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Acid-catalyzed intramolecular hydride shifts

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ACID-CATALYZED INTRAMOLECULAR HYDRIDE SHIFTS

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Master of Science

by

Surekha Podduturi

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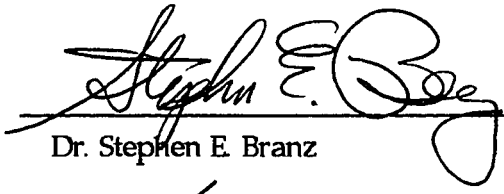

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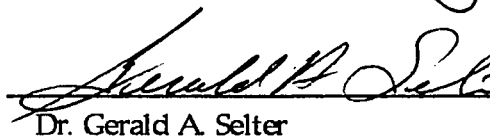

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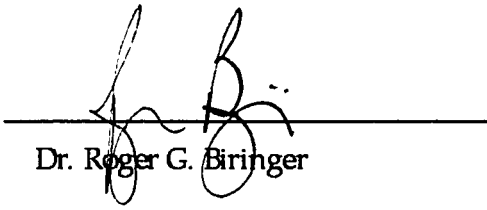

Dr. Roger G. Biringer

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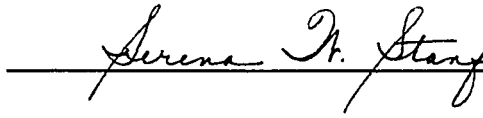
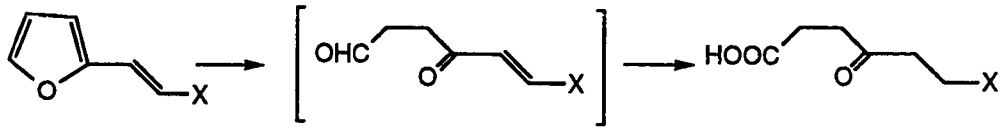


ABSTRACT

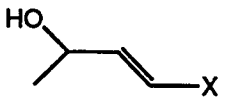
ACID-CATALYZED INTRAMOLECULAR HYDRIDE SHIFTS

by Surekha Podduturi

Our research work deals with an investigation of the mechanism of hydrolysis of 2-alkenylfurans **19**. Anticipated dicarbonyl compounds **23** were apparently the reaction intermediates in our abnormal hydrolysis which gave **24** as the products. There are three conceivable ways by which the intramolecular hydride can reduce the double bond of these intermediates to give the final products **24** (a 1,6-hydride shift, or a 1,5-hydride shift, or a 1,4-hydride shift followed by a 1,2-shift). Of the three possible mechanisms only the 1,6-shift had been ruled out experimentally when we began this study. Hydrolysis reactions of model compounds provided us with the experimental evidence necessary to distinguish between the remaining two possibilities. Work leading towards the synthesis of model compounds and their hydrolysis reactions is described.



19 **23** **24**



Model compounds

X = NO_2, COOH, CN

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Acknowledgements

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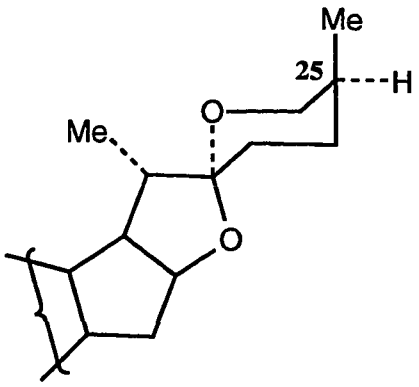
Introduction

1,2- and 1,3-Intramolecular hydride transfers are well documented, and have been recognized for many years.[1] In contrast, there are relatively few reports of intramolecular transfer of hydride to more remote electrophilic sites (long range intramolecular hydride transfer). Most examples of such reactions are restricted to transannular migrations,[2] and are driven by the formation of carbocations in medium sized rings or rigid polycyclic compounds in which the reaction sites are in close proximity.[3] Such rearrangements are due to the special geometric features of these molecules. Nevertheless, several examples of non-transannular intramolecular hydride shifts have appeared in the literature. An example of an acid catalyzed 1,5-hydride shift in a flexible system is the isomerization of steroidal sapogenins[4] at C-25.



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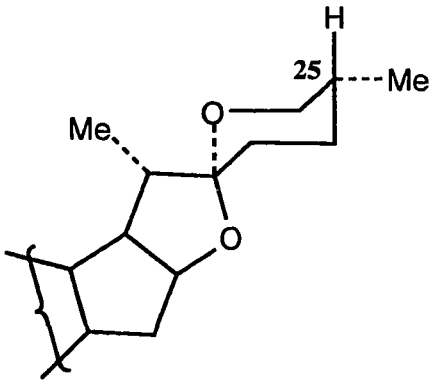

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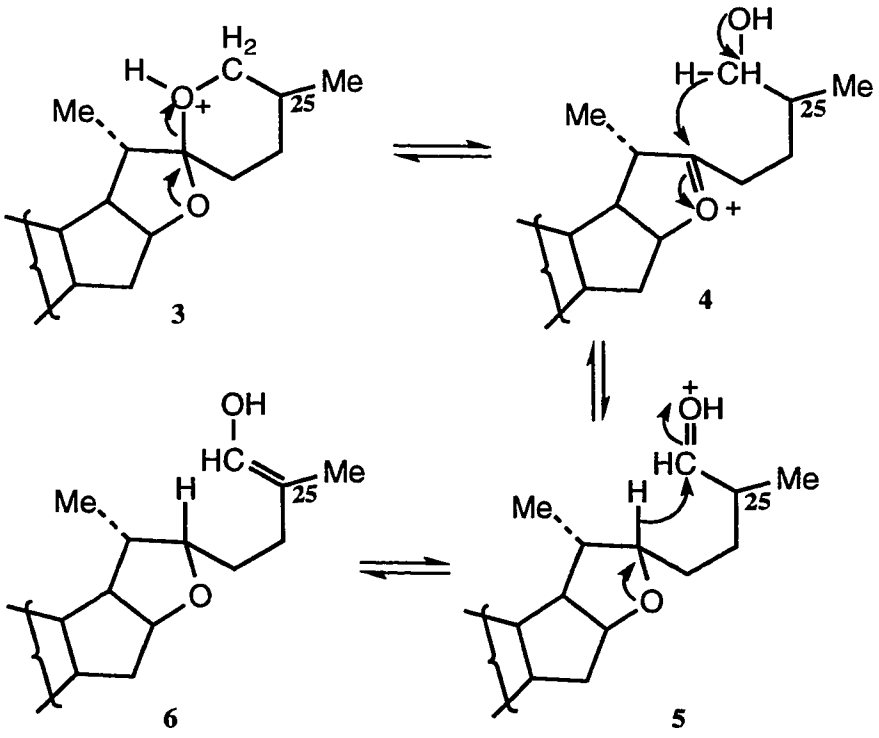
The interconversion of normal (**1**) and the iso (**2**) sapogenins presumably takes place by a redox mechanism (shown in **Scheme I**).

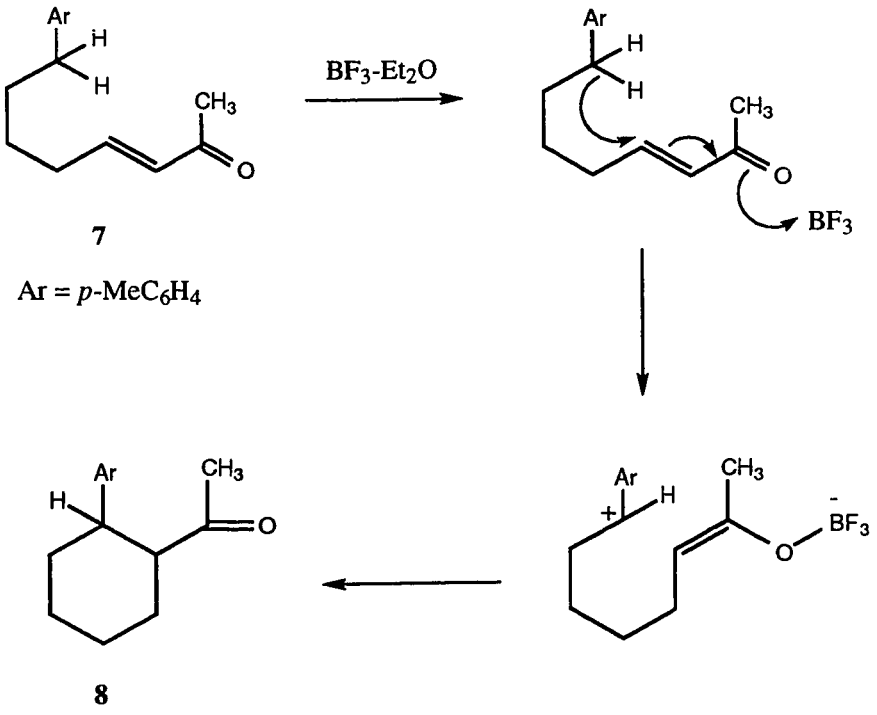
Scheme I



The key step in the mechanism is a reversible hydride shift involving the oxonium ions **4** and **5**. Since the protonated aldehyde **5** is in equilibrium with the corresponding enol **6**, change of configuration at C-25 is simply established.

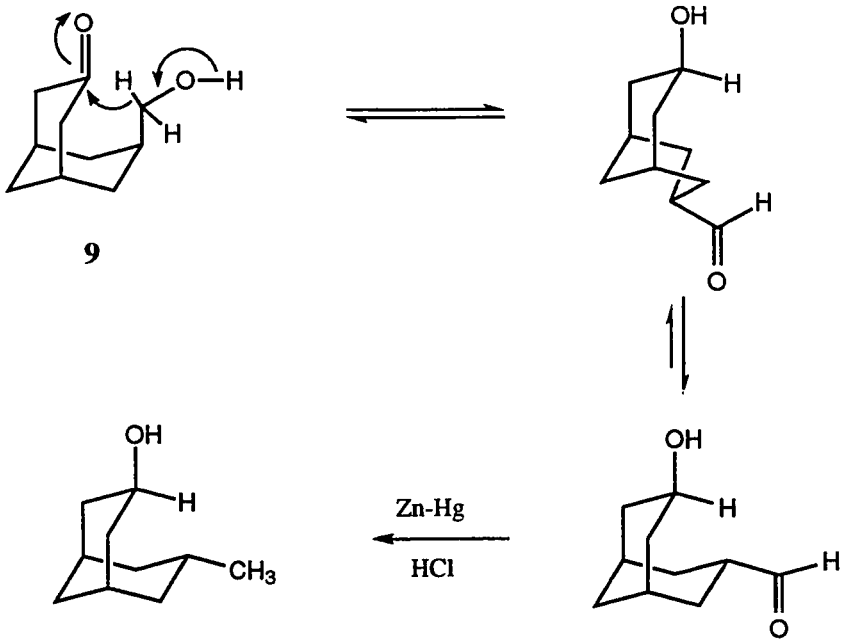
The principal driving force for many of the rearrangements involving a hydride shift is the generation of a more stable carbocation. For example, the acid catalyzed rearrangement of the α,β-unsaturated ketone **7** is shown in **Scheme II**.[5] The mechanism involves a 1,5-hydride shift (as shown by deuterium labelling) resulting in a stable acyclic carbocation.

Scheme II



In another example, Huang-Minlon reduction[6] of 7α-hydroxymethyl-bicyclo-[3.3.1]-nonane-3-one (**9**) gave 7β-methylbicyclo-[3.3.1]-nonan-3β-ol (**10**) as a result of a transannular 1,6-hydride shift followed by epimerization alpha to the newly formed aldehyde. This rearrangement allows for the relief of steric strain prior to the reduction (shown in **Scheme III**).

