

## SYNTHESIS OF REDUCED FURANS AND 3(2H)-DIHYDROFURANONES WITH MANIPULABLE FUNCTIONALITY

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Abstract - Recent advances in the synthesis of functionalized, naturally occurring or synthetically useful reduced furans and 3(2H)-dihydrofuranones are reviewed.

## INTRODUCTION

In the last several years, many interesting reduced furans and furanones have appeared in the chemical literature. Although several methods have been employed to synthesize simple reduced furans, functionalized derivatives require more selective conditions and it is this methodology which will be reviewed. The discussion will be divided as follows:

## I. SYNTHESIS OF FUNCTIONALIZED TETRAHYDROFURANS

## 1. CYCLIZATION METHODS

- 1.1 Acid-catalyzed cyclizations
- 1.2 Halogen-induced cyclizations
- 1.3 Cyclizations via oxymercuration - demercuration
- 1.4 Organo-selenium induced cyclizations
- 1.5 Cyclizations via epoxide ring opening
- 1.6 Cyclizations via Michael additions
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## II. SYNTHESIS OF FUNCTIONALIZED 2,5-DIHYDROFURANS

## 1. CYCLIZATION ROUTES

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- 1.3 Addition/cyclization routes

## 2. REDUCTIVE METHODS

## 3. CLAISEN REARRANGEMENT OF FURANOID GLYCAL

4. TRANSFORMATIONS OF CARBOHYDRATE PRECURSORS

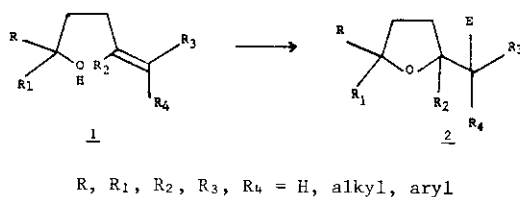
III. SYNTHESIS OF FUNCTIONALIZED 3(2H)-DIHYDROFURANONES

1. HYDRATION OF ACETYLENIC DIOLS
2. NAZAROV-TYPE CYCLIZATIONS
3. INTRAMOLECULAR MICHAEL-DIECKMANN CONDENSATIONS
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5. INTRAMOLECULAR CYCLIZATION OF UNSATURATED ALCOHOLS

I. SYNTHESIS OF FUNCTIONALIZED TETRAHYDROFURANS

1. CYCLIZATION METHODS

The most common approach to tetrahydrofurans involves an electrophilic process (Scheme 1).

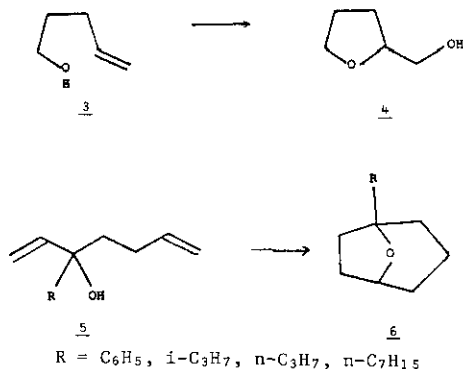


Scheme 1

Treatment of 4-pentenol derivative 1 with an electrophilic reagent  $E^+$ , followed by intramolecular interception of the resultant intermediate by the hydroxyl group, affords the corresponding tetrahydrofuran (2). In addition to acids ( $E^+ = H^+$ ), the most commonly used electrophiles for this cyclization include oxygen,<sup>1,2</sup> halogen,<sup>3,4</sup> mercury,<sup>5</sup> and selenium<sup>6-8</sup> reagents.

1.1 Acid-Catalyzed Cyclizations

A simple example of an acid-catalyzed cyclization is the conversion of 4-penten-1-ol (3) to tetrahydrofurfuryl alcohol 4 with sulfuric acid<sup>9,10</sup> (Scheme 2).

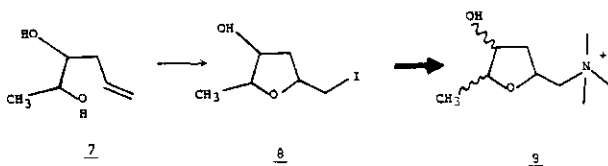


Scheme 2

A general preparative method for the synthesis of bicyclic ethers possessing a tetrahydrofuran ring is based on a variation of this process.<sup>11</sup> Treatment of the dienols 5 with a mixture of formic acid and 70% sulfuric acid at room temperature gave 60 - 70% yields of the corresponding ethers (6) (Scheme 2). These reactions are severely limited in scope, however, because of the highly acidic reaction conditions required for cyclization.

### 1.2 Halogen-Induced Cyclizations

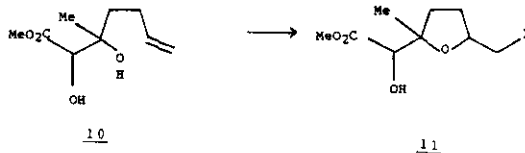
Reaction of diol 7 with iodine in an aqueous methanol solution effected iodoetherification to produce iodide 8 which was further transformed into an isomeric mixture of muscarines (9)<sup>12</sup> (Scheme 3).



Scheme 3

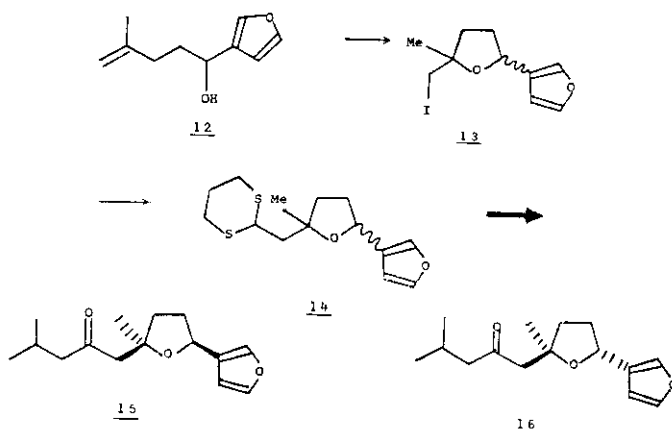
The same research group used this process as a general route to 5-substituted-2-dimethylaminoalkyl tetrahydrofurans.<sup>13</sup>

Similarly, reaction of glycolate 10 with iodine afforded the interesting functionalized tetrahydrofuran 11<sup>14</sup> (Scheme 4).



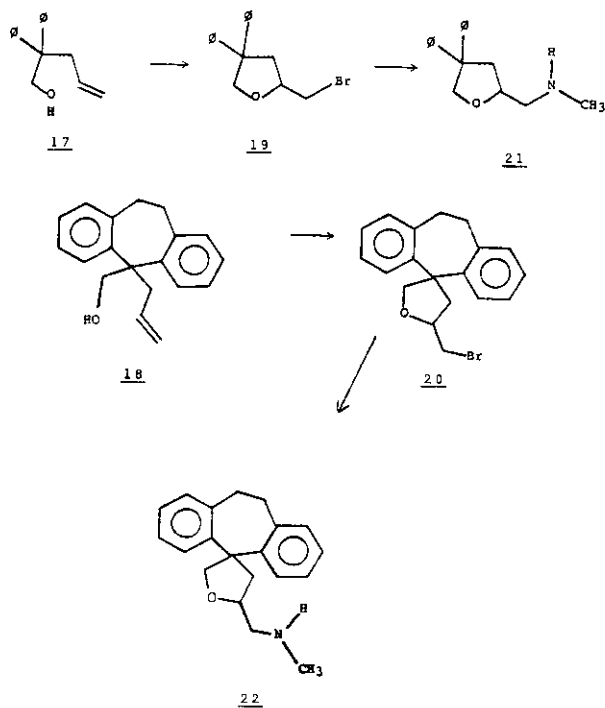
Scheme 4

N-Iodosuccinimide (NIS) is a precursor for the generation of electrophilic iodine under mild conditions. This reagent was used by Kondo and Matsumoto<sup>15</sup> in the total synthesis of (+)-ipomeamarone (15) and (+)-epiipomeamarone (16). Both 15 and epimer 16 were isolated from *Myoporium deserti*,<sup>16</sup> a well-known phytoalexin which exists in mold-damaged sweet potatoes.<sup>17</sup> Thus, when alcohol 12 was stirred in the dark with an equimolar amount of N-iodosuccinimide and sodium bicarbonate at room temperature for one and a half hours, oxidative cyclization occurred, giving a stereoisomeric mixture of iodides (13) in 94% yield. Reaction of 13 with the anion of 1,3-dithiane afforded adduct 14 in 54% yield. After lithiation of dithiane 14 with n-butyllithium and alkylation of the resultant anion with isobutyl chloride, removal of the dithiane functionality with a mixture of silver nitrate and N-chlorosuccinimide in aqueous acetonitrile gave 15 and 16 in 84% overall yield (Scheme 5).



Scheme 5

A similar cyclization process employing bromine in place of iodine was used to prepare the potent antidepressants 21 and 22<sup>18-20</sup> (Scheme 6).

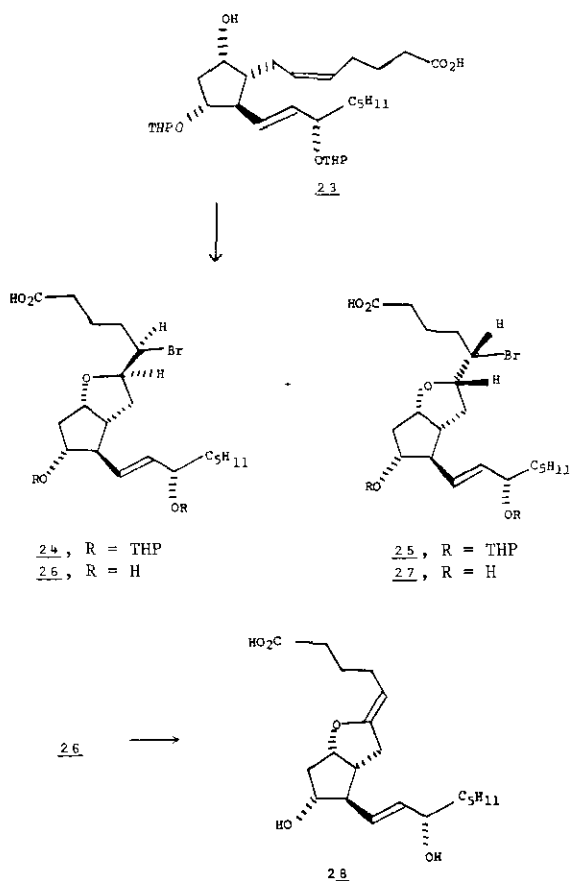


Scheme 6

Treatment of unsaturated alcohols 17 and 18, at room temperature, with a solution of pyridine/bromine in carbon tetrachloride gave bromides 19 and 20, in 36% and 85% yields, respectively. Reaction of the bromides in dimethyl sulfoxide solution with methylamine afforded 21 and 22 in 62%

and 68% yields, respectively. The stereochemical aspects of these cyclizations have been examined by Monkovic, et al.<sup>20</sup>

Haloetherification with *N*-bromosuccinimide (NBS) is the most general and most useful route to cyclic bromoethers. These bromoethers can be reduced to saturated cyclic systems or oxidized to the analogous unsaturated compounds by base-catalyzed elimination. An important feature of the latter reaction is its selectivity, the elimination proceeding towards the oxygen atom of the tetrahydrofuran ring to afford enol ethers by E<sub>2</sub> *trans* mechanism. This reaction has considerable utility in the synthesis of many natural products as illustrated by Corey's synthesis of prostacyclin (PGI,  
28)<sup>21</sup> (Scheme 7).

