INVESTIGATIONS INTO THE INTRAMOLECULAR GEMINAL ACYLATION REACTION

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Investigations into the Intramolecular Geminal Acylation Reaction

By

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Abstract

The geminal acylation reaction, initially introduced by Kuwajima and co-workers, has been developed into a synthetically useful method of creating cyclic diketones by reacting 1,2-bis[(trimethylsilyl)oxy]cyclobutene (**1**) with aldehydes, ketones, or acetals. To date, all examples of the reaction are intermolecular. The focus of this research was to develop methodology for an intramolecular geminal acylation. This process would lead to bridged compounds with two carbonyl functionalities.

Compounds that should be capable of performing an intramolecular geminal acylation have been synthesized. These compounds possess a reactive functionality similar to that of **1**, and an acetal moiety. Attempts at performing this reaction have been made and the results are quite promising. Several bridged diketones have been generated. There have been other compounds isolated that indicate that this reaction does proceed, however isolating the desired products has been problematic due to destruction of the bridged diketones within the reaction mixture.

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List of Abbreviations

APT	attached proton test
9-BBN	9-borabicyclo[3.3.1]nonane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
eq	equivalent(s)
Et	ethyl
GC-MS	gas chromatograph-mass spectrometer
h	hour(s)
HRMS	high resolution mass spectrum
IR	infrared
LDA	lithium diisopropylamide
Me	methyl
min	minute(s)
MS	mass spectrum
NMR	nuclear magnetic resonance
ORTEP	Oak Ridge thermal ellipsoids projection
PCC	pyridinium chlorochromate
*p*TsOH	*para*-toluenesulfonic acid
rt	room temperature
TFA	trifluoroacetic acid
THF	tetrahydofuran

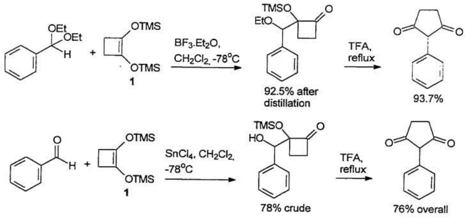
tlc	thin layer chromatography
TMSCl	chlorotrimethylsilane
TMS	trimethylsilyl
xs	excess

INTRODUCTION

The geminal acylation reaction is very useful to synthetic organic chemists. It is an efficient method of converting ketones, aldehydes or acetals into cyclic diketones. The reaction was termed geminal acylation because it essentially converts both carbon-oxygen bonds of one carbonyl into two carbon-carbon bonds, with the new carbon bonds being to carbonyl (acyl) groups.

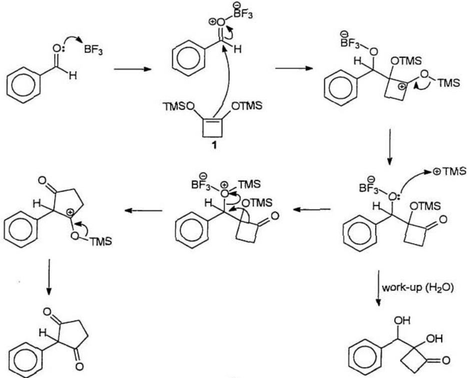
The original geminal acylation procedures published by Kuwajima and coworkers[1] are shown in Scheme 1. The geminal acylation reaction combines an acetal of an aldehyde or a ketone, or an underivatized aldehyde, with 1,2-bis[(trimethylsilyl)oxy]cyclobutene (**1**) in the presence of a Lewis acid followed by heating in trifluoroacetic acid (TFA) to generate a cyclic 1,3-diketone. This original procedure was unsuccessful in generating the geminal acylation products from ketones.

Scheme 1



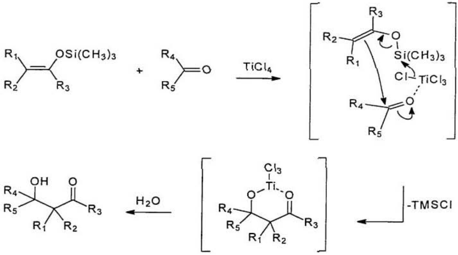
The original method utilized $BF_3 \cdot Et_2O$ with acetals and $SnCl_4$ with aldehydes. The reaction between **1** and a carbonyl-containing compound is a Mukaiyama-like aldol reaction. Refluxing the isolated cyclobutanone compound in TFA causes an acyl migration similar to a pinacol rearrangement to give the cyclic 1,3-diketone. The mechanism by which the geminal acylation products are produced is shown in Scheme 2. In this scheme the routes to both products isolated by Kuwajima are shown. The structure indicated by the work-up arrow is the result of the Mukaiyama-like aldol, and the final compound is the geminal acylation product of the pinacol-like rearrangement.

Scheme 2



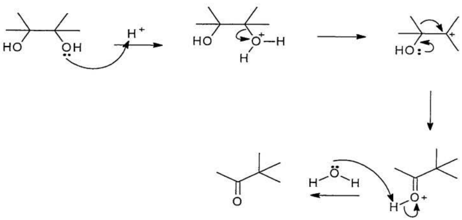
The Mukaiyama aldol reaction is a crossed-aldol reaction involving a carbonyl-containing compound and a silyl enol ether in the presence of $TiCl_4$.[2] The $TiCl_4$ activates the carbonyl site, and then the silyl enol ether acts as a nucleophile and attacks the activated carbonyl. The intermediate is stabilized by the formation of a titanium chelate. Mukaiyama was able to obtain crossed-aldol products with aldehydes at –78 °C. He noted that reactions with ketones proceeded very sluggishly at this temperature, and a reaction temperature of 0 °C or room temperature was required to obtain the desired compounds. This process is shown in Scheme 3. The initial step of the geminal acylation is similar to that of the Mukaiyama reaction except that there are two trimethylsilyloxy groups on the double bond in **1** and the Lewis acid utilized is different.

Scheme 3



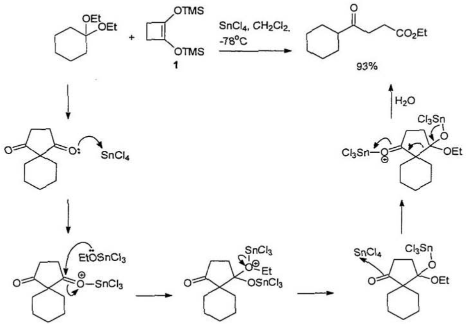
The pinacol rearrangement is an acid-catalyzed conversion of a diol to a ketone.[3] In a pinacol rearrangement, a carbocation is generated next to a carbon which has a hydroxyl group attached. An alkyl migration occurs to stabilize the carbocation and at the same time, a carbonyl group is generated. The classic example of this reaction is the conversion of pinacol to pinacolone, and hence this gives the reaction its name. This is shown in Scheme 4. This rearrangement is similar to the one that occurs in the geminal acylation reaction except that the oxygen functionality that becomes the carbonyl moiety is a trimethylsilyl ether instead of an hydroxyl group and the acid is usually $BF_3{\cdot}Et_2O$.

Scheme 4



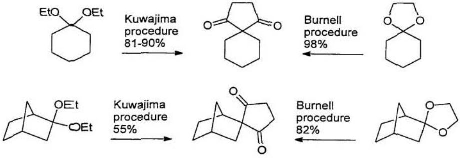
Kuwajima also reported a reductive succinoylation reaction.[1] When the acetals were treated under the conditions used for aldehydes in Scheme 1, γ-keto-esters were formed. The reaction proceeded to give the desired cyclic 1,3-diketone, but ring opening to the γ-keto-ester then occurred. This process is outlined in Scheme 5.

Scheme 5



Since Kuwajima's initial work, much time and effort has gone into developing this geminal acylation reaction. Examples of these modifications are shown in Schemes 6 and 7. One of the major improvements on Kuwajima's procedure was the modification that allowed the reaction to proceed to cyclic diketones without isolating the Mukaiyama-like aldol product. Wu and Burnell[4] were able to create the cyclic 1,3-diketones by utilizing a large excess of Lewis acid. This turned the reaction into a clean, efficient one-pot process. In most cases, the yields of the one-pot procedure were better than those obtained by the Kuwajima procedure. Scheme 6 shows some examples of this. Ayyanger's[5] group reported results similar to those achieved by Burnell.

Scheme 6



The scope of this reaction has also been expanded to include 1,2-bis[(trimethylsilyl)oxy]cyclopentene (**2**).[6] This generates cyclic 1,3-diketones that are in a six-membered ring as opposed to a five-membered ring. The reaction proceeds in an analogous fashion to that of **1** and gives good yields. It was also stated that the cyclic acetals derived from diols, like ethane-1,2-diol, seem to give higher yields and cleaner reactions.[6] An example of this reaction is shown in Scheme 7.

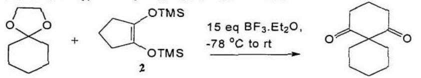
Jenkins and Burnell[7] achieved one of the most significant improvements to the geminal acylation reaction. This work outlined a procedure that used ketones to generate the desired diketone products. Mukaiyama had reported[2] that the aldol condensation with ketones and silyl enol ethers did not proceed at lower temperatures, however the desired reaction did proceed at room temperature. Jenkins and Burnell were able to create the cyclobutanone aldol products at room temperature and isolate them. The most favorable conditions for this step involved 1.5 molar equivalents of **1** and one molar equivalent of the Lewis acid at room temperature. Following this step, a small amount of water, usually a volume equal to that of the $BF_3{\cdot}Et_2O$, was added, followed by a large excess of

Lewis acid. It was speculated that the water hydrolysed some of the silyl ethers in the reaction medium, which favored the pinacol-like rearrangement instead of the conversion back to starting ketone. The result of this work was a procedure for generating cyclic 1,3-diketones directly from ketones in yields that were competitive with the one-pot procedure developed earlier. The advantage of this procedure was the reduction in the number of steps in synthetic routes by eliminating the need to create acetals. An example of this modification is also shown in Scheme 7.

Since the development of Jenkins' procedure, more investigations have been carried out with different ketones. Modifications to the ketone procedure have been made for α,β-unsaturated ketones and aromatic ketones.[8] It was found that geminal acylation reactions with these substrates take place in fair to good yields, however both steps occur under anhydrous conditions. Reactions have been performed using analogues with methyl substituents on the 3 and 4 positions of **1**.[9] Other investigations have shown that altering the Lewis acid in the reaction can improve yields, as was shown by Crane[10] by the use of BCl_3. BCl_3 was shown to improve the yields of 4,4-dimethyl-1,3-cyclopentanediones. Examples of each of these reactions are shown in Scheme 7.

Scheme 7

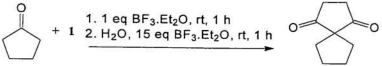
Use of 1,2-bis[(trimethylsily)oxy]cyclopentene (2):[6]



The yield obtained from this reaction was 89%. The same product was obtained from dimethyl acetal in a 80% yield.

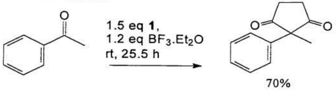
Scheme 7 cont.

Jenkins' modification for ketones:[7]

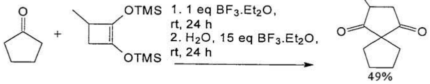


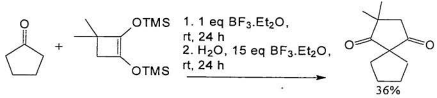
The yield from the ketone was 79%.[7] The yield from the corresponding ethane-1,2-diol acetal was 68%.[4]

Example of an aromatic ketone that does not require H_2O and excess Lewis acid:[8]

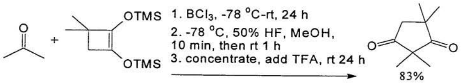


Examples of Reactions of methyl-substituted analogues of 1:[9]





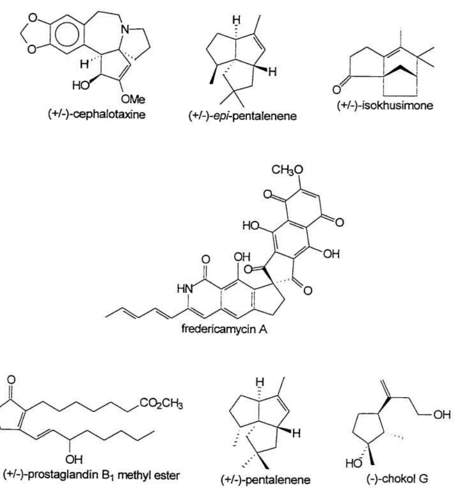
BCl_3 modification for dimethyl-analogue of 1:[10]



The yield of the same reaction with $BF_3.Et_2O$ was 22%.[9]

The geminal acylation reaction has been utilized in total syntheses of several challenging molecules. Some of these molecules are shown in Figure 1. Wu and Burnell[4,11] used this methodology in syntheses of (±)-isokhusimone, (±)-pentalenene and (±)-*epi*-pentalenene. (±)- Isokhusimone is a member of the zizaane sesquiterpene family of compounds, and pentalenene and *epi*-pentalenene are biogenetic precursors to the antibiotic pentalenolactone. Suzuki[12] employed the geminal acylation reaction in the synthesis of prostaglandin B_1 methyl ester, a mammalian regulatory compound, and Mariano[13] exploited the reaction to synthesize cephalotaxine. Cephalotaxine is the parent member of a family of alkaloids, several of which possess anticancer properties. The reaction was also utilized to create the spiro center of Fredericamycin A, a compound with only one stereogenic center and antitumor properties.[14] Recently, the reaction was used as a key transformation in a total synthesis of (-)-chokol G, a fungitoxic metabolite from the stomata of *Epichloe typhia*.[15] There are several other compounds that have been synthesized using the geminal acylation reaction that are not depicted in Figure 1.[16]

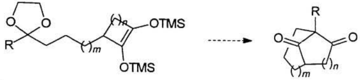
Figure 1. Compounds Synthesized using the Geminal Acylation Reaction



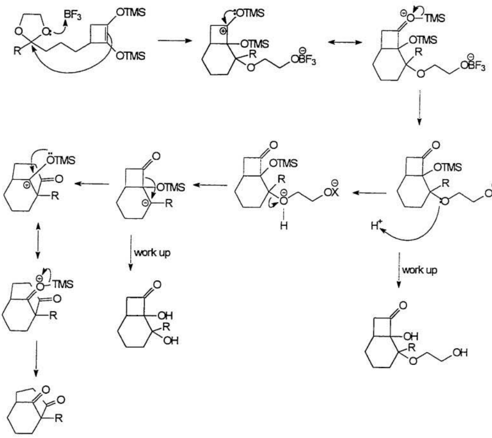
The synthetic utility of this reaction cannot be questioned. Therefore, more investigation into furthering the synthetic utility of this process was started by our group. It was thought that bridged 1,3-diketones could be generated using the geminal acylation method. By creating compounds that contained both a carbonyl moiety and functionality similar to **1**, it was hoped that an intramolecular geminal acylation could be performed to generate bridged 1,3-diketones in the manner outlined in Scheme 8. The mechanism by which these products were anticipated to form is shown in Scheme 9. The product indicated by the work-up arrow is the Mukaiyama-like aldol product that may or may not be isolated, and the final compound is the desired bicyclic 1,3-diketone.

Such methodology could find use in natural product synthesis. Potentially, this would be a method for creating bicyclic systems in which there are many sites for introducing substituents. It should be possible to create larger rings by increasing n and m in Scheme 8. One natural product that may be synthesized using such a methodology is vinigrol. Vinigrol[17] is a diterpenoid, isolated from a fungal strain identified as *Virgaria nigra*, that is being investigated for its medicinal purposes. It possesses antihypertensive and platelet aggregation-inhibiting properties. It has also been discovered that vinigrol, as well as salts derived from vinigrol, are tumor necrosis factor antagonists. Due to these properties, vinigrol is being tested as treatment for endotoxic shock, inflammations, infections, cachexia and to stop the progression of AIDS-related complex to full blown AIDS. To date there has been no total synthesis of this compound. Several groups have generated partial syntheses of vinigrol.[18] Scheme 10 outlines our proposed synthetic route, which utilizes an intramolecular geminal acylation step as the key transformation.

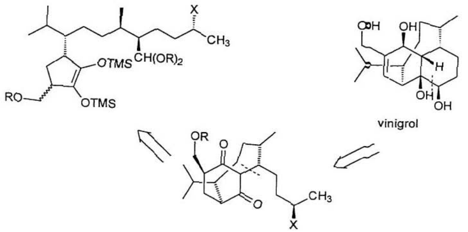
Scheme 8



Scheme 9



Scheme 10

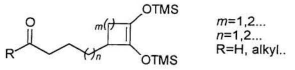


Results and Discussion

Synthesis of Substrates

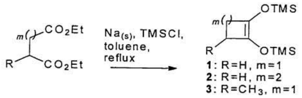
To begin investigating the intramolecular geminal acylation reaction, compounds must be synthesized that are capable of such a transformation. These compounds must contain a carbonyl moiety and a reactive functionality that is similar to **1** or **2**. Figure 2 illustrates the types of molecules that are required.

Figure 2 Molecules Required for the Intramolecular Geminal Acylation Reaction

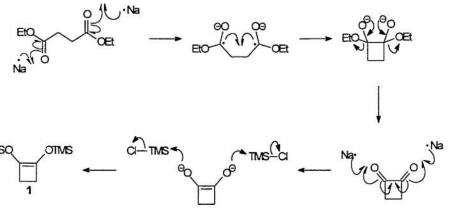


An acyloin condensation[19] is utilized to provide functionality that is similar to **1** and **2** from a diester. This is shown in Scheme 11. The acyloin condensation occurs via a series of single electron transfers from the sodium in the reaction mixture to form the ring structure, followed by trapping of the generated dianion with chlorotrimethylsilane (TMSCl). This mechanism is outlined in Scheme 12.

Scheme 11

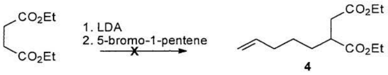


Scheme 12

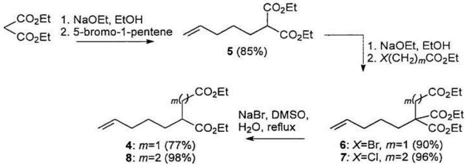


In order to generate the desired compounds shown in Figure 2, the R group in Scheme 11 must be a chain with either a carbonyl moiety or some other functionality that can be manipulated readily into a carbonyl moiety. The initial proposal for generating this type of compound is shown in Scheme 13. From previous work in our laboratory,[20a] it was known that treatment of diethyl succinate with lithium diisopropylamide (LDA) could remove a proton α to one of the ester carbonyls. Subsequent addition of iodomethane and work up generated diethyl 2-methyl succinate, which, in turn, underwent an acyloin condensation to provide **3**. It was thought that similar results could be achieved with a different alkyl halide. Diethyl succinate was treated with LDA, but addition of 5-bromo-1-pentene did not yield **4**. After many attempts and modifications, this alkylation was not achieved in synthetically useful yields, so a different approach was initiated. This approach is shown in Scheme 14. It should be noted that many of the attempts that were made with 5-bromo-1-pentene were repeated using iodomethane. There was no problem in performing this alkylation. The reactions performed with 5-bromo-1-pentene returned mainly diethyl malonate. It was speculated that the anion was being formed in the reaction medium, however, instead of performing an S_N2 reaction, an E2 reaction was occurring and the 5-bromo-1-pentene became pentadiene. The anion formed from diethyl succinate is a much stronger base than that of the diethyl malonate anion and hence may enhance the E2 reaction versus the S_N2 reaction.

Scheme 13



Scheme 14



This approach added several steps to the overall synthesis of the molecules, however each step proceeded very well and with very good yields. The first two steps in the syntheses of **4** and **8** were based on malonate chemistry by Adams and Kamm,[21] and **5**, **6** and **7** were obtained in greater than 85% yield. Diethyl malonate was treated with sodium ethoxide. This removed the acidic proton between the ester carbonyls and created an anion that performed a substitution reaction with 5-bromo-1-pentene to give **5**. Compound **5** was treated with sodium ethoxide to remove the other acidic proton between the ester carbonyls, and this time a substitution reaction occurred when the generated anion attacked ethyl bromoacetate to form triester **6**, or attacked ethyl 3-chloropropionate to form triester **7**. The ^1H nuclear magnetic resonance (NMR) spectrum was very useful for determining if the alkylation had occurred. In the formation of **5**, the CH_2 singlet from malonate disappeared and was replaced with a CH triplet at 3.33 ppm. The chemical shifts of the singlet and the triplet were slightly different, and it was possible to integrate both peaks to determine the ratio of starting material to product. A similar phenomenon occurred in the generation of **6** and **7** from **5**. The CH triplet at 3.33 ppm, visible in the spectrum of **5**, disappeared as **6** and **7** formed. Again this was very useful for determining the amount of conversion of starting material to product in these reactions. The nature of the halide did not seem to affect the reaction. Both the bromo- and the chloro-compounds provided products in very good yields.

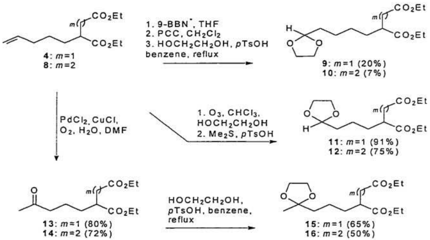
Both triesters were decarboxylated using the method of Krapcho and Lovey[22] to yield **4** and **8**. It was again very easy to determine if these decarboxylations had proceeded by ^1H NMR spectroscopy. In the formation of **4**, the CH_2 singlet of **6** at 2.97

ppm was replaced by a much more complex pattern consisting of a multiplet and two doublet of doublets. Similarly, in the generation of **8**, the symmetrical multiplet of 4 hydrogens centered at 2.25 ppm was converted into two different multiplets. One of these multiplets represented three hydrogen atoms and was located at 2.41ppm and the other corresponded to two hydrogen atoms and was positioned at 1.96 ppm.

Compounds **4** and **8** contained the diester functionality that was required in the acyloin condensation to generate the type of compound shown in Scheme 11. However, before the acyloin condensation could proceed, the terminal double bond had to be manipulated into a carbonyl moiety. The carbonyl had to be introduced at this point because after the acyloin condensation occurred, the resulting compounds became very unstable. The carbonyl required protection as an acetal because unprotected ketones and aldehydes are destroyed in the acyloin condensation. Scheme 15 depicts the method by which **4** and **8** were converted into precursors of compounds that should be capable of performing an intramolecular geminal acylation reaction.

