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Spiroperoxy Lactones from Furans in One Pot: Synthesis of (+)-Premnalane A

Ioannis Margaros, Tamsyn Montagnon, and Georgios Vassilikogiannakis*

Department of Chemistry, University of Crete, Vasilika Vouton, 71003 Iraklion, Crete, Greece

vasil@chemistry.uoc.gr

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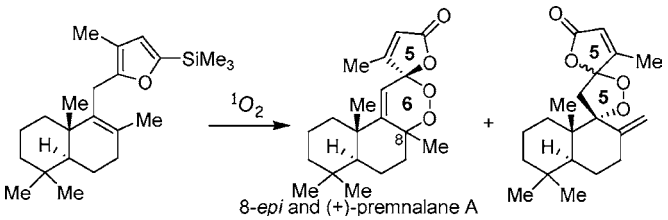
ABSTRACT



A [4+2]-cycloaddition between singlet oxygen and a furan, followed by an ene reaction and ketalization, in one synthetic operation, was used for the synthesis of (+)-premnalane A. The first example of a singlet oxygen ene reaction that furnishes exclusively a *Z*-double bond is noted.

Singlet oxygen ($^1O_2$) has considerable unmined potential as a synthetic tool. It is a highly reactive yet selective oxidant (protecting groups are rendered essentially redundant), which is readily generated. Furthermore, it is an excellent mediator of cascade reaction sequences. Recent work from our group has focused on designing and implementing such sequences, which use singlet oxygen's unique reactivity, to target a selection of different natural products.[1] It was in this context that we developed an interest in the rare γ-spiroperoxy lactone motif **F** (Scheme 1) of premnalane A,[2] an antibacterial natural product isolated from the shrub, *Premna oligtricha*, found in the Sidamo province of Ethiopia.[3]

Our first approach to the synthesis of premnalane A had, at its heart, a [4+2]-addition between $^1O_2$ and a diene; however, this approach failed.[4] In the light of this result, our strategy for the synthesis of premnalane A's unique γ-spiroperoxy lactone core was updated (Scheme 1). In the new proposal, two different modes of $^1O_2$ reaction, a [4+2]-cycloaddition and an ene reaction, were to be called upon to stitch up the spirolactone unit in an efficient one-pot operation. Thus, a [4+2]-cycloaddition[5] between the initial substrate's furan moiety and $^1O_2$, furnishing a 4-hydroxybutenolide portion (**A** → **B**, Scheme 1), would initiate the reaction sequence with an ene reaction following immediately afterward. There are a number of possible outcomes to the ene reaction resulting from the different orientations and pathways open to the intermediates. We deconvoluted these issues in our planning, by applying known mechanistic details regarding ene reactions (such as the cis-effect[6] and the large group effect[7]) to the premnalane A system. From hydroxybutenolide **B**, there are two possible sites for hydrogen abstraction, sites **a** and **b**. Precedent suggests that in the simplest systems abstraction from site **a** predominates;

(1) (a) Vassilikogiannakis, G.; Stratakis, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5465−5468. (b) Vassilikogiannakis, G.; Margaros, I.; Montagnon, T.; Stratakis, M. *Chem. Eur. J.* **2005**, *11*, 5899−5907. (c) Sofikiti, N.; Tofi, M.; Montagnon, T.; Vassilikogiannakis, G.; Stratakis, M. *Org. Lett.* **2005**, *7*, 2357−2359. (d) Georgiou, T.; Tofi, M.; Montagnon, T.; Vassilikogiannakis, G. *Org. Lett.* **2006**, *8*, 1945−1948. (e) Tofi, M.; Montagnon, T.; Georgiou, T.; Vassilikogiannakis, G. *Org. Biomol. Chem.* **2007**, *5*, 772−777.

(2) Premnalane A is our designation for the natural product **1** that was given only an IUPAC descriptor by the isolation team (see ref 3).

(3) Habtemariam, S.; Gray, A. I.; Lavaud, C.; Massiot, G.; Skelton, B. W.; Waterman, P. G.; White, A. H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 893−896.

(4) Margaros, I.; Montagnon, T.; Tofi, M.; Pavlakos, E.; Vassilikogiannakis, G. *Tetrahedron* **2006**, *62*, 5308−5317.

(5) 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.

