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The furan approach to oxacycles. Part 6: From THF to fused polyoxepanes

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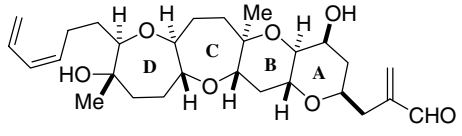
Abstract—We describe a stereoselective synthesis of cis or trans fused bisoxepane ring system with the iterative use of the furan approach, enlarging the scope of our methodology.

The so-called marine ladder toxins are a family of red tide toxins with highly complex architectures and very interesting biological properties including neurotoxicity and antimicrobial activity. Their unusual molecular architecture, a series of fused cyclic ethers having regular trans-syn-trans stereochemistry, has stimulated numerous iterative routes[1] and indeed represents challenging synthetic targets for organic chemists. Hemibrevetoxin B (**1**, Fig. 1) is the smallest member of the marine ladder toxins, which include the ciguatoxins, the brevetoxins, the maitotoxins, gymnocin and gambierol.[2]

We recently described a new methodology for the synthesis of oxacyclic compounds using either methoxyallene or furan as starting material.[3] The scope and limitations of this very powerful methodology are being determined and its application to the synthesis of cyclic natural products has been demonstrated by the enantioselective synthesis of (+)-(2*R*,3*S*,6*R*)-decarestrictine L.[3g]



1: Hemibrevetoxin B

Figure 1. Structure of Hemibrevetoxin B.

We now decided to further enlarge the scope of our methodology by targeting polyoxacyclic compounds. It was anticipated that the iterative use of our methodology would lead to polyoxacyclic compounds. We focused our attention on the synthesis of the bisoxepane system as a model study towards the CD ring system of Hemibrevetoxin B. The synthesis of cis fused bisoxepanes **3** and **4** was accomplished according to the reaction sequence shown in Scheme 1.

Starting from tetrahydrofuran we easily obtained cis-2,3-disubstituted oxepane **6**.[3b,d] Protection of the secondary alcohol of **6** gave 56% yield of the desired compound **7**,[4] together with 28% yield of alcohol **8**.[4] Compound **8** was casually our next target and could be obtained from **7** by selective removal of the TBS group. Compound **8** was easily converted into iodide **9**[4,5] in 89% yield. Lithiation of furan **10** and reaction with **9** afforded the alkylated furan **11**[4] (13%) together with free alcohol **12**[4] (74%). Oxidation of **11** with singlet oxygen followed by treatment with acetic anhydride in pyridine, afforded butenolide **13**[4] in 92% yield. Removal of the TBDPS group of **13** with TBAF gave tricyclic lactone **3**[4,6] through an intramolecular Michael addition (15%).

Alcohol **12** was protected to afford silylether **14** (94%). Oxidation of **14** with singlet oxygen followed by treatment with acetic anhydride in pyridine, afforded

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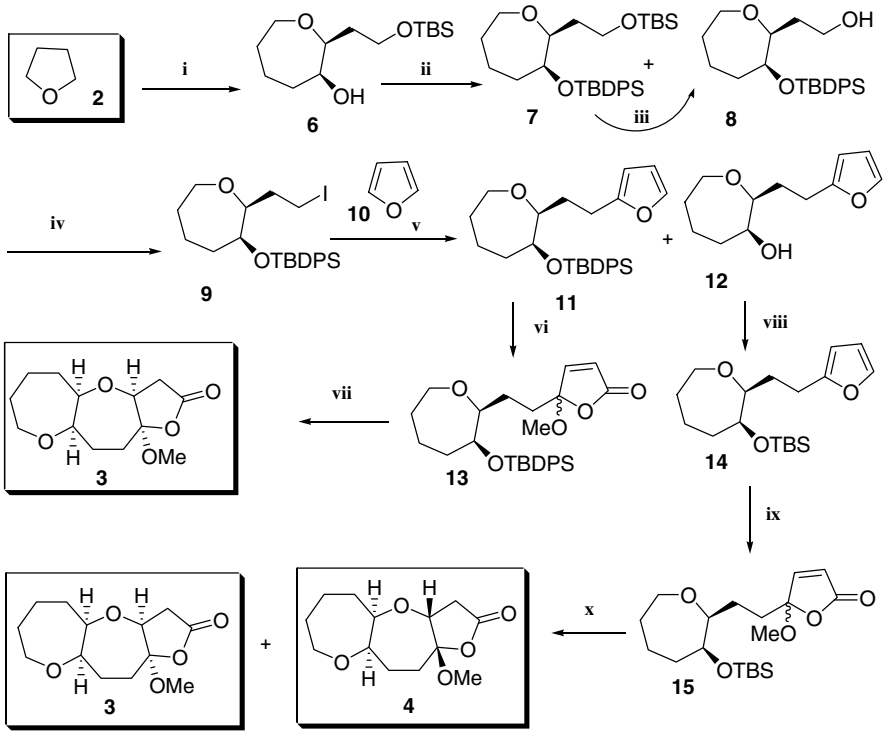
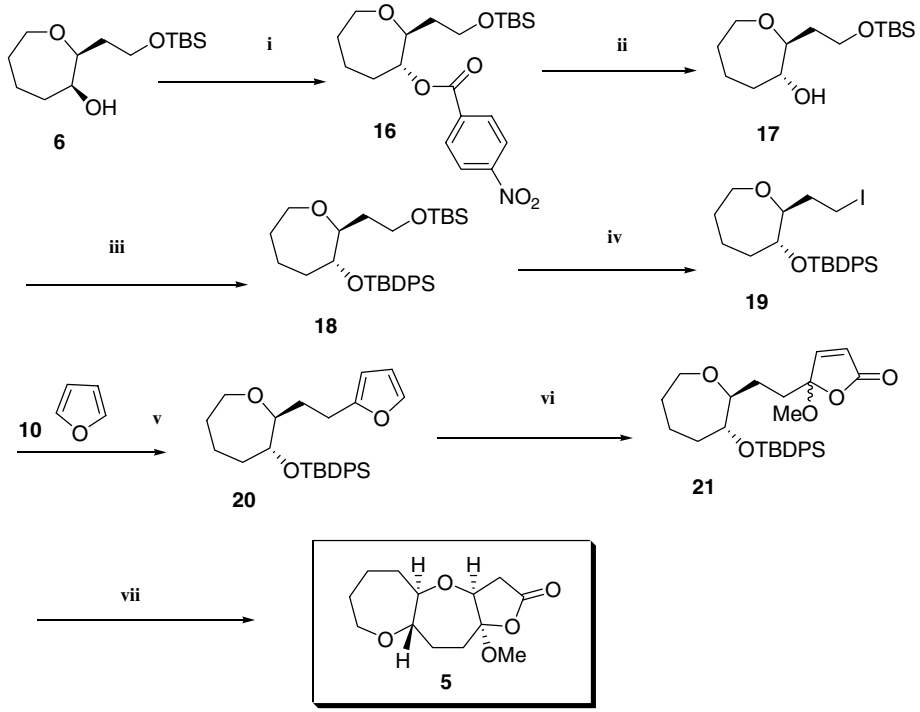


