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SYNTHETIC STUDIES TOWARDS RYANODINE

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Abstract - This paper describes the work carried out toward the total synthesis of ryanodine.

INTRODUCTION

STRUCTURE OF RYANODINE, RYANODOL AND ANHYDRORYANODOL. SYNTHETIC APPROACH.

The insecticide ryanodine (1), isolated from *Ryana speciosa Vahl*, is the ester of pyrrole-α-carboxylic acid and ryanodol (2) (Scheme 1). Since ryanodol contains twenty carbons it is classified as a diterpene. The structure of this complex natural product was elucidated by chemical degradation. During the course of this work (1), it was shown that ryanodol (2) could be easily converted into anhydroryanodol (3) which became the most important degradation product. The structure of ryanodol was later confirmed by X-ray analysis of one of its derivatives (2).

We now wish to report the investigation that we have carried out toward the total synthesis of ryanodine.

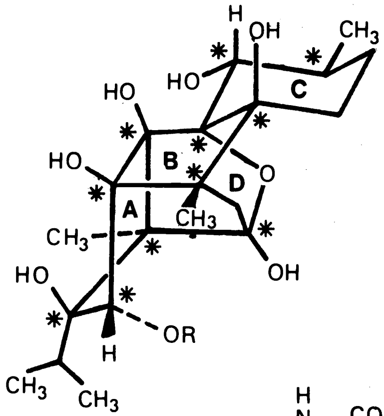
In our preliminary planning, we decided that the best strategy would be to develop a synthetic route to anhydroryanodol first. This decision was based on two facts: (a) anhydroryanodol is a much simpler compound than ryanodol; (b) we were convinced that it would eventually be possible to discover a simple method for the reconversion of anhydroryanodol into ryanodol. Consequently, our synthetic plan for the total synthesis of ryanodol is based on the skeleton of anhydroryanodol.

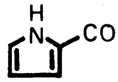
Anhydroryanodol (3) contains three carbocyclic rings A, B, and C plus the lactone ring D. Rings A and B are five-membered while ring C is six-membered. Each ring possesses a methyl group and ring A has in addition an isopropyl group. There are four tertiary hydroxyl groups attached to ring B, one of which forms part of the lactone ring. There are also two secondary alcohols, one in ring C and an allylic one in ring A. By comparison, the parent compound, ryanodol, contains one more carbocyclic ring and two additional tertiary alcohols. One of these hydroxyl groups is part of a ketol function which replaces the lactone function found in anhydroryanodol. Finally, ryanodol contains eleven contiguous asymmetric carbons, three more than anhydroryanodol.

In considering different synthetic strategies for the construction of anhydroryanodol, we became very much attracted by the approach described in Scheme 1. This approach appeared much superior to any other that we could conceive. Thus, all other routes were discarded and we decided to concentrate on that one alone. We were attracted by the tricyclic structure 4 for several reasons. Particularly attractive was the fact that on a simple ozonolysis of a double bond, 4 should be converted into 5 which is ideally built to undergo an internal aldol condensation to give 6. The alternative aldol condensations are all eliminated, one of them because of the presence of the bridgehead methyl group, the other two because they would form four-membered rings. In 6, rings B and C of anhydroryanodol can be easily recognized and ring D is also partially present. The carbonyl group in 6 can be used to introduce the secondary methyl group of ring C and to control its stereochemistry. Finally reduction of this carbonyl group to an equatorial alcohol completes ring C (cf. 7).

If structure 6 had another functional group (X) at C-1, a method of making the lactone ring D would in principle be readily available. For instance, if there were a ketone function at C-1 in structure 6, a Baeyer-Villiger oxidation reaction should give the lactone-containing structure 7. In order to complete the synthesis of anhydroryanodol from an intermediate such as 7, it is necessary that 7 also contains functional groups (Y and Z) at positions C-4 and C-5. These two functional groups should serve two purposes: they should facilitate the formation of the two carbon-carbon bonds for the construction of the five-membered ring A

SCHEME 1



1 R = 

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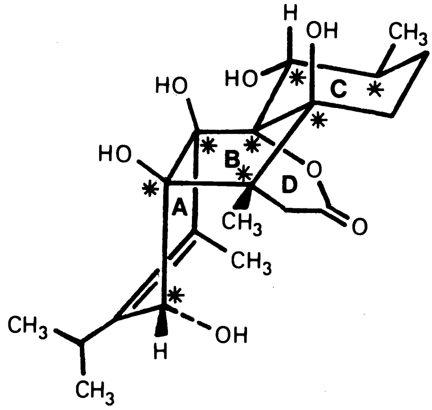

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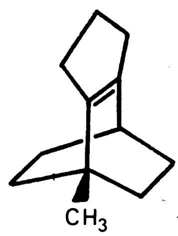

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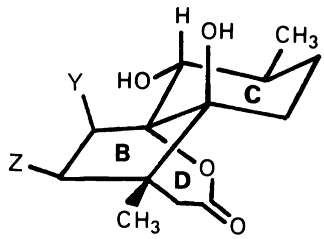

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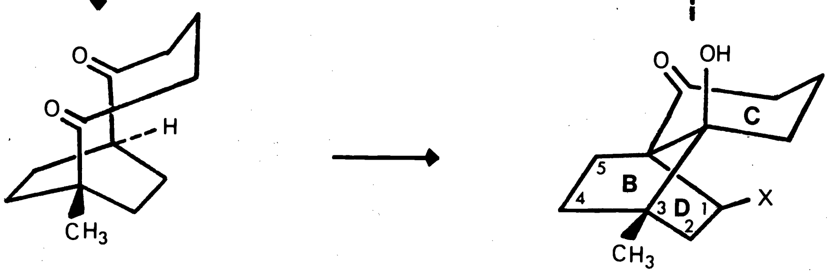

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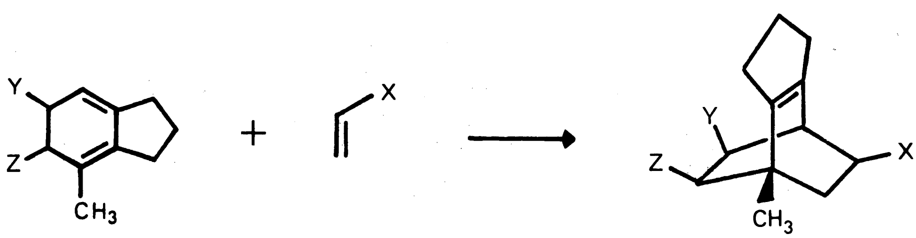
6



9

10

8

and they should be convertible to the two tertiary hydroxyl groups at C-4 and C-5 of anhydroryanodol.

These extra functional groups X, Y, and Z which are necessary to complete the synthesis of rings A and D of anhydroryanodol must therefore be already incorporated into structure 4. Thus, for the construction of anhydroryanodol, what is really needed initially is a compound which would have a structure such as 8. Indeed, structure 8 incorporates all the prerequired functional groups to build anhydroryanodol according to the scheme described above.

In order to complete this plan for the synthesis of anhydroryanodol it remained to consider the various synthetic routes for the preparation of compounds of type 8. Such tricyclic compounds are essentially bicyclo[2.2.2]octane derivatives which contain an extra five-membered ring, a tetrasubstituted double bond, a bridgehead methyl group, and three extra functional groups X, Y, and Z. The view that compounds of type 8 can be considered as bicyclo[2.2.2]octene systems immediately suggests that a Diels-Alder reaction could be utilized to prepare such a product (Note a). However, since each branch of the bicyclic system of 8 contains at least one functional group, the required diene for the Diels-Alder reaction would be more complex than usual. For instance, a diene such as 9 could react with dienophile 10 to give 8. This approach presents two major difficulties: (a) the diene 9 contains two extra functional groups Y and Z, 9 might therefore be either difficult to synthesize or might simply be very unstable; diene 9 should have a tendency to aromatize by losing one of the functional groups Y or Z, (b) since the diene 9 and the dienophile 10 are both asymmetric, it would be necessary to find ways to achieve some specificity to yield only adduct 8.

We felt that such problems might be overcome by selecting compound 11 which possesses all the requirements of diene 9 (Scheme 2). Compound 11 is an orthoquinone which has one of its carbonyl groups protected as a ketal. Since 11 is at the oxidation level of an orthoquinone, the anticipated problem of the aromatization of the diene is in principle solved. Also, we thought that the ketal protecting group should serve two important functions: (a) to stabilize 11 since the corresponding orthoquinone is known to be instable, (b) to bestow complete specificity to the Diels-Alder reaction with an unsymmetrical dienophile. Diene 11 can be compared with quinolacetate. This compound can act as a diene (12) and as a dienophile (13). Indeed, it is known that quinolacetate gives specifically dimer 14 very readily (4). Since diene 11 is much more substituted than quinolacetate (12), we could expect that 11 would be slow to dimerize. We also reasoned that diene 11 would prefer to react with a small active dienophile rather than to dimerize. Furthermore, by analogy with the dimerization of quinolacetate, the reaction of diene 11 with the unsymmetrical dienophile methyl vinyl ketone should be completely stereospecific. Quinolacetate can be considered as a vinyl homolog (cf. 13) of methyl vinyl ketone, thus both compounds should exhibit similar dienophile behavior. Consequently, it was possible to predict that if methyl vinyl ketone reacted with diene 11, it should give specifically the desired adduct 15.

The first practical goal therefore was to develop a synthesis of compound 11 so that its reaction with unsymmetrical dienophiles could be verified.

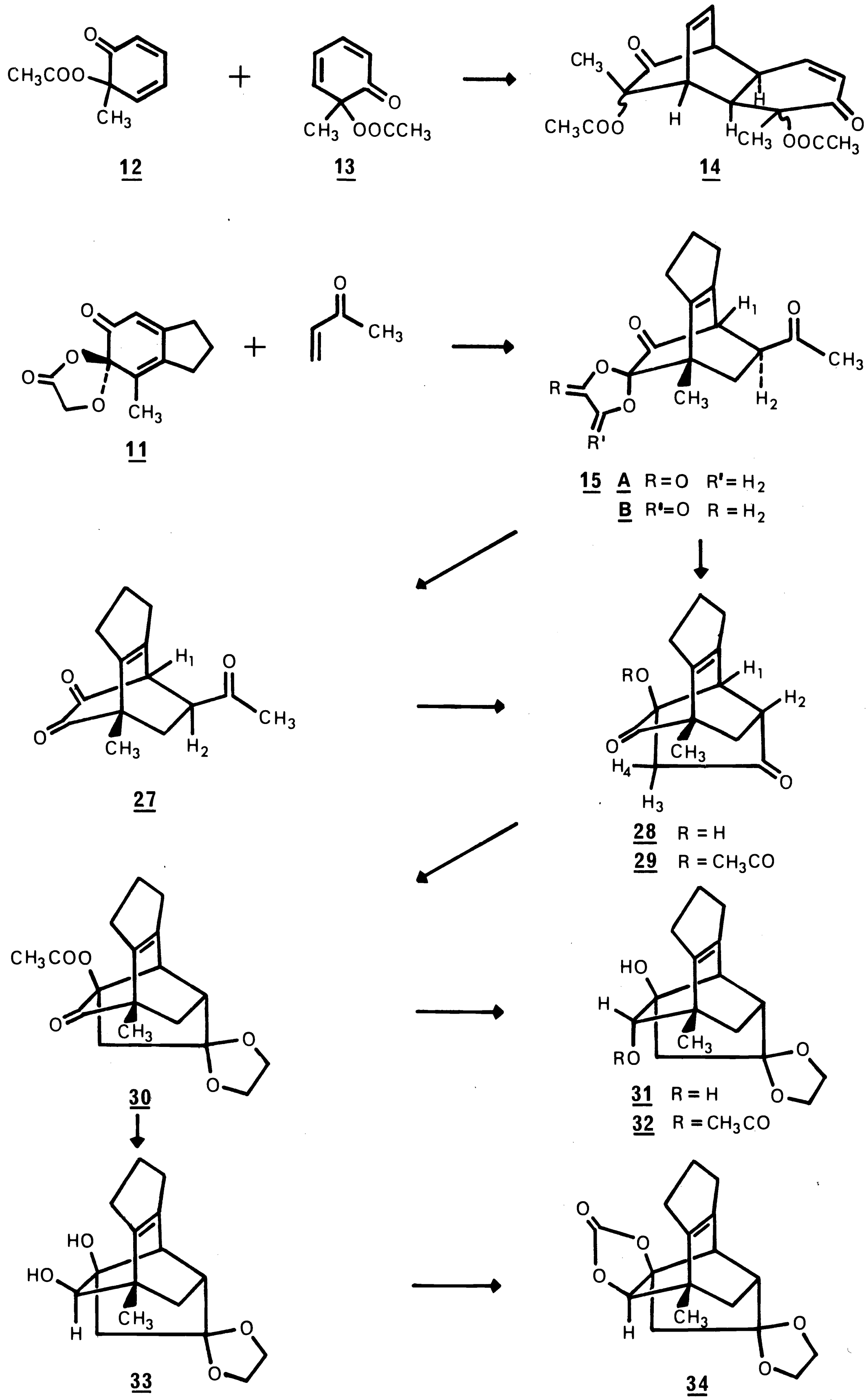
SYNTHESIS OF O-SPIRODIENONE LACTONE 11 AND REACTION WITH METHYL VINYL KETONE

5,6-Dimethoxyindane (16) was used as starting material (Scheme 3). This compound can be easily obtained in large quantity from veratraldehyde (5). It can also be prepared in one step from 5,6-dimethoxyindanone which is commercially available. 5,6-Dimethoxyindane (16) was first converted into the corresponding aromatic aldehyde 17 with α,α-dichloro-dimethyl ether in the presence of titanium tetrachloride in dichloromethane (6). Treatment of the dimethoxyaldehyde 17 with boron tribromide in dichloromethane (7) afforded 4-formyl-5,6-dihydroxyindane (18) in an overall yield for the two steps of ≃80%. 18 could be easily purified by recrystallization. The phenol aldehyde 18 was then selectively esterified with α-bromoacetylbromide in benzene containing pyridine to yield the mono bromoacetate derivative 19. This crude product 19 was then heated to reflux in tetrahydrofuran in the presence of anhydrous sodium carbonate to furnish the crystalline lactone aldehyde 20 in ≃80% yield from 18.

