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Synthesis of pentalongin and C(1)- and C(3)-substituted pentalongin using intramolecular Heck reaction

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ABSTRACT

An efficient and high yielding route for the synthesis of pentalongin and 1-alkyl, 1-aryl, and 3-alkyl substituted pentalongin has been demonstrated using intramolecular Heck reaction as a key step.

Pyranonaphthoquinones are widely distributed in plants, animals, bacteria, fungi, and algae, and are often associated with antitumor, antibacterial, and antiprotozoan activities.[1] The family of the pyranonaphthoquinones and 1*H*-naphtho-[2,3-*c*]pyran-5,10-dione derivatives is found in various natural products.[2] A particular group of pyranonaphthoquinone antibiotics bearing a C(3)–C(4) double bond that is 3,4-dehydro-pyranonaphthoquinone scaffolds include pentalongin (**1**),[3] dehydroherbarin (**2**),[4] anhydrofusarubin (**3**),[5] and 1,3-disubstituted-3,4-dehydro-pyranonaphthoquinones (**4**, Fig. 1),[6] also show significant antimicrobial activities.[7] Pentalongin is an unsubstituted, tricyclic 3,4-dehydro-pyranonaphthoquinone, which is used in Rwanda and Kenya as a traditional medicine for the treatment of malaria and skin diseases.[8]

Knowing these interesting biological activities of 3,4-dehydro-pyranonaphthoquinone series, we wish to develop a general synthetic route to pentalongin-based natural products. Several methods are available in the literature for the synthesis of pentalongin (**1**)[9,10] such as dehydration of psychorubrin,[9a] photochemical [2+2] addition of 2-chloro-1,4-naphthoquinone and acrolein dimethyl acetal, and subsequent treatment of the resulting 1,4-dimethoxymethyl-1,2-dihydrocyclobuta[*b*]naphthalene-3,8-dione with *p*-toluenesulfonic acid.[10a] De Kimpe and co-workers first reported the total synthesis of the naturally occurring pyranonaphthoquinone antibiotic pentalongin in 14% overall yield, they also reported the synthesis of 1-methylpentalongin by this procedure but they have failed to synthesize 3-methylpentalongin and they have proposed another pathway for the synthesis of 1-phenylpentalongin in overall 7% yield. Next they have reported another approach toward pentalongin by ring closure metathesis using Grubbs' first-generation catalyst in good yield.[11]

Recently our group reported a general methodology regarding pyran chemistry[12] and this prompted us toward the synthesis of pentalongin and its analogues by using intra-molecular Heck reaction[13] with 2-allyloxy compounds.

The synthesis of pentalongin (**1**), 1-methylpentalongin (**14**), and 1-phenylpentalongin (**15**) is presented in Schemes 1 and 2, starting from 1,4-dimethoxynaphthalene (**5**), which is readily available from 1,4-naphthoquinone through reductive methylation by means of $Na_2S_2O_4$ and methyl iodide.[14] The aldehyde group in **6** was introduced by dichloromethyl methyl ether formylation of the dimethoxynaphthalene. The 3-bromo substituent in **7** was introduced by electrophilic bromination of **6**[15] and here the disappearance of one of the aromatic C–H proton signals confirmed the formation of product **7**. Using this aromatic bromoaldehyde as the starting material we can synthesize a series of pentalongin-based antibiotics.

Alcohol **8a**[16] was prepared by the reduction of compound **7** with sodium borohydride in CH_3CN but alcohols **8b** and **8c**, were prepared from bromoaldehyde **7** using Grignard reaction. The allyl moiety was introduced using allyl bromide, in basic condition to give **9a–c**[17] in 87–92% yield. When these compounds **9a–c** were subjected to intramolecular Heck reaction afforded only compounds **10a–c** with exocyclic double bond in 79–84% yield[12] and no regioisomeric product possessing the endocyclic doublebond was formed during this Heck-type ring closure. Compounds **10a–c** on reaction with catalytic osmium(VIII) tetroxide and excess

