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Efficient Synthesis of the Components of the German Cockroach Sex Pheromone I

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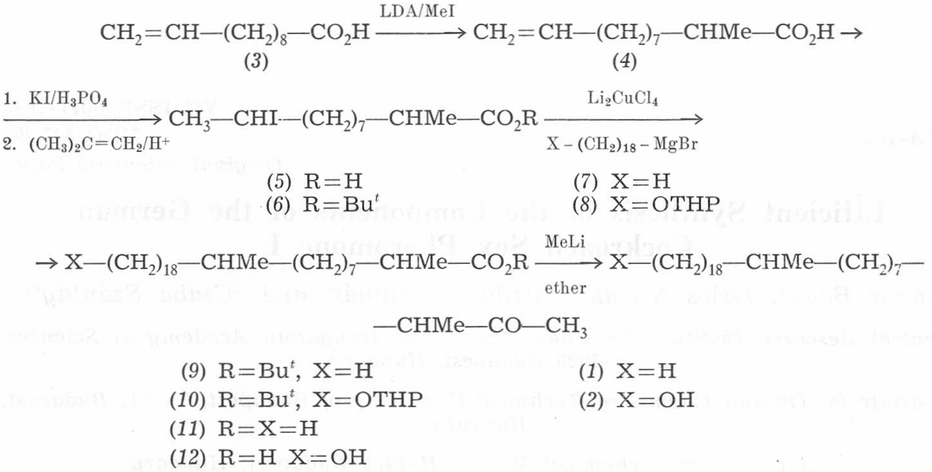
We wish to report a short (6 steps) synthesis of sex pheromones of the German cockroach, the 3,11-dimethyl-2-nonacosanone (*1*) and the 29-hydroxy-3,11-dimethyl-2-nonacosanone (*2*) using the halopolycarbon homologation as the key step. The *t*-butyl-2-methyl-10-iodo-undecanoate (*6*) synthetized from 10-undecenoic acid (*3*) by methylation and iodination was coupled with the Grignard reagent derived from stearyl bromide (*7*) and 18-bromooctadecanyl-tetrahidro-2-pyranyl ether (*8*) in the presence of dilithium tetrachlorocuprate. The natural pheromones (*1* and *2*) were finally obtained from the 2,10-dimethyl-octacosanon acid derivatives (*11* and *12*) with methyllithium in 23% (*1*) and 16% (*2*) overall yields.

The two components of the sex pheromone of the female German cockroach (*Blattella Germanica, L.*), the 3,11-dimethyl-2-nonacosanone (*1*) and 29-hydroxy-3,11-dimethyl-2-nonacosanone (*2*) were isolated and identified by Nishida and co-workers.[1,2] Several recent publications reported the synthesis of these compounds yielding diastereomeric mixtures.[3] Mori *et al.*[4] prepared all the four stereoisomers of both pheromone components in optically active form and established the 3*S*, 11*S* configurations of the natural pheromones. The natural pheromone and the synthetic stereoisomers showed essentially the same biological activity.

As a part of a project in which readily available starting materials are used in the synthesis of insect pheromones we elaborated a short (6 steps) synthesis of both pheromone components (*1* and *2*). As shown in Scheme I 10-undecenoic acid (*3*), easily obtained by the pyrolysis of ricinoleic acid, was chosen as starting material.

Treatment of *3* with 3 equiv. of lithium diisopropylamide generated the dianion which was quenched with 1 molar equiv. of methyl iodide.[5] The resulting methylated acid (*4*) was treated with a mixture of potassium iodide and phosphoric acid[6] to give the iodide compound *5*, which was converted to the corresponding *t*-butyl ester (*6*) by standard *t*-butyl ester synthesis.[7] This ester was then coupled with the Grignard reagent derived from stearyl

Scheme I



$$CH_2{=}CH{-}(CH_2)_8{-}CO_2H \; (3) \xrightarrow{LDA/MeI} CH_2{=}CH{-}(CH_2)_7{-}CHMe{-}CO_2H \; (4) \rightarrow$$

$$\xrightarrow[2.\ (CH_3)_2C{=}CH_2/H^+]{1.\ KI/H_3PO_4} CH_3{-}CHI{-}(CH_2)_7{-}CHMe{-}CO_2R \xrightarrow[X-(CH_2)_{18}-MgBr]{Li_2CuCl_4}$$

