AN ABSTRACT OF THE THESIS OF

Manuel Jose Arco for the degree of Doctor of Philosophy

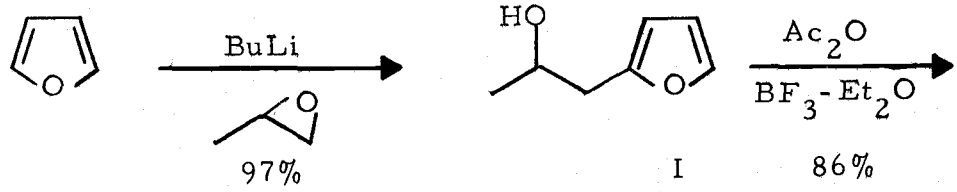
in Chemistry presented on August 15, 1975

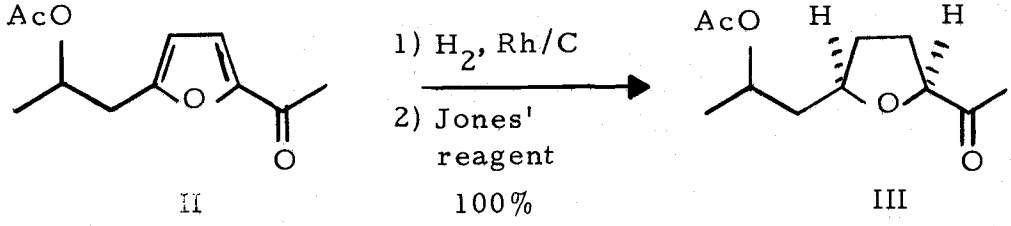
Title: THE SYNTHESIS OF NONACTIC ACID

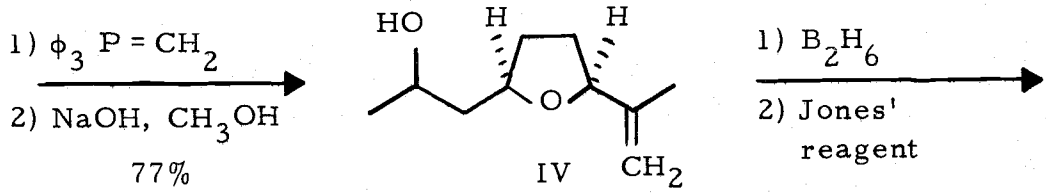
Abstract approved: Redacted for privacy

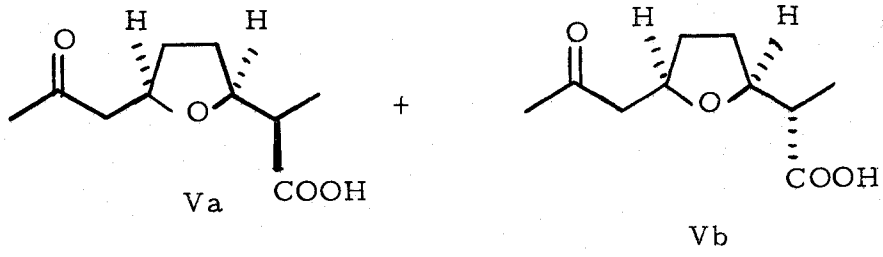
James D. White

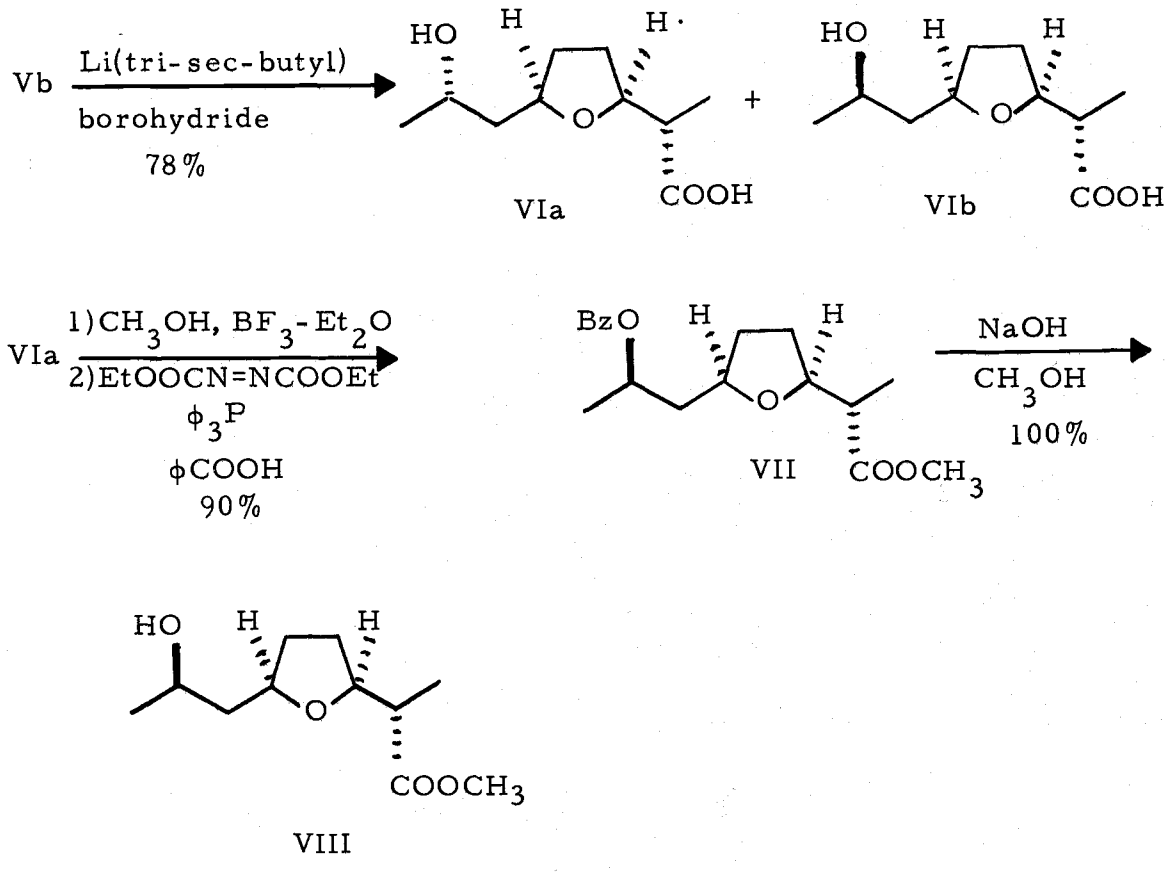
Alkylation of propylene oxide with 2-lithiofuran gave alcohol I, which was smoothly converted to acetylfuran II. Hydrogenation of II over rhodium on charcoal followed by Jones' oxidation afforded ketone III. Further transformation into IV was accomplished via a Wittig reaction followed by saponification with methanolic sodium hydroxide. Hydroboration of the resulting olefin IV followed by oxidative work-up with Jones' reagent gave a 2:1 mixture of Va and Vb. Reduction of Vb with lithium tri-sec-butyl borohydride gave a 9:1 mixture of VIa and VIb. Hydroxyacid VIa was further transformed into benzoate VII by esterification followed by an inversion of configuration at C-8. Methanolysis of VII afforded methyl nonactate VIII.


BuLi
97%
HO
I
Ac_2O
BF_3-Et_2O
86%


AcO
II
1) H_2, Rh/C
2) Jones' reagent
100%
AcO
H
H
III


1) ϕ_3 P = CH_2
2) NaOH, CH_3OH
77%
HO
H
H
IV
CH_2
1) B_2H_6
2) Jones' reagent


H
H
O
Va
COOH
+
H
H
O
COOH
Vb


Vb
Li(tri-sec-butyl)
borohydride
78%
HO
H
H
O
COOH
VIa
+
HO
H
H
O
COOH
VIb
VIa
1)CH3OH, BF3-Et2O
2)EtOOCN=NCOOEt
ϕ3P
ϕCOOH
90%
BzO
H
H
O
COOCH3
VII
NaOH
CH3OH
100%
HO
H
H
O
COOCH3
VIII

The Synthesis of Nonactic Acid

by

Manuel Jose Arco

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in charge of major

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Chairman of Department of Chemistry

Redacted for privacy

Dean of Graduate School

Date thesis is presented August 15, 1975

Typed by Mary Jo Stratton for Manuel Jose Arco

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My appreciation to Dr. Gary Trammell for his collaboration and for many enlightening discussions and helpful suggestions. Also to Mrs. Susan Berkhahn for her invaluable help with the translation of several articles.

I am grateful to Squibb Institute of Medical Research for providing us with several samples of Nonactin.

And last but not least, my deepest gratitude to Judy and David for their moral support, patience, and inspiration. To them I dedicate this thesis.

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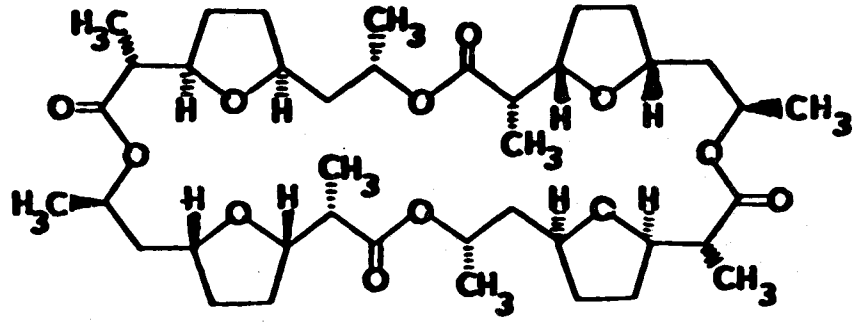
THE SYNTHESIS OF NONACTIC ACID

I. INTRODUCTION

In 1955, Corbaz et al.[1] reported the isolation of an Actinomycete metabolite which they named nonactin for its lack of both biological and optical activity toward their test organism. Later, Bennett et al.[2] isolated nonactin from Streptomyces chrysomallus. In addition to nonactin, higher homologs, mainly monactin, dinactin, and trinactin, were subsequently isolated from the same fermentation.[3, 4] The basic structure of the nactins is depicted in Figure 1.

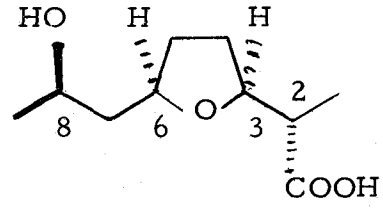


NONACTIN

Figure 1. Structure of nonactin.

A macrocyclic lactone skeleton is also found in other Streptomyces metabolites, including valinomycin, the enniatins, and the gramicidins.[5]

The subunit of nonactin is nonactic acid.[1] The higher homologs



(+) Nonactic Acid

2

Figure 2. Structure of nonactic acid.

differ in that the nonactic subunit is replaced by 1, 2, 3, or 4 homononactic acid units in which a C-8 ethyl group substitutes for methyl.

A study of the structure of nonactin by chemical techniques was completed in 1963 by Gerlach and Prelog[6] in an investigation notable for its perspicacity. The structure proposed by Gerlach and Prelog has been corroborated by an X-ray crystallographic study by Kilbourn and Dunitz[7] and by M. Dobler.[8] These X-ray studies reveal that the nonactin molecule in its K^+ complex has a crystallographic twofold rotation axis and has approximate S_4 symmetry.[9] The shape of the 32-membered ring can be compared conformationally to the

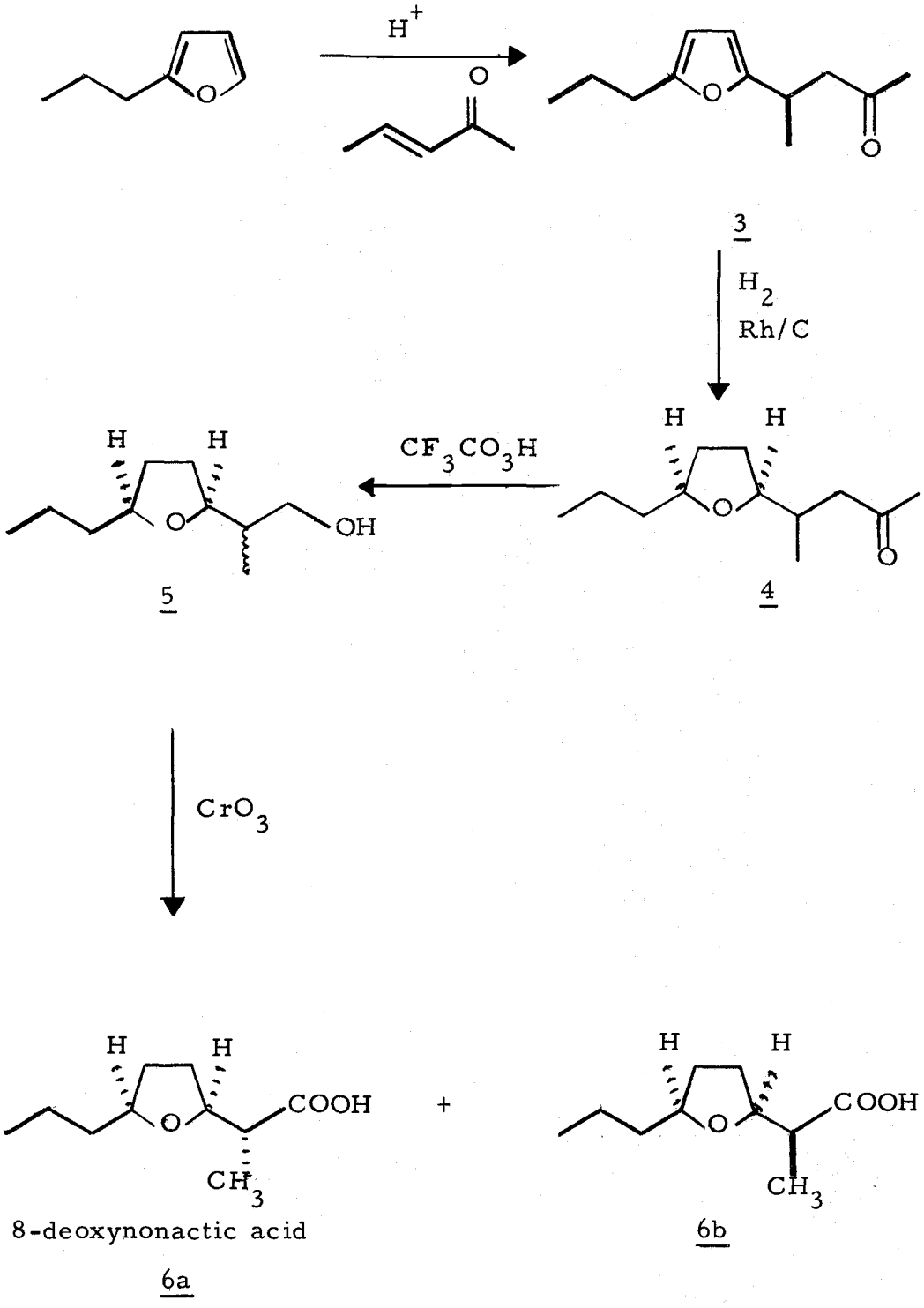
seam of a tennis ball, with the K^+ ion in the middle of the ball and hydrophobic groups on the outside.[8] In this arrangement the K^+ ion is surrounded by four oxygen atoms from furan and by four keto-oxygens in approximate cubic-8 coordination.[8]

The conformation of free nonactin is similar to that of the K^+ complex in that both have approximate S_4 symmetry. The uncomplexed molecule, however, is much flatter than the complexed species.[9]

Although essentially inactive as an antibacterial, nonactin has shown mild inhibition of gram positive organisms at high concentration and significant antitumor activity when injected subcutaneously.[9] Nonactin has also been found to affect ion transport and rate of respiration in the mitochondria,[9, 10] to induce ATPase activity, and to act as a potent uncoupler of oxidative phosphorylation.[11] The influence of nonactin in the regulation of metabolic behavior is hence well documented, making it a highly desirable target for synthetic studies.

A search of the chemical literature reveals only sporadic activity directed toward the synthesis of nonactic acid. In 1967 Gerlach and Huber[12] reported the synthesis of 8-deoxynonactic acid by the route shown in Scheme 1. Acid-catalyzed alkylation of 3-penten-2-one with 2-n-propylfuran gave 3 in 83% yield.

Scheme 1:



8-deoxynonactic acid

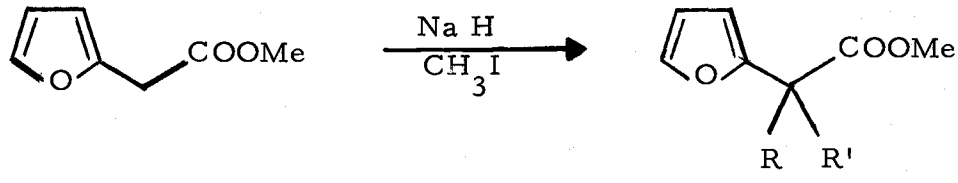
6a

6b

Hydrogenation of 3 over rhodium on charcoal afforded ketone 4 in 90% yield. Baeyer-Villiger oxidation of 4 gave an epimeric mixture of diols 5a and 5b which were separated on silica gel. Alcohol 5a, with the natural configuration at C-2, was oxidized with chromium trioxide into 8-deoxynonactic acid, 6a, with a yield of 40% from ketone 4.