Scheme III

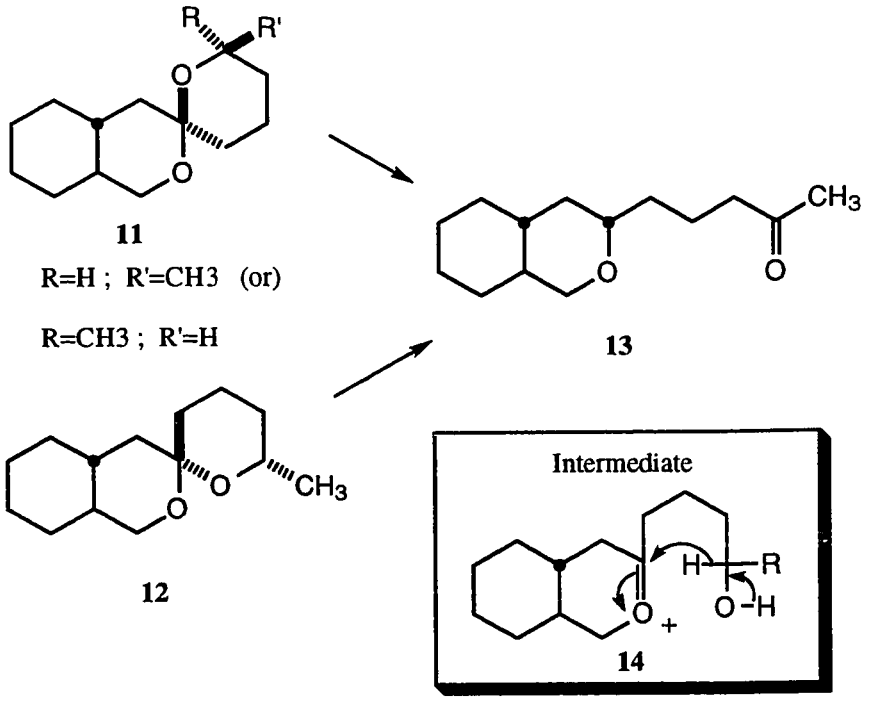


9

10

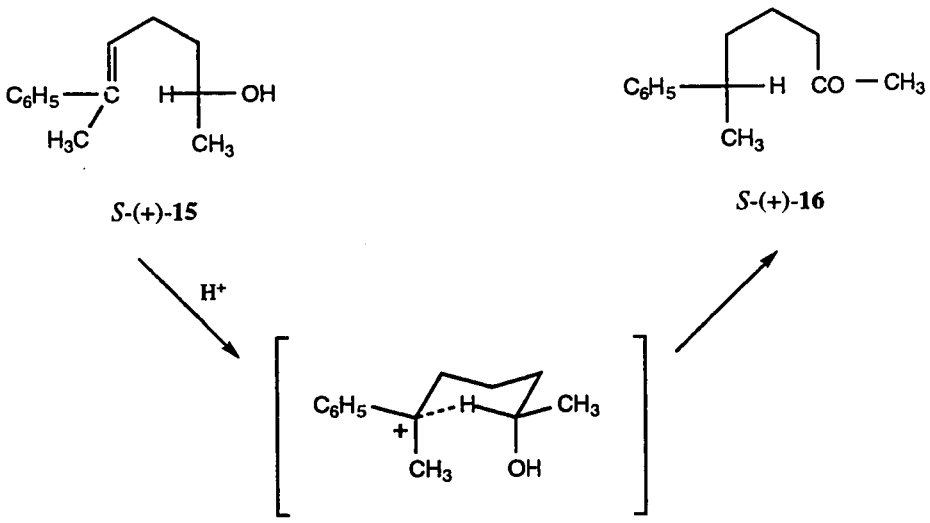
In a related case of acid catalyzed redox reactions of spiroketals,[7] evidence for stereoelectronic control was noted. The stereospecific formation of the more stable equatorial bicyclic ether **13** in **Scheme IV** is also consistent with stereoelectronic effects on the relative rates of equatorial and axial reduction of the intermediate oxonium ion **14**. The hydride transfer was assumed to take place with minimum energy only when the intermediate oxonium ion can develop an electron pair which will become antiperiplanar to the newly formed C–H bond in compound **13**, the final product.

Scheme IV



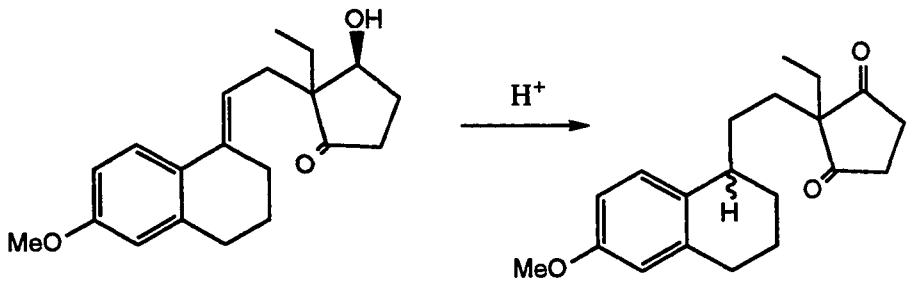
The stereoelectronic characteristics of a system can also favor a long range hydride shift. **Scheme V** illustrates a stereospecific 1,5-hydride shift in *S*-(+)-6-phenylhept-5-ene-2-ol (**15**) to yield *S*-(+)-6-phenylhept-2-one (**16**) via a six-membered transition state.[8] In this case a C=O is formed at the expense of a C=C, a thermodynamically favored transformation.

Scheme V



An example quite closely related to our own work is the intramolecular hydride shift of 13β-ethyl-17β-hydroxy-3-methoxy-8,14-secogona-1,3,5(10),9-tetraen-14-one (**17**)[9] (**Scheme VI**).

Scheme VI



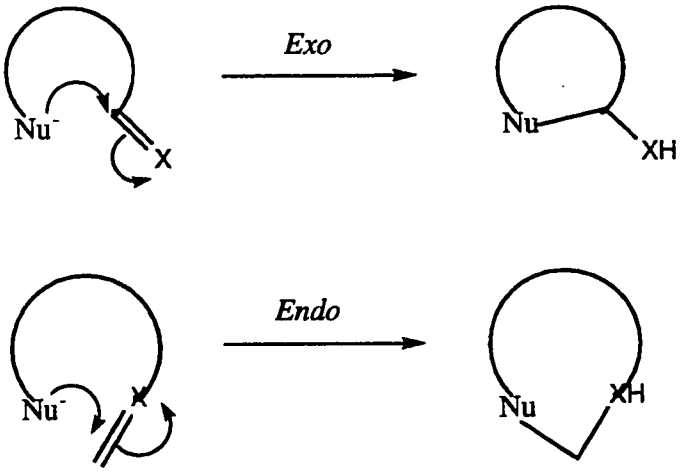
17 **18**

In this rearrangement, a 1,5-shift was responsible for the net reduction of the $\Delta^{9,11}$ double bond (shown by deuterium labelling).

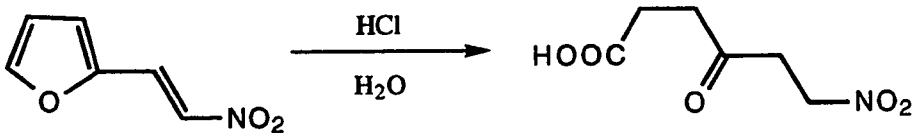
It is no surprise that these rearrangements are thermodynamically favorable, but this is not a good enough mechanistic explanation by itself as the corresponding intermolecular acid-catalyzed hydride shifts are unknown. By analyzing many examples, it seems clear that such intramolecular hydride shifts are kinetically favored by geometric arrangements which meet the stereoelectronic requirements of the transition states. Proximity and orbital alignment of the migrating hydride and the acceptor carbon orbitals can accelerate the hydride shift.

Baldwin[10,11] has indicated the significance of trajectory considerations in synthetic organic chemistry. He formulated a set of rules to predict the relative rates of intramolecular reactions and to characterize some of these as (kinetically) *favored* and others as (kinetically) *disfavored*. Intramolecular additions to carbonyls and other electrophilic groups were classified into two types, *exo* and *endo*. For example, in the case of intramolecular nucleophilic attack at an sp^2 carbon, Baldwin's Rules state that (a) 3-, 4-, 5-, 6-, and 7-*exo-trig* reactions are all *favored,* and (b) 3-, 4-, and 5-*endo-trig* reactions are *disfavored,* whereas 6- and 7-*endo-trig* reactions are *favored.* Sometimes two paths may both be kinetically accessible, but one may be favored over the other. For example, in our research work, a *6-exo-trig* path was proven to be favored over a

7-endo-trig, although either would provide a kinetically reasonable route to the final product.



Our research work began with a mechanistic investigation of the abnormal hydrolysis of 2-(2-nitrovinyl)furan (**19**) to 4-oxo-6-nitrohexanoic acid (**20**), which was first reported in 1909 by Thiele and Landers.[12] We have extended this work to other electron withdrawing groups in place of the nitro group.

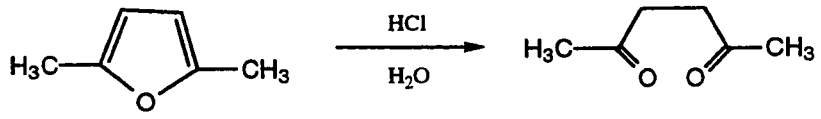


(1)

19 **20**

This hydrolysis reaction is abnormal because, under acid catalyzed conditions, furan rings such as **21** typically yield the corresponding

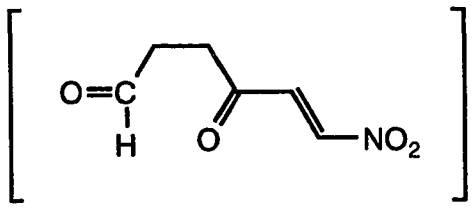
dicarbonyl compounds **22**,[13] as shown in eq 2. In eq 1 the product is an acid instead of the expected ketoaldehyde.



(2)

21 **22**

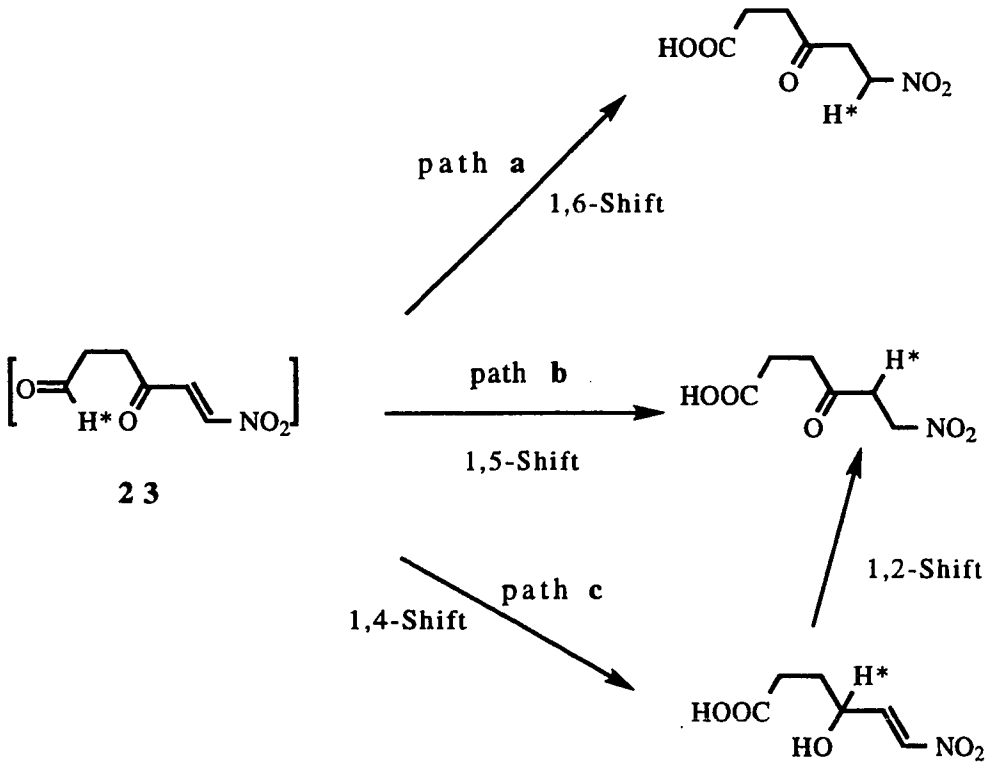
Even though the chemists who discovered these abnormal hydrolyses of furans recognized them as redox reactions, they did not have the modern spectroscopic tools and deuterium labelled substrates necessary to investigate them mechanistically. We have applied physical organic techniques and used deuterium labelled compounds to determine where the hydride has migrated. Examination of the rearrangement product **20** shows that there has been no net change in the oxidation state of the carbon skeleton. Hence, a redox reaction, assumed to be intramolecular in nature, has taken place. During the hydrolysis there has been a net hydride shift from C-1 to either C-5 or C-6. This observation leads to the assumption that the ketoaldehyde **23** has to be the reaction intermediate.



23

Assuming **23** is indeed the intermediate, there remain at least three distinct mechanistic possibilities for its conversion to the saturated 6-oxo-4-nitrohexanoic axid (**20**). They are shown in **Scheme VII**.

