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Synthesis of the core bicyclic system of hyperforin and nemorosone

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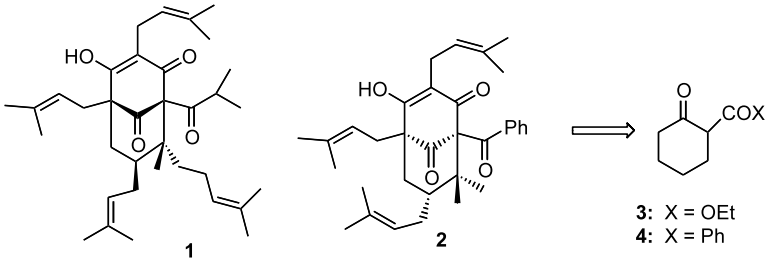
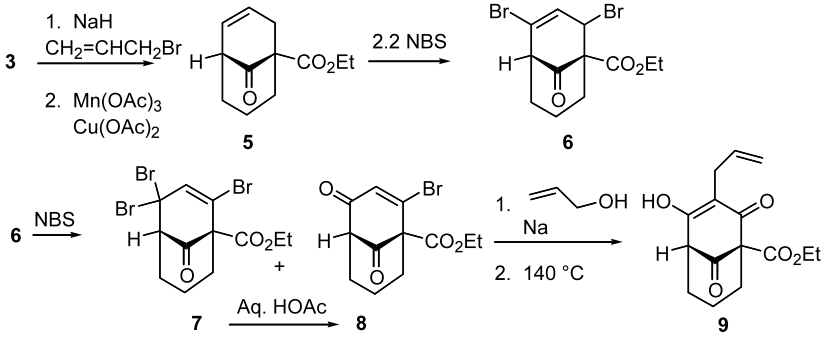
Abstract—A direct synthesis of analogs of hyperforin and nemorosone containing the key bicyclic unit was accomplished from 2-carboxyethylcyclohexanone and benzoylcyclohexanone. Key steps included a manganic acetate-mediated cyclization and the formation of the beta-bromo enone. © 2003 Published by Elsevier Science Ltd.

Natural products bearing a heavily substituted phloroglucinol subunit are common secondary metabolites.[1] Despite their abundance, this class of compounds has received little synthetic attention until the past three years.[2] The natural product hyperforin (**1**) was isolated from *H. perforatum*.[3] Recently, researchers have reported that hyperforin may be responsible for the beneficial effects of St. John's wort, a commonly used botanical dietary supplement, on mild depression.[4] Nemorosone (**2**) was recently isolated.[5] 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 units contained in **1** and **2**.



Our synthetic route began with the commercially available keto ester **3**. Alkylation with allyl bromide[6] followed by intramolecular cyclization using manganic triacetate and cupric acetate according to the method of Snider[7] gave keto ester **5** in 56% yield. The keto ester **5** was converted into the dibromide **6** in 85% yield using 2.2 equiv. of NBS and a catalytic amount of AIBN. Reaction



Scheme 1.

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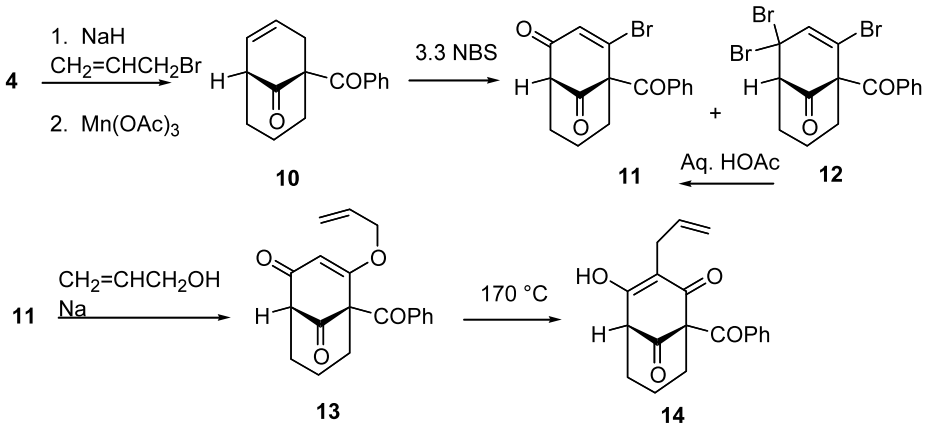

Scheme 2.

of **6** with 1.1 equiv. of NBS then produced a mixture of the bromo enone **8** and the tribromide **7**. The reaction of keto ester **5** with 3.3 equiv. of NBS afforded **7** and **8** directly, but the isolation was complicated by an unidentified polar byproduct that was not present when the conversion was conducted in two steps. The tribromide **7** could be transformed into enone **8** by heating in aqueous acetic acid. Overall, **8** could be obtained in 95% yield. The reaction of **8** 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 **9** in 45% overall yield. The structure of **9** was established by both proton and carbon NMR, IR and high resolution mass spectrometry (Scheme 1).[8]

We next examined a route to an analog of nemorosone. The diketone **4**[9] was alkylated with sodium hydride and allyl bromide in boiling THF in 60% yield. Cyclization with manganic acetate afforded **10** in 76% yield. Treatment of **10** with 3.3 equiv. of NBS and a catalytic amount of AIBN gave a mixture of enone **11** and tribromide **12**. Tribromide **12** was readily converted into **11** using hot aqueous acetic acid. Enone **11** was prepared in an overall yield of 52%. Displacement of the bromide in **11** using sodium allyloxide provided **13** which was heated in a sealed tube at 170°C to afford tetraketone **14** via a Claisen rearrangement. The structure assignment of **14** was supported by proton NMR, carbon NMR, IR and high resolution mass spectrometry (Scheme 2).[10]

The synthesis of **9** and **14** in good overall yields constitutes a useful preparation of analogs of hyperforin and nemorosonone.[9] The synthetic route is direct and is flexible enough to be extendable to a synthesis of the natural products.

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8. FTIR (thin film) 1733, 1710, 1678, 1572 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.98–5.90 (m, 1H), 5.35–5.21 (m, 2H), 4.18 (q, $J=9$ Hz, 2H), 3.53 (t, $J=4.5$, 1H), 3.33 (d, $J=6$ Hz, 2H), 2.51–2.31 (m, 2H), 2.14–1.95 (m, 2H), 1.79–1.73 (m, 2H), 1.27 (t, $J=4.5$ Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.73, 164.90, 164.52, 154.02, 135.38, 118.01, 110.85, 100.97, 61.79, 43.78, 28.54, 26.52, 20.66, 19.15, 14.39; HRMS (EI) m/z calcd for 278.11610, found 278.11542.
9. Compound **4** was prepared from the reaction of the morpholine enamine of cyclohexanone with benzoyl chloride.

10. FTIR (thin film) 1682, 1635, 1596, 1569 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, $J=8$ Hz, 2H), 7.61 (t, $J=7.5$, 1H), 7.50 (t, $J=7.8$, 2H), 6.02–5.89 (m, 1H), 5.36–5.20 (m, 2H), 4.57 (t, $J=5.4$, 1H), 3.32 (d, $J=6.3$, 2H), 2.59–2.50 (m, 1H), 2.40–2.30 (m, 1H), 2.13–2.03 (m, 2H), 1.79–1.67 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 198.27, 164.95, 164.74, 155.23, 135.51, 135.39, 133.87, 129.06, 128.89, 117.84, 111.88, 100.86, 45.24, 28.46, 26.70, 20.51, 18.57; HRMS (EI) m/z calcd for 310.12051, found 310.12098.