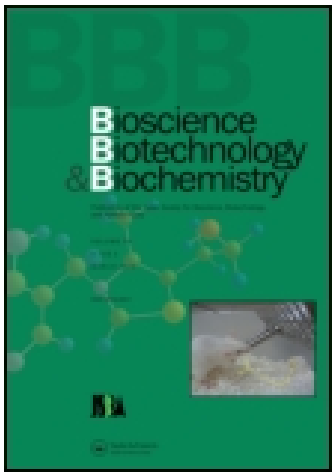

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Synthesis of (±)-Hiburipyranone, a Cytotoxic Metabolite of Marine Sponge Mycale adhaerens

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Synthesis of (±)-Hiburipyranone, a Cytotoxic Metabolite of Marine Sponge *Mycale adhaerens*

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Hiburipyranone, a cytotoxic metabolite of the marine sponge, *Mycale adhaerens*, was synthesized as a racemate.

Key words: cytotoxin; hiburipyranone; isocoumarin derivative; *Mycale adhaerens*

Hiburipyranone (**1**) was isolated in 1990 by Fusetani *et al.* from the marine sponge, *Mycale adhaerens*.[1] It has a 3,4-dihydroisocoumarin skeleton and was cytotoxic against P388 murine leukemia cells ($IC_{50}=0.19\,\mu g/ml$). Although the specific rotation of **1** has been reported [$[\alpha]_D$ −2.3° (*c* 0.028, MeOH)],[1] its absolute configuration at the C-3 position was not clarified. We undertook a synthesis of (±)-hiburipyranone as a part of our studies on isocoumarins, which have simple structures with many interesting activities.

Results and Discussion

Our starting material was methyl 3,5-dimethoxybenzoate (**2**) (Scheme 1). Reduction of **2** with lithium aluminum hydride gave alcohol **3a** as colorless needles (mp 46.0–47.0°C, 97%), and iodination of **3a** afforded **3b** as slightly yellow needles (mp 85.0–85.5°C, 81%). **3b** was then treated with ethyl valerate and lithium diisopropylamide to give **4a** (88%), which was hydrolyzed to carboxylic acid (**4b**; 88%). An intramolecular Friedel-Crafts reaction by heating **4b** with polyphosphoric acid afforded indanone (**5**) as colorless rods (mp 54.5–55.0°C, 90%).

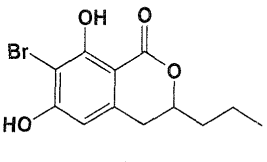

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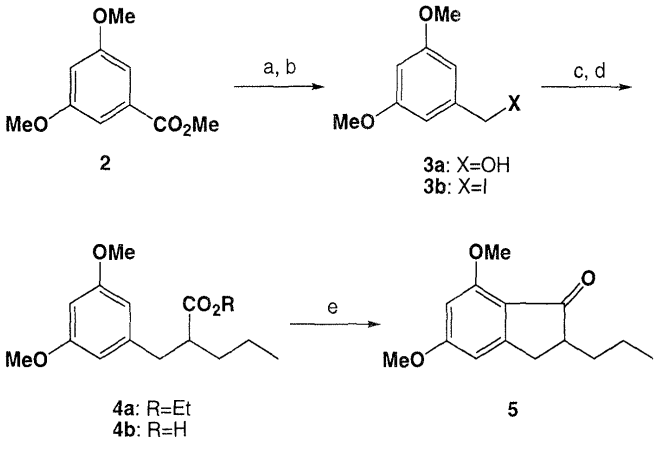
Fig. 1.



2 — **3a**: X=OH, **3b**: X=I — **4a**: R=Et, **4b**: R=H — **5**

Scheme 1.

a) $LiAlH_4$, Et_2O, 97%; b) I_2, PPh_3, imidazole, benzene, 81%; c) $CH_3(CH_2)_3CO_2Et$, LDA, HMPA, THF, 88%; d) KOH aq., MeOH, 88%; e) PPA, 90%.

