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Regioselective lactonization of naphthoquinones: synthesis and antitumoral activity of the WS-5995 antibiotics

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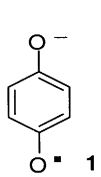
Abstract

An acid promoted quinolactonization of naphthoquinones has been developed, providing direct access to either *ortho* or *para* isomers as desired. Application of this methodology in syntheses of the antibiotics WS-5995A, WS-5995C and functional analogs is demonstrated. Preliminary antitumoral activity of the analogs is presented together with electrochemical analysis.

The search for new antibiotics continues at a steady pace, and quinonoid derived systems have been the subject of a number of promising leads. A central feature of conventional *p*-quinonoid based cytotoxins is their ability to generate semi-quinone radicals **1** following bioreduction, accelerated under hypoxic conditions.[1] Though less studied, the potential for *o*-quinone isomers to participate in similar chemistry via **2** also exists, providing the reduction potential lies within the window of opportunity for cellular activation. As part of our program directed towards free radical based chemotherapies,[2] we became interested in scrutinizing the differential cytotoxicities of quinone isomers. We opted to study the issue by preparing synthetic analogs of natural products, having the additional benefit of potentially accessing deselected natural products, a key feature of current trends in chemical genetics.[3] Though several pyranonaphthoquinone antibiotics have been identified, including nanaomycin A, kalafungin and eleutherin, relatively few members of the corresponding naphthoquinone lactones have been found.



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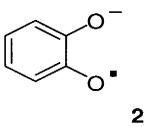

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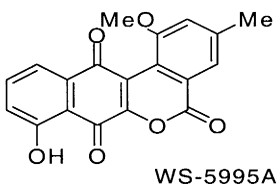
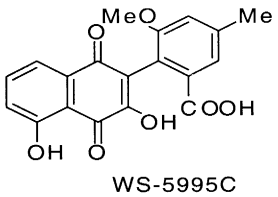


WS-5995A



WS-5995C

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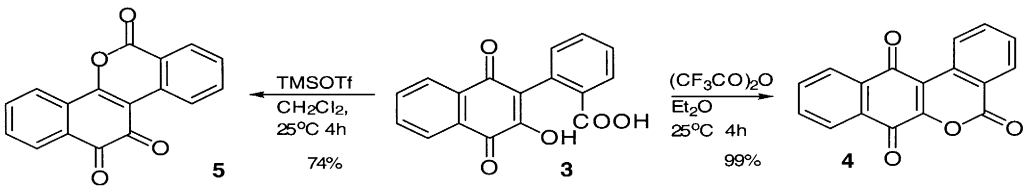
The structure of one member of this class, WS-5995A, isolated from *Streptomyces auranticolor* was determined in 1983,[4] which led to the subsequent discovery of the structural analogs including its open form WS-5995C.[5] These agents have demonstrated chemoprotective activity against *Eimeria tenella* infection.[6] Though the origin of their activity remains to be clarified, in an unrelated study it was shown that the bacterium *Streptomyces acidiscabies*, present in acidic soils, produces these compounds, and that they likely contribute to the observed pathogenicicty of this organism.[7] Our interest in this family was strengthened by their structural similarities with the gilvocarcin class of antitumor antibiotics, which participate in DNA intercalation, and may function as topoisomerase inhibitors.[8] We opted to develop an expeditious route to the core structure of the WS-5995 family, focusing on novel lactonization chemistry.

