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Stereoselective, Oxidative C–C Bond Coupling of Naphthopyran Induced by DDQ: Stereocontrolled Total Synthesis of Deoxyfrenolicin†

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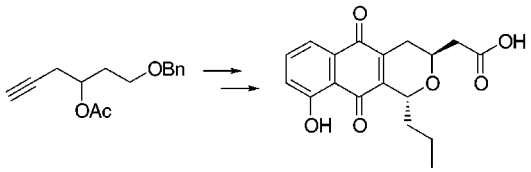
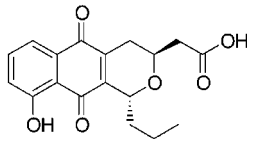
ABSTRACT

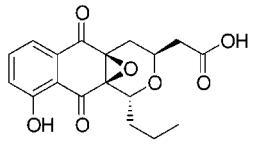


A formal total synthesis of pyranonaphthoquinone natural product deoxyfrenolicin 1 is described. The key step in the synthesis involves the use of stereoselective 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)-induced C–C bond coupling of the naphthopyran 10 with allyltriphenyltin to give exclusively 1,3-*trans* naphthopyran derivative 23. The naphthopyran 10 was obtained via oxa-Pictet–Spengler cyclization of substituted naphthalene 22, which was derived by regioselective benzannulation of chromium carbene complex 12 with acetylene 18. This newly developed synthetic route employing a tandem benzannulation/oxa-Pictet–Spengler cyclization/DDQ-induced coupling strategy should also be applicable to the synthesis of other pyranonaphthoquinone natural products such as kalafungin 4 and nanaomycin 5.

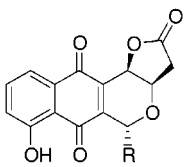
Deoxyfrenolicin **1**, isolated from cultures of *Streptomyces roseofulvus*, is a member of the relatively larger pyranonaphthoquinone family of natural products (Figure 1).[1,2] Many members in this family exhibit significant biological activity against fungi, cancers, and cocci.[1−4] The therapeutic potential of these natural products has attracted considerable attention from the synthetic organic chemistry community. Several approaches toward the synthesis of deoxyfrenolicin **1**,[5−10] frenolicin A **2**,[10] and frenolicin B **3**[10, 11] have been reported.



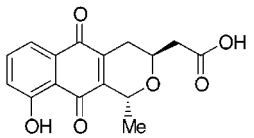
Deoxyfrenolicin **1**



Frenolicin A **2**



Frenolicin B **3** R = Pr
Kalafungin **4** R = Me



Nanaomycin **5**

Figure 1.

Our interest in developing a novel synthetic route to these pyranonaphthoquinone natural products stems from our

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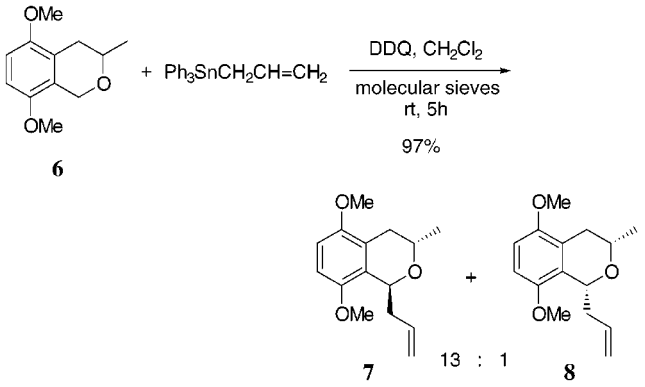
recent findings that benzopyran derivatives such as **6** undergo oxidative couplings with a variety of carbon nucleophiles in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[12] As shown in Scheme 1, treatment of 3-methyl-

Scheme 1



5,8-dimethoxyisochroman **6** with DDQ in dichloromethane at room temperature followed by addition of allyltriphenyltin gave rise to 1-allyl substituted isochromans **7** and **8** in 97% yield. The most important feature of this efficient C−C bond-forming reaction is the high stereoselectivity, providing predominantly the 1,3-*trans* isomer **7**. Application of this C−C bond coupling reaction into a naphthopyran system such as **10** would generate functionalized tricyclic compound **9**, which could serve as a late-stage precursor to deoxyfrenolicin **1** (Figure 2). The anticipated 1,3-*trans* stereochemistry for compound **9** will be the key to the success of our efficient synthesis of deoxyfrenolicin **1**.