Ketone **5** was treated with *t*-butyldimethylsilyl trifluoromethanesulfonate and 2,6-lutidine to give silyl enol ether **6** (Scheme 2). Contrary to our expectation, ozonolysis of **6** afforded keto carboxylic acid (**7**) only as a minor product. The major products were α-hydroxy ketone **8b** and its silyl ether **8a**. Instead of ozonolysis, some other methods were tried: Baeyer–Villiger oxidation[2] of **5** with mCPBA gave a mixture of many products, and Lemieux–Johnson oxidation[3] of **6** gave only desilylation product **5**. We therefore selected the first route. After the mixture of **7**, **8a**, and **8b** had been treated with 46% hydrofluoric acid to convert **8a** to **8b** and then with sodium periodate to oxidize **8b** to **7**, **7** was lactonized under acidic conditions to give isocoumarin derivative **9a** as colorless prisms (mp 102.0–103.0°C, 49% from **5** in 5 steps).

Demethylation of **9a** was accomplished by using boron tribromide[4] to give **9b** as colorless prisms (mp 146.0–147.0°C, 97%), whose enol lactone was then reduced in two steps to **11** as colorless prisms (mp 145.0–146.0°C, 62% in 2 steps). Finally, bromination of **11** with pyridinium hydrobromide perbromide[5] gave (±)-**1** as colorless needles (mp 191.5–193.0°C (sealed tube), 16%). In this step, 26% of starting material **11** was recovered, and undesired isomer **12** and dibromide **13** were also produced in 16% and 26% yields, respectively. However, **11** could be regenerated by debromination of the mixture of **12** and **13** with zinc powder in acetic acid in a quantitative yield. Considering the recovered and regenerated starting material, the yield of (±)-**1** was estimated to be 50%.

The ^{1}H-NMR, ^{13}C-NMR, and IR spectral data of our synthetic (±)-**1** were identical with those of natural **1**.[1]

Experimental

IR spectra were recorded on a JASCO A-102 spectrometer or JASCO FT/IR 230 spectrometer. ^{1}H-NMR spectra were determined with a JEOL JNM EX-90 (90 MHz), Bruker AC-300 (300 MHz) or JEOL JNM GSX-500 spectrometer (500 MHz). ^{13}C-NMR spectra were determined with a JEOL JNM GSX-500 instrument (125 MHz). Chemical shifts for ^{1}H-NMR are expressed in ppm based on the signal of $CHCl_3$ at 7.26 ppm or of DMSO-d_5

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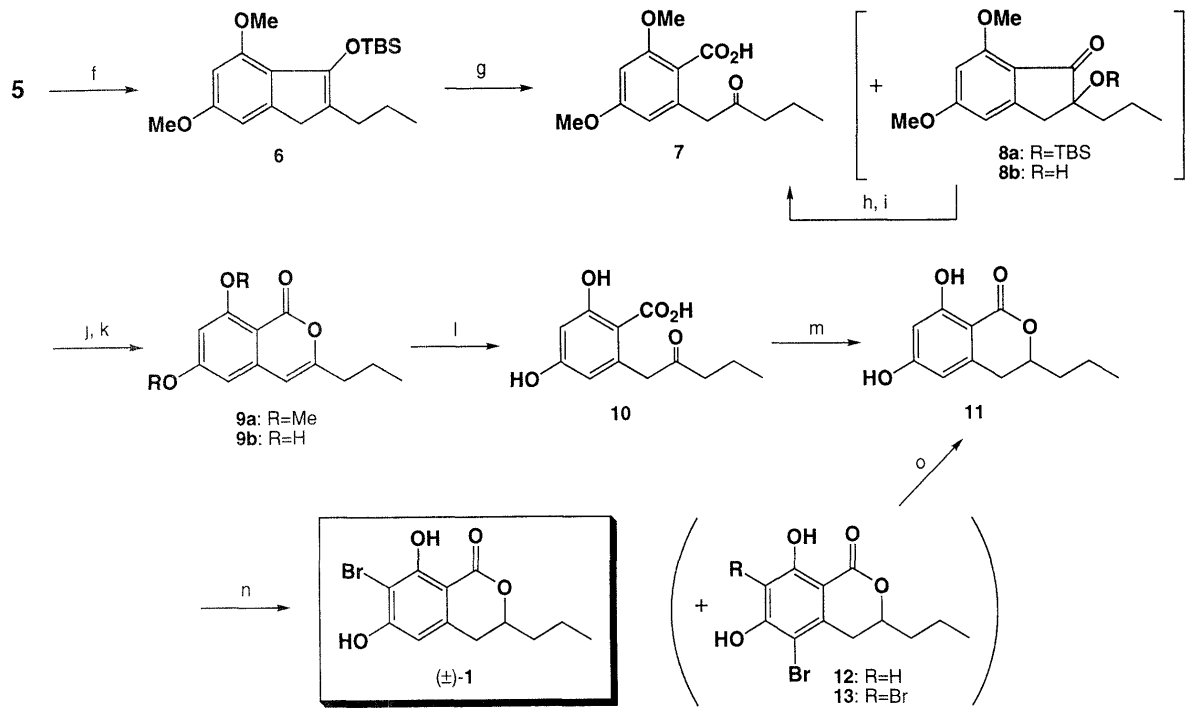

