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The synthesis of Fumonisin B1 analogs and silicon crosslinking agents

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The synthesis of Fumonisin B_1 analogs and silicon crosslinking agents

by

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Ames, Iowa

1992

DEDICATION

This dissertation is dedicated to my parents, John and Sharon Applegate. Throughout my life, their love, encouragement, and values have influenced me and made me the person I am today. Thank you, Mom and Dad.

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GENERAL INTRODUCTION

The synthesis of natural products and heterocyclic compounds has been and continues to be an important and active area of research in organic chemistry. This dissertation will examine strategies toward analogs of fumonisin B_1 and silicon heterocycles. Both the biological activity and unusual structure of fumonisin B_1 make it an interesting synthetic target. The use of silicon heterocycles as crosslinking agents in polymer chemistry make them challenging synthetic targets with industrial applications.

Explanation of Dissertation Format

This dissertation is divided into two papers with each paper preceded by an introduction. The two papers are intended to be separate, publishable articles. The first paper deals with the synthesis of fumonisin B_1 analogs. The second paper deals with the synthesis of nitrogen and oxygen silicon heterocycles. A general summary of both papers will follow the second paper.

PAPER I. THE SYNTHESIS OF FUMONISIN B_1 ANALOGS

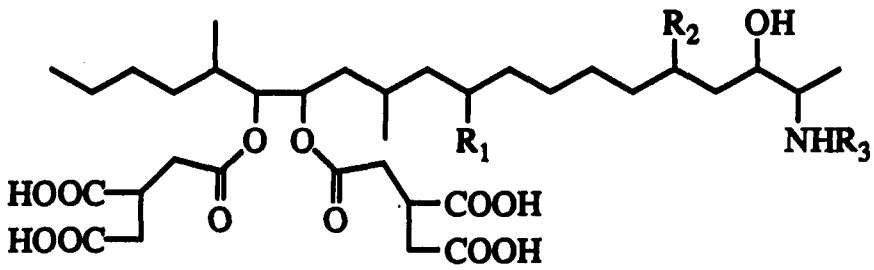
INTRODUCTION

The fungus *Fusarium moniliforme* Sheldon is one of the most important ear rot pathogens of corn. Dry, warm weather favors development of the disease. The infection occurs through injury of the kernels by insects, growth cracks, and weather. The infected kernels develop a white to pink color which become a powdery or cottony-pink mold as the disease progresses.[1] This mold can produce mycotoxins known as the fumonisins.

The toxicity of the mold was initially discovered when an isolate of *Fusarium moniliforme* from corn grown in Transkei, Africa was tested. This area of southern Africa has a high incidence of esophageal cancer in humans and the cause was unknown.[2] This isolate was found to be toxic to experimental animals and induced the neurotoxic disease leukoencephalomalacia in horses.[3] It was hepatocarcinogenic to rats[4] and mutagenic to *Salmonella* typhimurium.[5]

The carcinogenicity of the fungus accelerated the research on isolation of the toxins. The isolation and structural elucidation of the fumonisins, a family of related mycotoxins, was published in 1988.[6] Extraction of cultures of *Fusarium moniliforme* grown on sterilized corn with aqueous methanol yielded an active extract. Fractionation of the extract with macroreticular polystyrene resin (XAD-2), Sephadex LH-20, and reversed phase silica gel chromatography resulted in the isolation of a mixture of fumonisin B_1, B_2, A_1, and A_2. Recently, fumonisin B_3 was isolated.[7] Fumonisin B_1 is often abbreviated as FB_1.

Fumonisin



B_1 - $R_1 = OH, R_2 = OH, R_3 = H$

B_2 - $R_1 = H, R_2 = OH, R_3 = H$

A_1 - $R_1 = OH, R_2 = OH, R_3 = COCH_3$

A_2 - $R_1 = H, R_2 = OH, R_3 = COCH_3$

B_3 - $R_1 = OH, R_2 = H, R_3 = H$

Various spectroscopic methods such as liquid secondary ion mass spectrometry, carbon-13 NMR, proton NMR, two-dimension (2D) (^1H, ^1H) correlation spectroscopy, and electron impact mass spectroscopy were vital in elucidation of the structures.

As the scientific importance of fumonisins was realized, researchers began to develop experimental conditions for the optimal production of fumonisin in culture.[8] The study evaluated the effects of temperature and incubation on FB_1 production. The most effective growth culture is seven weeks at 25 °C. The FB_1 was also found to be heat stable. After boiling the culture for 30 minutes and oven-drying at 60 °C for 24 hours, there was no difference in the FB_1 concentration of

boiled and untreated culture materials. The boiled culture material also retained its cancer-promoting activity in rats. This data indicates that FB_1 is not destroyed by cooking and could enter the human food chain.

Scientists have developed improved methods for detecting fumonisins. Initially, high performance liquid chromatography (HPLC) analysis of its maleyl derivative (ultraviolet detection) and of its fluorescamine derivative (florescence detection) were used to detect FB_1.[9] Next, a quantitative and sensitive HPLC method for simultaneous determination of FB_1 and FB_2 in naturally contaminated corn and mixed feed was developed.[10] Derivatization of the primary amine moiety with o-phthalaldehyde yielded fluorescent products which were separated by reverse-phase isocratic chromatography using a methanol : phosphate buffer at an acidic pH to suppress ionization of the tricarballylic acid moieties. A more sensitive method for preparative scale isolation was published which allowed for separation of various fumonisin compounds using the mobile phase of chloroform : methanol : acetic acid (6:3:1).[11] Although these methods for laboratory use are reliable and successful, scientists began to develop more rapid and accurate tests which could be used to test for fumonisins.

The development of bioassays would be an easier method to use. The generation of antibodies which are reactive with Fumonisins B_1, B_2, and B_3 would be useful to monitor human and animal exposure in foods.[12] Fumonisin polyclonal antibodies were produced by using a conjugate of FB_1-CT (cholera toxin) as the immunogen. The sensitivity was sufficient to detect 0.5 to 1 ppm of fumonisin in corn or feed. This

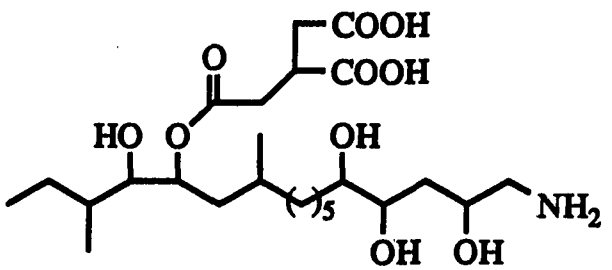
finding will allow use of the enzyme-linked immunosorbent assay (ELISA) for fumonisins in foods, feeds, and tissues. The examination of cultured mammalian cell lines indicated that this could be a useful method of bioassay.[13] The studies showed MDCK dog kidney epithelial cells are the preferred cell line for routine evaluation, and H4TG cell lines could be used although the culture growth was inconsistent. The MDCK cell line could detect 200 ng of fumosinin B_1 or B_2.

With the toxic effects of FB_1 known, a survey of fumonisin exposure of humans and animals was established. Forty toxic *Fusarium* isolates were tested for fumonisin production.[14] The fumonisin production was restricted to the species *F. moniliforme* (corn) and *F. proliferatum* (corn and sorghum). The contamination of commercial corn-based human foodstuffs was examined.[15] Cornmeal, corn grits, cornflakes, and miscellaneous products were examined from Canada, Egypt, Peru, South Africa and the United States. Cornmeal was positive for FB_1 in all five countries. Corn grits and cornflakes were examined only from South Africa and the United States, with positive results for corn grits and negative results for cornflakes. The most significant result was the high level of FB_1 in the United States foodstuffs relative to the other 5 countries (48.6% of samples had less than 500 ng/g and 51.4% had greater than 500 ng/g). These figures indicate humans are being exposed to fumonisins at a significant level.

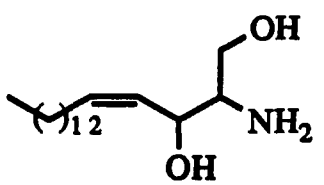
A safe level of consumption of contaminated grain was established for horses and swine. The minimum FB_1 feed levels were determined for inducement of leukoencephalomalacia (ELEM) and porcine

pulmonary endema (PPE).[16] Concentrations greater than 10 ppm in the feed induced ELEM and concentrations greater than 17 ppm in swine induced PPE.

Although new discoveries about fumonisins are being made, no one knows why fumonisins are carcinogenic. Fumonisins are structurally similar to the phytotoxin shown below produced by *Alternaria alternata*.[17]



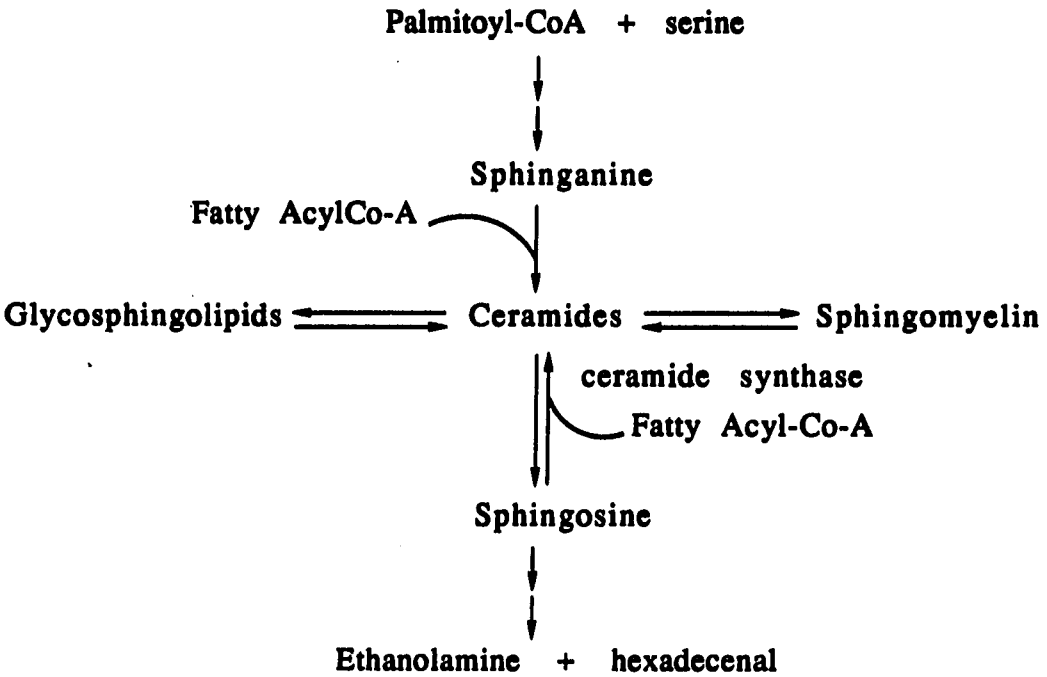
They are structurally similar to sphingosine.



Sphingosine

Fumonisins are considered tumor promoters because their culture material induces γ-glutamyl transaminase positive foci in rat liver which is a well established bioassay for tumor promoters.[18] Fumonisins are known inhibitors of sphingosine biosynthesis. Sphingosine is the chemical backbone of all sphingolipids, including sphingomyelin,

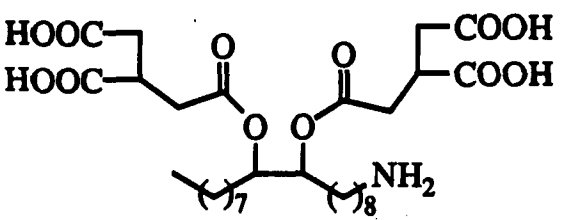
ceramides, and gangliosides. These lipids are involved in a number of cellular functions such as cell-cell communication, growth factor receptors, and transformation of cells. Interruption of sphingolipid biosynthesis could have adverse effects on an organism's health.



Fumonsins were found to alter the incorporation of radiolabelled serine into sphingosine. The site of action of the fumonisins appears to be ceramide synthase (sphingosine- and sphinganine-N-acyltransferase) in which fatty acyl-CoA combined with sphinganine or sphingosine to form dihydroceramide or ceramide. The interruption of sphingolipid biosynthesis may be responsible for the toxic effects of fumonisins. Sphingosine is a potent inhibitor of protein kinase C. It is known that tumor promoters stimulate protein kinase C; therefore, sphingosine may

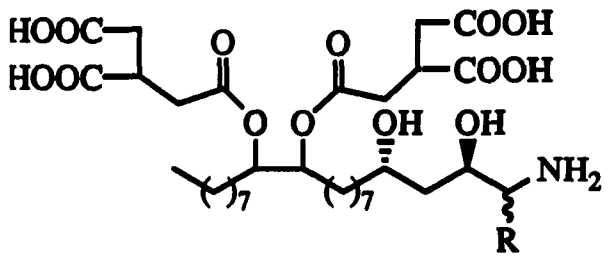
act as an antitumor agent. Since fumonisins inhibit biosynthesis of sphingosine, fumonisins may deregulate protein kinase C which then alters normal biochemical events. Another theory states that the tricarballylic acid sidechains of fumonisin may induce the toxicity. The sidechains may bind calcium and serve as a lipophilic calcium carrier. Calcium has been implicated in the mechanism of action of some tumor promoting agents.[19] Further examination of fumonisins is needed to determine the actual mode of activity.

From a chemical perspective, synthetic organic chemists can aid in this research by synthesizing analogs of fumonisin B_1. Those analogs of fumonisin which exhibit fumonisin activity will enable toxicologists to accurately study the effects of mycotoxins. Determination of the minimum structural requirements for activity may enable researchers to prepare inhibitors of fumonisins. Our strategy was to prepare analogs from commercially available reagents. Our first analog, I, had the tricarballylic acid moieties and the amine.



I

The second and third analogs II and III also included the 1,3-diol moiety.



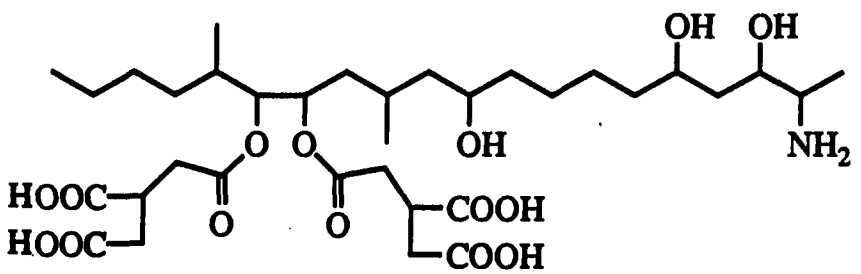
II, R = CH_3

III, R = H

Our strategy was based on the assumption that the alkyl groups on the backbone were not important for activity, but the tricarballylic acid moiety and the amine were significant. The first part of this dissertation will describe our synthetic strategy and the toxicological data of these analogs.

RESULTS AND DISCUSSION

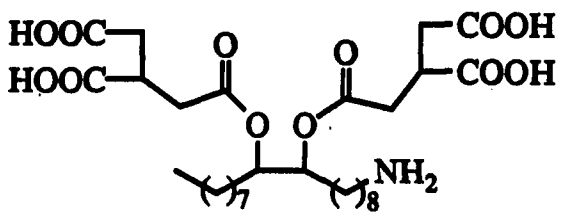
We have been pursuing a direct approach to analogs of fumonisin B_1. The absolute stereochemistry of the molecule is unknown, therefore, the synthesis of diastereomers is our goal. We felt that specific functionality was required for biological activity with the minimum being the tricarballylic side chains and the amine. The twenty carbon chain with methyl groups at C-5 and C-9 may not be that significant for biological activity. A commercially available amine with a long hydrocarbon chain was selected as the starting material. In relation to the tricarballylic side chain, no synthetic method of introduction of this subunit had been published. The synthetic goal was to introduce the tricarballylic acid functionality in a concise manner into an amine with a similiar number of carbons to the natural product, Fumonisin B_1.



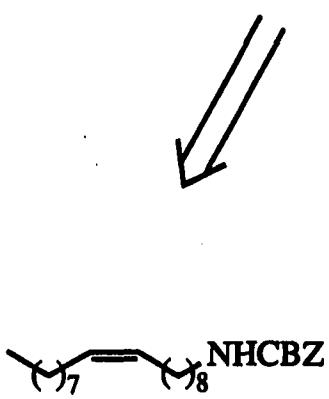
Fumonisin B_1

The first approach was to synthesize I from a compound with eighteen carbon backbone with a double bond at C-9 and C-10 and an

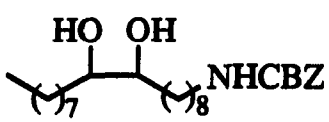
amine at C-1. Our strategy was to synthesize the compound from the protected amine with the synthesis proceeding through the olefin **1** or the diol **2**.



I



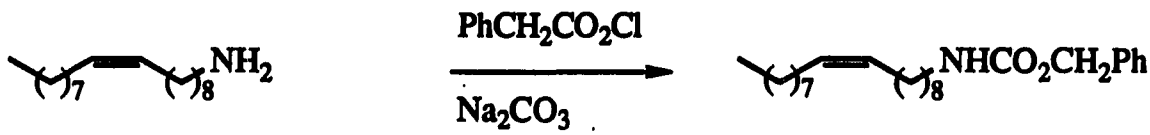
1



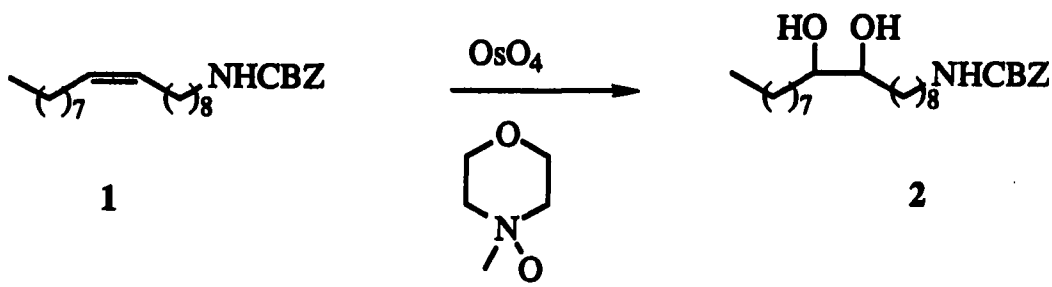
2

Our first approach began with commercially available oleylamine. Since the primary amine is a site of both nucleophilicity and a weakly acidic hydrogen, the amine was masked by acylation. The oleylamine was allowed to react with benzyl chloroformate and sodium carbonate[20] to yield the N-benzyloxycarbonyl oleylamine **1** in 75% yield.

