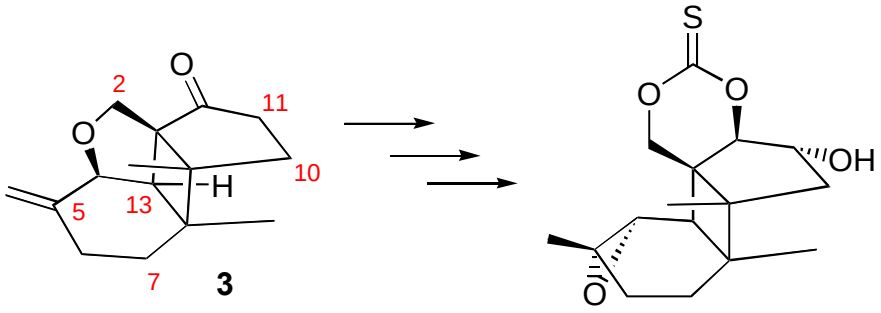
# CHAPTER IV: *ELABORATION OF THE FRAGMENTATION INTERMEDIATE.*

- *Introduction*

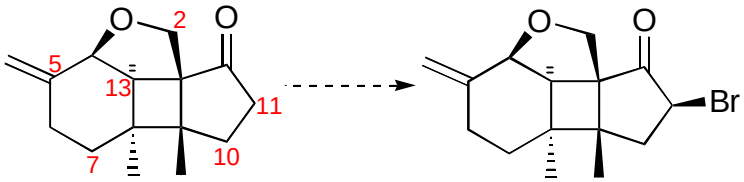



Once the tetracyclic structure of ketone **3** had been established (see chapter 2), its rigid structure could be coupled with face-selective reactions to introduce the remaining functionality for the preparation of the fragmentation precursor **1** (see chapter 1). The first goal was to introduce a hydroxy functionality in a stereoselective manner on the position alpha to the carbonyl (C-11). Subsequent elaboration of intermediate **3** would involve preparation of a *trans* diol (at C-11 and C-12), reduction of the allylic ether, introduction of an epoxide at C-4, C-5 and formation of the *cis*-fused cyclic thionocarbonate.

- *Functionalization alpha to the carbonyl:*

Introduction of the desired hydroxyl at C-11 required a way of placing this new functionality on the more hindered side of the molecule. Three strategies were investigated for this purpose.

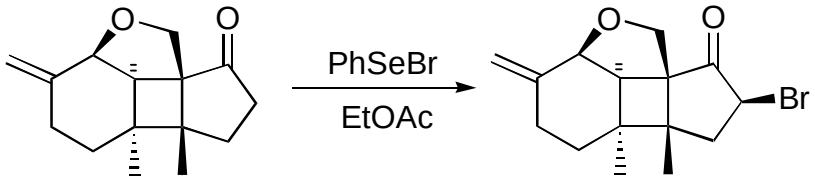
**1. Strategy I: α-Bromination**




**3** **112**

Bromination at the position activated by the carbonyl from the convex, less hindered side of the molecule would serve as a handle for nucleophilic attack and inversion of the configuration at that center. Once the bromine had been installed, intermolecular $SN_2$ displacement with an oxygen nucleophile would result in an alcohol with the desired α stereochemistry. Alternatively, one could set up for intramolecular displacement by reducing the ketone to an alcohol. Reduction would occur with hydride delivery from the less hindered, top side, of the bromoketone **112** yielding the alkoxide on the bottom face. Ideally, this alkoxide would displace the bromide prior to work-up to give an epoxide on the more hindered face of the compound. As a third option, a two step procedure could be used, with reduction of the carbonyl to an alcohol being followed by the displacement of the bromide in the formation of the same epoxide.

Bromination using standard reagents such as bromine or N-bromosuccinimide (NBS) gave only unreacted starting material. Reactions were attempted under basic or acidic conditions using stoichiometric or catalytic amounts of the reagents[162]. When the reaction was carried out in the presence of heat or under harsh conditions, base-line material was observed and no major product was isolated. The same was true when iodination was tried instead. Use of phenylselenium bromide[163] as the reagent solved the bromination problem. Taking advantage of solvent effects, one could select formation of the brominated product over the selenium derivative by carrying the reaction in a polar solvent, as was the case with ethyl acetate. The desired brominated product **112** was thus obtained in 72 % yield (PhSeBr, EtOAc, room temperature, 1h). 1D-proton difference NOE experiments aided on the relative stereochemistry assignment shown for the bromine at C-11 in compound **112**. An NOE observed between H-13 and H-11, which was not seen for compound **124**, confirms the S relative stereochemistry assignment for C-11. This assignment was further supported by the observation of NOEs between H-10α and H-13 and between H-10α and H-11 (see Addendum I for details).

