IR 3327 (OH), 2965, 2933, 2874, 1647, 1443, 1377, 1080, 1019, 898, 532 cm^{-1}; UV λ_{max} 260.0 nm; MS, m/z (% base) 180 (M$^+$, 6), 165 (2), 162 (4), 149 (68), 133 (16), 121 (100), 105 (45), 93 (42), 91 (38), 79 (22), 67 (16), 55 (18), 41 (19); GC retention index 14.25, minor isomer 14.07 (15%).

(2E,4E,6E)-2-Ethyl-4,6-dimethyl-2,4,6-octatrienal (8c). The reaction was performed as described for **6c**. Crude alcohol **8b** (2.5 g, containing 1.8 g of the *E,E,E* isomer) was converted to aldehyde **8c**, a yellow oil (2.4 g, purity 77% by GC): ^{1}H NMR δ 0.97 (3 H, t, J = 7.4), 1.63 (3 H, d, J = 7.1), 1.70 (3 H, br s), 1.98 (3 H, br s), 2.42 (2 H, q, J = 7.4), 5.51 (1 H, q, J = 6.9), 6.15 (1 H, br s), 6.53 (1 H, br s), 9.27 (1 H, s); ^{13}C NMR δ 14.0, 14.5, 16.4, 17.3 (CH$_3$), 18.5 (CH$_2$), 129.0, 142.7, 155.1 (CH=), 131.0, 131.7, 133.6 (>C=), 195.0 (CHO); IR 2966, 2935, 2875, 2710, 1681 (C=O), 1604, 1441, 1380, 1184, 1058, 805, 515 cm^{-1}; UV λ_{max} 312.8 nm; MS, m/z (% base) 178 (M$^+$, 43), 163 (36), 149 (60), 135 (24), 121 (100), 107 (63), 105 (56), 91 (57), 79 (34), 77 (31), 65 (13), 55 (16), 41 (21); GC retention index 14.28, minor isomer 14.07 (8%).

(2E,4E,6E,8E)-3,5,7-Trimethyl-2,4,6,8-decatetraene (1). Ethyltriphenylphosphonium bromide (3.4 g, 0.0091 mol) was slurried in THF (20 mL) and chilled over ice. Butyllithium (2.5 M in hexane) was added, under nitrogen, until the orange color persisted, and then an additional 3.6 mL (0.0091 mol) was added slowly, keeping the temperature below 10 °C. After stirring 5 min longer, crude aldehyde **7c** [1.5 g, containing 1.4 g (0.0085 mol) of the *E,E,E* isomer] was added dropwise, keeping the temperature below 10 °C. The mixture was allowed to warm to room temperature and was stirred for 1.5 h. Workup entailed dilution with 40 mL of hexane, addition of 40 mL of water, and separation of layers. The aqueous layer was washed three times with hexane, and the combined organic layers were washed three times with water. The mixture was dried over MgSO$_4$, and the solvent was removed by rotary evaporation. The product was passed through a 8 cm × 1 cm column of silica gel with hexane, and the solvent was again removed, affording a pale yellow oil (1.22 g). A portion of the product (0.51 g) was distilled (Kugelrohr, 0.060 Torr, 57 °C oven temperature) to give 0.46 g of a colorless oil (purity 84% after distillation, by GC). The calculated yield of **1** from the *E,E,E* isomer of distilled ester **7a** was 73% and overall from tiglic aldehyde (**5**), 40%. The proton NMR and mass spectra were as reported previously (Bartelt et al., 1990a): ^{13}C NMR data are presented in Table I; IR 3022, 2958, 2929, 2914, 2858, 1444, 1378, 1018, 961 (*E*, CH=CH), 897, 780, 520 cm^{-1}; UV λ_{max} 287.0, 222.8 nm (minor); GC retention index 13.83, minor isomer (2E,4E,6E,8Z) 13.26 (7%).

