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LETTERS

Synthesis of seven-membered oxacycles. Part 2: The furan approach

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Abstract—We describe an efficient new approach for the synthesis of seven-membered oxacycles that is based on the oxidation of a furan ring with singlet oxygen followed by an intramolecular Michael addition. © 2003 Elsevier Science Ltd. All rights reserved.

Seven-membered oxacycles are structural units that are present in a wide variety of bioactive natural products,[1] including the monocyclic zoapatanol,[2] the polycyclic hemibrevetoxin B[3] (Fig. 1) and more complex polyether toxins such as ciguatoxin[4] and brevetoxins A and B.[5] Because of their unusual molecular architecture, these molecules are challenging synthetic targets for organic chemists.

We recently described the synthesis of seven-membered oxacycles using methoxyallene as the key starting material.[6] The scope and limitations of this method are being explored, and the results will be published in due course. Prompted by the increasing interest in the synthesis of seven-membered oxacycles in recent years,[7] we have now developed a second approach. The two approaches share one of their starting materials, iodide **2** (Scheme 1), but differ in the other, which in the new method is furan (**1**).

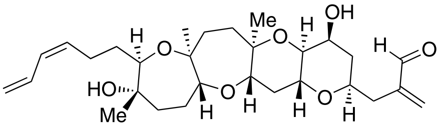
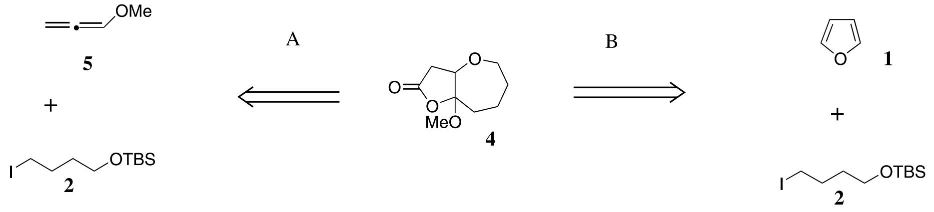


Figure 1. Hemibrevetoxin B.

Iodide **2** was easily obtained by reaction of THF with sodium iodide and TBSCl (Scheme 2). Lithiation of furan (**1**) and reaction with **2** afforded the alkylated furan **7** in 81% yield. Oxidation of **7** with singlet oxygen gave an 82% yield of hydroperoxide **8**,[8] which could be purified by column chromatography but was rather labile, undergoing slow decomposition even when stored at low temperature. Hence freshly purified **8** was immediately reacted with acetic anhydride in pyridine, affording butenolide **9** in 72% yield from **7**. Treatment of **9** with TBAF then not only removed its TBS group, but also led to the bicyclic compound **4**[8] through an intramolecular Michael addition (yield 63%). Finally, reduction of **4** in CH_2Cl_2 with Et_3SiH (3.0 equiv.) in the presence of TMSOTf (2.4 equiv.)[9] gave lactone **3** in 53% yield, presumably via oxonium ion intermediate **10**.

The structure of **4** was determined from its ^1H and ^{13}C NMR, NOE, NOESY, COSY and HMBC spectra (Fig. 2).



Scheme 1. Retrosynthetic analysis: A, the methoxyallene approach; B, the furan approach.

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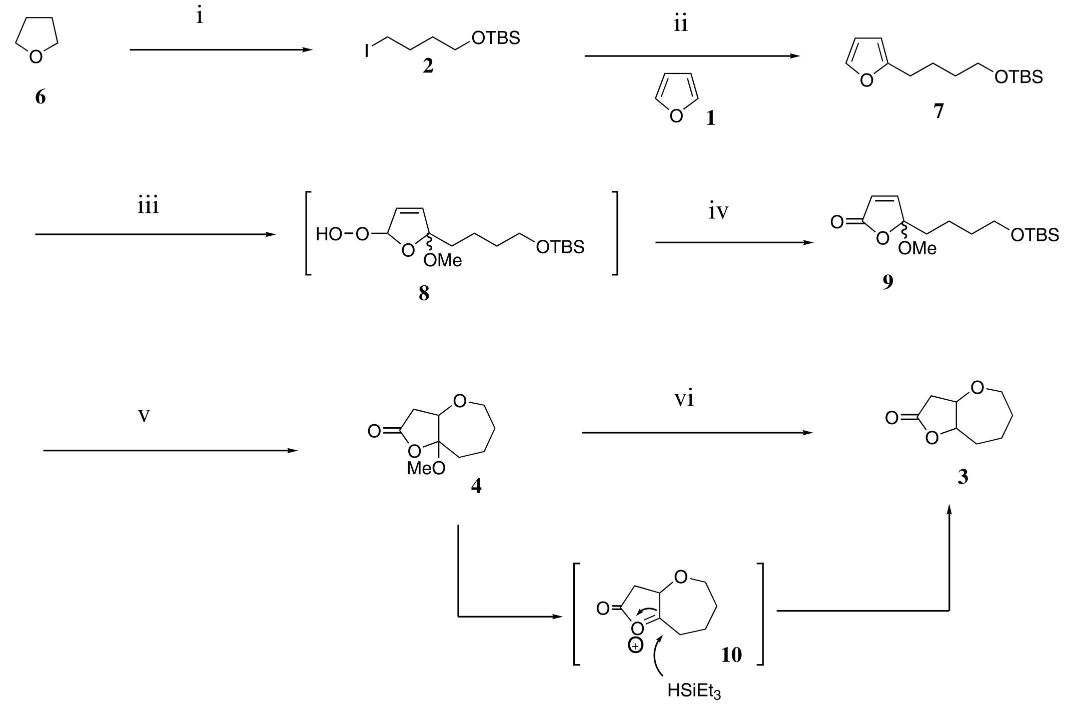

Scheme 2. *Reagents and conditions*: (i) NaI, TBSCl, CH_3CN, rt (72%); (ii) **1**, ^{t}BuLi, THF, −78 to 0°C (81%); (iii) $^1O_2$, MeOH, rose bengal, *hν* (82%); (iv) Ac_2O, py, DMAP (72%); (v) TBAF, THF, rt (63%); (vi) Et_3SiH, TMSOTf, CH_2Cl_2, rt, 6 h (52%).

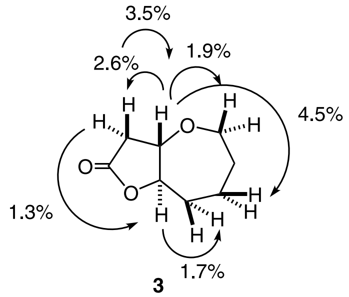

Figure 2. NOE correlations for **3**.

In conclusion, a new and efficient method for the synthesis of the oxepane ring from readily available starting materials yields a bicyclic lactone with a *trans* ring junction. The yield of this process is currently being optimized, and work is in progress on the use of lactone **3** as a building block for the synthesis of polycyclic ethers.

Acknowledgements

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