THE ESTER ENOLATE CLAISEN REARRANGEMENT

I. Stereochemical Control Through Stereoselective Enolate Formation

II. Construction of the Prostanoid Skeleton

Thesis by

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to bill weber
who got me started

to carla
who kept me going

when life gives you lemons
make lemonade

Acknowledgements

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Abstract

Part I:

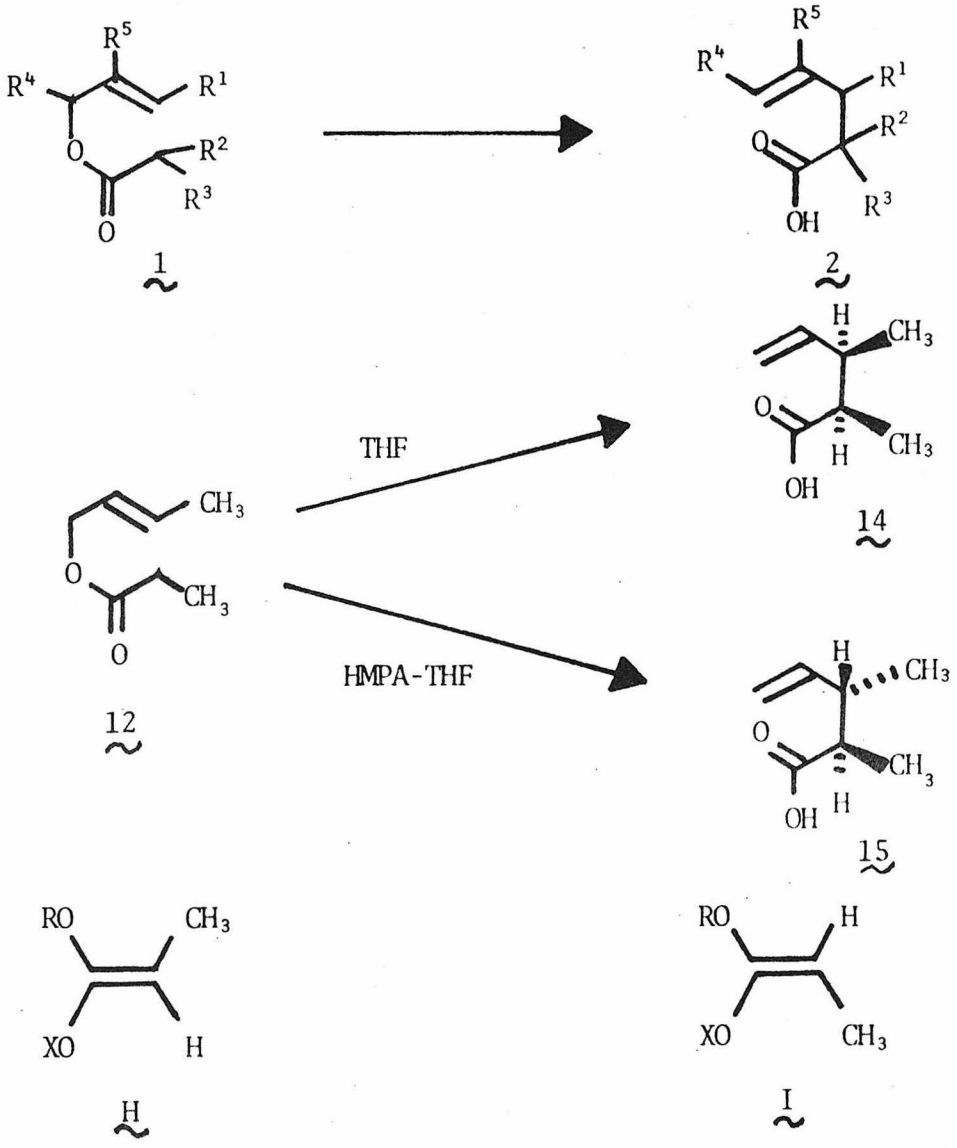
The [3,3]-sigmatropic rearrangement of a number of allylic esters 1, as the enolate anions or the corresponding silyl ketene acetals, produces the γ,δ-unsaturated acids 2 in 66 - 88% yield. The mild conditions allow rearrangement of acid sensitive and thermally labile esters. Rearrangement of ester 1g affords (E)-4-decenoic acid (2g) with greater than 99% stereoselectivity. (E)-Crotyl propanoate (12) leads to erythro-acid 14 when enolization is carried out in THF, but to the threo-acid 15 when the solvent is 23% HMPA-THF. Results with a variety of esters demonstrate that kinetic enolization with lithium diisopropylamide gives selective formation of the geometrical enolate H in THF and the isomeric enolate I in HMPA-THF. Similar results are obtained with 3-pentanone. (Scheme I)

Part II:

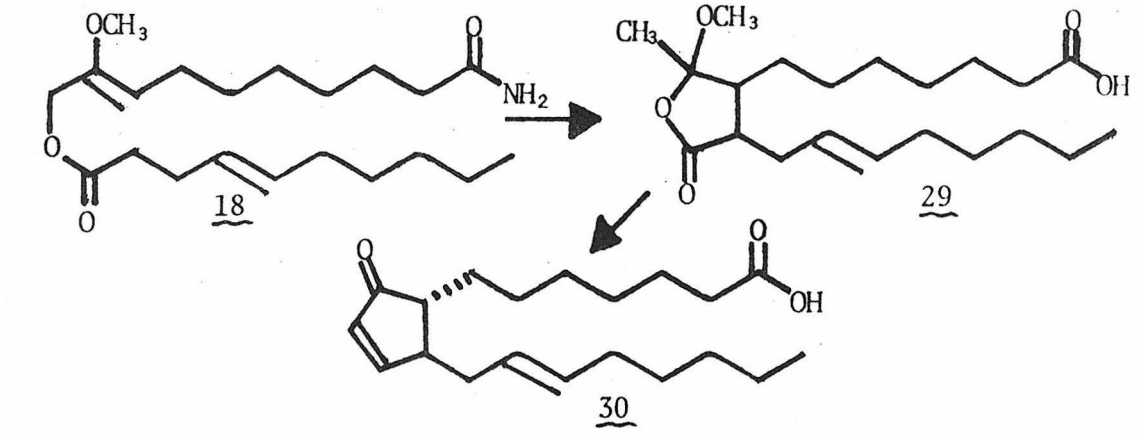
A convergent synthesis of the prostaglandin skeleton is described. The ester enolate modification of the aliphatic Claisen rearrangement is used to form the key C_8-C_{12} bond. Rearrangement of ester 18 provides the lactone 29 which is converted to the prostanoid 30. Similarly, the lactone 52, a potential intermediate in the synthesis of 12-methyl PGA_1, is obtained from ester 51. Preparation of ester 51 features Claisen rearrangement of ester 38, which leads to the dienoate 41 after

desulfenylation. Model studies of reduction of γ,δ-epoxy-α,β-unsaturated esters to δ-hydroxy-β,γ-unsaturated esters are described. This reduction is accomplished with lithium in ammonia at -78° for conversion of epoxy ester 50 to ester 51. (Scheme II)

Scheme I:



Scheme II: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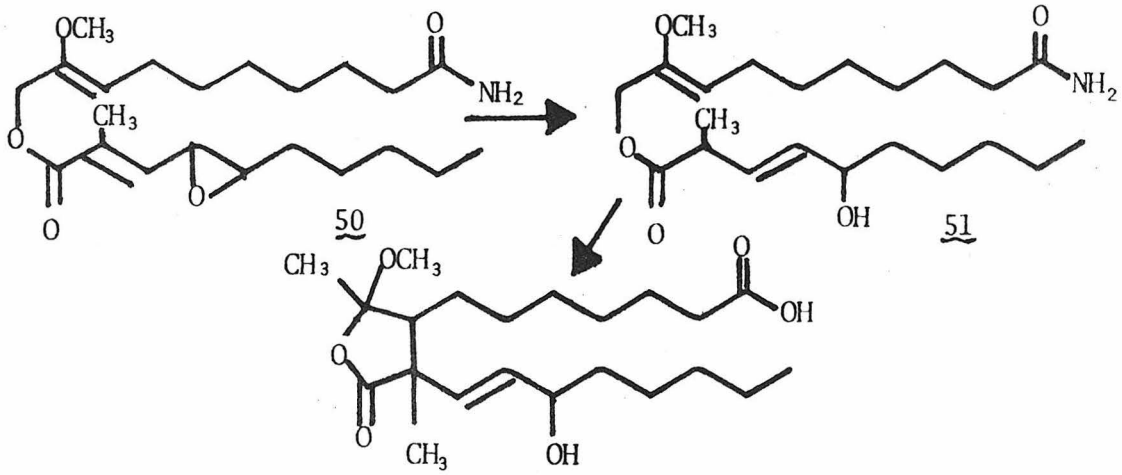
O
OH
30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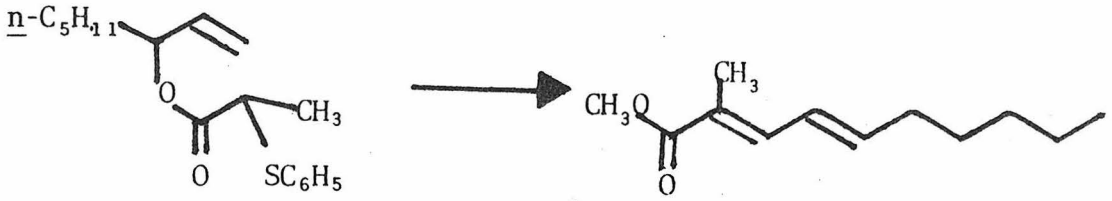
O
CH3
OH
52


n-C5H11
O
CH3
O
SC6H5
38
CH3
CH3O
O
41

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PART I

Stereochemical Control Through Stereoselective Enolate Formation[1]

Consideration of possible synthetic approaches to prostanoids suggested a convergent scheme which would incorporate the connection of a "top-half" and a "bottom-half" as a key step in the synthesis. Further analysis indicated that the required carbon-carbon bond could be generated by Claisen rearrangement of a properly designated substrate. This rearrangement would also result in the correct number of suitably functionalized carbon atoms for subsequent generation of the cyclopentanone ring system.

In order to take complete advantage of the convergence inherent in this scheme, the efficient use of both "halves" of the molecule in this key step was essential. The most popular procedures for the aliphatic Claisen rearrangement--vinyl ether,[2] ortho ester,[3] and amide acetal[4]--were not acceptable because of their use of one of the reaction partners in excess. These considerations led us to investigate the possibility that enolate anions derived from allyl esters would undergo a similar [3,3]-sigmatropic rearrangement.

Conceptually, this ester enolate Claisen rearrangement offered two major advantages. Connection of the two hydrocarbon fragments would be accomplished by ester formation. Such a reaction could be carried out in high yield under mild conditions and would require only equivalent amounts of either component. The generation of the required 1,5-diene system would occur through enolization under basic conditions rather than with the acid catalysis required in the vinyl ether[2] and ortho ester[3] rearrangements. These basic reaction conditions would be compatible with a variety of functional groups.

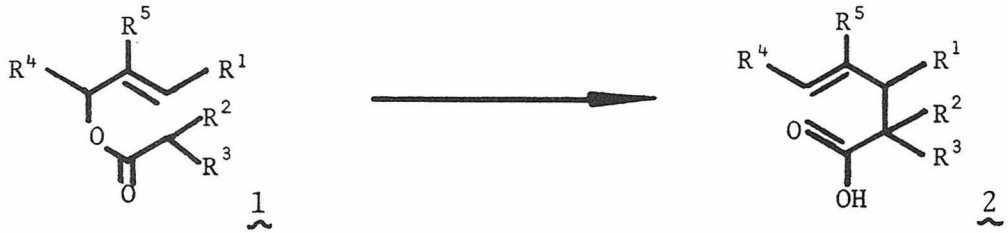
Base catalyzed rearrangement of a few allyl esters had been observed.[5] The special nature of the esters, the harshness of the conditions, and the low yields severely limited the usefulness of this procedure as a general synthetic transformation. A solution for these problems became apparent as a result of investigations by Rathke[6] which provided a method for the quantitative generation of ester enolates free from competing aldol-type condensation reactions. Indeed, the application of these methods to a variety of allyl esters resulted in enolate anions and/or the corresponding trimethylsilyl ketene acetals which underwent Claisen rearrangement under surprisingly mild conditions.[7]

Further development of these reaction conditions was necessary to avoid fragmentation of the enolate anions themselves and C-silylation by trimethylchlorosilane (TMSCl).[7] The use of tert-butyldimethylchlorosilane (TBSCl)[8] in the presence of hexamethylphosphoramide (HMPA) to trap the enolates afforded excellent yields of the corresponding silyl ketene acetals and the procedure presented here (see experimental section) appears to be quite general (TABLE I).

The advantage of the basic reaction conditions is demonstrated by the rearrangement of the ester 1j which would be impossible under the acidic conditions of the vinyl ether and ortho ester rearrangements.

An additional advantage in the use of TBSCl is worthy of note. The silyl esters (e.g., 3j) which result from rearrangement are sufficiently stable to permit isolation, but can be conveniently and mildly transformed into a variety of other functional groups,

TABLE I. Claisen Rearrangement of Allyl Ester Enolates



1 2

Ester	R^1	R^2	R^3	R^4	R^5	Procedure[a]	Yield(%)[b]
1a	H	H	H	H	H	B	66
1b	CH_3	H	H	H	H	B	70
1c	CH_3	CH_3	H	H	H	A(B)	75(75)
1d	CH_3	CH_3	CH_3	H	H	A(B)	80(78)
1e	CH_3	(E)-C_2H_5CH=CH	H	H	H	A	69
1f	n-C_6H_{13}	CH_3	H	H	CH_3	A	71
1g	H	H	H	n-C_5H_{11}	H	C	83
1h	H	CH_3	C_6H_5S	n-C_5H_{11}	H	C	88
1i	n-C_6H_{13}	(E)-C_2H_5CH=CH	H	H	CH_3O	C	77[c]
1j	n-C_6H_{13}	n-C_3H_7	H	H	CH_3O	C	80[c]
1k	CH_3	n-C_4H_9	Br	H	H	D	71[d]

Footnotes to TABLE I.

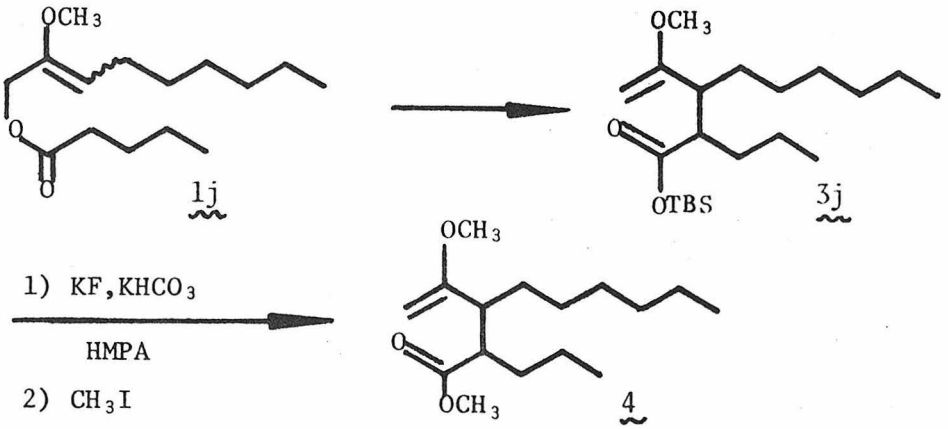
[a] A= rearrangement as the enolate anion prepared with LICA; B= rearrangement as the trimethylsilyl ketene acetal; C= rearrangement as the tert.-butyldimethylsilyl ketene acetal; D= rearrangement as the tert.-butyldimethylsilyl ketene acetal prepared by reaction of the α-bromo ester with Zn and TBSCl in THF-HMPA.

[b] Yield of acid after hydrolysis of the silyl ester.

[c] Yield of methyl ester prepared by cleavage of silyl ester with KF in HMPA followed by alkylation of carboxylate anion with iodomethane.

[d] R^3 = H in the product acid.

including alkyl esters (e.g., 4).



The temperatures required for the rearrangement itself are quite mild in comparison with the temperatures in excess of 100^0 which are required for the generation of, or the rearrangement of, the 1,5-diene system for the alternative procedures mentioned above. A few approximate half-lives (TABLE II) serve to demonstrate the remarkable ease with which the rearrangement occurs as well as a few effects of structure on reactivity. A distinct advantage of this facile rearrangement is that esters whose structure permits the possibility of competing thermal reactions can be employed in the rearrangement. For instance, no problem of Cope rearrangement of the silyl ester 3i generated in the rearrangement of 1i is encountered.

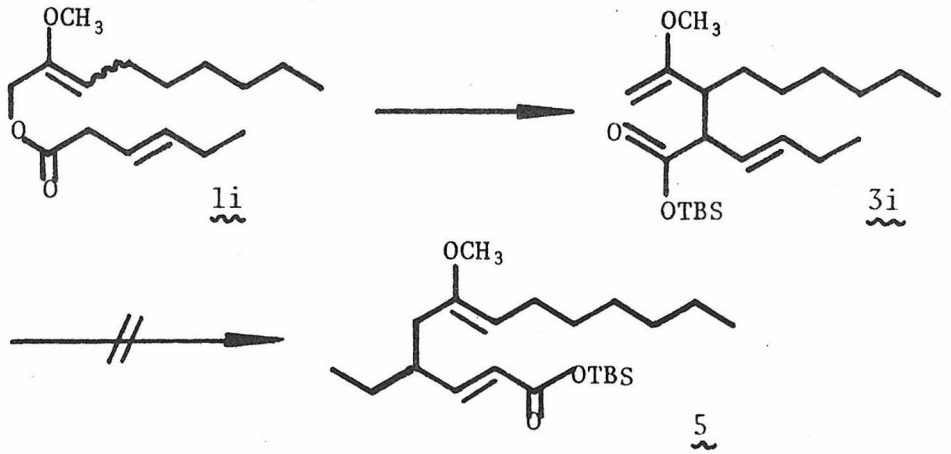
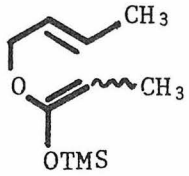
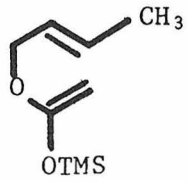
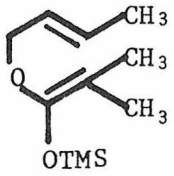
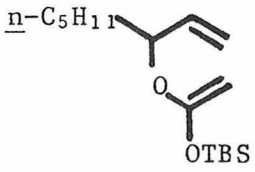
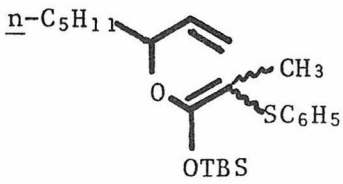


TABLE II. Half-Lives for Rearrangement of Silyl Ketene Acetals at 32°[a]

Ketene Acetal[b]	$t_{1/2}$ (min)[c]	Ketene Acetal[b]	$t_{1/2}$ (min)[c]
 4a	210 ± 30	 4c	5 ± 1
 4b	150 ± 30	 4d	<<1
 4g	6 ± 1	 4h	<1

[a] Not isolated but generated in situ as described in TABLE I and experimental section.

[b] TMS = $(CH_3)_3Si$; TBS=tert.-Bu $(CH_3)_2Si$.

[c] By NMR analysis of silicon methyl region as described in experimental section.

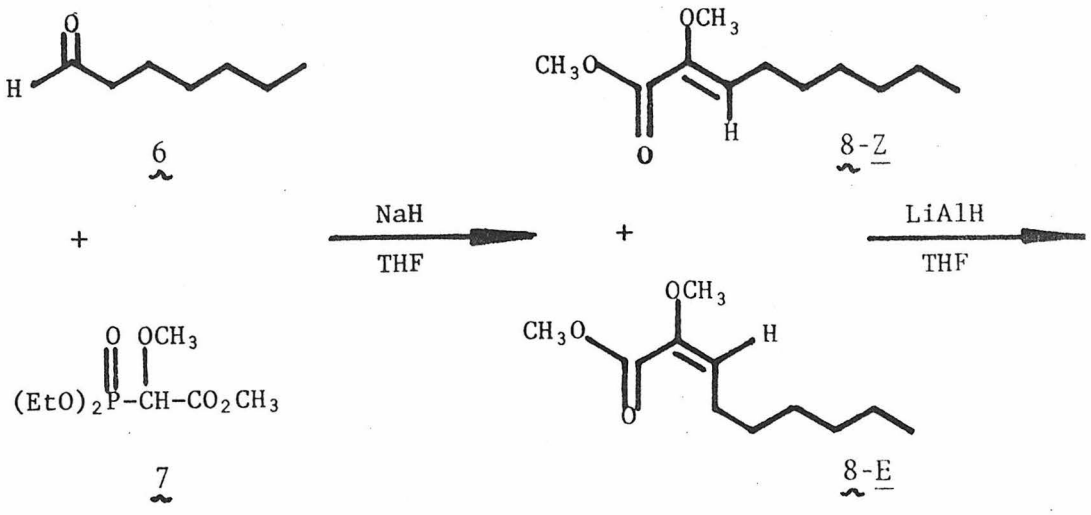
An alternative approach to silyl ketene acetals is demonstrated in the rearrangement of ester 1k. The reaction of this α-bromo ester with zinc and TBSCl in THF-HMPA generates the required silyl ketene acetal under quite mild conditions, and the rearrangement proceeds with the usual facility.[9]

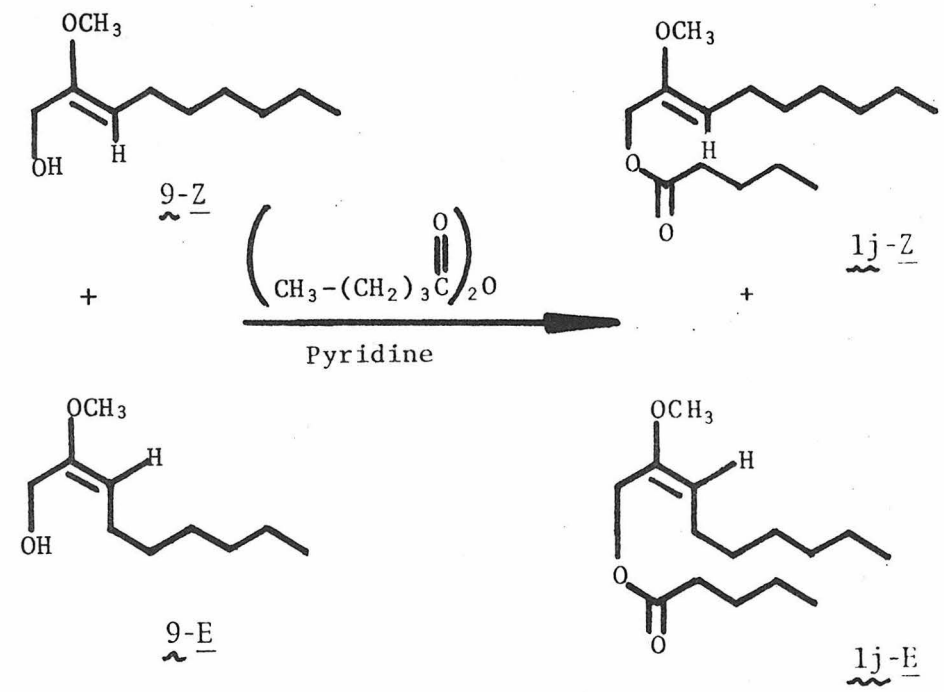
Methoxy substituted allyl alcohol synthons such as 9 employed in the esters 1i and 1j have proven to be highly useful in the synthesis of cyclopentanone derivatives[7,10] and deserve further comment. The 2-alkoxy-α,β-unsaturated esters such as 8 are readily available by the Wittig synthesis developed by Grell and Machleidt[11] (SCHEME I). This procedure results in approximately a 1:1 mixture of E- to Z-isomers which may be carried through the rearrangment sequence or separated by silica gel chromatography. Reduction by lithium aluminum hydride gives cleanly the allylic alcohols 9 which can be converted to stable esters such a 1j under a variety of non-acidic reaction conditions.

In the course of the Claisen rearrangement, both a new carbon-carbon double bond and a new carbon-carbon single bond are formed. To assess further the synthetic utility of the transformation, the stereochemical outcome at both of these sites was investigated.

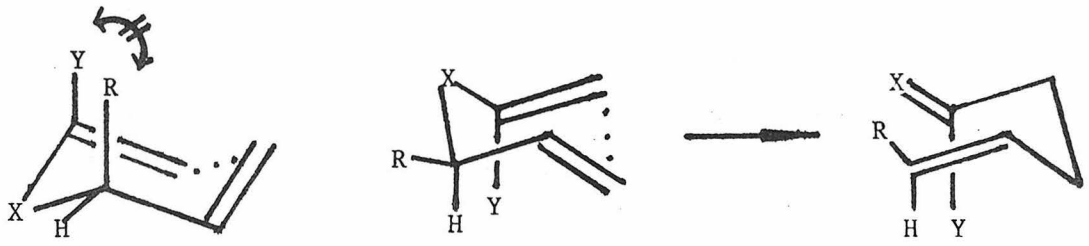
Ample theoretical considerations[12] and experimental evidence[3,13-17] on various [3,3]-sigmatropic rearrangements indicate quite clearly that, in the absence of any unusual steric constraints, the rearrangement proceeds through a chair-like transition state. An examination of non-bonded interactions readily indicates which of the two possible transition states A or B will be favored. The equatorial

SCHEME I.



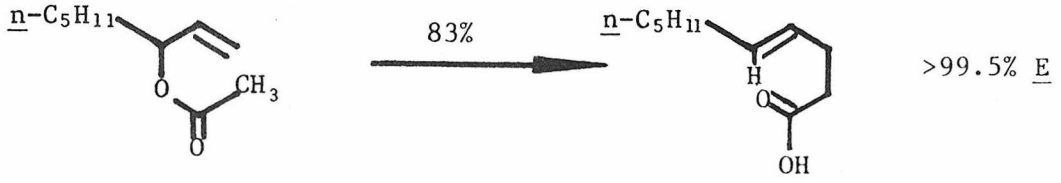


disposition of R puts transition state B at lower energy which results in predominant formation of the E-double bond.[17]

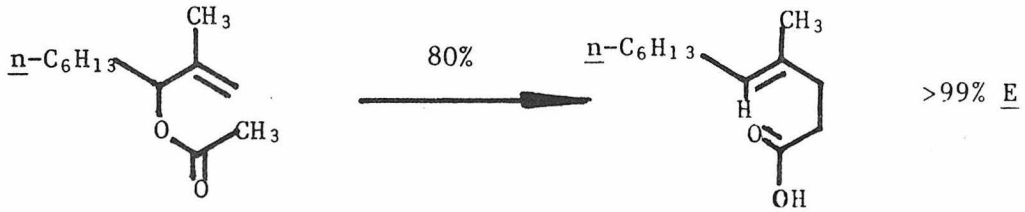


A B C

Not surprisingly, this predominance is found for the ester enolate Claisen rearrangement as well. The rearrangement of ester 1g leads to the acid 2g with greater than 99% stereoselectivity. Similar observations have been made by Katzenellenbogen[18] who finds greater than 98% stereoselectivity for formation of the E-trisubstituted double bond in acid 11.



