Pergamon

Tetrahedron 58 (2002) 7391–7395

TETRAHEDRON

A synthesis of a thysanone analog

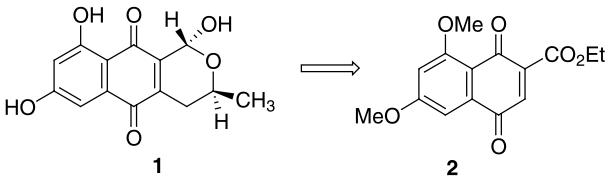
George A. Kraus* and Herbert Ogutu

Department of Chemistry, Iowa State University, 2759 Gilman Hall, Ames, IA 50011, USA

Received 17 June 2002; accepted 11 July 2002

Abstract—Hemiacetal **10** was prepared in 13 steps from dimethoxybenzaldehyde. Key steps included the salcomine oxidation of a phenol and a selective deprotection using boron trichloride.

In the process of screening microbial extracts for lead compounds that would be developed into chemotherapeutic agents for eventual control/cure of the common cold, Singh and co-workers isolated thysanone (**1**), a novel naphthoquinone. Thysanone is an effective inhibitor (IC_{50} 13 μg/mL) of human rhinovirus 3C-protease (Scheme 1).[1]



Scheme 1.

The positive strand RNA genome of human rhinoviruses (HRVs) is translated directly into a viral polyprotein (200 kD) precursor which undergoes a series of proteolytic cleavages to generate viral gene products. Processing of the polyprotein is dependent upon two virally encoded proteases ('3C-protease' and '2A-protease') which have no known cellular homologues. They represent attractive targets for the development of antiviral agents. Thysanone inhibits HRV-3C protease, thus curtailing viral replication.

To date, there has been one total synthesis of thysanone and a few syntheses of analogs.[2] The strategy used by Gill and co-workers in their total synthesis is quite different from our approach. As part of a program for the synthesis of tethered mixed mechanism antivirals (TMMA), we intend to connect thysanone with hypericin, a natural product with a broad range of antiviral activity.[3] To effect this connection, we have developed a synthesis of a thysanone analog with a hydroxymethyl group instead of a methyl group.

Our synthetic route began with known phosphonate **3**.[4] The anion of **3** (NaH, THF, 0°C) reacted with 2,4-dimethoxybenzaldehyde to provide the bis-ester adduct in 75% yield. The *tert*-butyl ester was then selectively cleaved with 90% aqueous trifluoroacetic acid to afford acid **4** in almost quantitative yield. Acid **4**, potassium acetate, and acetic anhydride were heated for 3 h to produce **5a** in 75% yield.[5] Diester **5a** was treated with acetyl chloride in methanol at 0°C to yield naphthol **5b** in almost quantitative yield (Scheme 2).

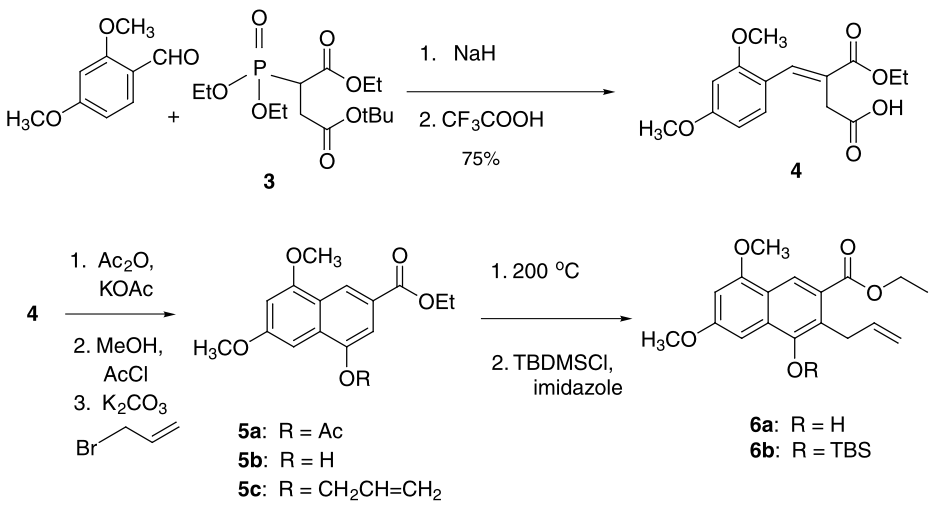
With **5b** in hand, we studied the oxidation of naphthol **5b** to naphthoquinone **2**. After several unsuccessful attempts (potassium dinitrodisulfonate (complex mixture),[6] phenyl iodo-*di*-trifluoroacetate (mixture of three products),[7] salcomine (no reaction),[8] and ceric ammonium nitrate (no reaction)[9]) we had to rethink our approach. The *O*-alkylation of naphthol **5b** was accomplished using allyl bromide and potassium carbonate. The reaction gave ether **5c** in 90% yield. Compound **5c** in DMF was purged with argon and heated in a sealed tube to 210°C. After several experiments, conditions were established wherein naphthol **6a** was produced in 75% yield. One of the side products of this reaction was a dihydronaphthofuran.[10] This by-product was likely produced via trace amounts of acid. This by-product could be minimized by washing the tube with base before conducting the Claisen rearrangement.

