EXPERIMENTS DIRECTED TOWARD THE TOTAL SYNTHESIS OF THE IONOPHORE ANTIBIOTIC X-537A

Thesis by

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Abstract

A synthetic approach to a portion of the carboxylic ionophore X-537A is discussed. A synthesis of the tetrahydropyran ring of this antibiotic via a Diels-Alder reaction followed by hydroboration is described.

Summary

A synthetic approach to a portion of the ionophore antibiotic X-537A is discussed. A synthesis of 6-carbomethoxy-3-ethyl-3-hydroxy-2-methyl-tetrahydropyran was accomplished via a Diels-Alder reaction between 3-methylene-2-pentanone and methyl acrylate, followed by hydroboration. Through optimization of the reaction conditions, yields of 50-55% could be achieved in the Diels-Alder reaction, substantially better than any previously reported yield for this type of cycloaddition. As compared with the tetrahydropyran ring of X-537A, the synthetic tetrahydropyran has the correct substitution pattern and the correct stereochemistry at C-2 and C-3. Several unsuccessful attempts to define the stereochemistry at C-6 are described and some possible methods for continuing the synthesis are discussed.

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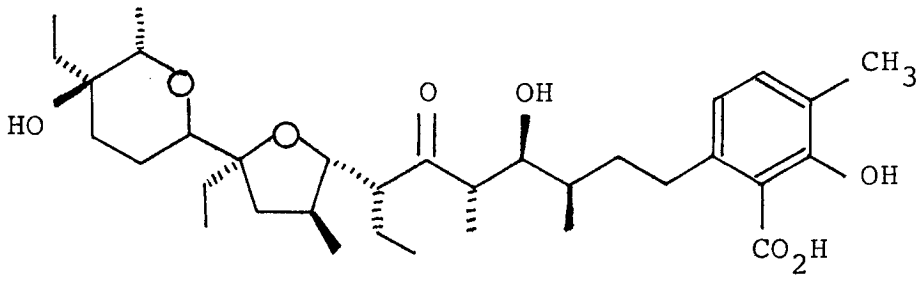
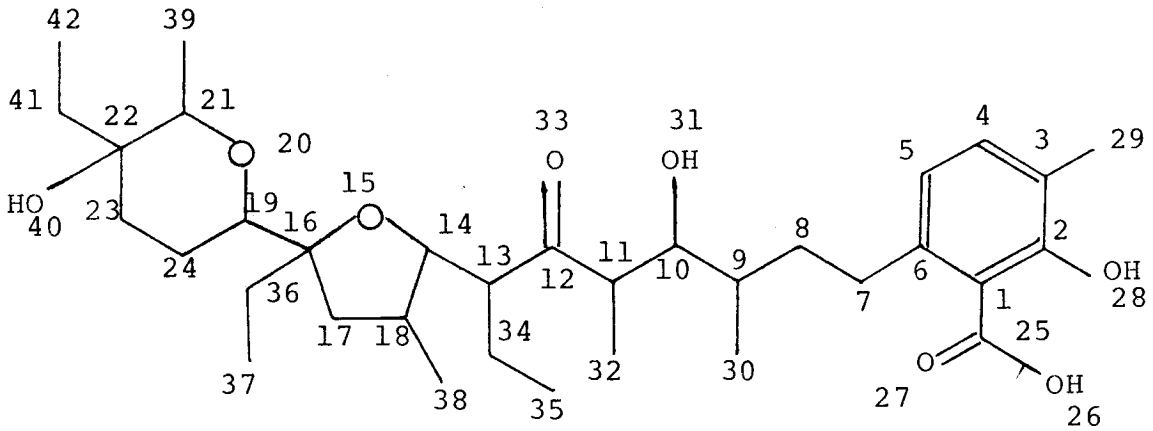
Introduction

The isolation of antibiotic X-537A from an unidentified Streptomyces strain was reported in 1951[1], and the structure and absolute configuration of the antibiotic were published in 1970[2-4]. X-537A, 1, is 3-methyl-6-[7(R)-ethyl-4(S)-hydroxy-3(R),5(S)-dimethyl-6-oxo-7-(5(S)-ethyl-3(S)-methyl-5-[5(R)-ethyl-5-hydroxy-6(S)-methyl-2(R)-tetrahydropyranyl]-2(S)-tetrahydrofuryl)-heptyl] salicylic acid.



1

This structure for X-537A was determined[2-4] by X-ray analysis of the barium salt, $(C_{34}H_{53}O_8)_2Ba \cdot H_2O$; subsequently, X-ray crystal structures of a silver salt[5], of a metal-free bromo derivative of the free acid[6], and of the sodium salt[7] have been reported. The numbering system commonly used for X-537A and its derivatives is that assigned by the crystallographers:



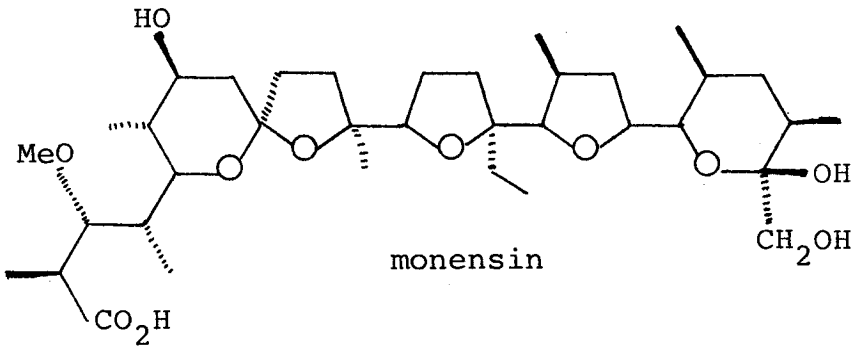
Westley, et al.[8-12] have studied the biosynthesis of X-537A by means of ^{13}C and ^{14}C incorporation experiments and have shown that the carbon skeleton of the antibiotic is derived from five acetate, four propionate, and three butyrate units. In the two most recent publications[11,12] concerning the biosynthesis of X-537A, the Streptomyces strain (previously referred to[1-10] only as "Streptomyces X-537A") has been renamed "Streptomyces lasaliensis", and the antibiotic X-537A renamed "lasalocid A". In this thesis, the older nomenclature will be retained and 1 referred to as X-537A.

X-537A is a member of a large class of antibiotics known as ionophores. The ionophoric antibiotics can be divided into two classes, differentiated by their charge at physiological pH. The first class is composed of neutral macrocyclic polypeptides or lactones which form positively-charged, lipid-soluble complexes with cations.

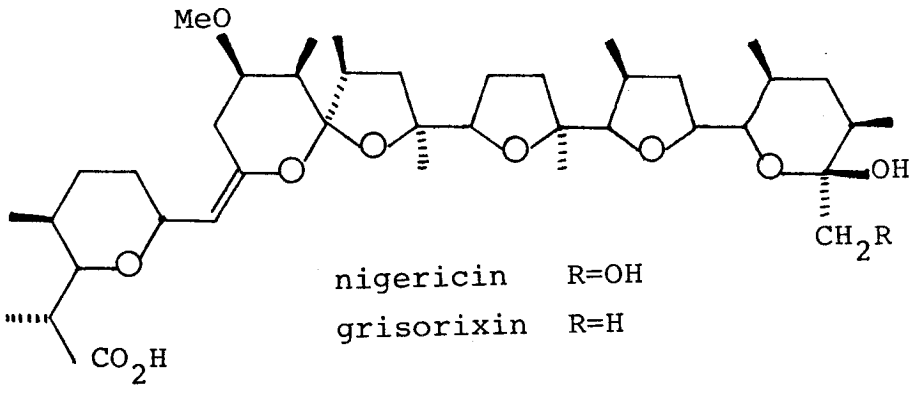
This class includes valinomycin[13], the actins[14], and the enniatins[15]. The second class is composed of monocarboxylic acids which are negatively charged at physiological pH and form neutral complexes with cations. Besides X-537A, this large group of antibiotics includes monensin[16], nigericin[17], grisorixin[18], septamycin[19], A204A[20], dianemycin[21], Ro 21-6150[22], X-206[23], alborixin[24], salinomycin[25], lysocellin[26], lonomycin[27], emericid[28], and A23187[29] (see Chart). As antibiotics, monensin and X-537A are currently in use agriculturally for the treatment of coccidial infections in chickens.

The ionophores derive their name from their ability to carry ions across lipid barriers, including artificial and biological membranes. As described by Pressman[30], ionophores catalyze transport by: (a) enveloping an ion at a membrane interphase; (b) diffusing across the membrane as a cation complex; (c) releasing the ion at the opposite interphase; and (d) diffusing back uncomplexed to the original interphase to complete the catalytic cycle. Thus ionophores function as carriers for cations in membranes.

