

A Photochemical Entry to Depsides:
Synthesis of Gustastatin

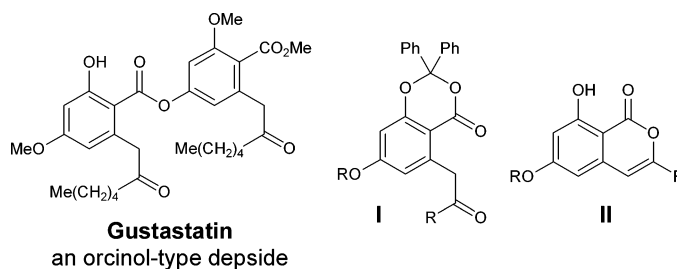
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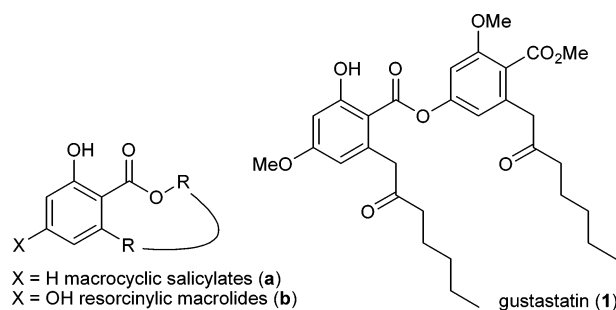
ABSTRACT



Herein, we propose a modular and general strategy to construct orcinol-type depsides based on the photolysis of functionalized benzodioxinones (I). Notably, resorcinylic esters are obtained without competing isocoumarin (II) formation, exemplified by the first total synthesis of gustastatin in 10 steps from commercially available trihydroxybenzoic acid.

Many biologically active natural products contain an *ortho*-functionalized salicylic or resorcinylic moiety. For example, members of the macrocyclic salicylate family (cf., **a**)¹ are potent inhibitors of the mammalian vacuolar ATPase with a potential novel mode-of-action,² whereas resorcinylic macrolides (cf., **b**) such as radicicol³ inhibit the molecular chaperone Hsp90.⁴ Another class of resorcinylic natural products, orcinol-type depsides, are composed of two (or more) resorcinylic acid derivatives that carry identical or different linear alkyl or 2-oxo-alkyl chains.⁵ A recent example is gustastatin (**1**), a compound isolated and characterized by Pettit and co-workers from the stems and twigs of the

Brazilian nut tree *Gustavia hexapetala*.⁶ These depsides and other lichen metabolites display a wide range of biological activities, yet their therapeutic potential remains largely unexplored.⁷



In a recent communication, we disclosed a general method for the synthesis of functionalized salicylates (**III**) under essentially neutral conditions through photolysis of benzodioxinones (I) [eq 1, X = H].⁸ The in situ generated quino-

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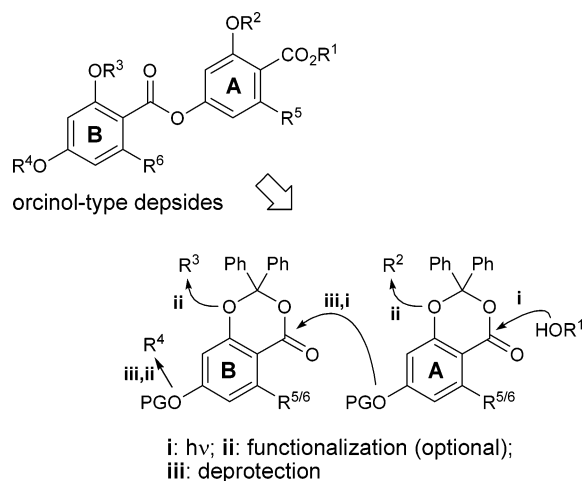
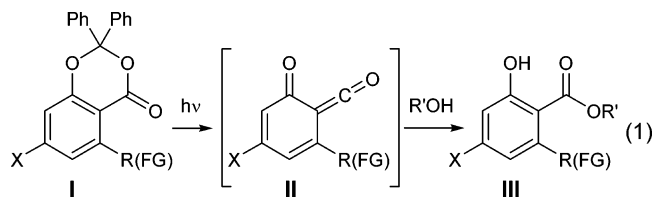


Figure 1. Photochemical approach to orcinol-type depsides.

ketenes (**II**)⁹ efficiently acylate a wide range of substrates, including sterically hindered and base-sensitive alcohols that are inert to other acylation methods.⁸ We envisioned that a similar reaction modality could benefit the synthesis of resorcinyl esters [eq 1, X = OR], an operation that is sometimes difficult to achieve with more conventional methods.^{10,11} Herein, we report the successful application of our methodology to the first total synthesis of gustastatin (**1**), an inhibitor of solid human tumor cell lines.

