The total synthesis of (+)-ryanodol. Part II. Model studies for rings B and C of (+)-anhydroryanodol. Preparation of a key pentacyclic intermediate

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This paper is dedicated to the memory of Professor Karel Wiesner

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This paper reports several model studies that were necessary for the rational conception of a simple four-step synthesis (**6** + (*S*)-**74** → **81***a*–*b* → **83** ↠ **87** → **89**) (Scheme 11) of the carbonate derivative **89** of the optically active pentacyclic dihydroxy ketoaldehyde **87**, an important key intermediate for the synthesis of (+)-ryanodol (**5**). The optically active vinyl ketone (*S*)-**74** that was used as starting material was prepared in four steps from *d*-carvone ((*S*)-**94**) (Scheme 13). The preparation of the other starting material, the *o*-spirolactone dienone **6**, was reported in Part I.

Key words: strategy, synthesis, ryanodol, key intermediate, diterpene.

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On rapporte plusieurs études modèles qui ont été nécessaires à la conception rationnelle d'une synthèse simple en quatre étapes (**6** + (*S*)-**74** → **81***a*–*b* → **83** ↠ **87** → **89**) (Schéma 11) d'un intermédiaire-clé important dans la synthèse du (+)-ryanodol (**5**) : le dérivé carbonate **89** du dihydroxy cétoaldéhyde pentacyclique **87** optiquement actif. La vinylcétone (*S*)-**74** optiquement active fut synthétisée à partir de la *d*-carvone ((*S*)-**94**) (Schéma 13). La synthèse de l'autre produit de départ, l'*o*-spirolactone diénone **6**, est rapportée dans la Partie I.

Mots clés : stratégie, synthèse, ryanodol, intermédiaire-clé, diterpène.

Our general strategy (1–3) for the construction of ryanodol (**5**) via anhydroryanodol (**4**) is summarized in Scheme 1. In this approach, the macrobicyclic diketone **2**, which can be obtained by oxidation of an appropriate precursor such as **1**, would undergo a transannular aldol condensation to produce the tricyclic hydroxyketone **3**. This compound would then be converted into ryanodol **5** via anhydroryanodol **4**.

This general strategy for the synthesis of ryanodol, which is based on an analysis of the skeleton of anhydroryanodol, is explained in detail in Part I (4). Our method for the preparation of a tricyclic compound such as **1**, which contains a bicyclo[2.2.2]octene unit, was also reported in that paper. More specifically, we have shown that the Diels–Alder reaction of methyl vinyl ketone with *o*-spirolactone dienone **6** gives a ≃1:1 mixture of adducts **7***a* and **7***b*, which are then converted under basic conditions into a single product, the tetracyclic hydroxydiketone **8**.

In this paper, we wish to report our studies demonstrating that the key transformation **1** → **2** → **3** can be realized in the laboratory. This work was carried out (1, 5) using the tricyclic hydroxydiketone **8** as a starting point. We also wish to report our detailed analysis and experimental studies (6–8), which led to the development of a very convenient strategy for the synthesis of a pentacyclic key intermediate that contains ring A of anhydroryanodol.

In the key transformation **1** → **2** → **3**, the oxidative cleavage of the tetrasubstituted double bond should produce two carbonyl groups that are expected to undergo a transannular aldol condensation; it was therefore desirable to avoid the presence of other carbonyl groups in the same molecule (*vide infra*). Consequently, the two carbonyl groups in the tetracyclic hydroxydiketone **8** were first modified before attempting the desired key transformation. Compound **8** was converted (Ac_2O, pyridine) into the diketoacetate **9** (Scheme 2), which was then selectively ketalized under standard conditions to give monoketal acetate **10**. It was then found that the reduction of **10** with lithium borohydride gave mainly the *trans* diol **11** together with a very small quantity of the *cis* diol **12**. When the reduction was carried out with lithium in liquid ammonia, the *cis* diol **12** was obtained as the major isomer. The configuration of the *cis* ketal diol **12** was rigorously established by its transformation into the five-membered carbonate **13** upon reaction with phosgene.

The *trans* ketal diol **11**, which was easily purified by crystallization, was selected for the cleavage study and it was first converted into ketal monoacetate **14** by acetylation (Ac_2O, pyridine). The diketone resulting from ozonolysis of ketal monoacetate **14** can exist in two different conformations, **15** and **16** (Scheme 3), which can each undergo a transannular aldol condensation yielding, respectively, the aldol diastereoisomers **17** and **18**. The ozonolysis of **14** 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

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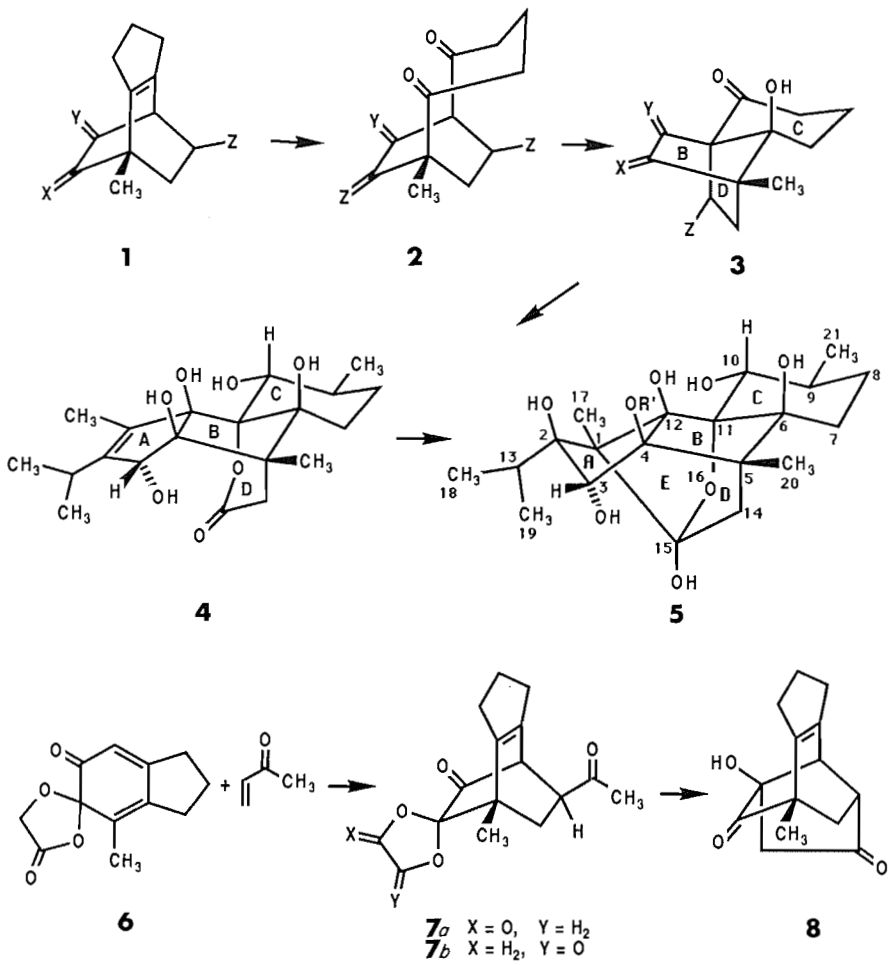
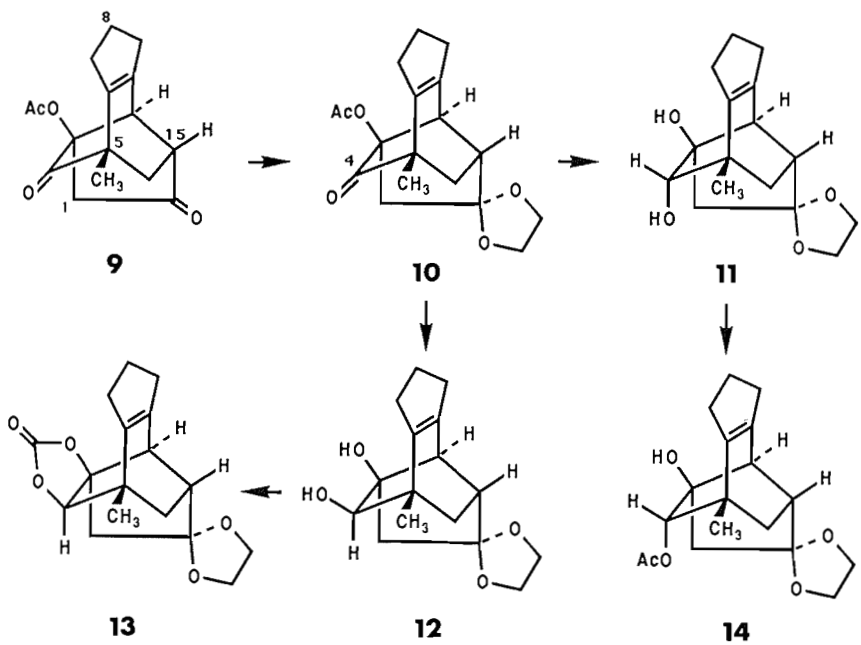
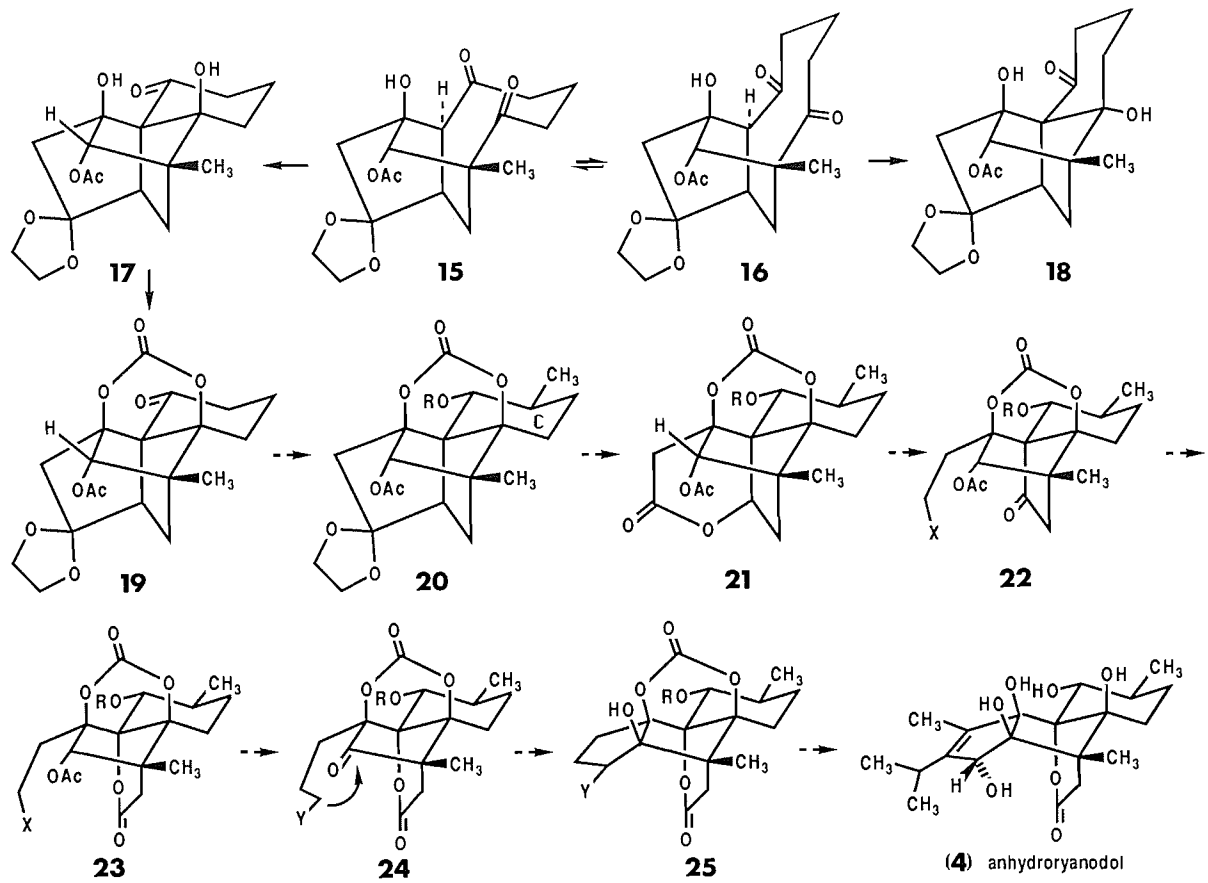


SCHEME 1



SCHEME 2



SCHEME 3

operations gave the dihydroxy ketoacetate **17** as the major product along with the isomer **18** (ratio 7:3), which were separated. The structure of **17** was firmly established by its reaction with phosgene, which afforded the crystalline six-membered carbonate derivative **19**.

The successful transformation of **14** into **17** proved that our basic synthetic strategy to build rings B and C of anhydroryanodol from the oxidative cleavage and the subsequent transannular aldol condensation of a tricyclic precursor containing a bicyclo[2.2.2]octene precursor was valid (1).

At this stage, we had to make a choice between two completely opposite directions for our future work. Either we accept compound **17** as a valuable key intermediate, or we consider the transformation **15** → **17** as a model experiment.

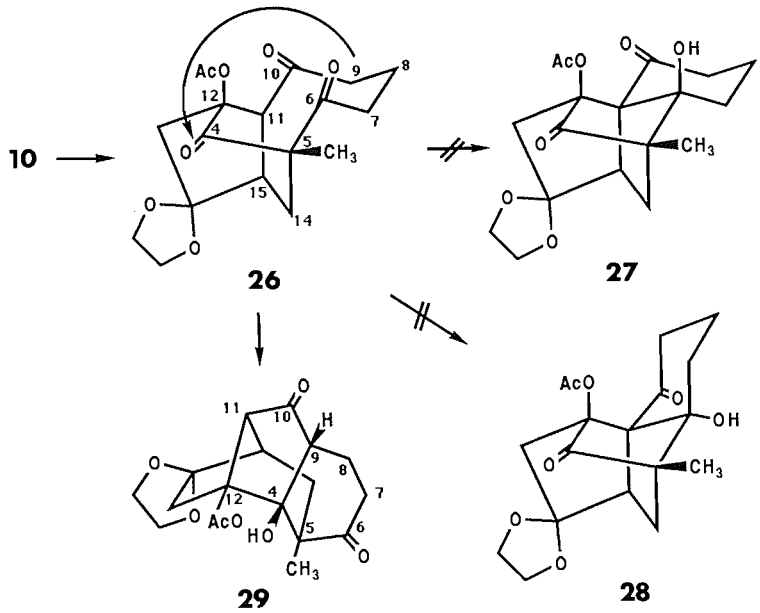
For instance, in the first case, one can imagine that after completing ring C, i.e., **19** → **20**, the removal of the ketal protecting group followed by Baeyer–Villiger oxidation would produce lactone **21**. This product could then be converted into ketone **22** (X to be determined), which in principle can also be oxidized via Baeyer–Villiger reaction to lactone **23**. Appropriate homologation of the side chain CH_2CH_2X and conversion of the secondary acetate at C_4[2] into a carbonyl group would then give an intermediate **24**, which would allow the formation of ring A, i.e., **25**. Anhydroryanodol would then be obtained from the tetracyclic intermediate **25**.

The proposed conversion **19** → **25** → anhydroryanodol, although certainly not easy to accomplish, is essentially a series of functional group transformations, which is quite attractive for producing a relatively simple synthesis of racemic anhydroryanodol. However, we deliberately refused to consider this route further because we felt that we would be missing a great opportunity to make a contribution to the development of knowledge in synthetic strategy.

One of the first priorities in doing organic synthesis is to discover simple schemes that avoid unnecessary steps. The preceding route already involves four extra steps, reduction of the carbonyl group at C_4, protection of the resulting secondary alcohol as an acetate (**10** → **11** → **14**), and, later on, removal of the acetate protecting group followed by reoxidation to a carbonyl group (**23** → **24**). These operations can in principle be eliminated by following one of the two alternative routes: (a) to simply carry out the ozonolysis and the transannular aldol condensation on a compound bearing a carbonyl group at C_4, i.e., **9** or **10**; (b) to transform the carbonyl group at C_4 into a hydroxyl group while forming the desired C_3—C_4 bond prior to the oxidative cleavage of the tetrasubstituted olefin. The second alternative meant that ring A would be constructed first. Both approaches were attractive because advantage was taken of the fact that our synthetic scheme generates intermediates that have the right level of oxidation at C_4 to produce ring A directly.

The first alternative route was tested with monoketal ketoacetate **10**. The ozonolysis of **10** was carried out and the expected

[2]The chemical abstract name for ryanodol: [3*S*-(3α,4β,4a*S*,6α,6aα,7α,8β,8aα,8bβ,9β,9aα] - hexahydro - 3,6a,9 - trimethyl - 7 - (1 - methyl-ethyl)-6,9-methanobenzo[1,2]pentaleno[1,6-*be*]furan-4,6,-7,8a,8b,9a(6a*H*,9*H*)-heptol) (Chem. Abstr. **101**, 6830CS (1984)). To facilitate the discussion on the synthetic strategy, the numbering system of ryanodol is used throughout, regardless of the skeleton considered.



SCHEME 4

triketone **26** (Scheme 4) was isolated in good yield as crystals. Heating triketone **26** in pyridine produced a tetracyclic transannular aldol product that, on the basis of its nmr spectra, was found to have the undesired structure **29**. A close examination of a molecular model of triketone **26** revealed that in addition to the two aldol condensations that we have previously discussed, and which lead to **27** and **28**, a third aldol condensation is possible between C_4 and C_9, yielding the isomeric aldol product **29**. Compound **29** is presumably produced preferentially because enolization at C_9 might be favored over that at C_{11}. Since **29** appears less strained than the bridged isomers **27** and **28**, which each contain a bicyclo[2.2.1]heptane unit, the former might also be preferentially formed because of a thermodynamically controlled aldol process. This result meant that the oxidative cleavage of the olefin cannot be performed in the presence of a carbonyl group at C_4, and the first alternative pathway was thus eliminated from further considerations.

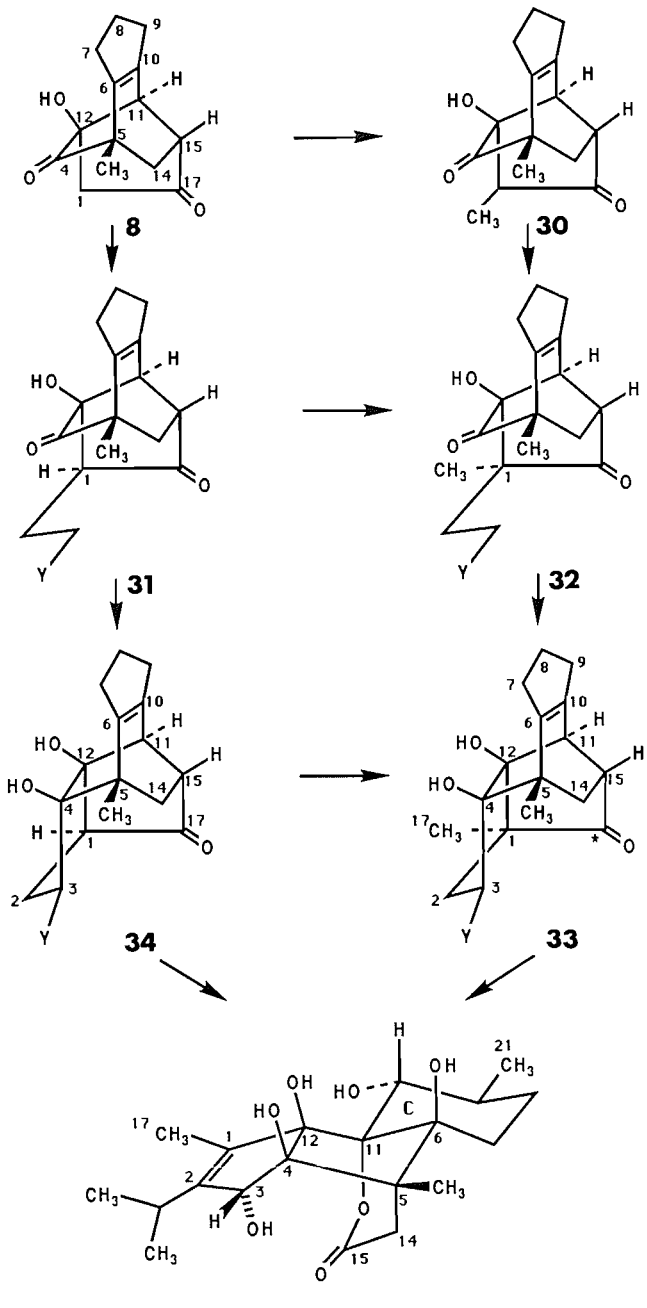
The second alternative route, which invokes the possibility of synthesizing ring A prior to the oxidative cleavage of the olefin, was then analysed in detail.

There are in principle two different approaches to building ring A from hydroxydiketone **8**. The first one is described by the route **8** → **32** → **33** → **4** (Scheme 5) and the second one by the route **8** → **31** → **34** → **4**. The first approach is interesting because there was a good possibility of generating the desired chirality at C_1 in **32** in a relatively simple manner. Indeed, with a dissymmetrical molecule like **8**, it is logical to expect a high degree of stereochemical control in the alkylation at C_1 and, depending on the course of this process, intermediate **32** would be produced from **8** from either of the monoalkylated products **30** or **31**. Once intermediate **32** is obtained, its conversion to pentacyclic intermediate **33** should be straightforward. The attractiveness of this route is the apparently facile construction of **33**. However, there might be a serious difficulty in this route because this compound has an extra carbon atom. By comparing the numbering system of anhydroryanodol (**4**) with that of **33**, it becomes clear that the carbonyl group (C*=O) in **33** is extra and will have to be removed eventually to produce anhydroryanodol. This means that some degradation chemistry will have to take place at a later stage. This appeared neither easy nor elegant; this route was not considered further on this basis, and also because the second approach appeared more promising.

The second approach, **8** → **31** → **34** → **4**, is interesting because the tetracyclic intermediate **34** does not have an extra carbon atom; the carbonyl group that corresponds to C_{17} can be eventually transformed into the methyl group of ring A of anhydroryanodol. The success of this route depends on the ease of controlling the configuration of the side chain at C_1 in **31**, which must be inside to produce ring A (cf. **31** → **34**). This approach was also quite interesting because there was a possibility of eliminating the alkylation step **8** → **31**. For instance, there was the possibility of producing intermediate **31** in two operations from the *o*-spirolactone dienone **6** and a methyl vinyl ketone derivative where the methyl group was replaced by a CH_2—CH_2—CH_2—Y group.

The next step was therefore to verify if substituted vinyl ketone could be used successfully in the Diels–Alder reaction and if the stereochemistry of the side chain at C_1 could be controlled.

The first study was carried out using ethyl vinyl ketone. The reaction of *o*-spirolactone dienone **6** with ethyl vinyl ketone proceeded as expected, producing a ≃1:1 mixture of adducts **35***a* and **35***b* isomeric at the spirolactone ring (Scheme 6). Treatment of crude **35***a* and **35***b* with sodium hydroxide in aqueous tetrahydrofuran gave a good yield (>60%) of two isomeric products in a 2:1 ratio; these were separated and identified as the *endo* and the *exo* epimers **36** and **37**. The assignment of configuration was carried out by ^1H nmr spectroscopy on their corresponding acetate derivatives **38** and **39**. In the major epimer **38**, H_1 appears as an octuplet (J = 2.3 and 7.2 Hz), whereas in the minor isomer **39**, H_1 appears as a quadruplet (J = 7.6 Hz). The additional coupling found in the major isomer **38** is the result of a W coupling between H_1 and H_{15}; such a coupling is not possible for the *exo* isomer **39**. This assignment was made unambiguous by observing the loss of W coupling in **38** on replacing the hydrogen at C_{15} by a deuterium atom. Monodeuterated **38** at C_{15} was obtained by repeating the epimerization – aldol condensation sequence **35***a*–*b* → **36** + **37**



SCHEME 5

using deuterated water as solvent. This produced **36** and **37** having two deuterium atoms (at C_1 and C_{15}). Treatment of dideuterated **36** and **37** under basic conditions with H_2O gave **36** and **37** monodeuterated at C_{15} only, which upon acetylation and chromatography yielded the corresponding C_{15} monodeuterated acetates **38** and **39**.

This study demonstrated that substituted vinyl ketones could be used with success. More importantly, it also showed that the most stable epimer at C_1 had the *endo* configuration. This last result was not expected and came as a surprise.[3] It had, however, a very favorable consequence. It meant that there was no need to imagine a special device or strategy for the control of the *endo* stereochemistry at C_1, and a synthesis of a pentacyclic intermediate such as **34** via an intermediate like **31** could be readily envisaged.

The ketal vinyl ketone **44** (Scheme 7) was studied next (7). It was prepared from ethyl acetoacetate by a standard route via the intermediates **40–43**. The reaction of dienophile **44** with *o*-spirolactone dienone **6** proceeded well to give a ≃1:1 mixture of **45***a* and **45***b* that, after treatment with aqueous base followed by acidification, gave the tetracyclic triketone **46** in an impressive yield of over 95%. Acetylation of **46** with acetic anhydride and pyridine gave a diacetate, which on treatment with aqueous sodium carbonate produced the acetate derivative **47**.