Scheme VII



path **a** 1,6-shift (*7-endo-trig* reaction)

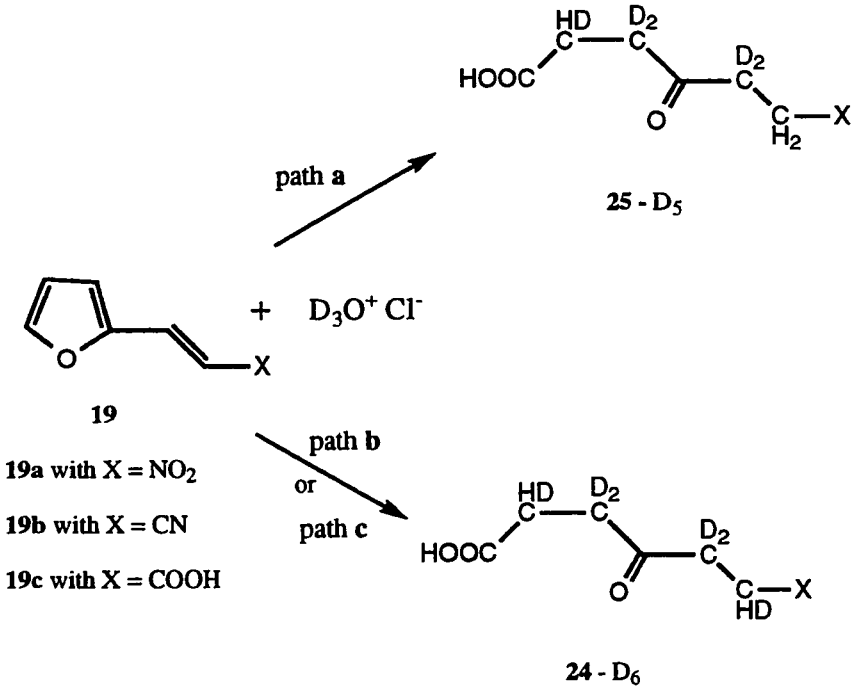
path **b** 1,5-shift (*6-exo-trig* reaction)

path **c** 1,4-shift (*5-exo-trig* reaction) followed by a 1,2 shift.

According to Baldwin's Rules, all the above are *favored* reaction types (but *6-exo-trig* is faster than *7-endo-trig*).

In their initial investigation of this rearrangement, Branz and Bansal[14] and Branz and Baliga[15] ruled out path **a** (**Scheme VII**) by means of a deuterium labelling experiment as shown in **Scheme VIII**.

Scheme VIII



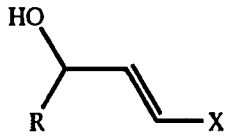
In the DCl hydrolysis of unlabelled substrate **19a**, NMR analysis clearly indicated that the product had retained only two carbon-bound hydrogens as in **24**, one next to the carboxyl and one next to the nitro group. The four hydrogens alpha to the keto group had exchanged with the deuterated solvent via enolization.

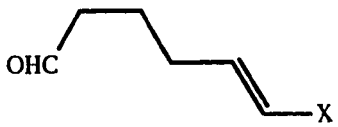
Branz and Baliga[15] investigated the relative rates of reactions in which the nitro group of the nitrovinylfuran **19a** was replaced with a nitrile (**19b**) or a

carboxylic acid (**19c**). The goal of their work was to investigate the importance of the electron withdrawing group in determining the mechanistic details in these hydride shifts.

The results in these cases paralleled those for the nitro group. The "overall" 1,5-shift pathway was followed regardless of the electron withdrawing group used. Having ruled out the 1,6-shift, there remained the other two possibilities: (1) a 1,5-shift, or (2) a 1,4- followed by a 1,2-shift (**Scheme VII**, paths **b** and **c** respectively). These two mechanisms are indistinguishable by isotopic labelling experiments because the migrating hydride would eventually be bound to the same carbon atom in either cases.

We planned to distinguish between these two mechanistic possibilities by synthesizing the model compounds **A** or **B**. Either one might provide enough information to choose between pathways **b** and **c** (as described in the Results and Discussion section of this thesis).





Model compound **A** Model compound **B**

(X = NO_2, COOH, CN)

Our long term goal is to synthesize a variety of compounds to acquire a clear picture of the stereoelectronic preferences of the migrating hydride.

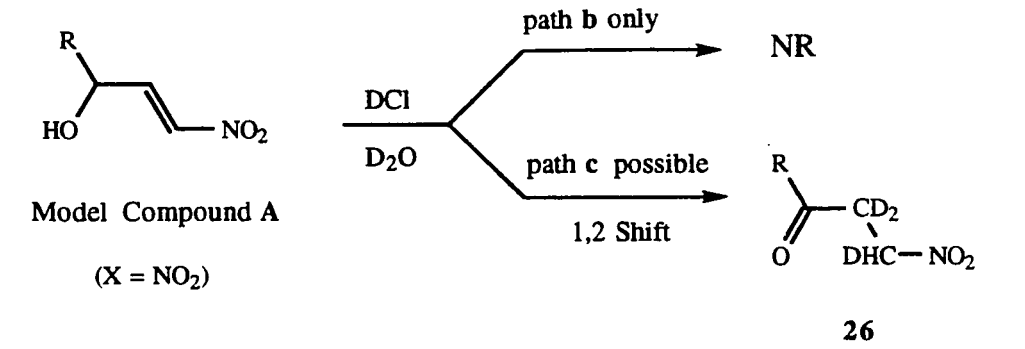
Results and Discussion

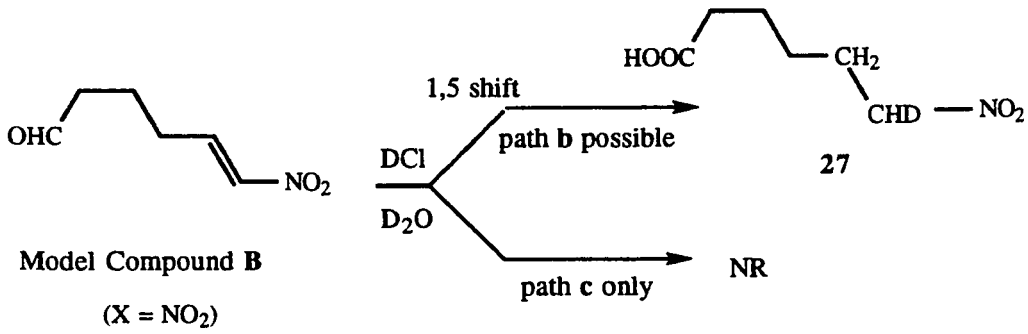
We planned to distinguish between path **b** and path **c** of **Scheme VII** (p. 10) by synthesizing the model compounds **A** and **B**. We were interested in these compounds because compound **A** models the second intermediate of path **c** and compound **B** models intermediate **23** except that only a 1,5-shift is possible. Hydrolysis of either one of these compounds might provide enough information to eliminate either path **b** or path **c**.

Scheme X illustrates our strategy. If the model compound **A** did not isomerize to the saturated ketone **26** under the reaction conditions utilized for the original hydrolysis, then path **c** in **Scheme VII** would be excluded. Similarly, if the model compound **B**, lacking the keto group, did not yield the saturated carboxylic acid **27**, then path **b** would be excluded. On the other hand, if both model compounds **A** and **B** rearranged to products **26** and **27** respectively, then the question would remain unanswered.

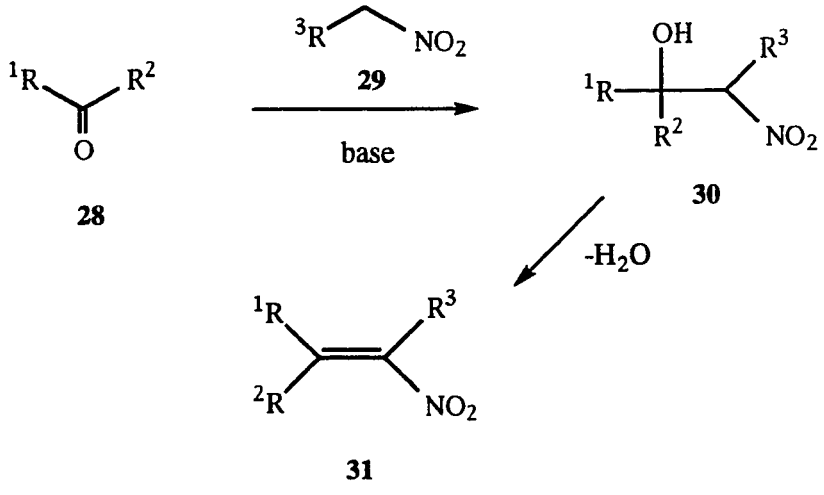
Most of our initial attempts at preparing either compound **A** or **B** (for $X = NO_2$) involved a Henry condensation to form the α,β-unsaturated nitro group. A Henry condensation[16] (**Scheme XI**) is the most general method for the preparation of nitroalkenes. Condensation of an aldehyde or ketone **28**, with a nitroalkane **29**, in presence of base, followed by dehydration of the resultant nitro alcohol **30**, yields a nitroalkene **31**.

Scheme X





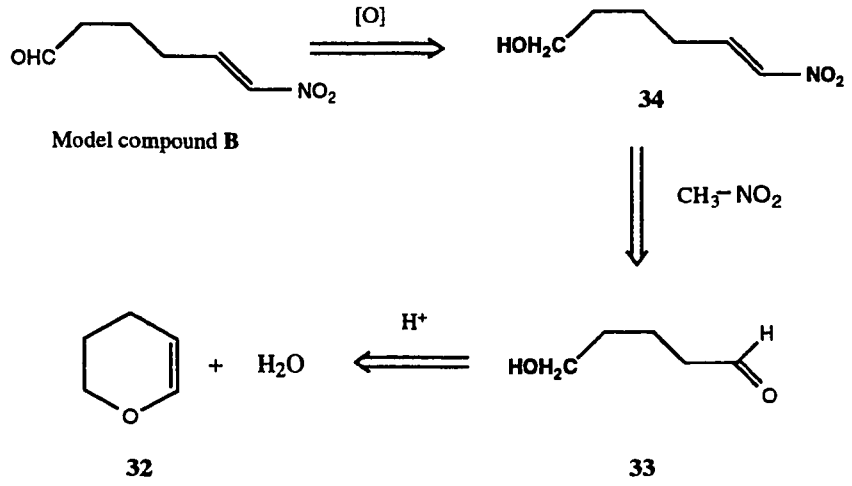
Scheme XI



Attempted Preparation of Model Compound B

Using the Henry condensation route, we designed a synthesis of the model compound **B** as shown in **Scheme XII.**

Scheme XII



The synthesis of compound **33** began with the hydrolysis of dihydropyran **32**.[17] The hydrolysis product was allowed to react with nitromethane in the presence of a catalyst, Amberlite IRA-400 (anion exchange resin; polymeric quaternary ammonium hydroxide).[18] This condensation reaction did not proceed as expected, but instead gave recovered starting material (as proved by NMR). Even when this reaction was repeated in ethylene glycol at reflux (bp 196-8 °C), the starting material was recovered unchanged. In another attempt,[19] KF was used as the basic catalyst. In this case isopropanol was used as a solvent, and a catalytic amount of

18-Crown-6 was added to accelerate the reaction. This reaction also yielded no product; only starting material was recovered. This nonreactivity of **33** can be explained by considering the tautomeric equilibrium shown in eq 3. 5-Hydroxypentanal (**33**) exists chiefly (95%) as 2-hydroxytetrahydropyran (**35**, cyclic structure) and only 5% as the acyclic structure **33**. The cyclic hemiacetal structure **35** is apparently very stable under the basic reaction conditions and therefore resisted attempts at direct condensation.

37 **39** (3)

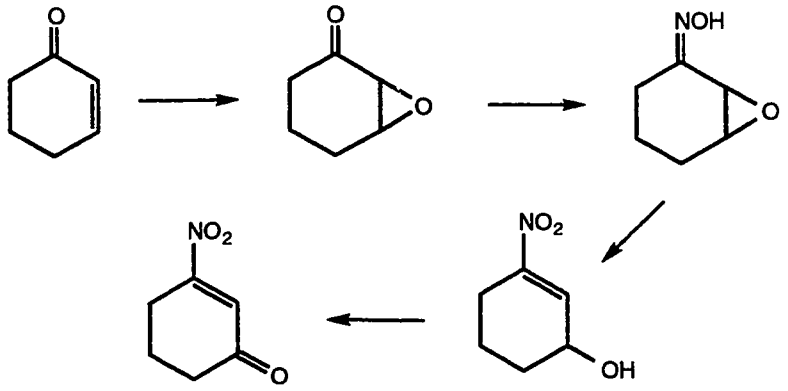
Attempted Preparation of Model Compound A

We first tried to synthesize model compound **A** by the method Corey[20] had used in the preparation of 3-nitro-2-cyclohexenone (**37**) (**Scheme XIII**). The intermediate compound **36** has functionality identical to our model compound **A**.