The retrosynthetic pathway is presented in Figure 2. Deoxyfrenolicin **1** could be derived from compound **9** via functional group manipulation. Key in the retrosynthetic analysis of naphthopyran **9** was the DDQ-induced introduction of a C-1 propyl group as discussed above. While an efficient process in the bicyclic system (Scheme 1), success of such a stereoselective reaction with a tricyclic naphthopyran substrate was yet to be proven. Compound **10** could be prepared from 2-substituted-1,4,5-trimethoxynaphthalene **11** via oxa-Pictet−Spengler cyclization.[13] Finally, preparation of **11** could be realized via a benzannulation reaction of chromium carbene complex **12** with properly functionalized terminal acetylene **13**.[14,15] The simplicity of this route using tandem benzannulation/oxa-Pictet−Spengler cyclization/DDQ-induced C−C coupling makes it an attractive approach to deoxyfrenolicin **1**.

The detailed synthesis of deoxyfrenolicin **1** is presented in Scheme 2 starting from 3-buten-1-ol. Installation of the benzyl protecting group on the alcohol of **14** using benzyl bromide, NaOH, and triethylamine,[16] followed by epoxidation of the terminal olefin with MCPBA in dichloromethane, gave rise to the epoxide **16** in 80% overall yield.[17] The reaction of **16** with lithium acetylide in DMSO at room temperature resulted in the regioselective ring opening of the epoxide, affording 91% of the terminal acetylene **17**,[18] of which the secondary alcohol could be efficiently blocked as either the methoxymethyl ether (MOM) or the acetate (Ac).

Our initial attempts to build the multisubstituted naphthalene **19** via the benzannulation reaction of chromium carbene complex **12** with the MOM-protected acetylene **13** fell short of expectation. While the chromium carbene complex **12** is readily accessible,[19] the benzannulation reaction in either benzene or THF solvent using reported procedures gave the expected product **19** in only about 10−25% yield.[20] Although the benzannulation reaction of chromium carbene complexes with acetylene is a well-studied process,[21] such a reaction with an acetylene bearing a MOM group at the β-position is not known.[22] We suspect that coordination of the MOM group with the oxophilic chromium carbene complex might have retarded the normal benzannulation processes.[21]

Selection of the MOM protecting group had a special purpose at the beginning of synthesis because naphthalene derivative **19** or **11** bearing a MOM ether at the C-2 substituent could be directly cyclized to give tricycle **10** using $TiCl_4$.[23] The low yield in the benzannulation reaction prompted us to consider other protecting groups. We were

