Tetrahedron. Vol 33, pp 385 to 387 Pergamon Press 1977 Printed in Great Britain

SYNTHESIS OF ALIPHATIC INSECT PHEROMONES FROM ALICYCLIC STARTING MATERIALS

(*Z*)-6-HENEICOSEN-11-ONE AND (*Z*)-8-DODECENYL ACETATE†

K. MORI,* M. UCHIDA‡ and M. MATSUI
Department of Agricultural Chemistry, The University of Tokyo, Yayoi 1-1-1, Bunkyo-ku, Tokyo 113, Japan

(*Received in Japan* 3 *July* 1976; *Received in the UK for publication* 28 *September* 1976)

Abstract—Both (*Z*)-6-heneicosen-11-one, the pheromone of Douglas fir tussock moth, and (*Z*)-8-dodecenyl acetate, the pheromone of oriental fruit moth, have been synthesized from cyclohexane-1,3-dione.

A strategy frequently employed in natural products synthesis is the construction and later fragmentation of an extra ring as a control synthon to give carbon chains existing in the final target molecule.[1] However, in the field of pheromone synthesis, especially with aliphatic pheromones, this concept has seldom been employed because of the accessibility of various types of aliphatic starting materials, although some of them are very expensive. As far as we know, the fragmentation strategy was used only in the syntheses of propylure[2] and the queen substance of honeybee.[3,4] Here we describe two additional examples of this concept which have been executed without using expensive starting materials.

The first example is the synthesis of (*Z*)-6-heneicosen-11-one (**1**), the pheromone of Douglas fir tussock moth (*Orgyia pseudotsugata*), isolated by Smith *et al.*[5] They reported its synthesis by constructing the carbon chain of **1** by the alkylation of undecanal dithianyl anion with 1-chloro-4-decyne.[6] Our synthesis started from cyclohexane-1,3-dione. It was converted to 3 - ethoxy - 2-cyclohexenone (**2**) by the known method.[7] The ketone (**2**) was treated with lithium and n-decyl bromide in THF[8] to give an α,β-unsaturated ketone (**3**) after acid hydrolysis. This procedure gave better result (65% yield of **3** from **2**) than the conventional Grignard reaction (45% yield of **3** from **2**). The ketone (**3**) was oxidized to yield an α,β-epoxy ketone (**4**). Its fragmentation according to Eschenmoser and Ohloff *et al.*[9] via the corresponding tosylhydrazone gave an acetylenic ketone (**5**) as crystals in 70% yield from **4**. The CO group was protected as an ethylene acetal to give **6**, which was alkylated with n-amyl bromide to give **7**. Regeneration of the CO group gave the alkylated acetylenic ketone (**8**). Semi-hydrogenation of **8** over Pd–$BaSO_4$ gave the pheromone (**1**). The over-all yield of the pheromone (**1**) from cyclohexane-1,3-dione was 15%.

The second example is the synthesis of (*Z*)-8-dodecenyl acetate (**9**). This was isolated by Roelofs *et al.* as the pheromone of oriental fruit moth (*Grapholithia molesta*).[10] The conventional synthesis of this type of pheromones employs the expensive heptamethylene glycol as a starting material. We used 1-bromo-2-hexyne (**10**) and cyclohexane-1,3-dione as two C_6 synthons. Alkylation of the diketone with the bromide (**10**) gave a crystalline product (**11**). This was cleaved with alkali and the product was reduced *in situ* by the Huang-Minlon reduction[11] to give an acetylenic acid (**12**). The reduction of **12** with LAH yielded an alcohol (**13**). This was hydrogenated over P-2 Ni[12] to give an olefinic alcohol (**14**). Acetylation of **14** afforded the pheromone (**9**) in 14% over-all yield from cyclohexane-1,3-dione.