We began by attempting to epoxidize the double bond of cinnamaldehyde (**38**) as shown in **Scheme XIV**.[21] We envisioned a parallel scheme, beginning with epoxidation, to give **39**, conversion to the epoxy oxime (**40**), and finally oxidation to compound **41** (which is model compound **A** for R = Ph). The *tert*-butyl hydroperoxide epoxidation of cinnamaldehyde

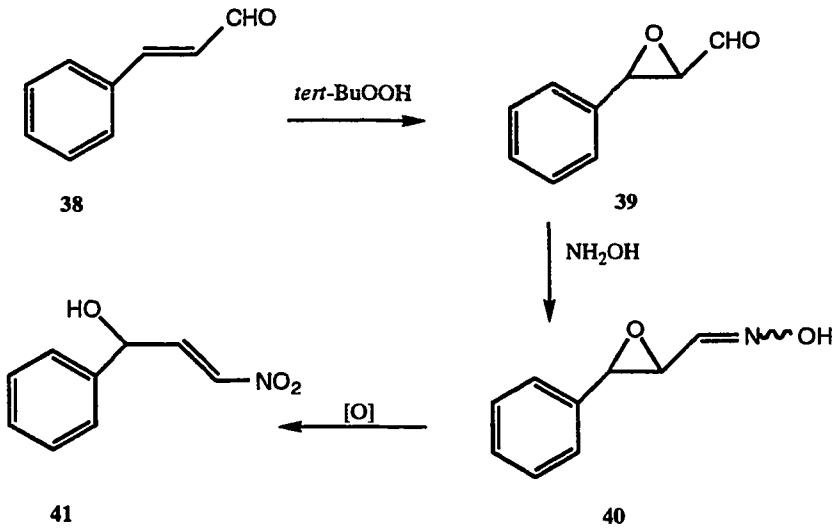
never went to completion, and it was very difficult to separate the epoxide from the cinnamaldehyde because of their similar boiling points.

Scheme XIII



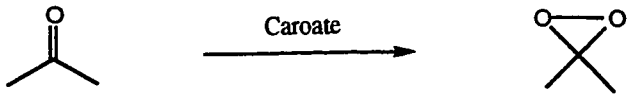
37 **36**

Scheme XIV



38 **39** **41** **40**

Next we tried Corey's method using crotonaldehyde (**42**) as shown in **Scheme XV**. By switching from a phenyl to a methyl group we were able to synthesize and purify the epoxide **43**[22] and the subsequent epoxyoxime **44**. In the final step, we decided to use dimethyl dioxirane (DD, **47**) for the oxidative rearrangement to **45**. DD has been found to be a very versatile oxidizing agent and has been used in place of peracids for many synthetic transformations.[23,24] We synthesized DD by oxidizing acetone with caroate using Adam's[25] procedure.



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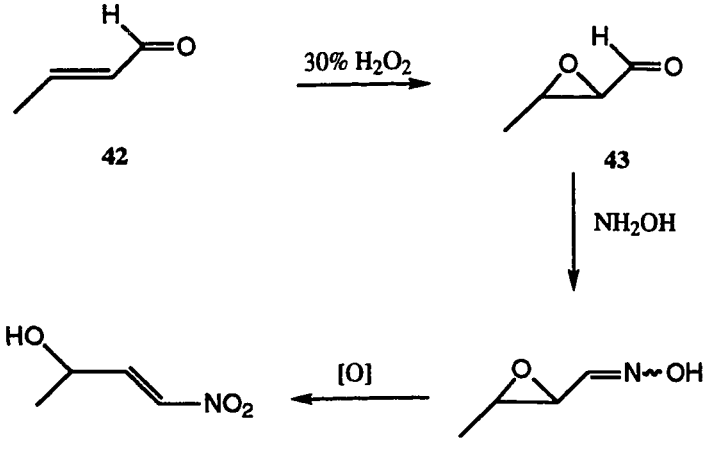
Scheme XV



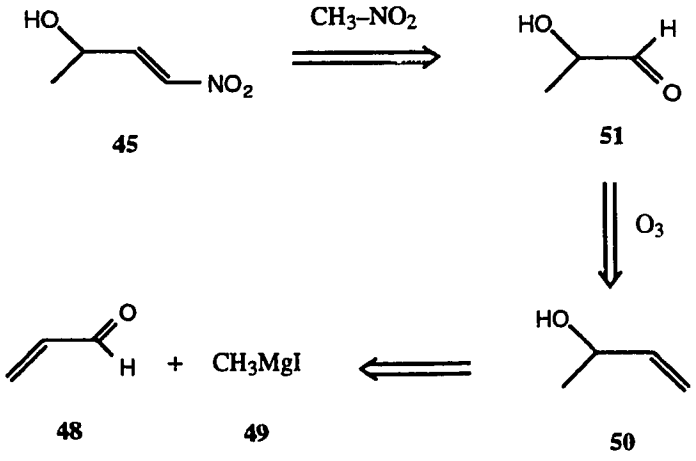
42 **43** **44** **45**

The reaction of DD with epoxyoxime **44** did not afford the expected product **45**, our model compound **A** for R = Me. Instead, only

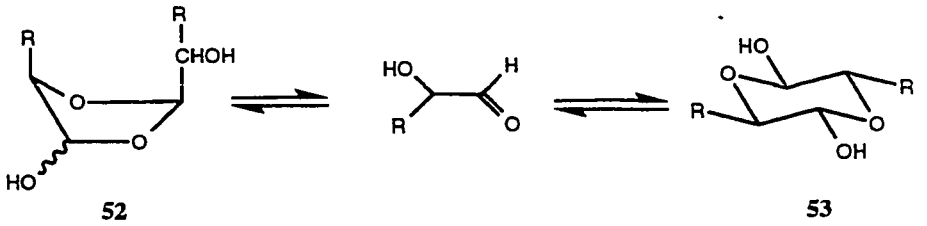
decomposition or polymerization byproducts were observed. The structure(s) of the decomposition products could not be determined.

Another approach for the synthesis of model compound **A** is shown in **Scheme XVI**. The key step in this retrosynthetic plan was the ozonolysis of an allylic alcohol to an α-hydroxyaldehyde.[26] We started with 3-buten-2-ol (**50**), which was prepared from methyl magnesium iodide (**49**), and acrolein (**48**). Attempts to ozonolyze the double bond were unsuccessful and we were unable to isolate the kinetically unstable ozonolysis product, α-hydroxybutyraldehyde (**51**).

Scheme XVI



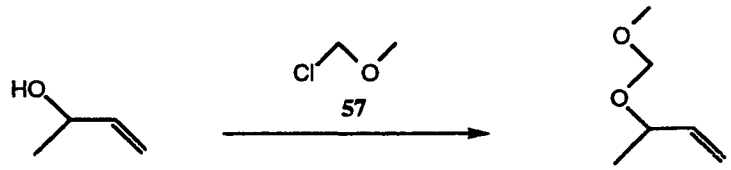
The fundamental problem with this approach is the known tendency for α-hydroxyaldehydes to dimerize as shown in eq 4.[27] These equilibria are known to favor the five and six membered ring dimers (**52** and **53** respectively) over the monomer.



52 53 (4)

Although NMR and GC clearly showed the disappearance of alkene in the ozonolysis, the product was not easily purified or characterized. Nevertheless, a Henry condensation was attempted with this crude starting material. Even though the IR spectrum of the crude product showed peaks consistent with the presence of a nitro group, the NMR spectrum did not indicate the presence of any desired product.

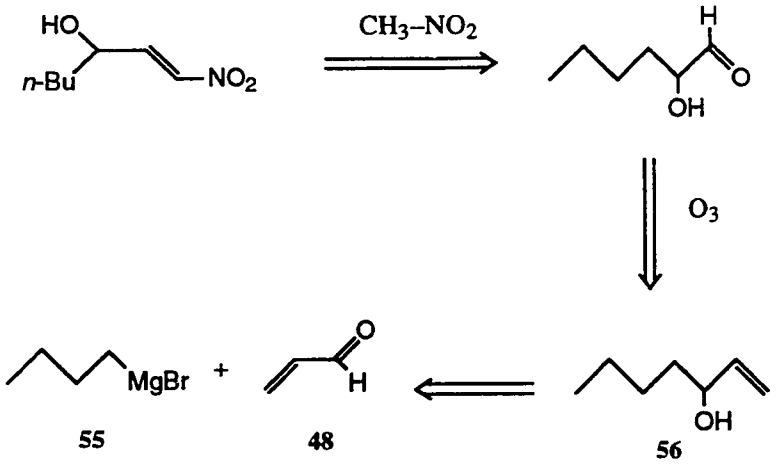
To avoid this dimerization problem we decided to protect the alcohol group of **50** as a methoxymethyl (MOM) ether **54**.



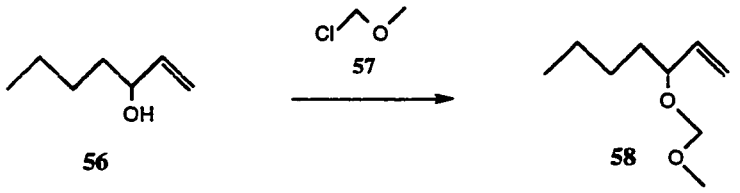
50 54

The above reaction yielded only 30% of the desired product (**54**) which was difficult to isolate pure. We suspected that a larger "R" group might give a more easily purified product. Hence, we tried changing the "R" group from a methyl to a *n*-butyl group as shown in **Scheme XVII**.

Scheme XVII



The starting material for the ozonolysis was 1-hepten-3-ol (**56**), which in turn was prepared from *n*-butyl magnesium bromide (**55**) and acrolein **48**. The result was the same; once again the α-hydroxyaldehyde appeared to exist primarily as a dimer. We again tried to protect the alcohol group of **56** as the MOM ether **58**.

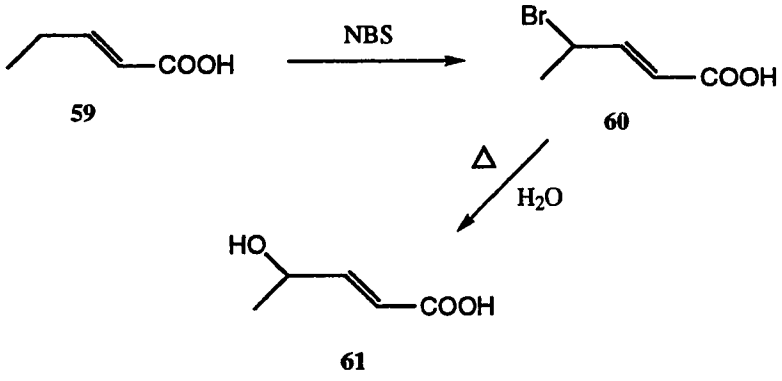


This reaction also proceeded in low yield and the product was difficult to isolate. The reason for the low yield in the case of R = Me might be the high volatility of the product, however the difficulties we experienced with the R = Bu are still unexplained.

Preparation of Model Compounds A

Frustrated by our inability to prepare model compound **A** with a nitro group, we shifted our attention to different electron withdrawing groups, such as a carboxylic acid or a nitrile. A synthetic plan for preparation of the model compound **A** with a carboxylic acid as the electron withdrawing group instead of nitro group is shown in **Scheme XVIII**.

Scheme XVIII



59 **60** **61**

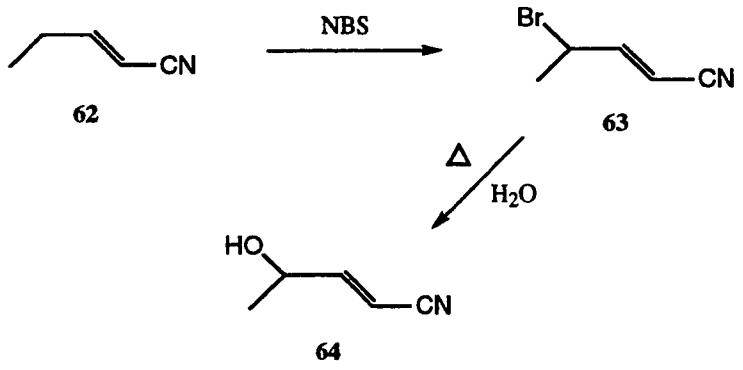
This scheme illustrates an essentially new synthetic strategy. Oxidation at the γ-carbon would follow formation of the α,β-unsaturated electron withdrawing group. We were unable to find any literature precedent for this new, more direct route.

Allylic bromination of *trans*-2-pentenoic acid (**59**) with N-bromo-succinimide resulted in the production of pure *trans*-4-bromo-2-pentenoic

acid (**60**) in high yield (90%). Hydrolysis of **60** in water gave *trans*-4-hydroxy-2-pentenoic acid (**61**) in excellent yield (90%).

We were also able to synthesize the model compound **A** with a nitrile group in place of the nitro group using a parallel approach (**Scheme XIX**).

