# Novel Synthesis of a 1,4-Dienic Macrolide Pheromone of *Cucujid* Grain Beetles

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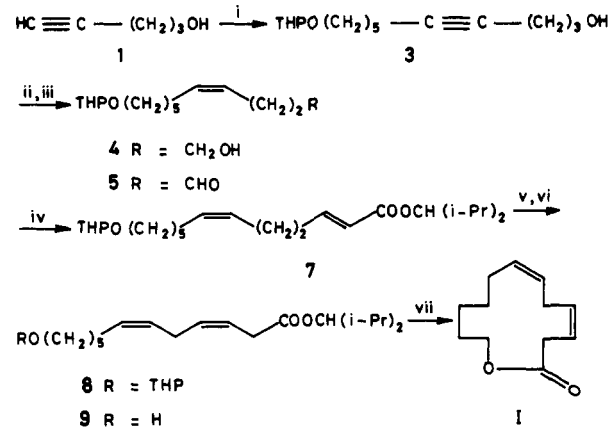
C-alkylation of 4-pentyn-1-ol (1) with 1-bromo-5-(tetrahydropyranyloxy)pentane, subsequent *cis*-hydrogenation, and PDC oxidation gave the $C_{10}$ aldehyde 5. Its Wittig–Horner olefination, base-catalyzed deconjugation to the corresponding (3*Z*) compound, and enzymatic macrolactonization furnished (3*Z*,6*Z*)-dodecanolide (I).

Various bioactive compounds possessing 1,4-dienic and macrolidic structures are abundant[1–4] in nature both individually or in conjunction with other compounds. The biological importance and challenge associated with their synthesis from readily available synthons makes the 1,4-dienic macrolides attractive targets. To this end, we have developed a novel synthetic strategy with (3*Z*,6*Z*)-dodecanolide (I) as the model compound. Compound I constitutes one of the aggregation pheromone components of the destructive *Cucujid* beetles in the genera *Cryptolestes* and *Oryzaephilus*. Its propensity to isomerize or decompose due to the presence of $\beta,\gamma$-unsaturated carbonyl functionality provides additional impetus for the present work.

For this, easily accessible 4-pentyn-1-ol (1) was chosen as the starting material. We have previously used[5–7] this synthon for the syntheses of several insect pheromones, jasmonoids, and marine natural products. Its choice for the preparation of 1,4-dienic compounds was envisaged from two considerations. First, suitable functionalization at its terminals would provide an easy access to 1,5-dienes. Secondly, if the required olefin at its alcohol terminus is generated *trans*-selectively by a Wittig–Horner reaction, the resultant $\alpha,\beta$-unsaturated ester can be deconjugated[8] to the corresponding skipped methylene carboxylic compounds. The presence of a hydroxy group at a suitable position of the compound then could be exploited for lactonization.

Chemoselective C-alkylation of 1 with 5-(bromotetrahydropyranyloxy)pentane (2) gave the $C_{10}$-diol derivative 3. However, use of 1 equiv of the alkylating agent in the above step led to a complex mixture presumably due to its poor solubility in the reaction mixture. After several trials, best results were obtained by using 0.5 equiv of 2. Stereospecific *cis*-semihydrogenation of 3 over P-2 Ni catalyst[9] followed by PDC oxidation[10] of the resultant alcohol 4 gave 5 in good yield. This on Wittig–Horner olefination with the hindered phosphonoacetate 6[8] furnished the conjugated ester 7. The (*E*) geometry of the incipient double bond was ascertained on the basis of the $^1$H-NMR coupling constants of the olefinic protons. Base-catalyzed deconjugation[8] with potassium disilazide gave the ester 8. After depyranylation, the resultant product 9 was subjected to alkaline hydrolysis which proved abortive. Furthermore, the lability of the target compound as well as the required hydroxy acid[13] warranted a mild lactonization protocol. Consequently, direct lactonization of 9 was tried with lipase as the catalyst. Biocatalysts have been efficiently used[11] for lactonization of long-chain hydroxy esters (>$C_{15}$–). But with the shortening of chain length, diolide formation predominates,[12] thereby reducing the yield of macrolides. In the present case, however, with porcine pancreatic lipase (PPL), the reaction could be carried out in benzene to provide the target compound (I) (78%) along with the unconverted starting material. Neither any improvement in yield of I nor any formation of diolide was noticed by increasing the reaction period or enzyme concentration. Probably, beyond the equilibrium point, the substrate concentration becomes too low for further conversion. The spectral data of I were in good agreement with those reported for a synthetic sample.[13]

**Scheme I**[a]




[a] (i) $LiNH_2$/$Br(CH_2)_5OTHP$/THF, (ii) $H_2$/P-2 Ni/EtOH, (iii) PDC/$CH_2Cl_2$, (iv) $(EtO)_2POCH_2CO_2CH(i\text{-}Pr)_2$(6)/NaH/THF, (v) K-disilazide/THF, (vi) MeOH/$H^+$; (vii) PPL/benzene.