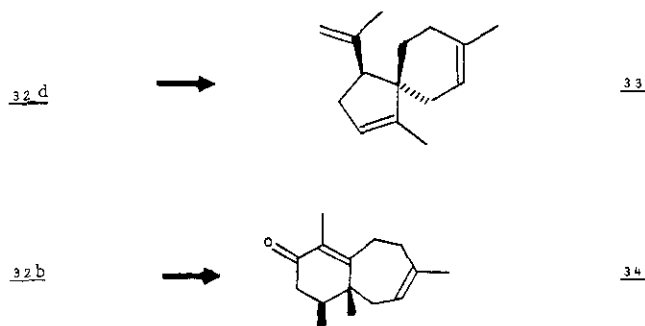
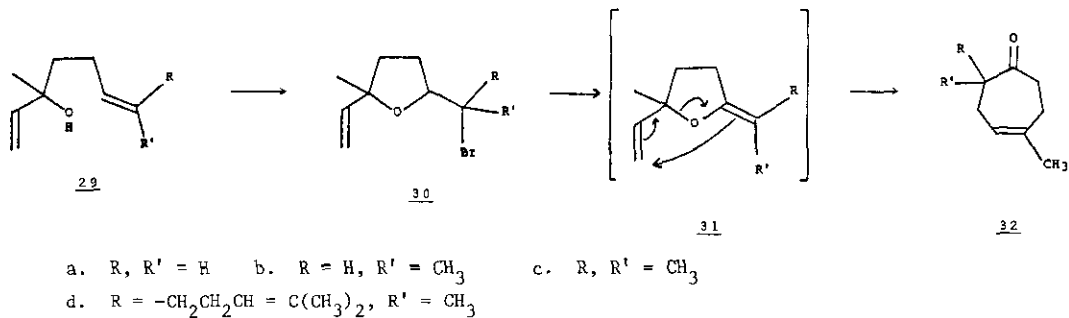


Scheme 7

Treatment of the 11,15-bis-tetrahydropyranyl ether of prostaglandin F<sub>2α</sub> (**23**) in tetrahydrofuran-chloroform solution with 1.1 equivalent of NBS at 23° for one hour afforded diastereomeric bromoethers **24** and **25**. Removal of the tetrahydropyranyl protecting groups with a mixture of acetic acid, water, and tetrahydrofuran at 45° for four hours allowed separation of the dihydroxy bromo-

ethers 26 and 27, which were formed in a 3:1 ratio in 81% overall yield. Dehydrobromination of bromoether 26 with excess potassium *tert*-butoxide in *tert*-butyl alcohol at 45° for one and a half hours followed by esterification of the acid function with diazomethane afforded the methyl ester of 28.

The sequence bromoetherification - dehydrobromination has been widely used to prepare both synthetic and naturally occurring 4-cycloheptenone derivatives (Scheme 8).



Scheme 8

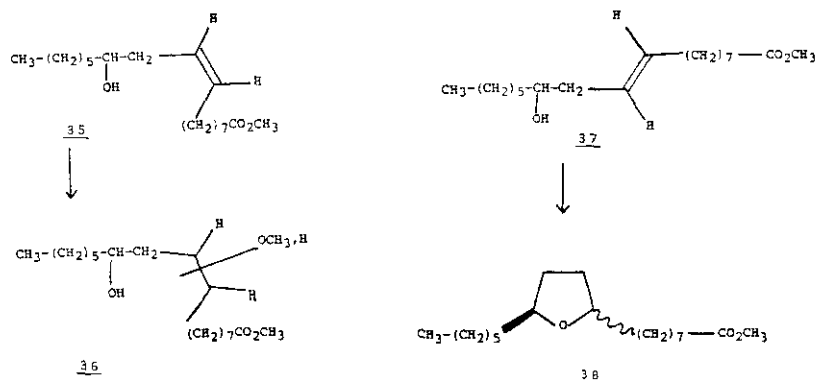
Hence, treatment of unsaturated alcohols 29 a-d with N-bromosuccinimide in carbon tetrachloride or methylene chloride at 0° to 25° gives practically quantitative yields of the corresponding bromoethers 30 a-d. Subsequent dehydrobromination of these materials in refluxing collidine generates the intermediate allyl vinyl ethers (31 a-d), which undergo a [3.3] sigmatropic rearrangement to produce cycloheptenones 32 a-d.

In this manner, karahanaenone (32 c) was prepared from linalool (29 c).<sup>22</sup> By further synthetic elaboration, Demole, et al.<sup>23,24</sup> converted cycloheptenone 32 d into  $\beta$ -acoratriene (33), and Gonzalez and co-workers<sup>25</sup> transformed cycloheptenone 32 b into perforenone (34).

Bromoetherification may also be effected with N,N-dibromodimethylhydantoin. This reagent was used to prepare prostacyclin analogs.<sup>26</sup> 2,4,4,6-Tetrabromocyclohexadienone (TBCO)<sup>27</sup> and *tert*-butyl hypobromite<sup>4</sup> also serve as efficient sources of bromonium ions.

## 1.3 Cyclization via Oxymercuration-Demercuration

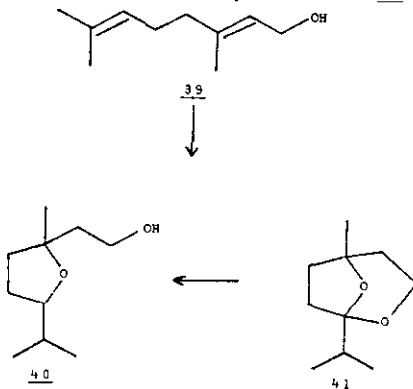
Another relatively mild method for the synthesis of tetrahydrofurans employs an intramolecular oxymercuration-demercuration process. Gunstone and Inglis<sup>28,29</sup> subjected a series of fatty acid esters to the oxymercuration-demercuration procedure and obtained some interesting results (Scheme 9).



Scheme 9

Treatment of the cis isomer of methyl ricinoleate (35) with mercury (II) acetate in methanol at room temperature for two to four days, followed by demercuration with sodium borohydride at 0°, primarily afforded products resulting from 1,2-addition to the olefin (36). However, under the same conditions, the trans isomer of methyl ricinoleate (37) gave a nearly quantitative yield of a cis, trans-mixture of the tetrahydrofuran derivative (38). In a similar manner, methyl cis- or trans-9-hydroxyoctadec-12-enoates produced nearly quantitative yields of the same isomeric cis, trans-tetrahydrofuran mixture (38). A related study<sup>30</sup> showed analogous results. This procedure has been used for the identification of various unsaturated fatty acid derivatives.<sup>31</sup>

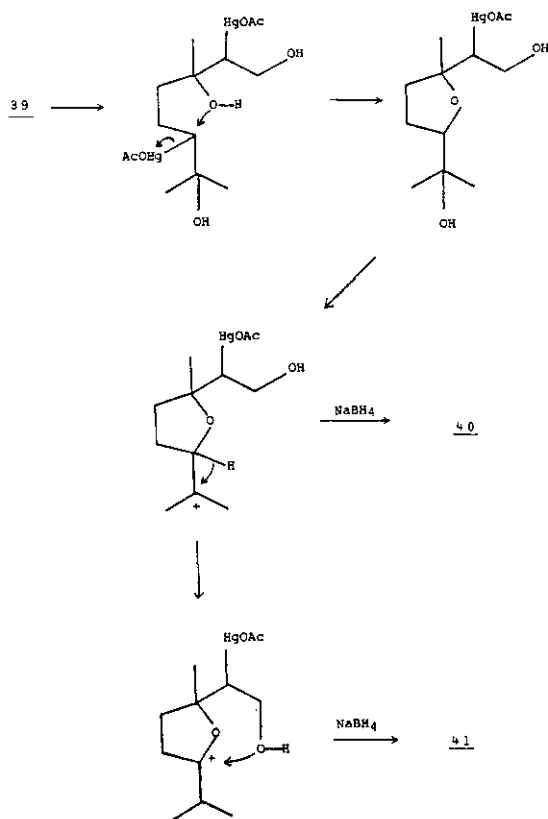
In a study of the oxymercuration of terpene alcohols, Brieger and Burrows<sup>32</sup> treated geraniol (39) with mercuric acetate and reduced the intermediate organomercurial with sodium borohydride. This process afforded tetrahydrofuran (40) and bicyclic ketal (41) in a 2:1 ratio in 55% yield (Scheme 10).



Scheme 10

Interestingly, 40 can be obtained quantitatively from 41 by treatment of the latter compound with a mixture of lithium aluminum hydride and aluminum chloride. Under the same reaction conditions, farnesol and linalool were resistant to the oxymercuration-demercuration procedure.

The products formed by the oxymercuration-reduction process may be rationalized mechanistically as arising via solvolysis of the presumed intermediate organomercury adduct (Scheme 11).

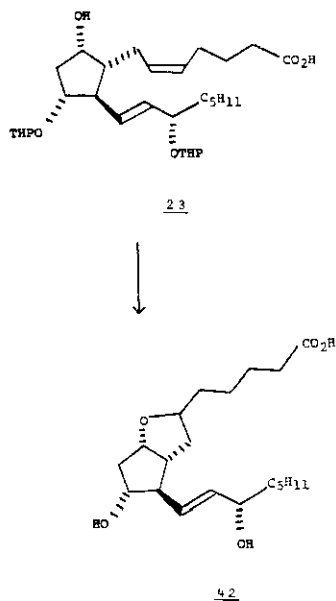


Scheme 11

A novel synthesis of 5,6-dehydroprostacyclin (42) also utilized an intramolecular version of the oxymercuration-demercuration process<sup>21</sup> (Scheme 12).

Reaction of the 11,15-bis-tetrahydropyranyl ether of prostaglandin  $\text{F}_{2\alpha}$  (23) with 1.2 equivalents of mercuric trifluoroacetate in a tetrahydrofuran-calcium carbonate mixture at room temperature for one hour, followed by reduction of the intermediate organomercurial with excess sodium borohydride at  $-20^\circ$  and removal of the alcohol protecting groups generated a C-6 epimeric mixture of 5,6-dihydroprostacyclin (42) in 90% overall yield.

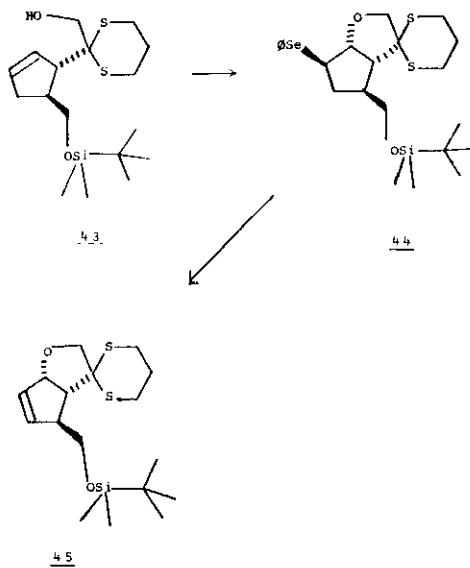




Scheme 12

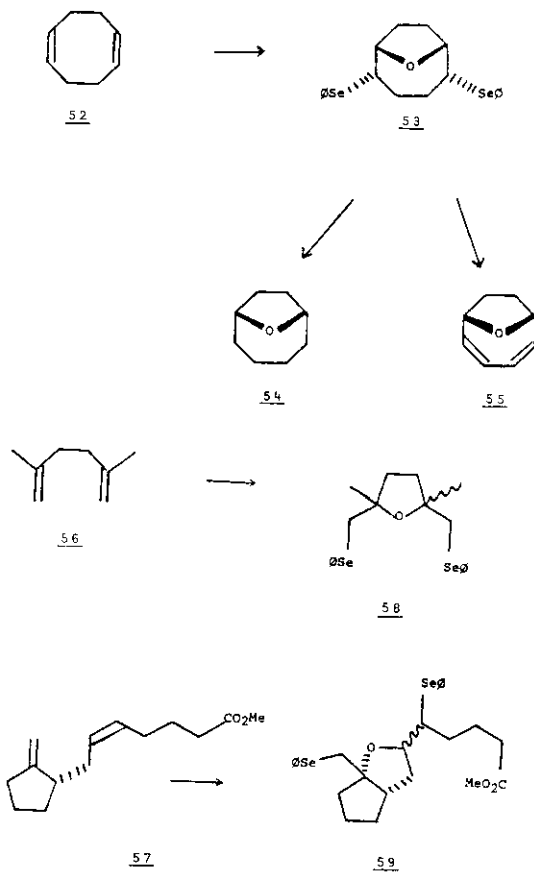
1.4 Organo-Selenium Induced Cyclizations

Very mild procedures for preparing functionalized tetrahydrofuran ring systems using phenylselenenyl chloride (PhSeCl) have recently been described.<sup>6-8</sup> The method is applicable to sensitive systems as illustrated for the synthesis of the potential prostaglandin precursor (45)<sup>6</sup> (Scheme 13).



Scheme 13



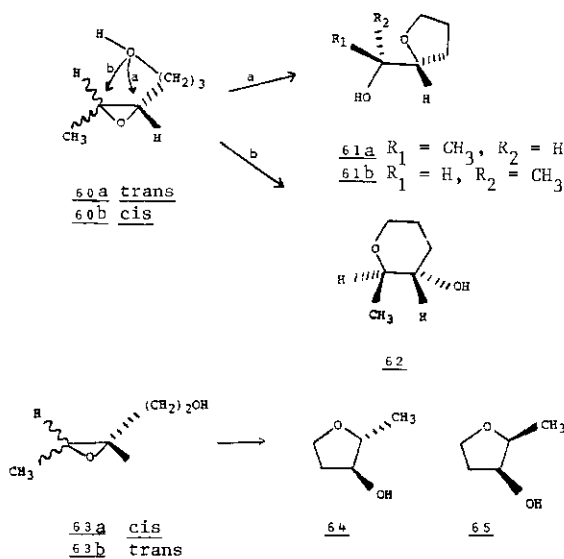


Scheme 15

natively, oxidation, utilizing ozone in methylene chloride at  $-78^{\circ}$ , followed by *syn* elimination of the derived selenoxide, furnished dienic ether **55** in 73% yield. In an analogous fashion, reaction of "PhSeOH" with 1,5-dienes **56** and **57** generated diselenide tetrahydrofurans **58** and **59** in 59% and 30% yield, respectively.

