EXAMINATION OF THE GEMINAL ACYLATION REACTION AND ITS APPLICATION TOWARDS THE SYNTHESIS OF A STEROID BACKBONE

RHEA LISE MELANSON

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EXAMINATION OF THE GEMINAL ACYLATION REACTION AND ITS APPLICATION TOWARDS THE SYNTHESIS OF A STEROID BACKBONE

by

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(B. Sc. Honours, Acadia University, 1998)

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Abstract

The geminal acylation reaction has been extensively studied in the Burnell research group. Acetals and ketones react with 1,2-bis((trimethylsilyl)oxy)cyclobutene (**2**) in the presence of a Lewis acid to give 2-substituted-1,3-diketones. Based on the knowledge that, on unsymmetrical diketones, the reaction occurs preferentially on the less sterically hindered center, competition studies were undertaken to investigate the outcome of the geminal acylation reaction on substrate mixtures. Not surprisingly, the less sterically hindered ketones of the mixtures were seen to yield the corresponding products in greater yields. Mixtures with higher concentrations of the hindered ketones still preferentially resulted in the formation of the products of the less hindered ketones. Substrate mixtures were selected to examine various other effects. It was found that β-substituents had a slight effect on the reaction, but not as great as an α-substituent. Cyclic ketones reacted faster than acyclic ones, with cyclohexanones reacting faster than cyclopentanones. Various nucleophiles were also examined, and it was found that **2** reacted faster than any other.

Selection of an appropriate diketone to react in a geminal acylation reaction could, in theory, give a compound which would cyclize to a steroid in a synthetically efficient manner. The D-ring and the A-ring of the steroid could be formed by sequential geminal acylations using 1,2-bis((trimethylsilyl)oxy)cyclobutene (**2**) and 1,2-bis((trimethylsilyl)oxy)cyclopentene (**55**), respectively. The preparation of this diketone

proceeded well and the first geminal acylation was performed in 95% yield. However, due to a shortage of time, the synthesis was not completed.

Most of the work done in the past on the geminal acylation reaction has been with 1,2-bis((trimethylsilyl)oxy)cyclobutene (**2**). In the course of this work, novel compounds were prepared, mostly by the reaction of an acetal with 1,2-bis((trimethylsilyl)oxy)cyclopentene (**55**).

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I would especially like to thank Jonathan Langille. This thesis would not have been possible without his encouragement, love and support. I know I wouldn't have made it through without him. The late night chats and kind words helped me more than he'll ever know. Words can't begin to express it.

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Thanks to my colleagues in the Burnell group and the organic groups for any help along the way. Thanks to Mark and Karen for wonderful lunchtime discussions and great friendship.

My parents have always been wonderfully supportive throughout my entire education. Thanks for everything, Mame et Pape.

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List of Schemes

List of Abbreviations and Symbols

APT	attached proton test
COSY	correlated spectroscopy
δ	chemical shift
d	doublet
DMSO	dimethylsulfoxide
2,4-DNP	2,4-dinitrophenylhydrazine
Et	ethyl
g	gram(s)
GC	gas chromatography
h	hour(s)
HETCORR	heteronuclear correlated spectroscopy
HRMS	high resolution (electron impact) mass spectrometry
Hz	hertz
IR	infrared (spectroscopy)
J	coupling constant (*J* value)
L	liter
m	multiplet (NMR); medium (IR)
M	molar (mol/L)
Me	methyl

mL	millilitre(s)
mmol	millimole(s)
mm Hg	millimeter(s) of mercury
mol	mole(s)
m.p.	melting point
MS	mass spectrometry
m/z	mass to charge ratio
NMR	nuclear magnetic resonance (spectroscopy)
Ph	phenyl
ppm	parts per million
***p*-TsOH**	*p*-toluenesulfonic acid
R_f	retention factor
r.t.	room temperature
s	singlet (NMR); strong (IR)
t	triplet
TBDMS	*tert*-butyldimethylsilyl
***t*-Bu**	*tert*-butyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMSO	trimethylsilyloxy
XS	excess

1. Introduction

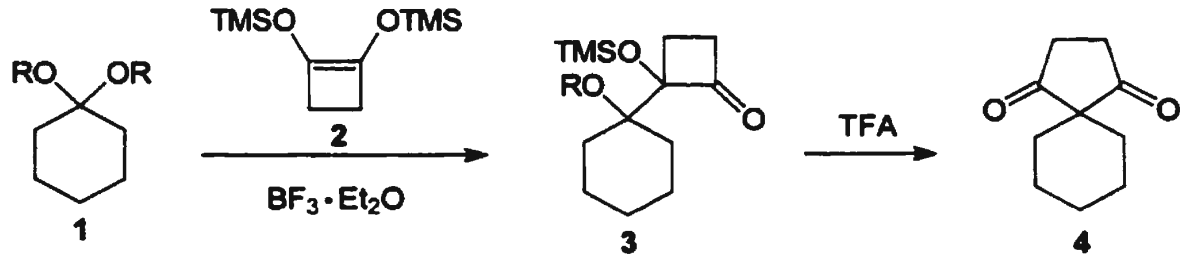
The synthesis of 2,2-disubstituted-1,3-diketones has proven to be a difficult task in organic synthesis.[1] The alkylation of enolates of 1,3-diketones can give either the *C*- or *O*-alkylated products. Poor yields are often obtained for the formation of cyclic 2,2-disubstituted-1,3-diketones by alkylation of cyclic 1,3-diketones.[2] The synthesis of spirocyclic 1,3-diketones has been achieved with acceptable yields, but the procedure involves a four-reaction sequence.[3] In this approach, the first step was an α-thioalkylation, which was followed by elimination and epoxidation. The resulting epoxide was then treated with a Lewis acid to induce rearrangement to a 1,3-diketone. Undoubtedly, a more straightforward, yet still high yielding, method to generate spirocyclic 1,3-diketones would be very useful.

The geminal acylation of acetals was first reported by Kuwajima's group.[4,5] The reaction of an acetal 1 with 1,2-bis((trimethylsilyl)oxy)cyclobutene[6] (2) in the presence of a Lewis acid gave a cyclobutanone derivative 3, which, when stirred in trifluoroacetic acid (TFA), yielded 2-substituted-1,3-cyclopentanedione 4 (Scheme 1). The Lewis acid most commonly used was boron trifluoride diethyl etherate ($BF_3 \cdot Et_2O$) but others, such as titanium tetrachloride, also worked well. The first step involved an aldol-type reaction

---

[1] House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972; pp 510-542.
[2] Garst, M. E.; McBride, B. J. *J. Org. Chem.* **1983**, *48*, 1362-1364.
[3] Bach, R. D.; Klix, R. C. *J. Org. Chem.* **1985**, *50*, 5438-5440.
[4] Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1977**, *99*, 961-963.
[5] Shimada, J.; Hashimoto, K.; Kim, B. H.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 1759-1773.

where **2** was added to acetal **1**. A pinacol-type rearrangement of **3** gave 2,2-disubstituted-1,3-cyclopentanedione **4**. TFA was chosen as the solvent for this second step, but it was shown that other conditions, such as *p*-toluenesulfonic acid (*p*-TsOH) in hot benzene, $BF_3 \cdot Et_2O$, and trimethylsilyl triflate in dichloromethane, were also capable of giving the desired product.[5]

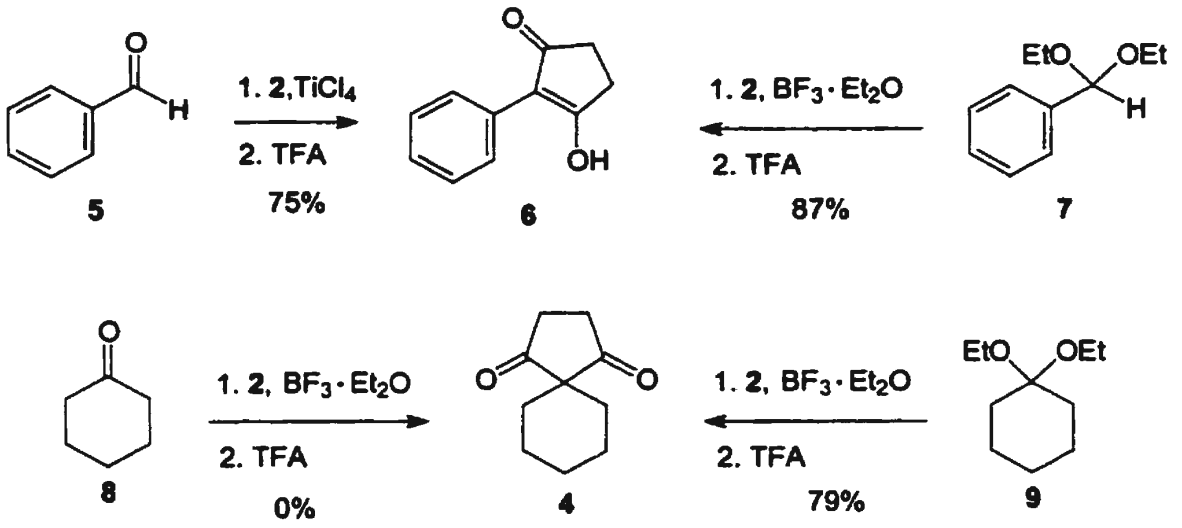


Scheme 1.

Although Kuwajima's group performed this reaction on aldehydes, in addition to the acetals of both aldehydes and ketones, it was reported that ketones did not react to give 2,2-disubstituted-1,3-cyclopentanediones. The problem was encountered in the first step. It has been shown that ketones are not good electrophiles for silyl enol ethers so that the reaction either does not occur[7] or is very sluggish.[8] For example, both benzaldehyde (**5**) and its diethyl acetal **7** reacted to give 1,3-diketone **6**, shown in its enol form (Scheme 2). Cyclohexanone (**8**) did not react with **2** but its diethyl acetal **9** did, giving the desired product **4**.

---

[6] Bloomfield, J. J.; Nelke, J. M. *Org. Synth. Coll. Vol. VI* **1988**, 167-172.
[7] Nakamura, E.; Shimizu, M.; Kuwajima, I.; Sakata, J.; Yokoyama, K.; Noyori, R. *J. Org. Chem.* **1983**, *48*, 932-945; Sato, T.; Otera, J.; Nozaki, H. *J. Am. Chem. Soc.* **1990**, *112*, 901-902.
[8] Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503-7509.



Scheme 2.

Subsequent work on the geminal acylation reaction has been very successful in improving the reaction conditions. Both our group[9,10] and Ayyangar's group[11] reported that using an excess of $BF_3 \cdot Et_2O$ gave the desired 1,3-cyclopentanedione product in one step, thereby eliminating the need for TFA. As such, the improved conditions consisted of addition of 10-15 equivalents of $BF_3 \cdot Et_2O$ to a solution of the acetal in dichloromethane at -78 °C, followed by addition of **2** and then allowing the reaction mixture to attain room temperature. Not only do these conditions reduce the number of steps, but they also improve the yields for most substrates.[10]

Although Kuwajima chose not to use cyclic acetals, opting instead for dimethyl, diethyl and dibenzyl acetals, our group attempted the geminal acylation reaction with

[9] Wu, Y.-J.; Burnell, D. J. *Tetrahedron Lett.* **1988**, *29*, 4369-4372.
[10] Burnell, D. J.; Wu, Y.-J. *Can. J. Chem.* **1991**, *69*, 804-811.
[11] Pandey, B.; Khire, U. R.; Ayyangar, N. R. *Synth. Commun.* **1989**, *19*, 2741-2747.

acetals derived from 1,2-ethanediol.[12] The results showed that unhindered cyclic acetals underwent the reaction just as well as acyclic dialkyl acetals. In fact, the yields were better due to the improvement of the reaction conditions stated above. The reaction of the diethyl acetal of cyclohexanone **9** proceeded in 79% yield, while the 1,2-ethanediol acetal **10** was produced in 96% yield. Hindered acetals greatly reduced the reactivity of the substrate. Thus, the reaction of the acetal of cyclohexanone derived from 2,3-butanediol **11** proceeded in 48% yield, while the acetal of cyclohexanone derived from 1,2-diphenyl-1,2-ethanediol **12** did not react at all (Figure 1). This could be useful as a protecting group on polyketones when the reaction is desired on one carbonyl group but not on the others present.[12] However, the use of cyclic acetals caused a problem in some cases due to the formation of a ketoester.[12] This was the result of an acid-catalyzed reaction of the desired 1,3-cyclopentanedione product with 1,2-ethanediol, which was released as the reaction progressed. For acetal **13**, this was a significant problem as none of product **14** was isolated. Only ketoester **15** was isolated in low yield (Scheme 3).

The effect of various functional groups on neighboring carbons was also examined.[12] For example, when there was a ketone next to the target acetal, as for compound **16**, the reaction was completely inhibited. An ester or lactone in the β-position also inhibited the reaction, however there was no significant effect when an ester was in the γ-position.

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[12] Wu, Y.-J.; Strickland, D. W.; Jenkins, T. J.; Liu, P.-Y.; Burnell, D. J. *Can. J. Chem.* **1993**, *71*, 1311-1318.

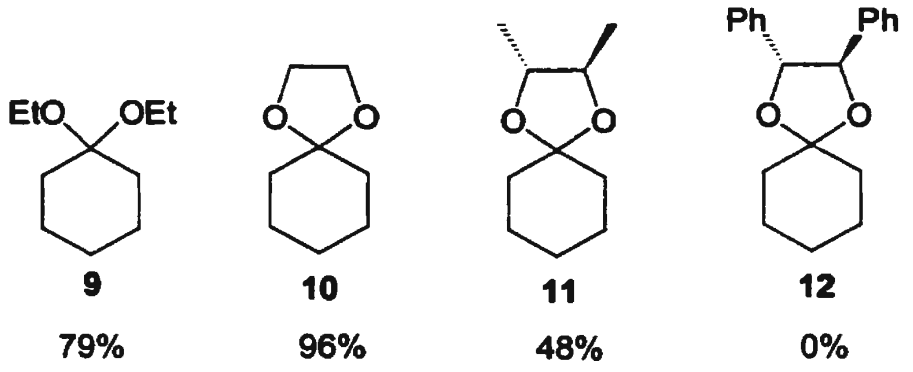
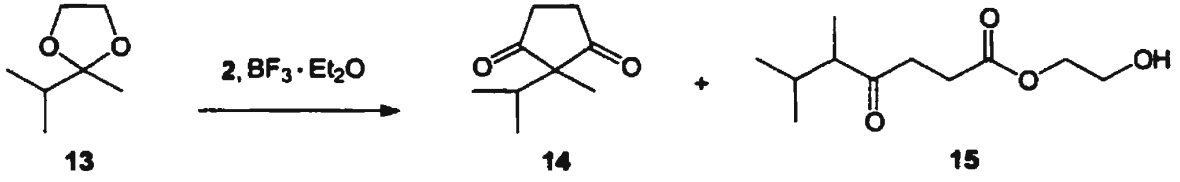


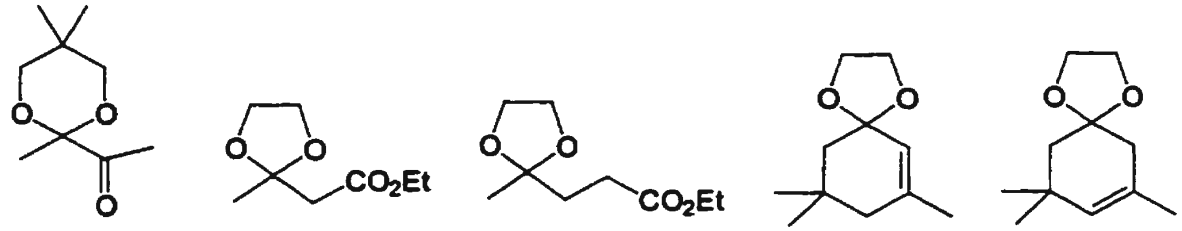
Figure 1. The effect of varying the acetal.



Scheme 3.

For example, the reaction of acetal **18** proceeded very well while acetal **17** did not react at all. Similarly, a reaction did not readily take place on the acetal of an α,β-unsaturated ketone **19**, but a double bond in the β,γ-position posed no difficulties. Acetal **20**, with a β,γ-double bond, reacted in 72% yield (Figure 2).

As mentioned previously, various groups have reported the difficulty with which ketones react with silyl enol ethers, when they react at all. As such, up to this point, the reaction of ketones in the geminal acylation reaction had been unsuccessful. Using the conditions optimized for acetals (i.e., excess $BF_3 \cdot Et_2O$) gave very poor results as mostly



16 0%

17 0%

18 91%

19 0%

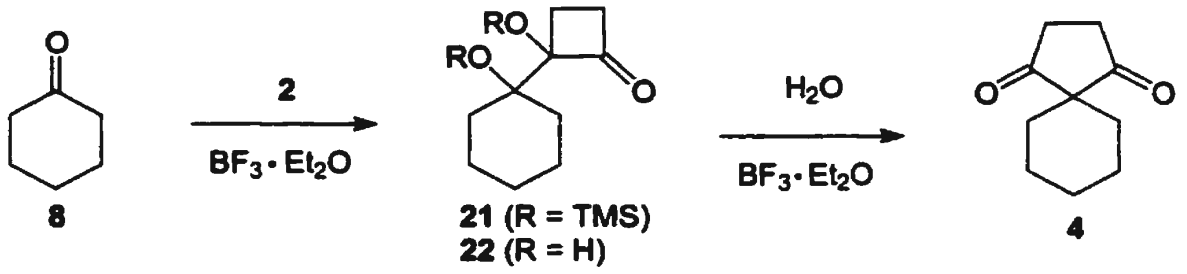
20 72%

Figure 2. The effect of neighboring functional groups on the geminal acylation reaction.

the starting ketone and the unrearranged intermediate were isolated.[13] It was discovered that the addition of water was necessary in order to get optimum yields when ketones were used as substrates. The new "ketone conditions", shown in Scheme 4, required only one equivalent of $BF_3 \cdot Et_2O$ followed by, after a time, a small volume of water and then excess $BF_3 \cdot Et_2O$. It was believed that the water was necessary to hydrolyze the (trimethylsilyl)oxy (TMSO) groups so that rearrangement to the 1,3-diketone could then take place. In the reaction of cyclohexanone (**8**), when cyclobutanone derivative **21** was treated with tetrabutylammonium fluoride, diol **22** was obtained, which rearranged to 1,3-cyclopentanedione **4** in anhydrous $BF_3 \cdot Et_2O$. Hence, hydrolysis to the diol was required in order to obtain a good yield of the desired cyclopentanedione, and this was accomplished by the addition of water in the second step.

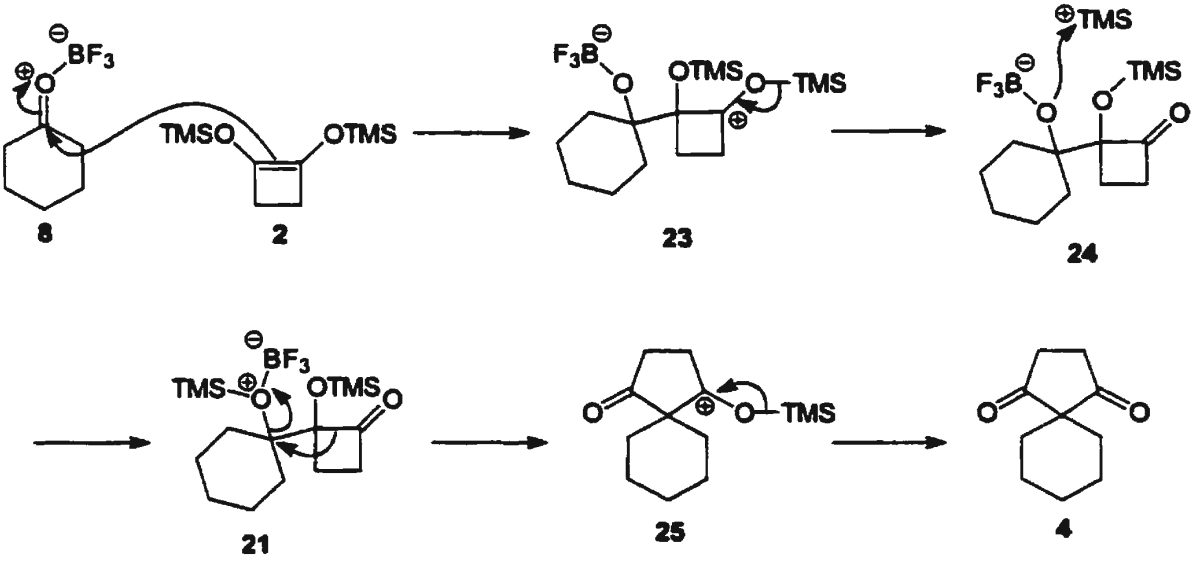
A proposed mechanism for the geminal acylation of cyclohexanone (**8**) is shown in Scheme 5. The first step is an aldol reaction, catalyzed by $BF_3 \cdot Et_2O$. 1,2-Bis((trimethylsilyl)oxy)cyclobutene (**2**) is added to the substrate giving intermediate **23**

[13] Jenkins, T. J.; Burnell, D. J. *J. Org. Chem.* **1994**, *59*, 1485-1491.

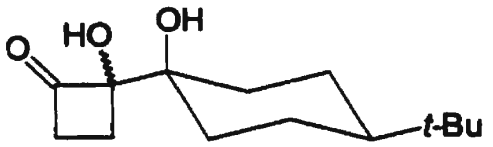


Scheme 4.

and then cyclobutanone **24**. The x-ray structure of cyclobutanone intermediate **26** (Figure 3) of the reaction of 4-*tert*-butylcyclohexanone suggested that it was formed by a mechanism involving an equatorial attack on the carbonyl group of **24**. A pinacol rearrangement of **21** gives the carbocationic compound **25**, which, in turn, yields the desired 2,2-disubstituted-1,3-cyclopentanedione **4** (Scheme 5).



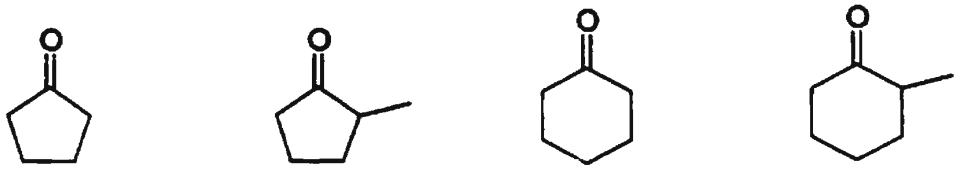
Scheme 5.



