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A double oxidation procedure for the preparation of halogen-substituted *para*-benzoquinone monoketals: asymmetric synthesis of (−)-harveynone

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ABSTRACT

The double oxidation of halophenols with hypervalent iodine reagents in methanol provides a simple procedure to prepare halo-1,4-benzoquinone monoketals. Seven examples of this procedure are reported as is the conversion of 3-iodo-4,4-dimethoxycyclohexa-2,5-dienone into the natural product, (−)-harveynone.

Halogen-substituted 1,4-benzoquinone monoketals are extremely valuable building blocks in natural product synthesis.[1–9] For example, we have utilised 3-iodo-4,4-dimethoxycyclohexa-2,5-dienone (**1a**) and 3-bromo-4,4-dimethoxycyclohexa-2,5-dienone (**1b**) as the cornerstones of racemic routes to bromoxone (**2**),[1] harveynone (**3**)[2] and tricholomenyn A (**4**) (Fig. 1).[3] Other groups have also used such compounds to prepare related and more complex natural products such as (−)-asperpentyn,[4] (+)-calafianin,[5] (+)-hexacyclinol,[6] (+)-ottelione[7] and (+)-panepophenanthrin.[8,9]

One of the most common ways of preparing halogen-substituted 1,4-benzoquinone monoketals is by electrochemical oxidation of 1,4-dimethoxybenzene derivatives **6a** and subsequent regioselective ketal hydrolysis (Scheme 1).[10] Alternatively, the corresponding phenol **6b** can be oxidised directly using thallium trinitrate or hypervalent iodine reagents.[11] In both cases, standard, but laborious procedures are often required to obtain the aromatic starting materials **6** (and thallium trinitrate is toxic and potentially explosive in methanol). We required large quantities of halogen substituted 1,4-benzoquinone monoketals for a complex natural product project and decided to investigate a more direct approach involving the double oxidation of substituted phenols **7** in methanol as solvent. Whilst this type of transformation has been reported using a number of substituted phenols,[12] it has been little explored using phenols with halide substituents, and not at all on simple halogenated phenols.[13] Given our experience in using hypervalent iodine reagents for the oxidation of alkyl substituted phenols,[14,15] we decided to further explore the scope of these reagents, initially using 3-iodophenol (**7a**) as substrate (Table 1).[16]

The first approach (entry i) utilised phenyliodo dichloride and gave none of the expected product **1a**, and the use of Koser's reagent was equally unsuccessful (entry ii). Success was achieved with phenyliodoso bis(trifluoroacetate) (PIFA, entry iii) and with phenyliodoso diacetate (PIDA, entry iv) giving iodo-dienone **1a** in 52–56% yield (unidentified minor by-products accounted for the material balance). Attempts to optimise the PIDA and PIFA processes were unsuccessful, despite changing the reaction

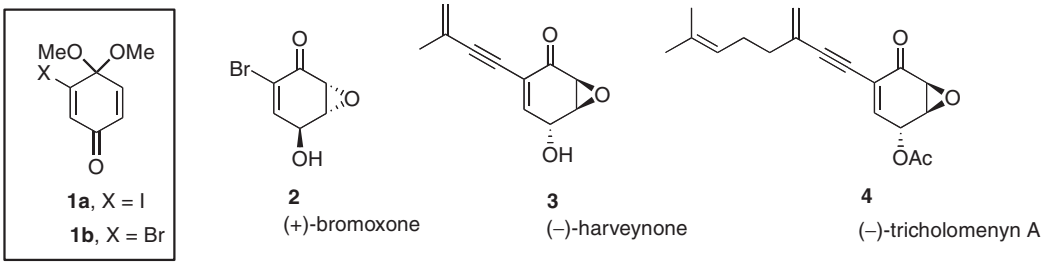

Figure 1.

