INSECT PHEROMONES

SYNTHESIS OF CHIRAL SEX PHEROMONE COMPONENTS OF SEVERAL SPECIES OF TROGODERMA (COLEOPTERA: DERMESTIDAE)

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Abstract—The (S)-enantiomers of (Z)- and (E)-14-methyl-8-hexadecen-1-ol, 1 and 4, respectively, and of (Z)- and (E)-14-methyl-8-hexadecenal, 6 and 7, respectively, which are sex pheromone components of dermestid beetles, have been synthesized in high optical purity starting from optically pure (S)-2-methyl-1-butanol. The preparation of 1 has been carried out using a new general method for reducing stereoselectively and in high yield ω -alkynols to the corresponding (E)-alkenols. The rotatory power of optically pure 1, 4, 6 and 7 has been established.

The dermestid beetles include many economically important insect pests which infest nearly all forms of stored products. Species in the dermestid genus *Trogoderma* which are pests of stored grains have received considerable attention regarding control and eradication.^{1,2} Therefore, several studies on their pheromones have been carried out.

The pheromone of female *T.inclusum* consists of four components, each active alone, two of which have been identified as (Z)(-)-14-methyl-8-hexadecen-1-ol (1) and methyl (Z)(-)-14-methyl-8-hexadecenoate (2).³ The absolute configuration of these compounds remained unknown until Mori⁴ synthesized (+)(S)-1 and (+)(S)-2 from (S)-2-methyl-1-butanol (3), thus establishing unequivocally that the absolute configuration of the naturally occurring compounds is *R*.

Two stereoisomers of 1 and 2, i.e. (E)-14-methyl-8hexadecen-1-ol (4) and methyl (E)-14-methyl-8-hex-

[†]Although the synthesis of (S)-1 has been previously described, ⁴ we thought it right to prepare again such compound since the literature data for it reported did not appear convincing. (S)-1 had been, in fact, prepared from (S)-2-methyl-1-butanol having 77% optical purity. The isomeric purity of this alcohol was, however, doubtful. It must be noted that commercially available amyl alcohol having a rotatory power corresponding to a 77% o.p. is a mixture of optically pure (S)-2-methyl-1-butanol and isoamyl alcohol.¹⁴

adecanoate (5), have been found in the multicomponent sex pheromone of the female dermestid beetle, *T.glabrum.*⁵ No measure of the optical rotation of 4 and 5 has so far been reported. Moreover, no stereospecific synthesis has been described, starting from chiral compounds with known absolute configuration and optical purity. Therefore, the relationship either between sign of the rotatory power and absolute configuration, or between biological activity and absolute stereochemistry of such pheromonal components has not been determined.

Very recently it was reported⁶ that (Z)-14-methyl-8hexadecenal (6) is the major sex pheromone component of female *T.inclusum* and *T.variabile* and that (E)-14methyl-8-hexadecenal (7), identified in female *T.glabrum*, has biological activity which is equal to that of the total airborne pheromone of such an insect.² Both 6 and 7 have been found in *T.granarium* in the 92:8 ratio, respectively.⁶

We have prepared stereospecifically the (S)-enantiomers of 1,† 4, 6 and 7, starting from optically pure (S)-2-methyl-1-butanol as part of a general programme,^{7,8} and in order to study the relationship between chirality and biological activity of insect pheromones.⁹⁻¹³

RESULTS AND DISCUSSION

According to a previously described reaction sequence,¹⁵ optically pure (S)-2-methyl-1-butanol (3)





 $([\alpha]_D^{25} - 5.82)^{16}$ was converted into (S)-5-methyl-1-heptene (8) $([\alpha]_D^{25} + 10.12)$ having 93.3% optical purity.¹⁵† Hydroboration of 8 gave on organoborane which reacted with bromine and subsequently with sodium methoxide to yield (S)-1-bromo-5-methylheptane (9) $([\alpha]_D^{25} + 8.05)$. Treatment of a DMSO solution of 9 with a DMSO solution of lithium acetylide-ethylenediamine complex gave (S)-7-methyl-1-nonine (10) $([\alpha]_D^{20} + 9.55)$ in 55% yield. A solution of 10 in HMPA was then treated with butyllithium and the resulting alkynyllithium was coupled with 1-iodo-7-tetrahydropyranyloxyheptane. The crude product was treated with p-toluenesulfonic acid to give (S)-14-methyl-8-hexadecyn-1-ol (11) $([\alpha]_D^{25} + 5.34 (CHCl_3))$ in 54% yield. Catalytic partial hydrogenation of 11 fol-

lowed by chromatography gave pure (S)-1 having $[\alpha]_D^{25}$ + 5.33 (CHCl₃). Oxidation of this alcohol according to Corey and Suggs¹⁷ gave, in 63% yield, pure (S)-6 having $[\alpha]_D^{25}$ + 6.05 (ether).