A rigorous chemical proof for the position of the lactone ring in aldehyde 20 was obtained in the following way. 5,6-Dimethoxyindane 16 was treated with bromine in carbon tetrachloride and it gave the bromoindane 21. Reaction of 21 with magnesium in ether afforded the expected Grignard derivative which by reaction with triethyl orthoformate followed by acid hydrolysis gave methoxyphenol aldehyde 22. Reduction of 22 with lithium aluminium hydride gave a phenol alcohol which was transformed into the cyclic carbonate 23 by reaction with phosgene in benzene containing pyridine. The formation of 23 shows that the remaining methoxy group in

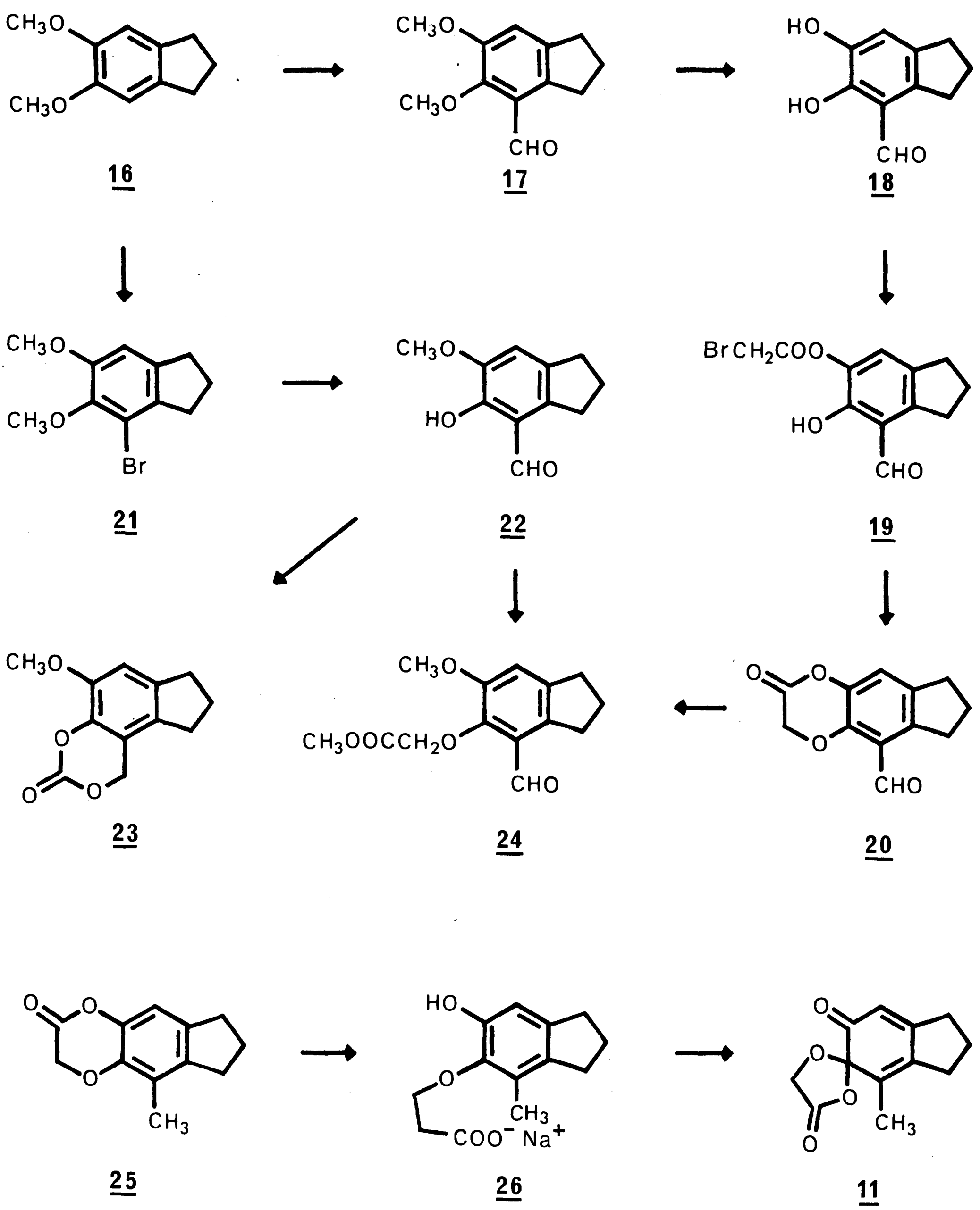
Note a. We have also considered different approaches (3).

SCHEME 2



CH3COO
CH3
12
13
CH3 OOCCH3
14
11
15 A R=O R'=H2
B R'=O R=H2
27
28 R=H
29 R=CH3CO
30
31 R=H
32 R=CH3CO
33
34

SCHEME 3


CH3O
CH3O
16
CH3O
CH3O
CHO
17
HO
HO
CHO
18
CH3O
CH3O
Br
21
CH3O
HO
CHO
22
BrCH2COO
HO
CHO
19
CH3O
O
O
O
23
CH3O
CH3OOCCH2O
CHO
24
O
O
O
CHO
20
O
O
O
CH3
25
HO
O
CH3
COO⁻ Na⁺
26
O
O
O
O
CH3
11

22 is at C-6. Alkylation of methoxyphenol aldehyde 22 with ethyl bromoacetate in tetrahydrofuran containing potassium carbonate gave a product which by hydrolysis in aqueous base followed by diazomethane esterification was transformed into the methyl ester 24. Lactone aldehyde 20 was then hydrolysed to its corresponding phenol carboxylic acid derivative which was esterified with diazomethane and further alkylated with dimethylsulfate in tetrahydrofuran containing anhydrous potassium carbonate. The resulting product was identical with compound 24 which had been obtained from methoxyphenol aldehyde 22. The structure of lactone 20 is thus secure.

Wolff-Kishner reduction of lactone aldehyde 20 gave crystalline lactone 25 in 80% yield. The lactone 25 was then hydrolysed with sodium hydroxide and the crude salt 26 was oxidized with N-bromosuccinimide in aqueous acetonitrile (8) to give the desired crystalline O-spirodienone lactone 11 (≈95% yield). The O-spirodienone lactone 11 was therefore very conveniently prepared in six steps (16 → 17 → 18 → 19 → 20 → 25 → 11) from 5,6-dimethoxyindane in an excellent overall yield (≈50%).

O-spirodienone lactone 11 is a stable crystalline compound. It did not dimerize even in refluxing benzene. However, it reacts with excess methyl vinyl ketone at room temperature within one hour to provide a one-to-one mixture of two isomers which were separated and identified as adducts 15A and 15B (Scheme 2).

A brief treatment of 15A or 15B with aqueous base followed by acidification gave the same tricyclic triketone 27. This result shows that the adducts 15A and 15B differ by the configuration of the lactone ring only. This is expected as the attack of the dienophile can be just as facile from above as from below the plane of the diene. The position of the methyl ketone side chain in compounds 15A, 15B, and 27 was easily established since H_1 and H_2 appear respectively as a doublet (J=2 Hz) and an octuplet (J=2, 6, and 9 Hz) in the nuclear magnetic resonance spectra of these compounds. The configuration of the methyl ketone side chain could not be established by spectral analysis but it was assigned *syn* to the double bond on the basis of the Alder *endo* rule (9). This rule predicts that the activating group of the dienophile must become *syn* to the double bond in the resulting adduct. Treatment of tricyclic ketone 27, with aqueous tetrahydrofuran containing sodium hydroxide gave the tetracyclic hydroxydiketone 28. Compound 28 was best prepared by treating directly the crude mixture 15A and 15B under the same basic conditions (80% yield). The direct conversion of 15A and 15B into 28 combines several steps in a single operation: (a) opening of the spirolactone to give a hemi-ketal, (b) breakdown of the hemi-ketal to give a carbonyl group, (c) epimerization of the methyl ketone side chain and (d) aldol condensation of the methyl ketone group with one of the carbonyls of the α-diketone system.

The structure of hydroxydiketone 28 was confirmed by carrying out a series of deuterium exchange experiments. If 28 was added to a deuterated basic medium, it incorporated two deuterium atoms to give 28 (D_3, D_4). Since H_2 was not exchanged, this result shows that the aldol condensation is an irreversible process. When 15A and 15B were placed in a deuterated basic medium, a trideuterated hydroxydiketone 28 (D_2, D_3, D_4) was isolated in which H_2 was totally exchanged for deuterium. These results were further confirmed by the treatment of trideuterated 28 (D_2, D_3, D_4) with ordinary aqueous sodium hydroxide which gave monodeuterated hydroxydiketone 28 (D_2) exclusively.

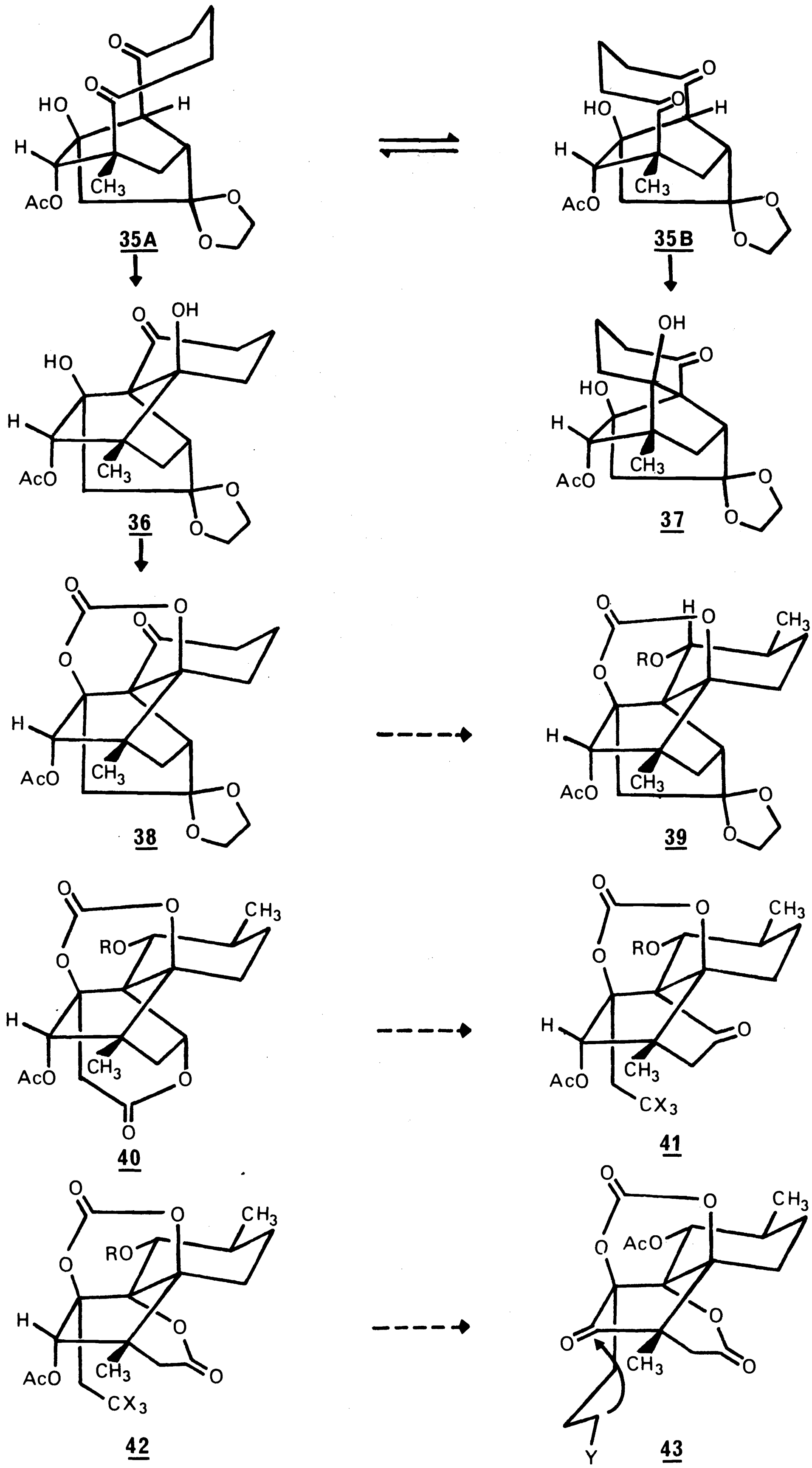
Compound 28 was transformed into the ketoacetate 29 by reaction with acetic anhydride catalyzed by pyridine or *p*-toluenesulfonic acid. 29 was selectively ketalized with ethylene glycol, benzene and *p*-toluenesulfonic acid to give ketal acetate 30. Reduction of ketal acetate 30 with lithium borohydride in tetrahydrofuran gave mainly the *trans* diol 31 together with a small quantity of the *cis* diol 33. The *cis* diol 33 was obtained as the major isomer when 30 was reduced with sodium in liquid ammonia containing ethanol. The *trans* diol 31 was further characterized by the preparation of the monoacetate 32 in acetic anhydride with pyridine. The diol 33 was shown to be the *cis* isomer by its reaction with phosgene in benzene containing pyridine which gave the five-membered carbonate 34.

The two primary objectives of the synthesis were thus successfully completed. A good practical synthesis of O-spirodienone lactone 11 was achieved and it was shown to undergo a specific Diels-Alder reaction with methyl vinyl ketone to give adducts 15A and 15B. The transformation of 15A and 15B into the tetracyclic hydroxydiketone 28 provides an excellent method to make one of the carbon-carbon bonds present in ring A of anhydroryanodol (3). Thus, this two-step sequence (11 → 15 → 28) is an exceptionally short route to intermediates which are ideally suited to verify that the ozonolysis and the subsequent internal aldol condensation can indeed result in compounds having rings B and C of the anhydroryanodol skeleton.

MODEL STUDIES FOR RINGS B AND C, AND SYNTHETIC STRATEGY FOR RING A

Since the oxidative cleavage of the tetrasubstituted double bond should produce two carbonyl groups which are expected to undergo an internal aldol condensation, the presence of other carbonyl groups would have to be avoided. It was mainly for this reason that ketal acetate 32 was chosen to study this crucial step of our synthetic plan.

SCHEME 4



The diketone resulting from ozonolysis of the ketal acetate 32 can exist in two different conformations: 35A and 35B (Scheme 4). Since the same aldol reaction can occur on each conformer, it is possible in principle to obtain two different aldol isomers, 36 from conformer 35A and 37 from conformer 35B. The ozonolysis of 32 was carried out in methanol, it was followed by a catalytic reduction with palladium-on-charcoal and by a short reflux in pyridine. This series of operations gave mainly the desired dihydroxyketoacetate 36 and a small quantity (≈30%) of the other isomer 37.

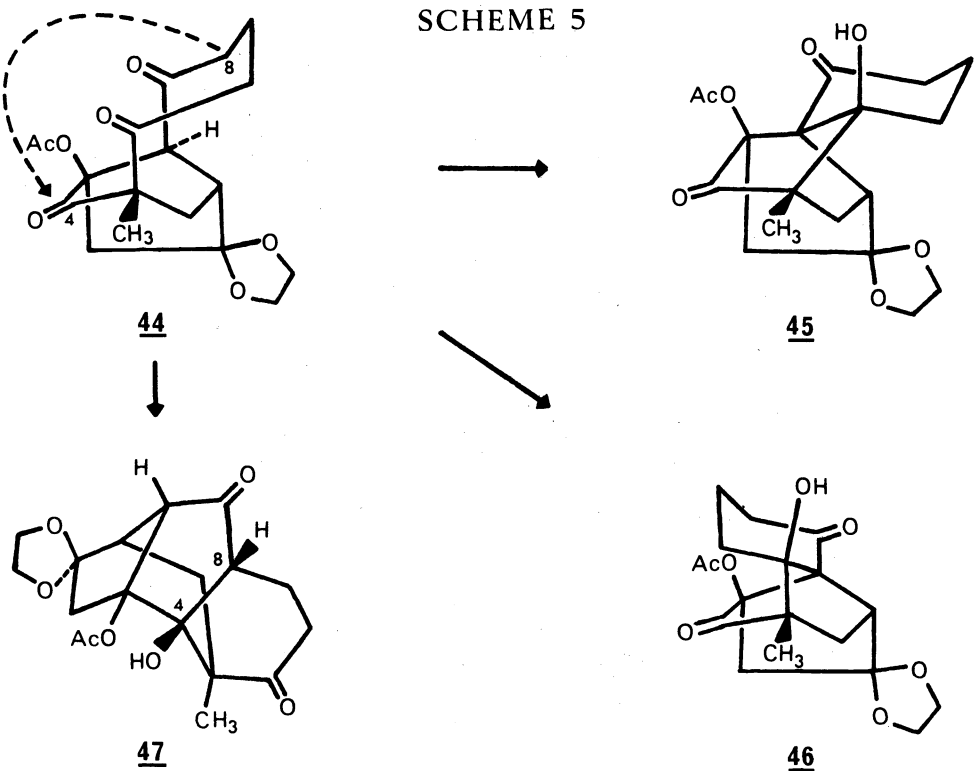
The structure of 36 was firmly established by its spectral and analytical properties, and by its reaction with phosgene which afforded the crystalline six-membered cyclic carbonate derivative 38. The transformation of 32 into 36 proved that our synthetic strategy to build rings B and C of anhydroryanodol from a bicyclo[2.2.2]octene precursor was indeed a valid one (10).