Chart: Carboxylic Ionophores

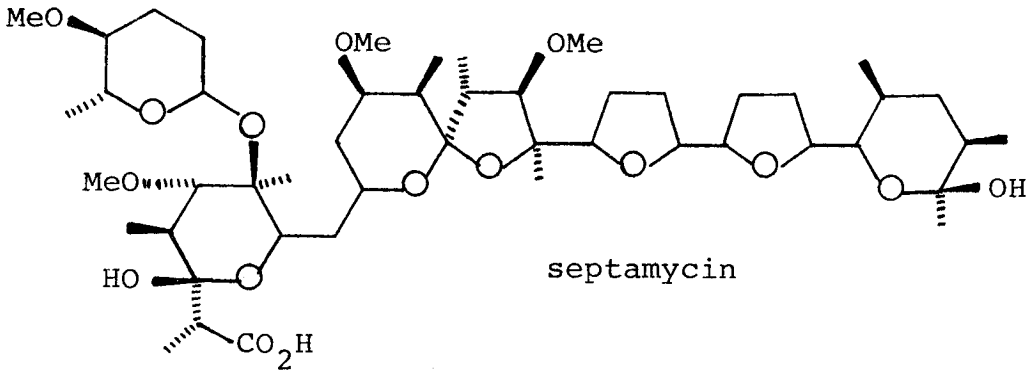


monensin

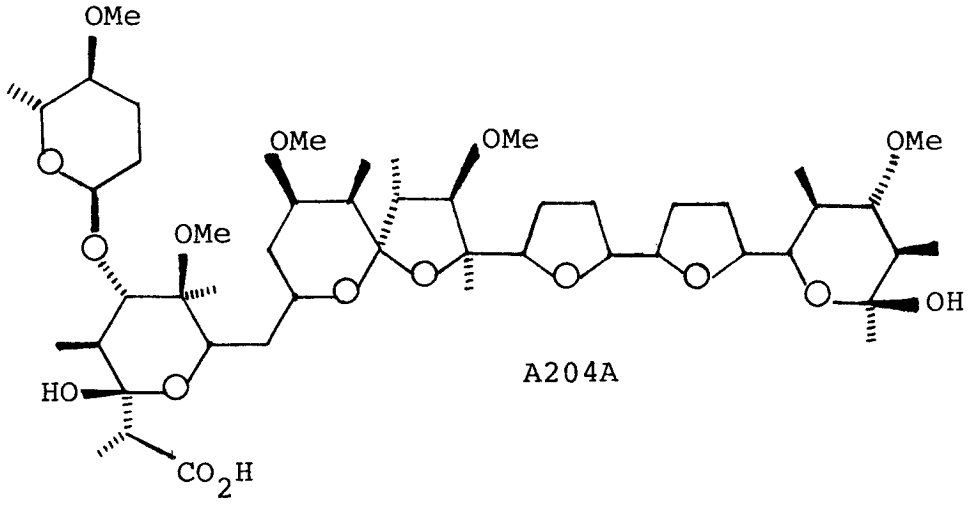


nigericin R=OH

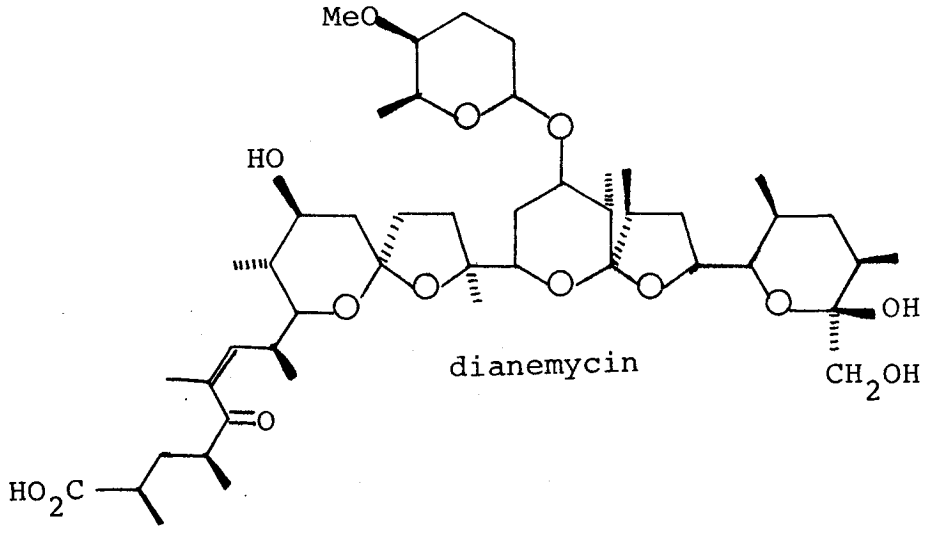
grisorixin R=H



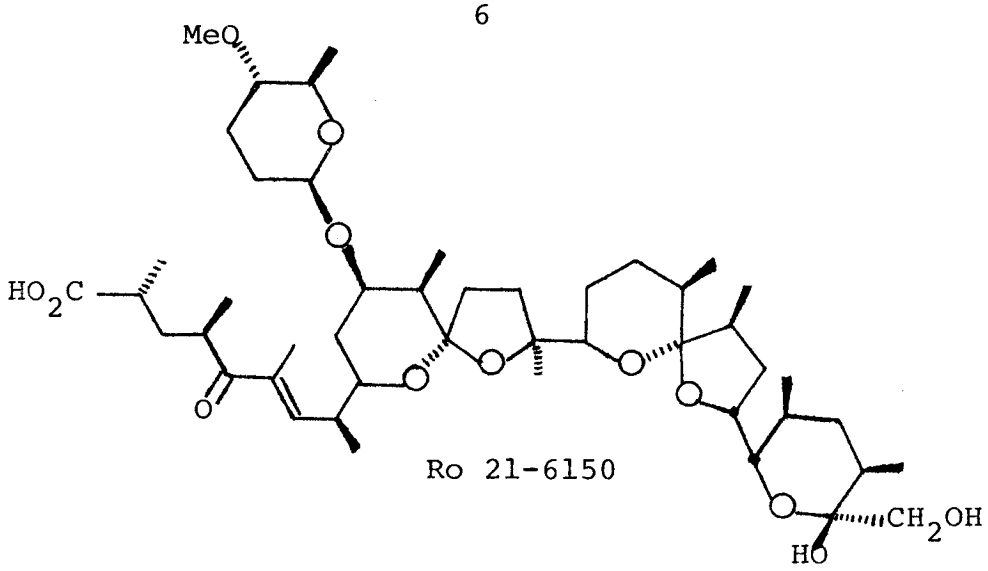
septamycin



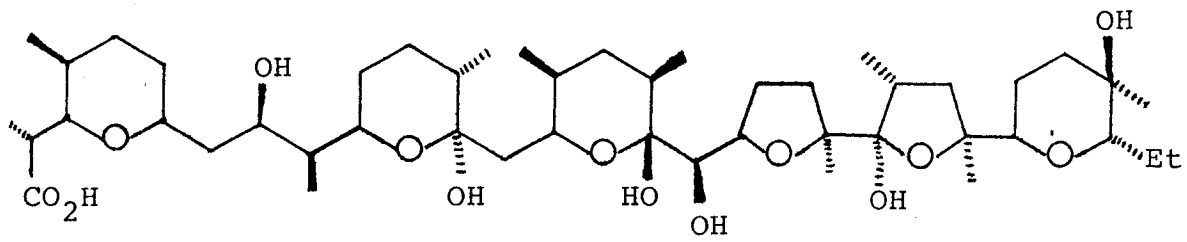
A204A



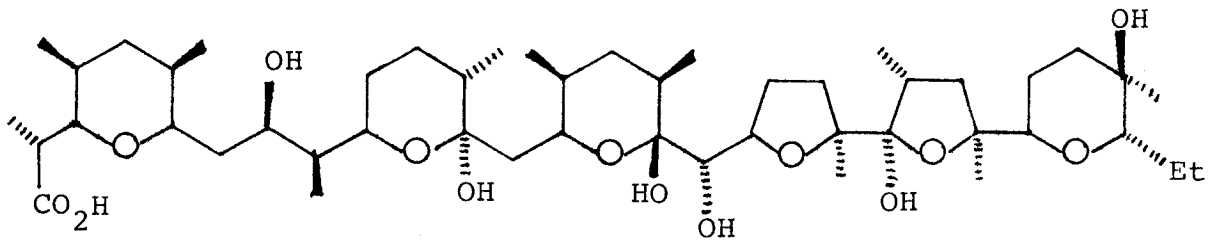
dianemycin



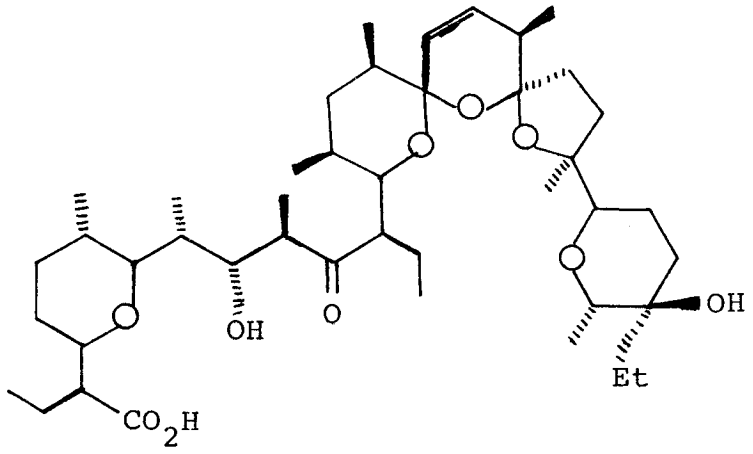
Ro 21-6150



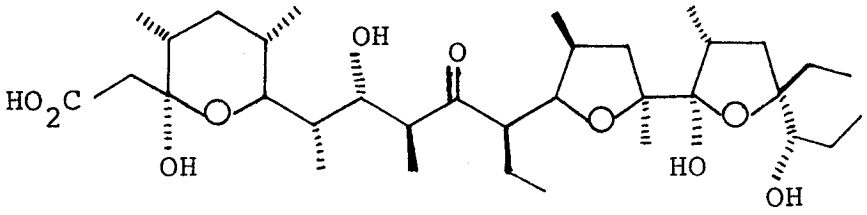
X-206



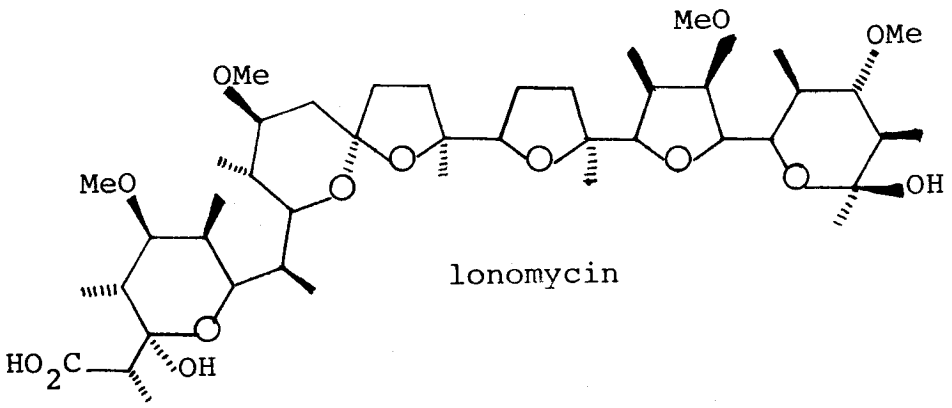
alborixin



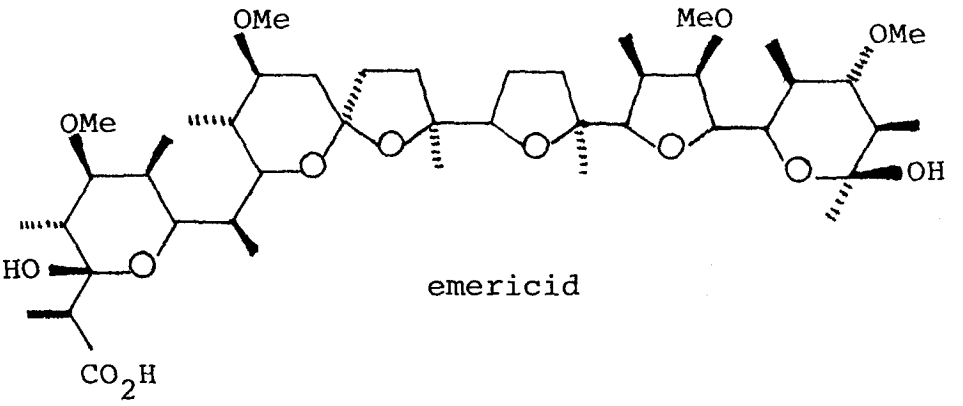
salinomycin



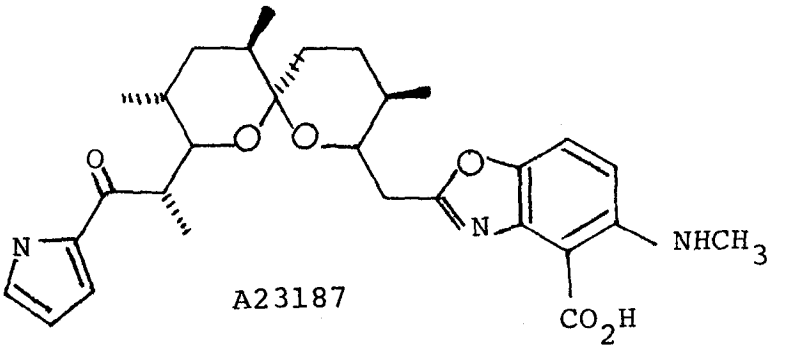
lysocellin



lonomycin



emericid



A23187

X-537A has several features which distinguish it from the other carboxylic ionophores, and it has been the subject of a number of diverse biochemical studies[30-36]. X-537A has been found to bind with both monocations and dications efficiently, by forming dimeric, sandwich-like complexes. With monocations, X-537A exhibits a selectivity: K^+, $Rb^+ > Na^+ > Cs^+ > Li^+$ [37]; with dications, the binding selectivity is: $Ba^{2+} > Sr^{2+} > Ca^{2+} > Mg^{2+}$ [30]. Binding of K^+ is more effective than binding of Ca^{2+}. With respect to transport across membranes, X-537A exhibits a preference: $Mg^{2+} > Ca^{2+} > Sr^{2+} > Ba^{2+}$, the reverse of its binding selectivity.

Another pharmacologically relevant property of X-537A is its ability to complex organic amines, such as ethanolamine and norepinephrine[30]. The ability of X-537A to complex these amines was substantially greater than that of monensin, dianemycin, and nigericin; in fact, X-537A is thus far the only natural ionophore which has demonstrated an ability to bind amines to a biochemically significant degree.

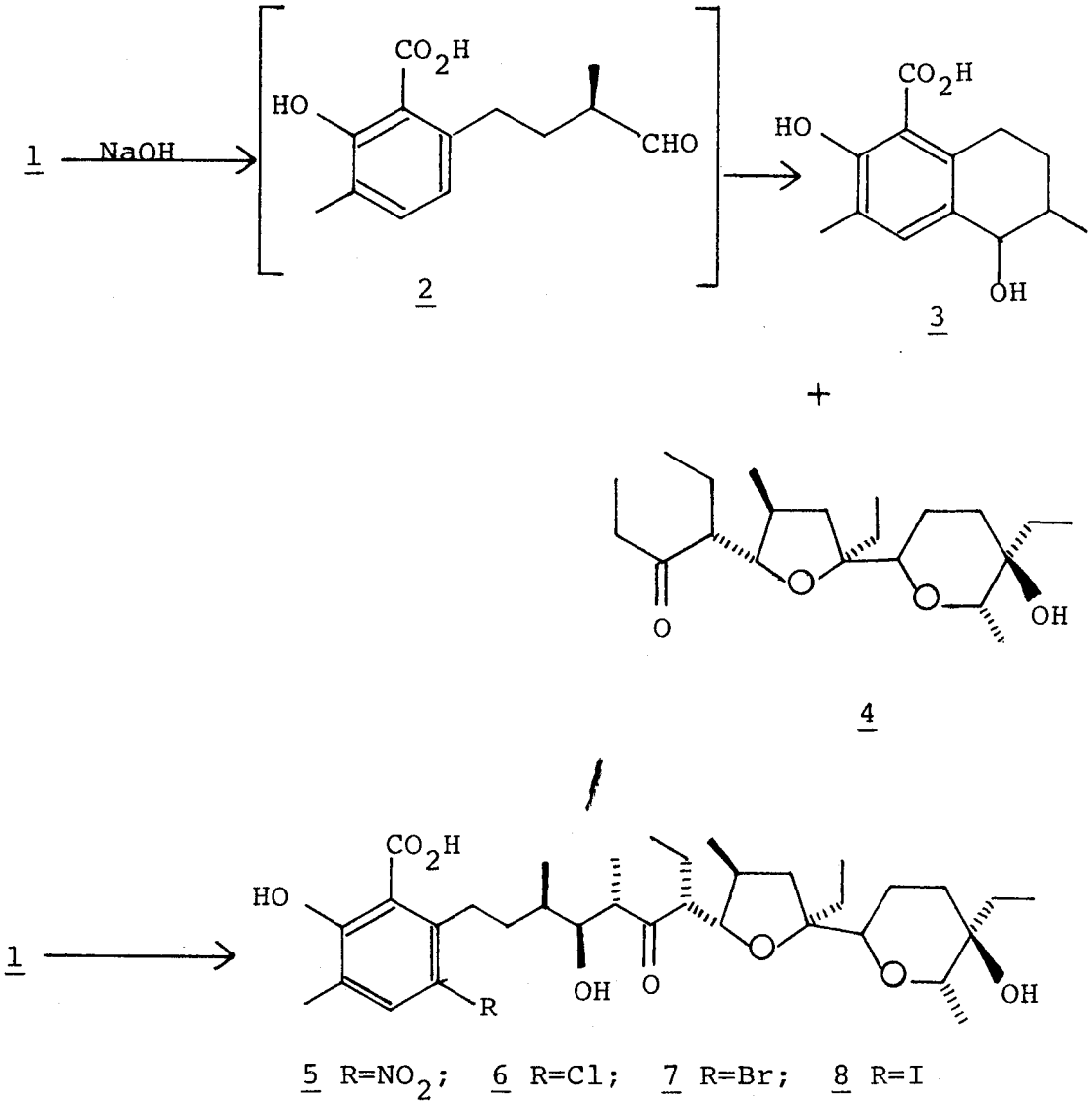
As a result of the observed affinity of X-537A for Ca^{2+}, its effect upon isolated sarcoplasmic reticulum vesicles was studied[31,32,34]. Not surprisingly, it was found that vesicles which had accumulated Ca^{2+} by an ATP-linked active transport mechanism lost this Ca^{2+} upon addition of X-537A to the medium. This effect appears to be due to the ability of X-537A to render sarcoplasmic reticulum membranes permeable to Ca^{2+}, so that passive transport down a concentration gradient occurs. This effect, coupled with the observed ability of X-537A to complex catecholamines, led to study of the effect of X-537A on muscle tissue[33]. It was found that X-537A initiates