(6) Stephenson, L.; Grdina, M. J.; Orfanopoulos, M. *Acc. Chem. Res.* **1980**, *13*, 419−425.

(7) For a review on regioselectivity in the ene reaction of $^1O_2$ with alkenes, see: Stratakis, M.; Orfanopoulos, M. *Tetrahedron* **2000**, *56*, 1595−1615.

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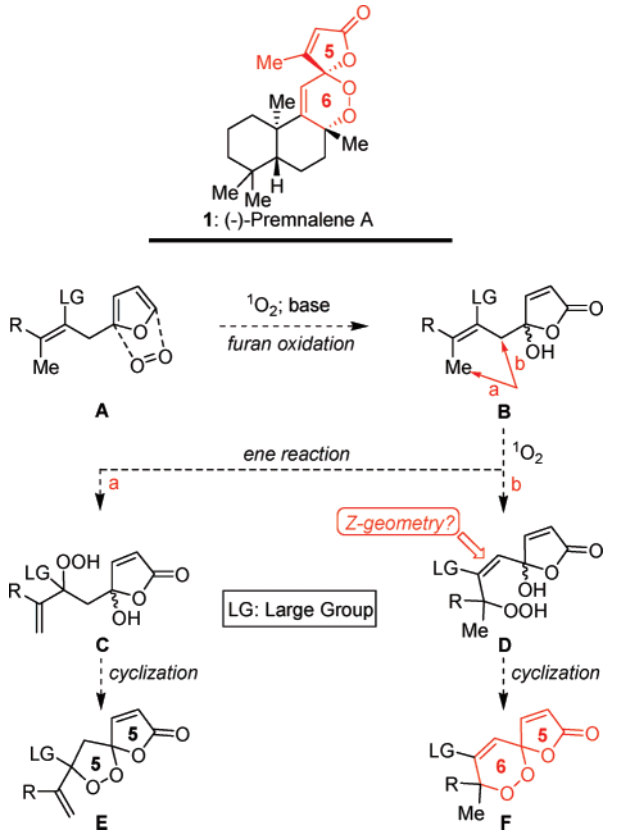
Scheme 1. The Concept

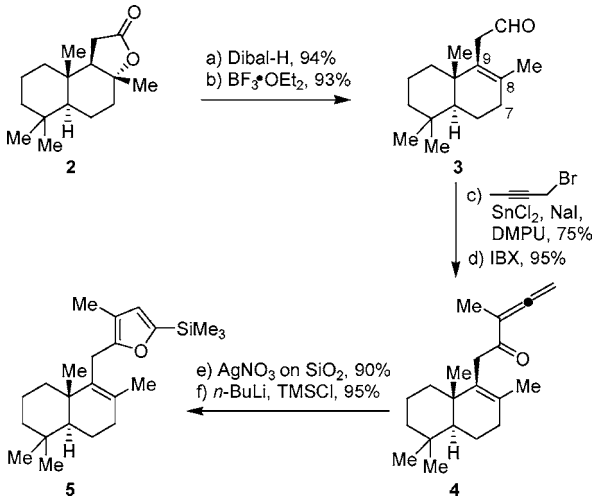


however, when the starting double bond is substituted with a large group (LG), abstraction of type **b** has been shown to eclipse site **a** abstraction (the so-called large group effect).[8] In the case of premnalane A, there is more than one large group (the decalin ring and the 4-hydroxybutenolide) as well as considerable restriction on the conformational and rotational freedom of various key bonds and positions. As a result, we were unsure of exactly how the premnalane A system might react. Finally, a very unusual feature was required from the sequence if success were to be ensured; the double bond formed in the ene reaction would need to have Z-geometry (intermediate **D**, Scheme 1) for the final cyclization step to be accomplished. This geometrical preference has not been reported previously, but we felt that the large steric demands of the 4-hydroxybutenolide and the decalin ring might conspire to help us attain this unprecedented geometry. Despite its risky nature, we felt the sequence held enough potential to be worth investigating in the laboratory.

The decalin system of (+)-sclareolide (**2**, Scheme 2), the chosen starting point for our synthetic investigation, is enantiomeric to that reported for premnalane A, but this difference in absolute stereochemistry was not relevant to our primary goal which was a thorough investigation of the proposed singlet oxygen-mediated reaction sequence.

(8) Orfanopoulos, M.; Stratakis, M.; Elemes, Y. *J. Am. Chem. Soc.* **1990**, *112*, 6417−6419.