(5) $R{=}H$ (6) $R{=}Bu^t$ (7) $X{=}H$ (8) $X{=}OTHP$

$$\rightarrow X{-}(CH_2)_{18}{-}CHMe{-}(CH_2)_7{-}CHMe{-}CO_2R \xrightarrow[ether]{MeLi} X{-}(CH_2)_{18}{-}CHMe{-}(CH_2)_7{-}$$

$$-CHMe{-}CO{-}CH_3$$

(9) $R{=}Bu^t$, $X{=}H$ (1) $X{=}H$
(10) $R{=}Bu^t$, $X{=}OTHP$ (2) $X{=}OH$
(11) $R{=}X{=}H$
(12) $R{=}H$ $X{=}OH$

bromide (7) in the presence of dilithium tetrachlorocuprate[8] at a low temperature (—20 °C).[9] As expected, this coupling reaction with the sterically congested secondary alkyl halide (6) was slow and gave compound 9 in moderate yield (46%). Pheromone component 1 was finally obtained by the hydrolysis of ester 9 followed by treatment of the resulting acid 11 with methyllithium[10] in 23% overall yield.

Iodo ester 6 also served as the key intermediate in the synthesis of pheromone component 2. Here, in the coupling reaction we used the Grignard reagent (8) of the 18-bromo-octadecanyl tetrahydropyran-2-yl ether[2b] which was generated from 1,18-octadecanediol[11] and prepared pheromone 2 by the acid catalysed hydrolysis of the ester and the protecting group, followed by the same reaction with methyl lithium as described above, *via* intermediates *10* and *12* in 16% overall yield from 10-undecenoic acid.

EXPERIMENTAL

Melting points and boiling points are uncorrected. Infrared spectra were recorded on a SPECTROMOM 2000 spectrophotometer. Proton (^{1}H-NMR) and carbon (^{13}C-NMR) magnetic resonance spectra were taken on a Varian S-100 XL instrument in deuterochloroform with tetramethylsilane as internal standard. MS measurements were obtained on a JEOL JMS-0156-2 GC/MS system.

2-Methyl-10-undecenoic Acid (4)

A solution of 10 g (54 mmol) 10-undecenoic acid in HMPT (15 ml) was added to the *in situ* generated lithium-diisopropylamide from 16.6 (160 mmol) diisopropyl-amine and equiv butyl-lithium in tetrahydrofuran (80 ml) at 0 °C. After 20 minutes 9.3 g (65 mmol) methyl iodide was added to the mixture without cooling. The temperature rose to 36 °C and the mixture was stirred for 2 h without cooling and heating, then poured to solution of hydrochloric acid (10%) and extracted with ether. The organic layer was separated and washed with 1 M hydrochloric acid, water and brine, then dried ($MgSO_4$). After removing the solvent, the residue was distilled to give (4) (9.1 g, 85%); b. p.: 100—104 °C (0.1 mm); ν_{max}: 1650, 1720 cm^{-1}; δ_H 5.6—6.0 (1H, m, =CH—), 4.85—5.15 (2H, m, =CH_2), 2.34 (1H, t, *J* 7Hz, 2-CH), 1.15 (3H, d, *J* 7Hz); (Found: C, 72.61; H, 11.36. $C_{12}H_{22}O_2$ requires C, 72.68; H, 11.18%).

10-Iodo-2-methylundecanoic Acid (5)

10 g Phosphorouspentoxide and 50 g potassium-iodide was dissolved in 21 ml phosphoric acid (ca 85%) and 19.8 g (100 mmol) *4* was added to the mixture and then stirred at 80 °C for 3 h. After cooling the reaction mixture was diluted with ether. The resulting dark solution was washed with water, acidified with sodium hydrogensulfite solution and dried (Na_2SO_4). After removing the solvent *in vacuo*, the residue was distilled to give the light yellow *5;* (26 g, 80%); b. p.: 135—140 °C (0.1 mm); ν_{max}: 1715, 1415, 1370, 1270 cm^{-1}; δ_H 4.1 (1H, m, 10-CH), 1.92 (3H, d, *J* 7Hz, 12-CH_3); 1.17 (3H, d, *J* 7Hz, 2'-CH_3); *m/z* 199 (42%, M^+-I), 185 (30%), 124 (11%), 84 (62%), 56 (100%); (Found: C, 44.09, H, 7.22 I, 38.68. $C_{12}H_{23}O_2I$ requires C, 44.18 H, 7.10 I, 38.90%).

