Synthesis of (±)-Dihydromahubanolide Using 2-Methylthio-4-pentenoic Acid Dianion

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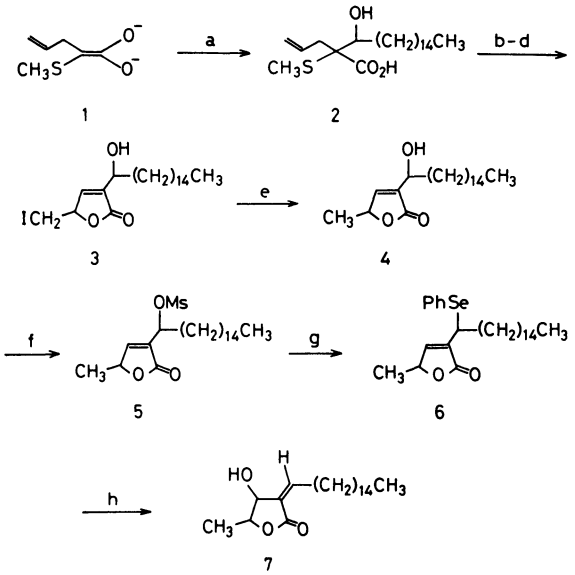
Synopsis. A new and mild method for the synthesis of (±)-dihydromahubanolide has been developed by the use of 2-methylthio-4-pentenoic acid dianion.

The several compounds isolated from the Japanese Lauraceae, *Lindera obtusiloba Blume*[1] and *Litsea japonica*[2] have the basic skeleton of the 3-alkylidene-4-hydroxydihydro-2(3*H*)-furanone, identical with the lactones from the Amazonian Lauraceae, *Licaria mahuba*.[3] A great deal of effort has been devoted to the development of novel methods for the construction of 3-alkylidene-4-hydroxydihydro-2(3*H*)-furanone unit[4] and for the total synthesis of these lactones.[5]

Recently we reported that the dianion **1** derived from 2-(methylthio)-4-pentenoic acid can be used as a building block to furnish 5-methylene-2(5*H*)-furanone from alkyl halides or aldehydes under extremely mild reaction conditions.[6]



Scheme 1. (a) n-$C_{15}H_{31}CHO$, THF, −40 °C, 7 h. (b) KI-I_2, $NaHCO_3$, H_2O. (c) MCPBA, CH_2Cl_2, −78 °C, 30 min. (d) $CaCO_3$, toluene, reflux. (e) n-Bu_3SnH, AIBN, benzene, reflux. (f) MsCl, CH_2Cl_2, Et_3N. (g) PhSeNa, EtOH, −10 °C. (h) 30% H_2O_2, CH_3CN, −40 °C—r.t., 43 h.

We now report a new route to (±)-dihydromahubanolide, isolated from the Amazonian Lauraceae, *Licaria mahuba*[3] starting from the dianion **1**. The preparation of hydroxy acid **2** was accomplished by the reaction of **1** with 1.1 equiv. of hexadecanal in THF.[6] Iodolactonization, oxidation with *m*-chloroperbenzoic acid (MCPBA), and subsequent dehydrosulfenylation[7] proceeded smoothly to give 5-iodomethyl-2(5*H*)-furanone **3** in good overall yield from the hydroxy acid **2**. The furanone **3** is extremely sensitive to a base; on treatment of **3** with amine bases or even sodium hydrogencarbonate, the compound **3** gave 5-methylene-2(5*H*)-furanone in high yield.[6] Reduction of **3** with 2 equiv. of tributyltin hydride[5d] cleanly gave the 5-methyl-2(5*H*)-furanone **4** in 90% yield. The mesylate **5** was smoothly transformed by reaction in dichloromethane at 0 °C with 1.2 equiv. of methanesulfonyl chloride in the presence of 1.3 equiv. of triethylamine. Treatment of **5** with sodium benzeneselenolate[8] in ethanol at −10 °C for 2 h gave the selenide **6** in 70% yield. Rearrangement of **6** with 30% hydrogen peroxide[9] in dichloromethane afforded a mixture of (±)-dihydromahubanolide and (±)-dihydroisomahubanolide (*Z*/*E* ratio 67 : 33 in 52% yield). Enhancement in *Z*-selectivity and increase in yield were observed when the oxidation was carried out at −10 °C and the mixture was slowly warmed to room temperature (43 h).[9,10] The IR and 200-MHz ^{1}H-NMR spectra were identical with those of the published spectra.[2,3,5] Although the stereochemical relationship between CH_3 and OH groups is still uncertain due to the overlapping of methyl signals (doublet) of four isomers at 1.34—1.50 ppm region, the present method provides the efficient stereoselective synthesis of (*Z*)-3-alkylidene-4-hydroxy-2(3*H*)-furanones.

