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Bicyclic β-Hydroxytetrahydrofurans as Precursors of Medium Ring Keto-Lactones

Helena M. C. Ferraz* and Luiz S. Longo, Jr.†

Instituto de Química, Universidade de São Paulo, CP 26077, CEP 05513-970, São Paulo, SP, Brazil

hmferraz@iq.usp.br

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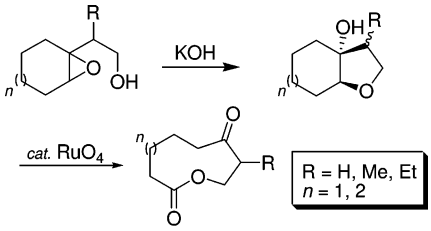

The reaction of a series of cis-fused bicyclic β-hydroxytetrahydrofurans with ruthenium tetraoxide, generated in situ from ruthenium trichloride and sodium periodate, afforded 9- and 10-membered keto-lactones in moderate to good yields, in a clean and straightforward fashion. The starting β-hydroxyethers were obtained from the corresponding 3-alkenols by two alternative procedures, depending on their pattern of substitution: (a) epoxidation by dimethyldioxirane, followed by base-catalyzed cyclization of the resulting epoxyalcohol, and (b) thallium trinitrate-mediated cyclization of the 3-alkenols, a method already described by our group.

Introduction

Medium ring compounds, those containing 8−11 atoms in the ring,[1] are the subject of continuous interest in organic synthesis, as they constitute the framework of many natural products. Thus, several efforts have been made toward the development of efficient strategies for the synthesis of these compounds, which can be carbocycles,[2,3] lactones,[4−6] cyclic ethers,[7] and nitrogen heterocycles,[8,9] among others.[10] More particularly, medium ring keto-lactones are found in some bioactive natural products, such as the polyketide metabolites diplodialides A and D,[11] cephalosporolides B and C,[12] and decarestrictines B, E, F, G, H, and J,[13] as well as the recently isolated[14] and synthesized[15] xestodecalactone A. Some representative examples are shown in Figure 1.

Cyclization reactions that lead to medium ring lactones are often inhibited by both entropic and enthalpic factors, as stated by Illuminati and Mandolini.[16] Therefore, several methods for circumventing this problem, as well as the competition between inter- and intramolecular reactions in the preparation of medium and macrolactones, have been developed.[17]

Ruthenium tetraoxide (RuO_4), first introduced in organic synthesis by Djerassi and Engle,[18] has a widespread application in organic transformations,[19] as attested by recent examples, such

† Present address: Universidade Federal de São Paulo/Campus Diadema, Rua Artur Riedel, 275, CEP 09972-270, Diadema, SP, Brazil.

(1) Roxburgh, C. J. *Tetrahedron* **1993**, *49*, 10749.
(2) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757.
(3) Minnaard, A. J.; Wijnberg, J. B. P. A.; de Groot, A. *Tetrahedron* **1999**, *55*, 2115.
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(9) Nubbemeyer, U. *Top. Curr. Chem*. **2001**, *216*, 125.
(10) Yet, L. *Chem. Rev.* **2000**, *100*, 2963.
(11) Wada, K.; Ishida, T. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1154.
(12) (a) Ackland, M. J.; Hanson, J. R.; Hitchcock, P. B.; Ratcliffe, A. H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 843 (b) Rukachaisirikul, V.; Pramjit, S.; Pakawatchai, C.; Isaka, M.; Supothina, S. *J. Nat. Prod.* **2004**, *67*, 1953.
(13) (a) Göhrt, A.; Zeeck, A.; Hütter, K.; Kirsch, R.; Kluge, H.; Thiericke, R. *J. Antibiot.* **1992**, *45*, 66. (b) Grabley, S.; Haummann, P.; Hütter, K.; Kirsch, R.; Kluge, H.; Thiericke, R. *J. Antibiot.* **1992**, *45*, 1176.
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(15) Bringmann, G.; Lang, G.; Michel, M.; Heubes, M. *Tetrahedron Lett.* **2004**, *45*, 2829.
(16) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.
(17) The general methodology for macrolactones synthesis can often be applied for medium ring lactones. For a recent review: Parenty, A.; Moreau, X.; Campagne, J. M. *Chem. Rev.* **2006**, *106*, 911.
(18) Djerassi, C.; Engle, R. R. *J. Am. Chem. Soc.* **1953**, *75*, 3838.