Scheme 2. Synthesis of the Key Precursor **5**



Our first task was to install the requisite furan moiety. To this end, we began by reducing the lactone functionality of **2** to the corresponding lactol using Dibal-H (94%, 8:1 lactol/open hydroxyaldehyde). Elimination of the tertiary alcohol using BF_3•OEt_2 (fast addition) furnished aldehyde **3** (contaminated with minor amounts of the $\Delta^{7,8}$ regioisomer, $\Delta^{8,9}$/$\Delta^{7,8}$ 18:1, Scheme 2) in 93% combined yield. The furan was then constructed in three steps using the method of Marshall[9] as modified by Winkler et al.[10] The organostannane, derived from 1-bromo-2-butyne,[11] was added to aldehyde **3** to afford a diastereomeric mixture of allenic alcohols in 75% yield. These alcohols were oxidized to the corresponding allenic ketone **4** using IBX (95% yield). Treatment of allenic ketone **4** with $AgNO_3$ on silica gel furnished the desired furan (90% yield). Before attempting the singlet oxygen cascade sequence, a silyl group was smoothly introduced onto the furan (**5**, 95%). This functionality has been shown to dramatically improve the yield of the transformation of furan-derived endoperoxides into 4-hydroxybutenolides (the first steps of the proposed reaction sequence).[12] The substrate for the singlet oxygen-mediated reaction sequence had now been successfully synthesized in a very straightforward manner (53% overall yield for six steps).

The stage was now set to investigate if we could assemble the entire endoperoxy-spirolactone unit in one-pot. We began by validating each key step. Neutralized $CDCl_3$ (K_2CO_3) was initially employed as the solvent to monitor the reaction's progress by ^1H NMR (Scheme 3). When furan **5** was treated with $^1O_2$ [generated by bubbling air gently through the

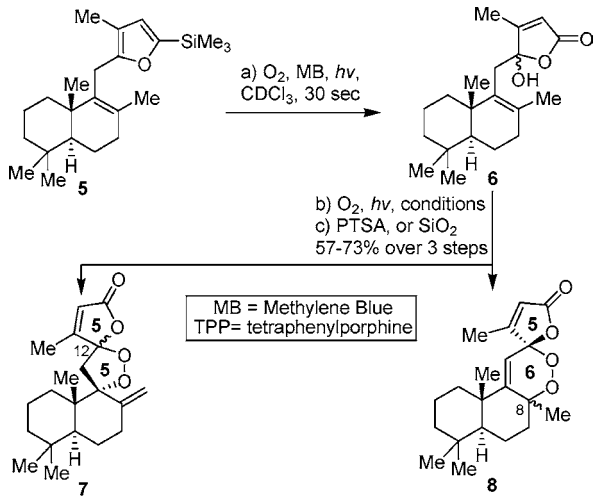
(9) (a) Marshall, J. A.; Wang, X.-J. *J. Org. Chem.* **1991**, *56*, 960−969. (b) Marshall, J. A.; Bartley, G. S. *J. Org. Chem.* **1994**, *59*, 7169−7171. (c) Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1995**, *60*, 5966−5968.

(10) Winkler, J. D.; Quinn, K. J.; MacKinnon, C. H.; Hiscock, S. D.; McLaughlin, E. C. *Org. Lett.* **2003**, *5*, 1805−1808.

(11) Mukaiyama, T.; Harada, T. *Chem. Lett.* **1981**, 621−624.

(12) For the introduction of the stabilizing effect of the silyl substituent, see: Adam, W.; Rodriguez, A. *Tetrahedron Lett.* **1981**, *22*, 3505−3508. For direct comparisons between photooxygenations of silyl- and unsubstituted furans, see: (a) Bury, P.; Hareau, G.; Kocieñski, P. J.; Dhanak, D. *Tetrahedron* **1994**, *50*, 8793−8808. (b) Shiraki, R.; Sumino, A.; Tadano, K.; Ogawa, S. *J. Org. Chem.* **1996**, *61*, 2845−2852.