Scheme 2.

f) TBSOTf, 2,6-lutidine, CH_2Cl_2; g) O_3, $NaHCO_3$, CH_2Cl_2; Me_2S; h) 48% HF, CH_3CN; i) $NaIO_4$, Et_2O–H_2O; j) conc. HCl, AcOH, 48% in 5 steps; k) BBr_3, CH_2Cl_2, 97%; l) 0.05 N NaOH aq., 92%; m) $NaBH_4$, Et_2O, H_2O; conc. HCl, H_2O, 67%; n) Pyr·HBr_3, pyridine, 16% (50%); o) Zn dust, AcOH, Δ, quant.

at 2.49 ppm, and those for ^{13}C-NMR are expressed in ppm based on the signal of $CDCl_3$ at 77.0 ppm. Column chromatography was performed on Merck Kieselgel 60 (Art. Nr. 7734). Preparative silica gel TLC was performed on Merck Kieselgel F-254. Melting point (mp) data are uncorrected.

3,5-Dimethoxybenzyl alcohol (**3a**). A solution of **2** (28.4 g, 145 mmol) in dry ether was added dropwise to a stirred and cooled suspension of lithium aluminum hydride (5 g, 132 mmol) in dry ether (125 ml) at −5–0°C under argon. The mixture was stirred at room temp. for 15 h. The excess reducing agent was then destroyed by successively adding of water (5 ml), a 15% aqueous sodium hydroxide solution (5 ml) and water (15 ml) to the stirred and ice-cooled mixture. It was then filtered, and the filter cake was washed several times with tetrahydrofuran. The combined filtrate and washings were dried with anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was recrystallized from hexane–ether (1 : 1–2 : 1) to give pure **3a** (23.7 g, 97%) as colorless needles; mp 46.0–47.0°C; IR (nujol) ν cm^{-1}: 3350, 1605, 1300, 1205, 1160, 1065, 1020, 840, 705; ^{1}H-NMR (90 MHz in $CDCl_3$) δ: 1.78 (1H, br., OH), 3.79 (6H, s, $-OCH_3$), 4.63 (2H, s, $-CH_2O-$), 6.39 (1H, t, J=2 Hz, 4-H), 6.51 (2H, d, J=2 Hz, 2- and 6-H). *Anal.* Calcd. for $C_9H_{12}O_3$: C, 64.27; H, 7.19%. Found: C, 64.47; H, 7.34%.

3,5-Dimethoxybenzyl iodide (**3b**). Iodine (1.13 g, 4.45 mmol) was added to a solution of alcohol **3a** (0.50 g, 2.98 mmol), triphenylphosphine (1.17 g, 4.47 mmol) and imidazole (0.44 g, 6.46 mmol) in dry benzene (20 ml) at 0°C. After stirring the mixture at room temp. for 20 min, a saturated aqueous sodium bicarbonate solution and sodium thiosulfate were added to the reaction mixture, which was then extracted with ether. The organic layer was washed with a saturated aqueous sodium bicarbonate solution, dried with anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was diluted with ether and stirred at room temp. for 1 h. The resulting precipitate of triphenylphosphine oxide was removed by filtration and washed with ether. The combined filtrate and washings were concentrated *in vacuo*, and the residue was chromatographed over silica gel (30 g). Elution with hexane–ethyl acetate (30 : 1–20 : 1) gave **3b** (0.67 g, 81%). An analytical sample was obtained by recrystallization from hexane–ethyl acetate to give pure **3b** as slightly yellow needles; mp 85.0–85.5°C; IR (nujol) ν cm^{-1}: 1610, 1590, 1470, 1430, 1320, 1200, 1160, 1070, 940, 820, 700; ^{1}H-NMR (90 MHz in $CDCl_3$) δ: 3.78 (6H, s, $-OCH_3$), 4.38 (2H, s, $-CH_2I$), 6.34 (1H, t, J=2 Hz, 4-H), 6.51 (2H, d, J=2 Hz, 2- and 6-H). *Anal.* Calcd. for $C_9H_{11}O_2I$: C, 38.64; H, 3.87%. Found: C, 38.87; H, 3.99%.

