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Synthesis of versatile bicyclo[5.4.0]undecane systems from tetrachlorocyclopropene

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Abstract—2,2,3,4-Tetrachloro-8-oxabicyclo[3.2.1]octa-2,6-diene, derived in a single step from the cyclocondensation of furan and tetrachlorocylopropene, serves as a key intermediate for the construction of bicyclo[5.4.0]undecane synthons. Conversion to a *meso*-1,3 diketone is followed by a high yielding Robinson annulation reaction. Studies on the reduction of the enone product reveals a powerful preference for formation of the *cis*-ring fusion.

The bicyclo[5.4.0]undecane system is an important structural moiety found in a variety of terpenoid natural products. We have been interested in several targets containing this system (Fig. 1) because of their unique and often potent biological activity.

Erinacine C[1] is an inducer of NGF, guanacastepene A[2] is a potent antibiotic and frondosin D[3] has shown powerful anti-HIV properties. The prevalence of this structure in many natural products has inspired a variety of efforts to develop general methods for the construction of these systems.

Recent efforts from these laboratories have shown that the oxabicyclo[3.2.1]octadiene derivatives prepared through the reaction of tetrahalocyclopropenes and furan are highly versatile synthons, which can be readily functionalized.[4] A direct strategy for the assembly of bicyclo[5.4.0]undecane building blocks would be the annulation of a six-membered ring on to these bicyclic systems followed by opening of the bridging ether. Herein, we report our efforts to apply a Robinson annulation[5] strategy to effect this conversion.

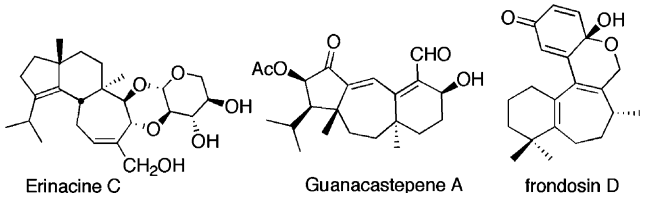
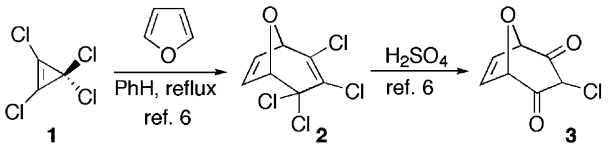


Figure 1. Natural products with a bicyclo[5.4.0]undecane ring system.

The inspiration for the use of the Robinson annulation was Tobey and Law's[6] synthesis of the 1,3-diketone **3** (Scheme 1) in just two steps from commercially available tetrachlorocyclopropene.

Cyclocondensation of **1** and furan proceeds through an initial Diels–Alder reaction[6,7] to produce **2** in high yield. Direct hydrolysis of **2** under strongly acidic conditions and elevated temperatures delivers the 1,3-dione **3**. Although the yield for this step is moderate (~50%), the chloro diketone is relatively easy to produce in multigram quantities. Intermediate **3** was attractive for the synthesis of bicyclo[5.4.0]undecane systems because such diketone moieties are highly effective in Robinson annulation reactions.[8] Moreover, since this hydrolysis converts the racemic adduct into a *meso*-compound, it may also be possible to execute the annulation with a



Scheme 1.

Keywords: Tetrachlorocyclopropene; Furan; Robinson annulation; Bicyclo[5.4.0]undecane.
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† Corresponding author concerning X-ray structural studies.

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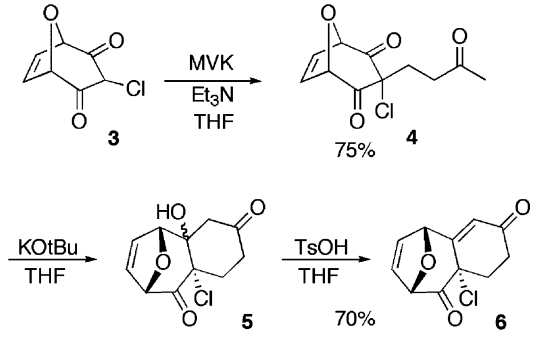
chiral catalyst (Hajos–Parrish reaction[9]) to produce nonracemic adducts.

