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A synthesis of puraquinonic acid

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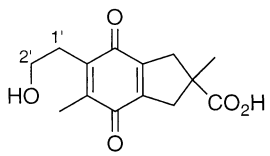
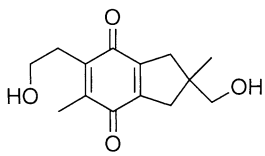
Abstract—2-Methyl-1,4-benzenediol (**10**) was acylated with α-chloroisobutyroyl chloride and converted by treatment with $AlCl_3$ into the indanone derivative **12**, which was elaborated into the substituted indane acid **24**. Oxidation then afforded racemic puraquinonic acid.

The fungal metabolite puraquinonic acid (**1**)[1] has the noteworthy property of inducing differentiation in HL-60 cells, and its structure may therefore offer some guidance for the design of antileukemia drugs.[2] The absolute configuration of **1**, which has $[\alpha]_D^{22}$ +1 (*c* 1.0, $CHCl_3$), is not known. Compounds **2** and **3**, which are structurally related to puraquinonic acid, have been isolated[3] from injured fruit bodies of the fungus *Russula delica*, but no evaluation of the biological properties of these metabolites has been reported. Recent work in this laboratory has resulted in a synthetic route to (±)-**1**,[4] starting from 2,5-dimethoxybenzoic acid (**4**), which was first elaborated into **5**. Then, Nazarov cyclization (**5**→**6**, concentrated H_2SO_4, 84%) served to generate the indanone **6**, which was acylated (**6**→**7**) and converted into puraquinonic acid. In this route (**4**→**5**→**6**→**7**→**1**, Scheme 1), the C(2′) oxygen had to be protected in the form of the heterocycle shown, in order to avoid cyclization of the type **8**→**9**[5] during the Nazarov cyclization (Scheme 2). We have now bypassed this inconvenient requirement, and report (Scheme 3) a much shorter route to **1** (15 steps versus 28).



1



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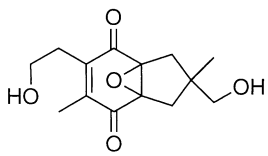
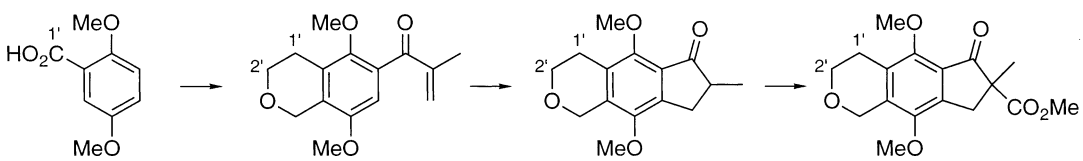


3

Acylation of **10** with α-chloroisobutyroyl chloride gave the diester **11** (88%), which is reported (no yield is given) in the patent literature[6] to undergo rearrangement and cyclization (**11**→**12**) on heating with $AlCl_3$. In our hands this transformation is easily accomplished (43%), and methylation (MeI, K_2CO_3, DMF) gave the



Scheme 1.

Keywords: antileukemia compound; Claisen rearrangement; quinone; oxidation; differentiation inducer.

