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A NEW SYNTHESIS OF dl-VARIOTIN

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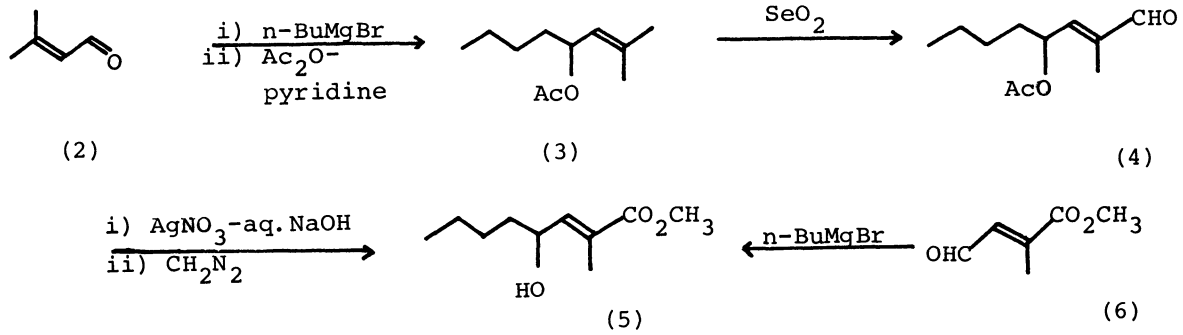
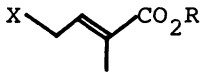
A new synthesis of dl-variotin (1) was accomplished by the reaction of 2-ethoxy-1-pyrroline and (2E,4E,6E)-8-hydroxy-6-methyl-2,4,6-dodecatrienoic acid (14), without protection of the hydroxyl group at C-8, utilizing 1-methyl-2-chloropyridinium iodide as a coupling reagent.

Variotin (1) is a well-known antifungal antibiotic isolated from the culture broth of Pacecilomyces variotin Bainier var. antibioticus,[1] and the structure was established by Yonehara and Takeuchi.[2]

In previous papers,[3,4] we have reported a useful method for the conversion of δ-alkoxy-α,β-unsaturated aldehydes, prepared from dienoxysilanes and acetals, to polyenals with 1,8-diazabicyo[5.4.0]undec-7-ene(DBU) in the presence of molecular sieves 3A, and also a new method for the preparation of N-acyl lactams from free carboxylic acids and lactim ethers using 2-halopyridinium salt as a coupling reagent. We now wish to report a new synthesis of dl-variotin (1) starting from 3-methyl-2-butenal (2) by employing the above mentioned two preparative methods in key steps.



(2) (3) (4) (5) (6)