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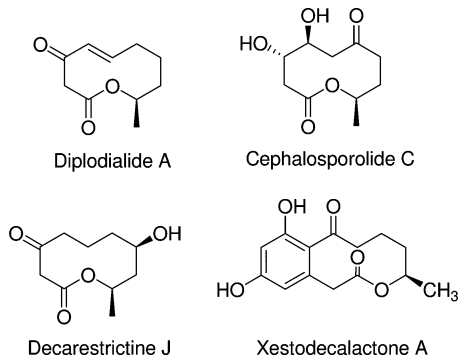
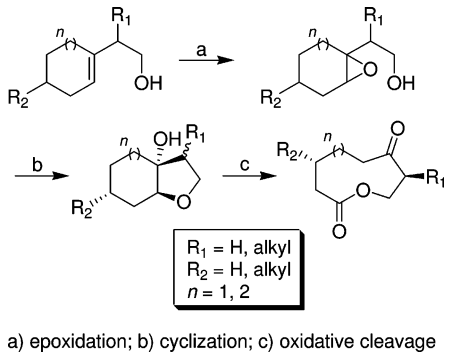


FIGURE 1. Structures of some naturally occurring medium ring keto-lactones.

SCHEME 1[a]



[a] (a) Epoxidation; (b) cyclization; (c) oxidative cleavage.

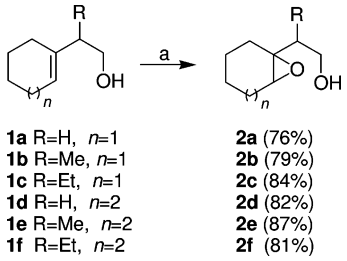
as the oxidation of saturated hydrocarbons,[20] the oxidative cleavage of alkenes,[21] the α-ketohydroxylation of alkenes,[22] the cis-dihydroxylation of alkenes,[23] and the oxidative polycyclization of polyenes.[24] In 1985, Torii et al.[25] reported a single example of the RuO_4-promoted oxidative cleavage of an enol ether, which led to a 10-membered ring keto-lactone.

In this work we wish to report an efficient procedure for synthesizing a series of bicyclic β-hydroxyethers, as well as their oxidative cleavage by catalytic RuO_4, which showed to be a clean and straightforward method for the synthesis of 9- and 10-membered keto-lactones (Scheme 1).[26]

Results and Discussion

Preparation of the Bicyclic β-Hydroxytetrahydrofurans. In a previous paper we reported the preparation of some cis-fused bicyclic β-hydroxyethers, through a thallium trinitrate (TTN) mediated cyclization of 3-alkenols bearing an alkyl group at the cyclohexene ring. Similar unsubstituted alkenols gave rise to ring contraction products.[27] In order to obtain the bicyclic β-hydroxyethers without a substituent in the cycloalkane ring, we employed the method described by Murai et al.,[28] which consists of a base-promoted cyclization of epoxyalcohols.

SCHEME 2[a]



[a] Reagents and conditions: 1.5 of equiv Oxone, 4.0 equiv of $NaHCO_3$, acetone/H_2O (1:1), rt, 5−20 min.

The 3-alkenols **1a**−**f**, used as starting materials, were prepared from commercially available cyclohexanone and cycloheptanone.[29] The epoxidation of the 3-alkenols **1a**−**f** was performed using Oxone and sodium bicarbonate, following a described protocol[30] (Scheme 2).

The epoxyalcohols **2a**−**f** thus obtained were submitted to treatment with 10 equiv of KOH in 75% aqueous DMSO solution.[28] The intramolecular reaction, i.e., the opening of the epoxide by the alkoxide anion, occurs preferentially over an intermolecular process, providing the reaction is performed at a high dilution rate. In this way, the expected bicyclic β-hydroxyethers **3a**−**f** were obtained in moderate to good yields (Table 1).

The other bicyclic β-hydroxyethers used in this work (**3g**−**j**) were prepared through the already mentioned TTN-mediated cyclization of 3-alkenols.[27]

The relative configurations of the diastereomeric β-hydroxyethers shown in Table 1 (entries 2, 3, 5, and 6) were proposed by comparison of their ^1H and ^{13}C NMR data with those of **3h** and **3j**.[27]

To check the behavior toward base-promoted cyclization of epoxides bearing a substituent in the cyclohexane ring, the 3-alkenol **1g**, prepared from 4-methyl-cyclohexanone,[27] was transformed into a 3:2 diastereoisomeric mixture of the epoxyalcohols **2g** and **2g′**. Treatment of these epoxides with KOH, under the same conditions used for the preparation of **3a**−**f**, led to a mixture of several products. Among them, the expected β-hydroxyethers **3g** and **3g′**, the spiro hydroxyether **4**, the allylic alcohol **5**, and the glycolic derivative **6** could be partially separated by flash chromatography and identified by ^1H and ^{13}C NMR (Scheme 3).

