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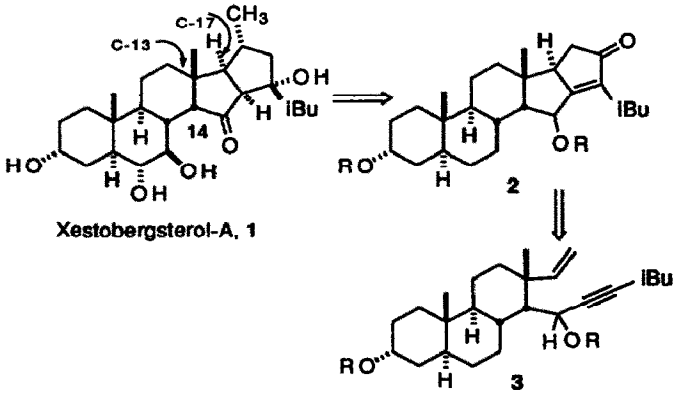
Synthesis of a Model for the Xestobergsterol D and E Rings Using the Pauson-Khand Reaction

Marie E. Krafft* and Xavier Chirico
The Florida State University, Department of Chemistry, Tallahassee, FL 32306-3006

Summary: An intramolecular Pauson-Khand reaction has been used to illustrate the incorporation of proper stereochemistry at the C/D/E rings of a xestobergsterol model system.

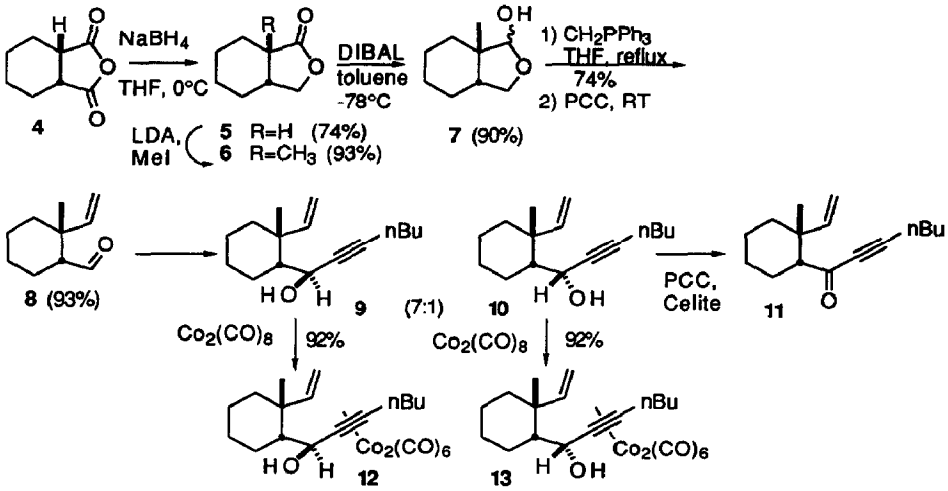
Xestobergsterol-A, (**1**), is a unique, pentacyclic steroid with a cis C/D ring junction. Xestobergsterol-A was isolated in 1992 from the crude extracts of the Okinawan sponge *Xestospongia berquista* Fromont, and it was reported that **1** strongly inhibited histamine release from rat peritoneal mast cells induced by anti-IgE in a dose dependent manner.[1] Our interest in **1** was stimulated by its potent biological activity and the unusual configuration of the C/D/E rings. We envisioned the use of an intramolecular Pauson-Khand[2,3] reaction, i.e. **3** to **2**, to construct the D and E rings of xestobergsterol (Scheme I). A critical stereochemical issue with such an approach is the configuration at the newly formed center at the D/E ring fusion (C-17) relative to the existing stereocenters at the C/D ring fusion (C-13 and C-14). We investigated this important question in the model study described below.

Enynes **9** and **10** were chosen as model substrates to investigate the Pauson-Khand[2,3] ring closures to generate the D and E rings. The steps leading to the alkynols **9** and **10** are described in Scheme 2 and were, for the most part, uneventful. Addition of 1-hexynyl lithium to aldehyde **8** gave rise to a 7:1 mixture of **9**:**10**, readily separable by silica gel flash chromatography. The assignment of the relative stereochemistry of



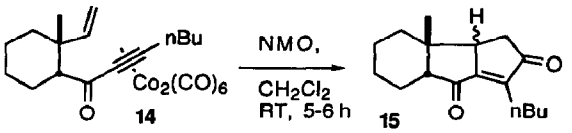
SCHEME 1

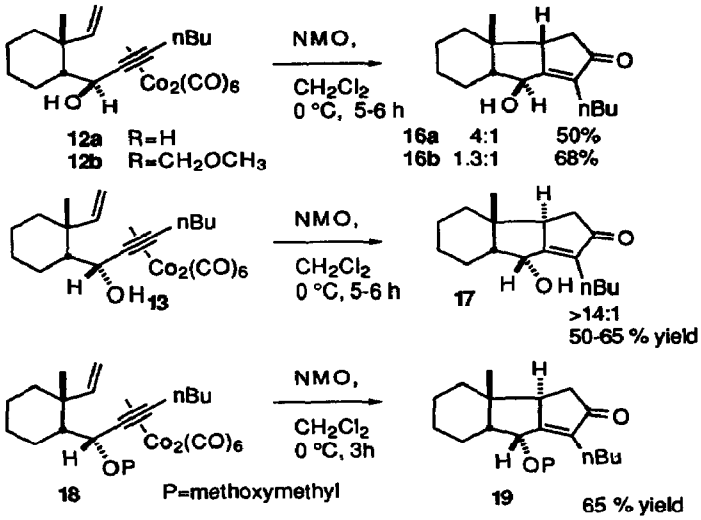
alcohols **9** and **10** is based on the stereochemistry of the cyclization products which was determined by NOE experiments. In order to obtain adequate material to study the effect of the propargylic center on the cycloaddition, a mixture of alcohols was oxidized (PCC, RT, 88%) to give **11**, and reduced (Dibal, toluene, -78 C, 77%) to provide a 1.5:1 ratio of **9**:**10**. Complexation of either alcohol was performed in methylene chloride at ambient temperature using 1.2 equivalents of $Co_2(CO)_8$. Each of the complexes **12** and **13** was isolated in 92% yield.



