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A New Synthesis of Defucogilvocarcin M

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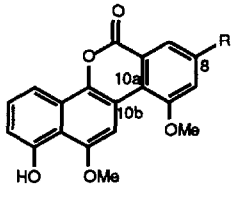
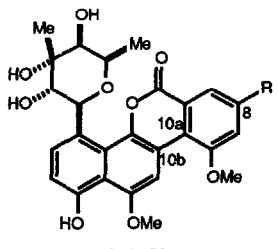
Abstract: A convergent synthesis of the title compound is described. The synthesis revolves around a MAD-mediated coupling of oxazoline **11** and naphthoquinone ketal **16** and requires eight steps via the longest linear sequence.

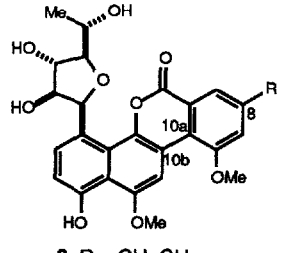
Defucogilvocarcin V (**1**)[1] and defucogilvocarcin M (**2**) are aglycones common to a family of C-aryl glycosides that include the gilvocarcins (**3**-**4**)[2] and chrysomycins (**5**-**6**).[3,4] These compounds display interesting biological properties including antibiotic (**1**, **3**-**6**) and antitumor (**1**, **3**, **5**, **6**) activity. The antitumor activity of **1**, **3**, and **5** has been attributed to a photochemical process which requires the presence of the C(8) vinyl group.[5] The phenomena responsible for the activity of **6** have yet to be established. A number of syntheses of **1**[6-9] and **2**[10,11] have been described. Three of these syntheses revolve around construction of the C(10a)-C(10b) bond using processes in which C(10a) and C(10b) behave as electrophile and nucleophile, respectively.[6-8] The remaining approaches involve construction of the same bond using either a quinone - aryl diazonium salt[9,10] coupling or a Suzuki biaryl synthesis.[11,12] This letter describes our effort in this area within the context of a synthesis of defucogilvocarcin M (**2**). Our approach involves construction of the C(10a)-C(10b) bond using a reaction in which C(10a) acts as a nucleophile toward a C(10b) electrophile.