(2E,4E,6E,8E)-3,5,7-Trimethyl-2,4,6,8-undecatetraene (2). The reaction was performed as for **1** except that propyltriphenylphosphonium iodide was employed as the Wittig salt. Aldehyde **7c** (0.75 g, containing 0.70 g of the *E,E,E* isomer) afforded 0.67 g of crude tetraene **2** after silica gel chromatography. Recovery was 95% after distillation (Kugelrohr, 0.050 Torr, 65 °C oven temperature). By GC, the purity of **2** was 83%. Calculated yields were 76% from the *E,E,E* isomer in distilled ester **7a** and 42% from starting material **5**: proton NMR and mass spectra were as reported previously (Bartelt et al., 1990a); ^{13}C NMR data are presented in Table I; IR 3014, 2963, 2932, 2916, 2872, 2859, 1442, 1379, 1025, 961 (*E*, CH=CH), 898, 518 cm^{-1}; UV λ_{max} 288.5, 224.0 nm (minor); GC retention index 14.76, minor isomer (2E,4E,6E,8Z) 14.02 (4%).

Nitidulid Pheromone Synthesis

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(2E,4E,6E,8E)-7-Ethyl-3,5-dimethyl-2,4,6,8-decatetraene (3). Conditions were as for 1. Aldehyde 8c (0.50 g, containing 0.39 g of the E,E,E isomer) afforded 0.35 g of crude tetraene 3 after silica gel chromatography. Recovery from distillation was 93% (Kugelrohr, 0.06 Torr, 62 °C oven temperature). By GC, purity of the distilled product 3 was 73%. Calculated yields were 59% from the E,E,E isomer in distilled ester 8a and 25% from starting material 5: ^{1}H NMR δ 1.19 (3 H, t, J = 7.5), 1.64 (3 H, t, J = 6.9), 1.73 (3 H, dd, J = 6.7, 1.5), 1.74 (3 H, d, J = 1.5), 2.00 (3 H, d, J = 1.0), 2.57 (2 H, q, J = 7.5), 5.54 (1 H, qqd, J = 6.9, 1.2, 1.2), 5.68 (1 H, dq, J = 15.6, 6.6), 6.00 (1 H, s), 6.11 (1 H, br s), 6.11 (1 H, dm, J = 15.6, ~1); ^{13}C NMR data are presented in Table I; IR 2965, 2933, 2914, 2875, 2858, 1448, 1376, 963 (E, CH=CH), 898, 517 cm^{-1}; UV λ$_{max}$ 286.8, 226.3 nm (minor); MS, m/z (% base) 190 (M$^+$, 49), 175 (29), 161 (74), 147 (14), 133 (100), 119 (88), 108 (13), 107 (28), 105 (52), 93 (27), 91 (47), 83 (12), 79 (20), 77 (25), 69 (16), 65 (15), 55 (68), 43 (5), 41 (54); GC retention index 14.28, minor isomer (2E,4E,6E,8Z) 13.68 (15%).

(2E,4E,6E,8E)-7-Ethyl-3,5-dimethyl-2,4,6,8-undecatetraene (4). Conditions were as for 2. Aldehyde 8c (1.0 g, containing 0.77 g of the E,E,E isomer) afforded 0.64 g of crude tetraene 4 after silica gel chromatography, and recovery from distillation was 88% (Kugelrohr, 0.07 Torr, oven temperature 62 °C). Purity was 71% by GC. Calculated yields were 52% from the E,E,E isomer in distilled ester 8a and 20% from starting material 5: proton NMR and mass spectra were as reported earlier (Bartlet et al., 1990b); ^{13}C NMR data are presented in Table I; IR 3013, 2964, 2933, 2874, 2859, 1453, 1376, 962 (E, CH=CH), 899, 515 (cm^{-1}; UV λ$_{max}$ 287.0, 227.2 nm (minor); GC retention index 15.15, minor isomer (2E,4E,6E,8Z) 14.41 (10%).

RESULTS AND DISCUSSION

The synthesis is outlined in Scheme I. The carbon chain is built from tiglic aldehyde (5) by two Wittig–Horner reactions (Boutagy and Thomas, 1974; Gallagher and Webb, 1974) and then is terminated with a Wittig reaction, according to the method of Sonnet (1974). Each Wittig–Horner condensation produces an ester that is sequentially reduced to an alcohol with LiAlH$_4$ and then oxidized to the corresponding aldehyde with activated MnO$_2$ (Fatiadi, 1976), thereby preparing the intermediate for the next chain extension. Either methyl or ethyl side chains can be introduced, depending on whether TEPP or TEPB is used as the Wittig–Horner reagent (although different reaction temperatures are required for these).

