

1983

New strategies in the synthesis of carbocyclic natural products

Peter Gottschalk
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**NEW STRATEGIES IN THE SYNTHESIS OF CARBOCYCLIC NATURAL
PRODUCTS**

Iowa State University

Ph.D. 1983

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New strategies in the synthesis of
carbocyclic natural products

by

Peter Gottschalk

A Dissertation Submitted to the
Graduate Faculty in Partial Fulfillment of the
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DOCTOR OF PHILOSOPHY

Department: Chemistry
Major: Organic Chemistry

Approved:

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In Charge of Major Work

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For the Major Department

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For the Graduate College

Iowa State University
Ames, Iowa

1983

TABLE OF CONTENTS

	Page
GENERAL INTRODUCTION	1
PART I: SYNTHETIC STUDIES TOWARD THE SYNTHESIS OF EUDESMANE LACTONES	2
INTRODUCTION	3
HISTORICAL	4
RESULTS AND DISCUSSION	12
EXPERIMENTAL	31
REFERENCES	53
PART II: PREPARATION OF β -HYDROXY- γ -LACTONES	56
INTRODUCTION	57
HISTORICAL	58
RESULTS AND DISCUSSION	62
EXPERIMENTAL	71
REFERENCES	76
PART III: USEFUL AND NOVEL STEREOSELECTIVE SYNTHESIS OF CARBOCYCLIC COMPOUNDS	78
INTRODUCTION	79
HISTORICAL	80
RESULTS AND DISCUSSION	83
EXPERIMENTAL	101
REFERENCES	106
ACKNOWLEDGEMENTS	107
GENERAL CONCLUSION	108

GENERAL INTRODUCTION

Organic synthesis plays a major role in the science of organic chemistry. Nature provides us with a limited supply of readily available chemicals. Transformation of these chemicals into the plethora of compounds required for modern living and research relies heavily on the creativity and skill of the synthetic chemist. Continuous research is required to find more efficient and convenient methods in the synthesis of chemical products. I hope this manuscript will be a contribution toward this effort.

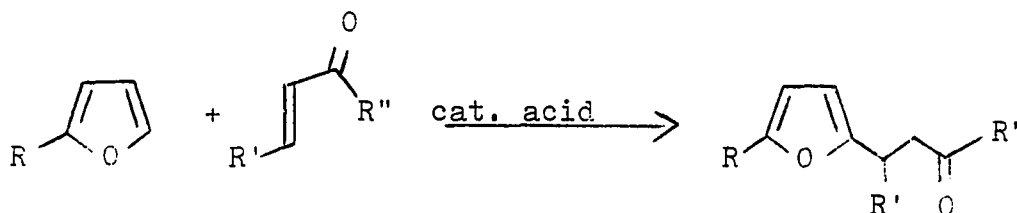
PART I: SYNTHETIC STUDIES TOWARD THE SYNTHESIS OF
EUDESMANE LACTONES

INTRODUCTION

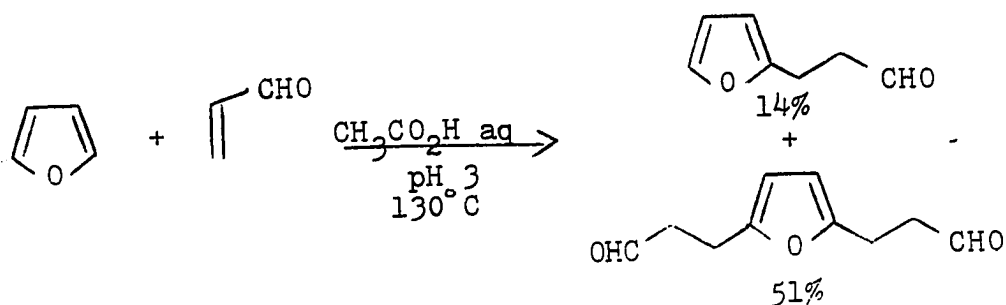
The eudesmane lactones represent a large group of natural products which have a wide range of biological activity. This manuscript will describe the efforts made towards the synthesis of such compounds. The key reaction illustrated will involve the conjugate addition of a furan unit to an enone with concomitant formation of an enol silyl ether regioselectivity.

HISTORICAL

During the investigation (1,2) of the Diels-Alder reaction it was found that furan would not react as the diene with activated dienophiles such as acrolein, crotonaldehyde, methyl vinyl ketone, and phenyl vinyl ketone. Traces of acid, however, promoted an alternate reaction resulting in the formation of a substituted furan. Various acid catalysts (3) were found to promote this exothermic reaction in moderate yield.



Webb and Borchardt (4) determined that this substitution reaction proceeded under general acid catalysis and was pH dependent. They recovered only polymeric material from the reaction of furan and acrolein in the presence of strong acid catalysts in the absence of water. Substitution products could be obtained if the reaction was run in aqueous acetic acid at elevated temperatures. This reaction was typical in that furan gave predominantly a 2,5-disubstituted product. The proposed mechanism was that of electrophilic substitution of the furan ring by



the protonated acrolein. The preponderance of the disubstituted furan was consistent with an electrophilic substitution mechanism in that 2-alkylfurans are more reactive than furan (5,6).

Subsequent workers contradicted the claim that strong acid catalysis led only to polymeric material. Alder and Schmidt (2) were able to obtain substitution products by the reaction of 2-methylfuran and methyl vinyl ketone in the presence of catalytic amounts of sulfuric acid. Yur'ev and coworkers (7) found sulfuric acid to be superior to hydrogen chloride, phosphoric acid, *p*-toluenesulfonic acid, and boron trifluoride etherate in promoting the reaction between 2-methyl- or 2-ethylfuran and mesityl oxide.

Functionalized furan systems were first studied by Glukhovtsev and coworkers (8-10). Their work showed that alcohols, nitriles, esters, and carboxylic acids survive the acidic reaction conditions (Table I). In addition, they found that furans with electron-withdrawing groups attached directly to the furan nucleus were

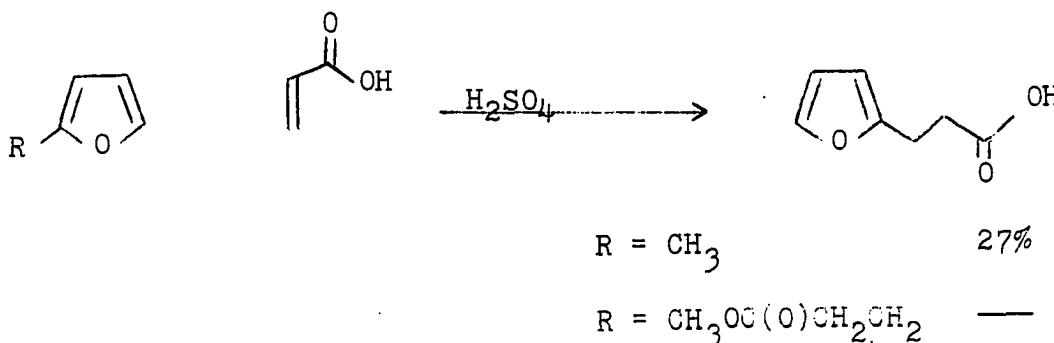
Table 1. Reactions of substituted furans

Furan	Product
	29%
	a) R = H 50% b) R = NCCH ₂ CH ₂ - 44% c) R = CH ₃ C(O)- 58%
	13.6%
	N. R.
	N. R.
	a) R = H 65% b) R = CH ₃ 60%

unreactive. All cases involved the use of 50% aqueous sulfuric acid as the catalyst except in the case of acrolein. Here, a better yield was obtained when acetic acid was used.

Reactions of various α,β -unsaturated ketones and aldehydes were explored by Yur'ev and coworkers (11). These data (Table 2) showed that this reaction was general for alkyl substituted acyclic enones and enals.

Other α,β -unsaturated carbonyl compounds do not, in general, undergo this substitution reaction with furans. Glukhovtsev and Zakharova (12) have reported the reaction depicted below. While Zamaraev and Tikhomirova



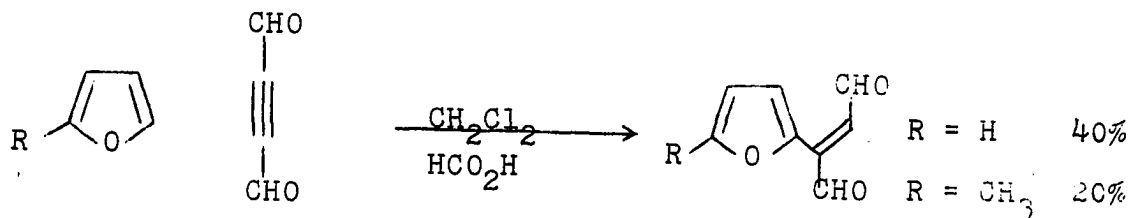
(13) could not induce methacrylic acid or its corresponding esters to react with 2-methylfuran, they found that acid chlorides would react with a variety of alkyl substituted furans in the absence of added catalyst. This was probably due to traces of hydrogen chloride

Table 2. Survey of enone reactivity

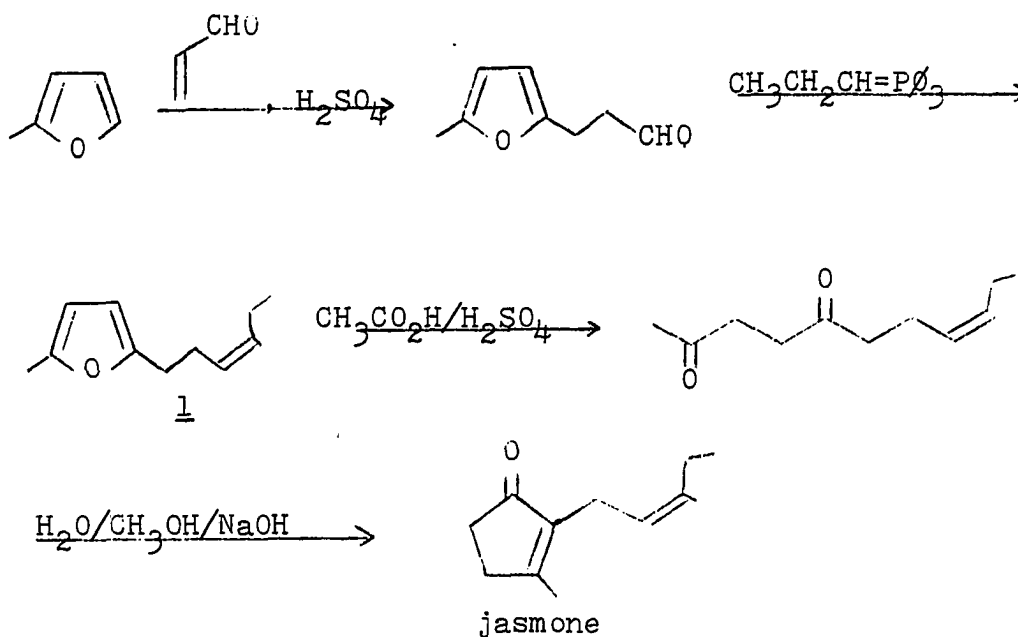
R ¹	R ²	R ³	R ⁴	%
H	H	H	Me	50
H	H	H	<i>i</i> -Bu	50
Me	H	H	Me	60
Et	H	H	Me	52
<i>n</i> -Pr	H	H	Me	44
<i>i</i> -Pr	H	H	Me	45
<i>n</i> -Hex	H	H	Me	49
H	H	Me	Me	-- ^a
Me	H	Me	Me	69
Me	Me	H	Me	56
Me	Et	H	Et	48
Me	Me	Me	Me	39

^aProduct was obtained but no yield was given.

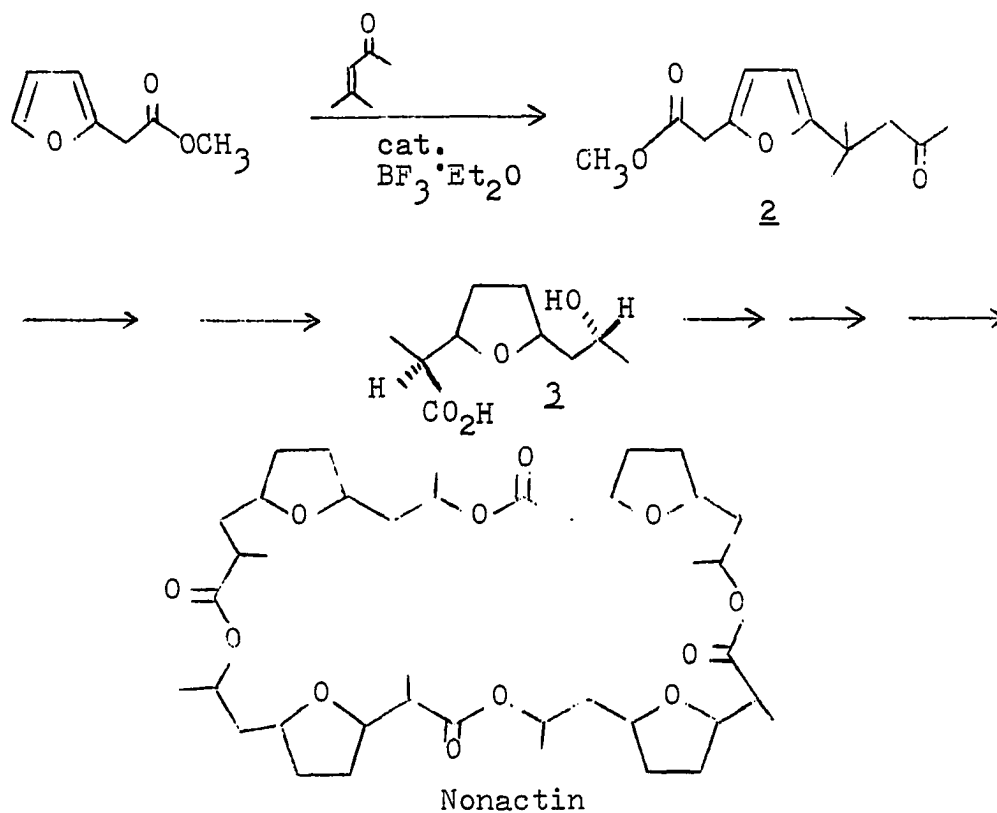
present in the acid chloride. No studies involving the use of α,β -unsaturated amides have been reported. Finally, acetylene dicarboxaldehyde was shown to react with furans in the presence of acid in modest yields (14).



Although this furan substitution reaction appeared to be quite generally applicable and operationally quite simple it had not been extensively used synthetically. In 1964, Zefirov and coworkers (15) used this reaction in the formation of a key furan intermediate (1) which was transformed into the fragrance compound jasmone. Seven years later



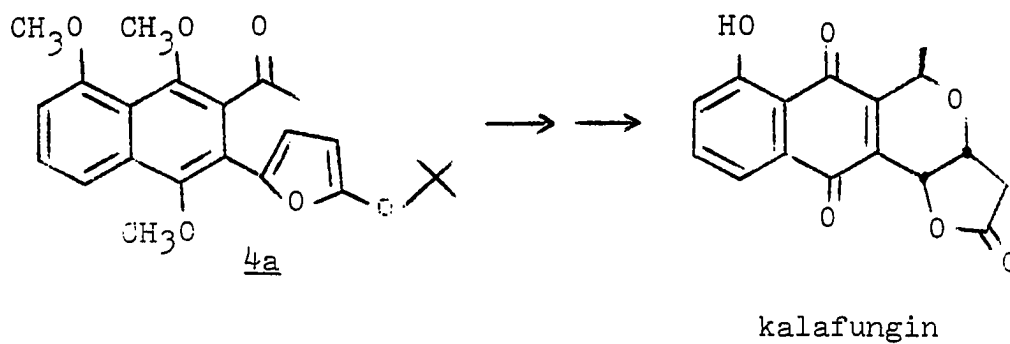
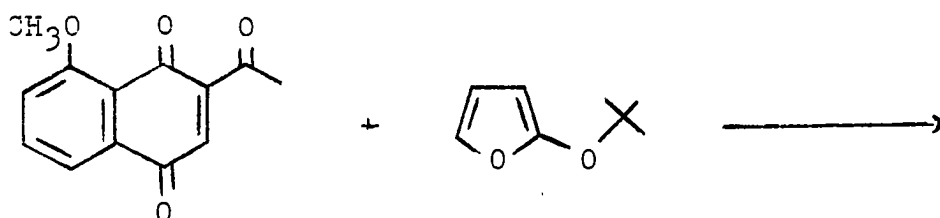
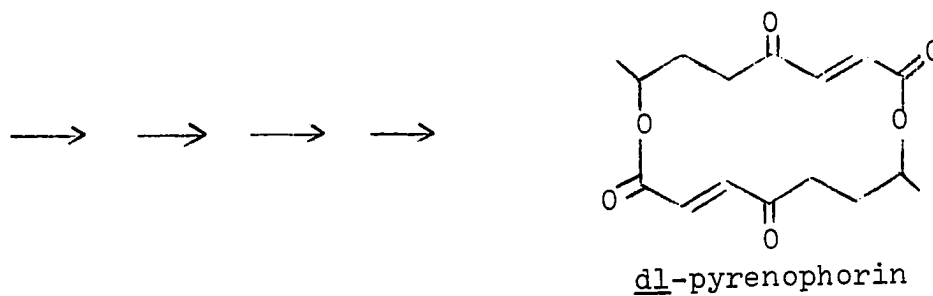
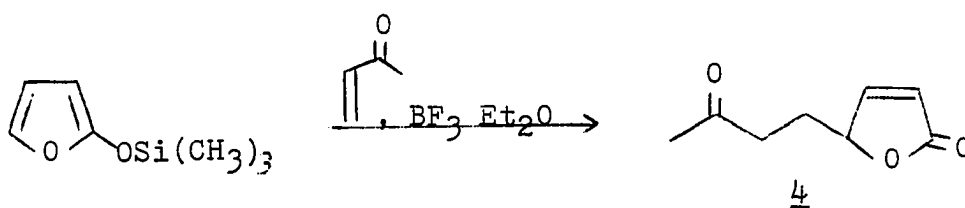
Beck and Henseleit (16) prepared compound (2) for use in the synthesis of (3), a key subunit of nonactin.



Asaoka and coworkers (17) have described the use of 2-trimethylsilyloxyfuran as a masked butenolide in these types of reactions. They synthesized (4) which was converted in several steps to dl-pyrenophorin. Finally, Kraus and Roth (18) have shown that certain electron-rich furans could add to quinones without the

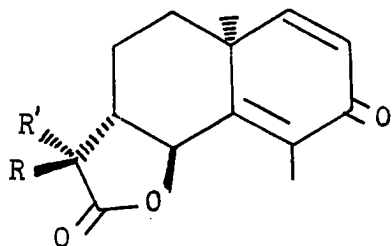
aid of a catalyst to give substituted butenolides.

Compound (4a) was synthesized in this manner and taken on to kalafungin.



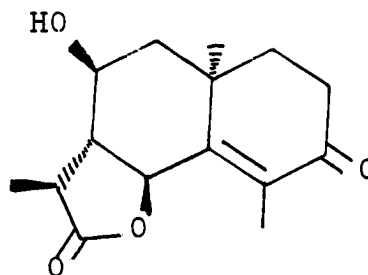
RESULTS AND DISCUSSION

Our intent was to devise a convenient synthetic approach to various sesquiterpene natural products such as the eudesmane lactones (19). These types of compounds have a 5,6,6-carbocyclic ring system in which the five-membered ring is in the form of a furan or a $\Delta^{2,3}$ - γ -lactone, otherwise known as a butenolide. Various examples (20) of these compounds are shown below.



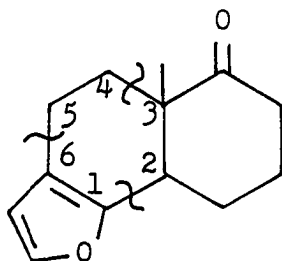
R = CH₃, R' = H α -Santonin

R = H, R' = CH₃ β -Santonin



Artemisin

Since furans could oxidatively be transformed into butenolides (21), our research focused primarily on the use of furans. Our retrosynthetic analysis produced three major bond disconnections. The bond

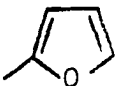
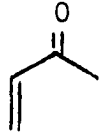
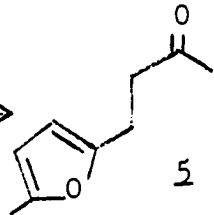
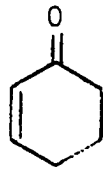
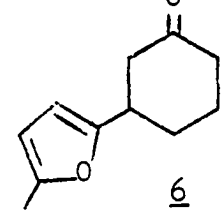
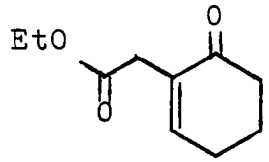
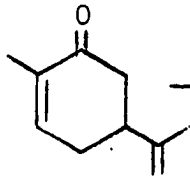
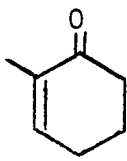


between C1 and C2 would be formed by reaction of a furan with an appropriately functionalized cyclohexenone unit. The central ring would then be formed by an appropriate two-carbon bridge. We focused our initial efforts on the synthesis of the bond between C1 and C2. We chose to do this by the acid catalyzed furan addition to enones. This reaction offered several advantages:

- 1) The reaction was operationally very simple, requiring no solvent.
- 2) Direct distillation from the reaction pot gave pure product.
- 3) The reaction was amenable to large scales.

