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Exploring *O*-stannyl ketyl and acyl radical cyclizations for the synthesis of γ-lactone-fused benzopyrans and benzofurans†

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The synthesis of a series of γ-lactone-fused benzopyrans and benzofurans, analogues of the pyrano-naphthoquinone antibiotics, is reported. Preparation of the heterocycles was achieved by either *O*-stannyl ketyl or acyl radical cyclization of benzaldehyde precursors followed by oxidation to give the pyrano- and furanobenzoquinone systems. The observed diastereoselectivity during *O*-stannyl ketyl radical cyclization is influenced by aromatic substitution *ortho* to the aldehyde, whilst acyl radical cyclization followed by stereoselective reduction of the resulting pyranones provides a complimentary approach to forming the required γ-lactone-fused benzopyran systems.

Introduction

The redox chemistry of quinones is often linked to their biological relevance, from the central involvement of coenzyme Q_{10} (ubiquinone) in the electron transport chain of eukaryotic organisms, through to the defence mechanism of the bombardier beetle. Not surprisingly, the presence of a quinonoid system in compounds such as **1–4** (Fig. 1) is crucial to their bioactivity, with doxorubicin **1** and mitomycin C **2** both being in clinical use for the treatment of a variety of cancers. The pyranoquinones kalafungin **3** and frenolicin B **4** are members of a large family of natural products that consistently show a broad range of antibiotic activities, many possessing cytotoxic properties.[1] A mechanism of action involving bioreductive alkylation was proposed by Moore and Czerniak for pyranoquinones such as **3** and **4**,[2] and is supported by more recent theoretical,[3] chemical[4] and biochemical studies.[5]

The tricyclic quinone **5** (Scheme 1) contains the essential structural features required for the bioactivity of pyrano-naphthoquinones **3** and **4**, based on their proposed bioreductive alkylation mode of action, and can thus be considered the pharmacophore for these natural products. The process involves an initial two-electron reduction of quinone **5** to

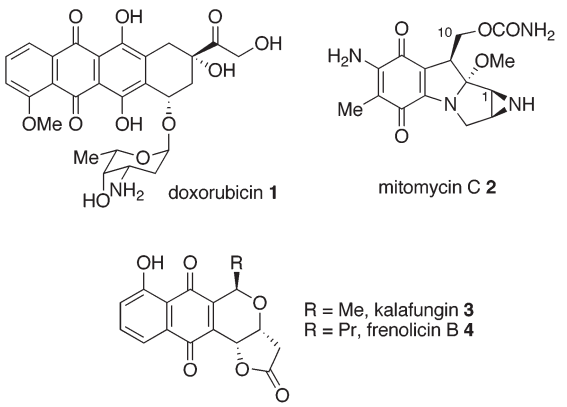
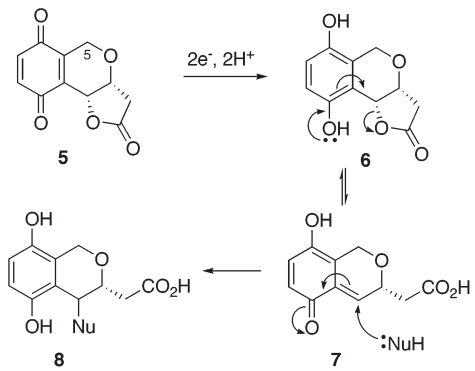


Fig. 1 Bioreductive alkylating agents.



Scheme 1 Mechanism of bioreductive alkylation for γ-lactone-fused pyranoquinones.

