Tetrahedron. Vol. 34, pp. 1385 to 1388. Pergamon Press 1978. Printed in Great Britain

PHEROMONE SYNTHESIS—II†

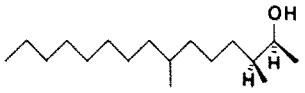
PREPARATION OF PINE SAWFLY (*HYMENOPTERA: DIPRIONIDAE*) SEX ATTRACTANTS AND ANALOGUES WITH POSSIBLE BIOLOGICAL ACTIVITY‡

GÖRAN MAGNUSSON
Organic Chemistry 2, Chemical Center, The Lund Institute of Technology, S-220 07 Lund 7, Sweden

(*Received in UK* 20 *October* 1977; *Accepted for publication* 31 *October* 1977)

Abstract—The pine sawfly pheromones, *erythro*-3,7-dimethylpentadecan-2-ol acetate and propionate, as well as the *threo*- and other analogues have been prepared by a stereospecific route for structure-activity tests.

Simple esters of *erythro* - 3,7 - dimethylpentadecan - 2 - ol (**1a**; C-7 stereostructure not reported) have been shown[1] to be components of the sex attractant of several species of pine sawflies (e.g. *Neodiprion sertifer*; *Hymenoptera*: *Diprionidae*). The pheromone appears to be stored in the insect as the alcohol (**1a**) and esterified prior to use.[1] Different species of the family *Diprionidae* apparently use different esters (e.g. acetate and propionate) of **1a** as one means of obtaining a species-specific pheromone;[1] in some species the pheromone may be an optical isomer of **1a**.[1]



1a

Biologically active diastereomeric mixtures of the isomers of **1** have been prepared by non-stereospecific routes during the structural elucidation[1] and later by others.[2] A stereospecific synthesis of **1a** was described in a preliminary report on the present project.[3]

Pine sawflies cause severe damage, at regular intervals, to Swedish pine forests; the pheromones of these insects have been under study in Sweden for some time.[4] Since the structure of a major sawfly pheromone is now known[1] this offered a possibility of investigating[5] receptor specificity towards different isomers and analogues. As part of this work, I now report the preparation of a series of compounds (Scheme 1) for testing. Biological evaluation is in progress and will be reported elsewhere.

There are four obvious positions (or combinations of these) in the molecule which may be important for receptor specificity: the acid moiety of the ester group and the three asymmetric C atoms 2,3 and 7. Since variation of the ester function seems to be used by the insects for species specificity, the most interesting (and indeed the easiest) part of the molecule to manipulate is that close to the ester group, i.e. the C-2/C-3 stereostructure.

An *erythro* (or *threo*) alcohol system of the present type should be most easily formed by fragmentation (under non-epimerising conditions) of a ring with substituents in a *cis* (or *trans*) arrangement. The method used here is based on the well-known stereospecificity of the Baeyer–Villiger reaction.[6] Opening of a "Baeyer–Villiger lactone" (from a cyclo-hexanone) with a suitable nucleophile should give a compound with a CO group in the position where the C-7 Me group will be placed in the final product and should make possible preparation of compounds with different substituents in the "C-7" position and of *nor*-compounds which lack substituents here.