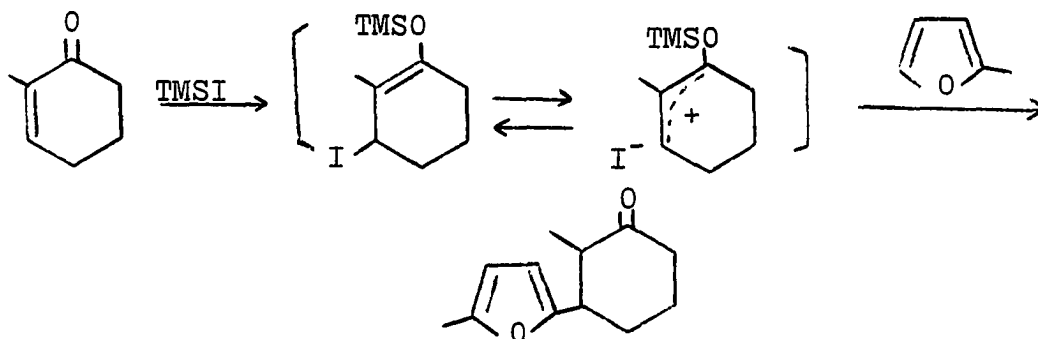
We found the literature conditions quite reproducible and were thus encouraged to try more complex enones. No cycloalkenones had previously been used in this reaction. Our preliminary results (Table 3) showed that although cyclohex-2-en-1-one worked well, all of the α -substituted cyclohexenones failed to react. Prolonged reaction times and elevated temperatures gave only polymeric residues. This was unfortunate in that all of the natural products of the type we wished to synthesize had a quaternary center at the ring juncture between the two cyclohexyl rings. Using an α -substituted cycloalkenone would have resulted in an extremely efficient synthesis of the desired bicyclic unit. At this point,

Table 3. Acid catalyzed furan addition to enones

Furan	Enone	Product
		 <u>5</u>
"		 <u>6</u>
"		N. R.
"		N. R.
"		N. R.

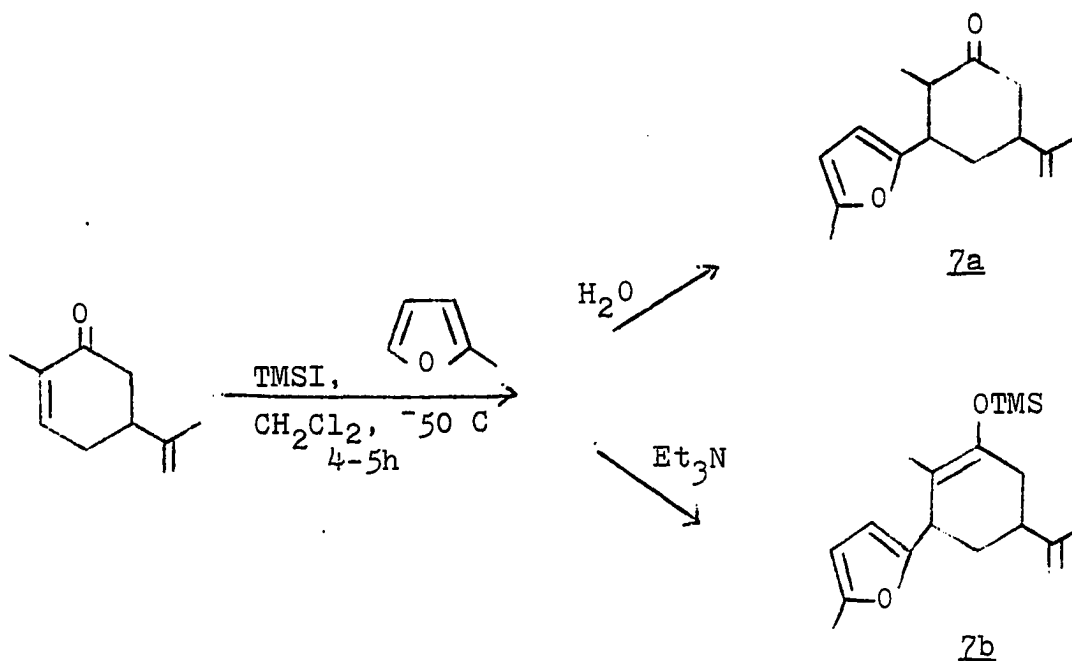
we decided to look at alternate ways of generating the allylic carbocationic intermediate.

Our new approach involved the use of iodotrimethylsilane (TMSI). It has been shown by Miller and McKean (22) that TMSI reacted with various enones to form the unstable γ -iodoenol silyl ethers. We presumed that in a polar aprotic solvent this compound would ionize giving us the desired allylic carbocation which would react with the furan.



Precedent for the idea was established by Marino and Linderman (23) who used the labile γ -iodoenol silyl ether to effect a carbocationic electrocyclic ring closure in a Nazarov-type cyclization to form various bicyclic systems. Concurrent with our own research, Godleski and Heacock (24) has independently observed that TMSI mediates the intramolecular cyclization of activated methylene compounds and intermolecular addition of amines to enones.

Using 1-carvone as our model enone we duplicated Marino's conditions using 2-methylfuran but observed only destruction of the reactants. We modified the procedure by using methylene chloride as the solvent and a low reaction temperature ($-78 - -50^{\circ}\text{C}$). With these modified conditions we isolated the furan addition product (7a) in quantitative yield upon aqueous work-up. We further reasoned that if we could devise an anhydrous work-up of this reaction, we would be able to isolate the enol silyl ether of the furan addition product, namely (7b). Hence, the reaction was monitored by infra-



red spectroscopy, and upon disappearance of the enone carbonyl stretch (1680 cm^{-1}) the reaction was quenched with anhydrous triethylamine. Dilution with hexane followed by filtration through celite gave enol silyl ether (7b) in quantitative yield. Acid hydrolysis converted (7b) to (7a). Isolation of the enol silyl ether was significant in that we had efficiently and regioselectively provided a handle for further functionalization.

The scope and limitations of this reaction were next explored yielding the results shown in Table 4. The reaction was quite general for a variety of α -substituted cycloalkenones and gave good yields of furan addition products. Some further advancements made by this research are illustrated with example (8a) in Table 4, where almost exclusive monosubstitution of furan was obtained. This required the use of a thirty-fold excess of furan. However, the traditional sulfuric acid catalyzed reaction gave the 2,5-disubstituted furan as the major product even with excess furan present (1). Unfortunately, under identical conditions, example (11b) was not as selective, affording a 1:1 mixture of mono:disubstituted furan. On reaction with 3-bromofuran one compound was exclusively obtained, namely that in which substitution had occurred at the 2-position of the furan.

Table 4. Iodotrimethylsilane mediated additions

R R^1 + Enone^a $\xrightarrow[\text{CH}_2\text{Cl}_2]{\text{TMSI}}$ Adduct^b

Entry	R	R ¹	Enone	% yield enol silyl ether (a)	% yield of ketone (b)
(8)	H	H	1	96 ^c	--
(9)	H	Br	1	100	95
(10)	CH ₃	H	1	100	89
(11)	H	H	2	--	50 ^d
(12)	H	Br	2	75	90
(13)	CH ₃	H	2	--	90
(14)	PhS	H	2	90	--
(15)	H	Br	3	70	95

^aEnone 1 = carvone, 2 = 1-acetylcyclohexene, 3 = 2-methylcyclohexenone.

^bThe adduct is either the β -furyl enol silyl ether or the β -furyl ketone.

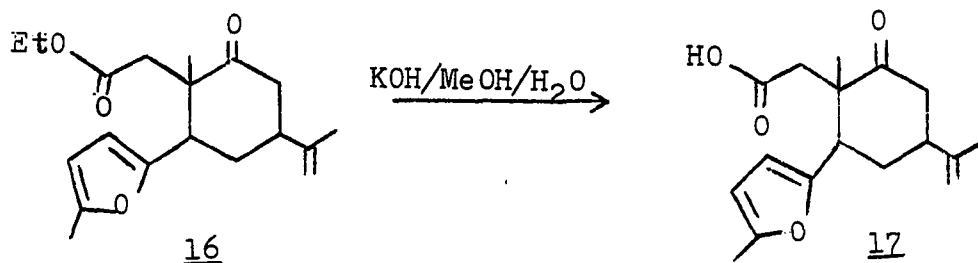
^c4% of a 2:1 enone:furan adduct was also obtained.

^d50% of a 2:1 enone:furan adduct was also obtained.

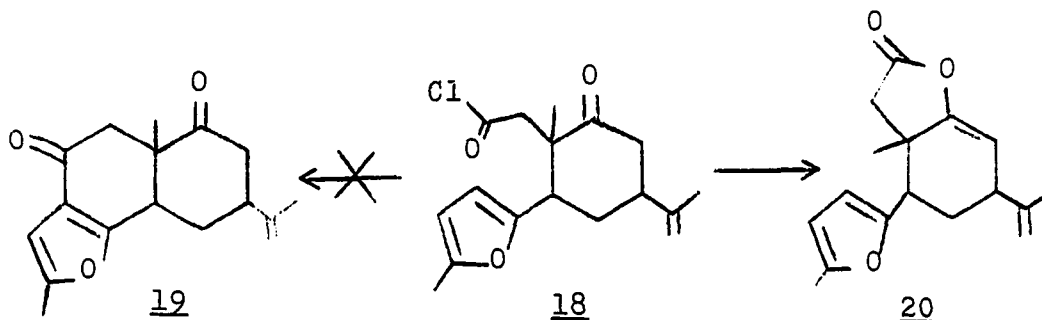
Precedent for this reactivity was established by Gol'dfarb and coworkers (25) who acylated 3-bromofuran and obtained a mixture of 2- and 2,5-disubstituted furans in a ratio of 4:1. Various other studies also noted this directing effect by bromine (5). In our studies using catalytic sulfuric acid, we also obtained both the 2- and the 2,5-substituted furans with the 2-substituted furan predominating. Enones other than l-carvone reacted poorly under the reaction conditions giving only polymeric materials as products. The major difference between these enones was the absence of the isopropenyl substituent of l-carvone. We hypothesized that this unit may be absorbing small amounts of hydrogen iodide which may have formed in the reaction and thereby thwarting acid catalyzed polymerization of the furan. We added one equivalent of 2-methyl-2-butene as an acid scavenger to subsequent reactions and obtained good yields of the desired products.

We now turned our attention toward the attachment of a two-carbon bridge which would give us the 5,6,6-carbocyclic ring system. We were able to regioselectively alkylate the enolate of (9a) formed by the use of fluoride ion as described by Kuwajima and coworkers (26) with ethyl bromoacetate. Saponification of (16) using

Quesada and coworkers' conditions (27) gave us the key intermediate we wished to use in the synthesis. Carboxylic



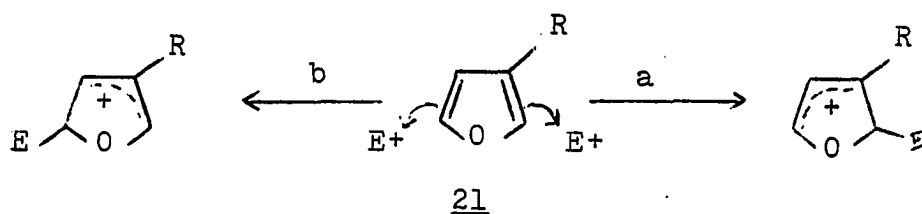
acid (17) was transformed to the acid chloride (28) which was taken directly on to the Friedel-Crafts cyclization with tin(IV) chloride. The small amount of material recovered from the reaction proved to be enol lactone (20).



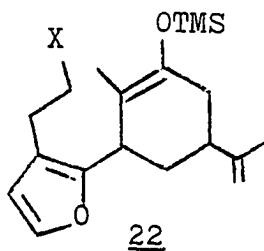
Using trifluoroacetic anhydride as the cyclizing agent gave similar results. Treatment of (17) with polyphosphoric acid resulted in complete destruction of the starting material. The ketonic carbonyl was clearly

adversely affecting our cyclization attempts here. Elimination or protection of this carbonyl would add extra steps to our synthesis. Considering the moderate yield in which we obtained (17)--30% from (19a) we decided not to pursue this sequence any further.

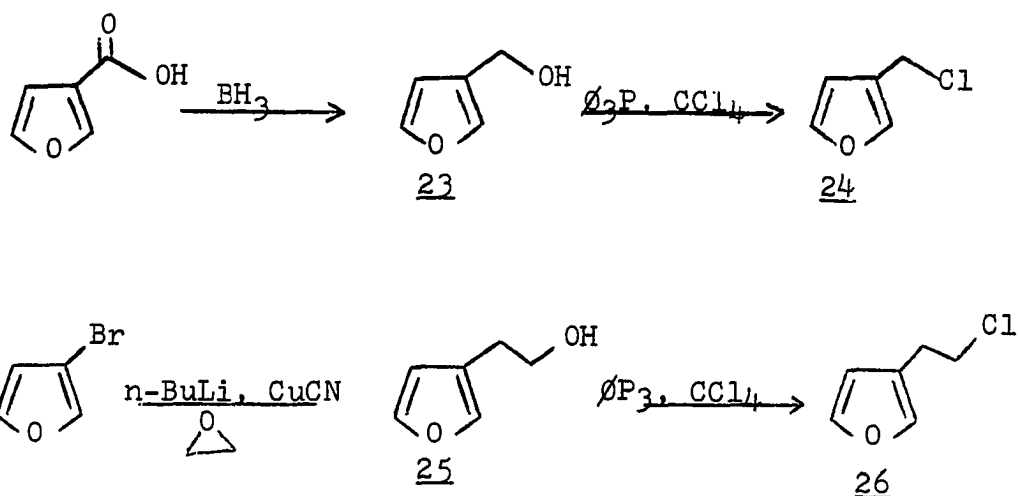
We briefly explored the use of 3-alkyl substituted furans in this reaction. Electrophiles could attack the furan nucleus (21) at either the 2- or the 5-position.



The carbocation resulting from process a would be more stable than that resulting from process b due to the inductive effect of the alkyl group R. Process a should be the lower energy pathway giving rise to 2,3-disubstituted furans. This would be an efficient means of providing the two carbon bridge (e.g. with R being $-\text{CH}_2\text{CH}_2\text{X}$, with X being a leaving group). Compound (22)



would be susceptible to ring closure under Kuwajima's conditions. Since we saw improved regioselective substitution of furan and 3-bromofuran at low temperature, we hoped we could see similar selectivity with the 3-alkylfurans. We synthesized compounds (24) and (26) as shown and subjected them to our normal reaction conditions with 1-carvone. Only 1-carvone could ultimately



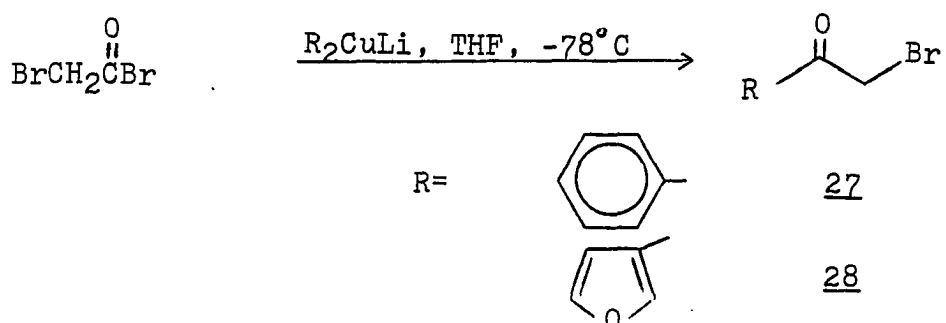
be recovered with no trace of any addition product. We surmised that these particular furans may have been unstable to the reaction conditions.

As an alternative strategy we chose to employ (9a) as the precursor for (22). It was known that 3-bromofuran rapidly underwent metal-halogen exchange with *n*-butyllithium at low temperature (29). Reaction with an appropriate 1,2-biselectrophile would give rise to (22). We were limited as to the nature of the 1,2-biselectrophile in that 3-furyllithium would only react effectively

with hard electrophiles, namely carbonyl compounds (30). Low temperature reaction (-78 C to 0°C) of 3-furyllithium with excess ethyl bromoacetate gave, hence with no surprise, only ethyl bromoacetate as the product. Anion exchange was presumed to be the cause of this failure. The more reactive carbonyl compounds chloroacetyl chloride and bromoacetyl bromide were tried next. The expected product should cyclize very well-based on previous experiments by Roth (31). Infrared analysis of the reaction product of 3-furyllithium with chloroacetyl chloride or bromoacetyl bromide showed no carbonyl absorbance. This was true when the reaction was done either via normal or inverse addition. This was not totally unexpected. Despite inverse addition, alkyl-lithiums react very rapidly with acid halides to yield tertiary alcohols (32). An added complication may be ketene formation (33). We nevertheless subjected (9a) to metal halogen exchange and reaction with chloroacetyl chloride. We conjectured that the steric bulk at the furan 2-position would hinder tertiary alcohol formation. This reaction gave no recognizable products.

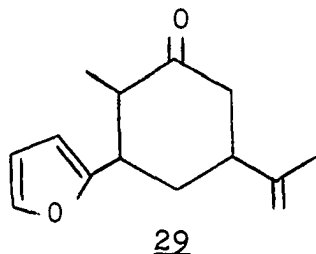
Organocuprates are known to form ketones on reaction with acid halides quite efficiently (34). We decided, therefore, to use the mixed or heterocuprates so as not to waste our starting material. We found no literature examples of a mixed cuprate having a furyllithium as

the transferable ligand. We formed the mixed cuprate using 3-furyllithium and copper(I) cyanide to investigate the reactivity of such a species. Cyanide ion as a non-transferable ligand has been used mainly in higher order cuprates such as $R_2CNCuLi_2$ (35). Using equimolar amounts of alkyllithium and copper(I) cyanide, we formed a complex which was reacted with chloroacetyl chloride. No recognizable products were obtained in this reaction, but we did obtain the desired products with bromoacetyl bromide in good yields. Anion exchange may have been



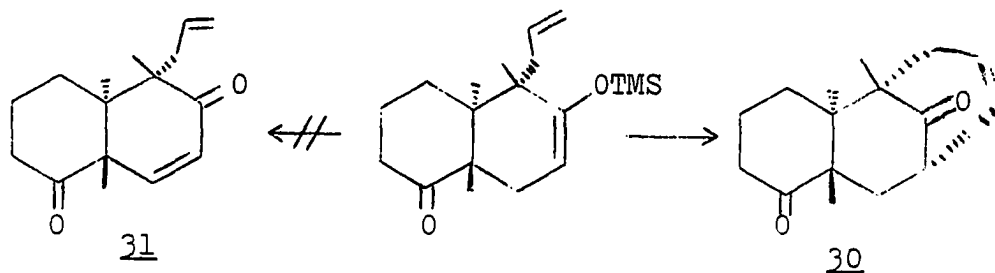
the problem with chloroacetyl chloride. Since bromine is less electronegative than chlorine, the protons in bromoacetyl bromide should be less acidic than those in chloroacetyl chloride. This would favor nucleophilic attack on bromoacetyl bromide as opposed to chloroacetyl chloride. Excited by these results we tried the cuprate reaction using (9a). We never obtained a homogenous

solution of this cuprate. Subsequent reaction with bromoacetyl bromide gave (29), after quenching with aqueous ammonium chloride, as the major product. Use of various coordinating compounds such as dimethyl-

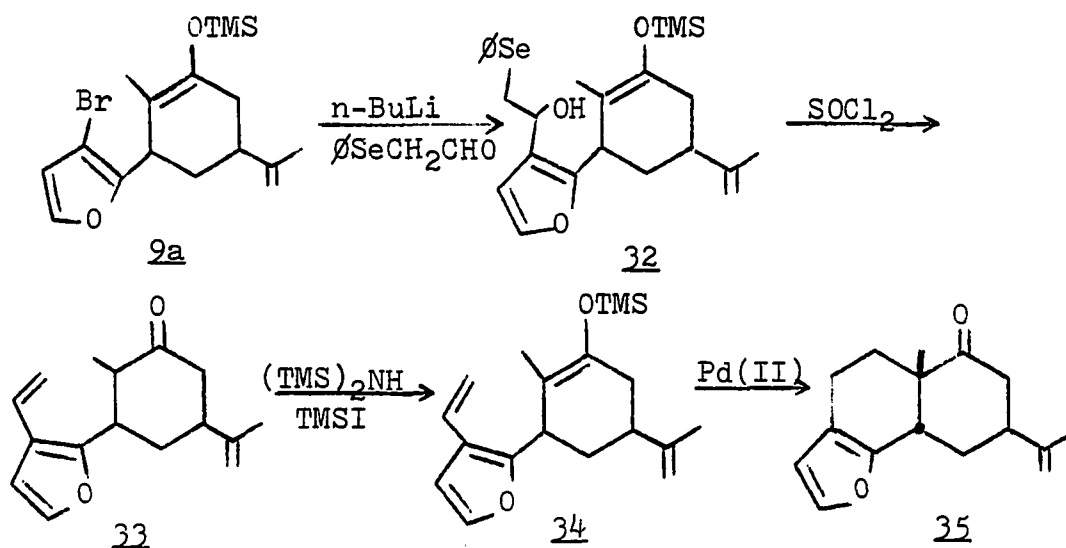


sulfide, hexamethylphosphorous triamide, or hexamethylphosphoric triamide did not promote cuprate solubility and all resultant reactions failed. We felt that either lithiated (9a) may have been too bulky to form an effective complex with copper(I) cyanide or that if the complex did form it was too insoluble to react.

