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Synthesis of the Spirocyclic Core of the Prunolides Using a Singlet Oxygen-Mediated Cascade Sequence

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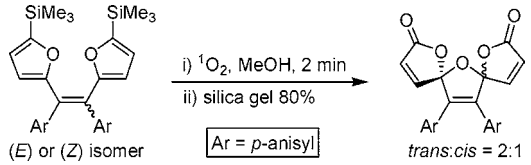
ABSTRACT



A highly efficient and rapid four-step synthesis of the bis-spiroketal core of the prunolide natural products, starting from furan itself, is described. The key step and culmination of the synthesis, responsible for zipping up the spirocyclic core, is a singlet oxygen-orchestrated cascade sequence in which a double photooxygenation of a 1,2-difuryl alkene precursor precedes dehydration and spirocyclization to furnish the intact prunolide core.

Static marine invertebrates are prolific producers of biologically promising and synthetically challenging cytotoxic natural products. In 1999, the existing cohort of secondary metabolites derived from this source was joined by a new class of spirocyclic compounds, the prunolides (A−C, **1**−**3**, Figure 1), isolated from a species of colonial ascidian collected off the Australian coast.[1] When the components of the *Synoicum prunum* cytotoxic extract were examined in detail, it was found that the newly identified prunolides were accompanied by the already known and biogenetically related antibiotic, rubrolide A (**4**, Figure 1). Rubrolide A (**4**) is the lead member of a group of closely related compounds isolated in 1991 and 2000.[2,3]

Our interest in the prunolides was initially piqued by their compact and intricate C_2-symmetric bis-spiroketal core, and by the recurrence of the butenolide motif. This latter characteristic suggested a possible singlet oxygen ($^1O_2$)-mediated entry to the synthesis of these molecules using one particular mode of furan photooxygenation.[4] The bis-spiroketal core, otherwise known only in unnamed marine natural product compound **5** (note: **5** differs from prunolides **1**−**3** in the bis-spiroketal's relative stereochemistry),[5] has not been previously synthesized. Our recent experience of employing $^1O_2$-facilitated reaction cascades in the synthesis of natural products[6] led us to conceive of and pursue a similarly ambitious strategy for the construction of the prunolides. Herein we report the result, a rapid and highly

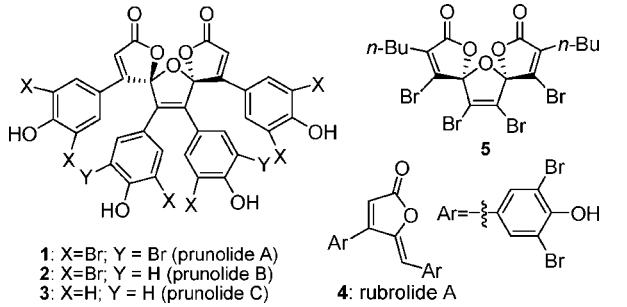


Figure 1. Structures for prunolides A−C (**1**−**3**), rubrolide A (**4**), and unnamed compound **5**.

(1) Carroll, A. R.; Healy, P. C.; Quinn, R. J.; Tranter, C. J. *J. Org. Chem.* **1999**, *64*, 2680−2682.
(2) Miao, S.; Andersen, R. J. *J. Org. Chem.* **1991**, *56*, 6275−6280.
(3) Ortega, M. J.; Zubía, E.; Ocaña, J. M.; Naranjo, S.; Salvá, J. *Tetrahedron* **2000**, *56*, 3963−3967.

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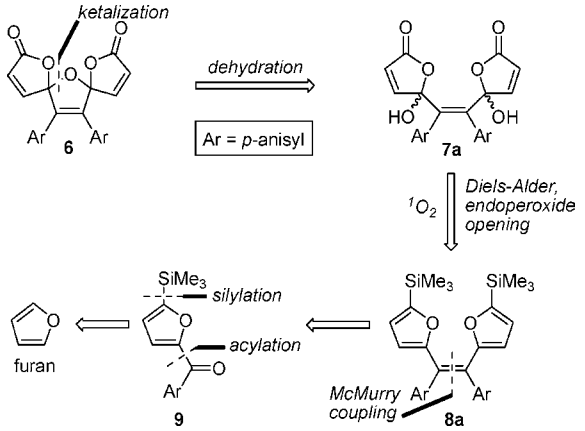
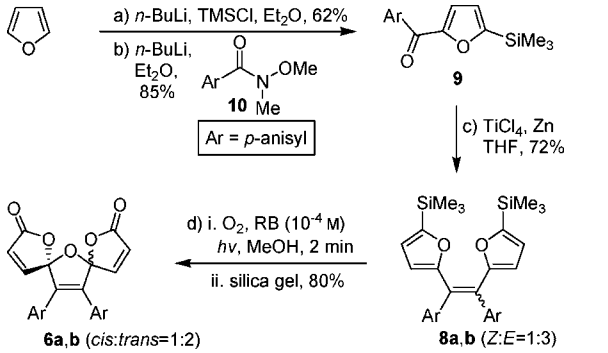
Scheme 1. Retrosynthetic Analysis for the Prunolide Core



