A radical-based approach to hydroxytetralones from unprotected phenols†‡

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Xanthates derived from unprotected 2-hydroxyacetophenones undergo smooth intermolecular addition to unactivated alkenes and subsequent cyclisation to give hydroxytetralones in good yield.

As part of an ongoing synthetic project, we examined a potentially short approach to pseudopteroxazole **1** proceeding by way of α-tetralone **2** (Scheme 1).[1] This key intermediate appeared to be easily accessible by a general route to α-tetralones we reported a few years ago.[2,3] In the present case, this would involve the radical addition of phenacyl xanthate **3** to commercially available diethyl acetal **4** of acrolein followed by cyclisation to the aromatic ring.

The synthesis of the xanthate component **3** was trivial and the first intermolecular radical addition to alkene **4** took place smoothly to give the expected adduct **5** in 77% yield (Scheme 2). We were, however, disappointed to find that, in contrast to the many previous cases we had studied, the ring-closure could not be accomplished despite all our efforts. The only product that could be isolated in poor yield was the reduced starting material **6**.[4]

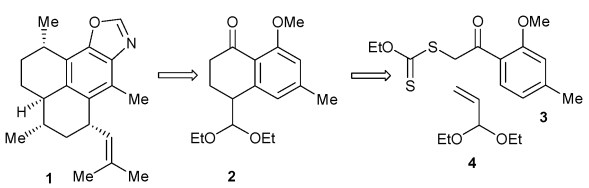
One possible explanation is that the dipole–dipole repulsion between the carbonyl and methoxy group forces the intermediate radical into adopting conformation **7b** that is unfavourable for cyclisation. The ring closure is perhaps also being hindered to a certain extent by the steric bulk of the acetal group.

In order to overcome this repulsion and encourage the radical to adopt a more propitious conformation, we considered the possibility of exploiting the intramolecular hydrogen bond that is bound to exist with the naked phenol. As indicated in structure **8**, such a relatively strong hydrogen bond would freeze the molecule in the desired conformation. Another, perhaps less obvious advantage, is that the hydrogen bond will slow down hydrogen abstraction from the phenol. Indeed, phenols are extensively used as stabilisers and inhibitors of radical chain reactions,[5] but a study by Ingold and co-workers revealed that hydrogen abstraction from phenols could be slowed 200-fold on going from CCl_4 to *t*-butanol as solvent.[6] This remarkable decrease in rate of hydrogen abstraction was attributed to hydrogen bonding with the more polar solvent. In our case, the stronger intramolecular hydrogen bond would hopefully eliminate any danger of complications arising from unwanted and uncontrolled hydrogen abstractions.

In the event, we were greatly relieved to find that both the intermolecular addition to acrolein acetal **4** and the ring closure were quite efficient and furnished the desired α-tetralone **11** in good overall yield (Scheme 3). The generality of the sequence was tested with three other olefins, vinyl acetate, **12** and **15**, which afforded the corresponding tetralones **11′**, **14** and **17**. In the case of **14**, the intermolecular adduct **13** was not isolated; the reaction mixture from the first step was simply diluted and treated with a stoichiometric amount of peroxide.

A major hurdle on the route to pseudopteroxazole **1** and substances with related structures has thus been removed. The synthetic utility of this approach can be gauged by the two transformations in Scheme 4. In the first, addition of xanthate **9** to vinyl acetate followed by cyclisation and saponification of the ester group in **19** furnished racemic shinanolone **20**, a natural product isolated from various plant sources.[7] The second example testifies to the mildness of the reaction conditions since the addition to alkene **21** derived from citronellene and cyclisation could be accomplished without harm to the epoxide group. An elaborate structure **23** could hence be assembled in only two steps. It is worth noting that tetralone **23** is closely related to the naturally occurring *seco*-pseudopteroxazole and erogorgiaene, the biosynthetic precursor of pseudopterosins and *seco*-pseudopterosins.[8]

A final interesting aspect is the flexibility inherent to this chemistry. Variations can be introduced through both partners in the process. The examples displayed in Scheme 5 illustrate some modifications in the xanthate component. For instance, addition of xanthate **24** to vinyl pivalate and cyclisation provides compound **26**, an advanced intermediate in the synthesis of 10-Norparvulenone **27**, which we recently described.[9] Eliminating the need to protect the phenolic group therefore shortens the synthesis by two steps and increases significantly the overall yield. The last example involving xanthate **28** and leading to tetralone **30**, albeit in modest yield,



