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Synthesis Directed Towards Putative Advanced Intermediates in Sarubicin A Biosynthesis

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Abstract 3,6-Dihydroxyanthranilamide, **5**, and its 5-propyl derivative, **15**, were synthesized The former was found to be very unstable, but the later was stable and could be reversibly oxidized to the analogous quinone 3,6-Dimethoxyanthranilamide was protected as an acetone acetaminal and formylated at C-5 to give **18** A hetero-Diels-Alder reaction with Danishefsky's diene and **18** was effected with the aid of sonication and $ZnCl_2$, yielding a model, **20**, for a putative C-glycoside intermediate in the biosynthesis of sarubicin A, **1** However, when **18** and the triethylsiloxydiene derived from 3-penten-2-one were treated under the same conditions no reaction occurred, while *p*-dimethylaminobenzaldehyde only gave an aldol product **23**

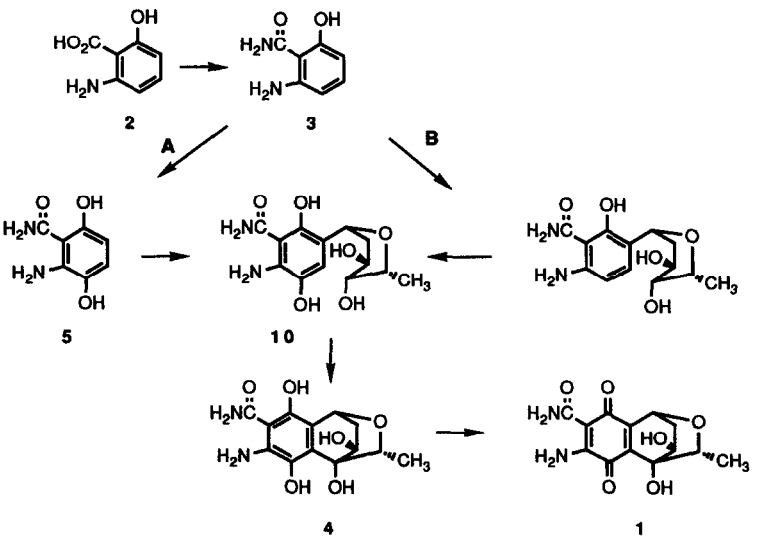
Sarubicin A, **1**,[1-3] a quinone antibiotic produced by several *Streptomyces* species, is derived from glucose,[4,5] 6-hydroxyanthranilic acid, **2**,[6] a new aromatic amino acid from the shikimic acid pathway, and molecular oxygen.[6] 6-Hydroxyanthranilamide, **3**,[7] has recently been shown to be an intermediate

Key biosynthetic steps beyond **3** should be oxygenation of the ring to introduce the C-4 oxygen, C-glycoside formation, presumably through a 2,6-dideoxy-4-ketosugar nucleoside, and cyclization, thus leading to the hydroquinone **4** Two permutations are outlined in Scheme 1, with the last step in the pathway expected to be oxidation to the final quinone A program to synthesize these compounds for advanced biosynthetic studies, as well as to provide entry into a putative biomimetic synthesis of **1** via C-glycosides was initiated

Results and Discussion

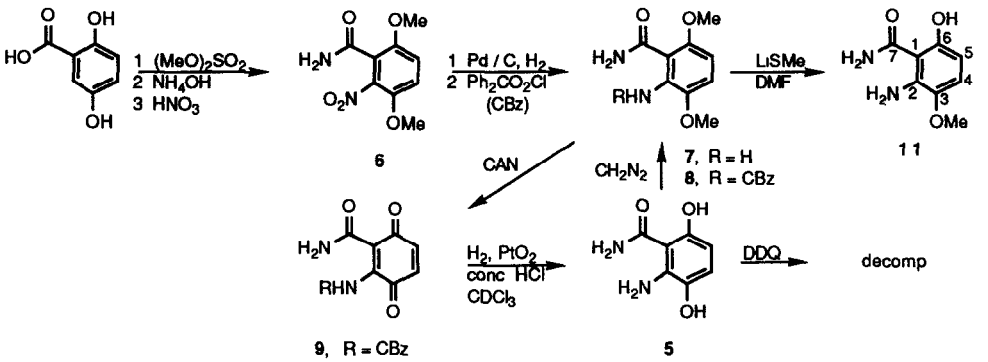
Initial efforts were directed towards synthesizing 3,6-dihydroxyanthranilamide, **5**, and its derivatives to determine their stability and suitability as synthetic intermediates 2-Nitro-3,6-dimethoxybenzamide, **6**,[8] was prepared from commercially available 2,5-dihydroxybenzoic acid Catalytic reduction of the nitro group of **6** produced the anthranilamide **7**, which was protected as a benzyl urethane to give **8** (88%) and then smoothly oxidized (89%) to the slightly unstable quinone **9** with ceric ammonium nitrate[9] (CAN) Reduction of **9** was expected to produce the putative hydroquinone intermediate **5** Indeed, when catalytic reduction and concomitant urethane deprotection was carried out in the presence of a small amount of concentrated HCl the hydroquinone product **5** could be detected by ^1H- and ^{13}C NMR spectroscopy, but it decomposed within 30 min *In situ* reoxidation with dichlorodicyanoquinone (DDQ) of initially formed