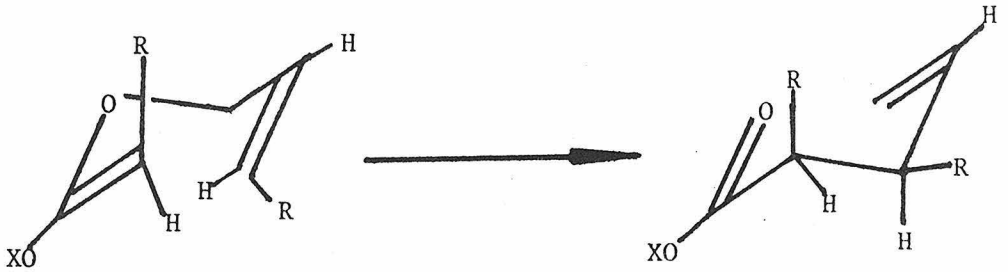
1g 2g



10 11

A second consequence of the chair-like transition state is that the stereochemistry about the newly formed carbon-carbon single bond can be predicted from the geometries of the double bonds in the starting 1,5-diene system. Although a priori it was not obvious that enolization would result in selective formation of one of the two isomeric enolates, the stereochemical consequence of rearrangement of either enolate isomer is predictable.[14-16] Silyl ketene acetal D (x = TBS) will give the acid F, while E will lead only to acid G. Similar arguments can be made for esters containing a cis-double bond in the allylic alcohol fragment.

D F



E G

Rearrangement of (E)- and (Z)-crotyl propanoate (12 and 13) was used to probe the stereochemical outcome of enolization (SCHEME II).

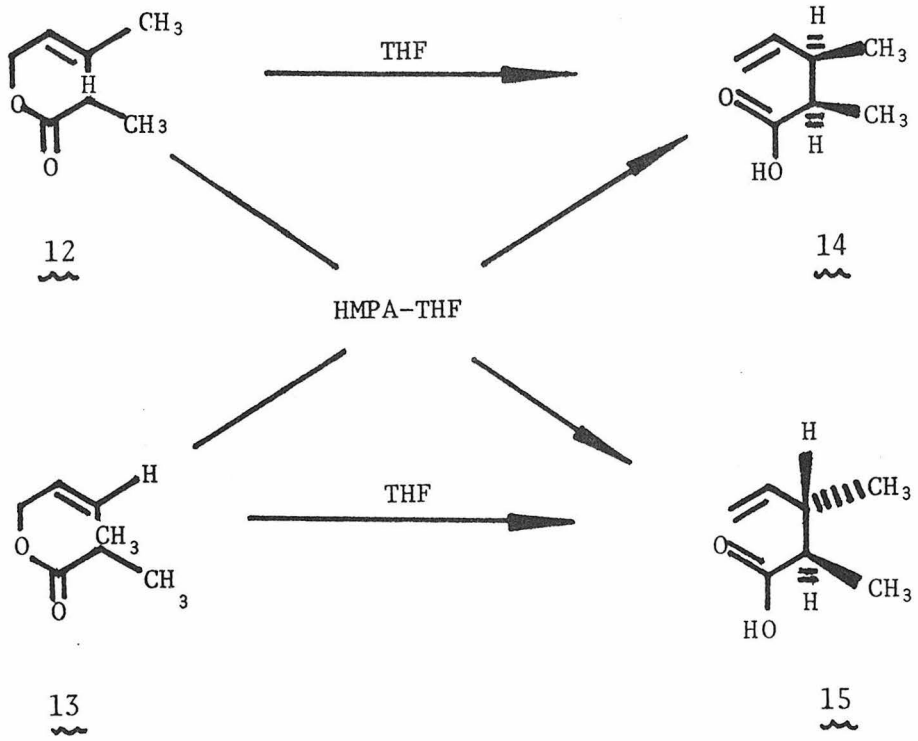
The data in TABLE III demonstrates the unanticipated effect of solvent polarity on the ratio of erythro 14 to threo 15 products obtained in the rearrangement. When (E)-crotyl propanoate (12) is enolized in tetrahydrofuran (THF) and allowed to rearrange as either the enolate anion or the derived silyl ketene acetal, selective formation of the erythro-acid 14 is observed. When the more coordinating solvent system, 23% HMPA-THF is employed, enolization takes an alternate course and the threo-acid 15 predominates. Rearrangement of (Z)-crotyl propanoate (13) gives the expected complete reversal of product ratios and verifies that the product determining step is indeed enolization.

These results indicate that in THF the Z-type enolate H is preferentially formed and trapped but when the solvent is 23% HMPA-THF, enolization leads to the geometrically isomeric E-type enolate anion I.

As was mentioned above, rearrangement of the enolate anion is only preparatively useful in specific cases. Only the enolate anion formed in THF from (E)-crotyl propanoate (12) rearranges in good yield. The low yields obtained with the other enolate anions probably reflect variable activation energies for rearrangement[15] and the known reactivity of ester enolates at temperatures above -78^{0}.[7,8] It is worthy of note, however, that the enolate anions show no tendency to interconvert.

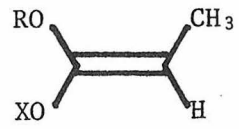
To evaluate these initial observations and to determine the generality of the process, the synthetically more interesting esters 1j were examined under similar conditions (SCHEME III and TABLE IV).

SCHEME II.



12 14

13 15



H

I

X = Li, TBS

TABLE III. Effect of Solvent on Rearrangement of (E)- and (Z)-Crotyl Propanoate (12 and 13).

Ester	Conditions[a]	Solvent[b]	Yield(%)[c]	14/15[d]	Enolate[e]
12	Anion	THF	86	92/8	H
12	Ketene Acetal	THF	79	87/13	H
12	Anion	HMPA-THF	21	13/87	I
12	Ketene Acetal	HMPA-THF	73	19/81	I
13	Anion	THF	6	25/75	H
13	Ketene Acetal	THF	75	11/89	H
13	Anion	HMPA-THF	--	--	--
13	Ketene Acetal	HMPA-THF	75	86/14	I

[a] The rearrangement was carried out as the enolate anion (Anion) or this anion was quenched with TBSCl before rearrangement (Ketene Acetal).

[b] THF=100% THF; HMPA-THF=23 vol% HMPA-THF.

[c] Isolated and distilled.

[d] Determined by glpc analysis of methyl esters as described in experimental section.

[e] The geometrical enolate which would lead to the predominate product assuming a chair-like transition state.

In this case the derived silyl esters were cleaved with potassium fluoride in HMPA[19] and the resulting carboxylate salts were esterified with methyl iodide.[20] Analysis of the mixture of methyl esters by NMR indicated that again the same stereoselectivity pertained. The isomeric products were easily separated by silica gel chromatography, but the stereochemistry could not be unambiguously assigned from the spectral data. The assignment in TABLE IV and SCHEME III is based on the outcome of experiments with crotyl propanoates 12 and 13.

This stereoselectivity is even more general. The silyl ketene acetals obtained by trapping simple ester enolates with TBSCl can be isolated in quantitative yield.[8] When this procedure is used to study the enolization of a variety of esters, a high degree of selectivity for formation of one enolate in THF and the isomeric enolate in HMPA-THF is observed in nearly every case (TABLE V). Only methyl phenylacetate (18b), in which the enolate is stabilized by conjugation with an aromatic ring, does not exhibit the changeover in stereoselectivity. Again, the stereochemistry of the ketene acetals 19 and 20 cannot be deduced from the spectral data (see TABLE VI) and is assigned by comparison with the results from the crotyl propanoates 12 and 13 (TABLE III and SCHEME II) and for 3-pentanone (vide infra).

The question quickly arises whether these results apply only to esters or whether the selective formation of either geometrical enolate of ketones is possible. The symmetrical ketone, 3-pentanone, in which no problem of regioselectivity arises, was chosen for study. Again, a high degree of selectivity for one enolate in THF and the other in HMPA-THF was observed (TABLE V). The silyl enol ethers were

SCHEME III.

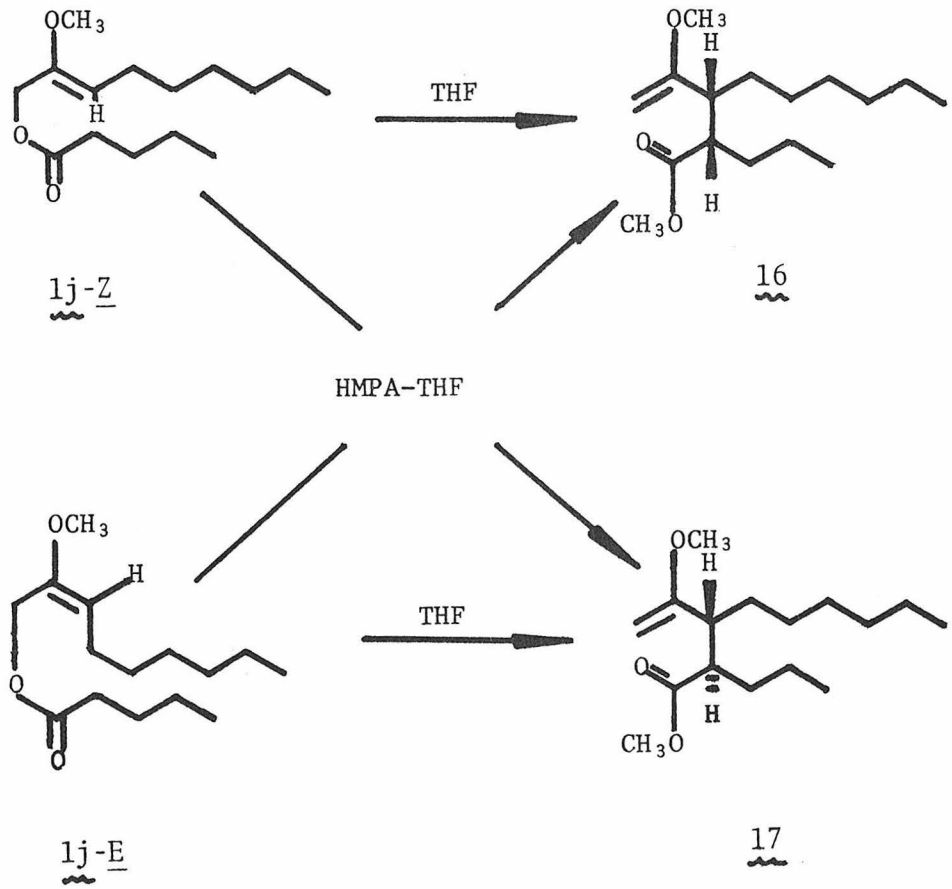

OCH3
H
O
O
THF
OCH3
H
O
CH3O
H
1j-Z
16
HMPA-THF
OCH3
H
O
O
THF
OCH3
H
O
H
CH3O
1j-E
17

TABLE IV. Effect of Solvent on Rearrangement of (Z)- and (E)-2-Methoxy-2-nonenyl Pentanoate (1j-Z and 1j-E).[a]

Ester	Solvent[b]	16/17[c]	Yield(%)[d] Major Isomer
1j-Z	THF	88/12	68
1j-Z	HMPA-THF	20/80	57
1j-E	THF	21/79	59
1j-E	HMPA-THF	85/15	69

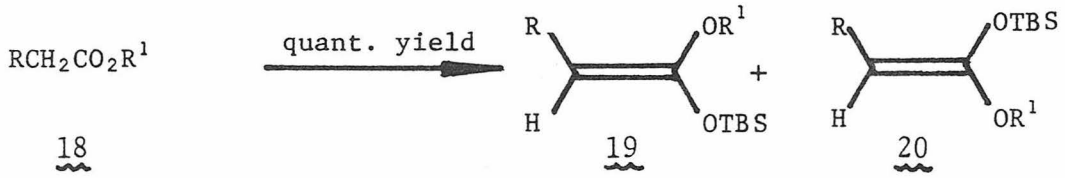
[a] Rearranged as the silyl ketene acetal (TBS); converted to methyl esters as described in experimental section.

[b] THF=100% THF; HMPA-THF=23 vol% HMPA-THF.

[c] From NMR analysis of methyl esters.

[d] After chromatographic separation.

TABLE V. Effect of Structure on Ratio of Enolates.[a]



18 19 20

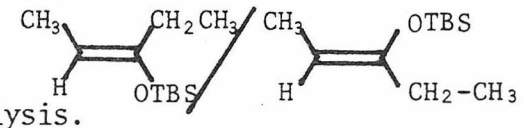
Ester	R	R^1	Solvent[b]	19/20[c]
18a	C_2H_5	CH_3	THF	91/9
18a	C_2H_5	CH_3	HMPA-THF	16/84
18b	C_6H_5	CH_3	THF	29/71
18b	C_6H_5	CH_3	HMPA-THF	5/95
18c	$(CH_3)_3C$	CH_3	THF	97/3
18c	$(CH_3)_3C$	CH_3	HMPA-THF	9/91
18d	C_2H_5	$(CH_3)_3C$	THF	95/5
18d	C_2H_5	$(CH_3)_3C$	HMPA-THF	23/77
	3-Pentanone		THF	77/23[d,e]
	3-Pentanone		HMPA-THF	5/95[d,e]

[a] Enolization with 1.1 equiv LDA at -78°, trapped with TBSCl, HMPA.

[b] THF = 100% THF, HMPA-THF = 23 vol% HMPA-THF.

[c] By NMR analysis of isolated mixture.

[d] Ratio represents:



[e] By NMR or VPC analysis.

TABLE VI. NMR Data for Silyl Ketene Acetals 19 and 20.[a]

Ketene Acetal	R	R^1	δ R	δ R^1	δ vinyl H	δ CH_3Si	δ $(CH_3)_3CSi$
19a	C_2H_5	CH_3	--	3.55(s)	3.72(t)[b]	0.18(s)	0.95(s)
20a	C_2H_5	CH_3	--	3.45(s)	3.43(t)[c]	0.12(s)	0.92(s)
19b	C_6H_5	CH_3	7.3(m)	3.73(s)	4.72(s)	0.30(s)	1.02(s)
20b	C_6H_5	CH_3	7.3(m)	3.67(s)	4.60(s)	0.23(s)	1.00(s)
19c	$(CH_3)_3C$	CH_3	1.06(s)	3.52(s)	3.75(s)	0.18(s)	0.95(s)
20c	$(CH_3)_3C$	CH_3	1.10(s)	3.43(s)	3.37(s)	0.15(s)	0.93(s)
19d	C_2H_5	$(CH_3)_3C$	--	1.32(s)	3.88(t)[d]	0.15(s)	0.92(s)
20d	C_2H_5	$(CH_3)_3C$	--	1.25(s)	3.90(t)[d]	0.12(s)	0.90(s)

[a] 10% solution in $CDCl_3$, internal standard $CHCl_3$, chemical shifts in ppm downfield from TMS.

[b] J = 7.2 Hz.

[c] J = 6.8 Hz.

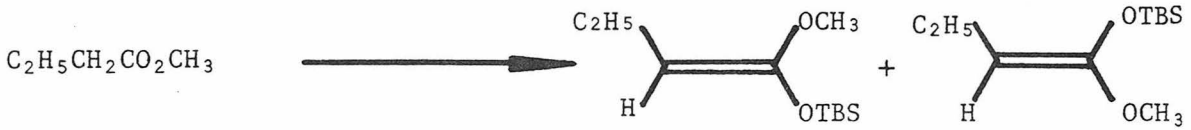
[d] J = 7 Hz.

easily separated by VPC and readily identified by NMR (see Experimental Section).[21,22] The unambiguous stereochemistry in this case reinforces the assignments for the esters above (TABLE V).

In order to gain further insight about the mechanism, methyl butanoate (18a) was subjected to enolization and trapping under a variety of conditions. The results recorded in TABLE VII point out a smooth change from one enolate (19a) with no HMPA present to predominately the other (20a) as the amount of HMPA increases to the point of saturation. There is no discrete molar quantity which effects the changeover in stereoselectivity. The kinetic nature of the stereoselectivity is supported by the fact that the enolate formed in THF maintains its integrity in the presence of HMPA (entry 2) and that the silyl ketene acetal formed in THF is stable for at least two hours in the reaction medium at 67° (entry 1). When the enolization is carried out in HMPA-THF, the trapping agent (TBSCl) may be present during the enolization or added afterward with no change in the outcome (entries 6 and 7).

It appears that the observed stereoselectivity results from the kinetic enolization of esters and ketones, and that this enolization takes a different course as a function of the solvent employed. One explanation for this dramatic solvent effect may lie in an analysis of the steric requirements for enolization. Two transition states J and K leading to the two enolates can be imagined. When the solvent is the less-coordinating THF, the interaction of the carbonyl oxygen with the lithium cation must be quite important, and the carbonyl oxygen becomes effectively bulkier than OR'. The resulting

TABLE VII. Effect of HMPA Concentration on Ester Enolate Isomer Ratio.[a]



18a 19a 20a

	Equiv. HMPA[b]	Solvent	19a/20a[c]
1.	0	100% THF	91/9[d]
2.	0	100% THF[e]	85/15
3.	0.5	3% HMPA-THF	89/11
4.	1.0	6% HMPA-THF	53/47
5.	2.0	11% HMPA-THF	23/77
6.	4.7[g]	23% HMPA-THF	16/84
7.	4.7[g]	23% HMPA-THF	16/84[f]

[a] Enolized with 1.1 equiv LDA in 0.3 M solution.

[b] Based on LDA.

[c] By NMR analysis.

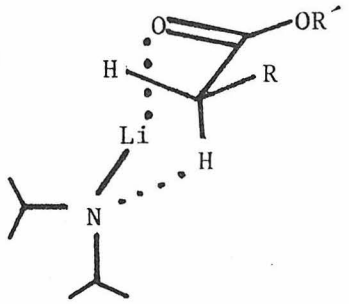
[d] No change after heating ketene acetals in reaction medium for 2 hr at 67°.

[e] Following enolization, 4.7 equiv HMPA added, stirred for 4 min at -78° then quenched with TBSCl.

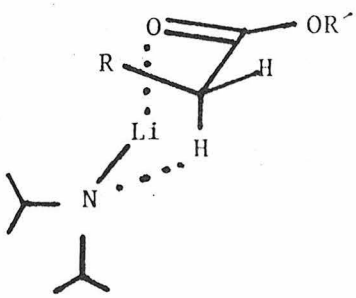
[f] A mixture of TBSCl and ester added to LDA solution.

[g] This quantity of HMPA is not entirely soluable at -78°.

non-bonded interactions would bestow a higher activation energy on transition state K and enolization would be expected to proceed through transition state J. The presence of HMPA, on the other hand,



J



K

should result in a greater degree of solvation of the lithium cation and an enhanced reactivity of the amide base. The lithium - carbonyl oxygen interaction should be much weaker and transition state K, in which R becomes eclipsed with the now sterically smaller carbonyl oxygen during enolization, should be favored.

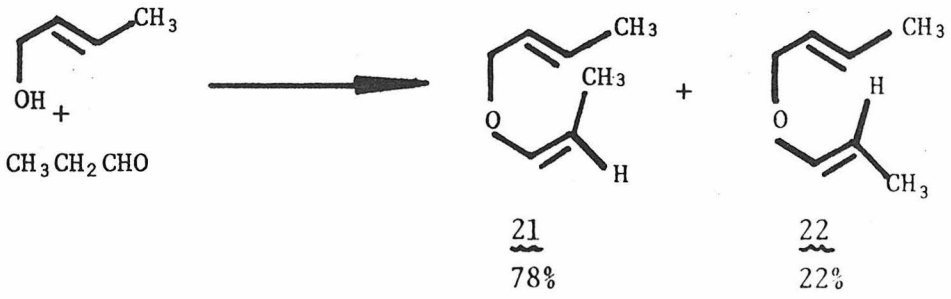
This degree of control over the stereochemistry of the 1,5-diene unit enormously expands the potential of the ester enolate Claisen rearrangement and provides the synthetic chemist with a powerful weapon with which to attack the problem of stereochemistry of acyclic molecules. The ability to generate selectively the desired stereochemistry in the rearranged products regardless of the stereochemistry present in the starting material places this modification in a unique

position among procedures for the aliphatic Claisen rearrangement.

The stereochemical outcome of the vinyl ether rearrangement has been investigated by Schmid[15] who notes a preponderance of the cis-propenyl ether 21 from the reaction of crotyl alcohol with propanal in the presence of phosphoric acid. A similar result was obtained in a study of the amide acetal rearrangement by Sucrow and Richter.[16] In this case a strong preference for formation of the Z-configuration 24 of the intermediate ketene O,N-acetal was inferred from the stereochemistry of the rearrangement products. The opposite stereochemistry of the ketene acetal portion of the molecule has been obtained by requiring this double bond to lie in a ring (e.g., 28). Cyclic ortho esters such as 26 have been successfully employed in this approach by Lythgoe.[23]

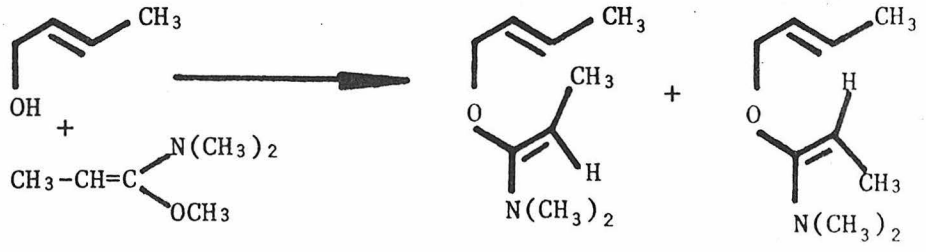
As well as extending the utility of the Claisen rearrangement, these results have general implications in other synthetic reactions. Recent reports have related enolate geometry to intermolecular reactions including aldol condensation[24-26] and alkylation reactions.[27] The rapidly increasing use of ketone and ester enolates as versatile intermediates in organic synthesis will undoubtedly unveil more of these relationships. The complementary conditions which have been described here for stereoselective enolization should find useful application in these areas as well.

SCHEME IV.



21
78%

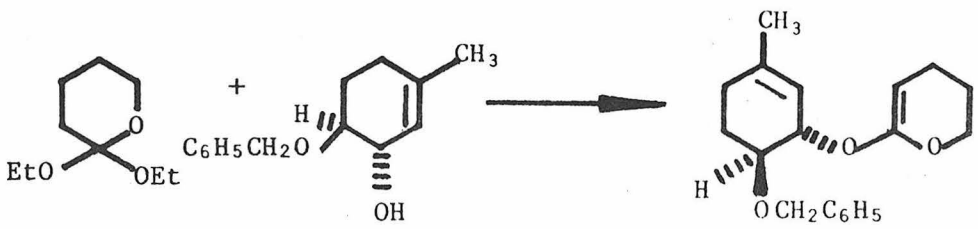
22
22%



23

24
95%

25
5%



26

27

28

Experimental Section[28]

(Z)-2-Buten-1-ol (Cis-Crotyl Alcohol). The following procedure gave the most consistent results. A solution of 7.0 g (0.1 mol) of 2-butyn-1-ol in 75 ml of methanol containing 500 mg of 5% $Pd/BaSO_4$ and 5 ml of s-collidine was stirred rapidly under 1 atm of hydrogen until 2440 ml (0.1 mol) of hydrogen was absorbed (2.25 hr). The reaction mixture was filtered with the aid of celite, and the filtrate was subjected to fractional distillation through a 30-cm vacuum-jacketed Vigreux column. The pot was maintained at 110° while the pressure was gradually lowered. Most of the methanol distilled at atmospheric pressure, with an additional portion distilling as the pressure was lowered to 90 mm. After a small forerun at this pressure, the material distilling at 72-80° (90 mm) was collected. This amounted to 5.6 g (78%). Analysis by VPC[28] (100° and 150°, ¼" x 8' 10% Carbowax 20 M, 60 ml/min, thermocouple) indicated that this material consisted of cis-crotyl alcohol contaminated with 1% methanol, 1% s-collidine and less than 1% trans-crotyl alcohol.

A similar reaction without s-collidine gave cis-crotyl alcohol containing 12% trans-crotyl alcohol and 10% n-butanol.

Methyl (E)-2-Methoxy-2-nonenoate (8-E); Methyl (Z)-2-Methoxy-2-nonenoate (8-Z). To a mechanically stirred suspension of sodium hydride (mineral oil-free) in 50 ml of dry THF was added dropwise over 30 min, 8.0 g (33.3 mmol) of methyl diethoxyphosphinylmethoxyacetate[11] (7). The mixture was stirred for an additional 45 min at 25° and then cooled to 0°. During 30 min, the reaction mixture was

treated with 3.8 g (33.3 mmol) of heptanal (6) in 5 ml of dry THF while vigorous stirring was maintained. Toward the end of the addition a gummy precipitate formed. The reaction mixture was allowed to warm to 25° and stirring was continued for 2 hr. After cautious addition of 25 ml of water, the product esters were isolated by ether extraction.[29] The slightly brown liquid residue was subjected to evaporative distillation at 45° (0.08 mm) and gave 5.7 g (85%) of the unsaturated esters. NMR analysis indicated that this was approximately a 1:1 mixture of double bond isomers. Separation of the isomers was accomplished by medium-pressure chromatography[28] of 2.0 g of the mixture on 2.5 x 50 cm of silica gel with 3% ether/petroleum ether at a flow rate of 2 ml/min. Elution with 930 ml gave 686 mg of the Z-isomer 8-Z. An analytical sample was prepared by evaporative distillation at 45° (0.08 mm): NMR ($CDCl_3$) δ3.66 (s, 3H, ether CH_3), 3.78 (s, 3H, ester CH_3), 6.29 (t, 1H, J = 7.5 Hz, vinylic H); ir ($CHCl_3$) 1720 (C = O), 1645 (C = C), 1430, 1275, 1090 cm^{-1}.

Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.99; H, 10.03.

Further elution with 120 ml of the same solvent system gave 245 mg of a mixture of the Z- and E-isomers. Continued elution with 990 ml of this solvent system gave 797 mg of the E-isomer 8-E. An analytical sample was prepared by evaporative distillation at 45° (0.08 mm): NMR ($CDCl_3$) δ3.62 (s, 3H, ether CH_3), 3.83 (s, 3H, ester CH_3), 5.37 (t, 1H, J = 7.5 Hz, vinylic H); ir ($CHCl_3$) 1720 (C = O), 1635 (C = C), 1435, 1370, 1240, 1145 cm^{-1}.

Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 66.03; H, 10.05.

Lithium Aluminum Hydride Reduction of Esters 8. A solution of 380 mg (10.0 mmol) of lithium aluminum hydride in 40 ml of dry ether was cooled to 0^0. This solution was subjected to the dropwise addition of 2.5 g (12.5 mmol) of either the Z- or E-ester 8-Z or 8-E in 5 ml of dry ether over 30 min. The cooling bath was removed and the reaction mixture was stirred at 25^0 for 1 hr. Following this, dropwise addition of 2 ml of ethyl acetate effected destruction of excess hydride. Work-up according to the Fieser procedure[30] afforded 2.1 g (quantitative crude yield) of a colorless oil. A portion of this material was purified by medium-pressure chromatography[28] on 1.25 x 50 cm of silica gel with 60% ether/petroleum ether at a flow rate of 1 ml/min. Elution with 100 ml gave a colorless oil (90%). An analytical sample was prepared by evaporative distillation at 50^0 (0.08 mm).

Z-2-Methoxynon-2-enol (9-Z): NMR ($CDCl_3$) δ3.66 (s, 3H, CH_3O), 4.10 (br s, 2H, $-CH_2O-$), 4.75 (t, 1H, J = 7 Hz, vinylic H); ir ($CHCl_3$) 3650-3400 (OH), 1675 (C = C), 1460, 1150, 1080, 885 cm^{-1}.

Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.70; H, 11.67.

E-2-Methoxynon-2-enol (9-E): NMR ($CDCl_3$) δ3.55 (s, 3H, CH_3O-), 4.16 (br s, 2H, $-CH_2O-$), 4.54 (t, 1H, J = 7.5 Hz, vinylic H); ir ($CHCl_3$) 3590 and 3450 (OH), 1670 (C = C), 1225, 1120, 1055, 1015 cm^{-1}.

Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.57; H, 11.59.

Preparation of Allyl Esters. A. From the Acid Chloride. The following esters were prepared by reaction of 1.0 equiv of the allylic alcohol[31] with 1.0 equiv of the required acid chloride[32] in the presence of 1.1 equiv of pyridine as an 0.3 M solution in dry dichloromethane:

(E)-2-Butenyl Propanoate (12). Yield 92%, bp 65-68° (35 mm): NMR ($CDCl_3$) δ1.13 (t, 3H, J = 7.5 Hz, CH_3), 1.72 (d, 3H, J = 5 Hz, vinylic CH_3), 2.34 (q, 2H, J = 7.5 Hz, $-CH_2C=O$), 4.52 (d, 2H, J = 6 Hz, $-CH_2O-$), 5.70 (m, 2, vinylic H's).