Introduction of the diol with catalytic osmium tetroxide and N-methylmorpholine N-oxide (NMO)[21] gave **2** in a 40% yield.

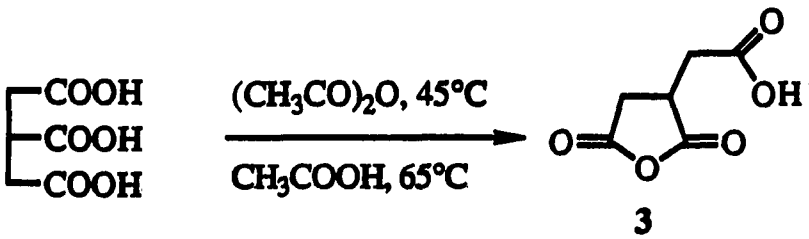


1



1 **2**

Two acylating reagents were prepared by the method of Whitesides.[22] The tricarballylic α,β-anhydride **3** was prepared by heating tricarballylic acid with acetic anhydride at 45 °C and glacial acetic acid at 65 °C to yield 75% of a white solid. The tricarballylic α,β-anhydride acid chloride **4** was formed in 40% yield by the reaction of **3** with excess thionyl chloride.



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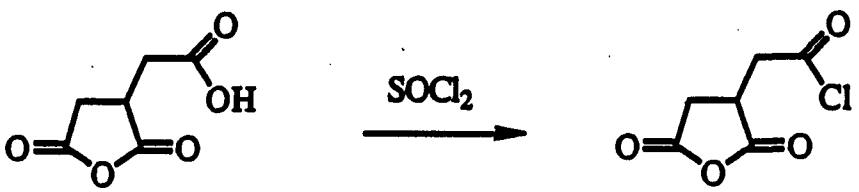
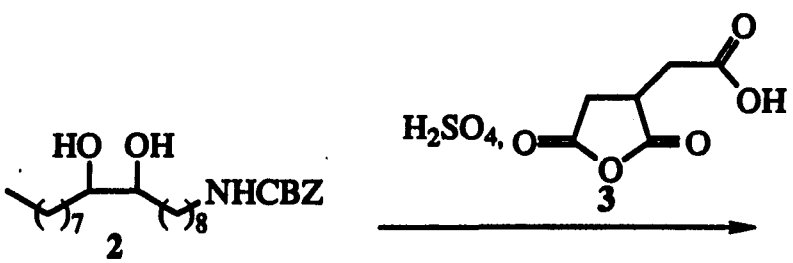
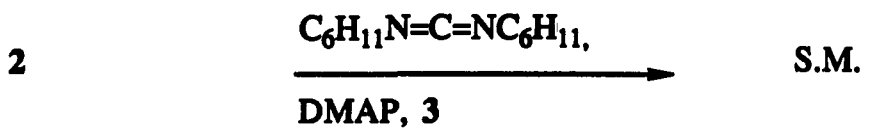
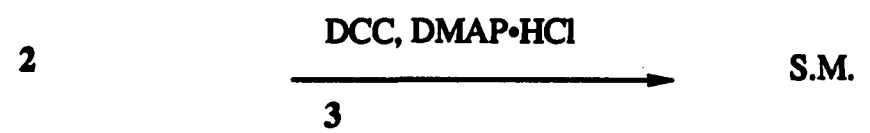


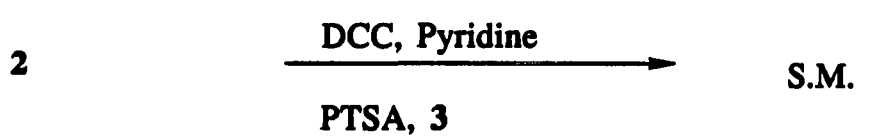
3 4

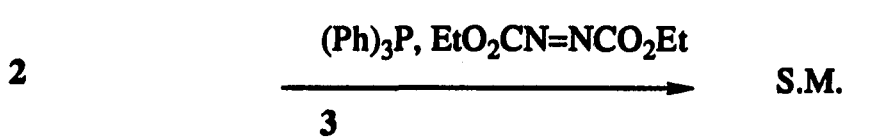
The first attempt involved Fischer esterification of compound 2 with 3 in the presence of sulfuric acid and was unsuccessful. Steglich esterification[23] which consisted of 1,3-dicyclohexylcarbodiimide (DCC), 4-dimethylaminopyridine (DMAP), diol 2 and anhydride 3 in methylene chloride at room temperature failed. The same conditions, but using p-toluenesulfonic acid (pTSA) or 4-dimethylaminopyridine hydrochloride (DMAP•HCl) as a catalyst in the reaction was ineffective.[24] Another well-known method of esterification, the Mitsunobu reaction,[25] involving triphenylphosphine, diethyl azodicarboxylate (DEAD), diol 2, and anhydride 3 was investigated with no success.





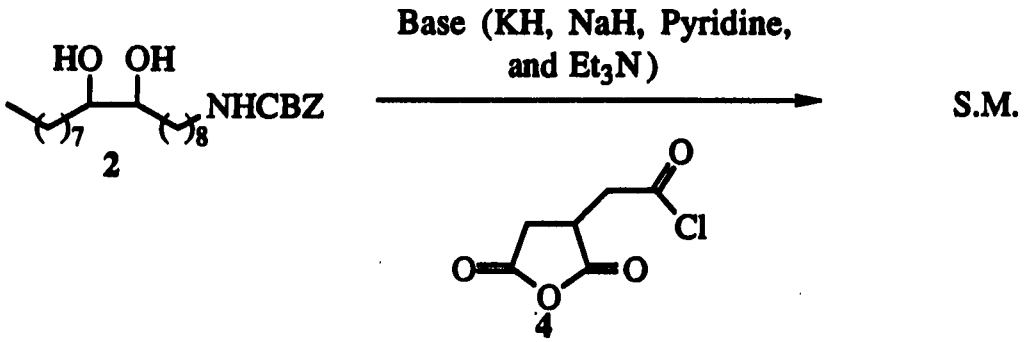




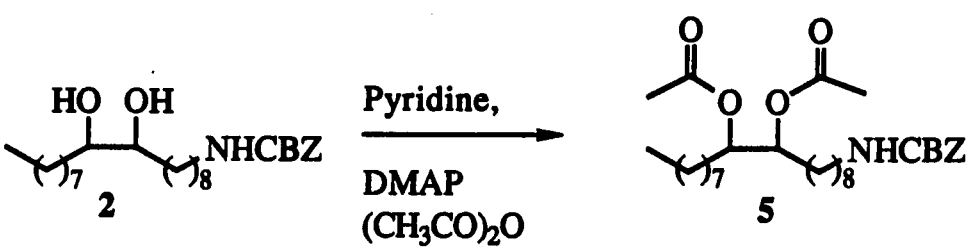


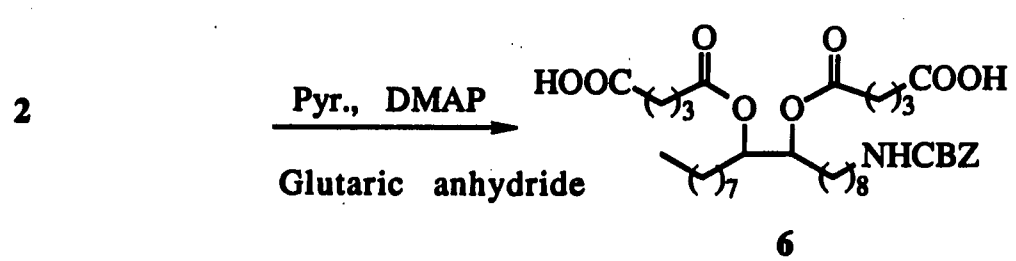
We next examined the use of tricarballylic α,β-anhydride acid chloride **4** as the acylating reagent. Examination of diol **2** with acid

chloride 4 in the presence of bases such as potassium hydride, sodium hydride, pyridine, and triethylamine showed no positive results.

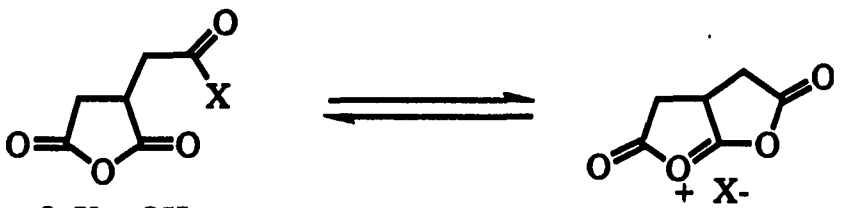


At this point in the research, we began to question if there was a potential problem with the acylating reagents 3 and 4 or the diol 2. The reaction of diol 2 with DMAP, pyridine and acetic anhydride afforded the bis-acetate 5 in a 60% yield. The reaction of 2 with glutaric anhydride yielded 60% of the diacid 6.





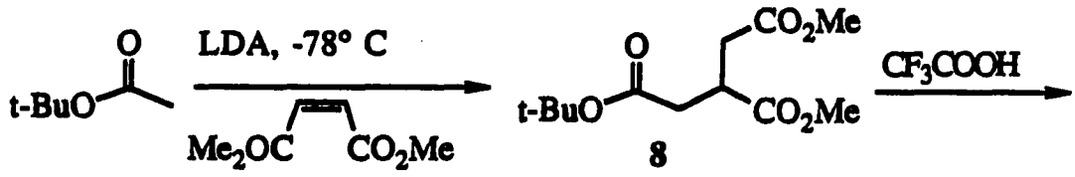
With the success of the esterification with acetic and glutaric anhydride, we felt that our original acylating reagents 3 and 4 could have been contributing to our problem. Bicyclic intermediate 7 may be responsible for our acylation problems.



3, X = OH
4, X = Cl

7

We began pursuing an acyclic acylation reagent to react with diol 2. Generation of the anion of *tert*-butyl acetate with lithium diisopropylamide (LDA) at -78 °C followed by Michael addition to dimethyl maleate yielded 80% of 1,2-dimethyl-3-*tert*-butylpropane-tricarboxylate 8. Hydrolysis of 8 in the presence of trifluoroacetic acid gave 1,2-dimethyl-1,2,3-propanetricarboxylic acid 9 in 78% yield. Reaction of diol 2, DCC, DMAP and 9 yielded 20% of tetramethyl ester derivative 10. Unfortunately, due to low yields and the failure to synthesize the dibenzyl ester of 1,2,3-propanetricarboxylic acid, we began to pursue a more efficient strategy.



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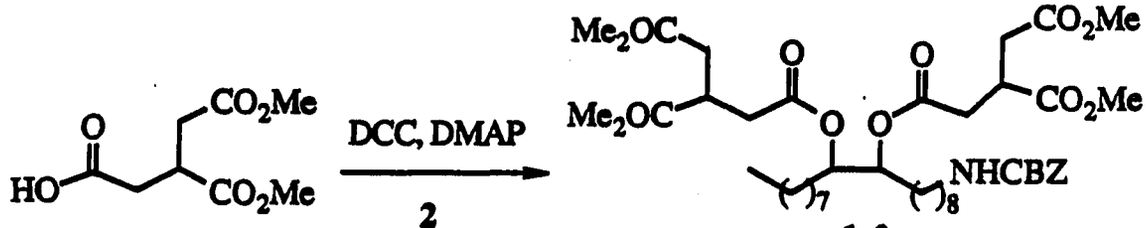
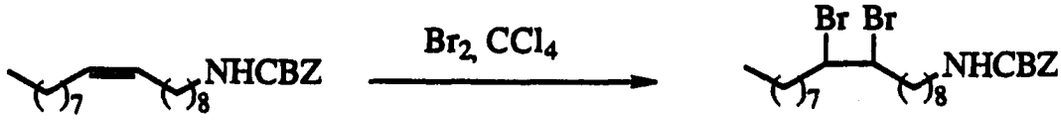


9 2 10

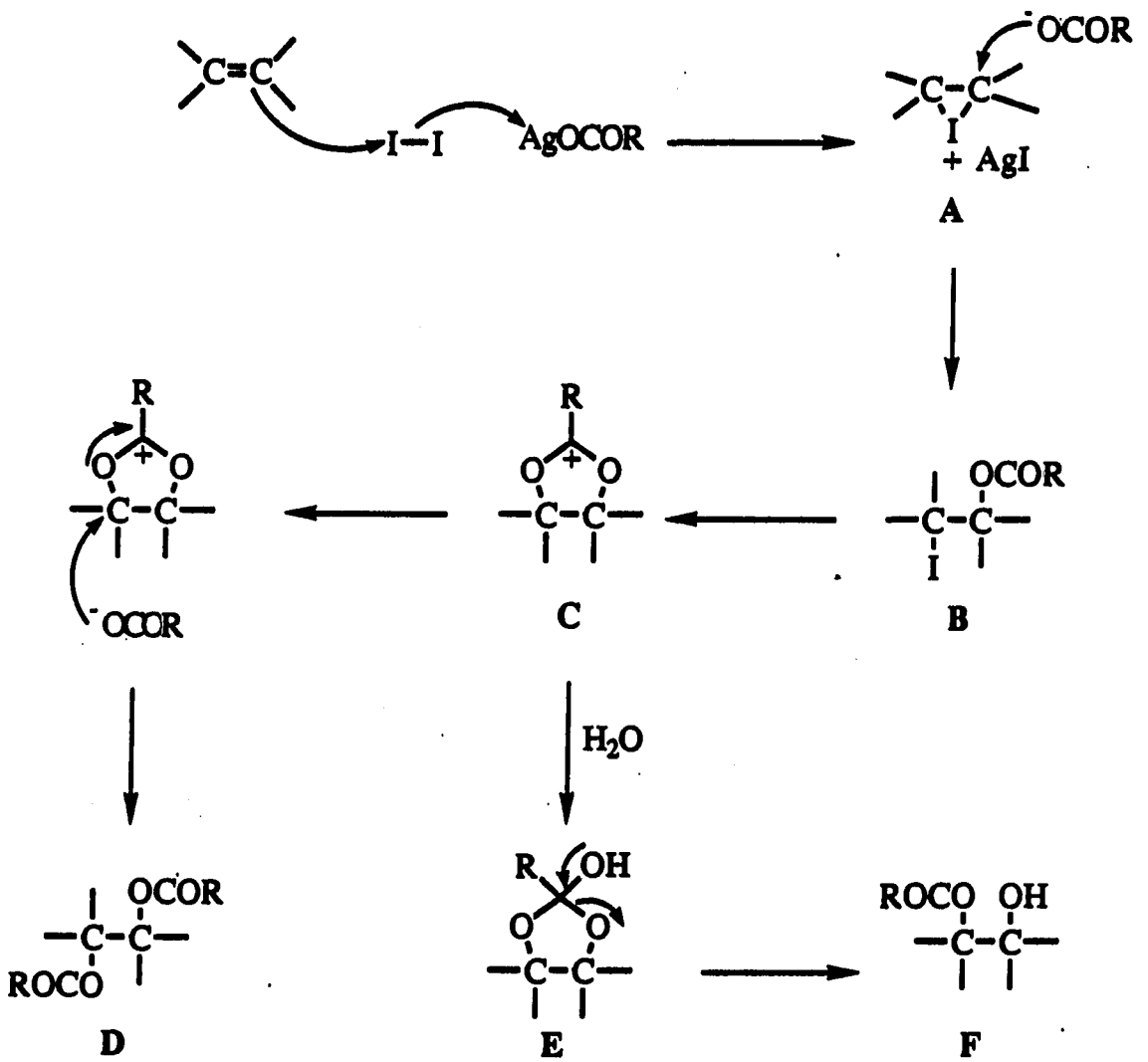
Our second strategy involved the use of N-benzyloxycarbonyl oleyl amine 1. Initially, formation of 54% of the dibromide[26] 11 by the reaction of 1 with bromine in carbon tetrachloride was pursued. Israel[27] reported reacting an α-bromo ketone with the monosodium salt of glutaric acid in good yields. The reaction of dibromide 11 with 2 equivalents of the monosodium salt of glutaric acid failed.



1 11

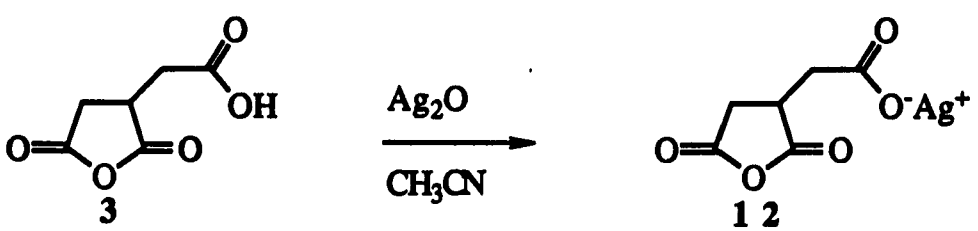
11 X

One method of esterification which had not been examined was the oxidation of alkenes with iodine and silver carboxylates. Under anhydrous Prevost conditions, this reaction directly yields the *trans*-diacyl derivative. In the presence of Woodward aqueous conditions, the monoester of the *cis*-glycol is obtained. The proposed mechanism[28] proceeds through the formation of an iodonium cation A which in the presence of silver carboxylate forms the *trans*-iodoacetate B.