At this stage of the investigation, we had arrived at a situation which had to be carefully analysed before continuing. Either the conversion 32 → 36 could be accepted as a model study to be carried out on a more appropriate intermediate, or 36 could be used to continue the synthesis to anhydroryanodol. For instance, after completion of ring C (36 → 39), the ketal group could be hydrolysed. A Baeyer-Villiger oxidation of the resulting ketone would afford lactone 40. This product could then be converted into ketone 41 which in principle can be oxidized to lactone 42. The proper functionalization of the CH_2-CX_3 side chain and the conversion of the secondary acetate group at C-4 into a carbonyl group would give an intermediate 43 which would allow the formation of the second carbon-carbon bond of ring A. The above theoretical conversions are very plausible and it is likely that the synthesis of anhydroryanodol could have been achieved by this specific route.

However, we decided not to try this route as a matter of principle based on the following points. One aim of this synthetic work was to discover schemes which avoid unnecessary steps. The scheme using 36 would involve four steps starting with the reduction of the carbonyl group at C-4 in 30, protection of the resulting secondary alcohol (32), later removal of the protecting group and reoxidation to the carbonyl group (43). These operations can in principle be eliminated by two alternatives which are (a) to simply carry out the ozonolysis on a compound bearing the C-4 carbonyl group, e.g. intermediate 28; (b) to transform the carbonyl group at C-4 into a hydroxyl group by forming the carbon-carbon bond necessary to complete ring A, prior to ozonolysis. Ring A would therefore have to be completed before the oxidative cleavage of the tetrasubstituted double bond.

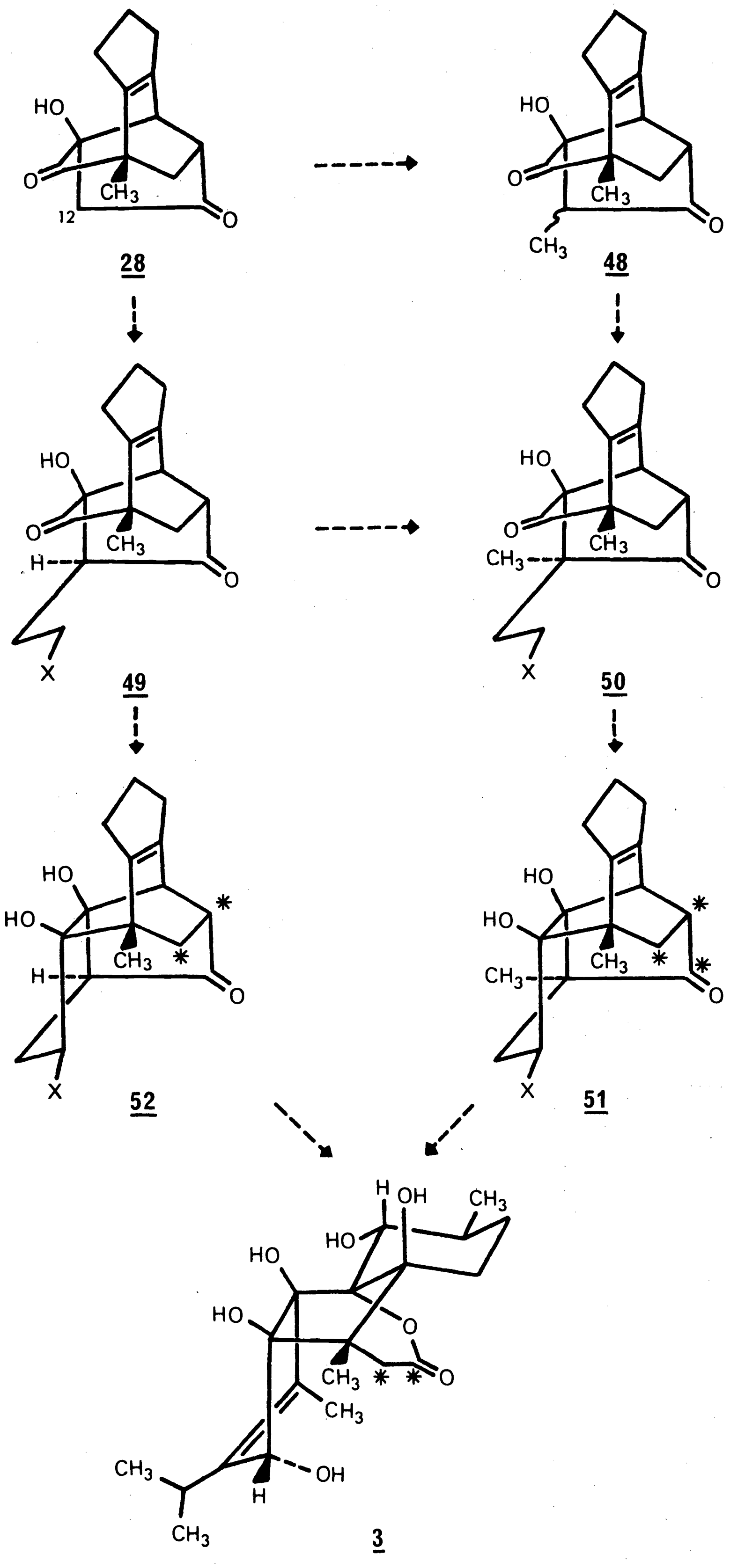
The ozonolysis reaction (O_3 in $CH_3COOC_2H_5$, Pd/C-H_2) was attempted on the carbonyl compound 30 and the crystalline triketone 44 could be isolated (Scheme 5). A close examination of structure

SCHEME 5



44 45 47 46

SCHEME 6



HO
O
CH3
12
O
28
HO
O
CH3
CH3
O
48
HO
O
CH3
H
O
X
49
HO
O
CH3
CH3
O
X
50
HO
HO
CH3
H
O
X
52
HO
HO
CH3
CH3
O
X
51
H
OH
CH3
HO
HO
HO
O
CH3
O
CH3
CH3
OH
H
CH3
3

44 indicates that in addition to the two condensations previously discussed which would give 45 and 46, another aldol condensation is possible between C-4 and C-8 leading to structure 47. In the formation of the latter, no new strained bridged system is introduced as in the previous two (45 and 46), therefore this undesired process is even favored. Indeed, when the triketone 44 was heated in pyridine, it gave exclusively the compound 47. This result definitely showed that the oxidative cleavage of the double bond cannot be performed in the presence of a carbonyl group at C-4, and eliminates the alternative (a).

The synthesis of ring A prior to the oxidative cleavage of the double bond was the next to be considered. There are in principle two different approaches to build ring A from hydroxy-diketone 28. The first one is described by the route 28 → 50 → 51 → 3 in Scheme 6. Based on a stereochemical point of view, 50 is the key intermediate of this approach. If the alkylation at C-12 of molecules of type 28 is specific, the stereospecific synthesis of 50 can be simply achieved by the proper sequential introduction of the methyl and the CH_2CH_2-X groups, thus *via* 48 or 49. The advantage of this route is the apparently facile stereospecific synthesis of 50. However, there is a serious objection to this route: intermediate 50 (or 51) has three carbons (C*) instead of two, with which to make the lactone ring D, meaning that one of them will eventually have to be removed to make anhydroryanodol. Such an operation appeared neither easy nor elegant and this approach was not further considered.

The second approach is described by the route 28 → 49 → 52 → 3. In this approach, there is no extra carbon, the carbonyl group of 52 being used to make the ring A methyl group of anhydroryanodol. It is clear that the success of this route depends on the ease of control of the configuration of the side chain which must be "inside" in 49 so that ring A can be formed. We were quite interested by this approach because there was a further possibility of eliminating the alkylation step: 28 → 49. For instance, compound 49 could be prepared in two operations from the O-spirodienone lactone 11 and a methyl vinyl ketone derivative where the methyl group was replaced by a $-CH_2-CH_2-CH_2-X$ group.

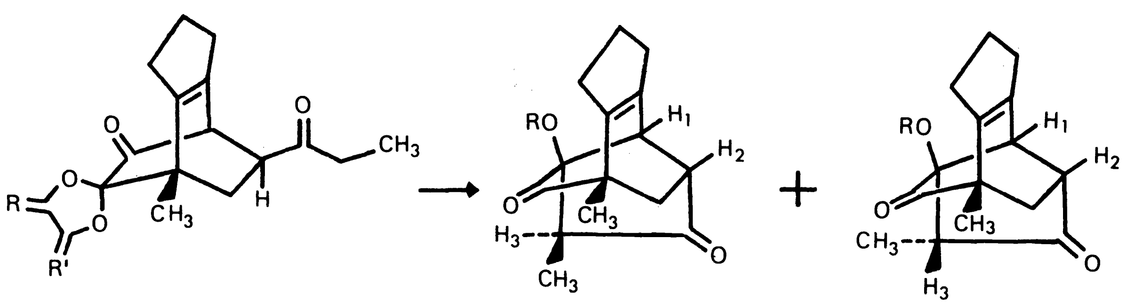
A study of the consequence of substitution on the methyl group of methyl vinyl ketone was therefore undertaken in order to develop a simple synthesis of ring A.

SYNTHETIC STUDIES TOWARDS RING A. SYNTHESIS OF A PENTACYCLIC INTERMEDIATE.

The first study with a substituted derivative of methyl vinyl ketone was carried out with ethyl vinyl ketone. Its reaction with diene 11 proceeded well giving the expected mixture (≃1:1) of 53A and 53B (Scheme 7). Treatment of the crude mixture of 53A and 53B with sodium hydroxide in aqueous tetrahydrofuran gave a good yield (>60%) of two products which were identified as the *endo* epimer 54 (75%) and the *exo* epimer 55 (25%). The assignment of configuration was made on their respective acetate derivatives 56 and 57. In the major isomer, H_3 appears as an octuplet (J=2 and 6 Hz), whereas in the minor isomer, H_3 appears as a quadruplet (J=6 Hz). The additional coupling found in the major isomer is the result of W coupling between H_3 and H_2. Only structure 56 has the correct geometry for W coupling through the carbonyl group. This assignment was further unambiguously proven by loss of W coupling in 56 on replacing the hydrogen at C-2 with deuterium using the deuterium exchange technique previously described for compound 28.

It was surprising to discover that the most stable epimer was the *endo* isomer. This unpredictable result had favourable consequences. It was possible to assume that any *endo* isomer such as 49 (Scheme 6) would be easily obtained, because it would be the most stable epimer. Thus, this result indicated that a synthesis of a pentacyclic system such as 52 could be realized.

