

Concise Three-Component Synthesis of  
Defucogilvocarcin M

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## ABSTRACT

Concise synthesis of defucogilvocarcin M was achieved via the [2 + 2 + 2] approach to  $\beta$ -phenylnaphthalene structure.

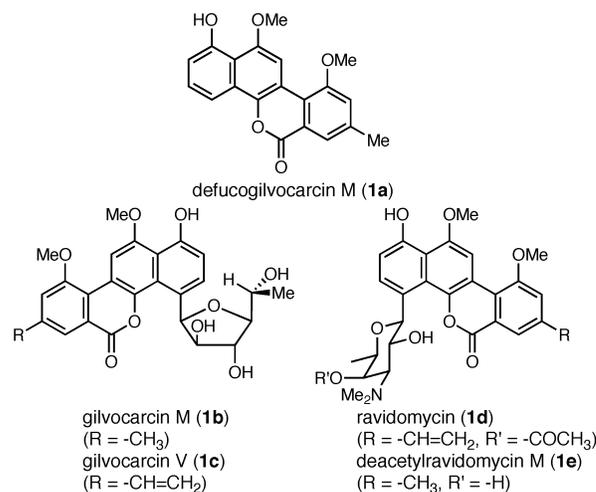
We report herein a new, efficient synthetic route to defucogilvocarcin M (**1a**), representing the chromophore of the gilvocarcin-class antibiotics (Figure 1).<sup>1–3</sup> The necessity of developing a new process emerged during our first synthesis of ravidomycin (**1d**), an amino sugar congener of this class of antibiotics. Although the synthesis was achieved by adopting the scheme that had been effective for the neutral

sugar congeners **1b** and **1c**, several problems arose as a result of the presence of a dimethylamino group in **1d**. More steps were required, and some transformations were capricious due to the deactivation of Lewis acids or transition metal catalysts.<sup>4</sup>

(1) For a review on the gilvocarcin-class antibiotics, see: Hua, H. H.; Saha, S. *Recl. Trav. Chim. Pays-Bas* **1995**, *144*, 341–355.

(2) For isolation and structure determination of the gilvocarcin-ravidomycin class antibiotics, see the following. (a) Gilvocarcin V and M: Horii, S.; Fukase, H.; Mizuta, E.; Hatano, K.; Mizuno, K. *Chem. Pharm. Bull.* **1980**, *28*, 3601–3611. Takahashi, K.; Yoshida, M.; Tomita, F.; Shibahara, K. *J. Antibiot.* **1981**, *34*, 271–275. Hirayama, N.; Takahashi, K.; Shibahara, K.; Ohashi, Y.; Sasade, Y. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1338–1342. (b) Ravidomycin: Findlay, J. A.; Liu, J.-S.; Radics, L.; Rakhit, S. *Can. J. Chem.* **1981**, *59*, 3018–3020. (c) Deacetylavidomycin M: Arai, M.; Tomoda, H.; Matsumoto, A.; Takahashi, Y.; Woodruff, B. H.; Ishiguro, N.; Kobayashi, S.; Omura, S. *J. Antibiot.* **2001**, *54*, 554–561. (d) Defucogilvocarcin V: Misra, R.; Tritch, H. R., III; Pandey, R. C. *J. Antibiot.* **1985**, *38*, 1280–1283. (e) Defucogilvocarcin M (Mer-1020dE): Nakashima, T.; Fujii, T.; Sakai, K.; Sameshima, T.; Kumagai, H.; Yoshioka, T. PCT Patent Appl. WO98/22612 A1, 1998.

(3) For the synthesis of defucogilvocarcins, see: (a) Patten, A. D.; Nguyen, N. H.; Danishefsky, S. J. *J. Org. Chem.* **1988**, *53*, 1528. (b) McGee, R. L.; Confalone, P. N. *J. Org. Chem.* **1988**, *53*, 3695–3701. (c) Jung, M. E.; Jung, Y. H. *Tetrahedron Lett.* **1988**, *29*, 2517–2520. (d) McKenzie, T. C.; Hassen, W.; Macdonald, S. J. F. *Tetrahedron Lett.* **1987**, *28*, 5435–5436. (e) Hart, D. J.; Merriman, G. H. *Tetrahedron Lett.* **1989**, *30*, 5093–5096. (f) Deshpande, P. P.; Martin, O. R. *Tetrahedron Lett.* **1990**, *31*, 6313–6316. (g) James, C. A.; Snieckus, V. *Tetrahedron Lett.* **1997**, *38*, 8149–8152.

