CHAPTER II: *SYNTHESIS OF THE TRICYCLO-UNDECANE COMMOM INTERMEDIATE*

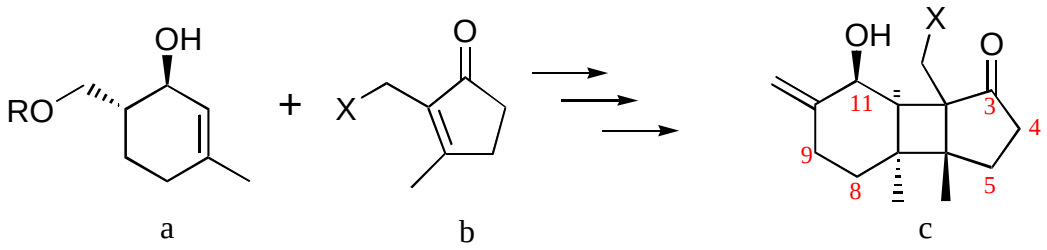
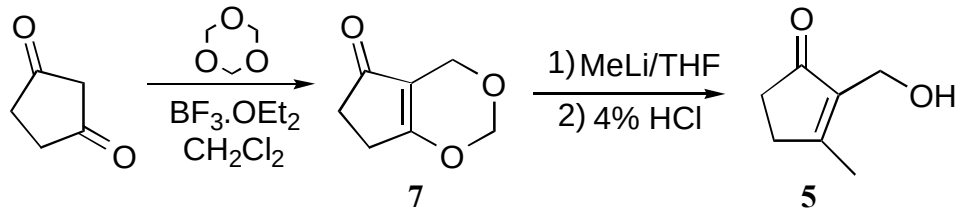


Figure 2.1

The synthesis of FS-2 required some way to control the many stereocenters present in the molecule, particularly the two adjacent quaternary centers at C-6 and C-7 (C-5 and C-6 in the trichothecene numbering system). The synthesis of a rigid intermediate with a well-defined geometry to enable face selectivity was envisioned to circumvent the need to introduce functionality in a stereoselective manner on a flexible molecule. This rigid intermediate could then be unraveled into FS-2 in the final step of the synthesis *via* a radical fragmentation. A tricycle [5.4.0.$0^{2,6}$] undecane skeleton (**c**) was designed as a precursor for simple model systems that could test the fragmentation theory and as an entry for the more advanced fragmentation intermediate needed for the synthesis of FS-2. This tricycle undecane skeleton required functionalization on its 2- and 3-positions for introduction of the cyclic thionocarbonate and a handle for introduction of a double bond at C-10 for later functional group elaboration. This common intermediate (**c**) was envisioned to arise in a convergent fashion from a [2+2] photo-addition reaction

between a five- and a six-membered ring intermediates (**a** and **b**) which would set the relative stereochemistry of the two adjacent quaternary centers upon formation of the four-membered ring.

- *Synthesis of the five and six-membered ring precursors*



7 **5**

The five- and the six-membered ring intermediates (**a** and **b**) were synthesized independently. The five-membered ring component, an α-hydroxymethyl cyclopentenone, was prepared following Smith's procedure[62] with only minor modifications.[63] Applying an acid catalyzed aldol reaction,[64] commercially available 1,3 cyclopentadione was treated with 1,3,5-trioxane in the presence of $BF_3.OEt_2$ (3 eq.) to give the 1,3-dioxin-vinylogous-ester **7** in 96% yield. It should be noted that an excess of $BF_3.OEt_2$ (3 eq.) was used in the reaction, rather then a catalytic amount (0.33 eq.), to minimize the formation of propellane side products.[62]

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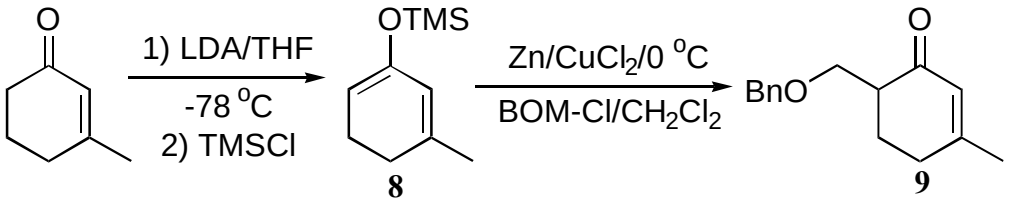
[62] Methodology developed by Bolte, M. L.; Crow, W. D.; Yoshida, S. *Aust. J. Chem.* **1982**, *35*, 1411. Amos Smith prepared compound **1** by the same procedure in Smith, A.; Dorsey, B. D.; Ohba, M.; Lupo-Jr., A. T.; Malamas, M. S. *J. Org. Chem.* **1988**, *53*, 4315.

[63] Smith used trioxane according to his table of results, but in the experimental there are reports only on the use of paraformaldehyde.

[64] A similar reaction on an enol system was previously investigated by Williams, P. H.; Ecke, G. G.; Ballard, S. A. *J. Am. Chem. Soc.* **1950**, *72*, 5738.

Addition of methyllithium or, in some experiments, a methyl Grignard reagent[65] to enone **7** (THF, -78° C, 90 min), followed by carbonyl transposition via acid hydrolysis of the intermediate (4% HCl, 0° C, 3.5 hrs) gave the desired allylic alcohol **5** in 79% yield. Derivatives of alcohol **5** could be easily prepared to activate the molecule towards nucleophilic substitution, as will be shown later for the ether coupling.



8 **9**

The six-membered ring moiety was prepared by alkylation of commercially available 3-methyl-2-cyclohexen-1-one. Initially the alkylation was attempted directly on the enolate in a basic medium, but the desired product **9** was not stable under alkaline conditions, giving mostly elimination side products.[65] To resolve the problem of product stability, an alternative approach to the alkylation was pursued using acidic conditions. A two step procedure in the presence of a Lewis acid was studied. The enone was first converted into its TMS enol ether **8** by kinetically controlled deprotonation of the ketone with LDA and trapping of the resulting lithium enolate with chlorotrimethylsilane (-78° C, THF, 40 min) in 98% yield according to the procedure of Rubottom[66] and Ainsworth.[67]

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[65] Brown E. and Nylund C. S. Progress Reports, **1979**, in this laboratory.
[66] Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1978**, *43*, 1599.
[67] Ainsworth, C.; Chen, F.; Kuo, Y. N. *J. Organomet. Chem.* **1972**, *46*, 59.

Alkylation of the known[68] enol-silyl ether **8** with BOM-Cl[69] was tried in the presence of several different Lewis acid systems ($TiCl_4$,[70] $BF_3.OEt_2$, TMSI,[71] TMSOTf,[72] $ZnBr_2$[73] and activated Zn[74]) in an attempt to optimize the yield of **9** and minimize the formation of undesired products. Titanium tetrachloride and $BF_3.OEt_2$ degraded the starting material (**8)** and no product (**9)** was obtained. When TMSI was used, product **9** could be isolated in 50-72% yield, but the reaction was not consistently reproducible. According to Noyori's procedure,[73] a solution of formaldehyde dibenzylacetal, enol-silyl ether **8** and 2,6-di-*tert*-butylpyridine was treated with 15-mol % of TMSOTf at 10^o C. Very little conversion was observed as evidenced by recovery of 81% of the starting material, 3-methyl-2-cyclohexen-1-one. The ketone was recovered due to hydrolysis of unreacted TMS-enolether **8** during purification of the products. The alkylation of the TMS-enol ether did not go to completion even after the reaction was conducted for 4 days, and more formaldehyde dibenzylacetal was added; instead, side products started to form.

The best results for alkylation were obtained using zinc bromide[73] (BOM-Cl, CH_2Cl_2, 0^o C, 3 hrs) in small-scale reactions (< 500 mg) which afforded **9** in 49% yield. When the procedure was tried on a larger scale poor yields (12-15 %) were obtained. It is

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[68] Iwata, C.; Takemoto, Y.; Nakamura, A.; Imanishi, T. *Tetrahedron Lett.* **1985**, *26*, 3227 reported the first preparation of this compound, in a table of results, but no characterization data was reported.

[69] An alternative where BOM-I was used instead of the chloride was reported with great success by Kucera, D. J.; O'Connor, S. J.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 5304 and also by Ditrich, K.; Reinhard, W.; Hoffman, R. W. *Liebigs Ann. Chem.* **1990**, 15.

[70] Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503.

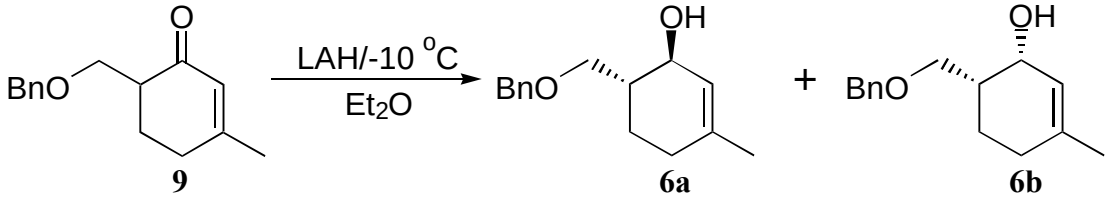
[71] Sakurai; Hosomi *Chem Lett.* **1983**, 405.

[72] Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, 2527.