Experimental

2-(1-Hydroxyhexadecyl)-2-methylthio-4-pentenoic Acid (2): To a solution of lithium diisopropylamine (22 mmol) in THF (60 ml) was added a solution of 2-methylthio-4-pentenoic acid (**1**) (1.46 g, 10 mmol) in 5 ml of THF at −78 °C. The reaction mixture was stirred at −78 °C for 1 h, and warmed to −40 °C over 8 h. After the solution was cooled to −78 °C,

Table 1. Stereochemistry in rearrangement of selenide **6**

	Reaction conditions		Solvent	Yield of **7** %	*Z*/*E* ratio of **7**[a]
	Temp/°C	Time			
H_2O_2 (3 equiv.)	−10	15 min	CH_3CN	Trace	—
H_2O_2 (3 equiv.)	−10—r.t.	2 h	CH_3CN	63	71/29
H_2O_2 (3 equiv.)	−10—r.t.	43 h	CH_3CN	82	77/23
H_2O_2 (3 equiv.)	−10—r.t.	18 h	CH_2Cl_2	52	67/33
MCPBA (1 equiv.)	−78—r.t.	20 h	CH_2Cl_2	73	75/25

a) The *Z* and *E* assignments are based on the differences of ^{1}H-NMR chemical shift of olefinic protons.[10]

a solution of hexadecanal (2.62 g, 10.9 mmol) in 15 ml of THF was added dropwise. The solution was stirred at −78 °C to −40 °C for 7 h and then quenched with saturated aqueous ammonium chloride (10 ml). The mixture was allowed to warm to room temperature, and was extracted with ether (4×50 ml). From the combined extracts was obtained the crude product which was purified by column chromatography (silica gel; eluent hexane–acetone, 3 : 1) to give 3.12 g (81%) of **2** as viscous liquid: ^{1}H-NMR ($CDCl_3$) δ 7.02 (br, 2H COOH and OH), 5.50—6.30 (m, 1H, CH=C), 4.80—5.30 (m, 2H, CH_2=C), 3.60—4.16 (m, 1H, CH), 2.20—2.90 (m, 2H, CH_2), 2.13 (d, J=6 Hz, 3H, CH_3), 0.70—2.00 (m, 31H, CH_2 and CH_3).

3-(1-Hydroxyhexadecyl)-5-iodomethyl-2(5H)-furanone (3): To a solution of **2** (3.00 g, 7.76 mmol) in water (60 ml) was added sodium hydrogencarbonate (1.96 g, 23.3 mmol), and stirring was continued at room temperature for 20 min. After a solution of iodine (1.97 g, 7.76 mmol) and potassium iodide (3.87 g, 23.3 mmol) in water (60 ml) was added over 1 h, the mixture was stirred at room temperature for 1 h, treated with 10% sodium thiosulfate solution (100 ml), and extracted with chloroform (4×50 ml). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give iodo lactone as an oil which was used without further purification. To a solution of this product (7.76 mmol) in dichloromethane (40 ml) at −78 °C was added a solution of MCPBA (1.68 g, 7.76 mmol) in dichloromethane (60 ml) over 20 min. After the addition was completed, the reaction mixture was stirred at −78 °C for 30 min, poured into water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give an oil. The oil was dissolved in toluene (120 ml), and powdered calcium carbonate (1.16 g, 11.6 mmol) was added. After the mixture was heated at reflux for 30 min, the product was isolated in the usual manner to afford an 82% yield of **3** (2.59 g; unstable) as colorless crystals which were purified by column chromatography (silica gel, eluent benzene to chloroform); mp 35.0—36.0 °C: ^{1}H-NMR ($CDCl_3$) δ 7.02—7.36 (m, 1H, CH=C), 4.76—5.20 (m, 1H, CH), 4.28—4.64 (m, 1H, CH), 2.92—3.70 (m, 3H, CH_2 and OH), 0.70 (m, 31H, CH_2 and CH_3).