Scheme 1



5 also resulted in decomposition, and attempts to trap **5** with acetic anhydride, or acetyl chloride were also unsuccessful, however, the dimethylhydroquinone **7** could be regenerated by trapping **5** with diazomethane, but only in 8% yield This proved the formation of **5** but the cummulative results revealed it to be quite unstable These results are outlined in Scheme 2

Scheme 2

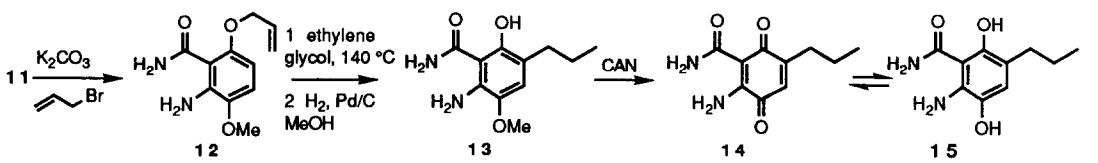


Given the instability of hydroquinone **5**, efforts were next directed towards synthesizing a 5-alkyl substituted analogue, as a model system for the putative biosynthetic intermediate **10**, in order to determine its relative stability H-5 of **7** had been found to readily exchange in methanol-d_4 under neutral conditions, but attempts at Friedel-Crafts alkyation were unsuccessful Mono-demethylation, however, with lithium thiomethoxide[6,10] in DMF yielded the stable, crystalline **11** The ^{1}H NMR spectrum of **11** contained a resonance at 10 12 ppm, which could be attributed to a hydrogen-bonded phenol at C-6 This was proven correct from the ^{13}C NMR spectrum by the use of deuterium-induced isotope shifts,[11] which distinguished between **11** and its C-3 isomer β-Isotope shifts (2 bonds) were observed for the C-2, C-6, and C-7 resonances, as were γ-isotope shifts (3 bonds) for the C-1 and C-5 resonances Interestingly, an isotope shift was also

observed for C-4, in this case due to deuterium at C-5 (exchange of H-5 was observed in the ^1H NMR spectrum, as had been the case for **7**) Significantly, no β-isotope shift was observed for C-3 and only a slight line broadening due to the N-D substitution at C-2 was detectable, indicating C-3 bears the methoxyl group A further distinction between the β-shift transmitted through the hetero-atoms and that arising from the C-D substitution at C-5 was made by increasing the exchange rate When the sample was heated to 320 K, only broadened resonances for C-6 and C-2 were observed, whereas the two lines for C-4 remain unchanged Independent confirmation of the ^{13}C assignments was obtained from a ^1H-^{13}C long-range correlation experiment (LR-HETCOSY) [12] In this case, three-bond correlations between C-1 and C-5 with the phenolic hydrogen were observed, while C-3 - in addition to the correlation with H-5 - also showed one with the methoxyl hydrogens

While neither **11**, nor its anion, could be alkylated using Friedel-Crafts conditions alkylation of C-5 was accomplished by the use of a Claisen rearrangement Thus, **11** was treated with allyl bromide and anhydrous potassium carbonate in DMF to yield **12** (83%), which was rearranged in 95% yield by heating at 140 °C in ethylene glycol using a previously base-washed flask Catalytic reduction (H_2, Pd/C, 95 5%) then gave the propyl-substituted **13**.Oxidation of **13** with CAN then gave the quinone **14** in 97% yield Catalytic reduction of **14** in chloroform with PtO_2 under a hydrogen atmosphere provided a faint yellow solution of **15** from the original deep red color of **14** After 24 hours, exposure of the solution of **15** to O_2 was found to be sufficient to reoxidize it within seconds back to **14**, as evidenced by instant reappearance of a deep red color The product was pure by TLC, which indicated that penta-substituted **15**, analogous to the proposed intermediate **10** (Scheme 1), was stable in the absence of O_2 - a marked contrast to that of the tetra-substituted **5** Reduction of **14** with sodium dithionite in DMSO d_6/D_2O in an NMR tube allowed direct observation of **15** by ^{13}C NMR After 4 hours the two quinone carbonyl resonances at 182 95 and 181 91 ppm had disappeared, and the aromatic resonances had increased from four to six This mixture was stable for at least a week at room temperature and, after exposure to air, the quinone could be reisolated by extraction into ethyl acetate These efforts are summarized in Scheme 3

