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Biomimetic Synthesis of Polycyclic Polyprenylated Acylphloroglucinol Natural Products Isolated from *Hypericum papuanum*

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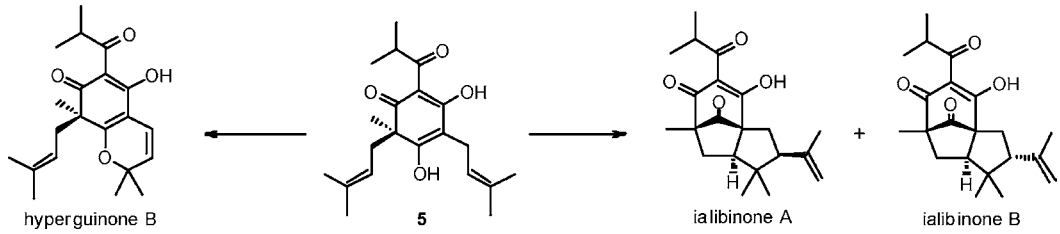
ABSTRACT



Biomimetic syntheses of three polycylic polyprenylated acylphloroglucinol natural products isolated from *Hypericum papuanum*, ialibinone A, ialibinone B, and hyperguinone B, have been accomplished by selective oxidative cyclizations of the proposed biosynthetic precursor 5, which was synthesized from phloroglucinol in three steps.

Polycyclic polyprenylated acylphloroglucinols (PPAPs) are a large family of natural products isolated from a wide range of plant species.[1] Many PPAPs have been shown to exhibit potent biological activities and are therefore highly attractive targets for synthesis.[2] They are biosynthetically derived from simpler monocyclic polyprenylated acylphloroglucinols, with the mechanism generally thought to involve cationic or radical cyclizations by reaction between the prenyl or prenyl-derived side chains and the electron-rich phloroglucinol core. Most PPAPs feature a bicyclo[3.3.1]nonane-2,4,9-trione core adorned with prenyl and/or geranyl side chains, such as garsubellin A[3] and hyperforin, the presumed active compound in the antidepressant St. John's wort.[4] A smaller group of PPAPs possess a bicyclo[3.2.1]octane-2,4,8-trione core, such as ialibinone A (**1**).[5] Many PPAP natural products have densely functionalized, highly oxygenated structures as a result of secondary cyclizations and oxidations and are therefore very challenging synthetic targets. We were interested in investigating some biomimetic cascade reaction approaches to PPAP natural products and decided to focus on the relatively simple family of compounds isolated from the leaves of *Hypericum papuanum*,[5a] a plant used in traditional medicine in Papua New Guinea. Several unique PPAP natural products have been isolated from this plant, including ialibinones A (**1**) and B (**2**)[5a] (Figure 1), which both contain a bicyclo[3.2.1]octane core and were found

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(1) For a review of PPAP natural products, see: Singh, I. P.; Bharate, S. B. *Nat. Prod. Rep.* **2006**, *23*, 558.

(2) For a review of the synthesis of PPAP natural products, see: Ciochina, R.; Grossman, R. B. *Chem. Rev.* **2006**, *106*, 3963.

(3) Fukuyama, Y.; Minami, H.; Kuwayama, A. *Phytochemistry* **1998**, *49*, 853.

(4) Mennini, T.; Gobbi, M. *Life Sci.* **2004**, *75*, 1021.

(5) (a) Winkelmann, K.; Heilmann, J.; Zerbe, O.; Rali, T.; Sticher, O. *J. Nat. Prod.* **2000**, *63*, 104. (b) Winkelmann, K.; Heilmann, J.; Zerbe, O.; Rali, T.; Sticher, O. *J. Nat. Prod.* **2001**, *64*, 701. (c) Winkelmann, K.; Heilmann, J.; Zerbe, O.; Rali, T.; Sticher, O. *Helv. Chim. Acta* **2001**, *84*, 3380.

