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# SYNTHESIS AND EVALUATION OF A PLEUROTIN ANALOG

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ABSTRACT. The photoenolization/Diels-Alder sequence provides a direct preparation of quinone **2** which exhibited activity against SR leukemia and colon cancers.

Pleurotin (**1**) is a novel quinone that has been isolated from *Pleurotis grieseus* . It exhibits activity against Erlich ascites carcinoma, L-1210 lymphoid leukemia and mammary tumors.[1] The only synthesis of **1** has been accomplished by Hart and coworkers.[2] As part of our study of the synthetic potential of hydrogen atom abstraction reactions,[3] we have developed a route to **2** which features a tandem photoenolization/Diels-Alder reaction sequence.[4]

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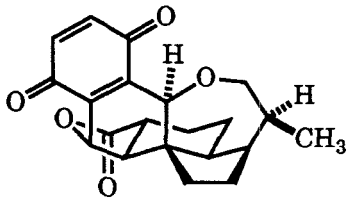
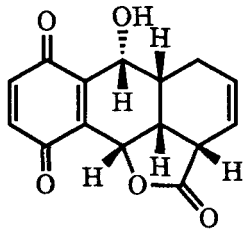


1

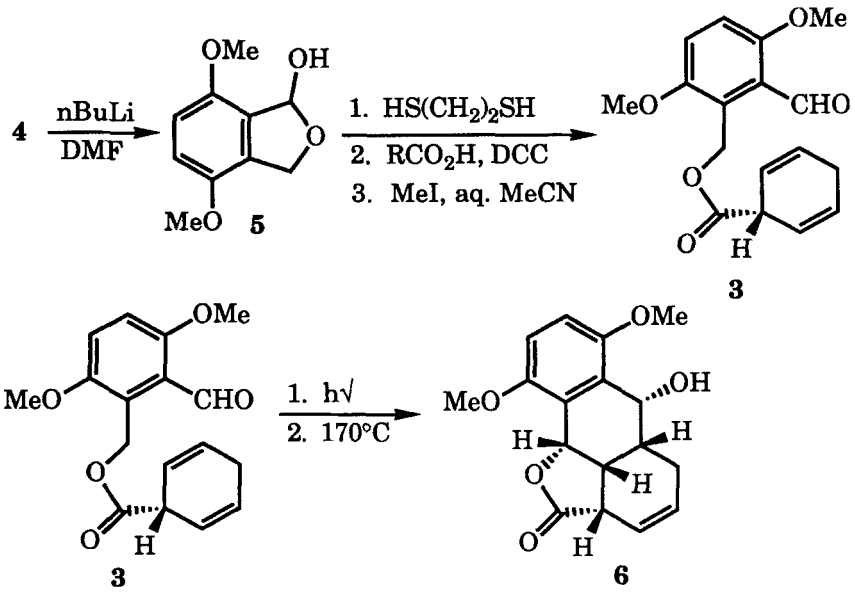


2

The "reductive alkylation" sequence proposed by Moore[5] involves a reactive quinone methide intermediate and has been used to explain the biological activity of pyranonaphthoquinone antibiotics such as frenolicin. Although the primary reason for selecting our synthetic pathway was to extend the scope of the photoenolization reaction, we recognized that intermediates early in our synthetic sequence posessed the benzylic C-O bonds common to compounds for which the Moore hypothesis had been invoked. Biological testing of some of our early intermediates would be possible after oxidation of the aromatic ring to a quinone.

Aldehyde **3** was synthesized as shown in Scheme 1. The reaction of the dianion of 2,5-dimethoxybenzyl alcohol (**4**) with DMF followed by mild aqueous hydrolysis afforded the hemiacetal **5**[6] in 66% yield. The attempted acylation of **5** failed; however, the reaction of hemicaetal **5** with 1,2-ethanedithiol and a catalytic amount of boron trifluoride etherate produced a thioketal alcohol in 91% yield which was acylated with 1,4-dihydrobenzoic acid[7] and dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP). Regeneration of the aldehyde using MeI in aqueous acetonitrile[8] produced aldehyde **3**. This reaction proceeded in 55% yield on a small scale; however,

Scheme 1



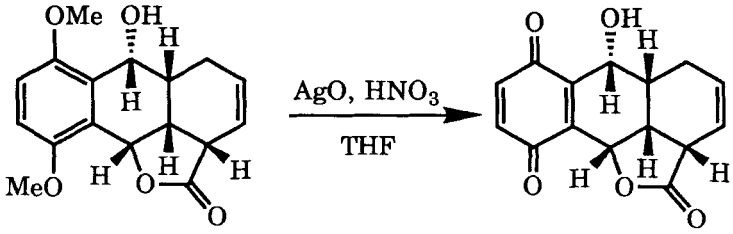

when **3** was prepared on a multigram scale, the method of Stork and Zhao[9] proved to be superior.