contraction of the smooth muscle of the rabbit aorta and increases the strength and rate of contraction of perfused rabbit heart. In in vivo studies on dogs, a dramatic 81% increase in contractile tension was observed, while the heart rate and aortic pressure were increased by much smaller amounts (3% and 10-16%, respectively). No conductive anomalies appeared on EKG traces, and no toxic manifestations were observed. Also, preliminary studies indicate that the hemodynamic responses of dogs in surgically-induced cardiac shock are even more striking. Thus, X-537A is emerging as a new cardiotonic or iontropic agent, which elicits response patterns that in many respects are more ideally suited for therapeutic applications to pathological conditions of the heart than the two iontropic drug classes in current use, the catecholamines and digitalis. At this time, prospects appear bright for the eventual therapeutic application of X-537A to humans.

There is little information available regarding the chemical properties of the carboxylic ionophores. Certain chemical transformations of X-537A and their effect on antibacterial activity have been reported[38,39]. For the most part, these studies have involved modifications of the -OH or -COOH functionalities of the molecule. Results have indicated that all the oxygen atoms involved in ligand formation with cations and intramolecular hydrogen bonding contribute to the biological activity of the antibiotic. In addition, treatment of X-537A with NaOH leads to retro-aldol cleavage of the β-keto alcohol system (Scheme 1). The aromatic aldehyde 2 spontaneously cyclizes under the reaction conditions to 3. This spontaneous cyclization was the first illustration of the ease of electrophilic substitution at C-5 of the aromatic ring. This position can be easily nitrated and halogenated, affording 5, 6, 7, and

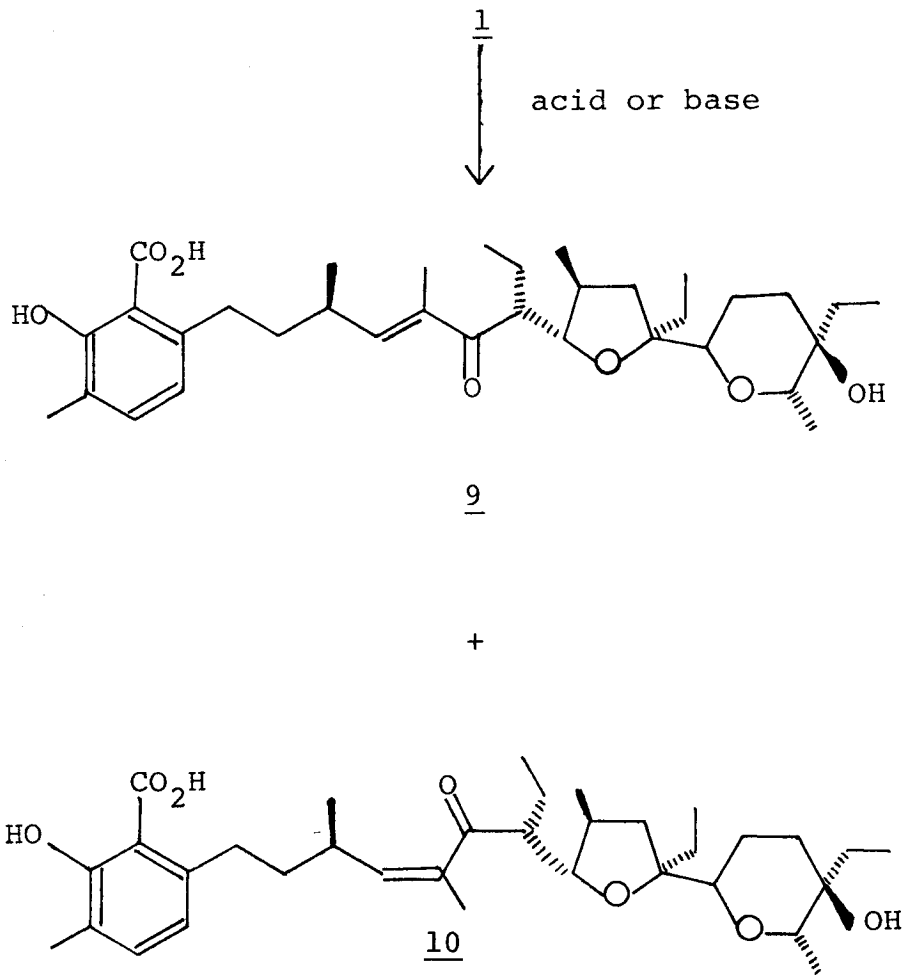
8. In addition, dehydration of 1 can be effected under acidic or basic conditions to give 9 and 10 (Scheme 1). Synthetic approaches to the carboxylic ionophores have not been reported.

Scheme 1



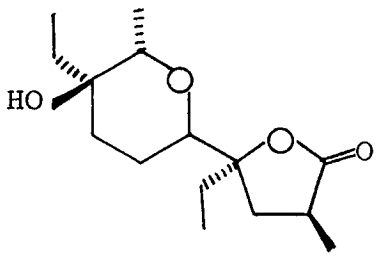
5 R=NO_2; 6 R=Cl; 7 R=Br; 8 R=I

Scheme 1 (Continued)



Discussion

In our approach to the total synthesis of X-537A, the tetrahydropyran-lactone 11 was envisaged as a key intermediate.

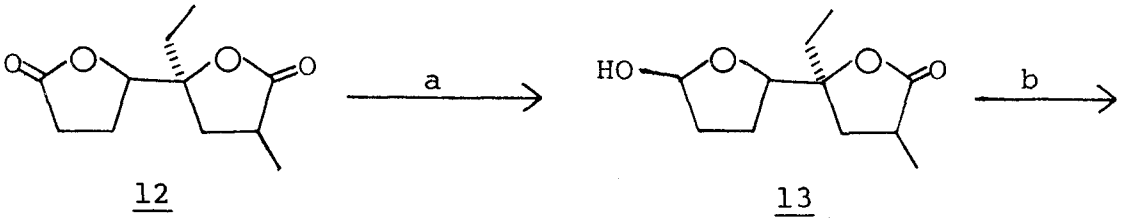


11

11 possesses five of the ten asymmetric centers of the antibiotic; in addition, the lactone carbonyl provides a convenient functionality which may be used for the attachment of the remainder of the molecule.

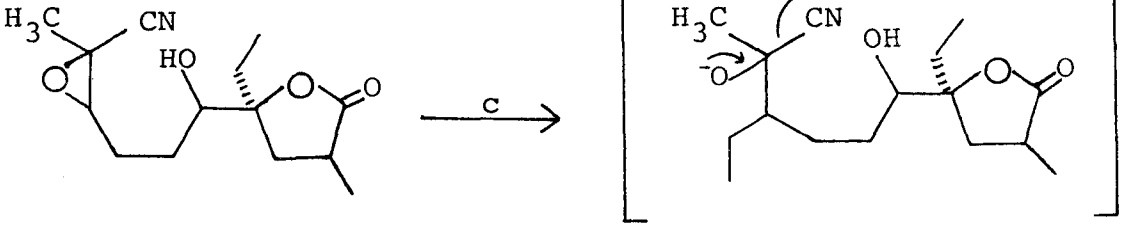
Initially, it was planned to obtain 11 through the dilactone 12 (Scheme 2). Thus, treatment of 12 with one equivalent of diisobutylaluminum hydride (DIBAH) would be expected to reduce selectively the less hindered carbonyl to give lactone-lactol 13[40]. Reaction of 13 with α -chloropropionitrile and potassium t-butoxide[41] should afford glycidonitrile 14, which would then be treated with lithium diethyl cuprate. Attack of the cuprate at the less hindered carbon of the epoxide, followed by elimination of CN^- by the intermediate alkoxide 15 would give keto alcohol 16. Cyclization and dehydration to dihydropyran 17, followed by hydroboration[42-45] would yield 11.

Scheme 2



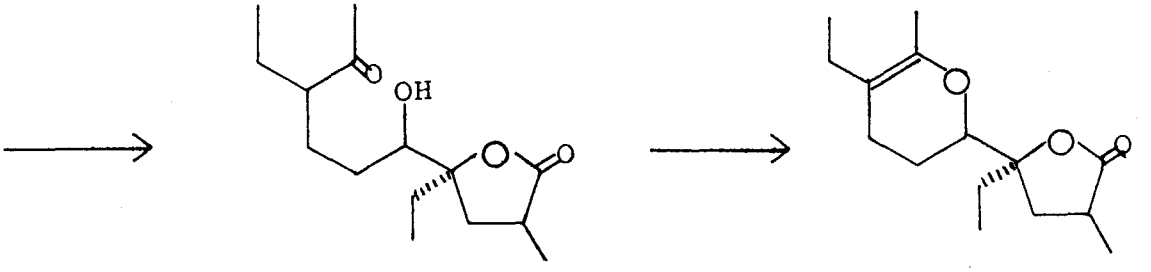
12

13



14

15



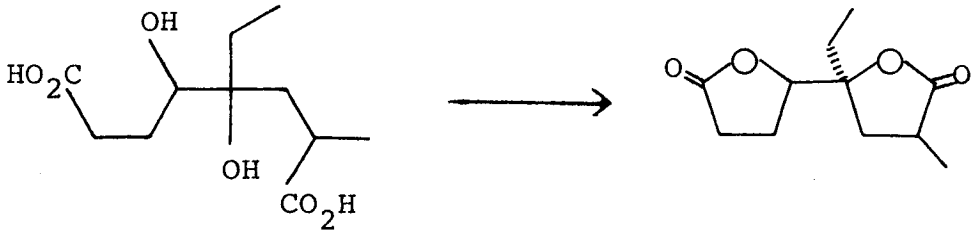
16

17

d → 11

a, DIBAH, -78°; b, $CH_3CH(Cl)CN$, KOt-Bu; c, $LiEt_2Cu$; d, B_2H_6, [O]

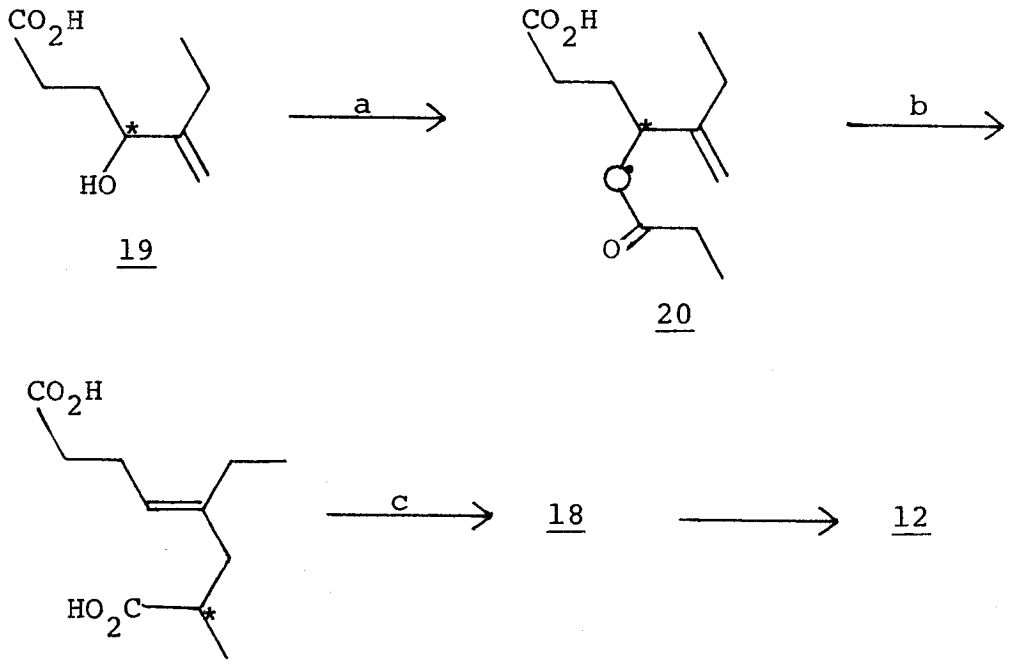
Dilactone 12 can, in principle, be derived from the diol diacid 18:



18 12

The proposed synthesis of 18 is shown in Scheme 3.