Compounds **9** and **10** were obtained by a hydroboration reaction and oxidation followed by protection of the aldehyde as a cyclic acetal.[23] The aldehydes were not isolated prior to the acetal formation. In an attempt to create these compounds, two different approaches were utilized. Initially, 9-borabicyclo[3.3.1]nonane (9-BBN) was used as the hydroborating reagent, and in other attempts, dicyclohexylborane was used. In both reactions, the yields were low and often there was starting material regenerated. Attempts to modify the reaction conditions to convert more of the starting material often led to complex mixtures in which nothing was identified. In all cases, pyridinium chlorochromate (PCC) was used to oxidize the primary alcohols to aldehydes and the acetal functionality was generated by an acid-catalyzed reaction with ethane-1,2-diol in benzene under reflux. All three of these steps were completed before the mixture was analyzed by spectroscopic methods. It was not difficult to determine when these products had formed by ^{1}H NMR because there was the presence of a very characteristic triplet at 4.85 ppm and 4.83 ppm for **9** and **10**, respectively.

Scheme 15



* These reactions were also performed with dicyclohexylborane.

Compounds **11** and **12** were created using an ozonolysis procedure[24] that was modified slightly from the literature. The ozonolysis was carried out in a mixed solvent of chloroform and ethane-1,2-diol. After the generated ozonide was reduced with dimethyl sulfide (Me_2S), a small amount of *para*-toluenesulfonic acid (*p*TsOH) was added, and this led to the production of the acetal directly. The products were obtained in very high yields, and, in most cases, the crude products did not require purification before they were used in the next steps. The disappearance of the signals for the double bond protons was clearly observed in the ^{1}H NMR of these reactions, as was the introduction of a CH triplet and the multiplet for the ethane-1,2-diol acetal protons of the products.

Finally, compounds **13** and **14** were formed using a Wacker oxidation.[25] Acetal formation then generated compounds **15** and **16**. The Wacker reaction was a clean and efficient process that converted the terminal olefin into a methyl ketone. By ^{1}H NMR, it was not difficult to determine that the olefinic protons were no longer present, and that a methyl ketone had been created. The methyl ketone singlets were located at 2.11 ppm for **13** and 2.14 ppm for **14**. The acetals were generated as they were in the production of **9** and **10**. Here it was easy to determine when the reaction had gone to completion because the singlets at $\approx$ 2.1 ppm for the methyl ketones disappeared and were replaced with singlets at 1.31 ppm and 1.30 ppm for **15** and **16**. The yields of these reactions were acceptable, and purification by column chromatography was not always needed.

As shown in Scheme 15, six compounds were produced that were reasonable precursors for an acyloin condensation followed by an intramolecular geminal acylation reaction. The chemistry of compounds **11**, **12**, **15** and **16** was explored more thoroughly than that of **9** and **10**. Compounds **9** and **10** were not as easily prepared on a large scale as the other four, and their yields were also lower. Therefore, the main focus of the remainder of this research was with the compounds derived by the ozonolysis and Wacker oxidation route.

Acyloin Condensations

Initially, some control reactions were performed to determine if these types of compounds would survive the harsh conditions of an acyloin condensation. The first reaction was designed to ascertain if acyloin reactions could proceed on a very small scale. This reaction employed normal acyloin condensation conditions to prepare **1**, but, usually when this experiment is performed in our laboratory, it is done so on a 120 mmol scale with diethyl succinate. In this case, the reaction was based on a six mmol scale. The reaction did proceed as expected and did generate **1**. However, the yield was low. The crude yield of this reaction was only 16% whereas the yield of purified **1** is usually 60-70%.[19]

The next reaction was to determine if the acyloin condensation would proceed in the presence of an acetal, and if the acetal would then react with the produced **1**. The reaction was performed as the first control reaction with the exception that the ethane-1,2-diol acetal of 2-pentanone was added with the diethyl succinate. Following the suction filtration step of the acyloin condensation mixture, the filtrate was cooled to –78 °C and 15 molar equivalents of $BF_3{\cdot}Et_2O$ were added. The mixture was stirred overnight and allowed to achieve room temperature. This reaction yielded 45% of the expected 1,3-diketone. This was proof that the acyloin condensation would occur in the presence of an acetal, that the acetal could survive the harsh conditions, and that both would react as expected. The ^{1}H NMR spectrum of the crude product revealed the presence of an aromatic side-product, which was presumed to have arisen from the toluene solvent.

Another reaction was performed to determine how the yields would compare if the acetal were added after the acyloin condensation. The reaction was set up like the previous one with the exception that the acetal of 2-pentanone was added after the suction filtration of the acyloin condensation. In this case, the yield of the reaction was 92%. There was also some evidence of the aromatic product as well. This suggested that, in the previous reaction, either some of the acetal must have been destroyed in the acyloin condensation, or the yield of **1** in acyloin condensations performed in the presence of an acetal is lower.

One other control reaction was carried out. In this reaction the acyloin condensation was performed just like the second control reaction. The difference in this case was that the toluene was removed by simple distillation before the geminal acylation step. The resulting residue was dissolved in dichloromethane and cooled to –78 °C, and fifteen molar equivalents of $BF_3{\cdot}Et_2O$ were added. This reaction yielded only 18% of the desired diketone, but there was no evidence of the aromatic product. The yield was much lower; it was speculated that much of the acetal was removed with the toluene in the distillation.

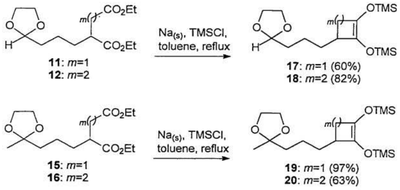
In summary, from these reactions it was concluded that:

1. Acyloin condensations can be performed on a small scale.
2. Acetals can survive the acyloin condensation conditions.
3. The expected geminal acylation reaction can proceed in toluene. Nevertheless, it does appear that the geminal acylation reaction works better in dichloromethane because a side reaction is eliminated.

The next step was to determine if compounds **11, 12, 15** and **16** would undergo an acyloin condensation. Scheme 16 depicts the expected products from the acyloin condensation. These compounds were expected to be very unstable in the presence of air. and because of their expected instability these compounds were not purified. In several instances, vacuum distillation of the acyloin products was attempted, however purified products were not obtained.

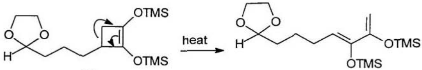
The transformations of **11, 12, 15** and **16** proceeded as expected to generate **17, 18, 19**, and **20**, respectively. The production of the acyloin compounds appeared, by ^{1}H NMR, to take place reasonably efficiently. The compounds were not purified, but the distinguishable resonances expected from the molecules were clearly visible in the ^{1}H NMR spectra. It was easy to determine that the ester multiplets around 4.1 ppm and 1.2 ppm were removed and the acetal resonances remained. It was also observed that trimethylsilyl (TMS) signals had been incorporated into the molecules.

Scheme 16



It should be noted that in the acyloin condensation to form **17**, an isomer was also created. Scheme 17 shows this conversion of **17** into **21**. It was suspected that during either the simple distillation to remove toluene or the vacuum distillation, **17** was heated too vigorously, and this resulted in the formation of **21**. Tendency for this type of transformation to occur had previously been observed in our laboratory.[20b] The signals for the olefinic protons were evident in the ^1H NMR spectrum of **21**.

Scheme 17



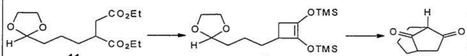
17 **21**

Initial Attempts at the Intramolecular Geminal Acylation Reaction.

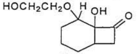
Initial attempts at the intramolecular geminal acylation reaction have proved to be promising. Many attempts to synthesize the desired bridged, 1,3-diketones were made. Some of the products that have been isolated have indicated that this type of chemistry will indeed work. However, some isolation problems were encountered, and the yields of the bridged 1,3-diketones are very low.

The geminal acylation reaction is a very complex reaction. It involves a Mukaiyama-like aldol reaction followed by a pinacol-like rearrangement. When looking back through the literature[8,9,10] on this reaction, it is not difficult to determine that different compounds react very differently under these conditions. Therefore, it is conceivable that, to achieve a bridged 1,3-diketone under these conditions, there are a lot of condition parameters that may need to be examined. Some of these conditions are: dilution, the mode and sequence of addition, the Lewis acid, the solvent, the temperature, the purity of the substrate, the reaction time, addition of TFA, work up method and the type of acetal used. Tables 2, 3, 4 and 5 summarize the different attempts that were made to carry out an intramolecular version of this reaction. It should be emphasized that progress with this project was occurring with all of the substrates at the same time and it is difficult to follow the rationale for changing the parameters if one focuses on the course of events for one substrate at a time.

Table 1: Intramolecular Geminal Acylation Attempts with **11** and **17**



11 → 17 → 22

	Reaction Conditions	Products
1	An acyloin condensation was performed with **11** (0.389 g, 1.35 mmol), TMSCl (0.79 mL, 6.2 mmol), toluene (25 mL) and $Na_{(s)}$ (0.14 g, 6.1 mmol). The toluene was removed by distillation. CH_2Cl_2 (30 mL) was added to the residue and it was cooled to –78 °C. $BF_3{\cdot}Et_2O$ (2.6 mL, 20 mmol) was added and the mixture was kept at –78 °C for 3 h. It was left to achieve rt overnight. The mixture was worked up• and the concentrate was passed through a Florisil column.	From the GC-MS, there were a lot of products formed. One of the isolated products with a crude yield of 7% was **23**.  **23**

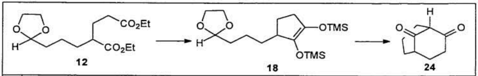
• Work up consisted of washing the organic mixture with H_2O, extracting the aqueous layers with CH_2Cl_2 and washing the combined organic layers with saturated $NaCl_{(aq)}$. The organic solution was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure.

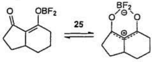
Table 1 cont.: Intramolecular Geminal Acylation Attempts with **11** and **17**

2	Compound **17** (0.0919 g, 0.267 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled to –78 °C. $BF_3{\cdot}Et_2O$ (0.51 mL, 4.0 mmol) was then added slowly. The mixture was left to achieve rt overnight. The mixture was worked up*.	The ^1H NMR spectrum was very complex. There were no products isolated from this mixture.
3	Compound **17** (0.175 g, 0.506 mmol) was dissolved in CH_2Cl_2 (5 mL) and stirred at –78 °C. $BF_3{\cdot}Et_2O$ (0.13 mL, 1.0 mmol) was added and the mixture was left stirring in the bath to achieve rt overnight. Work up* was performed the next day.	The ^1H NMR spectrum was not as messy as the previous reaction but still nothing was isolated from the mixture.
4	Compound **17** 0.178 g, 0.517 mmol) was dissolved in CH_2Cl_2 (5 mL). $BF_3{\cdot}Et_2O$ (0.08 mL, 0.6 mmol) was added and the mixture was stirred at rt for 2 h. H_2O (1 mL) was added and the mixture was stirred for 10 mins. $BF_3{\cdot}Et_2O$ (1.0 mL, 7.9 mmol) was then added and the mixture was stirred at rt overnight. The mixture was worked up*.	The ^1H NMR was complex, but similar to that of reaction three, so the two crude mixtures were combined and purification was attempted by column chromatography. The column fractions were not clean. By GC-MS, one of the products present in the mixture was **23** (0.007 g, 3%).
5	Compound **17** (0.156 g, 0.453 mmol) was dissolved in CH_2Cl_2 (5 mL) and stirred at –78 °C. A solution of $SnCl_4$ (0.24 g, 0.92 mmol in CH_2Cl_2 to make 1 mL) was added and the mixture was stirred to achieve rt overnight. The next day the mixture was worked up*.	The ^1H NMR spectrum was different from the others in that there was evidence of olefinic protons, however, nothing was isolated.
6	An acyloin condensation was performed with **11** (0.618 g, 2.14 mmol), TMSCl (1.25 mL, 9.85 mmol), toluene (25 mL) and $Na_{(s)}$ 0.22 g, 9.6 mmol). The mixture was suction filtered and the filtrate was cooled to –78 °C. $BF_3{\cdot}Et_2O$ (4.0 mL, 32 mmol) was added and the mixture was kept at –78 °C for 3 h. It was left to achieve rt overnight and then worked up*.	The ^1H NMR contains peaks that are characteristic of **23**. There are a lot of compounds present and column chromatography was unable to separate them into clean fractions. One of the fractions contained **23** (0.045 g, 10%).

* Work up consisted of washing the organic mixture with H_2O, extracting the aqueous layers with CH_2Cl_2 and washing the combined organic layers with saturated $NaCl_{(aq)}$. The organic solution was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure.

Table 2: Intramolecular Geminal Acylation Attempts with **18**



	Reaction Conditions	Products
1	A solution of **18** (0.610 g, 1.70 mmol) in CH_2Cl_2 (50 mL) was added to a solution of $BF_3{\cdot}Et_2O$ (4.3 mL, 34 mmol) in CH_2Cl_2 (800 mL) at a rate of 3.4 mL/h. Approximately 2 h after the addition, TFA (1.31 mL, 17.0 mmol) was added and the mixture was stirred for 2 h and the mixture was worked up*.	This reaction yielded **25**** in 7% yield. 
2	A solution of **18** (0.101 g, 0.282 mmol) in CH_2Cl_2 (50 mL) was added at a rate of 0.51mL/min to a solution of $BF_3{\cdot}Et_2O$ (0.71 mL, 5.6 mmol) in CH_2Cl_2 (700 mL). Following the addition, the mixture was worked up* and it appeared to contain OH peaks in its ^1H NMR spectrum. This was thought to be some of the cyclobutanone product obtained from the Mukaiyama-like aldol, so the mixture was diluted with CH_2Cl_2 (20 mL) and TFA (0.1 mL, 1.3 mmol) was added to try and invoke the pinacol-like rearrangement. After several additions with no obvious changes by tlc, the mixture was worked up* again.	This reaction yielded a lot of different products none of which were characterized.
3	A solution of **18** (0.113 g, 0.316 mmol) in CH_2Cl_2 (50 mL) was added to a solution of $BF_3{\cdot}Et_2O$ (0.06 mL, 0.5 mmol) in CH_2Cl_2 (700 mL) at a rate of 3.4 mL/min. TFA (0.24 mL, 3.0 mmol) was added 2 h after the syringe pump addition was complete and the mixture was stirred for 2 h. The mixture was then worked up*.	The ^1H NMR spectrum and the GC-MS chromatogram were identical with that of reaction 2.

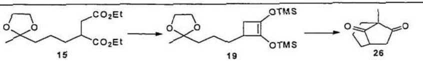
* Work up consisted of washing the organic mixture with H_2O, extracting the aqueous layers with CH_2Cl_2 and washing the combined organic layers with saturated $NaCl_{(aq)}$. The organic solution was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure

** **25** exists in its keto- enol- like form in solution, but exists in its cyclized form as a solid

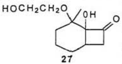
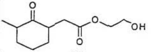
Table 2 cont.: Intramolecular Geminal Acylation Attempts with **18**

4	A solution of **18** (0.0978 g, 0.273 mmol)) in CH_2Cl_2 (50 mL) was added to a solution of BCl_3 (0.44 mL, 0.44 mmol) in CH_2Cl_2 (600 mL) at –78 °C. The mixture was stirred at –78 °C for 6.5 h and then left to achieve rt overnight. The next day it was cooled to –78 °C and a solution of HF (0.22 mL) in CH_3OH (0.47 mL) was added. The mixture was stirred at –78 °C for 10 min and then at rt for 1 h. The mixture was concentrated and TFA (0.83 mL, 8.6 mmol) was added. The mixture was stirred at rt for 24 h and then worked up*.	The crude ^1H NMR spectrum was very complex.
5	A solution of **18** (0.0758 g, 0.211 mmol) in CH_2Cl_2 (50 mL) was added to a solution of $BF_3{\cdot}Et_2O$ (0.05 mL, 0.4 mmol) in CH_2Cl_2 (600 mL) at –78 °C and kept at that temperature for 4.5 h. The mixture was allowed to achieve rt overnight. The mixture was worked up*.	The crude ^1H NMR spectrum was complex with no distinguishable peaks.
6	A solution of **18** (0.124 g, 0.346 mmol) in CH_2Cl_2 (50 mL) was added to a solution of $BF_3{\cdot}Et_2O$ (0.67 mL, 5.3 mmol) in $CHCl_2$ (600 mL) at –78 °C. The mixture was kept at –78 °C for 3.5 h and then allowed to achieve rt overnight. The mixture was worked up*.	The crude ^1H NMR spectrum shows evidence of **25**.
7	A solution of **18** (0.538 g, 1.50 mmol) in CH_2Cl_2 (50 mL) was added to a solution of $BF_3{\cdot}Et_2O$ (3.8 mL, 30 mmol) in $CHCl_2$ (500 mL). The mixture was stirred at rt for 3 h. TFA (1.2 mL, 16 mmol) was added and the mixture was stirred for another 2 h. It was worked up* and passed through a Florisil column.	This reaction yielded **25** (0.055 g, 18%).

Table 3: Intramolecular Geminal Acylation Attempts with **15** and **19**

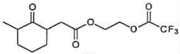


15 19 26

	Reaction Conditions	Products
1	An acyloin condensation was performed with **15** (0.396 g, 1.31 mmol), TMSCl (0.76 mL, 6.0 mmol), toluene (15 mL) and Na $_{(S)}$ (0.14 g, 6.1 mmol). The $Na_{(s)}$ was removed by suction filtration and the filtrate was cooled to –78 °C. $BF_3{\cdot}Et_2O$ (2.50 mL, 19.7 mmol) was added and it was kept a –78 °C for 4.5 h. The mixture was left to achieve rt overnight. It was worked up* and passed through Florisil.	This reaction yielded **26** (0.010 g, 5%).
2	An acyloin condensation was performed with **15** (0.587g, 1.94 mmol), TMSCl (1.1 mL, 8.7 mmol), toluene (25 mL) and Na $_{(S)}$ (0.20 g, 8.7 mmol). The mixture was suction filtered to remove the $Na_{(s)}$. The filtrate was cooled to –78 °C and $BF_3{\cdot}Et_2O$ (3.7 mL, 29 mmol) was added. It was kept at –78 °C for 7.5 h and allowed to achieve rt overnight. The mixture was worked up* and flushed through a Florisil column.	This reaction yielded **26** (0.070g, 7%) and **27** (0.021 g, 5%)  27
3	Compound **19** (0.225 g, 0.627 mmol) was dissolved in CH_2Cl_2 (5 mL). $BF_3{\cdot}Et_2O$ (0.10 mL, 7.0 mmol) was added at rt and the mixture was stirred for 10 min. H_2O (0.10 mL) was added and the mixture was stirred for 2.5 h. $BF_3{\cdot}Et_2O$ (1.2 mL, 7.0 mmol) was added and the mixture was stirred overnight to attain rt. The mixture was worked up*.	Crude ^{1}H NMR was very complex but there were some doublets present in the ^{1}H NMR spectrum that resemble the methyl signals of **28**  28

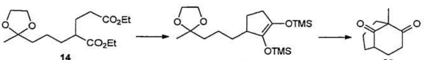
* Work up consisted of washing the organic mixture with H_2O, extracting the aqueous layers with CH_2Cl_2 and washing the combined organic layers with saturated $NaCl_{(aq)}$. The organic solution was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure.

Table 3 cont.: Intramolecular Geminal Acylation Attempts with **15** and **19**

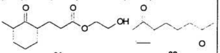
4	A solution of **19** (0.109 g, 0.304 mmol) in CH_2Cl_2 (50 mL) was added to a solution of $BF_3{\cdot}Et_2O$ (0.80 mL, 7.0 mmol) at 3.4 mL/h overnight. TFA (0.23 mL, 3.0 mmol) was added 3 h after the syringe pump addition was complete and the mixture was stirred for 7 h. It was then worked up*. There appeared to be OH peaks in the ^1H NMR spectrum so the mixture was diluted in CH_2Cl_2 (25 mL) and more TFA (2 mL) was added.	The ^1H NMR spectrum was a mixture of products that contained **27, 28, 29** and **15**. Compound **29** (0.013 g, 13%) was isolated after  **29** column chromatography.
5	A solution of **19** (0.316 g, 0.882 mmol) in CH_2Cl_2 (50 mL) was added to a solution of $BF_3{\cdot}Et_2O$ (2.2 mL, 7.0 mmol) in CH_2Cl_2 (800 mL) at 2.5 mL/h. TFA was added 2.5 h after the syringe pump addition was complete and 2 h later the mixture was worked up*.	Nothing of importance was visible in the ^1H NMR spectrum.
6	An acyloin condensation was performed with **15** (1.00 g, 3.32 mmol), TMSCl (1.93 mL, 15.2 mmol), toluene (25 mL) and $Na_{(S)}$ (0.35 g, 15 mmol). The mixture was suction filtered to remove the $Na_{(s)}$. The filtrate was cooled to –78 °C. $BF_3{\cdot}Et_2O$ (6.3 mL, 50 mmol) was added and the mixture was stirred for 7.5 h before achieving rt overnight. The mixture was worked up*.	**26** was isolated after column chromatography (0.080g, 16%).

* Work up consisted of washing the organic mixture with H_2O, extracting the aqueous layers with CH_2Cl_2 and washing the combined organic layers with saturated $NaCl_{(aq)}$. The organic solution was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure.

