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SYNTHESES OF OPTICALLY ACTIVE INSECT PHEROMONES, (2R,5S)-2-METHYL-5-HEXANOLIDE, (3S,11S)-3,11-DIMETHYL-2-NONACOSANONE, AND SERRICORNIN

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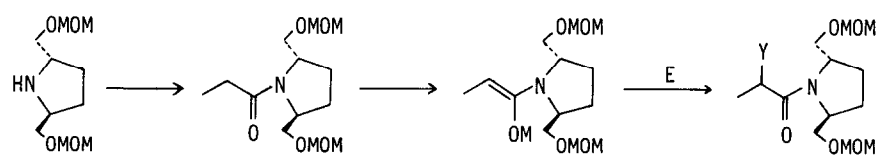
Summary: Three insect pheromones, (2R,5S)-2-methyl-5-hexanolide, (3S,11S)-3,11-dimethyl-2-nonacosanone, and serricornin, were synthesized in optically pure forms by using newly developed asymmetric reactions as key steps.

Optically active insect pheromones have been one of the challenging targets of organic synthesis because of i) the structural diversity for their often rather small molecules and ii) unique relationships between their stereochemistry and pheromone activity.[1] The latter especially demands the highly diastero- and enantioselective methods for their efficient synthesis. Recently, we found that the amide enolate (3) bearing optically active 2,5-bis(methoxymethoxymethyl)pyrrolidine (1) as a chiral auxiliary reacted with various electrophiles with excellent diastereo and/or diastereoface selectivity of >95% de (Scheme 1).[2] In this communication, we describe straightforward syntheses of (2R,5S)-2-methyl-5-hexanolide (4),[3] (3S,11S)-3,11-dimethyl-2-nonacosanone (5),[4] and serricornin (6),[5] which are sex pheromones of carpenter bee, German cockroach, and the female cigarette beetle, respectively, with full utilization of the two of the above asymmetric reactions; alkylation[2a] and aldol reaction.[2b]

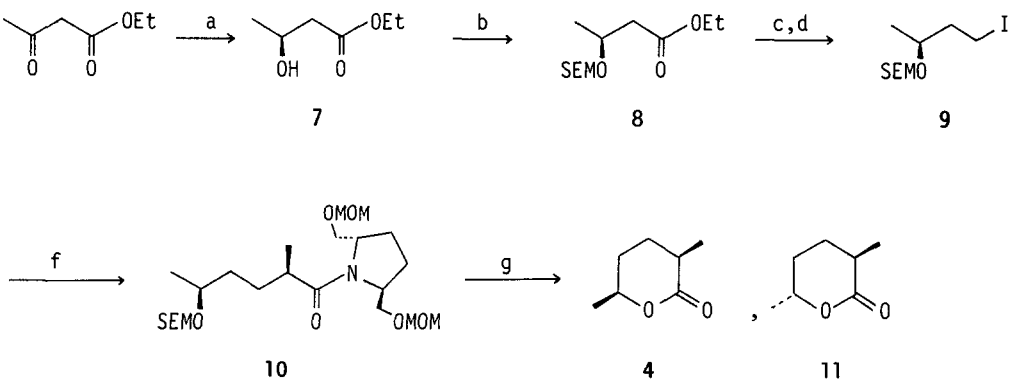


M= Li, E= RX, Y= R (2'S)
M= Zr, E= RCHO, Y= RCH(OH) (2'R,3'S)

Scheme 1

Synthesis of (2R,5S)-2-methyl-5-hexanolide (4) (Scheme 2). The synthesis was started from ethyl (S)-3-hydroxybutanoate (7) of 95% ee, prepared by the reduction of ethyl 3-oxobutanoate with Baker's yeast[6]. The hydroxyl group of 7 was protected as a β-trimethylsilylethoxymethyl (SEM) ether in 80% yield. The ether (8) was converted to the iodide (9) in 78% yield via conventional steps, LAH reduction followed by tosylation and iodination. The iodide (9) was treated with the lithiated (LDA, in THF, -78 °C) propionamide [(2R,5R)-3], derived from the corresponding amide (2), to introduce the remaining chiral center at C2,[2a] and the resulting amide (10) was hydrolyzed to a lactone [$[\alpha]_D^{23}$ -85° (c=0.68, $CHCl_3$); m.p. 48-48.5°C] in 76% yield,

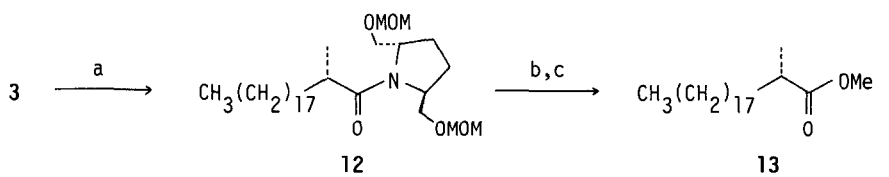
which was contaminated with 2.5% of trans-isomer (**11**). The minor **11** probably resulted from ethyl (R)-3-hydroxybutanoate in the starting material. The mixture was once recrystallized from hexane to give **4** as colorless needles. **4**; $[\alpha]_D^{23}$ -90° (c= 0.99, $CHCl_3$); m.p. 49-50 °C; ^1H NMR, δ ($CDCl_3$), 1.22(d, J=6.8Hz, 3H), 1.36 (d, J=6.2Hz, 3H), 4.4-4.6(1H, m). [Lit.,[3b] $[\alpha]_D^{20}$ -91.0 (c= 0.73, $CHCL_3$), m.p. 49-50° C].