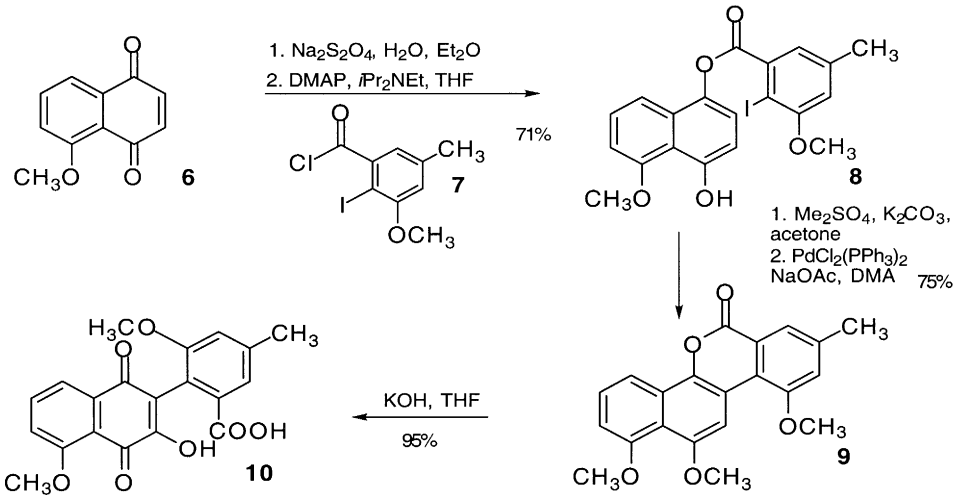
Accordingly, an appropriate model compound **3** was assembled to test the hypothesis.[9] A variety of acid catalyzed quinolactonizations were attempted using conventional methods, which would be expected to yield **4** via the mixed anhydride. Though unsuccessful with acetic anhydride, TFAA gave the product cleanly and in high yield (Scheme 1). More significantly, under the influence of Lewis acids, the alternate *ortho* quinone product **5** could be produced. This is presumably the result of enolization of the *p*-quinone carbonyl, encouraged by chelation of the phenol with the Lewis acid. Following attempts to optimize the yield of this isomer, TMS triflate was found to be most effective, giving good yields of the *o*-isomer, together with traces of the *p*-isomer. As expected, extended exposure of **5** to various acids resulted in isomerization to the more thermodynamically stable **4**, methanesulfonic acid proving most efficient (−78°C, CH_2Cl_2, 2 h, 95%).



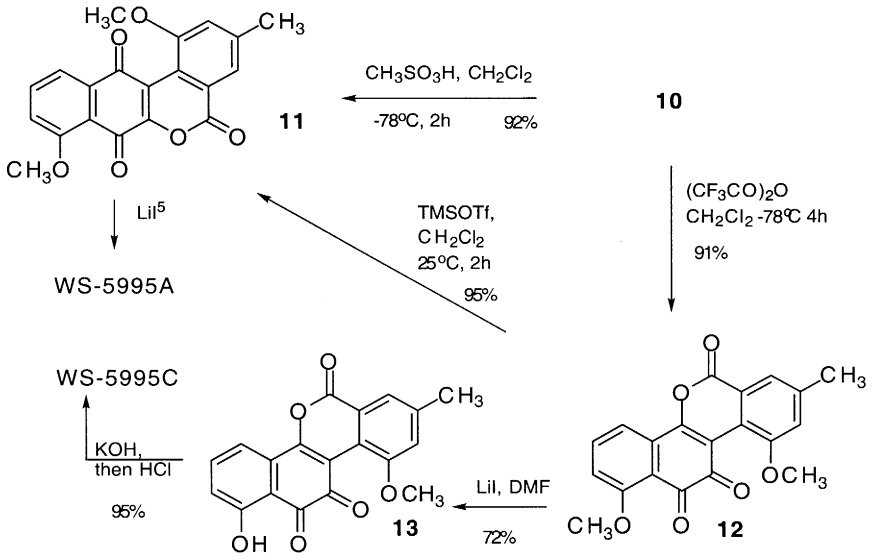
Scheme 1. Quinolactonization of benzoquinone model substrate