Table 4: Intramolecular Geminal Acylation Attempts with **16** and **20**



14 → 20 → 30

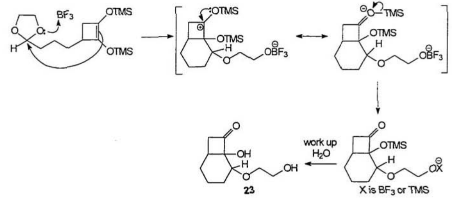
	Comments	Products
1	A solution of **20** (0.164 g, 0.439 mmol) in CH_2Cl_2 (50 mL) was added to a solution of $BF_3 \cdot Et_2O$ (1.1 mL) in CH_2Cl_2 (600 mL) at a rate of 3.4 mL/min. TFA (0.34 mL, 4.4 mmol) was added 3 h after the addition was finished and the mixture was left stirring for 4 h. The mixture was then worked up[•].	This reaction yielded a lot of products. These products included **30** (9%), **14** (2%), **31** (23%) and **32** (11%).  31 32
2	Compound **16** (1.25 g, 3.95 mmol), TMSCl (2.8 mL, 22 mmol), toluene (25 mL) and $Na_{(s)}$ (0.49 g, 21.3 mmol) underwent an acyloin condensation. The mixture was suction filtered and the filtrate was cooled to −78 °C. $BF_3 \cdot Et_2O$ (7.5 mL, 59 mmol) was added. The mixture attained rt overnight and the mixture was worked up[•].	This reaction yielded **30** (0.14 g, 23%) and **31** (0.22 g, 25%) after column chromatography.

From the results outlined in Tables 2 to 4, it is evident that after many attempts at this type of reaction there have been many disappointments, but some success. The intramolecular geminal acylation products derived from **11** and **12** have not been obtained. There have been some compounds isolated that suggest that the chemistry can indeed work. In the attempts with **15** and **16**, the expected products were isolated along with some side-products.

[•] Work up consisted of washing the organic mixture with H_2O, extracting the aqueous layers with CH_2Cl_2 and washing the combined organic layers with saturated $NaCl_{(aq)}$. The organic solution was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure.

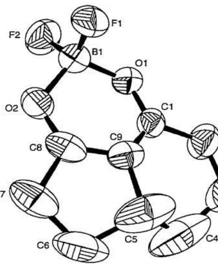
Table 1 describes in detail the attempts made at generating **22**. In most cases, the crude [1]H NMR spectra obtained were so complex that we were unable to determine if there was anything of importance present, and, even after column chromatography, it was not possible to elucidate the structures of any compounds. Reactions one, four and six did produce **23**. It was present in a mixture, but the spectra contained characteristic components of this compound. One distinguishing feature was the loss of the fragment ketene in the mass spectrum. This is very characteristic of cyclobutanone systems. The [1]H NMR spectrum also provided some features that seemed to be consistent with this structure. There were multiplets in the 3.5-4 ppm region, which is where the signals from the functionality derived from ethane-1,2-diol would be located. Isolation of this particular compound is a very good indication that this reaction has the capacity to do what is expected because this is the first step in our desired process. Scheme 18 shows the mechanism by which the Mukaiyama-like aldol reaction is expected to proceed and illustrates the derivation of **23**.

Scheme 18

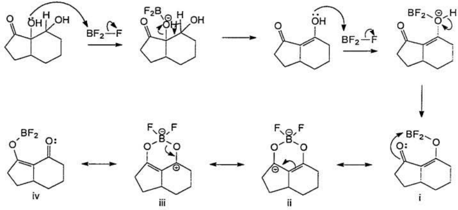


The intramolecular geminal acylation attempts with **18** provided a very interesting result. The column fractions obtained from reaction 1 were left to evaporate in order to better see the spots on the tlc plate before combining the fractions. In some of the tubes a white crystalline solid formed. The ^{1}H NMR and the ^{13}C NMR spectra were not consistent with literature values for **24**.[26] After performing other ^{1}H and ^{13}C NMR experiments and analyzing the data, the structure elucidation was still not clear. After many attempts at recrystallizing the solid, crystals were obtained and a single-crystal X-ray structure was obtained. The *ORTEP* representation is shown in Figure 3. The result was one that was not expected. A BF_2 group had been incorporated into the molecule from the Lewis acid. If the reaction proceeded as expected through the Mukaiyama-like aldol reaction, a fused ring structure could be obtained. There is a tertiary alcohol present that can perform an elimination reaction in the presence of acid. This ring structure and the postulated elimination step are shown in Scheme 19. When looking at the NMR spectra that had been obtained from **25** there was still some ambiguity. The carbon spectrum contained a carbonyl peak that was characteristic of a ketone. There was no ketone in the x-ray structure. There also appeared to be a quarternary double bond carbon that did not exist in the x-ray structure either. Finally, it was postulated that **25** exists in a cyclized form when it is a solid, but exhibits a keto-enol like tautomerization in solution. The x-ray structure is thought to be an average of resonance structures ii and iii in Scheme 19 and the NMR data obtained is either from resonance structures i, iv or the average of both i and iv as shown in Scheme 19.

Figure 3: X-Ray Structure of 25



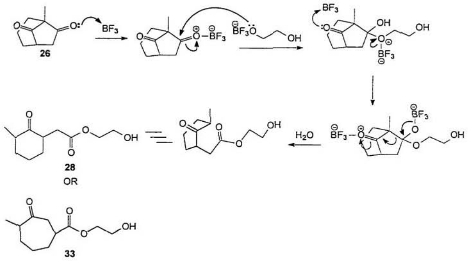
Scheme 19



The attempts at the intramolecular geminal acylation with **19** yielded positive results. Compounds at all stages of the reaction process were isolated, including the bridged 1,3-diketone, **26**. In reaction two of Table 3, **27** was isolated. This was the cyclobutanone compound that came from the Mukaiyama-like aldol reaction. It was generated in an analogous fashion to **23** in Scheme 18. Compound **27** was obtained in a much purer form than **23**. The minor impurity present was a small amount of **13**. The NMR spectra obtained show signals that are characteristic for **27**, including a resonance at 218 ppm for the cyclobutanone carbonyl in the ^{13}C NMR spectrum. It was also obvious in the ^{1}H NMR spectrum that an ethane-1,2-diol moiety was present in the compound because of a multiplet centered at 4.06 ppm. In reactions one, four and six, the bridged 1,3-diketone **26** was obtained. The ^{1}H NMR spectrum of **26** possesses a series of multiplets between 1.88 ppm and 2.95 ppm. The only other signal present is a methyl singlet at 1.06 ppm. All of the ^{13}C NMR resonances were present, including two ketone carbonyl peaks at 217.7 and 212.3 ppm. The other data obtained, including NMR correlation experiments and mass spectra fit this structure with no visible uncertainties.

The reactions involving **15** also yielded **28**. This is another good indication that the chemistry being attempted can indeed work. The keto-ester **28**, resulted from a reductive succinoylation reaction occurring after **26** formed. In Scheme 5, a reductive succinoylation reaction is described involving a 1,3-diketone. If the same mechanism is applied to the diketones that are generated from the intramolecular geminal acylation, compounds like **28** would be formed. Scheme 20 shows how these keto-esters could be generated from the bridged 1,3- diketones.

Scheme 20

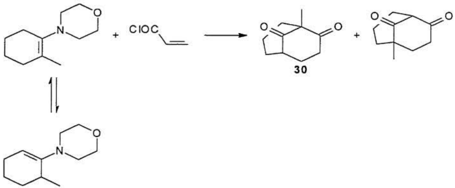


Compound **33** is another keto-ester that has the potential to form from a reductive succinoylation reaction of **26**. If the ethane-1,2-diol group attacked the other ketone carbonyl of **24**, the transformation would produce **33**. Although this compound was not isolated, it is possible that it was one of the minor components in the crude product mixtures.

Similar to the results of **15**, the results for **16** also appeared to be very promising. Again, the expected compound **30** was isolated. The ^{13}C NMR spectrum contained two ketone carbonyls and the ^{1}H NMR spectrum was similar to that of **26**. The ^{1}H NMR spectrum of **30** has a methyl singlet at 1.15 ppm and a series of multiplets between 1.68 and 2.90 ppm. The yields were still low, although in one instance **30** was obtained in a 23% crude yield.

Compound **30** had been previously prepared by a different procedure involving enamines.[26] The method by which Butkus and Bielinyte-Williams made **30** is shown in Scheme 21. They obtained a mixture of isomers by this route and the spectral data reported in the paper are very sketchy. The ^{13}C NMR data reported by Butkus, listed two ketone carbonyl peaks, neither of which matched the values that we obtained. Looking at the two isomers shown in Scheme 21, it was thought that the carbonyl peaks should be different. Also, they report data from a gated NMR spectrum for the tertiary carbons in both isomers. The value that they say came from **30** is not the value we obtained. We obtained the value that they propose came from the other isomer. We suggest that they have a mixture of both, but the major compound in their mixture is the isomer and not **30**.

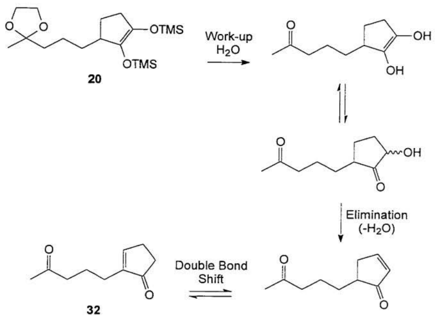
Scheme 21



The cyclopentanone intermediate expected from the Mukaiyama-like aldol step was not isolated in the experiments performed with **16**, but the reductive succinoylation product **31** was obtained. In the same manner as explained in Scheme 20, there are two expected reductive succinoylation products derived from 30. From the spectroscopic data, there does not appear to be any evidence for the keto-ester with an 8-membered ring. It is not known why only one of the two possible reductive succinoylation products was formed. From models of these molecules, it is apparent that the ketone carbonyl that is attacked is somewhat less hindered than the other ketone carbonyl. Six-membered rings are also more stable than eight-membered rings. These are two factors that might lead to the preference of one of the products to form over the other. In the paper by Butkus and Bielinyte-Williams[26] in which the preparation of **30** is described, hydrolysis of **30** is also detailed. They treated **30** and the isomer shown in Scheme 21 with 1 M HCl in hot methanol and achieved ring opened carboxylic acids that were similar to our ring-opened esters. The only structures that they reported are those with six-membered rings. There was no mention of any eight-membered ring structures. They did not even acknowledge that it was possible to obtain a ring-opening at the other carbonyl carbon under these conditions.

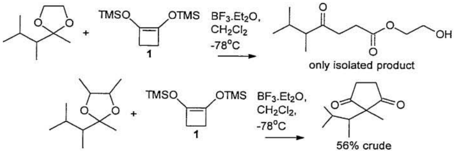
Another product was isolated in the reaction attempts with **16**. Compound **32** originates from **20**. If **20** did not react at all in the intramolecular geminal acylation reaction, the TMSO groups and the acetal would be hydrolyzed in the work up. This hydrolysis, followed by an elimination reaction and shifting of the double bond to its most stable position, gives rise to **32**. Scheme 22 depicts the formation of **32** from **20**.

Scheme 22



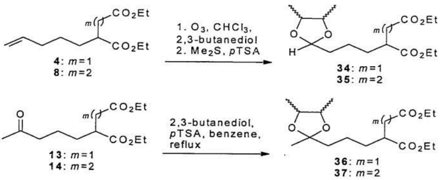
Compounds were isolated that indicated that the intramolecular geminal acylation reaction does indeed work. What was disappointing, however, was the formation of the reductive succinoylation products. Burnell and co-workers[4] had experienced such a phenomenon previously and had been able to overcome the problem. Scheme 23 outlines their results. By changing the acetal derived from ethane-1,2-diol for one derived from 2,3-butanediol, the desired geminal acylation product was isolated. It was thought that the extra steric hindrance due to the methyl groups prevented the diol from attacking one of the ketone carbonyls and generating the reductive succinoylation products. Based on this result, compounds were synthesized using 2,3-butanediol to create the acetals. The 2,3-butanediol was a mixture of stereoisomers.

Scheme 23



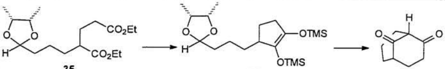
Acetals generated from 2,3-butanediol were obtained from compounds **4, 8, 13** and **14**. They were generated in the same manner as their corresponding ethane-1,2-diol acetals **11, 12, 15** and **16**. Scheme 24 outlines these syntheses.

Scheme 24



These acetals were then transformed via an acyloin condensation and more attempts were made at the intramolecular geminal acylation reaction. The investigations with the 2,3-butanediol acetals centered on compounds **35**, **36** and **37**. The reason that these three compounds were used was that spectroscopic data were available from the literature[26] for diketone **24**, which would arise from compound **35**, and the diketones expected from **36** and **37** had previously been isolated. The results obtained from the reactions performed with these acetals are summarized in Tables 5, 6 and 7.

Table 5: Intramolecular Geminal Acylation Attempts with **38**

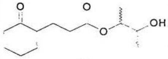


35 → **38** → **24**

	Reaction Conditions	Products
1	A solution of **38** (0.134 g, 0.347 mmol) in CH_2Cl_2 (50 mL) was added to a solution of $BF_3{\cdot}Et_2O$ (0.09 mL, 0.7 mmol) in CH_2Cl_2 (600 mL) at a rate of 0.51 mL/min at rt. Following the addition, the mixture was concentrated to approximately 100 mL and TFA (2.7 mL, 35 mmol) was added. The mixture was stirred for 1 h before work up*.	There was no sign of the desired product **24** (multiplet at 3.1ppm[26]) in the ^1H NMR spectrum.
2	A solution of **38** (0.124 g, 0.321 mmol) in CH_2Cl_2 (50 mL) was added to a solution of $BF_3{\cdot}Et_2O$ (0.08 mL, 0.6 mmol) and stirred for 1h at rt, The mixture was concentrated to approximately 50 mL TFA (0.27 mL, 3.5 mmol) was added. The mixture was stirred for 1 h and then worked up*.	There may be a small amount of **25**, but there was no evidence of **24** in the ^1H NMR spectrum.

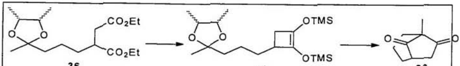
* Work up consisted of washing the organic mixture with H_2O, extracting the aqueous layers with CH_2Cl_2 and washing the combined organic layers with saturated $NaCl_{(aq)}$. The organic solution was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure.

Table 5 cont.: Intramolecular Geminal Acylation Attempts with **38**

3	A solution of **38** (0.0749 g, 0.193 mmol) in CH_2Cl_2 (50 mL) was added to a cooled solution of $BF_3{\cdot}Et_2O$ (0.05 mL, 0.4 mmol) in CH_2Cl_2 (600 mL) and stirred at –78 °C for 1 h. The bath was removed and the mixture was stirred for 2.5 h at rt. The mixture was worked up*.	There was no evidence of **24** or **25** in the crude ^{1}H NMR.
4	A solution of **38** (0.0761 g, 0.197 mmol) in CH_2Cl_2 (50 mL) was added to a stirring solution of BCl_3 (0.31 mL, 0.31mmol) in CH_2Cl_2 (600 mL) at –78 °C for 3.25 h and left to achieve rt overnight. The mixture was cooled to –78 °C and a solution of HF (0.16 mL) in MeOH (0.33 mL) was added and stirred at –78 °C for 10min. The mixture was then stirred at rt for 1 h. The mixture was concentrated and TFA (0.58 mL) was added. The mixture was left stirring at rt for 24 h and then worked up*.	The ^{1}H NMR spectrum showed a small amount of **25**, but there was no evidence of **24**. Compound **39** (0.011 g, 23%) was isolated after column purification.  **39**
5	A solution of **38** (0.070 g, 0.181 mmol) in CH_2Cl_2 (50 mL) was added to a solution of $BF_3{\cdot}Et_2O$ (0.05 mL, 0.4 mmol) in CH_2Cl_2 (600 mL) at –78 °C. The mixture attained rt overnight and it was worked up*.	The ^{1}H NMR spectrum showed no evidence of **24** or **25**, but it did contain a small amount of **39**.
6	A solution of **38** (0.0831 g, 0.214 mmol) in CH_2Cl_2 was added to a solution of $ZnCl_2$ (0.12 g. 0.88 mmol) in CH_2Cl_2 (600 mL) at –78 °C and kept at this temperature for 5.5 h. The mixture attained rt overnight and was worked up*.	There was no evidence of **24**, **25**, or **39** in the ^{1}H NMR spectrum.

* Work up consisted of washing the organic mixture with H_2O, extracting the aqueous layers with CH_2Cl_2 and washing the combined organic layers with saturated $NaCl_{(aq)}$. The organic solution was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure.

Table 6: Intramolecular Geminal Acylation Attempts with **40**

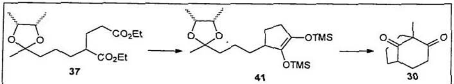


36 → **40** → **26**

	Reaction Conditions	Products
1	A solution of **40** (0.156 g, 0.403 mmol) in CH_2Cl_2 (50 mL) was added to a solution of $BF_3{\cdot}Et_2O$ (0.10 mL, 0.79 mmol) in CH_2Cl_2 (600 mL) with the syringe pump set at 0.51mL/min. Following the addition, the mixture was concentrated to approximately 100 mL and TFA (0.31 mL, 4.0 mmol) was added. The mixture was stirred for 1 h at rt and then worked up*.	The ^{1}H NMR spectrum contained peaks from **26** and **13**. There was no evidence of any reductive succinoylation products. This reaction yielded **26** (0.022 g, 36%) after purification by column chromatography.
2	Compound **40** (0.168 g, 0.434 mmol) was dissolved in toluene (25 mL) and cooled to –78 °C. $BF_3{\cdot}Et_2O$ (0.83 mL, 6.5 mmol) was added. The mixture was kept at –78 °C for 1 h and then attained rt overnight. The mixture was worked up*.	The ^{1}H NMR spectrum did not contain **26**. There was no evidence of any reductive succinoylation products.
3	Compound **40** (0.185 g, 0.479 mmol) was dissolved CH_2Cl_2 (25 mL) and cooled to –78 °C. $BF_3{\cdot}Et_2O$ (0.91mL, 7.2 mmol) was added and the mixture was kept at -78 °C for 1 h. The mixture attained rt overnight and was worked up*.	The ^{1}H NMR spectrum did not contain **26**. There was no evidence of any reductive succinoylation products.
4	A solution of **40** (0.112 g, 0.289 mmol) in CH_2Cl_2 (75 mL) was added to a solution of $BF_3{\cdot}Et_2O$ (0.55 mL, 7.0 mmol) in CH_2Cl_2 (600 mL) at –78 °C. The mixture was attained rt overnight. The mixture was worked up*.	The ^{1}H NMR spectrum contained a small amount of **26**. There was no evidence of any reductive succinoylation products.

* Work up consisted of washing the organic mixture with H_2O, extracting the aqueous layers with CH_2Cl_2 and washing the combined organic layers with saturated $NaCl_{(aq)}$. The organic solution was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure.

Table 7: Intramolecular Geminal Acylation Attempt with **41**



	Reaction Conditions	Products
1	A solution of **41** (0.17 g, 0.42 mmol) in CH_2Cl_2 (50 mL) was added to a solution of $BF_3 \cdot Et_2O$ (0.11 mL, 7.0 mmol) at 0.51mL/min at rt. Following the addition, the mixture was concentrated to approximately 100 mL and TFA (0.33 mL, 4.3 mmol) was added. The mixture was stirred for 1h and then worked up*.	The reaction yielded **30** (0.0060 g, 9%) and **14** (0.0062 g, 5%) after column purification. There was no evidence of the reductive succinoylation products.

The results obtained from the acetals derived from 2,3-butanediol were not what we expected. Based on previous work,[4c] it was hoped that the yields of the desired compounds **24**, **26** and **30** would increase. This was not the case. In the reactions to generate **24**, there was no evidence of the formation of any of the desired compound. There was also very little of **25** generated. This suggested that the reaction had not proceeded through the Mukaiyama-like aldol condensation. The unfortunate result is that **39** did form. This is a good indication that the molecules that did manage to generate **24** still underwent a reductive succinoylation reaction. The different acetal was unsuccessful in stopping the destruction of **24**.

The results obtained from reactions with **36** and **37** were a little bit different. The reaction mixtures were still complex by ^1H NMR, and, even after column

* Work up consisted of washing the organic mixture with H_2O, extracting the aqueous layers with CH_2Cl_2 and washing the combined organic layers with saturated $NaCl_{(aq)}$. The organic solution was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure.

chromatography it was difficult to detect anything. Small amounts of the desired compounds were generated, but the yields did not improve very much compared to the reactions performed with the ethane-1,2-diol acetals. We did not find evidence of any reductive succinoylation products in this set of reactions, however it was thought that the extra hindrance due to the methyl substituents on the acetal functionality was inhibiting the intramolecular geminal acylation reaction.

Considerations for Future Work.

The initial work with the intramolecular geminal acylation reaction appears to be promising. Some of the desired bridged 1,3-diketones have been obtained and other side-products have been isolated. The yields for these products are very low and not synthetically useful at this point. There is still much work required before this reaction will see use in natural product synthesis.

One idea that can be investigated is the use of methyl acetals in the reaction instead of those derived from ethane-1,2-diol or other diols. In this case, methanol would be liberated in the reaction mixture as opposed to ethane-1,2-diol. If the reaction is performed in the presence of 5Å Molecular Sieves, then maybe the methanol can be trapped before it can cause the reductive succinoylation reaction and destroy the bridged 1,3-diketones. The parameters that were manipulated in this research including dilution, the type of Lewis acid, and others, could once again be repeated in the presence of the Molecular Sieves.

Another facet of this research that needs to be continued is the work with the hydroboration reaction. The conditions employed here did not work well with these particular substrates. More work might go into improving this step and then into attempting intramolecular geminal acylation reactions that will generate larger ring systems.

Finally, it is anticipated that this methodology will be successful in finding its way into natural product synthesis. There are compounds that could be synthesized using this method as a key transformation, one of which is vinigrol.

Experimental Section

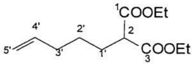
General Section:

Flash chromatography ("chromatography") was performed using 240-400 mesh silica gel. IR spectra were recorded on the Mattson FT-IR instrument as thin films. Relative intensities of the absorption bands are recorded using the following abbreviations: s (strong), m (medium), and w (weak). ^{1}H NMR spectra were obtained on a General Electric GE-300 NB spectrometer at 300MHz in $CDCl_3$ unless otherwise specified and shifts are relative to an internal trimethylsilane signal. Some of the NMR data were obtained on the Bruker Avance 500 MHz instrument with a TXI inverse detect gradient probe and these data sets are designated in the experimental section. The following abbreviations are used in the description of the ^{1}H NMR: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). The ^{13}C NMR spectra were recorded on the same instrument at 75 MHz, and shifts were measured relative to the solvent. The number of attached protons was determined by an attached proton test (APT) and heteronuclear correlations, follow each chemical shift in parentheses. Overlap may have prevented the reporting of all resonances when the spectral data of compounds were obtained from mixtures. NMR free induction decay data were processed using WinNuts (Acorn NMR software). Low resolution mass spectral data were recorded on the V.G. Micromass 7070HS instrument. High resolution mass spectra were obtained from the Dalhousie University mass spectrometry facility. Melting points were determined using a Fisher-Johns hot stage apparatus and were uncorrected. Mr. David Miller, who also carried out the structure elucidation, obtained data for the x-ray structure on the Rigaku AFC65 diffractometer. The GC-MS spectra were recorded on a Hewlett Packard (HP) 5890 Series 2 GC-MS.

