AN APPROACH TO THE PRODUCTION OF TETHERED β-TURN PEPTIDOMIMETICS BY GEMINAL ACYLATION

ANNE MARIE McCARTHY

An Approach to the Production of Tethered β-Turn Peptidomimetics by Geminal Acylation

by

Anne Marie McCarthy

B. Sc. (Memorial University of Newfoundland)

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Department of Chemistry

Memorial University of Newfoundland

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Abstract

The aim of this research was to develop a synthetic route to produce 5,6-fused-1-aza-2-oxobicycloalkane amino acids. Geminal acylation of a ketone or its acetal provides ready access to a 2,2-disubstituted 1,3-cyclopentanedione derivative. Double geminal acylation of diketones with long acyclic tethers between the carbonyls is envisaged as a core strategy for the development of synthetic access to tethered peptidomimetics. The focus of this research was to develop a route to 5,6-fused-1-aza-2-oxobicycloalkane amino acids which are β-turn peptidomimetics, with carbon-based bridgehead substituents. Geminal acylation of the acetal derived from hexadeca-1,15-diene-5,12-dione gave the 1,3-cyclopentanedione **52** in 29% yield along with numerous interesting side-products. A successful route to form lactams via Beckmann rearrangement was established. The development of this synthetic route, including the elucidation of the structures of side-products, is discussed in detail.

Acknowledgements

I would like to extend my deepest thanks to Dr. D. Jean Burnell for his much appreciated guidance and support. I would like to thank the Burnell, Bodwell and Georghiou groups, both past and present, for their help and friendship in the past few years. I am grateful to Mr. David O. Miller and Ms. Rosemarie Harvey for NMR and IR spectra and Dr. Brian Gregory and Ms. Marian Baggs for mass spectral data, as well as my supervisory committee, Dr. Graham Bodwell and Dr. Paris Georghiou. I would also like to thank my family and friends for all their love, support and encouragement over the years. Finally, a huge thank-you goes out to Memorial University of Newfoundland for financial support.

List of Abbreviations

b	broad (IR)
$BF_3 \bullet Et_2O$	borontrifluoride diethyletherate
CI	chemical ionization
δ	chemical shift
DMP	Dess-Martin Periodinane
CH_2Cl_2	dichloromethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
d	doublet (NMR)
EI	electron impact ionization
Et	ethyl
Et_3N	triethylamine
GC/MS	gas chromatography – mass spectrometry
HMBC	heteronuclear multiple bond connectivity
HMQC	heteronuclear multiple quantum correlation
h	hour(s)
Hz	hertz
IBX	2-Iodoxybenzoic Acid
IR	infrared (spectroscopy)
J	coupling constant (J value)

Me	methyl
m	multiplet (NMR), medium (IR)
mL	millilitre(s)
mmol	millimole(s)
mp	melting point
MS	mass spectrum
MSH	*O*-mesitylenesulfonylhydroxylamine
m/z	mass to charge ratio
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
ppm	parts per million
p-TsOH	*para*-toluenesulfonic acid
q	quartet (NMR)
rt	room temperature
s	singlet (NMR), strong (IR)
t	triplet (NMR)
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilane
TBSCl	chloro-*tert*-butyldimethylsilane
t-Bu	*tert*-butyl
TFA	trifluoroacetic acid

THF	tetrahyrofuran
TLC	thin-layer chromatography
TMS	trimethylsilane and trimethylsilyl
TMSCl	chlorotrimethylsilane
TMSOTf	trimethylsilyl triflate
vs	very strong (IR)
w	weak (IR)

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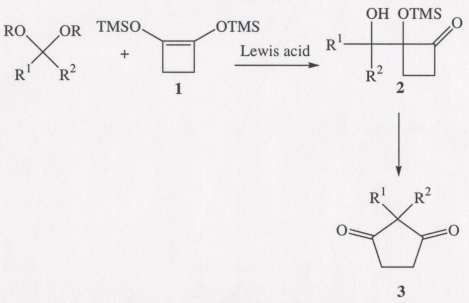
Introduction

Geminal acylation

Geminal acylation involves the replacement of the carbonyl moiety of a ketone, aldehyde or acetal by two geminally situated acyl groups. This reaction is a powerful carbon-carbon bond-forming reaction, and, consequently, it has engendered much interest for the synthesis of natural products and other structurally interesting molecules.

Kuwajima and co-workers[1] first studied this reaction and found that the reaction of an acetal or aldehyde with 1,2-bis[(trimethylsilyl)oxy]cyclobutene **1** led to the formation of pinacol **2,** either by Lewis acid-mediated aldol addition or by a fluoride mediated one (Scheme 1).

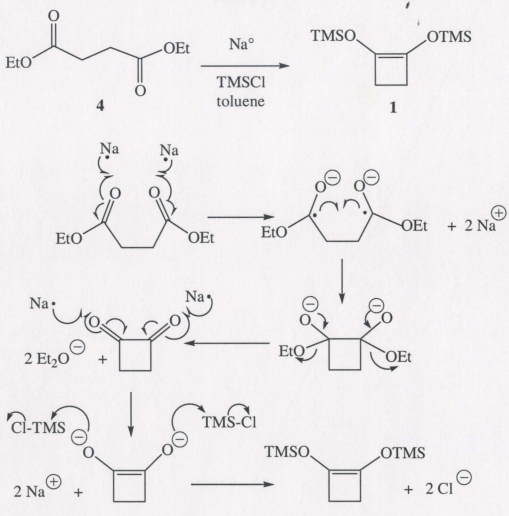
Scheme 1



Bis-(silylated) succinoin **1** was prepared by acyloin condensation of diethyl succinate

4 in the presence of chlorotrimethylsilane.[2] The reaction occurs via a series of single electron transfers from the sodium in the reaction mixture to form the ring structure, followed by trapping of the generated dianion with chlorotrimethylsilane (Scheme 2).

Scheme 2



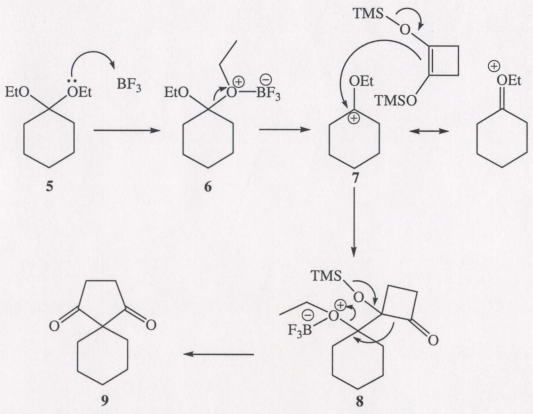
* The single electron transfer reactions depicted here are not concerted.

For the initial aldol reaction step of the geminal acylation reaction, $TiCl_4$ gives the most satisfactory results for the reaction with aldehydes and aliphatic acetals, but $BF_3 \bullet Et_2O$ is the reagent of choice for the more reactive acetals.[1] The aldol product **2** afforded the 2,2-disubstituted 1,3-cyclopentanedione, **3**, upon exposure to excess trifluoroacetic acid (TFA),

tetrabutylammonium fluoride (TBAF), or $TiCl_4$. Acetals are often the favored choice to use in geminal acylation since they coordinate more strongly with Lewis acids than their parent carbonyl precursors.[1] Kuwajima[1] claimed the aldol reaction between ketones and **1** could not be achieved under a variety of acidic or basic conditions.

Geminal acylation products are presumably formed via the mechanism shown in Scheme 3. The lone pair of electrons on an oxygen atom of the acetal **5** coordinates to the $BF_3 \bullet Et_2O$ making the acetal carbon susceptible to attack by the nucleophile in a Mukaiyama-like aldol reaction. This gives a cyclobutanone, **8** which participates in an acid-initiated acyl migration, similar to a pinacol rearrangement, to afford the desired 2,2-disubstituted-1,3-diketone **9**. This is not a concerted process as shown in Scheme 3.

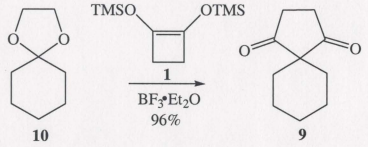
Scheme 3



Anderson and Lee[3] reported that the geminal acylation reaction often resulted in a cyclopentanedione product **3** along with 50-60% of the silylated **2** and its desilylated product. The desilylated product failed to rearrange under conditions of refluxing TFA or refluxing methanolic hydrogen chloride while the silylated product yielded the diketone **3** under the same conditions.

This reaction was initially developed as a two-step sequence that first required the isolation of intermediate **2** (Scheme 1).[1] Refinement of Kuwajima's original procedure by Wu and Burnell[4] showed that both reactions could be accomplished in a single operation, eliminating the isolation of the cyclobutanone intermediate and often achieving superior yields. This was done using two to three molar equivalents of 1,2-bis[(trimethylsilyl)oxy]cyclobutene **1** and a large excess of $BF_3 \bullet Et_2O$ as in forming **9** from acetal **10** (Scheme 4).

Scheme 4

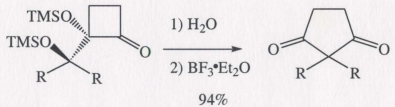


10 **9**

Kuwajima[1] claimed that ketones are non-reactive with **1** in the presence of $BF_3 \bullet Et_2O$ in the initial aldol condensation step. It had been proposed that ketones were not sufficiently reactive electrophiles for silyl enol ethers, causing the reaction to either not work or to be too sluggish. Jenkins and Burnell[5] proved the contrary in reporting an efficient preparation

of many 2,2-disubstituted 1,3-cyclopentanediones from a variety of ketones (Scheme 5). This was accomplished by using **1** with an equivalent amount of $BF_3 \bullet Et_2O$ followed by a small volume of water and a large excess of $BF_3 \bullet Et_2O$. The water and acid may have hydrolyzed one or both of the (trimethylsilyl)oxy groups, which in turn assisted the rearrangement step.

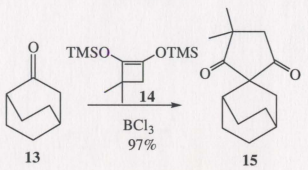
Scheme 5



11 **12**

Employing analogues of **1** bearing alkyl groups is an important extension of geminal acylation methodology since a variety of natural products contain cyclopentane moieties bearing a single methyl group or gem-dimethyl groups. Crane and Burnell[6] improved on this methodology by using BCl_3 rather than $BF_3 \bullet Et_2O$ for the geminal acylation reaction using **13** and **14** to form **15** (Scheme 6).

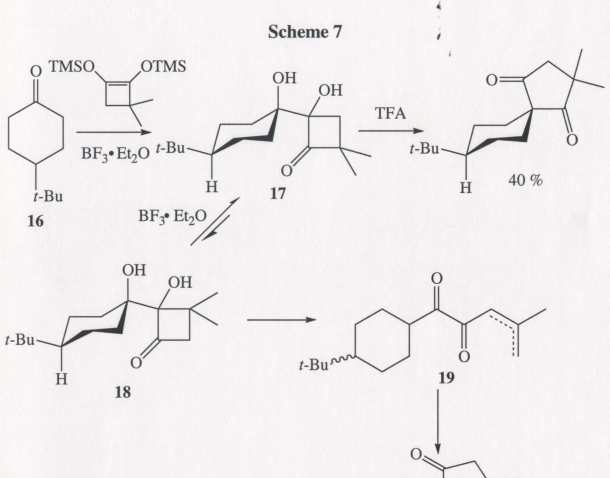
Scheme 6



13 **15**

It was concluded, based on NMR experiments, that $BF_3 \bullet Et_2O$ facilitates equilibration of the cyclobutanone intermediate **17** and leads to significant amounts of furanone by-products **20** (Scheme 7).

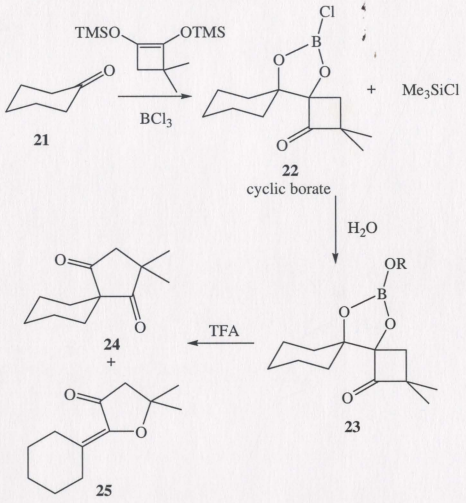
Scheme 7



BCl_3 is a superior reagent to $BF_3 \bullet Et_2O$ in that BCl_3 induces the initial aldol reaction and is incorporated itself into a cyclic borate **22**, which inhibits subsequent equilibration of the aldol products which in turn results in improved yields of the desired diketone product **24**

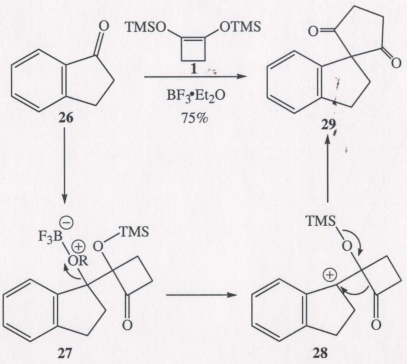
and less of the furanone by-product **25** (Scheme 8). Elliott and Burnell[7] found that using the ketone as the substrate, and not the acetal, in the BCl_3 method led to better yields.

Scheme 8



The geminal acylation reaction involving aromatic and α,β-unsaturated ketones such as **26** was found to proceed well under anhydrous conditions unlike saturated ketones, which required the addition of water to form the 1,3-cyclopentanedione (Scheme 9). Crane and Burnell[8] attributed this to benzylic or allylic stabilization of the positive charge, as in **28** for example, during the course of the rearrangement.