Encouraged by the regiocontrol observed in the model study, we sought to incorporate this methodology in the synthesis of natural and unnatural isomers of the WS-5995 family. Accordingly, substituted substrate **10** was prepared; methyl juglone **6** was reduced and esterified with acyl chloride **7**, prepared from dimethylanisole acid in five steps (Scheme 2).[10] The resulting iodo ester **8** was methylated, subjected to Pd catalyzed annulation, to give tetracycle **9**, then the quinone revealed to give **10**. As was found in the model series, exposure of the hydroxy acid to methane sulfonic acid gave the *p*-quinone **11**, however, in stark contrast to the model study, the alternate *o*-quinone **12** was produced exclusively using TFAA (Scheme 3). Interconversion of this isomer to **11** was effected either using MSA or TMSOTf, but extended exposure of **12** with TFAA did not result in isomerization. The origins of this apparent stabilizing effect are presumably related to the pendant methoxy functionality, and are the subject of an ongoing investigation. Regioselective demethylation of either **12** or **11** could be effected using lithium iodide, in the case of **11** giving the natural product WS-5995A, and in the case of **12**, the interesting analog **13**. Hydrolysis of the lactone in **13** resulted in concomitant formation of the natural product WS-5995C, which itself can be converted to WS-5995A using established methods.[5]

The described route allowed us to now scrutinize the redox chemistry of this intriguing class of natural products, and additionally explore the relative contribution to cytotoxicity this imparts. The electrochemical reduction potential of the quinone isomers was determined, and as expected marked differences exist, which could be expected to have an impact under biological conditions (Table 1).[11] Initial cytotoxicity assays against a murine cell line reveal that in addition to WS-5995, *ortho* quinone **12**



Scheme 2. Preparation of functionalized hydroxyquinone



Scheme 3. Synthesis of WS-5995 antibiotics and quinone isomers

and model quinone **4** are appreciably cytotoxic (Table 1). Additionally, comparison of **12** and **13** suggests that the hydrogen bonding phenolic group may attenuate the function of the *o*-quinone moiety.

It is well known that the differing reduction potentials of *o*- and *p*-quinones can play a dramatic role in electron transfer chemistry, and we are now investigating the antiproliferative capacity of the entire family of analogs under a variety of hypoxic and aerobic screens. Also of interest is the structural similarity of this class of agents to the ellagic acids, whose antiproliferative and chemoprotective ability has been noted.[12] Since ellagic acid had an IC_{50} of 10 μM in the current assay, additional efforts to determine the molecular mechanism of action of these agents is also underway.

In summary, substrate dependent regioselective acid catalyzed quinolactonization procedures have been developed and applied to the total synthesis of WS-5995A and C, and their quinone isomers. In-depth studies on the antitumoral and chemoprotective potential of these compounds, together with the scope of the quinolactonization procedure itself, will be reported in due course.

Table 1
Cytotoxicity of *o/p* quinones[#]

compound	IC_{50} (μM)	E^o (mV)^
WS-5995A	1	-370
WS-5995C	100	-1415
13	15	-550
12	2	-585
10	>15*	-1025
5	10	-360
4	5	-370
3	125	-1015

determined using MTS:PMS assay on L1210 mouse lymphoma cells.
^ all values relative to Ag/AgCl reference electrode *insolubility precluded studies at higher concentration

Acknowledgements

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9. Commercially available methoxynaphthol, was coupled with the acyl chloride derived from 2-iodobenzoic acid, giving the corresponding ester (90%), followed by Pd-mediated cyclization ($PdCl_2(PPh_3)_2$, NaOAc, DMA, 65%) and hydrolysis (KOH, THF 70%). All new compounds gave satisfactory spectroscopic and analytical data.
10. The desired acid was prepared from 3,5 dimethylanisole via (i) bromination (NBS, CCl_4) followed by (ii) in situ hydrolysis (K_2CO_3, dioxane, 40% over two steps) (iii) iodination (2 *n*BuLi, I_2, −78°C, 67%), and (iv) oxidation (Bu_4NMnO_4, Py, 95%).
11. We thank Sivashankar G. Sivakolundu for these determinations.
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