SCHEME 7

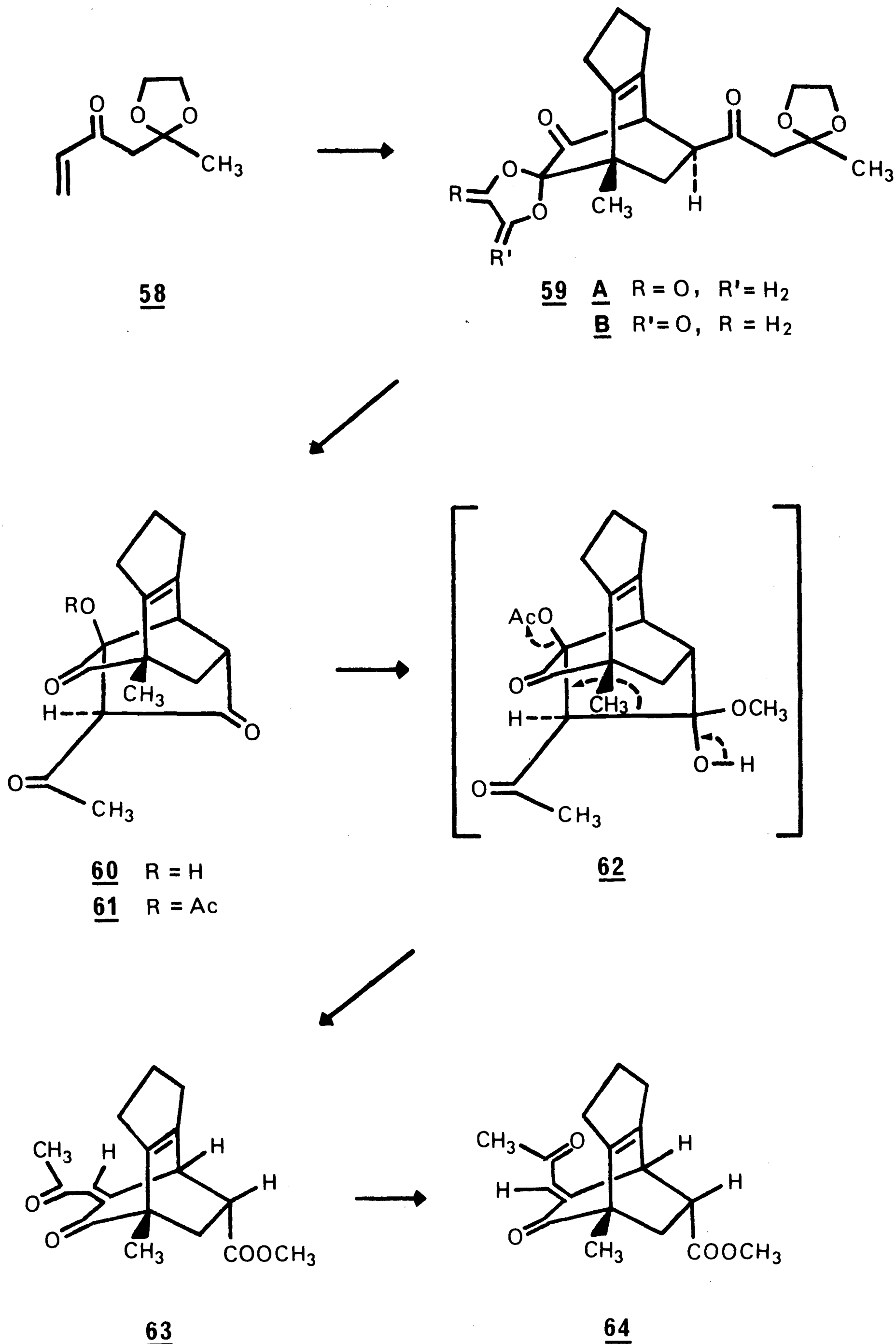


53 A R = O, R' = H_2
B R' = O, R = H_2

54 R = H
56 R = Ac

55 R = H
57 R = Ac

SCHEME 8



O
O
O
CH3
58
O
O
O
CH3
O
O
O
R
R'
CH3
H
59 A R = O, R' = H2
B R' = O, R = H2
RO
O
CH3
H
O
O
CH3
60 R = H
61 R = Ac
AcO
O
CH3
H
OCH3
O
H
O
CH3
62
CH3
H
H
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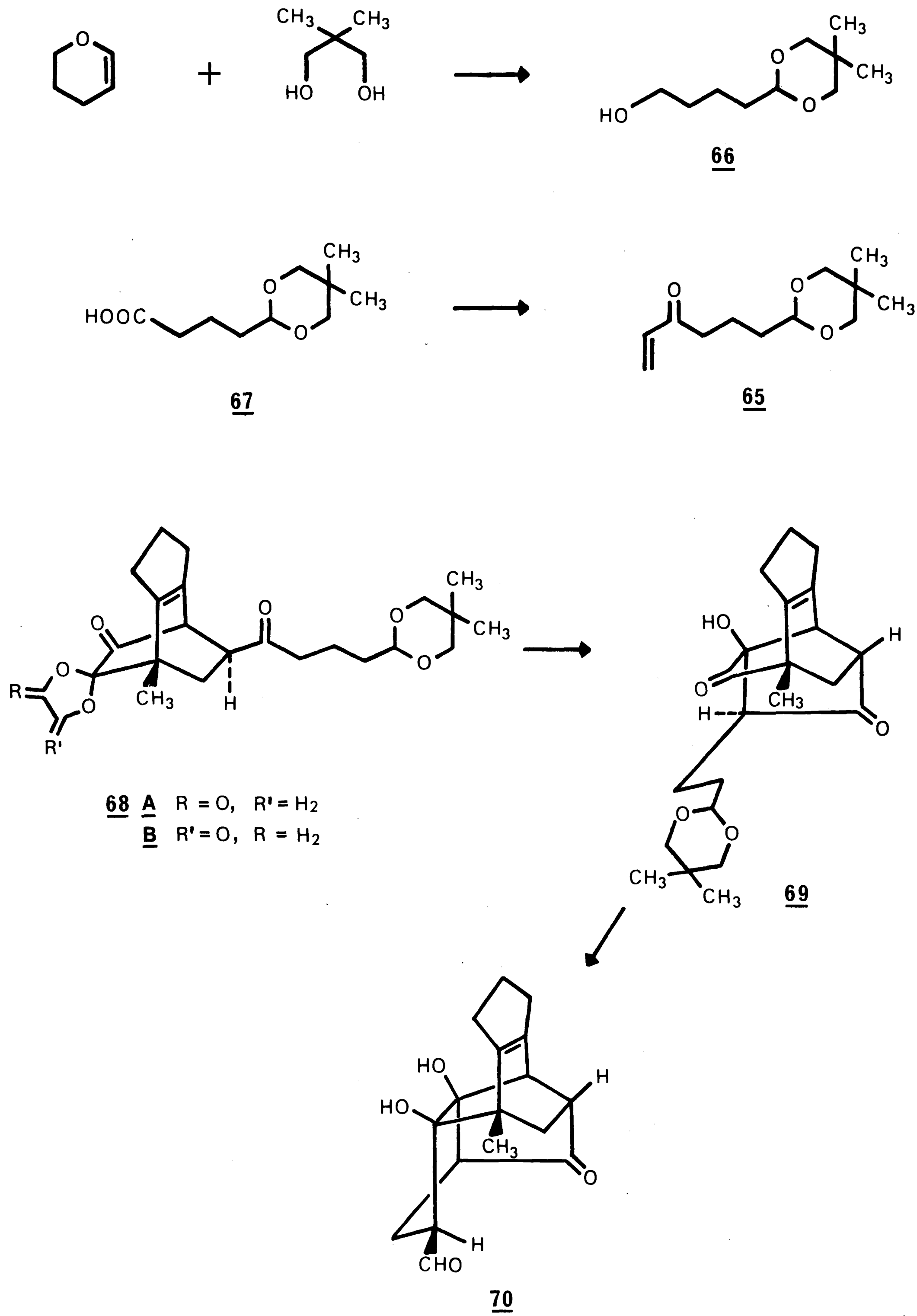
CH3
H
COOCH3
64

SCHEME 9



The next modified dienophile to be studied was the vinyl ketone 58 (Scheme 8) which was prepared by a standard route from methyl acetoacetate: It was felt that this dienophile would be a suitable one for the fabrication of ring A. Although we were not successful in achieving this goal, this study provided a rigorous chemical proof that compounds of type 49 are definitely more stable in the *endo* configuration.

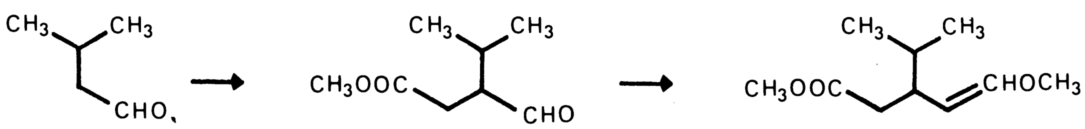
The reaction of 58 with diene 11 proceeded well to give a mixture of 59A and 59B which, after treatment with aqueous base followed by acidification, gave the tetracyclic β-diketone 60 in better than 95% yield. Acetylation of 60 with acetic anhydride and pyridine followed by mild treatment with aqueous sodium carbonate gave the acetate derivative 61. Treatment of 61 with anhydrous methanol containing *p*-toluenesulfonic acid gave the *cis* enedione 63. On pyrolysis at 100°, the enedione 63 was completely isomerized into the more stable *trans* enedione 64. Intermediate 62 explains the conversion of 61 into 63 and also illustrates that the specific formation of *cis* enedione 63 constitutes a chemical proof that the methyl ketone side chain is in the *endo* orientation in 61, otherwise, the more stable *trans* enedione 64 would have been first produced.

The dienophile 65 having an acetal function was studied next (Scheme 9). This compound was prepared in three steps. Reaction of dihydropyran with 2,2-dimethylpropanediol gave the acetal alcohol 66 which was oxidized with Jones reagent to give the crystalline carboxylic acid 67. Treatment of the lithium salt of 67 with vinyl lithium gave the vinyl ketone 65. Reaction of a slight excess of 65 with diene 11 in refluxing benzene gave a quantitative yield of adducts 68A and 68B (≈1:1). The crude product 68 was treated under the usual basic condition to yield the crystalline *endo* isomer 69 in ≈70% yield. Compound 69 was then heated to reflux in a mixture of acetone and hydrochloric acid (3N) to give the crystalline pentacyclic dihydroxyketone aldehyde 70 in 25% yield. The low yield in the last step is due to the fact that the acetal function in 69 is difficult to hydrolyse. Under more vigorous acidic conditions, compound 70 cannot survive. We had thus developed an especially simple three-step procedure to build a pentacyclic system containing a five-membered ring which should eventually become ring A of anhydroryanodol.

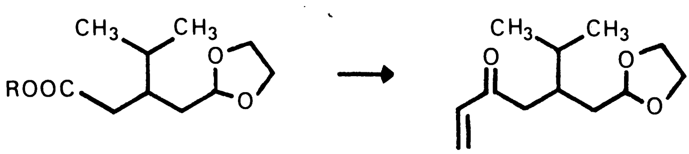
It was again decided to regard this series as a model study for two reasons: firstly, the acetal function of the dienophile had to be modified in order to be hydrolysed under milder conditions: secondly, there remained another possibility to take advantage of the dienophile to solve yet another important problem. If compound 70 were accepted as an intermediate, the subsequent introduction of an isopropyl group in ring A would have to be considered. No doubt a method could have been discovered to do so, but it appeared much more interesting to introduce that group directly in the dienophile.

The dienophile 71 which has a dioxolane acetal was selected and its synthesis was next undertaken (Scheme 10). The eneamine derived from di-isobutylamine and isobutyraldehyde (11, 12) was condensed with methyl bromoacetate to give the aldehyde ester 72. Wittig reaction gave 73 which was converted into the acetal ester 75 using standard methods. Basic hydrolysis of 75 gave the carboxylic acid 74. The lithium salt of 74 gave the vinyl ketone 71 on reaction with vinyl lithium.

SCHEME 10



72 73



74 R = H
75 R = CH_3

71

Diene 11 was reacted in boiling benzene with a slight excess of vinyl ketone 71 to give a quantitative yield of adducts 76A and 76B (Scheme 11). Treatment of this crude material with sodium hydroxide in aqueous tetrahydrofuran gave a mixture of epimers (77) at C-3 and C-4. This crude mixture was heated in aqueous acetic acid and then treated with sodium hydroxide in aqueous tetrahydrofuran. It gave the crystalline pentacyclic dihydroxyketoaldehyde 78 in 23% yield from diene 11. Compound 78 gave the five-membered cyclic carbonate 80 on reaction with phosgene in the presence of pyridine in benzene. On reaction with acetic anhydride and *p*-toluenesulfonic acid, 78 gave the two epimeric orthoester derivatives 81A and 81B which could be separated by chromatography.

An extremely simple synthesis of a pentacyclic system containing the isopropyl side chain of ring A was in hand. Furthermore, in this process, we had obtained an even more fascinating result which could not have been predicted: only one product (78) was produced whereas in principle, two isomers, 78 and 79, should have been formed, each in 50% theoretical yield.

The determination of the relative configuration of the isopropyl group was carried out on the derivatives 81A and 81B. In both n.m.r. spectra, H_3 appears as a quadruplet (J=6 and 2 Hz). Molecular models showed that the dihedral angle between H_3 and H_4 is 30° in structures of type 78 as opposed to 90° in structures of type 79 having the opposite configuration for the isopropyl group. Coupling between H_3 and H_4 should thus be observed in derivatives 81A and 81B and its value should be about 6 Hz. The additional coupling of 2 Hz was again explained by the occurence of W coupling between H_3 and H_2. This overall assignment was confirmed by the synthesis of 81A and 81B having a deuterium atom at C-2. In those compounds, H_1 appears as a singlet and H_3 as a doublet (J=6 Hz).

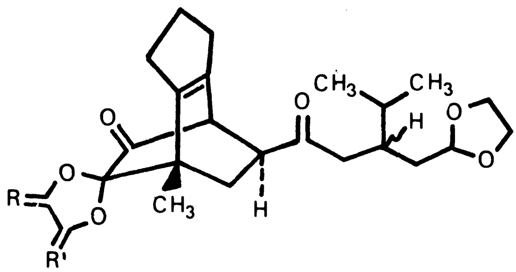
The sole formation of product 78 can be understood if it is assumed that only one of the two *endo* isopropyl isomers from 77 can undergo the internal aldol condensation. The four isomers of 77 were separated by column chromatography and the two major isomers were assigned the *endo* structures 77A and 77C. The minor isomers were assigned the *exo* structures 77B and 77D because they could be correlated with 77A and 77C respectively by equilibration under basic conditions. *Endo* isomer 77A was converted into 78 in almost quantitative yield. A similar attempt to convert 77C into the pentacyclic isomer 79 failed. Isomer 77C gave a complex mixture, from which 79 could not be isolated. The failure of this aldol condensation reaction is presumably due to the severe pseudo-1,3-diaxial interactions of the isopropyl group with the two tertiary hydroxyl groups which are present in structure 79. Other factors might also be operative.

The specific formation of 78 may appear to be a disadvantage as the theoretical yield cannot be higher than 50%, but it can become extremely advantageous if an optically active dienophile is used. To illustrate this point, let us assume that the optically active dienophile 71A is available and that its absolute configuration is known (Scheme 12). In practice, the dienophile 71A has no real preference for a particular face of racemic diene 11. The reaction will therefore give an almost equal amount of adducts 82A-B which result from an alpha attack and adducts 83A-B which come from an attack from the beta face of racemic diene 11. On treatment with base, these adducts will give respectively the optically active isomers 84 and 85. Adducts 84 and 85 are mirror images except for the fact that they have the same configuration at C-4 and are therefore diastereoisomers. In one diastereoisomer, 84, the relative configuration of the isopropyl group at C-4 allows the formation of the pentacyclic product 86A, while in the other diastereoisomer, 85, formation of 87 is not allowed. Thus, 71A will give the optically active pentacyclic intermediate 86A, having the absolute configuration shown.

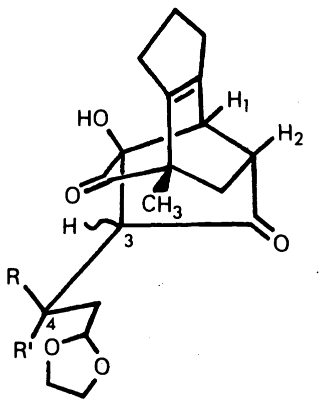
The next step of this investigation was to find a method to obtain an optically active dienophile of known absolute configuration and to verify if optically active pentacyclic product could be obtained from it. The monoterpene carvone was selected as starting material because it presented several advantages: (a) both optically active forms *d* and *ℓ* are commercially available, (b) the absolute configuration of the *d* and the *ℓ* forms are well established and (c) a very simple synthesis of the dienophile could be devised using carvone as a starting point.

Scheme 13 describes the preparation of the optically active dienophiles of 71. *d*-Carvone (88A) was reduced catalytically over platinum to give the dihydro derivative 89 (13). Ozonolysis of 89 (O_3 in $CH_3COOC_2H_5$; Pd/C-H_2) gave the aldehyde carboxylic acid 90 which was transformed into the acetal carboxylic acid 91 ((CH_2-OH)$_2$-*p*-TsOH in benzene; NaOH in CH_3OH). Crude 91 was then esterified (CH_3I, K_2CO_3 in acetone) (14) and the resulting methyl ester product 92 was purified by distillation (≃70% yield from carvone). Hydrolysis of 92 (NaOH in CH_3OH) gave pure acetal carboxylic acid 91 which was finally converted (LiH in THF and CH_2=CHLi) into optically active dienophile 71A ($[\alpha]_{578}$ = +0.6°). Diene 11 was then heated with a slight excess of 71A in benzene. The resulting crude product was treated with an aqueous solution of sodium hydroxide in tetrahydrofuran. It was then heated with aqueous acetic acid at 70° and the treatment with aqueous sodium hydroxide in tetrahydrofuran was repeated. Chromatography of the product gave pure dihydroxyketoaldehyde 86A ($[\alpha]_{578}$=+142.2°).