#### 1.5 Cyclizations via Epoxide Ring Opening

The synthesis of functionalized tetrahydrofurans *via* electrophilic oxygen reagents which produce epoxide intermediates has received much attention. Model studies by Coxon et al.<sup>37</sup> (Scheme 16) showed that reaction of *trans*-4,5-epoxyhexan-1-ol (**60 a**) with boron trifluoride etherate in ether at room temperature gave tetrahydrofuran **61 a** in 84% yield *via* path a and the *trans*-tetrahydropyran **62** in 16% yield *via* path b. The stereochemistry of both products was shown to be the result of inversion of configuration at the site of hydroxyl attack. The isomeric *cis*-epoxide (**60 b**)



Scheme 16

gave the tetrahydrofuran 61 b as the sole product in 97% yield.

The reaction of cis- or trans-3,4-epoxypentanol (63 a,b) with the same reagent system, however, gave results which contrasted with those for the rearrangement of epoxides 60 a,b, producing trans-tetrahydrofuran (64) and cis-tetrahydrofuran (65) in an 11:1 ratio regardless of epoxide geometry.

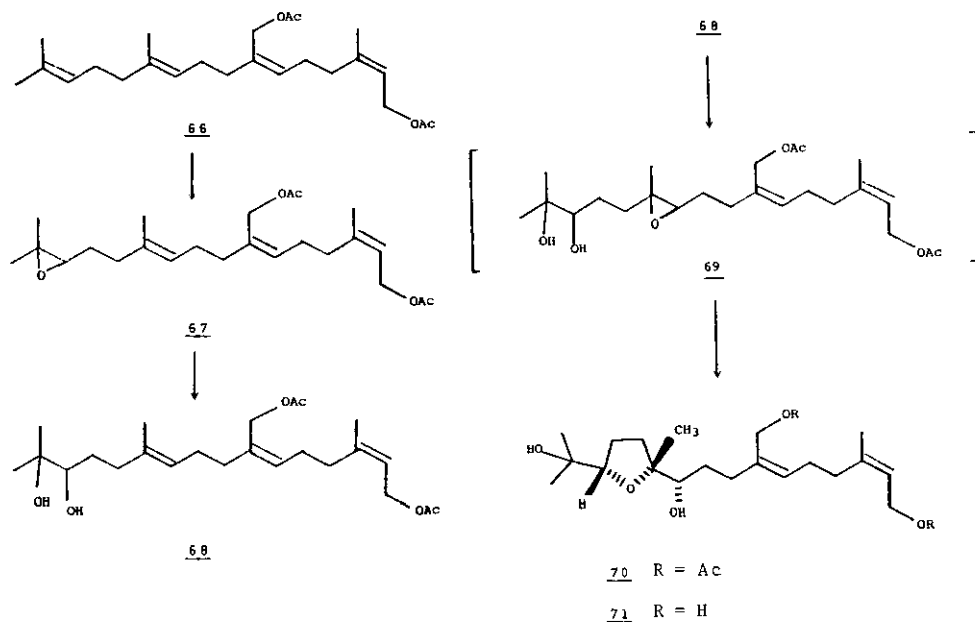
Coxon et al.<sup>38,39</sup> also examined the acid-catalyzed rearrangement of cis- and trans-1-acetoxy-3,4-epoxypentanes and 1-acetoxy-4,5-epoxyhexanes and observed that the corresponding tetrahydrofurans were formed with retention of configuration at the epoxide carbon atoms.

In related work, the biomimetic synthesis of ligantrol (71), a linear polyoxygenated diterpene from Liatris elegans,<sup>40</sup> was achieved by Takahashi et al.<sup>41</sup> using an epoxide intermediate (Scheme 17).

Reaction of 18-hydroxygeranylnerol diacetate (66) with *m*-chloroperbenzoic acid generated terminal epoxide 67 which was then hydrolyzed to the corresponding diol (68) with perchloric acid in aqueous tetrahydrofuran. Treatment of diol 68 with *m*-chloroperbenzoic acid produced a mixture of ligantrol acetate (70) along with an epimer, via the intermediacy of epoxide 69. Hydrolysis of 70 in methanolic potassium carbonate afforded ligantrol (71).

Other examples of this type of synthetic strategy in the literature include the synthesis of the  $\alpha$ -bisabolol oxides A and B<sup>42</sup> and linalool oxides A and B<sup>43-46</sup> using epoxide intermediates.

One of the most impressive applications of epoxides to form functionalized tetrahydrofurans is evident in the elegant investigations which led to the total synthesis of the ionophore lalacaloid



Scheme 17

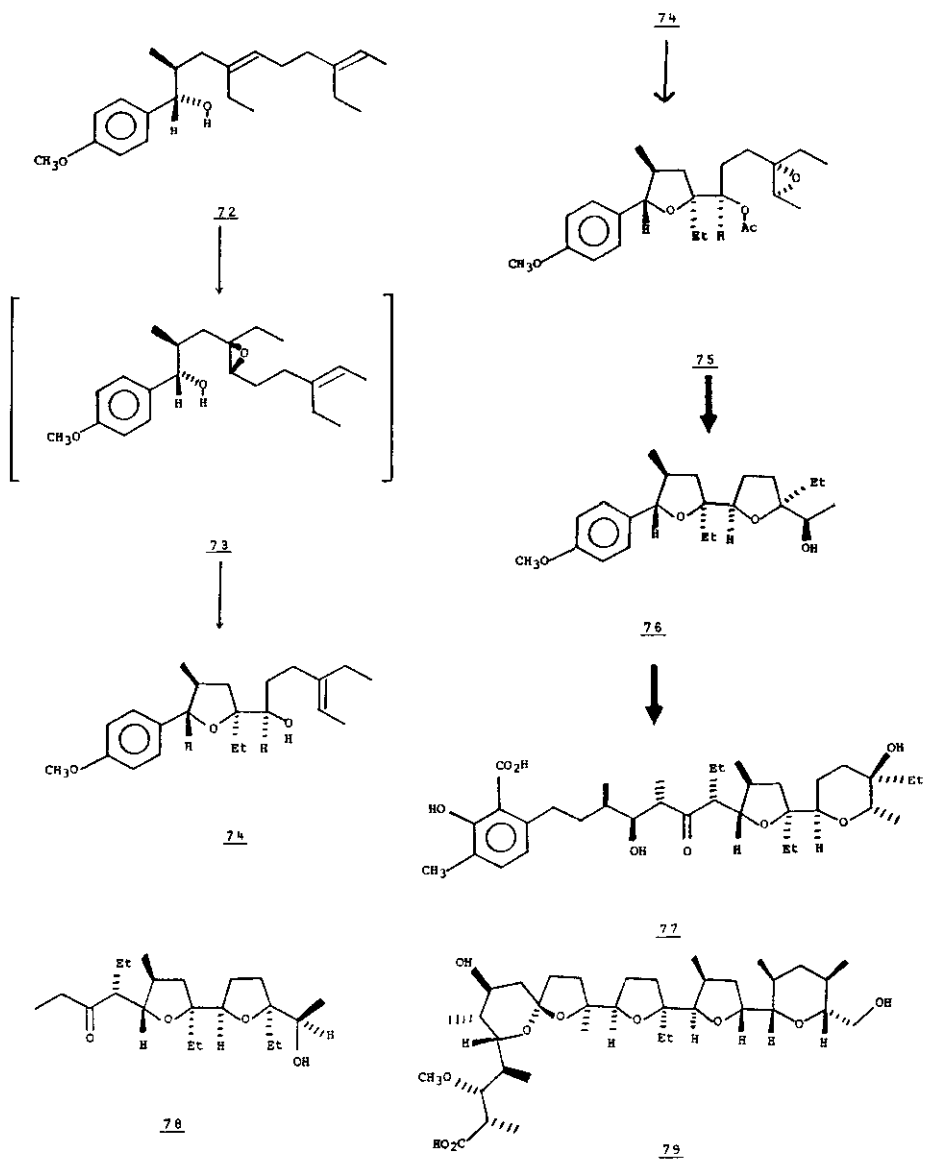
A (77) by Kishi and associates.<sup>47</sup> The epoxide route allowed the stereospecific construction of six out of ten chiral centers in this complex molecule (Scheme 18).

Treatment of alcohol 72 with tert-butylhydroperoxide in benzene containing vanadyl acetylacetonate and sodium acetate<sup>48,49</sup> at room temperature, generated an epoxide (73) along with its stereoisomer in an 8:1 ratio.<sup>50</sup> Reaction of 73 with acetic acid produced tetrahydrofuran 74 in 75% overall yield. Epoxidation of 74 under the conditions previously described, followed by acetylation, generated epoxide 75. The stereochemistry of the epoxide was inverted by a three-step procedure,<sup>47</sup> and then the resultant material was treated with acetic acid at room temperature to produce tetrahydrofuran 76 in 45% overall yield from 75. The stereoselectivity of the transformation of 74 to 76 and its stereoisomer was 5:1. After several steps, intermediate 76 was converted to lasalocid A (77).

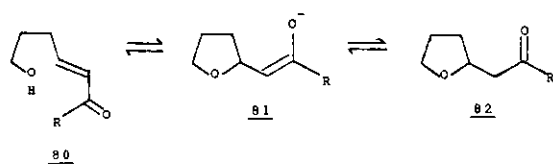
The use of analogous epoxidation-solvolysis procedures led to the ingenious total synthesis of isolalalocid ketone (78)<sup>51</sup> and monensin (79).<sup>52-54</sup> Synthetic ionophores have also been prepared.<sup>55,56</sup>

#### 1.6 Cyclizations via Intramolecular Michael Additions

Another useful method for the construction of tetrahydrofuran rings involves intramolecular Michael additions in  $\epsilon$ -hydroxy- $\alpha,\beta$ -unsaturated systems such as 80 (Scheme 19).



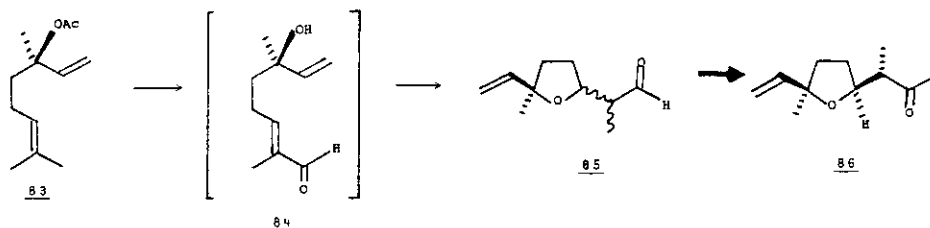
Scheme 18



Scheme 19

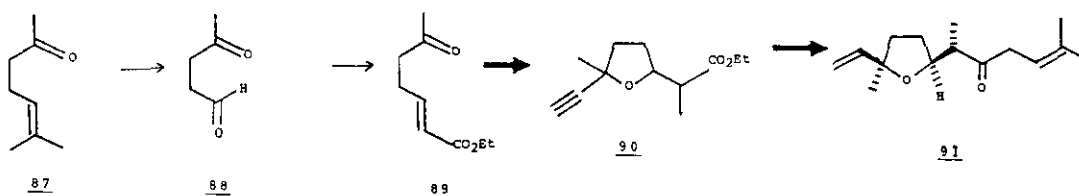
The alkoxide ion generated from 80 can attack the vinylogous  $\beta$ -carbon of the system in an intramolecular fashion to produce 81 which may then be protonated to afford a tetrahydrofuran derivative (82). In practice, care must be taken to avoid unfavorable equilibria which could lead to regeneration of starting materials or to undesired side reactions.

Nordavanone (86), a  $C_{11}$ -terpenoid from the oil of *Artemisia pallens*, was synthesized in a non-stereospecific manner using the intramolecular Michael reaction<sup>57</sup> (Scheme 20).



Scheme 20

Selenium dioxide oxidation of (-)-linalyl acetate (83), followed by base-catalyzed hydrolysis, produced an intermediate (84) which subsequently cyclized in 30% overall yield to give an isomeric mixture of aldehydes (85). Reaction of 85 with methylmagnesium iodide and subsequent oxidation of the resulting alcohols with chromic acid produced Nordavanone (86) along with three other diastereomers. Davanone (91),<sup>58</sup> also isolated from the oil of *Artemisia pallens*, was synthesized non-stereospecifically by Birch, et al.<sup>59</sup> by a related pathway (Scheme 21).