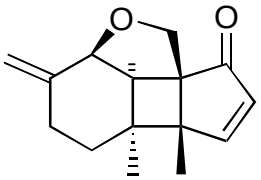



**3** **112**

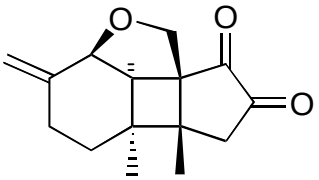
[162] Reaction with NBS was tried in the presence of $H_2O_2$ and/or UV light for initiation. Some of the reactions were tried in analogous substrates without the ether ring present as well. The results were the same as was observed for compound **3**.

[163] Abul-Haji, Y. J. *J. Org. Chem.* **1986**, 51, 3380.

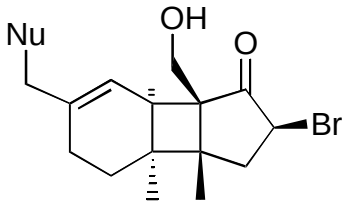
Attempts to invert the bromine by direct displacement using KOH, benzoate and superoxide[164] were unsuccessful. For reactions where KOH and benzoate were used, the elimination product, enone **113**, was the major product. When superoxide was used, the oxidation product dienone **114** was obtained as the single product in 49% yield ($KO_2$, DMSO, 18-crown-6 ether, 3Å molecular sieves). Other minor side products included addition of hydroxide to the allylic ether and opening of the 5-membered ring to give a derivative of the type of compound **115**. Formation of the desired inverted product was not observed under $SN_2$ conditions.




**113**



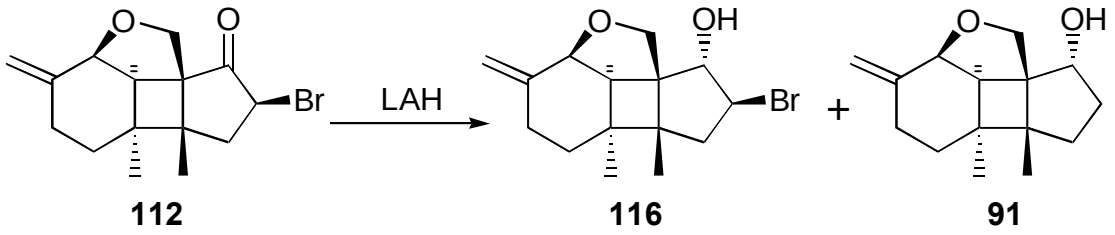

**114**




**115**

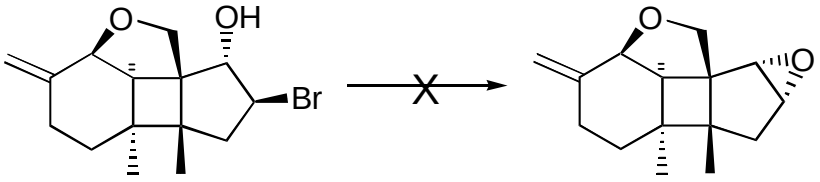
Reduction of the ketone in an attempt to prepare the epoxide in one step was also unsuccessful, but bromohydrin **116** was stable and could be isolated in 63% yield ($LiAlH_4$, $Et_2O$, $0^o$ C, 1h) along with product **91**, derived from over-reduction, where the bromide was removed.

[164] Corey, E. J.; Nicolaou, K. C.; Shibasaki, M.; Hachida, Y.; Shiner, C. S. *Tetrahedron Lett*. **1975**, 3183.




**112** **116** **91**

Attempts to induce the formation of the epoxide by regenerating the alkoxide in compound **116** through the use of bases such as $^{t}$BuOK, NaOMe or KOH or attempts to employ silver-assisted methods were unsuccessful. Mostly, recovery of unreacted bromohydrin along with elimination products evidenced by the increase of signal in the vinylic region of the $^{1}$H NMR or decomposition of the starting material, as was the case for the silver assisted reactions, was observed. Alternative methods also involved reaction of bromoketone **112** with methoxide[165] or hydrazine[166] to attempt formation of the epoxide *via* a ketal or an aminal type intermediate, again with no success. This result can be attributed to the increase of ring strain upon formation of the epoxide thus disfavoring this pathway.

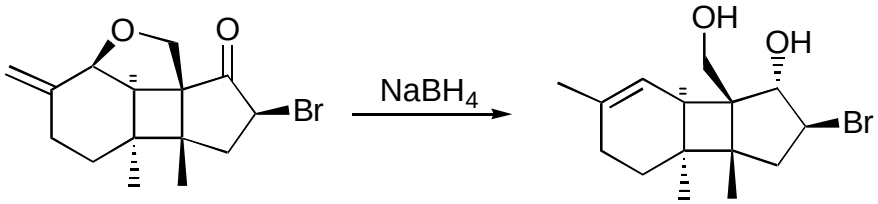



**116** **117**

[165] Hassner, A.; Catsoulacos, P. *J. Org. Chem*. **1966**, 31, 3149.