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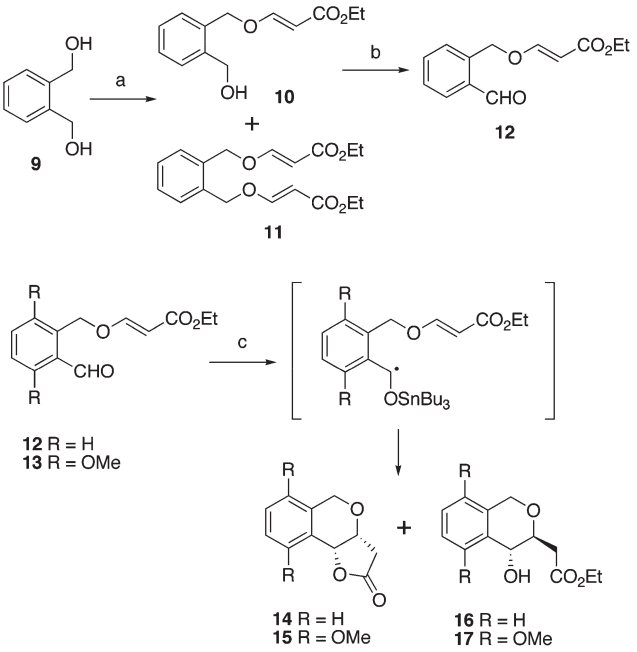
hydroquinone **6**, this being followed by opening of the γ-lactone to form the reactive *ortho*-quinone methide **7**, which upon reaction with a nucleophile leads to the alkylated product **8**. Some of the biological effects of doxorubicin **1** have been attributed to a related one-electron bioreductive process that generates reactive oxygen species,[6] whilst mitomycin C **2** acts as a sequence specific cross-linker of DNA *via* alkylation at C-1 and C-10.[7] In the later case, reduction of the quinone in **2** initiates a cascade involving loss of methanol, opening of the aziridine ring and loss of carbamate to form the alkylating species.

Surprisingly, the proposed pharmacophore **5** of the pyranoquinones has not itself been prepared previously, although a number of analogues having substituents on the benzoquinone ring[8,9] or at C-5 on the pyran ring[10–15] are known. Apart from the alkoxycarbonylative annulation methodology[16] and Lewis acid-catalyzed aryldioxolanylacetate rearrangement,[12] preparation of the fused benzopyran-γ-lactone structural motif contained in **6**, which may then serve as a precursor to quinone **5**, usually involves formation of each of the heterocyclic rings in separate steps. Examples include using sequential Wittig-oxa-Michael reactions followed by lactonization,[8] Sharpless dihydroxylation to form the γ-lactone followed by oxa-Pictet-Spengler reaction[10] and 2-alkoxyfuran addition to 2-acetylbenzoquinone with subsequent acid-catalyzed rearrangement.[13,15]

As part of an ongoing program exploring the use of *O*-stannyl ketyl radical cyclizations for the synthesis of a range of structure classes, including prostanoids and dioxaspirononanes,[17] we have also applied this approach to the synthesis of tricyclic systems related to **6** en route to frenolicin B **4**.[18] This method enabled both the pyran and *cis*-fused γ-lactone rings to be formed in a single step, with excellent diastereoselectivity, from a benzaldehyde precursor. The ability to rapidly access heterocycles such as **6** using this method gave us the incentive to explore the scope of this approach further for the synthesis of analogous systems that may potentially act as bioreductive alkylating agents. Additionally, it was anticipated that during the course of these studies factors affecting the diastereoselectivity during *O*-stannyl ketyl radical cyclization of benzaldehyde substrates would be assessed to establish more efficient and predictable outcomes in these multi-bond forming processes.

Results and discussion

To assess the viability of this approach we firstly prepared the cyclization precursor benzaldehyde **12** in two steps from benzene dimethanol **9**[19] (Scheme 2). When benzaldehyde **12** was treated with tributyltin hydride (0.05 M) and AIBN in benzene at reflux a mixture of *cis*-**14** and *trans*-**16** products were formed along with benzyl alcohol **10** resulting from reduction of the intermediate *O*-stannyl ketyl radical. Lowering the concentration of tributyltin hydride to 0.02 M gave improved conversion to cyclized products **14** and **16** (Table 1).



