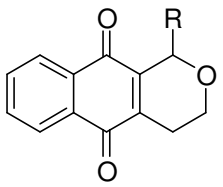
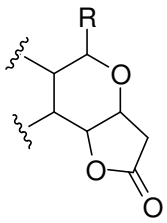
PART I: SYNTHESIS OF (±)-ISAGARIN, (±)-MARTICIN AND (±)-ISOMARTICIN BY PALLADIUM(II) CATALYSIS

INTRODUCTION

Natural products derived from microorganism are very important sources of biologically active compounds especially those systems with a pyranonaphthoquinone skeleton which are isolated from various strains of bacteria and fungi. This class displays activities against a variety of Gram-positive bacteria, pathogenic fungi and yeasts, as well as antiviral activity. In addition, they have been proposed to act as bioreductive alkylating agents (Moore, 1977). Some of the more recently discovered examples are structurally fairly complex and provide significant synthetic challenges.

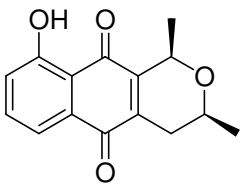
The core skeleton of pyranonaphthoquinone compounds is the naphtho[2,3-c]pyran-5,10-dione ring system (1) and some members of the family containing an additional γ-lactone ring (2) fused to the dihydropyran moiety as the basic subunit.



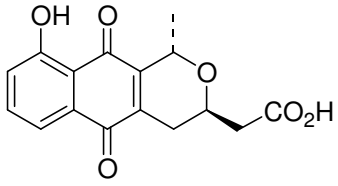


Naphtho[2,3-c]pyran-5,10-dione (1) **γ-lactone ring (2)**

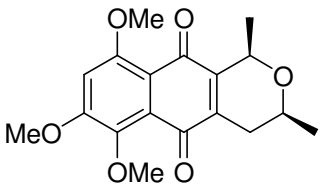
The diversity of chemical structures found within the pyranonaphthoquinone family of antibiotics has prompted syntheses of members of this class, for example: elutherin (3) (Dotz *et al*., 2000), nanaomycin A (4) (Semmelhack *et al*., 1985; Decker. *et al*., 1987; Kreaus et al., 1987) , ventiloquinone E (5) (Giles *et al*., 1991; Bergeron et al., 1992), ventiloquinone G (6) (Namura. *et al*., 1987), ventiloquinone J (7) (Giles. *et al*., 1991), frenolicin B (8) (Kreaus *et al*., 1993), arizonin C1 (9) (Brimble *et al*., 1995), granaticin (10) (Namura *et al*., 1987). Recently, the syntheses of pyranonaphthoquinones were reviewed. (Brimble *et al*., 2000).



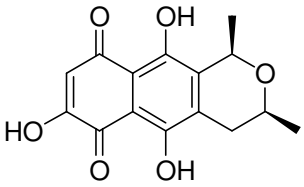
Elutherin (3)



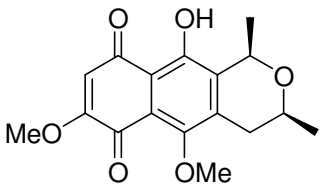
Nanaomycin A (4)



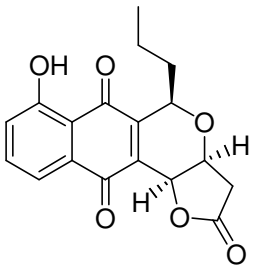
Ventiloquinone E (5)



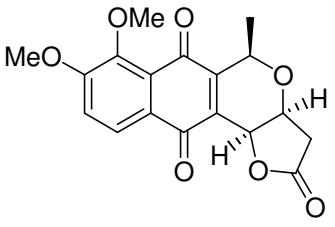
Ventiloquinone G (6)



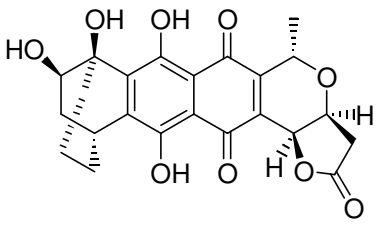
Ventiloquinone J (7)



Frenolicin B (8)

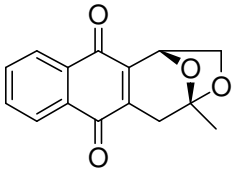


Arizonin C1 (9)