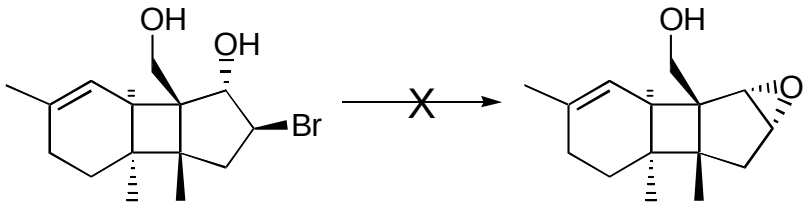
[166] Catsoulacos, P.; Hassner, A. *J. Org. Chem.*, **1967**, 32, 3723 and Numazawa, M.; Nagaoka, M. *J. Org. Chem*. **1982**, 47, 4024.

Another attempt to reduce the carbonyl, this time using $NaBH_4$ (EtOH, R.T., 70 % yield), gave only one product (bromo-diol **118**) that was the result of reduction of the ketone along with reduction of the allylic ether.




**112** **118**

Bromo-diol **118** lacked the 5-membered ether ring, and should be less strained than the parent compound **116**, so it was possible that the epoxide would form in this system. Furthermore, reaction of this substrate would avoid the need to reduce the allylic ether in the presence of the epoxide in a later step, as would be the case in the original system.



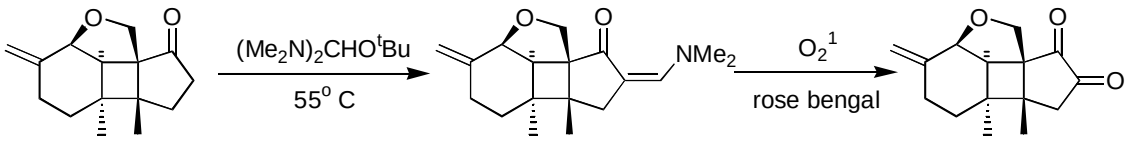

**118** **119**

This approach was also unsuccessful, so the focus of the investigation was diverted to another strategy.

## 2. Strategy II: α-Oxidation

The second strategy involved preparation of a system at one oxidation-level higher (diketone), followed by reduction to a diol in a stereocontrolled manner.

Preparation of diketone **114** followed the procedure developed by Wasserman[167] where first the enamino-ketone **120** was prepared by treatment of ketone **3** with Brederick's reagent followed by singlet oxygen oxidation of the vinylogous amide.



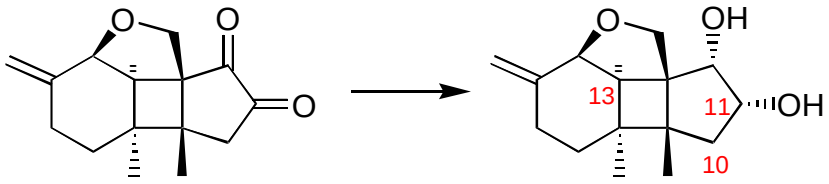

**3** **120** **114**

The formation of the vinylogous amide **120** was performed in the presence of excess reagent with no solvent ($(Me_2N)_2CHO^tBu$, 55° C, 30 h) and the reaction progress could be monitored by $^1H$ NMR of the crude mixture in $CDCl_3$. One could follow the appearance of a signal at δ 8.00 ppm due to the proton on the enamine double bond and the N-methyls at δ 2.85 and 2.90 ppm. The infrared spectrum ($CCl_4$ solution) of a sample purified by flash chromatography with diethyl ether also showed peaks at 1685 and 1596 $cm^{-1}$ associated with the vinylogous amide. The oxidation step followed without purification of the intermediate **120**, by dissolving the crude mixture in $CH_2Cl_2$, addition of a sensitizer (Rose Bengal) and irradiation with a sun lamp in the presence of a positive

[167] Wasserman, H. H.; Ives, J. L. *J. Am. Chem. Soc.* **1976**, 98, 7868.

pressure of oxygen for approximately 3h. The diketone **114** was thus obtained in 56% yield for the two steps.