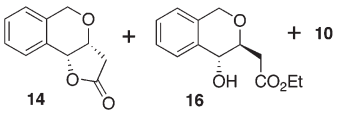
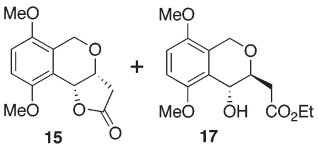
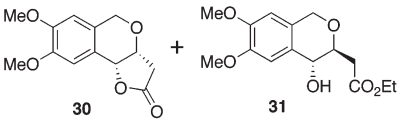
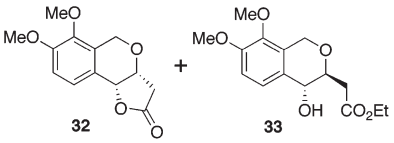
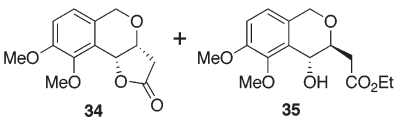
Scheme 2 *Reagents and conditions*: (a) ethyl propiolate, NMM, CH_2Cl_2, 1.5 h (**10** 45%; **11** 47%); (b) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, 3 h (98%); (c) Bu_3SnH, AIBN, benzene, reflux, 5 h (**15** 13%, **17** 46%).

Under these conditions the required γ-lactone-containing product and the *trans*-product are formed in equal amounts (**14** : **16** 1 : 1). When the *para*-dimethoxy substituted benzaldehyde **13** was reacted under similar conditions, however, the diastereoselectivity of the cyclization changed in favour of the *trans*-product **17** (**15** : **17** 1 : 3.4).[18] The conversion of *trans*-product **17** to lactone **15** can be effected by exposure to potassium carbonate.[18]

To further understand the factors influencing the stereoselectivity of these *O*-stannyl ketyl radical cyclizations the isomeric dimethoxybenzaldehydes **22**, **28** and **29** were prepared as outlined in Scheme 3. Thus, reduction of phthalide **18** gave the symmetrical diol **19**[20] that upon alkylation formed benzyl alcohol **20**, along with dialkylated product **21**. Oxidation of alcohol **20** then gave benzaldehyde **22** in 41% yield over the three steps. A similar sequence of reactions beginning from phthalide **23** initially gave diol **24**[21] that upon alkylation formed isomeric benzyl alcohols **25** and **26**. Separation of the isomers was best achieved after their subsequent oxidation to the corresponding benzaldehydes **28** and **29**. With these substrates in hand, the influence of substitution pattern on the *O*-stannyl ketyl radical cyclization could be assessed.

The *ortho*-dimethoxybenzaldehydes **22** and **28**, in which the methoxy substituents are remote to the aldehyde group, both gave a near 1 : 1 mixture of *cis*- and *trans*-products (Table 1, entries 3 and 4) that are comparable to the unsubstituted system **12**. The *ortho*-dimethoxy isomer **29** in which the aldehyde group has a neighbouring methoxy group gave a preference for *trans*-product **35** (entry 5), with the *cis*-/*trans*-product ratio very similar to that formed from the *para*-dimethoxy substituted system **13**. With dimethoxybenzaldehydes **13**, **22**, **28**

