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The furan approach to oxacycles: synthesis of medium-size 2,3-disubstituted oxacycles

Manuel Pérez, Pilar Canoa, Generosa Gómez, Carmen Terán and Yagamare Fall*

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Vigo, 36200 Vigo, Spain

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Abstract—We describe an efficient new approach for the synthesis of medium-size oxacycles that is based on the oxidation of a furan ring with singlet oxygen followed by an intramolecular Michael addition. This present study enlarges the scope of the furan approach strategy for the synthesis of oxepanes.

Marine polycyclic ethers of the brevetoxin (Fig. 1) and ciguatoxin family are interesting synthetic targets due to their unusual molecular architecture and potent biological activity.[1] They are challenging synthetic targets in terms of medium-size ring construction and have provided a stimulus for the development of a plethora of new reactions and strategies for the construction of polycyclic systems, culminating with the total syntheses of brevetoxins A and B by Nicolaou et al.[2] and of ciguatoxin by Hirama et al.[3]

We recently described two new strategies for the synthesis of seven-membered oxacycles using methoxyallene[4] or furan[5] as the key starting material. We now report the results of our investigation aimed at determining the scope and limitations of the furan approach. A series of 2-alkylfurans **6** were prepared from commercially available diols **4** and oxidized with singlet oxygen to give after removal of the silyl protecting group, bicyclic lactones **9a**–**e**, which on reaction with LAH afforded 2,3-disubstituted oxacycles **3a**–**e** (Scheme 1).

Monosilylation[6] of commercially available diol **4** afforded alcohol **5**,[7] which was easily converted into iodide **2**.[7,8] Lithiation of furan **1** and reaction with **2** afforded the alkylated furan **6**.[7] Oxidation of **6** with singlet oxygen followed by treatment with acetic anhydride in pyridine, afforded butenolide **7**.[7,9] Reaction of **7** with TBAF then not only removed its silyl group, but also led

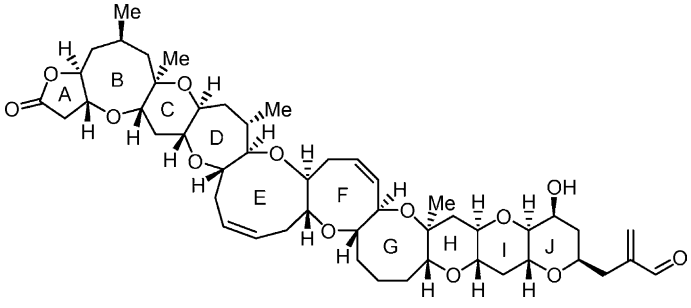

Figure 1. Brevetoxin A.

Keywords: 2,3-Disubstituted oxacycles; Oxepanes; Tetrahydrofurans; Tetrahydropyranes; Furan; Polyoxacycles; Toxins.
* Corresponding author. Tel.: +34-986-81-23-20; fax: +34-986-81-22-62; e-mail: yagamare@uvigo.es

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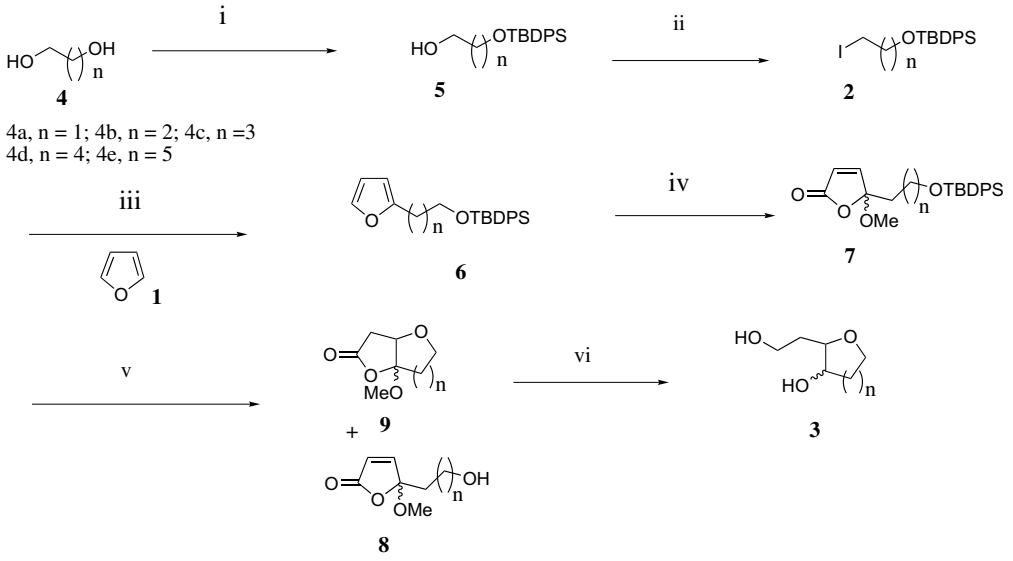
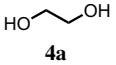
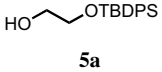
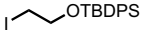
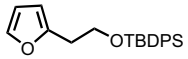
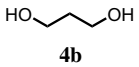
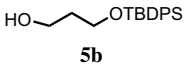
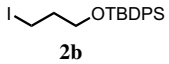
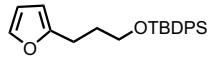
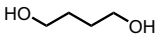
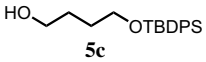
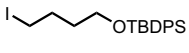
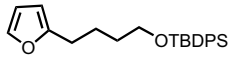
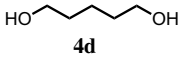
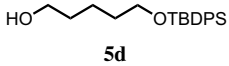
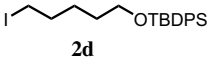
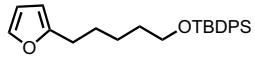
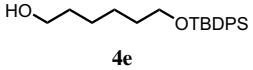
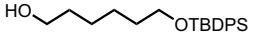
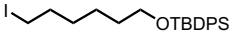
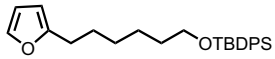