We were hoping that the methyl ketone side chain in **46** could be used to induce the formation of ring A through an internal aldol condensation. However, all our attempts in this direction were unsuccessful. This is presumably due to the fact that compound **47** is too reactive and easily undergoes other reactions. For instance, treatment of **47** with anhydrous methanol containing *p*-toluenesulfonic acid provided mainly the *cis* enedione methyl ester **49**. This transformation can be explained by the addition of methanol to the five-membered ketone group, producing intermediate **48**, which undergoes on acid-catalyzed Grob type fragmentation (9). The *endo* methyl ketone side chain in **46** is responsible for the formation of the *cis* geometry of the enedione **49**. On heating at 150°C, *cis* enedione **49** was quantitatively converted into the more stable *trans* enedione **50**. When triketone alcohol **46** was treated with water under acidic conditions, the five-membered lactone **51** was isolated. Treatment of **51** with potassium *tert*-butoxide in *tert*-butanol furnished the *trans* enedione carboxylic acid **52**, which was transformed into the corresponding *trans* enedione methyl ester **50** by reaction with diazomethane. The formation of **51** must first take place via the addition of water at C_{17} followed by a fragmentation similar to that described by **47** → **48** → **49**, producing *in situ* the *cis* enedione carboxylic acid **53**, which underwent an intramolecular Michael addition to yield the five-membered lactone **51**. In the following step, it is anticipated that the basic elimination would produce directly the more stable *trans* enedione carboxylic acid **52**.

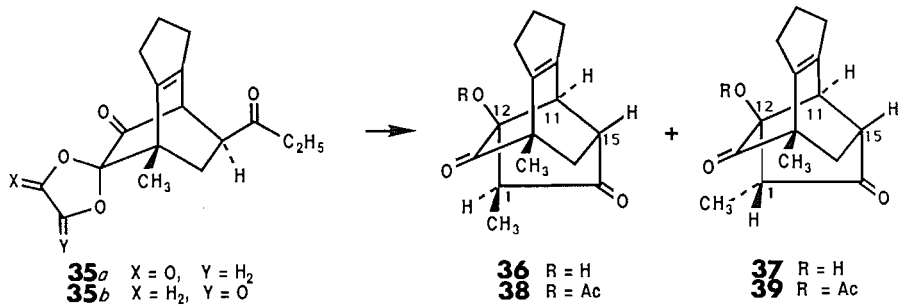
In conclusion, this study did not prove to be successful in providing a synthetic route for the construction of ring A, but it provided a rigorous chemical proof that compounds of type **31** are definitely more stable in the *endo* configuration.

We also learned from this study that the functional group of the side chain should be at a more remote position than C_2 in order to induce the formation of ring A while preventing fragmentation as previously observed. This left two possibilities, a functional group either at C_3 or linked to C_3.

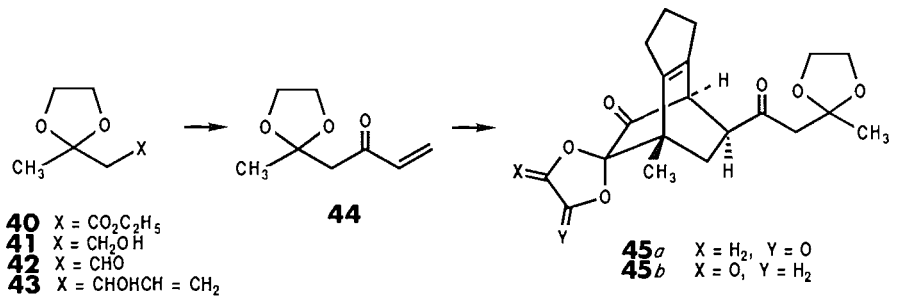
An example of the second possibility is the vinyl ketone **58** (Scheme 8), which possesses a masked aldehyde linked to C_3. Compound **58** was prepared in three steps (6). Reaction of dihydropyran with 2,2-dimethylpropanediol gave the acetal alcohol **54**, which upon oxidation with Jones reagent gave the crystalline carboxylic acid acetal **55**. Treatment of the lithium salt of **55** with vinyllithium gave the vinyl ketone acetal **58**. In large-scale preparation, it was found more convenient to prepare vinyl ketone **58** via the intermediates **56** and **57**.

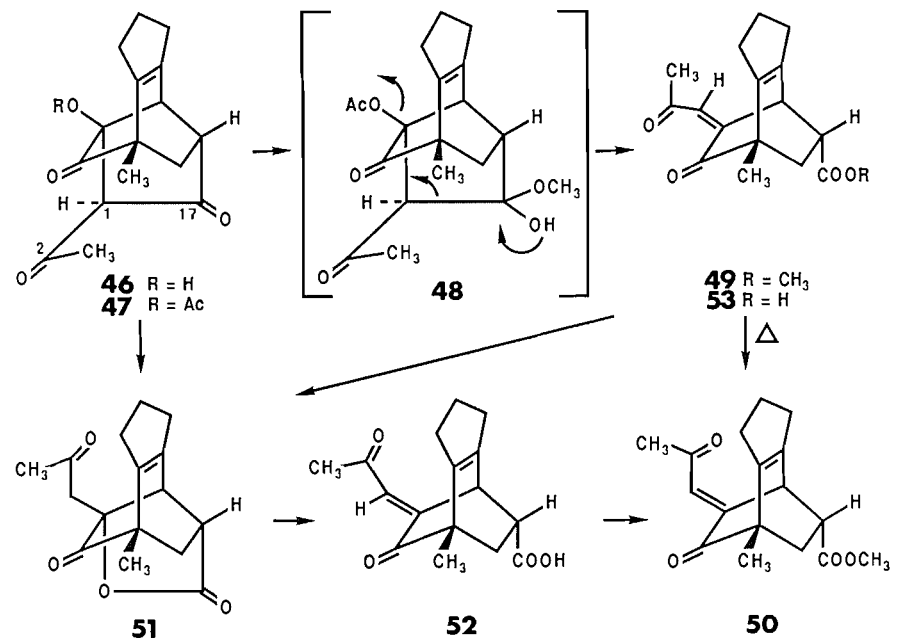
Diels–Alder reaction of **58** with *o*-spirolactone dienone **6** gave a quantitative yield of adducts **59***a* and **59***b* in a ≃1:1 ratio. This mixture was then treated under the now "usual" basic conditions to furnish the crystalline tetracyclic *endo* epimer **60** in 70% yield. The next step for the construction of ring A

[3]After the facts, it is, however, relatively easy to rationalize this result by an examination of molecular models of **38** and **39**: the methyl group appears to be more severely crowded in **39** (cf. steric interaction between CH_3 and H_{11}) than in **38**.



SCHEME 6



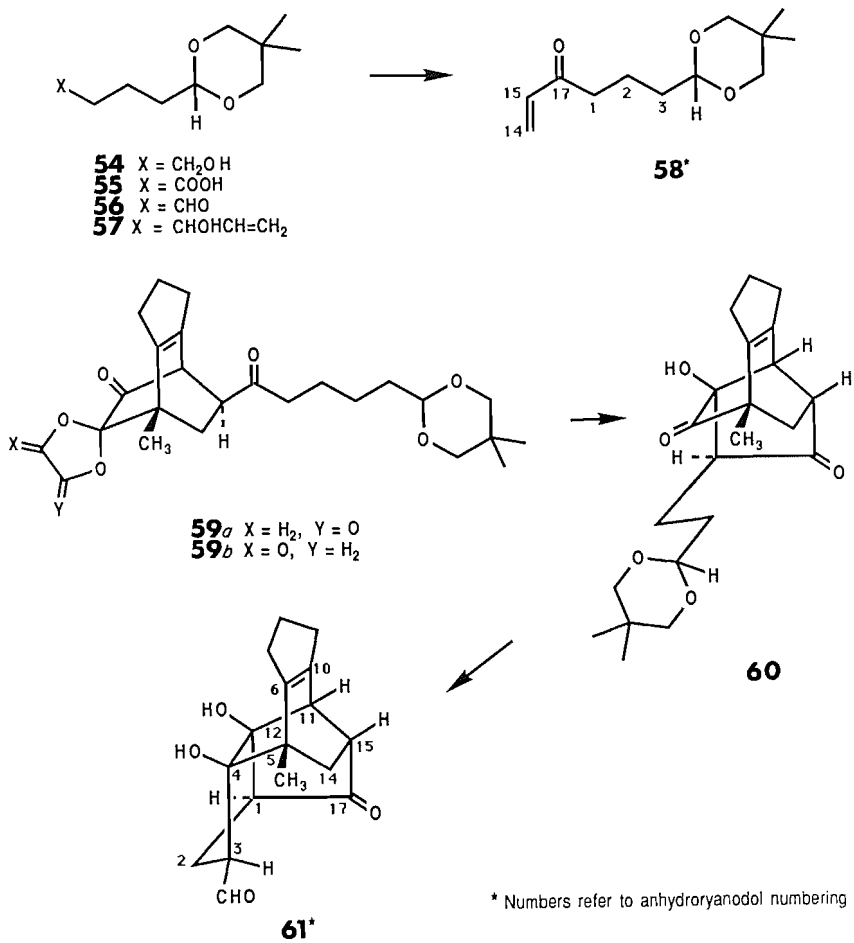


SCHEME 7

consisted of the deprotection of the aldehyde function to verify if the anticipated intramolecular aldol condensation would take place. When compound **60** was heated to reflux in a mixture of acetone and 3 M hydrochloric acid, hydrolysis and aldol condensation took place in a single operation, yielding directly the crystalline pentacyclic dihydroxyketone aldehyde **61**. However, the yield was only 25% and this was attributed mainly to the vigorous acidic conditions needed for the acetal hydrolysis.[4] Nevertheless, we had in hand an exceptionally short and simple synthesis of a pentacyclic intermediate containing ring A of anhydroryanodol. Indeed, the three steps, **58** + **6** → **59***a*–*b* → **60** → **61**, required very simple experimental conditions.

It was decided to regard this work as a model study essentially for two reasons. First, the acetal function of the dienophile had to be modified in order to be hydrolyzed under milder conditions. Second, there was also the possibility of taking further advantage of the dienophile. If a compound like **61** were accepted as an intermediate, the subsequent introduction of the isopropyl group had to be considered at a later stage. However, our strategy provided us with the opportunity of simplifying this task by pre-introducing this isopropyl group in the dienophile. We also retained the possibility of having a functional group

[4]A model study indicated that 2-alkyl-5,5-dimethyl-1,3-dioxanes require strong acidic conditions (>3 M HCl) for hydrolysis, and under such conditions compound **61** is not very stable.



SCHEME 8

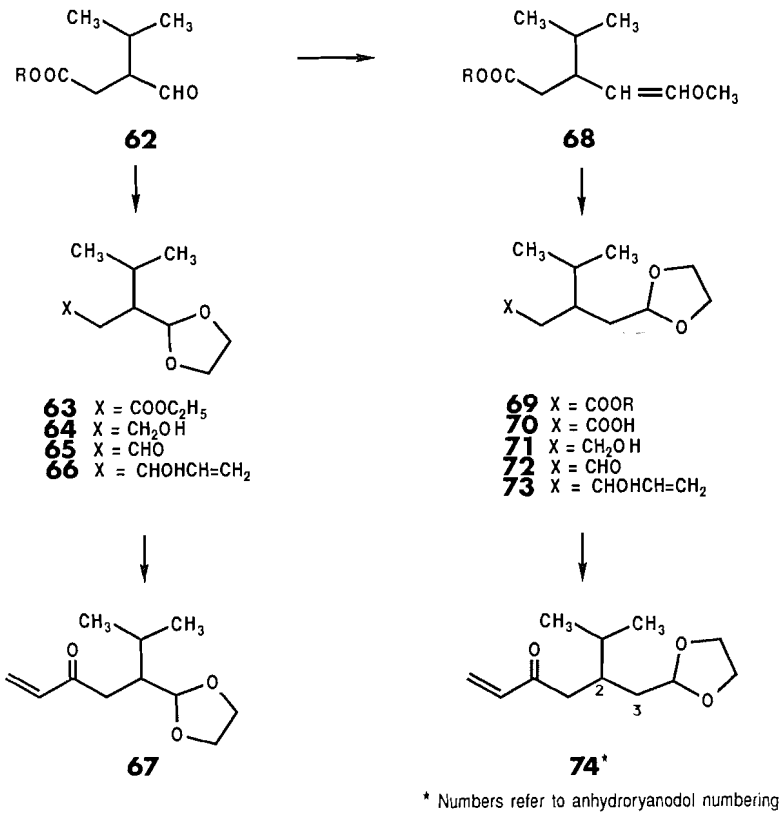
directly at C_3 or attached to C_3, and on that basis it was decided to study the dienophiles **67** and **74** (Scheme 9).

The racemic dienophiles **67** and **74** were (6) prepared from the same intermediate, the aldehyde ester **62**. Compound **62** was obtained from the condensation of the eneamine derived from diisobutylamine and isovaleraldehyde (10) with ethyl bromoacetate. Acetalization of **62** with ethylene glycol gave the acetal ester **63**, which was converted into the dienophile **67** via the intermediates **64–66** using standard conditions. Using methoxymethyl triphenylphosphorane as a reagent, the aldehyde **62** underwent a Wittig reaction to give a mixture of the *trans* and the *cis* (ratio 70:30) enol ether **68**, which can be separated by chromatography. Treatment of the isomeric mixture of enol ether **68** with ethylene glycol (PTSA, benzene) gave the homologated acetal ester **69** (R = CH_2CH_3). Basic hydrolysis of ester **69** gave the corresponding carboxylic acid **70**, which on reaction with 2 moles of vinyllithium furnished the vinyl ketone dienophile **74** having an isopropyl group at C_2 and an acetal group attached to C_3. Dienophile **74** was more conveniently prepared in large scale via the alternative route **69** → **71** → **72** → **73** → **74**.

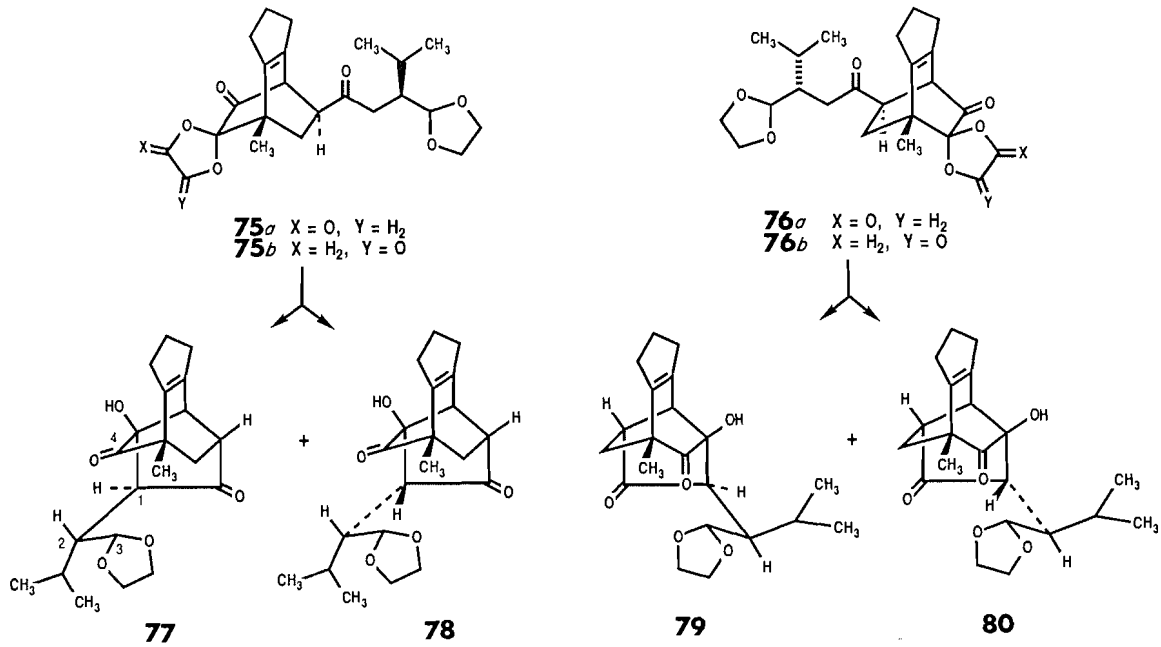
The Diels–Alder reactions of **67** and **74** were next investigated. In both dienophiles, there is a chiral center and this will lead to the formation of diastereoisomers isomeric at C_2 and at the spirolactone moiety. For instance, the condensation of racemic dienophile **67** with *o*-spirolactone dienone **6** is expected to produce a mixture of four racemic diastereoisomers, i.e., 50% of **75***a* and **75***b* in a ≃1:1 ratio and 50% of **76***a* and **76***b* also in a ≃1:1 ratio (Scheme 10). These relative proportions are due to the fact that the chiral center at C_2, which carries the isopropyl group, is far from the vinyl ketone and it should not influence the ratio of isomers **75** and **76**. Also, our previous Diels–Alder studies have shown that the *o*-spirolactone moiety of the dienophile **6** has essentially no influence on the relative formation of the *a* and *b* spirolactone isomers in the Diels–Alder adducts. This mixture of four adducts should be convertible into a mixture of four racemic aldol condensation products **77–80**, which are diastereoisomeric at C_1 and C_2. Indeed, isomers **75***a* and **75***b* can each give a mixture of **77** and **78** whereas isomers **76***a* and **76***b* can each give a mixture of **79** and **80**. However, since the *endo* epimers are expected to predominate over the *exo* epimers, it is expected that the *endo* epimers **77** and **79** should be formed predominantly and with approximately equal ease.

The Diels–Alder reaction of vinyl ketone **67** with *o*-spirolactone dienone **6** was carried out and gave the expected mixture of **75***a–b* and **76***a–b* as indicated by ^{1}H nmr spectroscopy. Treatment of this mixture under basic conditions gave the expected mixture of aldol products **77–80** from which one isomer was obtained pure, by a simple crystallization, in 35% yield. This crystalline product has either the *endo* structure **77** or **79**. The next step in this investigation was the determination of the orientation of the isopropyl group in the crystalline product. This would then be followed by the hydrolysis of the acetal functions at C_3 and attempts to induce the formation of the desired C_3—C_4 bond via a reductive cyclization process involving the C_3-aldehyde function and the C_4-carbonyl group.

There was no doubt a greater chance of success in pursuing



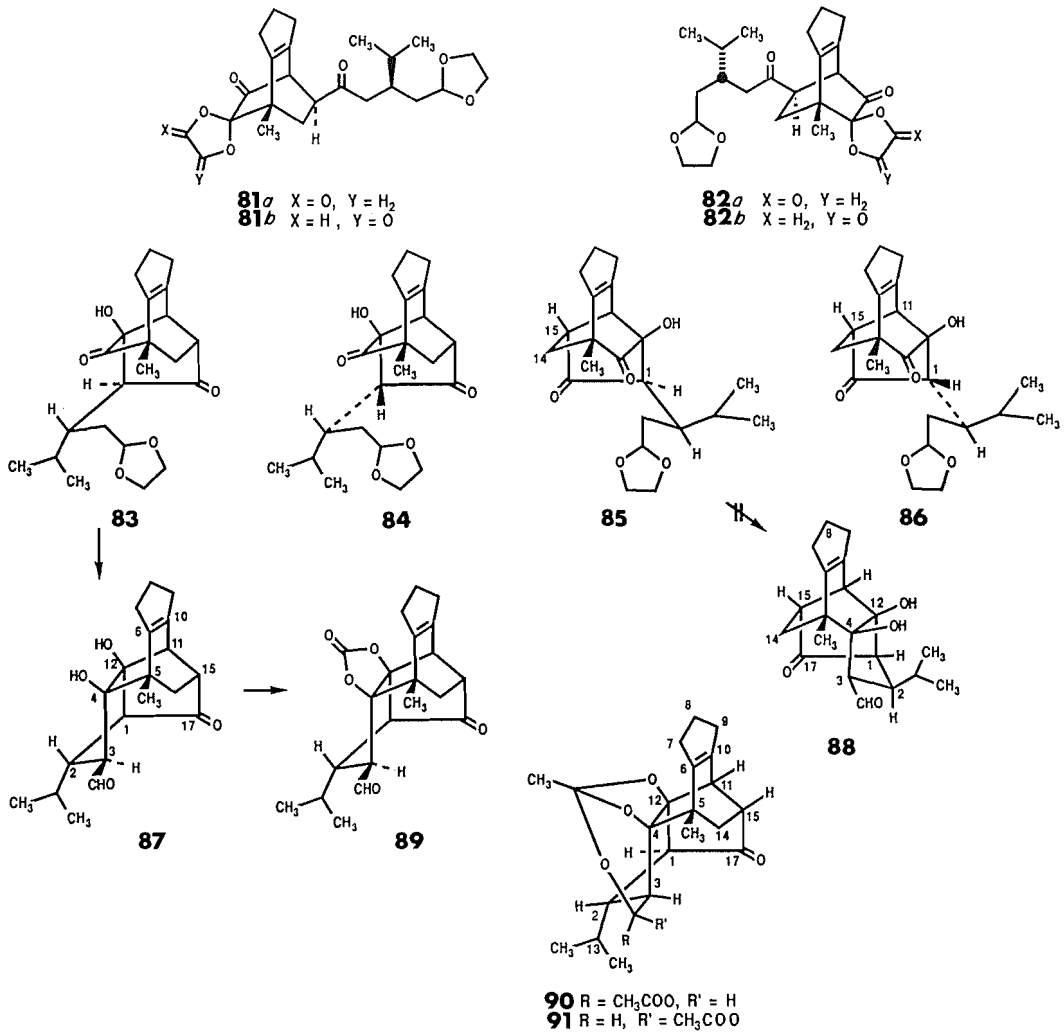
SCHEME 9



SCHEME 10

this route, but it was not investigated further because a concurrent study with the homologated dienophile **74** provided a very simple access to a pentacyclic system containing ring A. The strategy followed was essentially the same as that previously described in Scheme 8, except for the fact that the new dienophile i.e., **74**, had an isopropyl group, and a dioxolane rather than a dioxane acetal.

o-Spirolactone dienone **6** was reacted with racemic dienophile **74** to produce a quantitative yield of racemic adducts **81***a–b* and **82***a–b* (Scheme 11). Treatment of this crude mixture with sodium hydroxide in aqueous tetrahydrofuran gave a mixture of the four racemic diastereoisomers **83–86**. This mixture was heated in aqueous acetic acid and then treated with sodium hydroxide in aqueous tetrahydrofuran. This gave the racemic



SCHEME 11

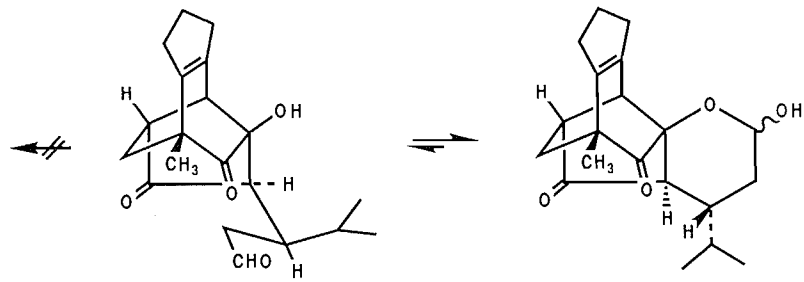
pentacyclic dihydroxyketone aldehyde **87**, which was isolated by crystallization in 23% yield from *o*-spirolactone dienone **6**. On reaction with phosgene, compound **87** gave the corresponding five-membered carbonate derivative **89**. On reaction with acetic anhydride and *p*-toluenesulfonic acid, compound **87** gave the two epimeric orthoester derivatives **90** and **91**, which could be separated by chromatography.

The relative orientation of the isopropyl group was determined by examining the ^{1}H nmr spectra of orthoester derivatives **90** and **91**, which have an almost completely rigid conformation (7). This assignment is due to the fact that in both compounds, H_1 appears as a doublet of doublets (J = 6 and 2 Hz). Molecular models show that the dihedral angle between H_1 and H_2 is near 30° in derivatives **90** and **91** and this explains the J value of 6 Hz. If these derivatives had a configuration for the isopropyl group opposite to that shown in structures **90** and **91** (cf. **88**), the dihedral angle between H_1 and H_2 would be near 90°, and the J value would have been much smaller than 6 Hz. The additional coupling of 2 Hz is due to the occurrence of W coupling H_1 and H_{15}. This overall assignment was confirmed by the synthesis of derivatives **90** and **91** having a deuterium atom at C_{15}. In those monodeuterated compounds, H_{11} and H_1 appear as a singlet and a doublet (J = 6 Hz) respectively.

The preparation of **90** and **91** monodeuterated at C_{15} was carried out by the technique previously described for deuterium incorporation in compounds **8** (4), **36**, and **37**. Starting with the mixture **81–82**, the aldol condensation was repeated using deuterated water; this produced a mixture of **83–86** bis-deuterated at C_1 and C_{15}. This mixture was then treated under basic conditions using unlabelled water to produce a mixture of **83–86** monodeuterated at C_{15}. This mixture was resubmitted under the acidic and basic conditions previously described to produce monodeuterated **87**, which was then converted into **90** and **91** having each one deuterium at C_{15}.

An extremely simple, four-step synthesis (**74** + **6** → **81–82** → **83–86** ↠ **87**) of a pentacyclic intermediate containing the isopropyl side chain of ring A was in hand. This intermediate, **87**, also had the required hydroxyl groups at C_4 and C_{12}, the tertiary methyl group at C_5, and the tetrasubstituted olefin between C_6 and C_{10}. It had two additional functional groups, the aldehyde at C_3 and the carbonyl at C_{17}, both of which are essential for the completion of rings A and D of anhydroryanodol.