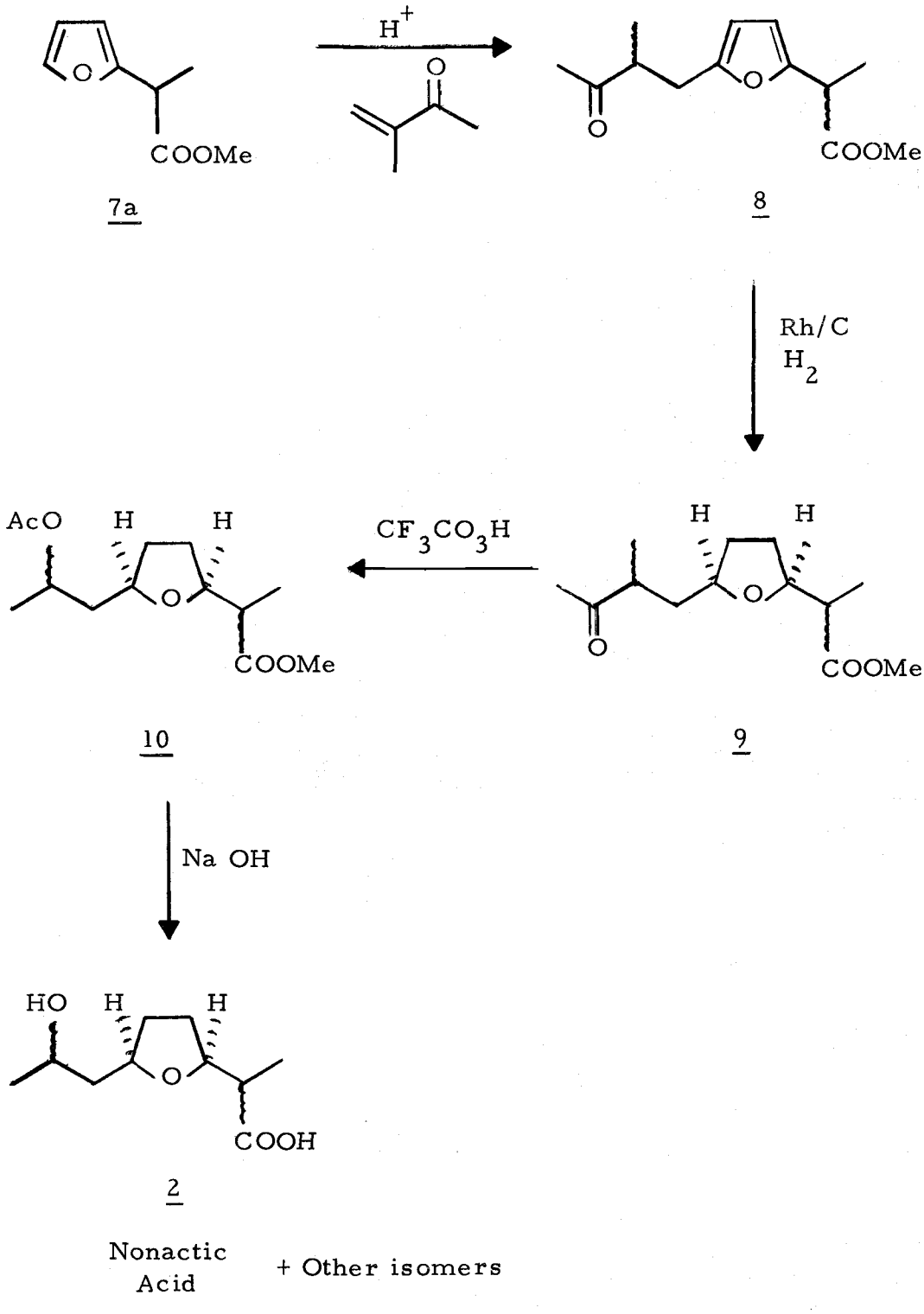
An analogous approach depicted in Scheme 2 was used by Beck and Henseleit[13] in preparing nonactic acid. Alkylation of methyl furylacetate with methyl iodide gave a mixture of mono- and dialkylated esters, 7a and 7b. Ester 7a was further alkylated with 2-methyl-2-butene-3-one in the presence of boron trifluoride-etherate complex to give 8. Hydrogenation of 8 with rhodium over alumina afforded 9. Baeyer-Villiger oxidation of keto-ester 9 gave 10, which was saponified to give all four possible diastereomers of 2.

Scheme 2:



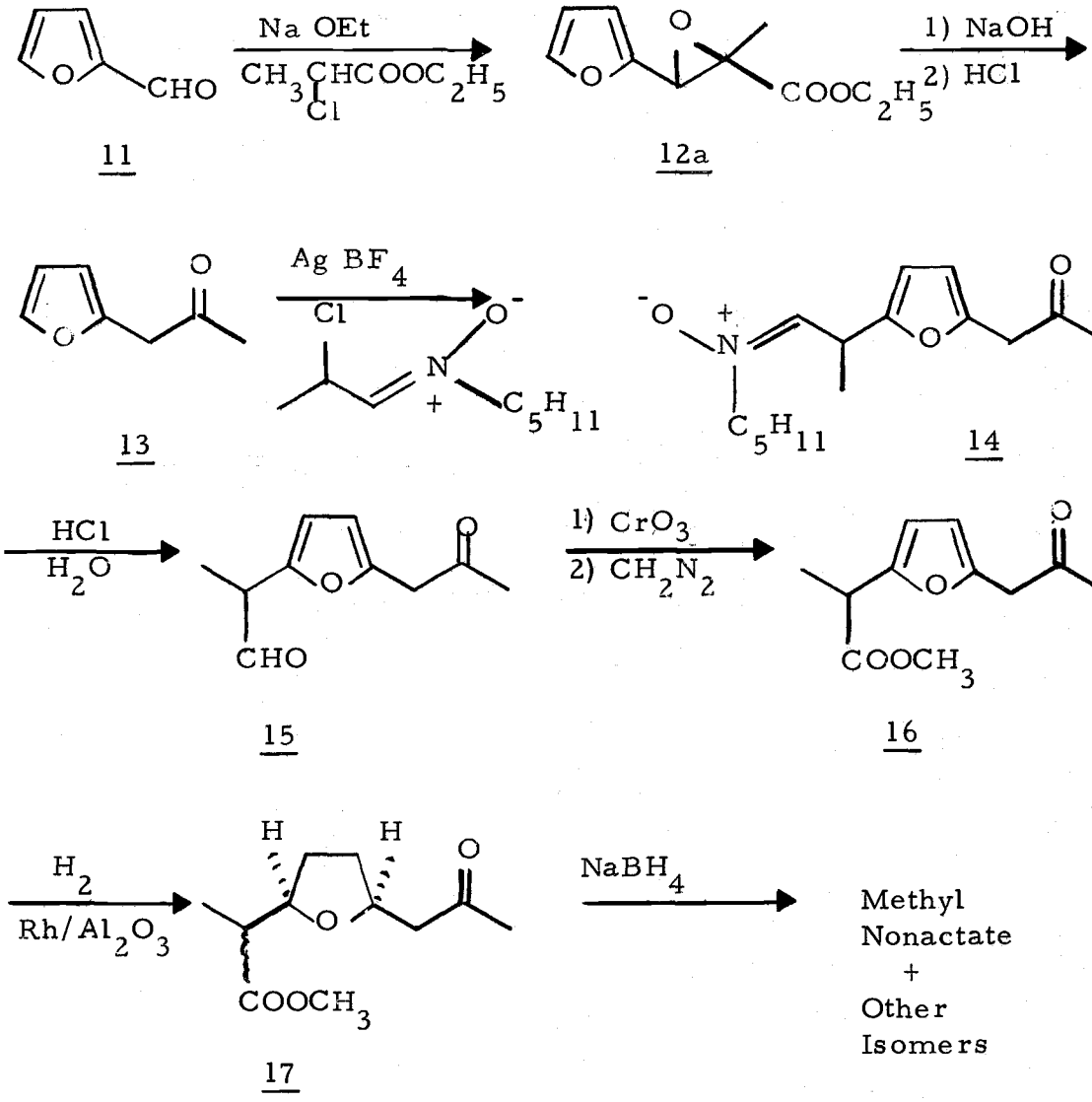
7a R = H R' = CH_3

7b R = R' = CH_3

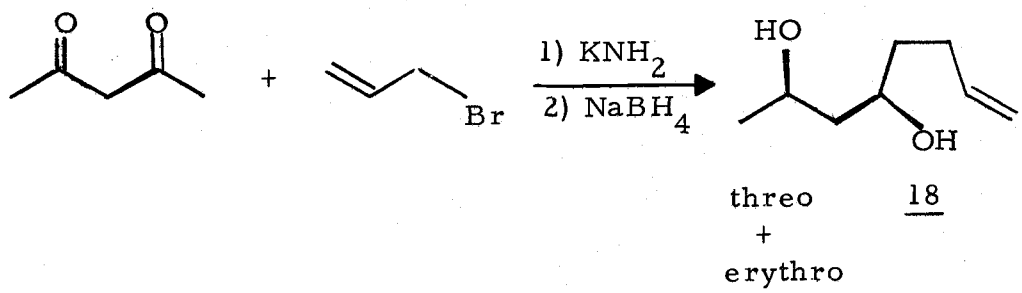

H+
COOMe
7a
8
Rh/C
H2
AcO
H
H
CF3CO3H
9
10
Na OH
HO
COOH
2
Nonactic Acid
+ Other isomers

Syntheses of methyl nonactate, albeit in poor yield, have recently been reported by Gerlach and Wetter.[14] The synthetic plans adopted by these workers are outlined in Scheme 3 and Scheme 4.

Scheme 3:

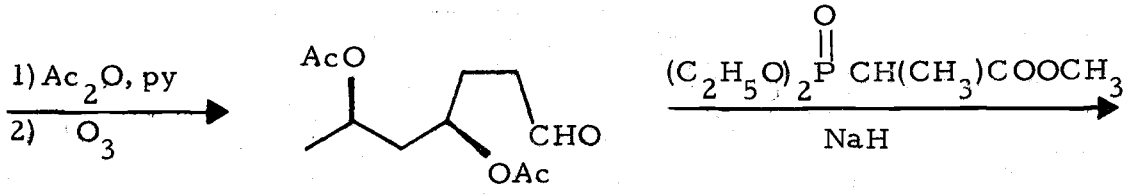


Scheme 4:

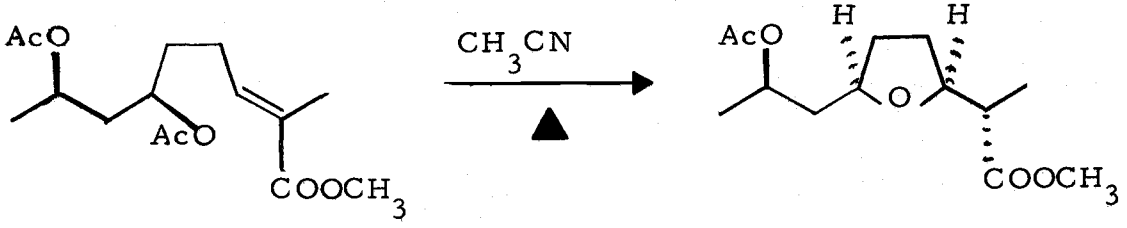


threo + erythro

18

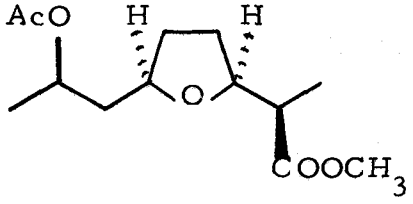


19



20

21a



21b

+ Trans-fused Products

Our own synthetic efforts to find a short and efficient route to non-actic acid are described in detail in the section which follows.

II. RESULTS AND DISCUSSION

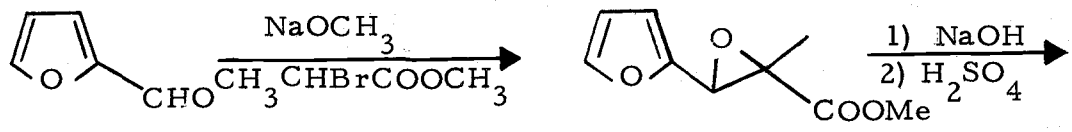
In planning the synthesis of nonactic acid, it seemed desirable to choose a route that would allow the maximum degree of stereochemical control. A close look at 2 reveals that two of its four asymmetric centers are located on the alpha carbons of a tetrahydrofuran ring with the hydrogens at the junction cis to each other. This observation set the strategy and development of our approaches to nonactic acid. We felt that in beginning the synthesis with furan, or with a furan derivative, our stereochemical problem was in a sense half-solved, since catalytic hydrogenation of furan and its derivatives have been shown to proceed in a cis fashion.[13]

Additional simplification of the stereochemical problem can occur by stereomutation at C-2. Gerlach and Prelog[4] found that degradation of Nonactin with alcoholic potassium hydroxide afforded a mixture of nonactic and 2-epinonactic acid. Esterification of the acids with diazomethane allowed separation of the corresponding methyl esters formed. Saponification of chromatographically pure methyl nonactate and methyl 2-epinonactate gave a mixture of nonactic and 2-epinonactic acid in a 5:1 ratio. This experiment suggested that the correct stereochemistry at C-2 could be attained even in the most unfavorable case when the starting material was the pure 2-epi compound, since equilibration resulted primarily in material bearing

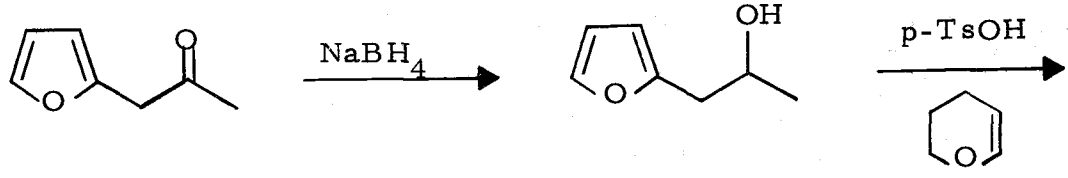
the natural configuration at C-2. We also felt that asymmetry might be successfully induced at C-8 via hydride reduction of a precursor ketone.[15] If the predominant configuration obtained at this center was the one opposite to the natural configuration at C-8 in nonactic acid, we were then prepared to perform an inversion of configuration at this center. On the other hand, advantageous as our choice of starting material was, it was clear that associated with it was the problem not only of functionalizing furan at C-2 and at C-5, but also dealing with compounds that would be very sensitive to acids and to air.

Our first attempt to synthesize nonactic acid is recorded in Scheme 5.

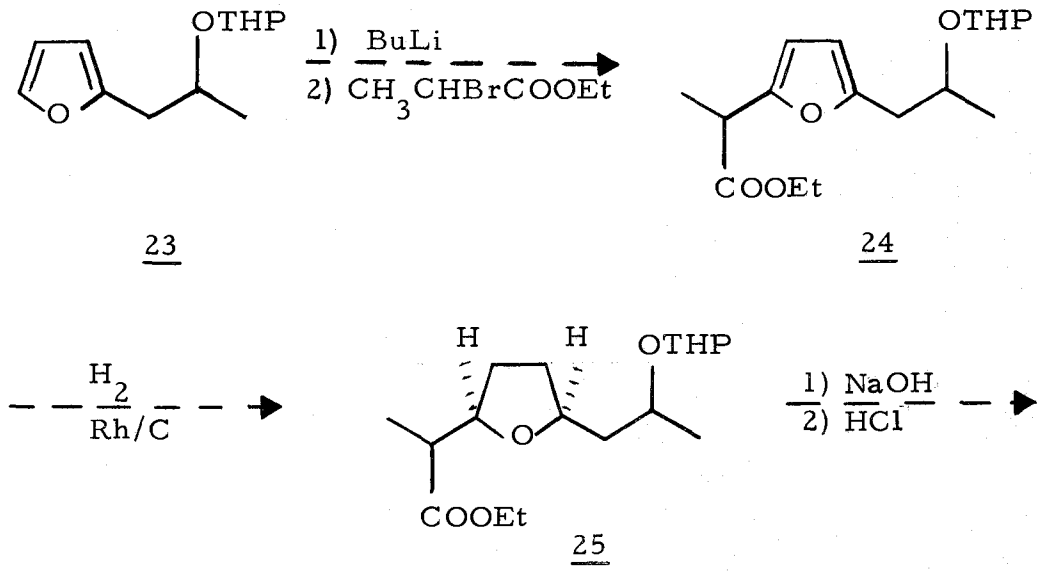
Scheme 5:



12b



13 22



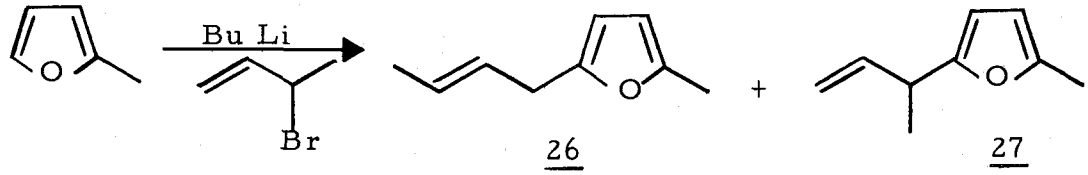
Nonactic Acid + Isomers

Treatment of readily available furfuraldehyde with ethyl 2-bromopropionate in the presence of equimolar amount of sodium methoxide gave glycidic ester 12b[16] as a 40:60 cis:trans mixture (methyl ester at δ 3.76 and 3.83, and methine at δ 3.97 and 4.28) in 48% yield. Saponification of 12 with methanolic sodium hydroxide followed by acidification resulted in the evolution of carbon dioxide[17] with production of 13 in 80% yield. Reduction of 13 with sodium borohydride gave 22 which, upon stirring at room temperature with dihydropyran and a few crystals of p-toluenesulfonic acid,[18] was converted smoothly into 23.

