INVESTIGATIONS INTO THE TOTAL SYNTHESIS OF INSECT ANTIFEEDANT CLERODANES

J.M. LUTEIJN

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Proefschrift
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van doctor in de landbouwwetenschappen,
op gezag van de rector magnificus,
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hoogleraar in de veeteeltwetenschap,
in het openbaar te verdedigen
op vrijdag 12 februari 1982
des namiddags te vier uur in de aula
van de Landbouwhogeschool te Wageningen.

ter nagedachtenis aan mijn vader

aan mijn moeder

voor Mena

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Verder iedereen die hierboven niet met name is genoemd, en het mede mogelijk heeft gemaakt dat ik dit proefschrift heb kunnen voltooien.

CONTENTS.

THIS THESIS IS PARTLY BASED ON THE FOLLOWING PUBLICATIONS.

1 Preparation and reactions of *cis*-5,10-methanoxymethano-1-methyl-$\Delta^{1,9}$-2-octalone as an intermediate in the total synthesis of clerodane diterpenes.
J.M. Luteijn, M. van Doorn, and Ae. de Groot,
Tetrahedron Lett., (1980), *21*, 4127.

2 The preparation of (±) 18,19-epoxy-14,15,16-trisnorclerodan-13-oic acid as a key intermediate in the total synthesis of clerodane type diterpenes.
J.M. Luteijn and Ae. de Groot,
Tetrahedron Lett., (1980), *21*, 4129.

3 Stereospecific formation of a *trans*-decalin as an intermediate for the synthesis of clerodane insect antifeedants.
J.M. Luteijn and Ae. de Groot,
Tetrahedron Lett., (1981), *22*, 789.

4 The stereospecific synthesis of 9α-acetoxymethyl-8α,8'-epoxy-3α, 4,4-trimethyl-trans-decalin-1α-ol acetate, a model for the investigation of structure-activity relationships of the insect antifeedant neoclerodanes.
J.M. Luteijn and Ae. de Groot,
J. Org. Chem., (1981), *47*, 3448.

5 The assignment of ^{13}C NMR shift data in clerodanes and related structures.
J.M. Luteijn, A. van Veldhuizen, and Ae. de Groot,
Submitted for publication in Organic Magnetic Resonance.

LIST OF ABBREVIATIONS.

Ac	acetyl
9-BBN	9-borabicyclononane
Bu	butyl
Bz	benzene
m-CPBA	*meta*-chloroperbenzoic acid
DAP	4-dimethylaminopyridine
DBN	diazabicyclononene
DIBAL-H	diisobutylaluminium hydride
DME	dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
Et	ethyl
HMPT	hexamethylphosphoric triamide
LDA	lithium diisopropylamide
Me	methyl
MED	2-methyl-2-ethyl-1,3-dioxolan
PCC	pyridiniumchlorochromate
Ph	phenyl
Py	pyridine
THF	tetrahydrofuran
Ts	tosyl

INTRODUCTION.

Among the still growing group of clerodane type diterpenes, those compounds possessing insect antifeedant activity have drawn much attention.

Surprisingly, at the beginning of our investigations, only a few attempts towards the total synthesis of clerodanes had been made. During the last few years the number of investigators studying the synthesis of these diterpenes steadily increased and in 1979 Takahashi *et al.* achieved the first success in this field with the total synthesis of annonene (see chapter 2.7). However, up to the time of writing no total synthesis of physiologically active clerodanes has been reported.

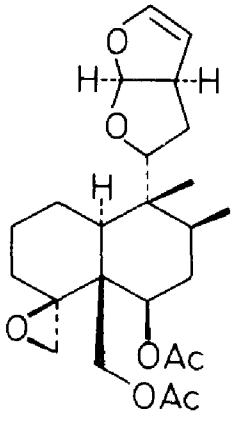
The main object of the investigations described in this thesis was to develop synthetic methods for the construction of the clerodane basic skeleton. This skeleton should contain functionalities that allow the total synthesis of the highly oxygenated clerodanes. At a later stage these results could be employed in the synthetic approach to the interesting insect antifeedant clerodanes. This also offered the possibility to arrive at analogous compounds which may contribute to the knowledge of structure-activity relationships of the antifeedant activity.

1 NOMENCLATURE, BIOSYNTHESIS, OCCURRENCE, AND BIOLOGICAL ACTIVITY OF THE CLERODANES.

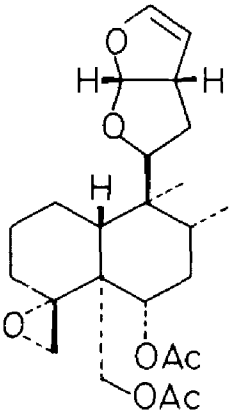
1.1 NOMENCLATURE

During the last decade the occurrence of over two hundred different clerodanes in a widespread number of plant of plant families has been reported in the literature[1]. Although the first clerodanes were isolated in the previous century[2], their structural elucidation could only recently be accomplished. In 1961 the structure and absolute configuration of clerodin (*'1'*), a bitter principle isolated from the Indian bhat tree (*Clerodendron infortunatum*), was published[3]. This compound, the first clerodane with a fully established structure, gave its name to this entire subgroup of diterpenes. In addition, the absolute configuration of all other clerodanes was related to the absolute configuration of clerodin. Clerodanes with an opposite absolute configuration (corresponding to the mirror image of *'1'*) were named *ent*-clerodanes[4] (*enantio*-clerodanes).

Scheme 1.1



'1'



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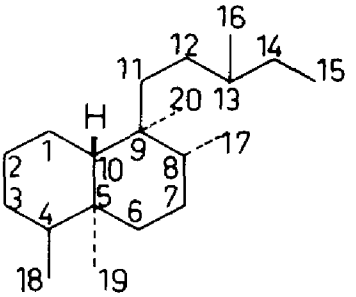

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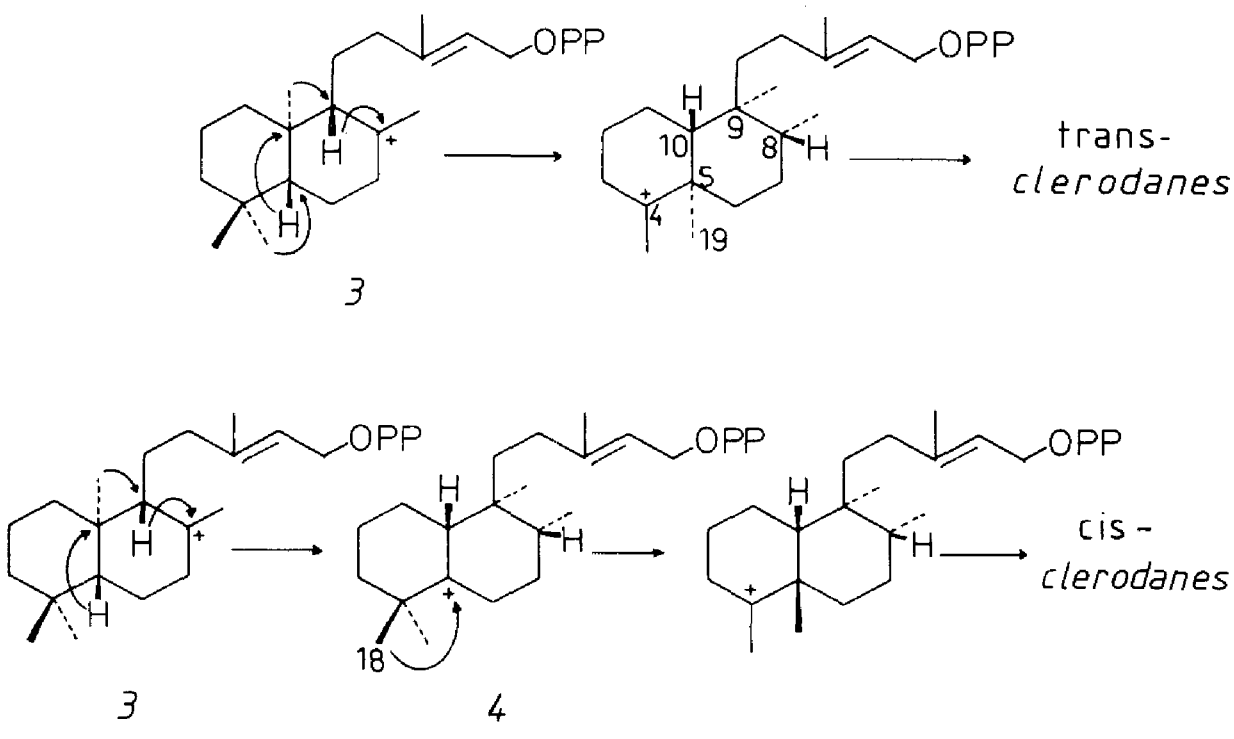
Recently the absolute configuration of clerodin was reexamined[5,6] and it was shown that its absolute configuration had to be reversed, due to an error in the early X-ray analysis. This inevitably led to implications for the nomenclature of all clerodanes and it was suggested to rename those clerodanes which possess the new clerodin chirality (as illustrated by *1*) as *neo*-clerodanes and those with opposite chirality as *ent-neo*-clerodanes.
Thus the *neo*-clerodane basic skeleton is represented by structure *2*[7] (scheme 1.1)

1.2 BIOSYNTHESIS

Clerodanes are biogenetically closely related to the labdanes and in fact they are believed to arize from a labdane type precursor (*3*) which itself is formed by the proton initiated cyclization of geranylgeranyl pyrophosphate. The clerodane skeleton is then constructed through a series of successive hydride and methyl shifts

Scheme 1.2



as indicated[8] in scheme 1.2. These migrations may possibly take place in a concerted manner and give rise to the *trans* clerodanes. Characteristically all the migrating groups are situated *anti* to the leaving group.

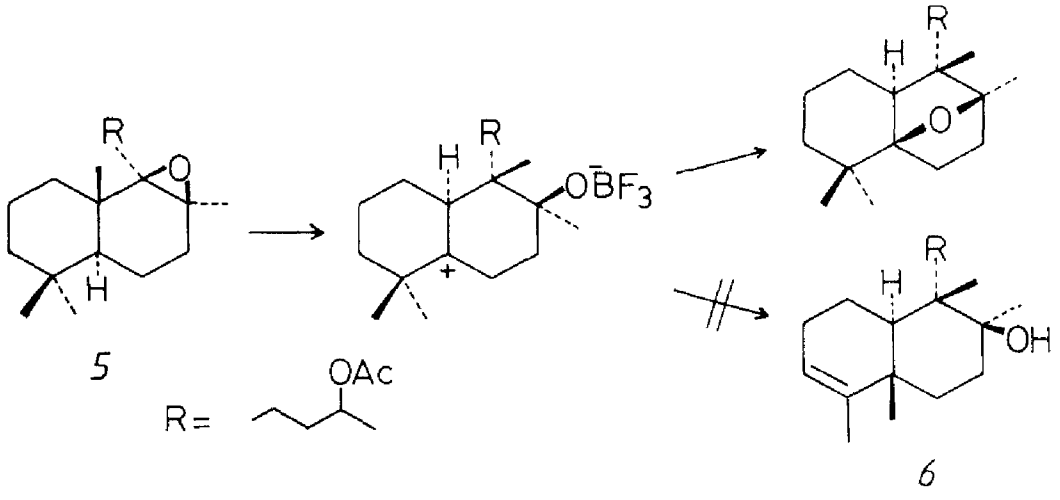
A number of clerodanes, however, have a *cis* A/B ring junction[9] and in consequence the formation of these compounds cannot be assumed as proceeding *via* a concerted reaction.

A brief pause is necessary after the second hydride shift to *4* in order to enable the subsequent *syn* rearrangement of C-18 (instead of C-19), to generate the *cis* ring fusion (scheme 1.2).
A few cases are known in which this last methyl shift does not occur, thus leading to 'half' rearranged diterpenes[10,11].

Further transformations are largely oxidative. Oxigenation patterns that are frequently encountered involve C-15 as an alcohol or as part of a lactone. Other clerodanes are oxygenated at almost every available site (see, for example, clerodendrin A (*11*) in scheme 1.5).

The mechanism of the methyl-hydride rearrangements has been studied *in vitro*. Hadley and Halsall[12] investigated the Lewis acid catalyzed rearrangements of a number of model compounds. In the case of the epoxide *5* migration of the angular methyl group occurred readily (scheme 1.3), indicating that the migrating group does not ne-

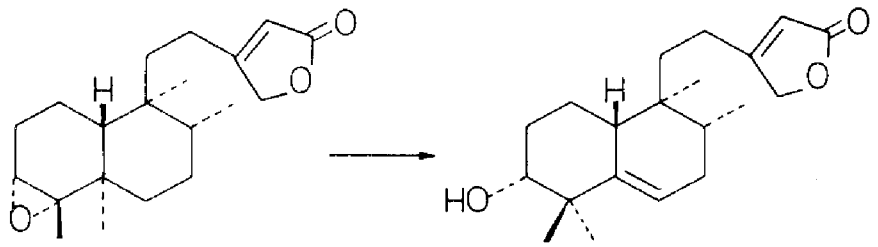
Scheme 1.3



cessarily have to be situated *anti* to the leaving group. The driving force of this migration is probably the elimination of a 1,3-diaxial interaction.
Further rearrangement to the clerodane skeleton did not occur however, probably because this would reintroduce a 1,3-diaxial interaction. Even the incorporation of a hydroxy group at C-3, in order to stabilize an adjacent carbonium ion could not bring about the migration of a methyl group from C-4 to C-5.

This unfavourable 1,3-diaxial interaction is additionally emphasized by the reverse migration of the methyl group from C-5 to C-4 on treatment of the clerodane epoxide *7* with acid[13] (scheme 1.4).

Scheme 1.4



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1.3 OCCURRENCE

As mentioned above, more than two hundred different clerodanes have been identified. They have been isolated from genera of some fifteen plant families. The following table gives an overview of plant species from which clerodanes have been isolated[1] (Table 1.1).

There is often a great resemblance in structure of the clerodanes isolated from the same genus. Typically, the clerodanes from the genus *Teucrium* all are highly oxygenated compounds which possess, with only a few exceptions, a spirolactone at C-9 and incorporate C-13 - C-16 as a furan[7] (as represented in *8*). They all belong to

Table 1.1 Occurrence of clerodanes in plant species

Family	Species
Araucariaceae	*Araucaria bidwillii*
Caesalpiniaceae	*Gossweilerodendron balsamiferum* Harms
Cistaceae	*Cistus labdaniferus*
	C. populifolius
	C. monosplensis
Compositae	*Annona coriacea*
	Baccharis conferta
	B. crispa Sprengel
	B. genistelloides (Lam.) Pers
	B. tricuneata
	B. trimera
	Conyza ivaefolia Less.
	Fleischmania sinclarii Benth.
	Haplopappus ciliatus
	Hinterhubera imbricata Cuatr.
	Nidorella agria
	N. residifolia
	Olearia heterocarpa
	O. muelleri (Sond) Benth
	Printzia laxa
	Solidago altissima
	S. arguta Ait
	S. elongata Nutt
	S. gigantea Ait
	S. juncea Ait
	Symphiopappus itatiayensis
Cucurbitacea	*Jateorhiza palmata* Miers
	Melothria maderospatana
Dicrastylidacea	*Cyanostegia angustifolia* Turcz.
Euphorbiaceae	*Croton californicus*
	C. caudatus

	C. corylifolius Lam.
	C. eleuteria
	C. lucidus
	C. oblongifolius
	C. subliratus Kurz.
	C. verreauxii Baill.
	Mallotus repandus
Hamamelidacereae	*Callicarpa maingayi*
Hepaticeae	*Gymnocolea inflata*
Labiatae	*Ajuga iva*
	A. nipponensis Makino
	A. remota
	A. reptans
	Leonurus cardiaca
	L. marrubiastrum L.
	Salvia splendens
	Stachys annua
	Teucrium chamaedrys
	T. cubense
	T. eriocephalum
	T. flavum
	T. fragile
	T. fruticans
	T. gnaphalodes l'Her
	T. homotrichum
	T. hyrcanum
	T. intricatum
	T. montanum
	T. polium subsp. *capitatum*
	T. polium subsp. *aureum* Sicily
	T. polium subsp. *aureum* Spain
	T. scorodonia subsp. *euganeum*
	T. spinosum
	T. viscidum
Leguminosae	*Hardwickia pinnata*
Menispermaceae	*Dioscoreophillum cumminsii*
Sapindaceae	*Dodonea attenuata* A. Cunn.
	D. boroniaefolia G. Don

	D. linearis Benth.
	D. viscosa
Saxifragaceae	*Ribes nigrum*
Scrophulariaceae	*Linaria japonica* Miq.
Verbenaceae	*Caryopteris divaricata* Maxim
	Clerodendron calamitosum
	C. infortunatum
	C. tricotomum Thunb.

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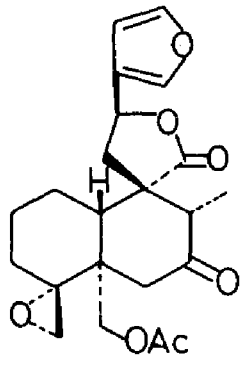
the *trans* series. The clerodanes from the genus *Baccharis* all have an α,β-unsaturated lactone containing C-4 and C-5, as well as a trans A/B ring fusion (e.g. *9*). They differ from each other in oxidation state at other sites of the ring and in the side chain. The clerodanes isolated from the genus *Leonurus* to date all belong to the *cis* series.

Sometimes the same clerodanes are found in totally different species: clerodin has been isolated from *Clerodendron infortunatum*[1], *Caryopteris divaricata*[1] and *Ajuga remota*[14]. Hardwickiic acid (*10*) has been isolated[1] from *Hardwickia pinnata*, *Annona coriacea*, *Ribes nigrum*, and *Printzia laxa*.



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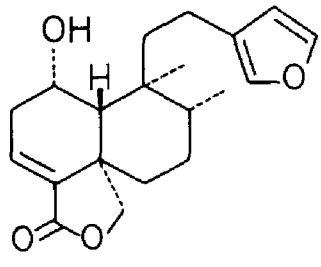

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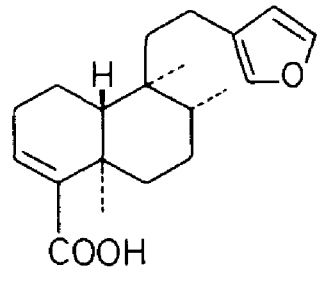

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A resemblance in structure of secondary plant products may be of interest for the chemotaxonomy of plant species. The examples men-

tioned above make it clear that a classification on the occurrence on the basis of the occurrence of certain diterpenes alone will hardly be possible, but they may provide a valuable contribution[15].

1.4 BIOLOGICAL ACTIVITY OF CLERODANES.

Many of the plants from which clerodanes have been isolated are used in folk medicine (e.g. *Baccharis tricuneata*[16], *Baccharis crispa* Sprengel[17], *Croton californicus*[8], *Leonurus cardiaca*[18], *Mallotus repandus*[19], *Teucrium chamaedreys*)[20]. In most cases, however, no relationship between the occurrence of clerodanes and pharmacological activity has been demonstrated. An exception must be made for the clerodanes isolated from *Croton sublyratus*, which showed significant inhibitory activity against ulcers in rats[21].

Table 1.2 Activity of clerodane insect antifeedants

compound	activity* (ppm)
Clerodin (*1*)	50
Clerodendrin A (*11*)	200
Clerodendrin B (*12*)	200
Caryoptin (*13*)	200
Epicaryoptin (*14*)	200
Caryoptinol (*15*)	200
Dihydroclerodin (*16*)	50
Dihydrocaryoptin (*17*)	80
Dihydrocaryoptin (*18*)	100
Clerodin hemiacetal (*19*)	50
Caryoptin hemiacetal (*20*)	200
Ajugarin I (*21*)	300**
Ajugarin II (*22*)	300**

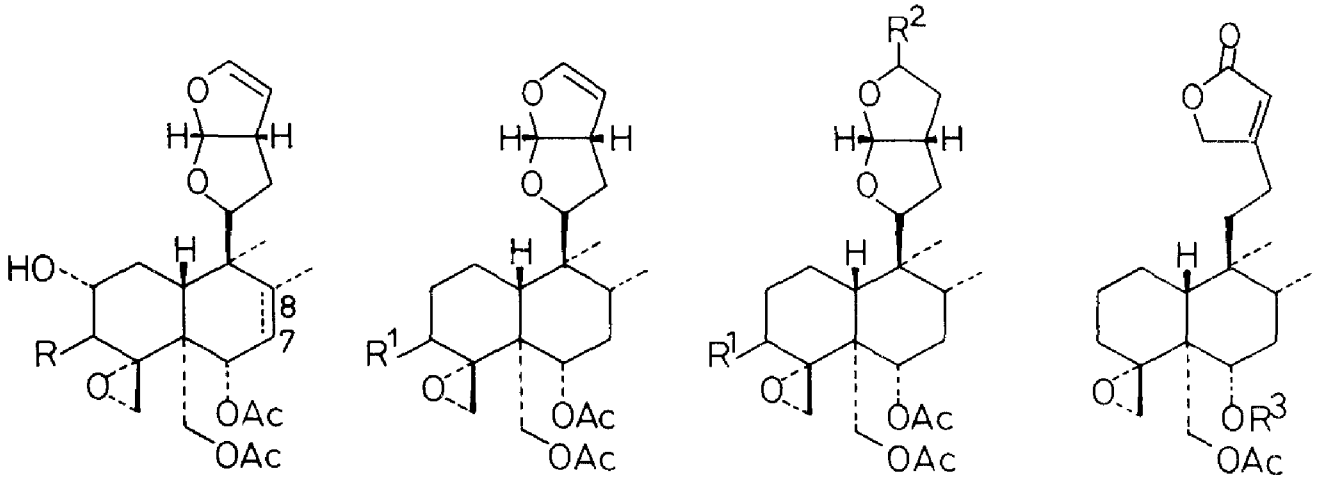
* Minimum concentration showing 100% activity within 24 h against *Spodoptera litura*.

** Tested against *S. littoralis*.

A more general feature is the bitter taste of the clerodanes; the bitterness of columbin, a *cis*-clerodane from the colombo root, is still perceptible at concentrations of 1:60,000[22]. For this reason the clerodanes are often classified as "bitter principles", a pharmacological term which denotes a group of secondary plant products with a very bitter taste but without any significant pharmacological activity'[24].

Considerable attention has been paid to the insect antifeedant properties of some clerodanes. This is in fact one of the most salient features of this group of diterpenes. Table 1.2 summarizes the clerodanes for which insect antifeedant activity has been demonstrated. (Formulas are represented in scheme 1.5).

Scheme 1.5



During laboratory testing the antifeedant activity of these clerodanes persisted for more than 24 h, and then the larvae eventually starved to death. The term 'absolute antifeedant' was therefore

proposed for these diterpenes. In contrast, other compounds, such as the furocoumarin derivative bergaptene, only retarded feeding for some 2 h and therefore these compounds are called 'relative antifeedants'[25].

During the last few decades insect antifeedants have attained considerable attention, especially in connection with their possible application in crop protection[27,28]. Little is known however about the fundamental chemoreception processes at molecular level of this feeding deterrency[29]. A lively debate is in progress concerning which part of the clerodane molecule is responsible for the physiological activity. Kojima and Kato[30] showed that the perhydrofurofuran unit (as is present in *e.g.* clerodin (*1*), was the active center; Jackson and Ley[31] suggest that the epoxy diacetate (which is present in both clerodin (*1*) and in ajugarin I (*21*) could also be responsible for at least part of the activity.

In order to probe this activity in greater detail, part of the investigations in this thesis concern the synthesis and testing of a number of model compounds (see chapter 5 and 9).

1.5 REFERENCES AND NOTES

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7 There is, however, a risk of confusion in this new nomenclature since the *neo*-clerodanes are related biogenetically to *ent*-labdanes and the *ent-neo*-clerodanes to the *normal* labdanes. (see also chapter 1.2). Piozzi therefore suggests to adopt the previous nomenclature again, which would mean that clerodin (*1*) belongs to the *ent*-clerodane series; Piozzi, F., Heterocycles (1981), *15*, 1489.
Since all synthetic compounds described in this thesis are racemates, the prefixes *neo* or *ent-neo* will be omitted in the discussions.

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2 SYNTHETIC STUDIES ON CLERODANES. A LITERATURE SURVEY.

2.1 INTRODUCTION

During the last few years a number of synthetic approaches towards clerodanes have appeared in the literature. Only one of these methods was carried through to a successful total synthesis.

Two distinct strategies become apparent on studying the results in the field of attempts to totally synthesize clerodanes. The aim of most investigators is to synthesize simple, low oxygenated clerodanes and eventually synthesize intermediates from which a larger group of these diterpenes can be made. A second group of investigators is more interested in the physiologically active clerodanes. Their synthetic efforts are directed towards the synthesis of the insect antifeedant clerodanes (see chapter 1.4) or model compounds for the investigation of structure-activity relationships. Most efforts to date remained without success, however, due to the many chiral centers and oxygenated functionalities in these molecules.

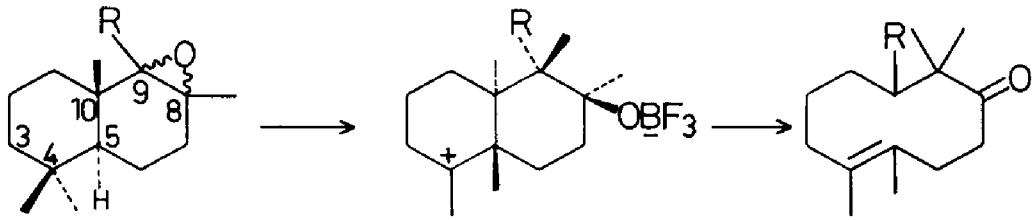
The diversity in synthetic approaches and the variety of target molecules make it difficult to discern a general pattern in the publications on clerodane synthesis. A chronological enumeration of the papers which have appeared in this field is therefore given.

2.2 HADLEY AND HALSALL'S BIOGENETIC-TYPE APPROACH OF THE CLERODANE BASIC SKELETON.

Since clerodanes may be formed in nature from a labdane type precursor (see chapter 1.2) an obvious way to their total synthesis is to mimic nature. Therefore Hadley and Halsall[1] studied the Lewis acid catalyzed rearrangements of various labdane epoxides and epoxides of model compounds. As mentioned before, they were able to bring about the migration of the C-10 methyl to C-9 and the C-5 hydrogen to C-10. The final step, *i.e.* the migration of the C-4 methyl to C-5 proved much more difficult to achieve, probably because of the introduction of a 1,3-diaxial interaction between the C-5 and the

C-9 methyl groups. As a result of this interaction the last migration either did not take place at all (see scheme 1.3) or gave rise to further rearrangements (scheme 2.1).

Scheme 2.1



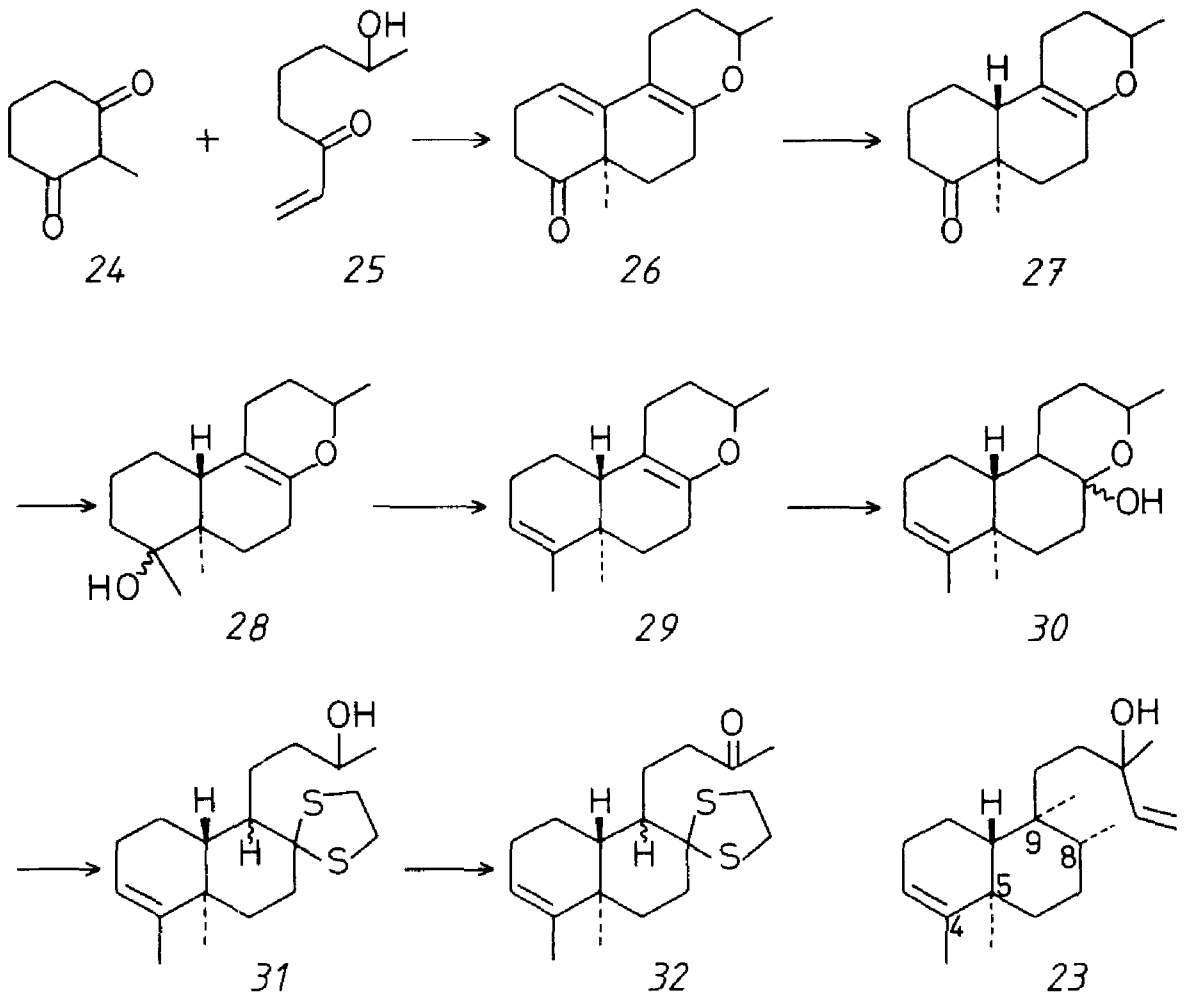
The main problem in this approach is the control over which proton is lost. In this case the proton at C-10 is lost instead of the C-3 proton. In nature this problem is solved by an enzyme system.

2.3 APSIMON'S SYNTHESIS OF A VERSATILE SYNTHON FOR CLERODANE APPROACHES.

The approach by ApSimon and Yamasaki[2] was directed towards the synthesis of low oxygenated clerodanes, *e.g.* kolavelool (*23*). Robinson annulation of 2-methyl-1,3-cyclohexanedione (*24*) with the hydroxy α,β-unsaturated ketone *25* afforded the key substance *26*. Hydrogenation of this compound gave the *trans* decalone *27*. Once this *trans* A/B ring system was constructed, further investigations towards the completion of the molecule were investigated. Addition of a methyl Grignard reagent afforded the alcohol *28* which was dehydrated to *29* by refluxing in methanol in the presence of hydrogen chloride. This product was hydrated to the hemiacetal *30*, followed by thioketalization to give *31*. Finally this thioketal was oxidized to the ketone *32* (scheme 2.2).

Although an elegant solution was found for the construction of the A/B ring system and the introduction of the methyls at C-4 an C-5, the possibilities for the introduction of the methyl groups at C-8 and C-9 remained undiscussed.

Scheme 2.2

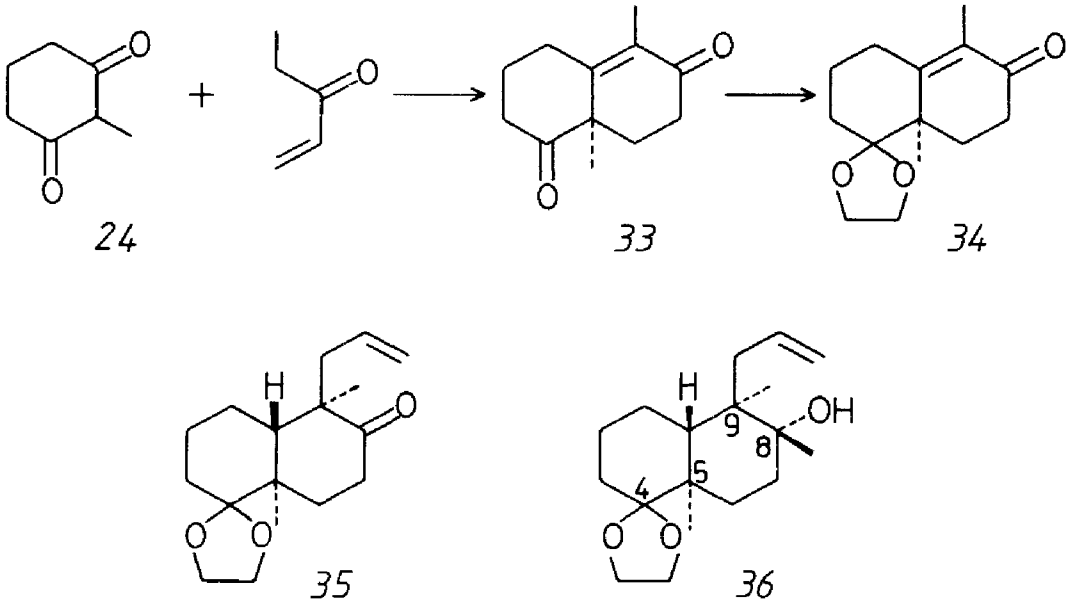


2.4 THE FORMATION OF A POTENTIAL INTERMEDIATE IN THE SYNTHESIS OF CLERODANES BY ARDON-JIMENEZ AND HALSALL.

After the unsuccessful biogenetic-type pathway for the total synthesis of clerodanes (chapter 2.2) Halsall's group started an alternative approach to this goal[3]. Like ApSimon they started with an annulation reaction. 2-Methyl-1,3-cyclohexanedione (*24*) was reacted with ethyl vinyl ketone to give the octalone *33*. Protection of the C-4 keto function gave *34*. Reductive alkylation using allyl bromide as alkylating agent afforded the *trans* A/B ring system *35* with functionalities suitably placed for the further synthesis of low oxyge-

nated clerodanes. Finally a methyl substituent at C-8 was introduced by addition of methyllithium to ketone *35* to give the alcohol *36* (scheme 2.3).

Scheme 2.3

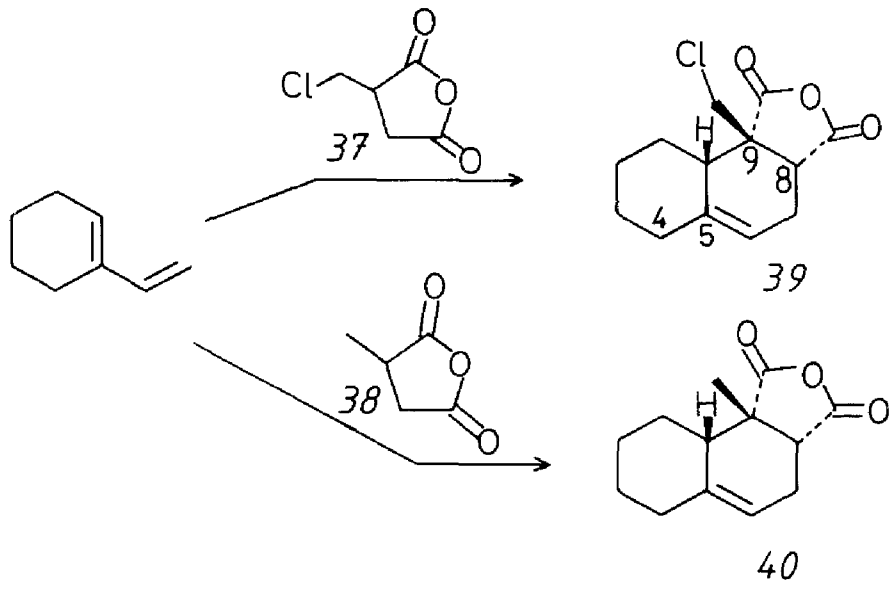


The authors did not work out the completion of the clerodane side chain at C-9 and the transformation of the tertiary alcohol at C-8 into an equatorial methyl. However, this method does seem to offer a better perspective for the total synthesis of clerodane type diterpenes than the ApSimon approach.

2.5 THE STEREOSPECIFIC FORMATION OF A BICYCLIC INTERMEDIATE USEFUL FOR SYNTHESIS OF CLERODANES BY TOKOROYAMA *ET AL.*

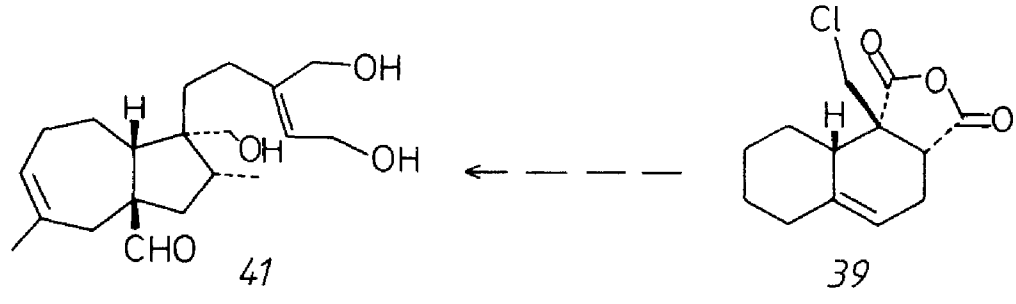
Tokoroyama and coworkers[4] studied the Diels-Alder reactions of 2-vinylcyclohexene and various substituted maleic anhydrides in order to obtain intermediates for the total synthesis of clerodanes. Thus, reaction of 2-vinylcyclohexene with the chloromaleic anhydride *37* and citraconic anhydride (*38*) afforded *39* and *40* respectively (scheme 2.4).

Scheme 2.4



Although intermediate *39* may serve as a precursor for the synthesis of clerodanes with highly oxygenated functionalities at C-8 and C-9, the authors remain vague about the introduction of the substituents at C-4 and C-5. In a later paper they described the total synthesis of portulal[5] (*41*) starting from the chloride *39*, thus proving the usefulness of their intermediates (see scheme 2.5).

