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Singlet-Oxygen-Mediated One-Pot Synthesis of 3-Keto-tetrahydrofurans from 2-(β-Hydroxyalkyl) Furans

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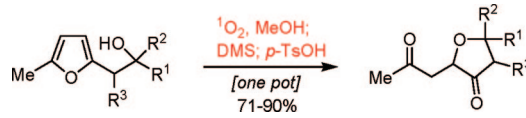
ABSTRACT



Photooxygenation of 2-(β-hydroxyalkyl) furans affords, in one synthetic operation and in high yields, 3-keto-tetrhydrofuran motifs via intramolecular Michael-type addition to the 1,4-enedione intermediate.

As a continuation of our intrest in the development and application of tandem and cascade reaction sequences, mediated by singlet oxygen ($^1O_2$), for the synthesis of natural products and important natural products motifs,[1] we sought to explore the potential of the photooxygenation of 2-(β-hydroxyalkyl) furans[2] as means to prepare 3-keto-tetrahydrofuran motifs. The 3-keto-tetrahydrofuran motif is of interest because it exists in a wide variety of natural products including the scabrolides[3] and pectenotoxins (PTXs).[4]

The new approach to 3-keto-tetrahydrofurans that is successfully developed herein is particularly advantageous as a result of the atom economy and intrinsic efficiency of the cascade reaction sequence that is employed. Furthermore, the 2-(β-hydroxyalkyl) furan precursors, with a wide variety of appended substituents and functionalities, are readily accessible; thus, a highly effective method has been delineated.

Previous studies emanating from our laboratories had shown what happened if a furan photooxygenation substrate had a γ- or δ-hydroxyl appended on the 2-alkyl substituent; the corresponding spiroketal was furnished via intramolecular trapping.[5] On the other hand, it has been known for some time that an α-hydroxyl at the 2-alkyl substituent leads to rapid fragmentation of the substrate yielding the corresponding 4-hydroxy butenolide.[6] Despite these seemingly comprehensive investigations, the effect of placing the hydroxyl at the β-position (**A**, Scheme 1) had never been probed prior to this study.

Obviously, an intramolecular nucleophilic opening of ozonide **B** (Scheme 1), of the sort seen with the γ- and δ-hydroxyls, is unlikely because it would require an unfavorable 4-*exo*-cyclization compared to 5-*exo*- and 6-*exo*-cyclizations observed in the previous cases.[5a] Drawing on experience garnered during the synthesis of the litseavertiicillol family of natural products,[7] it was interesting to wonder whether, when employing MeOH as the photooxygenation solvent, the analogous 1,4-enedione (see **F**, Scheme 1) might

(1) For a recent account, see: Montagnon, T.; Tofi, M.; Vassilikogiannakis, G. *Acc. Chem. Res.* **2008**, *41*, 1001–1011.

(2) For general reviews of furan photooxygenation, see: (a) Gollnick, K.; Griesbeck, A. *Tetrahedron* **1985**, *41*, 2057–2068. (b) Feringa, B. L. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 469–488.

(3) (a) Sheu, J.-H.; Ahmed, A. F.; Shiue, R.-T.; Dai, C.-F.; Kuo, Y.-H. *J. Nat. Prod.* **2002**, *65*, 1904–1908. (b) Ahmed, A. F.; Su, J.-H.; Kuo, Y.-H.; Sheu, J.-H. *J. Nat. Prod.* **2004**, *67*, 2079–2082.

(4) For original isolation, see: (a) Yasumoto, T.; Murata, M.; Oshima, Y.; Sano, M.; Mastumoto, G. K.; Clardy, J. *Tetrahedron* **1985**, *41*, 1019–1025. For total synthesis of PTX4 and PTX8, see: (b) Evans, D. A.; Rajapakse, H. A.; Stenkamp, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 4569–4573. (c) Evans, D. A.; Rajapakse, H. A.; Chiu, A.; Stenkamp, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 4573–4576.

