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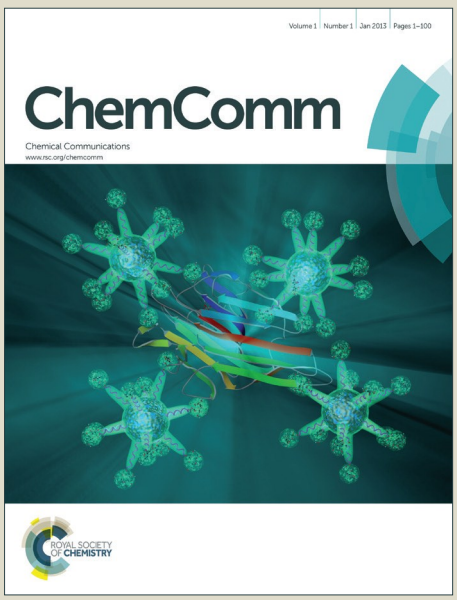

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Isotetronic Acids from an Oxidative Cyclization

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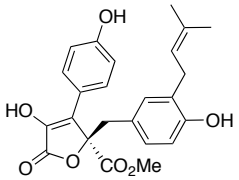
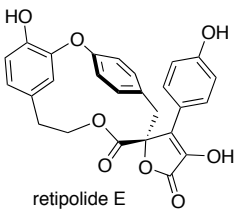
Abstract. Oxidation of α,β-unsaturated methyl ketones with selenium dioxide leads to a cascade of reactions culminating in the formation of isotetronic acids.

Isotetronic acids (2-hydroxybutenolides) are a common structural motif in natural products derived from marine and terrestrial fungi, bacteria, marine algae and plants. For example, butyrolactone I was isolated in 1977 from cultures of *Aspergillus terreus* var. *africans*[1] whereas retipolide E is the putative biosynthetic precursor[2,3] of a number of structurally related isotetronic acids isolated from the fruiting bodies of North American *Retiboletus sp.* fungi.



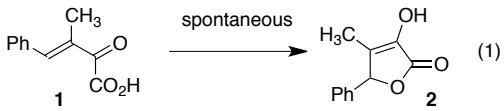
butyrolactone I



retipolide E

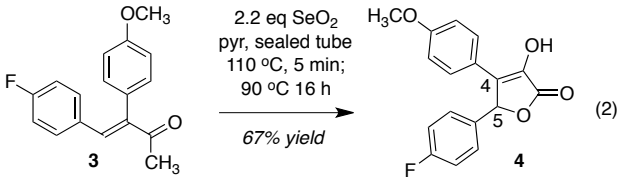
Useful pharmacological activities are sometimes associated with this substructure, for example butyrolactone I is a potent inhibitor of CDK1 and CDK2, both of which play a key role in mammalian cell cycle progression, and it has consequently been of interest as a lead for cancer chemotherapeutic drug development.[4,5] This has generated considerable interest in the synthesis of this type of structure that has most often been prepared through aldol addition of a α-ketoester to an aldehyde followed by spontaneous lactonization.[6] The α-ketoesters are typically not commercially available. Langer and coworkers developed a distinct approach to 4-alkoxycarbonyl isotetronates whereby oxalyl chloride was condensed with 1,3-bis(trimethylsilyloxy)alk-1-enes.[7] In both approaches the isotetronic acid was disconnected into fragments of the appropriate oxidation state.

Herein we report a synthesis of this chemotype that makes use of a different strategy. We had observed that α-ketoacid **1** was stable in



1 **2** (1)

solution over several days at room temperature, but underwent spontaneous cyclization to isotetronic acid **2** upon removal of the solvent (Eq 1). We postulated that under the appropriate conditions methyl enones that are very simple to prepare would undergo oxidative cyclization to isotetronic acids. After screening conditions, we determined that exposure of enones to a modest excess of selenium dioxide in pyridine resulted in a reaction cascade culminating in the formation of the isotetronates in moderate to good yield as illustrated in Eq 2.[8] Methyl enone **3** that was prepared in 63% yield by means of piperidine catalyzed aldol condensation was heated in pyridine solution with selenium dioxide in a re-sealable sealed tube. Workup led to isotetronic acid **4** in 67% yield following chromatographic purification. The reaction presumably takes place through the initial oxidation of the methyl group in **3** to the carboxylate that undergoes cyclization spontaneously under the reaction conditions.