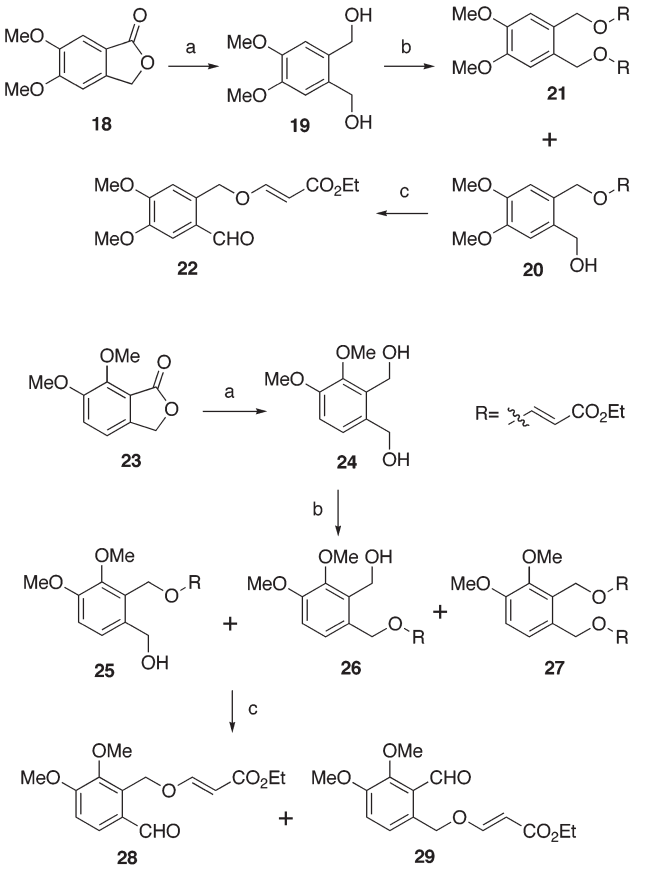
Table 1 *O*-Stannyl ketyl radical cyclization products from benzaldehydes **12**, **13**, **22**, **28** and **29**

Entry	Substrate	Products[a,b]
1	**12**	 **14** + **16** + **10** 29 : 29 : 42[c] 38 : 40 : 22 (73%)
2	**13**	 **15** + **17** 22 : 78 (59%)[d]
3	**22**	 **30** + **31** 54 : 46 (63%)
4	**28**	 **32** + **33** 54 : 46 (65%)
5	**29**	 **34** + **35** 25 : 75 (69%)

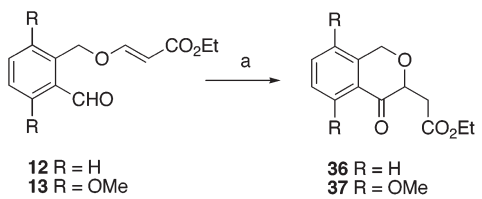
[a] Conditions: Bu_3SnH (0.02 M, 1.5 equiv.), AIBN (0.1–0.3 equiv.), benzene, reflux, 5 h. [b] Ratio and yield of cyclized products obtained by integration of ^1H NMR spectrum of the mixture after filtration through 10% KF/silica. In each case, 15–25% of the products resulting from reduction were also observed. [c] $[Bu_3SnH]$ = 0.05 M. [d] Isolated yield.

and **29** having similar electronic features, the change in stereoselectivity may be a result of the steric influence of the methoxy groups. Thus, when a methoxy group is *ortho* to the aldehyde (Table 1, entries 2 and 5) then *trans*-products are favoured. Conversely, less hindered aldehyde groups (entries 1, 3 and 4) tend to give similar amounts of *cis*- and *trans*-products. The preference for *trans*-product formation from benzaldehydes **13** and **29** may also result from electrostatic repulsion between the oxygen of the intermediate *O*-stannyl ketyl group and adjacent methoxy substituent being minimized in the transition state leading to *trans*-products **17** and **35**. Samarium diiodide has been used to effect reductive cyclization of benzaldehydes,[22] however, under these conditions a strong preference for *trans*-product formation is observed and as such has not been attempted in the present study.

With the goal of more efficiently accessing the required γ-lactone-containing product **15** from benzaldehyde **13**, we considered an approach that involved a diastereoselective

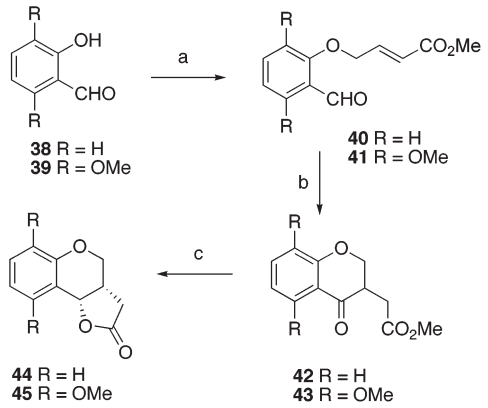


Scheme 3 *Reagents and conditions*: (a) $LiAlH_4$, THF, 0 °C, 2.5 h (**19** 80%; **24** 93%); (b) ethyl propiolate, NMM, CH_2Cl_2, 1.5 h (**20** 56%, **21** 24%; **25** + **26** 60%, **27** 21%); (c) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, 2–3 h (**22** 91%; **28** + **29** 90%).

