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Synthesis of a model system for the preparation of phloroglucinol containing natural products

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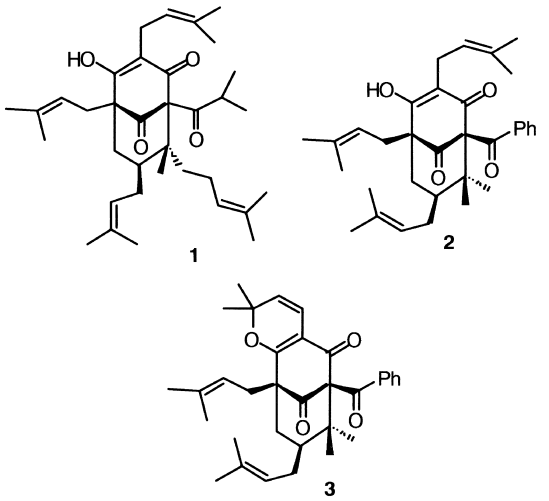
Abstract—A model system for the synthesis of phloroglucinol containing natural products was synthesized. Key steps include a manganic acetate-mediated cyclization and the facile conversion of an alkene into a β-bromoenone.

Natural products bearing a heavily substituted phloroglucinol subunit are common secondary metabolites.[1] Recently, this class of compounds has received considerable synthetic attention.[2] The natural product hyperforin (**1**) was isolated from *H. perforatum*.[3] Nemorosone (**2**) was recently isolated.[4] Their challenging structure and potentially-useful biological activity combine to make these compounds attractive synthetic objectives. Hyperforin is a reactive compound that undergoes cyclization reactions in the presence of oxygen. The enolic β-diketone subunit reacts with the prenyl groups to form hydroxyalkyl tetrahydrofuran units or pyran units as in **3**.[5]

Recently, researchers have reported that hyperforin may be responsible for the beneficial effects of St. John's wort, a botanical dietary supplement, on mild depression.[6] Other studies related to the pharmacology of hyperforin have also been reported.[7] In order to understand the effect that changes in structure exert on the biological activity of hyperforin, we have developed an efficient synthesis of the core unit contained in **1**.

Our initial approach began with diketone[8] **4**. Initially, the Michael addition of acrolein using base catalysis (DBU, CH_2Cl_2; TMG, CH_2Cl_2; powdered KOH; Triton B, *tert*-butanol; K_2CO_3, proline, MeOH, acetone) proceeded in low yield. The product was co-produced with the dimer of acrolein. The use of sodium methoxide in methanol at −78°C with a trace of hydroquinone improved the yield of the reaction to 55% yield.[9] Cyclization to the bicyclic hydroxy diketone with HCl in acetone followed by oxidation of the mixture of diastereomeric alcohols using PCC afforded the triketone **5** in 62% yield. Conversion of triketone **5** into the corresponding enol silyl ether followed by palladium catalyzed oxidation[10] provided enone **6**. Unfortunately, all attempts to transform either enone **6** or its corresponding epoxide into β-diketone **7** using palladium catalysts[11] afforded either starting material or decomposition products (Scheme 1).



Our next approach began with keto ester **8**. Alkylation of **8** with allyl bromide and intramolecular cyclization using manganic triacetate and cupric acetate using the Snider[12] protocol provided keto ester **9** in 60% yield. The [3.3.1]bicyclononane ring system was the major product. The isomeric [3.2.1]bicyclooctane was produced in less than 5% yield.[13] Allylic oxidation of the alkene in **9** using PCC, SeO_2 or PDC was not selective. After several experiments, the bicyclic keto ester **9** was converted into the dibromide **10** in 85% yield using 2.2 equiv. of NBS and a catalytic amount of AIBN. The structural assignment of dibromide **10** was supported by the absence of coupling between the bridgehead hydrogen and the methine hydrogen alpha to the bromine atom. The reaction of **10** with