(Z)-2-Butenyl Propanoate (13). Yield 86%, bp 76-79°(60 mm): NMR ($CDCl_3$) δ1.13 (t, 3H, J = 7.5 Hz, CH_3), 1.72 (d, 3H, J = 5 Hz, vinylic CH_3), 2.34 (q, 2H, J = 7.5 Hz, $-CH_2C=O$), 4.65 (d, 2H, J = 5 Hz, $-CH_2O-$), 5.70 (m, 2H, vinylic H's).

(Z)-Methyl-2-nonenyl Propanoate (1f). Yield 63%, bp 75° (0.5 mm): NMR ($CDCl_3$) δ1.65 (br s, 3H, vinylic CH_3), 1.97 (m, 2H, vinylic CH_2), 2.35 (q, 2H, J = 7 Hz, $-CH_2CO_2-$), 4.47 (br s, 2H, $-CH_2O-$), 5.45 (br t, 1H, vinylic H); ir ($CHCl_3$) 1727 (C = O), 1380, 1345, 1280, 1185, 1085, 1015, 940 cm^{-1}.

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.42; H, 11.35.

1-Hexyl-2-propenyl 2-(Phenylthio)propanoate (1h). Yield 88%, evaporatively distilled at 110° (0.05 mm): NMR ($CDCl_3$) δ1.53 (d, 3H, J = 7 Hz, CH_3), 3.87 (q, 1H, J = 7Hz, -CHS-), 5.3 (m, 4H, CH_2=CH-CH-O-), 7.33 (m, 5H, phenyl); ir ($CHCl_3$) 1725 (C = O), 1380, 1260, 1165, 985, 930 cm^{-1}.

Anal. Calcd for $C_{17}H_{24}O_2S$: C, 69.82; H, 8.27; S, 10.96. Found: C, 69.90; H, 8.35; S, 10.89.

(Z)-2-Methoxy-2-nonenyl Pentanoate (1j-Z). Yield 78%, evaporatively distilled at 60° (0.003 mm): NMR ($CDCl_3$) δ3.60 (s, 3H, CH_3O), 4.57 (s, 2H, $-CH_2O-$), 4.86 (t, 1H, J = 7 Hz, vinylic H); ir ($CHCl_3$) 1725 (C = O), 1675 (C = C), 1460, 1165, 960 cm^{-1}.

Anal. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found: C, 70.31; H, 11.03.

(E)-2-Methoxy-2-nonenyl Pentanoate (1j-E). Yield 91%, evaporatively distilled at 60° (0.006 mm): NMR ($CDCl_3$) δ3.53 (s, 3H, CH_3O), 4.62 (s, 2H, $-CH_2O-$), 4.65 (t, 1H, J = 7 Hz, vinylic H). ir ($CHCl_3$) 1730 (C = O), 1670 (C = C), 1260, 1170, 1070 cm^{-1}.

Anal. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found: C, 70.35; H, 10.84.

2-Butenyl 2-Bromohexanoate (1k). Yield 98%, evaporatively distilled at 50° (0.05 mm): NMR ($CDCl_3$) δ1.73 (d, 3H, J = 5 Hz, vinylic CH_3), 4.20 (t, 1H, J = 7 Hz, -CHBr), 4.60 (d, 2H, J = 5 Hz, $-CH_2O-$), 5.7 (m, 2H, vinylic H's); ir ($CHCl_3$) 1735 (C = O), 1380, 1150, 970 cm^{-1}.

Anal. Calcd for $C_{10}H_{17}BrO_2$: C, 48.21; H, 6.88; Found: C, 48.40; H, 6.76.

B. From the p-Nitrophenyl Ester. Esters of E-3-hexenoic acid were prepared by reaction of 1.0 equiv of the alcohol in dry triethylamine solution with 1.0 equiv of p-nitrophenyl E-3-hexenoate, which was prepared as follows: A solution of 10 mmol of p-nitrophenyl trifluoroacetate in 6 ml of dry triethylamine was cooled to 0^0 and treated with 10 mmol of 3-hexenoic acid. This mixture was stirred for 30 min at 0^0 and 30 min at 25^0. Benzene extraction[29] including a base wash afforded p-nitrophenyl E-3-hexenoate as an orange oil: NMR ($CDCl_3$) δ1.02 (t, 3H, J = 7, CH_3), 2.13 (m, 2H, $-CH_2-$), 3.32 (d, 2H, J = 5 Hz, CH_2), 5.68 (m, 2H, -CH=CH-), 7.32 (d, 2H, J = 9 Hz, aromatic), 8.30 (d, 2H, J = 9 Hz, aromatic). The following esters were prepared in this manner:

2-Butenyl (E)-3-Hexenoate (1e). Yield 43%, bp $70-72^0$ (2 mm): NMR ($CDCl_3$) δ1.00 (t, 3H, J = 7 Hz, CH_3), 1.72 (d, 3H, J = 5 Hz, vinylic CH_3), 2.03 (m, 2H, vinylic CH_2), 3.03 (d, 2H, J = 5 Hz, $-CH_2CO_2-$), 4.53 (d, 2H, J = 5 Hz, $-CH_2O-$), 5.63 (m, 4H, vinylic H's); ir ($CHCl_3$) 1728 (C = O), 1685, 1380, 1170, 965 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.35; H, 9.53.

(Z)-2-Methoxy-2-nonenyl (E)-3-Hexenoate (1i-Z). Yield 31%, evaporatively distilled at 65^0 (0.002 mm): NMR ($CDCl_3$) δ3.05 (m, 2H, $-CH_2CO_2-$), 3.60 (s, 3H, CH_3O), 4.57 (s, 2H, $-CH_2O-$), 4.87 (t, 1H, J = 7 Hz, -CH=C-O-), 5.53 (m, 2H, -CH=CH-); ir ($CHCl_3$) 1728 (C = O), 1675, 1460, 1155, 970 cm^{-1}.

Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.64 H, 10.55.

(E)-2-Methoxy-2-nonenyl (E)-3-Hexenoate (1i-E). Yield 65%, evaporatively distilled at 60° (0.006 mm): NMR ($CDCl_3$) δ3.05 (d, 2H, J = 5 Hz, $-CH_2CO_2-$), 3.52 (s, 3H, CH_3O), 4.62 (s, 2H, $-CH_2O-$), 5.57 (m, 2H, -CH=CH-); ir ($CHCl_3$) 1728 (C = O), 1670, 1465, 1160, 970 cm^{-1}.

Anal. Calcd. for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.61; H, 10.66.

Claisen Rearrangement of Esters 1a-f (TABLE I). A. As the Enolate Anion. A stirred solution of 1.70 g (12.1 mmol) of dry N-isopropylcyclohexylamine in 20 ml of dry THF was cooled to 0° and treated with 5.0 ml (11.1 mmol) of n-butyl lithium in hexane solution over several minutes. After the mixture was stirred for an additional 10 min following the addition, the solution was cooled to -78° and 10 mmol of the appropriate ester (1a-f) was added dropwise over 2-3 min. After an additional 2 min, the cooling bath was removed and the reaction mixture was allowed to warm to 25°. This solution was stirred for the indicated period of time, and then the reaction mixture was poured into 20 ml of 5% aqueous sodium hydroxide solution. The aqueous solution was washed with two 15-ml portions of ether (washings discarded), acidified with conc hydrochloric acid, and then the product acid was isolated by dichloromethane extraction.[29] Distillation at reduced pressure afforded the pure acid in the indicated yield (TABLE I).

B. As the Trimethylsilyl Ketene Acetal. The esters 1a-f (TABLE I) were enolized at -78° as described in A previously. Within 5 min after the addition of the ester was complete, 1.2 g (11.1 mmol) of TMSCl was added in one batch. The cooling bath was then removed and the reaction mixture was allowed to warm to 25° over 30 min. Stirring at either 25° or 67° was continued as indicated for each particular ester. Following this, 3 ml of methanol was added and the reaction mixture was stirred for 10 min at 25° to effect hydrolysis of the silyl ester. The reaction mixture was then added to 20 ml of 5% aqueous sodium hydroxide solution and the product was isolated as described in A. The distilled acids prepared by this procedure contained 1-2 mol% 2-trimethylsilyl-substituted acid. This impurity could be removed as described below.

4-Pentenoic Acid (2a). From allyl acetate (1a); procedure B, 2 hr at 67°, 66%; bp 70-72° (4 mm): ir (film) 3600-2400, 1711 (C = O) cm^{-1}; NMR ($CDCl_3$) δ2.5 (m, 4H, $-CH_2-$), 5.85-6.25 (m, 3H, $-CH=CH_2$), 11.9 (s, 1H, $-CO_2H$).

3-Methyl-4-pentenoic Acid (2b). From crotyl acetate (1b); procedure B, 1.5 hr at 67°, 70%; bp 75-76° (4 mm): ir (film) 3600-2400, 1710 (C = O), 1640, 1000, 920 cm^{-1}; NMR ($CDCl_3$) δ1.10 (d, 3H, J = 7 Hz, CH_3), 2.2-3.0 (m, 3H, $-CH_2-CH-$), 4.85-6.15 (m, 3H, $-CH=CH_2$), 11.5 (s, 1H, $-CO_2H$).

Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.06; H, 8.87.

2,3-Dimethyl-4-pentenoic Acid (2c). From crotyl propanoate (1c); procedure A, 1 hr at 25°, 75%; procedure B, 0.5 hr at 67°, 75%; bp 81-82° (3 mm): ir (film) 3600-2400, 1710 (C = O), 1644, 1000, 920 cm^{-1}; NMR ($CDCl_3$) δ1.0-1.3 (overlapping d's, 6H, CH_3), 2.1-2.7 (m, 2H, methines), 4.82-6.05 (m, 3H, $-CH=CH_2$), 11.43 (s, 1H, $-CO_2H$).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.43; H, 9.28.

2,2,3-Trimethyl-4-pentenoic Acid (2d). From crotyl isobutyrate (1d); procedure A, 10 min at 25°, 80%; procedure B, 10 min at 25°, 78%; bp 52° (0.07 mm): ir (film) 3600-2400, 1705 (C = O), 1643, 1000, 923 cm^{-1}; NMR ($CDCl_3$) δ1.01 (d, 3H, J = 7 Hz, CH_3), 1.13 and 1.15 (s, 3H, CH_3), 2.52 (m, 1H, methine), 4.85-6.1 (m, 3H, $-CH=CH_2$), 12.05 (s, 1H, $-CO_2H$).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.71; H, 10.12.

(E)-2-(1-Methyl-2-propenyl)-3-hexenoic Acid (2e). From crotyl (E)-3-hexenoate (1e); procedure A, 3 hr at 25°, 69%; evaporatively distilled at 90° (0.05 mm): ir (film) 3600-2400, 1710 (C = O), 1645, 1000, 975, 920 cm^{-1}; NMR ($CDCl_3$) δ0.80-1.15 (m, 6H, CH_3), 1.8-3.1 (m, 4H, allylic H's), 4.8-6.0 (m, 5H, vinylic H's), 11.2 (s, 1H, $-CO_2H$).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.42; H, 9.68.

2,4-Dimethyl-3-hexyl-4-pentenoic Acid (2f). From 2-methyl-2-nonenyl propanoate (1f); procedure A, 20 hr at 25°, 71%; evaporatively distilled at 100-120° (0.05 mm): ir (film) 3600-2400, 1710 (C = O), 1650, 900 cm^{-1}; NMR ($CDCl_3$) δ0.8-1.5 (m, 16H), 1.54 and 1.65 (brs, 3H, vinylic CH_3), 2.1-3.5 (m, 2H, methines), 4.8, (m, 2H, vinylic H's), 11.20 (s, 1H, $-CO_2H$).

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.67; H, 11.26.

Removal of α-Silyl Impurities in Carboxylic Acids Prepared by Procedure B. A 2.0-g portion of the 4-pentenoic acid obtained by procedure B was esterified with excess diazomethane in ether solution and then refluxed with 5 wt% sodium methoxide in methanol for 2 hr. Water (20 ml) was added and the methanol was distilled over 1 hr. The reaction mixture was extracted with 20 ml of ether (extract discarded) and then acidified with conc hydrochloric acid. The product acid was isolated by dichloromethane extraction.[29] Distillation at 65° (4 mm) afforded 1.70 g of pure, colorless 4-pentenoic acid (1a) (57% overall yield from allyl acetate).

In exactly the same manner, pure 3-methyl-4-pentenoic acid (1b) was prepared in an overall yield of 50% from crotyl acetate.

Determination of Rearrangement Half-lives. After addition of TMSCl or TBSCl to the reaction mixture to quench the enolate anion, a 300 μl aliquot was withdrawn and placed in an NMR tube. The region from δ=1.5 to -1.0 was scanned. A peak at δ≈0.27 (assigned to the CH_3Si of the ketene acetal) gradually disappeared and a new peak of

$\delta \sim 0.33$ (assigned to the CH_3Si of the silyl ester) appeared at the same rate. When the two peaks reached the same height, the elapsed time was taken to be the half-life for the rearrangement. This method was used to follow the reaction with both trimethylsilyl and tert.-butyldimethylsilyl derivatives.

Lithium Diisopropylamide (LDA). Hexane-free LDA was prepared by dropwise addition of 1 equiv of n-butyl lithium in hexane to a stirred solution of 1.5 equiv of dry diisopropylamine in dry hexane (~2M) at 0^0. Following the addition, the viscous mixture was stirred for an additional 10 min, after which the hexane and excess amine were removed under reduced pressure at 0^0. The flask was refilled with argon and the residual white solid was redissolved in sufficient dry THF at 0^0 to give approximately an 0.3 M solution. When dissolution was complete, the ice bath was replaced by a dry-ice/acetone (-78^0) bath.

(E)-4-Decenoic Acid (2g). A solution of 11.0 mmol of LDA in 30 ml of dry THF was cooled to -78^0 and then 3.0 ml of dry HMPA was added. To this solution was added dropwise 1.70 g (10.0 mmol) of 3-acetoxy-1-octene[33] (1g) and 1.65 g (11.0 mmol) of TBSCl in 2 ml of dry THF over 5 min. The slightly yellow solution was stirred at -78^0 for an additional 2 min after which the cooling bath was removed, and the reaction mixture allowed to warm to 25^0 over 30 min. The reaction mixture was stirred at 25^0 for an additional 2 hr and the product silyl ester was isolated by pentane extraction.[29] The crude, oily silyl ester was dissolved in 25 ml of THF, treated with 5 ml of

10% hydrochloric acid, and the mixture was stirred at 25° for 45 min to effect hydrolysis of the silyl ester. The reaction mixture was then poured into 30 ml of 5% aqueous sodium hydroxide solution and extracted with two 30-ml portions of ether (extracts discarded). After acidification with conc hydrochloric acid, the product acid was isolated by ether extraction.[29] Evaporative distillation of the residual oil (1.5 g) at 70° (0.003 mm) afforded 1.41 g (83%) of acid 1g: NMR ($CDCl_3$) δ1.13 (m, 6H, $-CH_2-$), 1.98 (m, 2H, $-CH_2$), 2.20 (m, 4H, $-CH_2CH_2CO_2-$), 5.25 (m, 2H, -CH=CH-), 11.0 (s, 1H, $-CO_2H$); ir ($CHCl_3$) 3500-2400 (OH), 1710 (C = O), 1285, 970 cm^{-1}.

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.51; H, 10.73.

Comparison of the methyl ester with an authentic sample of methyl (Z)-4-decenoate[34] by VPC[28] (300 ft x 0.03 in open tubular column, TCEP, 110°, 20 ml/min, flame ionization) indicated that less than 0.5% of the Z-isomer was present.

(E)-2-Methyl-2-(phenylthio)-4-decenoic Acid (2h). A solution of 20.5 mmol of LDA in 75 ml of dry THF was cooled to -78°. To this rapidly stirred solution was added a mixture of 5.0 g (17.1 mmol) of ester 1h in 5 ml of dry THF over a 10 min period. Following the addition, the mixture was stirred at -78° for 5 min. After the addition of 7.5 ml of dry HMPA, 6.1 ml (20.5 mmol) of TBSCl in hexane was added and the cooling bath was removed after 2 min. The mixture was then allowed to warm to 25° and was stirred for 2 hr. The silyl ester was isolated by petroleum ether extraction[29] and amounted to 6.9 g of a yellow oil. This oil was stirred with a

solution of 15 ml of 5% hydrochloric acid and 75 ml of THF at 25° for 45 min to effect hydrolysis of the silyl ester. Petroleum ether extraction[29] afforded 5.5 g of a yellow oil which was purified by chromatography on 150 g of acidic silica gel[28] with 20% ether/petroleum ether. After elution with 250 ml of this solvent mixture, continued elution with 350 ml gave 4.4 g (88%) of the acid 2h. An analytical sample was prepared by evaporative distillation at 140° (0.005 mm): NMR ($CDCl_3$) δ1.40 (s, 3H, CH_3), 2.00 (m, 2H, allylic CH_2), 2.48 (m, 2H, allylic CH_2), 3.80 (m, 2H, vinylic H's), 7.37 (m, 5H, phenyl), 10.5 (br s, 1H, $-CO_2H$); ir ($CHCl_3$) 3300-2400, 1740 (shoulder), 1695 (C = O), 10.70, 975 cm^{-1}.

Anal. Calcd for $C_{17}H_{24}O_2S$: C, 69.82; H, 8.27; S, 10.96. Found: C, 69.86; H, 8.22; S, 10.95.

Methyl (E)-2-(1-Hexyl-2-methoxy-2-propenyl)-3-hexenoate (2i-Methyl Ester). A solution of 4.10 mmol of LDA in 10 ml of dry THF was cooled to -78°. To this rapidly stirred solution was added 1.0 g (3.73 mmol) of the ester 1i (a mixture of isomers) in 1 ml of dry THF over a 1.5 min period. After an additional 1 min, 2.64 ml (4.10 mmol) of TBSCl in HMPA was added, and the reaction mixture was stirred for an additional 5 min. The cooling bath was then removed, and the reaction mixture was allowed to warm to 25° over 30 min. The mixture was then stirred at reflux (67°) for 2 hr and cooled to 25°. Pentane extraction afforded the silyl esters as an orange oil (1.5 g). This oil was dissolved in 8 ml of HMPA and was treated with 560 mg (5.6 mmol) of $KHCO_3$ and 527 mg (5.6 mmol) of $KF \cdot 2H_2O$. The reaction mixture was stirred vigorously for 30 min, after which 1.07 g (7.5

mmol) of methyl iodide was added. Stirring was continued for 15 hr after which the methyl esters were isolated by pentane extraction.[29] The residual orange oil (1.0 g) was purified by medium-pressure chromatography[28] on 2.5 x 50 cm of silica gel with 4% ether/petroleum ether at a flow rate of 2 ml/min. After elution with 300 ml, continued elution with 20 ml of the same solvent system gave 361 mg (34%) of the more mobile isomer as a colorless oil. An analytical sample was prepared by evaporative distillation at 70-80° (0.005 mm): Rf = 0.49 (silica gel, 10% ether/petroleum ether); NMR ($CDCl_3$) δ3.45 (s, 3H, ether CH_3), 3.68 (s, 3H, ester CH_3), 3.87 (m, 2H, CH_2=C-O-), 5.40 (m, 2H, -CH=CH-); ir ($CHCl_3$) 1752 (C = O), 1660, 1615, 1165, 1070, 970 cm^{-1}.

Anal. Calcd for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71. Found: C, 72.25; H, 10.74.

Continued elution with 30 ml gave 225 mg (21%) of a mixture of the two isomers. Finally elution with an additional 60 ml gave 220 mg (21%) of the less mobile isomer. An analytical sample was prepared by evaporative distillation (70-80°/0.005 mm): Rf = 0.33 (silica gel, 10% ether/petroleum ether); NMR ($CDCl_3$) δ3.47 (s, 3H, ether CH_3), 3.60 (s, 3H, ester CH_3), 3.88 (br s, 2H, CH_2= C-O), 5.45 (m, 2H, -CH=CH-); ir ($CHCl_3$) 1752 (C = O), 1660, 1615, 1165, 1070, 975 cm^{-1}.

Anal. Calcd for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71. Found: C, 72.34; H, 10.66.

2-Butyl-3-methyl-4-pentenoic Acid (2k). To a stirred suspension of 520 mg (8.0 mmol) of zinc dust and 720 mg (4.80 mmol) of TBSCl in 30 ml of dry THF and 6 ml of dry HMPA, was added 1.0 g (4.01 mmol) of the α-bromo ester 1k over a 10-min period. Following the addition, the reaction mixture was stirred at reflux for 1.5 hr, cooled to room temperature, and then diluted with 300 ml of pentane containing 2 ml of pyridine. The pentane solution was filtered and then washed with three 30-ml portions of ice water, dried ($MgSO_4$), and evaporated at reduced pressure. The resulting oil (1.2 g) was stirred with 5 ml of 10% hydrochloric acid in 25 ml of THF for 45 min to effect hydrolysis of the silyl ester. The mixture was diluted with 20 ml of 5% aqueous sodium hydroxide solution and washed with two 50-ml portions of ether (washings discarded). This solution was acidified with conc hydrochloric acid and the product acid was isolated by ether extraction.[29] This afforded 499 mg (73%) of a colorless oil which was homogeneous by TLC (silica gel, 50% ether/petroleum ether). An analytical sample was prepared by evaporative distillation at 60° (0.05 mm): NMR ($CDCl_3$) δ1.07 (d, 2H, J = 6 Hz, CH_3), 2.30 (m, 2H, methines), 4.8-6.0 (m, 3H, $-CH=CH_2$), 10.4 (brs, 1H, CO_2H); ir ($CHCl_3$) 3400-2400, 1705 (C = O), 1645, 1415, 990, 920 cm^{-1}.

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.49; H, 10.69.

Stereochemistry of the Rearrangement. Enolization and Claisen rearrangement was studied under four sets of conditions (TABLES III and IV).

A. Enolization in THF; Rearrangement as the Silyl Ketene Acetal. A solution of 1.1 equiv of LDA in dry THF (0.3 M) was cooled to -78°. To this rapidly stirred solution was added 1.0 equiv of the ester, dropwise over 4 min. Following the addition, the reaction mixture was stirred for 2.5 min and then quenched with 1.1 equiv of TBSCl in HMPA. After an additional 2 min at -78°, the reaction mixture was allowed to warm to 25° during 20 min and was then stirred at reflux (67°) for 1-2 hr.

B. Enolization in 23% HMPA-THF; Rearrangement as the Silyl Ketene Acetal. To a stirred solution of 1.1 equiv of LDA in dry THF at -78° was added sufficient dry HMPA to adjust the solvent composition to 23 vol% HMPA-THF. This slightly yellow, non-homogeneous solution was treated with the dropwise addition of 1.0 equiv of the ester over 4 min. After an additional 2.5 min at -78°, 1.1 equiv of TBSCl in hexane was added. The reaction mixture was stirred for an additional 2 min at -78°, allowed to warm to 25° over 20 min and then stirred at reflux (67°) for 1-2 hr.

C. Enolization in THF; Rearrangement as the Enolate Anion. The enolization was carried out as described in A above. In this case, however, no TBSCl was added. The reaction mixture was allowed to warm to 25° over 20 min and was then stirred at 25° for 1 hr.

D. Enolization in 23% HMPA-THF; Rearrangement as the Enolate Anion. Enolization was carried out as described in B above. In this case, however, no TBSCl was added. The reaction mixture was allowed to warm to 25° over 20 min and was then stirred at 25° for 1 hr.

Rearrangement of (E)- and (Z)-2-Butenyl Propanoate (12 and 13).

After rearrangement as described above (5.0 mmol), the reaction mixtures obtained in C and D were diluted with 30 ml of 5% aqueous sodium hydroxide solution, and this solution was extracted with two 30-ml portions of ether (extracts discarded). The basic solution was then acidified with conc hydrochloric acid and ice. The cold, acidic aqueous phase was extracted with four 20-ml portions of ether. The combined ethereal extracts were washed with 20-ml portions of water and saturated brine and dried ($MgSO_4$). The solvents were then distilled through a 30-cm, vacuum-jacketed, Vigreux column and evaporative distillation of the residue at 90^0 (2 mm) afforded a mixture of the erythro 14 and threo 15 acids.

For the reactions in A and B, after 1 hr at 67^0 the silyl esters were isolated by pentane extraction.[29] The residue was dissolved in 15 ml of THF and treated with 3 ml of 10% hydrochloric acid. This mixture was stirred for 45 min at 25^0 and then worked up as described for C and D above. Evaporative distillation afforded a mixture of the acids 14 and 15.

Treatment of 64-mg (0.5 mmol) portions of each of the acid mixtures with 5 ml of ether containing 1.5 mmol of diazomethane[35] served to convert the acids to the corresponding methyl esters. These mixtures were analyzed by VPC[28] (90^0, 1/8 in x 27 ft 15% Carbowax 20 M, 20 ml/min, flame ionization). The erythro-ester 14 had a retention time of 54 min; the threo-ester 15, 58 min. There were no other volatile compounds in the mixtures. The data obtained from this analysis is recorded in TABLE III.

Rearrangement of (E)- and (Z)-2-Methoxy-2-nonenyl Pentanoate (1j-E and 1j-Z). Esters 1j-E and 1j-Z were rearranged only as described in A and B above (1.95 mmol). The silyl esters were isolated as described for the rearrangement of (E)- and (Z)-2-butenyl propanoate (12 and 13). The crude mixture of silyl esters was then stirred with 490 mg (4.90 mmol) $KHCO_3$ and 367 mg (3.90 mmol) of $KF \cdot 2H_2O$ in 5 ml of HMPA for 18 hr to effect cleavage of the silyl esters. Following this, 364 µl (831 mg, 5.85 mmol) of methyl iodide was added and the mixture was stirred for an additional 1.5 hr at room temperature. The methyl esters were then isolated by pentane extraction[29] including a base wash. The ratio of the two isomers in this mixture could be determined from peak heights of the ester methyl signals in the NMR spectra. The two isomers were cleanly separated by medium-pressure chromatography[28] on 1.25 x 50 cm of silica gel with 5% ether/petroleum ether at a flow rate of 1 ml/min. Analytical samples were prepared by evaporative distillation at 60^0 (0.08 mm). The more mobile isomer was tentatively assigned the erythro-configuration 16 (see discussion): Rf = 0.50 (silica gel, 10% ether/petroleum ether). NMR ($CDCl_3$) δ3.51 (s, 3H, ether CH_3); 3.70 (s, 3H, ester CH_3), 3.95 (m, 2H, CH =C); ir ($CHCl_3$) 1725 (C = O), 1660 and 1610 (C = C), 1190, 1160, 1115, 1060 cm^{-1}.

Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 71.11; H, 11.25.

The less mobile isomer was assigned the threo-configuration 17 (see discussion): Rf = 0.35 (silica gel, 10% ether/petroleum ether); NMR ($CDCl_3$) δ3.49 (s, 3H, ether CH_3), 3.63 (s, 3H, ester CH_3), 3.88 (m, 2H, CH_2=C); ir ($CHCl_3$) 1730 (C = O), 1655 and 1615 (C = C),

1285, 1190, 1160, 1120, 1065 cm .

Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 70.98; H, 11.25.

The data obtained from these rearrangements is recorded in TABLE IV.

Ozonization of Erythro-Acid 14. A solution of 754 mg (5.9 mmol) of the acid mixture containing 90% erythro-acid 14 (VPC analysis of methyl esters, see above) in 25 ml of ethyl acetate and 25 ml of acetic acid was cooled to -10°. Ozone[36] was passed through the solution until no more ozone was absorbed. The reaction mixture was then purged with argon to remove dissolved ozone and was treated with 10 ml of 15% aqueous hydrogen peroxide solution. This solution was stirred at 25° for 16 hr. The solvents were then removed at reduced pressure and the residue was dissolved in 50 ml of 3% aqueous sodium hydroxide solution. This basic solution was extracted with three 30-ml portions of ether (extracts discarded) and acidified with 40 ml of 2N aqueous sulfuric acid. This acidic solution was continuously extracted with ether for 16 hr, after which evaporation of the ether extract afforded 830 mg of a white solid. One recrystallization of this material from 20 ml of water gave 543 mg of meso-2,3-dimethylsuccinic acid (70% based on amount of erythro-acid 14 initially present: mp 202-204° dec (Lit[37] 209°).