At this point we had hoped to metalate the C-5 position of the furan ring in 23 by hydrogen-metal exchange with butyllithium, this

to be followed by alkylation of the resulting lithiofuran derivative with ethyl 2-bromopropionate to give 24. Compound 24 could have easily been reduced to its tetrahydrofuran analogue 25 by catalytic hydrogenation over rhodium on charcoal, and deprotected to give presumably all four diastereomers of 2. However, an attempt to carry out the metalation-alkylation sequence on 23 according to the procedure of Levine et al.[19] resulted in the isolation of starting materials along with some higher molecular weight material. The infrared spectrum of the latter showed strong band at 3500 cm^{-1}. We attributed this band to a hydroxyl group that could have arisen by attack at the ester carbonyl of ethyl 2-bromopropionate with two moles of furyl lithium.[19,20]

Even though the coupling of the lithiofuran 23 with ethyl 2-bromopropionate had not occurred as expected, we were still attracted to the possibility of adding the requisite three carbon chain to the furan ring via a metalation-coupling sequence. Thus we turned our attention toward model systems using 2-methyl furan, and furan itself. We observed that when 2-methylfuran was treated with butyllithium, followed by addition of 3-bromo-1-butene, work up of the solution afforded a 2:1 mixture of 26 and 27 in 50-60% yield.



26 27

This established that 5-lithio-2-methylfuran was being generated, and that it would displace a secondary, allylic bromide. We set out to take this observation into account and to modify our system accordingly by: 1) reducing the reactivity of the carbonyl carbon; 2) increasing the ability of the leaving group to depart; and 3) reducing the affinity of the lithio furan derivative toward the carbonyl ester.

In practice, one, two, or all three modifications above were utilized. Posner et al.[21] have shown that organolithium cuprates are quite useful, among other reasons, because they tend not to react with saturated carbonyl compounds, whereas the corresponding alkyl lithium species react in a matter of seconds.[22] We decided to utilize this observation by preparing 5-(2-methylfuryl)-lithium cuprate, and allowing it to react with ethyl 2-bromopropionate, carefully following the procedure for coupling dialkyl lithiumcuprates and alkyl halides developed by Whitesides et al.[23] Unfortunately, we were able only to isolate the starting bromoester. We noticed, however, that there was scarcely any polymerization. This indicated that either Posner's observation was indeed valid in our case, or that the organo lithiumcuprate was not been formed. To test the second hypothesis the previous experiment was repeated up to formation of the organo lithiumcuprate. At this point oxygen containing nitrogen was admitted into the reaction flask. Upon work-up a low boiling substance was isolated and assigned structure 28 based on its 100 MHz

nuclear magnetic resonance and mass spectrum. This material

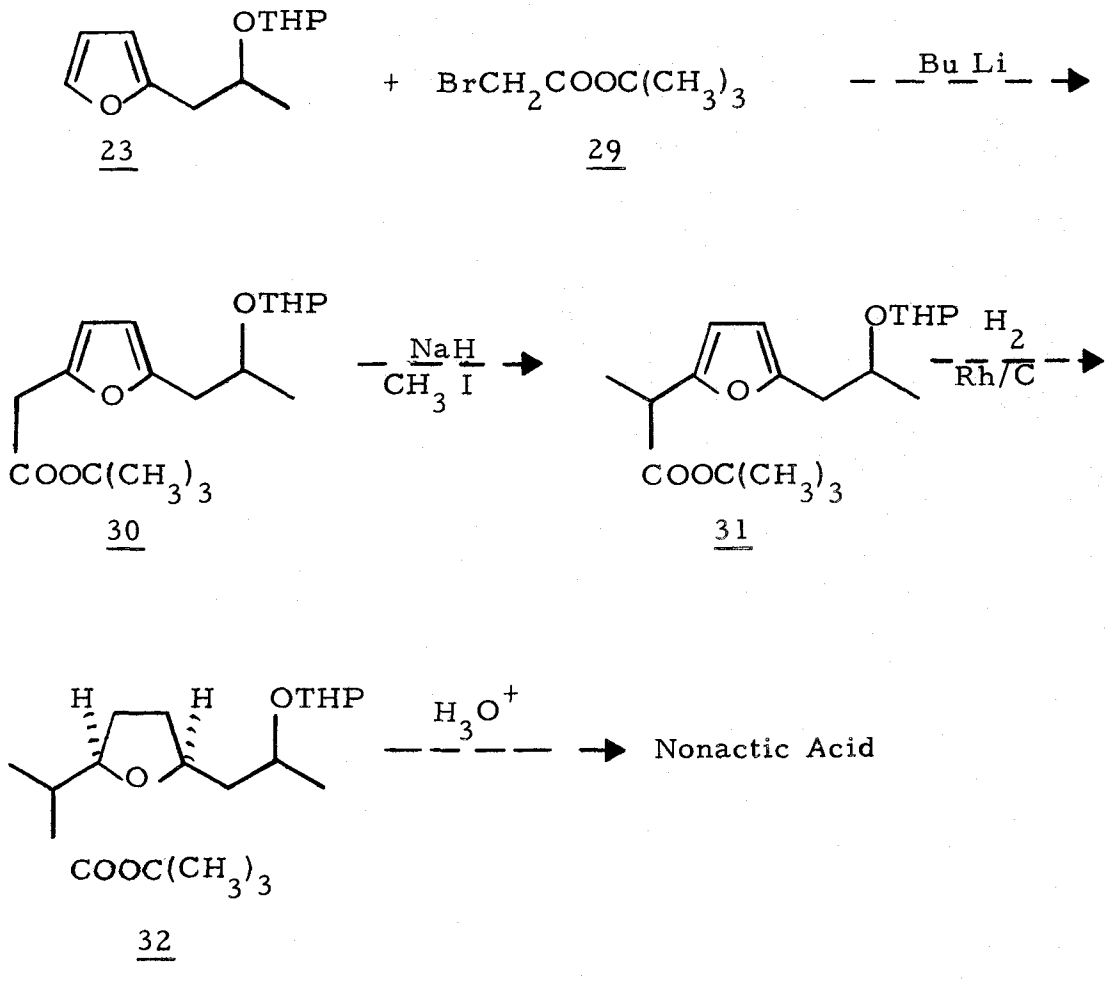
28

presumably derives from oxidative coupling, which suggests that indeed our organo lithiumcuprate reagent was being generated. There is precedence in the chemical literature for this type of process in the work of Whitesides et al.[23] The coupling process appears to occur by the removal of two electrons from the initial organometallic cluster to form a transient dicationic species that collapses to give two lithium cations, the coupled product, and the organo copper compound. Any oxidant which has an oxidation potential larger than about 1.2 volts versus the standard calomel electrode will suffice to effect the oxidative coupling. For example, such oxidants as nitrobenzene, iron (III) salts, air, etc. will effect the coupling process.[22]

We had no aversion to abandoning the alkylation of the bromo ester since it is a potent lachrymator and carcinogen. In its place we decided to use tert-butyl 2-bromoacetate 29.[24] We felt that the reaction at the carbonyl ester should be minimized on electronic as well as steric grounds by the use of this hindered ester. The missing methyl group in 30 could be incorporated in a later step by alkylation

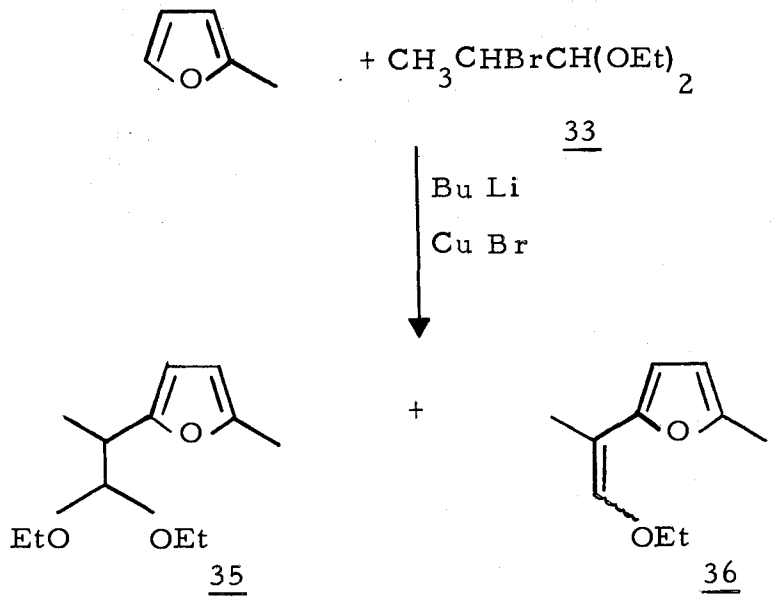
with sodium hydride and methyl iodide, and the synthesis completed by hydrogenation of 31 and deprotection of 32 to 2. The reaction of 5-lithio-2-methylfuran with tert-butyl 2-bromoacetate gave, on work up, a polymeric substance whose infrared spectrum showed a strong band at 3600 cm^{-1} (OH), and no absorption in the carbonyl region. This evidence suggested that instead of displacing the halide in 29, lithiofuran 23 as before had added across the carbonyl double bond.

Scheme 6:



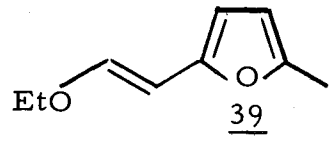
23 29 30 31 32

We next focused our attention on 33 as a potential alkylating agent. Bromoacetal 33 appeared to be an excellent substitute for ethyl 2-bromopropionate for two reasons. First, the carbonyl was masked as an acetal, readily removable by mild acid hydrolysis, and the resulting aldehyde would be easily oxidized to the corresponding carboxylic acid. Secondly, the proton attached to C-2 was no longer acidic, minimizing proton abstraction by the basic lithiofuran, 23. Treatment of 5-(2-methylfuryl) lithiumcuprate with 33 gave a 2:1 mixture of 35 and 36 in a 50% yield.

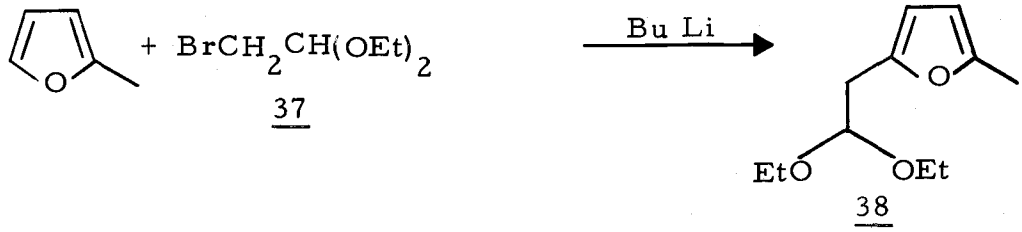


This result was encouraging despite the minor complication due to the formation of 36. We felt that enol ether 36 could be hydrolyzed along with 35 to the corresponding aldehyde. The reaction of 5-lithio-2-methylfuran with 37 was also investigated and in this case a 47% yield

of acetal 38 was obtained without any detected formation of 39.

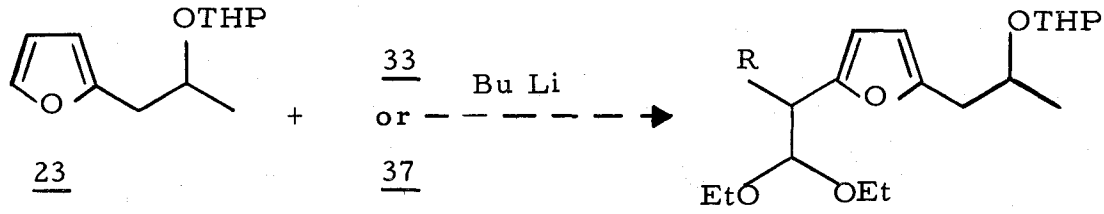


39



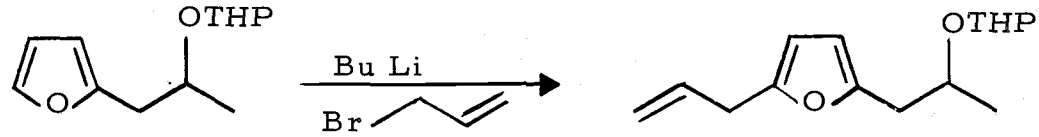
38

We were quite disappointed, however, when we extended these efforts to the reaction of 23 with 33 or 37



R = H 34
R = CH_3 34a

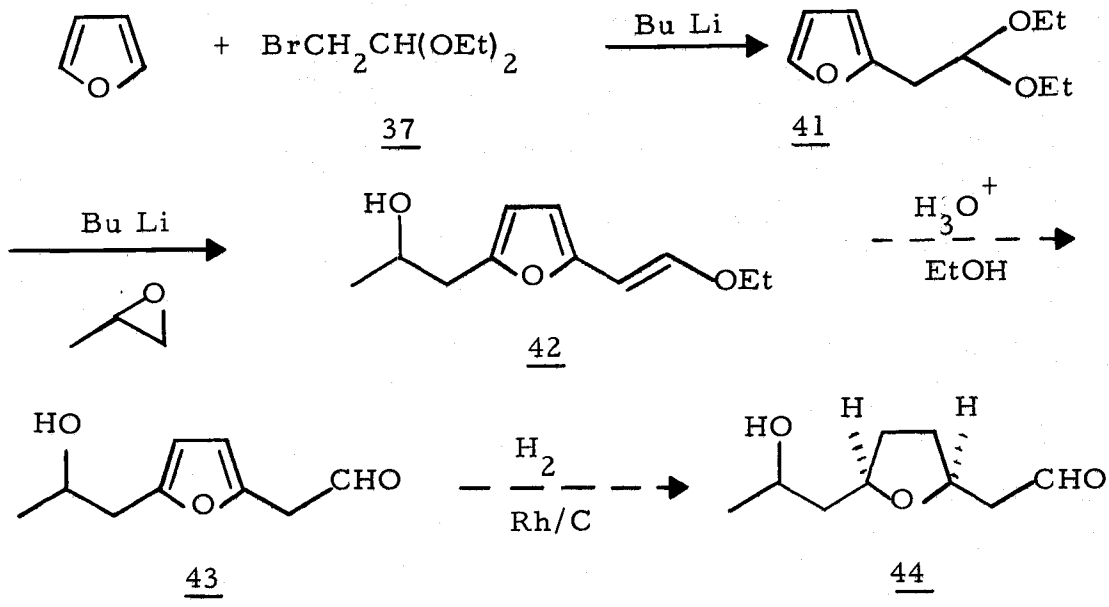
for unchanged starting materials were repeatedly isolated, despite the fact that other alkyl halides, for example allyl bromide, reacted with 23 to give 40.



23 40

In the meantime, we had also been searching for a different way to prepare 22 because the yield of the first two steps in Scheme 5 were quite modest. This was accomplished directly and efficiently by reaction of 2-lithiofuran with propylene oxide and hence allowed us to attach the 2-hydroxy-1-propyl side chain at a different stage of the synthesis. The order of side chain introduction in Scheme 5 was now changed to take advantage of our study with methylfuran, and these alterations are outlined in Scheme 8.

Scheme 8:



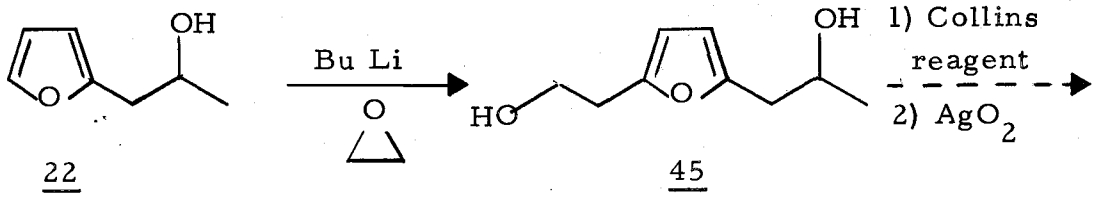
37 41 42 43 44

1) Na H, CH_3 I
2) Ag_2O, NaOH → Nonactic Acid

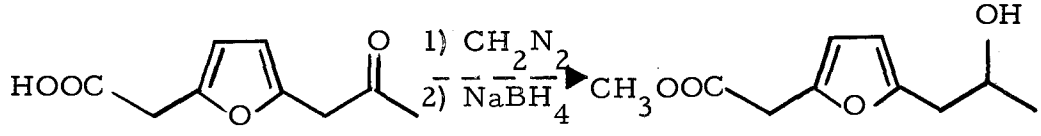
Acetal 41, obtained in 81% yield from 2-lithiofuran and 37, was converted into compound 42 in 43% yield. Enol ether 42, however, proved to be resistant to our hydrolytic attempts using dilute hydrochloric acid in aqueous ethanol. An increase in reaction time eventually led to polymerization.

The approach involving alkylation of α-bromo-acetals and α-bromoesters was abandoned at this point in favor of the route represented in Scheme 9.

Scheme 9:



22 45

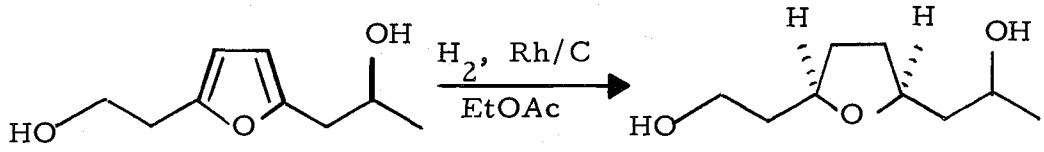


46 47

1) H_2, Rh/C
2) NaH, CH_3I

→ Methyl Nonactate

As anticipated, diol 45 was cleanly obtained in 80% yield by alkylation of ethylene oxide with the 5-dilithio derivative of 22. Attempted oxidation of 45 to 46 using Collins'[25, 26] or Jones'[27] reagents gave poor recovery in the former case and polymerization in the latter. Diol 45 was then reduced (H_2, Rh/C, ethyl acetate) to 48.