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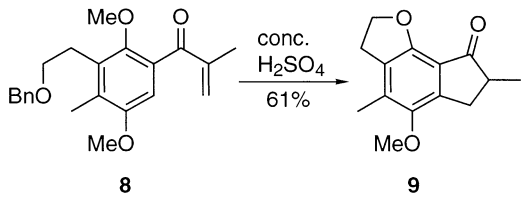
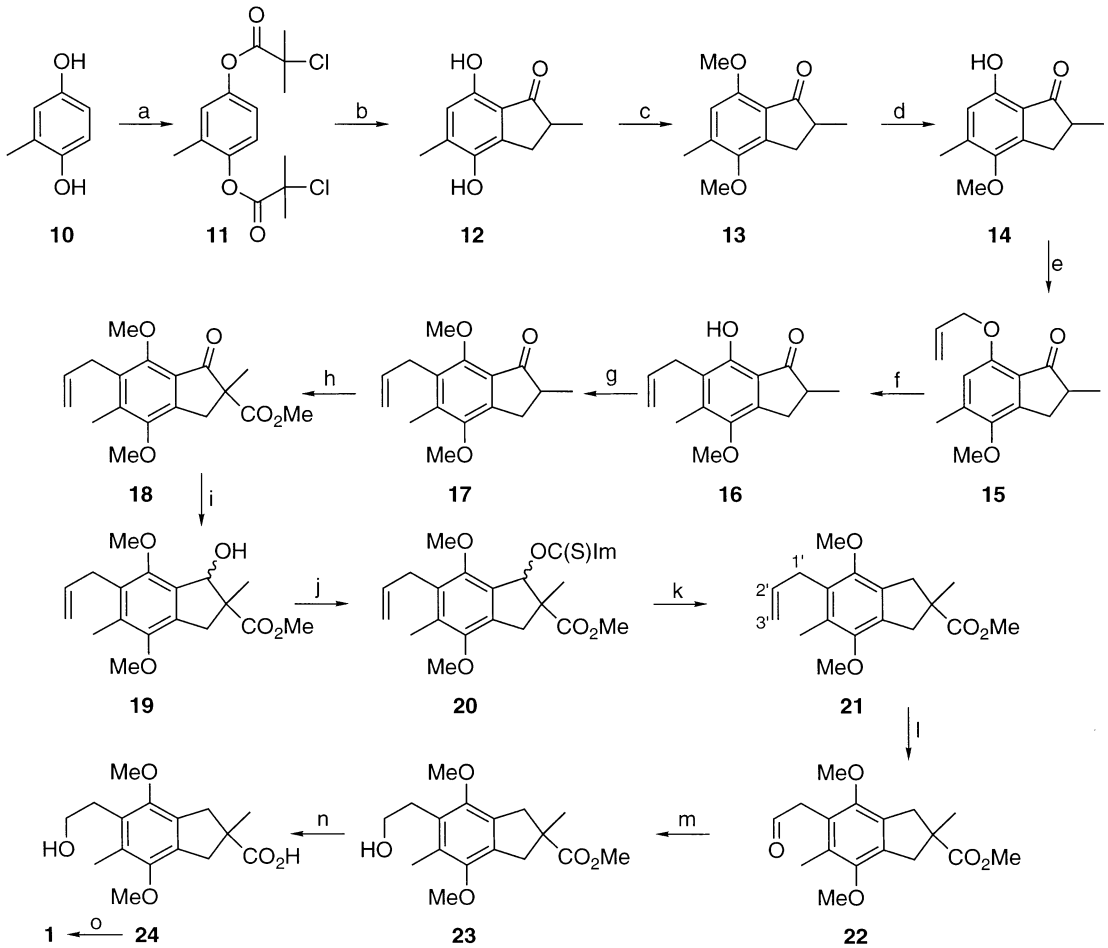


Scheme 2.

corresponding bis-methyl ether **13** (64%). Selective demethylation, directed by the carbonyl group, was then achieved on treatment with BCl_3 (−78°C to room temperature, 97%).[7] From that point, *O*-allylation (**14**→**15**, NaH, allyl bromide, DMF, 96%, or 99% after correction for recovered **14**), Claisen rearrangement (**15**→**16**, 200°C, 8 h, 67%, or 75% after correction for recovered **15**), and *O*-methylation (MeI, K_2CO_3, DMF, 93%) gave the highly substituted indanone derivative **17**; acylation with Mander's reagent [LDA, MeOC(O)CN, 88%] then provided ketoester **18**, which contains all the required skeletal carbons and the appropriate functionality for conversion into puraquinonic acid.

