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Synthesis of Puraquinonic Acid Ethyl Ester and Deliquinone via a Common Intermediate

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Abstract: Both compounds were prepared via a common intermediate. The key features included the direct synthesis of the indan skeleton and the radical addition to a quinone.

Natural products bearing the indan subunit are increasing in number and many exhibit interesting biological activity.[1] In some cases such as illudin A (**1**), the six-membered ring subunit bears a spiro cyclopropane.[2] In other cases such as puraquinonic acid (**2**, R = H) and deliquinone (**3**), there is a quinone (Figure 1).[3] Fomajorin (**4**) is a metabolite of basidiomycete *Heterobasidion annosum*.[4] Puraquinonic acid induces differentiation of HL-60 cells. Puraquinonic acid has been synthesized by Clive and co-workers using a clever variant of the Nazarov cyclization.[5] Although illudin A has not been synthesized, other members of this family have been prepared.[6] We recently communicated the synthesis of racemic deliquinone.[7] We report herein a full account of this work plus a synthesis of the ethyl ester of puraquinonic acid.

Our strategy for the synthesis of **2** and **3** centered on the preparation of indan ester **5** (X = H), a readily available compound.[8] We initially planned to construct quinone **6** from the ester **5** (X = H) by oxidation (Scheme 1). *m*-Chloroperbenzoic acid,[9] methylrhenium trioxide,[10] and palladium acetate[11] have been reported to convert 1,2-disubstituted aromatic rings directly into benzoquinones. Unfortunately, attempted oxidation of **5** (X = H) to quinone **6** using either methylrhenium trioxide or palladium acetate returned recovered starting material.

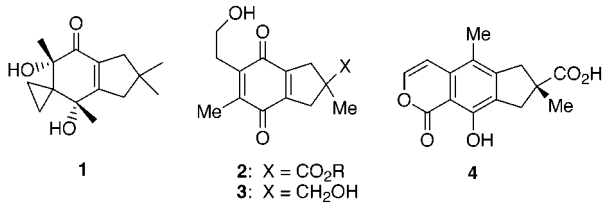
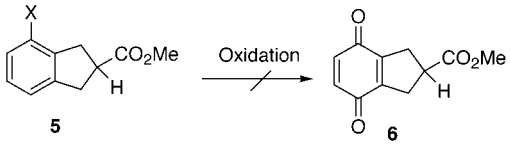
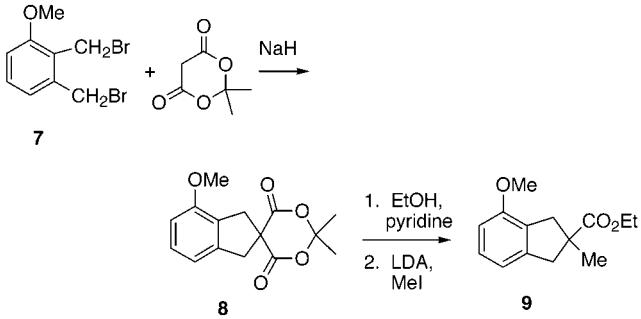


FIGURE 1.

SCHEME 1



SCHEME 2



The reaction of **5** (X = H) with *m*-chloroperbenzoic acid proceeded in modest yield and was not reproducible.

We next focused on a synthesis of indan ester **5** (X = OMe). This was achieved by the reaction of 2,3-dimethylanisole with 2 equiv of *N*-bromosuccinimide in carbon tetrachloride. The resulting dibromide **7** reacted with Meldrum's acid and sodium hydride in DMSO to provide the indan dilactone **8**.[12] The use of DMSO as the solvent was critical, since solvents such as ethanol afforded 2:1 adducts as significant byproducts. The reaction of **8** with ethanol and pyridine produced **5** (X = OMe) in 87% isolated yield. This compound was generated by ester formation followed by decarboxylation. The resulting ester was methylated using lithium diisopropylamide (LDA) and methyl iodide in THF at −78 °C to generate ester **9** in quantitative yield (Scheme 2).

