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CYCLOPROPYLCARBINYL RADICAL-MEDIATED RING EXPANSION TO SEVEN-MEMBERED CARBOCYCLES

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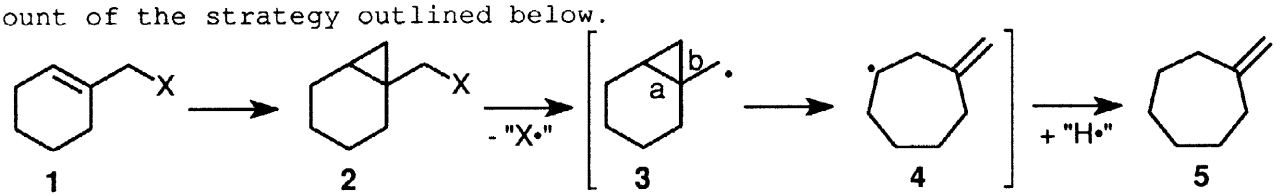
Abstract: *Radical-mediated ring expansion methodology is presented wherein 7-membered carbocycles can be prepared from the corresponding xanthate derivatives of bicyclo[4.1.0]heptan-1-methanol. In certain systems, an intermediate cycloheptyl radical appears to be kinetically favored over the cyclohexyl radical, but the direction of cyclopropylcarbinyl radical fragmentation is subject to substitution about the bicyclo[4.1.0]heptan-1-methyl ring.*

The frequent occurrence of seven-membered carbocycles in natural products has spawned the development of numerous synthetic routes to these rings systems. Typical approaches[1] include ring expansion, ring contraction, or rearrangements starting from more easily prepared ring sizes as well as cyclization of a straight chain precursor containing a nucleophilic and electrophilic site.

We were interested in exploring the applicability of radical **3** as part of a methodology for the preparation of seven-membered rings. Radical precursor **2** (where X is any group predisposed to homolytic bond cleavage) would be accessible via cyclopropanation of cyclohexene **1**. The utility of this approach is especially attractive when compound **1** is viewed antithetically as a Diels-Alder cycloadduct. Upon generation of cyclopropylcarbinyl radical[2] **3**, the strained cyclopropyl ring could fragment along the shared bond of the bicyclic system (bond "a") to yield 3-methylenecycloheptyl radical **4** which is subsequently trapped by reducing agent to yield ring-expanded product **5**, methylenecycloheptane. Alternatively, radical **3** could fragment along the bond exo to the cyclohexane ring (bond "b") to provide, after reduction, 2-methylmethylenecyclohexane. We report here a preliminary account of the strategy outlined below.



Our study began with the cyclopropanation of allylic alcohols **1**[3] and **6**[4] using 2.5 equivalents of Et_2Zn/CH_2I_2 (Et_2O; less reagent resulted in incomplete

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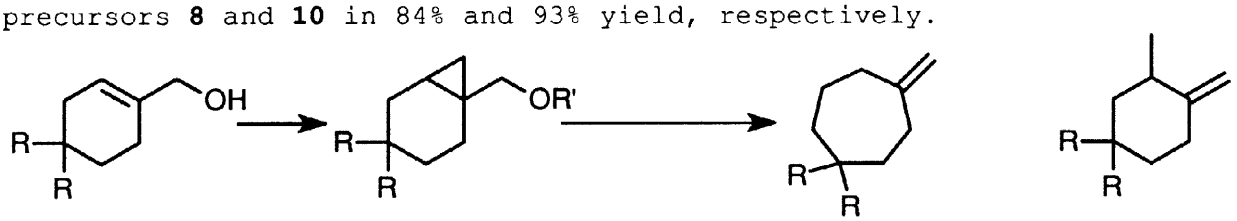
conversion). Activation of the resulting neopentyl alcohols (-OH → -Br[5] or -OH → -OTs[6]) proved difficult. Fortunately, alcohols **7** and **9** could be converted to their *S*-methylthiocarbonate (xanthate ester) derivatives, a functional group developed by Barton for radical deoxygenation.[7] Hence, reacting either 1° alcohol with DBU and CS_2 in DMF followed by alkylation with CH_3I provided radical precursors **8** and **10** in 84% and 93% yield, respectively.