(5) (a) Georgiou, T.; Tofi, M; Montagnon, T.; Vassilikogiannakis, G. *Org. Lett.* **2006**, *8*, 1945–1948. (b) Tofi, M.; Montagnon, T.; Georgiou, T.; Vassilikogiannakis, G. *Org. Biomol. Chem.* **2007**, *5*, 772–777.

(6) Lee, G. C. M.; Syage, E. T.; Harcourt, D. A.; Holmes, J. M.; Garst, M. E. *J. Org. Chem.* **1991**, *56*, 7007–7014.

(7) (a) Vassilikogiannakis, G.; Stratakis, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5465–5468. (b) Vassilikogiannakis, G.; Margaros, I.; Montagnon, T. *Org. Lett.* **2004**, *6*, 2039–2042. (c) Vassilikogiannakis, G.; Margaros, I.; Montagnon, T.; Stratakis, M. *Chem. Eur. J.* **2005**, *11*, 5899–5907.

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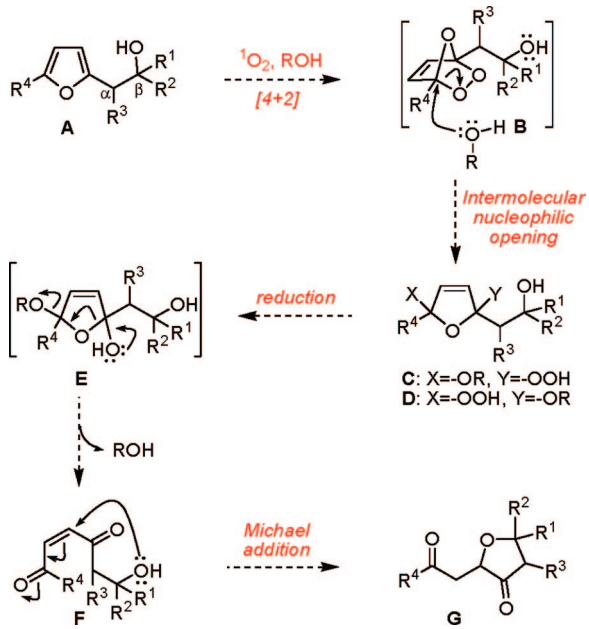
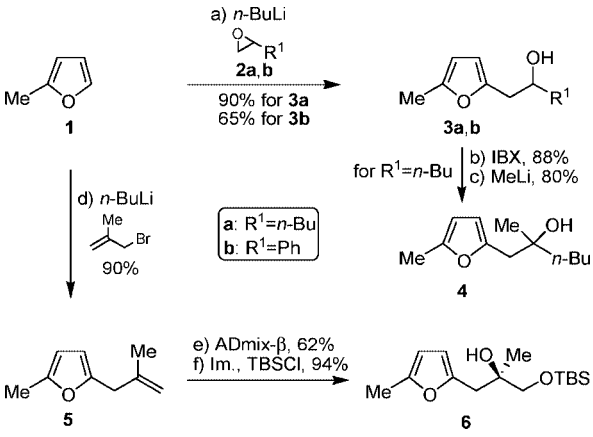
Scheme 1. Concept



be obtained. This unsaturated 1,4-enedione **F** might then become the subject of an intramolecular Michael-type addition to yield the final cyclized motif seen in **G** (Scheme 1).

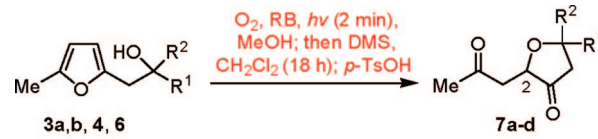
To test this hypothesis and gain proof of principle, furan **3a** (Scheme 2) was easily prepared upon nucleophilic

Scheme 2. Synthesis of Key Precursor **3a,b**, **4**, **6**



opening of 1,2-epoxyhexane (**2a**) by 2-methylfuryllithium. The resulting furan was then subjected to a standard set of $^1O_2$ photooxygenation conditions (rose bengal as photosensitizer, oxygen bubbling through the reaction mixture, and irradiation with visible spectrum light, Scheme 3) for 2 min. Following a change of solvent (removal of MeOH in vacuo and replacement with CH_2Cl_2), an in situ reduction of the hydroperoxides (analogous to **C** and **D**, Scheme 1) using

