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STUDIES ON STRUCTURALLY SIMPLE α,β-BUTENOLIDES—I

NEW SYNTHESES OF RACEMIC γ-HYDROXYMETHYL-α,β-BUTENOLIDE AND DERIVATIVES

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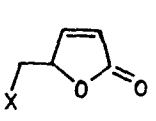
Abstract—Exhaustive approaches to the synthesis of racemic γ-heterosubstituted γ-methyl-α,β-butenolides are presented, starting mainly from C_3 synthons (glyceraldehyde, glycidaldehyde, acrolein and 2,3-epoxypropyl ethers). Good general methods for the preparation of γ-hydroxymethyl-α,β-butenolide **2**, several of its ether derivatives, as well as of γ-bromomethyl-α,β-butenolide **5**, are given. The reactivities of these structurally simple but highly functionalized compounds, convenient synthons for more complex molecules, are preliminarily explored.

INTRODUCTION

In recent years there has been a renewed interest in the synthesis of structurally simple α,β-butenolides. This ring system is widely present in secondary metabolites which show interesting physiological activities.[1,2] Some examples are the many sesquiterpenoid lactones, such as norparthenone; fungal metabolites, such as patulin, penicillic acid or the pulvinones; and metabolites of marine origin, such as the carotenoid pigments of phytoplankton (for example, peridinin), the antibiotic strobilin or the polyhalogenated algal metabolites known as fimbrolides. Methods for the synthesis of α,β-butenolides have been reviewed,[3] and in recent years some new syntheses of butenolides have been published.[4] However, the synthesis of γ-heteromethyl-α,β-butenolides **1** is virtually unexplored, except for a few isolated examples.[5]

γ-Hydroxymethyl-α,β-butenolide **2**, in its *S* configuration, is the aglycone of ranunculin **3**, a glucoside studied by Hill[6] and by one of us[7] several years ago. Both (±)-**2** and (−)-(*S*)-**2** or ether derivatives from them have recently been used as templates in the synthesis of natural products, the former for prostaglandin analogs by Pernet[8] and the latter for antileukaemic lignans by Koga.[5a,b] Their high concentration of functional groups on just five carbon atoms allows the use of butenolides of type **1** as useful synthons with good reactivity as Michael acceptors, although—and this has been overlooked in the literature—they can easily eliminate HX under the action of bases to give protoanemonin **4**. This elimination reaction is so easy that even ranunculin **3**, which is exceptionally stable towards acids, hydrolyzes in neutral or alkaline aqueous solution directly to its anhydroaglycone **4**.[7] Thus the aglycone (—)-(*S*)-**2** has only been isolated in very small amounts by enzymic hydrolysis.[9]

One of us described a long and inefficient synthesis of **2** from vinyl-acetylene[10] which was followed by Pernet[8] in his work on PG analogs. On the other hand, ethers of (−)-(*S*)-**2**, such as **1** (X = Ph_3CO or $PhCH_2O$) have been prepared by Koga in six steps from L-glutamic acid[5a] in low overall yields. The purpose of the present paper and successive ones is to describe new and efficient syntheses of γ-heteromethyl-α,β-butenolides of type **1**, both racemic and optically active. In the present paper particular emphasis will be placed on the racemic compounds γ-hydroxymethyl-α,β-butenolide **2** and γ-bromomethyl-α,β-butenolide **5**, their synthesis and their reactivity. The accompanying paper is devoted to the synthesis of optically active (−)-(*S*)-**2**, some ether derivatives and



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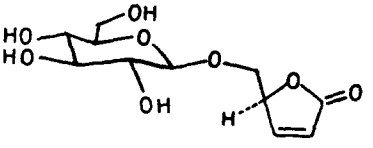

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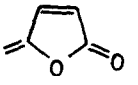


4

2 (X = OH)
5 (X = Br)
75 (X = MeO)
76 (X = Ph_3CO)
77 (X = $PhNHCO_2$)

Scheme 1.

several reactions of these chiral compounds. Preliminary communications on these subjects have already appeared.[11,12]

Retrosynthetic analysis of the target molecules **1**

A brief analysis yields three different synthetic approaches to butenolides **1**:

(i) Initial formation of the butanolide ring with final generation of the double bond. This was the approach used by Koga,[5a] who prepared γ-trityloxymethyl-α,β-butenolide from the corresponding saturated lactone using selenium chemistry, and in another synthesis of (−)-(*S*)-**2** and derivatives, published from these laboratories,[12] using D-ribonolactone as the starting material. In both cases optically active products were obtained.

(ii) Use of furan derivatives as precursors. Actually, oxidation of furfuryl alcohol by peracetic acid was believed to give **2** as a minor by-product,[13] while lead tetraacetate is used for the oxidation of furanoterpenoids to the corresponding α,β-butenolides.[14] On the other hand, condensation of 2-*tert*-butoxyfuran with carbonyl compounds yields γ-ylidene-α,β-butenolides.[15]

(iii) Generation of conveniently functionalized (*Z*)-2-pentenoic acids **6** or pentanoic acids **7** *via* condensation of appropriate C_3 and C_2 synthons.

A fourth, non-trivial (see below) approach is the replacement of X in previously formed butenolides of type **1**. In the present paper we explore approach (iii), as well as this apparently simple fourth approach.

Use of glyceraldehyde as the C_3 *synthon*

One obvious precursor for butenolide **2** is (*Z*)-4,5-dihydroxy-2-pentenoic acid, **6** (X = Y = OH, R = H). Therefore, the use of glyceraldehyde as the C_3 synthon was considered. Previous work by one of us has shown that attempted Knoevenagel condensation of glyceraldehyde dimer **8** and malonic acid or esters gives polymeric products,[16] while the use of glyceraldehyde acetonide **9** has been reported[17] to result in the *E* condensation product **10**, rather than the *Z* isomer, but in very low yield. However, in previous work,[10] it was found that dimer **8** reacts smoothly with the Wittig reagent **11** in benzene to afford methyl ester **12** in 80% yield. We have now found that in cold methanol this Wittig reaction gave **12** as the major product, together with a small amount of **2** (identified by PMR) which could not be separated. Similarly, the acetonide **9** reacted with **11** in dichloromethane to give exclusively the *E* ester **13**, as described by Kuhn,[18] but in methanol as solvent this Wittig reaction gave also the *Z* ester **14**, which could be isolated in 28% yield. Careful hydrolysis of **14** gave a low (12%) yield of **2**, which is extremely soluble in water, and this is probably the reason for the low yield of its isolation.

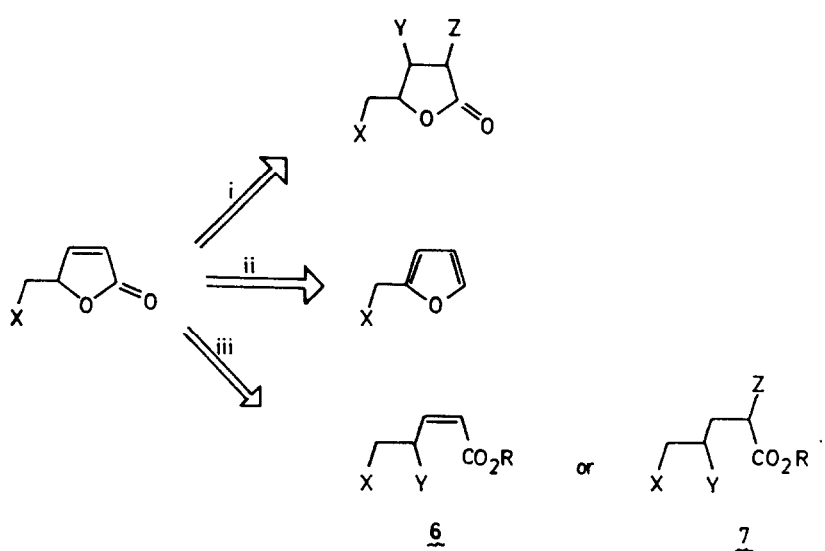
A substantial improvement in the yield of **2** was reached when taking into account the formal equivalence between *E* and *Z* alkenes under UV irradiation. Usually photolactonization of (*E*)-4-hydroxy-2-alkenoic acids or esters is carried out under acid catalysis[19] and, as mentioned above, butenolides of type **1** are stable towards these conditions. Thus, unsensitized irradiation of **12** in acidified methanol for 1.5 h using a 400 W medium pressure mercury lamp gave **2** in 48.5% yield, together with a 32% recovery of unreacted **12**, which could be recycled. Irradiation for longer periods resulted in disappearance of the ethylenic protons in the PMR spectrum of the crude irradiated mixture.

Use of glycidaldehyde as the C_3 *synthon*

Glycidaldehyde **15** can be easily prepared (but not easily isolated: 10% yield) from acrolein by epoxidation with hydrogen peroxide in mild alkaline medium.[20] Wittig olefination of **15** with the phosphorane **11** in dichloromethane afforded the *E* ester **16** in 57% yield. The same reaction performed in methanol gave a 2:3 mixture of *E* **16** and *Z* **17** condensation products in 46% overall yield. The same mixture of stereoisomers could be obtained in 23% overall yield from acrolein, avoiding the difficult isolation of **15**, by reacting **11** with the crude product from the epoxidation reaction, fairly diluted in methanol.

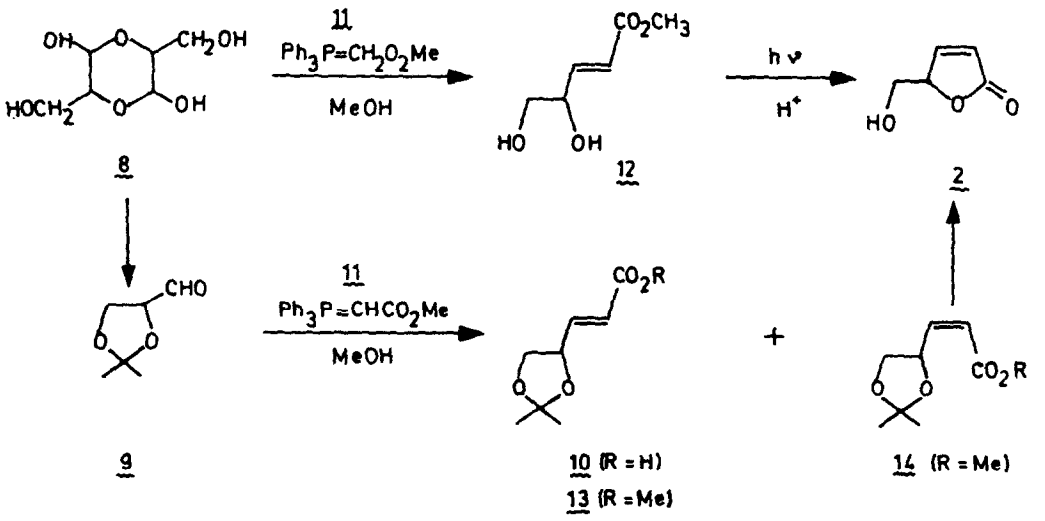
Separation of **16** and **17** required the use of preparative tlc, since the *Z* isomer decomposed (protoanemonin?) upon attempted column chromatography on silica gel, while 2-methoxyfuran was collected instead of **17** under preparative glc. The stereochemical assignment of epoxyesters **16** and **17** was confirmed by their spectral data.

Since the preparation of **17** just described, and parti-

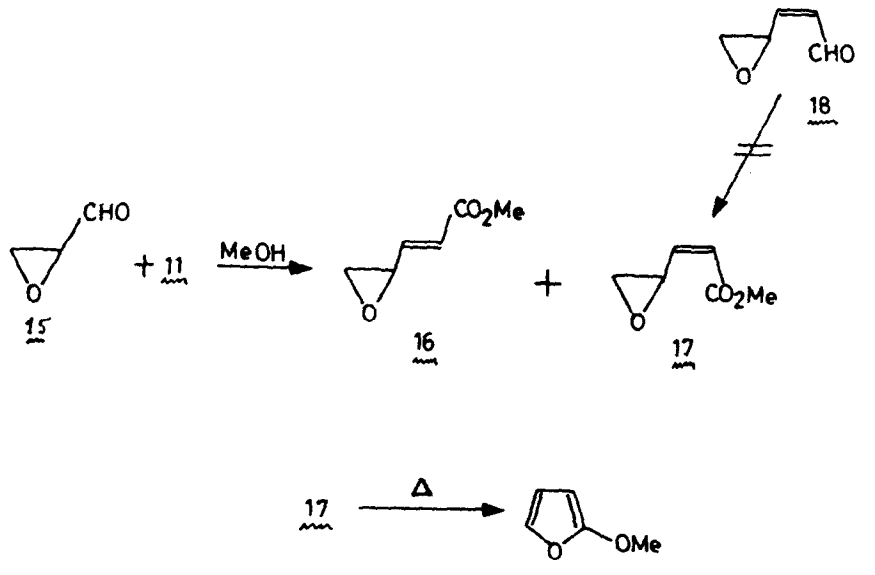


6 7

Scheme 2.



Scheme 3.



Scheme 4.

cularly its isolation by preparative tlc, are not very convenient from the synthetic point of view, we tried a different approach to arrive at this compound. The *Z* epoxyaldehyde **18** can be obtained from cyclopentadiene by sensitized photooxidation.[21] Furthermore, **18** is now commercially available from Fluka. We therefore tried several oxidations of **18** under neutral, mild conditions, but unsuccessfully. Thus, **18** did not react with atmospheric oxygen, while Corey's method for the oxidation of α,β-unsaturated aldehydes to methyl esters by active manganese dioxide in methanol under hydrocyanic acid catalysis[22] gave the desired epoxyester in low, unreproducible yields. The use of silver(II) oxide[22] under the same conditions, instead of manganese dioxide, resulted in the formation of polymers.

As expected, treatment of **17** with a catalytic amount of perchloric acid in aqueous dioxane or aqueous acetone gave **2** in 75% yield. However, when methanol was used as solvent, a complex mixture of products resulted. Among them we have identified the *E* ester **19**, *cis*- (**20**) and *trans*- (**21**) β,γ-dimethoxy-δ-valerolactones, as well as small amounts of ketoesters **22** and **23**. Plausible mechanisms for these reactions are given in Fig. 1, in which route (a) takes into account the observed nucleophilic attack at C_4 of the protonated oxirane ring, while route (b) shows the formation of acetylacrylate derivatives by hydride migration when the protonated oxirane ring opens in the alternative direction (structure **24**, *arrows*). The possible anchimeric assistance by the very near carboxyl oxygen atom, which *a priori* cannot be excluded, is shown in routes (a') and (b').

In striking contrast with this complex behaviour, treatment of the *E* isomer **16** with methanol under acid catalysis gave exclusively the *E* addition product **19** in 64% yield. Finally, the mixture of **16** and **17** obtained in the aqueous-methanolic Wittig reaction, directly treated with a catalytic amount of perchloric acid in acetone, gave a mixture of butenolide **2** and acetonide-ester **13** which could be separated by distillation.

