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A xanthate-based free radical approach to defucogilvocarcin M

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ABSTRACT

A formal total synthesis of the aglycon of gilvocarcin M is described. The synthesis is based on the construction of the key naphthalene **7** via a free radical addition–cyclization protocol followed by aromatization of the resulting α-tetralone. This highly functionalized aromatic system is coupled to the corresponding acid chloride **6** to afford ester **4**, which by treatment with a catalytic amount of palladium (0) produced defucogilvocarcin M (**1a**).

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C-Arylglycosides represent a wide class of natural products with interesting biological activities.[1] The strong C–C bond between the carbohydrate and the aromatic moiety provides to these structures higher resistance to enzymatic and acidic hydrolysis.[2] The gilvocarcin-class C-arylglycosides **1b–d** (Fig. 1) display important antibiotic and antitumor activity[1] and due to their unique molecular architecture, these compounds represent interesting synthetic targets. Considerable effort[3] has been devoted to achieve the synthesis of these molecules, however, only one total synthesis of the gilvocarcins has been completed so far.[4]

On the other hand, several syntheses of defucogilvocarcin M (**1a**) have been described. Different strategies have been applied to achieve this goal, including Pechmann condensation,[5a] Suzuki cross-coupling,[5b] 1,4-addition of a lithiated oxazoline,[5c] Stille coupling,[5d–f] Fischer carbene–alkyne reaction,[5g] directed remote metalation,[5h] [2+2+2] cycloaddition,[5i] or a palladium-catalyzed biaryl bond construction.[5j] The latter strategy, developed by Martin, involves the construction of ester **4** as the key intermediate and a final Pd (0)-catalyzed biaryl coupling to afford the benzyl-protected aglycon (**5**) of gilvocarcin M (Scheme 1).

In our continuous interest in developing new routes to C-arylglycoside-class compounds,[3b,6] herein we report a formal total synthesis of defucogilvocarcin M. Our strategy relies on the preparation of the known ester **4** via a free radical addition–cyclization sequence.

The general features of our retrosynthetic plan are depicted in Scheme 2. Defucogilvocarcin M would be obtained from naphthol **7** and acid chloride **6** via an esterification and a palladium-catalyzed biaryl coupling. Tetralone **8**, the substrate for the projected naphthol **7**, might be constructed using a free radical sequence from a substituted acetophenone (**9**) and a suitable olefin (**10**). To this end, we turned our attention to the xanthate-based free radical addition-cyclization sequence developed by Zard (Scheme 3)[7] which has been previously applied to the synthesis of α-tetralones[8] and of C-arylglycosides.[6] It is worth noting that this protocol would afford the tetralone **8** framework containing the properly masked hydroxyl groups of **7**.

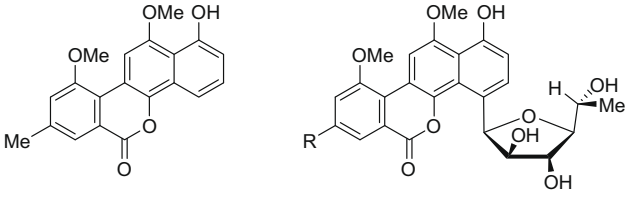
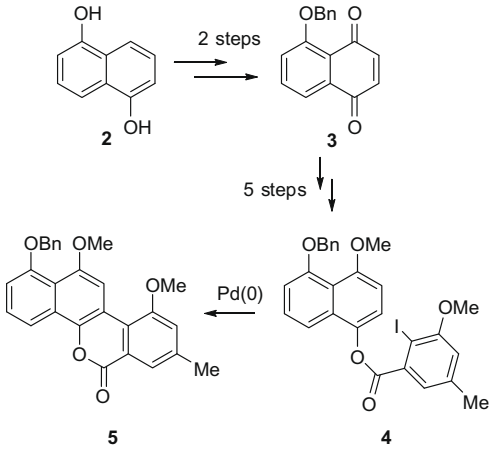


Figure 1. Gilvocarcins (**1b–d**) and defucogilvocarcin M (**1a**).



Scheme 1. Martiń's strategy.