General Procedure for Alkylation of Diethyl Malonate and Derivatives. Compounds **5**, **6**, and **7** were prepared using the method Adams and Kamm.[21] Absolute ethanol was dried over sodium metal and freshly distilled into the reaction flask, and all reactions were performed under an inert atmosphere of nitrogen.

Compound **4** is located with the geminal decarboxylation products, following compound **7**.

Diethyl 2-(4-pentenyl)propanedioate (5)

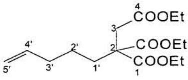


5

Absolute ethanol (45 mL) was distilled into a three-necked flask bearing a stopper and a septum. The flask was fitted with a condenser. The flask was charged with $Na_{(s)}$ (2.94 g, 0.128 mol) and the mixture was stirred and heated until the solid had dispersed. The mixture did not reach reflux temperature. Diethyl malonate (20.0 mL, 0.132 mol) was added dropwise over 45 minutes and then 5-bromo-1-pentene (15.0 mL, 0.127 mol) was added to the mixture dropwise over 50 minutes. The mixture was heated under reflux and this temperature was maintained until it was neutral to pH paper. The reaction mixture was stirred overnight at rt. Aqueous work up consisted of adding 50 mL of ether to the mixture, washing the organic solution with H_2O (2 x 50 mL), extracting the aqueous layers with ether (2 x 50 mL) and, washing the combined organic layers with saturated

$NaCl_{(aq)}$ (50 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was vacuum distilled to yield 22.3 g of **5** (77% yield, 85% yield based on recovered diethyl malonate) as a colorless liquid: bp 83-85.5°C (0.6 mmHg). IR: ν_{max} 3078 (w), 1753 (s), 1736 (s), 1731 (s), 1641 (w) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.79 (1H, m, H-4'), 5.01 (2H, m, H-5'), 4.22 (4H, q, *J*=7.0 Hz, O**CH₂**CH₃), 3.33 (1H, t, *J*=7.5 Hz, H-2), 2.10 (2H, m, H-3'), 1.92 (2H, m, H-1'), 1.44 (2H, m, H-2'), 1.26 (6H, t, *J*=7.0 Hz, OCH_2**CH_3**). ^{13}C NMR ($CDCl_3$): δ 169.4 (0, C-1 and C-3), 137.9 (1, C-4'), 114.9 (2, C-5'), 61.2 (2C, 2, O**CH_2**CH_3), 51.9 (1, C-2), 33.2 (2, C-3'), 28.1 (2, C-1'), 26.5 (2, C-2'), 14.0 (2C, 3, OCH_2**CH_3**). MS *m/z* (%): 229 (1, M^++1), 173 (12), 160 (22), 137 (25), 136 (20), 109 (19), 108 (28), 81 (25), 80 (19), 73 (14), 68 (12), 67 (24), 55 (40), 54 (29), 41 (34), 39 (17), 29 (100), 27 (35). HRMS calcd for $C_{12}H_{20}O_4$: 183.1021 (M^+-OEt); found: 183.1022.

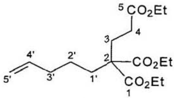
Diethyl 2-carboxyethyl-2-(4-pentenyl)butanedioate (6)



6

Absolute ethanol (22 mL) was distilled into a three-necked flask bearing a stopper and a septum. The flask was fitted with a condenser. The flask was charged with $Na_{(s)}$ (1.42 g, 61.8 mmol), and the mixture was stirred and heated until the solid had dispersed. The mixture did not reach reflux. Compound **5** (14.6 g, 63.9 mmol) was added dropwise over 40 minutes. Ethyl bromoacetate (6.9 mL, 0.062 mol) was added to the mixture dropwise over 20 minutes. The mixture was then heated under reflux and this temperature was maintained until the mixture was neutral to pH paper. The reaction mixture was stirred overnight at rt. Aqueous work up consisted of adding ether (50 mL) to the mixture, washing the organic layer with H_2O (2 x 50 mL), extracting the aqueous layers with ether (2 x 50 mL) and, washing the combined organic layers with saturated $NaCl_{(aq)}$ (50 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure to yield 15.5 g of **6** (80% yield, 90% yield based on recovered **5**) as a yellowish liquid. IR: ν_{max} 3078 (w), 1737 (s), 1632 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.77 (1H, m, H-4'), 5.00 (2H, m, H-5'), 4.21 (4H, q, *J*=7.1 Hz, O**CH₂**CH₃), 4.21 (2H, q, *J*=7.1 Hz, O**CH₂**CH₃), 2.97 (2H, s, H-3), 2.04 (4H, m, H-1'and H-3'), 1.34 (2H, m, H-2'), 1.27 (6H, t, *J*=7.1 Hz, OCH₂**CH₃**), 1.25 (3H, t, *J*=7.1 Hz, OCH₂**CH₃**). ^{13}C NMR ($CDCl_3$): δ 170.3 (0, C-1), 170.2 (0, C-4), 137.7 (1, C-4'), 114.9 (2, C-5'), 61.3 (2C, 2, O**CH₂**CH₃), 60.5 (2, O**CH₂**CH₃), 55.3 (0, C-2), 37.4 (2, C-3), 33.5 (2, C-3'), 32.4 (2, C-1'), 23.5 (2, C-2'), 13.9 (3, OCH₂**CH₃**), 13.8 (2C, 3, OCH₂**CH₃**). MS *m/z* (%): 269 (11, M^+-OEt), 222 (18), 195 (13), 173 (21), 149 (12), 148 (10), 93 (22), 79 (12), 67 (15), 55 (16), 41 (21), 29 (100), 27 (22). HRMS calcd for $C_{16}H_{26}O_6$: 269.1389 (M^+-OEt); found: 269.1381.

Diethyl 2-carboxyethyl-2-(4-pentenyl)pentanedioate (7)

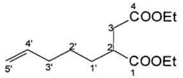


7

Absolute ethanol (21mL) was distilled into a three-necked flask bearing a stopper and a septum. The flask was fitted with a condenser. The flask was charged with $Na_{(s)}$ (1.40 g, 60.9 mmol), and the mixture was stirred and heated until the solid had dispersed. The mixture did not reach reflux. Compound **5** (14.3 g, 62.6 mmol) was added dropwise over 45 minutes. Ethyl 3-chloropropionate (8.33 g, 61.0 mmol) was added to the mixture dropwise over 25 minutes. The mixture was heated under reflux, and this temperature was maintained until it was neutral to pH paper. The reaction mixture was stirred overnight at rt. Aqueous work up consisted of adding ether (50 mL) to the mixture, washing the organic layers with H_2O (2 x 100 mL), extracting the aqueous layers with ether (2 x 100 mL) and, washing the combined organic layers saturated $NaCl_{(aq)}$ (100 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. This yielded 19.3 g of **7** (96% crude yield), a yellowish-brown liquid that was clean enough by ^{1}H NMR to use without purification. IR: ν_{max} 1733 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.77 (1H, m, H-4'), 5.01 (2H, m, H-5'), 4.20 (4H, q, *J*=7.1 Hz, $\mathbf{OCH_2}CH_3$), 4.13 (2H, q, *J*=7.1 Hz, $\mathbf{OCH_2}CH_3$), 2.25 (4H, m, H-3 and H-4), 2.07 (2H, q, *J*=7.1 Hz, H-3'), 1.88 (2H, m, H-1'), 1.31 (2H, m, H-2'), 1.27 (6H, t, *J*=7.1 Hz, $OCH_2\mathbf{CH_3}$), 1.26 (3H, t, *J*=7.1 Hz, $OCH_2\mathbf{CH_3}$). ^{13}C NMR ($CDCl_3$): δ 172.7 and 171.1 (3C, 0, $\mathbf{CO_2}Et$), 137.8 (1, C-4'), 115.0 (2, C-5'), 61.2 and 60.5 (3C, 2, OCH_2CH_3), 56.7 (0, C-2), 33.7 (2, C-3'), 32.3 (2, C-1'), 29.5 and 27.6 (2C, 2, C-3 and C-4), 23.2 (2, C-2'), 14.0 (3C, 3, OCH_2CH_3). MS *m/z* (%): 283 (23, M^+-OEt), 260 (14), 237 (14), 236 (34), 209 (20), 190 (17), 186 (26), 181 (14), 173 (27), 163 (31), 162 (17), 155 (13), 140 (15), 135 (25), 127 (19), 107 (15), 99 (14), 95 (10), 93 (34), 81 (10), 79 (14), 67 (27), 55 (28), 54 (33), 43 (16), 41 (32), 29 (100). HRMS calcd for $C_{17}H_{28}O_6$: 328.1886; found: 328.1884.

General Procedure for Decarboxylation. Compounds **4** and **8** were generated using the method of Krapcho and Loveys.[22] Compounds **6** and **7** were treated with dimethyl sulfoxide (DMSO), H_2O, NaBr and heated under reflux to convert the triesters into diesters.

Diethyl 2-(4-pentenyl)butanedioate (4)

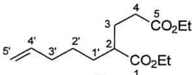


4

NaBr (4.26 g, 41.4 mmol), **6** (12.1 g, 38.5 mmol), H_2O (2.1 mL, 0.120 mol), and DMSO (100 mL) were placed in a round-bottomed flask fitted with a condenser and a drying tube. The mixture was heated under reflux gently in an oil bath. The reaction was monitored by thin layer chromatography (tlc) until it appeared as though all of the starting material was consumed, approximately 24 h. The mixture was then cooled to rt and ether (50 mL) was added. The organic solution was washed with H_2O (2 x 100 mL), the aqueous layers were extracted with ether (3 x 100 mL), and the combined organic layers were washed with saturated $NaCl_{(aq)}$ (100 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography to yield **4** (7.17 g, 77% yield) as a colorless liquid: bp 116-119 °C (3 mmHg). IR: ν_{max} 3078 (w), 1775 (w), 1737 (s), 1641 (w) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.79 (1H, m, H-4'), 5.00 (2H, m, H-5'), 4.16 (4H, m, O**CH$_2$**CH$_3$), 2.84 (1H, m, H-2), 2.72 (1H, dd, J=16.2, 9.3 Hz, H-3), 2.43 (1H, dd, J=16.2, 5.1 Hz, H-3), 2.07 (2H, m, H-3'), 1.55 (4H, m, H-1'and H-2'), 1.26 (6H, m, OCH$_2$**CH$_3$**). ^{13}C NMR ($CDCl_3$): δ 174.9 and 171.9 (0, C-1 and C-4), 138.1 (1, C-4'), 114.8 (2, C-5'), 60.5 (2C, 2, O**CH$_2$**CH$_3$), 41.1 (1, C-2), 36.1 (2, C-3), 33.4 (2, C-3'), 31.3 (2, C-1'), 26.1 (2, C-2'), 14.2 (3, OCH$_2$**CH$_3$**), 14.1 (3, OCH$_2$**CH$_3$**). MS m/z (%): 197 (10, M$^+$-OEt), 151 (12), 150 (21), 128 (14), 95

(17), 81 (22), 67 (12), 55 (24), 54 (23), 43 (10), 41 (34), 39 (22), 29 (100), 27 (41). HRMS calcd for $C_{13}H_{22}O_4$: 197.1178 (M+-OEt); found: 197.1180.

Diethyl 2-(4-pentenyl)pentanedioate (8)



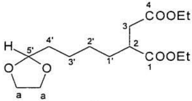
8

NaBr (6.34 g, 61.6 mmol), **7** (18.4 g, 56.0 mmol), H_2O (3.0 mL, 0.17 mol), and DMSO (100 mL) were placed in a round-bottomed flask, fitted with a condenser and a drying tube. The mixture was heated under reflux gently in an oil bath. The reaction was monitored by tlc until it appeared as though all of the starting material was consumed which was approximately 24 h. The mixture was then cooled to rt and ether (50 mL) was added. The organic mixture was washed with H_2O (2 x 50 mL), the aqueous layers were extracted with ether (3 x 50 mL), and the combined organic layers were washed with saturated $NaCl_{(aq)}$ (50 mL). The organic layer was dried over anhydrous $MgSO_4$ and solvent removal was achieved under reduced pressure. This yielded **8** (14.1 g, 98% crude yield) as a dark orange-brown liquid. Compound **8** was clean enough by ^{1}H NMR to use without purification: bp 116-119 °C (3 mmHg). IR: ν_{max} 3077 (m), 1732 (s), 1641 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.87 (1H, m, H-4'), 5.07 (2H, m, H-5'), 4.24 (2H, q, *J*=7.1 Hz, O**CH₂**CH₃), 4.22 (2H, q, *J*=7.1 Hz, O**CH₂**CH₃), 2.41 (3H, m, H-2 and H-4), 2.14 (2H, br q, *J*=7.0 Hz, H-3'), 1.96 (2H, m, H-3), 1.61 (4H, m, H-1'and H-2'), 1.35 (6H, t, *J*=7.1 Hz, OCH₂**CH₃**). ^{13}C NMR ($CDCl_3$): δ 175.5 and 173.0 (0, C-1 and C-4), 138.3 (1, C-4'), 114.7 (2, C-5'), 60.3 (2, O**CH₂**CH₃), 60.2 (2, O**CH₂**CH₃), 44.6 (1, C-2), 33.5 (2, C-3'), 32.0 (2, C-3), 31.6 (2, C-1'), 27.1 (2, C-4), 26.4 (2, C-2'), 14.2 (2C, 3, OCH₂**CH₃**). MS *m/z* (%): 211 (36, M^+-OEt), 165 (24), 164 (100), 155 (26), 142 (24), 141 (16), 137 (33), 136 (27), 127 (12), 122 (15), 119 (12), 114 (47), 113 (11), 109 (23), 108 (12), 101 (17), 99 (14), 95 (60), 94 (33), 93 (22), 88 (14), 86 (11), 83 (11), 81 (21), 79 (13), 73 (18), 71 (15), 69 (14), 68 (15), 67 (44), 55 (47), 54 (46), 43 (22), 41 (58), 39 (25), 29 (100). HRMS calcd for $C_{14}H_{24}O_4$: 256.1674; found: 256.1691.

General Procedure for Hydroboration, Oxidation and Acetal Formation.

Compounds **9** and **10** were synthesized from compounds **4** and **8**. Two different methods[23] were employed to produce these compounds, neither of which was very good. Initially, the method of Brown was employed which utilized 9-BBN and secondly, dicyclohexylborane was used as the borane reagent. In all instances, the hydroboration and oxidation reactions were carried out under an inert atmosphere of nitrogen. The CH_2Cl_2 was distilled over CaH_2 and the tetrahydrofuran (THF) was distilled over $Na_{(S)}$.

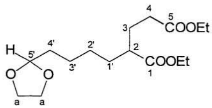
Diethyl 2-(5-oxopentyl)butanedioate, ethylene acetal (9)



9

9-BBN (3.8 mL of 0.5 M solution in THF) was placed in a 25 mL round-bottomed flask. At rt, a solution of **4** (0.456 g, 1.88 mmol in 2 mL of THF) was added and stirred for 2 h. This mixture was transferred via a canula into a vigorously stirring solution of PCC (1.51 g, 7.00 mmol in 8 mL of CH_2Cl_2). The mixture was heated under reflux for 2 h. It was cooled to rt, passed through a Florisil column and concentrated. The residue was then combined with ethane-1,2-diol (0.67 g, 0.011 mol), a small amount of *p*TsOH and benzene (40 mL). The flask was fitted with a Barrett apparatus and heated under reflux for 5 days. The mixture was cooled to rt and the benzene was removed under reduced pressure. CH_2Cl_2 (25 mL) was added to the residue, and the organic solution was washed with saturated $NaHCO_{3(aq)}$ (2 x 25 mL), the aqueous layers were extracted with CH_2Cl_2 (2 x 25 mL) and the combined organic layers were washed with saturated $NaCl_{(aq)}$ (50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography to yield **9** (0.11 g, 20% yield) as a colorless liquid: IR: ν_{max} 1733 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 4.85 (1H, t, *J*=4.7 Hz, H-5'), 4.17 (2H, q, *J*=7.2 Hz, O**CH$_2$**CH$_3$), 4.14 (2H, q, *J*=7.2 Hz, O**CH$_2$**CH$_3$), 3.91 (4H, m, H-a), 2.84 (1H, m, H-2), 2.71 (1H, dd, *J*=16.3, 9.3 Hz, H-3), 2.43 (1H, dd, *J*=16.3, 5.1 Hz, H-3), 1.31 to 1.71 (8H, m, H-1', H-2', H-3', and H-4'), 1.27 (3H, t, *J*=7.2 Hz, OCH$_2$**CH$_3$**), 1.26 (3H, t, *J*=7.2 Hz, OCH$_2$**CH$_3$**). ^{13}C NMR ($CDCl_3$): δ 174.8 and 171.9 (0, C-1 and C-4), 104.3 (1, C-5'), 64.7 (2C, 2, C-a), 60.4 (2C, 2, O**CH$_2$**CH$_3$), 41.1 (1, C-2), 36.0 (2, C-3), 33.5, 31.7, 26.7, and 23.7 (4C, 2, C-1', 2', 3', and 4'), 14.1 (2C, 3, OCH$_2$**CH$_3$**). MS *m/z* (%): 257 (2, M^+-OEt), 73 (100), 45 (11), 29 (11). HRMS calcd for $C_{15}H_{26}O_6$: 302.1729; found: 302.1731.

Diethyl 2-(5-oxopentyl)pentanedioate, ethylene acetal (10)

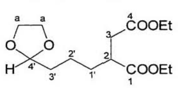


10

BH_3.THF (0.64 mL of 1.0 M solution in THF) and cyclohexene (0.13 mL, 1.28 mmol) were stirred in an ice-water bath for 1 h. Compound **8** (0.165 g, 0.643 mmol) was added and the ice-bath was removed. The mixture was stirred at rt for 2 h. This mixture was transferred via a canula into a vigorously stirring solution of PCC (0.51 g, 2.37 mmol in 3 mL of CH_2Cl_2). The mixture was then heated under reflux for 2 h. It was cooled to rt, flushed through a Florisil column and concentrated. The residue was combined with butane-1,2-diol (0.20 g, 3.22 mmol), a small amount of *p*TsOH in benzene (80 mL). The flask was fitted with a Barrett apparatus and heated under reflux for 4 days. The mixture was cooled to rt, and the benzene was removed under reduced pressure. CH_2Cl_2 (25 mL) was added to the residue and the organic solution was washed with saturated $NaHCO_{3(aq)}$ (2 x 25 mL), the aqueous layers were extracted with CH_2Cl_2 (2 x 25 mL) and the combined organic layers were washed with saturated $NaCl_{(aq)}$ (1 x 50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated. Purification of the residue was attempted by column chromatography and yielded **10** (0.014 g, 7% yield) as a colorless liquid. Compound **10** was still impure, therefore ^1H and ^{13}C NMR were the only spectroscopic analyses obtained. ^1H NMR (500 MHz, $CDCl_3$): δ 4.83 (1H, t, *J*=4.8 Hz, H-5'), 4.14 (4H, m, O$\mathbf{CH_2}$$CH_3$), 2.94 (4H, m, H-a), 2.34, 1.87, 1.64 and 1.41 (13H, m, H-2, 3, 4, 1', 2', 3'and 4'), 1.26 (6H, m, $OCH_2$$\mathbf{CH_3}$). ^{13}C NMR (125 MHz, $CDCl_3$): δ175.5 and 173.0 (2C, 0, C-1 and C-5), 104.5 (1, C-5'), 64.8 (2C, H-a), 60.4 and 60.3 (2, O$\mathbf{CH_2}$$CH_3$), 44.7, 33.6, 32.2, 32.0, 27.2, and 23.9 (C-2, 3, 4, 1', 2',3', and 4'), 14.3 and 14.2 (3, $OCH_2$$\mathbf{CH_3}$).

General Procedure for Ozonolysis and Acetal Formation. The ozonolysis procedure was based on the method of Pappas[24] with some modifications. The ozone was generated using a Welsbach T-408 ozonator.

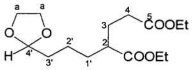
Diethyl 2-(4-oxobutyl)butanedioate, ethylene acetal (11)



11

Butane-1,2-diol (1.26 g, 20.3 mmol), **4** (0.478 g, 1.97 mmol) and $CHCl_3$ (25 mL) were stirred in a round-bottomed flask at –78 °C. $O_{3\,(g)}$ was bubbled through the solution until a blue color persisted (approximately 20 min). The $O_{3\,(g)}$ inlet was then removed, and the flask was taken out of the dry ice/acetone bath. The mixture was purged with $N_{2(g)}$ for 30 minutes. Me_2S (3 mL) was added along with a small portion of *p*TsOH. The mixture was stirred at rt for 3 days. The organic mixture was washed with saturated $NaHCO_{3\,(aq)}$ (2 x 100mL), the aqueous layers were extracted with CH_2Cl_2 (2 x 100mL), the organic layers were washed with saturated $NaCl_{\,(aq)}$ (100mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to yield homogeneous **11** (0.52 g, 91% crude yield) as a colorless liquid. IR: ν_{max} 1731 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.85 (1H, t, *J*=4.6 Hz, H-4'), 4.15 (4H, m, O**CH$_2$**CH$_3$), 3.91 (4H, m, H-a), 2.84 (1H, m, H-2), 2.72 (1H, dd, *J*=16.2, 9.4 Hz, H-3), 2.44 (1H, dd, *J*=16.2, 5.0 Hz, H-3), 1.40 to 1.83 (6H, m, H-1', H-2'and H-3'), 1.27 (3H, t, *J*=7.1 Hz, OCH$_2$**CH$_3$**), 1.26 (3H, t, *J*=7.2 Hz, H-OCH$_2$**CH$_3$**). ^{13}C NMR ($CDCl_3$): δ 174.7 and 171.8 (0, C-1 and C-4), 104.1 (1, C-4'), 64.8 (2C, 2, C-a), 60.5 (2C, 2, O**CH$_2$**CH$_3$), 41.1 (1, C-1), 36.0 (2, C-3), 33.5 (2, C-3'), 31.7 (2, C-1'), 21.3 (2, C-2'), 14.1 (2C, 3, OCH$_2$**CH$_3$**). MS *m/z* (%): 243 (8, M^+-OEt), 73(100). HRMS calcd for $C_{14}H_{24}O_6$: 288.1573; found: 288.1574.