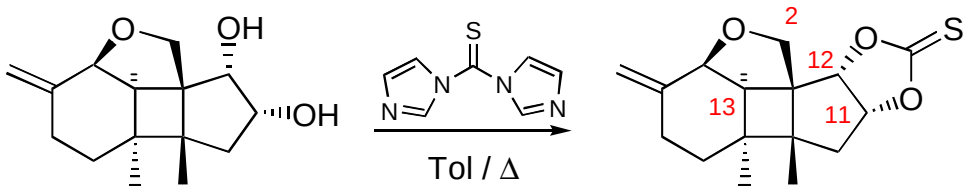
Reduction (complete, not partial) of the diketone could have three possible results: formation of the alpha-*cis* diol, or the two possible *trans* diols. Reports in the literature[168] suggested that reduction of diketones tend to give *trans* products due to OH direction. Various reducing agents were used to determine the product distribution outcome. Elucidation of the relative stereochemistry of the diol products was done via NMR studies: 1D-proton difference NOE aided by 2D-proton COSY or selective single frequency decoupling experiments. Studies conducted using $LiAlH_4$, $NaBH_4$, $ZnBH_4$, selectride, Red-Al and other common reducing agents gave only the *cis* product **121** ($^3J$ = 5.5 Hz between the diol methine hydrogens at C-11 and C-12). An NOE observed between H-11 and H-12 confirms the *cis* relative stereochemistry assigned for diol **121** and the absence of NOEs between H-13 and H-11 or between H-13 and H-12 supports the S* assignment for C-12 and the R* relative stereochemistry assignment for C-11. These assignments were further supported by comparison with the results for the NOE experiments conducted on the *trans* diol **126** (see Addendum I for details).




**114** **121**

[168] Hashimoto, S.; Sakata, S.; Sonegawa, M.; Ikegami, S. *J. Am. Chem. Soc.* **1988**, *110*, 3670.

The relative stereochemistry of compound **121** was further confirmed by preparation of the rigid derivative **122**. This cyclic thionocarbonate was prepared by reaction of diol **121** with thiocarbonyl diimidazole, in toluene, at reflux. The desired product **122** was isolated, after purification, in 75% yield. Coupling constant of 6.8 Hz between the hydrogens at C-11 and C-12[169], along with 1D-proton difference NOE experiments results supported the *cis* relative stereochemistry assignment. An NOE observed between H-2 and H-12 confirmed the S relative stereochemistry assigned for C-12. The absence of NOEs between H-12 and H-13 and between H-11 and H-13 further supported the assignment (see Addendum I for details).

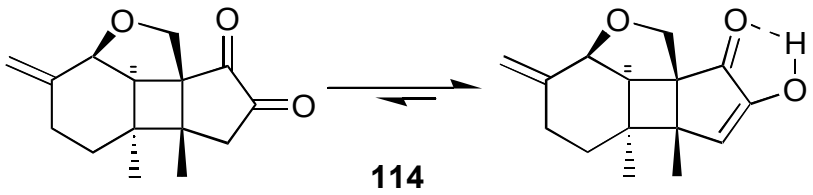



**121** **122**

Compound **122** could be submitted to radical fragmentation conditions to verify if any selectivity would be achieved for the formation of one possible secondary radical over the other. For this molecule, strain release would be the only factor inducing selectivity. Unfortunately, the thiocarbonate was never prepared in large enough quantity for the experiment to be attempted.

[169] Predicted coupling constant for *cis* ring junction, based on molecular mechanics using MacroModel v4.5, was 6.6 Hz with a dihedral angle of 21.1°.

Further NMR analysis suggested that the stable form of diketone **114** is its enol-ketone tautomer as shown by the presence of proton signals at δ 8.53 ppm corresponding to the OH and a singlet at δ 6.59 ppm corresponding to the olefinic hydrogen. Monte Carlo simulations[170] of the two tautomeric forms of compound **114** favored the enol form by 20 Kcal/mol. The predominance of the enol-ketone tautomer was supported further by the infrared data with absorptions observed at 3602 $cm^{-1}$ for the OH, and 1699 $cm^{-1}$ for the enone.




**114**

Another approach to synthesize the *trans* diol was to effect a Luche reduction[171] of compound **114**. The idea was to first perform a 1,2-reduction of the "enone portion" followed by reduction of the remaining ketone with $NaBH_4$ *via* complexation with the freshly prepared hydroxyl. This two-step reduction should force the system into a *trans* configuration. Attempts to isolate the Luche reduction intermediate were unsuccessful, probably due to equilibration of the keto-alcohol through its various tautomeric forms[170,172], and reduction of the crude Luche-reaction product afforded only *cis* diol **121**.

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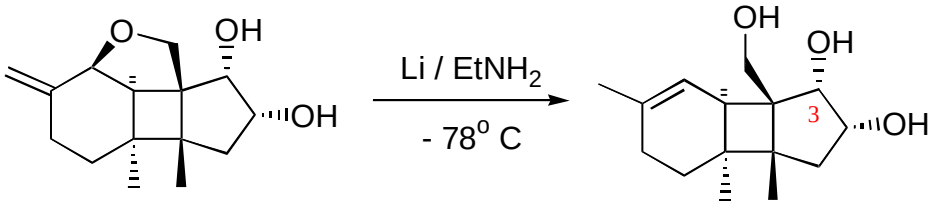
[170] Energy minimizations were carried out using MacroModel v4.5, developed by Prof. Clark Still at Columbia University. Conformational analysis were conducted using the Monte Carlo simulation package along with MM2 force fields.