1: -R = -H
6: -R = -O(CH$_2$)$_2$O-

7: -R = -H; -R' = -H
8: -R = -H; -R' = -C(S)SCH$_3$
9: -R = -O(CH$_2$)$_2$O-; -R' = -H
10: -R = -O(CH$_2$)$_2$O-; -R' = -C(S)SCH$_3$

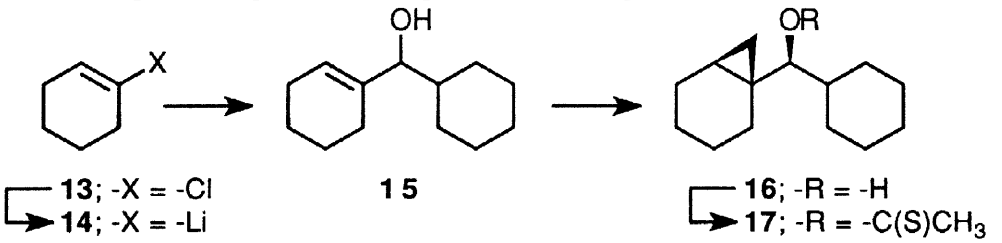
11a: -R = -H
12a: -R = -O(CH$_2$)$_2$O-

11b: -R = -H
12b: -R = -O(CH$_2$)$_2$O-

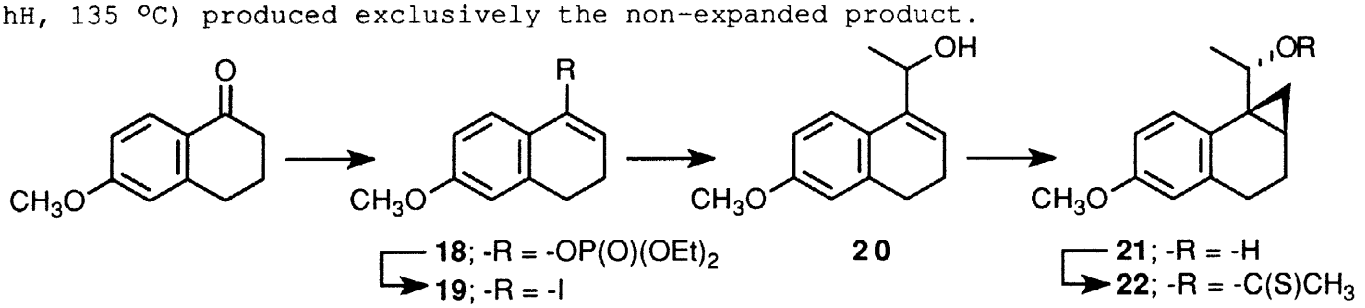
Radical deoxygenation of primary alcohols, via their xanthate ester, can typically be accomplished with tributylstannane (Bu_3SnH) in refluxing xylene (130 °C) or *p*-cymene (150 °C).[7] Indeed, radical formation was accomplished by heating a sealed tube containing xanthate ester **8** or **10** and *n*-Bu_3SnH in benzene at 135 °C. The distribution of 6- versus 7-membered ring product at various concentrations of Bu_3SnH is shown in the **Table**. Under these relatively high temperature conditions, it is evident that radical **4** is kinetically favored. Moreover, cycloheptane products (**11a**, **12a**) increase with higher concentrations of reducing agent with near exclusive formation of **11a** at [Bu_3SnH] ≥ 0.80 M (**Table**: entries 2 and 3). Surprisingly, **12a** was not selected as the major product even at higher [Bu_3SnH]. It is also interesting to note that the seemingly remote acetal moiety affects the fragmentation pathway, presumably by destabilizing the developing β- versus γ-radical. We were unable to lower the reaction temperature for **10** → **11** by application of the Et_3B/air protocol.[8]