Diethyl 2-(4-oxobutyl)pentanedioate, ethylene acetal (12)

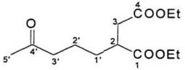


12

Butane-1,2-diol (16.3 g, 0.262 mol), **8** (6.69 g, 26.1 mmol) and $CHCl_3$ (150 mL) at –78 °C. $O_{3\,(g)}$ was bubbled through the solution until a blue color persisted (approximately 20 min). The $O_{3\,(g)}$ was then removed and the flask was taken out of the dry ice/ acetone bath. The mixture was purged with $N_{2(g)}$ for 30 minutes. Me_2S (36 mL) was added along with a small portion of *p*TsOH. The mixture was stirred at room temperature for 3 days. The mixture was washed with 2 x 100 mL of saturated $NaHCO_{3\,(aq)}$, extracted with 2 x 75 mL of CH_2Cl_2, washed with 1 x 100 mL of saturated $NaCl_{\,(aq)}$, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Column chromatography of the residue yielded **12** (5.90 g, 75%). The crude yield of this reaction was much higher, and it was thought that some of the acetal hydrolyzed on the column. Compound **12** was a colorless liquid. IR: ν_{max} 1736 (s), 1731 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 4.85 (1H, t, *J*=4.7 Hz, H-4'), 4.15 (4H, m, O**CH₂**CH₃), 3.91 (4H, m, H-a), 2.23 to 2.44 (3H, m, H-2 and H-4), 1.89 (2H, H-4), 1.41 to 1.74 (6H, m, H-1', H-2' and H-3'), 1.27 (3H, t, *J*=7.1 Hz, H-OCH_2**CH_3**), 1.27 (3H, t, *J*=7.1 Hz, H-OCH_2**CH_3**). ^{13}C NMR ($CDCl_3$): δ 175.2 and 172.7 (0, C-1 and C-5), 104.1 (1, C-4'), 64.7 (2C, 2, C-a), 60.2 (2, O**CH_2**CH_3), 60.1 (2, O**CH_2**CH_3), 44.5 (1, C-2), 33.5, 32.0 and 21.5 (2, C-1', C-2' and C-3'), 32.0 (2, C-3), 27.0 (2, C-4), 14.1 (2C, 3, OCH_2**CH_3**). MS *m/z* (%): 302 (3, M^+), 257 (24, M^+-45), 73 (100). HRMS calcd for $C_{15}H_{26}O_6$: 302.1729; found: 302.1738.

General Procedure for Wacker Oxidation. The Wacker oxidation performed on compounds **4** and **8** were based on the method of Tsugi.[25] The $O_{2(g)}$ was bubbled directly into the stirred mixture as opposed to a positive pressure of the gas above the mixture as cited in the literature reference. This seemed to give better yields.

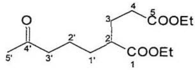
Diethyl 2-(4-oxopentyl)butanedioate (13)



13

CuCl (1.21 g, 12.2 mmol), $PdCl_2$ (0.22 g, 1.2 mmol), DMF (110 mL) and H_2O (15 mL) were placed in a three-necked round-bottomed flask. $O_{2(g)}$ was bubbled directly into the stirring mixture for 2 h. To this mixture, **4** (2.85 g, 11.7 mmol) was added. The mixture was stirred with continued bubbling overnight at rt. The organic mixture was washed with 3M HCl (100 mL) and saturated $NaCl_{(aq)}$ (50 mL). The aqueous layers were extracted with CH_2Cl_2 (2 x 50 mL) and then the combined organic layers were washed with saturated $NaCl_{(aq)}$ (2 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. After column chromatography, **13** (2.42 g, 80% yield) was isolated as a colorless liquid: IR: ν_{max} 1734 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.12 (4H, m, O**CH₂**CH₃), 2.79 (1H, m, H-2), 2.69 (1H, dd, *J*=16.1, 9.0 Hz, H-3), 2.38 to 2.45 (3H, m, H-3' and H-3), 2.11 (3H, s, H-5'), 1.46 to 1.66 (4H, m, H-1' and H-2'), 1.24 (6H, m, OCH_2**CH_3**). ^{13}C NMR ($CDCl_3$): δ 207.8 (0, C-4'), 174.3 and 171.5 (0, C-1 and C-4), 60.3 (2, O**CH_2**CH_3), 60.3 (2, O**CH_2**CH_3), 42.8 (2, C-3'), 40.8 (1, C-2), 35.7 (2, C-3), 30.9 (2, C-1'), 29.6 (3, C-5'), 20.8 (2, C-2'), 13.9 (3, OCH_2**CH_3**), 13.9 (3, OCH_2**CH_3**). MS *m/z* (%): 213 (71, M$^+$-45), 167 (16), 155(30), 139 (23), 128 (15), 97 (11), 43 (100), 29 (42). HRMS calcd for $C_{13}H_{22}O_5$: 258.1467; found: 258.1464.

Diethyl 2-(4-oxopentyl)pentanedioate (14)



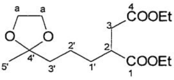
14

CuCl (0.05 g, 0.5 mmol), $PdCl_2$ (0.02 g, 0.1 mmol), DMF (5 mL) and H_2O (0.7 mL) were placed in a three-necked round-bottomed flask. $O_{2(g)}$ was bubbled directly into the stirring mixture for 2 h. To this mixture, **8** (0.127 g, 0.496 mmol) was added. The mixture was stirred with continued bubbling overnight at rt. The organic solution was washed with 3M HCl (50 mL) and saturated NaCl $_{(aq)}$ (50mL), The aqueous layers were extracted with CH_2Cl_2 (2 x 50 mL) and then the combined organic layers were washed with saturated $NaCl_{(aq)}$ (50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography to yield **14** (0.097 g, 72% yield) as a colorless liquid: IR: ν_{max} 1731(s) cm^{-1}. ^{1}H NMR ($CDCl_3$): 4.16 (2H, q, *J*=7.1 Hz, O**CH$_2$**CH$_3$), 4.14 (2H, q, *J*=7.2 Hz, O**CH$_2$**CH$_3$), 2.28 to 2.47 (5H, m, H-2, H-4 and H-3'), 2.14 (3H, s, H-5'), 1.88 (2H, m, H-3), 1.56 (4H, m, H-1' and H-2'), 1.28 (3H, t, *J*=7.2 Hz, OCH$_2$**CH$_3$**), 1.27 (3H, t, *J*=7.1 Hz, OCH$_2$**CH$_3$**). ^{13}C NMR ($CDCl_3$): δ 208.3 (0, C-4'), 175.2 and 172.9 (0, C-1 and C-5), 60.3 (2C, 2, O**CH$_2$**CH$_3$), 44.4 (2, C-2), 43.2 and 31.8 (2, C-4 and C-3'), 31.5 and 21.3 (2, C-1' and C-2'), 29.8 (3, C-5'), 27.0 (2, C-3), 20.8 (2, C-2'), 14.2 (2C, 3, OCH$_2$**CH$_3$**). MS *m/z* (%): 227 (5, M$^+$-45), 215 (11), 181 (18), 169 (47), 153 (41), 142 (22), 141 (23), 138 (15), 137 (28), 135 (13), 127 (11), 125 (11), 115 (15), 114 (51), 113 (12), 111 (23), 110

(160, 109 (20), 101 (14), 99 (17), 98 (11), 95 (12), 93 (10), 81 (13), 71 (11), 67 (13), 55 (22), 43 (100), 41 (11), 29 (33). HRMS calcd for $C_{14}H_{24}O_5$: 272.1624; found: 272.1629.

General Procedure for Butane-1,2-diol Acetal Formation. The acetals were generated by an acid-catalysed reaction of the methyl ketones with a large excess of butane-1,2-diol in benzene, assisted by the azeotropic removal of water. The acid used as the catalyst was *p*TsOH.

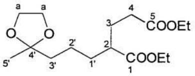
Diethyl 2-(4-oxopentyl)butanedioate, ethylene acetal (15)



15

Butane-1,2-diol (1.79 g, 28.8 mmol), **13** (1.50 g, 5.81 mmol), a small amount of *p*TsOH and benzene (85 mL) were placed in a Barrett apparatus. The mixture was heated under reflux for 30 h. The reaction mixture was cooled to rt and concentrated under reduced pressure. The organic residue was washed with saturated $NaHCO_{3\,(aq)}$ (2 x 50 mL), the aqueous layers were extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic layers were washed with saturated $NaCl_{\,(aq)}$ (50 mL). The organic solution was dried over anhydrous $MgSO_{4(s)}$ and the solvent was removed under reduced pressure. The crude mixture was purified by column chromatography to yield **15** (1.14 g, 65%) as a colorless liquid. IR: ν_{max} 1734 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 4.16 (4H, m, **OCH_2**CH_3), 3.93 (4H, m, H-a), 2.84 (1H, m, H-2), 2.71 (1H, dd, *J*=16.2, 9.3 Hz, H-3), 2.43 (1H, dd, *J*=16.2, 4.9 Hz, H-3), 1.37 to 1.71 (6H, m, H-1', H-2', and H-3'), 1.31 (3H, s, H-5'), 1.27 (3H, t, *J*=7.1 Hz, OCH_2**CH_3**), 1.26 (3H, t, *J*=7.1 Hz, OCH_2**CH_3**). ^{13}C NMR ($CDCl_3$): δ 174.9 and 172.0 (0, C-1 and C-4), 109.8 (0, C-4'), 64.6 (2C, 2, C-a), 60.5 (2C, 2, **OCH_2**CH_3), 41.2 (1, C-2), 38.8 (2, C-3'), 36.0 (2, C-3), 32.0 (2, C-1'), 23.8 (3, C-5'), 21.4 (2, C-2'), 14.2 (3, $OCH_2\mathbf{CH_3}$), 14.1 (3, $OCH_2\mathbf{CH_3}$). MS *m/z* (%): 287 (6, M^+-CH_3), 87 (100), 43 (25). HRMS calcd for $C_{15}H_{26}O_6$: 287.1494 (M^+-CH_3); found: 287.1497.

Diethyl 2-(4-oxopentyl)pentanedioate, ethylene acetal (16)

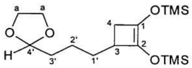


16

Butane-1,2-diol (3.31 g, 53.3 mmol), **14** (2.76 g, 10.1 mmol), a small amount of *p*TsOH and benzene (150 mL) were combined in a Barrett apparatus. The mixture was heated under reflux for 7 days. The mixture was cooled to rt and concentrated under reduced pressure. The organic residue was washed with saturated $NaHCO_{3\,(aq)}$ (2 x 50 mL), the aqueous layers were extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic layers were washed with of saturated $NaCl_{\,(aq)}$ (50 mL). The organic solution was then dried over anhydrous $MgSO_{4(s)}$ and concentrated under reduced pressure. The crude mixture was purified by column chromatography to yield **16** (1.58 g, 50% yield) as a colorless liquid. IR: ν_{max} 1731 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.15 (4H, m, $O\mathbf{CH_2}CH_3$), 3.92 (4H, m, H-a), 2.22 to 2.42 (3H, m, H-2 and H-4), 1.88 (2H, m, H-3), 1.42 to 1.63 (6H, m, H-1', H-2' and H-3'), 1.30 (3H, s, H-5), 1.26 (3H, t, J=7.2 Hz, $OCH_2\mathbf{CH_3}$), 1.25 (3H, t, J=7.0 Hz, $OCH_2\mathbf{CH_3}$). ^{13}C NMR ($CDCl_3$): δ 175.5 and 172.9 (0, C-1 and C-5), 109.8 (0, C-4'), 64.6 (2C, 2, C-a), 60.3 (2, $O\mathbf{CH_2}CH_3$), 60.2 (2, $O\mathbf{CH_2}CH_3$), 44.7 (1, C-2), 38.8, 32.4 and 21.7 (2, C-1', C-2' and C-3'), 32.0 (2, C-4), 27.1 (2, C-3), 23.7 (3, C-5'), 14.2 (2C, 3, $OCH_2\mathbf{CH_3}$). MS *m/z* (%): 301 (3, M^+-15), 87 (100), 43 (30). HRMS calcd for $C_{16}H_{28}O_6$: 316.1886; found: 316.1881.

General Procedure for the Acyloin Condensation. The acyloin condensation was performed under an inert atmosphere of nitrogen. The toluene used as the solvent had previously been distilled over CaH_2 and stored over Molecular Sieves to ensure that there was no water present. The suction filtration was carried out under an inert atmosphere of nitrogen.

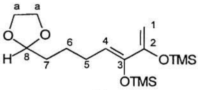
3-(4-Oxobutyl)-1,2-bis[(trimethylsilyl)oxy]cyclobutene, ethylene acetal (17)



17

Compound **11** (1.77 g, 6.14 mmol), toluene (6 mL) and TMSCl (3.6 mL, 2.8 mmol) were placed in an addition funnel. The funnel was placed in a three-necked round-bottomed flask. The flask was fitted with a mechanical stirrer and charged with toluene (19 mL) and $Na_{(s)}$ (0.65 g, 28.3 mmol). The $Na_{(s)}$ and toluene were heated under reflux and stirred vigorously for 2 h. The mixture in the dropping funnel was then added over 45 min. The mixture was then heated under reflux for 2 h. The mixture was left stirring under $N_{2(g)}$ overnight. The mixture was heated under reflux for 16.5 h. The mixture was suction filtered and the filtrate was then distilled to remove the toluene. Vacuum distillation of the residue yielded a yellowish-brown liquid that was not pure. It contained mainly **17** (1.28 g, 60% yield), but there was also evidence of **21** in the ^1H NMR data. ^1H NMR ($CDCl_3$): δ 4.85 (1H, m, H-4'), 3.85 to 3.97 (4H, m, H-a), 2.26 and 1.47 (9H, m, CH and CH_2), 0.20 (18H, m, TMS).

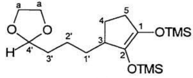
8-Oxo-2,3-bis[(trimethylsilyl)oxy]-1,3-octadiene, ethylene acetal (21)



21

21 was present in a mixture with compound **17**. ^{1}H NMR ($CDCl_3$): δ 5.31 (1H, t, J=7.4 Hz, H-4), 4.85 (1H, m, H-8), 4.65 (1H, s, H-1), 4.29 (1H, s, H-1), 3.91 (4H, m, H-a).

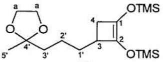
3-(4-Oxobutyl)-1,2-bis[(trimethylsilyl)oxy]cyclopentene, ethylene acetal (18)



18

Compound **12** (1.32 g, 4.36 mmol) was placed in the addition funnel with TMSCl (2.7 mL, 21 mmol) and toluene (5 mL). The solution was slowly added to a stirred and heated mixture of toluene (25 mL) and $Na_{(S)}$ (0.48 g, 20.9 mmol). Over the next 4 days, the mixture was heated under reflux for approximately 24 h. It was then cooled to rt, suction filtered, and concentrated under vacuum. This yielded **18** (1.29 g, 82%) as a yellowish-brown liquid. The ^{1}H NMR showed mainly the desired compound, but there were some impurities present. ^{1}H NMR ($CDCl_3$): δ 4.86 (1H, t, J=4.7 Hz, H-4'), 3.91 (4H, m, H-a), 1.09 to 2.41 (11H, m, CH and CH_2), 0.16 (18H, m, TMS).

3-(4-Oxopentyl)-1,2-bis[(trimethylsilyl)oxy]cyclobutene, ethylene acetal (19)

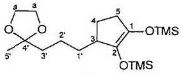


19

Compound **15** (0.41 g, 1.35 mmol) was placed in an addition funnel with TMSCl (0.80 mL, 6.30 mmol) and toluene (8 mL). The solution was slowly added to a vigorously stirred and heated mixture of $Na_{(s)}$ (0.15 g, 6.52 mmol) and toluene (32 mL).

The mixture was heated under reflux for approximately 19 h. The mixture was cooled to rt and suction filtered. The filtrate was concentrated under vacuum to yield **19** (0.48 g, 97% crude yield) as a yellowish-brown liquid. The ^{1}H NMR shows evidence of mainly the desired compound as well as a small amount of **13** and some other impurities in the baseline. ^{1}H NMR ($CDCl_3$): δ 3.94 (4H, m, H-a), 2.28 to 2.42 and 1.20 to 1.73 (9H, m, CH and CH_2), 1.31 (3H, s, H-5'), 0.20 (9H, s, TMS), 0.19 (9H, s, TMS).

3-(4-Oxopentyl)-1,2-bis[(trimethylsilyl)oxy]cyclopentene, ethylene acetal (20)



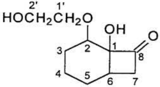
20

Compound **16** (1.04 g, 3.29 mmol) was placed in an addition funnel with toluene (5 mL) and TMSCl (1.95 mL, 15.4 mmol) and slowly added to a stirred and heated mixture of toluene (30 mL) and $Na_{(s)}$ (0.36 g, 0.016 mol). The mixture was heated under reflux for 21 h. It was suction filtered and the filtrate was concentrated under vacuum to yield **20** (0.76 g, 63% crude yield) as a yellowish-brown liquid. The ^{1}H NMR spectrum shows mainly the desired compound with very little impurity. ^{1}H NMR ($CDCl_3$): δ 3.94 (4H, m, H-a), 1.70 to 2.42 (11H, m, CH and CH_2), 1.32 (3H, s, H-5'), 0.19 (9H, s, TMS), 0.18 (9H, s, TMS).

General Procedure for Attempts at the Intramolecular Geminal Acylation

These reactions were carried out under anhydrous conditions. The glassware was dried in the oven. The reactions were performed under an inert atmosphere of nitrogen, and the solvents were freshly distilled over CaH_2.

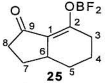
1-Hydroxy-2-(2-hydroxyethoxy)bicyclo[4.2.0]octane-2-one (23)



23

Toluene (6 mL), TMSCl (0.79 mL, 6.22 mmol), and **11** (0.39 g, 1.35 mmol) were placed in an addition funnel. The funnel was fitted into a three-necked flask and the flask was charged with toluene (19 mL) and $Na_{(s)}$ (0.14 g, 6.09 mmol). The mixture in the flask was stirred and heated under reflux and then the solution in the addition funnel was added gradually. The mixture was heated under reflux for a total of 19.5 h. The mixture was suction filtered and the solvent was removed by distillation. The residue was diluted with CH_2Cl_2 (30 mL) and cooled to –78 °C. $BF_3{\cdot}Et_2O$ (2.6 mL, 21 mmol) was added, and the mixture was stirred and allowed to warm to rt overnight. The organic mixture was washed with H_2O (2 x 25 mL) and the aqueous layers were extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were washed with saturated $NaCl_{(aq)}$ (25 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The concentrate was passed through a Florisil column. The solvent was removed under reduced pressure and this yielded a mixture of products, one of which was thought to be **23**. MS (From GC-MS) *m/z* (%):199 (M^+-1, 1), 181 (29), 182 (78), 165 (14), 156 (13), 155 (41), 154 (100), 153 (13), 142 (15), 141 (30), 140 (54), 139 (98), 138 (15), 137 (10), 127 (14), 126 (27), 125 (18), 122 (10), 121 (18), 114 (18), 113 (30), 112 (73), 111 (14), 101 (17), 100 (37), 99 (13).

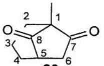
2-Borondifluoroxybicyclo[4.3.0]non-1-ene-9-one (25)



25

At rt, a solution of **18** (0.610 g, 1.70 mmol, in 50 mL of CH_2Cl_2) was added to a solution of $BF_3{\cdot}Et_2O$ (4.3 mL, 34 mmol in approximately 800 mL of CH_2Cl_2) at a rate of 3.4 mL/h with a syringe pump. TFA (1.31 mL, 17.0 mmol) was added 4 h after the addition was completed and the mixture was stirred at rt for an additional 2 h. Most of the CH_2Cl_2 was removed under reduced pressure, and the organic residue was washed with H_2O (2 x 50 mL), the aqueous layers were extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic layers were washed with saturated NaCl $_{(aq)}$ (25 mL). The organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography, which yielded **25** (0.023 g, 7% yield) as a white solid: mp 98-100°C. ^{1}H NMR ($CDCl_3$): δ 2.91(2H, m), 2.55 (3H, m), 2.13 (2H, m), 1.72 (2H, m), 0.81 to 1.30 (2H, m) all CH and CH_2's. ^{13}C NMR ($CDCl_3$): δ 199.0 (0, C-9), 186.2 (0, C-2), 116.6 (0, C-1), 36.0 (1, C-6), 33.7, 31.0, 30.1, 30.0 and 21.9 (CH_2). MS *m/z* (%): 200 (M^+, 15), 172 (100), 171 (23), 144 (24), 143 (22).