Introduction of the two-carbon side chain was the next objective. It was achieved by demethylation of the aryl methyl ether using 2-phenylethylthiol and aluminum trichloride.[13] With reagents such as boron trichloride or iodotrimethylsilane, cleavage of the ester was competitive with demethylation. Alkylation of the phenol produced the ether **10**. Claisen rearrangement at 200 °C in DMF cleanly provided phenol **11** in 77% yield from **9** (Scheme 3).

Phenol **11** was viewed as a key intermediate for both the synthesis of deliquinone and the synthesis of

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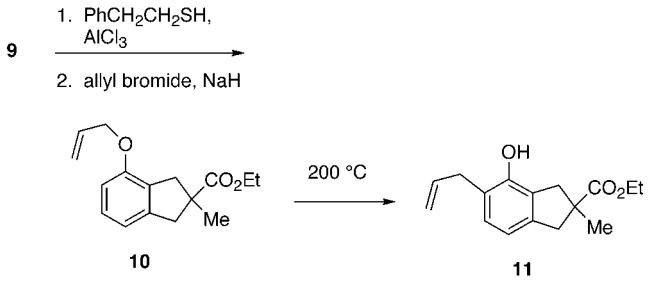
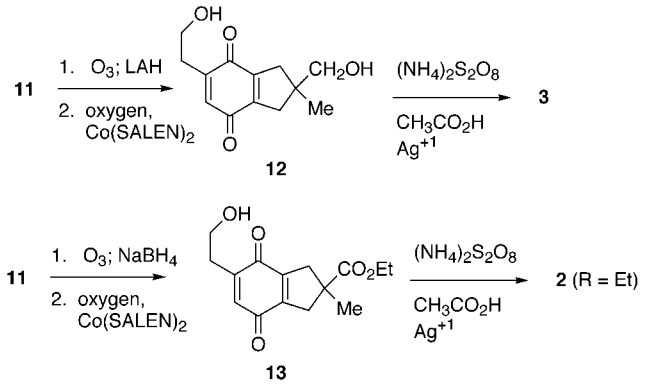
SCHEME 3



SCHEME 4



puraquinonic acid. Ozonolysis followed by reductive workup of the ozonolysis product with excess lithium aluminum hydride afforded a triol. This triol could be converted to quinone **12** using salcomine ($Co(SALEN)_2$) and oxygen.[14] Reaction of quinone **12** with ammonium persulfate, acetic acid, and a catalytic amount of silver nitrate at 70 °C produced quinone **3** in 68% yield. This reaction proceeds by way of a radical intermediate. Ammonium persulfate oxidizes the silver(I) salt to a silver(II) salt, which decarboxylates to give the methyl radical.[15] The use of organometallic reagents such cuprates or organozinc reagents failed to introduce the methyl group.

Similarly, the product from the ozonolysis of **11** was reduced with sodium borohydride to afford ester **13** in 70% yield. This compound reacted with ammonium persulfate, silver nitrate, and acetic acid to provide the ethyl ester of puraquinonic acid in 72% yield (Scheme 4).

In summary, the synthesis of deliquinone and the synthesis of the ethyl ester of puraquinonic acid were achieved by a direct and flexible route. The direct assemblage of the indan unit and the persulfate-mediated quinone alkylation are key features of this route.

Experimental Section

Preparation of Dilactone 8. 2,3-Dimethylanisole (13.8 g, 100 mmol) and *N*-bromosuccinimide (37.38 g, 210 mmol) were dissolved in dry carbon tetrachloride (1000 mL), and the mixture was refluxed under argon for 3 h while being exposed to a 275 W high-intensity sunlamp. The solution was cooled to room temperature, the suspended succinimide was removed by filtration, and the solvent was evaporated. The residue was recrystallized from diethyl ether−pentane to give compound **7** as white crystals in 87% (25.5 g) yield.

Sodium hydride (60% in mineral oil, 4.6 g, 2.2 equiv) was washed with dry pentane and suspended in DMSO (75 mL). Meldrum's acid (15.8 g, 110 mmol) in DMSO (30 mL) was added to the stirred slurry (after homogenization; 10 min, stirring at room temperature) followed by 2,3-bis(bromomethyl)anisole (14.7 g, 50 mmol) in DMSO (30 mL). The reaction mixture was stirred at 50 °C for 3 h, poured into 0.04 M aqueous HCl (500 mL, 0 °C), and extracted with ethyl acetate (3 × 150 mL). The combined extracts were washed with water, dried over Na_2SO_4, and evaporated. The residue was recrystallized from diethyl ether to furnish compound **8** as white crystals in 80% (11 g) yield.