Ethyl 2-(3,5-dimethoxybenzyl)pentanoate (**4a**). A solution of *n*-butyllithium in hexane (1.69 M, 16.0 ml, 27.0 mmol) was added dropwise to a solution of diisopropylamine (3.8 ml, 27.1 mmol) in dry tetrahydrofuran (24 ml) at −40 ~ −30°C under argon. After stirring the solution at −20°C for 10 min, hexamethylphosphoric triamide (4.5 ml, 25.9 mmol) was added at −30°C. To this solution was added a solution of ethyl valerate (4.4 ml, 29.6 mmol) in dry tetrahydrofuran (16 ml) at −78°C. After stirring at this temp. for 1 h, a solution of **3b** (6.0 g, 21.6 mmol) in dry tetrahydrofuran (16 ml) was added to this solution and stirring was continued at the same temp. for a further 2.5 h. The reaction mixture was poured into water and extracted with ether. The organic layer was successively washed with water, saturated aqueous sodium bicarbonate solution and brine. It was then dried with anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed over silica gel (200 g), and elution with hexane–ethyl acetate (50 : 1–10 : 1) gave **4a** (5.31 g, 88%) as a colorless oil; n_D^{17} = 1.4981; IR (film) ν cm^{-1}: 2950, 1730, 1600, 1460, 1210, 1190, 1160, 1060, 830, 700; ^{1}H-NMR (90 MHz in $CDCl_3$) δ: 0.89 (3H, t, J=6 Hz, 5-H), 1.18 (3H, t, J=7 Hz, $-CO_2CH_2CH_3$, 1.10–1.60 (4H, m, 3- and 4-H), 2.5–3.0 (3H, m, 2-H and Ar-CH_2), 3.77 (6H, s, $-OCH_3$), 4.09 (2H, q, J=7 Hz, $-CO_2CH_2CH_3$), 6.32 (3H, s, Ar-H). *Anal.* Calcd. for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63%. Found: C, 68.33; H, 8.63%.

2-(3,5-Dimethoxybenzyl)pentanoic acid (**4b**). A solution of potassium hydroxide (85%, 5.94 g, 90 mmol) in water (5 ml) was added to a stirred and ice-cooled solution of **4a** (6.30 g, 22.5 mmol) in methanol (30 ml). After stirring at 50°C for 22 h, the reaction mixture was diluted with water (15 ml), and methanol was evaporated *in vacuo*. The aqueous solution was washed with pentane, and the pentane solution was extracted with a 1 N aqueous sodium hydroxide solution. The combined aqueous layer was acidified with concentrated sulfuric acid and back-extracted with ether. The ethereal extract was then washed with brine, dried with anhydrous magnesium sulfate and concentrated *in vacuo* to give **4b** (5.0 g, 88%) which was used in the next step without further purification. For analysis, a small portion of this compound was purified by preparative silica gel TLC to give pure **4b** as a colorless oil; n_D^{19} = 1.5168; IR (film) ν cm^{-1}: 3000, 1710, 1600, 1460, 1430, 1300, 1210, 1160, 1060, 930, 840, 700; ^{1}H-NMR (90 MHz in $CDCl_3$) δ: 0.90 (3H, t, J=7 Hz, 5-H), 1.10–1.75 (4H, m, 3- and 4-H), 2.55–3.05 (3H, m, 2-H and Ar-CH_2), 3.77 (6H, s, $-OCH_3$), 6.34 (3H, s, Ar-H).

5,7-Dimethoxy-2-propylindan-1-one (**5**). A mixture of **4b** (13.4 g,

53.2 mmol) and polyphosphoric acid (Merck, Art. 807471, 228 g) was stirred at 80°C for 1.5 h. After cooling, the reaction mixture was diluted with water, and extracted with ether and ethyl acetate. The combined organic layer was successively washed with a saturated aqueous sodium bicarbonate solution and brine, dried with anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed over silica gel (300 g), and elution with hexane–ethyl acetate (10 : 1–2 : 1) gave crude **5** which was recrystallized from hexane–ethyl acetate to give pure **5** (11.2 g, 90%) as colorless prisms; mp 54.5–55.0°C; IR (nujol) ν cm^{-1}: 1690, 1590, 1210, 1160, 830, 720; ^{1}H-NMR (90 MHz in $CDCl_3$) δ: 0.93 (3H, t, J=6 Hz, 3′-H), 1.20–2.10 (4H, m, 1′- and 2′-H), 2.40–2.90 (1H, m, 2-H), 2.68 (1H, dd, J=18 Hz, 4.5 Hz, 3-H), 3.15 (1H, dd, J=18 Hz, 9 Hz, 3-H), 3.87 (3H, s, –OCH_3), 3.90 (3H, s, –OCH_3), 6.30 (1H, d, J=2 Hz, Ar-H), 6.45 (1H, d, J=2 Hz, Ar-H). *Anal.* Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74%. Found: C, 71.60; H, 7.80%.