Initial studies involved the conversion of the known chloro diketone **3** into a bicyclo[5.4.0]undecane system. Our initial efforts to effect a Michael addition between **3** and methyl vinyl ketone were frustrated by the sensitivity of **3** to the typical hydroxide or alkoxide bases used to promote this reaction. Evidence was observed for products arising from a ring-opening retro-Claisen reaction. Fortunately, it was found that triethylamine was an excellent base and produced a single Michael adduct **4** in 75% isolated yield (Scheme 2).

An important issue in this reaction was the relative configuration of the newly formed stereogenic center. It was presumed that the conformation produced by the bridging ether would bias attack of electrophiles to the *exo*-face, *syn* to the oxabridge. An X-ray structure of Michael adduct **4** verified this preference (Fig. 2).

Subjecting the trione **4** to an alkoxide base resulted in a highly effective ring closure reaction. Interestingly, the alkoxide bases that caused decomposition of dione **3** were compatible with the trione **4**, perhaps because of steric shielding of the endocyclic carbonyls from nucleophilic attack. The base catalyzed process led to the formation of aldol product **5** along with minor amounts of the annulation product **6**. Treatment of the crude mixture with tosic acid resulted in complete dehydration to give the desired enone **6** in 70% isolated yield.



Scheme 2.

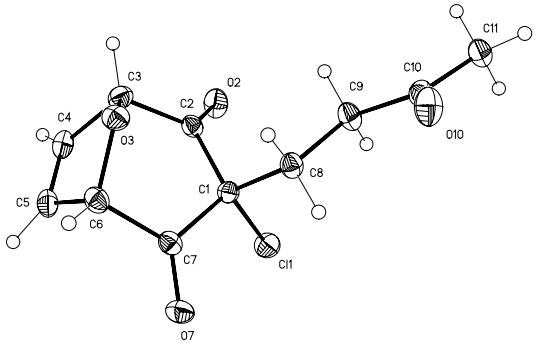
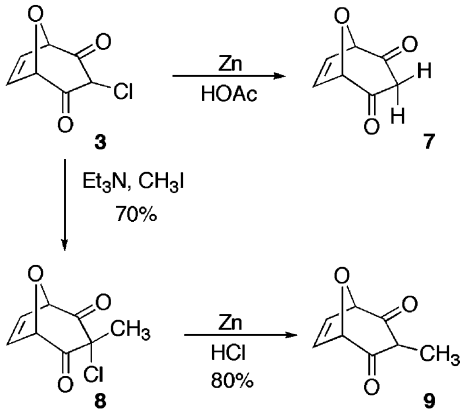


Figure 2. X-ray structure of **4**.



Scheme 3.

The effectiveness of this process encouraged the investigation of more relevant compounds that have an angular methyl group rather than the angular halogen atom as in **6**. Exchange of chlorine for a methyl group in compound **3** was envisioned to give a more valuable *meso*-diketone (Scheme 3).

Initially, this transformation was envisioned as a one-step operation whereby reduction of the chloro diketone to the enolate would be followed by direct alkylation. Unfortunately, it was not possible to produce the enolate directly with zinc or magnesium, although reduction to the parent diketone **7** under acidic conditions was possible. However, the isolation of **7** was difficult owing to high water solubility and ready deprotonation and unfortunately, useful quantities of the unsubstituted compound could not be obtained.

An alternative route involved initial alkylation with methyl iodide to produce **8**. Interestingly, the activated proton in **3** is so acidic that triethylamine can be used as a base for this alkylation. X-ray analysis (Fig. 3) once again showed that the bias of the bridged bicyclic system had forced the small electrophile exclusively to the *exo*-face.

This compound was smoothly reduced by zinc and hydrochloric acid to produce diketone **9** in good yield. Conversion of this compound to the analogous bicyclic building block proved relatively straightforward (Scheme 4).