In order to prepare the (S)(E)-stereoisomers of 1 and 6, i.e. (S)(E)-14-methyl-8-hexadecen-1-ol (4) and the corresponding aldehyde 7 we attempted to reduce stereoselectively the O-tetrahydropyranyl ether of 11 according to the procedure described by Wharten and Jacobson for preparing high molecular weight (E)-alkenols. Unfortunately, owing to the low solubility of the acetylenic compound in liquid ammonia, the yield was rather low. A much higher yield and a very high degree of stereoselectivity was however obtained by reacting directly the alkynol 11 with a large excess of LAH in a mixture of diglyme and tetrahydrofurane.[‡] Careful hydrolysis of the mixture followed by chromatography afforded pure (S)-4, $[\alpha]_{D}^{25}$ + 5.11 (CHCl₃), in 85% yield. Solution of (S)-4 with pyridinium chlorochromate gave pure (S)-7, $[\alpha]_D^{25}$ + 5.62 (ether), in 73% yield.

In continuation, the enantiomeric purity of the synthesized compounds was investigated. Since it is a reasonable assumption that no racemization has occurred at any synthetic step later than 10, the examination was conducted on this compound. Thus, it was partially

⁺Mori⁴ reported $\{\alpha\}_{D}^{23}$ + 6.42 for (S)-5-methyl-1-heptene prepared from (S)-3.

[‡]An analogous procedure previously described for reducing low molecular weight alkynes¹⁹ has been also usefully employed to prepare in *ca.* 100% stereoselectivity and high yield high molecular weight (E)-alkenes from the corresponding alkynes.⁹

[§]This method has been also employed to prepare in 100% stereoselectivity and *ca.* 90% yield other (E)- ω - and (E)- β -alkenols, i.e. (E)-7-dodecen-1-ol a precursor of the sexpheromone of false codling moth,^{20,21} (E)-7-hexadecen-1-ol, and (E)-3-dodecen-1-ol.



hydrogenated and the rotatory power of (S)-7-methyl-1nonene (12) so obtained, $[\alpha]_{D}^{25} + 9.46$, was compared with that of optically pure 12, $[\alpha]_{D}^{25} + 10.24$.²²

The synthesized alkene proved to be 92.5% optically pure. This percentage thus represents the optical purity of the final products.

On this basis, the sample of (S)-1 having $[\alpha]_D^{2+} 5.31$ (CHCl₃) which was prepared by Mori⁴ is also 92.5% instead of less than 77% optically pure.[†]

The values of the rotatory power of optically pure 1, 4, 6 and 7 are reported in the Table. These values, in case it is possible to measure the value of the rotatory power of the naturally occurring compounds, may be very useful to establish the optically purity of these substances. Moreover, the data can establish whether the chiral quality of the pheromonal messengers gives rise to the species-specificity in the chemical communication of the dermestid beetles.[‡]

The biological study of our synthetic products by

(S)-1-Bromo-5-methylheptane (9). A soln of B_2H_6 in THF (0.6 mole, 500 ml) was added to a stirred and ice-cooled soln of **8** (38.6 g, 0.3 mole) in dry THF (500 ml). The mixture was stirred for 1 hr at 0° and 6 hr at room temp. MeOH (10 ml) was slowly added to destroy the excess of B_2H_6 . Then Br_2 (23.7 ml) was added during 1 hr to the stirred mixture cooled at -10° . Finally a soln of MeONa (obtained from 13.6 g of Na and 270 ml of MeOH) was added during 90 min at 0°. The mixture was stirred for an additional 20 min; subsequently it was diluted with water (250 ml) and sat K_2CO_3 soln (250 ml) and extracted with pentane. The extract was washed with water, sat NaHCO₃ aq, sat NaCI aq, dried over Na₂SO₄ and fractionally distilled to yield 51.0 g (86%) of 9: b.p. 80-81°/18 torr; n_D^{25} 1.4519; $[\alpha]_D^{25} + 8.05$ (neat). (Found: C, 49.92; H, 8.92. $C_8H_{17}Br$ requires: C, 49.75; H, 8.87%).

