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A CONCISE TOTAL SYNTHESIS OF THE AGLYCONE OF THE GILVOCARCINS

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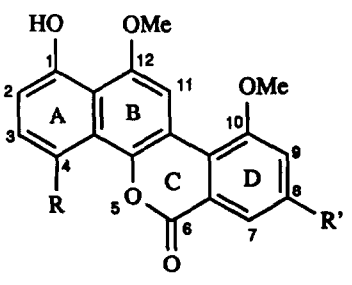
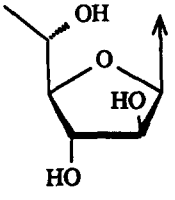
Abstract: A brief and convergent synthesis of the aglycone of the gilvocarcins M and E (and formally V) involving, in the key step, a Pd-mediated *intramolecular* biaryl coupling, is reported.

6*H*-Benzo[*d*]naphtho[1,2-*b*]pyran-6-ones bearing oxygenated substituents at C-1, 10 and 12, and an alkyl (methyl, ethyl) or vinyl group at C-8 constitute the common aglycone of a number of *C*-aryl glycoside antibiotics including, in particular, the gilvocarcins (M, 1a; E, 2a; V, 3a),[1] ravidomycin,[2] and others.[3] Several of these antibiotics exhibit significant antitumor activity:[3] for example, gilvocarcin V is a DNA-intercalating agent of unusual potency[4] whose activity is enhanced by low-energy visible light irradiation;[4b,5] the therapeutic potential of this compound is further supported by its remarkably low toxicity. The complexity of the aglycone as well as the presence of an unusual C-C linkage between a sugar and an aromatic unit make these natural products particularly attractive synthetic targets. Our interest in the field of *C*-aryl glycosides[6] prompted us to develop a short and convergent synthesis of the aglycone of the gilvocarcins which would permit the attachment of the hexofuranosyl unit at an early stage and thus give access to a variety of analogs of the natural product. A number of syntheses of the aglycones 1b - 3b ("defucogilvocarcins") have already been reported; the critical linkage between rings B and D of the tetracyclic system has been created by way of a nucleophilic aromatic substitution,[7] the Pechman reaction,[8] a Meerwein coupling,[9] a conjugate addition to a naphthoquinone ketal,[10] or a Suzuki biaryl coupling.[11] Pioneering investigations on the synthesis of *C*-glycofuranosylated benzonaphthopyranones related to 3a have been performed by Daves and coworkers;[12] a total synthesis of the gilvocarcins remains, however, to be achieved.