Compound **8**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.77 (s, 3H), 1.79 (s, 3H), 3.63 (s, 2H), 3.72 (s, 2H), 3.79 (s, 3H), 6.71 (d, J = 8.0 Hz, 1H), 6.80 (d, J = 7.5 Hz, 1H), 7.20 (t, J = 7.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.8, 28.9, 43.3, 45.5, 52.2, 55.1, 105.1, 108.6, 116.0, 126.4, 129.4, 141.1, 155.6, 170.5; HRMS calcd for $C_{15}H_{16}O_5$ 276.0997, found 276.1002.

Ethyl 4-Methoxy-2-methylindan-2-carboxylate 9. Compound **8** (3.0 g, 10.87 mmol) was dissolved in dry ethanol (1.5 mL)−pyridine (15 mL) containing copper powder (0.125 g, 2 mmol) and boiled under argon for 4 h. After removal of pyridine, the residue was diluted with ether and filtered through Celite pad. Solvent was removed, and the residual green liquid was purified by SGC by using 1:9 ethyl acetate/hexane to afford the ester as a colorless oil in 86% yield (2.05 g).

The ester (1 equiv, 1.9 g, 8.63 mmol) in dry THF (10 mL) was added to LDA (1.1 equiv) solution at −78 °C and stirred for 1 h at the same temperature. Methyl iodide (5 equiv) was added to the reaction mixture at −78 °C and warmed to room temperature. The reaction mixture was quenched with saturated ammonium chloride solution, extracted with ether (3 × 100 mL), dried over $MgSO_4$, and evaporated. The residue was purified by SGC by using 0.5:9.5 ethyl acetate/hexane to obtain ester **9** as a colorless oil in 96% yield (1.95 g).

Compound **9**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 (t, J = 5.4 Hz, 3H), 1.40 (s, 3H), 2.84 (d, J = 11.7 Hz, 1H), 2.88 (d, J = 12.03 Hz, 1H), 3.43 (d, J = 12.3 Hz, 1H), 3.54 (d, J = 11.9 Hz, 1H), 3.84 (s, 3H), 4.21 (q, J = 5.3 Hz, 2H), 6.70 (d, J = 6.0 Hz, 1 H), 6.84 (d, J = 5.6 Hz, 1H), 7.17 (t, J = 5.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4, 25.6, 40.9, 44.4, 49.3, 55.2, 60.8, 108.1, 117.1, 128.1, 128.9, 143.3, 156.2, 177.7; HRMS calcd for $C_{14}H_{18}O_3$ 234.1255, found 234.1259.

Ethyl 2-Methyl-4-(2-propenyloxy)indan-2-carboxylate 10. To a mixture of phenethylthiol (1.75 mL, 3 equiv) and dichloromethane (10 mL) was added aluminum chloride (1.75 g, 3 equiv) at 0 °C. The resulting solution was warmed to room temperature, and ester **9** (1.023 g, 4.37 mmol) in dichloromethane (10 mL) was added with stirring. After being stirred for 8 h, the reaction mixture was poured into ice−water, acidified with dilute HCl, extracted with dichloromethane, and dried over $MgSO_4$. After removal of solvent, the residue was purified by SGC by using 1:9 ethyl acetate/hexane to obtain the phenol as a colorless oil in 93% yield (0.895 g).

To a stirred suspension of sodium hydride (8.36 mmol, 1.1 equiv, 60% dispersion in mineral oil, which had been washed with pentane) in anhydrous DMF (10 mL) at 0 °C was added a solution of the phenol (1.67 g, 7.60 mmol) in DMF (10 mL), and the resulting solution was stirred at room temperature for 0.5 h. The solution was again cooled to 0 °C, allyl bromide (2 equiv, 1.3 mL) was added, and stirring was continued to reach room temperature (1 h). The reaction mixture was then poured into saturated brine (25 mL) and extracted with ether (4 × 75 mL). The organic phases were combined, washed with saturated brine (50 mL), and dried ($MgSO_4$). Evaporation of the solvent yielded a red oil that was purified by SGC by using 1:19 ethyl acetate/hexane to obtain compound **10** as a colorless oil in 96% yield (1.88 g).