[73] Paterson, I.; Fleming, I. *Tetrahedron Lett.* **1979**, *20*, 2179.

important to note that one must sublime the catalyst (flame, under vacuum) just prior to use because any HBr present in the system is enough to compromise the reaction. Another solution was sought for situations when large-scale versions of the reaction were needed. Activated zinc,[74] in the form of Simmon-Smith's catalyst (Zn, CuCl, CH_2I_2, BOM-Cl, CH_2Cl_2, 0^o C, 10 hrs) was used with success, giving 58% yield on large scale reactions up to 24 g.

Contrary to previous reports,[65] compound **9** was stable after purification. Compound **9** degrades rapidly under the reaction conditions; therefore, it requires immediate purification via flash chromatography using 1 % diethyl ether in methylene chloride as the eluent. Product **9** was found to be particularly prone to degradation when zinc bromide was used as the catalyst.

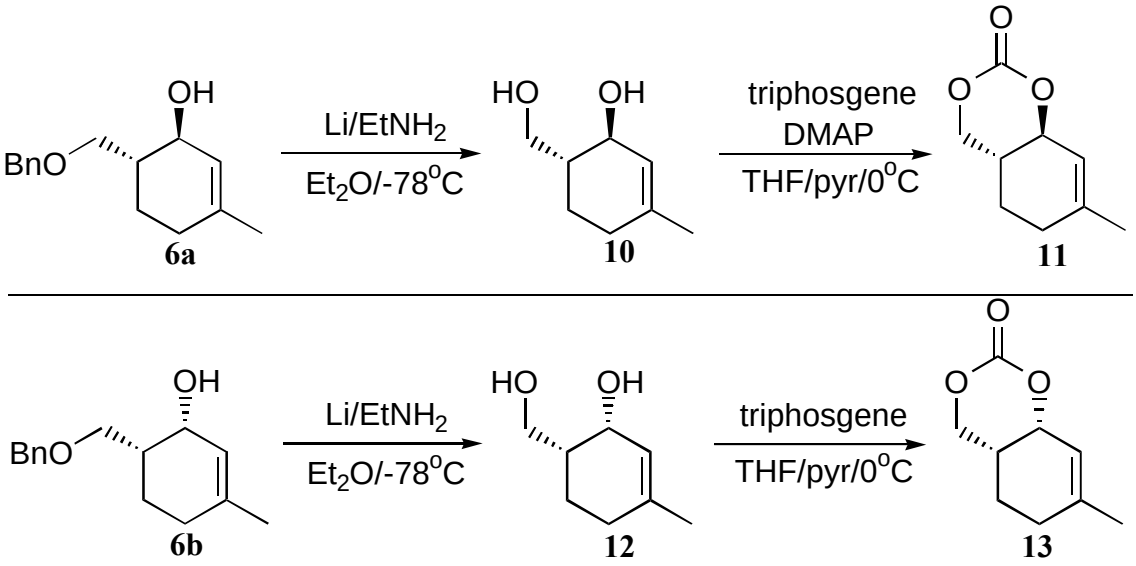


9 **6a** **6b**

Reduction of compound **9** was accomplished with good selectivity using lithium aluminum hydride as the reducing agent (Et_2O, -10^o C, 3 hrs). A mixture of *cis* and *trans* alcohols was obtained in 85% yield. The ^{1}H NMR integration ratios of the crude reaction mixture indicated a 7:1 distribution in favor of the desired *trans* product **6a** (threo). The

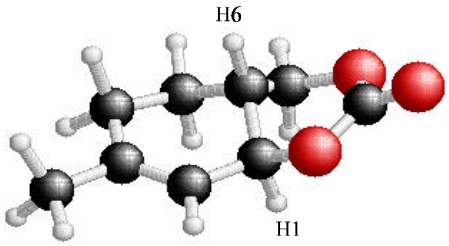
[74] Shono, T.; Nishigushi, I.; Komaniura, T.; Sasaki, M. *J. Am. Chem. Soc.* **1979**, *101*, 984.

two isomers **6a** and **6b** could be separated by flash chromatography using 5 % diethyl ether, 1 % benzene in methylene chloride as the eluent.

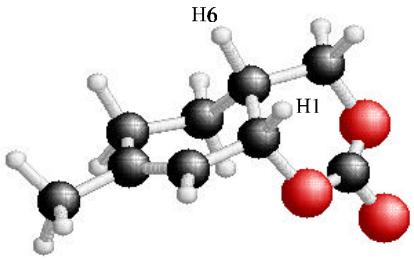


The relative stereochemistry of the two alcohols was tentatively assigned based on their ^{3}J coupling constants (*trans* 8.4 Hz and *cis* 4.0 Hz) of protons attached to C-1 and C-6 in the ^{1}H NMR. These stereochemical assignments of **6a** and **6b** were further supported by converting each product to its corresponding cyclic carbonate, where the coupling constants could be used for assignment in a more confident fashion once the two systems were locked in a rigid geometry. The conversion of the two alcohols **6a** and **6b** to the cyclic carbonates **11** and **13** was done independently by first deprotection of the benzyl protecting group with Li/$EtNH_2$ (Et_2O/ -78^{o} C) to give the respective diols, *trans* (**10)** in 97% yield and *cis* (**12)** in 90% yield. These diols were in turn converted to the corresponding cyclic carbonates by treatment with triphosgene. The best conditions for this transformation were 4-dimethylaminopyridine, pyridine, THF, 0^{o} C, 7 hrs for the *trans* system **11** (93% yield) and pyridine, THF, 0^{o} C, 7 hrs for the *cis* system **13** (89% yield).

The reaction gave very poor yields for the *cis* product (**13**) when 4-DMAP was used. When ^{3}J coupling constants of the protons attached to C-1 and C-6 were examined they were found to be 9.5 Hz for compound **11** and 4.3 Hz for compound **13**.



Compound 9
trans-carbonate



Compound 10
cis-carbonate

According to the Karplus[75] equation and based on the predicted dihedral angles of the energy minimized structures[76] for these two compounds (*trans* 124.9° and 48.4° for the *cis*), their coupling constants were predicted to be 10.5 Hz for the *trans* compound and 3.2 Hz for the *cis*). Based on these observations compound **11** was assigned as the *trans* carbonate and compound **13** as the *cis* carbonate.

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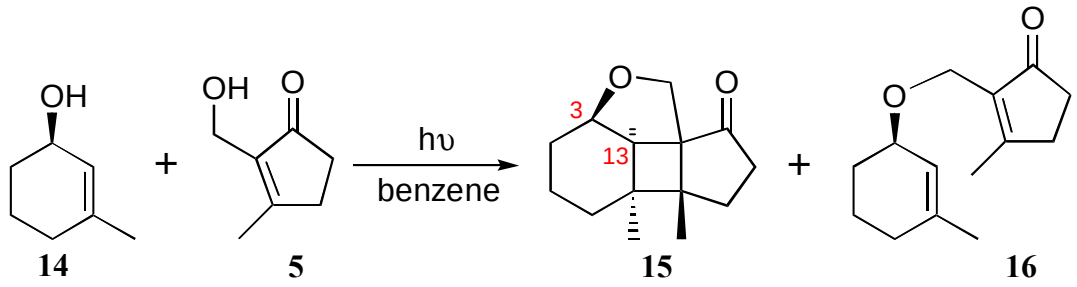
[75] Karplus, M. *J. Chem. Phys*. **1959**, *30*, 11.

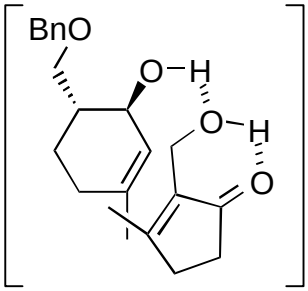
[76] Energy minimizations were performed using MacroModel version 4.5 developed by Prof. Clark Still at Columbia University. Conformational searches were conducted using the Monte Carlo simulation package and the MM2 minimization force field. One conformation was found for the *trans* compound and 3 conformations were found for the *cis* system within 50 Kcal/mol. The lowest energy in each case was used to evaluate the angles. The *trans* compound was found to be more stable by ΔE=0.12 Kcal/mol.

- *Intermolecular photoaddition*



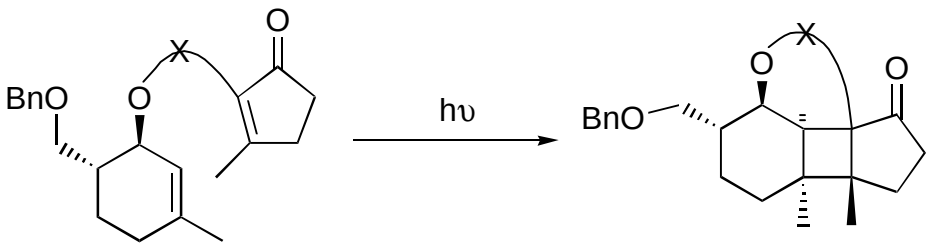
With the two precursors in hand, initial studies[65] to couple the five- and six-membered rings involved an intermolecular photo-addition. The reaction was carried out under the following conditions: alcohol **14** (10 eq.), alcohol **5** (1 eq.), benzene (0.02 M on alcohol **5**) and UV photo-irradiation of the deoxygenated solution for 20 hrs at room temperature. This gave a 7% yield of the head-to-head product **15** as was evidenced by the absence of vinylic protons on the ^{1}H NMR and shift of the enone IR band from 1696 cm^{-1} to that of a ketone at 1729 cm^{-1}. Evidence for the formation of the four-membered ring consisted of the presence of a resonance at δ 2.27 ppm, a doublet (J = 6.3 Hz) corresponding to H-13, coupled to a multiplet at δ 3.99-3.93 ppm associated with H-3, in the ^{1}H NMR spectrum. There was no evidence for the formation of head-to-tail products.