Thus we had arrived at a very interesting point in our investigation. We decided that the pentacyclic compound **87** should be considered seriously as a real intermediate for our synthesis. Yet, further analysis revealed that we could take additional advantage of our dienophile **74**! This analysis started by examining in more detail the chemistry that is taking place in the course of the formation of the pentacyclic intermediate **87**. We



SCHEME 12

were interested in understanding why the other isomer **88** was not isolated. For instance, was it due to the fact that **87** crystallizes more readily than **88** or because only the former is being formed in the second aldol condensation process?

The tetracyclic diastereoisomeric mixture **83**–**86** was purified by chromatography (7). Isomers **83** and **85** were isolated pure and isomers **84** and **86** were obtained as a mixture from which isomer **86** could be isolated pure by crystallization. The relative configuration of the four isomers could be established by ^{1}H nmr spectroscopy and by the following reactions and chemical correlations. Equilibration[5] under basic conditions indicated that **83** and **84** are epimeric at C_1 and, since the former is the most stable epimer, **83** and **84** must have, respectively, the *endo* and the *exo* configuration. Similarly, equilibration showed that **85** and **86** are epimeric at C_1 and, since the former isomer is more stable, it has the *endo* orientation. Interestingly, when isomer **83** was submitted to the acidic and basic conditions necessary for the formation of the pentacyclic system, compound **87** was isolated in essentially quantitative yield. On the other hand, when compound **85** (or **86**) was submitted to the same reaction conditions, a complex mixture of products was formed, from which we did not succeed in isolating the anticipated pentacyclic isomer **88**. These experiments determined the relative configuration of the isopropyl group in isomers **83** and **85** since the configuration of this group has been established in compound **87** (*vide supra*). They also demonstrated that the specific formation of **87** is due to the fact that the aldehyde intermediate derived from **83** undergoes a quantitative internal aldol condensation, whereas that from **85**, under the same conditions, does not.

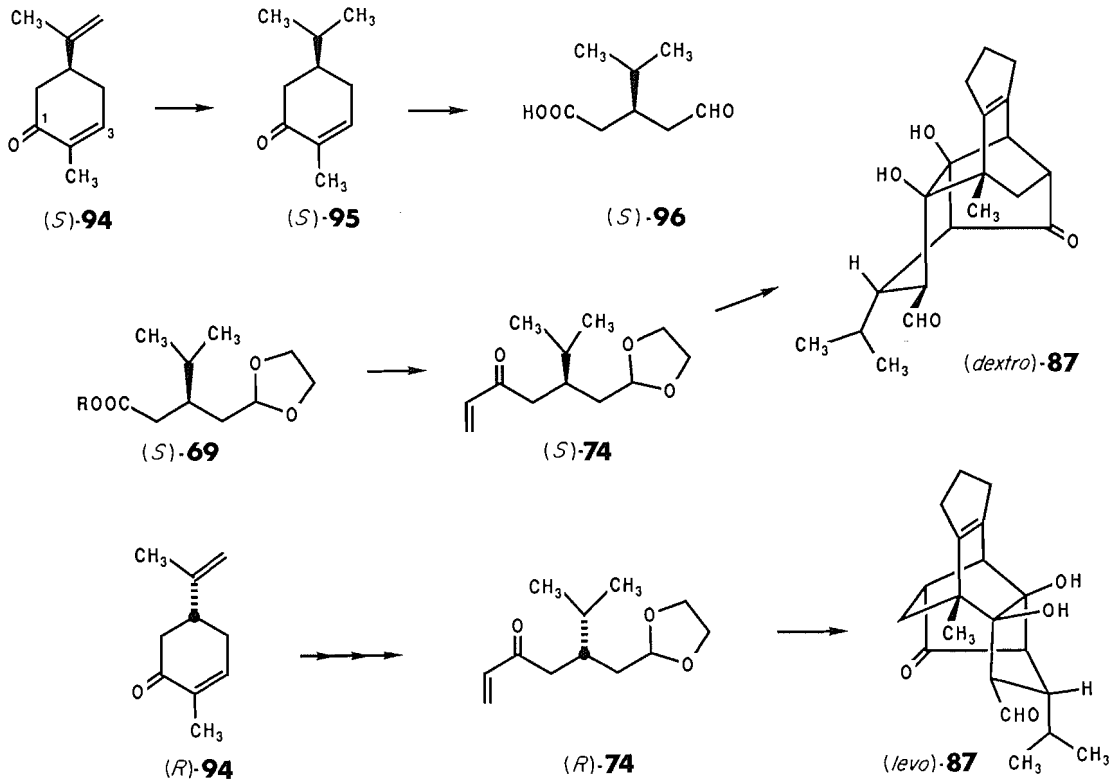
It is sometimes difficult to speculate on why a reaction takes place and more difficult on why a reaction does not take place. However, examination of molecular models suggests the following two alternative explanations. The isopropyl group is much more sterically hindered in isomer **88** than in **87**. On that basis, it is possible that in the case of **88** the equilibrium of the reaction is towards the retroaldol rather than the aldol product. It is also possible that the aldehyde **92** (Scheme 12) derived from **88** would prefer to exist in the form of the cyclic hemiacetal **93**, which has an isopropyl group in the equatorial orientation.[6] This would slow the rate of enolate formation from the aldehyde **92**, which is necessary for the aldol condensation, and, as a result, other competing reactions would take place and predominate. In the case of the aldehyde derived from **87**, formation of a cyclic hemiacetal would not occur because the isopropyl group would have to take an axial orientation. Thus enolization of the aldehyde would take place readily, followed by the internal aldol condensation.

The fact that the pentacyclic compound **88** is not formed and that the process leads to the specific formation of the pentacyclic isomers **87** has the disadvantage that the yield of the reaction cannot be higher than 50%. On the other hand, this approach has the advantage that if an optically active dienophile is used, the optically active enantiomer of pentacyclic **87** should be produced. To illustrate this point, let us assume that the dienophile would be optically active and would have the absolute configuration described by formula **74** (Scheme 13), i.e., having the *S* configuration. Optically active dienophile (*S*)-**74** has no preference for a particular face of the racemic diene **6**; the reaction will therefore take place with equal ease from the α and the β faces the racemic diene **6**, producing a 50:50 mixture of optically active **81***a*–*b* and **82***a*–*b* having the absolute configuration shown and where the *a*/*b* ratio due to the spirolactone isomerism will also be near 1:1. On treatment with base, optically active **81***a*–*b* will produce optically active *endo* and *exo* epimers having the absolute configuration described by structures **83** and **84**. Similarly, **82***a*–*b* will produce a mixture of optically active *endo* and *exo* epimers **85** and **86**. In the next step, **83** will be transformed into optically active **87** having the absolute configuration shown, whereas **85** cannot be converted into **88**. As a result, starting with dienophile **74** with the *S* absolute configuration leads to the optically active pentacyclic **87** having the absolute configuration shown. This also means that if one starts with dienophile **74** having the opposite *R* absolute configuration, the mirror image enantiomer of **87** would be produced. However, the absolute configuration of ryanodol is known and corresponds to formula **5**; consequently, we need the pentacyclic compound having the absolute configuration described by **87**. Thus we must synthesize an optically active dienophile **74** having the *S* absolute configuration.

The next step in our work was to find a method of obtaining an optically active dienophile of known absolute configuration in order to produce an optically active pentacyclic product. The monoterpene carvone was selected as starting material because

[5]More specifically, on treatment of **83** under basic equilibrating conditions for 18 h, **84** is not isolated but **83** was reisolated in only 85% yield. This indicates that **84** is much less stable than **83** and that **83** decomposed slightly under these conditions. Basic equilibration of **86** gave a mixture of **85** and **86** in 43% yield, where **85** predominates. Similar treatment of a mixture of **84** and **86** gave a mixture of **85** and **86**. This result confirms that isomer **84**, which can be characterized by nmr, is, however, unstable under basic conditions. It may also explain the unstability of isomer **83** because it is slowly converted into **84**, which is not stable under these conditions.

[6]These explanations were confirmed much later with the evidence of hemiketal formation (see **93**): nmr observation of anomeric proton signals at 5.38 (dd, J = 6 and 3 Hz) and 6.18 (dd, J = 12 and 3 Hz).



SCHEME 13

it presented several advantages. Both optically active forms *d* and *ℓ* are commercially available and their absolute configuration is well established as being *S* and *R* respectively (11). Also we were able to conceive and realize a very simple synthesis of the dienophile starting from carvone.

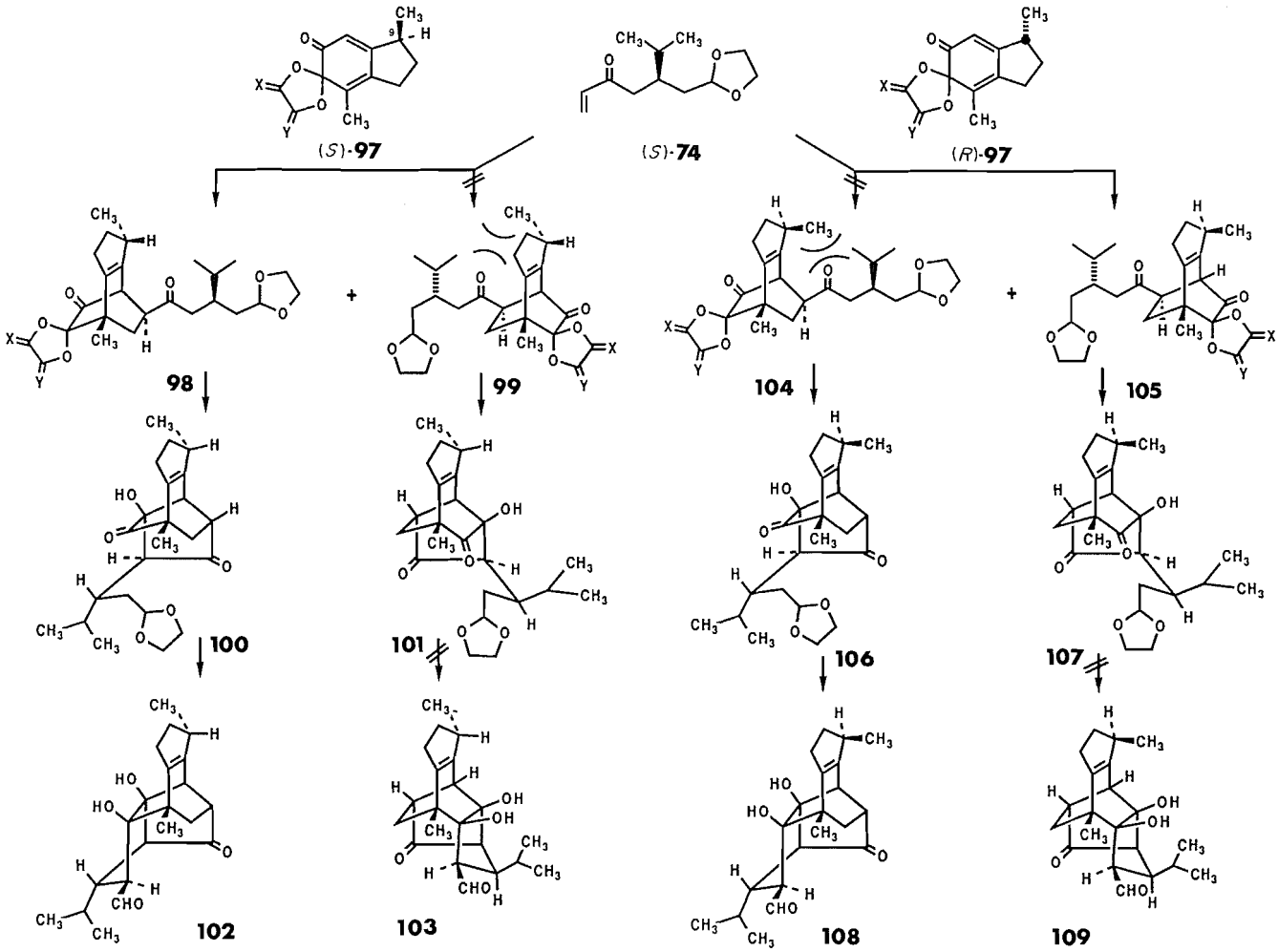
Scheme 13 describes the preparation of the optically active dienophile (*S*)-**74**. *d*-Carvone ((*S*)-**94**) was reduced catalytically (12) over platinum with hydrogen to give the dihydro derivative (*S*)-**95**. Ozonolysis of (*S*)-**95** (O_3 in CH_3COOEt; H_2–Pd/C) gave the aldehyde carboxylic acid (*S*)-**96**, which was transformed into the optically active acetal methyl ester (*S*)-**69** (R = CH_3) by successive acetalization (ethylene glycol, cat. PTSA in benzene; NaOH in CH_3OH) and esterification (CH_2N_2 or CH_3I, K_2CO_3 in acetone (13)). Using the methods previously described for the preparation of racemic material, acetal ester (*S*)-**69** was converted into optically active dienophile (*S*)-**74**, which was found to be dextrorotatory ($[\alpha]_{578}$ +0.6°). *o*-Spirolactone diene **6** was then heated with a slight excess of (*S*)-**74** in benzene. The crude Diels–Alder adduct was treated with an aqueous solution of sodium hydroxide in tetrahydrofuran to effect the first aldol condensation. It was then treated with aqueous acetic acid at 70°C followed by a treatment of the resulting crude material with aqueous sodium hydroxide in tetrahydrofuran. This produced, after chromatography, the crystalline pentacyclic dihydroxyketone aldehyde, which is dextrorotatory, i.e., (*dextro*)-**87** ($[\alpha]_{578}$ +142.2°). Starting with *ℓ*-carvone, i.e., (*R*)-**94**, a small quantity of the levorotatory dienophile (*R*)-**74** was also prepared and, following a sequence similar to that described above, (*R*)-**74** was converted into the crystalline levorotatory pentacyclic dihydroxyketone aldehyde, which is the mirror image of (*dextro*)-**87**, i.e., (*levo*)-**87** ($[\alpha]_{578}$ −137.5°). The pentacyclic key intermediate was thus available in both optically active forms. However, as previously mentioned, we needed (*dextro*)-**87** since its absolute configuration corresponds to that of ryanodol. In practice, it was easier to isolate the pentacyclic intermediate as the five-membered carbonate derivative **89** ($[\alpha]_D$ +121.3°) (Scheme 11). However, the overall yield of this product (**89**) from diene **6** was 27%. This 27% yields represents 54% of the theoretical yield. Our synthetic scheme being convergent, it meant that using ≈50 g of diene **6** with 50 g of dienophile (*S*)-**74** leads to approximately 25 g of (*dextro*)-**89**. It was thus relatively easy to obtain a large quantity of (*dextro*)-**89**, and we prepared approximately 100 g of it.[7]

Before preparing a large quantity of the optically active pentacyclic intermediate (*dextro*)-**89**, we carried out one additional study. So far, our investigation has led to improvement of the dienophile, but further analysis of our synthetic route revealed that there was also the possibility of improving the diene. This could be done by introducing, in the diene, the secondary methyl group that is found in ring C of ryanodol. This meant that the Diels–Alder reaction would take place with an *o*-spirolactone diene having a secondary methyl group at C_9. Since this diene would have a chiral center,[8] it could be optically active, having either the absolute configuration (*S*)-**97** or the opposite (*R*)-**97** (Scheme 14). This is theoretically interesting because each, the diene and the dienophile, have one chiral center.

This new situation can be analyzed by considering the combination of optically active dienophile (*S*)-**74** with the two

[7]When this material was prepared, Fourier transform nmr was not yet available. So, a large quantity of material was required for further investigation.

[8]*o*-Spirolactone diene **6** has one chiral center due to the spirolactone ring. However, as previously discussed, this chiral center is not important because it does not influence the Diels–Alder reaction and it is destroyed in the following step.



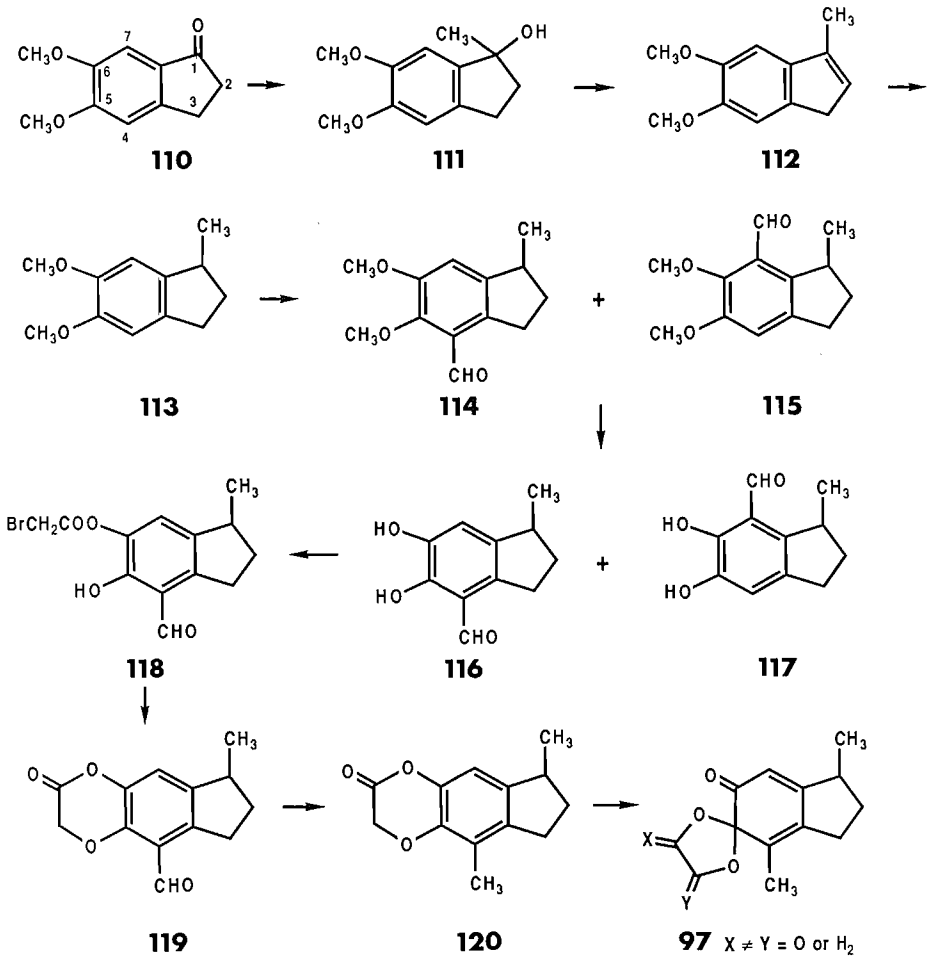
SCHEME 14

enantiomeric dienes (*S*)-**97** and (*R*)-**97**. The combination of (*S*)-**74** with (*S*)-**97** can theoretically produce **98** and **99**, which can lead to the formation of the tetracyclic intermediates **100** and **101** respectively. Then, due to the chirality of the isopropyl group, **101** would not be converted into **103** whereas **100** would lead to the formation of the pentacyclic intermediate **102**. Furthermore, it is also possible that **98** would be produced but not **99**, and this would be due to the fact that, in the transition state leading to **99**, the secondary methyl group of the diene comes close to the carbonyl group of the dienophile (cf. **99**). This is not the case during the formation of **98**, and it is possible that this steric interaction might be large enough to completely prohibit the formation of **99**. If this is true, it means that not only **103** but also **99** would not be formed and the net result would be that the theoretical yield for the production of **102** would be 100% rather than 50%.

Further advantage could also be drawn from this situation by examining the combination of optically active dienophile (*S*)-**74** with the other enantiomeric diene, i.e., (*R*)-**97**. This combination can theoretically lead to **104** and **105**, which can then yield **108** and **109** via **106** and **107** respectively. However, because of the additional steric hindrance caused by the secondary methyl group in the Diels–Alder reaction, **104** would not be produced, and only **105** would be observed. Then, **105** would be converted into **107**. However, due to the relative chirality of the isopropyl group, **107** would not yield **109**. The net result would be that the combination of (*S*)-**74** with (*R*)-**97** would not be productive. The interesting conclusion of this analysis is that it would not be necessary to resolve the diene, this resolution would be achieved by the dienophile (*S*)-**74**! Indeed, (*S*)-**74** would react with a racemic mixture of (*S*)-**97** and (*R*)-**97** producing a mixture of optically active Diels–Alder adducts **98** and **105** only, of which only the former (i.e., **98**) can lead to a pentacyclic optically active intermediate (i.e., **102**).

This interesting conclusion is valid only if the steric hindrance caused by the secondary methyl group is large enough to completely inhibit the formation of **99** and **104**. If not, it is expected that a mixture of the four Diels–Alder adducts would be produced where **98** and **105** should predominate. Since **99** and **105** cannot produce a pentacyclic product, a mixture of **102** (from **98**) and **108** (from **104**) would be produced, both optically active and where the former would predominate.

The preparation (8) of racemic *o*-spirolactone diene **97** is shown in Scheme 15. The reaction of 5,6-dimethoxyindanone (**110**) with methyllithium gave a crude mixture of **111** and **112**. Dehydration of **111** took place in the work-up and, upon purification by chromatography, crystalline methylindene **112** was isolated. Catalytic hydrogenation of **112** (PtO_2/H_2, CH_3COOH) gave methylindane **113**, which was converted into the racemic *o*-spirolactone dienone **97** by a route essentially identical to that



SCHEME 15

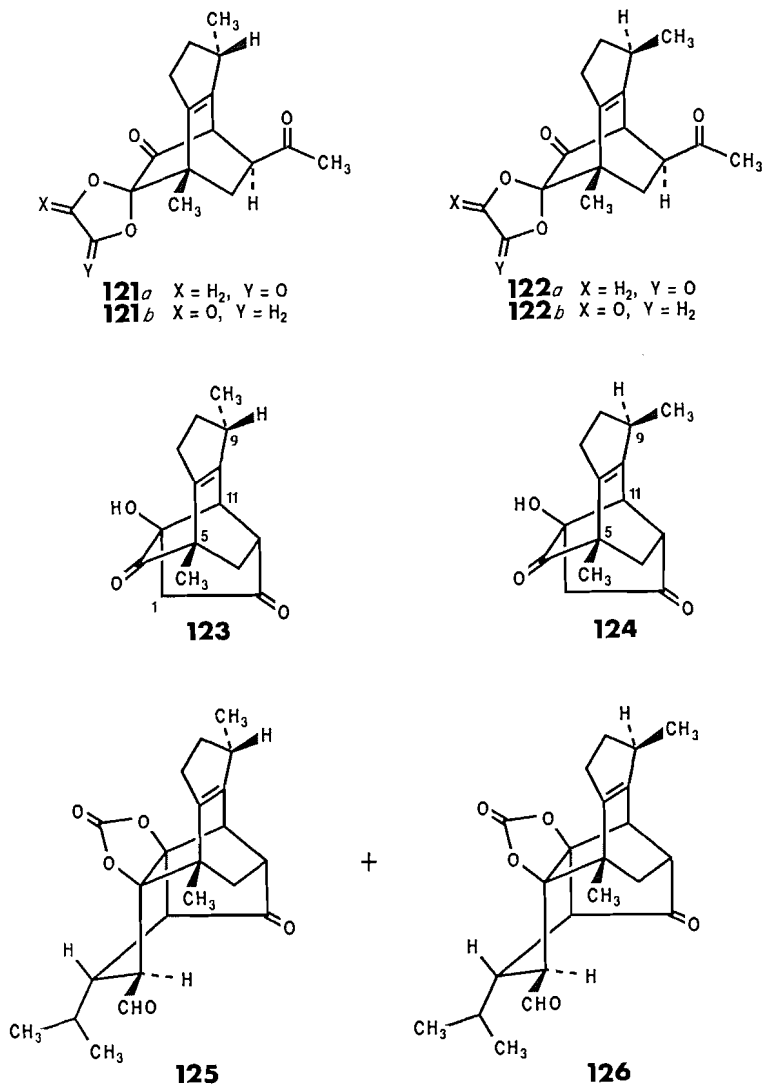
previously developed for the preparation of *o*-spirolactone dienone **6** (4). In this series, however, the chemistry was somewhat more complicated because the methylindane **113** is dissymmetric.

Reaction of methylindane **113** with dichloromethyl methyl ether and titanium tetrachloride in benzene (14) gave a 2:1 mixture of isomeric dimethoxyindane aldehydes **114** and **115**. Treatment of this mixture with boron tribromide (15) gave a 2:1 mixture of dihydroxyindane aldehydes **116** and **117**. Using the technique of fractional crystallization, **116** and **117** were obtained pure in low yield of 12 and 1% respectively. Nevertheless, this provided **116** in sufficient quantity to test our hypothesis. Reaction of **116** with bromoacetyl bromide in pyridine gave the bromoacetate **118**, which was then converted using potassium carbonate into the lactone aldehyde **119**. Catalytic reduction and hydrogenolysis of **119** with hydrogen in the presence of palladium-on-charcoal in acetic acid yielded the lactone indane **120**. Finally, treatment of lactone **120** with sodium hydroxyde followed by oxidation with *N*-bromosuccinimide (16) provided the racemic *o*-spirolactone dienone **97** ($X \neq Y = O$ or H_2).