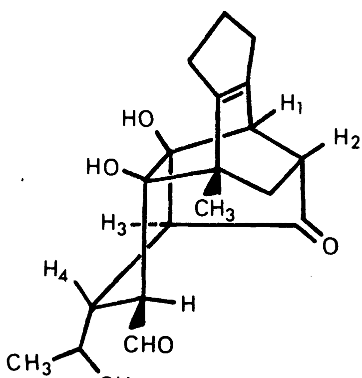
SCHEME 11



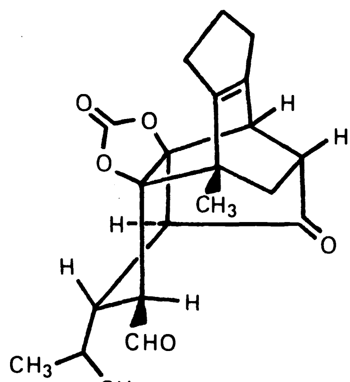
76 A R = O, R' = H_2
B R' = O, R = O_2



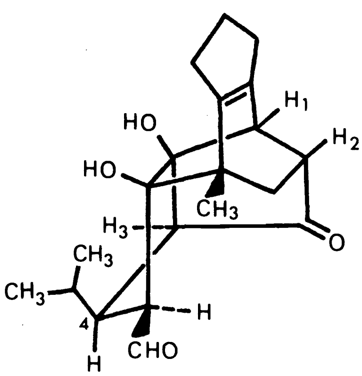
77 A R' = $CH(CH_3)_2$, R = H (endo)
B R' = $CH(CH_3)_2$, R = H (exo)
C R = $CH(CH_3)_2$, R' = H (endo)
D R = $CH(CH_3)_2$, R' = H (exo)



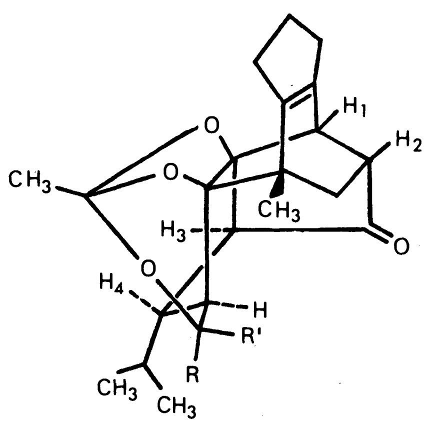
78



80

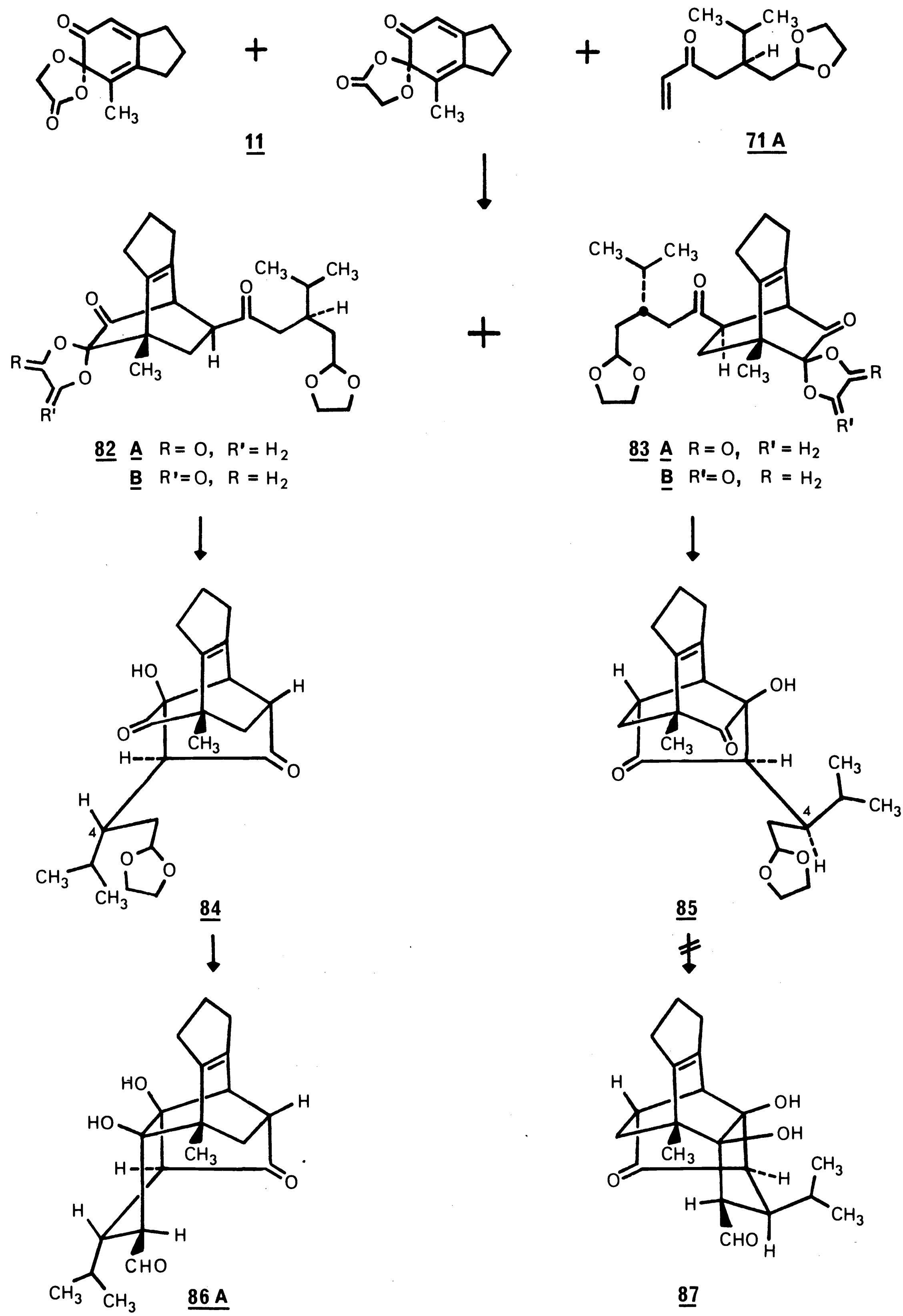


79

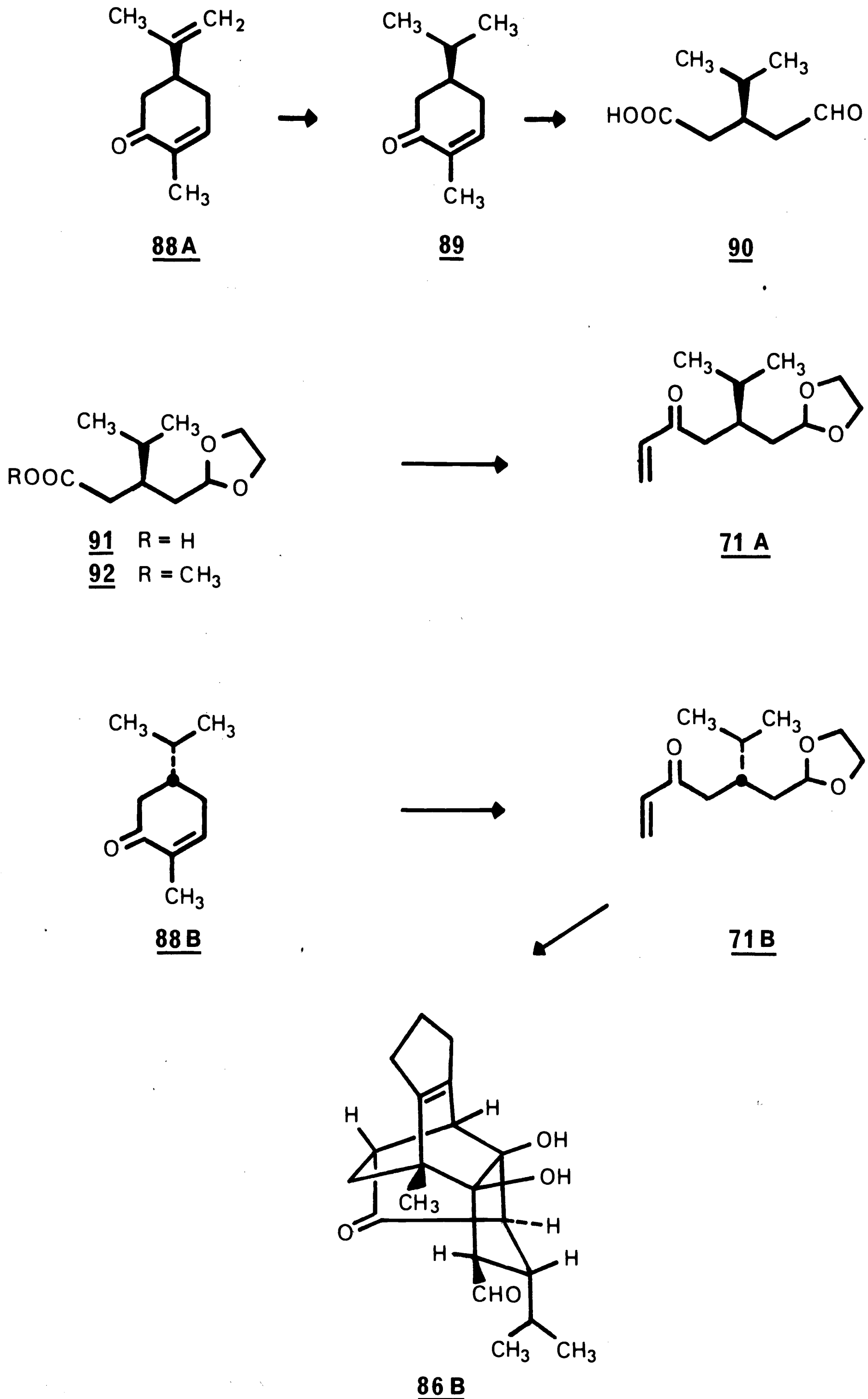


81 A R = AcO, R' = H
B R' = AcO, R = H

SCHEME 12



SCHEME 13



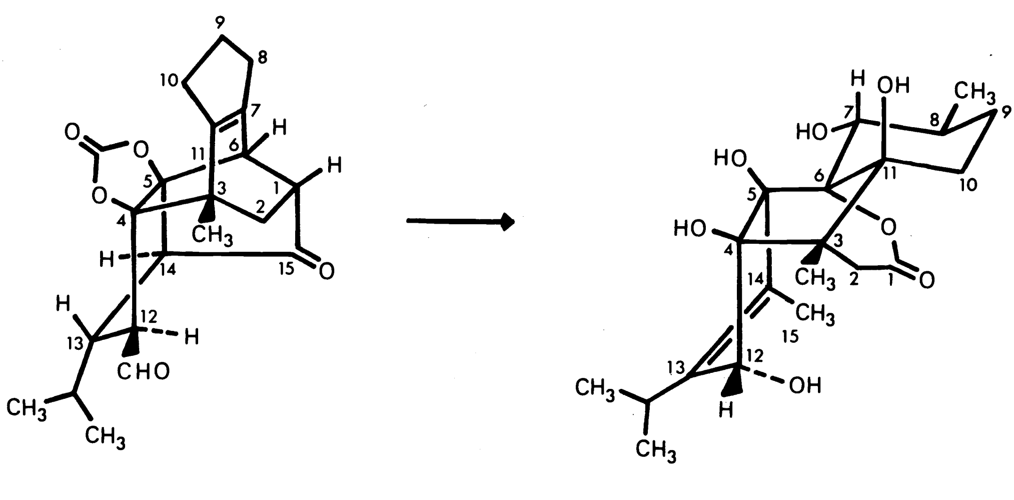
Using ℓ-carvone (88B) as starting material, the ℓ dienophile 71B ($[\alpha]_{578}$ = -0.6°) was obtained and its combination with diene 11 led to pure dihydroxyketoaldehyde 86B ($[\alpha]_{578}$ = -137.5°). Thus, the pentacyclic dihydroxyketoaldehyde was available in both optically active forms 86A and 86B. The absolute configuration of ryanodine is known (1) and it is illustrated by structure 1. The optically active form of the pentacyclic intermediate which corresponds to 1, 86A, was prepared in large quantity. In practice, it was easier to isolate the pentacyclic intermediate as the five-membered carbonate derivative, the overall yield of this product from diene 11 being 27%. Since the theoretical yield is only 50%, this represents 54% of the theoretical yield.

SYNTHETIC STUDIES TOWARDS ANHYDRORYANODOL

The synthesis of the optically active pentacyclic carbonate intermediate 93 (Scheme 14) was now complete. However, several operations had yet to be performed before this compound could be transformed into anhydroryanodol. These were: a) introduction of an oxygen atom between C-1 and C-15 to give a lactone ring or its equivalent, b) cleavage of that lactone ring or its equivalent, c) conversion of C-15 into a methyl group, d) oxidation to obtain a carbonyl function at C-1, e) introduction of an oxygen atom between C-6 and C-1 to give the lactone ring of anhydroryanodol, f) oxidative cleavage of the double bond between C-7 and C-11 and internal aldol condensation, g) introduction of a methyl group at C-8, h) reduction of the newly generated ketone function at C-7, i) introduction of a double bond between C-13 and C-14 and j) conversion of the aldehyde group at C-12 into an *endo* hydroxyl group. Appropriate reagents and reactions conditions had to be found to carry out these ten operations as well as the order in which these operations should be performed.

Three out of the ten operations, steps a, e, and f, could be considered the major ones. A variety of reagents and/or methods was available for each of the other transformations However, the key steps a and e might be difficult to realize because there were very few general methods to carry out such operations and it could be anticipated that these methods might simply not work in our series of compounds. Nevertheless, step f, the oxidative cleavage and the aldol condensation, being the lynchpin on which the overall synthetic scheme is based, was the most important one. This transformation had first to be verified and several experiments were carried out in this direction.

SCHEME 14



93 **Anhydroryanodol (3)**

Compound 93 was first converted (Scheme 15) into the dimethoxyacetal 94 (CH_3OH, $(CH_3O)_3CH$, H^+). Ozonolysis (CH_3OH; $(CH_3)_2S$) of 94 gave an 87% yield of a mixture of the isomeric aldol condensation products 95 (28%) and 96 (72%). If the same reaction was carried out in the presence of an equivalent of *p*-toluenesulfonic acid the proportion of the desired isomer 95 was raised to 70%. The ozonolysis of the dihydroxyacetal 97 which is obtained from the basic hydrolysis of 94 was next investigated. Oxidation of 97 would give a diketone which should exist primarily in the conformation 98, with internal hydrogen bonding between the carbonyl groups and the two tertiary hydroxyl groups stabilizing this conformation. It was therefore anticipated that 97 would afford the desired aldol product 99 in good yield. Although ozonolysis of 97 gave only the isomer 99, the yield was only 28% and several other products were observed in this reaction. This result was explained by the presence in 97 and 99 of a vicinal diol grouping which is known to be very sensitive to oxidative reagents. The structure of 99 was rigorously established by the formation of the orthoacetate aldehyde 100 ($HClO_4$, $(CH_3CO)_2O$; Na_2CO_3, H_2O). The monoacetate derivative 101 appeared to offer a good compromise for a satisfactory oxidative cleavage - aldol sequence. While one tertiary hydroxyl group remained to stabilize the desired conformer (98, H'=CH_3CO) for the aldol reaction, the resulting product should resist further oxidation because of the presence of the acetate group. 101 was prepared in 60% yield from the dihydroxyketoaldehye 92 ($(CH_3CO)_2O$, CH_3COONa) and upon ozonolysis gave the desired monoacetate 102 in 50% yield. Simply heating 102 in benzene under reflux in the presence of a catalytic amount of *p*-toluenesulfonic acid afforded the previously described orthoacetate 100 in 80% yield. The orthoacetate aldehyde 100 was then converted into the dimethoxyorthoacetate 103. Reduction of 103 with lithium tri-*t*-butoxyaluminium hydride afforded the equatorial alcohol 104 which was analyzed as its acetate derivative 105. This stereospecific reduction illustrated, as expected, that no difficulty should be encountered with step h.