The absence of the head-to-tail product can be justified by arguing that the exciplex is pre-organized due to hydrogen bonding between the two reagents as shown in the scheme on the right. Other isolated compounds included the unreacted starting materials: alcohol **14 (**47%) and alcohol **5** (80%), along with the byproduct ether **16** (8%). The observation that ether **16** is formed during the course of



this reaction is further support for the idea that hydrogen bonding is in effect between the five- and six-membered ring reagents. The low yield of the desired photoaddition product **15** obtained under these conditions prompted us to investigate intramolecular analogs of the same reaction.

- *Intramolecular photoaddition*



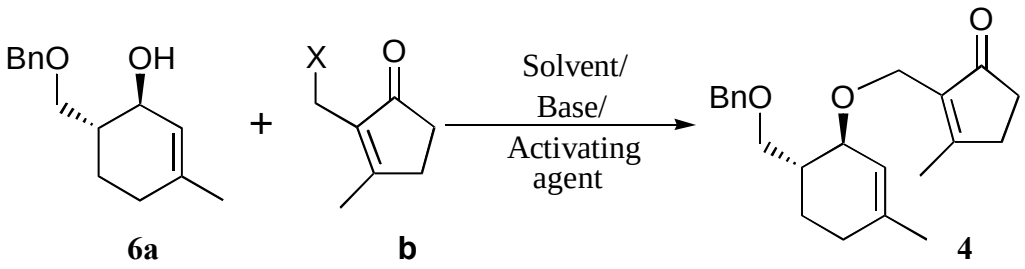
Intramolecular reactions are preferred over crossed-cyclo-additions because they minimize undesired homo-dimerizations and allow for regio-control of the photoaddition. The intermolecular version of the reaction would also offer better control over the relative stereochemistry of the four newly formed stereocenters by transferring chirality from the six-membered ring alcohol **6a** to the product. Wender supports this prediction in a report where he states "When the ground state alkene is facially differentiated, addition of the excited state enone will occur preferentially to the less encumbered face of the alkene".[77] This statement is based on assumptions that the stereochemistry integrity of ground state

[77] Wender, P. In *Photochemistry in Organic Synthesis*; Coyle, J. D., Ed.; Royal Soc. of Chem.: London, **1986**; Vol. 57, p 163.

cyclic alkenes is preserved, and also that the exo product is favored unless there are geometric constraints in the molecule that would favor the endo product.

In an attempt to tether the five- and six-membered ring precursors **5** and **6a** for an intramolecular version of the photoaddition, three main strategies were pursued: ether link, ester link and silicon tether. All three strategies will be discussed, but ultimately, the ether link strategy gave the most promising results and the Williamson ether synthesis was incorporated in the final photoaddition scheme.

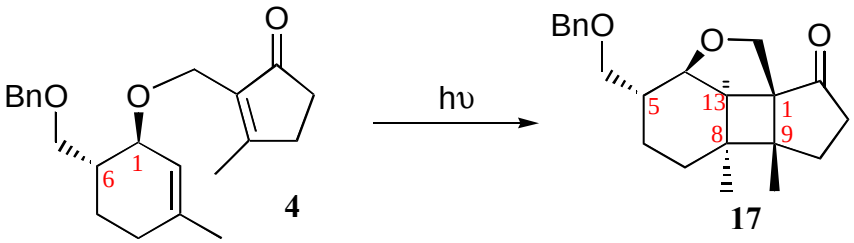
1. Ether tether strategy: Williamson ether synthesis



6a **b** **4**

The Williamson ether synthesis methodology was the first ether link strategy pursued. The best coupling results were obtained using the six-membered ring alcohol **6a** as the nucleophile and activating the five-membered ring component towards substitution. The benefits of using the five-membered ring as the electrophile are two fold: one does not have to worry about SN_2' reactions competing with the desired direct displacement on the six-membered ring and the displacement is expected to occur on the primary site of the electrophile thus minimizing steric effects.

Following successful ether formation, the intramolecular photoaddition reaction of compound **4** could follow two pathways in which both faces of the double bonds could react to give two isomeric *syn* products. In order to induce the face selectivity, only the *trans* alcohol **6a** was used. Thus the oxygen stereochemistry at C-1 of the substrate **4** would induce formation of the 1R*, 8R*, 9S*, 13S* relative stereochemistry in photoadduct **17**. The alkyl group at C-6 would further ensure this face selectivity by increasing the steric hindrance on the opposite side of the molecule.



4 **17**

During the course of optimizing the ether synthesis, several issues had to be examined: best leaving group, activation of the electrophile, solvent effects and choice of base. On trying to select the best leaving group, two issues were considered: the ease of preparation of the derivative and the effect of the leaving group in the coupling reaction. Attempts included the derivatization of alcohol **5** as its mesylate (X = OMs), chloride (X = Cl), bromide (X = Br) and iodide (X = I). The mesylate (MsCl, Et_3N, CH_2Cl_2, 0^o C) was prepared in 40 % yield. The chloride ($SOCl_2$, $CHCl_3$, room temperature) was obtained in 96 % yield. The bromide was prepared in a two step process starting from formation of the mesylate and displacement with bromide (LiBr, acetone, 0^o C) to obtain the desired derivative in 46% yield (18% overall from alcohol **5**). The iodide was also prepared in a

two step process (NaI, acetone, room temperature) giving the desired product in 61% yield (25% overall from alcohol **5**).

With the derivatives in hand, coupling of the mesylate (10 eq. of alcohol **6a**, 1 eq. mesylate, ^{t}BuOK) gave ether **4** in 24 % yield. For the reactions involving the halide electrophiles, silver triflate was used as an activating agent (in CH_2Cl_2, and base). Under these reaction conditions the iodide derivative reacts only slightly better (38 % yield of **4**) than the bromide (34 % yield of **4**) and the chloride (35 % yield of **4**). Since there was not much difference on the efficiency of the different leaving groups, the chloride derivative was chosen because it could be prepared in higher yield.

Various silver salts were investigated to determine which one would work best in activating the electrophile in the Williamson ether synthesis. Silver nitrate, silver carbonate and silver tetrafluoroborate were tried unsuccessfully. The best results were obtained using a silver triflate catalyst to activate chloride **18** towards coupling. Under these conditions AgCl starts precipitating immediately upon addition so, provided there is free silver salt in solution, activation of the chloride is not the rate-determining factor. Note that excess silver triflate (3 eq.) was necessary, possibly because some of the silver salt complexes to the oxygens in the product during the course of the reaction.

The solvent of choice was methylene chloride, a non-coordinating solvent. Experiments that utilized coordinating solvents such as THF or acetonitrile led to no reaction, even when ten equivalents of silver triflate were used. Attempts were also made with benzene as an option for solvent, but ether formation proceeded in low yield (<10%).

Base was required to scavenge any acid formed during the course of the reaction; experiments conducted in the absence of base gave poor results. Four bases were tried,

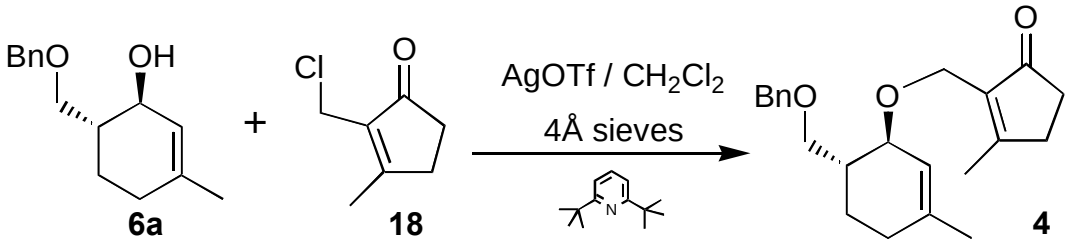
triethylamine, pyridine, 2,6-lutidine and 2,6-di-*tert*-butylpyridine. When only one equivalent of the silver salt is used with one equivalent of either TEA, pyridine or 2,6-lutidine, no product formed, which suggests that the base complexes with the salt. To prevent this complexation, the more hindered base, 2,6-di-*tert*-butylpyridine was used successfully. It is worth mentioning that chloride **18** is unstable to nucleophilic bases probably due to degradation leading to diene type elimination products. This is evidenced by the increased signal in the vinylic region of the ^{1}H NMR.

The possibility that the reaction catalyzed by silver triflate involved substitution of the halide in compound **b** and formation of a triflate intermediate (X = OTf) prior to coupling with alcohol **6a** was investigated. Attempts to pre-form the triflate of alcohol **5** *in situ* (triflic anhydride, CH_2Cl_2, 0^o C, 30 min), followed by addition of alcohol **6a** and di-tert-butylpyridine was unsuccessful, yielding only 24% of the desired ether **4**. Optimization was focussed again on the chloride displacement reaction.

Studies involving changes in the order of addition of the reagents, testing the stability of the reagents in the reaction mixture and stoichiometric dependence of the reaction led to the conclusion that, provided the base was hindered enough, the only variable that affected reaction yield was the slow addition of chloride **18**. The slow addition requirement probably reflects the fast activation of the chloride generating an unstable electrophile. It is important to keep the chloride concentration low throughout the course of the reaction to maximize ether formation.

Attempts to scale up the reaction were not as successful. This could be due to surface area restraints that seem to play an important role in this reaction. Consequently, the yield was higher if several small reactions (300 mg) were conducted side by side rather

than one large-scale reaction. It is also important that no moisture be present in the reaction media to prevent the nucleophilic attack of water on the activated chloride. For that reason, the reaction was always conducted in the presence of 4Å molecular sieves.