In conclusion cyclohexane-1,3-dione was shown to be a versatile C_6-synthon in the synthesis of aliphatic insect pheromones. Very recently a synthesis of racemic brevicomin, a bicyclic acetal pheromone, appeared in which 2 - ethyl - 3 - methyl - 2 - cyclohexenone served as the starting material to give the required carbon skeleton after fragmentation.[13]

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra refer to films unless otherwise specified and were determined on a Jasco IRA-1 spectrometer. NMR spectra were recorded as CCl_4 solns at 60 MHz with TMS as an internal standard on a Hitachi R-24A spectrometer. GLC analyses were performed on a Yanaco G80 gas chromatograph.

3-*n-Decyl-2-cyclohexenone* (**3**). A mixture of **2** (7 g) and n-decyl bromide (13.3 g) was added dropwise to a suspension of Li (0.87 g) in dry THF (15 ml) at 20–30° with stirring under N_2. After the addition, the mixture was stirred for 1 hr at room temp. The excess Li was filtered off. The filtrate was poured into ice-dil H_2SO_4 and extracted with ether. The ether soln was washed with $NaHCO_3$ aq and NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 7.7 g (65.3%) of **3**, b.p. 130–132°/0.3 mm, n_D^{23} 1.4792; ν_{max} 2920, 2860, 1670, 1625, 1470, 1455, 1430, 1375, 1350, 1330, 1260, 1195, 1135, 960, 885, 760, 720 cm^{-1}; δ 0.90 (3 H, t, J = 6 Hz), 1.29 (18 H, br. s), 1.50–2.40 (6 H, m), 5.77 (1 H, br. s). (Found: C, 80.76; H, 11.71. $C_{16}H_{28}O$ requires: C, 81.29; H, 11.94%).

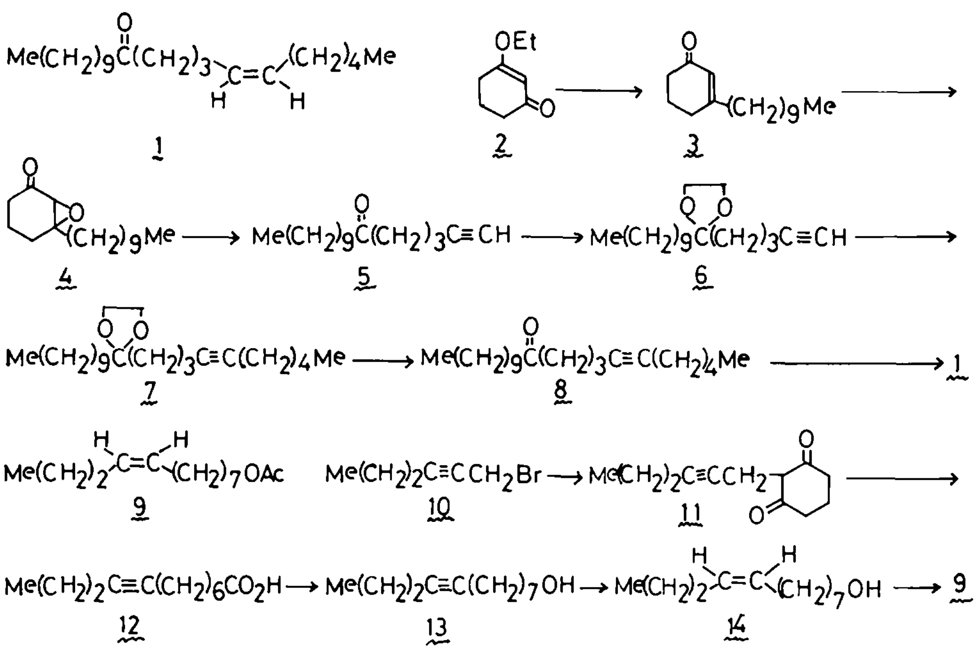
3-*n-Decyl-2,3-epoxycyclohexanone* (**4**). 30% H_2O_2 (16 ml) was added dropwise to a stirred and ice-cooled soln of **3** (9.6 g) in MeOH (40 ml) at 10°. Subsequently 6 N NaOH (3.5 ml) was added to the mixture during 5 min period. After stirring for 3 hr at 20–25°, the mixture was poured into water and extracted with ether. The ether soln was washed with water and NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 8.1 g (80.4%) of **4**, b.p. 125–126°/0.2 mm, n_D^{23} 1.4642; ν_{max} 2920, 2860, 1720, 1470, 1410, 1380, 1355, 1330, 1260, 1190, 1160, 1070, 970, 900, 820, 780, 730 cm^{-1}; δ 0.88 (3 H, t, J = 6 Hz), 1.26 (18 H, br. s), 1.40–2.50 (6 H, m), 2.91 (1 H, s). (Found: C, 76.41; H, 11.24. $C_{16}H_{28}O_2$ requires: C, 76.14; H, 11.18%).