Ozonization of Threo-Acid 15. As described above for the erythro-acid 14, 606 mg (4.73 mmol) of a mixture containing 90% of the threo-acid 15 was treated with ozone and then aqueous hydrogen peroxide.

After continuous extraction, 648 mg of a white solid was obtained. One recrystallization from water gave 453 mg (73% based on the amount of threo-acid 15 initially present) of d,l-2,3-dimethylsuccinic acid: mp 118-121° (Lit[37] 129°).

Preparation of Silyl Ketene Acetals of Simple Esters (TABLE V).

A. Enolization in THF. A solution of 5.5 mmol of LDA in 15 ml of dry THF was cooled to -78°. To this rapidly stirred solution was added 5.0 mmol of the ester 18 over 4 min. Following the addition, the reaction mixture was stirred at -78° for 2.5 min and then treated with 3.59 ml (5.5 mmol) of TBSCl in HMPA. After an additional 2 min at -78°, the reaction mixture was allowed to warm to 25° over 30 min. Pentane extraction[29] then afforded a quantitative yield of a mixture of the ketene acetals 19 and 20.

B. Enolization in 23 vol% HMPA-THF. A solution of 5.5 mmol of LDA in 15 ml of dry THF was cooled to -78° and 4.5 ml of HMPA was added. To this rapidly stirred solution was added 5.0 mmol of the ester 18, dropwise over 4 min. After an additional 2.5 min at -78°, 1.59 ml (5.5 mmol) of TBSCl in hexane was added. This mixture was stirred for 2 min at -78° and then allowed to warm to 25° over 30 min. Pentane extraction[29] afforded a quantitative yield of a mixture of ketene acetals 19 and 20.

These mixtures of ketene acetals obtained in A and B were subjected to NMR analysis. Only signals which could be assigned to the two possible isomeric ketene acetals 19 and 20 were present (TABLE VI). The ratios of the isomers were determined by integration

and are recorded in TABLE V.

C. Enolization of Methyl Butyrate (18a) in the Presence of Varying Amounts of HMPA (TABLE VII). Methyl butyrate (18a) was enolized as described in B in dry THF containing varied concentrations of HMPA. When 2 equiv or less of HMPA was present (entries 1-5), the enolates were quenched with TBSCl in HMPA. When more than 2 equiv of HMPA was present, the enolates were quenched with TBSCl in hexane (entry 6). A variety of other experiments were performed with methyl butyrate 18a. These are described in Footnotes to TABLE VII. The resulting mixtures of silyl ketene acetals 19a and 20a were analyzed by NMR as described above.

Preparation of the Silyl Enol Ethers of 3-Pentanone. The tert.-butyldimethylsilyl enol ethers of 3-pentanone were prepared by enolization as described for the esters 18 in A and B above. The isomer ratios were determined by NMR analysis and by VPC[28] analysis (110 , 8 ft x ¼ in 4% SE-30, 60 ml/min, thermocouple, not corrected for sensitivities). The data obtained is recorded in TABLE V. These isomers were preparatively separated under the same conditions. The structures were readily assigned by NMR[21 22] analysis.

(E)-3-(Tert.-Butyldimethylsilyloxy)-2-pentene. Retention time = 7.5 min; NMR ($CDCl_3$) δ0.13 (s, 6H, CH_3Si), 0.95 (s, 9H, $(CH_3)_3CSi$), 1.03 (t, 3H, J = 7 Hz, CH_3), 1.55 (d, 3H, J = 7 Hz, vinylic CH_3), 2.10 (q, 2H, J = 7 Hz, <1 Hz homoallylic coupling, $-CH_2-$), 4.60 (q, 1H, J = 7 Hz, vinylic H).

(Z)-3-(Tert.-Butyldimethylsilyloxy)-2-pentene. Retention time = 8.5 min; NMR ($CDCl_3$) δ0.13 (s, 6H, CH_3Si), 0.99 (s, 9H, $(CH_3)_3CSi$), 1.05 (t, 3H, J = 7 Hz, CH_3), 1.56 (d of t, 3H, J = 6.5 and 1.5 Hz, vinylic CH_3), 2.06 (q, 2H, J = 7 Hz, broadened by allylic and homo-allylic coupling >1 Hz, $-CH_2-$), 4.54 (q of t, 1H, J = 7 and 1 Hz, vinylic H).

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(28) Boiling points are uncorrected. Infrared (ir) spectra were determined on a Perkin-Elmer 237B grating infrared spectrometer and nuclear magnetic resonance (NMR) spectra were recorded using a Varian T-60 spectrometer. Chemical shifts are reported as δ values in parts per million relative to TMS (δ TMS = 0.0 ppm) as an internal standard. Deuteriochloroform for NMR and chloroform for ir spectra were filtered through neutral alumina before use.

Vapor phase chromatographic (VPC) analyses were determined on either a Hewlett-Packard 5750 equipped with a flame ionization detector or a Varian 920 equipped with a thermal conductivity detector using helium as the carrier gas under the indicated conditions. The indicated liquid phase was absorbed on 60-80 mesh Chromosorb W AW DMCS.

Silica gel columns used the 0.05-0.2 mm silica gel manufactured by E. Merck & Co., Darmstadt, Germany. Acidic silica gel refers to Silicar CC-4 Special "For Column Chromatography", sold by Mallinckrodt Chemical Works, St. Louis, Missouri. Preparative medium-pressure chromatography was performed using glass columns of the indicated length and diameter with fittings supplied by Laboratory Data Control, Riviera Beach, Fla., and an instrument minipump supplied by Milton Roy Co., St. Petersburg, Florida (instrumentation designed by R. H. Mueller, these laboratories, and copies are available on request). The columns were packed with silica gel H "for TLC acc. to Stahl" (10-40 μ) manufactured by E. Merck & Co., Darmstadt, Germany. Solvents were degassed under water aspirator vacuum prior to use.

Analytical thin layer chromatography was conducted on 2.5 x 10 cm Pre-coated TLC Plates, Silica Gel 60 F-254, layer thickness 0.25 mm manufactured by E. Merck & Co., Darmstadt, Germany.

"Dry" solvents were dried immediately prior to use. Ether and tetrahydrofuran (THF) were distilled from lithium aluminum hydride; pyridine, triethylamine, diisopropylamine, N-isopropylcyclohexylamine, trimethychlorosilane (TMSCl), hexamethylphosphoramide (HMPA), and benzene were distilled from calcium hydride; dichloromethane, methyl iodide, and hexane were distilled from phosphorous pentoxide. "Petroleum ether" refers to the "Analyzed Reagent" grade hydrocarbon fraction, bp 30-60°, which is supplied by J. T. Baker Co., Phillipsburg, N. J., and was not further purified.

Standard solutions of tert.-butyldimethylchlorosilane (TBSCl) in hexane (ca. 3.3 M) or HMPA (ca. 1.5 M) were employed.

Reactions were run under an argon atmosphere arranged with a mercury bubbler so that the system could be alternately evacuated and filled with argon and left under a positive pressure.

Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

(29) In cases where the products were isolated "by solvent extraction", the procedure generally followed was to dilute the reaction mixture with the indicated solvent or to extract the aqueous solution with several portions of the indicated solvent; then the combined organic layers were washed with several portions of water followed by saturated brine. The organic layer was dried over anhydrous sodium or magnesium sulfate, then filtered, and the solvent was evaporated from the filtrate under reduced pressure (water aspirator) using a rotary evaporator. The use of the terms "base wash" or "acid wash" indicate washing the organic solution with saturated aqueous sodium bicarbonate

solution or with dilute aqueous hydrochloric acid, respectively, prior to the aforementioned wash with water.

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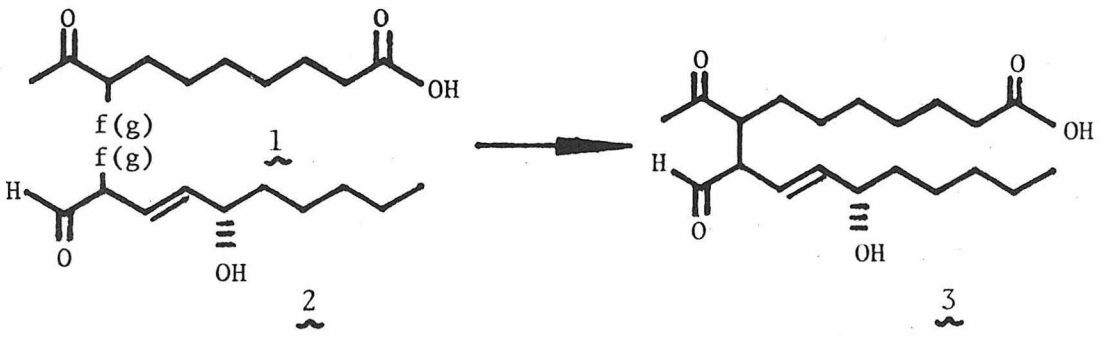
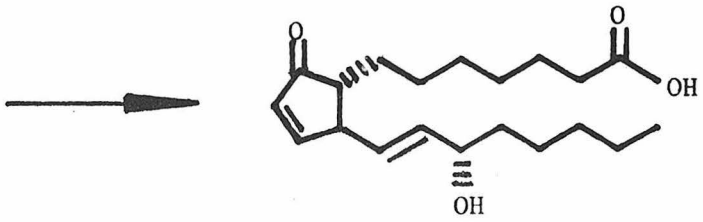
PART II

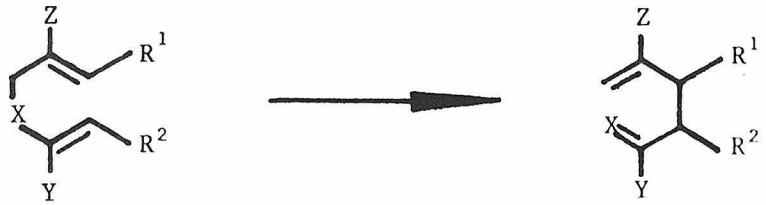
Construction of the Prostanoid Skeleton[1]

No family of molecules since the steroids has attracted the interest and effort of synthetic chemists as strongly as have the prostaglandins. Recent efforts have involved the search for flexible synthetic schemes which will allow preparation of a variety of analogs. We report here a synthetic approach which incorporates connection of a "top-half" and a "bottom-half" of the prostanoid skeleton in a key carbon-carbon bond forming reaction.





An intriguing possibility for this approach was formation of the carbon-carbon bond with an aliphatic Claisen rearrangement. This reaction (5 → 6) would not only provide an efficient means for formation of the desired bond but also would result in the proper number of suitably functionalized carbon atoms for subsequent formation of the cyclopentanone ring system.



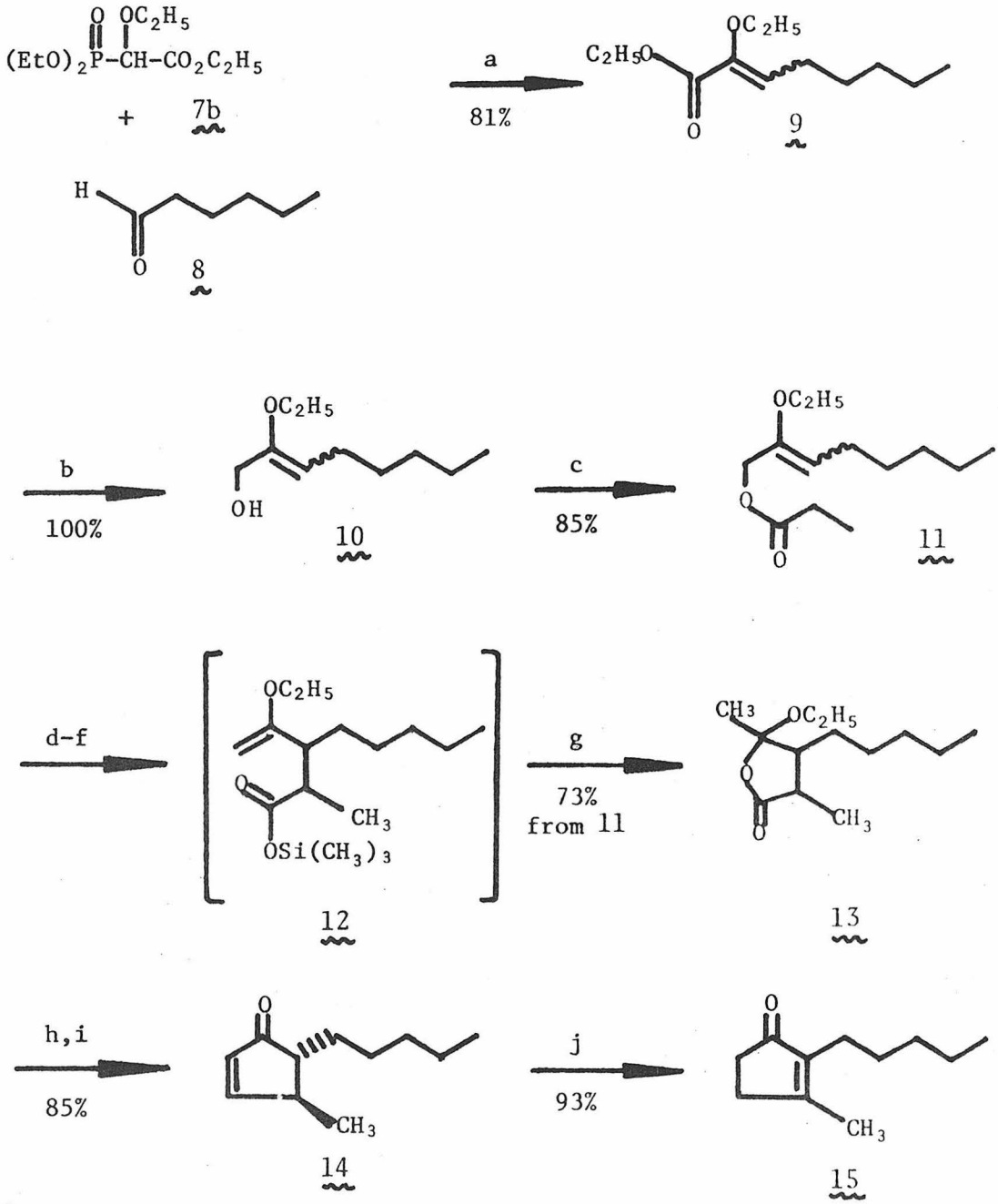
5 6

The requirements that only one equivalent of each half of the molecule be employed in construction of the precursor 5 and that conditions of the reaction be compatible with a variety of functional groups prompted development of the ester enolate Claisen rearrangement.[2,3]

To demonstrate the viability of this approach, synthesis of dihydrojasmone (15), a virtual touchstone of cyclopentenone syntheses, was undertaken. The successful route is described in SCHEME I.[2]

Phosphonates such as 7b, introduced by Grell and Machleidt,[4] are a useful source of functionalized allylic alcohols such as 10. When the ester 11 was subjected to enolization with lithium isopropylcyclohexylamide (LICA) and the enolate was trapped with trimethyl-

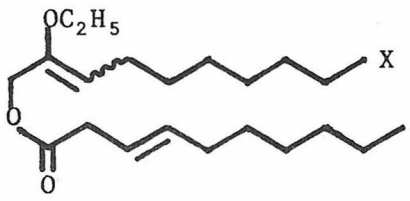
SCHEME I. Synthesis of Dihydrojasmone (15).[a]



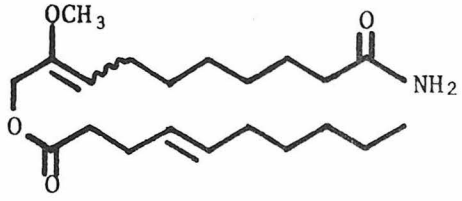
[a] a, NaH, THF; b, LiAlH , ether; c, propanoic anhydride, pyridine; d, LICA, THF, -78°; e, TMSCl; f, 65°, 7 hr; g, CH_3SO_3H, EtOH; h, DIBAH, toluene, -78°; i, NaOH, aq CH_3OH, 25°; j, KOH, aq CH_3OH, reflux.

chlorosilane (TMSCl), rearrangement[3] occurred without incident to give silyl ester 12. The enol ether functionality not only serves as an ultimate source of a methyl ketone for aldol condensation but also is a convenient handle for reduction of the silyl ester carbon to the aldehyde oxidation state. This reduction is accomplished by conversion of the silyl ester 12 to the lactone 13 with a trace of acid in ethanol followed by reaction with diisobutylaluminum hydride (DIBAH).[5] Finally, aldol condensation[6] and double bond migration[7] complete this synthesis of dihydrojasmone (15).[8]

This same approach was then used for the construction of the prostaglandin skeleton, with initial efforts focused on preparation and transformations of esters 16 - 18.



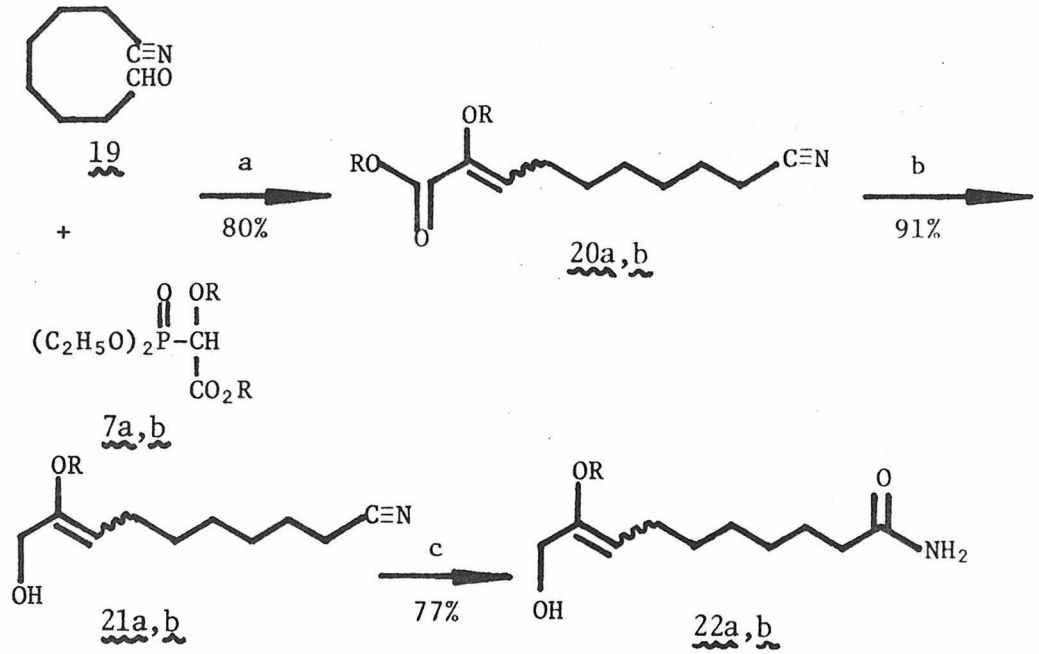
16 X = C≡N
17 X = $CONH_2$



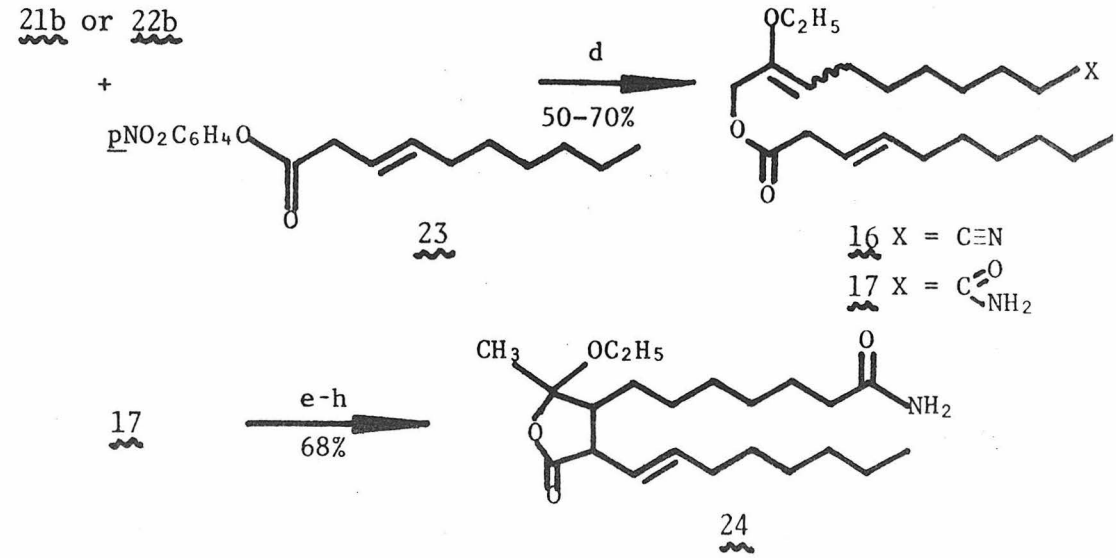
18

Use of readily available 7-cyanoheptanal (19)[9] as a substrate in the Wittig reaction produced equivalent amounts of the geometrical isomers of ester 20 (SCHEME II). The methoxy series was adopted in later stages of these studies because it offered the advantage of simpler interpretation of NMR spectra of intermediates in the synthesis. Selective reduction of the cyano esters 20 with lithium borohydride[10] in tetrahydrofuran (THF) provided the desired alcohols 21.

SCHEME II. Preparation and Transformations of Esters 16 and 17.[a]



a series, R = CH_3; b series, R = C_2H_5



[a] a, NaH, THF; b, $LiBH_4$, THF; C, H_2O_2, NaOH, aq C_2H_5OH; d, Et_3N, 25^0; e, LICA, THF, -78^0; f, TMSCl; g, 67^0, 3.5 hr; h, CH_3SO_3H, C_2H_5OH.

An alternate masked carboxylic acid function, the primary amide 22, was available by hydration of the nitrile in the presence of the enol ether with basic hydrogen peroxide. Reaction of the alcohol 21 or 22 with the p-nitrophenyl ester[11] of the acid in triethylamine was the most satisfactory procedure for preparation of esters of these γ,δ-unsaturated acids.

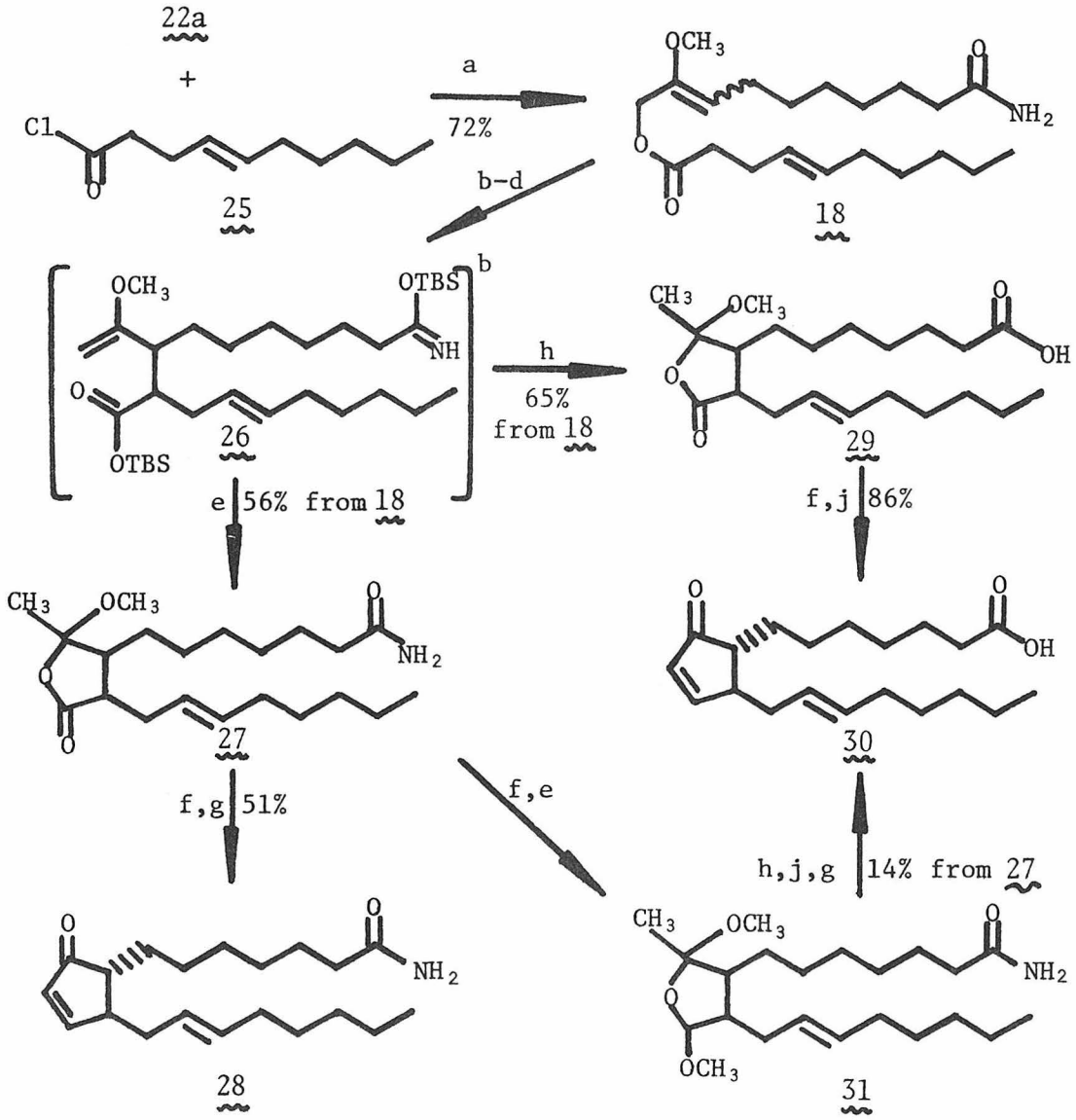
With the esters 16 and 17 in hand, their further conversion to cyclopentenone derivatives was investigated. Enolization, silylation and Claisen rearrangement of cyano ester 16 resulted in a mixture of products containing C-silylated nitrile. The silylation of aliphatic nitriles has now been studied and formation of C-silylated products, even with one equivalent of base and trialkylchlorosilane, has been demonstrated.[12] Because of this problem, use of the nitrile as a masked carboxylic acid was abandoned in favor of the primary amide. Rearrangement of amide-ester 17 proceeded in good yield to provide a intermediate silyl ester which was directly transformed to the lactone 24 with a trace of methanesulfonic acid in ethanol.

Attempted reduction of amide-lactone 24 with one equivalent of diisobutylaluminum hydride[5] resulted in complete recovery of the starting lactone; apparently the reagent is consumed by reaction with the acidic amide proton. The reduction was accomplished with two equivalents of hydride reagent, but treatment of the reduction product with aqueous base to cause aldol condensation[6] produced neither cyclopentenone nor β-ketol. A possible reason for this is that the acidity of the β,γ-unsaturated aldehyde was resulting in extensive conjugation of the double bond.

If this were indeed the case, isolation of the double bond was a possible solution. This suggested preparation of ester 18 (SCHEME III). Moving the double bond to a position where it would not interfere with the aldol condensation also simplified ester formation; now, the acid chloride 25 served well for preparation of the ester. Rearrangement of ester 18, using lithium disopropylamide (LDA) and tert.-butyldimethylchlorosilane (TBSCl),[3,13] led to the silyl ester 26 which, as above, could be converted with acid into the lactone 27. Reduction with two equivalents of DIBAH[5] and aldol condensation[6] with aqueous methanolic sodium hydroxide provided the cyclopentenone 28. This verified that the trouble with these reactions on lactone 24 was the position of the double bond.