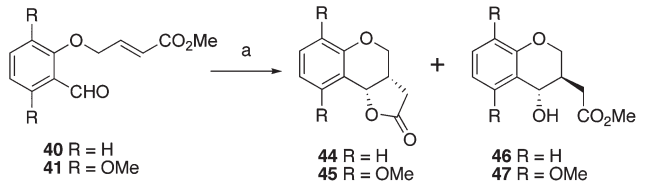


Scheme 4 *Reagents and conditions*: (a) *tert*-dodecanethiol (0.3 equiv.), ACCN (0.3 equiv.), PhMe, reflux, 22 h (**37** 23% [48% recovered **13**]).

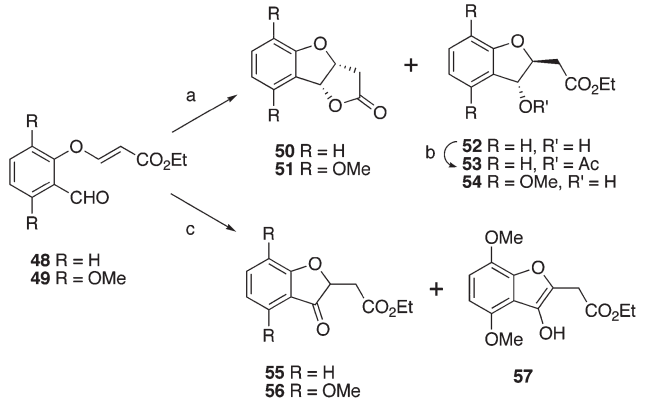
reduction of ketone **37** (Scheme 4). To prepare the required ketone we envisaged the direct formation of **37** from benzaldehyde **13** using an acyl radical cyclization under conditions of polarity reversal catalysis.[23,24] Firstly using the unsubstituted benzaldehyde **12**, treatment with *tert*-dodecanethiol and 1,1′-azobis(cyclohexanecarbonitrile) (ACCN) resulted in only 30% conversion to ketone **36** after 18 hours in toluene at reflux. Similar treatment of the dimethoxybenzaldehyde **13** gave 50% conversion after 22 hours, with ketone **37** being isolated in 23% yield (44% based on recovered **13**). Longer reaction times with further addition of initiator and/or catalyst failed to complete the conversion of benzaldehyde **13** to ketone **37** without further decomposition taking place. We



Scheme 5 *Reagents and conditions*: (a) methyl-4-bromobut-2-enoate, K_2CO_3, DMF, 16–20 h (**40** 61%; **41** 80%); (b) *tert*-dodecanethiol (3.0 equiv.), ACCN (1.5 equiv.), PhCl, 100 °C, 20 h (**42** 68% [26% recovered **40**]; **43** 64%); (c) (i) $CeCl_3{\cdot}7H_2O$, $NaBH_4$, CH_2Cl_2, MeOH, –78 °C, 45 min; (ii) *p*TsOH·H_2O, $CHCl_3$, 2 h (**44** 69%; **45** 84%).



Scheme 6 *Reagents and conditions*: (a) Bu_3SnH, AIBN, benzene, reflux, 2 h (**44** + **46** 92%; **45** 39%, **47** 40%).



Scheme 7 *Reagents and conditions*: (a) Bu_3SnH, AIBN, benzene, reflux, 2–3 h (**50** + **52** 86%; **51** 71%, **54** 25%); (b) Ac_2O, pyridine, DMAP, CH_2Cl_2, 1.5 h; (c) *tert*-dodecanethiol (3.0 equiv.), ACCN (1.5 equiv.), PhCl, 100 °C, 18 h (**56** 47%, **57** 11%).

