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# $\gamma$-Spiroketal $\gamma$-Lactones from 2-($\gamma$-Hydroxyalkyl)furans: Syntheses of *epi*-Pyrenolides D and Crassalactone D

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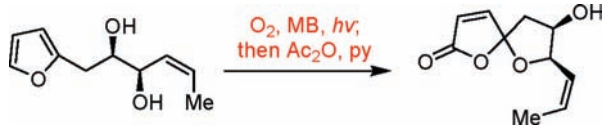
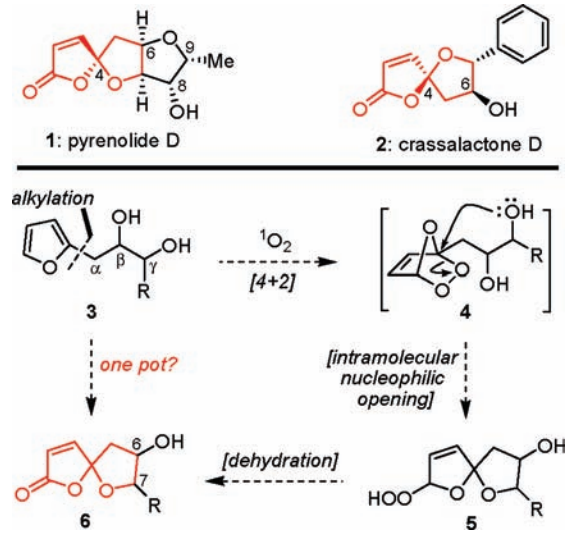
## ABSTRACT




**Photooxygenation of 2-($\gamma$-hydroxyalkyl)furans followed by dehydration affords, in one synthetic operation and in high yield, $\gamma$-spiroketal $\gamma$-lactones. This newly developed technology was successfully applied to the synthesis of three different epimers of pyrenolide D, as well as to the first synthesis of the anticancer natural product crassalactone D and its C4-epimer.**

As a continuation of our interest 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 photooxygenation of 2-($\gamma$-hydroxyalkyl)furans[2] as a means of preparing $\gamma$-spiroketal $\gamma$-lactones. $\gamma$-Spiroketal $\gamma$-lactones are important because they exist in a wide variety of key biologically active natural products, including pyrenolide D[3] (**1**, Scheme 1, $IC_{50} = 4$ $\mu$g/mL against HL-60), crassalactone D[4] (**2**, Scheme 1, $ED_{50} = 1.1$ $\mu$g/mL against P-388, 3.3 $\mu$g/mL against KB, 4.0 $\mu$g/mL against Col-2, 3.2 $\mu$g/mL against BCA-1 and 3.1 $\mu$g/mL against ASK), and the stemoninine family.[5]

**Scheme 1.** The Concept




A crucial common feature of the $\gamma$-spiroketal $\gamma$-lactone moieties of pyrenolide D and crassalactone D is the presence of an oxygen atom at C6 (part of a THF ring in the case of **1** and as a free −OH in the case of **2**). Previous studies have

(1) For recent accounts, see: (a) Montagnon, T.; Tofi, M.; Vassilikogiannakis, G. *Acc. Chem. Res.* **2008**, *41*, 1001–1011. (b) Margaros, I.; Montagnon, T.; Tofi, M.; Pavlakos, E.; Vassilikogiannakis, G. *Tetrahedron* **2006**, *62*, 5308–5317.

(2) For a general review of furan photooxygenation, see: Feringa, B. L. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 469–488.

(3) For isolation see: (a) Nukina, M.; Hirota, H. *Biosci. Biotech. Biochem.* **1992**, *56*, 1158. For total synthesis, see: (b) Engstrom, K. M.; Mendoza, R. M.; Villalobos, N. M.; Yin, Y. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 1128–1130. For synthesis of analogues, see: (c) Robertson, J.; Stevens, K.; Naud, S. *Synlett* **2008**, 2083–2086.

