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Biomimetic Total Synthesis of (±)-Garcibracteatone

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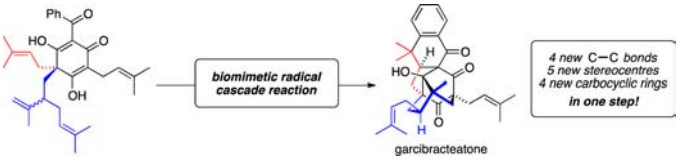
ABSTRACT



The polycyclic polyprenylated acylphloroglucinol natural product garcibracteatone has been synthesized in four steps from phloroglucinol, using a strategy based on biosynthetic speculation. The key biomimetic transformation is a cascade of 7-*endo*-*trig* and 5-*exo*-*trig* radical cyclizations followed by a terminating aromatic substitution reaction.

Polycyclic polyprenylated acylphloroglucinols (PPAPs) represent a large class of natural products isolated from plants of the Clusiaceae and Hypericaceae families.[1] Many PPAPs show potent biological activities, and their complex molecular structures have therefore attracted considerable recent attention from the synthetic community.[2] Garcibracteatone (**1**, Figure 1) is a PPAP natural product whose isolation from the bark of *Garcinia bracteata* was reported in 2005.[3] *It is the most structurally complex PPAP natural product isolated to date, with a highly compact polycyclic ring system containing seven stereocenters, five of which are quaternary.*

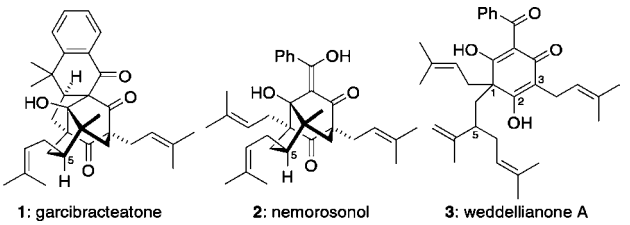


Figure 1. PPAP natural products of interest in this work.

The structure of garcibracteatone was elucidated on the basis of 2D NMR studies. The relative stereochemistry of garcibracteatone at C-5 was not rigorously determined but was predicted to be as shown in Figure 1 by comparison with the related and coisolated PPAP natural product nemorosonol (**2**).[4] A biosynthetic link between **1**, **2**, and a possible common precursor, weddellianone A (**3**), was proposed in the isolation paper. Weddellianone A has been previously isolated from *Clusia weddelliana*, although its

(1) For reviews of the isolation and pharmacology of PPAP natural products, see: (a) Singh, I. P.; Bharate, S. B. *Nat. Prod. Rep.* **2006**, *23*, 558–591. (b) Ciochina, R.; Grossman, R. B. *Chem. Rev.* **2006**, *106*, 3963–3986.

(2) For recent reviews of PPAP natural product synthesis, see: (a) Richard, J.-A.; Pouwer, R. H.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2012**, *51*, 4536–4561. (b) Njardarson, J. T. *Tetrahedron* **2011**, *67*, 7631–7666. For a review of biomimetic approaches to PPAP synthesis, see: (c) Dakanali, Theodorakis, E. A. In *Biomimetic Organic Synthesis*; Poupon, E., Nay, B., Eds.; WILEY-VCH: 2011; pp 433–467. For selected recent syntheses of PPAP natural products, see: (d) Kuramochi, A.; Usuda, H.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 14200–14201. (e) Siegel, D. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 1048–1049. (f) Rodeschini, V.; Ahmad, N. M.; Simpkins, N. S. *Org. Lett.* **2006**, *8*, 5283–5285. (g) Tsukano, C.; Siegel, D. R.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8840–8844. (h) Nuhant, P.; David, M.; Pouplin, T.; Delpech, B.; Marazano, C. *Org. Lett.* **2007**, *9*, 287–289. (i) Shimizu, Y.; Shi, S.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1103–1106. (j) Simpkins, N. S.; Taylor, J. D.; Weller, M. D.; Hayes, C. J. *Synlett* **2010**, 639–643. (k) Qi, J.; Beeler, A. B.; Zhang, Q.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2010**, *132*, 13642–13644. (l) Garnsey, M. R.; Lim, D.; Yost, J. M.; Coltart, D. M. *Org. Lett.* **2010**, *12*, 5234–5237. (m) Zhang, Q.; Mitasev, B.; Qi, J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2010**, *132*, 14212–14215. (n) Biber, N.; Möws, K.; Plietker, B. *Nat. Chem.* **2011**, *9*, 938–942. (o) Zhang, Q.; Porco, J. A., Jr. *Org. Lett.* **2012**, *14*, 1796–1799.

