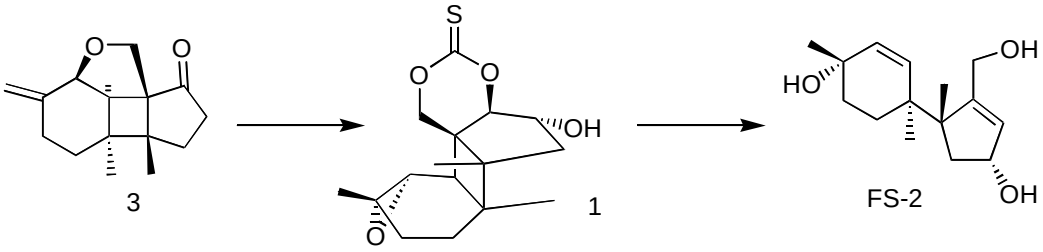
CHAPTER III: *RADICAL FRAGMENTATION - MODEL SYSTEMS*

- *Introduction*



The synthesis of intermediate **3** enabled the investigation of the radical fragmentation theory originally proposed in chapter 1. A number of model systems were constructed from this intermediate, which could serve as a handle to determine what factors controls the selectivity of the fragmentation at the different steps of the reaction regarding thermodynamics and strain factors.

This chapter will first present background information on radical fragmentation reactions in general and discuss specific considerations that may affect the reactions proposed in this synthesis. This involves the selectivity of the cyclic thiocarbonate fragmentation to generate the primary or secondary radical, the fragmentation of the cyclobutyl carbinyl radical to give exocyclic or endocyclic bond cleavage, and the opening of the epoxide. The preparation of the model compounds will then be discussed along with the results of the fragmentation reactions.

- *Radical Fragmentation Background*

Reactions involving radical intermediates have been known since the beginning of the century,[117] but they were not often incorporated in synthetic plans because they were regarded as unpredictable and complex. Radicals react at a high absolute rate, which may suggest low selectivity, but it is the relative rates between the competing reaction paths that are important for selectivity.

Radicals can react with another radical or with a non-radical molecule. Radical-radical reactions occur by combination or disproportionation at rates approaching the diffusion controlled limit. These reactions are undesirable for most synthetic applications and can be avoided or limited by conducting the experiments under high dilution.[118] Radical-molecule reactions occur with a wide spectrum of rates and can be both chemo and regioselective.

Radical-molecule reactions allow for bond formation and bond cleavage to occur in a neutral environment. Under these conditions most functional groups may be left unprotected. The products of these reactions can be more predictable than the outcome of complex polar reactions. Steric crowding,[119] particularly on the radical center, is often tolerated. The reaction is not subjected to large solvent effects or ion pairing and aggregation issues. The choice of solvents is based on boiling point and hydrogen donating ability, and the volume of solvent used can dramatically influence the product

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[117] Gomberg, M. *J. Am. Chem. Soc*. **1900**, 22, 757.
[118] Curran, D. Synthesis **1988**, 417.
[119] Barton, D. R.; Motherwell, R. S. H. *Pure and Appl. Chem*. **1981**, 53, 15.

ratio when one or more second order reactions are involved as a consequence of changes in reagent concentration.

Radical reactions can be advantageous over polar reactions in that they are less prone to rearrangement. In the example shown in Figure 3.1 Lange[120] observed the formation of ring expansion product **44** when he submitted compound **43** to radical fragmentation conditions. When the same substrate **43** was submitted to cationic solvolysis conditions (AgOAc, TFA), skeletal rearrangements were observed with products **45** and **46** deriving from both possible four-membered ring bond-migrations.

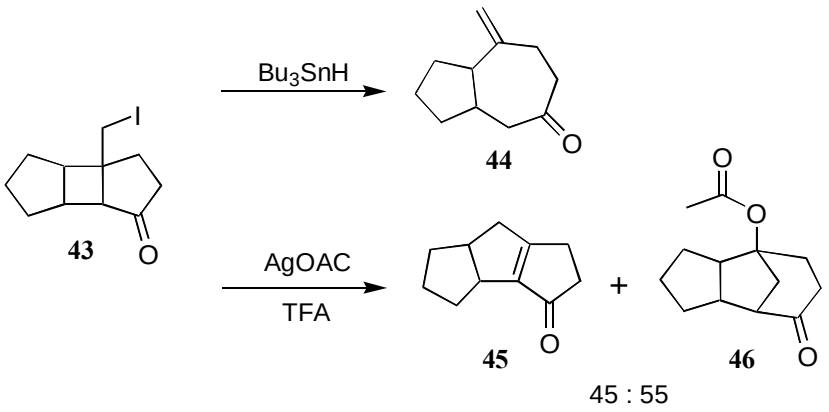


Figure 3.1

The product of a radical reaction is another radical; therefore tandem or sequential reactions are a natural development. It is possible to effect radical additions to unactivated alkenes and to introduce functionalization at remote positions. Barton[121] took

[120] Lange, G. L.; Gottardo, C. *J. Org. Chem.* **1995**, 60, 2183.
[121] Barton, D. H. R.; Beaton, J. M.; Geller, L. E.; Pechet, M. M. *J. Am. Chem. Soc* **1961**, *83*, 4076.

advantage of radical reactions in the synthesis of steroids where he used a 1,5-H migration to introduce functionalization at unactivated areas of the steroid skeleton (see Figure 3.2).

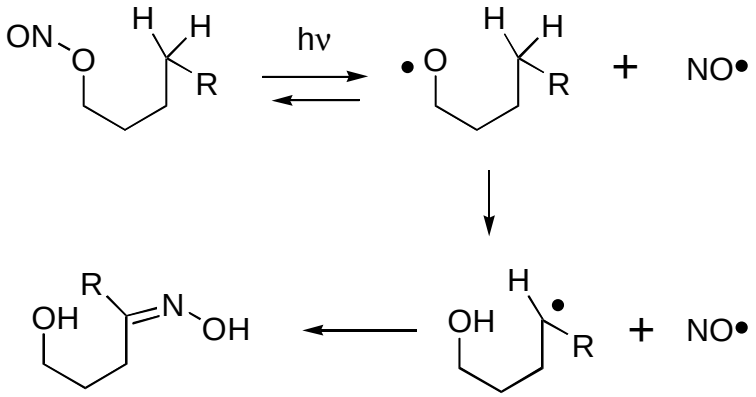
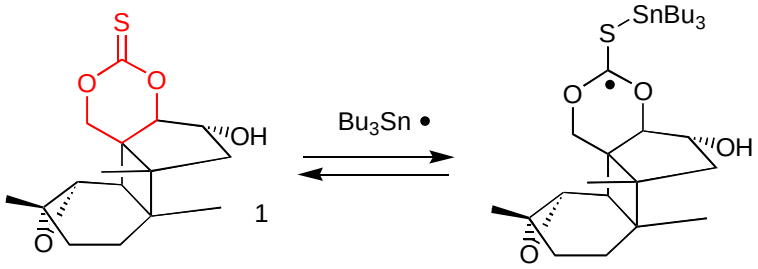


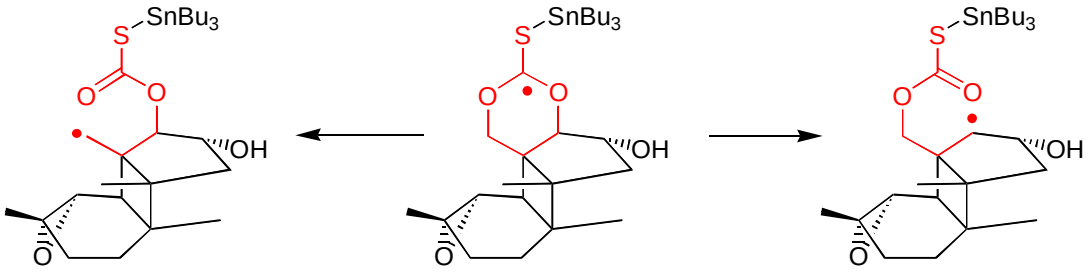
Figure 3.2

1. Fragmentation of Thionocarbonates

The fragmentation mechanism of the thionocarbonate system is well understood.[122] It involves rapid, reversible addition of the stannyl radical to the thiocarbonyl group followed by slower fragmentation of the adduct radical with cleavage of the carbon-oxygen bond.



Carbon-oxygen bonds are usually very strong (BDE_{298K} ~83 Kcal/mol),[123] therefore they do not readily undergo β-fission. However under favorable conditions the C-O bond can be broken as in the transformation of a weak C=S bond into a strong C=O.



For the fragmentation precursor of FS-2 (shown above), the product of the addition of the stannyl radical to the thiocarbonyl group is locally symmetric. Fragmentation can occur in either direction to generate a primary alkyl radical or a secondary alkyl radical. A number of factors have been discussed in the literature as being important for determining the relative rates that establish the selectivity in this fragmentation; such as orbital overlap,[118] stability of the product radicals[124] or release of strain.[125]

For example, in sugars, primary versus secondary radical selectivity always favors formation of the secondary radical. Barton[124] argues that the failure to form primary derivatives is due to lesser stability of primary relative to secondary radicals. Figure 3.3

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[122] Crich, D.; Beckwith, A. L. J.; Chen, C.; Yao, Q. W.; Davidson, I. G. E.; Longmore, R. W.; Deparrodi, C. A.; Quinterocortes, L. and Sandovalramirez, J. *J. Am. Chem. Soc*. **1995**, 117, 8757.
[123] Hartwig, W. *Tetrahedron* **1983**, 39, 2609.
[124] Barton, D. R. and Subramarian, R. *J. Chem. Soc. Perkin Trans. I* **1977**, 1718.
[125] Ruchardt, C. *Angew. Chem. Int. Ed. Eng.* **1970**, 9, 830.

illustrates the fragmentation of a five-membered ring cyclic thionocarbonate.[126] Formation of the secondary radical **48** was the preferred pathway for this reduction reaction supporting Barton's hypothesis. Along with the product deriving from the primary radical (**49**), other side products included reduction of the thiocarbonyl (compound **50**) and compound **51** which is a product of the Schönberg rearrangement.[127]

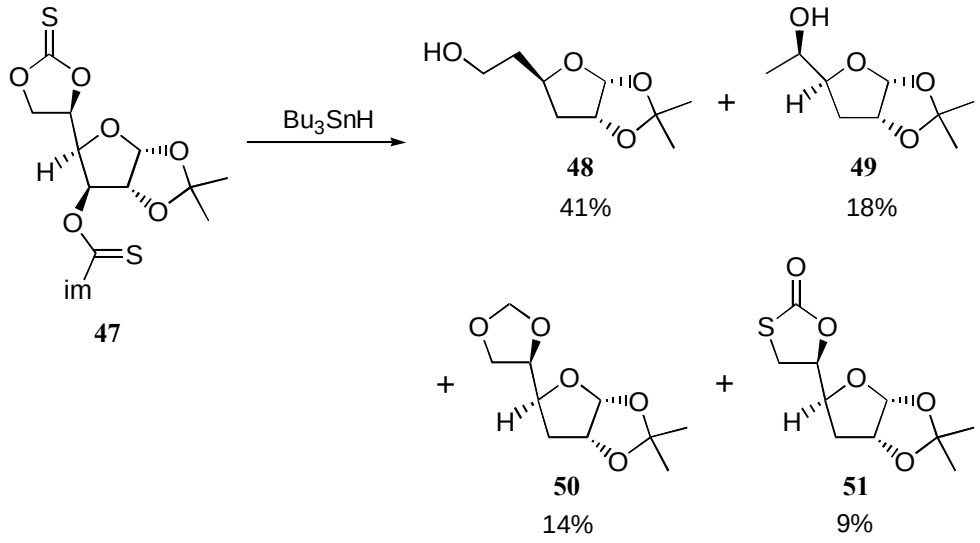

Figure 3.3

The stability of the radical, however, does not always determine the selectivity of the reaction. Studies of Barton-McCombie reactions on the taxol skeleton[128] serve to illustrate the role of strain in determining selectivity. In the example below (Figure 3.4), the presence of an acetate substituent in the eight-membered ring of compound **55** was important for determining the outcome of the reaction. When the acetate group was next

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[126] De Bernardo, S.; Tenge, J. P.; Sasso, G. and Weigele, M. *Tetrahedron Lett*. **1988**, 29, 4077.