Phenol **6a** was readily silylated (*tert*-butyldimethylsilyl chloride, imidazole, CH_2Cl_2) to produce **6b**. Unfortunately, treatment of **6b** with DIBAL resulted in recovered starting material. LAH reduction of **6b** afforded alcohol **7** in 95% yield. PCC oxidation of **7** proceeded in 90% yield to give aldehyde **8**.[11] The dihydroxylation of **8** using a catalytic amount of osmium tetroxide with NMO as the oxidant directly afforded a lactol in 75% yield. The lactol was dissolved in methanol containing a catalytic amount of concentrated sulfuric acid. Instead of replacing the hydroxyl group at C-1 with a methoxyl group, a cyclic acetal was formed. Additionally, the TBS ether was cleaved to give naphthol **9**. Potassium dinitrodisulfonate, ceric ammonium

Keywords: thysanone analog; hemiacetal; chemotherapeutic agents.

* Corresponding author. Tel.: +1-515-294-7794; fax: +1-515-294-0105; e-mail: gakraus@iastate.edu

0040–4020/02/$ - see front matter
PII: S0040-4020(02)00823-2



Scheme 2.

nitrate, and phenyl iodo-*di*-trifluoroacetate did not oxidize naphthol **9**. However, when naphthol **9** was treated with a catalytic amount of salcomine in the presence of oxygen, a naphthoquinone was formed in 60% yield. Selective demethylation at C-9 *peri* to the carbonyl C-10 was achieved with 1.1 equiv. of boron trichloride, at 0°C in methylene chloride.[12] In addition to the demethylation, the acetal also opened, resulting in hemiacetal **10** (Scheme 3).

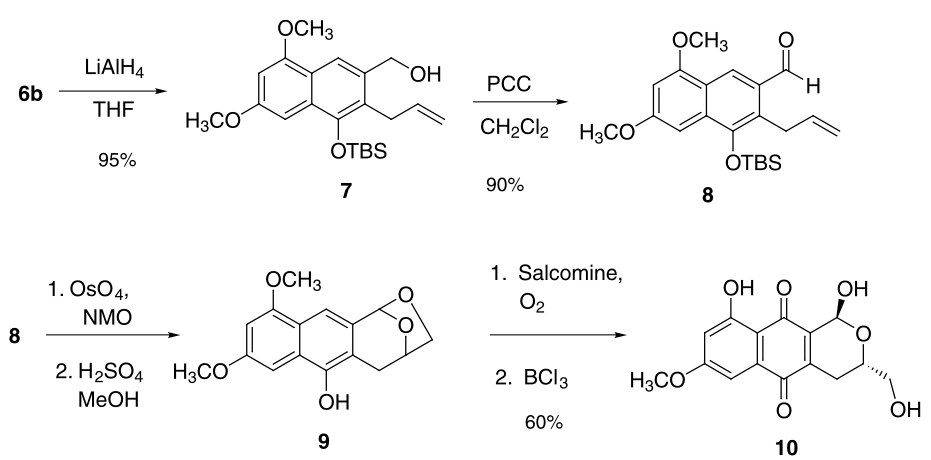
The stereochemistry of **10** was assigned in analogy to that of thysanone, which exists as a single stereoisomer with the hydroxyl group in the axial orientation. The synthesis by Gill and co-workers[2] generated the hemiacetal unit by hydrolysis of a benzylic bromide. This hydrolysis afforded a single isomer whose NMR spectrum was identical to that of natural thysanone.