Scheme 3. Validation of Proposed Reaction Sequence: Synthesis 2,5-Substituted-3-keto-tetrahydrofurans



substrate	R^1	R^2	*p*-TsOH (time)	yield (%)	product (dr)
3a	*n*-Bu	H	0.5 h	83	**7a** (3.3:1)
3b	Ph	H	3.5 h	86	**7b** (2.5:1)
4	*n*-Bu	Me	0.5 h	90	**7c** (2:1)
6	CH_2OTBS	Me	1.0 h	85	**7d** (1.2:1)

dimethylsulfide (DMS) afforded the desired enedione (analogous to **F**), as seen by ^1H NMR, which could be coaxed into cyclizing in the desired manner upon addition of catalytic amounts of *p*-TsOH and after 30 min of stirring. Removal of MeOH before the addition of DMS is important for the fast elimination of MeOH from intermediate of type **E** (**E** → **F**, Scheme 1). The overall yield of this one-pot multistep sequence was 83%, and the final product **7a** (dr = 3.3:1, Scheme 3) was obtained in a highly pure form, such that no chromatographic purification was needed.

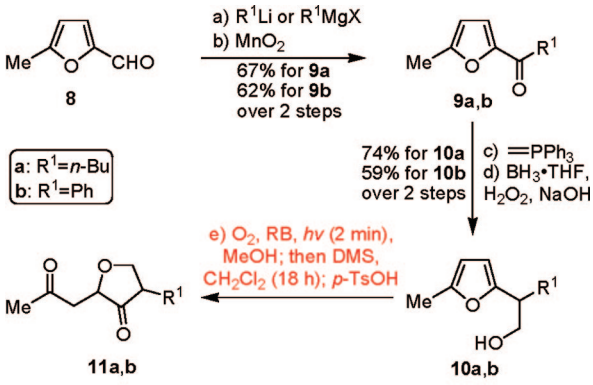
Once this proof of principle had been obtained, the scope and limitations of this synthetic technology needed to be delineated. To this end, a range of different 2-(*β*-hydroxyalkyl) furans were synthesized. First was furan **3b**, prepared by nucleophilic opening of styrene oxide **2b** (Scheme 2) and chosen as a target substrate in order to ascertain whether the cyclization of the enedione (of type **F**) was faster than the possible dehydration of the benzylic hydroxyl in the presence of *p*-TSOH. Under the experimental conditions reported above, clean formation of the intemediate *cis*-endione of type **F** (R^1 = Ph, R^2 = H, R^3 = H, R^4 = Me) was observed by ^1H NMR. Treatment of this intermediate with catalytic amount of *p*-TSOH for 30 min resulted in isomerizion to the corresponding *trans* geometrical isomer. Further stirring for 3 h gave clean conversion to the cyclized product **7b** (dr = 2.5:1, Scheme 3). NOE experiments revealed that the relative stereochemistry of the minor diastereoisomer of **7b** is *syn* while the major one is *anti*. It should be noted that similar NOE experiments had proven inconclusive in the case of **7a**.

Having established that the technology works very efficiently for secondary alcohols, such us **3a** and **3b**, it was hoped that it might be extended to include tertiary alcohols, such as **4** and **6**. Alcohol **4** was readily prepared by IBX oxidation of **3a** followed by addition of MeLi (70% over two steps). Homochiral alcohol **6** was synthesized by alkylation of 2-methylfuran with 3-bromo-2-methylpropene followed by Sharpless asymmetric dihydroxylation and selective protection of the primary alcohol as the TBS ether. Protection of the primary alcohol was essential in order to avoid the fast intramolecular nucleophilic opening of ozonide of type **B**, which leads to the formation of a [5,5]