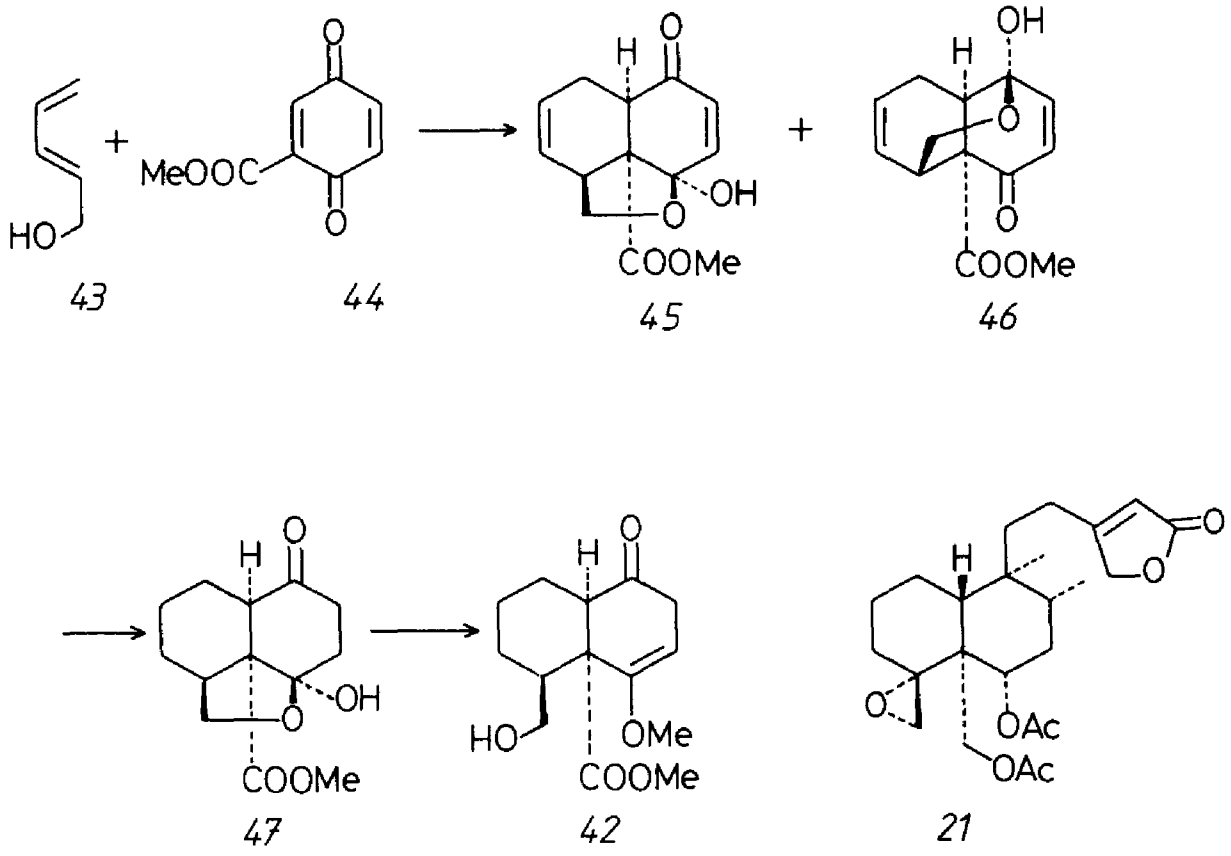
Scheme 2.5



2.6 A DIELS-ALDER APPROACH TO THE SYNTHESIS OF AJUGARIN I ACCORDING TO GOLDSMITH AND COWORKERS.

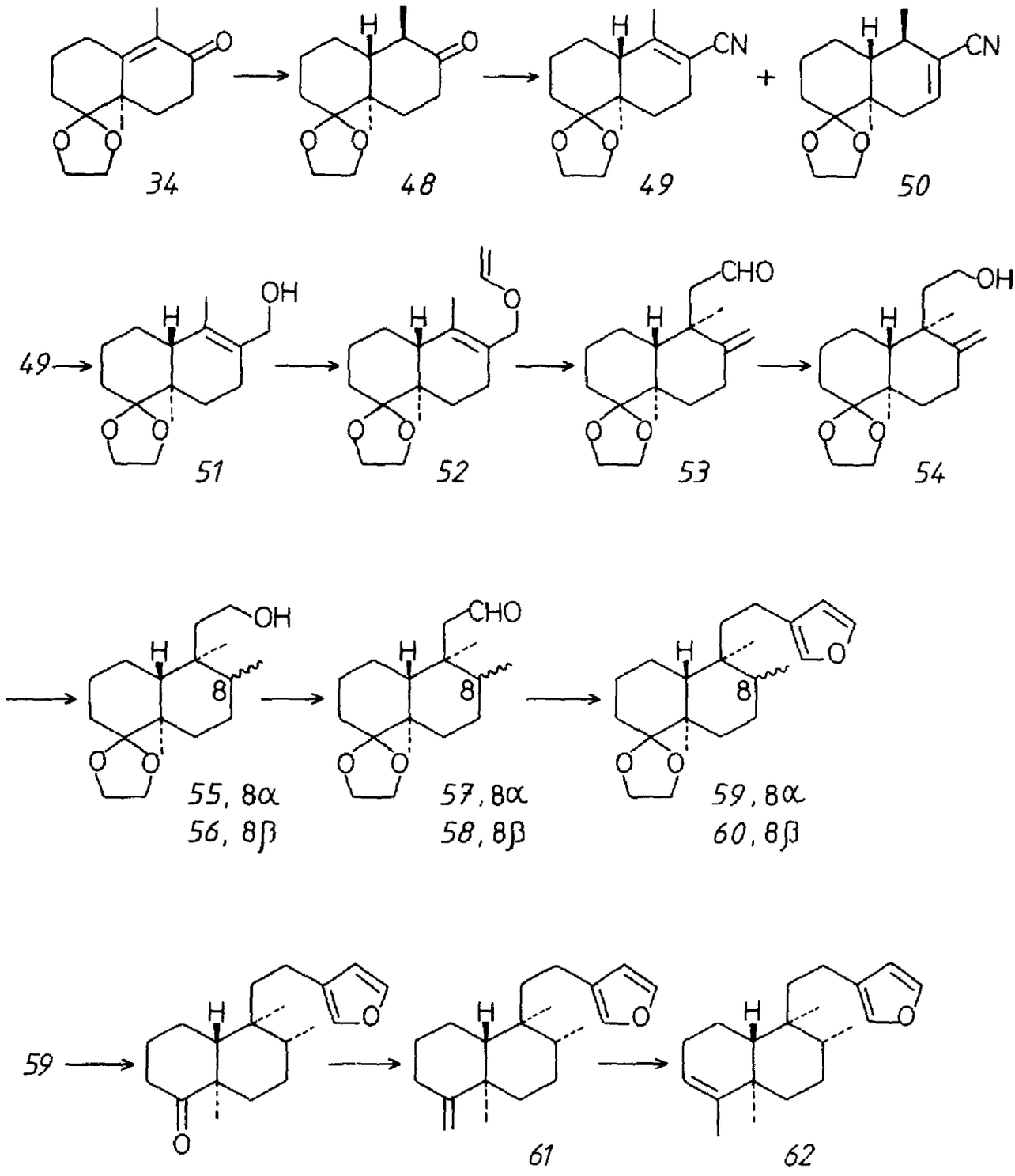
In an approach towards the insect antifeedant clerodane ajugarin I (*21*), Goldsmith[6] described the synthesis of the decalone *42*. Cycloaddition of 2,4-pentadien-1-ol (*43*) and carbomethoxy-*p*-benzoquinone (*44*) afforded a mixture of the hemiacetals *45* and *46*. This mixture was transformed into the γ-keto unsaturated acetal *47*. Reductive cleavage of this product afforded *42* which was presented as a useful intermediate for the synthesis of ajugarin I (scheme 2.6).

Scheme 2.6



In accompanying experiments the authors were able both to epimerize the *cis* decalin system into the *trans* and to introduce the C-8 methyl group. They did not investigate, however, the stereospecific introduction of the clerodane side chain (*i.e.* C-10 - C-16). Furthermore the transformation of the hydroxymethyl at C-4 into an epoxide remained an unsolved problem.

Scheme 2.7



2.7 THE FIRST CLERODANE TOTAL SYNTHESIS BY TAKAHASHI AND COWORKERS.

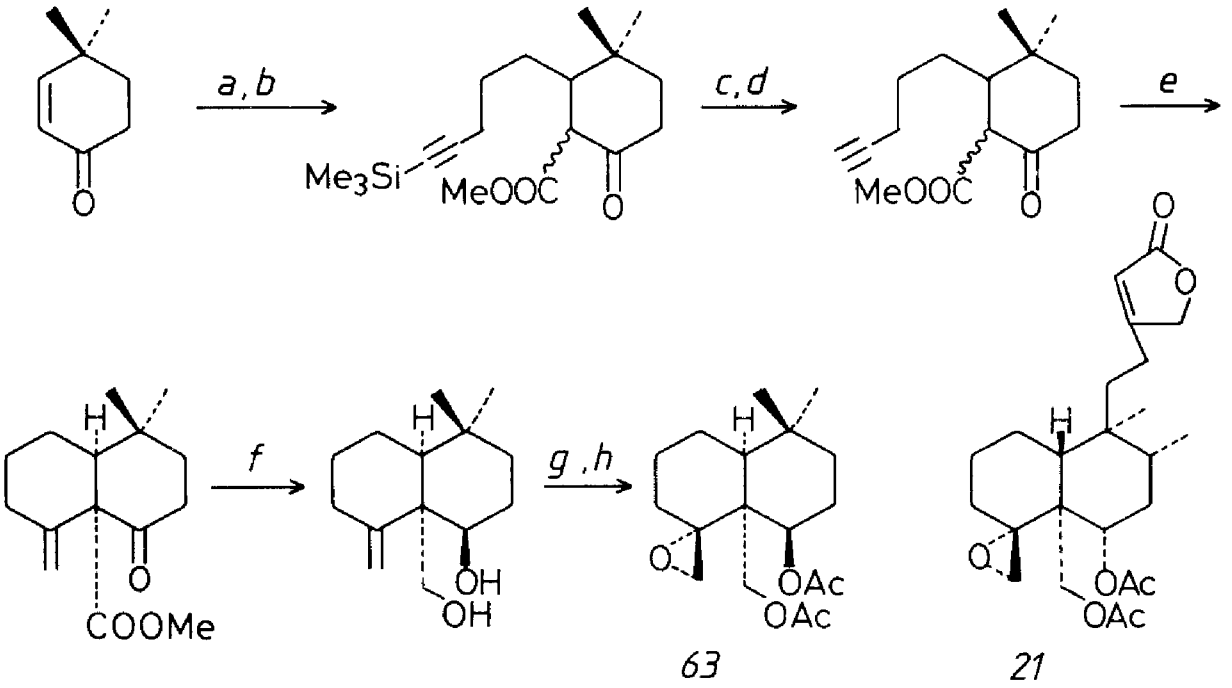
In 1979 the first total synthesis was published by Takahashi *et al*[7]. Just as Ardon-Jimenez and Halsall they started from the Wieland-Miescher ketone *34*. This ketone was reduced by lithium in ammonia to give the *trans* decalone *48*. Treatment of this ketone with potassium cyanide followed by dehydration gave the isomeric nitriles *49* and *50*. The nitrile *49* was converted into the allyl alcohol *51* by reduction with diisobutylaluminium hydride followed by sodium borohydride reduction of the intermediate aldehyde. The alcohol *51* was transformed into the vinyl ether *52* and subjected to a Claisen rearrangement to afford the aldehyde *53* as the major product. This aldehyde was reduced with sodium borohydride to give the alcohol *54* which in turn was hydrogenated (H_2/Pd) to give a 1:1 mixture of the C-8 epimers *55* and *56*. This mixture was not separated at this stage but oxidized to the aldehydes *57* and *58*. Treatment with furyllithium, followed by acetylation and reductive removal of the acetoxy group with calcium in ammonia gave *59* and *60*, which could be separated by chromatography on silica gel. Deacetylation of *59* followed by reaction with methylenetriphenylphosphorane afforded the exocyclic olefin 61 which could be transformed into the clerodane annonene *62* (scheme 2.7).

Although this approach did actually afford the natural product and introduced the C-9 side chain in a stereoselective and very elegant way, it suffered from the disadvantage that it contained two non-stereoselective steps which reduced the yield considerably and made it necessary to carry out some difficult separations. Furthermore this approach does not seem to be very appropriate to synthesize the highly oxygenated and physiologically active clerodanes.

2.8 SYNTHESIS OF A SUBSTITUTED *CIS* DECALIN AS A POTENTIAL INSECT ANTIFEEDANT BY JACKSON AND LEY.

In order to probe the insect antifeedant activity of a number of clerodanes, Jackson and Ley[8] started a programme of synthesis of a number of model compounds. They reported the stereospecific synthesis of a *cis* decalin containing a number of substituents that are also found in the antifeedant-active clerodanes. Their synthesis is outlined briefly in scheme 2.8.

Scheme 2.8



a: $Me_3Si\text{-}C{\equiv}C\text{-}(CH_2)_3MgI$, Cu^I, Et_2O; *b*: $ClCO_2Me$; *c*: $AgNO_3$; *d*: KCN; *e*: $SnCl_4$; *f*: $LiAlH_4$; *g*: $VO(acac)_2$-*t*-BuOOH; *h*: Ac_2O, Py, DAP.

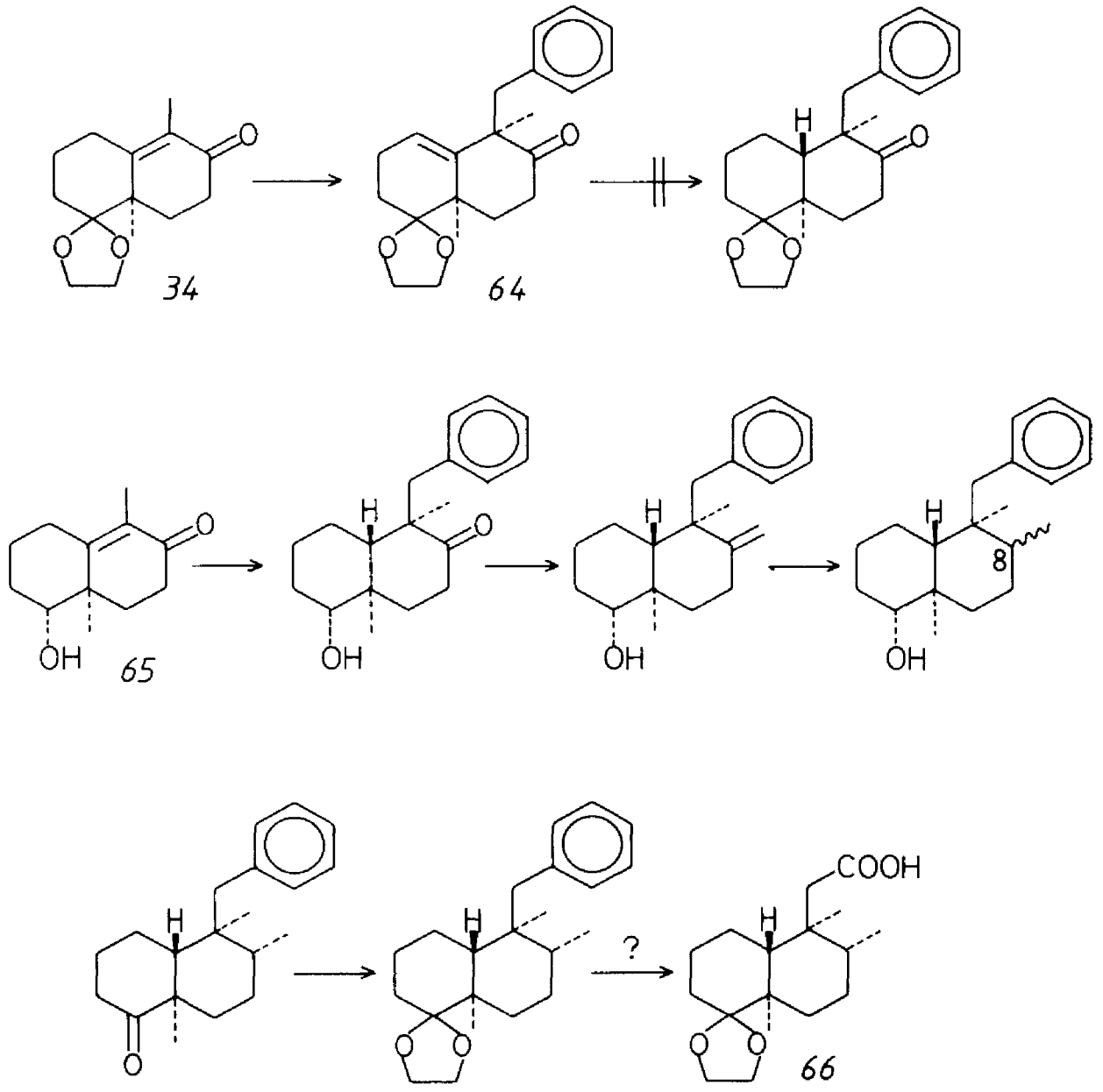
Since all antifeedant clerodanes contain a *trans* fused A/B ring system (*e.g.* ajugarin I, *21*), the *cis* decalin *63* is a poor model for structure-activity studies. In one case, however, this compound did show weak antifeedant activity, which might be an indication that this activity is situated in the epoxy diacetate moiety.

2.9 STUDIES ON THE SYNTHESIS OF *TRANS* CLERODANES AND CONGENERS BY SARMA AND CHATTOPADHYAY.

The approach published by Sarma and Chattopadhyay[9] resembles to some extent the synthetic studies by Ardon-Jimenez and Halsall (see chapter 2.5). They started with octalone *34* and used a dienolate alkylation to introduce a side chain presursor at C-9, which afforded *64*. Reduction of the double bond in ring A, however, was unsuc-

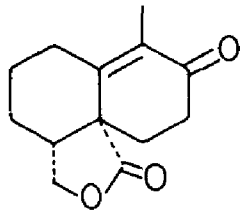
cessful. A reductive alkylation was therefore carried out on decalone *65*. A Wittig reaction introduced the C-8 methylene, which in turn was hydrogenated to afford the desired C-8 α methyl as the major and the C-8 β methyl as the minor product. Further reactions involved the oxidation of the C-4 hydroxyl followed by ketalization. Ozonolysis of the aromatic ring was used to functionalize the side chain precursor at C-9. The desired acid *66* could not be isolated, however, from the reaction mixture (see scheme 2.9).

Scheme 2.9

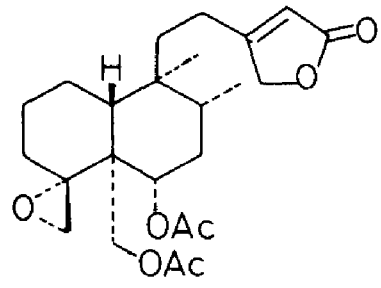


2.10 FORMATION OF A SYNTHON FOR CLERODANE ANTIFEEDANT SYNTHESIS BY GOLDSMITH AND COWORKERS.

Two years after their first paper in this field (chapter 2.6) Goldsmith's group[10] published the octalone *67* as a new intermediate for the total synthesis of ajugarin I (*21*).



67



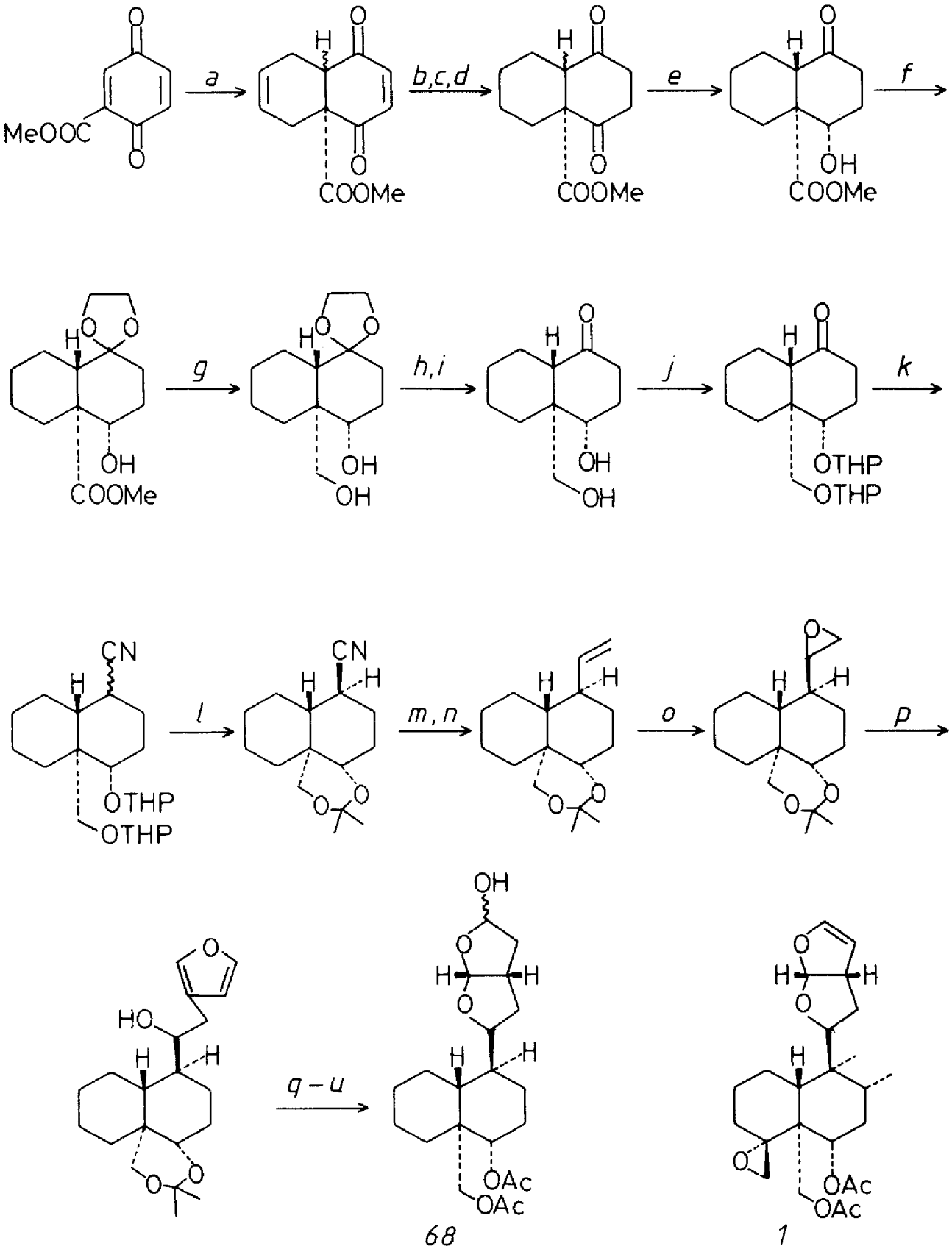
21

It is not clear which further transformations are planned to synthesize the target molecule. Anyway, the tentative conclusion may be drawn that their first approach towards ajugarin I was not pursued any further.

2.11 THE STEREOCONTROLLED SYNTHESIS OF A CLERODIN HOMOLOG BY KOJIMA AND KATO.

In contrast to Jackson and Ley (chapter 2.9) Kojima and Kato[11] expect that the antifeedant activity of clerodanes such as clerodin (*1*) is situated in the furofuran structural element. They therefore synthesized the clerodin homolog *68* for structure-activity studies. The synthesis of this homolog is outlined briefly in scheme 2.10. The initial steps show some analogy to the strategy of Goldsmith's ajugarin I approach.

Scheme 2.10



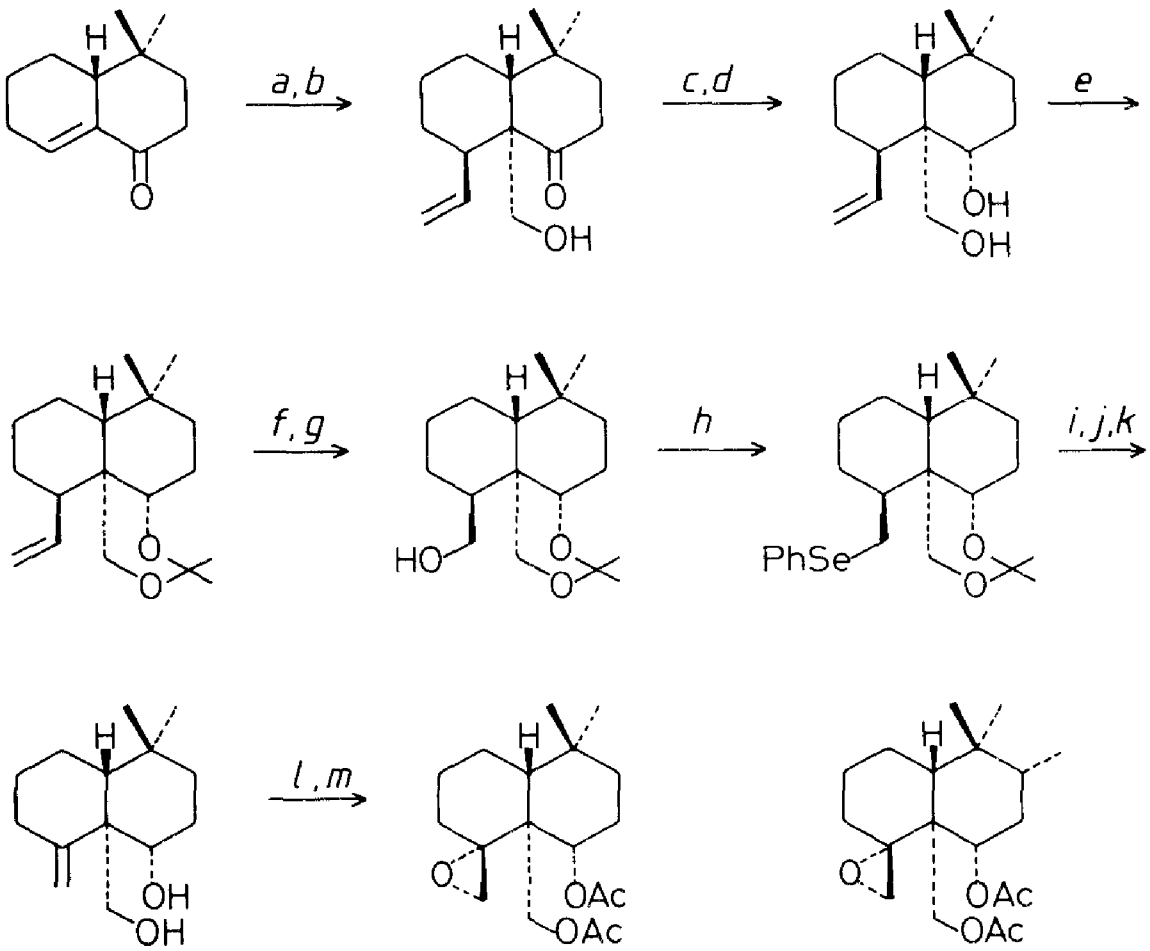
a: butadiene, $SnCl_4$; *b*: Zn, HOAc; *c*: MeO^-; *d*: H_2/Pd; *e*: $NaBH_4$; *f*: TsOH, glycol, Δ; *g*: $LiAlH_4$; *h*: H_3O^+; *i*: OH^-; *j*: dihydropyran, TsOH; *k*: TosMIC, *t*-BuO^-; *l*: TsOH, acetone dimethylacetal; *m*: Dibal H; *n*: Wittig; *o*: *m*-CPBA; *p*: 3-furyllithium; *q*: H_3O^+; *r*: Br_2, MeOH; *s*: H_2, Ra-Ni; *t*: $HClO_4$; *u*: Ac_2O, Py.

The results of the insect antifeedant tests of compound *68* will be discussed in chapter 9 of this thesis.

2.12 THE SYNTHESIS OF A *TRANS* DECALIN AS A POTENTIAL INSECT ANTIFEEDANT BY LEY *ET AL*.

Shortly after we had published the synthesis of the model compound *69* for structure-activity investigations of the antifeedant

Scheme 2.11



70 *69*

a: $(CH_2{=}CH)_2CuMgX$; *b*: H_2CO; *c*: *t*-$BuMe_2SiCl$, imidazole, DMF; *g*: $LiAlH_4$; *e*: $Me_2(OMe)_2C$; TsOH; *f*: O_3, MeOH; *g*: $NaBH_4$; *h*: N-PSP, n-Bu_3P; *i*: O_3, CH_2Cl_2; *j*: Δ, CCl_4, Et_2NH; *k*: TFA; *l*: *t*-BuOOH, $VO(acac)_2$; *l*: Ac_2O, Py, DAP.

clerodanes (see chapter 5), Ley *et al*[12]. achieved the synthesis of a similar compound (*70*). The synthesis of this epoxy diacetate is outlined in scheme 2.11.

Compound 70 showed strong insect antifeedant activity against *Locusta migratoria*.

2.13 REFERENCES.

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2 ApSimon, J.W., and Yamasaki, K., Chemistry Lett., (1977), 1453.

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10 Goldsmith, D.J., John, T.K., and Van Middlesworth, F., Synthetic Commun., (1980), 511.

11 Kojima, Y., and Kato, N., Tetrahedron Lett., (1980), 5033.

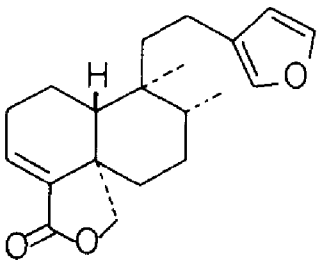
12 Ley, S.V., Simpkins, N.S., and Whittle, A.J., J. Chem. Soc., Chem. Commun., (1981), 1001.

3 *THE FORMATION OF SUBSTITUTED DECALONES AS INTERMEDIATES IN THE TOTAL SYNTHESIS OF* TRANS *CLERODANES.*

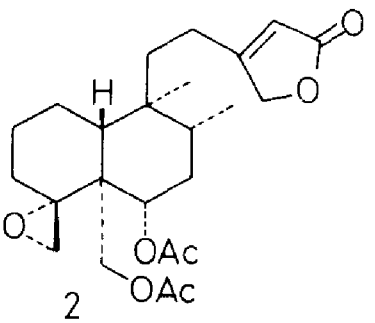
3.1 INTRODUCTION

Those members of the class of clerodanes that possess physiological activity have drawn most attention in research, not only from the biological, but also from the chemical point of view. The many asymmetric centers and the variety of functional groups make their structural elucidation often very laborious. Even more complex is the total synthesis of these compounds; again the numerous chiral centers together with the various oxidation states pose the main problems to the synthetic chemist.
Aware of these difficulties we initially elected to investigate the synthesis of less complex clerodanes (for which no physiological activity has been reported). The experience acquired in these studies eventually enabled the synthetic plans to be extended to the more challenging physiological active compounds.

Hautriwaic acid (18→19) lactone (1)[1] seemed to be a suitable target molecule for the preliminary investigations. This compound contains only four chiral centers and possesses an array of carbon atoms at oxidation states that enables extension to the synthesis of the complex physiologically active *trans* clerodanes (*e.g.* ajugarin I (2))[2].



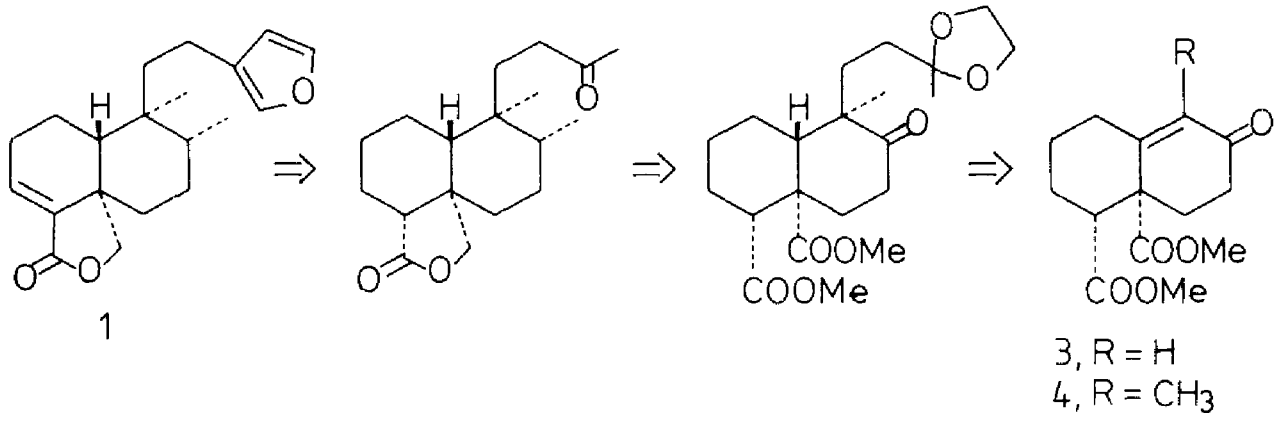
1



2

Our approach towards the total synthesis of 1 has been founded on the initial construction of a suitably substituted bicyclic intermediate with the side chain (carbon atoms 11-16) being completed in the final stages. Our first retrosynthetic plan (scheme 3.1) started with the readily available octalones 3 and 4. In this approach the substituents at C-9* should be introduced *via* alkylation of the dienolate anion generated from these octalones. A 3-oxo-butyl substituent (protected as its ethylene ketal) was chosen as the precursor of the C-9 side chain since an elegant conversion of alpha methyl ketones into furanes as present in 1 was described in a recent paper[3]. Furthermore the transformation of the *vic* ester groups into an α,β-unsaturated lactone had to be investigated.

Scheme 3.1



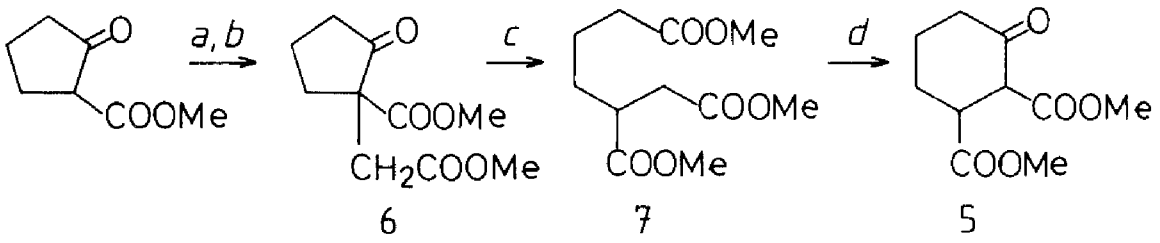
3.2 THE CONSTRUCTION OF THE A/B RING SYSTEM.

Octalones of type 3 or 4 are best prepared *via* a Robinson annulation reaction of a suitably substituted cyclohexanone. In 1958 Sen and Bagchi[4] described the synthesis of 2,3-diethoxycarbonyl-cyclohexanone. The corresponding dimethyl ester was prepared as follows in an analogous fashion. Reaction of bromoacetic methyl ester with the enolate anion of 2-methoxycarbonyl-cyclopentanone gave 6.

* In order to avoid confusion, the numbering corresponding to that of the clerodane diterpenes is used throughout the discussion. In the experimental part, however, the numbering corresponding to the IUPAC rules is used.

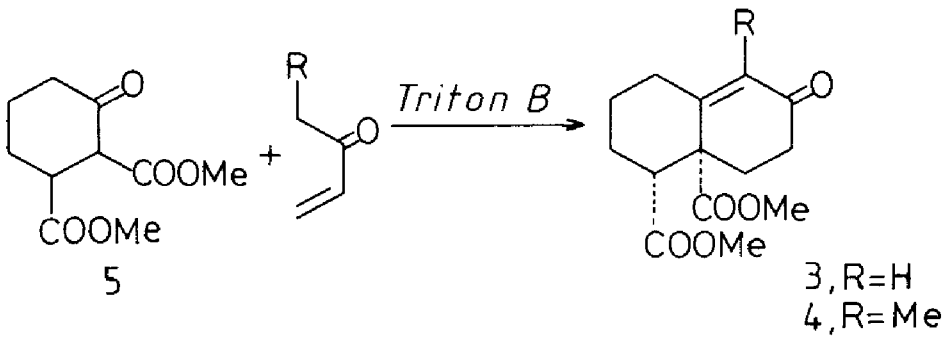
Treatment of this product with sodium methoxide gave the acyclic triester 7. Dieckmann condensation of this compounds gave 5 (scheme 3.2)[5]. The overall yield of these reactions was 72-75%. In all cases the methyl ester derivatives were used because of the simplicity of their ^{1}H-NMR spectra.

Scheme 3.2



a: MeO^-, MeOH; *b*: $BrCH_2COOMe$; *c*: MeO^-, MeOH; *d*: Na,Bz.

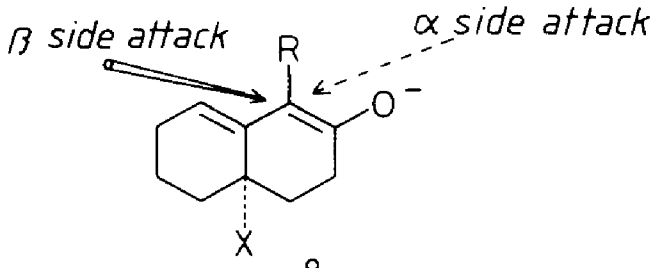
As mentioned above octalones 3 and 4 could be prepared in high yield by a Robinson annulation of the ketodiester 5 and methyl vinyl ketone and ethyl vinyl ketone respectively, in the presence of Triton B. The methoxycarbonyl groups at C-4 and C-5 were assumed to possess relative *cis* stereochemistry. This was based upon the findings of Dutt *et al.*[6], who carried out a similar annulation reaction.



3.3 THE DIENOLATE ALKYLATION OF SUBSTITUTED OCTALONES.

The next step in the synthetic plan involved the stereospecific introduction of the substituents at C-9. Initially the dienolate alkylation method was chosen for this purpose. The expected steric course of this reaction should lead to an axially orientated methyl group an equatorially orientated side chain precursor at C-9.

McQuillin and Simpson[7] found that the stereochemical outcome of this type of alkylations is strongly dependent on the nature of the substituent X in the dienolate anion 8. In the case of X representing an ethoxycarbonyl group, alkylation was found to take place from the α** side. When X was a methyl group, the major alkylation product arose from substitution in the conversed fashion.



8

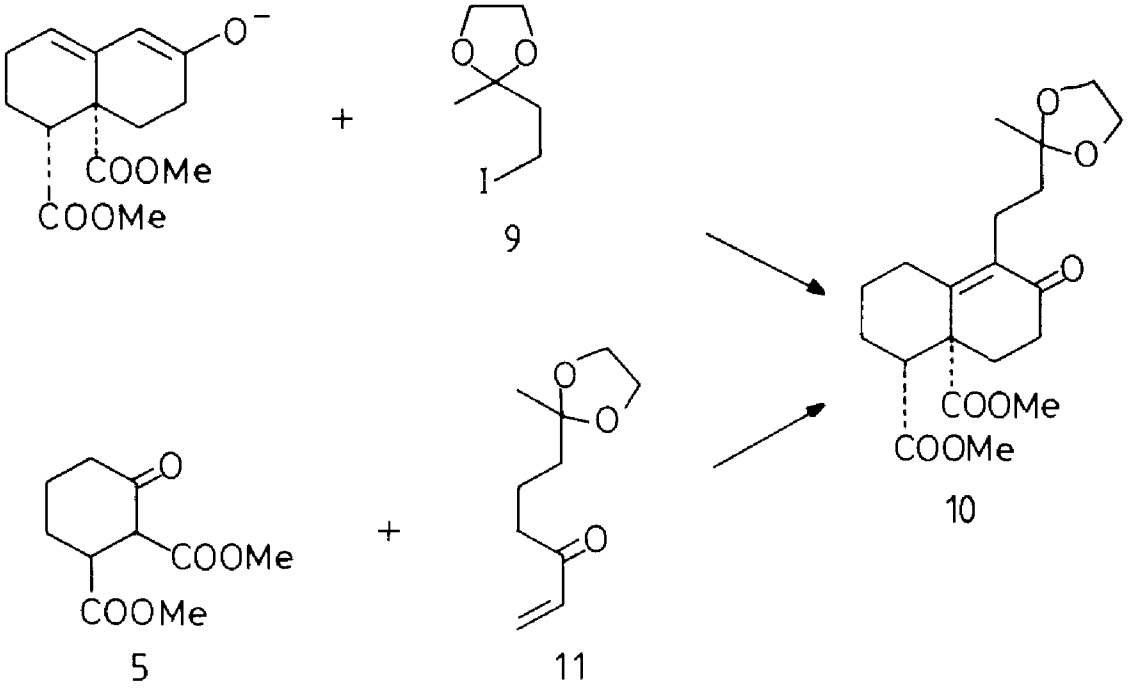
The influence of the ester group was attributed to its polar nature and to its effect in stabilising the transition state leading to α substitution.
It was expected that this effect would decrease in more polar media and therefore the authors used dioxan as the solvent in their experiments.

Application of the foregoing to clerodane total synthesis implied that the precursor of the side chain should be introduced first, followed by alkylation with methyl iodide.

** When the rings of a quasi planar parent structure are denoted as projections into the plane of the paper, an atom or group attached to the ring is termed α if it lies *below* the plane of the paper or β if it lies *above* the plane of the paper.
(Nomenclature in Organic Chemistry, Pergamon Press (1979), rule F-6.2).

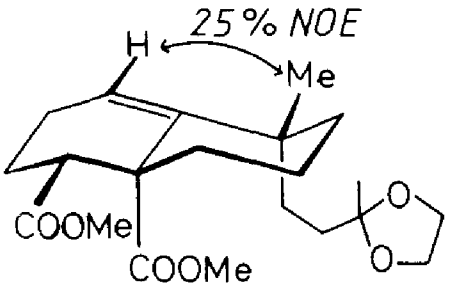
The required side chain precursor was introduced by alkylation of the dienolate anion of 3 with 2-methyl-2-(2'-iodoethyl)-dioxolan(9) (see also the retrosynthetic plan in scheme 3.1). The same octalone could also be prepared by a Robinson annulation of ketodiester 5 and enone 11 (scheme 3.3).

Scheme 3.3



Subsequent treatment of 10 with sodium 2-methyl-2-butoxide in benzene, followed by methyl iodide predominantly gave monoalkylation and a dialkylated side product. The monoalkylated product was isolated in 42% yield by column chromatography on silica gel. The stereochemistry of the product could be elucidated by intramolecular nuclear Overhauser effect (NOE) studies. Irradiation of the methyl singlet at 1.11 ppm in the ^{1}H-NMR spectrum caused a 28% increase of the integrated area of the olefinic C-1 H at 5.77 ppm. This effect can only be explained by assuming an equatorial position of the C-9 methyl[8], as indicated in structure 12.

These results showed that the stereochemistry at C-9 was opposite to what was expected on the basis of the findings of McQuillin and Simpson, in spite of the use of a non polar solvent in the alkyla-

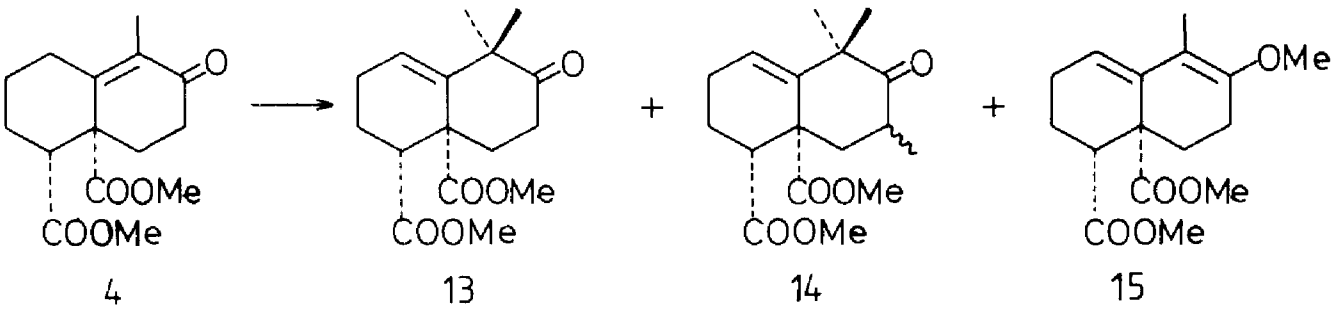


12

tion step. The same reaction was also carried out in *t*-butanol with potassium *t*-butoxide as the base. This afforded the same product, thus showing that in this case the stereochemistry of the alkylation products is independent on the nature of the solvent and is always a result of β attack of methyl iodide.

From the foregoing it was concluded that the methyl group at C-9 should be introduced first, followed by dienolate alkylation with iodide 9. In order to investigate the feasability of dienolate alkylations of 4, this compound was alkylated by methyl iodide in *t*-butanol using potassium *t*-butoxide as the base. Analysis of the reaction mixture showed the formation of the monoalkylated product 13 (43%) alongside a small amount of dialkylated product 14(5%) and

Scheme 3.4



some O-alkylated product 15. The latter could be hydrolysed with dilute acid to give the starting compound (see scheme 3.4).

Alkylation of the dienolate anion generated from 4, with iodide 9 was unsuccessful, however, in that only starting material was recovered.

The use of other alkylating agents as potential precursors of the side chain was considered but rejected. Allyl bromide was undesirable since ring A also contains an olefinic moiety after addition, and chemical distinction between this double bond and the allyl side chain might be difficult to achieve. For similar reasons the use of bromo acetic acid methyl ester as alkylating agent did not seem attractive.