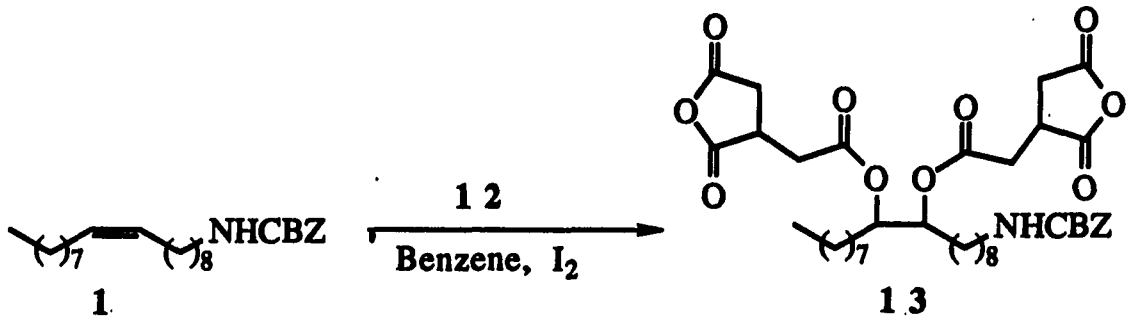


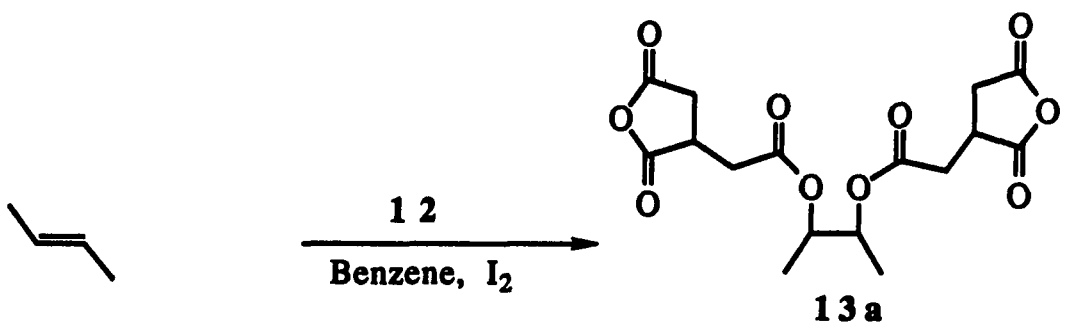
Through neighboring group participation, **B** forms a resonance stabilized cation **C** which undergoes attack by the carboxylate ion to form the *trans*-diacyl derivative **D** (Prevost conditions). In the presence of water, **C** forms the hydroxy acetal **E** which affords the *cis* hydroxy-acyl derivative **F**.

We quantitatively formed the silver salt[29] of tricarballylic α,β-anhydride **12** by reacting the tricarballylic α,β-anhydride **3** with silver(I) oxide in the dark until the black silver oxide had disappeared. This salt **12** was rigorously dried for 2 days in the presence of phosphorous pentoxide.

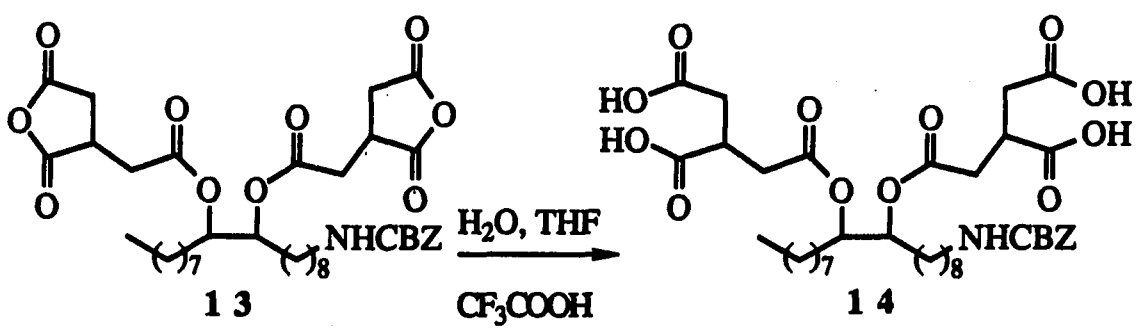


The N-benzyloxycarbonyl oleylamine **1** was reacted with two equivalents of **12** in the presence of one equivalent of iodine in boiling benzene for 2 days.[30] The Prevost conditions yielded the anhydride **13** in 90% yield. The ^1H NMR was reasonable, but the ^{13}C NMR was complex due to the large number of methylenes. The reaction of *trans*-2-butene and **12** under the Prevost conditions yielded 80% of the anyhdride **13a** which had a much simpler ^{13}C spectrum. Both of these compounds were characterized and the data supported the success of the Prevost reaction.

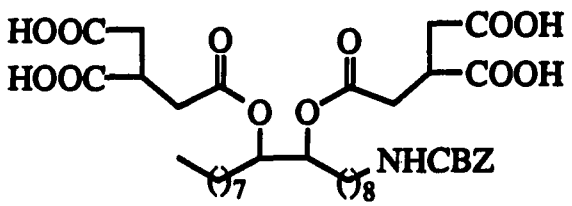




With the key carbon-oxygen bond formation finished, the last steps of the synthesis would seem to be trivial. Hydrolysis of anhydride **13** with a mixture of tetrahydrofuran, water, and trifluoroacetic acid (10:1:catalytic) at room temperature opened the anhydride to the tetraacid **14** in a quantitative yield.



The removal of the N-benzyloxycarbonyl protecting group was not as simple as originally expected. Examination of various hydrogenation conditions was conducted. Hydrogenation with palladium on carbon (Pd/C) in ethanol/water[31] failed. The use of a hydrogen transfer reagent such as cyclohexene[32] in the reaction failed.



14

$\xrightarrow[H_2O, EtOH]{H_2, Pd/C}$ S.M.

14

$\xrightarrow[Cyclohexene]{H_2, Pd/C}$ S.M.

The use of formic acid, methanol, and Pd/C[33] failed along with ammonium formate[34] and Pd/C. Attempts with trimethylsilyl iodide (TMSI)[35] and trifluoromethanesulfonic acid[36] failed.

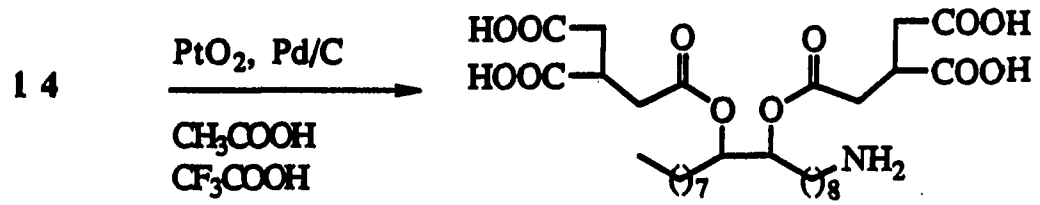
14 $\xrightarrow[MeOH,Pd/C]{4.4\% HCOOH}$ S.M.

14 $\xrightarrow[MeOH,Pd/C]{HCO_2NH_4,}$ S.M.

14 $\xrightarrow{TMSI, CH_2Cl_2}$ S.M.

14 $\xrightarrow[CH_2Cl_2]{CF_3SO_3H}$ S.M.

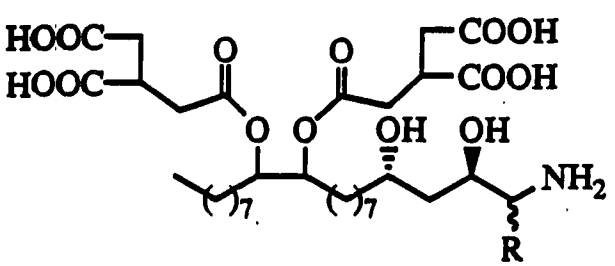
The reaction of 14 with hydrogen, platinum(IV) oxide, palladium on carbon, trifluoroacetic acid and acetic acid[37] afforded 90% of I.



I

Purification of I was effected by high performance liquid chromatography (HPLC) on a C-18 column.

The synthesis of I, achieved by the introduction of the tetraacid functionality in one step, paved the way for analogs II and III. The introduction of the 1,3-diol moiety will give insight into the relationship of functionality and toxicological activity.



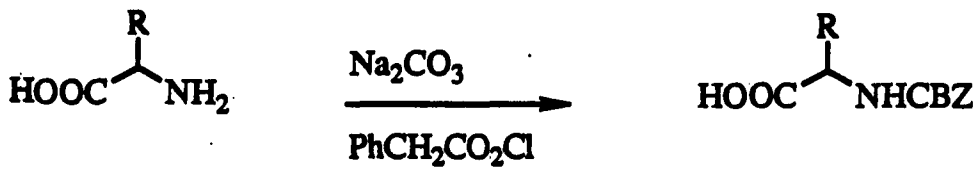
II, R = CH_3

III, R = H

The synthesis of II and III began with commercially available oleic acid. Addition of two equivalents of methyllithium[38] to oleic acid with an acidic workup provided a 98% yield of ketone 15.

15

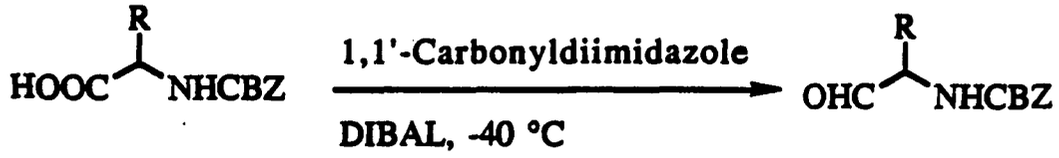
The key carbon-carbon bond forming step was an aldol condensation of **15** with an N-protected α-aminoaldehyde. The N-protected α-amino acids were prepared by reacting either dl-alanine or glycine with benzylchloroformate and sodium carbonate at room temperature to provide N-benzyloxycarbonyl alanine **16** and N-benzyloxycarbonyl glycine **17** in 87% and 89% yields, respectively.



R = CH_3 — **16**, R = CH_3

R = H — **17**, R = H

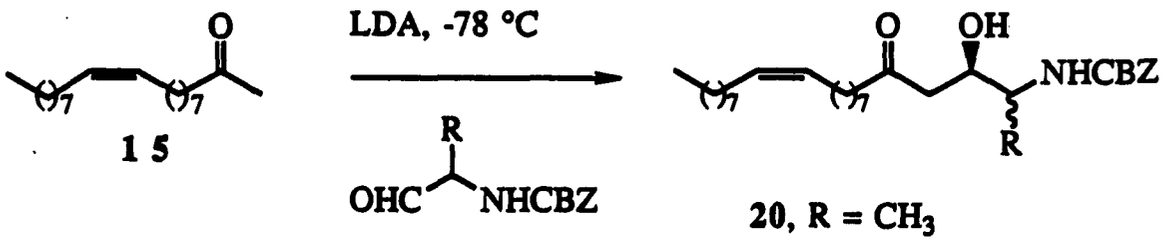
The carboxylic acids **16** and **17** were reduced at -40 °C in the presence of 1,1'-carbonyldiimidazole and diisobutylaluminum hydride (DIBAL)[39] to afford 55% of **18** and 65% of **19**. The aldehydes were used immediately since they decomposed within 24 hours. Since purification on a silica gel column only accelerated the decomposition, they were used without purification.



16, R = CH_3 **18**, R = CH_3

17, R = H **19**, R = H

The aldol condensation of ketone **15** with **18** and **19** was done at -78 °C to afford a 54% yield of β-hydroxy ketone **20** and a 45% yield of β-hydroxyketone **21**. Unfortunately, these aldol condensations have low diastereoselectivity.[40]



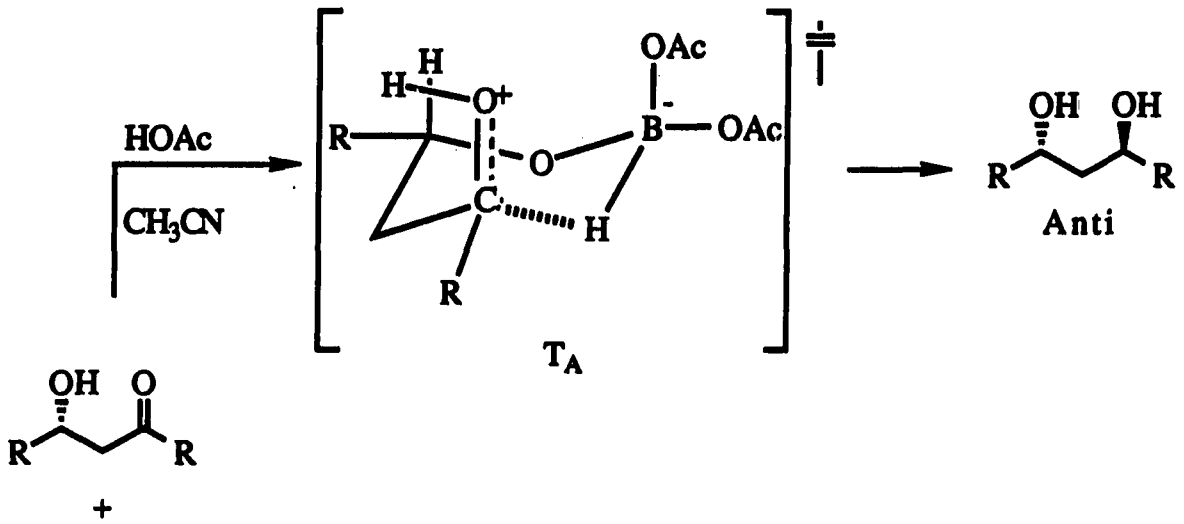
15 **20**, R = CH_3

18, R = CH_3 **21**, R = H

19, R = H

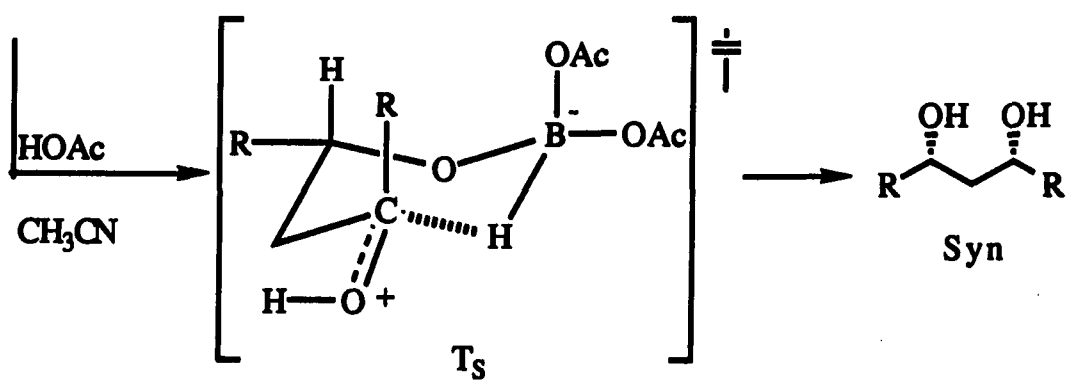
The directed reduction of the β-hydroxy ketones **20** and **21** was examined. The work of Evans[41] with tetramethylammonium trisacetoxyborohydride as the reducing agent was used due to the fact that these reductions exhibit both good levels of diastereoselection and generality. Both anti and syn aldol adducts give high levels of anti reduction products. The diasteroselectivity is rationalized via two chair-like transition states T_A and T_S. The T_S transition state has 1,3-

diaxial interactions which destabilize it compared to the nonbonding interactions in transition state T_A, favoring the anti product.



+

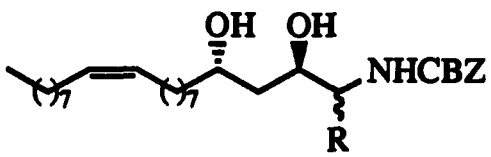
Me_4 $NBH(OAc)_3$



The reaction of **20** or **21** with tetramethylammonium trisacetoxy-borohydride in acetonitrile/acetic acid at 0 °C for two days produced diols **22** or **23** in 70% and 63% yields, respectively.

20, R = CH_3

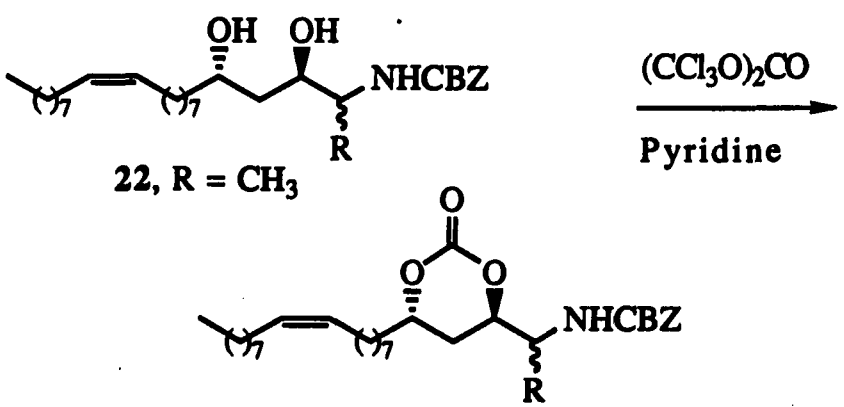
21, R = H



22, R = CH_3

23, R = H

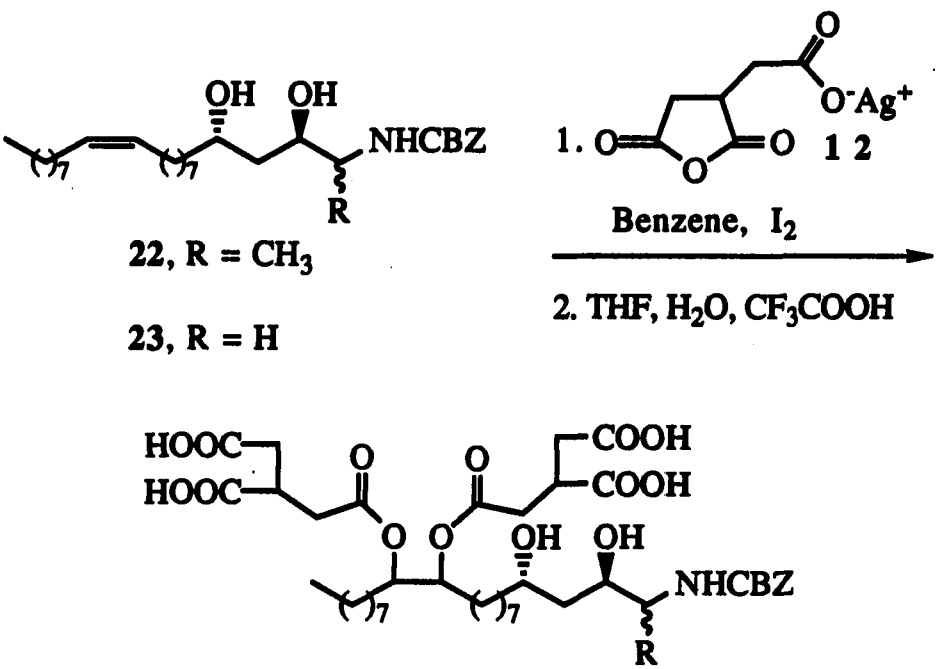
To confirm the stereochemistry of the reduction, the diol **22**, was treated with triphosgene and pyridine in CH_2Cl_2 to give a 20% yield of carbonate **24**.[42] The carbonate was used in a NOESY experiment to confirm the anti stereochemistry.



