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ABSOLUTE CONFIGURATIONS OF (-)-14-METHYLHEXADEC-8-*cis*-EN-1-OL AND METHYL (-)-14-METHYLHEXADEC-8-*cis*-ENOATE, THE SEX PHEROMONE OF FEMALE DERMESTID BEETLE[a]

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Abstract—The absolute configurations of the title compounds were determined to be 14*R* by synthesizing their antipodes of known configuration.

The insect pheromones are usually optically inactive aliphatic compounds.[1,2] Some of them, however, are dissymmetric and optically active such as *Trogoderma inclusum* pheromones with an asymmetric tertiary carbon,[3] *Ips confusus* pheromones as asymmetric secondary alcohols,[4] and *Acanthoscelides obtectus* pheromone as an asymmetric allene.[5] Determination of absolute configuration of each of these dissymmetric pheromones has not been attempted except for (+)-*cis*-verbenol[4] which belongs to a well-known family of bicyclic monoterpenes of plant origin. The limited availability of natural and oily phermones was the major obstacle to stereochemical studies by degradation or by X-ray crystallographic analysis. In such a case, a synthesis starting from a compound of known absolute configuration can be the most reliable method for stereochemical assignment. Herein we report such an example.[6]

(-)-14-Methylhexadec-8-*cis*-en-1-ol (1) and methyl (-)-14-methylhexadec-8-*cis*-enoate (2) were isolated from a female dermestid beetle, *Trogoderma inclusum* Le Conte, as the components of the sex attractant.[3] Although two syntheses of their racemates were reported,[3,7] their absolute configuration remained unknown. We planned to solve this problem by synthesizing optically active pheromones (1 and 2) from the levorotatory primary amyl alcohol (3) of fusel oil. The absolute configuration of this active amyl alcohol (3) was related to that of L-(+)-isoleucine,[8] while that of D-(-)-isoleucine was revealed by X-ray crystallographic analysis to be 3*R*.[9] Therefore (-)-2-methylbutan-1-ol (3) possesses 2*S* configuration. The sign of the optical rotation of the synthesized pheromones (1 and 2) would then enable us to establish unequivocally the absolute configurations of the natural (-)-pheromones.

(*S*)-(-)-2-Methylbutan-1-ol (3)[†] was converted to the corresponding bromide (4)[11] by treatment with phosphorus tribromide. The Grignard reagent derived from 4 was coupled with allyl bromide to give an olefin (5). Anti-Markownikoff hydrobromination of the terminal olefin *via* hydroboration-bromination[12] yielded a bromide (6). This in HMPA was added to a THF-ether solution of the lithium salt of 9-tetrahydropyranyloxy-1-nonyne (7)[‡] to give an acetylenic tetrahydropyranyl ether (8).[13] The tetrahydropyranyl protective group was removed by treatment with *p*-toluenesulfonic acid in methanol to give an acetylenic alcohol (9). This was dissolved in methanol and hydrogenated over Pd-$BaSO_4$ in the presence of quinoline[14] to give (*S*)-14-methylhexadec-8-*cis*-en-1-ol (1) after chromatographic purification over silicic acid impregnated with silver nitrate. The Jones chromic acid oxidized it to a carboxylic acid (10) which was treated with diazomethane to give the methyl ester (2) with 14 *S*-configuration.

These two (*S*)-pheromones were both dextrorotatory. Therefore the 14 *R*-stereochemistry was assigned to the natural and levorotatory (magnitude unspecified) pheromones. This is opposite to the 3 *S*-stereochemistry of the common and widely distributed amino acid L-(+)-isoleucine. The comparison of this 14 *R* configuration with the 11 *S* stereochemistry of the *Cecropia* juvenile hormone (11)[15] seems to suggest the participation of a similar stereochemical process in the biosynthesis of this part of these molecules of insect origin.