Wittig–Horner olefinations are known to be predominantly E directed (Boutagy and Thomas, 1974). This was the case with the present compounds also because the final tetraenes were spectrally and chromatographically identical with standards of 1, 2, and 4 on which the all-E configuration had been confirmed by nuclear Overhauser experiments (Bartlet et al., 1990a,b). The Wittig reaction, used for the final step, normally produces predominantly Z double bonds from unstabilized ylides [discussed by March (1985)]. However, with the triene aldehydes 7c and 8c, the reaction produces E double bonds stereoselectively, as evidenced by the large coupling constants (15.4–15.7 Hz) between olefinic protons in the NMR spectra and by the strong IR bands at 961–963 cm^{-1} in the major products.

Overall yields of the desired all-E isomers for the seven-step procedure were 40–42% for the 3,5,7-trimethyl tetraenes, and purities of the distilled products were 83–84%. For the 7-ethyl-3,5-dimethyl tetraenes, overall yields of the all-E isomers were 20–25% and the purities after distillation, 71–73%. The synthetic tetraenes have been stored in the freezer diluted ca. 5:1 with pentane for nearly a year without evidence of degradation.

Byproducts and side reactions were not a serious problem with the scheme. A small amount of Z isomer was formed during each Wittig–Horner reaction (evidenced by shorter GC retentions but almost identical mass spectra, compared with the E isomer). Fortunately, the proportion of these (unwanted) isomers always decreased during the subsequent reduction and oxidation steps (see Experimental Procedures). Apparently, the reaction conditions allowed some isomerization of double bonds, and the thermodynamically more stable E configuration became more abundant. Residual starting materials could be avoided in the products of the Wittig–Horner reaction by using a 5–10% excess of phosphonate reagent relative to the aldehyde. While residual aldehyde would be difficult to remove, any excess TEPP or TEPB disappeared upon workup with water and/or in the subsequent reduction step with LiAlH$_4$. The major impurity in all final tetraene products was the E,E,E,Z isomer (4–15%), formed in the Wittig reaction. For tetraene 1, for example, this impurity had a mass spectrum almost identical with that of 1 but had a coupling constant between olefinic protons of 11.6 Hz in the NMR spectrum.

The base and solvent used for the Wittig–Horner reaction affected product quality. Two combinations of base and solvent were compared: butyllithium with tetrahydrofuran (THF) and NaOEt with ethanol. The latter pair was less satisfactory because it led to a greater number of minor products and side reactions (six GC peaks of >1% the area of that for 6a, versus just two for butyllithium and THF). Also, butyllithium was a strong enough base so that a salt such as ethyltriphenylphosphonium bromide could be used as color indicator for complete deprotonation of the phosphonate. Finally, the refluxing temperature of THF was adequate to smoothly drive the reaction with TEPB (to form ester 8a). Thus, this base–solvent pair worked well regardless of whether a methyl or ethyl side chain was being added.

The tetraenes were never seen to crystallize or solidify at any temperature; during distillation the receiver flask was kept at dry-ice temperature, but no solid formed. As an alternative to crystallization, the tetraenes can be purified by HPLC on a AgNO$_3$-coated silica column (Bartelt et al., 1990a; Heath and Sonnet, 1980), although this procedure would be impractical for large batches. The isomers with Z double bonds appear to be biologically inert, in any case; thus, further purification of the tetraene products is probably unnecessary for field use. Alcohols 7b and 8b did crystallize from hexane at −10 °C, and purification at this stage should be possible, if desired.

The other, previous, approach for making these tetraenes was to couple a monounsaturated Wittig salt (such as that from 4-bromo-2-pentene) with aldehyde 6c, creating the double bond in the 6-position as the final reaction (Bartelt et al., 1990a). This approach was less satisfactory than that in Scheme I for several reasons: Yields of the unsaturated phosphonium salts were low, allylic rearrangement of the salts was a problem (for example, the salt intended for making 2 also produced 3), and the final Wittig reaction created both E and Z isomers of the 6-position double bond in about equal proportions.