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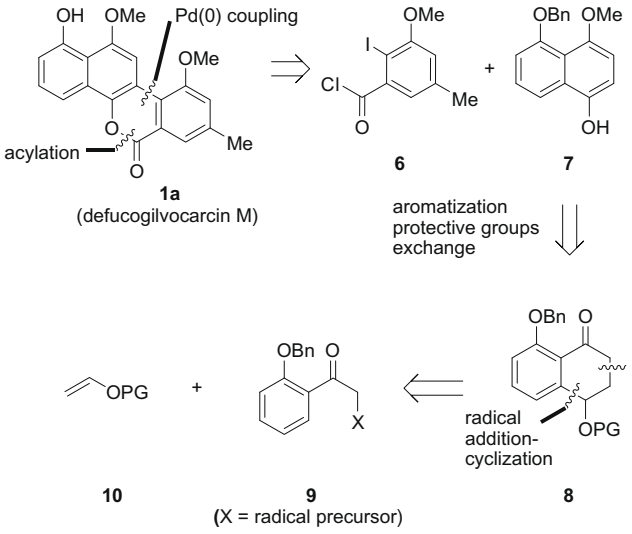
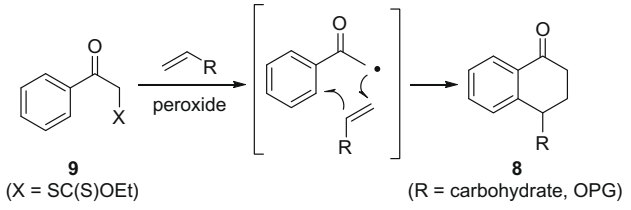


Scheme 2. Retrosynthetic analysis.

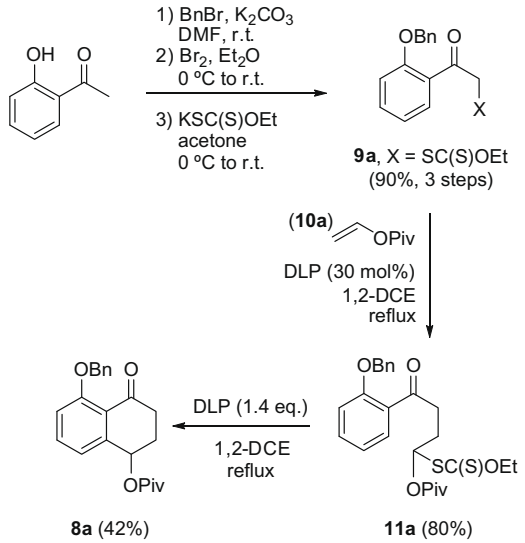
Thus, our synthesis starts with the preparation of the required radical precursor **9a** from commercially available 2-hydroxyacetophenone in three steps (90% overall yield), as depicted in Scheme 4. With the desired precursor in hand, we proceeded to carry out the radical addition onto olefin **10**. In this regard, Zard[9] has shown that vinyl pivalate (**10a**) serves as an effective radical trap and that the ester moiety could be resistant to several reactions conditions in subsequent transformations. Thus, when a mixture of **9a** and vinyl pivalate in refluxing 1,2-dichloroethane was treated with a substoichiometric amount (30 mol %) of dilauroyl peroxide (DLP), a smooth reaction took place to afford adduct **11b** in 80% yield. The latter was then allowed to react with 1.4 equiv of DLP and the expected ring closure took place to form the desired α-tetralone (**8a**) in 42% yield.[10] Although the moderate yield may appear to be disappointing, this transformation would be quite difficult to accomplish by other means. Interestingly, when we attempted the radical sequence with the iodine derivative **9b**[11] (X = I, not shown) under the same reaction conditions,[12,13] we observed nothing but starting material or reduction product.[14]

As depicted in Scheme 5, the aromatization of the α-tetralone **9a** was accomplished by applying a 2-step protocol (α-bromination followed by the elimination of the bromine atom).[15] However, the bromination step using either Br_2 or $PyHBr_3$ yielded a complex mixture of products and indeed, low yields of the desired aromatic compound. In contrast, when a cold (0 °C) solution of the α-tetralone in a mixture of diethyl ether and acetonitrile was treated with 1.1 equiv of NBS, followed by the elimination of the bromine atom with DBU in dichloromethane, the desired naphthol **12** was obtained in 30% overall yield (87% corrected yield, based on recovered starting material).[16] The treatment of **12** with iodomethane and potassium carbonate in dry DMF at 80–90 °C furnished naphthalene **7** in 68% yield. Reduction of the pivaloyl ester followed by the treatment of the crude naphthol with acid chloride **6**[4b,17] afforded the known compound **4**.[5b,5j]

