Novel Oxidative Conversion of β,γ-Unsaturated Acids into Butenolides: Synthesis of Heritonin and Heritol†

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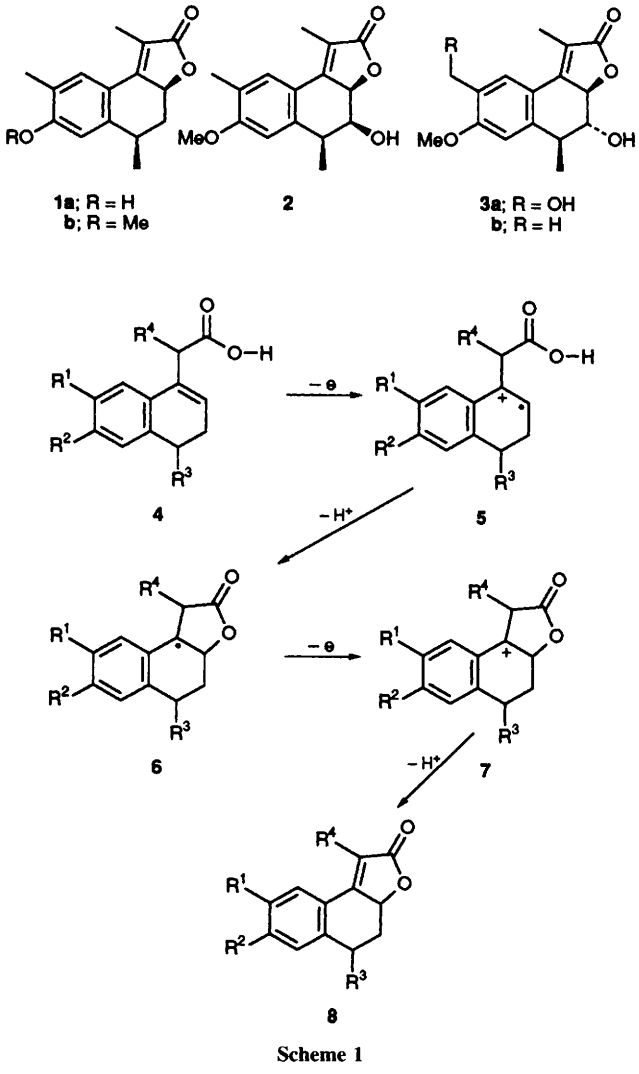
A novel strategy of converting β,γ-unsaturated esters to butenolides involving oxidative cyclisation with ceric ammonium nitrate at room temperature is described.

Interest in the synthesis of butenolides, as a consequence of their natural abundance in a variety of natural products including biologically active molecules, has been the focus of current interest and continues to stimulate development of new strategies.[1,2]

In continuation of our work in the synthesis of biologically active molecules *viz*. heritol **1a**,[3,4a] heritonin **1b**,[3,4b] heritianin **3b**, vallipin **2**,[4b] vallapianin **3a**[4b] and related compounds isolated recently from the mangrove plant *Heritiera littoralis* by Miles and coworkers, we became interested in the development of methodologies to generate these unusual skeletons. We have recently reported[2] an efficient entry into butenolides from β,γ-unsaturated esters *via* diols involving transesterification with concomitant dehydration. Although palladium mediated direct conversion of β,γ-unsaturated acids to butenolides has been reported to proceed in poor to moderate yields,[5] a recent publication reports that these results could not be duplicated.[6]

We reasoned that it should be possible to directly convert β,γ-unsaturated acid **4** to butenolide **8** if one can selectively and effectively generate the cation radical **5**. Intramolecular trapping of the cation radical would generate the butyrolactone **6** which on further oxidation and loss of proton would generate butenolide **8**.



Scheme 1

The concept of atom economy as a strategy for synthetic efficiency has been of recent interest and is practised and described by Trost.[7] This paper describes our contribution of atom economy as a strategy to construct butenolides efficiently.

We describe a novel, mild and efficient methodology based on the above mentioned strategy to convert β,γ-unsaturated acids to butenolides. The propensity of ceric ammonium nitrate (CAN) to act as a single electron oxidant is well documented in literature.[8] Thus, when acid of general formula **4** was subjected to treatment with CAN, butenolides **8** were obtained in good to excellent yields (Table 1).‡

The β,γ-unsaturated acids **4** were prepared easily by the saponification of the corresponding esters **10** which in turn were prepared from corresponding ketones in high yields. Typical procedure is as follows: To a mixture of CAN (0.2 mmol) and $NaHCO_3$ (0.2 mmol) in 20 ml of dry acetonitrile was added the acid **4** (0.1 mmol) during a period of 5 min. After completion of the reaction, monitored by TLC, the reaction mixture was filtered through celite and concentrated to a residue which was chromatographed on silica gel with (9 : 1) petroleum : ethyl acetate as eluent.

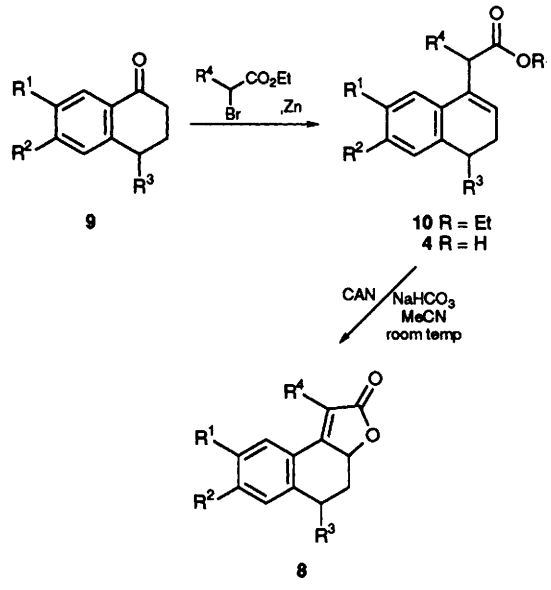


Table 1

Entry	R^1	R^2	R^3	R^4	**10** yield (%)	**4** yield (%)	**8** yield (%)
1	H	H	H	H	87	82	67
2	H	H	H	Me	90	86	72
3	H	H	H	Et	92	84	87
4	H	H	H	Pr^i	89	89	92
5	Me	H	Me	Me	80	78	74
6	OMe	Me	H	Me	90	81	70
7	Me	OMe	Me	Me	85	89	36

To delineate the generality and efficacy of our methodology, we chose to incorporate bulky groups on the butenolide moiety. A notworthy feature of this transformation is obvious from Table 1 in that on progressing from R = H to Pr^{i} (entries 1–4), there is a steady increase in the bulk of R and there is a corresponding steady increase in the yield of formation of butenolides.

This trend although surprising from the point of view of *peri* interactions may help the approach of the carboxylic acid to the double bond. This effect also may be attributed to the 'Thorpe–Ingold' effect which helps the cyclisation to proceed in high efficiency. This observation is in stark contrast to the poor yields obtained in intramolecular Wittig–Horner-reactions ascribed to *peri* interactions.[9]

To extend the scope of the methodology we have synthesized a variety of butenolides using the above protocol (see Table 1). We have successfully employed the above concept towards the synthesis of natural products heritonin **1a** (entry 7). Since the conversion of heritonin to heritol has been already reported by us earlier,[3] this constitutes a total formal synthesis of heritol.

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Footnotes

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‡ The spectral (IR, NMR ^{13}C, mass) properties of the compounds were consistent with the assigned structures. All new compounds were characterised by elemental analyses as well.

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