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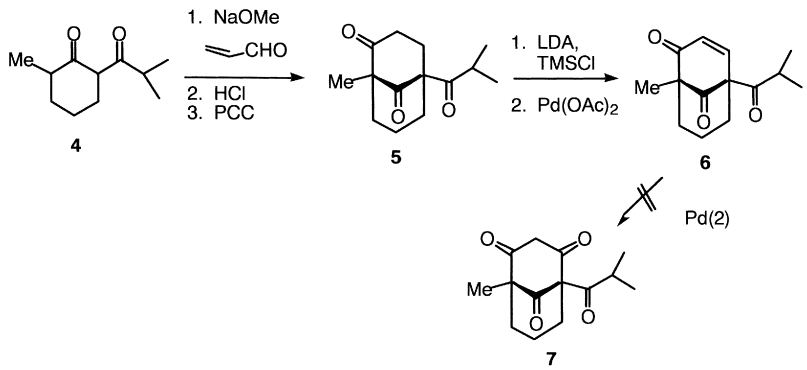
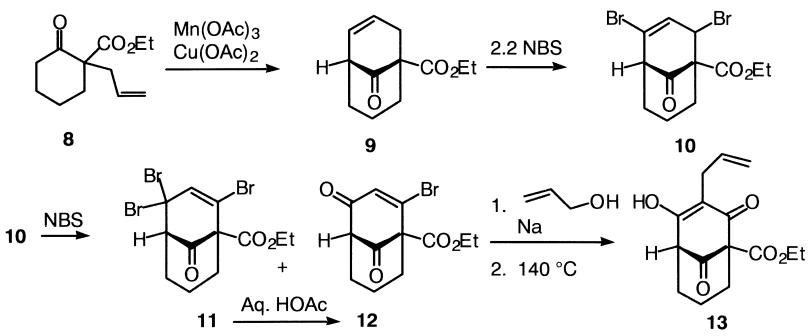
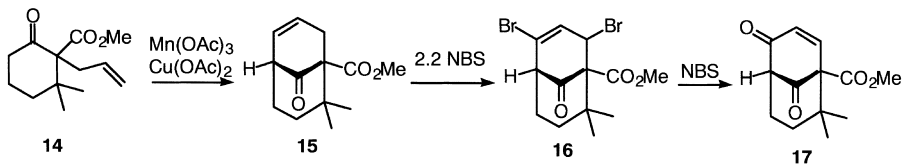


Scheme 1.



Scheme 2.

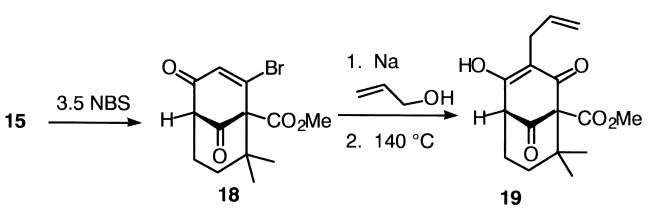


Scheme 3.

1.1 equiv. of NBS then produced a mixture of the bromo enone **12** and the tribromide **11**. Interestingly, the reaction of keto ester **9** with 3.3 equiv. of NBS afforded **11** and **12** directly, but in lower yield. The tribromide **11** was transformed into enone **12** with aqueous acetic acid at 115°C. Overall, **12** could be obtained in 95% yield. The reaction of **12** with the sodium salt of allyl alcohol followed by heating in a sealed tube in toluene at 140°C to effect the Claisen rearrangement provided triketone **13** in 45% overall yield from **12**. The structure of **13** was established by proton NMR, carbon NMR, IR, and mass spectrometry (Scheme 2).[14]

The next objective was the preparation of an advanced intermediate bearing the geminal dimethyl group. We were concerned that the geminal dimethyl group might inhibit the formation of the tribromide analogous to compound **11**. The starting material was the known keto ester **14**. This compound had been prepared in three steps by Rothberg in his synthesis of dehydroambliol-A.[15] Intramolecular cyclization with manganic triacetate and copper acetate produced predominately the [3.3.1]bicyclononane ring system **15**. The product from the reaction of **15** with 2.2 equiv. of NBS was the dibromide **16**. To our surprise, treatment of **16** with another equivalent of NBS afforded enone **17**. Apparently, the effect of geminal dimethyl substitution is to render the allylic bromide moiety in **16** more susceptible to conversion to **17** (Scheme 3).

Bromination of **15** with 3.5 equiv. of NBS in the presence of molecular sieves directly afforded the bromo enone **18** in 55% yield. In this case, the tribromide was not isolated. The ^{13}C NMR spectrum supported the production of one regioisomer. The structure for **18** was assigned because the chemical shift of the bridgehead hydrogen in **18** was similar to that of the bridgehead hydrogen in a model system.[16] Substitution of the bromide with sodium allyloxide followed by a Claisen rearrangement at 140°C produced β-diketone **19** from **18** (Scheme 4).



Scheme 4.

The use of the bromination/hydrolysis strategy efficiently introduces the β-diketone subunit into the bicyclic ring system. With suitably protected prenyl groups at the bridgehead and the three-carbon bridge, this strategy is expected to be applicable to the synthesis of **1** or **2**. Compounds **13** and **19** have been submitted for biological evaluation.