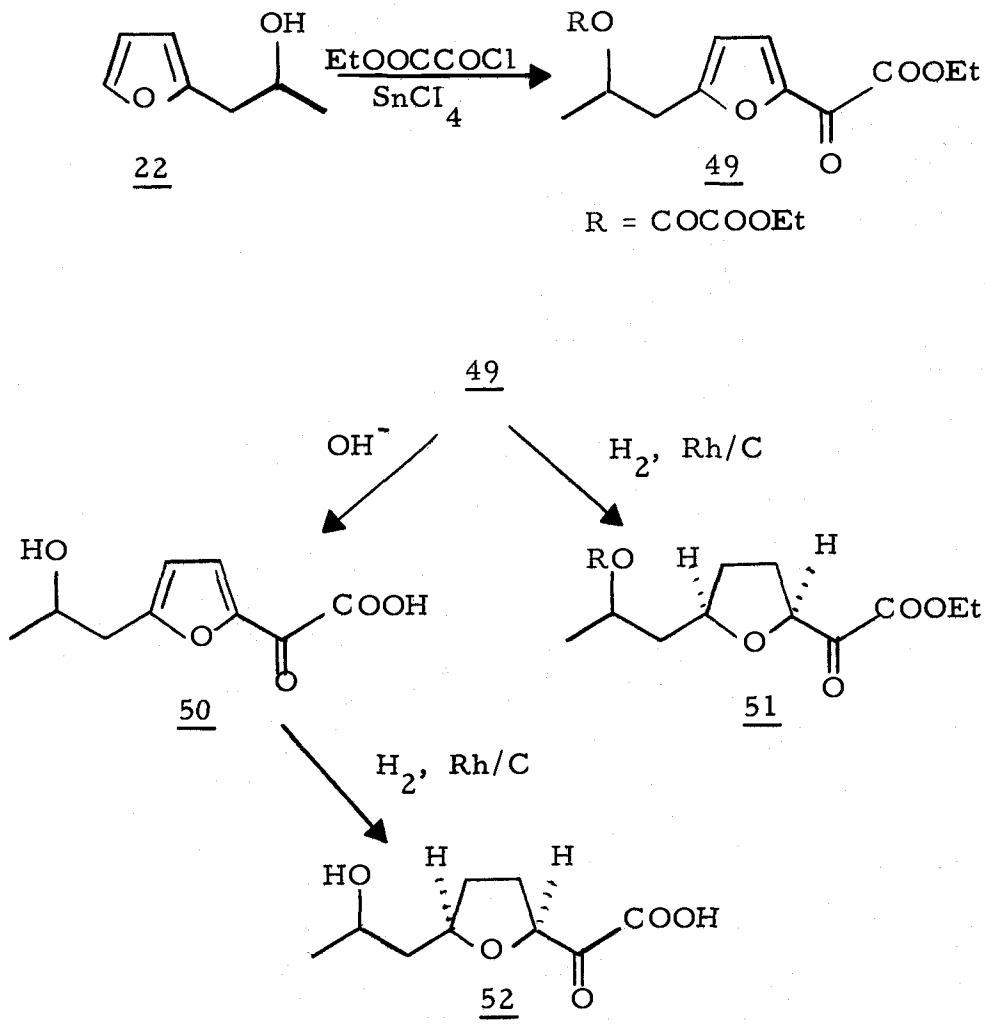


45 48

Attempted oxidation of 48 with Collins reagent still gave low mass recovery. The reaction of 48 with Jones' reagent on the other hand gave a disappointingly complex mixture. The reason for this complex mixture is not understood in the light of subsequent results obtained in our laboratories.

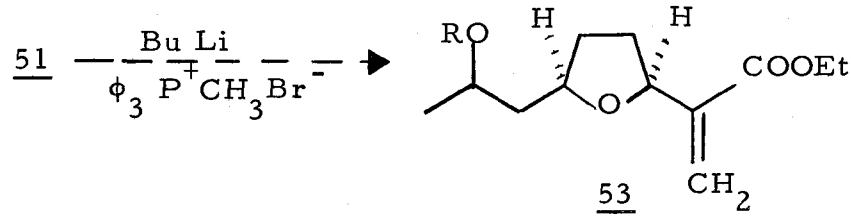
At this point, the strategy involving alkylation of furan via its lithium derivative did not look promising, and we turned to an alternate approach for introducing the propionic side chain that is characteristic of all the nactins. A search of the literature revealed that the acylation of furan and its derivatives at position 2 generally proceeds smoothly and in good yield.[28, 29, 30] Therefore the approach in Scheme 10 was briefly pursued as a potential route to nonactic acid.

Scheme 10:



The reaction of 22 with ethyl chloroglyoxylate in the presence of anhydrous stannic chloride afforded a dark viscous oil which was assigned structure 49 on the basis of its infrared and proton magnetic resonance spectra. In general, the yield of crude product from this reaction was highly variable, ranging from 15 to 50%. Ester 49 gave a broad band on thin layer chromatography (silica gel or alumina),

and it polymerized upon an attempted distillation under vacuum. In an effort to purify 49 the conversions indicated in Scheme 10 were carried out. However, neither 50, 51, nor 52 turned out to be any more tractable. Glyoxylate 51 was reacted with triphenylphosphonium bromide and butyl lithium under Wittig conditions[31] in hopes of forming 53, which could have been converted to nonactic acid by hydrogenation and deprotection.

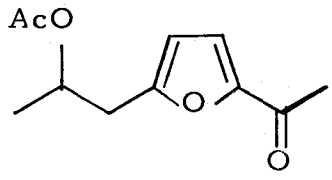


53

R = COCOOEt

On work-up, however, a complex mixture was isolated which showed no vinyl hydrogen in the nmr spectrum.

Our vain efforts with 51 led us to consider the related ketone, 54, as a possible intermediate to nonactic acid



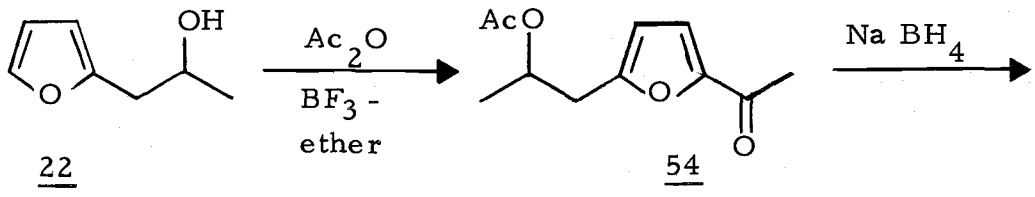
54

Ketoester 54 does not contain all the carbon atoms present in nonactic acid and therefore our problem at this stage would be the conversion

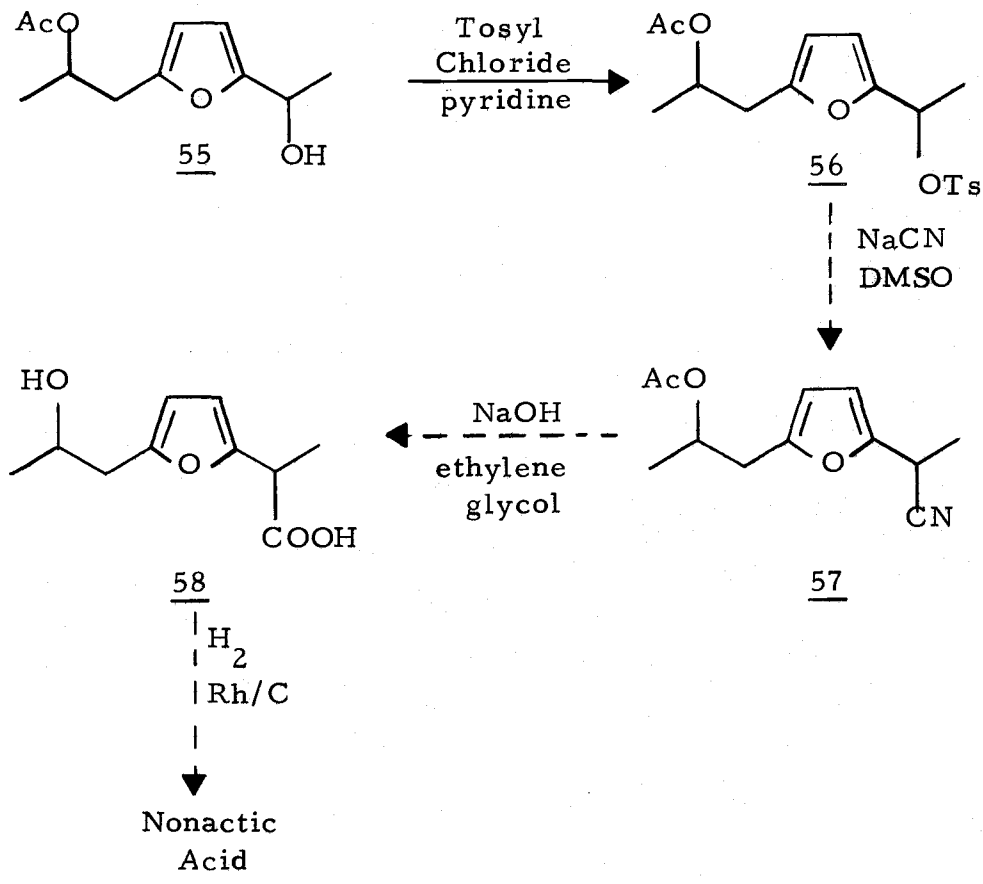
$$R'COR \longrightarrow R'CH(R)CO_2H \qquad (1)$$

One carbon homologation of the type expressed by equation (1) is a fairly routine operation in organic synthesis, for which methodology is currently available.[32-41] Treatment of 22 with acetic anhydride in the presence of 10% boron trifluoride-etherate, using the conditions developed for acylation of furans by Levine and Heid,[42] gave 54 in 60% yield. By lowering the temperature of the initial reaction mixture from 0° to -25° we were able to increase the yield of ketone 54 to 86%. We had planned beyond this juncture to adhere to the sequence outlined in Scheme 11, since this route looked attractive for its simplicity as well as for the convenience of introducing the missing carbon at the same oxidation level as it appears in nonactic acid. Also, the displacement of sulfonate esters by sodium cyanide in dimethyl sulfoxide is well documented, and is a reaction that generally affords good yields.[43]

Scheme 11:



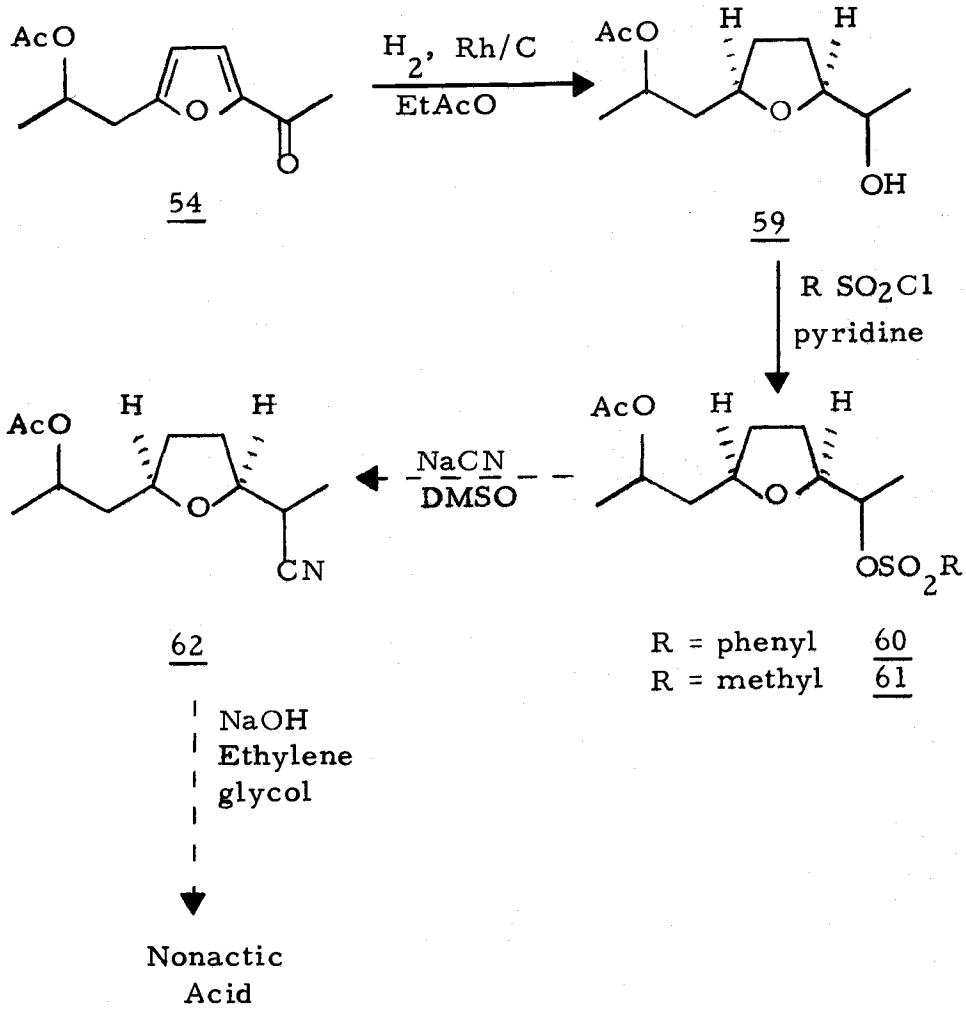
22 54



Toward this goal, 54 was reduced with sodium borohydride in a mixture of glyme and tert-butanol to give 55 (ir 360 cm^{-1}; nmr 1.24, d, 3H, J=6) as a mixture of epimers. Treatment of alcohol 55 with tosyl chloride in pyridine afforded, in addition to a small amount of starting material, a new substance, which from its infrared spectrum (1180-1190 cm^{-1}, st. d, and 1370 cm^{-1}, s)[44] was assigned structure 56. This mixture was stirred at room temperature with sodium cyanide in dimethyl sulfoxide for 36 hours. Work-up followed by thin layer chromatography (silica gel) afforded a very complex mixture,

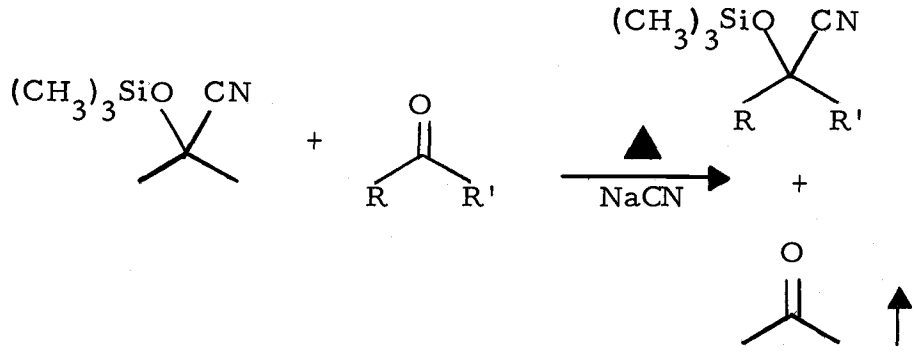
and thus the displacement of furyl tosylate 56, with cyanide ion was not pursued further.

An alternate approach in which displacement could be carried out on a tetrahydrofuryl system was next considered and it was therefore decided to reduce 54 to 59.

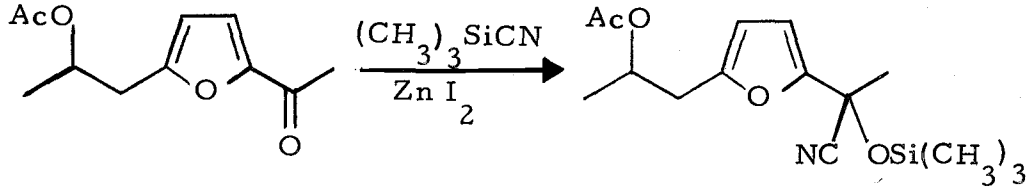


Tetrahydrofuran derivative 59 was obtained quantitatively from 54 by hydrogenation over rhodium on charcoal for 24 hours, and 59 was then converted to its sulfonate ester 60 (p-toluenesulfonyl chloride in pyridine). However, an attempt to prepare 62 from 60 by displacement with sodium cyanide in dimethyl sulfoxide at room temperature for six days[45] gave unchanged starting material. Mesylate ester 61 was also prepared (methanesulfonyl chloride in pyridine), but its displacement to give 62 under somewhat more vigorous conditions (60° for 96 hours) did not occur.

An alternative method to convert ketone 54 into a nitrile was also explored. Evans et al.[46] have observed that aldehydes and ketones react rapidly and smoothly with trimethyl silylcyanide to give silyloxy nitriles. The formation of the cyanohydrin derivatives is catalyzed by Lewis acids, by cyanide ion, or can be carried out via the exchange process illustrated below.



Treatment of ketone 54 with trimethyl silylcyanide[47] in the presence of a few crystals of anhydrous zinc iodide gave after one hour an 86% yield of siloxy nitrile 63 (determined by nmr).



