A Total Synthesis of (−)-Sacculatal

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Synopsis. The total synthesis of a tumor promoter, (−)-sacculatal (**1**), has been completed.

According to the recent study in chemical carcinogenesis, there are two successive stages, initiation and promotion, that are induced by chemical substances, initiater and promoter, respectively. Among them, control of the latter stage is much more important to prevent cancer because of its reversibility. (−)-Sacculatal (**1**), a diterpene dialdehyde isolated from the liverworts *Trichocoleopsis sacculata* and *Pellia endiviifolia* by Asakawa and his co-workers, was at first known as a constituent of pungent taste of liverworts.[1a] Later on, in connection with skin irritant property of these plants, (−)-sacculatal (**1**) was found to have tumor promoting activity by testing ornithine decarboxylase (ODC) activity, which was estimated as 1/100 active as 12-*O*-tetradecanoylphorbol 13-acetate.[1b] As a part of our program directed toward total syntheses of biologically active sacculatane type natural products,[3] we disclose herein our synthesis of natural (−)-sacculatal (**1**) starting from (4a*S*,5*S*,8a*S*)-(−)-5β,8aβ-dimethyl-5α-(4-methyl-3-pentenyl)-3,4,4a,-5,6,7,8,8a-octahydro-1(2*H*)-naphthalenone (**3**), an advanced common intermediate for sacculatane synthesis.[3b]

Results and Discussion

The (−)-ketone **3** {[α]$_D$ −8.2° (*c* 3.0 in MeOH); 80% enantiomeric excess} was formylated with ethyl formate in the presence of sodium hydride in benzene to give the keto aldehyde **4**, which was oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dioxane to introduce an unsaturation furnishing the enone **5**. The formyl carbonyl group was selectively protected as an ethylene acetal to afford the acetal **6**. Although two intermediary aldehydes, **4** and **5**, were used without purification because of their instability, the overall yield of **6** from the ketone **3** was 69%. Finally, a protocol of Magnus[4] was employed in order to introduce a formyl group at the electronically less reactive and sterically congested C-1 position. Addition of methoxy(trimethylsilyl)methyllithium afforded in almost quantitatively the fragile single adduct **7** whose stereochemistry has not yet been determined. After extensive efforts to eliminate trimethylsilanol,

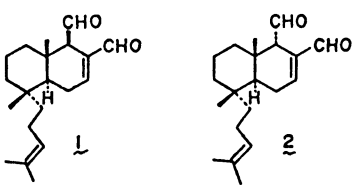
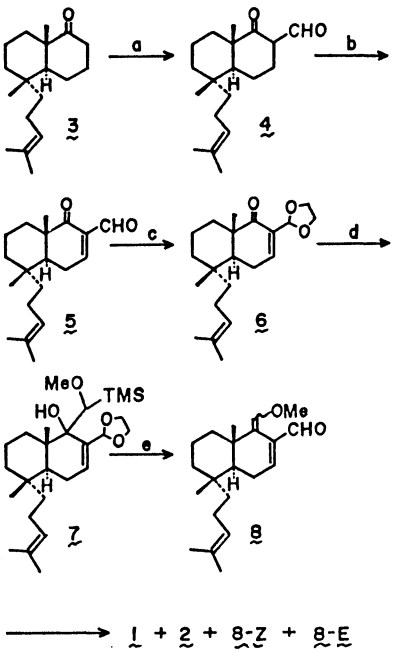


Fig. 1.



⟶ 1 + 2 + 8-Z + 8-E

Scheme 1. Total synthesis of (−)-sacculatal (**1**). (a): HCO_2Et, NaH, benzene, (b): DDQ, dioxane, (c): Ethylene glycol, cat. *p*-TsOH, benzene, (d): $TMSCH_2OMe$, *s*-BuLi, THF, (e): Et_2O saturated with 46% aqueous HF.

treatment of the adduct **7** in ether saturated with 46% hydrogen fluoride[5] underwent facile deprotection of acetal and subsequent elimination of trimethylsilanol followed by slow hydrolysis of the resulting enol ethers **8** to afford (−)-sacculatal (**1**) (26%), isosacculatal (**2**) (16%), and the precursory enol ethers **8-Z** and **8-E** (20%). Attempts to eliminate trimethylsilanol with KH simply gave decomposition products. Isomerization of sacculatal (**1**) to isosacculatal (**2**) was unavoidable because of A$^{(1,2)}$ strain of formyl group at C-1β in addition to peri repulsion between proton at C-8β. The product which exhibited a singlet proton at δ 7.36 in ^{1}H NMR spectrum was assigned to be the (*E*)-enol ether **8-E**. The spectral data of synthetic (−)-sacculatal (**1**) (^{1}H NMR and IR), as well as the optical rotation and mp values {[α]$_D$ −30° (*c* 0.48, $CHCl_3$) (lit,[1a] [α]$_D$ −31.4° (*c* 3.5, $CHCl_3$)}; mp 65—66 °C (lit,[1a] mp 65—66 °C)], are identical with those of the natural sample.