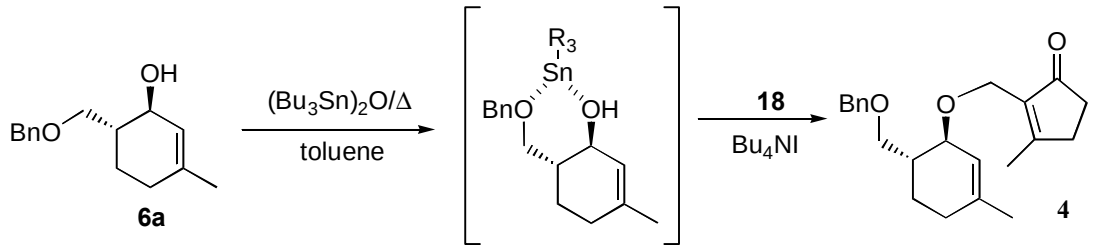


The optimized reaction conditions for the Williamson ether synthesis involves slow addition of the chloride **18** (1 eq.) to a solution protected from light containing alcohol **6a** (1 eq.), 2,6-di-*tert*-butyl-pyridine (3 eq.), silver triflate (3 eq.) and 4Å molecular sieves, in methylene chloride. Under these conditions, provided the scale was no more than 300 mg, compound **4** was consistently isolated in 57% yield.

2. Ether tether strategy: failed alternatives

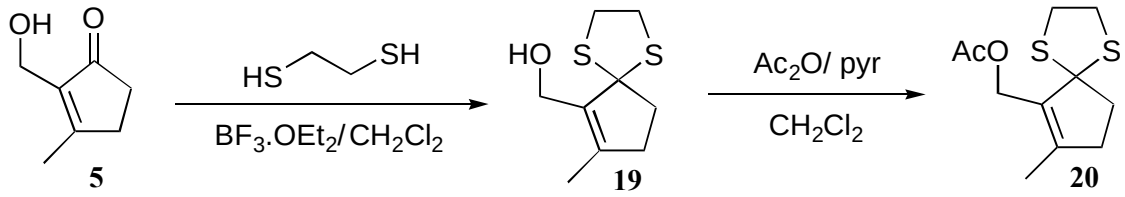
Attempts to overcome the low yield obtained for the Williamson ether synthesis strategy involved experiments under different ether forming conditions or modification of the five-membered ring coupling-partner. These options are presented below.

The first approach involved formation of the tin-oxide derivative[78] of alcohol **6a** in an attempt to make the oxygen of the alcohol more nucleophilic.

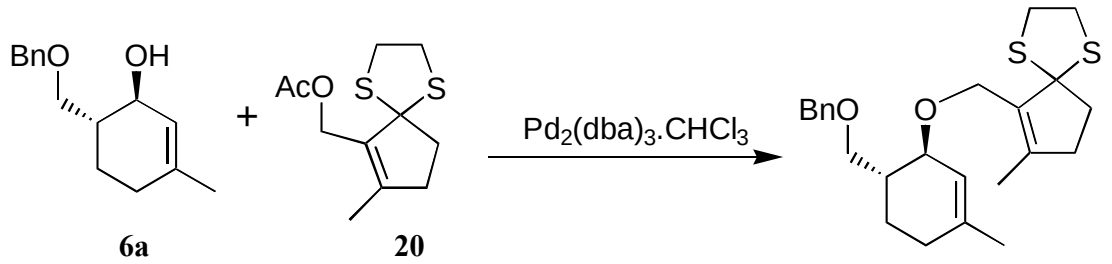


Alcohol **6a** was first treated with bis-(tributyltin)-oxide, (toluene, reflux, 4 hrs, 4Å molecular sieves) and then reacted with chloride **18**, in the presence of Bu_4NI, (80^o C). After 70 hrs only unreacted starting material was recovered.

Trost[79] and Hirama[80] successfully applied oxygen nucleophiles in intramolecular palladium-coupling reactions. Attempts to effect the intermolecular version of this reaction and form the ether through a π-allyl intermediate was conducted in two fronts.

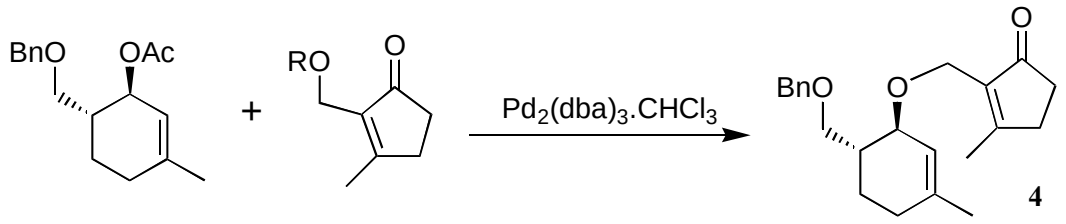


[78] Alais, J.; Veyrieres, A. *J. Chem. Soc. Perkin Trans. I* **1981**, 377. This reaction was first tried by Nylund, C. S., see ref 4.
[79] Trost, B. M.; Tenaglia, A. *Tetrahedron Lett.* **1988**, *29*, 2927.
[80] Suzuki, T.; Sato, O.; Hirama, M. *Tetrahedron Lett.* **1990**, *31*, 4747.



6a **20**

The first possibility was to form the π-allyl on the five-membered ring and use the six-membered ring as the nucleophile. This required masking of the ketone in the five-membered ring in order to form the π-allyl complex effectively, introducing an extra step to the reaction sequence. It also resulted in an increase of the ring strain on the π-allyl complex and of the steric hindrance around the reaction center. The carbonyl in compound **5** was first protected as a thioketal to give compound **19** by treatment with 1,2-ethane dithiol (methylene chloride, room temperature, $BF_3.OEt_2$, 8 hrs. 80% yield). The allylic alcohol portion of the molecule was activated as an acetate by treatment with acetic anhydride to give compound **20** (pyridine, CH_2Cl_2, room temperature, 16 hrs, 77% yield) which was then reacted with $Pd_2(dba)_3.CHCl_3$ (THF, PPh_3, room temperature, 15 min) to form the π-allyl complex. This intermediate was transferred *via cannula* into a solution containing alcohol **6a** and sodium hydride in THF. No coupling product was isolated even after the reaction proceeded for 20 hrs at room temperature.



R = H comp. **5**

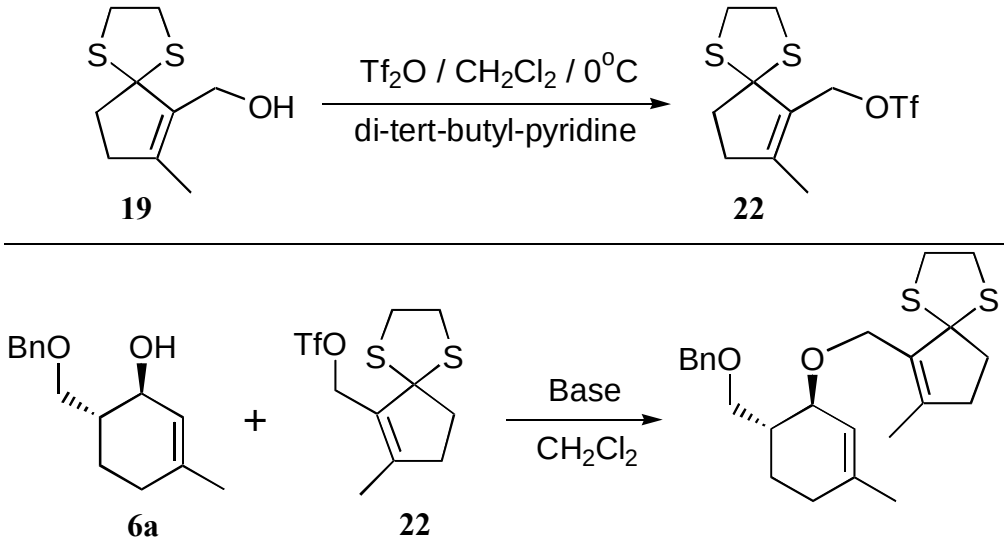
R = Bu_3Sn comp. **21**

The second possibility for the palladium coupling was the reverse of the previous strategy. The π-allyl-palladium complex was formed on the six-membered ring and the five-membered ring acted as the nucleophile. This approach should be favored since the nucleophile attacking the complex would be located on a primary center. Attack of the π-allyl should be selective with the nucleophile approaching from the least hindered side, giving ether **4**. Two versions of the coupling were tried against the possibility that the dipolar moment of the carbonyl on **5** would interfere with the nucleophilic attack of the palladium complex: one with the carbonyl protected as the thioketal (compound **19**), and the other with the carbonyl unprotected (compound **5**). In addition, following suggestions that hard nucleophiles are generally poor reaction partners for π-allyl-palladium complexes, the tin ether[78] of alcohol **5** was pre-formed and used as the nucleophile (compound **21**). The stannyl derivative experiment, as was also observed in Trost's experiments,[81] gave the same result as the respective alcohol.

Alcohol **6a** was first acetylated (Ac_2O, pyridine, CH_2Cl_2, room temperature, 4 hrs, 66% yield) then submitted to π-allyl formation. Treatment of the acetyl derivative of **6a** with $Pd_2(dba)_3{\cdot}CHCl_3$ (THF, PPh_3, room temperature), then addition of alcohol **5** or

alcohol **19** (reflux for 2 hrs) resulted in recovery of the five-membered ring piece intact. Attempts to form the π-allyl complex by treatment with $Pd(Ph_3P)_4$ in THF, or with $Pd(PPh_3)_4$ and $Ph_2PCH_2CH_2PPh_2$ in CH_2Cl_2 resulted in no reaction and both starting materials were recovered with no evidence of formation of the complex. Due to the lack of success with the palladium coupling strategy, this approach was abandoned.

