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CARBOCYCLIC FRENOLICIN ANALOGUES: NOVEL ANTICOCCIDIAL AGENTS

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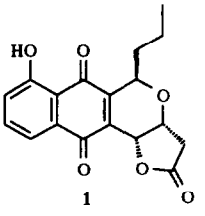
Abstract. Carbocyclic analogues of the antibacterial natural product frenolicin B have been synthesised. These analogues were active against parasitic protozoa of the genus *Eimeria* and represent a new series of anticoccidial agents. The synthesis of simplified analogues helped to define a possible pharmacophore for frenolicin.

Introduction. The pyranonaphthoquinone Frenolicin B **1** represents a promising lead in the search for new agents to combat coccidiosis,[1] an endemic parasitic disease of poultry caused by protozoa of the genus *Eimeria*. With the aim of increasing our understanding of the SAR pertaining to frenolicin B **1**, substitution of the pyran oxygen by a methylene unit was identified as an important modification. A short, flexible route was sought that would allow the synthesis of a number of analogues rapidly.



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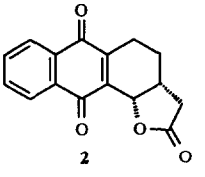

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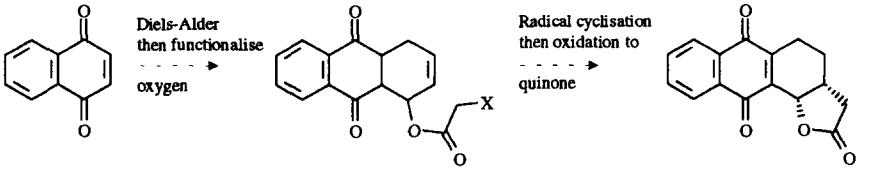
Carbocycle **2** was selected as a prototype target and we based our synthetic planning around a key Diels-Alder reaction to construct the fused cyclohexyl ring (Scheme 1). We planned to take advantage of the double bond thus introduced to annulate the final lactone ring using a radical cyclisation.

Scheme 1



Chemistry. The cycloaddition reaction of naphthoquinone and 1-trimethylsilyloxybutadiene proceeded efficiently at room temperature (79%) to give adduct **3** as a single diastereomer (Scheme 2).

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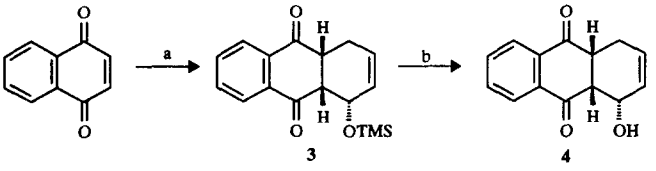
The stereochemistry of this intermediate was never established due to its insignificance to the course of the synthesis but theoretical considerations predict an endo transition state giving rise to the *anti* relationship as depicted in Scheme 2.

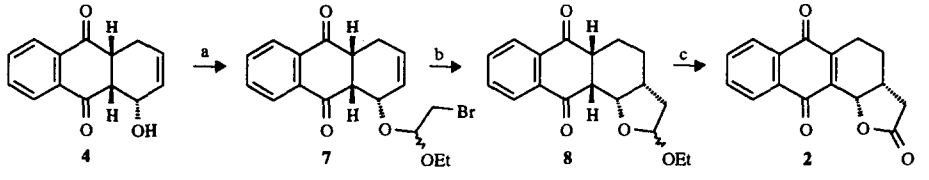
Scheme 2



a. TMSOCH=CHCH=CH_2, CH_2Cl_2, RT; b. TsOH, MeOH, RT.

Desilylation of **3** was cleanly accomplished (80%) with toluenesulfonic acid in methanol to give the sensitive alcohol **4**. Various attempts to refunctionalise this alcohol were hampered by the tendency of the product to undergo elimination and immediate oxidation, generating anthroquinone. However, selection of a well established strategy[2] led us to treat alcohol **4** with *N*-bromosuccinimide (NBS) in neat ethylvinyl ether[3] (Scheme 3) which successfully gave bromoacetal **7** as a 1:1 mixture of diastereomers (40%).

Scheme 3



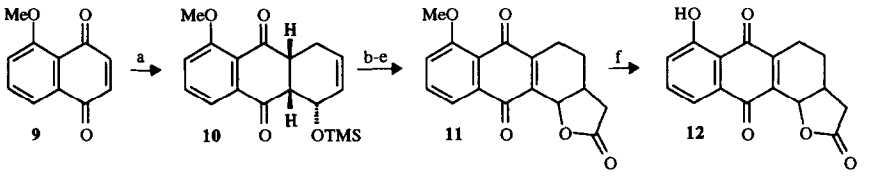
a. EtOCH=CH_2, NBS; b. Bu_3SnH, AIBN, toluene, Δ; c. CrO_3, H_2SO_4, H_2O/acetone

Treatment of compound **7** with tri-*n*-butyltin hydride and 2,2'-azobisisobutyronitrile (AIBN) in refluxing toluene[2,3] generated a reactive radical which underwent addition to the double bond generating a 50% yield of the desired tetrahydrofuran **8** as the major product (also a 1:1 mixture of diastereomers). Jones' oxidation was all that was then necessary to convert acetal **8** into the target molecule **2** through a sequence of one hydrolysis and two oxidations.