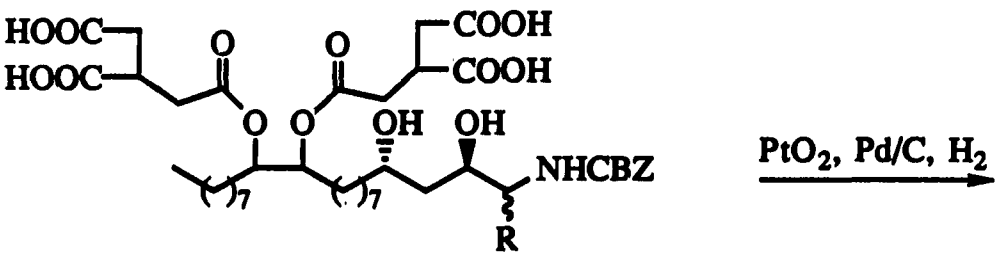
22, R = CH_3

24, R = CH_3

The final steps of the synthesis of analog II and analog III are the same as those for analog I. The diols **22** and **23** were heated with

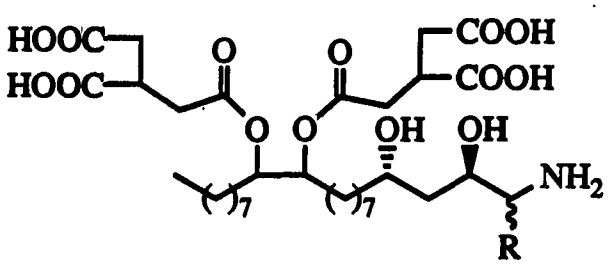


the silver salt of tricarballylic α,β-anhydride **12** in benzene providing 70% of **25** and 64% of **26**. Hydrolysis of **25** and **26** with tetrahydrofuran, water and catalytic trifluoroacetic acid gave **27** and **28** in quantitative yield. Hydrogenation of **27** and **28** with platinum oxide, palladium on carbon, trifluoroacetic acid and acetic acid in the presence of hydrogen yielded analog II and analog III. Purification of II and III was effected by HPLC.



27, R = CH_3

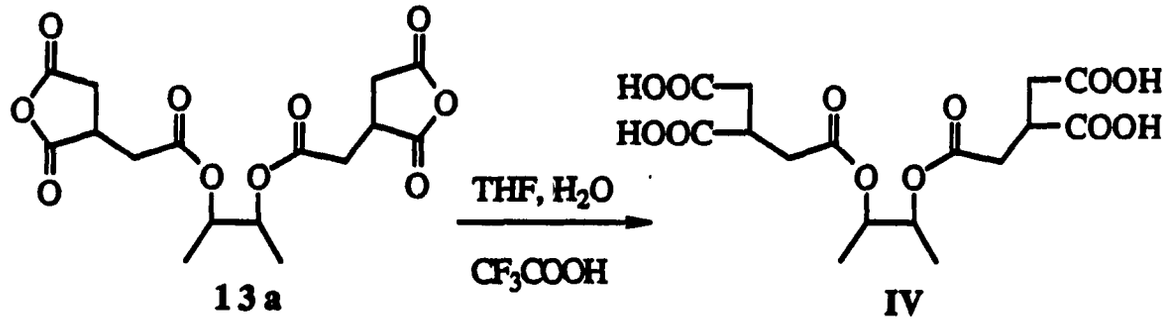
28, R = H



II, R = CH_3

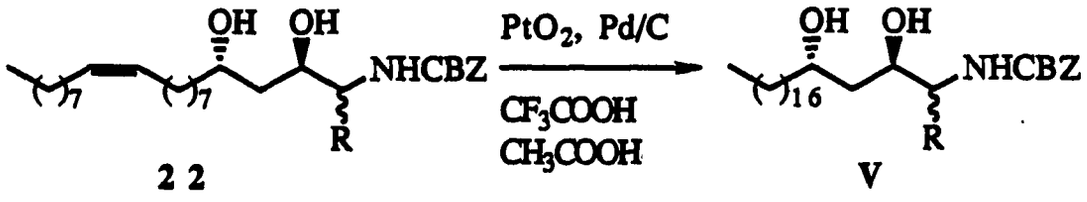
III, R = H

To determine a little more about the required structural features of fumonisin for toxicological activity, simple analogs were prepared with specific functionality. The hydrolysis of **13a** with the standard conditions gave the analog **IV** which has only the tetraacid moiety.



13a IV

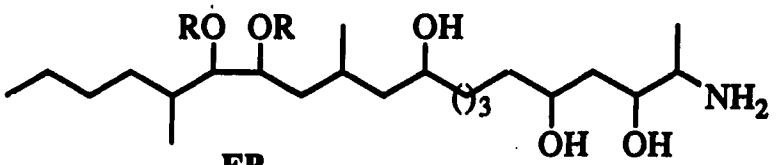
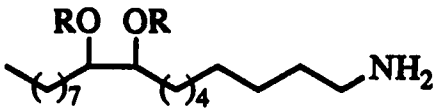
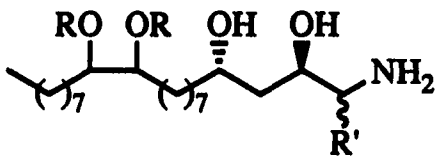
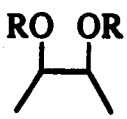
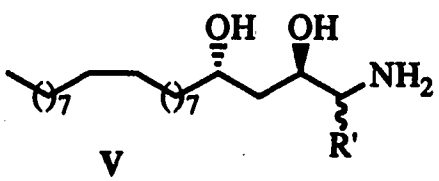
Hydrogenation of the diol 22 under the platinum oxide and palladium on carbon conditions yielded 60% of analog V which had only the 1,3-diol and the amine.



22 V

Toxicological testing of the analogs of Fumonisin B_1 was done by Dr. Don Reynolds of Veterinary Medicine at Iowa State University. Some of our analogs have shown similar toxicity to FB_1 (Table 1). The initial results of testing show that analog I and analog III have similar toxicity to FB_1. Analog II has greater toxicity by approximately 35 ppm. Analog IV was non-toxic and analog V has greater toxicity by approximately 20 ppm.

Table 1. Toxicity Studies

Compound	LCD_{50} (ppm)
 **FB_1**	50 - 100
 **I**	50 - 100
 **II** R' = CH_3	10 -15
III R' = H	50 - 100
 **IV**	500 - 1000
 **V**	25 - 30

R = -$COCH_2CH(CO_2H)CH_2CO_2H$

CONCLUSION

The synthesis of the fumonisin B_1 analogs was done in a concise manner. These analogs have been tested for their toxicity with fumonisin B_1 as a standard. As organic chemists, we can further contribute to this research by synthesizing an analog similar to hydrolyzed fumonisin B_1. A serine analog would be interesting due to the structural similarity to sphingosine. The testing of these analogs would allow us to know even more about the structural relationship and toxicity.

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Benzene was distilled from lithium aluminum hydride. Dichloromethane and acetonitrile were distilled from calcium hydride. All reactions were conducted under nitrogen atmosphere and all extracts were dried over anhydrous sodium sulfate. Apparatus for experiments requiring anhydrous conditions was flame-dried under a stream of nitrogen or dried in a 150 °C oven for 12 h and cooled under a stream of nitrogen. Flash chromatography was performed on EM Science Kieselgel 60 (mesh 230-400). Thin layer chromatography was performed using EM Science Kieselgel F_{254} prepared plates with a thickness of 0.25 mm. The solvent systems were suitable mixtures of hexanes (H) and ethyl acetate (EA) unless otherwise noted. The abbreviation sg represents silica gel. Infrared spectra were obtained on a Perkin-Elmer 1320 spectrophotometer and are reported in cm^{-1}. Proton nuclear magnetic resonance spectra (300 MHz) were obtained using a Nicolet Magnetics Corporation NMC-1280 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), ABq (AB quartet), and m (multiplet); a br suffix indicates a broadened pattern. Carbon-13 NMR spectra (75.46 MHz) were obtained on a Nicolet NMC-

spectrometer and are reported in δ relative to $CDCl_3$ (77.00 ppm). High resolution mass spectra were obtained on a Kratos model MS-50 spectrometer. Low resolution mass spectra were obtained on a Finnegan 4023 mass spectrometer. Elemental analyses were performed by Galbraith Laboratories. The purity of all title compounds was judged to be ≥ 95% by ^1H NMR spectral determination.

N-benzyloxycarbonyl oleylamine (1). To a solution of oleylamine (2.0 g, 7.47 mmol) in 29.9 mL of Et_2O and 37 mL of H_2O was added Na_2CO_3 (1.03 g, 9.71 mmol). After stirring for 30 minutes, benzylchloroformate (1.33 g, 7.47 mmol) was added and the reaction was stirred for 12 hours. The ether layer was separated from the aqueous layer, washed with saturated NaCl, dried with Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography on sg (3:1 H:EA) to provide 1 (2.26 g, 5.62 mmol) in 75% yield: R_F = .46 (3:1 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ .87 (t, J = 6 Hz, 3H), 1.27-1.25 (br, 24H), 2.00 (q, J = 6.0 Hz, 4H), 3.17 (q, J = 6.6 Hz, 2H), 5.08 (s, 2H), 5.34 (dt, J = 5.4 Hz, 2H), 7.30-7.39 (m, 5H); IR (CH_2Cl_2) 3440 2920, 2820, 1780, 1510, 1450, 1220 cm^{-1}.

N-benzyloxycarbonyl-9,10-dihydroxyoctadecylamine (2). To a solution of OsO_4 (0.11 g, .43 mmol) and NMO (2.61 g, 26 mmol) in 111.5 mL of acetone and 27.8 mL of H_2O was added carbamate 1 (9.0 g, 22.3 mmol) in 39.2 mL of acetone. The reaction was followed until TLC analysis indicated no carbamate 1 remained. Florosil (16.7 g) and sodium dithionite (4.54 g, .026 mmol) were added with stirring for 60 minutes. Reaction was filtered, precipitate was washed with acetone,

and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography on sg (2:1 H:EA) to yield 40% of 2 (3.88 g, 8.9 mmol): R_F = .20 (2:1 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ .88 (t, J = 6.6 Hz, 3H), 1.27 (br, 24H), 1.43-1.51 (m, 4H), 3.18 (q, J = 6.6 Hz, 2H), 3.43-3.37 (m, 1H), 3.63-3.55(m, 1H), 5.09 (s, 2H) 7.34-7.37 (m, 5H); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 22.63, 25.94, 26.60, 29.52, 31.21, 31.82, 33.63, 41.06, 66.57, 74.47, 74.66, 128.03, 128.45, 136.56, 170.8.

General Procedure for Esterification of Diol 2. To a solution of diol 2 (1 equiv) in dry CH_2Cl_2 (0.1M) at 0 °C was added pyridine (2.2 equiv) and DMAP (0.5 equiv). The reaction was warmed to room temperature and anhydride (2.2 equiv) in dry THF (2.5 M) was added to the solution. The reaction was monitored until TLC analysis indicated no diol 2 remained. The reaction was poured into water, the aqueous layer was washed with CH_2Cl_2, dried, and concentrated in vacuo. The residue was purified by sg chromatography.

1,1'[1-(N-benzyloxycarbonyl-8-aminooctyl)-2-(octyl)-1,2-ethanediyl]ester Acetic acid (5): R_F = .32 (7:1 H:EA); (300 MHz, $CDCl_3$) δ .87 (t, J = 6.1 Hz, 3H), 1.25 (br, 24H), 1.42-1.51 (m, 4H), 2.04 (s, 3H), 2.07 (s, 3H), 3.17 (q, J = 6.6 Hz, 2H), 4.93-5.11 (m, 2H), 5.09 (s, 2H), 7.32-7.34 (m, 5H); IR ($CDCl_3$) 3470, 2940, 2880, 1750, 1720, 1530, 1460 cm^{-1}.

1,1'[1-(N-benzyloxycarbonyl-8-aminooctyl)-2-(octyl)-1,2-ethanediyl]ester Glutaric acid (6): R_F = .20 (10% MeOH); ^1H NMR (300 MHz, $CDCl_3$), δ .80 (t, J = 5.6 Hz, 3H), 1.18 (br, 24H), 1.36-1.44 (m, 4H), 1.79-1.98 (m, 4H), 2.24-2.41 (m, 8H), 3.05-3.15 (m, 2H), 4.87-

4.97 (m, 2H), 5.02 (s, 2H), 7.25-7.30 (m, 5H); ^{13}C NMR (75.46 MHz, $CDCl_3$), δ 13.91, 19.91, 22.51, 25.41, 26.51, 26.58, 29.26, 33.23, 40.97, 66.45, 74.11, 127.92, 128.15, 128.34 128.76, 136.51, 156.46, 172.49, 177.76; IR (CH_2Cl_2) 3450, 2920, 2860, 1750, 1710, 1510, 1450 cm^{-1}.

3-*tert*-Butyl-1,2-dimethyl ester 1,2,3-propane-tricarboxylic acid (8): To a solution of LDA (2.75 mmol, prepared from *n*-BuLi (2.75 mmol) and diisopropylamine (3.25 mmol) in 8 mL of THF at -78 °C) was added a solution of t-butyl acetate (0.29 g, 2.5 mmol) in 2 mL of dry THF. The solution was stirred at -78 °C for 30 minutes. Dimethyl maleate (0.39 g, 2.75 mmol) in 1.37 mL of THF was added quickly and the reaction was stirred at -78 °C for 30 minutes. Acetic acid/CH_2Cl_2 (10%) was added to the -78 °C solution to quench the reaction. The reaction was warmed to room temperature, diluted with water, extracted with CH_2Cl_2, dried and concentrated in vacuo to afford 80% of **8** (0.48 g, 1.84 mmol) after sg chromatography (3:1 H:EA): R_F = .10 (4:1 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H), 2.37-2.81 (m, 4H) 3.17-3.27 (m, 1H), 3.68 (s, 3H), 3.70 (s, 3H).

2,3-Dimethylester 1,2,3-propanetricarboxylic acid (9). To a solution of triester **8** (0.276 g, .82 mmol) in 1.0 mL of CH_2Cl_2 was added trifluoroacetic acid (0.473 g, 4.1 mmol). After TLC analysis indicated no triester **8** remained, the reaction was concentrated. The residue was dissolved in Et_2O, the ether layer was extracted with cold $NaHCO_3$, the aqueous layer was acidified with 1N HCl, and the aqueous layer was extracted with CH_2Cl_2. The CH_2Cl_2 layer was concentrated to yield 78% of **9** (0.130 g, .63 mmol): ^1H NMR (300 MHz, $CDCl_3$) δ 2.68 (dd,

J = 12.0, 6.3 Hz, 2H), 2.77 (dd, J = 12.0, 6.6 Hz, 2H), 3.21-3.29 (m, 1H), 3.69 (s, 3H), 3.72 (s, 3H).

1,1'[1-(N-benzyloxycarbonyl-8-aminooctyl)-2-(octyl)-1,2-ethanediyl]ester-2,2',3,3' tetramethylester 1,2,3-propanetricarboxylic acid (10). To a solution of diol **2** (0.105 g, .24 mmol), acid **9** (0.090 g, 0.44 mmol), and DMAP (0.004 g, 0.038 mmol) in 1.1 mL of CH_2Cl_2 at 0 °C was added DCC (0.099 g, 0.48 mmol). The reaction was warmed to room temperature. After TLC analysis indicated no diol **2** remained, the reaction was filtered through Celite. The filtrate was washed with 0.5 N HCl, washed with $NaHCO_3$, dried, and concentrated in vacuo. The crude product was purified by sg chromatography to yield 20% of **10** (0.038 g, 0.04 mmol): ^1H NMR (300 MHz, $CDCl_3$) δ .87 (t, J = 6.1 Hz, 3H), 1.25 (br, 24H), 1.41-1.54 (m, 4H) 2.55-2.68 (m, 4H), 2.73-2.84 (m, 4H), 3.13-3.31 (m, 4H), 3.68 (s, 6H), 3.69 (s, 6H), 4.92-5.03 (m, 2H), 5.09 (s, 2H), 7.31-7.37 (m, 5H); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 173.34, 171.64, 170.97, 170.87, 170.73, 170.50, 156.25, 136.55, 128.72, 128.34, 127.92, 74.52, 74.49, 66.40, 52.59, 52.30; IR ($CDCl_3$) 3440, 3050, 2920, 1740 (broad), 1510, 1440, 1260, 1160 cm^{-1}.