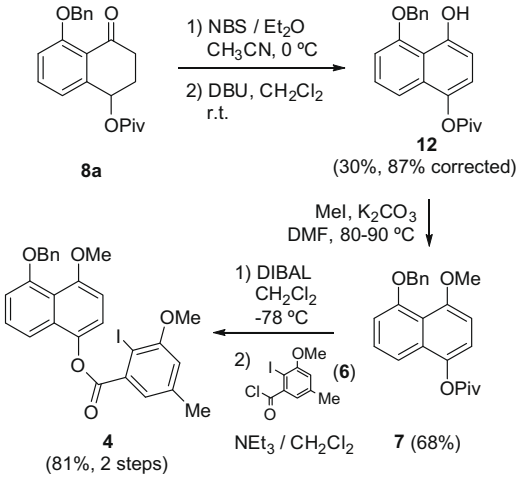
With key ester **4** assembled and the iodine atom properly placed to achieve the palladium-catalyzed cyclization, the formal total synthesis of the aglycon of gilvocarcin M was completed (Scheme 6). In this context, the final transformations, as described by Martin,[5j] included the treatment of **4** with 20 mol% of $PdCl_2(PPh)_2$ and sodium acetate in *N*,*N*-dimethylacetamide (DMA), which led to the benzyldefucogilvocarcin **5** in 65% yield.



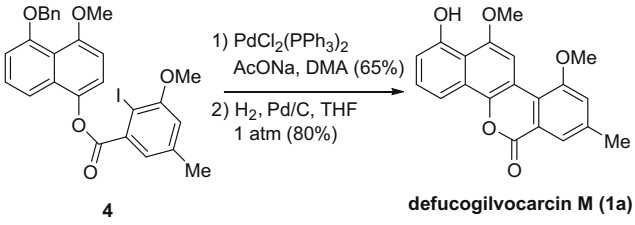
Scheme 3. Radical sequence for the preparation of key α-tetralone.



Scheme 4. Synthesis of compound **9a**.



Scheme 5. Preparation of key ester **4**.



Scheme 6. Completion of the synthesis of defucogilvocarcin M.

Final hydrogenation of the latter in the presence of 10% Pd/C allowed us to prepare defucogilvocarcin **1a** in good yield (80%). All the spectroscopic and physical data of compound **1a** fully matched with those reported by Suzuki[5i] and Snieckus.[5h]

In summary, we have accomplished a formal total synthesis of defucogilvocarcin M. The described route is based on the preparation of the key aromatic skeleton by using a xanthate-based free radical sequence. This route is also highly convergent and could be applied to the synthesis of other aglycons.

Acknowledgments

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Supplementary data

Supplementary data (experimental details for all reactions and spectral data for new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.076.

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10. The radical cyclization was also performed using different reaction conditions, but lower yields of **8a** were obtained (DCP/chlorobenzene: 15% yield; Et_3B/O_2/CH_2Cl_2: 27% yield).
11. Iodine derivative was prepared by reaction of known 2'-benzyloxy-2-bromoacetophenone with NaI in acetone. For the preparation of the bromo derivative, see: Black, M.; Cadogan, J. I. G.; McNab, H.; MacPherson, A. D.; Roddam, V. P.; Smith, C.; Swenson, H. R. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2483.
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13. The Et_3B/O_2 system was also applied unsuccessfully to this reaction. For triethylborane-mediated radical reactions, see: Yorimitsu, H.; Oshima, K. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M., Eds.; Wiley-VCH: Weinheim, 2001; pp 11–27.
14. It has been reported that in the presence of Et_3B, α-carbonyl radicals could evolve the corresponding boron enolates. This is probably the reason why nothing but reduction product in the attempted radical addition of **9b** to vinyl pivalate was observed. For examples on boron enolates, see: (a) Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1041; (b) Beraud, V.; Gnanou, J. C.; Walton, B.; Maillard, B. *Tetrahedron Lett.* **2000**, *41*, 1195.
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16. When we forced the bromination reaction to completion by adding extra amounts of NBS, the starting material disappeared completely, but a number of by-products were formed and the global yields (after treatment with DBU) were considerably lower (40–50%). So, we decided to keep the amount of NBS at 1.1 equiv and to recycle the unreacted starting material.
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