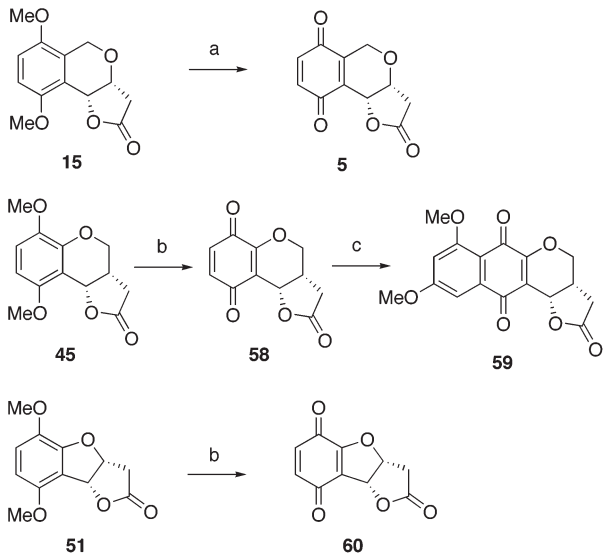
considered that competitive abstraction of hydrogen at the activated benzylic ether positions in **12** and **13** by the thiyl radical may be inhibiting efficient intramolecular hydroacylation to form the expected ketones **36** and **37**. In accord with this, the analogous carbocyclic ketone products are obtained efficiently using this method[24a] and we have observed that increasing steric hindrance by the introduction of further substitution at the benzylic ether position in **13** gives improved conversion to the corresponding ketone using the thiyl radical catalysed process.[24b]

We then turned to the isomeric benzaldehyde **40** (Scheme 5), prepared from salicylaldehyde **38**,[25] to further investigate the acyl radical cyclization process. When **40** was heated in the presence of thiol and initiator the ketone product **42**[25] was isolated in 68% yield. Similarly, the dimethoxy-substituted system **41** underwent acyl radical cyclization efficiently to form ketone **43** in 64% yield. Complete consumption of benzaldehyde **41** was evident after 20 h, supporting the proposition that the presence of readily abstractable hydrogen at the benzylic ether position in previous substrates **12** and **13** significantly hinders the efficiency of these thiyl radical-catalysed reactions. As anticipated, ketones **42** and **43** could be stereoselectively reduced under Luche conditions ($CeCl_3$–$NaBH_4$–MeOH) to form the corresponding lactones **44** and **45** in 69% and 84% yields, respectively. The presence of *trans*-alcohol products under these conditions was not evident.

Direct formation of the γ-lactone-fused benzopyrans **44** and **45** should also be possible using the previously described *O*-stannyl ketyl radical cyclization conditions. Thus, upon treatment of benzaldehyde **40** with tributyltin hydride an inseparable 1.4 : 1 mixture of lactone **44** and alcohol **46** (Scheme 6) was obtained in a combined 92% yield, in accord with previous reports.[26] Incorporation of methoxy substituents onto the aromatic ring in benzaldehyde **41** led to only a slight change in the diastereoselectivity with **45** and **47** being isolated in 39% and 40% yields, respectively. In contrast to the β-alkoxy acrylate systems described earlier (Table 1), the isomeric crotonate systems **40** and **41** showed no evidence of undergoing competitive reduction and shorter reaction times were required suggesting that the barrier to radical cyclization may be less significant for **40** and **41**.

We then sought to further explore both the *O*-stannyl ketyl and acyl radical cyclization approach for the formation of benzofuran systems having an appended γ-lactone ring (Scheme 7). Such systems, when converted to benzoquinones, should potentially be able to act as bioreductive alkylating agents in a manner similar to that proposed for the benzopyran systems (Scheme 1). The 6,5,5-ring systems in **50**/**51** resemble the ring system contained in mitomycin C **2** and may be considered as a 'hybrid' of the mitomycin C **2** and pyranonaphthoquinone **3** pharmacophores.