A different strategy for the ether synthesis involved modification of the five-membered ring coupling-partner based on the premise that the dipole moment of the ketone was favoring elimination side products and deactivating substitution pathways.

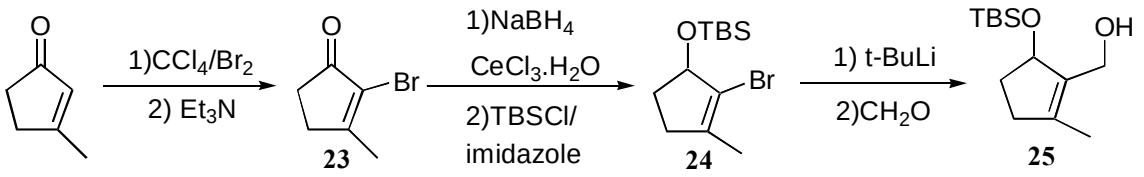


One attempt involved masking the ketone as a thioketal. The thioketal derivative was activated towards coupling by reaction with triflic anhydride (di-*tert*-butyl-pyridine, CH_2Cl_2, 0^o C, 30 min) followed by addition of alcohol **6a**, then the reaction mixture was

[81] Trost, B. M.; Tenaglia, A. *Tetrahedron Lett.* **1988**, *29*, 2931.

allowed to slowly warm to room temperature. Even after 4 hrs, only 8% yield of an ether could be isolated.

Another attempt to modify the five-membered ring component (**5**) involved reduction of the enone to an allylic alcohol and protection as a silyl ether.



Compound **25** could be obtained from 3-methylcyclopentenone by first treating the starting material with bromine in carbon tetrachloride, followed by elimination in the presence of triethylamine to give the α-keto-bromide **23** in 66% yield.[82] Reduction of the carbonyl according to Luche's procedure[83] ($CeCl_3.7H_2O$, $NaBH_4$, EtOH, room temperature) and protection of the resulting allylic alcohol by reaction with TBSCl in the presence of imidazole[84] (DMAP, CH_2Cl_2, 0^o C) occurred smoothly giving the desired silyl ether precursor **24** in 76% yield. Transmetallation[85] with t-BuLi in pentane-ether at -78^o C, followed by trapping the anion with para-formaldehyde gave the requisite five-membered ring compound **25** in 68% yield.

Incorporation of **25** into the ether coupling schemes required activation of its alcohol functionality as either the chloride or the mesylate. However, preparation of these

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[82] Smith, A.; Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982**, *47*, 1855-1869.
[83] Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
[84] Tanner, D.; Somfai, P. *Tetrahedron* **1988**, *44*, 619.

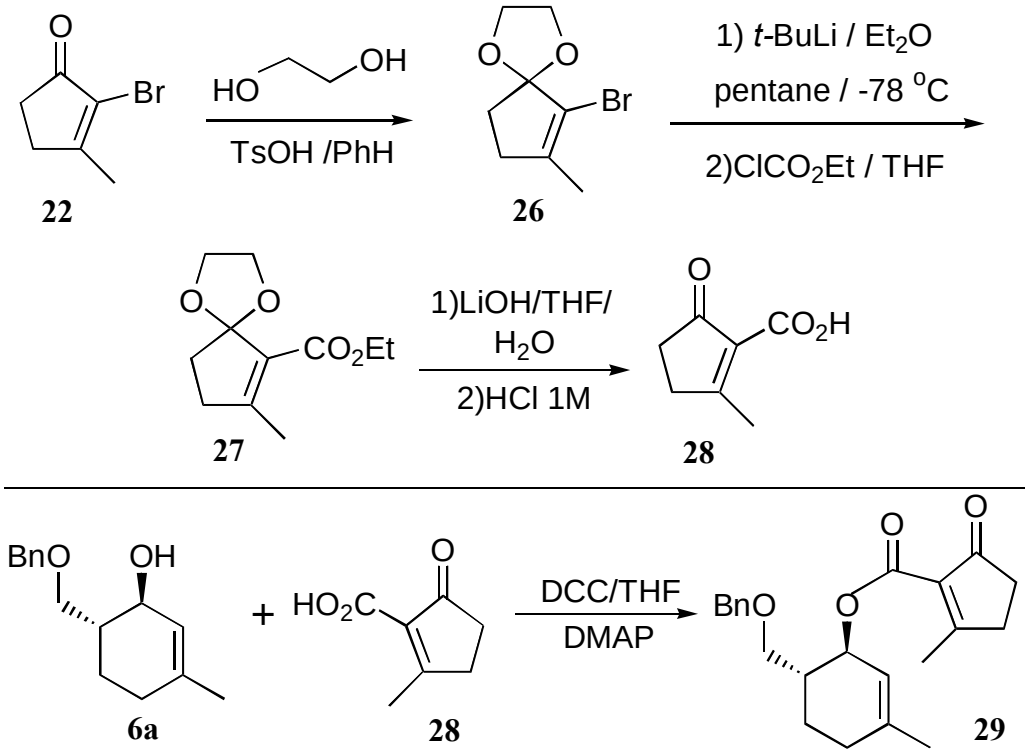
derivatives using the procedures discussed previously produced mostly degradation products along with byproducts deriving from silicon group migration.

3. The ester tether strategy

The second strategy pursued to tether the precursors for the intramolecular photoaddition scheme was to use an ester link, a two oxidation-level higher version of the ether coupling. An advantage of the ester link is that there are many reagents available for the coupling. A disadvantage is that the ester introduces rigidity into the tethering chain, which may hinder proper alignment of the double bonds in the subsequent photochemistry step. Two substrates were prepared, a one-carbon chain ester (compound **29**) that was analogous to the ether tether, and a two-carbon chain ester (compound **32**) designed to add flexibility to the tether. Ester formation was accomplished in acceptable yields for both the one and two carbon chain esters, but the photochemistry of these substrates was not successful.

Preparation of the one carbon chain ester (compound **29**) was accomplished by first synthesizing the carboxylic acid derivative of the five-membered ring piece (compound **28**), and then coupling it with alcohol **6a**.

[85] (a) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404; (b) Negishi, E.-I.; Swanson, D. R.; Rousset, C. J. *J. Org. Chem.* **1990**, *55*, 5406.

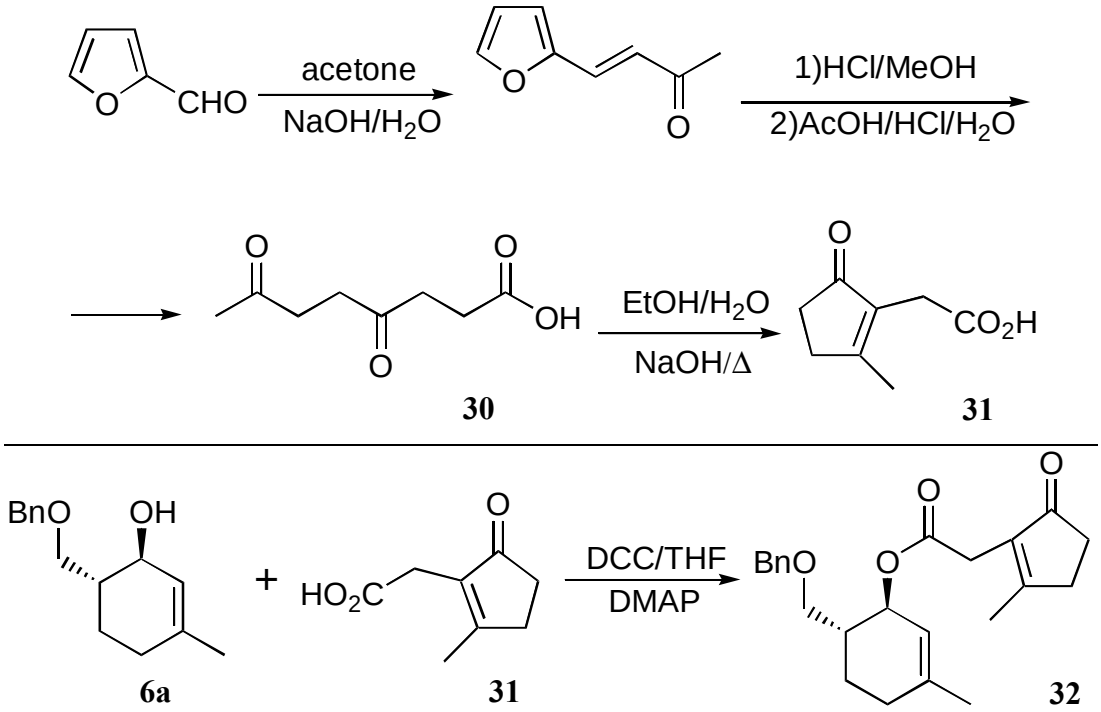


Protection of the carbonyl of 2-bromo-3-methylcyclopentenone **22** as the ketal[86] proceeded smoothly by treatment of the substrate with ethylene glycol in the presence of p-toluene sulfonic acid in benzene, under reflux (90% yield). Transmetallation[85] with t-butyllithium in pentane-ether at -78° C followed by trapping the anion with ethyl chloroformate gave ester **27** in 90% yield. Hydrolysis into the carboxylic acid **28** using LiOH[87] (THF, H_2O, 15° C), followed by acidic work-up (1M HCl) gave the five-membered ring substrate **31** in 78% yield. Note that the ketal protecting-group was also

[86] Daignault, R. A.; Eliel, E. L. *Org. Syn. coll.* **1973**, *vol 5*, 303.
[87] Ziegler, F. E.; Harran, P. G. *J. Org. Chem.* **1993**, *58*, 2768.

removed during the course of the hydrolysis. Esterification[88] of carboxylic acid **28** with alcohol **6a**, using DCC and DMAP in THF gave the desired ester **29** in 41% yield.