(4) Tuchinda, P.; Munyoo, B.; Pohmakotr, M.; Thinapong, P.; Sophasan, S.; Santisuk, T.; Reutrakul, V. *J. Nat. Prod.* **2006**, *69*, 1728–1733.

(5) Lin, L.; Zhong, Q. X.; Cheng, T. Y.; Tang, C. P.; Ke, C. Q.; Lin, G.; Ye, Y. *J. Nat. Prod.* **2006**, *69*, 1051–1054.

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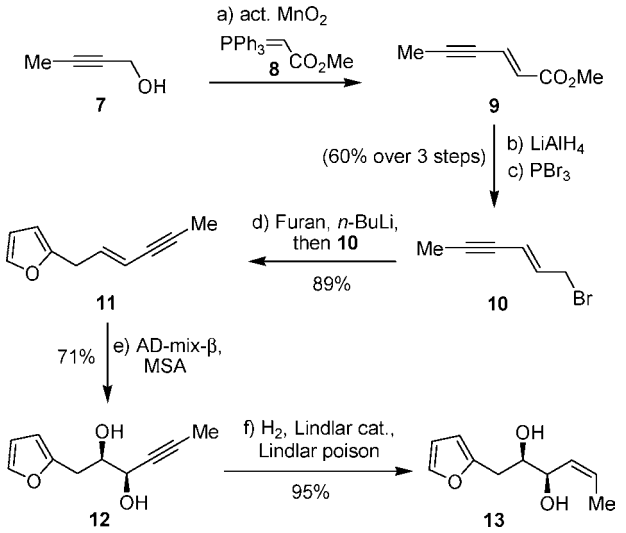
explored the outcome of furan photooxygenation sequences wherein a substrate is used that bears a $\beta$-,[6] $\gamma$- or $\delta$-hydroxyl[7] appended to the 2-alkyl substituent. In this new study, the substrate bears two adjacent hydroxyls at both $\beta$- and $\gamma$-positions of the 2-alkyl substituent (**3**, Scheme 1). An intramolecular nucleophilic opening of a furan endoperoxide[8] (**4**, Scheme 1) might be expected to afford the corresponding [5,5] spirocyclic hydroperoxide **5**, which should then be possible to dehydrate yielding the desired $\gamma$-spiroketal-$\gamma$-lactone **6** as the final result of the one-pot reaction sequence.

The photooxygenation precursor **3** (Scheme 1) bearing the requisite adjacent oxygen functionalities at the $\beta$ and $\gamma$ positions of the alkyl side chain can be easily generated by alkylation of furan with an allylic bromide and dihydroxylation of the resultant double bond. The required double-bond geometry for the alkylating agent can be found by examining the relative stereochemistry at the C6 and C7 positions of the final products (i.e., *trans*-geometry in the case of pyrenolide D but *cis*-geometry for crassalactone D).

Beginning with pyrenolide D (**1**) as the target, the synthesis of the requisite photooxygenation precursor furan **13** is described in Scheme 2. Thus, oxidation of 2-butyn-1-ol (**7**)

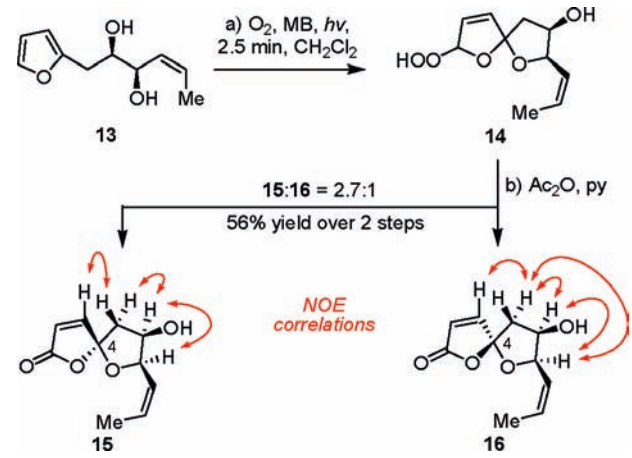
**Scheme 2.** Synthesis of the Photooxygenation Precursor **13**




followed by in situ[9] Wittig reaction with stabilized ylide **8** affords ester **9** accompanied by its easily separable *cis* isomer (*trans*/*cis* = 4:1). Reduction of ester **9** with $LiAlH_4$, followed by bromination of the resulting allylic alcohol using $PBr_3$, gave allylic bromide **10**. Furyllithium alkylation with allylic bromide **10** gave rise to the monosubstituted furan **11**, which then became the subject of a Sharpless dihydroxylation[10] and subsequent Lindlar hydrogenation to furnish the desired furan **13**.