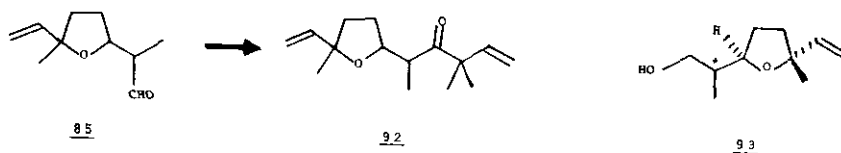


Scheme 21

Ozonolysis of enone 87 produced levulinaldehyde (88), which underwent a Wittig reaction with ethoxycarbonylethylidene triphenylphosphorane to afford mainly *trans*-ester (89). Subsequent treatment of 89 with lithium acetylide, followed by cyclization using sodium hydride in refluxing benzene gave tetrahydrofuran 90. Finally, partial hydrogenation of the acetylene moiety, saponification of the ester function, and reaction of the resultant intermediate with  $\gamma,\gamma$ -dimethylallyllithium gave a mixture of Davanone (91) and its stereoisomers. Another synthesis<sup>60</sup>, using racemic linalyl acetate (dl-83) as the starting material, also afforded 91 along with isomers.

The non-stereospecific synthesis of a related sesquiterpene ketone, artemone (92) was also carried out<sup>61</sup> by the Michael sequence from racemic aldehyde 85 (Scheme 22). The total synthesis of diastereomeric mixtures of lilac alcohols a and b (93) has similarly been achieved (Scheme 22).

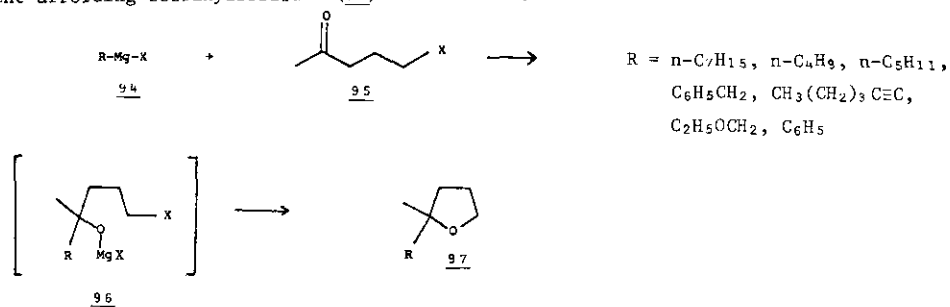
Mixtures of all possible stereoisomers were obtained.<sup>62-65</sup>



Scheme 22

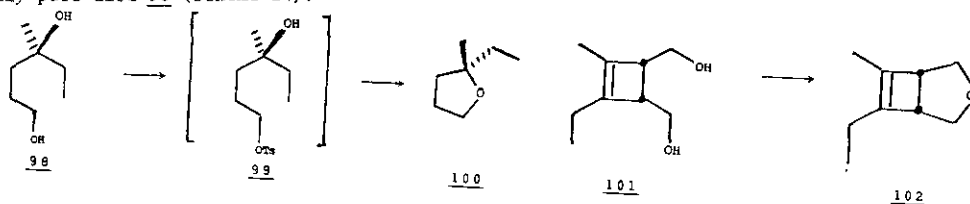
### 1.7 Cyclizations via Intramolecular Dehydration, Dehydrohalogenation, and Tosylate Displacement

The formation of tetrahydrofurans by classical procedures, such as intramolecular dehydrohalogenation, dehydration, and tosylate displacement are synthetically useful in certain instances. An interesting approach related to dehydrohalogenation is the reaction of Grignard reagents (94) with  $\gamma$ -bromo- or chloro-2-pentanone (95) in refluxing ether or tetrahydrofuran containing hexamethylphosphoric triamide (HMPA).<sup>66</sup> The intermediate alkoxide (96) undergoes intramolecular displacement affording tetrahydrofurans (97) in 50 - 75% yield (Scheme 23).



Scheme 23

Jacobus<sup>67</sup> studied the mechanism and stereochemistry of tetrahydrofuran formation using the optically pure diol 98 (Scheme 24).



Scheme 24

Treatment of 98 with one equivalent of *p*-toluenesulfonyl chloride in pyridine afforded 100 via tosylate intermediate 99. As expected, intramolecular displacement occurred with retention of configuration at the chiral center.

The interesting tetrahydrofuran 102, a useful intermediate in the synthesis of the antibiotic methylenomycin-A, was similarly prepared in 86% yield by reaction of diol 101 with one equivalent



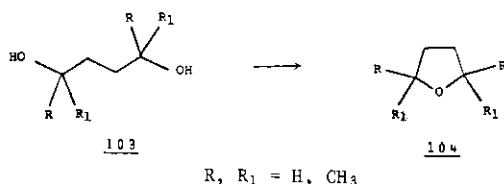
of p-toluenesulfonyl chloride in pyridine<sup>68</sup> (Scheme 24).

Dehydration of 1,4-diols using acid catalysts<sup>69-72</sup> often gives low yields of tetrahydrofurans.

Furthermore, when the starting material is an optically active alcohol, racemization occurs.<sup>67</sup>

A related method, dehydration of 1,4-diols using hot dimethyl sulfoxide,<sup>67,73</sup> is limited to unfunctionalized precursors, but does afford good yields of products.

An interesting approach to simple tetrahydrofurans has recently been developed by Nalesnik and Holy,<sup>74</sup> utilizing a palladium (II) chloride-copper (II) chloride-copper (II) nitrate-oxygen catalyst system (Scheme 25).



Reaction of diols (103) with this homogeneous catalyst system at 150<sup>o</sup> produced tetrahydrofurans (104) in 70 - 95% yield. Although the mechanism of the reaction is not known, the role of the palladium (II) was considered to be that of a simple Lewis acid.

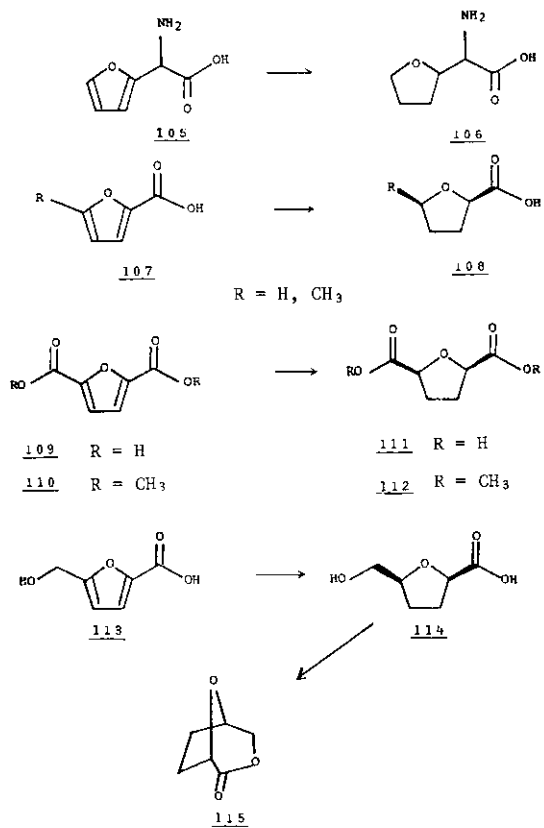
## 2. REDUCTIVE METHODS

Catalytic hydrogenation of aromatic furan derivatives is a very useful method for obtaining the corresponding tetrahydrofurans, and has been widely employed in organic synthesis (Scheme 26).

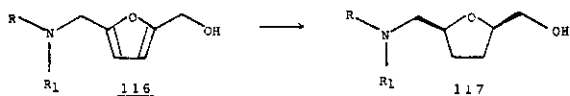
Joullié and Divanfard<sup>75</sup> demonstrated that hydrogenation of 105 in a mixture of methanol, acetic acid, and water, containing a rhodium on charcoal catalyst, gave the novel tetrahydrofuran  $\alpha$ -amino acid (106) in 90% yield. Similarly, reduction of the furoic acids (107) in methanol-water containing a rhodium on charcoal catalyst produced the corresponding tetrahydrofuroic acids (108) in 96 - 100% yield.<sup>76</sup>

Moore and Kelly<sup>77</sup> hydrogenated furan-2,5-dicarboxylic acid (109) and its dimethyl ester (110) in aqueous solutions containing a rhodium on charcoal catalyst and obtained the corresponding *cis*-tetrahydrofuran derivatives 111 and 112 in 83% and 91% yields, respectively. Hydrogenation of 2-carboxy-5-(hydroxymethyl)furan (113) over rhodium on charcoal in water produced *cis*-tetrahydrofuran 114 which was converted immediately in 20% yield to the corresponding lactone (115)<sup>78</sup> (Scheme 26).

A series of 5-dialkylaminomethyltetrahydrofurfuryl alcohols (117) were prepared<sup>79</sup> by hydrogenation of aromatic precursors (116) in an autoclave over a nickel-chromium catalyst. The acyl derivatives of these substances possess hypotensive, cholinolytic, and anesthetic activity (Scheme 27).

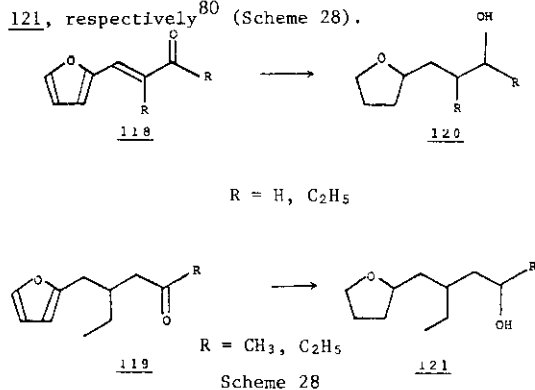


Scheme 26



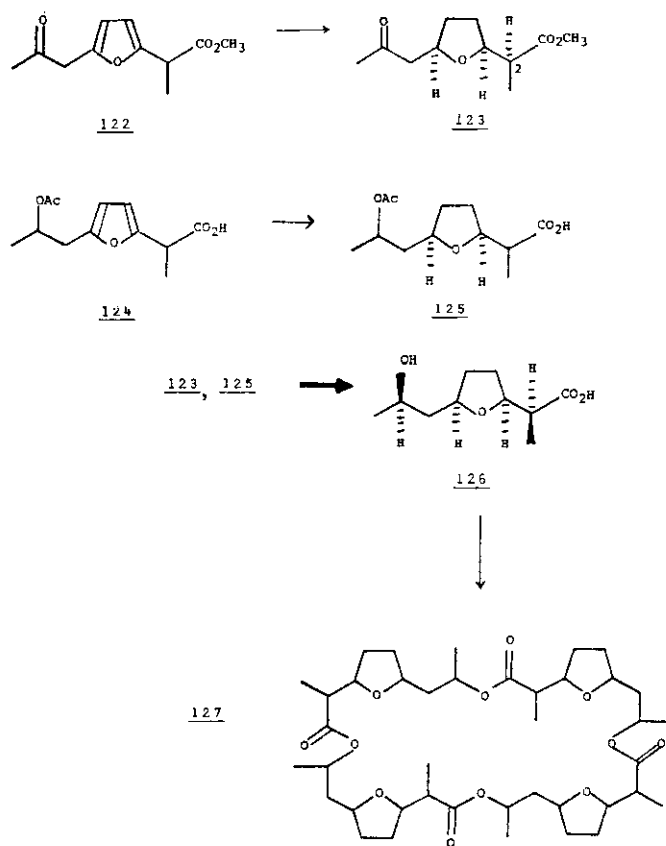
Scheme 27

Hydrogenation of 118 and 119 over Raney nickel catalyst at 100-130<sup>o</sup> produced the corresponding reduced furans 120 and 121, respectively<sup>80</sup> (Scheme 28).



Scheme 28

Perhaps the most interesting recent examples of the catalytic hydrogenation of aromatic furan derivatives are found in the synthesis of nonactic acid (126), a monomer of the naturally occurring ionophore macrolide nonactin (127)<sup>81</sup> (Scheme 29).