SCHEME 2

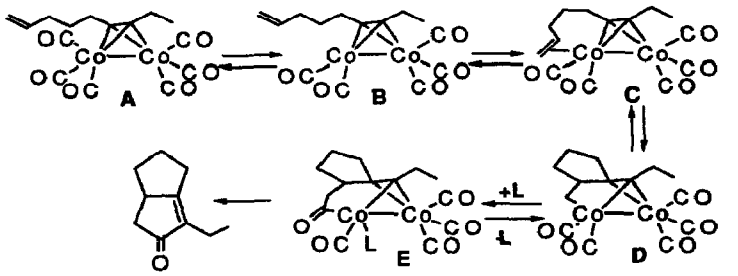
Reaction of ketone **11** with $Co_2(CO)_8$ followed by treatment of the resulting cobalt complex with excess NMO at ambient temperature resulted in the formation of a 1:1 mixture of enediones **15** in 70% yield. Cycloaddition of **12a** using 8-10 equivalents of N-methylmorpholine-N-oxide (NMO)[4,5] in CH_2Cl_2 at 0 °C gave rise to a 4:1 mixture of **16a** and the epimer at the 5:5 ring fusion in 50% yield. The stereochemistry of the tricycle was determined by ^1H NOE experiments. However, subjecting the cobalt complexed carbinol epimer **13** to the analogous cyclization conditions yielded cycloadduct **17** in 50-65% yield, with small amounts of the ring fusion epimer (the stereochemistry of **17** was also determined by NOE studies). *Tricycle **17** exhibits the desired relative stereochemistry between the two ring fusions.* However, methoxymethyl ether **18** undergoes cyclization more cleanly and yields the desired cycloadduct in 65% yield. No other cyclization isomer was detected by ^1H NMR. Interestingly, complex **18** undergoes cycloaddition at ambient temperature in the absence of an oxidizing agent. Further work on the origin of this effect is currently underway.





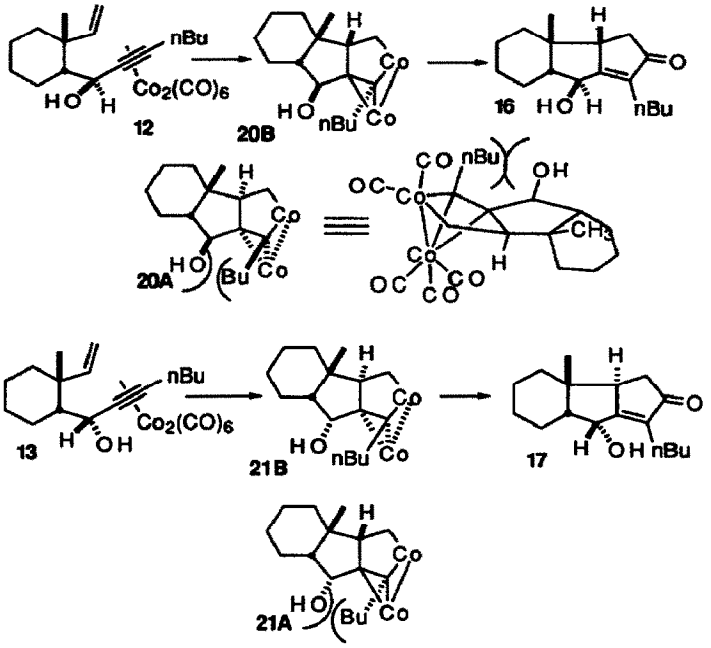
These results make it quite clear that, in this enyne system, the propargylic carbinol center[6] is the major factor which influences the stereochemical outcome of the cycloaddition. The resulting allylic functionality in cycloadducts **16**, **17** and **19** appears predominantly cis to the new ring fusion hydrogen.

An explanation is based on a consideration of the proposed mechanism of the Pauson-Khand cycloaddition which is shown in Scheme 3.[6a] Formation of the metallacycle is expected to occur so that the thermodynamically preferred cis fused bicyclo[3.3.0] ring system will be formed by placing the cobalt and the hydrogen at the ring fusion in a syn orientation. Transition states **20A**, **20B**, **21A**, and **21B** can be proposed for the cycloadditions of **12** and **13** respectively. (The ligands on cobalt have been left out for clarity.) Complex **20A** (which leads to the minor isomer) exhibits steric interactions between the group on



Scheme 3. Proposed Mechanism for the Pauson-Khand Reaction

the alkyne terminus and the group at the propargylic position and should be disfavored. This interaction is apparently eliminated in complex **20B** which would yield the observed isomer. An analogous argument may be used to explain the cyclization of **13** via transition state **21B** rather that **21A** to yield tricycle **17**. These observations are similar to those reported by Magnus.[6,7]



In summary, we have established the efficacy of the Pauson-Khand cycloaddition to provide the necessary relative stereochemistry at C-17 and C-13 of the tricycle, as exhibited in **1**, by taking advantage of steric interactions in the transition state resulting from propargylic substitution. Further work on the Pauson Khand reaction in this context and the synthesis of **1** is in progress and results will be reported in due course.

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