Kende and coworkers (36) recently reported a novel reaction of an olefin with an enol silyl ether mediated by palladium(II) which formed (30) instead of the expected (31). We sought to use this novel reaction in the



cyclization of (20). Vinylfuran (20) was synthesized



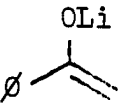
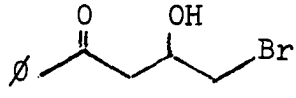

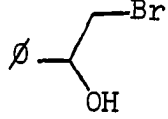
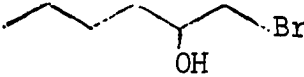
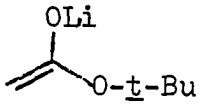
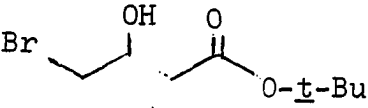
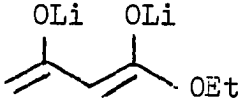
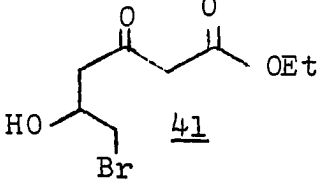
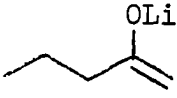
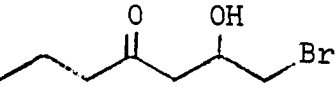
by reaction of the lithiated (9a) with phenylselenoacetaldehyde (37) to give (32). Formation of the vinylfuran with thionyl chloride (38) led also to the hydrolysis of the enol silyl ether which was regenerated. Product (34) was then submitted to palladium(II) mediated cyclization which gave a small amount of unidentifiable residue.

An important piece of information that we gained from the unsuccessful cyclization was that we could react lithiated (9a) with electrophiles and isolate the addition product consistently with the enol silyl ether intact. The optimal conditions for preventing the

hydrolysis of the sensitive enol silyl ether were to run the reaction in diethyl ether and work the reaction up by first diluting with hexane and then washing with brine. We now returned our attention to the development of a suitable 1,2-biselectrophile.

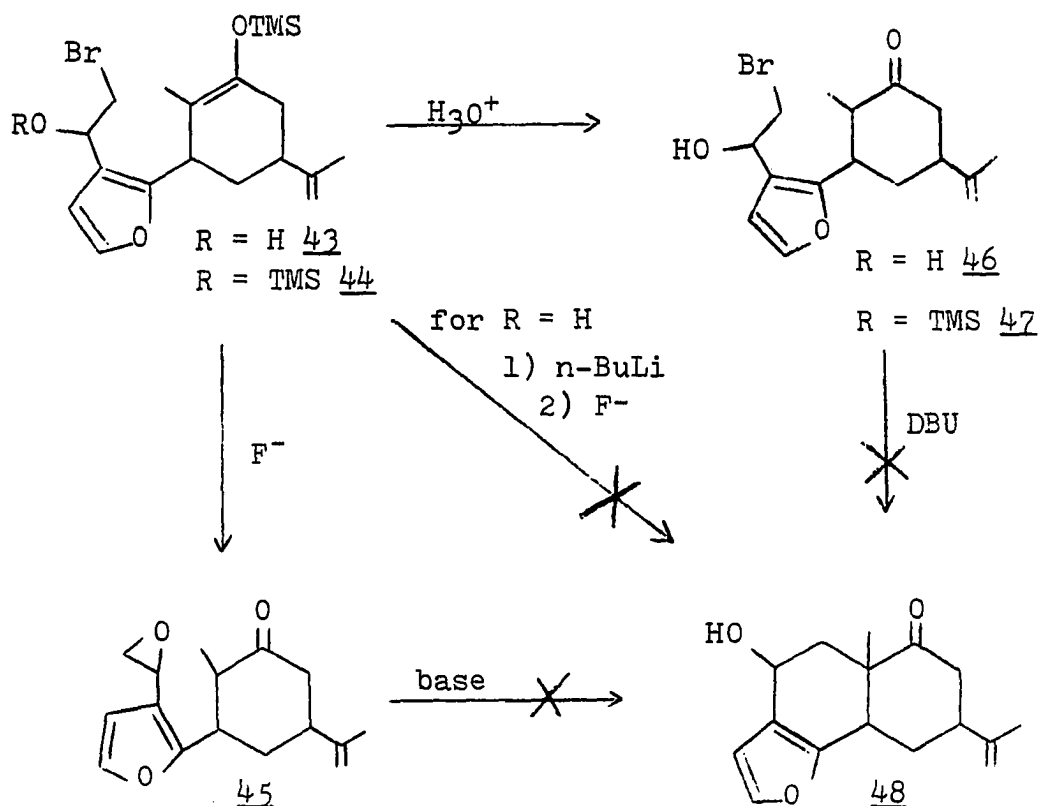
The simplest 1,2-biselectrophile we could envisage which met the previously discussed criteria was a 2-haloacetaldehyde. We thought that the ozonolysis of a 1,4-dihalo-2-butene would be a convenient source of a 2-haloacetaldehyde, since it has been shown that allylic halides undergo normal cleavage reactions with ozone (39). With chloride as the halide, ozonolysis followed by quenching with triphenylphosphine gave after distillation a small amount of 2-chloroacetaldehyde contaminated with a large amount of methylene chloride. Reaction of various alkyllithiums at low temperature with 2-chloroacetaldehyde gave complex mixtures of products. However, ozonolysis of 1,4-dibromo-2-butene led to the formation of 2-bromoacetaldehyde (36) in 50% yield. Methylene chloride was separated more effectively from the higher boiling 2-bromoacetaldehyde. Subsequent reaction with a variety of anions at low temperature gave the bromohydrins in good yields as seen in Table 5. Although 2-bromoacetaldehyde was known in the literature (40), it had never

Table 5. The reaction of anions with 2-bromoacetaldehyde (36)

Anion	Product	% Yield
	 <u>37</u>	100
	 <u>38</u>	100
n-BuLi	 <u>39</u>	60
	 <u>40</u>	82
	 <u>41</u>	85
	 <u>42</u>	60

been synthesized under anhydrous conditions. We felt that 2-bromoacetaldehyde generated in this manner served as a valuable two-carbon electrophile for water-sensitive anions.

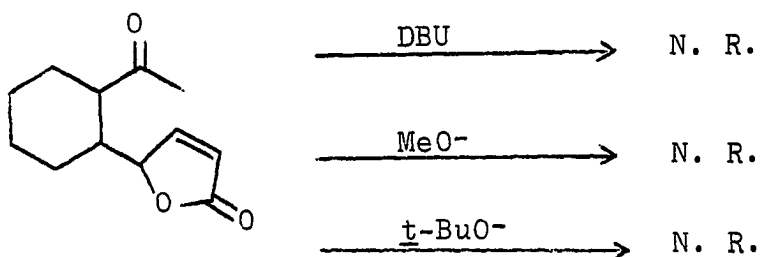
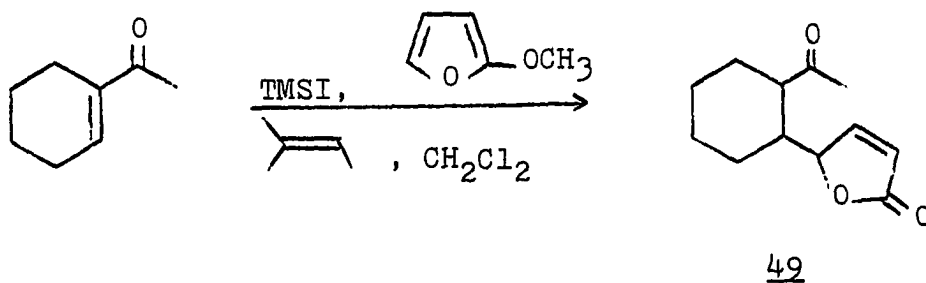
As expected, 2-bromoacetaldehyde reacted smoothly with lithiated (9a) to give bromohydrin (43) quantitatively.



Various attempts were made to cyclize intermediate (43). Epoxide (45) was the only compound obtained by reaction of (43) or (44) with tetrabutylammonium fluoride. Epoxides are known to undergo nucleophilic displacement by enolates,

but neither treatment with 1,8-diazabicyclo[5.4.0.]undec-7-ene in methylene chloride nor treatment with potassium *t*-butoxide in benzene or tetrahydrofuran gave the cyclized product (48). Base treatment of (46) gave no reaction at all.

One other attempt at forming a tricyclic system was made by using (49). It was obtained by the TMSI-promoted reaction of 2-methoxyfuran with 1-acetylcyclohexene. We hoped to effect an intramolecular Michael reaction but obtained either recovered starting material or no recognizable products.



EXPERIMENTAL

General

Diethyl ether and tetrahydrofuran (THF) were distilled from lithium aluminum hydride. Methylene chloride was distilled from P_2O_5 . All reactions were run under a nitrogen atmosphere, and all organic extracts were dried over Na_2SO_4 . Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were determined on a Beckman IR-4250 spectrometer. Nuclear magnetic resonance spectra were determined on a Varian EM-360 instrument for proton or on a Joel FX-90Q for carbon-13 in $CDCl_3$ with absorptions recorded in ppm downfield from internal tetramethylsilane. High resolution mass spectra were recorded on an AEI MS-902 high resolution mass spectrometer. Crystal structures were performed at Ames Laboratory by Dr. James Benson.

2-Methyl-5-(3-oxobutyl)-furan (5)

To a cooled mixture of 10 mmol methyl vinyl ketone and 7.0 mg hydroquinone was added a small drop of a 1:1 mixture of H_2SO_4/H_2O . 2-Methylfuran was added dropwise and the resultant dark orange solution was stirred for 1h. The reaction flask was then fitted with

a short path distillation head and the product was distilled at aspirator pressure (b.p. 56°C, 18 torr). One gram of a clear oil was collected (66%): IR (film) 3120, 2930, 1720, 1575, 1022, 781 cm^{-1} ; NMR (CDCl_3) δ 2.18 (s, 3H), 2.28 (s, 3H), 2.83 (bs, 4H), 5.85 (bs, 2H); carbon-13 NMR (CDCl_3) δ 206.601, 152.365, 150.024, 105.673, 105.478, 41.424, 29.328, 21.978, 13.007.

3-(5-Methyl-2-furyl)-cyclohexan-1-one (6)

The same procedure was used as in the previous synthesis of (5). A colorless oil was obtained in 67% yield: IR (film) 3120, 2960, 1715, 1570, 1225, 780 cm^{-1} ; NMR (CDCl_3) δ 1.40-3.30 (m, 12H), 2.22 (s, 3H), 5.85 (s, 2H); carbon-13 NMR (CDCl_3) δ 209.593, 155.097, 150.350, 105.543, 104.828, 45.456, 40.904, 37.392, 29.718, 24.126, 13.137.

General Procedure for TMSI Mediated Addition of Furans
to Enones

The enone (1.0 mmol) was dissolved in 3 mL dry CH_2Cl_2 and cooled to -78°C while under a nitrogen atmosphere. TMSI (1.05 mmol) was added with stirring and the reaction was allowed to stir 45 min. The furan (1.1 mmol) was added neat or as a 1M solution in CH_2Cl_2 followed by

addition of 2-methyl-2-butene (1.5 mmol for entries 4-9 in Table 3). Stirring was continued at -78°C or -20°C for entries 2, 5, 7, and 9 in Table 3) for 5-6h (36h for entry 2 in Table 3) until IR analysis showed loss of the enone absorbance at 1680 cm^{-1} . The reaction was quenched with triethylamine (1.5 mmol) and warmed to room temperature. The reaction mixture was diluted with hexane and filtered through Celite. The solvent was removed and the residue was again dissolved in hexane and filtered through Celite. A clear filtrate was obtained which gave the enol silyl ether as a yellow oil upon solvent removal. The ketones were formed by acid hydrolysis of the crude enol silyl ethers using 5 mL of 10% aqueous THF containing 1 drop of 2N HCl. The hydrolysis was allowed to proceed for 3-5h. The reaction was diluted with 20 mL diethyl ether and washed once with 5 mL of saturated aqueous NaHCO_3 . The organic was dried (Na_2SO_4). Removal of the solvent gave the following adducts: Adduct (8a) IR (film) 3100, 2980, 1255, 1180, 845 cm^{-1} ; NMR (CDCl_3) δ 0.21 (s, 9H), 1.40-3.00 (m, 11H), 3.40 (m, 1H), 4.72 (bd, 2H), 5.87 (t, 1H), 6.18 (bs, 1H), 7.22 (bs, 1H). Adduct (9a) IR (film) 3085, 2970, 1250, 1185, 840 cm^{-1} ; NMR (CDCl_3) δ 0.20 (s, 9H), 1.43 (bs, 3H), 1.5-3.0 (m, 11H), 1.70 (bs, 3H), 3.50 (bt, 1H), 4.62 (bs, 2H),

6.28 (d, 1H), 7.18 (d, 1H); high resolution mass spectrum for $C_{17}H_{25}BrO_2Si$ requires m/e 368.08072, found m/e 368.08168. Adduct (9b) NMR ($CDCl_3$) δ 0.90 (d, 3H), 1.73 (d, 3H), 1.9-2.3 (m, 3H), 2.30-3.00 (m, 3H), 3.68 (m, 1H), 4.70 (bs, 2H), 6.25 (d, 1H), 7.20 (dd, 1H ($J = 2Hz, 2Hz$)); low resolution mass spectrum for $C_{14}H_{17}BrO_2$ requires m/e 296, found m/e 296. Adduct (10a) IR (film) 3080, 2980, 1250, 1180, 840 cm^{-1} ; NMR ($CDCl_3$) δ 0.22 (s, 9H), 1.5-1.9 (m, 8H), 2.1 (m, 1H), 2.23 (s, 3H), 2.3-2.8 (m, 2H), 3.35 (bt, 1H), 4.67 (bd, 2H), 5.78 (d, 2H). Adduct (10b) NMR ($CDCl_3$) δ 1.03 (d, 3H), 1.70 (bs, 3H), 2.0-3.0 (m, 7H), 2.20 (d, 3H), 4.67 (bs, 2H), 5.78 (d, 2H). Adduct (11b) IR (film) 3085, 2985, 1715, 840 cm^{-1} ; NMR ($CDCl_3$) δ 1.10-2.30 (m, 8H), 2.00 (s, 3H), 2.70 (m, 1H), 3.30 (m, 1H), 5.80 (m, 2H). Adduct (12b) IR (film) 2940, 1715, 1250 cm^{-1} ; NMR ($CDCl_3$) δ 1.20-1.90 (m, 9H), 1.95 (d, 3H), 2.90 (m, 1H), 6.23 (d, 1H), 7.16 (d, 1H). Adduct (13b) IR (film) 3120, 2940, 1710, 1000, 840 cm^{-1} ; NMR ($CDCl_3$) δ 1.32-2.00 (m, 8H), 2.03 (s, 3H), 2.20 (s, 3H), 2.73 (m, 1H), 3.30 (m, 1H), 5.70 (bs, 2H); high resolution mass spectrum for $C_{13}H_{18}O_2$ requires m/e 206.13068, found m/e 206.13010. Adduct (14a) IR (film) 3060, 2920, 1240, 1000, 830 cm^{-1} ; NMR ($CDCl_3$) δ 0.20 (s, 9H), 1.0-2.2 (m, 11H), 2.50 (m, 1H), 5.69 (d, 1H),

6.38 (t, 1H), 6.90 (s, 5H). Adduct (15b) NMR (CDCl₃)
δ 0.86 (d, 3H), 1.60-3.00 (m, 7H), 6.33 (d, 1H), 7.30 (d, 1H).

1-Methyl-2-(5-methyl-2-furyl)-4-(1-methylethenyl)-6-oxo-
cyclohexaneacetic Acid (17)

To 4 mL dry THF under a nitrogen atmosphere was added 1 g of molecular sieves (4 Å) followed by the addition of solid benzyltrimethylammonium fluoride (1.3 mmol). This mixture was stirred 8-10h at room temperature. The enol silyl ether (10a) (1.0 mmol) was added as a 1M solution in THF followed by addition of neat ethyl bromoacetate (1.1 mmol). The mixture was stirred 12h at room temperature, diluted with 5 mL diethyl ether, and filtered through Celite. Evaporation of the solvent gave a crude product which was placed under vacuum several hours to remove excess ethyl bromoacetate. The resultant viscous yellow oil was dissolved in 1 mL methanol. To this solution was added 1 mL of a 1M KOH solution with stirring. Stirring was continued at room temperature for 5h. The methanol was removed in vacuo and the residue was diluted with 10 mL brine and extracted 3 times with 15 mL portions of diethyl ether. The ether extracts were combined and extracted 3 times with 5 mL portions of 1N NaOH. The aqueous extracts were combined,

acidified with 6N HCl to pH 2-3, saturated with brine, and extracted 3 times with 10 mL portions of diethyl ether. The ether extracts were combined and dried (Na_2SO_4). The product was obtained as a viscous yellow oil (31%): NMR (CDCl_3) δ 1.10 (bs, 3H), 1.72 (bs, 3H), 1.80-3.50 (m, 11H), 2.27 (bs, 3H), 4.75 (bs, 2H), 5.85 (m, 2H), 10.32 (bs, 1H); Low resolution mass spectrum for $\text{C}_{17}\text{H}_{22}\text{O}_4$ requires m/e 290, found m/e 290.

1-Methyl-2-furyl-4-(1-methylethenyl)-6-oxo-cyclohexane
Acetyl Chloride (18)

To the carboxylic acid (17) (0.46 mmol) dissolved in 1mL freshly distilled acetonitrile was added carbon tetrachloride (1.84 mmol) followed by triphenylphosphine (0.51 mmol). Stirring was continued at room temperature for 6-7h. Analysis of an aliquot of the reaction solution by infrared spectroscopy revealed loss of the hydroxyl and the presence of the acid chloride carbonyl at 1780 cm^{-1} . The reaction was diluted with diethyl ether and filtered through Celite. The solvent was removed in vacuo and the crude residue was used directly in the next reaction.

Attempted Synthesis of Tricyclic Adduct (19)

The crude acid chloride (0.46 mmol) was dissolved in 10 mL methylene chloride and cooled to 0°C under a nitrogen atmosphere. Tin(IV) chloride was added dropwise and the reaction was allowed to stir 0.5h at 0°C. Analysis by TLC (silica gel, ether:hexane 1:1) showed only one spot at the origin. The reaction was quenched with 2 mL of 5M K₂CO₃ and diluted with diethyl ether. The organic layer was separated and dried over Na₂SO₄. Analysis of the residue left after removal of solvent revealed nothing recognizable in the NMR spectrum.

