A Stereoselective Synthesis of (±)-endo-Brevicomin, a Pheromone Inhibitor Produced by Dendroctonus Bark Beetles

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endo-Brevicomin (1) was first isolated and synthesized by Silverstein et al. as a biologically inactive component of the frass of western pine beetle, Dendroctonus brevicomis, from which exo-brevicomin (1, Et=exo, instead of endo) was also isolated as the aggregation pheromone. Later Vité and Renwick found that the olfactory response of flying male and female southern pine beetles, D. frontalis, to the female-produced pheromone, frontalin (2), was inhibited under field conditions by endo-brevicomin (1). This suggested its use in pest control as a pheromone inhibitor. Since then several syntheses of 1 appeared with varying degrees of stereoselectively. This note describes a new and highly stereoselective synthesis of 1 using the (E)-olefination method of Kondo et al. Alkylation of the known phosphonate (3) with the known bromide (4) gave a new phosphonate (5). This was treated with lithium aluminum hydride to give an (E)-olefin (6). Oxidation of 6 with m-chloroperbenzoic acid gave an epoxide (7). This was hydrolyzed and cyclized with dilute perchloric acid to give (±)-endo-brevicomin (1). The product was gas chromatographically pure (>99%) and exhibited IR and NMR spectra completely identical with the published charts. The present synthesis is particularly simple and highly stereoselective compared with the existing methods.

EXPERIMENTAL

All bps 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. 

Diethyl 1-(1'-propenyl)-5-ethylenedioxyhexylphosphonate (5)
A solution of n-butyllithium in n-hexane (1.3 M, 47 ml) was added dropwise to a stirred and cooled solution of diethyl 2-butenylphosphonate (3, 9.6 g) in dry tetrahydrofuran (100 ml) at -60°C under nitrogen. The mixture was stirred for 1 hr at -60°C. Then a solution of 4-ethylenedioxypentyl bromide (4, 10.5 g) in dry tetrahydrofuran (25 ml) was added during 3 min at -60°C to -50°C. The mixture was stirred for 30 min at -60°C and then allowed to stand at room temperature for 1 hr. The mixture was poured into ice and brine. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic solution was dried over magnesium sulfate and concentrated in vacuo. The residue was distilled to give 6.9 g (43%) of 5, bp 160°C to 167°C (1.3 mmHg); νmax cm⁻¹: 3460 (m), 2995 (s), 1450 (m), 1385 (m), 1250 (s), 1070 to 1020 (s), 960 (s), 870 (m), 790 (m); NMR δ: 1.19 (3H, s), 1.27 (6H, t, J=7 Hz), 1.4-1.7 (6H, m), 3.82 (4H, s), 4.05 (4H, q, J=7 Hz), 5.4 (2H, m); Anal. Found: C, 56.42; H, 9.11. Calcd. for C₁₅H₂₉O₅P: C, 56.23; H, 9.12%.

(E)-6-Nonen-2-one ethylene ketal (6)
A solution of the phosphonate (5, 5.5 g) in dry ether (50 ml) was added dropwise to a stirred and ice-cooled suspension of lithium aluminum hydride (1 g) in dry ether (200 ml). The mixture was stirred for 1 hr at 10°C to 15°C. Then the excess of the hydride was decomposed by successive addition of water (1 ml), 15%
sodium hydroxide solution (1 ml) and water (3 ml). The ether layer was dried over potassium carbonate and concentrated in vacuo. The residue was distilled to give 1.9 g (61%) of 6, bp 75~78°C (3 mmHg); \( \delta^\text{H} \) 1.4451; IR \( \nu_{\text{max}} \) cm\(^{-1} \): 2950 (s), 2880 (s), 1460 (m), 1380 (s), 1260 (m), 1220 (m), 1060 (s), 965 (s), 945 (m), 860 (m); NMR \( \delta \) 0.96 (3H, t, \( J=7 \) Hz), 1.20 (3H, s), ~1.50 (2H), ~1.7~2.2 (4H), 3.84 (4H, s), 5.40 (2H, m); Anal. Found: C, 70.91; H, 10.72. Calcd. for \( \text{C}_{11}\text{H}_{20}\text{O}_{2} \): C, 71.69; H, 10.94%.

\((E)-6,7\)-Epoxynonan-2-one ethylene ketal (7)

\(m\)-Chloroperbenzoic acid (85% purity, 1.8 g) was added to an ice-cooled solution of the olefin (6, 1.6 g) in dichloromethane (20 ml) at 0~5°C. The mixture was stirred for 2 hr at 0~5°C, washed with sodium carbonate solution, dried over potassium carbonate and concentrated in vacuo. The residue was distilled to give 1.2 g (70%) of 7, bp 85~87°C (0.9 mmHg); \( \delta^\text{H} \) 1.4428; IR \( \nu_{\text{max}} \) cm\(^{-1} \): 2980 (s), 2880 (s), 1465 (m), 1385 (s), 1265 (m), 1230 (m), 1150 (m), 1120 (m), 1050 (s), 950 (m), 890 (s), 860 (m); NMR \( \delta \) 0.97 (3H, t, \( J=7 \) Hz), 1.22 (3H, s), ~1.50 (6H), 2.50 (2H, m), 3.85 (4H, s); Anal. Found: C, 65.50; H, 9.85. Calcd. for \( \text{C}_{11}\text{H}_{20}\text{O}_{4} \): C, 65.97; H, 10.07%.

\((\pm)-\text{endo-Brevicomin} \) (7-ethyl-5-methyl-6,8-dioxabicyclo [3.2.1] octane (I))

The epoxide (7, 1.1 g) was mixed with 0.1 \( m\)-perchloric acid (6 ml) and the mixture was vigorously stirred for 3 hr at room temperature (30~32°C). Then it was extracted with a small amount of ether. The ether extract was dried over potassium carbonate and concentrated at atmospheric pressure with a Vigreux column. The residue was distilled to give 634 mg (74%) of I, bp 115~118°C (115 mmHg); \( \delta^\text{H} \) 1.4454; IR \( \nu_{\text{max}} \) cm\(^{-1} \): 2960 (s), 2880 (s), 1470 (m), 1380 (s), 1350 (m), 1340 (w), 1330 (w), 1315 (w), 1290 (w), 1270 (m), 1245 (s), 1200 (m), 1190 (m), 1180 (s), 1150 (w), 1130 (w) 1115 (s), 1100 (m), 1080 (w), 1070 (w), 1055 (w), 1035 (s), 1000 (s), 970 (m), 940 (w), 900 (m), 870 (m), 850 (s), 820 (w), 810 (w), 795 (w), 785 (w); NMR \( \delta \) (100 MHz, \( \text{CCl}_4 \)) 0.98 (3H, t, \( J=7 \) Hz), 1.30 (3H, s), ~1.4~2.0 (8H, m), 3.86 (1H, df, \( J_1=4, J_2=7.5 \) Hz), 4.02 (1H, br.s); MS \( m/e \) : 156 (M\(^+\)), 43 (base peak); GLC (column, LAC 2R~446, 1.5 m × 3 mm i.d. at 60°C, carrier gas, \( N_2 \), 1.0 kg/cm\(^2\)): \( t_R \) 13.4 min (>99%), 9.4 min (<1%). Anal. Found: C, 68.94; H, 10.12. Calcd. for \( \text{C}_{11}\text{H}_{16}\text{O}_2 \): C, 69.19; H, 10.32%.

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**REFERENCES**