Another fact that frustrated the dienolate alkylation approach was the inertness of the double bond in ring A of both compounds 12 and 13 towards catalytic hydrogenation as planned for the formation of the *trans* fused decalone system.

3.4 LACTONE FORMATION FROM A *VIC* DIESTER GROUP

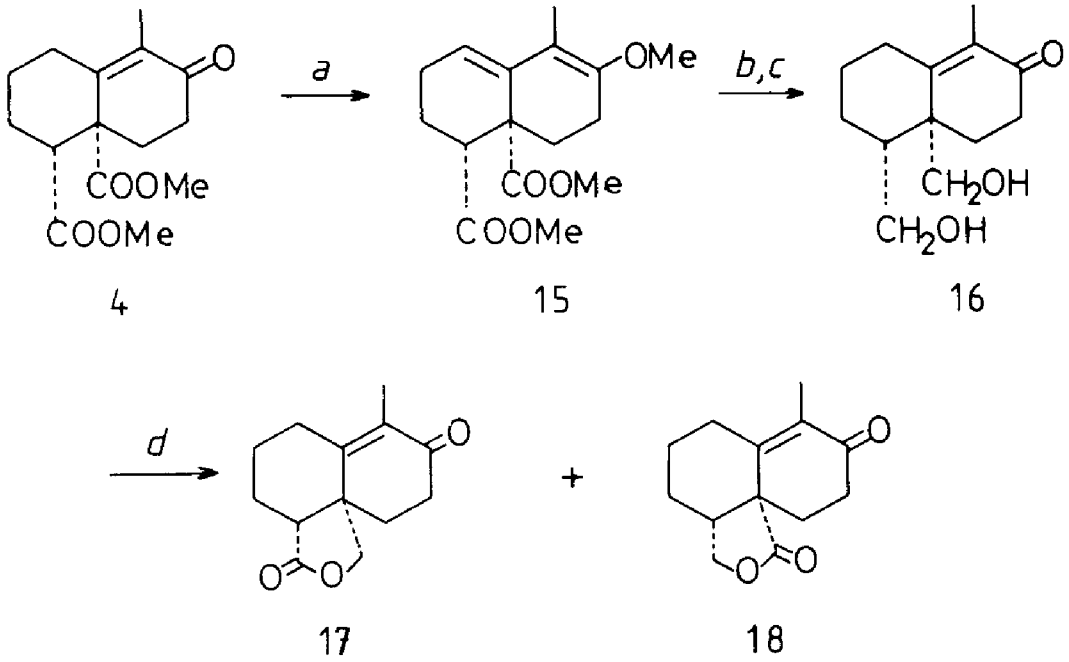
Besides the investigations into the usefulness of the dienolate alkylation approach, we also studied the possibilities of transforming the two ester groups into a lactone, as is necessary for the synthesis of 1.
Compound 4 was chosen as a model for this study. First the enone system was protected as the dienol ether 15 by reaction of 4 with trimethyl *ortho* formate in methanol in the presence of boron trifluoride. The ester groups were reduced with lithium aluminium hydride to give, after hydrolysis, diol 16. Oxidation of this compound with Jones' reagent[9] gave a 1:1 mixture of the two isomeric lactones 17 and 18 which proved difficult to separate by column chromatography (see scheme 3.5).

The low yield of the desired lactone 17 and its difficult separation from the isomer 18 made this approach quite unattractive.

3.5 THE REDUCTIVE ALKYLATION OF SUBSTITUTED OCTALONES.

It had become clear from the foregoing that our retrosynthetic plan had to be revised. In the first place a way had to be found

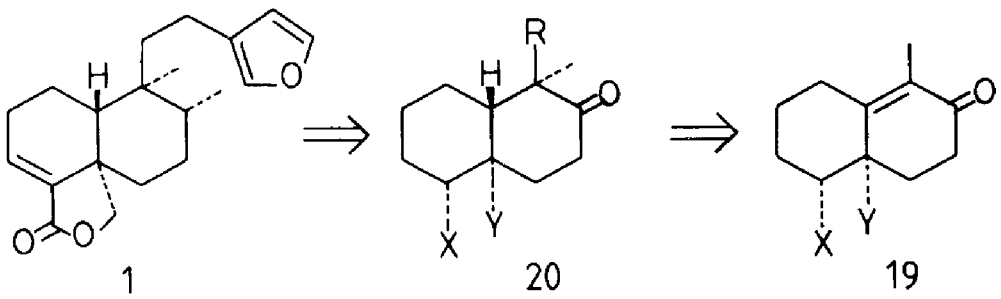
Scheme 3.5



a: $HC(OMe)_3$, MeOH, BF_3; *b*: $LiAlH_4$; *c*: H_3O^+; *d*: Jones' reagent.

for the stereochemically correct introduction of the substituents at C-9, combined with the reduction of the octalone system to a *trans* fused decalone. Secondly a more selective procedure had to be developed for the formation of lactones as are found in 1.

Scheme 3.6

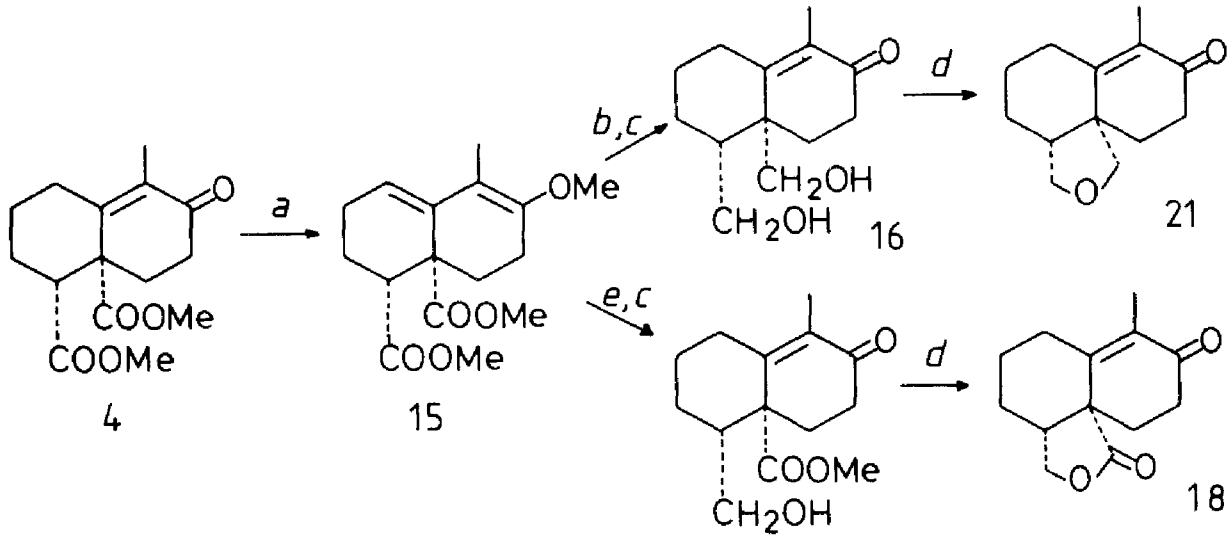


An alternative approach to the *trans* fused decalone system can start with octalones of type 19 in which the side chain precursor at C-9 is introduced *via* a reductive alkylation-step (scheme 3.6). Analogous reductive alkylations[10] are known to give the *trans* decalin structure and proceed *via* β attack of the alkylating agent (*i.e.* structure 19→20), thus affording the right stereochemistry at C-9 with respect to *trans* clerodanes such as 1.
The main problem in this approach is the proper choice of X and Y, both oxidized one carbon substituents that must survive conditions of reductive alkylation and other chemical manipulations. On the other hand their selective and rapid conversion into an α,β-unsaturated lactone must remain possible.

3.6 THE FORMATION OF A CYCLIC ETHER FOR THE PROTECTION OF THE FUNCTIONALITIES AT C-18 AND C-19.

Preliminary experiments had made it clear that enone 4 was unsuitable in the reductive alkylation step since the ester groups

Scheme 3.7



a: $HC(OMe)_3$, MeOH, BF_3; *b*: $LiAlH_4$; *c*: H_3O^+; *d*: H_3O^+, Δ; e: $LiAlH_4$, 0.5 molar eq.

gave rise to undesired side reactions which led to the formation of numerous products. Conversion of the ester groups into a more stable cyclic ether seemed to circumvent these complications. Octalone 4 was protected as its dienolether 15 and reduced with lithium aluminium hydride to give diol 16. Dehydration of 16 by refluxing in concentrated aqueous hydrochloric acid afforded 21 (see scheme 3.7).

The overall yield of these conversions was 80-85%. The facile ether formation in the dehydration step emphasizes the *cis* orientation of the substituents at C-4 and C-5. On use of 0.5 molar equivalent of lithium aluminium hydride in the reduction of 15, lactone 18 was formed in 84% yield after refluxing in concentrated hydrochloric acid. This indicated that the ester group at C-4 is reduced preferentially. The synthesis of 18 *via* a more laborious route was described recently by Goldsmith *et al.*[11], also in connection with clerodane total synthesis (see also chapter 2.10). The use of 18 was not explored further because better results were expected with the cyclic ether 21.

3.7 THE USE OF THE CYCLIC ETHER AS A PROTECTIVE GROUP IN REDUCTIVE ALKYLATION REACTIONS, AND ITS SUBSEQUENT TRANSFORMATION INTO AN α,β-UNSATURATED LACTONE.

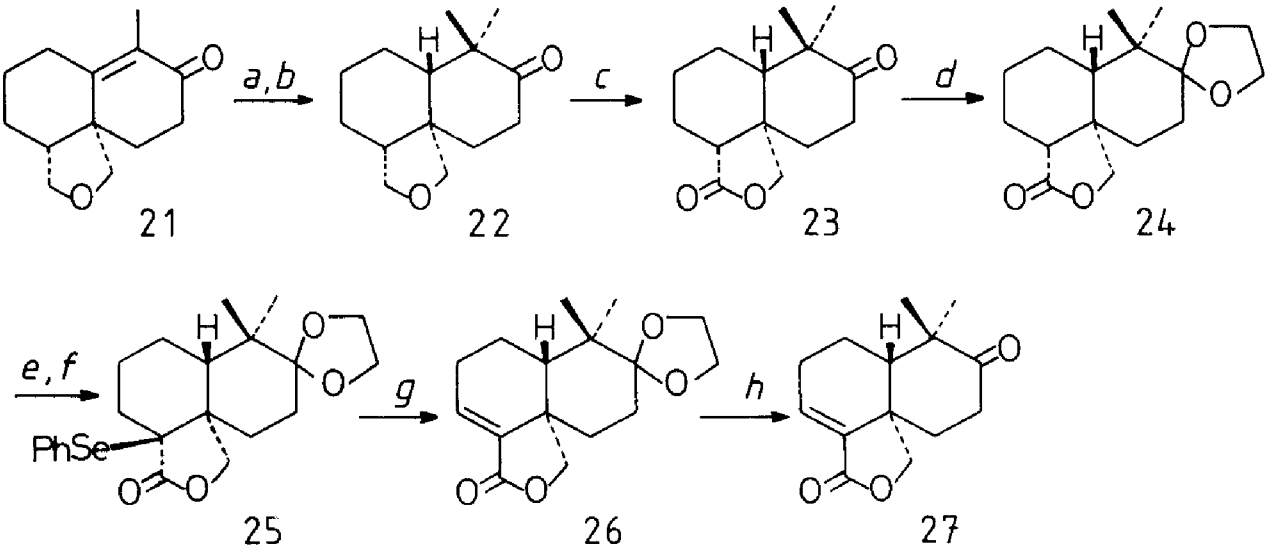
In order to probe the scope of the cyclic ether moiety as a potential protective group for C-18 and C-19 in the synthesis of 1, the following series of transformations was carried out.

Reductive alkylation of 21 with lithium in ammonia using methyl iodide as the alkylating agent afforded 22 in 94% yield. The stereochemistry at the ring junction was assumed to be *trans*. Evidence confirming this assumption was obtained at a later stage (see chapter 4.4 and 6).

The cyclic ether could be converted quantitatively and regiospecifically into lactone 23 either by treatment with bromine solution[12] or with ruthenium tetroxide[13].

The introduction of the unsaturation in ring A in 23 was achieved in the following way. First the oxo group at ring B was protected as its ethylene ketal to give 24. This compound was then treated with lithium diisopropylamide (LDA), followed by the addition of diphenyl diselenide to afford 25. Oxidation of this selenide to its corresponding selenoxide, followed by elemination, gave the α,β-unsaturated lactone 26[14]. The latter was hydrolysed to ketone 27 (see scheme 3.8).

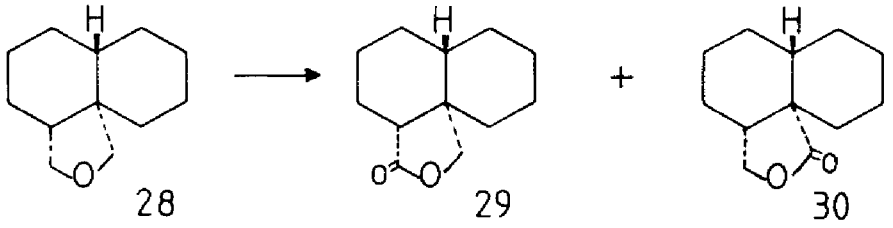
Scheme 3.8



a: Li, NH_3, 1 eq. H_2O; *b*: MeI; *c*: RuO_4, or Br_2, H_2O, pH7; *d*: MED, TsOH; *e*: LDA; *f*: PhSeSePh; *g*: $NaIO_4$; *h*: acetone, H_3O^+.

The overall yield of these conversions was 37-40%.
The high degree of regiospecifity in the oxidation of 22 to 23 is probably owing to the 1,3-diaxial interaction between the substituents at C-5 and C-9 which prevents the oxidizing agent from approaching the angular substituent. This regiospecifity decreased in the absence of a substituent at ring B. Thus oxidation of 28 with ruthenium tetroxide gave the isomeric lactones 29 and 30 in a ratio of 88:12 respectively[15] (scheme 3.9).

Scheme 3.9



The experiments described above show that octalone 21 can be expected to be a promising intermediate for the synthesis of *trans* clerodanes that possess a lactone at ring A. The cyclic ether was shown to be stable under the conditions of reductive alkylation reactions and stability towards *e.g.* organometallic reagents, mild oxidation and reduction was anticipated. Conversion into an α,β-unsaturated lactone can be effectuated at a strategical moment in the sequence of transformations in the synthesis under study. As will be shown later (chapter 5.3) this cyclic ether can also be cleaved in a very effective way, which opens a unique synthetic route towards antifeedant-active clerodanes, such as ajugarin I (2). This makes octalone 21 a key intermediate in the synthesis of a large number of clerodanes.

3.8 EXPERIMENTAL SECTION

Infrared spectra were recorded on a Perkin-Elmer 237 spectrometer. UV spectra were obtained on a Perkin-Elmer 550 spectrometer. ^{1}H NMR spectra were recorded on a Varian EM-390 or a Perkin-Elmer R 24 B spectrometer with tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded with a Varian XL-100 spectrometer in the pulse FT mode using $CDCl_3$ as solvent and tetramethylsilane as internal standard. Mass spectra and exact mass measurements were obtained with an AEI MS 902 spectrometer. GCMS spectra were obtained from a VG Micromass 7070F spectrometer. GC analyses were carried out on a Hewlett Packard 5700 A chromatograph. The column used for determining product purity and for monitoring reactions was a 2 m

column packed with 3.3% SE-30 on Chromosorb W. Column chromatography was carried out over Merck Silica gel 60 (70-230 mesh ASTM). All melting and boiling points are uncorrected. Relative intensities of mass spectrometrical fragmentations are in parentheses.

In the experimental part the numbering according to the IUPAC rules is utilized.

2,3-dimethoxycarbonyl-1-cyclohexanone (5).

This compound was prepared in 72-75% yield employing the method of Sen and Bagchi[4] described for the corresponding diethylester. A preparation of 5 via a different route has been reported[5].
B.p 105-110°C (0.5 mm); IR (neat) 3500, 1730, 1650, 1610 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.70-2.3 (m,6H), 3.33 (m,1H); 3.57 (s,3H), 3.67 (s,3H), 11.16 (s,1H); MS m/e 214 (8), 182 (8), 155 (81), 123 (100).

cis-*5,10-Dimethoxycarbonyl-*$\Delta^{1,9}$*-octalin-2-one* (3).

To a stirred solution of 5 (21.2 g, 0.1 mol) in methanol (250 mL) was added methyl vinyl ketone (7.0 g, 0.1 mol) (freshly distilled) and benzyl-trimethyl-ammonium hydroxide (Triton B) (5 mL of a 40% solution in methanol). The mixture was stirred for 16 h. at room temperature. Concentrated hydrochloric acid (5 mL) was added and the solvent was distilled off.

The residue was dissolved in 200 mL of ether and washed with saturated brine solution and with aqueous sodium bicarbonate solution. The organic layer was dried over anh. magnesium sulfate and concentrated to give 3 (22 g, 83%); m.p. 95-96°C (recrystallized from ether); IR ($CHCl_3$) 1725, 1660, 1610 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.8-2.9 (m, 11H), 3.67 (s,3H), 3.70 (s,3H), 5.87 (s,1H); MS m/e 266 (4), 2 34 (12), 206 (45), 179 (18), 147 (100).

cis-*5,10-Dimethoxycarbonyl-1-methyl-*$\Delta^{1,9}$*-octalin-2-one* (4).

This compound was prepared analogous to 3 in 80-85% yield by using ethyl vinyl ketone in the annulation reaction; m.p 60-61°C (recrystallized from ether); IR (KBr) 1725, 1655, 1590 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.81 (s,3H), 1.1-3.8 (m,11H), 3.66 (s,3H), 3.69 (s,3H); MS m/e 280 (21), 248 (8), 220 (41), 161 (100).

Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; h, 7.19. Found: C, 64.56; H, 7.25.

cis-*5,10-Dimethoxycarbonyl-1-(3',3'-ethylenedioxy-butyl)-$\Delta^{1,9}$-octalin-2-one* (10).

Sodium hydride (490 mg, 20.5 mmol) was added under nitrogen to dry dimethylsulfoxide (50 mL). After stirring for 4 h a solution of 3 (5.45 g, 20.5 mmol) in 20 mL of dimethylsulfoxide was added and the dark red solution was stirred for another 3 h. 2-(2'-Iodoethyl)-2-methyl dioxolan (9) (6.3 g, 30 mmol) was added. After stirring overnight 50 mL of water was added and the mixture was extracted with ether. The ethereal extract was dried over anh. magnesium sulfate and concentrated to give the crude product. Crystallization from ether afforded pure 10 (3.2 g, 41%) m.p. 93-96°C; IR ($CHCl_3$) 1730, 1680, 1610 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.31 (s,3H), 1.5-2.7 (m,11H), 3.70 (s,3H), 3.72 (s,3H), 3.80(s,4H); MS m/e 380 (4), 365 (10), 318 (40),259 (31), 87 (100).

Anal. Calcd for $C_{20}H_{28}O_7$:C, 63.14; H, 7.42. Found: C, 62.88; H, 7.39.

7,7-Ethylenedioxy-3-oxo-1-octene (11).

To a stirred suspension of sodium hydride (3.0 g, 0.125 mol) in tetrahydrofuran (50 mL, freshly distilled from benzophenone-sodium) was added under nitrogen 2-(3-oxo)-butyl-phenyl-sulfoxide (22.1 g, 0.123 mol) in hexamethyl phosphoric acid triamide (HMPA) (22 g, 0.123 mol). After the evolution of hydrogen had ceased n-butyllithium (80 mL of a 1.5 N solution) was added and the solution became red. After 15 min. iodide 9 (27 g, 0.19 mol) was added. The red color of the solution turned yellow, indicating the disappearance of the dianion. The mixture was worked up by the addition of water and extraction with hexane. The hexane extracts were dried over anh. magnesium sulfate. Evaporation of the solvent gave 30 g of crude product which was refluxed in carbon tetrachloride for 6 h. The solvent was distilled off and the residue was chromatographed on silica gel to afford 11 (4.5 g, 20%) (oil); IR (neat) 1690, 1620 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.30 (s,3H), 1.68 (m,4H), 2.60 (m,2H), 3.86 (s,4H), 5.73 (dd, J=9,5Hz, 1H), 6.19 (d, J=5Hz, 1H), 6.20 (d, J=9Hz, 1H); MS m/e 169 (m^+-15) (10), 124 (4), 99 (45), 87 (100).

Synthesis of 10 via *a Robinson annulation reaction*.

A mixture of enone 11 (4.5 g, 0.025 mol) and ketodiester 1a

(5.15 g, 0.024 mol) was refuxed in 100 mL of methanol in the presence of Triton B (3 mL of a 40% solution in methanol). After 16 h the mixture was allowed to cool to room temperature and the solvent was distilled off. The residue was chromatographed on silicagel with ether-hexane (1:1) as the eluant to give 10 (7.6 g, 83%).

1α-(3',3'-ethylenedioxybutyl)-5α,10α-dimethoxycarbonyl-1β-methyl-$\Delta^{8,9}$-octalin-2-one (12).

To a solution of 10 (690 mg, 2.52 mmol) in dry benzene (20 mL) was added under nitrogen sodium 2-methyl-2-butoxide (6 mL of a 0.5 N solution in benzene). After stirring for 1 h methyl iodide (1.5 g, 10 mmol) was added and the mixture was stirred for 1 h. Water was added and the benzene layer was washed with brine solution and dried over anh. magnesium sulfate. The solvent was distilled off and the residue was chromatographed over silica gel with ether as the eluant to give 12 (450 mg, 45%) m.p. 84-86°C; IR (neat) 1730, 1710 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.10 (s,3H), 1.14 (s,3H), 1.2-2.8 (m,13H), 3.60 (s,3H) 3.66 (s,3H), 3.80 (s,4H), 5.76 (s,br,1H); MS m/e 394 (2), 379 (4), 332 (5), 279 (40), 220 (20), 87 (100).

Anal. Calcd for $C_{21}H_{30}O_7$:C, 63.94; H, 7.66. Found: C, 63.36; H, 7.44.

Alkylation of 4 with methyl iodide.

To a solution of 4 (3.50 g, 12 mmol) in 30 mL of dry *tert*-butanol was added under nitrogen potassium *tert*-butoxide (1.40 g, 12.5 mmol) and the mixture was stirred for 2 h. Methyl iodide (2.0 g, 13.5 mmol) was added and the stirring was continued for 1 h. The *tert*-butanol was distilled off and water and ether were added to the residue. The ether layer was separated and the aqueous layer was extracted with ether. The combined ethereal layers was extracted with ether. The combined ethereal layers were dried over anh. magnesium sulfate and concentrated. The residue was chromatographed over silica gel with ether-hexane (1:2) as eluant to give *cis*-5,10-dimethoxycarbonyl-1,1,3-trimethyl-$\Delta^{8,9}$octalin-2-one (14) (0.17 g, 5%) (oil); IR (neat) 1730, 1710 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.14 (s,3H), 1.20 (d, J=6Hz, 3H), 1.25 (s,3H), 1.3-2.6 (m,8H), 3.67 (s,6H), 6.85 (s,br, 1H); MS m/e 308 (27), 293 (9), 175 (100).

Further elution gave *cis*-5,10-dimethoxycarbonyl-1,1-dimethyl-$\Delta^{8,9}$-octalin-2-one (13) (1.57 g, 44%) (oil); IR (neat) 1730, 1710 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.15 (s,3H), 1.25 (s,3H), 1.6-2.9 (m,9H), 3.68 (s,6H), 5.85 (s,br,1H); MS m/e 294 (10), 279 (3), 276 (10), 263 (2), 244 (11), 175 (100).

Further elution with ether gave *cis*-5,10-dimethoxy carbonyl-2-methoxy-1-methyl-3,4,5,6,7,10-hexahydronaphtalene (15) (0.58 g, 16%) (oil); IR (neat) 1730 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.2-2.8 (m,9H), 1.72 (s,3H), 3.53 (s,3H), 3.62 (s,3H), 3.70 (s,3H), 5.57 (s,br,1H); MS m/e 294 (26), 262 (11), 234 (11), 175 (100).

This product decomposed on treatment with dilute acid to give the starting enone 4.

cis-*5,10-Dimethoxycarbonyl-2-methoxy-1-methyl-3,4,5,6,7,10-hexahydronaphtalene* (15).

To a mixture of 4 (56 g, 0.20 mol) and trimethyl orthoformate (26 g, 0.25 mol) in 350 mL of absolute methanol was added BF_3-MeOH complex (5 mL of a 14% solution in methanol). After stirring for 6 h triethylamine (2.5 mL) was added and the methanol was evaporated under reduced pressure. A sample of the resulting light-yellow oil (250 mg) was purified by column chromatography on silica gel with ether-hexane (1:1) as eluant to afford 238 mg of a colorless oil; IR (neat) 1730 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.72 (s,3H), 1.2-2.7 (m,9H), 3.52 (s,3H), 3.63 (s,3H), 3.67 (s,3H), 5.57 (m,$W_{½}$=9Hz, 1H); MS m/e 294(22), 262(12), 234(12), 175(100); UV (ether) λ_{max} 243 nm.

Anal. Calcd for $C_{16}H_{22}O_2$: m/e 294.147. Found: m/e 294.149.

cis-*5,10-Dihydroxymethyl-1-methyl-$\Delta^{1,9}$-octalin-2-one* (16).

The crude 15 (59.7 g) was dissolved in anhydrous ether (250 mL) and added dropwise with stirring to a suspension of lithium aluminium hydride (9.5 g, 0.25 mol) in 150 mL of anhydrous ether. The mixture was refluxed for 1 h and the excess lithium aluminium hydride was destroyed by the addition of ethylacetate. Hydrochloric acid (500 mL of a 6N solution) was added and the ether was evaporated. The resulting aqueous solution was used without further purification to produce 21. A sample of 5 mL of the aqueous solution was extracted with methylene chloride. The extract was dried over anhydrous magnesium sulfate and concentrated to afford the diol 16 (400 mg); IR (neat) 3350, 1650, 1595 cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ 1.2-2.8

(m, 11H), 1.76 (s, 3H), 3.4-4.1 (m, 4H), 4.50 (br,s,2H); MS m/e 224, 206, 176.

cis-*5,10-Diacetoxymethyl-1-methyl-$\Delta^{1,9}$-octalin-2-one*.

Since no satisfactory elementary analysis was obtained of diol 16 this compound was converted into its diacetate. A mixture of 16 (400 mg, 1.8 mmol), pyridine (2 mL), and acetic anhydride (1 mL) was stirred for 6 h. The volatile compounds were distilled off under reduced pressure and the residue was chromatographed on silica gel using ether as the eluant to give the diacetate of 16 (540 mg, 89%), m.p. 73-74°C; IR ($CHCl_3$) 1730, 1660, 1610, 1250 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.5-2.9 (m,11H), 1.83 (s,3H), 2.03 (s,3H), 2.07 (s,3H), 3.96 (dd, J=7,11Hz,1H), 4.28 (d, J=12Hz,1H), 4.36 (dd, J=11,3Hz,1H), 4.50 (d,J=12Hz,1H); MS m/e 308 (26), 266 (3), 248 (3), 206 (13), 188 (20), 176 (100), 175 (100).

Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 65.93; H, 7.89.

Lactone formation by oxidation of diol 16.

To a solution of diol 16 (2.5 g, 11.2 mmol) in 50 mL of acetone was added slowly with stirring a solution of sodium bichromate (1.2 g) and sulfuric acid (2.0 mL) in 7 mL of water. The green precipitate was removed by filtration and the acetone was distilled off under reduced pressure. The residue was dissolved in ether and washed with aqueous sodium bicarbonate solution and with brine solution. The organic layer was dried over anh. magnesium sulfate and concentrated. The residue was chromatographed on silica gel with ether-hexane as the eluant to give 3aβ,4,5,6,9,10-hexahydro-7-methyl-1*H*-naphto[1,8aα-c]furan-3,8-dione (17) (1.05 g, 43%), m.p. 132-135°C; IR (KBr) 1750, 1660, 1595 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.81 (s,3H), 1.4-3.0 (m,12H), 4.17 (dd, J=1,13Hz,1H), 4.36 (d, J=13Hz, 1H); MS m/e 220 (94), 192 (28), 180 (10), 176 (15), 162 (100), 121 (44).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.59; H, 7.36. Further elution gave 18 (1.00 g, 41%).

3,3aβ,4,5,6,8,9,10-octahydro-7-methyl-8-oxo-1H-*naphto[1,8aα-c] furan* (21).

The aqueous solution of 16 was refluxed under nitrogen for 6 h.

During this time a yellow oil separated. After cooling to room temperature ether was added and the aqueous layer was extracted with ether. The combined organic layers were washed with saturated sodium bicarbonate solution and dried over anh. magnesium sulfate. Evaporation of the solvent gave an oil which solidified upon standing. Distillation gave 21 (35 g, 84% overall yield) as white solid; mp 40-41°C, bp 132-135°C (0.3 mm); IR (KBr) 1670, 1612 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.79 (s,3H), 1.4-2.9 (m,11H), 3.69 (d, J=9Hz, 1H), 3.69 (dd, J=9, 4Hz, 1H), ^{13}C NMR δ 197.5 (s), 155.9 (s), 132.2 (s), 73.7 (d), 70.2 (d), 48.3 (d) 47.2 (s), 33.9 (t), 32.5 (t), 28.8 (t), 28.8 (t), 28.3 (t), 24.0 (t), 11.1 (q); MS m/e 206(100), 176(83).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.51; H, 8.74.

3aβ,4,5,6,9,10-*Hexahydro*-7-methyl-3H-*naphto*-[*1,8aα-c*]*furan*-*1,8-dione* (18).

To a suspension of lithium aluminium hydride (190 mg, 5 mmol) in anhydrous ether (10 mL) was added dropwise with stirring a solution of 15 (2.9 g, 10 mmol) in 20 mL of anhydrous ether. The mixture was refluxed for 1 h and water was added (10 mL) followed by the addition of concentrated hydrochloric acid (50 mL).
The ether was distilled off and the resulting aqueous solution was refluxed for 6 h. The mixture was allowed to cool to room temperature and extracted with ether. The extract was washed with aqueous sodium bicarbonate solution, then with brine solution and dried over anh. magnesium sulfate. Evaporation of the solvent gave a white solid which was crystallized from ethanol to give 18 (1.85 g, 84%), m.p. 114-116°C; IR (KBr) 1760, 1650, 1605 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.3-3.0 (m,11H), 1.86 (s,3H), 4.06 (d, 9Hz, 1H), 4.52 (dd, J=5,9Hz, 1H); MS m/e 220 (100), 192 (61), 176 (35), 161 (21), 134 (140).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.12; H, 7.55.

3,3aβ,4,5,6,6aβ,7,8,9,10-decahydro-7,7-dimethyl-8-oxo-1H-*naphto*[*1,8aα-c*])*furan* (22).

A solution of 21 (4.12 g, 20 mmol) in tetrahydrofuran (75 mL) (freshly distilled from benzophenone-sodium) and water (360 mg, 20 mmol) was added dropwise under nitrogen to a stirred solution of

lithium (560 mg, 80 mmol) in ammonia (250 mL, distilled from sodium). The mixture was stirred for 15 min and then methyl iodide (15 g, 105 mmol) was added. After 15 min 10 g of ammonium chloride was added. The ammonia was allowed to evaporate and the residue was treated with ether and water. The ether layer was separated and the aqueous layer was washed with ether. The combined ether layers were washed with saturated brine and dried over anh. magnesium sulfate. Evaporation of the solvent afforded an oil. Column chromatography on silica gel with ether-hexane (1:1) afforded 22 (4.14 g, 94%) which crystallized upon standing; mp 71-73°C; IR (neat) 1695 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.86 (s,3H), 1.07 (s,3H), 1.2-2.8 (m,12H), 3.41 (d, J=8Hz, 1H), 3.80 (dd J=8, 4Hz, 1H), 3.83 (s,2H); MS m/e 222(100), 123(81).

Anal. Calcd for $C_{14}H_{22}O_2$; C, 75.63; H, 9.97. Found: C, 75.71; H, 9.78.

3aβ,4,5,6,6aβ,7,9,10-Octahydro-7,7-dimethyl-1H-*naphto[1,8aα-c] furan-3,8-dione* (23).

To a solution of 20 (500 mg, 2.26 mmol) in 20 mL of carbon tetrachloride was added ruthenium dioxide (30 mg) and a solution of sodium *meta*-periodate (1.2 g) in 20 mL of water. The mixture was stirred vigorously overnight during which time the ruthenium dioxide dissolved and the organic layer attained a bright-yellow color of ruthenium tetroxide. The organic layer was separated and ether was added to destroy the ruthenium tetroxide. The resulting black suspension was filtered through a short column of silica gel. Evaporation of the solvent afforded 23 (520 mg. 98%), m.p. 120-123°C; IR ($CHCl_3$) 1770, 1705 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 0.89 (s,3H), 1.88 (s,3H), 1.2-2.8 (m,12H), 4.39 (s,2H); MS m/e 236 (90), 194 (42), 192 (36), 136 (46), 135 (44), 55 (100).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.30; H, 8.73.

8,8-Ethylenedioxy-3,3aβ,4,5,6,6aβ,7,8,9,10-decahydro-7,7-dimethyl-3-oxo-1H-*naphto[1,8aα-c]furan* (24).

Ketone 21 (500 mg, 2.12 mmol) was dissolved in 2-ethyl-2-methyl-1,3-dioxolan (MED) (10 mL). *p*-toluene-sulfonic acid (10 mg) was added and the mixture was stirred for 2 days.

The solvent was evaporated and the residue was taken up in ether, washed with aqueous sodium bicarbonate solution and dried over anh. magnesium sulfate. The ether was distilled off under reduced pressure to give 24 (580 mg, 98%), m.p. 198°C; IR (CCl_4) 1760 cm^{-1}; ^{1}H-NMR δ 0.88 (s.3H), 0.88 (s,3H), 1.1-2.2 (m,12H), 3.98 (s,4H), 4.26 (d, J=12Hz, 1H), 4.37 (d, J=12Hz, 1H); MS m/e 280 (0.5), 99 (100), 86 (40).

Anal Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.63; H, 8.57.

*8,8-Ethylenedioxy-3,5,6,6aβ,7,8,9,10-octahydro-7,7-dimethyl-3-oxo-*1H-*naphto[1,8aα-c]furan* (26).

To a mixture of diisopropylamine (202 mg, 2 mmol) and tetrahydrofuran (10 mL) (freshly distilled from benzophenone-sodium) was added with stirring under nitrogen n-butyllithium (1.45 mL of a 1.4 N solution in hexane). The mixture was cooled to -78°C and a solution of 24 (560 mg, 2 mmol) in 10 mL of dry tetrahydrofuran was added. After 1 h a solution of diphenyldiselenide (685 mg, 2.2 mmol) in 8 mL of dry tetrahydrofuran was added dropwise and the stirring was continued for 2 h. The reaction mixture was allowed to warm to room temperature and evaporated to dryness. The residence was taken up in 25 mL of methanol and a solution of sodium *meta*-periodate (1.2 g) in 20 mL of water was added and the mixture was stirred for 2 h. Most of the methanol was distilled off under reduced pressure and the aqueous solution was extracted with ether. The extract was dried over anh. magnesium sulfate. GCMS analysis revealed the product to consist of the α,β-unsaturated lactone 24 (90%) next to some starting material (10%). Chromatography on silica gel with ether-hexane (1:1) as the eluant afforded 24 (40 mg, 7%). Further elution gave 26 (450 mg, 81%), m.p. 120-122°C; IR ($CHCl_3$) 3030, 1770, 1652 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.81 (s,3H), 0.94 (s,3H), 1.1-2.4 (m,9H), 3.81 (dd, J=7,3Hz,1H), 4.00 (s,4H), 4.32 (d, J=7Hz, 1H), 6.75 (dd, J=6,3Hz, 1H); MS m/e 278 (0.2), 206 (4), 196 (9), 99 (100),86 (35).

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.84; H, 8.05.

5,6,6aβ,7,9,10-Hexahydro-7,7-dimethyl-1H-*naphto[1,8aα-c]furan-3,8-dione* (27).

Lactone 26 (400 mg, 1.44 mmol) was dissolved in acetone (10 mL). This mixture was stirred overnight in the presence of 1 drop of concentrated hydrochloric acid. The solvent was distilled off under reduced pressure and the residue was crystallized from ethanol yielding 27 (320 mg, 95%), m.p. 116-119°C; IR (KBr), 1765, 1695, 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.95 (s,3H), 1.21 (s,3H), 1.1-2.8 (m,9H), 4.01 (dd, J=8,1Hz, 1H), 4.11 (d, J=8Hz, 1H), 6.83 (dd, J=8,4Hz, 1H); MS m/e 234 (82), 204 (100), 177 (57), 161 (18), 133 (24).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.47; H, 7.75.

3.9 REFERENCES AND NOTES

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4 THE STEREOSPECIFIC INTRODUCTION AND FUNCTIONALIZATION OF AN ALLYL GROUP AS A SIDE CHAIN PRECURSOR IN CLERODANE TOTAL SYNTHESIS.

4.1 INTRODUCTION.

In the previous chapter we used the reductive alkylation method for the synthesis of a *trans*-fused decalone. The same reaction was chosen for the introduction of the side chain precursor at C-9 of the clerodane molecule. The investigations were primarily concentrated on the total synthesis of *trans* clerodanes with side chains that contain one cyclic unit, such as a furan or a butenolide, as it is found in hautriwaic acid (18→19) lactone (1) and in ajugarin I (2), respectively.

Alkylation with allyl bromide seemed to offer good perspectives since the allyl group can readily be functionalized by a variety of methods (*e.g.* ozonolysis, epoxidation and hydroboration).

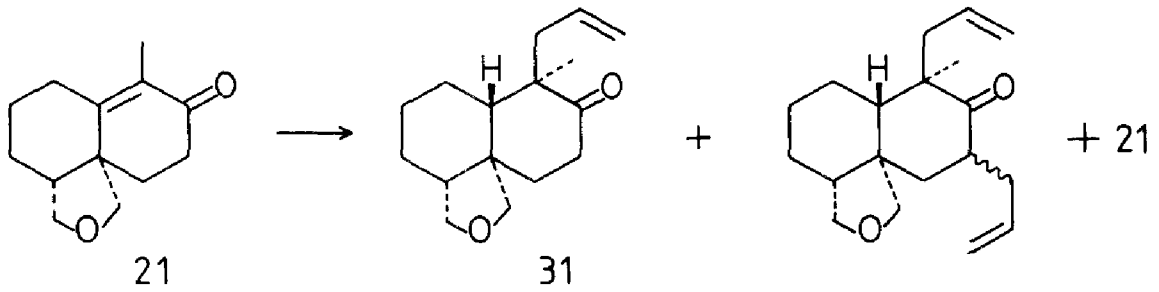
Ardon Jimenez and Halsall[1] described investigations on a similar subject (see chapter 2.5) and by studying their results several other alkylating agents could be rejected beforehand as possible side chain precursors, since they would probably lead to poor yields or undesired products.

4.2 THE STEREOCHEMISTRY OF THE REDUCTIVE ALKYLATION OF OCTALONE 21.

Reductive alkylation of 21 with allyl bromide gave the mono alkylated product 31 in 70-85% yield alongside some polyalkylated product and some starting material (see scheme 4.1).

From similar reductive alkylations[1] the orientation of the allyl group was expected to be β. Bearing in mind the unexpected stereochemistry of the dienolate alkylation, however (see chapter 3.3), further proof was required for this assumption.

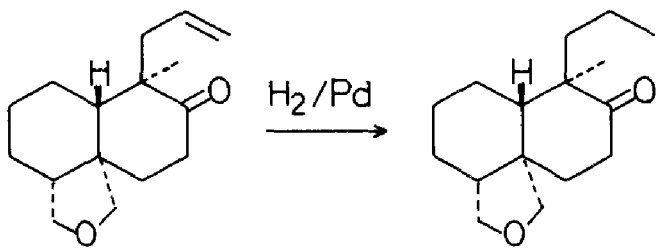
Scheme 4.1



21 31

Williams and Bhaccha[2] examined the solvent effect in some steroids on the chemical shift in the ^{1}H-NMR spectrum of methyl groups adjacent to carbonyl. They observed an upfield shift of about 0.3 ppm for axially orientated methyl groups at the alpha position of a carbonyl on changing the solvent from chloroform to benzene. For equatorially orientated methyls no change in chemical shift was observed in the same experiment.

First these experiments were repeated for compound 22. Since this compound possesses both an equatorially and an axially orientated methyl group alpha to a carbonyl, an indication could be obtained whether in the molecules under study the solvent effect had the same order of magnitude. Next the solvent effect experiments were carried out for 31. The π system of the allyl group being in the vicinity of the carbonyl, could possibly influence however the outcome of the experiments. Therefore 31 was hydrogenated to the 9 propyl derivative 32 in which this possible complication is absent.



31 32

The results of the solvent shift experiments are summarized in table 4.1.

Table 4.1

compound no		22	31	32
δ-Me ($CDCl_3$) (ppm)	α	0.86	0.87	0.82
	β	1.07		
δ-Me (C_6D_6) (ppm)	α	0.64	0.56	0.58
	β	1.01		
Δ[δ-Me($CDCl_3$)-δMe(C_6D_6)]	α	0.22	0.31	0.24
	β	0.06		

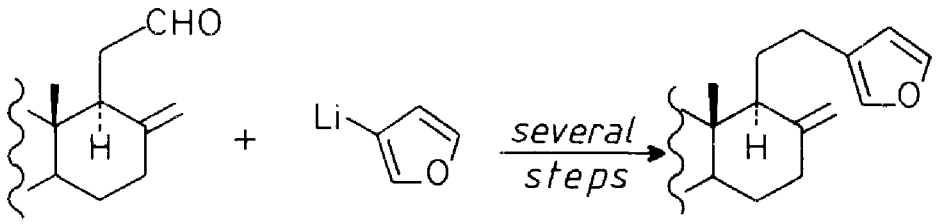
The values for the differences in chemical shift on changing the solvent from $CDCl_3$ to C_6D_6 strongly suggest an axial orientation for the methyl substituent at C-9 in the compounds 31 and 32 and consequently an equatorial orientation for the allyl and the propyl substituents at C-9 respectively.