The formation of the cyclic ethers **3g**, **3g′**, and **4** can be rationalized considering a stereoselective diaxial opening of the oxirane ring. Thus, the isomer **2g**, bearing the epoxide and the methyl group in a cis relationship, can be cyclized through the more stable conformer **I** (Figure 2). This 5-endo-trig-like cyclization affords exclusively the β-hydroxyether **3g**. On the

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(20) Drees, M.; Strassner, T. *J. Org. Chem.* **2006**, *71*, 1755 and references cited therein.
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(22) (a) Plietker, B. *Eur. J. Org. Chem.* **2005**, 1919. (b) Plietker, B. *J. Org. Chem.* **2004**, *69*, 8287 and references cited therein.
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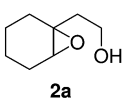
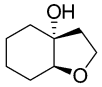
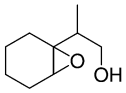
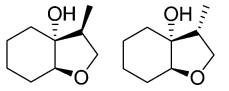
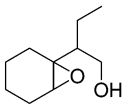
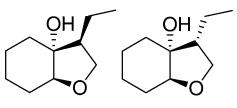
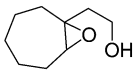
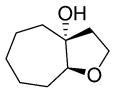
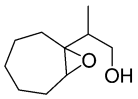
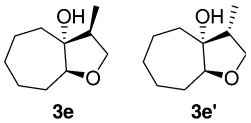
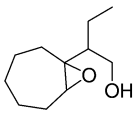
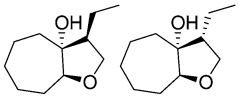
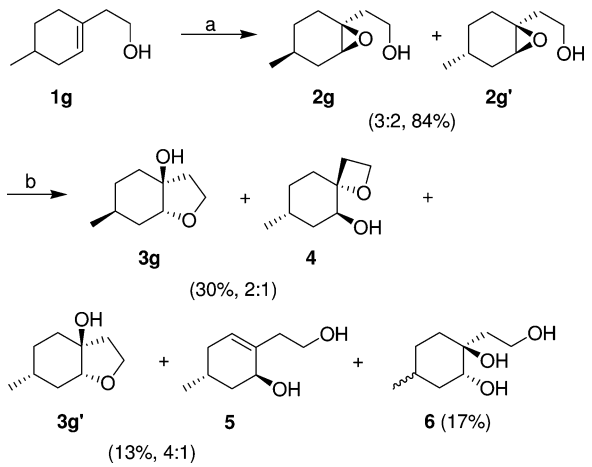
(28) Murai, A.; Ono, M.; Masamune, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1226.
(29) For experimental details and full characterization data of **1a**, **1b**, and **1d** see ref 27. For a general procedure for the preparation of **1c**, **1e**, and **1f**, see Supporting Information.
(30) Ferraz, H. M. C.; Muzzi, R. M.; Vieira, T. O.; Viertler, H. *Tetrahedron Lett.* **2000**, *41*, 5021.

TABLE 1. Base-Promoted Cyclization of Epoxyalcohols 2a−f[a]

Entry	*Substrate*	*Products*	*Yield (ratio)*
1	 **2a**	 **3a**	38%[b]
2	 **2b**	 **3b** **3b'**	83% (3:2)[c]
3	 **2c**	 **3c** **3c'**	75% (3:1)[c]
4	 **2d**	 **3d**	68%
5	 **2e**	 **3e** **3e'**	75% (2:3)[c]
6	 **2f**	 **3f** **3f'**	86% (7:3)[c]

[a] Reagents and conditions: 1.0 mmol epoxyalcohol, 10 equiv KOH, 20 mL of 75% aq DMSO, 110−120 °C, 2 h. [b] Minor amounts of the corresponding glycolic derivative were observed in the crude product of the reaction. [c] Ratio determined by GC and/or ^{1}H NMR of the crude product.

SCHEME 3[a]



[a] Reagents and conditions: (a) 1.5 equiv of Oxone, 4.0 equiv of $NaHCO_3$, acetone/H_2O (1:1), rt, 10 min; (b) 10 equiv of KOH, 20 mL of 75% aq DMSO, 110−120 °C, 2 h.

other hand, the cyclization of the trans isomer **2g′** can give either the hydroxyether **3g′**, from the conformer **III**, or the spiro ether **4**, by a 4-exo-trig-like cyclization of **IV**, since both the conformations probably have similar stabilities (Figure 2). The

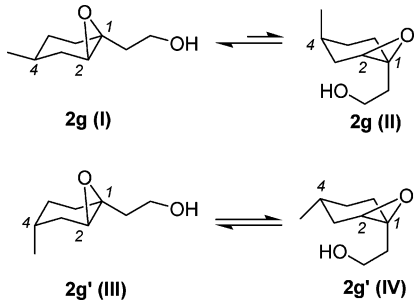


FIGURE 2. Conformers of the epoxides **2g** and **2g′**.

allylic alcohol **5** should be formed from the trans isomer **2g′**, by abstraction of the C_6-equatorial proton,[31] while a direct hydroxide opening of the oxirane ring of **2g** and/or **2g′** could give the triol **6**.

