Synthesis of (*R*)-(-)-10-Methyl-2-tridecanone, the Pheromone of the Southern Corn Rootworm[†]

Shuji SENDA* and Kenji MORI**

Department of Agricultural Chemistry, The University of Tokyo,
Bunkyo-ku, Tokyo 113, Japan

Received September 14, 1982

(*R*)-(-)-10-Methyl-2-tridecanone, the pheromone of *Diabrotica undecimpunctata howardi* Barber, was synthesized from (*R*)-(+)-citronellyl acetate.

The pheromone of the southern corn rootworm, *Diabrotica undecimpunctata howardi* Barber, was recently identified by Tumlinson *et al.* as 10-methyl-2-tridecanone **1**, with a chiral center at C-10.^{1,2)} The two enantiomers of this compound have been synthesized by Sonnet.³⁾ Field trapping experiments in the United States indicate that males of this species respond only to the (*R*)-enantiomer, thus establishing the absolute configuration of the pheromone to be *R*.^{1,3)}

Herein we report a short synthesis of (*R*)-(-)-**1**, employing (*R*)-(+)-citronellol as the chiral starting material. The use of optically

pure (*R*)-(+)-citronellic acid or (*R*)-(+)-citronellol in our pheromone synthesis is well documented.^{4,5)} Ozonolysis of 100% optically pure (*R*)-(+)-citronellyl acetate **3** yielded **4** in a 60% yield.^{cf.5)} Huang Minlon reduction of **4** with hydrazine hydrate and potassium hydroxide in diethylene glycol, with removal of the product by steam-distillation, gave (*R*)-(+)-3-methylhexanol **5a** in an 82% yield. The corresponding tosylate **5b** was converted to an iodide **6**, $[\alpha]_D^{24} -14.1^\circ$ (CHCl₃). The achiral part of **1** was prepared from ($\pm$)-3-butyn-2-ol **7**. Alkylation of ($\pm$)-**7** with *n*-propyl iodide and lithium amide in liquid ammonia yielded

[†] Pheromone Synthesis. Part LVI. Part LV, K. Mori, S. Kuwahara and H. Ueda, *Tetrahedron*, in press.

* Research Fellow on leave from Nitto Denko Co., Ltd. (1982~1984).

** Address correspondence to this author.

($\pm$)-**8**. This was submitted to the acetylene zipper reaction,⁶⁻⁹ employing an excess of potassium 3-aminopropylamide (KAPA)^{10,11} in 3-aminopropylamine, to give ($\pm$)-6-heptyn-2-ol **9a** in an 80% yield. The corresponding tetrahydropyranyl ether **9b** was alkylated with (*R*)-(-)-**6**, employing *n*-butyllithium as the base, to give (2*RS*,10*R*)-**10a**. Removal of the protecting group afforded (2*RS*,10*R*)-(-)-**10b** in a 75% yield. Hydrogenation of (2*RS*,10*R*)-(-)-**10b** over palladium-charcoal gave (2*RS*,10*R*)-(-)-**11** in a 93.5% yield. Finally **11** was oxidized with the Jones chromic acid to give (*R*)-(-)-10-methyl-2-tridecanone **1**, $[\alpha]_D^{23} -1.4^\circ$ (CHCl₃) in a 74% yield. This completed the convergent synthesis of the pheromone of the natural enantiomer of the southern corn rootworm in 8 steps from (*R*)-(+)-citronellyl acetate **3** (12% overall yield) or in 7 steps from ($\pm$)-3-butyn-2-ol **7** (13.5% overall yield). The optical purity of the pheromone **1** should be 100%, since there was no synthetic operation which might have caused racemization.

EXPERIMENTAL

All boiling points were uncorrected. IR spectra refer to films. NMR spectra were recorded at 60 MHz in CCl₄ with TMS as an internal standard unless otherwise stated.