The constitution and stereochemistry of δ-lactones **20**

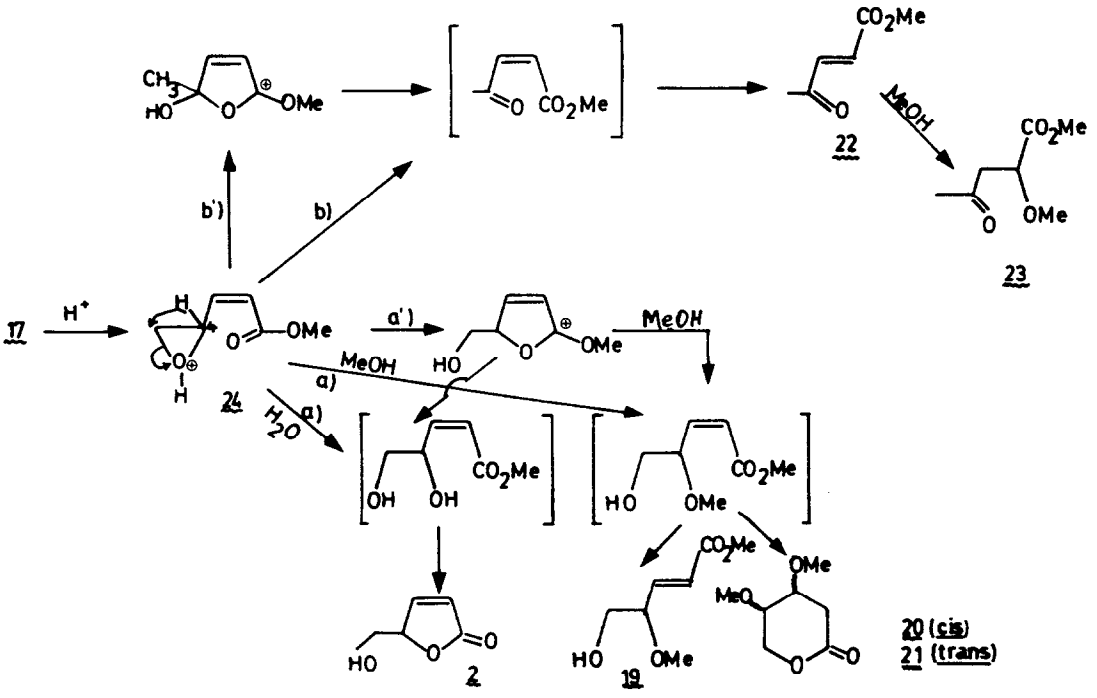
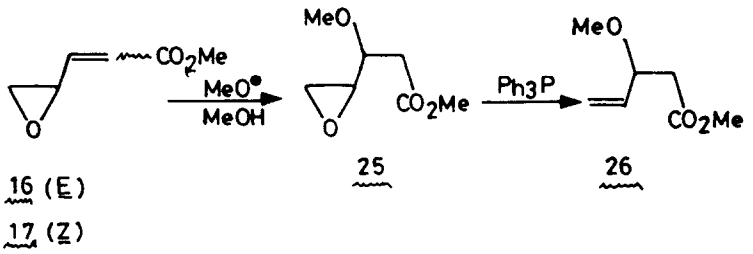


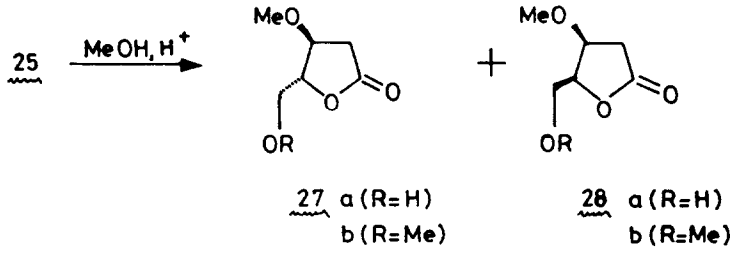
Fig. 1.

and **21** have been established by chemical correlation with natural products of known configuration, as reported elsewhere.[23]

The constitution of the *E* ester **19**, i.e. the presence of a primary hydroxyl and a secondary methoxyl group, was firmly established by its ^{13}C NMR spectrum, which in the off-resonance mode showed a doublet at 81.0 ppm for C_4 and a triplet at 63.7 ppm for C_5. Comparison of this data with those of diolester **12** (doublet at 71.4 ppm for C_4 and triplet at 65.2 for C_5) confirms that acid-catalyzed opening of the oxirane ring in epoxyesters **16** and **17** takes place by attack of the nucleophile at C_4, as shown in Fig. 1, thus preventing the formation of γ-lactones of type **1** from the *Z* epoxyester **17** for nucleophiles other than water.

In order to have S_N2 conditions, which should favor the alternative oxirane ring opening, we next reacted epoxyesters **16** and **17** with methanolic sodium methoxide. However no ring opening occurred, and from both isomers, using either catalytic or equimolar sodium methoxide, the Michael adducts **25** were obtained as a chromatographically separable mixture of *erythro* and *threo* diastereoisomers in up to 36% overall yield. We could not assign the configuration of these two Michael adducts, although their constitution **25** was confirmed spectroscopically and by conversion to **26**, identified by





Scheme 5.

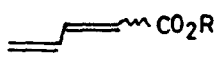
PMR. Treatment of **25**, as a mixture of diastereomers, with acid in methanol afforded the separable lactones **27** and **28**, identified by chemical correlation with natural products of known configuration, as reported elsewhere,[23] and unmistakably assigned as γ-lactones from their IR band at 1790 cm^{-1}.

Comparison between the reactions of the unsaturated epoxyesters **16–17** and the saturated epoxyesters **25** with acid in methanol allows us to conclude that the acrylate group of the former pair behaves as a vinyl substituent and hence stabilizes the secondary, allylic cationic center which develops at C_4 upon opening of the protonated oxirane ring, probably under stereoelectronic control, while in the case of **25** the absence of this acrylate unit results in the normal S_N2 steric control leading to substitution at the primary position. The stabilizing ability of the acrylate residue is also the driving force for the hydride migration which leads ultimately to **22** and **23** upon opening of the protonated oxirane ring of the unsaturated epoxyester **17** in the alternative direction (Fig. 1, structure **24**, *arrows*). The absence of this process in the *E* isomer **16** supports the anchimeric assistance by the very close oxygen atom of the ester group in the case of the *Z* isomer **17**, as shown in Fig. 1, routes (a') and (b').

We should finally mention that photolactonization of the *E* epoxyester **16** in acidified aqueous acetone yielded hydroxymethylbutenolide **2** (27%), while part of the remaining starting material was recovered as dihydroxyester **12** (18%), which is also photolactonizable.

Use of acrolein as the C_3 synthon

An alternative way for the preparation of epoxyester **17** would start from acrolein, by Wittig or Knoevenagel condensation to a diene derivative **29**, followed by epoxidation of its terminal double bond. On the other hand, addition of X–Y to this double bond would also open the way to other derivatives of type **6**, which could eventually lactonize to butenolides **1**. Again, the stereochemistry of **29** appears to be the important factor. Thus, Wittig reaction of acrolein with the phosphorane **11** in dichloromethane gave the *E* ester **30**, but the yield of isolated product was quite low (24%) because compounds of type **29** polymerize during distillation, and in



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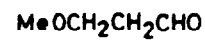


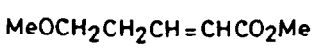
32

30 (E) (R=Me)

31 (Z) (R=Me)

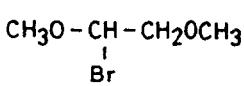
35 (E) (R=Na)

42 (E) (R=H)

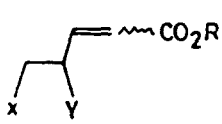


33 (E)

34 (Z)



39



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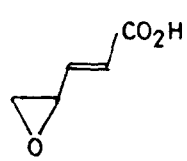


46

36 (E) (X=I, Y=OH, R=H)

37 (E) (X=Br, Y=OH, R=Me)

38 (E) (X=Br, Y=OMe, R=Me)

40 (Z) (X=Br, Y=OH, R=Me)

41 (Z) (X=Br, Y=OMe, R=Me)

43 (E) (X=Br, Y=OH, R=H)

44 (E) (X=Y=Br, R=H)

Scheme 6.

our hands ester **30** polymerized even at −10°. When the Wittig olefination was carried out in methanol, spinning band distillation allowed the isolation of the *Z* ester **31** in only 3% yield, while the yield of the *E* isomer **30** was 20%. Also isolated were 3-methoxypropanal **32** (< 1%) and a 2:3 mixture of the isomeric esters **33** and **34**. Epoxidation of the *E* diene **30** by *m*-chloroperbenzoic acid (*m*-CPBA) gave the terminal epoxyester **16** in 63% yield. However, the same reaction performed on the *Z* isomer **31** gave unidentified products, together with a trace of butenolide **2**.

Other butenolides of type **1**, particularly halogenated derivatives **1** (X = halogen) can conceivably be prepared from dienes **29**. Indeed, the reaction of sodium pentadienoate **35** with aqueous iodine and potassium iodide has been claimed[24] to yield γ-iodomethyl-α,β-butenolide **1** (X = I). However, in our hands this reaction gave only the *E* iodohydrin **36** in 18% yield, together with much unchanged starting material. We have prepared other halohydrins from dienes **29**. Thus, bromohydroxylation of the terminal double bond of **30** by *N*-bromosuccinimide (NBS) in aqueous 1,2-dimethoxyethane (DME) gave **37**, impurified with important amounts of the unexpected by-product **38**, identical with the compound formed upon treatment of **30** with NBS in methanol. Obviously, formation of **38** in the former reaction requires bromination of DME to **39**, which upon hydrolysis would release the required methanol. Pure **37** was obtained in 68% yield by reaction of **30** with NBS in the presence of water (heterophase).

However, the reaction in heterophase between the *Z* isomer **31**, NBS and water did not give the expected *Z* bromohydrin **40**; instead, a mixture of its *E* isomer **37** and γ-bromomethyl-α,β-butenolide **5** was obtained. The isomerization of the α,β-double bond was largely suppressed when performing an analogous reaction in homogeneous phase. Thus, reaction of **31** with NBS in methanol yielded the *Z* unsaturated ester **41**, impurified by small amounts of the *E* isomer **38**. Again, the best yield of the bromobutenolide **5** was obtained from the *E* bromohydrin **37**, rather than from the scarcely available derivatives of *Z* configuration, by photolactonization. Thus, irradiation of **37** in acidified methanol yielded the bromobutenolide **5** in 41% yield.

The best route to **5** starts from (*E*)-2,4-pentadienoic acid **42**, an easily polymerizable compound which can be obtained from acrolein by Knoevenagel condensation with malonic acid as described by Doebner.[25] Thus, reaction of **42** with either NBS or, preferably, bromine in aqueous sodium bicarbonate gave the water-soluble bromohydrin **43** in up to 64% yield. Repeated irradiations of **43** in acidified water yielded the butenolide **5** in 75% isolated yield on a 16 g scale preparation.

The bromohydroxylation of **42** in alkaline aqueous solution is worth commenting upon more deeply. When using bromine (1.2 equiv.) and sodium bicarbonate the by-products isolated from this reaction were the dibromoacid **44** (13% yield) and, somewhat surprisingly, (*E*)-4-bromo-2-butenal **45** (formed in up to 10% yield). Formation of the latter can be rationalized as shown in Fig. 2(a). In more basic conditions, i.e. using sodium hydroxide, the epoxyacid **46** was isolated in 16% yield, together with much gummy material. On the other hand, when bromohydroxylation of **42** was performed in aqueous dioxane, in order to suppress these side reactions brought about by the presence of base, no bromohydrin **43** could be isolated; instead, dibromoacid **44** (54% yield) was exclusively formed. Finally, when using two equiv. of bromine in aqueous sodium bicarbonate, subsequent treatment of the crude reaction products with 4-methylbenzenesulfonic acid in benzene under reflux gave several products, including the dibrominated butenolide **47** (8% yield), probably formed as shown in Fig. 2(b). The other products formed in this last reaction will be fully described elsewhere.[26]

Use of epichlorohydrin as the C_3 *synthon*

Recalling the retrosynthetic analysis shown above, it is worth noting that another approach to butenolides of type **1** (X = OR) which combines features from routes (iii) and (i) would start from epichlorohydrin (or some 3-alkoxy-1,2-epoxypropane easily derived from it) and malonyl derivatives. Indeed, the reaction of 1,2-epoxy-3-phthalimidopropane with diethyl malonate has been reported[27] to yield α-ethoxycarbonyl-γ-phthalimidomethyl-γ-butyrolactone, from which the corresponding butenolide **1** (X = phthalimido) could probably be formed through approach (i).

We first tried the preparation of **1** (X = Cl) from epichlorohydrin itself, but its reaction with dimethyl malonate **48** gave a complex mixture of products, mainly polymers. However, reaction of 3-*n*-butoxy-1,2-epoxypropane **49** with ester **48** gave the γ-lactone **50** in 51% yield. Chlorination of the active α position of **50** by sulfuryl chloride (see Ref. 27) yielded **51**, which was hydrolyzed and decarboxylated to the chlorolactone **52**. Dehydrochlorination of **52** to the desired butenolide was unsuccessfully tried by several methods (DBN in toluene under reflux;[28] potassium *tert*-butoxide in *tert*-butanol; sodium carbonate in xylene under reflux;[29] sodium ethoxide in ethanol). Therefore the chlorine atom of **52** was replaced by treatment with sodium benzenethiolate in ethanol. The resulting thioether **53** was oxidized by sodium metaperiodate in aqueous methanol to sulfoxide **54**, which without further purification was pyrolyzed in boiling toluene to afford butenolide **55**. All compounds **50–54** showed to be mixtures of diastereomers.

Similarly, 1,2-epoxy-3-phenoxypropane **56** (prepared from epichlorohydrin and sodium phenoxide[30]) was converted into **57**. However reaction of **57** with sulfuryl chloride resulted in chlorination at the benzene ring of the side chain substituent, and when three equiv. of sulfuryl chloride were used the final product was the trichloroderivative **58** rather than the expected **59**. Compound **58** was converted, via **60**, **61** and **62**, into the corresponding butenolide **63**. The preparation of the non-chlorinated butenolide **64** was achieved by reaction of **57** with benzenesulfenyl chloride, hydrolysis and decarboxylation of the resulting **65** to **66**, oxidation of this sulfide to **67** and pyrolysis of the latter to **64**.