Furan **13** was then subjected to a standard set of $^1O_2$ photooxygenation conditions (methylene blue as photosensitizer, oxygen bubbling through the reaction mixture, and irradiation with visible spectrum light) for 2.5 min to afford an equimolar mixture of the four possible diastereomeric spiro-hydroperoxides **14** (Scheme 3). Treatment of the crude

**Scheme 3.** Photooxygenation of Furan **13** to $\gamma$-Spiroketal $\gamma$-Lactones **15** and **16**




hydroperoxides **14** with acetic anhydride in pyridine[11] gave a chromatographically separable diastereomeric mixture of $\gamma$-spiroketal $\gamma$-lactones (**15**/**16** = 2.7:1) in 56% yield over the two steps. NOE experiments proved that the stereochemistry of the major diastereoisomer **15** is identical to that of pyrenolide D, while the stereochemistry of the spiro center (C4) of the minor diastereoisomer **16** is the opposite to that of the natural product (see NOEs, Scheme 3). The formation of amounts of the minor stereoisomer **16** did not present an obstacle to the synthesis since the isomerization of 4-*epi*-pyrenolide D to natural pyrenolide D under acidic conditions (8 N aq HCl) is known.[3b]

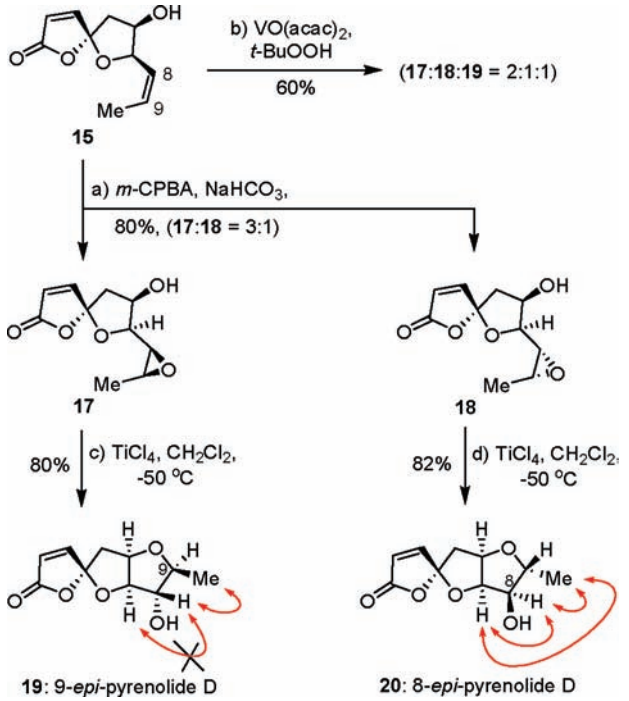
With $\gamma$-spiroketal $\gamma$-lactone **15** in hand, we hoped to complete the synthesis of **1** via epoxidation of the *cis* C8−C9 double bond followed by a 5-*endo* epoxide opening. *m*-CPBA epoxidation afforded a separable mixture of **17** and **18** in a 3:1 ratio and in 80% total yield (Scheme 4). The stereochemistry of the two epoxides remained uncertain at this stage (NOE experiments are not useful because of rotation of the epoxy side chain). An alternative epoxidation of **15** using $VO(acac)_2$ and *t*-BuOOH was also examined. This resulted in the formation of a 2:1 mixture of the expected epoxides **17** and **18**, accompanied by a substantial amount of a new product **19**, whose $^1H$ and $^{13}C$ NMR data are very similar, but not identical, to that of pyrenolide D. At this stage, it was thought that the new product **19** might be a diastereoisomer of pyrenolide D which came from 5-*endo* opening of the stereochemically incorrect epoxide **18**.