[127] (a) Schönberg, A.; Vargha, L. v. *Ber. Dtsch. Chem. Ges.* **1930**,. *63*, 178; (b) Schönberg, A.; Vargha, L. v.; Paul, W. *Liebigs Ann. Chem.* **1930**,. *483*, 107.

to the carbonyl the major product (**56**) was derived from the tertiary radical; when the acetate group was not present the major product (**53**) was derived from the secondary radical and the product derived from the tertiary radical (**54**) was obtained in only 8% yield. This change in selectivity can be explained by the increase in ring strain as a consequence of conformational changes induced in the ring by the presence of the acetate. This result is contrary to Barton reports[119,124] that: tri-butyltinhydride mediated deoxygenation of diol-thionocarbonates proceeded regioselectively to introduce hydride at the more substituted carbon due to a preference to form the more stable radical.

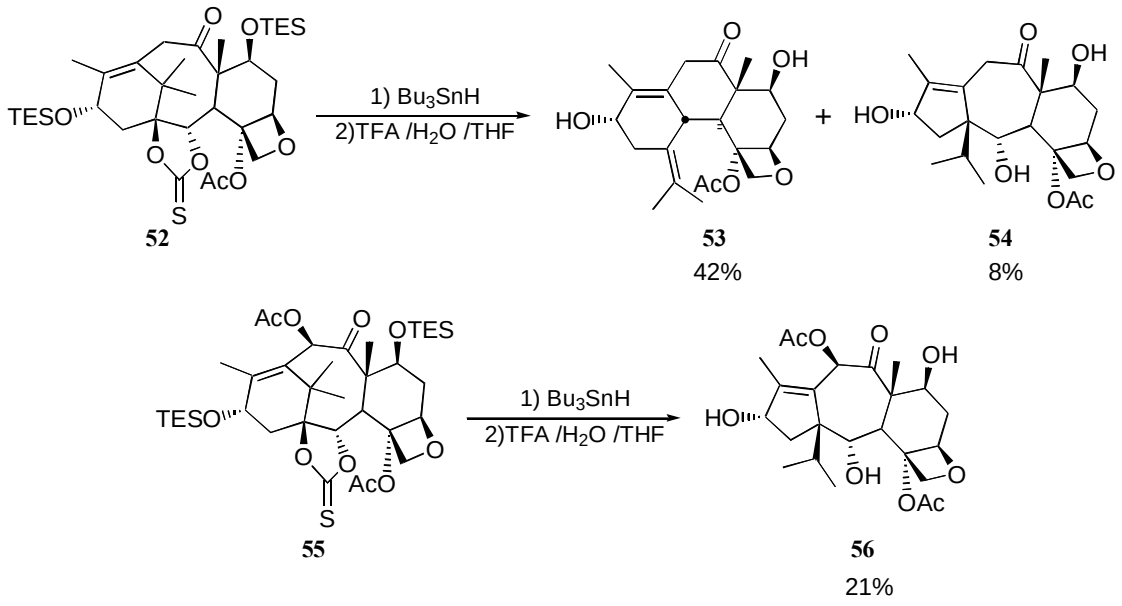
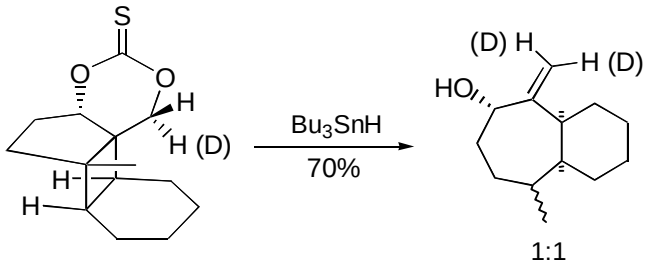


Figure 3.4

[128] Chen, S. H.; Huang, S.; Gao, Q.; Golik, J. and Farina, V. *J. Org. Chem*., **1994**, 59, 1475.

In the example below, Ziegler[129] observed that radical fragmentation of the six-membered ring thiocarbonate gave rise to a product that derived from a primary radical. The system then underwent cyclobutylcarbinyl fragmentation to yield the ring expansion product. The experiment was repeated after introduction of a deuterium label at a specific position. Scrambling of the label was observed indicating that preference for formation of the primary radical was not due to bond overlap in a concerted process. Also, examination of structural models suggests that both C-O bonds have good orbital overlap for fragmentation.



[129] Ziegler, F. E.; Zheng, Z. L. *J. Org. Chem*, **1990**, 55, 1416.

Further studies of this reaction, in a simplified system, showed that the four-membered ring was not required for the observed course of bond cleavage of the cyclic thionocarbonate.

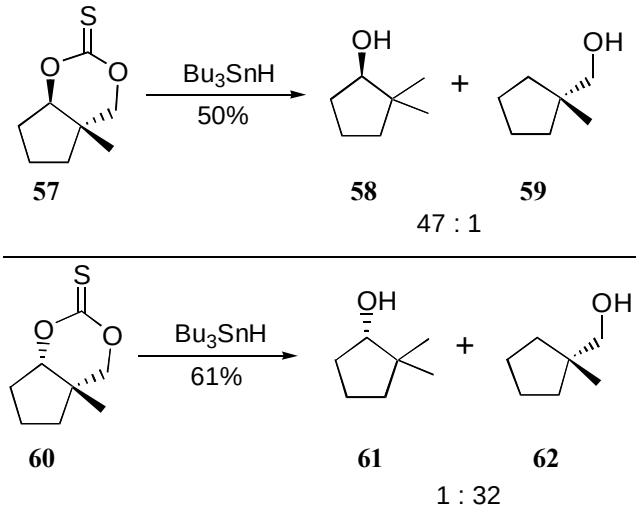


Figure 3.5

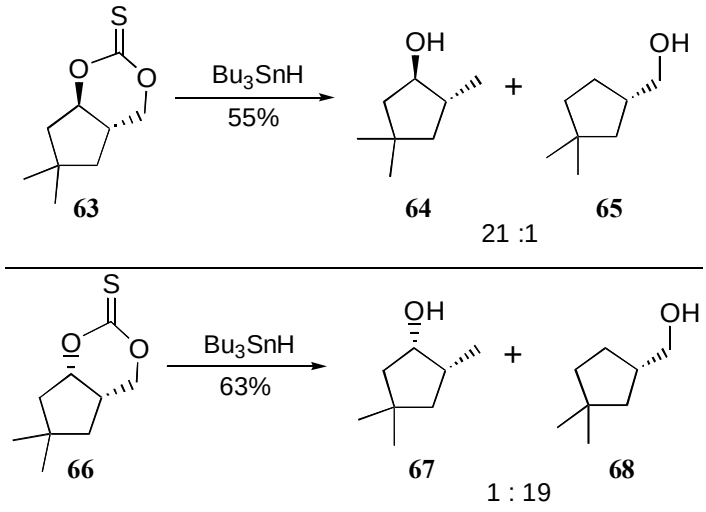


Figure 3.6

The stereochemistry at the ring junction between the five-membered ring and the cyclic thionocarbonate controls the selectivity of the fragmentation reaction (Figures 3.5 and 3.6). When the ring junction between the cyclic thionocarbonate and the five-membered ring is *trans* (compounds **57** and **63**), fragmentation of the cyclic thionocarbonate will favor the product deriving from the primary radical (compounds **58** and **64**) at a ratio of 47:1 and 21:1 respectively. When the ring junction is *cis* (compounds **60** and **66**), the major product is derived from the secondary radical (compounds **62** and **68**) at a ratio of 1:32 and 1:19 respectively. Experimental results suggest that local steric aspects do not play a role in the selectivity, as the reaction is successful with (Figure 3.5) and without (Figure 3.6) the methyl group substitution at the ring junction. The observed *cis*-*trans* selectivity suggests that relief of strain during the fragmentation reaction, due to difference in the conformation adopted by the molecules, is the causative agent.

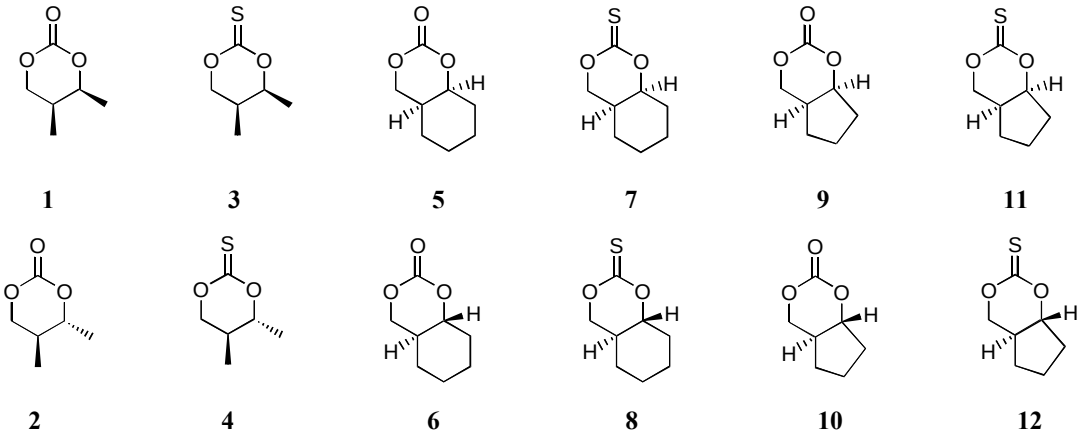
Barton reports[124] suggest that the stability of the radicals is the dominant factor in determining selectivity, while the experiments conducted in the Ziegler lab support Ruchardt's theory[125] that strain plays a crucial role in determining the selectivity in the radical formation. Given these different views, a more in depth analysis of the selectivity issues for thionocarbonate fragmentation was explored.

Initially, an attempt to model the transition state for the radical cleavage reaction was done using the software package MacroModel.[130] The transition state was mimicked by stretching the bond that would eventually cleave to generate the radical. The simulations were carried out on the carbonate equivalent of the 6-5 thionocarbonate

[130] MacroModel v 4.5 developed by Prof. Clark Still at Columbia University.

simplified model system shown above. Primary and secondary radical formation was examined. These studies concluded that bond-angle-bending strain plays a major role in the regioselectivity of these reactions.

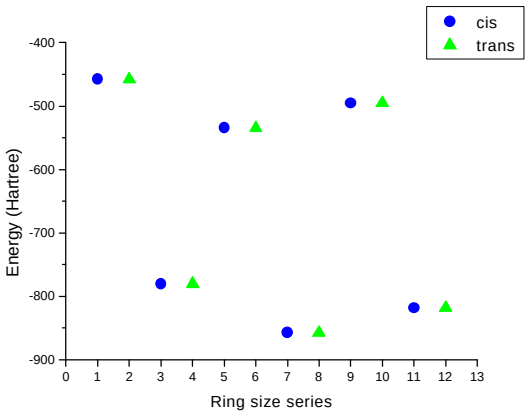
In an attempt to get a better understanding of what was determining the selectivity, *ab initio* calculations were used to evaluate the fragmentation reaction. The *ab initio* method offers the opportunity to examine the energy, charge distribution and geometry of each of the intermediate radicals and transition states involved in the fragmentation. Geometry calculations were conducted on a simplified version of the fragmentation system. Initially, a series of molecules were examined to determine if there was something inherently different about the 6-5 ring system (molecules **9**-**12**) versus a 6-6 ring system (molecules **5**-**8**) or a dimethyl substituted six-membered ring thionocarbonate (molecules **1**-**4**), in the context of *cis* versus *trans* substitution. Details about how the calculations were carried out and the specific results obtained can be found in Addendum 4. Here will be presented the conclusions derived from the calculations.



1 **3** **5** **7** **9** **11**

2 **4** **6** **8** **10** **12**

The results from the *ab initio* calculations conducted on compounds **1** through **12** demonstrated that *cis* and *trans* molecules have similar energies (Figure 3.7a). The charge distribution results indicated that charge was not a factor in determining the selectivity. Angle-offset[131] calculations showed that the carbonates display a smaller offset than the respective thionocarbonates except for the 6-5 series (compounds **9**, **10**, **11** and **12**) in which the offset associated with *cis* thionocarbonate **11** is smaller than its carbonate counterpart (Figure 3.7b).