Scheme 29

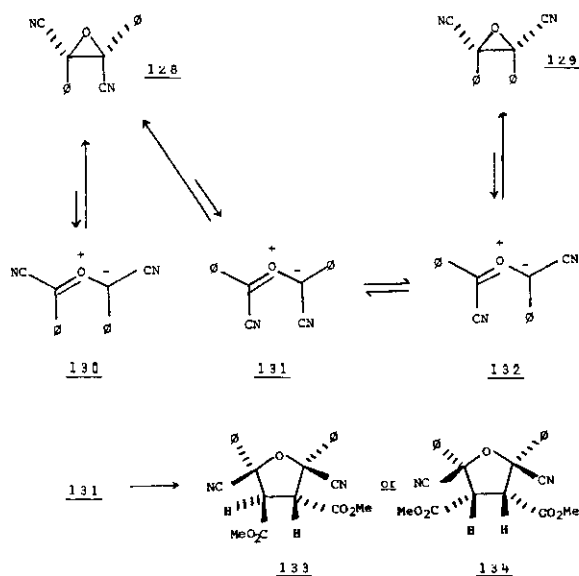
Gerlach and Wetter<sup>82</sup> reduced keto-ester 122 with a rhodium on alumina catalyst to produce 123 with the correct *cis*-stereochemistry of the ring substituents, but the desired product was obtained as a mixture with its C-2 epimer.

At about the same time, Schmidt and co-workers<sup>83-85</sup> synthesized nonactin from the precursor 125, obtained as a mixture of diastereomers by hydrogenation of intermediate 124 over rhodium on alumina. Both intermediates (123 and 125) were further transformed into nonactic acid (126)<sup>82-87</sup> and nonactin (127). Other routes to nonactic acid have also been published.<sup>88,89</sup>

### 3. CYCLOADDITION REACTIONS

The thermal or photoinduced formation of carbonyl ylids from oxiranes and their subsequent [3+2] cycloaddition reactions with dipolarophiles is both a theoretically interesting and often practical route to highly substituted tetrahydrofuran rings. Significant work in this area by Huisgen

and his associates<sup>90,91</sup> demonstrated that trans-dicyanostilbene oxide (128) and the corresponding cis-isomer (129) establish an equilibrium at 100-120° via a conrotatory ring opening process<sup>91</sup> to generate the carbonyl ylids 130-132 (Scheme 30).



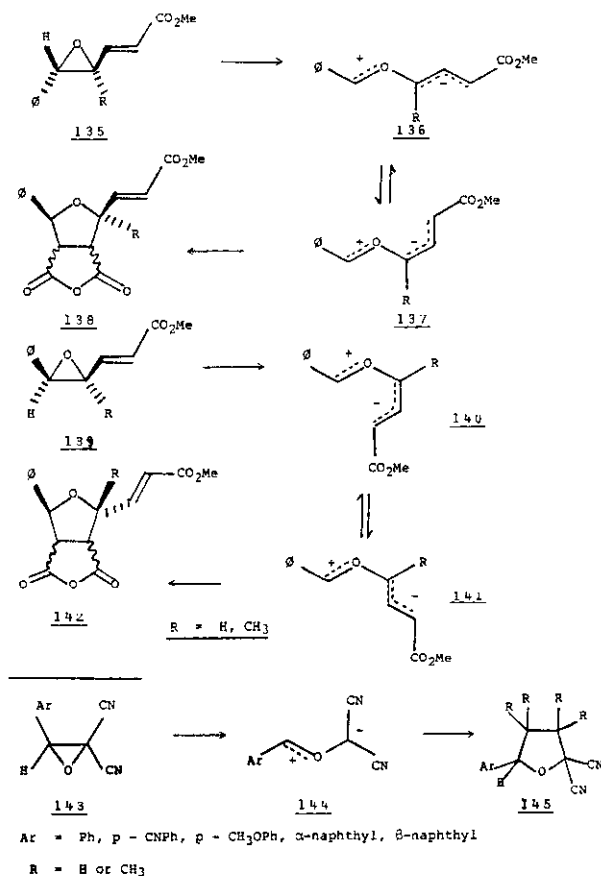
Scheme 30

This equilibrium process favored the formation of cis-dicyanocarbonyl ylid (131), as evidenced by spectroscopic analysis of the adducts obtained by addition of dipolarophiles. Isomerization of trans-ylid 132 to cis-ylid 131 precedes the 1,3-dipolar cycloaddition process, and, accordingly, reaction of ylid 131 with dimethyl fumarate and dimethyl maleate produced cycloadducts 133 and 134 in 85% and 65% yields, respectively. Addition of a variety of acetylenic or olefinic dipolarophiles produced 2,5-dihydrofurans or tetrahydrofurans, respectively in 23 - 97% yields. Related studies were also carried out on cis- and trans- $\alpha$ -cyanostilbene oxides.<sup>91,92</sup>

The thermolysis of vinyloxiranes was studied by Eberbach and Burchardt<sup>93,94</sup> (Scheme 31).

Brief thermolysis of trans-vinyloxirane (135) in bromobenzene at 156° generated the oxapentadienyl ylids 136 and 137 through conrotatory ring opening processes. Trapping of the ylids with maleic anhydride produced an isomeric mixture of adducts (138). Analogously, thermolysis of cis-vinyloxirane (139) led via ylids 140 and 141 to the corresponding isomeric mixture of adducts (142). Both adducts 138 and 142 were obtained in 80%- 85% yields.

Photolysis<sup>95,96</sup> of a series of dicyanooxiranes (143) in benzene solution produced the corresponding carbonyl ylids (144) which could be trapped efficiently with ethylene, 2,3-dimethyl-2-butene, or isobutylene to give tetrahydrofuran adducts (145) in 34 - 90% yields. The stereospecificity of this reaction was demonstrated by generation of the ylid in the presence of cis-



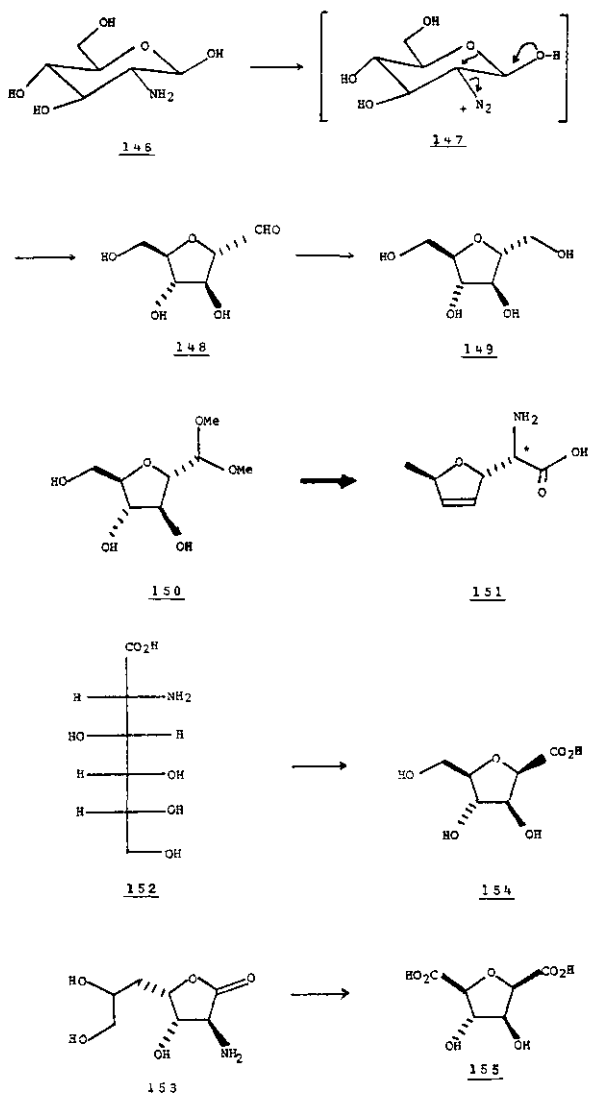
Scheme 31

or trans-2-butene and isolation of the corresponding adducts, exhibiting retention of the initial olefin geometry.

A related study<sup>97</sup> on the photolysis of cis- and trans-stilbene oxides revealed that carbonyl ylids were also formed and that these intermediates could be trapped stereoselectively in high yield with electron-deficient olefins. An investigation by Huisgen and Markowski<sup>98</sup> demonstrated that photolysis of cis- and trans- $\alpha$ -cyano-stilbene oxides afforded ylids by an initial disrotatory oxirane ring opening process. The ylids were then trapped as tetrahydrofuran adducts.

#### 4. TRANSFORMATIONS OF CARBOHYDRATE PRECURSORS

The deamination of 2-amino-deoxyaldoses and the corresponding acids with nitrous acid is one of the oldest known reactions in carbohydrate chemistry, and has been extensively investigated<sup>99,100</sup> (Scheme 32).



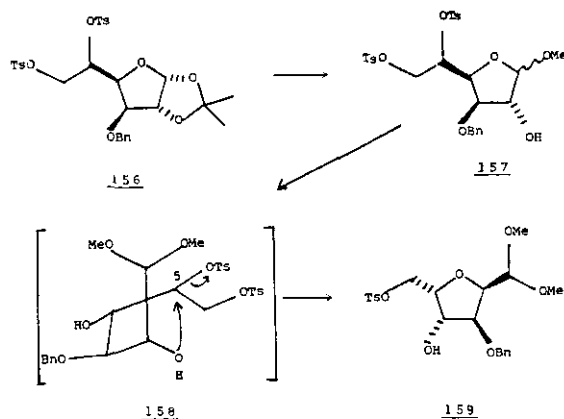
Scheme 32

The deamination of 2-amino-2-deoxy-D-glucose (**146**) with nitrous acid affords 2,5-anhydro-D-mannose (**148**) via diazonium salt **147**.<sup>101-103</sup> Reduction of the labile "chitose" (**148**) with sodium borohydride gave **149** in 71% overall yield.<sup>101-103</sup>

Joullié and Chen are currently investigating the total synthesis of the 5(R),2(S), $\alpha$ (S,R)-furanomycins (**151**) from dimethyl acetal **150**, obtainable, in turn, from **146** in 70% overall yield.<sup>76</sup>

In a similar manner, deamination of 2-amino-2-deoxy-D-gluconic acid (**152**)<sup>104</sup> and 2-amino-2-deoxy-D-idolactone (**153**)<sup>105,106</sup> with nitrous acid produced the carboxylic acids **154** and **155**, respectively.

An extremely powerful method for the synthesis of furan rings from acyclic carbohydrate precursors was developed by Defaye<sup>107,108</sup> (Scheme 33).



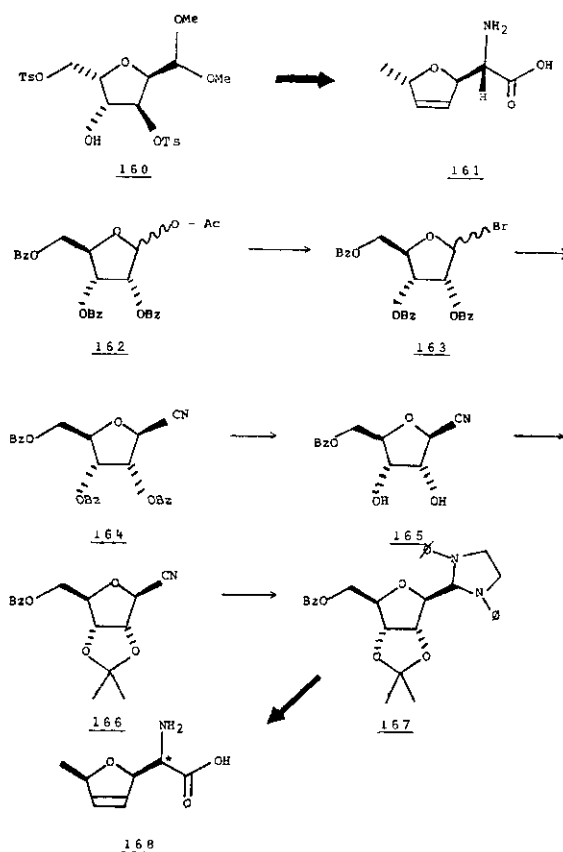
Scheme 33

Thus, reaction of 3-O-benzyl-1,2-O-isopropylidene-5,6-di-O-p-tolylsulfonyl- $\alpha$ -D-glucofuranose (**156**) in refluxing methanolic hydrogen chloride generates acetal **157** which undergoes ring opening to produce intermediate **158**. Subsequent intramolecular cyclization with inversion of configuration at C-5 gives the acetal **159** in 80% yield. Matsui and co-workers<sup>109</sup> utilized this method for the preparation of several 2,5-anhydroaldose dimethyl acetals.

Joullié and co-workers recently described an efficient asymmetric total synthesis of naturally occurring 5(S),2(R), $\alpha$ (S)-furanomycin (**161**) from intermediate **160**,<sup>110</sup> analogously derived via the Defaye rearrangement of an appropriately functionalized precursor (Scheme 34).