1a,b R' = CH_3
2a,b R' = CH_2CH_3
3a,b R' = $CH{=}CH_2$

Series a: R =

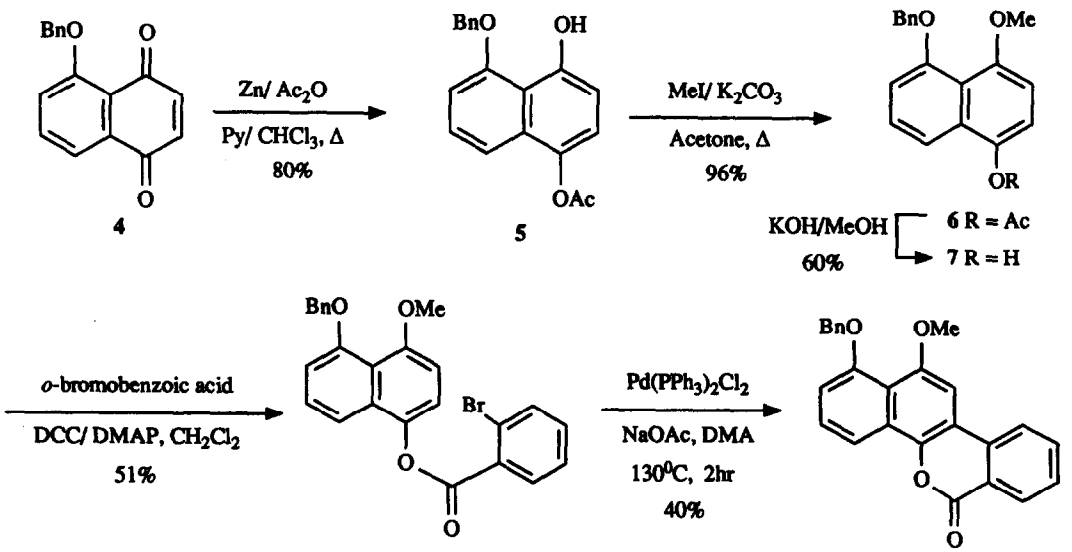


Series b: R = H

The synthesis of the tetracyclic aglycone would be considerably shortened and simplified if the linkage between rings B and D could be generated by way of an *intramolecular* aryl coupling: only one of the two aromatic reaction partners would indeed need to be activated. The successful, Pd-mediated cyclization of aryl

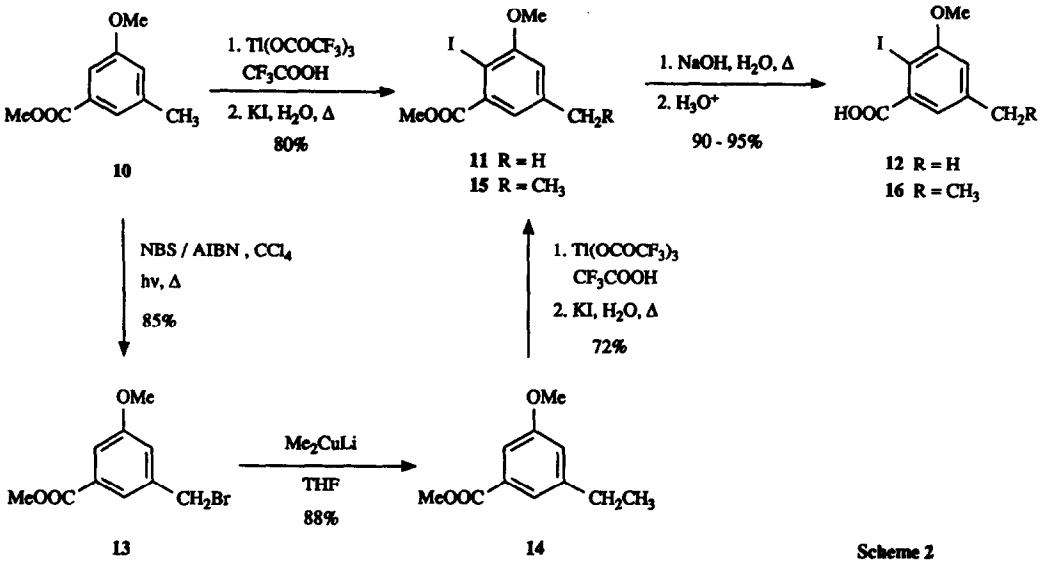
o-bromonaphthoates en route to naphthyl isoquinoline alkaloids such as ancistrocladine[13] constitutes evidence that an intramolecular approach to the "defucogilvocarcins" should be feasible. The precursors required for the critical coupling reaction are a selectively protected 4-methoxy-1,5-naphthalenediol (e.g., **7**) and an *o*-halogenobenzoic acid derivative (e.g., **12** or **16**).

The 1,4,5-naphthalenetriol derivative **6** (m.p. 119-120°)[14] in which all three oxygen atoms are differentiated was obtained in two steps (Scheme 1) from benzylated juglone **4** [15] by way of the efficient reduction-selective acetylation process described by Giles and coworkers.[16] Deacetylation of **6** and DCC-mediated esterification of the resulting naphthol **7** with *o*-bromobenzoic acid as a model for ring D of the natural products, afforded benzoate **8**. The treatment of **8** with $Pd(PPh_3)_2Cl_2$ (0.2 mol equiv) in *N,N*-dimethylacetamide at 130° C in the presence of sodium acetate (see ref. 13) promoted the desired cyclization and gave compound **9** (m.p. 182-183°)[17] in 40% yield. This result clearly demonstrated the viability of the proposed approach to the aglycone of the gilvocarcins.