1-*Hexadecyn-6-one* (**5**). *p*-Tosylhydrazide (3.7 g) was added in one portion to a stirred and ice-cooled soln of **4** (5 g) in CH_2Cl_2 (20 ml) and AcOH (10 ml) at 0–2°. The mixture was stirred for 3 hr at 0–2° and for another 3 hr at room temp. Then it was poured into water and extracted with n-hexane. The n-hexane soln was

---

†Pheromone Synthesis—XIV. Part XIII, K. Mori, *Tetrahedron* **33**, 289 (1977).

‡Research Fellow on leave from Otsuku Pharmaceutical Co., Ltd., Tokushima Factory.



washed with water, NaHCO$_3$ aq and NaCl aq, dried (MgSO$_4$) and concentrated *in vacuo*. The residue was distilled to give 3.3 g (70%) of **5**, b.p. 122–123°/0.8 mm. This oil solidified and the solid was recrystallized from light petroleum to give prisms, m.p. 27–28°; ν_{max} 3300, 2920, 2850, 2120, 1710, 1470, 1440, 1410, 1370, 1130, 1090, 760, 720 cm^{-1}; δ 0.88 (3 H, t, J = 6 Hz), 1.27 (18 H, br.s), 1.50–2.05 (3 H, m), 2.05–2.20 (4 H, m); GLC (Column, 5% SE-30 in glass tube, 2 m × 3 mm i.d. at 200°; Carrier gas, N$_2$, 1.0 kg/cm^2): R$_t$ 3.6 min. (Found: C, 80.91; H, 11.78. $C_{16}H_{28}O$ requires: C, 81.29; H, 11.94%).

6-*Ethylenedioxy*-1-*hexadecyne* (**6**). A mixture of **5** (3 g), ethylene glycol (0.9 g) and *p*-TsOH (5 mg) in dry C_6H_6 (100 ml) was heated under reflux for 6 hr with continuous removal of water. After cooling, it was washed with NaHCO$_3$ aq and NaCl aq, dried (MgSO$_4$) and concentrated *in vacuo*. The residue was distilled to give 3 g (83.3%) of **6**, b.p. 120–125°/0.3 mm, n_D^{23}1.4570; ν_{max} 3020, 2940, 2860, 2130, 1470, 1440, 1380, 1320, 1220, 1140, 1100, 1060, 950, 930, 840, 730 cm^{-1}; δ 0.88 (3 H, t, J = 6 Hz), 1.26 (18 H, br. s), 1.50–1.90 (5 H, m), 2.00–2.50 (2 H, m), 3.84 (4 H, s); GLC (Column, 5% SE-30, 2 m × 3 mm i.d. at 220°; Carrier gas, N$_2$, 1.0 kg/cm^2): R$_t$ 3.7 min (86% purity). (Found: C, 77.08; H, 11.38. $C_{18}H_{32}O_2$ requires: C, 77.09; H, 11.50%).