Scheme 1. Reagents and conditions: (i) Refs. 3b and d; (ii) TBDPSCl, Imid, DMAP, DMF, rt (56% **7**; 21% **8**); (iii) AcOH/THF/H_2O (3:1:1) (88%); (iv) PPh_3, I_2, Imid, THF, 0 °C (89%); (v) **10**, bipy, *n*-BuLi, THF, 0 °C–rt (13% **11**; 74% **12**); (vi) (a) $^1O_2$, MeOH, rose Bengal, *hv*; (b) Ac_2O, py, DMAP (92%, 2 steps); (vii) TBAF, THF, rt (15%); (viii) TBSOTf, 2,6-lutidine, CH_2Cl_2, −10 °C (94%); (ix) (a) $^1O_2$, MeOH, rose Bengal, *hv*; (b) Ac_2O, py, DMAP (63%, 2 steps); (x) TBAF, THF, rt (19% **3**; 7% **4**).

butenolide **15** in 63% yield (2 steps). Treatment of **15** with TBAF led to the previously obtained tricyclic lactone **3** (19%) together with tricyclic lactone **4** (7%).

The cis-2,3-disubstituted oxepane **6** was subjected to a Mitsunobu reaction[7] to afford trans-2,3-disubstituted oxepane **17**[4] (Scheme 2). Alcohol **17** underwent the same



Scheme 2. Reagents and conditions: (i) *p*-NO_2PhCO_2H, Ph_3P, DIAD, THF, rt (78%); (ii) K_2CO_3, MeOH, rt (88%); (iii) TBDPSCl, Imid, DMAP, DMF (77%); (iv) (a) AcOH/THF/H_2O (3:1:1) (85%); (b) PPh_3, I_2, Imid, THF, 0 °C (95%); (v) **10**, bipy, *n*-BuLi, THF, 0 °C–rt (87%); (vi) (a) $^1O_2$, MeOH, rose Bengal, *hv*; (b) Ac_2O, py, DMAP (56%, 2 steps); (vii) TBAF, THF, rt (25%).

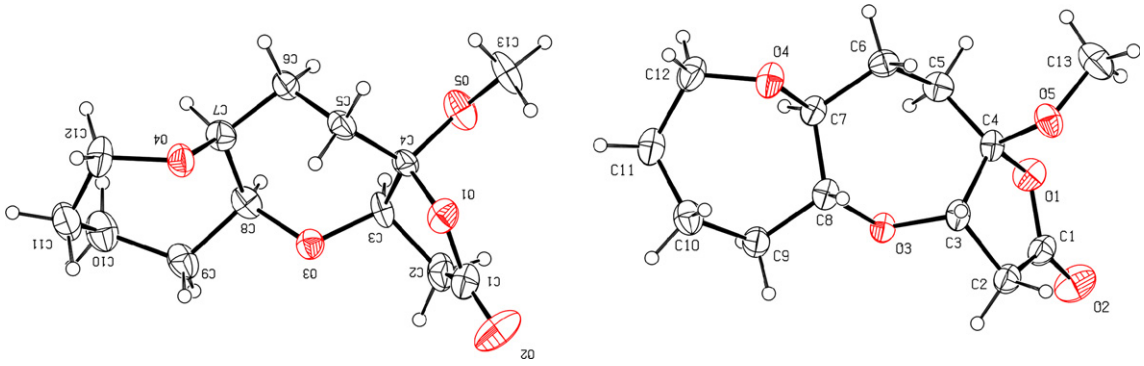


Figure 2. X-ray structures of **3** (left) and **5** (right).

reaction sequence described previously in Scheme 1 and ultimately gave only one tricyclic lactone **5**.[4,6]

The stereochemistries of **3** and **5** were unambiguously assigned using X-ray crystallographic analysis (Fig. 2). The stereochemistry of **4** is as indicated in Scheme 1, taking into account that the final intramolecular Michael addition occurs giving rise to a cis ring junction.[8]

In conclusion, we have demonstrated that iterative use of the furan approach leads to the stereoselective synthesis of polyoxacyclic compounds. Work is now in progress towards the optimization of the yields and the enantioselective synthesis of polycyclic natural products using this model study.

Acknowledgements

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