In summary, we have completed the total synthesis of a tumor promoter, (−)-sacculatal (**1**).

Experimental

General. Melting point is uncorrected. Anhydrous solvents were distilled from sodium (benzene) or lithium aluminum hydride (tetrahydrofuran). All infrared spectra were obtained with a JASCO A-3 spectrophotometer for solutions

in carbon tetrachloride. ^{1}H NMR spectra were recorded with a JEOL PMX-60 SI (60 MHz) or FX-90Q (90 MHz) instrument. Chemical shifts were reported δ values relative to tetramethylsilane. Mass spectra were obtained with a JEOL JMS DX-300 mass spectrometer at 70 eV and relative intensities were reported. Optical rotations were recorded on a JASCO DIP-4S polarimeter for solutions in chloroform unless otherwise specified. Preparative medium-pressure liquid chromatographies (MPLC) were carried out on a JASCO PRC-50 system.

(4a*S*,5*S*,8a*S*)-(+)-5β,8aβ-Dimethyl-2-formyl-5α-(4-methyl-3-pentenyl)-3,4,4aα,5,6,7,8,8a-octahydro-1(2*H*)-naphthalenone (4). To a stirred slurry of sodium hydride (60%, 54 mg, 1.35 mmol) in anhydrous benzene (1 mL) were added a solution of the ketone **3** (51.8 mg, 0.198 mmol) in benzene (2 mL) and then ethyl formate (80 μL, 0.99 mmol). After stirring at room temperature for overnight under nitrogen, the resulting solution was poured into dil. HCl, and extracted with ether (30 mL×2). The combined extracts were washed with water and brine and dried. Evaporation of the solvents afforded the keto aldehyde **4** (67.4 mg), which was used soon for the next reaction without purification. The sample purified by MPLC exhibited $[\alpha]_D$ +22.3° (*c* 0.546, methanol); IR ν 1700, 1640, 1590, 1455 cm^{-1}; ^{1}H NMR (60 MHz) δ=0.88 (s, 3H), 1.23 (s, 3H), 1.6 (s, 3H), 1.7 (s, 3H), 1.0—2.5 (m, 16H), 5.09 (br t, 1H), 8.43 (d, *J*=4 Hz, 1H); MS *m*/*z* 290 (M$^+$, 9), 138 (19), 58 (41), 43 (100); Calcd for $C_{19}H_{30}O_2$: M, 290.22449. Found: *m*/*z* 290.22419.

(4a*S*,5*S*,8a*S*)-(+)-5β,8aβ-Dimethyl-2-formyl-5α-(4-methyl-3-pentenyl)-4a,5,6,7,8,8a-hexahydro-1(4*H*)-naphthalenone (5). To a solution of the crude keto aldehyde **4** (67.4 mg) in dioxane (3 mL) was added DDQ (freshly recrystallized from dichloromethane, 134 mg, 0.59 mmol) in one portion. The resulting solution was stirred for 1 h, and extracted with ether (30 mL×2). The combined organic layer was washed with water and brine. After evaporation of the solvents, the residue was passed through silica-gel short column with the aid of hexane/ethyl acetate. Evaporation of the solvents gave the enone **5** (162 mg), which was used without purification for the next reaction. The pure enone **5** after MPLC purification exhibited $[\alpha]_D$ +75.5° (*c* 0.249); IR ν 1705, 1680, 1620, 1450, 1380 cm^{-1}; ^{1}H NMR (90 MHz) δ=1.02 (s, 3H), 1.12 (s, 3H), 1.57 (s, 3H), 1.68 (s, 3H), 1.0—2.5 (m, 13H), 5.0 (br t, 1H), 7.92 (m, 1H), 10.0 (s, 1H); MS *m*/*z* 288 (M$^+$, 12), 273 (29), 245 (31), 189 (17), 175 (18), 162 (19), 150 (23), 137 (22), 109 (37), 69 (52), 58 (74), 43 (100); Calcd for $C_{19}H_{28}O_2$: M, 288.20891. Found: *m*/*z* 288.20891.