Oxidative Cleavage of the Bicyclic *β*-Hydroxytetrahydrofurans. With the *β*-hydroxyethers **3a−j** in hand, we turned our attention to the study of the oxidative cleavage of these substrates by catalytic RuO_4. The reaction was performed with RuO_4 generated in situ from ruthenium trichloride ($RuCl_3 \cdot nH_2O$) and excess sodium periodate ($NaIO_4$) in a biphasic solvent system containing water, carbon tetrachloride, and acetonitrile (3:2:2 ratio, respectively).[32]

The hydroxyethers **3a−f** afforded the corresponding 9- and 10-membered ring keto-lactones **7a−f**, as outlined in Table 2. The typical workup protocol, addition of distilled water, extraction with CH_2Cl_2, and then filtration of the concentrated organic extracts on a silica gel pad (protocol A), furnished the keto-lactones **7a** and **7b** in low yields (entries 1 and 2). In spite of these yields, no impurities or byproducts were observed by GC analysis of the crude products. A somewhat modified workup, quenching with a saturated aqueous sodium thiosulfate ($Na_2S_2O_3$) solution,[33] extraction with CH_2Cl_2, and filtration on Celite (protocol B), allowed a significant improvement in the yields of the keto-lactones **7a** and **7b**. Similarly, the *β*-hydroxyethers **3e** and **3f** led to the corresponding 10-membered ring keto-lactones **7e** and **7f** in better yields using protocol B (entries 5 and 6).

As previously reported,[26] the *β*-hydroxyethers **3g−j** led to the corresponding nine-membered keto-lactones **7g−j**. These results are summarized in Scheme 4.[34]

Bakke and Froehaug[35] postulated that the order of reactivity of carbon−hydrogen bonds vicinal to an ether toward oxidation by RuO_4 is CH_2 > CH. The same behavior was reported for the oxidation of tetrahydrofuran and tetrahydropyran derivatives.[36] However, our results demonstrated an inversion of this regiochemistry in the oxidation of the *β*-hydroxyethers **3a−j**,

(31) Performing the reaction with 4.0 equiv of NaH in anhydrous THF led to the exclusive formation of the allylic alcohol **5** along with recovered starting material after 3 h under reflux. It is noteworthy that **5** was the only regioisomer observed with either KOH or NaH.

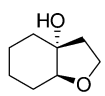
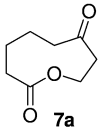
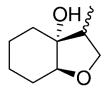
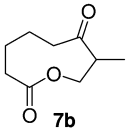
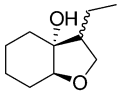
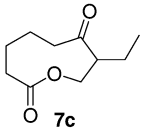
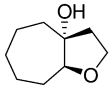
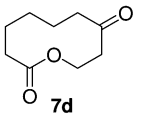
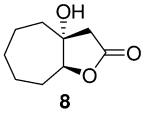
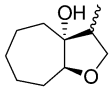
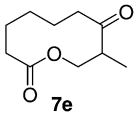
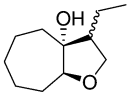
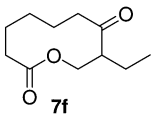
(32) The use of acetonitrile, as established by Sharpless and co-workers, represents a great improvement in the reaction protocol, since this solvent can prevent coordination of low-valent ruthenium species with carboxylic acids formed as byproducts during the course of the reaction. Carlsen, H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(33) A saturated aqueous solution of sodium sulfite (Na_2SO_3) is also used in the workup protocols of ruthenium tetraoxide-mediated oxidations (see ref 22).

(34) For the ^{1}H and ^{13}C NMR spectra of the keto-lactones **7g−j** see ref 26.

(35) Bakke, J. M.; Froehaug, A. E. *J. Phys. Org. Chem.* **1996**, *9*, 310.

TABLE 2. RuO_4-Catalyzed Oxidative Cleavage of β-Hydroxyethers 3a−f[a]

Entry	Substrate	Product	Protocol[c] (yield)
1	 **3a**	 **7a**	A (16%) B (52%)
2[b]	 **3b+3b'**	 **7b**	A (26%) B (76%)
3[b]	 **3c+3c'**	 **7c**	A (62%)
4	 **3d**	 **7d**  **8**	B (78%) (9:1)[d]
5[b]	 **3e+3e'**	 **7e**	A (49%) B (63%)
6[b]	 **3f+3f'**	 **7f**	A (66%) B (86%)