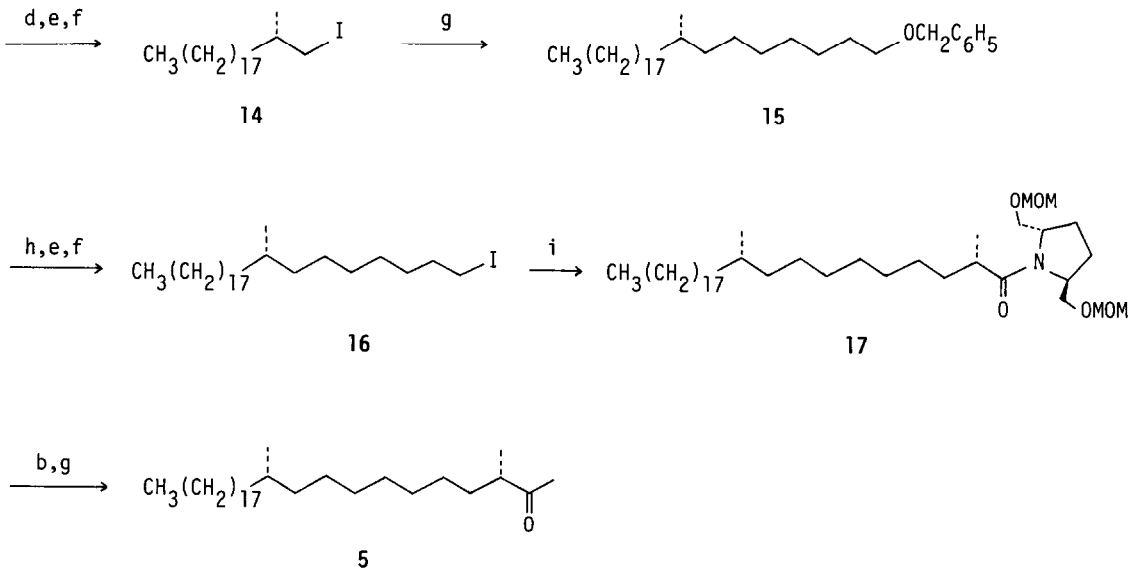


a) Baker's yeast, b) $Me_3SiCH_2CH_2OCH_2Cl$ (SEMCl), $EtNPr^i_2$, CH_2Cl_2, c) LAH, THF, 0° C, d) TsCl, pyridine, rt, e) NaI, acetone, rt, f) (2R,5R)-**3**, THF, -78° C, g) 1 mol dm^{-3} HCl, reflux.

Scheme 2

Synthesis of (3S,11S)-3,11-dimethyl-2-nonacosanone (**5**) (Scheme 3). Lithiated (2S,5S)-**3** was first treated with 1-bromooctadecane at -20° C to give the alkylated (2S)-amide (**12**) of 95% de in 70% yield. Hydrolysis of the amide (**12**) followed by treatment with diazomethane gave the methyl ester [**13**,[•] $[\alpha]_D^{25}$ 10.5° (c= 1.08, $CHCl_3$)] in 74% yield. The ester (**13**) was converted to the iodide (**14**) in 85% yield via the same procedure as described above. Then, the iodide (**14**) was coupled with 6-benzyloxyhexylmagnesium bromide under the presence of dilithium tetrachlorocuprate[7] to give the benzyl ether (**15**) which, on successive treatment with H_2/Pd-C, tosyl chloride-pyridine, and NaI-acetone, provided the elongated iodide (**16**) in 60% yield. This iodide (**16**) was again treated with lithiated (2S,5S)-**3** to afford the compound (**17**) containing all requisite chiral centers in the proper absolute configuration in 84% yield. The compound (**17**) was transformed in 42% yield into **5** by hydrolysis followed by treatment with methyl lithium. **5**; m.p. 43.5-45 °C; $[\alpha]_D^{23}$ 5.5° (c= 0.12, hexane); ^1H NMR, δ ($CDCl_3$), 0.89 (m, 6H), 1.08 (d, J= 7Hz, 3H), 1.26 (m, 48H), 2.13 (s, 3H), 2.45 (m, 1H). [Lit.,[4] m.p. 44-45 °C, $[\alpha]_D^{21}$ 5.98° (c= 0.9, hexane)].