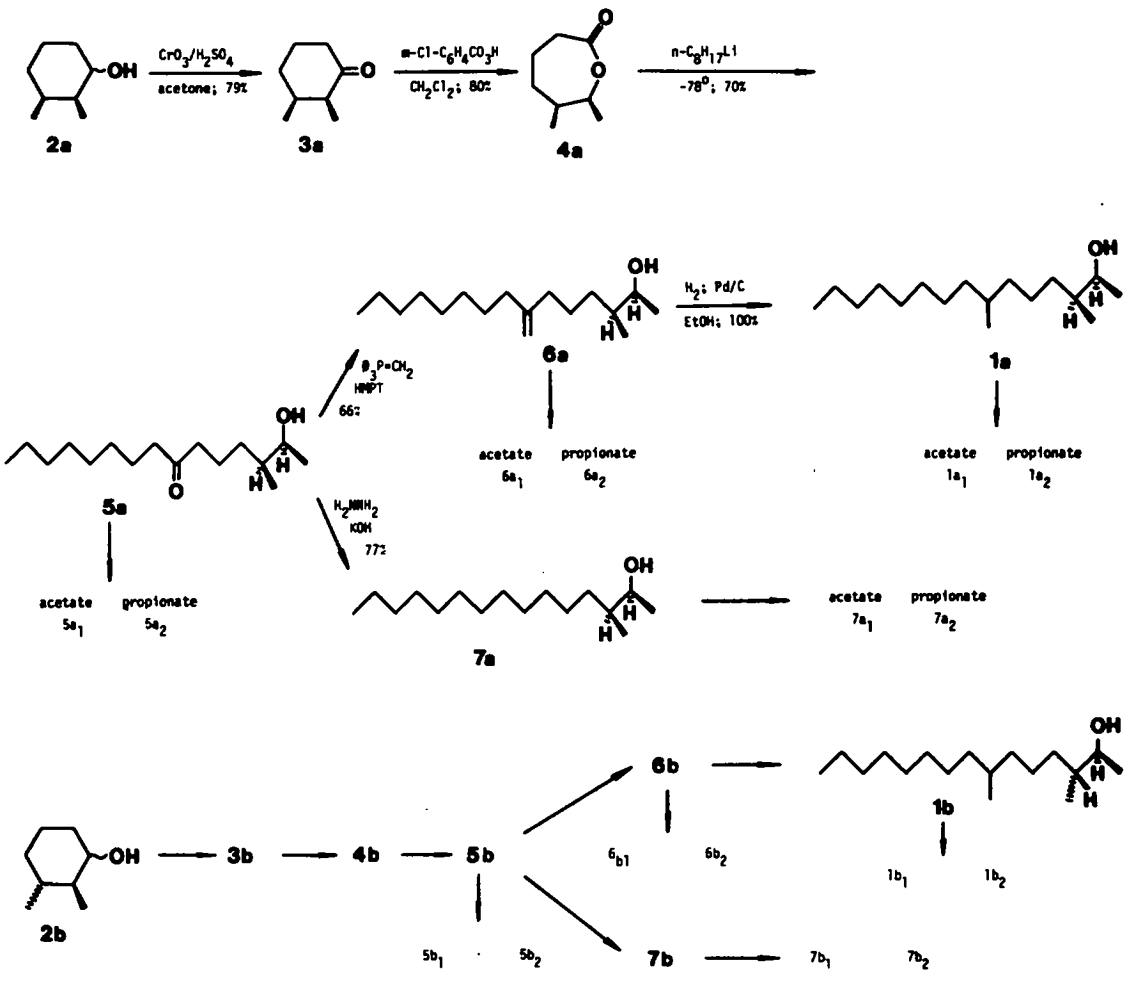
A suitable starting material for the synthesis is the commercially available[7] diastereomeric mixture of dimethylcyclohexanols (**2**). This can be separated by distillation into two fractions containing the two *cis*-dimethyl (**2a**) and the two *trans*-dimethyl alcohols (**2b**) respectively. Jones oxidation gave the corresponding ketone (**3a** or **3b**)[8] without any epimerisation (GLC). Baeyer–Villiger oxidation of the ketone **3** gave the lactone (**4a** or **4b**). The ^{13}C NMR spectrum of **4a** showed no signals attributable to **4b** (and vice versa) which means that the lactone-forming step also goes without epimerisation of the starting ketone. Only very weak signals from other material (unidentified) were detected in the ^{13}C NMR spectra which means furthermore that the Baeyer–Villiger reaction is almost totally regiospecific. The protons at C-6 in **4a** and **4b** give rise respectively to a sharp quartet and to a broad pentet (δ 4.61 and 4.25 ppm). In the most stable conformation(s) of **4a** (inspection of Dreiding-models), the angle between the protons on C-5 and C-6 was close to 90°. According to the Karplus equation this should mean a coupling constant close to 0 Hz. This corroborates the *cis*-dimethyl assignment in **4a**.

Reaction of the lactone **4** with one equivalent of octyllithium at low temperature gave the keto–alcohol (**5a** or **5b**). At room temperature, the main product is the diol (and unreacted lactone **4**) formed by reaction of the lithium alcoholate of **5** with a second molecule of octyllithium. Presumably, at low temperature the hemiacetal salt formed initially is sufficiently stable that ring-opening and subsequent reaction with octyllithium is minimised.

Reaction of the keto–alcohol **5** with methylenetriphenylphosphorane gave the corresponding olefinic alcohol (**6a** or **6b**). Standard Wittig conditions gave only 24% yield (after column chromatography). However, adding one molar equivalent of hexamethylphosphoric triamide (HMPT) per molar equivalent of Li

†Part I, see Ref. 3.