Scheme 9

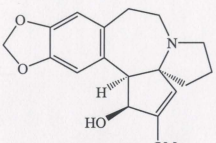


Syntheses employing geminal acylation

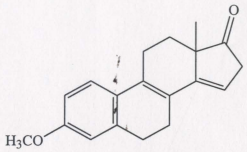
Geminal acylation is a powerful carbon-carbon bond forming reaction, and its synthetic utility is evident in the syntheses of numerous natural products (Figure 1). An anticancer agent with a unique pentacyclic structure, cephalotaxine, was prepared by Mariano's group[9] by employing geminal acylation to produce the 1,3-diketone intermediate (Scheme 10). Wu and Burnell synthesized estrone[10], isokhusimone[4], and pentalenene[11] by utilizing geminal acylation. Wu and Burnell[10] illustrated the synthetic utility of geminal acylation methodology for the formation of a five-membered ring when they proposed a route to the steriodal diene dehydroestrone - a key intermediate in the Torgov estrone synthesis (Scheme 11). Isokhusimone (Scheme 12) is a zizaane sesquiterpene derivative that can

potentially serve as a common intermediate for all such sesquiterpenes. Wu and Burnell[4] successfully employed a Lewis acid-catalysed spiro-annulation with 1,2-bis[(trimethylsilyl)oxy]cyclobutene to yield isokhusimone. The synthesis of pentalenene (Scheme 13), a biosynthetic precursor to the antibiotic sesquiterpenoid pentalenolactone, also employed this method.[11] (-)-Chokel G, a fungitoxic metabolite from the stromata of *Epichloetyphia,* was also synthesized via a geminal acylation route (Scheme 14).[12] Fredericamycin A is of considerable interest due to its antitumor properties. Bach's group[13c] completed the total synthesis (Scheme 15) of this antibiotic by utilizing geminal acylation to introduce the unusual spirodiketone functionality as did both Julia and co-workers[13b] and Parker's group.[13a]

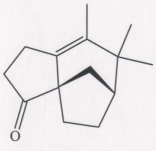
Figure 1: Natural products synthesized via geminal acylation routes



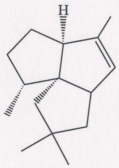
Cephalotaxine
Marino (1996)



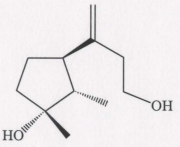
Dehydroestrone
Wu & Burnell (1988)



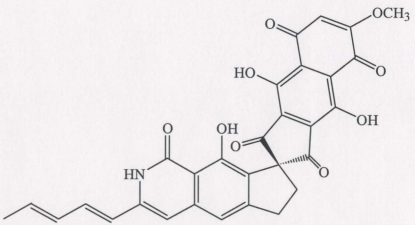
Isokhusimone
Wu & Burnell (1990)



(±)-Pentalenene
Wu & Burnell (1994)

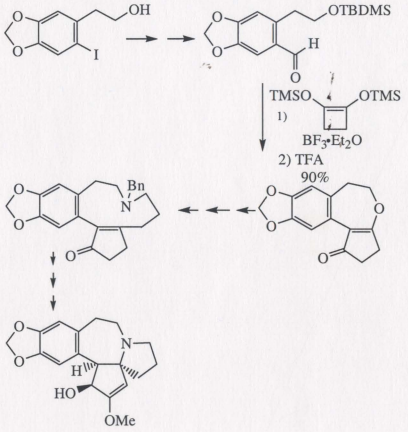


(-)-Chokel G
Ogasawera & co-workers (1998)

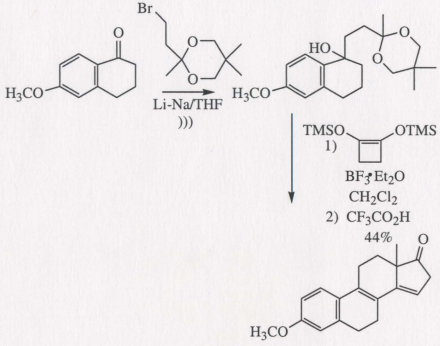


Fredericamycin A
Julia & co-workers (1993)
Bach (1994)
Parker (1985)

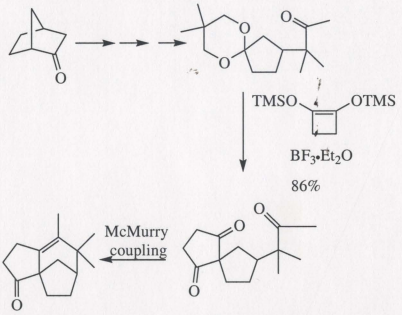
Scheme 10: Outline of Cephalotaxine Synthesis:[9]



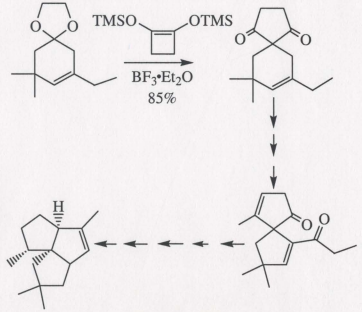
Scheme 11: Outline of Estrone Synthesis:[10]



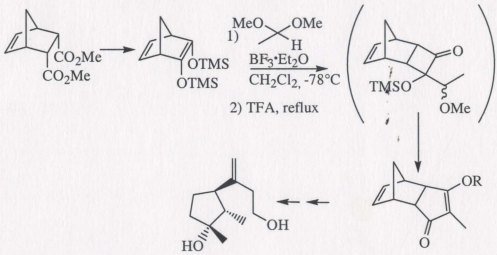
Scheme 12: Outline of Isokhusimone Synthesis:[4a, b]



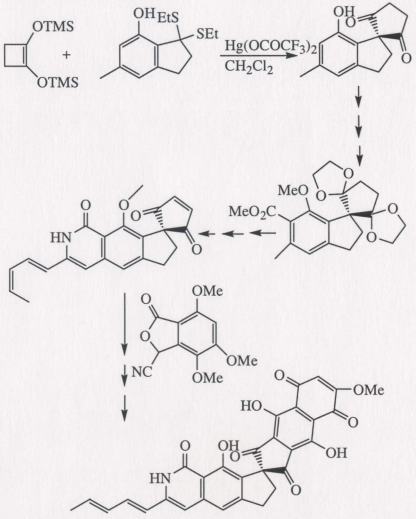
Scheme 13: Outline of (±)-Pentalenene Synthesis:[11]



Scheme14: Outline of Chokel G Synthesis:[12]



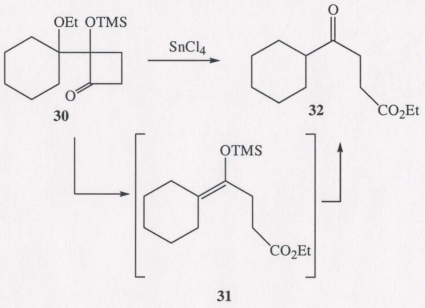
Scheme 15: Outline of Fredericamycin A Synthesis:[13c]



Reductive Succinoylation

Kuwajima[1] reported numerous cases in which the cyclobutanone ring underwent acid-catalysed cleavage to furnish a γ-ketoester such as **32** (Scheme 16). This process, known as reductive succinoylation, was accomplished in a single operation using tin(IV) chloride, and the ease of ring cleavage was related to the structure of the substrate. It was found that aldol adducts derived from cyclohexananone and cyclopentanone ketals rearrange smoothly in the presence of a small amount of the catalyst while acetone adducts proved quite stable and ring enlargement to the diketone only occurred under forcing conditions. Adducts formed from acetals were found to be inert to $SnCl_4$.

Scheme 16

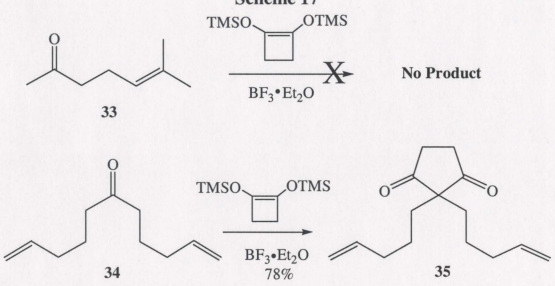


Wu and Burnell[4c] found that the yields of their geminal acylation products ranged from modest to zero when a series of acetals derived from ketones with α-methyl groups was employed. One reason proposed for the poor yields was the tendency for the 1,2-ethanediol

generated during the reaction to participate in ring-opening reductive succinoylation to give a ketoester. The best yields were obtained from unhindered cyclohexanones. It was found that steric hindrance reduced yields considerably. Acetals derived from more hindered ketones proved unreactive, and this led to the conclusion that this sensitivity to substitution places serious limits on the use of geminal acylation.

Geminal acylation with γ,δ-unsaturated acyclic ketones or acetals had been recognized as problematic for some time. In attempts to geminally acylate 6-methyl-5-hepten-2-one **33** (Scheme 17), Jenkins and Burnell[5] obtained none of the desired product. However when the double bond was one carbon further away, as in 1,10-undecadien-6-one **34** acceptable yields of the desired product **35** were obtained.

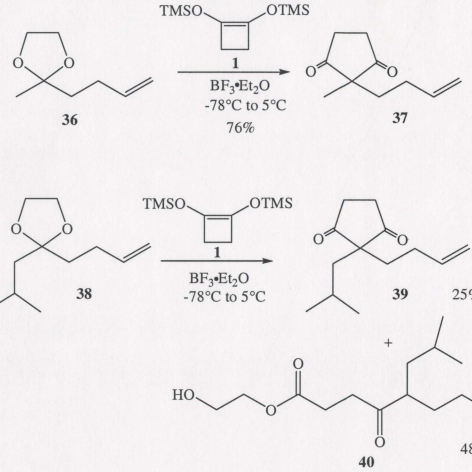
Scheme 17



Curran and co-workers[14] showed that this was the result of acid-promoted cyclization on to the double bond, which occurs at temperatures just above 0 °C. Elliott and Burnell[7] did work in this area based on Curran's example of quenching the reaction at 5 °C. The procedure was

successful in obtaining the desired diketone **37** from **36** in 76% yield (Scheme 18). The same procedure proved to be inadequate for acetal **38** giving only a 25% yield of the desired product **39** and 48% of the γ-ketoester **40** which results from acid-mediated rupture of the cyclopentanedione via reductive succinoylation. Attempts to prevent this through the use of different acetals and variation of the reaction conditions failed.

Scheme 18



β-Turn Peptidomimetics

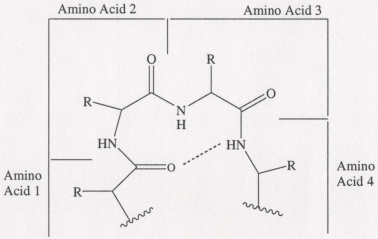
Peptides and proteins play a key role in many medical disorders. There is a growing number of biologically active peptides that have potential for the development of new

therapeutics. Small linear peptides are active as hormones, neurotransmitters, and neuromodulators and are thus of much interest to medicinal chemists. The geminal acylation reaction has the potential to be useful for the production of mimics for the turn regions present in naturally occurring peptides. Native peptides pose numerous limitations in medical applications such as poor transport properties, rapid excretion by the liver and kidneys, rapid metabolism and low oral activity.[15] All these disadvantages prevent peptides from becoming drugs and stimulate the quest for peptide mimics. In addressing these limitations, the modification of peptides into mimetics with specific physical, chemical and biological characteristics were developed, resulting in a class of compounds known as peptidomimetics. These compounds act as substitutes for peptides in their interaction with receptors and generally show higher metabolic stability, better bioavailability, and longer duration of action.[16] Peptidomimetics are typically derived from peptides by partly or completely removing the amide bonds while retaining essential amino acid side chains in a defined spatial relationship. A generally applicable and successful method for the development of peptidomimetics has been the production of conformationally restricted analogues that enable peptides to have improved metabolic stability since they are more resistant toward proteases. The first of two important factors to consider in peptidomimetic design is that a complementary fit must take place between the desired peptidomimetic and the receptor. Second, by the placement of certain structural elements such as functional groups, polar regions and hydrophobic regions must be in positions that favor interactions like hydrogen bonding, electrostatic interactions and hydrophobic interactions.[17]

α-Helices, β-sheets, and reverse turns are the three basic building blocks for all secondary and tertiary peptide structures and are the result of intramolecular hydrogen bonding. Research in the area of mimetics has focused strongly on two turns: α-turns and β-turns. The α-turn is a three amino acid residue reverse turn. In α-turns, the carbonyl of the first amino acid is aligned to form an intra-chain hydrogen bond with the amide hydrogen of the third amino acid residue, resulting in a pseudo-seven membered ring. α-Turns are not as widespread as β-turns.

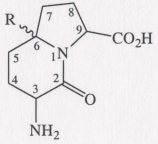
A β-turn is a segment composed of four amino acids (*i* to *i+3*) that occurs when a peptide strand changes its direction. It is stabilized by a hydrogen bond between the carbonyl group of the first amino acid and the NH group of the fourth and results in a U-shaped structure containing a central amide (Figure 2).[18] The β-turn is common to many biologically active, cyclic peptides and for this reason it is the most frequently imitated secondary structure.

Figure 2: Classical view of a β-turn.