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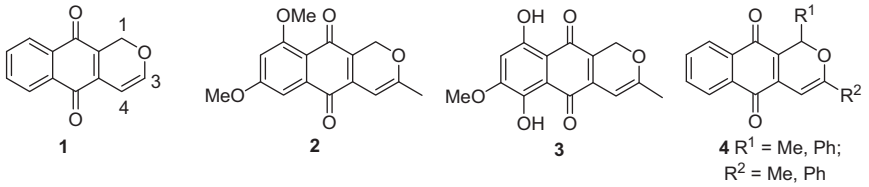
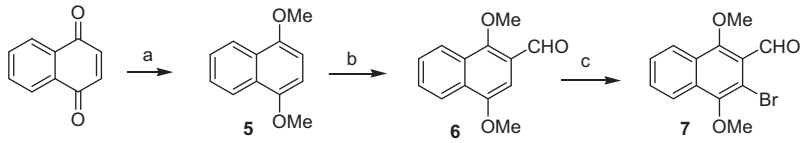
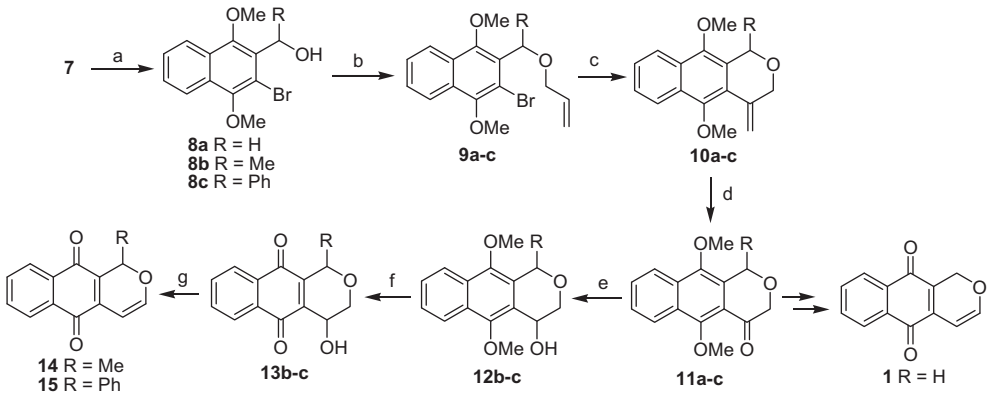


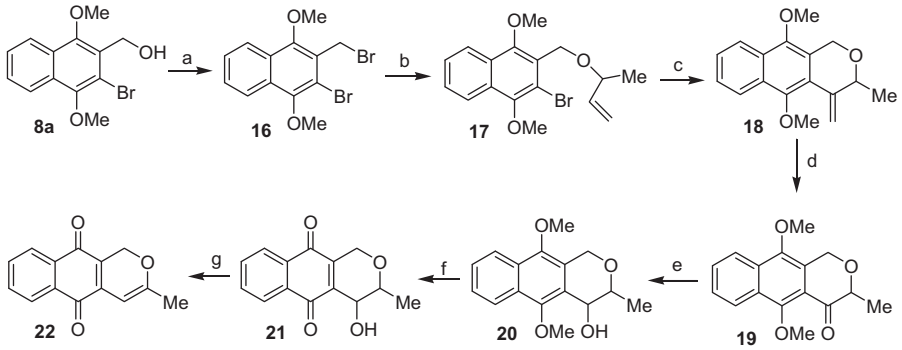
Figure 1. Some biologically active 3,4-dehydro-pyranonaphthoquinones.



Scheme 1. Synthesis of the aromatic bromoaldehyde **7**. Reagents and conditions: (a) 5.0 equiv $Na_2S_2O_4$, Et_2O/EtOAc/H_2O, 10:1:10, 25 °C, 30 min; 2.1 equiv NaH, 2.2 equiv MeI, DMF, −15 °C, 1 h, 82%; (b) 1.1 equiv $TiCl_4$, 1.1 equiv $CHCl_2OCH_3$, CH_2Cl_2, 0 °C, 4 h, 94%; (c) 1.1 equiv Br_2, CH_2Cl_2, 25 °C, 1 h, 75%.