1. Experimental

1.1. Data for compounds

1.1.1. 5-(1-Oxo-2-methylpropyl)-1-methylbicyclo[3.3.1]-nonane-2,9-dione (5). A solution of 1.96 g (35 mmol) of acrolein and 4.55 g (25 mmol) of **4** in 10 mL of diethyl ether was added dropwise at −60°C over a period of 2 h to sodium methoxide (prepared from 10 mg of Na in 15 mL of MeOH) containing 10 mg of hydroquinone. The resulting mixture was kept at −60°C for another hour and then warmed to rt (25°C). Neutralization with AcOH followed by removal of the solvent under reduced pressure gave a residue that was dissolved in 20 mL of ether. The ether layer was washed successively with brine, satd. $NaHCO_3$, and brine, and dried over anhydrous $MgSO_4$. The residue after concentration in vacuo was purified by silica gel column chromatography using 5:1 hexane–ethyl acetate to provide the adduct.

A solution of 3.29 g (13.8 mmol) of adduct in acetone (40 mL) containing 6N HCl (4 mL) was heated under reflux for 40 min. After removing the acetone, the residue was dissolved in 20 mL of ethyl acetate. The ethyl acetate layer was washed successively with brine, satd. $NaHCO_3$, and brine and dried. The crude material was purified by column chromatography using 4:1 hexane–ethyl acetate to provide the aldol.

To a solution of 238 mg (1 mmol) of the aldol in CH_2Cl_2 (10 mL) were added 431 mg (2 mmol) of PCC and Celite (431 mg) at rt. The mixture was stirred at rt for 3 h. It was then filtered and concentrated. The crude material was purified by column choromatography using 4:1 hexane–ethyl acetate to provide the triketone **5**.

^{1}H NMR (300 MHz, $CDCl_3$) 1.13 (dd, J=6, 6.3 Hz, 6H), 1.20 (d, J=6 Hz, 3H), 1.60–1.78 (m, 4H), 1.97–2.03 (m, 1H), 2.26–2.38 (m, 2H), 2.40–2.49 (m, 1H), 2.65–2.72 (m, 1H), 2.82–2.90 (m, 1H), 2.94 (septet, J=6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) 17.3, 19.6, 20.5, 20.6, 22.8, 38.2, 38.3, 39.5, 42.8, 63.0, 211.7, 211.7, 213.7. HRMS (EI) m/z calcd for 236.1413, found 236.1412.

1.2. Oxidative cyclization with $Mn(OAc)_3$ and $Cu(OAc)_2$

To a stirred solution of $Mn(OAc)_3$ dihydrate (2 equiv.) and $Cu(OAc)_2$ monohydrate (1 equiv.) in degassed glacial acetic acid at rt, was added a solution of keto ester (1 equiv.) in glacial acetic acid. The mixture was stirred at 80°C for 16 h. After normal aqueous work-up, the crude material was purified by column chromatography.

1.2.1. Compound 9. Identical to that reported in Ref. 12.

1.2.2. Compound 15. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82–5.78 (1H, m), 5.57–5.51 (1H, m), 3.65 (3H, s), 3.07–2.81 (3H, m), 2.06–1.97 (2H, m), 1.57–1.53 (1H, m), 1.19–1.10 (1H, m), 1.07 (3H, s), 1.03 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.8, 171.2, 129.5, 127.0, 64.8, 51.9, 46.7, 42.8, 36.2, 33.4, 28.5, 25.6, 25.0.

1.3. Dibromination with NBS

To a solution of alkene (1 equiv.) in CCl_4, was added AIBN (0.1 equiv.) and NBS (2.2 equiv.). The flask was fitted with a reflux condenser and irradiated with a sun lamp. After 30 min (monitored by TLC), the mixture was allowed to cool to rt and filtered. The crude material was purified by column chromatography to yield the pure dibromide.

1.3.1. Compound 10. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.52 (1H, d, J=3.0 Hz), 5.71 (1H, d, J=3.0 Hz), 4.28 (2H, q, J=9.0 Hz), 3.21 (1H, t, J=3.0 Hz), 2.60–1.66 (6H, m), 1.31 (3H, t, J=9.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.7, 168.7, 132.3, 120.3, 63.0, 62.4, 56.2, 52.3, 36.6, 31.2, 16.7, 14.1.

1.3.2. Compound 16. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (1H, dd, J=12.0, 3.0 Hz), 5.67 (1H, d, J=12.0 Hz), 3.74 (3H, s), 3.48–3.51 (1H, m), 2.42–2.50 (1H, m), 2.08 (1H, tt, J=12.0, 3.0 Hz), 1.85 (1H, dt, J=12.0, 3.0 Hz), 1.31 (3H, s), 1.10–1.20 (1H, m), 1.05 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 168.5, 137.1, 124.6, 65.5, 63.5, 63.1, 52.7, 44.4, 34.2, 30.9, 25.9, 22.9.