Reverse-turn mimics are usually cyclic or bicyclic dipeptide analogues, which, due to their constrained structure, force a peptide chain to fold back upon itself.[19] Many of these molecules feature the 1-azabicyclo[4.3.0]nonane skeleton (Figure 3). This basic ring system can also encompass heteroatom analogues in which a carbon is replaced by sulfur, oxygen, or nitrogen. This can pose a disadvantage of reduced stability under acidic conditions. All of the compounds reported in literature have substitution at C-6 as R = H. Consequently, the production of analogues with R ≠ H is a fertile area for investigation and pharmacological interest. Compounds with this azabicyclo[4.3.0]nonane skeleton have proved useful as β-turn mimics. Many others are still known only as potential β-turn mimics based on conformational analysis.

Figure 3:
Azabicyclo[4.3.0]
nonane skeleton



Numerous examples of β-turn peptidomimetics can be found in the scientific literature. Moeller[20] synthesized a thyrotrophin releasing hormone (TRH) analogue **41** (Figure 4). The release of thyroid-stimulating hormone from the anterior pituitary gland is controlled by the hypothalamic tripeptide TRH. TRH also displays effects in the brain, blood and spinal cord. It was found that both potency and binding were dependent on the ring

fusion stereochemistry. The *R* isomer was found to be much more potent than the *S* isomer.

Compound **42** (Figure 4) was designed by Kahn[21] as a non-peptide mimic of an immunostimulating peptide, tuftsin. The naturally-occurring tetrapeptide displays immunostimulatory activity. This non-peptide mimic blocks tuftsin's stimulating effect in sheep red-blood cells assay in a dosage-dependent fashion.

(-)-A58365A **43** (Figure 4) is a natural product synthesized by Clive[22] and is a powerful inhibitor of angiotensin converting enzyme (ACE). As a result, the synthesis of analogues of this compound are important for the design of blood pressure lowering drugs.

Nagai and co-workers[23] synthesized **44**, a gramicidin S (GS) analogue, in which a sulfur atom is incorporated into the 1-azabicyclo[X.Y.0] alkane skeleton. GS is a cyclic decapeptide antibiotic that contains two β-turns in its structure. The antibiotic activity of this analogue was found to be the same as that of natural GS when **44** was incorporated in the turn region of GS.

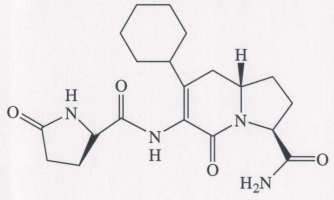
The peptide L-prolyl-L-leucylglycinamide (PLG) has been shown to control dopamine neurotransmission within the central nervous system. Compound **45** (Figure 4) was found to display a pharmacological profile similar to PLG in terms of activity in binding to dopamine receptors.[24]

Elliott and Burnell[7] disclosed for the first time a method to produce 6-alkyl-substituted analogues of the 1-azabicyclo[4.3.0] nonane system **46** (Figure 4). The synthetic sequence was geminal acylation using 1,2-bis[(trimethylsilyl)oxy]cyclobutene or methylated analogues followed by Beckmann rearrangement and cyclization of the amidic nitrogen onto

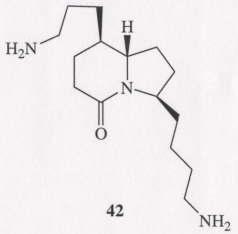
the terminal double bond. The biological activities of 6-substituted compounds such as **46** have not been determined.

These examples illustrate that there is a wide variety of potential targets for β-turn peptidomimetics which contain the 1-azabicyclo[4.3.0]nonane (indolizidine) skeleton.

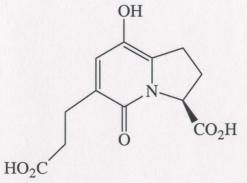
Figure 4: Examples of β-turn peptidomimetics.



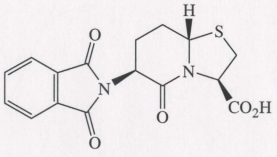
41



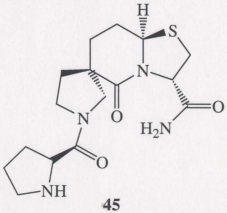
42



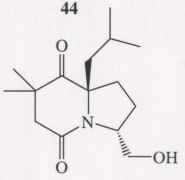
43



44



45



46

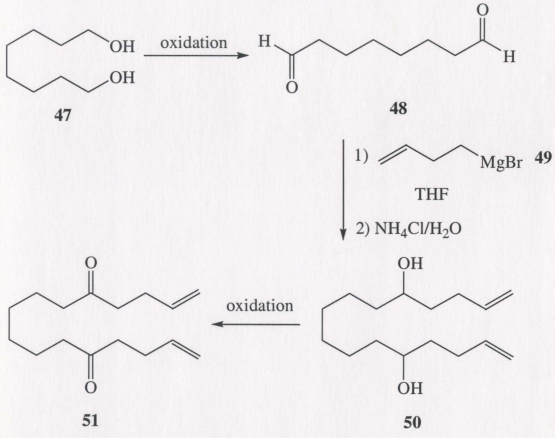
The aim of this project is to provide a synthetic route to produce tethered β-turn peptidomimetics. This project will provide molecules of considerable biochemical interest since the site of the incorporation of the first peptidomimetic moiety would restrict the site where the second might be incorporated since they are joined. The biochemical ramification of such tethering is unknown since these molecules have not been previously made.

Results and Discussion

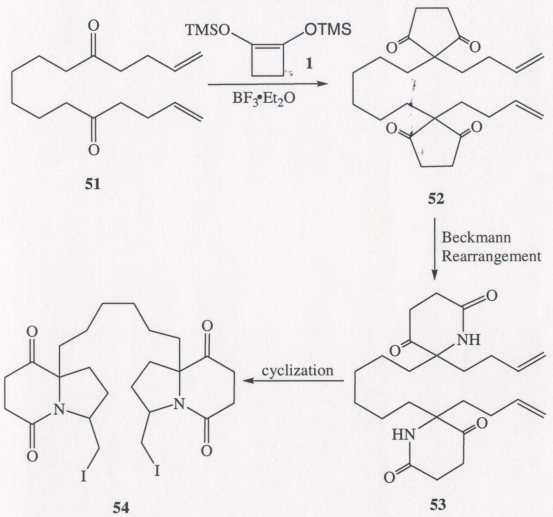
Initial Attempt to synthesize a tethered β-turn peptidomimetic

A synthetic route to produce a tethered β-turn peptidomimetic was proposed based on previous work in that area by Burnell and coworkers.[7] It was first proposed that the 5,6-fused bicyclic system, **54**, could be synthesized by the route outlined in Scheme 19.

Scheme 19



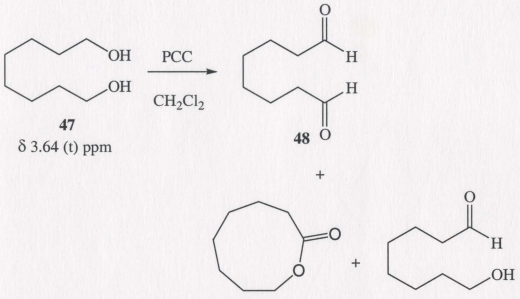
Scheme 19 (continued)



The synthetic sequence began with 1,8-octanediol **47**. An oxidation was performed to give **48**. In initial attempts, pyridinium chlorochromate was used as the oxidant.[25] This proved to be unsatisfactory since the extraction of the product from the gum-like crude mixture was inefficient. Only a minimal amount of the desired product **48** was obtained . This product was contaminated with mono-aldehyde **56** and the corresponding lactone **55** (Scheme 20). Both of these compounds exhibit diagnostic signals in the ^{1}H NMR spectrum of the crude mixture. Triplets at δ 4.07 and 2.37 ppm were attributable to the methylene hydrogens adjacent to the oxygen and carbonyl groups of the lactone **55**. The CH_2-OH signal of 1,8-

octanediol appeared as a multiplet at δ 3.64 ppm. The presence of the hydroxyaldehyde **56** was supported by the presence of a triplet at δ 3.66 ppm. The lactone **55** was likely derived by cyclization of the hydroxyaldehyde **56** to give a lactol, which underwent further oxidation to provide the lactone.

Scheme 20



47
δ 3.64 (t) ppm

48

55
δ 4.07 (t) ppm
δ 2.37 (t) ppm

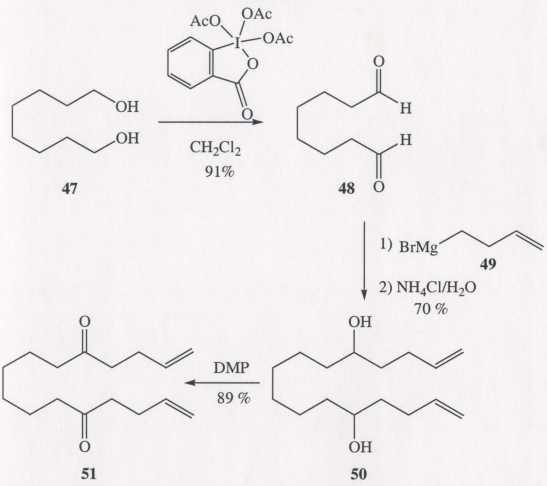
56
δ 3.66 (t) ppm

A modified Swern oxidation was also attempted using a combination of DMSO/P_2O_5/Et_3N.[26] This reaction produced the desired product, but it was contaminated with DMSO and a salt of Et_3N. Contamination was especially prevalent in large scale reactions. It was hoped that dialdehyde **48** could be obtained which was sufficiently homogeneous to use in the next step without purification.

The oxidation was improved in both yield and purity of the crude dialdehyde by using

Dess-Martin periodinane[27] as the oxidizing agent (Scheme 21). The desired product **48** was confirmed by its ^{1}H NMR spectrum, which included a triplet at δ 9.78 ppm corresponding to the aldehyde, and a carbonyl resonance at δ 202.9 ppm in the ^{13}C NMR spectrum. No characteristic peaks were present for either the mono-aldehyde product **56** or the lactone **55**.

Scheme 21



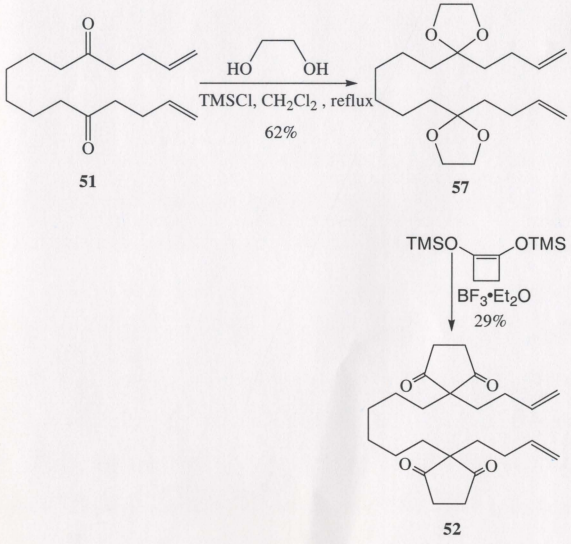
This procedure was quite successful, but often resulted in the presence of an impurity evident from NMR signals in the aromatic region, tentatively identified as 1-acetoxy-1,2-benziodoxol-3(1*H*)-one.[27] It had been reported that work-up with saturated aqueous sodium bicarbonate containing sodium thiosulfate or solely aqueous 1 M NaOH would hydrolyze this product completely to water-soluble 2-iodosobenzoate; however, this was not the case

in using the 1,8-octanediol substrate **47**. This problem was finally overcome by washing the product with saturated aqueous sodium bicarbonate containing sodium hydroxide. This method appeared to quench any Dess-Martin periodinane by-product and afforded 1,8-octanedial in 91% yield. A double Grignard reaction was performed between 1,8-octanedial **48** and the organomagnesium reagent derived from 4-bromo-1-butene **49**. The 16-carbon diol **50** was obtained in 56% yield. During the double Grignard reaction, both the *meso* and the racemic diol were presumably produced. However, no doubling of signals was observed in the ^{13}C NMR spectrum, which showed only eight carbon signals. This is likely a consequence of the distance between the elements of asymmetry. The ^{13}C NMR spectrum provides strong support that the desired molecule was obtained. The disappearance of the aldehyde signal of **48** at δ 202.6 ppm and the appearance of the alkene signals at δ 138.8 and 115.2 ppm are particularly telling. Subsequent oxidation of **50** with Dess-Martin periodinane furnished the diketone **51** in 89 % yield.

The next step of the sequence was a geminal acylation reaction on **51** with 1,2-bis[(trimethylsilyl)oxy]cyclobutene **1**. Several products were formed. The problem did not appear to be that of an incomplete reaction since no starting diketone was apparent by TLC. Prior to preparative thin layer chromatography, the mass recovery of material was more than 100%. The ^{1}H NMR spectrum of the crude mixture displayed a cluttered alkane region, which may indicate polymerization. It was proposed that this resulted in the formation of insoluble material. After preparative thin layer chromatography was performed, many products were isolated, but only in very small amounts. The desired product **52** was obtained

in only 8% yield. It was decided to attempt the reaction again using the corresponding acetal **57**. Acetals are often more reactive since they coordinate more strongly to the Lewis acid than the parent carbonyl.[1] The double acetal was synthesized employing a method by Chan,[28] which involved the use of ethylene glycol and chlorotrimethylsilane (Scheme 22). Reactions that employed *p*-TsOH to form acetals were avoided due to concerns about adverse reaction with the double bonds.