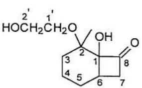
1-Methylbicyclo[3.2.1]octane-7,8-dione (26)



26

A mixture of toluene (5 mL), TMSCl (1.93 mL, 15.2 mmol), and **15** (1.00 g, 3.32 mmol) was added to an addition funnel which was placed in a three-necked, round-bottomed flask. The flask was charged with toluene (20 mL) and $Na_{(S)}$ (0.35 g, 15.2 mmol). The toluene and $Na_{(S)}$ mixture was stirred vigorously and heated under reflux. The mixture in the addition funnel was added slowly and continually heated and stirred for 9 h. It was left stirring under $N_{2\,(g)}$ overnight. The reaction mixture was heated under reflux for 3.5 h and then cooled to rt. The mixture was suction filtered, and the filtrate was cooled to –78 °C. $BF_3{\cdot}Et_2O$ (6.3 mL, 50 mmol) was added, and the mixture was stirred and allowed to achieve rt overnight. The organic mixture was washed with H_2O (2 x 50 mL), the aqueous layers were extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic layers were washed with saturated $NaCl_{(aq)}$ (50 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography and yielded **26** (0.08 g, 16% yield) as a white solid: mp 65-66°C. ^{1}H NMR ($CDCl_3$): δ 2.95 (1H, m, H-5), 2.66 (2H, m, H-6), 2.20 (2H, m, H-4), 1.88 (4H, m, H-2 and H-3), 1.06 (3H, s, $\mathbf{CH_3}$). ^{13}C NMR ($CDCl_3$): δ 217.7 and 212.3 (0, C-7 and C-8), 59.3 (0, C-1), 45.7 (1, C-5), 44.9 (2H, C-2), 42.9 (2, C-6), 35.7 (2, C-4), 18.2 (2H, C-3), 12.1(3, $\mathbf{CH_3}$). MS *m/z* (%): 153 (M^++1, 11), 152 (M^+, 100), 137 (30), 124 (38), 109 (12), 96 (30), 95 (20), 83 (12), 82 (23), 81 (61), 79 (11), 69 (47), 68 (27), 67 (53), 55 (42), 54 (28), 53 (16), 41 (70), 39 (48).

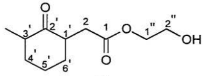
1-Hydroxy-2-(2-hydroxyethoxy)-2-methylbicyclo[4.2.0]octan-2-one (27)



27

Toluene (6 mL), TMSCl (1.1 mL, 8.7 mmol), and **15** (0.587 g, 1.94 mmol) were placed in an addition funnel. The funnel was placed in a three-necked round-bottomed flask. Toluene (19 mL) and $Na_{(s)}$ (0.20 g, 8.70 mmol) was placed in the flask and this was stirred and heated under reflux for 2 h. The mixture in the addition funnel was slowly added, and the reaction mixture was stirred and heated for 4 h. The mixture was left under an inert atmosphere of nitrogen overnight. It was stirred and heated for an additional 4.5 h the next day before being cooled to rt and suction filtered. The filtrate was cooled to –78 °C and $BF_3{\cdot}Et_2O$ (3.7 mL, 29 mmol) was added. The mixture was kept at this temperature for 7.5 h and left to achieve rt overnight. The organic mixture was washed with H_2O (2 x 50 mL), the aqueous layers were extracted with CH_2Cl_2 (2 x 50 mL), and the combined organic layers were washed with saturated NaCl $_{(aq)}$ (50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to approximately 50 mL and then passed through a Florisil column. The solvent was removed under reduced pressure and the mixture was purified by column chromatography. This yielded **27** (0.021g, 5% yield) as a yellow oil. IR: ν_{max} 1745 (s) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.90 to 4.22 (4H, m, H-1' and H-2'), 2.53 (1H, dd, *J*=18.3, 7.4 Hz, H-7), 2.34 (1H, m, H-6), 2.09 (2H, m, H-5 and H-7), 1.88 (1H, m, H-3), 1.64 (1H, m, H-5), 1.23 to 1.69 (3H, m, H-3 and H-4),0.92 (3H, s, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 218.3 (0, C-8), 115.2 (0, C-1), 65.6 and 64.9 (2, C-1' and C-2'), 53.4 (0, C-2), 41.9 (2, C-7), 38.4 (1, C-6), 35.3 (2, C-3), 27.7 (2, C-5), 17.7 (2, C-4), 13.0 (3, $\mathbf{CH_3}$). MS *m/z* (%): 215 (M^++1, 1), 196 (47), 168 (62), 167 (15), 153 (67), 139 (18), 126 (17), 125 (52), 113 (100), 112 (11), 99 (76), 16 (95), 86 (16), 81 (23), 20 (17), 79 (12), 73 (13), 69 (33), 67 (17), 55 (45), 54 (18), 43 (27), 41 (83), 40 (11), 39 (42), 34 (29), 28 (17), 27 (44).

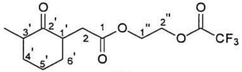
2-Hydroxyethyl-3-methyl-2-oxocyclohexanebutanoate (28)



28

At rt, a solution of **19** (0.109g, 0.304 mmol, in 50 mL of CH_2Cl_2) was added to a solution of BF_3·Et_2O (0.80 mL, 6.3 mmol in approximately 600 mL of CH_2Cl_2) at a rate of 3.4 mL/h. TFA (0.23 mL, 3.0 mmol) was added to the reaction mixture 3 h after the syringe pump addition was complete, and the mixture was stirred at rt for an additional 7 h. The mixture was concentrated under reduced pressure, and the organic residue was washed with H_2O (2 x 50 mL), the aqueous layers were extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic layers were washed with saturated NaCl $_{(aq)}$ (100 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. Purification of the residue was attempted by column chromatography and this yielded a mixture of components one of which was thought to be **28**. ^{1}H NMR ($CDCl_3$): δ 4.23 and 3.83 (4H, m, H-1" and H-2"), 0.85 to 3.11 (14 H, m, all other H's). There are a lot of signals reminiscent of methyl groups in the range of 1-1.5 ppm.

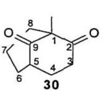
2-Trifluoroacetoxyethyl 3-methyl-2-oxocyclohexanebutanoate (29)



29

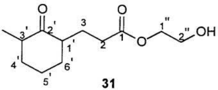
A solution of **19** (0.109g, 0.304 mmol, in 50 mL of CH_2Cl_2) was added to a solution of BF_3·Et_2O (0.80 mL, 6.3 mmol in approximately 600 mL of CH_2Cl_2) at a rate of 3.4 mL/h at rt. TFA (0.23 mL, 3.0 mmol) was added to the reaction mixture 3 h after the syringe pump addition was complete, and the mixture was stirred at rt for an additional 7 h. The mixture was concentrated under reduced pressure, and the organic residue was washed with H_2O (2 x 50 mL), the aqueous layers were extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic layers were washed with saturated $NaCl_{(aq)}$ (100 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. Purification of the residue was attempted by column chromatography and this yielded a fraction that appeared to have hydroxyl moieties present. It was uncertain whether this was unrearranged cyclobutanone intermediate (the Mukaiyama aldol product) or a keto-ester (reductive succinoylation product). This column fraction was dissolved in CH_2Cl_2 (5 mL),TFA (2.0 mL) was added and the mixture was stirred at rt overnight. This organic mixture was washed with H_2O (2 x 25 mL), the aqueous layers were extracted with CH_2Cl_2 (2 x 25 mL) and the combined organic layers were washed with saturated $NaCl_{(aq)}$ (100 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated to yield **29** (0.013 g, 13% yield) as a yellow liquid. The ^1H NMR spectrum showed that there was a small amount of methyl ketone **13** present. ^1H NMR ($CDCl_3$): δ 4.56 and 4.38 (2H, m, H-1" and H-2"), 0.85 to 2.92 (13H, m, all other H's) 1.03 (3H, d, *J*=6.5 Hz). MS *m/z* (From GC-MS): 197 (M^+-$OCOCF_3$, 100), 196 (10), 154 (27), 153 (73), 152 (33), 96 (16), 82 (10), 81 (19), 69 (16), 68 (12), 67 (15), 57 (15), 56 (29), 55 (54), 54 (17).

1-Methylbicyclo[3.3.1]nonane-2,9-dione (30)



Toluene (5 mL), TMSCl (2.8 mL, 22 mmol), and **14** (1.25 g, 3.95 mmol) were added to an addition funnel, which was placed in a three-necked, round-bottomed flask. The flask was charged with toluene (20 mL) and $Na_{(S)}$ (0.49 g, 21 mmol). The toluene and $Na_{(S)}$ mixture was stirred vigorously and heated under reflux. The solution in the addition funnel was added slowly and the mixture was continually heated and stirred for 3 h. It stirred under $N_{2\,(g)}$ overnight at rt. The mixture was heated under reflux for 3 h and then cooled to rt. The mixture was suction filtered, and the filtrate was cooled to –78 °C. $BF_3{\cdot}Et_2O$ (7.5 mL, 59 mmol) was added and the mixture was stirred and allowed to attain rt overnight. The organic mixture was washed with H_2O (2 x 50 mL), the aqueous layers were extracted with CH_2Cl_2 (2 x 100 mL) and the combined organic layers were washed with saturated $NaCl_{(aq)}$ (100 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography and yielded **30** (0.14 g, 23% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.90 (1H, m, H-5), 2.64 (1H, m, H-3), 2.38 (1H, m, H-3), 2.27 (1H, m, H-6), 2.20 (1H, m, H-4), 2.07 (2H, m, H-7), 1.81 (1H, m, H-4), 1.60 to 1.75 (3H, m, H-6 and H-8), 1.15 (3H, s, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 213.4 and 212.6 (0, C-2 and C-9), 63.4 (0, C-1), 44.5 (1, C-5), 43.2 (2, C-6), 39.1 (2, C-3), 36.1 (2, C-7), 22.0 (2, C-4), 19.3 (2, C-8), 16.8 (3, CH_3). MS *m/z* (%): 166 (M^+, 50), 138 (11), 111 (100), 110 (35), 109 (13), 93 (14), 81 (11), 69 (16), 67 (23), 55 (52), 53 (12), 43 (58), 41 (47), 39 (32).

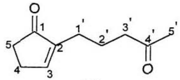
3-Methyl-2-oxocyclohexanepropanoic acid, 2-hydroxyethyl ester (31)



31

A solution of **20** (0.164 g, 0.439 mmol in 50 mL of CH_2Cl_2) was added to a solution of $BF_3 \cdot Et_2O$ (1.1 mL, 8.7 mmol in approximately 600 mL of CH_2Cl_2) at rt and at a rate of 3.4 mL/h. TFA (0.34 mL, 4.4 mmol) was added to the reaction mixture 3 h after the syringe pump addition was complete. The mixture was stirred at rt for 4 h. Most of the solvent was removed under reduced pressure and the organic residue was washed with H_2O (2 x 50 mL), the aqueous layers were extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic layers were washed with saturated NaCl $_{(aq)}$ (50 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography. This yielded several products including **31** (0.023 g, 23% yield) as a clear, colorless liquid. Compound **31** was a mixture of diastereomers in a ratio of 2:1. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.21 and 3.82 (4H, m, H-1" and H-2"), 2.34 to 2.59 (4H, m, H-2, H-1' and H-3'), 1.93, 1.56 and 1.35 (8H, m, H-2, H-4', H-5' and H-6'), 1.07 (3H, d, CH_3, J= 6.9 Hz, minor diastereomer) 1.00 (3H, d, J= 6.5 Hz, major diastereomer). ^{13}C NMR (125 MHz, $CDCl_3$, major diastereomer): δ 216.7 (0, C-2'), 174.1 (0, C-1), 66.0 and 61.2 (2, C-1" and C-2"), 49.8 and 45.6 (1, C-1' and C-3'), 37.4. 35.3, 32.1, 25.4, and 24.7 (2, C-2, C-3, C-4', C-5', and C-6'), 14.4 (3, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$, minor diastereomer): δ 213.9 (0, C-2'), 173.4 (0, C-1), 66.2 and 61.0 (2, C-1" and C-2"), 48.2 and 42.7 (1, C-1' and C-3'), 35.1, 32.8, 31.9, 26.1 and 20.5, (2, C-2, C-3, C-4', C-5', and C-6'), 15.4 (3, CH_3). MS *m/z* (%): 228 (M^+, 1), 210 (12), 167 (62), 166 (91), 139 (23), 138 (27), 124 (15), 112 (26), 111 (16), 110 (18), 109 (18), 99 (24), 97 (16), 96 (25), 95 (22), 94 (11), 86 (22), 83 (13), 81 (23), 82 (10), 81 (23), 69 (26), 68 (20), 67 (23), 59 (25), 58 (17), 55 (68), 45 (34), 43 (100), 41 (63).

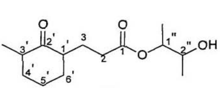
2-(4-Oxopentyl)-2-cyclopentenone (32)



32

A solution of **20** (0.164 g, 0.439 mmol in 50 mL of CH_2Cl_2) was added to a solution of $BF_3 \cdot Et_2O$ (1.1 mL, 8.7 mmol in approximately 600 mL of CH_2Cl_2) at rt and at a rate of 3.4 mL/h. TFA (0.34 mL, 4.4 mmol) was added to the reaction mixture 3 h after the syringe pump addition was complete. The mixture was stirred at rt for 4 h. Most of the solvent was removed under reduced pressure and the organic residue was washed with H_2O (2 x 50 mL), the aqueous layers were extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic layers were washed with saturated NaCl $_{(aq)}$ (50 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography and this yielded several products including **32** (0.0082 g, 11% yield). ^1H NMR ($CDCl_3$): δ 7.35 (1H, m, H-3), 2.60, 2.39 to 2.48, 2.17, and 1.77 (10H, m, CH_2), 2.17 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$): δ 210.0, and 208.7 (0, C-1 and C-4'), 158.1 (1, C-3), 145.7 (0, C-2), 43.2, 34.5, 30.0, 26.5, 24.1, and 21.9 (CH_2 and CH_3). MS *m/z* (%): 166 (M^+, 27), 123 (43), 109 (77), 96 (34), 95 (18), 81 (23), 79 (20), 71 (17), 67 (22), 55 (24), 45 (13), 43 (100), 41 (36).

1,2-Dimethyl-2-hydroxyethyl-2-oxocyclohexanepropanoate (39)

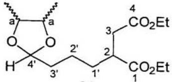


39

A solution of **38** (0.0761 g, 0.197 mmol) in CH_2Cl_2 (50 mL) was added to a stirring solution of BCl_3 (0.31 mL, 0.31mmol) in CH_2Cl_2 (600 mL) at –78 °C for 3.25 h and left to attain rt overnight. The mixture was cooled to –78 °C and a solution of HF (0.16 mL) in MeOH (0.33 mL) was added and stirred at –78 °C for 10min. The mixture was then stirred at rt for 1 h. The mixture was concentrated and TFA (0.58 mL) was added. The mixture was left stirring at rt for 24 h. The organic solution was washed with H_2O (50 mL) and $NaHCO_{3(s)}$ was added until the mixture was neutral. The aqueous layers were extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by column chromatography and yielded **39** (0.0109 g, 23%) as a mixture of diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.90 and 3.91 (2H, m, H-1" and H-2", major isomer), 4.77 and 3.76 (2H, m, H-1" and H-2", minor isomer), 1.17 to 2.52 (22H, m, all other H). ^{13}C NMR ($CDCl_3$, both diastereomers): δ 221.2 (0, C-2'), 173.0 (0, C-1), 74.9, 74.3, 70.0, 69.4, 48.9, 49.8, 38.1, 34.5, 34.4, 29.5, 29.3, 29.0, 28.8, 23.0, 22.7, 20.7, 19.1, 17.8, 16.4, 14.0. MS *m/z* (%): 224 (M^+-18, 5), 154 (14), 153 (57), 153 (42), 135 (27), 124 (28), 107 (67), 97 (53), 96 (27), 84 (60), 83 (23), 73 (71), 67 (29), 55 (100), 45 (47), 43 (55), 41 (93).

General Procedure for 2,3-Butanediol Acetal Formation. The acetals were generated by an acid-catalysed reaction of the methyl ketones with a large excess of a mixture of meso and *d/l* 2,3-butanediol in benzene and assisted by the azeotropic removal of water from the equilibrium. The acid used as the catalyst was *p*TsOH.

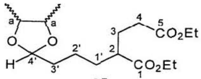
Diethyl 2-(4-oxobutyl)butanedioate, 2,3-butanediol acetal (34)



34

$CHCl_3$ (50 mL), 2,3-butanediol (3.68 g, 40.8 mmol) and **4** (0.976 g, 4.03 mmol) were placed in a round-bottomed flask. The mixture was cooled to –78 °C and $O_{3\,(g)}$ was bubbled into the solution until a blue color persisted (approximately 20 min). The flask was removed from the dry ice/acetone bath, and the $O_{3\,(g)}$ bubbler was removed. The mixture was purged with $N_{2\,(g)}$ for 30 min, and Me_2S (3 mL) and a small amount of *p*TsOH were added. The mixture was stirred at rt for 5 days. The organic mixture was then washed with saturated $NaHCO_{3\,(aq)}$ (2 x 25 mL), the aqueous layers were extracted with CH_2Cl_2 (2 x 25 mL), and the combined organic layers were washed with saturated $NaCl_{\,(aq)}$ (1 x 25 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified column chromatography to yield **34** (1.37 g, 71% yield) as a colorless liquid. Compound **34** was a mixture of stereoisomers. ^{1}H NMR ($CDCl_3$): δ 5.16, 5.02 and 4.85 (1H, m, H-4', stereoisomers), 4.16 and 3.58 (6H, m, O**CH$_2$**CH$_3$ and H-a), 2.82 (1H, m, H-2), 2.70 (1H, dd, *J*=16.3 and 9.5 Hz, H-3), 2.43 (1H, dd, *J*=16.3 and 4.8, H-3), 1.14 to 1.73 (18H, m, all other H's).

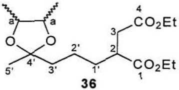
Diethyl 2-(4-oxobutyl)pentanedioate, 2,3-butanediol acetal (35)



35

Compound **8** (1.02 g, 3.96 mmol), 2,3-butanediol (3.62 g, 40.2 mmol) and $CHCl_3$ (50 mL) were placed in a round-bottomed flask. The flask was cooled to –78 °C and $O_{3\,(g)}$ was bubbled into the solution until a blue color persisted (approximately 20 min). The flask was taken out of the cooling bath, and the $O_{3\,(g)}$ bubbler was removed. The mixture was purged with $N_{2\,(g)}$ for 30 min, and Me_2S (3 mL) and a small amount of *p*TsOH were added. The mixture was stirred at rt for 5 days. The organic mixture was washed with saturated $NaHCO_{3\,(aq)}$ (2 x 25 mL), the aqueous layers were extracted with CH_2Cl_2 (2 x 25 mL), and the combined organic layers were washed with saturated $NaCl_{\,(aq)}$ (25 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography to provide **35** (0.80 g, 61% yield) as a pale yellow liquid. There were still impurities present in the compound. ^{1}H NMR ($CDCl_3$): δ 5.15, 5.02 and 4.86 (t, H-4', stereoisomers), 4.14 and 3.59 (6H, m, $\mathbf{OCH_2}CH_3$ and H-a), 2.18 to 2.43 (3H, m, H-2 and H-4), 1.12 to 1.97 (20H, m, all other H's).

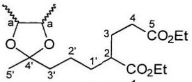
Diethyl 2-(4-oxopentyl)butanedioate, 2,3-butanediol acetal (36)



36

2,3-Butanediol (2.70 g, 30.0 mmol), **13** (1.54 g, 5.96 mmol), benzene (100 mL) and a small amount of *p*TsOH were combined in a flask. The flask was fitted with a Barrett apparatus and heated under reflux for 6 days. Fresh benzene and *p*TsOH were added twice. The mixture was concentrated under reduced pressure. The organic residue was washed with saturated $NaHCO_{3\,(aq)}$ (2 x 25 mL), the aqueous layers were extracted with CH_2Cl_2 (2 x 25 mL), and the combined organic layers were washed with saturated $NaCl_{(aq)}$ (25 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The residue was separated by column chromatography. This yielded **36** (1.52 g, 77%) of a slightly yellow liquid. The compound was still slightly impure. ^{1}H NMR ($CDCl_3$): δ 4.18 and 3.61 (6H, m, O**CH$_2$**CH$_3$ and H-a), 2.90 (1H, m, H-2), 2.71 (1H, dd, *J*= 16.4, 9.1, H-3), 2.43 (1H, dd, *J*=16.4, 4.5, H-3), 1.12 to 1.68 (21H, m, all other H's).

Diethyl 2-(4-oxopentyl)pentanedioate, 2,3-butanediol acetal (37)

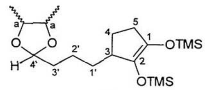


37

Benzene (80 mL), 2,3-butanediol (2.45 g, 27.2 mmol), **14** (1.39 g, 5.10 mmol) and a small portion of *p*TsOH were combined in a flask. The flask was fitted with a Barrett apparatus and the solution was heated under reflux for 8 days. Fresh benzene and *p*TsOH were added on several occasions. The mixture was cooled to rt and concentrated under reduced pressure. The organic residue was washed with saturated $NaHCO_{3\,(aq)}$ (2 x 25 mL), the aqueous layers were extracted with CH_2Cl_2 (2 x 25 mL) and the combined organic layers were washed with saturated $NaCl_{(aq)}$ (25 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The residue was separated by column chromatography. This yielded **37** (0.73 g, 41 %) as a colorless liquid. Compound **37** was isolated as a mixture of stereoisomers. ^{1}H NMR ($CDCl_3$): δ 4.17 and 3.61 (6H, m, $\mathbf{OCH_2}CH_3$ and H-a), 2.35 (3H, m, H-2 and H-4), 1.15 to 1.98 (23H, m, all other H's).

General Procedure for the Acyloin Condensation. The acyloin condensation was performed under an inert atmosphere of nitrogen. The toluene used as the solvent had previously been distilled over CaH_2 and stored over Molecular Sieves to ensure that there was no water present. The suction filtration was carried out under an inert atmosphere of nitrogen.

3-(4-Oxobutyl)-1,2-bis{(trimethylsilyl)oxy]cyclopentene, 2,3-butanediol acetal (38)

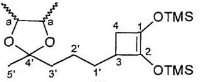


38

Toluene (5 mL), TMSCl (1.5 mL, 0.012 mol) and **35** (0.846 g, 2.56 mmol) were placed in an addition funnel. The funnel was placed in a three-necked round-bottomed flask. The flask contained toluene (20 mL) and Na $_{(s)}$ (0.28 g, 12 mmol). The toluene and Na $_{(s)}$ mixture was stirred and heated under reflux. The mixture in the addition funnel was added slowly and the mixture was heated for 4 h. The mixture was heated for approximately 16 h over the next 2 days. The reaction mixture was suction filtered and the solvent was removed under vacuum to yield **38** (0.62 g, 63%) as an orange-brown liquid. ^{1}H NMR ($CDCl_3$): δ 5.12, 5.03 and 4.87 (1H, m, H-4', stereoisomers), 4.11 (2H, m, H-a), 1.14 to 2.42 (18H, m, all other H's), 0.19 and 0.18 (18H, 2s, O**TMS**).