3-(1-Hydroxyhexadecyl)-5-methyl-2(5H)-furanone(4): The mixture of **3** (1.86 g, 4 mmol), azobisisobutyronitrile (0.656 g, 4 mmol), and tributyltin hydride (2.32 g, 8 mmol) in benzene (40 ml) was heated at reflux for 2 h under argon. After cooling, the mixture was poured onto 10% hydrochloric acid (50 ml), and extracted with benzene (4×50 ml). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. Chromatography on silica gel (eluent hexane–ether, 5 : 1 to ether) gave **4** in 91% yield (1.23 g); ^{1}H-NMR ($CDCl_3$) δ 7.14—7.30 (m, 1H, CH=C), 4.80—5.08 (m, 1H, CH), 4.32—4.52 (m, 1H, CH), 2.60—3.00 (m, 1H, OH), 0.70—1.90 (m, 34H, CH_2 and CH_3). IR (Nujol) 3400 (OH), 1740, 1720 (C=O) cm^{-1}. MS (20 eV) *m/e* 338 (M^+), 320 ($M^+ - H_2O$). Preparative TLC on silica gel (Merck 60-F254s; hexane–ethyl acetate, 4 : 1) gave an analytical sample as colorless plates; mp 78—80 °C. Found: C, 74.03; H, 11.18%. Calcd for $C_{21}H_{38}O_3$: C, 74.51; H; 11.31%.

5-Methyl-3-[1-(phenylseleno)hexadecyl]-2(5H)-furanone (6): To a solution of **4** (1.26 g, 3.73 mmol) in dichloromethane (30 ml) was added triethylamine (0.49 g, 4.85 mmol) at 0 °C, and the mixture was stirred for 10 min under argon. After the addition of methanesulfonyl chloride (0.50 g, 4.40 mmol) was completed, the mixture was stirred at 0 °C for 3 h. The usual workup gave mesylate **5** in 90% yield (1.39 g). To a solution of sodium benzeneselenolate prepared from diphenyl diselenide (0.255 g, 0.750 mmol) and sodium borohydride (0.057 g, 1.50 mmol) in ethanol (30 ml) was added at −10 °C the mesylate **5** (0.417 g, 1 mmol) in ethanol (10 ml). After the mixture was stirred for 2 h at −10 °C, the solution was poured onto dilute hydrochloric acid and extracted with ether (4×30 ml). The ethereal extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. Chromatography on silica gel first with hexane and then with benzene as eluent gave 0.335 g of **6** in 70% yield: ^{1}H-NMR ($CDCl_3$) δ 7.12—7.52 (m, 5H, CH, and aromatic), 6.44—6.60 (m, 1H, CH=C), 4.50—4.92 (m, 1H, CH), 3.74—4.04 (m, 1H, CH), 0.70—1.92 (m, 34H, CH_2 and CH_3). IR (Nujol) 1740 (C=O), 1680 (C=C), 745, 725, 695 cm^{-1}. Preparative TLC on silica gel (hexane–ethyl acetate, 3 : 1) gave an analytical sample as pale yellow crystals; mp 45—47 °C. Found: C, 67.61; H, 8.98%. Calcd for $C_{27}H_{42}O_2Se$: C, 67.90; H, 8.87%.

(±)-Dihydromahubanolide (7): To a solution of **6** (0.33 g, 0.69 mmol) in acetonitrile (30 ml) was added at −10 °C 30% H_2O_2 (0.178 g, 1.57 mmol). The mixture was slowly warmed to room temperature (43 h) with stirring. The usual workup gave **7** in 82% yield (0.19 g) as a ratio of 77 : 23 of *Z*/*E* mixture. The analytical sample was obtained by silica gel column chromatography (hexane–ethyl acetate, 2 : 1); mp 39.0—50.0 °C (broad). TLC analysis (Merck silica gel plate 60-F254; hexane–ethyl acetate, 3 : 1) indicated a single spot (R_f=0.25). IR (nujol) 3400 (OH), 1740 (C=O), 1675 (C=C) cm^{-1}. MS (20 eV) *m/e* 338 (M^+), 320 ($M^+ - H_2O$). Found: C, 74.32; H, 11.56%. Calcd for $C_{21}H_{38}O_3$: C, 74.51; H, 11.31%.

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11) The 200 MHz ^{1}H-NMR analysis showed a mixture of (±)-dihydrmabubanolide A and B. However, the cis and trans ratio was not determined by 200 MHz ^{1}H-NMR due to the fact that they could not be separated by preparative TLC.