Compound Number	Total Offset	Energy (Hartree)
1	0.7587	-457.6375
2	0.7741	-457.6393
3	0.8198	-780.2564
4	0.8298	-780.2582
5	0.7533	-534.5498
6	0.6915	-534.5501
7	0.8147	-857.1689
8	0.7375	-857.1689
9	0.8878	-495.5063
10	1.2122	-495.4997
11	0.3847	-818.1251
12	1.2646	-818.1182

Figure 3.7 (a) Energy calculation

[131] Angle-offset calculations based on the minimized geometries obtained from the *ab initio* calculations mimc the effect of bond-angle-strain energy associated with these molecules. See Addendum IV for more details.

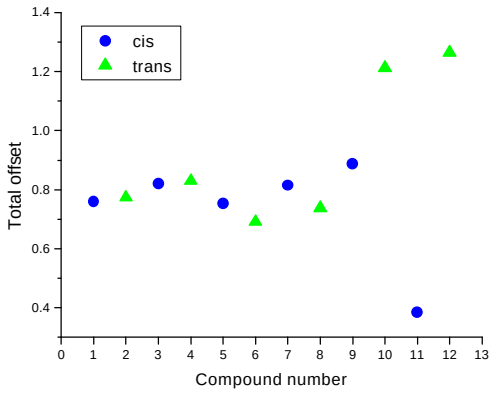
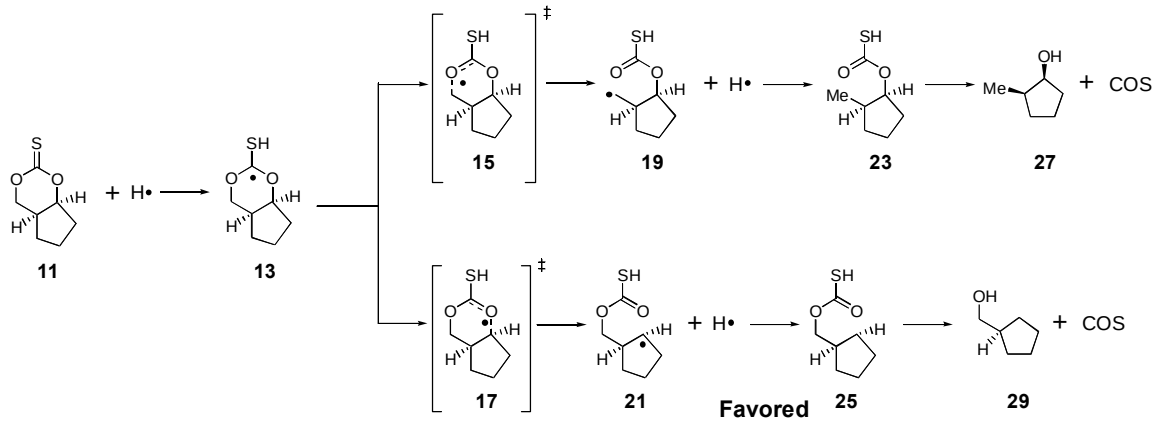
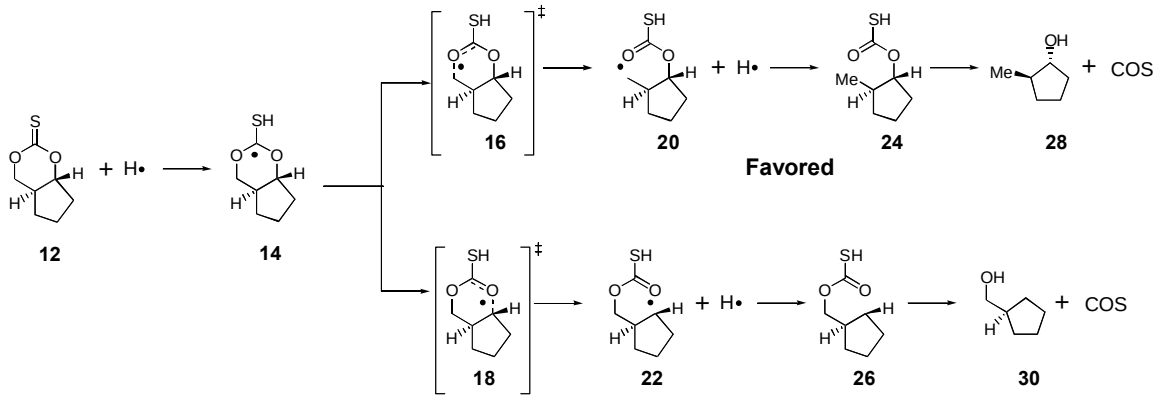


Figure 3.7 (b) Angle-offset estimation

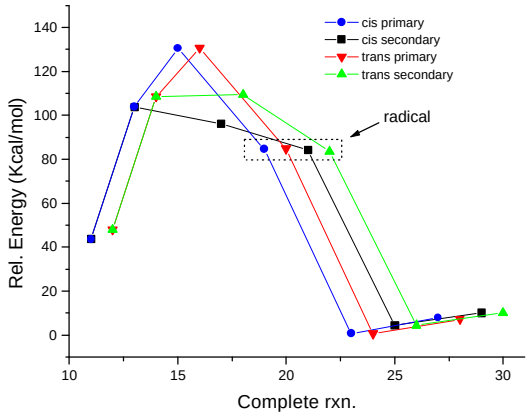
Additionally, the fragmentation reaction itself was examined starting from molecule **11**, representing the *cis* configuration and **12**, representing the *trans* configuration.





Simple thermodynamical analysis of the reactions (see the graph and chart in Figure 3.8) would indicate preference for the formation of the secondary radical (**21** and **22**) in both the *cis* and the *trans* series. Secondary radical **21** is more stable than primary radical **19** by 6.36 x 10^{-4} Hartrees (0.399 Kcal/mol) which should give an approximate 2:1 selectivity[132] at 25 ^{o}C for formation of the secondary radical. Meanwhile, the secondary radical **22** is more stable than the primary radical **20** by 2.04 x 10^{-3} Hartrees (1.28 Kcal/mol) which should give an approximate 6:1 selectivity at 25 ^{o}C for formation of the secondary radical. This agrees with what is expected based on stability of secondary *versus* primary radical analysis but is not in agreement with the experimental observation that the primary radical (**20**) is the preferred product for the *trans* system.

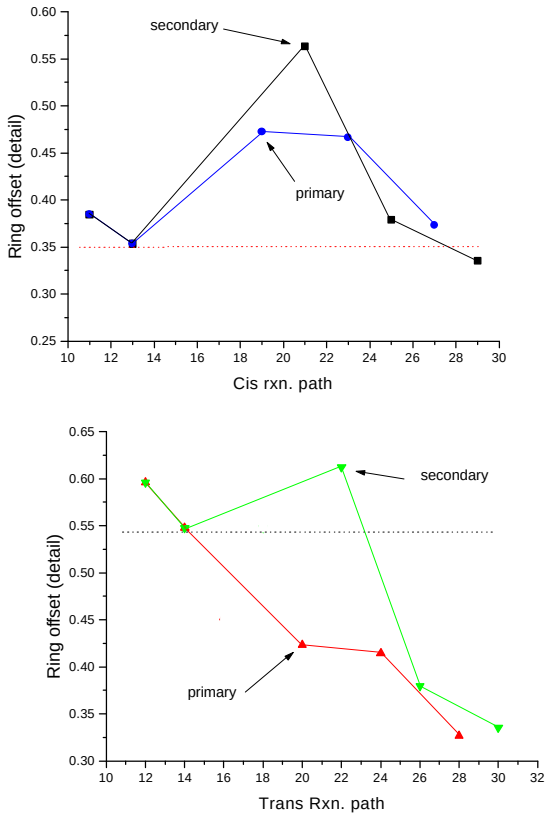
[132] Based on $\Delta G = - RT \ln K$ where R= 1.9872 cal/molK.



Compd. Number	Energy (Hartree) ab initio		Rxn. Energy (Hartree) ab initio	Rxn. Energy (Kcal/mol) relative
11	-818,1251	H-H	-819,2519	43,6499
12	-818,1182	H-H	-819,2450	47,9797
13	-818,6578	H•	-819,1560	103,8280
14	-818,6504	H•	-819,1486	108,4716
15	-818,6152	H•	-819,1134	130,5599
16	-818,6489	H•	-819,1134	130,5599
17	-818,6699	H•	-819,1681	96,2352
18	-818,6489	H•	-819,1471	109,4129
19	-818,6884	H•	-819,1867	84,5823
20	-818,6881	H•	-819,1863	84,8082
21	-818,6891	H•	-819,1873	84,1807
22	-818,6901	H•	-819,1884	83,5281
23	-819,3204		-819,3204	0,6843
24	-819,3205		-819,3206	0,5713
25	-819,3145		-819,3145	4,3489
26	-819,3145		-819,3145	4,3489
27	-309,0482	COS	-819,3088	7,9195
28	-309,0497	COS	-819,3103	7,0033
29	-309,0447	COS	-819,3053	10,1157
30	-309,0447	COS	-819,3053	10,1157
H•	-0,4982			
COS	-510,2606			
H-H	-1,1268			

Figure 3.8

For the *cis* reaction, analysis of the offset-from-the-ideal-angle associated with the ring portion of each intermediate of the fragmentation process showed an increase in the offset for the formation of both radicals. Formation of the primary radical (**13** to **19**) resulted in a change in ring-offset of 0.12, while the formation of the secondary radical (**13** to **21**) resulted in a change in ring-offset of 0.21, as shown in the graph in Figure 3.9.



Compound Number	Total Strain	Ring Strain
11	0,3847	0,3847
12	1,2646	0,5961
13	1,1524	0,3535
14	1,3420	0,5476
15	1,7867	0,3979
16	1,5677	0,4528
17	6,5950	2,9316
18	1,2623	0,5476
19	0,9894	0,4723
20	0,9370	0,4230
21	1,1768	0,5634
22	1,2241	0,6124
23	0,9933	0,4667
24	0,9351	0,4144
25	0,9949	0,3792
26	0,9949	0,3792
27	0,9197	0,3733
28	0,8803	0,3266
29	0,8493	0,3352
30	0,8493	0,3352

Figure 3.9 (a) Ring Offset-cis rxn path; (b) Ring Offset-trans rxn path

For the *trans* reaction, the two possible radicals show opposite trends. Formation of the primary radical (**14** to **20**) is favored due to decrease in ring-offset of 0.13. Formation of the secondary radical (**14** to **22**) is unfavorable due to an increase of ring-offset of 0.07 (see Figure 3.9).

Based on these observations, it may be concluded that the *trans* series selectivity is controlled by the release of the offset-from-the-ideal-angle associated with the ring portion of the intermediates, while thermodynamics (*via* formation of the more stable secondary radical) controls the *cis* series selectivity. The *trans* series has greater overall offset-from-

the-ideal-angle than the *cis* series and therefore changes in the offset are proportionally more important and thus play a bigger role in defining selectivity towards formation of the primary radical and overcomes the thermodynamical tendencies of the system.

2. Beta-oxygen effect

The reaction rate of radical formation is accelerated by the presence of an oxygen substituent beta to the site of radical formation. Barton[133] first reported the β-oxygen effect where he stated that "various thiocarbonyl esters bearing alkoxy or acyloxy groups in the β-position underwent deoxygenation upon treatment with tri-butyltinhydride at lower temperatures than the corresponding unsubstituted species". He explained this result by stating that the "β-bonded oxygen has a marked effect in stabilizing carbon radicals thus permitting homolytic fission not seen otherwise".

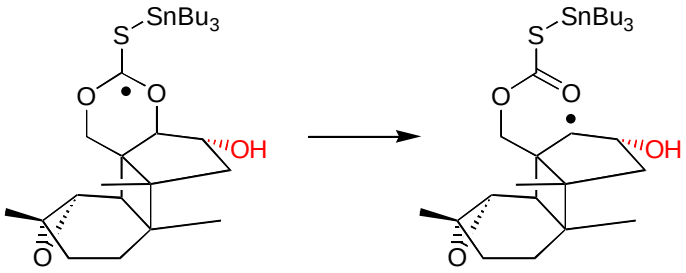


Figure 3.10

Beckwith[122] further investigated Barton's results and found that the β-oxygen effect was small, corresponding to a difference of only 1 Kcal/mol in activation energy at

110 °C. The observed reaction rates were faster for OH substituted substrates, but this was highly dependent on the conformation of the molecule. He observed that compounds that had a flexible frame did not exhibit the Barton β-oxygen effect and that in conformationally rigid species, stereochemistry played an important role in the magnitude of the effect. Further studies indicated that the results could be explained in terms of differing torsional and ring strain energies present in the various radicals. Beckwith suggested that relief of unfavorable dipolar interactions between synclinal carbon-oxygen bonds also played an important role and may be dominant in certain cases. This relief of dipolar interactions may be the underlying reason for the rate differences originally noted by Barton for highly functionalized acyclic systems, rather than stabilization effects. In the competition experiment shown in Figure 3.11, an axial xanthate was found to be more reactive than an equatorial xanthate when neither is subject to severe 1,3-diaxial steric interactions.