(3) Thoison, O.; Cuong, D. D.; Gramain, A.; Chiaroni, A.; Hung, N. V.; Sevenet, T. *Tetrahedron* **2005**, *61*, 8529–8535.

(4) Initial isolation of nemorosonol: (a) Monache, F. D.; Monache, G. D.; Pinherio, R. M.; Radics, L. *Phytochemistry* **1988**, *27*, 2305–2308. Correction of relative stereochemistry of nemorosonol by X-ray crystallography: (b) Cerrini, S.; Lamba, D.; Monache, F. D.; Pinherio, R. M. *Phytochemistry* **1993**, *32*, 1023–1028.

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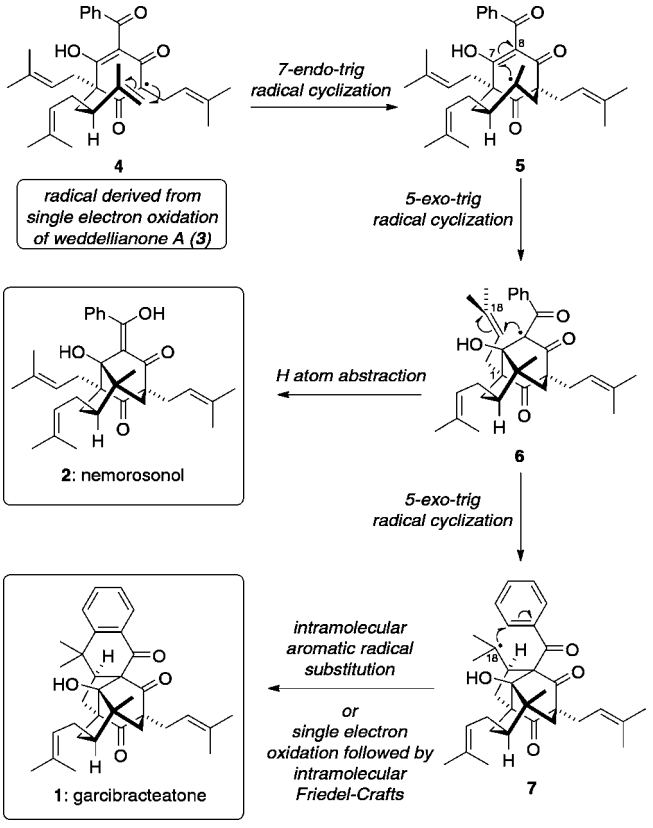
relative stereochemistry at C-1 and C-5 was not determined.[5] Herein, we propose that **1** and **2** are derived in nature from **3** via highly selective, predisposed radical cyclizations. As delineated in Scheme 1, oxidation of the $\Delta^{2,3}$ enol of **3** would form the stabilized radical **4** that could undergo a 7-*endo-trig* cyclization with the pendant lavandulyl side chain to give the tertiary radical **5**. A subsequent 5-*exo-trig* radical cyclization of **5** onto the $\Delta^{7,8}$ enol would give the diketo radical **6**, which could abstract a hydrogen atom from a suitable donor to form nemorosonol (**2**). Alternatively, **6** could undergo a second 5-*exo-trig* cyclization onto the $\Delta^{17,18}$ of the C-1 prenyl group to give tertiary radical **7**. Garcibracteatone (**1**) could then be formed from **7** either via an intramolecular aromatic radical substitution reaction or, alternatively, by single electron oxidation to give a carbocation that could participate in an intramolecular Friedel–Crafts reaction.

Scheme 1. Proposed Biosynthesis of Garcibracteatone and Nemorosonol from Weddellianone A



It was our intention to apply the biosynthetic proposal outlined in Scheme 1 to a concise biomimetic synthesis of garcibracteatone (**1**). In addition to providing evidence for our proposed biosynthetic pathway, such a synthesis would also demonstrate the ability of radical cyclizations to rapidly generate complex PPAP natural products.

We have previously applied an oxidative radical cylization approach to the simpler PPAP natural products ialibinones A and B[6] using $PhI(OAc)_2$ as the oxidant.[7] A similar synthesis of ialibinones A and B has also been reported by Simpkins,[8] who used $Mn(OAc)_3$ and $Cu(OAc)_2$ as reagents for the key radical cascade sequence. The $Mn(OAc)_3$/$Cu(OAc)_2$ system for inducing oxidative radical cyclizations of enolizable carbonyl compounds has been investigated extensively by Snider,[9] and it has been specifically applied in studies toward the synthesis of PPAPs by Kraus[10] and Porco.[11] The work of Porco is particularly relevant to this synthesis of garcibracteatone, as he showed the potential for forming complex polycyclic ring systems via cyclizations of dearomatized phloroglucinols.

