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Progress towards the synthesis of papuaforin A: selective formation of α-bromoenones from silyl enol ethers

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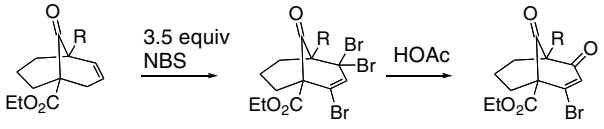
Abstract—The selective one-pot conversion of enol silyl ethers into α-bromoenones allows a direct preparation of a tricyclic intermediate to papuaforin A.

The antidepressant activity of *Hypericum perforatum*, commonly known as St. John's wort, has drawn much attention.[1–4] St. John's wort is used as a natural remedy to treat moderate to mild depression. Studies of the constituents of St. John's wort and other plants from the family Guttiferae identified a novel class of natural products, polycyclic polyprenylated acylphloroglucinols (PPAPs). Due to their significant biological activity and challenging structures, members of this class have become attractive synthetic targets and are shown in Figure 1.[5] Hyperforin (**1**) was isolated from *H. perforatum*,[6] and is thought to be responsible for the antidepressant and antibacterial activities of St. John's wort.[6–10] Nemorosone (**2**) shows cytotoxic activity against epithelioid carcinoma (HeLa), epidermoid carcinoma (Hep-2), prostate cancer (PC-3), and central nervous system cancer (U251).[11] Papuaforin A (**3**), extracted from *Hypericum papuanum* (Papua New Guinea), shows moderate cytotoxic activity towards the KB cell line ($IC_{50} = 4.9$ μg/mL) and modest antibacterial activity against *Micrococcus luteus*, *Staphylococcus epidermidis*, and *Bacillus cereus*.[12] As part of a program to synthesize bioactive constituents from *Hypericum* and *Echinacea* species,[13] we report herein the construction of an advanced intermediate for the synthesis of papuaforin A.

The 2,2-dimethyl-2*H*-pyran ring contained in **3** is formed by cyclization of a prenyl side chain onto the β-diketone. Initial experiments to prepare this β-diketone focused on the allylic bromination of an alkene to produce the tribromide shown below which readily hydrolyzed to a β-bromo enone. Unfortunately, when more highly congested systems were evaluated (R = alkyl), the enone (the product of dibromination followed by hydrolysis) rather than the β-bromo enone became the major product.



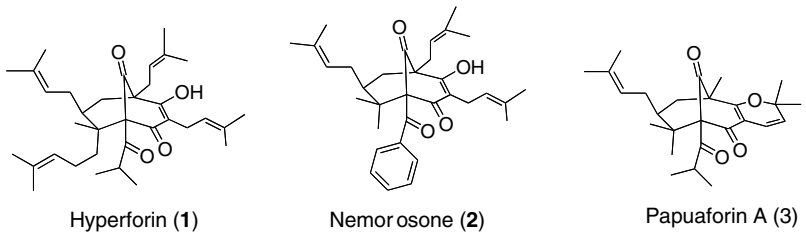


Figure 1. Polycyclic polyprenylated acylphloroglucinols (PPAPs).

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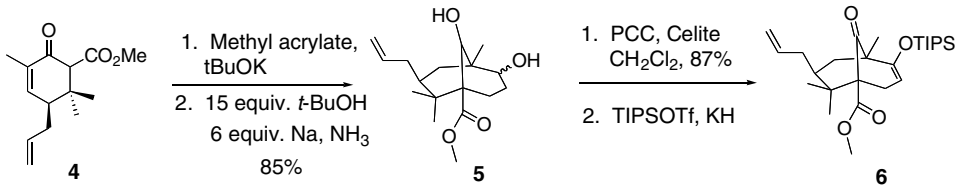
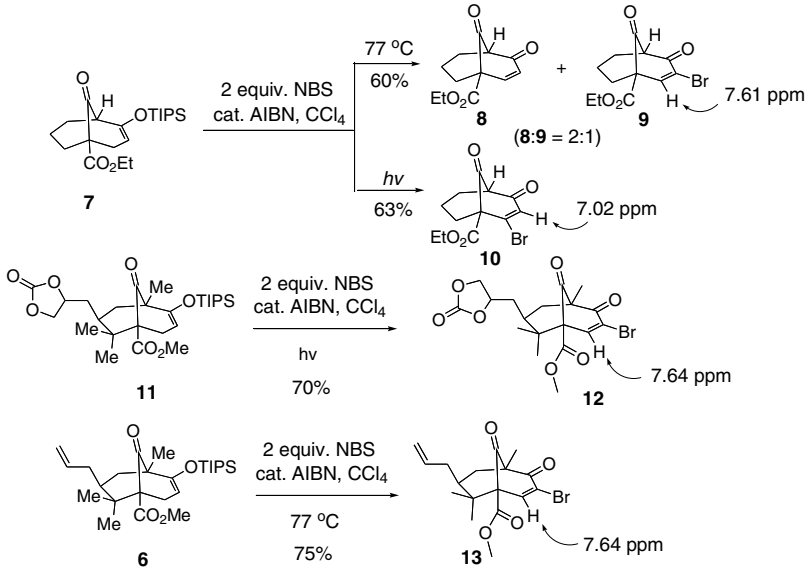


Scheme 1. Synthesis of silyl enol ether **6**.