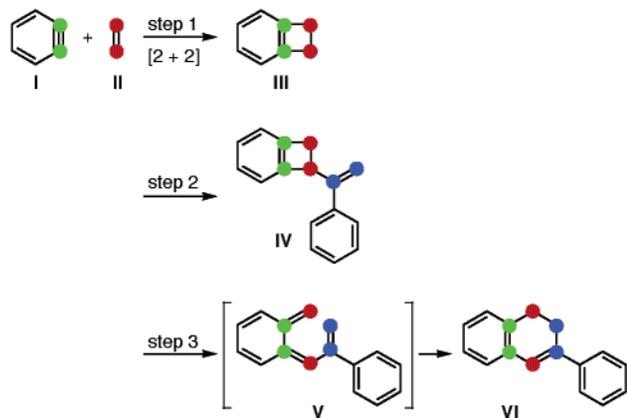


**Figure 1.** Gilvocarcin-class antibiotics (M and V represent the C(8) substituent (R) methyl and vinyl, respectively).

Thus, we decided to pursue synthetic routes that would be viable in the presence of such basic functionality. Our idea was to exploit molecular strain in several pericyclic processes to avoid the use of catalysts or promoters.

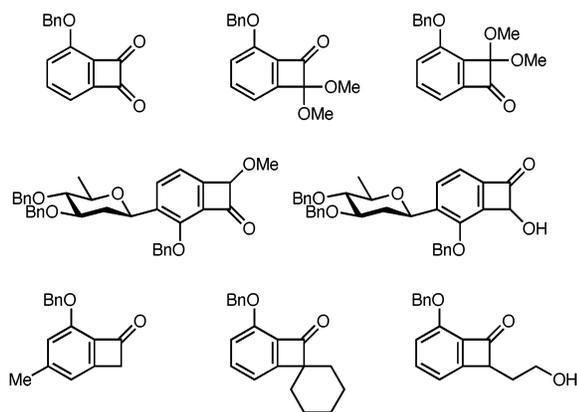
As the prelude to a second-generation total synthesis of ravidomycin (**1d**), we now describe a flexible, efficient access to its chromophore, using a [2 + 2 + 2] cycloaddition/pericyclic cyclization approach (Scheme 1). A three-step

### Scheme 1. [2 + 2 + 2] Route to $\beta$ -Phenyl-naphthalene Cores



process was envisioned that identified the  $\beta$ -phenyl-naphthalene as a key structural motif: The first stage would involve [2 + 2] cycloaddition of the benzyne **I** to the olefin **II** to give the benzocyclobutene **III**. The second step would introduce an additional two carbons in the form of a styryl unit to give **IV**, and finally, sequential pericyclic reactions would form the dihydronaphthalene **VI**. Through the release of molecular strain in the whole process, spontaneous conversion would hopefully occur to furnish the requisite  $\beta$ -phenyl-naphthalene structure.

Our plan was predicated upon the known regioselective [2 + 2] cycloaddition of  $\alpha$ -alkoxybenzynes with ketene silyl acetals,<sup>5</sup> which provides a generous repertoire of benzo-

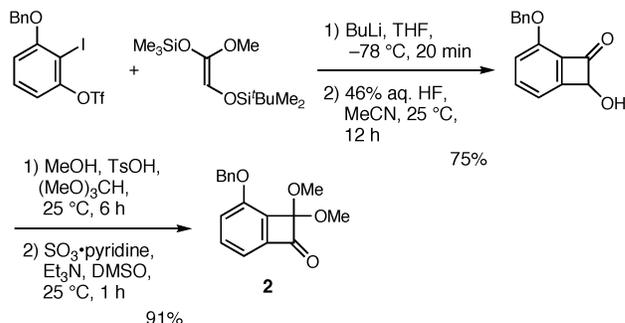


**Figure 2.** Various benzocyclobutenones available.

cyclobuten(di)one derivatives with varying oxidation patterns, including the ones that possess C-glycoside motifs (Figure 2).