Our synthesis of garcibracteatone commenced with a Friedel–Crafts reaction between anhydrous phloroglucinol (**8**) and benzoyl chloride to give 2,4,6-trihydroxybenzophenone (**9**) in 47% yield (Scheme 2).[12] Diprenylation of **9** with prenyl bromide in aqueous KOH then formed **10** in 34% yield.[13] Alkylation of **10** using (±)-lavandulyl iodide[14] (**11**) with NaH in DMF gave **12** as an inseparable mixture of two diastereomers, with each diastereomer existing as a mixture of two tautomers. The modest yield for this reaction (29%, or 50% based on recovered **10**) reflects the sterically crowded nature of the all-carbon quaternary center formed at C-1, as well as the low S_N2 reactivity of the alkyl iodide (competing E2 elimination was observed). Oxidation of **12** under the standard $Mn(OAc)_3$/$Cu(OAc)_2$ conditions then furnished a mixture of (±)-garcibracteatone (**1**, 14% isolated yield) and (±)-5-*epi*-garcibracteatone (**13**, 8% isolated yield) that was separable by flash chromatography on silica gel.[15]

The structures of **1** and **13** were elucidated via 2D NMR spectroscopy and later confirmed by X-ray studies,[16] and the data for **1** matched those of the previously isolated natural product. The relative stereochemistry of **1** at C-5 is therefore confirmed to be as shown in Scheme 2. The formation of a mixture of **1** and **13** is inevitable by this strategy due to the nondiastereoselective alkylation of **10**

(5) Porto, A. L. M.; Machado, S. M. F.; de Oliveira, C. M. A.; Bittrich, V.; Amaral, M. E.; Marsailoi, A. J. *Phytochemistry* **2000**, *55*, 755–768.

(6) Winkelmann, K.; Heilmann, J.; Zerbe, O.; Rali, T.; Sticher, O. *J. Nat. Prod.* **2000**, *63*, 104–108.

(7) George, J. H.; Hesse, M. D.; Baldwin, J. E.; Adlington, R. M. *Org. Lett.* **2010**, *12*, 3532–3535.

(8) Simpkins, N. S.; Weller, M. D. *Tetrahedron Lett.* **2010**, *51*, 4823–4826.

(9) For a review of $Mn(OAc)_3$-mediated oxidative radical cyclizations, see: Snider, B. B. *Chem. Rev.* **1996**, *96*, 339–363.

(10) (a) Kraus, G. A.; Nguyen, T. H.; Jeon, I. *Tetrahedron Lett.* **2003**, *44*, 659–661. (b) Kraus, G. A.; Dneprovskaia, E.; Nguyen, T. H.; Jeon, I. *Tetrahedron* **2003**, *59*, 8975–8978.

(11) Mitasev, B.; Porco, J. A., Jr. *Org. Lett.* **2009**, *11*, 2285–2288.

(12) Lin, C.-M.; Huang, S.-T.; Lee, F.-W.; Kuo, H.-S.; Lin, M.-H. *Bioorg. Med. Chem.* **2006**, *14*, 4402–4409.

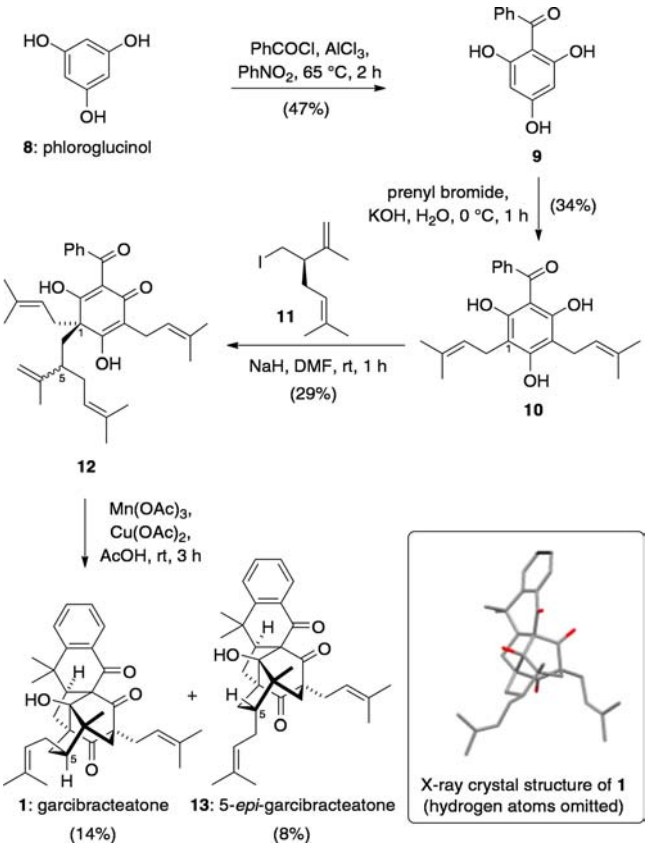
(13) Qi, J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 12682–12683.