26

Figure 3. The cyclobutanone intermediate **26** that would be the result of equatorial attack.

As mentioned previously, the bulkiness of the acetal group is a factor in the reaction. α-Substituents on the original ketone also have a significant effect on the yield. Work with ketones showed that addition of an α-methyl group reduced the yield by approximately 30%.[13] For example, the yields in the reactions of cyclopentanone (**27**) and 2-methyl-1-cyclopentanone (**28**) were 79% and 55%, respectively. The reactions of cyclohexanone (**8**) and 2-methyl-1-cyclohexanone (**29**) also showed this effect (Figure 4). Ketones with neighboring quaternary centers do not react with **2**. Although this limits the use of the reaction, it also ensures that the 2,2-disubstituted-1,3-cyclopentanediones do not react further.

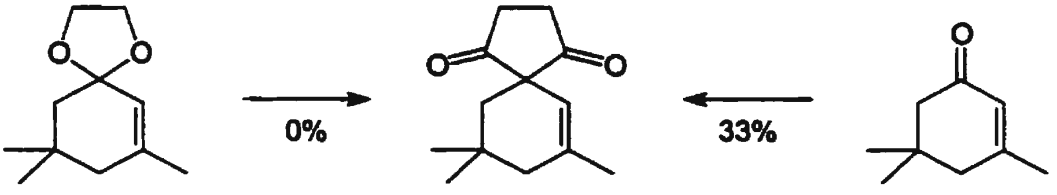


27 79%　　**28** 55%　　**8** 94%　　**29** 62%

Figure 4. The effect of α-methyl substituents on the yield.

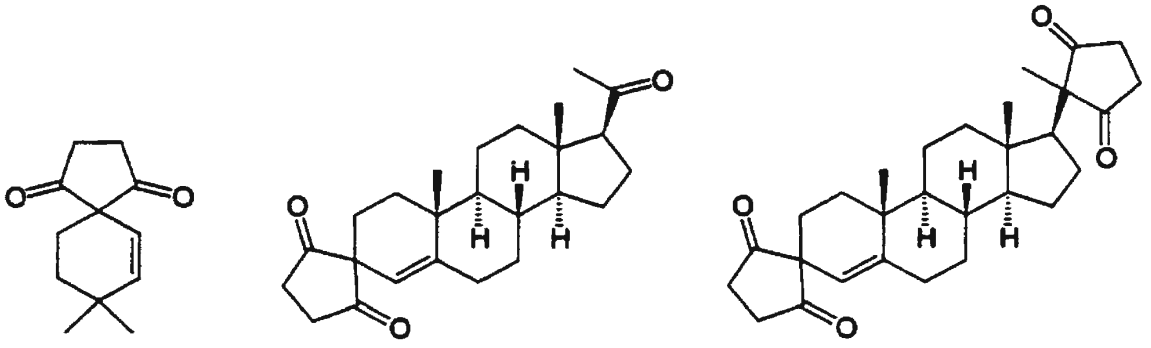
In some cases where the acetal did not react at all, the corresponding ketone was used to synthesize the desired compound.[13] Recall that acetal **19** did not react due to its α,β-double bond. Ketone **31**, on the other hand, gave diketone **30** in 33% yield (Scheme 6). Some α,β-unsaturated ketones reacted very well in the geminal acylation reaction. A yield of 71% was obtained when 4,4-dimethyl-2-cyclohexen-1-one was converted to diketone **32** (Figure 5). Even more striking was the reaction of progesterone. The reaction took place on the α,β-unsaturated ketone preferentially to give **33** in 66% yield. This selectivity was most likely due to the hindering effect of the α-substituents of the non-conjugated ketone. Reaction at this more sterically-hindered carbon was still possible since 5% of the doubly geminally acylated product **34** was isolated.

A double bond in the γ-position was shown to be potentially problematic in the geminal acylation reaction.[13] When the reaction of 6-methyl-5-hepten-2-one with **2** and $BF_3 \cdot Et_2O$ was attempted, none of the desired product **35** was observed by nuclear magnetic resonance spectroscopy (NMR). However, when the double bond was one carbon further away, as in 1,10-undecadien-6-one, acceptable yields of **36** were achieved (Figure 6). When the double bond was in the γ-position, cyclization occurred in some



19 **30** **31**

Scheme 6.



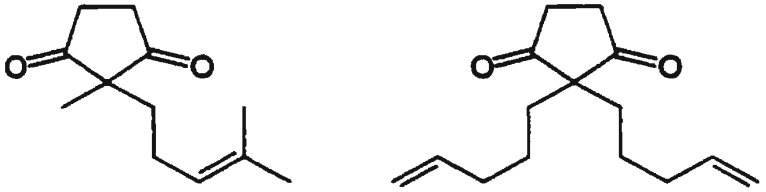
32
71%

33
66%

34
5%

Figure 5. The products of the reaction of α,β-unsaturated ketones.

cases. Curran and Balog[14] used the geminal acylation reaction on acetals **37** and **40**, which have γ-triple bonds, as a facile way of generating polycyclic enediones **39** and **42**, respectively. The reactions were tandem, where, once 1,3-cyclopentanediones **38** and **41** were formed, 5-*exo-dig* or 6-*endo-dig* cyclizations ensued (Scheme 7).

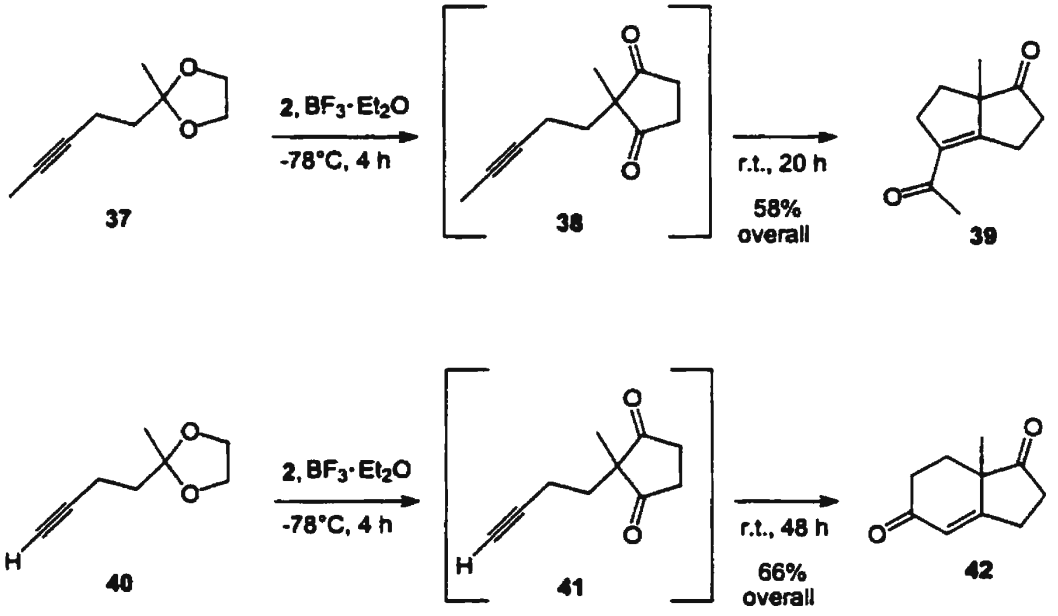


35
0%

36
78%

Figure 6. The reactions of unsaturated ketones.

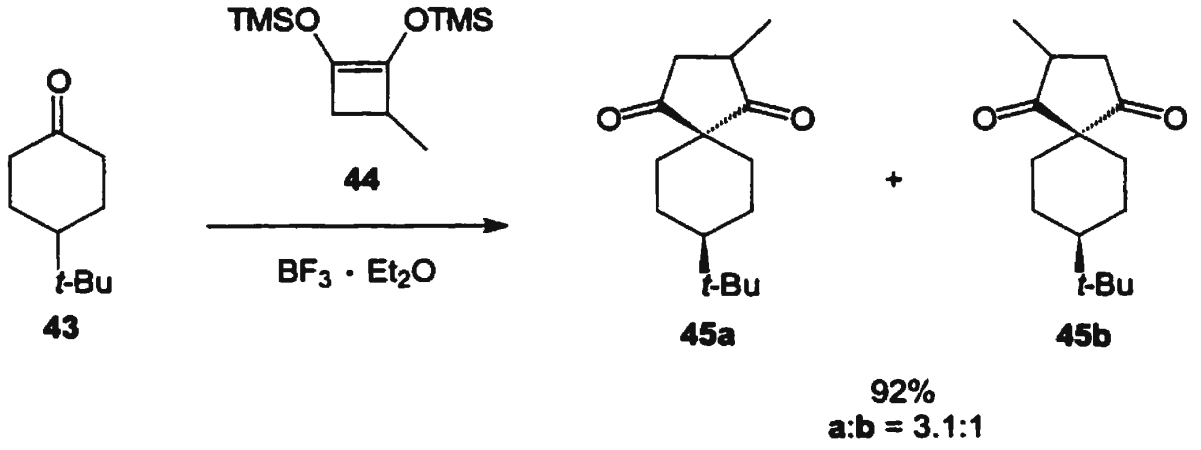
[14] Balog, A.; Curran, D. P. *J. Org. Chem.* **1995**, *60*, 337-344.



Scheme 7.

The geminal acylation reaction of ketones with methyl-substituted analogues of **2**, that is, 3-methyl-1,2-bis((trimethylsilyl)oxy)cyclobutene (**44**) and 3,3-dimethyl-1,2-bis((trimethylsilyl)oxy)cyclobutene (**46**), have been examined.[15] In some cases, acetals did not react as well with these analogues and, as expected, the best results were obtained with unencumbered ketones. The presence of methyl substituents on the 1,3-cyclopentanedione ring introduced stereochemical complexity, as shown in Scheme 8. The presence of multiple stereogenic centers had the potential to lead to a mixture of many diastereomers. Fortunately, some selectivity was observed, as in the reaction of 4-*tert*-butyl-1-cyclohexanone (**43**) where one diastereomer was produced preferentially over the other. It is worth noting that when the reaction was performed with the

corresponding acetal of **43**, the diastereomeric ratio had a tendency to shift in favor of **45b**. This was the case for most ketone/acetal pairs.

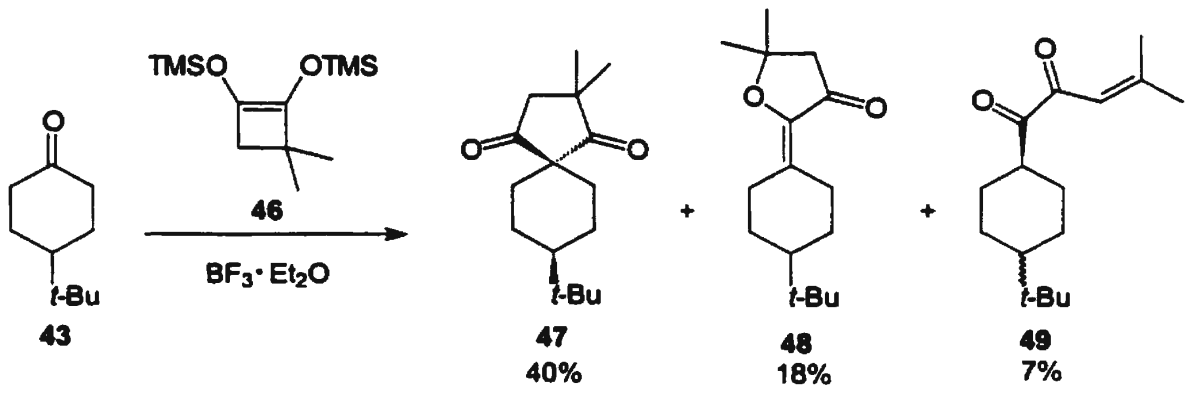


Scheme 8.

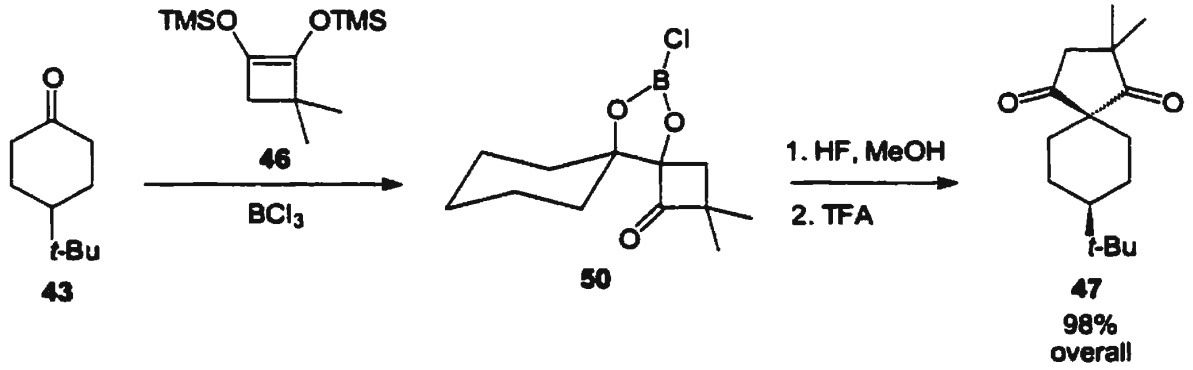
Expectedly, the yields in the reactions of ketones with **46**, the dimethyl analogue, were not as good as with **44**, presumably due to steric interactions. The stereoselectivity, however, was very high. In some cases, such as in the reaction of **43**, only one diastereomer, **47**, was observed (Scheme 9). Unwanted side reactions producing furanone **48** and dione **49** were troublesome,[15] but this problem was later overcome by the use of BCl_3 as the Lewis acid.[16] A three-step, one-pot procedure was developed in which none of the furanone side product was formed, hence increasing the yield of the desired 4,4-dimethyl-1,3-diketone **47** from 40% to 98%. The use of BCl_3 was just as stereoselective as $BF_3{\cdot}Et_2O$. As shown in Scheme 10, cyclobutanone intermediate **50** incorporated the boron. The diol was formed by addition of hydrofluoric acid in

[15] Crane, S. N.; Jenkins, T. J.; Burnell, D. J. *J. Org. Chem.* **1997**, *62*, 8722-8729.
[16] Crane, S. N.; Burnell, D. J. *J. Org. Chem.* **1998**, *63*, 5708-5710.

methanol and then addition of TFA yielded 4,4-dimethyl-1,3-diketone **47** without forming any furanone.



Scheme 9.



Scheme 10.

Although α,β-unsaturated ketones previously gave lower than desirable yields, their reaction with **46** gave surprisingly good results, as did α-aromatic ketones.[17] Examples of the products obtained when α,β-unsaturated ketones reacted with **2** and **46**

[17] Crane, S. N.; Burnell, D. J. *J. Org. Chem.* **1998**, *63*, 1352-1355.

are shown in Figure 7. Both corresponding pairs of diketones, that is **51** and **52**, and **30** and **53**, showed a significant improvement in yield for the reaction of the dimethyl analogue **46**.

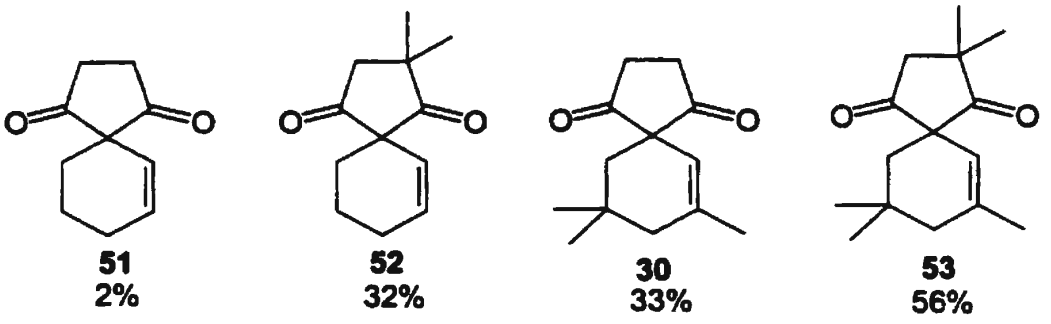
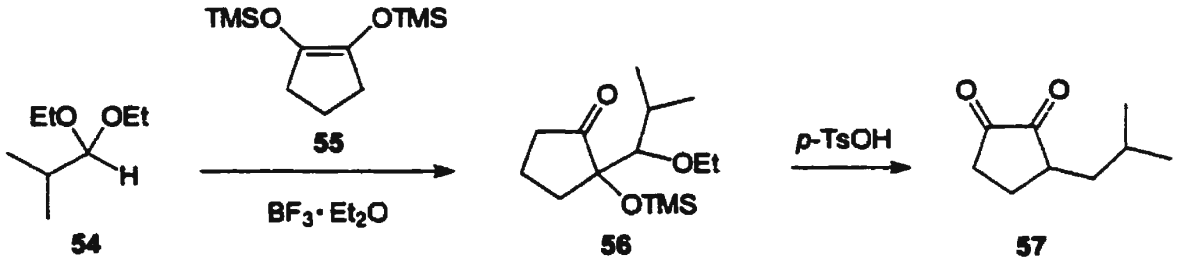


Figure 7. The reaction of α,β-unsaturated ketones with **2** and **46**.

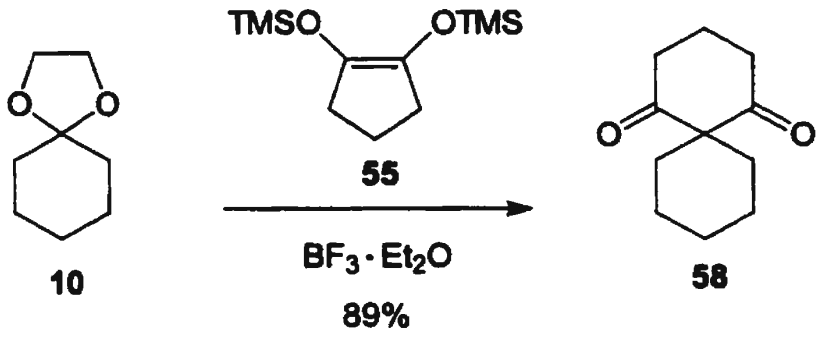
The use of 1,2-bis((trimethylsilyl)oxy)cyclopentene (**55**) in the geminal acylation reaction was studied by Pattenden and Teague.[18] They reported that, instead of a 2-substituted-1,3-cyclohexanedione, 3-substituted-1,2-cyclopentanedione **57** was obtained. Their proposed reaction sequence is shown in Scheme 11. Acetal **54** reacted to give cyclopentanone intermediate **56**, which supposedly rearranged to give 1,2-dione **57**. Later work by our group showed that 2-substituted-1,3-cyclohexanediones can be produced in very good yields.[19] For example, acetal **10** gave spiro diketone **58** in 89% yield (Scheme 12).

The geminal acylation reaction can be quite useful in the synthesis of natural products, especially since it is such a convenient method for generating a spiro center. In

[18] Pattenden, G.; Teague, S. *Tetrahedron Lett.* **1982**, *23*, 1403-1404.
[19] Wu, Y.-J.; Burnell, D. J. *Tetrahedron Lett.* **1989**, *30*, 1021-1024.

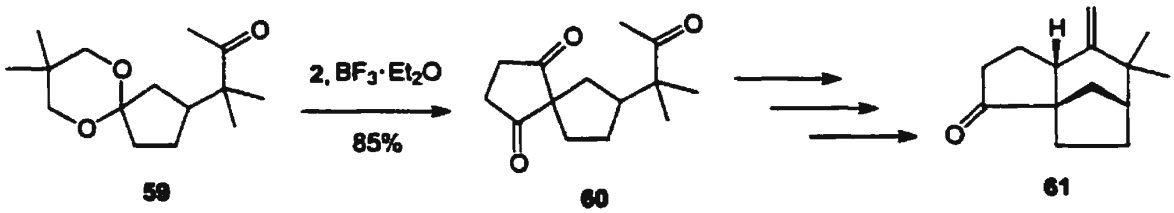


Scheme 11.



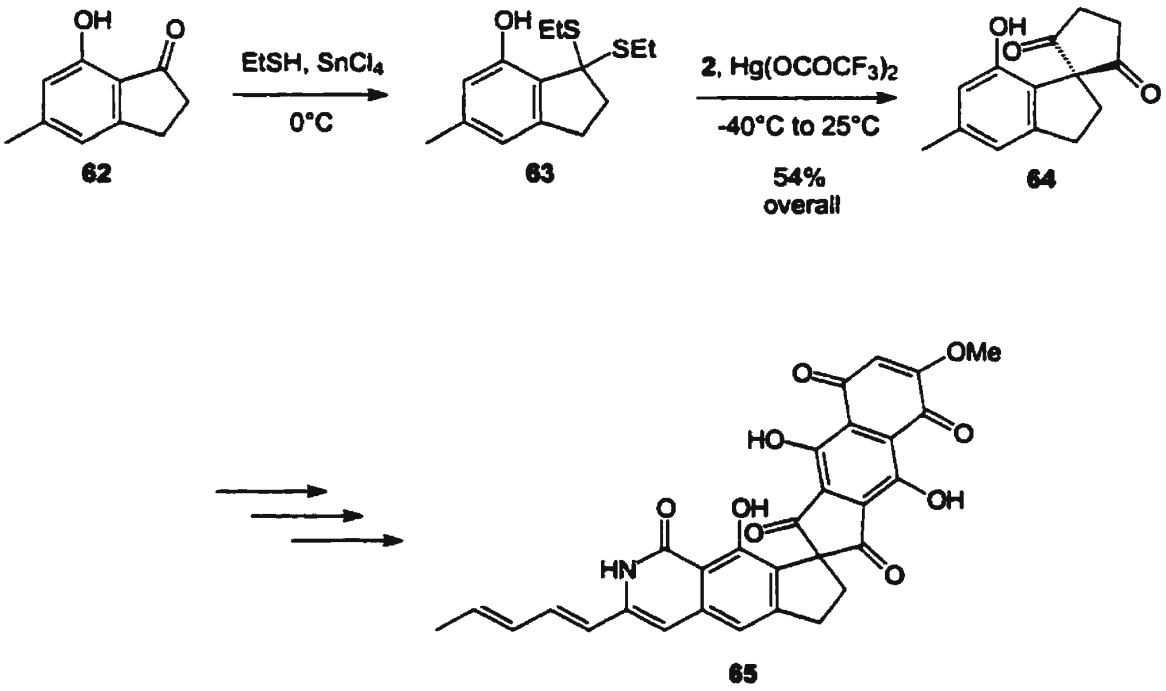
Scheme 12.

the synthesis of (±)-isokhusimone (**61**) by Wu and Burnell,[9] the geminal acylation was one of the key steps of the 8-step sequence. Acetal **59** reacted with **2** while the encumbered ketone was unreactive, giving the desired product **60** in 85% yield (Scheme 13).