4.3 FUNCTIONALIZATION OF THE ALLYL SIDE CHAIN PRECURSOR BY OZONOLYSIS.

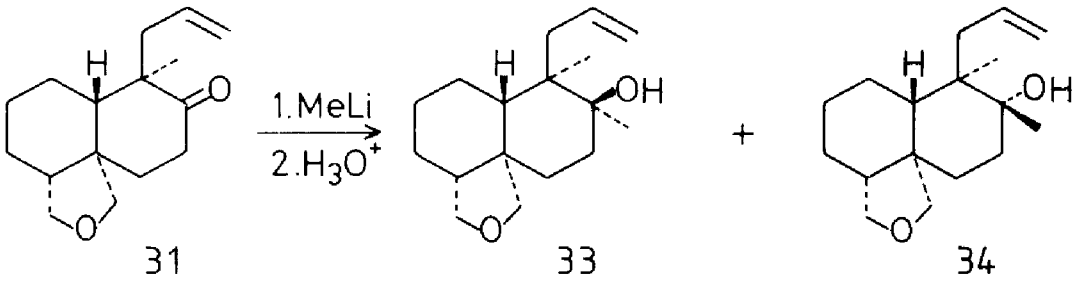
The conversion of the allyl group into a six carbon side chain containing a furan moiety as is found in 1, was based upon the strategy of Bell *et al*[3]. in their synthesis of lambertianic acid, a labdane-type diterpene[4].

They reacted a two carbon substituent containing an aldehyde, with 3-furyllithium to obtain the six carbon side chain after the reduction of the intermediate alcohol (see scheme 4.2).
The allyl group in 31 can be degradated to a 2-oxoethyl substituent on reaction with ozon. Subsequent reaction with 3-furyllithium was expected to give rise to undesired side reactions since this molecule contains a second carbonyl at C-8. Therefore the methyl group at C-8 was introduced at this stage by reacting 31 with methylli-

Scheme 4.2



thium to give the isomeric alcohols 33 and 34 in a 1:1 ratio, which were separated by column chromatography.

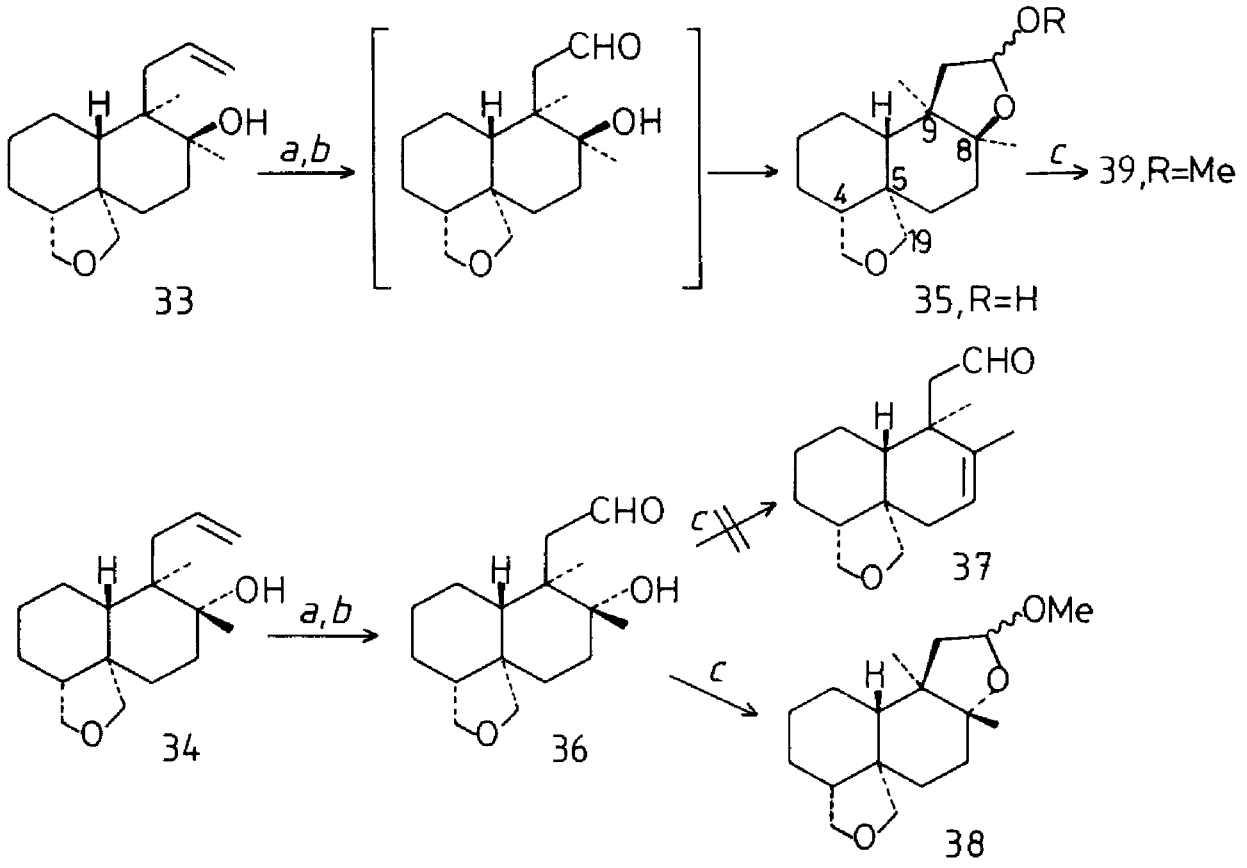


31 33 34

Due to steric hindrance towards carbonyl addition, alpha deprotonation was a serious competition reaction[5]; only 50% conversion had taken place. By repeated addition of methyllithium to the hydrolysed products, 95% conversion could be achieved.

Ozonolysis of 33, followed by catalytic hydrogenation of the intermediate ozonide did not give the desired hydroxy aldehyde, but afforded the ring closed hemiacetal 35 instead. Reaction of the β-alcohol 34 in a similar way afforded the hydroxy aldehyde 36 in 76% yield. At this stage 36 had to be dehydrated to 37 in order to be able to bring about an equatorial methyl at C-8 after reduction of the double bond. All efforts to dehydrate, 36 however, remained without success. Reaction with phosphoryl chloride in pyridine, as well as refluxing 36 in benzene in the presence of acid gave rise to the formation of numerous products. Refluxing the same compound in methanol in the presence of *p*-toluene sulfonic acid afforded the acetal 38 (see scheme 4.3).

Scheme 4.3

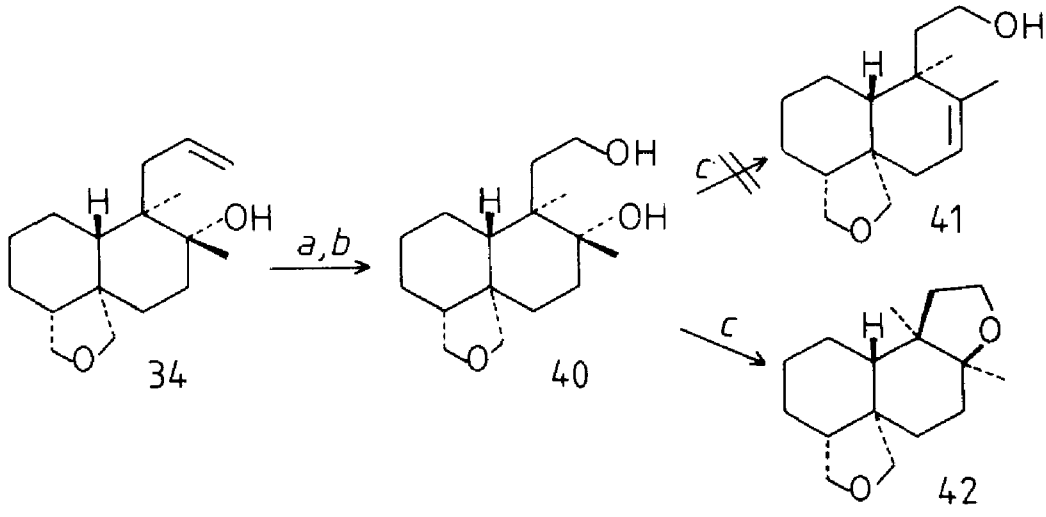


a: O_3; *b*: H_2/Pd; *c*: TsOH, MeOH, Δ.

The stereochemistry of the ring junction at C-8 and C-9 followed from a comparison of the ^{1}H-NMR spectra of 38 and 39 (the latter compound was prepared by refluxing 35 in the presence of acid). It was found empirically that the C-19 protons appear as a singlet[6] whenever ring strain is absent in the molecule. By introducing distorsion in the A/B ring system the chemical shifts of these protons move to a different position, thus resulting in an AB pattern. In the case of 35 and 39 no ring torsion will be present, which is reflected by the spontaneous hemiacetal formation to 35. In these compounds the C-19 protons appeared as a singlet and the ring junction at C-8 and C-9 was assumed to be *cis*. In the case of 38 the C-19 protons appeared as an AB pattern as a result of the relatively highring torsion caused by a *trans* ring junction at C-8 and C-9.

Since hemiacetal and acetal formation of the above mentioned ozonolysis products blocked the further elaboration of these molecules, an alternative route was investigated. It was presumed that reduction of the ozonolysis products to the corresponding diols would circumvent the problems of ring closure reactions. Reduction of the ozonolysis product of 33 with lithium aluminium hydride, however, again afforded hemiacetal 35. On the other hand, reaction of 34 in a similar way produced diol 40 in 76% yield. Making use of the fact that tertiary alcohols are more prone to dehydration than primary alcohols, it was hoped that alcohol 41 could be obtained by selective dehydration of 40. Heating of diol 40 in the presence of anhydrous copper(II) sulfate did not give the desired alcohol but the cyclic ether 42 instead (scheme 4.4).

Scheme 4.4



a: O_3; *b*: $LiAlH_4$; *c*: $CuSO_4$, Δ.

The C-19 protons in 42 appeared as a singlet in the ^{1}H-NMR spectrum, indicating that no ring strain was present in the molecule and hence a *cis* ring junction at C-8 and C-9 was assumed. This can be explained by supposing the formation of a carbonium ion at C-8, followed by ether formation to 42.

Since all efforts to functionalize the allyl group by means of an ozonolysis reaction were frustrated by undesired ring closure

reactions, we turned to a different approach in which ring closure reactions at C-8 would be less probable.

4.4 FUNCTIONALIZATION OF THE ALLYL SIDE CHAIN PRECURSOR BY HYDROBORATION.

In order to be able to construct an equatorial methyl group at C-8 (as is found in most clerodanes), the hydroxy group at this position should be dehydrated first to an exocyclic or an endocyclic olefin, followed by catalytic hydrogenation.

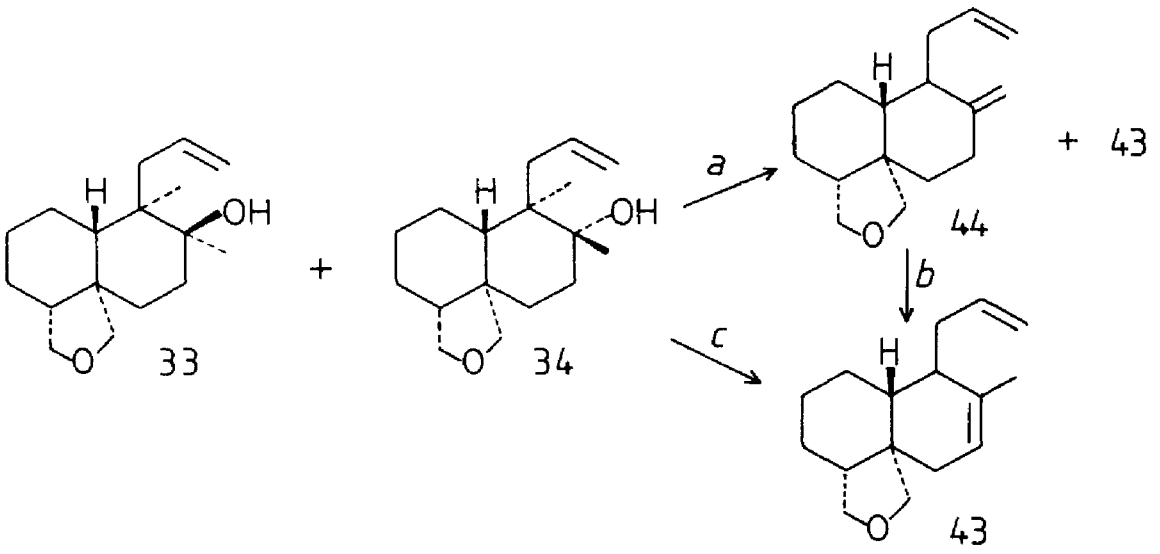
In the previous experiments the dehydration was planned *after* the modification of the allyl group at C-9. By carrying out the dehydration step *prior* to the reactions involving the side chain precursor, the functionality at C-8 probably would not lead any longer to cyclization reactions.

During the last decade a number of organoborane reagents which react very specifically with unhindered double bonds, have become available. The use of these reagents offered good perspectives for the selective functionalization of the allyl group.

In the dehydration of 33 and 34, however, we had to proceed with caution. In the preceding paragraph was shown that the creation of a carbonium ion at C-8 led to ring closure reactions. Furthermore, Hadley and Halsall[7] showed that the formation of carbonium ions in similar molecules gave rise to rearrangements of the carbon skeleton (see chapter 2.2). Since the acid catalysed dehydration of the alcohols 33 and 34 proceeds *via* a similar carbonium ion, this reaction had to be circumvented. Alcohol dehydration using phosphoryl chloride in pyridine proceeds *via* the E2 mechanism, so this reaction was studied first. GCMS analysis showed the formation of two isomeric products in a 1:1 ratio, both with parent ion $M^+ = 246$. These products could be isolated in a low yield from the reaction mixture. Separation of this isomeric mixture was unsuccessful. On treatment with boron trifluoride etherate in ether, one isomer was converted into the other. On the basis of spectroscopic evidence the latter product was assigned structure 43. The other isomer was probably the exocyclic olefin 44. The low yield of 43 induced us to try the initially rejected acid catalysed dehydration. An attempt to dehydrate a mixture of the isomeric alcohols 33 and 34 on treat-

ment with *p*-toluene sulfonic acid in refluxing benzene was unsuccessful in that only starting material was recovered. On use of boron trifluoride etherate as the catalyst, diene 43 was obtained in an excellent yield (93%) (see scheme 4.5).

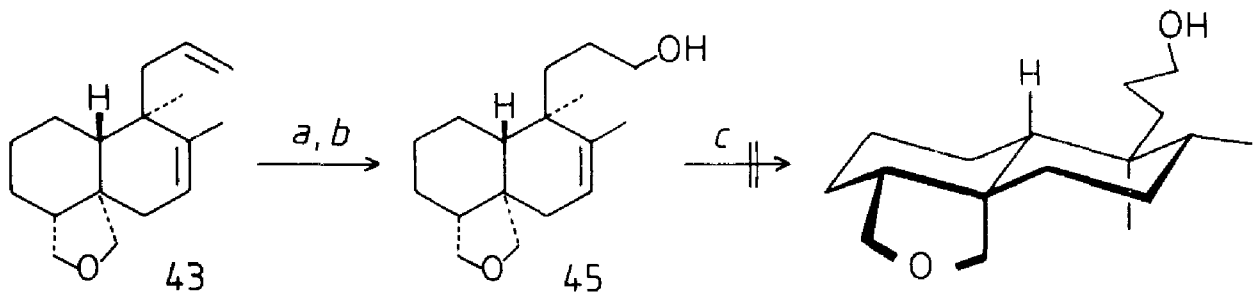
Scheme 4.5



a: PCl_3; *b*: BF_3 etherate, ether; *c*: BF_3 etherate, Bz, Δ.

The selective functionalization of the allyl group could indeed be accomplished by hydroboration of 43 with 9-BBN (9-borabicyclo [3.3.1]nonane, followed by treatment with alkaline hydrogen peroxide to afford the alcohol 45. Due to steric factors the endocyclic double bond was not attacked by the bulky 9-BBN. It was expected that catalytic hydrogenation of 45 would proceed from the less hindered (β) side of the molecule, thus affording the required equatorial methyl group at C-8. The same steric factors that enabled the selective functionalization of the allyl group now worked against us by preventing the hydrogenation of the double bond (see scheme 4.6).

Scheme 4.6

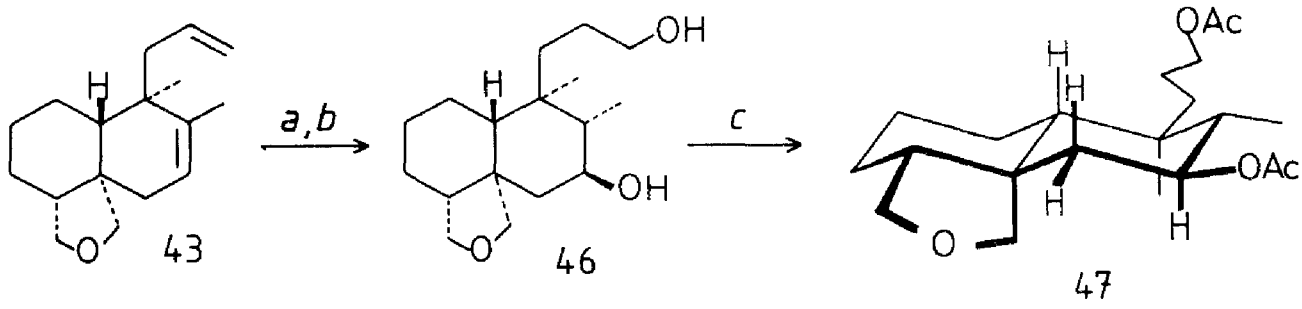


a: 9-BBN; *b*: H_2O_2, OH^-; *c*: H_2, Pd.

This problem could be solved in the following way.

Treatment of 43 with diborane afforded, after oxidation of the intermediate organoborane, diol 46 in 83% yield. Hydroboration-oxidation is known to involve overall *syn* addition, so the hydrogen at C-8 and the hydroxyl at C-7 occupy either both the α or both the β orientation. In order to elucidate the stereochemical outcome of the hydroboration reaction, diol 46 was converted into the diacetate 47. In the ^{1}H-NMR spectrum of 47 the C-7 proton displayed an apparent triplet (J=11Hz) with a doublet (J=2Hz) superposed on it. These values indicate an α orientation for the C-7 proton (two diaxial and one axial-equatorial couplings) and hence an equatorial position for C-17 (see scheme 4.7).

Scheme 4.7

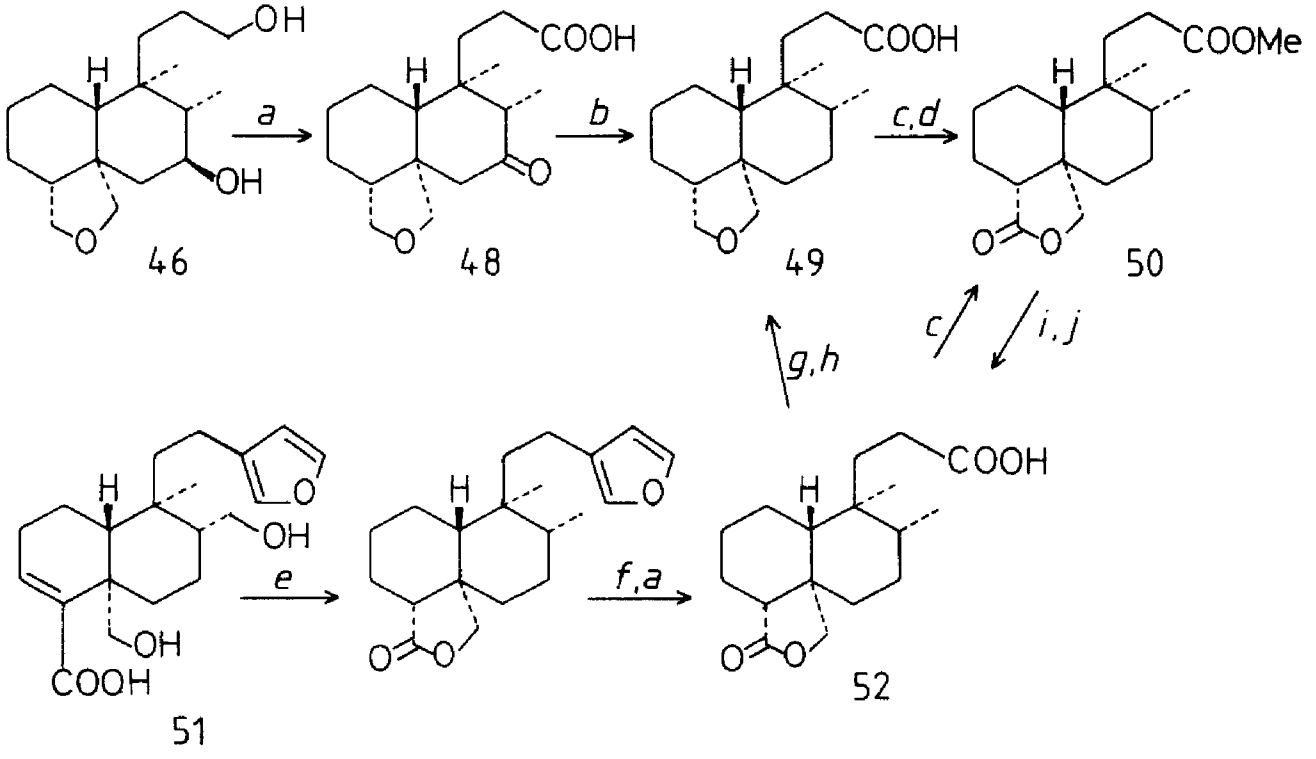


a: B_2H_6; *b*: H_2O_2, OH^-; *c*: Ac_2O, Py.

The diborane reaction provides a unique method for the stereospecific introduction of the C-8 methyl group together with the functionalization of C-7. In the next chapter two other methods are shown for the stereospecific introduction of the C-8 methyl which involves the simultaneous functionalization of C-6.

In order to bring about the distinction between the substituents at C-7 and C-13, diol 46 was oxidized to the keto carboxylic acid 48 in 67% yield. Wolff-Kishner reduction of this compound afforded the carboxylic acid 49 in 55% yield. Esterification and oxidation with ruthenium tetroxide gave the lactone 50. The compounds 49 and 50 have been synthesized before by Payne and Jefferies[8]; not in a total synthesis of clerodanes, but the other way round, namely by the selective degradation of the *trans* clerodane 51 (see scheme 4.8).

Scheme 4.8



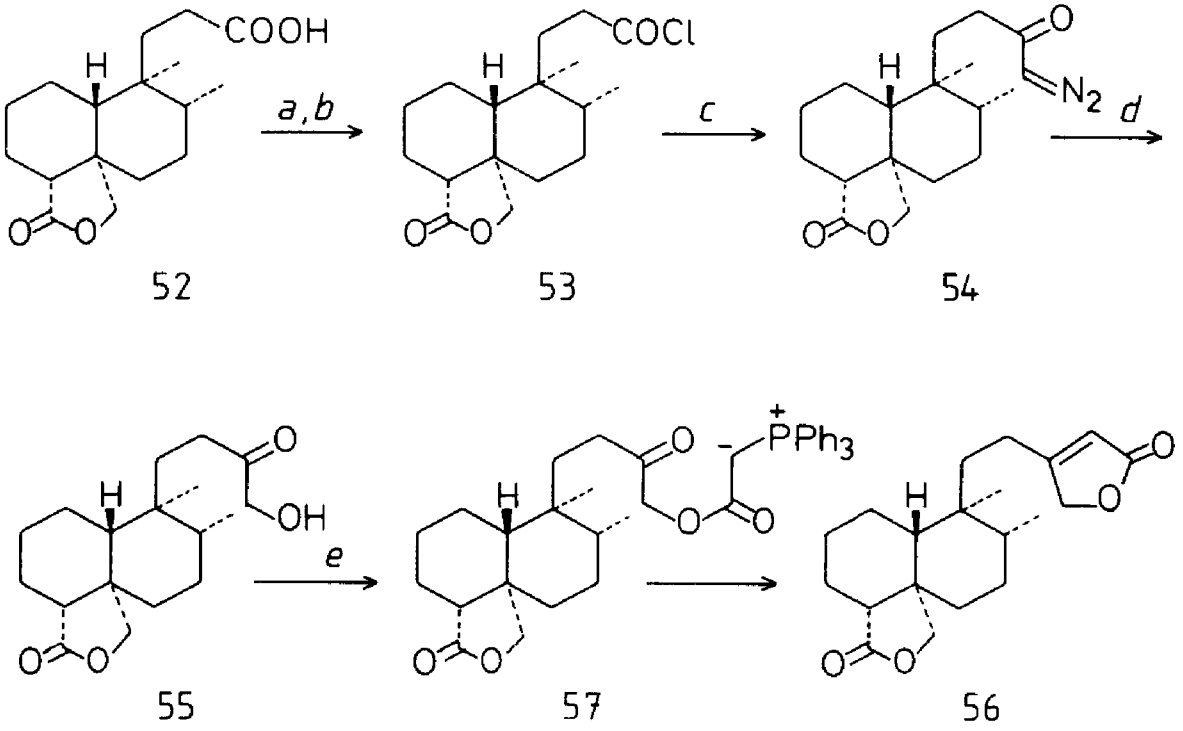
a: Jones' reagent; *b*: Wolff-Kishner redn.; *c*: CH_2N_2, ether; *d*: RuO_4, CCl_4; *e*: several steps; *f*: O_3, CH_2Cl_2; *g*: $LiBH_4$; *h*: TsOH; *i*: H_2O, OH^-; *j*: H_3O^+.

The ^{1}H-NMR spectra of 49 and 50 were superimposable on the spectra of the corresponding compounds derived from the natural product 51[9]. The spectroscopic resemblance of our synthetic products to those derived from 51 afforded additional proof about the correctness of our stereochemical assignments, particulary of the *trans* A/B ring junction.

4.5 STUDIES ON THE COMPLETION OF THE SIDE CHAIN.

For obvious reasons the original plan for the termination of the clerodane side chain, which was based upon the methodology of Bell *et al.* (see scheme 4.2), could no longer be used.
A solution to this problem was found in the cardenolide chemistry. In this field a number of methods have been developed for the extension of a carboxylic acid to a butenolide moiety[10].

Scheme 4.9



a: KOH, MeOH; *b*: $(COCl)_2$; *c*: CH_2N_2, ether; *d*: SO_2, H_2O;
e: $(Ph)_3P{=}C{=}C{=}O$, Bz, Δ.

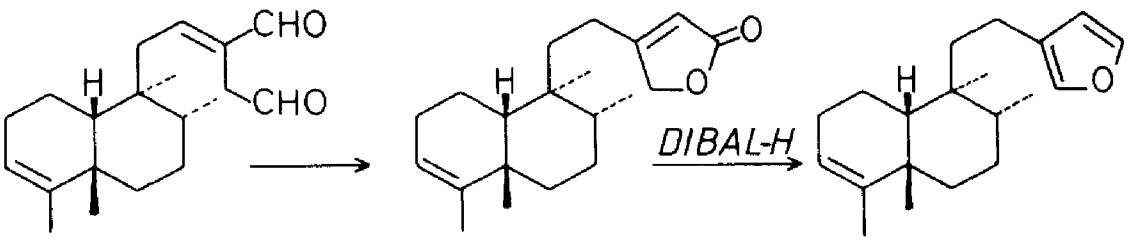
The reduction of butenolides into furans has been described by Minato *et al*[11]. Adapting these methods for the termination of the clerodane side chain, we carried out the following transformations.

The methyl ester 50 was hydrolysed to give the carboxylic acid 51. Treatment of the potassium salt of this compound with oxalyl chloride afforded the acid chloride 53 which in turn was reacted with diazomethane to give the diazoketone 54. The latter could readily be hydrolysed to the alpha hydroxy ketone 55 on treatment with sulfur dioxide in water. The entire sequence, when carried out without purification of the intermediates, gave 55 in about 60% yield. The product was accompanied by the methyl ester 50 (29%).

In a recent paper Bohlman[12] described a very elegant method for the conversion of alpha hydroxy ketones into butenolides. Thus reaction of 55 with triphenylphosphoranylidene-ketene[13] in refluxing benzene gave the butenolide 56 in 93% yield. This reaction proceeds by the initial attack of the hydroxyl group on the ketene to afford the intermediate phosphorous ylide 57, which cyclizes to give the unsaturated five-ring lactone (see scheme 4.9).

The further transformation of butenolides into furans has been described in the literature[11] and has found application[15] in the partial synthesis of LJ-furan (58), starting from linaridial (59). Both 58 and 59 belong to the *cis* clerodane series (scheme 4.10).

Scheme 4.10

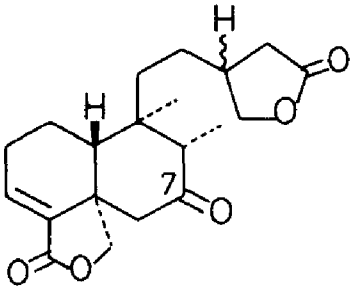


59 58

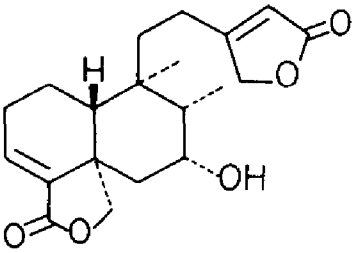
This method however involves the reduction of the butenolide with diisobutylaluminium hydride (DIBAL-H) and is inconsistent with the presence of a second carbonyl in the molecule. This imposes special conditions on the strategy of the planned total synthesis. Further investigations to effectuate these conversions have not been studied as yet.

4.6 STUDIES ON THE TOTAL SYNTHESIS OF C-7 FUNCTIONALIZED CLERODANES.

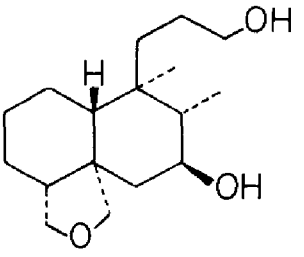
A relatively large number of clerodanes (including some physiologically active ones) possess a side chain which contains a lactone moiety (*e.g.* 60[16] and 61[17]).



60



61



46

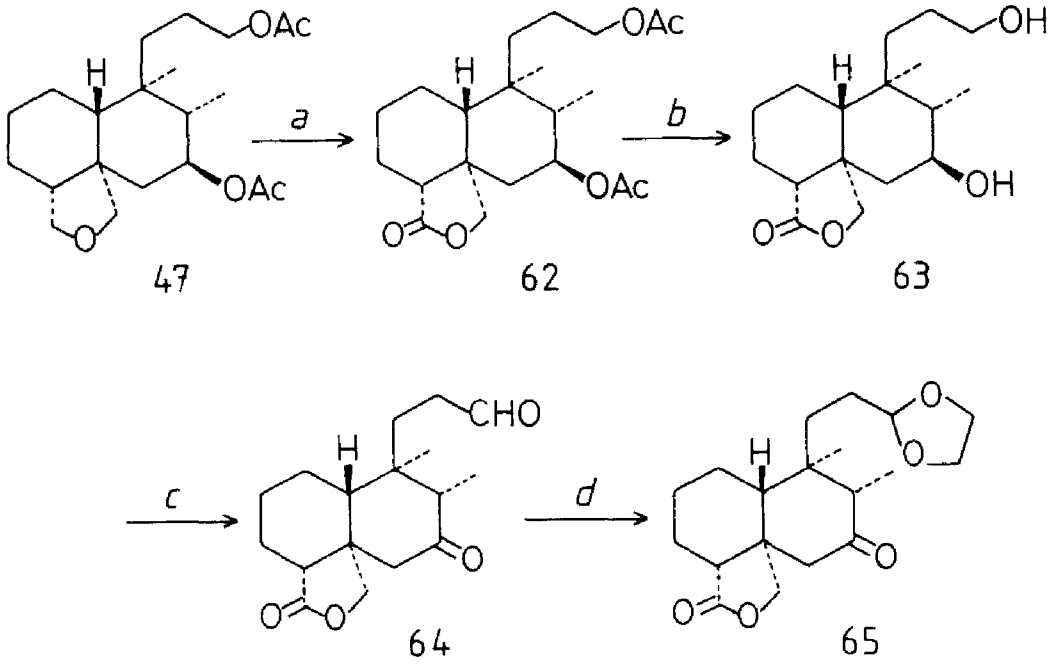
The diol 46 opened perspectives as a starting compound to totally synthesize this type of compounds, in which C-7 is oxidized to a ketone or an equatorial hydroxy group respectively. In the previous paragraphs we showed that each of the tranformations leading to these structures belong to the potentialities of our strategy. In addition the reduction of the C-7 ketone in 60 using sodium borohydride as the reductant, has been shown to give an α hydroxyl group.

The main problem in the total synthesis of the clerodanes under study is that the completion of the side chain must be compatible with the construction of the α,β-unsaturated lactone at C-4 and C-5. This imposes certain conditions on the sequence in which each transformation must be carried out. Firstly the ruthenium tetroxide oxidation is inconsistent with the presence of alcohols, olefinic moieties, acetals and ketals, aldehydes, ethers *etc.* in the rest of the

molecule since these groups will also be oxidized by the reagent. Ketones, carboxylic acids and esters usually are not attacked by ruthenium tetroxide so all functionalities must be protected by transforming them into one of these groups.

Oxidation of the diacetate 47 gave lactone 62 in high yield. For the introduction of the double bond in ring A no other hydrogen atoms situated alpha to a carbonyl should be present since in the first reaction step addition of phenyl selenide at these sites would occur. Therefore 62 was hydrolysed to diol 63 which in turn was oxidized to the keto aldehyde 64 by pyridinium chlorochromate. The next step involved the protection of both the aldehyde and the ketone as acetal and ketal respectively. This protection, however, was unsuccessful and led to the formation of a mixture of products. GCMS analysis showed the presence of the monoprotected compound 65 (scheme 4.11) as the major product.

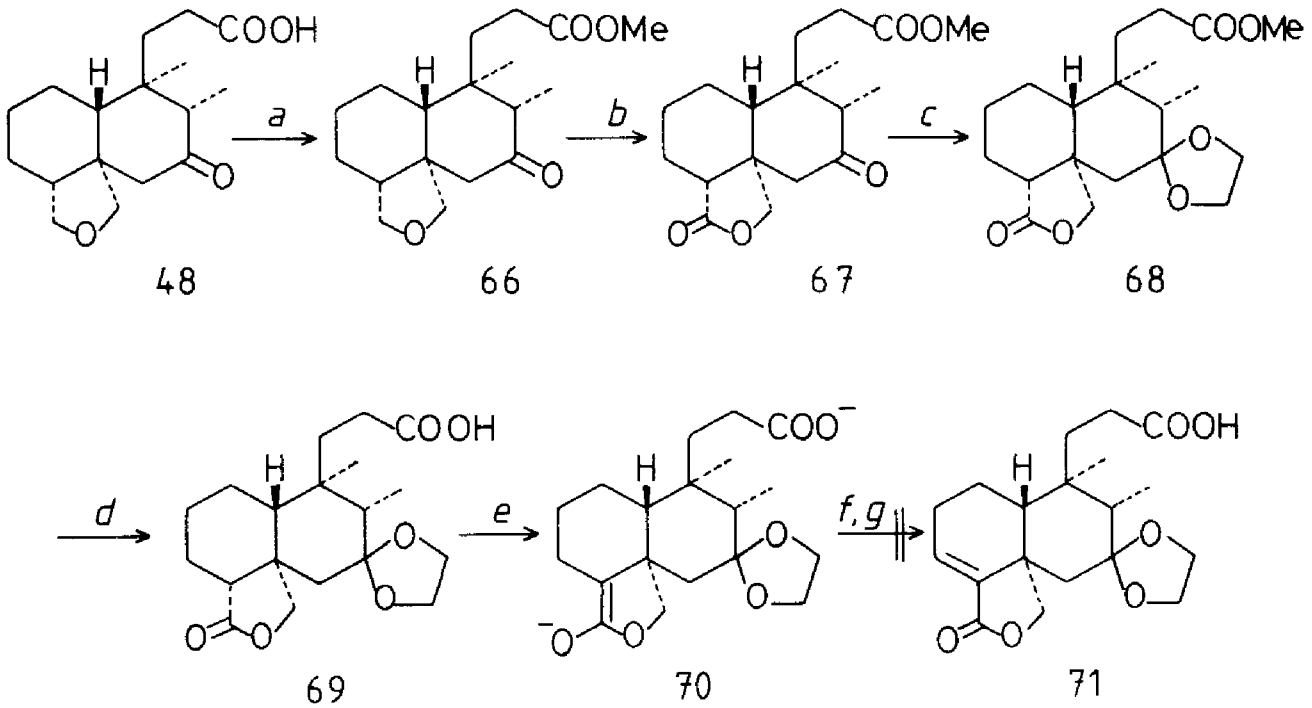
Scheme 4.11



a: RuO_4; *b*: OH^-, H_2O; *c*: PCC; *d*: TsOH, glycol, Bz, Δ.

In an alternative approach the keto ester 66 was oxidized with ruthenium tetroxide to the lactone 67. In contrast to the results from the previous experiments, the ketone at C-7 could be protected as the ethylene ketal 68. Saponification of the ester afforded the carboxylic acid 69. Reaction of this acid with 2 equivalents of LDA was expected to give the dianion 70. This was based upon the assumption that the carboxylate anion would probably deactivate proton abstraction at its alpha position. Subsequent addition of diphenyldiselenide and oxidation did not give, however, the α,β-unsaturated lactone 71 (see scheme 4.12).

Scheme 4.12



a: CH_2N_2, ether; *b*: RuO_4; *c*: TsOH, glycol, Bz, Δ; *d*: OH^-, H_2O; *e*: 2eq. of LDA; *f*: PhSeSePh; *g*: $NaIO_4$.

Further alterations in the reaction sequence in order to construct the α,β-unsaturated lactone have not been studied so far since at this moment we began to focus our attention on the antifeedant active clerodanes, as will be described in the next chapter.

4.7 EXPERIMENTAL SECTION.

General experimental conditions were as given in chapter 3.8.

*7β-Allyl-3,3aβ,4,5,6,6aβ,7,8,9,10-decahydro-7αmethyl-8-oxo-*1H*-naphto[1,8aα-c]furan* (31).

To a solution of lithium (290 mg, 41 mmol) in ammonia (50 mL) (distilled from sodium) was added with stirring under nitrogen a solution of enone 21 (4.12 g, 20 mmol) in tetrahydrofuran (50 mL) (freshly distilled from benzophenone-sodium). A solution of water (360 mg, 20 mmol) in tetrahydrofuran (10 mL) was added by which the blue color of the solution just disappeared. After 10 min. allyl bromide (14 g, 116 mmol) was added and the ammonia was allowed to evaporate overnight. Ether and water were added and the mixture was stirred. The two layers were separated and the aqueous layer was extracted with ether. The combined ethereal layers were washed with brine solution and dried over anh. magnesium sulfate. The ether was distilled off under reduced pressure and the residue was chromatographed over silica gel with ether-hexane (1:1) as the eluant to afford the polyalkylated product (350 mg, 6%) (oil); IR (neat) 3080, 1700, 1630 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.86 (s,3H), 1.1-2.6 (m,15H), 3.41 (d, J=8Hz, 1H), 3.85 (dd, J=8,4Hz, 1H), 3.97 (s,2H), 4.96 (d, J=12Hz, 2H), 5.05 (s,2H), 5.55 (br.2H); MS m/e 288 (33), 273 (100), 247 (21).

Further elution gave 31 (3.9 g, 78%), m.p. 76-77°C (crystalized from ether); IR (KBr) 3080, 1700, 1630; ^{1}H-NMR ($CDCl_3$) δ 0.86 (s,3H), 1.1-2.6 (m,14H), 3.46 (d, J=8Hz, 1H), 3.93 (dd, J=8,4Hz, 1H), 3.95 (s,2H), 4.99 (d, J=12Hz, 1H), 5.06 (s,1H), 5.60 (br,1H); MS m/e 248 (15), 233 (100), 123 (30), 110 (41).

Anal. Calcd for $C_{16}H_{24}O_2$:C, 77.37; H, 9.74. Found: C, 77.41; H, 9.82.

Finally the starting material 21 eluted (165 mg, 4%).

*3,3aβ,4,5,6,6aβ,7,8,9,10-decahydro-7α-methyl-8-oxo-7β-propyl-*1H*-naphto-[1,8aα-c]furan* (32).

The ketone 31 (100 mg, 0.4 mmol) was dissolved in methanol (5 mL). Palladium on charcoal (20 mg) was added and the mixture was hydrogenated for 1 h. Filtration of the catalyst followed by evaporation

of the solvent afforded 32 (89 mg, 89%) (oil); IR (neat) 1695 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.82 (s,3H), 0.89 (t,br,3H), 1.0-2.6 (m,16H), 3.95 (d,J=8Hz, 1H), 3.88 (s,2H), 3.90 (dd, J=8,4Hz, 1H); MS m/e 250 (44), 235 (100).

7β-Allyl-3,3aβ,4,5,6,6aβ,7,8,9,10-decahydro 8β-hydroxy-7α,8α-dimethyl-1H-*naphto[1,8aα-c]furan* (33) and *7β-Allyl-3,3aβ,4,5,6,6aβ,7,8,9,10-decahydro-8α-hydroxy-7α,8β-dimethyl*-1H -*naphto[1,8aα-c]furan* (34).