54 63

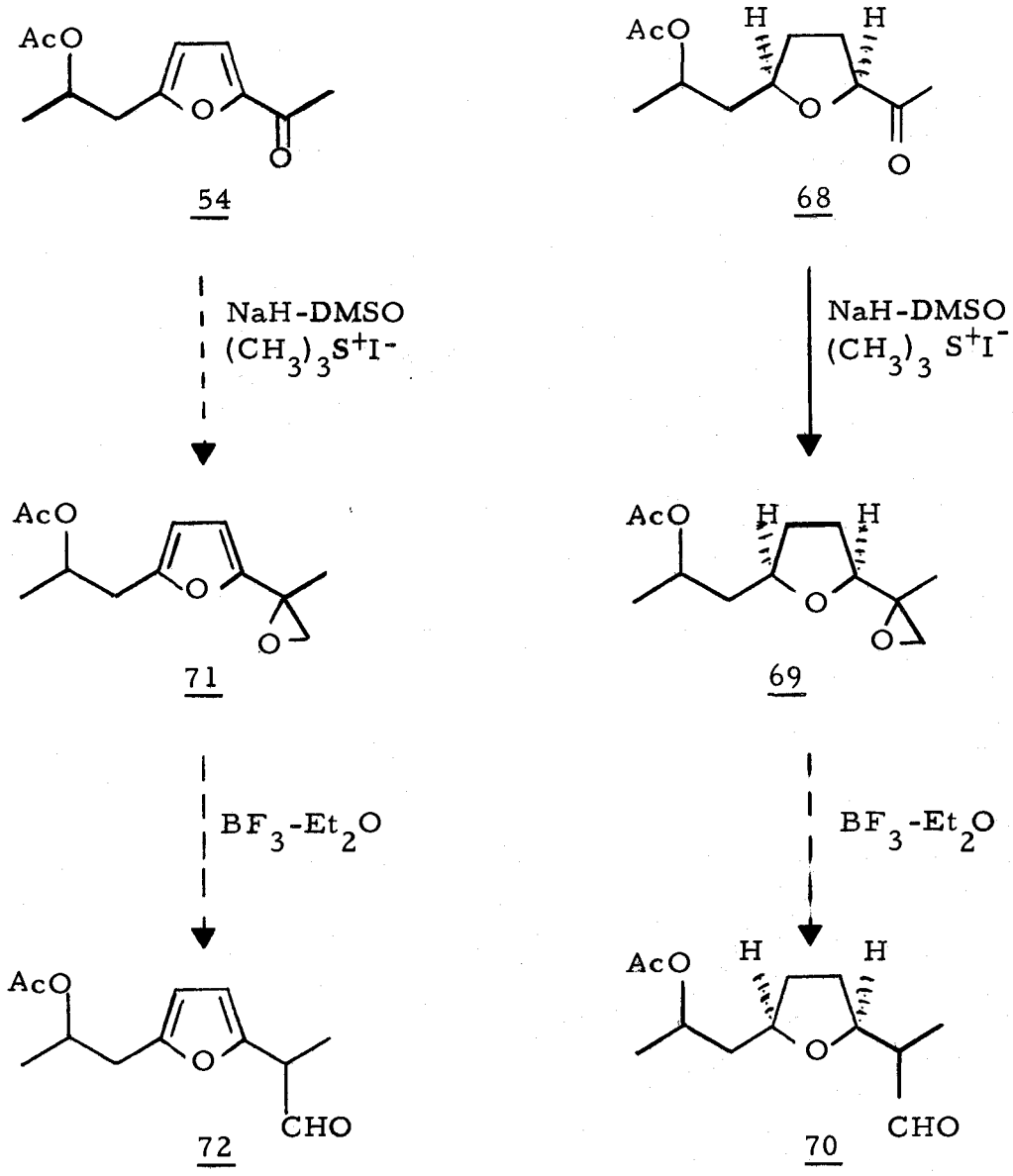
We had hoped to transform 63 into 57 and convert the latter to non-actic acid as outlined in Scheme 11. However, attempts to reductively cleave the siloxyl group of 63 (Pd/C, H_2) proved unrewarding.

Two other widely used methods for homologating ketones (according to equation (1) on p. 24) are the sulfonium methylide condensation developed by Corey and Chaykovsky[48] and the Darzens condensation.[49] These two methods are related by the nature of the intermediate generated--in the former case an epoxide and in the latter an α, β -epoxy-ester. Both the epoxide and the glycidic ester can be converted to an aldehyde by further elaboration.

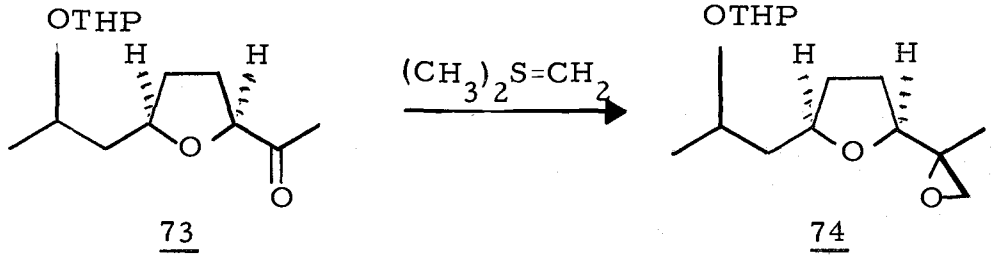
The method of Corey and Chaykovsky consists of generating dimethylsulfonium methylide from a solution of methylsulfinyl carbanion and trimethylsulfonium iodide. The ylid behaves as a nucleophile and functions to transfer methylene to electrophilic unsaturated linkages, including α, β unsaturated systems. We

experimented with this ylid using ketones 54 and 68, in both cases hoping to rearrange the epoxides obtained to the corresponding aldehydes as shown in Scheme 12.

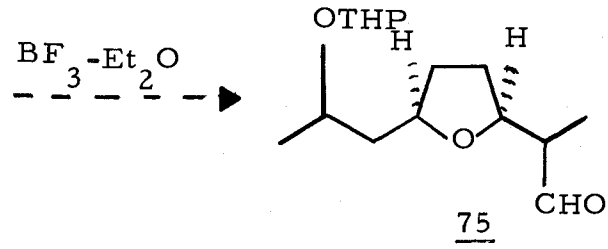
Scheme 12:



Treatment of 68 with two equivalents of dimethyl sulfonium methylide afforded epoxide 69 in 70% yield. When ketone 73 was used in place of 68, a 75% yield of 74 was realized.

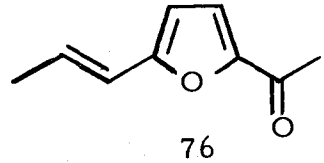


73 74



75

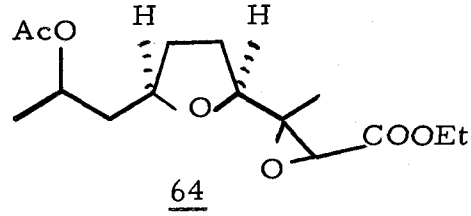
Unfortunately, neither 69 nor 74 could be converted into the desired aldehydes 70 or 75 by treatment with boron trifluoride-etherate complex. Therefore, we concentrated on homologating 54. However, the reaction of ketone 56 with dimethyl sulfonium methylide was incomplete and considerable amount of starting material was isolated. An increase in the ratio of ylid to ketone from 2:1 to 4:1 gave unexpectedly 76 as the main product.



76

The Darzens condensation, developed around the turn of the century, involves the condensation of an aldehyde or ketone with an

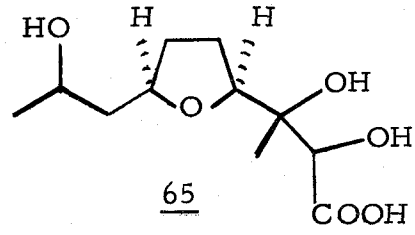
α-halo ester to produce an α, β -epoxy ester (glycidic ester). Usually the glycidic esters isolated can be converted into aldehydes or ketones having a higher carbon content than the original carbonyl compound. This transformation occurs after hydrolysis to and decarboxylation of the epoxy acid.[50] The most frequently used condensing agent is sodium ethoxide, although other bases, in particular sodium amide and potassium tert-butoxide, have enjoyed widespread use. A recent report by Yamamoto et al.[51] described the use of lithium dicyclohexylamide as the base in the generation of polyhalomethyl lithium carbonyl adducts. This method was successfully extended by Yamamoto and his co-workers to a Darzen's condensation of methyl 2-bromoacetate and cyclohexanone to afford the corresponding glycidic ester in 92% yield. Application of this condensation to ketone 54 resulted in considerable amount of starting material being recovered. On the other hand, addition of lithium dicyclohexylamide to a mixture of ketone 68 and ethyl 2-bromo-acetate gave, after work up, a substance identified as 64.



64

Glycidic ester 64, when treated with sodium hydroxide and acidified, failed to decarboxylate even when heated to reflux. A carboxylic acid was isolated and tentatively assigned structure 65, which could have

originated by hydrolysis of epoxide 64.

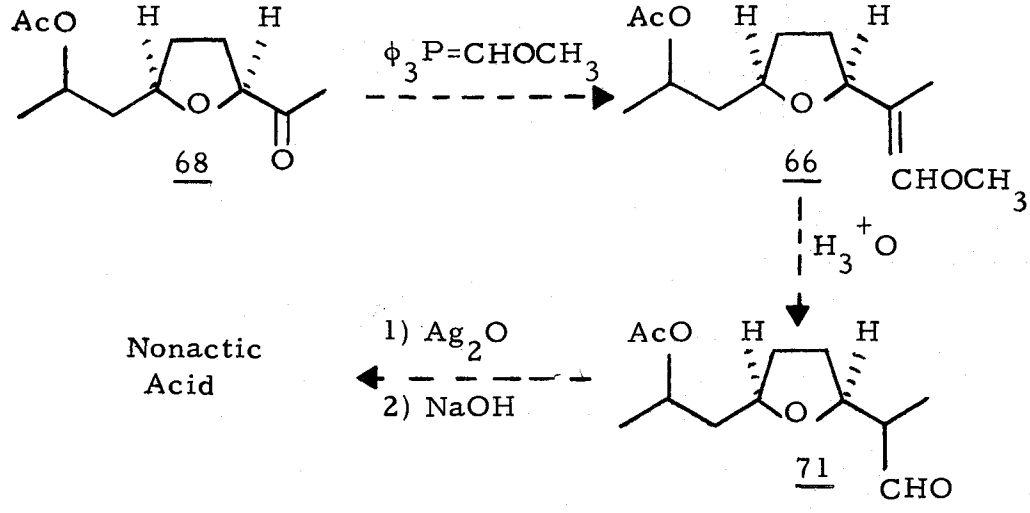


65

Our unsuccessful attempts to decarboxylate 65 therefore prompted us to abandon this approach.

A widely used method for the synthesis of olefins in preparative organic chemistry is based on the pioneering work of G. Wittig who, in 1953, found that the reaction of benzophenone with methylene-triphenylphosphorane gave 1, 1-diphenylethylene and triphenylphosphine oxide in almost quantitative yield.[52] The Wittig reaction of 68 suggests two approaches and these are illustrated in Scheme 13 and Scheme 14.

Scheme 13:

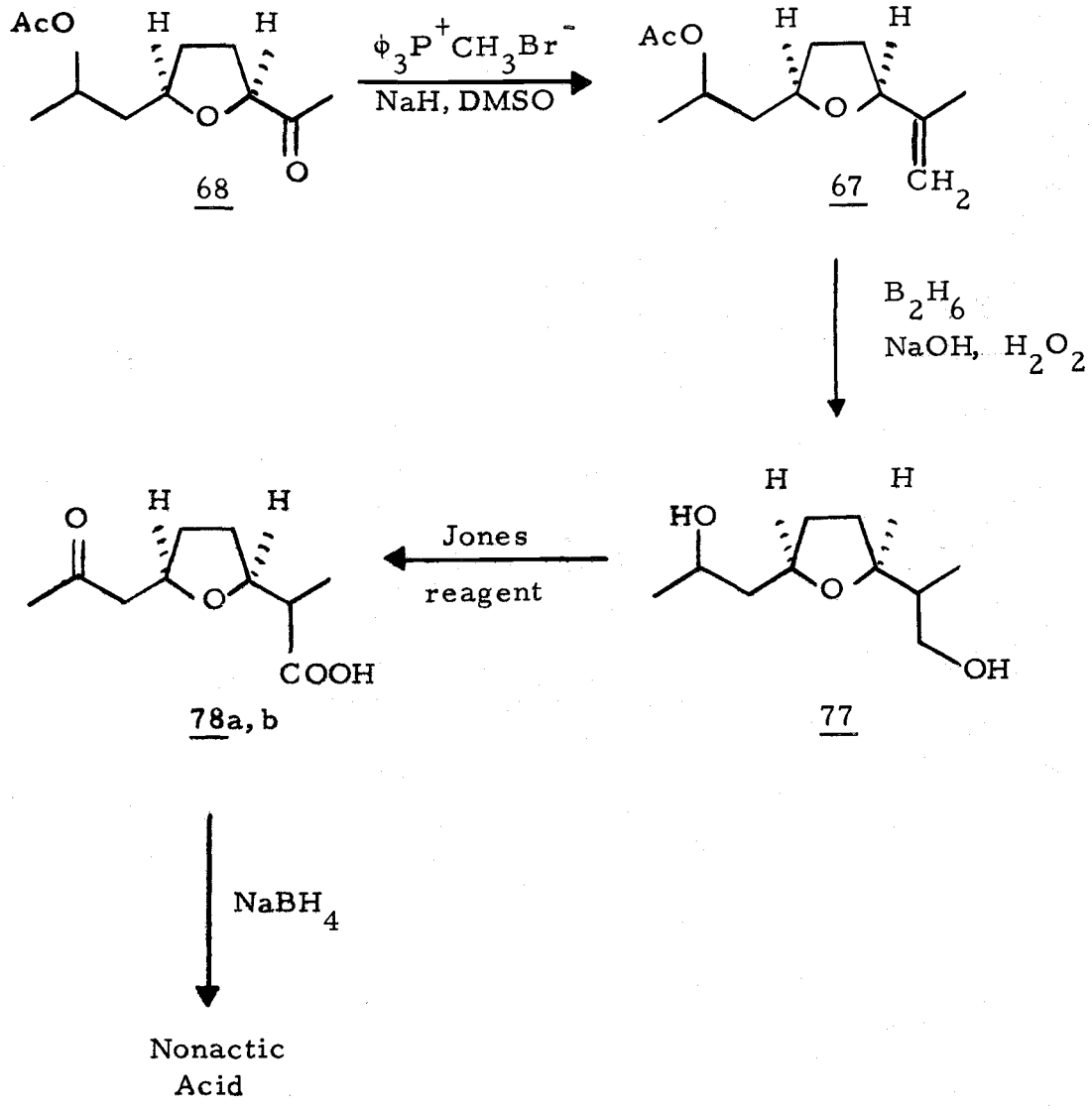


68

66

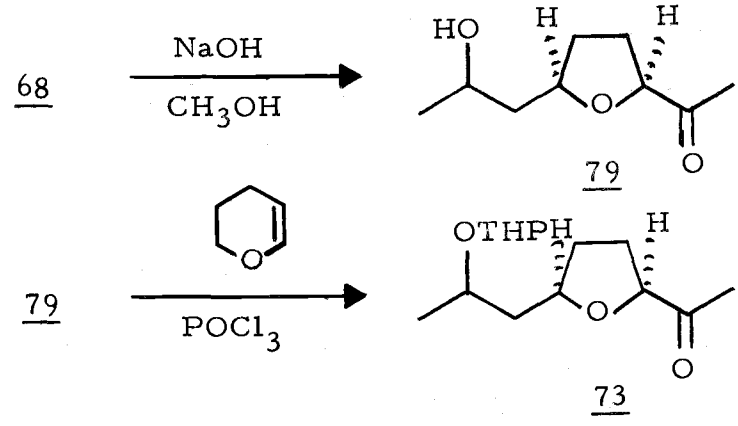
71

Scheme 14:


AcO
H
H
O
O
68
$\phi_3P^+CH_3Br^-$
NaH, DMSO
AcO
H
H
O
67
CH_2
B_2H_6
NaOH, H_2O_2
H
H
HO
O
OH
77
Jones
reagent
O
H
H
O
COOH
78a, b
$NaBH_4$
Nonactic
Acid

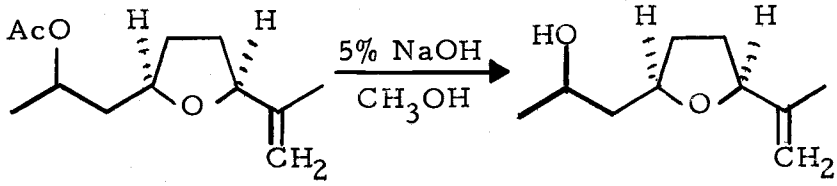
We selected Scheme 13 for examination before Scheme 14 for the simple reason that enol ether 66 is a masked carbonyl and hence at a higher oxidation state than olefin 67, although both 66 and 67 would require further oxidation to nonactic acid.

Although benzophenone reacts with methoxymethylenetriphenylphosphorane to give 1, 1-diphenylvinyl methyl ether in 83% yield,[53] when the same reaction conditions are applied to either cyclohexanone or acetophenone using 100% excess of the reagent, the yields are much lower (typically around 35%).[48] Ketone 68 was treated with methoxymethylenetriphenylphosphonium chloride and n-butyllithium but the nmr spectrum of the crude oil isolated suggested that very little, if any, of 66 was present. Pettit has shown that protection of a hydroxyl group as its tetrahydropyranyl ether versus its acetate can have a beneficial effect on the yield of Wittig reactions[56] and for this reason we converted 68 into 79 by saponification with alcoholic sodium hydroxide followed by reprotection with dihydropyran.



However, in spite of this interchange, the reaction of 79 with methoxymethylenetriphenylphosphonium chloride led to a complex mixture.