Bobek and Farkas<sup>111</sup> reported that reaction of 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose (**162**) with hydrogen bromide in benzene gave bromide **163**. This halide, upon reaction with mercuric cyanide in nitromethane produced 2,3,5-tri-O-benzoyl- $\beta$ -D-ribofuranosyl cyanide (**164**) in 88% overall yield from **162**. Moffatt and his associates<sup>112</sup> treated **164** with ammonium hydroxide in methanol-chloroform at 0° and obtained the diol (**165**) in 85% yield. The diol functionality of **165** was then protected by reaction with 2,2-dimethoxypropane and acetone containing p-toluenesulfonic acid (95% yield). The resultant compound (**166**), when reduced with Raney nickel in acetic acid-pyridine-water containing sodium hypophosphite and 1,2-dianilinoethane, gave the corresponding 2,5-diphenylimidazolidine derivative (**167**) in 78% yield. Compound **167** was transformed into C-glycosyl nucleosides by Moffatt and co-workers,<sup>112</sup> and has also served as an excellent precursor in Robins and Parker's<sup>113</sup> total synthesis of the 5(R),2(R), $\alpha$ (R,S)-furanomycins (**168**) (Scheme 34). Since many sugars are economical starting materials and also contain a rich array of chiral functionality, their transformation into optically active natural products, or useful intermediates leading to such substances, constitutes an extremely powerful and important method of modern

organic synthesis.



Scheme 34

## 5. MISCELLANEOUS REACTIONS

The synthesis of functionalized tetrahydrofurans has been effected through the use of carbenoid intermediates,<sup>114,115</sup> free-radical intermediates,<sup>116-119</sup> dioxolanes,<sup>120-122</sup> and the Prins reaction.<sup>123-125</sup> Since these methods are either poor from a preparative standpoint, often resulting in complex mixtures of products, or lack generality, they will not be discussed further in this review.

### II. SYNTHESIS OF FUNCTIONALIZED 2,5-DIHYDROFURANS

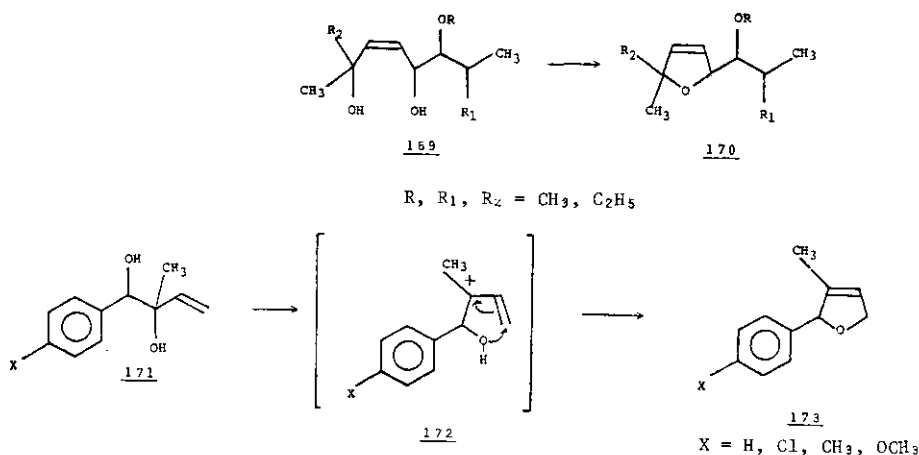
Functionalized 2,5-dihydrofurans are useful intermediates in the total synthesis of several natural products.

#### 1. CYCLIZATION ROUTES

##### 1.1 Intramolecular Dehydration

The classical procedure of intramolecular dehydration is still of current interest as a preparative method for the synthesis of simple 2,5-dihydrofuran ring systems (Scheme 35).



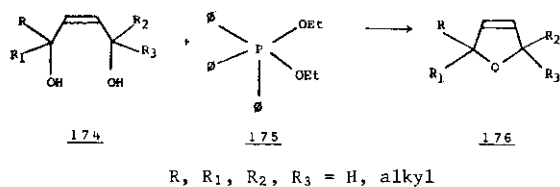


Scheme 35

A typical example of this type of reaction is the treatment of unsaturated 1,4-diols (169) with hot dilute sulfuric acid.<sup>126</sup> The 2,5-dihydrofurans (170) are produced in moderate yield as a 1:1 mixture of *cis* and *trans* isomers. Obviously, the harsh conditions required for this reaction drastically limit its scope.

An interesting variation on the normal 1,4-dehydration route, studied by Dana, et al.,<sup>127, 128</sup> revealed that 2,5-dihydrofurans (173) could be obtained in 9%-67% yield by acid-catalyzed dehydration of the 1,2-diols (171). Treatment of these diols with refluxing dilute sulfuric acid generates an allylic carbonium ion (172), which can be attacked by the neighboring hydroxyl group to produce the corresponding 2,5-dihydrofurans (173). Again, it should be emphasized that only alkyl or aryl groups can tolerate the harshness of the highly acidic reaction conditions, and this method also is of an obviously limited scope.

A very mild method which effects intramolecular 1,4-diol dehydration was recently disclosed by Evans and Grote<sup>129</sup> (Scheme 36).



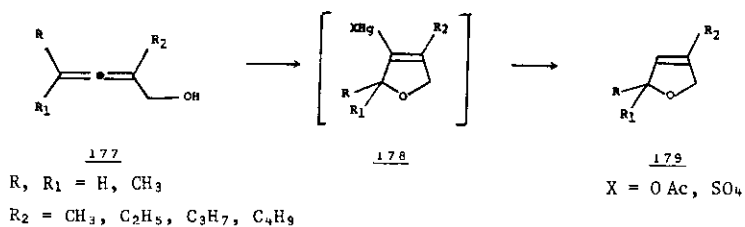
Scheme 36

The procedure consists of heating chloroform solutions of unsaturated 1,4-diols (174) with triphenyldiethoxyphosphorane (175) to afford the corresponding 2,5-dihydrofurans (176).

### 1.2 Cyclization of Allenic Alcohols

Gelin, et al.<sup>130</sup> found that oxymercuration-demercuration of allenic alcohols can produce 2,5-dihy-

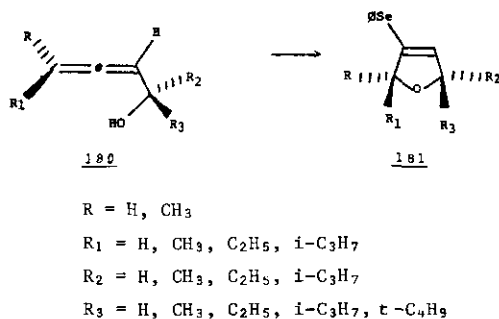
dofurans in good yields (Scheme 37).



Scheme 37

Thus, reaction of allenic alcohols (177) with mercuric acetate or sulfate in aqueous or methanolic media generated intermediate organomercury derivatives (178), which, upon treatment with sodium borohydride, afford 2,5-dihydrofurans (179) in 48%-90% isolated yields.

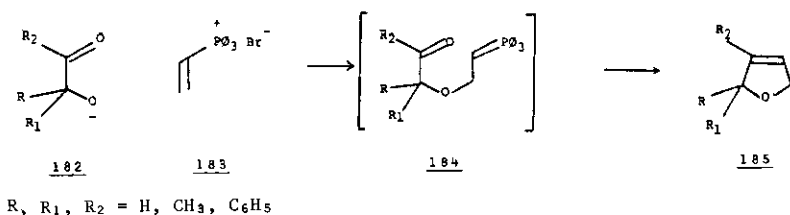
Along similar lines, Beaulieu, et al.<sup>131</sup> very recently demonstrated that treatment of allenic alcohols (180) with phenylselenenyl chloride (PhSeCl) in methylene chloride at room temperature caused an analogous electrophilically induced cyclization, giving 3-phenylseleno-2,5-dihydrofurans (181) in 70%-98% yield with high stereospecificity (Scheme 38).



Scheme 38

### 1.3 Addition/Cyclization Routes

An elegant approach to 2,3-substituted-2,5-dihydrofurans was developed by Schweizer<sup>132</sup> and Liehr<sup>133</sup> (Scheme 39).

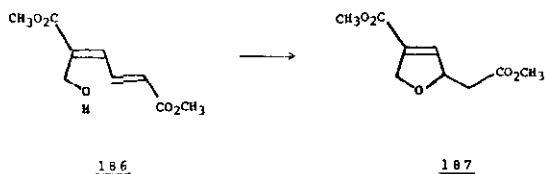


Scheme 39

In this method, the alkoxide derived from  $\alpha$ -hydroxyketone (182) is treated with vinyltriphenylphosphonium bromide (183) to generate an intermediate ylid (184), which undergoes an intramolecular Wittig reaction to produce 2,5-dihydrofuran (185) in modest yields. Although the reaction was

reported over a decade ago, the general scope of this 2,5-dihydrofuran synthesis has not as yet been determined.

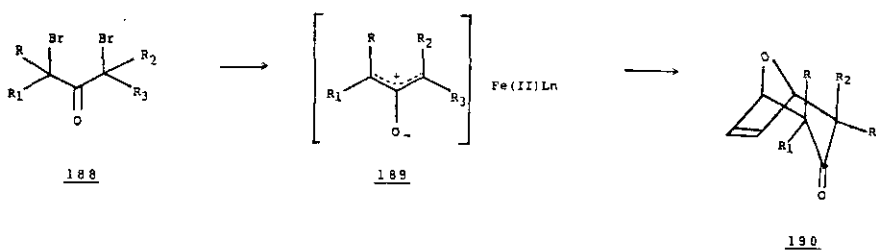
Stotter and co-workers<sup>134</sup> reported an interesting intramolecular Michael addition which produced a 2,5-dihydrofuran in high yield (Scheme 40).



Scheme 40

Treatment of (186) in warm *tert*-butyl alcohol with a catalytic amount of potassium *tert*-butoxide caused cyclization to occur and the resultant 2,5-dihydrofuran diester (187) was isolated in 90% yield.

An extremely powerful technique for the synthesis of bicyclic ring systems incorporating a 2,5-dihydrofuran moiety has been developed and exploited by Hoffmann<sup>135</sup> and Noyori<sup>136-139</sup> (Scheme 41).



Scheme 41

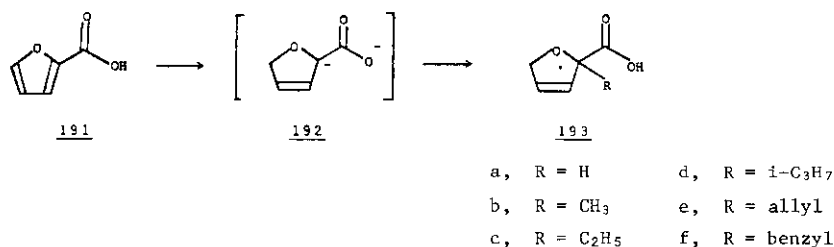
Reaction of an  $\alpha,\alpha'$ -dibromoketone (188) with a reducing agent such as diiron nonacarbonyl,  $\text{Fe}_2(\text{CO})_9$ , generates a highly reactive 2-oxyallyl-iron (II) intermediate (189) which undergoes [3+4] cyclocoupling reactions with furan to produce adducts (190) in excellent yields. Adducts such as (190) have served as intermediates for the total synthesis of a wide variety of natural products, including troponoids,<sup>140</sup> thujaplicins,<sup>141</sup> and C-nucleosides.<sup>142-144</sup>

## 2. REDUCTIVE METHODS

Perhaps one of the best-known and most preparatively useful methods for the synthesis of 2,5-dihydrofurans is the Birch-type reduction<sup>145</sup> of aromatic furan-2-carboxylic acids with lithium in liquid ammonia solution (Scheme 42).

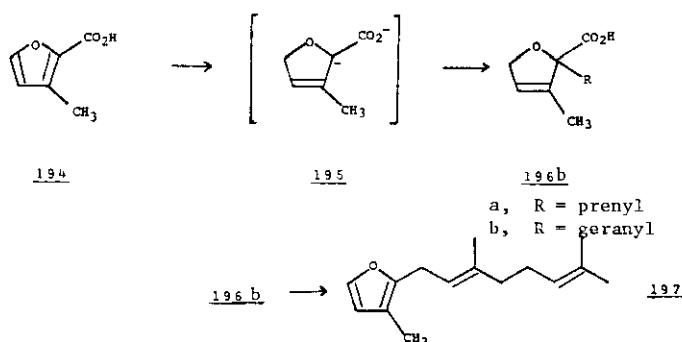
Birch and Slobbe<sup>146</sup> reported that rapid addition of 2-furoic acid (191) to 2.5 equivalents of lithium in liquid ammonia at  $-78^\circ$ , followed by quenching after three minutes with ammonium chloride produced 2,5-dihydrofuroic acid (193a) in 80% yield. Alternatively, the intermediate dianion (192) could be intercepted with alkyl halides to produce the corresponding acids (193b-f)

in 68%-95% yields.