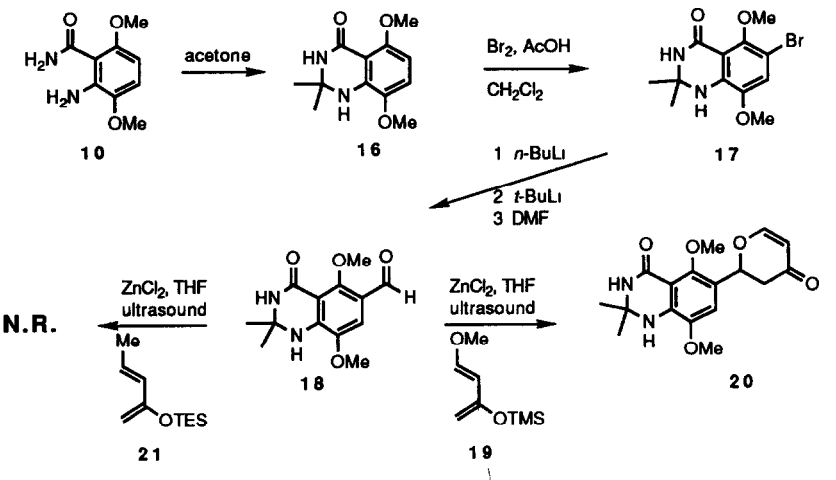
Scheme 3



Methodology was next developed which could be used to provide a series of C-glycosides analogous to **14** Of the approaches to the synthesis of C-aryl glycosides available in the recent literature,[13] Lewis acid mediated cyclocondensation of aldehydes[14,15] was adapted to the synthesis of ourtargets For preparation of the requisite aldehyde by lithiation, the presence of five acidic protons attached to the hetero-atoms of **10** presented a significant obstacle However, condensation with acetone led quantitatively to the acetaminal **16**, which simultaneously protected the aniline and the amide nitrogens and removed two acidic protons Bromination of **16** was next carried out in a mixture of Br_2 in acetic acid and CH_2Cl_2 Neutralization and reduction of excess Br_2, and of any N-brominated products which may have resulted, was affected with freshly prepared $Na_2S_2O_3$ in 5% $NaHCO_3$ The acetaminal protecting group was found to be very labile under the workup conditions but could be restored merely by heating the crude residue in acetone for 15 min, and **17** crystallized from the solution in 90% yield Treatment of **17** successively with *n*-BuLi (2 eq)

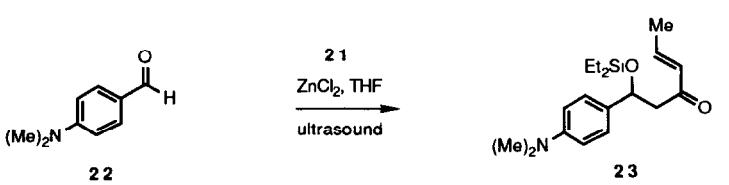
followed by *t*-BuLi (2 7 eq) at -78 °C generated the tri-lithio derivative, which was quenched with dimethylformamide after 2 5 hours to give analytically pure penta-substituted aldehyde **18** (79%) These efforts are summarized in Scheme 4

Scheme 4



It was anticipated that cycloaddition of aldehyde **18** and an appropriate diene could provide the pyran skeleton and the requisite *cis* relative stereochemistry between the methyl group and the C-8 hydrogen at the C-glycoside junction of **1** Cyclization of **18** with Danishefsky's diene[16] **19** was unsuccessful in the presence of various Lewis acids[14-17], but succeeded with $ZnCl_2$/ultrasound[18] catalysis in THF at room temperature The cycloaddition took place over a 2 hour period to yield the cycloadduct **20**, after deprotection of the silyl enol ether with trifluoroacetic acid Characteristic enone resonances at δ 7 49 and 5 46 (J = 6 Hz) as well as the benzylic resonance at δ 5 78 were observed in the ^{1}H NMR spectrum, and a resonance at 192 ppm in the ^{13}C NMR spectrum could be assigned to the enone carbonyl

The triethylsiloxydiene **21**[14] was next prepared from 3-penten-2-one Although *o*-methoxybenzaldehyde underwent a smooth cycloaddition with the diene **21** in the presence of $ZnCl_2$,[16] Reaction of **21** with **18** under the sonication conditions gave no reaction A model system was tested at this point to determine the electronic effect of the amino group on the reactivity of the benzaldehyde *p*-N,N-Dimethylbenzaldehyde, **22**, was mixed with **21** and $ZnCl_2$ in THF Reaction occurred only with sonication, in this case yielding an aldol product, apparently followed by a silyl group transfer to yield enone **23** The ^{13}C NMR spectrum for **23** exhibited a carbonyl resonance at 198 ppm, and resonances at 143 4 (β C) and 133 2 (α C) ppm, consistent with an enone system A coupling or 17 Hz between the α and β hydrogens in the ^{1}H NMR spectrum, indicating a *trans* relationship, further supported this assignment



The results obtained with the two *p*-aminobenzaldehyde derivatives **18** and **22** indicate that the amino group deactivates the aldehyde sufficiently to prevent a cycloaddition reaction with the less reactive diene **21** [19] Attempts to avoid this by derivatizing **18** with acetic anhydride or trifluoroacetic anhydride in triethylamine, or with methyl chloroformate or ethyl chloroformate in triethylamine, only resulted in extensive decomposition Apparently, the presence of the aldehyde of **18** is sufficient to deactivate the hindered amino group

The synthetic efforts presented here have demonstrated the feasibility of constructing the pyran skeleton of the 5-substituted C-glycoside targets While **18** did not prove to be sufficiently reactive, appropriate early derivatization of the amino group may provide increased solubility and reactivity sufficient for successful cycloaddition with the diene **21** The demonstration of the increased stability of the penta-substituted hydroquinone **15** over that of tetra-substituted **5** provided impetus for further synthetic efforts to construct C-glycosides in order to probe the advanced steps in the biosynthesis of **1** Additional efforts will be reported in the future While the results so far do not allow a distinction to be made between the putative pathways presented in Scheme 2, the chemical viability of pathways **A** and **B** have been established Given the clear differences in stability between **15** and **5**, pathway **B** seems more probable

Experimental

General Procedures ^{1}H NMR and ^{13}C NMR spectra were taken on a Bruker AM 400 or AC 300 spectrometer Sonications were carried out with a Branson 2000 Water Bath Sonicator High resolution mass spectra were taken on a Kratos MS 50 TC spectrometer Melting points were obtained on a Büchi melting point apparatus and are uncorrected Elemental analyses were performed by Desert Analytics (Tucson, AZ) Flash chromatography was carried out on silica gel (EM Reagents, Keiselgel 60, 230-400 mesh) or Silicar CC-4 (Mallinkrodt) Ion exchange resins were purchased from Sigma Chemical Company (St Louis, MO) All solvents were distilled prior to use