Scheme 22



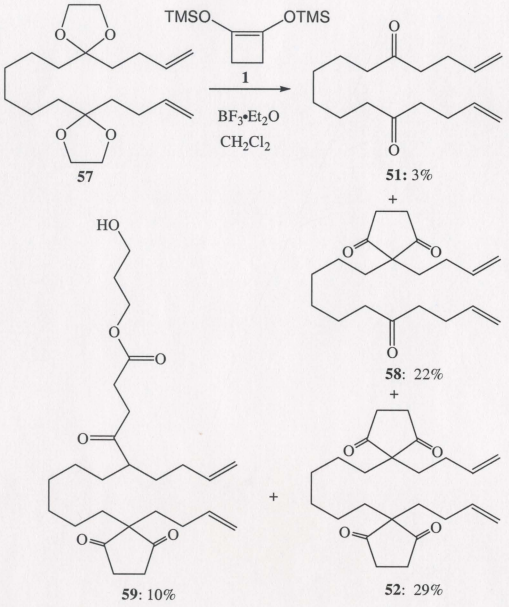
51 **57** **52**

The geminal acylation reaction on the diacetal **57** was slightly more successful, resulting in a 29% yield of **52**. Various modifications of the reaction conditions were tried, such as variations in the reaction time and temperature, but no improvement in yield was achieved. It was proposed that increasing the number of equivalents of 1,2-bis[(trimethylsilyl)oxy]cyclobutene **1** might result in a better yield of the diketone product. However, when the number of equivalents of **1** was increased from four to eleven in the reaction of acetal **57**, the yield was once again 29%.

The geminal acylation reaction of **57** afforded diketone **51** (3%), the doubly reacted product **52** (29%), the mono-reacted product **58** (22%), and the mono-reductive succinoylation product **59** (10%) (Scheme 23). From the ^{1}H NMR spectrum of the reaction mixture it was clear that the starting acetal **57** was consumed since the acetal singlet at δ 3.92 ppm was no longer present. The doubly reacted product **52** showed a singlet at δ 2.72 ppm, which corresponds to the hydrogens of the 1,3-cyclopentanedione ring, and the olefinic signal was shifted upfield to δ 5.63 ppm from δ 5.82 ppm for the diacetal **57**. The ^{13}C NMR spectrum exhibited signals for ten unique carbon atoms as expected, with the quarternary carbon signal at δ 60.8 ppm. The ^{1}H NMR spectrum for the mono-reacted product **58** showed two multiplets for the alkene hydrogens, one of which is near the ketone (δ 5.70 ppm) and one near the cyclopentanedione (δ 5.85 ppm). This unsymmetrical molecule showed 18 signals in its ^{13}C NMR spectrum. The unsymmetrical mono-reductive succinoylation product **59** also gave two multiplets for the alkene hydrogens, as in the mono-reacted product. The

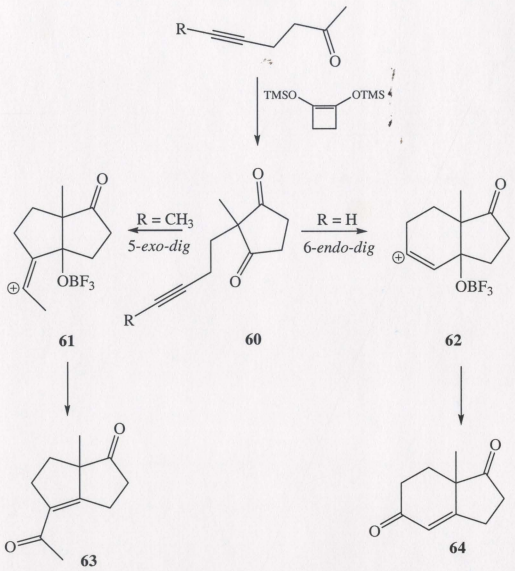
ester portion of the product gave new signals in the ^{1}H NMR spectrum at δ 4.23 and 3.82 ppm, and the ^{13}C NMR spectrum included a new signal at δ 173.3 ppm, which is consistent with an ester. The presence of the mono ring-opened product suggested that the double reductive succinoylation product might have formed as well, but it would be very polar due to the presence of eight oxygen atoms. As a result, this material may not have been isolated from thin layer chromatography and would have accounted for the loss of some material.

Scheme 23



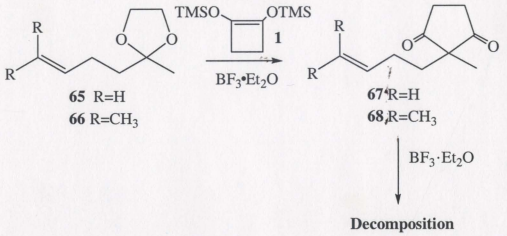
Curran and co-workers[14] claimed that as steric crowding in the vicinity of the acetal carbon increases, the yield of geminal acylation product decreases. It was proposed that the failure is caused by a breakdown in the initial Mukaiyama-aldol step. They also reported poor yields when diketone products had unsaturation in the δ-position.[14] The promotion of cationic π-cyclization of alkynyl and alkenyl 1,3-cyclopentanediones was found to be effected by the nucleophilic additives, and Lewis acids such as $BF_3 \bullet Et_2O$. They reported that the cyclopentanedione **60** (Scheme 24) could be observed by TLC and sometimes even isolated. However, it underwent a cyclization process involving the alkyne and the ketone. The mechanism of this process is not entirely known, but the regioselectivity of the reactions was consistent with the involvement of vinyl cation intermediates, as summarized in Scheme 24. Alkynyl ketone cyclization was promoted by $BF_3 \bullet Et_2O$ and occurred either by a 5-*exo-dig* process, to lead to **61** which subsequently formed **63**, or via a 6-*endo-dig* process to lead to **62** to result in **64**. The more stable cation is generated by 6-*endo-dig* and is presumably more favorable.

Scheme 24



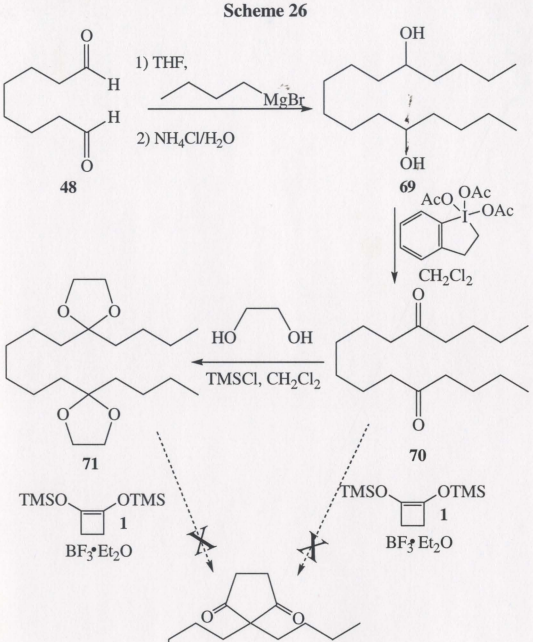
Curran and co-workers[29] reported that by controlling the reaction time and temperature, conversions of **65** to **67** and **66** to **68** both occurred smoothly (Scheme 25). However, extended exposure of **67** or **68** to $BF_3 \bullet Et_2O$ without any nucleophile resulted in complete decomposition. Despite Curran's disclosure of reducing π-catalysed cyclization by controlling reaction time and temperature, his conditions failed to produce results differing from previous attempts when employing hexadeca-1,15-diene-5,12-dione **51** or its acetal **57**.

Scheme 25



To test the hypothesis that Lewis acid-catalyzed π cyclization was responsible for the poor yields of geminal acylation products the corresponding 1,3-cyclopentanedione **72** without the unsaturation in the δ position was targeted (Scheme 26). A Grignard reaction was carried out on 1,8-octanedial **48** with the organomagnesium reagent derived from bromobutane. The resulting diol **69** was oxidized using Dess-Martin periodinane to give diketone **70**. Trials were done on both this diketone and its corresponding acetal **71** which was prepared from **70** upon reaction with ethylene glycol in the presence of chlorotrimethylsilane. Neither the diketone **70** nor the diacetal **71** gave any 1,3-cyclopentanedione **73** upon treatment with **1** and BF_3•Et_2O under standard conditions. The ^1H NMR spectrum of the recovered material showed signals only for the starting diketone **70**. No signals were present that could be attributed to the desired product **72**.

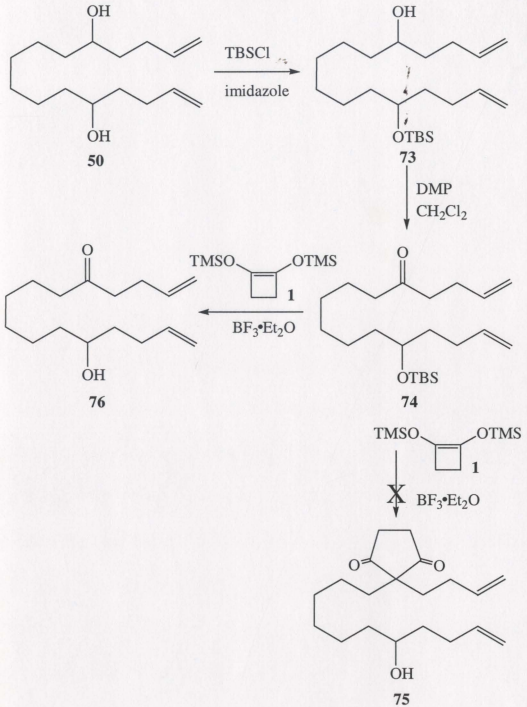
Scheme 26



The geminal acylation reaction was also performed on the mono-protected product **74**. It was thought that better yields may be obtained by doing one geminal acylation at a time. Initially, mono-protection the diol **50** as a silyl ether was attempted by treating the diol

with TBSCl and imidazole.[30] The substrate was slow to react and required heating at reflux for 12 hours to yield **73** in 35% yield. There was also 23% of the starting diol **50** recovered, but no doubly protected diol was obtained. The Dess-Martin oxidation proceeded efficiently to give **74**. Reacting **74** with **1** and $BF_3 \cdot Et_2O$ failed to produce any of the mono-1,3-cyclopentanedione **75** as did its corresponding acetal. 12-Hydroxy-hexadeca-1,15-dien-5-one **76** was recovered in both cases (Scheme 27).

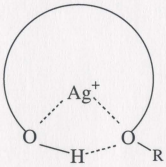
Scheme 27



The mono-protection of the diol by a method of Bouzide and Sauvé[31] was assessed. They mono-benzylated symmetrical primary and secondary diols in the presence of silver(I) oxide. This method had resulted in very good yields of mono-protected products, and not mixtures

of starting material, mono, and bis-reacted products. They proposed that selectivity was the result of complexation of the diol's oxygen atoms with the silver atom, a Lewis acid, as shown in Scheme 28. The coordination increases the acidity of one hydroxylic hydrogen, the one not involved in intramolecular hydrogen bonding, which thus favors benzylation.

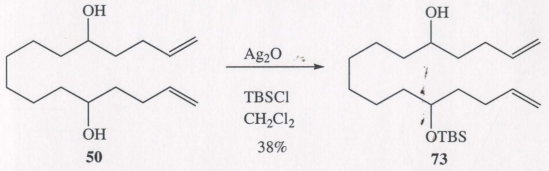
Scheme 28



R = H, benzyl, alkyl

Based on the success of this method, mono-protection of diol **50** was attempted. As a modification to Sauvé's procedure, however, it was decided to employ a silyl ether as the protecting group, which to the best of our knowledge had not been previously attempted. This reaction was successful in producing the desired mono-protected alcohol **73** in 38% yield when using *tert*-butyldimethylsilyl chloride (Scheme 29). After filtering the crude product through neutral alumina to remove the silver(I) oxide, there was no starting material recovered or bis-reacted product obtained.

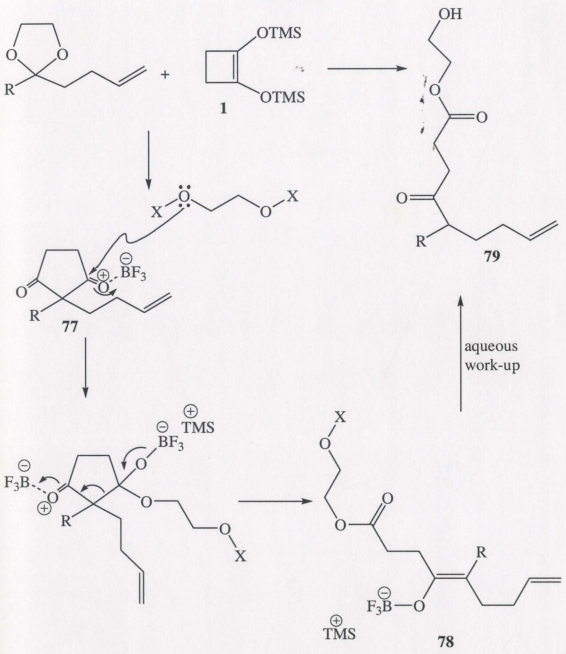
Scheme 29



Reductive Succinoylation

The mono-reductive succinoylation-1,3-cyclopentanedione product **59** (Scheme 23) was also obtained in the geminal acylation reaction of the diacetal **57**. Kuwajima *et al.*[1] reported the process of reductive succinoylation; a process in which the cyclopentandione ring underwent acid-catalysed cleavage to produce a γ-ketoester. This process was presumed to occur via the mechanism shown in Scheme 30. The Lewis acid complexed to one of the carbonyl oxygen atoms of the diketone **77**, after which nucleophilic attack occurred. Regeneration of a carbonyl group occurred with the collapse of the ring to generate an enol **78**. Aqueous work-up resulted in **79**.