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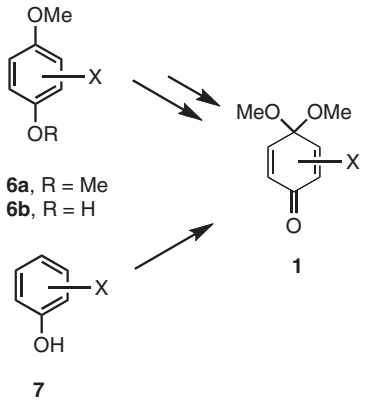
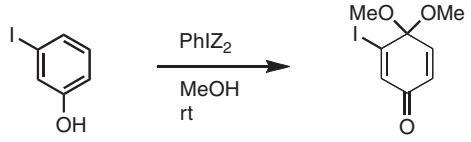


Scheme 1.

Table 1
Double oxidation of 3-iodophenol (**7a**)[a]



i.	$PhICl_2$	0%
ii.	PhI(OH)OTs	0%
iii.	$PhI(OCOCF_3)_2$	52%
iv.	$PhI(OAc)_2$	56%[b,c]

[a] Reaction carried out on a 1.0 mmol scale using redistilled MeOH, unless stated otherwise.
[b] 54% at −20 °C.
[c] 34% using reagent grade MeOH.

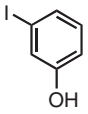
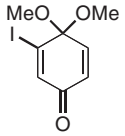
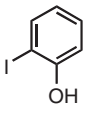
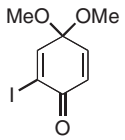
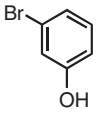
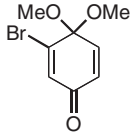
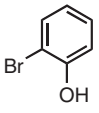
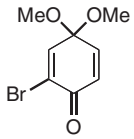
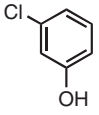
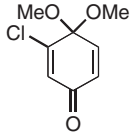
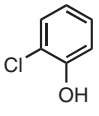
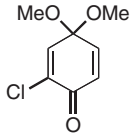
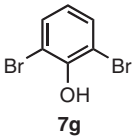
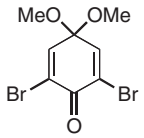
temperature, the concentration and the use of mixed solvents and basic additives. However, we were delighted to have developed such a straightforward route to 3-iodo-4,4-dimethoxycyclohexa-2,5-dienone (**1a**) and briefly explored the utility of the PIDA process with other commercially available halogenated phenols (Table 2).

As can be seen, a range of mono-iodo (entries i and ii), mono-bromo- (entries iii and iv) and mono-chloro- (entries v and vi) dienones were prepared, as was 2,6-dibromo-4,4-dimethoxycyclohexa-2,5-dienone (**1g**). In all cases the standard procedure developed for the iodo example **1a** was employed—it is likely that better yields could be obtained after further optimisation.

As a simple demonstration of the synthetic utility of these halogen-substituted 1,4-benzoquinone monoketal building blocks, we revisited the synthesis of harveynone. (−)-Harveynone (**3**) was isolated from *Curvularia harveyi* and shown to possess anti-cancer properties by inhibiting microspindle formation.[21] In addition, (+)-harveynone has been isolated as a phytopathogenic metabolite of grey tea blight, *Pestalotiopsis theae*.[22] In 1996, our group reported the first total synthesis of harveynone, in racemic form,[2] and subsequently the groups of Johnson (1997),[9c] Ogasawara (1998),[23] Negishi (2000),[24] Maycock (2000),[4] Lee (2009),[25a] Banwell (2009)[9b] and Ryu (2010)[25b] reported other approaches. Using 3-iodo-4,4-dimethoxycyclohexa-2,5-dienone (**1a**) as starting material, we have now completed a short and efficient synthesis of (−)-harveynone (**3**) as shown in Scheme 2.

