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Synthesis of a Novel, Highly Symmetric Bis-Oxa-Bridged Compound

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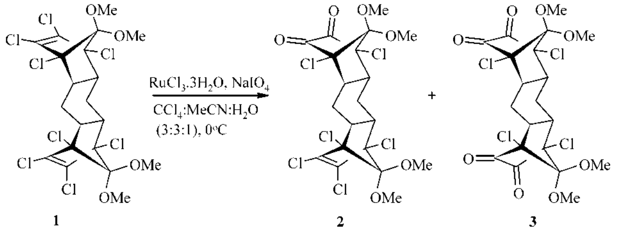
The synthesis and chemistry of aesthetically pleasing, strained polycyclic unnatural compounds continues to fascinate and pique the imagination of chemists because of their unusual geometries, marvelous structural architecture, and intriguing chemistry, leading to a great deal of physical−organic, theoretical, and spectroscopic investigations.[1] The unfavorable thermodynamic stability due to high strain which poses a formidable synthetic challenge for designing a rational strategy for their creation, generated a lot of interest among synthetic chemists, and culminated in the synthesis of a wide class of strained systems, mostly carbocyclic compounds.[1,2] Another equally enthralling synthetic task is the preparation of relatively less explored heterocyclic strained compounds, which have started receiving considerable current interest due to the exciting as well as more useful properties exhibited by them compared to that of carbocyclic analogues.[3] The rigid "heterologues" decked with heteroatoms such as oxygen, nitrogen, or sulfur could serve not only as potentially promising metal binders but also as prospective building blocks for the synthesis of complex polycyclic unnatural and natural products.

As a consequence of our ongoing efforts aimed at selective utilization of halogens in Diels−Alder adducts of tetrahalo-5,5-dimethoxycyclopentadiene,[4,5] we have recognized the feasibility of ruthenium-catalyzed oxidation of 1,2-dihaloalkenes to α-diketones on a variety of norbornyl derivatives,[5] which have been serving as highly potent and inextricable templates in organic synthesis.[6] We envisioned that a bis-α-diketone (**3**, Scheme 1), prepared using our methodology,[5] would have wide synthetic applications due to its unique topology as well as functional group disposition. We herein report an elegant application wherein a one-pot synthesis of a highly oxygenated strained bis-oxa-bridged compound is delineated from the bis-α-diketone and generalized to other substrates.

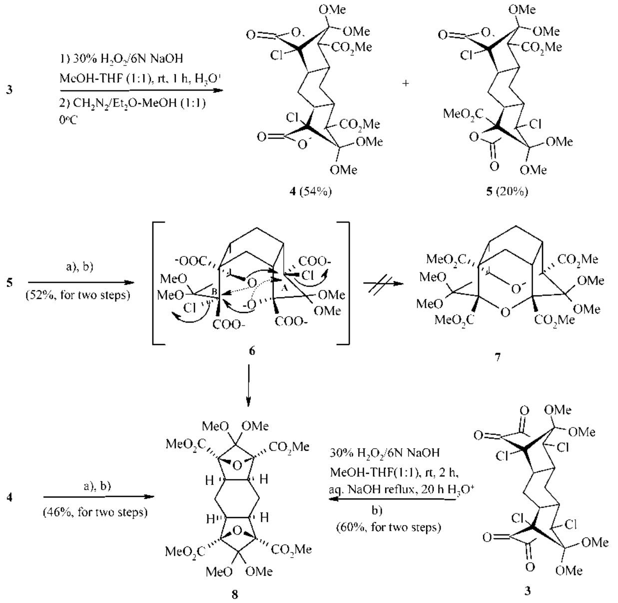
The bis-adduct **1** was prepared by following the literature procedure.[7] We have recently reported that when **1** was subjected to the ruthenium-catalyzed oxidation conditions, either a mixture of mono-diketone **2** (42%) and bis-diketone **3** (10%) or only bis-diketone **3** (65%) were formed, depending on the reaction conditions.[5] At this juncture, we decided to expend efforts to improve the yield of **3** because of its importance as a potential building block. Several rounds of optimization efforts lead us to prepare exclusively bis-diketone **3** in quantitative yield simply by adding an aqueous solution of 11% $RuCl_3$ and 2.5 equiv of $NaIO_4$ in one portion to the substrate in $MeCN-CCl_4$ at 0 °C (Scheme 1).