‡Presented at the Euchem Conference; *Structure, Synthesis and Biosynthesis of Mono- and Sesquiterpenoids*. Varenna, Italy (25–31 Aug. 1977).



Scheme 1.

bromide (which is present in the reaction mixture) increased the yield to 66%. This is presumably due to the formation of a rather insoluble (in ether), crystalline[3] LiBr/HMPT-complex (the complex showed only HMPT signals in ^1H NMR (D_2O) and formed a precipitate with silver nitrate) making the reaction mixture essentially "salt-free" (for further details, see Ref. 3).

Huang-Minlon reduction of the keto-alcohol 5 gave the straight-chain alcohol (7a or 7b) lacking substituents at C-7. This gives an opportunity to test the importance of the C-7 Me group for biological activity.

A series of 16 esters (Scheme 1 and experimental) for structure-activity tests was prepared by acylation of the alcohols 5, 6 and 7 with acetic and propionic anhydride; the esters of 1 were obtained by subsequent catalytic hydrogenation of the esters of 6.

EXPERIMENTAL

All GLC was carried out on a 50 m SE-30 glass capillary column. ^1H NMR spectra were recorded on Jeol PMX-60 and Jeol MH-100 instruments. ^{13}C NMR spectra were recorded on a Jeol FX-60 instrument. TMS was used as internal standard. IR spectra refer to liquid films. Mass spectra were recorded on a Varian MAT 311 instrument (Department of Clinical Chemistry, University Hospital, Lund).

†s, singlet; d, doublet; t, triplet; q, quartet; p, pentet.

cis- and trans-2,3-Dimethylcyclohexanone (3a *and* 3b).[8] Commercial[7] 2,3-dimethylcyclohexanol (ratio 2a/2b:2/1) was separated by repeated distillation (1 m column, packed with glass helices; heating mantle; high reflux ratio) into two main fractions (b.p. 32 mm, 94–95°: 2b and 99–100°: 2a). Oxidation in acetone with Jones reagent followed by distillation gave the ketones 3a and 3b (b.p. 11 mm, 60° and 58° respectively). Distillation of the alcohol mixture and oxidation were conveniently followed by GLC. No epimerisation at C-2 was detected.

Baeyer–Villiger oxidation of 3a *and* 3b

The ketone (3a or 3b; 7.0 g; 55 mmol) was dissolved in CH_2Cl_2 (20 ml) and added at room temp. to a soln of *m*-chloroperbenzoic acid (13.0 g; 76 mmol) in CH_2Cl_2 (100 ml). The soln started to boil (reflux condenser) after a few min and was allowed to react for 2 hr. Cooling with ice and removal of the precipitated *m*-chlorobenzoic acid by filtration, followed by evaporation and distillation gave the pure lactone (4a or 4b) in 80% yield. No epimerisation was detected (^1H and ^{13}C NMR).

cis-5-Methyl-6-heptanolide (4a), b.p. 59–60°/0.1 mm; IR: 1730, 1285, 1248, 1180, 1096, 1026, 1006 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.61 (1H, q,† J = 6.5 Hz), 1.33 (3 H, d,† J = 6.5 Hz), 0.94 (3 H, d, J = 6.5 Hz) ppm; ^{13}C NMR ($CDCl_3$): δ 175.6, 78.1, 36.0, 35.0, 34.7, 20.0, 17.9, 10.3 ppm.

trans-5-Methyl-6-heptanolide (4b), b.p. 63–64°/0.1 mm; 1735, 1276, 1249, 1180, 1096, 1039, 1000 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.25 (1H, broad p, J = 6 Hz), 1.31 (3H, d, J = 6.5 Hz), 0.93 (3H, d, J = 6.5 Hz) ppm; ^{13}C NMR ($CDCl_3$): δ 175.2, 80.6, 38.6, 36.4, 33.9, 21.3, 20.0, 18.3 ppm; MS, *m/e*: 142 (M), 99; Mol. wt., obs. 142.0990, calc. for $C_8H_{14}O_2$ 142.0993.