(14) See Supporting Information for synthesis of (±)-lavandulyl iodide (**11**) from (±)-lavandulol.

(15) No other products were isolated from the reaction mixture, perhaps indicating decomposition of the starting material by overoxidation.

(16) CCDC 881560 (**1**) and CCDC 881559 (**13**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Scheme 2. Biomimetic Synthesis of Garcibracteatone and 5-*epi*-Garcibracteatone



with lavandulyl iodide (**11**). However, this lack of control of the C-5 stereocenter is more than offset by the remarkable overall increase in molecular complexity during the final biomimetic radical cyclization step, in which four carbon−carbon bonds, four rings, and five stereocenters are formed with complete control of relative stereochemistry. We believe that the mechanism of this cascade reaction closely mirrors our biosynthetic proposal as outlined in Scheme 1, with initial exposure of **12** to $Mn(OAc)_3$ generating the first stabilized diketo radical intermediate, and the $Cu(OAc)_2$ additive facilitating the final aromatic substitution step. A related intramolecular aromatic radical substitution in the termination of a $Mn(OAc)_3$/$Cu(OAc)_2$-mediated radical cyclization cascade has been previously reported by Snider.[17]

The isolation of two structurally related PPAP natural products, doitunggarcinone A (**14**) and doitunggarcinone B (**15**),[18] from *Garcinia propinqua* has recently been reported (Figure 2). These compounds have identical molecular frameworks to garcibracteatone (**1**) and nemorosonol (**2**) respectively, but with different substituents and relative stereochemistry at C-5.

(17) Snider, B. B.; Kwon, T. *J. Org. Chem.* **1990**, *55*, 4786–4788.

(18) Tantapakul, C.; Phakhodee, W.; Ritthiwigrom, T.; Cheenpracha, S.; Prawat, U.; Deachathai, S.; Laphookhieo, S. *J. Nat. Prod.*, ASAP (DOI: 10.1021/np300487w).

(19) See Supporting Information for a full comparison of NMR data for these natural products.

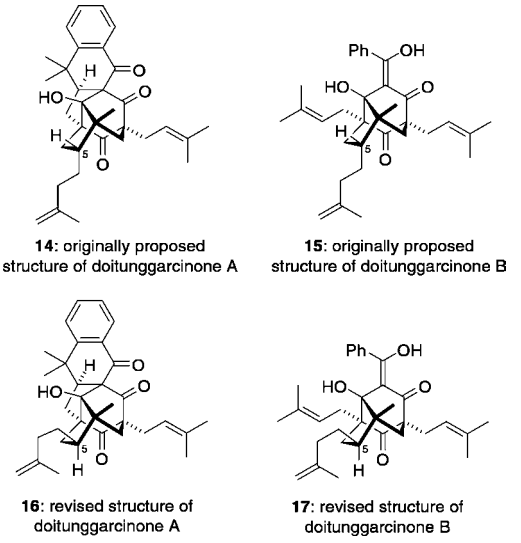


Figure 2. Structure revision of doitunggarcinones A and B.

However, after comparison of the ^1H and ^{13}C NMR data for the newly reported natural products with the corresponding data for garcibracteatone (**1**), 5-*epi*-garcibracteatone (**13**), and nemorosonol (**2**), we suggest that the C-5 relative stereochemistry of doitunggarcinones A and B should be revised to as shown in structures **16** and **17**.[19]

In conclusion, we have developed a four-step synthesis of the highly complex PPAP natural product garcibracteatone (**1**) that confirms its C-5 relative stereochemistry and also leads us to suggest a structure revision for the related compounds doitunggarcinones A and B. The synthesis features eight carbon−carbon bond forming events in four steps, and the use of protecting groups is avoided. The success of the strategy highlights the power of biomimetic synthesis as applied to the rapid generation of molecular complexity; indeed, it is difficult to imagine how else the ornate garcibracteatone structure could be accessed. Furthermore, the efficiency and inherent selectivity of the radical cascade reaction strongly suggests that a similar process is involved in the biosynthesis of the natural product.

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Supporting Information Available. Synthetic procedures and analytical data for compounds **1** and **9**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.