Scheme 13.

Fredericamycin A (**65**) is also a prime candidate for the use of the geminal acylation reaction. Bach's group completed the total synthesis of this antibiotic and utilized the geminal acylation in doing so.[20] The spiro center was created in the first few steps in order to avoid potential problems later in the synthesis. Dithioacetal **63**, made from indanone **62**, underwent spiroannulation using mercuric trifluoroacetate as a Lewis acid to afford the 2,2-disubstituted-1,3-diketone **64** in 54% yield from **62** (Scheme 14).



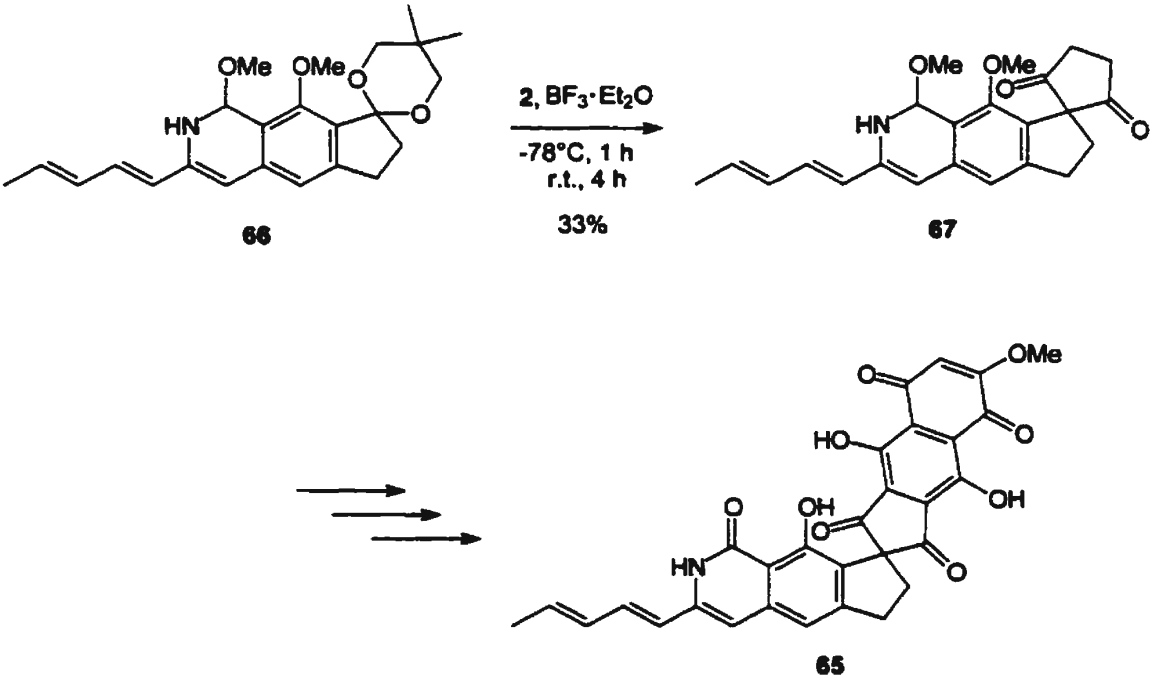
Scheme 14.

The total synthesis of fredericamycin A (**65**) was also reported by Julia and coworkers.[21] The geminal acylation was carried out on acetal **66**, using 3 equivalents of

[20] Wendt, J. A.; Gauvreau, P. J.; Bach, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 9921-9926.
[21] Saint-Jalmes, L.; Lila, C.; Xu, J. Z.; Moreau, L.; Pfeiffer, B.; Eck, G.; Pelsez, L.; Rolando, C.; Julia, M. *Bull. Soc. Chim. Fr.* **1993**, *130*, 447-449.

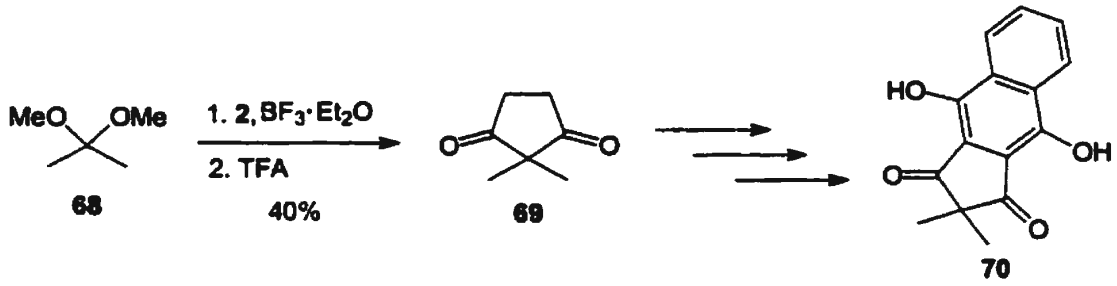
2 and 10 equivalents of the Lewis acid. As shown in Scheme 15, the desired spiro diketone **67** was produced in 33% yield.

Previously, the geminal acylation reaction had been used by Parker's group to create the tricyclic section **70** of fredericamycin A (**65**).[22] Once again, the reaction was used very early in the synthesis. Dimethyl acetal **68** reacted with **2** to give the desired 1,3-cyclopentanedione **69** in 40% yield, using TFA for the rearrangement (Scheme 16).



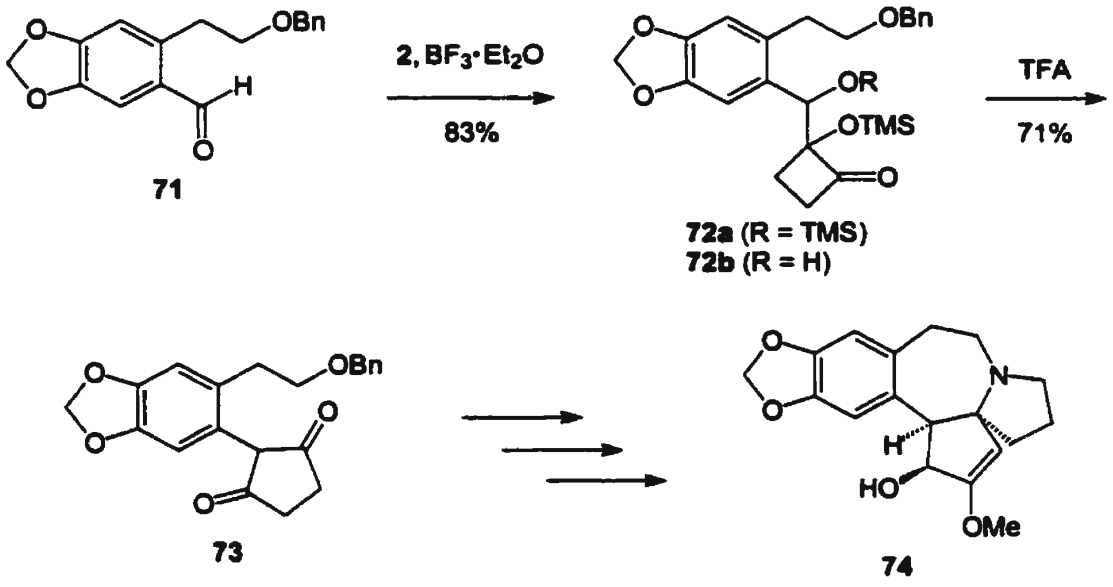
Scheme 15.

[22] Parker, K. A.; Koziski, K. A.; Breault, G. *Tetrahedron Lett.* **1985**, *26*, 2181-2182.



Scheme 16.

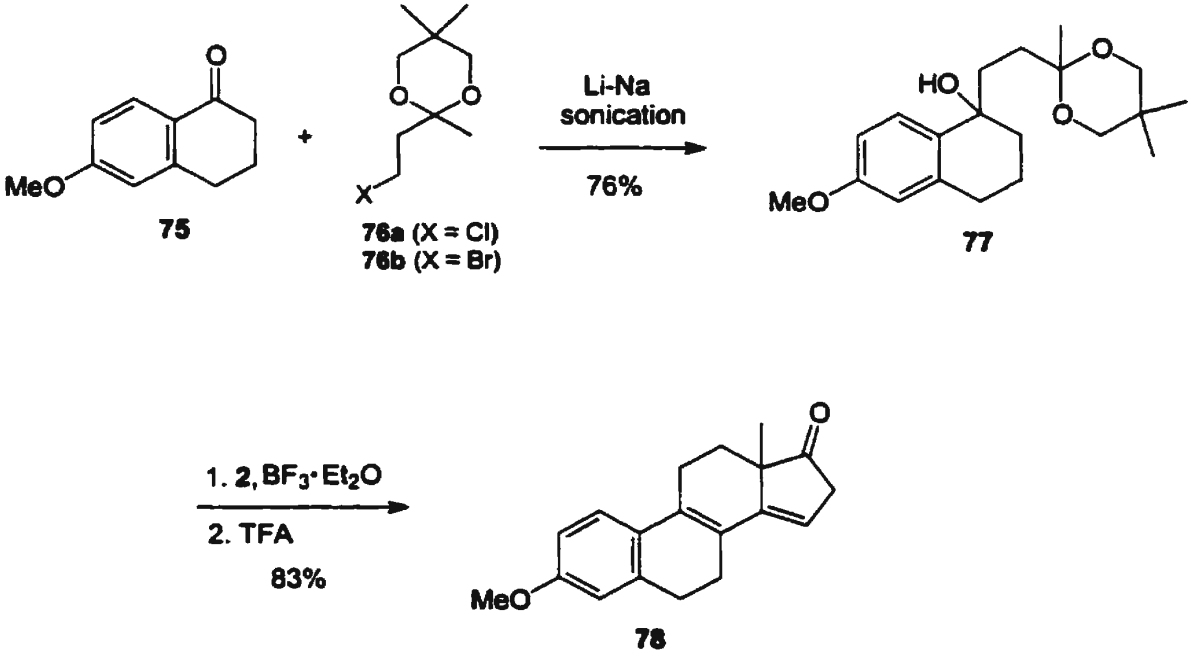
The anticancer agent cephalotaxine (**74**) was recently prepared by Mariano's group.[23] The aldol reaction onto aldehyde **71** was achieved in 83% yield, followed by the rearrangement of intermediate **72** by TFA in 71% yield. Thus, 1,3-diketone **73** was obtained in 60% yield from **71** (Scheme 17).



Scheme 17.

[23] Lin, X.; Kavazh, R. W.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 7335-7347.

Finally, the geminal acylation reaction can be used to generate the D-ring of steroidal compounds. Burnell and Wu reported a two-step synthesis of 3-methoxyestra-1,3,5,8,14-pentaen-7-one (**78**) from 6-methoxy-1-tetralone (**75**).[24] As shown in Scheme 18, the initial step was a Barbier reaction, which was followed by geminal acylation of acetal **77** in 83% yield.



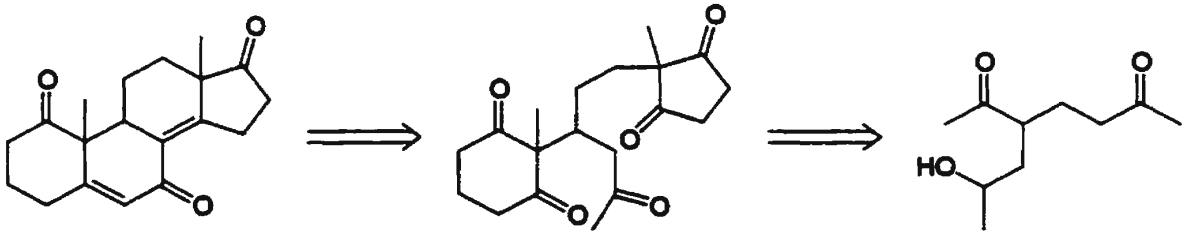
Scheme 18.

The geminal acylation reaction performed on unsymmetrical ketones gave interesting products. In the synthesis of (±)-isokhusimone (**61**), shown in Scheme 13, the geminal acylation occurred at only the acetal position. The ketone had two methyl groups in the α-position and, as such, it was too sterically hindered for the reaction to occur at this position. The reaction of progesterone was also interesting. The products of

[24] Burnell, D. J.; Wu, Y.-J. *Can. J. Chem.* **1989**, *67*, 816-819.

this geminal acylation reaction were shown previously, in Figure 5. To produce the major product **33**, the reaction occurred at only the less hindered ketone. However, the reaction can take place at both ketones since 5% of **34** was also isolated.

The idea that one center of an unsymmetrical diketone can react preferentially over another could be useful in the total synthesis of some compounds. For example, a carefully chosen diketone could undergo a geminal acylation reaction with **2**, followed by a reaction with **55** to generate quickly and efficiently a 5-membered ring and a 6-membered ring (Scheme 19). This methodology could be applied toward an efficient synthesis of steroid **79**. A diketone similar to **81** should react with **2** at its less hindered carbonyl to generate first a 5-membered ring. Subsequent reaction with **55** would produce the 6-membered ring. Oxidation of the secondary alcohol to the ketone would afford compound **80**, which could lead to steroid **79** by an acid-catalyzed aldol condensation.



79 **80** **81**

Scheme 19.

The proposed synthesis would take advantage of the geminal acylation reaction's preference for less hindered ketones. It would be interesting to examine other systems

where the reaction may occur preferentially at one center over another. Additionally, the effect of β-substituents, as well as linear and cyclic ketones, and cyclopentanones and cyclohexanones, could be investigated. A comparison of the reactivity of **2**, **46** and **55** with ketone mixtures could also be examined.

2. The Study of Ketone and Nucleophile Mixtures in the Geminal Acylation Reaction

When this work was begun, the geminal acylation reaction had previously been performed on ketones and acetals, both cyclic and linear, using **2** and **55** as nucleophiles. However, no study had been performed to investigate whether or not the reaction proceeded preferentially on one type of functional group over the other when a mixture was present in the reaction flask. Also, if the geminal acylation reaction was performed on a compound with both an acetal and ketone functionality, it would be synthetically interesting to discover which center, if either, would react chemoselectively.

The effect of varying the ketone and its surroundings was examined. As such, it was of interest to determine the effect of substitution at both the α-position and β-position, connectivity and ring size as well as the preference for ketones or acetals in the course of the geminal acylation reaction. It is also possible to vary the nucleophile so the reaction was performed on a single ketone with mixtures of **2** and **55**, and **2** and **46**.

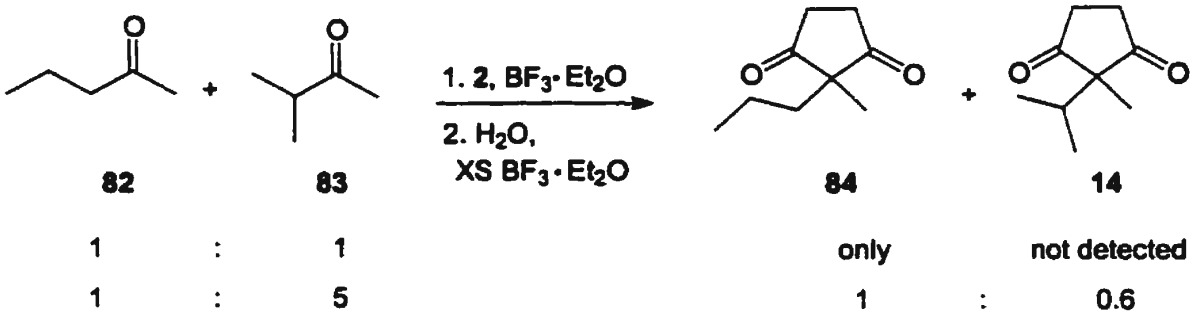
In order to examine the reactivity of the geminal acylation reaction on different systems, the reaction must be performed on either an unsymmetrical diketone or a mixture of two different ketones. Since there were various effects to be examined, many different diketones would have had to be prepared. It would have been necessary to synthesize diketones where one ketone is cyclic and the other is not, where one ketone is hindered and the other is not, and so on. It was, therefore, decided that mixtures of ketones instead of difunctional molecules would be used for this study.

The reactions were performed as for any other geminal acylation reaction. After the work-up, the samples were analyzed by gas chromatography-mass spectrometry (GC-MS), which gave ratios of the products obtained. The samples were identified by their mass spectra, and integration of the total ion chromatogram gave the relative peak areas, which was assumed, for investigative purposes, to be a reasonable measure of relative abundance.

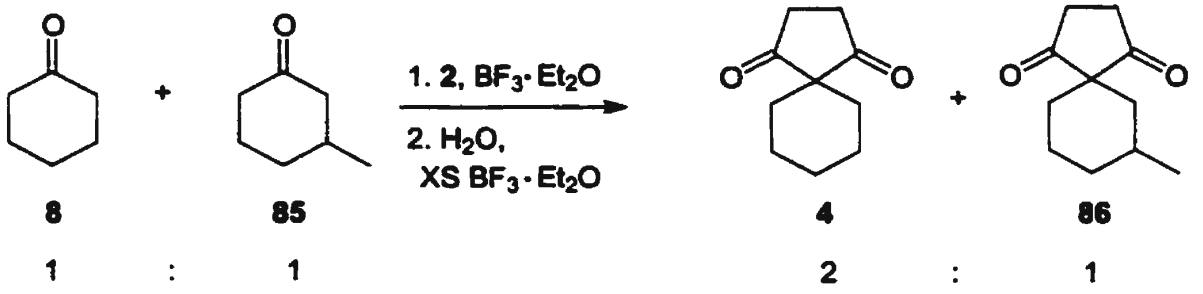
The first reaction to be examined was that of a mixture of 2-pentanone (**82**) and 3-methyl-2-butanone (**83**) as shown in Scheme 20. In this case, only one of the ketones has an α-methyl substituent. When a 1:1 mixture of the two ketones was reacted with one molar equivalent of **2**, only dione **84** was observed as the product. This was as expected since it was the product of the less hindered ketone. The reaction was repeated with a 1:5 mixture of the two ketones where the concentration of the more hindered, and subsequently less reactive, ketone **83** was increased. The major product was still dione **84**, but with its increased concentration, ketone **83** did react to give some of dione **14**.

Having examined the effect of an α-methyl substituent, it was of interest to determine if there was a significant effect from a β-substituent. A 1:1 mixture of cyclohexanone (**8**) and 3-methylcyclohexanone (**85**) was used to examine the effect of a methyl at the β-position. When the ketone mixture was reacted with one equivalent of **2**, both products were observed. Twice as much of dione **4** was produced as dione **86** (Scheme 21). Although there seems to be a slight effect due to a β-substituent, it is not nearly as great as the effect of an α-substituent. Synthetically, this difference could not

be reasonably used to provide chemoselective reactions in molecules with more than one ketone, whereas an α-substituent could.



Scheme 20.

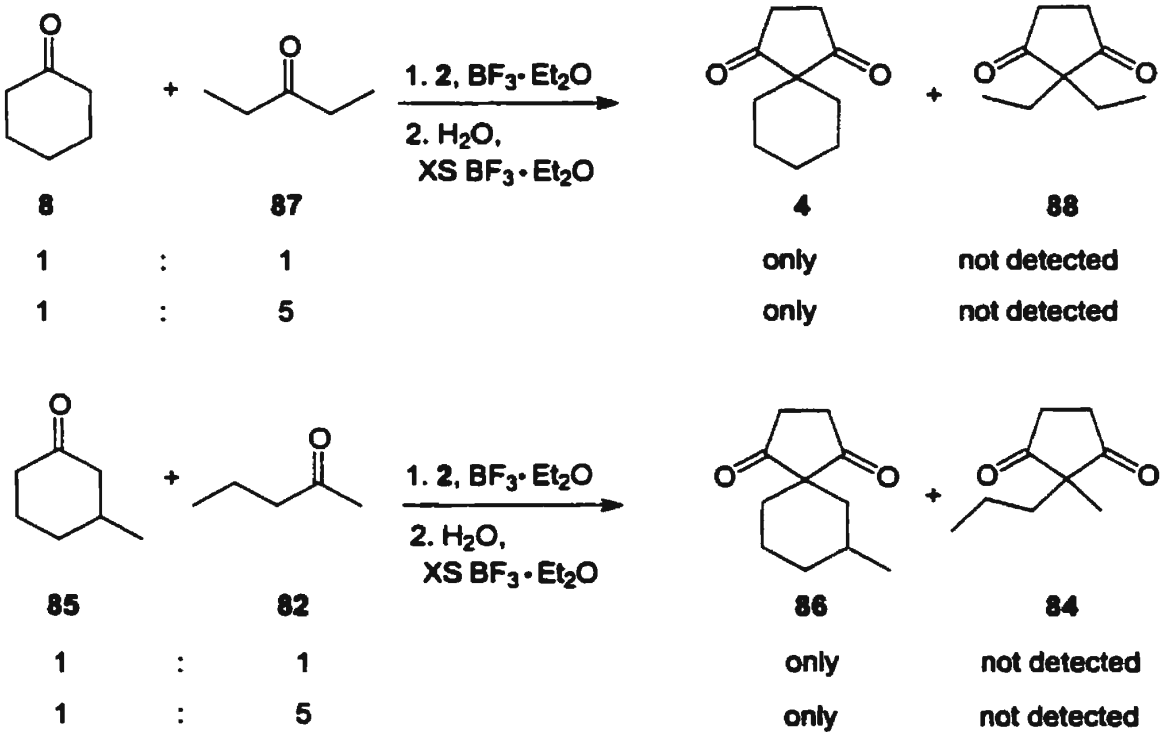


Scheme 21.

The reactivity difference between some cyclic and linear ketones was also examined. A 1:1 mixture of cyclohexanone (**8**) and 3-pentanone (**87**) was reacted with one equivalent of **2**. Only the spirocyclic dione **4** was detected, as shown in Scheme 22. Even when the concentration of the less reactive 3-pentanone (**87**) was increase by five-fold, none of its product **88** was observed. The reaction was repeated with a different ketone mixture. A mixture of 3-methylcyclohexanone (**85**) and 2-pentanone (**82**), both

1:1 and 1:5, gave only the spirocyclic dione **86** and none of dione **84**. Once again, the product of the linear ketone was not observed. Cyclic ketones may react better because the rest of the molecule is held away from the reaction center. Linear ketones, being less rigid, can sterically hinder the reaction.

