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Synthesis of pyranonaphthoquinone antibiotics involving the ring closing metathesis of a vinyl ether

Tuyen Nguyen Van and Norbert De Kimpe*

Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, Ghent University, Coupure links 653, B-9000 Ghent, Belgium

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Abstract—The synthesis of two antibiotic pyranonaphthoquinones was performed by a straightforward synthetic route utilizing ring closing metathesis. Vinylation of 3-(1-propenyl)-2-hydroxymethyl-1,4-dimethoxynaphthalene under iridium catalysis and subsequent ring closing metathesis of 3-(1-propenyl)-2-vinyloxymethyl-1,4-dimethoxynaphthalene with Grubbs' catalyst paved the way to the natural antibiotics pentalongin and psychorubrin.

1. Introduction

Pyranonaphthoquinone antibiotics are a diverse family of naturally occurring 1*H*-naphtho[2,3-*c*]pyran-5,10-diones, which are found in bacteria, fungi, aphides and higher plants.[1] Some pyranonaphthoquinones have been found to possess antimicrobial, antiparasitical and anticancer properties.[2,3] Accordingly, they have recently attracted considerable synthetic attention.[4,5] The synthesis of a particular smaller group of naturally occurring pyranonaphthoquinones, such as pentalongin **1**,[6,7] psychorubrin **2**,[6,7] dehydroherbarin **3**,[8] 1,3-disubstituted-3,4-dehydropyranonaphthoquinones **4**[9] and harounoside **5**,[10] was accomplished by us in efforts towards the discovery of biologically active pyranonaphthoquinone derivatives (Fig. 1).

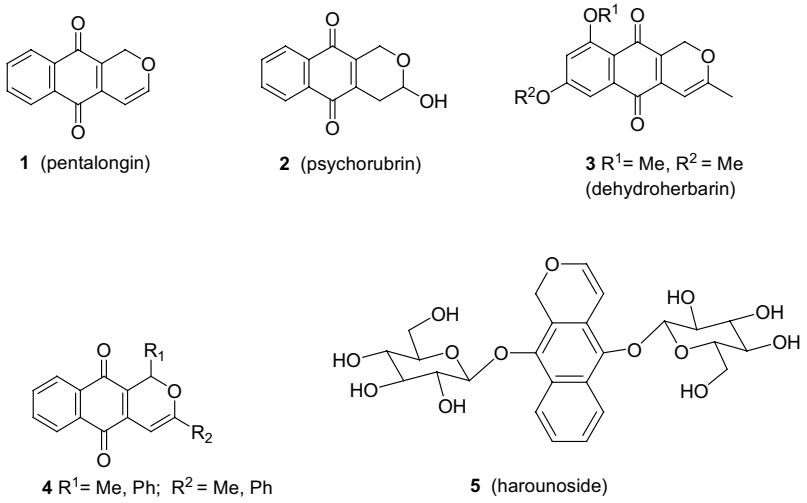

Figure 1.

Keywords: Pentalongin; Psychorubrin; Iridium-catalyzed vinylation; Ring closing metathesis (RCM).
* Corresponding author. Tel.: +32-092645951; fax: +32-092646243; e-mail: norbert.dekimpe@UGent.be

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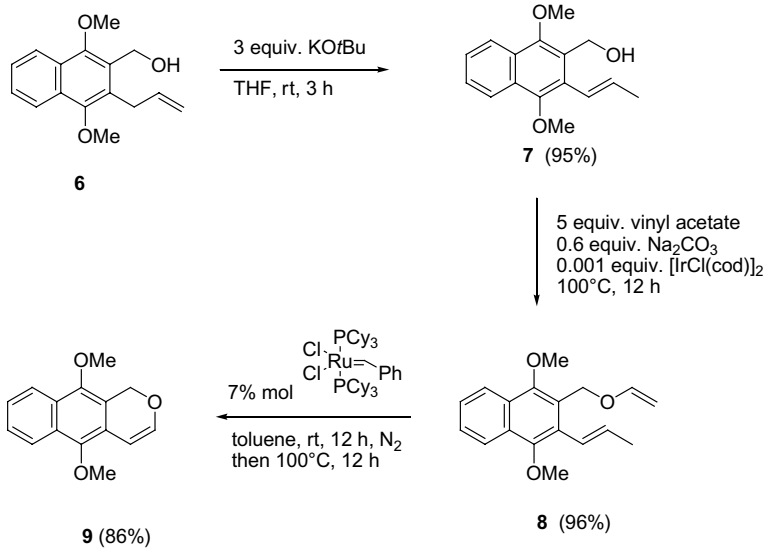
Pentalongin **1** is a natural product from the Central-East African medicinal plant *Pentas longiflora*, which is used in Rwanda and Kenya in the traditional medicine for the treatment of malaria and skin diseases.[11] Also psychorubrin is a naturally occurring pyranonaphthoquinone with significant antitumour activity, which was isolated from *Psychotria rubra* (Fig. 1).[12]