Scheme 1

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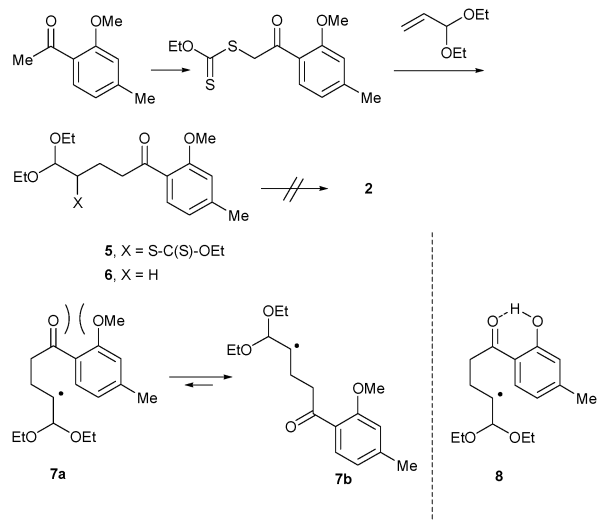
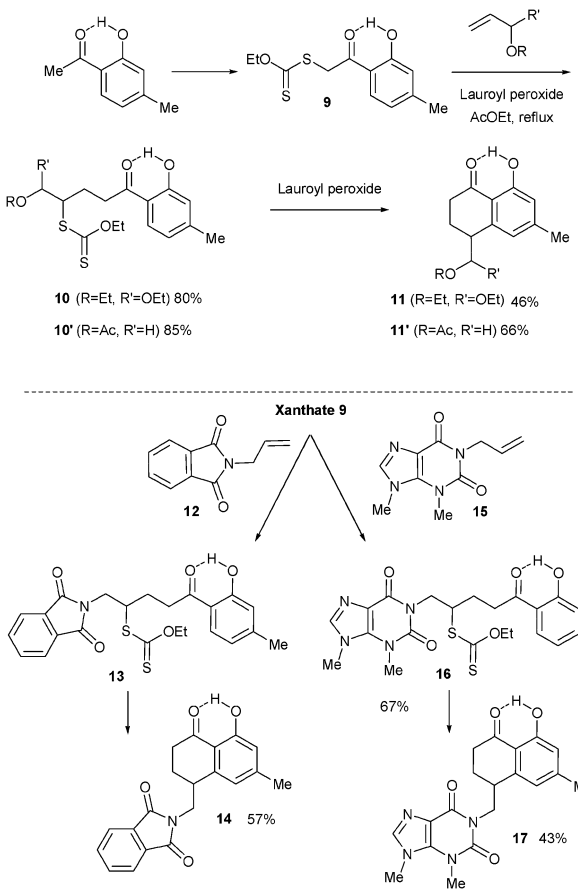
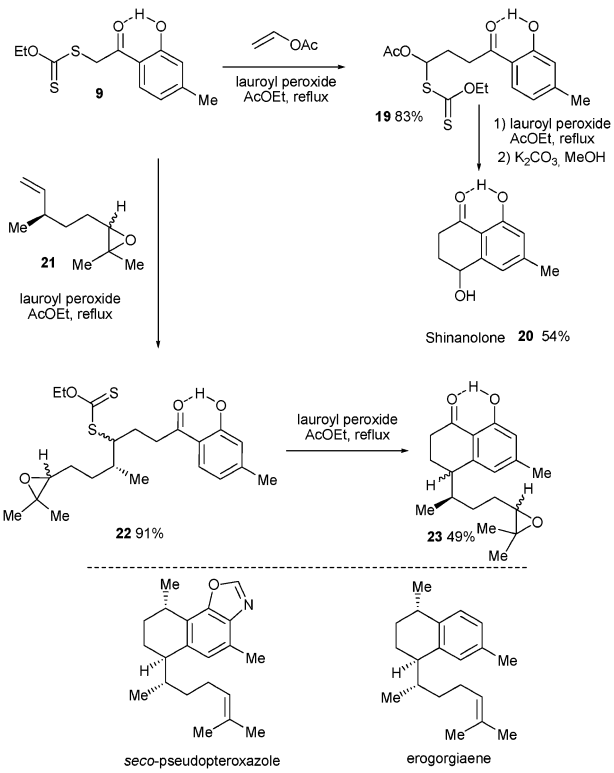
‡ Electronic supplementary information (ESI) available: Experimental details, spectroscopic data and NMR spectra. See DOI: 10.1039/c0cc00680g



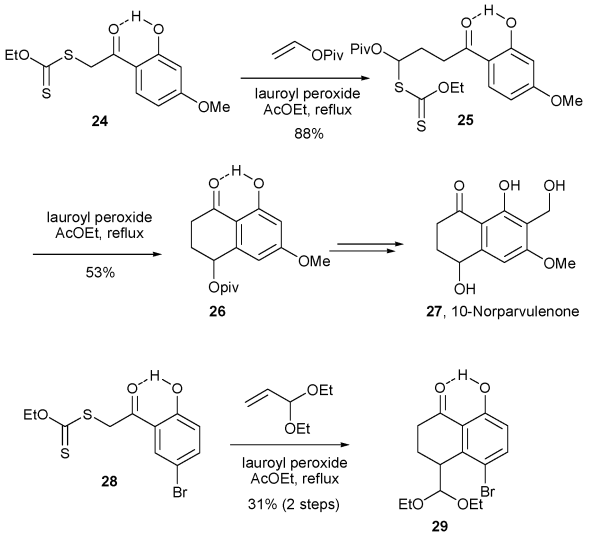
Scheme 2



Scheme 3



Scheme 4



Scheme 5

the ring closure being somewhat sensitive to steric hindrance, underscores the tolerance to the presence of halogen in the structure and hints at the possibility of using an organometallic reaction, such as a Heck coupling, to close the last ring present in pseudopteroxazole **1** and its congeners.

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