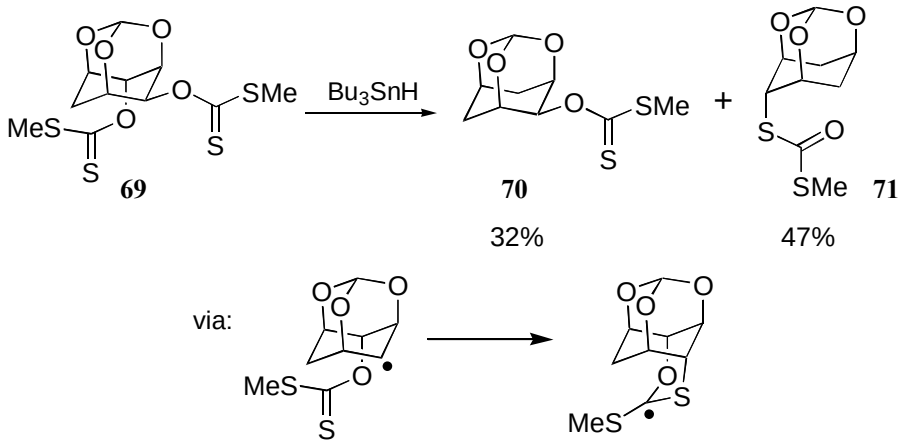
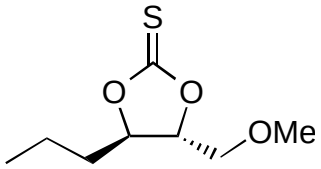


Figure 3.11

[133] Barton, D. H. R.; Hartwig, W.; Motherwell, W. B. *J. Chem. Soc. Chem. Comm.* **1982**, 447.

Compound **69** has one xanthate group which has two synclinal β-oxygens substituents and another xanthate which has two antiperiplanar β-oxygens. The xanthate, adjacent to two synclinal β-oxygens, cleaved faster to give compound **71** in 47% yield. Cleavage of the xanthate adjacent to two antiperiplanar oxygens was slower affording compound **70** in 32% yield. This ratio of roughly 1:1.5 in favor of cleavage of the equatorial xanthate suggests that the original β-oxygen effect is at least in part stereoelectronic in nature (relief of the dipolar interactions) and is maximized when the scissile C-O bond is synclinal to the β–oxygen bond.

Contrary to the results from other conformationally rigid compounds mentioned earlier, Beckwith did not observe β-oxygen effects for the cyclic thionocarbonate shown below.



Given this observation, the fragmentation of the FS-2 precursor should experience no β-oxygen effect because it is also a rigid cyclic thiocarbonate. However, if there were a significant β-oxygen effect, one would expect that for the *cis* ring-junction fragmentation precursor, the selectivity towards the secondary site would be enhanced and for the *trans* ring-junction fragmentation precursor, the selectivity towards primary site would be diminished.

3. Fragmentation of Cyclobutylcarbinyl systems

Under normal circumstances, ring opening of a cyclobutylcarbinyl radical is not reversible,[134] especially in [3.2.0]bicyclohept-2-enyl radicals (**74**). The rate of ring closure of 5-pentenyl radical (**73**) was measured to be ~ 250 s^{-1} at 80° C and it was observed only when the cyclized form was stabilized by substituents.[134],[135] Substitution at the radical center has little effect on the magnitude of the fragmentation rate constant.

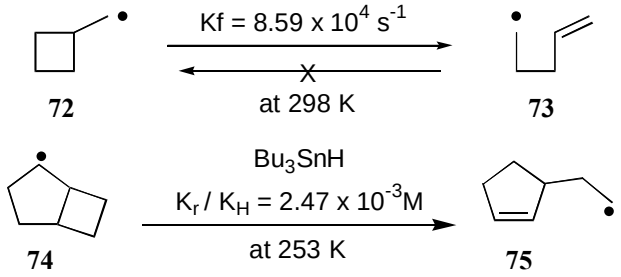


Figure 3.12

The cyclobutylcarbinyl radicals in this study were generated from the fragmentation of cyclic thionocarbonates (as shown in Figure 3.13, in red) and can fragment further to give either endocyclic or exocyclic bond cleavage.

[134] Beckwith, A. L. J.; Moad, G. *J. Chem. Soc. Perkin Trans. II*, **1980**, 1083.
[135] Castaing, M.; Pereyre, M.; Ratier, M.; Blum, P. M.; Davies, A. G. *J. C. Soc. Perkin II* **1979**, 287.

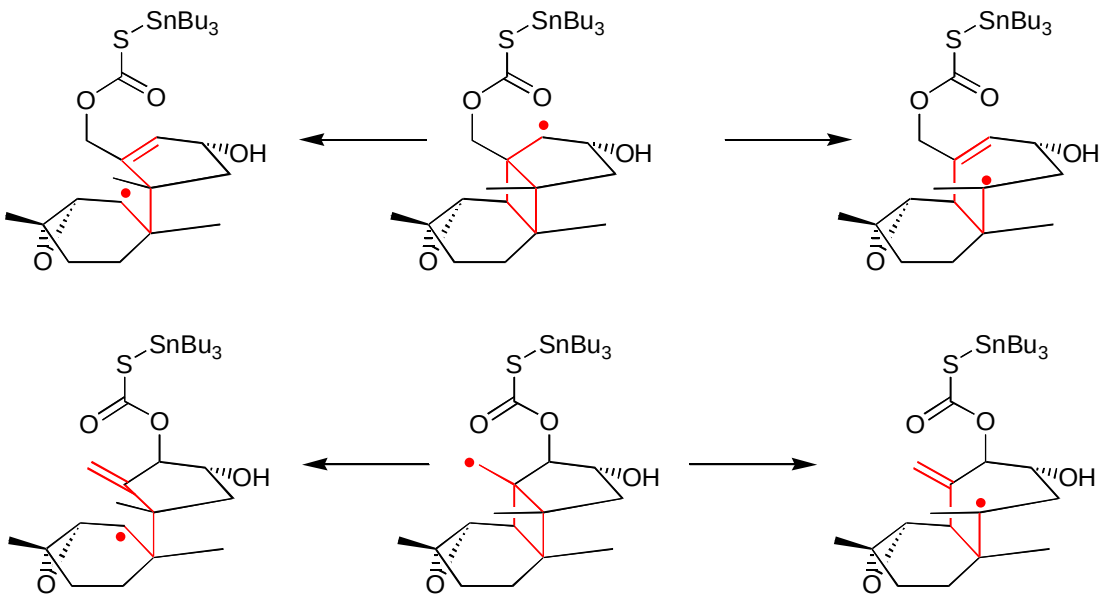


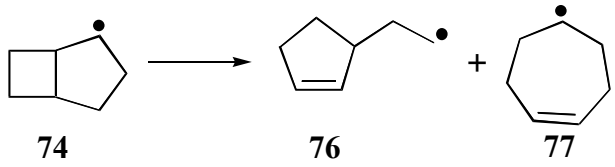
Figure 3.13

Based on thermodynamic calculations, Beckwith[134] demonstrated that the ring expansion product **77** arising from the fragmentation of [3.2.0]bicyclohept-2-enyl radicals **74** (endocyclic bond cleavage) is 2.0 Kcal/mol more stable than compound **76** (exocyclic bond cleavage). He proposed that the regiospecific ring opening of the bicyclic system to give the less stable product **76** is consistent with the view that β-fission requires efficient overlap between the semi-occupied orbital and the sigma orbital of the bond to be cleaved.[136] This is the opposite of what is seen in cationic examples where formation of the more stable cation directs the reaction towards endocyclic bond fragmentation[137].

---

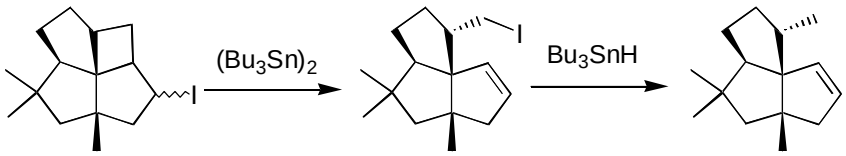
[136] Batey, R. A.; Grice, P.; Harling, J. D.; Motherwell, W. B.; Rzepa, S. *J. Chem. Soc. Chem. Comm.* **1992**, 942.

[137] (a) Shubin, V. G. *Top. Curr. Chem.* **1984**, *116-117*, 267. (b) Olah, G. A.; Liang, G.; Mo, Y. K. *J. Am. Chem. Soc.* **1972**, *94*, 3544. (c) Prelog, V.; Trayham, J. G. In *Molecular Rerrangements*; de Mayo, P., Ed.; Wiley - Interscience: New York, **1963**, 593.



74 **76** **77**

Beckwith's prediction is supported by the results observed in a synthesis of (±)-silphinene (**80**),[138] where β-scission of the four-membered ring of compound **78** provided regiospecific introduction of the double bond in the natural product. No product deriving from the competing tertiary radical was observed.

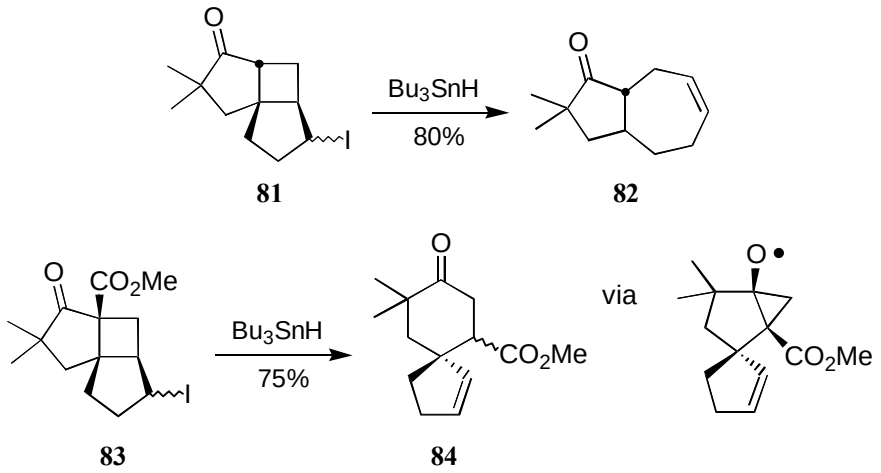


78 **79** **80**

Crimmins[139] explored the selectivity of the fragmentation of cyclobutyl carbinyl radicals by looking at substituent effects. When there were no substituents in the δ-position relative to the radical center (compound **81**), ring expansion was observed to give the more stable tertiary radical with cleavage of the endocyclic bond to give compound **82** in 80% yield. If instead, there was an electron-withdrawing substituent α to the carbonyl (δ to the radical center) as in the example shown for compound **83**, the product resulting from the exocyclic bond fragmentation (compound **84**) was obtained.

---

[138] Crimmins, M. T.; Mascarella, S. W. *Tetrahedron Lett.* **1987**, *28*, 5063.
[139] Crimmins, M. T.; Dudek, C. M.; Cheung, A. W. H. *Tetrahedron Lett.* **1992**, 33, 181.



In the example shown in Figure 3.14 cyclobutylcarbinyl fragmentation of iodide **85** yielded only ring expansion products.[140] The more stable allylic radical was favored over formation of the secondary radical deriving from exocyclic bond cleavage. This selectivity was not based on orbital overlap, since good overlap is possible for breaking both bonds. Based on this experiment one could argue that the stability of the final radical determined the outcome of the reaction. Since there is no obvious difference in stability between the two possible allylic radicals, the final product was determined by the rate of hydrogen atom transfer. The slowest reducing system (SmI_2 / solvent) allowed for the formation of the more stable double bond and product **86** was the major product observed. For the faster reducing system (tri-butyltinhydride) the exocyclic double bond was favored and compound **87** was the major product observed.

[140] Lange, G. L.; Gottardo, C. *Tetrahedron Lett.* **1994**, 35, 6607.