3 **4** (2)

The scope of the reaction is illustrated in Table 1. The reaction succeeds in the case of electron-rich or electron-poor aryl groups at C4 or C5 (**4** – **9**). An ester group at C4 is well tolerated (**10** – **13**). Note that allylic oxidation of the ester group apparently does not represent an appreciable side reaction (**13**). C4 benzoyl isotetronates **14** and **15** both formed in good yield. Compounds **5** and **6** have been mentioned in the literature,[10] as have **10**, **11**,[7] **14** and **15**.[12]

We were curious to learn what would be the reaction outcome for substrates that offered a second site at which oxidation could take place, so the two tetrasubstituted alkenes **16a** and **16b** w

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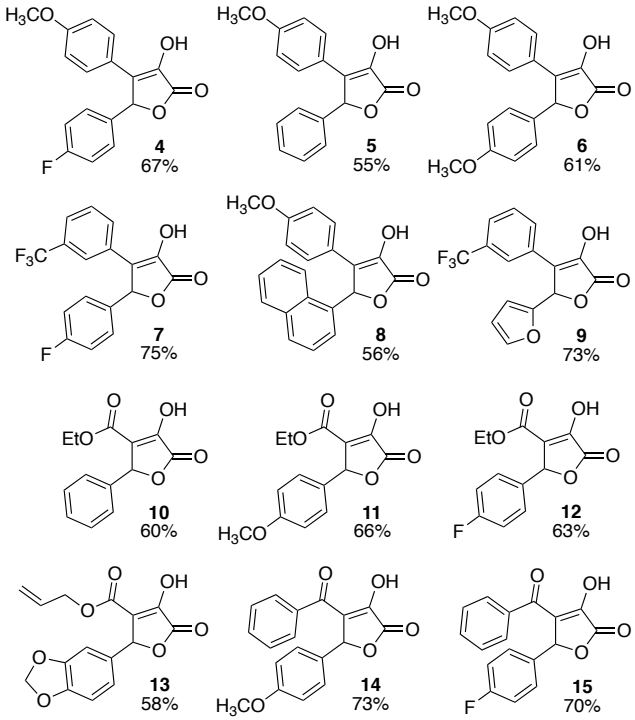
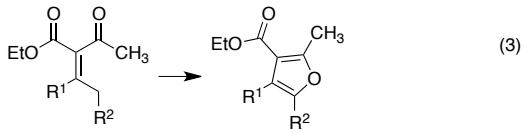
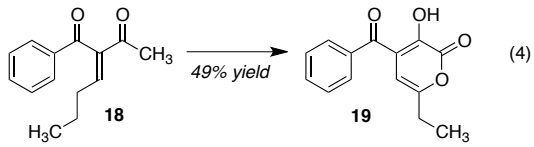
subjected to the reaction conditions using 2.2 equiv of selenium dioxide (Eq 3). 3-Carboethoxyfurans **17a**[13] and **17b**[14] were formed as the major products in modest yield, indicating that oxidation of the allylic methylene group to the alcohol in each case took place faster than oxidation of the acetyl methyl group.

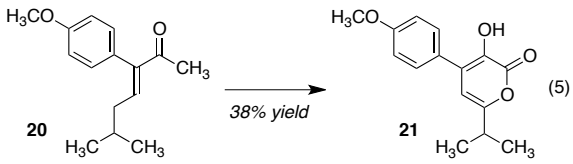
Table 1. Examples of the oxidative cyclization



Plausible mechanisms of the oxidative cyclization leading to the isotetronic acids are either an intramolecular oxa-Michael addition of the carboxylate carbonyl oxygen atom of the transiently formed α-ketoacid with simultaneous proton transfer from the carboxylate to the enol, or perhaps an oxa-Nazarov 4 π conrotation of the same α-ketoacid.[15]