1 R = $CH{=}CH_2$
2 R = Me



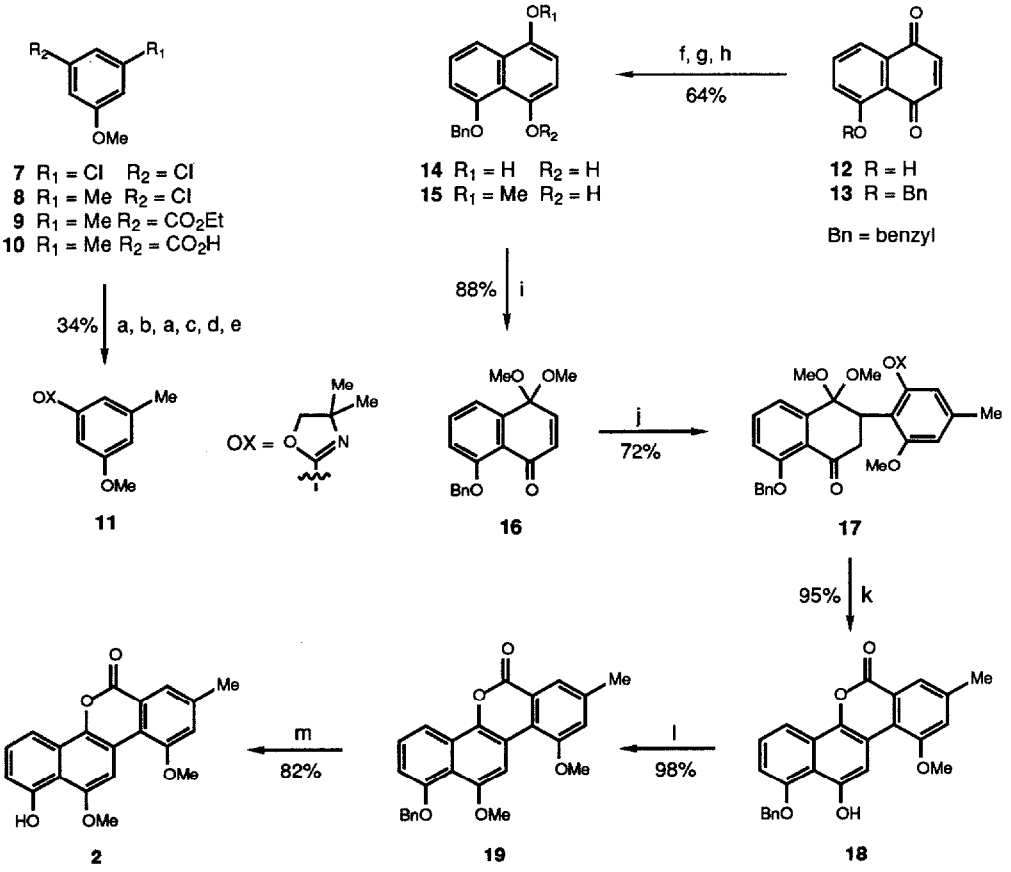
5 R = $CH{=}CH_2$
6 R = Me



3 R = $CH{=}CH_2$
4 R = Me

The key reaction in our synthesis of **2** involved the MAD-mediated conjugate addition[13] of an aryl lithium derived from oxazoline **11** to naphthoquinone monoketal **16**, a process recently developed by Swenton for use with quinone monoketals.[14] Oxazoline **11** was prepared in four steps from commercially available 3,5-dichloroanisole (**7**). Thus, sequential treatment of **7** with Rieke magnesium in tetrahydrofuran and dimethyl sulfate gave **8** in 53% yield.[15] Treatment of

chloride **8** with Rieke magnesium gave the corresponding Grignard reagent, which afforded ester **9** upon exposure to six equivalents of ethyl chloroformate. Saponification of **9** using potassium hydroxide in aqueous methanol gave carboxylic acid **10** (m.p. 130-131°C) in 71% overall yield from **8**.[16] Sequential treatment of **10** with thionyl chloride, 2-amino-2-methyl-1-propanol and thionyl chloride gave oxazoline **11** (87%). Napthoquinone ketal **16** was prepared in four steps from juglone (**12**). Thus, juglone was converted to benzyl ether **13** using a known procedure.[17] Reduction of **13** using sodium hydrosulfite gave **14** (m.p. 157-159°C) in 90% yield. Methylation of the least hindered hydroxyl group was accomplished in 95% yield using dimethyl sulfate and potassium carbonate in acetone under reflux. The resulting phenol **15** (m.p. 118-119°C) was converted to **16** (m.p. 106-108°C) in 88% yield using well established electrochemical procedures.[18]



(a) Rieke Mg, THF, rt (b) Me_2SO_4, THF, rt (c) $ClCO_2Et$ (6.0 equiv) (d) KOH, MeOH-H_2O (3:1), Δ (e) $SOCl_2$, PhH, Δ; $HOCH_2C(Me)_2NH_2$, CH_2Cl_2; $SOCl_2$ (f) BnBr, Ag_2O, $CHCl_3$ (g) $Na_2S_2O_4$, H_2O, Et_2O (h) Me_2SO_4, K_2CO_3, acetone, Δ (i) anodic oxidation, MeOH, 2% $LiClO_4$ (j) **11** + *n*-BuLi, THF; add to **16** + MAD, PhMe, -78°C (k) HCl, THF, H_2O, Δ (l) Me_2SO_4, K_2CO_3, CH_2Cl_2, Δ (m) H_2, Pd/C, THF

The coupling of **11** and **16** was performed as follows. Addition of the aryllithium derived from *o*-metalation of **11** (*n*-butyllithium in tetrahydrofuran at -45°C)[19] to a solution of methyl aluminium bis-(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD)

and naphthoquinone ketal **16** in toluene at -78°C gave tetralone **17** (72%) after purification by column chromatography over silica gel. Ketal and oxazoline hydrolysis, aromatization, and lactone formation were effected by treating **17** with 0.6 M hydrochloric acid in tetrahydrofuran-water (8:1) under reflux. The resulting phenol **18** (95%) gave spectral data in accord with expectation and a melting point (234-237°C) in agreement with that reported by Jung.[11] The synthesis of defucogilvocarcin M (**2**) was completed by methylation of the **18** (98%) followed by hydrogenolysis (82%) of the resulting benzyl ether **19** (218-219°C).

In summary, a synthesis of defucogilvocarcin M (**2**) has been accomplished using a convergent approach that requires only eight steps via the longest linear sequence. We are in the process of applying this strategy to the synthesis of naturally occuring C-aryl glycosides as well as derivatives thereof. These studies as well as other approaches to **1** and **2** will be reported in due course.

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