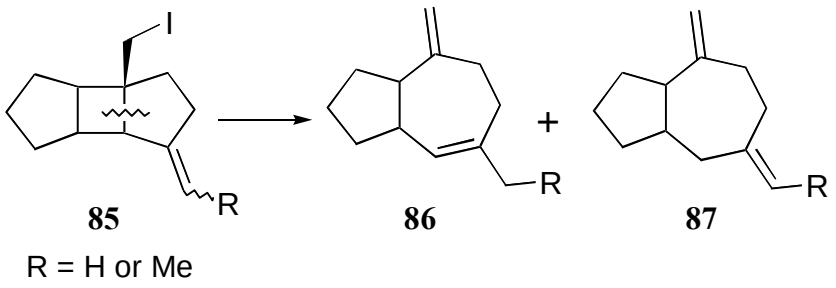


Figure 3.14

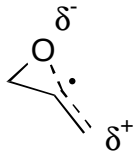
The results presented in this section are in agreement with the observation that cyclobutylcarbinyl radicals bearing substituents at the γ-position undergo ring opening to afford preferentially the more stable radical.[134] This can be explained on the basis that during bond fission the transition state is very product-like. The α-carbon has undergone little re-hybridization but the γ carbon is transformed from sp^3 to sp^2 hybridization and the resulting change in configuration relieves ring-strain. So for these radicals the rate and mode of fragmentation is dependent on strain release, orbital overlap and stability of the products formed.

4. Fragmentation of oxiranylcarbinyl radicals

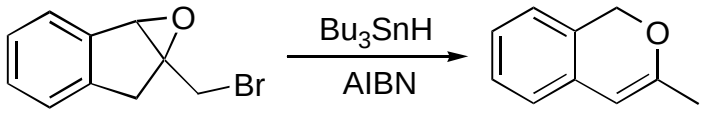
In theory, oxiranylcarbinyl radicals can fragment in two possible ways: by breaking the C-O bond or the C-C bond. Based on simple bond dissociation energy, one would predict that epoxides would fragment the C-C bond preferentially by 5 Kcal/mol.[141]

[141] Lee, M. S.; Jackson, J. E. *Abstr Pap Am Chem Soc*. **1993**, *205*, 104.

However, if the dipolar nature of the transition state[142] is important in determining the course of the reaction, cleavage of the C-O bond would be the preferred pathway. Pasto[143] calculated that the activation barriers for fragmentation of the oxiranylcarbinyl radicals are 3.57 Kcal/mol for C-O bond cleavage and 14.7 Kcal/mol for breaking the C-C bond. This gives a difference of 11.13 Kcal/mol (or 6.7 Kcal/mol according to Jackson calculations)[144] in favor of C-O fragmentation (which would roughly correspond to 98% of C-O bond breaking to 2% of C-C bond breaking at 25 ^{o}C).



Experimentally it has been verified that the C-O bond is usually the preferred cleavage site, especially for alkyl substituted epoxides. However, C-C bond cleavage has been observed to occur when the cleaved radical product is stabilized by the presence of vinyl or aryl groups,[145] as shown below.



[142] Nonhebel, D. C.; Suarez, E. *Chem. Soc. Rev* **1993**, 347.
[143] Pasto, D. J. *J. Org. Chem.* **1996**, *61*, 252.
[144] Jackson (see ref. 141) calculated the activation barrier for C-O bond cleavage at 4.8 Kcal/mol and for C-C cleavage at 11.5 Kcal/mol.
[145] Murphy, J. A.; Patterson, C. W. *Tetrahedron Lett.* **1993**, 34, 867.

If the desired exocyclic bond cleavage is the favored pathway for the fragmentation of the cyclobutylcarbinyl radical under study, an oxiranylcarbinyl radical will be the product of the reaction. This product can fragment further to give C-O or C-C bond cleavage as shown on Figure 3.15. Cleavage of the C-O bond is expected to be the preferred pathway since there is no vinyl or aryl stabilization to favor C-C cleavage.

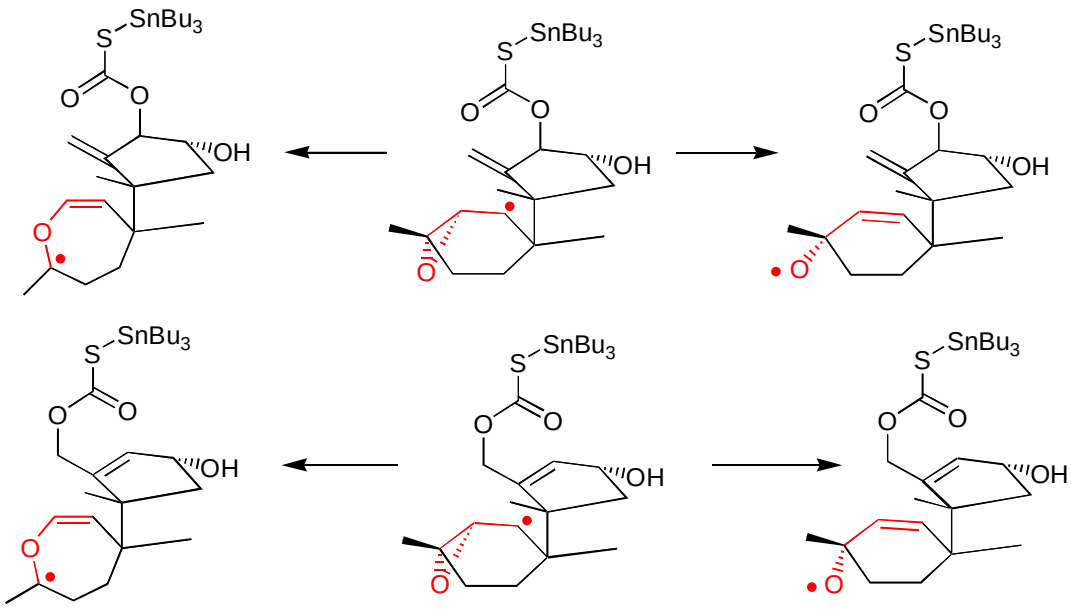
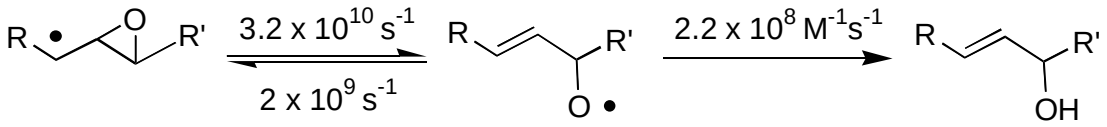


Figure 3.15

Rawal[146] measured the C-O bond cleavage rate at 3.2 x 10^{10} s^{-1} at 30° C as shown below. Ziegler's experiments[147] demonstrated that the opening of oxiranylcarbinyl radical is reversible, reporting the rate of the reverse reaction at 2 x 10^{9} s^{-1} at 80° C. Jackson and Pasto's calculations corroborates these results, predicting fast equilibrium between the

[146] Krishnamurthy, V.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 1572.

closed form and the C-O cleaved form based on the low activation barrier and the "near thermo-neutrality" of the system (ΔH = -2.6 Kcal/mol). Additionally, Scaiano measured the quenching step for alkoxide radicals at 2.2 x 10^8 M^{-1} s^{-1}.[148]

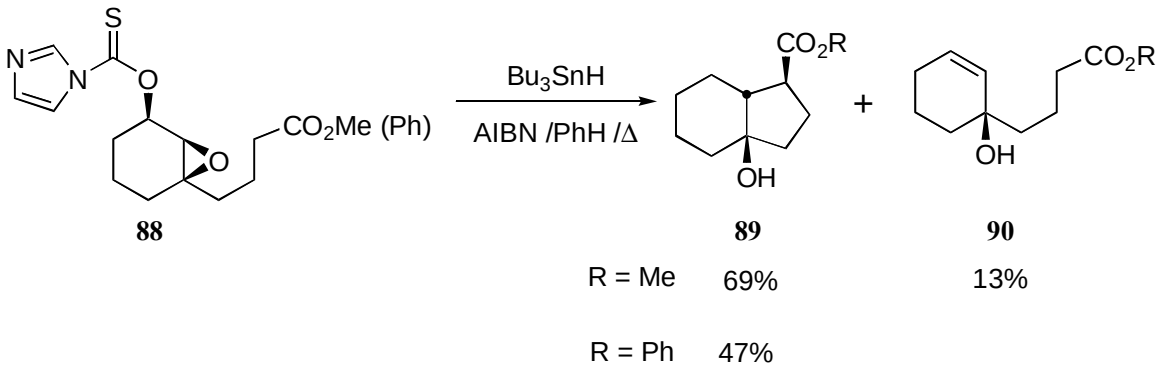


The reactivity of the alkoxide radical formed upon fragmentation must be examined. It is possible for this radical to undergo hydrogen shift or cyclize; further fragmentation of the six-membered ring was not considered a real possibility in the system under investigation.

Some literature examples were examined in order to illustrate the reactivity of alkoxide radicals. For instance, in the example below,[149] when compound **88** was submitted to fragmentation conditions the radical which derived from C-O cleavage of the oxiranylcarbinyl radical could be quenched as allylic alcohol **90** or could undergo 1,5-hydrogen shift, which was then followed by 1,5-cyclization to give the alcohol **89**.

---

[147] Ziegler, F. E.; Petersen, A. K. *J. Org. Chem.* **1994**, 59, 2707 and Ziegler, F. E.; Petersen, A. K. *J. Org. Chem.* **1995**, *60*, 2666.
[148] Scaiano, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 5399.
[149] Rawal, V. H.; Newton, R. C.; Krishnamurthy, V. *J. Org. Chem.* **1990**, 55, 5181.

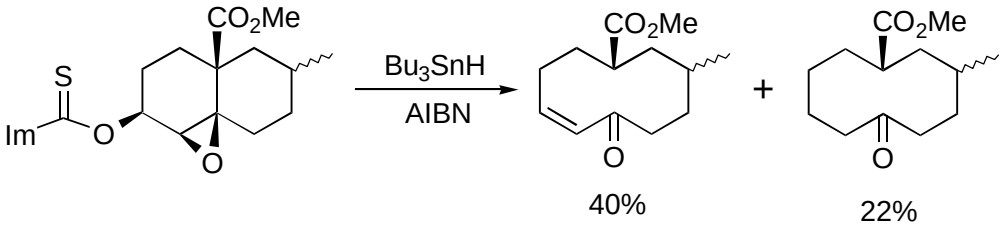


88 **89** **90**

R = Me 69% 13%

R = Ph 47%

The possibility of further fragmentation of the alkoxide radical is considered in the two examples below. In the first example, [150] in Figure 3.16, the ester group directs the fragmentation of the six-membered ring from the oxygen-centered radical towards ring expansion.



40% 22%

Figure 3.16

For the second example,[151] in Figure 3.17, epoxide fragmentation is followed by fragmentation of the external bond of the cyclohexane. The final product was derived from exocyclic bond cleavage, likely due to the greater stability of the tertiary radical. Exocyclic bond fragmentation also results in greater strain release for the system.

[150] Corser, D. A.; Marples, B. A.; Zaidi, N. A. *Tetrahedron Lett.* **1989**, 30, 3343.

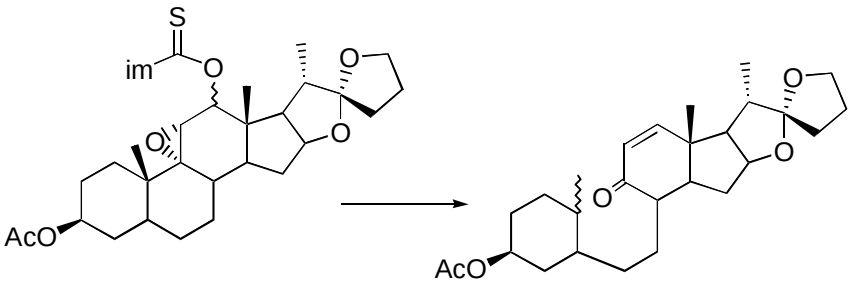


Figure 3.17

To address the issue of further cyclization of the alkoxide radical, an example was found in which the possibility of cyclization was in competition with fragmentation of cyclopropylcarbinyl radical as shown in the Figure 3.18. In this example, [152] β-scission of the C-C bond was shown to occur faster than the radical could cyclize. Based on this result and on direct competition experiments between fragmentation of cyclopropylcarbinyl and oxiranylcarbinyl radicals where only products deriving from epoxide fragmentation were observed,[153] C-O bond cleavage should also be faster than the competing cyclization reaction.