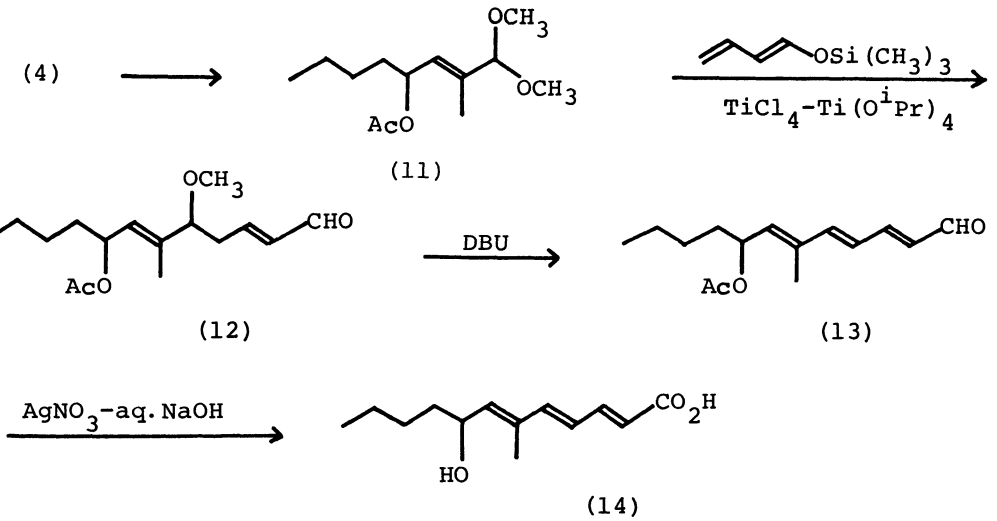
7) X=Br R=CH_3

8) X=OAc R=CH_3

9) X=OH R=H

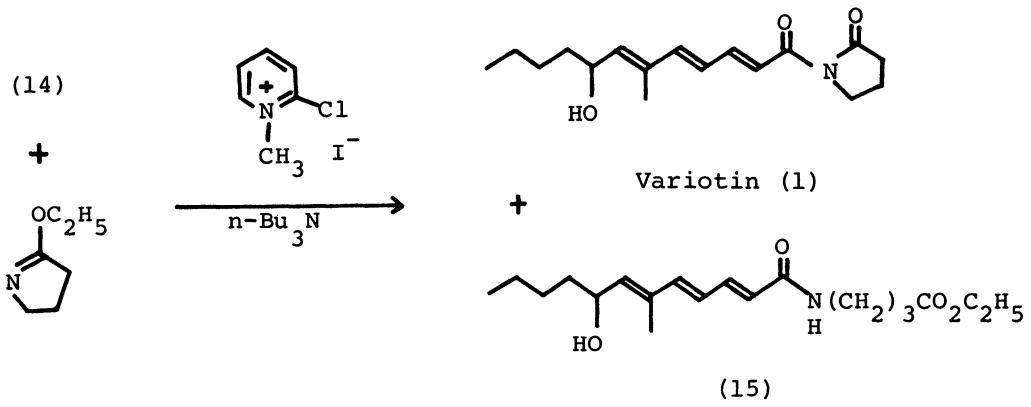
10) X=OH R=CH_3

The reaction of 3-methyl-2-butenal (2) with butylmagnesium bromide in ether at 0°C for 3hr, followed by acetylation with acetic anhydride-pyridine, gave 4-acetoxy-2-methyl-2-octene(3) in 81% yield after distillation. The allylic oxidation of 3 with 1.5 molar amounts of selenium dioxide[5] in refluxing xylene afforded (E)-4-acetoxy-2-methyl-2-octenal (4) in 43% yield. In order to determine the configuration of C_2-double bond of 4, the aldehyde (4) was converted into methyl 4-hydroxy-2-methyl-2-octenoate (5)[6] by the oxidation with silver oxide and subsequent treatment with ethereal diazomethane at 0°C in 76% yield based on 4. On the other hand, authentic methyl (E)-4-hydroxy-2-methyl-2-octenoate (5) was derived from methyl (E)-4-bromo-2-methyl-2-butenoate (7)[7] according to the following procedure. Treatment of 7 with potassium acetate in refluxing C_2H_5OH[8] afforded acetoxy ester (8). Hydrolysis of 8 with CH_3OH-20%KOH solution gave (E)-4-hydroxy-2-methyl-2-butenoic acid (9) in 59% yield based on 7. Treatment of 9 with diazomethane gave the hydroxy methyl ester (10) in 85% yield, which on oxidation with pyridinium chlorochromate[9] in CH_2Cl_2 afforded methyl (E)-2-methyl-4-oxo-2-butenoate (6)[10,11] in 75% yield. The reaction of 6 with butylmagnesium bromide in ether gave authenic



(2E)-octenoate(5) in 60% yield. The spectral data of the hydroxy ester (5) derived from 4 were identical with those of the authentic sample obtained by the above route.