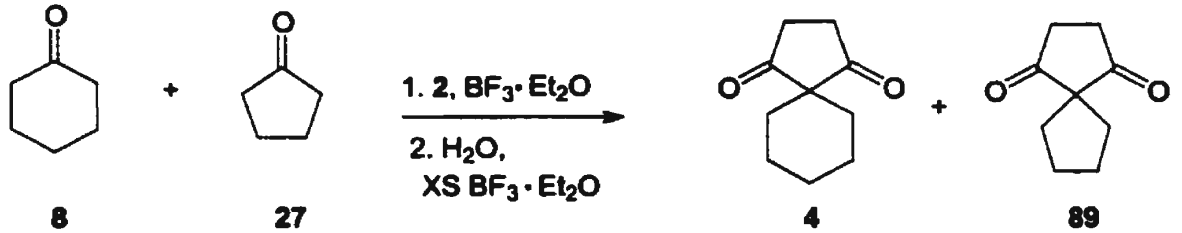
Although cyclic substrates reacted preferentially to acyclic ones, it was of interest to discover if the size of the ring had any effect. The geminal acylation reaction was performed on a 5:1 mixture of cyclohexanone (**8**) and cyclopentanone (**27**). The major



Scheme 22.

product was dione **4**, with none of **89** being detected. The reaction was performed a second time with a 1:2 mixture of cyclohexanone (**8**) and cyclopentanone (**27**), so that the concentration of the less reactive ketone was twice that of the more reactive one. Again,

only dione **4** was detected (Scheme 23). This showed that cyclohexanones are significantly more reactive than cyclopentanones in the geminal acylation reaction. This result could be synthetically significant in that cyclohexanones could be geminally acylated selectively in the presence on cyclopentanones.

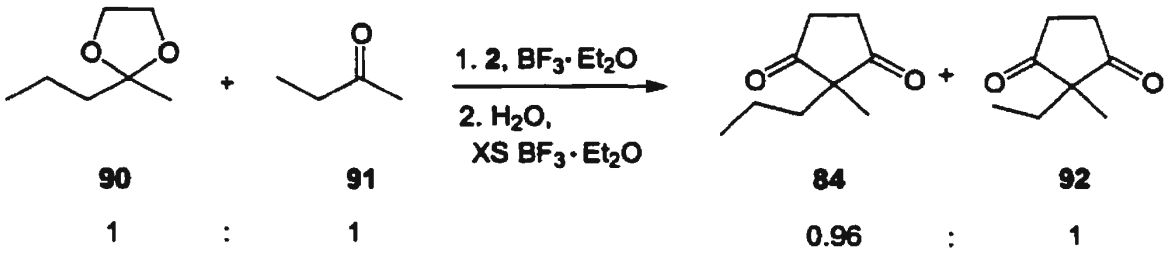


8		**27**	**4**	**89**
5	:	1	only	not detected
1	:	2	only	not detected

Scheme 23.

In the past, when a geminal acylation of a ketone did not proceed as desired, the reaction was performed on the corresponding acetal, often producing satisfactory results. The reaction of a mixture of a ketone and an acetal was therefore of interest in order to determine if acetals react preferentially over ketones. The mixture could not be composed of a ketone and its corresponding acetal because it would be impossible to determine from which starting material the dione originated. Also, under the conditions used for these geminal acylation reactions, the acetals are deprotected to generate ketones. Therefore, loss of starting material cannot be used to determine how the dione is being produced. To solve this problem, a 1:1 mixture of acetal **90** and 2-butanone (**91**) was used since the two compounds differ by only one carbon. Diones **84** and **92** were

obtained in nearly equal amounts (Scheme 24). In this case, acetal **90** did not appear to react significantly faster than ketone **91**, even if in other instances acetals seem to react when ketones do not.

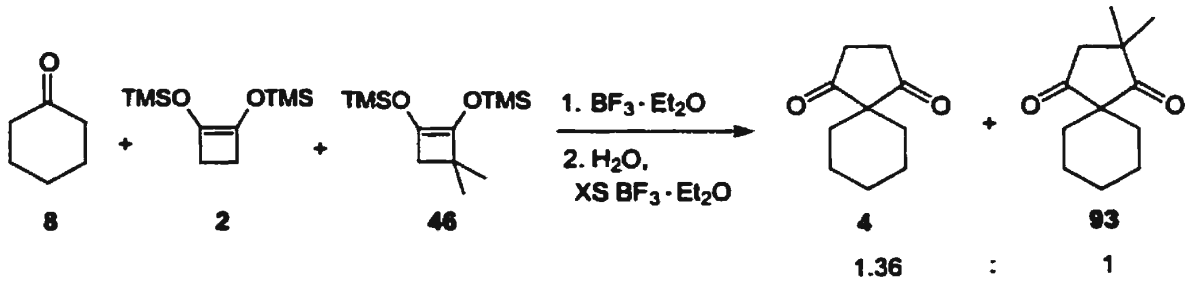


90 1 : **91** 1 → **84** 0.96 : **92** 1

Scheme 24.

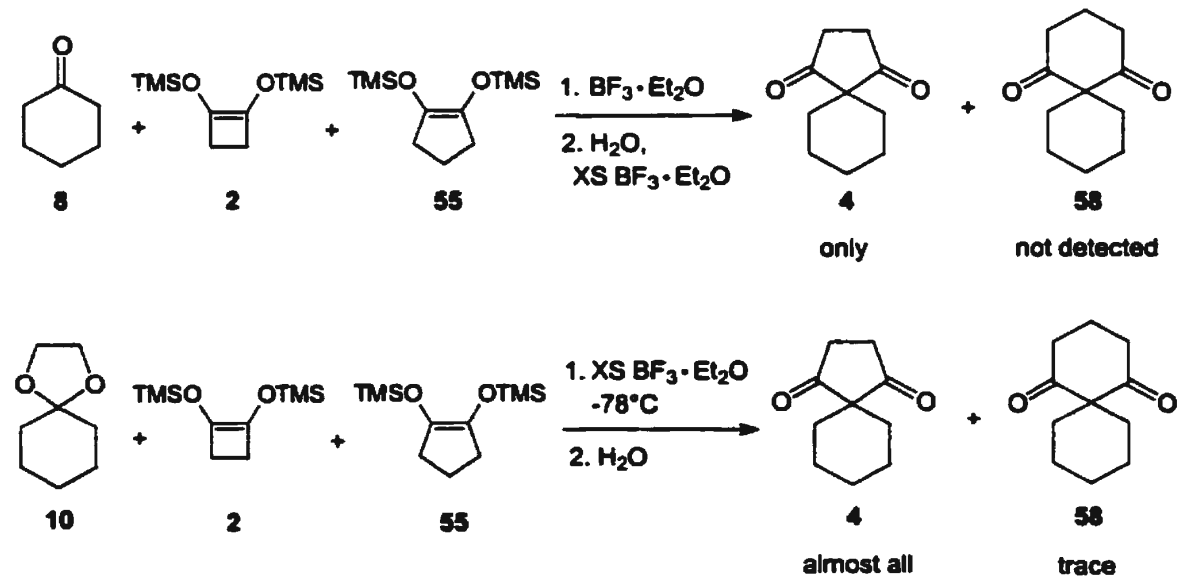
The study was expanded by keeping the ketone constant and adding a 1:1 mixture of nucleophiles **2** and **46**. The reaction of cyclohexanone (**8**) with this mixture gave two products in a ratio of 1.36:1, with spirocyclic dione **4** being the major product (Scheme 25). The formation of dione **93** proceeded very well in comparison to the formation of **4**. The two methyl groups do not seem to have a great steric effect on the course of this geminal acylation reaction. The pronounced difference in reactivity of **46** in this case, relative to that shown in Scheme 9, was presumably a result of the lack of steric interaction with the ketone.

The same reaction as in Scheme 25 was repeated with a 1:1 mixture of **2** and **55**. Cyclohexanone (**8**) was, once again, used as the ketone. The only product observed was



Scheme 25.

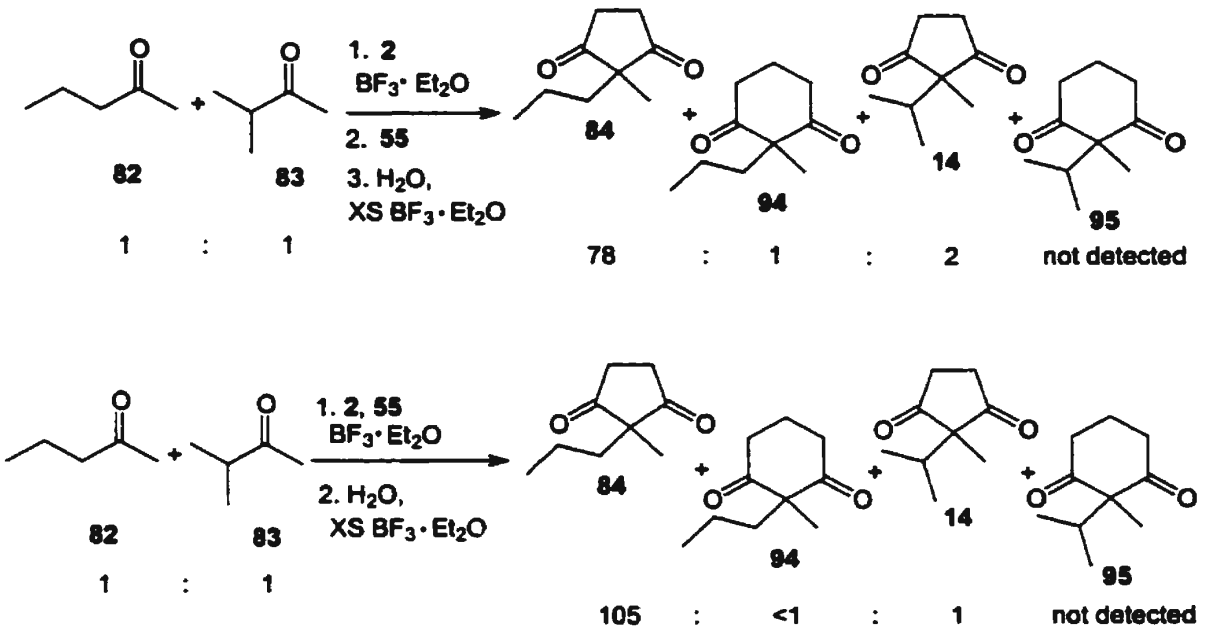
dione **4**. The absence of dione **58** was as expected since **2** is much more reactive than **55** (the reactions of **2** are often performed at -78 °C whereas the reactions of **55** are conducted at 0°C or room temperature) and often gives better yields. The geminal acylation of acetal **10** was performed with a 1:1 mixture of **2** and **55**. A trace amount of dione **58** was observed but dione **4** was almost exclusively formed (Scheme 26).



Scheme 26.

Often, **55** reacted faster with acetals than ketones so if the product of **55** was to be observed at all, it was not surprising that it was in the reaction with the acetal.

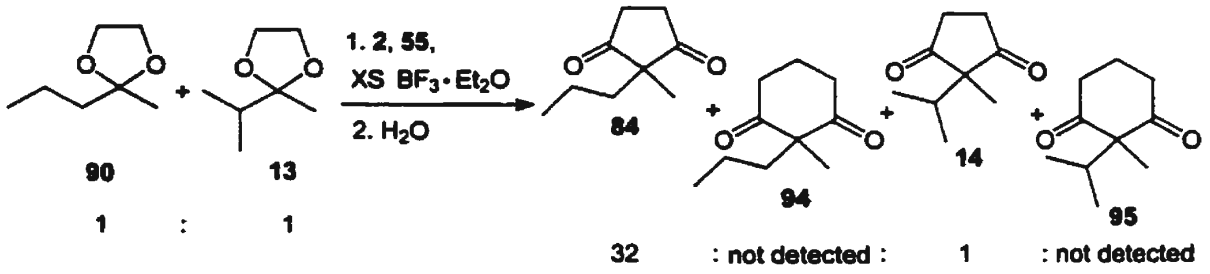
As shown in Scheme 19 in Chapter 1, two successive geminal acylations on a diketone could be very useful in the novel synthesis of a steroid backbone. The results for the mixture shown in Scheme 20 show that the less hindered ketone should react first. The more hindered ketone would then still be available to react with a second equivalent of nucleophile. This type of reaction sequence was attempted with a 1:1 mixture of 2-pentanone (**82**) and 3-methyl-2-butanone (**83**), as shown in Scheme 27. One equivalent of **2** was added, which should react with the less hindered ketone **82** to give dione **84**. After 30 minutes, one equivalent of **55** was added, which should react with the remaining ketone **83** to give dione **95**. Three of the four possible products were observed, with dione **84** being the major product. The more hindered ketone did react with **2** to give some dione **14**. When **55** was added, some unreacted ketone **82** reacted to give a small amount of dione **94**, but no dione **95** was observed. The reaction was repeated using the same concentrations of ketones and nucleophiles, but the nucleophiles were added simultaneously. Scheme 20 shows that 2-pentanone (**82**) reacted more quickly than 3-methyl-2-butanone (**83**), while Scheme 26 shows that **2** reacted better than **55**. If both nucleophiles were added simultaneously, the two more reactive starting materials, i.e., **82** and **2**, should react first, leaving **83** and **55** to react second. The results of this experiment were very similar to the previous one where the nucleophiles were added separately. Once again, **84** was the major product but none of **95** was observed.



Scheme 27.

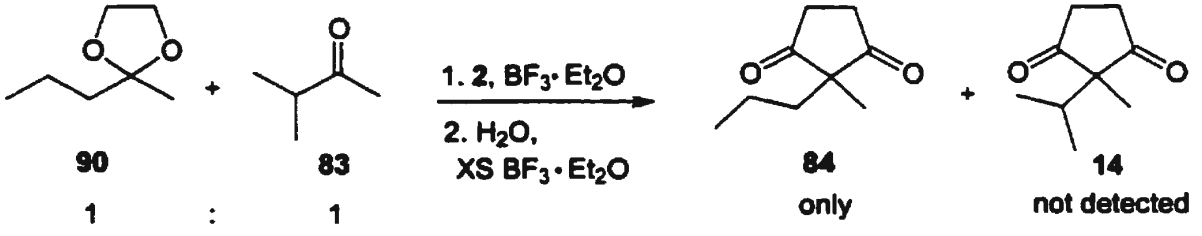
In order to form dione **95**, the reaction was attempted using acetals instead of ketones. A 1:1 mixture of acetal **90** and acetal **13** was reacted with a 1:1 mixture of **2** and **55** using acetal conditions. The results were similar to those previously obtained with the ketone mixtures. Nucleophile **2** reacted with both acetals to give dione **84** and dione **14** in a 32:1 ratio. Nucleophile **55** did not react with either acetal so dione **95** was not produced (Scheme 28). The reaction of **55** with acetal **13** alone occurs in 84% yield under the usual conditions.[19]

The reaction of one final mixture was performed. As will later be discussed in Chapter 3, the first geminal acylation in the synthesis of a steroid backbone was on an acetal. In diketone **81** shown in Scheme 19, the less hindered ketone was actually an acetal. Thus, it was of interest to react **2** with a mixture of the less hindered acetal **90** and



Scheme 28.

the hindered ketone **83** since these two molecules mimic both ends of the compound on which the first geminal acylation was to be performed. It was very promising to discover that only dione **84** was formed (Scheme 29). The first geminal acylation reaction in the synthesis of the steroid backbone should proceed as expected according to these results.



Scheme 29.

The various reactions performed on ketone and nucleophile mixtures has given more insight into the geminal acylation reaction. It is now known with a higher degree of certainty that α-methyl substituents have a significant effect on the reaction. β-Substituents may affect the results slightly, but not to the extent of α-substituents. The reaction occurs preferentially on rings rather than chains and on 6-membered rings rather than 5-membered rings. In this study, the geminal acylation reaction did not proceed

better on acetals than on ketones. The more reactive nucleophile was shown to be **2**, although the methyl groups of **46** did not seem to have a significant effect on the reaction.

2.1 General Experimental Procedures

All reactions were performed under oxygen-free nitrogen. Dichloromethane was dried and distilled from calcium hydride and stored over Molecular Sieves. THF was distilled from sodium/benzophenone immediately before use. Acetals were prepared by heating the appropriate ketone, 1,2-ethanediol and a catalytic amount of *p*-TsOH in benzene under reflux.

Thin layer chromatography (TLC) was done on Macherey-Magel Polygram® SIL G/UV_{254} precoated silica plates. Silica gel 60 (230-400 mesh) was used for flash column chromatography. Melting points were measured using a Fisher-Johns melting point apparatus and are uncorrected.

Nuclear magnetic resonance (NMR) spectra were obtained from a General Electric GN-300NB spectrometer at 300.1 MHz for ^{1}H NMR and 75.5 MHz for ^{13}C NMR. $CDCl_3$ was used as the solvent. Chemical shifts are reported in ppm and are relative to tetramethylsilane (δ = 0.0 ppm) for ^{1}H NMR and $CDCl_3$ (δ = 77.00 ppm) for ^{13}C NMR. The assignment of signals was achieved by performing other NMR experiments such as ^{1}H-COSY, ^{13}C-APT and ^{13}C-HET-CORR.

Gas chromatography-mass spectrometry (GC-MS) for the mixtures was performed on a Hewlett Packard 5710A gas chromatograph using a Finnigan MAT ion

trap detector. Infrared (IR) spectra were acquired on a Mattson Polaris FT-IR spectrophotometer using NaCl cells. Samples were usually thin films, however solids were measured as Nujol mulls. Low resolution electron impact mass spectrometry (MS) was performed on a V.G. Micromass 7070HS mass spectrometer at 70 eV. High resolution electron impact mass spectrometry (HRMS) were performed at the Department of Chemistry, Dalhousie University. At time of printing, HRMS data was not yet available for many samples.

2.2 Experimental

General procedure for geminal acylation of ketone or acetal mixtures

To a solution of ketones/acetals in dichloromethane, was added $BF_3 \cdot Et_2O$. The nucleophile was added dropwise as a solution in dichloromethane. Once nucleophile addition was complete, water was added after a period of time (t_1), followed by, after a time (t_2), $BF_3 \cdot Et_2O$. The reaction mixture was left overnight (t_3). Work-up consisted of washing with water (2 × 50 mL), re-extracting with dichloromethane (2 × 50 mL) and washing with brine (75 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Table 1 shows the amounts used and reaction times.

Reaction of 10 with 2 and 55 (acetal conditions)

To a solution of **10** (0.31 g, 2.2 mmol) in dichloromethane (30 mL) cooled to -78 °C, was added $BF_3 \cdot Et_2O$ (4.10 mL, 32.5 mmol). A solution of **2** (0.75 g, 3.3 mmol) and **55** (0.80 g, 3.3 mmol) in dichloromethane (8 mL) was added dropwise to the reaction mixture. After allowing the solution to warm to room temperature over 23 hours, water (10 mL, 0.55 mol) was added. After 4 hours, work-up consisted of separating the layers, extracting the aqueous layer with dichloromethane (2 × 15 mL) and washing the combined organic layers with brine (2 × 30 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum to give a dark brown liquid (0.305 g).

Reaction of 90 and 13 with 2 and 55 (acetal conditions)

A solution of **90** (0.26 g, 2.0 mmol) and **13** (0.26 g, 2.0 mmol) in dichloromethane (30 mL) was cooled to -78 °C. $BF_3 \cdot Et_2O$ (3.8 mL, 30 mmol) was added followed by dropwise addition of **2** (0.46 g, 2.0 mmol) and **55** (0.49 g, 2.0 mmol) in dichloromethane (8 mL). The reaction mixture was allowed to reach room temperature overnight. After 17 hours, water (10 mL, 0.55 mol) was added. After 4 hours, work-up consisted of separating the layers, extracting the aqueous layer with dichloromethane (2 × 25 mL) and washing the combined organic layers with brine (2 × 50 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum to give a dark brown liquid (0.324 g).

Table 1. Reagents and reaction times for geminal acylations of ketone or acetal mixtures.

