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Synthetic studies toward geranylated PPAP natural products oblongifolin A, oblongifolin D, and enervosanone

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ABSTRACT

A concise approach of general utility toward mono- and di-geranylated PPAP frameworks employing 'reconstructive aldol cyclization' as the key step is delineated.

The plant family *Clusiaceae* (*Guttiferae*), which in turn consists of many genera and species, has been receiving attention for centuries as they are mentioned in folk medicine for alleviating a variety of disorders. Recent investigations into the chemical constituents of this family have revealed it to be a rich repository of polycyclic polyprenylated acylphloroglucinol (PPAP) natural products, a novel and growing group of complex natural products embodying a bicyclo[3.3.1]nonane-2,4,9-trione core.[1,2] A notable feature of PPAPs is the presence of a dense and varied oxy-functionalization pattern together with generous and strategic placement of hydrophobic prenyl arms on its bicyclic nucleus. Indeed, PPAPs are constituted through mixed biosynthesis involving the polyketide and mevalonate pathways. Many PPAPs have been shown to exhibit a very wide ranging bioactivity profile that includes anticancer, antibacterial, antidepressant, anti-HIV, antimalarial, antiulcer, and anti-neurodegenerative among others.[1,2] Prototypical examples of some prominent PPAP natural products are clusianone **1**, nemorosone **2,** and hyperforin **3**, all embodying a bicyclo[3.3.1]nonane frame and each laced with **3** or **4** prenyl substituents (Fig. 1). Considering their structural and bioactivity attributes, it is natural that PPAPs have drawn considerable attention from the synthetic community world-wide[1,3] as well as from our group[4] and two very recent reviews[1b,c] summarize the noteworthy achievements in the arena.

A subclass of novel natural products representing an interesting structural variant among PPAPs, wherein one or more geranyl substituents are present at C5, C7, or C8 positions, have surfaced recently.[2m–o] Notable examples of such entities include monogeranylated oblongifolin A **4**[2o] and enervosanone **6**[2m] and di-geranylated oblongifolin D **5**.[2o] These geranylated PPAPs **4**-(Fig. 1) and many of their recently reported siblings also exhibit impressive biological activity.[5] Recent reports[6] that a higher prenylated moiety like the geranyl group with extended reach and conformational flexibility can provide enhanced affinity for biological membranes and interactions with cellular targets in some bioactive compounds[6b,c] have further kindled interest in geranylated PPAPs. However, barring one report[4f] from our group outlining an Effenberger cyclization based approach to the C8-geranylated PPAP framework, there have been no other endeavors targeted toward geranylated PPAPs. We report here a tactical variant of our general methodology[4b,d] toward PPAPS that provides convenient access to the C5 and C7 mono-geranylated and C5, C7-di-geranylated core present in natural products **4**–**6**, respectively.

Following our earlier forays toward PPAPs, the present approach toward geranylated bicyclo[3.3.1]nonane framework also emanated from dimedone derived enol ether **7**. The initial aim was to install the geranyl substituents at the C5 and/or C7 position with requisite relative stereochemistry required for oblongifolins A **4** and D **5**.[20] Geranylation of **7** with geranyl bromide proceeded smoothly and led to geranylated enol ether **8**. Hydrolysis to dimedone derivative **9** with a reactive 1,3-dicarbonyl functionality lend itself amenable toward implementing a quaternization protocol in a stereocontrolled manner.[7] Sequential Michael addition to methyl acrylate and prenylation of **9** in a single pot operation led to the installation of the quaternary center with requisite stereochemistry