The known syntheses of pentalongin **1** and psychorubrin **2** are based upon the construction of the 1*H*-naphtho[2,3-*c*]pyran skeleton by ring closure of 2-allyl-3-hydroxymethyl-1,4-dimethoxynaphthalenes[6] and 2-allyl-3-hydroxymethyl-1,4-naphthoquinones[13] by oxidative olefin cleavage or by intramolecular base-catalyzed condensation of 3-bromomethyl-1,4-dimethoxy-2-naphthaleneacetic acid followed by selective reduction.[7] In continuation of our interest in the efficient synthesis of this class of compounds, we now report a new synthetic pathway for pyranonaphthoquinones, using Grubbs' first generation catalysts for the ring closing step.

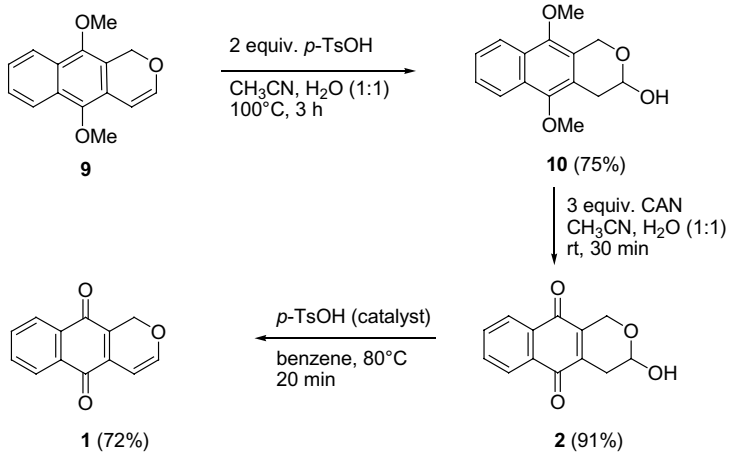
The synthesis of precursors of pentalongin **1** and psychorubrin **2** starting from 2-allyl-3-hydroxymethyl-1,4-dimethoxynaphthalene **6**[6] and proceeding to the reduced and protected form of pentalogin (**9**) is outlined in Scheme 1. Isomerization of the allylic double bond in the easily accessible compound **6**[6] was carried out by treatment with potassium *tert*-butoxide in tetrahydrofuran to give 2-hydroxymethyl-1,4-dimethoxy-3-(1-propenyl)-naphthalene **7** in 95% yield as the (*E*)-isomer, exclusively.[8] Vinylation of compound **7** at the oxygen atom was carried out with vinyl acetate in the presence of chloro(1,5-cyclootadiene)iridium(I) dimer ([IrCl-(cod)]$_2$) as catalyst.[14] For example, a mixture of compound **7**,vinyl acetate, sodium carbonate and [IrCl(cod)]$_2$ (molar ratio 1:5:0.6:0.001) was stirred in toluene at 100 °C for 12 h to afford vinyl ether **8**[15] in excellent yield (96%) as the (*E*)-isomer. This compound was converted into compound **9** by ring closing metathesis.

Treatment of compound **8** with 7% mol of Grubbs' first generation catalyst in toluene at room temperature for 12 h under nitrogen, and then at 100 °C for an additional 12 h afforded compound **9**[7,16] in good yield (86%), culminating in the synthesis of this pyranonaphthoquinone precursor **9** in three efficient steps. It was found that these conditions were most appropriate for this conversion despite the known thermal lability of the catalyst. To our knowledge, the use of Grubbs' first generation catalyst for the ring closing reaction of enolic ethers is limited and known to be problematic.[17–20] Attempts were initially made to employ ruthenium catalysts for the ring closure of vinyl ethers, but these reactions failed and gave only dimerization products. However, the ring closing reaction of such vinyl ethers was successful by using the Schrock molybdenum catalyst.[18] It has been suggested that the carbene resulting from the rapid reaction between the vinyl ether moiety and the ruthenium catalyst is inert towards further metathesis.[21] However recently, the ring closing reaction of vinyl ethers containing alkoxy substituents by using Grubbs' first generation catalyst was performed successfully by Wong. Probably, the neighbouring alkoxy groups may exert an influence on the chemoselectivity of the metathesis process between the ruthenium catalyst and the olefin.[22] Very recently, de Koning has also succeeded in achieving the ring closing metathesis reaction of phenolic vinyl ethers containing neighbouring alkoxy groups by using Grubbs' second generation catalyst.[23]

As outlined in Scheme 2, 5,10-dimethoxy-1*H*-naphtho[2,3-*c*]pyran **9** was hydrated by treatment with *p*-toluenesulfonic acid in aqueous acetonitrile at 100 °C for 3 h, affording hemiacetal **10**[7,24] in 75% yield after purification by flash chromatography on silica gel.