N-benzyloxycarbonyl-9,10-dibromooctadecyl-amine (11). To a solution of carbamate **1** (1.0 g, 2.48 mmol) in 12.7 mL of CCl_4 at 10 °C was added dropwise a solution of bromine (0.376 g, 2.35 mmol) in 5 mL of CCl_4. After TLC analysis indicated no carbamate **1** remained, the reaction was concentrated in vacuo. The residue was dissolved in hexane, washed with $NaHCO_3$, washed with H_2O, and washed with

sodium thiosulfate. The organic layer was dried, concentrated in vacuo and purified by sg chromatography (10:1 H:EA) to yield 54% of **11** (0.76 g, 1.35 mol): RF = 0.29 (10:1 H:EA); ^{1}H NMR (300 MHz, $CDCl_3$) δ .88 (t, J = 6.3 Hz, 3H), 1.25 (br, 24H) 1.78-1.94 (m, 2H), 1.94-2.10 (m, 2H), 3.12-3.23 (m, 2H), 4.16-4.24 (m, 2H), 5.09 (s, 2H), 7.33-7.36 (m, 5H).

Silver salt of tricarballylic α,β-anhydride (12). To a solution of acid **3** (1.0 g, 6.36 mmol) in 15.1 mL of dry MeCN was added Ag_2O (0.737 g, 3.18 mmol). The reaction was stirred in the dark for 2 days until all the Ag_2O disappeared. The reaction was filtered, the beige solid was washed with MeCN, and dried in the presence of phosphorous pentoxide.

General Procedure for the Prevost Reaction: To a solution of olefin (1 equiv) in dry benzene (0.33 M) was added iodine (1 equiv) and silver salt **12** (2 equiv). The reaction was heated in boiling benzene for 2-3 days. The reaction was filtered, the silver salt precipitate was washed with benzene and concentrated.

1,1'[1-(N-benzyloxycarbonyl-8-aminooctyl)-2-(octyl)-1,2-ethanediyl]ester 2,3-tricarballylic anhydride (13): ^{1}H NMR (300 MHz, $CDCl_3$) δ .87 (t, J = 6.3 Hz, 3H), 1.24 (br, 24H), 1.43-1.51 (m, 4H), 2.76-3.22 (m, 10H), 3.24-3.39 (m, 2H), 4.97-5.05 (m, 2H), 5.08 (s, 2H), 7.32-7.36 (m, 5H); IR ($CHCl_3$) 3450, 2910, 1860, 1760, 1710, 1510 cm^{-1}.

1,1'[1-(methyl)-2-(methyl)-1,2-ethanediyl]ester 2,3-tricarballylic anhydride (13a): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (d, J = 1.8 Hz, 3H), 1.21 (d, J = 1.8 Hz, 3H), 2.76-3.20 (m, 8H), 3.24-3.37 (m,

2H), 4.83-4.89 (m, 2H); ^{13}C NMR (75.46 Hz, $CDCl_3$), δ 165.97, 165.41, 163.51, 69.34, 36.65, 33.65, 31.05, 19.03; IR (Neat) 2980, 1850, 1780, 1730 cm^{-1}; MS (CI-NH_3) *m/e* 176, 194, 248, 290, 388 (M+ NH_4).

1,1][1-(N-benzyloxycarbonyl-11-amino-8,10-dihydroxydodecyl)-2-(octyl)-1,2-ethanediyl]ester 2,3-tricarballylic anhydride (25): ^1H NMR (300 MHz, $CDCl_3$) δ .87 (t, J = 6.2 Hz, 3H), 1.23 (br, 33H), 2.61-2.91 (m, 8H), 3.22-3.40 (m, 3H), 3.72-3.91 (m, 2H), 4.80-5.08 (m, 2H), 5.11 (s, 2H), 7.32-7.35 (m, 5H); IR (Neat) 3355, 2926, 2854, 1852, 1783, 1724, 1525, 1411 cm^{-1}.

1,1'[1-(N-benzyloxycarbonyl-11-amino-8,10-dihydroxyundecyl)-2-(octyl)-1,2-ethanediyl]ester 2,3-tricarballylic anhydride (26): ^1H NMR (300 MHz, $CDCl_3$) δ .87 (t, J = 5.2 Hz, 3H), 1.25 (br, 26H), 1.49-1.54 (m, 4H), 2.61-2.84 (m, 8H), 2.91-3.30 (m, 6H), 5.02-5.16 (m, 4H), 7.31-7.35 (m, 5H); IR (neat) 3363, 2926, 2854, 1852, 1781, 1716, 1259, 1190 cm^{-1}; MS (CI-NH_3) *m/e* 193, 284, 649, 807 (M+NH_4).

General Procedure for the Hydrolysis of the dianhydride. To a solution of anhydride (1 equiv) in THF (0.5 M) and water (5 M) was added 1 drop of trifluoroacetic acid. After stirring at room temperature for 48 hours, the reaction was quenched with trifluoroacetic anhydride to remove the excess water. The reaction was concentrated in vacuo.

1,1'[1-(N-benzyloxycarbonyl-8-aminooctyl)-2-(octyl)-1,2-ethanediyl]ester 1,2,3-propanetricarboxylic acid (14): ^1H NMR (300 MHz, $CDCl_3$) δ .86 (t, J = 5.9 Hz, 3H), 1.28 (br, 24H), 1.45-1.51 (m, 4H), 2.72-2.87 (m, 8H), 3.14-3.21 (m, 2H), 3.24-3.35 (m, 2H), 4.97-

5.04 (m, 2H), 5.13 (s, 2H), 7.32-7.34 (m, 5H); IR ($CDCl_3$) 3500-3000 (broad), 2920, 1780, 1720, 1220, 1160 cm^{-1}.

1,1'[1-(N-benzyloxycarbonyl-11-amino-8,10-dihydroxydodecyl)-2-(octyl)-1,2-ethanediyl]ester 1,2,3-propanetricarboxylic acid (27): ^1H NMR (300 MHz, $CDCl_3$) δ .872 (t, J = 5.6 Hz, 3H), 1.25 (br, 29H), 1.44-1.52 (m, 4H), 2.71-2.86 (m, 8H), 3.144-3.61 (m, 5H), 4.96-5.14 (br, 4H), 7.32-7.34 (br, 5H); IR ($CDCl_3$) 3500-3000 (broad), 2930, 1780, 1720, 1260, 1170 cm^{-1}.

1,1'[1-(N-benzyloxycarbonyl-11-amino-8,10-dihydroxyundecyl)-2-(octyl)-1,2-ethanediyl]ester 1,2,3-propanetricarboxylic acid (28): ^1H NMR (300 MHz, $CDCl_3$) δ .86 (t, J = 6.3 Hz, 3H), 1.24 (br, 26H), 1.46-1.61 (m, 4H), 2.33-2.84 (m, 8H), 3.10-3.36 (m, 6H), 4.82-5.13 (m, 4H), 7.27-7.35 (m, 5H); IR (Neat) 3500-3000 (broad), 2927, 1780, 1733, 1263, 1172.

1,1'[1-(methyl)-2-(methyl-1,2-ethanediyl]ester 1,2,3-propanedtricarboxylic acid (IV): ^1H NMR (300 MHz, $CDCl_3$) δ 1.12-1.30 (m, 6H), 2.17-2.81 (m, 8H), 3.31-3.41 (m, 2H), 5.01-5.12 (m, 2H); IR (Neat) 1733 cm^{-1}; MS (CI-NH_3); 406 (M), 424 (M+NH_4).

General Procedure for the Hydrogenation Reaction. To a suspension of PtO_2 (10 mol%), 10% Pd/C (10 mol%) in CF_3COOH (0.05 M) under hydrogen atmosphere was added the N-benzyloxycarbonyl compound (1 equiv) in CH_3COOH (0.045 M). After completion of addition, the reaction was stirred for 48 hours. The reaction was filtered through a pad of Celite which remained wet with CF_3COOH, and the filtrate was concentrated in vacuo.

1,1'[1-(8-aminooctyl)-2-(octyl)-1,2-ethanediyl]ester 1,2,3-propanetricarboxylic acid (I): ^{1}H NMR (300 MHz, CD_6O) δ .82 -.91 (m, 3H), 1.27 (br, 24H), 1.50-1.59 (m, 4H), 2.54-2.87 (m, 8H), 3.18-3.24 (m, 2H), 3.80-3.85 (m, 2H), 4.96-5.08 (m, 2H); MS (H_2O-Glyceral) (+) (FAB) *m/e* 113, 140, 270, 460, 618 (M+1); MS (Positive Electrospray) *m/e* 618.7 (M+1).

1,1'[1-(11-amino-8,10-dihydroxydodecyl)-2-(octyl)-1,2-ethanediyl]ester 1,2,3-propanetricarboxylic acid (II): ^{1}H NMR (300 MHz, CD_6O) δ .81-.88 (m, 3H), 1.26 (br, 29H), 1.51-1.62 (m, 4H), 2.52-2.83 (m, 8H), 3.10-3.26 (m, 2H), 3.43-3.64 (m, 1H), 3.75-3.87 (m, 1H), 3.95-4.10 (m, 1H), 4.85-5.20 (m, 2H); MS (H20-Glyceral) (-) (FAB) *m/e*113, 205, 546, 704 (M-1); MS (Positive Electrospray) *m/e* 706.7 (M+1).

1,1'[1-(11-amino-8,10-dihydroxyundecyl)-2-(octyl)-1,2-ethanediyl]ester 1,2,3-propanetricarboxylic acid (III): ^{1}H NMR (300 MHz, CD_6O) δ .81-.90 (m, 3H), 1.26 (br, 26H), 1.50-1.63 (m, 4H), 2.55-2.79 (m, 8H), 3.10-3.27 (m, 2H), 3.46-3.54 (m, 2H), 3.65-3.88 (m, 1H), 3.96-4.11 (m, 1H), 4.89-5.16 (m, 2H); MS (H20-Glyceral) (+) (FAB) *m/e* 109, 140, 159, 306, 324, 456, 498, 692 (M+1).

2-Amino-3,5-dihydroxydocosane (V): ^{1}H NMR (300 MHz, $CDCl_3$) δ .876(t, J = 6.1Hz, 3H), 1.26 (br, 40H), 1.50-1.63 (m, 4H), 3.41-3.64 (m, 1H), 3.73-3.86 (m, 1H), 3.94-4.04 (m, 1H).

Nona-dec-10-en-2-one (15): To a solution of oleic acid (2.0g, 7.08 mmol) in 47.2 mL of dry Et_2O at 0 °C was added 10.3 mL of methyllithium (1.37 M in hexane). The reaction was stirred for 1.5

hours at 0 °C and for 4 hours at room temperature. The reaction was slowly added to a suspension of ice and 50 mL of 10% HCl. The aqueous layer was extracted with Et_2O. The combined Et_2O layers were washed with $NaHCO_3$, dried, and concentrated in vacuo to yield 98% of **15** (1.94 g, 6.93 mmol): R_F = .42 (10:1 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ .787 (t, J = 6.1 Hz, 3H), 1.178 (br, 16H), 1.928 (m, 4H), 2.014 (s, 3H), 2.309 (t, J = 7.2 Hz, 2H), 5.235 (m, 2H); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 13.84, 28.90, 28.95, 29.12, 29.34, 29.49, 29.57, 31.72, 43.39, 129.40, 129.60, 208.05; IR (Neat) 3002, 2923, 2852, 1718, 1463, 1358 cm^{-1}.

General Procedure for N-protection of Amino Acids. To solution of amino acid (1 equiv) in Et_2O (0.25 M) and water (0.20 M) was added Na_2CO_3 (2.5 equiv). After 30 minutes, benzylchloroformate (1 equiv) was added and the reaction was stirred for 12 hours. The organic and aqueous layer were separated and the aqueous layer was acidified to pH=3 with 1N HCl. The aqueous layer was extracted with ether, the combined organics were dried, and concentrated in vacuo.

N-benzyloxycarbonylalanine (16): ^1H NMR (300 MHz, CD_6O) δ 1.40 (d, J = 7.5 Hz, 3H), 4.18-4.30 (m, 1H), 5.06 (s, 2H), 7.32-7.40 (m, 5H); IR (CH_2Cl_2) 3440, 1720, 1510 cm^{-1}.

N-benzyloxycarbonylglycine (17): ^1H NMR (300 MHz, CD_6O) δ 3.89 (d, J = 6.3 Hz, 2H), 5.08 (s, 2H), 7.26-7.38 (m, 5H).

General Procedure for the Reduction of N-protected Amino Acids. To a solution of N-benzyloxycarbonyl amino acid (1 equiv) in THF (0.20 M) at 0 °C was added 1,1'-carbonyldiimidazole. After 30 minutes, the solution was cooled to -40 °C and DIBAL (1.0 M in

hexane) (2.5 equiv) was added dropwise. After 40 minutes at -40 °C, the reaction was quenched with 1N HCl and it was slowly warmed to room temperature. The aqueous layer was extracted with ethyl acetate. The combined organics were washed with water, washed with $NaHCO_3$, washed with saturated NaCl, dried and concentrated in vacuo.

N-benzyloxycarbonylalaninal (18): ^1H NMR (300 MHz, $CDCl_3$) δ 1.38 (d, J = 7.5 Hz, 3H), 4.25-4.38 (m, 1H), 5.127 (s, 2H), 7.34-7.37 (m, 5H); IR ($CDCl_3$) 3440, 3000, 1720, 1500, 1230 cm^{-1}.

N-benzyloxycarbonylglycinal (19): ^1H NMR ($CDCl_3$) δ 4.14 (d, J = 7.2 Hz, 2H), 5.134 (s, 2H), 7.370-7.30 (m, 5H), 9.65 (s, 1H).

General Procedure for the Aldol Condensation. To a solution of LDA (1.1 equiv, prepared from *n*-BuLi (1.1 equiv) and diisopropylamine (1.2 equiv) in THF (0.25 M) at -78 °C was added a solution of ketone (1 equiv) in THF (2 M). The solution was stirred at -78 °C for 90 minutes. The aldehyde (1 equiv) in THF (2 M) was added to the -78 °C reaction. Acetic acid/CH_2Cl_2 (10%) was added to quench the -78 °C reaction. After warming to room temperature, the aqueous layer was extracted with CH_2Cl_2. The combined organics were dried and concentrated in vacuo.

N-benzyloxycarbonyl-2-amino-3-hydroxydocos-13-en-5-one (20): R_F = .29 (2:1 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ .919 (t, J = 6.7, 3H), 1.12 (d, J = 6.9 Hz, 3H), 1.306 (br, 24H), 2.01-2.08 (m, 4H), 2.40 (t, J = 7.32 Hz, 2H), 2.50 (d, J = 6.3 Hz, 2H), 3.61-3.72 (m, 1H), 4.00-4.07 (m, 1H), 5.08 (s, 2H), 5.37 (m, 2H), 7.29-7.35 (m, 5H); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 14.06, 14.91, 22.61, 23.42, 27.14, 29.02, 29.24, 29.44,

29.62, 29.68, 31.82, 43.50, 45.61, 50.32, 64.89, 66.68, 69.92, 126.83, 127.35, 127.96, 128.01, 128.34, 128.40, 129.63, 129.91, 136.34, 155.99, 211.66; IR (Neat) 3311, 2919, 2848, 1707, 1685, 1544, 1464 cm^{-1}; MS (CI-NH_3) *m/e* 169, 197, 225, 298, 488 (M+1), 505 (M+NH_4).

N-benzyloxycarbonyl-1-amino-2-hydroxyhenicos-12-en-4-one (21): R_F = .28 (2:1 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ .882 (t, J = 6.3 Hz, 3H), 1.271 (br, 24H), 2.00 (m, 4H), 2.41 (t, J = 7.3 Hz, 2H), 2.58 (d, J = 6.9 Hz, 2H), 3.11-3.23 (m, 1H), 3.31-3.49 (m, 2H), 4.07-4.18 (m, 1H), 4.110 (s, 2H), 5.34 (m, 2H), 7.32-7.39 (m, 5H); IR ($CDCl_3$) 3444, 3053, 1717 (broad), 1516, 14653, 1267 cm^{-1}; MS (CI-NH_3) *m/e* 474 (M+1), 491 (M+NH_4).

General Procedure for the Reduction of β-hydroxyketone. To a solution of $Me_4NBH(OAc)_3$ (5 equiv) in CH_3COOH (1.25 M) and MeCN (1.25 M) at -20 °C was added a solution of β-hydroxyketone (1 equiv) in MeCN (2 M). The reaction was stirred for 2 days at -20 °C. The reaction was warmed to room temperature after the addition of a 0.5 N potassium sodium tartrate (3 mL/mm) solution. The solution was diluted with $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2. The combined organics were washed with water, dried and concentrated in vacuo.

N-benzyloxycarbonyl-2-amino-3,5-dihydroxydocos-13-ene (22): R_F = .27 (2:1 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ .897 (t, J = 6.7 Hz), 1.12 (d, J = 6.6 Hz, 3H), 1.28 (br, 24H), 1.99-2.10 (m, 4H), 3.76-3.88 (m, 1H), 3.82-3.92 (m, 1H), 3.93-3.980 (m, 1H), 5.08 (s, 2H), 5.363 (m, 2H), 7.32-7.35 (5H); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 14.02, 14.93, 22.58,

27.11, 29.22, 29.42, 29.47, 29.57, 29.68, 31.79, 37.38, 38.96, 51.40, 66.68, 68.90, 70.79, 127.96, 128.01 128.30, 129.67, 129.82, 136.26, 156.27; IR (Neat) 3432, 2925, 2853, 1699, 1507 cm^{-1}; MS (CI-NH_3) *m/e* 108, 125, 169, 225, 298, 490 (M+1), 507 (M+NH_4).