3-t-Butyldimethylsilyloxy-4,6-dimethoxy-2-propylindene (**6**). To a stirred and ice-cooled solution of **5** (1.14 g, 4.87 mmol) and 2,6-lutidine (2.2 ml, 18.9 mmol) in dry dichloromethane (30 ml) was added *t*-butyldimethylsilyl trifluoromethanesulfonate (2.0 ml, 8.71 mmol). The mixture was stirred at 0°C for 1 h, poured into an ice-cooled aqueous sodium bicarbonate solution and extracted with dichloromethane. The organic layer was washed with brine, dried with anhydrous magnesium sulfate and concentrated *in vacuo* to give **6** (3.67 g) as a slightly yellow oil; IR (film) ν cm^{-1}: 1625, 1605, 1255; ^{1}H-NMR (300 MHz in $CDCl_3$) δ: 0.16 (6H, s, –$SiCH_3$), 0.94 (3H, t, J=7.3 Hz, 3′-H), 1.04 (9H, s, –SiBu^t), 1.51 (2H, tq, J=7.8 Hz, 7.3 Hz, 2′-H), 2.32 (2H, t, J=7.8 Hz, 1′-H), 3.78 (3H, s, –OCH_3), 3.82 (3H, s, –OCH_3), 6.36 (1H, d, J=1.9 Hz, Ar-H), 6.56 (1H, d, J=1.9 Hz, Ar-H).

This oil was used in the next step without further purification.

4,6-Dimethoxy-2-(2-oxopentyl)benzoic acid (**7**). Ozone was bubbled into a mixture of crude **6** (3.67 g) and sodium bicarbonate (0.2 g, 2.38 mmol) in dichloromethane (50 ml) at −78°C. After the mixture had turned slightly blue in color, oxygen was passed into the solution to remove the excess ozone. Dimethyl sulfide (0.6 ml, 8.19 mmol) was then added to the reaction mixture, and the whole was gradually warmed to room temp. and stirred at this temp. overnight. The reaction mixture was poured into 0.5 N hydrochloric acid and extracted with dichloromethane and ether. The organic layer was washed with brine, dried with anhydrous magnesium sulfate and concentrated *in vacuo* to give a yellow oil (2.21 g), whose TLC analysis revealed it to be a mixture of **8a**, **8b** and a small amount of **7** (**8a**/**8b** = 1 : 1–1 : 2). This crude mixture was diluted with acetonitrile (50 ml), and 46% hydrofluoric acid (1.6 ml) was added to the solution at 0°C. After stirring at room temp. for 7 h, sodium bicarbonate (4 g) was added, and the mixture was concentrated *in vacuo* to afford a residue that was acidified with 1 N hydrochloric acid and extracted with ether and ethyl acetate. The combined organic layer was successively washed with water and brine, dried with anhydrous sodium sulfate and concentrated *in vacuo* to give a crude mixture (1.27 g) of **8b** and a small amount of **7**. A small amount of **8b** was isolated for analysis by silica gel chromatography and recrystallization; mp 42.5°C; IR (nujol) ν cm^{-1}: 3400, 1700, 1600, 1580, 1330, 1220, 1160; ^{1}H-NMR (90 MHz in $CDCl_3$) δ: 0.86 (3H, t, J=7 Hz, 3′-H), 1.05–1.85 (4H, m, 1′- and 2′-H), 2.64 (1H, br., –OH), 3.07 (1H, d, J=17 Hz, 3-H), 3.12 (1H, d, J=17 Hz, 3-H), 3.88 (3H, s, –OCH_3), 3.91 (3H, s, –OCH_3), 6.31 (1H, br., Ar-H), 6.45 (1H, br., Ar-H). *Anal.* Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25%. Found: C, 67.37; H, 7.32%.