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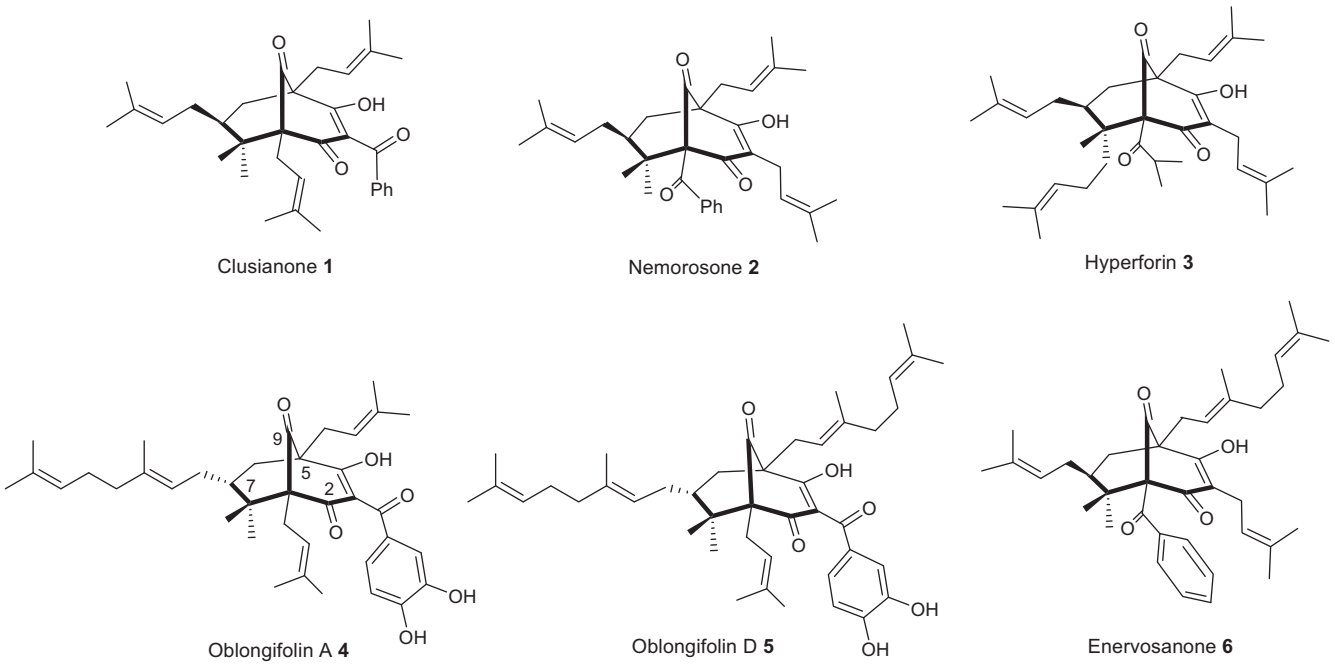