Scheme 3



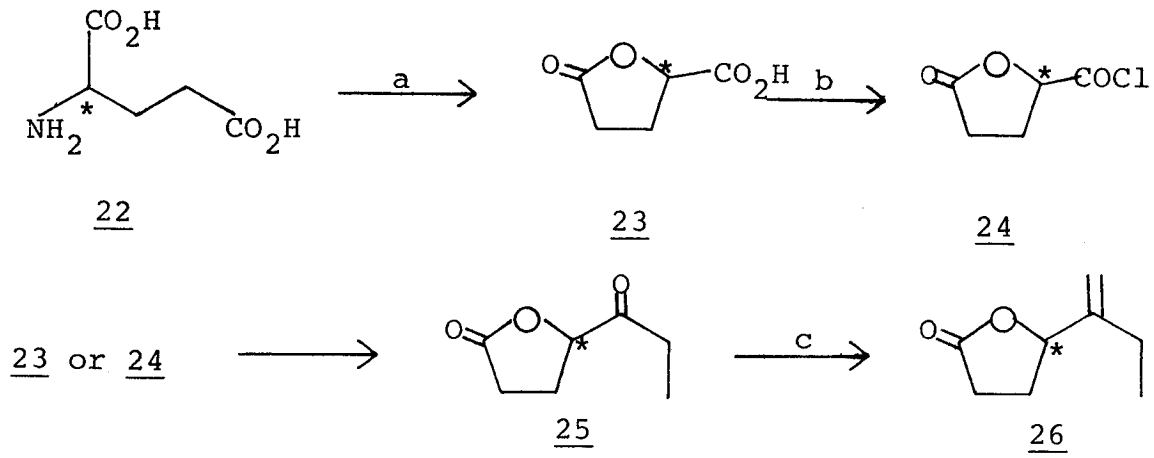
19 20 21 18 12

a, CH_3CH_2COCl; b, enolate Claisen; c, $KMnO_4$

If compound 19, of known configuration at the starred carbon, were esterified with propionyl chloride and the resulting ester 20 induced to undergo an enolate-Claisen rearrangement[46,47], 21 would be obtained. It was hoped that the stereoselectivity which has been demonstrated[46,47] for this rearrangement would allow the transfer of stereochemistry from 20 to 21 as indicated. Oxidation of the olefin in 21 with potassium permanganate[48] would then give 18.

A possible approach to 19 is shown in Scheme 4.

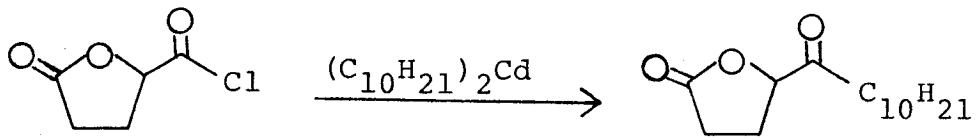
Scheme 4



a, $NaNO_2$, aqueous HCl; b, $SOCl_2$; c, Ph_3PCH_2

Nitrous acid deamination of glutamic acid 22 to lactone acid 23 is known to proceed with retention of configuration at the chiral center[49-53]. Using the methods of Plieninger et al.[50], both lactone acid 23 and the corresponding acid chloride 24 were obtained in excellent yield. It was planned that if either 23 or 24 could be converted to ethyl ketone 25, reaction with methylenetriphenylphosphorane would give lactone olefin 26. 26 is the lactonized form of acid alcohol 19. This route seemed particularly attractive due to the ready availability of glutamic acid of known configuration.

Unfortunately, all attempts to prepare ethyl ketone 25 (or the analogous methyl ketone) from 23 or 24 were unsuccessful. Iwaki et al.[53] were able to obtain ketone 27 by reaction of acid chloride 24 with didecylcadmium, but no experimental details were reported.



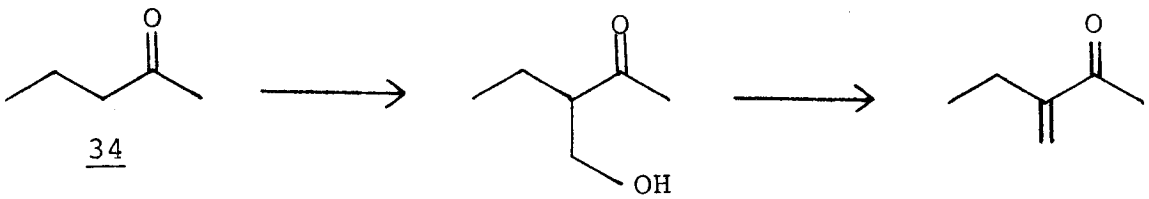
24 27

Although the synthesis of ketones from acid chlorides via cadmium reagents is a well-known reaction[54-57], numerous attempts to condense 24 with diethylcadmium under a variety of conditions yielded only trace amounts of ethyl ketone 25. Reaction of acid chloride 24 with lithium diethyl cuprate (or lithium dimethyl cuprate)[58,59] was similarly

unsuccessful. Finally, reaction of free acid 23 with ethyl lithium (or methyl lithium) was tried without success[60]. In all these experiments, destruction of the starting material was the major reaction. Following these disheartening results the dilactone route to 11 was abandoned.

A new synthesis of 11 was devised, in which the tetrahydropyran portion of the molecule, having the correct substitution and stereochemistry, is prepared prior to construction of the lactone ring. This approach, which has demonstrated considerable promise, is shown in Scheme 5.

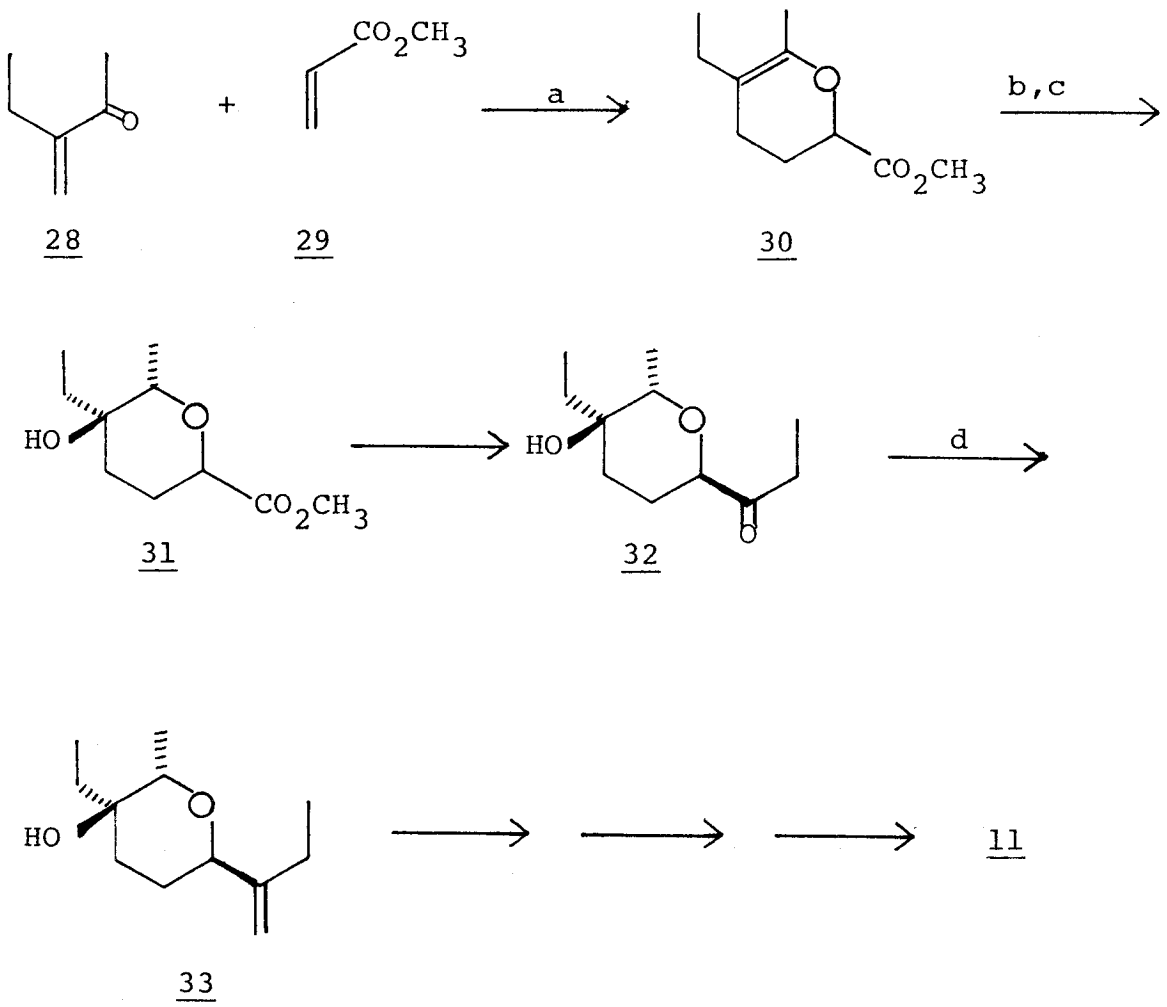
The starting material for this synthesis, α,β -unsaturated ketone 28 was prepared by the method of Colonge and Cumet[61]. Thus, reaction of 2-pentanone 34 with formaldehyde and a small amount of sodium hydroxide affords keto alcohol 35 in 50-55% yield. Enone 28 is obtained in 60-65% yield by heating 35 in the presence of iodine; the unsaturated ketone distills from the reaction mixture as it forms.



34 35 28

The Diels-Alder reaction of 28 with methyl acrylate 29 merits some discussion, as it is the key to this synthetic approach. Diels-Alder reactions of this type, in which the

Scheme 5

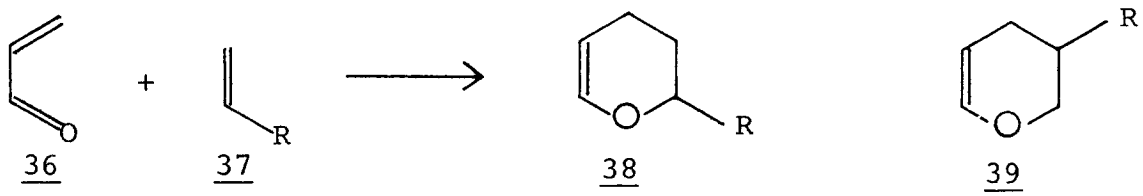


28 29 30 31 32 33 11

a, benzene, hydroquinone, 200°, sealed tube;
b, $BH_3 \cdot THF$; c, ^-OH, H_2O_2; d, Ph_3PCH_2

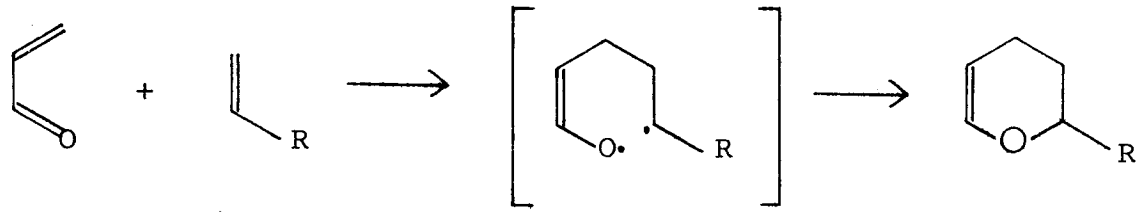
diene component is an α,β-unsaturated carbonyl compound, are well known[62,63] and have recently been reviewed[64].