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## Experimental Section

All bp's are uncorrected. The IR spectra were scanned as thin films, and only the pertinent bands are provided in $cm^{-1}$. Anhydrous reactions were carried out under an atmosphere of argon and with freshly dried solvents. Unless otherwise mentioned, all organic extracts were desiccated over anhydrous $Na_2SO_4$.

**10-(Tetrahydropyranyloxy)dec-4-yn-1-ol (3).** To a suspension of $LiNH_2$ (0.26 mol) in liquid $NH_3$ (500 mL) was added 1 (10.5 g, 0.125 mol) at −78 °C. After 30 min, 2 (15.8 g, 0.063 mol) in THF (80 mL) was slowly introduced into it. After the mixture was stirred for 4 h at the same temperature, $NH_4Cl$(s) was added and the mixture left overnight for the removal of $NH_3$(g). After addition of water (100 mL), the reaction mixture was extracted with ether (4 × 50 mL). The ether layer was washed with water and brine and dried. Removal of solvent and column chromatography (silica gel, 0–20% EtOAc/hexane) of the residue gave pure 3: yield 14.88 g (93% based on 2); bp 170 °C/3 mm; IR 3440, 2220, 1080, 880, 810; $^1$H-NMR δ 1.5 (br s, 14H), 1.8–2.2 (m, 4H), 2.6 (s, 1H, $D_2O$ exchangeable), 3.5–3.7 (m, 6H), 4.53 (s, 1H). Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.82; H, 10.30. Found: C, 70.68; H, 10.42.

**(4*Z*)-10-(Tetrahydropyranyloxy)dec-4-en-1-ol (4).** The above compound (4.0 g, 0.016 mol) was semihydrogenated over P-2 Ni catalyst in the presence of ethylenediamine (0.03 mL) in ethanol (30 mL) to give 4: yield 3.84 g (94%); bp 110 °C/0.1 mm; IR 3440, 3010, 1080, 880, 810; $^1$H-NMR δ 1.5 (br s, 14H), 1.9–2.4 (m, 4H), 3.08 (s, 1H, $D_2O$ exchangeable), 3.4–3.7 (m, 6H), 4.53 (s, 1H), 5.2–5.5 (m, 2H). Anal. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found: C, 70.34; H, 11.15.

**(4*Z*)-10-(Tetrahydropyranyloxy)dec-4-en-1-al (5).** To a stirred solution of 4 (3.8 g, 0.015 mol) in $CH_2Cl_2$ (50 mL) was added PDC (8.46 g, 0.023 mol) in one lot. After being stirred for 24 h at room temperature, the reaction mixture was worked up[10] and the product purified by flash chromatography to furnish pure 5: yield 3.05 g (81%); IR 3010, 2720, 1715, 880, 810; $^1$H-NMR δ 1.2–1.5 (m, 12H), 1.9–2.2 (m, 4H), 2.4–2.5 (m, 2H), 3.2–3.8 (m, 4H), 4.6 (br s, 1H), 5.2–5.6 (m, 2H), 9.72 (t, $J$ = 1.5 Hz, 1H). Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.82; H, 10.30. Found: C, 70.59; H, 10.10.

**2′,4′-Dimethyl-3′-pentyl (2*E*,6*Z*)-12-(Tetrahydropyranyloxy)dodeca-2,6-dienoate (7).** To a stirred suspension of NaH (0.72 g, 50% suspension, 0.015 mol) in THF (50 mL) was added 6 (4.41 g, 0.015 mol) in THF (15 mL) at room temperature. After 0.5 h, it was cooled to 0 °C and 5 (3.0 g, 0.012 mol) in THF (20 mL) was introduced into it. After being stirred for 1 h at 0 °C and 4 h at room temperature, the reaction was quenched with aqueous saturated $NH_4Cl$ solution. The organic layer was separated, the aqueous portion extracted with ether (3 × 50 mL), and the combined organic layer washed with water and brine. Removal of solvent in vacuo and column chromatography of the residue (silica gel, 0–20% EtOAc in hexane) furnished 7: yield 3.83 g (81%); bp 150–154 °C/0.1 mm; IR 3005, 1720, 1640, 980, 880, 810; $^1$H-NMR δ 0.88 (d, $J$ = 6 Hz, 12H), 1.2–1.7 (m, 14H), 1.8–2.4 (m, 6H), 3.3–3.7 (m, 4H), 4.53 (t, $J$ = 6 Hz, 1H, overlapped with a singlet, 1H), 5.2–5.4 (m, 2H), 5.72 (d, $J$ = 16 Hz, 1H), 6.88 (dt, $J$ = 16 Hz, 6 Hz, 1H). Anal. Calcd for $C_{24}H_{42}O_4$: C, 73.05; H, 10.73. Found: C, 73.17; H, 10.85.