Compound **10**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.31 (t, J = 7.1 Hz, 3H), 1.41 (s, 3H), 2.85 (d, J = 16.0 Hz, 1H), 2.93 (d, J = 16.5 Hz, 1H), 3.51 (d, J = 16.5 Hz, 1H), 3.55 (d, J = 16.1 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 4.56 (d, J = 5.0 Hz, 2H), 5.28−

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5.48 (m, 2H), 6.03−6.15 (m, 1H), 6.7 (d, J = 8.1 Hz, 1H), 6.85 (d, J = 7.4 Hz, 1H), 7.15 (t, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 25.4, 40.9, 44.3, 49.2, 60.6, 68.5, 109.3, 117.0, 117.1, 127.9, 129.1, 133.5, 143.3, 155.2, 177.5; HRMS calcd for $C_{16}H_{20}O_3$ 260.1412, found 260.1416.

Ethyl 4-Hydroxy-2-methyl-5-(2-propenyl)indan-2-carboxylate 11. Compound **10** (1 g, 3.84 mmol) in anhydrous DMF (8 mL) was heated in sealed tube at 200 °C for 7 h. After removal of DMF under reduced pressure, the residue was purified by SGC by using 1:9 ethyl acetate/hexane to yield the compound **11** as a colorless oil in 82% yield along with starting compound in 8%.

Compound **11**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (t, J = 5.3 Hz, 3H), 1.4 (s, 3H), 2.78 (d, J = 11.8 Hz, 1H), 2.82 (d, J = 11.9 Hz, 1H), 3.37−3.49 (m, 4H), 4.18 (q, J = 5.3 Hz, 2H), 4.9 (s, 1H), 5.15−5.21 (m, 2H), 5.97−6.07 (m, 1H), 6.74 (d, J = 5.6 Hz, 1H), 6.93 (d, J = 5.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4, 25.7, 35.4, 40.3, 44.3, 49.9, 60.9, 116.6, 117.1, 122.9, 127.5, 129.3, 137.0, 142.2, 150.9, 177.7; HRMS calcd for $C_{16}H_{20}O_3$ 260.1412, found 260.1416.

4,7-Dihydro-4,7-dioxo-2-methyl-5-(2-hydroxyethyl)indan-2-methanol 12. Ozone was bubbled through a solution of compound **11** (0.26 g, 1 mmol) in dichloromethane (8 mL) at −78 °C for 7 min. Argon was passed through the ozonide solution at room temperature for 5 min, dichloromethane was removed under reduced pressure at room temperature, immediately the ozonide in anhydrous THF (5 mL) was added dropwise to lithium aluminum hydride (3 equiv) in THF (2 mL) at 0 °C, and stirring was continued for 0.5 h at 0 °C. The reaction mixture was then decomposed by addition of a few drops of water followed by 10% sulfuric acid. The reaction mixture was then extracted with ethyl acetate (3 × 25 mL) and dried (Na_2SO_4). Solvent was removed under reduced pressure, and the residue was purified by SGC by using 1:1 ethyl acetate/hexane to furnish the triol as a viscous oil in 63% yield (0.14 g).

To a stirred solution of the triol (0.044 g, 0.2 mmol) in acetonitrile (5 mL) was added salcomine hydrate (0.4 equiv). Oxygen was bubbled through the solution for 5 min, and then the solution was stirred for an additional 24 h in the oxygen atmosphere. Acetonitrile was removed under reduced pressure, and the residue was purified by SGC by using 3:1 ethyl acetate/hexane to yield the compound **12** as a yellow viscous liquid in 98% yield.

Compound **12**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.17 (s, 3H), 1.65 (br s, 1H), 1.72 (br s, 1H), 2.48 (d, J = 19.0 Hz, 1H), 2.54 (d, J = 19.5 Hz, 1H), 2.68 (t, J = 6.1 Hz, 2H), 2.81−2.88 (m, 2H), 3.51 (br s, 2H), 3.82 (dd, J = 10.6, 5.5 Hz, 2H), 6.57 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.1, 32.7, 40.5, 40.7, 43.1, 61.3, 70.1, 134.6, 146.6, 147.3, 147.4, 186.5, 186.8; HRMS calcd for $C_{13}H_{16}O_4$ 236.10486, found 236.1050.