Six of the intermediates (6a–c and 7a–c) are previously known compounds (Patel and Pattenden, 1985; Venkataraman and Cha, 1987; Jones et al., 1977), but reagents used in their preparation differed somewhat from those reported here. Patel and Pattenden (1985) and Venkataraman and Cha (1987) used (carbethoxyethylidene)-triphenylphosphorane as the reagent to form 6a and 7a, but the reaction required 48 h at the reflux temperature of methylene chloride (Patel and Pattenden, 1985). The more reactive phosphonate anion from TEPP produced complete reaction within 2 h at room temperature. Three

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different oxidizing agents have been used to prepare the aldehydes: activated manganese dioxide (Patel and Pattenden, 1985; Venkataraman and Cha, 1987), pyridinium chlorochromate (Jones et al., 1977), and the periodinane reagent of Dess and Martin (1983) (Bartelt et al., 1990a). While all three were satisfactory, MnO_2 is readily available in activated form, is easy to use, and is very selective for allylic alcohols. Despite the need to use a large (ca. 6-fold) molar excess of reagent, it was the reagent of choice in this synthesis.

LITERATURE CITED

Bartelt, R. J.; Dowd, P. F.; Plattner, R. D.; Weisleder, D. Aggregation Pheromone of Driedfruit Beetle, *Carpophilus hemipterus*: Wind-Tunnel Bioassay and Identification of Two Novel Tetraene Hydrocarbons. *J. Chem. Ecol.* **1990a,** *16,* 1015–1039.

Bartelt, R. J.; Dowd, P. F.; Plattner, R. The Aggregation Pheromone of *Carpophilus lugubris*: Toward New Pest Management Tools for the Nitidulid Beetles. In *Naturally Occurring Pest Bioregulators*; Hedin, P. A., Ed.; American Chemical Society: Washington, DC, 1990b, in press.

Bax, A.; Morris, G. A. An Improved Method for Heteronuclear Chemical Shift Correlation by Two-Dimensional NMR. *J. Magn. Reson.* **1981,** *42,* 501–505.

Boutagy, J.; Thomas, R. Olefin Synthesis with Organic Phosphonate Carbanions. *Chem. Rev.* **1974,** *74,* 87–99.

Dess, D. B.; Martin, J. C. Readily Accessible 12-I-5 Oxidant for the Conversion of Primary and Secondary Alcohols to Aldehydes and Ketones. *J. Org. Chem.* **1983,** *48,* 4155–4156.

Doddrell, D. M.; Pegg, D. T.; Bendall, M. R. Distortionless Enhancement of NMR Signals by Polarization Transfer. *J. Magn. Reson.* **1982,** *48,* 323–327.

Fatiadi, A. J. Active Manganese Dioxide Oxidation in Organic Chemistry: Part I. *Synthesis* **1976,** 65–104.

Gallagher, G., Jr.; Webb, R. L. Tetrasubstituted Acrylates: The Wittig-Horner Reaction of Ketones with Triethyl 2-Phosphonopropionate. *Synthesis* **1974,** 122–124.

Heath, R. R.; Sonnet, P. E. Technique for in situ Coating of Ag^+ onto Silica Gel in HPLC Columns for the Separation of Geometical Isomers. *J. Liq. Chromatogr.* **1980,** *3,* 1129–1135.

Jones, T. H.; Meinwald, J.; Hicks, K.; Eisner, T. Characterization and Synthesis of Volatile Compounds from the Defensive Secretions of Some "Daddy Longlegs" (Arachnida: Opiliones: *Leiobunum* spp.). *Proc. Natl. Acad. Sci. U.S.A.* **1977,** *74,* 419–422.

March, J. *Advanced Organic Chemistry,* 3rd ed.; Wiley: New York, 1985; pp 845–854.

Patel, P.; Pattenden, G. Natural Polyene alpha-Pyrones: Total Synthesis of Citreomontanin from *Penicillium pedomontanum. Tetrahedron Lett.* **1985,** *26,* 4789–4792.

Poole, C. F.; Schuette, S. E. *Contemporary Practice of Chromatography*; Elsevier: Amsterdam, 1984; 708 pp.

Pretsch, E.; Seibl, J.; Simon, W.; Clerc, T. *Tables of Spectral Data for Structure Determination of Organic Compounds*; Springer-Verlag: Berlin 1983.

Sonnet, P. E. *cis*-Olefins from the Wittig Reaction. *Org. Prep. Proc. Int.* **1974,** *6,* 269–273.

Venkataraman, H.; Cha, J. K. Total Synthesis of Citreomontanin and Its $C_{18}Z$ Polyene Isomer. *Tetrahedron Lett.* **1987,** *28,* 2455–2458.