Hemiacetal **10** was prepared in 13 steps from dimethoxybenzaldehyde. This compound will be useful for structure–activity studies as well as for the synthesis of tethered antiviral agents.

1. Experimental

1.1. Data for compounds

1.1.1. 2-(2,4-Dimethoxy-benzylidene)-succinic acid 1-ethyl ester (4). To a suspension of 1.46 g (36.5 mmol) sodium hydride (60% dispersion, hexane washed) in 50 mL of dry THF was added phosphonate **3** (12.2 g, 36 mmol) dropwise. The reaction mixture was stirred for 2 h at 0°C under argon. A solution of 2,4-dimethoxybenzaldehyde (5.82 g, 35.0 mmol) in 30 mL THF was prepared in a 250 mL flask. The anion solution was added dropwise with stirring to the aldehyde solution at 0°C under argon. The cooling bath was removed and the reaction mixture was stirred and allowed to warm to rt overnight. After 18 h, water (20 mL) was added and the solvent was removed in vacuo. The residue was partitioned between water and methylene chloride. The organic phase was collected, dried over sodium sulfate, filtered and evaporated to dryness in vacuo. The product was purified by flash column chromatography using hexanes and ethyl acetate (30:1). The pure



Scheme 3.

product was obtained in 75% yield as a viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (t, J=7.2 Hz, 3H), 1.46 (s, 9H), 3.40 (s, 2H), 3.82 (s, 3H), 3.83 (s, 3H), 4.25 (q, J=7.2 Hz, 2H), 6.46 (d, J=2.4 Hz, 1H), 6.50 (dd, J_1=8.4 Hz, J_2=2.4 Hz, 1H), 7.26 (d, J=8.4 Hz, 1H), 7.91 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 14.4, 28.2, 35.5, 55.5, 55.6, 60.9, 80.9, 98.5, 104.4, 117.2, 125.2, 130.6, 137.2, 159.1, 161.9, 167.9, 170.9. MS (*m*/*z*) 350 (M+), 294, 249, 166, 148, 89, 61, 43. HRMS calcd for $C_{19}H_{26}O_6$ 350.1729, found 350.1735.

The *tert*-butyl ester (5.2 g, 14.86 mmol) was dissolved in 20 mL of trifluoroacetic acid/water (9/1) at rt. The mixture was stirred, and the progress of the reaction monitored by TLC. When the reaction was complete, the solvent was removed under reduced pressure to give crude compound **4**. The crude product was partitioned between 10% aqueous sodium hydrogen carbonate (100 mL) and ethyl acetate (50 mL). The aqueous phase was separated, acidified with concentrated hydrochloric acid to pH 2, and extracted with ethyl acetate (3×30 mL). The organic extract was dried and evaporated under reduced pressure to give pure **4**, a white solid, in almost quantitative yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, J=7.2 Hz, 3H), 3.52 (s, 2H), 3.83 (s, 3H), 3.84 (s, 3H), 4.34 (q, J=7.2 Hz, 2H), 6.47 (d, J=2.4 Hz, 1H), 6.55 (dd, J_1=8.4 Hz, J_2=2.4 Hz, 1H), 7.31 (d, J=8.4 Hz, 1H), 7.99 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 14.3, 34.3, 55.7, 55.8, 62.0, 98.8, 104.9, 116.6, 123.3, 130.9, 139.6, 159.2, 164.5, 168.9, 178.3. MS (*m*/*z*) 294 (M+), 294, 249, 166, 148, 89, 61, 43. HRMS calcd for $C_{15}H_{18}O_6$ 294.2998, found 294.2986.

