

Synthesis of a novel, bowl-like bis γ -lactone

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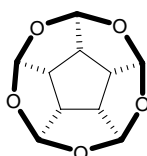
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Abstract—Synthesis of a compound with bowl-like, symmetrical molecular architecture, starting from a Diels–Alder adduct **7**, derived from a reaction between 2,5-dihydro-2,5-dimethoxyfuran and 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene, is reported.

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Syntheses of bowl-like molecular architectures with oxygen atoms at the apex positions, called oxa-bowls, have attracted considerable interest.¹ Such aesthetically pleasing but synthetically challenging molecules, endowed with interesting physicochemical properties, are potential targets for exploration into new avenues of application. One such emerging application is in the area of neuroscience where the metal binding property of an oxapentacyclic amine derivative is exploited as a neuroprotective agent in focal ischemia due to its calcium channel antagonism activity.² Hence, the quest for polycyclic cage compounds, bearing one or more heterocycles, through novel and efficient pathways continues.³

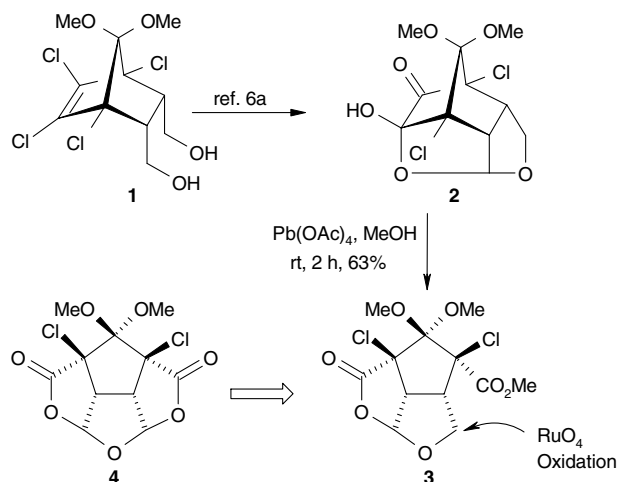


Oxa-bowl
Pentaoxa[5]peristylane

We have previously reported an efficient ruthenium-catalyzed methodology for the synthesis of norbornyl α -diketones,⁴ serving as versatile building blocks for the construction of natural as well as unnatural products.⁵ During the course of our studies directed towards the synthesis of γ -lactones from norbornyl α -diketones,⁶ we demonstrated that one of the products obtained in 30% yield in the ruthenium-catalyzed oxidation of diol **1** was an interesting derivative **2**.^{6a} We envisaged that this could serve as a potential precursor for the bowl-like molecule **4** through oxidation as indicated in

Scheme 1, either at the tetracyclic hemiacetal stage **2** or at the tricyclic monolactone stage **3** obtained after cleavage of the precursor. We herein, report our efforts in this direction and provide an account of a de novo synthesis of bowl-like bis γ -lactone **4**.

The tetracyclic hemiacetal **2** was subjected to cleavage using lead tetraacetate in methanol to give tricyclic monolactone **3** (**Scheme 1**). Although ruthenium-catalyzed oxidation of the tetrahydrofuran moiety at the α -position is generally very easy,⁷ tricyclic monolactone **3**, under usual reaction conditions, was recovered in 73% yield. A similar observation was also noted for the tetracyclic hemiacetal **2**.

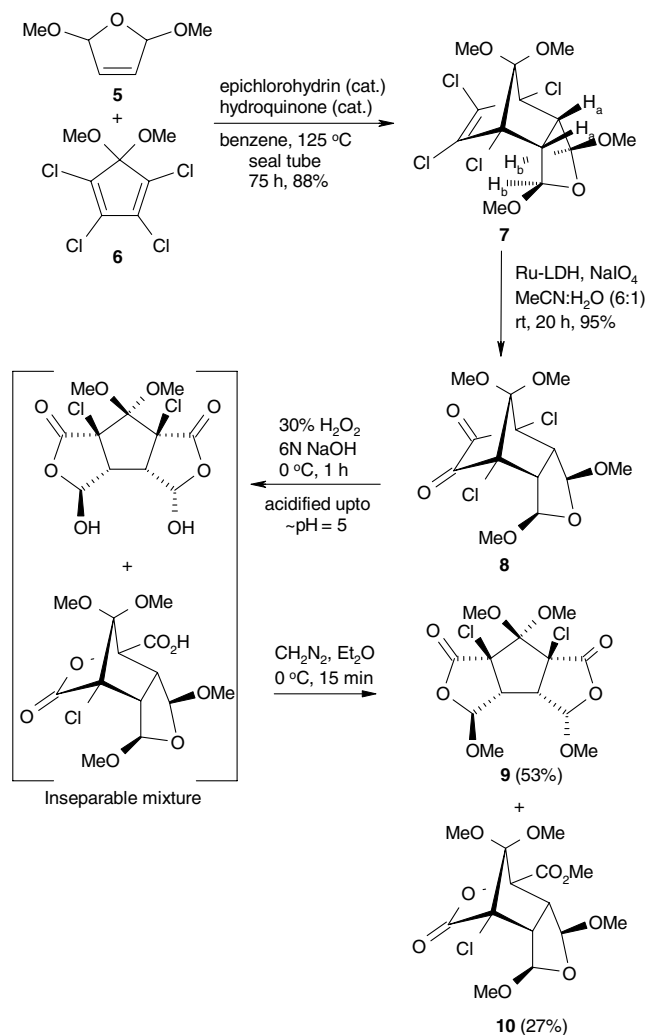


Scheme 1.