spiroketal.[1,5a] Application of the developed protocol to furan **4** furnished cleanly, in 90% yield, 3-keto-tetrahydrofuran **7c** as a 2:1 mixture of diastereoisomers. The analogous procedure transformed furan **6** into 3-keto-tetrahydrofuran **7d** in 85% yield and as a 1.2:1 mixture of diastereoisomers (Scheme 3). Once again, *cis*−*trans* isomerization of the intermediate enedione (of type **F**), prior to the cyclization that afforded **7d**, was observed by ^{1}H NMR. Removal of the TBS group from 3-keto-tetrahydrofuran **7d** with TBAF gave a 2.2:1 mixture of diastereomeric primary alcohols. This finding is consistent with the easy epimerization of the stereogenic center α to the ketone (C2, Scheme 3). On the basis of NOE experiments, the minor stereoisomer of 3-keto-tetrahydrofuran **7d** (dr = 1.2:1) has the *syn* stereochemistry. The C-ring of the pectenotoxins[8] exhibits this relative stereochemistry.

Next we sought to clarify the ease with which different substitution patterns could be targeted using this newly developed methodology. To this end, furans **10a,b** were synthesized using the four-step sequence shown in Scheme 4 in order to attempt the synthesis of 2,4-disubstituted-3-keto-tetrahydrofurans. Application of the developed $^1O_2$-protocol in substrates **10a** and **10b** resulted in the clean formation of 2,4-disubstituted-3-keto-tetrahydrofurans **11a** and **11b**, respectively, in high yields and as mixtures of two diastereoisomers (Scheme 4). In contrast to the previously investigated cases (e.g., **7b** and **7d**), NOE studies proved in the case of **11a** that the relative stereochemistry of the major diastereoisomer was *syn*. In the case of **10b**, completion of the **E** → **F** transformation (Scheme 1) was observed after 5 h of treatment with DMS. Prolonged reaction times (18 h) led to complete *cis*−*trans* isomerization of this intermediate (type **F**). Similar *cis*−*trans* isomerization of the intermediate type **F** enedione was observed after 20 min of treatment with *p*-TsOH. Prolonged treatment with *p*-TsOH (6 h) cleanly afforded the cyclized product **11b**.

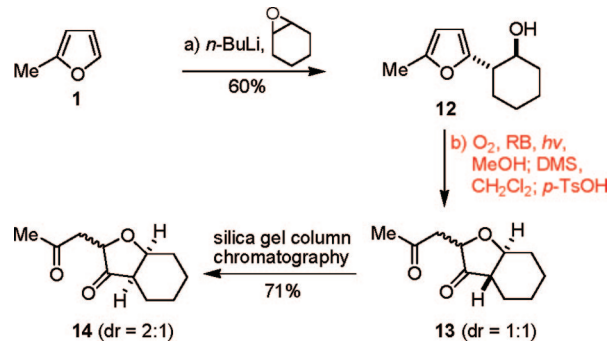
Scheme 4. Synthesis of 2,4-Disubstituted-3-keto-tetrahydrofurans



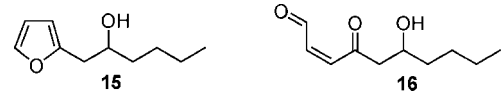
substrate	R^1	*p*-TsOH (time)	yield (%)	product (dr)
10a	*n*-Bu	20 min	83	**11a** (1.9:1)
10b	Ph	6 h	89	**11b** (1.5:1)

With these results in hand, it seemed pertinent to next explore whether the protocol could be extended to the preparation of 2,4,5-trisubstituted-3-keto-tetrahydrofurans. Furan **12** was synthesized via stereoselective nucleophilic opening of cyclohexene oxide with 2-methylfuryllithium (Scheme 5). Application of the newly developed tandem sequence, with furan **12** as substrate, then afforded the expected *trans*-fused bicycle **13** as an 1:1 mixture of diastereoisomers. Fast epimerization of the *trans*-fused bicycle **13**, to the more thermodynamically stable *cis*-fused isomer **14** (dr = 2:1), was observed upon purification using silica gel. In this instance particularly the potential of this method is highlighted because a relatively complex fused bicyclic motif has been accessed directly from a simple substrate using a dependable and high-yielding cascade sequence. Similar [6,5]-fused bicyclic motifs can be found in a variety of natural products, including (+)-phyllanthocin,[9] (+)-phyllanthocindiol,[9] (+)-phyllantoside,[10] and phyllantostatins.[11]