[171] Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, 103, 5454.

[172] Molecular modeling using MacroModel placed all 5 tautomers within 1 Kcal/mol of each other.

Due to the difficulty in synthesizing the *trans* diol the new alternative focused on the preparation of the *cis* diol cleanly and use the primary alcohol, derived from reduction of the allylic ether, in compound **123** as a handle to invert the stereochemistry at C-3 of the triol. Dissolving metal reduction of the allylic ether **121** gave the desired triol **123** in 35% yield. This low yield was probably due to difficulties encountered during the purification of the highly polar final product.




**121** **123**

The first approach considered (see Figure 4.1) was to prepare the cyclic sulfite of the *cis* diol (an epoxide equivalent) and invert one of the hydroxyl centers (C-11 or C-12) by the intramolecular formation of a cyclic carbonate[173] or a phenylurethane[174]. Formation of the six-membered ring should be favored over formation of the seven-membered ring and inversion should occur at C-12 to give the desired stereochemical framework.

[173] Bartlett, P. A.; Meadows, J. D.; Brown, E. G.; Morimoto, A.; Jernstedt, K. K. *J. Org. Chem.* **1982**, 47, 4013.
[174] Roush, W. R.; Brown, R. J.; DiMare, M. *J. Org. Chem*. **1983**, 48, 5083.

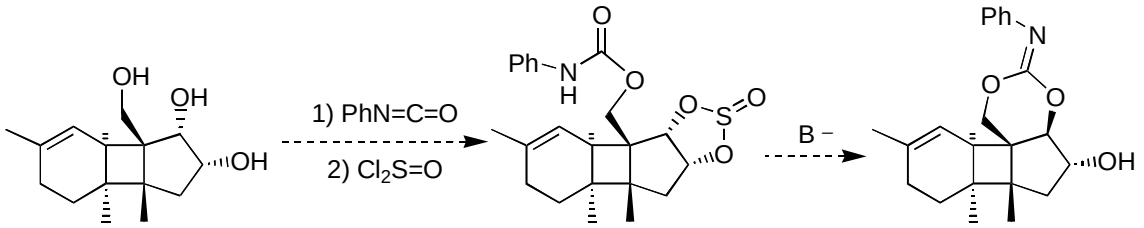



**Figure 4.1**

The second approach (see Figure 4.2) would be to activate the electrophile instead of the nucleophile. This could be accomplished by methylating the thionocarbonate and allowing a proximate pivaloate, or other ester group, to assist in the elimination.

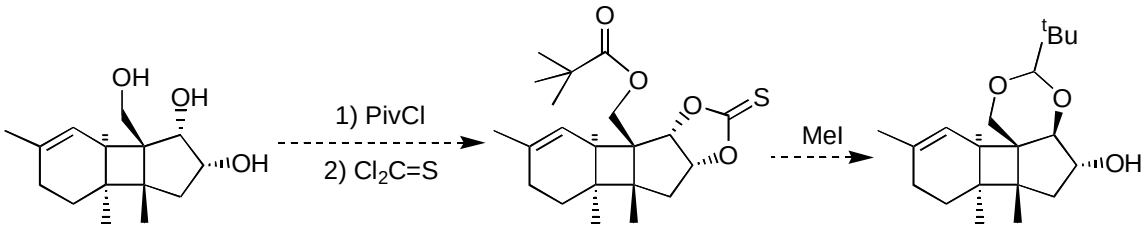
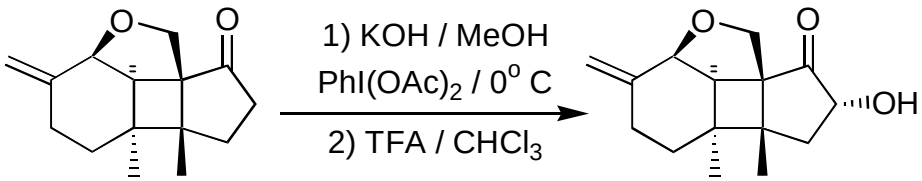



**Figure 4.2**

These ideas were not entertained for long because a more direct approach became available, the possibility of the direct installation of the hydroxy group in the concave face of the molecule.

## 3. Strategy III: The Moriarty Route

A solution to the need to install a hydroxyl in the concave face of the molecule was found in the work of Moriarty[175]. Treatment of ketone **3** with KOH, MeOH and iodoso benzene diacetate gave the alcohol-ketal **125**, which upon hydrolysis gave the desired compound **124** with the alcohol in the alpha face of the molecule.