Scheme 42

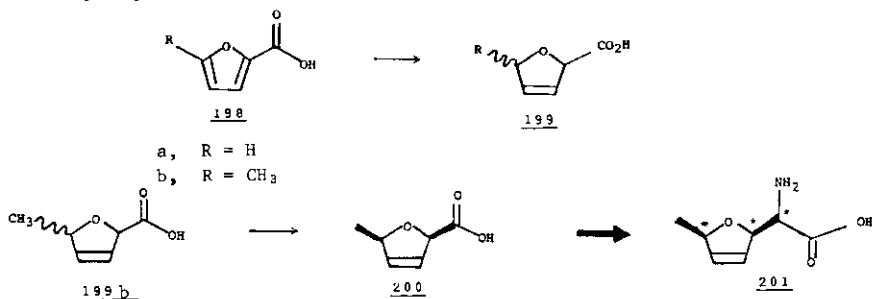
The same authors<sup>147</sup> carried out the reduction of 3-methyl-2-furoic acid (194) with lithium in liquid ammonia and then treated the intermediate dianion (195) with either prenyl bromide or geranyl bromide (Scheme 43).



Scheme 43

The corresponding alkylation products (196a,b) were obtained in 75% and 60% yields, respectively. Reaction of (196b) with 1.2 equivalents of lead tetraacetate in warm benzene solution induced oxidative decarboxylation, producing rose furan (197) in 70% yield.

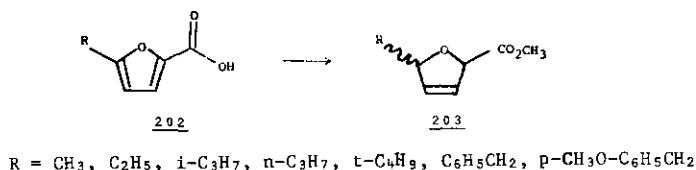
Joullié and Divanfard<sup>148</sup> studied the reduction of 2-furoic acid (198a) and 5-methyl-2-furoic acid (198b), and found that 90% yields of the corresponding 2,5-dihydrofuroic acids (199a,b) could be obtained by addition of three equivalents of finely divided lithium to a solution of the acids in methanol and dry liquid ammonia at -33° (Scheme 44).



Scheme 44

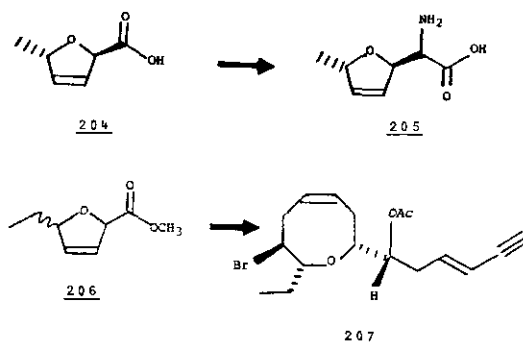
Fractional distillation of the acid mixture (199b), afforded pure cis-5-methyl-2,5-dihydro-2-furoic acid (200). This compound served as a precursor for the total synthesis of the cis series of furanomycins (201).<sup>76</sup>

In a similar manner, Masamune, et al.,<sup>149</sup> reduced a series of 5-substituted-2-furoic acids (202) with three equivalents of lithium or sodium metal in a methanol-liquid ammonia mixture and then esterified the crude 2,5-dihydrofuroic acids to obtain the corresponding methyl esters (203) as ca. 1:1 cis and trans mixtures in 40%-85% yield (Scheme 45).



Scheme 45

The Birch reduction of 3-furoic acids<sup>150-152</sup> does not produce 2,5-dihydrofuran derivatives. Masamune and Ono<sup>153</sup> have converted the trans- acid 204 (to which they had mistakenly assigned the cis geometry) into the  $\alpha$ -amino acid antibiotic dl-furanomycin (205) (Scheme 46).



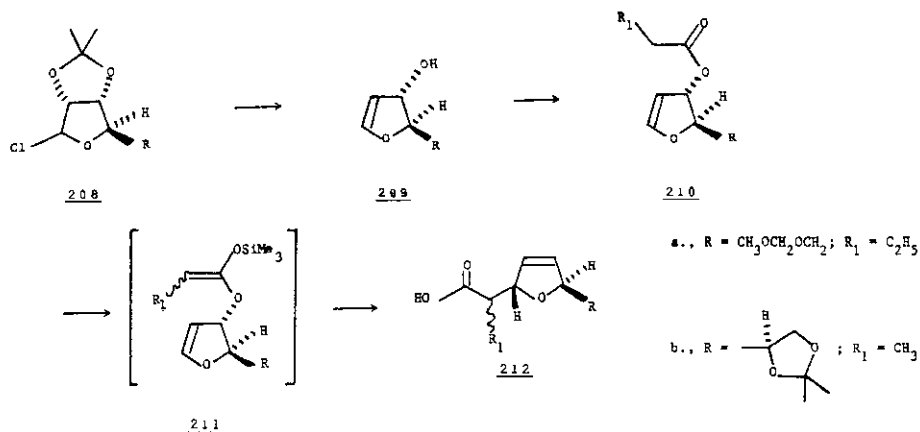
Scheme 46

The same group<sup>154</sup> used the isomeric ester mixture (206) as a key intermediate in their total synthesis of laurencin (207), a naturally occurring bromoether (Scheme 46).

### 3. CLAISEN REARRANGEMENT OF FURANOID GLYCAL

A very elegant approach to functionalized 2,5-dihydrofurans which are potentially useful for the construction of complex ionophore natural products such as lasalocid A (77) has been developed by Ireland and his associates<sup>155,156</sup> (Scheme 47).

The key step was an ester enolate Claisen rearrangement on a furanoid glycal precursor. The synthesis began with the reductive fragmentation of furanosyl chlorides (208a,b).<sup>155</sup> Treatment of a solution of the chlorides (208a,b) in liquid ammonia at  $-78^{\circ}$  with excess lithium metal gave 75%-80% yields of the corresponding glycals (209a,b). Reaction of the lithium alcohates

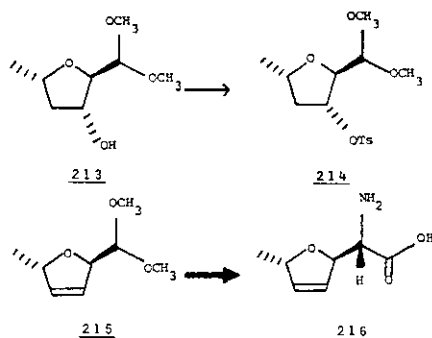


Scheme 47

of these compounds with either butanoyl chloride or propanoyl chloride in tetrahydrofuran-hexamethylphosphoramide solvent mixtures then afforded the respective esters (210a,b). These esters were deprotonated with lithium diisopropylamide, and the enolates thus generated were silylated with trimethylsilyl chloride. The resultant silyl ketene acetals (211), when warmed to 35°, rearranged rapidly to the corresponding 2,5-dihydrofurans (212) in 52%-73% overall yields from (208).<sup>156</sup> It is interesting to note that the ratio of diastereomers at the  $\alpha$ -carbon can be controlled by the intermediate enolate (211) geometry, which, in turn, is affected by the solvent system used. Also, the rearrangement process occurs with retention of configuration as the silyl ketene moiety shifts from C-3 to C-5.

#### 4. TRANSFORMATIONS OF CARBOHYDRATE PRECURSORS

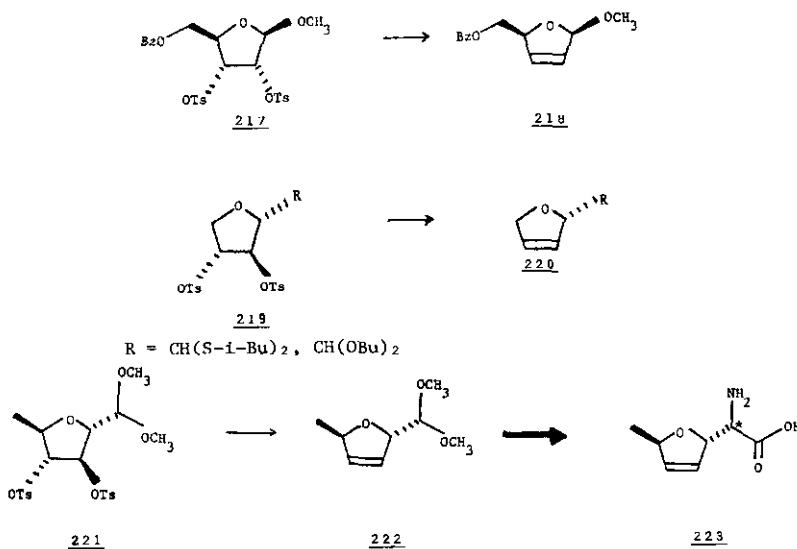
Joullié and co-workers have utilized two efficient routes for the preparation of chiral 2,5-dihydrofurans from appropriately functionalized carbohydrate precursors (Scheme 48), and employed the hydrofurans in a total synthesis of furanomycin.<sup>76,110</sup>



Scheme 48

Furanose 213, obtainable from D-glucose in 62% overall yield, was treated with p-toluenesulfonyl chloride in pyridine at 0° to produce tosylate (214). Reaction of this compound with sodium methoxide in refluxing methanol generated the chiral 2,5-dihydrofuran acetal (215) in 72% overall yield via a *trans*-E<sub>2</sub> elimination process.<sup>157</sup> In turn, acetal 215 was recently transformed into naturally occurring 5(S),2(R),α(S)-furanomycin (216).<sup>110</sup>

Another useful procedure for the synthesis of chiral 2,5-dihydrofurans from carbohydrate precursors was developed by Tipson and Cohen<sup>158</sup> (Scheme 49).



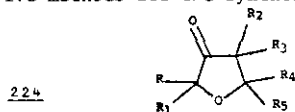
Scheme 49

When tosylates 217 and 219 were heated with sodium iodide and powdered zinc in dimethylformamide, the corresponding 2,5-dihydrofurans (218 and 220), were obtained.<sup>158-165</sup> This procedure has been used extensively in carbohydrate chemistry for the preparation of unsaturated heterocycles.<sup>166-169</sup>

Joullié and co-workers treated ditosylate 221 with five equivalents of sodium iodide and ten equivalents of powdered zinc in hot dimethylformamide and obtained 2,5-dihydrofuran acetal (222) in 86% yield, a potential precursor in the total synthesis of the 5(R),2(S),α(S,R)-furanomycins (223).<sup>76</sup>

### III. SYNTHESIS OF FUNCTIONALIZED 3(2H)-DIHYDROFURANONES

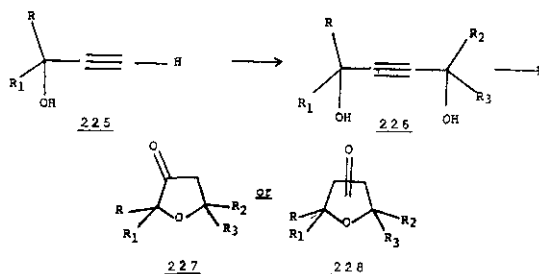
There are several preparative methods for the synthesis of the 3(2H)-dihydrofuranone (224) ring system.



R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> = H, alkyl, cycloalkyl, alkenyl, aryl

## 1. HYDRATION OF ACETYLENIC DIOLS

The synthesis of simple 2,5-disubstituted- or 2,2,5,5-tetrasubstituted 3(2H)-dihydrofuranones is usually carried out by reaction of sodium or lithium acetylide<sup>170-175</sup> with a ketone or aldehyde to produce an acetylenic alcohol (225) which is subsequently treated with a carbonyl compound in the presence of base to generate acetylenic diols (226) (Scheme 50).



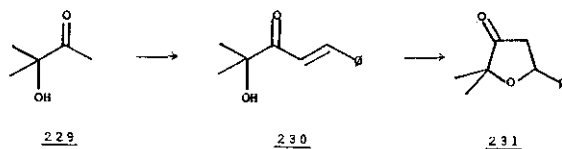
R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> = H, alkyl, aryl

Scheme 50

Mercury catalyzed hydration of the resultant diols (226) in the presence of acid affords the furanones (227) in moderate to high yields.<sup>174-180</sup> It should be noted that if R ≠ R<sub>2</sub> and R<sub>1</sub> ≠ R<sub>3</sub>, isomeric mixtures of furanones (228) are always obtained.<sup>174,175,181,182</sup>

## 2. NAZAROV-TYPE CYCLIZATIONS

The Nazarov-type cyclization<sup>183</sup> of α'-hydroxy-α,β-unsaturated ketones is an interesting and often useful method to construct certain types of furanones (Scheme 51).