Scheme XIX

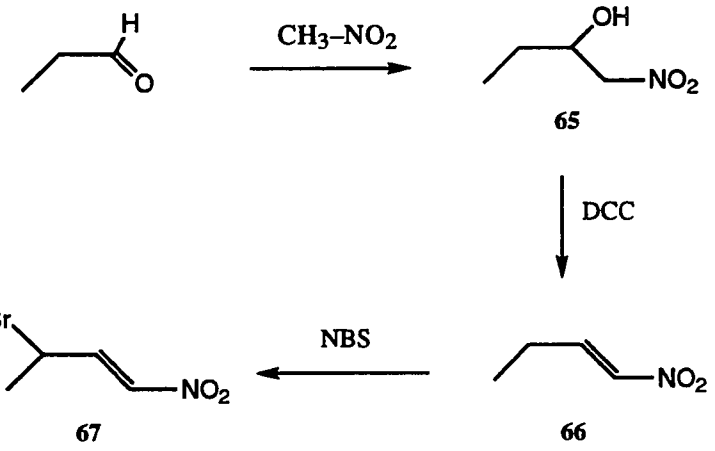


Here we started with *cis*-2-pentenonitrile (**62**). NBS bromination gave a mixture of *cis*- and *trans*-4-bromo-2-pentenonitrile (**63**) (90%). The final hydrolytic substitution gave *trans* product **64** in lower yield (57%) than the corresponding acid because of the tendency of the unsaturated nitrile to polymerize.

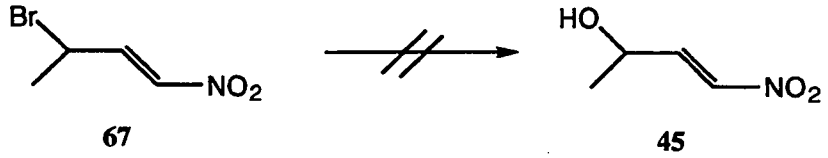
Our success with this "bromination/hydrolysis" methodology lead us to apply it to the model compound **A** (with a nitro group) which had resisted our previous synthetic attempts. **Scheme XX** shows our synthetic strategy. The necessary nitroalkene **66** was commercially available, but quite

expensive. Therefore it was synthesized by the Henry condensation method. Allylic bromination of nitroalkene **66** with NBS afforded bromoalkene **67**. The simple hydrolytic conversion to the alcohol, which had worked so well for the carboxylic acid and the nitrile, failed in this case.

Scheme XX

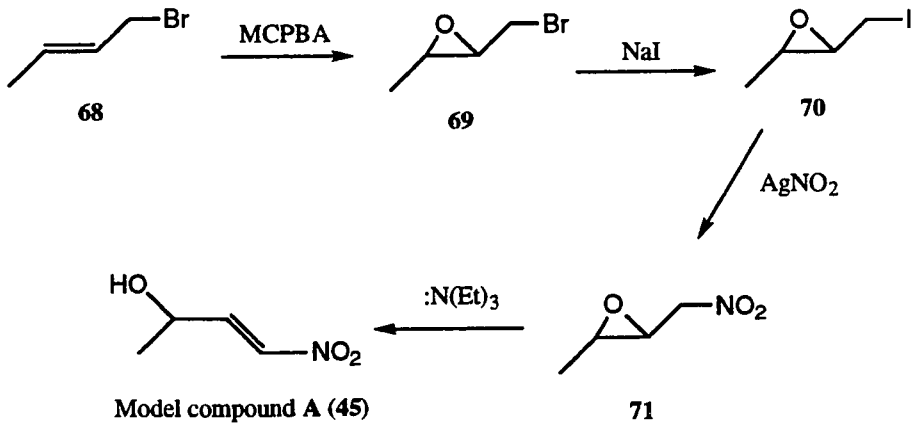


We varied solvent, concentration, base, temperature, and time, but all to no avail. In each and every attempt, the NMR showed the presence of an addition product (conjugate addition of water), and none of the substitution product.



Finally we returned to the literature and found a method based on the ring opening of a β,γ-epoxynitroalkane as shown in **Scheme XXI**.[28]

Scheme XXI

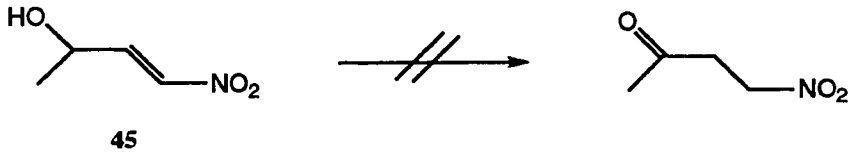


Epoxidation of crotyl bromide (**68**) gave 2,3-epoxy-1-bromobutane (**69**), which was converted to 2,3-epoxy-1-nitrobutane (**71**) in a two step procedure. It was necessary to form the iodoepoxide **70**, as nitration of the bromoepoxide was too slow to be of synthetic value. Compound **71**, in the presence of a catalytic amount of triethylamine, rearranged to *trans*-4-nitro-3-buten-2ol (**45**) (model compound **A** with R = Me). In the last step, care was taken not to use excess base which could have polymerized the product.

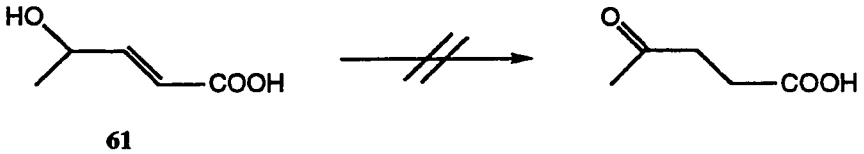
Attempted Rearrangement of Model Compounds A

Having synthesized the model compound **A** with three different electron withdrawing groups (**45**, **61** and **64**), we performed separate hydrolyses

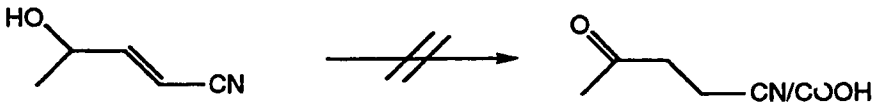
under the same reaction conditions that were used for the original hydrolysis of the nitrovinylfuran. None of the three model compounds showed any evidence of products resulting from 1,2 hydride shifts. This analysis was done by NMR spectroscopy.



45



61



64

We had authentic samples of each product except that with the nitro group. NMR spectra of all three crude reaction products showed no singlets attributable to the anticipated acetyl methyl groups of the 1,2-hydride shift products. The spectra of the crude products did show many peaks indicating either substitution (substitution of the hydroxy group by chloride) or addition (addition of HCl/H_2O to the double bond) or both substitution and addition products.

As the model compounds **45**, **61** and **64** do not undergo 1,2-hydride shifts to keto compounds, the nitrovinylfuran and γ-ketopimelic acid cannot be undergoing a 1,4-shift followed by a 1,2-shift as postulated by path **c** (**Scheme VII**, p. 10). These results clearly eliminate path **c** as a mechanistic possibility. By this process of elimination, path **b** (**Scheme VII**) remains as the only explanation for these "abnormal" furan hydrolyses. Therefore, the redox/rearrangements of nitrovinylfuran and the analogous carboxy and cyano analogs are indeed occurring by 1,5-hydride shifts.

Conclusions

Our experiments have shown that the model compounds **45, 61** and **64** did not isomerize to saturated ketones under the reaction conditions utilized for the original hydrolyses of nitrovinylfuran (**19a**), carboxyvinylfuran (**19b**), and cyanovinylfuran (**19c**). Spectroscopic evidence indicates the formation of addition and substitution products, but there is absolutely no evidence for any 1,2-hydride shifts in any of these model hydrolyses. Therefore path **c** has been eliminated as a mechanistic possibility. Because Bansal[14] and Baliga[15] had previously ruled out path **a**, path **b** (1,5-hydride shift) remains as the only reasonable mechanistic explanation for the abnormal hydrolyses of alkenylfurans.

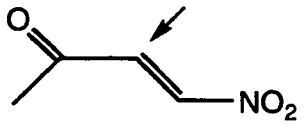
From our results we can also analyze the relative importance of stereoelectronic and electronic factors in controlling these hydride migrations. As our reactions are acid catalyzed, we do not know whether the hydride shift occurs prior to or following protonation of the substituents. In either case (neutral or protonated) we can predict the position for the hydride attack (α or β to the substituent) as described below.

Predictions for electronic control of hydride addition with neutral functional groups: These predictions are based upon the magnitude of the difference between the Hammet substituent constants (σ_p, sigma-*para*) of the carbonyl group and the nitro, cyano and carboxyl groups incorporated in the model compounds **45, 61** and **64**.[29] Hammet defined a series of substituent constants

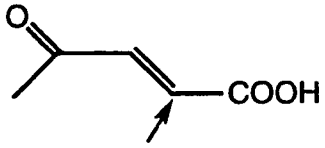
σ, which represent the effect of each substituent on the ionization of *meta* and *para* substituted benzoic acid under standard conditions. Substituents with large σ_p values are the better electron withdrawing groups. The σ_p values of the substituents of the model compounds are shown in **Table 1.**

Table 1. σ_p Values of Different Substituents

Substituent	σ_p value
—CO-R	0.50
$-NO_2$	0.75
—CN	0.66
—COOH	0.45



45



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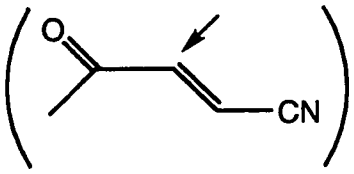
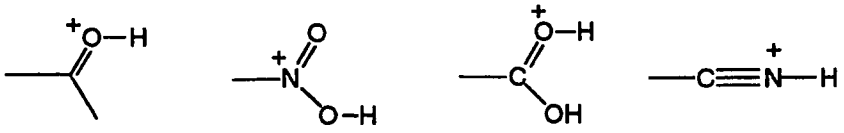


64

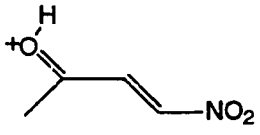
Based on σ_p constants, we can predict the "electronic preferences" for alkenes **45** and **61**. The hydride should attack beta to the nitro group in **45**, whereas the hydride attack should be alpha to the carboxylic acid in **61**. In the cyanoalkene **64**, the preferred site of hydride attack is difficult to predict. If the nitrile is hydrolyzed to a carboxylic acid before the hydride attack, then the hydride would be located alpha to the nitrile (carboxylic acid) in the product, whereas if the nitrile group is hydrolyzed after the hydride attack, then the hydride would be located beta to the nitrile group in the product.

Predictions for electronic control of the hydride addition with protonated functional groups: In the cases of protonated substituents, the sites of hydride attack can be predicted by taking the pK_a values into consideration as shown below.

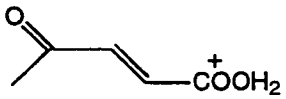


pK_a	-7	-11	-6	-10

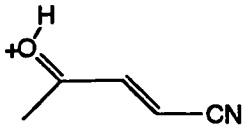
From the above pK_a values the preferred protonated structures for $(\mathbf{45\text{-}H})^+$, $(\mathbf{61\text{-}H})^+$, and $(\mathbf{64\text{-}H})^+$ are shown below.



(45-H)$^+$



(61-H)$^+$



(64-H)$^+$

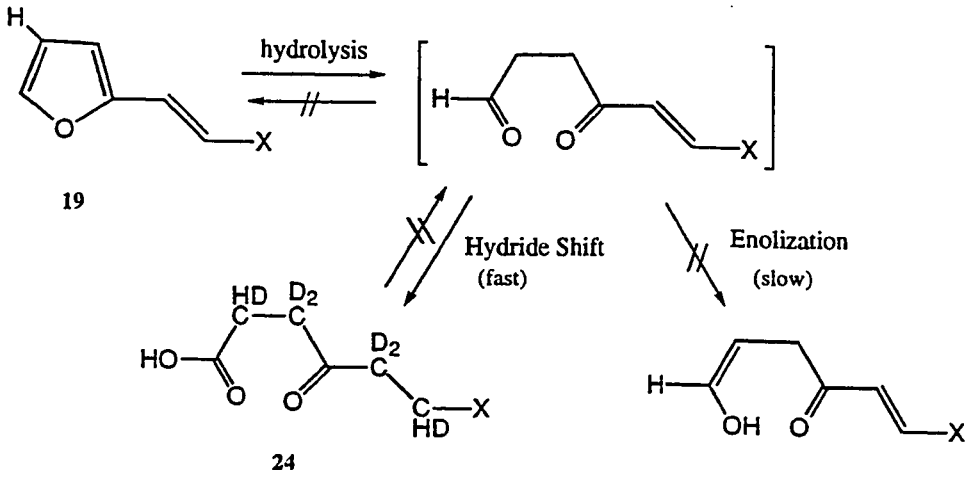
In these cases, we expect hydride attack beta to the protonated substituent. The predictions for the sites of hydride attack are exactly the opposite of those for the neutral substituents.

Our work has shown that there is no evidence for the rearranged product when hydroxyalkenes **45, 61** or **64** are subjected to hydrolytic reaction conditions. With the original alkenylfurans, the hydride migration was always beta to the electron withdrawing group regardless of the substituent used. These results lead to the conclusion that it is not the nature of the electron withdrawing group (electronic control) which is directing the hydride shift. Indeed, what we have proven is that it is the *exo*-selectivity (stereoelectronic control) that is directing the hydride migration in these acid catalyzed hydrolyses of alkenylfurans.