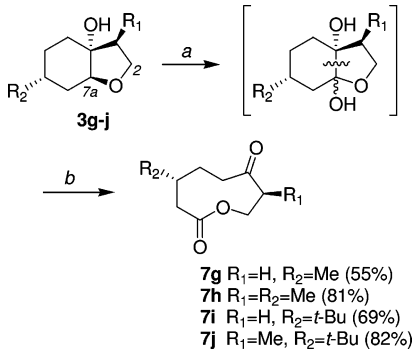
[a] Reagents and conditions: 1.0 mmol β-hydroxyether, 3.0 mol % $RuCl_3 \cdot nH_2O$, 4.1 equiv $NaIO_4$, $H_2O/CCl_4/CH_3CN$ (7 mL, 3/2/2, respectively), rt, 90 min. [b] Diastereoisomeric mixtures of the β-hydroxyethers were used (see ratios in Table 1). [c] Protocol A: addition of distilled water, extraction with CH_2Cl_2, and filtration on a silica gel pad. Protocol B: quenching with saturated aqueous $Na_2S_2O_3$ solution, extraction with CH_2Cl_2, and filtration on Celite. [d] Ratio determined by GC of the crude product.

since carbon 7a (CH) was oxidized preferentially to carbon 2 (CH_2), leading to an α-hydroxy-hemiketal (as suggested in Scheme 4), whose oxidative cleavage could be performed either by RuO_4 or by $NaIO_4$.

It is noteworthy that the oxidation of the β-hydroxyether **3d** (Table 2, entry 4) led to the 10-membered lactone **7d** along with approximately 10% of the bicyclic lactone **8** (assumed structure). The presence of such an oxidation product, even in small amounts, was observed exclusively for the substrate **3d**.

Although the mechanism of the oxidative cleavage is not completely understood, the presence of the angular hydroxyl group in the bicyclic ethers seems to play an important role in the chemoselectivity displayed by RuO_4, when compared to the

SCHEME 4[a]



7g R_1=H, R_2=Me (55%)
7h R_1=R_2=Me (81%)
7i R_1=H, R_2=*t*-Bu (69%)
7j R_1=Me, R_2=*t*-Bu (82%)

[a] Reagents and conditions: (a) 2.4 mol % $RuCl_3 \cdot nH_2O$, 4.1 equiv of $NaIO_4$, $H_2O/CCl_4/CH_3CN$ (7 mL, 3:2:2, respectively), rt, 75 min, workup by protocol A; (b) oxidative cleavage.

results obtained by Kitagawa et al.[37] These authors reported that the $RuO_4/NaIO_4$ oxidation of the octahydro-3,6-dimethylbenzofurans, which differ from **3h** essentially by the absence of the hydroxyl group, led to the corresponding bicyclic lactones, by the anticipated oxidation of the secondary carbon. In our substrates, it is reasonable to consider the initial formation of a ruthenate ester with the angular hydroxyl group. This ester might then participate in a syn methine hydrogen abstraction, followed by oxidation at that position, to afford the diol depicted in Scheme 4.

The octahydro-3,6-dimethylbenzofuran-3-ols **9a** and **9b**,[38] which are also β-hydroxyethers but bear the hydroxyl group in a position different from that of the ethers **3a**−**j**, were submitted to the same oxidative treatment, in order to verify the role of the hydroxyl group in the chemoselectivity of the reaction. The only isolated product from **9a** was 2-acetyl-5-methyl-cyclohexanone (**10**),[39] again through an oxidation of the tertiary carbon 7a. The ether **9b** also led to the β-diketone **10**, together with minor amounts of **11** and **12**, produced by oxidation of the secondary carbon C_2.[40]

The different reactivities of **9a** and **9b** are in agreement with the literature information concerning the steric requirements for the oxidation of cyclic hydrocarbons by RuO_4 (reactivity of C−H bonds: equatorial tertiary ≫ axial tertiary > equatorial secondary > axial secondary).[41] The tertiary equatorial C−H bond of **9a**, as well as those of the ethers **3a**−**j**, is oxidized faster than the tertiary axial C−H bond of **9b**. Therefore, the less reactive ether **9b** allows the oxidation of both tertiary and secondary carbons. Unfortunately, we could not clarify the role of the hydroxyl group in the course of the reaction.

A possible mechanism for the oxidation of **9a** and **9b** by RuO_4 is suggested in Scheme 5. The oxidation can occur either in the tertiary carbon 7a or in the secondary carbon 2. Preferential oxidation of the C_7−H bond of both **9a** and **9b** leads to the hemiketal intermediate **I**, which undergoes oxidation to **II** and further cleavage to the β-diketone **10**. Alternatively, the oxida-

(36) Smith, A. B., III; Scarborough, R. M., Jr. *Synth. Commun*. **1980**, *10*, 205.

(37) Kitagawa, I.; Tsujii, S.; Nishikawa, F.; Shibuya, H. *Chem. Pharm. Bull.* **1983**, *31*, 2639.

