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Combined Directed Metalation - Cross Coupling Strategies. Total Synthesis of the Aglycones of Gilvocarcin V, M and E

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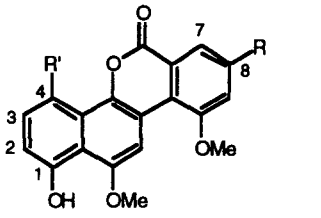
Abstract: Using the versatile Directed ortho and remote Metalation protocols linked with Suzuki-Miyaura cross coupling, efficient syntheses of defucogilvocarcin V, M, and E, **2-4** have been achieved. © 1997 Elsevier Science Ltd.

The gilvocarcins (**1-4**) represent a notable group of naphtho[b,d]benzopyran-6-one natural products isolated from various strains of *Streptomyces*,[1] which, in view of their challenging structural features as well as significant antibiotic and antitumor activity,[2] have elicited considerable synthetic interest.[3] Previous routes incorporate aromatic nucleophilic addition of Grignards to 2-MeO-aryloxazolines,[3c,d] classical Pechmann condensation[3e] and diazonium Meerwein[3i] coupling as key steps. In the continuation of efforts to demonstrate the synthetic advantages of directed *ortho*[4] and remote[5] metalation strategies linked to transition metal catalyzed cross coupling reactions,[6] we report the total synthesis of defucogilvocarcin V (**2**) and its methyl (**3**) and ethyl (**4**) analogues. This route, proceeding *via* the remote anionic Fries rearrangement (**5**), provides an

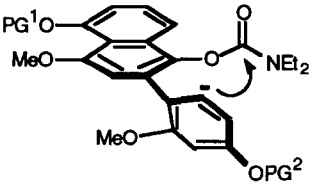


1 R = vinyl, R' =

2 R = vinyl, R' = H

3 R = Me, R' = H

4 R = Et, R' = H



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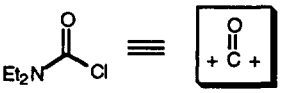

carbonyl dication equivalent

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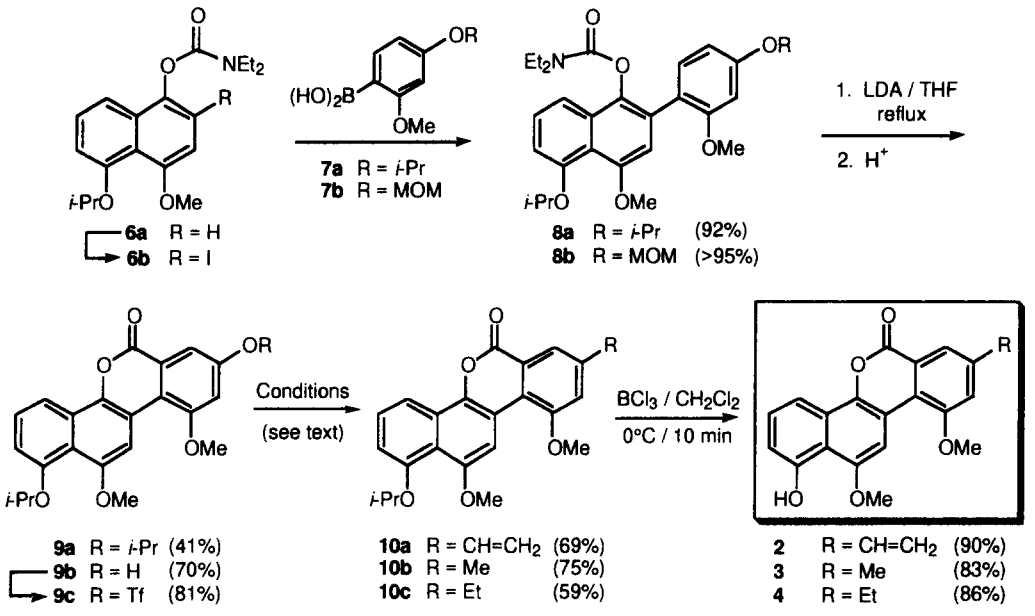
Dedicated to Dieter Seebach, colleague and friend, on his 60th birthyear for his incessant abilities to trail blaze consequential problems in organic synthesis.

efficient route to these systems and anticipates further utility of remote metalation tactics in the preparation of analogues and similar structural types.

