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An *ortho*-quinone methide based strategy towards the rubromycin spiroketal family†

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A method for the generation/*in situ* hetero-Diels–Alder cycloaddition of a trisubstituted *ortho*-quinone methide (*o*-QM) is described. Heating of *ortho*-hydroxybenzylamines was found to be a more effective strategy for the formation of *o*-QMs than use of the corresponding *N*-substituted quaternary salts hitherto employed. This method was used to synthesise the spiroketal core of the rubromycins.

A number of spiroketal containing natural products exist where either one, or both of the rings is benzannelated.[1] Amongst these, the rubromycin family **1–6** (Fig. 1) has received considerable interest from the synthetic community.[2]

Initial curiosity of these molecules is presumably on account of their attractive biological activities, notably γ-rubromycin **3** is a telomerase and HIV-1 reverse transcriptase inhibitor at micromolar concentrations (IC_{50} = 2.64 and 19.9 μm respectively).[3] In contrast α-rubromycin **1** is far less potent (IC_{50} > 200 μm in each case), testament to the pharmacological importance of the spirocyclic core. Moreover, the beguiling and challenging molecular architectures of the rubromycins has prompted the development of a variety of innovative cyclisation methods to be developed for the construction of the biologically key spirocyclic core.[2] A number of successful total syntheses of γ-rubromycin **3** have been published based upon these.[4] For a number of years we have been intrigued by the possibility of a general synthetic route to the rubromycin family *via* a hetero-Diels–Alder cycloaddition approach that would nominally bring together an enol ether **8** (masked naphthazarin) and an isocoumaryl *ortho*-quinone methide[5] (*o*-QM) **9** (Scheme 1). Syntheses employing such a union would obviously be highly attractive in terms of overall brevity and subsequent analogue synthesis. To this end, we have previously reported on methods for the construction of benzannelated spirocycles generating an *o*-QM under basic conditions at low temperature[6] as well as *via* thermolytic extrusion of AcOH[7] from the same *ortho*-hydroxybenzyl acetate starting materials. Herein, we describe our synthesis of a fully elaborated *o*-QM precursor which has the potential for later conversion to the isocoumarin portion of the rubromycins and our efforts to employ this molecule in hetero-Diels–Alder reactions with enol ethers. Our synthesis began with conversion of vanillin (**10**) into the ester **13** (Scheme 2) according to the route of Reiβig[8] *via* *O*-silylation of the phenol with *tert*-butyldimethylsilyl chloride followed by protection of the aldehyde as an acetal using 1,3-propanediol, $HC(OMe)_3$ and *n*-Bu_4NBr_3 as catalyst.[9] The subsequent *ortho*-lithiation of **12** according to the published procedure[8] was found to be highly temperature

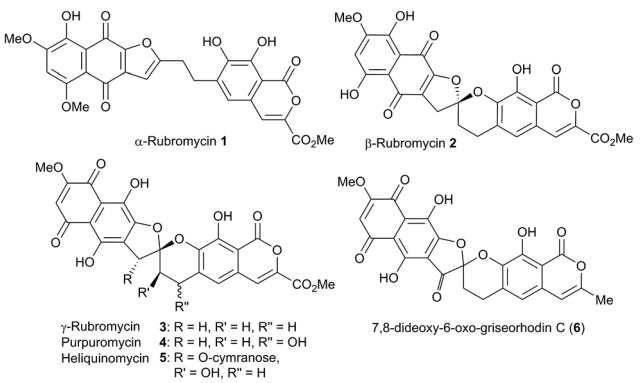
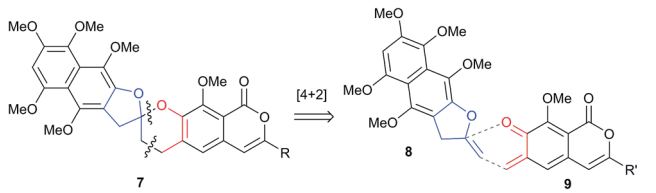


Fig. 1 Selected members of the rubromycin family.



Scheme 1 Proposed cycloaddition based strategy to the rubromycins.