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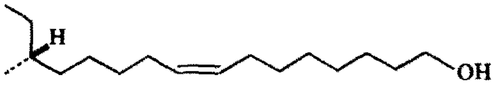
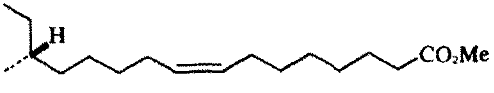
[a] Pheromone Synthesis-I

[†] Our material showed $[\alpha]_D^{23} - 4{\cdot}54°$ (neat). The purest sample of $[\alpha]_D^{20} - 5{\cdot}90°$ is recorded.[10] Hence our material was of 77% optical purity. Our synthetic products were therefore presumed to be in the same order of optical purity. This caused no trouble in the present work, for not the magnitude but the sign of the optical rotation was the important factor.

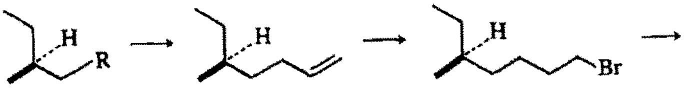
[‡] This was prepared from heptamethylene chlorohydrin (i) in the usual manner *via* the tetrahydropyranyl ether (ii), and the iodide (iii). The latter was reacted with sodium acetylide in liquid ammonia to give 7.



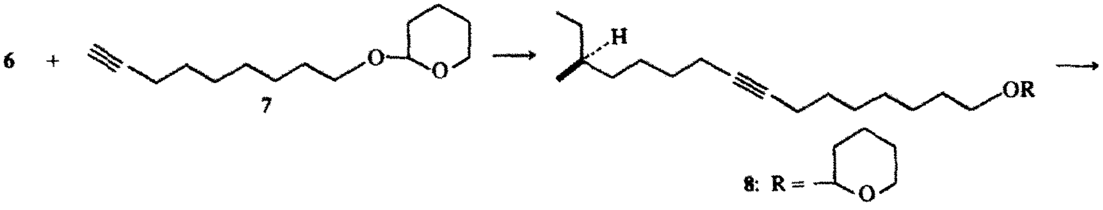
(*R*)-(−)-**1**



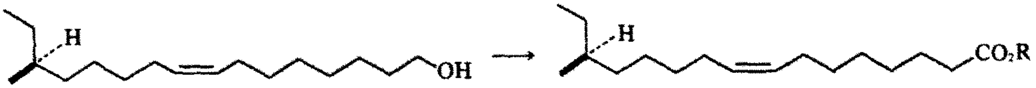
(*R*)-(−)-**2**



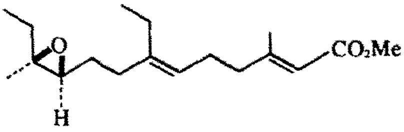
3: R = OH
4: R = Br
5
6



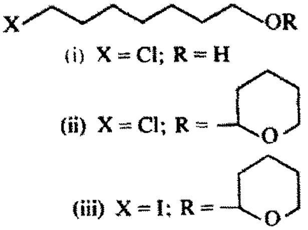
7
8: R =
9: R = H



(*S*)-(+)-**1**
10: R = H
(*S*)-(+)-**2**: R = Me



11: 10*R*, 11*S*



(i) X = Cl; R = H
(ii) X = Cl; R =
(iii) X = I; R =

EXPERIMENTAL

All b.ps were uncorrected. IR spectra refer to films and were determined on a Jasco IRA-1 spectrometer. NMR spectra were recorded at 60 or 100 MHz with TMS as an internal standard. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. GLC analyses were performed on a Yanaco G 80 gas chromatograph.