Scheme 5. Synthesis 2,4,5-Trisubstituted-3-keto-tetrahydrofurans



When the developed tandem reaction sequence was applied to monosubstituted furan **15**, no 3-keto-tetrahydrofuran formation was observed. This failure was attributed to the fast decomposition of the unstable intermediate 1,4-keto-aldehyde **16**.



In all of the substrates examined thus far, the final Michael-type attack (**F** → **G**, Scheme 1) occurs onto a monosubsti-

(8) For the classical syntheses of the C-ring of pectenotoxins based on a 5-*exo* epoxide opening, see: (a) Halim, R.; Brimble, M. A.; Merten, J. *Org. Lett.* **2005**, *7*, 2659–2662. (b) O'Connor, P., D.; Knight, C. K.; Friedrich, D.; Peng, X.; Paquette, L. A *J. Org. Chem.* **2007**, *72*, 1747–1754. (c) Aho, J. E.; Salomaki, E.; Rissanen, K.; Pihko, P. M. *Org. Lett.* **2008**, *10*, 4179–4182.

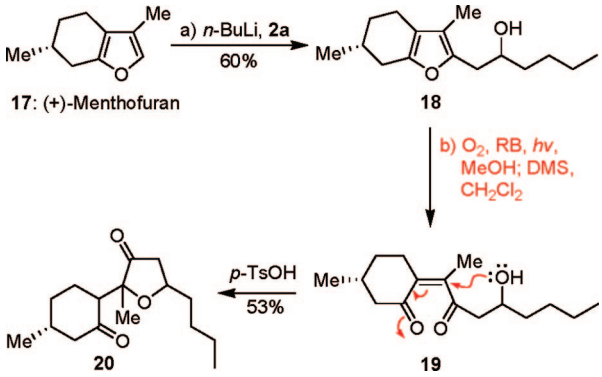
(9) For total synthesis, see: Smith, A. B., III; Fukui, M.; Vaccaro, H. A.; Empfield, J. R. *J. Am. Chem. Soc.* **1991**, *113*, 2071–2092.

(10) For total synthesis, see: Smith, A. B., III; Rivero, R. A.; Hale, K. J.; Vaccaro, H. A. *J. Am. Chem. Soc.* **1991**, *113*, 2092–2112.

(11) For total synthesis, see: Smith, A. B., III; Hale, K. J.; Vaccaro, H. A.; Rivero, R. A. *J. Am. Chem. Soc.* **1991**, *113*, 2112–2122.

tuted olefinic carbon. In order to expand the limitations of the newly developed protocol, 2-(β-hydroxyalkyl) furan **18** (Scheme 6) was synthesized starting from commercially

Scheme 6. Application of Developed Protocol for 2-(β-Hydroxyalkyl)-3-substituted Furan **18**



available (+)-menthofuran (**17**). The important characteristic of this substrate is the substitution at the 3-position of the furan (with a methyl group). Gratifyingly, application of the developed technology to furan **18** led to the formation of desired compound **20** (as a mixture of three diastereoisomers). The less polar and major diastereoisomer is separable from the other two by column chromatography and has the *anti* relative stereochemistry in the 3-keto-tetrahydrofuran ring (based on NOE studies). The major diastereoisomer of the remaining more polar inseparable mixture (dr = 3:1) also has the *anti* relative stereochemistry in the 3-keto-tetrahydrofuran ring.

In summary, a rapid and highly efficient synthesis of a range of variably substituted 3-keto-tetrahydrofuran motifs starting from readily accessible furan precursors has been developed and explored. This new strategy for the one-pot synthesis of 3-keto-tetrahydrofurans from furans makes use of an attractive singlet-oxygen-mediated cascade reaction sequence.

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Supporting Information Available: Experimental procedures, full spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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