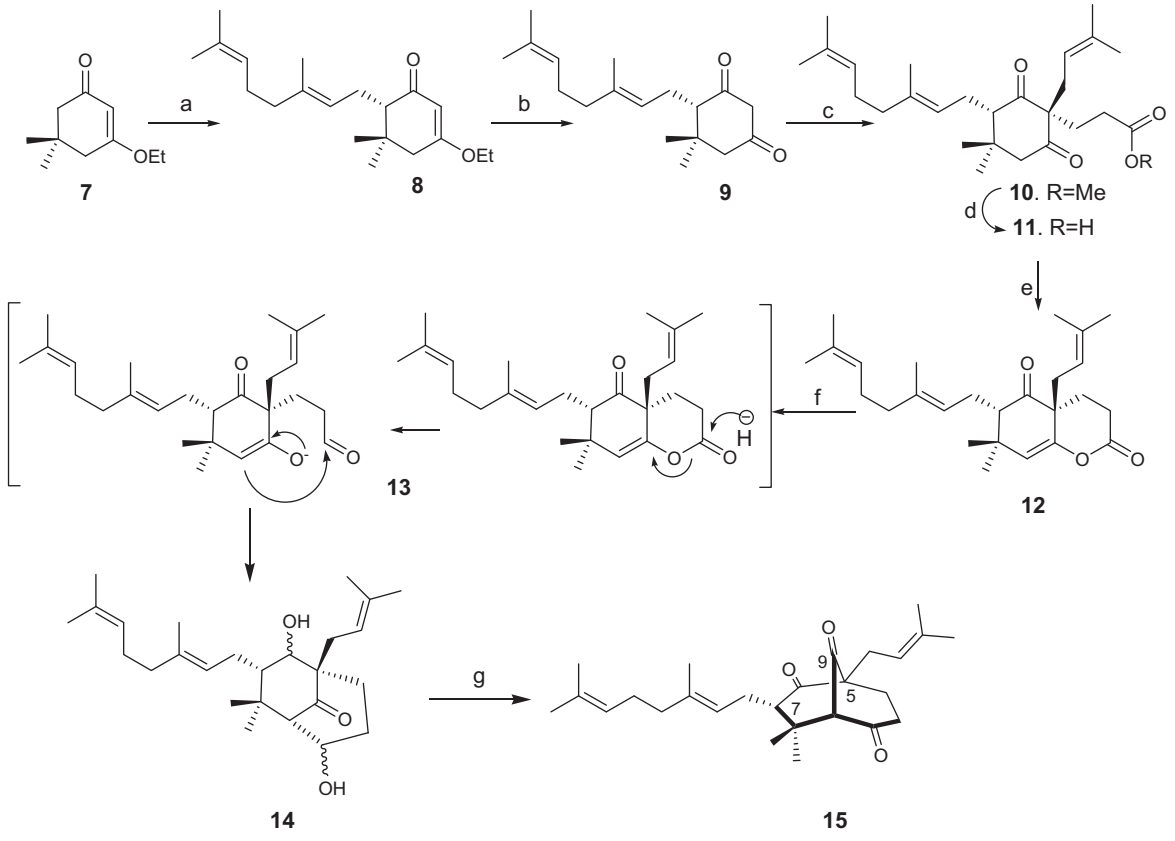
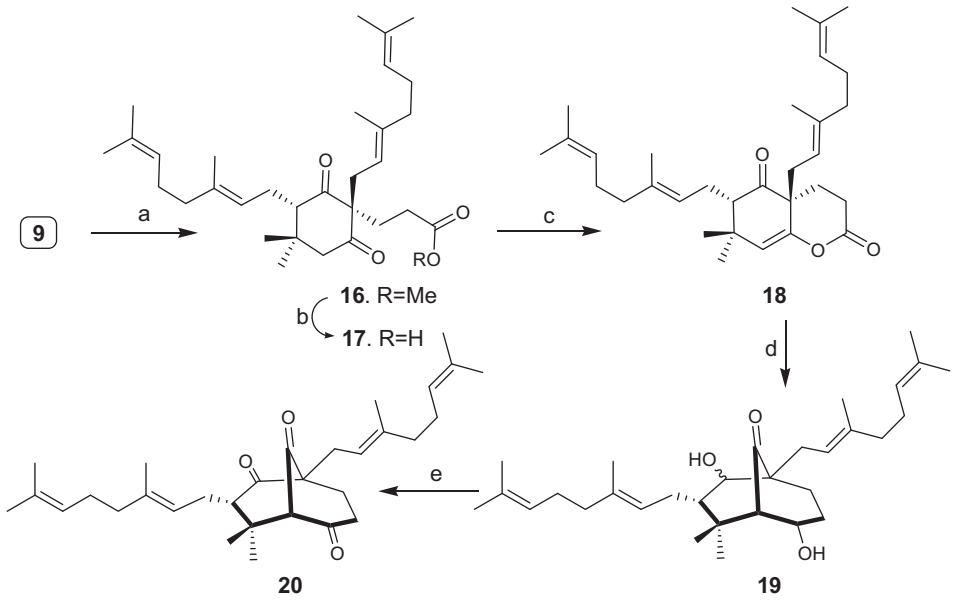