To a stirred solution of 31 (4.96 g, 20 mmol) in ether 50 mL (distilled from sodium hydride) was added methyllithium (21 mmol, 15 mL of a 1.4 N solution in ether) at 0°C. After stirring for 10 min. water was added and the ethereal layer was separated. The aqueous layer was extracted with ether and the combined organic layers were dried (anh. magnesium sulfate). The ether was distilled off and the residue was dissolved in anhydrous ether. This solution was treated again with methyllithium and worked up as described above. After repeating this procedure another three times, GC analysis showed the presence of only 5% of starting material. The crude product was chromatographed on silicagel with ether-hexane (1:1) as the eluant to afford 33 (2.31 g, 44%) (oil) IR (neat) 3450, 3080, 1630; ^{1}H-NMR ($CDCl_3$) δ 0.65 (s,3H), 1.20 (s,3H), 1.1-2.4 (m,14H), 3.36 (d, J=8Hz, 1H), 3.71 (s,2H), 3.88 (dd, J=8,4Hz, 1H), 4.96 (d, J=12Hz, 1H), 5.09 (s,1H), 6.0 (m,1H) MS m/e 264 (4), 249 (11), 223 (8), 221 (17), 205 (100).
Further elution gave the starting compound 31 (250 mg, 5%). Finally the α alcohol 34 was eluted (2.50 g, 47%9 (oil); IR (neat) 3450, 3080, 1625; ^{1}H-NMR ($CDCl_3$), 0.80 (s,3H), 1.36 (s,3H), 1.2-2.3 (m,14H), 3.35 (d, J=8Hz, 1H), 3.76 (s,2H), 3.85 (dd, J=8,4Hz, 1H), 4.96 (d, J=12Hz, 1H), 5.08 (s,1H), 6.0 (br,1H); MS m/e 264 (6), 249 (6), 224 (16), 221 (18), 205 (100).

3aα,11bβ-Dimethyl-1,2,3a,4,5,8,8aβ,9,10,11,11aβ,11b-dodecahydro-2-hydroxy-6H-*furo[3',4'-4aα,5]naphto[2,1-b]furan* (35).

Alcohol 33 (1.0 g, 3.8 mmol) was dissolved in methylene chloride (40 mL) and cooled to -78°C. The solution was magnetically stirred and ozone was bubbled through until the mixture attained a persisting blue color. Residual ozone was removed by flushing the system

with nitrogen. The mixture was allowed to warm to room temperature and the ozonide was reduced with hydrogen, using palladium on charcoal as the catalyst. The catalyst was removed by filtration and the solvent was distilled off to give 35 (0.70 g, 70%), mp. 176-180°C; IR (KBr) 3400 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.72 (s,3H), 1.25 (s,3H), 1.2-2.5 (m,14H), 3.39 (d, J=8Hz, 1H), 3.71 (s,2H), 3.87 (dd, J=8,5Hz, 1H), 4.2 (s,br,1H), 5.48 (t, J=6Hz, 1H); MS m/e 266 (3), 265 (6), 264 (6), 251 (100), 205 (10).

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 71.94; H, 9.70.

3,3aβ,4,5,6,6aβ,7,8,9,10-Decahydro-8α-hydroxy-7α,8β-dimethyl-7β-(2-oxoethyl)-1H-*naphto[1,8aα-c]furan* (36).

The alcohol 34 (1.0 g, 3.8 mmol) was ozonolysed and hydrogenated in the same way as described for 33. This afforded 36 (0.75 g, 75%), m.p 120-124°C; IR (KBr) 3350, 2760, 1700 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.00 (s,3H), 1.30 (s,3H), 1.3-2.0 (m,12H), 2.26 (d, J=4Hz, 2H), 2.55 (s,br,1H), 3.33 (d, J=8Hz, 1H), 3.72 (s,2H), 3.80 (dd, J=8,4Hz, 1H), 9.80 (t, J=4Hz, 1H); MS m/e 266 (5), 264 (3), 251 (25), 238 (45), 206 (91), 178 (100).

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 71.06; H, 9.58.

1,2,3a,4,5,8,8aβ,9,10,11,11aβ,11b-Dodecahydro-2-methoxy-3aβ,11bα-dimethyl-6H-*furo[3',4'-4aα,5]naphto[2,1-b]furan* (38).

Aldehyde 36 (400 mg, 1.5 mmol) was refluxed in methanol (10 mL) in the presence of *p*-toluene sulfonic acid for 1h. The mixture was allowed to cool and the methanol was distilled off under reduced pressure. The residue was dissolved in ether and washed with saturated aqueous sodium bicarbonate solution, dried over anh. magnesium sulfate and concentrated to afford 38 (340 mg, 85%) (oil); IR (neat): no specific absorbtions; ^{1}H-NMR ($CDCl_3$) δ 0.73 (s,3H), 1.1-2.0 (m,14H), 1.40 (s,3H), 3.37 (d, J=8Hz, 1H), 3.40 (s,3H), 3.69 (d, J=8Hz, 1H), 3.82 (d, J=8Hz, 1H), 3.82 (dd, J=8,4Hz, 1H), 5.10 (t, J=6Hz, 1H); MS m/e 280 (29), 165 (48), 249 (63), 248 (36), 207 (36), 178 (100).

1,2,3a,4,5,8,8aβ,9,10,11,11aβ,11b-Dodecahydro-2-methoxy-3aα,11bα-dimethyl-6H-*furo[3',4'-4aα,5]naphto[2,1-b]furan* (39).

Treatment of hemiacetal 35 as described for 36 afforded 39 (380 mg, 90%) (oil); IR: no specific absorbtions found; ^{1}H-NMR ($CDCl_3$) 0.71 (s,3H), 1.19 (s,3H), 1.1-2.0 (m,13H), 2.34 (dd, J=14,6Hz, 1H), 3.36 (s,3H), 3.39 (d. J=8Hz, 1H), 3.71 (s,2H), 3.89 (dd, J=8,4Hz, 1H), 4.93 (t, J=6Hz, 1H); MS m/e 280 (5), 265 (58), 248 (50), 85 (100).

3,3aβ,4,5,6,6aβ,7,8,9,10-Dodecahydro-8α-hydroxy-7β-(2-hy-droxyethyl)-7α,8β-dimethyl-1H-*naphto[1,8aα-c]furan* (40).

Alcohol 34 (1.3 g, 5 mmol) was dissolved in ether and reacted with ozone at -78°C. At the end of the reaction residual ozone was removed by flushing the system with nitrogen. The mixture was allowed to warm to room temperature and added to a magnetially stirred suspension of lithium aluminium hydride (200 mg). Ethyl acetate was added (to destroy any excess of lithium aluminium hydride), followed by dilute hydrochloric acid. The reaction mixture was worked up as usual to afford diol 40 (1.1 g, 82%) (oil); IR (neat) 3400 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.78 (s,3H), 1.19 (s,3H), 1.2-2.1 (m,14H), 3.35 (d, J=7Hz, 1H), 3.72 (dd, J=7,4Hz, 1H), 3.75 (m,2H); MS m/e 268 (0.4), 250 (0.8), 235 (100).

1,2,3,4,5,8,8aβ,9,10,11,11aβ,11b-Dodecahydro-3aα-11bα-dimethyl-6H-*furo[3',4'-5aα,6]naphto[2,1-b]furan* (42).

Diol 40 (1.0 g, 3.7 mmol) was heated with anhydrous copper (II) sulfate in an atmosphere of nitrogen at 140°C for 1h. After cooling to room temperature, ether and water were added and the reaction mixture was worked up in the usual manner to give 42 (900 mg, 96%). Crystallization from ethanol gave the analytical sample, m.p. 68-70°C; IR: no specific absorbtion observed; ^{1}H-NMR ($CDCl_3$) 0.72 (s,3H), 1.03 (s,3H), 1.1-2.2 (m.14H), 3.37 (d, J=8Hz, 1H), 3.72 (s,2H), 3.83 (m,2H), 3.87 (dd, J=8,5Hz, 1H); MS m/e 250 (1), 249 (1), 235 (100), 205 (3).

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.82; H, 10.44.

Dehydration of 33 and 34 with phosphoryl chloride-pyridine.

To a mixture of the alcohols 33 and 34 (100 mg, 0.38 mmol) and pyridine (2 mL) was added at 0°C phosphoryl chloride (0.1 mL) and the mixture was stirred for 1h. Water (10 mL) and hydrochloric acid (5 mL of a 6N. aqueous solution) were added and the mixture was extracted with ether. The extract was washed with brine solution and dried (anh. magnesium sulfate). GCMS analysis showed the presence of two isomeric products with M^+ m/e 246, which could not be separated by TLC. Evaporation of the solvent afforded an oil (19 mg, 20%) which was dissolved in ether (5 mL) and treated with boron trifluoride etherate (0.1 mL). The mixture was stirred for 1h and analysed by GC, which showed the disappearance of the second peak.

7α-Allyl-3,3aβ,4,5,6,6aβ,7,10-octahydro-7β,8-dimethyl-1H-*naphto[1,8aα-c]furan* (43).

To a mixture of the alcohols 33 and 34 (3.75 g, 14.2 mmol) and benzene (50 mL) was added boron trifluoride etherate (1 mL). The mixture was refluxed in an atmosphere of nitrogen under a Dean-Stark trap. Separation of the water began immediately. Refluxing was continued for 4h. The mixture was cooled, washed with 10% aqueous sodium bicarbonate, and dried over anhydrous magnesium sulfate. Removal of the solvent gave a yellow oil which was chromatographed on silica gel with hexane-ether (5:1) as the eluant to afford 43 (3.25, 93%) (oil); IR (neat) 3070, 1632 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.76 (s,3H), 1.64 (s,3H), 1.2-2.0 (m,8H), 2.11 (d, J=7Hz, 2H), 3.14 (d, J=8Hz, 1H), 3.56 (d, J=7Hz, 1H), 3.80 (d, J=7Hz, 1H), 3.88 (dd, J=8,4Hz), 4.97 (d, J=12Hz, 1H), 5.03 (s,1H), 5.39 (d,br, J=7Hz, 1H), 5.55 (m,1H); MS m/e 246 (1.5), 205 (85), 187 (16), 123 (31), 95 (100). This diene was identical (as shown by GC, GCMS and IR) to the compound of the preceeding experiment.

3,3aβ,4,5,6,6aβ,7,10-Octahydro-7β-(3-hydroxypropyl)-7α,8-dimethyl-1H-*naphto[1,8aα-c]furan* (45).

To a mixture of diene 43 (1.70 g, 7.0 mmol) and tetrahydrofuran (30 mL) (freshly distilled from benzophenone-sodium) was added under nitrogen a solution of 9-BBN (16 mL of a 0.5 N solution in tetrahydrofuran). After stirring for 1h a solution of sodium hydroxide (1 g, 25 mmol) in water (10 mL) was added, followed by hydrogen

peroxide (2 mL of a 30% aqueous solution). After 1h most of the tetrahydrofuran was distilled off and the residue was extracted with ether. The extract was dried (anh. magnesium sulfate) and concentrated to afford an oil which was chromatographed on silicagel with ether-hexane (1:1) as the eluant to give 45 (1.55 g, 83%) (oil); IR (neat) 3350 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.81 (s,3H), 1.67 (s,3H), 1.2-2.3 (m,14H), 3.51 (d, J=8Hz, 1H), 3.63 (t,br,sH), 3.64 (d, J=8Hz, 1H), 3.86 (d, J=8Hz, 1H), 3.96 (dd, J=8,4Hz, 1H), 5.44 (d, J=6Hz, 1H); MS m/e 264 (24), 205 (31), 151 (18), 123 (31), 95 (100).

9β-Acetoxy-7β-(3-acetoxypropyl)-3,3aβ,4,5,6,6aβ,7,8β,9α,10-decahydro7α,8α-dimethyl-1H-*naphto[1,8aα-c]furan* (47).

To a solution of diene 43 (0.98 g, 4 mmol) in tetrahydrofuran (15 mL) (freshly distilled from benzophenone-sodium) was added under nitrogen borane-tetrahydrofuran complex (4 mL of a 2N solution in tetrahydrofuran) and the mixture was stirred for 4h. Ethanol was added (to destroy any excess of diborane) followed by aqueous sodium hydroxide (10 mL of a 2N solution) and hydrogen peroxide (3 mL of a 30% solution in water). Water was added (50 mL) and the mixture was extracted with ether. The extract was washed with brine solution and dried (anh. magnesium sulfate). Evaporation of the solvent afforded 46 (1.05 g, 97%) as a viscous oil; IR (neat) 3400 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.57 (s,3H), 0.95 (d, J=6Hz, 3H), 1.0-2.1 (m,15H), 3.4-4.0 (m,5H), 3.69 (s,2H); MS m/e 264 (M^+-18) (4), 249 (5), 233 (3), 223 (38), 221 (22), 205 (100).

The crude diol was dissolved in pyridine (5 mL) and acetic anhydride (1 mL) was added. The mixture was stirred for 4h. The mixture was evaporated to dryness and chromatographed on silicagel with ether as the eluant to give 47 (1.30 g, 90%) (oil); IR (neat) 1728, 1230 cm^{-1} ($CDCl_3$) δ 0.62 (s,3H), 0.82 (d, J=6Hz, 3H), 1.2-2.0 (m,15H), 2.02 (s,6H), 3.37 (d, J=7Hz, 1H), 3.78 (s,2H), 3.84 (dd, J=7,5Hz, 1H), 4.03 (t,br,2H), 4.85 (ddd, J=11,11, 4Hz, 1H); MS m/e 366 (0.5), 349 (0.4), 323 (0.6), 306 (27), 262 (25), 251 (19), 246 (13), 205 (100).

3,3aβ,4,5,6,6aβ,7,8β,9,10-Decahydro-7α,8α-dimethyl-9-oxo-1H-*naphto[1,8aα-c]furan-7β-propanoic-acid* (48).

A mixture of 46 (1.18 g, 4.1 mmol) and acetone (30 mL) was added slowly to a solution of sodium bichromate (1.2 g) and sulfuric acid

(2.5 mL) in water (10 mL) at a temperature of 0°C. The green precipitate was filtered off and most of the acetone was distilled off under reduced pressure. Water was added (20 mL) and the mixture was extracted with chloroform. The organic layer was washed with 10% aqueous sodium bicarbonate solution and dried (anh. magnesium sulfate). Evaporation of the solvent afforded 48 (820 mg, 67%); IR (KBr), 3000 (br), 1690; ^{1}H-NMR (CD_3OD) δ 0.53 (s,3H), 0.90 (d, J=7Hz, 3H), 1.1-2.4 (m,14H), 2.69 (q, J=7Hz, 1H), 3.40 (d, J=8Hz, 1H), 3.41 (d, J=8Hz, 1H), 3.79 (d, J=8Hz, 1H), 3.83 (dd, J=8,4Hz, 1H); MS m/e 294 (6), 232 (85), 222 (94), 221 (65), 176 (45), 175 (45), 123 (100).

3,3aβ,4,5,6,6aβ,7,8β,9,10-Decahydro-7α,8α-dimethyl-1H-*naphto[1,8aα-c]furan-7β-propanoic acid* (49).

The keto carboxylic acid 48 (600 mg, 2.05 mmol) was dissolved in triethylene glycol (10 mL). Hydrazine hydrate (0.5 mL) and potassium hydroxide (480 mg) were added and the mixture was heated in an atmosphere of nitrogen at 90°C during 0.5 h. The temperature was risen to 150°C for 1h. and then to 190°C. After 1.5h. the reaction mixture was cooled, aq. hydrochloric acid (8 mL, 4N) was added and the mixture was extracted with ether. The ether layers were washed with 10% aqueous sodium bicarbonate solution and dried (anh. magnesium sulfate). Evaporation of the solvent gave the crude product which was purified by column chromatography over silicagel with ether as the eluant to give the pure 49 (315 mg, 55%) (oil); IR (neat), 3000 (br), 1690 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.54 (s,3H), 0.69 (d, J=6Hz, 3H), 1.1-2.4 (m,17H), 3.37 (d, J=8Hz, 1H), 3.72 (s,2H), 3.87 (dd, J=8,4Hz, 1H); MS m/e 280 (2), 262 (2), 249 (5), 248 (6), 235 (14), 207 (100).

3,3aβ,4,5,6,6aβ,7,8β,9,10-Decahydro-7β,8β-dimethyl-3-oxo-1H-*naphto[1,8aα-c]furan-7β-propanoic acid methylester* (50).

The carboxylic acid 49 (315 mg) was dissolved in ether (20 mL) and diazomethane solution in ether was added until the yellow color persisted. The excess of diazomethane was removed by flushing the system with nitrogen and the ether was distilled off to afford the methyl ester of 49 (330 mg, 99%) (oil); IR (neat) 1730 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.53 (s,3H), 0.70 (d, J=6Hz, 3H), 1.1-2.4 (m,17H), 3.36 (d, J=7Hz, 1H), 3.65 (s,3H), 3.73 (s,2H), 3.87 (dd, J=7,4Hz, 1H); MS m/e 294 (3), 264 (4), 263 (7), 249 (24), 207 (100).

The methyl ester was dissolved in carbon tetrachloride (10 mL) and ruthenium dioxide (30 mg) and a solution of sodium *meta*-periodate (1 g) in water (10 mL) were added. The mixture was stirred vigorously overnight and the organic layer was separated. Ether was added and the solution was dried (anh. magnesium sulfate). The drying agent and the ruthenium dioxide were filtered off and the filtrate was concentrated to give 50 (330 mg, 95%)(oil); IR (neat) 1768, 1725, 1165 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.62 (s,3H), 0.83 (d, J=6Hz, 3H), 1.0-2.4 (m,17H), 3.66 (s,3H), 4.22 (d, J=9Hz, 1H), 4.27 (d, J=9Hz, 1H); MS m/e 308 (3), 290 (8), 277 (5), 242 (16), 239 (9), 221 (100), 163 (82), 87 (90).

3,3aβ,4,5,6,6aβ,7,8β,9,10-Decahydro-7β,8β-dimethyl-3-oxo-1H-*naphto[1,8aα-c]furan-7β-propanoic acid* (52).

The methyl ester (50) (100 mg, 0.325 mmol) was dissolved in methanol (3 mL) and a solution of potassium hydroxide (100 mg) in methanol (10 mL) was added. The mixture was stirred for 2h. Aqueous hydrochloric acid was added (3 mL, 1N) and the methanol was distilled off. Ether was added and the solution was washed with brine solution and dried (anh. magnesium sulfate). Evaporation of the solvent afforded 52 (87.5 mg, 92%) as an amorphous solid; IR ($CDCl_3$) 3000, 1770, 1700 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.63 (s,3H), 0.84 (d, J=6Hz, 3H), 1.0-2.4 (m,17H), 4.22 (d, J=9Hz, 1H), 4.26 (d, J=9Hz, 1H). MS m/e 294(2), 276(2), 221(100).

7β-(4-Hydroxy-3-oxo-butyl)-3,3aβ,4,5,6,6aβ,7,8β,9,10-decahydro-7α,8α-dimethyl-3-oxo-1H-*naphto[1,8aα-c]furan* (55).

To a solution of the carboxylic acid 52 (87.5 mg, 0.298 mmol) in methanol (1 mL) was added a solution of potassium hydroxide (16.6 mg, 0.298 mmol) in methanol (1 mL). The methanol was distilled off under reduced pressure. Carbon tetrachloride (2 mL) was added and distilled off to remove any residual methanol. Carbon tetrachloride (3 mL) was added followed by two drops of pyridine and the mixture was cooled to 0°C. The suspension was stirred magnetically and oxalyl chloride (0.2 mL) was added. After stirring overnight the mixture was filtered and the filtrate was evaporated to dryness to afford the acid chloride 53; (84 mg) (oil); IR (neat) 1790, 1768.

The acid chloride was dissolved in ether (20 mL) and added to a dry solution of diazomethane in ether (20 mL). After 1h. the solution was evaporated to dryness to afford the crude diazoketone 54 (87 mg).
This diazoketone was dissolved in acetone (3 mL) and water was added (5 mL). The mixture was cooled to 0°C and a saturated solution of sulfur dioxide in water (30 mL) was added with stirring. After 1h most of the acetone was distilled off and the aqueous solution was extracted with ether. The extract was dried over anh. magnesium sulfate and the ether was removed under reduced pressure to afford an oil (85 mg) which was chromatographed over silica gel with ether-ethylacetate (9:1) as the eluant to afford the methyl ester 50 (21 mg, 23%).

Further elution gave the hydroxy ketone 55 (51 mg, 55%) (oil); IR (neat) 3450, 1768, 1725 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.62 (s,3H), 0.84 (d, J=6Hz, 3H), 1.1-2.4 (m,17H), 3.25 (s,1H), 4.24 (s,4H); MS m/e 308(1.5), 277(44), 259(72), 231(16), 221(100).

7β-[2-(2,5-Dihydro-5-oxo-3-furanyl)ethyl]-3,3aβ,4,5,6,6aβ,7,8β,9,10-decahydro-7α,8α-dimethyl-3-oxo-1H-*naphto[1,8aα-c]furan* (56).

The hydroxy ketone 55 (51 mg, 0.165 mmol) was dissolved in benzene. Triphenylphosphoranylidene ketene (50 mg, 0.172 mmol) was added and the mixture was refluxed for 1h. The mixture was allowed to cool and the benzene was distilled off under reduced pressure. The residue was chromatographed on silica gel with ether-ethylacetate (9:1) as the eluant to afford 56 (51 mg, 93%) (oil); IR (neat) 1768, 1735, 1630 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 0.65 (s,3H), 0.86 (d, J=6Hz, 3H), 1.2-2.4 (m,17H), 4.25 (d, J=9Hz, 1H), 4.31 (d, J=9Hz, 1H), 4.78 (d, J=2Hz, 2H), 5.88 (q, J=2Hz, 1H); MS m/e 332(1.5), 314(7), 221 (100).

9β-Acetoxy-7β-(3-acetoxypropyl)-3,3aβ,4,5,6,6aβ,7,8β,9α,10-decahydro7α,8α-3-oxo-1H-*naphto[1,8aα-c]furan* (62).

To a solution of the diacetate 47 (500 mg, 1.37 mmol) in carbon tetrachloride (10 mL) was added ruthenium dioxide (10 mg) and a solution of sodium *meta*-periodate (600 mg) in water (10 mL). The mixture was stirred vigorously overnight and worked up as described for the synthesis of 23 to afford 62 (499 mg, 96%) (oil); IR (neat) 1768, 1728, 1231 cm^{-1}; ^{1}H-NMR ($CDCl_3$), 0.66 (s,3H), 0.84 (d, J=6Hz,

3Hz), 1.1-2.0 (m,15H), 2.03 (s,6H), 4.00 (t,br,2H), 4.23 (d, J=9Hz, 1H), 4.36 (d, J=9Hz, 4.86 (ddd, J=11,11,4Hz, 1H); MS (8eV) m/e 380 (6), 320 (56), 279 (42), 260 (95), 219 (100).

3aβ,4,5,6,6aβ,7,8β,10-Octahydro-7α,8α-dimethyl-7β-(3-oxo-propyl)-1H-*naphto[1,8aα-c]furan-3,9-dione* (64).

To a solution of diacetate 62 (480 mg, 1.26 mmol) in methanol (19 mL) was added a solution of potassium hydroxide (200 mg) in water (10 mL). The mixture was stirred overnight, acidified, and extracted with chloroform. The extract was dried over magnesium sulfate and concentrated to afford the diol 63 (450 mg) (viscous oil); IR (neat) 3350, 1755 cm^{-1}. The crude diol was dissolved in methylene chloride (20 mL) and pyridinium chlorochromate (1.2 g, 5.5 mmol) was added. The mixture was stirred at room temperature for 6h. during which time a black polymer separated. Ether (20 mL) was added and the organic layer was decanted from the polymer, which in turn was washed three times with ether. The combined phases were washed with 5% aqueous hydrochloric acid and with 5% aqueous sodium bicarbonate, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to afford 64 (260 mg, 70%), as an amorphous solid; IR (KBr) 1768, 1710, 1700 cm^{-1}; MS m/e 292 (10) 274 (8), 235 (100).

7β-(3,3-Ethylenedioxypropyl)-3aβ,4,5,6,6aβ,7,8β,10-octahydro-7α,8α-dimethyl-1H-*naphto[1,8aα-c]furan-3,9-dione* (65).

To a solution of the keto aldehyde 64 (200 mg, 0.69 mmol) in benzene (20 mL) was added ethylene glycol (0.2 mL) and *p*-toluene sulfonic acid (10 mg). The mixture was refluxed overnight under a Dean-Stark trap. The benzene layer was washed with 5% aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 65 (185 mg, 80%) (oil); IR (neat) 1768, 1700 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.61 (s,3H), 0.98 (d, J=6Hz, 3H), 1.2-2.7 (m,15H), 3.95 (m,4H), 3.98 (d, J=9Hz, 1H), 4.32 (d, J=9Hz, 1H), 4.86 (t,br,1H); MS m/e 336 (0.6), 321 (0.5), 291 (0.4), 235 (90), 99 (50), 73 (100).

3aβ,4,5,6,6aβ,7,8,10-Octahydro-7α,8α-dimethyl-1H-*naphto[1,8aα-c]furan-3,9-dion-7β-carboxylic acid methyl ester* (67).

The ketocarboxylic acid 48 (500 mg, 1.70 mmol) was dissolved in methanol and refluxed for 2h. in the presence of boron trifluoride-methanol complex (0.2 mL of a 12% solution in methanol). The solvent was distilled off and the residue was taken up in 10 mL of ether and washed with 5% aqueous sodium bicarbonate. The ethereal solution was dried (anh. magnesium sulfate) and concentrated to give 66 (510 mg, 97%) (oil); IR (neat) 1730, 1700 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.55 (s,3H), 0.92 (d, J=6Hz, 2H), 1.1-2.7, 3.40 (d, J=8Hz, 1H), 3.48 (d, J=9Hz), 3.69 (s,3H), 3.74 (d, J=9Hz, 1H), 3.83 (dd, J=5,8Hz); MS m/e 308 (8), 249 (50), 236 (33), 221 (100), 207 (38). This methyl ester was dissolved in carbon tetrachloride and oxidized with ruthenium tetroxide as described for the oxidation of 47 to 62, which gave the lactone 67 (500 mg, 91%) (oil); IR 1768, 1728, 1700 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.61 (s,3H), 0.98 (d, J=6Hz, 3H), 1.1-2.7 (m,15H), 3.71 (s,3H), 3.97 (d, J=9Hz, 1H), 4.32 (d, J=9Hz, 1H); MS m/e 322 (4), 291 (4), 235 (100).

9,9-Ethylenedioxy-3,3aβ,4,5,6,6aβ,7,8β,9,10-decahydro-7α,8α-dimethyl-3-oxo-1H-*naphto[1,8aα-c]furan-7β-propanoic acid* (69).

The lactone 67 (500 mg, 1.55 mmol) was reacted with ethylene glycol in a similar way as described for keto aldehyde 64 to give 68 (500 mg, 85%); IR (KBr) 1768, 1730 cm^{-1}. The ester was dissolved in methanol (10 mL) and 10% aqueous potassium hydroxide solution (10 mL) was added. After stirring overnight the mixture was acidified (aqueous hydrochloric acid) and the methanol was distilled off. The aqueous layer was extracted with chloroform. The extract was dried (anh. magnesium sulfate) and concentrated to give 69 (450 mg, 97%) as an amorphous solid; IR (KBr) 2900 (br), 1768, 1695 cm^{-1}; MS m/e 352 (45), 280 (7), 235 (5), 223 (19), 181 (40), 86 (100).

Attempted dehydrogenation of 69.

The carboxylic acid 69 (350 mg, 1.0 mmol) was dissolved in tetrahydrofuran (20 mL freshly distilled from benzophenone-sodium) and cooled to -78°C. Lithium diisopropylamide (2.10 mmol in 10 mL of tetrahydrofuran) was added with stirring in an atmosphere of nitrogen. Tetramethylenediamine (230 mg, 2.1 mmol) was added. After

stirring for 3h. diphenyldiselenide (310 mg, 1.03 mmol) in tetrahydrofuran (5 mL) was added and the mixture was allowed to warm to room temperature. The solvent was distilled off and the residue was taken up in methanol (10 mL) and treated with a solution of sodium *meta*-periodate (250 mg) in water (10 mL). After stirring overnight the methanol was distilled off and the residue was extracted with chloroform. The extract was dried (anh. magnesium sulfate) and evaporated to dryness. The residue was analysed (^{1}H-NMR, IR and MS) and was shown to contain only the starting compound 69.

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5 *THE STEREOSELECTIVE SYNTHESIS OF A SUBSTITUTED TRANS DECALIN AS A MODEL FOR THE INVESTIGATION OF STRUCTURE-ACTIVITY RELATIONSHIPS OF THE INSECT ANTIFEEDANT CLERODANES.*

5.1 INTRODUCTION.

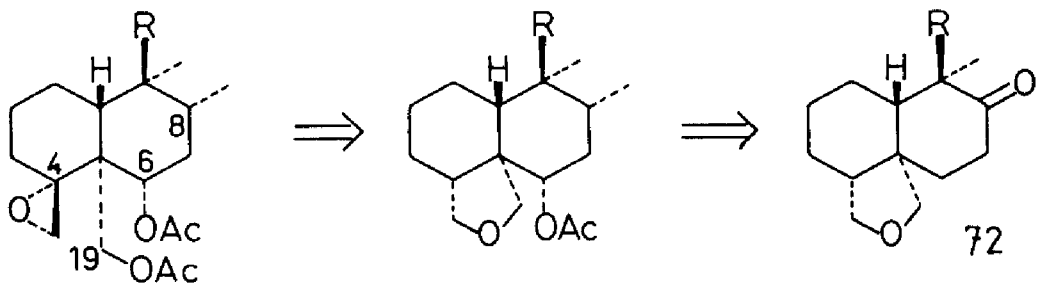
All insect antifeedant clerodanes possess a spiro epoxide at C-4 and acetate functions at C-6 and C-19 (see chapter 1.4). Being interested in the synthesis of these diterpenes and model compounds for structure-activity investigations, we had to probe the usefulness of the previously described compounds as intermediates in this approach.

Starting from the readily available decalones of type 72 we had to develope acceptable solutions for the following aspects:

i. The introduction of an equatorial methyl group at C-8 (one method was shown in the preceding chapter).
ii. The introduction of an equatorial acetate at C-6.
iii. The efficient and stereoselective transformation of the cyclic ether into a spiroepoxide at C-4 and an acetate at C-19 (see the retrosynthetic plan in scheme 5.1).

Especially the latter aspect is one of the most crucial tranformations in our synthetic plan.

Scheme 5.1



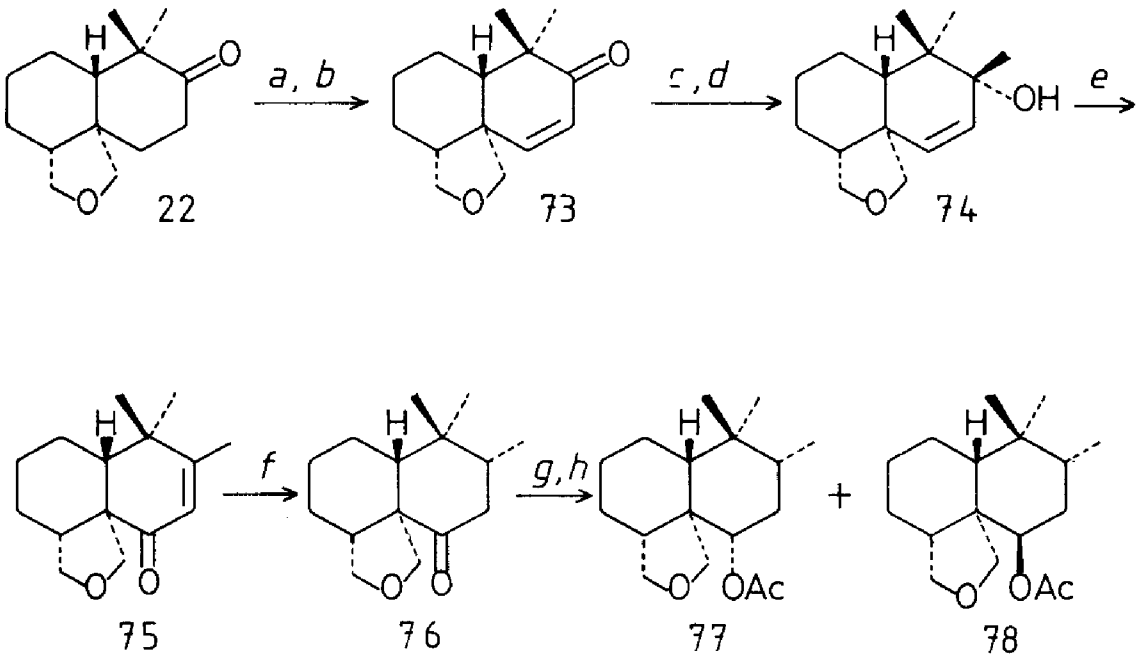
5.2 THE STEREOSELECTIVE FUNCTIONALIZATION OF C-6 AND C-8.

The decalone 22 was chosen as a model compound to probe a series of reactions aiming the combined introduction of a methyl at C-8 and an acetate at C-6. The method for alkylative 1,3-carbonyl transposition which was developed by Dauben and Michno[1] seemed to be very suited for this purpose.

Treatment of 22 with bromine in acetic acid, followed by dehydrobromination with lithium bromide and lithium carbonate in refluxing dimethylformamide gave the α,β-unsaturated ketone 73.

Addition of methyllithium to 73 gave, after hydrolysis, the tertiary alcohol 74. The stereochemistry at C-8 was not rigorously proven, but tentatively assigned on the assumption that β-attack of methyl lithium had taken place. Oxidation of the allylic alcohol with pyridinium chlorochromate afforded the α,β-unsaturated ketone 75. The overall yield of these transformations was 86%. The olefinic moiety in 75 was reduced with lithium in ammonia[2]. This reaction was expected to lead to the energetically more favoured product, *i.e* with the C-8 methyl group in an equatorial position. ^{1}H-NMR

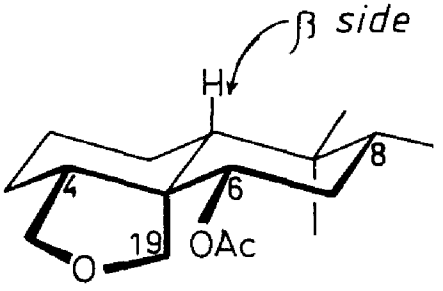
Scheme 5.2



a: Br_2, AcOH; *b*: LiBr, Li_2CO_3; DMF, Δ; *c*: MeLi; *d*: H_2O; *e*: PCC; *f*: H_2, Pd/C; *g*: $NaBH_4$, 2-propanol; *h*: Py, Ac_2O, DAP.

spectrometry, however, showed two different secondary methyl groups in the reaction product in a 1:1 ratio, centered at 0.95 and 0.88 ppm, thus indicating the presence of both the equatorial and the axial C-8 methyl. This mixture of isomers could not be separated by GC or TLC.

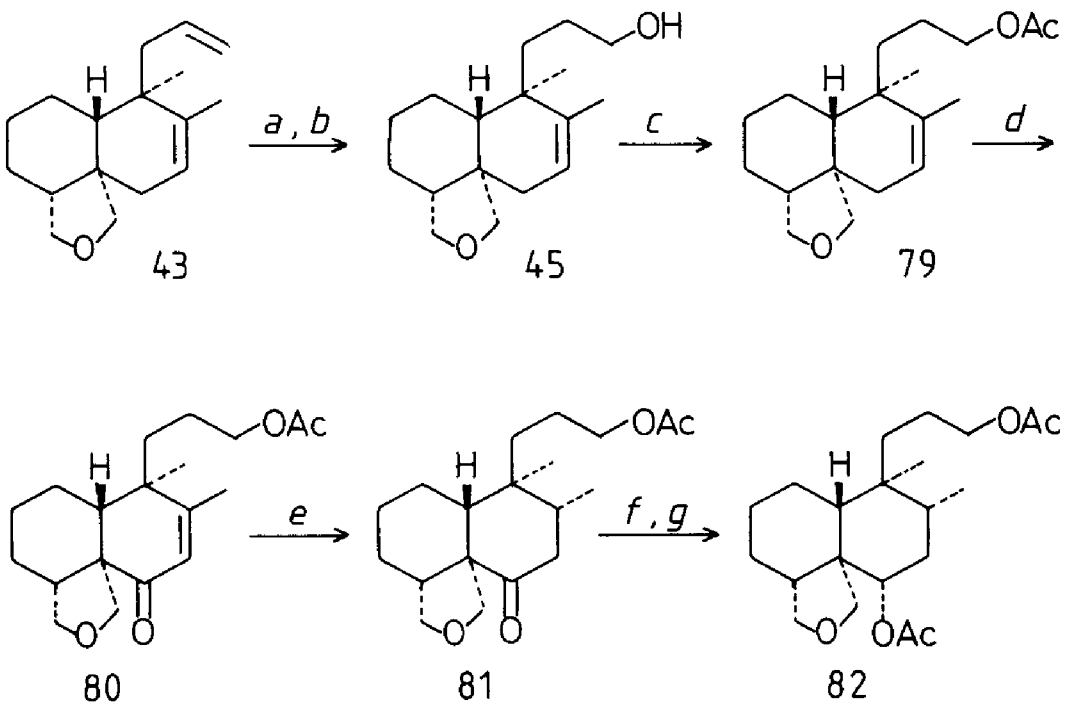
In contrast, catalytic hydrogenation of 75 using palladium on charcoal as the catalyst gave a single product. Evidence for the stereochemistry at C-8 in the hydrogenated product was found for $J_{7,8}$ in the ^{1}H-NMR spectrum. The C-7 protons display a double doublet at 2.65 ppm. with coupling constants of 13 and 13 Hz. These values render obvious the equatorial attachment of the C-8 methyl group. Hence catalytic hydrogenation of 75 produces exclusively the desired ketone 76 as a result of addition of hydrogen from the less hindered side of the molecule. Reduction of 76 with sodium borohydride in 2-propanol at 0°C gave a 9:1 mixture of the equatorial and the axial alcohols respectively. They were converted into the corresponding acetates by treatment with acetic anhydride/pyridine/4-dimethylaminopyridine (DAP). The two isomeric acetates could easily be separated by column chromatography on silica gel. Acetate 77 was thus obtained in 82% yield and the isomer 78 in 9% yield. On use of the more bulky diisobutyl aluminium hydride for the reduction of 76 the equatorial and axial alcohols were formed in a ratio of 94:6.



77

We wanted to investigate the possibilities for the oxidation of C-6 in model compounds with substituents at C-9 which can be used for the construction of the clerodane side chain. In chapter 4 we demonstrated the usefulness of an allyl group as a possible side chain precursor. It was therefore important to develop a method towards the above mentioned objectives which would be consistent with the presence of this group or could be combined with its further transformation. If the alkylative 1,3-carbonyl transposition was to be used, one of the first steps should then be the transformation of the allyl group in order to avoid the loss of its functionality in the catalytic hydrogenation step which must be used in the subsequent reaction (see scheme 5.1). Since future transformations of the side chain require a terminally functionalized three carbon substituent at C-9 (see chapter 4), hydroboration is most appropriate for the functionalization of the allyl group. This reaction, how-

Scheme 5.3



a: 9-BBN; *b*: H_2O_2, OH^-; *c*: Ac_2O, Py; *d*: CrO_3, AcOH; *e*: H_2, Pd/C; *f*: $NaBH_4$; *g*: Py, Ac_2O, DAP.

ever, seems to be inconsistent with the presence of other double bonds or carbonyl functions in the molecule so this would require a laborious series of protection and deprotection reactions.

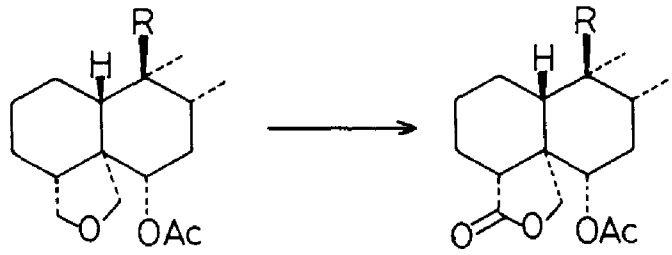
A solution was found in the selective hydroboration[3] of the allyl substituent at C-9 in diene 43 (see also chapter 4.4) using 9-BBN. Subsequent oxidation afforded the alcohol 45 which was protected as the acetate to give 79.
Oxidation of C-6 could now be achieved *via* allylic oxidation[4] (chromium trioxide in acetic acid), thus affording enone 80 in 55% yield. Catalytic hydrogenation of 80 under the same conditions as in the case of 75, again proceeded stereoselective and gave the keto acetate 81 in 97% yield. Reduction of 81 with sodium borohydride proceeded less stereoselective than in the case of 76: the equatorial and axial C-6 hydroxyl groups were formed in a ratio of 4:1 respectively. The mixture of the two isomers was acetylated to give, after column chromatography on silica gel the equatorial acetate 82 in 66% yield (see scheme 5.3).

These reactions provided a *second* stereospecific method for the introduction of the C-8 methyl, together with the stereoselective introduction of an equatorial acetate at C-6. The latter reactions are consistent with a side chain precursor at C-9 in the form of a three carbon substituent being protected as an acetate. It was expected that any other side chain precursor which contains an ester functionality, would also survive the same sequence of reactions (see chapter 7).

5.3 STUDIES ON THE FUNCTIONALIZATION OF C-18 AND C-19.

Further investigations concerned the transformation of the cyclic ether moiety into more accessible groups for the construction of the functionalities as present in ajugarin I and clerodin. Our first efforts in this direction started with the well known ruthenium tetroxide ether oxidation[5]. Thus oxidation of 77 afforded the lactone 83 and diacetate 82 gave lactone 84.

Our initial synthetic plan towards the epoxy diacetate 85 involved alpha bromination of the lactone moiety, followed by selective

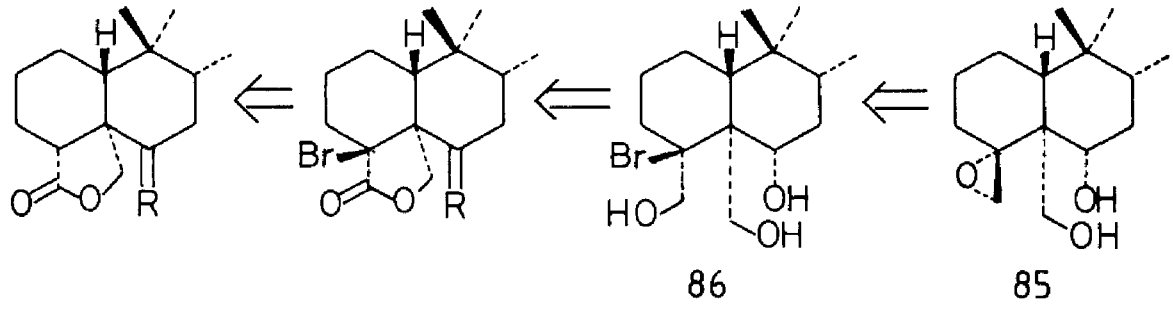


77, R = Me
82, R = -$(CH_2)_3OAc$

83, R = Me
84, R = -$(CH_2)_3OAc$

reduction to give the triol 86. The halohydrin function in this molecule can be transformed into the epoxide 85 (see scheme 5.4).