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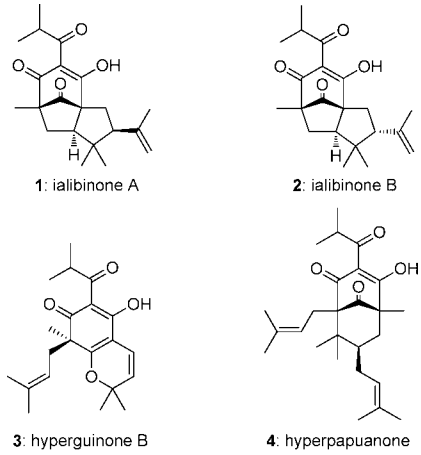


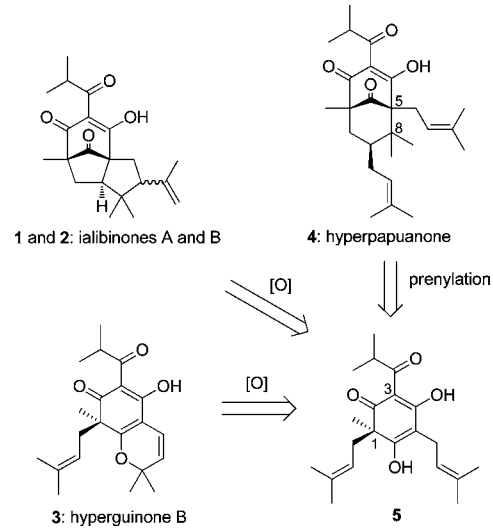
Figure 1. Representative PPAP natural products from *H. papuanum*.

to exhibit antibacterial activity against *Bacillus cereus*, *Staphylococcus epidermidis*, and *Micrococcus luteus*. Hyperguinone B (**3**)[5b] is a bicyclic compound featuring a 2,2-dimethyl-2*H*-pyran ring, while hyperpapuanone (**4**)[5b] and papuaforins A−E[5b] all contain the more common bicyclo[3.3.1]nonane core.

Ialibinones A (**1**) and B (**2**) and hyperguinone B (**3**) are presumably all derived from a common monocyclic precursor **5** by various oxidative cyclizations (Scheme 1). Similarly, hyperpapuanone (**4**) might arise via prenylation of the C-1 prenyl group of **5**, followed by an electrophilic cyclization of the resultant carbocation intermediate to form the C(5)−C(8) bond. Although **5** has not itself been isolated as a natural product, its biosynthesis by diprenylation of a 1-methyl-3-acylphloroglucinol derivative is likely. Ialibinones A (**1**) and B (**2**), hyperguinone B (**3**), and related PPAP natural products from *Hypericum papuanum* were all isolated in optically active form. This optical activity presumably derives from an asymmetric prenylation of the 1-methyl-3-acylphloroglucinol precursor, catalyzed by an aromatic prenyl transferase enzyme. The aim of this project was therefore to synthesize the proposed common intermediate **5** in racemic form and then to investigate oxidative cyclizations of this compound with a view to racemic synthesis of complex PPAP natural product structures.

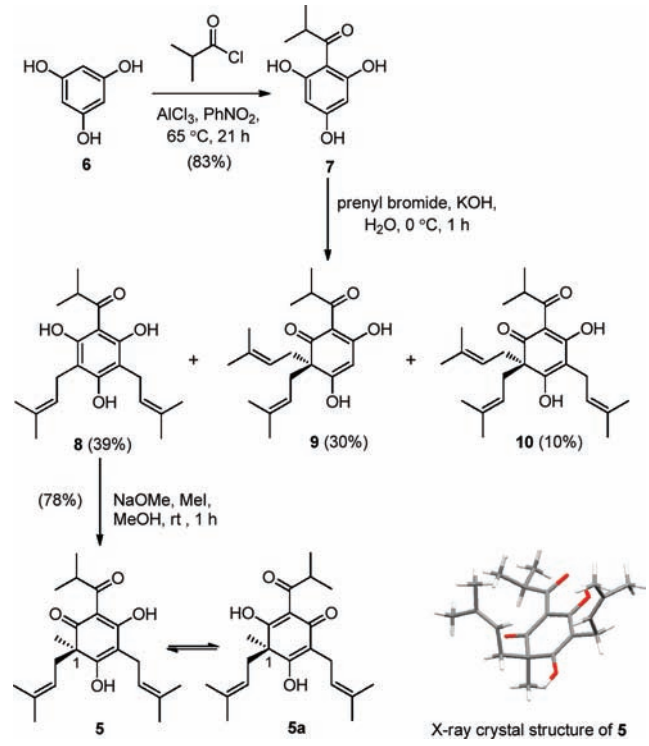
The synthesis of the proposed biosynthetic intermediate **5** commenced with a Friedel−Crafts reaction of anhydrous phloroglucinol (**6**) with isobutyryl chloride and $AlCl_3$ in nitrobenzene, which gave (2-methylpropionyl)phloroglucinol[6] (**7**) in 83% yield (Scheme 2). Prenylation of **7** with prenyl bromide in aqueous KOH[7] gave a mixture of the desired *m*-diprenylacylphloroglucinol **8** (39%), together with the *gem*-diprenylated acylphloroglucinol **9** (30%, mixture of four tautomeric forms) and the triprenylated acylphloroglucinol **10** (10%). These products could be