Scheme 2. Synthesis of pentalongin **1** and its C(1)-substituted derivatives **14** and **15.** Reagents and conditions: (a) (i) R = H; 2 equiv $NaBH_4$, CH_3CN, 25 °C, 3 h, 96%; (ii) R = Me; 1.2 equiv MeMgBr, Et_2O, 0 °C, 4 h, 81%; (iii) R = Ph; 1.2 equiv PhMgBr, Et_2O, 0 °C, 4 h, 82%; (b) 2 equiv allyl bromide, 3 equiv NaH, THF, 0 °C, 5 h, 87–92%; (c) 0.25 equiv PPh_3, 1.2 equiv Cs_2CO_3, 10 mol % $Pd(OAc)_2$, DMF, 85–90 °C, 2 h, 79–84%; (d) 0.01 equiv OsO_4, 2.4 equiv $NaIO_4$, THF–H_2O (2:1), 70 °C, 18 h, 82–85%; (e) 1.1 equiv $NaBH_4$, MeOH–CH_2Cl_2 (1:1), 25 °C, 16 h, 74–78%; (f) 3 equiv CAN, CH_3CN–H_2O (1:2), 0 °C, 15 min, 25 °C, 15 min, 93–94%; (g) Catalytic *p*-TsOH, benzene, reflux, 1 h, 76–78%.



Scheme 3. Synthesis of 3-methylpentalongin **22**. Reagents and conditions: (a) 0.5 equiv PBr_3, CCl_4, 25 °C, 1 h, 66%; (b) (i) 3 equiv NaH, 2 equiv but-3-en-2-ol, THF, 40 °C, 30 min; (ii) 1 equiv **16**, 40 °C, 3 h, 79%; (c) 0.25 equiv PPh_3, 1.2 equiv Cs_2CO_3, 10 mol % $Pd(OAc)_2$, DMF, 85–90 °C, 2 h, 83%; (d) 0.01 equiv OsO_4, 2.4 equiv $NaIO_4$, THF–H_2O (2:1), 70 °C, 18 h, 81%; (e) 1.1 equiv $NaBH_4$, MeOH–CH_2Cl_2 (1:1), 25 °C, 16 h, 76%; (f) 3 equiv CAN, CH_3CN–H_2O (1:2), 0 °C, 15 min, 25 °C, 15 min, 91%; (g) Catalytic *p*-TsOH, benzene, reflux, 1 h, 67%.

of sodium periodate lead to the formation of ketones **11a–c**. From the keto compound **11a** we can easily synthesize our targeted molecule pentalongin **1**, which is reported in the literature.[18] Sodium borohydride reduction followed by oxidation with cerium(IV) ammonium nitrate of the ketones **11b,c** afforded the pyranonaphthoquinone derivatives **13b** and **13c**. Finally dehydration of compounds **13b,c** using *p*-toluenesulfonic acid in benzene under reflux condition gave 1-methylpentalongin **14** and 1-phenylpentalongin **15** as sole products in overall 25–27% yield (Scheme 2) which are known compounds.[11a]

For the synthesis of 3-methylpentalongin (**22**) we used alcohol **8a** which was first brominated with phosphorus tribromide in carbon tetrachloride to yield dibromonaphthalene **16** in 66% overall yield, which is the literature known compound.[17] This

dibromonaphthalene when treated with but-3-en-2-ol in the presence of NaH in THF yielded the O-allylated compound **17** in 79% yield with some unwanted side products which can be separated in column chromatography. With this allyl compound **17** similar reactions were performed as described in Scheme 1, to get 3-methyl pentalongin **22** in overall 17% yield (Scheme 3).

In short we have designed an efficient and general strategy for the synthesis of pentalongin and C(1)-and C(3)-substituted pentalongin. The advantage of using our synthetic strategy is that all these products can be synthesized from the same aromatic bromoaldehyde using intramolecular Heck reaction as a key step. We are gratified to prove that this methodology has the potential to be of great benefit in the convergent synthesis of a number of pyranonaphthoquinone-based natural products.

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Supplementary data

Supplementary data (detailed experimental procedures and spectral data for all the unknown compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.061.

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