In order to verify this suspicion and before undertaking any NOE studies on compound **19**, the 5-*endo* opening of epoxides

(6) Tofi, M.; Koltsida, K.; Vassilikogiannakis, G. *Org. Lett.* **2009**, *11*, 313–316.

(7) (a) Feringa, B. L.; Butselaar, R. J. *Tetrahedron Lett.* **1982**, *23*, 1941–1942. (b) Feringa, B. L.; Butselaar, R. J. *Tetrahedron Lett.* **1983**, *24*, 1193–1196. (c) Georgiou, T.; Tofi, M.; Montagnon, T.; Vassilikogiannakis, G. *Org. Lett.* **2006**, *8*, 1945–1948. (d) Tofi, M.; Montagnon, T.; Georgiou, T.; Vassilikogiannakis, G. *Org. Biomol. Chem.* **2007**, *5*, 772–777.

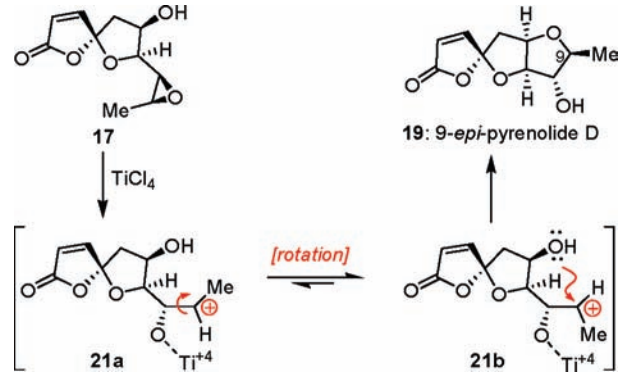
**Scheme 4.** From $\gamma$-Spiroketal $\gamma$-Lactones **15** to 9-*epi*- and 8-*epi*-Pyrenolide D




**17** and **18** under acidic conditions was attempted in the hope that this would furnish pyrenolide D (**1**). After much experimantation it became obvious that employing Brønsted acids, such as PPTS and CSA, which had previously been used[12] for similar 5-*endo* cyclizations, left epoxide **17** completely untouched. A careful observation of the literature substrates[12] revealed the presence of a phenyl group which stabilizes the developing positive charge during the epoxide opening. For this reason, Lewis acidic conditions were next tested to see whether they could accomplish the desired 5-*endo* cyclization. Treatment of **17** with $AlMe_3$ gave a mixture of unidentified byproducts, while the use of $ZnCl_2$ resulted in a 60% conversion of the starting epoxide **17** to the previously synthesized compound **19**. Complete conversion of epoxide **17** to **19** (80% yield) was achieved by employing $TiCl_4$ at −50 °C (Scheme 4). Extensive NOE studies now proved that compound **19** was in fact identical to pyrenolide D except in the stereochemistry at C9 (see NOEs, Scheme 4). Application of the developed epoxide opening conditions ($TiCl_4$, −50 °C) to **18** afforded, in 82% yield, compound **20** which differed from pyrenolide D only in the stereochemisty at the C8 position (see NOEs, Scheme 4).