(S)-7-Methyl-1-nonine (10). A degassed soln of LiC=CH-ETDA (Ventron Alfa) (35 g, 0.38 mole) in dry DMSO (150 ml) was added under N₂ to a magnetically stirred mixture of 9 (40 g, 0.207 mole) in dry DMSO (500 ml) cooled at $< 5^{\circ}$. The mixture was stirred for additional 24 hr at room temp., then water (400 ml) was slowly added. The resulting mixture was diluted with excess of water (11.) and extracted with ether. The extract

Table 1. Maximum rotatory powers of (E)(S)- and (Z)(S)-14-methyl-8-hexadecen-1-ol and of (E)(S)- and (Z)(S)-14methyl-8-hexadecenal

Compound		[~] ²⁵ _{D max}
(Z)(S)-14-Methyl-8-hexadecen-1-ol	(<u>1</u>)	+ 5.76 <u>+</u> 0.23 (c 4.687, CHCl ₃)
(E)(S)-14-Methyl-8-hexadecen-1-ol	(<u>4</u>)	+ 5.52 <u>+</u> 0.23 (c 2.823, CHC1 ₃)
(Z)(S)-14-Methyl-8-hexadecenal	(<u>6</u>)	+ 6.54 <u>+</u> 0.23 (c 4.958, ether)
(E)(S)-14-Methyl-8-hexadecenal	(<u>7</u>)	+ 6.06 <u>+</u> 0.23 (c 3.553, ether)

Professor R. Zocchi, Istituto Sperimentale per la Zoologia Agraria, Florence, will be published elsewhere. The synthesis of the (R)-enantiomers of the above compounds is in progress in our laboratory.

EXPERIMENTAL

General. All b.ps are uncorrected. IR refer to films and were determined on a Perkin-Elmer 225 spectrometer. NMR spectra were recorded as CCl₄ solns at 60 MHz with TMS as an internal standard. MS spectra were determined on a Varian Mat CH-7 spectrometer. Optical rotations were measured on a Schmidt-Haensche polarimeter. GLC analyses were performed on a C.Erba Fractovap G.T. and on a Perkin-Elmer F-30 gas chromatograph.

(S)-5-Methyl-1-heptene (8). Commercially available (S)-3 was distilled through a 90 cm column filled with metal helices to give optically pure 3 having $[\alpha]_D^{25} - 5.82$.¹⁶ According to a previously described reaction sequence¹⁵ which involves (S)-1-chloro-2-methylbutane and (S)-2-methylbutylmagnesium as intermediates, compound 3 was converted into (S)-8 in 55% overall yield b.p. 114°; n_D^{25} 1.4077; $[\alpha]_D^{25} + 10.12$ (neat). Lit.¹⁵ b.p. 114°; n_D^{25} 1.4077; $[\alpha]_{Dmax}^{25} + 10.84$.

was washed with sat NaCl aq, dried and concentrated. The residue was fractionally distilled to give 15.7 g (55%) of 10: b.p. 166–167°; n_D^{25} 1.4255; $[a_1]_D^{26}$ + 9.55 (neat); δ 5.16 (2H, m, seemingly t), 3.51 (2H, t), 3.20 (1H, s), 1.97 (4H, m), ~1.33 (19H, br), 0.88 (3H, t) and 0.88 ppm (3H, t). GLC analysis (2m × 0.29 cm Silicone gum rubber 2.5% on Chromosorb G AW-DMCS 80–100 mesh) showed that compound 10 was >99% pure. (Found: C, 86.90; H, 13.12. C₁₀H₁₈ requires: C, 86.95; H, 13.05%).