Our results allow us to extend earlier conclusions based on deuterium labelling experiments (Bansal,[14] **Scheme VIII**). The fact that a single hydrogen atom is retained adjacent to the newly formed carboxyl group of **24** (proved by NMR) reveals that the rate of hydride transfer should be much faster than the

rate of enolization, and that the hydride transfer is irreversible (shown in Scheme XXII).

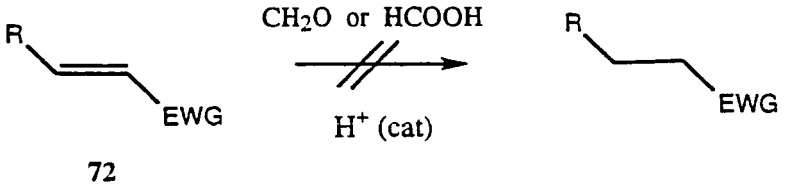
Scheme XXII



19 24

Future work

In the future, we would like to do some intermolecular competition experiments to learn more about the electronic preferences for the hydride transfer. Baliga[15] already attempted to accomplish this task by using the systems like 72 with one electron withdrawing group. As she did not observe any intermolecular reduction of the double bond, she was unable to directly determine the "electronic" effects of various substituents on the reaction.



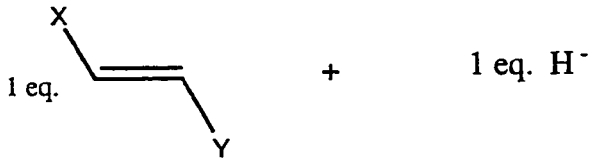
72

EWG = NO_2, COOH, CN

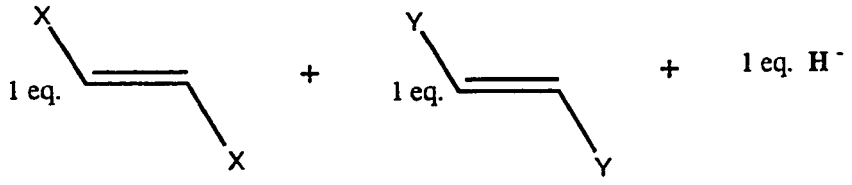
R = Me, Ph

Assuming that α,β-disubstituted alkenes will be more susceptible to hydride reduction, future work might involve the use of systems with two electron withdrawing groups, to perform internal and normal competition experiments as shown below (X≠Y).

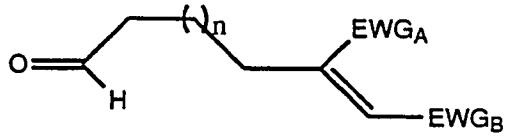
Internal competition:



Normal competition:



In addition to these competition experiments, future work might also involve synthesis of model compounds with a tethered hydride donor and different electron withdrawing groups on either end of the double bond. Such compounds will enable us to learn about the relative abilities of different electron withdrawing groups to activate the conjugated alkene as a hydride acceptor.



Different chain lengths will allow us to gain a better understanding of the stereoelectronic preferences of the hydride transfer.

Experimental Section

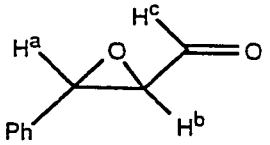
General Procedures. IR spectra were recorded on a Perkin-Elmer 1620 FTIR Spectrophotometer. Band positions are reported in reciprocal centimeters (cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded in parts per million (ppm) relative to TMS, on a 300 MHz QE Plus Spectrometer. Capillary GC analyses were performed on an HP 5880 with FID detector and a DB-5 column.

5-Hydroxypentanal (33).[17] Dihydropyran (50 g, 0.60 mol) and 0.2 N HCl (200 mL, 40.0 mmol) were heated to reflux. After 40 minutes of refluxing, the water insoluble layer had disappeared. After another 20 min, the refluxing mixture had turned brown. The acidic mixture was neutralized by adding 0.4 N NaOH and then distilled under reduced pressure to yield 5.8 g (10%) of 33, bp 57-59 °C/3 mm (lit.[17] bp 54-55 °C/3 mm). The reported yield for this procedure[17] was 40 g (65%). By NMR the product exists as a mixture of 2-hydroxytetrahydropyran (cyclic structure, 95%) and 5-hydroxypentanal (acyclic structure, 5%).
^{1}H-NMR (300 MHz, $CDCl_3$) 5.42 (broad s, 1H), 4.87 (broad s, 1H), 4.06-3.97 (m, 1H), 3.59-3.48 (m, 1H), 1.89-1.75 (m, 2H), 1.55-1.47 (m, 4H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) 93.9, 63.3, 31.7, 25.0, and 20.1 ppm.

Attempted Preparation of 6-Nitro-5-hexen-1-ol (34). The procedure of Melvin and Abbott[18] was followed. Nitromethane (0.50 g, 8.2 mmol), 2-hydroxy-tetrahydropyran (0.30 g, 2.9 mmol), Amberlite IRA-400 (0.20 g, ion exchange resin), and ethanol (40 mg, 0.87 mmol) were mixed in a flask and stirred

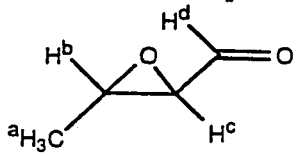
overnight. After the reaction was complete, the resin was removed by filtration and washed with ethanol. The washings were combined and distilled under reduced pressure. No reaction was observed and the starting material was recovered (proved by NMR). The same reaction was performed several times varying temperature, solvent, base, and reaction times. In each case, starting material was recovered.

2,3-Epoxycinnamaldehyde (39).[21] To a 300-mL round bottom flask equipped with a Beckman pH meter, a dropping funnel, a magnetic stirrer, and a thermometer were added methanol (50 mL) and *tert*-butyl hydroperoxide (9.60 g of 70% aqueous solution, 79.4 mmol). The pH meter was adjusted to 10.5 $\pm$ 0.2 (the pH for methanol solvent as determined by pH meter was generally about 1 unit higher than that determined by indicator paper) by the addition of 1 N NaOH and maintained at that pH as cinnamaldehyde (8.25 g, 62.5 mmol) was added at 35-40 °C over 1 h. Stirring was continued for another 5 h. Additional 1 N NaOH (3-5 mL) was added during the course of the reaction to maintain the desired pH. The reaction mixture was then diluted with water (200 mL) and extracted with chloroform (3 x 25 mL). The extracts were then combined, washed with saturated NaCl solution (1 x 50 mL), dried ($MgSO_4$), concentrated, and finally distilled under reduced pressure. The yield of 2,3-epoxy-cinnamaldehyde was 5.8 g (65%), bp 75-77 °C/0.5 mm (lit.[21] bp 66-68 °C/0.2 mm). The presence of unreacted cinnamaldehyde (~10%), which codistills with the product, was unavoidable even with prolonged reaction times.



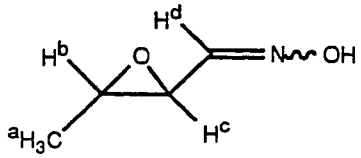
^{1}H-NMR (300 MHz, $CDCl_3$) 9.12 (d, J_{bc} = 7.8 Hz, 1H_c, *E*), 7.6-7.2 (m, 5H, *E*), 4.52 (d, J_{ab} = 2.2 Hz, 1H_a, *E*), 3.39 (dd, J_{bc} = 7.8 Hz, J_{ab} = 2.2 Hz, 1H_b, *E*) ppm. Cinnamaldehyde peaks: 9.65 (d, J = 8.0 Hz, 1H), 7.5-7.4 (m, 3H), 7.4-7.3 (m, 3H), 6.65 (dd, J = 16.1 Hz, J = 8.0 Hz, 1H) ppm.

2,3-Epoxybutanal (43).[22] In a 500-mL round bottom flask equipped with a condenser and an addition funnel were placed water (60 mL) and hydrogen peroxide (24.0 g of 30% aqueous solution, 212 mmol). While stirring at 35-40 °C, crotonaldehyde (14.0 g, 200 mmol) was added over 0.5 h at pH 8-8.5 (pH was maintained by the addition of 1 N NaOH). After 3-5 h at the same temperature and pH, gas chromatography showed the disappearance of the starting material and the appearance of one large peak (*E* isomer, >95%) followed by a small peak (*Z* isomer, <5%). As the product was very soluble in water it was very difficult to purify by extraction with ether. CH_2Cl_2 was found to be a better solvent for extraction. After 20-30 extractions the yield was 6.85 g (42%), bp 30-33 °C/2.0 mm (lit.[22] bp 60-61 °C/80 mm, 56%).



^{1}H-NMR (300 MHz, $CDCl_3$) 9.02 (d, J_{cd} = 5.3 Hz, 1H_d, *E*) 3.33 (dd, J_{cd} = 5.3 Hz, J_{bc} = 1.8 Hz, 1H_c, *E*), 3.11 (qd, J_{ab} = 6.1 Hz, J_{bc} = 1.8 Hz, 1H_b, *E*), 1.45 (d, J_{ab} = 6.1 Hz, 3H_a, *E*) ppm; IR (film) 1726 cm^{-1} (CHO).

2,3-Epoxy-1-butoxime (44). A general procedure for the preparation of oximes[30] was followed. A solution of 2,3-epoxybutanal (300 mg, 3.49 mmol) in ether (2 mL) was treated with hydroxylamine hydrochloride, $NH_2OH{\cdot}HCl$, (241 mg, 3.40 mmol) and sodium bicarbonate (0.19 g, 2.3 mmol; must be limiting reagent to avoid epoxide opening). The mixture was stirred vigorously at 15-20 °C after adding water (0.05 mL) to initiate the reaction. After 2-5 min of CO_2 evolution, the ether solution was pipetted away from the insoluble salt, dried ($MgSO_4$), then concentrated. The resulting crude epoxyoxime (305 mg, 131% ?) was pure enough to continue to the next reaction. [Note: Payne,[22] noted that the glycidaldehyde oxime polymerized explosively after a 1-2 h period at room temperature. In our case the product turned dark after several hours. We never attempted this reaction on a large scale.]



^{1}H-NMR (300 MHz, $CDCl_3$) 7.06 (d, J_{cd} = 8.2 Hz, 1H_d), 3.29 (dd, J_{cd} = 8.2 Hz, J_{bc} = 2.6 Hz, 1H_c), 3.12 (qd, J_{ab} = 5.2 Hz, J_{bc} = 2.6 Hz, 1H_b), 2.00 (s, 1H), 1.40 (d, J_{ab} = 5.2 Hz, 3H_a) ppm; IR (film) 1651 cm^{-1} (C=N). [A peak at 1716 cm^{-1} indicated some residual aldehyde, but there was no corresponding evidence in the NMR.]

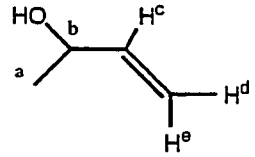
Dimethyl Dioxirane (DD), (47).[25] A 5-L, 3-neck, round bottom reaction flask was equipped with an efficient mechanical stirrer, addition funnel for solids, and a condenser (loosely packed with glasswool) connected to a receiver, which in turn was connected to a trap and an aspirator. The reaction flask

was charged with a mixture of water (170 mL), acetone (130 mL, 3.04 mol), and sodium bicarbonate (39.0 g, 0.464 mol), and cooled to 5-10 °C. While vigorously stirring and cooling, caroate (peroxy monosulfate, 80.0 g, 0.130 mol) was added in five portions at 30 min intervals. Three minutes after the start of the last addition, a slight vacuum (80-100 torr) was applied through the aspirator. The cooling bath was removed and, while vigorously stirring, the dimethyl dioxirane along with acetone was distilled and collected in a precooled (-78 °C) receiving flask. The resulting DD solution (100 mL, 0.085 M, 6.5% yield) was dried with anhydrous K_2CO_3.
^{1}H-NMR (300 MHz, acetone-d_6) showed in addition to the huge solvent signal, a small singlet at 1.65 ppm for the DD methyl protons. It was difficult to calculate the ratio of DD/acetone from the ^{1}H or ^{13}C spectra. Therefore, an assay for the dioxirane content was done by oxidation of phenyl methyl sulfide.[28]

Attempted Preparation of 4-Nitro-3-buten-2-ol (45).[28] The procedure of Murray and Jayaraman[24] was followed. Freshly prepared 47 (20 mL of a 0.085 M solution, 1.7 mmol of DD) was mixed with epoxyoxime 44 (0.21 g, 2.1 mmol) in acetone (20 mL) and stirred for 4 h. Decomposition resulted even at reduced reaction times.