2,5-Dimethoxy-6-nitrobenzamide, 6 To a solution of 2,5-dihydroxybenzoic acid (29 00 g, 188 0 mmol) in ethanol (65 mL) and 50% aqueous KOH (25 mL) was added alternately portions of dimethyl sulfate (145 mL, 1530 mmol) and 50% aqueous KOH (150 mL) while maintaining the temperature at 50-60 °C After addition was complete the mixture was heated to 95 °C for 5 min to hydrolyze any excess dimethyl sulfate The mixture was cooled to 0 °C, diluted with water and extracted with ether The organic layer was washed with 1N NaOH, water, sat brine, dried over $MgSO_4$ and concentrated *in vacuo* to yield a light yellow, clear oil Distillation (106-107 °C/ 0 7 mm Hg) produced 33 03 g (89 9%) of the ester ^{1}H NMR ($CDCl_3$, 400 MHz) d 7 31 (d, J = 3 0, Hz, 1 H), 7 00 (dd, J = 8 9, 3 0 Hz, 1 H), 6 90 (d, J = 8 9 Hz, 1 H), 3 87 (s, 3 H), 3 84 (s, 3 H), 3 77 (s, 3 H), ^{13}C NMR ($CDCl_3$, 100 6 MHz) d 166 44, 153 42, 152 98, 120 49, 119 49, 115 92, 113 83, 56 70, 55 76, 52 00, MS (70 ev) *m/z* 196, M^+ (100), 181 (58), 165 (72), 150 (30), 129 (31), 86 (61), HRMS Calc for $C_{10}H_{12}O_4$ 196 07356 Found 196 07350 Methyl 2,5-dimethoxybenzoate (15 55 g, 80 0 mmol) was dissolved in concentrated NH_4OH (95 mL) and stirred overnight at room temperature The white mixture was cooled to 0°C and filtered, and the white residue washed with cold water and crystallized from hot water to give 13 79 g (96 0%) of white needles mp 141 0 -142 0 °C, ^{1}H NMR (acetone-d_6, 400 MHz) d 7 87 (br s, 1 H), 7 75 (d, J = 3 2 Hz, 1 H), 7 02 (dd, J = 9 0, 3 2 Hz, 1 H), 6 92 (d, J = 9 0 Hz, 1 H), 6 44 (br s, 1 H), 3 92 (s, 3 H), 3 82 (s, 3 H), ^{13}C NMR ($CDCl_3$, 100 6 MHz) d 166 91, 153 77, 152 14, 121 31, 120 00, 115 60, 112 99, 56 43, 55 78, MS (70 ev) *m/z* 181 (100), 165 (25), 135 (44), HRMS Calc for $C_9H_{11}NO_3$ 181 07393 Found 181 07393

To 2,5-dimethoxybenzamide (13 53 g, 74 75 mmol) was added 70% HNO_3 (240 mL, pre-cooled to -25°C) The mixture was allowed to stir to 15 °C over 50 min whereupon the yellow slurry was poured into cold water and filtered

Washing the yellow residue with water followed by crystallization from acetone yielded 15 36 g (91 8%) of **6** as yellow needles mp 225 0 - 226 0 °C, IR (KBr) 3382, 1654, 1531, 1370, 1270, 1054 cm^{-1}, ^1H NMR ($CDCl_3$, 300 MHz) d 7 90 (br s, 1 H), 7 75 (br s, 1 H), 7 33 (d, J = 9 3 Hz, 1 H), 7 28 (d, J = 9 3 Hz, 1 H), 3 82 (s, 3 H), 3 80 (s, 3 H), ^{13}C NMR ($CDCl_3$, 75 4 MHz) d 163 44, 149 33, 144 07, 139 11, 120 88, 115 43, 115 14, 57 09, 56 76, MS (70 ev) *m/z* 226 (100), 179 (38 9), 150 (62 5), 135 (38 2), 120 (92 8), 95 (67 2), 76 (73 7), Anal Calc for $C_9H_{10}N_2O_5$ C, 47 79, H, 4 46, N, 12 38 Found C, 47 49, H, 4 38, N, 12 26

3,6-Dimethoxyanthranilamide, 7 To a solution of 2,5-dimethoxybenzamide, **6**, (2 91 g, 12 9 mmol) in methanol (250 mL) was added 10% Pd/charcoal (100 mg), and the solution stirred under hydrogen for 3 h, until H_2 uptake had ceased The catalyst was filtered, and the clear, colorless solution evaporated *in vacuo* to yield a purple-white powder Crystallization from CH_2Cl_2/hexanes gave 2 43 g (96 5%) of **7** as colorless crystals mp 129 0 - 130 0 °C, IR ($CHCl_3$) 3530, 3400, 3000, 1640, 1610, 1570, 1240 cm^{-1}, ^1H NMR (methanol-d_4, 400 MHz) d 6 81 (d, J = 8 9 Hz, 1 H), 6 20 (d, J = 8 9 Hz, 1 H), 3 81 (s, 3 H), 3 79 (s, 3 H), ^{13}C NMR (DMSO-d_6, 100 6 MHz) d 169 50, 152 35, 141 42, 141 18, 111 73, 104 83, 96 25, 55 88, 55 72, MS (70 ev) *m/z* 196 (100), 179 (28 1), 164 (66 4), 136 (31 5), 89 (15 8), 61 (26 2), Anal Calc for $C_9H_{12}N_2O_3$ C, 55 10, H, 6 12, N, 14 29 Found C, 55 33, H, 5 95, N, 14 17