Aldehyde **3** was converted into **6** in 50% yield by irradiation followed by heating at 170 °C. In practice, it was most expedient to take the mixture of **6** and the benzocyclobutenol from the irradiation step and subject this material directly to the thermolysis step. Kametani and coworkers examined a related thermal cyclization of an ester of a benzocyclobutenol and suggested that a tricyclic lactone bearing a trans ring juncture was initially formed and was isomerized to a cis-lactone at 210 °C.[10]

The structure of **6** was supported by both a COSY and a NOESY 2D-NMR experiment. Additionally, molecular mechanics calculations were preformed on **6** (the endo product) and the exo

product. These calculations indicated that the endo adduct **6** was less stable than the exo adduct by approximately 1.6 Kcal/mole.

Compound **6** contains four of the six rings and three of the correct stereogenic centers of pleurotin. Lactone **6** also contains the benzylic lactone and benzylic alcohol moieties as well as a protected quinone. Oxidation of **6** with silver(II) oxide and nitric acid in THF[11] afforded the desired benzoquinone **2**.




**6** **2**

The biological testing of quinone **2** was carried out at the National Cancer Institute. This compound has comparable reactivity with pleurotin against SR leukemia cell line ($\log_{10}$ $GI_{50}$ = -5.33) and most colon cancer cell lines ($\log_{10}$ $GI_{50}$ ranging from -4.65 to -4.77). The mean value of $\log_{10}$ $GI_{50}$ of pleurotin is about -5.51 against leukemia cell lines and -5.17 against colon cancer cell lines.

The successful photoenolization reaction not only extends the synthetic utility of this little-used photoreaction but also demonstrates that benzylic heteroatom substituents do not disrupt the reaction.[12] Since our initial report, both Wagner and Saa have reported examples which reinforce our results.[13]

## Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. H:EA refers to

hexanes:ethyl acetate solvent mixtures for TLC and silica gel flash chromatography (sgc). The purity of all title compounds was determined to be >95% by 300 MHz proton NMR and/or elemental analysis.

**1,3-Dihydro-1-hydroxy-4,7-dimethoxyisobenzofuran (5)**

To the solution of 29.4 g (175 mmol) of 2,5-dimethoxybenzyl alcohol in 600 mL of dry THF was added 140 mL of *n*-BuLi (2.5 M) at -15 °C under argon. The resulting solution was boiled for 6 h and then cooled to 0 °C with ice-water bath. DMF (15 mL) was then introduced into the solution and the mixture was stirred for 12 hr. After the reaction was quenched with 200 mL of saturated $NH_4Cl$ solution and 50 mL of 1N HCl, the solution was stirred overnight. The white precipitate was collected and the aqueous layer was then extracted with ethyl acetate (200 mL three times). The combined organic layer was washed with brine and dried with $MgSO_4$. The solvent was then concentrated to about 30 mL and the white solid was collected by filtration to yield 22.7 g (66%) of **5** after recrystallization from ether. NMR ($CDCl_3$) δ (ppm) 6.78 (d, J = 7.4 Hz, 1 H), 6.74 (d, J = 7.4 Hz, 1 H), 6.58 (dd, $J_1$ = 7.2 Hz, $J_2$ = 2.1 Hz, 1 H), 5.30 (dd, $J_1$ = 13.2 Hz, $J_2$ = 2.1 Hz, 1 H), 5.00 (d, J = 13.2 Hz, 1 H), 3.84 (s, 3 H), 3.80 (s, 3 H), 3.07 (d, J = 7.2 Hz, 1 H); IR ($CH_2Cl_2$) 3560, 2940, 1500, 1300, 1020 $cm^{-1}$; MS: m/e 196.1, 178.1, 163.0, 77.0; HRMS: m/e for $C_{10}H_{12}O_4$ calcd. 196.07356, measured 196.07402; TLC (1:1 = H:EA) $R_f$ = 0.33; m.p. = 156-7 °C.

**2-(2-Hydroxymethyl-3,6-dimethoxyphenyl)-1,3-dithiolane**

The hemiacetal **5** (8.9 g, 45 mmol) and 1,2-ethanedithiol (5.5 mL, 60 mL) was mixed in 150 mL of $CH_2Cl_2$. $BF_3 \cdot Et_2O$ (0.5 mL, 4 mmol) was added to the solution at 0 °C. The resulting mixture was stirred for 12 h at rt. To the above mixture, 10 mL of 2 M NaOH solution was added and the mixture was stirred for another 2 h. Then the mixture was diluted with 200 mL of $CH_2Cl_2$ and washed with 50 mL of 2 N HCl and brine (50 mL x 2), dried with $MgSO_4$. Sgc purification gave 11.21 g (41.2 mmol) of a white solid in 91% yield. CMR ($CDCl_3$) δ (ppm) 153.05, 151.63, 131.14, 124.36, 111.42, 111.08, 56.50, 55.90, 55.26, 46.23, 40.11; TLC (2:1 = H:EA) $R_f = 0.26$.