**3** **124**

The procedure developed by Moriarty represents, in essence, an intramolecular double displacement in one step. More specifically, in this example, the enolate adds to the iodoso benzene from its least hindered face giving the β-substituted iodoso adduct. Methoxide attacks the carbonyl, again from the least hindered side of the molecule, resulting in an alkoxide in the opposite face that displaces the iodoso benzene substituent in an intramolecular $SN_2$ fashion. Another methoxide attacks the resulting methoxy-epoxide in the more electron rich site to give the hydroxy-ketal **125** (73% isolated yield). The new hydroxyl substituent is in the concave face of the molecule.

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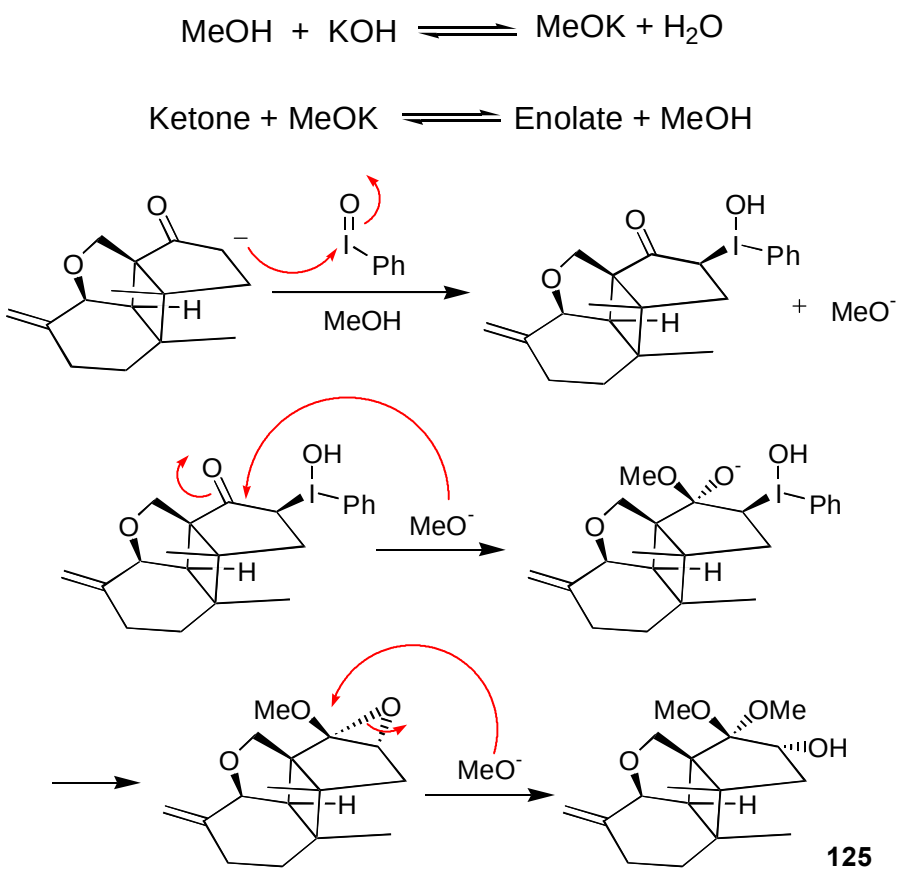
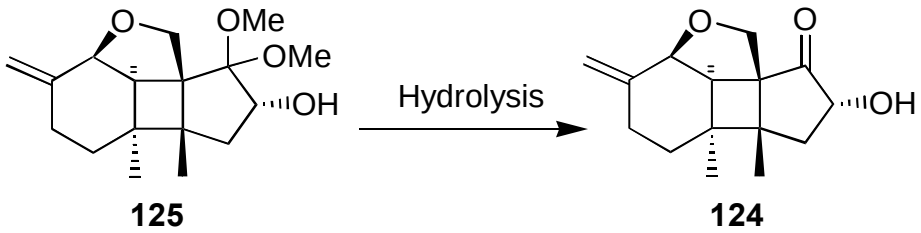
[175] Moriarty, R. M.; Gupta, S. C.; Hu, H.; Berenschot, D. R.; White, K. B. *J. Am. Chem. Soc*. **1981**, 103, 686; Moriarty, R. M.; Hu, H.; Gupta, S. C. *Tetrahedron Lett*. **1981**, 22, 1283; Moriarty, R. M.; Hu, H. *Tetrahedron Lett*. **1981**, 22, 2747; Moriarty, R. M.; Hou, K.-C. *Tetrahedron Lett*. **1984**, 25, 691; Moriarty, R. M.; Berglund, B. A.; Pen Masta, R. *Tetrahedron Lett.* **1992**, *33*, 6065.




Hydrolysis of the ketal was a delicate issue because of the risk of equilibrating the hydroxy-ketone **124** into its tautomers. The best results[176] were obtained under cold acidic conditions[177] using trifluoroacetic acid in a water-chloroform mixture at 0° C.