Scheme 3. Validation of the Proposed Reaction Sequence and Synthesis of (+)-premnalene A (**8b**)



conditions	7:8	7a:7b	8a:8b
$CDCl_3$, MB, 8 °C	2:1	10:1	1:1
MeOH, MB, 8 °C	4:1	1:3	1:1
toluene, TPP, 8 °C	1.3:1	1.7:1	1:1
toluene, TPP, 65 °C	1.2:1	1:1	1:1

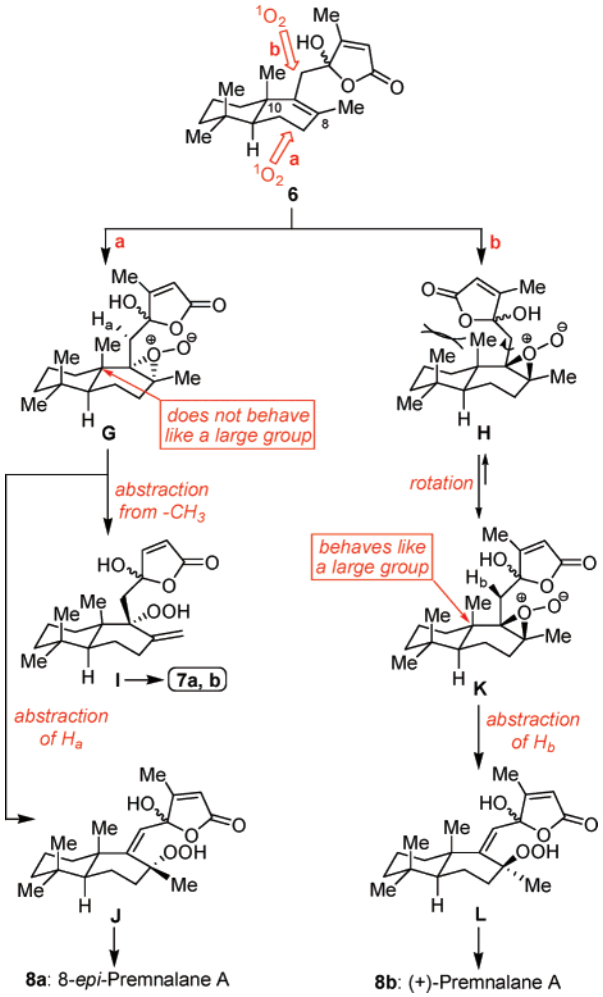
reaction solution containing catalytic amounts (10^{-4} M) of the sensitizer methylene blue, at 8 °C, in the presence of visible spectrum light] for 30 s we observed the smooth formation of the 4-hydroxybutenolide **6** (by ^{1}H NMR). If the irradiation time was extended to 3 min we observed the formation of allylic hydroperoxides from an ene reaction, (**I**, **J**, and **L**, Scheme 4). These hydroperoxides were cyclized in the desired manner on treatment with catalytic PTSA (**7**/**8**, 2:1; overall yield for three steps, 62%). The two different γ-spiroperoxy lactones, **7** and **8**, could be separated readily by column chromatography. Thus, we had validated each individual step of our proposed cascade reaction sequence, and, in so-doing, synthesized (+)-premnalane A (**8b**). That one of the diastereoisomers of **8** was indeed (+)-premnalane A was confirmed by X-ray crystallography (Figure 1).[13] Furthermore, extensive NOE studies clarified that in the case of **7**, both spirocycle isomers at C-12 were present, whereas, with **8**, only one spirocycle stereochemistry was observed, but both stereoisomers of the C-8 center were present (Figure 1).

We next attempted to complete the sequence as a one-pot operation. This objective was readily achieved; if neutralized $CDCl_3$ was replaced with untreated $CHCl_3$, furan **5** could be transformed directly into the endoperoxy spirolactone products **7** and **8** (after 2.5 min of irradiation followed by treatment for 30 min with catalytic amount of SiO_2) in an overall yield of 73% (**7**/**8**, 2:1).