**(2-Formyl-3,6-dimethoxyphenyl)methyl 2,5-cyclohexadiene-1-carboxylate (3).**

The thioacetal alcohol (544 mg, 2 mmol), dihydrobenzoic acid (248 mg, 2 mmol) and DMAP (25 mg) were dissolved in 8 mL of dry $CH_2Cl_2$. The solution was then cooled to 0° C with ice bath and the DCC (453.2 mg, 2.2 mmol) was added to the solution with 3 mL of $CH_2Cl_2$. The solution was warmed to rt and stirred for 5 h. After filtration, the filtrate was concentrated and the residue was purified to give 470 mg of the thioacetal ester. $^1H$ NMR ($CDCl_3$) δ (ppm) 6.89 (d, J = 9.0 Hz, 1 H), 6.84 (d, J = 9.0 Hz, 1 H), 6.37 (s, 1 H), 5.85 (d, J = 1.8 Hz, 4 H), 5.51 (s, 2 H), 3.83 (s, 3 H), 3.79 (m, 1 H), 3.77 (s, 3 H), 3.56 (m, 2 H), 3.34 (m, 2 H), 2.68 (m, 2 H); IR ($CH_2Cl_2$) 3040, 2930, 2860, 1710, 1478, 1260, 1075 $cm^{-1}$; TLC (3:1 = H:EA) $R_f = 0.37$.

The ester (200 mg) obtained above was dissolved in 15 mL of MeCN-$H_2O$ (4:1) mixture and to this solution 5 mL of MeI was added.

The mixture was then stirred at rt for 28 hr and the solvent was evaporated. The residue was purified by sgc (EA:H = 3:1) to give 90 mg of **3** in 55% yield. **3**: $^1$H NMR ($CDCl_3$) δ (ppm) 10.56 (s, 1 H), 7.11 (d, J = 9.0 Hz, 1 H), 6.99 (d, J = 9.0 Hz, 1 H), 5.83 (m, 4 H), 5.49 (s, 1 H), 3.88 (s, 3 H), 3.81 (s, 3 H), 3.70 (m, 1 H), 2.67 (m, 2 H); IR ($CDCl_3$) 3040, 2960, 2840, 1735, 1690, 1265 cm$^{-1}$; MS: m/e 302.1, 195.1, 179.1, 79.1; HRMS: m/e for $C_{17}H_{18}O_5$ calcd. 302.11542, measured 302.11476; TLC (3:1 = H:EA) $R_f$ = 0.37.

**2a,5,5a,6,10b,10c-hexahydro-6-hydroxy-7,10-dimethoxy-(2aα,5aα,6β,10bα,10cα)-2H-anthra[9,1-bc]furan-2-one (6)**

A benzene solution (18 mL) of benzaldehyde **3** (90 mg) was degassed with argon for 30 min and was then photolyzed with a Rayonet reactor equipped with black-light lamps (λ = 360 nm) for 4 h with stirring. Evaporation of benzene gave the residue which was purified by sgc (3:1 = H:EA and then 2:1 = EA:H). The reaction was then heated to 165°C for 40 hr. After removal of the solvent, the residue was purified by sgc (EA:H = 6:4) to give a 50% yield of compound **6** (45 mg).

: NMR ($CDCl_3$) δ (ppm) 6.88 (s, 2 H), 6.29 (d, J = 8.4 Hz, 1 H), 6.07 (m, 2 H), 5.26 (sb, 1 H), 3.84 (s, 3 H), 3.80 (s, 3 H), 3.43 (m, 1 H), 3.18 (ddt, $J_1$ = 10.8 Hz, $J_2$ = $J_3$ = 8.4 Hz, 1 H), 2.52 (m, 1 H), 2.35 (dd, $J_1$ = 18.6 Hz, $J_2$ = 4.5 Hz, 1 H), 1.95 (sb, J = 8.1 Hz, 1 H), 1.77 (s, 1 H); IR ($CDCl_3$) 3600, 2960, 2840, 1762, 1260 cm$^{-1}$; MS: m/e 302.1, 284.1, 209.1, 188.1, 165.1; HRMS: m/e for $C_{17}H_{18}O_5$ calcd. 302.11542, measured 302.11610; TLC (2:1 = EA:H) $R_f$ = 0.33.

**2a,5,5a,6,10b,10c-hexahydro-6-hydroxy-(2aα,5aα,6β,10bα,10cα)-2H-anthra[9,1-bc]furan-2, 7, 10-trione (2)**

To a mixture of lactone **6** (61 mg, 0.20 mmol) and AgO (100 mg, 0.80 mmol) in 2 mL of THF at rt was added 6N $HNO_3$ (200 μL). The mixture was stirred at rt for 20 min. After the addition of 8 mL of chloroform and 2 mL of water, the aqueous layer was extracted with chloroform. The combined organic layers were washed once with brine, were dried over sodium sulfate and were concentrated in vacuo to afford 17 mg (28% yield) of quinone **2** as a waxy solid. TLC (1:1 H:EA) $R_f$ = 0.28.

NMR ($CDCl_3$) δ (ppm) 1.90 (bt, J=7 Hz, 1H), 2.26-2.57 (m, 3H), 3.16-3.24 (m, 1H), 3.40 (dt, J=1, 12 Hz, 1H), 4.95 (bs, 1H), 5.89 (d, J=9 Hz, 1H), 5.95-6.06 (m, 2H), 6.36 (bs, 2H).

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