Scheme 30

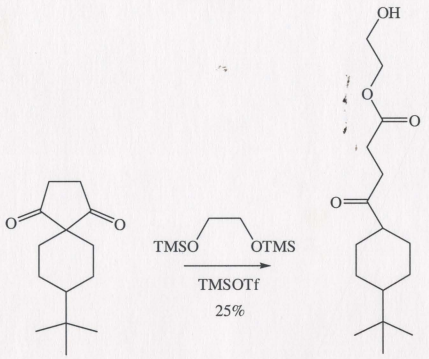


Wu and Burnell[4] had found that, when employing a series of acetals derived from ketones bearing α-methyl groups and 1,2-ethanediol, the yields of their geminal acylation products ranged from modest to non-existent. One reason proposed for the poor yields was the tendency for the 1,2-ethanediol generated during the reaction to participate in reductive

succinoylation.

In reality there should be no ethylene glycol present in the reaction medium until work-up. The reaction pathway does involve the removal of the acetal as well as both (trimethylsilyl)oxy groups from the 1,2-bis[(trimethylsilyl)oxy]cyclobutene. It is proposed that these groups join to form 1,2-bis[(trimethylsilyl)oxy]ethane, which poses the question as to how this silylated ethylene glycol can open the ring. Hwu[32] reported a procedure for making acetals using 1,2-bis[(trimethylsilyl)oxy]ethane and trimethylsilyl triflate. This purportedly works via the TMS part of the triflate, essentially TMS^+, adding to the carbonyl. The carbonyl is then activated towards attack by the modestly nucleophilic oxygen atoms of the 1,2-bis[(trimethylsilyl)oxy]ethane. Attempts were made in this research to encourage acid-catalysed ring opening of 8-*tert*-butylspiro[4.5]decane-1,4-dione **80** using 1,2-bis[(trimethylsilyl)oxy]ethane and trimethylsilyl triflate (Scheme 31). This route was effective in producing the ring-opened product **81** in 25% yield. Starting material was recovered in 15% yield. The ^{1}H NMR spectrum revealed signals at δ 4.23 and 3.82 ppm which are indicative of the ester-type product. There were no other products evident from the ^{1}H NMR spectrum of the crude mixture. It was expected that two ring-opened products would be obtained, one axial and the other equatorial. The doubling of the ester carbon peaks in the ^{13}C NMR spectrum suggests that both were indeed formed. From these results it was concluded that the geminal acylation reaction proceeded in a way which was consistent with the proposed mechanism (Scheme 30).

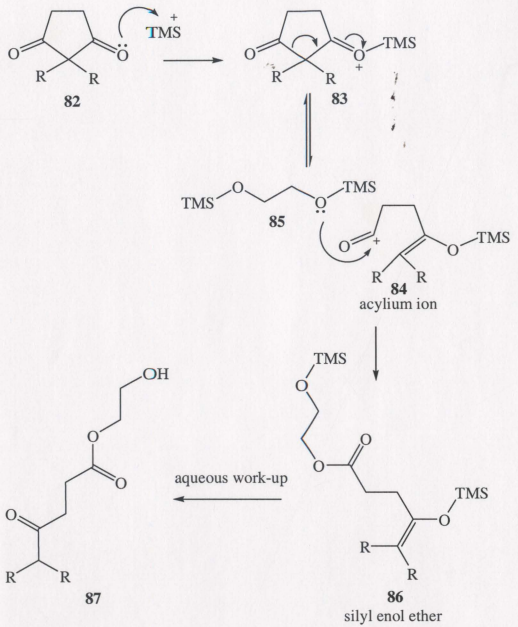
Scheme 31



80 **81**

It is proposed that the geminal acylation reaction involves the generation of TMS^+ which leads to the production of 1,2-bis[(trimethylsilyl)oxy]ethane **85**. It is feasible then that the TMS^+ could add to one carbonyl group thereby causing the ring to open. Attack of the resulting acylium ion **84** by the 1,2-bis[(trimethylsilyl)oxy]ethane **85** then affords the product **87** upon aqueous work-up. (Scheme 32).

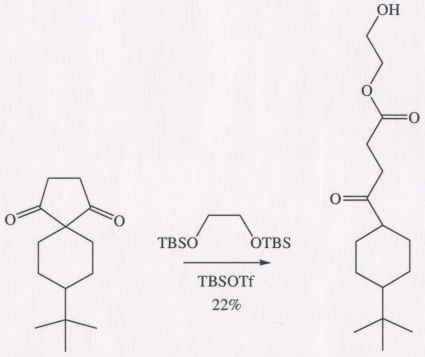
Scheme 32



It was proposed that the use of a bulkier silyl group would avoid the problem of ring-opening. To investigate this, 1,2-bis[(*tert*-butyldimethylsilyl)oxy]ethane was produced. It was proposed that the bulkier TBS group might not activate the carbonyl as well as TMS, and thus it might not be as susceptible to attack by the oxygen atoms of the ethylene glycol. If this were to be successful, then it would be only a matter of ensuring that the 1,2-bis[(*tert*-

butyldimethylsilyl)oxy]cyclobutene were reactive enough to participate in the geminal acylation reaction. 8-*tert*-Butylspiro[4.5]decane-1,4-dione **80** was added to 1,2-bis[(*tert*-butyldimethylsilyl)oxy]ethane and *tert*-butyldimethylsilyl triflate, and was stirred at -78 °C (Scheme 33). It was disappointing that this resulted again in the formation of ring opened product **81**.

Scheme 33



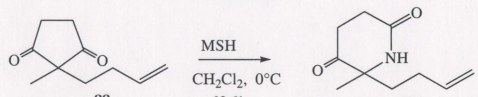
80 **81**

In seeing this result it was concluded that drastic modifications would need to be made to the geminal acylation reaction for it to be successfully applied to the synthetic problem at hand. It appeared that the problem arose from the ethylene glycol derivative causing the desired product to open, hence a much different protecting group must be employed to eliminate this problem.

Beckmann Rearrangement Investigation

Concurrent with the work on the geminal acylation reaction described above, some work was done to extend the methodology to the synthesis of lactams. More specifically, Beckmann rearrangements of diketones obtained from the geminal acylation reaction were studied. Previously in the Burnell lab, it was established that conventional Beckmann conditions, such as using hydroxylamine-*O*-sulfonic acid in refluxing formic acid,[33] led to the destruction of the starting material when the substrate contained an alkene δ to the 1,3-cyclopentanedione.[7] Diketones derived from 1,2-bis[(trimethylsilyl)oxy]cyclobutene **1** underwent a double Beckmann rearrangement and hydrolysis process. As a result, a gentler aminating reagent, *O*-mesitylenesulfonylhydroxylamine (MSH) was employed.[7] Using MSH and **88** (Scheme 34), oxime formation and migration occurred under very mild conditions, 0° C in CH_2Cl_2, to produce lactam **89**.

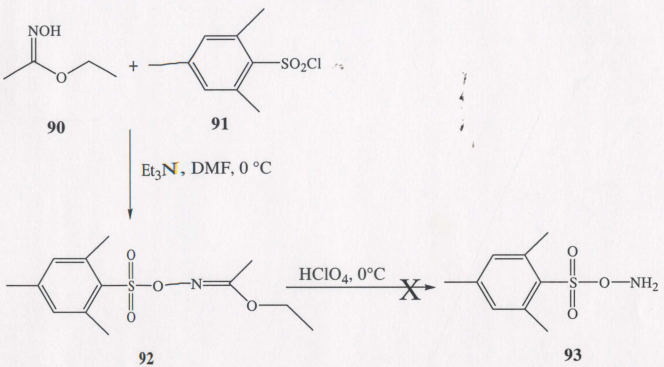
Scheme 34



88 **89**

Based on these results, it was decided to use this methodology to produce lactams. Unfortunately, MSH is not commercially available. It is prepared from ethyl acetohydroxymate **90** and 2-mesitylenesulfonylchloride **91** as shown in Scheme 35.[34] MSH, **93** can be stored below 0° C, but only for a short period of time before decompostion.

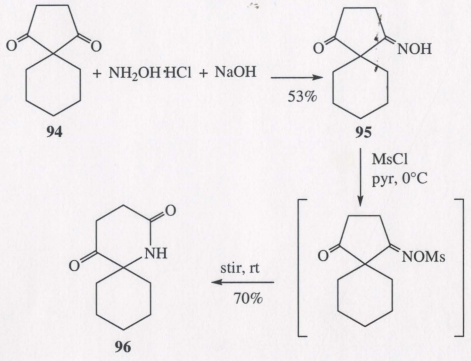
Scheme 35



It was found that it was difficult to produce this reagent reproducibly. Numerous attempts to repeat it were made but only once was the intermediate **92** obtained, and its conversion to **93** failed. An alternative, more reliable process to form the lactam was required. It was decided to attempt a method where the oxime was formed first, followed by its mesylation and subsequent rearrangement. Initial attempts were performed on dione **94** using standard conditions of reacting the ketone and hydroxylamine hydrochloride in the presence of sodium hydroxide in 95% ethanol and water (Scheme 36).[35] A mixture of hydroxylamine hydrochloride and sodium hydroxide was used in the reaction as opposed to solely hydroxylamine because the free amine was not particularly stable. This produced the desired oxime **95** in moderate yield. Mesyl chloride was then added to the oxime. The mesylate was not isolated. Rearrangement seemed to take place spontaneously to form the

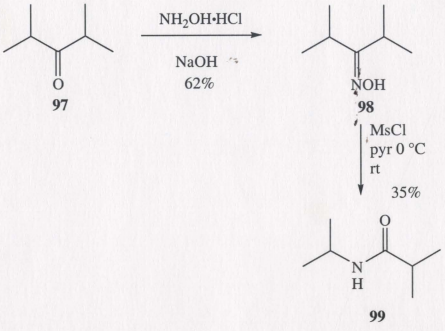
corresponding lactam **96**.

Scheme 36

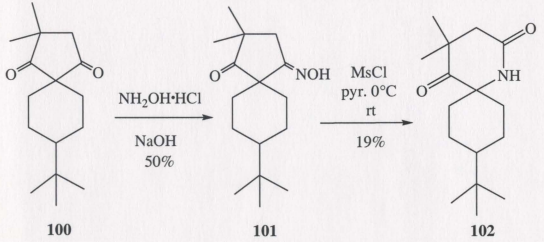


Overall, the reaction sequence gave moderate yields. 2,4-Dimethyl-3-pentanone **97** (Scheme 37) and 8-*tert*-butyl-2,2-dimethylspiro[4.5]decane-1,4-dione **100** (Scheme 38) were then tested under the same conditions and the method was found to be successful in both cases. Despite the low yields, the results were quite pleasing in the second case where the reaction occured only at the less hindered carbonyl group to give mono-reacted **101**. The lactam **102** that was subsequently obtained also had the nitrogen inserted in the correct position. Seeing these results it was decided to exercise this method to form the lactam in the synthetic sequence to produce a tethered lactam.

Scheme 37

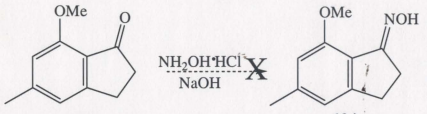


Scheme 38



Indanone **103** failed to form the oxime **104** and only returned starting material (Scheme 39). This may be attributed to the stability of the system due to the conjugation of the ketone and the benzene ring and was not foreseen as a problem in the case of 1,3-cyclopentanedione **52**.

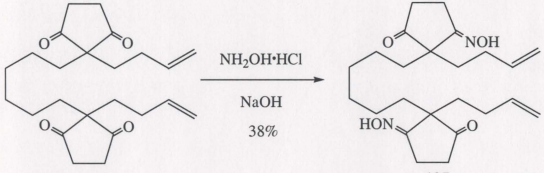
Scheme 39



103 **104**

Upon finding success with this method, the oxime of the bis-1,3-cyclopentanedione, **52** was formed (Scheme 40). This was successful and resulted in a 38% yield of double oxime **105**. This result was pleasing due the possibility that four oximes could have formed. The presence of two diastereomers was detectable in the ^{13}C NMR spectrum, which exhibited a doubling of some of the signals.

Scheme 40

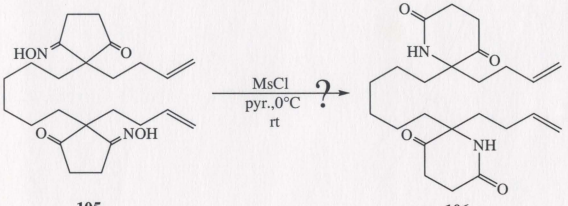


52 **105**

The rearrangement of the oxime **105** to the desired lactam was attempted on the very small amount of material that was on hand (Scheme 41). The crude material obtained from the rearrangement was only enough to give a poorly-resolved ^{1}H NMR spectrum. In comparison to the ^{1}H NMR spectrum of the starting material, it appeared that the peaks at δ 2.85 and 2.55 ppm, which corresponded to the hydrogens next to the oxime and the

carbonyl disappeared and a peak at δ 2.91 ppm appeared. Despite not having enough product to characterize lactam **106,** it can be concluded with some degree of confidence that the desired product was present. However, due to lack of 1,3-cyclopentanedione **52** this route was not repeated.

Scheme 41



105 **106**

Conclusions and Considerations for Future Work

The initial goal of employing geminal acylation to form a tethered peptidomimetic was slow but promising. Some of the desired 1,3-cyclopentandione **52** was obtained, but many other products were also isolated. The yields for each of these products were low. Through the course of this research, it was determined that the problems with the geminal acylation stemmed from using ethylene glycol to form the acetal. This resulted in problems associated with ring-opening that may have formed highly polar, doubly ring-opened material that could not be isolated from the column. One idea to be investigated is the use of another acetal. Bulkier acetals may prove to be more effective by prohibiting the attack of the carbonyl which may have caused the destruction of the desired cyclopentanedione product.