With hope of improvements in the yield of premnalane A (**8b**), we sought to investigate the effect of changes to the

(13) CCDC 658553 contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Scheme 4. Mechanistic Rationale



reaction conditions on the one-pot operation. Changes in solvent could indeed engineer the desired changes in the

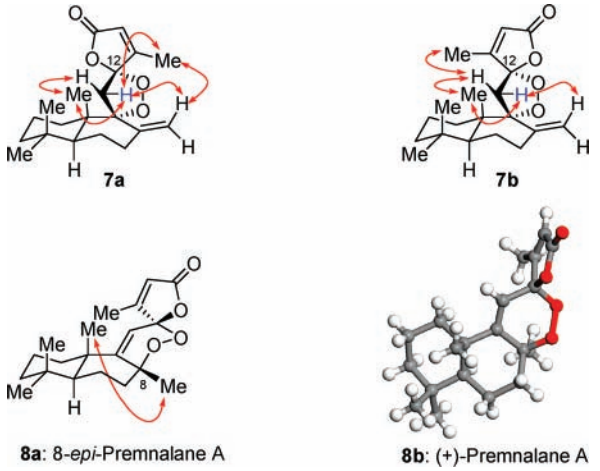


Figure 1. Selected NOE's observed for **7a**, **7b**, and **8a** and ORTEP representation obtained for (+)-premnalene A (**8b**).

product distribution. Thus, when $CHCl_3$ was exchanged with highly polar MeOH, the undesired [5,5]-spirocycle **7** was strongly favored over the desired [6,5]-spirocyclic compound **8** (**7**/**8**, 4:1); however, when a nonpolar solvent such as toluene was employed the ratio improved significantly in favor of the desired [6,5]-spirocyclic compound **8** (**7**/**8**, 1.3:1). Increasing the reaction temperature (from 8 to 65 °C) made no significant change in the [5,5]-spirocyclic to [6,5]-spirocyclic product ratio. Within the product distribution, the two diastereomeric relationships are also of interest. The **8a**/**8b** ratio remains unchanged, independent of reaction conditions; this feature is in stark contrast to the **7a**/**7b** ratio, which varies according to the reaction conditions. Presumably, in the case of **7a**/**b**, the spirocyclic center may equilibrate so that the ratio is dependent on the conditions, whereas, with **8a**/**b** the C-8 center is fixed during the course of the reaction.

Tracing the source of each of these four different reaction products provides an interesting analysis of the competing factors at work in this series of reactions (Scheme 4). Thus, singlet oxygen may approach either one of the two faces of the double bond in the ene reaction (approach **a** or **b**). The face opposite the C-10 methyl group is favored because it avoids a steric clash between the incoming electrophile and the aforementioned methyl group (see Scheme 4, approach **a**, **6** → **G**). The resultant perepoxide sits so that stabilization from its interaction with allylic hydrogens is maximized, as shown in intermediate **G**.[6] From the final product distribution we know that hydrogen abstraction then occurs mainly from the C-8 methyl group (**G** → **I**). In other words, in this case the decalin ring system (C-10) is not behaving like a large group and the large group effect[8] is not observed (minor amounts of the product wherein H_a is abstracted are also seen, **G** → **J**). Cyclization of **I** then furnishes a mixture of spirocycles **7a**,**b** (variable ratios depending on reaction conditions) at the newly formed spirocycle center, while cyclization of the minor isomer **J** furnishes 8-*epi*-premnalane A (**8a**) only. Returning to the original approach of singlet oxygen to the double bond, when approach **b** is followed we see a different set of influences. Here, the C-10 methyl group on the decalin bridge now sits adjacent to, and on the same face as, the perepoxide (oriented as shown in intermediate **H** to maximize allylic interactions[6]). Thus it forces the decalin substituent (C-10) to act as a large group, and the large group effect is observed in the subsequent ene reaction.[8] In other words, only hydrogen H_b is abstracted (**K** → **L**). Furthermore, to avoid steric clashes between the 4-hydroxybutenolide and the decalin skeleton (shown in intermediate **H**), H_b is abstracted in such a manner that the double bond formed from this reaction has exclusively the *Z*-geometry (**L** but also **G** → **J**). A double bond with Z-geometry arises from the ene reaction of $^1O_2$, and a double bond is, to the best of our knowledge, without precedent[7] and as such provides an appropriate climax to this ambitious one-pot reaction sequence. The hydroperoxide product **L** then cyclizes to give a single spirocycle stereoisomer, (+)-premnalane A (**8b**).

In conclusion, we have synthesized (+)-premnalane A using a remarkable $^1O_2$-mediated one-pot reaction sequence which first employs a [4+2]-cycloaddition between $^1O_2$ and a furan, then a $^1O_2$ ene reaction, and, finally ketalization. Furthermore, we have also noted the first example of an ene reaction of this type that furnishes exclusively a *Z*-double bond.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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