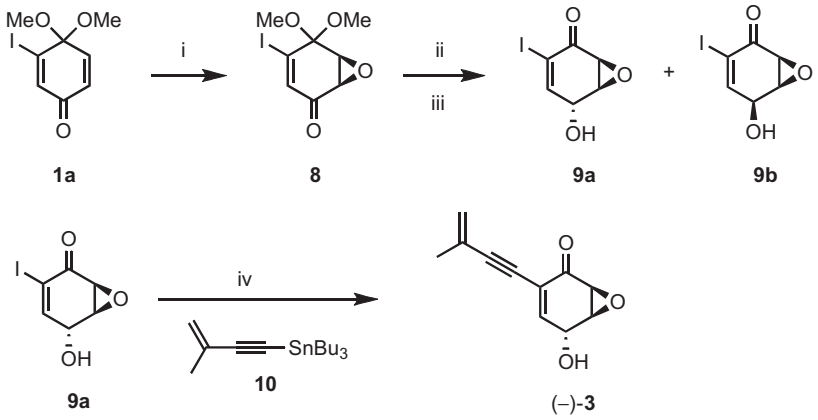
Thus, employing the L-diisopropyl tartrate (DIPT) epoxidation procedure developed by Porco and co-workers,[26] we were able to obtain the crucial epoxide **8** in 84% yield and 93:7 er {chiral HPLC

Table 2
Products obtained from the double oxidation using PIDA[a]

Entry	Phenol **7**	Quinone **1**	Yield (%)
i	 **7a**	 **1a**[2,17]	56
ii	 **7b**	 **1b**[7]	63
iii	 **7c**	 **1c**[1b,8]	24
iv	 **7d**	 **1d**[18]	52
v	 **7e**	 **1e**[19]	38
vi	 **7f**	 **1f**[11a]	64
vii	 **7g**	 **1g**[20]	41

[a] Using substrate **7** (0.8–1.6 mmol), redistilled MeOH (0.25 mmol/mL), rt, 30 min.

using a Chiralpak® AS™ chiral column, 2.1 mm ID × 150 mm; 2% IPA in hexane, flow rate 0.3 mL/min; $[\alpha]_D$ 156 (*c* 2.06, $CHCl_3$)}. It is noteworthy that the reaction was too slow at −78 °C (>500 h), and when carried out at temperatures above −65 °C the er began to deteriorate (−55 °C, er = 90:10). Following the racemic route,[2] stereoselective reduction was achieved using DIBAL-H (*anti*:*syn* = 85:15) and deprotection was effected with Montmorillonite K10.[27] These two steps could be telescoped and the required *anti*-product, 'iodoxone' **9a** isolated by column chromatography. As before,[2] we were able to carry out a Stille coupling between iodoxone **9a** and alkynylstannane **10**, although by using $Pd(PhCN)_2Cl_2/AsPh_3$[4] we were able to improve on our earlier yield (83% vs 74% using $PdCl_2(PPh_3/CuI$[2]). This sequence delivered (−)-harveynone (**3**) {$[\alpha]_D$ −164; lit.[23] $[\alpha]_D$ −200, consistent with the 93:7 er obtained during the epoxidation step}.[28] We believe that



Scheme 2. Reagents and conditions: (i) TrOOH, NaHMDS, L-DIPT, PhMe, −65 °C, 84%, 93:7 er; (ii) DIBAL-H, THF, −78 °C then; (iii) Montmorillonite K10, CH_2Cl_2, rt, 93% (over two steps), **9a**/**9b** = 85:15; (iv) 5 mol % $Pd(PhCN)_2Cl_2$, 10 mol % $AsPh_3$, THF, rt, 83%.

this is the shortest and the most efficient route to (−)-harveynone (**3**) (five steps, 32% overall yield) proceeding without the need for protection of the secondary alcohol group.

In summary, we have shown that a range of halogen-substituted quinone monoketals **1a–g** can be readily accessed, albeit in modest yields, via hypervalent iodine oxidation using PIDA in methanol. Furthermore, we have demonstrated the synthetic utility of this class of compound by carrying out a short synthesis of (−)-harveynone (**3**) starting from 3-iodo-4,4-dimethoxycyclohexa-2,5-dienone (**1a**). We are currently utilising halogen-substituted quinone monoketals **1a–g** to prepare more complex epoxyquinol natural products.