Figure 1. Representative PPAP natural products.

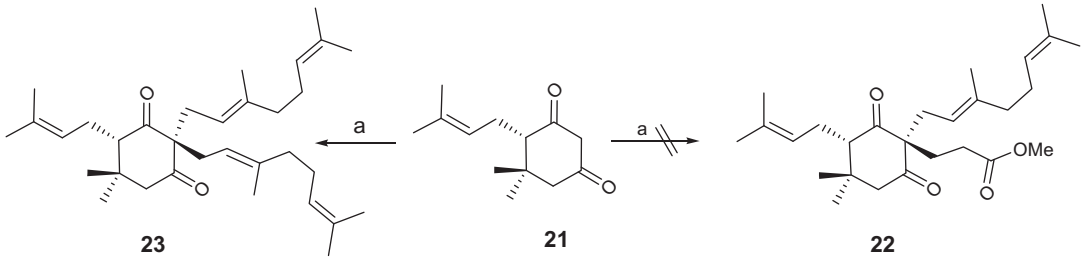


Scheme 1. Reagents and conditions: (a) LDA, geranyl bromide, THF, −78 °C → −5 °C, 12 h, 92%; (b)10% HCl, acetone–water (10:1), 25 °C, 12 h, 95%; (c) DBU (0.3 mole), THF, methyl acrylate (1.1 equiv), 5 h, then prenyl bromide (1.1 equiv), 3 h, 67%; (d) KOH, MeOH–H_2O (10:1), 65 °C, 4 h, 96%; (e) Ac_2O–NaOAc, 140 °C, 3 h under N_2, 81%; (f) DIBAL-H (3 equiv), 0 °C, 2 h; (g) PCC, SiO_2, DCM, 25 °C, 86% after 2-steps.

and delivered **10** (Scheme 1). 1,3-Stereoinduction by the pre-existing geranyl arm in **9**, as observed in related cases by us earlier,[4b,c] and the chosen sequence of the tandem Michael addition-alkylation reactions secured the stereochemistry depicted in **10**. Ester hydrolysis in **10** to acid **11** and enol-lactonization following a classical protocol led to **12**. A reconstructive aldol protocol in **12** was trig-



Scheme 2. Reagents and conditions: (a) DBU (0.5 equiv), THF, methyl acrylate (1.1 equiv), 5 h, then geranyl bromide (1.1 equiv), 3 h, 62%; (b) KOH, MeOH–H_2O (10:1), 65 °C, 4 h, 82%; (c) Ac_2O–NaOAc, 140 °C, 2 h under N_2, 82%; (d) DIBAL-H (3 equiv), 0 °C, 1.5 h; (e) PCC, SiO_2, DCM, 25 °C, 87% after 2-steps.