(*S*)-6-Acetoxy-4-methylhexanal **4**. Ozone was bubbled for 3 hr into a stirred and cooled solution of (*R*)-(+)-citronellyl acetate (30 g, $[\alpha]_D^{22} +3.79^\circ$ ($c=3.068$, CHCl₃)) in methanol (250 ml) containing sodium bicarbonate (2 g) at -56°C until the solution turned blue due to the presence of an excess of ozone. Nitrogen was bubbled into the solution to drive off the dissolved ozone. Dimethyl sulfide (30 ml) was then carefully added dropwise to a stirred and cooled (dry ice-acetone) solution. The stirring was continued overnight at ambient temperature. The mixture was concentrated *in vacuo*, diluted with water and extracted with ether. The ether solution was washed with water and brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue was distilled to give 15.7 g (60%) of **4**, bp $75\sim77^\circ\text{C}$ (0.5 mmHg); $n_D^{23} 1.4334$; $[\alpha]_D^{21} +3.31^\circ$ ($c=2.915$, CHCl₃); IR $\nu_{\text{max}} \text{ cm}^{-1}$: 2960 (m), 2930 (m), 2710 (w), 1740 (s), 1240 (s), NMR δ 0.92 (3H, d, $J=6\text{ Hz}$), 1.2~1.7 (5H, m), 1.95 (3H, s), 2.3~2.5 (2H, m), 3.99 (2H, t, $J=6\text{ Hz}$), 9.76 (1H, d, $J=2\text{ Hz}$); GLC (column, 5% PEG 20M, 2 m $\times$ 4 mm at $130^\circ\text{C}+5^\circ\text{C}/\text{min}$; carrier gas, N₂, 1 kg/cm²): t_R 4.7 min (98.5%). *Anal.* Found: C, 62.68; H, 9.23. Calcd. for C₉H₁₆O₃: C, 62.76; H,

9.36%.

(*R*)-(+)-3-Methyl-1-hexanol **5a**. 80% Hydrazine hydrate (20 ml) was added to a solution of **4** (12.5 g) in diethylene glycol (70 ml) and the mixture was heated under reflux for 1 hr. To this was added 50% potassium hydroxide aqueous solution (20 g) and the heating was continued under reflux for 30 min. The bath temperature was gradually raised to 210°C to give a low bp distillate. The mixture was heated under reflux for 1 hr. It was then steam-distilled by slowly adding water (50 ml). The combined distillates and the residue in the flask were extracted with ether. The ether solution was washed with dilute hydrochloric acid, saturated sodium bicarbonate solution, water and brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue was distilled to give 6.91 g (82%) of **5a**, bp $99\sim102^\circ\text{C}$ (97 mmHg); $n_D^{23} 1.4203$; $[\alpha]_D^{23} +1.54^\circ$ ($c=4.00$, CHCl₃); $\alpha_D^{23} +1.45^\circ$ (neat, $l=1\text{ dm}$); IR $\nu_{\text{max}} \text{ cm}^{-1}$: 3350 (m), 2970 (s), 2930 (s), 2880 (s), 1055 (m); NMR δ 0.7~1.0 (6H, m), 1.0~1.8 (7H, m), 3.25 (1H, s); 3.35 (2H, t, $J=6\text{ Hz}$); GLC (column, 5% FFAP, 2 m $\times$ 4 mm at $80^\circ\text{C}+5^\circ\text{C}/\text{min}$; carrier gas, N₂, 1.2 kg/cm²): t_R 3.3 min (99.6%). *Anal.* Found: C, 71.97; H, 13.83. Calcd. for C₇H₁₆O: C, 72.35; H, 13.88%.

(*R*)-3-Methylhexyl tosylate **5b**. Tosyl chloride (11.5 g) was added to a solution of **5a** (5.8 g) in dry pyridine (60 ml) with stirring and ice-cooling. The stirring was continued for 3 hr. The mixture was then poured into an ice-dilute hydrochloric acid solution and extracted with ether. The ether solution was washed with dilute hydrochloric acid, saturated cupric sulfate and brine, dried over magnesium sulfate and concentrated *in vacuo* to give an oily **5b** in a quantitative yield, IR $\nu_{\text{max}} \text{ cm}^{-1}$: 1595 (m), 1360 (s), 1185 (s), 1175 (s), 940 (s); NMR δ 0.76 (3H, d, $J=6\text{ Hz}$), 2.36 (3H, s), 3.92 (2H, t, $J=6\text{ Hz}$), 7.16 (2H, d, $J=8\text{ Hz}$), 7.58 (2H, d, $J=8\text{ Hz}$). This was employed for the next step without further purification.