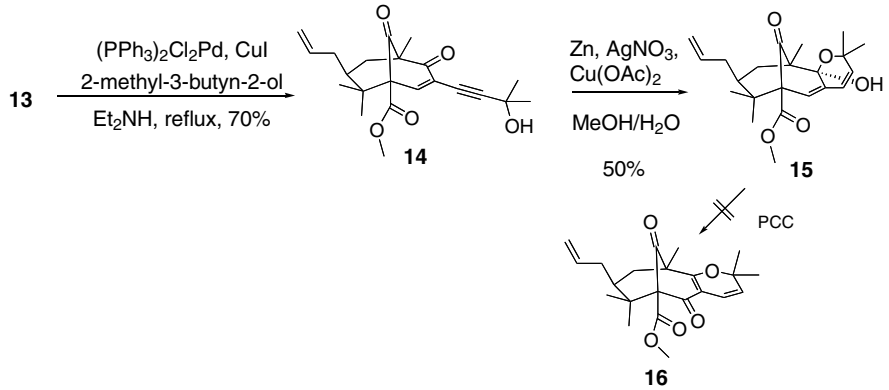


Scheme 2. Synthesis of bromoenones.

To generate an α-bromoenone, the TIPS enol ether **6** was prepared as shown in Scheme 1 from keto ester **4**[14] by Michael addition followed by Birch reduction/cyclization[15] to generate diol **5**. This compound was oxidized with PCC and the resulting diketone was silylated to provide **6** using KH and triisopropylsilyl triflate.[16]

Initial model studies were conducted on silyl enol ether **7**, prepared from the diketo ester and triisopropylsilyl triflate. As shown in Scheme 2, the radical bromination of **7** under thermal conditions afforded a mixture of enone **8** and α-bromoenone **9** in a 2:1 ratio in 60% yield. In contrast, bromination under photochemical conditions generated β-bromoenone **10** in 63% yield, as evidenced by the resonance at 7.02 ppm. Photochemical bromination of **11** produced α-bromo ketone **12** in 70% yield. Its structure was supported by a resonance at 7.64. The additional steps involved in forming the carbonate and later regenerating the allyl group, prompted us to examine the selective bromination of **6**, the precursor to **11**. The radical bromination under photochemical conditions was not clean, but the thermal conditions allowed a 75% yield of α-bromoketone **13**.[17]

The approach to **3** from **13** began with the Sonogashira reaction shown in Scheme 3. This reaction failed when conducted under the typical reaction conditions;



Scheme 3. Synthesis of an advanced intermediate.

however, when diethylamine was used as the solvent, a 70% yield of acetylenic ketone **14** was obtained. Reduction[18] of the triple bond to afford **15**[19] was achieved in 50% yield. The assignment of the stereochemistry of the hemiketal is tentative, but the resistance of the hydroxyl group to acetylation supports the assignment of the hydroxyl group to the more hindered face. Pyridinium chlorochromate oxidation[20] has been used to convert a tertiary allylic alcohol to the rearranged enone. Unfortunately, PCC oxidation of **15** did not produce the desired ketone **16**.

The radical bromination of enol silyl ethers generates α-bromoenones in good yields. Compound **13** was transformed into a tricyclic intermediate to **3** via Sonogashira coupling and reduction. The conversion of **15** into **16** by rearrangement followed by oxidation is in progress.

Acknowledgments

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14. Compound **4** was prepared from 3-methoxy-2,5,5-trimethylcyclohexenone (Clark, R. D.; Ellis, J. E.; Heathcock, C. H. *Synth. Commun.* **1973**, *3*, 347–54) by alkylation (LiTMP, allyl bromide, THF), LAH reduction followed by 10% aq HCl, and carboalkoxylation (LiTMP, $CNCO_2Me$).
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16. *Representative experimental for conversion of ketones to bromoenones*: To a stirred solution of KH (2 g, 30% in mineral oil, 15 mmol, mineral oil was removed with hexane prior to use) in THF (20 mL) were added a solution of the diketone (1.46 g, 5 mmol) and triisopropylsilyl triflate (2.7 mL, 10 mmol) in THF (10 mL), and stirred for 12 h. The reaction was diluted with saturated $NaHCO_3$ (20 mL) and extracted with ethyl acetate (15 mL × 3). The combined organic phase was washed with water, brine, and dried over $MgSO_4$. The residue was purified by silica gel chromatography (EtOAc/hexanes, 1:30) to give the silylated compound. This compound was dissolved in CCl_4 (20 mL), followed by the addition of NBS (3.56 g, 10 mmol) and AIBN (82 mg, 0.5 mmol). The mixture was boiled for 1 h, cooled to rt, diluted with aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (20 mL × 2). The combined organic layers were washed with brine and dried over $MgSO_4$. The residue was purified by chromatography on silica gel (EtOAc/hexanes, 1:7) to furnish **13** (1.31 g, 71%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (s, 1H), 5.67–5.53 (m, 1H), 5.04–4.98 (m, 2H), 3.80 (s, 3H), 2.31–2.25 (m, 1H), 2.02–1.96 (m, 1H), 1.74–1.63 (m, 2H), 1.51–1.41 (m, 1H), 1.31 (s, 3H), 1.20 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 191.5, 167.6, 146.4, 136.1, 125.5, 117.7, 71.1, 63.2, 53.0, 45.0, 42.0, 40.4, 34.0, 24.1, 16.7, 16.6; HRMS *m*/*z* calcd for 368.0623, found 368.0629.
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