Ketones/Acetals	Nucleophile	Reagents	Reaction times	Product mixture
(g, mmol)	(g, mmol)	(mL, mmol)	(h)	(g)
82 (0.18, 2.09)	**2** (0.390, 1.79)	$BF_3 \cdot Et_2O$ (0.39, 3.14)	$t_1 = 2.5$	Dark brown liquid
83 (0.18, 2.09)		H_2O (0.41, 22)	$t_2 = 0.33$	(0.085)
		$BF_3 \cdot Et_2O$ (4.0, 32)	$t_3 = 20$	
82 (0.23, 2.67)	**2** (0.543, 2.36)	$BF_3 \cdot Et_2O$ (0.46, 3.64)	$t_1 = 2.25$	Dark brown liquid
83 (1.05, 12.1)		H_2O (0.50, 28)	$t_2 = 0.25$	(0.129)
		$BF_3 \cdot Et_2O$ (4.6, 37)	$t_3 = 20$	
8 (0.23, 2.35)	**2** (0.465, 2.02)	$BF_3 \cdot Et_2O$ (0.38, 3.02)	$t_1 = 3.33$	Dark brown liquid
85 (0.26, 2.32)		H_2O (0.40, 22)	$t_2 = 0.5$	(0.592)
		$BF_3 \cdot Et_2O$ (3.4, 27)	$t_3 = 19$	

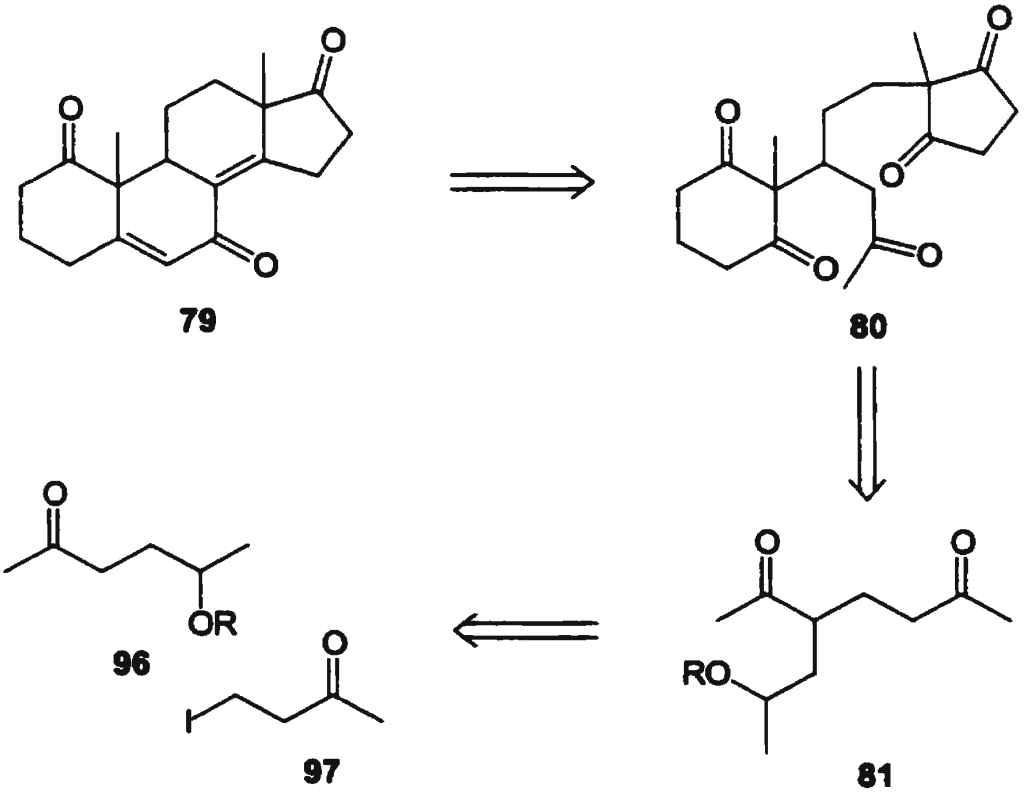
8 (0.22, 2.24)	**2** (0.447, 1.94)	$BF_3 \cdot Et_2O$ (0.34, 2.70)	$t_1 = 4$	Brown liquid
87 (0.20, 2.32)		H_2O (0.34, 19)	$t_2 = 0.5$	(0.2428)
		$BF_3 \cdot Et_2O$ (3.0, 24)	$t_3 = 20.5$	
8 (0.22, 2.24)	**2** (0.457, 1.99)	$BF_3 \cdot Et_2O$ (0.38, 3.02)	$t_1 = 6.5$	Dark brown liquid
85 (0.86, 10.0)		H_2O (0.40, 22)	$t_2 = 0.5$	(0.434)
		$BF_3 \cdot Et_2O$ (3.4, 27)	$t_3 = 13$	
85 (0.22, 1.96)	**2** (0.361, 1.57)	$BF_3 \cdot Et_2O$ (0.34, 2.67)	$t_1 = 2.5$	Dark brown liquid
82 (0.17, 1.97)		H_2O (0.40, 22)	$t_2 = 0.33$	(0.216)
		$BF_3 \cdot Et_2O$ (2.9, 25)	$t_3 = 19$	
85 (0.27, 2.41)	**2** (0.519, 2.25)	$BF_3 \cdot Et_2O$ (0.45, 3.57)	$t_1 = 2.5$	Dark brown liquid
82 (0.92, 10.7)		H_2O (0.50, 28)	$t_2 = 0.33$	(0.288)
		$BF_3 \cdot Et_2O$ (4.5, 36)	$t_3 = 24$	
8 (0.23, 2.35)	**2** (0.449, 1.95)	$BF_3 \cdot Et_2O$ (0.38, 3.02)	$t_1 = 4$	Dark brown liquid
27 (0.20, 2.38)		H_2O (0.40, 22)	$t_2 = 0.5$	(0.478)
		$BF_3 \cdot Et_2O$ (3.4, 27)	$t_3 = 21$	

8 (0.98, 10.0)	**2** (0.440, 1.91)	$BF_3 \cdot Et_2O$ (0.38, 3.02)	$t_1 = 6.5$	Dark brown liquid
27 (0.18, 2.14)		H_2O (0.40, 22)	$t_2 = 0.5$	(1.136)
		$BF_3 \cdot Et_2O$ (3.4, 27)	$t_3 = 13.5$	
8 (0.23, 2.35)	**2** (0.463, 2.01)	$BF_3 \cdot Et_2O$ (0.38, 3.02)	$t_1 = 4$	Dark brown liquid
85 (0.34, 4.04)		H_2O (0.40, 22)	$t_2 = 0.5$	(0.497)
		$BF_3 \cdot Et_2O$ (3.5, 28)	$t_3 = 18$	
90 (0.26, 2.00)	**2** (0.420, 1.82)	$BF_3 \cdot Et_2O$ (0.30, 2.38)	$t_1 = 2$	Dark brown liquid
91 (0.14, 1.94)		H_2O (0.30, 17)	$t_2 = 0.25$	(0.293)
		$BF_3 \cdot Et_2O$ (3.8, 30)	$t_3 = 18$	
8 (0.21, 2.14)	**2** (0.47, 2.04)	$BF_3 \cdot Et_2O$ (0.38, 3.02)	$t_1 = 4$	Yellow liquid
	46 (0.52, 2.00)	H_2O (0.40, 22)	$t_2 = 0.66$	(0.390)
		$BF_3 \cdot Et_2O$ (3.5, 28)	$t_3 = 20$	
8 (0.21, 2.16)	**2** (0.75, 3.26)	$BF_3 \cdot Et_2O$ (0.33, 2.62)	$t_1 = 3$	Brown liquid
	55 (0.80, 3.28)	H_2O (0.33, 18)	$t_2 = 0.5$	(0.259)
		$BF_3 \cdot Et_2O$ (4.10, 33)	$t_3 = 22$	

82 (0.19, 2.21)	**2** (0.468, 2.03)	$BF_3 \cdot Et_2O$ (0.38, 3.02)	$t_1 = 3.25$	**Brown liquid**
83 (0.19, 2.21)	**55** (0.488, 2.00)	H_2O (0.40, 22)	$t_2 = 0.5$	**(0.201)**
		$BF_3 \cdot Et_2O$ (3.5, 28)	$t_3 = 14$	
82 (0.19, 2.26)	**2** (0.267, 2.03)	$BF_3 \cdot Et_2O$ (0.38, 3.02)	$t_1 = 3.75$	**Dark brown liquid**
83 (0.19, 2.26)	**55** (0.490, 2.01)	H_2O (0.40, 22)	$t_2 = 0.5$	**(0.170)**
		$BF_3 \cdot Et_2O$ (3.5, 28)	$t_3 = 18$	
90 (0.29, 2.23)	**2** (0.455, 1.98)	$BF_3 \cdot Et_2O$ (0.38, 3.02)	$t_1 = 4$	**Dark brown liquid**
83 (0.19, 2.21)		H_2O (0.40, 22)	$t_2 = 0.5$	**(0.139)**
		$BF_3 \cdot Et_2O$ (3.4, 27)	$t_3 = 21$	

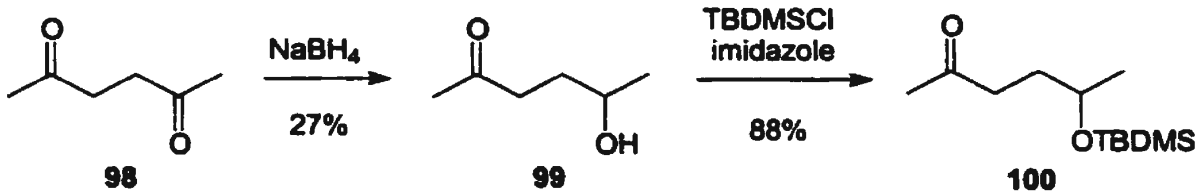
3.0 Progress toward the Synthesis of a Steroid Backbone

The results of the study of substrate mixtures were promising, so much so that the synthesis of a steroid backbone was believed to be possible using the geminal acylation reaction. The retrosynthetic sequence is shown in Scheme 30. Steroid **79** could be obtained from the aldol cyclization of **80**, which could, in turn, be made from two successive geminal acylations on **81**, followed by deprotection of the ketone. Diketone **81** should be readily made by the alkylation of ketone **96** with iodoketone **97**.



Scheme 30.

Ketone **96**, shown more precisely in Scheme 31 as ketone **100**, where the protecting group is specified as a *tert*-butyldimethylsilyl (TBDMS) ether, was prepared in two steps. In order to reduce only one of the carbonyl groups of 2,5-hexanone (**98**) using sodium borohydride, the reaction was closely monitored by TLC. The desired alcohol was produced in 27% unoptimized yield. Subsequent protection with *tert*-butylchlorodimethylsilane and imidazole proceeded easily to give the protected alcohol **100**.

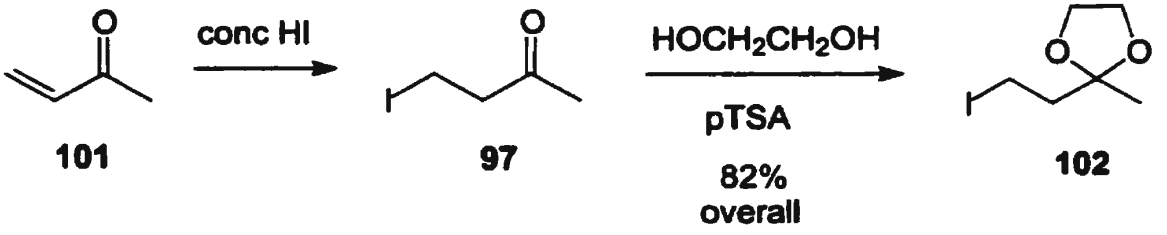


Scheme 31.

The next step involved alkylation of ketone **100**. The method used for the preparation of this starting material was that of Stowell's group.[25] 3-Buten-2-one (**101**) was reacted with concentrated hydriodic acid in benzene. Following a quick work-up without isolation of iodoketone **97**, 1,2-ethanediol and *p*-TsOH were added to the solution in benzene (Scheme 32). Iodoacetal **102** was purified by passing the extracted mixture through an alumina column. Stowell's group reported isolating iodoacetal **102** in 56% yield. The yield was improved to 82% by modifying the extraction performed after the first step. By simply re-extracting the aqueous layer with a small amount of benzene,

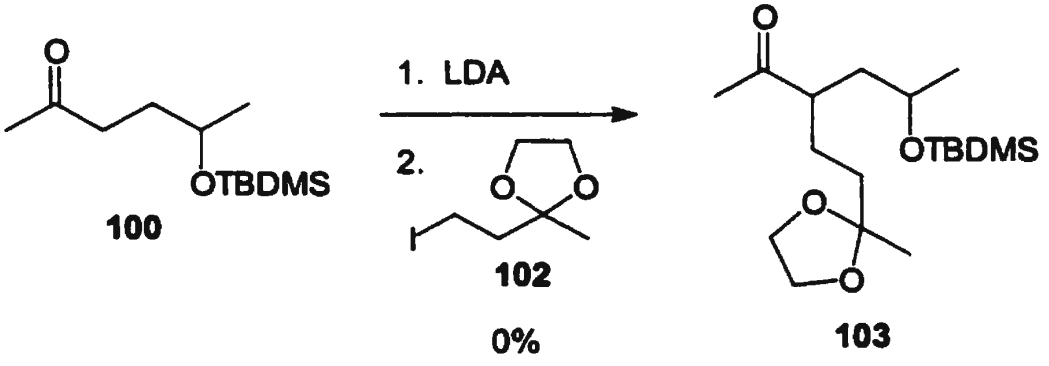
[25] Stowell, J. C.; King, B. T.; Hauck, H. F., Jr. *J. Org. Chem.* **1983**, *48*, 5381-5382.

the yield of isolated product was increased by 26%, an amount that is significant since this compound is a starting material in this synthesis.



Scheme 32.

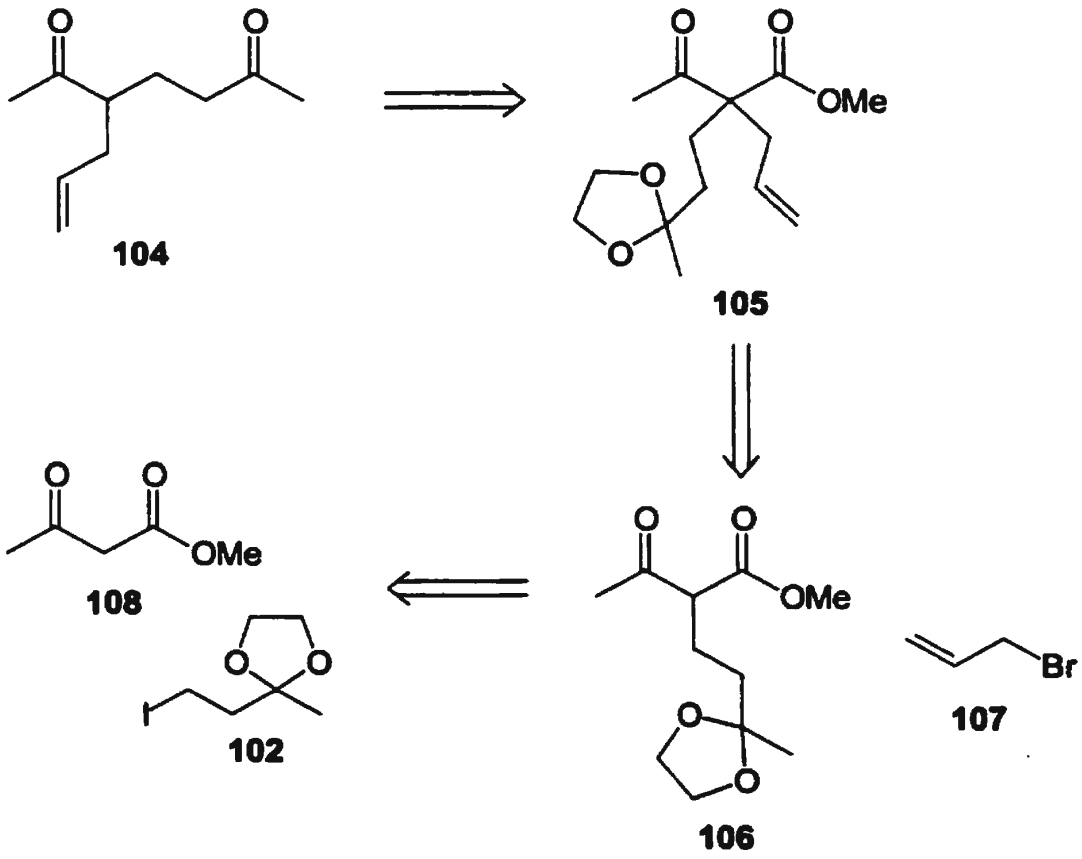
The alkylation of ketone **100** with iodoacetal **102** did not proceed as desired (Scheme 33). All attempts to force this reaction to work failed. The reaction times, solvent and temperature were varied unsuccessfully. Although in low yield, the only identifiable product obtained was that of alkylation of the kinetic enolate. At this point, it was necessary to revise the synthetic route.



Scheme 33.

The new method for the preparation of the protected diketone **81** was as shown in Scheme 34. Diketone **104** was very similar to diketone **81**. The terminal double bond

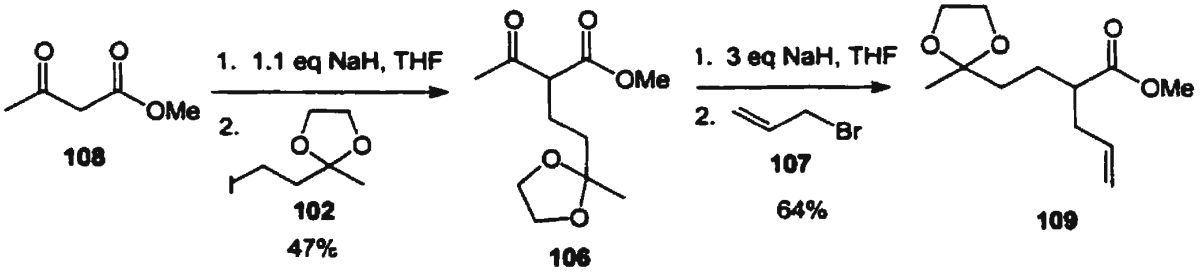
acted as a protecting group for the methyl ketone, which was previously protected as a TBDMS ether. Diketone **104** can be prepared by the decarboxylation of β-ketoester **105**. The alkylation of methyl acetoacetate (**105**) with iodoacetal **102** to give β-ketoester **106**, followed by an alkylation with allyl bromide (**107**) would give the desired α,α-disubstituted-β-ketoester **105**.



Scheme 34.

Methyl acetoacetate (**108**) was alkylated with iodoacetal **102** using sodium hydride as the base. This reaction proceeded to give the desired product in 47% yield,

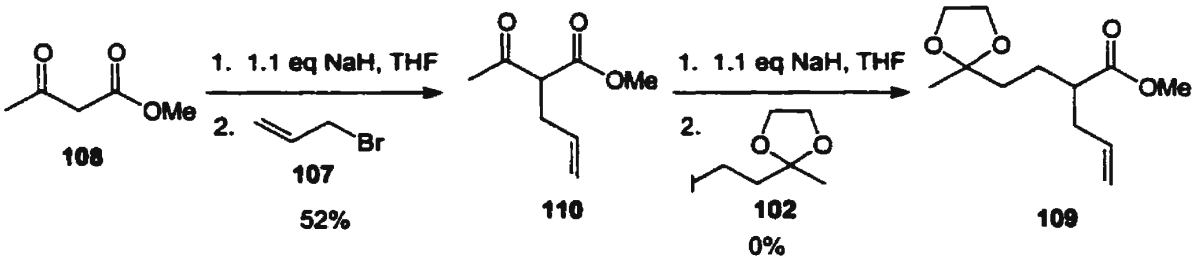
and 50% of iodoacetal **102** was recovered. The alkylation of β-ketoester **106** with allyl bromide (**107**) gave ester **109** in 64% yield (Scheme 35). The loss of the methyl ketone function was surprising, but the results were reproducible as the reaction was repeated several times. An explanation will be given later in this chapter.



Scheme 35.

Since the first alkylation did not proceeded as well as hoped, the order of the two alkylations was changed. The reaction of methyl acetoacetate (**108**) with allyl bromide (**107**) gave β-ketoester **110** in 52% yield. Subsequent alkylation with iodoacetal **97** was unsuccessful (Scheme 36). Allyl bromide (**107**) was a better electrophile than iodoacetal **102**. Thus, it was determined that the order first attempted was preferable since a more sterically hindered enolate will react preferentially with the better electrophile.

Although the formation of ester **109** was unforeseen, that is, the loss of the methyl ketone was unexpected, this did not hinder the synthesis of the desired diketone **104**.

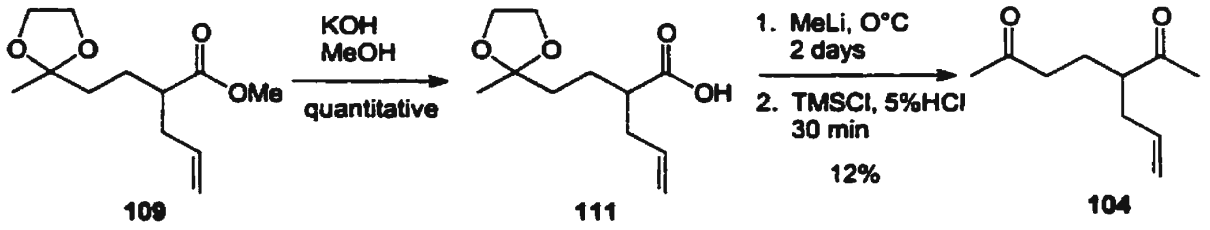


Scheme 36.

Since decarboxylation would have been necessary later in the synthesis to remove the ester group, this group was used to regenerate a methyl ketone using the chemistry shown in Scheme 37. The ester was hydrolyzed by potassium hydroxide in methanol quantitatively giving carboxylic acid **111**. Neutralization during work-up was performed very carefully since any amount of acid would hydrolyze the acetal, the presence of which was essential in the next step. The methyl ketone **104** was prepared from carboxylic acid **111** using first methyllithium, then chlorotrimethylsilane and hydrochloric acid.[10,26] The first equivalent of methyllithium deprotonates the acid while the second acts as a nucleophile. Chlorotrimethylsilane and hydrochloric acid are necessary as quenching conditions so that a methyl ketone is obtained and not a tertiary alcohol. This reaction proceeded in 12% yield to give diketone **104**. This yield was not optimized since work done concurrently on other reactions was more fruitful and this route was abandoned.

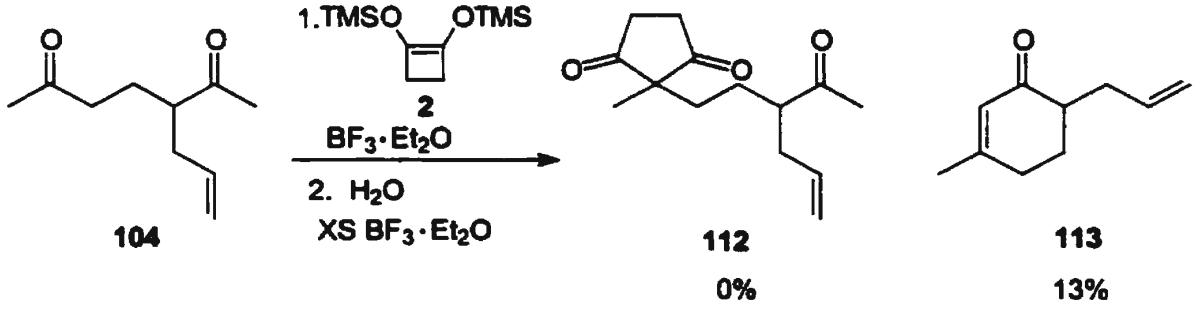
Having produced a small amount of diketone **104**, the geminal acylation with **2** was attempted. Unfortunately, the reaction did not give the desired product **112** (Scheme

[26] Rubottom, G. M.; Kim, C. *J. Org. Chem.* **1983**, *48*, 1550-1552.



Scheme 37.