Methyl Magnesium Iodide (49). This Grignard reagent was prepared on a 0.2 mol scale by the method used for the preparation of phenyl magnesium bromide.[31] After the reaction was complete, the reaction mixture was used for the next reaction without analysis or purification.

3-Buten-2-ol (50).[32] The reaction procedure was based on that used for the synthesis of triphenylmethanol.[31] Acrolein (10.2 g, 182 mmol) was used as the starting material. After the workup 7.72 g (59%) of 3-buten-2-ol was obtained sufficiently pure so that distillation was unnecessary.



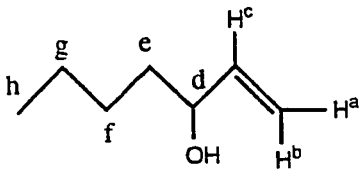
^{1}H-NMR (300 MHz, $CDCl_3$) 5.90 (ddd, J_{ce} = 18.1 Hz, J_{cd} = 10.0 Hz, J_{bc} = 6.4 Hz, $1H_c$), 5.21 (dt, J_{ce} = 18.1 Hz, $J_{be,\ de}$ = 1.9 Hz, $1H_e$), 5.06 (dt, J_{cd} = 10.0 Hz, $J_{de,\ bd}$ = 1.9 Hz, $1H_d$), 4.29 (distorted quintet, $J_{ab,\ bc}$ = 6.4 Hz, $1H_b$), 2.52 (broad s, 1H), 1.28 (d, J_{ab} = 6.7 Hz, $3H_a$) ppm.

Attempted Preparation of 2-Hydroxypropanal (51).[26] 3-Buten-2-ol (15 mL of a 0.200 M solution in CH_2Cl_2, 2.20 g, 30.6 mmol) was cooled to -78 °C in dry ice/acetone bath. A stream of O_3 gas (generated with a Welsbad II ozonizer) was bubbled through the solution until a light blue color persisted. The solution was then purged with nitrogen gas until it became colorless. The mixture was then treated with excess dimethyl sulfide and stirred at -78 °C for 1 h. The mixture was slowly warmed to room temperature and stirred for two more hours. The solvent was evaporated under vacuum, then the crude product was analyzed by NMR. There were no peaks attributable to the alkene starting material or to the aldehyde product.

Butyl Magnesium Bromide (55). This Grignard reagent was prepared on a

0.2 mol scale by the method used for the preparation of phenyl magnesium bromide.[31] After the reaction was complete, the reaction mixture was used for the next reaction without analysis or purification.

1-Hepten-3-ol (56).[33] The procedure was the same as that used for the preparation of 50 (0.181 mol scale). After the workup, 13.6 g (66%) of 1-hepten-3-ol was obtained sufficiently pure so that distillation was unnecessary.



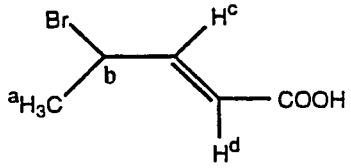
^{1}H-NMR (300 MHz, $CDCl_3$) 5.85 (ddd, J_{bc} = 17.0 Hz, J_{ac} = 10.4 Hz, J_{cd} = 6.4 Hz, $1H_c$), 5.20 (dt, J_{bc} = 17.0 Hz, $J_{ab,\,bd}$ = 1.4 Hz, $1H_b$), 5.08 (dt, J_{ac} = 10.4 Hz, $J_{ab,\,ad}$ = 1.4 Hz, $1H_a$), 4.07 (distorted quartet, $J_{cd,\,de}$ = 6.4 Hz, $1H_d$), 1.57-1.49 (m, $2H_e$), 1.41-1.37 (m, $4H_{f,\,g}$), 0.90 (virtual t, J_{hg} = 4.5 Hz, $3H_h$) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) 141.3, 114.4, 73.1, 36.7, 27.5, 22.6, 14.0 ppm.

Chloromethyl Methyl Ether (57). The procedure of Marvel and Porter[34] was followed on a 0.84 mol scale to yield 34 g (50%) following distillation. ^{1}H-NMR (300 MHz, $CDCl_3$) 5.47 (s, 2H), 3.50 (s, 3H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) 84.6, 57 4 ppm.

3-(Methoxymethoxy)-1-butene (54). The procedure of Kluge, Untch, and Fried[35] was followed. To a 100-mL round bottom flask equipped with a reflux condenser were added 3-buten-2-ol (800 mg, 11.1 mmol) and NaH (800 mg of a

50% mineral oil dispersion; 16.7 mmol) under nitrogen. The mineral oil was removed by washing with pentane (2 x 25 mL). After removing the pentane, a solution of chloromethyl methyl ether (1.35 g, 16.8 mmol) in anhydrous ether (6 mL) was added dropwise over 10 min and then heated to reflux. After 1 h, the resulting mixture was cooled to room temperature then poured into water (100 mL). The product was isolated by extraction with ether (3 x 20 mL). The ether layer was dried ($MgSO_4$), then concentrated to yield a mixture which included the starting material and the product (0.70 g total recovery, ~15% product).

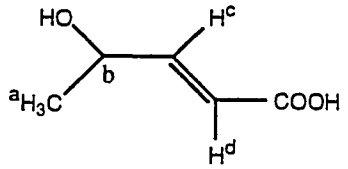
4-Bromo-2-pentenoic Acid (60).[36] The procedure of Greenwood, Kellert, and Sedlak[37] was followed. A 50-mL round bottom flask, equipped with a stirrer and a reflux condenser, was charged with 2-pentenoic acid (2.50 g, 25.0 mmol), N-bromosuccinimide (3.85 g, 21.6 mmol), benzoyl peroxide (30 mg, catalyst), and CCl_4 (15 mL). The reaction mixture was stirred and heated to reflux in a nitrogen atmosphere for 3-4 h while being illuminated with a 40 W bulb. The reaction was followed by TLC (8:2, hexane/ether). When the reaction was complete, succinimide (ppt) was floating on the top of the solvent. The crude product (96% yield) was recrystallized from toluene. The recrystallized product was washed with pentane to remove the toluene. The yield of 60 was 3.16 g (80.1%), mp 78 °C (lit.[36] mp 76 °C).



^{1}H-NMR (300 MHz, $CDCl_3$) 11.47 (broad s, 1H, *E*), 7.14 (dd, J_{cd} = 15.5 Hz, J_{bc} = 8.1 Hz, $1H_c$, *E*), 5.95 (dd, J_{cd} = 15.5 Hz, J_{bd} = 0.8 Hz, $1H_d$, *E*), 4.72 (dqd, J_{bc} = 8.1

Hz, J_{ab} = 6.7 Hz, J_{bd} = 0.8 Hz, 1H_b, *E*), 1.84 (d, J_{ab} = 6.7 Hz, 3H_a, *E*) ppm; IR (film) 2692 (COOH), 1688 (C=O), 1638 (C=C), 936 cm^{-1} (C-Br).

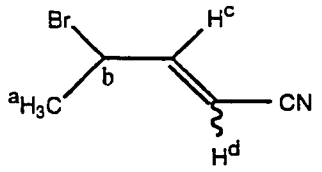
4-Hydroxy-2-pentenoic Acid (61).[38] In a 25-mL round bottom flask, 3-bromo-2-pentenoic acid (1.04 g, 5.81 mmol) was heated overnight (18-20 h) in water (10-15 mL) at 80-90 °C. The resulting water layer was saturated with NaCl and then extracted with ether (3 x 20 mL). The crude product (0.64 g, 95%) was obtained with a minor (2-5%) organic byproduct, which was removed by trituration with pentane. The final purification was done by column chromatography (silica gel, gradient elution with hexane/ether). The chromatographed product weighed 0.62 g (92%), bp 81-85 °C/<0.8 mm. A trace amount of acetic acid was used in the column chromatography to assist in the rapid elution of the hydroxypentenoic acid.



^{1}H-NMR (300 MHz, $CDCl_3$) 7.07 (dd, J_{cd} = 15.5 Hz, J_{bc} = 4.4 Hz, 1H_c, *E*), 6.05 (dd, J_{cd} = 15.5 Hz, J_{bd} = 1.7 Hz, 1H_d, *E*), 4.55 (dqd, J_{ab} = 6.6 Hz, J_{bc} = 4.4 Hz, J_{bd} = 1.7 Hz, 1H_b, *E*), 1.36 (d, J_{ab} = 6.6 Hz, 3H_a, *E*) ppm, [OH peaks not observed; presumably very broad]; IR (film) 3390 (OH), 2923 (COOH), 1702 (C=O), 1656 cm^{-1} (C=C); MS (70 ev; EI) *m/z* 115 (2, M-1), 101 (20, M-15), 73 (100, M-43); MS (70 ev; CI, NH_3) *m/z* 151 (14, M+NH_4+NH_3), 134 (100, M+NH_4).

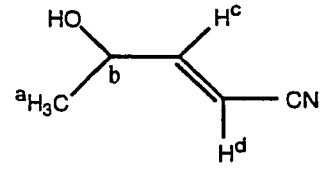
4-Bromo-2-pentenonitrile (63).[39] The procedure was the same as that used for the synthesis of 60 (180 mmol scale). The crude product weighed 25.2 g (88%).

The product was distilled under reduced pressure to yield 21.7 g (76%) of 66:44 mixture of *E*/*Z* isomers, bp 40-42 °C/0.5 mm.



^{1}H-NMR (300 MHz, $CDCl_3$) 6.80 (dd, J_{cd} = 16.1 Hz, J_{bc} = 8.0 Hz, 1H_c, *E*), 6.61 (t, J_{cd} = 10.7 Hz, J_{bc} = 10.7 Hz, 1H_c, Z), 5.55 (dd, J_{cd} = 16.1 Hz, J_{bd} = 1.1 Hz, 1H_d, *E*), 5.30 (d, J_{cd} = 10.7 Hz, 1H_d, Z), 5.03 (dq, J_{bc} = 10.7 Hz, J_{ab} = 6.7 Hz, `H_b, Z), 4.67 (dqd, J_{bc} = 8.0 Hz, J_{ab} = 6.8 Hz, J_{bd} = 1.1 Hz, 1H_b, *E*), 1.83 (d, J_{ab} = 6.7 Hz, 3H_a, Z), 1.82 (d, J_{ab} = 6.8 Hz, 3H_a, *E*) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) 153.7 (*E*), 153.2 (Z), 116.2 (*E*), 113.8 (Z), 100.2 (*E*), 98.6 (Z), 44.0 (*E*), 42.5 (Z), 25.0 (Z), 24.1 (*E*) ppm.

4-Hydroxy-2-pentenonitrile (64).[40] The procedure was the same as that used for the synthesis of 61 (12 mmol scale). To avoid polymerization, care should be taken not to overheat the reaction, and the reaction should be stopped as soon as the water insoluble layer disappears. After passing the crude product through a chromatographic column (silica gel, gradient elution with hexane/ether), the recovered product weighed 0.70 g (58%), bp 77-79 °C/0.5 mm (lit.[40] bp 76-78 °C/0.5 mm). Because the product tended to polymerize the yield was low compared to that of 61.



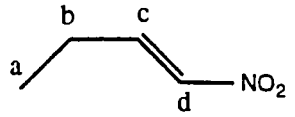
^{1}H-NMR (300 MHz, $CDCl_3$) 6.80 (dd, J_{cd} = 16.3 Hz, J_{bc} = 3.9 Hz, 1H_c, *E*), 5.66 (dd, J_{cd} = 16.3 Hz, J_{bd} = 2.0 Hz, 1H_d, *E*), 4.46 (qdd, J_{ab} = 6.8 Hz, J_{bc} = 3.9 Hz, J_{bd}

= 2.0 Hz, $1H_b$, *E*), 1.31 (d, J_{ab} = 6.8 Hz, $3H_a$, *E*) ppm; minor peaks attributable to the *Z* isomer (1-2%) were also found in the ^{1}H-NMR; ^{13}C-NMR (75 MHz, $CDCl_3$) 158.3, 117.4, 97.8, 66.8, 22.1 ppm; IR (film) 3420 (OH), 2228 (CN), 1461 cm^{-1} (C=C); MS (70 ev; EI) *m/z* 96 (8, M-1), 82 (52, M-15), 54 (100, M-43); MS (70 ev; CI, NH_3) *m/z* 132 (27, M+NH_4+NH_3), 115 (100, M+NH_4).

1-Nitro-2-butanol (65).[18] Nitromethane (39.1 g, 0.640 mol), propanal (29.0 g, 500 mmol), and Amberlite IRA 400 (7.50 g, catalyst) were mixed in ethanol (40 mL) and stirred vigorously for 18-20 h. There was an initial rise in temperature to 55 °C, but for most of the reaction temperature was kept at about 30-35 °C. At the end of the reaction, the catalyst resin was removed by filtration then washed with ethanol (2 x 20 mL). The washes were then combined with the reaction mixture, concentrated, and distilled at reduced pressure to afford pure 70 (32.4 g, 54.5%) bp 73-75 °C/1 mm.
^{1}H-NMR (300 MHz, $CDCl_3$) 4.5-4.3 (m, 2H), 4.3-4.2 (m, 1H), 3.45 (broad s, 1H), 1.57 (quintet, J = 6.7 Hz, 2H), 1.1 (t, J = 6.7 Hz, 3H) ppm.