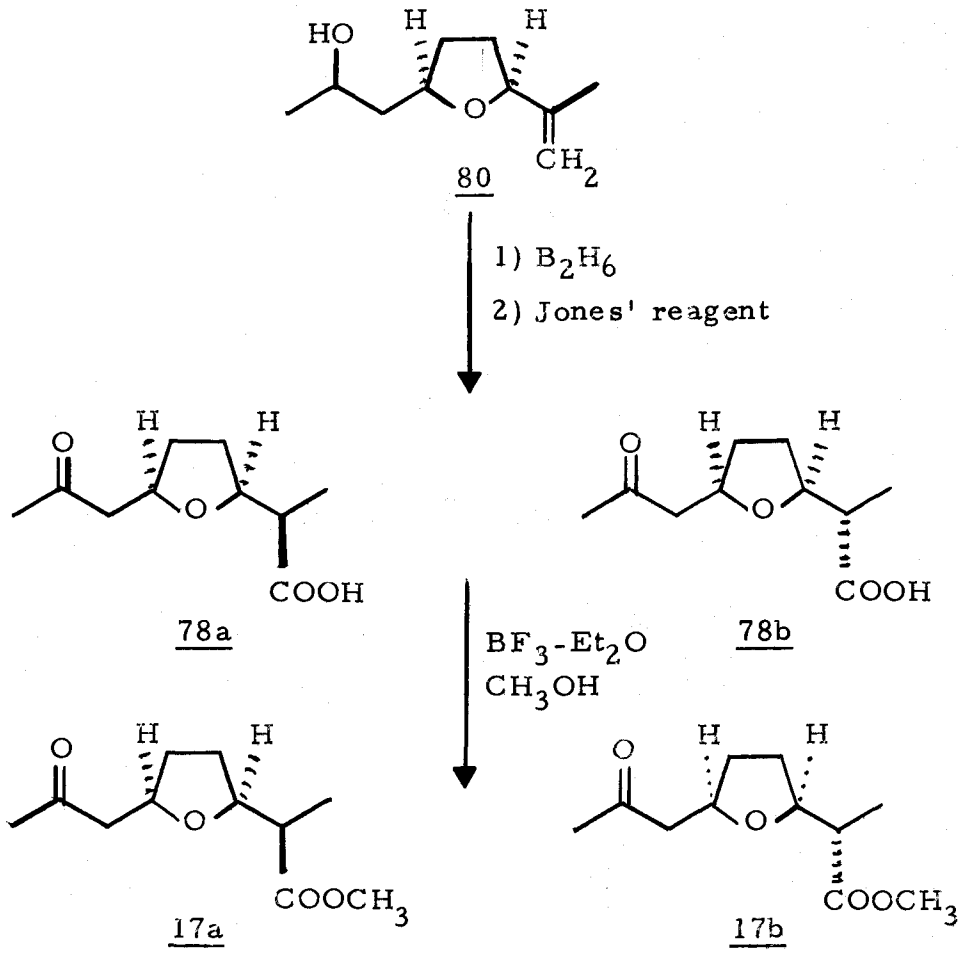
In contrast to reactions with methoxytriphenylphosphorane, treatment of 68 with methyltriphenylphosphonium bromide and sodium hydride in dimethyl sulfoxide[57] proceeded smoothly to afford 67 (ir 880 cm^{-1}; nmr 1.74 s, 3H, 4.8 and 5.0 singlets). In addition to 67, a saponified product 80 was isolated. Treatment of 67 with a 5% methanolic sodium hydroxide solution gave 80 quantitatively.



67 80

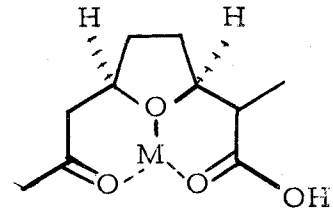
Hydroboration of 67 (1.0 M B_2H_6 in THF),[58] followed by oxidative work-up with basic hydrogen peroxide, afforded 77, $bp_{0.01}$ 82-84 (lit.[5] $bp_{0.01}$ 80). Diol 77 was oxidized with Jones' reagent to a mixture of ketoacids 78, epimeric at C-2. Alternatively hydroboration of 80 followed directly by titration of the intermediate borane with Jones' reagent gave a 2:1 mixture of ketoacids 78a and 78b. Conversion of 78a and 78b into their methyl esters was accomplished by treatment with boron trifluoride-etherate in excess methanol.[59] The boron trifluoride-etherate alcohol reagent is both mild and effective in meeting the esterification requirements of a great

number of different classes of carboxylic acids and it avoids strongly acidic conditions[60] or the cumbersome and dangerous operations associated with the distillation of diazomethane.[61]



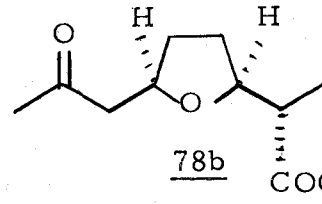
To complete the synthesis of nonactic acid, it remained for us to reduce the C-8 carbonyl of 17b. Our first attempt to accomplish this transformation was carried out using sodium borohydride in methanol as the reducing agent. The products isolated from this reaction were methyl nonactate, 82a, and methyl 8-epi-nonactate, 82b, in a 1:3 ratio. Similarly, other attempts with a variety of

reducing agents gave material with the prevailing unnatural configuration at C-8. Inspection of molecular models of 78b revealed that an intermediate such as 81, in which the oxygen atoms are complexed with the reducing agent, would favor hydride delivery from the less hindered side, affording predominantly the C-8 epimer.



81

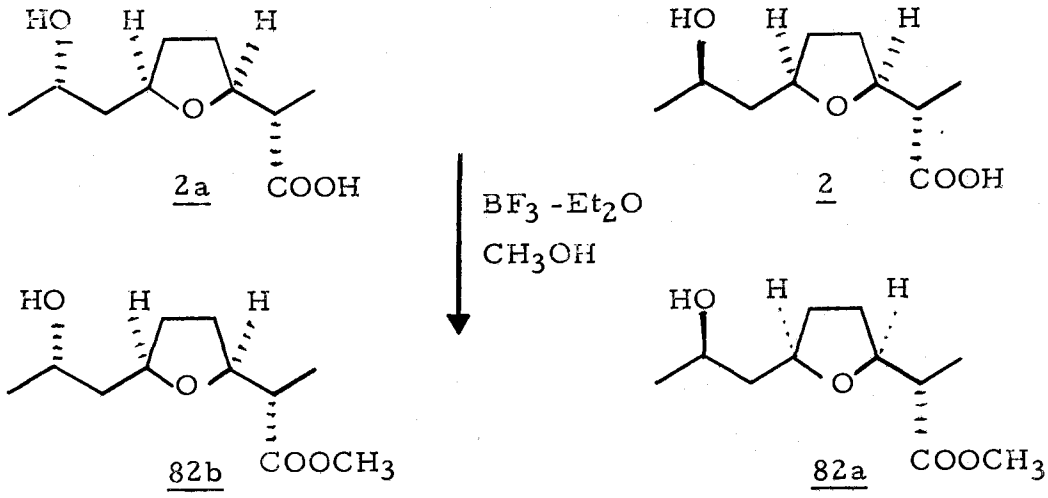
Therefore, we attempted to maximize the amount of C-8 epimer in the reduction step by the use of the bulky lithium tri-sec-butylborohydride. Reduction of 78b with this reagent gave hydroxy acids 2 and 2a. Esterification (CH_3OH-BF_3-Et_2O) followed by chromatography on silica gel (2:1 pentane:ethyl acetate) afforded pure methyl nonactate 82a and methyl 8-epinonactate 82b in a 1:9 ratio.



78b

Li (tri-sec-butyl-borohydride)

2a
8-epi nonactic acid + 2
nonactic acid



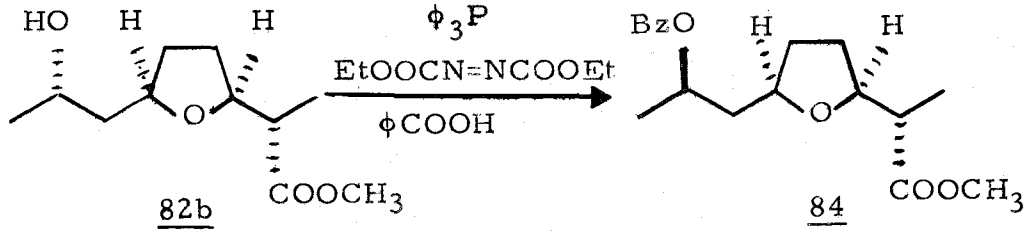
O. Mitsunobu et al.[62] and A. K. Bose et al.[63] have observed that the reaction of alcohols with carboxylic acids in the presence of equimolar amounts of diethyl azodicarboxylate and triphenyl phosphine led to the formation of carboxylic esters with high stereospecificity. An alkoxy phosphonium salt, 83, was assumed to be the intermediate of the reaction, from which the alkyl group was transferred to the carboxylate anion (with inversion of configuration) in concert with the release of triphenylphosphine oxide.

$$[\phi_3\overset{+}{P}OR \quad RCOO^-]$$

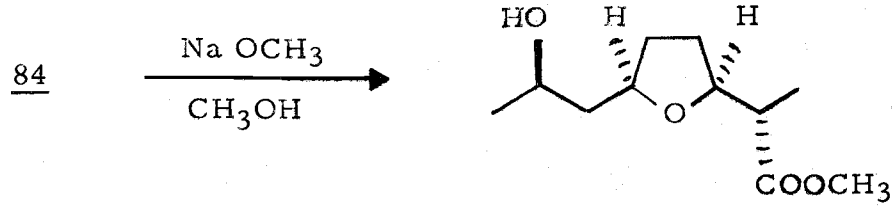
83

Application of this observation to methyl 8-epinonactate 82b, (triphenyl phosphine, diethyl azodicarboxylate, benzoic acid) led to the formation of benzoate 84 in 90% yield as the only product. Cleavage of the benzoate ester 84 (sodium methoxide, room temperature) gave quantitatively methyl nonactate as the only detectable isomer. Since methyl

nonactate has previously been converted to its acid, this constitutes a formal total synthesis of nonactic acid.



82b 84



82a

Methyl
Nonactate

III. EXPERIMENTAL

General

Melting points (mp) were determined on a Kofler hot stage microscope and are uncorrected as are boiling points (bp). Infrared (ir) spectra were recorded on Perkin Elmer 137 spectrophotometer. Nuclear magnetic resonance (nmr) spectra were obtained on Varian Associates EM-360 and HA-100 instruments. Peak positions are given in parts per million (δ) downfield from the internal standard TMS. The abbreviations s, d, t, q, p, and m refer to singlet, doublet, triplet, quartet, quintet, and multiplet respectively. The coupling constant (J) is measured in Hertz. Mass spectra (ms) and exact mass determinations were provided by Dr. Susan Rottschaefer at the University of Oregon. The abbreviation M^+ refers to the molecular ion. Thin layer chromatograms (tlc) were made on Merck silica gel 60F-254 or on alumina. Merck silica gel (0.05-20 mm) and Fischer Florisil (100-200 mesh) were used for column chromatography. Analytical vpc was performed on a Varian aerograph model 700 gas chromatograph using a 5' x 0.25" SE-30 (20% on Chrom G) column.

Methyl 2,3-epoxy-3-(2-furyl)-2-methylpropionate (12b)

A solution of 6.9 g of sodium (0.3 mole) in 75 ml of anhydrous

methanol was added during three hours to a mixture of 57.0 g (0.31 mole) of ethyl 2-bromopropionate, 20.0 g (0.21 mole) of furfuraldehyde and 25 ml of anhydrous methanol at 0°. Stirring was maintained throughout addition. When the addition was complete, the reaction was allowed to warm to room temperature and stirring was continued overnight. The methanol was removed under reduced pressure at room temperature and the residue was dissolved in 150 ml of ether and 100 ml of distilled water. The ether extracts were washed with saturated aqueous sodium bicarbonate, dried ($MgSO_4$), and distilled through a spinning-band column yielding 15.5 g (85 mmole, 42%) of glycidic ester (12b), bp 83-85° (1.5 torr): ir (film) 3150, 1740, 1450, 1380, 1200, 1150, 750 cm^{-1}; nmr ($CDCl_3$) 1.65 and 1.74 (s, 3H), 3.76 and 3.83 (s, 3H), 3, 97 and 4.28 (s, 1H), 6.35 (br, 2H), 7.38 and 7.43 (s, 1H).

2-Acetonylfuran (13)

Methyl 2, 3-epoxy-3-(2-furyl)-2-methylpropionate 12b (15.5 g, 83 mmole) was dissolved in 30 ml of 15% sodium hydroxide and 10 ml of methanol. After five minutes, 40 ml of 7N sulfuric acid was added in small increments. When all the CO_2 had evolved, the mixture was extracted with three 50-ml portions of ethyl ether. The ether extracts were washed with saturated aqueous sodium bicarbonate and evaporated in vacuo at room temperature. The remaining syrup was

distilled through a spinning-band column yielding 8.4 g (68 mmole, 80%) of 2-acetonylfuran, bp 34-36° (1 torr): ir (film) 1710, 1600, 1500, 1360, 1170, 890, 740 cm^{-1}; nmr ($CDCl_3$) 2.22 (s, 3H), 3.75 (s, 2H), 6.22 (d, 1H, J=3), 6.36 (dd, 1H, J=3, 1), 7.39 (d, 1H, J=1).

1-(2-Furyl)-2-propanol (22)

(a) A solution of 6.8 g (55 mmole) of 2-acetonylfuran in 15 ml of isopropyl alcohol was added dropwise to a suspension of 3.2 g (84 mmole) of sodium borohydride in 20 ml of a 1:1 mixture of absolute ethanol and isopropyl alcohol. Stirring was maintained throughout addition. When addition was complete, the mixture was allowed to warm to room temperature and stirring was continued for another hour. The reaction mixture was poured onto ice and 50 ml of distilled water was added. The aqueous layer was saturated with sodium chloride and extracted with ethyl ether. The ether extracts were dried over sodium sulfate and the solvent was evaporated. The residue was distilled through a spinning band column yielding 5.2 g (41 mmole, 75%) of alcohol (22), bp 47-50° (0.3 torr): ir (film) 3500, 1600, 1500, 1150, 1080, 1010, 950, 890, 740 (br) cm^{-1}; nmr ($CDCl_3$) 1.20 (d, 3H, J=6), 2.76 (d, 2H, J=6), 2.12 (s, br, 1H), 4.08 (m, 1H), 6.1 (d, 1H, J=3), 6.3 (d of d, 1H, J=3, 1), 7.36 (d, 1H, J=1); mass spectrum m/e 126.068 (M^+, calc. for $C_7H_{10}O_2$ 126.068).

(b) A solution of n-butyllithium in tetrahydrofuran (50 ml) was prepared from n-butyl chloride (5.42 g, 60 mmole) and finaly cut lithium metal (0.875 g, 125 mmole) at -25°. Furan (4.1 g, 60 mmole) was added at -15° and the solution was stirred for 6 1/2 hours. Propylene oxide (3.48 g, 60 mmole) in tetrahydrofuran (15 ml) was added. The solution was stirred at -15° for two hours and then allowed to warm to room temperature while stirring was continued overnight. The solution was poured onto ice and sodium chloride was added. The aqueous layer was extracted repeatedly with ether. The extracts were combined with the original organic layer, washed with saturated aqueous sodium chloride, dried ($MgSO_4$), and distilled, affording 7.7 g (58 mmole, 98%) of (22).

1-(2-Furyl)-2-propyl 2-tetrahydropyranyl ether (23)

A solution of 5.2 g (41 mmole) of 1-(2-furyl)-2-propanol in 10 ml of benzene was added to 7 ml of freshly distilled dihydropyran in a round bottom flask fitted with a reflux condenser with drying tube. A few crystals of p-toluenesulfonic acid were added and the mixture was stirred for 1 hour. Two grams of potassium carbonate were added to the cooled mixture which was allowed to stand overnight. The reaction mixture was filtered, evaporated in vacuo at room temperature, and distilled at reduced pressure yielding 7.2 g

(36 mmole, 89%) of diastereomeric ethers (23), bp 62-65° (0.3 torr): ir (film) 3200, 3000, 1580, 1495, 1120, 1080, 1040, 875, 735 cm^{-1}; nmr ($CDCl_3$) 1.20 and 1.30 (d, 3H, J=6), 1.45-1.95 (br, 6H), 2.86 and 2.80 (d, 2H, J=6), 3.54 (m, 1H), 4.1 (m, 2H), 4.5 and 4.8 (m, 1H), 6.12 and 6.16 (d, 1H, J=3), 6.31 (t, 1H, J=3), 7.34 (s, 1H), mass spectrum m/e 210.126 (M , calcd. for $C_{12}H_{18}O$ 210.123).

2-(3-But-1-enyl)-5-methylfuran (26)

Tetrahydrofuran (10 ml) was placed in a three-necked, round bottom flask fitted with a mechanical stirrer, a condenser, and a pressure-equalized addition funnel. The air was swept out of the flask with dry, prepurified nitrogen and a steady flow of the gas was maintained throughout the reaction. Lithium metal, finely cut (0.315 g, 45 mmole) was introduced, and the suspension was cooled to -25°. A mixture of n-butyl chloride (1.84 g, 20 mmole) in tetrahydrofuran (10 ml) was placed in the addition funnel. Two or three milliliters were added to the stirred suspension to start the reaction. When the reaction had started as indicated by the appearance of cloudiness, the remaining chloride solution was added while the cooling bath was maintained at -35°. After the addition of the alkyl halide, the mixture was stirred for one hour with the cooling bath at -25°, and then stirring was continued for four hours at -15°. 3-Bromo-1-butene (2.7 g, 20 mmole) in tetrahydrofuran (4 ml) was added. Stirring was

continued for one hour at -15° and then the cooling bath was removed while the mixture was stirred for an additional three hours. The mixture was poured over crushed ice and the two layers were separated. The aqueous layer was extracted with ether, and the ether extracts were added to the tetrahydrofuran layer. The combined organic layers were dried ($MgSO_4$), evaporated, and distilled in a Kugelrohr apparatus (oven temperature 77° at 0.2 torr), yielding 1.6 g (60%) of (26) and (27) (separated on preparative VPC) in a 1:2 ratio: (26): ir (film) 3150, 1650, 1560, 920, 780 cm^{-1}; nmr ($CDCl_3$) 1.29 (d, 3H, J=7), 2.22 (s, 3H), 3.46 (m, 1H), 5.08 (d, 1H, J=17), 5.04 (d, 1H, J=9), 5.85 (s, 2H), 5.94 (m, 1H); mass spectrum m/e 136 (M^+). (27): ir (film) 3100, 1580, 1020, 970, 780 cm^{-1}; nmr ($CDCl_3$) 1.66 (d, 3H, J=4), 2.22 (s, 3H), 3.30 (m, 2H), 5.56 (m, 2H), 5.84 (s, 2H); mass spectrum m/e 136 (M^+).