As the lactone 27 or the cyclopentenone 28, the molecule could not be subjected to reaction conditions sufficiently vigorous to effect hydrolysis of the primary amide. This hydrolysis was attempted at the intermediate stage. Lactone 27 was reduced as before and the reduction product was protected as the acetal 31. Saponification of the primary amide, acidic hydrolysis of the acetals and finally, aldol condensation in aqueous alcoholic base gave the cyclopentenone-acid 30 in low yield. An alternate point in the synthetic scheme where saponification was possible was immediately after Claisen rearrangement. Basic hydrolysis of the silyl ester 26, followed by neutralization gave the lactone-acid 29 in good yield. Reduction, again with two equivalents of DIBAH,[6] and aldol condensation using piperidinium acetate[14] in refluxing benzene provided the cyclopentenone-acid 30 in more satisfactory overall yield.

SCHEME III. Synthesis of Prostanoic Acid Derivatives 28 and 30.[a]

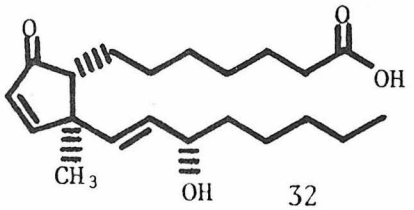


[a]a, Et_3N, CH_2Cl_2, 25°; b, LDA, THF, -78°; c, TBSCl; d, 67°, 3 hr; e, CH_3SO_3H, CH_3OH; f, DIBAH, Et_2O, -78°; g, aq NaOH, CH_3OH, 25°; h, aq NaOH, CH_3OH, reflux 16 hr, then neutralize, i, HOAc, piperidine, C_6H_6; j, aq HCl.

[b]TBS = tert.-butyldimethylsilyl.

Having demonstrated that the prostaglandin skeleton could be constructed in this manner, we refocused attention on the problematic double bond in the lower side chain. An alternate solution would be to block apparent conjugation of the double bond during the aldol condensation; a methyl group should serve this purpose well. The 12-methyl was also attractive because it should block *in vivo* deactivation of the PGA *via* migration of the enone double bond to produce the less active PGB structure.

Our synthetic approach to 12-methyl PGA_1 (32) would also give us the opportunity to investigate a sequence in which generation of the allylic alcohol functionality in the lower side chain is coupled to enolate formation necessary for the Claisen rearrangement. Two electron reduction of α,β-unsaturated-γ,δ-epoxy esters such as 33 should give the enolate 34. Silylation would provide the silyl ketene acetal 35. If the alcohol portion of this molecule were an allylic alcohol, this process could be followed by Claisen rearrangement.



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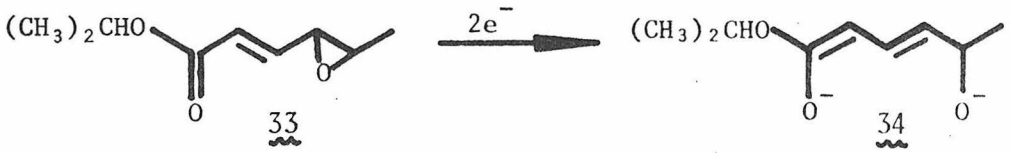
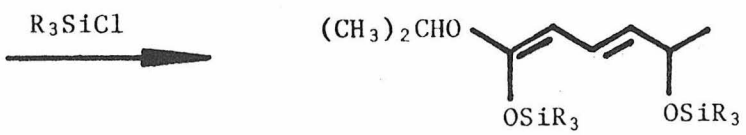


33 34



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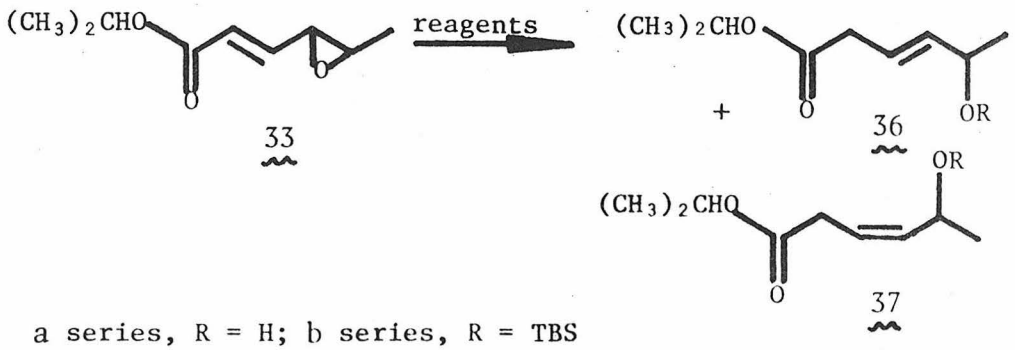
Epoxy esters such as 33 are readily available by peracid oxidation[15] of the corresponding dienoic esters. Several reduction methods were examined and are outlined in TABLE I.

Initial efforts were directed toward finding a system in which both reduction and silylation were possible in the same reaction mixture so that the reduction and Claisen rearrangement could be performed in a single step. A promising system for this transformation was sodium in THF-hexamethylphosphoramide (HMPA).[16,17] During initial attempts, reductions employing these conditions produced a myriad of products but little or none of the desired reduction product. Only under very specific conditions, two to three equivalents of the Na-HMPA-THF solution added in one portion to a rapidly stirred solution of ester 33 in HMPA-THF at -78° followed by addition of TBSCl, could even low yields of the reduction products be obtained. The intermediate silyl ketene acetal 35, which is formed under these conditions, is readily hydrolyzed to the siloxy esters 36b and 37b for analysis. Quenching the reaction mixture with solid ammonium chloride gave nearly identical yield of the alcohols 36a and 37a and demonstrated that the problems were arising during reduction, not silylation. A second distinct disadvantage of this method of reduction was that it produced the trans-isomer 36b and the cis-isomer 37b in nearly equal proportions (VPC analysis).

Reduction with a mixture of zinc and TBSCl in HMPA-THF had proven useful in the preparation of silyl ketene acetals from α-bromo esters,[3] but this method failed to reduce the epoxy ester 33. Finally a high yield of alcohols 36a and 37a was realized by reduction with

TABLE I. Reduction of Epoxy Ester 33.



33 36 37

a series, R = H; b series, R = TBS

Entry	Reagents	R	Yield(%)[a]	36/37[b]
1	1) 2 equiv Na, HMPA, THF, -78° 2) TBSCl 3) HOAc, H_2O	TBS	37	60/40
2	1) 3 equiv Na, HMPA, THF, -78° 2) NH_4Cl	H	42	-
3	1) Zn, TBSCl, HMPA, THF, 67°	-	0	-
4	1) 3 equiv Li, NH_3, THF, -78° 2) NH_4Cl	H	79	89/11

[a]After isolation and chromatography. [b]By VPC Analysis.

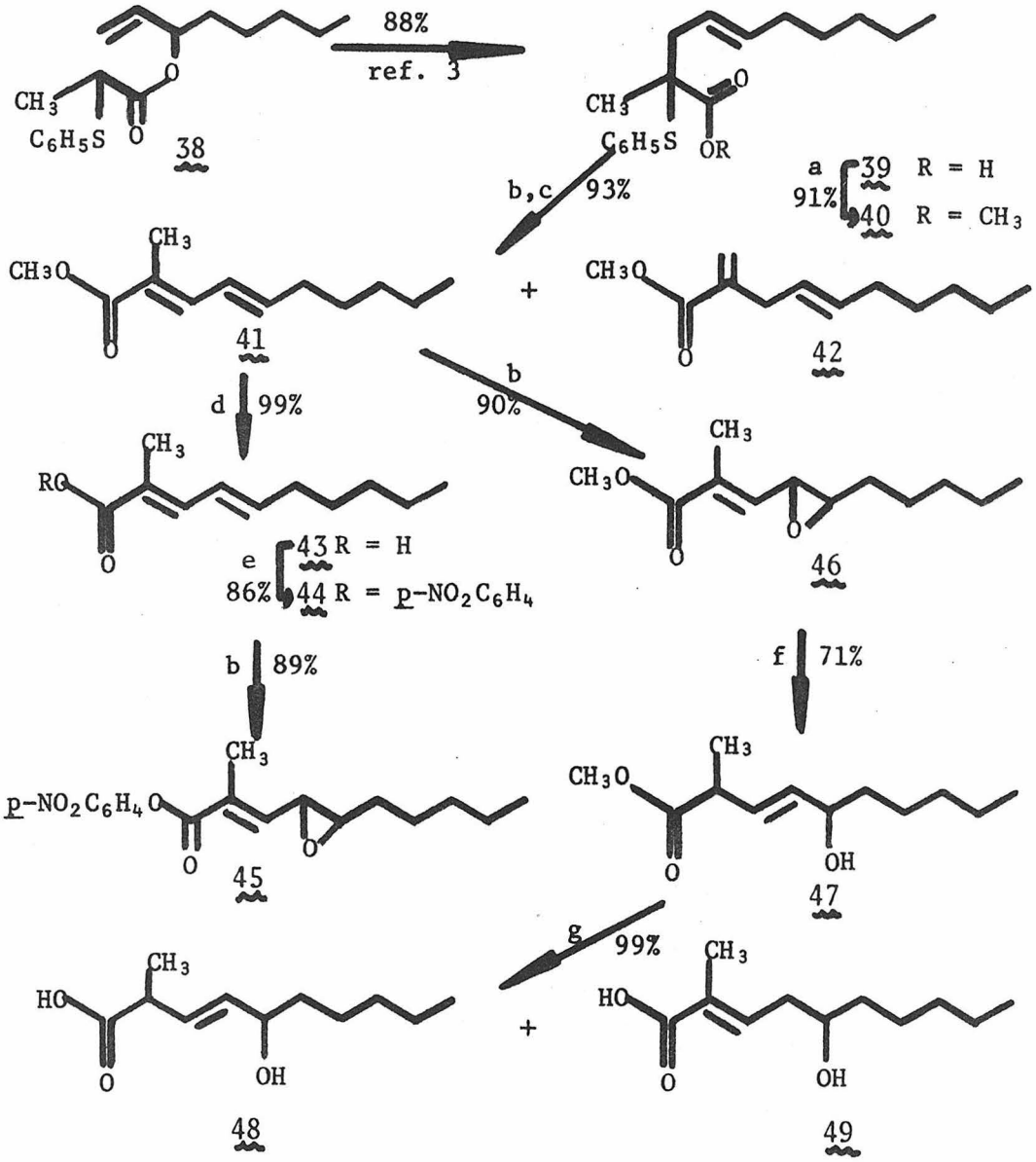
lithium in ammonia-THF. The best results were obtained when the reduction was performed with 3 equivalents of lithium at -78° for 1 min, and then the reaction mixture was quenched with solid ammonium chloride. In this case an 89:11 ratio of 36a and 37a was obtained (VPC analysis). These isomers were easily separated by silica gel chromatography after conversion[18] to the corresponding silyl ethers 36b and 37b.

The stereochemical assignment for these two isomers rests on infrared spectral data.[19] The major isomer exhibits a medium band at 970 cm^{-1}, indicative of a trans-disubstituted ethylene. No such band is present in the ir spectrum of the minor isomer.

Since the one step process was effectively ruled out by the necessity of performing the reduction in ammonia, enolization of the reduction products had to be examined. Enolization of both the hydroxy esters 36a and 37a and the siloxy esters 36b and 37b with LDA followed by trapping with TBSCl gave the silyl ketene acetal 35. Competing elimination was not a problem.

Efforts then turned to synthesis of the epoxy ester 50 or its reduced derivative 51. The acid fragment for these esters was prepared as described in SCHEME IV. The α-(phenylthio) ester 40 was readily available via Claisen rearrangement of allylic ester 38[3] followed by esterification. Desulfenylation[20] by mild heating of the sulfoxides obtained by oxidation with MCPBA produced a mixture of unsaturated esters 41 and 42 in the ratio 78:22. The mixture of diasteriomeric sulfoxides obtained in the oxidation was separated by silica gel chromatography, and the sulfoxides were independently pyrolized. The more mobile isomer gave the olefins in a 68:32 ratio

SCHEME IV. Preparation of the Acid Fragment for Ester 50.[a]



[a] a, NaH, CH_3I, THF; b, MCPBA, $CHCl_3$; c, 60^0, 2 hr; d, KOH, CH_3OH; e, p-nitrophenyl trifluoroacetate, Et_3N; f, 3 equiv Li, NH_3, THF, -78^0; g, LiOH, aq CH_3OH.

(41:42) and the less mobile isomer, in a 90:10 ratio.

This synthesis of ester 41 also serves to demonstrate the possibility of employing the Claisen rearrangement for formation of a carbon-carbon double bond. The sulfur functionality serves to mask this double bond until a convenient stage is reached in the synthesis.

Oxidation of ester 41 with MCPBA[15] produced the epoxy ester 46 in high yield. The presence of only one geometrical isomer of this epoxy ester is clearly demonstrated by NMR analysis. This indicates that ester 41 is cleanly the (E,E)-isomer. Attempts to saponify the epoxy ester 46 in order to obtain the corresponding acid were not encouraging. This sensitive epoxy acid was obtained in varying states of purity and attempted purification led to extensive decomposition.

The alternative approach of using the acid portion in already reduced form was also investigated. Epoxy ester 46 was reduced under the same conditions described above and gave a mixture of two separable components (93:7). The major component was assigned the trans-stereochemistry 47 based on results obtained with ester 33. The minor isomer was tentatively assigned cis-stereochemistry. Saponification of ester 47 gave a mixture of acids containing 70% of the unsaturated acid 48 and 30% of the conjugated isomer 49.

Since the difficulty in both of these approaches arose during attempted saponification of the methyl ester in order to prepare some activated ester derivative suitable for esterification, saponification of the ester at an earlier, less sensitive stage was desirable.

Hydrolysis of the dienoic ester 41 proceeded without difficulty.

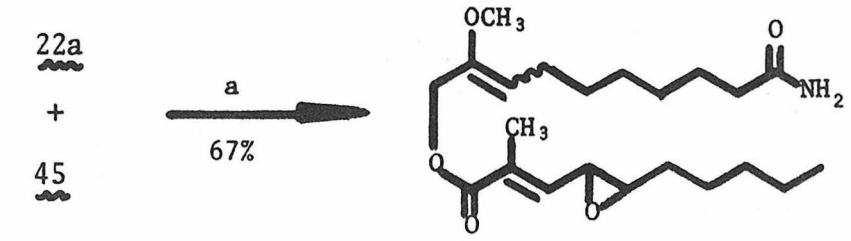
The p-nitrophenyl ester 44[11] of the resulting acid 43 was sufficiently stable to permit partial purification by rapid chromatography on silica gel. This derivative was also readily oxidized with MCPBA[15] to provide the epoxy ester 45. When stirred with the alcohol 22a in THF-triethylamine, epoxy ester 45 was converted to the target ester 50 through ester exchange (SCHEME V).

Reduction of ester 50 to hydroxy ester 51 proceeded normally. The minor isomer (cis?) found in the reduction of ester 46 was not detected but was probably present in the mixture.

Initial attempts to carry this ester on to 12-methyl PGA_1 (32) met with serious difficulties. Rearrangement and basic hydrolysis gave the lactone 52 in only 30% yield. The unsaturated acid 43 was a major side product. Reduction of lactone 52 with three equivalents of DIBAH proceeded smoothly but attempted aldol condensation did not produce cyclopentenone under mild (piperidinium acetate[14]) or harsh (aqueous methanolic sodium hydroxide[6]) conditions. In view of these difficulties and in face of a report that 12-methyl PGA_2 was inactive,[21] the synthesis was not pursued further.

Although difficulties arose in late stages of some of the syntheses described here, the potential of the ester enolate Claisen rearrangement in convergent synthesis of complex organic molecules has been demonstrated. Particularly, the compatibility of this reaction with a wide variety of functionality should make it a useful addition to the synthetic chemist's armory of reactions.

SCHEME V. Preparation and Transformations of Ester 50.[a]



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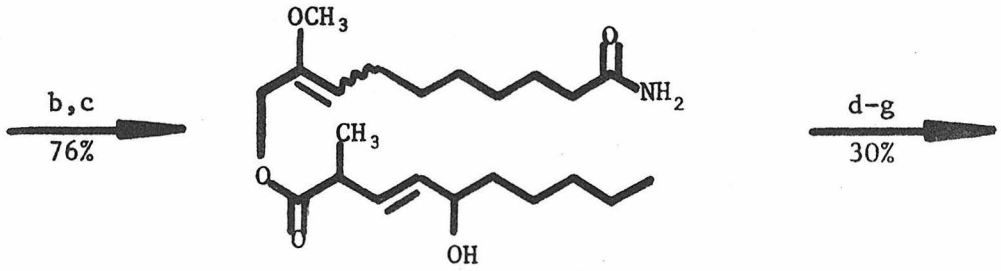

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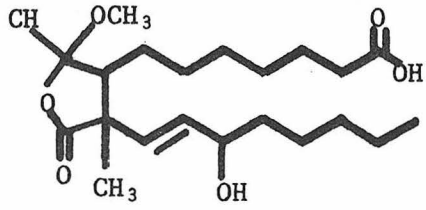

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[a] a, Et_3N, THF, 50^0, 57 hr; b, 3 equiv Li, NH_3, THF, -78^0; C, NH_4Cl; d, LDA, THF, -78^0; e, TBSCl; HMPA; f, 67^0, 3 hr; g, NaOH, aq CH_3OH, then neutralize.

Experimental Section[22]

Methyl Diethoxyphosphinylmethoxyacetate (7a). The procedure of Grell and Machleidt[4] was followed to prepare the phosphonate 7a from methyl dimethoxyacetate: bp 110° (0.3 mm) ; NMR ($CDCl_3$) δ1.33 (t, 6H, J=7 Hz, CH_3CH_2O-), 3.52 (s, 3H, ether CH_3O-), 3.83 (s, 3H, ester CH_3O-), 4.22 (m, 5H, $CHCO_2$- and CH_3CH_2O); ir (neat) 1750 (C = O), 1260, 1120, 1015, 970 cm^{-1}.

Anal. Calcd for $C_8H_{17}O_6P$: C, 40.00; H, 7.13. Found C, 40.12; H, 7.08.

Ethyl 2-Ethoxy-2-octenoate (9). A stirred suspension of 2.78 g (0.116 mol) of sodium hydride (mineral oil free) in dry THF was treated during 30 min with the dropwise addition of 30.0g (0.112 mol) of phosphonate 7b. Following the addition, the reaction mixture was stirred for an additional 30 min and then cooled to 0°. Hexanal (11.2 g, 0.112 mol) was added dropwise to this solution over a 30-min period. Near the end of the addition, a gummy precipitate formed. The reaction mixture was stirred for an additional 30 min at 25° and then treated with 50 ml of water. Benzene extraction,[23] including an aqueous ammonium chloride wash, followed by distillation of the residue afforded 19.5 g (81%) of a mixture (1:3) of unsaturated esters 9: bp 60-63° (0.08 mm); NMR ($CDCl_3$) δ0.87 (br t, 3H, $-CH_2CH_2CH_3$), 1.33 (t, 6H, J=7 Hz, $-OCH_2CH_3$), 3.73 (br t, 2H, J=7 Hz, $=COCH_2CH_3$), 4.24 and 4.21 (q's, 2H, J=7 Hz, $CO_2CH_2CH_3$), 6.24 and 5.26 (t's, 1H, ratio 1:3, J=7 and 7.5 Hz, vinylic H's); ir ($CHCl_3$) 1725, (C = O), 1640 (C = C), 1380,1160, 1040 cm^{-1}.

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.08; H, 9.80.

2-Ethoxy-2-octenyl Propanoate (11). To a suspension of 2.0 g (53 mmol) of lithium aluminum hydride in 120 ml of dry ether was added 10.0 g (47 mmol) of the esters 9 over a 30-min period. Following the addition, the reaction mixture was stirred for an additional 15 min before excess hydride was destroyed by addition of ethyl acetate. Workup according to the procedure of Fieser[24] afforded 7.75 g of crude alcohols 10 which were used without further purification. This material was treated with 15 g of propanoic anhydride in 20 ml of dry pyridine at 25° for 20 hr. Distillation of the reaction mixture gave 8.9 g (85%) of the ester 11: bp 72-85° (0.1 mm); NMR ($CDCl_3$) δ2.33 (q, 2H, J=7 Hz, $CH_3\underline{CH_2}CO_2$-), 3.65 (q, 2H, J=7 Hz, $CH_3\underline{CH_2}O$-), 4.57 and 4.62 (s's 2H, $-OCH_2C{=}C$), 4.64 and 4.86 (t's, 1H, J=7 Hz, vinylic H's); ir (neat) 1725 (C = O), 1640 cm^{-1} (C = C).

Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.58; H, 10.50.

5-Methoxy-3,5-dimethyl-4-pentyloxacyclopentan-2-one (13). A solution of 7.1 mmol of LICA in 20 ml of dry THF was cooled to -78°. To this rapidly stirred solution was added 1.50 g (6.6 mmol) of ester 11 over 3 min. Following the addition, 0.850 ml (6.7 mmol) of TMSCl was added in one portion and the reaction mixture was stirred at -78° for an additional 3 min. The cooling bath was removed and the reaction mixture was allowed to warm to 25°. The mixture was then stirred at

reflux for 7 hr to effect rearrangement. After cooling to 25° the reaction mixture was treated with 2 ml of ethanol and sufficient methanesulfonic acid to obtain pH 1-2. Extraction[23] with petroleum ether afforded 1.6 g of a yellow oil which was evaporatively distilled at 80° (0.2 mm) to give 1.1 g (73%) of the lactone 13. A portion of this material (400 mg) was purified further by medium-pressure chromatography[22] on 2.5 x 50 cm of silica gel with 50% dichloromethane/benzene. Elution with 550 ml of this solvent system gave the analytical sample: NMR ($CDCl_3$) δ1.10 (t, 3H, J=7 Hz, CH_3), 1.40 (d, 3H, J=8 Hz, $\underline{CH}_3CH$-), 3.63 (q, 2H, J=7 Hz, $-CH_2O$-); ir (neat) 1792 cm^{-1} (C = O).

Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.46; H, 10.49.

4-Methyl-5-pentyl-2-cyclopentenone (14). A solution of 450 mg (2.0 mmol) of lactone 13 in 10 ml of dry toluene was cooled to -78°. To this stirred solution was added 2.4 ml (2.3 mmol) of DIBAH in benzene over 5 min. The reaction mixture was stirred for 30 min at -78° and then treated with 0.5 ml of methanol and allowed to warm to 25°. Benzene extraction[23] gave 440 mg of a colorless oil which was dissolved in 10 ml of methanol and treated with 10 ml of 5% aqueous sodium hydroxide solution. This mixture was stirred at 25° for 20 min after which benzene extraction[23] and evaporative distillation of the residue at 80° (1 mm) gave 280 mg (85%) of colorless cyclopentenone 14: NMR ($CDCl_3$) δ0.90 (br t, 3H, J=7 Hz, $\underline{CH}_3CH_2$-), 1.22 (d, 3H, J=7 Hz, $\underline{CH}_3CH$-), 6.14 (dd, 1H, J=6 and 2 Hz, =CHC=O), 7.55 (dd, 1H, J=6 and

and 2.5 Hz, CH=C-C=O); ir (neat) 1710 (C = O), 1580 cm^{-1} (C = C).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.49; H, 10.90.

3-Methyl-2-pentyl-2-cyclopenten-1-one (15). A mixture of 118 mg (0.711 mmol) of cyclopentenone 14 and 200 mg of potassium hydroxide in 10 ml of water and 5 ml of methanol was stirred at reflux for 40 min. Extraction[23] with dichloromethane and evaporative distillation of the residue at 80° (1 mm) gave 110 mg (93%) of colorless dihydrojasmone (15): NMR δ0.88 (br t, 3H, J=7 Hz, CH_3), 1.2 (m, 6H), 2.05 (s, 3H, $C=CCH_3$); ir (neat) 1700 (C = O), 1650 cm^{-1} (C = C).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.55; H, 10.95.

Methyl 9-Cyano-2-methoxy-non-2-enoate (20a). To a mechanically stirred suspension of 2.64 g (0.11 mol) of sodium hydride (mineral oil free) in 150 ml of dry THF was added 24.0 g (0.10 mol) of phosphonate 7a over 40 min. The mixture was stirred for an additional hour and then cooled to 0°. During 30 min, the reaction mixture was treated with 13.9 g (0.1 mol) of 7-cyanoheptanal (9) while vigorous stirring was maintained. Toward the end of the addition a gummy precipitate formed. The reaction mixture was allowed to warm gradually to 25° over 1 hr. After cautious addition of 80 ml of water, ether extraction[23] gave a slightly orange liquid which was subjected to short path distillation to give 17.9 g (80%) of the cyano esters 20a, bp 120-128° (0.015 mm). NMR analysis indicated that this was approximately an equal mixture of

double bond isomers. A portion of this material (378 mg) was purified further by medium-pressure chromatography[22] on 1.25 x 50 cm of silica gel with 30% ether/petroleum ether at a flow rate of 1 ml/min. Elution with 150 ml gave 174 mg of the Z-isomer. An analytical sample was prepared by evaporative distillation at 110° (0.001 mm): NMR ($CDCl_3$) δ3.67 (s, 3H, ether CH_3O-), 3.78 (s, 3H, ester CH_3O-), 6.23 (t, 1H, J=7 Hz, vinylic H); ir ($CHCl_3$) 2250 (C≡N), 1720 (C = O), 1651 (C = C), 1270, 1120, 990 cm^{-1}.

Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 64.09; H, 8.43; N, 6.26.

Further elution with 10 ml of the same solvent system gave 68 mg of a mixture of the E- and Z-isomers. Continued elution with 80 ml of this solvent system gave 123 mg of the E-isomer. An analytical sample was prepared by evaporative distillation at 110° (0.001 mm): NMR ($CDCl_3$) δ3.58 (s, 3H, ether CH_3O-), 3.78 (s, 3H, ester CH_3O-), 5.20 (t, 1H, J=7 Hz, vinylic H); ir ($CHCl_3$) 2250 (C≡N), 1725 (C = O), 1640 (C = C), 1376, 1170, 1130 cm^{-1}.

Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 64.00; H, 8.48; N, 6.19.

10-Hydroxy-9-methoxydec-8-enenitrile (21a). To a vigorously stirred suspension of 685 mg (18 mmol) of sodium borohydride and 1.56 g (18 mmol) of anhydrous lithium bromide[10] in 20 ml of dry THF was added 2.0 g (8.89 mmol) of the cyano ester 20a. This mixture was stirred at 25° for 52 hr. At the end of this period, 20 ml of water was added and the reaction mixture was stirred for 40 min. After addition of

another 20-ml portion of water, ether extraction[23] gave 2.1 g of a colorless oil which still contained some ester (ir analysis). This material was subjected again to the same treatment and gave 1.59 g (91%) of the crude cyano alcohol 21a as a colorless liquid. A portion of this material was purified by medium-pressure chromatography[22] on 1.25 x 50 cm of silica gel with 80% ether/petroleum ether at a flow rate of 1 ml/min followed by evaporative distillation at 100° (0.001 mm) and gave the analytical sample: NMR ($CDCl_3$) δ3.54 and 3.65 (s, 3H total, CH_3O), 4.13 (br s, 2H, $-CH_2O-$), 4.6 (m, 1H, vinylic H's); ir ($CHCl_3$) 3600 and 3470 (OH), 2250 (C ≡ N) 1670 (C = C), 1465, 1140, 1110, 1055, 1015 cm^{-1}.

Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.87; H, 9.59; N, 7.01.