Octyllithium reaction of **4a** *and* **4b**

The lactone (**4a** or **4b**; 5.80 g; 41 mmol) was dissolved in dry ether (60 ml) and cooled in an acetone-dry ice bath. Octyllithium (42 mmol in ether; N_2-atmosphere) was added dropwise to the cooled lactone soln (magnetic stirring). After 30 min the cold reaction was poured into dil. HCl (2 M; 80 ml). The aqueous soln was extracted with ether and the ether extract was washed with sat. $NaHCO_3$aq (50 ml) and water (50 ml). Drying (Na_2SO_4), evaporation and distillation gave a fore-run (octanol and hexadecane), a main fraction (**5a** and **5b**; 70% yield) and a diol (from reaction of the lactone with 2 moles of octyllithium).

erythro-2-*Hydroxy*-3-*methyl-pentadecan*-7-*one* (**5a**), b.p. 139–140°/0.2 mm; IR 3440, 1716, 1465, 1412, 1381, 726 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.71 (1H, dq, J = 6.1 and 3.6 Hz), 1.11 (3H, d, J = 6.1 Hz) ppm; MS, *m/e*:256 (M), 238.

threo-2-*Hydroxy*-3-*methyl-pentadecan*-7-*one* (**5b**), b.p. 139–140°/0.3 mm; IR: 3440, 1715, 1463, 1412, 1382, 726 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.63 (1H, broad p, J = 6 Hz), 1.11 (3H, d, J = 6.0 Hz) ppm.

Wittig reaction of **5a** *and* **5b**

The hydroxy ketone (**5a** or **5b**; 1.54 g; 6 mmol) was dissolved in dry ether (20 ml) and added to a soln of methylenetriphenylphosphorane (from BuLi and methyltriphenylphosphonium bromide; 6.40 g; 18 mmol) in ether (150 ml) at room temp. The mixture was stirred for 15 min and hexamethylphosphoric triamide (HMPT; 3.21 g; 18 mmol) was added. Stirring overnight at room temp. followed by acidic work-up and column chromatography (SiO_2, 80 g; EtOAc/hexane 1/14, 300 ml, followed by EtOAc/hexane 1/2) gave the pure hydroxy olefin (**6a** or **6b**) in 66% yield. In a run in which the HMPT-addition was omitted, only 24% yield of **6a** was obtained.

erythro-7-*Hydroxy*-6-*methyl*-2-*octyl*-1-*octene* (**6a**), IR: 3360, 3078, 1647, 1464, 1381, 890 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.68 (2H, broad s), 3.68 (1H, dq, J = 6.2 and 3.3 Hz), 1.14 (3H, d, J = 6.2 Hz) ppm.

threo-7-*Hydroxy*-6-*methyl*-2-*octyl*-1-*octene* (**6b**). IR: 3370, 3080, 1647, 1462, 1380, 890 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.68 (2H, broad s), 3.62 (1H, broad p, J = 6 Hz), 1.12 (3H, d, J = 6.0 Hz) ppm.

Huang–Minlon reduction of **5a** *and* **5b**

KOH (0.4 g) was dissolved in diethylene glycol (4 ml) with magnetic stirring and heating with a small flame. The soln was cooled to 90° and the hydroxy ketone (**5a** or **5b**; 0.48 g) was added using a few drops of ether which was evaporated afterwards with a stream of N_2. Hydrazine hydrate[9] (99.5% 0.3 ml) was added and the mixture was slowly heated to 180° (oil-bath; magnetic stirring; gas evolution) and kept refluxing for 1 hr. Volatile compounds were allowed to distil off and the reflux was continued (oil-bath: 210°) for 2 hr. The mixture was cooled and water (5 ml) was added. Extraction with hexane, drying (Na_2SO_4), evaporation and column chromatography (SiO_2, 80 g; EtOAc/hexane, 1/2) gave **7a** or **7b** in 77% yield.

erythro-2-*Hydroxy*-3-*methyl-pentadecane* (**7a**), IR: 3365, 1470, 1382, 930, 725 cm^{-1}; H NMR ($CDCl_3$): δ 3.70 (1H, dq, J = 6.4 and 3.4 Hz), 1.15 (3H, d, J = 6.4 Hz) ppm.

threo-2-*Hydroxy*-3-*methyl-pentadecane* (**7b**), IR: 3365, 1472, 1383, 930, 725 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.64 (1H, broad p, J = 6 Hz), 1.10 (3H, d, J = 6.2 Hz) ppm.