Sodium periodate (1.29 g, 6.03 mmol) was added to a solution of this crude mixture (1.27 g) in ether–water (1 : 1, 10 ml) at 0°C. After vigorously stirring at 0°C for 5 h, the mixture was diluted with water, saturated with ammonium sulfate and extracted with ether. After the organic layer had been extracted with a 1 N aqueous sodium hydroxide solution, the aqueous layer was acidified with concentrated hydrochloric acid, saturated with ammonium sulfate and back-extracted with ether. It was then dried with anhydrous sodium sulfate and concentrated *in vacuo* to give crude **7** (993 mg). This was used in the next step without further purification. An analytical sample was obtained by recrystallization from hexane–ethyl acetate as colorless prisms; mp 85.0–87.0°C; IR (nujol) ν cm^{-1}: 3290, 1690, 1605, 1340, 1240, 1220, 1160; ^{1}H-NMR (90 MHz in $CDCl_3$) δ: 0.94 (3H, t, J=7 Hz, 5′-H), 1.64 (2H, m, 4′-H), 2.55 (2H, br., 3′-H), 3.70–4.20 (2H, br., Ar-CH_2), 3.86 (3H, s, –OCH_3), 4.00 (3H, s, –OCH_3), 6.40 (1H, d, J=2 Hz, Ar-H), 6.49 (1H, d, J=2 Hz, Ar-H). *Anal.* Calcd. for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81%. Found: C, 63.24; H, 6.83%.

6,8-Dimethoxy-3-propylisocoumarin (**9a**). A solution of **7** (993 mg) in concentrated hydrochloric acid (3 ml) and acetic acid (5 ml) was stirred at room temp. for 30 min. The reaction mixture was poured into ice-cooled water, adjusted to pH 8 by adding 15% aqueous sodium hydroxide, and extracted with ethyl acetate. The organic layer was successively washed with saturated aqueous sodium bicarbonate and brine, dried with anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was diluted with ethyl acetate and filtered through silica gel to give a crude product which was recrystallized from hexane–ethyl acetate to give pure **9a** (582 mg, 48% from **5**); mp 102.0–103.0°C; IR (nujol) ν cm^{-1}: 1720, 1660, 1600, 1570, 1360, 1210, 1160; ^{1}H-NMR (90 MHz in $CDCl_3$) δ: 0.96 (3H, t, J=7 Hz, 3′-H), 1.70 (2H, tq, J=7.5 Hz, 7 Hz, 2′-H), 2.44 (2H, t, J=7.5 Hz, 1′-H), 3.86 (3H, s, –OCH_3), 3.95 (3H, s, –OCH_3), 6.08 (1H, s, 4-H), 6.31 (1H, d, J=2 Hz, Ar-H), 6.41 (1H, d, J=2 Hz, Ar-H). *Anal.* Calcd. for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50%. Found: C, 67.55; H, 6.53%.

6,8-Dihydroxy-3-propylisocoumarin (**9b**). Boron tribromide (1.04 ml, 11.0 mmol) was added dropwise to a stirred and cooled solution of **9a** (1.30 g, 5.24 mmol) in dry dichloromethane (26 ml) at −78°C. The mixture was gradually warmed to room temp. during 1 h and stirred at room temp. for 8.5 h. It was then poured into ice-cooled water, stirred for 10 min and extracted with dichloromethane. The organic layer was washed with water, dried with anhydrous sodium sulfate and concentrated *in vacuo*. Recrystallization from hexane–ethyl acetate gave pure **9b** (1.12 g, 97%); mp 146.0–147.0°C; IR (nujol) ν cm^{-1}: 3200, 1670, 1620, 1250, 1180; ^{1}H-NMR (90 MHz in $CDCl_3$) δ: 0.98 (3H, t, J=7 Hz, 3′-H), 1.50–1.85 (2H, m, 2′-H), 2.48 (2H, t, J=7 Hz, 1′-H), 5.66 (1H, br., 6-OH), 6.16 (1H, s, 4-H), 6.27 (1H, d, J=2 Hz, Ar-H), 6.39 (1H, d, J=2 Hz, Ar-H), 11.14 (1H, s, 8-OH). *Anal.* Calcd. for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49%. Found: C, 65.46; H, 5.54%.