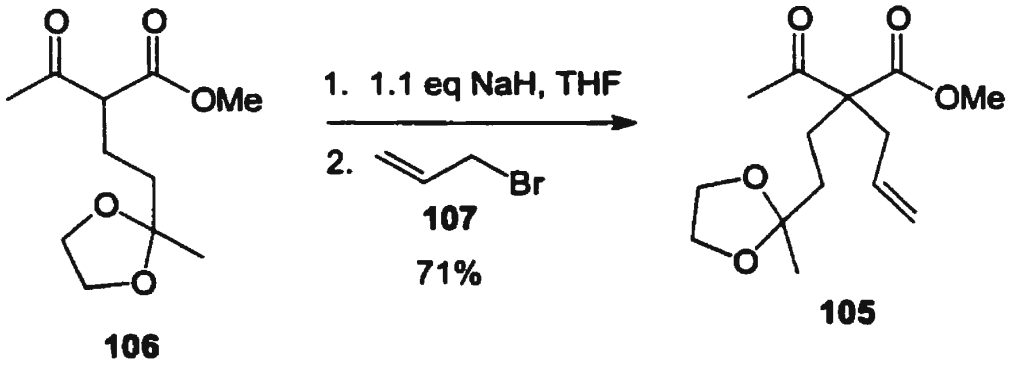
38). Under the acidic conditions, an internal aldol condensation occurred to produce cyclohexenone **113**. Although disheartening, work towards the diketone continued. Once the diketone was made by another route, the first geminal acylation would be performed on an acetal. The reaction may proceed better on an acetal than a ketone.



Scheme 38.

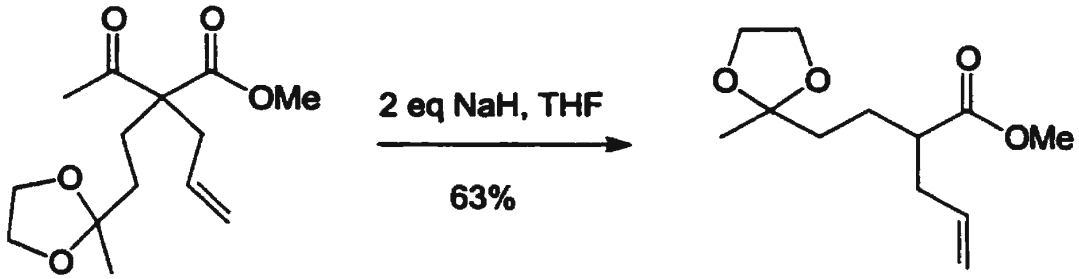
As the route in Scheme 37 was being attempted, a closer examination of the puzzling loss of the methyl ketone was performed. The alkylation of β-ketoester **106** with allyl bromide (**107**) was repeated using only 1.1 equivalents of base (Scheme 39). This reduced amount of base led to the formation of β-ketoester **105** with the retention of the methyl ketone. This led to the conclusion that β-ketoester **105** was originally

produced but the excess base was the cause of the deacylation. To test this hypothesis, β-ketoester **105** was subjected to excess base, keeping all conditions identical with the past reaction with the exception of the absence of the electrophile. The reaction, shown in Scheme 40, gave ester **109** in 63% yield. A reverse-Claisen type mechanism for the deacylation is proposed in Scheme 41. The hydride ion acts as a base and deprotonates the acyl group, giving enolate **114**. From **114**, enolate **116** and presumably ketene **115** are produced, although no evidence is obtained for the formation of **115**. Upon work-up, enolate **116** gives ester **109**, which is isolated.



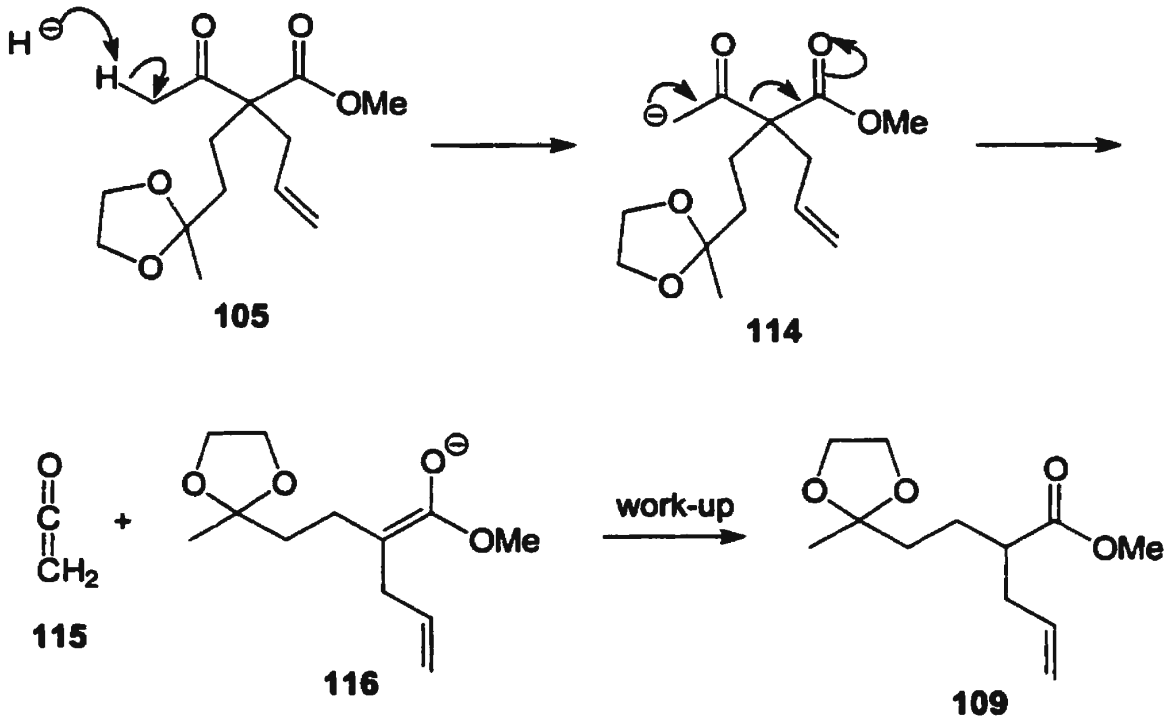
106 **105**

Scheme 39.



105 **109**

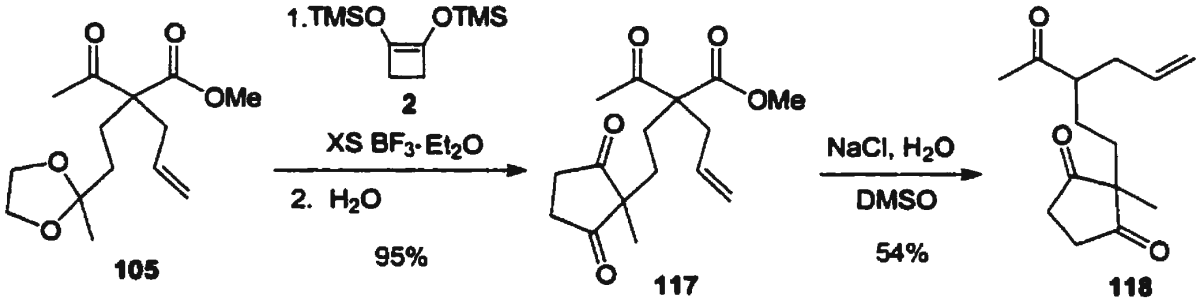
Scheme 40.



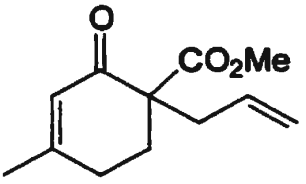
Scheme 41.

Having succeeded in the second alkylation without decarbonylation, it was now time to attempt the first geminal acylation. The reaction proceeded very well, originally giving **117** in approximately 80% yield (Scheme 42). A small amount of cyclohexenone **119** (Figure 8) was observed the first few times this reaction was performed. Seemingly without altering the reaction conditions, later attempts at this reaction produced **117** in 95% yield without formation of by-product **119**. Before the second geminal acylation could be performed, decarboxylation of the ester group must take place since it is highly unlikely that the reaction could take place next to a quaternary carbon. The method of

Krapcho and Lovey[27] was used for this reaction. After failed attempts using sodium bromide, the reaction was found to proceed well using sodium chloride in water and dimethylsulfoxide (DMSO). As such, the desired product was obtained in 54% yield.



Scheme 42.

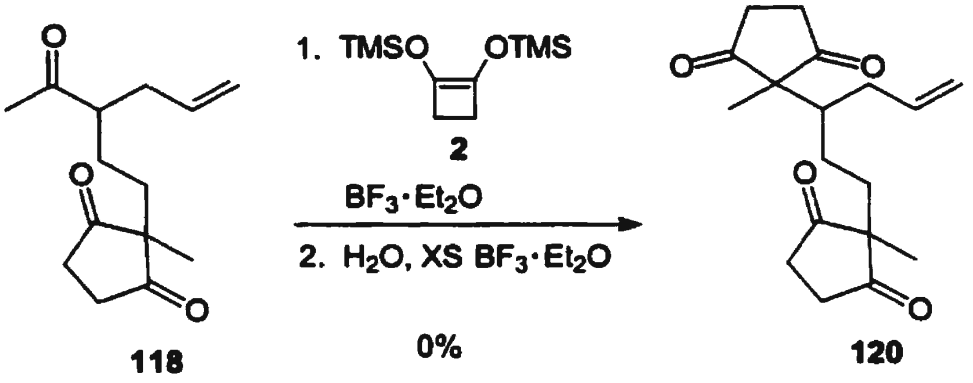


119

Figure 8. The internal aldol condensation product of **105**.

Since reactions with **2** usually work better than those with **55**, the second geminal acylation was tried first with **2**. The reasoning for this is that if the reaction did not occur with **2**, it would be very unlikely to proceed at all with **55**. When this reaction was attempted, only starting material was recovered (Scheme 43). At this point, work on the synthesis of the steroid backbone ceased due to time restraints.

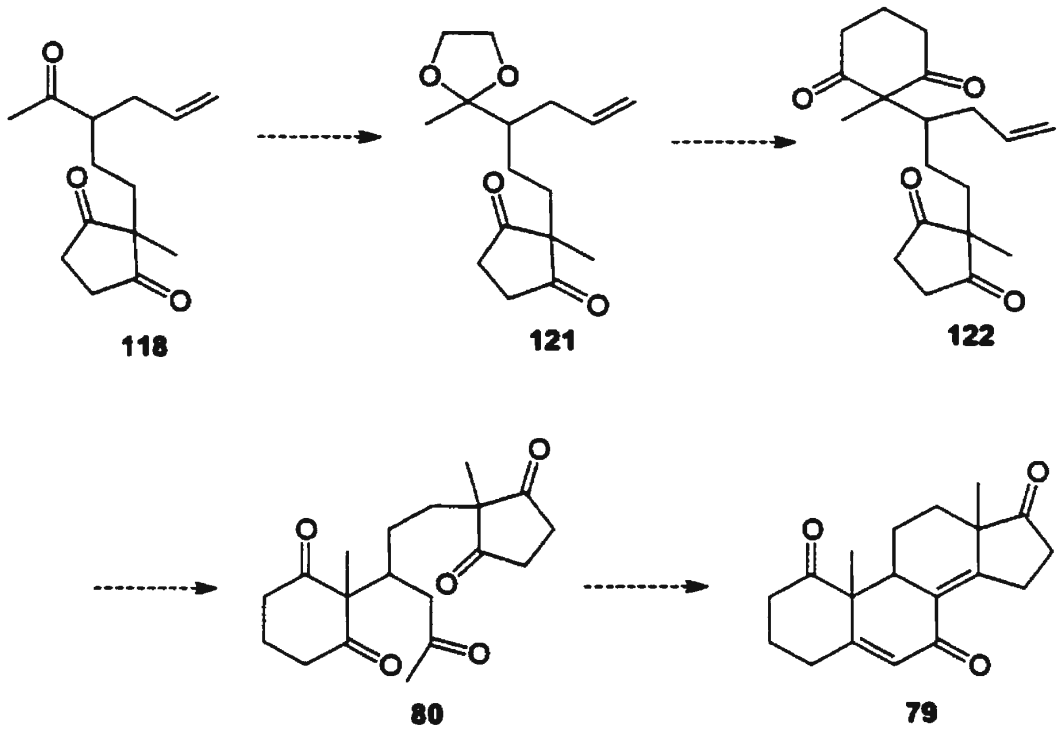
[27] Krapcho, A. P.; Lovey, A. J. *Tetrahedron Lett.* **1973**, *12*, 957-960.



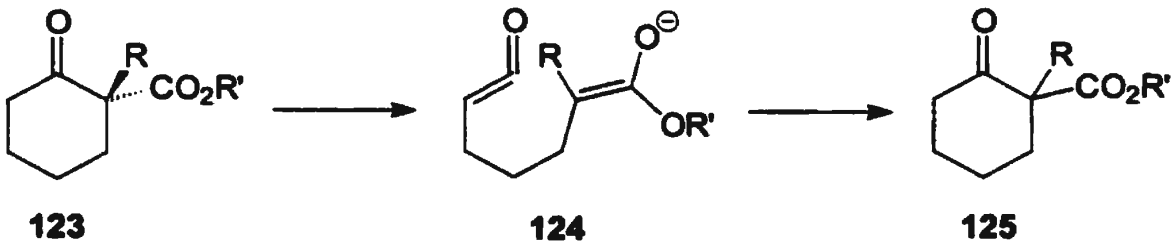
Scheme 43.

The next logical step after the unsuccessful geminal acylation reaction of **118** with **2**, would be to generate the acetal. As the initial geminal acylation reaction worked well on acetal **105**, but not on ketone **104**, it is hoped that the second geminal acylation would occur on acetal **121**, to give compound **122**. Wacker oxidation of the terminal double bond would generate a ketone, thus giving **80**. Finally, if the cyclization does not occur under the Wacker conditions, a small amount of acid should induce cyclization to produce steroid **79** (Scheme 44).

Another experiment that would have been interesting to try is depicted in Scheme 45. In order to test the hypothesized mechanism of the decarbonylation, it would have been interesting to subject β-ketoester **123** to an excess of sodium hydride in THF. Starting with a stereogenic center as shown, once ketene **124** is produced, it should regenerate the ring and give **125** in racemic form. If R' is also chiral, then two diastereomers would be produced. The formation of diastereomers, which should be separable, would help to show that the proposed mechanism is plausible.



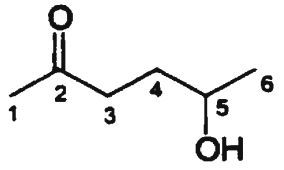
Scheme 44.



Scheme 45.

3.1 Experimental[28]

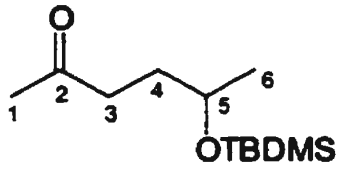
5-Hydroxy-2-hexanone (99)



To a solution of 2,5-hexanedione (5.63 g, 49.3 mmol) in methanol (50 mL) was added sodium borohydride (0.51 g, 15 mmol). Due to the liberation of heat, the reaction mixture was cooled in a cold water bath. The reaction was monitored by TLC and stopped after 15 minutes. The work-up consisted of addition of water (30 mL), extraction with dichloromethane (3 × 30 mL) and washing the organic layers with brine (60 mL). The combined aqueous layers were saturated with salt and re-extracted with ethyl acetate (4 × 30 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent was evaporated under reduced pressure. Flash column chromatography (80% ethyl acetate/hexanes, $R_f = 0.34$, vanillin dip visualization) yielded **99** as a yellow liquid (1.54 g, 27%) as well as the diol ($R_f = 0.23$) as a yellow liquid (4.29 g, 73%). For **99**: ^{1}H NMR ($CDCl_3$): δ 4.24 (1H, broad m, OH), 3.81 (1H, broad m, H-5), 2.60 (2H, t, J = 7.1 Hz, H-3), 2.18 (3H, s, H-1), 1.80-1.72 (2H, m, H-4), 1.21 (3H, d, J = 6.3 Hz, H-6). This compound was characterized after protection as **100**.

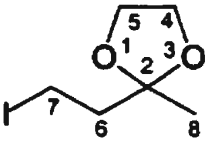
[28] General experimental procedures may be found on page 33.

5-(*tert*-Butyldimethylsilyl)oxy-2-hexanone (100)



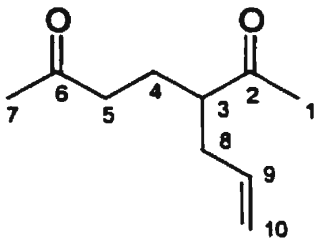
To a solution of **99** (0.44 g, 3.8 mmol) and imidazole (0.65 g, 9.5 mmol) in dichloromethane (10 mL), was added *tert*-butylchlorodimethylsilane (0.76 g, 5.0 mmol) dropwise by syringe. The next day, the mixture was washed with sodium bicarbonate solution (2 × 20 mL) and brine (10 mL) and dried over anhydrous magnesium sulfate. The solution was filtered and the solvent was evaporated under reduced pressure. Flash column chromatography (80% ethyl acetate/hexanes, R_f = 0.78, 2,4-DNP visualization) yielded **100** as a yellow liquid (0.773 g, 88%). IR: ν_{max} 3436 (m), 2961 (s), 2858 (s), 1718 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.73 (1H, m, H-5), 2.42-2.37 (2H, m, H-3), 2.04 (3H, s, H-1), 1.64-1.47 (2H, broad m, H-4), 1.03 (3H, d, J = 6.1 Hz, H-6), 0.78 (9H, s, $SiCCH_3$), -0.06 (3H, s, $SiCH_3$), -0.07 (3H, s, $SiCH_3$). ^{13}C NMR ($CDCl_3$): δ 209.3 (C-2), 67.7 (C-5), 39.9, 33.4, 26.0 ($SiC\underline{C}H_3$), 25.9, 23.9, -3.4 ($Si\underline{C}CH_3$), -4.2 ($SiCH_3$), -4.6 ($SiCH_3$). MS *m/z* (%): 173 (33), 147 (10), 83 (11), 81 (11), 75 (100), 73 (29), 55 (14), 45 (21), 43 (31), 32 (14), 28 (66).

2-(2-Iodoethyl)-2-methyl-1,3-dioxolane (102)



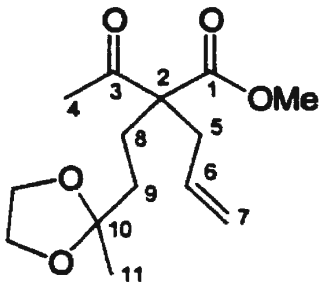
To a solution of 3-buten-2-one (5.00 g, 71.3 mmol) in benzene (60 mL) was added concentrated hydriodic acid (32.7 g, 143 mmol). The reaction mixture was stirred at room temperature for 2 hours, at which time the layers were separated. The organic layer was washed with saturated sodium bicarbonate solution (3 × 30 mL) and brine (30 mL). The combined aqueous layers were re-extracted with benzene (2 × 50 mL). After drying the combined organic layers over anhydrous magnesium sulfate and filtering, 1,2-ethanediol (4.89 g, 78.8 mmol) and *para*-toluenesulfonic acid (0.37 g, 1.9 mmol) were added to the benzene solution. The flask was equipped with a Barrett apparatus and the mixture was heated under reflux for 4 hours. The work-up consisted of washing with saturated sodium bicarbonate (2 × 50 mL), drying over anhydrous magnesium sulfate and removal of solvent. The residue was passed through an alumina column (10 cm × 1 cm) using hexanes as the eluant. Evaporation of the solvent under reduced pressure gave **102** as a brown liquid (14.2 g, 82%). ^{1}H NMR ($CDCl_3$): δ 3.95-3.92 (4H, m, H-4 and H-5), 3.19-3.13 (2H, m, H-7), 2.32-2.26 (2H, m, H-6), 1.30 (3H, s, H-8). ^{13}C NMR ($CDCl_3$): δ 109.7 (0, C-2), 64.8 (2, C-4 and C-5), 44.3 (2, C-6), 23.8 (3, C-8), -2.1 (2, C-7).

3-(2-Propenyl)-2,6-heptanedione (104)



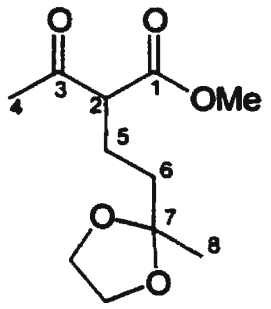
To a solution of **111** (0.341 g, 1.59 mmol) in THF (40 mL) cooled to 0 °C, was added methyllithium (17 mL, 1.4 M in diethyl ether, 24 mmol). The reaction was kept at 0 °C for 48 hours, at which time chlorotrimethylsilane (4.0 mL, 31 mmol) was added followed by 5% hydrochloric acid (10 mL). After 30 minutes, brine (20 mL) and ethyl acetate (20 mL) were added and the layers were separated. The remainder of the work-up consisted of extracting with ethyl acetate (2 × 50 mL), washing with sodium bicarbonate (50 mL) and brine (50 mL) and re-extracting with ethyl acetate (2 × 30 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent was evaporated under reduced pressure to give a brown liquid. Flash column chromatography (30% ethyl acetate/hexanes, R_f = 0.22, 2,4-DNP visualization) yielded **104** as a yellow liquid (0.0316 g, 12%). IR: ν_{max} 3507 (m), 3415 (m), 2931 (s), 1709 (s), 1641 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.70 (1H, m, H-9), 5.09-5.02 (2H, m, H-10), 2.58 (1H, m, H-3), 2.45-2.33 (2H, m, H-5), 2.14 (3H, s), 2.13 (3H, s), 1.93-1.70 (4H, m, H-4, H-8). MS *m/z* (%): 168 (0.6, M^+), 58 (11), 43 (100), 41 (14), 39 (13).

Methyl 2-(3-dioxolanobutanyl)-3-oxo-2-(2-propenyl)butanoate (105)



To a suspension of sodium hydride (0.74 g, 31 mmol) in THF (50 mL), was added **106** (6.43 g, 27.9 mmol) by syringe as a solution in THF (50 mL). After 30 minutes, allyl bromide (5.06 g, 41.8 mmol) was added by syringe as a solution in THF (50 mL). The reaction mixture was heated under reflux for 24 hours. After cooling, work-up consisted of washing with brine (2 × 50 mL) and re-extracting with ethyl acetate (6 × 50 mL), followed by drying the organic solution over anhydrous magnesium sulfate. Filtration and evaporation of the solvent under reduced pressure gave a yellow liquid, which was purified by flash column chromatography (30% ethyl acetate/hexanes, R_f = 0.29, 2,4-DNP visualization), yielding **105** as a yellow liquid (5.32 g, 71%). IR: ν_{max} 2982 (m), 2954 (m), 2882 (m), 1738 (s), 1714 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.65 (1H, m, H-6), 5.12-5.07 (2H, m, H-7), 3.96-3.90 (4H, m, OCH_2CH_2O), 3.73 (3H, s, OCH_3), 2.70-2.50 (2H, m), 2.13 (3H, s, H-4), 1.99-1.93 (2H, m), 1.60-1.40 (2H, m), 1.31 (3H, s, H-11). ^{13}C NMR ($CDCl_3$): δ 204.6 (C-3), 172.5 (C-1), 132.5 (C-6), 119.1 (C-7), 109.6 (C-10), 64.8 (OCH_2CH_2O), 63.1 (C-2), 52.5 (OCH_3), 36.0, 33.1, 26.9, 25.7, 24.0. MS *m/z* (%): 99 (11), 87 (100), 59 (10), 43 (10).