(S)-14-Methyl-8-hexadecyn-1-ol (11). An hexane soln of BuLi (75.9 ml, 0.167 mole) was added under N₂ to a magnetically stirred soln of 10 (23.2 g, 0.166 mole) in anhydrous HMPA (130 ml) cooled at 0°. The mixture was stirred for 30 min at 0°, then hexane was evaporated at 20 torr. Subsequently, a soln of 1-iodo-7-tetrahydropyranyloxyheptane§ (49.6 g, 0.152 mole) in dry THF (100 ml) was slowly added at 0° under N2. The mixture was stirred for 12 hr at room temp., then it was washed with sat NaCl aq., dried over Na₂SO₄ and concentrated. The residue was dissolved in MeOH (400 ml) containing p-TsOH (2g) and the resulting soln was refluxed for 2 hr concentrated in vacuo, diluted with water and extracted with ether. Distillation of the dried extract gave 23.1 g (54%) of 11: b.p. $133-134^{\circ}/0.15$ torr; $n_{\rm D}^{23}$ 1.4645; $[\alpha]_D^{25} + 5.34 \pm 0.23$ (ca. 2.994, CHCl₃); ν_{max} 3250, 2940, 2860, 1465, 1380, 1060, 750 and 725 cm⁻¹; MS: m/e 252 (M⁺). (Found: C, 81.17; H, 12.74. C₁₇H₃₂O requires: C, 80.95; H, 12.69%)

(Z)(S)-14-Methyl-8-hexadecan-1-ol (1). Compound 11 (4.18 g, 0.0165 mole) was hydrogenated over Lindlar catalyst (0.5 g) in MeOH (300 ml) containing quinoline (0.1 ml). Absorption of H₂ ceased after 20 min. The catalyst was filtered off and the filtrate was concentrated in vacuo to give crude 1, n_{D}^{25} 1.4587. GLC analysis (2 m Carbowax 20 M 8% + KOH 2% on Chromosorb W

[†]This result confirms that levorotatory primary amyl alcohol used by Mori⁴ was optically pure.

 $[\]ddagger$ Recently, it has been suggested²³ that the chiral quality of disparlure gives rise to differences in pheromone perception between gypsy moth and nun moth.

[§]Such compound was prepared according to the procedure described by Mori.⁴

60-80 mesh) showed the presence of less than 1% of 11. Compound I was purified by column chromatography over AgNO₃-silica gel (prepared from 75 g of Merck 70-230 mesh extra pure silica gel and 9.7 g of AgNO₃ in 75 ml of acetonitrile), in hexane. Elution with hexane yielded 3.8 g (90%) of pure 1: b.p. 132-133°/0.2 torr; n_D^{25} 1.4580; $[\alpha]_D^{25}$ + 5.33 ± 0.23 (*ca.* 4.58, CHCl₃); ν_{max} 3020, 1660, 1470, 1055 and 720 cm⁻¹; MS: *m/e* 254 (M⁺), 236 (M⁺-H₂O), 225 (M⁺-C₂H₃). Lit⁴: b.p. 150/0.1 torr; n_D^{25} 1.4568; $[\alpha]_D^{25}$ + 5.31 (*ca.* 4.58, CHCl₃).

(Z)(S)-14-Methyl-8-hexadecenal (6). A soln of 1 (4.58 g, 0.018 mole) in CH₂Cl₂ (5 ml) was added in one portion under N₂ to a magnetically stirred suspension of pyridinium chlorochromate (5.8 g, 0.027 mole in anhyd CH₂Cl₂ (40 ml). After 1.5 hr dry ether (150 ml) was added and the supernatant decanted from the black grum. The insoluble residue was washed thoroughly with anhyd ether (3 × 50 ml). The combined extracts were filtered through a short column of Florisil and the solvent was removed by evaporation at 20 torr. Fractional distillation of the residue afforded 2.89 g (63%) of 6: b.p. 138-139²/1 torr; n_D^{25} 1.4540; $[\alpha]_{25}^{25} + 6.05 \pm 0.23$ (ca. 4.958, ether); ν_{max} 2985, 2940, 2910, 2840, 2695, 1710, 1440, 1360 and 723 cm⁻¹; δ 9.71 (1H, t), 5.30 (2H, m, seemingly t, J = 5 Hz), 2.37 (2H, br), 2.00 (4H, br), 1.33 (17H, br), 0.87 (3H, t) and 0.87 ppm (3H, t); MS: *m/e* 252 (M⁺), 223

 $(M^{+}-C_{2}H_{5} \text{ or } M^{+}-CHO)$, 208 $(M^{+}-44)$, 44 $(H-O=CH-\dot{C}H_{2})$, 29 $(CHO^{+} \text{ or } C_{2}H_{5}^{+})$. (Found: C, 80.96; H, 12.69. $C_{17}H_{32}O$ requires: C, 80.95; H, 12.78%).