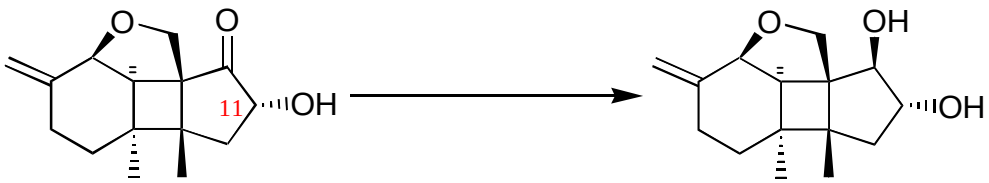

[176] Other reaction conditions attempted included dilute aqueous HCl, TsOH-MeOH and Acetic acid-THF-water.

[177] Ellison, R. A.; Lukenbach, E. R.; Chiu, C.-W. *Tetrahedron Lett.* **1975**, 16, 499.

The final product **124** was thus obtained in 62 % yield over the two steps. The stereochemistry assignment of the alcohol at C-11 was confirmed through a 2D-proton-proton NOESY experiment (see Addendum I for results).

- *Ketone Reduction:*

Once the relative stereochemistry of the hydroxyl group at C-11 was set, the next step was to convert the ketone into an alcohol with the beta configuration. To accomplish this transformation hydride delivery would have to occur from the concave side of the molecule.




**124** **126**

The objective was to use the hydroxyl as a handle for the reduction of the ketone. This transformation was attempted with various oxygen–complexing reducing agents such as $NaBH_4$, $ZnBH_4$, catechol borane[178], thexyl borane[179], cyclohexyl-borane[180], Alpine

[178] Kabalka, G. W.; Narayama, C.; Reddy, N. K. *Synth. Comm.* **1994**, *24*, 1019; *J. Chem. Soc. Chem. Comm*. **1993**, 1673.
[179] (a) Zweifel, G.; Pearson, N. R. *J. Am. Chem. Soc.* **1980**, *102*, 5919. (b) Negishi, E.; H.C.Brown *Synthesis* **1974**, 77.
[180] Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1971**, *93*, 4062.

borane[181] and Red-Al[182]. The reagents were expected to complex with the alcohol functionality and then reduce the ketone. In practice, however, most of these reagents lost some of their reducing potential once the complex was formed and more than one equivalent of reducing agent was needed for the reduction. In effect, it was the second equivalent that reduced the molecule while the first equivalent blocked the face of the molecule where it complexed. The reaction yields were low under all sets of conditions tried and the *cis* diol was the favored product.

Given the above results, a new strategy was designed to intentionally block the less hindered side of the molecule using Methylaluminum bis(2,6-di-tert-butyl-4-methylphenoxide) (MAD)[183], an aluminum complexing agent, followed by reduction of the ketone from the concave face with a small reducing agent such as NaH. The problem with sodium hydride was that it is a strong base and destroyed the starting material; the same was true for attempts using Clemmensen reduction (Zn(Hg)-HCl). Other reducing agents such as $LiBH_4$ and $AlH_3$[184] gave unreacted starting material and/or partial reduction of the olefin.

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[181] (a) Ramachandran, P. V.; Gong, B. Q.; Teodorovic, A. V.; Brown, H. C. *Tetrahedron Asym.* **1994**, *5*, 1075. (b) Ramachandran, P. V.; Gong, B. Q.; Teodorovic, A. V.; Brown, H. C. *Tetrahedron Asym.* **1994**, *5*, 1061; (c) Masamune, S.; Kim, B.; Petersen, J. S.; Sato, T.; Veenstra, S. J.; Imai, T. *J. Am. Chem. Soc.* **1985**, *107*, 4549.

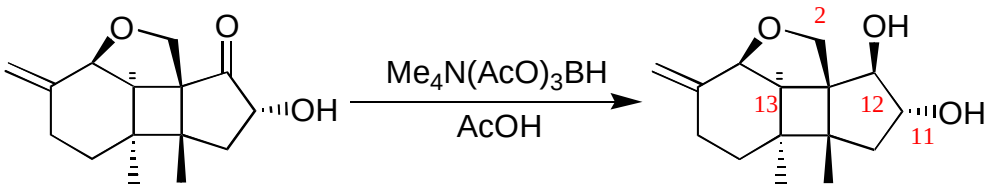
[182] Harashima, S.; Oda, O.; Amemiya, S. *Tetrahedron* **1991**, *47*, 2773.

[183] (a) Gerster, M.; Audergon, L.; Moufid, N.; Renaud, P. *Tetrahedron Lett*. **1996**, *37*, 6335; (b) Maruoka, K.; Nagahara, S.; Yamamoto, H. *Tetrahedron Lett.* **1990**, *31*, 5475; (c) Renaud, P.; Bourquard, T.; Carrupt, P.-A.; Gerster, M. *Helv. Chim. Acta* **1998**, *81*, 1048.

[184] Brown, H. C.; Hess, H. M. *J. Org. Chem*. **1969**, *34*, 2206.