Scheme 51

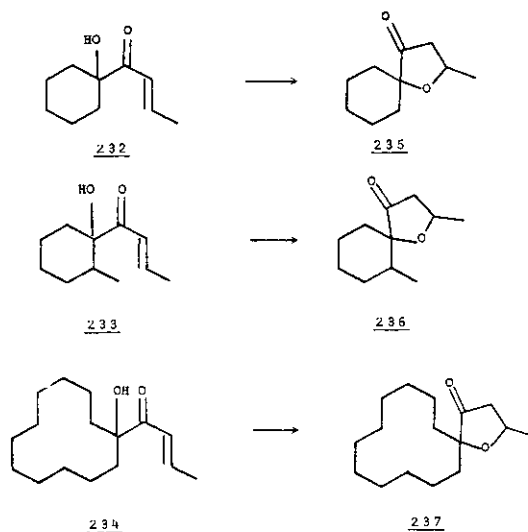
Aldol condensation of α-hydroxyketone 229 with an aromatic aldehyde such as benzaldehyde gives a good yield of α'-hydroxy-α,β-unsaturated ketone (230), cyclization of which with phosphoric acid<sup>183</sup> or p-toluenesulfonic acid<sup>184</sup> generates 3(2H)-dihydrofuranone 231 in 75 - 80% yields, via an acid-catalyzed intramolecular 1,4-addition reaction.

A method for the preparation of α'-hydroxyenones recently disclosed by Jacobson, et al.<sup>185,186</sup> provides a related route for the synthesis of novel spiro-furanones (Scheme 52).

Treatment of α'-hydroxyenones 232, 233 and 234 in refluxing toluene containing two equivalents of methanol with p-toluenesulfonic acid as catalyst produces the corresponding furanones 235, 236, and 237 in 90%, 78%, and 80% yields, respectively.

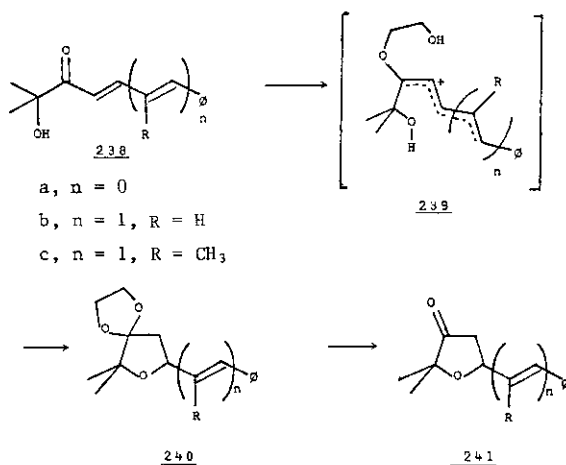
Joullié and Semple<sup>76</sup> discovered a very useful process for the preparation of 3(2H)-dihydrofuranone





Scheme 52

ethylene ketals (240a-c) from readily available  $\alpha'$ -hydroxyenones (238a-c) (Scheme 53).



Scheme 53

It was found that treatment of  $\alpha'$ -hydroxyenones (238a-c) with five equivalents of ethylene glycol and near stoichiometric amounts of p-toluenesulfonic acid in refluxing benzene with azeotropic removal of water produced ketals 240a-c in 65 - 100% yields. Interestingly, if  $\alpha'$ -hydroxydienone 238b was treated under the same conditions in the absence of ethylene glycol, furanone 241b was produced in disappointingly low yield (38%).

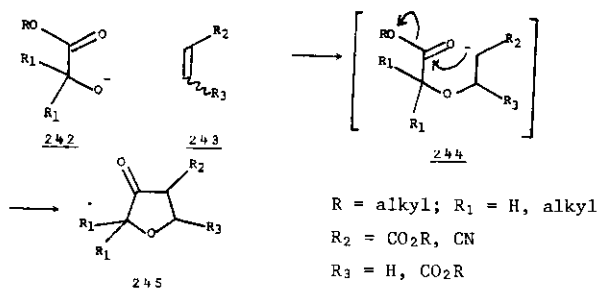
It was believed that the success of this novel reaction was due to the intermediacy of the extensively delocalized carbonium ion (239), formed by 1,2-addition of ethylene glycol to the carbonyl

group followed by dehydration. Subsequent ring closure in this intermediate (239) could occur by a relatively low energy pathway, to yield the observed products (240).

When ketals 240a,b were refluxed in acetic acid-water (2:1) for two hours, the corresponding furanones (241a,b) were formed in 98% yields. The ketals 240a-c and furanones 241a,b were found to be exceptionally versatile intermediates for the synthesis of several reduced furan natural products and analogs.<sup>76</sup>

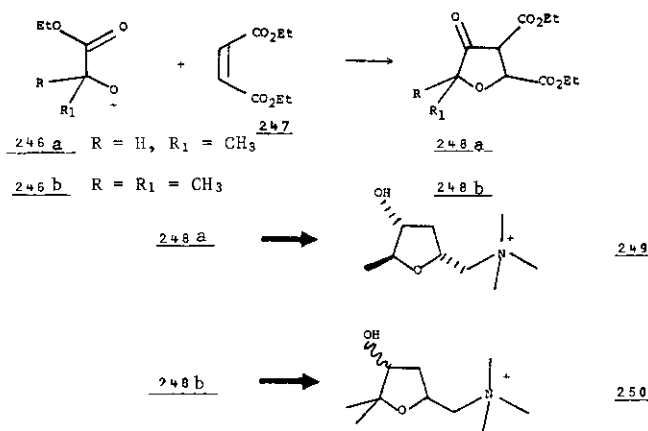
### 3. INTRAMOLECULAR MICHAEL-DIECKMANN CONDENSATION

A very powerful method for generating 3(2H)-dihydrofuranones is based on the Michael addition of anions derived from  $\alpha$ -hydroxyesters (242) to  $\alpha,\beta$ -unsaturated substrates (243) (Scheme 54).



Scheme 54

The intermediate anion 244 attacks the adjacent ester moiety via a Dieckmann condensation reaction, to produce a substituted furanone ring 245, which usually bears readily manipulable functionality. Early use of this reaction by Hardegger and co-workers<sup>187,188</sup> led to the synthesis of dl-allomuscaine (249)<sup>187</sup> and dl-2-methylmuscaine (250)<sup>188</sup> (Scheme 55).



Scheme 55

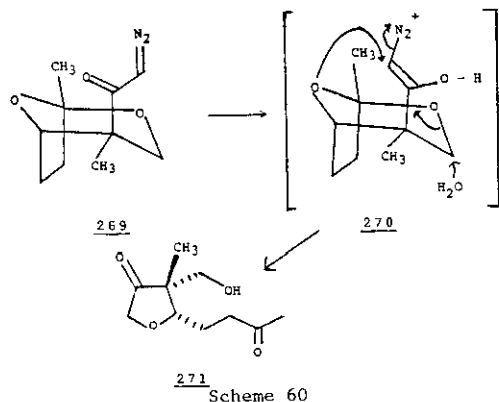
Thus, condensation of the sodium salt of ethyl lactate (246a) or ethyl  $\alpha$ -hydroxyisobutyrate (246b)





The mechanism of this interesting reaction involves an initial rearrangement of 263 to 266, as shown, followed by nucleophilic attack of the carbonyl group on the activated diazomethyl function, to generate intermediate 267. Addition of ethanol and a subsequent tautomeric shift gives furanone 268.

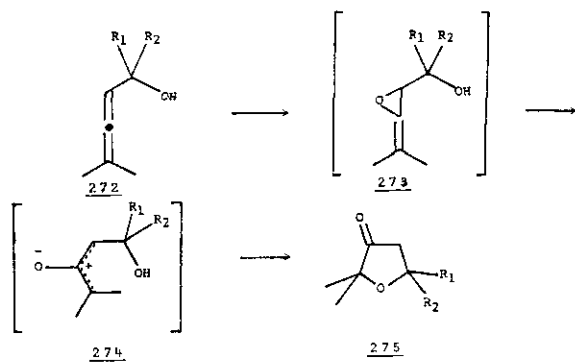
An unusual example of a diazoketone to furanone rearrangement occurs with  $\alpha$ -diazoketone 269<sup>200</sup> (Scheme 60).



Reaction of 269 with methanolic hydrochloric acid at room temperature for ten minutes afforded novel furanone 271 in 28% yield. The formation of this compound in an aqueous acidic medium can be rationalized mechanistically by an intramolecular attack of the oxygen atom on the  $\alpha$ -carbon as depicted with intermediate 270. Subsequent loss of nitrogen and tautomeric equilibration afforded the product (271).

#### 5. INTRAMOLECULAR CYCLIZATION OF UNSATURATED ALCOHOLS

Another route to furanones involves utilization of hydroxyallenes or  $\beta,\gamma$ -unsaturated hydroxyketones (Scheme 61).

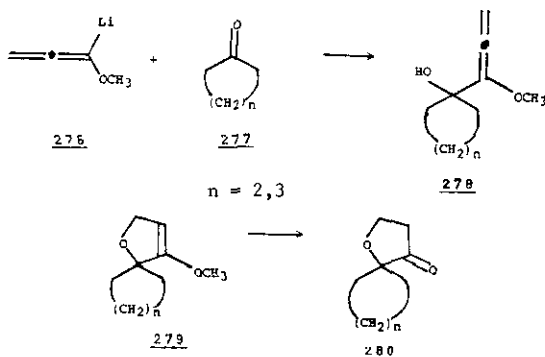


- a,  $R_1 = R_2 = H$   
 b,  $R_1 = CH_3, R_2 = H$   
 c,  $R_1 = R_2 = CH_3$

Scheme 61

Treatment of allenes 272a-c with a solution of hydrogen peroxide in benzonitrile led to oxyallyl zwitterion 274, via the intermediacy of epoxide 273. Nucleophilic attack by the hydroxyl group followed by a proton shift and tautomerization produced furanones 275a-c in 10%, 60%, and 100% yields, respectively.<sup>201</sup>

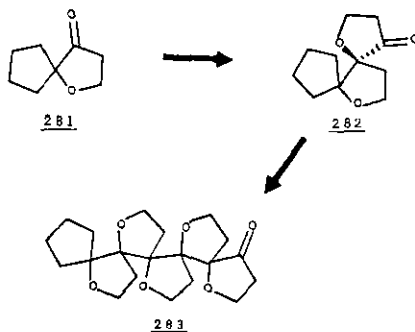
Magnus and Gange<sup>202</sup> reported a novel furanone synthesis using allene adducts (Scheme 62).



Scheme 62

Thus, reaction of  $\alpha$ -lithio- $\alpha$ -methoxyallene 276 with cyclic ketones 277 gave addition products 278 in 80 - 90% yields. Treatment of these compounds with potassium *tert*-butoxide and dicyclohexyl-18-crown-6 in refluxing *tert*-butyl alcohol effected their cyclization to spiro-enol ethers 279 which could be hydrolyzed to the corresponding 3(2H)-dihydrofuranones (280) in 65 - 75% overall yields by treatment with hydrochloric acid.

Magnus, et al.<sup>203</sup> extended this approach to the synthesis of the first "primary" helical molecule, based upon the shape (bond angles and bond lengths) of the tetrahydrofuran ring system (Scheme 63).

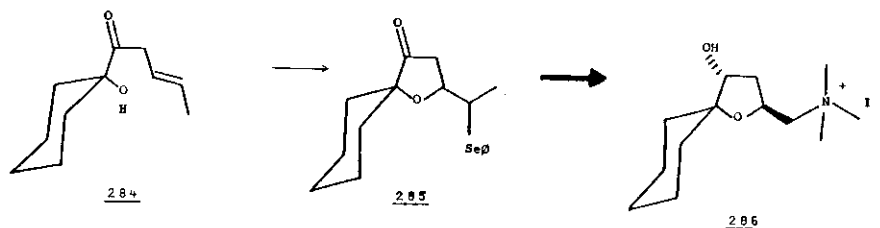


Scheme 63

Furanone 281 was subjected to the reaction sequence described above to generate the spiro-furanone

282 in 67% overall yield. Reiterative reactions with this same reagent system gave the polyoxa-polyspiroalkane 283. The steric congestion of spiro-compound 282 allows the  $\alpha$ -lithio- $\alpha$ -methoxyallene 276 to attack from only one diastereotopic face of the carbonyl group, and this fact accounts for the "helical" nature of the product (283).

Joullié and co-workers<sup>204</sup> treated the  $\beta,\gamma$ -unsaturated hydroxyketone 284 with phenylselenenyl chloride at  $-78^\circ$  and obtained furanone 285 in 80% yield (Scheme 64).



This compound was further transformed into the novel spiro muscarine analog 286.

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