Compound **39** is listed under the "Attempts at the Intramolecular Geminal Acylation" section following compound **32**.

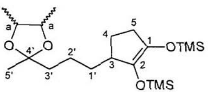
3-(4-Oxopentyl)-1,2-bis[(trimethylsilyl)oxy]cyclobutene, 2,3-butanediol acetal (40)



40

Toluene (5 mL), TMSCl (2.6 mL, 0.020 mol), and **36** (1.46 g, 4.42 mmol) were combined in an addition funnel. The funnel was placed in a three-necked round-bottomed flask. The flask was charged with $Na_{(s)}$ (0.44 g, 19 mmol) and toluene (20 mL). The mixture was stirred and heated under reflux and the contents of the addition funnel were added slowly. The mixture was heated under reflux for a total of 59 h. Extra toluene was added as needed. The mixture was suction filtered and concentrated under reduced pressure to yield **40** (1.39 g, 81%) as a orange liquid. ^{1}H NMR ($CDCl_3$): δ 4.19 and 3.61 (2H, m, H-a), 1.07 to 2.88 (18 H, m, all other H's), 0.19 (18H, m, **OTMS**).

3-(4-oxopentyl)-1,2-bis(trimethylsilyloxy)cyclopentene, ethylene acetal (41)



41

TMSCl (0.34 mL, 2.7 mmol), toluene (5 mL) and **37** (0.20 g, 0.58 mmol) were placed in an addition funnel. The funnel was placed in a three-necked round-bottomed flask. Toluene (20 mL) and $Na_{(s)}$ (0.06 g, 2.6 mmol) were placed in the flask and the liquid was heated under reflux and stirred. The solution in the addition funnel was added slowly, and the mixture was heated for approximately 52 h over the next 6 days. The mixture was suction filtered and concentrated under reduced pressure to yield **41** (0.18 g, 79%) as a orange liquid. ^{1}H NMR ($CDCl_3$): δ 2.32 and 3.61 (2H, m, H-a), 1.10 to 2.56 (m, all other H's), 0.18 (18H, m, **OTMS**).

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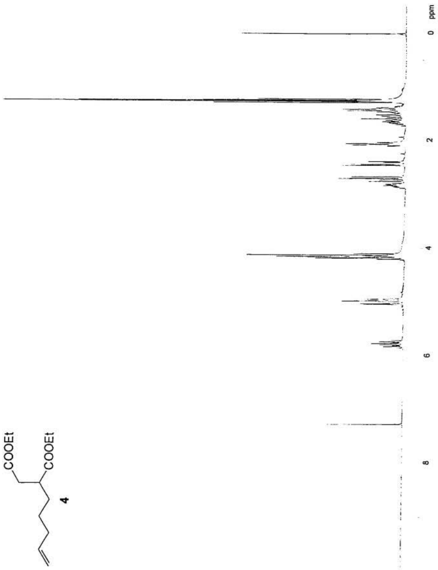
Appendix 1

^{1}H NMR and ^{13}C NMR Spectra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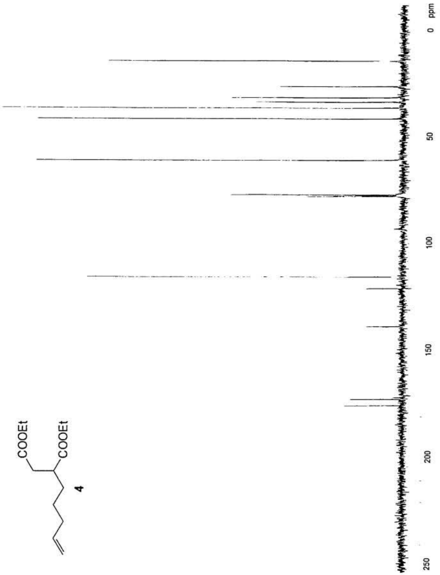
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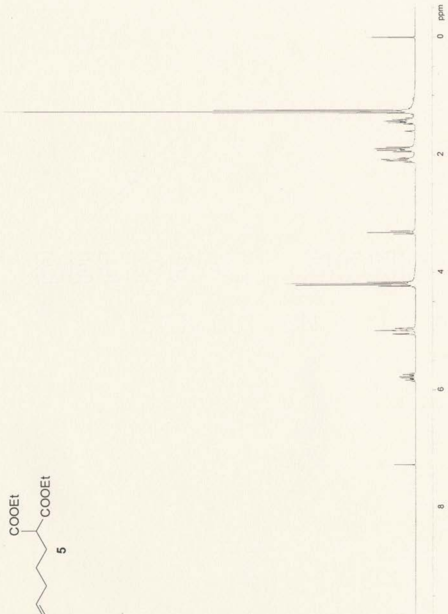
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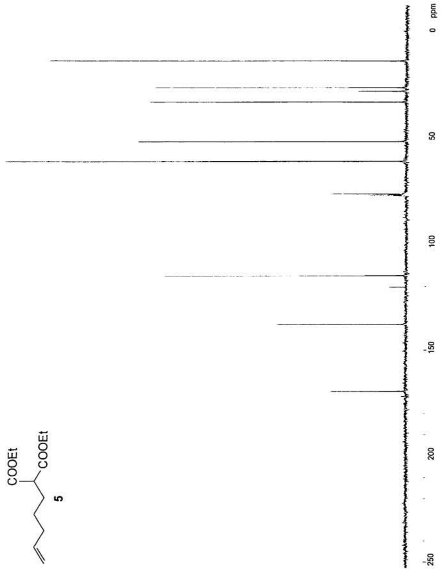
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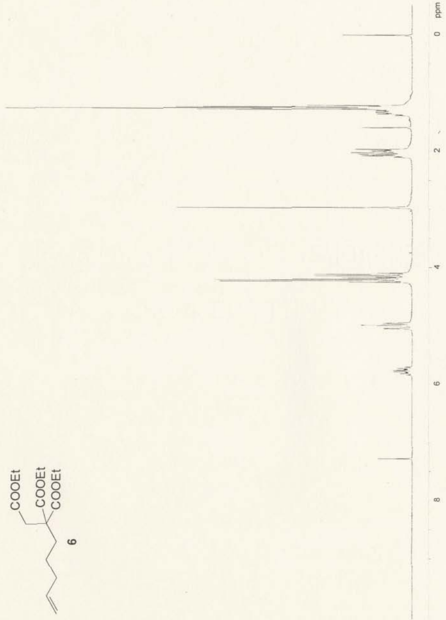

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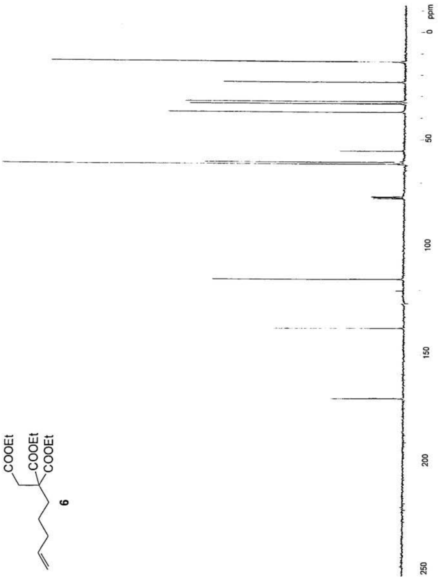
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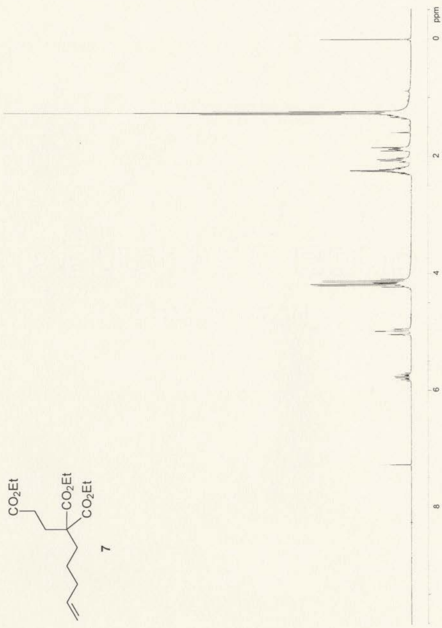
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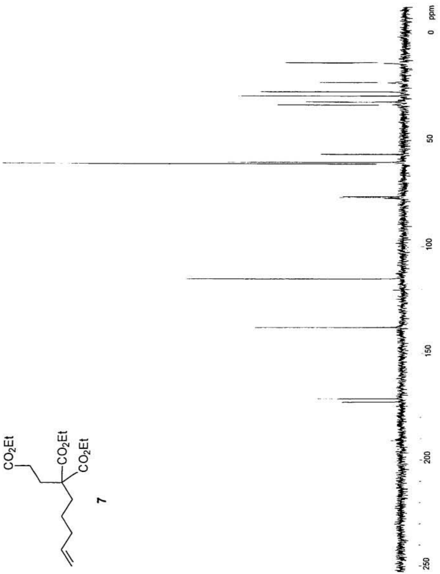

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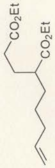

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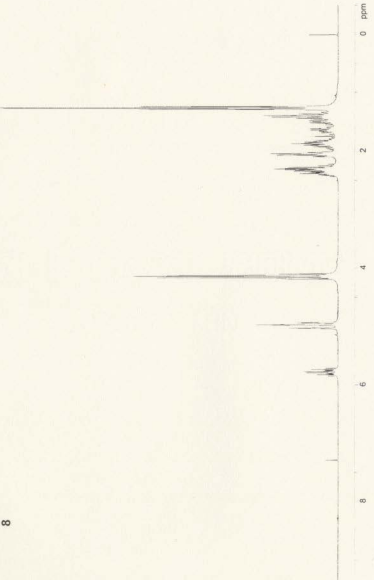

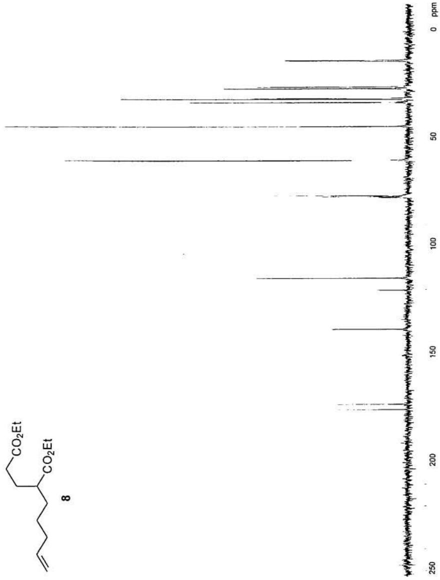
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200
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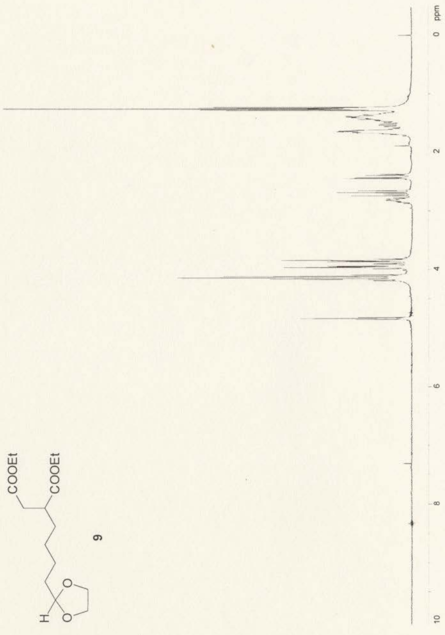

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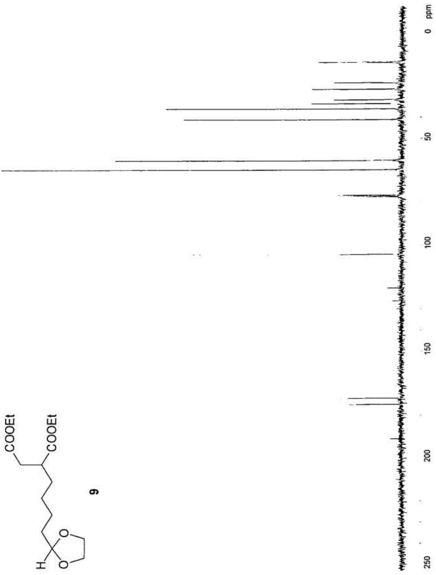

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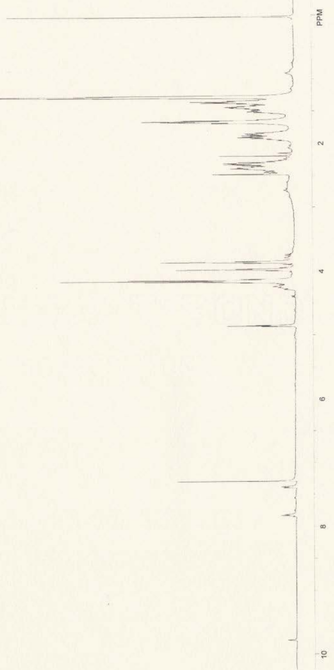
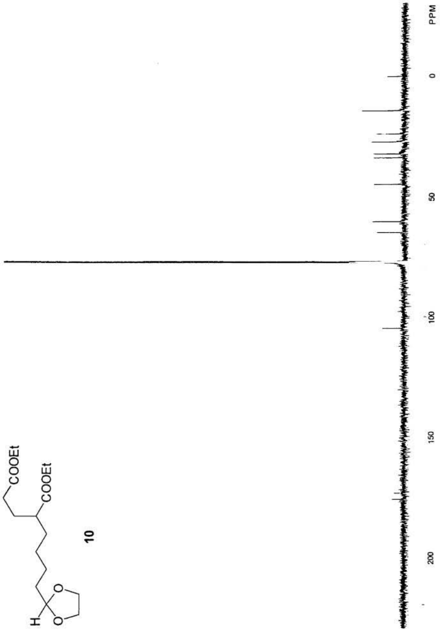
COOEt
H
O
O
9
250
200
150
100
50
0
ppm

10





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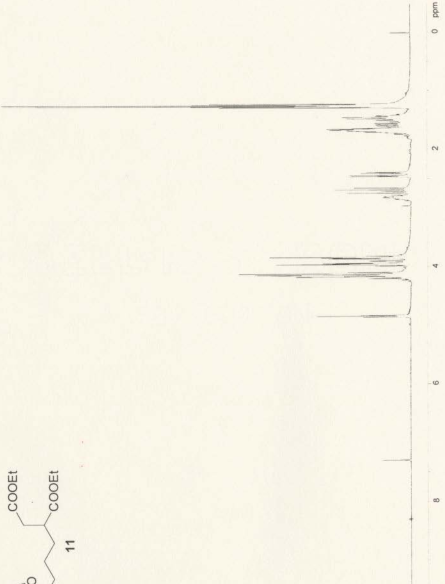
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COOEt
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6
4
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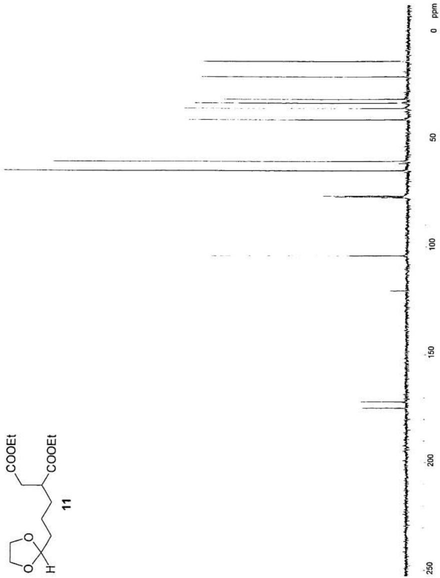
ppm



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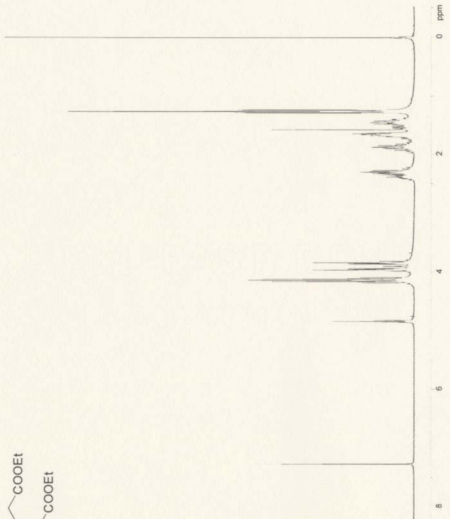
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COOEt
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ppm
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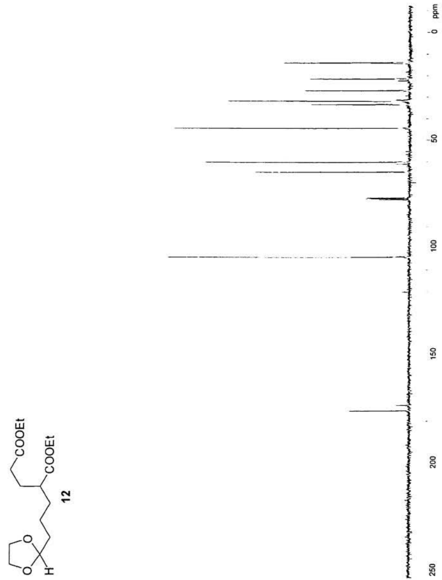

12

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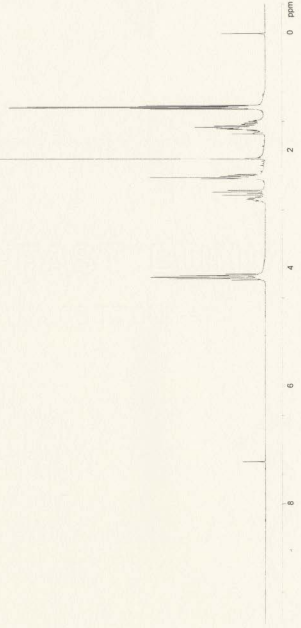

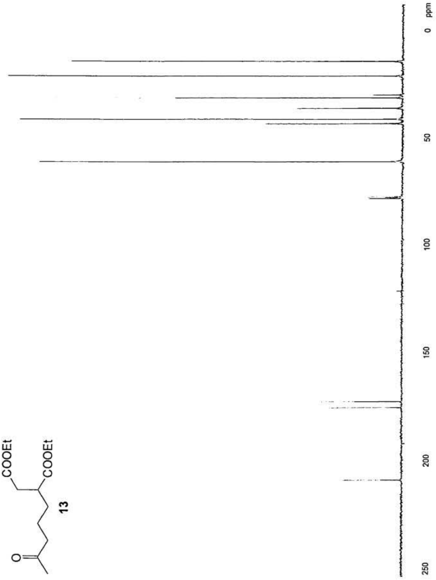
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COOEt
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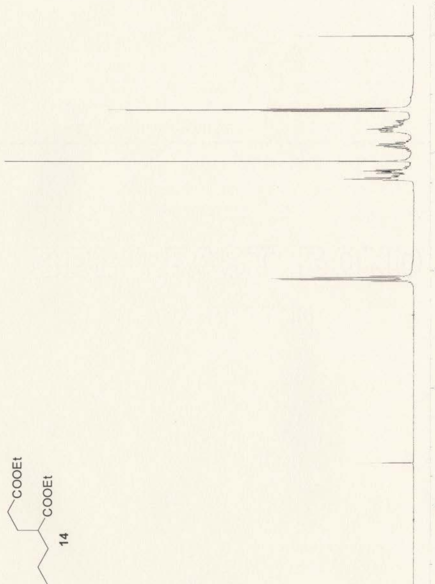
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COOEt
COOEt
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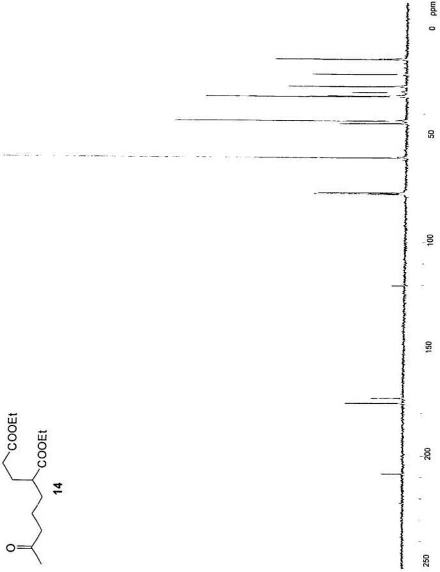
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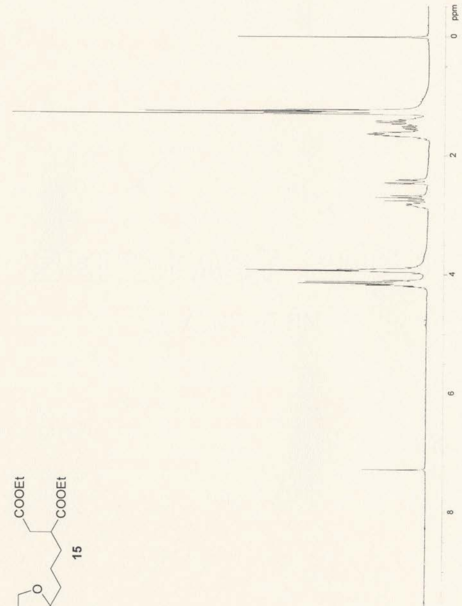
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COOEt
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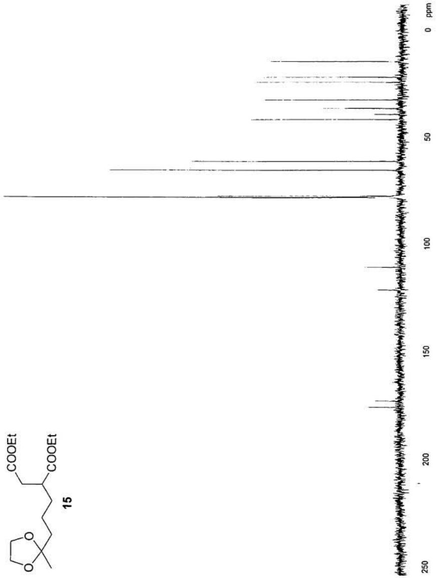
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COOEt
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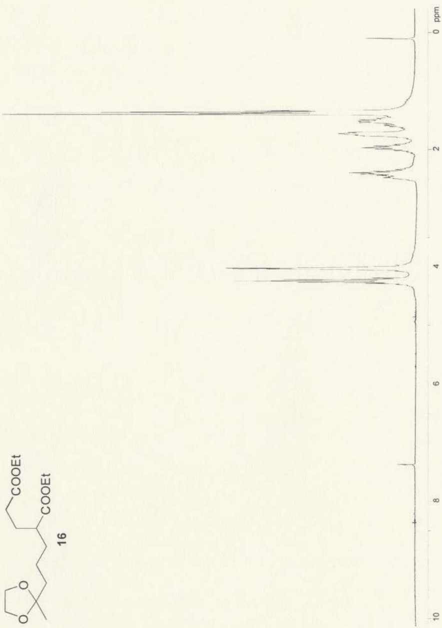
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COOEt
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4
6
8
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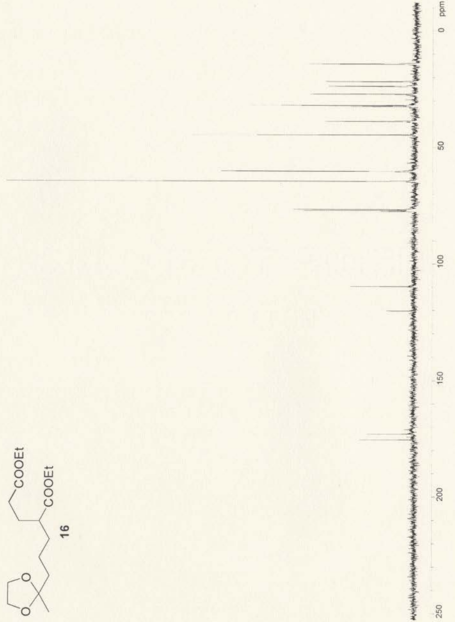
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COOEt
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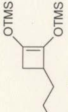