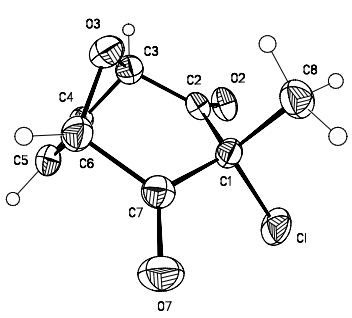
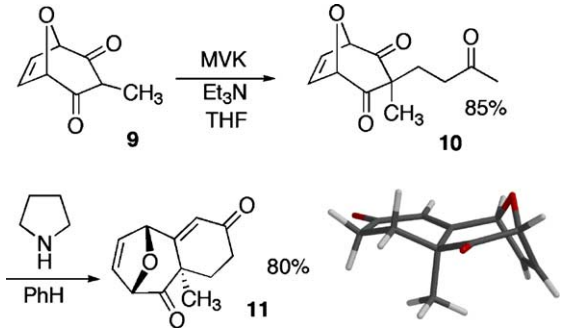


Figure 3. X-ray structure of **8**.



Scheme 4.

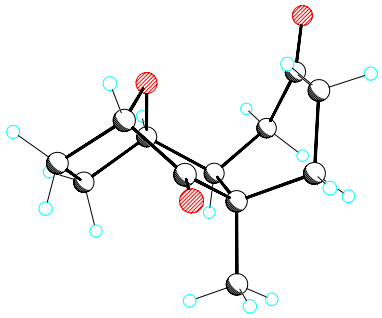
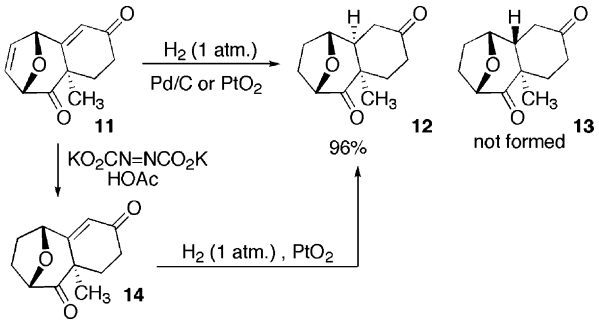


Figure 4. X-ray structure of ketone **12**.

Amine promoted Michael addition proceeded uneventfully to produce tri-ketone **10** in excellent yield. A variety of conditions were examined for the dehydrative aldol cyclization and the use of pyrrolidine was found to be far superior to the alkoxide bases employed previously. Under these conditions, the enone **11** was obtained in a single step in 80% yield. This substructure is common to both erinacine C and guanacastepene A and is available in only six steps from furan.

A final aspect we wished to examine in these preliminary studies was the stereoselectivity of the reduction of the enone. Controlling the ring fusion on bicyclo-[5.4.0]undecanes is often difficult[10] because there is very little energy difference between the alternative isomers. However, it seemed that the rigidity in the seven-membered ring imparted by the bridging ether may kinetically control the formation of this new center. Examination of an AM1 minimized structure[11] (see Scheme 4) suggested that approach to the *endo*-face of the enone was hindered by the two-carbon bridge of the oxabicyclo[3.2.1]octene ring as well as the *endo*-methyl group at the angular position. Reduction from the *exo*-face would deliver the *trans*-fused system common to the erinacines (Scheme 5).

Reduction of the diene under an atmosphere of hydrogen and either a palladium or platinum catalyst yielded a single product in very high yield. Determination of the relative stereochemistry by NMR methods was difficult and recourse was made to X-ray crystallography (Fig. 4).



Scheme 5.

The X-ray structure clearly revealed that reduction had occurred exclusively from the more hindered *endo*-face, giving the *cis*-fused product **12** instead of the anticipated **13**. In an attempt to reverse the selectivity and obtain the *trans*-fused compound as well, the nonconjugated alkene was selectively reduced with diimide. The conversion of these sp^2 centers to sp^3 should increase the steric shielding of the *endo*-face on the enone. However, reduction of **14** again delivered only the *cis*-fused isomer **12**.

In an attempt to explain this strong preference for the formation of the *cis*-isomer, computational studies were made on the two diketones. AM1 calculations[11] revealed that *cis*-isomer **12** is approximately 3.8 kcal/mol more stable than *trans*-isomer **13**, likely resulting from strain on the seven-membered ring. This large difference in thermodynamic stability may explain the strong preference for formation of the *cis*-fused product.

The adduct derived in a single step from furan and tetrachlorocyclopropene can be easily converted into various bicyclo[5.4.0]undecane building blocks through a key Robinson annulation. We are currently examining the asymmetric preparation of these compounds and their application to the synthesis of terpenoid natural products.

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