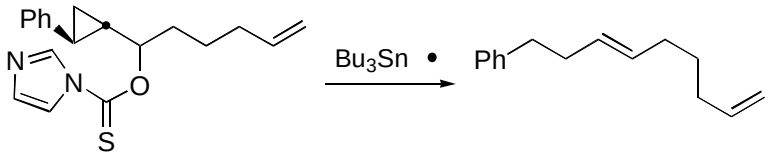
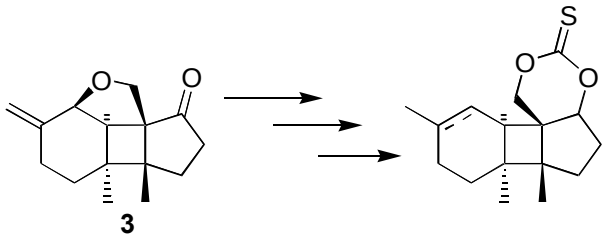


Figure 3.18

[151] Barton, D. H. R.; Motherwell, R. S. H.; Motherwell, W. B. *J. Chem. Soc. Perkin Trans. I* **1981**, 2363.
[152] Johns, A.; Murphy, J. A.; Patterson, C. W.; Wooster, N. F. *J. Chem. Soc. Chem. Comm.* **1987**, 1238.
[153] Newcomb, M.; Glenn, A. G. *J. Am. Chem. Soc.* **1989**, *111*, 275.

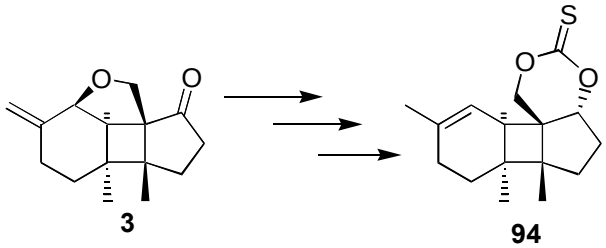
- *Preparation of the model systems*



3

The preparation of model systems to test the fragmentation step required the elaboration of intermediate **3** into a series of compounds containing the six-membered ring cyclic thionocarbonate fused to [3.2.0]bicycloheptane ring-system. This transformation required the reduction of the carbonyl, reduction of the cyclic ether and preparation of the cyclic thionocarbonate.

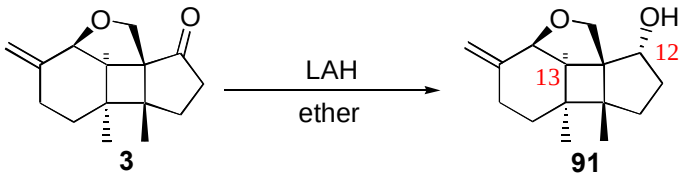
1. Model system 1



3 **94**

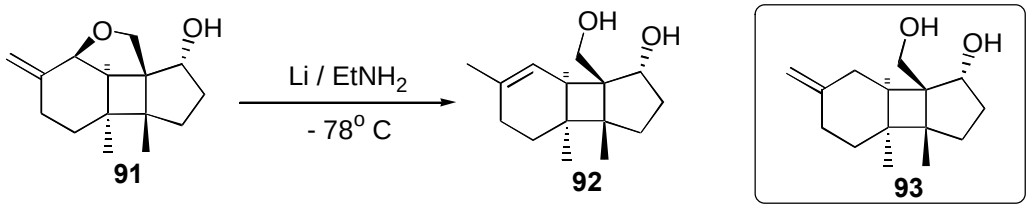
The first model system (cyclic thionocarbonate **94**) was constructed with the objective of determining the selectivity of the cyclic thionocarbonate fragmentation. The *trans* ring junction between the five-membered ring and the cyclic thionocarbonate should induce formation of the primary radical upon C-O bond cleavage. This model system

would also serve to verify if the cyclobutylcarbinyl radical would fragment *via* endocyclic or exocyclic bond cleavage.



3 **91**

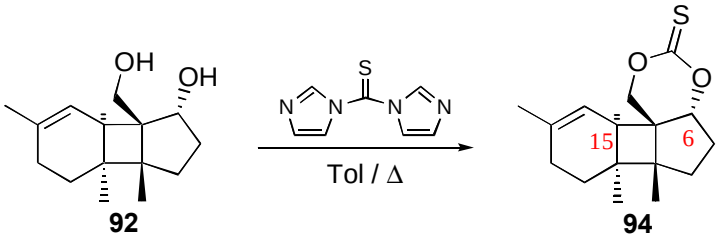
Reduction of the ketone in compound **3** was accomplished successfully using lithium aluminum hydride at 0° C (Et_2O, 89% yield) giving the desired alcohol **91**. Hydride was delivered from the less hindered face of the molecule to yield the hydroxyl group at C-12 in the α-configuration. No by-product due to reduction of the allylic ether was observed. The relative stereochemistry of the hydroxyl in the final product was confirmed by 1D-proton difference NOE experiments. The absence of an NOE between H-12 and H-13, which was seen for compound **100**, confirmed the R relative stereochemistry of the hydroxyl at C-12 (see Addendum I for details). A 2D-proton COSY experiment was used to aid in the peak assignments.



91 **92** **93**

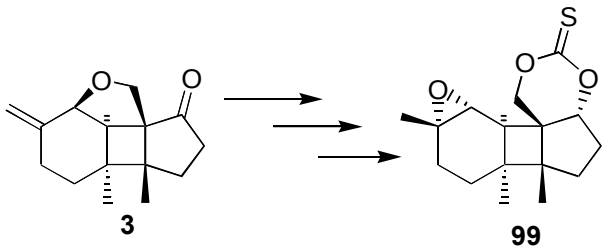
The allylic ether in alcohol **91** was reduced at -78° C by lithium in liquid ethylamine. This two-electron reduction generated an allylic radical that, upon further

reduction, gave olefin **92** in 91% yield with the double bond in the more stable position. When the reaction was carried out using liquid ammonia, instead of ethylamine a mixture of the desired product was isolated along with the terminal di-substituted double bond side-product **93** at an approximate 1:1 ratio.

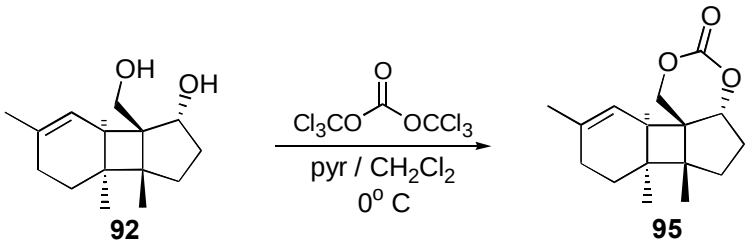


Preparation of the cyclic thionocarbonate **94** was carried out by reaction of diol **92** with thionocarbonyl diimidazole in toluene at reflux. More than one equivalent of the thionocarbonyl reagent was necessary for the reaction to go to completion, as the reagent apparently decomposed under these conditions. To prevent formation of the di-substituted product, a total of 2.3 equivalents of the reagent was added in three separate portions during the course of the reaction. The desired product **94** was obtained in 85% yield after it was separated from a small quantity of the di-substituted by-product. The absence of an NOE from H-6 to H-15 in the 1D-proton difference NOE experiments, compared to the results obtained for other compounds with similar structures, confirmed the R relative stereochemistry at C-6 for the cyclic carbonate portion of this fragmentation precursor (see Addendum I for details).

2. Model system 2



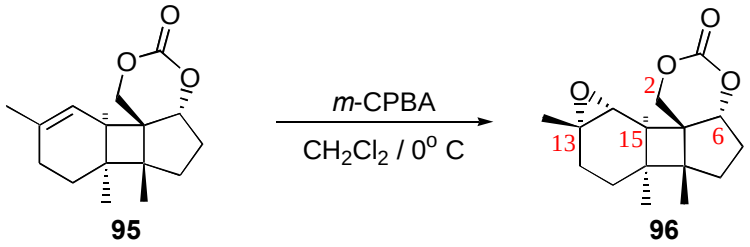
The second model system (epoxide **99**) represents a more advanced intermediate towards the synthesis of FS-2. The *trans* ring junction should once more induce formation of the primary radical upon C-O bond cleavage. The presence of the epoxide functionality enables an evaluation of the impact it may have on the system in terms of possible changes in the selectivity of the cyclobutylcarbinyl radical fragmentation.



Carbonate **95** was prepared by reaction of the diol **92** with triphosgene (pyridine, CH_2Cl_2 at 0^o C) and it was isolated in 90% yield. Attempts to directly convert the carbonate into a thionocarbonate by reaction of compound **95** with Lawesson's reagent[154]

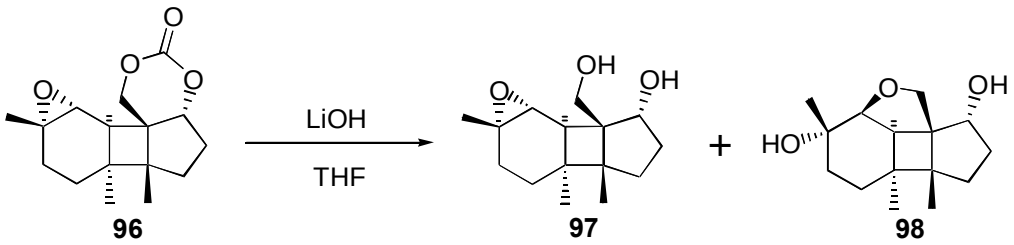
[154] Cava, M. P.; Levinson, M. J. *Tetrahedron* **1985**, *41*, 5061. Cherkasov, R. A. *Tetrahedron* **1985**, *41*, 2567. Clausen, K. *J. Chem. Soc., Perkin Trans. I* **1984**, 785. Jensen, O. E. *Tetrahedron* **1985**, *41*, 5595. Thomsen, I. *Org. Synth.* **1984**, *62*, 158.

(toluene, reflux) were only partially successful. The desired thionocarbonate product **94** was obtained, at best, in 30% yield and the remainder corresponded to base-line material.



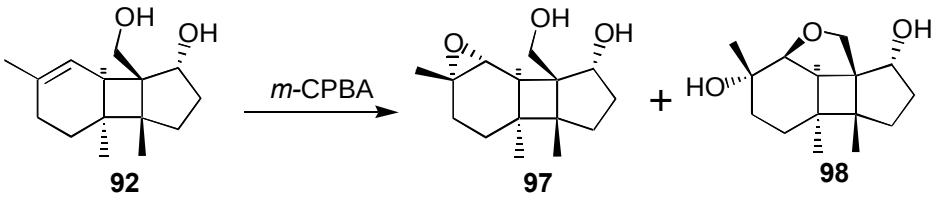
95 **96**

Diastereotopic face selective epoxidation of olefin-carbonate **95** was conducted by reaction with *meta*-chloroperbenzoic acid (*m*-CPBA) in CH_2Cl_2 at 0^o C and yielded epoxycarbonate **96** in 90 % yield. Oxidation occurred from the less hindered face to deliver the epoxide from the α-side of the molecule. 1D-proton difference NOE experiments were utilized to confirm the relative stereochemistry of the epoxide. An NOE observed between H-2α and H-14 confirmed the R relative stereochemistry at C-14. The absence of an NOE between H-6 and H-15 supported the assignment of the R relative stereochemistry for C-6 (see Addendum I for details). Since the attempts to directly convert the carbonate **95** into thionocarbonate **94** utilizing Lawesson's reagent were unsuccessful, it became necessary to investigate a new route to the installation of the thionocarbonate functionality *via* hydrolysis of the carbonate.



96 **97** **98**

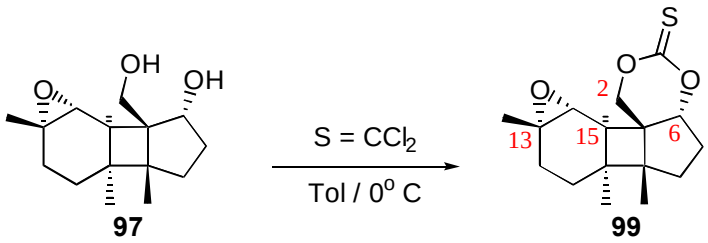
Attempts to hydrolyze carbonate **96** under mild basic conditions (LiOH in THF at 0^{o} C) resulted in a mixture of products. The desired compound, diol **97**, was obtained in 16% yield while tetrahydrofuran **98,** a product of cyclization of the primary alcohol onto the epoxide, was isolated in 79 % yield. Attempts to perform this reaction under acidic conditions gave similar results.