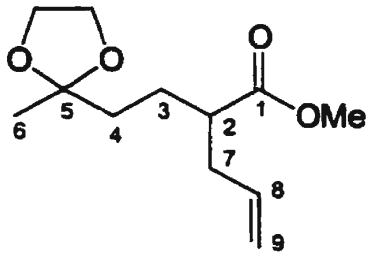
Methyl 2-(3-dioxolanobutanyl)-3-oxobutanoate (106)



To a suspension of sodium hydride (1.07 g, 44.5 mmol) in THF (50 mL), was added methyl acetoacetate (4.94 g, 42.6 mmol) by syringe as a solution in THF (50 mL). After 40 minutes, iodoacetal **102** (10.2 g, 42.3 mmol) was added by syringe as a solution in THF (50 mL). The reaction mixture was heated under reflux for 4 days. After cooling, work-up consisted of washing with brine (2 × 100 mL) and re-extracting with ethyl acetate (6-8 × 50 mL), followed by drying the organic solution over anhydrous magnesium sulfate. Filtration and evaporation of the solvent under reduced pressure gave a yellow liquid, which was purified by flash column chromatography (50% ethyl acetate/hexanes, $R_f = 0.38$, 2,4-DNP visualization), yielding **106** as a yellow liquid (4.54 g, 47%). IR: ν_{max} 2987 (s), 2954 (s), 2885 (s), 1737 (s), 1704 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.95-3.91 (4H, m, OCH_2CH_2O), 3.74 (3H, s, OCH_3), 3.50 (1H, t, $J = 7.1$ Hz, H-2), 2.24 (3H, s, H-4), 1.96 (2H, apparent q, $J = 8.7$ Hz, H-5), 1.67-1.60 (2H, m, H-6), 1.32 (3H, s, H-8). ^{13}C NMR ($CDCl_3$): δ 203.2 (0, C-3), 170.4 (0, C-1), 109.6 (0, C-7), 64.8 (2, OCH_2CH_2O), 59.4 (1, C-2), 52.6 (3, OCH_3), 36.5 (2, C-6), 29.1 (3, C-4), 23.9 (3,

C-8), 22.8 (2, C-5). MS *m/z* (%): 230 (0.05, M^+), 215 (2), 99 (25), 87 (100), 55 (11), 43 (87).

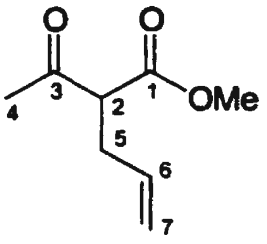
Methyl 5-dioxolano-2-(2-propenyl)hexanoate (109)



To a suspension of sodium hydride (0.46 g, 19 mmol) in THF (30 mL), was added **106** (1.41 g, 6.11 mmol) by syringe as a solution in THF (15 mL). After 30 minutes, allyl bromide (1.16 g, 9.59 mmol) was added by syringe as a solution in THF (15 mL). The reaction mixture was heated under reflux for 21 hours. After cooling, work-up consisted of washing with brine (2 × 50 mL) and re-extracting with ethyl acetate (6 × 50 mL), followed by drying the organic solution over anhydrous magnesium sulfate. Filtration and evaporation of the solvent under reduced pressure gave a yellow liquid, which was purified by flash column chromatography (30% ethyl acetate/hexanes, R_f = 0.38, 2,4-DNP visualization), yielding **109** as a yellow liquid (0.899 g, 64%). IR: ν_{max} 2953 (s), 2882 (s), 1732 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.74 (1H, m, H-8), 5.08-5.00 (2H, m, H-9), 3.95-3.90 (4H, m, OCH_2CH_2O), 3.67 (3H, s, OCH_3), 2.45 (1H, m), 2.40-2.18 (2H, m), 1.75-1.55 (4H, m), 1.30 (3H, s, H-6). ^{13}C NMR ($CDCl_3$): δ 170.2 (0, C-1), 135.5 (1, C-

8), 117.0 (2, C-9), 109.8 (0, C-5), 64.8 (2, OCH_2CH_2O), 51.6 (3, OCH_3), 45.4 (1, C-2), 36.7 (2), 36.6 (2), 26.3 (2, C-7), 23.9 (3, C-6). MS *m/z* (%): 99 (12), 87 (100), 43 (43).

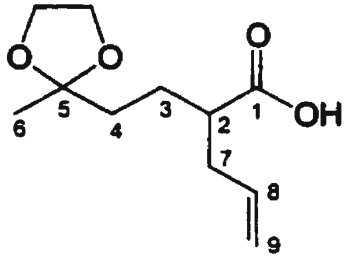
Methyl 3-oxo-2-(2-propenyl)butanoate (110)



To a suspension of sodium hydride (0.29 g, 9.5 mmol) in THF (30 mL), was added methyl acetoacetate (1.01 g, 8.68 mmol) by syringe as a solution in THF (15 mL). After 30 minutes, allyl bromide (1.06 g, 8.74 mmol) was added by syringe as a solution in THF (15 mL). The reaction mixture was heated under reflux for 22 hours. After cooling, work-up of the reaction consisted of washing with brine (2 × 25 mL) and re-extracting with ethyl acetate (4 × 25 mL). The combined organic layers were dried over anhydrous magnesium sulfate and filtered. Evaporation of the solvent under reduced pressure gave a slightly yellow liquid, which was purified by flash column chromatography (20% ethyl acetate/hexanes, $R_f = 0.22$, UV and 2,4-DNP visualization), yielding **110** as a clear, colorless liquid (0.769 g, 52%). IR: ν_{max} 2955 (m), 1751 (s), 1718 (s), 1643 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.74 (1H, m, H-6), 5.13-5.04 (2H, m, H-7), 3.74 (3H, s, OCH_3), 3.55 (1H, t, $J = 7.4$ Hz, H-2), 2.62-2.58 (2H, m, H-5), 2.24 (3H, s, H-4). ^{13}C NMR ($CDCl_3$): δ 202.6 (0, C-3), 169.9 (0, C-1), 134.3 (1, C-6), 117.7 (2, C-7), 59.2

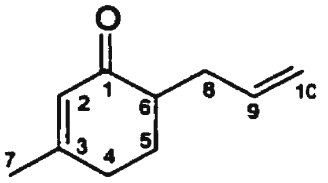
(1, C-2), 52.6 (3, OCH_3), 32.4 (2, C-5), 29.3 (3, C-4). MS *m/z* (%): 156 (0.5, M^+), 154 (3), 114 (13), 113 (21), 81 (12), 43 (100), 41 (17), 39 (13).

5-Dioxolano-2-(2-propenyl)hexanoic acid (111)



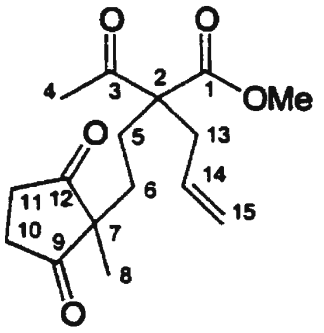
To a solution of **109** (0.350 g, 1.53 mmol) in 95% ethanol (50 mL), was added 10% potassium hydroxide solution (10 mL). The reaction mixture was heated under reflux for 22 hours. After cooling, the mixture was neutralized using 7% hydrochloric acid followed by addition of water (20 mL). Sodium chloride was added until the solution was saturated, at which point the aqueous solution was extracted with ethyl acetate (50 mL). The organic layer was washed with brine (50 mL) and then the combined aqueous layers were re-extracted with ethyl acetate (4 × 50 mL). The organic layers were dried over magnesium sulfate and, after filtration, the solvent was evaporated under reduced pressure to give **111** as an orange liquid (0.341 g, quantitative yield). The ^1H NMR spectrum of the crude product was obtained. ^1H NMR ($CDCl_3$): δ 5.74 (1H, m, H-8), 5.08-5.00 (2H, m, H-9), 3.96-3.93 (4H, s, OCH_2CH_2O), 2.50-2.20 (5H, m), 1.54-1.46 (2H, m), 1.32 (3H, s, H-6).

3-Methyl-6-(2-propenyl)-2-cyclohexen-1-one (113)



To a solution of **112** (0.15 g, 0.80 mmol) in dichloromethane (10 mL), was added $BF_3 \cdot Et_2O$ (0.15 mL, 1.2 mmol). A solution of **2** (0.20 g, 0.87 mmol) in dichloromethane (5 mL) was added slowly to the reaction mixture. After 4 hours, water (0.15 mL, 8.3 mmol) was added followed by, after another 1.25 hours, $BF_3 \cdot Et_2O$ (1.50 mL, 12 mmol). After 18 hours, work-up consisted of washing with water (2 × 20 mL), re-extracting with dichloromethane (2 × 20 mL) and washing the organic layer with brine (25 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Flash column chromatography (30% acetone/hexanes, R_f = 0.42, UV and 2,4-DNP visualization) yielded **113** as a yellow liquid (0.0155 g, 13%). ^1H NMR ($CDCl_3$): δ 5.86 (1H, s, H-2), 5.78 (1H, m, H-9), 5.15-5.09 (2H, m, H-10), 1.99 (3H, s, H-7), 2.46-1.90 (unresolved). ^{13}C NMR ($CDCl_3$): δ 199.6 (C-1), 165.3 (C-3), 136.2 (C-9), 127.3 (C-2), 117.6 (C-10), 39.3, 35.8, 34.0, 26.5, 23.2. MS *m/z* (%): 150 (12, M^+), 135 (13), 132 (17), 122 (12), 117 (14), 109 (47), 108 (15), 107 (13), 106 (12), 95 (15), 94, (18), 93 (50), 92 (23), 91 (12), 82 (16), 81 (100), 80 (49), 79 (90), 77 (18), 67 (14), 55 (12), 53 (28), 43 (22), 41 (47), 39 (14).

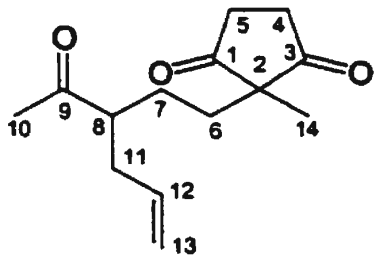
Methyl 2-(2-(2-methylcyclopentan-1,3-dion-2-yl)ethyl)-3-oxo-2-(2-propenyl)-butanoate (117)



To a solution of **105** (1.55 g, 5.74 mmol) in dichloromethane (140 mL), was added $BF_3{\cdot}Et_2O$ (10.8 mL, 85.8 mmol). After 5 minutes, **2** (1.96 g, 8.51 mmol) was added dropwise as a solution in dichloromethane (15 mL). The reaction was left stirring for 24 hours, at which time water (50 mL) was added. After another 20 hours, the reaction mixture was worked-up by separating the layers, re-extracting with dichloromethane (2 × 50 mL) and washing the organic layers with brine (75 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent was evaporated under reduced pressure. The resulting viscous yellow liquid was purified by flash column chromatography (50% ethyl acetate/hexanes, R_f = 0.47, 2,4-DNP visualization), yielding **117** as a viscous yellow liquid (2.98 g, 90%). IR: ν_{max} 3079 (m), 2955 (s), 2872 (m), 1726 (s), 1641 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.50 (1H, m, H-14), 5.14-5.08 (2H, m, H-15), 3.73 (3H, s, OCH_3), 2.87-2.71 (4H, m, H-10 and H-11), 2.56 (2H, m, H-13), 2.10 (3H, s, H-4), 1.68-1.63 (2H, m), 1.51-1.42 (2H, m), 1.11 (3H, s, H-8). ^{13}C NMR ($CDCl_3$): δ 216.0 (0, C-9 or C-12), 215.8 (0, C-9 or C-12), 203.8 (0, C-

3), 171.9 (0, C-1), 131.7 (1, C-14), 119.5 (2, C-15), 63.0 (0, C-2), 56.3 (0, C-7), 52.6 (3, OCH_3), 35.3 (2, C-13), 35.2 (2, C-10 and C-11), 28.7 (2), 26.6 (3, C-4) 25.8 (2), 20.0 (3, C-8). MS *m/z* (%): 295 (3), 294 (1.2, M^+), 156 (20), 138 (14), 125 (15), 113 (15), 108 (15), 95 (18), 80 (43), 79 (11), 69 (13), 67 (16), 55 (15), 43 (100), 41 (46), 39 (15), 27 (13).

2-Methyl-2-(4-oxo-3-(2-propenyl)-pentyl)-1,3-cyclopentanedione (118)



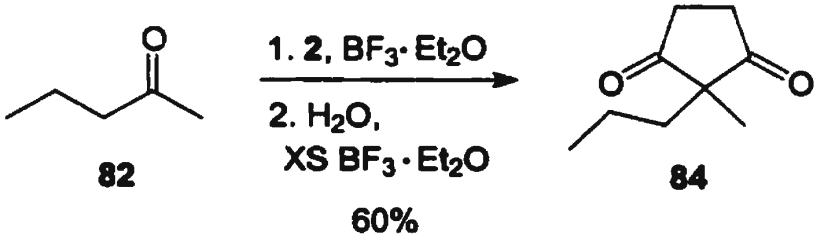
To a solution of **117** (0.0892 g, 0.30 mmol) in DMSO (2.0 mL), was added sodium chloride (0.02 g, 0.3 mmol) and water (0.16 mL, 8.9 mmol). The reaction mixture was heated to 140 °C in an oil bath for 24 hours. After allowing the mixture to cool, it was washed with water (2 × 5 mL) and brine (5 mL). The combined aqueous layers were re-extracted with ethyl acetate (4 × 10 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a brown liquid. Purification by flash column chromatography (50% ethyl acetate/hexanes, $R_f = 0.35$, vanillin dip) gave **118** as a yellow liquid (0.0381 g, 53%). IR: ν_{max} 3471 (m), 2931 (s), 2874 (m), 1722 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.60 (1H, m, H-12), 5.06-5.00 (2H, m, H-13), 2.83-2.71 (4H, m, H-4 and H-5), 2.44 (1H, m), 2.27 (1H, m), 2.10 (3H, s,

H-10), 1.90 (1H, m), 1.70-1.20 (4H, m), 1.10 (3H, s, H-14). ^{13}C NMR ($CDCl_3$): δ 216.24 (C-1 or C-3), 216.17 (C-1 or C-3), 210.9 (C-9), 134.8 (C-12), 117.5 (C-13), 56.6 (C-2), 52.4, 35.3 (C-4 and C-5), 32.4, 29.1, 25.3, 19.3.

4. Novel Compounds prepared using the Geminal Acylation Reaction

During the course of performing the studies on substrate mixtures, some novel compounds were prepared using the geminal acylation reaction. Since most work on this reaction in the past has employed 1,2-bis((trimethylsilyl)oxy)cyclobutene (**2**), most of the 1,3-cyclopentandiones had been previously prepared in our laboratory. 1,2-Bis((trimethylsilyl)oxy)cyclopentene (**55**), on the other hand, had been used very little, so that many novel compounds were prepared from this reagent.

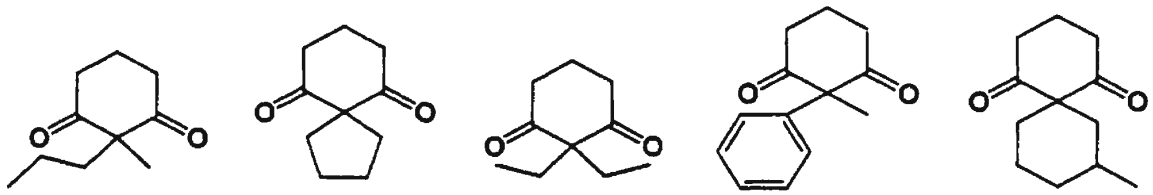
Surprisingly, the geminal acylation of 2-pentanone (**82**) with **2** had never been performed. The product of this reaction, 2-methyl-2-propyl-1,3-cyclopentanedione (**84**), was prepared in 60% yield.



Scheme 46.

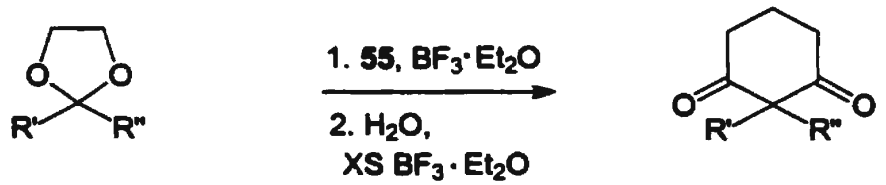
The five 1,3-cyclohexanediones shown in Figure 9 were all prepared from the geminal acylation of an acetal with **55**. The preparation of each of these diones is shown in Scheme 47. 2-Methyl-2-propyl-1,3-cyclohexanedione (**94**) was prepared in 46% yield. In each case, the product was purified by running the crude mixture through a short Florisil column. Two successive Florisil columns were unsuccessful in completely

purifying spiro[5.4]decane-1,5-dione (**126**) and 2,2-diethyl-1,3-cyclohexanedione (**127**). Due to a small amount of remaining impurity, MS and HRMS information were not obtained for these compounds. Difficulties were also encountered in the purification of 2-methyl-2-phenyl-1,3-cyclohexanedione (**128**). Purification was attempted by flash column chromatography, but it was discovered that the product had the same R_f as acetophenone. As a result, the yield reported was determined from the integration of the NMR spectrum. Finally, 8-methylspiro[5.5]undecane-1,5-dione (**129**) was prepared in 44% yield without any difficulties.



94	**126**	**127**	**128**	**129**
46%	31%	10%	11%	44%

Figure 9. Novel compounds prepared from geminal acylations with **55**.



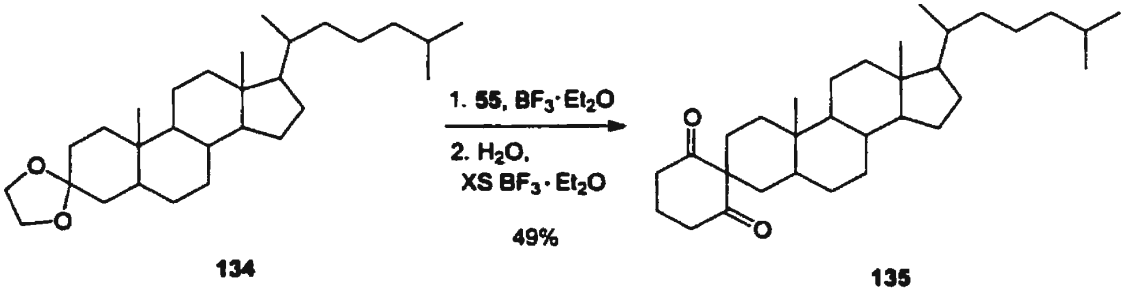
90 (R' = $CH_2CH_2CH_3$, R" = CH_3)
130 (R', R" = $CH_2CH_2CH_2CH_2$)
131 (R' = CH_2CH_3, R" = CH_2CH_3)
132 (R' = C_6H_5, R" = CH_3)
133 (R', R" = $(CH_2)_3CHCH_3CH_2$)

94 (R' = $CH_2CH_2CH_3$, R" = CH_3)
126 (R', R" = $CH_2CH_2CH_2CH_2$)
127 (R' = CH_2CH_3, R" = CH_2CH_3
128 (R' = C_6H_5, R" = CH_3)
129 (R', R" = $(CH_2)_3CHCH_3CH_2$)

Scheme 47.

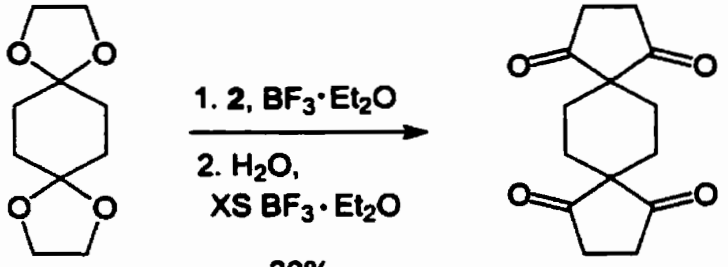
The geminal acylation of the 1,2-ethanediol acetal of 5α-cholestan-3-one **134** with **55** was performed successfully. After purification by passing the crude product

through a Florisil column, spiro[5α-cholestane-3-2'-cyclohexane]-1,3-dione (**135**) was produced in 49% yield.



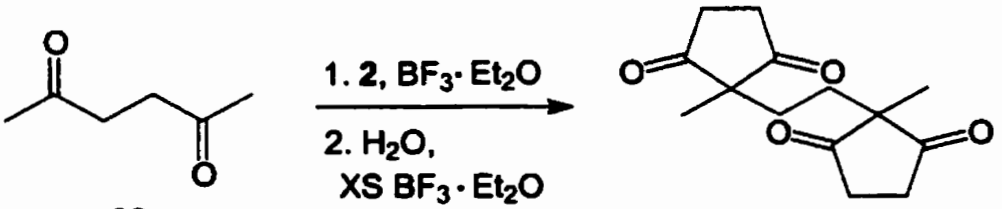
Scheme 48.

A geminal acylation reaction was also performed on a symmetrical diacetal and a symmetrical diketone. Diacetal **136** reacted with **2**, under acetal conditions, to give tetraone **137** in 40% yield. Although a ^1H NMR spectrum was obtained, tetraone **137** was not sufficiently soluble in any solvent to obtain a ^{13}C NMR spectrum. The same reaction was attempted with **55** but was unsuccessful. The reaction of diketone **98** proceeded in only 2% yield to give tetraone **138**. The reaction was not attempted with the diacetal of **98**, although this would have been interesting to try. However, the reaction of the diacetal of **98** with **55** was attempted but, as for the previous reaction with **55**, was unsuccessful.



136 **137**

Scheme 49.

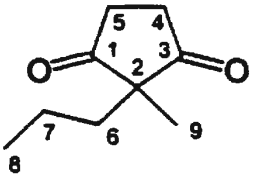


98 **138**

Scheme 50.