Alternate Attempted Synthesis of Tricyclic Adduct (19)

The carboxylic acid (17) (0.45 mmol) was dissolved in 4.5 mL CH₂Cl₂ and cooled to -20°C. Trifluoroacetic anhydride (0.5 mmol) was added dropwise with stirring. TLC analysis (silica gel, diethyl ether:hexane 1:1) of the reaction revealed the appearance of a new spot (R_f = 0.64) after 0.5h. Stirring was continued for 3h more with no apparent change in the TLC. The reaction was quenched with saturated aqueous NaHCO₃ and extracted 3 times with 5 mL portions of diethyl ether. The ether extracts were combined and dried with MgSO₄. Removal of

the solvent left a yellow oil which was assigned the structure (20): IR (film) 3080, 2940, 1800, 1720, 1220 900, 780, 725 cm^{-1} ; NMR (CDCl_3) δ 1.15 (bs, 3H), 2.28 (s, 3H), 1.5-3.5 (m, 12H), 4.30 (bs, 1H), 4.75 (m, 2H), 5.83 (bs, 2H); low resolution mass spectrum for $\text{C}_{17}\text{H}_{20}\text{O}_3$ requires m/e 272, found m/e 272.

3-Hydroxymethylfuran (23)

3-Furoic acid (50 mmol) was dissolved in 100 mL THF. The solution was cooled to 0°C and 50 mL of 1M BH_3 in THF was added dropwise. After the addition, the reaction was warmed to room temperature, and stirred for 24h. The reaction cooled to 0°C and quenched with 30 mL water followed by the addition of solid K_2CO_3 (11g). The resultant mixture was extracted three times with 75 mL diethyl ether and dried (Na_2SO_4). Removal of the solvent gave the desired product in 95% yield: NMR (CDCl_3) δ 2.85 (bs, 1H), 4.48 (bs, 2H), 6.41 (d, 1H), 7.42 (d, 2H).

3-Chloromethylfuran (24)

N-Chlorosuccinimide (7.5 mmol) was ground into a powder and dissolved in 25 mL of CH_2Cl_2 . The solution was cooled to 0°C and $(\text{CH}_3)_2\text{S}$ (9.0 mmol) was added over

3 min. A yellow suspension formed which was cooled to -20°C . 3-Hydroxymethylfuran (5 mmol) was added as a 2M solution in CH_2Cl_2 over 3 min. The reaction was then warmed to 0°C and stirring was continued for 2h. The reaction was then diluted with hexane (50 mL) and poured into ice water. The organic layer was separated, washed once with brine and dried (Na_2SO_4). Removal of the solvent gave the product in 55% yield: IR (film) 3150, 2960, 1040, 875 cm^{-1} ; NMR (CDCl_3) δ 4.41 (s, 2H), 6.35 (d, 1H), 7.32 (bs, 2H).

2-(3-Furyl)-ethanol (25)

To a solution of *n*-BuLi (13.6 mmol) in 8 mL dry THF at -78°C was added a 2M solution of 3-bromofuran in THF. The resultant solution was stirred 15 min and then transferred via cannula to a suspension of CuI (6.4 mmol) and $(\text{CH}_3)_2\text{S}$ (13.6 mmol) in 8 mL THF at -40°C . After 15 min, ethylene oxide (10 mmol) was added at once. The reaction was protected from light by covering with aluminum foil and was allowed to warm to room temperature overnight. The reaction was quenched with 15 mL saturated aqueous NH_4Cl and extracted 3 times with 25 mL of diethyl ether. The combined ether extracts were washed twice with brine and dried over Na_2SO_4 . The product was obtained in

quantitative yield after removal of the solvent: NMR (CDCl_3)
 δ 2.05 (bs, 1H), 2.63 (t, 2H), 3.73 (t, 2H), 6.22 (bs, 1H),
7.26 (m, 2H).

2-(3-Furyl)-1-chloroethane (26)

The alcohol (25) (8.6 mmol) was dissolved in 8 mL
 CCl_4 . Triphenylphosphine (11.2 mmol) was added, and the
reaction was refluxed for 1h. After cooling to room
temperature the dark solution was diluted with hexane (25 mL)
and filtered through Celite. Removal of solvent gave
the desired product in 55% yield: NMR (CDCl_3) δ 2.82 (t,
2H), 3.60 (t, 2H), 6.21 (bs, 1H), 7.25 (m, 2H).

Bromomethyl-3-furylketone (27)

To a dry 3-neck 25 mL flask containing CuCN (2.2 mmol)
was added 1 mL toluene. The solvent was then removed
under vacuum to azeotropically remove any water adsorbed
on the CuCN. After removal of the solvent, a nitrogen
atmosphere was introduced and THF (3 mL) and $(\text{CH}_3)_2\text{S}$
(4.0 mmol) were added sequentially, and the mixture
was cooled to -78°C . In a separate flask, $n\text{-BuLi}$ (2.2
mmol) was added to 1 mL dry THF at -78°C . A 1M solution
of 3-bromofuran (2.0 mmol) in THF was added dropwise and
then stirred at -78°C for 10 min. The resultant solution

of 3-furyllithium was transferred to the CuCN mixture via cannula. Stirring was continued an additional 45 min at -78°C while protecting the reaction from light by covering the flask with aluminum foil. Bromoacetyl bromide (2.2 mmol) was added rapidly to the clear tan solution, The reaction was allowed to warm to 0°C over 2h. The reaction was quenched with 10 mL saturated aqueous NH_4Cl and extracted three times with 10 mL portions of diethyl ether. The ether extracts were combined, washed once with saturated aqueous NaHCO_3 and dried (Na_2SO_4). Evaporation of solvent gave a yellow oil in 85% yield: IR (film) 3150, 1675, 1160, 870 cm^{-1} ; NMR (CDCl_3) δ 4.20 (s, 2H), 6.73 (d, 1H), 7.41 (dd, 1H (J = 2Hz, 1Hz)), 8.10 (d, 1H).

Phenacylbromide (28)

The preceding procedure was employed using a commercial solution of phenyllithium in cyclohexane (1.9M, 1.05 mL): NMR (CDCl_3) δ 4.63 (s, 2H), 7.45 (m, 3H), 7.88 (m, 2H).

1-Trimethylsilyloxy-2-methyl-3-(3-(1-hydroxy-2-phenyl-selenenyl ethyl)-2-furyl)-5-(1-methylethenyl)-1-cyclohexene (32)

A 1M diethyl ether solution of enol silyl ether (9a)

(1.0 mmol) was added dropwise to a solution of n-Buli (1.62M in hexane, 0.7 mL) in 2 mL diethyl ether at -78°C . After stirring 15 min a 1M diethyl ether solution of phenylselenoacetaldehyde (1.0 mmol) was added dropwise. The reaction was stirred 15 min at -78°C then warmed to 0°C , quenched with brine (5 mL) and diluted with hexane (5 mL). The organic phase was separated and dried (Na_2SO_4). Removal of solvent left a yellow oil which showed no carbonyl absorption with infrared analysis. The crude material (quantitative recovery) was taken on to the next step: IR (film) 3440, 3090, 2960, 1255, 1175, 845 cm^{-1} .

2-Methyl-3-(3-vinyl-2-furyl)-5-(1-methylethenyl)-1-cyclohexanone (33)

The hydroxyselenide (32) (1.0 mmol) was dissolved in 2 mL CH_2Cl_2 under a nitrogen atmosphere. The solution was cooled in a water bath at 15°C , and triethylamine (7.0 mmol) was added with stirring followed by slow addition of SOCl_2 (1.1 mmol) in 1.5 mL CH_2Cl_2 . The reaction was stirred for 30 min and then poured into saturated aqueous NaHCO_3 (5 mL). This mixture was extracted three times with 10 mL diethyl ether. These extracts were combined and dried (Na_2SO_4) while stirring with a small amount of activated charcoal. Filtration through Celite and

removal of solvent left a yellow oil which was purified by silica gel chromatography eluting first with hexane to remove the diphenyldiselenide formed and then eluting with diethyl ether. The product was isolated in 97% yield: NMR (CDCl₃) δ 0.83 (d, 3H), 1.82 (bs, 3H), 1.9-2.4 (3H, m), 2.4-3.0 (3H, m), 3.6 (m, 1H), 4.72 (bs, 2H), 5.0 (m, 1H), 5.2 (m, 1H), 5.5 (m, 1H), 6.45 (d, 1H), 7.27 (d, 1H).

1-Trimethylsilyloxy-2-methyl-3-(3-vinyl-2-furyl)-5-(1-methyl-ethenyl)-1-cyclohexene (34)

Ketone (33) (0.97 mmol) was dissolved in 20 mL CH₂Cl₂ under a nitrogen atmosphere, and cooled to -20°C. Hexamethyldisilazane (1.2 mmol) was added with stirring followed by TMSI (1.1 mmol). The reaction was allowed to warm slowly to room temperature. After stirring a total of 5-6h, the reaction was diluted with hexane (30 mL), washed once with saturated aqueous NaHCO₃ (5 mL) and once with brine (5 mL). The organic phase was dried over Na₂SO₄ mixed with a little K₂CO₃. Removal of the solvent left 0.89 mmol of crude product: NMR (CDCl₃) δ 0.2 (s, 9H), 1.48 (bs, 3H), 1.66 (bs, 3H), 1.5-2.5 (m, 5H), 3.50 (m, 1H), 4.65 (bs, 2H), 4.90 (d, 1H), 5.13 (m, 1H), 5.42 (d, 1H), 6.45 (d, 1H), 7.20 (d, 1H).

Attempted Formation of Tricyclic Compound (35)

To a suspension of Pd(OAc)₂ (0.76 mmol) in 6.0 mL of freshly distilled CH₃CN was added a solution of enol silyl ether (34) (0.76 mmol) in 2 mL of CH₂Cl₂/CH₃CN (1:1) at room temperature. Stirring was continued for 24h whereupon TLC analysis (silica gel, hexane:diethyl ether 2:1) showed the disappearance of starting material and the presence of a new compound (R_f=0.70). The solvent was removed in vacuo and the residue was washed with 10 mL diethyl ether. The ether solution was washed once with ice cold 1N HCl (2 mL), once with saturated aqueous NaHCO₃ (2 mL) and dried over Na₂SO₄. Removal of solvent left a small amount of residue which was unidentifiable by NMR analysis.

2-Bromoacetaldehyde (36)

A solution of 1,4-dibromo-trans-2-butene (40 mmol) in 60-70 mL CH₂Cl₂ was cooled to -78° C and treated with ozone until a blue color persisted (ca. 30 min). A nitrogen stream was passed through the solution until the blue color disappeared, giving a colorless solution. After a dried magnetic stirring bar was added to the flask, 40 mmol triphenylphosphine was added portionwise over 1 h while keeping the temperature at -78° C. After

the addition of triphenylphosphine, the solution was slowly warmed to 0°C. An aliquot of the slightly yellow solution was checked by NMR for the absence of ozonide. If the ozonide is still present (m, 3.5-4.0 δ) stirring was continued at 0°C until the reaction was complete. Methylene chloride was distilled off at 0°C at 90-100 mm Hg. The residue was then distilled at 1 mm Hg into a receiving flask which was cooled to -20°C. As the residue became viscous, it was heated with an oil bath at 50°C. Distillation yielded 11.26 g (56%) of 2-bromoacetaldehyde and methylene chloride (1:1.5). This solution was diluted with THF to a known molarity and stored under nitrogen in the freezer. Caution--the aldehyde is a lachrymator IR (film) 1728 cm^{-1} ; NMR (CDCl_3) δ 3.88 (d, 2H), 5.32 (s, CH_2Cl_2), 9.55 (t, 1H).

4-Bromo-3-hydroxy-1-phenyl-butan-1-one (37)

A solution of diisopropylamine (1.1 mmol) in THF was cooled to 0°C and *n*-BuLi (2.2M solution in hexane, 1 mL) was added dropwise. The reaction was stirred for 10 min after which it was cooled to -78°C. To this LDA solution was added a 1M THF solution of acetophenone (1.0 mmol). After stirring for 30 min a 1M THF solution

of 2-bromoacetaldehyde was added all at once. The reaction was stirred 15 min, then quenched with acetic acid (2.2 mmol). After diluting with water, the mixture was extracted three times with 10 mL portions of diethyl ether. The organic extracts were pooled and dried (Na_2SO_4). Removal of the solvent gave a yellow oil (100%) IR (TMS derivative, film) 3080, 2970, 1690, 1300, 840, 750, 685 cm^{-1} ; NMR (TMS derivative, CDCl_3) δ 0.10 (s, 9H), 3.15 (d, 2H), 3.37 (d, 2H), 3.42 (p, 1H), 7.35 (m, 3H), 7.83 (m, 2H).

(2-Bromo-1-hydroxy-ethyl)-benzene (38)

A commercial solution of phenyllithium (2.2M in cyclohexane, 1.1 mL) was added to THF and cooled to -78°C . The experimental procedure was continued as in the synthesis of bromohydrin (37). The product was obtained as a yellow oil (100%) IR (film) 3400, 1063, 755, 700 cm^{-1} ; NMR (CDCl_3) δ 3.5 (dd, 2H ($J = 6, 7$ Hz)), 4.07 (bs, 1H), 4.77 (dd, 1H ($J = 2.5, 2.5$ Hz)), 7.25 (s, 5H); high-resolution mass spectrum for $\text{C}_8\text{H}_9\text{BrO}$ requires m/e 199.98368, found m/e 199.98437.

1-Bromo-2-hexanol (39)

A commercial solution of n -BuLi (2.2M, 1.1 mL)

was used in a procedure analogous to that used in the synthesis of (38). The product was isolated as a clear oil (60%) IR (film) 3500, 2960, 2930, 2870, 1030 cm^{-1} ; NMR (CDCl_3) δ 0.90 (bt, 3H), 1.43 (m, 6H), 2.39 (bs, 1H), 3.49 (d, 2H), 3.63 (m, 1H); high-resolution mass spectrum of $\text{C}_8\text{H}_{18}\text{BrSiO}$ (TMS derivative - CH_3) requires m/e 237.03103, found m/e 237.03134.

t-Butyl-4-bromo-3-hydroxy-butyrate (40)

t-Butyl acetate was reacted with 2-bromoacetaldehyde in an analogous procedure as in the synthesis of bromohydrin (37). The product was obtained as a yellow oil (82%) IR (film) 3380, 2900, 1730 cm^{-1} ; NMR (CDCl_3) δ 1.47 (s, 9H), 2.53 (dd, 2H ($J = 6.0, 6.5$ Hz)), 3.48 (d, 2H), 4.16 (bp, 1H); high-resolution mass spectrum for $\text{C}_7\text{H}_{12}\text{BrO}_3$ (P - CH_3) requires m/e 222.99748, found m/e 222.99697.

Ethyl 6-bromo-5-hydroxy-3-oxo-hexanoate (41)

The analogous procedure used in the synthesis of (37) was used in the reaction of ethyl acetoacetate with 2-bromoacetaldehyde except that two equivalents of LDA and a reaction temperature of 0°C were required. The

product was obtained as a viscous yellow oil (85%)
 IR (film) 3460, 2980, 1735, 1715 cm^{-1} ; NMR (CDCl_3) δ
 1.26 (t, 3H), 2.80 (d, 2H), 3.40 (d, 2H), 3.47 (s, 2H),
 4.13 (q superimposed on m, 4H); high-resolution mass
 spectrum for $\text{C}_8\text{H}_{11}\text{BrO}_3$ (P - H_2O) requires m/e 234.98915,
 found m/e 234.98950.

1-Bromo-2-hydroxy-4-heptanone (42)

2-Pentanone was reacted with 2-bromoacetaldehyde
 in an analogous manner as in the synthesis of bromo-
 hydrin (37). The product was isolated as a clear oil
 (60%) IR (film) 3430, 2980, 1715 cm^{-1} ; NMR (CDCl_3) δ
 0.92 (bt, 3H), 1.52 (m, 2H), 2.48 (m, 4H), 3.43 (d, 2H),
 4.00 (bm, 1H); high-resolution mass spectrum for $\text{C}_4\text{H}_6\text{BrO}_2$
 (P - $\text{CH}_2\text{CH}_2\text{CH}_3$) requires m/e 164.95511, found m/e 164.95467.

1-Trimethylsilyloxy-2-methyl-3-(3-(1-hydroxy-2-bromoethyl)-
 2-furyl)-5-(1-methylethenyl)-1-cyclohexene (43)

To a cooled solution (-78°C) of $n\text{-BuLi}$ (2.1M, 0.52 mL)
 in 2 mL diethyl ether was added dropwise a 1M solution
 of enol silyl ether (9b) (1.0 mmol) in diethyl ether.
 The solution was stirred for 15 min. A solution of 2-bromo-
 acetaldehyde in THF (1M, 1.1 mL) was added rapidly and
 stirring was continued at -78°C for 10 min. The reaction

was warmed to 0°C, diluted with 15 mL hexane, and washed twice with 5 mL portions of brine. The organic portion was then dried (Na₂SO₄). Removal of solvent gave a yellow oil in 95% yield: IR (film) 3440, 3100, 2980, 1715, 1255, 840 cm⁻¹; NMR (CDCl₃) δ 0.20 (s, 9H), 1.42 (bs, 3H), 1.67 (bs, 3H), 1.7-3.0 (m, 5H), 3.50 (m, 3H), 4.63 (bs, 2H), 4.90 (m, 1H), 6.26 (d, 1H), 7.17 (d, 1H).

2-Methyl-3-(3-(1-hydroxy-2-bromoethyl)-2-furyl)-5-(1-methylethenyl)-cyclohexan-1-one (46)

Compound (43) (1.0 mmol) was dissolved 5 mL of 10% aqueous THF. One drop of 2N HCl was added and the reaction was stirred 3-4h at room temperature. The reaction was then diluted with diethyl ether (20 mL) and washed once with saturated aqueous NaHCO₃ (5 mL). The organic layer was dried over Na₂SO₄. Removal of solvent gave the product as a yellow oil in 95% yield. NMR (CDCl₃) δ 0.85 (d, 3H), 1.68 (bs, 3H), 1.70-2.30 (m, 3H), 2.30-3.20 (m, 4H), 3.50 (d, 2H), 4.67 (bs, 2H), 4.82 (m, 1H), 6.25 (d, 1H), 7.15 (d, 1H).

2-Methyl-3-(3-(1-trimethylsilyloxy-2-bromoethyl)-2-furyl)-5-(1-methylethenyl)-cyclohexan-1-one (47)

Compound (46) was dissolved in 1 mL CH₂Cl₂ and

cooled to 0°C. To this stirring solution was added Et₃N (1.2 mmol) followed by TMSCl (1.1 mmol). Stirring was continued, and the reaction was allowed to warm to room temperature over several hours. The reaction was diluted with hexane (20 mL) and filtered through Celite. The filtrate was concentrated to give the product in 95% yield: IR (film) 3100, 2980, 1715, 1255, 845 cm⁻¹; NMR (CDCl₃) δ 0.10 (s, 9H), 0.85 (d, 3H), 1.70 (bs, 3H), 1.80-2.30 (m, 3H), 2.30-2.90 (m, 4H), 3.38 (dd, 2H (J= 6 Hz, 7 Hz)), 4.72 (bs, 2H), 4.88 (m, 1H), 6.25 (d, 1H), 7.20 (d, 1H).

Attempted Formation of Tricyclic Adduct (48)

Method A: Bromohydrin (43) or (44) was treated with benzyltrimethylammonium fluoride in the same manner as in the synthesis of (16). Although not purified, the major product seemed to be epoxide (45) by NMR analysis.

Resonances at 3.05 and 3.65 ppm were indicative of a terminal epoxide: IR (film) 2960, 1710, 1450, 845 cm⁻¹; NMR (CDCl₃) δ 0.87 (d, 3H), 1.70 (bs, 3H), 2.10 (m, 3H), 2.70 (m, 5H), 3.05 (t, 1H), 3.65 (q, 1H), 4.70 (bs, 2H), 6.07 (d, 1H), 7.15 (d, 1H).

Method B: Bromohydrin (43) (0.47 mmol) was dissolved in 1 mL THF and cooled to 0°C. A solution of *n*-BuLi

(2.14M, 0.22 mL) was added dropwise and allowed to stir 5 min. This solution was then transferred via cannula to a mixture of benzyltrimethylammonium fluoride (0.61 mmol) and molecular sieves (0.5 g) in 3 mL THF. The reaction was stirred overnight and worked up analogously as in the synthesis of (14). Removal of the solvent gave a yellow oil having a very complex spectrum.