We reasoned that benzocyclobutenone **2**, among others, would be best suited for the present purpose; this could be readily prepared as reported (Scheme 2).<sup>5e</sup> Importantly, the

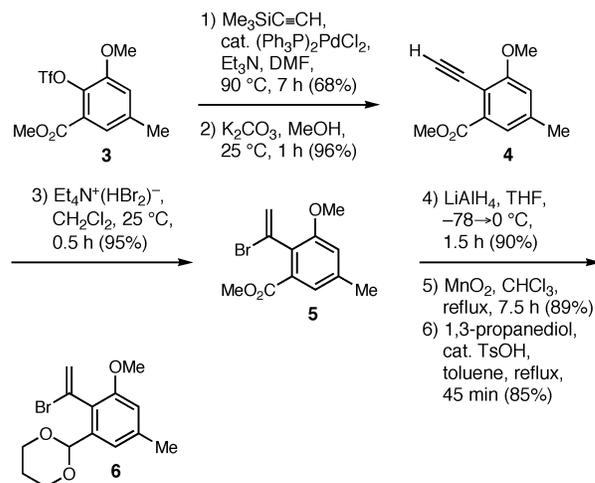
### Scheme 2. Preparation of Benzocyclobutenone **2**



strained carbonyl group in **2** would serve as an effective platform for the facile introduction of a styryl unit. Concerning the subsequent ring expansion step (see step 3 in Scheme 1), we had positive data accumulated for the related but simpler substrates.<sup>6,7</sup>

Scheme 3 shows how the styryl bromide **6** was prepared; it is the building block needed for introducing the styryl

### Scheme 3. Preparation of Styryl Bromide **6**



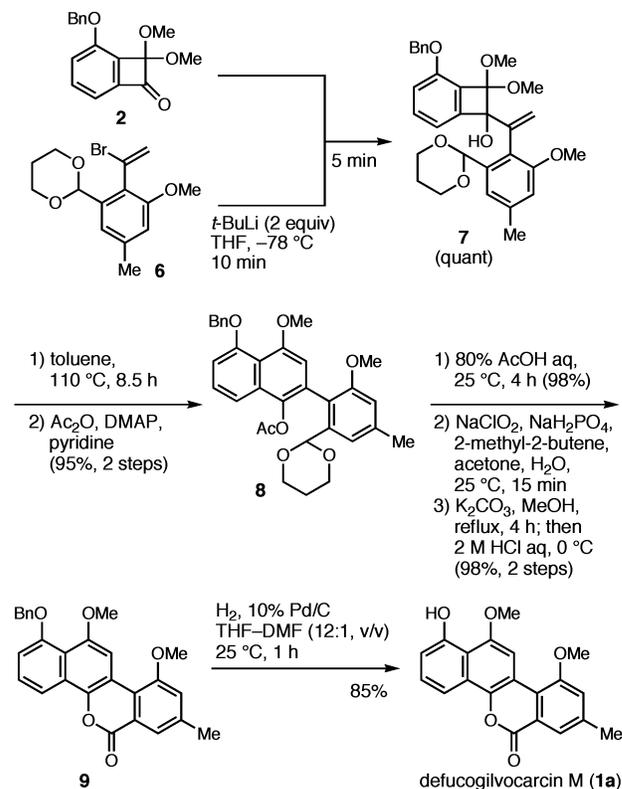
moiety. Triflate **3**<sup>8</sup> was subjected to Sonogashira reaction<sup>9</sup> with trimethylsilylacetylene to give, after desilylation, acetylene **4**. Selective addition of hydrogen bromide to the triple

(4) For the total synthesis of ravidomycin, see: (a) Futagami, S.; Ohashi, Y.; Imura, K.; Ohmori, K.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **2000**, *41*, 1063–1066. For the total synthesis of gilvocarcin M and V, see: (b) Matsumoto, T.; Hosoya, T.; Suzuki, K. *J. Am. Chem. Soc.* **1992**, *114*, 3568–3570. Hosoya, T.; Takashiro, E.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1994**, *116*, 1004–1015.

bond was then effected by using  $\text{Et}_4\text{N}^+(\text{HBr}_2)^-$ ,<sup>10</sup> giving the vinyl bromide **5** in excellent yield. Conversion of ester **5** into 1,3-dioxane acetal **6** was effected by reduction of the ester moiety with  $\text{LiAlH}_4$ , oxidation of the resulting benzyl alcohol, and acetalization of the aldehyde so formed.

Scheme 4 shows a short synthesis of defucogilvocarcin M (**1a**). Benzocyclobutenone **2**<sup>5e</sup> was coupled with the vinyl lithium species generated from vinyl bromide **6**, giving adduct **7** in quantitative yield (THF,  $-78^\circ\text{C}$ , 5 min), ready for the key ring enlargement. We were pleased to find that, upon thermolysis of **7** in refluxing toluene for 8.5 h, naphthalene **8** was obtained in 95% yield after acetylation of the crude products.<sup>11</sup> Note that the product was fully aromatized by the in situ elimination of a mole of methanol. Hydrolysis of the acetal moiety in **8** with 80% acetic acid (room temperature, 4 h) gave the corresponding aldehyde in 98% yield, which was oxidized with  $\text{NaClO}_2$  ( $\text{NaH}_2\text{PO}_4$ , 2-methyl-2-butene,  $\text{H}_2\text{O}$ , acetone, room temperature, 15 min) and converted to lactone **9** in 98% yield by methanolysis of the acetate followed by acidification. Final debenzoylation was cleanly effected by hydrogenolysis on 10% Pd-C in a THF/DMF solvent mixture (12/1, v/v), giving defucogilvocarcin