For the longer chain analog, furfural was used as the starting material for the synthesis of the five-membered ring precursor (compound **31**) which was then coupled to alcohol **6a**.



Furfural was condensed with acetone under basic conditions[89] (NaOH, H_2O, 80° C, 6 hrs, 53 % yield). The resulting furfurylidene-acetone was treated with HCl in methanol[90] to give the methyl ester of **30**, according to Marckwald's reaction.[91] This

[88] Ziegler, F. E.; Berger, G. D. *Syn. Comm.* **1979**, *9*, 539; also see Neises, B.; Steglich, W. *Ang. Chem. Int. Ed. Eng.* **1978**, *17*, 522 and Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, 4475.
[89] Midorikawa, H. *Bull. Chem. Soc. Japan* **1954**, *27*, 210.
[90] Birch, A. J.; Keogh, K. S.; Mandaprer, V. R. *Aust. J. Chem.* **1973**, *26*, 2671.
[91] (a) Hunsdiecker, H. *Chem. Ber.* **1942**, *75B*, 447, (b) Abeysekura, A. M.; Amaralinge, S.; Grunshaw, J.; Jayeweera, N.; Sinanayake, G. *J. Chem. Soc. Perkin Trans. I* **1991**, 2021.

intermediate was then transesterified in the presence of acetic acid, HCl and water, to give the carboxylic acid **30** in 45 % yield. An intramolecular Knöevenagel cyclization[92] in NaOH (EtOH, H_2O, reflux, 20 hrs) gave the desired carboxylic acid **31** in quantitative yield. Esterification[88] of carboxylic acid **31** with alcohol **6a**, using DCC and DMAP in THF at room temperature gave the desired ester **32** in 49 % yield.

Photoaddition reactions were tried on both the one[93] (compound **29**) and the two[94] (compound **32**) carbon-tethered systems. Optimization of the reaction conditions included use of different solvents (benzene, cyclohexane, acetonitrile, methylene chloride, tetrahydrofuran, acetone, methanol, ethylene glycol and glyme), glass filters[95,96] (quartz, Vycor, Corex, Pyrex and uranium) and the use of sensitizers[97] (acetone, E_τ= 79 Kcal/mol, acetophenone, E_τ= 74 Kcal/mol, and benzophenone, E_τ= 69 Kcal/mol). None of these conditions gave the desired [2+2]-photoaddition product with most of the reactions resulting on recovery of unreacted starting material or decomposition into baseline products.

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[92] (a) Johnson, W. S.; Gravestock, M. B.; McCarry, B. E. *J. Am. Chem. Soc.* **1971**, *93*, 4332; (b) McMurry, P. M. J.; Singh, R. K. *J. Org. Chem.* **1974**, *39*, 2316.

[93] UV absorption maximum at 220 nm in methanol.

[94] UV absorption maximum at 232 nm in methanol.

[95] UV cutoffs for glass width of 2mm: quartz (<200 nm), Vycor 7910 (<230 nm), Corex D (<270 nm), Pyrex 7740 (<290 nm), uranium (<320 nm).

[96] Coyle, J. D. *Photochemistry in Organic Synthesis*; Burlington House: London, **1986**.

[97] The energy for the first triplet state of cyclopentenones is reported to be at E_3=74 Kcal/mol in Turro, N. J. *Modern Molecular Photochemistry*; Benjamin/Cummings Pub. Co.: Menlo Park, Califronia, 1978.

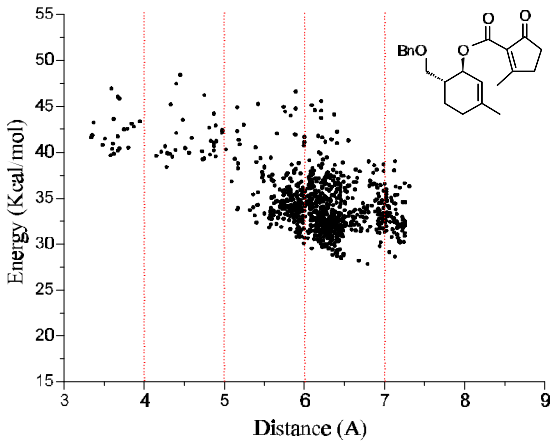
E - conformation Z - conformation

Figure 2.2

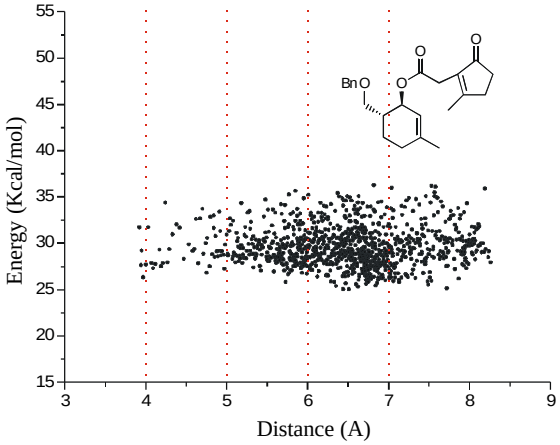
Most esters tend to favor E-conformations over Z-conformations (see Figure 2.2), thus setting the two double bonds in esters **29** and **32** involved in the photoaddition reaction far apart. This preference for the E-conformation for the ground state of esters **29** and **32** make the success of the [2+2] cyclization dependent on the lifetime of the excited state of the chromophore. The excited state must live long enough for conformational change to occur prior to cycloaddition and avoid other relaxation pathways that would lead to side reactions such as Norrish cleavage, etc. Also, [2+2] intramolecular addition of the ester with the longer tether (compound **32**) must be accompanied by formation of a six-membered ring, which is generally disfavored, entropically, on intramolecular photoadditions.[98] Attempts to run the reaction at a higher temperature favored the formation of products derived from these undesired "side reactions" (mostly baseline material).

Monte Carlo simulations were carried out in order to evaluate the population distribution of the different conformations that compounds **4**, **29** and **32** are able to adopt. Analysis of the results was based on the assumption that the excited state resembles the geometry of the ground state and that for the reaction to occur the double bonds must be

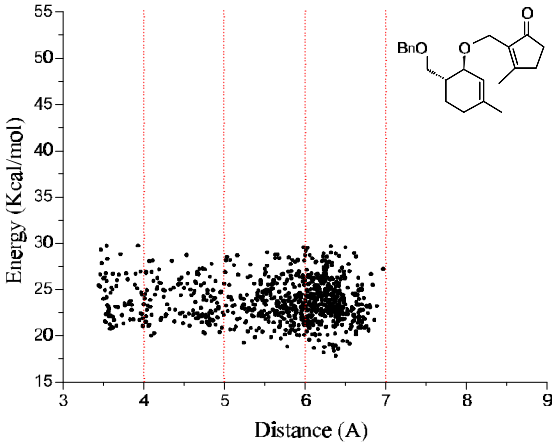
close in space in order to be able to interact. Since this is an intramolecular reaction, the distance between the two methylene-carbons next to a methyl in each double bond can represent the distance of the two olefins in each one of the compounds. The results comparing the distance between the olefins to the energy of the conformer are graphed below; conformations with shorter distances and lower relative energy are more likely to undergo the desired reaction.



compound 29



compound 32



compound 4

Monte Carlo simulation parameters included minimization of 10,000 conformations for each of the three compounds using the MM2 force field available with MacroModel. Structures within 20 Kcal/mol of the lowest energy structure for each compound were saved.

[98] "Rule of five" - Crimmins, M. T. *Chem. Rev.* **1988**, 1453.

The Monte Carlo simulation results indicate that a significant percentage of the possible conformations of ether **4** allow for the [2+2] photoaddition to occur. In contrast, the preferred conformations for esters **29** and **32** tend to place the two double bonds further apart and at higher relative energy. Assuming that the relative ground state energies reflect the relative excited state energies, the lifetime of the excited state is probably too short for the esters to adopt conformations where the distance between the olefins is small enough to result in reaction. [2+2] Photoaddition was successful for ether **4** (see section 5 in this chapter for more details) while it failed for the two esters **29** and **32**.