Another facet of this research was the study of Beckmann rearrangments of diketones obtained from the geminal acylation reaction. Despite not isolating pure tethered lactam **106** there is some room for optimism that it will ultimately be an effective method for the synthesis of the desired β-turn peptidomimetic.

Upon addressing the above complications, a route to form a chiral, non-racemic β-turn peptidomimetic can be considered. This can be approached by drawing on an already established method from previous work by Elliott and Burnell[7] where the 1,3-cyclopentanedione was asymmetrically reduced with Baker's yeast.

Experimental Section

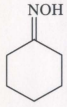
General Procedures:

Uncorrected melting points were determined using Fisher-Johns hot stage apparatus. IR spectra were recorded on the Bruker Tensor 27 either as thin films (liquids) or very thin uniform wafers (solids). ^{1}H NMR spectra were obtained in $CDCl_3$ on either a 300 MHz General Electric GE-300 NB spectrometer or a 500 MHz Bruker Avance spectrometer with a TXI inverse-detect gradient probe. Chemical shifts are reported in ppm and are specified relative to internal tetramethylsilane ($\delta = 0.00$ ppm) for ^{1}H NMR, and coupling constants are in Hz. The abbreviations used to describe multiplicities in the ^{1}H NMR spectra are as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and b (broad). The ^{13}C NMR spectra were recorded at 125 MHz on the Bruker Avance 500 MHz instrument, and the shifts are measured relative to solvent resonance ($\delta = 77.23$ ppm) for deuterated chloroform. Low resolution mass spectral data was recorded on the V.G. Micromass 7070 instrument.

Dichloromethane and toluene were distilled from calcium hydride and stored over 4 Å Molecular Sieves. THF was distilled from sodium metal/benzophenone immediately prior to use. Compound 1 was prepared by the method of Bloomfield and Nelke.[2] Flash chromatography used 240-400 mesh silica gel. IBX was synthesized based on a method of Santagostino *et al.*[36] Dess-Martin periodinane was made using a procedure developed by Dess and Martin.[28]

General procedure for oxime formation. Compounds **107**, **95**, **98**, and **105** were prepared based on a method of Lachman.[35]

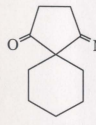
Cyclohexanone oxime (107)



107

Solid NaOH (9.93 g, 0.248 mol) was added in portions to a solution of cyclohexanone (4.43 g, 45.1 mmol), and hydroxylamine hydrochloride (3.18 g, 45.9 mmol) in 95% ethanol (16 mL) and H_2O (25 mL). The reaction mixture was heated to reflux for 5 min. The contents were cooled to room temperature then poured into a solution of concentrated hydrochloric acid (14 mL) and H_2O (88 mL). This was cooled in ice, and the crystals were collected by gravity filtration. The crystals were washed with H_2O (30 mL) and dried under vacuum to give **107** as a white solid (1.30 g, 25%). mp: 76-79°C. ^{1}H NMR ($CDCl_3$): δ 8.92 (1H, m), 2.51 (4H, m), 2.22 (4H, m), 1.63 (2H, m). ^{13}C NMR ($CDCl_3$): δ 160.9, 32.4, 27.0, 26.0, 25.8, 24.7.

Spiro[4.5]decane-1,4-dione monooxime (95)

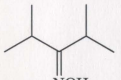


95

Solid NaOH (1.73 g, 43.2 mmol) was added in portions to a solution of cyclohexanone (1.25 g, 7.52 mmol), and hydroxylamine hydrochloride (0.448 g, 6.45 mmol) in 95% ethanol (14 mL) and H_2O (19 mL). The reaction mixture was heated to reflux for 5 min. The contents were cooled to room temperature then poured into

a solution of concentrated hydrochloric acid (4 mL) and H_2O (30 mL). This was cooled in an ice bath, and the crystals were collected by gravity filtration. The crystals were washed with H_2O (30 mL) and dried under vacuum to give **95** as a yellow crystalline solid (0.619 g, 53%). mp:142-144 °C. ^{1}H NMR ($CDCl_3$): δ 8.17 (1H, b s), 2.91 (2H, m), 2.54 (2H, m), 1.56 (10H, m). ^{13}C NMR ($CDCl_3$): δ 217.8, 166.8, 52.2, 34.5, 31.6, 25.4, 21.1, 20.9.

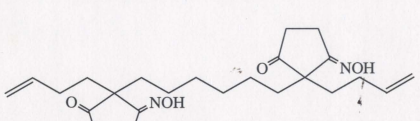
2,4-Dimethylpentan-3-one oxime (98)



98

Solid NaOH (1.83 g, 45.7 mmol) was added in portions to a solution of 2,4-dimethyl-3-pentanone (0.77 g, 6.8 mmol), and hydroxylamine hydrochloride (0.89 g, 12.8 mmol) in 95% ethanol (10 mL) and H_2O (6.5 mL). The reaction mixture was heated to reflux for 5 min. The contents were cooled to room temperature then poured into a solution of concentrated hydrochloric acid (2 mL) and H_2O (15 mL). This was cooled in an ice bath, and the precipitate was collected by gravity filtration. The crystals were washed with H_2O (30 mL) and dried under vacuum to give **98** as a colourless crystalline solid (0.55 g, 62%). mp: 38-41 °C. IR ν_{max} 3458 (b), 2965 (m), 2361 (s), 1457 (s), 847 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.66 (1H, b s), 3.20 (1H, m), 2.56 (1H, m), 1.15 (12H, m). ^{13}C NMR ($CDCl_3$): δ 169.1, 30.9, 27.7, 21.5, 19.0. MS *m/z* (%): 129 (10, M^+), 101 (18), 44 (100).

1,6-Bis((3-butenyl)-2,5-dioxocyclopentyl)hexane 2',2''-dioxime (105)



105

Solid NaOH (92.3 mg, 2.31 mmol) was added in portions to a solution of **52** (77.6 mg, 0.201 mmol) and hydroxylamine hydrochloride (26.5 mg, 0.381 mmol) in 95% ethanol (2 mL) and H_2O (1 mL). The reaction mixture was heated to reflux for 24 h. The contents were cooled to room temperature then poured into a solution of concentrated hydrochloric acid (0.1 mL) and H_2O (0.8 mL). This was cooled in ice and extracted with CH_2Cl_2 (2 × 5 mL). The organic layers were combined and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum. Flash chromatography was performed using 20% ethyl acetate/hexane as the eluting solvent to give **105** as a yellow solid (31.8 mg, 38%). mp: 113-116°C. IR ν_{max} 3373 (b), 2918 (s), 1731 (vs), 1641 (m), 935 (vs) cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.75 (2H, m*), 5.70 (2H, m), 4.94 (2H, m), 2.85 (4H, m), 2.70 (4H, s), 2.55 (4H, m), 1.76 (12H, m), 1.17 (6H, m). ^{13}C* NMR ($CDCl_3$): δ 220.4, 165.5, 137.9, 115.4, 56.7, 53.1, 38.4, 37.3, 36.6, 29.4, 29.2, 28.4, 23.9, 23.4, 22.9. MS *m/z* (%): 416 (5, M^+), 265 (26), 195 (100), 182 (93), 180 (55), 167 (57).

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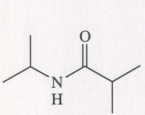
* The complexity if this signal was expected, and is consistent with the proposed structure. This material must be a mixture of diastereomers, with both a meso form and a racemic mixture. Hydrogen bonding, both intra- and intermolecular, should be possible. Furthermore, each oxime function can exist in an *E* and a *Z* geometrical isomer, and the geometrical isomerization should be an equilibrium process that may be slower then the NMR timescale.

General procedure for the rearrangement of oximes.

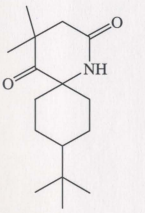
***N*-Isopropyl-2-methylpropanamide (99)**



99

A 0 °C solution of **98** (0.106 g, 0.822 mmol) in pyridine (8 mL) was charged with mesyl chloride (2.0 mL, 26 mmol). The reaction mixture was stirred and warmed to rt for 1 h. The mixture was then cooled to 0 °C and concentrated HCl (8 mL) in H_2O (20 mL) was added. The aqueous solution was extracted with ether (4 × 20 mL). The organic layers were combined and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to yield **99** (37.6 mg, 35%) as a yellow solid. mp: 71-75 °C. IR ν_{max} 3290 (b), 2966 (s), 1638 (s), 1545 (s), 1242 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.36 (1H, b s), 4.07 (1H, m), 2.30 (1H, m), 1.15 (12H, m) ^{13}C NMR ($CDCl_3$): δ 176.3, 41.2, 35.9, 22.9, 19.8. MS (EI) *m/z*: 129 (M^+).

1-Aza-9-*tert*-butyl-4,4-dimethylspiro[5.5]undecane-2,5-dione (102)



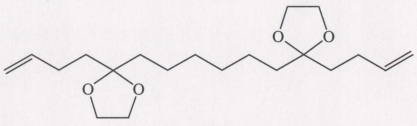
102

Solid NaOH (0.25 g, 6.2 mmol) was added in portions to a solution of 8-*tert*-butyl-2,2-dimethylspiro[4.5]decane-1,4-dione provided by Dr. Sheldon Crane (0.155 g, 0.619 mmol), and hydroxylamine hydrochloride (0.031 g, 0.45 mmol) in 95% ethanol (4 mL) and H_2O (5 mL). The reaction mixture was heated to reflux for 5 min. The contents were cooled to room temperature then poured into a solution of concentrated hydrochloric acid (3 mL) and H_2O (20 mL). This mixture was cooled in ice, and the precipitate was collected by gravity filtration. Pyridine

(1.15 mL) was added to the precipitate and the mixture was cooled to 0 °C. The solution was then charged with mesyl chloride (0.035 mL, 26 mmol) and the reaction mixture was stirred and maintained at rt for 17 h. The mixture was then cooled to 0 °C, and concentrated HCl (3 mL) in H_2O (10 mL) was added. The aqueous solution was extracted with ether (3 × 30 mL). The organic layers were combined and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to yield **102** (93.7 mg, 19%) as a beige solid. Mp: 251-253 °C. ^{1}H NMR ($CDCl_3$): δ 6.35 (1H, b s), 2.55 (2H, s), 1.79 (8H, m), 1.22 (6H, s), 1.15 (1H, m), 0.88 (9H, s). ^{13}C NMR ($CDCl_3$): δ 212.7, 170.4, 63.2, 46.8. 43.0, 42.6, 35.6, 32.7, 27.6, 24.9, 21.7.

General procedure for the protection of a ketone as an acetal. Compounds **57, 108,** and **109** were made based on a method by Chan.[28]

Hexadeca-1,15-diene-5,12-dione, bis(1,2-ethanediol) acetal (57)

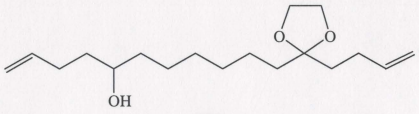


57

To a solution of 1,2-ethanediol (0.65 g, 11 mmol) in dry CH_2Cl_2 (10 mL) was added **51** (0.206 g, 0.823 mmol) followed by chlorotrimethylsilane (0.92 mL, 7.3 mmol). The reaction

mixture was heated to reflux for 48 h under N_2. Saturated aqueous $NaHCO_3$ solution (20 mL) was added and the resulting mixture was then extracted with ether (2 × 25 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. This was concentrated under reduced pressure to give **57** (0.17 g, 62%) as a yellow oil. IR ν_{max} 3076 (w), 2942 (b s), 1641 (m), 1047 (s), 908 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.81 (2H, m), 4.95 (4H, m), 3.92 (8H, s), 1.68 (8H, m), 1.51 (4H, m), 1.29 (8H, m). ^{13}C NMR ($CDCl_3$): δ 138.8, 114.3, 111.6, 65.1, 37.5, 36.5, 30.1, 29.8, 28.3, 23.9. MS *m/z* (%): 338 (1, M^+), 283 (100) 99 (28), 55 (58).

12-Hydroxyhexadeca-1,15-dien-5-one, (1,2-ethanediol) acetal (108)

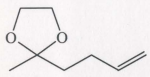


108

BF_3•Et_2O (0.33 mL, 2.60 mmol) was added to a solution of **74** (0.641 g, 1.75 mmol) in CH_2Cl_2 (20 mL) at 0 °C. This was stirred at rt for 2.5 h. 1,2-Ethanediol (0.97 mL, 17 mmol) and chlorotrimethylsilane (0.29 mL, 2.3 mmol) were added, and the mixture was heated under reflux for 46 h under N_2. Saturated aqueous $NaHCO_3$ solution (30 mL) was added and the resulting mixture was then extracted with ether (2 × 30 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. This was concentrated under reduced pressure to give a yellow oil **108** (0.396 g, 76%). IR ν_{max} 3303

(b), 2920 (s), 1642 (m), 1089 (m), 915 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.84 (2H, m), 4.96 (4H, m), 3.93 (4H, s), 3.61 (1H, m), 2.16 (5H, m), 1.48 (16H, m). ^{13}C NMR ($CDCl_3$): δ 138.9 (2C), 114.9, 114.4, 111.7, 71.7, 65.2 (2C), 37.7, 37.5, 36.7, 36.5, 30.3, 30.1, 29.8, 28.3, 25.8, 24.0. MS (CI, MeOH) *m/z*: 297 ($M^+ + 1$).