The regioselectivity of this cycloaddition reaction is not open to question. When α,β-unsaturated ketones or aldehydes 36 undergo the Diels-Alder reaction, either with themselves (thermal dimerization) or with other dienophiles 37, the products are always the 2-substituted dihydropyrans 38; 3-substituted dihydropyrans 39 are not formed.



36 37 38 39

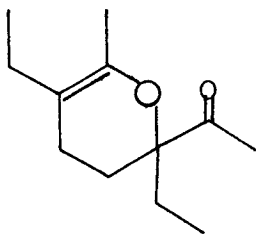
This selectivity cannot in general be explained by a polar mechanism, but has been explained[62,63] by invoking a diradical intermediate.



36 37 40 38

According to this mechanism, exclusive formation of 38 is due to formation and closure of the more stable radical intermediate 40. However, the existence of such diradical intermediates in thermal cycloadditions of this type is open to question. A more satisfactory explanation is provided by molecular orbital theory[64]. SCF calculations correctly predict the experimentally observed regioselectivity in the dimerization of acrolein, and also support an endo approach of the reactants with the C-C bond closing faster than the C-O bond.

Although it was thus certain that reaction of methyl acrylate 29 with enone 28 would give the desired adduct 30, finding experimental conditions under which the addition could be effected proved to be somewhat difficult. Typically[65-69] reactions of this type are carried out by heating the reactants in a sealed vessel without solvent at 170-200° for 1-2 hours in the presence of a polymerization inhibitor, such as hydroquinone. When this method was tried, only the dimer 41 was obtained[70].

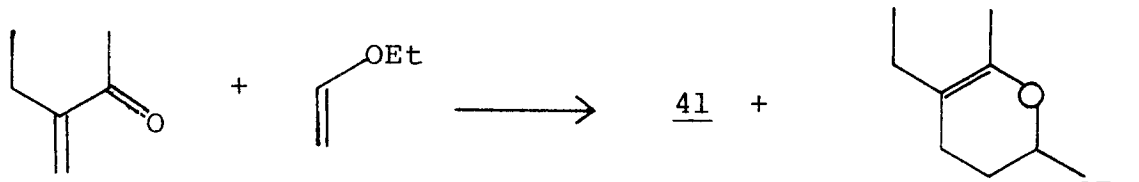


41

Various temperatures (170°, 180°, 190°, 200°) and various ratios of acrylate:enone (1:1, 2:1, 5:1, 10:1) were tried, but none of the desired adduct was found.

After these discouraging results, the addition of ethyl vinyl ether to 28 was attempted. The addition of vinyl ethers to α,β-unsaturated carbonyl compounds is known[62-66] to give higher yields of adduct than the addition of unsaturated esters. This has been explained[62,63] by stating that "electron-rich" dienophiles (such as vinyl ethers) add more readily to enones than do "electron-poor" dienophiles (such as acrylic esters). A more quantitative explanation can be provided by HOMO-LUMO theory[64]. Thus, the dominant interaction in Diels-Alder reactions of α,β -unsaturated carbonyl compounds with dienophiles is between the LUMO of the α,β-unsaturated carbonyl component, which acts as the acceptor, and the HOMO of the dienophile, which acts as donor. The HOMO of vinyl ethers is approximately 3eV higher than the HOMO of acrylonitrile and acrylic esters, and is therefore closer in energy to the LUMO of the heterodiene.

Reaction of enone 28 with ethyl vinyl ether using the conditions given in an Organic Syntheses preparation[71] afforded a mixture of dimer 41 and adduct 42.



28 42

By increasing the ratio vinyl ether:enone, it was possible to decrease the amount of dimerization, but it was only at a

ratio of vinyl ether:enone = 25:1 that dimerization was completely suppressed and only adduct 42 obtained in high yield.

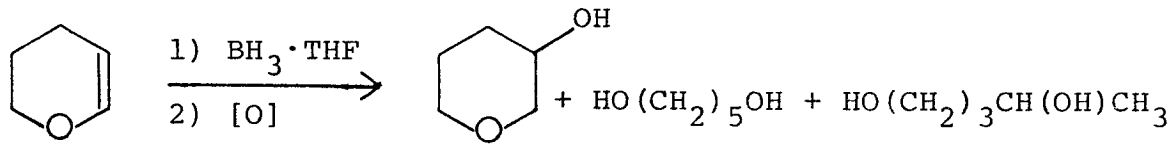
In the light of these results, particularly in view of the high ratio of dienophile:enone that was necessary to prevent dimerization, the reaction of 28 with methyl acrylate 29 was reinvestigated. It was found that mixtures of adduct 30 and dimer 41 were obtained at an acrylate:enone ratio of 25:1, but dimerization was almost negligible at ratios of 50:1. With this amount of methyl acrylate, however, a new problem presented itself. This was polymerization, which made isolation of the desired adduct a difficult and tedious procedure. Increasing the amount of hydroquinone in the reaction vessel did not prevent the polymerization.

In direct consequence, the effects of reaction time and of solvent were investigated, with the result that it is now possible to obtain adduct 30 in 50-55% yield, uncontaminated by dimer 41, by reacting methyl acrylate 29 with enone 28 (ratio 25:1) in benzene at 200° for 72 hours. This yield is substantially better than any heretofore reported for this type of reaction[62,63,67,69,72].

Hydroboration of carbomethoxy dihydropyran 30 proceeded to give the tetrahydropyran alcohol 31. Since the result of hydroboration is well known[42-45] to be overall cis addition of H_2O across the double bond, the desired cis relationship of the methyl and ethyl groups on the tetrahydropyran ring was thus established.

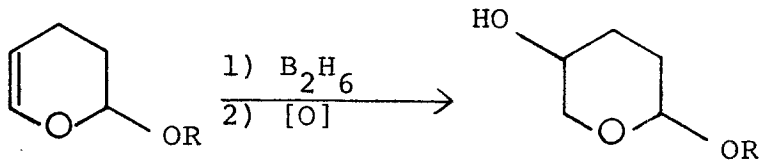
The yield in the hydroboration reaction was not very satisfactory (typically about 30%), and ring-opened, polyalcoholic products seem to be formed to a considerable extent. These by-products may be formed via elimination-

rehydroboration and redistribution-β-transfer reactions[44]. It has been observed that hydroboration of dihydropyran 43 with excess borane leads to the formation of acyclic diols[73].



43 36% 33% 22%

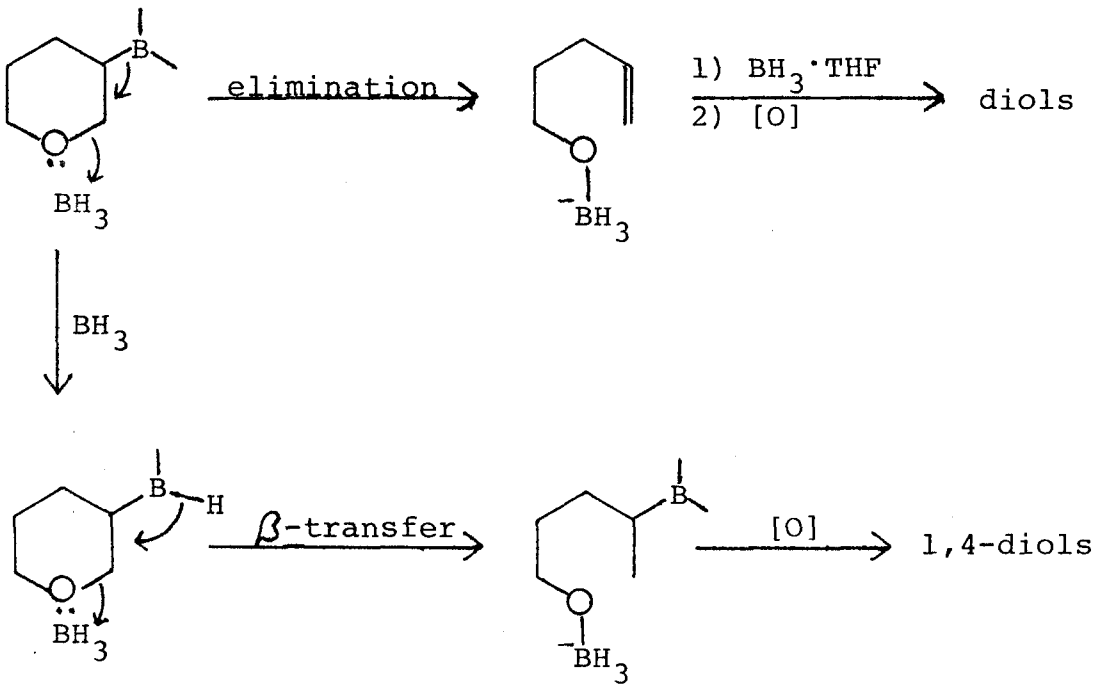
The proposed explanation for diol formation is shown in Scheme 6. This process is suggested to occur in the presence of either excess BH_3 or in the presence of BF_3. Thus, Zweifel and Plamondon[73] found that, in order to avoid diol formation, it was necessary not only to avoid excess borane but also to bubble the diborane (generated from sodium borohydride and boron trifluoride etherate) through a solution of sodium borohydride in diglyme to remove any BF_3 before use. Using this technique, they obtained[73] a 70% yield of 2-ethoxy-5-hydroxy tetrahydropyran 45 from the dihydropyran 44.



44 R=C_2H_5
46 R=CH_3

45 R=C_2H_5
47 R=CH_3

Scheme 6



However, Srivastava and Brown have reported[74] 70-80% yields of 2-methoxy-5-hydroxy tetrahydropyran 47 from 46, without taking any precautions to exclude excess borane or BF_3 from the reaction.

This reaction was examined and it was found that hydroboration of 44 with one equivalent of commercially obtained borane-tetrahydrofuran solution gave 65% yields of the desired product 45. Thus, the low yields of 31 do not seem to have been caused by choice of reagent. In addition,

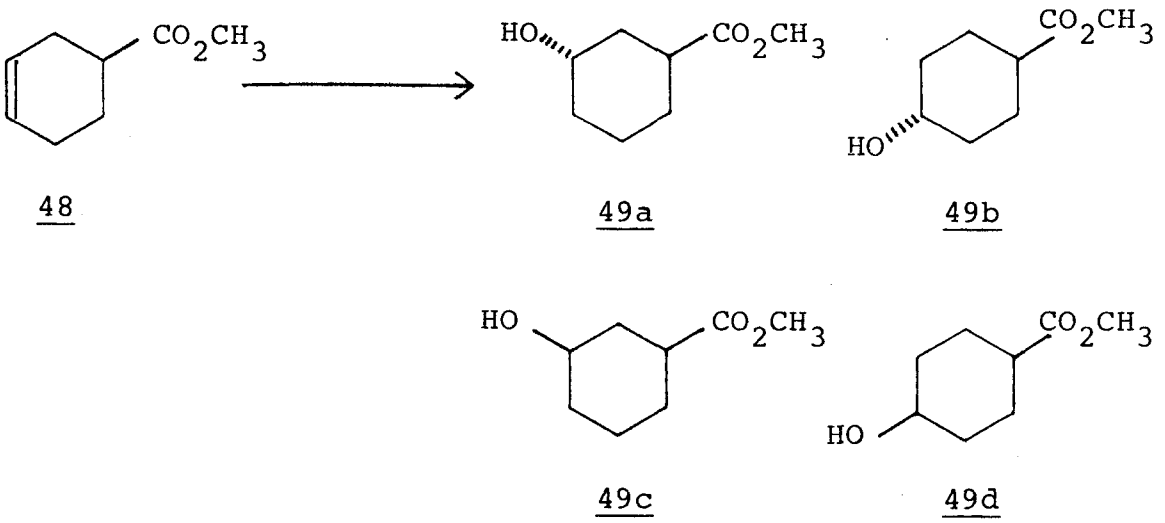
hydroboration of 30 using the conditions described by Zweifel and Plamondon[73], did not improve the yield of alcohol 31. It may be that the greater degree of substitution of the double bond in dihydropyran 30 renders it less reactive in the hydroboration reaction, thereby giving the ring-opening processes of Scheme 6 more opportunity to occur.

Once having obtained ester alcohol 31 with the alkyl substituents in the desired cis relationship, attention was focused on the stereochemical relationship between the hydroxyl and carbomethoxy functions, which must also be cis in the final product. Due to the anomeric effect[75-78], the alkoxy substituents in 44 and 46 occupy the axial position. The result is that the hydroboration products 45 and 47 are predominantly the trans isomers, the borane reagent having preferentially approached the olefin from the less hindered side.

In 2-carbomethoxydihydropyrans and 2-carbomethoxy-tetrahydropyrans, however, the carbomethoxy group is predominantly equatorial[79,80]. Examination of the NMR spectra of 30 and 31 confirms the equatorial disposition of the carbomethoxy group, as the α-proton can be assigned to the axial position on the basis of coupling considerations[81]. The influence of alkyl substituents on the steric outcome of hydroboration of substituted cyclohexenes has been studied[82]. The results varied according to the nature and position of the substituents, but cis or trans preferences were generally slight; for example, hydroboration of 4-t-butylcyclohexene gave an overall cis:trans ratio relative to the t-butyl group of 55:45. Klein et al.[83] studied the hydroboration of carbomethoxy cyclohexene 48 (Scheme 7). The product

ratios 49a:49b:49c:49d were 4:2:1:1, overall a 3:1 formation of trans product.