Consistent with previous reports benzaldehyde **48**[27] (Scheme 7) underwent *O*-stannyl ketyl radical cyclization efficiently to form an inseparable mixture of benzopyrans **50** and **52** in a combined 86% yield (**50** : **52** 34 : 66).[28] Acetylation of this mixture assisted separation of acetate **53** from lactone **50** to allow characterization of the products. The corresponding dimethoxy benzaldehyde **49** also cyclized efficiently to form *cis*-lactone **51** (71% yield) and *trans*-alcohol **54** (25% yield). In contrast to formation of the corresponding benzopyran systems (Table 1, entries 1 and 2) in which the incorporation of *para*-methoxy substituents led to the *trans*-product being favoured, introduction of methoxy substituents onto



Scheme 8 *Reagents and conditions*: (a) CAN, MeCN, H_2O, 30 min (93%); (b) PIFA, MeCN, H_2O, 1–2 h (**58** 76%; **60** 63%); (c) 1,3-dimethoxy-1-trimethylsiloxybuta-1,3-diene, CH_2Cl_2, 1.5 h, then SiO_2, air, 1 h (55%).

benzaldehyde **49** results in the *cis*-lactone **51** being formed in preference to the *trans*-alcohol **54** (**51** : **54** 2.8 : 1).

Benzaldehydes **48** and **49** also underwent acyl radical cyclization, with the unsubstituted system **48** only progressing to approximately 30% conversion to ketone **55** after 18 h at 100 °C in chlorobenzene. The dimethoxy benzaldehyde **49**, however, was completely consumed after the same reaction time to give ketone **56** and enol **57** in 47% and 11% yields, respectively. Interconversion of ketone **56** and enol **57** was not observed upon standing the purified materials in deuterated chloroform for two days.

Having prepared a series of benzopyran and benzofuran heterocycles, their conversion to the corresponding benzoquinones was effected as shown in Scheme 8. Thus, oxidation of benzopyran **15** using cerium(IV) ammonium nitrate (CAN) gave benzoquinone **5** in 93% yield. Attempted oxidation of the isomeric benzopyran **45** using CAN gave mixtures of products resulting from oxidative dimerization, however, using phenyliodine bis(trifluoroacetate) (PIFA) to effect oxidation of **45** led to the isolation of benzoquinone **58** in 76% yield. Further elaboration of benzoquinone **58** was undertaken by employing a regioselective Diels–Alder reaction to give the 'iso'-pyranonaphthoquinone system **59**. Finally, the benzofuran system **51** was also oxidized using PIFA to give furanobenzoquinone **60**, a novel hybrid of the mitomycin C and pyranonaphthoquinone pharmacophores.

Conclusions

The diastereoselectivity of *O*-stannyl ketyl radical cyclization of benzaldehydes with tethered acrylates has been investigated. The 6-*exo* cyclization of β-alkoxy acrylates having methoxy groups *ortho* to the aldehyde (**13** and **29**) tend to favour *trans* products, whereas an unsubstituted *ortho* position (**12**, **22** and **28**) leads to formation of a near equal mixture of *cis* (lactone) and *trans* products. A similar trend, though less pronounced, is observed for the isomeric crotonate systems **40** and **41**. During formation of benzofurans the opposite outcome is observed, with the addition of methoxy groups onto the aryl system favouring the formation of the *cis*-lactone product **51**. Furthermore, a complimentary approach that uses an acyl radical cyclization of the same benzaldehyde substrates followed by diastereoselective reduction of the resulting pyranones has provided a more efficient method for the preparation of the required *cis*-lactone products. These approaches have made available a series of benzopyran- and benzofuran-fused γ-lactones that have been converted to benzoquinones **5**, **58** and **60** and naphthoquinone **59**, which are expected to have potential as bioreductive alkylating agents.

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