Attempts to effect the reduction of the ketone using a modified version[185] of the Meerwein-Ponndorf-Verley reaction,[186] with $SmI_2$ and acetaldehyde (THF, -78° C) as part of the reduction scheme, was also unfruitful resulting in a 3:1 ratio of *cis*-*trans* diols.

A solution for the problem was found in the work of Evans[187] where he developed a borohydride reducing agent that provided a higher reducing potential once bound to the alcohol than the unbound species. Compound **124** was thus treated with tetramethylammonium triacetoxy-borohydride (AcOH, 0° C to room temperature) to yield upon isolation 75% of a 1:7 *cis*-*trans* mixture (NMR integration ratio) in favor of the desired *trans*-diol **126**.




**124** **126**

Compound **126** was separated from the *cis* diastereomer by flash chromatography to give the pure *trans* derivative. The reaction worked best when reduction was carried out soon after preparation of the keto-hydroxy intermediate **124** to minimize equilibration *via* tautomerization**.** Again the relative stereochemistry of the diol was confirmed through 1D-proton NOE difference experiments. An NOE observed between H-2β and H-11

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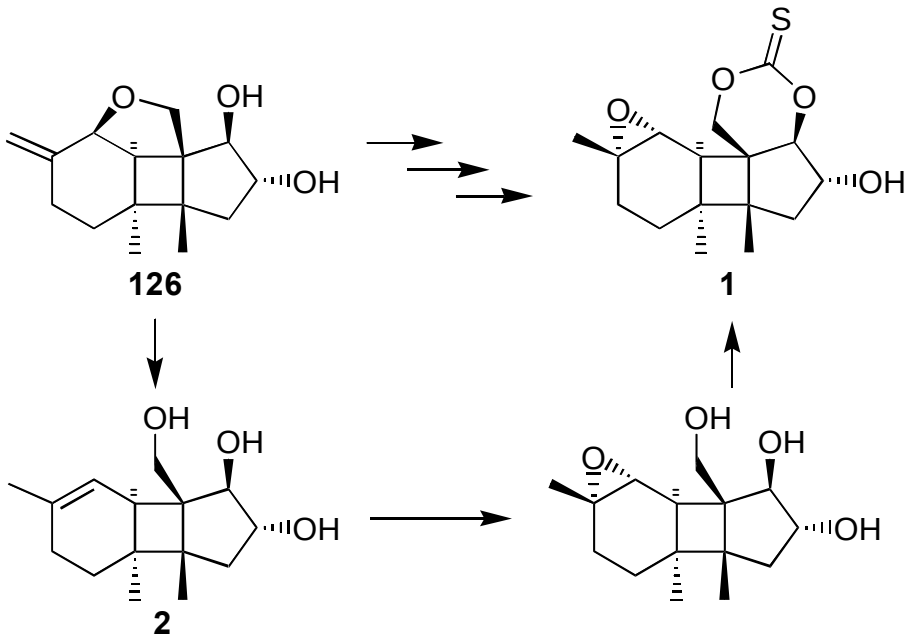
[185] Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447.
[186] Wilds, A. L. *Org. Rxns.* **1944**, *2*, 178.
[187] Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* 1988, 110, 3560; Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* 1983, 24, 273.

confirmed the R relative stereochemistry assignment at C-11 and an NOE observed between H-12 and H-13 confirmed the R relative stereochemistry assignment at C-12. These assignments were further supported by comparison with the results obtained for compound **121** (see Addendum I for details).

- *Future developments:*

With the stereochemistry of the diol established, most of the chemistry necessary to transform intermediate **126** into the fragmentation precursor **1** had been developed during the preparation of the model systems (see chapter 3). Unfortunately, the amount of substrate available was too small to carry out the remaining reactions and the preparation of more material was lengthy and difficult. At this point work in the project was interrupted; nonetheless, the initial results were promising. The fragmentation of the cyclic thionocarbonate portion of the molecule could be controlled *via* manipulation at the ring junction and this system would probably serve as a versatile entry for the synthesis of the trichothecene class of compounds.




Future developments for this project would begin with reduction of the allylic ether in compound **126**. This conversion could be accomplished by dissolving metal reduction as it was used in the reduction of the analogous compound **123**. Next, epoxidation of the triol **2** with *m*-CPBA should install the desired epoxide at C-10 and C-11 (triol numbering), as was the result for diol **92**. Again, the delivery of the oxygen should occur from the less hindered (alpha) face, instead of directed oxidation by the primary alcohol. This triol-epoxide could be converted to the cyclic thionocarbonate **1** by reaction with thiophosgene ($0^{o}$ C, slow addition of the reagent). The reaction should occur predominantly at the primary center followed by intramolecular cyclization. The cyclization step should favor formation of the six-membered ring over the seven-membered ring giving only the desired product required for the fragmentation step to unravel the trichothecene FS-2.