Method C: Ketone (46) (0.36 mmol) was dissolved in 5 mL CH_2Cl_2 and cooled to 0°C . 1,8-Diazabicyclo-[5.4.0]undec-7-ene (0.36 mmol) was added dropwise, and the reaction was allowed to warm to room temperature overnight. No change was observed with TLC analysis (silica gel, hexane:diethyl ether 2:1, $R_f = 0.45$). The reaction was diluted with 15 mL diethyl ether and filtered through Celite. Removal of the solvent gave a yellow oil which proved to be starting material by NMR analysis.

Method D: The crude epoxide (45) (0.36 mmol) was dissolved in 5 mL THF in a flask fitted with a reflux condenser. The solid complex of t-butanol/potassium t-butoxide (1:1) (0.4 mmol) was added with stirring, and the reaction was brought to reflux. Heating was continued for 2.5h. Analysis by TLC (silica gel, hexane:

diethyl ether 1:1) showed most of the material to be at the origin. The reaction was cooled, diluted with diethyl ether (15 mL), washed with brine (5 mL), and dried (Na_2SO_4). Removal of the solvent gave a viscous yellow oil which showed nothing recognizable based on NMR analysis.

1-Acetyl-2-(4-(2,3-dehydro)-butyrolactone)-cyclohexane (49)

This compound was formed by the reaction of 2-methoxyfuran and 1-acetylcyclohexene using the general procedure outlined in the synthesis of compounds (8 - 15): IR (film) 2940, 1760, 1715, 1300, 850 cm^{-1} ; NMR (CDCl_3) δ 1.00-2.10 (m, 9H), 2.80 (m, 1H), 5.32 (m, 1H), 6.05 (d, 1H), 7.43 (d, 1H).

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PART II: PREPARATION OF β -HYDROXY- γ -LACTONES

INTRODUCTION

A convenient preparation of β -hydroxy- γ -lactones will be described. This unit is not only found in a wide variety of natural products, but also serves as a synthon for furans.

HISTORICAL

Little work had been done in developing synthetic procedures for β -hydroxybutyrolactones until compounds containing this unit were recently isolated from natural sources. Some examples of these compounds are shown in Figure 1.

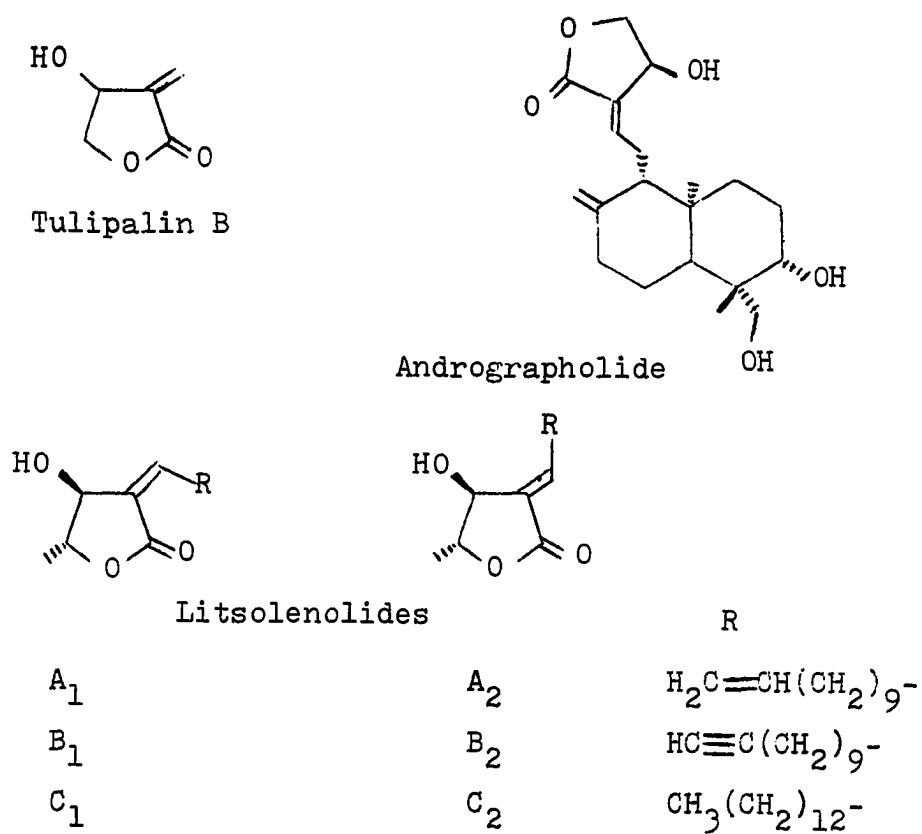
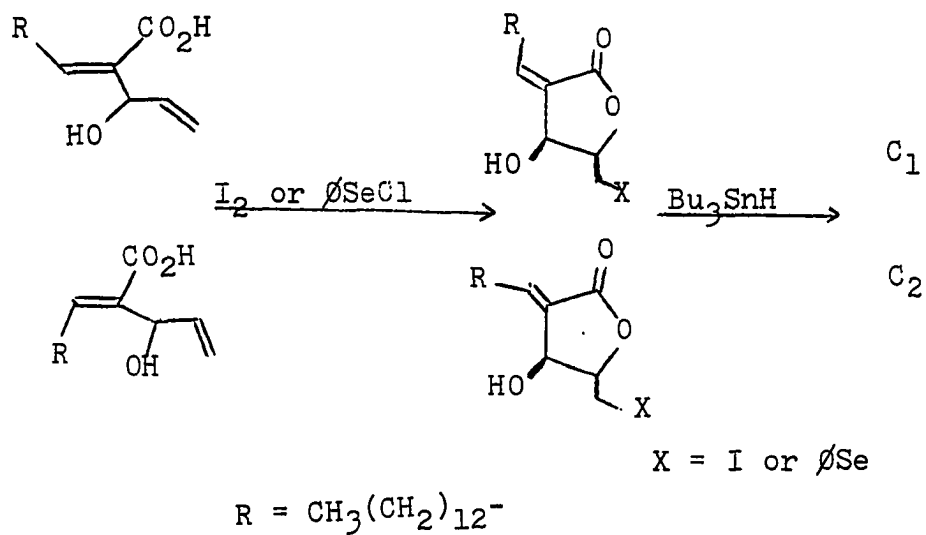
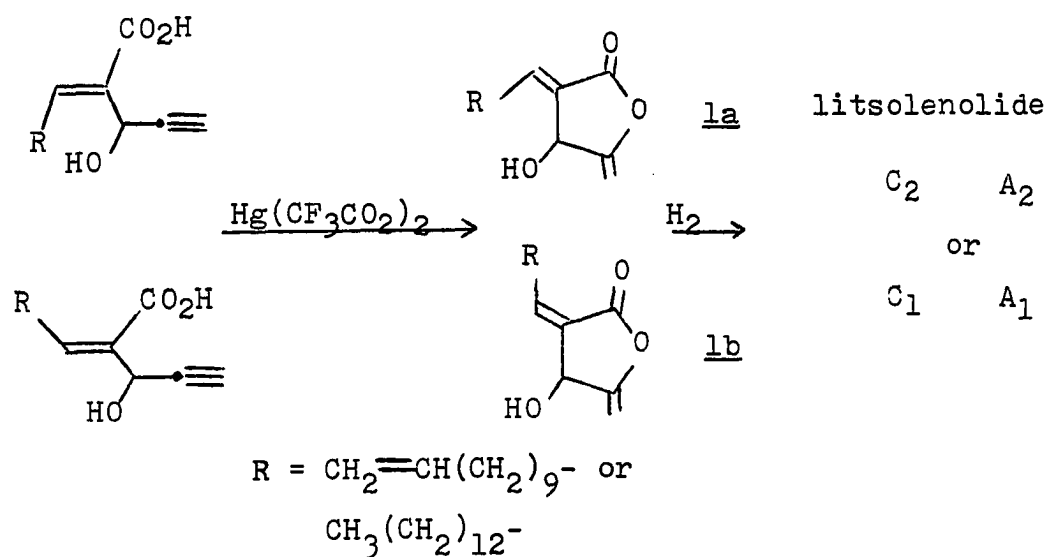
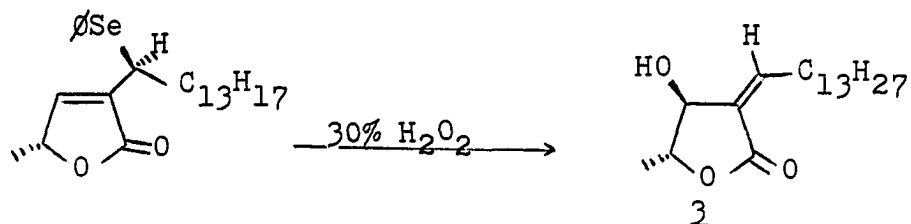


Figure 1. Natural Hydroxy Lactones

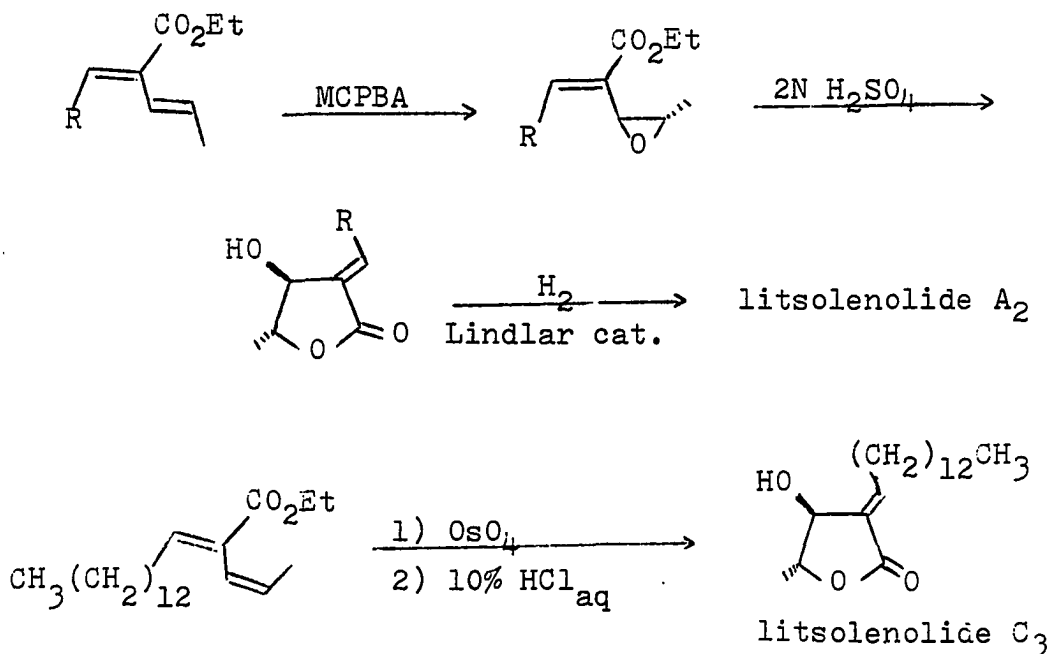
The majority of the work focused on the synthesis of litsolenolides. Rollinson and coworkers (1) have utilized an oxymercuration or iodolactonization strategy for the formation of the hydroxylactones (1a,b) and (2a,b). Wollenberg (2) has introduced the hydroxyl



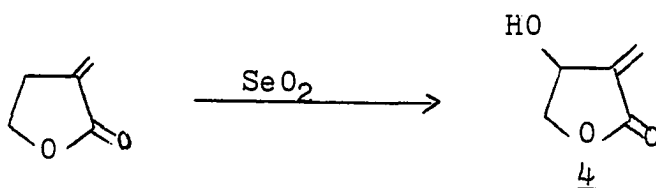
group via a 2,3 -sigmatropic rearrangement to obtain



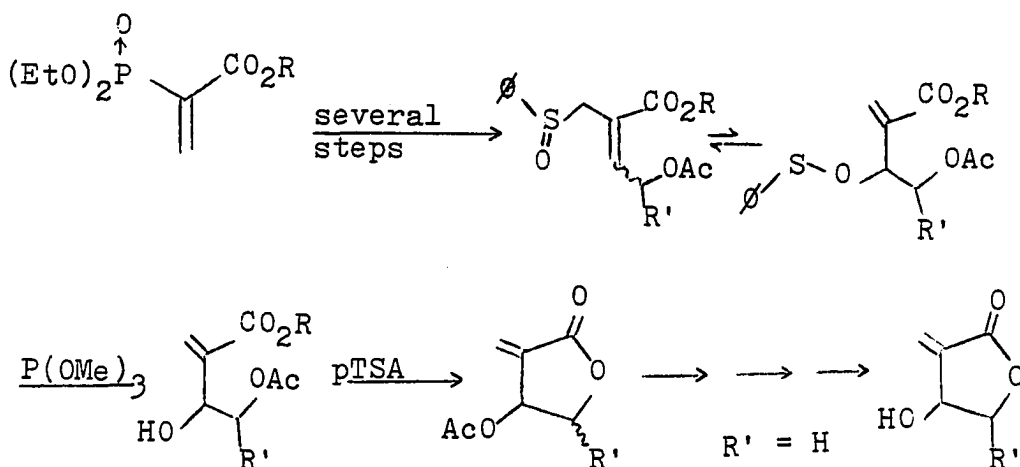
the naturally occurring hydroxy lactone litsolenolide C_1 (3). Kende and Toder (3) examined the alkylation and aldol reaction of deprotonated α -2-alkenoates to determine the stereochemical fate of the double bond. Some of the products were then taken on toward the synthesis of various litsolenolides. An intramolecular transesterification process was used to form the desired lactones.



Several groups have developed a synthesis of the α -methylene- β -hydroxybutyrolactone unit due to its presence as a structural feature in a variety of natural products (4). These syntheses invariably involved multistep procedures. Hutchinson (5) synthesized Tulipalin B (4) by allylic oxidation using selenium dioxide. The yield of (4) was described only as "modest". Corbet

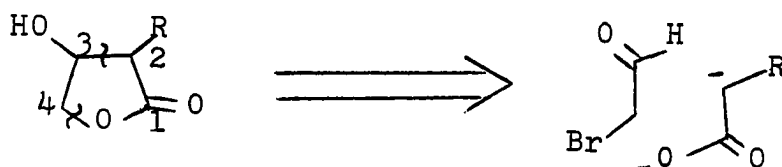


and Benezra have described a general method for the synthesis of α -methylene- β -hydroxylactones (6) involving the allylic sulfoxide--allylic sulfenate ester rearrangement and have used this to synthesize (4) (7) in 22% overall yield.

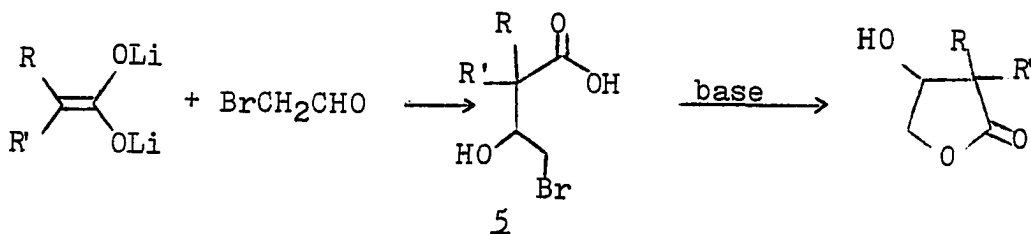


RESULTS AND DISCUSSION

Our synthesis of β -hydroxybutyrolactones utilized 2-bromoacetaldehyde to provide carbons 3 and 4 of the lactone ring. The dianion of a carboxylic acid (8)

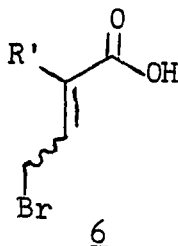


should react with the more electrophilic aldehyde portion of 2-bromoacetaldehyde giving intermediate (5). Treatment with one equivalent of base should form the carboxylate



preferentially which could displace the bromide. Using conditions developed by Pfeffer and coworkers (9), several dianions of carboxylic acids were formed. We reacted these with 2-bromoacetaldehyde and obtained a mixture of products. The acidic work-up conditions required to isolate the carboxylic acid (5) promoted dehydration,

giving (6) as the major product when R was hydrogen.

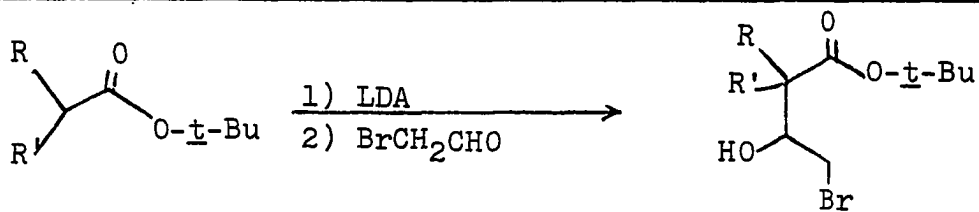


For R,R' not equal to hydrogen, the reaction afforded a mixture of (5) contaminated with a substantial amount of the starting acid. These compounds could not be easily separated from each other. These problems, in addition to the harsh conditions usually required for the formation of carboxylate dianions, caused us to look for a milder and more general methodology.

The next approach we tried involved the use of labile esters. Ester enolates reacted with 2-bromoacetaldehyde to give the bromohydrins in good yield (Table 1). The strongly basic saponification conditions used for simple esters could result in formation of an epoxide which could go on to form numerous side products. We decided, therefore, to investigate the use of t-butyl esters, since they could be cleaved with catalytic amounts of acid. The t-butyl esters were synthesized in good yield by the coupling of a carboxylic acid with t-butanol using the dehydrating agent dicyclohexylcar-

Table 1. Reaction of t-Butyl ester enolates with 2-bromoacetaldehyde

R	R'	%
H	H	94
∅	H	100
CH ₃	CH ₃	77
S∅	CH ₃	100

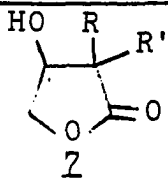


bodiimide (10). As expected, the anions of several t-butyl esters formed by the method of Rathke and Lindert (11) gave good yields of bromohydrins on reaction with 2-bromoacetaldehyde. The standard conditions for removal of the t-butyl group, namely catalytic p-toluenesulfonic acid in refluxing benzene (12), caused complete destruction of the hydroxyester. We decided to try TMSI which has been reported (13) to cleave t-butyl esters and t-butyl alcohols at low temperature. This procedure was tried on either the esters containing the free alcohol or the trimethylsilyl derivative. The carboxylic acid was obtained as evidenced by the infrared spectrum. Treatment of the crude acid with aqueous base gave hydroxylactones in variable yields contaminated with various side products.