Scheme 7



48 49a 49b 49c 49d

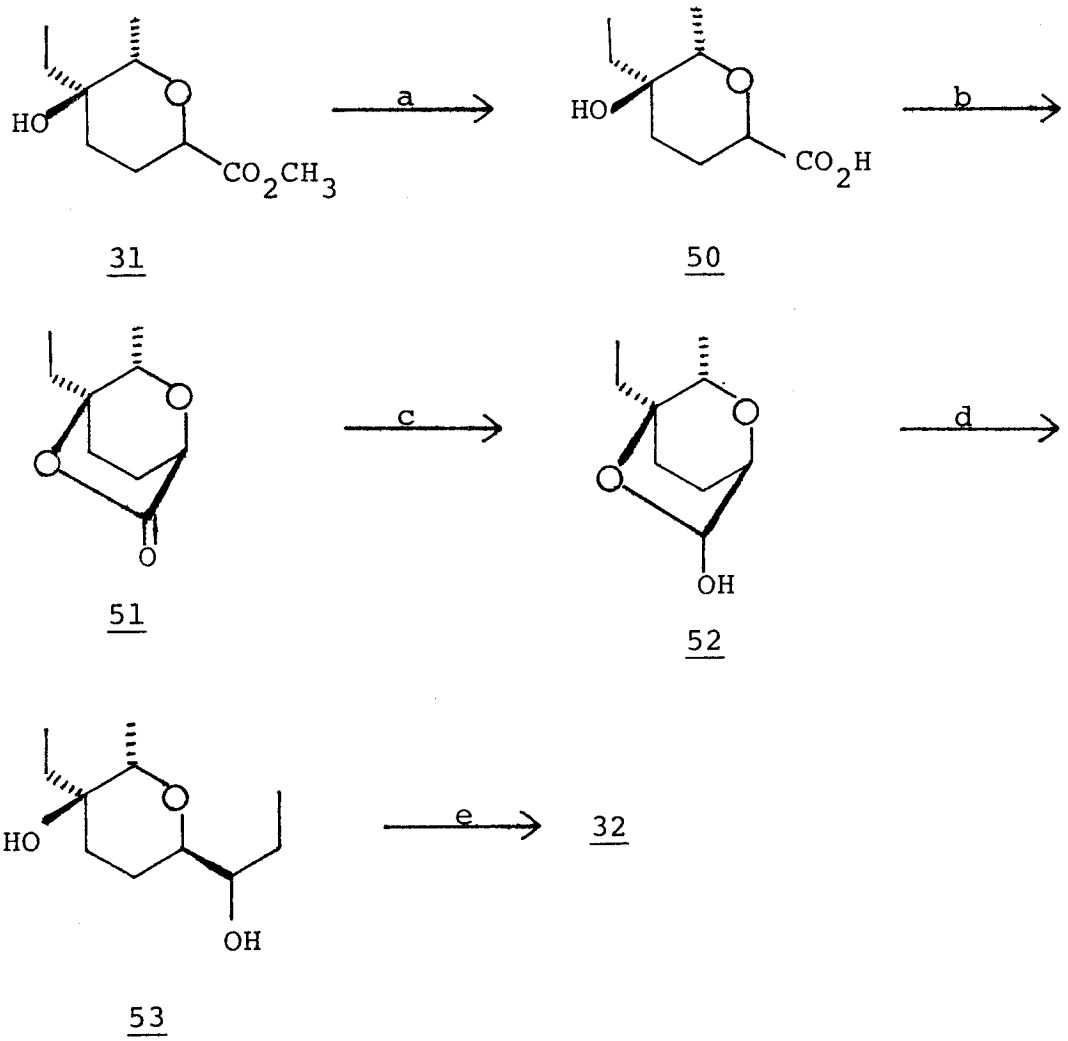
The predominant formation of 49a may be explained by an axial attack of boron, coupled with a polar factor in which the partial positive charge developing on the olefinic carbon to which the hydride is donated would tend to be as remote as possible from the electron-attracting carboxylate. The preference for trans product may be due to polar effects which make trans attack more favorable, or to a steric effect in which cis approach to the ring is more difficult than approach trans to the carboxylate[83].

Thus, it has proved difficult to predict the stereochemical outcome of the hydroboration of 30. The most likely possibility is that a mixture of cis and trans isomers (cis and trans here referring to the relation

between hydroxyl and carbomethoxy functions) is obtained. If this is the case, the two isomers do not appear (by thin-layer chromatography or gas chromatography) to be readily separable. In view of this stereochemical ambiguity, two separate lines of investigation were pursued.

The first, shown in Scheme 8, assures the correct stereochemical relationship of carboxyl and hydroxyl by formation of lactone 51. Reduction of 51 to lactol 52 with diisobutylaluminum hydride[40] and reaction of 52 with ethyl magnesium bromide would give diol 53, which could then be oxidized to ethyl ketone 32. Accordingly, ester alcohol 31 was hydrolyzed with lithium hydroxide in aqueous methanol[84] to acid alcohol 50. Unfortunately, attempts to lactonize 50 with acetic anhydride[85], dicyclohexylcarbodiimide[86], or p-toluenesulfonic acid[86] were unsuccessful.

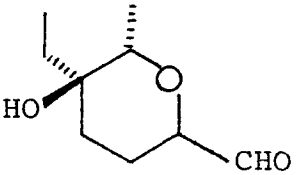
Scheme 8



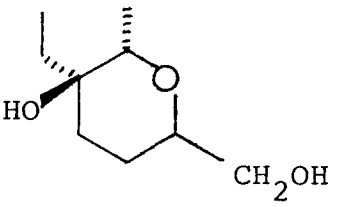
31 50 51 52 53 32

a, LiOH, aqueous MeOH; b, lactonize; c, DIBAH;
d, EtMgBr; e, [O]

The second approach involved continuation of the sequence in Scheme 5, with separation of isomers to be effected later at some convenient stage in the sequence. Several methods for the conversion of ester alcohol 31 to keto alcohol 32 can be envisaged. Thus, conversion of 31 to aldehyde 54 and reaction of 54 with ethyl magnesium bromide would give 53; oxidation would then yield 32.



54

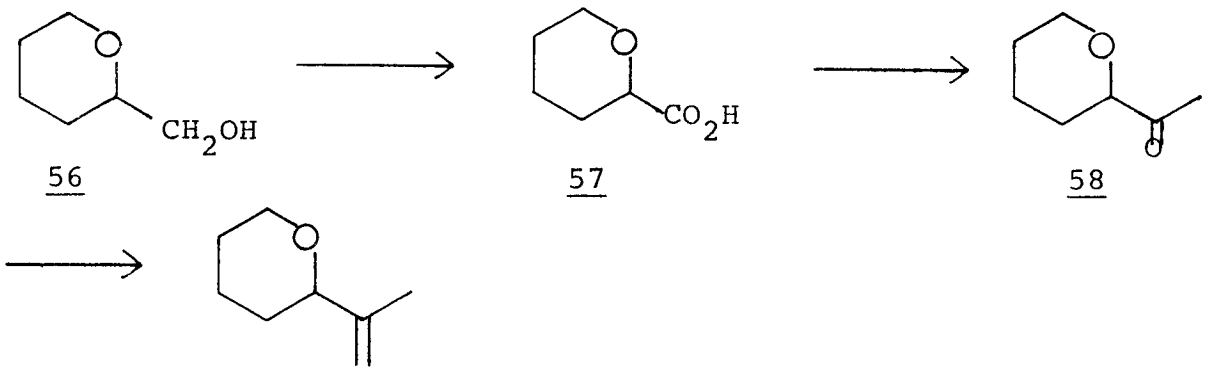


55

Aldehyde 54 was obtained by reduction of 31 with lithium aluminum hydride[69] to diol 55, which was then oxidized (chromium trioxide-pyridine[87]) to 54. This route to 54 was chosen, rather than direct reduction of 31 to 54 with diisobutylaluminum hydride[40], because a sample of diol 55 was desired for comparison with certain products of the hydroboration of 30. It has been established that 55 is not produced in the hydroboration.

Although this route is feasible, it is both inconvenient (aldehyde 54 decomposes fairly rapidly) and unnecessarily lengthy. A better route, involving direct conversion of acid 50 to ketone 32 was tried on a model compound. Thus, commercially obtained tetrahydropyran-2-methanol 56 was oxidized (Jones reagent) to acid 57. Reaction of 57 with two equivalents of methyl lithium[60]

gave ketone 58, which reacted as expected with methylenetriphenylphosphorane to give olefin 59.

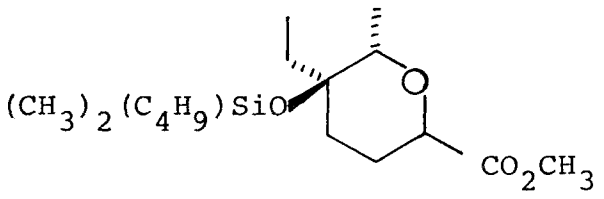


56 57 58

59

Similarly, acid 50 was treated with three equivalents of methyl lithium (the additional equivalent of lithium reagent is consumed by the alcohol proton) to yield the methyl ketone analog of 32. Assuming that ethyl lithium does not react anomalously, this route is the most efficient way to obtain 32.

It has thus far not been necessary to protect the alcohol function that was introduced in the hydroboration reaction. If or when protection of this group is required, it will be possible to prepare a silyl ether. Reaction of ester alcohol 31 with t-butyldimethylsilyl chloride[88] yielded the t-butyldimethylsilyl ether 60. The reaction was sluggish (due, no doubt, to the steric hindrance about the tertiary alcohol), but serves to demonstrate the feasibility of silyl ether protection. The use of either isopropyldimethylsilyl chloride or triethylsilyl chloride might be a better choice.



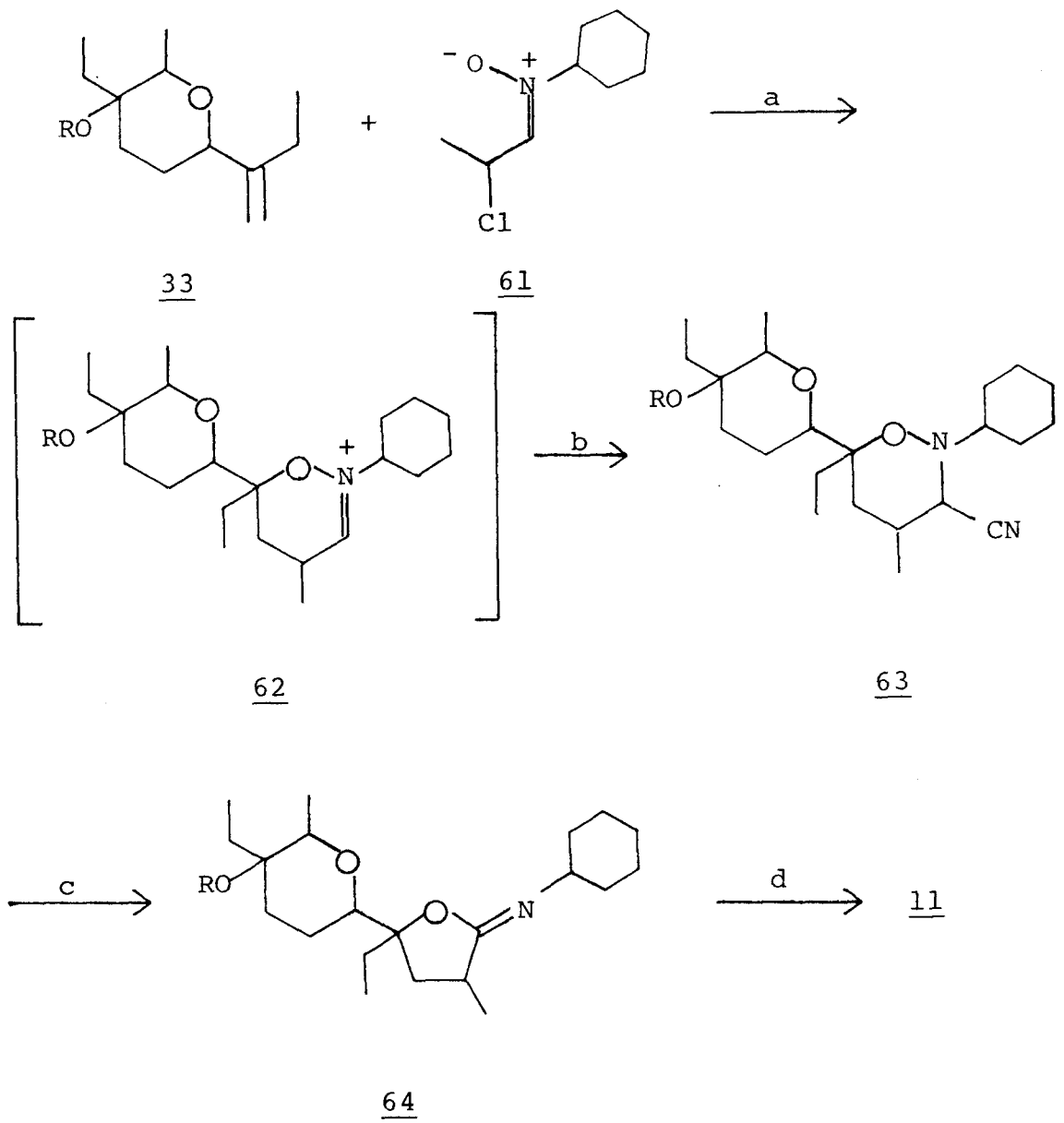
60

Although there are still stereochemical questions to be resolved, a synthesis of 32 has been accomplished. The conversion of ketone 32 to olefin 33 is not expected (based on the model reaction mentioned above and on unpublished results from our laboratory[89]) to present any difficulty. Thus, Scheme 5 represents a viable synthesis of the tetrahydropyran ring of X-537A. Further work on this approach will involve conversion of olefin 33 to the tetrahydropyran-lactone 11. At present, two methods are envisaged for carrying out this transformation.

