Synthesis of Syzygiol; A Skin-Tumor Promotion Inhibitor

Shingo SATO,* Heitaro OBARA, Akira ENDO,
Jun-ichi ONODERA, and Shigeru MATSUBA
Department of Materials Science and Engineering, Faculty of Engineering,
Yamagata University, Yonezawa 992
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Synopsis. Syzygiol, 3-hydroxy-2-(β-hydroxycinnamoyl)-5-methoxy-6,6-dimethyl-2,4-cyclohexadien-1-one (**1**) was synthesized via ceroptene (**5**).

Recently, the structure of syzygiol (**1**), a constituent of the seed of the Indonesian myrtaceous plant *Syzygium polycephaloides,* was reported by M. Nishizawa et al.[1] The structure of **1** was mainly established by an X-ray analysis, since this compound exists as a mixture of many tautomers in solution. The interesting tautomeric structures and the inhibitory activity against tumor promotion of **1** prompted us to synthesize this novel compound. We herein wish to report the brief synthetic method of **1** via ceroptene (**5**) as shown in Scheme 1.

The treatment of 1,3,5-benzenetriol with acetic acid–boron trifluoride (2/1), followed by a reaction with methyl iodide in the presence of sodium methoxide, afforded 2,6-diacetyl-3,5-dihydroxy-4,4-dimethyl-2,5-cyclohexadien-1-one (**2**) in 42% yield. Deacetylation of **2** with 80% H_2SO_4 followed by treatment with diazomethane afforded 2-acetyl-3-hydroxy-5-methoxy-4,4-dimethyl-2,5-cyclohexadien-1-one (**4**) in 72% yield. An aldol condensation of **4** with benzaldehyde in piperidine afforded ceroptene (**5**) in 79% yield (overall yield 24.0%, lit,[2] 2.0%). We could establish an efficient synthetic method of ceroptene, which was isolated from fronds of *Pityrogramma triangularis.*[2] Next, Bromination of **5** gave the bromide **6**[3] in 72% yield. Finally, hydrolysis of **6** in alkaline solution at r.t. afforded syzygiol (**1**) in 33% yield, which is readily crystallized from ethyl acetate to give pale-yellow plates. The pysicochemical data of synthetic **1** were completely identical with those of the natural specimen in all respects. The NMR spectra showed many complex signals arising from keto-enol tautomerism, just as has been reported.[1] Futhermore, the treatment of **1** with an acidic solution, followed by alkaline hydrolysis, afforded demethylated syzygiol (**7**) in 10% yield. Its ^1H NMR and UV spectra were much more complicated than those of **1**, due to the presence of an enolizable 1,3,5-triketone system (Fig. 1).

Experimental

All melting points are uncorrected. IR and UV spectra were recorded with a Hitachi 215 and a Hitachi 100-50 spectrometer, respectively. ^1H and ^{13}C NMR spectra were measured by a

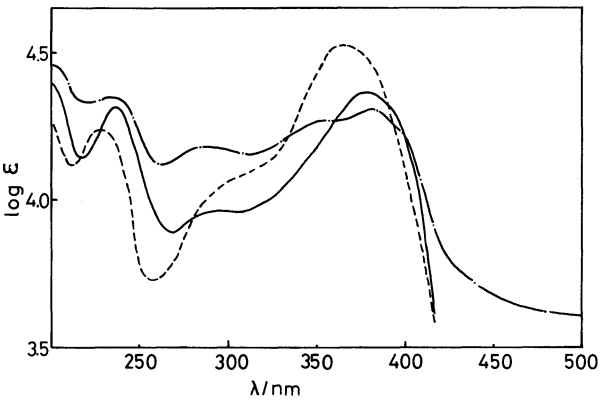
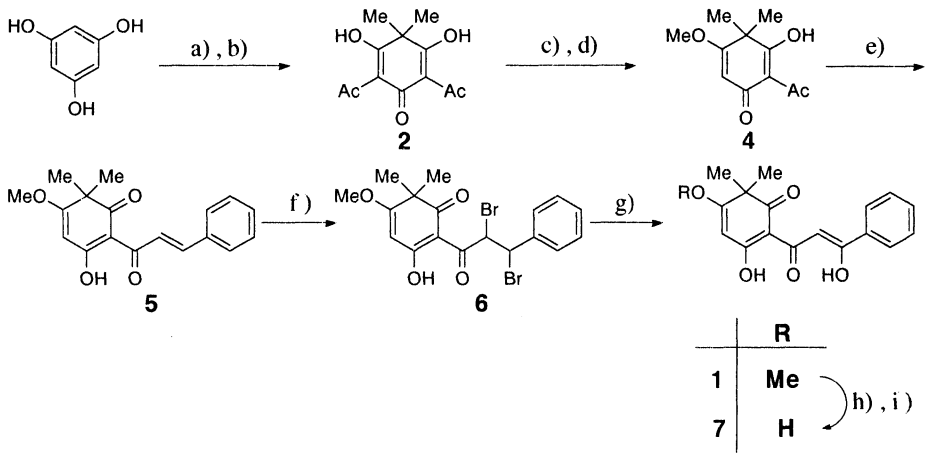