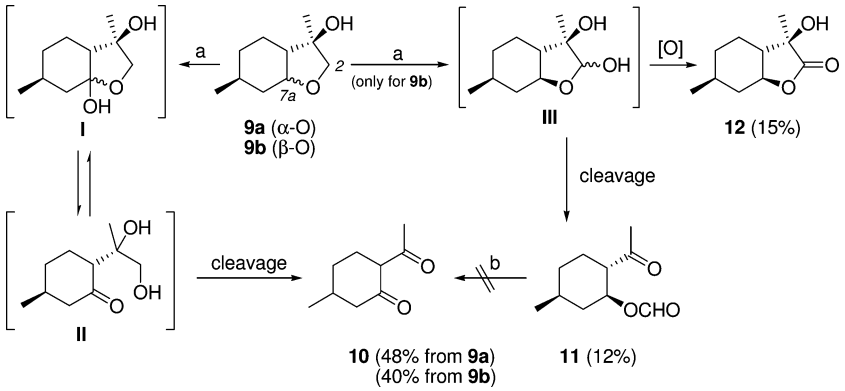
(38) Ferraz, H. M. C.; Grazini, M. V. A.; Ribeiro, C. M. R.; Brocksom, U.; Brocksom, T. J. *J. Org. Chem.* **2000**, *65*, 2606.

(39) Descotes, G.; Yvon, Q. *Bull. Soc. Chim. Fr*. **1968**, *8*, 3395. Diketone **10** exists predominantly in the enol form: Snider, B. B.; Shi, Z. *J. Am. Chem. Soc.* **1992**, *114*, 1790.

(40) For experimental details and full characterization data of products **11** and **12** see Supporting Information.

(41) Bakke, J. M.; Bethell, D. *Acta Chem. Scand.* **1992**, *46*, 644.

SCHEME 5[a]



[a] Reagents and conditions: (a) 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 **9a** and 4 h for **9b**; (b) 5.0 mol % $RuCl_3 \cdot nH_2O$, 4.1 equiv of $NaIO_4$, $H_2O/CCl_4/CH_3CN$ (3:2:2), rt, 4 h.

tion of C_2, which occurs only in the ether **9b**, gives the intermediate **III**, precursor of the minor products **11** and **12**. The possibility of a direct transformation of **11** to **10**[42] was excluded by submitting **11** to the same oxidative reactional conditions: after 4 h of reaction the starting material was recovered unchanged.

Conclusions

We have demonstrated that the oxidative cleavage of bicyclic β-hydroxyethers by catalytic RuO_4 is a mild and clean method for the preparation of 9- and 10-membered ring lactones, using $RuCl_3$ as the source of RuO_4 and $NaIO_4$ as the stoichiometric cooxidant. The bicyclic ethers were easily prepared from 3-alkenols in two steps, i.e., epoxidation with dimethyldioxirane followed by base-catalyzed cyclization of the resulting epoxy-alcohol. This method complements the thallium trinitrate-mediated cyclization of 3-alkenols described earlier by our group.[27] High regioselectivity was observed in the oxidation of the β-hydroxyethers by RuO_4, with large preference for the oxidation of the tertiary carbon−hydrogen bond, in contrast to the postulated order of reactivity of the carbon−hydrogen bonds in ethers.[35,36] The application of this methodology to the synthesis of natural medium ring lactones is in progress in our laboratory.

Experimental Section

General Procedure for the Base-Promoted Cyclization of Epoxyalcohols 2a−f. Preparation of the Bicyclic *β*-Hydroxy-ethers 3a−f. To a stirred solution of the epoxyalcohols **2a−f** (1 mmol) in 75% aqueous DMSO (20 mL) was added potassium hydroxide (10 equiv, 0.56 g, 10 mmol). The mixture was stirred at 110−120 °C for 2 h, and water (20 mL) was added dropwise. The aqueous phase was extracted with AcOEt (three times). The combined organic extracts were washed with H_2O followed by brine and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure.