10-Hydroxy-9-methoxydec-8-enamide (22a). A solution of 1.97 g (10.0 mmol) of the crude cyano alcohol 21a in 50 ml of ethanol was added in one portion to an ice-cooled, stirred mixture of 90 ml of 10% aqueous hydrogen peroxide and 3 ml of 40% aqueous sodium hydroxide solution. After 10 min the ice bath was removed and the reaction mixture was stirred at room temperature for 2 hr. Dichloromethane extraction[23] gave 1.65 g (77%) of a white solid. A portion of this material (130 mg) was purified further by medium-pressure chromatography[22] on 1.25 x 50 cm of silica gel with 50% acetone/ether at a flow rate of 1 ml/min. Elution with 265 ml of this solvent system gave 101 mg of a white solid. One recrystallization from ether containing a small amount of dichloromethane gave the analytical sample as a mixture of

double bond isomers: mp 51-58°; NMR ($CDCl_3$) δ3.53 and 3.65 (s, 3H total, CH_3O-), 4.09 (m, 2H, CH_2O-), 4.8 (m, 1H, vinylic H), 6.0 (br s, 2H, NH_2); ir ($CHCl_3$) 3700-3100 (several bands, OH, NH_2), 1675 (C = O), 1590, 1465, 1390, 1010 cm^{-1}.

Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83; N, 6.51. Found: C, 61.41; H, 9.88; N, 6.46.

Ethyl 9-Cyano-2-ethoxynon-2-enoate (20b). In a manner similar to that described for the methyl derivative 20a, phosphonate 7b and cyano aldehyde 19 were converted into a mixture of esters 20b (84%): bp 120-136° (0.1 mm); NMR ($CHCl_3$) δ2.33 (m, 4H, $=CCH_2$- and $-CH_2C{\equiv}N$), 4.25, 4.21 and 3.75 (q's, 4H total, J=7 Hz, $CH_3\underline{CH_2}O$-), 6.21 and 5.22 (t's, 1H total, J=7 Hz, vinylic H); ir (neat) 2250 (C ≡ N), 1725 (C = O), 1640 cm^{-1} (C = C).

Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.39; H, 9.13; N, 5.57.

9-Ethoxy-10-hydroxy dec-8-enenitrile (21b). In a manner similar to that described for cyano alcohol 21a, the mixture of esters 20b was reduced with lithium borohydride[10] to give the cyano alcohol 21b (100%): NMR ($CDCl_3$) δ3.66 (q, 2H, J=7 Hz, $CH_3\underline{CH_2}O$-), 4.12 (br s, 2H, $=CCH_2O$-), 4.4 (m, 1H, vinylic H); ir ($CHCl_3$) 3600 and 3470 (OH), 2240 (C ≡ N), 1665 (C = C), 1385, 1105, 1050, 1010 cm^{-1}.

Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.25; H, 10.09; N, 6.60.

9-Ethoxy-10-hydroxydec-8-enamide (22b). In a manner similar to that described for hydroxy amide 22a, the cyano alcohol 21b was converted into the hydroxy amide 22b (72%): NMR ($CDCl_3$) δ3.15 (br s, 1H, OH), 3.68 (q, 2H, J=7 Hz, $CH_3\underline{CH_2}O$-), 4.13 and 4.10 (s, 2H total, -$\underline{CH_2}OH$), 4.47 and 4.76 (t, 1H total, J=7.5 and 8 Hz, vinylic H), 6.2 (br s, 2H, NH_2); ir ($CHCl_3$), 3700-3150 (several bands, OH, NH_2), 1675 (C = O, C = C), 1590 cm^{-1}.

Anal. Calcd for $C_{12}H_{23}NO_3$: C, 62.85; H, 10.11; N, 6.11. Found: C, 62.79; H, 10.17; N, 6.14.

9-Cyano-2-ethoxy-2-nonenyl (E)-3-Decenoate (16). To a solution of 1.40 g (6.0 mmol) of p-nitrophenyl trifluoroacetate[11] in 3 ml of dry pyridine was added 1.0 g of (E)-3-decenoic acid[25]. This mixture was stirred for 2 hr at 25°. Pentane extraction[23] including an acid wash and a base wash, gave 1.37 (80%) of p-nitrophenyl (E)-3-decenoate (23) which was not purified further: NMR ($CDCl_3$) δ2.07 (m, 2H, $=CCH_2$), 3.30 (d, 2H, J=5 Hz, $=CCH_2CO_2$-), 5.65 (m, 2H, CH=CH), 7.25 (d, 2H, J=8 Hz, aromatic H's), 8.25 (d, 2H, J=8 Hz, aromatic H's); ir (neat) 1765 (C = O), 1620, 1595, 1530, 1495, 1350, 1115 cm^{-1}.

This crude p-nitrophenyl ester 23 was dissolved in 3 ml of dry triethylamine and was treated with 1.3 g (6.1 mmol) of the cyano alcohol 21b. This mixture was stirred at 25° for 16 hr. Pentane extraction[23] including a base wash, gave 1.6 g of an oil which was filtered through 7 g of silica gel with benzene to give 1.14 g (50%) of cyano ester 16 as a colorless oil: NMR ($CDCl_3$) δ2.96 (br d, 2H, J=4 Hz, -CH_2CO_2-), 3.63 (q, 2H, J=7 Hz, $CH_3\underline{CH_2}O$-), 4.48 (s, and t, 3H, J=7 Hz,

-OCH_2C=CH-), 5.50 (m, 2H, CH=CH); ir (neat) 2250 (C ≡ N), 1737 (C = O), 1668 cm^{-1} (C = C).

Anal. Calcd for $C_{22}H_{37}NO_3$: C, 72.69; H, 10.26; N, 3.85. Found: C, 72.69; H, 10.27; N, 3.78.

9-Carbamoyl-2-ethoxy-2-nonenyl (E)-3-decenoate (17). The p-nitrophenyl ester 23 (4.8 mmol) was added to 1.0 g (4.4 mmol) of the hydroxy amide 22b in 2 ml of dry triethylamine. This mixture was stirred for 36 hr at 25°. Ether extraction,[23] including a base wash, gave a yellow oil which was purified by chromatography on 10g of silica gel with 300 ml of benzene, then 200 ml of dichloromethane and finally 800 ml of ether. The ether fraction contained 1.4 g (83%) of a slightly yellow oil which solidified upon standing. A portion of this material was recrystallized from petroleum ether to afford the analytical sample: mp 53-54°; NMR ($CDCl_3$) δ3.03 (d, 2H, J=5 Hz, CH_2CO_2-), 3.68 (q, 2H, J=7 Hz, CH_3CH_2O-), 4.60 (s and t, 3H, J=7 Hz, CH_2C=CH-), 5.53 (m, 2H, CH=CH), 5.8 (br, 2H, NH_2); ir ($CHCl_3$) 1725 (ester C = O), 1675 (amide C = O), 1590, 1115, 1060, 965, 910 cm^{-1}.

Anal. Calcd for $C_{22}H_{39}NO_4$: C, 69.25; H, 10.30; N, 3.67. Found: C, 69.34; H, 10.27; N, 3.64.

4-(6-Carbamoylhexyl)-5-ethoxy-5-methyl-3-(1-octenyl)-oxacyclopentan-2-one (24). A solution of 1.64 mmol of LICA in 3 ml of dry THF was cooled to -78°. To this rapidly stirred mixture was added a solution of 206 mg (0.54 mmol) of ester 17 in 1 ml of dry THF over 35 sec. After an additional 2 min at -78°, 0.250 ml (1.95 mmol) of

TMSCl was added in one portion. The reaction mixture was stirred for an additional 3 min at -78° and then allowed to warm to 25°. The mixture was then stirred at reflux for 3.5 hr to effect rearrangement. After cooling to 25°, the mixture was treated with 0.1 ml of ethanol and sufficient methanesulfonic acid to give pH 1-2. Immediate dichloromethane extraction[23] afforded 227 mg of a yellow oil. This material was purified by medium-pressure chromatography[22] on 1.25 x 50 cm of silica gel with 20% acetone/benezene. Elution with 300 ml of this solvent mixture afforded 141 mg (68%) of the lactone-amide 24 as a colorless oil: NMR ($CDCl_3$) δ1.60 (s, 3H, $CH_3C(O)_2$-), 3.66 (q, 2H, J=7 Hz, $CH_3\underline{CH_2}O$-), 5.5-6.3 (br m, 4H, CH=CH and NH_2); ir ($CHCl_3$) 3700-3150 (several bands NH_2), 1765 (lactone C = O), 1675 (amide C = O), 1590 cm^{-1}.

Anal. Calcd for $C_{22}H_{39}NO_4$: C, 69.25; H, 10.30; N, 3.67. Found: C, 69.10; H, 10.30; N, 3.71.

(E)-4-Decenoyl Chloride (25). A solution of 1.37 g (8.05 mmol) of (E)-4-decenoic acid[3] in 15 ml of dry benzene was treated with 1.14 ml (1.90 g, 16 mmol) of thionyl chloride. This mixture was stirred at reflux for 1 hr. After the reaction mixture had cooled to 25°, the benzene and excess thionyl chloride were removed by rotary evaporation at reduced pressure followed by addition and similar removal of a second 15-ml portion of benzene. The residue was evaporatively distilled at 50-55° (0.05 mm) and gave 1.41 g (93%) of the acid chloride as a colorless liquid: NMR ($CDCl_3$) δ2.95 (m, 2H, C-2 H's), 5.45 (m, 2H, CH=CH); ir ($CHCl_3$) 1800 (C = O), 1405, 970, 915, 730, 685 cm^{-1}.

9-Carbamoyl-2-methoxy-2-nonenyl (E)-4-Decenoate (18). A solution of 1.37 g (6.37 mmol) of the hydroxy amide 22a and 3.53 ml (2.55 g, 25 mmol) of dry triethylamine in 25 ml of dry dichloromethane was cooled to 0^0. To this stirred solution was added 1.20 g (6.37 mmol) of the acid chloride 25 in 10 ml of dichloromethane. The reaction mixture was allowed to warm to 25^0 over 1 hr and then was stirred for 11 hr. Extraction[23] with 10% dichloromethane/ether, including a base wash, gave 2.02 g of a yellow oil which crystallized upon standing. This material was purified by medium-pressure chromatography[22] on 2.5 x 50 cm of silica gel with 40% acetone/ether at a flow rate of 2 ml/min. After elution with 210 ml of this solvent system, the next 160 ml afforded 1.69 g (72%) of the ester 18 as a white waxy solid containing two isomers. A portion of this material was recrystallized from hexane and gave white platelets: mp 52.5-60^0; NMR ($CDCl_3$) δ3.47 and 3.55 (s, 3H total, CH_3O), 4.57 (m, 2H, $-CH_2O-$), 4.8 (m, 1H, enol ether vinylic H), 5.42 (m, 2, CH=CH), 5.7 (br, 2H, NH_2); ir ($CHCl_3$) 3540, 3500 and 3420 (NH_2), 1730 (ester C = O), 1675 (amide C = O), 1590, 1160, 1120, 1070, 970 cm^{-1}.

Anal. Calcd. for $C_{21}H_{37}NO_4$: C, 68.63; H, 10.15; N, 3.81. Found: C, 68.64; H, 10.13; N, 3.84.

4-(6-Carbamoylhexyl)-5-methoxy-5-methyl-3-(2-octenyl)-oxacyclopentan-2-one (27). A solution of 1.5 mmol of LDA in 3.0 ml of dry THF was cooled to -78^0. To this rapidly stirred solution was added

184 mg (0.5 mmol) of the ester 18 in 1 ml of THF over 1 min. After an additional 2 min at -78°, 1.0 ml (1.52 mmol) of TBSCl in HMPA was added in one portion. This mixture was stirred at -78° for an additional 2 min after which the cooling bath was removed and the reaction mixture was allowed to warm to 25° over 20 min. The reaction mixture was then stirred at reflux for 3.5 hr. Extraction[23] with 75% ether/petroleum ether afforded 369 mg of a nearly colorless oil. This oil was dissolved in 3 ml of THF and 1 ml of methanol; one drop of methanesulfonic acid was added and the mixture was stirred for 35 min at 25°. Extraction[23] with 75% ether/petroleum ether, including a base wash, gave 198 mg of a colorless oil. This material was purified by medium-pressure chromatography[22] on 1.25 x 50 cm of silica gel with 25% acetone/ether at a flow rate of 1 ml/min. After elution with 110 ml of this solvent system, the next 10 ml gave 45 mg of a mixture of compounds which by NMR analysis appeared to contain 50% of the desired lactone. Continued elution with 65 ml of the same solvent system gave 102 mg (56%) of a mixture of diasteriomers of the lactone 27 as a colorless oil: NMR ($CDCl_3$) δ1.35 (br s, methylenes), 1.43 and 1.53 (s, 3H total, $CH_3C-(O)_2-$), 3.33 (br s, 3H, CH_3O-), 5.5 (br m, 4H, CH=CH and NH_2): ir ($CHCl_3$) 1765 (lactone (C = O), 1680 (amide C = O), 1590, 1385, 975, 910 cm^{-1}.

Anal. Calcd for $C_{21}H_{37}NO_4$: C, 68.63; H, 10.15; N, 3.81. Found: C, 68.72; H, 9.99; N, 3.62.

5-(6-Carbamoylhexyl)-4-(2-octenyl)-2-cyclopentenone (28).

A. Reduction with DIBAH. A solution of 102 mg (0.278 mmol) of

lactone 27 in 4 ml of dry ether was cooled to -78°. To this stirred solution was added 0.855 ml (0.612 mmol) of a solution of DIBAH in benzene over a period of 3 min. The reaction mixture was stirred at -78° for an additional 30 min, then 0.15 ml of methanol was added to the mixture and the cold bath was removed. After the reaction mixture had warmed to 25°, 0.15 ml of water and 0.2 g of Celite were added. The reaction mixture was stirred vigorously for 15 min. Anhydrous sodium sulfate (0.2 g) was again subjected to vigorous stirring for 15 min. The reaction mixture was then filtered with the aid of 75 ml of ether. The filtrate was evaporated at reduced pressure and gave 95 mg (92%) of a crude lactol which was not purified further.

B. Aldol Condensation. A solution of 69 mg (0.187 mmol of the crude lactol in 5 ml of ethanol and 5 ml of 5% aqueous sodium hydroxide solution was stirred for 20 min at 25°. Ether extraction[23] gave 53 mg of a colorless oil. This material was purified by medium-pressure chromatography[22] on 1.25 x 50 cm of silica gel with 30% acetone/ether at a flow rate of 1 ml/min. After elution with 120 ml of this solvent system, continued elution with 35 ml afforded 33 mg (51%) of the cyclopentenone 28 as a colorless oil: NMR ($CDCl_3$) δ2.05 (t, 2H, J=7 Hz, $CH_2C=O$), 5.42 (m, 2H, CH=CH), 5.73 (m, 2H, NH_2), 6.10 (dd, 1H, J=6 and 1 Hz, =CH-C=O), 7.56 (dd, 1H, J=6 and 2 Hz CH=C-C=O); ir ($CHCl_3$) 3550-3100 (several bands, NH_2), 1685 (enone and amide C = O), 1590, 970 cm^{-1}; uv(EtOH) λ_{max}= 219 mμ (ε= 10,000).

Anal. Calcd for $C_{20}H_{33}NO_2$: C, 75.19; H, 10.41; N, 4.38. Found: C, 75.05; H, 10.47; N, 4.41.

4-(6-Carboxyhexyl)-5-methoxy-5-methyl-3-(2-octenyl)-oxacyclopentan-2-one (29). A solution of 2.04 mmol of LDA in 7 ml of dry THF was cooled to -78°. To this stirred solution was added 1.8 ml of dry HMPA followed by 250 mg (0.679 mmol) of the ester 18 in 2 ml of THF over 4 min. The reaction mixture was stirred for an additional 2 min and then 0.59 ml (2.04 mmol) of TBSCl in hexane was added. After an additional 2 min at -78°, the cold bath was removed and the reaction mixture was allowed to warm to 25°. The mixture was then stirred at reflux for 3 hr. Extraction[23] with 75% ether/petroleum ether gave a non-mobile oil. This material was stirred at reflux in a solution of 1.2 g sodium hydroxide, 6 ml of water and 15 ml of methanol for 16 hr. The cooled reaction mixture was poured into 30 ml of water and extracted with three 25-ml portions of ether (extracts discarded). The basic solution was cooled to 0° and acidified by addition of 90 ml of 0.4 N H_2SO_4 with stirring. Dichloromethane extraction[23] gave 220 mg of an oil. This material was purified by medium-pressure chromatography[22] on 1.25 x 50 cm of silica gel with petroleum ether : dichloromethane : THF : acetic acid = 50:10:3:2 at a flow rate of 1 ml/min. After elution with 60 ml of this solvent system, continued elution with 50 ml gave 162 mg (65%) of a mixture of diasteriomers of the lactone-acid 29 as a colorless oil: NMR ($CDCl_3$) δ1.43 and 1.53 (s, 3H total, $CH_3C(O)_2$-), 3.36 (s, 3H, CH_3O-), 5.65 (m, 2H, CH=CH); ir ($CHCl_3$) 1765 (lactone C = O), 1710 (acid C = O), 1380, 975, 910 cm^{-1}.

Anal. Calcd for $C_{21}H_{36}O_5$: C, 68.45; H, 9.85. Found: C, 68.42; H, 9.72.

5-(6-Carboxyhexyl)-4-(2-octenyl)-2-cyclopentenone (30).

A. Reduction with DIBAH. A solution of 168 mg (0.450 mmol) of the lactone-acid 29 in 15 ml of dry ether was cooled to -78°. To this stirred solution was added 1.17 ml (1.01 mmol) of DIBAH in benzene over a 4-min period. The reaction mixture was then stirred at -78° for an additional 30 min. The mixture was then treated with 0.6 ml of methanol to quench excess hydride and was stirred for an additional 5 min at -78°. The reaction mixture was then rinsed into a mixture of 5 ml of acetic acid and 10 g of ice with 25 ml of ether. This mixture was stirred for 5 min, after which ether extraction[23] afforded 166 mg (quantitative crude yield) of a keto-aldehyde: NMR ($CDCl_3$) δ1.33 (m, $-CH_2-$), 2.16 and 2.23 (s, 3H total, $CH_3C=O$), 5.38 (m, 2H, CH = CH), 9.41 (br s, 1H, CO_2H), 9.69 (m, 1H, CHO).

B. Aldol Condensation. This keto-aldehyde was dissolved in 15 ml of dry benzene and was treated with 5.7 μl of acetic acid and 9.9 μl of piperidine. This mixture was stirred at reflux with continuous removal of water by means of a Dean-Stark apparatus charged with 4A molecular sieves. After 4.75 hr, TLC analysis indicated that some starting keto-aldehyde remained. The reaction mixture was again treated with 5.7 μl of acetic acid and 9.9 μl of piperidine and reflux was continued for 2 hr. Ether extraction,[23] including a wash with 20% aqueous sodium dihydrogen phosphate solution, gave 197 mg of a

slightly yellow oil. Purification by PTLC[22,26] on 13 x 20 x 0.2 cm of silica gel with hexane : dichloromethane : THF : acetic acid = 30:10:5:3 afforded 126 mg (86% from lactone 29, Rf = 0.23-0.38) of cyclopentenone 30 as a colorless oil: NMR ($CDCl_3$) δ5.44 (m, 2H, CH = CH), 6.15 (dd, 1H, J=6 and 1 Hz, =CHC=O), 7.60 (dd, 1H, J=6 and 2 Hz, CH=CC=O), 10.07 (br s, 1H, CO_2H); ir ($CHCl_3$) 3400-2600 (CO_2H), 1705 (enone and acid C = O), 1590, 950 cm^{-1}; uv(EtOH) λ_{max} = 219 mμ (ε= 9400).

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 74.90; H, 9.90.

3-(6-Carboxyhexyl)-2,5-dimethoxy-2-methyl-4-(2-octenyl)-oxacyclopentane (31). A solution of 133 mg (0.361 mmol) of the crude lactol, which resulted from reduction of lactone 27 (vide supra), in 7 ml of methanol was cooled to 0^0. To this solution was added one drop of methanesulfonic acid and the reaction mixture was stirred at 0^0 for 3 hr. Ether extraction,[23] including a base wash, gave 128 mg (93%) of a slightly brown oil. A portion of this material (75 mg) was purified by medium-pressure chromatography[22] on 1.25 x 50 cm of silica gel with 30% acetone/ether at a flow rate of 1 ml/min. After elution with 135 ml of this solvent, continued elution with 125 ml afforded 53 mg of a mixture of several diasteriomers of the bis acetal 31 as a colorless oil: NMR ($CDCl_3$) 3.27, 3.32, 3.37 and 3.40 (s, CH_3O), 4.65 (m, 1H, -OCHO-), 5.43 (m, 2H, CH=CH), 5.68 (m, 2H, NH_2); ir ($CHCl_3$) 1675 (amide C = O), 1590, 1380, 1100, 975 cm^{-1}.

Anal. Calcd for $C_{22}H_{41}NO_4$: C, 68.89; H, 10.77; N, 3.65. Found: C, 68.91; H, 10.76; N, 3.66.

Preparation of Cyclopentenone 30 from Bis Acetal 31. A solution of 128 mg (0.334 mmol) of the crude bis acetal 31 in 25 ml of methanol and 8 ml of 20% aqueous sodium hydroxide solution was stirred at reflux for 8 hr. The reaction mixture was poured into 150 ml of pH 7 buffer (Beckmann) containing a small amount of bromothymol blue. The blue solution was neutralized by dropwise addition of conc hydrochloric acid at 0° until a light green color was obtained. Dichloromethane extraction[23] gave 95 mg of a brown oil. This material was partially purified by filtration through 15 g of silica gel. Elution with 40 ml of ether gave 48 mg of an oil. This material was dissolved in 7.5 ml of THF and 3 ml of water. To this solution was added 0.3 ml of conc hydrochloric acid and the mixture was stirred at 25° for 1.5 hr. At the end of this period, 0.75 ml of 40% aqueous sodium hydroxide solution and 3 ml of methanol were added. The reaction mixture was stirred at 25° for 25 min. The reaction mixture was then poured into 20 ml of 5% hydrochloric acid. Ether extraction[23] gave 44 mg of an orange oil. Chromatography of this material on 15 g of silica gel with 30 ml of 75% ether/petroleum ether, 30 ml of 90% ether/petroleum ether, and finally 60 ml of ether gave 15 mg (14% from lactone 27) of the cyclopentenone acid 30.

Isopropyl 4,5-Epoxy-2-hexenoate (33). A solution of 5.8 g (37.7 mmol) of isopropyl sorbate in 100 ml of dichloromethane was cooled to 0°. To this solution was added 11.5 g (56.5 mmol) of 85%

m-chloroperbenzoic acid during a 10-min period. Following this addition, the reaction mixture was stirred at 0^0 for 30 min and at 25^0 for 4 hr. Excess peracid was then destroyed by dropwise addition of 10% aqueous sodium bisulfite solution and the product was isolated by ether extraction,[23] including a base wash. The residual liquid was purified by chromatography on 200 g of silica gel. After elution with 500 ml of 10% ether/petroleum ether and then 250 ml of 20% ether/petroleum ether, continued elution with the latter solvent system gave 4.9 g (76%) of the epoxy ester 33. An analytical sample was obtained by preparative VPC[22] (200^0, 1/4 in. x 8 ft. 10% Carbowax 20 M, 60 ml/min, thermocouple) followed by evaporative distillation at 40^0 (0.08 mm): NMR ($CDCl_3$) δ1.25 (d, 6H, J=6 Hz, $(CH_3)_2C$), 1.35 (d, 3H, J=6 Hz, C-6 H), 2.95 (q of d, 1H, J=5 and 2 Hz, C-5 H), 3.13 (dd, 1H, J=6 and 2 Hz, C-4 H), 5.07 (septet, 1H, J=6 Hz, $(CH_3)_2CHO$-), 6.07 (d, 1H, J=15 Hz, C-2 H), 6.67 (dd, 1H, J=15 and 6 Hz, C-3 H); ir ($CHCl_3$) 1710 (C = O), 1660 (C = C), 1110, 975, 915, 940, 830 cm^{-1}.

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.52; H, 8.36.

Reduction of Ester 33.

A. With Lithium in Ammonia. A mixture of 24 ml of dry THF and 96 ml of dry ammonia was cooled to -78^0. To this stirred solution was added 63 mg (9 mmol) of lithium wire in 6 freshly cut pieces. After 10 min at -78^0, a solution of 510 mg (3 mmol) of the ester 33 in 2 ml of dry THF was added to the rapidly stirred reaction mixture as fast as

possible. After 40 sec, the blue color faded and 9 g of solid ammonium chloride was added. Stirring was continued at -78° for 2 min, after which the cooling bath was removed and ammonia allowed to evaporate over 4 hr. Dichloromethane extraction[23] gave 480 mg of a colorless oil which was purified further by chromatography on 15 g of silica gel with 50% ether/petroleum ether. After elution with 40 ml of this solvent mixture, continued elution with 80 ml gave 410 mg (79%) of a mixture of alcohols 36a and 37a. Analysis by VPC[22] (160°, 1/4 in x 8 ft. 10% Carbowax 20 M, 60 ml/min, thermocouple) indicated that the mixture contained an 89:11 ratio of isomers: NMR ($CDCl_3$) δ1.22 (d, 6H, J=6 Hz, $(CH_3)_2C$), 1.25 (d, 3H, J=6 Hz, C-6 H's), 2.3 (br, 1H, OH), 3.00 (m, 2H, C-2 H's), 4.27 (m, 1H, C-5 H), 5.00 (septet, 1H, J=6 Hz, $(CH_3)_2CH$-), 5.67 (m, 2H, C-3 H and C-4 H); ir ($CHCl_3$) 3600 and 3400 (OH), 1720 (C = O), 1375, 1110, 1060, 970 cm^{-1}.

Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.70; H, 9.44.

Isopropyl (E)-5-(tert.-Butyldimethylsilyloxy)-3-hexenoate (36b); Isopropyl (Z)-5-(tert.-Butyldimethylsilyloxy)-3-hexenoate (37b). Following the procedure of Corey,[18] a mixture of 462 mg (2.69 mmol) of the alcohols 36a and 37a from the lithium in ammonia reduction above, 483 mg (3.22 mmol) of TBSCl, and 457 mg (6.73 mmol) of imidazole in 5 ml of dry DMF was stirred at 25° for 17 hr. Pentane extraction[23] gave 731 mg of a slightly yellow oil which was filtered through 15 g of silica gel with 80 ml of 5% ether/petroleum ether. This afforded 526 mg (68%) of a colorless oil. Analysis by VPC[22] (160 , 1/4 in x

8 ft 10% Carbowax 20 M, 60 ml/min, thermocouple) indicated that this consisted of two isomeric components. The minor isomer (10%) had a rention time of 11.5 min; the major isomer (90%) had a retention time of 13.0 min. These isomers were separated by medium-pressure chromatography[22] on 0.9 x 60 cm of silica gel with 5% ether/petroleum ether at a flow rate of 0.5 ml/min. The more mobile component was the minor isomer which was assigned the Z-stereochemistry 37b. An analytical sample was prepared by evaporative distillation at 50° (0.05 mm): NMR ($CDCl_3$) δ0.03 (s, 6H, $(CH_3)_2Si$), 0.87 (s, 9H, $(CH_3)_3CSi$), 1.18 (d, 3H, J=6 Hz, C-6 H's), 1.22 (d, 6H, J=6 Hz, $(CH_3)_2C$), 1.37 (d, 2H, J=5 Hz, C-2 H's), 4.5 (m, 1H, C-5 H), 5.00 (septet, 1H, J=6 Hz, $(CH_3)_2CH$-), 5.55 (m, 2H, C-3 H and C-4 H); ir ($CHCl_3$) 1725 (C = O), 1260, 1110, 915, 875, 835 cm^{-1}, no band at 970 cm^{-1}.

Anal. Calcd for $C_{15}H_{30}O_3Si$: C, 62.89; H, 10.55. Found: C, 62.94; H, 10.58.

The less mobile component was the major isomer and was assigned the E-stereochemistry 36b. An analytical sample was prepared by evaporative distillation at 50° (0.05 mm): NMR ($CDCl_3$) δ0.05 (s, 6H, $(CH_3)_2Si$), 0.90 (s, 9H, $(CH_3)_3CSi$), 1.20 (d, 3H, J=6 Hz, C-6 H's), 1.22 (d, 6H, J=6 Hz, $(CH_3)_2C$), 2.98 (d, 2H, J=5 Hz, C-2 H's), 4.27 (m, 1H, C-5 H), 5.02 (septet, 1H, J=6 Hz, $(CH_3)_2CHO$-), 5.65 (m, 2H, C-3 H and C-4 H); ir ($CHCl_3$) 1720 (C=O), 1260, 1110, 970, 910, 835 cm^{-1}.