2-(3-Butenyl)-2-methyl-[1,3]dioxolane (110)

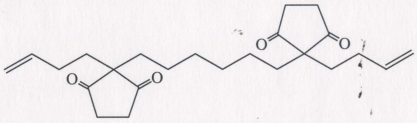


110

To a solution of 1,2-ethanediol (6.12 g, 98.6 mmol) in dry CH_2Cl_2 (70 mL) was added 5-hexene-2-one (1.2480 g, 12.72 mmol) followed by chlorotrimethylsilane (6.5 mL, 51 mmol). The reaction mixture was heated at reflux for 48 h under N_2. Saturated aqueous $NaHCO_3$ solution (100 mL) was added and the resulting mixture was then extracted with ether (2 × 80 mL). The combined organic layers were washed with brine (75 mL) and dried over anhydrous Na_2SO_4. This was concentrated under reduced pressure to give **110** (1.07 g, 59%) as a yellow oil. ^1H NMR ($CDCl_3$): δ 5.84 (1H, m), 4.98 (2H, m), 3.95 (4H, m), 2.16 (2H, m), 1.74 (2H, m), 1.33 (3H, s). ^{13}C NMR ($CDCl_3$): δ 138.7, 114.4, 110.0, 64.9, 38.5, 28.5, 24.1.

General procedure for geminal acylation. Compounds **52**, **58**, **88** were prepared based on methods previously developed in our group.[4,5,6,7]

1,6-Bis((3-butenyl)-2,5-dioxocyclopentyl)hexane (52)



52

Procedure A:

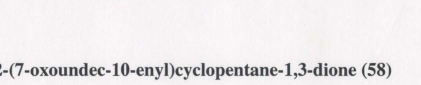
$BF_3 \bullet Et_2O$ (0.82 mL, 6.5 mmol) was introduced slowly to a solution of **51** (92 mg, 0.39 mmol) in dry CH_2Cl_2 (10 mL) at -78 °C. After 10 min, **1** (0.54 g, 2.4 mmol) in CH_2Cl_2 (3 mL) was added to the mixture. This was stirred at -78 °C for 3 h and then maintained at rt for 20 h. The mixture was diluted with ether (25 mL), water (25 mL) was added and the resulting mixture was then extracted with ether (3 × 20 mL). The combined organic layers were washed with brine (25 mL) and dried over anhydrous $MgSO_4$. Flash chromatography was performed eluting with 30% ethyl acetate/hexane to yield **52** (11.7 mg, 8%) as a yellow oil. IR ν_{max} 2929 (m), 2360 (m), 1724 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.64 (2H, m), 4.95 (4H, m), 2.72 (8H, s), 1.93 (4H, m), 1.75 (4H, m), 1.67 (8H, m), 1.18 (4H, m).^{13}C NMR ($CDCl_3$): δ 217.5, 137.6, 116.0, 60.8, 36.4, 36.0, 34.0, 29.5, 29.4, 24.4. MS *m/z* (%): 386 (3, M^+), 332 (67), 278 (59), 125 (79), 112 (100), 55 (88), 41 (86).

Procedure B:

$BF_3 \bullet Et_2O$ (1.20 mL, 9.47 mmol) was introduced slowly to a solution of **57** (0.184 g, 0.543 mmol) in dry CH_2Cl_2 (15 mL) at -78 °C. After 10 min, **1** (0.41 g, 1.8 mmol) was added to the mixture slowly. This was stirred at -78 °C for 4 h after which **1** (1.00 g, 4.38 mmol) was

added. This was stirred and warmed to and maintained at rt for 20 h. The mixture was diluted with ether (15 mL), water (15 mL) was added and the resulting mixture was then extracted with ether (3 × 40 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash chromatography was performed eluting with 30% ethyl acetate/hexane to yield **52** (60 mg, 29%) as a yellow oil.

2-(3-Butenyl)-2-(7-oxoundec-10-enyl)cyclopentane-1,3-dione (58)

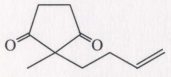


58

$BF_3 \bullet Et_2O$ (1.20 mL, 9.47 mmol) was introduced slowly to a solution of **57** (0.184 g, 0.543 mmol) in dry CH_2Cl_2 (15 mL) at -78 °C. After 10 min, **1** (0.41 g, 1.8 mmol) was added to the mixture slowly. This was stirred at -78 °C for 4 h after which **1** (1.00 g, 4.38 mmol) was added. This was stirred and maintained at rt for 20 h. The mixture was diluted with ether (15 mL), water (15 mL) was added and the resulting mixture was then extracted with ether (3 × 40 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash chromatography was performed eluting with 30% ethyl acetate/hexane to yield **58** (30.3 mg, 22%) as a yellow oil. IR ν_{max} 2925 (s), 1710 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.85 (1H, m), 5.70 (1H, m), 4.95 (4H, m), 2.71 (4H, s), 2.48 (2H, t, J = 7.4 Hz), 2.34 (4H, m), 1.92 (2H, m), 1.76 (2H, m), 1.58 (2H, m),

1.50 (4H, m), 1.18 (4H, m). ^{13}C NMR ($CDCl_3$): δ 217.5, 210.4, 137.6, 137.4, 116.0, 115.4, 60.8, 42.9, 42.0, 36.3, 36.2, 33.9, 29.8, 29.4, 28.9, 28.0, 24.4, 23.7. MS *m/z* (%): 318 (1, M^+), 167 (64), 112 (54), 83 (36), 55 (100).

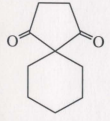
2-(3-Butenyl)-2-methylcyclopentane-1,3-dione (88)



88

To a -78 °C solution of 2-(3-butenyl)-2-methyl-[1,3]dioxolane (0.561 g, 3.94 mmol) in CH_2Cl_2 (50 mL), was added BF_3•Et_2O (5.0 mL, 39 mmol) dropwise. After 10 min **1** (1.53 g, 6.82 mmol) was introduced slowly. The mixture was stirred at -78 °C for 3 h before it was warmed to 5 °C. The mixture was stirred at this temperature for 10 min, and then the mixture was diluted with ether (30 mL) followed by H_2O (30 mL) and extracted with ether (3 × 40 mL). The combined organic layers were washed with brine (70 mL) and dried over anhydrous $MgSO_4$. The solution was concentrated under vacuum. Flash chromatography was performed eluting with 30% ethyl acetate/hexane to produce **88** (0.390 g, 60%) as a colourless liquid. ^1H NMR ($CDCl_3$): δ 5.65 (1H, m), 4.95 (2H, m), 2.78 (4H, m), 1.96 (2H, m), 1.77 (2H, m), 1.12 (3H, s). ^{13}C NMR ($CDCl_3$): δ 216.8, 137.6, 116.0, 56.5, 35.3, 34.4, 29.4, 20.3.

Spiro[4.5]decane-1,4-dione (94)

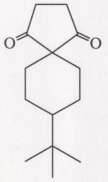


94

To a solution of cyclohexanone (0.418 g, 4.26 mmol) and BF_3•Et_2O (0.81 mL, 6.4 mmol) in CH_2Cl_2 (15 mL) at -78 °C was added **1** (1.51 g, 6.61 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at this temperature for 3 h before it was allowed to attain rt.

H_2O (0.70 mL) was added, and the mixture was cooled to -78 °C before more BF_3•Et_2O (10 mL, 79 mmol) was added. The mixture was allowed to attain rt overnight. Aqueous workup involved washing the mixture with H_2O (2 × 75 mL), back-extracting with CH_2Cl_2 (3 × 75 mL), washing the combined organic layers with brine (75 mL) and drying over anhydrous $MgSO_4$. The solvent was reduced in volume to 150 mL and the resulting solution was flushed through a column containing Florisil and activated charcoal to yield **94** (0.521 g, 74%) as a beige solid. mp: 60-62 °C. ^{1}H NMR ($CDCl_3$): δ 2.72 (4H, s), 1.65 (4H, m), 1.55 (4H, m), 1.46 (2H, m). ^{13}C NMR ($CDCl_3$): δ 216.2, 56.2, 34.6, 29.5, 29.3, 25.1, 20.7, 20.5.

8-*tert*-Butylspiro[4.5]decane-1,4-dione (80)



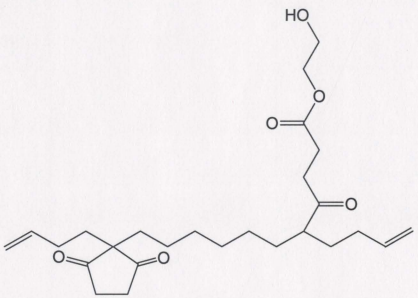
80

To a solution of 4-*tert*-butylcyclohexanone, (1,2-ethanediol) acetal (0.219 g, 1.10 mmol) and BF_3•Et_2O (0.23 mL, 1.8 mmol) in CH_2Cl_2 (10 mL) at -78 °C was added **1** (0.35 g, 1.6 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at this temperature for 3 h before it was allowed to attain rt. H_2O (0.50 mL) was added, and the mixture was cooled to -78 °C before more BF_3•Et_2O (3.6 mL, 28 mmol) was added. The mixture was allowed to attain rt overnight. Aqueous workup involved washing the mixture with H_2O (2 × 50 mL), back-extracting with CH_2Cl_2 (3 × 50 mL), washing the combined organic layers with brine (75 mL) and drying over anhydrous $MgSO_4$. The solvent was reduced in volume, and the resulting solution was flushed through a column containing Florisil® and activated charcoal to yield **80** (0.166 g, 68%) as a yellow solid. Mp: 81-83 °C

(lit. 82.5-84 °C). ^{1}H NMR ($CDCl_3$): δ 2.75 (4H, m), 1.64 (9H, m), 0.88 (9H, s). ^{13}C NMR ($CDCl_3$): δ 216.2, 216.1, 56.1, 47.2, 34.8, 34.6, 32.7, 30.4, 27.6, 21.9.

Formation of reductive succinoylation products.

2-Hydroxyethyl 1-((3-butenyl)-2,5-dioxocyclopentyl)-5-(3-butenyl)-4-oxoundecanoate (59)

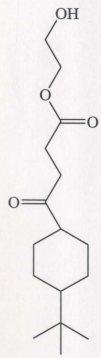


59

BF_3•Et_2O (1.20 mL, 9.47 mmol) was introduced slowly to a solution of **57** (0.181 g, 0.536 mmol) in dry CH_2Cl_2 (20 mL) at -78 °C. After 10 min **1** (0.45 g, 1.9 mmol) was added to the mixture slowly. This was stirred at -78 °C for 7.5 h before it was warmed to 5 °C. The mixture was stirred at this temperature for 10 min, and then the mixture was diluted with Et_2O (25 mL) followed by H_2O (25 mL) and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (50 mL) and dried over anhydrous $MgSO_4$. The

solution was concentrated under vacuum. Flash chromatography was performed eluting with 20% ethyl acetate/hexane to produce **59** (41.3 mg, 17%) as a yellow oil. IR ν_{max} 3768 (b), 2927 (m), 1716 (s), 1168 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.75 (1H, m), 5.63 (1H, m), 4.95 (4H, m), 4.23 (2H, m), 3.82 (2H, m), 2.76 (2H, m), 2.71 (4H, s), 2.60 (3H, m), 2.51 (2H, m), 2.23 (1H, b, s), 2.00 (2H, m), 1.95 (2H, m), 1.73 (4H, m), 1.59 (4H, m), 1.48 (2H, m), 1.17 (4H, m). ^{13}C NMR ($CDCl_3$): δ 217.6, 213.0, 173.3, 138.1, 137.6, 115.9, 115.4, 66.4, 61.3, 60.9, 51.4, 37.5, 36.6, 36.5, 34.2, 32.0, 31.9, 31.1, 30.0, 29.6, 28.2, 27.5, 24.7. MS *m/z* (%): 448 (8, M^+), 145 (36), 152 (33), 101 (100).

2-Hydroxyethyl 4-(4-*tert*-butylcyclohexyl)-4-oxobutanoate (81)



81

1,2-[(Bis)trimethylsilyloxy]ethane (0.19 mL, 0.77 mmol) and trimethylsilyl triflate (0.20 mL, 1.1 mmol) were added to a solution of **80** (0.166 g, 0.748 mmol) in CH_2Cl_2 (10 mL). This was stirred at rt under N_2 for 20 h. Saturated aqueous $NaHCO_3$ solution (15 mL) was added and the resulting mixture was then extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum. Flash chromatography was performed eluting with 20% ethyl acetate/hexane to produce **81** (52.4 mg, 24%), a brown liquid. IR ν_{max} 3467 (b), 2941 (m), 1707 (s), 1201 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.22 (2H, m), 3.82 (1H, m), 3.70 (1H, m), 2.77 (2H, m), 2.61, (2H, m), 2.30 (1H, m), 1.92 (4H, m), 1.32 (3H, m), 1.02

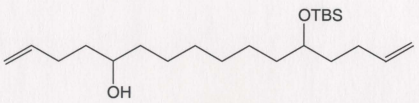
(3H, m), 0.85 (9H, s). ^{13}C NMR ($CDCl_3$): δ 212.8, 212.3, 173.3, 173.1, 70.7, 69.3, 66.4, 63.9, 61.3, 51.1, 47.6, 35.4, 35.2, 32.6, 29.1, 28.1, 27.6, 26.8. MS (CI, MeOH) *m/z*: 285 (M^+ + 1).

Procedure B:

1,2-[(Bis)-*tert*-butyldimethylsilyloxy]ethane (0.493 g, 1.69 mmol) and *tert*-butyldimethylsilyl triflate (0.40 mL, 1.74 mmol) were added to a solution of **80** (0.363 g, 1.63 mmol) in CH_2Cl_2 (20 mL). This was stirred at rt under N_2 for 24 h. Saturated aqueous $NaHCO_3$ solution (30 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (25 mL) and dried over anhydrous Na_2SO_4. Flash chromatography was performed eluting with 30% ethyl acetate/hexane to produce **81** (0.101 g, 22%) as a brown liquid.