Acylation of **5a** *and* **b**, **6 a** *and* **b**, *and* **7a** *and* **b**

The alcohol (150 mg) was dissolved in pyridine (6 ml) and the anhydride (acetic or propionic anhydride; 2 ml) was added. The mixture was stirred overnight at room temp. Addition of EtOH and evaporation (repeated until dryness) gave a crude product which was chromatographed (SiO_2, 40 g; EtOAc/hexane, 1/14) giving the pure ester in almost quantitative yield.

erythro-3-*Methyl*-7-*oxo-pentadec*-2-*yl acetate* (**5a$_1$**), IR: 1738, 1718, 1464, 1375, 1249, 951 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.83 (1H, dq, J = 6.4 and 4.2 Hz), 2.02 (3H, s), 1.14 (3H, d, J = 6.4 Hz) ppm.

erythro-3-*Methyl* -7-*oxo-pentadec*-2-*yl propionate* (**5a$_2$**), IR: 1740, 1720, 1463, 1380, 1196 cm^{-1}; H NMR ($CDCl_3$): δ 4.82 (1H, dq, J = 6.4 and 4.0 Hz) ppm.

threo-3-*Methyl*-7-*oxo-pentadec*-2-*yl acetate* (**5b$_1$**), IR: 1738, 1720, 1463, 1379, 1250, 950 cm^{-1}; H NMR ($CDCl_3$): δ 4.80 (1H, broad p, J = 6 Hz), 2.01 (3H, s), 1.12 (3H, d, J = 6.4 Hz) ppm; MS, *m/e*: 298 (M), 238 (M^- HOAc), 211, 140, 125, 96, 86; Mol. wt., obs: 298.2449, calc. for $C_{18}H_{34}O_3$: 298.2507; obs: 238.2299, calc. for $C_{16}H_{30}O$: 238.2296.

threo-3-*Methyl*-7-*oxo-pentadec*-2-*yl propionate* (**5b$_2$**), IR: 1737, 1719, 1462, 1379, 1195 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.80 (1H, broad p, J = 6 Hz) ppm.

erythro-6-*Methyl*-2-*octyl*-1-*octen*-7-*yl acetate* (**6a$_1$**), IR: 3072, 1741, 1648, 1463, 1377, 1250, 950, 891 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.84 (1H, dq, J = 6.4 and 4.4 Hz), 4.71 (2H, broad s), 2.01 (3H, s), 1.15 (3H, d, J = 6.4 Hz) ppm.

erythro-6-*Methyl*-2-*octyl*-1-*octen*-7-*yl propionate* (**6a$_2$**), IR: 3072, 1740, 1647, 1464, 1379, 1195, 890 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.87 (1H, dq, J = 6.6 and 4.6 Hz), 4.71 (2H, broad s), 2.32 (2H, q, J = 7.2 Hz) ppm.

threo-6-*Methyl*-2-*octyl*-1-*octen*-7-*yl acetate* (**6b$_1$**), IR: 3072, 1740, 1648, 1463, 1376, 1249, 950, 890 cm^{-1}: ^1H NMR ($CDCl_3$) δ 4.78 (1H, broad p, J = 6 Hz), 4.67 (2H, broad s), 2.01 (3H, s), 1.11 (3H, d, J = 6.4 Hz) ppm: MS, *m/e*: 296 (M), 254, 236 (M^-HOAc), 207, 180, 123, 94, 81: Mol. wt., obs: 236.2507, calc. for $C_{17}H_{32}$: 236.2503 (M^-HOAc).

threo-6-*Methyl*-2-*octyl*-1-*octen*-7-*yl propionate* (**6b$_2$**), IR: 3078, 1740, 1648, 1467, 1381, 1199, 891 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.87 (1H, broad p, J = 6 Hz), 4.74 (2H, broad s), 2.32 (2H, q, J = 7.1 Hz) ppm.

erthro-3-*Methyl-pentadec*-2-*yl acetate* (**7a$_1$**), IR: 1742, 1465, 1377, 1250, 950 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.86 (1H, dq, J = 6.6 and 4.6 Hz), 2.02 (3H, s), 1.07 (3H, d, J = 6.6 Hz) ppm.

erythro-3-*Methyl-pentadec*-2-*yl propionate* (**7a$_2$**), IR: 1742, 1466, 1380, 1197, 868 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.87 (1H, dq, J = 6.4 and 4.6 Hz), 2.32 (2H, q, J = 7.2 Hz) ppm.

threo-3-*Methyl-pentadec*-2-*yl acetate* (**7b$_1$**), IR: 1740, 1465, 1377, 1250, 950 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.80 (1H, broad p, J = 6 Hz), 2.01 (3H, s), 1.12 (3H, d, J = 6.0 Hz) ppm; MS, *m/e*: 240, 224 (M^- HOAc), 195, 125, 116, 111, 96, 86, 72; Mol. wt., obs: 224.2494, calc. for $C_{16}H_{32}$: 224.2504 (M^- HOAc).

threo-3-*Methyl-pentadec*-2-*yl propionate* (**7b$_2$**), IR: 1740, 1465, 1380, 1197, 865 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.82 (1H, broad p, J = 6 Hz), 2.29 (2H, q, J = 7.1 Hz) ppm.