N-benzyloxycarbonyl-1-amino-2,4-dihydroxyhenicos-12-ene (23): R_F = .21 (2:1 H:EA); ^1H NMR ($CDCl_3$) δ .881 (t, J = 6.6 Hz), 1.270 (br, 25H), 2.20 (m, 4H), 3.13-3.25 (m, 2H), 3.32-3.42 (m, 1H), 3.88-3.98 (m, 1H), 3.99-4.09 (m, 1H), 5.11 (s, 2H), 5.34 (m, 2H), 7.32-7.37 (m, 5H); IR (Neat) 3341, 2951, 2847, 1677, 1545, 1466 cm^{-1}; MS (CI-NH_3) *m/e* 476 (M+1), 493 (M+NH_4).

4-(N-benzyloxycarbonyl-1-aminoethyl)-6-(8-heptadecene)-2-oxo-1,3-dioxane (24): To a solution of diol 22 (0.30 g, 0.61 mmol) in 0.61 mL of dry CH_2Cl_2 at 0 °C was added pyridine (0.09g, 1.22 mmol). To the 0 °C reaction was added triphosgene (0.12g, 0.04 mmol). The reaction was monitored by TLC analysis until no diol remained. The reaction was poured into water and was concentrated in vacuo. The residue was dissolved in ethyl acetate and was washed with $NaHCO_3$. The ethyl acetate layers were dried with Na_2SO_4 and concentrated in vacuo. The reaction was purified by sg chromatography (2:1 H:EA) to yield 20% of 24 (0.063g, 0.12 mmol): R_F = .25 (2:1 H:EA); ^1H NMR ($CDCl_3$) δ .874 (t, J = 6.6 Hz, 3H), 1.267 (br, 27H), 1.82-1.88 (m, 2H), 1.99-2.03 (m, 4H), 3.83-3.96 (m, 1H), 4.34-4.43 (m, 1H), 4.49-4.60 (m, 1H), 5.085 (s, 2H), 5.342 (m, 2H), 7.30-7.36 (m, 5H); IR (Neat) 3316, 2951, 2922, 2852, 1733, 1716, 1690, 1541, 1464 cm^{-1}; MS (CI-NH_3) m/e 399, 533 (M+18).

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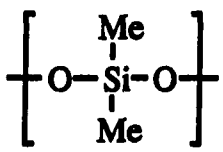
PAPER II. THE SYNTHESIS OF SILICON CROSSLINKING AGENTS

INTRODUCTION

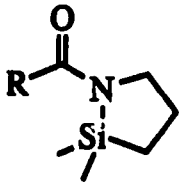
Organosilicon studies were initiated in the 1930's at Corning Glass Works. This early work lead to the development of "Fiberglass" tapes and fabrics for electrical insulation. The urgency of World War II pushed the Dow Corning research in the organosilicon area ahead to develop ignition sealing products, coating varnishes, silicone wire coatings, and lubricating gels. The development of these various polysiloxanes from the hydrolyzed chlorosilanes was innovative. The general structural building block is shown below.[1] These polysiloxanes



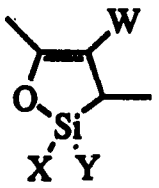
are polymer chains which can be further connected by branches. This branch joining the two chains is referred to as a crosslink. Crosslinking is distinguished by the occurrence of gelation at some point in the polymerization. The gel corresponds to the formation of an infinite network in which polymer molecules have been crosslinked to each other to form a macroscopic molecule. Crosslinking is extremely important from an industrial viewpoint. The physical behavior and mechanical properties of long chain polymers depend not only on chemical structure and chain mobility, but also on the association between adjacent molecules. Crosslinks between polymer chains represent permanent bonds. The effect of the bonds depends on the

chemical structure of the individual bonds, molecular mobility, morphology, and the distribution of the crosslinks.[2]

Two silicon heterocycles were targeted as potential crosslinking agents. One is the cyclic silylamide **1** and the other is the cyclic silyl enol ether **2**.

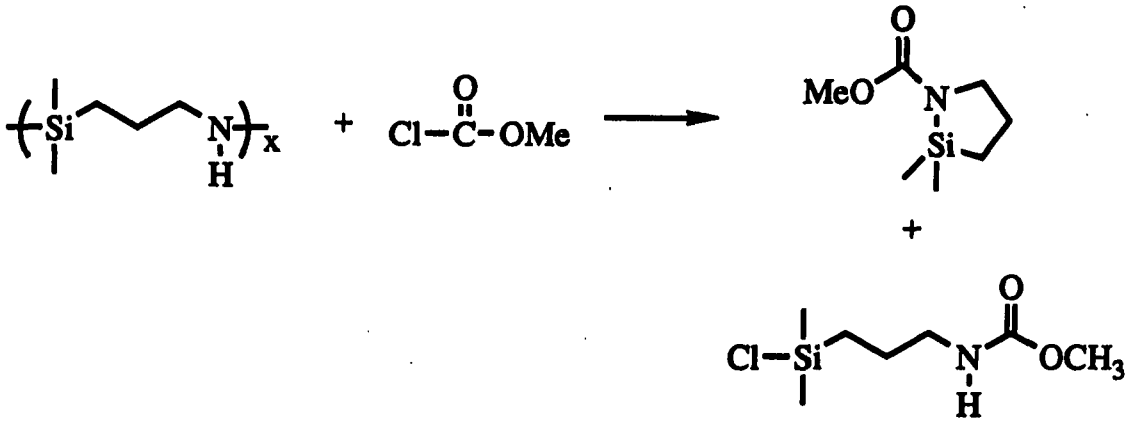


1

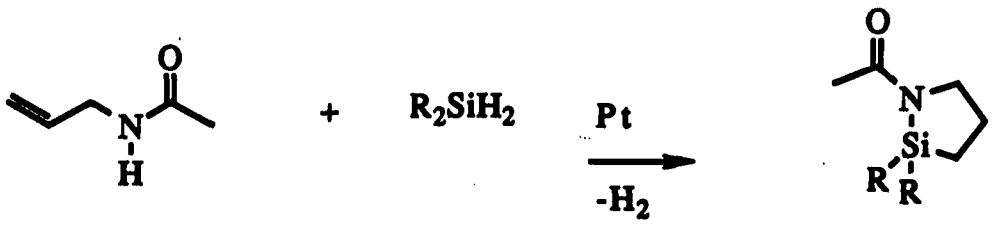


2

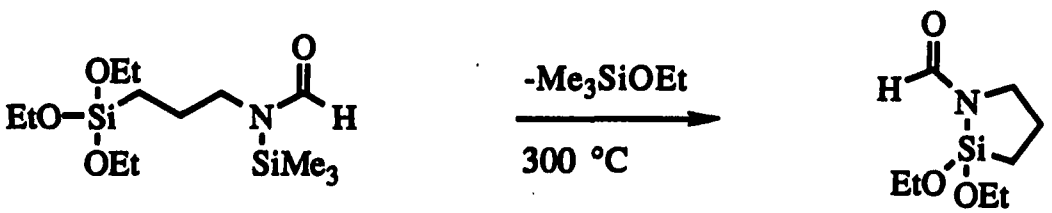
In the examination of the literature for syntheses of heterocycle **1**, three procedures were reported. Preparation of the analogous cyclic silylamide carbamate[3] was published in a 45% yield. An amide



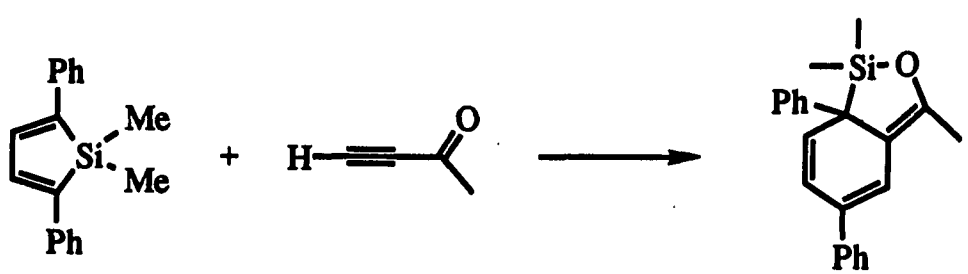
hydrosilation was reported in a General Electric patent.[4] A pyrolysis



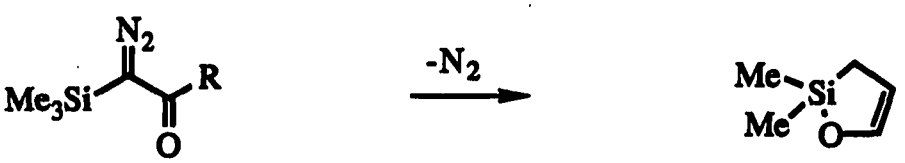
at 300 °C for ten minutes produced a cyclic silylamide in a 98% yield.



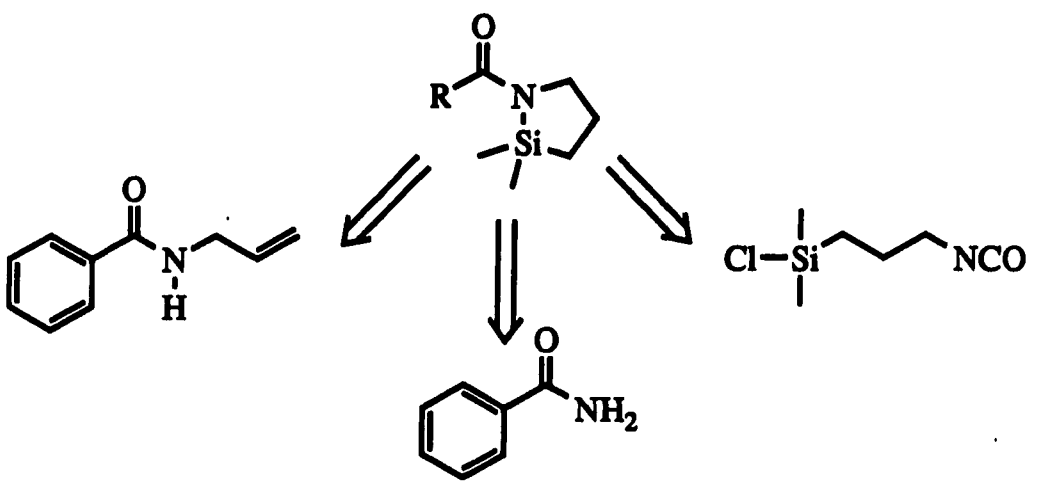
The cyclic silyl enol ethers have been reported in the literature. They have been produced by pyrolysis. Barton[6] reported the Diels-Alder addition of butyn-3-one to a silole to afford bicyclic silyl enol ether in over 85% yield. Thermal decomposition of alpha-diazo-



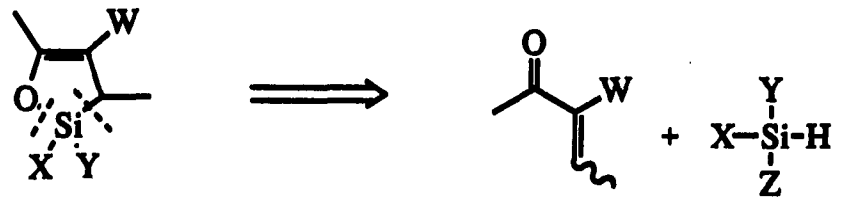
alpha-(trialkylsilyl)alkanes was found to be a useful route to 1-oxa-2-sila-4-cyclopentenes.[7]



Three general strategies for the synthesis of cyclic silylamide 1 were evaluated: the hydrosilation of allylbenzamide, silation of the dianion of a benzamide, or nucleophilic attack of an organolithium reagent on an isocyanate.



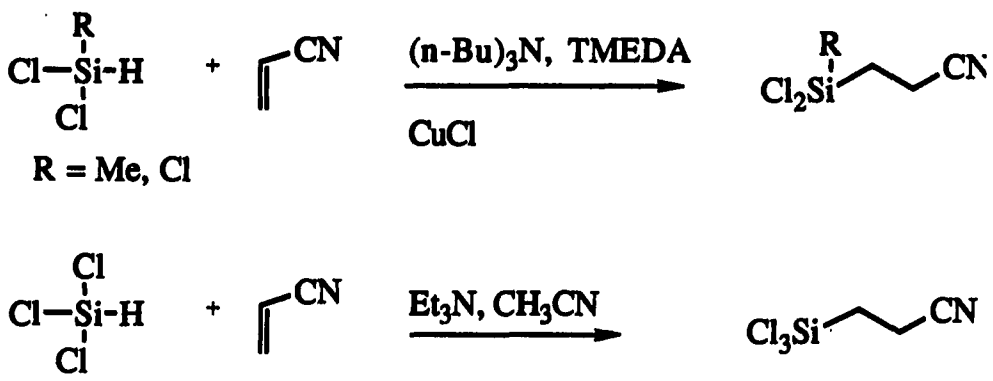
The cyclic silyl enol ether 2 could be approached by various strategies. The major bond formations will be between the oxygen-silicon and carbon-silicon bond.



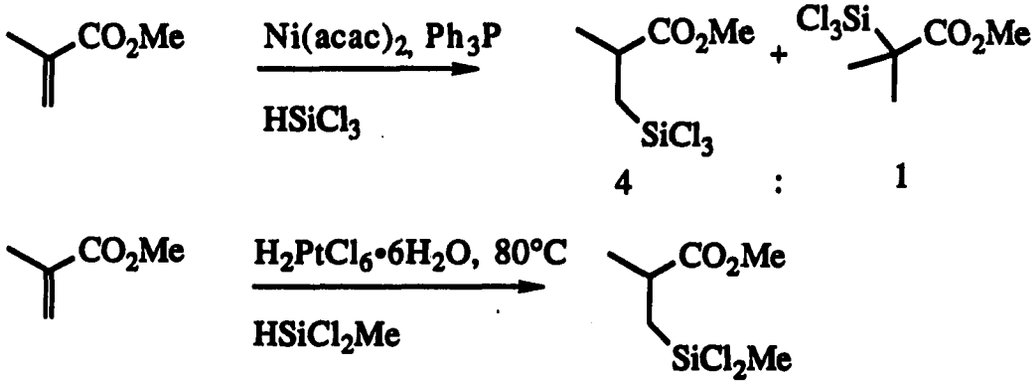
2

W = H, CO_2Et
X = Cl, Me, Ph
Y = Cl, Me, Ph
Z = Cl, CN

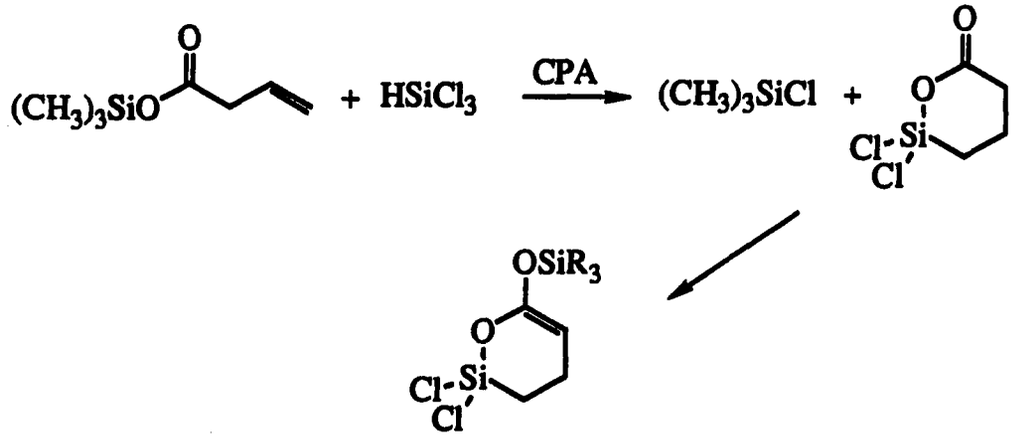
In the context of a synthesis of 2, the base catalyzed hydrosilation was initially explored. Bluestein[8] and Nozakura[9] reported the hydrosilation of acrylonitrile in the presence of a trialkylamine. Similar conditions were attempted on our two unsaturated ketones.



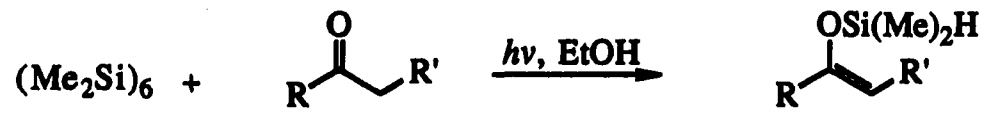
Metal catalysis was examined by Yurev in the hydrosilation of methyl methacrylate. Yurev[10] reported that nickel acetylacetonate ($Ni(acac)_2$) provided successful results. Speier[11] used chloroplatinic acid (CPA) to selectively provide the beta-adduct.



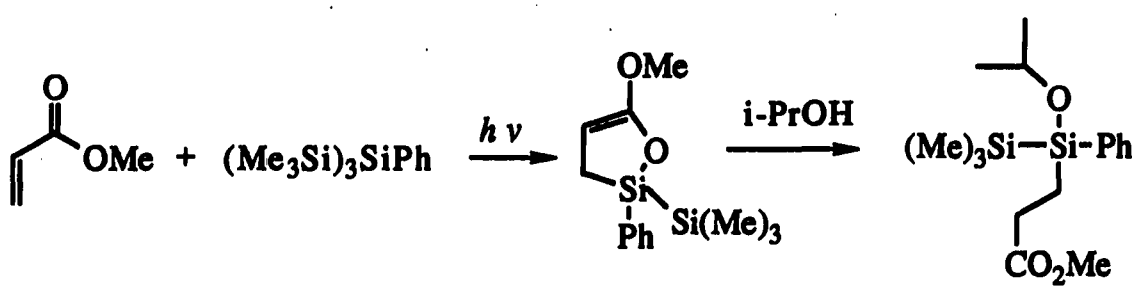
Various metal catalyzed hydrosilation conditions were examined for our system. Radical conditions[12] were explored, too. Mironov[13] synthesized 2-silalactones via an intramolecular hydrosilation. We will later describe our efforts to synthesize the six-membered cyclic silyl enol ether.



