A catalytic asymmetric protocol for the enantioselective synthesis of 3(2*H*)-furanones†

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3(2*H*)-Furanones can be prepared by a catalytic asymmetric protocol from enynones, which, if electron-rich, require only one reagent and involve two reactions in a single operation—a domino process.

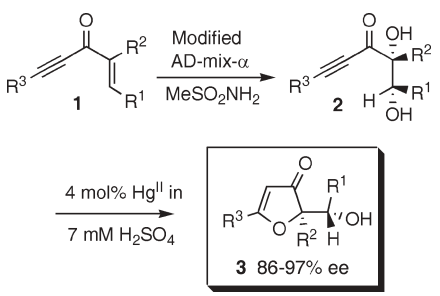
The construction of small and medium-sized *O*-heterocyclic rings is a cornerstone of natural product synthesis, but can be a demanding objective, particularly when the placement of multiple functionality with enantiocontrol must be addressed.[1] The tetrahydrofuran ring is central to numerous natural products of potent biological activity, including the zaragozic acids,[2] the calyculins,[3] serine–threonine protein phosphatase inhibitors, and especially polyether antibiotics such as monensin and halichondrin B.[4] Coordination to a metal of one or more tetrahydrofuran rings of a polyether natural product is often the central feature upon which specific biological activity depends. The 3(2*H*)-furanone ring system is found in a variety of natural products, including potent anti-tumour agents,[5] bacterial glycosides,[6] and sesquiterpenoids possessing anti-inflammatory activity.[7] The potent anti-tumour properties of many 3(2*H*)-furanones have been associated with their ability to act as Michael acceptors.[8] With one major exception,[8] methods of preparing the 3(2*H*)-furanone ring system are not general, and to our knowledge none is enantioselective.[9]

Herein, we report the first examples of the asymmetric dihydroxylation of enynones, and disclose a new catalytic sequence to 3(2*H*)-furanones **3** (Scheme 1), versatile precursors useful for the synthesis of natural products containing the dihydrofuran or tetrahydrofuran ring. The second of the two catalytic steps in this sequence is not needed for ynones **1** that contain a terminal alkoxy group; those 3(2*H*)-furanones **3** are formed from the ynone in a single reaction.

There are relatively few reports of enantioselective dihydroxylation of α,β-unsaturated ketones,[10] and in one case 1 mol eq. of OsO_4 and 2 mol eq. of $(DHQD)_2PHAL$ were required for a satisfactory ee to be obtained.[11] Despite the possible limitations indicated by such studies, it was reasoned that the increased electron density from an alkyne moiety adjacent to the keto group would render the flanking carbon–carbon double bond more akin to an α,β-unsaturated ester or even an isolated alkene, both of which are well known to afford products in high ee's using Sharpless's asymmetric dihydroxylation.[12] For the subsequent 5-*endo-dig* ring closure, studies on the Hg^{II}-catalysed rearrangement and ring-closure of 1-alkynyl-2,3-epoxy alcohols to give 2,3-dihydro-4*H*-pyran-4-ones[13] suggested that similar conditions might be effective, although the use of unprotected diols could, in principle, give either five-membered or six-membered rings.

Entries 1–3 in Table 1 are representative of the procedure and results. The required enynone precursors were obtained by addition of a terminal alkynyllithium (1.1 eq.) to the appropriate 2-alkenal in THF at 20 °C to give the corresponding enynol which was oxidised to the requisite enynone **1** using MnO_2. The dihydroxy-ynones **2a–2c** were obtained from Sharpless's asymmetric dihydroxylation using modified AD-mix-α containing 5 mol% of $(DHQ)_2PHAL$ and 1 mol% of potassium osmate.[14] Treatment of **2a–2c** with catalytic Hg(II), obtained by previously dissolving HgO in aqueous sulfuric acid, afforded the corresponding 3(2*H*)-furanones in high ee's. An alternative order of reaction (Table 1, entry 4) was tested by conducting asymmetric dihydroxylation on (*E*)-*N*-methoxy-*N*-methylcinnamamide (**4**) followed by protection as the acetal **5** (using acetone and catalytic *p*-TsOH) prior to addition of the alkynyllithium to give **2d** (Scheme 2). This sequence benefits from its convergence and also permits cyclisation to the 3(2*H*)-furanone with concomitant deprotection of the acetal group; **3d** was also obtained in excellent ee. The ethoxy-substituted enynones **1e** and **1f** (prepared by addition of lithium ethoxyacetylide to the requisite aldehyde, followed by oxidation of the enynol using MnO_2) spontaneously generated the 3(2*H*)-furanones **3e** and **3f**, respectively, when treated with AD-mix-α, representing a new domino process.

An X-ray crystal structure determination[15] of **3c** confirmed the constitution of the five-membered ring system and also the relative



Scheme 1 A catalytic enantioselective route to 3(2*H*)-furanones.