Fig. 1. Electronic spectra of **5** (---), **1** (——), and **7** (--·—) in ethanol.



a) $2AcOH \cdot BF_3$ b) NaOMe, MeI c) 80% aq H_2SO_4
d) CH_2N_2 e) PhCHO, Piperidine, 85°C f) Br_2, $CHCl_3$, 0°C
g) 20% aq NaOH, r.t. h) 10% HCl–MeOH i) 20% aq NaOH, MeOH

Scheme 1.

Hitachi R-600 and a Hitachi R-90H spectometer using tetramethylsilane as an internal standard, respectively. Mass spectra were obtained on a Hitachi RMU-6M spectometer.

2,6-Diacetyl-3,5-dihydroxy-4,4-dimethyl-2,5-cyclohexadien-1-one (2). 2,4-Diacetyl-1,3,5-benzenetriol was prepared from 1,3,5-benzenetriol by reaction with acetic acid–boron trifluoride (2/1) in 66% yield. To a solution of 2,4-diacetyl-1,3,5-benzenetriol (10.0 g, 47.6 mmol) in dry methanol (40 ml) was added 28% sodium methoxide solution (27.9 g, 145 mmol) in MeOH at 0°C. To the stirred mixture was added dropwise methyl iodide (20.5 g, 145 mmol) at 0°C; the stirring was continued at r.t. for 24 h. Then, an additional 28% sodium methoxide solution (18.6 g, 96.4 ml) in MeOH and methyl iodide (20.5 g, 145 mmol) were added; the mixture was then stirred at r.t. for 24 h. After the methanol in the reaction mixture was removed by a rotary evaporator, 200 ml of ice-cold 2 M HCl (1 M=1 mol dm^{-1}) was added to the residual reddish-brown syrup, and an aqueous mixture was extracted with petroleum ether three times. The combined extracts were washed with water and brine, dried over sodium sulfate (Na_2SO_4), and concentrated in vacuo to give pale-yellow crystals, which were recrystallized from petroleum ether to give 7.2 g (63.3%) of colorless prisms. Mp 58—60°C (lit,[4] 60—61°C); MS (25 eV) *m/z* 238 (M^+); IR (KBr) 3500, 3020, 2980, 2930, 1675, 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.47 (s) and 1.58 (s) (6 : 1, 6H, CH_3×2), 2.63 (s) and 2.74 (s) (1 : 1.2, 6H, Ac×2), 18.38 (s), 18.86 (s), and 19.27 (s) (1 : 4.3 : 4.3, 2H, chelated OH, contributions from tautomers[4]). Found: C, 60.79; H, 6.11%. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92%.

2-Acetyl-3,5-dihydroxy-4,4-dimethyl-2,5-cyclohexadien-1-one (3). A mixture of **2** and 10 ml of 80% H_2SO_4 was heated on a steam bath until the disappearance of the starting material on TLC (for ca. 20 min). The reaction mixture was poured onto ice and then extracted with ethyl acetate three times. The combined extracts were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo to give crude crystals, which were recrystallized from methanol to give 6.1 g (72.6%) of colorless prisms. Mp 170—172°C (lit,[4] 174—175°C); MS (25 eV) *m/z* 196 (M^+); ^1H NMR (DMSO-d_6) δ=1.29 (6H, s, CH_3×2), 2.49 (3H, s, Ac), 5.45 (1H, s, =CH–), 18.41 (1H, br.s, chelated OH). Found: C, 61.19; H, 6.37%. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16%.