2-Methyl-5-difuryl (28)

n-Butyllithium (60 mmole) in ether was prepared according to the method of Gilman. 2-Methylfuran (4.8 g, 60 mmoles) was added at -20°, and the mixture was warmed to room temperature and refluxed for four hours. The solution was cooled to 0° and 3.5 g (24 mmole) of cuprous bromide was added. After stirring for five minutes, the solution was refluxed for 72 hours while air was swept through the reaction flask. The mixture was quenched with aqueous ammonium

chloride and the organic layer was separated. The aqueous phase was washed with ether. The combined organic layers were dried ($MgSO_4$), evaporated, and distilled under vacuum yielding 1.0 g (6.1 mmoles, 25%) of (28), bp 41-43° (2.8 torr): ir (film) 3000, 1600, 1500, 1150, 890, 730 cm^{-1}; nmr ($CDCl_3$) 2.28 (s, 3H), 5.98 (d, 1H, J=3), 6.36 (d, 1H, J=3); mass spectrum m/e 162.067 (M^+, calc. for $C_{10}H_{10}O_2$ 162.068).

Tert-butyl bromoacetate (29)

A solution of 30.8 g (221 mmole) of bromoacetic acid in 50 ml of tetrahydrofuran was cooled to -15° and 3.5 ml of concentrated sulfuric acid was added. A slow stream of isobutylene was passed through the solution until the volume had increased by one third. The mixture was stoppered tightly in a pressure bottle, and shaken at room temperature overnight. The mixture was then poured into 20 ml of 0.5N sodium hydroxide and extracted with ethyl acetate. The extract was washed with water and saturated aqueous sodium chloride. Drying ($MgSO_4$) and removal of solvent gave the ester, 29, as a clear liquid. Distillation gave 24 g (112 mmole, 54%) of 29: ir (film) 3000, 1725, 1280, 1150, 950 cm^{-1}; nmr 3.73 (s, 2H), 1.46 (s, 9H).

2-(2,2-Diethoxyethyl)-5-methylfuran (38)

A solution of n-butyllithium in tetrahydrofuran (15 ml) was prepared from n-butyl chloride (1.84 g, 20 mmole) and lithium shavings

(0.29 g, 42 mmole) at -25°. 2-Methylfuran (1.68 g, 20 mmole) in tetrahydrofuran (4 ml) was added, and the solution was allowed to stir at -15° for six hours. Bromoacetal 39 (3.9 g, 20 mmole) was added, and the solution was stirred overnight at room temperature. The mixture was poured into cold water and was saturated with sodium chloride. The organic layer was retained, and the aqueous layer was extracted with ether (150 ml). The organic layers were combined, dried ($MgSO_4$), and evaporated. Distillation through a spinning-band column afforded 1.8 g (45%) of 40, bp 44-46° (0.4 torr): ir (film) 3000, 1500, 1120, 1060, 780 cm^{-1}; nmr ($CDCl_3$) 6.96 (d, 1H, J=3), 6.84 (d, 1H, J=3), 4.8-4.3 (d of q, 4H, J=7), 2.88 (d, 2H, J=6), 2.20 (s, 3H), 1.14 (t, 3H, J=7).

1-(2-Propenyl-5furyl)-2propyl 2-Tetrahydropyranyl Ether (40)

A solution of n-butyllithium in tetrahydrofuran (20 ml) was prepared from n-butyl chloride (0.92 g, 10 mmole), and lithium shavings (0.15 g, 22 mmole) at -35° as previously described. 1-(2-Furyl)-2-propyl 2-tetrahydropyranyl ether (23) (2.1 g, 10 mmole) was added and the mixture was stirred for four hours at -15°. A solution of allyl bromide (1.21 g, 10 mmole), in 1 ml of tetrahydrofuran, was added and the mixture was stirred for one hour at -15° and overnight at room temperature. The mixture was poured into ice, and sodium

chloride was added. The aqueous layer was extracted three times with ethyl ether. The organic layer was combined with the extracts, dried ($MgSO_4$), and evaporated. The remaining oil was distilled affording 0.92 g (37%) of 42, bp 85.88° at 0.25 torr. A pure sample of (42) was obtained by preparative gas chromatography: ir (film) 3150, 3000, 1560, 1130, 1020, 995, 910, 785 cm^{-1}; nmr ($CDCl_3$) 6.1-5.8 (m, 3H), 5.0-5.2 (m, 2H), 4.2-3.9 (m, 2H), 3.6-3.3 (m, 4H), 2.7 (dd, 2H, J=7), 1.8-1.3 (m, 6H), 1.10 and 1.20 (d, d, 3H, J=7); mass spectrum m/e 250 (M^+).

2-Furanacetaldehyde Diethyl Acetal (43)

A solution of n-butyllithium in tetrahydrofuran (200 ml) was prepared from n-butyl chloride (13.8 g, 150 mmole) and finely cut lithium metal (2.27 g, 320 mmole) at -25°. Furan (10.2 g, 150 mmole) was added and the solution was stirred at -15° for six hours. Bromoacetal (39) (29.6 g, 150 mmole) was added and the solution was stirred overnight at room temperature. The mixture was poured onto ice and sodium chloride was added. The layers were separated and the aqueous layer was extracted with ether. The ether extracts were combined with the organic layer, dried ($MgSO_4$), and evaporated. Vacuum distillation afforded 19.3 g (105 mmole, 70%) of (43): ir (film) 3120, 3000, 2920, 1580, 1120, 1050, 720 cm^{-1}; nmr ($CDCl_3$) 7.32 (d, 1H, J=1), 6.3 (d, d, 1H, J=3, 1), 4.8 (t, 1H, J=6), 3.8-3.3

(d q, 4H, J=6), 2.96 (d, 2H, J=6), 1.16 (t, 3H, J=6).

2-(2-Hydroxy-1-propyl)-5-(2-ethoxy-1-vinyl)-furan (42)

A solution of n-butyllithium in tetrahydrofuran (10 ml) was prepared from n-butyl chloride (4.14 g, 45 mmole) and lithium shavings (0.665 g, 95 mmole) at -25°. Compound (41) (2.76 g, 15 mmole) was introduced and the solution was stirred at -15° for six hours. Propylene oxide (0.87 g, 15 mmole) in tetrahydrofuran (1 ml) was added and the solution was allowed to warm to room temperature while stirring was continued overnight. The flask contents were poured over crushed ice and the two layers were separated. The aqueous layer, after saturation with sodium chloride, was extracted with ether and the ether extracts were added to the tetrahydrofuran layer. The combined organic layers were dried ($MgSO_4$), evaporated, and distilled in a Kugelrohr apparatus under vacuo affording 1.1 g (37%) of (44): ir (film) 3500, 3180, 3000, 1640, 1580, 1200, 1100, 1050, 930, 790 cm^{-1}; nmr ($CDCl_3$) 6.9 (d, 1H, J=14), 6.0 (d, 1H, J=3), 5.8 (d, 1H, J=3), 5.6 (d, 1H, J=14), 4.1 (m, 1H), 3.8 (q, 2H, J=6), 2.7 (d, 2H, J=6), 2.3 (s, 1H), 1.26 (t, 3H, J=6), 1.16 (d, 3H, J=6).

2-(2-Hydroxy-ethyl)-5-(2-hydroxy-propyl) furan (45)

A solution of n-butyllithium in tetrahydrofuran (180 ml) was

prepared from n-butyl chloride (16.5 g, 180 mmole) and lithium metal (2.62 g, 375 mmole) at -25°. Compound (22) (7.5 g, 59 mmole) was introduced and the solution was stirred at -15° for six hours. Ethylene oxide (7.9 g, 180 mmole) in tetrahydrofuran (10 ml) was added and the solution was stirred at -15° for two hours. The flask contents were allowed to warm to room temperature while stirring was continued overnight. The mixture was quenched with ice and the two layers were separated. The aqueous layer was extracted with ether, and the extracts were combined with the tetrahydrofuran layers. The combined organic layers were dried ($MgSO_4$), evaporated, and distilled affording 8.1 g (80%) of (45): ir (film) 3600-3400, 2950, 1560, 1050, 950, 790 cm^{-1}; nmr ($CDCl_3$) 5.96 (s, 2H), 4.05 (p, 1H), 3.75 (t, 2H, J=6), 3.06 (s, 2H), 2.75 (t, 2H, J=6), 2.65 (d, 2H, J=6), 1.16 (d, 3H, J=6).

2-(2-Hydroxy-ethyl)-5-(2-Hydroxy-propyl)tetrahydrofuran (48)

Diol (45) (2.7 g, 15.8 mmole) in 50 ml of anhydrous methanol was hydrogenated over rhodium on alumina at atmospheric pressure for four hours. The catalyst was filtered and the filtrate was evaporated to a clear liquid which, upon distillation, afforded 1.7 g (63%) of (50): bp 86-89° (0.15 torr), ir (film) 3500, 3000, 1160-1060, 950 cm^{-1}; nmr ($CDCl_3$) 4.0 (m, 3H), 3.75 (t, 2H, J=6), 3.5 (br s, 2H), 1.7 (m, 8H), 1.16 (d, 3H, J=6).

2-Ethylglyoxyl-5-(2-ethylglyoxyloxy-1-propyl)furan (49)

A mixture of 1-(2-furyl)isopropanol (126 mg, 1 mmole), ethyl chloroglyoxylate (300 mg, 2.1 mmole), and 2 ml of tetrachloroethylene was stirred for one hour at 0°. The mixture was cooled to -10° and stannic chloride (2.86 mg, 1.1 mmole) in 2 ml of tetrachloroethylene was added dropwise. Stirring was continued for 15 minutes. The mixture was quenched with iced-water and it was extracted repeatedly with methylene chloride. The organic layer was washed with dilute sodium carbonate, brine, and dried ($MgSO_4$). Evaporation of solvent left a dark viscous oil: ir (film) 1760 (s), 1740 (s), 1200 (s), 905 (s) cm^{-1}; nmr (CCl_4) 5.9 (br, s, 2), 5.2 (m, 1), 4.2 (q, 4, J=6), 2.9 (br, d, 2), 1.2-1.4 (m, 9).

2-α-[5-(2-Hydroxy-1-propyl)]furylglyoxylic acid (50)

Crude compound (49) (70 mg, 0.21 mmole) was stirred with an ethanolic potassium hydroxide solution for two hours at room temperature. Six N HCl was added dropwise until the solution turned acidic to litmus. The mixture was extracted with ether and the ether extracts were washed with water, dried ($MgSO_4$) and evaporated to yield 21 mg (0.1 mmole, 50%) of a yellow oil which was used without further purification (50): ir (film) 3500 (s), 1720 (m), 1260 (s), 110-1000 (br,

s) cm^{-1}; nmr ($CDCl_3$) 5.9 (br, s, 2), 3.2 (br, s, 2, exchangeable with D_2O), 2.5 (d, 2), 1.5-1.1 (br, d, 3).

2-Ethylglyoxyl-5-(2-ethylglyoxyloxypropyl)-tetrahydrofuran (51)

Crude compound (49) (500 mg) in 3 ml of absolute ethanol was hydrogenated over Rh/Al_2O_3 for four hours at atmospheric pressure. The catalyst was filtered and the solvent was evaporated under vacuum, leaving a dark glass-like substance assigned structure (51) on the basis of its ir and nmr spectra: ir (film) 1740 (s), 1755 (s), 1180 (s), 1050 (s) cm^{-1}; nmr (CCl_4) 5.0 (br, 1), 3.6-4.2 (br, 6), 1.35 (t, 6), 1.2 (d, 3).

2-Acetyl-5-(2-acetoxypropyl)-furan (54)

Alcohol (22) (630 mg, 5 mmole) and acetic anhydride (1.07 g, 11.5 mmole) were placed in a 10 ml flask equipped with reflux condenser fitted with a drying tube and a side arm fitted with a rubber septum. The reaction vessel was cooled to -25° with stirring. Boron trifluoride etherate was added at once by means of a syringe. The cold bath was removed after five minutes and stirring was continued for 20 minutes. The mixture was quenched with 6 ml of water and the contents of the flask were extracted with ether. The ether extracts were washed with saturated sodium carbonate, dried ($MgSO_4$) and

concentrated. The remaining liquid was distilled in an air-bath yielding 0.87 g (83%) of (54), bp 92-93° (0.1 torr): ir (film) 3120, 1730, 1680, 1580, 1500, 1250 cm^{-1}; nmr ($CDCl_3$) 7.12 (d, 1H, J=3), 6.25 (d, 1H, J=3), 5.2 (p, 1H), 2.96 (d, 2H, J=6), 2.4 (s, 3H), 2.0 s, 3H), 1.22 (d, 3H, J=6). Mass spectrum m/e 167.072 (M^+ - 43, calc for $C_9H_{11}O_3$ 167.071).

2-(1-Hydroxyethyl)-5-(2-acetoxypropyl)-furan (55)

To a slurry of sodium borohydride (0.54 g, 14 mmole) in 20 ml of a 1:1 mixture of glyme and t-butanol was added with stirring at 0° 1.99 g (9.5 mmole) of (54) in 10 ml of t-butanol. After stirring for three hours at room temperature the flask contents were poured into iced water. The mixture was extracted with ether, dried ($MgSO_4$), and distilled giving 1.6 g (80%) of alcohol (55) bp 92-93° at 0.15 torr: ir (film) 3500, 1740, 1560, 1360, 1250 cm^{-1}; nmr ($CDCl_3$) 6.1 (d, 1H, J-3), 5.98 (d, 1H, J=3), 5.15 (m, 1H), 4.8 (m, 1H), 2.82 (d, 2H, J=6), 2.3 (s, 1H), 1.98 (s, 3H), 1.46 (d, 3H, J=6), 1.20 (d, 3H, J=6).

2-(2-Acetoxypropyl)-5-(1-p-toluenesulfonylethyl)furan (56)

Alcohol (55) (212 mg, 1 mmole) was dissolved in dry pyridine (3 ml) at -20° and p-toluenesulfonyl chloride (380 mg, 2 mmole) was

added. The cold bath was removed and stirring was continued overnight. The flask contents were poured into iced water and the mixture was extracted with ether. The extracts were subsequently washed twice with aqueous copper sulfate, aqueous sodium bicarbonate, brine, dried ($MgSO_4$) and concentrated under vacuum at room temperature. The remaining liquid was shown to be a mixture of two components by thin layer chromatography. The major component was assigned structure (56) based on its infrared spectrum: 1725, 1580, 1380, 1180-1150 d, 890 cm^{-1}.

2-(1-Hydroxyethyl)-5-(2-acetoxypropyl)-tetrahydrofuran (59)

Compound (54) (420 mg, 2 mmole) in ethyl acetate (5 ml) was hydrogenated over 20 mg of rhodium over charcoal for 24 hours. After the catalyst was filtered, removal of the solvent left a clear liquid. Distillation in an air bath afforded 415 mg (96%) of alcohol (59): ir (film) 3500, 1740, 1380, 1250, 1050 (br) cm^{-1}; nmr ($CDCl_3$) 5.0 (m, 1H), 3.7 (m, 3H), 1.96 (s, 3H), 1.8-1.4 (m, 6H), 1.2 (d, 3H, J=6), 1.0 (d, 3H, J-6); mass spectrum m/e 171.101 (M^+-43, calcd for $C_9H_{15}O_3$ 171.102).

2-(2-Acetoxy-propyl)-5-(1-p-toluenesulfonyl-ethyl)-tetrahydrofuran (60)

Alcohol (59) (86 mg, 0.4 mmole) was dissolved in dry pyridine

(3 ml) at 0° and p-toluenesulfonyl chloride (161 mg, 0.8 mmole) was added. The cold bath was removed and stirring was continued overnight. The flask contents were poured into iced water and the mixture was extracted with ether. The extracts were washed with aqueous copper sulfate, aqueous sodium bicarbonate, brine, dried ($MgSO_4$), and concentrated under vacuum at room temperature. Thin layer chromatography on silica gel (1:1 cyclohexane:ethyl acetate) showed this oil to be a mixture of two components. The minor, slower moving substance was identified as starting alcohol (59). The second component was assigned structure (60): 3000, 1740, 1370, 1250, 1190-1180, 910 cm^{-1}.

2-(2-Acetoxy-1-propyl)-5-(1-mesyl-1-ethyl-tetrahydrofuran (61)

Compound (59) (320 mg, 1.47 mmole) in pyridine (3 ml) was cooled to -20°. Methanesulfonyl chloride (340 mg, 3 mmole) was added, and the solution was stirred for 16 hours. The flask contents were poured into 5 ml of iced water, and the mixture was extracted with ether. The ether extracts were washed with aqueous copper sulfate, brine, dried ($MgSO_4$), and concentrated under vacuum to give 430 mg (99%) of crude mesylate which showed a single spot on thin layer chromatography (silica, ethyl acetate): ir (film) 1740 (s), 1350 (s), 1250 (s), 1175 (s, d) cm^{-1}; nmr ($CDCl_3$) 5.1-4.4 (m, 2),

4.2-3.7 (m, 2), 3.03 and 3.06 (s, 3), 2.0 (s, 3), 1.3 (d, 3, J=7), 1.15 (d, 3, J=7).

Trimethylsilylcyanide

Trimethylchlorosilane (6.1 g, 55 mmole) and silver cyanide (2.5 g, 18.8 mmole) were stirred at room temperature for 72 hours. The flask contents were filtered through Celite and the precipitate was washed with 3-10 ml portions of anhydrous ether. The filtrate was distilled through a short Vigreaux column and the fraction boiling at 118-120° was collected. In this fashion, 1.55 g (80%) of title compound was obtained (lit. bp 117-118[47]): ir (film) 3200, 3000, 2200, 1600, 1245, 1050, 840 cm^{-1}.