1.1.2. 4-Acetoxy-6,8-dimethoxy-naphthalene-2-carboxylic acid ethyl ester (5a). The acid **4** (4.2 g, 14.3 mmol) and anhydrous potassium acetate (1.54 g, 15.7 mmol) were dissolved in acetic anhydride (50 mL). The solution was heated at reflux for 2 h. The solvent was removed in vacuo, and the product was purified by recrystallization from ethanol to give a pale yellow crystalline solid in 75% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (t, J=7.2 Hz, 3H), 2.46 (s, 3H), 3.92 (s, 3H), 3.99 (s, 3H), 4.44 (q, J=7.2 Hz, 2H), 6.54 (d, J=2.1 Hz, 1H), 6.67 (d, J=2.1 Hz, 1H), 7.81 (d, J=1.5 Hz, 1H), 8.80 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 14.7, 21.3, 55.6, 56.0, 61.3, 91.8, 98.8, 119.4, 122.5, 123.5, 124.6, 131.4, 145.6, 158.2, 161.2, 166.5, 169.5.

MS (*m*/*z*) 294 (M+), 294, 249, 166, 148, 89, 61, 43. HRMS calcd for $C_{17}H_{18}O_6$ 318.1103, found 318.1112.

1.1.3. 4-Hydroxy-6,8-dimethoxy-naphthalene-2-carboxylic acid ethyl ester (5b). To a solution of 1.84 g (5.79 mmol) of **5a** in 10 mL of methanol was added 94.2 mg (1.2 mmol) of acetyl chloride at 0°C. The mixture was stirred at 0°C and allowed to warm to rt. After 12 h, the solvent was removed in vacuo, and the product was purified by recrystallization from ethanol to give a grayish-white solid in 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (t, J=7.2 Hz, 3H), 3.96 (s, 3H), 3.99 (s, 3H), 4.46 (q, J=7.2 Hz, 2H), 6.55 (d, J=2.1 Hz, 1H), 7.15 (d, J=2.1 Hz, 1H), 7.56 (d, J=1.5 Hz, 1H), 8.50 (s, 1H). ^{13}C NMR ($CDCl_3$) 14.6, 55.8, 55.9, 61.3, 92.6, 98.9, 109.4, 118.2, 122.3, 124.7, 129.0, 150.8, 157.8, 160.3, 167.6.

1.1.4. 4-Allyloxy-6,8-dimethoxy-naphthalene-2-carboxylic acid ethyl ester (5c). To a stirred solution of 3.71 g (13.4 mmol) of **5b** in 50 mL of acetone was added 3.73 g (27 mmol) of potassium carbonate and 3.3 g (27 mmol) of allyl bromide. The resulting mixture was heated under reflux and the reaction was monitored by TLC. After 18 h, the reaction mixture was cooled, and then suction filtered through a pad of Celite. The filtrate was concentrated in vacuo, and the product was purified by flash column chromatography using hexanes and ethyl acetate (15:1), to give **5c**, a pale yellow solid, in 90% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (t, J=7.2 Hz, 3H), 3.95 (s, 3H), 3.99 (s, 3H), 4.42 (q, J=7.2 Hz, 2H), 4.78 (d, J_1=4.8 Hz, 2H), 5.35 (dd, J_1=10.1 Hz, J_2=1.5 Hz, 1H), 5.52 (dd, J_1=17.1 Hz, J_2=1.5 Hz, 1H), 6.13–6.26 (m, 1H), 6.55 (d, J=2.1 Hz, 1H), 7.17 (d, J=2.1 Hz, 1H), 7.43 (d, J=1.5 Hz, 1H), 8.52 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 14.7, 52.3, 55.6, 55.8, 69.3, 92.9, 98.7, 105.7, 117.3, 118.4, 121.8, 124.3, 130.1, 133.4, 153.3, 157.7, 160.3, 167.8. MS (*m*/*z*) 316 (M+), 271, 243, 227, 199, 139, 128. HRMS calcd for $C_{18}H_{20}O_5$ 316.1311, found 316.1314.