(S)-(+)-2-*Methylbutyl bromide* (**4**). PBr$_3$ (50 g) was slowly added to stirred and cooled (*S*)-**3** [40 g, $[\alpha]_D^{23}$ − 4·54° (neat)] at − 14 ~ − 16°. The mixture was stirred for 2 h at − 15 ~ 0°. Then it was warmed to 30° for 10 min and poured into ice-water. The organic layer was separated and the aqueous layer was extracted with light petroleum. The combined organic soln was washed with water and dil NaHCO$_3$ aq, dried (CaCl$_2$) and concentrated. The residue was distilled to give 20·0 g of **4**, b.p. 110 ~ 120°. An analytical sample boiled at 119°, $[\alpha]_D^{23}$ + 3·92° (neat); MS: *m/e* 150, 152 (M$^+$).

(S)-(+)-5-*Methylhept-1-ene* (**5**). A Grignard reagent was prepared from **4** (20 g) and Mg (3·2 g) in dry ether (60 ml). Allyl bromide (16·1 g) was added during 20 min to the Grignard reagent. The reaction was exothermic and the ether spontaneously refluxed. After 16 h at room temp, the mixture was poured into ice and NH$_4$Cl soln and extracted with ether. The extract was dried (CaCl$_2$) and concentrated. The residue was fractionally distilled with a Vigreaux column to give 8·0 g (71%) of **5**, b.p. 110 ~ 115°, n_D^{24} 1·4070; ν_{max} 3070 (w), 2960 (s), 2930 (s), 2890 (s), 1830 (vw), 1650 (m), 1470 (m), 1380 (w), 1000 (w), 920 (m) cm^{-1}; δ (60 MHz, CCl$_4$) 0·80 ~ 0·95 (5 H), 1·05 ~ 1·45 (5 H), 1·80 ~ 2·20 (2 H, q), 4·65 ~ 5·10 (2H, m), 5·35 ~ 6·05 (1 H, m); MS: *m/e* 112 (M$^+$, C$_8$H$_{16}$); $[\alpha]_D^{23}$ + 6·42° (neat).

(S)-(+)-5-*Methylheptyl bromide* (**6**). A soln of B$_2$H$_6$ in THF (1·12 M, 25 ml) was added to a stirred and ice-cooled soln of **5** (6·5 g) in dry THF (20 ml) at 0°. The mixture was stirred for 30 min at 0° and for 1 h at 20°. MeOH (1 ml) was added to destroy the excess of B$_2$H$_6$. Then Br$_2$(4 ml) was gradually added with stirring at − 5 ~ 0°. Finally a soln of NaOMe (from 2·3 g of Na) in MeOH (30 ml) was added during 45 min with stirring at < 5°. Then the mixture was diluted with H$_2$O (10 ml) and sat K$_2$CO$_3$ soln (10 ml) and extracted with light petroleum. The extract was washed with water, sat NaHCO$_3$ aq and sat NaCl aq, dried (CaCl$_2$) and concentrated. The residue was distilled to give 5·1 g

(46%) of **6**, b.p. 112 ~ 114°/60 mm or 86°/28 mm, n_D^{29} 1·4481; ν_{max} 2975 (vs), 2920 (vs), 2870 (s), 1460 (m), 1380 (m), 1250 (m), 1200 (w), 760 (w), 725 (w) cm^{-1}; δ (60 MHz, CCl_4) 0·6 ~ 1·0 (5 H), 1·0 ~ 1·5 (7 H), 1·5 ~ 2·0 (2 H), 3·30 (2 H, t, J = 6 Hz); $[\alpha]_D^{23\cdot5}$ + 7·97° (*c* = 3·73; $CHCl_3$). (Found: C, 50·25; H, 9·16. $C_8H_{17}Br$ requires: C, 49·75; H, 8·87%).

1 - *Tetrahydropyranyloxy - 7 - chloroheptane* (*ii*). *p*-TsOH (0·1 g) was added to a soln of heptamethylene chlorohydrin (i, 8·9 g) and dihydropyran (7·0 g) in ether (35 ml) and the mixture was left to stand for 3 h at room temp. Then it was diluted with ether and washed with K_2CO_3 aq. The organic soln was dried (K_2CO_3) and concentrated *in vacuo*. The residue was distilled to give 12·0 g (86%) of ii, b.p. 112 ~ 114°/0·2 mm, n_D^{24} 1·4594; ν_{max} 2950 (vs), 2880 (s), 1460 (m), 1360 (m), 1200 (m), 1140 (s), 1130 (s), 1080 (s), 1040 (vs) cm^{-1}. (Found: C, 61·67; H, 9·77. $C_{12}H_{23}O_2Cl$ requires: C, 61·39; H, 9·86%).