The selectivity of diene **97** was first examined by studying its reactivity with methyl vinyl ketone (Scheme 16). This cycloaddition provided a mixture of the four isomers **121***a–b* and **122***a–b*, which were separated by chromatography. The relative stereochemistries of these compounds were not firmly established. This mixture was also treated with sodium hydroxide in water and tetrahydrofuran to produce a 55:45 mixture of isomers **123** and **124**, which were obtained pure by chromatography. The ratio obtained clearly demonstrated that the secondary methyl group in **97** does not create sufficient steric interaction to prevent the formation of **122***a–b* over that of **121***a–b*. It was therefore clear that the reaction of optically active dienophile (*S*)-**74** with racemic diene **97** would not lead to the exclusive formation of **102** as anticipated. Nevertheless, since we had both components in our hand, the Diels–Alder reaction of racemic diene **97** and optically active dienophile (*S*)-**74** was carried out, and the resulting product was treated successively with base (NaOH, THF–H_2O), acid (CH_3COOH–H_2O), and base (NaOH, THF–H_2O) to produce a crude material that was reacted with phosgene in the presence of pyridine in benzene. Preparative thin-layer chromatography provided a ≃55:45 mixture of isomers **125** and **126** in a low yield of 10%. Each isomer was then obtained pure by fractional crystallization.

This approach was abandoned because it was difficult to produce a large quantity of racemic diene **97**, and a low yield of an isomeric mixture of pentacyclic material was isolated. This approach is, however, theoretically interesting because it corresponds to a new strategy in synthesis, where the novel aspect comes from the fact that the resolving agent remains part of the target molecule afterward. It is likely that such a procedure will eventually be used with complete success in another synthesis.

Before ending Part II, we wish to add that we also considered to some extent another type of dienophile. The strategy previously described using vinyl ketone dienophiles requires a

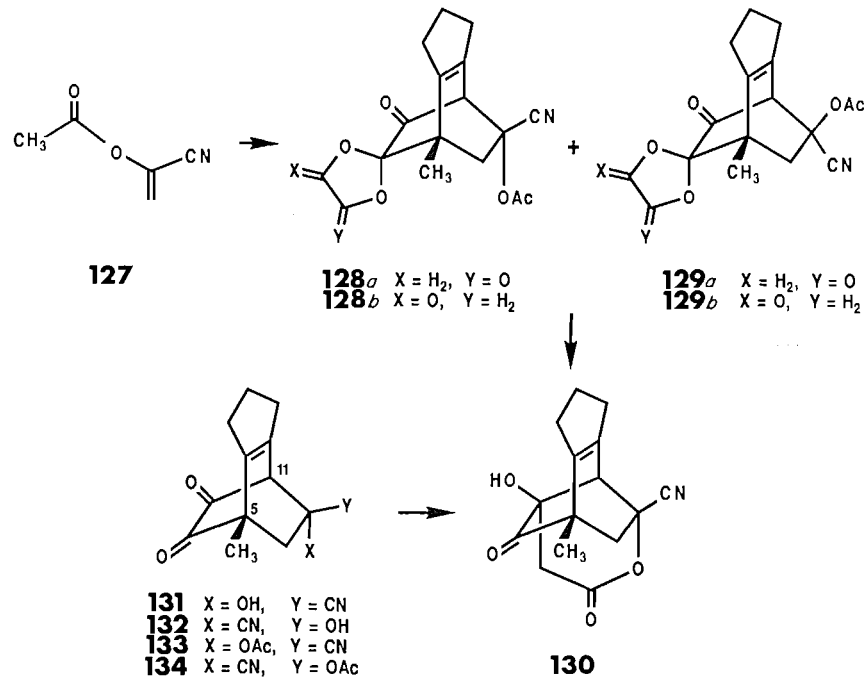


SCHEME 16

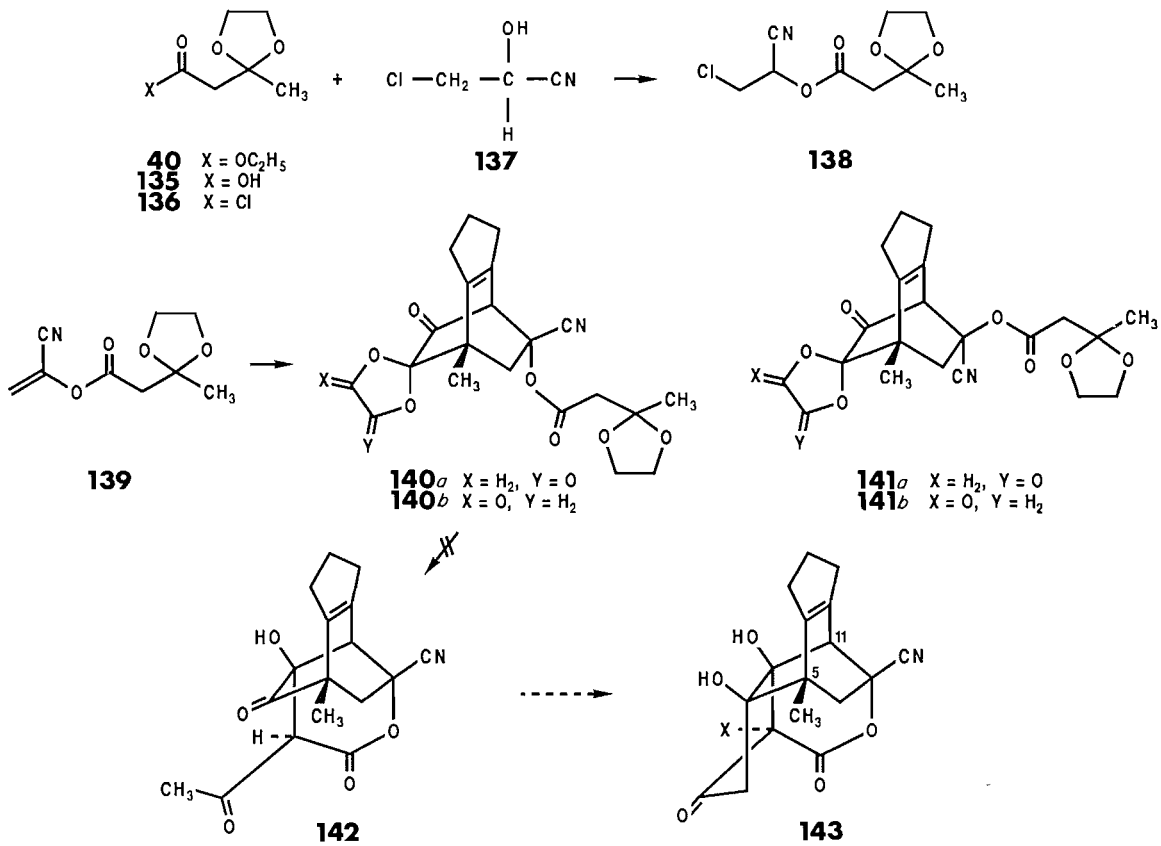
cleavage of a carbon–carbon bond between C_{15} and C_{17} (cf. Scheme 5) at a later stage, and we have considered ways either to prevent or at least to ease this task. For this reason, we considered, as dienophile, acrylonitrile having an ester group at carbon-2 (8*a*).

The first dienophile investigated was the known (17) 2-acetoxy-acrylonitrile (**127**) (Scheme 17). The Diels–Alder reaction of **127** with *o*-spirolactone dienone went smoothly, but without following the *endo* rule, yielding a mixture of four stereoisomers **128***a–b* and **129***a–b* that could, however, be separated by chromatography. The most polar of these Diels–Alder adducts (mp 191–192°C) was shown to have structure **128***b* by single crystal X-ray diffraction analysis (8*b*). It was then hoped that the two isomers that correspond to **128***a–b* would undergo an intramolecular aldol condensation to produce the cyanohydrin lactone **130**. However, in our hands, all attempts to produce **130** under either basic or acidic conditions failed. In acidic conditions, isomers **129***a–b* showed their interrelation, giving the same cyanohydrin diketone, which therefore had structure **132** and not **131**. The cyanohydrin diketone **132** was further characterized by acetylation (Ac_2O, pyridine) to an acetate derivative, which should have structure **134** and not **133**. The failure of these aldol condensation experiments might be due to the fact that the acetate group requires strong conditions to enolize. To facilitate the aldol condensation, the more complex acrylonitrile **139** was synthesized (8) (Scheme 18). Thus using a strategy similar to that described for the β-diketone **46** (Scheme 7), it was hoped that **139** would react with *o*-spirodienone lactone **6** to produce **140***a–b*, which would undergo, after acetal hydrolysis, an internal aldol condensation. This would produce **142**, which might thus undergo a second aldol condensation yielding ring A (i.e., **143**).

The synthesis of **139** was started with the dioxolane acetal **40** of ethyl acetoacetate. Basic hydrolysis of **40** gave the corresponding carboxylic acid **135**, which was then converted ($(COCl)_2$, pyridine, benzene) into the acid chloride **136**. Reaction of **136** with the cyanohydrin of chloroacetaldehyde (**137**) gave the corresponding ester **138**. Treatment of ester **138** with triethylamine gave the desired substituted acrylonitrile **139**. The Diels–Alder reaction of **139** with *o*-spirolactone dienone **6** gave a mixture of isomers **140***a–b and* **141***a–b* from which two isomers were isolated pure by fractional crystallization. The most polar (mp 189–190°C) of these adducts was shown to have structure **140***b* (X = O, Y = H_2) by single crystal X-ray diffraction analysis (8*b*). Again, it was hoped that the isomers that correspond to **140***a–b* would have produced the aldol product **142**. However, all attempts were unsuccessful and this approach was abandoned.



SCHEME 17



SCHEME 18

In conclusion, the chemistry described in Part II that is relevant to our total synthesis can be summarized in the following way. We have developed a simple synthesis of optically active dienophile (*S*)-**74** starting from carvone (*S*)-**94** (Scheme 13). Using this dienophile and racemic *o*-spirolactone dienone **6**, we have obtained, in four steps, the five-membered carbonate derivative **89** (Scheme 11) of the optically active pentacyclic dihydroxy ketoaldehyde **87**, having the desired absolute configuration, in 54% of a 50% theoretical yield, i.e., 27% overall yield.

Experimental

Apparatus, materials, and methods

Melting points were determined on a Büchi M-50 apparatus and are uncorrected. Ether, tetrahydrofuran, and 1,2-dimethoxyethane were dried by distilling over sodium benzophenone ketyl. Benzene, dichoromethane, dimethyl sulfoxide, and amines were distilled over calcium hydride. All reactions were performed under nitrogen or argon atmosphere. Analytical and preparative thin-layer chromatography (tlc) were carried out on glass plates precoated (0.25, 0.5, 1.0, and 2.0 mm) with silica gel 60 F-250 (Merck). Materials were detected by visualization under an ultraviolet lamp (254 or 350 nm) and (or) by spraying with sulfuric acid (50%) or a solution of phosphomolybdic acid or vanillin followed by heating on a hot plate. Column chromatography was performed with silica gel (Baker 60–200 Mesh) or Merck 60 (200–400 mesh)).

The infrared spectra (ir) were taken on a Perkin–Elmer 257 or 681 spectrophotometer. Proton nuclear magnetic resonance (^{1}H nmr) spectra were recorded (with chloroform or tetramethylsilane as internal standard) on a Varian A-60, a Bruker WP-60, a Bruker HX-90, or a Bruker WM-250 instrument. Carbon nuclear magnetic resonance (^{13}C nmr) spectra were measured on a Bruker HX-90 or WM-250 instrument. The following abbreviations have been used: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; qn, quintet; m, multiplet; br, broad. For most of the hydroxylated compounds, the multiplicity of the hydrogens attached to a carbinol was analyzed after D_2O exchange. The mass spectra were recorded on a Hitachi–Perkin–Elmer RMU-6 mass spectrometer and peak matching (hrms) on a VG Micromass ZAB-2F spectrometer. The ultraviolet spectra (uv) were recorded on a Varian Techtron 635 spectrophotometer. Microanalyses were carried out by Mr. J. Tamas, Laboratoire de Microanalyses, Université de Sherbrooke; Schwarzkopf Microanalytical Laboratories, New York; and by Dr. C. Daesslé, Organic Microanalyses, Montreal.

Diketoacetate ***9***

A solution of diketoalcohol **8** (2.5 g, 10.4 mmol) in a mixture of pyridine (3 mL) and acetic anhydride (4 mL) was heated for 0.5 h at 100°C. The volatile materials were removed under vacuum and the residue was crystallized from ether–pentane to give pure acetate **9** (2.6 g, 91%); mp 128–130°C; ir (CH_2Cl_2, ν cm^{-1}): 1745, 1720, and 1230; ^{1}H nmr ($CDCl_3$, δ ppm): 3.75 (d, 1H, J = 5 Hz, HC11), 3.07 (dd, 1H, J_{AB} = 19.4 Hz, J_W = 2.3 Hz, H_{exo}-C1), 2.66 (d, 1H, J_{AB} = 19.4 Hz, H_{endo}-C1), 2.68 (m, 1H, H-C15), 2.45 (m, 4H, allylic protons), 2.05 (s, 3H, CH_3CO_2), 2.00 (m, 2H), 1.82 (dd, 1H, J_{AB} = 13.8 Hz, J_{AX} = 11.6 Hz, H_{exo}-C14), 1.52 (dd, 1H, J_{AB} = 13.8 Hz, J_{BX} = 1.6 Hz, H_{endo}-C14), 1.27 (3H, s, CH_3-C5); ms *m/e*: 274 (M^+). *Anal.* calcd. for $C_{16}H_{18}O_4$: C 70.05, H 6.61; found: C 69.97, H 6.52.

Monoketal acetate ***10***

A mixture of diketoacetate **9** (2.4 g, 8.8 mmol), ethylene glycol (2 mL), and *p*-toluenesulfonic acid (20 mg) in benzene (50 mL) was refluxed for 4 h (Dean–Stark water separator). The cooled reaction mixture was then washed with aqueous sodium carbonate solution (1 M) and brine. Evaporation of the solvent gave a solid residue, which was crystallized from ether (2.55 g, 91%); mp 149–152°C; ir (CH_2Cl_2, ν cm^{-1}): 1745, 1730, 1230; ^{1}H nmr ($CDCl_3$, δ ppm): 3.88 (m, 4H), 3.52 (d, 1H, 4 Hz, H-C11), 2.8–1.4 (m, 11H), 1.98 (s, 3H, CH_3CO_2), 1.25 (s, 3H, CH_3-C5); ms *m/e*: 318 (M^+). *Anal.* calcd. for $C_{18}H_{22}O_5$: C 67.91, H 6.97; found: C 68.22, H 6.96.

Reduction of ketoacetate ***10***

(a) With lithium borohydride

To a cooled (0°C) solution of monoketal acetate **10** (2.4 g, 7.6 mmol) in tetrahydrofuran (120 mL) was added lithium borohydride (0.42 g, 20 mmol). The mixture was stirred for 2 h at 0°C, 1 h at 25°C, and 1 h at reflux temperature. Then was added lithium aluminum hydride (0.80 g, 20 mmol) and the reflux was pursued for 1 h. The cooled mixture was then cautiously reacted with moist ether, then water. The mixture was extracted with ether. The organic phase was dried ($MgSO_4$) and evaporated to give a mixture (≈95:5) of *trans* diol **11** and *cis* diol **12** respectively. The crude mixture was crystallized from ether to give pure *trans* ketal diol **11** (1.6 g, 76%); mp 145–147°C; ir (CH_2Cl_2, ν cm^{-1}): 3580, 3400, 1030; ^{1}H nmr ($CDCl_3$, δ ppm): 4.00 (m, 4H), 3.16 (d, 1H, J_W = 2 Hz, H-C4), 3.03 (d, 1H, J = 4 Hz, HC11), 2.8–1.6 (m, 11H), 1.13 (s, 3H, CH_3-C5); ms *m/e*: 278 (M^+). *Anal.* calcd. for $C_{16}H_{22}O_4$: C 69.04, H 7.97; found: C 68.90, H 8.15.

(b) With lithium in ammonia

To a solution of monoketal acetate **10** (2.0 g, 6.3 mmol) in tetrahydrofuran (15 mL) and dry ethanol (5 mL), at −78°C, was added liquid ammonia (freshly distilled, ~50 mL). Small pieces of lithium (total 1.0 g) were added to that mixture over a period of 1 h. The cold bath was then removed, the ammonia was evaporated, and the residue was reacted with ethanol (2 mL), then diluted with water and extracted with ether (3 × 50 mL). The combined organic layer were dried over magnesium sulfate, filtered, and the solvents evaporated to give a mixture (31:58) of *trans* ketal diol **11** and *cis* ketal diol **12** respectively. The two isomers were separated by crystallization or by chromatography (silica, Et_2O). *trans* Ketal diol **11** (0.53 g, 31%) (*vide supra*); *cis* ketal diol **12** (1.0 g, 58%); mp 115–117°C; ir (CH_2Cl_2, ν cm^{-1}): 3400, 1180, 1060, 1030; ^{1}H nmr ($CDCl_3$, δ ppm): 3.90 (m, 4H), 3.35 (s, 1H, H-C4), 2.95 (d, 1H, J = 4 Hz, HC11), 2.6–1.3 (m, 1H), 1.24 (s, 3H, CH_3-C5); ms *m/e*: 278 (M^+). *Anal.* calcd. for $C_{16}H_{22}O_4$: C 69.04, H 7.97; found: C 68.83, H 7.78.

Carbonate ***13***

To a solution of *cis* ketal diol **12** (0.5 g, 1.8 mmol) in a mixture of benzene (30 mL) and pyridine (0.5 mL) was added, at 25°C, a saturated benzene solution of phosgene (20 mL). After 15 min the mixture was filtered and evaporated. The oily residue was crystallized from ether–hexane to give carbonate **13** (0.45 g, 82%); mp 102–103°C; ir (CH_2Cl_2, ν cm^{-1}): 1795, 1210, 1190, 1065; ^{1}H nmr ($CDCl_3$, δ ppm): 4.15 (s, 1H, H-C4), 3.95 (m, 4H), 3.20 (d, 1H, J = 4 Hz, H-C11), 2.7–1.4 (m, 11H), 1.30 (s, 3H, CH_3-C5); ms *m/e*: 304 (M+). *Anal.* calcd. for $C_{17}H_{20}O_5$: C 67.10, H 6.75; found: C 66.68, H 6.48.

Ketal monoacetate ***14***

A solution of *trans* ketal diol **11** (4.3 g, 14.2 mmol) in pyridine (10 mL) was reacted overnight with acetic anhydride (12 mL) at room temperature. Evaporation of volatile materials under vacuum afforded monoacetate **14** as an oil (5.0 g, quant.); ir (CH_2Cl_2, ν cm^{-1}): 3420, 1720, 1030; ^{1}H nmr ($CDCl_3$, δ ppm): 3.92 (d, 1H, J_W = 2 Hz, H-C4), 3.90 (m, 4H), 3.07 (d, 1H, J = 4 Hz, H-C11), 2.6–1.7 (m, 11H), 2.17 (s, 3H, CH_3CO_2), 1.09 (s, 3H, CH_3-C5); ms *m/e*: 320 (M^+).

Dihydroxy ketoacetates ***17*** *and* ***18***

A solution of ketal monoacetate **14** (4.90 g, 15.3 mmol) in methanol (100 mL) was reacted, at −78°C, with a stream of ozone for 25 min. The mixture was then shaken for 3 h in an atmosphere of hydrogen in the presence of 10% palladium-on-carbon catalyst (50 mg). After filtration, the solvent was evaporated and the residue dissolved in pyridine (5 mL), refluxed for 20 min, and kept to dryness. The residue was purified by column chromatography on silica gel (ether) to give dihydroxy ketoacetates **17** and **18**.

Dihydroxyacetate ***17*** (3.10 g, 57%); mp 176–177°C; ir (CH_2Cl_2, ν cm^{-1}): 3450, 1735, 1690; ^{1}H nmr ($CDCl_3$, δ ppm): 5.24 (d, 1H J_W = 2 Hz, H-C4), 4.3 (br s, 1H, -OH), 3.90 (m, 4H), 3.35 (br signal, 1H, -OH), 2.8–1.2 (m, 11H), 2.21 (s, 3H, CH_3CO_2), 1.02 (s, 3H, CH_3-C5). *Anal.* calcd. for $C_{18}H_{24}O_7$: C 61.35, H 6.86; found: C 61.03, H 6.72.

Dihydroxyacetate ***18*** (1.10 g, 20%); mp 99–101°C; ir (CH_2Cl_2, ν cm^{-1}): 3450, 1715; ^{1}H nmr ($CDCl_3$, δ ppm): 4.70 (d, 1H, J_W = 2 Hz, H-C4), 3.85 (m, 4H), 3.50 (br signal, 1H, -OH), 2.4–1.1 (m, 11H), 2.12 (s, 3H, CH_3CO_2), 0.80 (s, 3H, CH_3-C5).

Carbonate derivative ***19***

To a solution of dihydroxyacetate **17** (0.50 g, 1.42 mmol) in a mixture of benzene (30 mL) and pyridine (0.5 mL) was added, at 25°C, a saturated benzene solution of phosgene (30 mL). After 4 h, the mixture was filtered and evaporated. Crystallization of the crude product (CH_2Cl_2–Et_2O) yielded carbonate **19** (0.46 g, 86%); mp 204–205°C; ir (CH_2Cl_2, ν cm^{-1}): 1760, 1740, 1715, 1230, 1060; ^{1}H nmr ($CDCl_3$, δ ppm): 4.90 (d, 1H, J_W = 2 Hz, H-C4), 3.88 (m, 4H), 3.50 (br signal, 1H, -OH), 2.45–1.1 (m, 11H), 2.12 (s, 3H, CH_3CO_2), 0.80 (s, 3H,

CH_3-C5); ms *m/e*: 378 (M^+). *Anal.* calcd. for $C_{19}H_{22}O_8$: C 60.31, H 5.86; found: C 60.12, H 6.07.

Triketone ***26***

A solution of monoketal ketoacetate **10** (0.80 g, 2.5 mmol) in ethyl acetate (50 mL) was reacted with a stream of ozone during 15 min. Then the mixture was shaken for 2 h in an atmosphere of hydrogen in the presence of 10% palladium-on-carbon catalyst (20 mg). After filtration, the solvent was evaporated and the solid residue was crystallized from ether to give triketone **26** (0.72 g, 82%); mp 212–218°C (dec.); ir (CH_2Cl_2, ν cm^{-1}): 1750, 1720, 1710, 1235; ^1H nmr ($CDCl_3$, δ ppm): 4.00 (m, 4H), 3.50 (m, 1H), 3.4–1.8 (m, 11H), 2.22 (s, 3H, CH_3CO_2), 1.32 (s, 3H, CH_3-C5). *Anal.* calcd. for $C_{18}H_{22}O_7$: C 61.70, H 6.33; found C 61.42, H 6.41.

Tetracyclic aldol product ***29***

Triketone **26** (0.50 g, 1.43 mmol) was refluxed in pyridine (2 mL) for 1 h. Evaporation of pyridine yielded a solid residue, which was crystallized from dichloromethane–ether mixture to give compound **29** (0.43 g, 86%); mp 240–243°C; ir (CH_2Cl_2, ν cm^{-1}): 3450, 1760, 1720; ^1H nmr ($CDCl_3$, δ ppm): 3.80 (m, 4H), 3.6–1.6 (m, 12H), 2.01 (s, 3H, CH_3CO_2), 1.18 (s, 3H, CH_3-C5). *Anal.* calcd. for $C_{18}H_{22}O_7$: C 61.70, H 6.33; found: C 61.45, H 6.26.

Diels–Alder adducts ***35****a and* ***35****b*

A solution of spirolactone dienone **6** (500 mg, 2.27 mmol) and ethyl vinyl ketone (267 mg, 3.18 mmol) in benzene (3 mL) was refluxed for 4 h under nitrogen. Removal of the volatile substances under vacuum and a rapid filtration on silica gel (hexane–EtOAc, 20%) furnished a 1:1 mixture (680 mg, quant.) of isomers **35***a* and **35***b*; ^1H nmr ($CDCl_3$, δ ppm): ~4.5 (two embodied AB patterns, 2H, J_{AB} = 14 Hz, -OCH_2CO_2), 3.63 (two d, 1H, J = 2 Hz, H-C11), 3.4–1.5 (m, 9H), 2.5 (q, J = 6 Hz, CH_3CH_2CO), 1.28 (s, 3H, CH_3-C5), 1.08 (t, 3H, CH_3CH_2CO). This mixture was used without any further purification for the next step.

Tetracyclic ketones ***36*** *and* ***37***

To a solution of the Diels–Alder adducts **35***a* and *b* (652 mg, 2.14 mmol) in tetrahydrofuran (25 mL) was added aqueous sodium hydroxide (1 M, 6 mL) and the mixture was stirred at room temperature for 20 h. The main part of the tetrahydrofuran was removed under reduced pressure and the residue was extracted with ether. Chromatography of the crude extract (540 mg, silica gel, benzene–ether 10%) furnished minor isomer *exo* **37** (110 mg, 20%) and major isomer *endo* **36** (more polar, 230 mg, 45%).