3*β*-Methyl-8aα*H*-octahydro-cyclohepta[*b*]furan-3aα-ol (3e) and 3α-Methyl-8aα*H*-octahydro-cyclohepta[*b*]furan-3aα-ol (3e′). The reaction was performed following the general procedure, using the epoxyalcohol **2e** (0.757 g, 4.45 mmol) in 75% aqueous DMSO (90 mL) and KOH (2.49 g, 44.5 mmol). The crude product was purified by flash chromatography (eluent, 50% AcOEt in hexanes) to give a 2:3 mixture of **3e** and **3e′** (0.566 g, 3.33 mmol, 75%), respectively (ratio determined by GC and ^{1}H NMR in the crude product). Analytical samples of the diastereomeric bicyclic β-hydroxyethers **3e** and **3e′** were obtained performing a second flash chromatography (gradient elution, 10−50% AcOEt in hexanes). **3e**: white solid; mp = 94.4−94.8 °C; IR (KBr) 3382 cm^{-1}; LRMS *m*/*z* (%) 170 (16, M$^+$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (d, J = 6.9 Hz, 3H), 1.26−1.66 (m, 6H, H−OH), 1.77−1.99 (m, 5H), 3.45 (dd, J = 8.1 and 11.4 Hz, 1H), 3.81 (dd, J = 2.7 and 11.4 Hz, 1H), 3.93 (t, J = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.8, 23.1, 25.7, 31.2, 33.7, 36.9, 44.1, 72.6, 82.9, 91.9. Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55%; H, 10.66%. Found: C, 70.64%; H, 10.65%. **3e′**: white solid; mp = 65.5−65.6 °C; IR (KBr) 3383 cm^{-1}; LRMS *m*/*z* (%) 156 (16, M$^+$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (d, J = 7.3 Hz, 3H), 1.27−1.37 (m, 2H), 1.50−1.92 (m, 8H, H−OH), 2.03−2.06 (m, 1H), 3.56 (dd, J = 2.8 and 8.3 Hz, 1H), 3.75 (dd, J = 3.0 and 11.2 Hz, 1H), 4.09 (dd, J = 5.5 and 8.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.7, 22.7, 25.4, 30.8, 33.2, 33.6, 48.1, 73.4, 84.3, 91.4. Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55%; H, 10.66%. Found: C, 70.55%; H, 10.62%.

3*β*-Ethyl-8aα*H*-octahydro-cyclohepta[*b*]furan-3aα-ol (3f) and 3α-Ethyl-8aα*H*-octahydro-cyclohepta[*b*]furan-3aα-ol (3f′). The reaction was performed following the general procedure, using the epoxyalcohol **2f** (0.389 g, 2.11 mmol) in 75% aqueous DMSO (42 mL) and KOH (1.18 g, 21.1 mmol). The crude product was purified by flash chromatography (eluent, 50% AcOEt in hexanes) to give a 7:3 mixture of **3f** and **3f′** (0.334 g, 1.82 mmol, 86%), respectively (ratio determined by GC and ^{1}H NMR in the crude product). Analytical samples were obtained performing a second flash chromatography (gradient elution, 10−50% AcOEt in hexanes). **3f**: white solid; mp = 110.5−110.6 °C; IR (KBr) 3380 cm^{-1}; LRMS *m*/*z* (%) 184 (6.3, M$^+$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (t, J = 7.5 Hz, 3H), 1.26−1.92 (m, 13H, H−OH), 3.48 (dd, J = 8.1 and 11.3 Hz, 1H), 3.80 (dd, J = 2.4 and 11.3 Hz, 1H), 4.04 (t, J = 7.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.2, 17.9, 23.1, 25.7, 31.2, 33.6, 37.3, 51.5, 71.6, 83.1, 92.3. Anal. Calcd for $C_{10}H_{18}O_2$: C, 71.70%; H, 10.94%. Found: C, 71.46%; H, 10.73%. **3f′**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J = 7.2 Hz, 3H), 1.15−1.97 (m, 13H, H−OH), 3.68 (dd, J = 4.0 and 8.6 Hz, 1H), 3.77 (dd, J = 2.5 and 10.8 Hz, 1H), 4.04 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9, 20.9, 22.4, 24.8, 30.4, 32.3, 33.1, 55.3, 70.0, 83.9, 90.6. Anal. Calcd for $C_{10}H_{18}O_2$: C, 71.70%; H, 10.94%. Found: C, 71.51%; H, 10.83%.

General Procedure for the Ruthenium Tetraoxide-Promoted Oxidative Cleavage of *β*-Hydroxyethers 3a−c,e,f (Protocol A). To 7.0 mL of a 3:2:2 mixture of $H_2O/CCl_4/CH_3CN$, respectively, was added 1 mmol of the β-hydroxyethers **3**, 4.1 mmol of $NaIO_4$,

(42) An example of the RuO_4-promoted oxidation of a formate ester to the corresponding ketone is described in ref 25.

and 2.4−3.0 mol % of $RuCl_3 \cdot nH_2O$,[43] according to the data shown in Table 2. The mixture was magnetically stirred at rt for 75−90 min, and 10 mL of distilled H_2O was added. The aqueous phase was extracted with CH_2Cl_2 (three times), and the combined organic phases were washed with brine (twice) and concentrated by removing part of the solvent under reduced pressure. The resulting residue was then filtered through a small silica gel pad (approximately 10 cm), washing with CH_2Cl_2. The filtrate was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure affording the corresponding keto-lactones.