The bis-diketone **3** was subjected to a dione cleavage reaction employing alkaline H_2O_2, an efficient method we have recently demonstrated for the cleavage of other norbornyl α-diketones.[5] Interestingly, the bis-diketone **3** afforded, upon subsequent treatment with diazomethane, a separable mixture of two products (**4** + **5**) in 74% yield (Scheme 2).[8] The peaks in ^1H NMR spectra revealed that **4** is less symmetric than **5**. In ^{13}C NMR, the major compound **4** (54%) showed a 12-line spectrum, while the minor compound **5** (20%) showed an 11-line spectrum. On the basis of the degree of symmetry shown in ^{13}C NMR, the major compound was unambiguously assigned the σ-symmetric pentacyclic bis-lactone structure **4**. The minor lactone, which is more symmetric, was assigned C_2-symmetric pentacyclic bis-lactone **5**.

Scheme 1. Ruthenium-Catalyzed Oxidation of Bis-adduct **1** to Bis-α-diketone **3**



Scheme 2. Synthesis of the Novel Bis-bridged Compound **8** via Alkaline H_2O_2 Cleavage of the Bis-diketone[a]



[a] Reagents and conditions: a) aq NaOH−MeOH, reflux, 24 h. H_3O^+, b) CH_2N_2, $Et_2O-MeOH$ (1:1), 0 °C.

A careful observation of the structural morphology of the minor C_2-symmetric pentacyclic bis-lactone **5** revealed that the intermediate **6**, which would be generated upon treatment of **5** with NaOH (Scheme 2), possesses suitably disposed alkoxide moieties that are expected to undergo intramolecular face-to-face S_N2 cyclization resulting in a cage compound **7**. On the other hand, a relatively strained bis-oxa-bridged compound **8** would result if the alkoxide moieties displace the respective chlorine atoms present in the same ring. To check the feasibility of this plan, the minor C_2-symmetric bis-lactone was refluxed with NaOH in aqueous MeOH for 24 h. Esterification of the crude product with diazomethane gave, contrary to our expectations, a strained novel bis-oxa-bridged compound **8** in 52% yield. Both ^1H and ^{13}C NMR spectra reveal a highly symmetrical structure. The four ester groups appeared as a singlet at 3.80 ppm, while two sets of peaks at 3.44 and 3.31 ppm were

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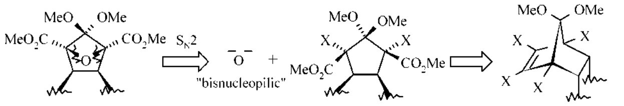
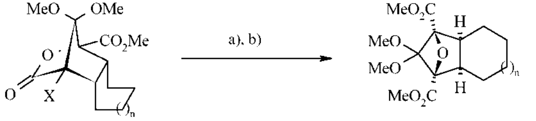
Scheme 3. Schematic Representation of Incorporation of Formal "Bisnucleopilic" (hypothetical) Oxygen Leading to Oxa-Bridged Derivatives



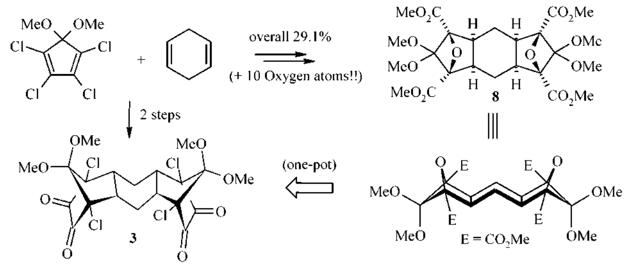
Scheme 4. Synthesis of Oxa-Bridged Derivatives **10** and **12**[a]



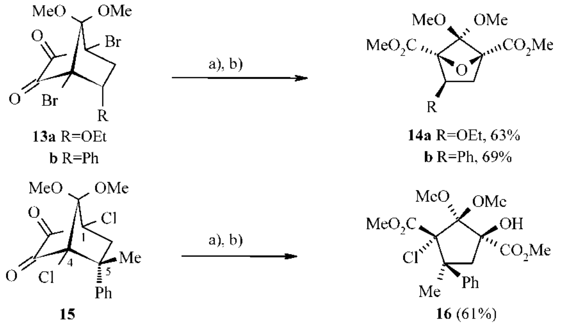
9a X=Cl (n=1) 89% **10** (n=1)
b X=Br (n=1) 90%
11 X=Cl (n=3) 92% **12** (n=3)

[a] Reagents and conditions: a) aq NaOH−MeOH, reflux, H_3O^+, b) CH_2N_2, 0 °C, Et_2O−MeOH (10:1).