The first, illustrated in Scheme 9, is based on work by Eschenmoser and his colleagues[90-95]. The chloronitrone 61 should undergo Ag^+-induced addition to the olefin 33 (cycloaddition of an N-alkyl-N-vinyl nitrosonium ion). The initially-formed adduct 62 is not isolated, but trapped with cyanide to give 63. Treatment of 63 with potassium t-butoxide causes rearrangement to imine 64, which yields lactone 11 upon hydrolysis. Preliminary model studies of this reaction in our laboratory have been inconclusive[96].

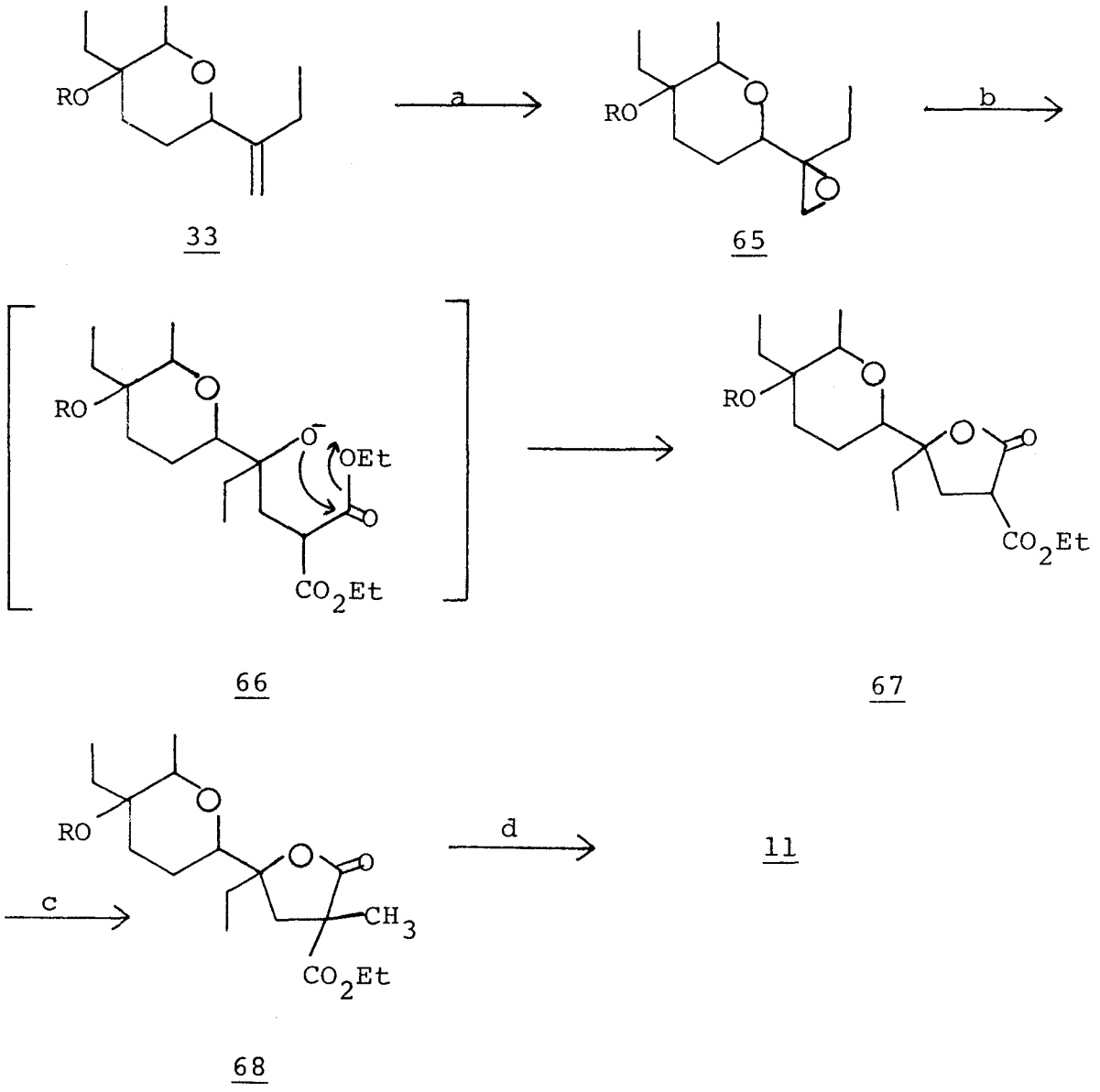
If the chloronitrone procedure should not prove feasible, an alternate, albeit less elegant, route to 11 from 33 is shown in Scheme 10. Epoxidation of 33 and treatment of epoxide 65 with malonic ester anion should yield lactone ester 67 directly[97], through the intermediacy of 66. Introduction of the methyl group and decarboxylation would give 11.

Scheme 9



a, $AgBF_4$; b, CN^-; c, KO<u>t</u>-Bu, <u>t</u>-BuOH; d, H_2O

Scheme 10



a, peracid; b, $CH_2(CO_2Et)_2$, EtO^-, EtOH; c, base, MeI; d, decarboxylate

Experimental

General Methods

Boiling points are uncorrected. Infrared (ir) spectra were determined on a Perkin-Elmer 237B grating infrared spectrometer and nuclear magnetic resonance (NMR) spectra were recorded using either a Varian T-60 or A 60A spectrometer. Chemical shifts are reported as δ values in parts per million relative to TMS (δ TMS = 0.0 ppm) as an internal standard.

Vapor phase chromatographic (VPC) analyses were determined on a Hewlett-Packard 5750 equipped with a flame ionization detector using helium carrier gas at a flow rate of 60 ml/min. Analytical VPC was conducted on a 6 ft x 0.125 in column packed with 4% SE-30 on 60-80 mesh Chromosorb W AW DMCS.

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

Silica gel columns used the 0.05-0.2 mm silica gel manufactured "for column chromatography" by E. Merck & Co., Darmstadt, Germany. Alumina used for column chromatography refers to the grade I, neutral variety manufactured by M. Woelm, Eschwege, Germany.

"Dry" solvents were dried immediately prior to use. Tetrahydrofuran (THF) was distilled from a dark purple solution of benzophenone dianion; ether was distilled from

lithium aluminum hydride; benzene and pyridine were distilled from calcium hydride; methylene chloride was distilled from phosphorous pentoxide; dimethylformamide (DMF) was dried over 4A molecular sieves and fractionally distilled at reduced pressure. "Petroleum ether" refers to the "Analyzed Reagent" grade hydrocarbon fraction, bp 30-60°, which is supplied by J.T. Baker Co., Phillipsburg, N.J., and was not further purified. Reactions employing "dry" solvents were conducted under anhydrous conditions in oven-dried glassware under an argon atmosphere.

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

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

3-hydroxymethyl-2-pentanone, 35

Following the procedure of Colonge and Cumet[61], a mixture of 344.4 g (4.0 mol) of 2-pentanone, 34 (Aldrich Chemical Co.), 128 ml (1.5 mol) of 37% aqueous formaldehyde, and 7.0 ml of 30% aqueous sodium hydroxide was prepared. Sufficient ethanol (ca. 150 ml) was added to give a homogeneous solution, which was stirred at room temperature for 100 minutes. During the first 15 minutes of stirring, the solution became warm and turned yellow. The color deepened to reddish-brown as the reaction progressed.

At the end of the stirring period, the solution was neutralized with 10% aqueous hydrochloric acid, causing a further color change from reddish-brown to pale yellow. The neutral solution was concentrated under reduced pressure on a rotary evaporator to yield 135 g of crude product as a viscous yellow liquid. The crude material was distilled in vacuo to yield 90 g (52%) of keto alcohol 35 as a clear liquid: bp 55.0-58.0° (1.0 mm) (literature[61] bp 95-97° (17 mm)); ir ($CHCl_3$) 3500-3400 (OH), 1700 (CO), 1460 cm^{-1}; NMR ($CDCl_3$) δ 1.0 (t, 3H, $C\underline{H}_3-CH_2-$), 1.3 (m, 2H, $CH_3-C\underline{H}_2-$), 2.2 (s, 3H, CH_3CO), 3.0 (m, 1H, α-H), 3.8 (d, 2H, $-C\underline{H}_2OH$), 4.2 (s, 1H, OH).

3-methylene-2-pentanone (2-ethyl-1-buten-3-one), 28

A mixture of 11.6 g (100 mmol) of 3-hydroxymethyl-2-pentanone 35 and 150 mg of iodine was prepared in a 25 ml roundbottom flask containing a magnetic stir bar. The flask was connected to a short-path distillation apparatus

having a 25 ml receiving flask cooled in an ice bath. The keto alcohol - iodine mixture was heated slowly, with stirring, and boiling began as the temperature of the oil bath reached 120°. The dehydration was continued until no more liquid distilled: maximum bath temperature = 180°; head temperature = 90-95°.

The distillate separated into two phases: methylene ketone (upper) and water (lower). The crude product was isolated by ether extraction, yielding 7.5 g of methylene ketone. Distillation of the crude material at atmospheric pressure under argon afforded 6.3 g (64%) of 3-methylene-2-pentanone 28 as a clear liquid: bp 118-120° (literature[61] bp 118-120°); ir (CCl_4) 1680 (CO), 1630, 1360, 1280, 1150, 1125, 940 cm^{-1}; NMR (CCl_4) δ 1.0 (t, 3H, $C\underline{H}_3-CH_2-$), 2.2 (s, 3H, CH_3CO), 3.3 (q, 2H, $CH_3-C\underline{H}_2-$), 5.5 (s, 1H, olefinic H), 5.8 (s, 1H, olefinic H).

2-carbomethoxy-5-ethyl-6-methyl-3,4-dihydro-2H-pyran, 30

A solution consisting of 1.5 g (15.3 mmol) of 3-methylene-2-pentanone, 28, 33.0 g (384 mmol) of methyl acrylate, 29 (Aldrich Chemical Co., purified by distillation), 0.5 g of hydroquinone, and 30 ml of dry benzene was prepared and placed in a heavy-wall glass tube (2 cm x 50 cm). The solution was degassed by the freeze-pump-thaw method and the tube was sealed under vacuum. The sealed tube was heated (sealed tube oven) to 200°, maintained at that temperature for 72 hours, and then allowed to cool to room temperature. The tube was opened and the contents were transferred to a roundbottom flask. Benzene and unreacted methyl acrylate were

removed on a rotary evaporator. The semi-solid residue was distilled *in vacuo* to yield 1.6 g (57%) of the Diels-Alder adduct 30 as a clear liquid, bp 120° (bath) (0.3 mm).

Analysis of this material by VPC at 175° indicated that the product was essentially free (less than 1%) of dimer 41. An analytical sample was prepared by evaporative distillation at 110° (0.1 mm): ir ($CHCl_3$) 1730 (CO), 1680 (olefin), 1430, 1380 cm^{-1}; NMR ($CDCl_3$) δ 1.0 (t, 3H, CH_3-CH_2-), 1.8 (s, 3H, olefinic CH_3), 2.0 (m, 6H), 3.8 (s, 3H, ester CH_3), 4.4 (m, 1H, α-H).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.91; H, 8.60.

6-carbomethoxy-3-ethyl-3-hydroxy-2-methyl-tetrahydropyran, 31

To a magnetically stirred, ice-cold solution of 1.42 g (7.72 mmol) of carbomethoxydihydropyran 30 in 25 ml of dry THF was added via syringe 6.4 ml (7.61 mmol) of a 1.19 M solution of BH_3-THF in THF (Aldrich Chemical Co.). The solution was stirred at 0° for three hours and then excess hydride was destroyed by the careful addition of 5 ml of water. The aqueous mixture was kept under argon throughout the following oxidation procedure.