t-*Butyl-10-iodo-2-methylundecanoate (6)*

A solution of 16.8 g (50 mmol) *5* in dichloromethane (150 ml), which contained 0.6 ml sulfuric acid, was saturated with isobutylene (volume raised with about 50 ml) and the closed flask was left to stand for 3 days at room temperature. Then the mixture was neutralized powdered potassium carbonate and the solvent removed *in vacuo*. The residue was dissolved in ether and washed successively with sodium hydrogencarbonate, water and brine, dried ($MgSO_4$). After removing the solvent, the crude *6* was purified by flash chromatography (benzene-acetone) (10—0.2) to afford (*6*) as a light yellow liquid (18.2 g, 93%); ν_{max}: 1730, (C=O), 1460, 1370, 1240, 1150 cm^{-1}; δ_H 4.13 (1H, q, *J* 7Hz, 10-CH), 2.2 (1H, m, 2-CH), 1.9 (3H, d, *J* 7Hz; 11-CH_3), 1.42 (9H, s, Bu^t), 1.1—1.75 (14H, m, CH_2), 1.07 (3H, d, *J* 7Hz, 2'-CH_3); (Found: C, 50.13, H, 8.22, I, 33.07, $C_{16}H_{31}O_2I$ requires C, 50.26, H, 8.17, I, 33.19%).

t-*Butyl-2,10-dimethyloctacosanoate (9)*

A solution of the Grignard reagent *7* was prepared from 4.0 g (12 mmol) stearyl bromide and 0.33 g (14 mmole) magnesium in tetrahydrofuran (60 ml) by reflux (2 h) in the usual manner. The cooled solution was added dropwise for 1.5 h under an inert atmosphere to a cooled (—20 °C) solution of 3.8 g (10 mmol) *6* in tetrahydrofuran (30 ml) containing 0.22 g (1 mmol) dilithium tetrachlorocuprate in tetrahydrofuran (10 ml). The mixture was held at 0 °C for 3 h, hydrolysed with 1 : 1 mixture of 10% ammonium chloride solution and brine, and extracted with ether. The ether extract was washed with ammonium chloride solution, sodium hydrogencarbonate, water and brine and dried (Na_2SO_4). After removing the solvent, the crude *9* was purified by flash chromatography (benzene-acetone) (10 : 0.2), as eluant ($R_f \approx 0.4$) to give *9* as a colourless liquid; (2.3 g, 46%); ν_{max}: 1730, 1460, 1370, 1150 cm^{-1}; δ_H: 2.1—2.3 (1H, m, 2-CH); 1.42 (9H, s, Bu^t), 1.1—1.8 (49H, m, CH_2), 1.06 (3H, d, *J* 7Hz, 2'-CH_3), 0.86 (3H, t, *J* 6Hz, CH_3) 0.83 (3H, d, *J* 7Hz, 10'-CH_3); Found: C, 80.31, H, 13.51. $C_{34}H_{68}O_2$ requires C, 80.24, H, 13.47%).

2,10-Dimethyloctacosanoic Acid (11)

A solution of 2.50 g (5 mmol) *9* and 0.25 g *p*-toluenesulfonic acid in 15 ml of benzene was refluxed for 30 minutes, then cooled and diluted with ether. The organic layer was washed with water and brine, and dried (Na_2SO_4). Removal of the solvent gave *11,* (1.95 g, 86%); m. p. 46—49 °C (lit.[3b] m. p. 49—51 °C); ν_{max}: 1705, 1460, 1380, 1230, 1140 cm^{-1}; δ: 2.1—2.3 (1H, m, 2-CH), 1.1—1.8 (49H, m) 1.03 (3H, d, *J* 7Hz, 2'-CH_3), 0.86 (3H t, *J* 6Hz, CH_3) 0.83 (3H, d *J* 7Hz 10'-CH_3); *m/z*: 452 (69%, M^+); 438 (7%), 199 (10%) 130 (11%) 74 (100%): (Found: C, 79.52 H, 13.41, $C_{30}H_{60}O_2$ C, 79.58, H, 13.35%).

3-11-Dimethyl-2-nonacosanone (1)

2.2 mmol methyl lithium in hexane was added to a cooled (0 °C) solution of 0.45 g (1 mmol) acid *10* in ether (20 ml) under an inert atmosphere and stirred at 0—5 °C for 5 h. The mixture was hydrolysed with 1 M hydrochloric acid, extracted with ether and the organic layer was washed with 1 M hydrochloric acid, sodium-hydrogencarbonate solution, water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude *1* was purified by column chromatography (benzene-acetone) (100 : 0.1) to afford pheromone *1* as a diastereomeric mixture (0.41 g, 91%); m. p.: 29—32 °C (lit.[1b] m. p. 29—31 °C); ν_{max}: 1715 cm^{-1}; δ_H 2.45 (1H, m, 3-CH), 2.10 (3H, s, CH_3CO), 1.1—1.6 (49H, m), 1.04 (3H, d, *J* 7Hz, 3'-CH_3), 0.86 (3H, t *J* 7Hz, CH_3) 0.83 (3H, d, *J* 6Hz, 11'-CH_3); δ_C: 212.40 (CO) 47.26 (2-CH), 27.19 (1-CH_3), 19.75 (3'-CH_3), 16.19 (11'-CH_3), 14.12 (29-CH_3); (Found: C, 82.68; H, 13.97, $C_{31}H_{62}O$ requires C, 82.59, H, 13.86%).