2-(2-Acetoxy-1-propyl)-5-(1-cyano-1-siloxy-1-ethyl)-furan (63)

To a stirred solution of ketone (54) (450 mg, 2.1 mmole) and trimethylsilyl cyanide (213 mg, 2.1 mmole) was added a catalytic amount of anhydrous zinc iodide. Stirring for one hour afforded an 86% yield of title compound (determined by nmr), which was used in the next experiment without further purification: ir (film) 3000, 1750, 1250, 840 cm^{-1}; nmr ($CDCl_3$) 6.3 (d, 1H, J=3), 5.95 (d, 1H, J=3), 5.0 (m, 1H), 2.75 (d, 2H, J=6), 1.84 (s, 3H), 1.76 (s, 3H), 1.15 (d, 3H, J=6).

2-(2-Acetoxy-1-propyl)-5-(1-carboethoxy-1,2-epoxy-2-propyl)tetrahydrofuran (64)

A well stirred solution of ethyl bromoacetate (1.79 g, 94%, 10 mmole) and ketone (68) (1.05 g, 5 mmole) in dry tetrahydrofuran (10 ml) was cooled to -78° and was treated with lithium dicyclohexylamide (10 mmole; prepared from dicyclohexylamine (1.81 g, 10 mmole) in dry tetrahydrofuran (10 ml) with n-butyl lithium (10 mmole, 4.1 ml, 2.4 M hexane solution)) at 0° dropwise over a period of five minutes. The mixture was allowed to stand for one hour at -78°. Water was added, and the mixture was extracted repeatedly with ether. The ether layer was washed with aqueous copper sulfate (until the original color of the copper sulfate solution persisted), brine, dried ($MgSO_4$), and concentrated. The residue was distilled under vacuum to give 1.4 g (90%) of (64): nmr (CCl_4) 5.0 m, 1), 4.1 (q, 2, J=6), 3.7 (s, 1), 2.0 (s, 3), 1.3 (s, 3).

2-(2-Acetoxy-1-propyl)-5-(2-propenyl) tetrahydrofuran (67)

Sodium hydride (1.2 mmole as a 50% dispersion in mineral oil) in a 50-ml three-necked flask was washed with several portions of pentane to remove the mineral oil. The system was flushed with prepurified nitrogen while being warmed gently. Five ml of dimethyl sulfoxide (freshly distilled from calcium hydride) was introduced via a

syringe, and the mixture was heated at 70-75° until the evolution of hydrogen ceased. The resulting solution of methyl sulfinyl carbanion was cooled in an ice-water bath, and 430 mg of methyltriphenylphosphonium bromide in 5 ml of dimethyl sulfoxide was added. The resulting solution of the ylid was stirred at room temperature for ten minutes. A solution of ketone (68) (214 mg, 1 mmole) in 5 ml of tetrahydrofuran (freshly distilled from lithium aluminum hydride) was added. After standing at room temperature for 24 hours, the solution was poured into 20 ml of water and the product was extracted with pentane. The pale yellow extracts were combined, washed with 50 ml of a 1:1 water-dimethyl sulfoxide solution and then with 50 ml of water, dried ($MgSO_4$), and chromatographed on silica gel. Elution with dichloromethane afforded 110 mg (52%) of (67): ir (film) 3200, 1735, 1250, 990, 870 cm^{-1}; nmr (CCl_4) 5.0 (s, 1H), 4.8 (s, 1H), 4.3-3.5 (m, 2H), 2.1 (s, 3H), 1.8 (s, 3H), 1.25 (d, 3H, J=6; mass spectrum m/e 212.141 (parent, calcd for $C_{12}H_{20}O_3$ 212.142). In addition, 39 mg (22%) of (80) identical with material prepared as described below, was eluted (9:1 dichloromethane-ethyl acetate).

2-(2-Hydroxy-1-propyl-5-(2-propenyl) tetrahydrofuran (80)

Acetoxy olefin 67 (110 mg, 0.52 mmole) was stirred at room temperature overnight with 10 ml of a 5% methanolic solution of

sodium hydroxide. Water (10 ml) was added, and the resulting solution was extracted with ether. The ether extracts were combined, washed with 50% aqueous sodium chloride, and dried ($MgSO_4$). Distillation afforded 89 mg (100%) of 80: ir 3600, 3180, 1560, 1080, 890 cm^{-1}; nmr 5.0 (br, s, 1H), 4.8 (br s, 1H), 4.3 (m, 1H), 4.15 (m, 1H), 1.8 (s, 3H), 1.2 (d d, 3H, J=6); mass spectrum m/e 170.131 (parent, calcd for $C_{10}H_{18}O_2$ 170.134).

2-Acetyl-5-(2-acetoxy-1-propyl) tetrahydrofuran (68)

Jones' reagent (8N) was added dropwise to a solution of (59) (391 mg, 1.8 mmole) in 15 ml of acetone at 0° until the orange end point persisted. The reaction mixture was stirred an additional 20 minutes and excess oxidant was destroyed by addition of isopropyl alcohol. The solution was filtered and the chromium salts were dissolved in water. The aqueous phase was saturated with sodium chloride and was extracted three times with ether. The filtrate was combined with the ether extracts and the organic layer was washed once with aqueous sodium bicarbonate, dried ($MgSO_4$), and concentrated in vacuo. The remaining liquid was distilled yielding 381 mg (98%) of ketone 68; ir (film) 1735 (s), 1710 (s), 1240 (s) cm^{-1}; nmr ($CDCl_3$) 5.0 (m, 1), 4.1 (m, 2), 2.1 (s, 3), 1.95 (s, 3), 1.23 (d, 3,

J=6). Mass spectrum m/e 214.121 (Parent, calcd for $C_{11}H_{18}O_4$ 214.115).

2-(2-Acetoxy-1-propyl)-5-(1,2-epoxy-2-propyl)tetrahydrofuran (69)

A 2.0 M solution of methyl sulfinyl carbanion was prepared from 421 mg of sodium hydride (10 mmole, 57% dispersion in mineral oil) in 5 ml dry dimethyl sulfoxide (distilled from calcium hydride) by heating to 70-75° with stirring until evolution of hydrogen ceased. The solution was cooled to room temperature, diluted with 5 ml dry tetrahydrofuran, and then cooled in a salt-ice bath. With stirring, a solution of trimethylsulfonium iodide (2.0 g, 10 mmole) in dimethyl sulfoxide (10 ml) was added over a period of about 3 minutes. After the addition of the salt was complete, the mixture was stirred for one minute. Ketone (68) (1.08 g, 5 mmole) in dimethyl sulfoxide (2 ml) was added at a rapid rate. Stirring was continued at salt-ice bath temperature for ten minutes and then for 60 minutes with the bath removed. The reaction mixture was diluted with 15 ml of distilled water and was extracted repeatedly with ether. The combined ether extract was washed with water, dried (K_2CO_3), and concentrated under vacuum to give a yellow oil. Distillation at reduced pressure afforded 800 mg (70%) of 69: ir (film) 1740 (s), 1250 (s), 1100-1000 (s) cm^{-1}; nmr (CCl_4) 5.0 (b, 1), 3.8 (b, 3), 2.5 (s, 2), 1.95 (s, 3), 1.25 (s, 3).

2-(2-Tetrahydropyranyloxy-1-propyl)-5-acetyltetrahydrofuran (73)

A solution of (79) (1.03 g, 5.66 mmole), dihydropyran (1.43 g, 17 mmole), and phosphorous oxychloride (0.1 ml) in methylene chloride (60 ml) was stirred for 3.5 hours in an ice bath. The solution was washed with 10% aqueous sodium carbonate, water, and brine. Evaporation of the solvent left an oil which was distilled under vacuum yielding 1.2 g (83%) of 73: ir (film) 1725 (s), 1070 (s), 1030 (s) cm^{-1}; nmr (CCl_4) 4.55 (br, 1), 4.2-3.2 (br, 5), 2.02 (s, 3), 1.6-1.25 (br, 6).

Trimethylsulfonium iodide

Equimolar amounts of dimethyl sulfide and methyl iodide were mixed and allowed to stand at room temperature overnight. The resulting solid white cake of the sulfonium salt was crushed and recrystallized from 95% ethanol. The recrystallized material was dried at 110° (0.05 torr) for 24 hours.

Methoxymethylenetriphenylphosphonium chloride

Triphenylphosphine (50 g, 0.19 mol) and chloromethyl methyl ether (16.1 g, 0.20 mol) were heated for 72 hours at 50° in 120 ml of anhydrous benzene. The solid obtained after filtration was recrystallized from chloroform-ethyl acetate and dried over P_2O_5 at 0.1 torr

for 24 hours, yielding 55 g (0.158 mol, 83%) of title compound, mp 195-200°, lit. 200-202°.

2-(2-Tetrahydropyranyloxy-1-propyl)-5-(1,2-epoxy-2-propyl)-1-tetrahydrofuran (74)

A 2.0 M solution of methyl sulfinyl carbanion was prepared from 252 mg sodium hydride (6 mmole, 67% dispersion in mineral oil) in 3 ml of dry dimethyl sulfoxide (distilled from calcium hydride) by heating to 70-75° with stirring until evolution of hydrogen ceased. The solution was cooled to room temperature, diluted with 3 ml dry tetrahydrofuran, and then cooled in a salt-ice bath. With stirring, a solution of trimethylsulfonium iodide (1.2 g, 6 mmole) in dimethyl sulfoxide (5 ml) was added over a period of about 3 minutes. After the addition of the salt was complete, the mixture was stirred for one minute longer. Ketone (73) (720 mg, 2.8 mmole) in dimethyl sulfoxide (1 ml) was added at a rapid rate. Stirring was continued at salt-ice bath temperature for ten minutes and then for 60 minutes with the bath removed. The reaction mixture was diluted with 15 ml of distilled water and was repeatedly extracted with ether. The combined ether extract was washed with water, dried (K_2CO_3), and concentrated under vacuum to give a yellow oil. Distillation under vacuum afforded 590 mg (75%) of 74: ir (film) 2980 (s), 1120 (s), 1070 (s), 1030 (s), 870 (m) cm^{-1} nmr CCl_4) 4.6 (br, 1), 4.0-3.2 (br, 6), 2.4 (d, 1, J=1), 1.25 (s, 3), 1.1 (d, 3, J=6).

2-(1-Propenyl)-5-acetylfuran (76)

A 2.0 M solution of methyl sulfinyl carbanion was prepared from 1.2 g of sodium hydride (10 mmole, 57% dispersion in mineral oil) in 13 ml of dry dimethyl sulfoxide by heating to 70-75° with stirring until evolution of hydrogen ceased. The solution was cooled to room temperature, diluted with 15 ml of tetrahydrofuran, and then cooled in a salt-ice bath. With stirring, a solution of trimethylsulfonium iodide (5.1 g, 25 mmole) in dimethyl sulfoxide (25 ml), was added over a period of three minutes. After the addition of the salt was complete, the mixture was stirred for one minute. A solution of 54 (1.05 g, 5 mmole) in dimethyl sulfoxide (3 ml) was added at rapid rate. Stirring was continued at salt-ice temperature for ten minutes, and then for 60 minutes with the ice bath removed. The reaction mixture was diluted with 60 ml of distilled water, and extracted repeatedly with ether. The combined ether extract was washed with water, dried (K_2CO_3), and concentrated under vacuum to give 0.52 g (70%) of ketone (76): nmr 7.2 (d, 1H, J=3), 6.5-6.1 (m, 3H), 2.4 (s, 3H0, 1.86 (d, 3H, J=4).

2-(2-Hydroxy-1-propyl)-5-(1-hydroxy-2-propyl)tetrahydrofuran (77)

A solution of 89 mg (0.5 mmole) of 80 in 3 ml of tetrahydrofuran was added dropwise to a cooled 1 M solution of diborane (2 ml) in

tetrahydrofuran. The reaction mixture was stirred for 1 hr at 0°, then for 2 hr at room temperature. Excess diborane was decomposed by dropwise addition of water (1 ml). A 3 M solution of sodium hydroxide (3 ml) was then added, followed by dropwise addition of 30% hydrogen peroxide (3 ml). The reaction mixture was stirred for 1 hr at room temperature and potassium carbonate was then added. The layers were separated, the aqueous solution was extracted three times with 25 ml of ether, and the combined organic layers were washed with water, dried ($MgSO_4$) and concentrated. Distillation afforded 75 mg (80%) of 77, bp 82-84° (0.01 torr), lit.[5] bp 80° (0.01 torr): ir (film): 3500, 2980, 1100 br, 950 cm^{-1}; nmr ($CDCl_3$) 4.2-3.8 (m, 3H), 3.6 (d d, 2H, J=6), 3.2 (br s, 2H), 1.6 (m, 7H), 1.18 (d, 3H, J=6), 0.95 (d, 3H, J=6).

2-Acetyl-5-(2-hydroxy-1-propyl) tetrahydrofuran (79)

Compound 68 (216 mg, 1 mmole) was stirred in 10 ml of 5% methanolic potassium hydroxide at room temperature for 20 hours. The solution was diluted to 50 ml with distilled water, saturated with sodium chloride, and extracted with ether. The ether extracts were dried ($MgSO_4$), evaporated, and distilled under vacuum to yield 105 mg (61%) of 79: ir (film) 3600, 3000, 1725, 1360, 1080 cm^{-1}; nmr $CDCl_3$) 4.1 (m, 3), 3.4 (s, 1), 2.14 (s, 3), 1.15 (d, 3, J=6); mass spectrum m/e 172.109 (M^+, calcd. for $C_9H_{16}O_3$ 172.109).

2-(5-Acetonyltetrahydrofuryl)
propionic acid (78a & 78b)

A solution of 120 mg (0.7 mmole) of 80 in 5 ml of tetrahydrofuran was added dropwise to a cooled 1 M solution of diborane (3 ml) in tetrahydrofuran. The reaction mixture was stirred for one hour at 0°, then two hours at room temperature. Jones' reagent was added dropwise with caution until the solution remained orange. The reaction mixture was stirred for 30 minutes and excess oxidant was destroyed by the addition of isopropyl alcohol. The mixture was concentrated under vacuum, filtered through Celite, and the filter cake rinsed with 15 ml of chloroform. The remaining solution was washed with 50% aqueous brine, and dried ($MgSO_4$). Evaporation of the solvent left 121 mg (89%) of a mixture of 78a and 78b.

Methyl 2-(5-acetonyltetrahydrofuryl)
propionate (17a & 17b)

The mixture of ketoacids 78a and 78b (121 mg, 0.62 mmole) in 10 ml of dry methanol and 0.4 ml of boron trifluoride etherate were stirred at room temperature for 16 hours. The reaction mixture was poured into 20 ml of water, saturated with sodium chloride, and extracted with 50 ml of chloroform. The extracts were washed with dilute sodium bicarbonate, 50% brine, and dried ($MgSO_4$). Vacuum distillation at 110° afforded 131 mg (99%) of a 2:1 mixture of 17a and

17b: ir 3000, 1730, 1710, 1100, 1050 cm^{-1}; nmr (CCl_4) 4.1 (m, 3H), 3.64 (s, 3H), 2.5 (m, 2H), 2.11 (s, 3), 1.20 and 1.10 (d, 3H, J=6); mass spectrum 214.108 (parent, calcd $C_{11}H_{18}O_4$ 214.106).

Methyl 8-epi-nonactate (81b)

A solution of ketoacid 78b (75 mg, 0.37 mmole) in 10 ml of dry tetrahydrofuran was cooled in an ice bath and lithium tri-sec-butylborohydride (800 μl of 1 M solution, 0.80 mmole) was added. After 6 hr at 0°, the mixture was quenched with 5 ml of water, acidified with 5% aqueous hydrochloric acid, and extracted with three 10-ml portions of ether. The ether extracts were dried ($MgSO_4$), filtered, and concentrated. A solution of the residue in 5 ml of methanol was treated with four drops of boron trifluoride etherate, and the solution was stirred overnight at room temperature. Concentration of the methanol solution gave a residue which was dissolved in 15 ml of methylene chloride and washed once with water, dried ($MgSO_4$), filtered and concentrated. Chromatography on silica gel with 2:1 pentane:ethyl acetate gave 30.2 mg (41%) of 82b: ir (film) 3509, 1739 cm^{-1}; nmr (CCl_4) 3.98 (3H, m), 3.66 (3H, s), 2.94 (1H, broad s), 2.52 (1H, p), 2.02 (2H, m), 1.56 (4H, m), 1.10 (3H, d, J=7), 1.08 (3H, d, J=7).

Methyl 8-benzoyloxynonactate (83)

A solution of methyl 8-epi-nonactate 82b (36.7 mg, 0.17 mmole) in 2 ml of dry tetrahydrofuran was stirred under nitrogen with triphenyphosphine (91.9 mg, 0.351 mmole), and benzoic acid (46.0 mg, 0.37 mmole). Diethylazodicarboxylate (59.2 mg, 0.34 mmole) was slowly added to the solution. After stirring overnight, the solution was concentrated and the residue was chromatographed on Florisil (10 g). Elution with benzene gave benzoate ester 83 (89.5%): ir (CCl_4) 1739 and 1718 cm^{-1}; nmr (CCl_4) 7.97 (2H, m), 7.40 (3H, m), 5.17 (1H, s, J=6), 4.0 (2H, m), 3.62 (3H, s), 2.46 (1H, p, J=7), 1.9 (4H, m), 1.6 (2H, m), 1.36 (3H, d, J-7), 1.07 (3H, d, J=7).

Methyl nonactate (82a)

Benzoate ester 83 (48.7 mg, 0.15 mmole) was stirred in 10 ml of dry methanol containing sodium methoxide (0.87 mmole). After 18 hours at room temperature, the solution was concentrated, mixed with water, and acidified with 5% equaous hydrochloric acid. The mixture was extracted with three portions of methylene chloride, and the combined extracts were dried ($MgSO_4$), filtered, and concentrated giving 32 mg (100%) of methyl nonactate 82a: ir (CCl_4) 3509, 1736 cm^{-1}; nmr (CCl_4) 3.97 (3H, m), 3.63 (3H, s), 2.59 (1H, s), 2.49 (1H, p), 1.99 (2H, m), 1.59 (4H, m), 1.12 (3H, d, J=7), 1.09 (3H, d, J=7).

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