9-*Tetrahydropyranyloxynon-1-yne* (**7**). The chloride (ii, 21·7 g) was added to a soln of NaI (18·0 g) in acetone (100 ml) and the mixture was heated under reflux for 24 h. Subsequently it was diluted with dil $NaHCO_3$ aq and extracted with n-hexane. The extract was dried ($MgSO_4$) and concentrated *in vacuo* to give 28·2 g (90%) of crude iodide (iii). This was dissolved in dry ether (30 ml) and added dropwise during 30 min to a stirred and cooled suspension of NaC≡CH (from 3·5 g of Na and gaseous HC≡CH) in liq NH_3 (400 ml) at −40°. The mixture was stirred at −35° for 2 h and left to stand overnight at room temp. The residue was mixed with ice-water and extracted with ether. The ether extract was washed with H_2O and sat NaCl aq, dried (K_2CO_3) and concentrated *in vacuo*. The residue was distilled to give 16·5 g (85%) of **7**, b.p. 107 ~ 110°/0·2 mm, n_D^{22} 1·4590. This was contaminated with the starting helogeno compounds as revealed by the low CH content determined by combustion analysis. ν_{max} 3300 (m), 2950 (vs), 2850 (vs), 2120 (w), 1465 (m), 1455 (m), 1365 (m), 1220 (m), 1200 (m), 1150 (s), 1130 (s), 1090 (s), 1040 (s), 1000 (m), 920 (m), 880 (m), 830 (m), 740 (m) cm^{-1}; TLC (silica gel G, ether): Rf 0·72.

(S)-(+)-14-*Methylhexadec-8-yn-1-ol* (**9**). A soln of n-BuLi in ether (1·66 M, 13·5 ml) was added to a stirred and ice-cooled soln of **7** (5·0 g) in dry THF (20 ml) below 10° under N_2. Subsequently a soln of **6** (4·5 g) in dry HMPA (35 ml) was added with stirring at 10 ~ 25°. After 30 min the mixture was poured into ice-water and extracted with n-hexane. The extract was washed with H_2O and sat NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residue (**8**) was dissolved in MeOH (100 ml) containing *p*-TsOH (0·2 g). The soln was heated at 60 ~ 65° for 1 h, concentrated *in vacuo*, diluted with water and extracted with ether. The extract was washed with sat $NaHCO_3$ aq and sat NaCl aq, dried (K_2CO_3) and concentrated *in vacuo*. The residue was distilled to give 1·45 g (32%) of crude 9, b.p. 142 ~ 148°/0·2 mm, n_D^{24} 1·4601; ν_{max} 3250 (m), 2940 (vs), 2860 (vs), 1465 (m), 1380 (m), 1300 (m), 1200 (m), 1060 (m), 990 (m), 750 (w), 730 (w) cm^{-1}; MS: *m/e* 252 (M^+); TLC (silica gel G, ether): Rf 0·80, 0·66 (main), 0·40, 0·10. $[\alpha]_D^{23\cdot5}$ + 5·23° (*c* = 2·79, $CHCl_3$). This was employed for the next step without further purification.