(*R*)-(-)-3-Methylhexyl iodide **6**. Sodium iodide (9.0 g) was added to a stirred and heated solution of **5b** (prepared from 4.67 g of **5a**) in acetone (30 ml). The mixture was stirred and heated under reflux for 5 hr. The stirring was continued overnight at room temperature. The mixture was then concentrated *in vacuo*, diluted with water and extracted with ether. The ether solution was washed with sodium thiosulfate solution and brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue was distilled to give 5.4 g (60% from **5a**) of **6**, bp $69\sim78^\circ\text{C}$ (22 mmHg); $n_D^{24} 1.4806$; $[\alpha]_D^{24} -14.1^\circ$ ($c=1.058$, CHCl₃); IR $\nu_{\text{max}} \text{ cm}^{-1}$: 2970 (s), 2930 (s), 2880 (m), 1460 (m), 1380 (m), 1220 (m), 1180 (m); NMR δ 0.85 (3H, d, $J=6\text{ Hz}$), 0.88 (3H, deformed t, $J=6\text{ Hz}$), 1.0~2.1 (7H, m), 2.9~3.3 (2H, m); GLC (column, 3% SE-30, 2 m $\times$ 4 mm at $80^\circ\text{C}+5^\circ\text{C}/\text{min}$; carrier gas, N₂, 1 kg/cm²): t_R 4.3 min (95.7%). *Anal.* Found: C, 37.73; H, 6.79. Calcd. for C₇H₁₅I: C, 37.19; H, 6.69%.

($\pm$)-3-Heptyn-2-ol **8**. Lithium amide was prepared in the usual manner from lithium (0.763 g) and liquid ammonia (100 ml). To this was added ($\pm$)-7 (3.4 g) with stirring at -28°C . After stirring for 30 min at -28°C , the mixture was cooled to -63°C . *n*-Propyl iodide (7.64 g) was added dropwise to the stirred mixture during a 15 min period. The stirring was continued for 3 hr at -63°C and for the next 2 hr at -28°C . The mixture was left to stand overnight at room temperature to remove the ammonia, mixed with an ice-water solution and extracted with ether. The ether solution was washed with sodium thiosulfate solution, brine, dilute hydrochloric acid, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue was distilled to give 2.01 g (41%) of ($\pm$)-**8**, bp $70\sim 75^{\circ}\text{C}$ (24 mmHg); IR ν_{max} cm^{-1} : 3360 (s), 2250 (w), 1160 (s), 1080 (s); NMR δ 0.99 (3H, t, $J=6$ Hz), 1.36 (3H, d, $J=6$ Hz), 2.90 (1H, br. s), 4.2~4.6 (1H, m); GLC (column, 5% FFAP, 2 m $\times$ 4 mm at $80^{\circ}\text{C}+10^{\circ}\text{C}/\text{min}$; carrier gas, N_2 , 1 kg/cm 2): t_R 3.3 min, (99.6%). *Anal.* Found: C, 74.49; H, 10.71. Calcd. for $\text{C}_7\text{H}_{12}\text{O}$: C, 74.95; H, 10.78%.

($\pm$)-6-Heptyn-2-ol **9a**. 20% Potassium hydride in mineral oil (12 g) was washed several times with *n*-pentane (dried over sodium) to remove the oil. To this was added 3-aminopropylamine (50 ml, dried and distilled over barium oxide). The mixture was stirred for 1 hr at room temperature to give a solution of KAPA with evolution of hydrogen (ca. 1.2 liters). 3-Heptyn-2-ol **8** (1.14 g) was added dropwise over 8 min to the stirred solution of KAPA at 0°C . The mixture was stirred for 2 hr at room temperature. It was then poured into an ice-water solution and extracted with ether. The ether solution was washed with dilute hydrochloric acid and brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue was distilled to give 0.91 g (80%) of ($\pm$)-**9a**, bp $95\sim 98^{\circ}\text{C}$ (75 mmHg); $n_D^{21.5}$ 1.4424 IR ν_{max} cm^{-1} : 3400 (s, br), 3320 (s), 2130 (w), 1130 (m), 1090 (m); NMR δ 1.15 (3H, d, $J=6$ Hz), 1.3~1.7 (4H, m), 1.82 (1H, t, $J=2$ Hz), 2.0~2.4 (2H, m), 2.96 (1H, br. s), 3.75 (1H, br); GLC (column, 5% FFAP, 2 m $\times$ 4 mm at $100^{\circ}\text{C}+10^{\circ}\text{C}/\text{min}$; carrier gas, N_2 , 1 kg/cm 2): t_R 2.4 min (98.2%). *Anal.* Found: C, 74.46; H, 10.73. Calcd. for $\text{C}_7\text{H}_{12}\text{O}$: C, 74.95; H, 10.78%.