Scheme 1. Proposed Biosynthetic Origin of Ialibinones A and B, Hyperguinone B, and Hyperpapuanone from **5**



separated by careful flash chromatography on silica gel or alternatively by selective extraction from basic aqueous solutions.

Scheme 2. Synthesis of Key Biomimetic Intermediate **5**

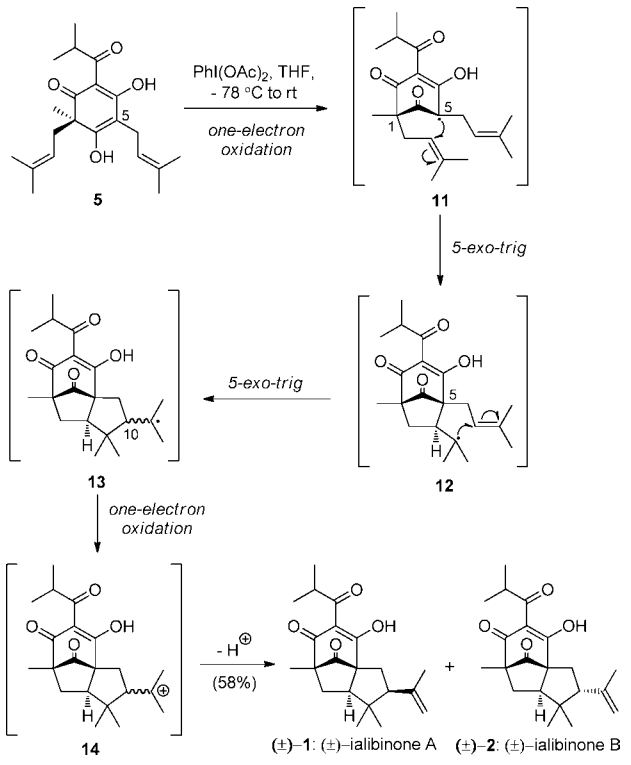


C-Methylation of **8** was then carried out by treatment with NaOMe and MeI in MeOH to give **5** in 78% yield. Both **5** and **8** are unstable with respect to aerial oxidation, with **8** giving the α-hop acid cohumulone[8] in quantitaive yield and

(6) Crombie, L.; Jones, R. C. F.; Palmer, C. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 317.
(7) Xiao, L.; Tan, W.; Li, Y. *Synth. Commun.* **1998**, *28*, 2861.

5 giving a complex mixture of products. In solution, **5** exists as a 3:1 mixture of two tautomeric forms, **5** and **5a**. However, crystallization of **5** from hexane gave colorless crystals of **5**, and X-ray studies confirmed the structure[9] and proved that methylation had occurred at C-1. With **5** in hand, the proposed biomimetic oxidative cyclizations were investigated. In the first instance, treatment of **5** with $PhI(OAc)_2$ in THF gave a 1:1 mixture of (±)-ialibinones A ((±)-**1**) and B ((±)-**2**) in combined yield of 58% (Scheme 3). Several alternative oxidizing systems (such as $Mn(OAc)_3/Cu(OAc)_2$ and CAN) were investigated, but all gave inferior results.[10]