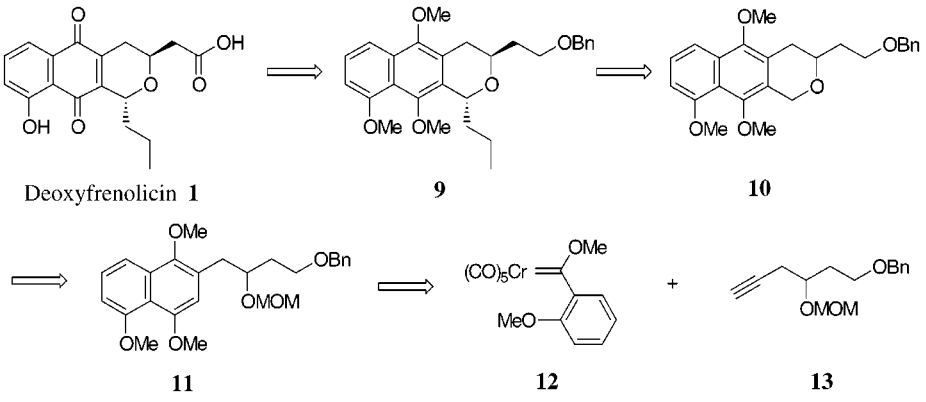
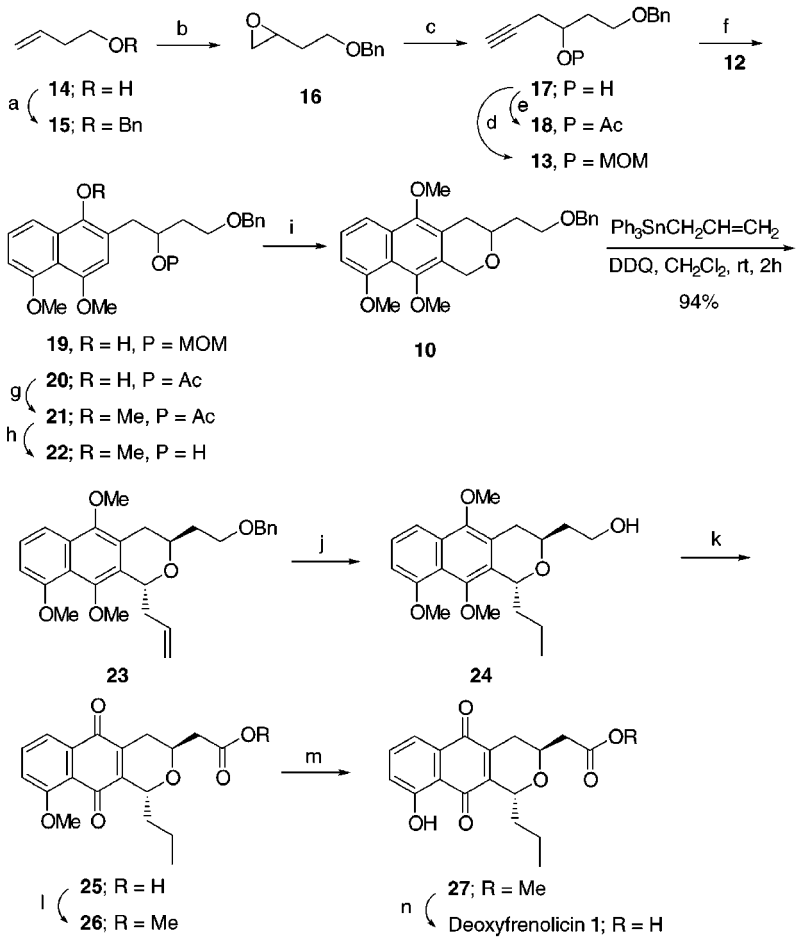


Figure 2.

Scheme 2[a]



[a] (a) $PhCH_2Br$, NaOH, Et_3N, hexane, reflux, 5h, 98%; (b) MCPBA, CH_2Cl_2, rt, 24 h, 91%; (c) LiC≡CH·EDA, DMSO, rt, 40 min, 91%; (d) $CH_2(OMe)_2$, P_2O_5, $CHCl_3$, rt, 79%; (e) AcCl, Ac_2O, Py, CH_2Cl_2, rt, 91%; (f) **12**, THF, 60 °C, 15 h, 74%; (g) MeI, K_2CO_3, acetone, reflux, 3 h, 81%; (h) K_2CO_3, MeOH, H_2O, rt, 6 h, 85%; (i) $CH_2(OMe)_2$, BF_3·Et_2O, Et_2O, rt, 85%; (j) H_2, Pd/C (10%), EtOH, rt, 2 days, 77%; (k) CrO_3, acetone, CH_3CO_2H, H_2O, rt, 40 min; (l) MeOH, H_2SO_4, rt, 12 h, 43% for last two steps; (m) BBr_3, CH_2Cl_2, −78 to 0 °C, 85%; (n) KOH, MeOH, rt, 3 h, 97%.[9]

delighted to find that the benzannulation reaction of **12** with the acetylene ester **18** proceeded smoothly, affording naphthol **20** in 74% isolated yield. It should be noted that the benzannulation reaction with this terminal acetylene is highly regioselective to give only 2-substituted naphthol, consistent with what had been reported in the literature.[14] Methylation of the phenol using iodomethane and K_2CO_3 gave 81% of 1,4,5-trimethoxynaphthalene **21**,[24] which was converted to alcohol derivative **22** in an 85% yield upon hydrolysis of the acetyl group (K_2CO_3, MeOH, H_2O). The oxa-Pictet−Spengler cyclization of **22** with dimethoxymethane was carried out in Et_2O using BF_3 etherate to give an 86% yield of the functionalized naphthopyran **10**.[25]