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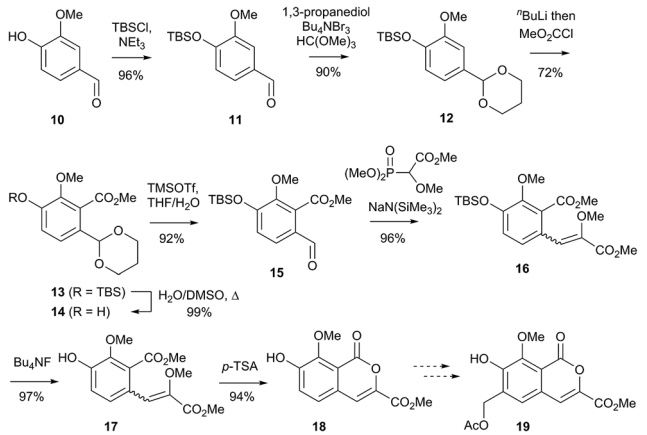
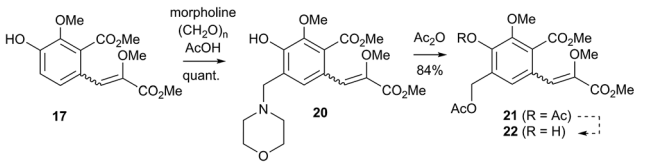


Scheme 2 Efforts towards a fully elaborated *o*-QM precursor.

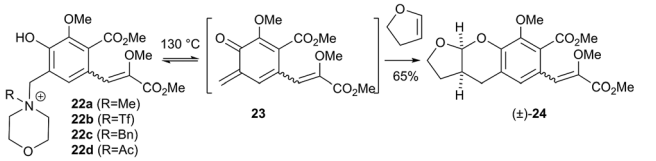
dependant. Optimal conditions were found to require deprotonation at −6 °C followed by subsequent trapping of the aryllithium formed with MeOCOCl and warming to 10 °C to give the arylester **13** in 72% yield on >30 g scale (lit.[8] 56%). Next a method for the selective deprotection of the aldehyde was needed that retained the silyl-protecting group on the phenol. An exhaustive screen of conditions to achieve acetal deprotection were examined however initially success was in finding a method for selective removal of the silyl protecting group using refluxing DMSO/H_2O to give phenol **14**. We were subsequently drawn to a report by Mohan *et al.*[10] describing how $Bi(OTf)_3$ could be used as a mild reagent for the deprotection of acetals in THF/H_2O. A second screening was therefore carried out using all the available metal triflates, present in the laboratory. $Sn(OTf)_2$ was found to catalyse the desired hydrolysis, leaving the silyl-protecting group intact, to give benzaldehyde **15** in 65%. Conscious that this reaction might be being caused by adventitious TfOH we also examined the use of TMSOTf in THF/H_2O. This far cheaper reagent combination led to the desired product in an improved 78% yield. Horner–Wadsworth–Emmons olefination of benzaldehyde **15** with $(MeO)_2P(O)CH(OMe)CO_2Me$[11] gave the enol ethers **16** in 96% yield as a 5 : 1 mixture of diasteromers in favour of the *Z*-isomer, following which, removal of the silyl-protecting group was achieved with TBAF to give the phenols **17**. Cyclisation of the phenols **17** was achieved using *p*-TSA to give the isocoumarin **18** present in the rubromycins in 94% yield. Our initial aim was then the conversion of isocoumarin **18** into the *ortho*-hydroxybenzyl acetate **19** which we hoped would be capable of generating an *o*-QM (*cf.* **9**) as per our previous reported procedures.[6,7] Multiple strategies were investigated including *O*-allylation/Claisen rearrangement and iodination/cross coupling. In each case whilst construction of a new C–C bond at C6 could be achieved, ultimate conversion to the *ortho*-hydroxybenzyl acetate **19** failed in each case. Attempted direct *ortho*-formylation *via* a myriad of known methods returned the starting material **18**. Combined, these failures were in large part due to the extreme insolubility of many of the intermediates coupled with the low nucleophilicity of the aromatic ring and fragility of the isocoumarin.



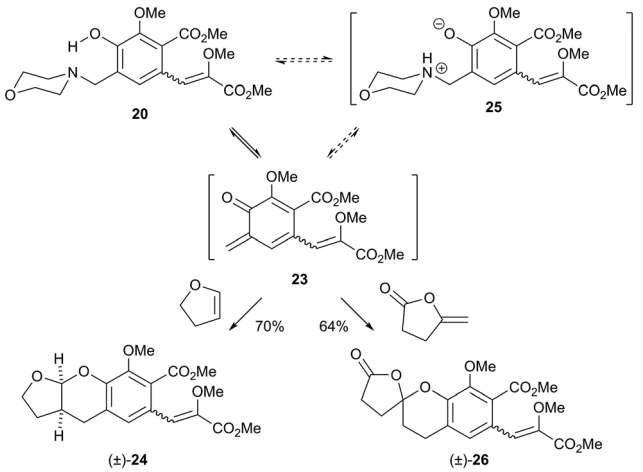
Scheme 3 Synthesis of a fully elaborated *o*-QM precursor.