($\pm$)-6-Heptyn-2-ol tetrahydropyranyl ether **9b**. 2,3-Dihydropyran (1.26 g) and *p*-toluenesulfonic acid (a trace amount) were added to a solution of **9a** (1.1 g) in dry tetrahydrofuran (20 ml). The solution was left to stand overnight at room temperature. It was then poured into water and extracted with ether. The ether solution was washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and concentrated *in vacuo* to give **9b** in a quantitative yield as an oil, IR ν_{max} cm^{-1} : 3320 (m), 2140 (w), 1135 (m), 1080 (s), 1035 (s), 1020 (s), 1005 (m). This was employed for the next step without further purification.

(2*RS*,10*R*)-(-)-10-Methyl-6-tridecyn-2-ol **10b**. A solution of *n*-butyllithium in *n*-hexane (2.2*N*, 3.5 ml) was added dropwise to a stirred and cooled solution of **9b** (970 mg) in dry tetrahydrofuran (10 ml) at -50°C under argon. The temperature was gradually raised and the stirring continued for 3.5 hr at $0\sim 3^{\circ}\text{C}$ to complete the formation of the acetylide. The temperature was then kept at -30°C . To the stirred and cooled mixture, hexamethylphosphoric triamide (HMPA, 5 ml) was added dropwise. Subsequently a solution of **6** (1.13 g) in dry tetrahydrofuran (5 ml) was added dropwise. The temperature was gradually raised and the stirring was continued overnight at room temperature. The mixture was poured into an ice-water solution and extracted with *n*-hexane. The extract was washed with water and brine, dried over magnesium sulfate and concentrated *in vacuo* to give crude **10a** as an oil. This was dissolved in methanol (20 ml) containing a trace amount of *p*-toluenesulfonic acid. The solution was stirred at $60\sim 65^{\circ}\text{C}$ for 4 hr and then at room temperature overnight. It was poured into water and extracted with ether. The ether solution was washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by chromatography over silica gel and distilled to give 700 mg (75.3%) of **10b**, bp $84\sim 90^{\circ}\text{C}$ (0.15 mmHg); n_D^{24} 1.4556; $[\alpha]_D^{24} -1.3^{\circ}$ ($c=3.159$, CHCl_3); IR ν_{max} cm^{-1} : 3370 (m), 2980 (s), 2940 (s), 1130 (m), 1085 (m); NMR δ 0.85 (3H, d, $J=6$ Hz), 0.87 (3H, deformed t, $J=6$ Hz), 1.13 (3H, d, $J=6$ Hz), 3.65 (1H, m); MS (m/z): 210 (M^+); GLC (column, 5% FFAP, 2 m $\times$ 4 mm at $150^{\circ}\text{C}+5^{\circ}\text{C}/\text{min}$; carrier gas, N_2 , 1 kg/cm 2): t_R 5.2 min (97.9%). *Anal.* Found: C, 79.76; H, 12.21. Calcd. for $\text{C}_{14}\text{H}_{26}\text{O}$: C, 79.93; H, 12.40%.