γ-Heteromethyl-α,β-butenolides from other butenolides

Besides the syntheses described in the preceding paragraphs, a simple approach to butenolides of type **1** would start from other butenolides, for instance by appropriate functionalization of the methyl group of α- or β-angelica lactones (**68** and **69**, respectively), or by replacement of X in some of the butenolides **1** hitherto described. However, both ways present some problems. Thus, reaction of **68** or **69** with NBS has been reported[31] to give low yields of the dibrominated derivative **70** as the only identified product. In our hands, this reaction gave a complex mixture of products in varying proportions, among them protoanemonin **4**, as well as **71**, **72** and

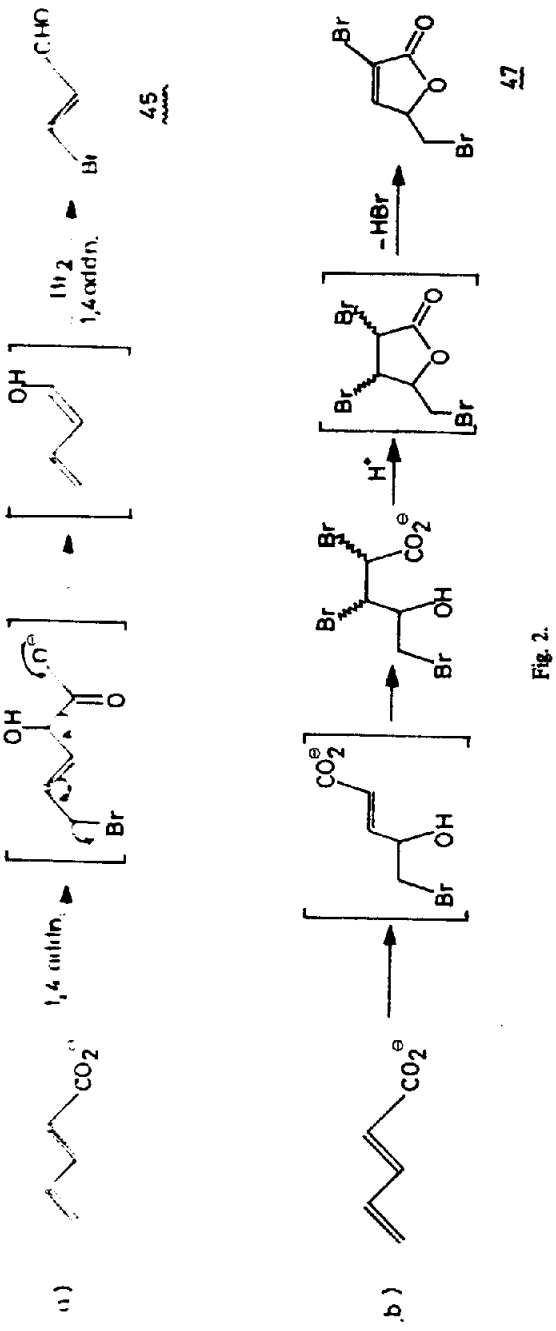
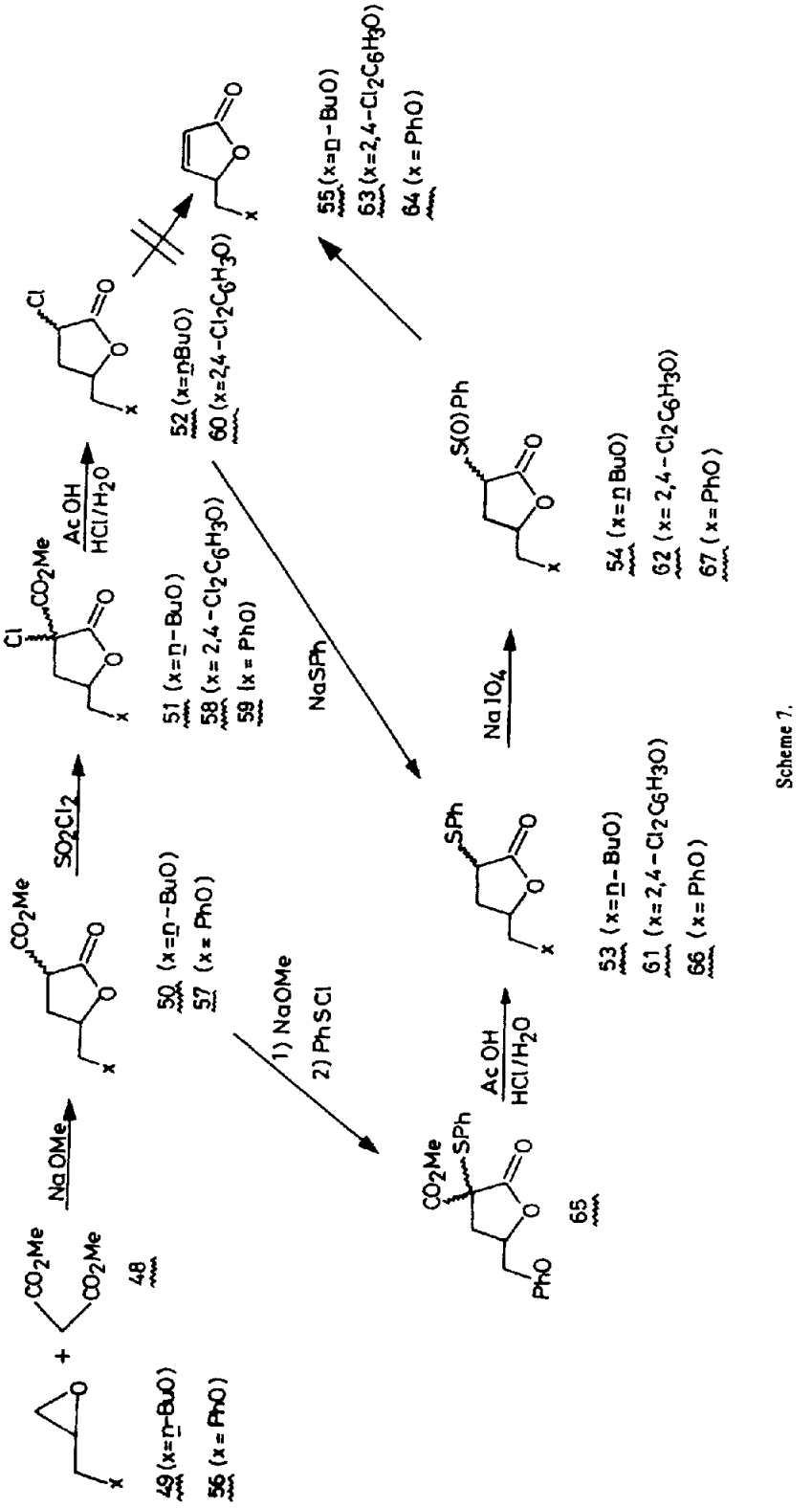


Fig. 2.


49 (x=n-BuO)
56 (x=PhO)
48
NaOMe
50 (x=n-BuO)
57 (x=PhO)
SO2Cl2
51 (x=n-BuO)
58 (x=2,4-Cl2C6H3O)
59 (x=PhO)
AcOH
HCl/H2O
52 (x=nBuO)
60 (x=2,4-Cl2C6H3O)
55 (x=n-BuO)
63 (x=2,4-Cl2C6H3O)
64 (x=PhO)
1) NaOMe
2) PhSCl
NaSPh
Na IO4
53 (x=n-BuO)
61 (x=2,4-Cl2C6H3O)
66 (x=PhO)
54 (x=n BuO)
62 (x=2,4-Cl2C6H3O)
67 (x=PhO)
65

Scheme 7.

73. We could only obtain the dibromolactone **70** by allylic bromination of γ-bromomethyl-α,β-butenolide **5** in heterophase, using NBS in the presence of water. Furthermore, attempted allylic oxidation of **68** by selenium dioxide gave only **4** and its spontaneously formed dimer **74**.

We next tried the preparation of ether derivatives **1** (X = OR) from γ-hydroxymethyl-α,β-butenolide **2**, and several nucleophilic substitutions on γ-bromomethyl-α,β-butenolide **5**. However, the sensitivity of both **2** and **5** towards bases, which cause elimination to **4**, limits the applicability of these reactions to cases in which neutral or acidic reaction conditions are required. Thus, treatment of **2** with diazomethane under boron trifluoride etherate catalysis gave **75**; reaction of **2** with trityl chloride in pyridine yielded **76**; and treatment of **2** with phenyl isocyanate afforded **77**.

Also attempted was the synthesis of ranunculin **3** from **2**, using the general method for the preparation of β-glucosides from alcohols.[32] Thus, reaction of acetobromoglucose **78** with **2** in the presence of silver oxide gave a mixture of tetra-*O*-acetylranunculin **79** and its 5-epimer **80** in 55% yield. Column chromatography on silica gel allowed the separation of a fraction containing **79** and **80** in a 3:1 ratio, as shown by its 200 MHz PMR spectrum. Comparison of this spectrum with that of a sample of **79** derived from natural ranunculin showed the identity of the major isomer in the synthetic mixture with the acetylated natural ranunculin, as shown in Table 1. However we were unable to isolate **79** from this mixture, and thus the synthesis of **3** could not be continued. Nevertheless, in the accompanying paper[33] a direct synthesis of **3**, accomplished in these laboratories, is described.

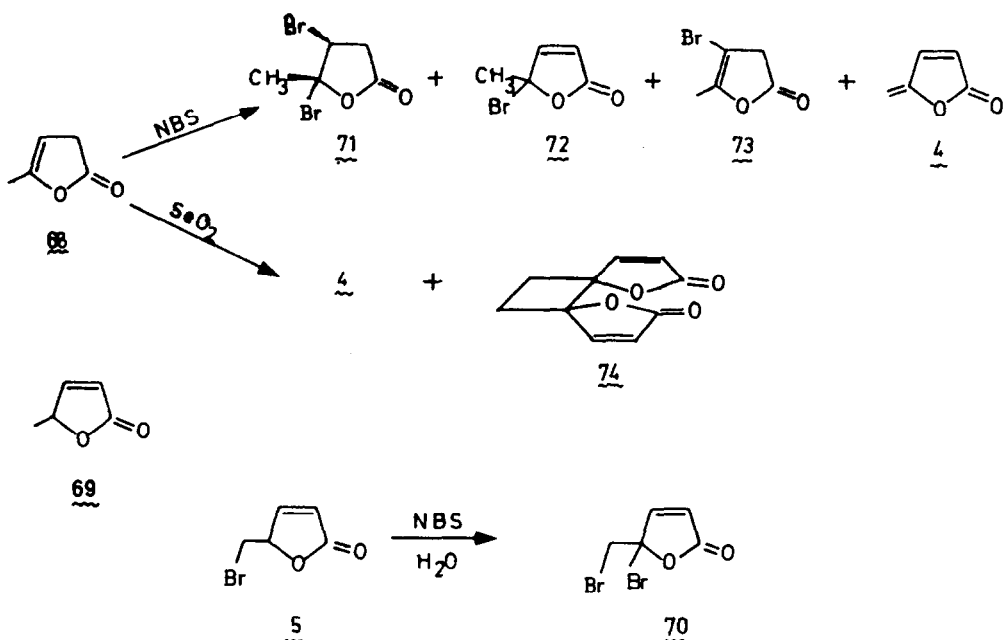
We finally explored the reactivity of γ-bromomethyl-α,β-butenolide **5** towards several nucleophiles, hoping that S_N2 substitution could give us an entry to other butenolides **1**. Thus, reaction of **5** with sodium benzenethiolate did give the expected substitution product **81**, along with some Michael addition product **82**.

Table 1. 200 MHz PMR data of the diagnostic protons **79** and **80**

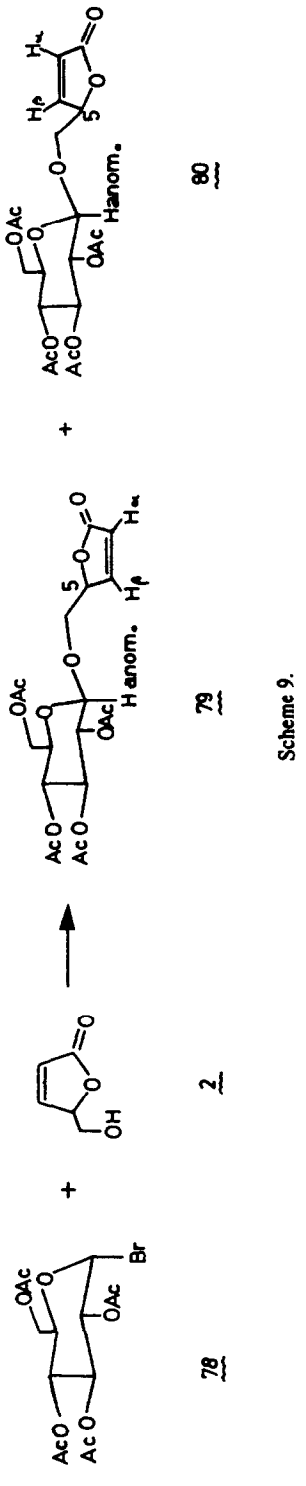
Hydrogen	Compound	δ/ppm	J/Hz
α	natural	7.47	5.8 and 1.6
α	major	7.48	5.7 and 1.6
α	minor	7.46	5.7 and 1.6
β	natural	6.20	5.7 and 2.1
β	major	6.19	5.7 and 2.1
β	minor	6.16	5.7 and 2.1
anomeric	natural	4.59	7.8
anomeric	major	4.60	7.8
anomeric	minor	4.54	7.8

However, reaction of **5** with triphenylphosphine resulted in formation of the rearranged salt **83**. This salt hydrolyzed spontaneously on standing in chloroform solution to the open-chain salt **84**. Both salts, when treated with base and 4-nitrobenzaldehyde in methanol gave open-chain condensation products, **85** from **83** and **86** from **84**. Neutral *O*-nucleophiles (i.e. ethanol) gave no reaction with **5**, while anionic *O*-nucleophiles, owing to their basicity, produced only dehydrobromination to protoanemonin **4**. On the other hand, *N*-nucleophiles were also unsuccessful. Thus, reaction of **5** with sodium azide or imidazole gave **4** even at low temperature, while the use of the more basic nucleophile piperidine resulted in the isolation of a small amount of the ring-opening product **87**.

Thus, we have observed all possible reactions of **5** with nucleophiles, i.e. substitution, Michael addition, double bond migration, dehydrobromination and ring opening. We feel that the key consideration to explain this variety of reactions is the acidity of the γ-proton of the lactone ring. The conjugate base of **1** is the aromatic anion **88**, which can either expel the leaving group X (depending on its nucleofugality) to give protoanemonin



Scheme 8.



Scheme 9.

4 or, upon reprotonation, can afford either the original α,β-butenolide 1 or the rearranged β,γ-butenolide (e.g. 83). In the latter case, attack of more nucleophile on the now more reactive carbonyl group of the enol lactone would produce not only ring opening but also enol to keto tautomerization to give ω-functionalized laevulinic acid derivatives, such as 87.

We feel that any factor enhancing the acidity of the γ proton in 1, such as reaction with a neutral nucleophile (this would place a cationic X in 1), would result in enhanced ability to isomerize the double bond. Thus, the more convenient nucleophiles should be non-basic, soft anions, while hard or basic anions result in dehydrobromination to 4. The drawback is that these soft anions can also give the Michael addition product (i.e. 82). Other butenolides 1 are being evaluated in these laboratories for their reactions with nucleophiles.

