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Efficient Entry into Medium-Ring Keto-Lactones. The Ruthenium Tetraoxide-Promoted Oxidative Cleavage of β-Hydroxyethers

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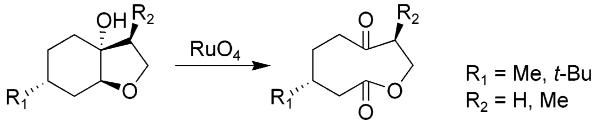
ABSTRACT



A new use of ruthenium tetraoxide is reported. The catalytic oxidative cleavage of hexahydro-benzofuran-3a-ols led to nine-membered ring keto-lactones in moderate to good yields and high purity. The reaction is clean and easily performed using catalytic amounts of ruthenium trichloride and an excess of sodium periodate as a cooxidant.

The synthesis of medium-ring compounds (those containing from 8 to 11 atoms) remains a challenge for organic chemists. Several efforts have been made toward the development of efficient methods for the preparation of these systems,[1] since they are encountered in many biologically important natural products such as the medium-ring ethers (+)-obtusenyne,[2] (+)-laurallene,[3] and (−)-isolaurallene,[4] besides the well-known brevetoxins[5] and taxol.[6] Medium-ring lactones are also found in nature. Examples are the octalactins A and B,[7] the nine-membered ring halicholactone and neohalicholactone,[8] and the cephalosporolides B and C.[9] Some of them are outlined in Figure 1.

Cyclization strategies toward medium-ring lactones are often inhibited due to entropic factors and transannular interactions. For instance, the rate of lactonization of ω-bromo alkanoic acid to the corresponding nine-membered ring lactone is almost zero.[10]

Many other methodologies for preparing medium-ring lactones have been reported[11] such as the ionic[12] and radical[13] cleavage of saturated bicyclic hemiketals, the oxidative

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(2) (a) Fujiwara, K.; Awakura, D.; Tsunashima, M.; Nakamura, A.; Honma, T.; Murai, A. *J. Org. Chem.* **1999**, *64*, 2616. (b) Howard, B. M.; Schulte, G. R.; Fenical, W.; Solheim, B.; Clardy, J. *Tetrahedron* **1980**, *36*, 1747. (c) King, T. J.; Imre, S.; Öztuna, A.; Thomson, R. H. *Tetrahedron Lett.* **1979**, 1453.

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(11) For a review concerning medium-ring lactones, see: Rousseau, G. *Tetrahedron* **1995**, *51*, 2777.

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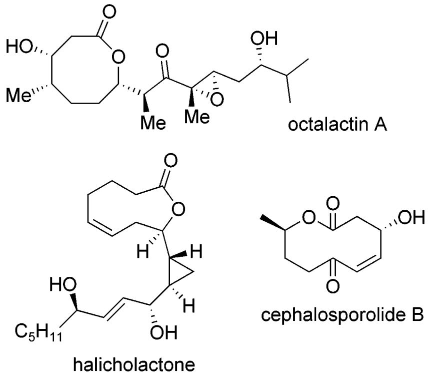
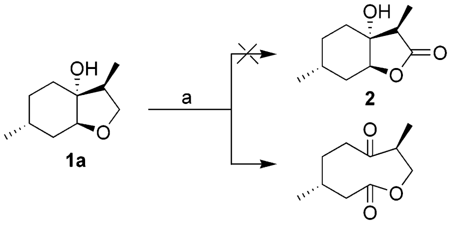


Figure 1. Natural medium-ring lactones.

cleavage of unsaturated bicyclic compounds promoted by ozone, PCC, or *m*CPBA,[14] and the cleavage of bicyclic 1,2-diols.[15] In 1985, Torii and co-workers reported a single example of the oxidative cleavage of an enol ether by ruthenium tetraoxide, which led to a ten-membered ring keto-lactone.[16]