We next investigated the effects of employing a secondary xanthate on the distribution of fragmentation products. Reacting cyclohexanone with PCl_5 in CH_2Cl_2[9] gave 1-chlorocyclohexene (**13**) which, upon treatment with lithium powder, generated 1-cyclohexenyllithium (**14**). Quenching with cyclohexanecarboxaldehyde afforded secondary alcohol **15** in 55% yield from cyclohexanone. Conversion to β-cyclopropyl alcohol **16** was accomplished in quantitative yield by treatment of **15** with Et_2Zn/CH_2I_2 in ether. We found it was critical to premix the Et_2Zn and CH_2I_2 at -78 °C and then allow the solution to warm to 0 °C before olefin addition. NMR and GC analysis of **16** indicated that only one stereoisomer was formed and X-ray

cystallography established *syn* stereochemistry. Xanthate ester **17** was prepared in 87% yield by deprotonation of **16** with KH (5 equiv.) followed by addition of CS_2 and then CH_3I. The rearrangement (same conditions as **8** and **10**) favored ring-expanded over non-expanded products by ≈3:1 (entry 10).



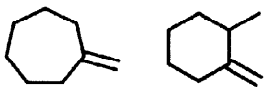
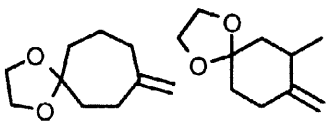
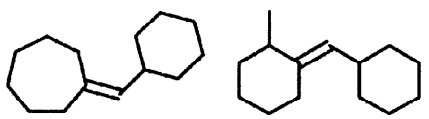
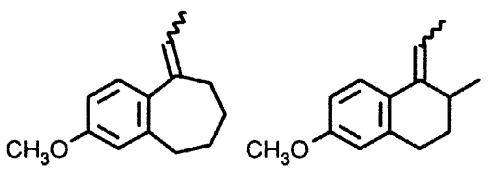
To probe whether geometric constraints would affect bond "a" or bond "b" selection, compound **22** was prepared. Diethyl phosphonate **18** was prepared by treatment of 6-methoxy-α-tetralone with LDA followed by trapping with diethylphosphoryl chloride. Treatment of this crude phosphonate with NaI and TMSCl provided vinyl iodide **19**[10] which proved to be prone to decomposition. The pure iodide was immediately subjected to *t*-butyllithium in ether followed by trapping with acetaldehyde to provide allylic alcohol **20** in 71% yield. Cyclopropanation (by the method described for **15**) produced an 11:1 mixture of diastereomers in 84%. The relative stereochemistry of the major isomer, isolated by recrystallization from CH_2Cl_2, is shown below. Xanthate ester **22** was prepared in 85% yield by sequential treatment of **21** with KH, CS_2 and CH_3I. In contrast to **8**, **10**, and **17**, cyclopropylcarbinyl fragmentation of **22** with Bu_3SnH (sealed tube, PhH, 135 °C) produced exclusively the non-expanded product.



The results shown in the **Table** clearly indicate that fragmentation pathways for cyclopropylcarbinyl radicals are dependent on the cyclohexyl ring substituents as well as the hybridization state of the ring carbons. For the all-sp^3 cyclohexyl system, there is evidence that the ring expansion product is kinetically favored over the non-expansion product. While the elevated temperature required (<135 °C was ineffective) to generate carbon-centered radicals from xanthates precludes an

accurate kinetic analysis of these systems, this methodology does show potential as an entry into 7-membered carbocyles.

Table: 7- vs. 6-membered ring distribution from Bu_3SnH reduction of xanthates.

entry[a]	precursor	[Bu_3SnH]	7-:6-ring	products
1	**8**	0.40	1:1	
2	**8**	0.80	>95:5	
3	**8**	1.00	>95:5	
4	**10**	0.05	32:68	
5	**10**	0.08	36:64	
6	**10**	0.11	38:62	
7	**10**	0.13	40:60	
8	**10**	0.20	41:59	
9	**10**	0.43	43:57	
10	**17**	0.10	73:27[b]	
11	**22**	0.06	0:100[b]	

[a] Entries 1-3 list product ratios determined by ^1H NMR; entries 4-10 list isolated product ratios. [b] *E/Z* olefin geometry was not determined.

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