The mixture was allowed to warm to room temperature and the organoborane was oxidized by the addition of 7.6 ml (7.6 mmol) of 1.0 M NaOH, followed by the cautious addition of 1.0 ml (11.6 mmol) of 30% hydrogen peroxide. Following the addition of the peroxide, which caused the reaction mixture to become quite warm, the mixture was stirred at room temperature for one hour.

The crude product was isolated by ether extraction, including a base wash. Silica gel chromatography (25% ethyl acetate - benzene) afforded 444 mg (29%) of ester alcohol 31. This material had only one component by TLC analysis (30% ethyl acetate - benzene) and was greater than 95% pure by VPC at 200°. An analytical sample was prepared by evaporative distillation at 85-90° (1.0 mm): ir ($CHCl_3$) 3450-3600 (OH), 1740 (CO), 1450, 1435 cm^{-1}; NMR ($CDCl_3$) δ 1.0 (t, 3H, CH_3-CH_2-), 1.3 (d, 3H, C-2 CH_3), 1.5-2.4 (m, 6H), 3.5 (q, 1H, C-2 H), 3.8 (s, 3H, ester CH_3), 4.2 (m, 1H, C-6 H).

Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.36; H, 8.91.

In a subsequent experiment, the diborane used was generated externally according to the procedure of Zweifel and Plamondon[73]. Oxidation of the organoborane and purification of the product were carried out as described above. Under these conditions, hydroboration of 1.47 g (8.0 mmol) of dihydropyran 30 yielded 450 mg (28%) of ester alcohol 31.

6-carboxy-3-ethyl-3-hydroxy-2-methyl-tetrahydropyran, 50

A solution of ca. 200 mg (1 mmol) of ester alcohol 31 in 20 ml (3 mmol) of 0.15 M aqueous methanolic lithium hydroxide[84] was stirred at room temperature for 72 hours. After acidification with aqueous hydrochloric acid, the product, 151 mg (ca. 80%) of acid alcohol 50, was isolated by ether extraction. Evaporative distillation at 150° (0.1 mm)

afforded analytically pure material: ir ($CHCl_3$) 3100-3600 (OH), 1725 (CO), 1450, 1365, 1100 cm^{-1}; NMR ($CDCl_3$) δ 1.0 (t, 3H, CH_3-CH_2-), 1.3 (d, 3H, C-2 CH_3), 1.4-2.4 (m, 6H), 3.5 (q, 1H, C-2 H), 4.2 (m, 1H, C-6 H), 5.8 (br s, 1H, -OH).

Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.25; H, 8.48.

Attempted Lactonization of acid alcohol 50

(A) with acetic anhydride

Following the procedure of Giudici and Bruice[85], a solution of 100 mg (0.53 mmol) of acid alcohol 50 in 10.0 ml (10.8 g; 160 mmol) of acetic anhydride was refluxed under argon for six hours and then allowed to stir at room temperature for 24 hours. The acetic anhydride was removed by short-path distillation under reduced pressure (water aspirator). The residue was taken up in ether and the crude product was isolated by ether extraction including a base wash. Evaporative distillation of the crude material at 150° (0.05 mm) afforded 70 mg of starting acid 50, characterized by TLC and ir spectrum. An additional 20 mg of starting material was recovered by acidification and ether extraction of the above-mentioned base wash. The total recovery of starting material was 90%.

(B) with dicyclohexylcarbodiimide

Following the method of Johnson, et al.[86], a solution

of 80 mg (0.43 mmol) of acid alcohol 50, 104 mg (0.504 mmol) of dicyclohexylcarbodiimide, and 20 ml of dry pyridine was stirred at room temperature under argon for five days. The solvent was removed under reduced pressure (rotary evaporator), the residue was taken up in ether, and the product was isolated by ether extraction, including an acid wash. This material was shown (TLC and ir spectrum) to be unchanged starting acid 50. The recovery was 76 mg (95%).

(C) with p-toluenesulfonic acid

Following the procedure of Johnson, et al.[86], a solution of 240 mg (1.28 mmol) of acid alcohol 50, 100 mg (0.53 mmol) of p-toluenesulfonic acid, and 50 ml of xylene was refluxed for one hour in a flask equipped with a reflux condenser and water separator. After cooling, the product was isolated by xylene extraction including a base wash. The product was again shown (TLC and ir spectrum) to be unaltered starting material. The recovery was 227 mg (95%).

3-ethyl-3-hydroxy-6-hydroxymethyl-2-methyl-tetrahydropyran, 55

To a stirred suspension of 40 mg (1.1 mmol) of lithium aluminum hydride in 25 ml of dry THF was added dropwise a solution of ca. 200 mg (1 mmol) of ester alcohol 31 in 25 ml of dry THF. The mixture was stirred at room temperature for 12 hours and then refluxed for 6 hours. After cooling, excess hydride was destroyed by the dropwise addition of ethyl acetate, followed by aqueous THF. The suspension was filtered and the product was isolated by continuous extraction of the

filtrate with ether for three days. Silica gel chromatography (50% ethyl acetate - benzene) afforded 130 mg (ca. 75%) of diol 55 as a viscous liquid. NMR and ir spectra indicated the absence of ester carbonyl and ester methyl functionalities. TLC analysis (50% ethyl acetate - benzene) showed only a single component of R_f = 0.15.

ir ($CHCl_3$) 3400-3600 (OH), 1450, 1255, 1090 cm^{-1}.

3-ethyl-6-formyl-3-hydroxy-2-methyl-tetrahydropyran, 54

Chromium trioxide - pyridine complex was prepared by the method of Ratcliffe and Rodehorst[87] using 120 mg (1.2 mmol) of chromium trioxide and 190 mg (2.4 mmol) of dry pyridine in 20 ml of dry methylene chloride. To the resulting burgandy solution was added a solution of 34 mg (0.20 mmol) of diol 55 in 5 ml of dry methylene chloride. This addition resulted in the immediate formation of a black precipitate.

After stirring for 15 minutes, the product was isolated as described by Ratcliffe and Rodehorst[87]. The yield was 20.6 mg (61%) of crude hydroxy aldehyde 54 which was not further purified. Spectral (ir) analysis indicated the absence of primary OH; TLC (50% ethyl acetate - benzene) showed only a single spot at the solvent front and no spot at R_f = 0.15 corresponding to starting material.

ir ($CHCl_3$) 1725 (CO), 1260, 1000-1100 cm^{-1}.

6-acetyl-3-ethyl-3-hydroxy-2-methyl-tetrahydropyran

To a stirred, ice-cold solution of 70 mg (0.37 mmol) of acid alcohol 50 in 10 ml of dry THF was added dropwise 0.7 ml (1.13 mmol; 3 equiv.) of a 1.62 M solution of methyllithium in ether. The ice bath was removed and the solution was stirred at room temperature for one hour.

The reaction was quenched by taking up the reaction mixture in a syringe and adding it dropwise to 50 ml of rapidly stirred ice water. The product was isolated by ether extraction, yielding 16 mg (23%) of the keto alcohol as a yellowish liquid with a strong odor. This material was not further purified. TLC analysis (30% ethyl acetate - benzene) showed one major component of R_f = 0.33 (the starting acid remains at the origin in this TLC system).

ir ($CHCl_3$) 3400-3600 (OH), 1715 (CO), 1100 cm^{-1}; NMR ($CDCl_3$) δ 1.0 (t, 3H, CH_3-CH_2-), 1.2 (d, 3H, C-2 CH_3), 1.5-2.0 (m, 6H), 2.2 (s, 3H, ketone CH_3), 3.5 (q, 1H, C-2 H), 4.2 (m, 1H, C-6 H).

6-carbomethoxy-3-ethyl-2-methyl-3-(tert.-butyldimethyl-silyloxy)-tetrahydropyran, 60

A solution of 67.5 mg (0.34 mmol) of ester alcohol 31, 114 mg (1.7 mmol; 5 equiv.) of imidazole, and 126 mg (0.84 mmol; 2.5 equiv.) of tert.-butyldimethylsilylchloride in 5 ml of dry DMF was stirred at room temperature for 48 hours. The solution was mixed with water and the product was isolated by ether extraction, affording a viscous oil. Analysis of the crude product by TLC (methylene chloride) showed one major component of R_f = 0.54 and a minor

component (starting material) at the origin. Purification by silica gel chromatography (methylene chloride) gave 68.7 mg (65%) of silyl ether 60. Analysis by VPC (250°) showed this material to be greater than 95% pure. The ir spectrum indicated absence of OH.

ir ($CHCl_3$) 1740 (CO), 1250 (O-Si), 1090 cm^{-1}; NMR ($CDCl_3$) δ 0.0 (s, 6H, $(CH_3)_2Si$-), 1.0 (m, 12H, CH_3-CH_2- and $(CH_3)_3C$), 1.3 (d, 3H, C-2 CH_3), 1.4-2.2 (m, 6H), 3.5 (q, 1H, C-2 H), 3.8 (s, 3H, ester CH_3), 4.2 (m, 1H, C-6 H).

Model Compounds

(A) 2-carboxytetrahydropyran, 57

To a stirred solution of 5.8 g (50 mmol) of 2-hydroxymethyltetrahydropyran (Aldrich Chemical Co.) in 100 ml of acetone was added dropwise sufficient Jones reagent such that the orange color of the oxidant persisted for 30 minutes. The temperature of the reaction mixture was maintained by external cooling at less than 40° throughout the addition.

Excess oxidant was destroyed by adding a few drops of isopropyl alcohol to discharge the orange color. The acetone was decanted from the solid residue and the residue was washed with several portions of acetone. Concentration of the acetone solution under reduced pressure (rotary evaporator) left a thick liquid. This material was dissolved in ether

and the crude product was isolated by ether extraction, including a base wash. The crude product (4.0 g; 62% crude yield) was purified by distillation in vacuo, affording 2.6 g (40%) of acid 57 as a clear, viscous liquid: bp 70-75° (0.5 mm) (literature[98] bp 110.5° (5 mm)); ir ($CHCl_3$) 3000-3500 (acid OH), 1720 (CO), 1440, 1095, 1050, 910 cm^{-1}.

(B) 2-acetyltetrahydropyran, 58

To a stirred, ice-cold solution of 400 mg (3.08 mmol) of carboxylic acid 57 in 20 ml of dry THF was added dropwise 3.8 ml (6.16 mmol; 2 equiv.) of a 1.62 M solution of methyllithium in ether. During the addition, particles of white solid appeared and then redissolved as more methyllithium was added. The ice bath was removed and the solution was stirred at room temperature for one hour, becoming slightly turbid during the final five minutes.

The reaction was quenched by taking up the reaction mixture in a syringe and adding it dropwise to 75 ml of rapidly stirred ice water. The crude product, isolated by ether extraction including a base wash, amounted to 397 mg (quantitative crude yield) of ketone 58. Analysis of this product by TLC (10% ether - petroleum ether) revealed one major component of R_f = 0.20 and a minor component (tertiary alcohol) of R_f = 0.07.

ir ($CHCl_3$) 1715 (CO), 1435, 1355, 1290, 1170, 1090, 1050, 900 cm^{-1}; NMR ($CDCl_3$) δ 1.4-2.0 (m, 6H), 2.2 (s, 3H, ketone CH_3), 3.7 (br m, 3H).

(C) 2-isopropenyltetrahydropyran, 59

To a cold (-78°) suspension of 1.1 g (3.1 mmol) of (methyl)-triphenylphosphonium bromide (Aldrich Chemical Co.) in 50 ml of dry ether was added 1.3 ml (3.1 mmol) of a 2.36 M solution of n-butyllithium in hexane. The cooling bath was removed and the mixture was stirred at room temperature for 90 minutes, by which time all the solid material had dissolved, giving an orange solution of methylenetriphenylphosphorane.

This solution was cooled to -78° and a solution of 397 mg (3.1 mmol) of ketone 58 in 20 ml of dry ether was added, with immediate formation of a creamy precipitate. The cooling bath was removed and the mixture was stirred for 45 minutes at room temperature before the reaction was quenched by the addition of 10 ml of methanol, giving an orange solution.

The solution was filtered through Celite and the reaction flask and Celite pad were washed with ether. Concentration of the filtrate under reduced pressure (rotary evaporator) afforded an orange liquid, which was chromatographed over alumina (pentane) to give ca. 300 mg (77%) of impure olefin 59. Analysis of this product by TLC (10% ether - petroleum ether) showed one major component of R_f = 0.64 and two minor components of R_f = 0.20 (ketone) and R_f = 0.07 (tertiary alcohol). Due to the impurity of this product, clean spectra could not be obtained, but the ir and NMR spectra were consistent with the assigned structure. In particular, the NMR spectrum clearly showed the presence of the olefinic hydrogens (δ 4.9, d, 2H, J = 4 Hz).

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