11-*Ethylenedioxy*-6-*heneicosyne* (**7**). A soln of n-BuLi in n-hexane (1.7 N, 6.6 ml) was added dropwise to a stirred and ice-cooled soln of **6** (2.8 g) in dry THF (15 ml) under N$_2$. The mixture was stirred for 15 min at room temp. A soln of n-amyl bromide (3 g) in dry HMPA (25 ml) was added to the stirred and ice-cooled mixture. After stirring for 1 hr under ice-cooling, the mixture was poured into water and extracted with n-hexane. The n-hexane soln was washed with water and NaCl soln, dried (MgSO$_4$) and concentrated *in vacuo*. The residue was distilled to give 2.8 g (80%) of **7**, b.p. 165–168°/0.3 mm, n_D^{24} 1.4612; ν_{max} 2940, 2860, 1470, 1440, 1380, 1330, 1310, 1210, 1130, 1090, 1060, 940, 930, 720 cm^{-1}; δ 0.92 (6 H, m), 1.23 (24 H, br. s), 1.20–1.80 (4 H, m), 1.90–2.30 (4 H, m), 3.83 (4 H, s); GLC (Column, 5% SE-30, 2 m × 3 mm i.d. at 220°; Carrier gas, N$_2$, 1 kg/cm^2): R$_t$ 17.9 min (93.4%); TLC (Merck Kieselgel F$_{254}$, C_6H_6-ether = 10:1): R$_f$ 0.68. (Found: C, 78.89; H, 12.08. $C_{23}H_{42}O_2$ requires: C, 78.80; H, 12.08%).

6-*Heneicosyn*-11-*one* (**8**). 3 N HClO$_4$ (5 ml) was added to a soln of **7** (1.5 g) in THF (15 ml) and the mixture was left to stand overnight in a refrigerator. Then it was concentrated *in vacuo*, diluted with water and extracted with ether. The ether soln was washed with NaHCO$_3$ aq and NaCl aq, dried (MgSO$_4$) and concentrated *in vacuo*. The residue was distilled to give 1.16 g (88.5%) of **8**, b.p. 145–150°/0.2 mm, n_D^{24} 1.4568; ν_{max} 2920, 2840, 1710, 1470, 1440, 1410, 1370, 1330, 1130, 1090, 740 cm^{-1} δ 0.92 (6 H, m), 1.27 (24 H, br. s), 1.95–2.25 (4 H, m), 2.30–2.60 (4 H, m); GLC (Column, 5% SE-30, 2 m × 3 mm i.d. at 220°; Carrier gas, N$_2$, 1 kg/cm^2): R$_t$ 5.5 (0.9%), 10.0 (99.1%) min; TLC (Merck Kieselgel F$_{254}$,C_6H_6-ether = 10:1): R$_f$ 0.83. (Found: C, 82.32; H, 12.43. $C_{21}H_{38}O$ requires: C, 82.28; H, 12.50%).

(*Z*)-6-*Heneicosen*-11-*one* (**1**). 5% Pd-BaSO$_4$ (150 mg) and quinoline (2 drops) were added to a soln of **8** (0.9 g) in MeOH (15 ml) and the mixture was shaken under H$_2$ (atm press) at room temp. When H$_2$ uptake ceased, the mixture was filtered to remove Pd and the filtrate was concentrated *in vacuo*. The residue was dissolved in ether. The ether soln was washed with dil HCl, NaHCO$_3$ aq and NaCl aq, dried (MgSO$_4$) and concentrated *in vacuo*. The residue was distilled to give 0.78 g (86%) of **1**, b.p. 138–140°/0.2 mm, n_D^{25} 1.4541; ν_{max} 3020, 2940, 2860, 1720, 1470, 1420, 1380, 1130, 1090, 720 cm^{-1}; δ 0.90 (6 H, m), 1.28 (24 H, br. s), 1.97 (4 H, m), 2.32 (4 H, t), 5.36 (2 H, m); MS: *m*/*e* 124 (100%), 167 (33%), 169 (57%), 197 (29%), 308 (7%) = M$^+$; GLC (Column, 5% SE-30, 2 m × 3 mm i.d. at 220°; Carrier gas, N$_2$, 1 kg/cm^2); R$_t$ 1.8 (0.6%), 2.3 (0.6%), 4.6 (1.0%), 5.2 (1.5%), 9.4 (96.3%) min; TLC (Merck Kieselgel F$_{254}$, C_6H_6-ether = 10:1): R$_f$ 0.80. (Found: C, 81.99; H, 12.95. $C_{21}H_{40}O$ requires: C, 81.75; H, 13.07%).