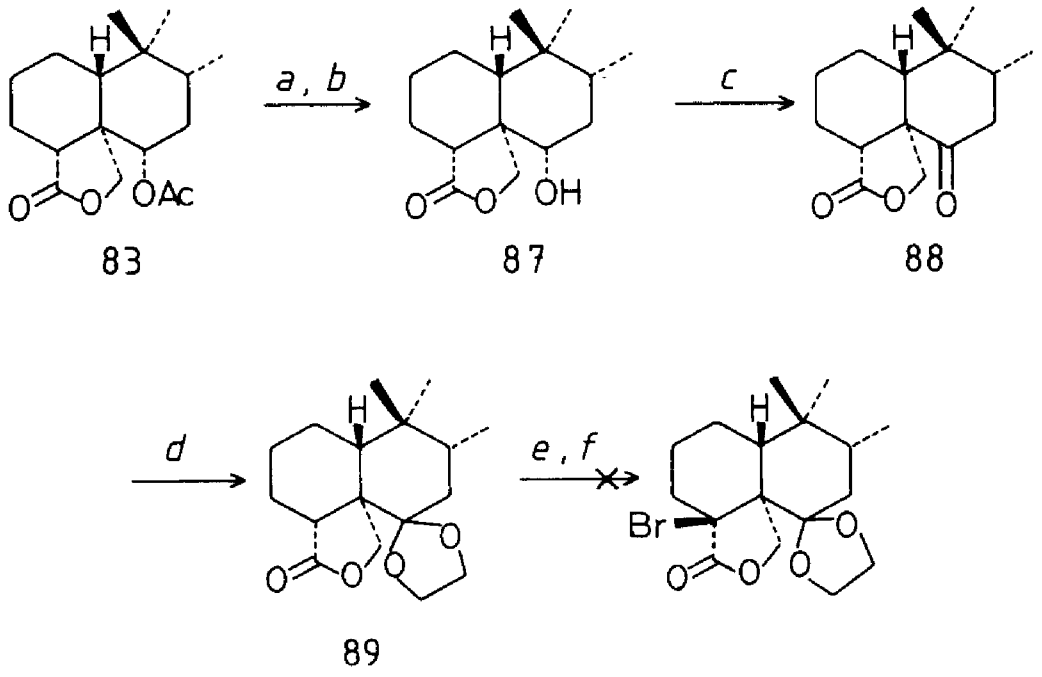
Scheme 5.4



86 85

The acetate 83 was therefore hydrolysed to the corresponding alcohol 87 and oxidized to ketone 86[6], which in turn was protected as the ethylene ketal 89. Subsequent alpha bromination using LDA followed by the addition of 1,2-dibromoethane, was unsuccessful. The steric bulk of the ethylenedioxygroup probably prevented bromination of C-4 (see scheme 5.5). In the absence of a substituent at C-6, alpha bromination of the lactone moiety could readily be accomplished[7].

Scheme 5.5



83 87 88

89

a: OH^-, H_2O; *b*: H_3O^+; *c*: Jones' reag.; *d*: TsOH, glycol, Bz, Δ; *e*: LDA; *f*: $BrCH_2CH_2Br$.

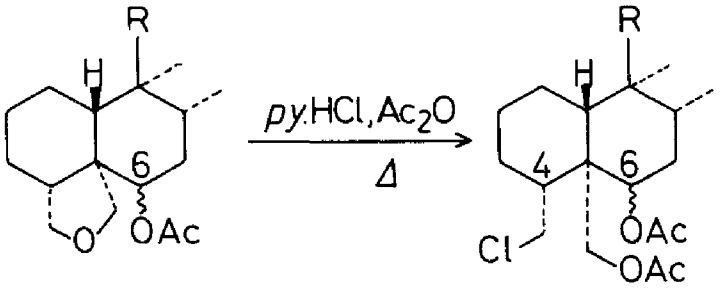
Before trying alternative approaches for the alpha bromination of the lactone, we investigated the possibilities of an ether cleavage reaction in order to construct suitable substituents at C-4 and C-5.

Karger and Mazur described a very efficient method for the transformation of ethers into a tosylate and an acetate function by reaction with acetyl-*p*-toluenesulfonate[8]. Using this method for the cleavage of the ether moiety in 77, however, only starting material was recovered from the reaction mixture.

Ether cleavage by pyridine hydrochloride[9] in refluxing acetic anhydride was more successful; the chloro diacetate 90 was produced in 80% yield (scheme 5.6).

In a similar way 78 and 82 afforded the ring opening products 91 and 92 respectively in comparable good yields.

Scheme 5.6



77, R=Me, 6α-OAc

78, R=Me, 6β-OAc

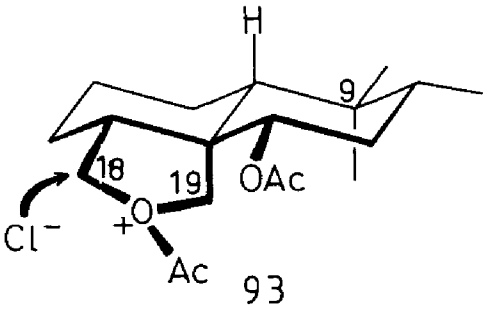
82, R= $(CH_2)_3OAc$, 6α-OAc

90, R=Me, 6α-OAc

91, R=Me, 6β-OAc

92, R= $(CH_2)_3OAc$, 6α-OAc

The very high regiospecificity in this reaction can be explained by assuming the formation of the intermediate acylium ion 93, followed by nucleophylic attack of chlorine at C-18. Nucleophylic attack at C-19 is unfavourable because of steric reasons (especially the 1,3-diaxial interaction between C-19 and the axially orientated methyl at C-9).



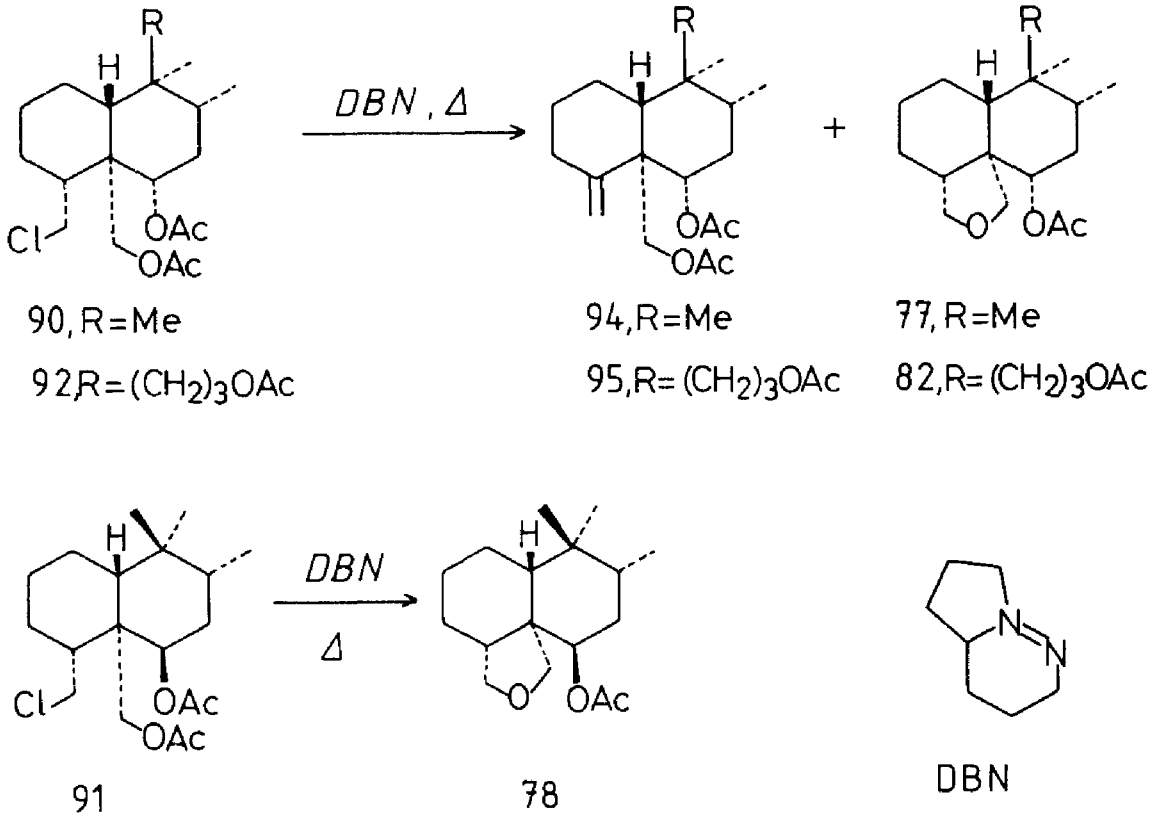
93

Elimination of hydrogen chloride, followed by epoxidation of the exocyclic double bond is now the obvious way for the construction of the desired functionalities.

On heating of 90 in the presence of diazabicyclo-undeceen (DBU) at 150°C no elimination of hydrogen chloride was observed and the

starting material was recovered unchanged. The planned reaction could be effectuated by heating 90 in diazabicyclononene (DBN) (a smaller amidine base) and the exocyclic olefin 94 was thus formed in 75% yield, alongside a small amount of 77, resulting from ring closure. On treatment of the chlorodiacetate 91 with DBN, the cyclic ether 78 was slowly obtained as the only observable product. In this case the axial acetate at C-6 probably prevents the base from approaching C-4 as is essential to the formation of the exocyclic olefin. Treatment of 92 with DBN afforded the exocyclic olefin 95 in 75% yield, accompanied by a small amount of the ring-closure product 82 (see scheme 5.7).

Scheme 5.7

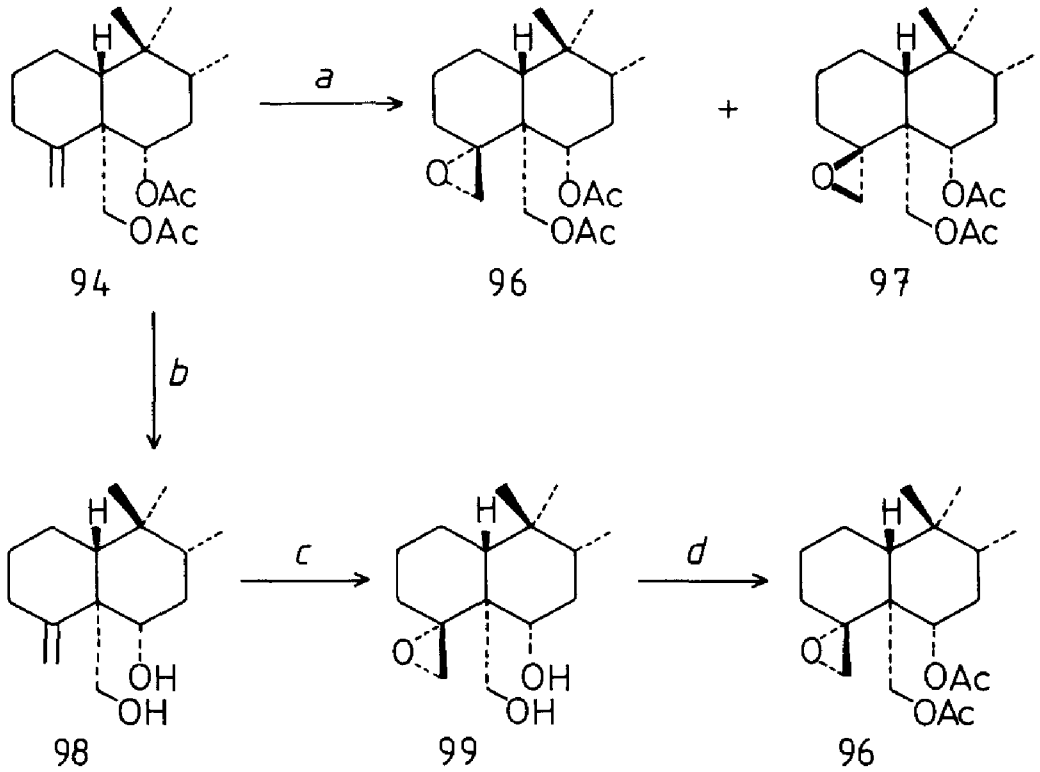


The final step in the synthesis of the model compounds involved the epoxidation of the exocyclic double bond. On treatment of 94 with *m*-chloroperbenzoic acid in ether two isomeric epoxides were formed in a ratio of 1:1. Separation could be accomplished by column chromatography on silica gel. The ^{1}H-NMR spectrum of the first elu-

ted compound showed an AB system (J=4.5Hz) with A and B resonating at 2.53 and 2.71 ppm respectively. In the ^{13}C-NMR spectrum the epoxide ring showed signals at 60.7 (s) and 45.6 (t) ppm. The epoxide protons of the second eluted compound showed an AB pattern with A centered at 2.96 and B at 2.19 ppm with coupling constants of 4Hz. Furthermore long range (W) coupling of the A proton with a proton at C-3 was observed. In the ^{13}C-NMR spectrum the epoxide showed signals at 65.0 (s) and 48.5 (t) ppm. These values strongly suggest that the latter compound possesses structure 96; the NMR data of the epoxide ring being similar to those found for ajugarin I[10]. Consequently the former compound has to be assigned structure 97.

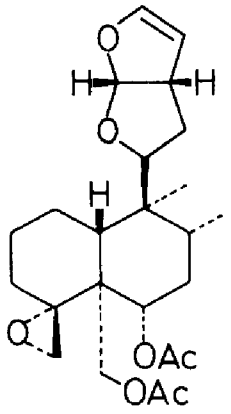
A stereospecific method for the preparation of 96 was achieved *via* epoxidation of diol 98. Hydrolysis of 94 afforded 98 which in turn was treated with VO(acac)$_2$-*tert*-butylhydroperoxide[11]. Subsequent acetylation of the epoxy diol 99 gave 96 as sole product (see scheme 5.8).

Scheme 5.8

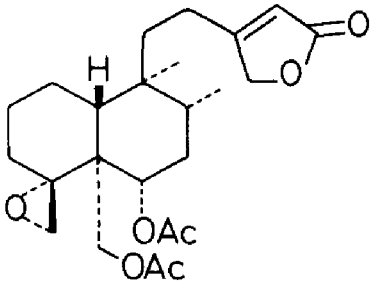


a: m-CPBA; *b*: OH^-, MeOH; *c*: VO(acac)$_2$, *t*-BuOOH, CH_2Cl_2; *d*: Py, Ac_2O, DAP.

Compound 96 represents the decalin unit as is present both in clerodin (100) and in ajugarin I (2).



100



2

Testing the epoxy diacetate 96 for insect antifeedant activity can possibly give a better insight into the relation of this structural unit with the physiological activity of the above mentioned clerodanes[12]. The testing results for 96 as well as for 97 are mentioned in chapter 9 of this thesis.

5.4 EXPERIMENTAL SECTION

General experimental conditions were as given in chapter 3.8.

3,3aβ,4,5,6,6aβ,7,8-Octahydro-7,7-dimethyl-8-oxo-1H-*naphto[1,8aα-c]furan* (73).

Ketone 22 (3.5 g, 15.9 mmol) in acetic acid (25 mL) was treated dropwise with a solution of Br_2 (2.55 g, 15.9 mmol) in ether (15 mL) at room temperature. Dilution with water and extraction with ether, gave the crude *3β-bromo-3,3aβ,4,5,6,6aβ,7,8,9α,10-decahydro-7,7-dimethyl-8-oxo*-1H-*naphto[1,8aα-c]furan* as an oil (4.50 g); IR ($CHCl_3$) 1722 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.96 (s,3H), 1.19 (s,3H), 1.3-2.2 (m,9H) 2.26 (dd, J=13,6Hz, 1H), 3.48 (d, J=8Hz, 1H), 3.95 (dd, J=9,4Hz, 1H), 4.00 (s,2H), 505 (dd, J=13,6Hz, 1H); MS m/e 302-300, 221. The crude bromoketone (4.50 g) was dissolved in DMF and heated at 160°C with LiBr (1.5 g) and Li_2CO_3 (1.5 g) for 6h under nitrogen. The

mixture was poured into water and extracted with ether. The extract was washed with brine and dried over anh. magnesium sulfate. Evaporation of the solvent gave a light-yellow oil. Column chromatography on silica gel with etherhexane (1:1) as the eluant afforded 73 (3.3 g, 94%); mp 64-65°C; IR (neat) 1670, 1615 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.88 (s,3H), 1.15 (s,3H), 1.2-2.3 (m,8H), 3.57 (d, J=8Hz, 1H), 3.71 (d, J=8Hz, 1H), 4.02 (dd, J=9,4Hz, 1H), 4.12 (d, J=9Hz, 1H), 5.87 (d, J=10Hz, 1H), 6.90 (d, J=10Hz, 1H); MS m/e 220(70), 175(63), 147(100).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.50; H, 9.10.

3,3aβ,4,5,6,6aβ,7,8-Octahydro-8α-hydroxy-7,7,8β-trimethyl-1H-*naphto[1,8aα-c]furan* (74).

To a stirred solution of 73 (2.25 g, 10.5 mmol) in 20 mL of anhydrous ether at -78°C was added under nitrogen an ethereal solution of methyllithium (11.2 mmol, 8 mL of a 1.40 M solution in ether). The mixture was allowed to warm to room temperature and quenched with 15 mL of water. The ether layer was separated and the aqueous layer was extracted with ether. The combined organic layers were washed with brine and dried over anh. magnesium sulfate. Evaporation of the solvent gave 74 as a colorless oil (2.44 g, 97%); IR (neat) 3420 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.75 (s,3H), 0.90 (s,3H), 1.0-2.0 (m,8H), 1.18 (s,3H), 2.12 (br,1H), 3.42 (d, J=8Hz, 1H), 3.61 (d, J=8Hz, 1H), 3.93 (dd, J=8,4Hz, 1H), 3.98 (d, J=8Hz, 1H), 5.37 (d, J=10Hz, 1H), 5.70 (d, J=10Hz, 1H); MS m/e 236(100), 221(47), 218(36), 203(84).

Anal. Calcd for $C_{15}H_{24}O_2$: m/e 236.178. Found: m/e 236.179.

3,3aβ,4,5,6,6aβ,7,10-Octahydro-7,7,8-trimethyl-10-oxo-1H-*naphto[1,8aα-c]furan* (75).

To a stirred solution of pyridine chlorochromate (4.50 g, 21 mmol) in 30 mL of methylene chloride was added a solution of 74 (2.44 g, 10.35 mmol) in 20 mL of methylene chloride. The mixture was stirred for 6 h at room temperature, during which time the solution became dark brown and a dark polymer separated. The solution decanted from the black polymer, which in turn was washed with ether. The combined organic layers were washed successively with 2N aqueous sodium hydroxide, 2N hydrochloric acid, and saturated sodium bicarbonate so-

lution. Removal of the solvent gave an oil which was purified by column chromatography on silica gel with ether as the eluant to afford 75 (2.30 g, 95%); mp 56-58°C; IR ($CDCl_3$) 1665, 1640 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 0.96 (s,3H), 1.12 (s,3H), 1.1-2.4 (m,8H), 1.91 (s,3H), 3.44 (d, J=8Hz,1H), 3.76 (d, J=9Hz, 1H), 4.03 (d, J=9Hz, 1H), 4.19 (dd, J=8, 4Hz, 1H), 5.71 (s,1H); MS m/e 234(23), 110(100).

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46; m/e 234.1620. Found: C,76.69; H, 9.16; m/e 234.1630.

*3,3aβ,4,5,6,6aβ,7,8β,9,10-Decahydro-7,7,8α-trimethyl-10-oxo-*1H-*naphto[1,8aα-c]furan* (76).

A solution of 75 (2.0 g, 8.55 mmol) in 20 mL of methanol and 4 mL of triethylamine was hydrogenated at 40 psi using 10% palladium on charcoal as catalyst. After the hydrogen uptake had ceased (4h), the catalyst was removed by filtration. Evaporation of the solvent gave 1.95 g (97%) of 76 as a colorless oil. The product was shown to be pure by GC. IR (neat) 1697 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 0.77 (s,3H), 0.94 (s,3H), 0.95 (d, J=6Hz, 3H), 1.1-2.9 (m,9H), 2.13 (dd, J=13,4Hz, 1H), 2.65 (dd, J=13,13Hz, 1H), 3.35 (d, J=8Hz, 1H), 3.80 (dd, J=8,5Hz, 1H), 4.00 (d, J=9Hz, 1H), 4.06 (d, J=9Hz, 1H). ^{13}C NMR δ 212.5 (s), 72.7 (t), 69.0 (t), 60.6 (s), 54.1 (d), 45.4 (d), 43.7 (t), 40.3 (d), 37.1 (s), 28.6 (t), 27.3 (q), 25.7 (t), 22.2 (t), 16.6 (q), 15.3 (q). MS m/e 236 (100).

Anal. Calcd for $C_{15}H_{24}O_2$: m/e 236.1776. Found: m/e 236.1785.

Reduction of 75 with lithium-ammonia.

To a stirred solution of lithium (21 mg, 3 mmol) in ammonia (25 mL, distilled from sodium) was added under nitrogen enone 75 (250 mg, 1.07 mmol) and ethanol (1 eq.) in tetrahydrofuran (10 mL, freshly distilled from benzophenone-sodium). The ammonia was allowed to evaporate and water was added. Extraction with ether followed by the same workup as described for 22 gave an oil (230 mg), which was purified by column chromatography on silica gel with ether-hexane (1:1) as the eluant to afford 200 mg (80%) of a colorless oil. This product was judged to be pure 76 as indicated by GC and TLC. However ^1H NMR analysis showed the presence of two different secondary methyls at 0.95 and 0.88 ppm in a 1:1 ratio, indicating that a non stereoselective reduction had taken place.

10α-Acetoxy-3,3aβ,4,5,6,6aβ,9,10β-decahydro-7,7,8α-trimethyl-1H-*naphto[1,8aα-c]furan* (77) and *10β-Acetoxy-3,3aβ,4,5,6,6aβ,7,8β,9,10α-decahydro-7,7,8α-trimethyl*-1H-*naphto[1,8aα-c]furan* (78).

A solution of sodium borohydride (350 mg, 9.1 mmol) in 2-propanol (5 mL) was added dropwise during 30 min to a stirred solution of ketone 76 (1.90 g, 8.0 mmol) in 2-propanol (5 mL) at 0°C. The solution was stirred for 6h. Hydrochloric acid (15 mL of a 2N solution) was added and most of the 2-propanol was distilled off under reduced pressure. The resulting aqueous layer was extracted with ether. The combined ethereal layers were washed with 10% aqueous sodium bicarbonate solution and dried over anh. magnesium sulfate. Evaporation of the solvent gave an oil (1.83 g, 96%) which was shown by ^{1}H-NMR to be a mixture of the 6α and 6β hydroxy compounds in a ratio of 9:1 respectively. These two isomers could not be separated by GC or by TLC. This isomeric mixture was treated with pyridine (3 mL), acetic anhydride (3 mL), and 4-*N,N*-dimethylaminopyridine (100 mg). After 6h the pyridine and acetic anhydride were distilled off under reduced pressure. The resulting oily residue was dissolved in methylene chloride (2 mL) and separated by column chromatography on silica gel with ether-hexane as eluant to give 78 (0.2 g, 9%); mp 95-96°C; IR ($CHCl_3$) 1730, 1234 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.51 (s,3H), 0.79 (d, J=6Hz, 3H), 0.92 (s,3H), 1.1-1.9 (m,11H), 2.08 (s,3H), 3.32 (d, J=8Hz, 1H), 3.63 (d, J=9Hz, 1H), 3.84 (dd, J=8,5Hz, 1H), 3.86 (d, J=9Hz, 1H), 4.95 (s, $W_{½}$=6½Hz, 1H); MS m/e 280(0.1), 220 (100), 205(55).

Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.81; H, 10.07. Found: C, 72.69; H, 10.29.

Further elution gave 77 (1.84 g, 82%); mp 87-88°C; IR ($CHCl_3$) 1728, 1235 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.53 (s,3H), 0.84 (d, J=6½Hz, 3H), 0.88 (s,3H), 1.2-1.9 (m,11H), 2.06 (s,3H), 3.35 (d, J=9Hz, 1H), 3.82 (dd, J=9,5Hz, 1H), 3.84 (d, J=9Hz, 1H), 3.94 (d, J=9Hz, 1H), 4.80 (dd, J=13,4Hz, 1H); ^{13}C NMR δ 171.1 (s), 80.5 (d), 74.0 (t), 67.3 (t), 50.9 (s), 50.6 (d), 46.3 (d), 40.7 (d), 36.7 (s), 34.6 (t), 29.9 (t), 27.6 (q), 24.5 (t), 21.7 (q), 21.0 (t), 16.0 (q), 15.3 (q); MS m/e = 280(0.1), 220(95), 205(100).

Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.81; H, 10.07. Found: C, 7.96; H, 10.07.

Reduction of 76 with diisobutyl aluminium-hydride.

To a solution of 76 (2 mg, 0.1 mmol) in 2 mL of anhydrous ether under nitrogen was added a solution of diisobutyl aluminium hydride (0.1 mL of a 25% solution in toluene, 0.18 mmol). The reaction mixture was stirred for 1h at room temperature. Hydrochloric acid was added (0.5 mL of a 2N solution) and the organic layer was separated and dried over anh. magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was acetylated as described above. GC analysis of the acetylated products showed the formation of 77 and 78 in a 94:6 ratio respectively.

7β(3-Acetoxypropyl)-3,3aβ,4,5,6,6aβ,7,10-octahydro-7α,8-dimethyl-1H-naphto-[1,8aα-c]furan (79).

The alcohol 45 (5.3 g, 20 mmol) was acetylated (pyridine-acetic anhydride) and worked up in the usual manner to afford the acetate 79 (5.8 g, 95%) (oil); IR (neat) 1730, 1235 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.75 (s,3H), 1.0-2.0 (m,14H), 1.56 (s,3H), 2.02 (s,3H), 3.39 (d, J=8Hz, 1H), 3.53 (d, J=8Hz, 1H), 3.73 (d, J=8Hz, 1H), 3.78 (dd, J=8, 5Hz, 1H), 3.95 (t,br,2H), 5.33 (d, J=8Hz, 1H); MS m/e 306 (8), 246 (7), 205 (48), 95 (100).

7β(3-Acetoxypropyl)-3,3aβ,4,5,6,6aβ,7,10-octahydro-7α,8-dimethyl-10-oxo-1H-naphto[1,8aα-c]furan (80).

Acetate 79 (5.5 g, 1.8 mmol) was dissolved in acetic acid (60 mL) and acetic anhydride (8 mL) and anhydrous sodium chromate (15 g) was added. The mixture was stirred for 16h at 60°C. Water was added and the mixture was extracted with ether. The combined ether extracts were washed with saturated aqueous sodium bicarbonate solution and dried (anh. sodium sulfate). Evaporation of the solvent afforded 80 (3.16 g, 55%) (oil); IR (neat) 1730, 1665, 1620, 1230 cm^{-1}; ^{1}H-NMR ($CDCl_3$), 0.97 (s,3H), 1.1-2.3 (m,12H), 1.89 (s,3H), 2.03 (s,3H), 3.48 (d, J=8Hz, 1H), 3.80 (d, J=8Hz, 1H), 4.00 (t,br, 2H), 4.03 (dd, J=8,3Hz, 1H), 4.23 (dd, J=8,6Hz, 1H), 5.87 (s,1H); MS m/e 320 (28), 277 (19), 260 (7), 29 (100).

7β-(3-Acetoxypropyl)-3,3aβ,4,5,6,6aβ,7,8β,9,10-decahydro-7α,8α-dimethyl-10-oxo-1H-naphto[1,8aα-c]furan (81).

Enone 80 (3.0 g, 9.4 mmol) was hydrogenated in the same way as described for 75, using palladium on charcoal as catalyst, to give

81 (2.9 g, 97%) (oil); IR 1730, 1700, 1230 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.80 (s,3H), 0.91 (d, J=6Hz, 3H), 1.1-2.2 (m,13H), 2.03 (s,3H), 2.11 (dd, J=1,4Hz, 1H), 2.67 (dd, J=13,13Hz, 1H), 3.12 (d, J=8Hz, 1H), 3.35 (d, J=8Hz, 1H), 3.80 (dd, J=8,5Hz), 4.02 (m,3H); MS m/e 322 (35), 304 (31), 203 (100).

10α-Acetoxy-7β(3-acetoxypropyl)-3,3aβ,4,5,6,6aβ,7,8β,9,10β-decahydro-7α,8α-dimethyl-1H-*naphto[1,8aα-c]furan* (82).

Ketone 81 (2.7 g, 8.4 mmol) was reduced with sodium borohydride and acetylated in the same way as described for ketone 76. Column chromatography on silica gel using ether as the eluant afforded 82 (2.1 g, 66%), (oil); IR (neat) 1730, 1233 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.53 (s,3H), 0.69 (d, J=6Hz, 3H), 1.1-1.9 (m,15H), 2.05 (s, 6H), 3.35 (d, J=8Hz, 1H), 3.80 (dd, J=8,3Hz, 1H), 3.86 (d, J=9Hz, 1H), 3.96 (d, J=9Hz, 1H), 4.00 (t,br,2H), 4.75 (dd, J=13,5Hz, 1H); MS m/e 323 (0.5) (M^+-43), 306 (15), 205 (100), 203 (36).

10α-Acetoxy-3,3aβ,4,5,6,6aβ,7,8,9,10β-decahydro-7,7,8α-tri-methyl-3-oxo-1H-*naphto[1,8aα-c]furan* (83).

Acetate 77 (140 mg, 0.5 mmol) was oxidized with ruthenium tetroxide in the same way as described for the preparation of lactone 23. After the usual workup lactone 83 (140 mg, 95%) was obtained, m.p. 146°C; IR (KBr) 1765, 1728, 1225 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.57 (s,3H), 0.89 (d, J=6Hz, 3H), 0.90 (s,3H), 1.2-2.0 (m,11H), 2.00 (s,3H), 4.33 (d, J=9Hz, 1H), 4.41 (d, J=9Hz, 1H), 4.70 (dd, J=12,5Hz, 1H); MS m/e 294 (15), 234 (100).

Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.35; H, 8.93.

10α-Acetoxy-7β(3-acetoxypropyl)-3,3aβ,4,5,6,6aβ,7,8β,9,10β-decahydro-7α,8α-dimethyl-3-oxo-1H-*naphto[1,8aα-c]furan* (84).

The diacetate 82 (600 mg, 1.6 mmol) was oxidized with ruthenium tetroxide in the same way as described for the preparation of lactone 23. After the usual workup lactone 84 (580 mg, 93%) was obtained (oil); IR (neat) 1765, 1725, 1230 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.60 (s,3H), 0.83 (d, J=6Hz, 3H), 1.1-2.2 (m,15H), 2.03 (s,6H), 4.00 (t,br,2H), 4.35 (d, J=9Hz, 1H), 4.42 (d, J=9Hz, 1H), 4.70 (dd, J=12,5Hz, 1H); MS m/e 380 (11), 320 (23), 279 (5), 260 (16), 219 (100).

3,3aβ,4,5,6,6aβ,7,8β,9,10β-Decahydro-10α-hydroxy-7,7,8α-trimethyl-3-oxo-1H-naphto[1,8aα-c]furan (87).

The lactone 83 (600 mg, 2.04 mmol) was dissolved in methanol (15 mL) and a solution of potassium hydroxide (400 mg) in water (5 mL) was added. The mixture was stirred for 6h. Most of the methanol was distilled off under reduced pressure and the residue was acidified and extracted with ether. The extract was dried (anh. magnesium sulfate) and concentrated to afford 87 (490 mg, 95%); IR (neat) 3400, 1765 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.53 (s,3H), 0.87 (d, J=6Hz,3H), 1.1-2.3 (m,11H), 3.50 (dd, J=12,4Hz, 1H), 3.77 (s,br,1H), 4.29 (d, J=10Hz, 1H), 4.39 (d, J=10Hz, 1H); MS m/e 252 (3), 234 (100).

3aβ,4,5,6,6aβ,7,8β,9-Octahydro-7,7,8α-trimethyl-1H-*naphto[1,8aα-c]furan-3,10-dione* (88).

To a solution of 87 (490 mg, 1.95 mmol) in acetone (40 mL) was added a solution of sodium bichromate (200 mg) in 4N sulfuric acid (4 mL). Most of the acetone was distilled off and the residue was extracted with ether. The extract was washed with brine and dried over anh. magnesium sulfate and concentrated to give 88 (450 mg, 92%); IR (neat) 1765, 1698 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.80 (s,3H), 0.97 (s,3H), 0.98 (d, J=6Hz, 3H), 1.1-2.0 (m,9H), 2.24 (dd, J=14,4Hz, 1H), 2.69 (dd, J=14,13 Hz, 1H), 4.34 (d, J=9Hz, 1H), 5.54 (d, J=9Hz, 1H); MS m/e 250 (14), 222 (20), 207 (10), 139 (100).

10,10-Ethylenedioxy-3,3aβ,4,5,6,6aβ,7,8β,9,10-decahydro-7,7,8α-trimethyl-3-oxo-1H-*naphto[1,8aα-c]furan* (89).

The ketone 88 (450 mg, 1.8 mmol) was dissolved in benzene and refluxed in the presence of ethylene glycol (400 mg) and *p*-toluene sulfonic acid (20 mg) under a water trap. After 16h. the mixture was allowed to cool and washed with saturated aqueous sodium bicarbonate solution. The benzene layer was dried over anh. magnesium sulfate and concentrated to give 89 (500 mg, 95%); IR (neat) 1765 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.57 (s,3H, 0.87 (d, J=6Hz, 3H), 0.90 (s, 3H), 1.0-2.2 (m,10H), 2.46 (dd, J=10,7Hz, 1H), 3.96 (s,4H), 4.35 (s,2H); MS m/e 294 (3), 248 (67), 219 (73), 27 (76), 103 (100).

Attempted alpha bromination of lactone (89).

To a solution of 89 (295 mg, 1 mmol) in dry tetrahydrofuran (8 mL) was added under nitrogen at -78°C lithium diisopropylamide (2 mL

of a 0.5N solution in tetrahydrofuran). After stirring for 4h 1,2-dibromoethane (350 mg) was added and the mixture was allowed to warm to room temperature. After the usual workup only starting material could be recovered.

9α-Acetoxymethyl-8α-chloromethyl-3α,4,4,-trimethyl-trans-*decalin-1α-ol acetate* (90).

A mixture of 77 (1.68 g, 6.0 mmol), pyridine hydrochloride (4 g, 33 mol), and acetic anhydride (10 mL) was heated under reflux for 18h. The acetic anhydride was evaporated under reduced pressure. The resulting dark brown residue was taken up in 3 mL of methylene chloride and chromatographed on silica gel with ether-hexane (1:1) as the eluant to give 90 (1.72 g, 80%); mp 97-98°C; IR (KBr) 1720, 1230 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.66 (s,3H), 0.83 (d, J=6Hz, 3H), 0.88 (s,3H), 1.2-2.0 (m,11H), 2.00 (s,3H), 2.04 (s,3H), 3.47 (dd, J=11, 9Hz, 1H), 3.96 (dd, J=11,3.5Hz, 1H), 4.20 (d, J=13Hz, 1H), 4.73 (d, J=13Hz, 1H), 4.75 (dd, J=12,4Hz, 1H); MS m/e 323 (M^+-Cl)(0.5), 240-238(30), 227-225(100).

Anal Calcd. for $C_{19}H_{31}ClO_4$: C, 63.58; h, 8.71. Found: C, 63.31; H, 8.87.

Further elution gave 77 (210 mg, 13%).

9α-Acetoxymethyl-8α-chloromethyl-3α,4,4-trimethyl-trans-*decalin-1β-ol acetate* (91).

The acetate 78 (150 mg, 0.53 mmol) was refluxed for 18h in acetic anhydride (2 mL) and pyridine hydrochloride (05. g, 4.2 mmol). Workup as described above afforded 91 (130 mg, 69%); mp 116-118°C; IR (KBr) 1725, 1230 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.70 (s,3H), 0.79 (d, J=7Hz, 3H), 0.93 (s,3H), 1.2-2.0 (m,11H), 2.03 (s,3H), 2.13 (s,3H), 3.10 (dd, J=11,9Hz, 1H), 3.62 (dd, J=11,2Hz, 1H), 4.33 (s,2H), 5.20 (s, $W_{1/2}$=7Hz, 1H); MS m/e 323 (M^+-Cl)(0.5), 317-315(0.2), 258-256(19), 240-238(46), 227-225(100).

Anal. Calcd for $C_{19}H_{31}ClO_4$: C, 63.58; H, 8.71. Found: C, 63.70; H, 8.79.

9α-Acetoxymethyl-4β(3-acetoxypropyl)-8α-chloromethyl-3α,4α-dimethyl-trans-*decalin-1α-ol acetate* (92).

The acetate 82 (600 mg, 1.6 mmol) was refluxed for 16h. in ace-

tic anhydride (3 mL) in the presence of pyridine hydrochloride (1.0 g, 8.2 mmol). Workup as described above afforded 92 (540 mg, 76%) (oil); IR (neat) 1725, 1230 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.70 (s,3H), 0.81 (d, J=6Hz, 3H), 1.1-1.9 (m, 15H); 2.05 (s,9H), 3.49 (dd, J=10,9Hz, 1H), 3.96 (dd, J=10,3Hz, 1H), 4.03 (s,br,2H), 4.25 (d, J=13Hz, 1H), 4.75 (dd, J=12,5Hz), 4.80 (d, J=13Hz, 1H); MS m/e 348 (M^+-96/98) (0.7), 324/326 (15), 288 (17), 223/225 (61), 187 (100).

Attempted ether cleavage of 77 by acetyl-p-toluene-sulfonate.

A mixture of 77 (28 mg, 0.1 mmol) and acetyl-*p*-toluene-sulfonate (43 mg, 0.2 mmol) in acetonitrile (1 mL) was refluxed overnight. The acetonitrile was evaporated under reduced pressure and ether and water were added. The ether layer was separated and dried over anh. magnesium sulfate. Analysis (GC, TLC and ^{1}H-NMR) showed only starting material.

9α-Acetoxymethyl-8-methylene-3α,4,4-trimethyl-trans-*decalin-1α-ol acetate* (94).

A mixture of 90 (1.3 g, 3.64 mmol) and diazabicyclononene (DBN) (2 mL) was heated at 140°C under nitrogen for 6h. The resulting brown reaction mixture was dissolved in 2 mL of methylene chloride and chromatographed on a silica gel column with ether-hexane as the eluant to afford 94 (880 mg, 75%) as a colorless oil which crystallized upon standing; mp 83-84°C; IR (neat) 1730, 1641, 1240 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.69 (s,3H), 0.86 (s,3H), 0.87 (d, J=6Hz, 3H), 1.1-2.2 (m,10H), 1.93 (s,3H), 1.97 (s,3H), 4.24 (d, J=12Hz, 1H), 4.47 (s,1H), 4.71 (s,1H), 4.76 (d, J=12Hz, 1H), 5.10 (dd, J=11,5Hz, 1H); MS m/e 262 (M^+-60)(4), 249(3), 232(12), 220(13), 202(86), 187 (100).

Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.90; H, 9.09.

Further elution gave 90 (185 mg, 18%).

Reaction of 91 with DBN.

The chlorodiacetate 91 (100 mg, 0.28 mmol) was dissolved in diazabicyclononene (DBN), (1 mL) and heated at 140°C overnight. Workup as described afforded 91 (70 mg, 89%) as sole product.

*9α-Acetoxymethyl-4β(3-acetoxypropyl)-8-methylene-3α,4α-dimethyl-*trans-*decalin-1α-ol acetate* (95).

The chloride 92 (220 mg, 0.5 mmol) was dissolved in diazabicyclononene (DBN), (1 mL) and heated at 140°C overnight. Workup as described above afforded 95 (140 mg, 71%); IR (neat) 1730, 1680, 1240 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.72 (s,3H), 0.81 (d, J=6Hz, 3H), 1.1-2.2 (m,14H), 1.97 (s,3H), 2.00 (s,3H), 2.04 (s,3H), 4.00 (t,br,2H), 4.25 (d, J=12Hz, 1H), 4.47 (s,1H), 4.73 (s,1H), 4.74 (d, J=12Hz,1H), 5.03 (dd, J=11Hz, 1H); MS m/e 348 (M^+-60) (1), 306 (2), 288 (16), 187 (100).

9α-Acetoxymethyl-8α,8'-epoxy-3α,4,4-trimethyl-trans-*decalin-1α-ol-acetate* (96) and
9α-Acetoxymethyl-8α,8'-epoxy-3α,4,4-trimethyl-trans-*decalin-1α-ol-acetate* (97).