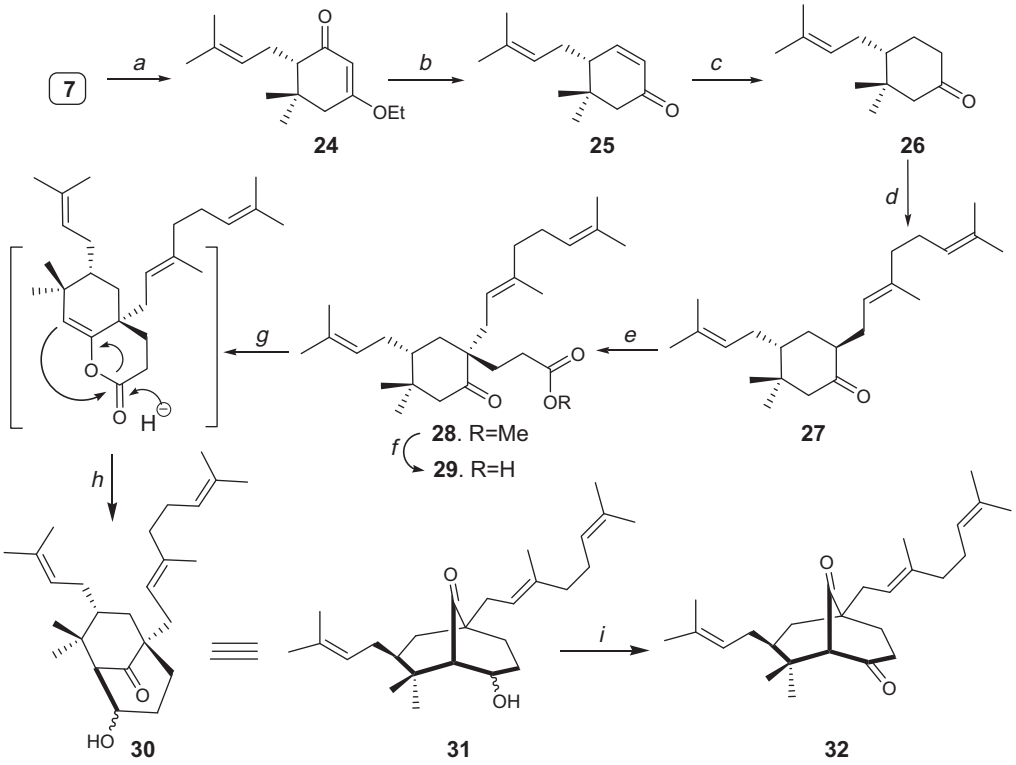


Scheme 3. Reagents and conditions: (a) DBU (0.5 equiv), THF, geranyl bromide, 25 °C, 5 h, then methyl acrylate (1.1 equiv), 2 h, 80%.

gered through DIBAL-H mediated reduction to the thermodynamically controlled re-aldolization cyclized to a bicylco[3.3.1]nonane framework bearing diol **14** through concurrent reduction of the bystander carbonyl group. PCC oxidation of the diol **14** smoothly delivered the triketone **15** bearing the C5-prenyl and C7-geranyl substituent pattern and in particular the C7-geranyl group in the desired 'endo' stereochemistry required for oblongifolin A.

Build-up of the digeranylated framework present in oblongifolin D was next on the agenda and the monogeranylated dimedone **9** served as the starting point. Quaternization in **9** was now implemented through a tandem Michael addition of methyl acrylate and alkylation with geranyl bromide in a single pot operation to furnish **16** (Scheme 2). Stereochemistry of **16** was again dictated by the 1,3-stereoinduction and the chosen sequence of the tandem Michael addition and alkylation. Ester hydrolysis in **16** to the acid **17** and enol-lactonization smoothly delivered the enol-lactone **18** (Scheme 2). Reconstructive aldolization in **18** though retro-aldol and re-aldol steps, induced by DIBAL-H reduction of **18**, led to the dihydroxylated bicyclo[3.3.1]nonane framework **19** through collateral carbonyl reduction. Bicyclic diol **19**, apparently a mixture of hydroxyl diastereomers, was oxidized by PCC to a single bicyclo[3.3.1]nona-2,6,9-trione **20** embodying the core structure of oblongofolin D (Scheme 2). Interestingly, both **15** and **20** have generous substitution on their bicyclic framework for further evolution toward the targeted natural products.

As we turned our attention to enversanone **6**,[2m] it became clear that the strategy that proved successful in the case of oblongifolins A & D required tweaking in the case of **6** as the C7 prenyl substituent in this case was 'exo' disposed. An obvious solution toward this end was to reverse the sequence of tandem Michael addition-alkylation in **21** to first mono geranylation and then Michael addition to deliver **21** which would eventuate in 'exo' C7 prenyl substituent at the end of the sequence (Scheme 3). When an attempt was made to execute this tandem protocol on **9**, it only delivered the *gem*-digeranylated **23** and not the required **22** perhaps due to the very reactive nature of the 1,3-carbonyl moiety present in it (Scheme 3). Our repeated failures to access **22** forced us to redesign our strategy. For this purpose, dimedone derived enol ether **7** was readily prenylated to **24** and further enone transposition through reduction and acid hydrolysis led to **25** (Scheme 4). Conjugate reduction in **25** led to **26** (Scheme 4). A regio- and stereocontrolled geranylation in **26** could now be implemented under kinetically controlled conditions to deliver mono-geranylated product **27**. The anion derived from **27** readily underwent Michael addition to methyl acrylate to furnish **28** and set-up the quaternary center in a stereocontrolled manner through 1,3-stereoinduction. Acid hydrolysis of **28** and enol-lactonization of the resultant carboxylic acid **29** delivered **30** (Scheme 4). DIBAL-H reduction of **30** triggered the reconstructive aldol cyclization to result in bicyclo[3.3.1]nonane framework **31** with 'exo' disposed C7 prenyl group. Oxidation of **31** led to