2 - (2' - *Hexynyl*) - *cyclohexane* - 1,3 - *dione* (**11**). Cyclohexane - 1,3 - dione (7.8 g) was dissolved in a soln of KOH (3.9 g) in 50% MeOH (22 ml). 1-Bromo-2-hexyne (12.4 g) was added to the soln and the mixture was heated under reflux for 7 hr. Then the mixture was concentrated *in vacuo* and the residue was mixed with 5% NaOH aq (100 ml). The neutral impurities were extracted with ether. The aqueous layer was evacuated to remove the dissolved ether and acidified carefully with ice-dil HCl to pH 4. The ppt was collected on a filter and recrystallized from EtOH to give 6 g (45%) of **11** as needles, m.p. 148–150°, ν_{max} (Nujol) 2920, 2860, 2800–2100, 1570, 1460, 1370, 1310, 1280, 1230, 1200, 1150, 1100, 1070, 1010, 900, 860, 760 cm^{-1}; δ 0.98 (3 H, t, J = 6 Hz), 1.30–2.90 (12 H, m), 3.31 (1 H, br. s). (Found: C, 74.75; H, 8.18, $C_{12}H_{16}O_2$ requires: C, 74.97; H, 8.39%).

8-*Dodecynoic acid* (**12**). Powdered KOH (7.8 g) was dissolved in diethylene glycol (70 ml). To this were added **11** (7.2 g), 80% $N_2H_4 \cdot H_2O$ (9 ml) and MeOH (6 ml). The mixture was heated at 125° for 12 hr. Then the inner temp. was raised to 195° to remove volatile materials (water, $N_2H_4 \cdot H_2O$ and MeOH). The mixture was kept at 195° for 8 hr. After cooling, the mixture was diluted with water, acidified with dil HCl and extracted with ether. The ether soln was washed with water and NaCl soln, dried (MgSO$_4$) and concentrated *in vacuo*. The residue was distilled to give 4.8 g (65%) of **12**, b.p. 127–128°/0.65 mm, n_D^{23} 1.4617; ν_{max} 3600–3000, 2920, 2860, 2800–2000, 1710, 1460, 1440, 1420, 1380, 1290, 1260, 1230, 1150, 1080, 930, 880 cm^{-1}; δ 0.97 (3 H, t, J = 6 Hz), 1.20–2.60 (16 H, m, 1.28, 1.43, 1.72, 1.77, 2.10, 2.22, 2.33) (Found: C, 73.08; H, 10.18. $C_{12}H_{20}O_2$ requires: C, 73.42; H, 10.27%).

8-*Dodecyn*-1-*ol* (**13**). A soln of **12** (3 g) in dry ether (30 ml) was added dropwise during 1 hr to a stirred and ice-cooled suspension of LAH (1.2 g) in dry ether (50 ml). The mixture was stirred for 1 hr at room temp. Water was carefully added to destroy excess LAH. The mixture was poured into ice-dil H_2SO_4. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether soln was washed with NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 2.4 g (86%) of **13**, b.p. 99–100°/0.6 mm, n_D^{23} 1.4626; ν_{max} 3320, 2940, 2870, 1460, 1440, 1380, 1340, 1290, 1060, 880 cm^{-1}; δ 0.96 (3 H, t, J = 6 Hz), 1.36 (12 H, br. s), 2.10 (4 H, m), 3.52 (2 H, t, J = 6 Hz), 3.83 (1 H, s). (Found: C, 78.78; H, 11.70. $C_{12}H_{22}O$ requires: C, 79.01; H, 12.05%).