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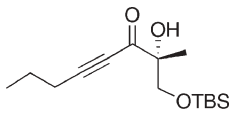
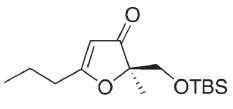
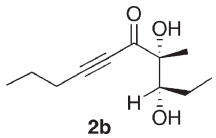
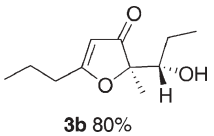
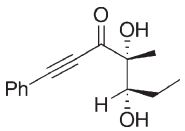
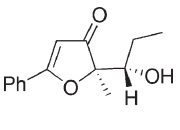
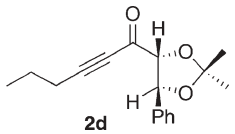
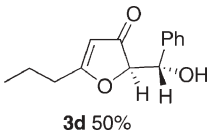
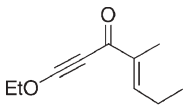
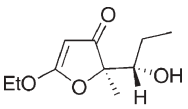
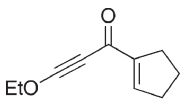
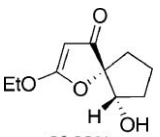
† Electronic supplementary information (ESI) available: Representative procedures and crystallographic data for **3c**. See DOI: 10.1039/b701548h

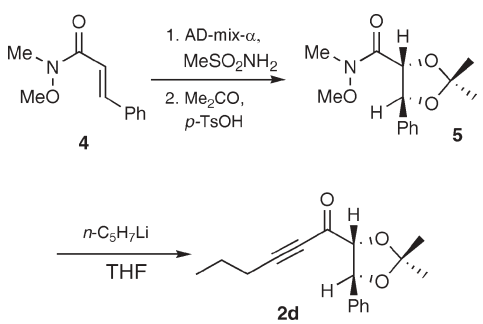
Table 1 Synthesis of 3(2*H*)-furanones

	Ynone	3(2*H*)-Furanone (yield)	ee (%)
1[a]	 **2a**	 **3a** 92%	90[b]
2[a]	 **2b**	 **3b** 80%	92[c]
3[a]	 **2c**	 **3c** 95%	97[c]
4[a]	 **2d**	 **3d** 50%	97[c]
5	 **1e**	 **3e** 50%	95[c]
6	 **1f**	 **3f** 62%	ND[d]

[a] Reaction conditions: 4 mol% HgO dissolved in 7 mM aqueous H_2SO_4. [b] Enantiomeric purity was determined by derivatisation of the alcohol (obtained by desilylation of **3a**) as the Mosher ester. [c] Enantiomeric purity was determined by HPLC analysis using a Chiralcel OD column (entries 2, 4 and 5) or Chiralcel OJ column (entry 3). [d] Not determined.

configuration of its substituents (Fig. 1). In the present investigation, albeit preliminary, 2,3-dihydro-4*H*-pyran-4-ones, arising from the alternative 6-*endo-dig* mode of cyclisation, were not found.

The cyclisation protocol is consistent with the presence of an unprotected carboxylic acid group (Scheme 3), and was used to



Scheme 2 Preparation of the acetal **2d**.

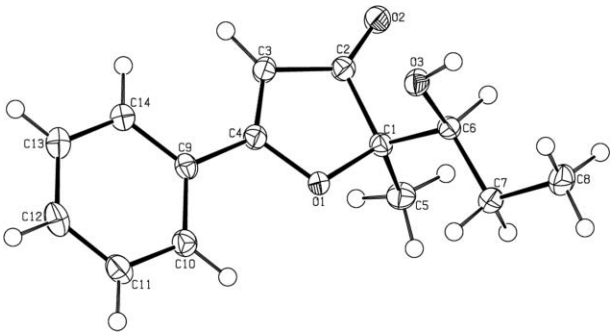
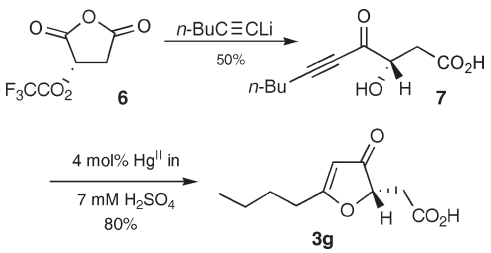


Fig. 1 A representation showing the relative configuration of **3c**.



Scheme 3 Synthesis of 3(2*H*)-furanone **3g**, an inhibitor of germination.

prepare the natural product **3g**, isolated from the flowers of *Erigeron annuus* and shown in a seed assay to be twice as potent at inhibiting germination as 4-hydroxybenzoic acid.[16] The sequence also enables the previously unknown absolute configuration of the 3(2*H*)-furanone natural product to be assigned as **3g** ($[\alpha]_D$ = +25 (*c* 0.094 in MeOH); lit.[16] $[\alpha]_D$ = +29 (*c* 0.07 in MeOH)).

In conclusion, the first examples of a new protocol for the catalytic asymmetric synthesis of 3(2*H*)-furanones (in either enantiomeric form) are described. To our knowledge, the protocol is also the first route to 3(2*H*)-furanones that is both catalytic and asymmetric. The dihydroxylation–cyclisation sequence does not require hydroxy group protection, and can be used to generate quaternary centres (without recourse to chiral auxiliaries). In a variant of that two-fold catalytic protocol, a convergent assembly involving addition of an alkynyllithium to a protected dihydroxylated Weinreb amide would permit those fragments to contain absolute configurations in any of the substituents (R^1–R^3 in Scheme 1) and for their stereochemistry to be imported into the cyclised product and hence into subsequent intermediates. The resulting compounds containing 3(2*H*)-furanone rings are versatile and functionalised intermediates that should have potential in the total synthesis of *O*-heterocyclic natural products.

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Notes and references

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