Major isomer endo ***36***: mp: 135–136°C; ir (CH_2Cl_2, ν cm^{-1}): 3510, 1742, 1715; ^1H nmr ($CDCl_3$, δ ppm): 3.30 (d, 1H, J = 5.0 Hz, H-C11), 3.21 (br s, 1H, -OH), 2.73 (dddd, 1H, J = 11.6, 5.0, 2.4, 1.7 Hz, H-C15), 2.53 (qd, 1H, J = 7.5, 2.4 Hz, H_{exo}-C1), 2.55 (m, 2H), and 2.42 (m, 2H) (allylic protons), 2.04 (m, 2H, H_2-C8), 1.86 (dd, 1H, J_{AB} = 14.0 Hz, J_{AX} = 11.6 Hz, H_A-C14), 1.57 (dd, 1H, J_{AB} = 14.0 Hz, J_{BX} = 1.7 Hz, H_B-C14), 1.24 (s, 3H, CH_3-C5), 1.00 (d, 3H, J = 7.5 Hz, CH_3-C1); ms *m/e*: 246 (M^+).

Minor isomer exo ***37***: mp: 110–111°C; ir (CH_2Cl_2, ν cm^{-1}): 3510, 1742, 1718; ^1H nmr ($CDCl_3$, δ ppm): 3.30 (d, 1H, J = 5.0 Hz, H-C11), 2.83 (br s, 1H, OH), 2.65 (ddd, 1H, J = 11.5, 5.0, 1.7 Hz, H-C15), 2.55 (m, 2H) and 2.44 (m, 2H) (allylic protons), 2.02 (m, 2H, H_2-C8), 1.85 (dd, 1H, J_{AB} = 14 Hz, J_{AX} = 11.5, H_A-C14), 1.57 (dd, 1H, J_{AB} = 14 Hz, J_{BX} = 1.7 Hz, H_B-C14), 1.28 (s, 3H, CH_3-C5), 1.18 (d, 3H, J = 7.7 Hz, CH_3-C1); ms *m/e*: 246 (M^+).

Diketoacetate endo ***38***

A solution of diketoalcohol *endo* **36** (100 mg, 0.41 mmol) and *p*-toluenesulfonic acid (7 mg) in acetic anhydride was heated at 70°C for 2 h. After evaporation of acetic anhydride, the residue was extracted with ether, washed with dilute sodium bicarbonate, and the extract was dried ($MgSO_4$) and filtered. Evaporation of ether left a solid residue, which was recrystallized from ether–hexane (112 mg, 95%); mp 102–103°C; ir (CH_2Cl_2, ν cm^{-1}): 1745, 1725, 1235; ^1H nmr ($CDCl_3$, δ ppm): 3.79 (d, 1H, J = 5.1 Hz, H-C11), 3.23 (qd, 1H, J = 7.3, 2.3 Hz, H_{exo}-C1), 2.75 (dddd, 1H, J = 11.7, 5.1, 2.3, 1.7 Hz, H-C15), 2.45 (m, 4H, allylic protons), 2.06 (s, 3H, CH_3CO_2), 1.98 (m, 2H, H_2-C8), 1.84 (dd, 1H, J_{AB} = 13.9 Hz, J_{AX} = 11.7 Hz, H_A-C14), 1.49 (dd, 1H, J_{AB} = 13.9 Hz, J_{BX} = 1.7 Hz, H_B-C14), 1.23 (s, 3H, CH_3-C5), 1.06 (d, 3H, J = 7.3 Hz, CH_3-C1); ms *m/e*: 288 (M^+). *Anal.* calcd. for $C_{17}H_{20}O_4$: C 70.81, H 6.99; found: C 70.66, H 6.94.

Diketoacetate exo ***39***

Acetylation of diketoalcohol *exo* **37** (40 mg, 0.16 mmol) was done as for compound **36** (*vide supra*). Filtration on silica gel (hexane–EtOAc, 20%) gave pure acetate **39** (44 mg, 94%); ir (CH_2Cl_2, ν cm^{-1}): 1745, 1725, 1230; ^1H nmr ($CDCl_3$, δ ppm): 3.42 (d, 1H, J = 5.0 Hz, H-C11), 2.66 (ddd, 1H, J = 11.8, 5.0, 1.5 Hz, H-C11), 2.61 (q, 1H, J = 7.6 Hz, H_{endo}-C1), 2.44 (m, 4H, allylic protons), 2.04 (s, 3H, CH_3CO_2), 1.93 (m, 2H, H_2-C8), 1.84 (dd, 1H, J_{AB} = 13.8 Hz, J_{AX} = 11.8 Hz, H_A-C14), 1.46 (dd, 1H, J_{AB} = 13.8 Hz, J_{BX} = 1.5 Hz, H_B-C14), 1.28 (s, 3H, CH_3-C5), 1.25 (d, 3H, J = 7.6 Hz, CH_3-C1); ms *m/e*: 288 (M^+).

Monodeuterated diketoacetates 15-d-endo ***38*** *and* exo ***39***

To a stirred solution of compounds **35***a* and *b* (crude Diels–Alder adducts) (860 mg, 2.98 mmol) in tetrahydrofuran (50 mL) was added a solution of sodium hydroxide (1 M in D_2O, 14 mL). After 2 h at room temperature, the organic solvent was evaporated and the mixture was extracted with ether (3 × 20 mL). The combined organic layers were washed with water (2 × 10 mL), brine, and dried over magnesium sulfate. After evaporation of ether the crude dideuterated isomers **36** and **37** (485 mg, *m/e*: 248 (M^+)) were dissolved in THF (15 mL) and stirred with a solution of potassium hydroxide (1 M in H_2O, 5 mL) for 2 h at room temperature. After the usual ether extraction, the mixture was purified by chromatography (*vide supra*) to give monodeuterated (15-*d*) *endo* **36** (242 mg, 34% from **35**) and monodeuterated (15-*d*) *exo* **37** (17 mg, 11% from **35**). These compounds were acetylated separately (*vide supra*) to produce monodeuterated acetates **38** and **39**.

Monodeuterated diketoacetate 15-d endo ***38***: ^1H nmr: identical with the unlabelled **38** (*vide supra*) except for the following: 3.79 (s, 1H, H-C11), 3.23 (q, 1H, J = 7.2 Hz, H-C1); ms *m/e*: 289 (M^+).

Monodeuterated diketoacetate 15-d exo ***39***: ^1H nmr: identical with the unlabelled **39** (*vide supra*) except for the following: 3.42 (s, 1H, H-C11); ms *m/e*: 289 (M^+).

*Ethyl 3,3-ethylenedioxy-butanoate (****40****)*

A mixture of ethyl acetoacetate (200 g, 1.54 mol), ethylene glycol (150 mL, 2.68 mol), and *p*-toluenesulfonic acid (250 mg) in benzene (2.5 L) was refluxed for 24 h (Dean–Stark water separator), then cooled and washed with aqueous sodium bicarbonate (5%) and water. The organic layer was dried ($MgSO_4$), filtered, and solvent removed under reduced pressure. The crude product (255 g, 93%) did not need purification; ir ($CHCl_3$, ν cm^{-1}): 1724, 1180, 1042; ^1H nmr ($CDCl_3$, δ ppm): 4.10 (q, 2H, J = 7.2 Hz, -OCH_2CH_3), 3.89 (s, 4H, 2 × -OCH_2-), 2.50 (s, 2H, -CH_2CO_2-), 1.40 (s, 3H, CH_3-), 1.23 (t, 3H, J = 7.2 Hz, -OCH_2CH_3); ms *m/e*: 159 ($M^+ - CH_3$).

*3,3-Ethylenedioxy-1-butanol (****41****)*

A solution of ethyl acetoacetate ketal (**40**) (50.0 g, 0.287 mol) in dry ether (200 mL) was slowly added to a suspension of lithium aluminum hydride (12 g, 0.31 mol) in ether (1 L) (smooth reflux). The mixture was refluxed for 1 h, then cooled (0°C) and reacted with a slow addition of moist ether (350 mL), then water, (350 mL) until the formation of a white precipitate. The organic layer was decanted, dried ($MgSO_4$), filtered, and the solvent evaporated. The oily residue was distilled under reduced pressure (28 g, 75%); ir ($CHCl_3$, ν cm^{-1}): 3420, 1380, 1050; ^1H nmr ($CDCl_3$, δ ppm): 3.96 (s, 4H, OCH_2CH_2O), 3.72 (t, 2H, J = 6.0 Hz, CH_2OH), 3.35 (s, 1H, -OH), 1.92 (t, 2H, J = 6.0 Hz, -CH_2CH_2OH), 1.32 (s, 3H, CH_3-); ms *m/e*: 117 ($M^+ - 15$).

*3,3-Ethylenedioxy-butanal (****42****)*

A solution of 3,3-(ethylenedioxy)butanol (**41**) (13.2 g, 0.10 mol) in dimethyl sulfoxide (60 mL) was reacted with *N,N'*-dicyclohexylcarbodiimide (41.2 g, 0.20 mol) in the presence of pyridinium trifluoroacetate (10.0 g, 0.05 mol). After a few minutes of efficient mechanical stirring, an exothermic reaction took place together with orange coloration. After 1 h, benzene was added to precipitate di-

cyclohexyl urea, which was separated by filtration. The solvents were evaporated under reduced pressure and the liquid residue was distilled under vacuum to give 3,3-ethylenedioxy-butanal (**42**), (10.3 g, 78%), bp 42°C/0.5 Torr; 1 Torr = 133.3 Pa); ir ($CHCl_3$, ν cm^{-1}): 2720, 1720, 1055; ^1H nmr ($CDCl_3$, δ ppm): 9.73 (t, 1H, J = 3 Hz, CHO), 4.01 (s, 4H, OCH_2CH_2O), 2.70 (d, 2H, J = 3 Hz, CH_2CHO), 1.42 (s, 3H, CH_3-); ms *m/e*: 115 ($M^+ - 15$).

*5,5-Ethylenedioxy-1-hexen-3-ol (**43**)*

Magnesium turnings (8.0 g, 0.32 mol) and one crystal of iodine were covered with dry tetrahydrofuran (40 mL). Vinyl bromide (50.0 g, 0.46 mol) was then added dropwise until an exothermic reaction took place (~3 mL). The addition was continued in order to maintain a good reflux. After the addition was completed, the mixture was refluxed for 45 min. A solution of ketal aldehyde **42** (37.2 g, 0.28 mol) in THF (70 mL) was then added dropwise to the mixture and the reflux was continued for 45 min. The reaction mixture was poured onto ice and brine (1.5 L), neutralized to pH 7 (2 M HCl), and extracted with dichloromethane (4 × 200 mL). Evaporation of the solvents yielded pure alcohol **43** (42 g, 92%) as an oil; ir ($CHCl_3$, ν cm^{-1}): 3500, 1650, 1380, 1060; ^1H nmr ($CDCl_3$, δ ppm): 6.2–4.9 (m, 3H, olefinic), 4.42 (m, 1H, *H*-C-OH), 4.00 (s, 4H, OCH_2CH_2O), 3.50 (br s, -OH), 2.00 (br s, 1H) and 1.80 (br s, 1H) (CH_2CHOH), 1.39 (s, 3H, CH_3-); ms *m/e*: 143 ($M^+ - 15$).

*5,5-Ethylenedioxy-1-hexen-3-one (**44**)*

A solution of allylic alcohol **43** (10.0 g, 63.4 mmol) in acetone (150 mL) was reacted at −30°C under good stirring with Jones reagent (dropwise, 23.7 mL, 63.5 mmol). After the addition, the mixture was warmed to room temperature and decanted. After evaporation of the acetone, the residue was dissolved in ether (300 mL), then washed with aqueous sodium bicarbonate solution and brine. The organic layer was dried ($MgSO_4$), filtered, and the ether evaporated. The oily residue was chromatographed on silica gel (benzene–ether, 98:2) to give vinyl ketone **44** (4.4 g, 44%) as an oil; ir ($CHCl_3$, ν cm^{-1}): 1680, 1610, 1050; ^1H nmr ($CDCl_3$, δ ppm): 6.52–5.70 (m, 3H, olefinic), 3.98 (s, 4H, $-OCH_2CH_2O-$), 2.95 (s, 2H, CH_2-CO), 1.44 (s, 3H, CH_3-); ms *m/e*: 141 ($M^+ - 15$).

*Isomers **45**a and **45**b*

Spirolactone dienone **6** (2.59 g, 11.8 mmol) was dissolved in benzene (4 mL) and reacted with ketal vinyl ketone **44** (2.20 g, 14.1 mmol) at reflux temperature for 45 min. Evaporation of benzene and removal of the excess of dienophile **44** under vacuum left an oily residue (4.4 g, ~quant.) containing two products (~1:1), isomers **45***a* and *b*, which were not separated; ir ($CHCl_3$, ν cm^{-1}): 1820, 1740, 1715; ^1H nmr ($CDCl_3$, δ ppm): 4.70 (d, 0.5H) and 4.35 (d, 0.5H), 4.65 (d, 0.5H) and 4.34 (d, 0.5H) (two embodied AB patterns), (J_{AB} = 14.5 Hz) (spirolactonic methylene), 3.94 (s, 4H, OCH_2CH_2O), 3.5–1.6 (m, 10H), 2.82 (s, 2H, CH_2-CO-), 1.38 (s, 3H, CH_3-COO-), 1.26 (s, 3H, CH_3-C5); ms *m/e*: 376 (M^+).

*Tetracyclic triketone **46***

A crude mixture of isomers **45***a* and *b* (4.44 g, 11.8 mmol) in tetrahydrofuran (16 mL) was stirred at 25°C with aqueous sodium hydroxide (1 M, 240 mL) for 24 h. The basic aqueous mixture was successively extracted with ether (2 × 75 mL), acidified with aqueous hydrochloric acid (2 M, 130 mL), then extracted with ether (4 × 100 mL). This acidic extract was dried ($MgSO_4$) and filtered, and solvents were evaporated under reduced pressure to give pure tetracyclic hydroxytriketone **46** (3.147 g, 97%); ir ($CHCl_3$, ν cm^{-1}): 3520, 1710, 1655, 1610; ^1H nmr ($CDCl_3$, δ ppm): 3.93 (br s, 1H, OH), 3.32 (d, 1H, J = 4 Hz, H-C11), 2.9–1.6 (m, 10H), 2.15 (s, 3H, CH_3-CO), 1.26 (s, 3H, CH_3-C5); ms *m/e*: 246 ($M^+ - CO$). *Exact Mass* (hrms) calcd. for $C_{16}H_{18}O_4 - CO$: 246.121; found: 246.125.

*Monoacetate derivative **47***

A solution of tetracyclic ketone **46** (3.25 g, 11.8 mmol) in pyridine (40 mL) and acetic anhydride (45 mL) was stirred in the absence of light for 24 h. The volatile substances were then evaporated under vacuum and the solid residue purified by crystallization and chromatography (3.1 g, 73%); mp 185–189°C (chloroform–hexane); ir ($CHCl_3$, ν cm^{-1}): 1760, 1725, 1645; ^1H nmr ($CDCl_3$, δ ppm): 3.93 (d, 1H, J = 5 Hz, H-C11), 2.9–1.7 (m, 10H), 2.41 (s, 3H, CH_3CO_2), 2.22 (s, 3H, CH_3CO), 2.10 (s, 3H, CH_3—C=), 1.27 (s, 3H, CH_3-C5).

A solution of that crystalline diacetate (0.619 g, 1.72 mmol) in tetrahydrofuran (13 mL) was reacted with aqueous sodium carbonate (5%, 30 mL) at room temperature for 6 h. The aqueous mixture was first washed with ether (3 × 15 mL), acidified with hydrochloric acid (2 M, 18 mL), and extracted again with ether to give monoacetate **47** (0.491 g, 90%) as a mixture of epimers in position 1; ir ($CHCl_3$, ν cm^{-1}): 1760, 1730, 1660, 1615; ^1H nmr ($CDCl_3$, δ ppm): 3.79 (d, 1H, H-C11), 2.9–1.6 (m, 10H), 2.12 (s, 3H, CH_3CO-), 2.08 (s, 3H, CH_3CO_2), 1.26 (s, 3H, CH_3-C5); ms *m/e*: 288 ($M^+ - 28$). *Exact Mass* (hrms) calcd. for $C_{18}H_{20}O_5 - CO$: 288.136; found: 288.131.

cis- *and* trans-*Enedione methyl esters **49** and **50***

A solution of crude monoacetate **47** (0.258 g, 0.817 mmol) and *p*-toluenesulfonic acid (5 mg) in dry methanol (6 mL) was stirred at 55–60°C for 6 h. The mixture was then poured into aqueous sodium bicarbonate (5%, 25 mL) and extracted with ether. The organic layer was dried and evaporated. By nmr, the crude residue (181 mg) showed a proportion of 86:14 for the *cis*/*trans* isomers **49** and **50**. Chromatography (benzene–ether 2:1) of this mixture on silica gave pure isomers **49** (more polar) and **50** (less polar).

*cis Enedione **49*** (102 mg, 43%); ir ($CHCl_3$, ν cm^{-1}): 1730, 1700, 1635; ^1H nmr ($CDCl_3$, δ ppm): 5.72 (s, 1H, olefinic), 3.67 (s, 3H, CO_2CH_3), 3.55 (d, 1H, J = 3 Hz, H-C11), 2.9–1.5 (m, 9H), 2.18 (s, 3H, CH_3CO), 1.24 (s, 3H, CH_3-C5); ms *m/e*: 288 (M^+).

*trans Enedione **50*** (43 mg, 20%); uv (λ max, ethanol): 251 nm (ε 8200); ir ($CHCl_3$, ν cm^{-1}): 1730, 1680, 1620; ^1H nmr ($CDCl_3$, δ ppm): 6.80 (s, 1H, olefinic), 4.91 (d, 1H, J = 3 Hz, H-C11), 3.67 (s, 3H, CO_2CH_3), 3.0–1.6 (m, 9H), 2.28 (s, 3H, CH_3CO), 1.32 (s, 3H, CH_3-C5); ms *m/e*: 288 (M^+). *Anal.* calcd. for $C_{17}H_{20}O_4$: C 70.80, H 6.99; found: C 70.65, H 7.05.

trans *Enedione methyl ester **50** by isomerization of* cis *isomer **49***

Pure *cis*-enedione methyl ester **49** (150 mg, 0.52 mmol, neat) was heated at 150°C in a sealed tube for 1.5 h. Chromatography (benzene–ether 2:1) of the crude product on silica gel furnished *trans* enedione methyl ester **50** (105 mg, 70%) and unreacted starting material (30 mg, 20%).

*Tetracyclic lactone **51***

A solution of tetracyclic triketone **46** (196 mg, 0.72 mmol) in methanol (5 mL) was poured into an aqueous solution of sulfuric acid (8 M, 40 mL) in a separatory funnel. The mixture was shaken for 2 min, then rapidly extracted with ether (4 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent evaporated. The solid residue was crystallized (ether–hexane) to give tetracyclic lactone **51** (100 mg, 49%); mp 95–96°C; ir ($CHCl_3$, ν cm^{-1}): 1785, 1730, 1710 (sh); ^1H nmr ($CDCl_3$, δ ppm): 3.95 (d, 1H, J = 4 Hz, H-C11), 3.25 (d, 1H, J_{AB} = 15 Hz) and 2.38 (d, 1H, J_{AB} = 15 Hz), 2.9–1.6 (m, 9H), 2.19 (s, 3H, CH_3CO), 1.29 (s, 3H, CH_3-C5); ms *m/e*: 274 (M^+). *Anal.* calcd. for $C_{16}H_{18}O_4$: C 70.05, H 6.62; found: C 69.74, H 6.49.

trans *Enedione carboxylic acid **52***

Lactone **51** (51 mg, 0.186 mmol) was dissolved in a solution of potassium (16 mg) in *tert*-butanol (10 mL) and stirred under nitrogen for 23 h at room temperature. The mixture was then poured onto water (20 mL) and extracted with ether (2 × 10 mL) to remove a neutral fraction (16 mg). The aqueous basic layer was acidified (HCl, 1 M, pH 4) and extracted with ether (3 × 25 mL). Evaporation of the solvent furnished crude acid **52** (36 mg, 70%); ir ($CHCl_3$, ν cm^{-1}): 3500–2500 (br), 1710, 1680, 1620; ^1H nmr ($CDCl_3$, δ ppm): 11.6 (br s, $-CO_2H$), 6.82 (s, 1H, olefinic), 5.00 (d, 1H, J = 3 Hz, H-C11), 2.9–1.5 (m, 9H), 2.28 (s, 3H, CH_3CO), 1.31 (s, 3H, CH_3-C5).

trans *Enedione methyl ester **50** by esterification of acid **52***

A solution of acid **52** (60 mg, 0.22 mmol) in ether at 0°C was reacted with a slight excess of diazomethane in ether (~2 mL). After 2 min of stirring, the volatile substances were evaporated and the crude product

was purified by thin-layer chromatography on silica gel (benzene–ether 2:1) to yield the known *trans* methyl ester **50** (30 mg, 48%) (*vide supra*).

*Alcohol **54** and acid **55***

Dihydropyran (88 g, 1.0 mol) and 2,2-dimethylpropanediol (125 g, 1.20 mol) were refluxed in toluene (500 mL) in the presence of *p*-toluenesulfonic acid (20 mg). After 24 h, the mixture was cooled and washed with water (3 × 50 mL). Evaporation of toluene left an oil (188 g) containing acetal alcohol **54** and the mono THP derivative of 2,2-dimethylpropanediol in a proportion of 4:1. Separation of these isomers is delicate and was performed at a later stage (*vide infra*). The analytical data for the major desired alcohol **54** come from reduction of acid **55** (*vide infra*). The crude product (1.88 g, 10.0 mmol) in dry acetone (60 mL) was cooled at −20°C and reacted with Jones reagent (3.75 mL, 10.0 mmol) over a period of 30–40 min. Isopropanol (1 mL) was added to the mixture and the organic layer was decanted, diluted with water (20 mL), and extracted with ether. The combined organic layers were washed with water, dried ($MgSO_4$), and solvents evaporated to leave an oil that was crystallized to give ketal acid **55** (1.60 g, 80%); mp 92–93°C; ir ($CHCl_3$, ν cm^{-1}): 3500–2500 (br), 1720; ^1H nmr ($CDCl_3$, δ ppm): 11.2 (s, 1H, CO_2H), 4.45 (br t, 1H, J = 5 Hz, HCO_2-), 3.5 (m, 4H, $(CH_2O)_2$), 2.42 (m, 2H, CH_2CO_2H), 1.7 (m, 4H), 1.16 (s, 3H, -CH_3), 0.70 (s, 3H, -CH_3). *Anal.* calcd. for $C_{10}H_{18}O_4$: C 59.39, H 8.97; found: C 59.35, H 9.16.

*Alcohol **54** from acid **55***

A solution of ketal acid **55** (2.02 g, 10.0 mmol) in dry ether (50 mL) was added to a mixture of lithium aluminum hydride (700 mg) in ether (25 mL) and refluxed for 12 h. The excess hydride was destroyed by slow addition, at 0°C, of moist ether and water and the mixture was extracted with ether to give pure alcohol **54** as an oil (1.69 g, 90%); ir ($CHCl_3$, ν cm^{-1}): 3590, 3450, 1140, 1030; ^1H nmr ($CDCl_3$, δ ppm): 4.45 (br t, 1H, J = 5 Hz, H-CO_2), 3.5 (m, 6H, 3 × CH_2O-), 1.6 (m, 6H), 1.18 (s, 3H, CH_3), 0.73 (s, 3H, CH_3). *Anal.* calcd. for $C_{10}H_{20}O_3$: C 63.79, H 10.71; found: C 63.70, H 10.69.

*Vinylketone **58** (via acid **55**)*

To a solution of acid **55** (2.02 g, 10.0 mmol) in dry ether (150 mL) was added, under nitrogen, a solution of vinyllithium (~2 M in THF, 10 mL, 20 mmol). After 40 min at 25°C, the mixture was hydrolyzed (pH ≃ 6, 2 M H_2SO_4) and extracted with ether. The purity of the crude oily product was largely related to the quality of the lithium reagent. Flash chromatography of the crude product (silica gel, benzene) furnished fragile enone **58** (1.1 g, 52%); ir ($CHCl_3$, ν cm^{-1}): 1700, 1620; ^1H nmr ($CDCl_3$, δ ppm): 6.5–5.7 (m, 3H, olefinic), 4.45 (br t, 1H, J = 5 Hz, HCO_2), 3.50 (m, 4H, $(CH_2O)_2$), 2.65 (m, 2H, CH_2CO), 1.75 (m, 4H), 1.20 (s, 3H, CH_3), 0.70 (s, 3H, CH_3).

*Aldehyde **56***

A solution of acetal alcohol **54** (1.88 g, 10.0 mmol) in dichloromethane (4 mL) was added at 15°C to a mixture of Collins reagent prepared from chromic oxide (8 g, 80 mmol) and pyridine (13 mL) in dichloromethane (350 mL). After 20 min, the mixture was poured onto ice-water and extracted with dichloromethane. The organic layer was washed several times with water, dried, and the solvents were evaporated. The residual colored oil was purified by chromatography on Florisil (benzene) to give pure aldehyde **56** (1.1 g, 60%); ir ($CHCl_3$, ν cm^{-1}): 2820, 2720, 1730; ^1H nmr ($CDCl_3$, δ ppm): 9.84 (t, 1H, J = 2 Hz, -CHO), 4.48 (br t, 1H, J = 5 Hz, HCO_2), 3.52 (m, 4H, $(CH_2O)_2$), 2.50 (m, 2H, CH_2CHO), 1.70 (m, 4H), 1.18 (s, 3H, CH_3), 0.71 (s, 3H, CH_3).