The acetoxy aldehyde (4) was easily converted into its dimethyl acetal (11) in 89% yield on treatment with $HC(OCH_3)_3$-CH_3OH in the presence of p-toluenesulfonic acid. The reaction of 1-trimethylsiloxy-1,3-butadiene with 11 in the coexsistence of $TiCl_4$ and $Ti(O^iPr)_4$ smoothly proceeded at -40°C to afford (2E,6E)-8-acetoxy-5-methoxy-6-methyl-2,6-dodecadienal (12) in 85% yield. The δ-methoxyl group of 12 was easily eliminated with 4 molar amounts of DBU at room temperature in the presence of molecular sieves 3A to give (2E,4E,6E)-8-acetoxy-6-methyl-2,4,6-dodecatrienal (13) in 75% yield. The hydroxy acid (14) was obtained in 92% yield on oxidation of 13 with silver oxide at room temperature for 24hr. [14: IR(neat): 3300, 1690, 1620 cm^{-1}; UV: $\lambda_{max}^{C_2H_5OH}$ 296 nm (ε 2.6 × 10^4); MS: m/e 225(M^+ + 1), 206, 139; NMR($CDCl_3$) δ7.2-7.7 (m, 1H), 6.3-6.8(m, 4H), 5.90(d, J=16Hz, 1H), 5.70(br.d, 1H), 4.3-4.7(br, 1H), 1.86(s, 3H), 1.1-1.8(6H), 0.85(3H)].



(15)

The hydroxy acid (14) and 2-ethoxy-1-pyrroline were treated with 1-methyl-2-chloropyridinium iodide and tributylamine in toluene at 85°C for 30 min to give dl-variotin (1) in 30∿37% yield, together with the hydroxy amide (15)[12] (10∿18% yield). [1: IR(neat): 3400, 1740, 1670, 1600 cm^{-1}; UV: $\lambda_{max}^{C_2H_5OH}$ 320 nm (ε 2.6 × 10^4); MS: m/e 291(M^+), 273, 206; NMR($CDCl_3$): δ7.3-7.7(m, 2H), 6.4-6.7(m, 2H), 5.70(br.d, 1H), 4.3-4.8(b, 1H), 3.90(t, 2H), 2.65(quasi t, 2H), 2.50(s, 1H), 1.85(s, 3H), 1.8-2.4(m, 2H), 1.1-1.8(6H), 0.9(3H)]. Spectral data of synthetic dl-variotin (1) were consistent with those in the literature.[13]

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6) 5: bp 95°C/0.04 mmHg; IR(neat): 3400, 1720, 1650 cm^{-1}; NMR($CDCl_3$): 6.68(br.d, 1H), 4.3-4.8(br, 1H), 3.74(s, 3H), 2.64(br.s, 1H), 1.87(d, J=1.5Hz, 3H), 0.9-1.8(9H).

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10) 6: bp 89-90°C/15 mmHg (lit,[11] bp 76-78°C/12 mmHg); IR(neat): 1720, 1680, 1630, 1260 cm^{-1}; NMR($CDCl_3$): δ10.28(d, J=8Hz, 1H), 6.85(quasi d, 1H), 3.88(s, 3H), 2.35(d, J=1.5Hz, 3H); 2,4-Dinitrophenylhydrazone: mp 206-207°C(lit,[11] 204-205°C).

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12) 15: IR(neat); 3300, 1740, 1650, 1610 cm^{-1}; UV $\lambda_{max}^{C_2H_5OH}$ 294 nm (ε 4.0×10^4); MS: m/e 337(M^+), 319, 252; NMR($CDCl_3$): δ7.1-7.6(m, 1H), 6.1-6.6(m, 3H), 5.95(d, J=16Hz, 1H), 5.65(br.d, 1H), 4.2-4.7(br, 1H), 4.15(q, 2H), 3.15-3.80(m, 3H), 2.2-2.6(m, 2H), 1.85(s, 3H), 1.25(t, 3H), 1.1-2.2(8H), 0.9(3H).

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