4,6-Dihydroxy-2-(2-oxopentyl)benzoic acid (**10**). A mixture of **9b** (20 mg, 0.091 mmol) and a 0.05 N aqueous sodium hydroxide solution (5.46 ml, 0.273 mmol) was stirred at 80–100°C for 2 h. After cooling, it was acidified with hydrochloric acid, saturated with ammonium sulfate and extracted with chloroform. The extract was dried with anhydrous sodium sulfate and concentrated *in vacuo* to give **10** (20 mg, 92%). This was used in the next step without further purification. An analytical sample was obtained by recrystallization from hexane–ethyl acetate (1 : 5) as colorless needles; mp 140.0–143.0°C (sealed tube); IR (nujol) ν cm^{-1}: 3200 (br.), 1660, 1630, 1270, 1250, 1170, 840; ^{1}H-NMR (500 MHz in DMSO-d_6)*1 δ: 0.86 (3H, br., 5′-H), 1.44 (2H, br., 4′-H), 1.79 (2H, br., 1′-H of B form), 2.38 (2H, br., 3′-H of A form), 2.90 (1H, br., 4-H of B form), 3.10 (1H, br., 4-H of B form), 3.88 (2H, br., 1′-H of A form), 6.17 (2H, s, Ar-H), 6.21 (1H, br., 4-OH of A form or 6-H of B form), 7.25 (1H, br., 4-OH of A form or 6-H of B form), 10.20 (1H, br., 6-OH of A form or 8-OH of B form), 10.50 (1H, br., 6-OH of A form or 8-OH of B form), 11.22 (1H, br., –CO_2H). *Anal.* Calcd. for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92%. Found: C, 60.21; H, 5.91%.

6,8-Dihydroxy-3-propyl-3,4-dihydroisocoumarin (**11**). Sodium borohydride (65 mg, 1.71 mmol) was added portionwise to a solution of **10** (15 mg, 0.063 mmol) in ethanol (2 ml) and water (6 ml). After stirring the mixture at room temp. for 2 h, it was diluted with water (30 ml), acidified with concentrated hydrochloric acid and stirred for a further 2 h. It was then saturated with ammonium sulfate, extracted with chloroform, dried with anhydrous sodium sulfate and concentrated *in vacuo*. The residue was subjected to preparative silica gel TLC, and **11** (9.4 mg, 67%) was obtained as colorless crystals. An analytical sample was obtained by recrystallization to give pure **11** as colorless needles; mp 145.0–146.0°C; IR (nujol) ν cm^{-1}: 3240, 1630, 1260, 1170, 1120; ^{1}H-NMR (500 MHz in $CDCl_3$) δ: 0.97 (3H,

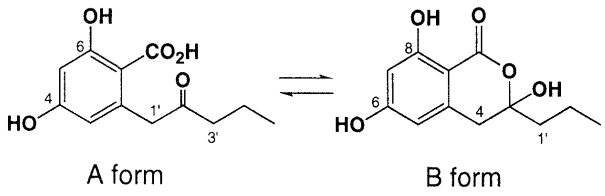

Fig. 2.

*1 It seems that **10** existed as a 1 : 1 mixture of A form and B form in DMSO-d_6.

t, J=7.4 Hz, 3′-H), 1.43–1.64 (2H, m, 2′-H), 1.67 (1H, m, 1′-H), 1.86 (1H, dddd, J=5.0 Hz, 7.5 Hz, 10.0 Hz, 14.0 Hz, 1′-H), 2.82 (1H, dd, J=4.0 Hz, 16.3 Hz, 4-H), 2.87 (1H, dd, J=10.8 Hz, 16.3 Hz, 4-H), 4.53 (1H, m, 3-H), 5.96 (1H, br., 6-OH), 6.20 (1H, m, Ar-H), 6.30 (1H, d, J=2.0 Hz, Ar-H), 11.20 (1H, s, 8-OH). *Anal.* Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35%. Found: C, 64.76; H, 6.38%.

7-Bromo-6,8-dihydroxy-3-propyl-3,4-dihydroisocoumarin (*Hiburipyranone*; **1**). A solution of pyridinium hydrobromide perbromide (124.8 mg, 0.390 mmol) in pyridine (4 ml) was added to a solution of **11** (84.8 mg, 0.382 mmol) in pyridine (8 ml) at 0°C. After stirring the mixture at 0°C for 2 h, the reaction mixture was poured into cold 2 N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with brine, dried with anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was subjected to preparative silica gel TLC with hexane–ethyl acetate–acetic acid, and **1** (18.4 mg, 16%), **12** (18.2 mg, 16%), **13** (38.2 mg, 26%), and recovered **11** (21.7 mg, 26%) were obtained. Analytical samples were obtained by recrystallization from hexane–ethyl acetate to give pure **1**, **12**, and **13**.