Scheme 1.



Scheme 2.

Psychorubrin **2** was prepared in 91% yield by treatment of hemiacetal **10** with cerium(IV) ammonium nitrate (CAN) in aqueous acetonitrile at room temperature for 30 min.[6] Finally, pentalongin **1** was obtained in 72% yield by treatment of psychorubrin **2** with *p*-toluenesulfonic acid in benzene at 80 °C for 20 min.[7,12,13] All attempts to carry out the direct oxidation of compound **9** to pentalongin **1** by using several oxidative reagents such as CAN, AgO, HNO_3 and CrO_3 failed. This problematic oxidation of certain pyranonaphthalene derivatives was already observed by us[6] and others.[25]

In conclusion, by using a new synthetic approach, that is, a RCM strategy, the naturally occuring antibiotics pentalogin **1** and psychrubrin **2** were synthesized in high yield. This protocol now opens a new way for the synthesis of other pyranonaphthoquinone antibiotics.

Acknowledgements

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15. (*E*)-3-(1-Propenyl)-2-vinyloxymethyl-1,4-dimethoxynaphthalene **8**. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 1.97 (3H, dd, $J = 6.6$ and 1.6 Hz, CH_3), 3.82 (3H, s, OMe), 3.86 (3H, s, OMe), 4.14 (1H, dd, $J = 6.9$ and 2.3 Hz, CH═CH_aH$_b$), 4.40 (1H, dd, $J = 6.9$ and 2.0 Hz, CH═CH$_a$$H_b$), 4.93 (2H, s, OCH_2), 6.25–6.34 (1H, m, CH_3CH═CH), 6.56–6.68 (2H, m, overlap., Me─CH═CH─), 7.48–7.54 (2H, m, H-6 and H-7), 8.07–8.13 (2H, m, H-5 and H-8). ^{13}C NMR ($CDCl_3$, 67 MHz): δ 19.7 (Me), 60.6 (OMe), 62.7 (CH_2O), 63.7 (OMe), 87.0 (OCH═CH), 122.6 (CH═), 122.7 (CH═), 123.8 (═C_{quat}), 123.9 (CH═), 126.0 (═C_{quat}), 126.7 (CH═), 127.4 (CH═), 128.3 (═C_{quat}), 129.4 (CH═), 132.8 (═C_{quat}), 150.0 (O─CH═$\underline{C}$H), 151.4 (═C─OMe), 152.4 (═C─OMe). IR (NaCl): 2916; 2854:1640 (C═C), 1607 (C═C), 1451; 1354:1191, 1061, 1051 cm^{-1}. MS m/z (%): no M$^+$, 257 [(M−vinyl)$^+$, 20], 242 (20), 241 (100), 210 (14), 149 (10). Anal. Calcd for $C_{18}H_{20}O_3$: C 76.03, H 7.09; found C 76.12, H 7.20.
16. 5,10-Dimethoxy-1*H*-naphtho[2,3-*c*]pyran **9**. White powder, mp 138–139 °C, ^{1}H NMR, ^{13}C NMR and MS data were identical to data reported in the literature.[7]
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24. 3,4-Dihydro-5,10-dimethoxy-1*H*-naphtho[2,3-*c*]pyran-3-ol **10**. ^{1}H NMR ($CDCl_3$, 270): δ 2.97 (1H, dd, $J = 16.8$ and 5.3 Hz, $ArCH_aH_b$), 3.29 (1H, dd, $J = 16.8$ and 4.0 Hz, $ArCH_aH_b$), 3.89 (3H, s, OMe), 3.90 (3H, s, OMe), 4.99 and 5.19 (each 1H, each d, $J = 15.5$ Hz, CH_2–O), 5.42 (1H, dd, $J = 5.3$ and 4.0 Hz, CH–OH), 7.45–7.51 (2H, m, H-7 and H-8), 8.01–8.08 (2H, m, H-6 and H-9). ^{13}C NMR ($CDCl_3$, 67 MHz): δ 29.6 (C-4), 60.2 (C-1), 61.3 (OMe), 61.5 (OMe), 92.4 (C-3), 121.4 (=C_{quat}), 121.9 (=CH), 122.1 (=CH), 123.5 (=C_{quat}), 125.8 (2 × =C_{quat}), 127.0 (=C_{quat}), 127.7 (=C_{quat}), 147.1 (=C–OMe), 149.9 (=C–OMe). IR (NaCl): 3390 (OH), 1590; 1450:1355, 1265, 1068 cm^{-1}. MS m/z (%): 260 (M^+, 10), 243 (17), 229 (20), 215 (100), 216 (15), 200 (10). Anal. Calcd for $C_{15}H_{16}O_4$: C 69.22, H 6.20; found C 69.12, H 6.09.
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