(2*RS*,10*R*)-(-)-10-Methyl-2-tridecanol **11**. 10% Palladium-charcoal (50 mg) was added to a solution of **10b** (300 mg) in 99% ethanol (30 ml). The mixture was shaken under a hydrogen atmosphere for 3 hr at room temperature. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was chromatographed over silica gel and distilled to give 285.8 mg (93.5%) of **11**, bp $75\sim 80^{\circ}\text{C}$ (0.4 mmHg); $n_D^{24.5}$ 1.4392; $[\alpha]_D^{24.5} -1.1^{\circ}$ ($c=3.161$, CHCl_3); IR ν_{max} cm^{-1} : 3360 (m), 2870 (s), 2930 (vs), 2820 (s), 1460 (m), 1380 (m), 1120 (m); NMR δ 0.82 (3H, d, $J=6$ Hz), 0.86 (3H, deformed t, $J=6$ Hz), 3.55 (1H, m); MS (m/z): 214 (M^+); GLC (column, 5% FFAP, 2 m $\times$ 4 mm at 180°C ; carrier gas, N_2 , 1 kg/cm 2): t_R 2.8 min (92.7%). *Anal.* Found: C, 78.14; H, 13.83. Calcd. for $\text{C}_{14}\text{H}_{30}\text{O}$: C, 78.41; H, 14.11%.

(10*R*)-(-)-10-Methyl-2-tridecanone **1**. The Jones chromic acid reagent (8*N*, 0.4 ml) was added to a solution of **11** (240 mg) in acetone (10 ml) with stirring and ice-cooling. The mixture was stirred for 2 hr. The excess oxidant was destroyed by the addition of a small amount of 2-propanol. The mixture was concentrated *in vacuo*. The residue was mixed with water and extracted with

ether. The ether solution was washed with water and brine dried over magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed over silica gel and distilled to give 175 mg (74%) of **1**, bp (bath temperature) 105~115°C (3 mmHg); n_D^{23} 1.4330; $[\alpha]_D^{23}$ -1.4° ($c=3.017$, CHCl_3); IR ν_{max} cm^{-1} : 2960 (s), 2930 (vs), 2850 (s), 1720 (s), 1460 (m), 1360 (m), 1160 (m); NMR δ 0.86 (3H, d, $J=6$ Hz), 0.94 (3H, deformed t, $J=6$ Hz), 1.0~1.8 (17H, br), 1.98 (3H, s), 2.1~2.4 (2H, m); MS (m/z): 212 (M^+); GLC (column, 5% FFAP, 2 m $\times$ 4 mm at 180°C; carrier gas, N_2 , 1 kg/cm²); t_R 2.3 min (98.3%). *Anal.* Found: C, 78.87; H, 13.28. Calcd. for $\text{C}_{14}\text{H}_{28}\text{O}$: C, 79.18; H, 13.29%.

Acknowledgments. We thank Shiono Perfumery Co., Ltd., for the gift of (*R*)-(+)-pulegone from which (*R*)-(+)-citronellyl acetate was prepared. Our thanks are due to Mrs. Y. Naito of this Department for elemental analyses. We are grateful to Nitto Denko Co., Ltd. for their financial support.

REFERENCES

- 1) J. H. Tumlinson, "Les Colloques de l'INRA" ed. by Institut National de la Recherche Agronomique, Paris, Les Médiateurs Chimiques Agissant sur le Comportement des Insectes, Versailles, 16~20 November 1981, pp. 193~201.
- 2) P. L. Guss, J. H. Tumlinson, P. E. Sonnet and J. R. McLaughlin, in preparation (cited in ref. 1).
- 3) P. E. Sonnet, *J. Org. Chem.*, **47**, 3793 (1982).
- 4) K. Mori, S. Masuda and T. Suguro, *Tetrahedron*, **37**, 1329 (1981).
- 5) K. Mori and S. Kuwahara, *Tetrahedron*, **38**, 521 (1982).
- 6) C. A. Brown and A. Yamashita, *J. Am. Chem. Soc.*, **97**, 891 (1975).
- 7) C. A. Brown and A. Yamashita, *J. Chem. Soc., Chem. Commun.*, 959 (1976).
- 8) C. A. Brown and E. Negishi, *J. Chem. Soc., Chem. Commun.*, 318 (1977).
- 9) M. M. Midland and R. L. Halterman, *Tetrahedron Lett.*, **22**, 4171 (1981).
- 10) C. A. Brown, *J. Org. Chem.*, **39**, 3913 (1974).
- 11) C. A. Brown, *J. Chem. Soc., Chem. Commun.*, 222 (1975).