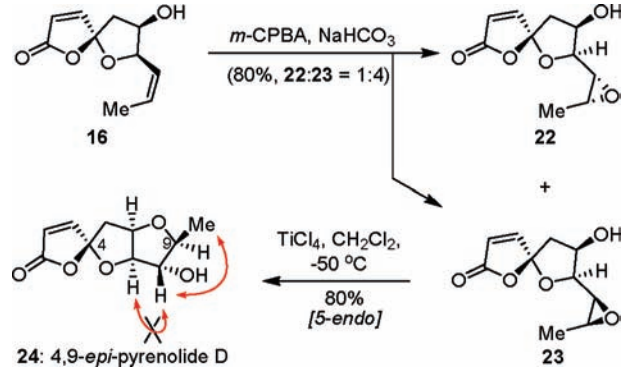
A possible mechanistic explanation for the unexpected stereochemical outcomes for the 5-*endo* cyclizations of epoxides **17** and **18** is the formation of the carbocation intermediate **21a** (starting from **17**, Scheme 5), which has a long enough lifetime to allow for rotation around the C8−C9 bond. Thus, the less hindered carbocation **21b** is attained, which then undergoes a cyclization reaction to give 9-*epi*-pyrenolide D (**19**). Invoking this mechanistic rationale invalidates the careful choice of a *cis* C8−C9 double bond in the epoxidation substrate, since exactly the same stereochemical outcome is now expected regardless of the geometry of the starting C8−C9 double bond.

**Scheme 5.** Mechanistic Rationale for 5-*Endo* Cyclization




A similar stereochemical outcome was observed when the establised conditions (*m*-CPBA epoxidation followed by treatment with $TiCl_4$) were applied to $\gamma$-spiroketal $\gamma$-lactone **16** and its major epoxidation product **23**. This sequence led to the formation of the expected diastereoisomer of pyrenolide D (**24**, Scheme 6).

**Scheme 6.** From Spirolactone **16** to 4,9-*epi*-Pyrenolide D




Despite not having been able to synthesize pyrenolide D (**1**) itself during the course of our successful syntheses of a number of pyrenolide D epimers (**19**, **20**, and **24**), a very

(8) For the first isolation of reasonable quantities of highly sensitive furan endoperoxides, see: (a) Gollnick, K.; Griesbeck, A. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 726–727. For nucleophilic opening of furan endoperoxides, see: (b) Foote, C. S.; Wuesthoff, M. T.; Wexler, S.; Burstain, I. G.; Denny, R.; Schenck, G. O.; Schulte-Elte, K. H. *Tetrahedron* **1967**, *23*, 2583–2599. (c) Peters, K.; Peters, E. M.; Schnering, H. G.; Griesbeck, A.; Gollnick, K. *Z. Kristallogr.* **1984**, *168*, 153. (d) Gollnick, K.; Griesbeck, A. *Tetrahedron* **1985**, *41*, 2057–2068.

(9) Wei, X.; Taylor, R. J. *Tetrahedron Lett.* **1998**, *39*, 3815–3818.

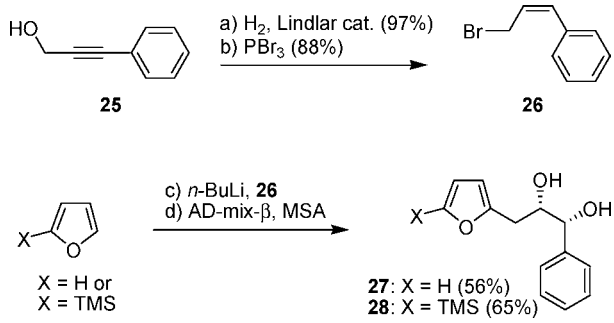
(10) For a review, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.

(11) (a) Naya, K.; Shimizu, M.; Nishio, H.; Takeda, M.; Oka, S.; Hirota, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1071. (b) Fall, Y.; Vidal, B.; Alonso, D.; Gomez, G. *Tetrahedron Lett.* **2003**, *44*, 4467–4469.

(12) Harris, M. J.; O'Doherty, A. G. *Tetrahedron* **2001**, *57*, 5161–5171.

reliable strategy for the synthesis $\gamma$-spiroketal $\gamma$-lactones had been developed. We next sought to apply this rapid and efficient method to the synthesis of the recently isolated[4] and biologically active member of the crassalactone family of natural products, crassalactone D (**2**). In a four-step, high-yield reaction sequence, two different photooxygenation precursors **27** and **28** were synthesized (Scheme 7).