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One would expect that the extension of this oxa-Pictet−Spengler cyclization with alkyl aldehyde will give 1-alkylnaphthopyran directly. Such an approach was previously employed in the synthesis of other related pyranonaphthoquinones.[26] Unfortunately, only the 1,3-*cis* isomer of the naphthopyran derivative was obtained. For that purpose, this approach will not directly lead to the requisite 1,3-*trans* stereochemistry of deoxyfrenolicin **1**.

The oxidative coupling reaction of **10** with allyltriphenyltin in CH_2Cl_2 in the presence of DDQ provided the allyl-substituted naphthopyran **23** in 95% yield. This outcome is significant for the following reasons. The oxidative C−C coupling reaction with naphthopyran is as efficient as the benzopyran system. Nearly identical yields were obtained from both compounds **10** and **6**. The reaction is highly stereoselective, resulting in the exclusive formation of the *trans* isomer, which has exactly the same stereochemistry as that of deoxyfrenolicin **1**. No *cis* isomer was detected from the reaction. The C_1-C_3 *trans* stereoselectivity is unique in our approach because most previous reported syntheses suffered more or less from this stereochemical control.[5−9,11]

With the basic framework built and the proper substituents installed, the final stage of the synthesis basically involves functional group manipulation. The benzyl protecting group was removed under hydrogenation conditions using 10% Pd/C catalyst in ethanol, and under such conditions, the terminal double bond was also reduced to provide compound **24** in 77% overall yield. The primary alcohol in **24** can be oxidized to carboxylic acid using CrO_3 in acetone and an acetic acid solvent mixture.[27] To our surprise, the central benzene ring bearing two methoxy groups was also oxidized to the quinone, affording compound **25** in a single-step operation. While CrO_3 is a known strong oxidant, oxidative demethylation of 1,4-dimethoxybenzene to 1,4-benzoquinone using CrO_3 is not precedented in the literature. To facilitate isolation, the carboxylate **25** was converted to methyl ester **26** using MeOH and H_2SO_4 in 43% overall yield for last two steps. The deprotection of the methyl ether **26** was effected by BBr_3 in CH_2Cl_2 to provide deoxyfrenolicin methyl ester **27** in 85% yield.[28] The spectroscopy data (NMR, IR, MS) for compound **27** were in good agreement with those reported in the literature.[5,9] The final hydrolysis of the methyl ester has been reported by use of KOH to afford deoxyfrenolicin **1**.[9]

Ichihara et al. reported that the conversion of deoxyfrenolicin **1** to frenolicin A **2** could be effected by *tert*-butyl hydroperoxide and Triton B.[10] The same authors have also reported that simple reflux of deoxyfrenolicin **1** in $CHCl_3$ afforded frenolicin B **3** in quantitative yield.[10] Therefore the current synthesis of deoxyfrenolicin **1** also constitutes a formal synthesis of frenolicin A **2** and frenolicin B **3**.

In conclusion, we have developed an efficient approach toward deoxyfrenolicin **1** and similar analogues such as frenolicin A and B. We have demonstrated that the DDQ-induced, oxidative C−C bond coupling reaction provided an efficient, stereoselective entry into the functionalized naphthopyran system. The convergent approach to deoxyfrenolicin using a tandem benzannulation/oxa-Pictet−Spengler cyclization/DDQ-induced coupling strategy should be also applicable to the synthesis of other pyranonaphthoquinone natural products such as kalafungin **4** and nanaomycin **5**.

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Supporting Information Available: Experimental procedures for the preparationof compounds **15**−**27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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