Scheme 4. Reagents and conditions: (a) LDA, prenyl bromide, THF, −78 °C → −5 °C, 12 h, 77%; (b) DIBAL-H, THF, 0 °C, 2 h and then 50% HCl, acetone–water (3:1), 25 °C, 30 min, 67% after two steps; (c) K-selectride, THF, −55 °C, 4 h, 87%; (d) LDA, geranyl bromide, THF, −78 °C, 91%; (e) K^{t}OBu, THF, methyl acrylate (1.1 equiv), 0.5 h, 75%; (f) KOH, MeOH–H_2O (10:1), 25 °C, 8 h, 87%; (g) Ac_2O–NaOAc, 120 °C, 4 h under N_2, 67%; (h) DIBAL-H (3 equiv), 0 °C, 2 h, 82%; (i) PCC, SiO_2, DCM, 25 °C, 95%.

the desired bicyclo[3.3.1]nonan-3-9-dione **32** for further elaboration.

In summary, we have advanced the utility of a general 'reconstructive aldol cyclization' based approach to PPAPs and report here the first synthesis of the geranylated bicyclo[3.3.1]nonane core present in oblongifolins A and D and enversanone.

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7. All new compounds were characterized on the basis of their spectroscopic data (IR, ^{1}H, ^{13}C, MS). Spectral data for some of the key compounds are as follows: 15: IR (neat) 1742, 1715, 1702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.16–5.12 (m, 1H), 5.7–5.03 (m, 1H), 4.94–4.91 (m, 1H), 3.4 (s, 1H), 2.45–2.36 (m, 5H), 2.10–1.94 (m, 6H), 1.68–1.58 (cluster of s, 15H), 1.48–1.41 (m, 1H), 1.32 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.6, 206.1, 204.3, 136.8, 135.7, 131.5, 124.0, 121.5, 117.33, 78.6, 63.4, 61.4, 40.0, 37.6, 36.2, 32.1, 31.1, 27.2, 26.7, 25.9, 25.7, 22.3, 20.0, 17.7, 17.6, 15.9; HRMS(ES): *m*/*z* Calcd for $C_{26}H_{38}O_3$ (M+Na): 421.2719. Found: 421.2724. 20: IR (neat) 1739, 1714, 1702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.17–5.12 (m, 1H), 5.05–5.03 ((m, 1H), 4.96–4.92 (m, 1H), 3.4 (s, 1H), 2.58–2.38 (m, 5H), 2.19–1.95 (m, 12H), 1.66–1.58 (cluster of s, 18H), 1.31, (s, 3H), 0.83 (s, 3H);); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.4, 205.9, 204.1, 139.3 (2c), 136.9, 131.5, 124.1, 121.6, 119.3, 117.2, 78.8, 63.5, 61.2, 57.90, 39.9 (2C), 37.6, 37.4, 36.2, 32.1, 30.8, 27.0, 26.7, 26.6, 25.9, 25.6, 22.4, 19.9, 17.6, 16.1; *m*/*z* Calcd for $C_{31}H_{46}O_3$ (M+Na): 489.3345. Found: 489.3354; 31: IR (neat) 1725, 1702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.22(t, 1H), 5.08 (br s, 3H), 2.88 (s, 1H), 2.77–2.50 (m, 2H), 2.24–1.80 (m, 12H), 1.71 (s, 3H), 1.67 (s, 3H), 1.60 (br s, 9H), 1.42–1.22 (m, 1H), 1.06 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.4, 208.4, 138.1, 133.09, 131.4, 124.2, 122.7, 119.4, 79.3, 49.4, 45.5, 42.6, 42.4, 40.1, 39.5, 35.2, 29.8, 29.5, 26.7 (2C), 25.8, 25.7, 21.2, 17.9, 17.7, 16.2; *m*/*z* Calcd for $C_{26}H_{40}O_2$ (M+Na): 407.2926. Found: 407.2931.