EXPERIMENTAL

M.ps were determined on a Reichert m.p. microscope and are uncorrected, UV spectra on a Perkin–Elmer mod. 550 UV-vis. spectrophotometer, IR spectra on a Perkin–Elmer mod. 720 spectrophotometer, PMR spectra at 60 MHz on a Perkin–Elmer R-12 A, at 80 MHz on a Bruker WP-80 and at 200 MHz on a Varian XL-200 spectrometers, ^{13}C NMR spectra on a Varian FT-80 or on a Bruker WP-80 spectrometers, both at 20 MHz, and mass spectra were recorded under electron impact at 70 eV on a Hewlett–Packard 5930 A spectrometer. Glc analyses were performed on Perkin–Elmer F-21 or Sigma-1 chromatographs, the silica gel used for column chromatography was Merck Art. 7734 (70–230 mesh) or Merck Art. 9385 (230–400 mesh), and for preparative tlc was Merck G seg. Stahl (60). Distillation of small amounts were effected on a rotational distillator Buchi, mod. KRV 65/30 (only external or oven temp. given), and for large scale efficient separations a spinning band distillation apparatus Perkin–Elmer, mod. 251 Auto Annular Still was used. High scale (100–750 ml) irradiations were effected using a 400 W medium pressure mercury lamp (Applied Photophysics mod. 3040) on a quartz reactor (Applied Photophysics mod. 3230) under nitrogen bubbling. Small scale irradiations were performed using the same lamp and quartz immersion well and attaching to it one or more standard UV cells containing the solution to be irradiated, through which nitrogen was bubbled. Microanalyses were performed at Consejo Superior de Investigaciones Científicas in Barcelona.

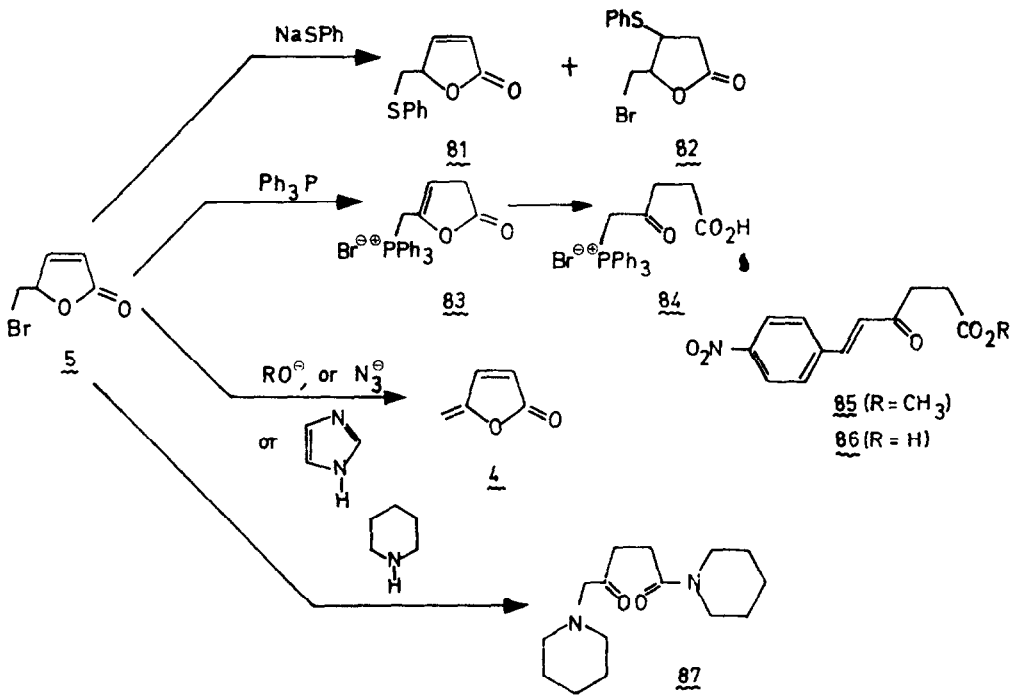
Methyl (E)-*4,5-dihydroxy-2-pentenoate* **12**

The unpublished spectra of this compound, which was obtained as previously described,[10] are as follows. 60 MHz PMR ($CDCl_3$): δ 3.6 (2H, m), 3.7 (3H, s), 4.1 (2H, br s), 4.35 (1H, m), 6.1 (1H, dd, J = 16, J' = 1) and 6.9 (1H, dd, J = 16, J' = 4.6). ^{13}C NMR ($CDCl_3$): δ 51.5q, 65.2t, 71.4d, 121.0d, 146.8d and 166.9s.

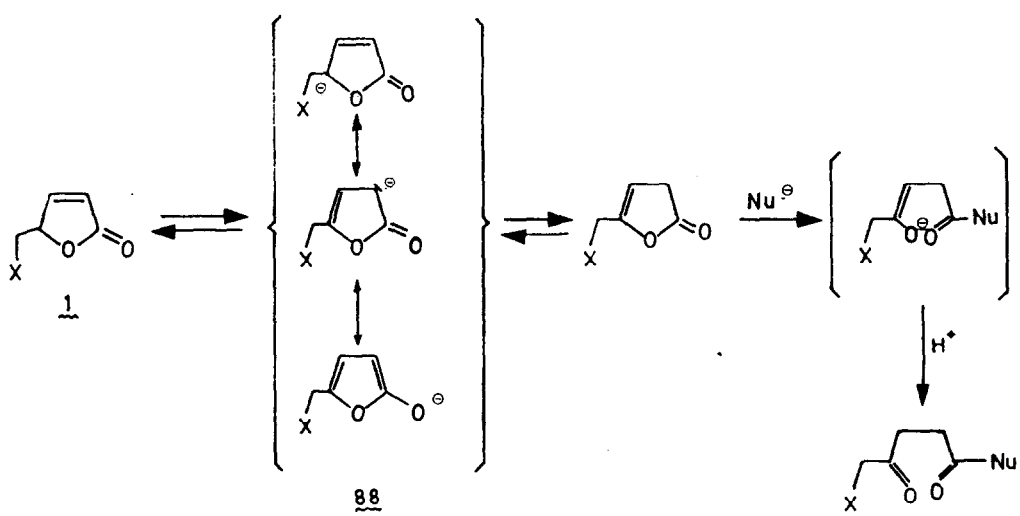
Wittig condensation of 2,2-*dimethyl*-1,3-*dioxolane*-4-*carboxaldehyde* **9** *with methoxycarbonylmethylenetriphenylphosphorane* **11**

(a) *In dichloromethane*: *Methyl* (E)-3-(2,2-*dimethyl*-1,3-*dioxolan*-4-*yl*)-2-*propenoate* **13**. The reaction of **9** and **11** in dichloromethane gave, as reported,[18] **13**. The unpublished spectra of this compound are as follows. 60 MHz PMR (CCl_4): δ 1.32 (3H, s), 1.38 (3H, s), 3.6 (3H, s), 3.5–3.6 (1H, m), 4.0 (1H, t, J = 6.5), 4.4 (1H, q, J = 6.5), 5.86 (1H, dd, J = 16, J' = 1) and 6.7 (1H, dd, J = 16, J' = 5). IR (CCl_4): $\bar{\nu}$ 3000, 2950, 2900, 1725, 1660, 1440, 1380, 1300, 1200, 1060 and 980 cm^{-1}.

(b) *In methanol*: *Methyl* (Z) - 3 - (2,2 - *dimethyl* - 1,3 - *dioxolan* - 4 - *yl*) - 2 - *propenoate* **14**. The reaction of **9** and **11** was performed as above, but in methanol as solvent and operating at room temp. Distillation gave **14** in 28% yield, b.p. < 110–115°/14 mm. 60 MHz PMR (CCl_4): δ 1.35 (3H, s), 1.4 (3H, s), 3.5 (1H, dd, J = 8.5, J' = 6.5), 3.7 (3H, s), 4.3 (1H, dd, J = 8.5, J' = 6.5), 5.4 (1H, dq, J_q = 6.5, J_d = 2), 5.65 (1H, dd, J = 11, J' = 2) and 6.4



Scheme 10.



Scheme 11.

(1H, dd, J = 11, J' = 6.5). IR (CCl_4): $\bar{\nu}$ 2950, 2880, 2820, 1730, 1660, 1440, 1380, 1320, 1260, 1200 and 1060 cm^{-1}.

5-Hydroxymethyloxol-3-en-2-one **2**

A solution of 3.46 g (23.7 mmole) of **12** and 12.5 ml of 48% HBr in 700 ml MeOH was irradiated under stirring for 1.5 h. Solid $NaHCO_3$ (5 g) was added, and after stirring for another 0.5 h the solution was filtered, the solvent was eliminated and the residue (4.12 g) was chromatographed on silica gel (60 g). Elution with $CHCl_2$:Et_2O (7:3) afforded unmodified **12** (1.10 g, 31.8% recovery) and then 1.31 g (48.5%) of **2**, bp < 140°/1 mm (lit.[10] < 130°/15 mm). UV and IR identical to Ref. 10. 60 MHz PMR identical to Ref. 9. MS: *m/e* (%) 115 (M + 1, 2), 114 (4), 97 (4), 84 (77), 83 (16) and 55 (100).

Methyl (E)-*4,5-epoxy-2-pentenoate* **16**

To a solution of 3.8 g (11.4 mmole) of **11** in 30 ml of CH_2Cl_2 was added dropwise a solution of 1.0 g (13.9 mmole) of glycidaldehyde[20] **15** in 10 ml of CH_2Cl_2 and the mixture was heated under reflux for 2 h. After standing overnight at room temp., repeated distillation of solvent and addition of ether until no more Ph_3PO precipitated gave a residue (1.514 g) which by distillation afforded **16** (1.02 g, 57.4%), b.p. <78–80°/18 mm. 60 MHz PMR ($CDCl_3$): δ 2.6 (1H, dd, J = 6, J' = 2.5), 2.9 (1H, dd, J = 6, J' = 4), 3.35 (1H, m), 3.65 (3H, s), 6.0 (1H, d, J = 16) and 6.55 (1H, dd, J = 16, J' = 6.5). IR (CCl_4): $\bar{\nu}$ 3070, 3010, 2970, 2930, 1720, 1660, 1440, 1390, 1310, 1280, 1200, 1160, 1130, 1040, 1015, 980, 925 and 840 cm^{-1}. Found: C, 56.20; H, 6.63. $C_6H_8O_3$ requires: C, 56.25; H, 6.29%.

Methyl (Z)-4,5-*epoxy*-2-*pentenoate* **17**

To a solution of 10.68 g (32 mmole) of **11** in 225 ml of MeOH cooled in an ice–salt bath was added dropwise a solution of 2.33 g (32 mmole) of **15** in 5 ml of MeOH. After stirring for 3 h, solvent removal, addition of ether and filtration of the precipitated Ph_3PO, followed by evaporation of solvent, gave a residue which upon distillation afforded a 3:2 mixture (PMR) of **17** and **16**, b.p. <78–80°/14 mm (1.87 g, 46%). Preparative tlc on silica gel, eluting with hexane:ether (2:1) allowed the isolation of 0.13 g (9%) of **16**, identical to that described above, and 0.27 g (18%) of **17**, b.p. <79°/14 mm, from 0.67 g of mixture. Spectral and analytical data for **17**. 60 MHz PMR ($CDCl_3$): δ 2.58 (1H, dd, J = 5.5, J' = 2.6), 3.02 (1H, dd, J = 5.5, J' = 4), 3.7 (3H, s), 4.45 (1H, m), 5.64 (1H, d, J = 10.2) and 5.95 (1H, dd, J = 10.2, J' = 7.3). IR (CCl_4): $\bar{\nu}$ 3070, 3010, 2970, 2930, 1720, 1645, 1440, 1420, 1340, 1300, 1200, 1140, 1110, 1005, 925 and 900 cm^{-1}. Found: C, 55.93; H, 6.47. $C_6H_8O_3$ requires: C, 56.25; H, 6.29%.

Oxidation of (Z)-4,5-*epoxy*-2-*pentenal* **18**

To a stirred suspension of active MnO_2 (5.32 g, 61.2 mmole) and NaCN (0.75 g, 15.3 mmole) in a solution of 0.30 g (3.06 mmole) of **18** (Fluka) in 25 ml of anh. MeOH was added dropwise in a solution of glacial AcOH (0.28 g, 4.59 mmole) in 5 ml of anh. MeOH and the mixture was stirred for 5 h. After filtering and solvent removal under vacuum without warming, the residue was taken up in ether, washed with water and dried. Elimination of solvent gave a residue (0.18 g) which upon distillation gave 0.040 g (10%) of **17**, b.p. <80°/16 mm, impurified by unknown substances, as shown by PMR.

Reaction of **17** *with perchloric acid in aqueous acetone*

A solution of 1.0 g (7.8 mmole) of **17**, 0.14 ml (7.8 mmole) of water and 3 drops of conc. $HClO_4$ in 20 ml of acetone was boiled under reflux for 20 h. After neutralization with satd. aqueous $NaHCO_3$ filtration and solvent removal under vacuum, the residue was taken up in $CHCl_3$, dried and the solvent was evaporated. The resulting oil was distilled yielding 0.67 g (75%) of **2**, b.p. < 120–125°/0.35 mm, identical to that described above.

Reaction of **16** *with perchloric acid in aqueous methanol: methyl* (E)-5-*hydroxy*-4-*methoxy*-2-*pentenoate* **19**

A solution of 0.5 g (3.9 mmole) of **16** and 4 drops of 60% aqueous $HClO_4$ in 10 ml of MeOH was boiled under reflux for 20 h. Working up as above gave 0.40 g (64%) of **19**, b.p. <160°/14 mm. 60 MHz PMR (CCl_4): δ 2.9 (1H, br s), 3.34 (3H, s), 3.3–3.7 (3H, m), 3.68 (3H, s), 5.95 (1H, dd, J = 15, J' = 1) and 6.75 (1H, dd, J = 15, J' = 5.5). IR (CCl_4): $\bar{\nu}$ 3620, 3000, 2950, 2875, 2825, 1740, 1680, 1440, 1400, 1360, 1310, 1280, 1200, 1060 and 980 cm^{-1}. ^{13}C NMR ($CDCl_3$): δ 51.1q, 56.9q, 63.7t, 81.0d, 122.5d, 144.4d and 165.9s. Found: C, 52.19; H, 7.82. $C_7H_{12}O_4$ requires: C, 52.49; H, 7.55%.

Reaction of **17** *with perchloric acid in aqueous methanol*

A solution of 2.43 g (19 mmole) of **17** and 5 drops of 60% aqueous $HClO_4$ in 50 ml of MeOH was boiled under reflux for 20 h. Working-up as above gave 0.15 g of fraction A, b.p. <140°/14 mm, and 0.60 g of fraction B, b.p. <160°/14 mm. Column chromatography of fraction A afforded 80 mg (3.3%) of *methyl* (E)-*acetylacrylate* **22** (identical with an authentic sample prepared according to Ref. 35) and 40 mg (1.3%) of *methyl* 2-*methoxy*-4-*oxopentanoate* **23**, 60 MHz PMR (CCl_4): δ 2.1 (3H, s), 2.65 (2H, d, J = 6.5), 3.3 (3H, s), 3.65 (3H, s), 4.0 (1H, t, J = 6.5). Column chromatography of fraction B (CH_2Cl_2–Et_2O) gave:

trans-4,5-*dimethoxyoxan*-2-*one* **21** (330 mg, 11%), b.p. <155–160°/14 mm. 60 MHz PMR ($CDCl_3$: δ 2.75 (2H, dd, J = 4, J' = 2.5), 3.40 (3H, s), 3.44 (3H, s), 3.6–3.9 (2H, m) and 4.45 (2H, d, J = 2.5); IR (CCl_4): $\bar{\nu}$ 3025, 2950, 2925, 2850, 1740, 1460, 1410, 1370, 1320, 1260, 1220, 1160 and 1110 cm^{-1}. Found: C, 52.63; H, 7.77. $C_7H_{12}O_4$ requires: C, 52.49; H, 7.55%.