Ethyl 4,7-Dihydro-4,7-dioxo-2-methyl-5-(2-hdroxyethyl)-indan-2-carboxylate 13. Ozone was bubbled through a solution of compound **11** (0.26 g, 1 mmol) in absolute ethanol (6 mL) at −78 °C for 5−7 min. The ozonide solution was then added dropwise to sodium borohydride in ethanol at 0 °C, and stirring was continued at the same temperature for 1 h. The ethanol was removed under reduced pressure at room temperature, and the residue was acidified with cold dilute hydrochloric acid, extracted with ethyl acetate (3 × 25 mL), and dried over Na_2SO_4. After removal of solvent, the crude product was purified by SGC by using 1:3 ethyl acetate/hexane to afford the diol ester in 72% yield (0.19 g).

To a stirred solution of diol ester (0.08 g, 0.3 mmol) in acetonitrile (5 mL) was added salcomine hydrate (0.4 equiv). Oxygen was bubbled through the solution for 5 min, and then the solution was stirred for an additional 24 h in the oxygen atmosphere. Acetonitrile was removed under reduced pressure, and the residue was purified by SGC by using 3:1 ethyl acetate/hexane to yield compound **13** as a yellow viscous liquid in 98% yield.

Compound **13**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (t, J = 5.3 Hz, 3H), 1.39 (s, 3H), 1.68 (t, J = 4 Hz, 1H), 2.68−2.75 (m, 4H), 3.35 (m, 2H), 3.83 (dd, J = 8.5, 4.4 Hz, 2H), 4.18 (q, J = 5.4 Hz, 2H), 6.59 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4, 26.2, 32.7, 42.2, 42.5, 47.3, 61.3, 61.5, 134.6, 146.1, 146.3, 146.6, 176.5, 186.0, 186.3; HRMS calcd for $C_{15}H_{18}O_5$ 278.1154, found 278.1157.

Preparation of Compounds 2 and 3. A mixture of quinone (**13**, 0.055 g, 0.2 mmol or **12**, 0.024 g, 0.1 mmol), acetic acid (1.5 equiv), silver nitrate (0.2 equiv), and ammonium persulfate (1.2 equiv) in 1 mL of 1:1 acetonitrile/water was heated at 65−70 °C for 3−4 h. The solution was diluted with methylene chloride. The organic layer was washed with water, dried over sodium sulfate, and concentrated in vacuo. The crude residue was purified by preparative thin-layer chromatography using 1:1 and 3:1 ethyl acetate/hexane to furnish the compounds **2** and **3** as viscous brown liquid in 64% and 68% yield, respectively, along with the starting compounds **13** and **12** in 13% and 15% yield.

Compound **2** (R = Et): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, J = 7.1 Hz, 3H), 1.37 (s, 3H), 1.78 (br s, 1H), 2.07 (s, 3H), 2.67−2.80 (m, 4H), 3.34 (d, J = 16.3 Hz, 2H), 3.77 (br t, J = 5.8 Hz, 2H), 4.17 (q, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.4, 14.4, 26.2, 30.1, 42.5, 42.6, 47.2, 61.4, 61.7, 141.5, 142.9, 145.6, 146.0, 176.6, 186.0, 186.5; HRMS calcd for $C_{16}H_{20}O_5$ 292.1310, found 292.1312.

Compound **3**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.17 (s, 3H), 2.07 (s, 3H), 2.49 (d, J = 16.1 Hz, 1H), 2.54 (d, J = 17.7 Hz, 1H), 2.77−2.86 (m, 4H), 3.50 (br s, 2H), 3.76 (dd, J = 11.4, 5.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.4, 25.1, 30.1, 40.7, 40.8, 43.0, 61.7, 70.2, 141.5, 142.8, 146.8, 147.2,186.5, 187.0; HRMS calcd for $C_{14}H_{18}O_4$ 250.1205, found 250.1208.

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Supporting Information Available: NMR spectra of obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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