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Combining Two-Directional Synthesis and Tandem Reactions: Synthesis of Trioxadispiroketals

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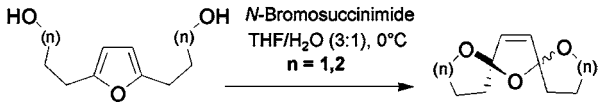
ABSTRACT



A tandem bromonium ion-promoted cyclization of two pendant hydroxyl groups onto a central furan core provides a highly direct route to both the [5,5,5]- and the [6,5,6]-trioxadispiroketal ring systems.

The trioxadispiroketal functionality is present in a number of biologically active marine natural products such as the spirolides,[1] the pinnatoxins[2] **2**, the pteriatoxins[3] **3**, and the azaspiracids[4] **1** (Figure 1), as well as the antibiotic polyether ionophores.[5] As such, this functionality is of synthetic interest. However, due to its low occurrence relative to other spirocyclic groups, limited research has been carried out into the assembly of such structures. Our group has a continuing interest in combining two-directional synthesis with tandem reactions to create efficient strategies for the synthesis of complex molecules, as exemplified by our recent syntheses of perhydrohistrionicotoxin[6] and hippodamine.[7] With the aim of developing efficient synthetic routes to the aforementioned marine natural products, we herein report the development of a novel trioxadispiroketalization procedure. Our methodology employs a bromonium source to effect an oxidative tandem cyclization of two proximal hydroxyl groups onto a central furan core[8] allowing direct access to the [5,5,5]-trioxadispiroketal **8** and the [6,5,6]-trioxadispiroketal **14** ring systems (Schemes 1 and 2).

To begin our synthesis of the [5,5,5]-trioxoxadispiroketal analogue, 5-hydroxymethyl-2-furaldehyde **4** was subjected to Taylor's tandem oxidation/Wittig procedure.[9] Stirring compound **4** with 2.4 equiv of (methoxycarbonylmethylen)-triphenylphosphorane **5** and 10 equiv of manganese(iv) oxide at room temperature for 4 days gave diester **6** as a 6.6:1 mixture of (*E*,*E*)- and (*E*,*Z*)-isomers in 87% yield overall after column chromatography. Reduction of the α,β-unsaturated ester functionalities in compound **6** using 20 equiv of lithium borohydride,[10] which was generated *in situ* from lithium chloride and sodium borohydride, gave a complex mixture of diols that were shown by NMR to contain

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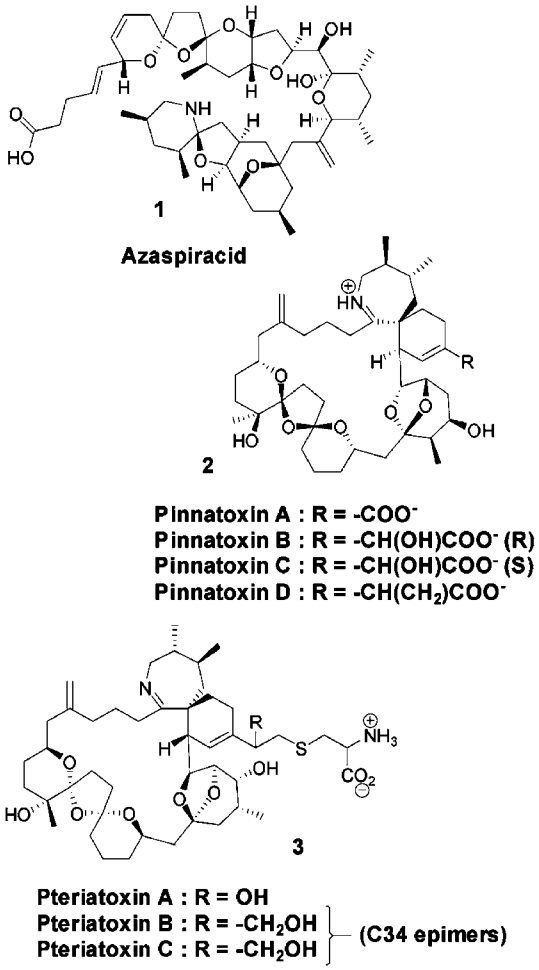
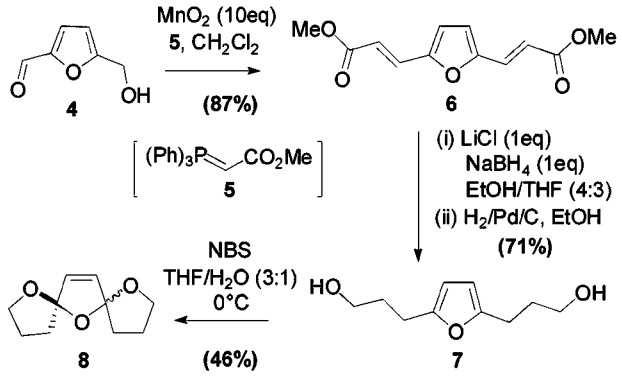