1.1.5. 3-Allyl-4-hydroxy-6,8-dimethoxy-naphthalene-2-carboxylic acid ethyl ester (6a). A flame-dried pressure tube, cooled under a stream of argon, was charged with 1.58 g (5 mmol) of ether **5c** and dissolved in 5 mL of dimethylformamide. The solution was degassed with argon for 10 min. The pressure tube was sealed and placed in an oil bath. The temperature of the oil bath was raised to 210°C, and the solution stirred at this temperature for 6 h. The tube was cooled to rt and the solvent removed under reduced pressure. The resulting crude product was purified by flash column chromatography using hexanes and ethyl acetate (10:1) to afford naphthol **6a** in 78% yield as the major product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (t, J=7.2 Hz, 3H), 3.88 (d, J=1.8 Hz, 2 H), 3.92 (s, 3H), 3.99 (s, 3H), 4.43 (q, J=7.2 Hz, 2H), 5.19 (dd, J_1=4.2 Hz, J_2=1.5 Hz, 1H), 5.24 (dd, J_1=17.1 Hz, J_2=1.5 Hz, 1H), 6.07–6.20 (m, 1H), 6.50 (d, J=2.1 Hz, 1H), 7.05 (d, J=2.1 Hz, 1H), 8.37 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 14.6, 32.0, 55.6, 55.8, 61.1, 92.2, 98.4, 116.4, 118.7, 119.0, 120.5, 125.8, 128.5, 136.6, 149.9, 157.4, 160.2, 168.3. MS (*m*/*z*) 316 (M+), 269, 255, 243, 227, 211, 199, 139, 128. HRMS calcd for $C_{18}H_{20}O_5$ 316.1311, found 316.1314.

1.1.6. 3-Allyl-4-(*tert*-butyldimethyl-silyloxy)-6,8-dimethoxy-naphthalene-2-carboxylic acid ethyl ester (6b). Naphthol **6a** (377 mg, 1.2 mmol) was dissolved in methylene chloride (20 mL) and treated with *tert*-butyl dimethylsilyl chloride (270 mg, 1.8 mmol), imidazole (123 mg, 1.8 mmol), and dimethylaminopyridine (20 mg). The mixture was stirred for 18 h at rt after which the solvent was removed in vacuo. The residue was purified by flash column chromatography (hexane–ethyl acetate 25:1) to give silyl ether **6b** in 92% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.21 (s, 6H), 1.13 (s, 9H), 1.44 (t, J=7.2 Hz, 3H), 3.88 (d, J=6.6 Hz, 2H), 3.92 (s, 3H), 3.96 (s, 3H), 4.37 (q, J=7.2 Hz, 2H), 4.89 (dd, J_1=5.1 Hz, J_2=1.5 Hz, 1H), 4.97 (dd, J_1=15.1 Hz, J_2=1.5 Hz, 1H), 5.86–5.97 (m, 1H), 6.50 (d, J=2.1 Hz, 1H), 7.05 (d, J=2.1 Hz, 1H), 8.40 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ −2.7, 14.6, 19.0, 26.0, 30.0, 32.2, 55.6, 55.8, 61.0, 94.3, 98.0, 115.0, 119.7, 120.6, 126.2, 127.1, 131.7, 137.7, 148.4, 157.5, 159.7, 168.7. MS (*m*/*z*)

316 (M+), 269, 255, 243, 227, 211, 199, 139, 128. HRMS calcd for $C_{24}H_{34}O_5Si$ 430.6093, found 430.6085.