6-Hydroxy-3-methoxyanthranilamide, 11 To a solution of **7** (1 60 g, 8 2 mmol) in dry DMF (70 mL) was added lithium thiomethoxide[10] (1 81 g, 8 21 mmol), and the solution stirred at 80 °C for 14 h The volatiles were removed at aspirator pressure, and the residue dissolved in methanol and then diluted with ethyl acetate Saturated NH_4Cl was added immediately, and the phases separated Washing the organic layer with sat brine, followed by drying over Na_2SO_4 and concentration *in vacuo* yielded a green oil Crystallization from ethyl acetate produced 1 28 g (86 0%) of a light green powder mp 158 0 - 159 0 °C, IR (KBr) 3400, 3180, 1641, 1618, 1576, 1453, 1406, 1223, 1133, 823 cm^{-1}, ^1H NMR (DMSO-d_6, 400 MHz) d 10 11 (s, 1 H), 7 49 (br s, 2 H), 6 69 (d, J = 8 6 Hz, 1 H), 6 42 (br s, 2 H), 6 00 (d, J = 8 6 Hz, 1 H), 3 68 (s, 1 H), ^{13}C NMR (DMSO-d_6, 100 6 MHz) d 170 19, 150 83, 141 70, 139 99, 113 30, 102 63, 100 14, 56 05, MS (70 ev) *m/z* 182 (85), 165 (97), 150 (100), 122 (29), 94 (25), HRMS Calc for $C_8H_{10}N_2O_3$ 182 06920 Found 182 06920

3-Methoxy-6-(2-propenoxy)-anthranilamide, 12 To a solution of **11** (1 73 g, 9 51 mmol) in DMF (100 mL) was added powdered K_2CO_3 (2 36 g, 17 10 mmol) followed by allyl bromide (0 812 mL, 10 46 mmol) The green mixture was stirred for 3 h at room temperature After dilution with ethyl acetate, the mixture was washed with sat $NaHCO_3$ and then sat brine The organic layer was dried over Na_2SO_4 and concentrated to a dark oil, and crystallization from CH_2Cl_2/hexanes yielded 610 mg of **12** as brown crystals Chromatography of the mother liquor through a Silicar CC-4 column eluting with 1 3 ethyl acetate/CH_2Cl_2, followed by crystallization, gave an additional 285 mg The combined yield was 854 mg (82 9%) mp 119 0 - 120 0 °C, IR (KBr) 3400, 3000, 1651, 1634, 1557, 1404, 1257 cm^{-1}, ^1H NMR ($CDCl_3$, 400 MHz) d 7 92 (br s, 1 H), 6 69 (d, J = 8 5 Hz, 1 H), 6 54 (br s, 1 H), 6 09 (d, J = 8 5 Hz, 1 H), 6 05 (m, 1 H), 5 42 (ddd, J = 16 9, 1 4, 1 2 Hz, 1 H), 5 32 (ddd, J = 10, 1 4, 1 2 Hz, 1 H), 4 55 (dt, J = 6, 1 2 Hz, 2 H), 3 82 (s, 3 H), ^{13}C NMR ($CDCl_3$, 100 6 MHz) d 170 61, 152 14, 143 21, 142 31, 132 69, 118 63, 111 59, 103 42, 97 79, 70 43, 55 99, MS (FAB$^+$) m/z 223 (M^++1), UV MeOH) 343 2 (4 280), 254 4 (sh, 6 673), 233 6 (14 593), 209 6 nm (16 851), HRMS Calc for $C_{11}H_{14}N_2O_3$ 222 10052 Found 222 10050

6-Hydroxy-3-methoxy-5-propylanthranilamide, 13 The allyl ether **12** (400 mg, 1 80 mmol) was dissolved in ethylene glycol (45 mL) and heated to 145 °C for 20 min whereupon the dark brown solution was poured into CH_2Cl_2 and water (100 ml) added The aqueous phase was extracted 3 times with CH_2Cl_2, and the organics combined, washed with water, sat brine, and then dried over Na_2SO_4 Removal of the solvent *in vacuo* provided a single compound

as a brown cake in 99% yield which was greater than 95% pure by ^{1}H NMR analysis Attempts at crystallization led to some decomposition to an unidentifiable product This was therefore used without further purification mp 86 0° - 88 0 °C, ^{1}H NMR ($CDCl_3$, 300 MHz) d 11 75 (s, 1 H), 7 12 (br s, 2 H), 6 79 (s, 1 H), 6 00 (m, 1 H), 5 10 (m, 1 H), 5 05 (m, 1 H), 4 12 (br s, 2 H), 3 81 (s, 3 H), 3 35 (dt, J = 6 5, 1 2 Hz, 2 H), ^{13}C NMR ($CDCl_3$, 75 4 MHz) d 172 92, 153 10, 141 26, 136 88, 133 61, 118 47, 117 47, 115 48, 105 15, 56 73, 33 67, MS (FAB$^+$) *m/z* 223 (M^++1), HRMS Calc for $C_{11}H_{14}N_2O_3$ 222 10052 Found 222 10052