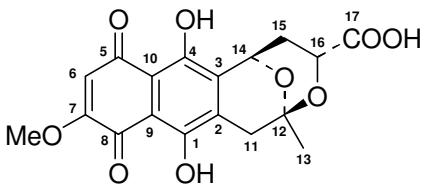


Granaticin (10)

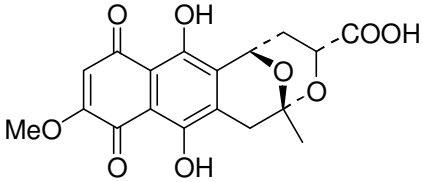
Some members of pyranonaphthoquinone class contain an oxabicyclic moiety connected to naphthoquinone such as (-)-isagarin (11), (+)-marticin (12) and (+)-isomarticin (13) (De Kimpe *et al*., 1998; Holenstein *et al*., 1984).



(-)-Isagarin (11)



(+)-Marticin (12)



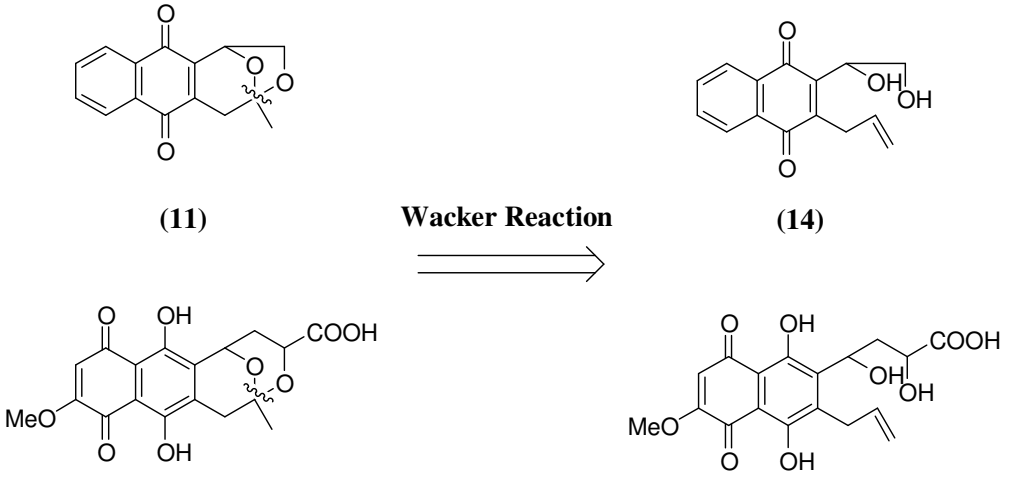
(+)-Isomarticin (13)

The tetracyclic naphthoquinone (-)-isagarin (11), 1,4-epoxy-4-methyl-1,2,4,5-tetrahydronaphtho[2,3-d]oxepin-6,11-dione, was isolated from the roots of *Pentas longiflora* and subsequently synthesized by De Kimpe *et al.* in 1999.

(±)-Marticin (12) and (±)-isomarticin (13) were isolated from the acid fraction extract of the fungal culture strains: *Fusarium martii, Fusarium. solani* and *Fusarium spp.* (Holenstein *et al*., 1983; Tatum *et. al*., 1983). Marticin (12) and isomarticin (13) contain three stereogenic centers (C-12, C-14 and C-16). The stereochemistry at the C-14, C-16 and C-12 position of (±)-marticin (12) was recently revised to be *S*, *S* and *R* whereas the stereochemistry at the C-14, C-16 and C-12 position of (±)-isomarticin (12) was recently revised to be *R*, *R* and *R*, respectively (Holenstein.*et al*. in 1984).

Our group has reported the formation of the dioxabicyclic skeleton of several natural products by palladium-catalysed reactions. For example: the synthesis of brevicomin (Kongkathip *et al*., 1984), frontalin (Kongkathip *et al*., 1985) and

amberketal (Kongkathip *et al*., 1999). Isagarin (11), marticin (12) and isomarticin (13) contain a dioxabicyclic ring and might be prepared via Wacker reaction ($PdCl_2/CuCl_2/O_2$) as shown in Scheme 1.



Scheme 1

The objectives of this research are

i) to synthesize (±)-isagarin (11)

ii) to synthesize (±)-marticin (12) and (±)-isomarticin (13)

iii) to investigate the intramolecular cyclization reaction by Wacker reaction ($PdCl_2/CuCl_2/O_2$) for the construction of the dioxabicyclic skeleton of these target molecules