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Double Ring Expansions: A New Method for Making Medium and Large Cyclic Ketones

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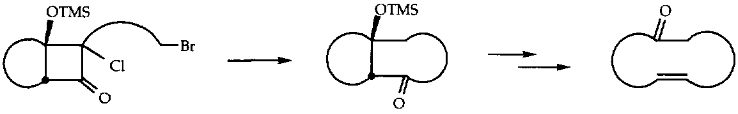
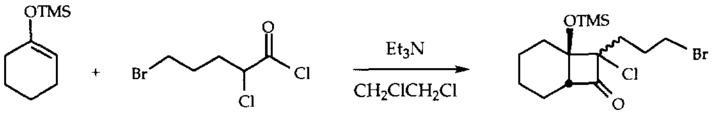
Summary: *A method for making medium and large cyclic ketones by free radical ring expansion of cyclobutanones with sequential Grob fragmentation is described.*

The construction of medium and large rings by means of ring expansion is important in organic synthesis.[1] Free radical mediated ring expansion is a rapidly developing part of this effort.[2] In our continuing exploration of this area, we have developed β-keto ester and cyclobutanone systems for ring expansion of cyclic ketones.[3,4] The cyclobutanone system has special advantages for *cis*-fused medium rings. This method can be extended to larger rings by coupling with a second, ring-expanding, Grob fragmentation (Scheme 1). Two ring expansion methods: side chain incorporation and zero-bridge cleavage,[1a] are employed in this new sequence (Scheme 1). In this paper, we provide results of ring transformations from trimethylsilyloxy substituted cyclobutanones to illustrate the possibilities that exist here.

Scheme 1



Trimethylsilyloxy substituted cyclobutanones are easily prepared by [2 + 2] cycloaddition of ω-bromoalkyl ketenes with cyclic TMS enol ethers.[5] The cycloaddition gives a mixture of



1

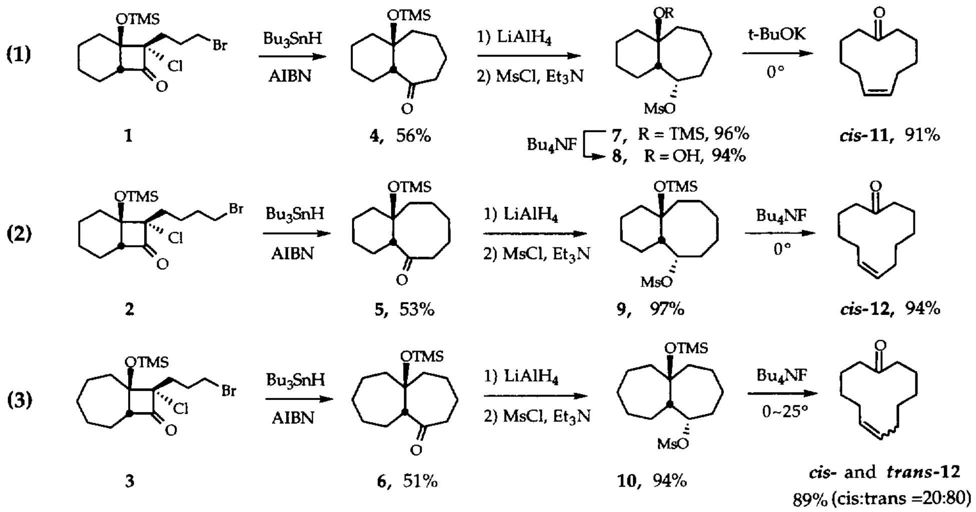
(eq 1)

temp.(°C)	yield (exo:endo)
90	43% (45:55)
25	48% (70:30)
-20~0	44% (>95:5)

exo- and *endo*-bromoalkyl substituted cyclobutanone **1** (eq 1). Our previous studies showed that the *exo*-bromoalkyl cyclobutanones undergo ring expansion.[4b] In the present series, we found the exo : endo ratio from the cycloaddition can be significantly increased by lowering the reaction temperature (eq 1). Thus, ω-bromoalkyl ketene, generated *in situ* by treatment of the α-chloro acid chloride with triethylamine, reacts with the cyclic TMS enol ether to give adducts in the ratio of 45:55 (exo : endo) at 90 °C. The ratio is improved to 70:30 at 25 °C and 95:5 at -20 to 0 °C, while the yield is relatively stable at the different temperatures (eq 1). Acid-sensitive, trimethylsilyloxy-substituted cyclobutanones can be purified by chromatography on basic alumina at 0 °C.