Also isolated from this chromatography were cis-4,5-*dimethoxyoxan*-2-*one* **20** (10 mg, 0.3%), the unsaturated ester **19** (117 mg, 4%), identical to that described above, and the butenolide **2** (30 mg, 1%), also identical to that described above.

Methyl 4,5-*epoxy*-3-*methoxypentanoate* **25**

To a stirred solution of 160 mg (6.9 meq.) of sodium in 6 ml of MeOH was added dropwise a solution of 1.06 g (8.3 mmole) of a mixture of diastereomeric epoxyesters **16** and **17** in 1 ml of MeOH. After stirring under reflux for 4 h and allowing to stand overnight at room temp., the mixture was neutralized by addition of 3 drops of glacial AcOH. Solvent removal and vacuum distillation gave a fraction, b.p. 80–85°/14 mm (600 mg), which by column chromatography on silica gel, eluting with CH_2Cl_2–Et_2O (24:1), afforded 64 mg (6%) of the *E* epoxyester **16**, and 478 mg (36%) of **25**, b.p. <90–95°/14 mm, as a mixture of *erythro* and *threo* diastereomers. IR (CCl_4): $\bar{\nu}$ 3060, 3000, 2950, 2850, 1730, 1440, 1410, 1360, 1250, 1200, 1170, 1120, 1020, 1000, 920 and 880 cm^{-1}. Found: C, 52.15; H, 7.60. $C_7H_{12}O_4$ requires: C, 52.49; H, 7.55%.

Column chromatography on silica gel, eluting with CH_2Cl_2–Et_2O (47:3), allowed the separation of both diastereomers of **25** from the above mixture. The 60 MHz PMR (CCl_4) of these isomers, from which no configurational assignment was possible, are as follows:

Diastereomer A: δ 2.4–2.9 (6H, m), 3.32 (3H, s) and 3.6 (3H, s).

Diastereomer B: δ 2.4–3.3 (6H, m), 3.38 (3H, s) and 3.6 (3H, s).

Methyl 3-*methoxy*-4-*pentenoate* **26**

A mixture of 1.0 g (6.25 mmole) of **25**, 1.637 g (6.25 mmole) of dry Ph_3P and 60 mg of hydroquinone was melted by heating at 90–100° for 10 min. Distillation afforded a fraction, b.p. <160–190°/1 atm, which by column chromatography on silica gel, eluting with CH_2Cl_2–Et_2O (4:1), gave 202 mg (22.5%) of **26**. 60 MHz PMR ($CDCl_3$): δ 2.55 (2H, dd, J = 6.5, J' = 2), 3.3 (3H, s), 3.7 (3H, s), 4.05 (1H, q, J = 6.5) and 5.0–5.7 (3H, m).

Reaction of **25** *with perchloric acid in methanol*

A solution of 2.73 g (17 mmole) of **25** and 4 drops of $HClO_4$ in 48 ml of MeOH was boiled under reflux for 20 h. Neutralization by addition of $NaHCO_3$, filtration and solvent removal gave 1.3 g of crude reaction mixture, which was chromatographed on silica gel, eluting with CH_2Cl_2–Et_2O. The fractions eluted were:

(a) trans-4-*methoxy*-5-*methoxymethyloxolan*-2-*one* **27b**, 300 mg (11%), slightly impurified by **23**, which could not be completely purified by a second column chromatography. 60 MHz PMR (CCl_4): δ 2.32 (1H, dd, J = 16, J' = 6.5), 3.31 (3H, s), 3.38 (3H, s), 3.55 (2H, d, J = 3.5), 4.0 (1H, m) and 4.42 (1H, m). IR (CCl_4): $\bar{\nu}$ 3000, 2950, 2900, 2850, 1790, 1740, 1460, 1400, 1360, 1200, 1160, 1120, 1100, 1040, 1020, 950 and 900 cm^{-1}. GC/MS: *m/e* (%) 160 (M, 2), 145 (8), 132 (71), 131 (12), 117 (6), 115 (19), 101 (24), 100 (29), 87 (12), 85 (19), 84 (8), 83 (27), 75 (12), 73 (55), 72 (31), 71 (72), 59 (42), 58 (100), 55 (14), 45 (63) and 43 (27).

(b) cis-4-*methoxy*-5-*methoxymethyloxolan*-2-*one* **28b**, 240 mg (8.8%), b.p. <170°/14 mm. 60 MHz PMR (CCl_4): δ 2.55 (2H, d, J = 4.5), 3.34 (3H, s), 3.38 (3H, s), 3.6 (2H, m), 4.08 (1H, m) and 4.48 (1H, m). IR (CCl_4): $\bar{\nu}$ 3000, 2950, 2900, 2850, 1790, 1740, 1460, 1410, 1360, 1300, 1130, 1070, 1020, 960 and 940 cm^{-1}. Found: C, 52.57; H, 7.80. $C_7H_{12}O_4$ requires: C, 52.49; H, 7.55%.

(c) 123 mg (4.5%) of ester **19**, identical to that described above.

(d) trans-4-*methoxy*-5-*hydroxymethyloxolan*-2-*one* **27a**, 174 mg (7%), b.p. <140°/0.5 mm. 60 MHz PMR ($CDCl_3$): δ 2.75 (2H, m), 3.0 (1H, br s), 3.38 (3H, s), 3.75 (2H, m), 4.1 (1H, m) and 4.5 (1H, m). IR ($CHCl_3$): $\bar{\nu}$ 3600 (broad), 2975, 2875, 1790, 1600, 1460, 1360, 1170, 1120, 1080 and 940 cm^{-1}. Found: C, 49.63; H, 7.28. $C_6H_{10}O_4$ requires: C, 49.31; H, 6.90%.

(e) cis-5-*hydroxymethyl*-4-*methoxyoxolan*-2-*one* **28a**, 250 mg (10%), slightly impurified by butenolide **2**. Purification was completed by preparative tlc on silica gel plates. 60 MHz PMR ($CDCl_3$): δ 2.75 (2H, d, J = 4.5), 3.30 (1H, br s), 3.38 (3H, s), 3.95 (2H, d, J = 4.5), 4.28 (1H, m) and 4.65 (1H, m). IR ($CHCl_3$): $\bar{\nu}$ 3600 (broad), 2975, 2875, 1790, 1600, 1460, 1370, 1170, 1100, 1020 and 900 cm^{-1}. GC/MS: *m/e* (%) 118 (M-28, 9), 117 (5), 115 (28), 103 (12), 85 (14), 84 (56), 83 (17), 73 (26), 71 (54), 59 (38), 58 (100), 55 (26), 45 (53), 43 (74), 31 (32) and 29 (33).

Photolactonization of **16**

A solution of 100 mg (0.78 mmole) of **16**, 1 ml of acetone and 3

drops of conc. HCl in 3 ml of water was irradiated for 4 h. After solvent removal, the residue was taken up in 10 ml of $CHCl_3$, dried and evaporated. Column chromatography of the residue (110 mg) on 7.0 g of silica gel, eluting with $CHCl_3$–Et_2O (7:3) afforded 21 mg (18%) of ester **12**, and 24 mg (27%) of butenolide **2**, both identical to the compounds described above.

Methyl (E)-2-,4-*pentadienoate* **30**

To a stirred solution of 11.52 g (34.4 mmole) of **11** in 50 ml of CH_2Cl_2 containing a trace of benzoic acid was added dropwise over 1 h a solution of 6.0 g (107 mmole) of freshly distilled acrolein in 10 ml of CH_2Cl_2. After boiling the mixture under reflux for 24 h the solvent was boiled off through a 30 cm Vigreux column, pentane was added to the residue and the precipitate of Ph_3PO was filtered off. Distillation of solvent (Vigreux column) gave a residue (2.83 g) which was distilled evaporatively, with cooling of the receiving balls at −30°, to yield 930 mg (24%) of **30**, b.p. <70°/14 mm. 60 MHz PMR ($CDCl_3$): δ 3.65 (3H, s), 5.3–5.7 (2H, m), 5.8 (1H, d, J = 16), 6.1–6.8 (1H, m) and 7.2 (1H, dd, J = 16, J′ = 9.7). IR (CCl_4): $\tilde{\nu}$ 3025, 2975, 1720, 1640, 1600, 1440, 1320, 1275, 1200, 1140, 1020, 1010, 920 and 890 cm^{-1}. UV (EtOH): λ 247 nm (log ε 4.2). MS: *m/e* (%) 113 (M + 1, 23), 112 (69), 111 (18), 97 (15), 81 (42), 68 (14), 53 (38), 45 (100).

Wittig condensation of acrolein and **11** *in methanol*

To a stirred solution of 356 g (1.06 mole) of **11** in 3.5 l. of MeOH was added dropwise over 3 h. 176 g (3.14 mole) of freshly distilled acrolein. After stirring at room temp. for 14 h and at 45° for 8 h, the mixture was poured on 1.2 l. of water. Continuous extraction with 1.5 l. of pentane, followed by concentration to 100 ml, filtration of the precipitated Ph_3PO and finally distillation of the residue (condenser cooled at −20°, receiver flasks at −40°) gave a forerun (3.0 g), then 26.64 g (22%) of a mixture of **30** and **31**, b.p. 46–65°/16 mm, and finally 14.85 g (10%) of a mixture of *methyl* (*E*)- (**33**) and (*Z*)- (**34**) *5-methoxy-2-pentenoates*, b.p. 80–86°/16 mm, tentatively identified from the 60 MHz PMR spectrum of the mixture, as well as from its MS. Spinning band distillation of the fraction having b.p. 46–65°/16 mm gave 383 mg (0.14%) of *3-methoxypropanal* **32**, b.p. 62–70°, 60 MHz PMR ($CDCl_3$): δ 2.7 (2H, dt, J_t = 6, J_d = 2), 3.35 (3H, s), 3.7 (2H, t, J = 6) and 9.8 (1H, t, J = 2). In addition, the *E* ester was isolated later, and in an intermediate fraction, 3.28 g (2.7%) of *methyl* (Z)-2,4-*pentadienoate* **31**, b.p. 82–82.5°/99 mm. 60 MHz PMR ($CDCl_3$): δ 3.55 (3H, s), 5.3–5.8 (3H, m), 6.45 (1H, t, J = 11.3) and 7.2–7.9 (1H, m).

Epoxidation of **30** *and of* **31**

To a stirred solution of 300 mg (2.68 mmole) of **30** in 15 ml of $CHCl_3$ was added dropwise over 75 min a solution of *m*-chloroperbenzoic acid (*m*-CPBA) (544 mg, 85% purity, 2.68 mmole) in 15 ml of $CHCl_3$, and the mixture was boiled under reflux for 3 h and stirred at room temp. for 24 h. After concentration and filtration of the precipitated *m*-chlorobenzoic acid, the filtrate was washed with 20% aq. $NaHSO_3$, 10% aq. $NaHCO_3$ and brine. Drying, solvent removal and distillation afforded 216 mg (63%) of **16**, b.p. <75–76°/14 mm, identical to that described above.

The same reaction performed on **31** on the same scale gave resinous products. When performed at room temp. for 8 days, solvent evaporation yielded a crude mixture which showed in its PMR spectrum some of the absorptions of **2**, together with many others. No defined products could be isolated after work-up.

(E)-2,4-*pentadienoic acid* **42**

This easily polymerizable compound was prepared according to known procedures and showed m.p. 66–68° (lit.: 72°[36] or 80°[25]). It should be kept in a refrigerator for no more than one month after its preparation. The unpublished spectra of this compound are as follows: 60 MHz PMR ($CDCl_3$): δ 5.3–5.7 (2H, m), 5.9 (1H, d, J = 16), 6.2–6.9 (1H, m), 7.4 (1H, dd, J = 16, J′ = 9.3) and 11.4 (1H, s). UV (H_2O/$NaHCO_3$): λ 243 nm (log ε 4.3). MS: *m/e* (%) 98 (M, 76), 97 (50), 81 (22), 80 (10), 70 (43), 69 (26), 54 (100), 53 (39).

Reaction of sodium (E)-2,4-*pentadienoate* **35** *with aqueous iodine and potassium iodide*: (E)-*4-hydroxy-5-iodo-2-pentenoic acid* **36**

Following strictly the procedure described by Staninets *et al.*[24] for the preparation of iodomethyl-α,β-butenolide **1** (X = I), to a solution of 0.86 g (10 mmole) of $NaHCO_3$ and 1.0 g (10.2 mmole) of **42** in 15 ml of water was added a solution of 2.6 g (10.2 mmole) of iodine in 30 ml of water containing enough KI to keep the I_2 dissolved, and the stoppered mixture was heated at 50° for 15 days. After cooling, remaining acid **24** (326 mg, 33% recovery) was extracted with CH_2Cl_2 and continuous extraction with Et_2O of the aqueous layer gave 444 mg (18%) of crude **36**, which was partially purified by column chromatography on 10 g of silica gel, eluting with Et_2O, yielding finally 286 mg (11.6%) of solid **36**, m.p. 69–71°. 60 MHz PMR (CD_3COCD_3): δ 3.4 (2H, d, J = 6), 4.45 (1H, m), 6.1 (1H, dd, J = 15, J′ = 1.5), 7.0 (1H, dd, J = 15, J′ = 5) and 7.3 (2H, s). MS: *m/e* (%) 242 ($I^{\cdot}$, 1), 225 (2), 189 (7), 169 (4), 142 (12), 141 (8), 128 (20), 127 (30), 115 (23), 101 (48), 98 (13), 97 (100), 83 (12), 73 (51), 69 (40), 68 (17), 55 (54), 53 (26), 51 (15), 50 (14).

Methyl (E)-*5-bromo-4-hydroxy-2-pentenoate* **37**

A mixture of 3.0 g (26.8 mmole) of **30**, 4.76 g (26.7 mmole) of NBS and 50 ml water was stirred gently at room temp. for 1 h. Extraction with CH_2Cl_2, drying, solvent removal and column chromatography of the residue (5.57 g) on 30 g of silica gel, eluting with C_6H_6:Et_2O (9:1) gave 3.78 g (68%) of 37.80 MHz PMR ($CDCl_3$): δ 2.75 (1H, br s), 3.43 (1H, dd, J = 10, J′ = 6.6), 3.62 (1H, dd, J = 10, J′ = 4.6), 3.75 (3H, s), 4.56 (1H, m), 6.17 (1H, dd, J = 16, J′ = 1.5) and 6.93 (1H, dd, J = 16, J′ = 4.6). ^{13}C NMR ($CDCl_3$): δ 36.9t, 51.7q, 70.1d, 122.5d, 145.8d and 166.7s. IR (film): $\tilde{\nu}$ 3450 (broad), 1710 and 1650 cm^{-1}. UV (EtOH): λ 211 nm (log ε 4.5). MS: *m/e* (%) 209–211 (M + 1, 1), 191–193 (1), 177–179 (13), 176–178 (7), 149–151 (5), 129 (7), 121–123 (17), 115 (100), 113 (25), 97 (20), 93–95 (10), 87 (70), 86 (10), 83 (17) and lower *m/e*. Found: C, 34.36; H, 4.30; Br, 38.56. $C_6H_9BrO_3$ requires: C, 34.48; H, 4.34; Br, 38.23%.