Reduction of the ketone carbonyl ($NaBH_4$, MeOH, 91%) and radical deoxygenation (**19**→**20**→**21**, 80% overall) took the route to a stage where the 2′,3′ double bond had to be cleaved. This seemingly straightforward operation was initially troublesome, as ozonolysis resulted in destruction of the starting material, and treatment with OsO_4–$NaIO_4$ under standard conditions[8] gave the required aldehyde **22** in low yield (ca. 22%). However, use of OsO_4–$LiIO_4$ in an aqueous phosphate buffer at pH 6.6[9] afforded **22** in 98% yield, and $NaBH_4$ reduction (96%) led to alcohol **23**. Simple hydrolysis (LiOH, aqueous THF, 93%) liberated the parent acid **24**,[4] which we had previously[4] oxidized [$Ce(NH_4)_2(NO_3)_6$, 2,6-pyridinedicarboxylic acid *N*-oxide,[10] 77%] to racemic puraquinonic acid.

In the present route, formation of the five-membered ring at an early stage avoids complications engendered by the presence of the (2′-oxyethyl) side chain, and a considerable shortening of the synthesis results. Our



Scheme 3. (a) α-Chloroisobutyroyl chloride, pyridine, 88%; (b) $AlCl_3$, 25°C for 20 min, then 190°C for 10 min, 43%; (c) MeI, K_2CO_3, DMF, 5 h, 64%; (d) BCl_3, −78°C to room temperature, 5 h, 97%; (e) NaH, allyl bromide, DMF, 0°C to room temperature, 1.5 h, 96%, or 99% after correction for recovered **14**; (f) degassed decalin, 200°C, 8 h, 67%, or 75% after correction for recovered **15**; (g) MeI, K_2CO_3, DMF, 12 h, 93%; (h) LDA, THF, −78°C, MeOC(O)CN, 88%; (i) $NaBH_4$, MeOH, 0°C, 40 min, 91%; (j) $Im_2C{=}S$, DMAP, $ClCH_2CH_2Cl$, room temperature, 12 h, 97%; (k) Bu_3SnH, AIBN, PhMe, 1.5 h, reflux, 83%; (l) EtOAc, $LiIO_4$–Li_3PO_4–buffer, pH 6.6, 1% aqueous OsO_4, 17 h, 98%; (m) $NaBH_4$, MeOH, 0°C, 1 h, 97%; (n) $LiOH{\cdot}H_2O$, 1:1 dioxane–water, room temperature, 3 h, 93%; (o) $Ce(NH_4)_2(NO_3)_6$, 2,6-pyridinedicarboxylic acid *N*-oxide, 77%.

attempts to effect oxidative cleavage of the allyl side chain of **21** illustrate the significant improvement that can be achieved in the Lemieux–Johnson oxidation by controlling the pH.

All new compounds were characterized spectroscopically, including accurate mass measurements.[11]