1.4. Bromination with NBS and hydrolysis to β-bromo enones

To a solution of dibromide (1 equiv.) in CCl_4, was added AIBN (0.1 equiv.) and NBS (1.2 equiv.). The flask was fitted with a reflux condenser and irradiated with a sun lamp. After 30 min (monitored by TLC), the mixture was allowed to cool to rt and filtered. The crude material was a mixture (1:1) of tribromide and enone. Then 50% aqueous AcOH was added and boiled for 2 h. After aqueous workup, the enone was purified by column chromatography.

1.4.1. Compound 11. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (1H, s), 4.24–4.35 (2H, m), 3.56–3.58 (1H, m), 2.56–2.63 (1H, m), 1.60–2.31 (5H, m), 1.30 (3H, t, J=9.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.1, 167.7, 139.3, 120.4, 66.4, 63.7, 62.5, 58.9, 36.9, 34.8, 17.2, 14.2.

1.4.2. Compound 12. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (1H, s), 4.32 (2H, q, J=6.0 Hz), 3.41 (1H, t, J=3.0 Hz), 2.36–1.61 (6H, m), 1.35 (3H, t, J=9.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 193.5, 167.3, 146.3, 137.1, 68.6, 62.7, 61.8, 33.7, 32.9, 17.8, 14.2.

1.4.3. Compound 17. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (1H, d, J=12.0 Hz) 6.52 (1H, dd, J=9.0 Hz), 3.78 (3H, s), 3.37 (1H, t, J=3.0 Hz), 2.16–2.27 (1H, m), 1.95–2.02 (1H, m), 1.81 (1H, dt, J=12.0, 3.0 Hz), 1.37 (3H, s), 1.27–1.34 (1H, m), 1.11 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2, 197.4, 168.3, 148.2, 131.9, 68.4, 62.3, 52.8, 42.2, 34.7, 27.8, 26.4, 22.9.

1.4.4. Compound 18. To a solution of bicyclic olefin and crushed molecular sieves in dry CCl_4, was added dry NBS (3.5 equiv.) and AIBN (0.3 equiv.). The flask was fitted with a reflux condenser and irradiated with a sun lamp. After 1 h (monitored by TLC), the mixture was allowed to cool to rt and filtered. The crude material was purified by column chromatography to yield the bromo enone in 55% yield.

1.4.5. Compound 18. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (1H, s), 3.79 (3H, s), 3.36–3.38 (1H, m), 2.47–2.49 (1H, m), 2.15–2.23 (1H, m), 1.98–2.03 (1H, m), 1.48 (3H, s), 1.36–1.45 (1H, m), 1.31 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.8, 193.5, 166.7, 146.1, 137.5, 74.0, 60.6, 52.5, 42.7, 34.7, 28.4, 26.7, 22.2.

1.5. Addition of sodium allyloxide and thermal Claisen rearrangement

To a solution of allyl alcohol (20 equiv.) at 0°C, was added freshly cut sodium metal (1.2 equiv.). Enone (1 equiv.) in allyl alcohol was added and the mixture was allowed to stir for 1 h. After aqueous work-up, the crude material was purified by column chromatography. The allyl enol ether was then dissolved in dry toluene and placed in a sealed tube, where it was heated at 140°C for 7 h. Compound was purified by column chromatography.

1.5.1. Compound 13. FTIR (film) 1733, 1710, 1678, 1572 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98–5.90 (1H, m), 5.35–5.21 (2H, m), 4.18 (2H, q, J=9.0 Hz), 3.53 (1H, t, J=4.5 Hz), 3.33 (2H, d, J=6 Hz), 2.51–2.31 (2H, m), 2.14–1.95 (2H, m) 1.79–1.73 (2H, m) 1.27 (3H, t, J=4.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 164.9, 164.5, 154.0, 135.4, 118.01, 110.9, 101.0, 61.8, 43.8, 28.5, 26.5, 20.7, 19.2, 14.4. HRMS (EI) m/z calcd for 278.11542, found 278.11610.

1.5.2. Compound 19. FTIR (film) 1737, 1701, 1650, 1572 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94–5.89 (1H, m), 5.37–5.27 (2H, m), 3.67 (3H, s), 3.35–3.33 (1H, m), 3.31–3.28 (2H, m), 2.20–2.16 (1H, m), 2.01–1.94 (1H, m), 1.72–1.64 (1H, m), 1.39–1.30 (1H, m), 1.25 (3H, s), 1.19 (3H, s). HRMS (EI) m/z calcd for 292.1311, found 292.1316.

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16. The model system is shown below