We designed a modular and general approach to the orcinol-type depside system, creating opportunities to access natural as well as designed members for further exploration. Our underlying concept is based on the mild functional group-tolerant photolysis of functionalized benzodioxinones [eq 1], appropriately sequenced according to the format



shown in Figure 1: (1) irradiation of a protected *p*-hydroxy benzodioxinone (ring A) in the presence of an alcohol (step

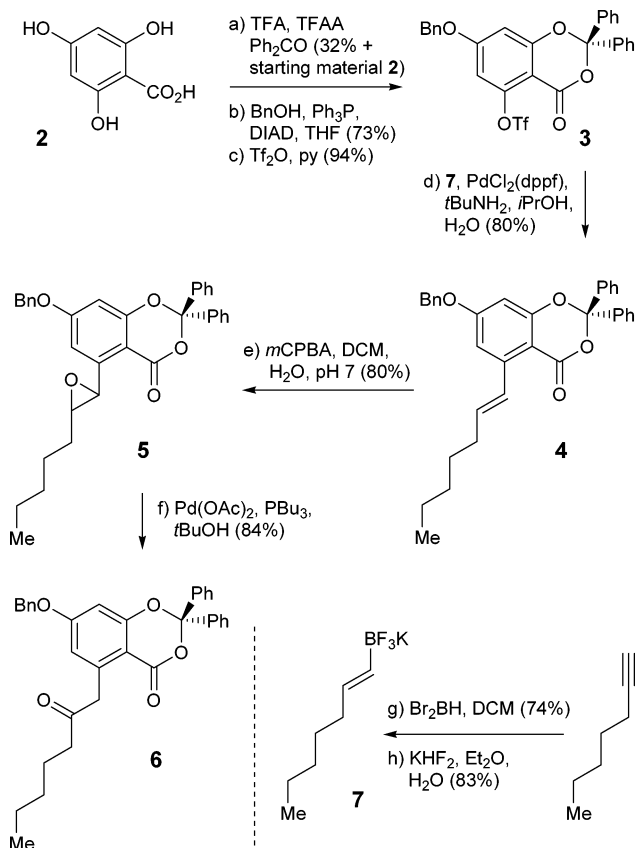
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(11) For an elegant solution to benzofused resorcinyl macrolides via de novo aryl synthesis from ynolides, see: Yang, Z.-Q.; Geng, X.; Solit, D.; Pratilas, C. A.; Rosen, N.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 7881–7889.

Scheme 1



i); (2) optional functionalization of the liberated *o*-phenol (step ii); (3) deprotection of the *p*-phenol (step iii); (4) repeating this sequence with a liberated *p*-phenol A-ring donor and benzodioxinone B-ring acceptor (steps i, iii, ii). This concept was reduced to practice exemplified by the synthesis of gustastatin (**1**) described below.

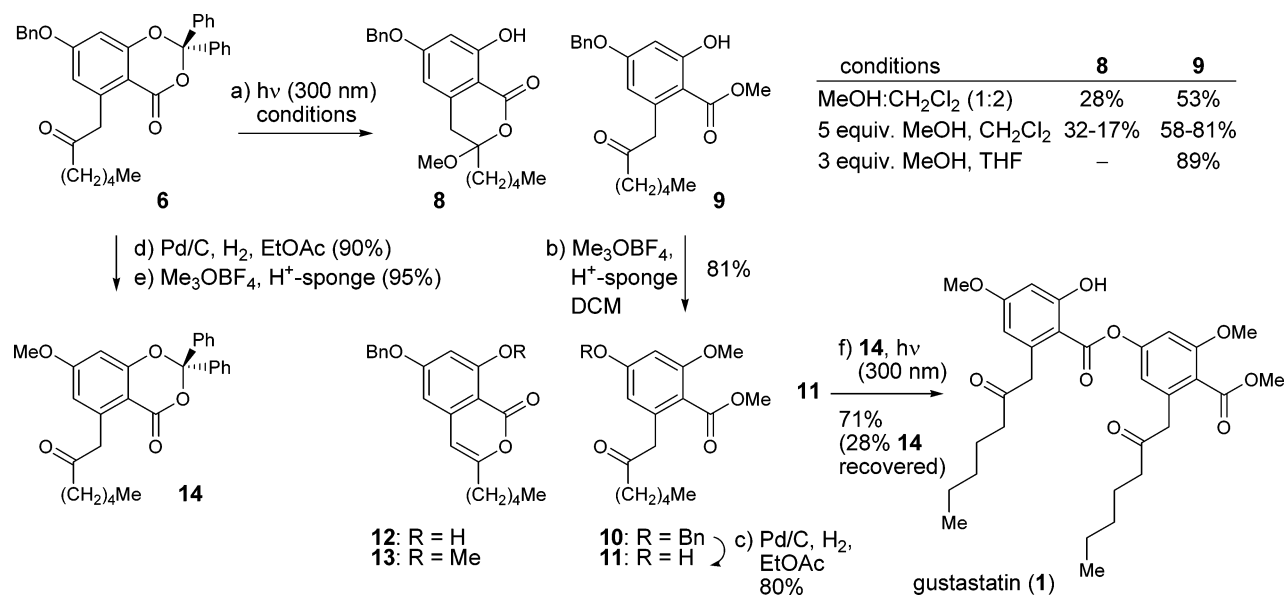
The synthesis of functionalized benzodioxinones commences from cheap 2,4,6-trihydroxybenzoic acid **2** (Scheme 1). Condensation of this material with benzophenone, followed by selective benzylation of the *p*-hydroxyl under Mitsunobu¹² conditions and triflation of the remaining *o*-hydroxyl furnished benzodioxinone **3**.¹³ Our next objective entailed the introduction of the 2-oxo-heptyl chain, a feat we failed to accomplish in one step via cross-coupling of aryl triflate **3** with a methyl ketone enolate.¹⁴ Instead, we resorted to an oxidative functionalization of the heptenyl appendage in benzodioxinone **4**, a compound conveniently prepared by palladium-catalyzed cross-coupling of air-stable and storable heptenyltrifluoroborate salt **7** (prepared from 1-heptyne as shown)¹⁵ with aryl triflate **3** under conditions reported by Molander and Bernardi (80% yield).¹⁶ While various attempts to functionalize the β -carbon of the styryl