(4a*S*,5*S*,8a*S*)-(−)-5β,8aβ-Dimethyl-2-(1,3-dioxolan-2-yl)-5α-(4-methyl-3-pentenyl)-4aα,5,6,7,8,8a-hexahydro-1(4*H*)-naphthalenone (6). A solution of the crude enone **5** (162 mg) in anhydrous benzene (5 mL) in the presence of ethylene glycol (0.3 mL) and a catalytic amount of *p*-toluenesulfonic acid was refluxed for 30 min using a Dean-Stark water separator. After cooling to room temperature, the resulting solution was poured into aqueous $NaHCO_3$, and the product was extracted with ether (30 mL×2). Evaporation of the solvent followed by MPLC separation (silica gel, 4:1 hexane/ethyl acetate) afforded the enone acetal **6** (45 mg, 69% in overall 3 steps), which exhibited $[\alpha]_D$ −4.76° (*c* 0.315); IR ν 1680, 1620 cm^{-1}; ^{1}H NMR (60 MHz) δ=1.0 (s, 3H), 1.1 (s, 3H), 1.6 (s, 3H), 1.68 (s, 3H), 1.0—2.5 (m, 13H), 3.98 (br s, 4H), 5.02 (br t, 1H), 5.57 (s, 1H), 7.1 (t, *J*=4 Hz, 1H); MS *m*/*z* 332 (M$^+$, 64), 317 (56), 243 (33), 203 (30), 180 (37), 154 (37), 109 (68), 73 (100), 69 (70), 55 (34), 45 (45), 41 (66); Calcd for $C_{21}H_{32}O_3$: M, 332.23502. Found: *m*/*z* 332.23442.

(4a*S*,5*S*,8a*S*)-5β,8aβ-Dimethyl-2-(1,3-dioxolan-2-yl)-1-[methoxy(trimethylsilyl)methyl]-1,4,4aα,5,6,7,8,8a-octahydro-1-naphthalenol (7). To a stirred solution of methoxytrimethylsilylmethane (106 μL, 0.68 mmol) in anhydrous THF (1 mL) was added a hexane solution of *s*-BuLi (1.02 M†, 0.66 mL, 0.67 mmol) at −65 °C under nitrogen. After stirring for 30 min at −30 to −25 °C, a solution of the enone acetal **6** (45 mg, 0.136 mmol) in anhydrous THF (4 mL) was added. The resulting solution was stirred at −25 to 0 °C for 30 min and then at 0 °C for further 30 min. The reaction was quenched by addition of aqueous NH_4Cl and the product was extracted with ether (30 mL×2). Evaporation of the solvent left the trimethylsilyl alcohol **7**, an oil (77 mg), which was used without purification. IR ν 3500, 1385, 1250 cm^{-1}; ^{1}H NMR (60 MHz) δ=0.12 (s, 9H), 0.92 (s, 6H), 1.6 (s, 3H),1.68 (s, 3H), 1.0—2.5 (m, 14H), 3.35 (s, 3H), 3.4 (s, 1H), 3.95 (m, 4H), 5.05 (br t, 1H), 5.37 (s, 1H), 6.67 (t, *J*=3 Hz, 1H).