Methyl (E)-*5-bromo-4-methoxy-2-pentenoate* **38**

To a stirred solution of 256 mg (2.4 mmole) of **30** in 10 ml of anh. MeOH was added 350 mg (2.35 mmole) of NBS. After stirring for 1 h at room temp., solvent removal and column chromatography of the residue (205 mg) on 2.0 g of silica gel, eluting with C_6H_6–Et_2O (98:2), afforded 120 mg (23%) of **38**. 80 MHz PMR ($CDCl_3$): δ 3.4 (3H, s), 3.4 (2H, d, J = 6), 3.78 (3H, s), 4.03 (1H, dq, J_q = 6, J_d = 1.5), 6.12 (1H, dd, J = 16, J′ = 1.5) and 6.84 (1H, dd, J = 16, J′ = 6). ^{13}C NMR ($CDCl_3$): δ 32.8, 51.6, 57.5, 79.7, 124.0, 144.4 and 166.6. IR (film): $\tilde{\nu}$ 1720 and 1660 cm^{-1}. UV (EtOH): λ 240 nm (log ε 3.2). MS: *m/e* (%) 221–223 (M − 1, 1), 191–193 (6), 163–165 (6), 159–161 (4), 143 (6), 129 (100), 112 (7), 111 (4), 101 (29), 97 (9), 93–95 (3) and lower *m/e*. Found: Br, 36.02. $C_7H_{11}BrO_3$ requires: Br, 35.83%.

Reaction of **30** *with NBS in DME–water*

A mixture of 290 mg (2.26 mmole) of **30**, 2.5 ml of DME, 0.5 ml of water and 402 mg (2.26 mmole) of NBS was stirred at room temp. for 4 h. Water (7 ml) was then added, and extraction with CH_2Cl_2, drying and solvent removal gave a residue (350 mg) which was chromatographed on 5.0 g of silica gel, eluting with C_6H_6–Et_2O (10:1) to yield 61 mg (12%) of **38** and 62 mg (13%) of **37**, both identical to those described above.

Reaction of **31** *with NBS and water in heterophase*

Reaction in heterophase of the *Z* ester **31** (200 mg, 1.5 mmole) with NBS and water as described above for **30**, followed by chromatography on silica gel, afforded 11% of *5-bromomethyl-oxol-3-en-2-one* **5**, identical to that described below, and 13% of the *E* bromohydrin **37**, identical to that described above.

Reaction of **31** *with NBS in methanol: methyl* (Z)-*5-bromo-4-methoxy-2-pentenoate* **41**

Following the procedure described above for the preparation of **38** from **30**, 100 mg (0.9 mmole) of the *Z* ester **31** gave, after chromatography on silica gel, 43 mg (24%) of **41**, slightly impurified by its *E* isomer **38**. Data given for **41**. 80 MHz PMR

($CDCl_3$): δ 3.32 (3H, s), 3.47 (2H, d, J = 5), 3.68 (3H, s), 5.00 (1H, m), 5.8–6.2 (2H, m). IR (film): $\bar{\nu}$ 2950, 1720, 1650, 1600, 1530, 1420, 1400, 1210, 1110, 1040, 980 and 820 cm^{-1}. MS: *m/e* (%) 191–193 (M − 31, 5), 159–161 (7), 143 (69), 131–133 (8), 129 (100), 127 (22), 112 (15), 111 (83), 101 (64), 97 (9), 93–95 (14) and lower *m/e*. Found: Br, 35.37. $C_7H_{11}BrO_3$ requires: Br, 35.83%.

Bromohydroxylation of **42** *in aqueous sodium bicarbonate by bromine* (1.2 *eq.*): (E)-*5-bromo-4-hydroxy-2-pentenoic acid* **43**

To a solution of 30.0 g (306 mmole) of **42** in 1.0 l. of excess aqueous $NaHCO_3$ was added dropwise over 2 h at room temp. 16.8 ml (58.2 g, 363 mmole) of Br_2 under stirring. Acidification to pH 2 with 40% H_2SO_4 and extraction with CH_2Cl_2 followed by solvent removal yielded 27.0 g of extractable by-products and starting acid **42**, identified as described later, and devoid of the water-soluble product **43**. Repeated extractions of the remaining aqueous phase with Et_2O, drying and solvent removal gave 37.7 g (63.2%) of **43** as a colourless oil from which crystals deposited on standing. After drying on a tile they showed m.p. 86–87° (lit.[37] 92–93°). The unpublished spectra of this compound are: 60 MHz PMR ($CDCl_3 + CD_3COCD_3$): δ 3.5 (2H, d, J = 6), 4.6 (1H, m), 6.15 (1H, dd, J = 16, J' = 1.5), 7.0 (1H, dd, J = 16, J' = 5), 7.3 (2H, s). IR (KBr): $\bar{\nu}$ 3500–2500 (broad), 1690 and 1660 cm^{-1}. MS: *m/e* (%) 194–196 (M, 1), 177–179 (3), 176–178 (4), 149–151 (20), 101 (78), 97 (9), 93–95 (25), 83 (24), 73 (73), 69 (24), 55 (100) and 45 (49). UV (aq. $NaHCO_3$): λ 225 nm (log ε 3.6).

The other products formed in this reaction were isolated from or identified in the CH_2Cl_2 extract mentioned above. Rapid chromatography technique[40] of 590 mg of this extract on 50 g of silica gel (230–400 mesh), eluting with hexane–EtOAc, gave 27 mg of liquid (E)-*4-bromo-2-butenal* **45** (2.7%), identified by its PMR spectrum (see Ref. 38), and 100 mg (15% recovery) of unaltered **42**. The PMR spectrum of intermediate fractions showed them to contain in addition (E)-*4,5-dibromo-2-pentenoic acid* **44**, identical to that described below. Integration of the PMR diagnostic signals of these three compounds showed them to be present in the original CH_2Cl_2 extract in proportions corresponding to the following conversions from **42**: 10%, (**45**), 13% (**42**) and 10% (**44**).

5-Bromomethyloxol-3-en-2-one **5**

(a) *By photolactonization of* **37**. A solution of 400 mg (1.8 mmole) of **37** in 20 ml of MeOH containing 8 drops of conc. methanolic HCl was irradiated for 2 h and 15 min. Elimination of MeOH to dryness, addition of $CHCl_3$, washing with 10% aq. $NaHCO_3$, drying and solvent removal was followed by column chromatography of the residue (333 mg) on 6.0 g of silica gel, eluting with C_6H_6–EtOAc (19:1), which gave 138 mg (41%) of **5** as a colourless liquid, partly decomposed upon attempted distillation.

(b) *By photolactonization of* **43**. A solution of 24.0 g (123 mmole) of **43** in 700 ml of water containing 12 ml of conc. HCl was irradiated for 2 h, and then was extracted with 3 × 50 ml of CH_2Cl_2, which does not extract the water-soluble starting material **43**. After subjecting the aqueous layer to 3 more irradiation-extraction cycles, the combined organic extracts were washed (aq. $NaHCO_3$), dried and evaporated, yielding 16.2 g (74.4%) of **5**, identical to that described above.

80 MHz PMR ($CDCl_3$): δ 3.56 (1H, dd_{AB}, J = 11.8, J' = 6), 3.76 (1H, dd_{AB}, J = 11.8, J' = 5), 5.34 (1H, m), 6.31 (1H, dd, J = 5.5, J' = 1.5) and 7.59 (1H, dd, J = 5.5, J' = 2). ^{13}C NMR ($CDCl_3$): δ 30.2, 80.4, 123.2, 154.0 and 171.9. IR (film): $\bar{\nu}$ 1760 and 1600 cm^{-1}. UV (EtOH): λ 208 nm (log ε 4.3). MS: *m/e* (%) 176–178 (M, 10), 148–150 (6), 147–149 (60), 97 (44), 93–95 (7), 83 (64), 69 (14), 68 (13), 55 (100), 54 (9) and lower *m/e*. Found: C, 33.95; H, 3.10; Br, 44.68. $C_5H_5BrO_2$ requires: C, 33.93; H, 2.85; Br, 45.05%.

Reaction of **42** *with bromine in dioxane–water*: (E)-*4,5-dibromo-2-pentenoic acid* **44**

To a stirred solution of 2.0 g (21 mmole) of **42** in 100 ml of dioxane and 15 ml of water were added at once 3.3 g (20 mmole) of Br_2. After stirring at room temp. for 20 h, reduction to 1/3 its original volume and extraction with Et_2O, drying and solvent elimination gave 2.94 g (54%) of **44**, which was further purified by column chromatography, but did not crystallize. Distillation (b.p. <150–160°/0.5 mm) gave a low yield (20%) of still oily material. 60 MHz PMR ($CDCl_3$): δ 3.5–4.0 (2H, m), 4.75 (1H, m), 6.05 (1H, d, J = 16), 7.0 (1H, dd, J = 16, J' = 9) and 11.35 (1H, s). MS: *m/e* (%) 257–259–261 (M + 1, 0.3:0.6:0.3), 239–241–243 (0.6:1.2:0.6), 211–213–215 (1.7:2.7:1.7), 177–179 (100), 147–149 (5), 133–135 (10), 121–123 (10), 98 (49), 97 (92), 80–82 (32) and 79–81 (27), and lower *m/e*.

(E)-*4,5-Epoxy-2-pentenoic acid* **46**

To a stirred solution of 1.0 g (10.2 mmole) of **42** in 50 ml of 24% aq. NaOH was added 0.51 ml (1.6 g, 10 mmole) of Br_2. After stirring for 1 h at room temp. acidification to pH 6 was effected by addition of conc. H_2SO_4. Extraction with CH_2Cl_2, drying and solvent removal yielded 182 mg (16%) of **46** as an oil. 60 MHz PMR (CD_3COCD_3): δ 2.3 (1H, dd, J = 6, J' = 3), 2.6 (1H, dd, J = 6, J' = 5), 3.1 (1H, m), 5.7 (1H, d, J = 16), 6.2 (1H, dd, J = 16, J' = 6) and 8.0 (broad, 1H). IR (film): $\bar{\nu}$ 3500–2800 (broad), 1700, 1660, 1420, 1260, 1200, 1160, 980, 920 and 840 cm^{-1}.

Reaction of **42** *with bromine* (2 *equiv.*) *in aqueous sodium bicarbonate: isolation of 3-bromo-5-bromomethyloxol-3-en-2-one* **47**

To a stirred solution of 2.0 g (20.4 mmole) of **42** and 16 g (208 mmole) of $NaHCO_3$ in 100 ml of water was added 6.4 g (40 mmole) of Br_2 over 1 h and the mixture was stirred for one further hour at room temp. Then addition of 16 N H_2SO_4 (to pH 2), filtration of the yellow precipitate, concentration of the filtrate to 1/3 its volume and extraction of both the aqueous phase and the yellow solid with Et_2O, followed by drying and solvent removal of the combined Et_2O extracts gave 2.4 g of an oil. A solution of 1.7 g of this oil and 20 mg of TsOH in 300 ml of C_6H_6 was boiled under reflux for 6 h. After cooling overnight and filtering the precipitated TsOH, evaporation of the filtrate gave 1.6 g of oil. Chromatography of 600 mg of this oil on 30 g of silica gel, eluting with hexane–EtOAc gave 118 mg (8.5%) of **47** as an oil. 60 MHz PMR ($CDCl_3$): δ 3.5–4.0 (2H, AB part of ABX system, $J_{AB} = -12$, $J_{AX} = 6.5$, $J_{BX} = 5.3$), 5.2 (1H, m, X part of ABX system) and 7.6 (1H, d, J = 2). IR (film): $\bar{\nu}$ 1780 cm^{-1}. MS: *m/e* (%) 254–256–258 (M, 15:30:15), 226–228–230 (5:10:5), 225–227–229 (7:17:9), 212–214–216 (9:18:9), 175–177 (42), 161–163 (54), 133–135 (50), 105–107 (58), 93–95 (45), 92–94 (15), 91 (58), 79 (58), 53 (100), 51 (100), 50 (91), 43 (50), 42 (50) and 39 (83). UV (EtOH): λ 239 nm (log ε 3.3). Found: C, 23.40; H, 1.59; Br, 62.37. $C_5H_4Br_2O_2$ requires: C, 23.47; H, 1.57; Br, 62.45%.

Also isolated from this chromatography was a solid, m.p. 149–151°, identified as *c-4-bromo-c-5-bromomethyl-r-3-hydroxy-oxolan-2-one*. The identification of this compound will be given elsewhere.[26]

Methyl 5-butoxymethyl-2-oxooxolane-3-carboxylate **50**

To a boiling solution of sodium methoxide (166 mmole) in MeOH (90 ml), dimethyl malonate **48** (21.93 g, 166 mmole) was added dropwise, followed after 0.5 h by butoxymethyloxirane **49** (21.58 g, 166 mmole), and the mixture was boiled under reflux for 18 h. After cooling to room temp., neutralization with AcOH (9.4 ml, 166 mmole), filtration and solvent removal, water was added and the residue was extracted with $CHCl_3$. The organic layer was separated, dried and distilled, affording 19.46 g (51.2%) of **50**, b.p. 122–123°/0.2 mm. 60 MHz PMR ($CDCl_3$): δ 0.97 (3H, m), 1.49 (4H, m), 2.55 (2H, m), 3.48 (5H, m), 3.73 (3H, s) and 4.67 (1H, m). IR (CCl_4): $\bar{\nu}$ 3000, 2950, 2900, 1790, 1750, 1460, 1440, 1350, 1280, 1160, 1150 and 1130 cm^{-1}. MS: *m/e* (%) 230 (M, 0.5), 199 (0.8), 171 (0.6), 157 (4), 143 (16), 111 (21), 87 (35), 57 (100), 56 (10), 55 (35), 43 (18), 41 (53), 29 (63), 27 (41) and 15 (35). Found: C, 57.24; H, 7.73. $C_{11}H_{18}O_5$ requires: C, 57.37; H, 7.89%.

Methyl 5-butoxymethyl-3-chloro-2-oxooxolane-3-carboxylate **51**

Sulfuryl chloride (17 ml, 210 mmole) was added dropwise on **50** (33.64 g, 146 mmole) at 0° under stirring, and the mixture was then boiled under reflux for 5 h. Removal of excess SO_2Cl_2 under vacuum gave 38.62 g (100%) of **51**. 60 MHz PMR ($CDCl_3$): δ 0.97 (3H, m), 1.50 (4H, m), 2.82 (2H, m), 3.58 (4H, m), 3.90 (3H, s) and 4.80 (1H, m). IR ($CHCl_3$): $\bar{\nu}$ 3000, 2975, 2900, 1800, 1770, 1740, 1440, 1420, 1350, 1250, 1180 and 1130 cm^{-1}. MS: *m/e* (%) 265–267

(M+1, 1.4:0.5), 229 (3), 191–193 (9:3), 177 (33), 143 (30), 113 (20), 111 (15), 89 (11), 87 (37), 85 (20), 59 (22), 57 (100), 56 (20), 55 (14), 43 (20), 41 (50), 39 (19) and 29 (35). Found: C, 50.34; H, 6.75; Cl, 14.73. $C_{11}H_{17}ClO_5$ requires: C, 49.90; H, 6.49; Cl, 13.39%.