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Scheme 2



bond by hydroboration/oxidation or oxymercuration failed, a palladium-catalyzed epoxy-ketone rearrangement of styryl epoxide **5** (**4**, pH 7 buffered *m*CPBA, 80%)¹⁷ provided the desired β -ketone **6** as the only detectable isomer in 84% yield.¹⁸ Consistent with the proposed oxidative addition/ β -hydride elimination mechanism,¹⁸ epoxide **5** was recovered unchanged when treated with tributylphosphine alone under otherwise identical reaction conditions.

With an appropriately functionalized benzodioxinone at hand, we next explored the potential of our photochemical acylation methodology to assemble the depside gustastatin (Scheme 2). The synthesis of the requisite A-ring methyl resorcinyllate **11** necessitated the photolysis of benzodioxinone **6** in the presence of methanol. When this reaction was performed in dichloromethane (varying amounts of methanol), the desired product **9** could be isolated in acceptable yields between 53% and 81%, but substantial amounts of 3-methoxy-dihydroisocoumarin **8** were also produced under these conditions. Changing the solvent to THF completely suppressed the formation of this byproduct, and methyl resorcinyllate **9** was obtained in 89% yield.¹⁹ It is important to mention that attempted formation of methyl benzoate **9** via conventional methanolysis (K₂CO₃, MeOH) only led to isocoumarin formation (i.e., **12**),²⁰ underscoring the mild conditions of the photochemical alternative.⁸ Facile isocou-

marin formation was also evident during the methylation of the *o*-phenol in **9**. Extensive experimentation revealed that a reagent combination composed of Meerwein's salt and proton sponge was uniquely able to avoid the formation of **12/13**, delivering desired methyl ether **10** as the only product in 81% yield.²¹ Finally, hydrogenolytic debenzylation cleanly liberated *p*-phenol **11**.

The gustastatin B-ring substrate, benzodioxinone **14**, was prepared in two steps from common intermediate **6** via debenzylation (H₂, Pd/C, 90%) and methylation of the liberated *p*-phenol with Meerwein's salt and proton sponge (95%).²¹ Irradiation (300 nm) of benzodioxinone **14** (2 equiv) with *p*-phenol **11** (1 equiv) in dichloromethane completed the synthesis of gustastatin (**1**), obtained in 71% isolated yield (benzodioxinone **14** was recovered in 28%).²² This material was identical to the natural product by IR, UV, ¹H and ¹³C NMR spectroscopy, and high-resolution mass spectrometry.

In summary, we have accomplished the first total synthesis of the antitumor agent gustastatin in 10 steps (longest linear sequence) from commercially available 2,4,6-trihydroxybenzoic acid. A key step in our approach involved a mild photochemical formation of resorcinylic esters without competing isocoumarin formation. This approach provides the blueprint to a general and modular synthesis of natural and unnatural orcinol-type depsides.

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(19) Under these conditions, benzhydrol (34%) and diphenyl-(tetrahydrofuran-2-yl)-methanol (33%) were also isolated, resulting from photochemistry of benzophenone, the stoichiometric byproduct from the initial benzodioxinone photolysis.

(20) Isocoumarin formation is a common problem associated with *o*-(2-oxo-alkyl)-substituted resorcinyllates, requiring the use of masked ketones in synthetic sequences. For selected examples, see: (a) Reference 10a. (b) Elix, J. A.; Jayanthi, V. K. *Aust. J. Chem.* **1987**, 40, 1851–1859. (c) Elix, J. A.; Wardlaw, J. H. *Aust. J. Chem.* **1997**, 4799–486.

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(22) In principle, equimolar amounts of reactants could be employed, although previous observations⁸ indicated that optimal yields are obtained with an excess of one of the reactants. Optimization studies have not been performed in this particular case.

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Supporting Information Available: Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for all new compounds and gustastatin (**1**). This material is available free of charge via the Internet at <http://pubs.acs.org>. OL047507P