(S)-(+)-14-*Methylhexadec-8-en-1-ol* (**1**). 5% Pd-$BaSO_4$ (250 mg) and quinoline (3 drops) were added to a soln of **9** (1·65 g) in MeOH (30 ml) and the mixture was shaken under H_2 at room temp. H_2 uptake ceased after 30 min (120 ml). The catalyst was filtered off and the filtrate was concentrated *in vacuo* to give crude I, ν_{max} 3350 (m), 3050 (m), 2940 (vs), 2870 (vs), 1470 (m), 1380 (w), 1205 (m), 1065 (m), 995 (m), 810 (w), 790 (w), 740 (m) cm^{-1}; TLC: four spots. This was chromatographed over SiO_2—$AgNO_3$ (prepared from 30 g of Mallinckrodt AR 100 mesh SiO_2 and 2·5 g of $AgNO_3$ in 7 ml of H_2O, 8·5 × 3 cm) in n-hexane. Elution with n-hexane yielded 1·40 g (85%) of **1**, b.p. 150 ~ 151°/0·1 mm, n_D^{25} 1·4568; ν_{max} 3350 (s), 3050 (m), 2940 (vs), 1660 (w), 1470 (m), 1380 (m), 1060 (m), 970 (vw), 730 (w) cm^{-1}; δ (100 MHz, CCl_4) 0·88 (3 H, t, J = 6 Hz), 0·88 (3 H, d, J = 6 Hz), ~ 1·34 (19 H, br), 2·00 (4 H, br, d), 2·67 (1 H, s), 3·52 (2 H, t, J = 6 Hz), 5·28 (2 H, m, seemingly t, J = 5 Hz); MS: *m/e* 254 (M^+), 236, 225, 208, 194, 180, 166, 151; GLC (5% LAC 2R-446 on Diasolid, 1·5 m × 3 mm i.d. at 200°, Carrier gas N_2, 1·0 kg/cm^2): Rt 11·6 min (99%; 1% impurity at Rt 5·6 min); TLC (silica gel G, ether): Rf 0·66; $[\alpha]_D^{25}$ + 5·31° (*c* 4·58, $CHCl_3$). (Found: C, 79·90; H, 13·01. $C_{17}H_{34}O$ requires: C, 80·24; H, 13·47%).

Methyl (S)-(+)-14-*methylhexadec-8-enoate* (**2**). Jones CrO_3 (0·7 ml) was added to a soln of **1** (550 mg) in acetone (10 ml) and the mixture was left to stand for 5 min at room temp. The excess of CrO_3 was destroyed with MeOH. Then the mixture was concentrated *in vacuo*, diluted with water and extracted with ether. The ether extract was washed with H_2O and sat NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residue (**10**) was treated with ethereal CH_2N_2. The soln was concentrated and the residual oil was chromatographed over Woelm grade II neutral alumina (30 g, 9·5 × 2·2 cm) in n-hexane. Elution with n-hexane and n-hexane-ether (9:1) yielded 339 mg (56%) of **2**, b.p. 125 ~ 127°/0·1 mm, n_D^{25} 1·4483; ν_{max} 3020 (m), 2930 (s), 2860 (s), 1750 (s), 1470 (m), 1440 (m), 1380 (m), 1250 (m), 1200 (m), 1175 (m), 1130 (m), 1085 (w), 1030 (w), 970 (w), 880 (w), cm^{-1}; δ (100 MHz, CCl_4) 0·88 (3 H, t, J = 6 Hz), 0·88 (3 H, d, J = 6 Hz), ~ 1·34 (17 H, br), 2·00 (4 H, br. d), 2·22 (2 H, t, J = 7 Hz), 3·62 (3 H, s), 5·28 (2 H, m, seemingly t, J = 5 Hz); MS: *m/e* 282 (M^+), 253, 251, 250, 213, 85, 74, 70; GLC (5% LAC 2R-446 on Diasolid, 1·5 m × 3 mm id at 180°, Carrier gas N_2, 1·0 kg/cm^2): Rt 16·5 min; $[\alpha]_D^{25}$ + 3·75° (*c* = 1·975, $CHCl_3$). (Found: C, 76·24; H, 12·48. $C_{18}H_{34}O_2$ requires: C, 76·54; H, 12·13%).

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