The successful strategy outlined above was also applied to the synthesis of phenolic carbocycle **12** (Scheme 4). In this case the dienophile required was 5-methoxynaphthoquinone **9**, prepared in one step from commercially available 5-hydroxynaphthoquinone by treatment with methyl iodide and silver(I)oxide.[4] The subsequent cycloaddition was much slower due to the presence of the methoxy group and only gave a modest 22% yield

under reflux. The stereochemistry and regiochemistry of adduct **10** have been assigned by reference to theoretical considerations and by analogy with the work of Chigr *et al.*.[5] Further elaboration to the lactone **11** proceeded smoothly utilising the chemistry already developed. A final deprotection, effected by aluminium trichloride[6] was necessary in order to give the frenolicin analogue **12**.

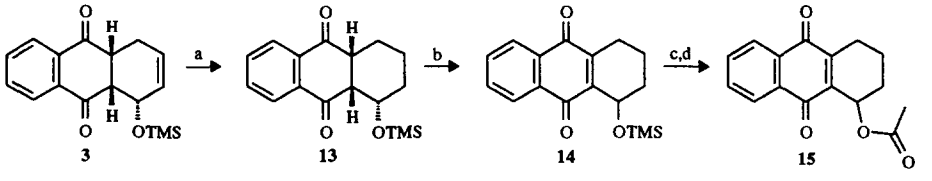
Scheme 4



a. TMSOCH=CHCH=CH_2, CH_2Cl_2, reflux; b. TsOH, MeOH, RT; c. EtOCH=CH_2, NBS; d. Bu_3SnH, AIBN, toluene, Δ; e. CrO_3, H_2SO_4, H_2O/acetone; f. $AlCl_3$, CH_2Cl_2, 0 C (10% over 5 steps).

One more analogue was prepared in this carbocyclic series, in order to test the limits of simplification that could be achieved whilst retaining antiprotozoal activity (Scheme 5). The double bond of adduct **3** was first hydrogenated, a transformation that was better carried out using Wilkinson's catalyst since palladium on charcoal caused overreduction of one of the ketone groups. The quinone oxidation level was easily achieved by treatment of **13** with manganese dioxide, subsequent desilylation and reprotection provided acetate **15** in good yield (12% overall from 3).

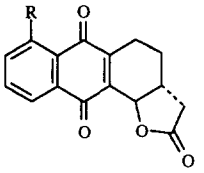
Scheme 5



a. H_2, $(Ph_3P)_3RhCl$, toluene, RT; b. MnO_2, ether, RT; c. Toluenesulfonic acid, MeOH, RT; d. Ac_2O, pyridine, CH_2Cl_2, Δ

Results and Discussion. The carbocyclic analogues prepared using the chemistry described above were tested in an *in vitro* assay which measures the ability of compounds to disrupt the infectious activity of *Eimeria* sporozoites. The relative potency of test compounds relative to frenolicin are shown in Table 1.

Table 1. Relative potencies of test compounds compared with frenolicin



Compound	R	lactone/acetate	Relative potency (frenolicin B = 1)
2	H	lactone	0.167
12	OH	lactone	0.033
15	H	acetate	0.001

Despite the radical simplifications made, analogues **2** and **12** retain an encouraging degree of antiprotozoal activity. In particular, carbocyclic analogue **2**, lacking both hydroxy and propyl substituents is within 6-fold of the potency of frenolicin B. Optimisation of this new carbocyclic template should easily bridge the gap. Surprisingly, reintroduction of the phenolic hydroxy group led to a further decrease in activity, suggesting that a complex interdependence of different parts of the molecule is important for activity. Finally, opening of the lactone to give the corresponding acetate **15** has a disastrous effect on potency, suggesting that a reversible leaving group α to the quinone may be a key structural feature of the frenolicin pharmacophore.

Conclusions. Carbocylic analogues of the anticoccidial frenolicin B are readily available using a strategy that relies on a Diels Alder reaction and a radical cyclisation to construct key C-C bonds. Screening results suggest that this structurally distinct class of analogues has the potential for potent anticoccidial activity.

References and Notes

1. Omura, S., Tsuzuki, K., Iwai, Y., Kishi, M., Watenabe, S., Shimizu, H. *J. Antibiotics* **1975**, *38*, 1447.
2. Stork, G., Mook, R., Jr., Biller, S.A., Rychnovsky, S.D. *J.Am.Chem.Soc.* **1983**, *105*, 3741.
3. Ueno, Y., Moriya, O., Chino, K., Watenabe, M., Okawara, M. *J.Chem.Soc.Perkin Trans. 1* **1986**, 1351.
4. Greene, A.E., Drian, C.L., Crabbe, P. *J.Am.Chem.Soc.* **1980**, *102*, 7583.
5. Chigr, M., Fillion, H., Rougny, A. *Tet. Lett.* **1987**, *28*, 4529.
6. Li, T.-t., Ellison, R.H. *J.Am.Chem.Soc.* **1978**, *100*, 6263.