*Allylic alcohol **57***

To magnesium turnings (2.45 g, 0.10 mol) in dry tetrahydrofuran (30 mL) were added successively a crystal of iodine and a solution of vinyl bromide (10.5 g, 0.10 mol) in tetrahydrofuran. When the magnesium had almost disappeared, ketal aldehyde **56** (14.9 g, 80.0 mmol) in tetrahydrofuran (20 mL) was added dropwise. After 12 h at room temperature the mixture was poured onto ice-water, neutralized (pH 7) with hydrochloric acid (1 M), and extracted with dichloromethane. Chromatography of the crude extract (Florisil, benzene) furnished allylic alcohol **57** (15.9 g, 93%) as a colorless oil; ir ($CHCl_3$, ν cm^{-1}): 3600, 3450, 1650; ^1H nmr ($CDCl_3$, δ ppm): 6.1–4.9 (m, 3H, olefinic), 4.45 (br t, 1H, HCO_2), 4.1 (br m, 1H, OH), 3.80 (m, *H*-COH), 3.50 (m, 4H, $(CH_2O)_2$), 2.0–1.3 (m, 6H), 1.18 (s, 3H, CH_3), 0.70 (s, 3H, CH_3).

*Enone **58***

To a cooled (−20°C) and well-stirred solution of allylic alcohol **57** (2.14 g, 10.0 mmol) in dry acetone (60 mL) was added, dropwise, Jones reagent (3.75 mL, 10 mmol). After 2 h and addition of isopropanol (1 mL) the mixture was warmed to room temperature, diluted with water, and extracted with ether. The combined organic layers were washed with aqueous sodium bicarbonate, dried ($MgSO_4$), and evaporated under reduced pressure. The colorless oily residue (1.95 g, 91%) was stored in the cold. The ir and nmr data have been given (*vide supra*).

*Diels–Alder adducts **59***a* and **59***b*

Spirolactone dienone **6** (1.00 g, 4.54 mmol) was dissolved in benzene (5 mL) and reacted with vinyl ketone acetal **58** (975 mg, 4.60 mmol) at reflux temperature for 15 h. Evaporation of benzene left an oily residue (1.9 g, ~98%) containing two products (~1:1), isomers **59***a* and *b*, which were not separated ir (CH_2Cl_2, ν cm^{-1}): 1820, 1740, 1710; ^1H nmr ($CDCl_3$, δ ppm): 4.70 (d, 0.5H) and 4.32 (d, 0.5H), 4.65 (d, 0.5H) and 4.30 (d, 0.5H) (two embodied AB patterns, J_{AB} = 14.5 Hz) (spirolactonic methylene), 4.45 (br t, 1H, J = 5 Hz, HCO_2), 3.7–3.2 (m, 5H, $(CH_2O)_2$ and H-C11), 3.2–1.4 (m, 15H), 1.23 (s, 3H, CH_3-C5), 1.18 (s, 3H), and 0.70 (s, 3H) (two methyl groups of acetal moiety).

Tetracyclic endo *epimer **60***

To a crude mixture of Diels–Alder adducts **59***a* and *b* (982 mg, 2.27 mmol) in tetrahydrofuran (150 mL) was added aqueous sodium hydroxide (1 M, 9.1 mL). After 4 h of vigorous stirring at room temperature, the solvent was evaporated and the aqueous residue was extracted with ether. Evaporation of the ether furnished a solid residue, which was recrystallized from ether–hexane to give pure *endo* isomer **60** (606 mg, 71%); mp 142–143°C; ir (CH_2Cl_2, ν cm^{-1}): 3500, 1745, 1720; ^1H nmr ($CDCl_3$, δ ppm): 4.50 (br t, 1H, J = 5 Hz, HCO_2), 3.55 (m, 4H, $(CH_2O)_2$), 3.26 (d, 1H, J = 5 Hz, H-C11), 3.0–1.4 (m, 14H), 1.26 (s, 3H, CH_3-C5), 1.20 (s, 3H) and 0.70 (s, 3H) (two methyl groups of acetal moiety); ms *m/e*: 374 (M^+). *Anal.* calcd. for $C_{22}H_{30}O_5$: C 70.52, H 8.07; found: C 70.19, H 8.22.

*Pentacyclic aldehyde **61***

To a solution of tetracyclic diketoacetal **60** (174 mg, 0.46 mmol) in acetone (25 mL) was added hydrochloric acid (3 M, 12 mL) and the mixture was refluxed for 3 h. Acetone was then partly evaporated and the residue was extracted with ether. Chromatography (benzene–ether 1:1) of the crude product on silica gel furnished crystalline pentacyclic aldehyde **61** (33 mg, 25%); mp 147–149°C; ir (CH_2Cl_2, ν cm^{-1}): 3500, 2720, 1740, 1720; ^1H nmr ($CDCl_3$, δ ppm): 9.64 (d, 1H J = 1 Hz, CHO), 3.22 (d, 1H, J = 5 Hz, H-C11), 3.0–1.4 (m, 15H), 1.29 (s, 3H, CH_3); ms *m/e*: 288 (M^+). *Anal.* calcd. for $C_{17}H_{20}O_4$: C 70.81, H 6.99; found: C 70.96, H 6.91.

*Ethyl 3-formyl-4-methylpentanoate (**62**, R = C_2H_5)*

A mixture of diisobutylamine (103 g, 0.79 mol) and isovaleraldehyde (43 g, 0.5 mol) in benzene (250 mL) was refluxed for 12 h (Dean–Stark water separator). Benzene was evaporated and the residue distilled under reduced pressure to give the corresponding enamine (91.6 g, 93%); bp 82°C/1 Torr; ir ($CHCl_3$, ν cm^{-1}): 1650, 1465, 1120, 945; ^1H nmr ($CDCl_3$, δ ppm): 5.80 (br d, 1H, J = 15 Hz, N—C*H*=), 3.95 (dd, 1H, J = 15 and 8 Hz, N—CH=C*H*—), 2.70 (br s, 2H, CH_2), 2.58 (br s, 2H, CH_2), 2.40–1.40 (m, 3H, 3 × -CH-), 0.82 (apparent t, 18H, J = 7.5 Hz, 6 × CH_3-CH). The purified enamine (91.6 g) in acetonitrile (300 mL) was refluxed with ethyl bromoacetate (98 g, 0.55 mol) for 15 h. Water (50 mL) was then added to the mixture and the reflux was continued for 5 h. The cooled reaction mixture was then poured onto cold brine (800 mL) and extracted with ether.

Evaporation of the dried extract left an oil that was distilled under reduced pressure to give ethyl 3-formyl-4-methylpentanoate (**62**, R = C_2H_5) (68 g, 79%); bp 92°C/3 Torr; ir (CH_2Cl_2, ν cm^{-1}): 2720, 1730, 1200; ^1H nmr ($CDCl_3$, δ ppm): 9.96 (br s, 1H, CHO), 4.15 (q, 2H, J = 7 Hz, OCH_2CH_3), 3.0–2.0 (m, 4H), 1.22 (t, 3H, J = 7 Hz, OCH_2CH_3), 1.05 (d, 3H, J = 6 Hz, CH_3CH), 0.95 (d, 3H, J = 6 Hz, CH_3CH); derivative: 2,4-dinitrophenylhydrazone: mp 96.5°C. *Anal.* calcd. for $C_{15}H_{20}O_6N_4$: C 51.13, H 5.59, N 15.90; found: C 51.39, H 5.47, N 15.70.

*Ethyl 3-(1,3-dioxolan-2-yl)-4-methylpentanoate (**63**)*

A mixture of aldehyde ester **62** (R = C_2H_5) (51.5 g, 0.33 mol), ethylene glycol (74 g, 1.2 mol), and *p*-toluenesulfonic acid (20 mg) was refluxed (Dean–Stark water separator) for 24 h. The cooled mixture was then washed with sodium bicarbonate and water and the solvent was evaporated. Distillation of the residue furnished pure acetal **63** (56 g, 91%); bp 96°C/1.5 Torr; ir (CH_2Cl_2, ν cm^{-1}): 1730, 1180, 1170; ^1H nmr ($CDCl_3$, δ ppm): 4.85 (br d, 1H, J = 3 Hz, H-CO_2), 4.09 (q, 2H, J = 7 Hz, -OCH_2CH_3), 3.83 (m, $(CH_2O)_2$), 2.25 (br s, 2H, CH_2CO_2), 2.5–1.6 (m, 2H), 1.21 (t, 3H, J = 7 Hz, OCH_2CH_3), 0.90 (br d, 6H, J = 6 Hz, 2 × CH_3CH). *Anal.* calcd. for $C_{11}H_{20}O_4$: C 61.08, H 9.32; found: C 60.99, H 9.39.

*3-(1,3-Dioxolan-2-yl)-4-methylpentanol (**64**)*

To a mixture of lithium aluminum hydride (9.5 g, 0.25 mol) in dry ether (600 mL) was added dropwise a solution of acetal ester **63** (54 g, 0.25 mol) in dry ether (500 mL). After a stirring period of 14 h at 25°C, the mixture was refluxed for 1 h, then cooled (0°C), and moist ether was added slowly to the mixture. After addition of water, the mixture was extracted with ether. Evaporation of the solvent left pure alcohol **64** (38.2 g, 88%); ir (CH_2Cl_2, ν cm^{-1}): 3600, 3450, 1050; ^1H nmr ($CDCl_3$, δ ppm): 4.82 (br d, 1H, J = 4 Hz, H-CO_2), 3.92 (m, 4H, $(CH_2O)_2$), 3.68 (br t, 2H, J = 7 Hz, CH_2OH), 2.98 (s, 1H, OH), 2.2–1.5 (m, 2H), 1.63 (t, 2H, J = 7 Hz, CH_2CH_2OH), 0.92 and 0.86 (two d, J = 6.5 Hz, $(CH_3)_2CH$). *Anal.* calcd. for $C_9H_{18}O_3$: C 62.04, H 10.41; found: C 61.75, H 10.48.

*3-(1,3-Dioxolan-2-yl)-4-methyl pentanal (**65**)*

Following exactly the same procedure as previously described for oxidation of alcohol **54** (*vide supra*, aldehyde **56**), alcohol **64** (1.74 g, 10.0 mmol) was oxidized to aldehyde **65**. The crude product was chromatographed (silica gel, benzene) to give pure aldehyde **65** (1.07 g, 62%) together with starting material (3.40 mg, 19%) (eluted with benzene–ether 2:1); ir (CH_2Cl_2, ν cm^{-1}): 2720, 1720, 1120, 1050; ^1H nmr ($CDCl_3$, δ ppm): 9.65 (t, 1H, J = 2.5 Hz, CHO), 4.96 (d, 1H, J = 4 Hz, H-CO_2), 3.86 (m, 4H, $(CH_2O)_2$), 2.33 (br s, CH_2CHO), 2.5–1.5 (m, 2H), 1.02 and 0.95 (two d, J = 6.5 Hz, $(CH_3)_2CH$).

*Allylic alcohol **66***

Following exactly the same procedure previously described for allylic alcohol **57** (*vide supra*), allylic alcohol **66** was obtained from aldehyde **65** (13.6 g, 80.0 mmol) in a pure form after chromatography on Florisil (hexane–ether 9:1) (14.9 g, 94%); ir (CH_2Cl_2, ν cm^{-1}): 3600, 3450, 1125; ^1H nmr ($CDCl_3$, δ ppm): 6.1–5.5 (m, 1H) and 5.4–4.8 (m, 2H) (olefinic), 4.78 (d, 1H, J = 4 Hz, HCO_2), 4.3–3.5 (m, 2H, CH-OH), 3.80 (m, 4H, $(CH_2O)_2$), 2.1–1.3 (m, 4H), 0.88 (d, 6H, J = 6.5 Hz, $(CH_3)_2CH$). *Anal.* calcd. for $C_{11}H_{20}O_3$: C 65.97, H 10.07; found: C 65.70, H 10.28.

*Enone **67***

Following exactly the same procedure previously described for enone **58** (*vide supra*), enone **67** was obtained from allylic alcohol **66** (2.0 g, 10 mmol) as a sensitive colorless oil. An analytical sample was prepared by thin-layer chromatography (benzene) (1.81 g, 90%); ir (CH_2Cl_2, ν cm^{-1}): 1720, 1620; ^1H nmr ($CDCl_3$, δ ppm): 6.4–5.5 (m, 3H, olefinic), 4.82 (d, 1H, J = 3 Hz, HCO_2), 3.80 (m, 4H, $(CH_2O)_2$), 2.8–2.1 (m, 2H, (CH_2CO), 2.0–1.4 (m, 2H), 0.88 (d, 3H, J = 6 Hz) and 0.82 (d, 3H, J = 6 Hz) ($(CH_3)_2CH$). *Anal.* calcd. for $C_{11}H_{20}O_3$: C 66.70, H 9.15; found: C 66.70, H 9.08.

*Ethyl 3-isopropyl-5-methoxy-4-pentenoate (**68**, R = C_2H_5)*

Sodium hydride (~50% oil, 3.12 g, 65 mmol) was washed with dry hexane (3 × 50 mL), then dissolved in dry dimethyl sulfoxide (33 mL). After stirring for 45 min at 60°C the mixture was cooled at ~15°C and reacted with a solution of (methoxymethyl)triphenylphosphonium chloride (22.3 g, 65 mmol) in dry dimethyl sulfoxide (70 mL). After 15 min at 25°C, the deep red mixture was treated with a solution of ester aldehyde **62** (R = C_2H_5) (8.6 g, 50 mmol) in dimethyl sulfoxide (25 mL), and stirring was continued for 17 h. The mixture was then poured onto ice-water (200 mL) and extracted several times with pentane. Solvent was evaporated from the dried extract and a rapid filtration (silica gel, hexane) of the crude product removed the residual triphenylphosphine oxide. A mixture of isomers, *cis* and *trans* (*30:70*) enol ethers **68** (R = C_2H_5), (6.79 g, 68%) was obtained pure after distillation under reduced pressure; bp 85°C/2 Torr; ir (CH_2Cl_2, ν cm^{-1}): 1730, 1675, 1660, 950; ^1H nmr ($CDCl_3$, δ ppm): 6.25 (d, 0.7H, J = 12 Hz, *trans*-CH_3O-CH=CH), 5.92 (d, 0.3H, J = 6 Hz, *cis*-CH_3OCH=CH), 4.7–4.2 (m, 1H, CH_3OCH=CH-), 4.10 (q, 2H, J = 7 Hz, OCH_2CH_3), 3.53 (s, 0.9H, *cis*-OCH_3), 3.48 (s, 2.1H, *trans*-OCH_3), 2.30 (m, 3H, -CH_2CO_2- and -$CHCH_2CO_2$), 1.66 (m, 1H, $CH(CH_3)_2$), 1.20 (t, 3H, J = 7.5 Hz, OCH_2CH_3, 0.85 (d, 3H, J = 6 Hz) and 0.81 (d, 3H, J = 6 Hz) ($(CH_3)_2CH$). *Anal.* calcd. for $C_{11}H_{20}O_3$: C 65.97, H 10.07; found: C 65.75, H 10.07.

*Ketal ester **69** (R = CH_2CH_3)*

A mixture of isomers **68** (R = CH_2CH_3) (10.0 g, 50 mmol), ethylene glycol (6.2 g, 100 mmol), and *p*-toluenesulfonic acid (10 mg) was refluxed in benzene (100 mL) for 24 h (Dean–Stark). The cooled mixture was then washed with aqueous sodium bicarbonate and water. Evaporation of the solvent from the dried extract furnished crude ketal ester **69** (R = CH_2CH_3), which was purified by distillation under reduced pressure (10.8 g, 94%); bp 96°C/1.5 Torr; ir (CH_2Cl_2, ν cm^{-1}): 1730, 1180, 1040; ^1H nmr ($CDCl_3$, δ ppm): 4.88 (t, 1H, J = 5 Hz, HCO_2), 4.10 (q, 2H, J = 7 Hz, -OCH_2CH_3), 3.85 (m, 4H, $(CH_2O)_2$), 2.4–1.5 (m, 6H), 1.25 (t, 3H, -OCH_2CH_3), 0.85 (d, 6H, J = 6 Hz, $(CH_3)_2CH$). *Anal.* calcd. for $C_{12}H_{22}O_4$: C 62.24, H 9.56; found: C 62.83, H 9.34.

*Ketal acid **70***

To a solution of acetal ester **69** (4.6 g, 20 mmol) in ethanol (100 mL) was added, at 25°C, aqueous sodium hydroxide (50 mL, 1 M). After 2 h of stirring, the main part of the ethanol was evaporated and the aqueous basic layer was first washed with ether (2 × 50 mL), then acidified (pH ~5) with hydrochloric acid (55 mL, 1 M) and extracted with ether (4 × 50 mL). Evaporation of the solvent furnished pure acid **70** (3.98 g, 98%); ir (CH_2Cl_2, ν cm^{-1}): 3500–2400 (br), 1710, 1150; ^1H nmr ($CDCl_3$, δ ppm): 11.18 (s, 1H, CO_2H), 4.90 (t, 1H, H-CO_2), 3.90 (m, 4H, $(CH_2O)_2$), 2.5–1.5 (m, 6H), 0.88 (d, 6H, J = 6 Hz, $(CH_3)_2CH$). *Anal.* calcd. for $C_{10}H_{18}O_4$: C 59.42, H 8.95; found: C 59.55, H 9.13.

*Alcohol **71***

This reduction was done as for ester **63** (*vide supra*, compound **64**). Thus, ester **69** (7.45 g, 32.4 mmol) furnished ketal alcohol **71** (6.0 g, 98%); ir ($CHCl_3$, ν cm^{-1}): 3600, 3450, 1050; ^1H nmr ($CDCl_3$, δ ppm): 4.91 (br t, 1H, J = 5 Hz, HCO_2), 4.05–3.5 (m, 6H, $(CH_2O)_2$ and CH_2OH), 2.77 (br s, 1H, OH), 1.8–1.3 (m, 6H), 0.80 (d, 6H, J = 6 Hz, $(CH_3)_2CH$).

*Aldehyde **72***

To a solution of chromic oxide – pyridine complex (25.0 g, 95 mmol) in dry dichloromethane (250 mL) was added rapidly a solution of alcohol **71** (3.05 g, 16 mmol) in dichloromethane (50 mL). After 30 min of vigorous stirring at 25°C, the mixture was poured onto ice-water and extracted with dichloromethane. The organic layer was dried over magnesium sulfate and the solvent was evaporated. The crude colored residue was filtered through a short pad of silica gel to give pure aldehyde **72** as a colorless oil (2.77 g, 95%); ir (CH_2Cl_2, ν cm^{-1}): 2720, 1720, 1122; ^1H nmr ($CDCl_3$, δ ppm): 9.79 (t, 1H, J = 3 Hz, CHO), 4.90 (t, 1H, J = 5 Hz, HCO_2), 3.90 (m, 4H, $(CH_2O)_2$), 2.6–1.2 (m, 6H), 0.90 (d, 6H, J = 6.5 Hz, $(CH_3)_2CH$).

*Allylic alcohol **73***

Following exactly the same procedure previously described for the

formation of allylic alcohol **57** (*vide supra*), allylic alcohol **73** was obtained from aldehyde **72** (4.13 g, 23 mmol) as a colorless oil (4.9 g, 98%); ir (CH_2Cl_2, ν cm^{-1}): 3600, 3450, 1650; ^1H nmr ($CDCl_3$, δ ppm): 6.1–4.8 (m, 3H, olefinic), 4.91 (br t, 1H, J = 5 Hz, H-CO_2), 3.90 (m, 4H, $(CH_2O)_2$), 3.81 (m, 1H, *H*COH), 2.1–1.1 (m, 6H), 0.86 (d, 6H, J = 6 Hz, $(CH_3)_2CH$).

Dienophile 74

(a) From ketal acid 70

To a stirred suspension of lithium hydride (680 mg, 0.085 mol) in tetrahydrofuran (200 mL) was added dropwise a solution of ketal acid **70** (15.15 g, 0.075 mol) in tetrahydrofuran (40 mL). After 2 h at 75–80°C, the mixture was cooled at 0°C, treated with vinyllithium (2.9 M in THF, 36 mL, 0.10 mol), then warmed (50–55°C) for 1 h. It was then poured onto an ice – hydrochloric acid mixture (200 mL, 1 M), and extracted with ether. The organic layers were combined, washed with aqueous sodium carbonate solution (5%) and brine, dried, and the solvents evaporated to give a crude neutral extract. Acidification (pH 6) of basic aqueous washings and extraction (ether) gave unreacted starting ketal acid **70** (6.1 g, 40%). Chromatographic purification (silica gel, hexane, benzene–ether mixtures) of the crude neutral extract furnished enone **74** as a sensitive colorless oil (7.37 g, 78% based on reacted acid **70**); ir (CH_2Cl_2, ν cm^{-1}): 1690, 1615, 1410, 1140; ^1H nmr ($CDCl_3$, δ ppm): 6.4–5.6 (m, 3H, olefinic), 4.85 (t, 1H, J = 5 Hz, HCO_2), 3.85 (m, 4H, $(CH_2O)_2$), 2.7–2.4 (m, 2H, CH_2CO), 2.3–1.4 (m, 4H), 0.86 (br d, 6H, J = 6 Hz, $(CH_3)_2CH$).

(b) From alcohol 73

Following exactly the same procedure previously described for the formation of enone **58** (*vide supra*), oxidation of alcohol **73** (4.91 g, 22 mmol) by Jones reagent (8.6 mL, 23 mmol) gave enone **74** (3.77 g, 81%) as a pure colorless oil; ir and nmr data have been given (*vide supra*).

Diels–Alder adducts 75a + b and 76a + b

A solution of spirolactone dienone **6** (4.30 g, 19.5 mmol) and enone **67** (4.64 g, 23.4 mmol) in benzene (60 mL) was refluxed for 9 h. Evaporation of benzene left an oily residue containing compounds **75***a* and *b*, **76***a* and *b*, which were not separated; ^1H nmr ($CDCl_3$, δ ppm): 4.85 (br d, 1H, J = 3.5 Hz, H-CO_2), 4.70 (d, 0.5H) and 4.32 (d, 0.5H), 4.65 (d, 0.5H) and 4.30 (d, 0.5H) (two embodied AB patterns, J_{AB} = 14 Hz) (spirolactonic methylene), 3.82 (br s, 4H, $CH_2O)_2$), 3.60 (m, 1H, H-C11 for 4 isomers), 3.2 (m, 1H, H-CCO), 3.0–1.3 (m, 12H), 1.25 (br s, 3H, CH_3-C5), 0.93 (d, 3H, J = 7 Hz) and 0.88 (d, 3H, J = 7 Hz) $(CH_3)_2CH$).

Tetracyclic ketal diketones 77–80

To a crude mixture of Diels–Alder adducts **75***a* + *b* and **76***a* + *b* (3.00 g, 7.2 mmol) in tetrahydrofuran (200 mL) was added an aqueous solution of potassium hydroxide (1 M, 28.7 mL). After 20 h of stirring at 25°C, tetrahydrofuran was evaporated and the aqueous residue was extracted with ether. The crude extract (1.83 g) showed three acetalic protons as doublets at δ 5.25 (J = 9 Hz) (major one), 5.08 (J = 6 Hz), and 4.75 (J = 7 Hz). Crystallization of the crude mixture (ether) furnished ketal diketone **77** (or **79**) (750 mg, 29%) plus a mixture of **77** and *exo* epimer **78** (or **80**). This mixture was submitted to the same basic treatment and gave an additional crop of crystalline *endo* **77** (or **79**) (153 mg, 6%) (total 35% yield in isomer *endo* **77** (or **79**); mp 204–206°C; ir ($CHCl_3$, ν cm^{-1}): 3500, 1735, 1710, 1210 cm^{-1}; ^1H nmr ($CDCl_3$, δ ppm): 5.25 (d, 1H, J = 9 Hz, HCO_2), 4.0–3.6 (m, 4H, $(CH_2O)_2$), 3.26 (d, 1H, J = 5 Hz, H-C11), 3.01–1.6 (m), 1.25 (s, 3H, CH_3-C5), 0.90 (d, 6H, J = 6.5 Hz, $(CH_3)_2CH$); ms *m/e*: 360 (M^+). *Anal.* calcd. for $C_{21}H_{28}O_5$: C 69.98, H 7.83; found: C 69.88, H 7.76.

Diels–Alder racemic adducts 81a + b and 82a + b

A solution of spirolactone dienone **6** (0.935 g, 4.22 mmol) and racemic dienophile **74** (1.117 g, 5.26 mmol) in benzene (6 mL) was refluxed for 16 h under nitrogen. Benzene was then evaporated to leave a mixture containing essentially 4 components (hardly separated on tlc after multiple elutions). Rapid filtration on silica gel (hexane–Et_2O 30%) removed the unreacted dienophile to give a pure mixture of adducts **81** and **82** (1.84 g, 99%); ir ($CHCl_3$, ν cm^{-1}): 1815, 1735, 1710 cm^{-1}; ^1H nmr ($CDCl_3$, δ ppm): 4.80 (m, 1H, HCO_2), ~4.5 (two embodied AB patterns, J = 14 Hz, OCH_2CO_2), 3.85 (m, 4H, $(CH_2O)_2$), 3.60 (m, 1H, H-C11), 3.4–1.4 (m, 15H), 1.27 (s, 3H, CH_3C5), 0.85 (br d, 6H, J = 7 Hz, $(CH_3)_2CH$). This mixture was used for the next step without any further purification.