t-*Butyl-29-(2'-tetrahydropyranyloxi)-2,10-dimethyloctacosanoate (10)*

The Grignard reagent of *8* was prepared from 18-bromooceadecanyl tetrahydropyranyl ether[2b] by the modified method of Babler and Invergo[12]. A flame--dried flask was charged with 0.58 g (24 mmole) Mg turnings and a small crystal of iodine. The mixture was flameheated for some minutes under nitrogen, then approximately 10% of the solution of 4.23 g (12 mmol) 18-bromooctadecanyl tetrahydropyranyl ether in anhydrous tetrahydrofuran (40 ml) were added at 80 °C. After initiation of the reaction (dark iodine colour was dischanged), the remaining bromide solution was added dropwise over 30 min while the mixture was refluxed. The cooled solution was added dropwise 1.5 h under an inert atmosphere to a cooled (—20 °C) solution of 3.8 g (10 mmol) *6* in tetrahydrofurane (30 ml) containing 0.22 g (1 mmol) dilithium tetrachlorocuprate in tetrahydrofuran (10 ml)[8]. The resulting mixture was held at 0—5 °C for 4 h and worked up as described above. The crude product was purified by chromatography (benzene-acetone) (10 : 0.2) to yield *10* as a colourless liquid (2.8 g, 38%); ν_{max}: 1730, (C=O) 1460, 1370, 1150, 1030 cm^{-1}; δ_H: 4.45 (1H, m, OCHO), 3.1—3.9 (4H, m, CH_2O), 2.05—2.3 (1H, m, 2-CH), 1.43 (9H, s, Bu^t), 1.1—1.8 (55H, m), 1.06 (3H, d, *J* 7Hz, 2'-CH_3), 0.83 (3H, d, *J* 7Hz, 10'-CH_3); Found: C, 76.17, H, 12.31. $C_{39}H_{76}O_4$ requires C, 76.91, H, 12.58%).

29-Hydraxy-2,10-dimethyloctacosanoic Acid (12)

A solution of 2.0 g (3.3 mmol) *10* and 0.2 g *p*-toluenesulfonic acid in 15 ml of benzene was refluxed for 30 minutes, then the solvent was evaporated in vacuo. The residue was diluted with 30 ml methanol and 3 ml water, heated and stirred at 60° for 2 h. The solvent was evaporated in vacuo again and then the residue was taken up with ether. The organic layer was washed with water and brine and dried (Na_2SO_4). Removal of the solvent gave *12*, (1.25 g, 80%); ν_{max} 3350, 1705 cm^{-1}; δ_H: 3.52 (2H, t, *J* 6Hz, CH_2O), 2.1—2.3 (1H, m, 2-CH), 1.1—1.8 (49H, m), 1.03 (3H, d, *J* 7Hz, 2'-CH_3), 0.83 (3H, d, *J* 7Hz, 10'-CH_3); (Found: C, 76.29; H, 13.12. $C_{30}H_{60}O_3$ requires C, 76.86, H, 12.90%).

29-Hydroxy-3,11-dimethyl-2-nonacosanone (2)

3.2 mmol methyl lithium in hexane was added to a cooled (0 °C) solution of 0.47 g (1 mmol) *12* in ether (40 ml) under an inert atmosphere and stirred at 0—5 °C for 2 h, and then at room temperature for 3 h. The mixture was worked up as described for compound *1*. The crude *2* was purified by column chromatography (benzene-acetone) (10 : 2) on silica (Merck) to afford a pure *2*, (0.4 g 85%), m. p.: 37—40 °C. Recrystallization from petroleum ether (40 °C) at —30 °C gave the diastereomeric mixture of pheromone *2*, m. p. 40—42 °C (lit.[2b] m. p.: 40—41 °C); ν_{max}: 3350, 1712, 1042 cm^{-1}; δ_H: 3.55 (2H, t, *J* 6Hz, CH_2—O), 2.45 (1H, m, 3-CH), 2.06 (3H, s, CH_3CO), 1.1—1.6 (49H, m), 1.04 (3H, d, *J* 7Hz, 3'-CH_3), 0.83 (3H, d, *J* 6Hz, 11'-CH_3); *m/z* 466 (2.2%, M^+), 72 (100%); Found: C, 79.58, H, 13.53. $C_{31}H_{62}O_2$ requires C, 79.76, H, 13.39%).