The use of a dimethylsilylene to undergo an insertion reaction into various unsaturated ketones was investigated. Dimethylsilylene has been reported to react with carbonyl compounds[14] to form enol



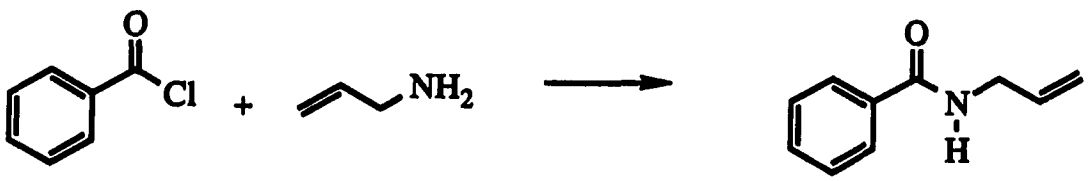
silyl ethers. Kumada reported the reaction of trimethylsilylphenyl-silylene with methyl acrylate.[15]



The compounds which will be discussed in the next section of the dissertation are now being tested as crosslinking agents by the Dow Corning Corporation.

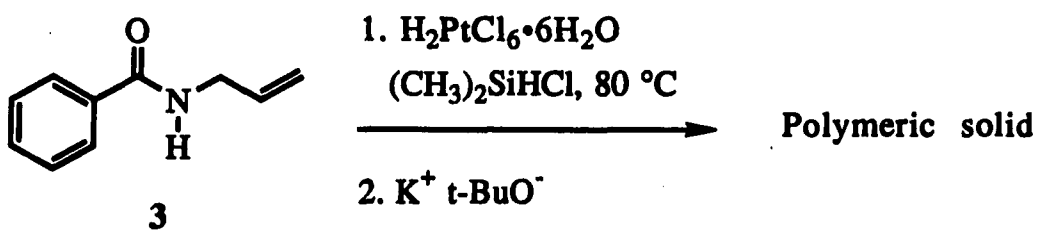
RESULTS AND DISCUSSION

Our work in the synthesis of silicon heterocycles began with the cyclic silylamide **1**. We initially examined the hydrosilation of **3** with dimethylchlorosilane followed with potassium *tert*-butoxide to promote the cyclization to **1**. Our starting material benzamide **3** was synthesized from benzoyl chloride and allylamine in a 95% yield.



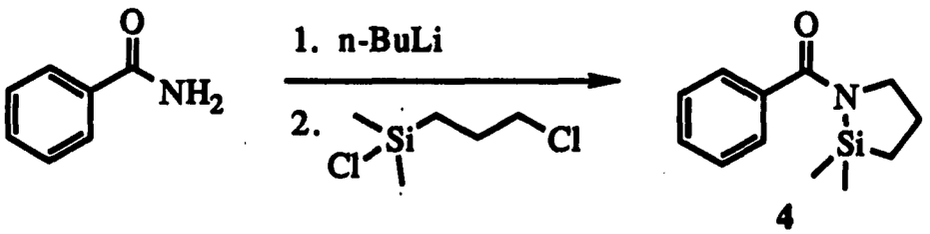
3

Allylbenzamide **3** was placed in a sealed tube in the presence of chloroplatinic acid (CPA), dimethylchlorosilane and CH_2Cl_2 at 80 °C. Potassium *tert*-butoxide was added to the resulting silylated product to generate the anion of the amide which then nucleophilically displaced the chloride to give a polymeric solid. This polymeric solid was insoluble in standard organic solvents.



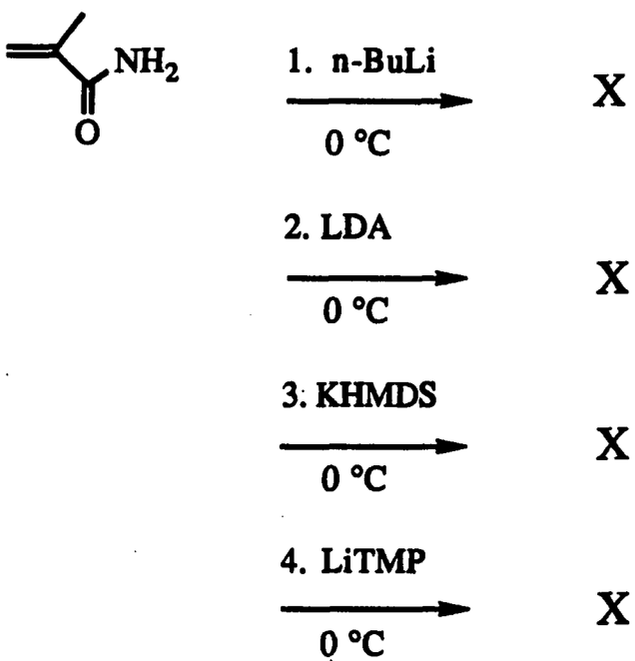
3

We next explored the generation of the dianion of benzamide with n-butyllithium at 0 °C in tetrahydrofuran followed by quenching at 0 °C with chloropropyldimethylchlorosilane. This reaction formed 100% of the cyclic silylamide **4**. We then attempted to generate the dianion of

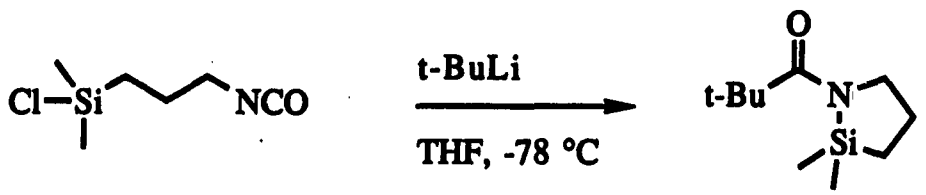


4

methacrylamide with *n*-butyllithium, lithium diisopropylamide (LDA), potassium 1,1,1,3,3,3-hexamethyldisilazide (KHMDS), or lithium 2,2,6,6,-tetramethylpiperidide (LiTMP), but the bases underwent Michael addition to the unsaturated amide.

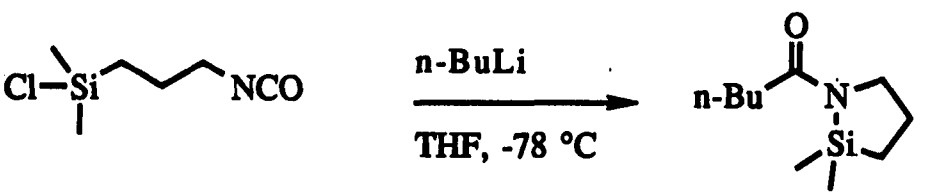


Finally, we pursued the strategy of having the chlorosilane built into the starting material. To commercially available 3-isocyanatopropylchlorodimethylsilane in tetrahydrofuran at -78 °C was added *tert*-butyllithium. We expected addition to the isocyanate. The resulting amide anion displaced the chloride to give cyclic silylamide **5**



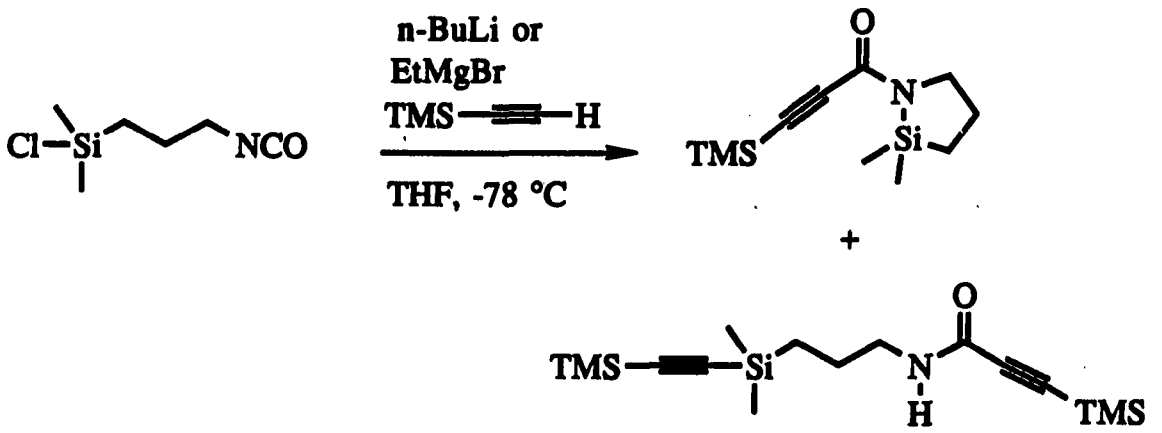
5

in a 100% yield. Using the same conditions with *n*-butyllithium at -78 °C, we isolated 90% of the cyclic silylamide **6**.

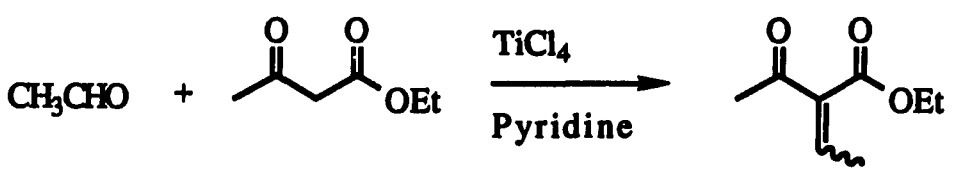


6

Reaction of lithium or magnesium trimethylsilylacetylide with the isocyanate gave unusual results. The desired cyclic silylamide formed in a 30% yield, but the major product by GC-MS/FT-IR was the bis addition product.

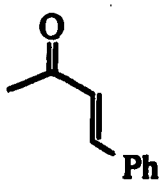


The cyclic silyl enol ether **2** was our next synthetic target. We initially needed to synthesize β-ketoester **7** [16]. Ethyl acetoacetate, acetaldehyde and tetrahydrofuran were added to a solution of titanium tetrachloride at 0 °C. Addition of pyridine followed by aqueous work up provided a 60% yield of **7**.



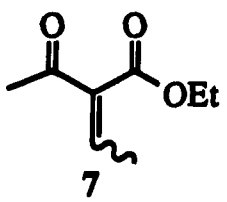
7

Initially, the base catalysis conditions of Bluestein[8] and Nozakura[9] were explored. Reaction of *trans*-4-phenyl-3-buten-2-one, trichlorosilane, cuprous chloride, and triethylamine at room temperature returned starting material. The same conditions were attempted on



$HSiCl_3$, Et_3N / $CuCl$, Et_2O → S.M.

compound 7 since it would expected to be a better Michael acceptor; however, the reaction yielded an unidentifiable product. Heating a mixture of trichlorosilane, triethylamine and compound 7 also failed.



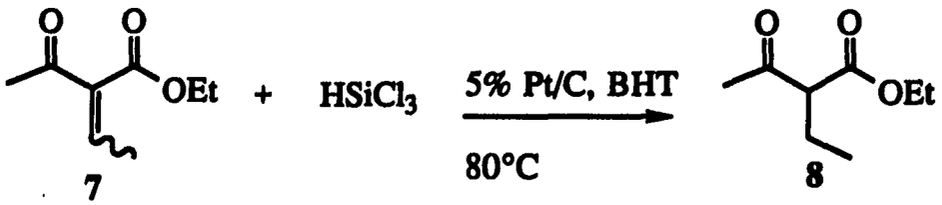
7

$HSiCl_3$, Et_3N / $CuCl$, Et_2O → X

7 → $HSiCl_3$, Et_3N / 80°C → X

These reactions were also attempted with toluene as a solvent, but the same results occurred.

Hydrosilation with metal catalysts was attempted after the failure of our first approach. β-Keto ester 7 was heated in benzene with trichlorosilane, and 5% Pt/C to give the reduction product 8 in a quantitative yield. The reaction was pursued with CPA and Wilkinson's catalyst with the same result. Heating 7 at 80 °C with nickel acetylacetonate and triphenylphosphine yielded a polymeric solid.

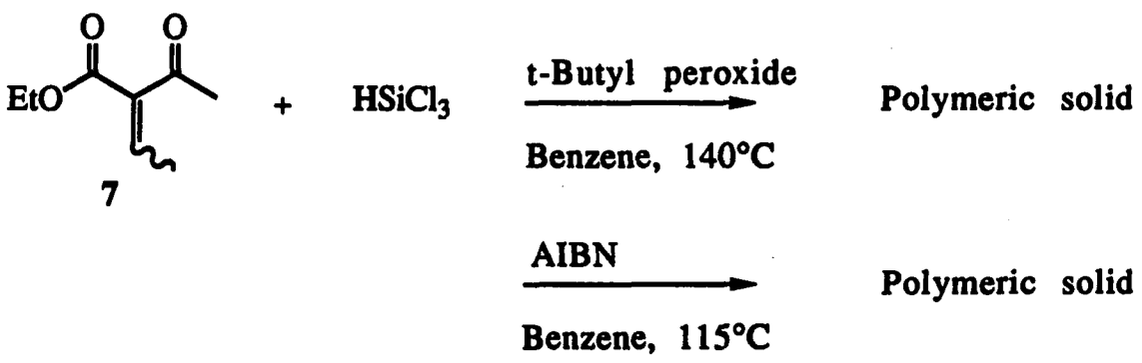


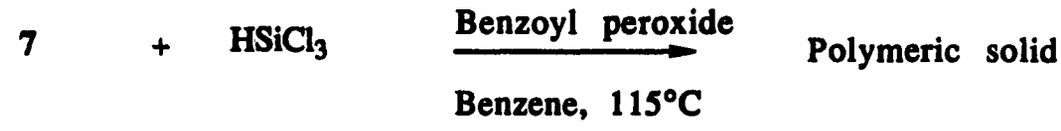
$H_2PtCl_6 \cdot 6H_2O$, 80°C → **8**

$(Ph_3P)_3RhCl$, 80°C → **8**

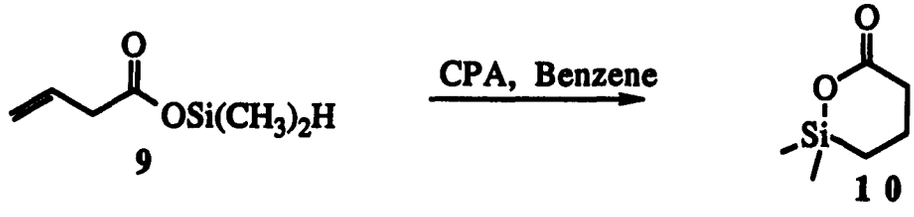
$Ni(acac)_2$, Ph_3P → Polymerization

Our third approach involved the hydrosilation under radical conditions. Heating **7** in presence of trichlorosilane with radical initiators such as *tert*-butylperoxide, 2,2'-azabisiobutyronitrile (AIBN), or benzoyl peroxide yielded a polymeric solid.

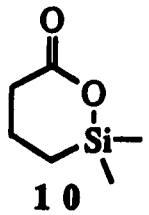




The fourth approach involved the initial work of Mironov.[13] We attempted to synthesize the six-membered ring cyclic enol silyl ether. The reaction of vinyl acetic acid with triethylamine and dimethylchlorosilane at 0 °C yielded 64% of ester **9**. The silyl ester **9** was reacted with CPA and benzene at 80 °C to yield 82% of the silalactone **10**



Several conditions were examined to form the enol silyl ether of silalactone **10**. Diisopropylethylamine was added to a 0 °C solution of silalactone **10** in CH_2Cl_2 with addition of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) after 15 minutes. The crude reaction mixture seemed to have several products by NMR. The reaction of **10** with LDA and *tert*-butyldimethylchlorosilane (TBDMSCl) failed. After considering that the *tert*-butyldimethylsilyl group could be sterically too demanding, the same conditions were examined with trimethylsilyl trifluoromethanesulfonate (TMSOTf) and trimethylchlorosilane (TMSCl) with no success.



10

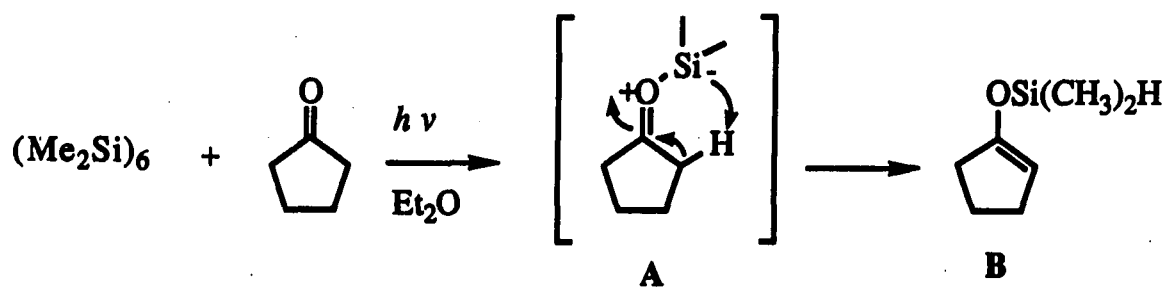
Hunig's Base, TBSOTf, 0°C - RT → X

LDA, TBSCl, -78°C → X

Et_3N, TMSOTf, -78°C → X

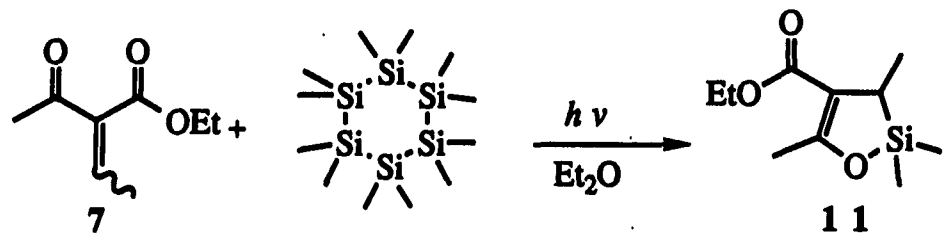
LDA, TMSCl, -78°C → X

The fifth approach proved successful. As Ando[14] had reported, dimethylsilylene does react with carbonyl compounds to generate enol silyl ethers. Initial reaction with the carbonyl results in zwitterion A which undergoes hydrogen-abstraction to yield the enol silyl ether B.