4.1 Experimental[28]

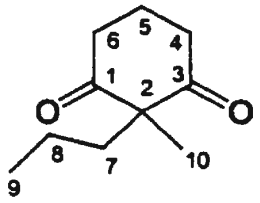
2-Methyl-2-propyl-1,3-cyclopentanedione (84)



To a solution of 2-pentanone (0.221 g, 2.57 mmol) in dichloromethane (9 mL), was added $BF_3 \cdot Et_2O$ (0.32 mL, 3.1 mmol). A solution of **2** (0.89 g, 4.3 mmol) in dichloromethane (4 mL) was added slowly to the reaction mixture. After 2.5 hours, water (0.35 mL, 19 mmol) was added followed, after another 15 minutes, by $BF_3 \cdot Et_2O$ (4.85 mL, 38 mmol). After 17 hours, work-up consisted of washing with water (2 × 50 mL), re-extracting with dichloromethane (2 × 50 mL) and washing with brine (75 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and most of the solvent was evaporated under reduced pressure. The resulting dark liquid was flushed through a short Florisil column with charcoal, using dichloromethane as the solvent. Evaporation of the solvent under reduced pressure gave **84** as a yellow liquid (0.238 g, 60%). IR: ν_{max} 3467 (m), 2964 (s), 2876 (s), 1722 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.76 (4H, s, H-4 and H-5), 1.64-1.59 (2H, m, H-6), 1.22-1.14 (2H, m, H-7), 1.12 (3H, s, H-9), 0.86 (3H, t, J = 7.2 Hz, H-8). ^{13}C NMR ($CDCl_3$): δ 216.9 (0, C-1 and C-2), 56.8 (0, C-2), 38.0 (2, C-6), 35.3 (2, C-4 and C-5), 18.9 (3, C-9), 18.0 (2, C-7), 14.3 (3, C-8). MS

m/z (%): 154 (15, M^+), 125 (100), 112 (56), 97 (20), 67 (54), 55 (14), 43 (14), 39 (14), 28 (17), 27 (21). HRMS calcd for $C_{11}H_{18}O_5$: 154.0994; found: 154.1002.

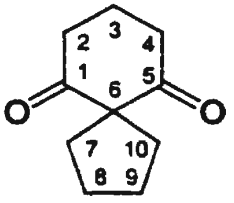
2-Methyl-2-propyl-1,3-cyclohexanedione (94)



To a solution of 2-methyl-2-propyl-1,3-dioxolane (**90**) (0.320 g, 2.45 mmol) in dichloromethane (30 mL) cooled to -78 °C, was added $BF_3{\cdot}Et_2O$ (4.6 mL, 37 mmol). A solution of **55** (0.97 g, 4.0 mmol) in dichloromethane (8 mL) was added dropwise to the reaction mixture. After allowing to warm to room temperature over 14 hours, water (10 mL, 0.55 mol) was added. After 4 hours, work-up consisted of extracting with dichloromethane (3 × 15 mL) and washing with brine (2 × 30 mL). The organic layer was dried over magnesium sulfate and filtered, and most of the solvent was removed under vacuum. The resulting brown liquid was passed through two successive Florisil columns and then evaporated under reduced pressure to give **94** as a yellow liquid (0.188 g, 46%). IR: ν_{max} 2963 (s), 2874 (s), 1697 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.77-2.55 (4H, m, H-4 and H-6), 2.01 (1H, m, H-5), 1.86 (1H, m, H-5), 1.78-1.73 (2H, m, H-7), 1.22 (3H, s, H-10), 1.20-1.10 (2H, m, H-8), 0.88 (3H, t, J = 7.2 Hz, H-9). ^{13}C NMR ($CDCl_3$): δ 210.4 (0, C-1 and C-3), 65.9 (0, C-2), 40.0 (2, C-7), 37.9 (2, C-4 and C-6), 18.5 (3, C-10), 18.1 (2, C-8), 17.8 (2, C-5), 14.4 (3, C-9). MS *m/z* (%): 168 (22, M^+), 149 (16), 139

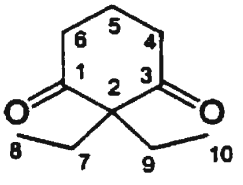
(15), 126 (59), 112 (15), 111 (100), 97 (52), 93 (20), 79 (22), 71 (33), 69 (76), 67 (32), 55 (47), 43 (51), 41 (86). HRMS calcd for $C_{11}H_{18}O_5$: 168.1150; found: 168.1145.

Spiro[5.4]decane-1,5-dione (126)



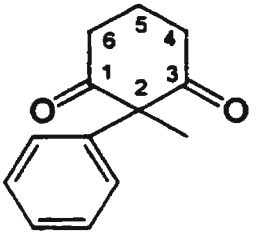
To a solution of 1,4-dioxaspiro[4.5]decane (**130**) (0.288 g, 2.25 mmol) in dichloromethane (30 mL) cooled to -78 °C, was added $BF_3 \cdot Et_2O$ (4.25 mL, 33.8 mmol). A solution of **55** (0.83 g, 3.4 mmol) in dichloromethane (8 mL) was added dropwise to the reaction mixture. After allowing the mixture to reach room temperature over the next 24 hours, water (10 mL, 0.55 mol) was added. After another 5 hours, work-up consisted of extracting with dichloromethane (3 × 15 mL) and washing the combined organic layers with brine (2 × 30 mL). The organic layer was dried over magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The resulting brown liquid was passed through two successive Florisil columns and the solvent was evaporated under vacuum to give **126** as a yellow liquid (0.115 g, 31%). IR: ν_{max} 2956 (s), 2870 (s), 1694 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.67 (4H, t, H-2 and H-4, J = 6.8 Hz), 2.08-2.02 (4H, m), 1.97 (2H, quintet, H-3, J = 6.8 Hz), 1.69-1.65 (4H, m). ^{13}C NMR ($CDCl_3$): δ 209.0 (C-1 and C-5), 72.7 (C-6), 38.1, 33.3, 26.6, 17.9.

2,2-Diethyl-1,3-cyclohexanedione (127)



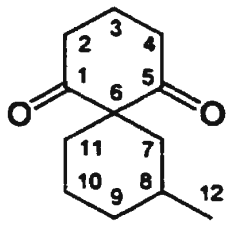
To a solution of 2,2-diethyl-1,3-dioxolane (**131**) (0.257 g, 1.98 mmol) in dichloromethane (30 mL) cooled to -78 °C, was added $BF_3 \cdot Et_2O$ (3.73 mL, 29.6 mmol). A solution of **55** (0.72 g, 2.9 mmol) in dichloromethane (8 mL) was added dropwise. The reaction mixture was allowed to reach room temperature over 13 hours, at which point water (10 mL, 0.55 mol) was added. After 4 hours, work-up consisted of extracting with dichloromethane (3 × 15 mL) and washing with brine (2 × 30 mL). The organic layer was dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The crude mixture was passed through a short Florisil column, yielding **127** as a yellow liquid (0.032 g, 10%). IR: ν_{max} 2964 (m), 2933 (m), 1722 (m), 1693(s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.61 (4H, t, J = 6.6 Hz, H-4 and H-6), 1.95 (2H, quintet, J = 6.6 Hz, H-5), 1.81 (4H, q, J = 7.5 Hz, H-7 and H-9), 0.75 (6H, t, J = 7.5 Hz, H-8 and H-10). ^{13}C NMR ($CDCl_3$): δ 211.5 (C-1 and C-3), 39.8, 29.9, 29.2, 17.2, 9.8.

2-Methyl-2-phenyl-1,3-cyclohexanedione (128)



A solution of 2-methyl-2-phenyl-1,3-dioxolane (**132**) (0.429 g, 2.61 mmol) in dichloromethane (30 mL) was cooled to -78 °C. To this solution was added $BF_3 \cdot Et_2O$ (6.19 mL, 39.2 mmol), followed by a solution of **55** (0.98 g, 4.0 mmol) in dichloromethane (8 mL). The reaction mixture was allowed to warm to room temperature over 18 hours, at which time water (10 mL, 0.55 mol) was added. After 4 hours, the reaction mixture was extracted with dichloromethane (3 × 15 mL) and the combined organic layers were washed with brine (2 × 30 mL). The organic layer was dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure to give a brown liquid. Flash column chromatography (20% acetone/hexanes, $R_f = 0.54$, UV and phosphomolybdic acid spray visualization), gave a yellow liquid, an inseparable mixture of product **128** and acetophenone. A calculation was performed from the NMR spectrum to show that **128** was produced in 11% yield. ^1H NMR ($CDCl_3$): δ 7.36-7.27 (3H, m, Ar-H), 7.02-6.98 (2H, m, Ar-H), 2.85-2.74 (2H, m, H-4 or H-6), 2.61-2.51 (2H, m, H-4 or H-6), 1.90 (1H, m, H-5), 1.71 (1H, m, H-5), 1.44 (3H, s, CH_3).

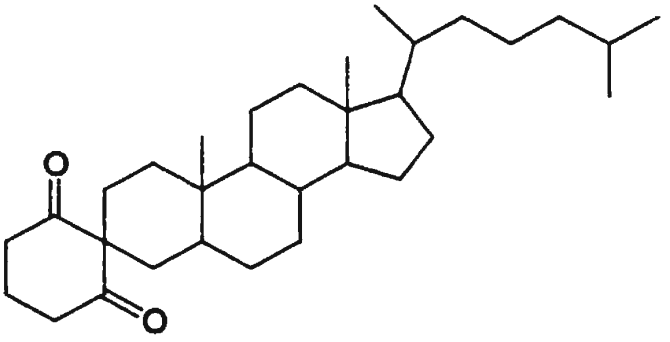
8-Methylspiro[5.5]undecane-1,5-dione (129)



To a solution of 7-methyl-1,4-dioxaspiro[4.5]decane (**133**) (0.321 g, 2.05 mmol) in dichloromethane (30 mL) cooled to -78 °C, was added $BF_3 \cdot Et_2O$ (3.9 mL, 31 mmol). A solution of **55** (0.85 g, 3.5 mmol) in dichloromethane (8 mL) was added dropwise to the reaction mixture. After warming to room temperature over 16 hours, water (10 mL, 0.55 mol) was added. After 4 hours, work-up consisted of extracting with dichloromethane (3 × 15 mL) and washing the combined organic layers with brine (2 × 30 mL), followed by drying the organic layer over anhydrous magnesium sulfate, filtering and evaporating the solvent under reduced pressure. Flash column chromatography (30% acetone/hexanes, R_f = 0.43, phosphomolybdic acid spray visualization) yielded **129** as an orange liquid (0.175 g, 44%). IR: ν_{max} 3402 (m), 2950 (s), 2870 (s), 1693 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.72 (2H, t, J = 7.0 Hz), 2.67 (2H, t, J = 7.0 Hz), 2.18-2.03 (2H, m), 1.90 (2H, quintet, J = 7.0 Hz, H-3), 1.72-1.47 (6H, m), 1.30 (1H, dd, J = 13.5, 12.1 Hz), 0.90 (3H, d, J = 6.3 Hz, H-12). ^{13}C NMR ($CDCl_3$): δ 209.8 (C-1 or C-5), 209.6 (C-1 or C-5), 68.6 (C-6), 39.1, 37.6, 37.3, 34.4, 30.8, 28.6, 23.0, 22.6, 18.6. MS *m/z* (%): 195 (12), 194 (88, M^+), 151 (18), 138 (66), 126 (66), 125 (66), 123 (38), 109 (20), 98 (28), 97 (25), 95 (74), 93 (20), 82 (20), 81 (59), 79 (25), 70 (56), 69

(25), 67 (37), 55 (68), 53 (33), 43 (56), 42 (100), 41 (98), 39 (62), 27 (57). HRMS calcd for $C_{11}H_{18}O_5$: 194.1307; found: 194.1320.

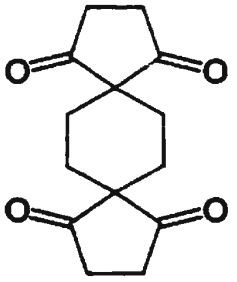
Spiro[5α-cholestane-3-2'-cyclohexane]-1,3-dione (135)



To a solution of the 1,2-ethanediol acetal of 5α-cholestan-3-one **134** (0.10 g, 0.24 mmol) in dichloromethane (30 mL) cooled to -78 °C, was added $BF_3{\cdot}Et_2O$ (0.46 mL, 3.6 mmol). A solution of **55** (0.23 g, 0.94 mmol) in dichloromethane (8 mL) was added dropwise to the reaction mixture. After allowing the mixture to warm to room temperature over 21 hours, water (10 mL, 0.55 mol) was added. After 4 hours, work-up consisted of extracting with dichloromethane (3 × 15 mL) and washing with brine (2 × 30 mL). The organic layer was dried over magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The crude product was passed through a Florisil column using dichloromethane as the eluant, yielding **135** as a white solid (0.055 g, 49%): m.p. 168-170°C. IR (Nujol): ν_{max} 1719 (m), 1691 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.84-2.54 (4H, m, $COCH_2$), 2.0-0.8 (unresolved), 0.75 (3H, s), 0.63 (3H, s). ^{13}C NMR

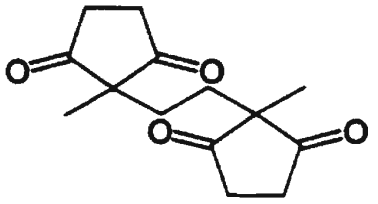
($CDCl_3$): δ 210.0, 209.6, 68.4, 56.6, 56.4, 54.1, 42.7, 42.1, 40.1, 39.7, 37.4, 37.3, 36.4, 36.0, 35.9, 35.6, 35.0, 34.4, 31.9, 28.9, 28.4, 28.2, 25.5, 24.4, 24.0, 23.0, 22.8, 21.1, 18.9, 18.7, 12.3, 11.8.

Dispiro[4.2.4.2]tetradecan-1,4,9,12-tetraone (137)



A solution of 1,4,9,12-tetraoxadispiro[4.2.4.2]tetradecane (**136**) (0.387 g, 1.93 mmol) in dichloromethane (30 mL) was cooled to -78 °C. To this solution was added $BF_3 \cdot Et_2O$ (7.25 mL, 57.6 mmol), followed a solution of **2** (1.39 g, 6.03 mmol) in dichloromethane (8 mL), added dropwise. After allowing the mixture to warm to room temperature over 20 hours, water (10 mL, 0.55 mol) was added. After 4 hours, work-up consisted of extracting with dichloromethane (3 × 15 mL) and washing with brine (2 × 30 mL). The organic layer was dried over magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The resulting yellow solid was washed with pentane, diethyl ether and methanol, and dried under vacuum, yielding **137** as a white solid (0.143 g, 30%): m.p. 265°C (decomposed). IR (Nujol): ν_{max} 1722 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.78 (8H, s), 1.88 (8H, s).

2-Methyl-2-(3-(2-methylcyclopentane-1,3-dion-2-yl)propyl)-cyclopentane-1,3-dione (138)



To a solution of 2,5-hexanedione (**98**) (0.243 g, 2.13 mmol) in dichloromethane (9 mL), was added $BF_3 \cdot Et_2O$ (0.30 mL, 2.4 mmol). A solution of **2** (1.38 g, 5.99 mmol) in dichloromethane (4 mL) was added slowly to the reaction mixture. After 2.3 hours, water (0.30 mL, 16 mmol) was added followed by, after another 15 minutes, $BF_3 \cdot Et_2O$ (1.9 mL, 15 mmol). After 18 hours, work-up consisted of washing with water (2 × 50 mL), re-extracting with dichloromethane (2 × 50 mL) and washing with brine (75 mL). The combined organic layers were dried over anhydrous magnesium sulfate and filtered, and most of the solvent was evaporated under reduced pressure. The resulting dark liquid was flushed through a short Florisil column with charcoal, using dichloromethane as the eluant. Evaporation of the solvent under reduced pressure gave a yellow liquid with a precipitate. After allowing the precipitate to settle overnight, suction filtration gave **138** as a white solid (0.0097 g, 2%): m.p. 184-186°C. IR: ν_{max} 1719 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.82-2.71 (8H, symmetrical m), 1.52 (4H, s), 1.09 (6H, s). ^{13}C NMR ($CDCl_3$): δ 215.7, 56.3, 35.1, 28.7, 19.1. MS *m/z* (%): 251 (0.1, M+1), 139 (12), 138 (100), 125 (30), 113 (30), 112 (14), 110 (40), 97 (16), 96 (14), 95 (31), 82 (18), 69 (31), 55 (20), 43 (17), 41

(84), 34 (21), 29 (13), 28 (31), 27 (30). HRMS calcd for $C_{14}H_{18}O_4$: 250.1205; found: 250.1201.

Appendix

^{1}H NMR spectra for selected compounds appearing in the body of this text.

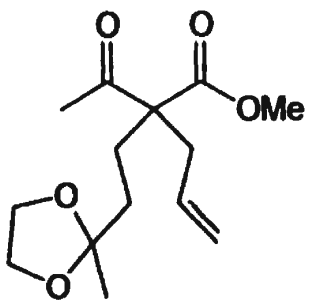
84
8
6
4
2
0 ppm

9q

100
OTBDMS
O
8
6
4
2
0 ppm

102

104

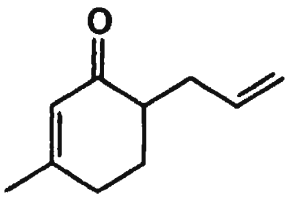


105

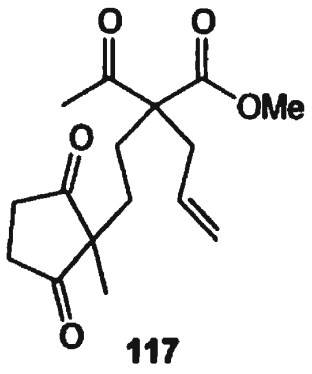
106
OMe
O
O
O
O
8
6
4
2
0 ppm

109
OMe
O
O
O
8
6
4
2
0 ppm

110
O
O
OMe
8
6
4
2
0 ppm

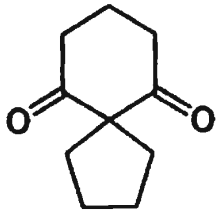


113



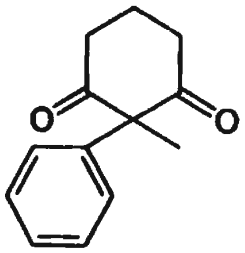
117

118



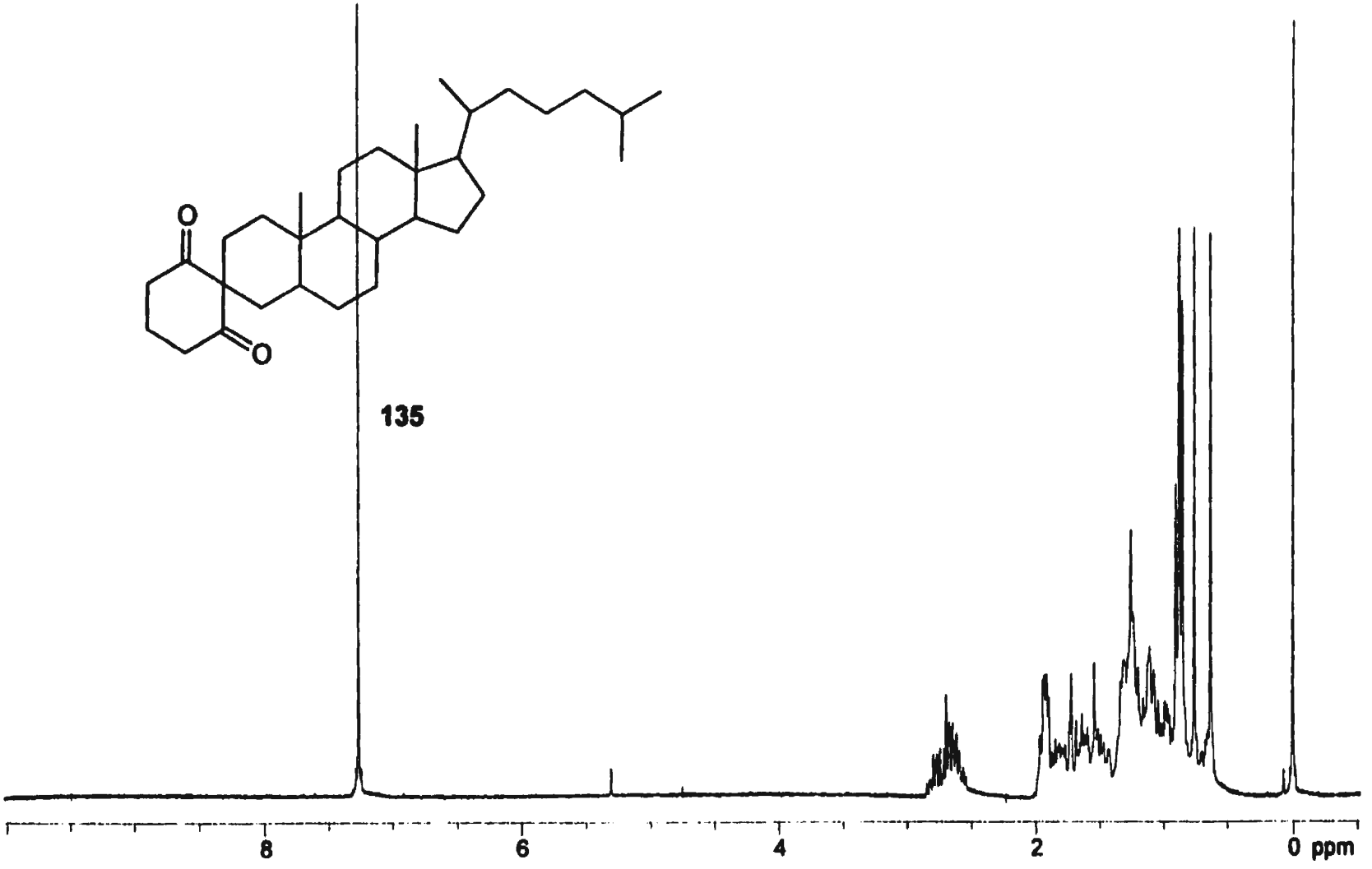
126

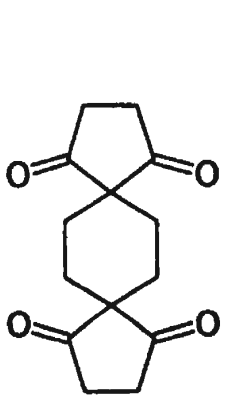
127



128

129


O
O
135
8
6
4
2
0 ppm



137

138