1.1.7. [3-Allyl-4-(*tert*-butyldimethylsilyloxy)-6,8-dimethoxynaphthalen-2-yl]-methanol (7). A solution of **6b** (570 mg, 1.32 mmol) dissolved in 20 mL of THF was added dropwise to a stirred suspension of lithium aluminum hydride (150 mg, 3.96 mmol) and 20 mL THF at 5°C under argon. The reaction was stirred under these conditions for 1.5 h and then quenched with the sequential dropwise addition of the following: water (0.15 mL), 15% sodium hydroxide solution (0.15 mL), and water (0.45 mL). This mixture was stirred for 6 h at rt and then suction filtered through a short pad of Celite and silica gel. The filtering pad was washed with three 5 mL portions of ethyl acetate. The filtrate was combined with the ethyl acetate wash, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude mixture of **7**. The residue was purified by flash column chromatography using hexanes and ethyl acetate (10:1), to afford **7** in 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.23 (s, 6H), 1.11 (s, 9H), 3.68 (br d, J=5.7 Hz, 2H), 3.91 (s, 3H), 3.95 (s, 3H), 4.78 (s, 2H), 4.90 (br dd, J_1=17.1 Hz, J_2=1.8 Hz, 1H), 5.00 (br dd, J_1=10.2 Hz, J_2=1.8 Hz, 1H), 5.90–6.03 (m, 1H), 6.47 (d, J=2.1 Hz, 1H), 6.95 (d, J=2.1 Hz, 1H), 7.85 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ −2.6, 19.0, 26.3, 30.9, 55.5, 55.7, 64.4, 94.2, 97.5, 115.2, 115.6, 121.5, 125.1, 129.2, 135.5, 137.3, 148.3, 156.7, 157.8. MS (*m*/*z*) 388 (M+), 370, 312. HRMS calcd for $C_{22}H_{32}O_4Si$ 388.2070, found 388.2076.

1.1.8. 3-Allyl-4-(*tert*-butyldimethylsilyloxy)-6,8-dimethoxynaphthalene-2-carbaldehyde (8). To a solution of **7** (0.53 g, 1.36 mmol) in methylene chloride (20 mL) was added a finely ground portions of a mixture of pyridinium chlorochromate (0.52 g, 2.72 mmol) and Celite (1.18 g) over a period of 30 min at rt. The reaction mixture was stirred for 18 h at rt, after which it was diluted with methylene chloride and filtered through a short pad of Celite. The Celite pad was washed with two 10 mL portions of methylene chloride which were combined with the filtrate, dried over sodium sulfate, and evaporated under reduced pressure. The residue was purified by flash column chromatography (hexane–ethyl acetate 10:1) giving **8** in 90% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.23 (s, 6H), 1.12 (s, 9H), 3.96 (br d, J=5.7 Hz, 2H), 3.91 (s, 3H), 3.98 (s, 3H), 4.90 (br dd, J_1=17.1 Hz, J_2=1.8 Hz, 1H), 4.97 (br dd, J_1=10.2 Hz, J_2=1.8 Hz, 1H), 5.90–6.03 (m, 1H), 6.49 (d, J=2.1 Hz, 1H), 6.98 (d, J=2.1 Hz, 1H), 7.85 (s, 1H), 10.16 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ −3.6, 14.4, 22.9, 26.3, 29.3, 30.3, 55.7, 55.9, 94.8, 98.2, 115.5, 125.3, 125.9, 129.2, 130.7, 137.5, 148.5, 158.1, 160.9, 193.1. MS (*m*/*z*) 386 (M+), 369, 329, 301, 296, 260. HRMS calcd for $C_{22}H_{30}O_4Si$ 386.1913, found 386.1919.