Acknowledgements

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11. Characterization data for key compounds: The symbols s′, d′, t′ and q′ in ^{13}C spectra refer to 0, 1, 2, and 3 attached protons, respectively. **17**: FTIR ($CHCl_3$ cast) 1707 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.29 (d, $J=7.3$ Hz, 3 H), 2.28 (s, 3 H), 2.62–2.72 [m containing d at δ 2.64 ($J=4.2$ Hz), 2H in all], 3.32–3.40 (m, 1H), 3.46 (dt, $J=5.8$, 1.6 Hz, 2H), 3.78 (s, 3H), 3.91 (s, 3H), 4.90 (dq, $J=17.1$, 1.8 Hz, 1H), 5.00 (dq, $J=10.2$, 1.7 Hz, 1H), 5.85–5.96 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.8 (q′), 16.5 (q′), 30.5 (t′), 31.6 (t′), 42.4 (q′), 60.1 (q′ or d′), 62.3 (d′ or q′), 115.1 (t′), 126.8 (s′), 132.0 (s′), 136.0 (d′), 139.2 (s′), 144.6 (s′), 151.2 (s′), 152.5 (s′), 206.0 (s′); exact mass m/z calcd for $C_{16}H_{20}O_3$ 260.1412, found 260.1407. **18**: FTIR ($CDCl_3$ cast) 1745, 1707 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.52 (s, 3H), 2.30 (s, 3H), 2.94 (d, $J=17.3$ Hz, 1H), 3.47 (dq, $J=5.8$, 1.6 Hz, 2H), 3.64 (d, $J=17.3$ Hz, 1H), 3.70 (s, 3H), 3.79 (s, 3H), 3.91 (s, 3H), 4.90 (dq, $J=17.2$, 1.6 Hz, 1H), 5.03 (dq, $J=10.2$, 1.6 Hz, 1H), 5.86–5.96 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.8 (q′), 21.2 (q′), 30.6 (t′), 36.6 (t′), 52.6 (q′), 56.4 (s′), 60.2 (q′), 62.3 (q′), 115.3 (t′), 125.1 (s′), 132.6 (s′), 135.8 (d′), 140.2 (s′), 143.6 (s′), 151.1 (s′), 153.2 (s′), 172.6 (s′), 200.0 (s′); exact mass m/z calcd for $C_{18}H_{22}O_5$ 318.1467, found 318.1466. **21**: FTIR ($CHCl_3$ cast) 1733 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.36 (s, 3H), 2.16 (s, 3H), 2.88 (dd, $J=16.0$, 2.2 Hz, 2H), 3.38–3.50 [m containing dd at δ 3.46 ($J=15.8$, 4.7 Hz), 4H in all], 3.70 (s, 3H), 3.72 (s, 3H), 3.73 (s, 3H), 4.91 (dq, $J=17.1$, 1.9 Hz, 1H), 5.00 (dq, $J=10.0$, 1.8 Hz, 1H), 5.89–5.97 (m, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 11.8 (q′), 25.2 (q′), 31.0 (t′), 41.2 (t′), 41.4 (t′), 50.0 (s′), 52.1 (q′), 59.9 (q′), 60.4 (q′), 114.7 (t′), 129.1 (s′), 130.3 (s′), 131.4 (s′), 132.5 (s′), 136.7 (d′), 151.0 (s′), 177.9 (s′), two signals overlap in this spectrum; exact mass m/z calcd for $C_{18}H_{24}O_4$ 304.1675, found 304.1679. **22**: FTIR ($CDCl_3$ cast) 1727 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.37 (s, 3H), 2.12 (s, 3H), 2.89 (dd, $J=15.9$, 3.3 Hz, 2H), 3.47 (d, $J=15.8$ Hz, 1H), 3.50 (d, $J=15.8$ Hz, 1H), 3.71 (overlapping singlets, 6H in all), 3.72 (t, $J=2.0$ Hz, 2H), 3.74 (s, 3H), 9.68 (t, $J=2.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.6 (q′), 25.1 (q′), 30.9 (q′), 41.2 (t′), 41.6 (t′), 42.5 (t′), 50.1 (s′), 52.2 (q′), 60.0 (q′), 123.5 (s′), 129.5 (s′), 131.1 (s′), 134.3 (s′), 151.0 (s′), 151.2 (s′), 177.7 (s′), 199.6 (d′); exact m/z calcd for $C_{17}H_{22}O_5$ 306.1467, found 306.1472. **23**: FTIR ($CDCl_3$ cast) 3427, 1731 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.36 (s, 3H) 1.90 (br s, 1H), 2.21 (s, 3H), 2.84–2.97 [m containing a dd at δ 2.87 ppm ($J=16.1$, 3.3 Hz) and a t at δ 2.92 ($J=6.8$ Hz), 4H in all), 3.44 (d, $J=15.9$ Hz, 1H), 3.48 (d, $J=15.8$ Hz, 1H), 3.70 (s, 3H), 3.73–3.79 (m, containing two singlets at δ 3.73 and δ 3.76, 8H in all); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.2 (q′), 25.3 (q′), 30.6 (t′), 41.2 (t′), 41.6 (t′), 50.1 (s′), 52.2 (q′), 60.0 (q′), 60.1 (q′), 62.8 (t′), 128.9 (two overlapping s′), 131.0 (s′), 132.9 (s′), 150.98 (s′), 151.09 (s′), 177.6 (s′); exact mass m/z calcd for $C_{17}H_{24}O_5$ 308.1624, found 308.1619.