92 **97** **98**

Meta-chloroperbenzoic acid is usually thought of as a hydroxy-directed oxidizing agent due to formation of hydrogen bonds between a proximate hydroxyl and the reagent. Esters are generally used to prevent alcohols from directing the epoxidation,[155] which is why the epoxidation was originally carried out on the carbonate substrate **95**. Due to the problems associated with the hydrolysis of the carbonate and with the direct conversion to the thionocarbonate, the direct oxidation of diol **92** was attempted. Epoxidation of compound **92** with *m*-CPBA under buffered conditions ($NaHCO_3$, $CHCl_3$ and 0^{o} C) gave

compound **97** in 69% yield along with cyclic ether **98** in 17% yield. Oxidation occurred from the less hindered side of the molecule and no neighboring group effects were observed. The ^{1}H NMR spectrum of this epoxide product was identical to the ^{1}H NMR spectrum of the epoxide derived from hydrolysis of carbonate **96**, confirming that they had the same relative stereochemistry. Once diol **97** was isolated, it had to be used immediately to prevent cyclization to tetrahydrofuran **98**.



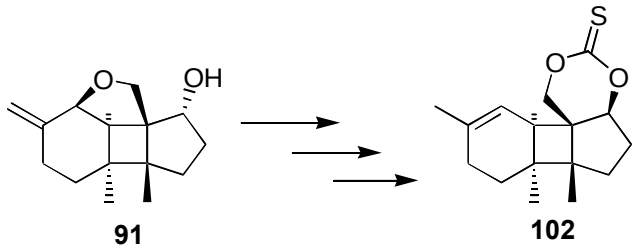
97 **99**

Reaction of diol **97** with thiophosgene (pyridine, toluene, 0° C) yielded the cyclic thionocarbonate **99** in 46 % yield. Attempts to perform the transformation with thionocarbonyl diimidazole at reflux temperature (as was done for compound **94**) failed, resulting in products derived from the opening of the epoxide. The ring opening was probably due to the high temperature necessary for the conversion; when the reaction was attempted at lower temperatures, only starting material was recovered. 1D-proton difference NOE experiments, along with 1D-proton decoupling experiments, confirmed the relative stereochemistry of the cyclic thionocarbonate and the epoxide. An NOE observed between H-2α and H-14 confirmed the R relative stereochemistry for the C-14

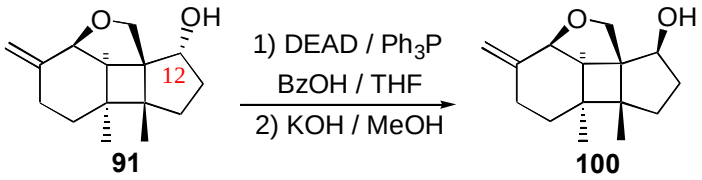
[155] Swern, D.; Dickel, G. B. *J. Am. Chem. Soc.* **1954**, *U*, 1957.

at the epoxide functionality. The absence of an NOE between H-6 and H-15 supported the R relative stereochemistry assignment at C-6 (see Addendum I for details).

3. Model system 3



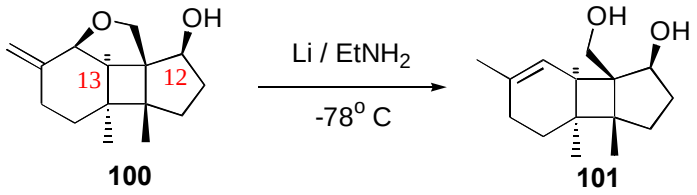
The third model system (cyclic-thionocarbonate **102**) enabled the examination of the selectivity of the fragmentation of the cyclic thionocarbonate in the environment of the *cis* ring junction. It also serves as a handle to determine if the fragmentation of the cyclobutyl carbinyl radical follows the same selectivity found in the first model system.



Mitsunobu inversion[156] of the hydroxyl group at C-12 was accomplished in two steps. First, reaction of α-alcohol **91** with triphenylphosphine and benzoic acid accompanied by slow addition of diethylazodicarboxylate (DEAD) generated the inverted

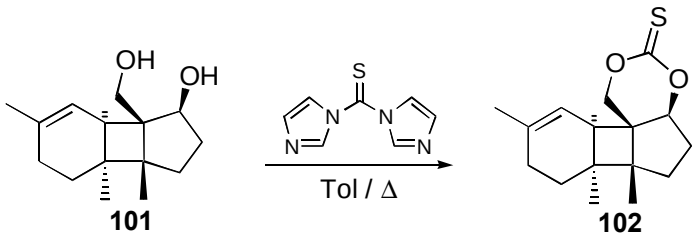
[156] Mitsunobu, O. *Synthesis* **1981**, 1.

benzoic ester at C-12 in 78% yield. Basic hydrolysis (KOH, MeOH at room temperature) of the newly generated ester gave alcohol **100** with the alcohol on the β-face of the molecule in 75% yield. 1D-proton difference NOE experiments were compared to those from α-alcohol **91**. An NOE observed between H-12 and H-13, which was absent on compound **91**, confirmed the S relative stereochemistry assignment for C-12 and agreed with the relative stereochemistry assignment shown for compound **100** (see Addendum I for details).



100 **101**

Reduction of the allylic ether portion of compound **100** followed the same procedure used for reduction of ether **91** (lithium in liquid ethylamine at -78° C), giving diol **101** in 97% yield.

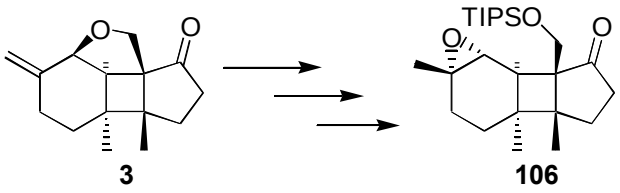


101 **102**

The final step for the assembly of thiocarbonate **102** required the transformation of the diol into a cyclic thionocarbonate. Reaction of diol **101** with thiocarbonyl diimidazole

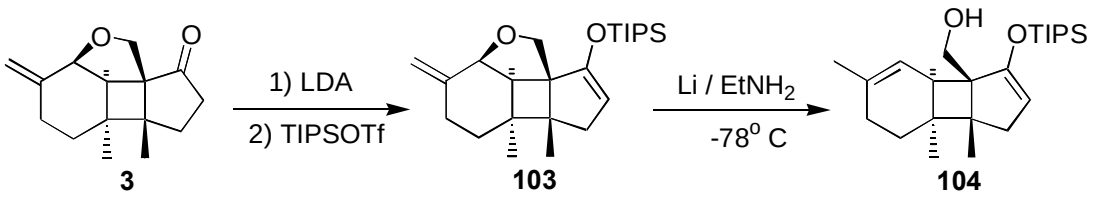
in toluene at reflux yielded the desired product in 95% yield. No di-substituted by-product was observed because the formation of the desired product was rapid contrary to the results obtained for the *trans* ring-system.

4. Model system 4



3 **106**

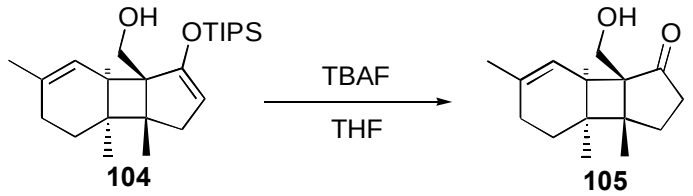
The concept for the fourth model system (ketone **106**) was to generate the secondary radical from a ketone by reaction with samarium diiodide. This study examines the importance of the thionocarbonate on the fragmentation. The cyclobutylcarbinyl radical is generated in the same position as if there were a *cis*-fused cyclic thionocarbonate in the molecule but through a different route.



3 **103** **104**

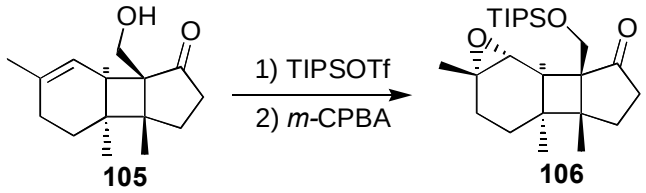
Ketone **3** was protected by reaction with lithium diisopropylamide (LDA, THF, -78° C) then immediately treated with triisopropylsilyl triflate to form the TIPS enolether **103** in 87% yield. Reduction of the allylic ether was carried out with lithium wire in liquid ethylamine yielding silyl-enolether **104** in 95% yield. No reduction of the ketone was

observed under these conditions. Migration of the TIPS group to the primary alcohol was the major contaminant observed.



104 **105**

Deprotection of the ketone was accomplished by submitting silyl-enolether **104** to tetrabutyl ammonium fluoride in aqueous THF at 0^{o} C, giving keto-alcohol **105** in 73% yield.



105 **106**

The primary alcohol in compound **105** was initially protected in the form of the tri isopropylsilyl ether (imidazole, DMAP, CH_2Cl_2, TIPSOTf) to prevent its participation during the epoxidation step. The reaction proceeded in 81% yield after purification of the product by silica gel flash chromatography. Epoxidation proceeded as desired (*m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0^{o} C) with oxidation occurring from the less hindered side to give the epoxide on the α-face of the molecule. Keto-epoxide **106** was thus obtained in 62% yield.

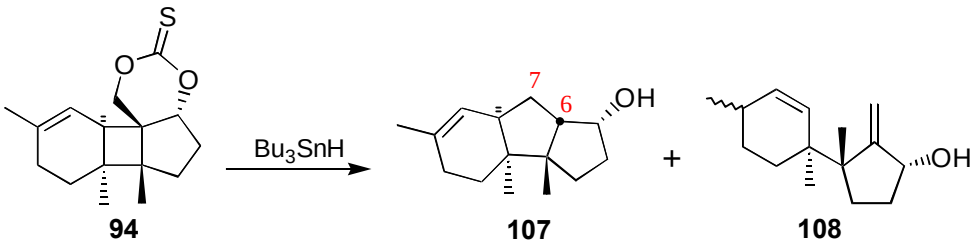
- *Fragmentation of the model systems*

Radical fragmentation experiments were conducted under high dilution conditions (10^{-3} M), using the tributyltin hydride method.[118] Dry toluene was used as the solvent at reflux temperature and AIBN as the radical initiator. The reaction solution was degassed by freeze-pump-thaw technique prior to each experiment in order to suppress side products due to reaction with oxygen. A solution of the substrate dissolved in toluene was heated to reflux and a second solution containing Bu_3SnH and AIBN was added to the reaction mixture over a period of 6 hours.

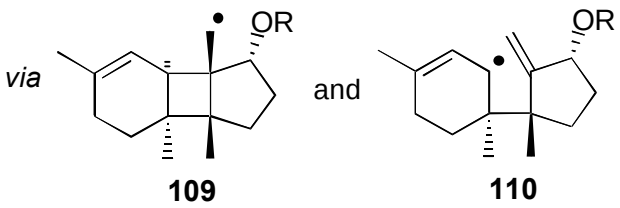
The yields reported below are in percent of isolated products after purification by flash chromatography. The method chosen for the reaction work-up plays an important role on determining the amount and purity of the products. The oxidative work-up developed by Curran[157] was utilized with most success. The procedure consists of iodine oxidation to convert all tin by-products or excess tin hydride into tin halides, followed by treatment with DBU in wet ether to form a white solid which is then separated by filtering through a silica gel column using ether as the solvent.

[157] Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140.