**Scheme 7.** Synthesis of the Photooxygenation Precursors **27** and **28**

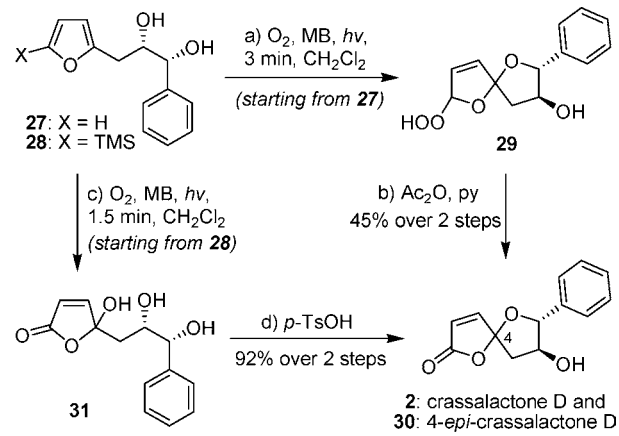



Photooxygenation of furan **27** under standard conditions (methylene blue as photosensitizer, oxygen bubbling through the reaction mixture, and irradiation with visible spectrum light) for 3 min afforded a mixture of the four possible diastereomeric spiro-hydroperoxides **29**. Treatment of this mixture with $Ac_2O$ in pyridine afforded a mixture of the natural product crassalactone D (**2**) and its 4-epimer (Scheme 8, **2**/**30** = 1.5:1) in 45% overall yield. Very careful chromatographic separation afforded pure crassalactone D (**2**), whose $^1H$ and $^{13}C$ NMR were identical to the natural compound, and its 4-epimer **30**.

The moderate overall yield (45%) of the last two steps (**27** → **29** → **2** + **30**) prompted us to turn our attention to the photooxygenation of 2-silylfuran **28**. It is known[13] that 2-silylfuran photooxyganation leads to the formation of 4-hydroxybutenolides. Indeed, 1.5 min photooxygenation of 2-silylfuran **28**, under the same conditions that had been

(13) For the silyl stabilization concept, see: (a) Adam, W.; Rodriguez, A. *Tetrahedron Lett.* **1981**, *22*, 3505–3508. For use in the regiospecific synthesis of 4-hydroxybutenolides, see: (b) Katsumura, S.; Hori, K.; Fujiwara, S.; Isoe, S. *Tetrahedron Lett.* **1985**, *26*, 4625–4628. For direct comparisons between the photoxygenations of silyl- and unsubstituted furans, see: (c) Bury, P.; Hareau, G.; Kocieński, P.; Dhanak, D. *Tetrahedron* **1994**, *50*, 8793–8808. (d) Shiraki, R.; Sumino, A.; Tadano, K.; Ogawa, S. *J. Org. Chem.* **1996**, *61*, 2845–2852.

**Scheme 8.** Photooxyganation of Furans **27** and **28** to Crassalactone D and Its 4-Epimer




previously used, afforded a mixture of two diastereomeric hydroxybutenolides **31**, which were ketalized in situ upon treatment with *p*-TsOH to furnish a mixture of crassalactone D (**2**) and its 4-epimer **30** in excellent overall yield (92%, Scheme 8). Complete ketalization was observed after 30 min of treatment with *p*-TsOH, and the **2**/**30** ratio afforded was 1:1.8. Prolonged treatment with *p*-TsOH (18 h) gave the previously observed thermodynamic ratio of **2**/**30** = 1.5:1.

In summary, a rapid and highly efficient strategy, beginning with a simple furan aklylation, proceeding with double bond dihydroxylation, and ending with a singlet oxygen ($^1O_2$) furan oxidation, has been introduced for the preparation of the important $\gamma$-spiroketal $\gamma$-lactone motif. This strategy was successfully applied to the syntheses of three different epimers of pyrenolide D, as well as to the first synthesis of crassalactone D and its 4-epimer.

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**Supporting Information Available:** Experimental procedures, full spectroscopic data, and copies of $^1H$ 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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