Scheme 1. Reagents and conditions: (i) NaH, TBDPSCl, THF, rt; (ii) PPh_3, I_2, Imid, THF, 0 °C; (iii) **1**, bipy, ^{n}BuLi, THF, 0 °C to rt; (iv) (a) $^1O_2$, MeOH, rose bengal, *hv* (b) Ac_2O, py, DMAP; (v) TBAF, THF, rt; (vi) LAH, $BF_3 \cdot OEt_2$, Et_2O, rt.

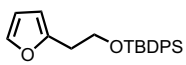
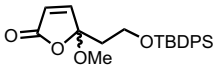
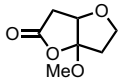
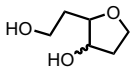
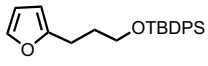
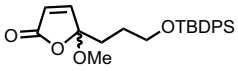
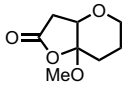
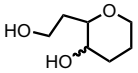
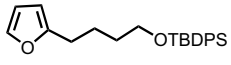
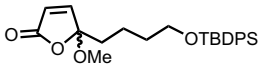
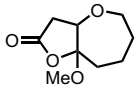
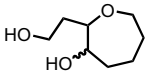
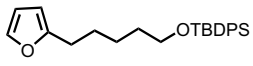
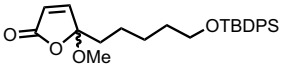
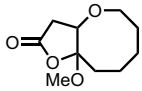
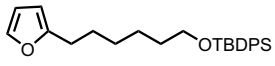
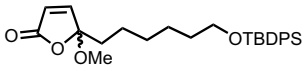
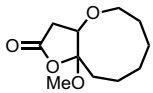
Table 1.

Entry	4	5	Yield (%)	2	Yield (%)	6	Yield (%)
1	 **4a**	 **5a**	65	 **2a**	90	 **6a**	70
2	 **4b**	 **5b**	73	 **2b**	66	 **6b**	85
3	 **4c**	 **5c**	71	 **2c**	97	 **6c**	94
4	 **4d**	 **5d**	30	 **2d**	94	 **6d**	74
5	 **4e**	 **5e**	21	 **2e**	93	 **6e**	71

to the bicyclic lactone **9**[7] through an intramolecular Michael addition. Opening of lactone **9** using LAH in the presence of $BF_3 \cdot OEt_2$ afforded 2,3-disubstituted oxacycle **3**.[7] Furans **6** could be synthesized in large scale from cheap commercial diols **4** and the results of their synthesis and subsequent transformation into **3** are summarized in Tables 1 and 2, respectively.

From the results of Table 2 it can be concluded that the present methodology is convenient for the synthesis of five-, six- and seven-membered oxacycles (2,3-disubstituted tetrahydrofuran **3a**, tetrahydropyran **3b** and oxepane **3c**, entries 1, 2 and 3). Formation of eight- and nine-membered oxacycles **9d** and **9e** was not observed, the key message being that with unsubstituted side chains, eight- and nine-membered rings cannot be made using this method. We are currently looking for an alternative for the synthesis of **9d** and **9e**. Diols **3a**, **3b** and **3c** were obtained as a mixture of *cis*- and *trans*-isomers, which could be separated by column chromatography only in the case of **3b**. Work is now in progress for the assignment of the stereochemistry of isomers **3b**

Table 2.

Entry	6	7	Yield (%)	9	Yield (%)	3	Yield (%)
1	 **6a**	 **7a**	86	 **9a**	73	 **3a**	54
2	 **6a**	 **7b**	89	 **9b**	81	 **3b**	89
3	 **6a**	 **7c**	90	 **9c**	78	 **3c**	74
				8c	16		
4	 **6a**	 **7d**	91	 **9d**	0	—	
				8d	71		
5	 **6a**	 **7e**	86	 **9e**	0	—	
				8e	57		

as well as the stereoselective obtention of the *cis*- and *trans*-isomers from **3a**–**c**, which are interesting building blocks for an iterative approach to polycyclic ethers.[10]

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