Synthesis of Pyranonaphthoquinone Antibiotics Involving the Phthalide Annulation Strategy

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Abstract: The synthesis of the pyranonaphthoquinone antibiotic pentalongin was performed using the phthalide annulation strategy. Annulation of the cyanophthalide onto 6*H*-pyran-3-one resulted in a hongconin analogue, which upon further elaboration was converted into the natural product.

Key words: annulations, natural products, quinones, phthalide, pentalongin

Pyranonaphthoquinone antibiotics are a diverse family of naturally occurring 1*H*-naphtho[2,3-*c*]pyran-5,10-diones found in bacteria, fungi, aphides and higher plants.[1] Due to their promising biological activities,[2,3] they attracted considerable synthetic attention.[4,5] Among these pyranonaphthoquinones, pentalongin is of special interest. It is a natural product isolated from the Central East African medicinal plant *Pentas longiflora*, which is used in Rwanda and Kenya in the traditional medicine for the treatment of malaria and skin diseases.[6] Pentalongin was found to be responsible for the antifungal properties of the plant extract.[7] In addition, it reveals the tricyclic backbone of many other pyranonaphthoquinone antibiotics.

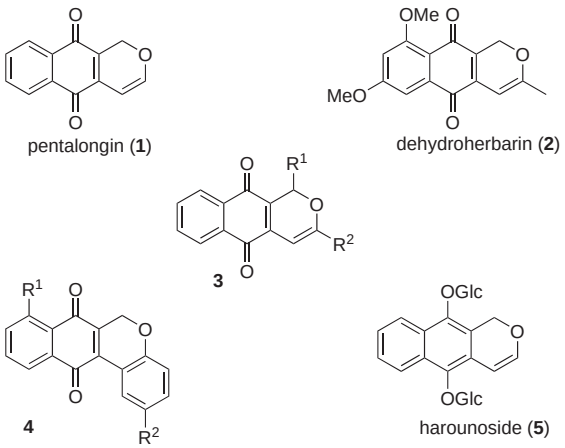

Figure 1

In the past years, our department has managed to synthesise a particular group of pyranonaphthoquinones such as pentalongin (**1**),[8,9] dehydroherbarin (**2**)[10] 1,3-disubstituted-3,4-dehydropyranonaphthoquinones **3**[11] tetracyclic pentalongin derivatives **4**[12] and harounoside (**5**, Figure 1).[13]

The naphtho[2,3-*c*]pyran skeleton was constructed before by ring closure of 2-allyl-3-hydroxymethyl-1,4-dimethoxynaphthalenes[10] and 2-allyl-3-hydroxymethyl-1,4-naphthoquinones,[14] by intramolecular base-catalysed condensation of 3-bromomethyl-1,4-dimethoxy-2-naphthaleneacetic acid,[15] by palladium-catalysed intramolecular cyclisation of 2-bromo-3-aryloxymethyl-1,4-naphthoquinone,[12] by ring-closing metathesis of a vinyl ether,[9] by using chloromethylation of substituted-2-naphthylacetic acid[16] and by reaction of 2-(1-hydroxyalkyl)-l,4-naphthoquinones with enamines or imines.[17] In this report, a novel efficient route towards pentalongin is described, utilising a phthalide annulation strategy, which allows the synthesis of novel pyranonaphthoquinone derivatives which are not accessible by other routes.

A brief look at the retrosynthetic scheme reveals the necessity of the construction of the Michael acceptor 6*H*-pyran-3-one (**9**). The annulated compound **7** is a hongconin analogue, a compound from traditional Chinese medicine shown to exhibit antianginal activity.[18] Further elaboration via pyranonaphthoquinone **6** will result in pentalongin (**1**, Scheme 1). Firstly, it was necessary to construct 6*H*-pyran-3-one (**9**). The literature revealed an existing synthesis of the 6*H*-pyran-3-one using palladium coupling of tri-*n*-butylvinyltin with allyloxyacetyl chloride and subsequent ring-closing metathesis in a total yield of 17%[19] and a synthesis using a Hg(II) ring closure from the appropriate alkyne in 21% yield.[20] In an attempt to avoid the toxic tin or mercury reagent and the low yielding results, an alternative pathway was devised (Scheme 2). In the first step, the nucleophilic attack of allyl alcohol at butadiene monoxide **10** resulted in the desired 1-allyloxybut-3-en-2-ol (**11**). The alcohol **11** could easily be ring-closed by using Grubbs' second-generation catalyst towards dihydropyranol (**12**) in 73% yield.