Scheme 3. Biomimetic Synthesis of Ialibinones A and B

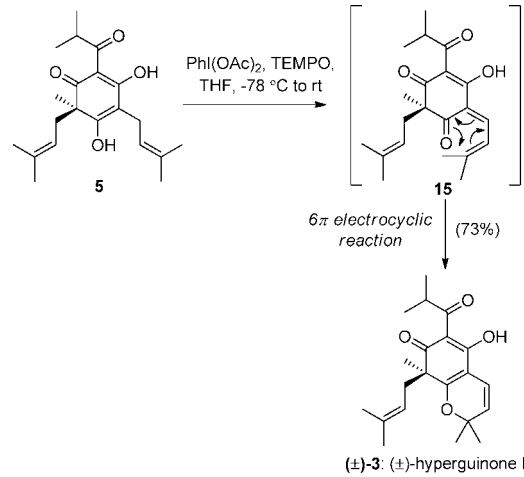


The reaction presumably proceeds via initial single-electron oxidation of **5** to give the stabilized α-keto radical intermediate **11**, with the radical character centered at C-5. A stereoselective 5-*exo*-*trig* cyclization of this radical onto the pendant C-1 prenyl group would then give tertiary radical **12**, which could undergo a second 5-*exo*-*trig* cyclization onto the C-5 prenyl group to give tertiary radical **13** (as a mixture of C-10 epimers). Finally, a further single-electron oxidation of **13** would give tertiary carbocation **14** and then (±)-**1** and (±)-**2** by loss of a proton.[11]

The resultant 1:1 mixture of (±)-ialibinones A and B could be separated by HPLC to give materials with ^1H and ^{13}C spectroscopic data identical to those previously reported.[5a] This is the first synthesis of ialibinones A and B, although an approach to the 6−5−5 ring system has been reported,[12] and structurally related semisynthetic products of hop constituents have also been described.[13] Ialibinones A and B both exist as a 1.8:1 mixture of enol tautomers (the major tautomer is shown). The ^1H NMR spectra of these tautomers all show resonances at around 18 ppm in $CDCl_3$, indicating complete enolization. The first 5-*exo*-*trig* radical cyclization (**11** → **12**) clearly proceeds with a high degree of stereocontrol, which could be explained by invoking a chairlike transition state for this reaction. Alternatively, this first radical cyclization could be nonstereoselective but reversible, with only the *cis* adduct **12** being aligned for a second radical cyclization onto the C(5) prenyl group. The second 5-*exo*-*trig* cyclization is not stereoselective.

Treatment of **5** with $PhI(OAc)_2$ in the presence of TEMPO gave (±)-hyperguinone B ((±)-**3**) in 73% yield (Scheme 4). This reaction presumably proceeds via a selective hydride abstraction by the in situ generated TEMPO cation to generate the *o*-quinone methide intermediate **15**, which undergoes a 6π-electrocyclization to give the 2,2-dimethyl-2*H*-pyran ring of **3**. The selectivity of this process is noteworthy, as **5** contains two prenyl groups that could potentially be oxidized and three phenolic oxygen atoms which could cyclize to form a 2,2-dimethyl-2*H*-pyran ring. However, hyperguinone B is the only observable reaction product, formed as a 3:1 mixture of enol tautomers.

Scheme 4. Synthesis of Hyperguinone B



The same oxidative conditions of $PhI(OAc)_2$ and TEMPO were used to selectively oxidize the triprenylated acylphlo-

(8) (a) Hoek, A. C.; Hermans-Lokkerbol, A. C. J.; Verpoorte, R. *Phytochem. Anal.* **2001**, *12*, 53. (b) For oxidation of deoxyhumulone to humulone under aerobic conditions, see: Fung, S. Y.; Zuurbier, K. W. M.; Paniego, N. B.; Scheffer, J. J. C.; Verpoorte, R. J. *Phytochemistry* **1997**, *44*, 1047.