1.1.9. 8,10-Dimethoxy-1,3,4,5-tetrahydro-1,4-epoxy-2-naphthoxepin-6-ol (9). To a magnetically stirred solution of **8** (364 mg, 0.94 mmol) and *N*-methylmorpholine *N*-oxide (165 mg, 1.41 mmol) in 25 mL of 10% water in acetone (v/v) was added a solution of osmium tetroxide (4.7 mL, 0.094 mmol) in *tert*-butyl alcohol (0.02 M, 1.0 g of osmium tetroxide in 196 mL of *tert*-butyl alcohol containing 0.5% *tert*-butyl hydroperoxide). The reaction progress was monitored by tlc analysis. After 42 h of stirring at rt, tlc analysis indicated the complete disappearance of **8** and the appearance of a new, more polar spot. A 1:1 (w/w) mixture of sodium hydrosulfite and sodium sulfite (700 mg) was then added to the reaction mixture and stirring continued for 30 min. The mixture was then filtered through a short pad of Celite on a 150 mL sintered-glass funnel. The Celite pad was washed with three 15 mL portions of acetone. The filtrate, combined with the acetone wash, was dried over sodium sulfate. The solvent was removed under reduced pressure, and the product was purified by flash column chromatography using hexanes and ethyl acetate (1:1) to afford a hemiacetal in 72% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.23 (s, 3H), 0.26 (s, 3H), 1.11 (s, 9H), 2.79 (br d, J=17.1 Hz, 1H), 3.32 (br dd, J_1=17.1 Hz, J_2=1.5 Hz, 1H), 3.69 (br dd, J_1=7.2 Hz, J_2=1.8 Hz, 1H), 3.89 (s, 3H), 3.94 (s, 3H), 4.00 (td, J_1=6.3 Hz, J_2=1.8 Hz, 1H), 4.94–4.98 (m, 1H), 6.12 (s, 1H), 6.45 (d, J=2.4 Hz, 1H), 6.89 (d, J= 2.4 Hz, 1H), 7.62 (s, 1H), ^{13}C NMR (300 MHz, $CDCl_3$) δ −3.4, −3.1, 19.0, 26.3, 31.8, 55.5, 55.8, 68.2, 72.4, 93.6, 97.7, 101.2, 112.3, 117.7, 121.6, 129.7, 132.0, 148.6, 158.1. MS (*m*/*z*) 420 (M+), 402, 345, 315, 273, 228. HRMS calcd for $C_{22}H_{32}O_6Si$ 420.1968, found 420.1973.

To a solution of hemiacetal (340 mg, 0.81 mmol) in 20 mL of methanol was added 2 drops of 6 M sulfuric acid. The mixture was heated at reflux for 1 h, after which the solvent removed under reduced pressure. The residue was directly subjected to flash column chromatography (hexane–ethyl acetate 1:1), affording **9** in 75% yield as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.79 (br d, J=16.5 Hz, 1H), 3.31 (br dd, J_1=16.2 Hz, J_2=5.1 Hz, 1H), 3.73 (br dd, J_1=7.5 Hz, J_2=1.5 Hz, 1H), 3.92 (s, 3H), 3.96 (s, 3H), 4.03 (td, J_1=7.5 Hz, J_2=1.5 Hz, 1H), 4.98–5.02 (m, 1H), 6.18 (s, 1H), 6.48 (d, J=2.1 Hz, 1H), 6.89 (d, J=2.1 Hz, 1H), 7.57 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 25.5, 54.9, 55.3, 65.6, 68.6, 76.5, 92.0, 97.4, 108.5, 116.6, 121.2, 125.2, 131.0, 148.9, 156.6, 157.7. MS (*m*/*z*) 288 (M+), 258, 230, 215, 187. HRMS calcd for $C_{16}H_{16}O_5$ 288.0998, found 288.1002.

1.1.10. 1,9-Dihydroxy-3-hydroxymethyl-7-methoxy-3,4-dihydro-1*H*-benzo[*g*]isochromene-5,10-dione (10). To a solution of **9** (124 mg, 0.43 mmol) in 25 mL acetonitrile was added bis(salicylidene)ethylenediiminocobalt(II) (salcomine) (5 mg, 0.15 mmol). Oxygen was bubbled into the solution for 2 h and the mixture was stirred at rt for 18 h. The reaction mixture was diluted with 10 mL acetonitrile and filtered through a short pad of Celite. The solvent was removed in vacuo and the crude product was purified by flash column chromatography (ethyl acetate–hexane 2:1) to give a quinone, a crystalline yellow solid, in 60% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (br d, J=19.5 Hz, 1H), 3.05 (br ddd, J_1=19.5 Hz, J_2=4.5 Hz, J_3=2.4 Hz 1H), 3.67 (br dd, J_1=7.8 Hz, J_2=1.8 Hz, 1H), 3.92 (s, 3H), 3.96 (s, 3H), 4.02 (td, J_1=6.0 Hz, J_2=2.4 Hz, 1H), 4.89–4.92 (m, 1H), 6.39 (s, 1H), 6.73 (d, J=2.4 Hz, 1H), 7.23 (d, J=2.4 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 26.2, 29.6, 56.4, 56.7, 69.1, 71.5, 93.2, 103.6, 104.6, 136.0, 136.6, 143.0, 162.3, 164.9, 180.7, 185.3. MS (*m*/*z*) 302 (M+), 303, 284, 271, 255, 227. HRMS calcd for $C_{16}H_{14}O_6$ 302.0790, found 302.0795.