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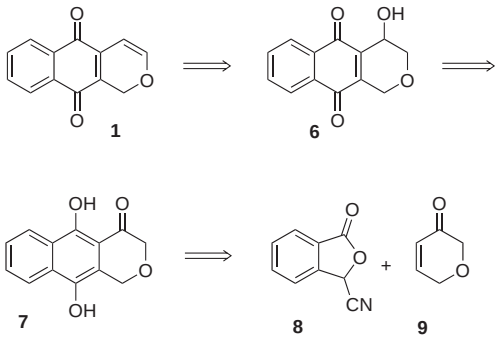
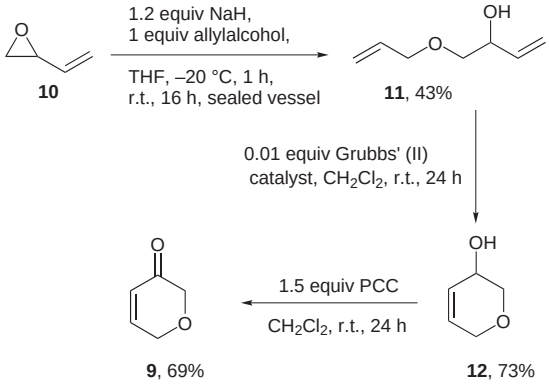