The crude allyl anthranilamide (400 mg, 1 80 mmol) was dissolved in methanol (30 mL) in a base-washed flask and a catalytic amount of 10% Pd/C was added The flask was placed on a hydrogenation apparatus at 1 atmosphere and stirred for 6 h until hydrogen uptake had ceased Filtration of the catalyst and removal of the solvent *in vacuo* provided a brown cake (395 mg) Decolorization by passage through a short Silicar CC-4 column followed by crystallization from CH_2Cl_2/hexanes yielded 375 mg (95 5%) of colorless crystals mp 115 0 - 116 0 °C, IR ($CHCl_3$) 3480, 2962, 1646, 1625, 1459, 1229 cm^{-1}, ^{1}H NMR (CD_2Cl_2, 300 MHz) d 11 96 (s, 1 H), 7 05 (br s, 2 H), 6 82 (s, 1 H), 4 04 (br s, 2 H), 3 80 (s, 3 H), 2 51 (t, J = 7 8 Hz, 2 H), 1 55 (tq, J = 7 8, 7 3 Hz, 2 H), 0 92 (t, J = 7 3 Hz, 3 H), ^{13}C NMR (CD_2Cl_2, 75 4 MHz) d 173 40, 153 86, 141 48, 133 41, 121 64, 118 26, 105 43, 57 16, 31 97, 23 30, 14 09, MS (70 ev) *m/z* 224 (36 3), 207 (93 4), 192 (80 7), 178 (100), 163 (24 6), 135 (17), 107 (10), UV (MeOH) 337 6 (3 676) 241 6 (12 478), 262 4 (sh 6 336), 205 6 nm (11 565), Anal Calc for $C_{11}H_{16}N_2O_3$ C, 58 91, H, 7 19, N, 12 49 Found C, 59 16, H, 7 12, N, 12 17

2-Amino-3-carboxamido-5-propyl-1,4-benzoquinone, 14 To a solution of the phenol **13** (100 mg, 0 446 mmol) in acetonitrile (25 mL) was added ammonium cerium (IV) nitrate (492 mg, 0 897 mmol) in water (5 mL) over 30 s The intense orange solution was diluted with ethyl acetate, washed 2 times with sat brine, and then dried over Na_2SO_4 Removal of the solvents under reduced pressure yielded a dark red solid which was passed through a Silicar CC-4 column, eluting with 60 40 ethyl acetate/hexanes The fractions containing the quinone were combined, and the solvent removed *in vacuo* to yield 90 mg (97 0%) of a deep red solid mp 139 0 - 140 0 °C, IR ($CHCl_3$) 3488, 3424, 1647, 1590, 1551, 1345 cm^{-1}, ^{1}H NMR (DMSO-d_6, 300 MHz) d 7 25 (br s, 2 H), 6 61 (s, 1 H), 4 10 (br s, 2 H), 2 46 (t, J = 7 0 Hz, 2 H), 1 56 (qt, J =7 4 Hz, 7 0, 2 H)), 0 97 (t, J = 7 4 Hz, 3 H), ^{13}C NMR (DMSO-d_6, 75 4 MHz) d 182 94, 181 91, 169 69, 154 26, 153 07, 128 34, 98 55, 31 50, 21 15, 13 68, UV (MeOH) 447 (1 065), 325 0 (1 055), 264 (8 807), 208 nm (10 300), MS (70 ev) *m/z* 208 (11 6), 163 (100), 148 (23 4), 106 (19 2), 68 (35 1), HRMS Calc for $C_{10}H_{12}N_2O_3$ 208 08486 Found 208 08480

Reduction and Reoxidation of Quinone 14 **a** The quinone **14** (8 0 mg, 0 0385 mmol) was dissolved in $CHCl_3$ and methanol (1 0 mL each) and PtO_2 (0 5 mg) added to the intense red solution The flask was purged with H_2, and stirred for 30 min A small aliquot was removed for TLC analysis after 2 h Application to silica gel resulted in the appearance of a red spot, indicating reoxidation of the substrate After development (2 1 ethyl acetate/$CHCl_3$), the quinone was apparent as the only spot (R_f 0 38) The light yellow mixture was stored under H_2 for 48 h, and the vessel was then purged with O_2, which caused the dirty yellow solution to instantly turn red Filtration and concentration yielded the quinone **14**

b To a solution of **14** in DMSO-d_6 (500 mL) in an Ar purged 5 mm NMR tube was added $Na_2S_2O_4$ (14 0 mg, 0 0804 mmol) dissolved in D_2O (100 mL) The tube was sealed and vortexed to give a light yellow solution After 4 h a ^{13}C NMR spectrum (75 4 MHz) was obtained The solution was kept at room temperature for 1 week, during which time ^{13}C NMR spectra were periodically obtained After 7 d, the solution was poured into ethyl acetate A red solution resulted, which was washed with sat brine, and dried over Na_2SO_4 Concentration of the solution *in vacuo* yielded the

quinone **14**, which was contaminated with a faint spot at lower R_f and some material that remained at the origin when analyzed by TLC (R_f 0 50, impurity R_f 0 44, 3 1 ethyl acetate/hexane) Hydroquinone **15** ^{13}C NMR (DMSO-d_6, 75 4 MHz) d 172 29, 162 20, 149 73, 143 32, 120 09, 113 61, 98 02, 31 7, 23 6, 14 61, (impurities 72 61, 19 25, 15 07)