5-Butoxymethyl-3-chlorooxolan-2-one **52**

A solution of **51** (38.62 g, 146 mmole) and conc. HCl (73 ml) in glacial AcOH (146 ml) was boiled under reflux for 4 h. Solvent removal under vacuum, helped by addition of some benzene in late stages, and distillation of the residue gave 29.30 g (97.3%) of **52**, b.p. 117–120°/0.3 mm. 60 MHz PMR ($CDCl_3$): δ 1.00 (3H, m), 1.52 (4H, m), 2.62 (2H, m), 3.62 (4H, m) and 4.75 (2H, m). IR ($CHCl_3$) $\bar{\nu}$ 3000, 2950, 2900, 1790, 1430, 1340, 1160, 1120 and 940 cm^{-1}. MS: *m/e* (%) 207–209 (M+1, 1.6:0.6), 206–208 (1.1:0.6), 163–165 (1.4:0.5), 133–135 (7:3), 120–122 (13:5), 119–121 (5:3), 100 (13), 87 (47), 85 (19), 63 (10), 57 (100), 55 (18), 43 (24), 41 (49), 39 (19) and 29 (27). Found: C, 52.26; H, 7.40; Cl, 17.32. $C_9H_{15}ClO_3$ requires: C, 52.30; H, 7.33; Cl, 17.15%.

5-Butoxymethyl-3-phenylthiooxolan-2-one **53**

Under anhydrous conditions and in a N_2 atmosphere, sodium (0.63 g, 27 mmole) was reacted with abs. EtOH (35 ml). Then 3.00 g (2.8 ml, 27 mmole) of benzenethiol in 10 ml EtOH was added dropwise, and the stirred mixture was boiled under reflux for 45 min. After cooling to room temp., a solution of 5.00 g (24 mmole) of **52** in 15 ml of abs. EtOH was added dropwise, and the mixture was boiled under reflux for 17 h. Filtration and washing the precipitate with $CHCl_3$ was followed by evaporation of the combined filtrate and washings. The residue was poured on water and extracted with $CHCl_3$, the organic phase was dried, filtered and after solvent removal the residue was chromatographed on silica gel, giving diphenyl disulfide (hexane) and **53** (CH_2Cl_2), yield of distilled product 5.62 g (83%), b.p. 200–206°/0.8 mm. 60 MHz PMR ($CDCl_3$): δ 0.95 (3H, m), 1.45 (4H, m), 2.42 (2H, m), 3.43 (4H, m), 3.90 (1H, t, J = 9.3), 4.50 (1H, m) and 7.40 (5H, m). IR (film): $\bar{\nu}$ 3000, 2975, 2900, 1780, 1590, 1480, 1440, 1380, 1350, 1170, 1130, 960, 940, 740 and 690 cm^{-1}. MS: *m/e* (%) 280 (M, 3), 113 (17), 110 (10), 109 (15), 71 (10), 69 (13), 65 (11), 57 (100), 55 (21), 45 (10), 43 (18), 41 (31) and 39 (11). Found: C, 64.27; H, 7.37; S, 11.18. $C_{15}H_{20}O_3S$ requires: C, 64.24; H, 7.20; S, 11.43%.

5-Butoxymethyloxol-3-en-2-one **55**

A solution of 5.90 g (28 mmole) of $NaIO_4$ in 80 ml of water kept at 0° was added at 0° to a solution of 6.68 g (24 mmole) of **53** in 175 ml of MeOH at 0° under stirring. After 0.5 h at 0°, the mixture was stirred for 19 h at room temp. After filtering and washing with MeOH, the filtrate was evaporated and the residue was poured on water and extracted with $CHCl_3$. The organic phase was dried, filtered and after solvent removal afforded 6.54 g (91.7%) of crude 5-butoxymethyl-3-phenylsulfinyloxolan-2-one **54**. 60 MHz PMR ($CDCl_3$): δ 0.97 (3H, m), 1.50 (4H, m), 2.52 (2H, m), 3.72 (5H, m), 4.72 (1H, m) and 7.64 (5H, broad s). IR (film): $\bar{\nu}$ 2975, 2950, 2900, 1760, 1470, 1440, 1340, 1180, 1120, 1080, 1040, 950, 740 and 680 cm^{-1}.

Without further purification, a solution of this crude sulfoxide **54**, (6.54 g, 22 mmole) in 75 ml of toluene was boiled under reflux for 5 h. Vacuum removal of solvent and addition of Et_2O, washing the organic with saturated aq. $NaHCO_3$, drying and solvent removal gave a residue which upon distillation and chromatography of the fraction having b.p. 104–106°/0.4 mm on silica gel afforded diphenyl disulfide (hexane–CH_2Cl_2, 20:1) and then the butenolide **55**, which was redistilled, b.p. <130–136°/0.7–0.8 mm (3.41 g, 91% yield). 60 MHz PMR (CCl_4): δ 0.98 (3H, m), 1.48 (4H, m), 3.55 (4H, m), 5.10 (1H, m), 6.10 (1H, dd, J = 6, J' = 2) and 7.60 (1H, dd, J = 6, J' = 1.3). IR (film): $\bar{\nu}$ 3000, 2975, 2900, 1760, 1470, 1380, 1340, 1160, 1130, 960, 920, 890, 860 and 820 cm^{-1}. MS: *m/e* (%) 171 (M+1, 0.5), 97 (3), 87 (19), 84 (33), 57 (93), 55 (19), 43 (16), 42 (10), 41 (100), 39 (31), 29 (90) and 27 (44). Found: C, 63.34; H, 8.61. $C_9H_{14}O_3$ requires: C, 63.50; H, 8.31%.

Methyl 5-phenoxymethyl-2-oxooxolane-3-carboxylate **57**

This product, b.p. 190°/0.9 mm, was obtained in 50% yield from 21 mmole of 3-phenoxy-1,2-epoxypropane **56** and the stoicheiometric amount of $NaCH(COOMe)_2$, operating as described above for **50**. 60 MHz PMR (CCl_4): δ 2.59 (2H, m), 3.67 (1H, broad s), 3.75 (3H, s), 4.09 (2H, m), 4.79 (1H, m) and 7.13 (5H, m). IR (film): $\bar{\nu}$ 3000, 1780, 1740, 1600, 1590, 1500, 1460, 1440, 1350, 1290, 1240, 1160, 1080, 1040, 1020, 980, 940, 750 and 680 cm^{-1}.

Methyl 5-(2,4-dichlorophenoxy)methyl-3-chloro-2-oxooxolane-3-carboxylate **58**

This compound was obtained upon reaction of 10.77 g (43 mmole) of **57** and 21.33 g (158 mmole) of SO_2Cl_2, operating as described above for **51**, in quantitative yield (crude material). 60 MHz PMR ($CDCl_3$): δ 3.25 (2H, m), 4.11 (3H, s), 4.54 (2H, m), 5.30 (1H, m), 7.30 (1H, d, J = 9.3) and 7.69 (2H, m). IR (film): $\bar{\nu}$ 3000, 1790, 1760, 1730, 1590, 1480, 1450, 1430, 1390, 1340, 1290, 1260, 1180, 1100, 1060, 1010, 970, 860 and 790 cm^{-1}. MS: *m/e* (%) 352–354–356 (M, 3:4:1), 191–193 (100:34), 164 (40), 162 (66), 155 (60), 149–147 (74:26), 145 (26), 135 (26), 133 (37), 131 (26), 125 (29), 115 (45), 111 (47), 75 (42), 63 (34), 59 (92), 53 (53) and 43 (45).

5-(2,4-Dichlorophenoxy)methyloxol-3-en-2-one **63**

The sequence described above for the preparation of **55** from **51** was followed.

5-(2,4-Dichlorophenoxy)methyl-3-chlorooxolan-2-one **60** was obtained in 97.7% yield from 15.58 g (44 mmole) of **58**. 60 MHz PMR ($CDCl_3$): δ 2.87 (2H, m), 4.27 (2H, m), 4.87 (2H, m), 6.95 (1H, dd, J = 8.7, J' = 2) and 7.35 (2H, m). IR (film): $\bar{\nu}$ 2975, 1790, 1590, 1580, 1560, 1490, 1460, 1400, 1350, 1300, 1270, 1250, 1200, 1170, 1110, 1070, 950, 920, 870, 800 and 760 cm^{-1}.

5-(2,4-Dichlorophenoxy)methyl-3-phenylthiooxolan-2-one **61** was obtained in 76.5% yield from 9.94 g (34 mmole) of **60** and 39 mmole of sodium benzenethiolate. 60 MHz PMR ($CDCl_3$): δ 2.60 (2H, m), 4.10 (3H, m), 4.70 (1H, m), 6.75 (1H, d, J = 8.7) and 7.34 (7H, m).

5-(2,4-Dichlorophenoxy)methyl-3-phenylsulfinyloxolan-2-one **62** was obtained in quantitative yield (crude material) from 7.73 g (21 mmole) of **61** by oxidation with 5.16 g (24 mmole) of $NaIO_4$. 60 MHz PMR ($CDCl_3$): δ 2.69 (2H, m), 4.30 (3H, m), 5.07 (1H, m), 7.25 (3H, m) and 7.80 (5H, broad). IR (film): $\bar{\nu}$ 3100, 2950, 1780, 1570, 1480, 1440, 1400, 1340, 1300, 1260, 1190, 1170, 1090, 1070, 1060, 940, 800, 740 and 690 cm^{-1}.

5-(2,4-Dichlorophenoxy)lethyloxol-3-en-2-one **63** was obtained in 64% yield by pyrolysis of 4.40 g (11.4 mmole) of **62** in 57 ml anh. toluene. M.p. 80–81° (from Et_2O). 60 MHz PMR ($CDCl_3$): δ 4.25 (2H, dd, J = 5.3, J' = 1.3), 5.36 (1H, m), 6.22 (1H, dd, J = 6, J' = 2), 6.82 (1H, d, J = 8), 7.22 (2H, m) and 7.62 (1H, dd, J = 6, J' = 1.3). IR (KBr): $\bar{\nu}$ 1770, 1580, 1480, 1450, 1380, 1330, 1300, 1290, 1260, 1240, 1160, 1100, 1060, 1020, 930, 870, 810, 780 and 730 cm^{-1}. MS: *m/e* (%) 258–260–262 (M, 9:7:2), 179 (7), 177 (28), 175 (50), 163 (11), 161 (19), 149 (29), 147 (68), 145 (71), 133 (32), 112 (27), 111 (100), 109 (97), 97 (60), 83 (64), 77 (24), 75 (81), 74 (71), 73 (76), 69 (69), 63 (67), 62 (50), 55 (81), 53 (43), 51 (31), 50 (42), 43 (84), 42 (41), 41 (81), 39 (68) and 31 (45). Found: C, 50.87; H, 3.23; Cl, 27.12. $C_{11}H_8Cl_2O_3$ requires: C, 50.98; H, 3.12; Cl, 27.37%.

5-Phenoxymethyl-3-phenylthiooxolan-2-one **66**

A solution of 4.13 g (16.5 mmole) of **57** in 18 ml of anh. MeOH was added dropwise at room temp. to a solution of 16 mmole of sodium methoxide in 6 ml of anh. MeOH. After cooling at 0°, 4 g (28 mmole) of benzenesulfenyl chloride was added dropwise, and the mixture was stirred at room temp. for 16 h. Filtering off the precipitate of NaCl and solvent removal gave a residue which was poured into water and extracted with $CHCl_3$. Drying, filtering and evaporating the organic layer gave 7.62 g of crude material containing *methyl 5-phenoxymethyl-3-phenylthio-2-oxooxolane-3-carboxylate* **65** and diphenyl disulfide (PMR control) which was used in the next step without further purification.

A solution of this crude material and 10.5 ml of conc. HCl in 31 ml of glacial AcOH was boiled under reflux for 5 h. Solvent removal, partition between water and $CHCl_3$ and drying the organic layer, followed by solvent removal and chromatography of the residue on silica gel, eluting with CH_2Cl_2, afforded 3.64 g (81% yield from **57**) of *5-phenoxymethyl-3-phenylthiooxolan-2-*

one **66**. 60 MHz PMR ($CDCl_3$): δ 2.59 (2H, m), 4.02 (3H, m), 4.77 (1H, m) and 7.27 (10H, m). IR (film): $\bar{\nu}$ 3075, 2975, 2950, 2900, 1770, 1600, 1590, 1500, 1480, 1450, 1440, 1340, 1300, 1250, 1180, 1120, 1090, 1060, 1040, 1020, 940, 880, 870, 810, 750, 730 and 690 cm^{-1}.

5-Phenoxymethyloxol-3-en-2-one **64**

The sequence described above for the preparation of **55** from **53** was followed.

5 - Phenoxymethyl - 3 - phenylsulfinyloxolan - 2 - one **67** was obtained in quantitative yield from 1.10 g (4 mmole) of **66** and 5 mmole of $NaIO_4$. 60 MHz PMR ($CDCl_3$): δ 2.47 (2H, m), 4.01 (3H, m), 4.81 (1H, m), 7.00 (5H, m) and 7.50 (5H, broad).IR (film): $\bar{\nu}$ 3100, 2950, 1760, 1600, 1590, 1500, 1440, 1350, 1300, 1240, 1180, 1080, 1050, 970, 940, 750 and 680 cm^{-1}.

Pyrolysis of this sulfoxide (2.06 g, 6.5 mmole) followed by chromatography gave 0.84 g (67.7%) of *5-phenoxymethyloxol-3-en-2-one* **64**, m.p. 82–83°. 60 MHz PMR ($CDCl_3$): δ 4.20 (2H, d, J = 5.3), 5.35 (1H, m), 6.20 (1H, dd, J = 6, J' = 2), 7.14 (5H, m) and 7.60 (1H, dd, J = 6, J' = 1.3). IR (KBr): $\bar{\nu}$ 3100, 1760, 1600, 1590, 1490, 1460, 1400, 1340, 1300, 1280, 1260, 1250, 1170, 1160, 1120, 1100, 1050, 1000, 960, 940, 900, 880, 760 and 700 cm^{-1}. MS: *m/e* (%) 190 (M, 0.6), 107 (55), 94 (9), 79 (33), 77 (100), 65 (18), 55 (18), 51 (43), 50 (17), 43 (16), 41 (18), 39 (39) and 29 (10). Found: C, 69.37; H, 5.29. $C_{11}H_{10}O_3$ requires: C, 69.45; H, 5.31%.