2-Acetyl-3-hydroxy-4,4-dimethyl-5-methoxy-2,5-cyclohexadien-1-one (4). To a stirred solution of **3** (1.0 g, 5.1 mmol) in ethyl acetate (10 ml) was added an ethereal solution of diazomethane dropwise at r.t. until the disappearance of the starting material on TLC (toluene–ethylacetate–acetic acid=6 : 1 : 0.2). The reaction mixture was concentrated in vacuo, and the crude product was crystallized from toluene to give 1.06 g (99%) of **4** as colorless prisms. Mp 106—107°C (lit,[2] 107—109°C); MS (25 eV) *m/z* 210 (M^+); IR (KBr) 3450 (br.), 3000, 2950, 1645, 1615, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.38 (6H, s, CH_3×2), 2.62 (3H, s, Ac), 3.83 (3H, s, OMe), 5.44 (1H, s, =CH–), 18.39 (1H, br.s, chelated OH). Found: C, 62.87; H, 6.97%. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71%.

Ceroptene; 2-Cinnamoyl-3-hydroxy-5-methoxy-6,6-dimethyl-2,4-cyclohexadien-1-one (5). A mixture of compound **4** (1.57 g, 7.48 mmol), benzaldehyde (2.27 ml, 22.45 mmol), and piperidine (3 ml) was heated at 85°C for 30 min. After cooling, the reaction mixture was poured into 10 ml of 2 M HCl, and extracted with ethyl acetate three times. The combined extracts were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo to give crude crystals, which were recrystallized from methanol to give 1.76 g (79%) of **5** as yellow prisms. Mp 137—138°C (lit,[2] 138—140°C); MS (25 eV) *m/z* 298 (M^+); IR (KBr) 3450 (br.), 1640, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.40 (s) and 1.49 (s) (5 : 1, 6H, CH_3×2), 3.76 (s) and 3.83 (s) (1 : 5.6, 3H, Ac, contributions from tautomers), 5.50 (1H, s, =CH–), 7.27—7.75 (5H, m, ArH), 7.92 and 8.33 (each 2H, d, *J*=15.6 Hz, *trans* –CH=CH–), 18.92 (1H, s, chelated OH). Found: C, 72.21; H, 6.27%. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08%.

2-(2,3-Dibromo-3-phenylpropionyl)-3-hydroxy-5-methoxy-6,6-dimethyl-2,4-cyclohexadien-1-one (6). To a stirred solution of **5** (1.86 g, 6.24 mmol) in chloroform (8 ml) was slowly added bromine dropwise at 0°C until the disappearance of the starting material on TLC. The reaction mixture was concentrated in vacuo. The residue was purified by silica-gel column chromatography with toluene, and then toluene–ethyl acetate–acetic acid (10 : 1 : 0.1) to give 2.07 g (72.4%) of **6** as orange prisms. Mp 138—140°C; MS (25 eV) *m/z* 378 ($M-Br^+$); IR (KBr) 3450 (br.), 1645, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.42 (s) and 1.45 (s) (1 : 1, 6H, CH_3×2, contribution from tautomers), 3.88 (3H, s, OCH_3), 5.54 (1H, s, =CH–), 5.58 and 6.92 (each 1H, d, *J*=12.0 Hz, –CHBrCHBr–), 7.30—7.46 (5H, m, ArH), 17.41 (1H, s, chelated OH). Found: C, 47.44; H, 3.99%. Calcd for $C_{18}H_{18}O_4Br_2$: C, 47.19; H, 3.96%.