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To overcome this problem we considered starting from Diels–Alder adduct **7**, derived through a reaction between 2,5-dihydro-2,5-dimethoxyfuran **5** and 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene **6** (Scheme 2). Interestingly, 2,5-dihydro-2,5-dimethoxyfuran, an inexpensive and stable commercially available form of (*Z*)-2-butenedial, though frequently used as a C₄ building block,⁸ has not been evaluated as a dienophilic partner in the Diels–Alder reaction.⁹ Commercial 2,5-dihydro-2,5-dimethoxyfuran is a mixture of *cis* and *trans* diastereoisomers, so, in principle formation of three *endo*-diastereomeric adducts is possible. The Diels–Alder reaction between 2,5-dihydro-2,5-dimethoxyfuran **5** and diene **6**,¹⁰ performed using benzene as solvent in a sealed-tube at 125 °C, furnished a single stereoisomer **7** (Scheme 2). This is presumably because of epimerization or *cis*–*trans* equilibration of **5** under the reaction conditions and preferential reaction of the *cis*-isomer through an *endo*-transition state with both methoxy groups oriented on the β -face for steric reasons.

The structural assignment of adduct **7** was based on analysis of the ¹H and ¹³C NMR spectra. The symmetrical nature of the adduct was evident from the presence



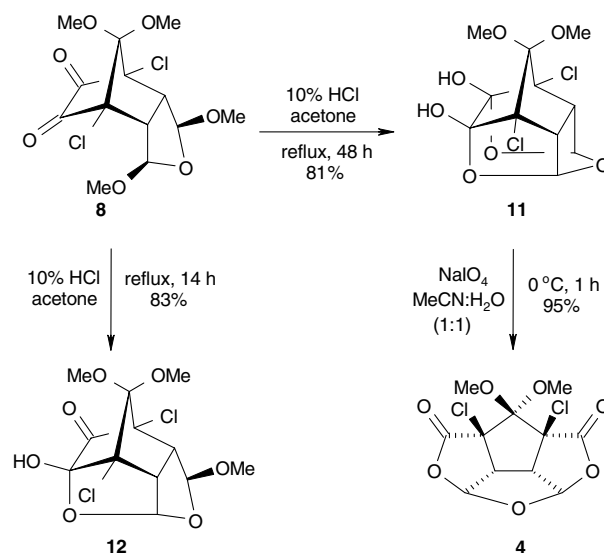
Scheme 2.

of five and eight signals in the ¹H and ¹³C NMR spectra, respectively. The relative stereochemistries of the OMe groups present in 2,5-dimethoxytetrahydrofuran moiety of **7** was assigned mainly based on the fact that the coupling constant between H_a and H_b was zero as anticipated for a dihedral angle of about 90°.

The 1,2-dihaloalkene moiety in **7** was first transformed to the corresponding α -diketone **8** in excellent yield using a recyclable supported ruthenium catalyst and NaIO₄ as stoichiometric co-oxidant.^{4b} The symmetrical nature of the α -diketone was apparent from the ¹H and ¹³C NMR spectra. The alkaline H₂O₂ mediated cleavage of α -diketone **8** to the corresponding dicarboxylic acid followed by treatment with HCl, contrary to our expectation, furnished a mixture of inseparable compounds which were characterized as **9** and **10** after methylation with diazomethane and chromatographic separation (Scheme 2). Treatment of **9** with acidic reagents such as HCl and Amberlyst-15 also failed to give the target compound **4**.

We then reversed the strategy; hydrolysis of the cyclic ketal moiety prior to the α -diketone cleavage furnished caged bis-hemiacetal **11** in 81% yield (Scheme 3). The intermediate mono-hemiacetal **12** was also isolated in 83% yield and characterized by intercepting the reaction after 14 h. Oxidative cleavage of the glycolic bond employing NaIO₄ in 1:1 MeCN–H₂O furnished the title compound **4** in excellent yield. A set of four signals in the ¹H and a seven-line ¹³C NMR spectra confirmed the structure which was further secured unequivocally through single crystal X-ray analysis (Fig. 1).¹¹

In conclusion, we have demonstrated that the Diels–Alder reaction between 2,5-dihydro-2,5-dimethoxyfuran and 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene leads to a single diastereomer. The adduct was transformed into the corresponding α -diketone **8** in excellent yield using a recyclable supported ruthenium catalyst. Acid catalyzed hydrolysis of the α -diketone furnished



Scheme 3.

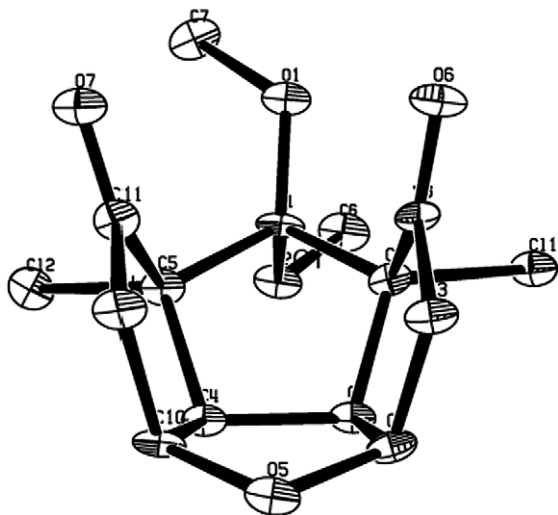


Figure 1. ORTEP diagram of **4**.

a symmetrical cage-compound **11** which was subjected to oxidative cleavage of the glycolic bond employing NaIO_4 to obtain bowl-like bis- γ -lactone **4** in an excellent overall yield (73% from adduct **7**).

Acknowledgements

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