Anal. Calcd for $C_{15}H_{30}O_3Si$: C, 62.89; H, 10.55. Found: C, 63.00; H, 10.58.

Reduction of Ester 33.

B. With Sodium in HMPA-THF, Followed by Silylation with TBSCl.

A solution of sodium in HMPA-THF was prepared according to the procedure of House.[17] Titration of an aliquot of this solution with sec-butanol in xylene indicated that it was 0.35 M in sodium. Addition of a second aliquot to water followed by titration with standard HCl to a phenolphthalein endpoint indicated that the solution was 0.32 M in total base.

A solution of 170 mg (1 mmol) of ester 33 in 13.7 ml of THF was cooled to -78°. To this rapidly stirred solution was added 5.88 ml (2.0 mmol) of the Na-HMPA-THF solution in one portion. Decolorization occurred after 70 sec. After an additional 2 min at -78° the yellow solution was treated with 0.65 ml (2.2 mmol) of TBSCl in hexane and was stirred at -78° for an additional 2 min. The cooling bath was then removed and the reaction mixture was stirred at 25° for 20 min. Pentane extraction[23] gave a yellow oil which was dissolved in 5 ml of THF and treated with 1 ml of 70% aqueous acetic acid solution. This solution was stirred at 25° for 1 hr to effect hydrolysis of the silyl ketene acetal. Pentane extraction,[23] including a base wash, gave a nearly colorless oil which was purified by chromatography on 10 g of silica gel with 10% ether/petroleum ether. Elution with 35 ml of this solvent mixture gave 113 mg (39%) of a mixture of silyl ethers 36b and 37b. Analysis by VPC[22] (160°, 1/4 in x 8 ft 10% Carbowax 20 M, 60 ml/min, thermocouple) indicated that this material consisted of a mixture of Z-silyl ether 37b (40%) and E-silyl ether 36b (60%).

C. With Sodium in HMPA-THF Followed by Protonation. A solution of sodium in HMPA-THF[17] was prepared as in B above. Titration of total base with standard HCl indicated that the solution was 0.256 M in sodium. A solution of 170 mg (1.0 mmol) of ester 33 in 43 ml of dry THF and 4 ml of dry HMPA was cooled to -78°. To this rapidly stirred solution was added 11.7 ml (3.0 mmol) of the Na-HMPA-THF solution in one portion. The blue color persisted and was discharged after 1 min by addition of 9 g of solid ammonium chloride. After an additional 2 min at -78°, the reaction mixture was allowed to warm to 25° over 30 min. Pentane extraction gave 127 mg of a yellow oil which was purified by chromatography on 15 g of silica gel with 50% ether/petroleum ether. After elution with 54 ml of this solvent mixture, continued elution with 40 ml gave 73 mg (42%) of a mixture of alcohols 36a and 37a.

D. With Zinc in HMPA-THF.[3] A mixture of 340 mg (2.0 mmol) of epoxy ester 33, 600 mg (4 mmol) of TBSCl, and 0.5 g of zinc dust in 10 ml of dry THF and 2.5 ml of dry HMPA was stirred at reflux for 16 hr. Pentane extraction[23] gave a colorless oil. NMR analysis indicated that this material consisted of only the starting ester 33.

Enolization of Hydroxy Esters 36a and 37a. A solution of 2.2 mmol of LDA in 20 ml of dry THF was cooled to -78°. To this solution was added 4.0 ml of dry HMPA. This rapidly stirred solution was treated with the dropwise addition of 172 mg (1.0 mmol) of a mixture of the hydroxy ester 36a (90%) and 37a (10%) in 2 ml of dry THF over 4 min.

Following the addition, the reaction mixture was stirred at -78° for an additional 2 min and then 0.65 ml (2.2 mmol) of TBSCl in hexane was added in one portion. After an additional 2 min, the reaction mixture was allowed to warm to 25 and was stirred for 30 min. Pentane extraction[23] gave a slightly yellow oil which contained none of the starting esters and was identified as the ketene acetal 35 (NMR analysis). This material was dissolved in 5 ml of THF and was treated with 1 ml of 70% aqueous acetic acid. After 1.5 hr, VPC[22] analysis (160°, 1/8 in x 6 ft, 4% SE-30, 60 ml/min, flame ionization) employing hexadecane as an internal standard (corrected for sensitivities) indicated that the siloxy esters 36b and 37b were present in 56% yield. VPC[22] analysis (160°, 1/4 x 8 ft, 10% Carbowax 20 M, 60 ml/min, thermocouple) demonstrated that the mixture consisted of 90% of the E-ester 36b and 10% of the Z-ester 37b.

Enolization of the Siloxy Esters 36b and 37b. A solution of 0.6 mmol of LDA in 5 ml of dry THF was cooled to -78° and 1.0 ml of dry HMPA was added. To this rapidly stirred mixture was added a solution of 143 mg (0.5 mmol) of a mixture of the silyl ether 36b (90%) and 37b (10%) and 90 mg (0.6 mmol) of TBSCl in 0.5 ml of dry THF over 4 min. After an additional 2 min at -78°, the reaction mixture was allowed to warm to 25° and was stirred for 30 min. Pentane extraction[23] gave a slightly yellow oil which contained none of the starting esters 36b or 37b (NMR analysis). The ketene acetal was hydrolized and the reaction mixture analyzed as described above. The silyoxy esters were present in 64% yield. This consisted of ester 36b (90%) and ester 37b (10%).

Methyl (E)-2-Methyl-2-(phenylthio)-4-decenoate (40). A solution of 3.37 g (11.53 mmol of (E)-2-methyl-2-(phenylthio)-4-decenoic acid[3] in 40 ml of dry HMPA was treated with 353 mg of sodium hydride (mineral oil free) in small portions over a 10-min period. Following the addition, the reaction mixture was stirred at 25° for 1.25 hr and then treated with 2.49 ml (5.68 g, 40 mmol) of iodomethane in one portion. This mixture was stirred at 25° for 3 hr and then diluted with 100 ml of 5% hydrochloric acid solution. Ether extraction,[23] including a wash with 10% aqueous sodium thiosulfate solution, gave 3.40 g of a slightly yellow oil. This material was purified by chromatography on 170 g of silica gel with 5% ether/petroleum ether. After elution with 540 ml of this solvent system, continued elution with 360 ml gave 3.21 g (91%) of the methyl ester 40. An analytical sample was prepared by evaporative distillation at 120° (0.05 mm): NMR ($CDCl_3$) 1.38 (s, 3H, CH_3), 2.00 (m, 2H), 1.8-2.9 (4H), 5.43 (m, 2H, CH=CH), 7.4 (m, 5H, C_6H_5); ir ($CHCl_3$) 1725 (C = O), 1435, 1375, 1025, 970 cm^{-1}.

Anal. Calcd for $C_{18}H_{26}O_2S$: C, 70.56; H, 8.55; S, 10.46. Found: C, 70.62; H, 8.62; S, 10.49.

Methyl (E,E)-2-Methyl-2,4-decadienoate (41); Methyl (E)-2-Methylene-4-decenoate (42). A solution of 3.0 g (9.80 mmol) of the α-(phenylthio) ester 40 in 125 ml of dichloromethane was cooled to 0°. To this stirred solution was added a solution of 1.99 g (9.80 mmol) of 85% m-chloroperbenzoic acid in 25 ml of dichloromethane over a period

of 1 hr. Following the addition, the reaction mixture was stirred at 0° for an additional hour. Ether extraction,[23] including a base wash, gave a mixture of sulfoxides. This material was dissolved in 65 ml of carbon tetrachloride and was stirred at 60° for 2 hr. The reaction mixture was cooled to 25° and the solvent was removed at reduced pressure. The residue was partially purified by passage through 100 g of silica gel with 200 ml of 30% ether/petroleum ether and afforded 2.0 g of a colorless oil. VPC[22] analysis (200°, 1/4 in x 8 ft 10% Carbowax 20 M, 60 ml/min, thermocouple) indicated that this material consisted of only two volatile components. The minor component (retention time = 3.5 min) accounted for 22% of the mixture and the major component (retention time = 7.5 min), 78%. These isomers could be separated by medium-pressure chromatography[22] on 2.5 x 50 cm of silica gel with 2% ether/petroleum ether at a flow rate of 2 ml/min. After elution with 380 ml of this solvent system, continued elution with 300 ml gave 387 mg (20%) of the minor component which was identified as the α-methylene ester 42. An analytical sample was prepared by evaporative distillation at 60° (0.1 mm): NMR ($CDCl_3$) δ0.5-1.5 (9H), 2.0 (m, 2H, C-6 H's), 3.0 (m, 2H, C-3 H's), 3.77 (s, 3H, CH_3O), 5.50 (m, 3H, vinylic H's), 6.15 (br s, 1H, vinylic H syn to ester); ir ($CHCl_3$) 1715 (C = O), 1630 (C = C), 1435, 1140, 975, 950 cm^{-1}.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.38; H, 10.18.

After elution with an additional 20 ml of the same solvent system, continued elution with 430 ml gave 1.411 g (73%) of the major isomer which was identified as the fully conjugated isomer 41. An

analytical sample was prepared by evaporative distillation at 60° (0.05 mm): NMR ($CDCl_3$) δ0.7-1.6 (9H), 1.90 (br s, 3H, vinylic CH_3), 2.2 (m, 2H, C-6 H's), 3.72 (s, 3H, CH_3O-), 6.23 (m, 2H, C-4 H and C-5 H), 7.13 (br d, 1H, J=8 Hz, C-3 H); ir ($CHCl_3$) 1700 (C = O), 1640 and 1610 (C = C), 1435, 1110, 970 cm^{-1}.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.42; H, 10.16.

In a separate experiment it was possible to separate and independently pyrolize the two diastereomeric sulfoxides. The mixture of sulfoxides from oxidation of 2.0 g (6.54 mmol) of the ester 40 was subjected to chromatography on 200 g of silica gel. After elution with 400 ml of 30% and 300 ml of 40% ether/petroleum ether, continued elution with 225 ml of 50% ether/petroleum ether gave 712 mg of the more mobile sulfoxide contaminated with decomposition products. Further elution with 150 ml of the same solvent mixture gave 346 mg of the less mobile sulfoxide, also contaminated with decomposition products. Rapid rechromatography on 50 g of silica gel with 60% ether/petroleum ether afforded pure samples of each of the sulfoxides.

The more mobile isomer (Isomer A, Rf^{22}=0.21, 30% ether/petroleum ether, 523 mg) was characterized by the following spectral data: NMR ($CDCl_3$) δ1.17 (s, 3H, CH_3), 1.9 (m, 2H, $=CCH_2$-), 2.60 (d, 1H, J=7 Hz, C-3 H), 2.88 (d, 1H, J=6 Hz, C-3 H), 3.60 (s, 3H, CH_3O), 5.43 (m, 2H, CH=CH), 7.48 (s, 5H, C_6H_5); ir ($CHCl_3$) 1720 (C = O), 1370, 1080, 1035, 970 cm^{-1}.

The less mobile isomer (Isomer B, Rf^{22}=0.12, 30% ether/petroleum ether, 144 mg) was characterized by the following spectral data:

NMR ($CDCl_3$) δ1.38 (s, 3H, CH_3), 1.9 (m, 2H, $=CCH_2-$), 2.37 (d, 1H, J=7 Hz, C-3 H), 2.60 (d, 1H, J=6 Hz, C-3 H), 3.63 (s, 5H, C_6H_5); ir ($CHCl_3$) 1725 (C = O), 1375, 1085, 1045, 975, 910 cm^{-1}.

Each sulfoxide was heated in carbon tetrachloride at 60° for 2 hr. The products were isolated as described above and analyzed by VPC[22] (200°, 1/4 in x 8 ft 10% Carbowax 20 M, 60 ml/min, thermocouple). The following results were obtained.

Sulfoxide	41/42	Yield of Olefins
Isomer A (High Rf)	68/32	99% from Sulfoxide
Isomer B (Low Rf)	90/10	97% " "
Original Mixture	78/22	93% from ester 40

Methyl 4,5-Epoxy-2-methyl-2-decenoate (46). The unsaturated ester 41 (3.1 g, 15.8 mmol) was dissolved in 100 ml of chloroform and 40 mg of 3-tert.-butyl-4-hydroxy-5-methylphenyl sulfide,[27] a free radical inhibitor, was added. To this solution was added 4.02 g (19.8 mmol) of 85% m-chloroperbenzoic acid and the resulting solution was stirred at 25° for 6 hr. Ether extraction,[23] including a base wash and a 10% aqueous sodium bisulfite wash, gave the crude epoxy ester 46 which was purified by medium-pressure chromatography[22] on 2.5 x 50 cm silica gel with 10% ether/petroleum ether at a flow rate of 2.7 ml/min. After elution with 560 ml of this solvent mixture, continued elution with 300 ml afforded 3.0 g (90%) of the epoxy ester 46 as a colorless oil. An analytical sample was prepared by evaporative distillation at 70° (0.1 mm): NMR ($CDCl_3$) δ0.5-1.7 (11H),

1.98 (d, 3H, J=1.5 Hz, C-2 CH_3), 2.88 (m, 1H, C-5 H), 3.33 (dd, 1H, J=2 and 8 Hz, C-4 H), 3.75 (s, 3H, CH_3O-), 6.30 (br d, 1H, J=8 Hz, C-3 H); ir ($CHCl_3$) 1715 (C = O), 1655 (C = C), 1435, 1315, 1260, 1160, 1105, 915, 870 cm^{-1}.

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.84; H, 9.42.

Methyl (E)-5-Hydroxy-2-methyl-3-decenoate (47). A mixture of 24 ml of dry THF and 96 ml of dry ammonia was cooled to -78°. To this stirred solution was added 63 mg (9 mmol) of lithium wire in 6 pieces. This solution was stirred for 10 min at -78° and then 636 mg (3.0 mmol) of epoxy ester 46 in 2 ml of THF was added in one portion. The blue color persisted for 1 min at which time it was discharged by addition of 9 g of solid ammonium chloride. After an additional 2 min at -78°, the cooling bath was removed, 75 ml of hexane was cautiously added to the reaction mixture, and the ammonia was allowed to evaporate over 4 hr. Ether extraction[23] gave 595 mg of a colorless oil which was purified by chromatography on 50 g of silica gel with 40% ether/petroleum ether. After elution with 80 ml of this solvent system, continued elution with 20 ml gave 26 mg (4%) of a minor isomer which was tentatively assigned Z-stereochemistry of ester 47. An analytical sample was prepared by evaporative distillation at 90° (0.05 mm): NMR ($CDCl_3$) δ0.9-1.5 (12H), 1.97 (m, 2H, C-6 H's), 2.5 (m, 2H, C-2 H and OH), 3.68 (s, 3H, CH_3O-), 4.28 (m, 1H, C-5 H), 5.57 (m, 2H, C-3 H and C-4 H); ir ($CHCl_3$) 3600-3400 (OH); 1725 (C = O), 1455, 1005, 970 cm^{-1}.

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.36; H, 10.32.

After elution with an additional 10 ml of the same solvent system, continued elution with 85 ml gave 440 mg (69%) of the major E-isomer 47. An analytical sample was prepared by evaporative distillation at 90° (0.05 mm): NMR ($CDCl_3$) δ0.5-1.9 (15H), 3.13 (m, 1H, C-2 H), 3.68 (s, 3H, CH_3O-), 4.07 (m, 1H, C-5 H), 5.67 (m, 2H, C-3 H and C-4 H); ir ($CHCl_3$) 3600 and 3550-3400 (OH), 1725 (C = O), 1455, 1045, 970 cm^{-1}.

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.22; H, 10.30.

Attempted Hydrolysis of Hydroxy Ester 47. A solution of 140 mg (0.654 mmol) of epoxy ester 44 and 157 mg (6.54 mmol) of lithium hydroxide[28] in 4.7 ml of methanol and 1.6 ml of water was stirred at 25° for 2.5 hr. After dilution with water and acidification with conc hydrochloric acid, ether extraction[23] gave 129 mg (99%) of a nearly colorless oil. TLC[22] analysis (ether) indicated that this consisted of two acid components, the more mobile of which quenched fluoresence. An ether solution of 32 mg of this material was treated with excess diazomethane[29] for 20 min at 0°. The excess diazomethane was destroyed by dropwise addition of acetic acid after which ether extraction[23] gave 33 mg of a colorless oil. This material showed only one spot by TLC analysis (50% ether/petroleum ether). Purification was accomplished by medium-pressure chromatography[22] on 0.9 x 60 cm silica gel with ether at a flow rate of 0.5 ml/min. After elution with 26 ml of this solvent, continued elution with an additional 14 ml afforded 31 mg (91%) of a

colorless oil. NMR analysis indicated that this consisted of 70% of ester 47 [δ3.68 (s, CH_3O)] and 30% of another methyl ester [δ3.73 (s, CH_3O) and 6.90 (br t, J=7 Hz, vinylic H)] which was tentatively assigned the structure of the methyl ester arising from conjugated acid 49. Similar results were obtained when the saponification was attempted with potassium hydroxide in methanol.

(E,E)-2-Methyl-2,4-decadienoic Acid (43). A mixture of 3.0 g (15.3 mmol) of the methyl ester 41 and 1.5 g of potassium hydroxide in 10 ml of methanol was stirred at reflux for 1.5 hr. The reaction mixture was then diluted with 100 ml of water and extracted with two 50-ml portions of ether (extracts discarded). After acidification of the basic solution with conc hydrochloric acid, ether extraction[23] gave 2.76 g (99%) of the acid 43 as white crystals, mp 53-56°. The analytical sample was prepared by two recrystallizations of this material from petroleum ether at -20°: NMR ($CDCl_3$) δ0.6-1.8 (9H), 1.93 (br s, 3H, C-2 CH_3), 2.2 (m, 2H, C_6H_5), 6.2 (m, 2H, C-4 H and C-5 H), 7.3 (d, 1H, J=10 Hz, C-3 H), 11.0 (br s, 1H, CO_2H); ir ($CHCl_3$) 3500-2500 (CO_2H), 1680 (C=O), 1630 (C=C), 1250, 1035, 970 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.34; H, 9.75.

9-Carbamoyl-2-methoxy-2-nonenyl (E)-4,5-Epoxy-2-methyl-3-decenoate (50).

A. p-Nitrophenyl 2-Methyl-2,4-Decadienoate (44). A solution of 2.65 g (14.56 mmol) of unsaturated acid 43 in 20 ml of dry triethylamine

was cooled to 0°. To this solution was added 3.42 (14.56 mmol) of p-nitrophenyl trifluoroacetate[11] in one portion. This homogeneous solution was stirred at 0° for 30 min, during which an orange lower layer separated. Stirring was then continued for 3 hr at room temperature. Ether extraction,[23] including a base wash and a 20% aqueous monosodium phosphate wash, gave an orange oil which was passed through 50 g of silica gel with 300 ml of dichloromethane. This afforded 3.8 g (86%) of the p-nitrophenyl ester 44 as a slightly yellow oil: NMR ($CDCl_3$) δ0.6-1.6 (9H), 2.07 (br s, 3H, C-2 CH_3), 2.2 (m, 2H, C-6 H's), 6.3 (m, 2H, C-4 H and C-5 H), 7.32 (d, 2H, J=9 Hz, aromatic), 8.28 (d, 2H, J=9 Hz, aromatic).

B. p-Nitrophenyl 4,5-Epoxy-2-methyl-2-decenoate (45). The p-nitrophenyl ester 44 (3.8 g, 12.54 mmol) was dissolved in 100 ml of chloroform. To this solution was added 3.19 g (15.68 mmol) of 85% m-chloroperbenzoic acid and 40 mg of 3-tert.-butyl-4-hydroxy-5-methylphenyl sulfide.[27] This mixture was stirred for 2 hr at 25° and for 2 hr at reflux. Ether extraction,[23] including a 10% aqueous sodium bisulfite wash and a base wash, followed by passage of the residue through 40 g of silica gel with 240 ml of dichloromethane, gave 3.55 g (89%) of the epoxy ester 45 as a slightly yellow oil: NMR ($CDCl_3$) δ0.5-1.9 (11H), 2.13 (d, 3H, J-1.5 Hz, C-2 CH_3), 3.0 (m, 1H, C-5 H), 3.45 (dd, 1H, J=2 and 8 Hz, C-4 H), 6.60 (br d, 1H, J=9 Hz, C-3 H), 7.30 (d, 2H, J=9 Hz, aromatic), 8.30 (d, 2H, J=9 Hz, aromatic).

C. Preparation of Ester 50. A solution of 1.76 g (8.2 mmol) of the hydroxyamide 22a and 2.62 g (8.2 mmol) of the p-nitrophenyl ester 45 in 5 ml of dry THF and 5 ml of dry triethylamine was stirred at 50° for 57 hr. Extraction[23] with 30% dichloromethane/ether, including a base wash, gave 3.2 g of an orange semi-solid. This material was purified by medium-pressure chromatography[22] on 2.5 x 50 cm of silica gel with 30% acetone/ether at a flow rate of 2 ml/min. After elution with 300 ml of this solvent system, continued elution with 240 ml gave 2.17 g (67%) of the epoxy ester 50 as a nearly colorless oil which solidified upon standing. A portion of this waxy solid was dried at reduced pressure to provide the analytical sample: NMR ($CDCl_3$) δ0.5-1.9 (19H), 2.02 (s, 3H, vinylic CH), 2.10 (m, 4H, $=CCH_2C-$ and CH_2CONH_2), 2.8 (m, 1H, C-5 H, epoxide), 3.33 (dd, 1H, J=2 and 8 Hz, C-4 H, epoxide), 3.50 and 3.60 (s, 3H total, CH_3O-), 4.62 and 4.65 (s, 2H total, $=CCH_2O-$), 5.5 (br, 2H, NH_2), 6.30 (br d, 1H, J=8 Hz, $CH=C-CO_2-$); ir ($CHCl_3$) 3530, 3490 and 3400 (NH_2), 1710 (C = O, ester), 1675 (C = O, amide), 1590, 1310, 1155, 870 cm^{-1}.

Anal. Calcd. for $C_{22}H_{37}NO_5$: C, 66.81; H, 9.43; N, 3.54. Found: C, 66.90; H, 9.48; N, 3.49.

9-Carbamoyl-2-methoxy-2-nonenyl 5-Hydroxy-2-methyl-3-decenoate (51). A mixture of 24 ml of dry THF and 96 ml of dry ammonia was cooled to -78°. To this stirred solution was added 21 mg (3 mmol) of lithium wire in 3 pieces. This solution was stirred for 10 min at -78°, after which 395 mg (1 mmol) of the epoxy ester 50 in 2 ml of dry THF was added in one portion. The blue color persisted for 1 min after which it was discharged by addition of 9 g of solid ammonium chloride. After

an additional 2 min at -78°, the cooling bath was removed and the ammonia was allowed to evaporate over 4.5 hr. Dichloromethane extraction[23] gave 345 mg of a yellow oil which was purified by medium-pressure chromatography[22] on 1.25 x 50 cm of silica gel with 30% acetone/ether. After elution with 110 ml of this solvent system, continued elution with 75 ml afforded 290 mg (73%) of the hydroxy ester 51. A portion of this material was dried at reduced pressure to provide the analytical sample: NMR ($CDCl_3$) δ0.5-1.9 (22H), 2.08 (m, 4H, $=CCH_2C-$ and $\underline{CH_2}CONH_2$), 3.1 (m, 1H, $-CHCO_2-$), 3.50 and 3.57 (s, 3H total, CH_3O-), 4.05 (m, 1H, $-\underline{CH}OH$), 4.53 and 4.60 (s, 2H total, $=CCH_2O-$), 5.63 (m, 4H, CH=CH and NH_2); ir ($CHCl_3$) 3600-3250 (OH and NH_2), 1725 (C = O, ester), 1675 (C = O, amide), 1590, 1460, 970, 915 cm^{-1}.

Anal. Calcd for $C_{22}H_{39}NO_5$: C, 66.47; H, 9.89: N, 3.52. Found: C, 66.44; H, 9.76; N, 3.45.

4-(6-Carboxyhexyl)-3-(3-hydroxyoctenyl)-5-methoxy-3,5-dimethyloxacyclopentan-2-one (52). A solution of 2.78 mmol of LDA in 10 ml of dry THF was cooled to -78°. Following addition of 2.4 ml of dry HMPA, 285 mg (0.718 mmol) of the ester 51 in 2 ml of THF was added dropwise over 4 min to the rapidly stirred solution. After an additional 2 min at -78°, 0.840 ml (2.87 mmol) of TBSCl in hexane was added in one portion and stirring was continued for 2 min at -78°. The cooling bath was removed and the reaction mixture was allowed to warm to 25°, after which the mixture was stirred at reflux for 3 hr. Extraction[23] with 75% ether/petroleum ether gave 508 mg of a yellow oil. This material was

stirred at reflux with 1.2 g of sodium hydroxide in 6 ml of water and 15 ml of methanol for 16 hr. After dilution with water, the reaction mixture was extracted with two 50 ml portions of ether (extracts discarded) and then acidified by addition of 80 ml of 0.4 N sulfuric acid to the ice-cooled, stirred solution. Dichloromethane extraction[23] gave 237 mg of a brown semi-solid. This was purified by medium-pressure chromatography[22] on 1.25 x 50 cm of silica gel with petroleum ether : dichloromethane : THF : acetic acid = 50:10:3:2. Following elution with 40 ml of this solvent system, continued elution with 10 ml gave 40 mg of the unsaturated acid 41. Continued elution with 40 ml gave 44 mg of material which was tentatively identified as the tert.-butyl-dimethylsilyl ether of the desired lactone 52: NMR ($CDCl_3$) δ0.07 (s, 6H, $(CH_3)_2Si$), 0.92 (s, 9H, $(CH_3)_3CSi$), 2.13 (m, 2H, $-CH_2CO_2-$), 3.37 (s, 3H, CH_3O-), 4.07 (m, 1H, CHOSi), 5.63 (m, 2H, CH=CH).

After elution with an additional 295 ml of the same solvent system, continued elution with 200 ml gave 65 mg (30%) of the desired lactone-acid 52 as a colorless oil. A portion of this material was dried at reduced pressure and provided the analytical sample: NMR ($CDCl_3$) δ0.6-2.0 (28H), 2.3 (m, 2H, CH_2CO_2-), 3.36 (s, 3H, CH_3O), 4.12 (m, 1H, -CH-OH), 5.7 (m, 2H, CH=CH), 6.2 (br, 2H, OH and CO_2H); ir ($CHCl_3$) 3600-3400 (OH), 3200-2600 (CO_2H), 1760 (C = O, lactone), 1710 (C = O, acid), 1380, 1030, 970, 910 cm^{-1}.

Anal. Calcd for $C_{22}H_{38}O_6$: C, 66.30, H, 9.61. Found: C, 66.52; H, 9.67.

References and Notes

(1) (a) Grateful acknowledgement is made for support of this work by the National Science Foundation and the National Institutes of Health.

(b) National Science Foundation Predoctoral Fellow, 1972-75.

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(22) Boiling points are uncorrected. Infrared (ir) spectra were determined on a Perkin-Elmer 237B grating infrared spectrometer and nuclear magnetic resonance (NMR) spectra were recorded using a Varian T-60 spectrometer. Chemical shifts are reported as δ values in parts per million relative to TMS (δ TMS = 0.0 ppm) as an internal standard. Deuteriochloroform for NMR and chloroform for ir spectra were filtered through neutral alumina before use.

Vapor phase chromatographic (VPC) analyses were determined on either a Hewlett-Packard 5750 equipped with a flame ionization detector or a Varian 920 equipped with a thermal conductivity detector using helium as the carrier gas under the indicated conditions. The indicated liquid phase was absorbed on 60-80 mesh Chromosorb W AW DMCS.