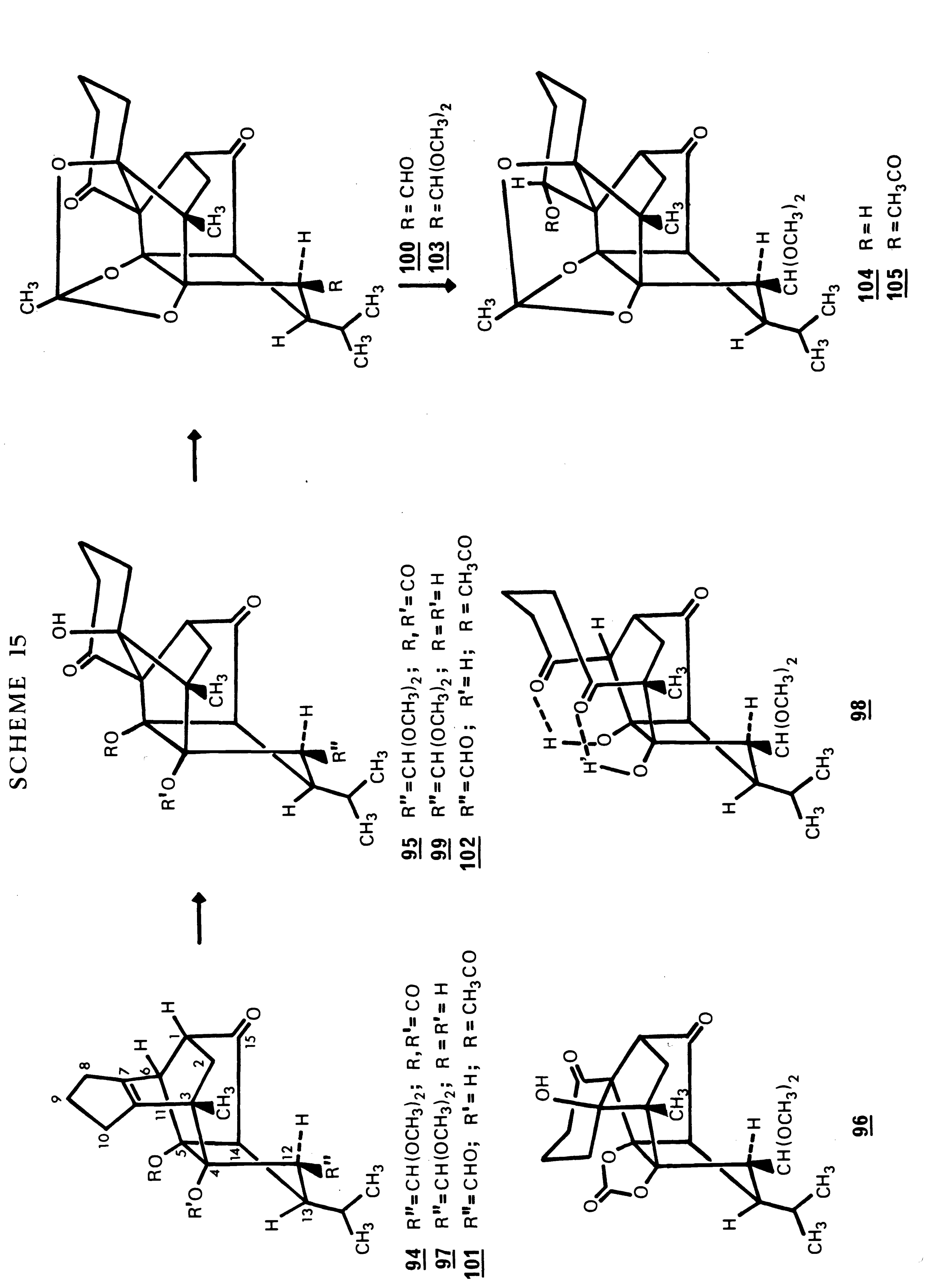
The preceding results showed that it was indeed possible to perform the oxidative cleavage and the desired aldol condensation on a pentacyclic system which contains ring A. However, it was necessary to be able to successfully execute step f stereospecifically and in high yield. Such a result could only be obtained on pentacyclic compounds into which the oxygen atom between C-1 and C-15 had previously been inserted (step a).

The introduction of an oxygen atom between C-1 and C-15 is an important operation and it is clear that it could be directly achieved by a Baeyer-Villiger oxidation reaction. Most reagents used gave the desired epoxylactone 106 (Scheme 16), but the isomeric lactone 107 was always present in significant quantity. However, the use of 40% peracetic acid gave 106 (85%) and 107 (15%) in excellent yield. Retroepoxidation (WCl_6, 2 BuLi in THF) (15) was carried out on the crude mixture of 106 and 107 and the crystalline olefin lactone 108 was obtained by chromatography in an overall yield of 75% from 94.

Ozonolysis of 108 (CH_3OH; $(CH_3)_2S$) gave the desired product 109 in 95% yield. Treatment of 109 with sodium hydride in anhydrous tetrahydrofuran yielded the hemi-orthocarbonate sodium salt 110 which was analyzed by infrared spectroscopy. Upon addition of acid, the salt 110 gave back the alcohol carbonate 109. The formation of 110 is a good proof that the aldol condensation had taken place in the desired direction.

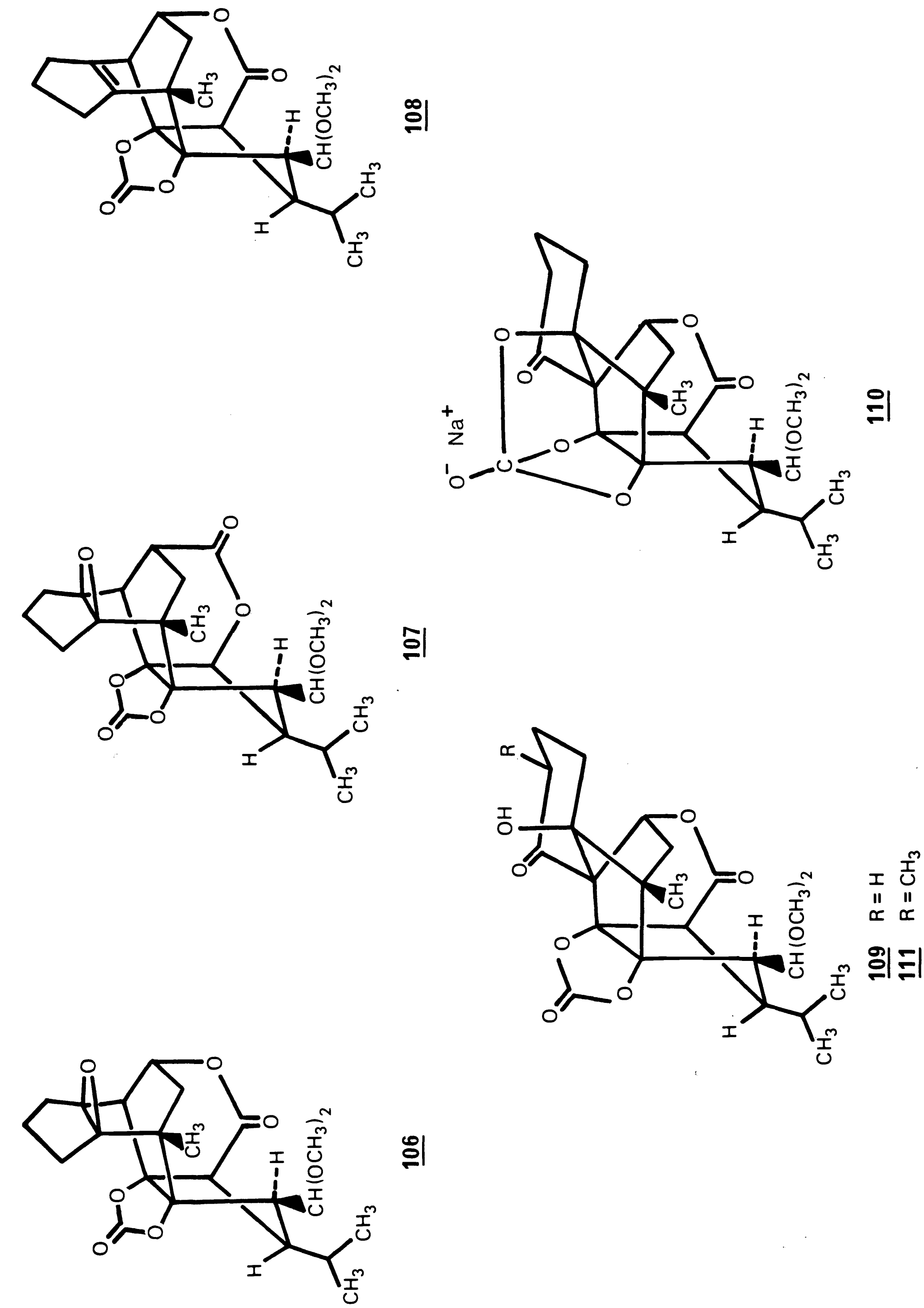
Using compound 109 as a model, it was possible to show that the introduction of a methyl group at C-8, step g, could be carried out without difficulty. Reaction of 109 with methyl formate gave the expected hydroxy-methylene derivative which was transformed into the thiobutyl enol ether derivative and reduced to yield the desired methyl derivative 111 (16).

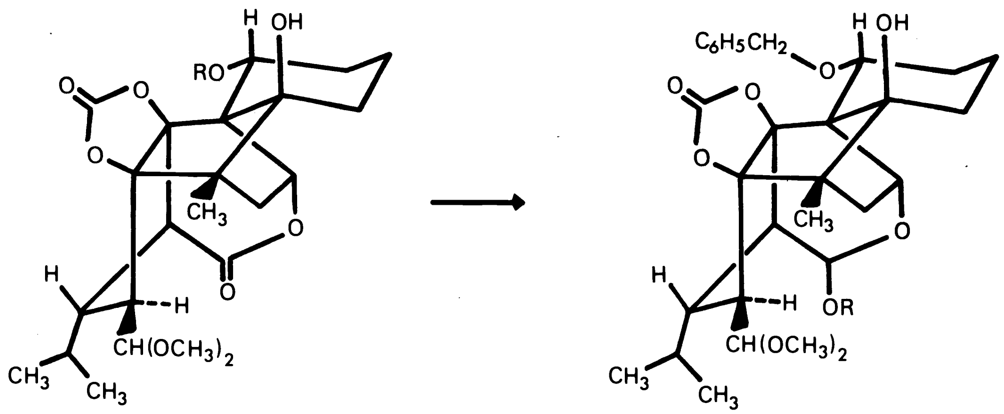
The ketone function of compound 109 was reduced ($NaBH_4$ in CH_3OH-THF) to give the equatorial alcohol 112 (Scheme 17) which was then protected by the formation of the benzyl ether 113 (NaH, $C_6H_5CH_2Br$ in THF). The next logical operation to be studied was step b, i.e., the cleavage of the lactone ring. Standard methods such as hydrolysis of the lactone ring or its reduction to the diol were not successful. Consequently, an attempt to solve this problem by a new strategy was undertaken. Lactone 113 was reduced (DIBAL in toluene) to give in good yield the lactol 114 which was further converted into the crystalline *p*-nitrobenzoate derivative 115 by reaction with *p*-nitrobenzoyl chloride and pyridine. It had been anticipated that this product, upon treatment with sodium hydride in anhydrous toluene, would form the orthocarbonate salt 116 which would then undergo a Grob type fragmentation (17) to yield the enol ether 117. This reaction was carried out and the product obtained had the expected spectroscopic properties for structure 117. It had been further hoped that on mild acid hydrolysis, the enol ether would be hydrolysed to give the hydroxy aldehyde 118 which could then undergo an aldol condensation to yield the aldehyde alcohol 119. However, when compound 117 was treated under acidic conditions (HCl in H_2O-THF), the desired product 119 was not observed, the lactol 114 being produced instead in a yield of 80%. This result could be explained if the carbonate carbonyl was first protonated, being the most basic group in 117, and then the reversed cyclization (See arrow in 117) occured immediately to give a carbonium ion which was then hydrated. Thus, in structure 117, the enol ether function would not behave normally, i.e., to undergo protonation of the double bond followed by hydration of the resulting carbonium ion. This rationalization was supported by the fact that treatment of 117 with glacial acetic acid gave a good yield of the lactol



SCHEME 15
94 R''=CH(OCH3)2; R,R'=CO
97 R''=CH(OCH3)2; R=R'=H
101 R''=CHO; R'=H; R=CH3CO
95 R''=CH(OCH3)2; R,R'=CO
99 R''=CH(OCH3)2; R=R'=H
102 R''=CHO; R'=H; R=CH3CO
100 R=CHO
103 R=CH(OCH3)2
104 R=H
105 R=CH3CO
96
98

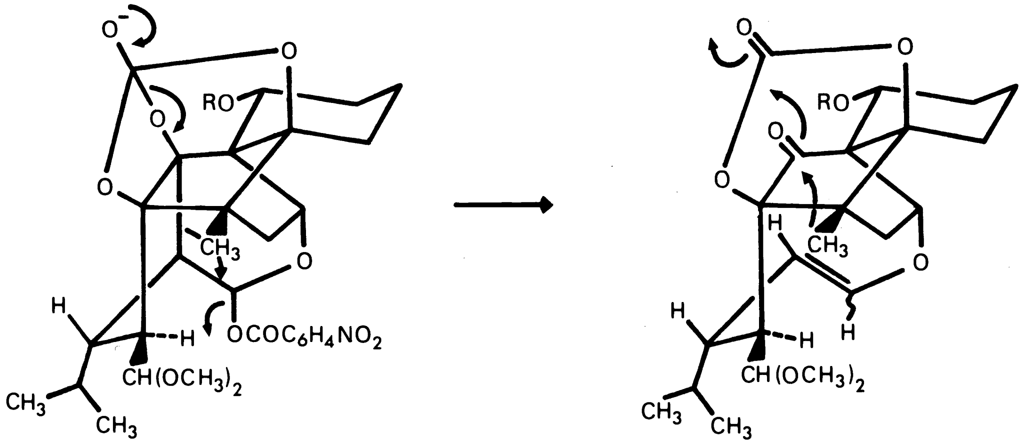
SCHEME 16





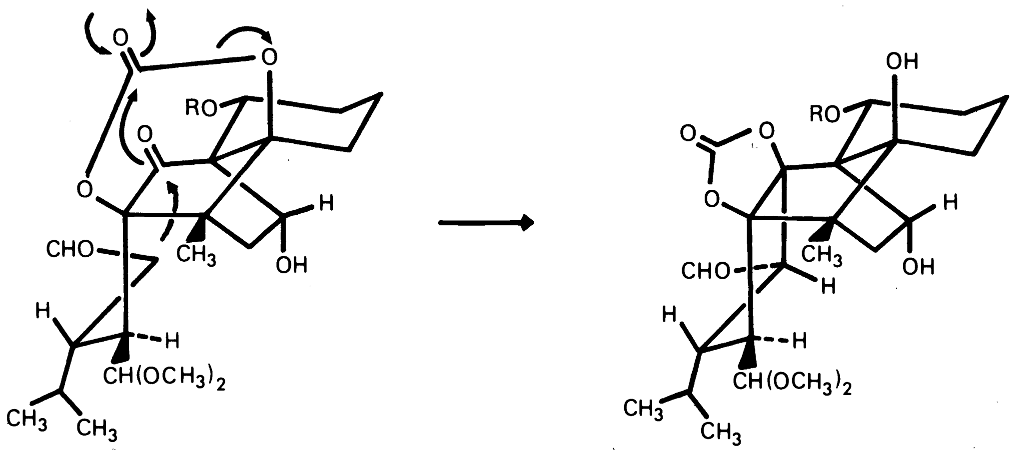
112 R = H
113 R = $C_6H_5CH_2$

114 R = H
115 R = p-$O_2NC_6H_4CO$
120 R = CH_3CO



116 R = $C_6H_5CH_2$

117 R = $C_6H_5CH_2$



118 R = $C_6H_5CH_2$

119 R = $C_6H_5CH_2$

SCHEME 17

acetate 120. An authentic sample of 120 was prepared by acetylation of 114 with acetic anhydride and pyridine.

It was concluded from this study that the olefin lactone 108 had to be one of the intermediates for the synthesis of anhydroryanodol. The product 109 resulting from the oxidation of 108 was, however, regarded only as a model study since no convenient method could be found to solve step b, i.e., the cleavage of the lactone ring. Studies were therefore carried out on the olefin lactone 108 to overcome this problem as well as that of the oxidation at C-1, so that the important step e, introduction of an oxygen atom between C-6 and C-1 could then be undertaken.