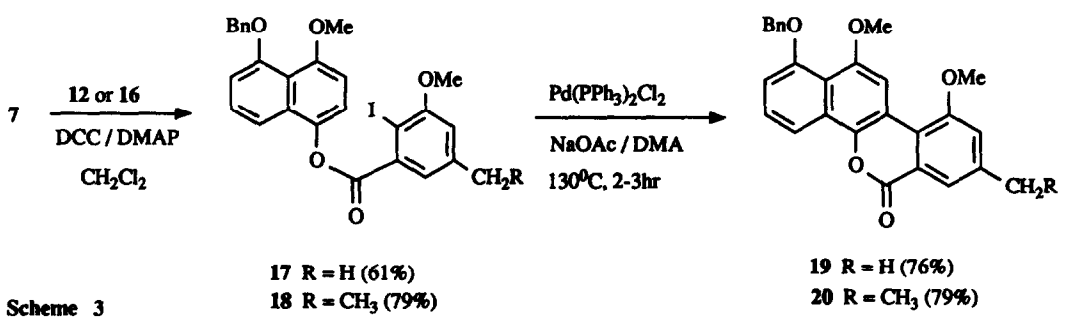
Scheme 1

The substituted benzoic acid needed as the precursor of ring D of the aglycone must contain a halogen *ortho* with respect to both the carboxyl and the methoxy groups. A procedure for the regioselective synthesis of 2-iodobenzoate **11** (in three steps from **10**; **10** was obtained by methylation of 3-hydroxy-5-methylbenzoic acid[18]) has been described by Jung and Jung.[11] However, the thallation[19] of **10** was found to proceed highly regioselectively,[20] to give, after treatment of the resulting arylthallium derivative with aqueous KI,[21] compound **11** [11,22] in high yield, thereby providing a shorter and more convenient route to the required *o*-iodo acid **12** (m.p. 155-156°, Scheme 2). Furthermore, the methyl group of **10** could be readily converted into an ethyl group by benzylic bromination followed by methylation of the resulting bromide (**13**) with Me_2CuLi. The 5-ethyl analog of **10**, compound **14**, was then iodinated by the same procedure, and the ester function of **15** was saponified to generate the ring D precursor of defucogilvocarcin E, compound **16** (m.p. 114-115°).



Scheme 2

Esterification of naphthol 7 with benzoic acid derivatives 12 or 16 afforded functionalized substrates 17 (oil) and 18 (m.p. 97-98°); both of these esters underwent internal biaryl coupling in excellent yield on reaction with $Pd(PPh_3)_2Cl_2$ under the same conditions as before, thereby leading to benzonaphthopyranones 19 and 20 (Scheme 3). The melting points of 19 and 20 (identical to those reported by Jung[11] and McGee[8a] for the same compounds) and their ^{1}H-NMR spectra[23] established their identity as *benzylated defucogilvocarcins M* and *E*, respectively. Furthermore, since the conversion of 20 into defucogilvocarcin V has already been reported,[8a] the present work constitutes also a formal synthesis of the 8-vinyl analog.



Scheme 3

The novel approach to the aglycone of the gilvocarcins presented in this paper provides one of the shortest routes to these aromatic systems: defucogilvocarcin E is available in 7 steps (including the final debenzylation[8a]) in 23% overall yield (unoptimized) from juglone (8 steps, 27%, from 3-hydroxy-5-methylbenzoic acid). The application of the same methodology to the preparation of the corresponding *C*-glycosylated benzonaphthopyranones is now under investigation.

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23. The chemical shifts of the ^{1}H-NMR signals of **19** and **20** match those of the benzylated defucogilvocarcins M [11] (data provided by Prof. Jung) and E [8a] to ±0.04 ppm and the coupling constants are identical.

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