The moderate success of the previous method encouraged us to use the even more labile trimethylsilyl esters. Aqueous sodium bicarbonate would cleave the ester and allow the resultant carboxylate anion to form the lactone by bromide displacement. The trimethylsilyl esters were formed from the carboxylic acids under mild conditions using triethylamine and chlorotrimethylsilane. As with the t-butyl esters, these were deprotonated with lithium diisopropylamide and were reacted with 2-bromoacetaldehyde. Since the resultant trimethylsilyl ester

would be unstable to aqueous work-up, we decided to attempt cyclization without isolation of the intermediate silyl ester. We attempted a one-pot procedure for lactone synthesis by quenching with water. Ester hydrolysis followed by closure to the lactone would be expected under the basic conditions. Quenching with either water or saturated aqueous sodium bicarbonate gave a mixture of products. A major side product appeared to be the amide formed from the reaction of diisopropylamine with the trimethylsilyl ester. This problem was overcome by quenching the reaction with acetic acid to protonate the alkoxide and amine. Subsequent addition of saturated aqueous sodium bicarbonate and vigorous stirring of the two-phase reaction for several hours gave good yields of butyrolactones. The product was determined to be a β -hydroxybutyrolactone contaminated with the β -trimethylsilyloxy butyrolactone presumably arising from silyl transfer. Treatment of this mixture with tetra-*n*-butylammonium fluoride in methylene chloride gave pure β -hydroxybutyrolactones in good yield (Table 2) as mixtures of diastereomers. This methodology seemed quite general except for a few special cases. Esters containing anion stabilizing groups in the α -position gave some butenolide as a side product. Trimethylsilyl bromoacetate failed

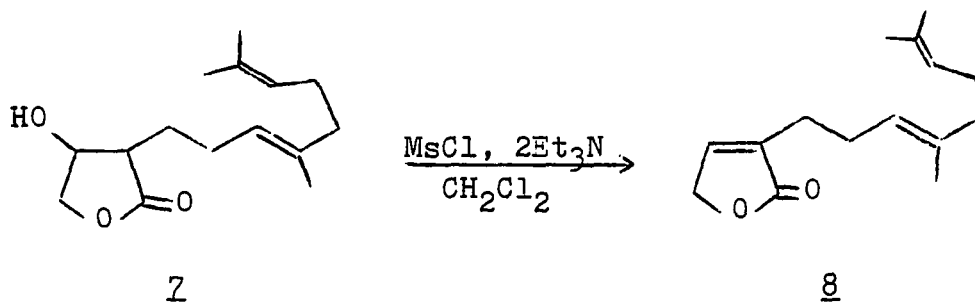
Table 2. The synthesis of β -hydroxybutyrolactones

$R(R')CHCO_2SiMe_3 + LDA + BrCH_2CHO \longrightarrow$				
entry	R	R'	% yield	Z
a	CH ₃	CH ₃	61	
b	n-Bu	H	90	
c	H ₂ C=CHCH ₂	H	62	
d	C ₆ H ₅ O	H	80	
e	C ₆ H ₅ S	H	65 ^a	
f	C ₆ H ₅ Se	CH ₃	75	
g	Br	Br	--	
h	H(CH ₂ C(CH ₃)=CHCH ₂) ₂ CH ₂	H	99	

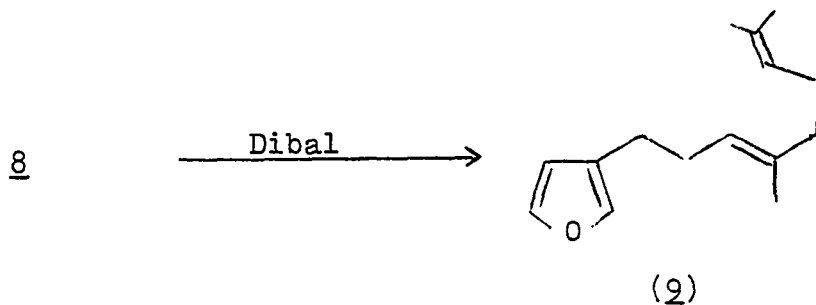
^aA 30% yield of the corresponding butenolide was also obtained.

to give any recognizable products, presumably due to the instability of the bromoanion (14). Bistrimethylsilyl adipate also gave a complex mixture of products possibly due to competitive intramolecular attack of ester enolate with unreacted ester.

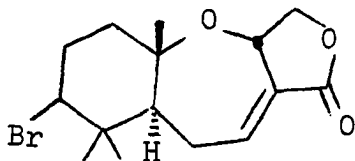
The β -hydroxybutyrolactones may be further transformed into butenolides and subsequently into furans. Treatment of (7) with methanesulfonyl chloride and two equivalents of triethylamine gave butenolide (8). Takahashi (15)



has converted the isomeric butenolide into dendrolasin (9) by reduction with diisobutylaluminum hydride. Analogously, we obtained dendrolasin in 30% overall yield from (7) after treatment of the crude reduction product with acid.

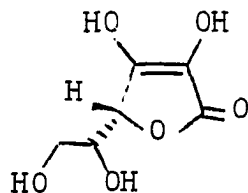


Compound (7) was a 1:1 mixture of diastereomers which were separated by flash chromatography (16). Such substituted β -hydroxybutyrolactones have been isomerized from the cis to the trans isomer by treatment with sodium methoxide in methanol (17). Treatment of the cis isomer of (7) with potassium t-butoxide/t-butanol complex in tetrahydrofuran did lead to the formation of the trans isomer. The trans compound was verified by comparison with the proton NMR spectrum of pure trans compound independently synthesized by Prestwich and Shieh (18). They used this compound in the synthesis of d-aplysistatin (10). Our synthesis of trans hydroxylactone (7), therefore, constitutes a formal total synthesis of dl-aplysistatin.

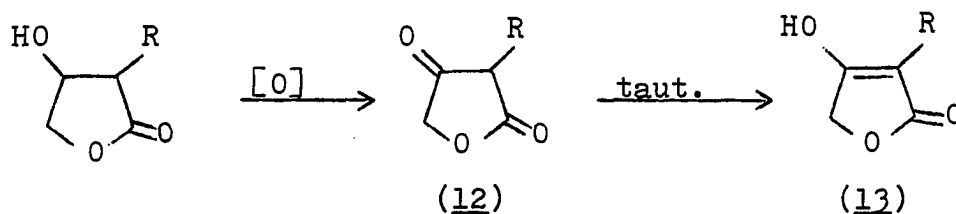


(10)

We also examined the oxidation of β -hydroxybutyrolactones to tetronic acids such as (11). Oxidation of

ascorbic acid 11

the alcohol to a ketone would give the β -ketolactone (12) which would exist as the hydroxybutenolide (13). Oxidations



of β -hydroxycarbonyl compounds to β -dicarbonyl compounds have generally been quite problematic, but Smith and Levenberg have reported good results using the Swern oxidation (19). Neither these conditions nor the related Moffat oxidation conditions (20) gave us the desired product. Complete destruction of starting material was observed in each case. Bartlett and Jernstedt (21) have used the Jones oxidation in a similar case. Our system again failed to give any of the desired product.

EXPERIMENTAL

General

Diethyl ether and tetrahydrofuran (THF) were distilled from lithium aluminum hydride. Methylene chloride was distilled from P_2O_5 . All reactions were run under a nitrogen atmosphere, and all organic extracts were dried over Na_2SO_4 . Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were determined on a Beckman IR-4250 spectrometer. Nuclear magnetic resonance spectra were determined on a Varian EM-360 instrument for proton or on a Joel FX-90Q for carbon-13 in $CDCl_3$ with absorptions recorded in ppm downfield from internal tetramethylsilane. High resolution mass spectra were recorded on an AEI MS-902 high resolution mass spectrometer.

General Procedure for the Synthesis of β -Hydroxy- γ -
Lactones

Diisopropylamine (0.15 mL, 1.1 mmol) was added to 1 mL THF and cooled to $0^\circ C$. n -Buli (2.05M in hexane, 0.54 mL) was added dropwise with stirring. After 15 min, the solution was cooled to $-78^\circ C$ and a 1M solution of

the silyl ester (1.0 mmol) in THF was added dropwise. After the reaction was stirred for 30 min, 1.1 mL of a 1M solution of 2-bromoacetaldehyde in THF was added at once. After stirring 5 min the reaction was quenched with 0.13 mL (2.3 mmol) of acetic acid and the resultant suspension was warmed to 0°C. A saturated solution of aqueous NaHCO₃ (3 mL) was added and the 2 phase system was stirred vigorously for 5h. The ice bath was allowed to warm to ambient temperature. The reaction mixture was diluted with brine (5 mL) and was extracted three times with 10 mL portions of diethyl ether. The residue obtained after drying and solvent removal proved to be a mixture of β-hydroxy and β-silyloxy-γ-lactone.

Complete conversion to the hydroxy lactone was accomplished by dissolving the crude product in 3 mL of CH₂Cl₂ and adding 0.5 mL of a 1M THF solution of tetra-n-butylammonium fluoride. The reaction was stirred at ambient temperature until TLC (silica gel, diethyl ether:hexane 1:1) analysis showed disappearance of high R_f material (15-20 min). The solution was diluted with 5 mL diethyl ether and washed once with water (3 mL) and once with brine (3 mL). The aqueous layers were combined and reextracted with 3 mL of diethyl ether. Purification was effected by filtration through a small

amount of silica gel eluting with diethyl ether to give the following adducts:

Adduct (7a) IR (film) 3460, 2970, 1770, 1100 cm^{-1} ; NMR (CDCl_3) δ 1.23 (s, 6H), 3.92-4.50 (m, 4H); high resolution mass spectrum for $\text{C}_6\text{H}_{10}\text{O}_3$ requires m/e 130.06300, found m/e 130.06335.

Adduct (7b) IR (film) 3460, 2960, 1775, 1170 cm^{-1} ; NMR (CDCl_3) δ 0.93 (bt, 3H), 1.12-2.00 (m, 9H), 2.30-2.62 (m, 1H), 3.90 (bs, 1H), 4.00-4.67 (m, 3H).

Adduct (7c) IR (film) 3460, 2970, 1780, 1255, 840, cm^{-1} ; NMR (CDCl_3) δ 2.30-2.70 (m, 3H), 3.63 (bs, 1H), 4.00-4.60 (m, 3H), 4.92-5.32 (m, 2H), 5.50-6.20 (m, 1H); high resolution mass spectrum for $\text{C}_7\text{H}_{10}\text{O}_3$ requires m/e 142.06300, found m/e 142.06352.

Adduct (7d) IR (film) 3490, 1770, 1165, 750, 690 cm^{-1} ; NMR (CDCl_3) δ 3.20 (bs, 1H), 3.80-4.30 (m, 4H), 6.70-7.30 (m, 5H).

Adduct (7e) IR (film) 3460, 1780, 1590, 1490, 1230, 1100, 905, 725 cm^{-1} ; NMR (CDCl_3) δ 3.62 (bs, 1H), 4.00-5.00 (m, 4H), 6.80-7.50 (m, 5H).

Adduct (7f) IR (film) 3440, 2980, 1770, 1020, 740 cm^{-1} ; NMR (CDCl_3) δ 1.58 (s, 3H), 3.81 (bs, 1H), 4.10-4.40 (m, 3H), 7.10-7.80 (m, 5H); high resolution mass spectrum for $\text{C}_{11}\text{H}_{12}\text{O}_3\text{Se}$ requires m/e 271.99512,

found m/e 271.99562.

Adduct (7h) (trans) IR (film) 3460, 2940, 1770, 1180, 1025 cm^{-1} ; NMR (CDCl_3) δ 1.62 (bs, 6H), 1.70 (bs, 3H), 1.80-2.30 (m, 8H), 2.48 (m, 1H), 3.09 (bs, 1H), 4.00-4.60 (m, 3H), 5.12 (bt, 2H).

Adduct (7h) (cis) IR (film) 3460, 2930, 1765, 1450, 1375, 1140, 1040, 975 cm^{-1} ; NMR (CDCl_3) δ 1.63 (bs, 9H), 2.00 (m, 8H), 2.40 (m, 1H), 2.78 (bs, 1H), 4.23 (d, 2H), 4.47 (m, 1H), 5.13 (bt, 2H).

Dendrolasin (9)

Adduct (7h) (0.29 mmol) was dissolved in 1 mL CH_2Cl_2 and cooled to 0°C . Triethylamine (0.6 mmol) was added followed by addition of neat methanesulfonylchloride (0.3 mmol). The reaction was stirred and allowed to warm slowly to room temperature over 5h. The reaction was diluted with 5 mL of diethyl ether and was washed once with saturated aqueous NaHCO_3 (2 mL) and then once with brine. The organic layer was dried over Na_2SO_4 . The crude butenolide was sufficiently pure to be taken on to the next step.

Butenolide (9) (0.30 mmol) was dissolved in 3.5 mL of THF and was added to a flask and cooled to -20°C .

Dibal (1M solution in hexane, 0.40 mL) was then added. TLC analysis (silica gel, hexane:diethyl ether 1:1) after 1h revealed the disappearance of starting material. The reaction was quenched with 0.03 mL acetic acid and was diluted with 5 mL CH_2Cl_2 and was warmed to room temperature. After washing with 2 mL saturated aqueous NaHCO_3 followed by 2 mL brine, the organic phase was dried over Na_2SO_4 . Removal of the solvent left a viscous yellow oil which contained only a small amount of furan by NMR analysis, but a large hydroxyl stretch by infrared analysis. This material was dissolved in 3 mL of CH_2Cl_2 and treated with a catalytic amount of pTSA· H_2O for 3h until TLC analysis (hexane:diethyl ether 1:1) showed one major spot ($R_f = 0.85$). The solution was diluted with hexane and filtered through 3 g of silica gel eluting with hexane. Removal of the solvent left 20.5 mg of a colorless oil which was shown to be dendrolasin (32% yield).

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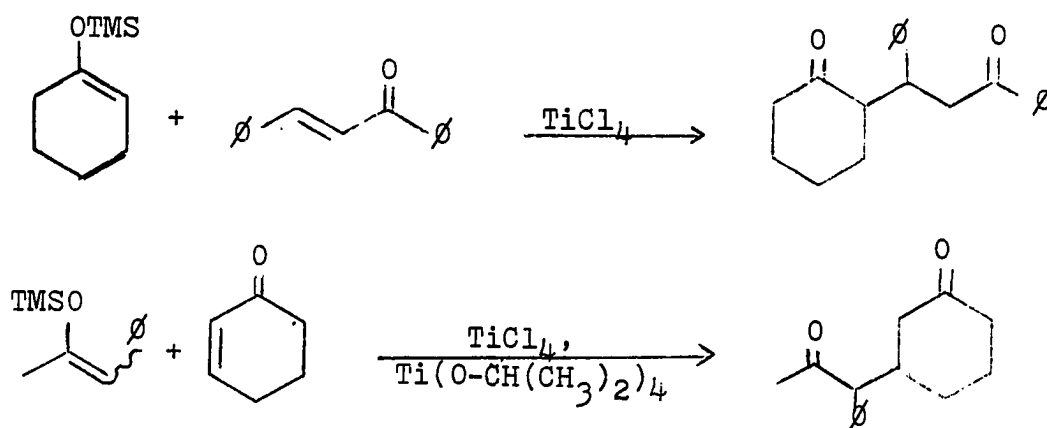
PART III: USEFUL AND NOVEL STEREOSELECTIVE SYNTHESSES OF
CARBOCYCLIC COMPOUNDS

INTRODUCTION

A novel approach toward the stereoselective synthesis of carbocyclic ring systems will be described using a similar procedure as in PART I. Though giving an alternate stereochemistry than expected, this approach allows the rapid formation of multicyclic systems.

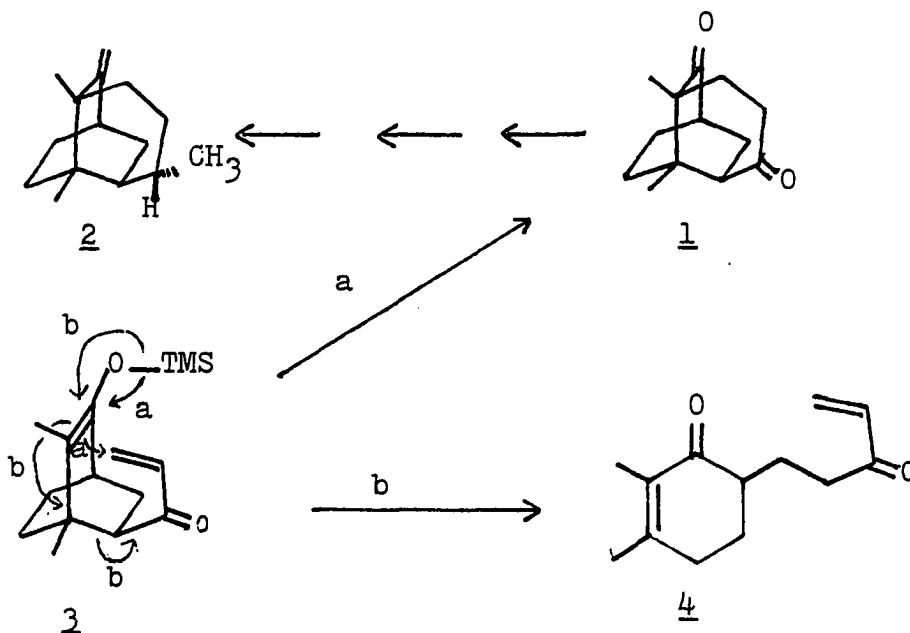
HISTORICAL

Several examples of 1,4-additions of enones with silyl enol ethers mediated by Lewis acids have been reported. The most common Lewis acid employed was TiCl_4 . Its use in these reactions has been discussed in a review by Mukaiyama (1). Reactions were typically conducted at low temperatures in methylene chloride using either TiCl_4 or a mixture of TiCl_4 and $\text{Ti}(\text{O}-\text{CH}(\text{CH}_3)_2)_4$ for the more Lewis acid sensitive compounds. Good yields of 1,5-dicarbonyl products were obtained in this manner.



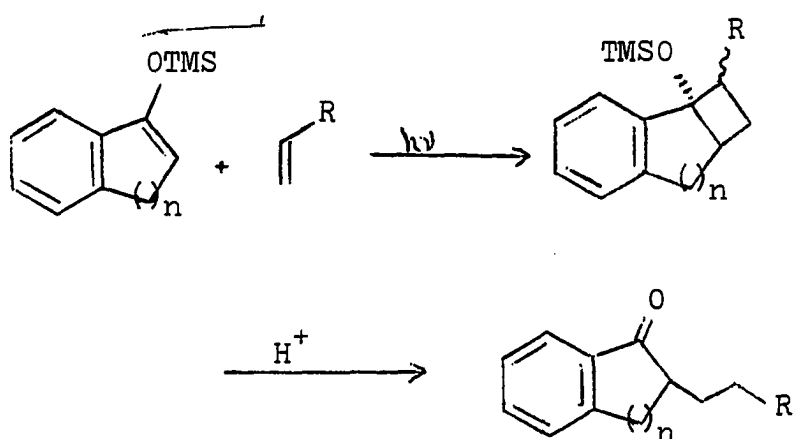
Despite the apparent generality of this reaction, conjugate addition of enones with silyl enol ethers has not been extensively used synthetically. Recently,

Jung and Pan (2) have incorporated this reaction in their synthesis of (1) which was taken on to dl-Seychellen (2) (3).



The key step was an intramolecular 1,4-addition of the enone with the silyl enol ether in (3). Several Lewis acids were tried with TiCl_4 giving the highest yield of (1). This key intermediate, however, was formed in only 5% yield. The major product was (4) formed through a retro Michael reaction via path b. Nevertheless, (1) was taken on to (2) in an elegant but highly inefficient synthesis. It was hypothesized that the constraints of the rigid bicyclic system provided poor orbital overlap necessary for the proper bond formation.

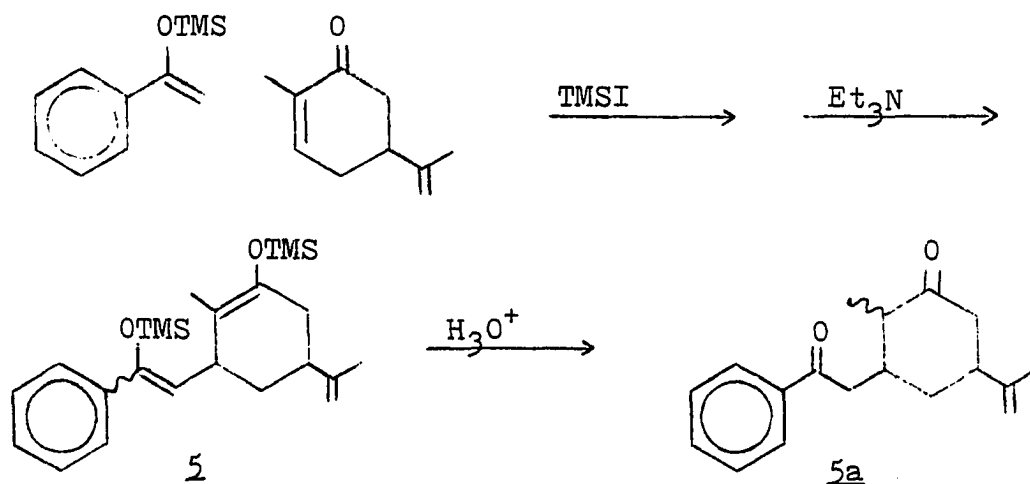
Adducts similar to those obtained by Mukaiyama have also been made through the photochemical reaction of an enone with a silyl enol ether. Mizuno and coworkers (4) have isolated the resultant 2 + 2 cycloaddition product which gave them the Michael adduct upon treatment with acid. The reaction seemed general and provided an alternative to the use of Lewis acids.