To a solution of quinone (24 mg, 0.079 mmol) in dry methylene chloride (10 mL) under argon, 1 M boron trichloride solution in methylene chloride (0.095 mL, 0.095 mmol) was added at 0°C. The reaction mixture was stirred at 0°C for 1 h and at rt for 2 h. After the reaction was complete, the reaction mixture was diluted with methylene chloride, washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluting with 2:1 ethyl acetate/hexane) to give **10**, an orange solid, in 58% yield. ^{1}H NMR (300 MHz, d_6-acetone) δ 2.38 (br dd, J_1=19.5 Hz, J_2=10.2 Hz, 1H), 2.70 (br dd, J_1=19.5 Hz, J_2=3.6 Hz, 1H), 3.72 (t, J=5.1 Hz, 2H), 3.98 (s, 3H), 4.26–4.34 (m, 1H), 6.00 (s, 1H), 6.76 (d, J=2.4 Hz, 1H), 7.11 (d, J=2.4 Hz, 1H).

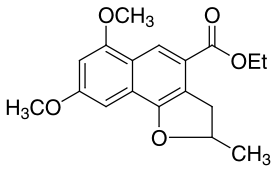
^{13}C NMR (300 MHz, $CDCl_3$) δ 24.4, 56.0, 59.9, 64.6, 66.4, 85.9, 106.0, 107.5, 136.6, 145.8, 156.8, 159.2, 164.6, 175.9, 185.2. MS (*m/z*) 302 (M+), 303, 284, 271, 255, 227. HRMS calcd for $C_{15}H_{14}O_7$ 306.0740, found 306.0744.

Acknowledgments

We thank the National Institutes of Health and the Roy J. Carver Charitable Trust for support of this work.

References

1. Singh, S. B.; Cordingley, M. G.; Ball, R. G.; Smith, J. L.; Dombrowski, A. W.; Goetz, M. A. *Tetrahedron Lett.* **1991**, *32*, 5279.
2. (a) Donner, C. D.; Gill, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 938–948. (b) Gill, M.; Donner, C. D. *Tetrahedron Lett.* **1999**, *40*, 3921. (c) Brimble, M. A.; Elliott, R. J. R. *Tetrahedron* **2002**, *58*, 183–189. (d) Singh, S. B.; Graham, P. L.; Reamer, R. A.; Cordingley, M. G. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3143–3146.
3. Wills, N. J.; Park, J.; Wen, J.; Kesavan, S.; Kraus, G. A.; Petrich, J. W.; Carpenter, S. Wen. *Photochem. Photobiol.* **2001**, *74*, 216–220.
4. Owton, W. M.; Gallagher, P. T.; Juan-Montesinos, A. *Synth. Commun.* **1993**, *23*, 2119.
5. Boger, D. L.; Turnbull, P. *J. Org. Chem.* **1998**, *63*, 8004.
6. Achari, B.; Bandyopadhyay, S.; Basu, K.; Pakrashi, S. C. *Tetrahedron* **1985**, *41*, 107.
7. Tamura, Y.; Yakura, T.; Tohma, H.; Kikuchi, K.; Kita, Y. *Synthesis* **1989**, 127.
8. (a) Bloomer, J. L.; Stagliano, K. W. *Tetrahedron Lett.* **1993**, *34*, 757. (b) Corey, E. J.; Martinez, E. J. *Org. Lett.* **1999**, *1*, 75.
9. Hewson, A. T.; Sharpe, D. A.; Wadsworth, A. H. *Synth. Commun.* **1989**, *19*, 2095.
10. The structure assigned to the by-product was



11. Zhu, J.; Beugelmans, R.; Bourdet, S.; Chastanet, J.; Roussi, G. *J. Org Chem.* **1995**, *60*, 6389.
12. Demuynck, M.; DeClerq, P.; Vandewelle, M. *J. Org. Chem.* **1979**, *44*, 4863.