Scheme 5



Scheme 6. One-Pot Synthesis of Oxa-Bridged Compound **14** and α-Hydroxyester **16**[a]



[a] Regents and conditions: a) 30% H_2O_2/6N NaOH, MeOH, rt, 2 h. aq NaOH, reflux, 31 h, b) CH_2N_2, 0 °C, Et_2O−MeOH (1:1).

assigned for the four OMe groups. In ^{13}C NMR, a single peak was seen at 166.5 ppm for the carbonyl of all the ester groups. The four carbons bearing the oxygen bridge as well as the ester groups appeared at 91.6 ppm. Since it was not possible to explicitly rule out the structure **7** based on ^1H, ^{13}C NMR, IR, or CHN, a single-crystal X-ray analysis of the product was carried out to prove the strained but highly symmetric structure **8** unambiguously.[9] Obviously, **8** was formed as a result of intramolecular S_N2 displacement within each cyclopentane ring **A** and **B** (shown with dotted arrows) leading to a strained oxa-bridge on each cyclopentane ring. It is intriguing that a reaction pathway leading to a strained oxygen-bridged compound was favored over the alternative that would have led to a less strained cage compound.

The synthetic sequence in Scheme 2 depicts a beautiful orchestration of selective utilization of the two sets of chlorines along with an illustration of an unprecedented example of extracting fullest advantage of geometric constraints on the reactivity of the molecule. In contrast to majority of the applications known thus far of tetrachloro norbornyl derivatives where complete dechlorination is invariably followed,[6] the availability of "retained" bridgehead chlorines by our method facilitates smooth incorporation of oxa-bridges in a stepwise manner through a formal "bisnucleophilic" oxygen as shown in Scheme 3.

Further, the pathway leading to product **8** reveals that even σ-symmetric pentacyclic bis-lactone **4** should furnish the same product under the reaction conditions. Indeed, when **4** was subjected to aqueous alkaline conditions followed by esterification, **8** was obtained in 46% yield (Scheme 2). The tricyclic lactones **9** and **11** were also transformed smoothly into tricyclic oxa-bridged compounds **10** and **12** respectively in high yield (Scheme 4).

The next logical step was to develop a one-pot sequence directly from bis-diketone **3**, which is the precursor for both **4** and **5**. Treatment of **3** with aqueous alkaline H_2O_2 in MeOH−THF, initially at room temperature, and then at reflux temperature followed by esterification gave the product **8** in 60% overall yield (Scheme 2). Thus, **8** was prepared in just three steps with an overall yield of 29.1% starting from tetrachloro-5,5-dimethoxycyclopentadiene and 1,4-cyclohexadiene (Scheme 5). The two *syn* oxa-bridges in **8** constrain the central cyclohexane ring into boat form.

The one-pot procedure was extended to monosubstituted α-diketones **13a**,**b**, both of which furnished the oxa-bridged products **14a**,**b** (Scheme 6). On the other hand, dione **15** with steric encumbrance in the α-position (C-5) failed to furnish the oxa-bridged derivative. The reaction stopped at α-hydroxyester stage, giving **16** (Scheme 6).[10]

In conclusion, we have demonstrated a simple and efficient procedure for the conversion of a 2:1 Diels−Alder adduct between tetrachloro-5,5-dimethoxycyclopentadiene and 1,4-cyclohexadiene into a highly symmetric pentacyclic bis-oxa-bridged compound **8** via stepwise controlled oxidation and intramolecular S_N2 displacements, eventually adding up as many as 10 oxygen atoms!

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Supporting Information Available: Experimental details, spectral data, and crystallographic data for compound **8** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) All new compounds were satisfactorily characterized by spectroscopic methods and elemental analysis.
(9) X-ray data will be published in the future.
(10) α-Hydroxyester intermediate could be isolated and characterized in case of **9a** by giving shorter reaction time.

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