**2′,4′-Dimethyl-3′-pentyl (3*Z*,6*Z*)-12-(Tetrahydropyranyloxy)dodeca-3,6-dienoate (8).** Potassium metal (0.39 g, 0.01 mol) was added to a stirred solution of naphthalene (1.28 g, 0.01 mol) in THF (10 mL) under argon atmosphere. Stirring was continued until the metal dissolved completely (4–5 h). The green solution was cooled to 0 °C and treated with HMDS (1.61 g, 0.01 mol). The resultant solution was quickly transferred into a stirred and cooled (−78 °C) solution of 7 (2.76 g, 0.007 mol) in THF (15 mL). After the solution was stirred for 4 h at −78 °C, saturated aqueous $NH_4Cl$ solution was added followed by cold water (100 mL). The mixture was extracted with ether (4 × 30 mL) and the ether layer washed with water and brine and finally dried. The crude product obtained after concentration under vacuum on column chromatography (silica gel, 0–15% ethyl acetate in hexane) gave pure 8: yield 2.15 g (78%); IR 3005, 1740, 880, 810; $^1$H-NMR δ 0.86 (d, $J$ = 5.5 Hz, 12H), 1.2–1.4 (m, 8H), 1.5–1.7 (m, 6H), 1.8–2.0 (m, 2H), 2.7–3.1 (m, 4H), 3.3–3.8 (m, 4H), 4.57 (t, $J$ = 6.5 Hz, 1H, overlapped with a s, 1H), 5.2–5.7 (m, 4H). Anal. Calcd for $C_{24}H_{42}O_4$: C, 73.05; H, 10.73. Found: C, 72.88; H, 10.71.

**(3*Z*,6*Z*)-Dodecadienolide (I).** A solution of 8 (2.36 g, 6.0 mmol) and PPTS (0.2 g) in methanol (30 mL) was stirred at room temperature until completion of the reaction. Usual isolation gave pure 9: yield 1.46 g (79%); IR 3440, 1740; $^1$H-NMR δ 0.86 (d, $J$ = 6 Hz, 12H), 1.4–1.7 (m, 8H), 1.9–2.2 (m, partially $D_2O$ exchangeable, 3H), 2.75 (dd, $J$ = 5.5 Hz, 4.4 Hz, 2H), 3.02 (d, $J$ = 7 Hz, 2H), 3.6 (t, $J$ = 6 Hz, 2H), 4.53 (t, $J$ = 6 Hz, 1H), 5.3–5.4 (m, 2H), 5.5–5.6 (m, 2H). $^{13}$C-NMR δ 21.02, 21.55, 21.84, 22.12, 23.37, 25.18, 25.52, 26.70, 26.95, 39.16, 39.26, 51.63, 60.46, 61.97, 126.75, 129.30, 129.69, 132.89, 172.9. Anal. Calcd for $C_{19}H_{34}O_3$: C, 73.50; H, 11.04. Found: C, 73.68; H, 10.86.

A mixture of 9 (1.46 g, 4.7 mmol) and PPL (Sigma, type II, sp. act. 70 U/mg, 0.200 g) in benzene (10 mL) was stirred at room temperature until there was no further reaction (~18 h). The suspended enzyme particles were removed by filtration and the filtrate concentrated in vacuo and purified by chromatography to furnish I (0.712 g, 78%) and unchanged substrate (0.26 g, 18%): IR 1740; $^1$H-NMR δ 1.2-1.6 (m, 6H), 1.9–2.1 (m, 2H), 2.7–2.9 (m, 2H), 3.07 (d, $J$ = 6 Hz, 2H), 4.08 (t, $J$ = 7 Hz, 2H), 5.3–5.6 (m, 4H); $^{13}$C-NMR δ 26.63, 27.00, 28.42, 29.61, 63.207, 64.47, 121.14, 127.17, 130.18, 131.30, 171.53. Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.28; H, 9.42.

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