To initiate the synthesis, differentially protected trioxygenated naphthalene species **6a**[7] (**Scheme 1**) was metalated - iodinated (1. *s*-BuLi/TMEDA/THF/-78°C; 2. I_2) to give **6b** in 94% yield. Pd(0)-catalyzed Suzuki-Miyaura cross coupling with arylboronic acid **7a**[8] using an improved $Ba(OH)_2$ mediated procedure[9] furnished the biaryl **8a** in excellent yield. In the initial strategy, the C-8 *i*-Pr protection was chosen due to its known stability to the standard[5b] LDA remote metalation conditions.[10] In the event, the key remote metalation - carbamoyl migration - cyclization sequence proceeded smoothly on **8a** under standard conditions (1. 3 equiv LDA/THF/reflux/1 h; 2. HOAc/reflux/10 min) affording tetracyclic lactone **9a** in modest yield.[11]

Scheme 1



However, the required *double* deisopropylation under a variety of Lewis acid conditions (BCl_3, $TiCl_4$) failed leading only to mono C-1 deprotection.[12] The circumvention of this impasse necessitated consideration of differential protection of the C-1 and C-8 phenols. To this end, the MOM ether **7b**[13] was coupled with **6b** to give **8b** which, upon treatment with LDA under modified[14] conditions followed by 50% aq HOAc cyclization, furnished the desired phenol lactone **9b** in good yield over two steps. Compound **9b** was readily converted ($Tf_2O/Et_3N/CH_2Cl_2$/-78°C) to the corresponding triflate **9c** which upon treatment with vinyltributyltin under

modified[15] Stille conditions (2 mol % $Pd_2(dba)_3$/LiCl/(2-furyl)$_3$P/NMP/rt/5 h) gave **10a** in 69% yield. Selective deprotection with BCl_3 afforded defucogilvocarcin V (**2**), shown to be identical with the natural product by comparison of physical and spectroscopic data.[3d] To enliven cross coupling diversity, the triflate **9c** was subjected to Negishi coupling with MeZnBr (5 mol % $NiCl_2$dppp/THF/rt/12 h) and Suzuki - Miyaura coupling with BEt_3 (5 mol % $PdCl_2$dppf/K_3PO_4/THF/reflux/1 h) yielding the methyl (**10b**) and ethyl (**10c**) analogues respectively. Deprotection of these compounds with BCl_3 as before afforded defucogilvocarcins M[16] (**3**) and E[3e] (**4**) whose spectroscopic properties were identical with those reported.

In summary the total synthesis of defucogilvocarcin V (**2**) has been accomplished in nine steps and 14% overall yield from commercially available juglone which constitutes an advance in efficacy over previous methods.[17] In addition, the aglycones **3** and **4** have been prepared from triflate **9c**, the focal intermediate for all three final products. Thus, the versatility of the combined directed ortho- and remote - metalation and cross coupling strategy has been further demonstrated.[18,19]