**Scheme 4.** Total Synthesis of Defucogilvocarcin M



(5) For the [2 + 2] cycloaddition of benzynes and ketene silyl acetals, see: (a) Hosoya, T.; Hasegawa, T.; Kuriyama, Y.; Matsumoto, T.; Suzuki, K. *Synlett* **1995**, 177–179. (b) Hosoya, T.; Hasegawa, T.; Kuriyama, Y.; Suzuki, K. *Tetrahedron Lett.* **1995**, 36, 3377–3380. (c) Hosoya, T.; Hamura, T.; Kurayama, Y.; Miyamoto, M.; Matsumoto, T.; Suzuki, K. *Synlett* **2000**, 520–522. (d) Matsumoto, T.; Yamaguchi, H.; Hamura, T.; Tanabe, M.; Kuriyama, Y.; Suzuki, K. *Tetrahedron Lett.* **2000**, 41, 8383–8387. (e) Hamura, T.; Hosoya, T.; Yamaguchi, H.; Kuriyama, Y.; Tanabe, M.; Miyamoto, M.; Yasui, Y.; Matsumoto, T.; Suzuki, K. *Helv. Chim. Acta* **2002**, 85, 3589–3604.

(6) For our contribution in this area, see: Matsumoto, T.; Hamura, T.; Miyamoto, M.; Suzuki, K. *Tetrahedron Lett.* **1998**, 39, 4853–4856. Hamura, T.; Miyamoto, M.; Matsumoto, T.; Suzuki, K. *Org. Lett.* **2002**, 4, 229–232. Hamura, T.; Miyamoto, M.; Imura, K.; Matsumoto, T.; Suzuki, K. *Org. Lett.* **2002**, 4, 1675–1678. Hamura, T.; Tsuji, S.; Matsumoto, T.; Suzuki, K. *Chem. Lett.* **2002**, 280–281.

(7) (a) For reviews on related reactions, see: Moore, H. W.; Yerxa, B. R. *Chemtracts* **1992**, 5, 273–313. Liebeskind, L. S. *Tetrahedron* **1989**, 45, 3053–3060. (b) For leading references, see: Jackson, D. K.; Narasimhan, L.; Swenton, J. S. *J. Am. Chem. Soc.* **1979**, 101, 3989–3990. Liebeskind, L. S.; Iyer, S.; Jewell, C. F., Jr. *J. Org. Chem.* **1986**, 51, 3067–3068. Hickman, D. N.; Wallace, T. W.; Wardleworth, J. M. *Tetrahedron Lett.* **1991**, 32, 819–822. Perri, S. T.; Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1986**, 51, 3067–3068.

(8) Hosoya, T.; Takashiro, E.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1994**, 35, 4591–4594. Hosoya, T.; Takashiro, E.; Yamamoto, Y.; Matsumoto, T.; Suzuki, K. *Heterocycles* **1996**, 42, 397–414.

(9) Cousseau, J. *Synthesis* **1980**, 805–806.

(10) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467–4470.

(11) Protection of the phenol was necessary, because further conversion otherwise did not work. Upon hydrolysis of the acetal without protection of the phenol, spontaneous cyclization occurred to give the corresponding lactol, which failed to undergo oxidation to the desired lactone **9** under a variety of conditions, giving only the corresponding quinone instead.

**M (1a)** in 85% yield. All spectroscopic data of the synthetic material was fully consistent with the literature data.<sup>12</sup>

In conclusion, we have reported a short total synthesis of defucogilvocarcin M that now provides efficient access to the core skeleton of the gilvocarcin-ravidomycin class of antibiotics. Simplicity and efficiency of the overall process should contribute to the future realization of a new synthesis of ravidomycin and its congeners. Further studies along these lines are now in progress in our laboratories.

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**Supporting Information Available:** Spectroscopic and analytical data of the compounds in Schemes 3 and 4 and the synthetic sample of defucogilvocarcin M (**1a**). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(12) We thank Drs. Isshiki and Nakashima, Mercian Co., for authentic <sup>1</sup>H and <sup>13</sup>C NMR spectra of **1a**.