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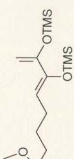

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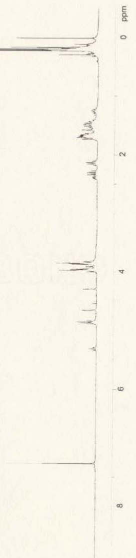

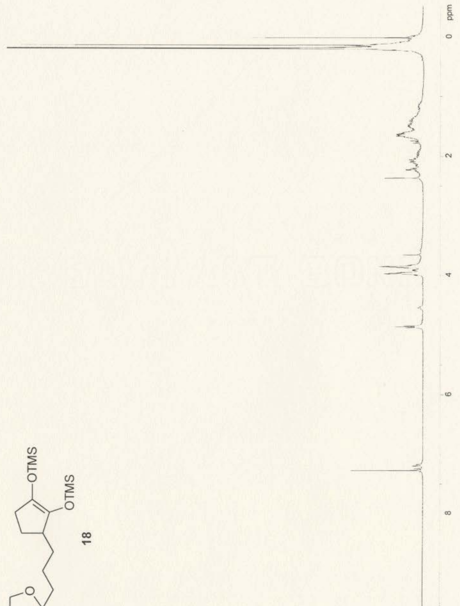
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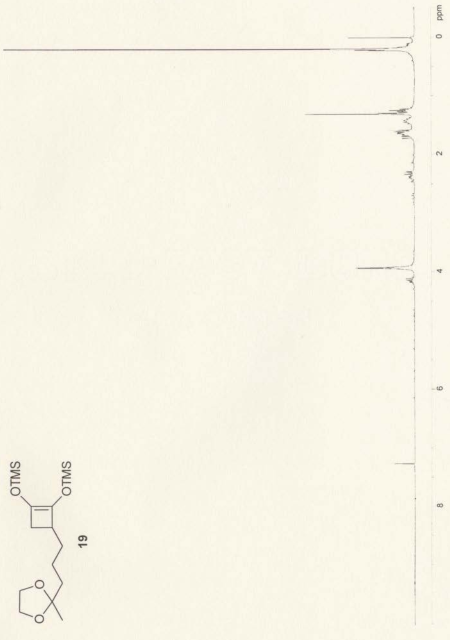
4
6
8



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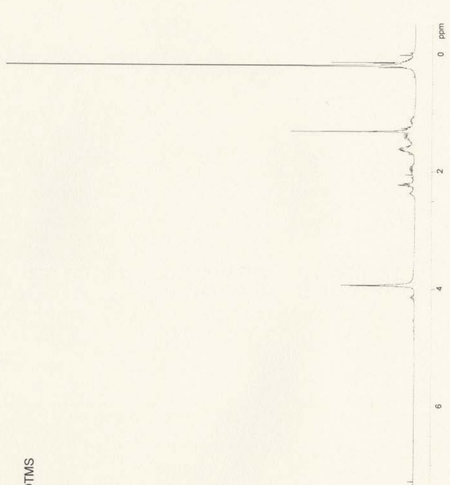
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OTMS
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ppm
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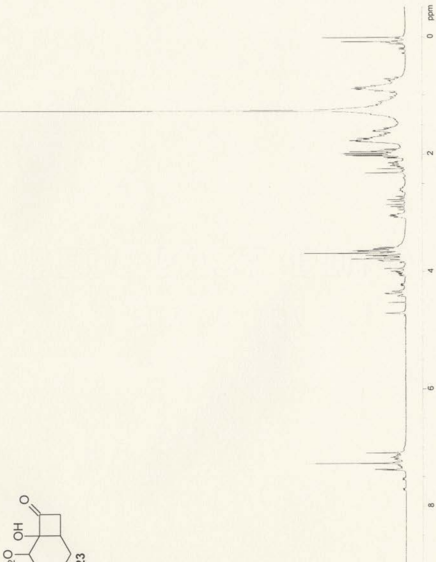
2
4
6
8



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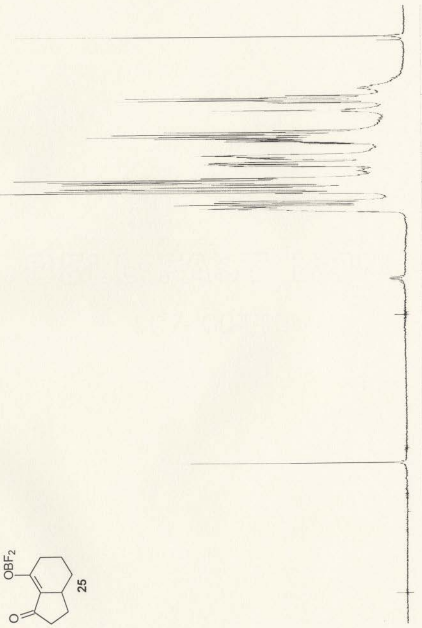

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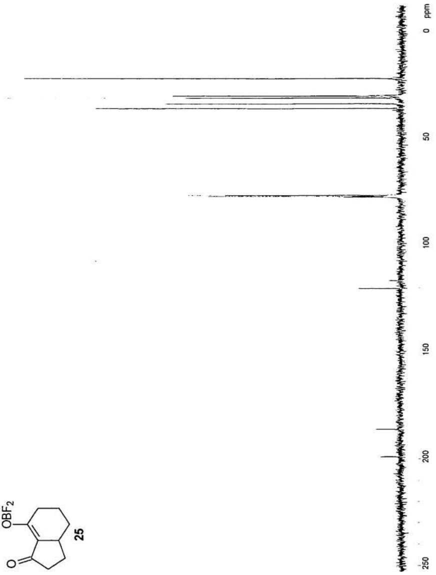
2
4
6
8



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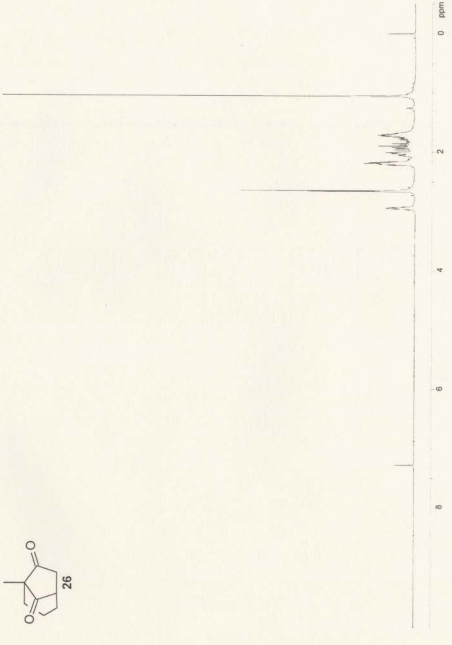

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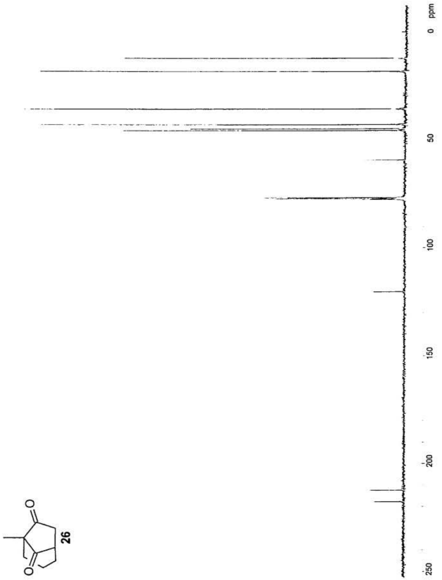
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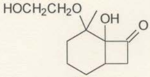
26
O
O



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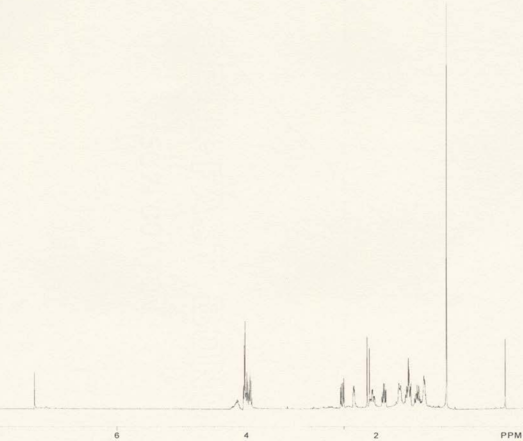


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OH
O
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PPM
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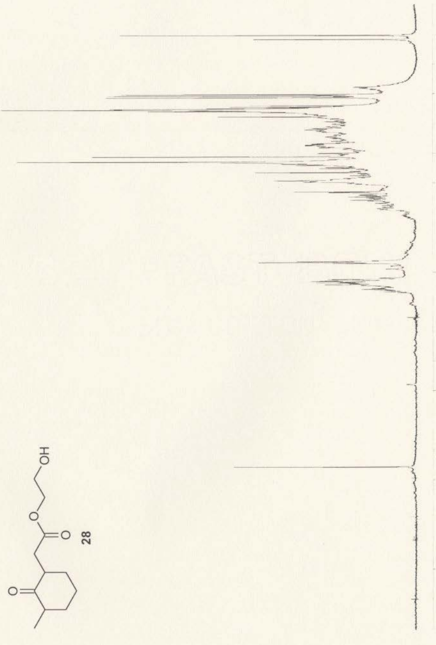
150
200



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6
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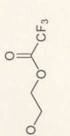

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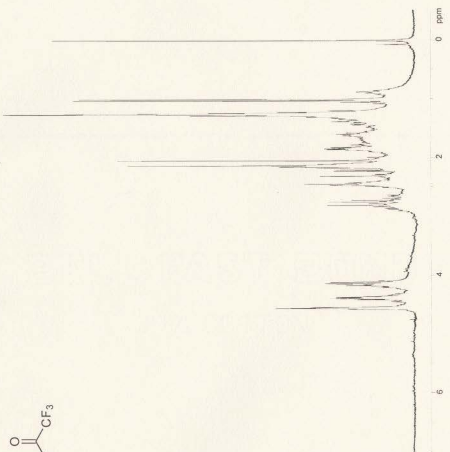

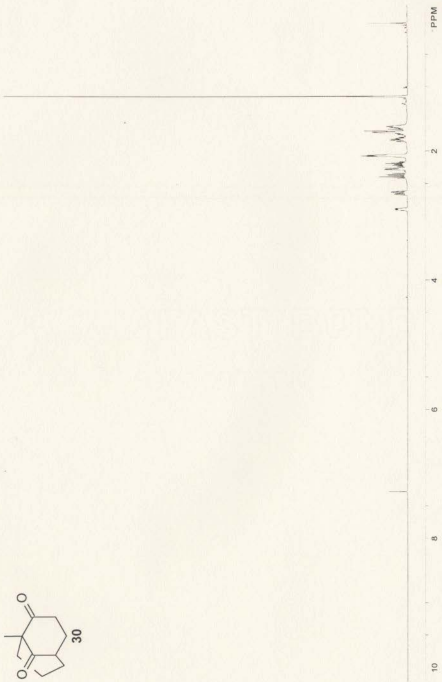
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8
10
30


PPM
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150
200
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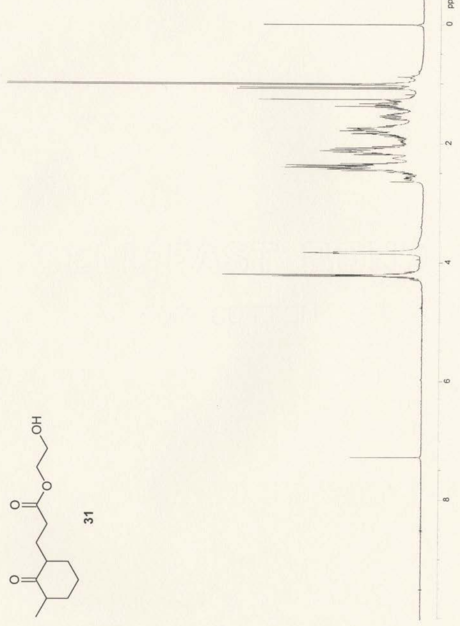
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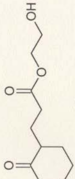

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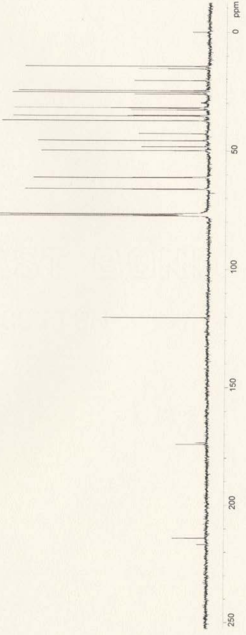

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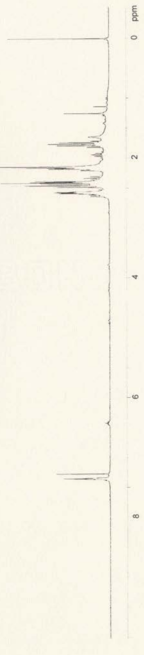

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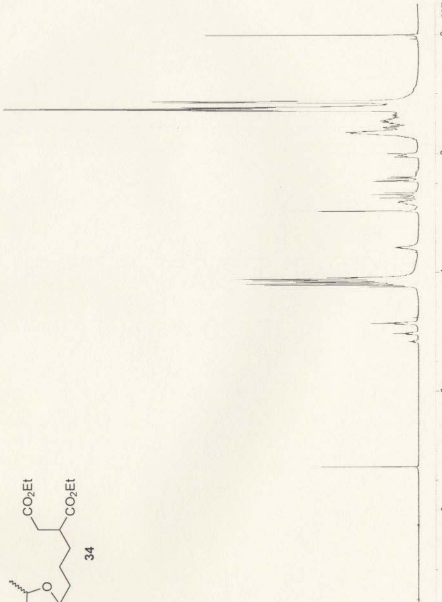
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CO2Et
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O
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CO2Et
O
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H
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2
4
6
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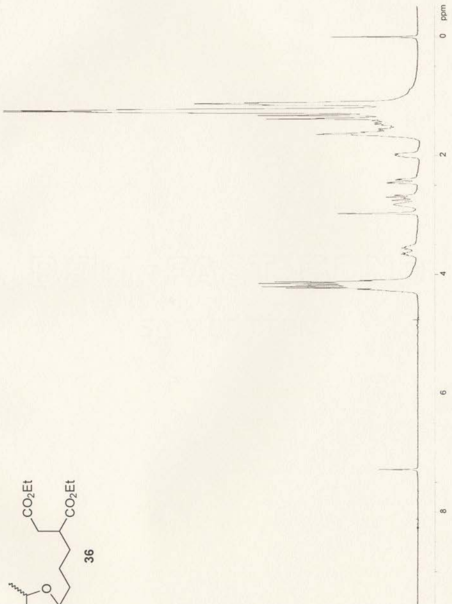
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CO2Et
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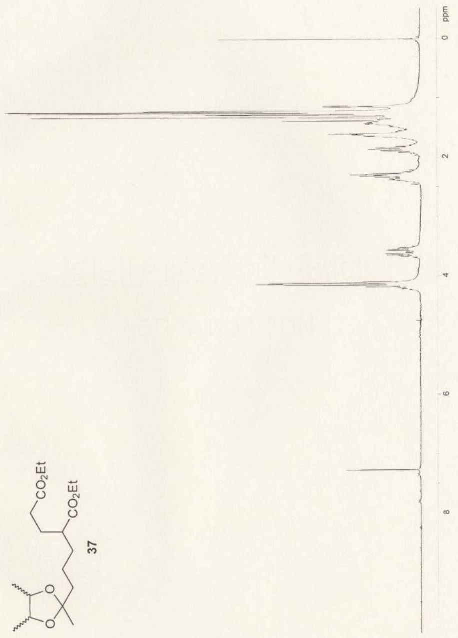

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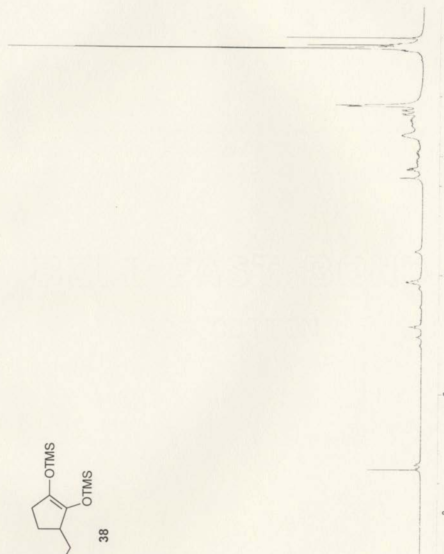

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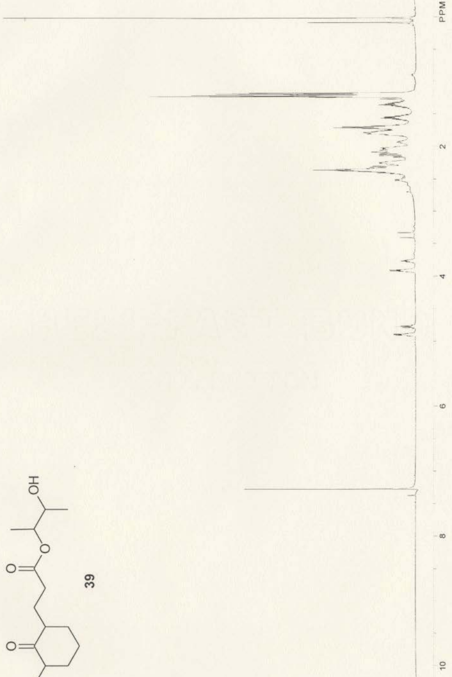

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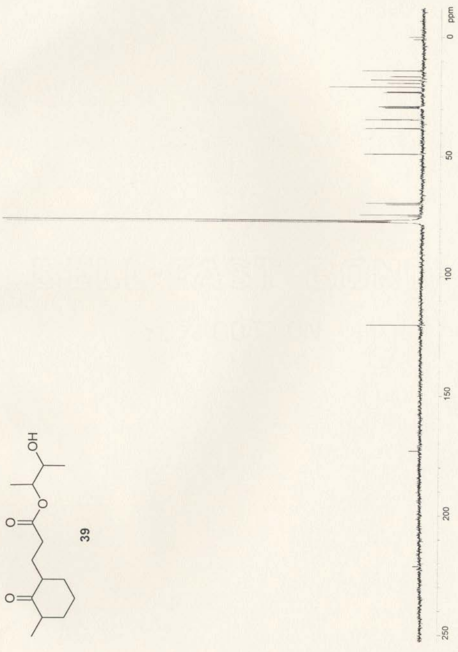
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O
O
O
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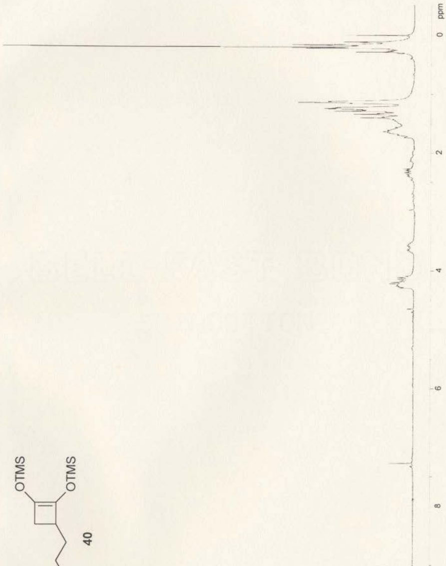
200
150
100
50
0
ppm



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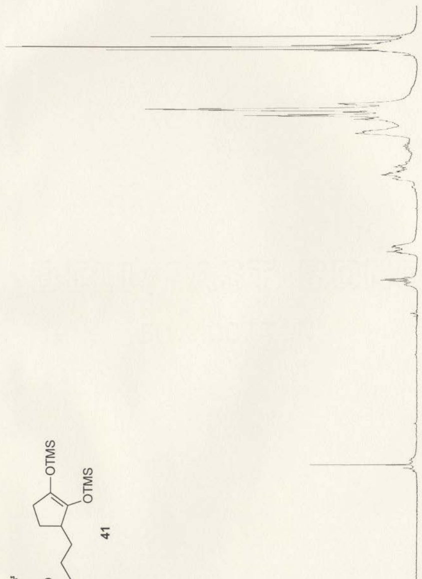
OTMS
OTMS
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ppm
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2
4
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