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REFERENCES

1. a) R. Nishida, H. Fukami, and S. Ishii, *Experientia* **30** (1974) 978.
   b) R. Nishida, H. Fukami, and S. Ishii, *Appl. Ent. Zool.* **10** (1975) 10.
2. a) R. Nishida, T. Sato, Y. Kuwahara, M. Fukami, and S. Ishii, *J. Chem. Ecol.* **2** (1976) 449.
   b) R. Nishida, T. Sato, Y. Kuwahara, H. Fukami, and S. Ishii, *Arg. Biol. Chem.* **40** (1976) 1407.
3. a) M. Schwarz, J. E. Oliver, and P. E. Sonnet, *J. Org. Chem.* **40** (1975) 2410.
   b) A. W. Burgstahler, L. O. Weigel, W. J. Bell, and M. K. Rust, *ibid.* **40** (1975) 3456.
   c) L. D. Rosenblum, R. J. Anderson, and C. A. Henrick, *Tetrahedron Lett.* (1976) 419.
   d) A. W. Burgstahler, L. O. Weigel, M. E. Sanders, C. G. Shaefer, W. J. Bell, and S. B. Vutoro, *J. Org. Chem* **42** (1977) 566.
   e) A. W. Burgstahler, M. E. Sanders, C. G. Shaefer, and L. O. Weigel, *Synthesis* (1977) 405.
   f) P. Place, M. L. Roumestant, and J. Gore, *Tetrahedron* **34** (1978) 1931.
   g) W. Seidel and H. J. Schäfer, *Chem. Ber.* **113** (1980) 351.
   h) R. I. Ishchenko, B. G. Kovalev, and V. M. Rastegaeva, *Zh. Org. Khim.* **18** (1982) 2272.
4. a) K. Mori, T. Suguro, and S. Masuda, *Tetrahedron, Lett.* (1978) 3447.
   b) K. Mori, S. Masuda, and T. Suguro, *Tetrahedron* **37** (1981) 1329.
   c) U. Jensen-Korte and H. J. Schäfer, *Liebigs, Ann. Chem.* (1982) 1532.
5. P. E. Pfeffer and L .S. Silbert, *J. Org. Chem.* **35** (1970) 262.
6. H. Stone and H. Shechter, *Org. Synth. Coll. Vol* **4** (1963) 543.
7. G. W. Anderson and F. M. Callahan, *J. Amer. Chem. Soc.* **82** (1960) 3359.
8. M. Tamura and J. Kochi, *Synthesis* (1971) 303.
9. a) L. Friedman and A. Shani, *J. Amer. Chem. Soc.* **96** (1974) 7101.
   b) D. Samain and C. Descoins, *Synthesis* (1978) 388.
   c) G. Dressaire and Y. Langlois, *Tetrahedron Lett.* (1980) 67.
   d) G. Cassani, O. Massardo, and P. Piccardi, *Tetrahedron Lett.* (1980) 3497.
10. H. O. House and T. M. Bare, *J. Org. Chem.* **33** (1968) 943.
11. a) N. L. Drake, H. W. Carhart, and R. Moringo, *J. Amer. Chem. Soc* **63** (1941) 617.
    b) R. H. Manske, *Org. Synth. Coll. Vol.* **2** (1943) 154.
12. J. H. Babler and B. J. Invergo, *J. Org. Chem.* **44** (1979) 3723.

POVZETEK

Učinkovita sinteza sestavin spolnega feromona iz nemškega ščurka

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Opisana je šeststopenjska sinteza spolnih feromonov iz nemškega ščurka, 3,11-dimetil-2-nonakozanona in 29-hidroksi-3,11-dimetil-2-nonakozanona. Ključna stopnja pri tej sintezi je homologizacija halopolikarbonske verige.

t-Butil-2-metil-10-jodoundekanoat je bil sintetiziran iz 10-undecenojske kisline z metiliranjem in jodiranjem ter nato pripajan z Grignardovim reagentom, ki nastane iz stearilbromida in 18-bromooktadekaniltetrahidro-2-piranil etra ob prisotnosti dilitijevega tetraklorokuprata. Naravna feromona smo nato pripravili iz derivata 2,10-oktakozanonske kisline z metillitijem v 23% oziroma 16% celokupnem izkoristku.