1. Model system 1



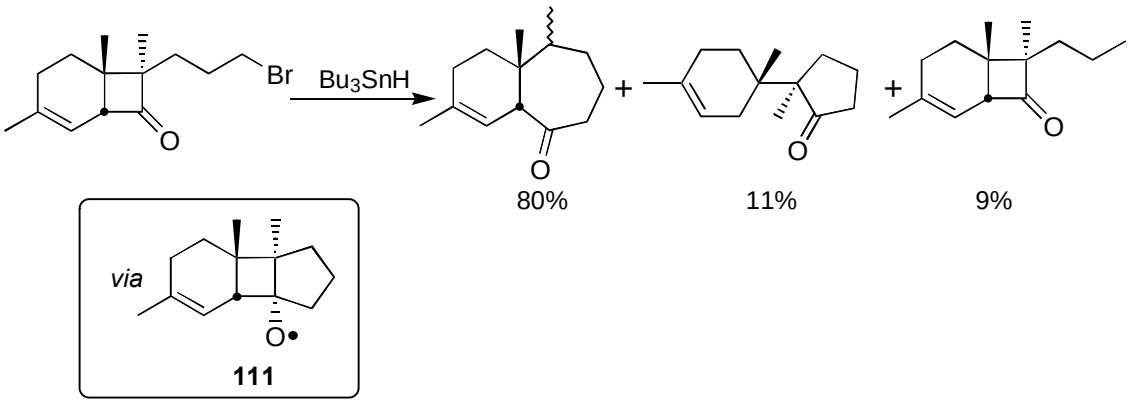
Fragmentation of *trans*-thionocarbonate **94** gave two products (**107** and **108**). Compound **107** was isolated in 47% yield and a ^{1}H NMR spectrum with 3 methyl singlet resonances at δ 0.79, 0.92 and 1.65 ppm (vinyl methyl) and one vinylic proton at δ 5.45 ppm was recorded. The structure was confirmed by conversion of the hydroxyl to acetate by treatment with excess acetic anhydride in pyridine. Observation of the shift of the ddd from δ 4.33 to 5.21 ppm (J = 6.5 Hz and 6.5 Hz) corresponding to the H-6, adjacent to the secondary alcohol, supports the structural assignment. Allylic alcohol **108** was isolated in 18% yield as a 3:1 mixture of diastereomers according to GC-MS analysis. The structure was confirmed by ^{1}H NMR which showed vinylic protons from δ 5.1 to 6.0 ppm corresponding to 4 protons (by integration) and a secondary hydroxyl at δ 4.41 ppm exchangeable with D_2O.



Both products **107** and **108** were derived from the fragmentation of the *trans* cyclic thionocarbonate to generate the radical at the primary center of intermediate **109** as expected. No product deriving from fragmentation to give the secondary radical was isolated or detected in the ^{1}H NMR spectra of the crude reaction mixture. The cyclobutylcarbinyl radical intermediate **109** fragmented further *via* cleavage of the exocyclic bond of the cyclobutane ring to give the more stable allylic radical **110**. No products deriving from ring expansion to give the tertiary radical were observed. The major product, tricyclo-dodecenol **107** derived from 1,5-cyclization of the allylic radical **110** with the terminal double bond generated after fragmentation of the four-membered ring. This hypothesis is corroborated by deuterium incorporation at C-6 when the fragmentation reaction was conducted with Bu_3SnD.

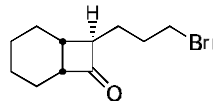
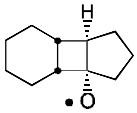
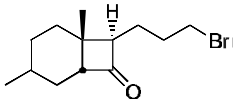
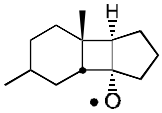
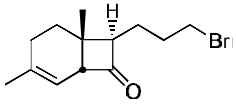
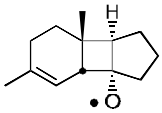
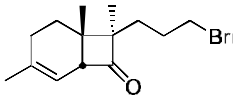
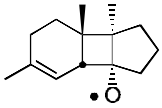
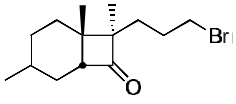
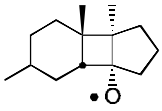
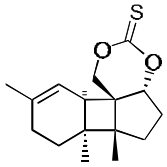
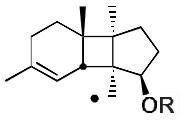
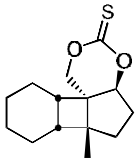
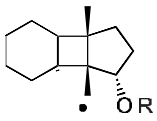
The results presented here for model system 1 were as predicted by Molecular Modeling calculations (see Addendum 4) and in agreement with previous examples studied in this lab. These results, however, are surprising in light of previous reports on four-membered ring fragmentations by Dowd[158] and Ziegler.[129] The ring expansion products were favored in both previous examples, rather than cleavage of the bond leading to the trichothecene skeleton.

[158] Zhang, W.; Dowd, P. *Tetrahedron*, **1993**, 49, 1965.



Dowd[158] studied 5-4-6 ring systems with an oxygen-centered radical, such as intermediate **111**, which is similar to intermediate **109** studied in the FS-2 synthesis. The cyclobutane ring can cleave to give a tertiary (ring expansion) or secondary allylic radical (trichothecene skeleton). For this oxygen-centered radical, the selectivity was found to favor the ring expansion product by an 8:1 ratio. He also studied the fragmentation of other related compounds.[159] The table below summarizes a comparison between other oxygen-centered radicals studied by Dowd (entries 1-5) and the carbon-centered radicals from the current study (entries 6 and 7).

[159] Dowd, P.; Zhang, W *J. Org. Chem.* **1992**, *57*, 7163. See also ref 158.

	Substrate	Radical Intermediate	Product Distribution: Ring Expansion	Exocyclic Fragmentation	Reduction
(1)			65%	16%	19%
(2)			49%	14%	37%
(3)			62%	X	38%
(4)			80%	11%	9%
(5)			68%	22%	10%
(6)			X	65%	X
(7)			80%	X	X

Dowd demonstrated that the ring-expansion product is actually 1 Kcal/mol more strained than the trichothecene like product based on molecular mechanics calculations. Thus, it is not relief of strain that dictates the product distribution observed experimentally.

Comparison of the results obtained for entries 4 and 5 suggests that removal of the double bond in the six-membered ring favors cleavage of the bond leading to the trichothecene-like skeleton. Formation of the tertiary radical was favored over formation of the allylic radical in an 8:1 ratio (entry 4) while formation of the secondary radical was favored over formation of the allylic radical in a > 62:1 ratio (entry 3). Analysis of the results obtained for entries 3, 4 and 5 of the table indicates that the stability of the final radical does not determine the selectivity of the bond cleavage.

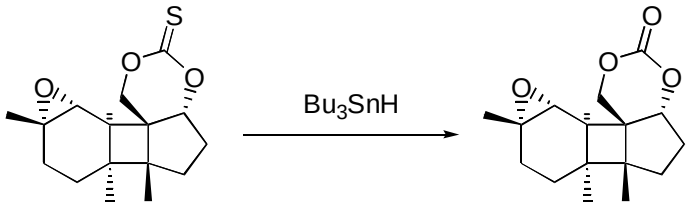
For the carbon-centered radicals, the product distribution suggests that the stability of the final radical determines the selectivity. Formation of the tertiary radical was favored over the secondary radical alternative in entry 7 and formation of the allylic radical was favored over the tertiary in entry 6. The possibility that the oxygen substituent, beta to the radical center, plays a role in deciding the selectivity was considered. However, the oxygen is adjacent to the radical at the starting point of the transformation and should not influence the final radical.

The release of strain is similar for both oxygen-centered radical **111** and carbon-centered radical **109**. The difference in the fragmentation selectivity for the two molecules may be a consequence of an early transition state for the oxygen-centered radical and a late transition state for the carbon-centered radical. If this is the case, bond overlap may play an important role for the oxygen-centered system while the stability of the product-radical may play an important role in determining the selectivity of the carbon-centered system.

Based on the result of the fragmentation of compound **94** into compound **107**, it was concluded that the lifetime of the allylic radical is long enough to allow 1,5 cyclization

to occur prior to termination. In competition with the cyclization is the reduction of the allylic radical generating compound **108**. The allylic radical favors the canonical structure with the more stable tertiary radical resulting in the product with the less stable di-substituted double bond.

2. Model system 2



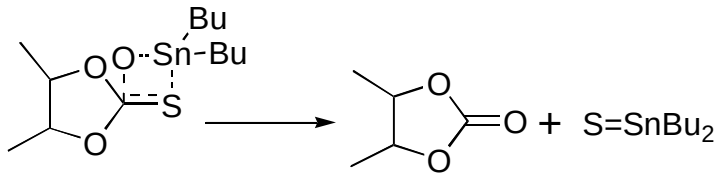
99 **96**

Isomerisation of the thionocarbonate **99** to the carbonate **96** was observed upon fragmentation of the second model system. The cyclic carbonate was isolated in 78% yield from the reaction mixture and was found to be identical to the product deriving from epoxidation of carbonate **95** with respect to TLC analysis, ^{1}H NMR and GC-MS trace. The fragmentation of compound **99** was carried out using the same stock solution used for compound **94**.

The isomerisation to compound **96** may be explained by postulating the formation of a 4-membered ring complex[160] in which the thiophilic tin atom changes its bonding

[160] Patroni, J. J.; Stick, R. V.; Tilbrook, D. M. G.; White, A. H.; Skelton, B. W. *Aust. J. Chem.* **1989**, 42, 2127.

partner with the carbon to form dibutyl tin sulfide. This transformation is driven by the conversion of the weak thionocarbonyl group into a stronger carbonyl group.



The other fragmentation reactions were not carried out due to lack of time or not enough material to characterize the reaction products.

- *Conclusion*

Starting from compound **3**, four model systems were built to test the selectivity of the radical fragmentation reaction proposed in the retrosynthetic analysis presented in chapter 1. Fragmentation experiments were conducted on two of the systems, model system 1 and 2. The results from model system 1 demonstrated that the stereochemistry at the ring junction between the six-membered cyclic thionocarbonate and the five-membered ring determined the selectivity of the cyclic thionocarbonate fragmentation. The *trans* stereochemistry led to formation of the primary radical (intermediate **109**). The resulting cyclobutylcarbinyl radical proceeded to cleave the bond leading to the more stable allylic radical, therefore unraveling the trichothecene-like skeleton. The results from model system 2 are unusual in that under these reaction conditions the thionocarbonate **99** isomerized into the carbonate **96**. This may suggest that there was some Bu_2SnO present

in the reaction mixture, either due to the presence of oxygen or air dissolved in the solution or due to aging of the Bu_3SnH reagent. Isomerisation to the carbonate was observed in two experiments, and in one case the reaction was run side by side to the fragmentation of the model system 1. No isomerisation of thionocarbonate **94** into carbonate **95** was observed which may suggest that the epoxide may play some role in the oxidation of the tin reagent. No other evidence for the oxidation was available since the experiment was not pursued.

This methodology offers a potential entry for the preparation of the family of trichothecene compounds *via* control of the stereochemistry at the ring junction of the cyclicthionocarbonates. The radical fragmentation of the cyclic thionocarbonate with the *cis* ring junction (Figure 3.19) can lead to the formation of trichothecenes with the FS-2 type skeleton *via* cleavage of the C-O bond leading to formation of the secondary radical. The radical fragmentation of the cyclic thionocarbonate with the *trans* ring junction (Figure 3.20) can lead to the formation of trichothecenes with the tricyclic type skeleton *via* cleavage of the C-O bond leading to formation of the primary radical followed by biomimetic cyclization[161] to assemble the final structure.

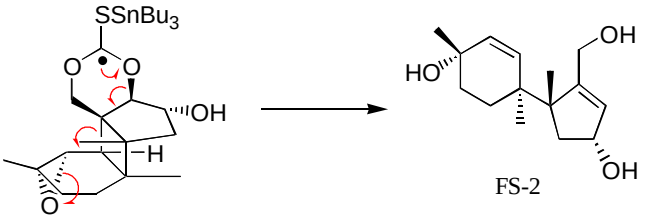


Figure 3.19

[161] (a) Masuoka, N.; Kamikawa, T. Tetrahedron Lett. 1976, 1691; (b) Masuoka, N.; Kanikawa, T.; Kubota, T. Chem. Lett. 1974, 751.

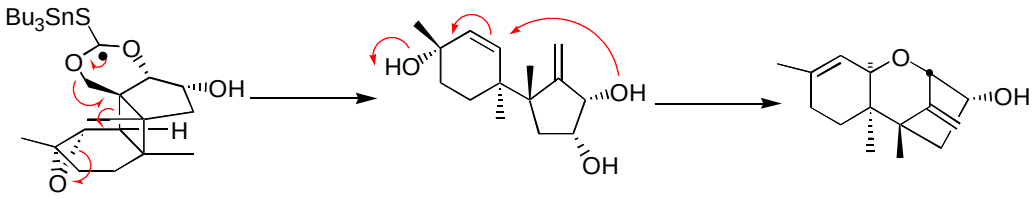


Figure 3.20

The selectivity observed for the fragmentation of model-system 1 encouraged the further development of intermediate **3** towards assemblage of the fragmentation precursor of FS-2. Work along this course is presented in detail in chapter 4.