(E)(S)-14-Methyl-8-hexadecen-1-ol (4). A mixture of THF (10 ml), diglyme (60 ml) and LAH (5 g, 0.131 mole) was heated under N_2 and a low boiling fraction (~7 ml) was distilled off. A soln of 11 (9.57 g, 0.038 mole) in diglyme (15 ml) was slowly added to the magnetically stirred mixture cooled at 10°. After keeping the temp. at 140° for 48 hr, the mixture was cooled and slowly hydrolysed under N2 with degassed ice-cold water. The aqueous slurry was neutralized with dil. HCl and extracted with pentane (300 ml in 6 portions). The pentane extracts were concentrated in vacuo. GLC analysis (2 m×0.29 cm Carbowax 20 M) of the residue showed that the product was contaminated by less than 4% of 11. Column chromatography on AgNO3-silica gel afforded 8.13 g (85%) of 4; b.p. 108–109°/0.03 torr; n_D^{25} 1.4584; $[\alpha]_{25}^{25}$ + 5.11 ± 0.23 (ca. 2.823, CHCl₃); ν_{max} 3350, 1665, 1460, 1440, 1380, 1055, 965 and 725 cm⁻¹; δ 5.16 (2H, m), 3.50 (2H, t), 3.25 (1H, s), 1.97 (4H, m), 1.33 (19H, br), 0.88 (3H, t) and 0.88 ppm (3H, t); MS: m/e 254 (M⁺), 236 (M⁺-H₂O), 225 (M⁺-C₂H₅), 208

 $(M^+-H_2O \text{ and } CH_2=CH_2)$, and 31 (CH₂=O-H). GLC analysis (2 m × 0.29 cm Carbowax 20 M); 2 m × 0.29 cm UCON LB-550 X on Chromosorb W 80-100 mesh) showed that 4 was isomerically pure. (Found: C, 79.93; H, 13.47. C₁₇H₃₄O requires: C, 80.24; H, 13.47%).

(E)(S)-14-Methyl-8-hexadecenal (7). According to the procedure described for the preparation of 6, compound 4 (4.50 g, 0.0177 mole) was oxidized to give 3.3 g (73%) of 7: b.p. 127-129°/0.5 torr; n_D^{25} 1.4534; $[a]_D^{25}$ 4.562 ± 0.23 (ca. 3.553, ether); ν_{max} 2940, 2910, 2840, 2695, 1713, 1440, 1360, 965 and 722 cm⁻¹; δ 9.70 (1H, t), 5.30 (2H, m), 2.37 (2H, br), 2.00 (4H, br), 1.33 (17H, br), 0.87 (3H, t) and 0.87 ppm (3H, t); MS: mle 252 (M⁺), 223

 $(M^{*}-C_{2}H_{5} \text{ or } M^{*}-CHO)$, 208 $(M^{*}-44)$, 44 $(H-O=CH-\dot{C}H_{2})$, 29 $(CHO^{*} \text{ or } C_{2}H_{5}^{*})$. (Found: C, 80.69; H, 12.88. $C_{17}H_{32}O$ requires: C, 80.95; H, 12.78%).

(S)-7-Methyl-1-nonene (12). Compound 10 (5 g, 0.036 mole) was hydrogenated over 5% Pd on BaSO₄ (1 g) in pentane (60 ml) containing quinoline (0.1 ml). The absorption of H₂ ceased after 1 hr. The mixture was filtered and the filtrate washed with 2 N HCl, water, and dried over Na₂SO₄. Fractional distillation afforded 4.33 g (87%) of 12: b,p. 162-162.5°; n_{D}^{25} 1.4197; $[\alpha]_{D}^{25}$ +9.46 (neat): ν_{max} 2080, 1820, 1642, 1460, 1380, 990, 905 and 725 cm⁻¹; δ 5.50 (1H, m), 4.79 (1H, m, seemingly d), 4.60 (1H, m), 1.98 (2H, br), 1.25 (9H, br), 0.86 (3H, t) and 0.86 ppm (3H, t). Lit.²²: b,p. 162-162.5°; n_{D}^{25} 1.4196; $[\alpha]_{Dmax}^{25}$ + 10.24.

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