

ing mixture poured into saturated aqueous sodium chloride (1200 mL). The layers were separated and the organic extract washed with saturated sodium chloride (600 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to a dark solid (31.0 g). Purification by preparative HPLC (Waters Prep 500, 9:1 hexane:ethyl acetate as eluant) afforded 6-hydroxy-3,4-dihydrobenzopyran-7-carboxaldehyde (18.80 g, 67.6%), m.p. 97°–100°.

#### EXAMPLE 3

##### 6-Acetoxy-3,4-dihydrobenzopyran-7-carboxaldehyde

To a solution of 6-methoxy-3,4-dihydrobenzopyran-7-carboxaldehyde (5.00 g, 28.1 mmol) in pyridine (15.0 mL) was added acetic anhydride (3.5 mL, 31.1 mmol) and the mixture allowed to stir at room temperature for 4 hours then poured into ice water (300 mL). The product which precipitated was collected by filtration, washed with water (75 mL) and air dried to afford 6-acetoxy-3,4-dihydrobenzopyran, (5.86 gm, 94.5%), m.p. 76°–77°.

#### EXAMPLE 4

##### 6-Acetoxy-7-hydroxymethyl-3,4-dihydrobenzopyran acetate

To a suspension of sodium borohydride (985 mg, 26.1 mmol) in ethyl acetate (55 mL) containing a small amount of absolute ethanol (0.2 mL) at 5° C. was added a solution of 6-acetoxy-3,4-dihydrobenzopyran-7-carboxaldehyde (5.68 g, 25.8 mmol) in ethyl acetate (55 mL) dropwise. Ethanol (4 mL) was added and the mixture allowed to warm to room temperature and stir for one hour. The reaction was quenched by the addition of 10% acetic acid (50 mL, dropwise) and the layers separated. The organic layer was washed sequentially with 7%  $\text{NaHCO}_3$  ( $3 \times 100$  mL) and water (100 mL), dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated to afford a thick yellow oil (5.35 g). The material was taken up in pyridine (15 mL), acetic anhydride (35 mL) was added, and the mixture heated to reflux for ten minutes. Upon cooling, the mixture was poured into ice water and the mixture extracted with ethyl acetate (100 mL). The organic extract was washed sequentially with 2.5N hydrochloric acid (100 mL), 7%  $\text{NaHCO}_3$  ( $2 \times 100$  mL), and brine (100 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to an oil. The crude product was purified by preparative HPLC (10% ethyl acetate/hexane as eluant) to afford 6-acetoxy-7-hydroxymethyl-3,4-dihydrobenzopyran acetate (3.89 g) as a pale yellow oil.

#### EXAMPLE 5

##### 6-Hydroxy-7-(2-hydroxymethylphenyl)thiomethyl-3,4-dihydrobenzopyran

To a solution of o-mercaptobenzylalcohol (289 mg, 2.06 mmol) in dry dimethylformamide (3 mL) was added sodium hydride (60% dispersion in mineral oil, 83 mg, 2.07 mmol) portionwise and the mixture allowed to stir for 30 minutes. To the resulting solution was added dropwise a solution of 6-acetoxy-7-hydroxymethyl-3,4-dihydrobenzopyran acetate (543 mg, 2.06 mmol) in dry dimethylformamide and the mixture allowed to stir at room temperature under nitrogen for three hours, heated to 50° for 30 minutes, then allowed to cool and stir overnight. The reaction was quenched with 2.5N sodium hydroxide (2 mL) and after stirring for 30 minutes, the mixture was poured into water (75 mL). The aqueous mixture was neutralized with 2N hydrochloric acid (2.5 mL), extracted with ether

( $2 \times 100$  mL) and the ether extract washed with brine ( $3 \times 100$  mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. The crude product was purified by preparative HPLC (2:1 hexane/ethyl acetate as eluant) to afford 6-hydroxy-7-(2-hydroxymethylphenyl)thiomethyl-3,4-dihydrobenzopyran as a pale off-white solid, m.p. 140°–141° C.

#### EXAMPLE 6

##### 6-Hydroxy-7-(4-acetylphenyl)thiomethyl-3,4-dihydrobenzopyran

To a solution of 6-acetoxy-7-hydroxymethyl-3,4-dihydrobenzopyran acetate (1.00 g, 3.78 mmol) in dry dimethylformamide (5 mL) was added a solution of potassium p-acetylthiophenoxide (720 mg, 3.8 mmol) in dimethylformamide (5 mL). The mixture was heated at 50° C. for 2.25 hours, then poured into ice water (75 mL). Sodium hydroxide (10% aqueous, 20 mL) was added, then mixture allowed to stir for 30 minutes, then acidified with 2N hydrochloric acid and extracted with ethyl acetate ( $3 \times 50$  mL). The combined extracts were washed with 7%  $\text{NaHCO}_3$ , and brine (2x), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. The crude product was purified by preparative HPLC (30% ethyl acetate hexane as eluant and recrystallized from ethyl acetate hexane to afford 6-hydroxy-7-(4-acetylphenyl)thiomethyl-3,4-dihydrobenzopyran as a white solid (172 mg), m.p. 192°–193° C.

#### EXAMPLE 7

##### 2-(2-Hydroxy-5-methoxybenzylthio)thiophene

To a suspension of 1.38 g (0.057 moles) Mg in 100 mL anhydrous ether was added 12.0 g (0.057 moles) 2-iodothiophene and the mixture was heated at reflux until the metal dissolved. The solution was cooled to 0°, 1.85 g (0.057 moles) of dry sulfur was added, and the mixture was heated at reflux for 1 hour. A solution of 5.80 g (0.0235 moles) of 1-acetoxy-2-acetoxymethyl-4-methoxybenzene in 25 mL dry tetrahydrofuran was added and the solution was heated at reflux for 1 hour.

The mixture was partitioned between ether and water, washed with  $\text{K}_2\text{CO}_3$ ,  $\text{NaCl}$  and dried over  $\text{Na}_2\text{SO}_4$ . The residue (14 g) was chromatographed on silica (15% ethyl acetate-hexane) to afford 4.0 g of a yellow oil that crystallized from 3:1 hexane-methylene chloride to yield 1.85 g of white needles (28%), m.p. 84°.

#### EXAMPLE 8

##### 2-(2-Hydroxy-3-methoxybenzylthio)thiophene

To a suspension of 0.360 g (14.8 mmol) Mg in 30 mL anhydrous ether was added 3.10 g (14.8 mmol) 2-iodothiophene and the mixture was heated at reflux until the metal dissolved. The solution was cooled to 0°, then 0.480 g (15.0 mmol) sulfur was added, and the mixture was heated at reflux for 1 hour. A solution of 1.50 g (6.10 mmol) of 2-acetoxy-1-acetoxymethyl-3-methoxybenzene in 5 mL dry tetrahydrofuran was added and the solution was heated at reflux for 1 hour.

The mixture was partitioned between ether and water, and the ether layer was washed with  $\text{K}_2\text{CO}_3$ ,  $\text{NaCl}$  and dried over  $\text{Na}_2\text{SO}_4$ . The residue was chromatographed on silica (15% ethyl acetate-hexane) and crystallized from petroleum ether-toluene to afford 0.980 g (47%) of white needles, m.p. 50°–51° C.

What is claimed is:

1. A compound of formula (I)