Procedures for the mono-protection of symmetrical diol 50. Compound **73** was prepared based on a method by Corey.[30] An alternative route was also employed based on a method by Sauvé.[31]

12-(*tert*-Butyldimethylsilyloxy)hexadeca-1,15-dien-5-ol (73)



73

Procedure A:[30]

Imidazole (71.1 mg, 1.04 mmol) and TBSCl (74.8 mg, 0.496 mmol) were added to a solution of **50** (11.7 mg, 0.459 mmol) in dry DMF (3.0 mL). This was stirred for 24 h at rt. H_2O (10 mL) was added and the resulting mixture was extracted with petroleum ether (3 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$. Flash chromatography was performed eluting with 20% ethyl acetate/hexane to give **73** (59.1 mg, 35%) as a yellow oil. IR ν_{max} 3365 (b), 2928 (s), 2857 (m), 1254 (m), 1069 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.83 (2H, m), 4.96 (4H, m), 3.59 (2H, m), 2.20 (8H, m), 1.41 (12H, m), 0.88 (6H, s), 0.08 (9H, s). ^{13}C NMR ($CDCl_3$): δ 138.9, 125.8, 114.8, 103.4, 71.6, 63.5, 37.7, 36.7, 33.0, 30.3, 30.1, 29.9, 29.6, 26.2, 26.0, 25.9, 18.5 (3C), -3.5, -5.1. MS (CI, MeOH): 369 (M^+ + 1).

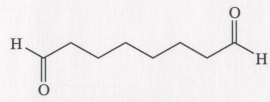
Procedure B:[31]

To a stirred solution of **50** (0.260 g, 1.02 mmol) in CH_2Cl_2 (15 mL) was added Ag_2O (0.389 g, 1.68 mmol) and TBSCl (0.214 g, 1.42 mmol). The solution was heated under reflux for 48 h. The mixture was filtered through a pad of neutral alumina, and the solvent was removed under reduced pressure to yield **73** (0.144 g, 38%) as a yellow oil.

General procedure for Dess-Martin oxidation.

Compounds **48**, **51**, **70** and **74** were prepared based on the method of Dess and Martin.[27]

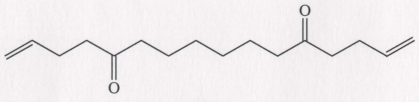
1,8-Octanedial (48)



48

To a solution of Dess-Martin periodinane[27,36] (16.4 g, 38.7 mmol) in dry CH_2Cl_2 (200 mL) was added 1,8-octanediol (2.49 g, 17.0 mmol). This was stirred for 22 h under N_2. The reaction mixture was diluted with ether (100 mL) and saturated aqueous $NaHCO_3$ solution (100 mL), was added followed by NaOH (8.5 g, 0.21 mol). The organic layer was washed with saturated $NaHCO_3$ (2 × 100 mL) and H_2O (2 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to give **48** as a yellow oil (2.19 g, 91%). IR ν_{max} 2932 (m), 2722 (w), 1720 (s), 1134 (w) cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.78 (2H, m), 2.45 (4H, m), 1.65 (4H, m), 1.35 (4H, m). ^{13}C NMR ($CDCl_3$): δ 202.9, 43.8, 28.9, 22.0.

Hexadeca-1,15-diene-5,12-dione (51)

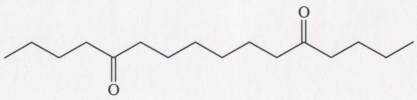


51

To a solution of Dess-Martin periodinane[27,36] (1.48 g, 3.49 mmol) in dry CH_2Cl_2 (25 mL) was added **50** (0.332 g, 1.31 mmol). This was stirred for 22 h under N_2. The reaction mixture was diluted with ether (30 mL) and 1 M NaOH solution (45 mL) was added. The organic layer was washed with H_2O (2 × 30 mL). The organic layer was dried over anhydrous $MgSO_4$, and

the solvent was removed under reduced pressure to give **51** as a white solid (0.296 g, 91%). Mp: 63-65°C. IR ν_{max} 3080 (w), 2930 (m), 1697 (s), 1086 (m), 916 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.82 (2H, m), 5.02 (4H, m), 2.50 (4H, t, J = 7.4 Hz), 2.41 (4H, t, J = 7.4 Hz), 2.34 (4H, m), 1.68 (4H, m), 1.30 (4H, m). ^{13}C NMR ($CDCl_3$): δ 210.5, 137.4, 115.4, 42.9, 42.0, 29.2, 28.0, 23.8. MS *m/z* (%): 250 (2, M^+), 153 (23), 111(15), 98 (14), 83 (59), 55 (100).

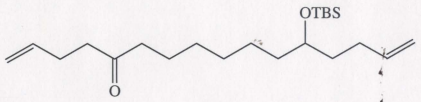
Hexadecane-5,12-dione (70)



70

To a solution of Dess-Martin periodinane[27,36] (0.94 g, 2.2 mmol) in dry CH_2Cl_2 (15 mL) was added **69** (0.247 g, 0.956 mmol). This was stirred for 22 h under N_2. The reaction mixture was diluted with ether (25 mL) and saturated aqueous $NaHCO_3$ solution (25 mL), was added followed by NaOH (0.25 g, 6.25 mmol). The organic layer was washed with saturated $NaHCO_3$ (2 × 20 mL) and H_2O (2 × 20 mL). The organic layer was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to give **70** as a yellow solid (0.163 g, 67%). Mp: 66-67°C. IR ν_{max} 2956 (m), 2931 (s), 1703 (s), 1379 (s), 1126 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.40 (8H, t, J = 7.3 Hz), 1.59 (8H, m), 1.36 (8H, m), 0.93 (6H, t, J = 8.5 Hz). ^{13}C NMR ($CDCl_3$): δ 211.7, 42.9, 42.8, 29.2, 26.2, 23.9, 22.6, 14.1. MS *m/z* (%): 155 (23), 85 (100), 58 (23), 57 (74), 41 (33), 29 (25). MS (EI) *m/z*: 254 (M^+).

12-(*tert*-Butyldimethylsilyloxy)hexadeca-1,15-dien-5-one (74)



74

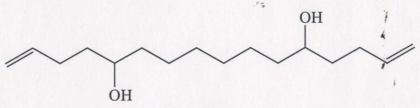
To a solution of DMP (0.21 g, 0.50 mol) in dry CH_2Cl_2 (5 mL) was added **73** (0.101 g, 0.274 mmol). This was stirred for 16 h under N_2. The reaction mixture was diluted with ether (20 mL) and saturated aqueous $NaHCO_3$ solution (15 mL) was added followed by solid NaOH (0.25 g, 6.25 mmol). The organic layer was washed with saturated aqueous $NaHCO_3$ solution (2 × 15 mL) and H_2O (2 × 15 mL). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to give a yellow oil **74** (0.093 g, 93%). IR ν_{max} 2929 (s), 2856 (m), 1717 (m), 1253 (m), 1057 (m), 834 (s), 773 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.84 (2 H, m), 5.04 (4H, m), 3.60 (1H, m), 2.50 (4H, t, J = 7.4 Hz), 2.40 (4H, t, J = 7.5 Hz), 1.53 (12H, m),1.30 (6H, m), 0.89 (9H, s). ^{13}C NMR ($CDCl_3$): δ 210.9, 138.3, 115.4, 63.5, 63.3, 43.1, 41.9, 33.1, 33.0, 29.7, 29.5, 28.0, 26.2, 26.0, 25.9, 24.0, 18.6 (3C), -3.5, -5.0. MS *m/z* (%): 255 (26), 147 (21), 75 (100), 69 (58), 55 (61). MS (CI, MeOH) *m/z*: 367 (M^+ + 1).

Procedure for Grignard reactions.

Compounds **50** and **69** were prepared based on the method of Newcomb and coworkers with some modifications.[37] The mechanical activation of the magnesium turnings was

accomplished using the procedure of Baker and coworkers.[38]

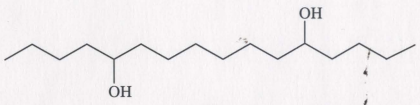
Hexadeca-1,15-diene-5,12-diol (50)



50

Magnesium turnings (1.19 g, 49.1 mmol) were stirred under an atmosphere of N_2 for 24 h. THF (20 mL) was added followed by a solution of 4-bromo-1-butene (4.21 g, 31.2 mmol) in THF (15 mL). The mixture was heated under reflux for 3 h, cooled to rt and then in an ice bath. A solution of **48** (1.82 g, 12.8 mmol) in THF (15 mL) was added dropwise and the mixture was stirred at rt for 16 h. The reaction mixture was poured into saturated aqueous NH_4Cl solution (50 mL). The aqueous layer was extracted with ether (4 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to yield **50** as a white solid (2.38 g, 73%). mp: 53-56 °C. IR ν_{max} 3320 (m), 2922 (s), 2847 (m), 1642 (m), 915 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ5.84 (2H, m), 5.02 (4H, m), 3.62 (2H, m), 2.18 (6H, m), 1.43 (16H, m). ^{13}C NMR ($CDCl_3$): δ 138.8, 115.2, 71.9, 37.7, 36.7, 30.3, 29.8, 25.8. MS (EI): 254 (M^+).

Hexadecane-5,12-diol (69)



69

Magnesium turnings (0.31 g, 12.6 mmol) were stirred under an atmosphere of N_2 for 24 h. THF (5 mL) was added followed by a solution of bromobutane (1.39 g, 10.1 mmol) in THF (10 mL). The mixture was heated under reflux 3 h, cooled to rt and then in an ice bath. A solution of **48** (0.51 g, 3.6 mmol) in THF (10 mL) was added dropwise and the mixture was stirred at rt overnight. The reaction mixture was poured into saturated aqueous NH_4Cl solution (20 mL). The aqueous layer was extracted with ether (4 × 20 mL). The combined organic layers were extracted dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to yield **69** as a yellow solid (0.58 g, 63%). mp: 58-60°C. IR ν_{max} 3323 (w), 2924 (s), 2854 (m), 1463 (m), 1043 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.62 (2H, m), 1.47 (18H, m), 0.92 (14H, m). ^{13}C NMR ($CDCl_3$): δ 72.2, 37.7, 37.4, 29.9, 28.1, 25.8, 22.9, 14.3. MS (CI, MeOH): 259 ($M^+ + 1$).

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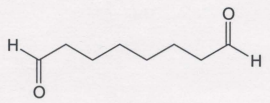
Appendix 1: ^{1}H NMR Spectra



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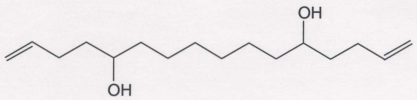

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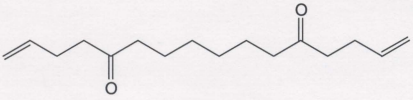

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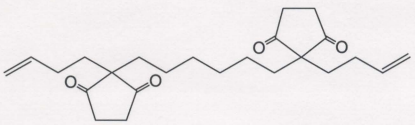

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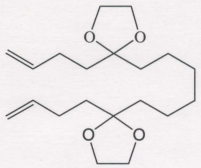

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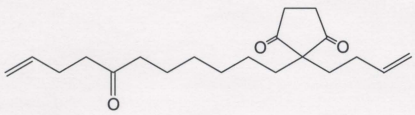

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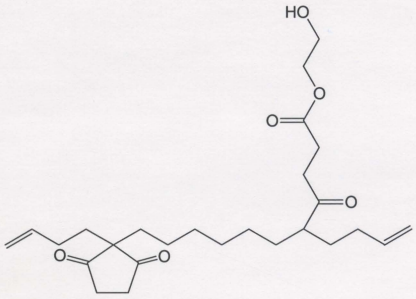

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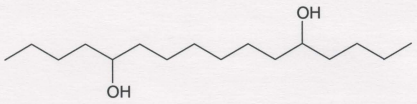

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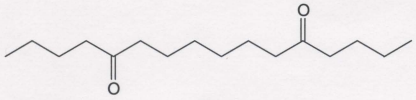

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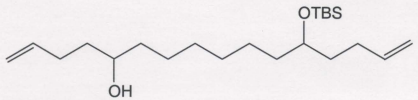

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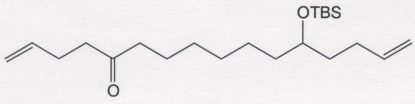

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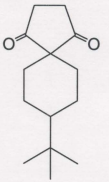

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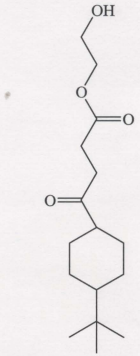

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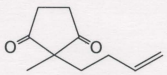

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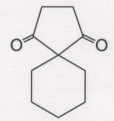

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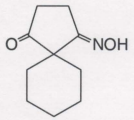

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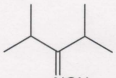

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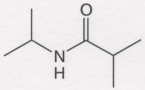

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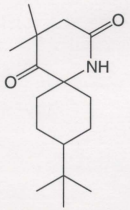

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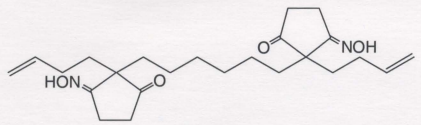

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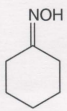

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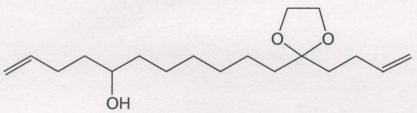

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