2,3-Dihydro-5,8-dimethoxy-2,2-dimethylquinazolin-4-(1H)-one, 16 The amide **10** (2 35 g, 12 0 mmol) was dissolved in acetone, (30 mL), *p*-toluenesulfonic acid (5 mg) added, and the solution stirred overnight at room temperature The solvent was removed under reduced pressure and the white powder recrystallized from $CHCl_3$/acetone/hexane to yield 2 80 g (99 0%) of white crystals mp 194 5 - 195 5 °C, IR (KBr) 3410, 3250, 2941, 1660, 1642, 1517, 1250, 1107, 798 cm^{-1}, ^1H NMR ($CDCl_3$, 300 MHz) d 7 79 (d, J = 8 9 Hz, 1 H), 6 22 (d, J = 8 9 Hz, 1 H), 6 16 (br s, 1 H), 4 75 (br s, 1 H), 3 86 (s, 3 H), 3 81 (s, 3 H), 1 52 (s, 6 H), ^{13}C NMR ($CDCl_3$, 75 4 MHz) d 163 04, 154 73, 140 29, 138 59, 113 83, 103 75, 99 42, 66 87, 56 12, 55 93, 29 18, MS (70 ev) *m/z* 236 (34), 221 (100), 206 (13), 191 (23), 180 (14), 164 (10), 150 (15), 122 (8), 91 (15), UV_{max} (MeOH) 352 0 (3 786), 278 4 (3 603), 235 2 (15 131), 216 8 nm (22 220), HRMS Calc for $C_{12}H_{16}N_2O_3$ 236 11618 Found 236 11620

6-Bromo-2,3-dihydro-5,8-dimethoxy-2,2-dimethylquinazolin-4-(1H)-one, 17 The acetaminal **16** was dissolved in CH_2Cl_2 (35 mL) and Br_2 in acetic acid (6 49 M, 1 50 mL, 9 74 mmol) added over 2 min Complete reaction could be observed by the appearance of a dark color when the Br_2 was in excess The brown solution was stirred for an additional 5 min, then poured slowly into a solution saturated in $Na_2S_2O_3$ and $NaHCO_3$ Extraction of the aqueous mixture into CH_2Cl_2, followed by washing the organic layer with water and with sat brine, and then drying over $MgSO_4$ and concentrating *in vacuo* yielded a dark oil Analysis of the mixture by ^1H NMR revealed partial hydrolysis of the acetaminal group during workup The residue was dissolved in acetone (10 mL), *p*-toluenesulfonic acid (5 mg) was added, and the solution stirred overnight Hexane (5 mL) was added and the solution was then cooled slowly to -78 °C to yield 2 72 g (90 3%) of white crystals mp 197 0 - 198 0 °C, IR (KBr) 3200, 2930, 1670, 1598, 1506, 1356, 1228, 1071, 994 cm^{-1}, ^1H NMR (DMSO-d_6, 300 MHz) d 7 95 (br s, 1 H), 7 08 (s, 1 H), 6 28 (br s, 1 H), 3 78 (s, 3 H), 1 36 (s, 6 H), ^{13}C NMR (DMSO-d_6, 75 4 MHz) d 160 51, 150 23, 143,06, 138 67, 116 66, 108 02, 102 32, 66 58, 61 00, 56 14, 28 25, MS (70 ev) *m/z* 314 (23), 299 (100), 286 (25), 271 (28), 230 (22), 221 (20), 91 (78), UV_{max} (MeOH) 356 8 (3 055), 299 2 (3 502), 236 0 (21 052), 224 0 nm (23 027), HRMS calc for $C_{12}H_{15}BrN_2O_3$ 314 02665 Found 314 02660

2,2-Dimethyl-5,8-dimethoxy-1,2,3,4-tetrahydro-4-oxoquinazoline-6-carboxaldehyde, 18 To a solution of **17** (1 25 g, 3 97 mmol) in dry THF cooled to -78 °C and under an Ar atmosphere, was added tetramethylethylenediamine (1 80 mL, 11 92 mmol), followed by *n*-butyllithium (1 6 M in hexanes 5 5 mL, 8 74 mmol) After 10 min, *t*-butyllithium (1 7 M in pentane, 7 0 mL, 11 92 mmol) was added and the canary-yellow heterogeneous mixture stirred at -78 °C for 2 5 h The stirred mixture was treated with DMF (3 1 mL, 40 mmol) and then allowed to warm to room temperature overnight After careful addition of ethanol (5 mL), the mixture was diluted with ethyl acetate and washed with sat $NaHCO_3$, water, and then sat brine Drying the solution over Na_2SO_4 and evaporation *in vacuo* yielded a yellow powder, which was triturated with acetone (3 mL) to give analytically pure **18** (830 mg, 79 1%) mp 275 5 - 277 0 °C, IR (KBr) 3255, 3180, 2970, 1675, 1655, 1613, 1522, 1405, 1230, 993, ^1H NMR (DMSO-d_6, 300 MHz) d 10 03 (s, 1 H), 8 05 (br s, 1 H), 7 38 (br s, 1 H), 7 08 (s, 1 H), 3 82 (s, 6 H), 1 42 (s, 6 H), ^{13}C NMR (DMSO-d_6, 75 4 MHz) d 186 78, 160 87, 160 43, 144 98, 142 34, 117 02, 108 28, 104 42, 66 83, 63 86, 55 72, 28 62, MS (70 ev) *m/z* 264, M^+ (32), 249 (100), 206 (36), 192 (9), 150 (8), 91 (31), UV_{max} (MeOH) 352 8 (10 860), 320 8 (11 860), 277 2 (7 160), 240 4 nm (16 060), Anal Calc for $C_{13}H_{16}N_2O_4$ C, 59 08, H, 6 10, N, 10 60, Found C, 59 16, H, 6 03, N, 10 53