Racemic tetracyclic ketones 83–86

To a stirred solution of Diels–Alder racemic adducts **81***a* + *b* and **82***a* + *b* (1.840 g, 4.22 mmol) in tetrahydrofuran (75 mL) was added aqueous sodium hydroxide solution (1 M, 14 mL). After 15 h at room temperature, the main part of THF was evaporated and the residue was extracted with ether (4 × 75 mL). Evaporation of the solvent gave an oily residue containing four compounds: **83**:**84**:**85**:**86** in the relative proportions (37:19:16:28) as given by the integration of the bridgehead proton (H-C11) of each component of the mixture. These compounds showed the following relative R_f values (benzene–ether 15%, solutions): **85** < **83** < **84** < **86**. By preparative thin-layer chromatography (benzene–ether 10%, 4 elutions) and crystallization, it was possible to obtain pure compounds **83**, **85**, and **86**.

Isomer 83: mp 57°C, ir ($CHCl_3$, ν cm^{-1}): 3530, 1745, 1715 cm^{-1}; ^1H nmr ($CDCl_3$, δ ppm): 4.84 (t, 1H, J = 4.5 Hz, HCO_2), 3.87 (m, 4H, $(CH_2O)_2$), 3.28 (d, 1H, J = 5.0 Hz, H-C11), 2.68 (m, 1H, H-C14), 2.6–1.6 (m, 13H), 1.27 (s, 3H, CH_3-C5), 0.88 (d, 6H, J = 7.3 Hz, $(CH_3)_2CH$); ms *m/e*: 374 (M^+). *Anal.* calcd. for $C_{22}H_{30}O_5$: C 70.55, H 8.07; found: C 69.50, H 8.36.

Isomer 84: obtained as a mixture (~1:1) with **86**: ^1H nmr ($CDCl_3$, δ ppm): 4.90 (t, 1H, J = 4.6 Hz, HCO_2), 3.90 (m, 4H, $(CH_2O)_2$), 3.48 (d, 1H, J = 5.2 Hz, H-C11), 2.7–1.6 (m, 14H), 1.25 (s, 3H, CH_3-C5); 0.93 (d, 3H, J = 6.7 Hz, CH_3CH), 0.84 (d, 3H, J = 6.7 Hz, CH_3CH).

Isomer 85: mp 78–80°C; ir ($CHCl_3$, ν cm^{-1}): 3500, 1740, 1715 cm^{-1}; ^1H nmr ($CDCl_3$, δ ppm): 4.88 (t, 1H, J = 4.4 Hz, HCO_2), 3.90 (m, 4H, $(CH_2O)_2$), 3.54 (s, 1H, OH), 3.17 (d, 1H, J = 4.9 Hz, HC15), 3.01 (dd, 1H, J_{vic} = J_W = 2.3 Hz, H_{exo}-C1), 2.70 (dddd, 1H, HC15), 2.50 (m, 2H) and 2.40 (m, 2H) (allylic protons), 2.00 (m, 2H, H_2C8), 1.80 (m, 6H), 1.27 (s, 3H, CH_3-C5), 0.88 (d, 3H, J = 7 Hz) and 0.85 (d, 3H, J = 7 Hz) $(CH_3)_2CH$); ms *m/e*: 374. *Anal.* calcd. for $C_{22}H_{30}O_5$: C 70.55, H 8.07; found C 69.53, H 8.38.

Isomer 86: mp 120–122°C; ir ($CHCl_3$, ν cm^{-1}): 3530, 3400, 1740, 1715; ^1H nmr ($CDCl_3$, δ ppm): 4.86 (t, 1H, J = 4.8 Hz, HCO_2), 3.90 (m, 4H, $(CH_2O)_2$), 3.43 (d, 1H, J = 5.3 Hz, HC11), 3.14 (s, 1H, -OH), 2.57 (ddd, 1H, HC15), 2.52 (m, 2H), and 2.41 (m, 2H) (allylic protons), 2.29 (m, 1H, $CH(CH_3)_2$), 2.14 (d, 1H, J = 3.9 Hz, H_{endo}-C1), 2.02 (m, 2H, H_2C8), 1.95–1.50 (m, 5H), 1.25 (s, 3H, CH_3-C5), 0.93 (d, 3H, J = 6.7 Hz) and 0.87 (d, 3H, J = 6.7 Hz) $(CH(CH_3)_2)$; ms *m/e*: 374 (M^+).

Racemic pentacyclic diol aldehyde 87

A solution of the preceding crude mixture of compounds **83–86** (1.975 g, 5.28 mmol) in aqueous acetic acid (70%, 50 mL) was heated at 70°C for 1 h. The solvents and volatile substances were removed by evaporation under reduced pressure, then the oily residue was dissolved in tetrahydrofuran (150 mL) and stirred (25°C, 15 h) in the presence of aqueous sodium hydroxide (1 M, 40 mL). After removal of the organic solvent, the aqueous residue was extracted with ether (5 × 100 mL). The organic layers were combined, dried, filtered, and evaporated. The residue was crystallized from chloroform – petroleum ether to give racemic pentacyclic diol aldehyde **87** (400 mg, 23% from dienone **6**); mp 198–199°C; ir ($CHCl_3$, ν cm^{-1}): 3500, 2710, 1725; ^1H nmr ($CDCl_3$, δ ppm): 9.57 (d, 1H, J = 3.1 Hz, -CHO), 3.14 (d, 1H, J = 5.1 Hz, H-C11), 2.75 (dd, 1H, J = 5.1, 3.0 Hz, H-C1), 2.65 (dd, 1H, J = 11.0, 3.1 Hz, H-C3), 2.70–2.38 (m, 5H, H-C2, allylic protons, $HC(CH_3)_2$), 1.44 (m, 2H, H_2C14), 1.28 (s, 3H, CH_3C5), 1.11 (d, 3H, J = 6.4 Hz) and 0.77 (d, 3H, J = 6.7 Hz) $(CH(CH_3)_2)$; ms *m/e*: 330 (M^+). *Anal.* calcd. for $C_{20}H_{26}O_4$: C 72.70, H 7.93; found: C 72.63, H 8.06.

Pentacyclic carbonate aldehyde 89

To a solution of diol aldehyde **87** (120 mg, 0.36 mmol) in benzene (10 mL) was added pyridine (4 mL) and a saturated benzenic solution of

phosgene (10 mL). After 15 min at room temperature the mixture was poured onto ice-water and extracted with ether. The crude product was crystallized from chloroform – petroleum ether to give carbonate aldehyde **89** (88 mg, 68%); mp 186–188°C; ir ($CHCl_3$, ν cm^{-1}): 1805, 1740, 1725; ^1H nmr ($CDCl_3$, δ ppm): 9.57 (d, 1H, J = 3.0 Hz, -CHO), 3.40 (d, 1H, J = 5.3 Hz, H-C11), 3.03 (dd, 1H, J = 6.7 Hz, 2.2 Hz, H-C1), 2.87 (m, 1H, H-C2), 2.74 (dd, 1H, J = 11.4, 3.0 Hz, H-C3), 2.50 (m, 5H, H-C15 and allylic protons), 2.1–1.8 (m, 3H, H_2C8 and $CH(CH_3)_2$), 1.56 (m, 2H, H_2C14), 1.36 (s, 3H, CH_3C5), 1.14 (d, 3H, J = 6.5 Hz) and 0.81 (d, 3H, J = 6.8 Hz) ($(CH_3)_2CH$); ms m/e: 356 (M^+).

*Orthoacetates **90** and **91***

A solution of diol aldehyde **87** (525 mg, 1.59 mmol) and *p*-toluenesulfonic acid (6 mg) in acetic anhydride (60 mL) was heated at 70°C for 3 h. Acetic anhydride was then evaporated and the oily residue was purified by preparative thin-layer chromatography (benzene–ether 9:1, three elutions) to give orthoacetates **90** (120 mg, 18%), and **91** (108 mg, 16%).

*Orthoacetate **90***: mp 157–158°C; ir ($CHCl_3$, ν cm^{-1}): 1735, 1370, 1230, 1040; ^1H nmr ($CDCl_3$, δ ppm): 6.06 (d, 1H, J = 2 Hz, *H*COAc), 4.09 (d, 1H, J = 5 Hz, H-C11), 3.68 (dd, 1H, J = 6.5, 2.0 Hz, H-C1), 2.7–1.5 (m, 13H), 2.15 (s, 3H) and 2.12 (s, 3H) (acetate and orthoacetate), 1.39 (s, 3H, CH_3-C5), 1.20 (d, 3H, J = 5.5 Hz) and 0.87 (d, 3H, J = 5.5 Hz) ($(CH_3)_2CH$); ms m/e: 414 (M^+). *Anal.* calcd. for $C_{26}H_{32}O_7$: C 68.40, H 7.06; found: C 68.50, H 7.20.

*Orthoacetate **91***: ir ($CHCl_3$, ν cm^{-1}): 1735, 1370, 1230, 1070, 1040; ^1H nmr ($CDCl_3$, δ ppm): 6.41 (d, 1H, J = 5.5 Hz, *H*COAc), 4.15 (d, 1H, J = 5 Hz, HC11), 3.65 (dd, 1H, J = 6.5, 2.0 Hz, H-C1), 2.8–1.2 (m, 13H), 2.15 (s, 3H) and 2.12 (s, 3H) (acetate and orthoacetate), 1.39 (s, 3H, CH_3C5), 1.26 (d, 3H, J = 6 Hz) and 0.78 (d, 3H, J = 6 Hz) ($(CH_3)_2CH$); ms m/e: 414 (M^+).

*Monodeuterated diol aldehyde **87**-d_1*

A crude mixture of tricyclic Diels–Alder adducts **81***a* + *b* and **82***a* + *b* (3.93 g, 9.1 mmol) in tetrahydrofuran (100 mL) was reacted with a solution of sodium hydroxide (1.22 g) in deuterium oxide (30.5 mL) at room temperature for 16 h. The main part of the tetrahydrofuran was evaporated and the aqueous residue extracted with ether. The crude extract (3.3 g, 96%) was dissolved in tetrahydrofuran (100 mL) and reacted with aqueous sodium hydroxide (1 M, 30 mL) for 6 h at room temperature. Evaporation of tetrahydrofuran and ether extraction of the aqueous residue gave crude monodeuterated (position 15) mixture **77–80** (2.5 g, 76%), which was dissolved in aqueous acetic acid (70%, 80 mL) and heated at 70°C for 45 min. Evaporation of the volatile substances left a residue that was dissolved in tetrahydrofuran (100 mL) and reacted with aqueous sodium hydroxide (1 M, 60 mL). After 16 h at room temperature the aqueous residue was extracted with ether to give an oily mixture, which was purified by chromatography and crystallization as previously described (*vide supra*, compound **87**) to give diol aldehyde **87**-d_1 (320 mg, 15%); ^1H nmr ($CDCl_3$) identical to nmr spectrum of **87** except for the following: 3.14 (s, 1H, H-C11), 2.75 (d, J = 5.1 Hz, HC1) and 2.33 (no multiplet).

*Monodeuterated orthoacetates **90**-d_1 and **91**-d_1*

A solution of monodeuterated diol aldehyde **87**-d_1 (280 mg, 0.85 mmol) was reacted with acetic anhydride and *p*-toluenesulfonic acid as previously described (see the preceding preparation) to give monodeuterated **90**-d_1 (82 mg, 21%, mp 156–157°C) and **91**-d_1 (90 mg, 23%).

*Orthoacetate **90**-d_1*: ^1H nmr ($CDCl_3$, δ ppm) same as for **90** except for the following: 4.09 (s, 1H, H-C11), 3.68 (d, 1H, J = 6.5 Hz, H-C1).

*Orthoacetate **91**-d_1*: ^1H nmr ($CDCl_3$, δ ppm) same as for **91** except for the following: 4.15 (s, 1H, H-C11), 3.65 (d, 1H, J = 6.5 Hz, H-C1).

*Basic treatment performed on isomers **83–86***

*On isomer **83***: To a stirred solution of isomer **83** (30 mg, 0.080 mmol) in tetrahydrofuran (3 mL) was added aqueous sodium hydroxide (0.75 mL, 1 M). After 18 h at 25°C, extraction of the reaction mixture with ether furnished unchanged starting material (26 mg, 86%) as shown by nmr and tlc analysis.

*On isomer **84***: same as for **83** with the following quantities: 14 mg of a mixture ~2:1 of **84** and **86**; NaOH, 1 M, 0.4 mL. Crude product (4 mg, 28%) showed the presence of **83**, **85**, and **86** by nmr.

*On isomer **85***: same as for **83** with the following quantities: isomer **85** (33 mg, 0.088 mmol), sodium hydroxide (0.8 mL, 1 M), tetrahydrofuran (3 mL). Crude product (10 mg, 30%) showed the presence of **85** and **86** (respectively ~2:1, by nmr).

*On isomer **86***: same as for **83**: isomer **86** (28 mg, 0.075 mmol), sodium hydroxide (0.8 mL, 1 M), tetrahydrofuran (3 mL). Crude product (12 mg, 43%) showed the presence of isomers **85** and **86** (respectively ~2:1, by nmr).

*Cyclization of isomer **83***

A solution of pure isomer **83** (30 mg, 0.080 mmol) in aqueous acetic acid (70%, 5 mL) was heated at 70°C for 45 min. Evaporation of the volatile substances left a residue that was dissolved in tetrahydrofuran (3 mL) and reacted with aqueous sodium hydroxide (1 mL, 1 M). After 16 h at room temperature, the mixture was extracted with ether to give pure diol aldehyde **87** (26 mg, 98%).

*(+)-Dihydrocarvone ((S)-**95**)*

A mixture of (+)-carvone ((*S*)-**94**) (50.0 g, 0.33 mol) and platinum oxide (0.10 g) was stirred under hydrogen at 25°C for 7 h. The catalyst was then removed by filtration through a short column of silica gel (ether). Evaporation of the solvent left colorless pure (+)-dihydrocarvone ((*S*)-**94**) (50 g, 99%); ir (neat, ν cm^{-1}): 1680, 1200; ^1H nmr ($CDCl_3$, δ ppm): 6.78 (m, 1H, H-C3), 2.7–1.3 (m, 6H), 1.77 (m, 3H, CH_3-C2), 0.88 (d, 6H, J = 5.5 Hz, $(CH_3)_2CH$). *(−)-Dihydrocarvone* ((*R*)-**95**): hydrogenation of (−)-carvone ((*R*)-**94**) (33.0 g, 0.217 mol) was done in the same way to furnish (−)-dihydrocarvone ((*R*)-**95**) (33 g, 99%).

*(3S)-3-Isopropyl-5-oxopentanoic acid ((S)-**96**)*

A solution of (+)-dihydrocarvone ((*S*)-**95**, 20.06 g, 131.5 mmol) in ethyl acetate (150 mL) was treated by a stream of ozone at −78°C until a blue color persisted (50 min approximately). The mixture was warmed at room temperature while a stream of nitrogen was bubbled through the yellowish solution. The reaction mixture was then cooled (ice water) and stirred in a hydrogen atmosphere in the presence of 10% palladium-on-charcoal (200 mg) catalyst. After 5 h, removal of the catalyst by filtration on Celite left the crude aldehyde acid (*S*)-**96** (20.5 g); ir (CCl_4, ν cm^{-1}): 3500–2800 br, 1770–1715 br; ^1H nmr ($CDCl_3$, δ ppm): 9.6 (m, 1H, CHO), 9.1 (br m, 1H, CO_2H), 2.8–1.2 (m, 6H), 0.90 (d, 6H, J = 6 Hz, $CH(CH_3)_2$).

*(3S)-5,5-Ethylenedioxy-3-isopropylpentanoic acid ((S)-**70**)*

To a solution of the crude aldehyde acid (*S*)-**96** (20.5 g, 130 mmol) in benzene (250 mL) were added ethylene glycol (25.2 g, 0.41 mol) and *p*-toluenesulfonic acid (0.50 g). The mixture was refluxed (Dean–Stark) for 16 h, then cooled, diluted with ether (200 mL), and washed with water (2 × 50 mL) and brine. Evaporation of the solvents left a crude mixture that was dissolved in methanol (150 mL) and reacted with aqueous sodium hydroxide (1 M, 150 mL) at 65°C for 4 h. Methanol was then evaporated under reduced pressure and the aqueous layer was washed with ether to remove neutral impurities. Acidification (pH 5, 0°C, 1 M HC1) of the basic aqueous layer and extraction with ether (4 × 100 mL) furnished ketal acid (*S*)-**70** (22.2 g, 99%): *vide supra* for spectroscopic data.

*(3R)-5,5-Ethylenedioxy-3-isopropylpentanoic acid ((R)-**70**)*

Same procedure as for (*S*)-**70** from aldehyde acid (*R*)-**96**.

*Methyl (3S) and (3R)-5,5-ethylenedioxy-3-isopropyl pentanoate ((S)-**69**, R = CH_3)*

(a) By esterification with diazomethane

A solution of ketal acid (*S*)-**70** (5.6 g, 27 mmol) or (*R*)-**70** (5.15 g, 25 mmol) in dry ether (100 mL) was reacted at −78°C with a slight excess of diazomethane in ether (~20 mg/mL, 100 mL). Evaporation of the solvent left ester (*S*)-**69** (R = CH_3, 5.3 g, 95%) or ester (*R*)-**69** (R

= CH_3, 5.18 g, 96%): ir (neat, ν cm^{-1}): 1740; ^1H nmr ($CDCl_3$, δ ppm): 4.93 (t, 1H, J = 5 Hz, HCO_2), 3.92 (m, 4H, $(CH_2O)_2$), 3.69 (s, 3H, OCH_3), 2.5–1.4 (m, 6H), 0.88 (d, 6H, $(CH_3)_2CH$); ms *m/e*: 216 (M^+). *Anal.* calcd. for $C_{11}H_{20}O_4$: (*S*)-**69** (R = CH_3): C 61.08, H 9.32; found: C 60.95, H 9.44; for (*R*)-**69** (R = CH_3): found: C 60.84, H 9.20; $[\alpha]_{578}^{25}$ for (*S*)-**69** (R = CH_3): +0.6°, neat, and for (*R*)-**69** (R = CH_3): −0.6°, neat.

(b) By esterification with methyl iodide

A mixture of the crude acetal acid (*S*)-**70** (142 g, 0.7 mol), anhydrous potassium carbonate (146 g), and methyl iodide (300 mL, 4.8 mol) in acetone (2 L) was refluxed for 25 h under nitrogen. The cooled mixture was then filtered and the solvent evaporated. The oily residue was dissolved in ether (1.4 L), washed twice with aqueous potassium carbonate (10%), twice with brine, and dried ($MgSO_4$). Evaporation of the solvent left an oil, which was distilled under reduced pressure (bp 84–86°C, 0.2 Torr, ~136 g, 90%) to give pure ketal ester (*S*)-**69** (R = CH_3).

Dienophile (S)-74

From ketal acid (*S*)-**70**. This reaction was done as for racemic dienophile **74** (*vide supra*). Dienophile **74** ($[\alpha]_{578}^{25}$ +0.7°, neat) was obtained in 75% yield based on reacted acid.

From ketal ester (*S*)-**69** (R = CH_3). This sequence was done exactly as for racemic material (*vide supra*, **69** → **74**) in an overall yield of ~80%.

Dienophile (R)-74

This material was obtained from ketal ester (*R*)-**69** (R = CH_3) as just described for dienophile (*S*)-**74** in the same overall yield of ~80% ($[\alpha]_{578}^{25}$ −0.6°, neat).

Pentacyclic diol aldehyde (dextro)-87

Starting from *o*-spirolactone dienone **6** (6.75 g, 30.6 mmol) and dienophile (*S*)-**74** (7.4 g, 34.8 mmol), the synthesis of (*dextro*)-**87** was done in the same way as described for racemic aldehyde **87** (*vide supra*); mp 165–165.5°C; $[\alpha]_{578}^{25}$ +142.2°.

Pentacyclic diol aldehyde (levo)-87

Starting from *o*-spirolactone dienone **6** (2.00 g, 9.13 mmol) and dienophile (*R*)-**74** (2.13 g, 10.04 mmol), aldehyde (*levo*)-**87** was obtained (0.52 g, 17%); mp 161–162°C; $[\alpha]_{578}^{25}$ −137.5°. *Anal.* calcd. for $C_{20}H_{26}O_4$: C 72.70, H 7.93; found: C 72.63, H 8.06.

Pentacyclic carbonate aldehyde (dextro)-89

This compound was synthesized from diol aldehyde (*dextro*)-**87** as for racemic **89** (*vide supra*); mp 186–188°C, $[\alpha]_D^{25}$ +121.3°.

5,6-Dimethoxy-1-methylindene (112)

To a solution of 5,6-dimethoxy-1-indanone (**110**) (100 g, 0.52 mol) in tetrahydrofuran (3.2 L) was added, at −55°C and under nitrogen, a solution of methyllithium in ether (1 mol, 500 mL). The mixture was then warmed to room temperature and stirred for 16 h. Water (100 mL) and hydrochloric acid (1 mol) were added to the cooled mixture and the organic layer was separated. The aqueous layer was then extracted (4 × 250 mL) with ether. The usual evaporation of the dried ($MgSO_4$) organic extract afforded a crude material, which was chromatographed on Florisil (benzene) to give pure compound **112** (96.4 g, 97%); mp 91–92°C (ether–hexane); ir ($CHCl_3$, ν cm^{-1}): 1610, 1580, 1490, 1340, 1270, 1220, 1130, 1060; ^1H nmr (CCl_4, δ ppm): 6.88 (br s, 1H, H-C7), 6.75 (s, 1H, H-C4), 5.99 (m, 1H, H-C2), 3.79 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.14 (m, 2H, H_2C3), 2.08 (m, 3H, CH_3-C1); ms *m/e*: 190 (M^+). *Anal.* calcd. for $C_{12}H_{14}O_2$: C 75.76, H 7.42; found: C 75.84, H 7.24.

5,6-Dimethoxy-1-methylindane (113)

A mixture of methylindene **112** (40 g, 0.21 mol) and platinum oxide (320 mg) in acetic acid (800 mL) was shaken in an hydrogen atmosphere for 48 h. The catalyst was removed by filtration and the acetic acid was evaporated under reduced pressure to leave an oil, which was filtered on Florisil (benzene as eluent) to give oily methylindane **113** (33.27 g, 83%): ir ($CHCl_3$, ν cm^{-1}): 1610; ^1H nmr (CCl_4, δ ppm): 6.17 (br s, 2H, aromatic), 3.72 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.2–1.5 (m, 5H), 1.22 (d, 3H, J = 7 Hz, CH_3-C1); ms *m/e*: 192 (M^+). *Anal.* calcd. for $C_{12}H_{16}O_2$: C 74.97, H 8.39; found: C 74.94, H 8.24.

Isomeric dimethoxyindane aldehydes 114 and 115

To a solution of methylindane **113** (7.50 g, 39 mmol) in dry dichloromethane (125 mL) was added, at 0°C, titanium tetrachloride (10.5 mL, 18.16 g, 95.7 mmol). To the red-violet mixture was then added a solution of dichloromethyl methyl ether (9.0 mL, 11.4 g, 100 mmol) in dichloromethane (25 mL). After stirring at 0°C for 15 min, at room temperature for 1 h, and at reflux for 4 h, the mixture was cooled and poured onto an ice–water mixture and stirred for 3 h. Separation of the organic layer and extraction of the aqueous phase with dichloromethane furnished an organic extract, which was dried (Na_2SO_4), filtered, and evaporated. The crude extract contained isomers **114** and **115** (respectively 2:1) together with unreacted starting material (~20%) as shown by nmr. As these aldehydes do not support chromatography, removal of the starting material was done by transforming these aldehydes to their corresponding Girard's T derivatives: a solution of the crude reaction mixture (4.58 g, ~20 mmol) in ethanol (35 mL) and acetic acid (3.5 mL) was reacted with Girard's T reagent (3.5 g, 20.8 mmol). After 1 h at reflux, the reaction mixture was cooled and diluted with brine (200 mL), and washed with ether (3 × 100 mL) to remove methylindane **113** and other impurities. Addition of hydrochloric acid (2 M, 20 mL) to the aqueous layer followed by ether extraction (5 × 100 mL) and a rapid filtration of the colored extract through a short path of silica gel (CH_2Cl_2) gave a pure mixture of aldehydes **114** and **115** (3.1 g, 68%).

Dihydroxyaldehydes 116 and 117

To a cooled (−70°C) solution of the purified mixture of compounds **114** and **115** (6.00 g, 27.3 mmol) in dry dichloromethane (250 mL) was added dropwise boron tribromide (6.0 mL, 62 mmol) over a period of 15 min. The mixture was then stirred at room temperature for 2 h, cooled again at −70°C, treated with methanol (10 mL), aqueous methanol (50%), and water (100 mL). After 4 h at room temperature, the organic layer was separated and the aqueous layer extracted with dichloromethane (4 × 100 mL). The combined extracts were washed with water, dried, and the solvent was evaporated. The crude extract (3.8 g) was filtered through a short path of Florisil (CH_2Cl_2). Fractional crystallization of the semicrystalline extract (3.0 g) (CH_2Cl_2 – Et_2O – hexane) furnished pure aldehydes **116** (630 mg, 12%) and **117** (49 mg, 1%).