In our first series of experiments, the olefinic lactone 108 (Scheme 18) was converted into the ketoester 121 (80% yield) by: a) selective hydrolysis of the lactone ring with lithium hydroxide, b) esterification of the resulting hydroxy carboxylic salt with trimethyloxonium tetrafluoroborate (18) and c) oxidation of the secondary alcohol with the Collins' reagent (19). All attempts to carry out the Baeyer-Villiger reaction, step e, on the ketoester 121 failed. The epoxy ketoester 122 could be easily obtained but it could not be further transformed into the desired lactone. The poor reactivity of the ketone function of 122 towards the Baeyer-Villiger reaction is very likely due to severe steric hindrance caused by the presence of both the epoxide oxygen and the *endo* carbomethoxy groups. An attempt to epimerize the *endo* carbomethoxy group of 122 under basic conditions (DBN, DME) gave instead the conjugated ester 123. The formation of the oxime derivative of 121 was also not successful. Under mild conditions, the oxime isolated had the undesired structure 124, further indicating that the formation of the conjugated ester was a very facile process. Ozonolysis of 121 gave the expected hydroxy diketone 125 (80% yield) which was then selectively reduced ($NaBH_4$, 90%) to the dihydroxydiketone 126. Treatment of 126 with diazomethane yielded the methyl orthocarbonate 127 (80% yield). Again the Baeyer-Villiger oxidation reaction on 126 and 127 was not successful, no reaction being observed in each case. Similarly, attempts to form their oxime derivatives gave only starting material.

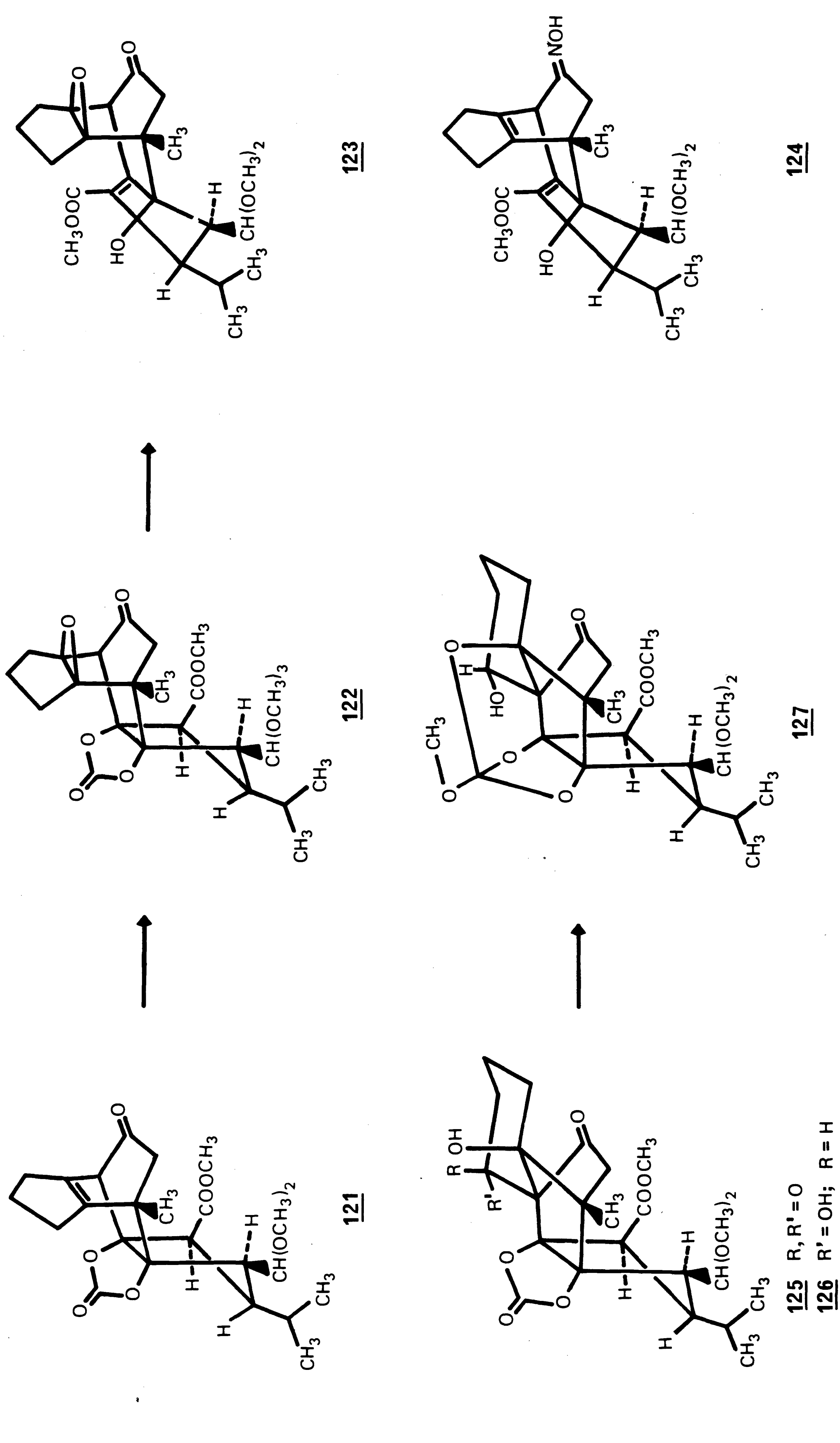
Convenient methods for steps b and d were available by this approach. The oxidative cleavage - aldol condensation, step f, could also be carried out and an interesting new method for the protection of the three tertiary hydroxyl groups had been discovered by the formation of the methyl orthocarbonate derivative 127. However, one of the key operations, the Baeyer-Villiger oxidation (step e), could not be achieved, the ketone function which should undergo this reaction in compounds such as 122 and 126 being simply too hindered.

Two different approaches were considered to solve the problem of step e: a) to use one of the encumbering groups to "build in" a transition state equivalent to a Baeyer-Villiger oxidation and b) to simply remove the hindering groups.

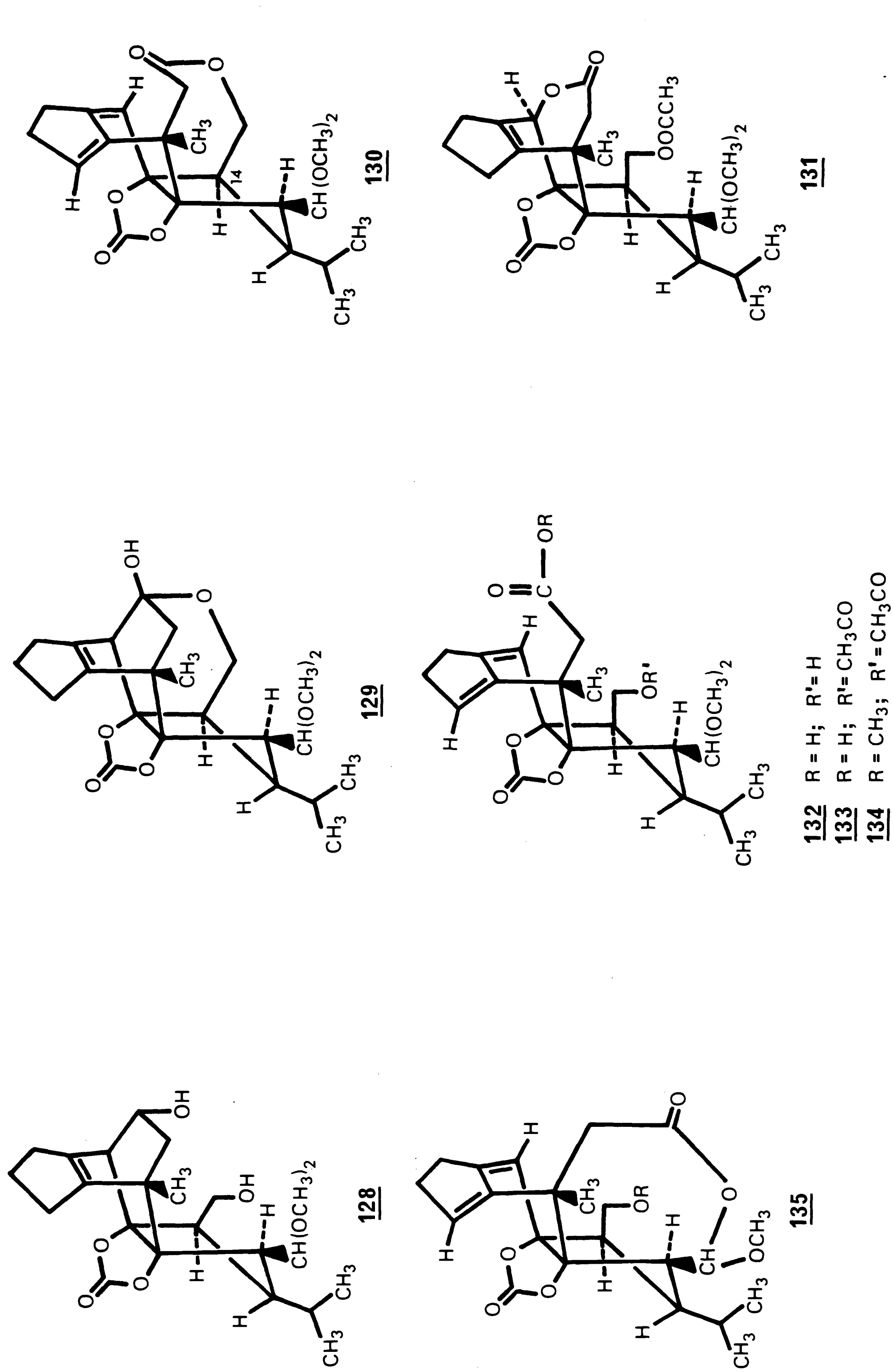
In the first approach (Scheme 19), the lactone olefin 108 was reduced ($LiBH_4$ in THF) to give the diol olefine 128. Oxidation of this diol with Jones reagent gave directly compound 129 in 80% yield. Thus, the secondary alcohol in 128 was preferentially oxidized and the remaining primary alcohol formed the hemiketal function with the resulting carbonyl group. Oxidation of hemi-ketal 129 was next investigated. Reaction of hemi-ketal 129 with ceric ammonium nitrate (20) yielded the diene lactone 130 in 80% yield. Consequently, the cleavage of the C_1-C_6 bond, half of step e, had been successfully achieved by using this new oxidative cleavage reaction. It remained to find a method to form the desired lactone ring (→131). Basic hydrolysis (LiOH in DME-H_2O) of 130 gave the corresponding hydroxy carboxylic acid 132 which was converted into the acetate carboxylic acid 133 by reaction with acetic anhydride and pyridine. 133 was further characterized as the methyl ester 134 which was obtained by reaction with diazomethane. It had been hoped that a treatment of the acetate carboxylic acid 133 with a strong acid such as *p*-toluenesulfonic in benzene would result in the formation of the desired lactone 131. However, the product formed under these conditions was the methoxylactone 135. This result indicated that the lactonization of the carboxylic acid with the enol ether, presumably obtained *in situ* by the elimination of methanol from the dimethoxy acetal protecting group, was a more facile process. It is in principle possible to avoid this undesired process either by changing the reaction conditions or by modifications of the dimethoxy acetal function into a more appropriate protecting group. However, we have not yet pursued this interesting approach further. One of the main reasons was the fact that the second route to solve step e (approach b) outlined below was also progressing well and became the preferred one.

In the second approach, we had arrived at the conclusion that the best manner to remove the steric hindrance caused by carbon-15 was to convert carbon-14 into an sp^2-hybridized carbon. The following reasons led us to select compound 136 as the next objective (Scheme 20). First, proper methods to complete ring A (steps c, i, and j) had to be developed for the first time; secondly, the cyclopentenone system should resist to reagents used in the Baeyer-Villiger reaction because the carbonyl group of this system is very hindered; and thirdly, the enone system should activate the other carbonyl group towards nucleophilic reagents. Indeed, it is plausible that the required intermediate for the Baeyer-Villiger oxidation (136 → 138) would be formed more easily because it would exist in the trapped form 137 (21).