Recently, we reported the preparation of a series of hexahydro-benzofuran-3a-ols (**1a**−**d**) by thallium trinitrate-promoted cyclization of homoallylic alcohols.[17] One of the possible synthetic applications of these ethers could be the construction of α,*β*-unsaturated lactones, an important class of natural products. For example, the cyclic ether **1a** could be transformed into isomintlactone,[18] through dehydration followed by allylic oxidation.[19] Nevertheless, the hydroxyl group of **1a** proved to be very resistant to several dehydration conditions. We decided then to run a prior oxidation of **1a** to the corresponding lactone **2**, which would easily undergo the desired dehydration. Thus, the cyclic ether **1a** was submitted to treatment with RuO_4 generated in situ from catalytic amounts of ruthenium trichloride ($RuCl_3 \cdot nH_2O$) and an excess of sodium periodate in a biphasic solvent system ($H_2O/CCl_4/CH_3CN$ = 3:2:2).[20] Somewhat surprisingly,[21] the isolated product was the nine-membered ring keto-lactone **3a**, obtained in very good yield (Scheme 1).

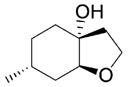
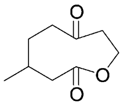
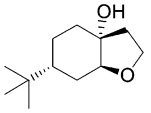
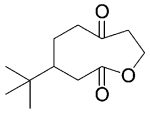
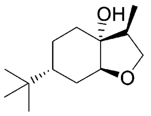
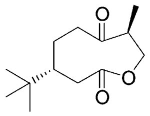
Scheme 1[a]



[a] Reagents and conditions: 2.4 mol % $RuCl_3 \cdot nH_2O$, 4.1 equiv of $NaIO_4$, $H_2O/CCl_4/CH_3CN$ (3:2:2), rt, 75 min (81%).

This result prompted us to submit the cyclic ethers **1b**−**d** to the same treatment. Thus, the keto-lactones **3b**−**d** were obtained in moderate to good yields, as shown in Table 1.

Table 1. RuO_4-Promoted Oxidative Cleavage of **1b**−**d**[a]

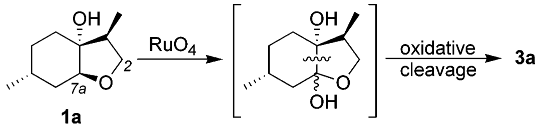
substrate	product	yield (%)
 **1b**	 **3b**	55
 **1c**	 **3c**	69
 **1d**	 **3d**	82

[a] Reagents and conditions: 2.4 mol % $RuCl_3.nH_2O$, 4.1 equiv of $NaIO_4$, $H_2O/CCl_4/CH_3CN$ (3:2:2), rt, 75 min.

It is noteworthy that the keto-lactones **3a**−**d** were obtained with a high degree of purity. No further purification was necessary, since neither significant impurities nor byproducts were detected in the ^1H and ^{13}C NMR spectra of the crude products.[22] Moreover, the simple filtration of the concentrated organic extracts on a small silica gel pad was sufficiently efficient to hold the ruthenium dioxide formed during the course of the reactions.

It has been postulated that the order of reactivity of C−H bonds toward the RuO_4-promoted oxidation of ethers is $CH_2 > CH$.[23] However, we observed an inversion of regiochemistry in the reaction of the cyclic ethers **1a**−**d** with RuO_4, since carbon 7a (CH) was oxidized in preference to carbon 2 (CH_2), as exemplified for **1a** in Scheme 2.

Scheme 2



Additional evidence of this inversion of regiochemistry was observed in the RuO_4-promoted oxidation of the

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[14] (a) Mahajan, J. R.; Araújo, H. C. *Synthesis* **1975**, 54. (b) Mahajan, J. R.; Araújo, H. C. *Synthesis* **1976**, 111.

[15] Bond, S.; Perlmutter, P. *Tetrahedron* **2002**, *58*, 1779.

[16] Torii, S.; Inokuchi, T.; Kondo, K. *J. Org. Chem.* **1985**, *50*, 4980.