(Z)-8-*Dodecen*-1-*ol* (**14**). P-2 Ni catalyst was prepared by adding a soln of $NaBH_4$ (60 mg) in 95% EtOH (2 ml) to a soln of $Ni(OAc)_2$ (400 mg) in 95% EtOH (20 ml). Ethylenediamine (244 mg) and **13** (1.8 g) were added to the catalyst suspension and the mixture was shaken under H_2 (atm press) at room temp. After 1 mol H_2 uptake, the catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was diluted with water and extracted with ether. The ether soln was washed with NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 1.3 g (72%) of **14**, b.p. 99–100°/1.1 mm, n_D^{23} 1.4552; ν_{max} 3300, 2920, 2860, 1460, 1380, 1050 cm^{-1}; δ 0.90 (3 H, t, J = 6 Hz), 1.32 (12 H, br. s), 2.00 (4 H, m), 3.20 (1 H, s), 3.50 (2 H, t, J = 6Hz), 5.38 (2 H, m); GLC (5% LAC-2R-446 Column, 1.5 m × 3 mm i.d. at 130°; Carrier gas, N_2, 1.0 kg/cm^2): R_t 12.7 (6%), 16.3 (92%), 18.2 min (2%). (Found: C, 78.20; H, 12.58. $C_{12}H_{24}O$ requires: C, 78.19; H, 13.13%).

(Z)-8-*Dodecenyl acetate* (**9**). Ac_2O (2 ml) was added to a soln of **14** (1 g) in dry C_5H_5N (3 ml) and the mixture was left to stand overnight at room temp. Then it was poured into water and extracted with ether. The ether soln was washed with dil HCl and NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 0.96 g (75%) of **9**, b.p. 97–98°/1.2 mm, n_D^{23} 1.4436; ν_{max} 2920, 2860, 1740, 1460, 1440, 1390, 1370, 1240, 1040 cm^{-1}; δ 0.90 (3 H, t, J = 6 Hz), 1.33 (16 H, br. s), 1.96 (3 H, s), 4.02 (2 H, t, J = 6 Hz), 5.35 (2 H, m); GLC (5% LAC-2R-446 Column, 1.5 m × 3 mm i.d. at 130°; Carrier gas, N_2, 1.0 kg/cm^2): R_t 11.7 (5.4%), 14.4 (93.4%), 17.0 min (1.2%). (Found: C, 74.08; H, 11.26. $C_{14}H_{26}O_2$ requires: C, 74.29; H, 11.58%).

Acknowledgements—We thank Mr. Y. Manabe of Otsuka Pharmaceutical Co., Ltd., Tokushima Factory, for his kind gift of cyclohexane-1,3-dione. We are grateful to Ms. H. Sasaki and Ms. Y. Naito, this Department, for elemental analyses.

REFERENCES

[1] E. J. Corey, *Pure Appl. Chem.* **14**, 19 (1967).

[2] M. Stoll and I. Flament, *Helv. Chim. Acta* **52**, 1996 (1969).

[3] M. Barbier, E. Lederer and T. Normura, *C.R. Acad. Sci., Paris* **251**, 1133 (1960.

[4] R. E. Doolittle, M. S. Blum and R. Boch, *Ann. Entomol. Soc. Am.* **63**, 1180 (1970).

[5] R. G. Smith, G. E. Daterman and G. D. Davis, Jr., *Science* **188**, 63 (1975).

[6] R. G. Smith, G. D. Davis, Jr. and G. E. Daterman, *J. Org. Chem.* **40**, 1593 (1975).

[7] W. F. Gannon and H. O. House, *Org. Synth. Col. Vol.* **5**, 539 (1973).

[8] P. J. Pearce, D. H. Richards and N. F. Scilly, *J. Chem. Soc.* Perkin I 1655 (1972).

[9] A. Eschenmoser, D. Felix and G. Ohloff, *Helv. Chim. Acta* **50**, 708 (1967).

[10] W. L. Roelofs, A. Comeau and R. Selle, *Nature* **224**, 723 (1969).

[11] H. Stetter, *Newer Methods of Preparative Organic Chemistry* (Edited by W. Foerst), Vol. 2, pp. 51–99. Academic Press, New York (1963).

[12] C. A. Brown and K. K. Ahuja, *J. Chem. Soc.* Chem. Comm. 553 (1973).

[13] P. J. Kocienski and R. W. Ostrow, *J. Org. Chem.* **41**, 398 (1976).