R	%(n = 1)	%(n = 2)
CO ₂ CH ₃	72	79
CN	40	86
COCH ₃	30	51

RESULTS AND DISCUSSION

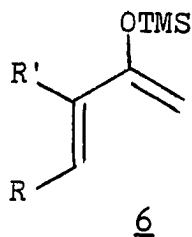
We sought to extend the iodotrimethylsilane (TMSI) mediated conjugate addition of furans to enones by reacting enones with other electron rich olefinic systems, namely, enol silyl ethers. Our initial study involved adding the enol silyl ether of acetophenone to l-carvone in a manner analogous to that in the furan case. The product obtained after quenching with triethylamine was quite complex by proton NMR analysis. It was thus hydrolyzed and chromatographed to give (5a) in 70% yield, along with



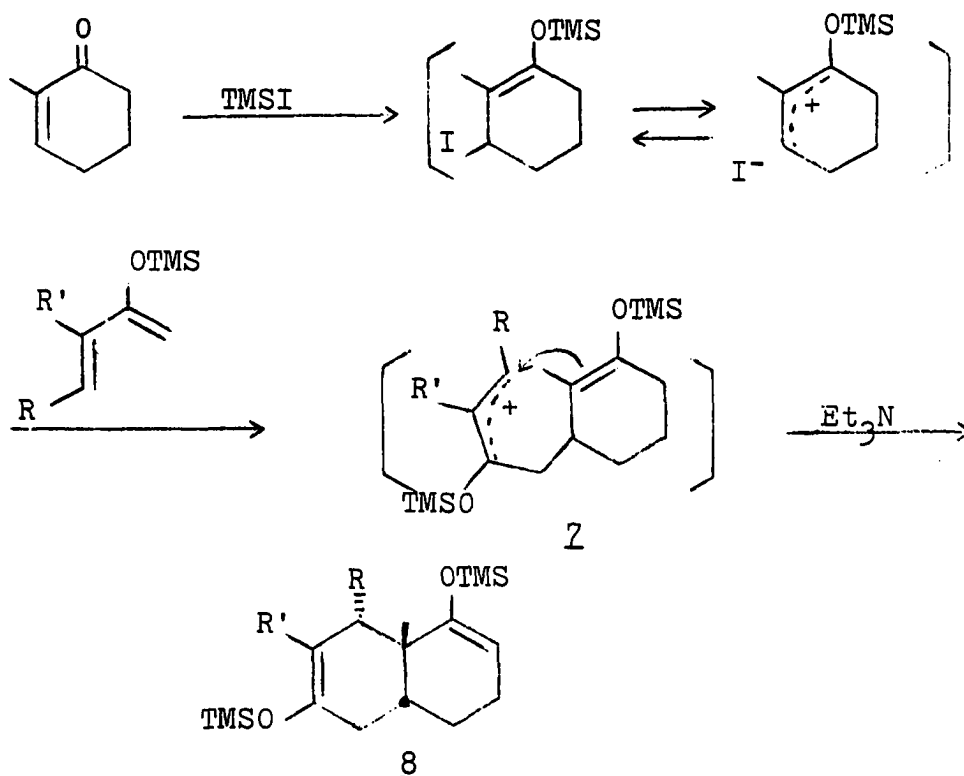
the recovery of some starting materials. The presence of starting material would explain the complexity of the proton NMR spectrum of the product after the basic

quench. The best yields of product were obtained using a one to two hour reaction time at -78°C as opposed to the six to seven hour reaction time at -78°C for furans. This reflects the increased electron density in the enol silyl ether double bond as opposed to the furans. Unreacted starting materials were always recovered when enol silyl ethers were used regardless of prolonged reaction times (up to seven hours) or elevated temperatures (up to -20°C). This made the direct use of dienol silyl ether intermediate (5) unlikely for further elaboration. Nevertheless, we have shown that enol silyl ethers will add in a Michael fashion to enones with the use of TMSI.

We now focused on using cross-conjugated dienol silyl ethers of type (6) in a way which would result

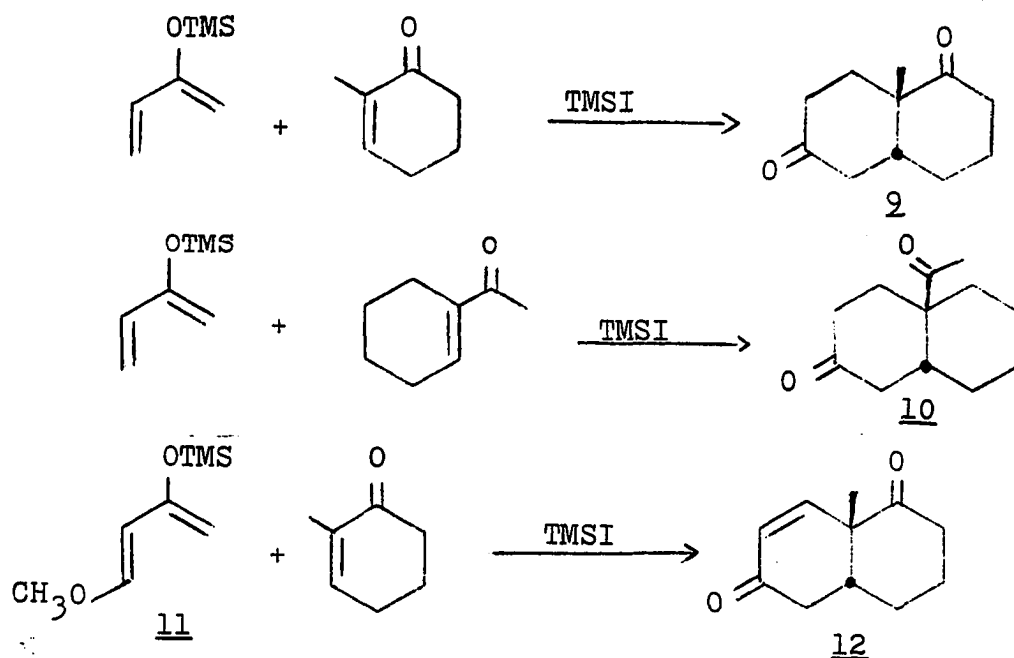


in an annulation procedure. This strategy involved a novel reaction sequence of a net tandem 1,4-addition. We envisaged the dienol silyl ether adding initially to form intermediate (7). We would then form another enol silyl ether and allylic carbocation pair which



should react this time intramolecularly to give (8) after quenching with triethylamine. The depicted stereochemistry in (9) was expected due to the intramolecular nature of the reaction. Such a reaction sequence was unprecedented in the literature.

Initially, 2-trimethylsilyloxy-1,3-butadiene was reacted with 2-methyl-2-cyclohexen-1-one or 1-acetylcyclohexene to give compounds (9) and (10) after acid hydrolysis and purification by silica gel chromatography. These reactions did not proceed as efficiently as in the

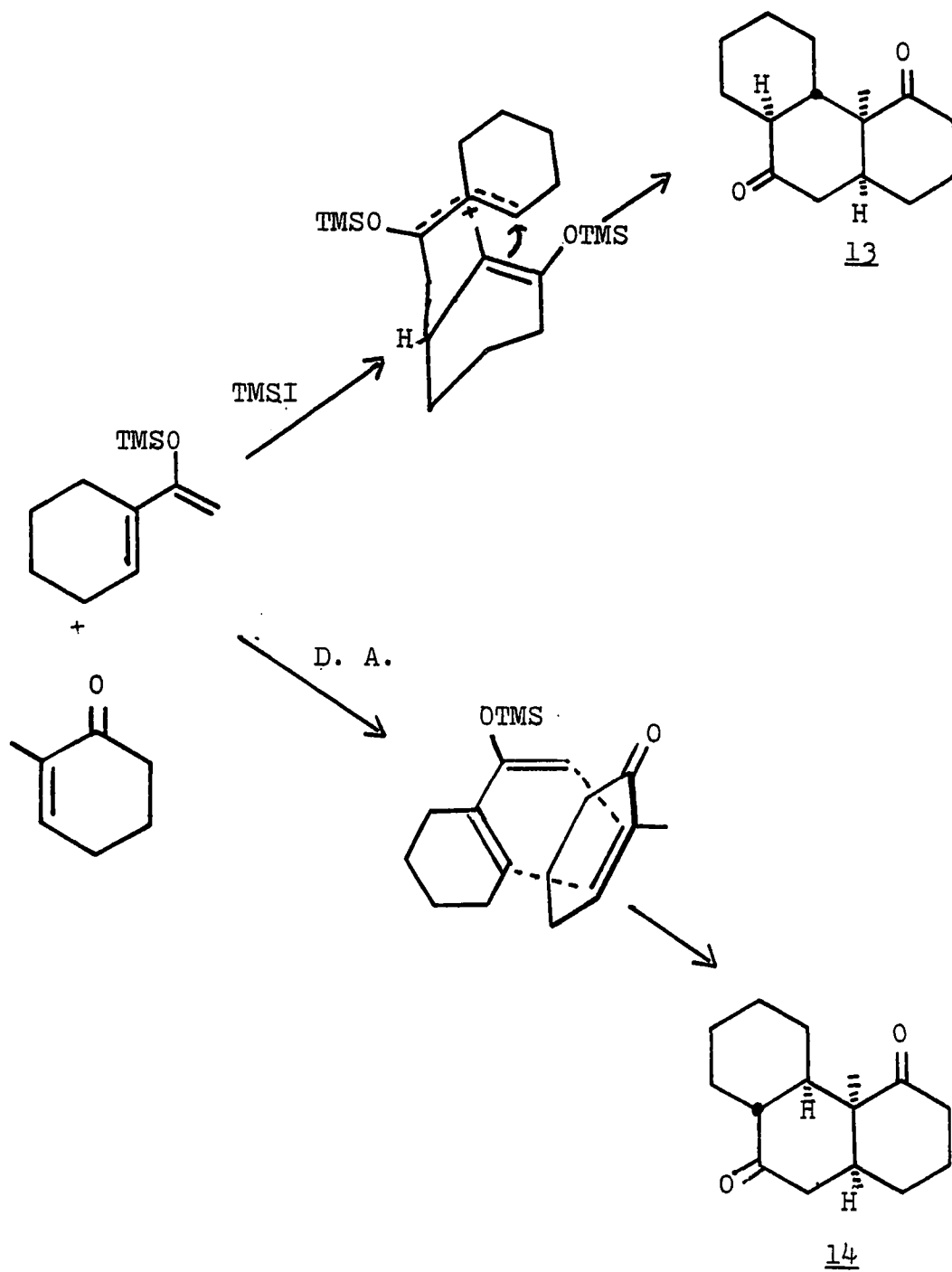


furan case in that some starting material was always recovered. These products were determined to be one diastereomer by NMR (proton and carbon-13) analysis. The *cis* ring junction was inferred through analysis of molecular models which showed that intramolecular of the allylic carbocation involved less strain in forming the *cis* as opposed to the *trans* ring junction. The structure of (**9**) was unequivocally proven by comparison with the literature data for (**9**) synthesized by another method (5). A melting point of 65-66°C was reported for (**9**) which compared quite favorably with our 66-67°C. The trans- isomer was reported to have a melting point of 57.5-59°C. Baudin and Pietrasanta (6) had found

that the stereochemistry of the ring junction of these types of bicyclic compounds can be determined by the chemical shift of the protons on the angular methyl group when using C_6D_6 as the solvent. The trans-isomer gave a chemical shift of 0.70 ppm (δ) downfield from tetramethylsilane while the cis-isomer gave a shift of 0.95 ppm. The chemical shift of the angular methyl group in our compound was 0.92 ppm and was thus determined to possess the cis-stereochemistry about the ring junction.

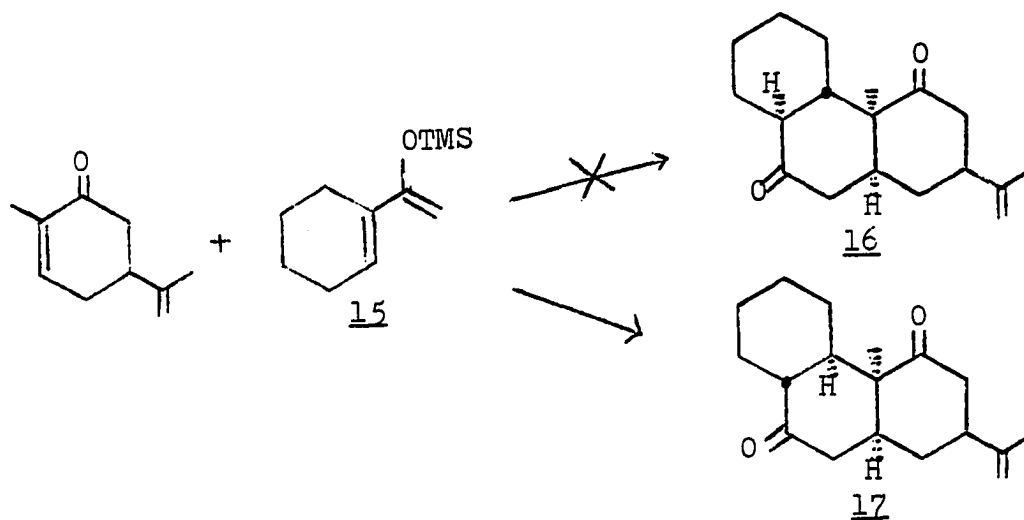
Danishefsky and Kitahara's diene (11) (7) would ultimately give rise to the difficultly formed hexahydronaphthalene system (12). Unfortunately, only a tarry residue was recovered from the reaction mixture. The use of 2-methyl-2-butene to moderate the amount of acid present produced the same results.

This reaction produced a Diels-Alder like product formed from the combination of a diene (the dienol silyl ether) and a dienophile (the enone). We hypothesized that this ionic analogue to the Diels-Alder reaction should give an alternate stereochemistry. The proposed transition state for the TMSI mediated reaction should give product (13) having a cis-ring junction. The angular methyl and adjacent hydrogen groups would



presumably have a trans relationship. The Diels Alder reaction, if carried out at low temperature with Lewis acid catalysis, should proceed via an endo-transition state (8) giving the relative stereochemistry found in (14). Neither reaction pathway determines the stereochemistry at C8. Since this center is epimerizable, we assumed a trans ring juncture would result.

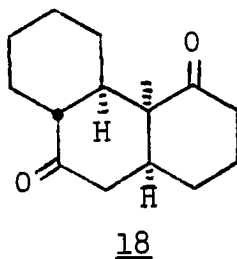
To test this hypothesis we treated l-carvone with TMSI then reacted the resultant intermediate with the dienol silyl ether of 1-acetylcyclohexene (15). The



expected product (16) would have the cis-anti-trans-stereochemical relationship found in terpenoid systems, and would provide an extremely rapid approach toward their synthesis. Two compounds were isolated after acid hydrolysis and purification with silica gel chromatography.

Both compounds gave similar NMR and IR data, but one of these was crystalline and consequently was subjected to X-ray crystallographic analysis. To our surprise, this compound proved to be (17) which was the expected Diels-Alder product (Figure 1). The non-crystalline compound was assumed to be a diastereomer of (17) having a β -isopropenyl group since the major difference between the two compounds in the proton NMR was the chemical shift of the olefinic protons.

In light of these results, we decided to reexamine this reaction using the simpler 2-methylcyclohexenone which would give only one diastereomer. Similar treatment with TMSI and the dienol silyl ether (15) gave adduct (18) in 35% isolated yield. The structure was unambiguously



assigned from X-ray crystallographic data to possess the cis-syn-trans-stereochemistry (Figure 2). This was in agreement with the result obtained from the use of 1-carvone. An analogous outcome was observed with

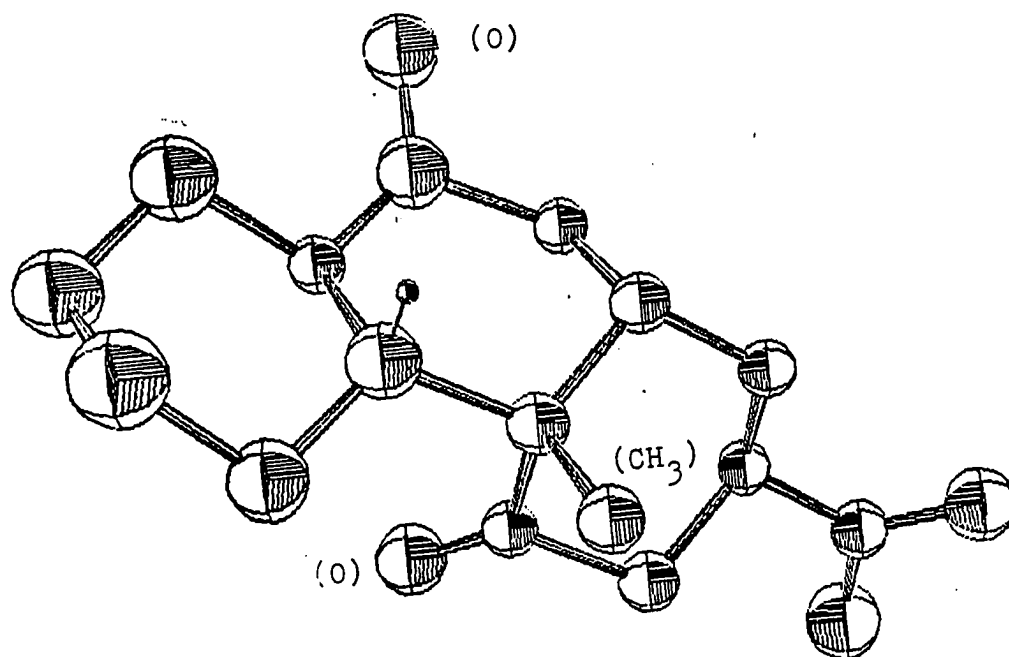


Figure 1. Tricyclic adduct (17a)

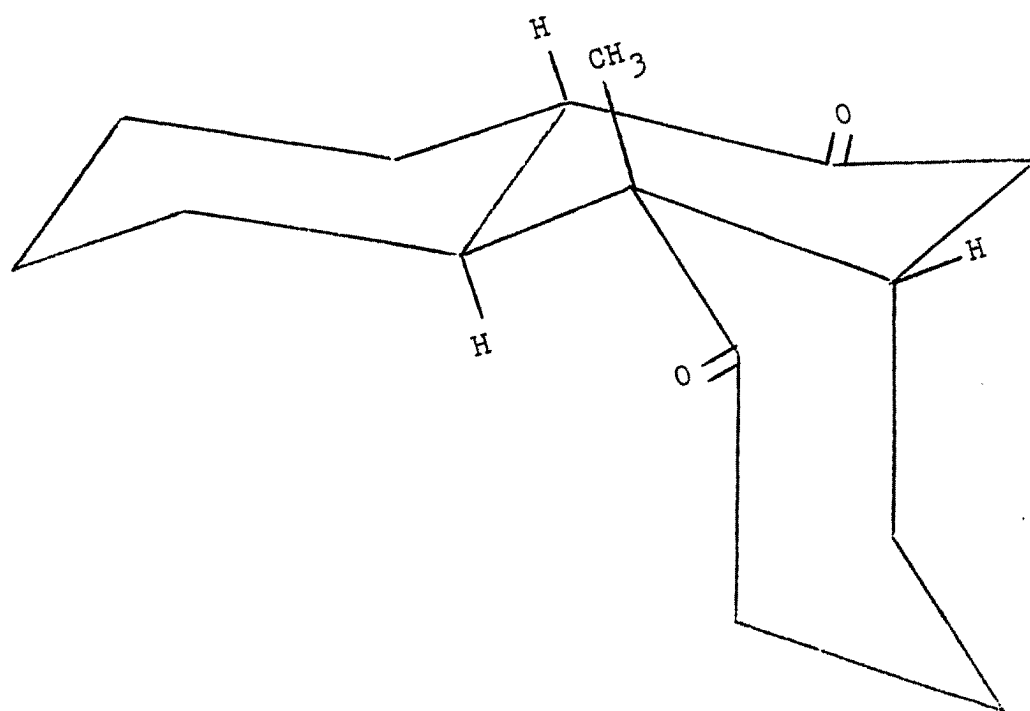
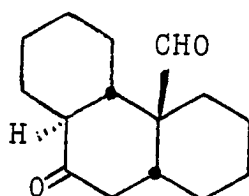


Figure 2. Expected Structure of Adduct (18)

the reaction of 1-acetylcyclohexene with its dienol silyl ether derivative resulting in a net dimerization. Dimerization of 1-acetylcyclohexene has been reported using basic conditions (9) to form a mixture of products. Our conditions formed adduct (19) (Figure 3) stereoselectively in good yield (Table 1). The reaction involving 2-bromo-2-cyclohexenone would have provided compound (21) from which a regioselectively formed enolate could have been formed through the use of zinc or magnesium metal. The product, however, consisted of a complex mixture by TLC analysis, and was not purified.