Reaction of 5-methyloxol-4-en-2-one (α-angelicalactone) **68** *with NBS*

To a solution of 2 g (20.4 mmole) of **68** in 24 ml anh. CCl_4 were added 1.57 g (28 mmole) of CaO, 1.95 g (23.2 mmole) of $NaHCO_3$ and 3.63 g (20.4 mmole) of NBS. The mixture was irradiated (Pyrex equipment) with a 500 W visible lamp at room temp. (water jacket) for 28 h under stirring. The mixture was filtered, the precipitate washed with CCl_4 and after solvent removal the residue (1.576 g) was distilled, giving 796 mg of several fractions, b.p. 58–64°/0.07–0.08 mm, which analyzed by PMR showed the presence of several compounds (glc gave aberrant peaks). One of the components was shown to be r-4, t-5-*dibromo*-c-5-*methyloxolan*-2-*one* **71**, identical PMR to that of the product of bromination of **68** by Br_2[7]. Another group of PMR peaks was due to protoanemonin **4** (this compound was available for comparison). Other peaks were assigned to *5-bromo-5-methyloxol-3-en-2-one* **72**: δ 2.19 (3H, s), 6.11 (1H, d, J = 6) and 7.79 (1H, d, J = 6). The remaining peaks were assigned to *4-bromo-5-methyloxol-4-en-2-one* **73**: δ 2.03 (3H, t, J = 2.6), 3.4 (2H, q, J = 2.6). Integration of the diagnostic signals from these four compounds showed them to be present in 45.5% (**71**), 29.5% (**72**), 18% (**73**) and 6.8% (**4**) (weight %). Compound **70** (see below) was clearly absent (see Ref. 31). The last fraction of this distillation (0.379 g), b.p. 105–113°/0.35 mm, crystallized to a solid, m.p. 53–56°, identified as *3-bromo-4-oxopentanoic acid* (lit.[39] m.p. 59°).

5-Bromo-5-bromomethyloxol-3-en-2-one **70**

A mixture of 100 mg (0.57 mmole) of **5**, 5 ml of CH_2Cl_2, 5 ml of water and 100 mg (0.56 mmole) of NBS was gently stirred at room temp. for 4 h. Separation of the organic phase and drying gave 122 mg of crude **70**, containing some succinimide. Chromatography on 3 g of silica gel, eluting with C_6H_6, gave 66 mg (45%) of pure **70**, identical in its PMR spectrum with the compound described by the Swiss group.[31]

Oxidation of **68** *by selenium dioxide*

A mixture of 1.01 g (10 mmole) of **68**, 1.41 g (13 mmole) of SeO_2 and 10 ml of dioxane was boiled under reflux for 6 h. After cooling to room temp., the mixture was filtered, and the precipitate was washed with CH_2Cl_2. Solvent elimination gave 1.21 g of a black solid residue which was extracted (Soxhlet) with $CHCl_3$. The extract (424 mg) showed the PMR peaks due to anemonin **74** and protoanemonin **4**. The insoluble residue could not be identified.

5-Methoxymethyloxol-3-en-2-one **75**

Three drops of BF_3–Et_2O and 5.96 ml of a 0.294*M* solution of CH_2N_2 (1.75 mmole) in Et_2O were simultaneously added to a solution of 0.2 g (1.75 mmole) of **2** in 3 ml of CH_2Cl_2. After standing for 1 h at room temp. and neutralization with satd. aq. $NaHCO_3$, the organic phase was dried and solvents evaporated. The residue, containing 60% unreacted **2** (PMR), was again treated as above (150% excess CH_2N_2). The crude product (0.11 g) was distilled giving 93 mg (42%) of **75**, b.p. <140°/14 mm. 60 MHz PMR (CCl_4): δ 3.4 (3H, s), 3.6 (2H, dd, J = 6, J' = 1.3), 5.05 (1H, m), 6.05 (1H, dd, J = 6, J' = 2) and 7.47 (1H, dd, J = 6, J' = 1.3). IR (CCl_4): $\bar{\nu}$ 2890, 2860, 2820, 1785, 1755, 1650, 1600, 1450, 1380, 1320, 1260, 1155, 1125, 1100 and 960 cm^{-1}. Found: C, 56.06; H, 6.60. $C_6H_8O_3$ requires: C, 56.25; H, 6.29%.

5 - Triphenylmethoxymethyloxol - 3 - en - 2 - one **76**

Freshly recrystallized (from C_6H_6–AcCl, 85:15) Ph_3CCl (1.22 g, 4.4 mmole) in 7.7 ml anh. pyridine was added to a solution of 0.5 g (4.4 mmole) of **2** in 3 ml of anh. pyridine, and the mixture was stirred at room temp. for 1 h. After standing for 3 days, filtration and solvent elimination under vacuum gave a residue from which Ph_3COH was crystallized by CH_2Cl_2–hexane treatment. Filtration, solvent removal and crystallization of the residue from C_6H_6–hexane gave 0.14 g (9%) of **76**, m.p. 162–164°. 60 MHz PMR ($CDCl_3$): δ 3.37 (2H, d, J = 5.3), 5.0 (1H, m), 6.10 (1H, dd, J = 5.3, J' = 2) and 7.30 (16 H, complex abs). IR (KBr): $\bar{\nu}$ 3080, 3030, 2920, 2870, 1765, 1600, 1490, 1445, 1330, 1215, 1150, 1110, 1085, 1050, 1020, 990, 950, 880, 860, 820, 790, 770, 755, 745, 705, 695 and 620 cm^{-1}. Found: C, 81.01; H, 5.53. $C_{24}H_{20}O_3$ requires: C, 80.88; H, 5.66%.

(5-Oxooxol-3-en-2-yl)methyl phenylcarbamate **77**

A solution of freshly distilled phenyl isocyanate (0.876 g, 7.35 mmole) in 6 ml of anh. C_6H_6 was added to a solution of 0.68 g (6 mmole) of **2** in 6 ml of anh. C_6H_6, and the mixture was boiled under reflux for 24 h. After cooling, filtration removed *N,N'*-diphenylurea and solvent removal from the filtrate gave a residue which was recrystallized from C_6H_6, yielding 0.47 g (34%) of **77**, m.p. 114–116°. 60 MHz PMR (CD_3COCD_3): δ 4.50 (2H, d, J = 4.7), 5.40 (1H, m), 6.25 (1H, dd, J = 6, J' = 2), 7.0–8.0 (6H, complex) and 8.87 (1H, broad s). IR (KBr): $\bar{\nu}$ 3350, 3310, 1745, 1725, 1600, 1540, 1445, 1345, 1330, 1320, 1235, 1225, 1160, 1080, 1070, 1060, 1040, 970, 920, 810, 750, 730 and 690 cm^{-1}. Found: C, 62.16; H, 4.77; N, 6.23. $C_{12}H_{11}NO_4$ requires: C, 61.80; H, 4.75; N, 6.01.

Tetra-O-acetylranunculin **79** *and tetra-O-acetyl-5-epiranunculin* **80**

To a solution of 200 mg (1.7 mmole) of **2** in 10 ml of $CHCl_3$ (EtOH-free) dried overnight over dryerite was added at once 405 mg (1.7 mmole) of Ag_2O and 87 mg (0.34 mmole) of iodine, and the mixture was stirred overnight under anh. conditions at room temp. Then a solution of 720 mg (1.7 mmole) of α-acetobromoglucose (dried overnight over dryerite) was added dropwise over 20 min and the mixture was stirred for 24 h. Aliquots showed the presence of unreacted **2** (tlc control), so addition of reactants was repeated three more times after 24, 72 and 96 h from the onset of the reaction until complete exhaustion of **2**. Filtration, solvent removal and column chromatography (rapid technique[40]) of the residue (2.63 g) on 50 g of silica gel, eluting with $CHCl_3$:Et_2O (3:2) yielded 418 mg (55.3%) of vitreous solid, consisting of a mixture of **79** and **80**, as shown by its 200 MHz PMR spectrum (Table 1).

5-Phenylthiomethyloxol-3-en-2-one **81**

A solution of 1.00 mmole of $NaSC_6H_5$ in 3 ml of anh. DME (prepared from 110 mg of C_6H_5SH and 96 mg of hexane-washed NaH, then decanting the excess NaH) at 0° was quickly added to a solution of 177 mg (1.0 mmole) of **5** in 3 ml of anh. DME under anh. conditions. Stirring for 30 min, concentration to 2 ml total volume, filtering and solvent removal gave a residue which was chromatographed on 20 g of silica gel, eluting with hexane–Et_2O, to give 17 mg (6%) of an oil, tentatively identified as *5-bromomethyl-4-phenylthiooxolan-2-one* **82** (MS: molecular ion at *m/e* 286–288, 17% rel. abundance) and later 52 mg (25.2%) of *5-phenylthiomethyloxol-3-en-2-one* **81**, eluted as an oil, b.p. < 120°/0.05 mm. 60 MHz PMR ($CDCl_3$): δ 2.95 (1H, dd, J = 13,

J' = 8), 3.35 (1H, dd, J = 13, J' = 6), 5.0 (1H, m), 6.0 (1H, dd, J = 6, J' = 2) and 7.1–7.4 (6H, m). IR (film): $\bar{\nu}$ 3100, 2950, 1760, 1600, 1580, 1490, 1440, 1325, 1230, 1180, 1100, 1070, 1025, 970, 920, 890, 820, 740 and 690 cm^{-1}. UV (EtOH): λ 251 nm (log ϵ 3.8). MS: *m/e* (%)207 (M + 1, 2), 206 (14), 124 (11), 123 (100), 110 (5), 109 (7), 83 (6), 77 (4) and 65 (7). Found: C, 63.69; H, 4.89; S, 15.48. $C_{11}H_{10}O_2S$ requires: C, 63.96; H, 4.89; S, 15.55%.

(5 - Oxooxol - 2 - en - 2 - yl)methyltriphenylphosphonium bromide **83**

A solution of 708 mg (4 mmole) of **5** in 20 ml anh. C_6H_6 was very slowly added over a 22 h period to a solution of 1.05 g (4 mmole) of $(C_6H_5)_3P$ in 20 ml anh. C_6H_6 and the mixture was stirred at room temp. for another 48 h. Decantation of oils and filtration of the white solid gave 1.11 g (63%) of **83**, m.p. 172–178° (dec.). 60 MHz PMR ($CDCl_3$): δ 3.0 (2H, d, J = 7), 5.3 (2H, d, J = 14), 6.0 (2H, m) and 7.6–8.1 (15H, m). IR (KBr): $\bar{\nu}$ 3080, 2900, 1800, 1710 (hydrolysis?), 1600, 1480, 1440, 1390, 1310, 1280, 1100, 1030, 1000, 990, 920, 820, 780, 740, 720 and 680 cm^{-1}. MS: *m/e* (%) 278 (Ph_3PO, 2), 277 (3), 262 (3), 183 (11), 98 (30), 78 (100), 77 (37), 69 (21), 63 (21), 52 (29), 51 (48), 50 (48) and 44 (52). Found: C, 62.77; H, 4.34; Br, 18.34; P, 6.74. $C_{23}H_{20}BrO_2P$ requires: C, 63.03; H, 4.57; Br, 18.19; P, 7.05%.

Treatment of the oils referred to above with $CHCl_3$ resulted in the precipitation of the ring opening product **84** (see below) in 6% yield (from **5**).

4 - Hydroxycarbonyl - 2 - oxobutyltriphenylphosphonium bromide **84**

A solution of **83** in $CHCl_3$ on standing for 7 days at room temp. yielded quantitatively the salt **84**, m.p. 231–233. 60 MHz PMR (CD_3OD): δ 2.1 (2H, t, J = 7.5), 2.6 (2H, t, J = 7.5), 4.5 (3H, s, exchanged protons) and 7.4–7.7 (15H, m). 60 MHz PMR (CD_3SOCD_3): 2.5 (overlapped with solvent), 3.0 (2H, t, J = 7.5), 6.7 (2H, d, J = 13), 7.6–7.9 (15H, m) and 8.3 (1H, s). IR (KBr): $\bar{\nu}$ 3200–2400 (broad), 2900, 2850, 1700, 1480, 1430, 1360, 1340, 1230, 1160, 1100, 1080, 990 and 820 cm^{-1}. MS: *m/e* 357 (9), 263 (19), 262 (100), 261 (23), 184 (23), 183 (78), 108 (47), 107 (32), 96 (19), 82 (19), 81 (17), 80 (21), 79 (12), 78 (20), 77 (33), 68 (20), 51 (69), 50 (36). Found: C, 60.31; H, 4.80; Br, 17.36; P, 6.73. $C_{23}H_{22}BrO_3P$ requires: C, 60.41; H, 4.84; Br, 17.47; P, 6.78%.

Methyl (E)-6-(4-nitrophenyl)-4-oxo-5-hexenoate **85**

A stirred suspension of 439 mg (1 mmole) of salt **83** and 54 mg (1 mmole) of NaOMe in 10 ml of anh. DME was heated at 60° for 2 h and allowed to cool to room temp. for 30 min. After adding 151 mg (1 mmole) of 4-nitrobenzaldehyde in 2 ml anh. DME, heating at 60° was resumed for 18 h. Filtering off Ph_3PO, and extracting the filtrate with CH_2Cl_2, followed by solvent removal, gave a residue (430 mg) which was chromatographed on 20 g of silica gel, eluting with CH_2Cl_2, to give 80 mg (30%) of **85**, m.p. 141–143 (lit.[41] 150°). The unpublished spectra of this compound are as follows. 60 MHz PMR ($CDCl_3$): δ 2.7 (2H, t, J = 6), 3.1 (2H, t, J = 6), 3.7 (3H, s), 6.8 (1H, d, J = 16), 7.65 (1H, d, J = 16), 7.7 (2H, d, J = 8) and 8.25 (2H, d, J = 8). IR (KBr): $\bar{\nu}$ 3100, 3000, 2870, 1800, 1730, 1680, 1620, 1600, 1510, 1440, 1420, 1350, 1200, 1160, 1100, 1060, 990, 970, 890, 840 and 740 cm^{-1}. UV (EtOH): λ 306 nm (log ϵ 4.3). MS: *m/e* (%) 263 (M, 2), 246 (7), 232 (10), 177 (14), 176 (100), 130 (50), 118 (24), 102 (80), 90 (34), 89 (23), 76 (50), 75 (28) and 63 (26).

(E) - 6 - (4 - Nitrophenyl) - 4 - oxo - 5 - hexenoic acid **86**

A mixture of 115 mg (0.25 mmole) of salt **84** and 20 mg (0.5 mmole) of NaOH in 3 ml of water was stirred at room temp. in heterophase for 2 h with a solution of 38 mg (0.25 mmole) of 4-nitrobenzaldehyde in 3 ml of CH_2Cl_2. Separation of the organic layer and solvent removal gave a residue (100 mg) from which yellow crystals deposited on standing (40 mg, 64%) which showed a PMR spectrum identical to that of **85**, except for the absence of the 3H singulet at δ 3.7.

5 - (N - Piperidyl) - 4 - oxopentanoic acid piperidide **87**

To a solution of 152 mg (0.86 mmole) of **5** in 5 ml of Et_2O was added dropwise 146 mg (1.72 mmole) of piperidine. The precipitate of piperidinium bromide (140 mg) was filtered off and solvent removal from the filtrate gave a residue (150 mg) which was chromatographed on 8 g of silica gel, eluting with Et_2O–CH_2Cl_2 (2:1), affording 29 mg (13%) of an oil, tentatively identified as **87**. 60 MHz PMR ($CDCl_3$): δ 1.3–1.7 (12H, m), 2.2–2.7 (8H, m) and 3.2–3.7 (6H, m). MS: *m/e* (%) 266 (M, 2), 182 (2), 181 (10), 168 (3), 154 (10), 140 (2), 138 (2), 121 (3), 119 (3), 112 (14), 98 (100) and lower *m/e*.

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