8-Methyl-oxonane-2,7-dione (7b). The reaction was performed following the general procedure, stirring a 3:2 mixture of the β-hydroxyethers **3b**/**3b′** (0.050 g, 0.318 mmol), $RuCl_3 \cdot nH_2O$ (3.0 mol %, approximately 0.002 g), and $NaIO_4$ (0.278 g, 1.30 mmol) in 2.8 mL of a 3:2:2 mixture of $H_2O/CCl_4/CH_3CN$ at rt for 90 min. The crude product was purified by flash chromatography (gradient elution, 0−30% AcOEt in hexanes) affording the keto-lactone **7b** (0.014 g, 0.082 mmol, 26%). **7b**: colorless oil; IR (film) 1743, 1711 cm^{-1}; LRMS *m*/*z* (%) 170 (0.4, M^+); ^1H NMR (500 MHz, $CDCl_3$) δ 1.05 (d, J = 6.8 Hz, 3H), 1.75−1.95 (m, 4H), 2.31−2.49 (m, 4H), 3.21−3.28 (m, 1H), 4.01 (dd, J = 9.5 and 10.7 Hz, 1H), 4.68 (dd, J = 7.2 and 10.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.2, 23.9, 24.5, 35.0, 41.5, 44.8, 66.9, 174.6, 213.8. Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29%. Found: C, 63.65%; H, 8.31%.

9-Methyl-oxecane-2,8-dione (7e). The reaction was performed following the general procedure, stirring a 2:3 mixture of the β-hydroxyethers **3e**/**3e′** (0.151 g, 0.888 mmol), $RuCl_3 \cdot nH_2O$ (3.0 mol %, approximately 0.006 g), and $NaIO_4$ (0.779 g, 3.64 mmol) in 7.0 mL of a 3:2:2 mixture of $H_2O/CCl_4/CH_3CN$ at rt for 90 min. The crude product was purified by flash chromatography (eluent, 20% AcOEt in hexanes) affording the keto-lactone **7e** (0.080 g, 0.44 mmol, 49%). **7e**: colorless oil; IR (film) 1738, 1713 cm^{-1}; LRMS *m*/*z* (%) 184 (4.7, M^+); ^1H NMR (500 MHz, $CDCl_3$) δ 1.02 (d, J = 6.8 Hz, 3H), 1.15−1.20 (m, 1H), 1.49−1.64 (m, 1H), 1.60−1.67 (m, 2H), 1.70−1.80 (m, 1H), 1.83−1.89 (m, 1H), 2.24−2.31 (m, 2H), 2.38 (ddd, J = 4.3, 5.5 and 14.2 Hz, 1H), 2.69 (ddd, J = 3.8, 9.1 and 14.8 Hz, 1H), 3.30−3.37 (m, 1H), 4.04 (t, J = 10.6 Hz, 1H), 4.34 (dd, J = 5.6 and 10.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.5, 22.2, 23.1, 25.2, 35.0, 41.9, 43.0, 67.3, 173.1, 214.7. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19%; H, 8.75%. Found: C, 65.41%; H, 8.67%.

General Procedure for the Ruthenium Tetraoxide-Promoted Oxidative Cleavage of β-Hydroxyethers 3a,b,d−f (Protocol B). To 7.0 mL of a 3:2:2 mixture of $H_2O/CCl_4/CH_3CN$, respectively, was added 1 mmol of the β-hydroxyethers **3**, 4.1 mmol of $NaIO_4$, and 3.0 mol % of $RuCl_3 \cdot nH_2O$,[43] according to the data shown in Table 2. The mixture was magnetically stirred at rt for 90 min, and 10 mL of a saturated aqueous solution of $Na_2S_2O_3$ was added. The resulting solution was filtered under Celite, washing with CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (three times), and the combined organic phases were washed with brine (twice) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure affording the corresponding keto-lactones.

Oxecane-2,8-dione (7d). The reaction was performed following the general procedure, stirring the β-hydroxyether **3d** (0.178 g, 1.14 mmol), $RuCl_3 \cdot nH_2O$ (3.0 mol %, approximately 0.007 g), and $NaIO_4$ (1.00 g, 4.67 mmol) in 8.0 mL of a 3:2:2 mixture of $H_2O/CCl_4/CH_3CN$ at rt for 90 min. The solvent was removed under reduced pressure, affording the keto-lactone **7d** contaminated with approximately 10% of the β-hydroxylactone **8** (assumed structure) in 78% overall yield. Spectral data for **7d** are in agreement with the literature.[44]

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Supporting Information Available: Experimental procedures and structural data information for the compounds not described within the Experimental Section: NMR spectra of 3-alkenols **1a**−**g**, epoxyalcohols **2a**−**g**, β-hydroxyethers **3a**−**g**, products **4**, **5**, and **6**, and keto-lactones **7a**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0626109

(43) Calculations for $RuCl_3 \cdot nH_2O$ were based on n = 1.

(44) Das, J.; Chandrasekaran, S. *Tetrahedron* **1994**, *50*, 11709.