One α,β -unsaturated aldehyde was tried (Table 1) in an attempt to form compound (22). In addition to significant amounts of recovered starting material, the



22

1,2-addition product (20) was isolated, as verified by the typical doublet of doublets at 2.75 ppm in the proton NMR. Compound (20) was further treated with methanesulfonyl chloride and two equivalents of triethylamine to give (23) as a structure proof. Thus, this

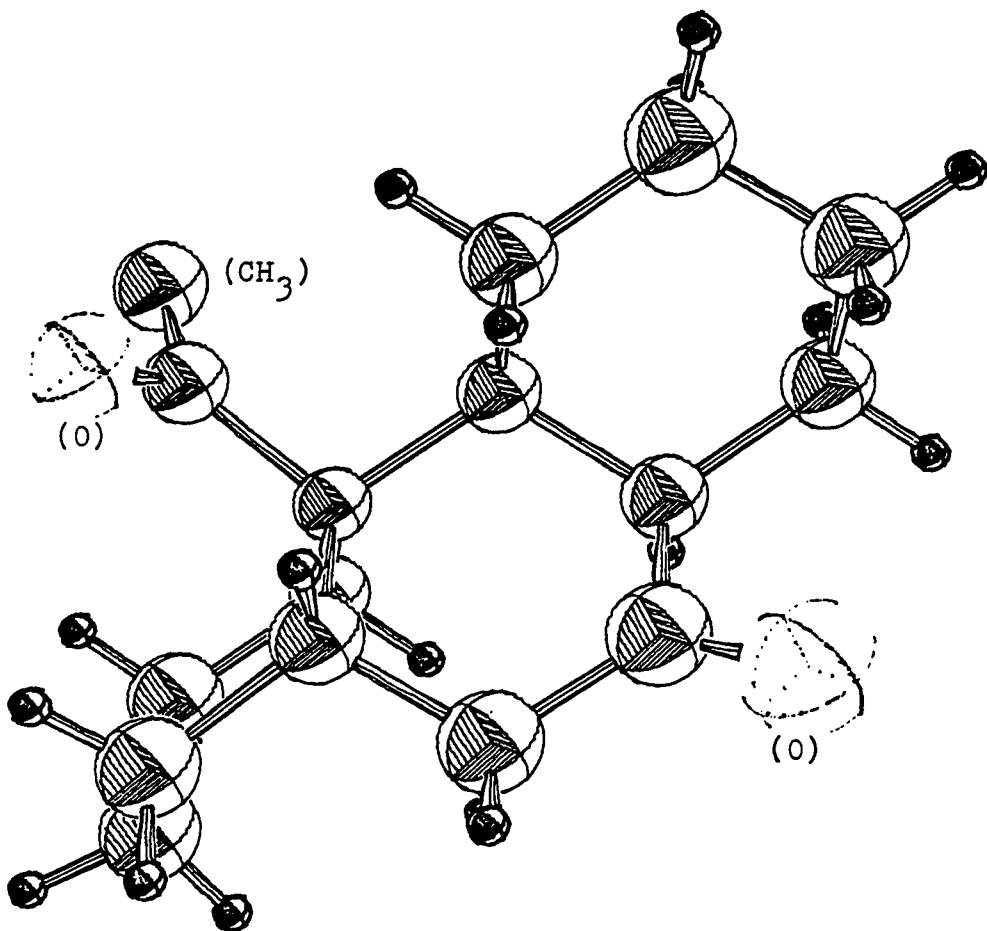
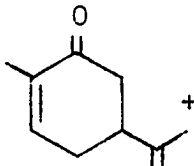
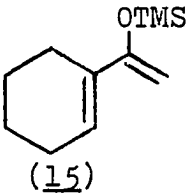
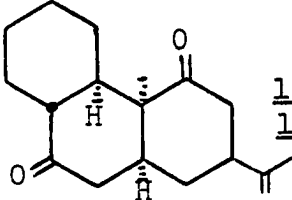
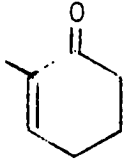
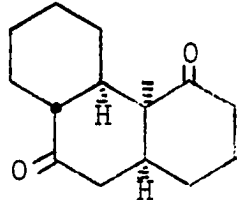
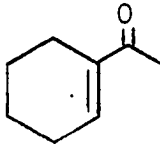
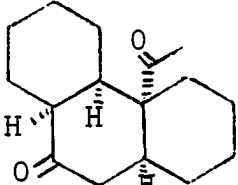
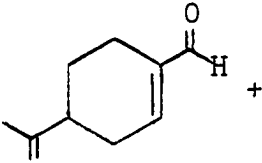
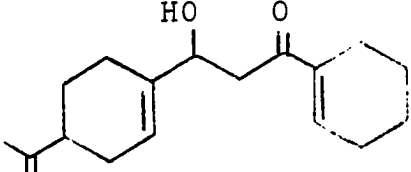
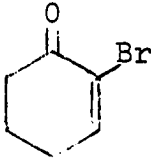
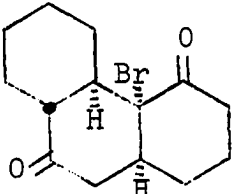
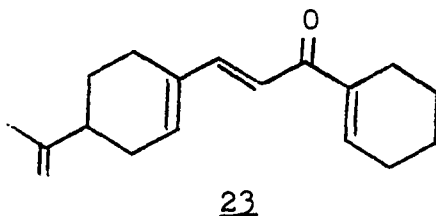


Figure 3. Tricyclic Adduct (19)

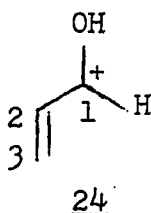
Table 1. Cyclization reactions involving dienol silyl ether (15)

Enone	(<u>15</u>)	Adduct	Yield
			<u>17a</u> (β) 34% <u>17b</u> (α) 25%
	"		<u>18</u> 35%
	"		<u>19</u> 77%
	"		<u>20</u> 20%
	"		<u>21</u>



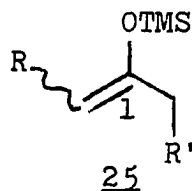
reaction appeared to be best suited for α,β -unsaturated ketones.

All of the tricyclic systems formed had the cis-syn-trans-stereochemistry which we predicted for the Diels-Alder product. The possibility existed that TMSI or traces of hydrogen iodide may have been acting as a Lewis acid, allowing a low temperature Diels-Alder reaction to occur. To determine whether or not this process was concerted, we examined the intermediate formed by the addition of TMSI to 1-methylcyclohexenone in CD_2Cl_2 by carbon-13 NMR at $-70^\circ C$. Olah and coworkers (10) have reported the chemical shifts of protonated acrolein (24) to occur



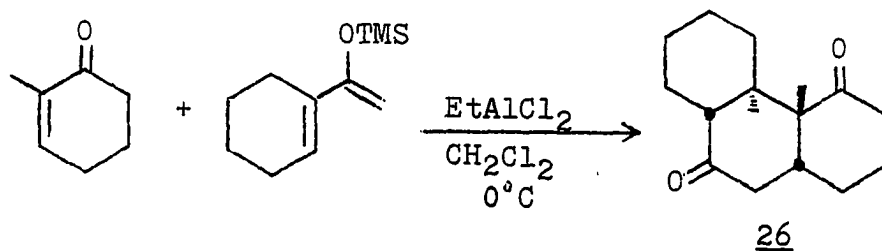
at 211.50 (C1), 176.5 (C2), and 133.10 (C3) ppm downfield from tetramethylsilane. The farthest downfield absorption we observed was at 120.217 ppm which would be consistent

with Cl of an enol silyl ether (25) (11). Furthermore,



a concerted reaction should have little or no solvent dependence. When the reaction was run in pentane instead of the more polar methylene chloride, no cyclization occurred. Only starting materials were recovered. With these results, we were confident in ruling out the Diels-Alder reaction.

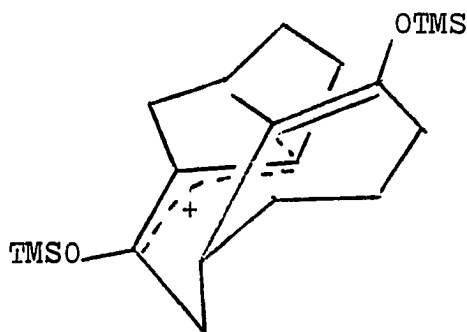
Since all the examples of this annulation reaction gave our predicted Diels-Alder products, we were curious whether the same product would be obtained under actual Diels-Alder conditions. Using the conditions described by



Rousch and Gillis (12), we effected the Diels-Alder reaction of 2-methylcyclohexenone and (15) using ethyl aluminum dichloride as the Lewis acid. A crystalline solid was recovered which gave spectroscopic features similar

to the adduct formed under the TMSI conditions. Differences were observed in the 2.5--3.0 ppm region of the 300 MHz proton NMR spectrum as well as in the carbon-13 NMR spectrum. The X-ray crystallographic data showed we had compound (26), having the cis-anti-trans-configuration (Figure 4). This product again was surprising in that this would result from a Diels-Alder reaction occurring through the less-favored exo-transition state.

The observed stereochemical outcome of the TMSI mediated reaction could be explained through the use of molecular models. The nucleophilic dienol silyl ether should come in axially to the cyclic enone. Bond formation between C1 and C2 to form the tricyclic cis-



anti-trans-isomer would have to proceed via a boat transition state. Formation of the cis-syn-trans-isomer would have proceeded through the more favorable chair

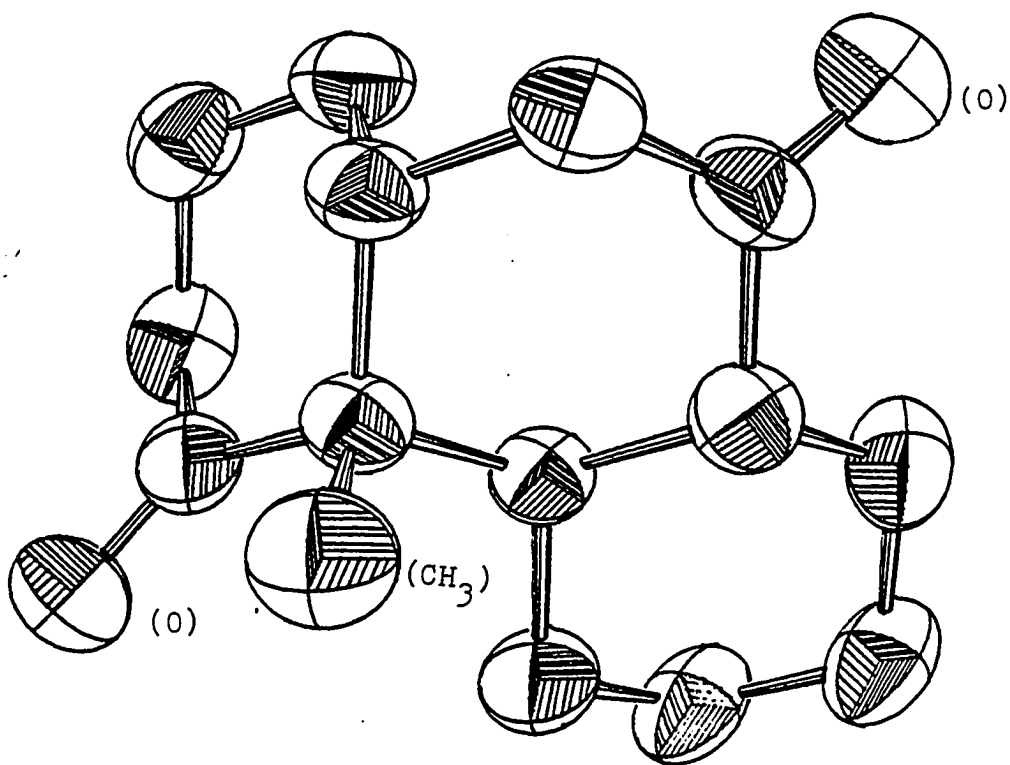
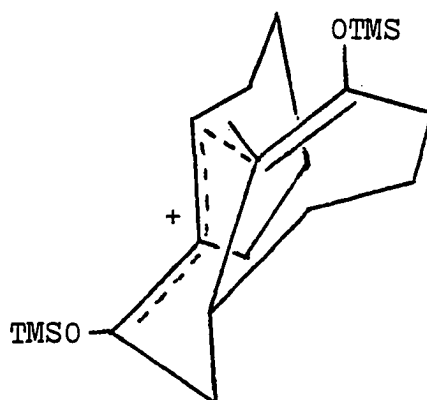


Figure 4. Tricyclic Adduct (26)

transition state. We could only speculate, on the other



hand, as to the reason for the stereochemical outcome of the Diels-Alder reaction. Examination of molecular models revealed no obvious severe non-bonded interactions involved in an endo-transition state. Possibly subtle steric factors influenced the course of the reaction leading to the exo-product.

The reaction of dienol silyl ethers with enones mediated by TMSI provided a unique and alternate annulation process. Although this reaction did not produce the cis-anti-trans-stereochemistry found in multicyclic terpenes, it still allowed the formation of various carbocyclic systems efficiently and stereoselectively.

EXPERIMENTAL

General

Diethyl ether and tetrahydrofuran (THF) were distilled from lithium aluminum hydride. Methylene chloride was distilled from P_2O_5 . All reactions were run under a nitrogen atmosphere, and all organic extracts were dried over Na_2SO_4 . Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were determined on a Beckman IR-4250 spectrometer. Nuclear magnetic resonance spectra were determined on a Varian EM-360 instrument for proton or on a Joel FX-90Q for carbon-13 in $CDCl_3$ with absorptions recorded in ppm downfield from internal tetramethylsilane. High resolution mass spectra were recorded on an AEI MS-902 high resolution mass spectrometer. Crystal structures were performed at Ames Laboratory by Dr. James Benson.

General Procedure for TMSI Mediated Annulation Reactions

The enone (1.0 mmol) was dissolved in CH_2Cl_2 and placed in a dry three-neck 25 mL round bottom flask. The solution was cooled to $-78^\circ C$, and TMSI (1.05 mmol) was added dropwise. After stirring for 30-45 min, a 1M solution of the dienol silyl ether (1.1 mmol) in CH_2Cl_2

was added dropwise. Stirring was continued at -78°C for 3.5h. The reaction was quenched with triethylamine (1.5 mmol), diluted with hexane (15 mL), and filtered through Celite. After removal of the solvent, hexane (10 mL) was again added and the mixture filtered through Celite. The solvent was removed and the remaining yellow oil was taken up in 10% aqueous THF (5 mL) to which had been added two drops of 1N HCl. The solution was stirred 3-4h to hydrolyze the enol silyl ether. This reaction was then diluted with diethyl ether (20 mL) and washed once with saturated aqueous NaHCO_3 (5 mL). After drying, the solvent was removed giving the cyclized adduct which was purified by column chromatography (silica gel). All solid adducts were recrystallized from diethyl ether-hexane:

Adduct (9) NMR (CDCl_3) δ 1.33 (s, 3H), 1.40-2.70 (m, 13H); NMR (C_6D_6) δ 0.90 (s, 3H), 1.00-1.65 (m, 6H), 1.65-2.50 (m, 7H); ^{13}C NMR (CDCl_3) δ 213.755, 210.828, 48.251, 45.781, 43.440, 38.107, 37.197, 33.360, 26.467, 23.605, 22.695; mp $66-67^{\circ}\text{C}$, high resolution mass spectrum for $\text{C}_{11}\text{H}_{10}\text{O}_2$ requires m/e 180.11503, found m/e 180.11452.

Adduct (10) IR (film) 2940, 1710, 1360 cm^{-1} ;
 NMR (CDCl_3) δ 1.10-1.80 (m, 8H), 1.80-2.80 (m, 10H), 2.22 (s, 3H); ^{13}C NMR (CDCl_3) δ 212.259, 210.568, 51.633, 44.936, 38.172, 37.782, 32.255, 28.288, 27.377, 24.646,

23.996, 21.068; high resolution mass spectrum for $C_{12}H_{18}O_2$ requires m/e 194.13060, found m/e 194.13044.

Adduct (17a) IR (film) 2940, 2860, 1700, 1120, 890, 725 cm^{-1} ; NMR ($CDCl_3$) δ 1.00-2.90 (m, 24H), 1.40 (s, 3H), 1.76 (bs, 3H), 4.70 (bs, 2H); mp 91.5-92.5°C.

Adduct (17b) IR (film) 2940, 1710, 1450 cm^{-1} ; NMR ($CDCl_3$) δ 0.90-3.00 (m, 24H), 1.43 (s, 3H), 1.72 (bs, 3H), 4.73 (d, 2H).

Adduct (18) IR (film) 2960, 2880, 1700, 1450 cm^{-1} ; NMR ($CDCl_3$) δ 1.00-3.20 (m, 22H), 1.49 (s, 3H); ^{13}C NMR δ 215.576, 211.544, 50.853, 50.202, 45.261, 43.960, 43.830, 40.384, 29.523, 27.052, 26.012, 25.456, 21.848, 21.458; mp 70-71°C.

Adduct (19) IR (film) 2940, 2860, 1700, 1440, 1350, 1130 cm^{-1} ; NMR ($CDCl_3$) δ 0.90-2.10 (m, 14H), 2.1 (s, 3H), 2.30-3.00 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 211.739, 211.284, 114.908, 55.600, 47.795, 44.806, 42.269, 31.915, 28.353, 27.052, 26.532, 26.077, 25.361, 23.801, 21.588, 19.962; mp 107-108°C.

Adduct (20) This crude material gave spectral data characteristic of an aldol product--IR (film) 3440 cm^{-1} ; NMR ($CDCl_3$) δ 2.95 (dd, 2H(J = 6Hz, 8Hz)). Further proof of this structure was obtained by conversion of (20) to (23).

4-Methylethenyl-1-(1-propene-3-oxo-3-(1-cyclohexenyl))-
cyclohexene (23)

Adduct (20) (ca. 0.54 mmol) was dissolved in 3mL CH_2Cl_2 and cooled to 0°C . Triethylamine (1.2 mmol) was added with stirring followed by methanesulfonyl chloride (0.54 mmol). The cooling bath was removed, and the reaction was stirred for 24h at room temperature. The reaction was diluted with diethyl ether and washed once with saturated aqueous NaHCO_3 (5 mL). The organic phase was collected and dried (Na_2SO_4). Chromatographic purification (silica gel) of the residue gave the trienone (23) as a viscous yellow oil IR (film) 2945, 1655, 1595, 1290, 1200 cm^{-1} ; NMR (CDCl_3) δ 1.23 (m, 2H), 1.63 (m, 5H), 1.75 (bs, 3H), 2.00-2.50 (m, 8H), 4.74 (bs, 2H), 6.22 (bt, 1H), 6.60 (d, 1H), 6.92 (bt, 1H), 7.30 (d, 1H); high resolution mass spectrum for $\text{C}_{18}\text{H}_{24}\text{O}$ requires m/e 256.18232, found m/e 256.18311.

4-Oxo-5-methyl-12-oxo-tetradecahydrophenanthrene (26)

2-Methyl-2-cyclohexen-1-one (1.0 mmol) was dissolved in CH_2Cl_2 (8 mL). Dienol silyl ether (15) (1.0 mmol) was then added with stirring as a 0.5M solution in CH_2Cl_2 . This solution was cooled to 0°C and a solution of ethyl-

aluminum dichloride (1.8M in toluene, 0.53 mL) was added dropwise. After the addition, the reaction was allowed to warm to room temperature. After 1.5 h, the reaction was quenched with 2 mL of 2M HCl, poured into diethyl ether (20 mL), and washed once with water (5 mL) and once with saturated aqueous NaHCO₃ solution (5 mL). The organic layer was separated and dried (Na₂SO₄). Removal of the solvent gave a white crystalline solid IR (film) 2940, 1705, 1450, 1250 cm⁻¹; NMR (CDCl₃) δ 0.80-3.00 (m, 22H), 1.32 (s, 3H); ¹³C NMR (CDCl₃) δ 213.560, 210.243, 52.674, 49.877, 47.795, 44.806, 44.025, 37.522, 27.637, 27.507, 26.207, 25.947, 25.556, 25.036, 15.478.

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GENERAL CONCLUSION

It was the purpose of this thesis work to develop new cyclization sequences to be used toward the synthesis of various carbocyclic terpenes. Three such sequences were discovered.

One sequence dealt with the 1,4-conjugate addition of various furans to certain cyclic enones mediated by iodotrimethylsilane.

Another sequence utilized the same general reaction except that dienol silyl ethers were employed instead of furans to yield bicyclic and tricyclic compounds. These compounds would be useful for the synthesis of several diterpene analogues such as the steroids or the quassinoids.

The final sequence dealt with β -hydroxy- γ -lactone synthesis. This was done with the novel reagent bromoacetaldehyde which we were able to produce in anhydrous form. We have ultimately improved the reaction sequence to entail a one-pot procedure resulting in good yields of the desired products. Such products could be used toward the synthesis of naturally occurring β -hydroxy- γ -lactones such as the litsolenolides.