(1*R*,4a*S*,5*S*,8a*R*)-(−)-5β,8aβ-Dimethyl-1β,2-diformyl-5α-(4-methyl-3-pentenyl)-1,4,4aα,5,6,7,8,8a-octahydronaphthalene [(−)-Sacculatal] (1), (1*S*,4a*S*,5*S*,8a*S*)-5β,8aβ-Dimethyl-1α,2-diformyl-5α-(4-methyl-3-pentenyl)-1,4,4aα,5,6,7,8,8a-octahydronaphthalene (Isosacculatal) (2), (4a*S*,5*S*,8a*S*)-5β,8aβ-Dimethyl-2-formyl-1*Z*-methoxymethylene-5α-(4-methyl-3-pentenyl)-1,4,4aα,5,6,7,8,8a-octahydronaphthalene (8-Z), and (4a*S*,5*S*,8a*S*)-5β,8aβ-Dimethyl-2-formyl-1*E*-methoxymethylene-5α-(4-methyl-3-pentenyl)-1,4,4aα,5,6,7,8,8a-octahydronaphthalene (8-E). A solution of the crude trimethylsilyl alcohol **7** (77 mg) in ether saturated with 46% aqueous hydrogen fluoride (5 mL) was stirred at room temperature for 6 h. The resulting solution was poured into cold aqueous $NaHCO_3$ and extracted with ether (30 mL×2). Evaporation of the solvent followed by MPLC separation of the residue (silica gel, 1:4 hexane/ethyl acetate) afforded (−)-sacculatal (**1**) (2.7 mg, 26.3%), isosacculatal (**2**) (1.6 mg, 15.6%) and a mixture of the enol ethers (**8-Z**) and (**8-E**) (2.1 mg, 19.6%) which were separated by repeated MPLC. (−)-Sacculatal (**1**) which crystallized spontaneously at −20 °C, exhibited mp 65—66 °C (lit,[1] mp 65—66 °C); $[\alpha]_D$ −30.1° (*c* 0.478) (lit,[1] −31.4°, *c* 3.5); IR ν 2700, 1725, 1685, 1640, 1385, 1240 cm^{-1}; ^{1}H NMR (90 MHz) δ=0.96 (s, 3H), 0.98 (s, 3H), 1.59 (s, 3H) 1.67 (s, 3H), 2.41 (m, 2H), 2.84 (br s, 1H), 1.0—2.0 (m, 11H), 5.05 (t, *J*=5 Hz, 1H), 7.11 (m, 1H), 9.46 (s, 1H), 9.49 (d, *J*=4.4 Hz, 1H); MS *m*/*z* 302 (M$^+$, 3), 274 (50), 259 (91), 231 (49), 121 (53), 91 (47), 69 (100), 55 (55), 41 (99); Calcd for $C_{20}H_{30}O_2$: M, 302.22453. Found: *m*/*z* 302.22263. Isosacculatal (**2**) exhibited IR ν 2700, 1685, 1650, 1450, 1380 cm^{-1}; ^{1}H NMR (90 MHz) δ=0.93 (s, 3H), 0.99 (s, 3H), 1.59 (s, 3H), 1.67 (s, 3H), 1.0—2.5 (m, 13H), 3.28 (br s, 1H), 5.04 (br t, 1H), 7.1 (m, 1H), 9.41 (s, 1H), 9.85 (d, *J*=2.6 Hz, 1H); MS *m*/*z* 302 (M$^+$, 18), 259 (34), 201 (38), 105 (47), 74 (64), 69 (70), 59 (100), 55 (51), 45 (58), 43 (54), 41 (94); Calcd for $C_{20}H_{30}O_2$: M, 302.22463. Found: *m*/*z* 302.22513. The enol ether (**8-Z**) exhibited IR ν 1700, 1640, 1605, 1220, 1130 cm^{-1}; ^{1}H NMR (90 MHz) δ=0.91 (s, 3H), 0.99 (s, 3H), 1.57 (s, 3H), 1.66 (s, 3H), 1.0—2.5 (m, 13H), 3.59 (s, 3H), 5.03 (br t, *J*=3.6 Hz, 1H), 5.97 (s, 1H), 6.53 (t, *J*=4 Hz, 1H), 9.65 (s, 1H); MS *m*/*z* 316 (M$^+$, 61), 302 (22), 301 (100), 199 (22), 163 (27), 145 (21), 119 (22), 109 (25), 105 (28), 91 (29), 81 (24), 69 (86), 55 (39), 41 (66); Calcd for $C_{21}H_{32}O_2$: M, 316.24013. Found *m*/*z* 316.24013. The enol ether (**8-E**) exhibited IR ν 2720, 1695, 1630, 1610, 1250, 1140 cm^{-1}; ^{1}H NMR (90 MHz) δ=0.91 (s, 3H), 1.05 (s, 3H), 1.59 (s, 3H), 1.67 (s, 3H), 1.0—2.5 (m, 13H), 3.64 (S, 3H), 5.06 (br t, *J*=3.6 Hz, 1H), 6.53 (m, 1H), 7.36 (s, 1H), 9.38 (s, 1H); mass spectrum *m*/*z* 316 (M$^+$, 52), 301 (82), 199 (22), 163 (23), 149 (54), 145 (21), 119 (23), 109 (32), 95 (27), 91 (34), 83 (22), 81 (26), 70 (23), 69 (100), 67 (21), 58 (54), 57 (35), 56 (21), 55 (56); Calcd for $C_{21}H_{32}O_2$: M, 316.24012. Found: *m*/*z* 316.24002.

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† 1 M=1 mol dm^{-3}.

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