1: mp 191.5–193.0°C (sealed tube); IR (KBr) ν cm^{-1}: 3080 (br.), 2960, 2930, 1610, 1500, 1430, 1380, 1310, 1260, 1240, 1190, 1150, 1130, 1070, 1040, 1000, 920, 830, 800, 770; ^{1}H-NMR (500 MHz in $CDCl_3$) δ: 0.98 (3H, t, J=7.3 Hz, 3′-H), 1.44–1.65 (2H, m, 2′-H), 1.69 (1H, m, 1′-H), 1.86 (1H, dddd, J=5.0 Hz, 7.5 Hz, 10.0 Hz, 14.0 Hz, 1′-H), 2.85 (1H, dd, J=6.0 Hz, 16.5 Hz, 4-H), 2.88 (1H, dd, J=1.0 Hz, 16.5 Hz, 4-H), 4.55 (1H, m, 3-H), 6.15 (1H, br., 6-OH), 6.44 (1H, s, 5-H), 11.99 (1H, s, 8-OH); ^{13}C-NMR (125 MHz in $CDCl_3$) δ: 13.8, 18.1, 32.8, 36.7, 79.1, 97.0, 102.5, 106.0, 140.2, 158.4, 160.3, 169.5. *Anal.* Calcd. for $C_{12}H_{13}O_4Br$: C, 47.86; H, 4.35%. Found: C, 47.48; H, 4.24%.

12: mp 172.5–173.5°C; IR (KBr) ν cm^{-1}: 3200, 3120, 1660, 1630, 1600, 1450, 1380, 1240, 840, 790, 750, 700; ^{1}H-NMR (500 MHz in $CDCl_3$) δ: 1.00 (3H, t, J=7.5 Hz, 3′-H), 1.46–1.68 (2H, m, 2′-H), 1.74 (1H, dddd, J=5.0 Hz, 6.0 Hz, 10.0 Hz, 14.0 Hz, 1′-H), 1.89 (1H, dddd, J=5.0 Hz, 7.9 Hz, 10.0 Hz, 14.0 Hz, 1′-H), 2.82 (1H, dd, J=11.7 Hz, 17.0 Hz, 4-H), 3.12 (1H, dd, J=3.4 Hz, 17.0 Hz, 4-H), 4.53 (1H, dddd, J=3.4 Hz, 5.0 Hz, 7.9 Hz, 11.7 Hz, 3-H), 6.10 (1H, br., 6-OH), 6.59 (1H, s, 7-H), 11.54 (1H, s, 8-OH).

13: mp 188.0–190.0°C; IR (KBr) ν cm^{-1}: 3330, 2950, 2930, 2870, 1640, 1600, 1420, 1380, 1320, 1300, 1260, 1240, 1200, 1120, 800, 760; ^{1}H-NMR (500 MHz in $CDCl_3$) δ: 1.00 (3H, t, J=7.3 Hz, 3′-H), 1.46–1.68 (2H, m, 2′-H), 1.74 (1H, dddd, J=5.0 Hz, 6.7 Hz, 10.0 Hz, 14.0 Hz, 1′-H), 1.89 (1H, dddd, J=5.0 Hz, 7.5 Hz, 10.0 Hz, 14.0 Hz, 1′-H), 2.81 (1H, dd, J=11.8 Hz, 17.0 Hz, 4-H), 3.18 (1H, dd, J=3.2 Hz, 17.0 Hz, 4-H), 4.54 (1H, dddd, J=3.2 Hz, 5.0 Hz, 7.5 Hz, 11.8 Hz, 3-H), 6.54 (1H, br., 6-OH), 12.16 (1H, s, 8-OH).

Regeneration of **11** *from* **12** *and* **13**. A mixture of **12** (5.2 mg, 0.073 mmol), **13** (10.9 mg, 0.0287 mmol), and zinc dust (608.5 mg, 9.31 g atm) in acetic acid (2 ml) was stirred and heated under reflux for 2 days. The reaction mixture was filtered through Celite, and the filter cake was washed with ethyl acetate. The combined filtrate and washings were concentrated *in vacuo*. The residue was subjected to preparative silica gel TLC with hexane–ethyl acetate (1 : 1) to give **11** (10.2 mg) in a quantitative yield.

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