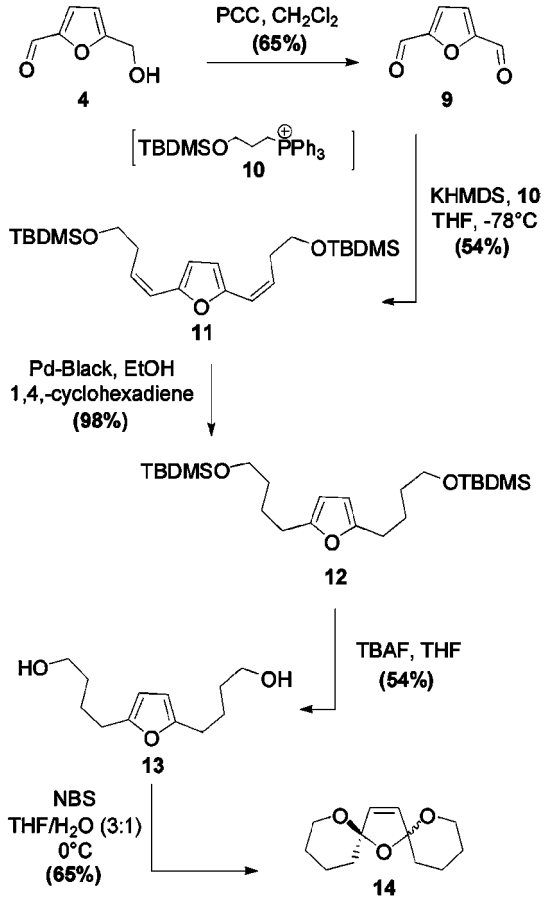
Figure 1. Naturally occurring trioxadispiroketals.

Scheme 1. Synthesis of the 5,5,5-Trioxadispiroketal Analogue



significant olefin character. Subsequent hydrogenation of this mixture under standard conditions achieved complete conversion of the diol mixture to give saturated cyclization precursor **7** in 71% overall yield from diester **6** after column chromatography. A solution of diol **7** in a (3:1) THF/H_2O solvent system was then treated with 1.2 equiv of *N*-bromosuccinimide at 0 °C[11] to effect oxidative cyclization, giving

Scheme 2. Synthesis of the 6,5,6-Trioxadispiroketal Analogue



dispiroketal **8** as an inseparable 1:1 mixture of *cisoidal* and *transoidal* isomers in 28.4% yield over three steps.

It was envisaged that the synthesis of [6,5,6]-trioxadispiroketal **14** could be achieved via an analogous strategy (Scheme 2). Oxidation of 5-hydroxymethyl-2-furaldehyde **4** using pyridinium chlorochromate gave 2,5-difuraldehyde **9** in 65% yield. Wittig olefination of this compound with 2 equiv of phosphonium ylide **10** homologated both side chains in one efficient step to give diolefin **11** in 54% yield. Hydrogenation of compound **11** was then achieved using a hydride transfer reduction procedure,[12] by stirring compound **11** in a suspension of palladium black and 1,4-cyclohexadiene in ethanol for 2 h to give compound **12** in 98% yield. Desilylation of this compound was effected by stirring in THF in the presence of 2.2 equiv of TBAF to give our desired diol cyclization precursor **13** in 54% yield. A solution of diol **13** in a (3:1) THF/H_2O solvent system was then treated with 1.2 equiv of *N*-bromosuccinimide at 0 °C to produce dispiroketal **14** as a 1:1 mixture of *cisoidal* and *transoidal* isomers in 65% yield. The two isomers were found to be separable by column chromatography; however, reequilibration was noted after a period of several hours in solution.

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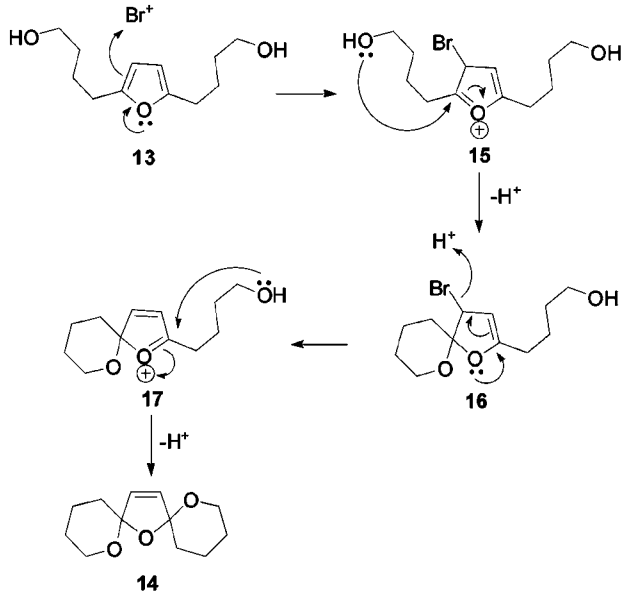
Scheme 3. Mechanism



A postulated mechanism for the tandem cyclization is shown in Scheme 3. It is proposed that the process begins with an electrophilic bromination of the central furan ring of **13**, thus revealing an electrophilic oxonium ion **15**. Subsequent nucleophilic attack from the proximal hydroxyl group in the side chain, followed by loss of a proton, forms the first spirocenter and gives intermediate **16**. Consequent E_2' elimination of the bromine substituent via the 5,4-central ring double bond reveals a second oxonium ion that undergoes an analogous nucleophilic attack from the remaining hydroxyl group in **17**. The loss of a proton completes the formation of the trioxadispiroketal ring system **14**.

In conclusion, the combination of two-directional synthesis building from a central furan core combined with a bromonium ion-mediated tandem spirocyclization has resulted in a very concise entry to trioxadispiroketal synthesis. Work directed at the application of this strategy for total synthesis is ongoing in these laboratories, and our results will be published in due course.

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Supporting Information Available: Experimental procedures, full characterization, and ^{1}H NMR and ^{13}C NMR spectra for compounds **6**−**8** and **11**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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