Aldehyde 116: mp 91.5–92.5°C; ir ($CHCl_3$, ν cm^{-1}): 3500, 3460, 2760, 1660, 1605; ^1H nmr (CCl_4, δ ppm): 11.28 (s, 1H, HO-C5), 10.0 (s, 1H, CHO), 6.94 (1H, s, H-C7), 5.73 (s, 1H, HO-C6), 3.2–1.5 (m, 5H), 1.22 (d, 3H, J = 7 Hz, CH_3Cl); ms *m/e*: 192 (M^+). *Anal.* calcd. for $C_{11}H_{12}O_3$: C 68.74, H 6.29; found: C 68.75, H 6.15. Irradiation of methyl signal (δ 1.22) resulted in an increase (15%) of aromatic signal at δ 7.01.

Aldehyde 117: mp 81–82.5°C; ir ($CHCl_3$, ν cm^{-1}): 3560, 2760, 1660, 1605; ^1H nmr (δ ppm): 11.41 (s, 1H, HO-C6), 10.10 (s, 1H, CHO), 7.01 (s, 1H, H-C4), 6.04 (s, 1H, HO-C5), 3.8–1.6 (m, 5H), 1.24 (d, 3H, J = 7 Hz, CH_3-C1); ms *m/e*: 192 (M^+). Irradiation of the methyl signal (δ 1.24) had no apparent effect on the intensity of the aromatic proton signal.

Bromoacetate 118

To a solution of 4-formyl-5,6-dihydroxy-1-methylindane (**116**) (1.42 g, 7.4 mmol) in dry benzene (30 mL) and pyridine (0.6 mL, 7.4 mmol) was added dropwise at 25°C a solution of bromoacetyl bromide (1.63 g, 8.1 mmol) in benzene (10 mL). After 3 h, the mixture was washed with water and the solvent was evaporated to leave a yellow oil sufficiently pure for the next step (2.35 g, crude 98%); ir ($CHCl_3$, ν cm^{-1}): 3600–3000 (br), 1760, 1660; ^1H nmr ($CDCl_3$, δ ppm): 11.39 (s, 1H, OH), 10.04 (s, 1H, CHO), 7.19 (s, 1H, H-C7), 4.10 (s, 2H, $BrCH_2$-), 3.3–1.4 (m, 5H), 1.22 (d, 3H, J = 7 Hz, CH_3-); ms *m/e*: 312 and 314 (M^+).

Lactone aldehyde 119

To a solution of bromoacetate **118** (2.51 g, 8.0 mmol) in tetrahydrofuran (60 mL) was added powdered potassium carbonate (10.0 g,

2.5 mmol). The mixture was refluxed for 48 h. After cooling, the mixture was centrifuged and decanted. The solid material was dissolved in water (100 mL), and the aqueous solution was acidified to pH 1 (2 M HCl) and extracted with ether (3 × 70 mL). The crude acid (2.0 g) was dissolved in benzene (50 mL) and refluxed (Dean–Stark, 4 h) in the presence of *p*-toluenesulfonic acid (25 mg). The cooled mixture was filtered through a short pad of silica gel. Evaporation of benzene left pure lactone **119** (1.69 g, 91%), which was crystallized from ether–hexane; mp 111.5–112°C; ir ($CHCl_3$, ν cm^{-1}): 2770, 1800, 1698, 1605, 1325, 1300, 1270, 1200; ^1H nmr ($CDCl_3$, δ ppm): 10.35 (s, 1H, CHO), 7.07 (br s, 1H, H-C7), 4.75 (s, 2H, $-OCH_2CO_2-$), 3.4–1.4 (m, 5H), 1.22 (d, 3H, J = 7 Hz, CH_3-); ms *m/e*: 232 (M^+). *Anal.* calcd. for $C_{13}H_{12}O_4$: C 67.23, H 5.21; found: C 67.13, H 5.15.

*Lactone **120***

A mixture of lactone aldehyde **119** (1.66 g, 7.1 mmol) and palladium-on-charcoal catalyst (10%, 440 mg) in acetic acid was shaken under hydrogen at 25°C for 24 h. Filtration of the catalyst and evaporation of the solvent left pure crystalline lactone indane **120** (1.55 g, 99%), which was recrystallized from hexane; mp 68–70°C; ir ($CHCl_3$, ν cm^{-1}): 1785, 1610; ^1H nmr (CCl_4, δ ppm): 6.70 (br s, 1H, H-C7), 4.49 (s, 2H, OCH_2CO_2), 3.3–1.4 (m, 5H), 2.11 (s, 3H, CH_3-C4), 1.22 (d, 3H, J = 7 Hz, CH_3Cl); ms *m/e*: 218 (M^+). *Anal.* calcd. for $C_{13}H_{14}O_3$: C 71.54, H 6.47; found: C 71.65, H 6.45.

*Spirolactones **97***

To a solution of lactone indane **120** (502 mg, 2.30 mmol) in acetonitrile (10 mL) was added aqueous sodium hydroxide (1 M, 2.7 mL). After 45 min of stirring at room temperature, a solution of *N*-bromosuccinimide (430 mg, 2.41 mmol) in aqueous acetonitrile (16 mL, 1:1) was rapidly added to the mixture. After 2.5 min, addition of brine and extraction with ether furnished a colored crude product, which was rapidly filtered on silica gel (benzene) to give a sensitive mixture of racemic lactones **97** (515 mg, ~95%); ir ($CHCl_3$, ν cm^{-1}): 1820, 1685, 1665, 1602; ^1H nmr ($CDCl_3$, δ ppm): 5.87 (br s, 1H, H-C7), 4.66 (br d, 1H, J = 14 Hz) and 4.39 (d, 1H, J = 14 Hz) (two embodied AB patterns, O-CH_2CO_2), 3.1–1.4 (m, 5H), 1.92 (br s, 3H, CH_3-C4), 1.22 (d, 3H, J = 7 Hz, CH_3Cl); ms *m/e*: 234 (M^+).

*Adducts **121**(a–b) and **122**(a–b)*

A solution of mixed dienones **97** (160 mg, 0.68 mmol) in excess methylvinylketone (0.3 mL) was refluxed for 20 min under nitrogen. Removal of the volatile substances under vacuum and careful chromatography of the oily residue (215 mg) on a thick layer of silica gel (carbon tetrachloride, ethyl acetate, benzene, hexane 1:1:5:3, two elutions) furnished four adducts (total yield ~65%). These compounds showed the following R_f values, 0.75, 0.70, 0.61, 0.56, and relative proportions 2:2:1:2.

Least polar isomer: mp 124–126°C; ir ($CHCl_3$, ν cm^{-1}): 1820, 1740, 1715; ^1H nmr (C_6H_6, δ ppm): 4.38 (d, 1H, J_{AB} = 14 Hz) and 3.77 (d, 1H, J_{AB} = 14 Hz) (AB pattern, OCH_2CO_2), 3.35 (d, 1H, J = 2 Hz, H-C11), 2.6–1.2 (m, 8H), 1.57 (s, 3H, CH_3CO), 1.00 (s, 3H, CH_3-C5), 0.77 (d, 3H, J = 7 Hz, CH_3-C9); ms *m/e*: 304 (M^+).

Second least polar isomer: mp 149–151°C; ir ($CHCl_3$, ν cm^{-1}): 1820, 1740, 1715; ^1H nmr (C_6H_6, δ ppm): 4.39 (d, 1H, J_{AB} = 14 Hz) and 3.77 (d, 1H, J_{AB} = 14 Hz) (AB pattern, OCH_2CO_2), 3.45 (d, 1H, J = 2 Hz, H-C11), 2.6–1.1 (m), 1.55 (s, 3H, CH_3CO), 1.15 (s, 3H, CH_3C5), 0.90 (d, 3H, J = 7 Hz, CH_3C9); ms *m/e*: 304 (M^+).

Third least polar isomer: mp 160–161°C; ir ($CHCl_3$, ν cm^{-1}): 1820, 1735, 1715; ^1H nmr (C_6H_6, δ ppm): 4.32 (d, 1H, J_{AB} = 14 Hz) and 3.76 (d, 1H, J_{AB} = 14 Hz) (AB pattern, OCH_2CO_2), 3.37 (d, 1H, J = 2 Hz, H-C11), 2.8–1.1 (m, 8H), 1.55 (s, 3H, CH_3CO), 1.01 (s, 3H, CH_3-C5), 0.77 (d, 3H, J = 7 Hz, CH_3C9); ms *m/e*: 304 (M^+).

Most polar isomer: ir ($CHCl_3$, ν cm^{-1}): 1820, 1745, 1715; ^1H nmr (C_6H_6, δ ppm): 4.34 (d, 1H, J_{AB} = 14 Hz) and 3.78 (d, 1H, J_{AB} = 14 Hz) (AB pattern, OCH_2CO_2), 3.48 (d, 1H, J = 2 Hz, H-C11), 2.8–1.1 (m, 8H), 1.55 (s, 3H, CH_3CO), 1.00 (s, 3H, CH_3-C5), 0.83 (d, 3H, J = 7 Hz, CH_3-C9); ms *m/e*: 304 (M^+).

*Isomers **123** and **124***

To a solution of the preceding Diels–Alder adduct mixtures (**121***a–b* and **122***a–b*) (200 mg, 0.66 mmol) in tetrahydrofuran (3 mL) was added aqueous sodium hydroxide (2.0 mL, 1 M). After 16 h of stirring at room temperature, the mixture was extracted with ether (5 × 20 mL). After evaporation of the solvents, the crude oily residue was chromatographed (preparative thick layer of silica gel, carbon tetrachloride, ether, benzene, 2:1:2) to give two products (55:45 of R_f values 0.30:0.25 respectively).

Less polar compound (**123** or **124**): R_f 0.30; mp 132–132.5°C; ir ($CHCl_3$, ν cm^{-1}): 3520, 1752, 1722; ^1H nmr ($CDCl_3$, δ ppm): 3.32 (d, 1H, J = 4.5 Hz, H-C11), 3.18 (br s, 1H, OH), 2.6–1.3 (m, 8H), 2.50 (br s, 2H, H_2Cl), 1.28 (s, 3H, CH_3-C5), 1.06 (d, 3H, J = 7 Hz, CH_3C9); ms *m/e*: 246 (M^+). *Anal.* calcd. for $C_{15}H_{18}O_3$: C 73.14, H 7.36; found: C 72.82, H 7.49.

More polar compound (**124** or **123**): R_f 0.25; mp 160–161°C; ir ($CHCl_3$, ν cm^{-1}): 3515, 1752, 1722; ^1H nmr ($CDCl_3$, δ ppm): 3.29 (d, 1H, J = 4.5 Hz, H-C11), 3.21 (br s, 1H, OH), 1.28 (s, 3H, CH_3-C5), 1.09 (d, 3H, J = 7 Hz, CH_3C9); ms *m/e*: 246 (M^+).

*Diels–Alder adducts **125** and **126***

A mixture of diene **97** (505 mg, 2.16 mmol) and optically active dienophile (*S*)-**74** (515 mg, 2.42 mmol) in benzene (4 mL) was refluxed for 12 h; then benzene was removed by evaporation to give an oily residue (1.0 g), which was dissolved in tetrahydrofuran (14 mL) and reacted with aqueous sodium hydroxide (5 mL, 1 M) for 24 h at 25°C. The mixture was then extracted with ether, washed with water, and ether was removed under reduced pressure to give a crude mixture (580 mg) that was dissolved in aqueous acetic acid (70%, 25 mL) and heated at 70°C for 1.5 h. Removal of acetic acid and ether extraction of the residue furnished a mixture of compounds (490 mg), which was dissolved in tetrahydrofuran (10 mL) and reacted with aqueous sodium hydroxide (1 M, 1.45 mL) for 16 h at 25°C. Extraction of the reaction medium with ether gave a crude mixture (400 mg) containing several compounds. This last mixture was dissolved in benzene (15 mL) and pyridine (0.25 mL) and reacted with an excess of phosgene in benzene during 1 h at room temperature. The mixture was then washed with water and extracted with ether. Chromatography of the crude extract on preparative thin layer (benzene–ether, 4:1) furnished a mixture (46 mg, 10%) of two compounds, isomers **125** and **126**, which were separated by fractional crystallization.

Isomer (***125*** or ***126***): mp 162–163°C; ir ($CHCl_3$, ν cm^{-1}): 2720, 1812, 1750, 1732; ^1H nmr ($CDCl_3$, δ ppm): 9.65 (d, 1H, J = 3 Hz, CHO), 3.40 (d, 1H, J = 5.5 Hz, H-C11), 3.2–1.5 (m), 1.35 (s, 3H, CH_3-C5), 1.14 (d, 3H, J = 7 Hz) and 0.80 (d, 3H, J = 7 Hz) ($CH(CH_3)_2$), 1.08 (d, 3H, J = 7 Hz, CH_3-C9). *Mol. Wt.* (ms) calcd. for $C_{21}H_{26}O_5$: 370.178; found 370.173.

Isomer (***126*** or ***125***): ir ($CHCl_3$, ν cm^{-1}): 2720, 1812, 1750, 1732; ^1H nmr ($CDCl_3$, δ ppm): 9.48 (d, 1H, J = 3 Hz, CHO), 3.38 (d, 1H, J = 5.5 Hz, H-C11), 3.2–1.5 (m), 1.35 (s, 3H, CH_3-C5), 1.14 (d, 3H, J = 7 Hz) and 0.80 (d, 3H, J = 7 Hz) ($CH(CH_3)_2$), 1.02 (d, 3H, J = 7 Hz, CH_3-C9); ms *m/e*: 370 (M^+).

*Diels–Alder adducts **128**a–b and **129**a–b*

A mixture of diene **6** (834 mg, 3.8 mmol) and acetoxy-2-acrylonitrile (1.0 g, 9.0 mmol) was heated at 127°C for 5 h. Removal of the dienophile under vacuum afforded a mixture of four compounds in the following proportion: 39:17:20:24, as determined by gas chromatography and increasing polarity. These were separated on a small scale by preparative thin-layer chromatography (carbon tetrachloride, ethyl acetate, benzene, 2:3:15).

Least polar compound (39%, R_f 0.70): mp 131–132°C; ir ($CHCl_3$, ν cm^{-1}): 1822, 1752; ^1H nmr ($CDCl_3$, δ ppm): 4.65 (d, 1H, J_{AB} = 15 Hz) and 4.38 (d, 1H, J_{AB} = 15 Hz) (AB pattern, OCH_2CO_2), 3.97 (s, 1H, H-C11), 2.7–2.0 (m, 8H), 2.12 (s, 3H, CH_3CO_2), 1.25 (s, 3H, CH_3C5); ms *m/e*: 331 (M^+). *Anal.* calcd. for $C_{17}H_{17}NO_6$: C 61.62, H 5.17, N 4.23; found: C 60.49, H 5.17, N 4.37.

Second least polar compound (17%, R_f 0.62): mp 182–182.5°C; ir ($CHCl_3$, ν cm^{-1}): 1822, 1752; ^1H nmr ($CDCl_3$, δ ppm): 4.70 (d, 1H, J_{AB} = 15 Hz) and 4.38 (d, 1H, J_{AB} = 15 Hz) (AB pattern, OCH_2CO_2), 3.99 (s, 1H, H-C11), 2.8–2.0 (m, 8H), 2.12 (s, 3H, CH_3CO_2), 1.25 (s, 3H, CH_3C5); ms *m/e*: 331 (M^+). *Anal.* calcd. for $C_{17}H_{17}NO_6$: C 61.62, H 5.17; found: C 62.17, H 5.16.

Third least polar compound (20%, R_f 0.55): ir ($CHCl_3$, ν cm^{-1}):

1822, 1752; ^{1}H nmr ($CDCl_3$, δ ppm): 4.65 (d, 1H, J_{AB} = 15 Hz) and 4.41 (d, 1H, J_{AB} = 15 Hz) (AB pattern, OCH_2CO_2), 4.14 (s, 1H, H-C11), 3.2–1.6 (m, 8H), 2.08 (s, 3H, CH_3CO_2), 1.25 (s, 3H, CH_3C5); ms *m/e*: 331 (M^+).

Most polar compound (24%, R_f 0.46): mp 191–192°C; ir ($CHCl_3$, ν cm^{-1}): 1822, 1752; ^{1}H nmr ($CDCl_3$, δ ppm): 4.70 (d, 1H, J_{AB} = 15 Hz) and 4.37 (d, 1H, J_{AB} = 15 Hz) (AB pattern, OCH_2CO_2), 4.16 (s, 1H, H-C11), 3.2–1.6 (m, 8H), 2.10 (s, 3H, CH_3CO_2), 1.25 (s, 3H, CH_3C5); ms *m/e*: 331 (M^+). *Anal.* calcd. for $C_{17}H_{17}NO_6$: C 61.62, H 5.17; found: C 60.99, H 5.25. Monocrystal X-ray diffraction analysis of this compound revealed that it had the structure shown by the formula **128***b* (Scheme 17). Complete X-ray data will be published elsewhere (8*b*).

Cyanohydrin diketone ***132***

(*a*) To Diels–Alder adduct **129***a* (or *b*) (least polar isomer, R_f 0.70, 18 mg, 0.054 mmol) in dimethoxyethane (1.5 mL) was added aqueous hydrochloric acid (0.2 mL, 1 M). After 12 h at 80°C, the mixture was extracted with ether to give a crude colored residue, cyanohydrin diketone **132** (17 mg); ir ($CHCl_3$, ν cm^{-1}): 3400, 1740; ^{1}H nmr ($CDCl_3$, δ ppm): 4.82 (br s, 1H, OH), 4.66 (s, 1H, HC11), 2.9–1.9 (m, 8H), 1.35 (s, 3H, CH_3-C5).

(*b*) With Diels–Alder adduct **129***b* (or *a*) (third least polar, R_f 0.55, 13 mg, 0.039 mmol), the same treatment gave the same cyanohydrin diketone **132** (9 mg).

Cyanohydrin diketone acetate ***134***

The preceding crude cyanohydrin diketone **132** (17 mg) was dissolved in pyridine (0.4 mL) and acetic anhydride (0.4 mL). After 20 h at room temperature, evaporation of the volatile materials left a residue that was dissolved in benzene, washed with water, and discolored with Norit. Removal of the solvent left a semicrystalline residue (18 mg). Crystallization from dichloromethane–ether gave an analytical sample of cyanohydrin acetate **134**; mp 210–210.5°C; ir ($CHCl_3$, ν cm^{-1}): 1752, 1740; ^{1}H nmr ($CDCl_3$, δ ppm): 4.24 (s, 1H, H-C11), 2.9–1.9 (m, 8H), 2.10 (s, 3H, CH_3CO_2), 1.37 (s, 3H, CH_3-C5); ms *m/e*: 273 (M^+). *Anal.* calcd. for $C_{15}H_{15}NO_4$: C 65.93, H 5.53; found: C 65.15, H 5.43.

3,3-Ethylenedioxy-butanoic acid ***(135)***

A mixture of ketal ester **40** (*vide supra*) (15.0 g, 86 mmol) and aqueous potassium hydroxide (100 mL, 1.1 M) was refluxed for 5 h. The cooled mixture was then extracted with ether and the aqueous layer was acidified (pH 5) at 0°C with hydrochloric acid (1 M) and extracted with ether (3 × 50 mL). Evaporation of the solvent furnished pure acid **135** (7.02 g, 56%) as a white solid; mp 48–50°C; ir ($CHCl_3$, ν cm^{-1}): 3600–2900 (br), 1710; ^{1}H nmr (CCl_4, δ ppm): 11.45 (s, 1H, CO_2H), 3.92 (s, 4H, OCH_2CH_2O), 2.60 (s, 2H, CH_2CO_2), 1.47 (s, 3H, CH_3); ms *m/e*: 131 ($M^+ - CH_3$). *Anal.* calcd. for $C_6H_{10}O_4$: C 49.31, H 6.90; found: C 48.89, H 7.00.

3,3-Ethylenedioxy-butanoyl chloride ***(136)***

To a cooled solution (6°C) of ketal acid **135** (17.5 g, 0.12 mol) in dry benzene (200 mL) and pyridine (10.7 mL, 0.132 mol) was added oxalyl chloride (16.8 g, 0.132 mol) in benzene (200 mL). After 3 h at room temperature the mixture was filtered and the solvent removed by evaporation. The residue was distilled under reduced pressure to furnish pure acid chloride **136** (18 g, 92%); bp 120°C (0.1 Torr); ir (CCl_4, ν cm^{-1}): 1811, 1100; ^{1}H nmr ($CDCl_3$, δ ppm): 3.96 (s, 4H, OCH_2CH_2O), 3.21 (s, 2H, CH_2CO_2), 1.43 (s, 3H, CH_3); ms *m/e*: 149 and 151 ($M^+ - 15$).

Ester ***138***

To a cooled (5°C) solution of acid chloride **136** (20.00 g, 120 mmol) in dry benzene (200 mL) and dry pyridine (9.50 g, 120 mmol) was added dropwise (10 min) a solution of 3-chloro-2-hydroxy propanenitrile (**137**) (12.65 g, 120 mmol) in benzene (200 mL). The mixture was warmed to room temperature, stirred for 12 h, and then decanted from the solid residue. The benzenic solution was washed with water and brine and the solvent evaporated. The oily residue was crystallized in the cold from ether–hexane to give pure ester **138** (22 g, 80%); mp 54–56°C; ir ($CHCl_3$, ν cm^{-1}): 1757, 1160, 1040; ^{1}H nmr ($CDCl_3$, δ ppm): 5.60 (t, 1H, *J* = 6 Hz, H-CCN), 4.00 (s, 4H, OCH_2CH_2O), 3.82 (d, 2H, H_2CCl), 2.74 (s, 2H, CH_2CO_2), 1.45 (s, 3H, $-CH_3$); ms *m/e*: 218 and 220 ($M^+ - 15$). *Anal.* calcd. for $C_9H_{12}NO_4Cl$: C 46.27, H 5.18, Cl 15.17; found: C 46.36, H 5.33, Cl 15.09.

2-(3,3-Ethylenedioxy-butanoyloxy)acrylonitrile ***(139)***

To a solution of chloronitrile **138** (20.70 g, 89 mmol) in dry ether (200 mL) was added a solution of triethylamine (10.50 g, 98 mmol) in ether (200 mL). After 72 h of stirring at room temperature the mixture was decanted from the solid residue, which was washed with ether and the combined etheral fractions were evaporated. The residual liquid was distilled under vacuum to give pure nitrile **139** (13.34 g, 76%); bp 100°C, 0.03 Torr; mp 31°C; ir ($CHCl_3$, ν cm^{-1}): 2225, 1770, 1635; ^{1}H nmr ($CDCl_3$, δ ppm): 5.80 (d, 1H, J_{AB} = 3 Hz) and 5.74 (d, 1H, J_{AB} = 3 Hz) (AB pattern, H_2C=), 4.00 (s, 4H, OCH_2CH_2O), 2.84 (s, 2H, CH_2CO_2), 1.50 (s, 3H, CH_3); ms *m/e*: 182 ($M^+ - 15$). *Anal.* calcd. for $C_9H_{11}NO_4$: C 54.82, H 5.62; found: C 54.47, H 5.48.

Diels–Alder adducts ***140***a–b *and* ***141***a–b

A mixture of diene **6** (834 mg, 3.78 mmol) and dienophile **139** (1.020 g, 5.18 mmol) was heated at 120°C under nitrogen for 40 h. Crystallization of the crude mixture containing four main compounds of very similar polarity gave a low yield (30%) of a crystalline mixture of two compounds (470 mg), which were separated by thin-layer chromatography (silica gel, carbon tetrachloride – ethyl acetate – benzene, 2:3:15) to give two pure adducts.

Least polar compound (R_f 0.64): mp 151–152°C; ir ($CHCl_3$, ν cm^{-1}): 1820, 1750; ^{1}H nmr ($CDCl_3$, δ ppm): 4.60 (d, 1H, J_{AB} = 14 Hz) and 4.33 (d, 1H, J_{AB} = 14 Hz) (AB pattern, OCH_2CO_2), 3.96 (s, 4H, OCH_2CH_2O), 3.92 (s, 1H, H-C11), 2.70 (s, 2H, CH_2CO_2), 2.7–1.8 (m, 10H), 1.49 (s, 3H, CH_3-), 1.24 (s, 3H, CH_3-C5); ms *m/e*: 417 (M^+). *Anal.* calcd. for $C_{21}H_{23}NO_8$: C 60.42, H 5.55; found: C 60.46, H 5.67.

More polar compound **140***b* (R_f 0.56): mp 189–190°C; ir ($CHCl_3$, ν cm^{-1}): 1820, 1750; ^{1}H nmr ($CDCl_3$, δ ppm): 4.58 (d, 1H, J_{AB} = 15 Hz) and 4.34 (d, 1H, J_{AB} = 15 Hz) (AB pattern, OCH_2CO_2), 3.96 (s, 5H, OCH_2CH_2O and H-C11), 2.73 (s, 2H, CH_2CO_2), 2.42 (s, 2H, H_2C14), 2.8–1.8 (m, 6H), 1.47 (s, 3H, CH_3-), 1.24 (s, 3H, CH_3C5); ms *m/e*: 417 (M^+). *Anal.* calcd. for $C_{21}H_{23}NO_8$: C 60.42, H 5.55; found: C 60.10, H 5.32. Monocrystal X-ray diffraction analysis of this compound revealed that it had the structure shown by **140***b* (X = O, Y = H_2). Complete X-ray data will be published elsewhere (8*b*).

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