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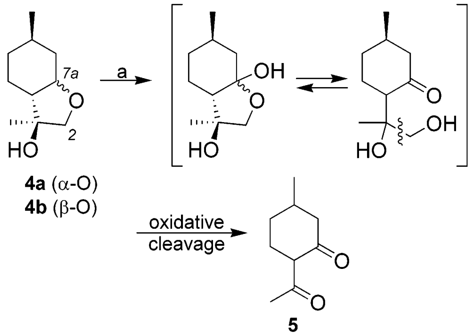
hexahydro-benzofuran-3-ols **4a** and **4b**,[24] which bear the hydroxyl group in another position. These ethers afforded, as the major product, the 2-acetyl-5-methyl-cyclohexanone (**5**), which is probably formed by the oxidation of the tertiary carbon 7a (Scheme 3).

Scheme 3 [a]

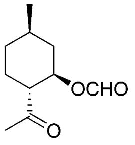


4a (α-O)
4b (β-O)

5

[a] Reagents and conditions: 5.0 mol % $RuCl_3 \cdot nH_2O$, 4.1 equiv of $NaIO_4$, $H_2O/CCl_4/CH_3CN$ (3:2:2), rt, 30 min for **4a** and 4 h for **4b** (48% for **4a** and 40% for **4b**).

The fact that the equatorial tertiary C−H bonds of **1a**−**d** and **4a** were oxidized faster than the axial tertiary C−H bond of **4b** agrees with the literature information about steric requirements for the oxidation reaction.[25] Moreover, the less reactive cyclic ether **4b** afforded minor amounts of the oxidation products of secondary carbon 2. The products **6** and **7** were obtained in 12 and 15% yields, respectively.



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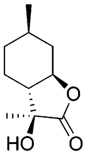

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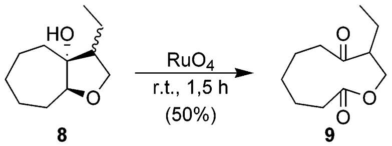
In a preliminary experiment, the oxidative cleavage of the β-hydroxyether **8** led to the ten-membered ring keto-lactone **9**, in a nonoptimized yield of 50% (Scheme 4).

Scheme 4



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Although the reaction mechanism remains unclear, the presence of the hydroxyl group in the cyclic ethers seems to play an important role in the chemoselectivity displayed by RuO_4.[26] It is of note that similar bicyclic ethers, without the hydroxyl group, afforded exclusively the corresponding products of oxidation of the secondary carbon.[27]

The results described herein represent a novel and efficient procedure for the synthesis of medium-sized lactones. At the moment, the application of this methodology to the synthesis of lactones of different sizes is in progress in our laboratory.

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Supporting Information Available: Experimental procedures for the RuO_4-promoted oxidative cleavage of β-hydroxyethers **1a**−**d** and **4a**−**b** and structural data and NMR spectra of keto-lactones **3a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[21] For examples of the chemoselectivity displayed by RuO_4 in the oxidation of tetrahydrofuran and tetrahydropyran derivatives, see: Smith, A. B., III; Scarborough, R. M., Jr. *Synth. Commun.* **1980**, *10*, 205.

[22] For ^1H and ^{13}C NMR spectra of keto-lactones **3a**−**d**, see Supporting Information.

[23] Bakke, J. M.; Frohaug, A. E. J. *Phys. Org. Chem.* **1996**, *9*, 310.

[24] Hexahydro-benzofuran-3-ols **4a** and **4b** were prepared by a previously reported procedure. Ferraz, H. M. C.; Ribeiro, C. M. R.; Grazini, M. V. A.; Brocksom, T. J.; Brocksom, U. *Tetrahedron Lett.* **1994**, *35*, 1497.

[25] Reactivity of C−H bonds in cyclohexane systems toward RuO4-promoted oxidations of hydrocarbons: axial secondary C−H, relative rate = 1; equatorial secondary C−H, relative rate = 9; axial tertiary C−H, relative rate = 47; and equatorial tertiary C−H, relative rate = 444. Bakke, J. M.; Bethell, D. *Acta Chem. Scand.* **1992**, *46*, 644.

[26]) Only substrate **4b** underwent oxidation of both tertiary and secondary C−H bonds.

[27]) Kitagawa, I.; Tsujii, S.; Nishikawa, F.; Shibuya, H. *Chem. Pharm. Bull.* **1983**, *31*, 2639.