Silica gel columns used the 0.05-0.2 mm silica gel manufactured by E. Merck & Co., Darmstadt, Germany. Acidic silica gel refers to Silicar CC-4 Special "For Column Chromatography", sold by Mallinckrodt Chemical Works, St. Louis, Missouri. Preparative medium-pressure chromatography was performed using glass columns of the indicated length and diameter with fittings supplied by Laboratory Data Control, Riviera Beach, Fla., and an instrument minipump supplied by Milton Roy Co., St. Petersburg, Florida (instrumentation designed by R. H. Mueller, these laboratories, and copies are available on request). The columns were packed with silica gel H "for TLC acc. to Stahl" (10-40 μ) manufactured by E. Merck & Co., Darmstadt, Germany. Solvents were degassed under water aspirator vacuum prior to use.

Analytical thin layer chromatography was conducted on 2.5 x 10 cm Pre-coated TLC Plates, Silica Gel 60 F-254, layer thickness 0.25 mm manufactured by E. Merck & Co., Darmstadt, Germany.

(22) continued:

"Dry" solvents were dried immediately prior to use. Ether and tetrahydrofuran (THF) were distilled from lithium aluminum hydride; pyridine, triethylamine, diisopropylamine, N-isopropylcyclohexylamine, trimethylchlorosilane (TMSCl), hexamethylphosphoramide (HMPA), benzene, and toluene were distilled from calcium hydride; dimethylformamide (DMF) was dried over 4 A molecular sieves and fractionally distilled at reduced pressure; methanol was dried over 3 A molecular sieves; ammonia was distilled from a blue solution of sodium directly into the reaction flask; dichloromethane, methyl iodide, and hexane were distilled from phosphorous pentoxide. "Petroleum ether" refers to the "Analyzed Reagent" grade hydrocarbon fraction, bp 30-60°, which is supplied by J. T. Baker Co., Phillipsburg, N. J., and was not further purified.

Diisobutylaluminum hydride (DIBAH) was used as a standard solution in benzene (ca. 1.0 M).

Lithium isopropylcyclohexylamide (LICA) and lithium diisopropylamide (LDA) were prepared as described previously.[3]

Standard solutions of tert.-butyldimethylchlorosilane (TBSCl) in hexane (ca. 3.3 M) or HMPA (ca. 1.5 M) were employed.

Reactions were run under an argon atmosphere arranged with a mercury bubbler so that the system could be alternately evacuated and filled with argon and left under a positive pressure.

Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

(23) In cases where the products were isolated "by solvent extraction", the procedure generally followed was to dilute the reaction mixture with the indicated solvent or to extract the aqueous solution with several portions of the indicated solvent; then the combined organic layers were washed with several portions of water followed by saturated brine. The organic layer was dried over anhydrous sodium or magnesium sulfate, then filtered, and the solvent was evaporated from the filtrate under reduced pressure (water aspirator) using a rotary evaporator. The use of the terms "base wash" or "acid wash" indicate washing the organic solution with saturated aqueous sodium bicarbonate solution or with dilute aqueous hydrochloric acid, respectively prior to the aforementioned wash with water.

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PROPOSITIONS

Abstract of Propositions

Proposition 1: Promotion of regioselective and stereoselective enolization of ketones and esters by means of a carboxylate ligand on the substrate molecule is proposed. Examples of stereoselective enolization of α,β-unsaturated esters and acids are cited. This selectivity can be traced to association of the lithium dialkylamide base with the carboxylate prior to proton removal. A series of molecules designed to test the generality of this selective enolization is suggested.

Proposition 2: An investigation of the reactions of N-alkylpyridinium salts and pyridine-N-oxides with organocuprate reagents is proposed. An electron transfer mechanism for organocuprate reactions is assumed. The reduction potential of the above N-substituted pyridine derivatives is within the range to make them potential substrates. Alkyl substituted 1,2- or 1,4-dihydropyridines are the expected products. These derivatives are potentially valuable intermediates for organic synthesis.

Proposition 3: The catalytic involvement of chiral crown ethers and cryptands in asymmetric synthesis is proposed. These ligands form stable complexes with metal cations and should impart chirality to associated achiral anions. Reaction with electrophiles should result in asymmetric induction catalyzed by the chiral ligand. Two basic types of reactions are suggested.

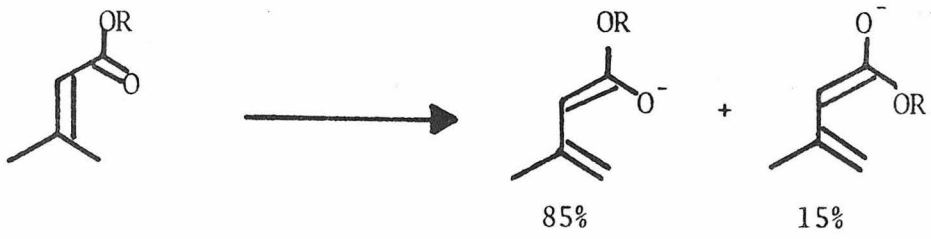
Proposition 4: Heterocyclic oxyselenation of olefins is proposed. Electrophilic reactions of reagents of the type PhSe-X with olefins are examined and the extension of these reactions to olefinic substrates which contain an intramolecular nucleophile is suggested. Lactonization, the simplest example, should lead to lactones with the phenylseleno functional group attached as a handle for further synthetic transformations.

Proposition 5: The preparation of a series of compounds whose chemistry should provide useful information for construction of "synthetic enzymes" is proposed. The chemistry of a series of molecules containing macropolycyclic ligands (cryptands) covalently attached to an organic functional group would be examined. The combination of "anion activation" by the ligand and juxtaposition of a reactive functional group should result in novel chemistry. Information gained should be useful for the ultimate preparation of molecular catalysts capable of promoting specific reactions on organic substrates.

Proposition 1

Promotion of regioselective and stereoselective enolization of ketones and esters by means of a carboxylate ligand on the substrate molecule is proposed.

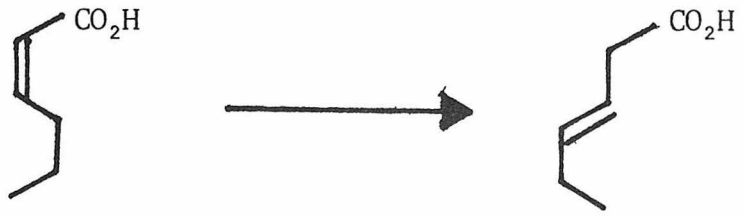
At least three unheralded instances of selective, kinetic enolization of α,β-unsaturated esters have been reported. The stereochemical composition of the products in the synthesis of juvenile hormone analogs by Fráter[1] can be traced back to the stereoselective enolization depicted in Eq. 1. Fráter also noted the apparent preference for proton removal from the alkyl group cis to the ester functionality (Eq. 2). Pfeffer and Silbert[2] demonstrated that deconjugation of α,β-unsaturated acids via protonation of the dianion formed with lithium diisopropylamide produced exclusively trans-double bonds from cis-acids but a mixture from trans-acids (Eq. 3).



85% 15% (1)

(2)

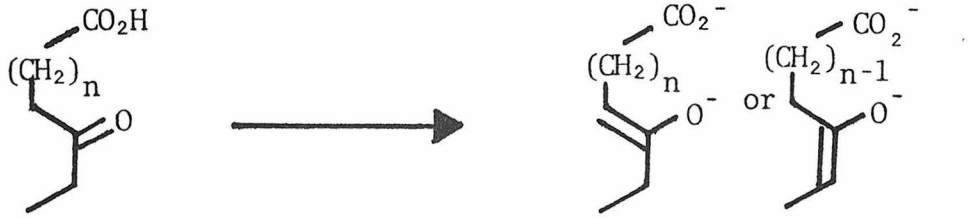
stereochemistry unknown



(3)

All of these results can be rationalized by a mechanism which involves coordination of the lithium dialkyl amide base with the carbonyl oxygen of the carboxylate or the ester prior to proton removal. The scope and limitations of this selectivity with α,β-unsaturated esters should be examined.

It should be possible to extend these results to regioselective enolization of ketones. Eqs. 4 - 6 depict systems worthy of examination.



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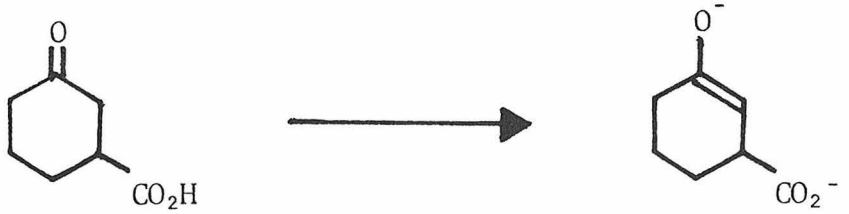

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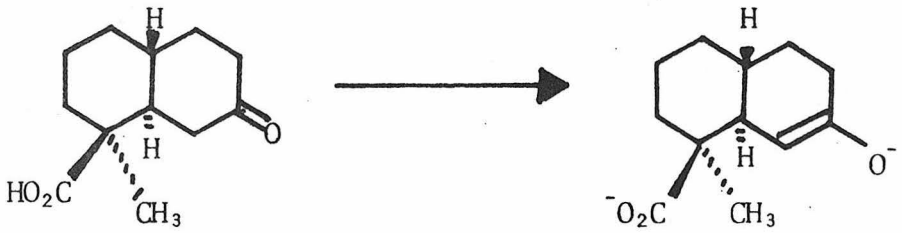

(6)

If the reliability of selective enolization can be demonstrated, a useful new tool for directed synthesis will be available.

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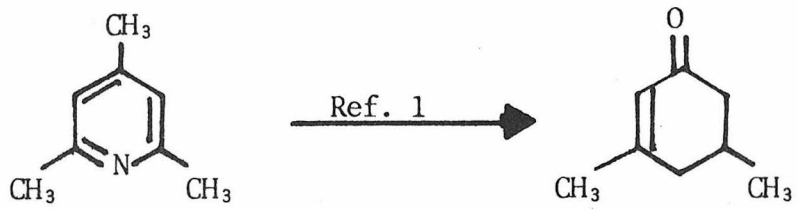
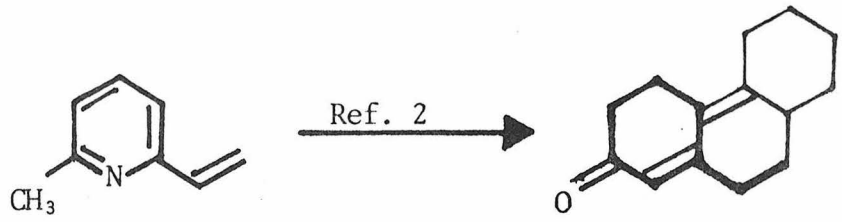
Proposition 2

An investigation of the reactions of N-alkylpyridinium salts and pyridine-N-oxides with organocuprate reagents is proposed.

Beyond its obvious role in the preparation of a variety of nitrogen heterocycles, the pyridine nucleus has not been heavily exploited by synthetic chemists. Two examples from carbocyclic chemistry serve to demonstrate its potential (Eqs. 1 and 2).

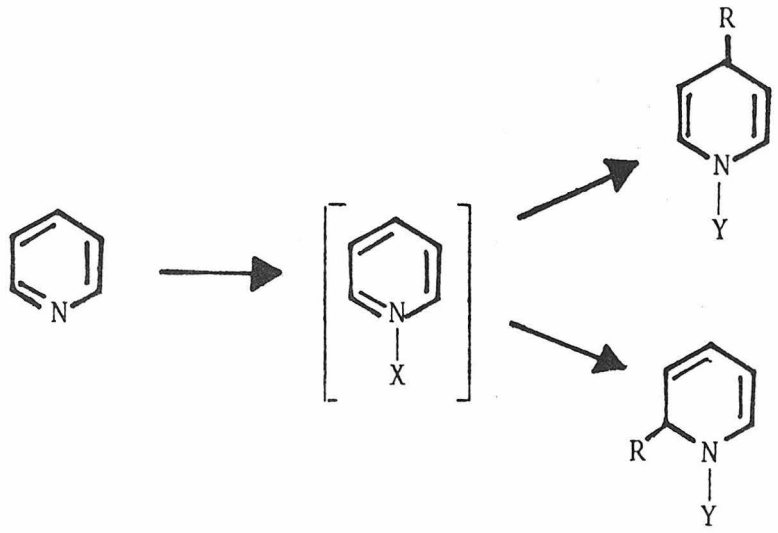


(1)



(2)

Both of these cyclohexenone products arise via metal-ammonia reduction to a 1,4-dihydropyridine. An alternative approach to the dihydropyridines might be by reaction with organocuprate reagents (R_2CuLi), a transformation which would couple the reduction with attachment of an alkyl group to the pyridine nucleus (Eq. 3).



(3)

All reactions of the organocuprate reagents can be accounted for by a mechanism in which electron transfer is the first step.[3,4] This suggests that the reduction potential of the substrate molecule is important. In fact, in the reaction of organocuprates with enones, only those enones with a reduction potential less negative than -2.4 V vs SCE react.[3] Limited evidence suggests that this is also true for other substrates.

Pyridine ($E_{1/2}$ = -2.61 V vs SCE) does not react with lithium dimethylcuprate. N-Alkylpyridinium salts ($E_{1/2}$ = ca. -1.0 V) and pyridine-N-oxides ($E_{1/2}$ = ca. -1.4 V) should react. Whether these substrates go on to give alkylated products after electron transfer and whether these products are 2- or 4-substituted dihydropyridine derivatives can't be answered at this point.

Investigation of the reaction of these two pyridine derivatives with organocuprates has two values. First, the results with these substrates have important bearing on the mechanism of organocuprate reaction and should suggest or rule out other substrates. Second, the

resulting dihydropyridines (should the reaction take this course) will be useful synthetic intermediates and will expand the potential of pyridine derivatives in organic synthesis.

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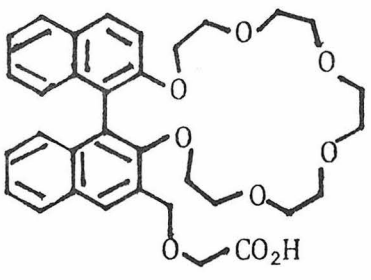
Proposition 3

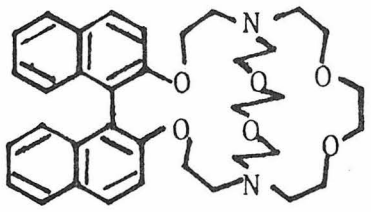
The catalytic involvement of chiral crown ethers and cryptands in asymmetric synthesis is proposed.

Asymmetric synthesis has been defined as "a reaction in which an achiral unit in an ensemble of substrate molecules is converted by a reactant into a chiral unit in such a manner that the stereoisomeric products are produced in unequal amounts."[1] Practicality demands efficient use of the chiral reagents in these reactions; chiral catalysts represent the ultimate in efficiency.

Chiral crown ethers[2] such as 1 and chiral cryptands[3] such as 2 are now available. These ligands form stable complexes with alkali and alkaline-earth metal cations and this complexation imparts chirality to the associated achiral anion. Since interaction of the ligand with the cation is through ion-dipole and related interactions but not covalent bonds, and because the ligand can be recovered unchanged, the ligand is playing a truly catalylic role.



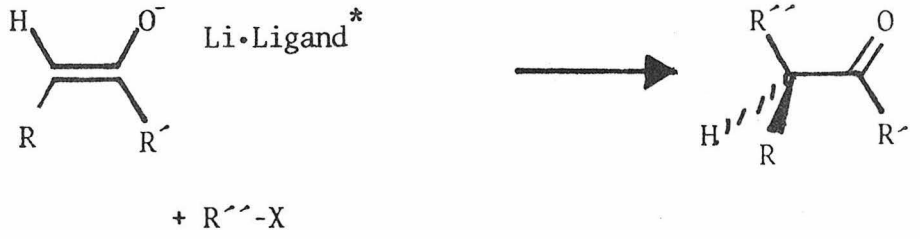
1



2

These ligands can be expected to promote asymmetric synthesis in two types of reactions. In the first, the substrate reacts with a complexed, nucleophilic reactant. Examples are hydride reduction of ketones (Eq. 1), alkyllithium additions to carbonyl compounds, and nucleophilic additions to activated double bonds. In the second type, the substrate is complexed and reaction with an electrophilic reactant produces the chiral unit. Alkylation of metallo-imines, aldol condensations, and alkylations of enolates (Eq. 2) are examples.

(1)



(2)

This chiral catalysis can be expanded through construction of specifically designed ligands to optimize the degree of asymmetric induction. Ligand design will also effect kinetics and thermodynamics of complexation which will control such variables as turnover number. Ultimately, the most effective catalysts may be those which have

chiral cavities large enough to contain both the substrate and the reactant in specific orientations.

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Proposition 4

Heterocyclic oxyselenation of olefins is proposed.

Electrophilic addition of reagents of the type PhSe-X (X = Cl, Br, RCO_2-) across carbon-carbon double bonds[1,2] has great potential in organic synthesis. This addition is mechanistically similar to other electrophilic additions but offers the advantage that the phenylseleno function is a useful handle on the molecule for further synthetic transformations. For instance, oxidation to the selenoxide followed by elimination introduces a double bond.

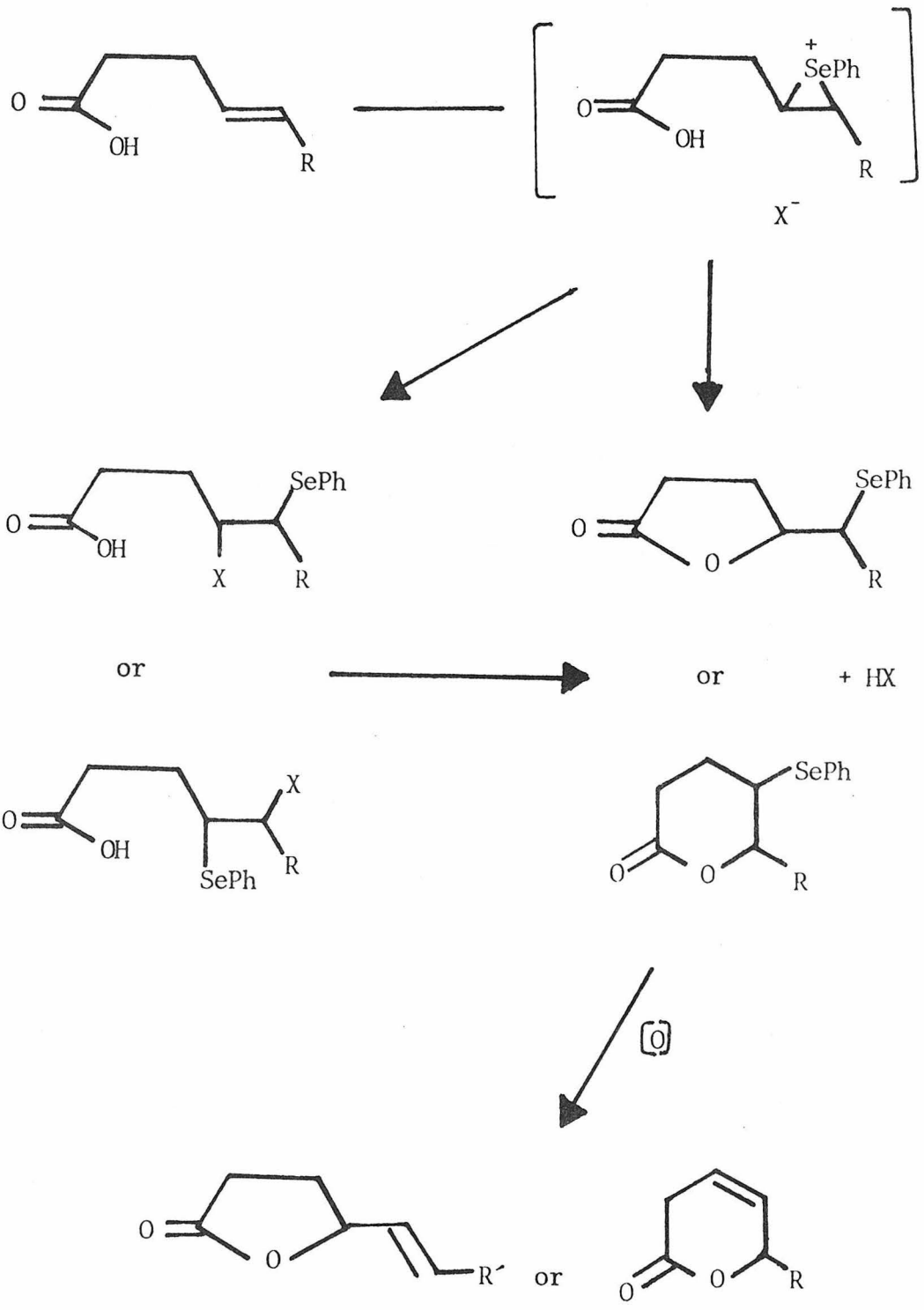
It should be possible to extend these reactions to cases in which the nucleophilic partner in the addition is part of the substrate molecule. The simplest example would be lactone formation with electrophilic organoselenium reagents. (see Scheme)

There are two possible pathways for formation of the lactone. Either direct attact by the carboxylate on the episelenonium ion (or its equivalent) or addition of PhSe-X to the olefin followed by solvolytic displacement of X by the carboxylate could result in lactonization.

The propensity to form 5- rather than 6-membered rings, as is noted for other lactonization procedures, will probably be found in this case also. Results with the simple acyclic cases suggest that elimination of the selenoxide should produce allylic rather than vinylic derivatives whenever possible.

Several experimental procedures will have reasonable chances for success in this lactonization. Addition of potassium acetate to a

Scheme:



mixture of PhSeBr and an olefin in acetic acid produces an acetate.[1] This may be occurring through direct addition of PhSeOAc or by acetolysis of the first-formed PhSeBr adduct. Addition of PhSeBr to the potassium salt of the olefinic acid in a suitable inert solvent should cause lactone formation by one of the above mechanisms. A second possibility lies in the use of benzeneselenyl trifluoroacetate.[2] Trifluoroacetate is a weak nucleophile and may permit direct opening of the episelenonium ion by the intramolecular carboxylate. This concept has proven useful in oxymercuration of olefins.[3] Finally, if lactonization is not realized by the above procedures, silver assisted solvolysis of the PhSeBr adduct should be effective.

If this heterocyclic oxyselenation is successful for preparation of lactones, it can probably be extended to the preparation of cyclic ethers and amines.

References:

1. K. B. Sharpless and R. F. Lauer, J. Org. Chem., 39, 429 (1974).
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Proposition 5

The preparation of a series of compounds whose chemistry should provide useful information for construction of "synthetic enzymes" is proposed.

The "crown ethers" and a related family of molecules, polyoxa-polyazamacropolycyclic ligands introduced subsequently by J.-M. Lehn,[1] hold promise in many areas of chemistry. Their well-known ability to form stable complexes which should allow metal ion selection and transport has already been heavily explored.[2] More recently, similar ligands capable of complexing organic molecules have been introduced.[3,4] Results in both of these areas suggest that it may ultimately be possible to prepare "synthetic enzymes" employing these ligands.

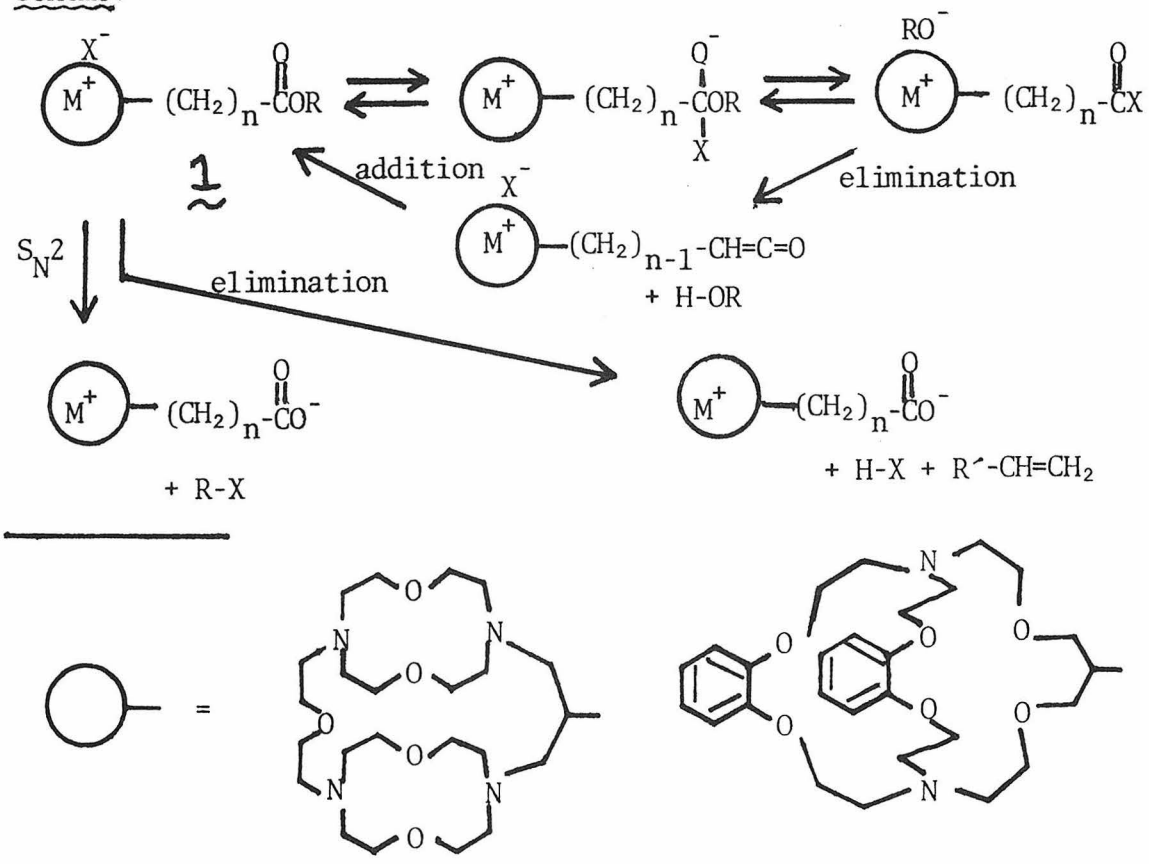
Specifically, it is proposed to prepare a series of molecules related to 1 (other organic functional groups as well as the ester would be examined) and to study their chemistry, some of which may be anticipated in the scheme.

Two effects are brought into play which should lead to interesting chemistry. As a consequence of the ligands forming stable complexes with metal cations, the associated anions become chemically activated and reactive. When this is coupled with the juxtaposition of the substrate by covalent attachment to the ligand, novel results can be expected.

Information on three points useful in later approaches to synthetic enzymes should be obtained: (1) Modes of reaction -- The serious geometrical and chemical stresses applied to the systems may lead to deviations

from the normal chemistry expected from these reagents. The reaction paths can be elucidated by product studies; (2) Reaction rates -- Rate enhancements of several orders of magnitude are found in the reactions of the activated anions formed in the presence of these ligands. For the proposed molecules, covalent attachment of the substrate to the ligand will make the reaction essentially "intramolecular" causing further dramatic increases in rate; (3) Substrate-reactivity relationships -- Several variables, including the ligand, the cation, the anion, and the reaction medium can be systematically varied to generate highly useful information about the reactivity of these molecules.

Scheme:



The synthesis of the molecules required for the study will be quite straightforward, following essentially the methods described by Lehn.[2]

The work described should map a portion of the frontier, putting organic chemists one step closer to acquiring the knowledge required to prepare synthetic molecules capable of mimicking the important biological enzymes. Such capabilities could revolutionize synthetic chemistry and, even more importantly, medicine.

References:

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2. J.-M. Lehn, Structure Bonding (Berlin), 16, 1 (1973).

3. J.-M. Lehn, J. Simon and J. Wagner, Ang. Chem. Int. Ed. Eng., 12, 578,579 (1973).

4. D. J. Cram and J. M. Cram, Science, 183, 803 (1974).