Syzygiol; 2-(β-Hydroxycinnamoyl)-3-hydroxy-5-methoxy-6,6-dimethyl-2,4-cyclohexadien-1-one (1). A mixture of **6** (0.40 g, 0.87 mmol), methanol (10 ml), and 20% NaOH aqueous solution (19 ml) was stirred at r.t. for 10 min. The reaction mixture was poured into ice-cold 2 M HCl (ca. 100 ml) and extracted with ethyl acetate three times. The combined extracts were washed with water and brine, dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by silica-gel column chromatography with toluene, and then toluen–ethyl acetate–acetic acid (10 : 1 : 0.1). Crystallization from ethyl acetate gave 91 mg (33.3%) of **1** as pale-yellow plates. Mp 150—151°C (lit,[1] 150—151°C); MS (25 eV) *m/z* 314 (M^+); IR (KBr) 3500 (br.), 3180, 3100, 3000, 2960, 1650, 1625, 1590 cm^{-1}; UV (95% ethanol) 238 (ε 20900), 380 (23800) nm; lit,[1] 238 (ε 21500), 380 (27900); ^1H NMR ($CDCl_3$) δ=1.32 (s), 1.40 (s), 1.52 (s), and 1.65 (s) (1.2 : 4.6 : 1 : 0.25, 6H, CH_3×2), 3.71 (s), 3.76(s), and 3.84 (s) (1 : 1 : 30, 3H, OCH_3), 4.64 (s) and 4.72 (s) (3.5 : 1, 1H, –COCH=C (OH)Ph), 5.44 (1H, s, =CH–), 7.40—7.58 (m) and 7.90—8.07 (m) (5H, ArH), 14.37 (1H, s, –COCH=C (OH)Ph), 17.35 (s), 17.47 (s), 17.78(s), and 17.86 (s) (1.5 : 8 : 1 : 2, 1H, chelated OH, contributions from tautomers); ^{13}C NMR (25 MHz, $CDCl_3$) δ=198.0 (23.0), 196.6 (17.8), 196.3 (14.1), 194.0 (14.9), 192.7 (20.1), 187.6 (22.9), 186.2 (22.7), 181.0 (13.9), 180.0 (20.1), 175.1 (25.1), 136.9 (14.5), 133.9 (25.1), 133.0 (36.3), 131.6 (41.7), 128.7 (19.2), 128.5 (100.0), 128.3 (98.5), 128.1 (78.9), 127.0 (19.7), 126.8 (83.1), 106.1 (14.4), 103.1 (14.2), 95.7 (35.5), 93.1 (33.3), 93.0 (36.5), 56.6 (34.4), 56.4 (36.6), 51.2 (31.5), 49.3 (25.2), 49.1 (25.4), 24.9 (47.2), and 24.5 (45.7). Found: C, 69.06; H, 5.91%. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77%.

2-(β-Hydroxycinnamoyl)-3,5-dihydroxy-6,6-dimethyl-2,4-cyclohexadien-1-one (7). A solution of **1** (200 mg, 0.637 mmol) in 10% HCl–methanol solution (5 ml) was refluxed for 1 h. The reaction mixture was poured into ice-cold water and extracted with ethyl acetate three times. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. To a solution of the residue in 3 ml of methanol, 20% NaOH aqueous solution (2 ml) was added; the mixture was then stirred at r.t. for 10 min. The reaction mixture was poured into ice-cold 2 M HCl (50 ml) and extracted with ethyl acetate three times. The combined extracts were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica-gel column chromatography with toluene, and then toluene–ethyl acetate–acetic acid (10 : 1 : 0.1). Crystallization from chloroform gave 20 mg (10.5%) of **7** as pale-yellow crystals. Mp 128—129°C; MS (25 eV) *m/z* 300 (M^+); UV (95% ethanol) 234 (ε 22000), 286 (15100), 356 (sh 18400), 380 (20000) nm; IR (KBr) 3450 (OH), 1685, 1640, 1595, 1520 cm^{-1};

^{1}H NMR (DMSO-d_6) δ=1.23 (s), 1.33 (s), and 1.55 (s) (21 : 11 : 1, 6H, CH_3×2), 4.54 (1H, s, =CH–), 5.49 (1H, s, –COCH=C (OH)Ph), 7.48—8.05 (5H, m, ArH), 14.30 (1H, br.s, –COCH=C (OH)Ph), 16.97 (br.s) and 17.78 (br.s) (1H, chelated OH, contributions from tautomers). Found: C, 68.48; H, 5.25%. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37%.

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