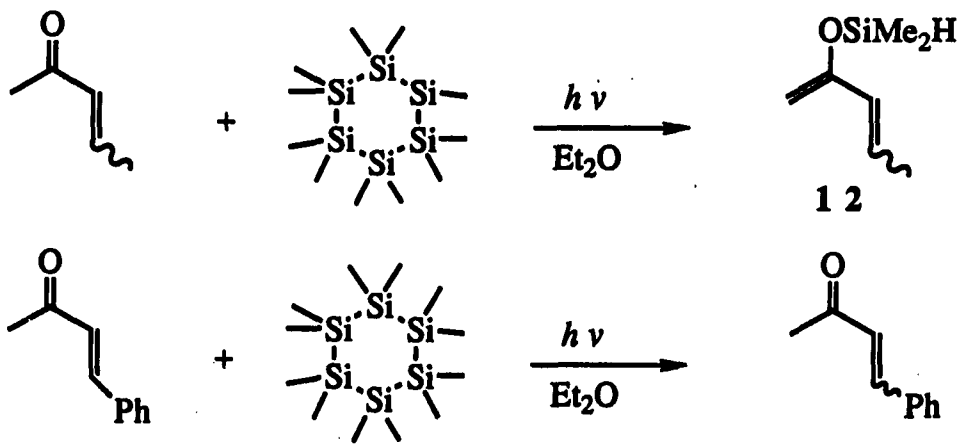
A B

We reacted the dodecamethylcyclohexasilane with unsaturated compound **7** in the hope that the zwitterion would undergo a conjugate addition. When **7** was photolyzed with dodecamethylcyclohexasilane for 2 hours with a Hanovia medium pressure mercury lamp, the desired cyclic enol ether **11** was isolated by preparative gas chromatography



7 11

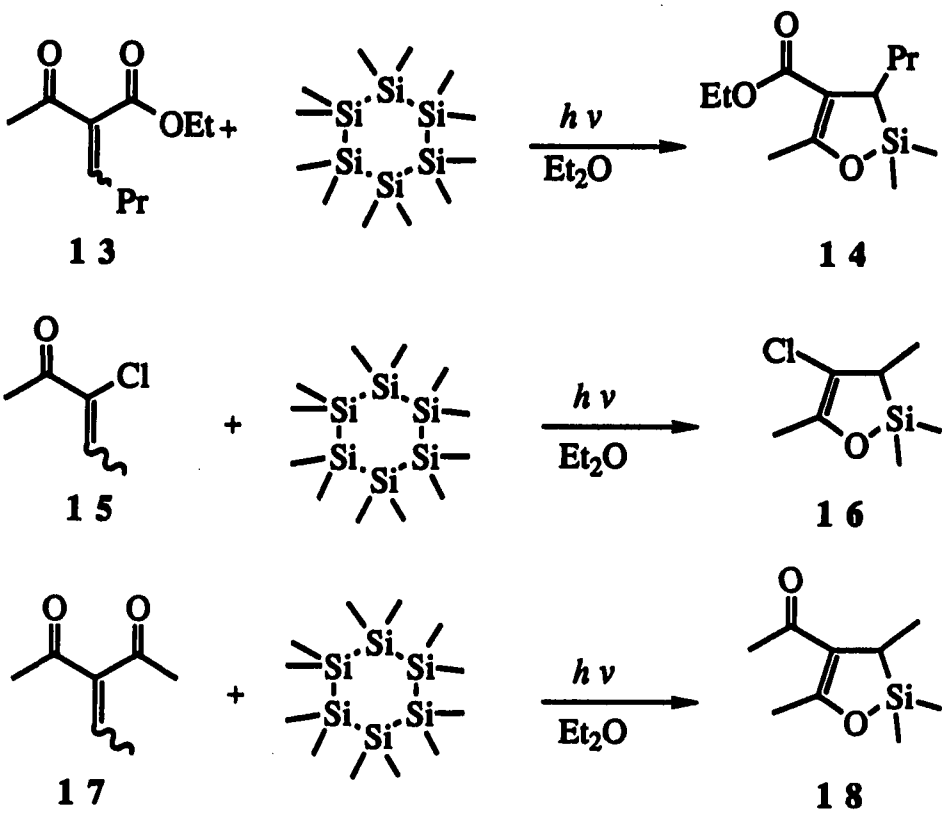
in a 19% yield. Other compounds were then studied. The photolysis of 3-penten-2-one afforded diene species **12** in 11% yield. Irradiation of *trans*-4-phenyl-3-buten-2-one resulted in only



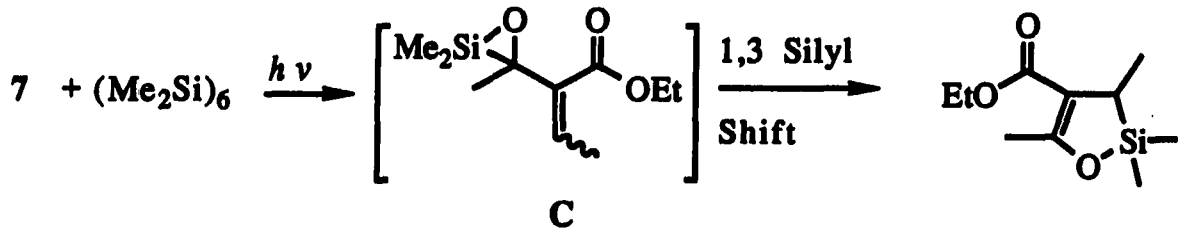
12

isomerisation to a mixture of cis/trans isomers. Keto ester **13** [16] was photolyzed to give 15% of the desired product **14**. Chloroketone **15** [17]

was prepared in a 71% yield by reacting 3-penten-2-one with chlorine, followed by triethylamine. The photolysis of **15** furnished 31% yield of **16**, but this compound decomposed when purification was attempted by preparative gas chromatography. Diketone **17** [18] reacted under the photolytic conditions to yield 32% of the cyclic silyl enol ether **18**.

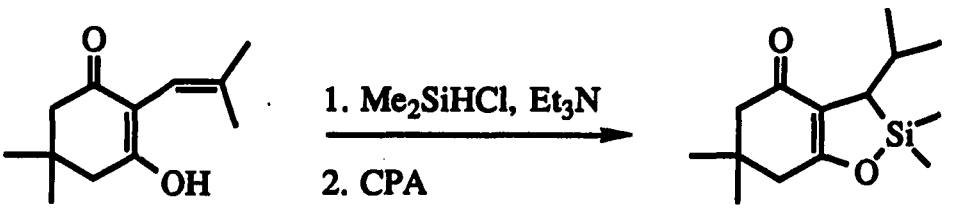


We postulated that **7** was reacting with dimethylsilylene to yield intermediate **C** which would undergo a 1,3 silyl shift to give the desired cyclic enol ether.



C

With the success of the silylene route, we began to examine the formation of the cyclic silyl enol ether by an intramolecular hydrosilation since dodecamethylcyclohexasilane would be too expensive to use on a large industrial scale. Diketone **19** was prepared from 5,5-dimethyl-1,3-cyclohexanedione, isobutryaldehyde, pyrrolidine, and 10% hydrochloric acid by the method of Yoshida.[19] Silation of alcohol **19** with triethylamine and chlorodimethylsilane returned starting material. Generation of the enol silyl ether in situ followed by removal of a minimum amount of ether, dilution with benzene and heating with CPA yielded 28% of bicyclic ketone **20**. One advantage to this route is



19 **20**

the ability to change the groups attached to the chlorosilane. Furthermore, Komarov[20] has published the vinylation of a CH acid such as 1,3-indandione with acetylene or phenylacetylene in the presence of

a mercury catalyst. This may be a better method of preparing compounds such as 19 on an industrial scale.

CONCLUSION

This chemistry has provided interesting methods for the synthesis of cyclic silylamides and cyclic silyl enol ethers. The instability of these heterocycles has made this work very challenging. The isolated compounds are short-lived, which encourages the pursuit of both structural variants of these heterocycles, and newer methods of preparation which will one day lead to increased stability.

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Benzene was distilled from lithium aluminum hydride. Dichloromethane and acetonitrile were distilled from calcium hydride. All reactions were conducted under nitrogen atmosphere and all extracts were dried over anhydrous sodium sulfate. Apparatus for experiments requiring anhydrous conditions was flame-dried under a stream of nitrogen or dried in a 150 °C oven for 12 h and cooled under a stream of nitrogen. Preparative gas chromatography was performed on a Varian 920 using 15-25% SE-30 on chromasorb W packed columns. Gas chromatographic analyses were performed on a Hewlett Packard 5790A using a 30 meter DB-5 capillary column. Mass spectra were recorded using a Hewlett Packard 5970B (GC/MS) operating at 70 eV. Infrared spectra were obtained on a Perkin-Elmer 1320 spectrophotometer or a Hewlett Packard 5965A (GC/IR) and are reported in cm^{-1}. Proton nuclear magnetic resonance spectra (300 MHz) were obtained using a Nicolet Magnetics Corporation NMC-1280 spectrometer. All chemical shifts are reported in δ relative to $CDCl_3$. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), ABq (AB quartet), and m (multiplet); a br suffix indicates a broadened pattern. Carbon-13 NMR spectra (75.46 MHz) were obtained on a Nicolet NMC-1280 spectrometer and

are reported in δ relative to $CDCl_3$ (77.00 ppm). The purity of all title compounds was judged to be ≥ 95% by ^1H NMR spectral determination.

N-allylbenzamide (3): To a solution of allylamine (3.71 g, 65 mmol) in 100 mL of CH_2Cl_2 at 0 °C was added benzoyl chloride (4.21 g, 30 mmol). After stirring overnight, the reaction was poured into 100 mL of H_2O with 5 mL of HCl. The layers were separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organics were washed with saturated NaCl solution. The solution was dried and concentrated in vacuo to give 4.64 g (95%) of a clear liquid: ^1H NMR (300 MHz, $CDCl_3$) δ 4.05-4.12 (m, 2H), 5.1-5.2 (m, 2H), 5.87-6.00 (m, 1H), 7.40-7.52 (m, 3H), 7.76-7.79 (m, 2H).

N-benzoyl-2,2-dimethyl-1-aza-2-silacyclopentane (4): To a solution of benzamide (0.363 g, 3 mmol) in 6 mL of THF at 0 °C was added *n*-BuLi (2.55mL, 6.3 mmol). After one hour, the chloropropyldimethylchlorosilane was added to the 0 °C reaction mixture with continued stirring for 2 hours. Hexane was added to precipitate the LiCl. The solution was filtered through Celite and concentrated in vacuo to give 0.65 g (100%) of a solid: ^1H NMR (300 MHz, $CDCl_3$) δ .076 (s, 6H), .58-.75 (m, 2H), 1.41-1.56 (m, 2H), 3.47-3.61 (m, 2H), 7.42-7.82 (m, 5H); IR (CH_2Cl_2) 3020, 2980, 2960, 1660, 1265 cm^{-1}.

General Procedure for the reaction of 3-isocyanato-propyldimethylchlorosilane with alkyllithium reagents: To a solution of 3-isocyanatopropyldimethylchlorosilane (0.44 g, 0.25 mmol) in 1 mL of dry THF at -78 °C was added dropwise an alkyl lithium (0.25

mmol) reagent. After stirring for 2.5 hours at -78 °C, the reaction mixture was diluted with dry hexane. The solution was filtered through Celite and concentrated in vacuo.

(N-Pivaloyl-2,2-dimethyl-1-aza-2-silacyclopentane (5): ^{1}H NMR (300 MHz, $CDCl_3$) δ .047 (s, 6H), .45-.52 (m, 2H), 1.19 (s, 9H), 1.45-1.53 (m, 2H), 3.15-3.24 (m, 2H); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ .057, 15.18, 23.25, 27.36, 38.23, 42.16, 177.99; IR (Gas) 2961, 1696, 1497, 1261, 830 cm^{-1}; GC-MS *m/e* 199, 100, 57.

N-(1-oxopentyl)-2,2-dimethyl-1-aza-2-silacyclopentane (6): ^{1}H NMR (300 MHz, $CDCl_3$) δ .094 (s, 6H), .43-.52 (m, 2H), .84-.97 (m, 7H), 1.25-1.35 (m, 2H), 2.15-2.28 (m, 2H), 3.18-3.32 (m, 2H); IR (CH_2Cl_2) 2960, 2920, 2880, 1660 cm^{-1}.

3-(carboethoxy)-2-pentanone (8): A solution of 3-carboethoxy-3-penten-2-one (0.050 g, 0.32 mmol), trichlorosilane (0.130 g, 0.96 mmol), 5% Pt/C (8 mg) and 2,6-di-tert-butyl-4-methylphenol (8 mg) were heated at 80 °C in a sealed tube for 18 hours. The reaction was concentrated in vacuo: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, J = 5.4 Hz, 3H), 1.49 (t, J = 6 Hz, 3H), 1.74-1.78 (m, 2H), 2.01 (s, 3H), 2.56 (q, J = 6.1 Hz, 2H). 4.0 (t, J = 5.5 Hz); IR (Neat) 2980, 1750, 1710, 1100 cm^{-1}.

General Procedure for the Photolysis Reaction. A quartz tube containing a solution of unsaturated ketone (1.5 equiv) and dodecamethylcyclohexasilane (1 equiv) in dry ether (0.085 M) was degassed with argon at -40 °C for 15 minutes. The reaction was photolyzed with a Hanovia medium pressure mercury lamp for 2-8

hours until gas chromatography showed partial completion of the reaction. The reaction was concentrated to a minimum amount of solvent prior to purification by preparative gas chromatography. The reported yields are uncorrected gas chromatography yields.

4-Carboethoxy-2,2-dimethyl-3,5-dimethyl-1-oxa-2-silacyclopent-4-ene (11): ^{1}H NMR (300 MHz, $CDCl_3$) δ .266 (s, 3H), .359 (s, 3H), 1.12 (d, J = 7.5 Hz, 3H), 1.29 (t, J = 7.0 Hz, 3H), 2.265 (d, J = 1.0 Hz, 3H), 4.18 (q, J = 7.2 Hz, 2H); IR (Gas) 2973, 1715, 1606, 1453, 1308, 1267, 1160, 1065 cm^{-1}; GC-MS *m/e* 214, 199, 169, 141, 75.

2-(Dimethylsilyloxy)-1,3-pentadiene (12): IR (Gas) 3121, 3037, 2144, 1595, 1315, 1263, 1025 cm^{-1}; GC-MS *m/e* 142, 127, 109, 99, 75, 61.

4-Carboethoxy-2,2-dimethyl-5-methyl-3-propyl-1-oxa-2-silacyclopent-4-ene (14): IR (Gas) 2968, 1715, 1606, 1465, 1306, 1262, 1152, 1073 cm^{-1}; GC-MS *m/e* 242, 227, 199, 169, 153, 125, 75.

4-Chloro-2,2-dimethyl-3,5-dimethyl-1-oxa-2-silacyclopent-4-ene (16): IR (Gas) 2968, 1647, 1383, 1258, 1161; GC-MS *m/e* 176, 161, 141, 125, 93, 75.

4-Acetyl-2,2-dimethyl-3,5-dimethyl-1-oxa-2-silacyclopent-4-ene (18): ^{1}H NMR (300 MHz, $CDCl_3$) δ .277 (s, 3H), .380 (s, 3H), 1.13 (d, J = 7.5 Hz, 3H), 2.24 (d, J = 1.2 Hz, 3H), 2.27 (s, 3H); IR (Gas) 2964, 1679, 1578, 1380, 1264, 1159, 1000 cm^{-1}; GC-MS *m/e* 184, 169, 97, 75.

3-(1-Methylethyl)-2,3,4,5,6,7-hexahydro-2,2,5,5-tetramethyl-4-oxo-1,2-benzoxasilole (20): To a solution of

diketone **19** (0.050 g, 0.25 mmol) in 1.0 mL of dry THF at 0 °C was added Et_3N (0.028 g, 0.27 mmol). The solution was stirred for 30 minutes at 0 °C. Chlorodimethylsilane (0.026 g, 0.27 mmol) was added dropwise and the solution was allowed to warm to room temperature. After 60 minutes, 0.75 mL of THF was removed and the reaction was diluted with 2.0 mL of dry benzene. To the reaction was added 30 μL of 3% CPA in amyl alcohol and the reaction was heated at 80 °C for 20 hours: ^1H NMR (300 MHz, $CDCl_3$) δ .22 (s, 3H), .55 (s, 3H), .83 (d, J = 6.9 Hz, 1H), .97 (d, J = 6.9 Hz, 1H), 1.07 (s, 3H), 1.11 (s, 3H), 2.22-2.25 (m, 2H), 2.31-2.34 (m, 2H); IR (Gas) 2965, 1675, 1545, 1365, 1135 cm^{-1}; GC-MS *m/e* 252, 237, 209, 153, 125, 75.

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GENERAL SUMMARY

The importance of synthetic organic chemistry to other scientific disciplines has been demonstrated in this dissertation. The first paper discusses the synthesis of FB_1 analogs and the toxicological testing results of these analogs. This paper has provided insight into the structural requirements needed for biological activity. This work could aid in the determination of a safe level of FB_1 in human food sources. These analogs could be used for the development of methods for the decomposition of FB_1 in food sources. The synthesis of radiolabelled analogs could be used to determine the mode of action in living systems. As more is discovered about FB_1, organic chemists will continue to find ways to contribute to this interdisciplinary research.

The synthesis of nitrogen and oxygen silicon heterocycles in the second paper demonstrates the contribution synthetic organic chemists can provide to the area of silicon research. The application of known organic transformations to organo-silicon chemistry will provide new approaches to silicon compounds. These compounds could make contributions in the areas of polymer chemistry and in the established areas of industrial silicon chemistry.

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