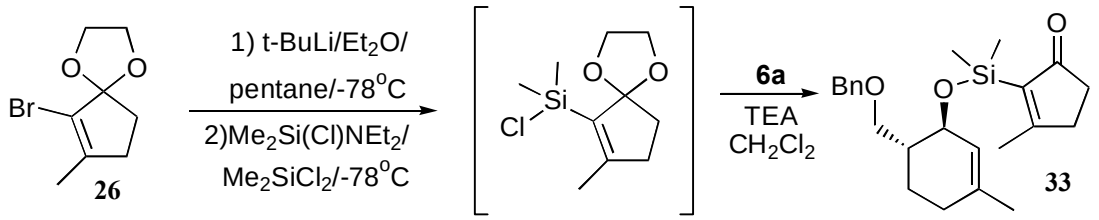
4. Silicon tether strategy

The third strategy pursued to tether the precursors for the intramolecular photoaddition scheme was to use a temporary silicon connection. This methodology has been employed successfully by Stork[99] and Crimmins.[100] The silicon atom adds the versatility of being able to be removed in an oxidative[101] or reductive[102] fashion, as required. The silicon-oxygen bond is longer than the carbon-oxygen bond adding more range of motion to the tether; this may help align the double bonds in the cyclization step. The major disadvantage to the silicon tether strategy is that the silicon-oxygen bond is

[99] Stork, G.; La Clair, J. *J. Am. Chem. Soc.* **1996**, *118*, 247.
[100] Crimmins, M. T.; Guise, L. E. *Tetrahedron Lett.* **1994**, *35*, 1657.
[101] Tamao, K.; Ishida, N.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2120.

often unstable to chromatography in silica gel, making it difficult to purify the intermediates. Two silicon-tethered substrates were envisioned: a two and a three-atom chain. The two-atom tether satisfies the "rule of five"[98] for the subsequent photoaddition reaction, but it requires the insertion of an additional carbon at C-2 (tricyclic-undecane numbering, see Figure 2.1) for the proper functionalization of "common intermediate **c** . The three-atom tether carries the necessary number of carbons for the thionocarbonate formation, but it requires the formation of a six-membered ring in the photochemical step.

For the two atom tether, vinyl bromide **26** was transmetallated with t-BuLi[85] (ether, pentane, -78° C) and then treated with $Me_2Si(NEt_2)Cl$[103,104] at -78° C. The crude reaction mixture was concentrated and the residue was treated with alcohol **6a** in the presence of triethylamine in methylene chloride at 0° C to give the desired product **33** in 13% yield.



Due to the low yield of this coupling and considering the additional steps required to introduce the carbon at C-2 to form the cyclic thionocarbonate, this system was abandoned in favor of pursuing the three-atom chain analog.

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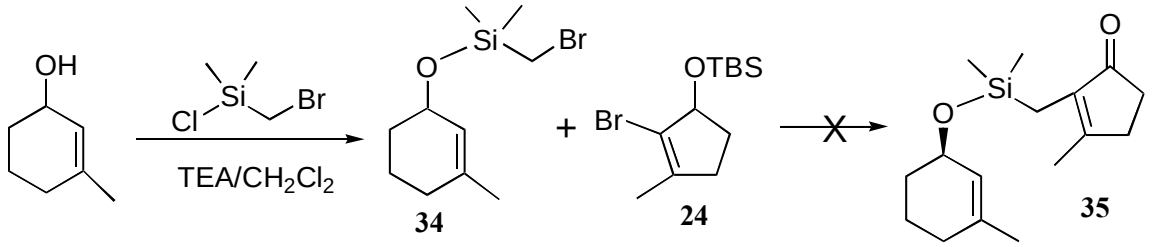
[102] (a) Stork, G.; Sofia, M. *J. Am. Chem. Soc.* **1986**, *108*, 6826; (b) Hale, M. R.; Hoveyda, A. H. *J. Org. Chem.* **1992**, *57*, 1643.
[103] Stork, G.; Keitz, P. F. *Tetrahedron Lett.* **1989**, *30*, 6981.



The bromide necessary to try the coupling for the three-atom chain compound was prepared from 3-methylcyclohexenone by reduction with $LiAlH_4$ (Et_2O, 0^o C, 30 min, 74 % yield), followed by treatment of the allylic alcohol with (bromomethyl)-chlorodimethylsilane[105] (triethylamine, CH_2Cl_2, 0^o C). Silylation gave the desired bromide **34** in 98 % yield. The higher-order vinylic-cuprate[106] of **24** was freshly prepared by addition of the alkyllithium derivative of **24**[85] to a solution containing 2-lithiothiophene and CuCN in THF at -78° C. The coupling with the six-membered ring halo-silicon intermediate **34** was performed by addition of the THF solution of the cuprate to **34** at -78° C; the reaction mixture was then allowed to warm to 0° C. The reaction was unsuccessful, giving none of the desired product. On a model system, the cuprate of geranyl bromide[107] could be coupled to **34** under the same conditions, which suggested that the difficulties observed for the desired coupling resided in the five-membered ring coupling-partner **24**. Further attempts to synthesize the silicon tether precursor were abandoned in favor of optimization of the Williamson ether synthesis, discussed earlier.

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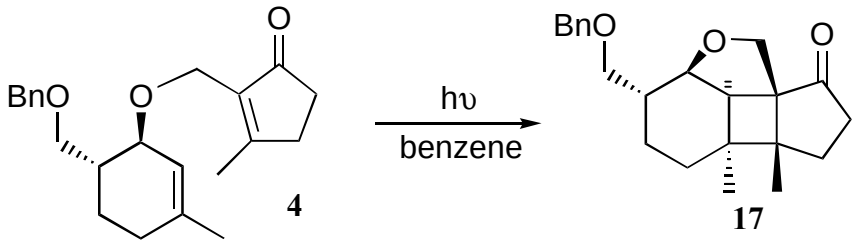
[104] Washburn, S. S.; W. R. Peterson, J. *J. Organomet. Chem.* **1970**, *21*, 59.
[105] Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500.
[106] Lipshutz, B. H.; Moretti, R.; Crow, R. *Org. Syn.* , *Coll vol VIII*, 33 (or Lipshutz, B. H.; Moretti, R.; Crow, R. *Org. Syn.* **1990**, *69*, 80).

5. Photoaddition

The product of the Williamson ether synthesis, compound **4**, was submitted to photoaddition conditions to promote [2+2] cyclization in order to produce the desired tricycle[5.4.0.0^{2,6}]undecane **17**.



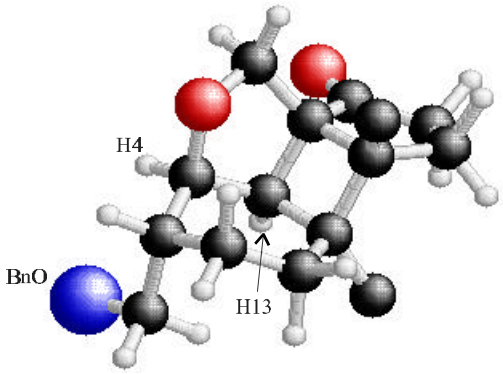
4 **17**

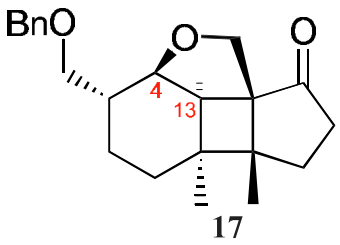
Irradiation of compound **4** was conducted using a medium pressure 450 W Hanovia UV lamp, at 8.75 mM concentration, in benzene. Other than [2+2] cyclization, enones can also undergo photoreduction, oxetane formation, Norrish type I cleavage and Norrish type II cleavage. The benzene[108] solvent probably acts as a filter, preventing the above side reactions (Norrish type I cleavage products were observed in other solvent systems such as cyclohexane). Three products were obtained, a [2+2] photoadduct, and two other products that could not be separated from each other by flash chromatography.

Only one isomer of the cyclized [2+2] photoadduct product was observed as evidenced by the presence of only two methyl singlets at δ 1.11 and 1.09 ppm in the ^{1}H NMR and the presence of 19 of 22 resolved peaks in the ^{13}C NMR. This isomer was

[107] Taylor, R. J. K. *Synthesis-Stuttgart* **1985**, *4*, 364.

tentatively assigned with the relative stereochemistry shown in compound **17** assuming that the stereochemistry of the ether would bias the face selectivity to cause the five-membered ring to approach the six-membered ring from the same side as the oxygen in the ether tether. This face selectivity should also be enforced by the presence of a bulky group (the benzyl ether) on the opposite side of the substrate. The assignment of compound **17** also presumes that most intramolecular photocycloadditions result in a *cis* ring fusion between five- and four-membered rings due to ring strain.[100] The assignment is supported by the measured ^{3}J between the protons at C-4 and C-13 of 6.0 Hz for the cyclized [2+2] photoadduct indicating a *cis* relationship between the two hydrogens.





17

Energy Minimization

This assignment was in agreement with the ^{3}J value (6.9 Hz) for compound **17** predicted by MM2 energy minimization.[109] The identity of compound **17** was later

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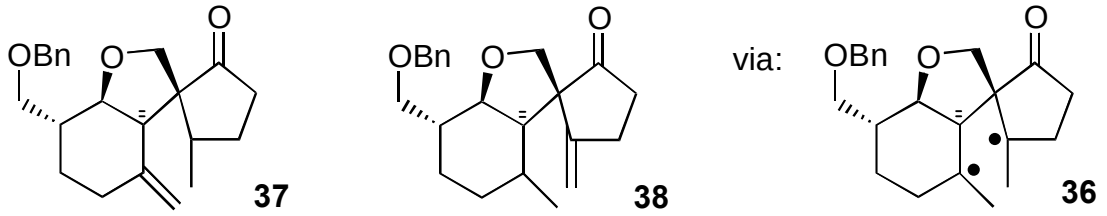
[108] UV absorption maximum at. 200 nm (ε 6300) and 255 nm (ε 200).

[109] Energy minimizations were performed using MacroModel version 4.5 developed by Prof. Clark Still at Columbia University. Conformational searches were conducted using the Monte Carlo simulation package and the MM2 minimization force field. Found 277 conformations within 50 Kcal/mol, mostly due to chain conformational changes. The lowest energy structure was used to evaluate the dihedral angle witch was 25.6 degrees.

confirmed by 1D-proton difference NOE experiments performed on products derived from this photoadduct, at subsequent steps in the synthesis. See chapter 3 for details.