With the *exo*-bromoalkyl cyclobutanones **1-3** in hand (Table 1), free radical ring expansion

Table 1. Double Ring Expansion of Cyclobutanones[7]

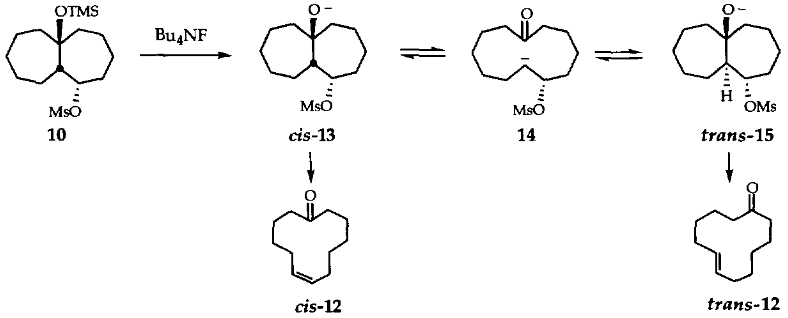


was carried out by slow addition[4b,i] of 2.5-3 eq of Bu_3SnH to the cyclobutanones in refluxing benzene, using AIBN as radical initiator. *Cis*-fused bicyclic ketones **4-6** were formed in good yield (Table 1). Release of four-membered ring strain provides the driving force for this reaction.[6] The bicyclic ketones **4-6** are then prepared for Grob fragmentation by transformation to the corresponding sulfonates **7**, **9**, and **10**. In this sequence $LiAlH_4$ reduction at -42 °C is followed by treatment with methanesufonyl chloride and triethylamine.

Fluoride-induced Grob fragmentation has the advantage of avoiding strongly basic reaction conditions,[8] but the scope of this reaction has been reported to be limited to strained cyclic systems.[8b] In this work, when the silyl ether **7** is treated with 2 eq of Bu_4NF at 0-25 °C for 24 h, only the tertiary alcohol **8** is generated (Table 1, entry 1). This is then treated with *t*-BuOK at 0 °C to form cycloundecenone ***cis*-11**.[9] However, treatment of silyl ethers **9** and **10** with Bu_4NF leads to direct fragmentation (Table 1, entries 2 and 3). When silyl ether **9** is treated with 1 eq of

Bu_4NF at 0 °C, the product is exclusively cyclododecenone ***cis*-12**. Silyl ether **10** gives a mixture of ***cis*-** and ***trans*-12** in the ratio of 20:80 (cis : trans) when treated with 3 eq of Bu_4NF at 0 to 25 °C. ***Trans*-12** is generated from *trans*-fused alkoxy anion ***trans*-15**, which is derived from the *cis*-fused alkoxy anion ***cis*-13** through the intermediate transannular keto anion **14** (Scheme 2).

Scheme 2



In summary, we have developed a new method for making medium and large cyclic ketones by means of a cyclobutanone ring expansion reaction combined with the Grob fragmentation. Fluoride-induced Grob fragmentation using Bu_4NF was also found to be feasible for non-strained cyclic systems.

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(9) The ^{13}C NMR of ***cis*-11** showed only six lines, while the ^{1}H NMR spectrum of the DNP derivative of ***cis*-11** showed J_{AB} =9.3 Hz for the two vinyl protons. Both ***cis*-** and ***trans*-12** showed twelve lines in their ^{13}C NMR spectra. For ***cis*-12** the two vinyl protons have J_{AB} =11.1 Hz, while for ***trans*-12** the two vinyl protons have J_{AB} =15.2 Hz in the ^{1}H NMR spectra.

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