References and Footnotes

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3. For literature concerning structural determination and an organized review of the synthetic work, see: a) Hua, D. H.; Saha, S. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 341. Defucogilvocarcin V: b) MacDonald, S. J. F.; McKenzie, T. C.; Hassen, W. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1528. c) Patten, A. D.; Nguyen, N. H.; Danishefsky, S. J. *J. Org. Chem.* **1988**, *53*, 1003. d) Findlay, J. A.; Daljeet, A.; Murray, P. J.; Rej, R. N.; *Can. J. Chem.* **1987**, *65*, 427. e) McGee, L. R.; Confalone, P. N. *J. Org. Chem.* **1988**, *53*, 3695. Defucogilvocarcin M: f) Hart, D. J.; Merriman, G. H. *Tetrahedron Lett.* **1989**, *30*, 5093. g) Jung, M. E.; Jung, Y. H. *Tetrahedron Lett.* **1988**, *29*, 2517. h) Deshpande, P. P.; Martin, O. R. *Tetrahedron Lett.* **1990**, *31*, 6313. i) McKenzie, T. C.; Hassen, W.; McDonald, S. J. F. *Tetrahedron Lett.* **1987**, *28*, 5435. Defucogilvocarcin E: see ref. 3e.
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7. Considerable effort was expended in the preparation of **6a**, including the benzyne cycloaddition protocol of Suzuki (see Hosoya, T.; Takashiro, E.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1994**, *116*, 1004 and references cited therein) which was abandoned due to a) inability to scale up the procedure, b) expense and limited availability of starting 2-methoxyfuran and c) modest yield (50%) in the cycloaddition step. An alternate method was adopted based on a modification of the selective reductive acylation of juglone derivatives by Giles (Chorn, T. A.; Giles, R. G. F.; Green, T. R.; Hugo, V. I.; Mitchell, P. R. K.; Yorke, S. C. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1339).

8. Prepared from 4-bromo-3-methoxyphenol (Bos, M. E.; Wulff, W. D.; Miller, R. A; Chamberlin, S; Brandvold, T. A. *J. Am. Chem. Soc.* **1991**, *113*, 9293.) in two steps: 1. *i*-PrI/K_2CO_3/acetone/reflux (98%); 2. a. *n*-BuLi/THF/-78°C, b. $B(OMe)_3$, c. H_3O^+ (67%).
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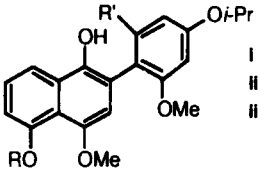
10. In a model study on *N,N*-diethyl-2-(4-isopropoxy-3-methoxyphenyl)-1-naphthyl-O-carbamate, the migration/acid mediated cyclization protocol proceeded in 76% with no detectable cleavage of the isopropyl group.
11. In addition to **9a**, decarbamoylated diisopropyl ether **i** and C-1 deisopropylated derivatives **ii** and **iii** were also isolated and characterized. These presumably result from LDA induced β-elimination assisted by C-12 OMe coordination. For an analogous deisopropylation, see ref. 5b.



i	R = *i*-Pr, R' = H	(13%)
ii	R = H, R' = H	(9%)
ii	R = H, R' = $CONEt_2$	(30%)

12. The structure was established by an NOE difference experiment. The *i*-Pr methine H (δ 4.86) showed a strong NOE to H_7 while H_2 showed no NOE. For a similar example of coordinative aryl ether cleavage, see Hua, D. H.; Saha, S.; Roche, D.; Maeng, J. C.; Iguchi, S.; Baldwin, C. *J. Org. Chem.* **1992**, *57*, 399.
13. Prepared analogously to **9a**: 1. NaH/MOMCl/DMF (91%); 2. a. *n*-BuLi/THF/-78°C, b. $B(OMe)_3$, c. H_3O^+ (72%).
14. Introduction of the base (2.5-3 equiv) in two portions separated by 1.5 h followed by cyclization gave **9b** in 70% yld.
15. Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.
16. Merriman, G. H. Ph.D. Thesis, Ohio State University, Columbus, Ohio, **1990**; *Diss. Abstr. Int. B*, **1991**, *51*, 5875, Order # 9111767.
17. Defucogilvocarcin V (**2**): 4 steps, 9% overall yld[3c] (not from a commercial material), 12 steps, 3% overall yld[3d] and 13 steps, 0.6% overall yld.[3e] Defucogilvocarcin M (**3**): 9 steps, 28% overall yield,[3f] 10 steps, 16% overall yld,[3g] 12 steps, 7% overall yld.[3i] Defucogilvocarcin E (**4**): 9 steps, 5% overall yld.[3e]
18. All new compounds show analytical and spectral data consistent with the depicted structures.
19. We are grateful to NSERC Canada and Monsanto/Searle for support under the Industrial Research Chair program.

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