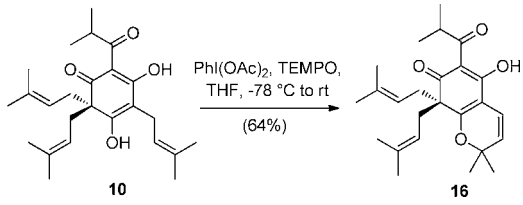
(9) Crystallographic data for the structure of **5** have been deposited with the Cambridge Crystallographic Data Centre (CCDC 780154). Copies of this data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

(10) For related radical cyclizations of dearomatized phloroglucinols using $Mn(OAc)_3$, see: Mitasev, B.; Porco, J. A. *Org. Lett.* **2009**, *11*, 2285.

(11) For a similar radical cyclization cascade reaction in the synthesis of tricycloillicinone, see: (a) Pettus, T. R. R.; Chen, X.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 12684. (b) Pettus, T. R. R.; Inoue, M.; Chen, X.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 6160. (c) Lei, X.; Dai, M.; Hua, Z.; Danishefsky, S. J. *Tetrahedron Lett.* **2008**, *49*, 6383.

roglucinol **10** to the bicyclic compound **16**, which is a close analogue of the natural product machuone[14] (Scheme 5).

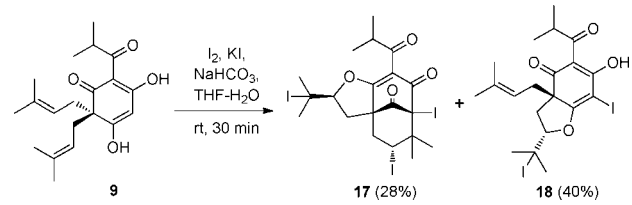
Scheme 5. Synthesis of **16** from **10**



Attempts to carry out electrophilic oxidative cyclizations of **5** to give PPAPs with bicyclo[3.3.1]nonane 2,4,9-trione cores (which are common to most PPAP natural products) were unsuccessful with reagents such as I_2 and *m*-CPBA. This is hardly surprising, since **5** contains two distinct prenyl groups of similar reactivity toward electrophiles and three enol groups which could react intramolecularly with any intermediate iodonium ions or epoxides via either C or O cyclization modes. In general, complex mixtures of oxygen heterocycles were formed. However, reaction of the *gem*-diprenylated acylphloroglucinol **9** under standard iodolactonization conditions generated **17** in 28% yield as a single diastereomer,[15] together with **18** in 40% yield (Scheme 6). Tri-iodide **17** features a bicyclo[3.3.1]nonane core fused to a tetrahydrofuran (relative stereochemistry assigned by observation of key NOEs) and is thus similar in structure to complex PPAP natural products such as garsubellin A.

(12) Srikrishna, A.; Beeraiah, B.; Gowri, V. *Tetrahedron* **2009**, *65*, 2649.
(13) John, G. D.; Shannon, P. V. R. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1633.
(14) Monache, F. D.; Monache, G. D.; Gacs-Baitz, E. *Phytochemistry* **1991**, *30*, 2003.
(15) For related electrophilic cyclizations of monocyclic polyprenylated acylphloroglucinols, see: (a) Raikar, S. B.; Nuhant, P.; Delpech, B.; Marazano, C. *Eur. J. Org. Chem.* **2008**, 1358. (b) Tsukano, C.; Siegel, D. R.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8840.

Scheme 6. Electrophilic Cyclizations of **5** with I_2



In summary, a series of oxidative cyclization reactions of monocyclic polyprenylated acylphloroglucinols have been investigated. By adopting a biomimetic approach and synthesizing the proposed biosynthetic intermediate **5**, a group of highly diverse polycyclic ring systems has been accessed. Oxidative radical cyclization of **5** with $PhI(OAc)_2$ gave (±)-ialibinones A ((±)-**1**) and B ((±)-**2**) via a selective radical cascade reaction to install the bicyclo[3.2.1]octane ring system. Synthesis of (±)-hyperguinone B ((±)-**3**) was carried out by oxidation of **5** with $PhI(OAc)_2$ and TEMPO, and treatment of *gem*-diprenylated acylphloroglucinol **8** with I_2 gave a compound with a bicyclo[3.3.1]nonane core (**17**). Further studies on oxidative cyclizations of more complex polyprenylated acylphloroglucinols are underway in these laboratories and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for compounds **1**−**3**, **5**, **7**−**9**, and **16**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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