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16. All compounds were fully characterised spectroscopically and by HRMS.
17. 3-Iodo-4,4-dimethoxycyclohexa-2,5-dienone (**1a**): To a solution of phenol **7a** (0.20 g, 0.91 mmol, 1.0 equiv) in freshly distilled MeOH (3.6 mL) was added phenyliodoso diacetate (0.62 g, 1.91 mmol) and the mixture was stirred until TLC analysis indicated the reaction was complete (20 min). The reaction was quenched with satd aq $NaHCO_3$ (50 mL) and then extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and the solvent removed in vacuo to give the crude product which was purified by flash column chromatography (SiO_2, 7:3 petroleum ether–Et_2O) to produce **1a** (140 mg, 56%) as a yellow solid, mp 39–41 °C (hexane); R_f 0.49 (1:1 petroleum ether–Et_2O); IR (thin film) ν_{max}/cm^{-1} 1670 (C=O), 1630 (C=C); δ_H (400 MHz, $CDCl_3$); 7.23 (1H, d, *J* 2.0, H-2), 6.97 (1H, d, *J* 10.0, H-5), 6.53 (1H, dd, *J* 10.0, 2.0, H-6), 3.26 (6H, s, H-7); δ_C (100 MHz, $CDCl_3$); 181.6 (C-1), 143.5 (C-2), 143.0 (C-6), 132.1 (C-5), 129.4 (C-3), 94.6 (C-4), 51.3 (C-7); *m*/*z* (ESI) found MH^+ 281, MNa^+ 303, $[MH-I]^+$ 154; HRMS (ESI) found MNa^+, 302.9485. 1.3 ppm error $C_8H_9INaO_3$ requires *MNa*$^+$, 302.9489 (found: C, 34.34; H, 3.17; $C_8H_9IO_3$ requires C, 34.31; H, 3.24).
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28. (−)-Harveynone (**3**): A solution of bis(benzonitrile)palladium(II) chloride (0.006 g, 0.016 mmol) and triphenylarsine (0.010 g, 0.032 mmol) in freshly degassed THF (8 mL) was added to a flask containing iodide **9a** (0.080 g, 0.32 mmol) and stannane **10** (0.223, 0.63 mmol) that had been subjected to 10 × vacuum–argon cycles. The mixture was then subjected to further 10 × vacuum–argon cycles and stirred at rt for 18 h at which point the reaction was considered complete by ^1H NMR analysis. The solvent was removed in vacuo and the residue was loaded onto a short plug of SiO_2 which was washed with hexane (50 mL) followed by EtOAc (100 mL). The EtOAc fraction was concentrated in vacuo and the residue was loaded onto a short plug of SiO_2 which was again washed with hexane followed by EtOAc. Again, the EtOAc fraction was concentrated in vacuo to give the crude product which was purified by flash column chromatography (SiO_2, 1:1 hexane–EtOAc) to give the title compound (−)-**3** (0.051 g, 83%) as an off-white solid, mp 69–71 °C (from hexanes; lit.[23] 78-79 °C); R_f 0.49 (1:1 petroleum ether–Et_2O); IR (thin film) ν_{max}/cm^{-1} 3450 (OH), 2207 (C≡C), 1691 (C=O), 1616 (C=C) cm^{-1}; $[\alpha]_D$ −164 (*c* 0.57, $CHCl_3$) {lit.[23] $[\alpha]_D$ −200.3, (*c* 0.40, $CHCl_3$)}; HRMS (*ESI*) found MNa^+, 213.0521. $C_{11}H_{10}NaO_3$ requires *MNa* 213.0522 (0.6 ppm error). High field NMR data were in accord with those published.[23]