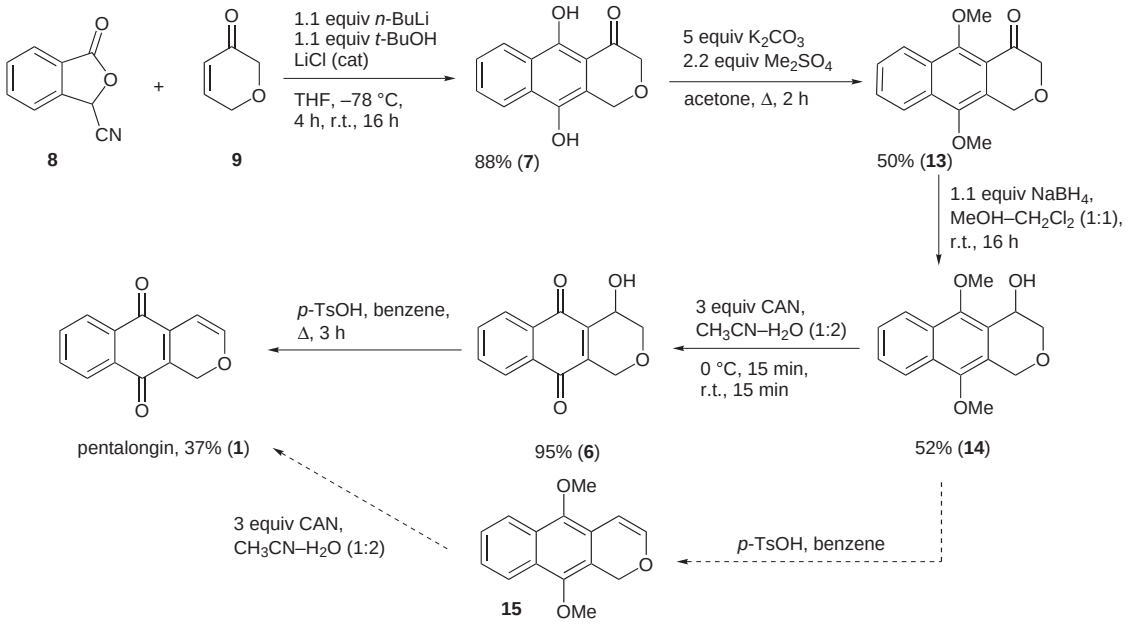
Scheme 1



Scheme 2

The subsequent oxidation towards 6*H*-pyran-3-one (**9**) was accomplished using a PCC-oxidation in dichloromethane to give the 6*H*-pyran-3-one (**9**) in 69% yield. The next step to work out was the phthalide annulation reaction (Scheme 3) with the heterocyclic compound **9**. This methodology is developed by Kraus et al.[21] and Hauser et al.[22] and became an often used procedure in the synthesis of naphthoquinones.[23] In spite of its usefulness, the reaction products are often difficult to characterise due to solubility problems and due to their capacity to form stabilised radicals, which make it impossible to run NMR spectra.[24] The only way to characterise these so-called 'silent NMR quinones' is to protect the naphthalene diols in order to avoid formation of radicals. The cyanophthalide annulation reaction was carried out using LiO*t*-Bu as the base and in the presence of LiCl to catalyse the reaction, resulting in the hongconin analogue **7**. All attempts to reduce the keto function in compound **7** to the corresponding alcohol failed. In view of the encountered problems it was necessary to protect the aromatic diol **7** as its double methyl ether **13**[25] using dimethyl sulfate and potassium carbonate in acetone. Subsequent reduction of **13** using sodium borohydride resulted in alcohol **14**. The problematic oxidation of the pyranonaphthalene **15** was already observed by us[10] and by others.[26] Therefore, the decision was made firstly to oxidise compound **14** towards the quinone **6**.[27] The oxidative demethylation was realised using cerium(IV) ammonium nitrate in aqueous acetonitrile and afforded the 4-hydroxynaphthoquinone **6** in 95% yield. Exceeding the reaction time of 15 minutes resulted in complex reaction mixtures. The final dehydration applying *p*-toluenesulfonic acid in benzene under reflux for three hours resulted in the target pentalongin (**1**) in 37% yield.

In conclusion, by using the phthalide annulation strategy, the naturally occurring pentalongin (**1**) was synthesised. Applying this synthetic pathway opens the door for new pentalongin derivatives and new naphthoquinone antibiotics, with the required cyclic enol ether moiety.



Scheme 3

Acknowledgment

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(25) **5,10-Dimethoxy-1*H*-benzo[*g*]isochromene-4-one (13):** yellowish oil; ^{1}H NMR (acetone-d_6): δ = 3.90 (3 H, s, OCH_3), 4.01 (3 H, s, OCH_3), 4.30 (2 H, s, CH_2C=O), 5.06 (2 H, s, CH_2O), 7.62 (1 H, ddd, *J* = 8.4, 7.0, 1.4 Hz, CH-7), 7.73 (1 H, ddd, *J* = 8.4, 7.0, 1.4 Hz, CH-8), 8.11 (1 H, dd, *J* = 8.4, 1.4 Hz, CH-9), 8.34 (1 H, dd, *J* = 8.4, 1.4 Hz, CH-6). ^{13}C NMR (acetone-d_6): δ = 62.13 (OCH_3), 63.14 (OCH_3), 64.46 (CH_2O), 74.50 (CH_2OC=O), 118.30 (C_{quat}), 122.01 (CH-9), 125.05 (CH-6), 126.84 (CH-7), 127.45 (C_{quat}), 129.08 (C_{quat}), 129.74 (CH-8), 131.74 (C_{quat}), 146.43 (C_{quat}), 155.64 (C_{quat}), 193.47 (C=O). IR (KBr): ν_{max} 1689 (C=O) cm^{-1}. MS (ES$^+$): *m/z* = 258 [M$^+$].
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(27) **4-Hydroxy-3,4-dihydro-1*H*-benzo[*g*]isochromene-5,10-dione (6):** ^{1}H NMR ($CDCl_3$): δ = 3.86 (1 H, dd, *J* = 12.2, 3.8 Hz, $CHC\mathit{H}_a\mathrm{H}_b$), 4.03 (1 H, dd, *J* = 12.2, 3.5 Hz, $CHCH_a\mathit{H}_b$), 4.49 (1 H, dd, *J* = 18.9, 1.65 Hz, $OC\mathit{H}_a\mathrm{H}_b$), 4.76 (1 H, dd, *J* = 18.9, 0.6 Hz, $OCH_a\mathit{H}_b$), 4.82 (1 H, m, CHOH), 7.76 (2 H, m, CH_7–CH_8), 8.09 (2 H, m, CH_6–CH_9). ^{13}C NMR ($CDCl_3$): δ = 60.18 (CH_2O), 63.23 (CHOH), 69.51 (CH_2), 126.38 (C-6 or C-9), 126.63 (C-9 or C-6), 131.83 (2 × C_{quat}), 134.28 (C-7 and C-8), 140.58 (C_{quat}), 143.74 (C_{quat}), 183.84 (C=O), 184.59 (C=O). IR (KBr): ν_{max} = 3468 (OH), 1661 (C=O) cm^{-1}. MS (ES$^+$): *m/z* (%) = 231 (15) [M + H$^+$], 213 (100) [M$^+$ – H_2O].