Aware that these issues might also prove problematic during any subsequent attempted *o*-QM formation from **19**, we therefore turned our attention to the more soluble and stable phenol **17** and its conversion into a suitable *ortho*-hydroxybenzyl acetate **22.** Once more a range of strategies were explored for the acetoxymethylenation of **17**. The low nucleophilicity of the phenolic ring was again apparent with none of the attempted reactions leading to **19** but in contrast to our reactions with isocoumarin **18**, Mannich reaction *via* the 4-methylenemorpholin-4-ium ion led smoothly to the amine **20** (Scheme 3). We then converted this to the diacetylated compound **21** through refluxing in Ac_2O according to the procedure of Kozlowski,[12] interestingly this process presumably proceeds *via* an *o*-QM (**23**). Selective hydrolysis of the phenolic acetate or methods to preferentially form the mono-acetylated compound **22** *e.g.* through refluxing in AcOH were sadly not forthcoming. *ortho*-Hydroxybenzylamines had previously been used as precursors for the generation of *ortho*-quinone methides *via N*-alkylation, acylation or oxidation followed either by heating or photolysis.[5] In particular we were intrigued by the findings of Wilson and co-workers that *N*-methylmorpholinium salts can be converted to *o*-QMs at 80 °C and encouraged by their isolation of a spiroketal byproduct during their synthesis of (±)-xyloketal D.[13] The amine **20** reacted with a range of electrophilic reagents (MeI, Tf_2O, BnBr, AcCl) to give the quaternary ammonium salts **22a–d** (Scheme 4).

Pleasingly when the iodomethane adduct **22a** was heated to 130 °C with 2,3-dihydrofuran (DHF), the fused acetal (±)-**24** was formed in 65% yield proving the intermediacy of the desired *o*-QM **23.** However a similar cycloaddition with γ-methylene-γ-butyrolactone did not give any of the expected[7] spirocycle. Furthermore we then attempted to induce the formation of **23** under our previously reported low temperature anionic conditions[6] in conjunction with DHF, since simple *exo*-enol ethers (*cf.* those akin to **8**) readily rearrange to their *endo*-cyclic isomers *via* thermal or protic conditions. Warming this reaction mixture from −78 → 20 °C after the addition of i-PrMgCl as base did not lead to the expected acetal (±)-**24** but instead to complex mixtures. Similar results were obtained with the salts **23b–d**



Scheme 4 Proof of *o*-QM formation.



Scheme 5 Synthesis of a spiroketal *via* *o*-QM cycloaddition.

even though we examined a large range of bases, temperatures and times. Unalkylated *ortho*-hydroxybenzylamines had previously been reported as precursors for *o*-QMs albeit only under photochemical conditions at room temperature or at vastly elevated temperatures.[5,14] For completeness we investigated if the amine **20** also formed *o*-QMs under thermal only conditions. This was indeed found to be the case. When the amine **20** was heated with DHF at 130 °C the fused acetal (±)-**24** was formed in an improved 70% yield (Scheme 5). Moreover when γ-methylene-γ-butyrolactone was used as the 2π partner, the desired spirocycle (±)-**26** was formed in 64% yield. This suggests that contrary to current thinking, the unalkylated amine is a more effective precursor for forming an *o*-QM (**23**) than the corresponding *N*-alkylated one. This indicates that protonation of the amine by the phenol is sufficient to initiate elimination. It is not clear if protonation is a discrete event (*i.e.* **20** → **25**) in the formation of an *o*-QM or if the whole process is more concerted, maybe even in a pericyclic like-manner (*i.e.* **20** → **23**).

Conclusions

In conclusion we have synthesised a highly decorated *ortho*-hydroxybenzylamine **20** that is capable of forming an *ortho*-quinone methide **23**. Notable in the synthesis of **20** is a method for the selective removal of a *tert*-butyldimethylsilyl group from a phenol in the presence of a 1,3-diol protected aldehyde. Orthogonal removal of this acetal protecting group without deprotection of the phenol was achieved using TMSOTf in THF/H_2O. These selective deprotection methods may prove useful in other syntheses. Finally, the *ortho*-hydroxybenzylamine **20** can be alkylated and heated with DHF to form a fused acetal (±)-**24**, however of greater note is the fact that *in lieu* of alkylation, the amine **20** appears to function as a more effective *o*-QM precursor. Cycloaddition with a model 2π-partner has given a spiroketal (±)-**26** similar to that found in the rubromycins. Future work will investigate this *o*-QM generation method and adapt this cycloaddition protocol to incorporate the entire rubromycin carbon skeleton.

Acknowledgements

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