Scheme 2. Synthesis of the Prunolide Core



efficient assembly of the intact prunolide core using a strategy that has a powerful one-pot $^1O_2$-orchestrated cascade sequence at its heart.

Our retrosynthetic analysis of the targeted core skeleton is outlined in Scheme 1. We envisaged initially unraveling the tightly bound spirocyclic core **6** to reveal the bis-hydroxy butenolide intermediate **7a**. Literature precedent[4] suggested that this compound **7a** might, in turn, be derived from 1,2-difuryl alkene **8a**. It was at this point that we opted to exploit the inherent symmetry of these molecules; thus, 1,2-difuryl alkene **8a** was retrosynthetically severed in two to reveal the aryl ketone **9**. Aryl ketone **9** was expected to be readily accessible from furan itself, via sequential silylation and acylation reactions.

It is very reasonable to ask why the silylated furan **8a** was selected as the photooxygenation precursor rather than its simpler unsubstituted congener (where H replaces $SiMe_3$). It is well known[4] that unsubstituted furans undergo the desired [4 + 2] cycloaddition with photochemically produced $^1O_2$; however, the transformation of the resulting endoperoxide to the corresponding hydroxyl butenolide by the action of a base[7] is frequently plagued with problems. This propensity toward a poor outcome was confirmed in our case when the unsubstituted analogue of **8** was employed in a test photooxygenation. The reaction failed, prompting us to include the silyl groups in our design from the outset.[8] The use of a stabilizing silyl group was first introduced by Adam and Rodriguez in 1981[9] and has since been successfully applied in many circumstances.[8,10] It should be noted that −CH(R)OH,[11] −CHO,[4b] or −COOH[12] substituents at the 2-position have also been employed to improve the outcome of the photooxygenation reactions of furans.

The starting point for our short synthesis of the prunolide core was furan, which was sequentially substituted, first with a trimethylsilyl group, and then with an aryl ketone, using standard ortho metalation conditions (Scheme 2). Thus, 2-lithiofuran, obtained upon treatment of furan with *n*-BuLi in refluxing ether, was quenched with trimethylsilyl chloride to afford 2-trimethylsilylfuran.[13] The same protocol was then employed to obtain the aryl ketone **9** from 2-trimethylsilylfuran, except this time the 2-lithiofuryl anion was quenched with Weinreb amide **10**.[14] Aryl ketone **9** was successfully dimerized using a McMurry coupling[15] to furnish 1,2-difuryl alkenes **8a** and **8b**, as a separable mixture of *Z*- and *E*-isomers, in good yield (72%; *Z*:*E* ≈ 1:3). The stage was now set for the first attempt at the crucial $^1O_2$-mediated cascade sequence.

The more polar and minor *Z*-isomer **8a**, in MeOH, was subjected to photooxygenation conditions consisting of the gentle bubbling of O_2 through the solution, which also contained the sensitizer, Rose Bengal (10^{-4} M), while visible light irradiation was applied for 2 min. The desired reaction cascade proceeded smoothly to afford an intermediary mixture of the labile diastereomeric bis-hydroxy butenolides (**7a**, Scheme 1, observed by ^1H NMR spectroscopy) that could be dehydrated, upon filtration through a short pad of silica gel, to give the desired, and readily separable, bis-spiroketals **6a** and **6b** in an 80% overall yield (**6a**:**6b** = cis:trans ≈ 1:2). The trans isomer (**6b**) representing the fully intact prunolide core where the spiroketal dipoles oppose one another was the much less polar product, while the cis isomer (**6a**) was the more polar congener because its dipoles

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(8) For direct comparisons between the photooxygenations of silyl- and unsubstituted furans, see: (a) Bury, P.; Hareau, G.; Kocieñski, P.; Dhanak, D. *Tetrahedron* **1994**, *50*, 8793−8808. (b) Shiraki, R.; Sumino, A.; Tadano, K.; Ogawa, S. *J. Org. Chem.* **1996**, *61*, 2845−2852.