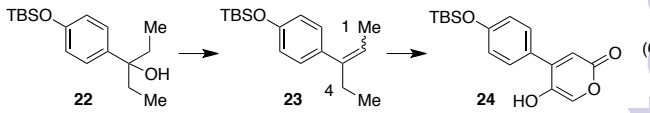






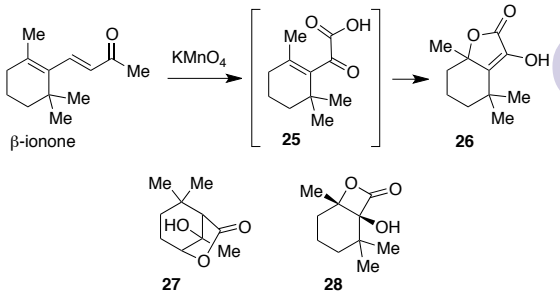
The oxidative cyclization of trisubstituted alkenes **18** and **20** took a different course and led to 3-hydroxypyrones **19** and **21**, respectively, as the major reaction products in modest yield (Eqs 4, 5). These products may have been formed from oxidation of the allylic methylene group to the alcohol, followed by oxidation of the methyl group to the acid, double bond isomerization and cyclization. The modest yields of the pyrones should be weighed against the ease of their synthesis and the speed with which these complex structures can be prepared from very simple starting materials.

Tertiary benzylic alcohol **22** was converted in 13% yield to 3-hydroxypyrone **24** as the major product (Eq 6). The difference in the outcome of this reaction and the reactions of Eqs 4 and 5 can be understood by considering that elimination of the alcohol under the reaction conditions presumably led to styrene **23** as the initial product. The C1 methyl group that is activated subsequently underwent oxidation to the carboxylate. Oxidation of the C4 methylene group to the ketone, followed by partial oxidation of the C5 methyl group and cyclization leads to the observed product. In a separate experiment, **22** was converted to **23** by exposure to methanesulfonyl chloride and Hünig's base in 64% yield. Exposure of **23** to selenium dioxide in pyridine in a second step led to **24** in 30% yield, or in 19% overall yield from **22**.



In summary, a convenient oxidative cyclization of methyl enones leads to isotetronic acids (Eq 2). Substrates with oxidizable allylic methylene or methyl groups lead either to furans (Eq 3), or to pyrones (Eqs 4-6). These results demonstrate a means through which simple molecules undergo a rapid increase in molecular complexity and suggest many opportunities for discovery.

As a historical footnote, during the execution of this work we became aware of only one oxidative cyclization related to ours. In 1898 during the course of his structural elucidation of the ionones, Tiemann reported that oxidation of ionone with potassium permanganate led to a compound melting at 130 °C that he named "oxyjonolacton" and to which he assigned structure **27**.[16] In subsequent years β-lactone **28** was described as Tiemann's "hydroxyionolactone".[17,18] In 1961 Brooks and coworkers, prompted by the implausibility of the structure **28**, repeated Tiemann's work and suggested that α-ketoacid **25** was one of the oxidation products formed from permanganate oxidation of β-ionone and that **26** (and not **28**) was the correct structure of "oxyjonolacton".[19] Brooks and coworkers made their structural assignment on the basis of infrared and ultraviolet spectroscopy



Scheme 1. Tiemann's reaction

and also the elemental analysis that suggested the correct molecular formula for **26**.[20] Moreover, the melting point of Brooks' **26** (129 – 131 °C) closely matched the one recorded by Tiemann for "oxyjonolacton". In 2007 Kamat and coworkers revisited Tiemann's and Brooks' work and with the benefit of X-ray crystallography, NMR and mass spectrometry were able to unambiguously show that **26** is indeed the correct structure of hydroxyionolactone.[21] This all leaves little doubt that Tiemann's reaction and ours are the same and allows us to trace the origins of our work to the late 19th century.

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18 To the best of our knowledge, Tiemann never showed a β-lactone structure for his "oxyjonolacton", so the origin of [illegible] remains unclear. Note also that **27** might have been an expected product of permanganate oxidation of α-ionone, whereas it is an unlikely oxidation product of β-ionone. Tiemann may have contributed to some of the confusion in *Chem. Ber.* 1898, **31**, 867–881 by showing the correct structure of α-ionone, but labelling it as β-ionone on p. 870, then showing the same structure on p. 874 labelled as α-ionone. On p. 881 he showed the correct structure for β-ionone but labelled it as α-ionone. On pp. 872–873 the oxidation of β-ionone to "oxyjonolacton" with permanganate is mentioned and structure **27** shown, referring to his preceding paper for the procedure. In a paper published posthumously, Tiemann correctly assigned structures to α- and β-ionone: F. Tiemann, *Chem. Ber.*, 1900, **33**, 3703–3710.; see pp. 3709–3710.

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20 It is interesting to note that Tiemann's elemental analytical data more closely matched the correct C/H ratio for **26** than for **27**, the structure he assigned.

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