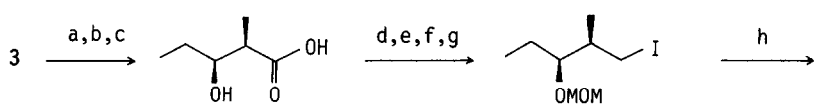


14 15 16 17 5

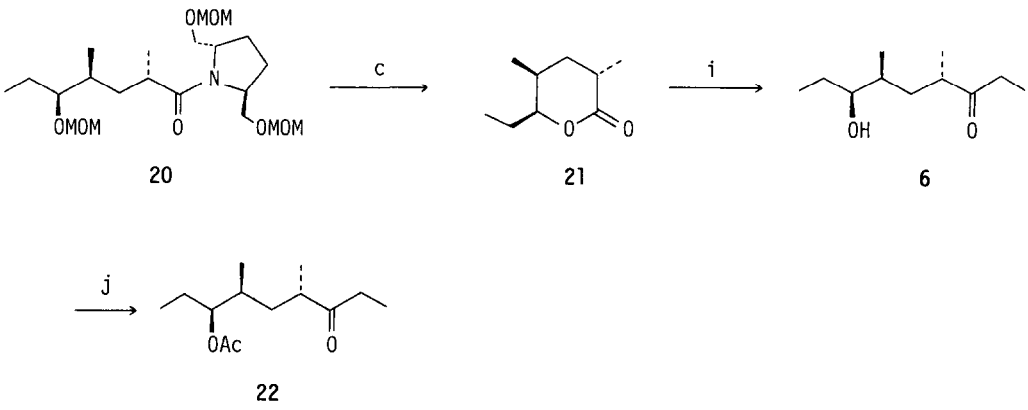
a) $CH_3(CH_2)_{17}Br$, -20 °C, b) 1 mol dm^{-3} HCl, reflux, c) CH_2N_2, ether, d) LAH, THF, 0 °C, e) TsCl, pyridine, rt, f) NaI, acetone, rt, g) $C_6H_5CH_2O(CH_2)_6MgBr$, Li_2CuCl_4, THF, -78°→rt, h) H_2/Pd, MeOH, i) (2S,5S)-**3**, LDA, THF, -78 °C→-20 °C, j) MeLi, ether, -78 °C.

Scheme 3

Synthesis of Serricornin (**6**) (Scheme 4). Aldol condensation of (2S,5S)-**3** with propanal and subsequent hydrolysis afforded (2R,3S)-2-methyl-3-hydroxypentanoic acid (**18**),[2c] which already carried two asymmetric centers at C6 and C7 (serricornine numbering) in proper absolute configuration. **18**; $[\alpha]_D^{23}$ -4.1° (c=1.72, $CHCl_3$); Lit.,[8] $[\alpha]_D^{26}$ -4.10 (c= 1.72, $CHCl_3$). The hydroxy acid (**18**) was transformed into the iodide (**19**) in 79% yield by the sequence, i) protection of hydroxyl and carboxyl group as respective MOM ether and MOM ester, ii) LAH reduction of the ester, iii) tosylation of the resulting alcohol, and iv) substitution of the tosyloxyl group by iodide. The iodide (**19**) was treated with lithiated (2S,5S)-**3** to set the remaining asymmetric center at C4. The resulting amide (**20**) was hydrolyzed to the lactone (**21**) in 70% yield from **19**, which is diastereomerically pure within the limits of detection by ^1H NMR (90 MHz). The lactone (**21**) was then treated with ethyl lithium in ether to give serricornin (**6**) in 73% yield, which was converted to its acetate (**22**) for identification. **22**; $[\alpha]_D^{25}$ -18.4° (c= 0,07, hexane); ^{13}C NMR, δ ($CDCl_3$), 7.85, 10.10, 14.45, 16.60, 24.20, 33.78, 34.16, 35.97, 43.58, 78.13, 214.88. [Lit.,[5] $[\alpha]_D^{21.5}$ -18.2° (c= 0.58, hexane), ^{13}C NMR, δ ($CDCl_3$), 7.87, 10.15, 14.43, 16.61, 24.20, 33.70, 34.25, 35.93, 43.53, 78.10, 214.94].



18 19



a)) Cp_2ZrCl_2, b) CH_3CH_2CHO, c) 1 mol dm^{-3} HCl, reflux, d) MOMCl, $EtNPr^i_2$, CH_2Cl_2, e) LAH, THF, 0 °C, f) TsCl, pyridine, g) NaI, acetone, rt, h) (2S,5S)-**3**, THF, -78 °C, i) EtLi, ether, -100 °C, j) Ac_2O, pyridine.

Scheme 4

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6) Reduction of ethyl 3-oxobutanoate with Baker's yeast, according to Mori's procedure, afforded ethyl (S)-3-hydroxybutanoate of 82-95% ee depending on the reaction conditions. The product of 95% ee was used in this study. The authors are grateful to Professor K. Mori, Tokyo University, for his kind offer of full experimental details on his procedure and information on the correct optical rotation of **4**.

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