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(10) For recent and representative examples, see: (a) Pommier, A.; Stepanenko, V.; Jarowicki, K.; Kocieñski, P. J. *J. Org. Chem.* **2003**, *68*, 4008−4013. (b) Tanaka, K.; Hata, T.; Hara, H.; Katsumura, S. *Tetrahedron* **2003**, *59*, 4945−4952. (c) Furuichi, N.; Hara, H.; Osaki, T.; Nakano, M.; Mori, H.; Katsumura, S. *J. Org. Chem.* **2004**, *69*, 7949−7959.

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(13) Carman, C. S.; Koser, G. F. *J. Org. Chem.* **1983**, *48*, 2534−2539.

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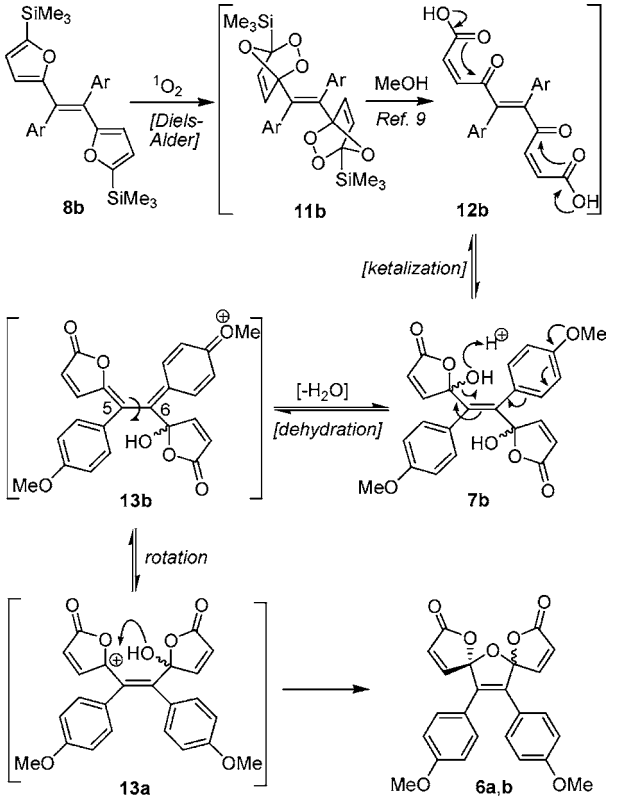
Scheme 3. Mechanistic Rationale for the One-Pot Cascade Sequence Converting the 1,2-Difuryl Alkenes **8a** and **8b** to Spiroketals **6a** and **6b**



are directionally reinforcing. Surprisingly, upon photooxygenation of the major *E*-isomer **8b**, a result identical to that obtained for **8a** was recorded with the facile formation of both isomers of **6** (**6a**:**6b** ≈ 1:2). Thus, the prunolide core **6b** could be accessed from both the *Z*- and the *E*-isomers of 1,2-difuryl alkene **8**.

The photooxygenation outcome can be explained on the basis of the following rationale (Scheme 3), using the (*E*)-difuryl alkene **8b** as the example substrate. The first step in the cascade sequence is a double [4 + 2]-cycloaddition between $^1O_2$ and the two furan moieties of **8b**. Silyl migration followed by methanolysis facilitates the collapse of the endoperoxide adduct **11b** to afford the open-chain carboxylic diacid **12b**.[9] Double ketalization of the carboxylic acids **12b** then affords the corresponding bis-hydroxy butenolide **7b**. Dehydration of the bis-hydroxy butenolide **7b**, mediated by the participation of the methoxy group, may furnish the intermediate cation **13b**. Rotation about the $\Delta^{5,6}$ central bond of **13b** then facilitates the requisite repositioning of the hydroxy butenolide unit such that the remaining hydroxyl group can attack the cation and accomplish the desired zipping up of the spiroketals (**13a**→**6a**,**b**). Exactly the same mechanism applies to the conversion of the *Z*-isomer **8a** into the spiroketals **6a** and **6b**, excluding the rotation around the $\Delta,^{5,6}$ which is not necessary in this instance for ring closure.

Hence, the compact and intricate core of the prunolide natural products was synthesized, starting from furan, using a remarkably efficient four-step reaction sequence culminating in a one-pot cascade orchestrated by $^1O_2$. Once again, the versatility and power of $^1O_2$ in the synthetic context was confirmed.

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Supporting Information Available: Experimental procedures, ^1H and ^{13}C spectra for all new compounds, and HRMS data for key compounds **6a**, **6b**, **8a**, and **8b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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