The two other products, which were inseparable by flash chromatography, derived from disproportionation of the diradical intermediate **36** followed by 1,5 hydrogen shift.

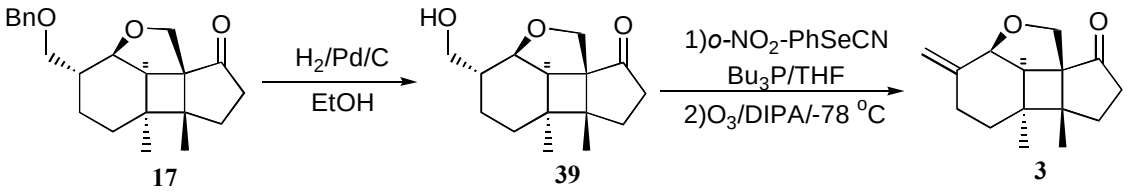


They were assigned as compounds **37** and **38**, which is supported in the ^{1}H NMR spectrum of the mixture of the two compounds (roughly 1:1), by a pair of doublets at δ 0.77 and 1.14 ppm (both J ~ 6.5 Hz), corresponding to the two methyl groups next to methine hydrogens. Additionally, four other peaks were observed at δ 4.64, 4.88, 5.22 and 5.28 ppm corresponding to the vinylic protons of the terminal olefins. Low-resolution GC-Ms traces indicated a mass of 340 for both compounds, as two separate peaks.

Product **17** was also photoreactive; therefore, the reaction could not be run to completion without degradation of the desired product. Best results were obtained when the reaction was run to 50 % conversion of the starting material, usually about 4 hours. After purification, the unreacted starting material could be resubmitted to the reaction conditions for further conversion. Product **17** was obtained in 78 % yield and the two byproducts together amounted to 9.5 % after three cycles of reaction.

- *Olefin formation*

Introduction of the double bond at C-5 could be accomplished by deprotection of the benzyl group followed by elimination of a water molecule. The double bond would be used later as a handle for the introduction of an epoxide as it is present in FS-2.



17 **39** **3**

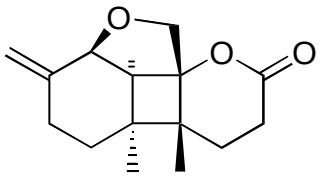
The benzyl-protecting group was removed by catalytic hydrogenation (H_2, Pd/ charcoal, in EtOH, at 40 psi) and alcohol **39** was obtained in 98% yield. The double bond formation could be accomplished by transforming the alcohol into the o-nitroselenide and inducing elimination upon oxidation, following Grieco's methodology.[110]

Grieco reported that substituents on the β and/or γ carbons of primary alkyl-phenyl-selenoxides result in low yields of terminal olefins. A solution for this problem was developed by Sharpless.[111] He verified that electron-withdrawing groups on the aromatic ring of alkyl-selenides enhance the rate of elimination of the respective selenoxides. Hence the use of an *o*-nitrophenyl substituent promotes the elimination of primary selenoxides yielding terminal olefins in high yield.

Alcohol **39** was first converted into a selenide using *o*-NO_2-phenyl selenium cyanide in the presence of tributyl phosphine in THF. The crude product was then

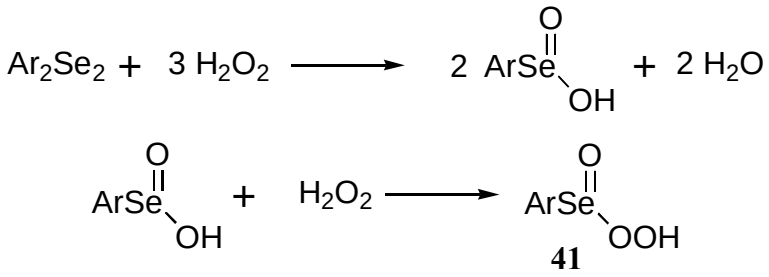
[110] Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.

oxidized to promote elimination giving the desired olefin **3**. The conventional method to carry out this oxidation involves the use of *m*-CPBA or H_2O_2.[112] However, these reagents were not compatible with the five-membered ring ketone present in the molecule. Attempted oxidation of the selenide using the literature conditions led to a mixture of the desired olefin **3** along with the Baeyer-Villiger product **40**.



40

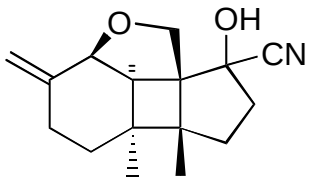
Other examples of Baeyer-Villiger reactions have been previously reported, along with epoxidation of olefins[113] under similar conditions. Both results were attributed to formation of benzeneperoxyseleninic acid **41** from organo selenides.[114]



[111] Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947.
[112] (a) Grieco, P. A.; Saki, Y.; Xler, D. *J. Am. Chem. Soc.* **1975**, *97*, 1597; (b) Grieco, P.; Noguez, J. A.; Masaki, Y. *Tetrahedron Lett.* **1975**, *48*, 4213.
[113] (a) Grieco, P. A.; Yokoyama, Y.; Gilman, S. *J. Chem. Soc. Chem. Comm.* **1977**, *23*, 870; (b) Grieco, P. A.; Yokoyama, Y.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1977**, *42*, 2034.
[114] McCullogh, J. *J. Am. Chem. Soc.* **1949**, *71*, 674.

The oxidation step could be effected by ozonolysis of the selenide intermediate thus preventing formation of the Baeyer-Villiger side product **40**.

Another byproduct that was observed during the course of optimizing this reaction was formation of cyanohydrin **42**.



42

This result also has precedent in the work of Grieco[115] in which he observed that, at room temperature in the presence of tributyl phosphine, aryl selenocyanates react rapidly with aldehydes to give cyano-selenides. When ketones were present in the media he observed rapid formation of cyanohydrins. Cyanohydrin formation could be reversed by treatment of the crude reaction mixture with base to regenerate the desired ketone **3**.

The best conditions found[116] to carry out this transformation were to first prepare the selenide with o-nitroselenyl cyanide in the presence of tri-n-butylphosphine with THF as the solvent. The THF was evaporated and the crude product was oxidized by ozonolysis in methylene chloride (-78^{o} C), in the presence of di-isopropylamine. This process provided the desired olefin **3** in 75 % yield for the two steps.

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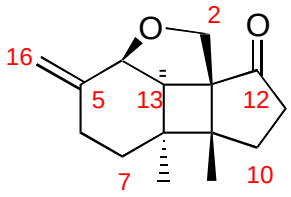
[115] Grieco, P. A.; Yokoyama, Y. *J. Am. Chem. Soc.* **1977**, *99*, 5210.
[116] Optimized by Nathan Yee in this laboratory.

The assignment of the structures for compounds **3**, **40** and **42** was based primarily on their ^{13}C NMR spectra and was supported by their ^{1}H NMR, infrared and mass spectra. These assignments relied heavily on the ^{13}C NMR spectra because their ^{1}H NMR spectra were very similar. Furthermore it was difficult to obtain a molecular ion for the cyanohydrin from the mass spectra (EI and CI), and the fragmentation pattern for the cyanohydrin was similar to that of the ketone. Analysis of the ^{13}C NMR showed that compound **42,** assigned as the cyanohydrin, had 16 peaks, no carbonyls, and showed a signal at δ 120.0 ppm in agreement with having a cyano group. The infrared bands seen at 2249 cm^{-1} and 3585 cm^{-1}, characteristic of cyanides and alcohols respectively, further confirmed the presence of the cyano and hydroxyl groups. Chemical evidence for the assignment of compound **42** was that this cyanohydrin could be converted to compound **3** by treatment with base (15 % aqueous NaOH). Compound **3** showed a characteristic carbonyl resonance in both the ^{13}C NMR (δ 217.6 ppm) and the infrared (1722 cm^{-1}) spectra. Evidence for lactone **40** comes primarily from an infrared band at 1745 cm^{-1} and is supported by the presence of a carbon resonance in the ^{13}C NMR at δ 171.5 ppm. The molecular ion M^{+} (248, EI) could be observed for this lactone, offering further support to the assigned structure.

- *Conclusion*



3

8,9–Dimethyl–5–methylidene-(1R*, 4R*, 8R*, 9S*, 13S*)–3-oxatetracyclo [6.4.1.$0^{1,9}$.$0^{4,13}$] tridecan-12-one (compound **3**) was synthesized. This compound fulfills the necessary requirements of the retrosynthetic-analysis for the synthesis of FS-2. It is a tricyclo [5.4.0.$0^{2,6}$] undecane carbon skeleton with two quaternary centers at C-8 and C-9, oxygen functionalization at C-2 and C-12 for introduction of the cyclic thionocarbonate and a handle for introduction of a double bond at C-5 to C-4.

Compound **3** was prepared in a convergent fashion, from a [2+2] intramolecular photo-addition reaction between a five-membered ring enone (compound **5**) and a six-membered ring olefin (compound **6a)**. The two precursors were tethered through an ether link *via* a Williamson ether synthesis using silver triflate to activate the electrophile. The *trans* stereochemistry of alcohol **6a** was used to control the relative stereochemistry of the four new stereocenters in the molecule, including the two adjacent quaternary centers.

After the photoaddition, the olefin functionality was unraveled by removal of the benzyl protecting group and elimination of a molecule of water following Grieco's methodology.

With compound **3** in hand, research was conducted on two fronts. The first was the preparation of model systems to test the scope of the radical fragmentation proposed

in the retrosynthetic plan. They will be discussed in chapter 3. The second was the further functionalization of the skeleton towards the synthesis of FS-2; this effort will be discussed in chapter 4.