6-(1,2-Dihydro-4-oxo-4H-pyran-2-yl)-2,3-dihydro-5,8-dimethoxy-2,2-dimethylquinazolin-4-(1H)-one, 20 To a heterogeneous mixture of **18** (50 0 mg, 0 189 mmol) in anhydrous THF under Ar in a thick-walled

conical vial was added **19** (123 µL, 90%, 0 568 mmol, Aldrich Chemical Co) followed by $ZnCl_2$ (1 0 M in THF, 190 µL, 0 189 mmol) The mixture was sonicated in a water bath at room temperature for 1 h until **18** had dissolved and was no longer detected by TLC (ethyl acetate, R_f 0 18) whereupon the homogeneous solution was treated with a trace trifluoracetic acid, and poured into sat $NaHCO_3$ The aqueous phase was extracted 3 times with ethyl acetate, and the organic layer washed with sat brine and then dried over Na_2SO_4 After filtration the solvent was removed *in vacuo* to yield a brown powder which was purified via silica gel chromatography (1 0 X 8 cm) eluting with ethyl acetate This afforded 40 mg (64%) of a yellow powder IR (KBr) 3200, 2870, 1662, 1656, 1616, 1517, 1509, 1279, 1250, 1222, 1069 cm^{-1}, ^1H NMR (CD_2Cl_2, 300 MHz) d 7 49 (dd, J = 6 03, 0 80 Hz, 1 H), 6 94 (s, 1 H), 6 37 (br s, 1 H), 5 78 (dd, J = 14 86, 3 25 Hz, 1 H), 5 46 (dd, J = 6 03, 1 37 Hz, 1 H), 4 95 br s, 1 H), 3 86 (s, 3 H), 3 79 (s, 3 H), 2 88 (dd, J = 16 84, 14 87, 1 H), 2 50 (ddd, J = 16 85, 3 30, 1 35, 1 H), 1 53 (s, 6 H), ^{13}C NMR (CD_2Cl_2, 75 4 MHz) d 192 31, 163 86, 162 21, 152 35, 142 90, 139 60, 119 74, 111 52, 107 25, 107 09, 76 40, 67 32, 63 04, 56 26, 43 36, 29 35, 29 25, UV_{max} (MeOH) 353 6 (5 911), 240 0 (24 632), 222 4 nm (24 546), HRMS (FAB^+) Calc for 333 14503, Found 333 14502

1-[4-(N,N-Dimethylamino)phenyl]-1-triethylsiloxy-4-hexene-3-one, 23 A mixture of *p*-N,N-dimethylaminobenzaldehyde, **22**, (50 0 mg, 0 335 mmol) and the triethylsiloxy diene **21** (132 mg, 0 670 mmol) was added to a small, thick-walled conical vial After purging with N_2, $ZnCl_2$ (1 0 M in THF, 0 50 mL, 0 503 mmol) was added, and the reaction stirred for 30 min Periodic analysis by TLC (2 1 ethyl acetate/hexanes, R_f aldehyde 0 51, diene 0 69) showed only starting material The mixture was then sonicated for 20 min in a water bath at 20 °C The reaction was monitored by TLC, and terminated by dilution with 5% $NaHCO_3$ followed by ethyl acetate when no more starting material could be detected Washing the organic layer with sat brine, drying with $MgSO_4$, and concentration of the solution *in vacuo* yielded a dark oil This was purified by passage through a small silica gel column eluting with 2 1 ethyl acetate/hexanes to yield 74 1 mg (64%) of **23** as a light yellow oil IR (Neat) 2953, 1688, 1675, 1616, 1522, 1350, 1073, 743 cm^{-1}, ^1H NMR ($CDCl_3$, 400 MHz) d 7 22 (d, J = 8 48, 1 H), (6 83 dq, J = 17 37, 6 92 Hz, 1 H), 6 68 (d, J = 8 45 Hz, 1 H), 6 12 (dq, J = 17 39, 1 50 Hz, 1 H), 5 13 (dd, J = 8 60, 4 10 Hz, 1 H), 3 07 (dd, J = 16 69, 8 77 Hz, 1 H), 2 94 (s, 6 H), 2 59 (dd, J = 14 69, 4 30 Hz, 1 H), 1 88 (dd, J = 6 92, 1 51 Hz, 1 H), 0 82 (t, J = 7 72 Hz, 9 H), 0 49 (q, J = 7 75 Hz, 6 H), ^{13}C NMR ($CDCl_3$, 100 6 MHz) d 198 58, 150 46, 143 36, 133 17, 133 02, 127 03, 112 43, 71 98, 51 30, 40 76, 18 39, 6 86, 4 98, UV_{max} (MeOH) 356 (1 300), 292 (4 511), 256 (25 585), 208 nm (29 633), HRMS (FAB^+) Calc for 348 23603 Found 348 23602

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19 One referee suggested that Zn^{2+} coordination with the less hindered NMe_2 of **18** might be responsible for the aldol product