Catalytic hydrogenation of **6a$_1$**, **a$_2$**, **b$_1$** *and* **b$_2$**

The olefinic ester (150 mg) was hydrogenated (atm pressure) in EtOH (8 ml) with Pd–C (10%) as catalyst. Filtration through Celite, evaporation and column chromatography (SiO_2, 40 g; EtOAc/hexane, 1/14) gave the saturated ester in quantitative yield.

erythro-3,7-*Dimethyl-pentadec*-2-*yl acetate* (**1a$_1$**), IR: 1743, 1465, 1377, 1250, 950 cm^{-1}; ^1H NMR (benzene-d_6): δ 4.96 (1H, dq, J = 6.4 and 4.4 Hz), 1.71 (3H, s), 1.09 (3H, d, J = 6.45 Hz) ppm; ^{13}C NMR (benzene-d_6): δ 169.6, 73.5, 38.0, 37.7, 33.2, 32.3, 30.5, 30.1, 29.8, 27.5, 25.0, 23.1, 20.9, 19.9, 17.1, 14.9, 14.4 ppm; MS, *m/e*: 254, 238 (M^- HOAc), 154, 140, 125, 116, 97.

erythro-3,7-*Dimethyl-pentadec*-2-*yl propionate* (**1a$_2$**), IR: 1740, 1465, 1380, 1194, 865 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.85 (1H, dq, J = 6.4 and 4.5 Hz), 2.31 (2H, q, J = 7.2 Hz) ppm.

threo-3,7-*Dimethyl-pentadec*-2-*yl acetate* (**1b$_1$**), IR: 1742, 1468, 1375, 1250, 950 cm^{-1}; ^1H NMR (benzene-d_6): δ 4.88 (1H, broad p, J = 6 Hz), 1.75 (3H, s), 1.06 (3H, d, J = 6.39 Hz) ppm; ^{13}C NMR (benzene-d_6): δ 169.3, 73.8, 37.6, 33.1, 32.3, 30.4, 30.1, 29.8, 27.5, 24.9, 23.0, 20.9, 19.9, 15.8, 14.7, 14.3 ppm; MS, *m/e*: 254, 238 (M^- HOAc), 154, 140, 125, 116, 96, 86; Mol. wt., obs: 238.2655, calc. for $C_{17}H_{34}$: 238.2660.

threo-3,7-*Dimethyl-pentadec*-2-*yl-propionate* (**1b$_2$**), IR: 1741, 1468, 1381, 1196, 867 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.82 (1H, broad p, J = 6 Hz), 2.28 (2H, q, J = 7.0 Hz) ppm.

Acknowledgement—This work was supported by the Swedish Natural Science Research Council.

REFERENCES

[1]D. M. Jewett, F. Matsumura and H. C. Coppel, *Science* **192**, 51 (1976).

[2]P. J. Kocienski and J. M. Ansell, *J. Org. Chem.* 42, 1102 (1977).
[3]G. Magnusson, *Tetrahedron Letters* 2713 (1977).
[4]G. Ahlgren, G. Bergström, J. Lövqvist, A. Jansson and T. Norin, *J. Chem. Ecol.*, in press.
[5]Joint project with Dr. J. Löfqvist, Lund (Entomology), Prof. T. Norin, Stockholm (Organic chemistry) and Dr. G. Bergström, Gothenburg (Ecological chemistry).
[6]H. O. House, *Modern Synthetic Reactions*, 2nd Edn, W. A. Benjamin, Menlo Park, California (1972) and Refs. cited.
[7]Fluka AG, CH-9470 Buchs, Switzerland (see also Ref. 8).
[8]H. E. Ulery and J. H. Richards, *J. Am. Chem. Soc.* 86, 3113 (1964).
[9]L. F. Fieser and M. Fieser, *Reagents for Organic Synthesis*, Vol. 1, p. 434. Wiley, New York (1967).