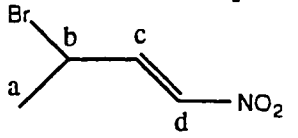
1-Nitro-1-butene (66).[41] A solution of nitroalcohol 65 (5.95 g, 50.0 mmol) and dicyclohexyl carbodiimide, DCC, (12.4 g, 60.8 mmol) in ether (30 mL) was mixed with CuCl, cuprous chloride (0.120 g, 1.21 mmol) then stirred under nitrogen for 15-16 h at 30-35 °C. At the end of the reaction, pentane (60 mL) was added at 0 °C and the urea was removed by filtration. The filtrate was washed thoroughly with 2% HCl (1 x 50 mL), H_2O (1 x 100 mL), saturated NaCl solution (1 x 50 mL), dried ($MgSO_4$), then carefully concentrated. The

crude product still containing a little urea, was then distilled under reduced pressure to give 3.33 g (65%) of a colorless liquid.



^{1}H-NMR (300 MHz, $CDCl_3$) 7.34 (dt, J_{cd} = 13.4 Hz, J_{bc} = 6.7 Hz, $1H_c$, *E*), 6.98 (dt, J_{cd} = 13.4 Hz, J_{bd} = 1.8 Hz, $1H_d$, *E*), 2.33 (qd, J_{ab} = 6.8 Hz, $J_{ab,\,bc}$ ~ 6.8 Hz, J_{bd} = 1.8 Hz, $2H_b$, *E*), 1.14 (t, J_{ab} = 6.8 Hz, $3H_a$, *E*) ppm; minor peaks attributable to the *Z* isomer (<5%, stereochemical assignment based on J_{cd} = 10.1 Hz) were also found in the ^{1}H-NMR; IR (film) 3107 (=C–H) and 1649 (C=C), 1526 and 1355 cm^{-1} (NO_2).

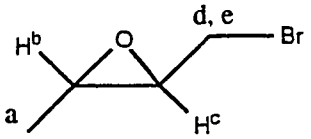
3-Bromo-1-nitro-1-butene (67). The procedure was the same as that used for the synthesis of60[37] (27 mmol scale), except that the reaction time was prolonged from 3 h to 10 h. The reaction was followed by TLC (8:2, hexane/ether). The crude yield of colorless liquid was 3.60 g (75%).



^{1}H-NMR (300 MHz, $CDCl_3$) 7.35 (dd, J_{cd} = 14.0 Hz, J_{bc} = 8.0 Hz, $1H_c$), 7.12 (d, J_{cd} = 14.0 Hz, $1H_d$), 4.75 (distorted quintet, J_{bc} = 8.0 Hz, J_{ab} = 7.1 Hz, $1H_b$), 1.9 (d, J_{ab} = 7.1 Hz, $3H_a$).

1-Bromo-2,3-epoxybutane (69).[42] A 250-mL three neck flask equipped with a magnetic stirrer was charged with crotyl bromide (5.00 g, 37.1 mmol). *meta*-Chloroperoxybenzoic acid (8.00 g, 46.4 mmol) dissolved in CH_2Cl_2

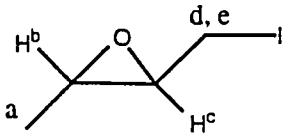
(100 mL) was added to this solution with vigorous stirring (0.5 h). The mixture was heated to reflux for 2 h then stored overnight. The contents of the flask were cooled in an ice bath and the precipitated *meta*-chlorobenzoic acid was removed by filtration. The organic layer was washed with freshly prepared 20% bisulfite solution (2 x 25 mL), 10% sodium bicarbonate solution (2 x 25 mL), dried ($MgSO_4$), then concentrated. Distillation under reduced pressure afforded 3.57 g (64%) of the epoxide, bp 55-58 °C/<1 mm.



^{1}H-NMR (300 MHz, $CDCl_3$) 3.40 (d, J_{ce} = 5.9 Hz, $1H_e$, *E*), 3.34 (d, J_{cd} = 5.9 Hz, $1H_d$, *E*) 3.00 (td, $J_{cd, ce}$ = 5.9 Hz, J_{bc} = 2.0 Hz, $1H_c$, *E*), 2.96 (qd, J_{ab} = 5.2 Hz, J_{bc} = 2.0 Hz, $1H_b$, *E*) 1.35 (d, J_{ab} = 5.2 Hz, $3H_a$, *E*) ppm; minor peaks attributable to Z isomer (<5%) were also present; ^{13}C-NMR (75 MHz, $CDCl_3$) 58.0, 56.5, 32.5, 17.2 ppm.

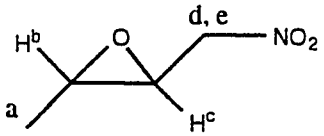
2,3-Epoxy-1-iodobutane (70).[43] A 100-mL round bottom flask was charged with anhydrous sodium iodide (4.00 g, 26.5 mmol) and acetone (50 mL), then heated to reflux for 0.5 h. 2,3-Epoxy-1-bromobutane (3.00 g, 19.9 mmol) was added to the solution. Heating was maintained for an additional 15-20 h with stirring. The mixture was cooled to room temperature, filtered through a fritted funnel. The inorganic salts on the filter were washed with acetone (2 x 10 mL). These washes were combined, concentrated, then dissolved in ether. The ether layer was washed successively with water (1 x 100 mL), freshly prepared 10% sodium bisulfite solution (1 x 40 mL), 5% sodium bicarbonate solution (1 x 40 mL), and saturated sodium chloride solution

(1 x 25 mL). The organic layer was dried ($MgSO_4$), then concentrated under vacuum. The crude product (2.8 g, 71% yield) was pure enough to use as the starting material for the preparation of 71.



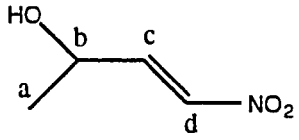
^{1}H-NMR (300 MHz, $CDCl_3$) 3.22 (dd, J_{de} = 10.0 Hz, J_{cd} = 6.3 Hz, 1H_d, *E*), 3.09 (dd, J_{de} = 10.0 Hz, J_{ce} = 6.3 Hz, 1H_e, *E*), 2.97 (td, $J_{cd, ce}$ = 6.3 Hz, J_{bc} = 2.0 Hz, 1H_c, *E*), 2.91 (qd, J_{ab} = 5.2 Hz, J_{bc} = 2.0 Hz, 1H_b, *E*), 1.32 (d, J_{ab} = 5.2 Hz, 3H_a, *E*) ppm; minor peaks attributable to *Z* isomer (<5%) were also present; ^{13}C NMR (75 MHz, $CDCl_3$) 59.1, 58.5, 17.4, 5.3 ppm.

2,3-Epoxy-1-nitrobutane (71).[43] A 50-mL round bottom flask was charged with 1-iodo-2,3-epoxybutane (2.00 g, 10.1 mmol) and ether (10 mL). Silver nitrite (1.80 g, 11.7 mmol), protected from light, was added with stirring. The mixture was stirred at room temperature overnight (protected from light). The silver iodide precipitate was filtered then washed with ether (2 x 10 mL). The washes were combined then concentrated. The crude product (1.10 g, 93%) was pure enough to use as the starting material for the preparation of 45.



^{1}H-NMR (300 MHz, $CDCl_3$) 4.66 (dd, J_{de} = 14.1 Hz, J_{cd} = 3.6 Hz, 1H_d, *E*), 4.32 (dd, J_{de} = 14.1 Hz, J_{ce} = 7.6 Hz, 1H_e, *E*), 3.33 (ddd, J_{ce} = 7.6 Hz, J_{cd} = 3.6 Hz, J_{bc} = 2.1 Hz, 1H_c), 3.00 (qd, J_{ab} = 5.2 Hz, J_{bc} = 2.1 Hz, 1H_b, *E*), 1.40 (d, J_{ab} = 5.2 Hz, 3H_a, *E*) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) 77.0, 53.6, 53.5, 16.9 ppm; IR (film) 1554 (asymmetric NO_2 stretch), 1376 cm^{-1} (symmetric NO_2 stretch).

4-Nitro-3-buten-2-ol (45).[28] With stirring and ice cooling, dichloromethane (5 mL) containing triethylamine (5.0 mg, 0.05 mmol, catalytic amount) was added dropwise to a solution of 1-nitro-2,3-epoxybutane (800 mg, 6.84 mmol) in dichloromethane (5 mL). The mixture was stirred at 18 °C for 1.5 h. The solvent was removed under vacuum and the residue was passed through a chromatography column (silica gel, gradient elution with hexane/ether) to yield pure 0.52 g (65%) of 4-nitro-3-buten-2-ol, bp 80-85 °C/<1 mm (lit.[28] bp 85-86 °C/1 mm).



^{1}H-NMR (300 MHz, $CDCl_3$) 7.27 (dd, J_{cd} = 13.2 Hz, J_{bc} = 3.7 Hz, $1H_c$), 7.18 (dd, J_{cd} = 13.2 Hz, J_{bd} = 1.5 Hz, $1H_d$), 4.66 (qdd, J_{ab} = 6.7 Hz, J_{bc} = 3.7 Hz, J_{bd} = 1.5 Hz, $1H_b$), 1.42 (d, J_{ab} = 6.7 Hz, $3H_a$) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) 145.1, 138.9, 64.7, 22.6 ppm; IR (film) 1529 (asymmetric NO_2 stretch), 1355 cm^{-1} (symmetric NO_2 stretch); MS (70 ev; CI, NH_3) *m/z* 134 (28, M+NH_3).

Attempted Rearrangement of 4-Hydroxy-2-pentenoic Acid (61) Under Hydrolysis Reaction Conditions. 4-Hydroxy-2-pentenoic acid (0.50 g, 4.3 mmol) was dissolved in conc. HCl (10 mL) then heated at 55-60 °C for 1h. The reaction mixture was then extracted with ether (2 x 10 mL). The combined ether extracts were washed with water (1 x 10 mL), saturated NaCl solution (1 x 10 mL), dried ($MgSO_4$), then concentrated. Even though the original hydrolytic conditions[14,15] for the substituted furans utilized conc. HCl, the reaction was repeated with 1 N HCl. Attempts to purify the crude product (0.38 g for conc. HCl, 0.41 g for 1 N HCl) by column

chromatography (silica gel, various eluents) were unsuccessful. In both cases the crude product did not show any peaks between 1.7 and 2.8 ppm at all stages of purification. An authentic sample of levulinic acid (2-oxopentenoic acid, the anticipated product of a rearrangement reaction) showed two triplets at 2.76 and 2.64 ppm, and one singlet at 2.21 ppm.

Attempted Rearragement of 4-Hydroxy-2-Pentenonitrile (64) Under Hydrolysis Reaction Conditions. 4-Hydroxy-2-pentenonitrile (0.50 g, 5.2 mmol) was dissolved in hot conc. HCl (10 mL) then heated at 55-60 °C for 1h. The reaction mixture was then extracted with ether (2 x 10 mL). The combined ether extracts were washed with water (1 x 10 mL), saturated NaCl solution (1 x 10 mL), dried ($MgSO_4$), then concentrated. Even though the original hydrolytic conditions[14,15] for the substituted furans utilized conc. HCl, the reaction was repeated with 1 N HCl. Attempts to purify the crude product (0.45 g for conc. HCl, 0.41 g for 1 N HCl) by column chromatography (silica gel, various eluents) were unsuccessful. In both cases, ^{1}H-NMR of the crude product did not show any peaks between 1.6 and 2.8 ppm at all stages of the purification.

Attempted Rearrangement of 4-Nitro-3-buten-2-ol (45) Under Hydrolysis Reaction Conditions. 3-Hydroxy-1-nitro-1-butene (0.50 g, 4.3 mmol) was dissolved in hot conc. HCl (10 mL) then heated at 55-60 °C for 1h. The reaction mixture was then extracted with ether (2 x 10 mL). The combined ether extracts were washed with water (1 x 10 mL), saturated NaCl solution

(1 x 10 mL), dried ($MgSO_4$), then concentrated. Even though the original hydrolytic conditions[14,15] for the substituted furans utilized conc. HCl conditions, the reaction was repeated with 1 N HCl. Attempts to purify the crude product (0.42 g for conc. HCl, 0.39 g for 1 N HCl) by column chromatography (silica gel, various eluents) were unsuccessful. In both cases, ^{1}H-NMR spectrum of the crude product did not show any peaks between 1.6 and 3.5 ppm at all stages of the purification.

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