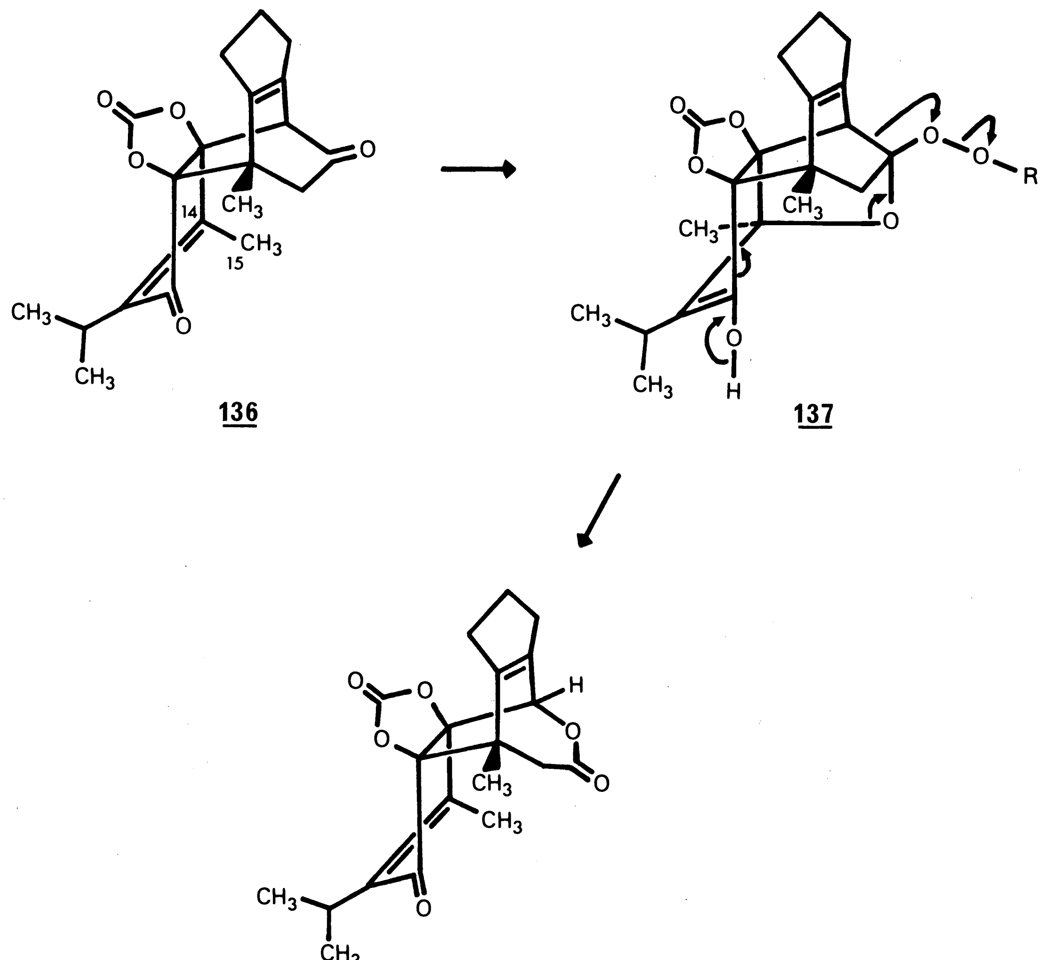
SCHEME 18



SCHEME 19



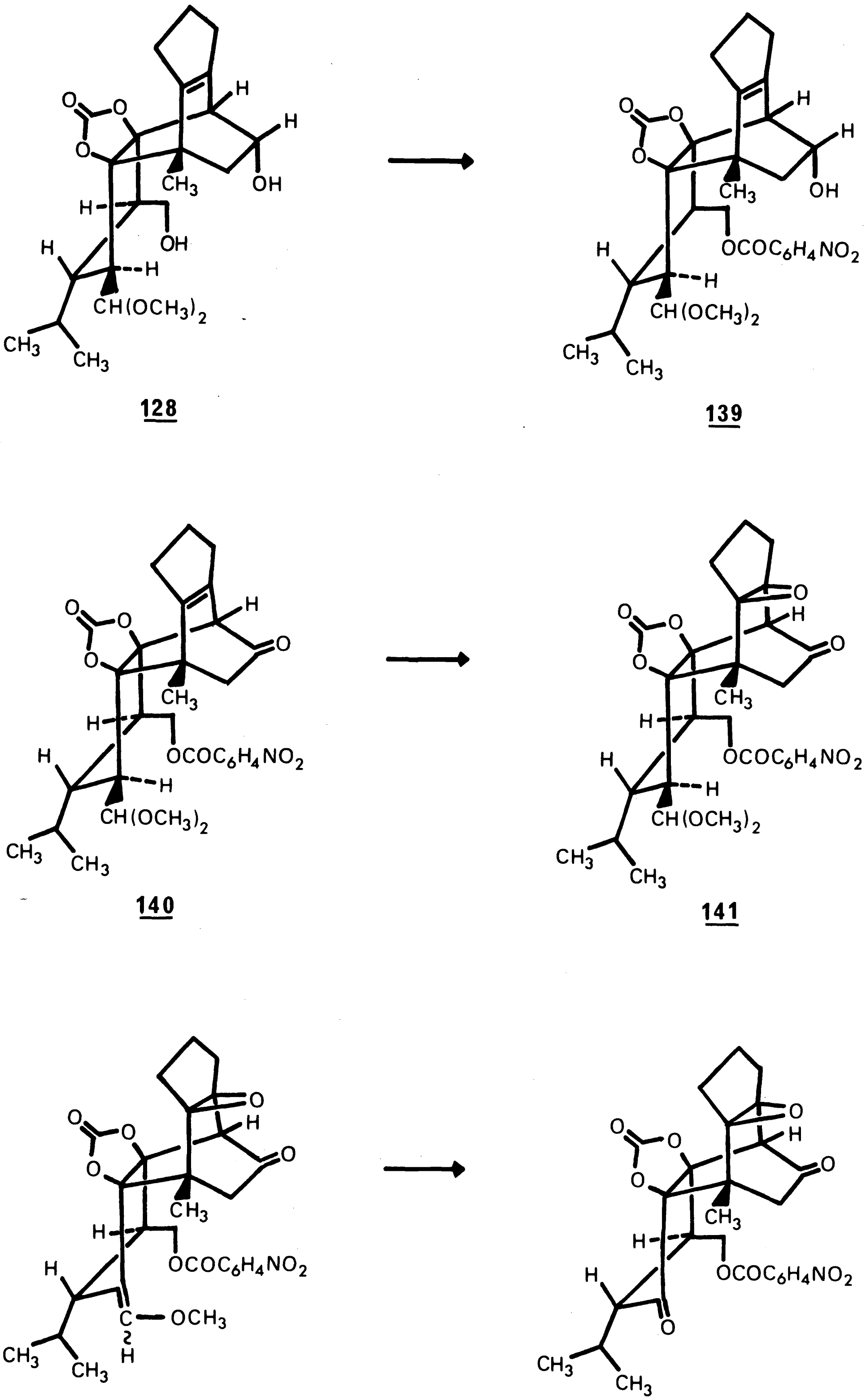
SCHEME 20



136 137 138

The diol olefin 128, obtained from the lactone olefin 108 (Scheme 18), was treated with *p*-nitrobenzoyl chloride in pyridine to give the mono-*p*-nitrobenzoate 139 (Scheme 21). Oxidation of 139 with Collins' reagent yielded the *p*-nitrobenzoate ketone 140 (95% yield from 128). The epoxide 141 was obtained by the reaction of *m*-chloroperbenzoic acid with the *p*-nitrobenzoate ketone 140. When 141 was heated to reflux in benzene containing a catalytic amount of *p*-toluenesulfonic acid, there was obtained a mixture of the isomeric enol ethers 142 which were smoothly transformed into the norketone 143 (70% yield from 140) by reaction with ozone (CH_2Cl_2; $(CH_3)_2S$). Reaction of 143 with an excess of diazomethane in ether at room temperature for a few hours gave the endocyclic enol ether 144 (Scheme 22). This smooth reaction indicates that the apparently unactivated five-membered ketone function undergoes enolization very easily. The formation of the enol acetate derivative 145 under mild conditions (CH_3COONa, $(CH_3CO)_2O$, 85°, 30 min) further illustrates this facile enolization of 143. Reaction of enol ether 144 with 1,5-diazabicyclo-[4.3.0]non-5-ene (DBN) in refluxing benzene afforded the dienol ether epoxide 146 (70% yield from 143). Under similar conditions, the enol acetate derivative 145 gave directly the enone epoxide 147 (50% yield from 143). The absence of dienol acetate 148 was rationalized by the premise that DBN should be basic enough to remove a proton from the methyl group of the acetate function, generating an anion which could then cleave to ketene and the enolate anion of the enone 147. Retroepoxidation of 146 (WCl_6, 2 BuLi in THF) gave the olefin 149 which afforded the desired olefin enone 136 upon reaction with boron trifluoride etherate. Thus, pentacyclic systems containing ring A of anhydroryanodol have been obtained by this relatively simple and direct route. Attempts to carry out a Baeyer-Villiger reaction or its equivalent, step e, on compounds 146, 147, 149, and 136 are presently under investigation.

SCHEME 21

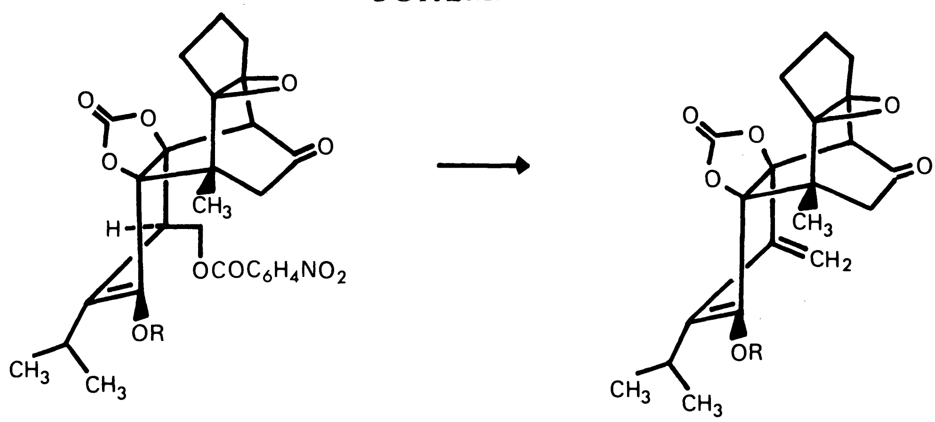


128 → 139

140 → 141

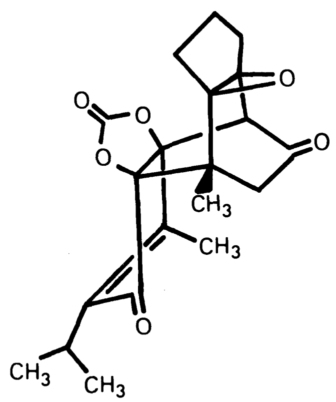
142 → 143

SCHEME 22

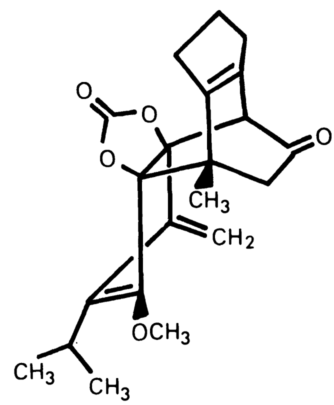


144 R = CH_3
145 R = CH_3CO

146 R = CH_3
148 R = CH_3CO



147



149

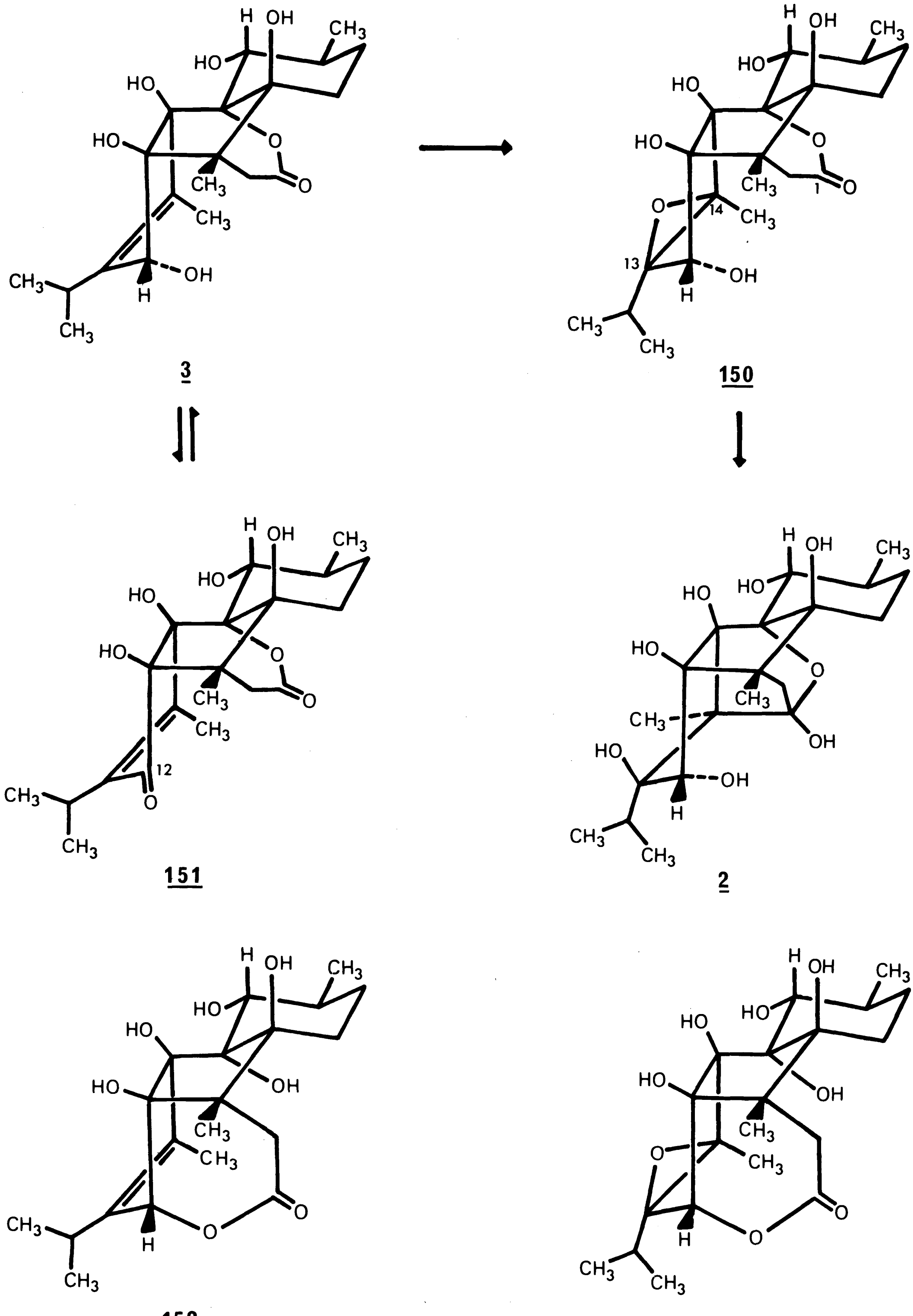
CONVERSION OF ANHYDRORYANODOL (3) INTO RYANODOL (2)

It has already been described in the introduction that our plan for the total synthesis was to first succeed the synthesis of anhydroryanodol (3) and then convert it into ryanodol (2). Since anhydroryanodol (3) is readily available from ryanodine (1), this desired reconversion could be concurrently undertaken, utilizing products derived from the natural source. Ryanodine (1) was therefore isolated and converted into ryanodol (2) and anhydroryanodol (3) (Note a).

Although different approaches were considered to effect the reconversion of ryanodol (2) from anhydroryanodol (3) (Scheme 23), we were especially attracted by an approach which involves, in principle, one single intermediate, the β-epoxide of anhydroryanodol (150). This simple route was very appealing for the following reasons: a) the specific synthesis of the epoxide 150 should present no difficulty because of the presence of the two tertiary hydroxyl groups at C-4 and C-5 which should direct the epoxidation on the β-face of the molecule which is also the less hindered side; b) it was also anticipated that chemical reduction of the epoxide of anhydroryanodol (150) would afford ryanodol (2) directly. It was hoped that under these conditions, the carbonyl group of the lactone function of 150 would first give a radical-anion (or a dianion), making C-1 nucleophilic enough to attack the epoxide ring at C-14, thus generating at the same time the C-13 tertiary hydroxyl group of ryanodol. Examination of molecular models further suggested that competitive opening of the epoxide ring at C-13 would be improbable due to severe steric hindrance in the resulting transition state. Our confidence in the above scheme was also based on several reports of successful reductive cyclizations (22).

Note a. We would like to express our appreciation to Professor K. Wiesner for a generous gift of powdered Ryania stems.

SCHEME 23



Direct epoxidation of anhydroryanodol (3) with *m*-chloroperbenzoic acid to give the desired epoxide 150 was unsuccessful, yielding instead the enone 151 which could also be prepared by the oxidation of 3 with manganese dioxide. The allylic alcohol had therefore to be protected before the epoxidation reaction could take place, and several experiments were carried out on anhydroryanodol (3) with this protection in mind. Although several products were obtained which were properly characterized, a simple direct solution was not readily found. In the course of this investigation, however, it was observed that the five-membered ketone function in enone 151 (or a derivative of 151) could be reduced in good yield with sodium borohydride to give anhydroryanodol (3) (or a derivative). This result indicated that the reduction of a carbonyl group at C-12 would be a simple method to complete step j (*vide supra*) in the synthesis of anhydroryanodol (3).

A simple solution to the synthesis of 150 became available when it was found that the lactone function present in anhydroryanodol (3) could be utilized to internally protect the allylic alcohol function. Basic treatment (NaOH 1N in THF) of 3 followed by acidification with acetic acid gave 3 (40%) and epianhydroryanodol (152) (60%) which were separated by chromatography. Epoxidation of 152 with *m*-chloroperbenzoic acid ($CHCl_3$, K_2CO_3, 72 h) gave the epoxide of epianhydroryanodol (153) in 55% yield. The yield was increased to 75% by using trifluoroperacetic acid in dichloroethane in the presence of sodium bicarbonate (45 min). It was also later found that anhydroryanodol (3), upon reaction with trifluoroperacetic acid, could be directly converted into the epoxide of epianhydroryanodol (153) in 75% yield. Thus, under these conditions 3 must first be isomerised to 152 before undergoing the epoxidation reaction.

Basic treatment (NaOH-1N in THF) of 153 followed by acidification with acetic acid gave a mixture of 150 (40%) and 153 (60%). Treatment of this mixture with lithium in liquid ammonia and tetrahydrofuran afforded ryanodol (2) in 35% yield. Under the same conditions, pure epoxide 153 also gave ryanodol (2) (30% yield), indicating that 153 must be partly epimerized to 150 prior to the reductive cyclization process. The product obtained was shown to be identical to an authentic sample of ryanodol (2) by melting point, mixed melting point, thin layer chromatography, and by proton and C-13 nuclear magnetic resonance spectroscopy. The synthetic material also exhibited the same chemical reactivity as authentic ryanodol. The yield of this reductive cyclization has yet to be optimized and the conversion of ryanodol (2) into ryanodine (1) remains to be investigated.

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