To a solution of diacetate 94 (700 mg, 2.18 mmol) in ether (15 mL) was added *meta*-chloroperbenzoic acid (2.5 mmol), 570 mg admixed with 30% *meta*-chlorobenzoic acid). The solution was allowed to stir for 16h. at room temperature and then washed with 10% aqueous sodium sulfite solution followed by saturated sodium bicarbonate solution. The ethereal solution was dried over anh. magnesium sulfate and concentrated under reduced pressure to afford an oil which was shown by GC to consist of the two isomeric epoxides. Separation of the mixture by column chromatography on silica gel with ether-hexane (4:1) as the eluant gave 97 (290 mg, 40%), mp 130-140°C; IR ($CHCl_3$) 1725, 1250 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.66 (s,3H), 0.83 (d, J=6Hz, 3H), 0.90 (s,3H), 1.0-1.9 (m,10H), 1.93 (s,3H), 2.02 (s,3H), 2.53 (d,4.5Hz, 1H), 2.71 (d, J=4.5Hz, 1H), 4.28 (d, J=12Hz, 1H); 4.65 (dd, J=11,5Hz, 1H), 4.81 (d, J=12Hz, 1H). ^{13}C-NMR 170.6 (s), 169.7 (s), 72.6 (d), 61.7 (t), 60.7 (s), 55.0 (t), 51.2 (d), 45.6 (s), 39.3 (d), 36.1 (s), 32.6 (t), 31.7 (t), 28.0 (q), 23.4 (t), 21.5 (t), 21.1 (q), 15.9 (q), 15.7 (q); MS m/e 323 (M^+-15)(0.5), 308(8), 295(30), 265 (49), 223(100).

Anal. Calcd for $C_{19}H_{30}O_5$: C, 67.43; H, 8.94. Found: C, 67.42; H, 8.66.

Further elution gave 96 (325 mg, 43%); mp 110-111°C; IR ($CHCl_3$) 1715, 1250 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.69 (s,3H), 0.86 (d, J=6Hz, 3H), 0.90 (s,3H, 1.0-1.9 (m,10H), 1.93 (s,3H), 2.09 (s,3H), 2.19 (d,

J=4Hz, 1H), 2.96 (dd, J=4,2Hz, 1H), 4.35 (d, J=12Hz, 1H), 4.73 (dd, J=11, 5Hz, 1H), 4.81 (d, J=12Hz, 1H); ^{13}C-NMR δ 171.0 (s), 170.1 (s), 72.6 (d), 65.0 (s), 6106 (t), 54.0 (d), 48.5 (t), 45.5 (s), 40.4 (d), 36.2 (s), 33,5 (t), 32.7 (t), 28.5 (q), 25.2 (t), 21.4 (t), 21.2 (q), 15.9 (q), 15.8 (q); MS m/e 338(0.5), 323(0.5), 308(8), 295(33), 265(56), 223(100).

Anal. Calcd for $C_{19}H_{30}O_5$: C, 67.43; H, 8.94. Found: C, 67.22; H, 8.72.

9α-Hydroxymethyl-8-methylene-3α,4,4-trimethyl-trans-*decalin-1α-ol* (98).

Diacetate 94 (110 mg, 0.34 mmol) was dissolved in dry ether (2 mL) and lithium aluminium hydride (50 mg, 1.3 mmol) was added under nitrogen. The mixture was stirred at room temperature for 1h. and water (0.5 mL) and 6N hydrochloric acid (1 mL) were added. The ether layer was separated and the water layer was extracted with ether. The combined ethereal extracts were dried over magnesium sulfate and concentrated to afford 98 (78 mg, 96%); mp. 126-128; IR ($CHCl_3$) 3340, 1640 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.61 (s,3H), 0.83 (s,3H), 0.88 (d, J=6Hz, 3H), 1.0-2.3 (m,10H), 3.26 (s,br,2H), 4.00 (m,3H), 4.96 (s,1H), 5.12 (s,1H); MS m/e 238, 220, 190, 120.

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.41; H, 10.73.

Stereospecific epoxidation of diol (98).

To a stirred solution of 98 (60 mg, 0.25 mmol) in methylene chloride (1 mL) was added $VO(acac)_2$ (10 mg) and *tert*-butylhydroperoxide (0.5 mmol, 55 μL of a 80% solution). The mixture was stirred overnight at room temperature and then chromatographed on a short silica gel column with ether as the eluant. The resulting clear oil was acetylated and worked up as described for 77 to afford 96 (65 mg, 77%) as the only product.

5.5 REFERENCES AND NOTES.

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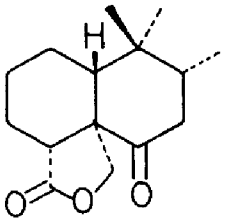
5 See chapter 3.7.

6 Ruthenium tetroxide oxidation of ketone 76 gave a 1:1 mixture of lactone 88 and the isomer *i*. Ruthenium tetroxide oxidation of acetate 77, however, did proceed in a regiospecific manner, affording lactone 83.



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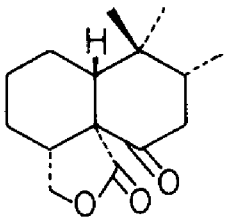

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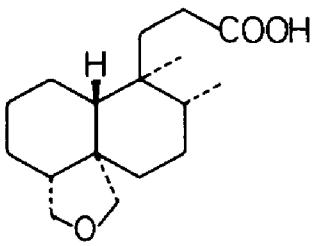
12 See also chapter 1.4.

6 *THE CRYSTAL STRUCTURE OF 9α-ACETOXYMETHYL-8α,8'-EPOXY-3α,4,4-TRIMETHYL-*TRANS*-DECALIN-1α-OL ACETATE.*

6.1 INTRODUCTION.

As described before, the reductive alkylation of octalone 21 to the decalone 22 or 31 was assumed to afford a *trans* A/B ring junction (see chapter 3.7 and 4.2). This assumption was based upon the results of analogous reductive alkylations which were reported in the literature. For our intermediates, however, no direct spectroscopic evidence could be obtained to support this assumption. At a later stage we were able to correlate the carboxylic acid 49 with a degradation product of a *trans* clerodane (51) (cf. chapter 4.4) which confirmed a *trans* A/B ring junction for our compounds. Some of the ^{13}C-NMR values of the epoxy diacetate 96, however, strongly differed from the values for corresponding carbon atoms in ajugarin I (2)[1]. Two different explanations may be given for this: either some of the ^{13}C-NMR assignments of ajugarin I had to be reversed (see also chapter 8) or we did obtain a *cis* decalin after all. Since an X-ray analysis of ajugarin I was available[2] there was no doubt about its structure. In addition the *trans* configuration of the clerodane 51 was assigned only on the basis of chemical evidence, which gave rise to some doubts about the correctness of our correlations.



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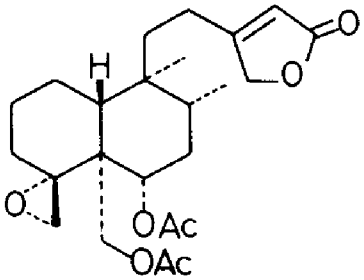

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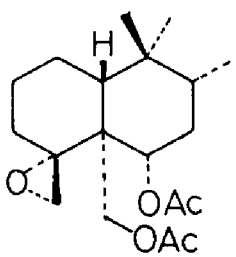


96

A definitive proof of our stereochemical assignments could be obtained by an X-ray analysis of the epoxy diacetate 96. This work was carried out by Dr. C.H. Stam and Mr. M. Konijn at the Laboratory of Crystallography of the University of Amsterdam.

6.2 RESULTS AND DISCUSSION.

Crystals of the title compound are monoclinic, space group $P2_1/n$ with 4 molecules in a unit cell of dimensions: a = 8.215(2), b = 10.850(2), c = 21.147(4) Å and β = 98.09(2)°.

1032 Intensities above the 2.5σ level were collected on a NONIUS CAD 4 automatic diffractometer employing graphite monochromatized CuK_α radiation.

The structure was solved by means of the symbolic addition program set SIMPEL[3]. Refinement proceeded by block-diagonal least-squares calculation anisotropic for C and O and isotropic for H. The H atoms were located in a ΔF-synthesis. The final R value was 0.054. The final coordinates are listed in table 1. Table 2 lists the bond distances and angles.

From the three dimensional structure which is given in fig. 1 it is clear that the A/B ring junction of the molecule is *trans*. Furthermore the correctness of the other stereochemical assignments is confirmed.

Table 1.
Fractional coordinates
Calculated standard deviations in parentheses.

	X	Y	Z
C(1)	-.0690(10)	.3729(9)	.2690(4)
C(2)	-.2266(12)	.3078(11)	.2807(5)
C(3)	-.1903(11)	.2005(11)	.3272(4)
C(4)	-.9853(9)	.2487(8)	.3876(3)
C(5)	.0736(8)	.3051(6)	.3804(4)
C(6)	.1645(8)	.3594(7)	.4425(3)
C(7)	.3125(8)	.4332(7)	.4328(4)
C(8)	.2741(9)	.5410(7)	.3875(4)
C(9)	.1813(9)	.5019(7)	.3217(3)
C(10)	.0352(8)	.4153(7)	.3330(3)
C(11)	-.1052(7)	.1774(6)	.4437(3)
C(12)	-.1908(9)	.2940(9)	.4364(4)
C(13)	.1808(10)	.2086(7)	.3529(3)
C(14)	.1659(6)	.0893(5)	.3826(3)
C(15)	.3074(10)	.0314(8)	.4045(4)
C(16)	.4370(7)	.0686(8)	.3965(4)
C(17)	.2729(14)	-.0837(9)	.4378(5)
C(18)	.2191(6)	.2602(5)	.4863(2)
C(19)	.1736(9)	.2604(8)	.5445(4)
C(20)	.1045(9)	.3469(6)	.5646(3)
C(21)	.2204(12)	.1460(9)	.5814(4)
C(22)	.4325(11)	.6146(8)	.3839(5)
C(23)	.1071(10)	.6218(8)	.2888(4)
C(24)	.2964(9)	.4462(7)	.2798(4)

Hydrogen atom parameters

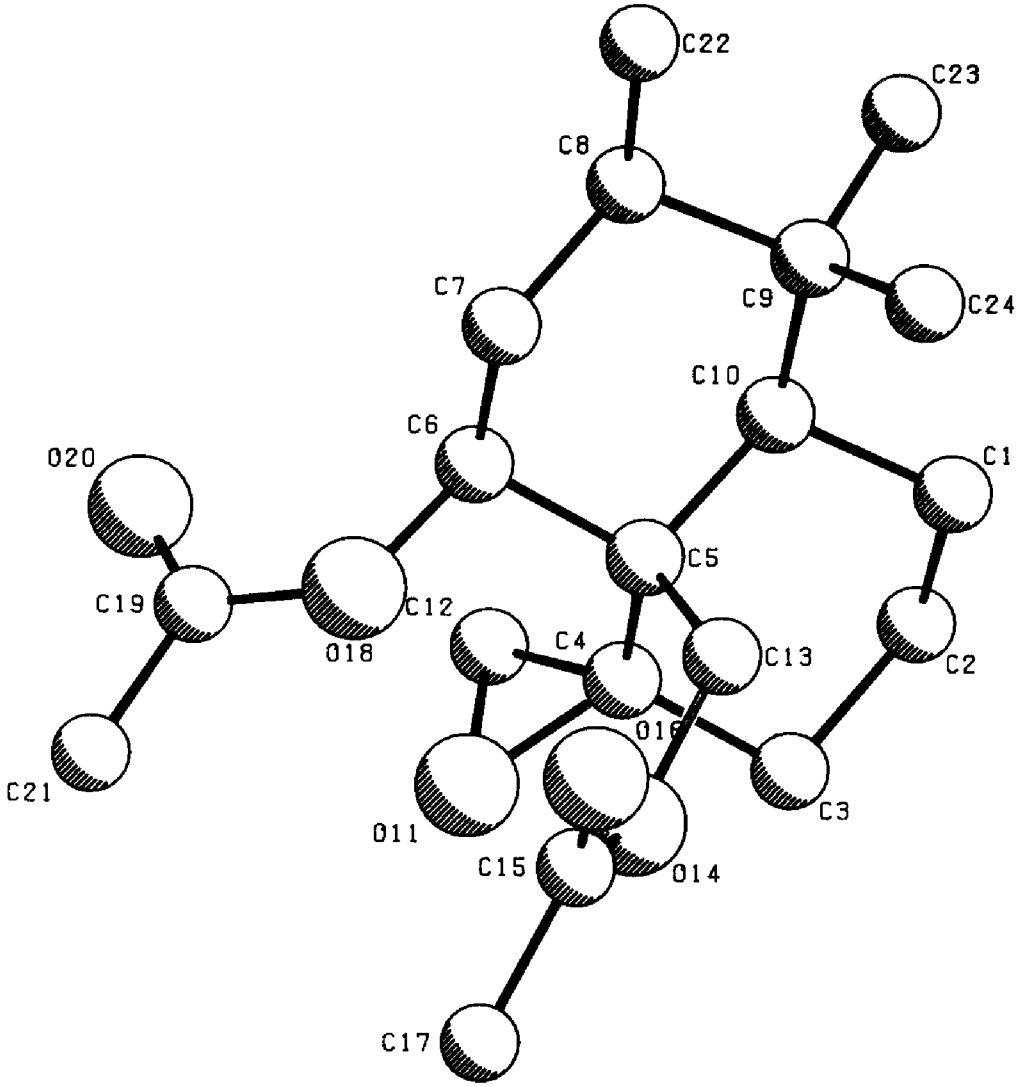
	X	Y	Z	U(A^2)
H(11)	.010(11)	.324(8)	.250(4)	.10(3)
H(12)	-.096(8)	.447(6)	.244(3)	.05(2)
H(21)	-.293(11)	.283(10)	.236(5)	.13(4)
H(22)	-.305(14)	.386(11)	.296(6)	.17(5)
H(31)	-.121(9)	.144(7)	.305(4)	.08(3)
H(32)	-.297(8)	.162(6)	.343(3)	.04(2)
H(6)	-.046(6)	.466(5)	.356(3)	.02(2)
H(71)	.371(8)	.468(7)	.479(3)	.07(3)
H(72)	.398(7)	.383(6)	.416(3)	.05(2)
H(8)	.193(7)	.594(6)	.408(3)	.05(2)
H(10)	.085(7)	.415(6)	.466(3)	.05(2)
H(121)	-.147(11)	.369(9)	.473(4)	.12(3)
H(122)	-.310(10)	.280(8)	.431(4)	.09(3)
H(131)	.299(10)	.233(8)	.360(4)	.10(3)
H(132)	.152(8)	.182(6)	.307(3)	.06(2)
H(171)	.212(10)	-.071(8)	.468(5)	.11(3)
H(172)	.206(11)	-.141(9)	.414(4)	.12(4)
H(173)	.378(12)	-.123(9)	.464(5)	.14(4)
H(211)	.180(11)	.089(9)	.556(5)	.13(4)
H(212)	.336(11)	.124(9)	.583(5)	.13(4)
H(213)	.194(18)	.151(14)	.627(7)	.25(7)
H(221)	.453(8)	.649(7)	.428(4)	.07(2)
H(222)	.513(10)	.551(8)	.366(4)	.10(3)
H(223)	.409(9)	.682(7)	.353(4)	.08(3)
H(231)	.051(9)	.597(8)	.238(4)	.09(3)
H(232)	.016(9)	.641(7)	.308(4)	.08(3)
H(233)	.194(8)	.691(6)	.289(3)	.05(2)
H(241)	.373(8)	.507(6)	.268(3)	.05(2)
H(242)	.375(9)	.361(7)	.300(3)	.07(3)
H(243)	.242(9)	.403(7)	.241(4)	.07(2)

Table 2
Bond distances (Å) and bond angles (°) with calculated standard deviations in parentheses.

C(1)	-C(2)	1.53(2)	C(2)	C(1)	C(10)	111.7(7)
C(1)	-C(10)	1.57(2)	C(1)	C(2)	C(3)	111.4(8)
C(2)	-C(3)	1.53(2)	C(2)	C(3)	C(4)	108.4(9)
C(3)	-C84)	1.49(2)	C(3)	C(4)	C(5)	115.0(7)
C(4)	-C(5)	1.54(1)	C(3)	C(4)	O(11)	115.9(8)
C(4)	-O(11)	1.43(1)	C(3)	C(4)	C(12)	116.9(7)
C(4)	-C(12)	1.47(2)	C(5)	C(4)	O(11)	117.0(6)
C(5)	-C(6)	1.53(1)	C(5)	C(4)	C(12)	120.9(7)
C(5)	-C(10)	1.56(1)	O(11)	C(4)	C(12)	59.9(5)
C(5)	-C(13)	1.53(2)	C(4)	C(5)	C(6)	113.8(7)
C(6)	-C(7)	1.49(1)	C(4)	C(5)	C(10)	105.3(6)
C(6)	-O(18)	1.45(1)	C(4)	C(5)	C(13)	109.8(6)
C(7)	-C(8)	1.52(1)	C(6)	C(5)	C(10)	106.6(6)
C(8)	-C(9)	1.55(1)	C(6)	C(5)	C(13)	110.5(5)
C(8)	-C(22)	1.54(1)	C(10)	C(5)	C(13)	110.7(6)
C(9)	-C(10)	1.57(1)	C(5)	C(6)	C(7)	113.3(6)
C(9)	-C(23)	1.56(1)	C(5)	C(6)	O(18)	109.4(6)
C(9)	-C(24)	1.51(1)	C(7)	C(6)	O(18)	107.5(6)
O(11)	-C(12)	1.45(2)	C(6)	C(7)	C(8)	113.5(6)
C(13)	-O(14)	1.45(1)	C(7)	C(8)	C(9)	112.9(7)
O(14)	-C(15)	1.34(1)	C(7)	C(8)	C(22)	109.2(6)
C(15)	-O(16)	1.17(1)	C(9)	C(8)	C(22)	114.2(8)
C(15)	-C(17)	1.48(1)	C(8)	C(9)	C(10)	108.5(6)
O(18)	-C(19)	1.34(1)	C(8)	C(9)	C(23)	106.5(6)
C(19)	-O(20)	1.20(2)	C(8)	C(9)	C(24)	111.5(6)
C(19)	-C(21)	1.49(2)	C(10)	C(9)	C(23)	108.0(6)
			C(10)	C(9)	C(24)	113.9(6)
			C(23)	C(9)	C(24)	108.1(6)

C(1)	C(10)	C(5)	111.5(7)	O(14)	C(15)	O(16)	123.2(8)
C(1)	C(10)	C(9)	112.1(6)	O(14)	C(15)	C(17)	110.1(8)
C(5)	C(10)	C(9)	117.8(5)	O(16)	C(15)	C(17)	126.7(9)
C(4)	O(11)	C(12)	61.4(6)	C(6)	O(18)	C(19)	119.1(6)
C(4)	C(12)	O(11)	58.7(6)	O(18)	C(19)	O(20)	122.2(8)
C(5)	C(13)	O(14)	110.9(6)	O(18)	C(19)	C(21)	113.4(7)
C(13)	O(14)	C(15)	116.4(6)	O(20)	C(19)	C(21)	124.4(8)

Fig. 1.
Three dimensional structure of 96.



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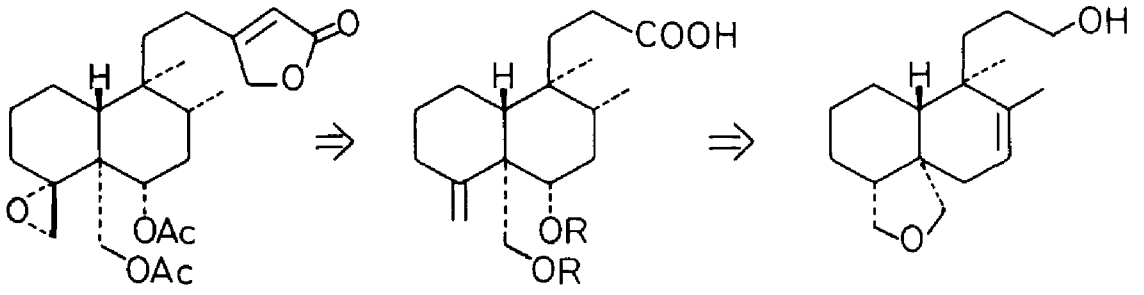
7 *INVESTIGATIONS INTO THE TOTAL SYNTHESIS OF AJUGARIN I.*

7.1 INTRODUCTION.

In chapters 4 and 5 we developed synthetic methods for the construction of a butenolide containing side chain and a *trans* decalin with epoxydiacetate substituents.

Next we wanted to develop a synthetic approach in which the decalin moiety and the side chain are constructed in the same molecule, thus leading to ajugarin I. The sequence of reactions again plays a crucial role in this approach. Since the epoxide is very sensitive towards most chemical reagents, the construction of this group was planned in the final stages. The first steps in the approach grossly parallel the synthesis of the triacetate 95 (cf. chapter 5.3). The synthesis of the side chain was based upon the transformation of a propanoic acid substituent at C-9[1]. The introduction of this substituent was planned in the first stages of the synthesis. This led us to the retrosynthetic plan which is outlined in scheme 7.1.

Scheme 7.1

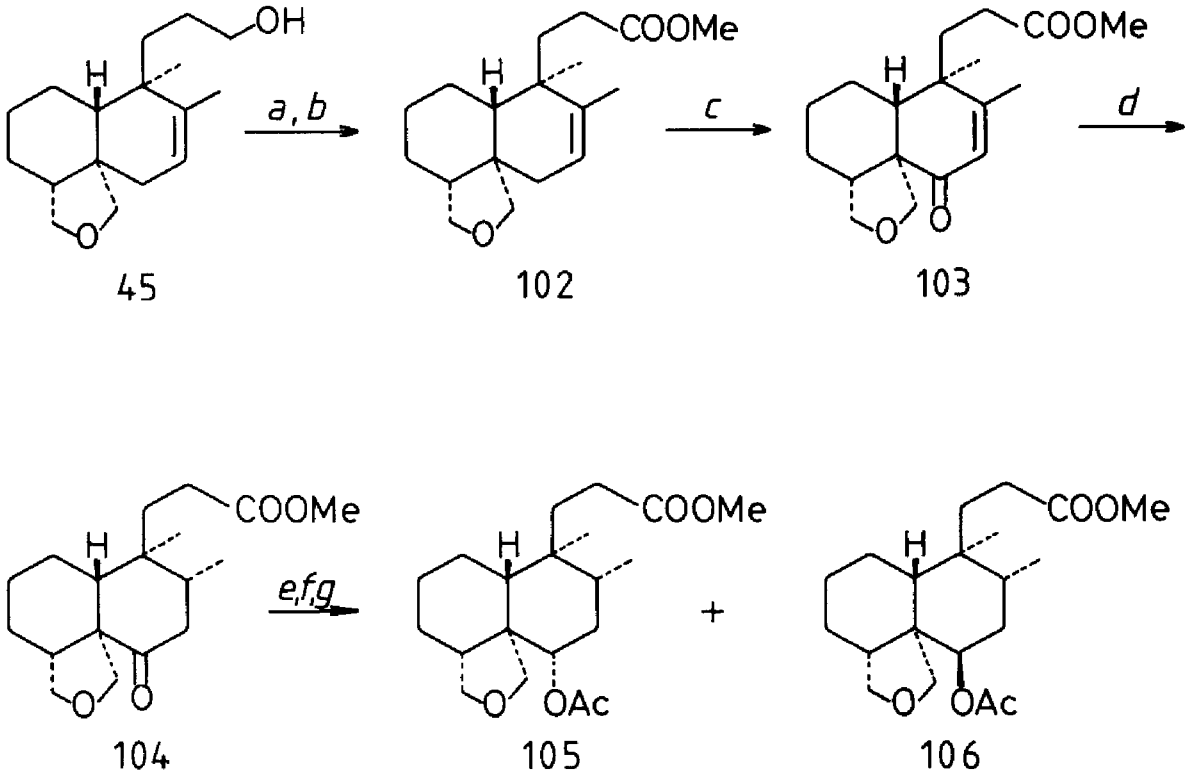


7.2 RESULTS AND DISCUSSION.

The alcohol 45 was chosen as the starting material. Oxidation with Jones' reagent afforded the carboxylic acid 101 in high yield,

which was converted into the methyl ester 102 on treatment with diazomethane. Allylic oxidation (chromic acid in acetic acid) of 102 gave the enone 103, which was hydrogenated to the ketone 104. Reduction of this compound with lithium tri-*t*-butoxy aluminium hydride gave a mixture of the equatorial and axial alcohols in a 4:1 ratio. Acetylation and separation on silica gel afforded the equatorial acetate 105 in 71% yield and the axial acetate 106 (18%) (scheme 7.2).

Scheme 7.2

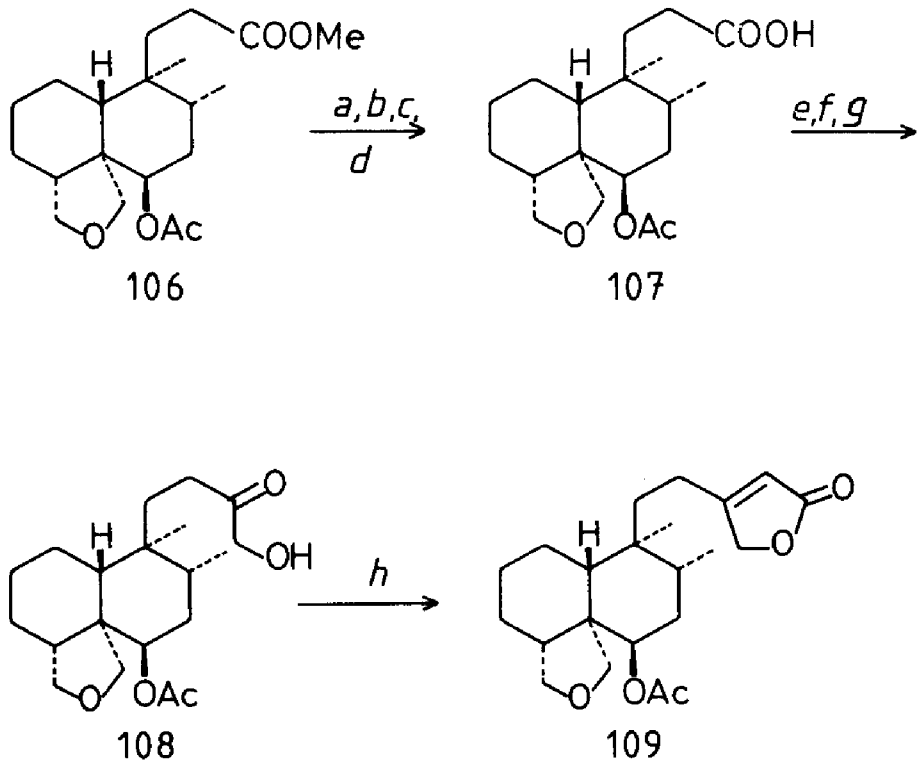


a: Jones' reagent; *b*: CH_2N_2; *c*: CrO_3,AcOH; *d*: H_2,Pd/C; *e*: $LiH(tBuO)_3Al$; *f*: H_3O^+; *g*: Py,Ac_2O, DAP.

In order to obtain model compounds for ^{13}C-NMR studies (cf. chapter 8), the propanoic acid methyl ester in 106 was transformed into a butenolide side chain in the following way[1].

Hydrolysis and reacetylation of 106 gave the carboxylic acid 107. This compound was treated with thionyl chloride, followed by reaction with diazomethane. The intermediate diazoketone was hydrolysed with aqueous sulfur dioxide solution to give the hydroxy ketone 108. The overall yield of these transformations was 53%. The butenolide 109 was prepared in 89% yield by reaction of 108 with triphenylphosphoranylidene ketene (cf. chapter 4.4) (see scheme 7.3).

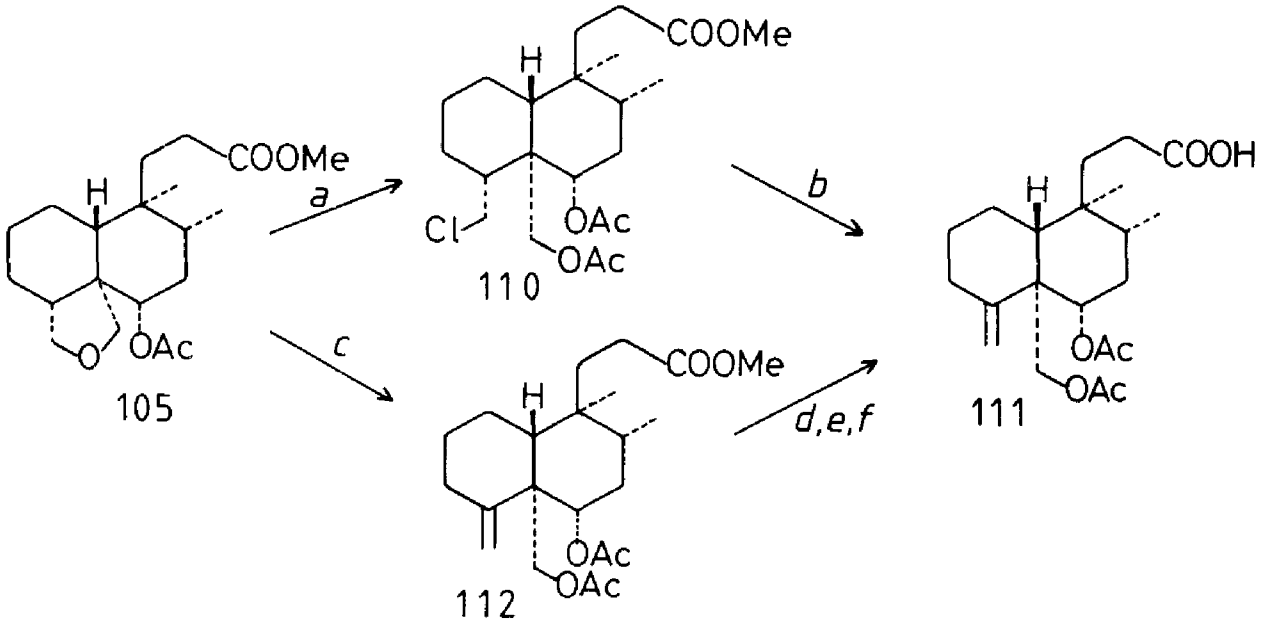
Scheme 7.3

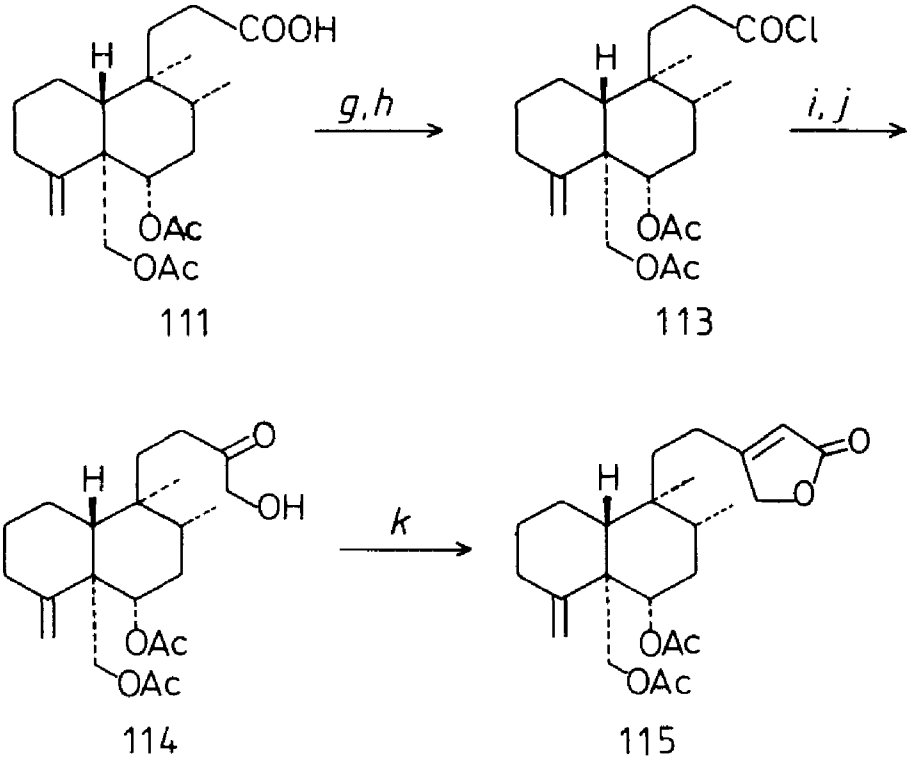


a: OH^-, H_2O,MeOH; *b*: H_3O^+; *c*: Ac_2O,Py; *d*: H_2O,Py; *e*: $SOCl_2$; *f*: CH_2N_2; *g*: H_2O,SO_2; *h*: $Ph_3P{=}C{=}C{=}O$.

After this side-track we continued with our original synthetic plans. Treatment of the acetate 105 with pyridine hydrochloride in refluxing acetic anhydride gave the chlorodiacetate 110 in high yield. Dehydrohalogenation of this compound with DBN in refluxing xylene afforded the carboxylic acid 111 in a relatively low yield (40%)[2]. On reaction of 105 with pyridine hydrobromide the olefin

Scheme 7.4



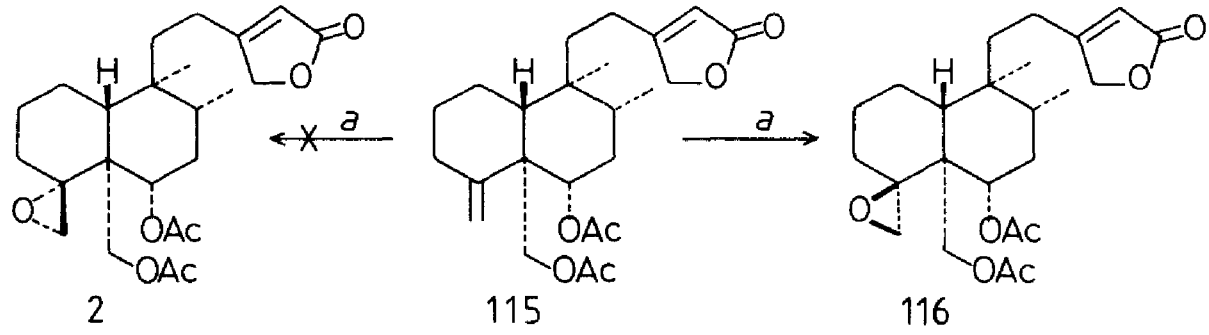


a: PyHCl,Ac_2O,Δ; *b*: DBN,δ; *c*: PyHBr,Ac_2O,Δ; *d*: OH^-,H_2O,MeOH; *e*: Py, Ac_2O DAP; *f*: H_2O,Py; *g*: KOH; *h*: $(COCl)_2$; *i*: CH_2N_2; *j*: H_2O,SO_2; *k*: $Ph_3P{=}C{=}C{=}O$.

112 was obtained in 66% yield next to some starting material (30%), thus avoiding the troublesome DBN reaction.
Hydrolysis followed by reacetylation gave 111. This carboxylic acid was converted into its potassium salt and reacted with oxalyl chloride to give the acid chloride 113. Reaction of his compound with diazomethane followed by hydrolysis of the intermediate diazoketone gave the hydroxy ketone 114. The overall yield of these conversions (*i.e.* 111→114) was 73%. Treatment of 114 with triphenylphosphoranylidene ketene gave the butenolide 115 in 92% yield (see scheme 7.4).

In chapter 5.3 we carried out the epoxidation of the 9β-methyl analogue of 115 (*i.e.* the diacetate 94). In that reaction both epimeric spiro epoxides were formed in the reaction with *m*-chloroperbenzoic acid. It was expected that in the present case again both isomers would be formed, thus leading to 116 and ajugarin I. Epoxidation of 115 with *m*-chloroperbenzoic acid in ether however afforded the epoxide 116 as sole product. The high stereospecificity in this reaction is probably owing to complexation of the butenolide moiety with the peracid, thus leading to an approach of the alkene from the β side of the molecule (scheme 7.5).

Scheme 7.5

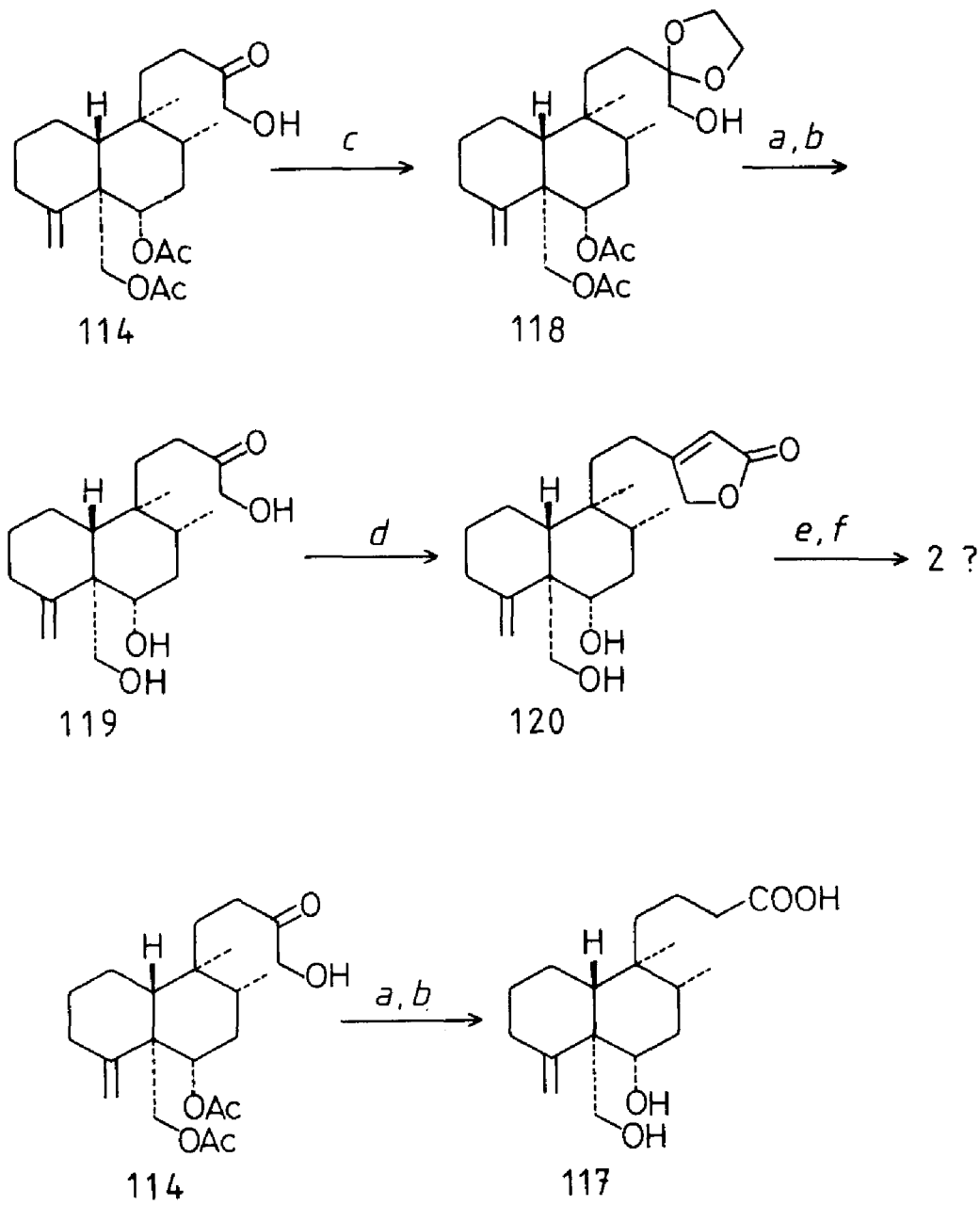


a: m-CPBA.

Alternatively the stereospecific epoxidation reaction using V^{5+} and *t*-butylhydroperoxide could be used to bring about the right stereochemistry at C-4 (cf. chapter 5.3). Therefore the acetates in

115 need to be hydrolysed first. Unfortunately both acid and base catalysed hydrolysis of 115 gave rise to the formation of numerous products. The butenolide proved unstable under basic conditions[3], while acidic conditions caused rearrangements of the olefinic bond.

Scheme 7.6



a: OH^-, H_2O; *b*: H_3O^+; *c*: MED, TsOH; *d*: $Ph_3P{=}C{=}C{=}O$; **e**: V^{5+}, *t*-BuOOH; *f*: Ac_2O, Py, DAP.

Base catalysed hydrolysis of the hydroxy ketone 114 was unsuccessful as well since a Favorskii rearrangement occurred[4], producing the carboxylic acid 117. Acid catalysed hydrolysis was expected to give the same complications as in the case of 115. The ketone 114 was therefore protected as the ethylene ketal 118 and the acetates were reduced with lithium aluminium hydride to give, after hydrolysis, the triol 119. Treatment of this product with triphenylphosphoranylidene ketene was expected to give the butenolide 120 since steric factors would probably favour reaction at the hydroxyl of the side chain precursor in the first step of the reaction mechanism (cf. chapter 4.4). However, only a very small amount of impure material could be obtained after extensive chromatography.
This product was further reacted with V^{5+} and *t*-butylhydroperoxyde and then acetylated. The ^{1}H-NMR spectrum of this compound revealed the presence of a small amount of epoxide as it is present in ajugarin I. Attempts to purify this mixture by HPLC was unsuccessful due to severe peak overlap. We have an indication however, that probably a small quantity of ajugarin I was formed.

From experiments in steroid chemistry it was shown that in certain cases the stereochemical outcome of molybdenum catalysed epoxidations[5] was opposite to that from peracid epoxidations[6]. On treatment of 115 with *t*-butylhydroperoxide in the presence of molybdenum hexacarbonyl, no reaction took place. The bulky metal complex probably was unable to approach the olefinic linkage.

7.3 EXPERIMENTAL SECTION.

General experimental details were as given in chapter 3.7.

3,3aβ,4,5,6,6aβ,7,10-Octahydro-7α,8-dimethyl-1H-*naphto[1,8aα-c]furan-7β-propanoic acid* (101).

To a solution of sodium bichromate (7.75 g, 26 mmol) in sulfuric acid (20 mL of a 8N solution) was added with stirring a solution of alcohol 45 (10.3 g, 39 mmol) in acetone (80 mL). After stirring for 1h, isopropanol (1 mL) was added to destroy the excess of bichromate. The greenish precipitate was filtered off and the acetone solution was concentrated. Ether was added and the solution was washed with brine and dried over anh. sodium sulfate. Evaporation of the

solvent gave 101 (10.3 g, 95%), m.p. 148-149°C; IR (KBr) 2900, 1720, 1698 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.80 (s,3H), 1.1-2.2 (m,14H), 1.62 (s,3H), 3.50 (d, J=9Hz, 1H), 3.61 (d, J=9Hz, 1H), 3.85 (d, J=9Hz, 1H), 3.91 (dd, J=9,4Hz, 1H), 5.47 (d, J=7Hz, 1H); MS m/e 278 (71), 260 (9), 247 (9), 205 (91), 187 (22), 95 (100).

Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.16; H, 9.20.

3,3aβ,4,5,6,6aβ,7,10-Octahydro-7α,8-dimethyl-1H-*naphto[1,8aα-c]furan-7β-propanoic acid methyl ester* (102).

To a solution of the carboxylic acid 101 (10.3 g, 37 mmol) in methanol (50 mL) was added a solution of diazomethane in ether until the yellow color persisted. The solvent was distilled off to give 102 (10.8 g, 100%) (oil); IR (neat) 1740 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.79 (s,3H), 1.1-2.3 (m,14H), 1.60 (s,3H), 3.43 (d, J=8Hz, 1H), 3.56 (d, J=9Hz, 1H), 3.64 (s,3H), 3.80 (d, J=9Hz, 1H), 3.90 (dd, J=4,8Hz, 1H), 5.46 (d, J=7Hz, 1H); MS m/e 292 (14), 261 (5), 205 (52), 187 (23), 95 (100).

3,3aβ,4,5,6,6aβ,7,10-Octahydro-7α,8-dimethyl-10-oxo-1H-*naphto[1,8aα-c]furan-7β-propanoic acid methyl ester* (103).

A mixture of 102 (9.8 g, 33.5 mmol), chromic acid (2.7 g, 27 mmol), acetic anhydride (1 mL) and acetic acid (100 mL) was stirred magnetically for 16h. Isopropanol (10 mL) was added to destroy the excess of oxidant. Water was added and the mixture was extracted with ether. The extract was dried over anh. sodium sulfate and concentrated. The residue was chromatographed on silica gel with ether-hexane (4:1) as the eluant to give the starting material (3,1 g, 29%). Further elution gave 103 (4.00 g, 39%), m.p. 90-91°C; IR (KBr) 1740, 1676, 1630 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.01 (s,3H), 1.1-2.2 (m,12H), 1.91 (s,3H), 3.47 (d, J=8Hz, H), 3.66 (s,3H), 3.80 (d,8Hz, 1H), 4.08 (d, J=8Hz, 1H), 4.20 (dd, J=5,8Hz, 1H), 5.90 (s,1H). MS m/e 306 (35), 263 (14), 245 (38), 233 (13), 219 (100), 182 (77).

Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.54; H, 8.26.

3,3aβ,4,5,6,6aβ,7,8β,9,10-Decahydro-7α,8α-dimethyl-10-oxo-1H-*naphto[1,8aα-c]furan-7β-propanoic acid methylester* (104).

The enone 103 (4.00 g, 13 mmol), was dissolved in methanol (50 mL)

and triethylamine (1 mL) and reduced with palladium on charcoal as the catalyst. After the hydrogen uptake had ceased (about 4h) the catalyst was filtered off and the filtrate was concentrated to give 104 (4.00 g, 96%) which was crystallized from ether, m.p. 86-87°C; IR (KBr) 1723, 1699 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.80 (s,3H), 0.91 (d, J=6Hz, 3H), 1.1-2.1 (m,13H), 2.11 (dd, J=4,13Hz, 1H), 2.67 (dd, J=13,13Hz, 1H), 3.35 (d, J=8Hz, 1H), 3.65 (s,3H), 3.80 (dd, J=8,5Hz, 1H), 3.97 (d, J=9Hz, 1H), 4.05 (d, J=9Hz, 1H); MS m/e 308 (21), 290 (24), 277 (15), 247 (8), 235 (8), 203 (100).

Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 70.17; H, 9.21.

10α-Acetoxy-3,3aβ,4,5,6,6aβ,7,8β,9,10β-decahydro-7α,8α-dimethyl-1H-*naphto[1,8aα-c]furan-7β-propanoic acid methyl ester* (105)
and
10β-Acetoxy-3,3aβ,4,5,6,6aβ,7,8β,9,10α-decahydro-7α,8α-dimethyl-1H-*naphto[1,8aα-c]furan-7β-propanoic acid methyl ester* (106).

To a magnetically stirred solution of ketone 104 (2.5 g, 8.1 mmol) in ether (60 mL) was added under nitrogen lithium tri-*tert*-butoxy aluminium hydride (1,8 g, 8.3 mmol). After stirring for 2h. aqueous hydrochloric acid was added and the ether layer was separated. The aqueous layer was extracted with ether and the combined organic layers were dried over anh. sodium sulfate and concentrated. The oily residue was dissolved in pyridine (20 mL) and acetic anhydride (4 mL). 4-Dimethylaminopyridine (DAP) (100 mg) was added and the mixture was stirred overnight. The solvents were distilled off and the residue was chromatographed on silica gel, using ether-hexane as the eluant to give 106 (542 mg, 19%), m.p. 121-123°C; IR (KBr) 1730, 1235 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.55 (s,3H), 0.76 (d, J=6Hz, 3H), 1.1-2.1 (m,15H), 2.09 (s,3H), 3.34 (d, J=8Hz, 1H), 3.62 (d, J=9Hz, 1H), 3.65 (s,3H), 3.83 (dd, J=4,8Hz, 1H), 3.84 (d, J=9Hz, 1H), 4.93 (s, 1H). MS m/e 306 (M^+-46) (9), 205 (100), 187 (42).

Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 68.32; H, 9.33.

Further elution gave 105 (2.2 g, 77%), m.p. 110-112°C; IR (KBr) 1730, 1235 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.60 (s,3H), 0.83 (d, J=6Hz, 3H), 1.1-2.1 (m,15H), 2.05 (s,3H), 3.37 (d, J=8Hz, 1H), 3.65 (s,3H), 3.83 (dd, J=4,8Hz, 1H), 3.86 (d, J=9Hz, 1H), 3.97 (d, J=9Hz, 1H), 4.87 (dd, J=5,14Hz, 1H); MS m/e 306 (M^+-46) (10), 205 (100), 187 (45).

Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 68.14; H, 9.05.

10β-Acetoxy-3,3aβ,4,5,6,6aβ,7,8β,9,10α-decahydro-7α,8α-dimethyl-1H-*naphto[1,8aα-c]furan-7β-propanoic acid* (107).

The ester 106 (500 mg, 1.42 mmol) was dissolved in methanol (20 mL) and a solution of potassium hydroxide (500 mg) in water (10 mL) was added. After stirring for 6h. the methanol was distilled off and the aqueous solution was acidified (conc. hydrochloric acid). The aqueous layer was extracted with ether. The extract was dried over anh. sodium sulfate and concentrated. The residue was dissolved in acetic anhydride (10 mL) and zinc chloride (50 mg) was added. After stirring for 4h. the solvent was distilled off and the residue was chromatographed on silica gel using ether as the eluant to give 107 (440 mg, 92%), m.p. 171-175°C; IR (KBr) 2900, 1720, 1235 cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ 0.60 (s,3H), 0.81 (d, J=6Hz, 3H), 1.1-2.2 (m,15H), 2.12 (s,3H), 3.36 (d, J=8Hz, 1H), 3.66 (d, J=9Hz, 1H), 3.82 (dd, J=5,8Hz, 1H), 3.83 (d, J=9Hz, 1H), 4.95 (s,1H); MS m/e 338 (0.5), 292 (6), 278 (85), 249 (16), 234 (7), 205 (100).

Anal. Calcd for $C_{19}H_{30}O_5$: C, 67.43; H, 8.93. Found: C, 66.87; H, 8.70.

10β-Acetoxy-7β-(4-hydroxybutan-3-one)-3,3aβ,4,5,6,6aβ,7,8β,9,10α-decahydro-7α,8α-dimethyl-1H-*naphto[1,8aα-c]furan* (108).

The carboxylic acid 107 (420 mg, 1.24 mmol) was dissolved in carbon tetrachloride (20 mL) and thionyl chloride was added (0.4 mL). After stirring for 1h. the solvent was distilled off together with the excess of thionyl chloride. The residue was dissolved in ether and added to a solution of diazomethane in ether. The ether and excess of diazomethane were distilled off, the residue was dissolved in acetone and added to an aqueous solution of sulfur dioxide. The mixture was stirred overnight. Most of the acetone was distilled off and the aqueous layer was extracted with ether. The extract was dried over anh. sodium sulfate and evaporated *in vacuo* to give an oily residue which was chromatographed on silica gel with ether as the eluant to give 108 (231 mg, 53%) (oil), IR (neat) 3400, 1730, 1715, 1235 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 0.60 (s,3H), 0.79 (d, J=6Hz, 3H), 1.1-2.3 (m,15H), 2.12 (s,3H), 3.34 (d, J=8Hz, 1H), 3.60 (d, J=9Hz,

1H), 3.80 (dd, J=4,8Hz, 1H), 3.81 (d, J=9Hz, 1H), 4.22 (s, 2H), 4.90 (s,1H); MS m/e 292 (M^+-60) (7), 261 (16), 243 (16), 205 (100).

10β-Acetoxy-7β-[2-(2(5H)-*furanone)ethyl]-3,3aβ,4,5,6aβ,7,8β,9,10α-decahydro-7α,8α-dimethyl*-1H-*naphto[1,8aα-c]furan* (109).

The alpha hydroxy ketone 108 (130 mg, 0.37 mmol) was dissolved in benzene (10 mL). Triphenylphosphoranylidene ketene (115 mg, 0.38 mmol) was added and the mixture was refluxed for 1h. in an atmosphere of nitrogen. The solvent was distilled off and the residue was chromatographed on silica gel with ether as the eluant to give 109 (124 mg, 89%), m.p. 166-169°C; IR (KBr) 1770, 1735, 1720, 1630, 1235 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.61 (s,3H), 0.81 (d, J=6Hz, 3H), 1.2-2.3 (m,15H), 2.14 (s,3H), 3.36 (d, J=8Hz, 1H), 3.66 (d, J=9Hz, 1H), 3.86 (dd, J=4,8Hz, 1H), 3.89 (d, J=9Hz, 1H), 4.78 (s, 2H), 4.98 (s, 1H), 5.84 (t, J=2Hz, 1H); MS m/e 316 (M^+-60) (47), 301 (14), 287 (19), 272 (12), 205 (100), 203 (80).

Anal. Calcd for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 69.67; H, 8.71.

1α-Acetoxy-9α-acetoxymethyl-8α-chloromethyl-3α,4α-dimethyl-trans-*decalin-4β-propanoic acid methyl ester* (110).

Acetate 105 (2.0 g, 0.57 mmol) was dissolved in acetic anhydride (20 mL), Pyridine hydrochloride (2.5 g) was added and the mixture was refluxed overnight. The solvent was distilled off *in vacuo* and the residue was chromatographed on silica gel with ether as the eluant to give 110 (1.96 mg, 80%), m.p. 158°C; IR (KBr) 1725, 1235 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 0.73 (s,3H), 0.80 (d, J=6Hz, 3H), 1.1-2.2 (m, 15H), 2.00 (s,3H), 2.04 (s,3H), 3.47 (dd,J=9,11Hz, 1H), 3.65 (s, 3H), 3.96 (dd, J=2,11Hz, 1H), 4.22 (d, J=12Hz, 1H), 4.72 (dd, J=5,11Hz, 1H), 4.76 (d, J=12H, 1H); MS m/e 310-312 (M^+-60-60) (9), 361 (7), 241-243 (7), 223-225 (100).

Anal. Calcd for $C_{22}H_{35}ClO_6$: C, 61.31; H, 8.19. Found: C, 61.36; H, 8.29.

Further elution gave the starting compound 105 (300 mg, 15%).

1α-Acetoxy-9α-acetoxymethyl-8-methylene-3α,4α-dimethyl-trans-*decalin-4β-propanoic acid* (111).

The chlorodiacetate 110 (180 mg, 0.42 mmol) was dissolved in

m-xylene (2 mL). Diazabicyclononene (DBN) (62 mg) was added under nitrogen. The mixture was stirred magnetically and heated at 140°C overnight. Methylene chloride (20 mL) was added and the dark brown solution was washed with aqueous hydrochloric acid. The organic layer was dried over anhydrous magnesium sulfate and chromatographed on silica gel with ether as the eluant to give 111 (640 mg, 40%), m.p. 166°C; IR (KBr) 2900, 1725, 1699, 1631, 1235; ^{1}H-NMR ($CDCl_3$) δ 0.79 (s,3H), 0.88 (d, J=6Hz,3H), 1.2-2.3 (m,14H), 2.00 (s,3H), 2.04 (s,3H), 4.26 (d, J=12Hz, 1H), 4.49 (s,1H), 4.77 (s,1H), 4.80 (d, J=12Hz, 1H), 5.06 (dd, J=5,12Hz, 1H); MS m/e 320 (M^+-60) (0.5), 278 (3), 260 (19), 229 (15), 187 (100).

Anal. Calcd for $C_{21}H_{32}O_6$: C, 66.29; H, 8.48. Found: C, 66.00; H, 8.44.

1α-Acetoxy-9α-acetoxymethyl-8-methylene-3α,4α-dimethyl-trans-*decalin-4β-propanoic acid methyl ester* (112).

A mixture of 105 (1.29 g, 3.66 mmol) and pyridine hydrobromide (2 g) in acetic anhydride was refluxed overnight. The solvent was removed in vacuo and the dark brown residue was chromatographed silica gel with ether-hexane (4:1) as the eluant to give 112 (950 mg, 66%) (oil); IR (neat) 1730, 1631, 1235 cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ 0.75 (s,3H), 0.83 (d, J=6Hz, 1H), 1.1-2.2 (m,14H), 2.00 (s,3H), 20.4 (s, 3H), 3.65 (s,3H), 4.21 (d, J=12Hz, 1H), 4.47 (s,1H), 4.71 (s,1H), 4.77 (d, J=12Hz, 1H), 5.03 (dd, J=5,12Hz, 1H); MS m/e 363 (M^+-31) (0.3), 334 (0.3), 292 (1.5), 274 (12), 229 (17), 187 (100).

Further elution gave the starting compound (105) (400 mg, 30%).

1α-Acetoxy-9α-acetoxymethyl-4β-(4-hydroxybutan-3-one)-8-methylene-3α,4α-dimethyl-trans-*decalin* (114).

The carboxylic acid 112 (400 mg, 1.05 mmol) was transformed into the alpha hydroxy ketone 114 by the procedure which was described in chapter 4.6 for the preparation of 55.

The yield of 114 was 306 mg (73%) (oil); IR (neat) 3400, 1720, 1640, 1240 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.79 (s,3H), 0.85 (d, J=6Hz, 3H), 1.2-2.2 (m,14H), 1.98 (s,3H), 2.01 (s,3H), 4.25 (d, J=12Hz, 1H), 4.24 (s,2H), 4.49 (s,1H), 4.78 (s,1H), 4.78 (d, J=12Hz, 1H), 5.04 (dd, J=5,12Hz, 1H), MS m/e 363 (M^+-31) (0.2), 334 (0.3), 294 (2), 274 (14), 261 (6), 243 (15), 225 (10), 187 (100).

1α-Acetoxy-9α-acetoxymethyl-4β-[2-(2(5H)-furanone)ethyl]-8-methylene-3α,4α-dimethyl-trans-*decalin* (115).

The alpha hydroxy ketone 114 (250 mg, 0.64 mmol) was transformed into the butenolide 114 by the procedure which was described for the preparation of 109. The yield was 229 mg (87%), m.p. 165-167°C; IR (KBr) 1780, 1730, 1630, 1240 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.76 (s,3H), 0.82 (d, J=6Hz, 3H), 1.2-2.2 (m,14H), 1.92 (s,3H), 1.98 (s,3H), 4.18 (d, J=12Hz, 1H), 4.43 (s,1H), 4.69 (s,1H), 4.70 (s,2H), 4.73 (d, J=12Hz, 1H), 5.00 (dd, J=5,12Hz, 1H), 5.77 (t, J=2Hz, 1H); MS m/e 358 (M^+-60) (0.4), 316 (4), 298 (15), 285 (6), 187 (100).

Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.81; H, 8.32.

1α-Acetoxy-9α-acetoxymethyl-8β,8'-epoxy-4β-[2-(2(5H)-furanone)ethyl]-3α,4α-dimethyl-trans-*decalin* (116).

To the olefin 115 (100 mg, 0.31 mmol) in ether (5 mL) was added *m*-chloroperbenzoic acid (0.35 mmol, 76 mg, admixed with 30% *m*-chlorobenzoic acid). After stirring for 24h. the ether was removed *in vacuo* and the residue was chromatographed to give the epoxide 116 (88 mg, 85%), m.p. 170-171°C; IR ($CHCl_3$) 1771, 1730, 1635, 1240 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.73 (s,3H), 0.80 (d, J=6Hz, 1H), 1.2-2.3 (m,14H), 1.95 (s,3H), 2.03 (s,3H), 2.54 (dd, J=4,5Hz, 1H), 2.60 (dd, J= 4,5Hz, 1H), 4.25 (d, J=12Hz, 1H), 4.63 (dd, J=5,12Hz, 1H), 4.72 (s,2H), 4.79 (d, J=12Hz, 1H), 5.80 (t, J=2Hz, 1H); MS m/e 404 (M^+-30) (1), 391 (5), 374 (5), 204 (43), 175 (100), 173 (63).

Anal. Calcd for $C_{24}H_{34}O_7$: C, 66.34; H, 7.89. Found: C, 66.14; H, 7.69.

1α-Acetoxy-9α-acetoxymethyl-4β-[3,3-ethylenedioxybutanol-4]-8-methylene-3α,4α-dimethyl-trans-*decalin* (118).

The alpha hydroxy ketone 114 (400 mg, 1.0 mmol) was dissolved in 2-methyl-2-ethyl-1,3-dioxolan (MED) and stirred overnight in the presence of *p*-toluene sulfonic acid (20 mg). The MED was distilled off under reduced pressure and the residue was chromatographed on a short column of silica gel, using ether as the eluant to give 118 (400 mg, 91%); IR (neat) 3400, 1730, 1240 cm^{-1}; ^{1}H-NMR (CCl_4) α 0.70 (s,3H), 0.80 (s,3H), 1.1-2.3 (m,14H), 1.93 (s,3H), 1.97 (s,3H), 3.42 (s,2H), 3.95 (s,4H), 4.20 (d, J=12Hz, 1H), 4.41 (s,1H), 4.70 (s,1H),

4.74 (d, J=12Hz, 1H), 4.98 (dd, J=5,12Hz, 1H); MS m/e 438 (0.1), 421 (0.4), 407 (100), 187 (31).

1α-Hydroxy-4β-(4-hydroxybutan-3-one)-9α-hydroxymethyl-8-methylene-3α,4α-dimethyl-trans-*decalin* (119).

The diacetate 118 (400 mg, 0.91 mmol) was dissolved in ether and lithium aluminium hydride (76 mg, 2 mmol) was added. After stirring for 2h. under nitrogen, water (1 mL) and aqueous hydrochloric acid (2 mL of a 6N solution) were added and the mixture was stirred overnight to give the triol 119 (225 mg, 80%); IR: 3400, 1725 cm^{-1}. Owing to the high polarity of the compound no satisfactory ^{1}H-NMR spectrum could be obtained.

Attempted formation of Ajugarin I.

The triol 119 (225 mg, 0.67 mmol) was dissolved in benzene (10 mL) and triphenylphosphoranylidene ketene (210 mg, 0.69 mmol) was added. The mixture was refluxed for 1 h. The benzene was distilled off and the mixture was purified by chromatography on silica gel with ether-ethyl acetate as the eluant to give an impure mixture (45 mg), IR (neat) 3400, 1770, 1750, 1635 cm^{-1}. This product was epoxydized with $V(acac)_2$/*t*-BuOOH and acetylated as described for the synthesis of 96 from 94 to give an impure mixture (13.5 mg); IR (neat) 1770, 1750, 1635, 1235 cm^{-1}; ^{1}H-NMR: contains Me (s), Me (d), 2Ac, ax. epoxide (2.19, d, J=4Hz; 2.97, dd, J=4,2Hz), butenolide. Attempts to purify the mixture by HPLC on Lichrosorb using methyl-*t*-butyl ether/hexane mixtures were unsuccessful.

Attempted molybdenum catalysed epoxidation of 115.

The olefin 115 (50 mg, 0.12 mmol) was dissolved in dry benzene. *t*-Butyl hydroperoxide (200 µL of a 1M solution in dry benzene) and molybdenum hexacarbonyl (10 mg) were added and the mixture was refluxed overnight. TLC analysis showed only starting material.

7.4 REFERENCES AND NOTES.

1 This method is described in chapter 4.5.
2 In reaction of the corresponding ethyl ester of chlorodiacetate 110 under the same conditions, no ester hydrolysis occurred. The

yields of this reaction remained very low, which is probably due to nucleophylic attack of DBN on the carbonyl of the propanoic ester.

3 See also: Inhoffen, H.H., Kreiser, W., and Panenka, R., Justus Liebigs Ann. Chem., (1971), *749*, 117.

4 Craig, J.C., Dinner, A., and Mulligan, P.J., J. Org. Chem., (1972), 3539.

5 Sharpless, K.B., and Verhoeven, T.R., Aldrichimica acta, (1979), *12*, 63.

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8 THE ASSIGNMENT OF ^{13}C SHIFT DATA IN CLERODANES AND RELATED STRUCTURES.

8.1 INTRODUCTION.

The correct assignment of ^{13}C-NMR shifts in the field of the clerodane type diterpenes remains a rather complicated task, especially where it concerns the methylene resonances. Lanthanide shift reagents cannot always be used since complexation at different sites of the molecule may occur, particulary in the highly oxygenated diterpenes. Selective proton decoupling to clarify the assignment of the methylene resonances is often impossible, since all methylene protons resonate in the same region (1.2-1.8 ppm). This forces one to use empirical rules[1] and comparison with analogous structures[2].

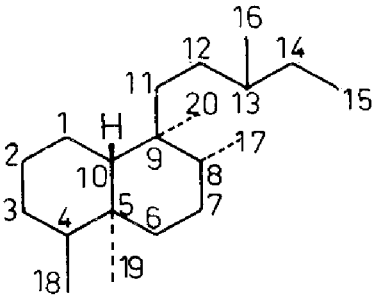
In this thesis the synthesis of a number of partial clerodane structure is described and the ^{13}C-NMR shifts of these compounds may constitute a valuable contribution to the complete and unambiguous assignment of the ^{13}C resonances of these natural products.

8.2 RESULTS AND DISCUSSION.

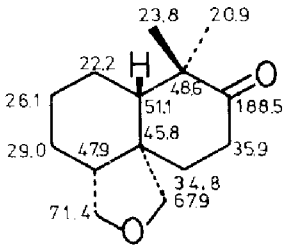
In the scheme the structures of a number of relevant synthetic intermediates are given, together with the assigned ^{13}C-NMR resonances. These assignments have been made on the basis of chemical shift theory[1], and also by considering the changes in chemical shifts produced by the change of substituents and comparison with the shift data for related structures[2]. In addition a number of clerodanes is presented with their ^{13}C-NMR shifts, which could now be assigned by using the information which was obtained from the partial structures.

Compounds *1* and *2* have the same decalone skeleton, but differ in substitution at C-9. On changing from an equatorial methyl at this position to an equatorial allyl group, a 5.5 ppm upfield shift for C-10 and a 3 ppm downfield shift for C-9 is observed. The allyl group in *2* strongly deshields C-8, thus emphasizing the strong interaction between these groups. This phenomenon had already been noticed on observation of the low reactivity of the C-8 carbonyl in chemical reactions[3] (cf. chapter 4.2).

Scheme



Clerodane numbering



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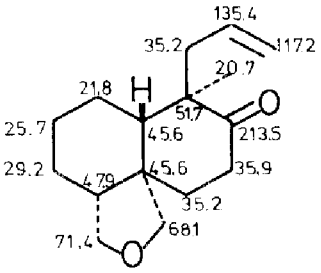

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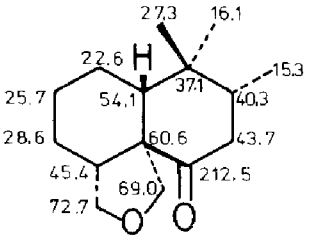

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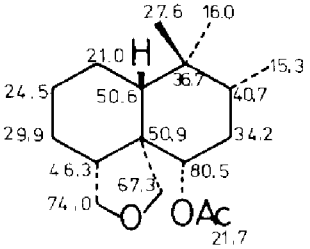

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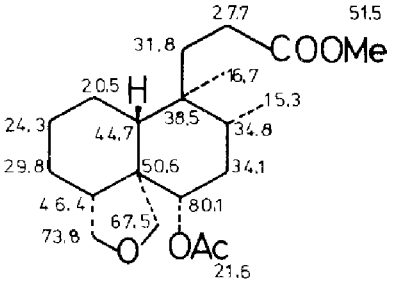

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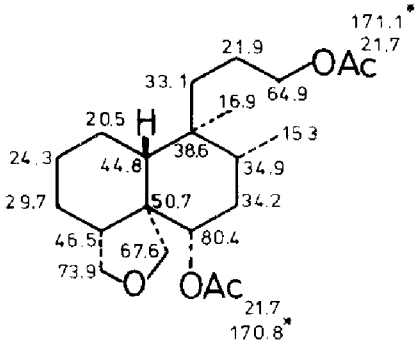

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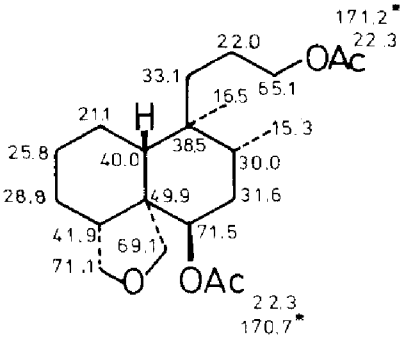

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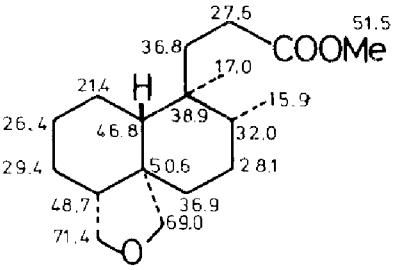

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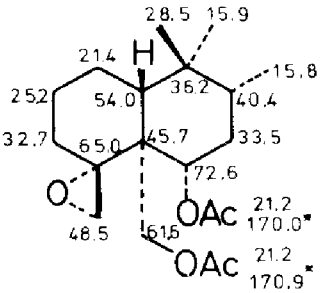

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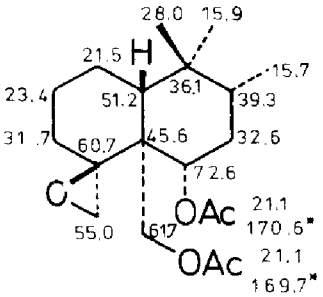

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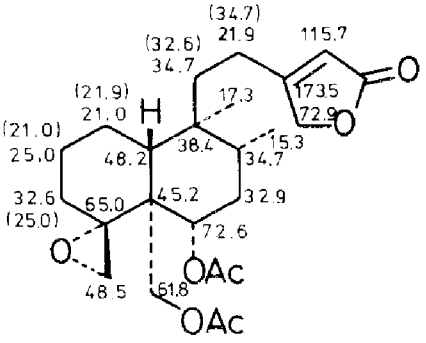

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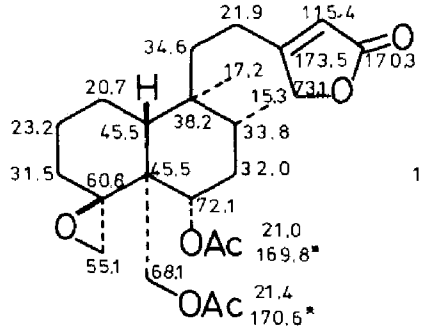

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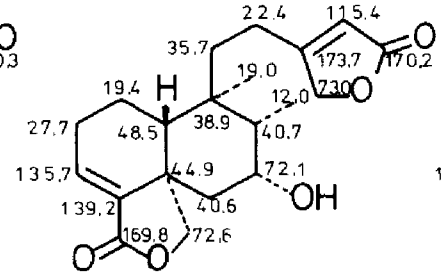

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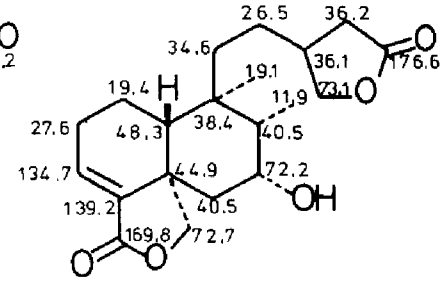

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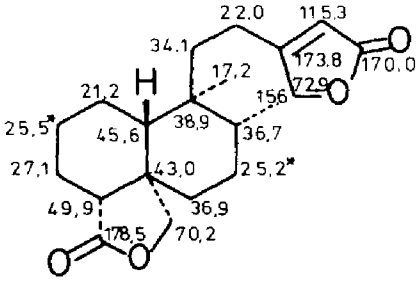

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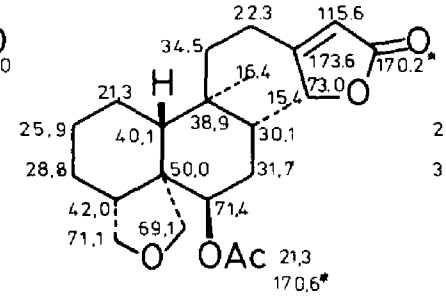

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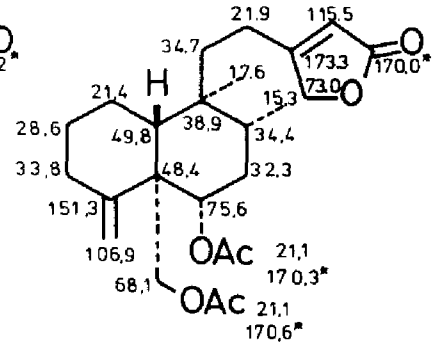

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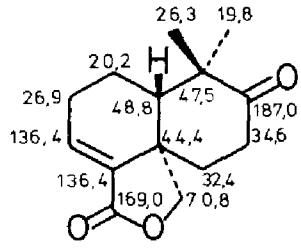

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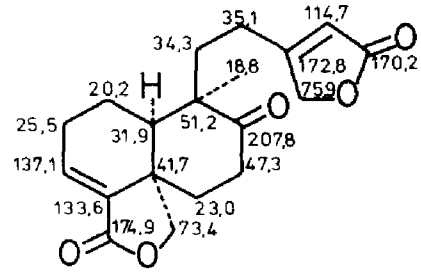

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Structures *3-8* only differ in substituents at C-6 and C-9. Making use of the shift values which were found for the partial structures of the first two compounds (*3* and *4*) the shifts for the more complex structures could be assigned. On changing an equatorial methyl at C-9 in the partial structure *4* for a substituent of 3 carbons or more, an upfield shift of 6 ppm. is observed for C-8 and C-10, whereas C-9 undergoes a downfield shift of 2 ppm. Exactly the same changes can be detected when we compare the partial structures *9* and *10* with *11* and *12* respectively.

On comparing the diacetates *6* and *7*, a shielding effect of almost 5 ppm by the C-6 acetate in *7* on the *peri* carbons C-4, C-8 and C-10 is observed.

A number of methylene resonances which were reported for ajugarin I[4] (*11*) strongly differed from the values we had assigned for the corresponding carbons in the partial structure *9*. There could be no doubt about the correctness of these structures since an X-ray analysis was available for both compounds.

On transposing a number of the values for the methylene carbons in ajugarin I, a more satisfactory assignment could be obtained, which is given in *11* (the original assignments by Kubo *et al.*[4] are in parenthesis). In this new assignment however, we came to an unusual high field resonance for C-12 (21.9 ppm). No arguments for this phenomenon can be found on the basis of empirical parameters[1] which lead to a shift of 30-35 ppm. The latter value is in good agreement with the original assignment. Further evidence was thus required to support our new assignment. In 1978 Wagner *et al.*[5] reported the structural elucidation of two clerodanes, *13* and *14*, together with the ^{13}C-NMR resonances. The only chemical difference between these two diterpenes was the unsaturation at C-13 and C-14. Wagner did not assign, however, the methylene resonances. Using the information we had at our disposal from the other structures, the assignments could readily be made. This again led to the unusual high field resonance for the C-12 methylene in *13*. This information enabled us to assign the ^{13}C resonance in the other compounds.

The ^{13}C shifts we had obtained for the butenolide containing side chain throw serious doubts on the correctness of the assignments which Tschesche and Streuff[6] had made for the *cis* clerodane *19*. Most probably the assignments for C-12 and C-6 should be reversed. However, since no related partial structures of *cis* decalones are

available, the correct assignment remains in doubt.

The examples given above emphasize that the assignment of ^{13}C-NMR chemical shifts to rather complex molecules such as clerodanes, will hardly be possible on the basis of empirical rules alone.

The synthesis of partial structures can afford valuable information enabling a proper and unambiguous assignment.

8.3 EXPERIMENTAL SECTION.

The spectra were recorded on Varian XL-100 and Bruker CXP-300 spectrometers, operating in the Fourier transform method. Multiplicaties were determined by recording the proton coupled spectra or by using the single frequency off resonance method. Assignments that may be interchanged are starred. $CDCl_3$ was used as solvent with TMS as internal standard (δ=0).

8.4 REFERENCES.

1 Wehrli, F.W., Wirthlin, T., Interpretation of ^{13}C-NMR spectra, Heyden, 1978.

2 Wehrli, F.W., Progress in the Chemistry of Organic Natural Products, (1979), *36*, 1.

3 Ardon-Jimenez, A., Halsall, T.G., J. Chem. Soc. Perkin I, (1978), 1461.

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6 Tschesche, R., Streuff, B., Chem. Ber., (1978), *111*, 2130.

9 *STRUCTURE-ACTIVITY RELATIONSHIPS OF THE INSECT ANTIFEEDANT CLERODANES.*

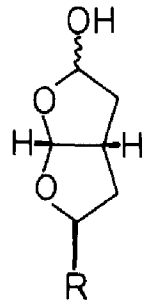
9.1 INTRODUCTION.

On comparison of the insect antifeedant clerodanes (for structural formulas, see chapter 1.4) one can detect a resemblance in structural elements. Eleven out of thirteen of these compounds possess a furofuran unit and furthermore all compounds have the epoxy diacetate groups in common.

It was concluded[1] that the furofuran ring is the active center of the molecule. In fact, Kojima and Kato[2] synthesized a number of perhydrofurofuran derivatives (structures 1-10) showing antifeedant activity against the larvae of *Spodoptera litura* (cf. chapter 2.9). The antifeedant activity of these model compounds was only 1/10-1/20 of that of the natural products. They correlated this low activity with the degree of rigidity of the perhydrofuran ring. It was suggested that the methyl groups at C-8 and C-9 in the natural products would sterically block the free rotation of the furofuran ring. This is reflected by the chemical reactivity of this moiety; on treatment of clerodin (11) with methanol in the presence of acid, the monomethanol adduct 12 was obtained whereas compounds 1-5 afforded a trimethanol adduct with general structure 13 when reacted under the same conditions.

These results however, cannot explain the antifeedant activity of ajugarin I[3] (14). In this molecule the activity is most probably localized in the decalin moiety of the molecule. The alternative possibility that in this compound the butenolide containing side chain alone is responsible for the physiological activity must be excluded. A large number of clerodanes contains the same structural element and no antifeedant activity has ever been reported for these compounds in the literature so far[4].

This leads us to the epoxy diacetate groups as the most salient feature of all antifeedant clerodanes. Evidence for the assumption



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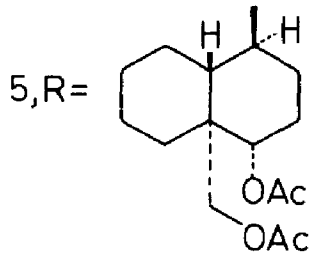
2, R = Ph
3, R = 2-MePh
4, R = 2,6-diMePh



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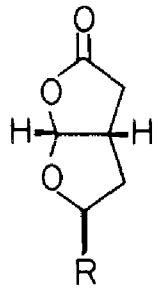
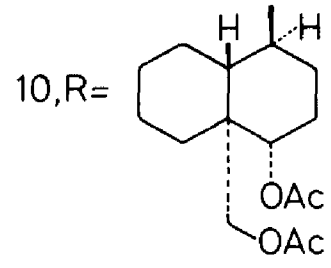


6, R = *t*-Bu
7, R = Ph
8, R = 2-MePh
9, R = 2,6-diMePh



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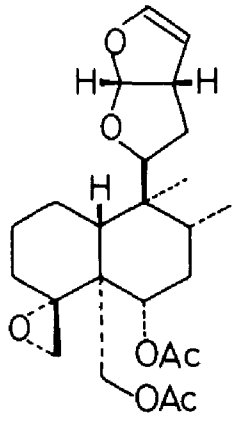

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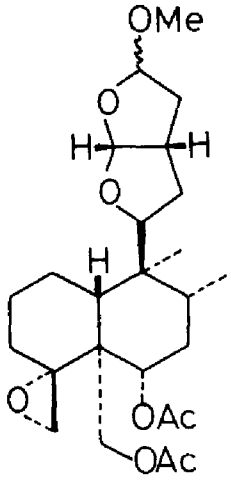

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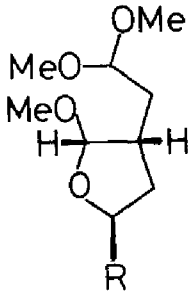

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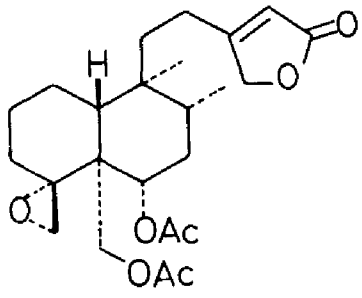

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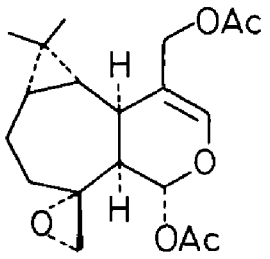
that the spiro epoxide plays an important role in the physiological activity is found by studying the results published by Hosozawa *et al.*[5] on a number of clerodin derivatives. They found that the antifeedant activity strongly decreased on cleavage of the epoxide ring in clerodin (11) whilst at the same time the furofuran ring was left intact.

The possible importance of the epoxy acetate functions is emphasized further by the presence of similar structural elements in plagiochiline A (15)[6], a sesquiterpene with strong antifeedant activity against *Spodoptera exempta*. Jackson and Ley[7] reached similar conclusions and tried to synthesize a *trans* decalin possessing the epoxy diacetate groups in question (see also chapter 2.7). From the testing results of this compound a better insight might possibly be obtained on the relationship of the decalin portion of the antifeedant clerodanes with regard to their physiological activity. Their synthetic efforts however resulted in the formation of the *cis* decalin 16. Since the spatial structure of this compound is quite different from the decalin moiety in *e.g.* clerodin (11) and ajugarin I (14), this compound is a poor model for investigating structure-activity relationships. When tested against *Locusta migratoria* weak antifeedant activity was observed. The feeding of *Spodoptera littoralis* was not deterred by the compound. In chapter 5 we described the synthesis of the *trans* decalin 17. This compound represents the decalin moiety as it is present in both clerodin and ajugarin I. It should therefore be interesting to test this compound for insect antifeedant activity.



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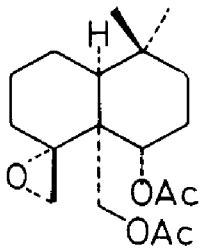

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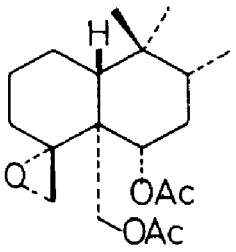


17

9.2 EXPERIMENTS TO DETERMINE ANTIFEEDANT ACTIVITY*.

To test the antifeedant activity of compounds 17-19, larvae of three different insect species were used: *Spodoptera littoralis (Boisd.)*, *S. exigua (Hübner)* (both polyphagous insects) and *Pieris brassicae L.* (oligophagous).

* These experiments were carried out at the Department of Animal Physiology of the Agricultural University, Wageningen. We are grateful to Ir. R.B.M. Geuskens and Prof.dr. L.M. Schoonhoven for these results.

The insects were reared on an agar diet at a temperature of 25°C for *S. littoralis* and *S. exigua* or 20°C for *P. brassicae*. Fifth instar larvae were used in the feeding tests. The weights of the larvae at the beginning of the tests are given in Table 1.

Table 9.1 Weights of the larvae at the beginning of the test.

	no of larvae	range of larval weight	avarage weight
S. littoralis	20	95 - 265 mg	190 mg
S. exigua	20	60 - 200 mg	120 mg
P. brassicae	20	60 - 275 mg	175 mg

To determine the antifeedant activity for the model compounds, the 'styropor method'[8] was used. Lamellae (6x3 cm) of 'styropor' (foamed polystyrene) of density 0.015 (P_{15}) were used as the carrier material for the testing compounds. These testing compounds were dissolved in ethanol (96%) and a solution of sucrose (0.250 M in water) was added. The ratio of ethanol-water was 1:1. The styropor lamellae were dipped into the solutions and allowed to dry for 30 min. at 50°C and then weighed individually. They were offered to the larvae in large boxes of synthetic material, each containing ten compartments of 10x7x3 cm. In each compartment one lamella and one larva were placed (no-choice experiment). Furthermore a moistened cotton wad in a small plastic cover was added to fulfil the drinking need of the insect. Fig. 9.1 and 9.2 show the experimental set-up at the beginning and at the end of the feeding tests.

Before the beginning of the test the larvae were starved for 3h. and then weighed. A testing period of 24 h. was used and then the lamellae were removed, dried at 50°C for 30 min[9] and weighed. In the control experiment the same number of larvae was under identical conditions offered lamellae which were only treated with sucrose as the feeding stimulant. All tests were carried out at 25°C.

Fig. 9.1 Experimental set-up at the beginning of the test.

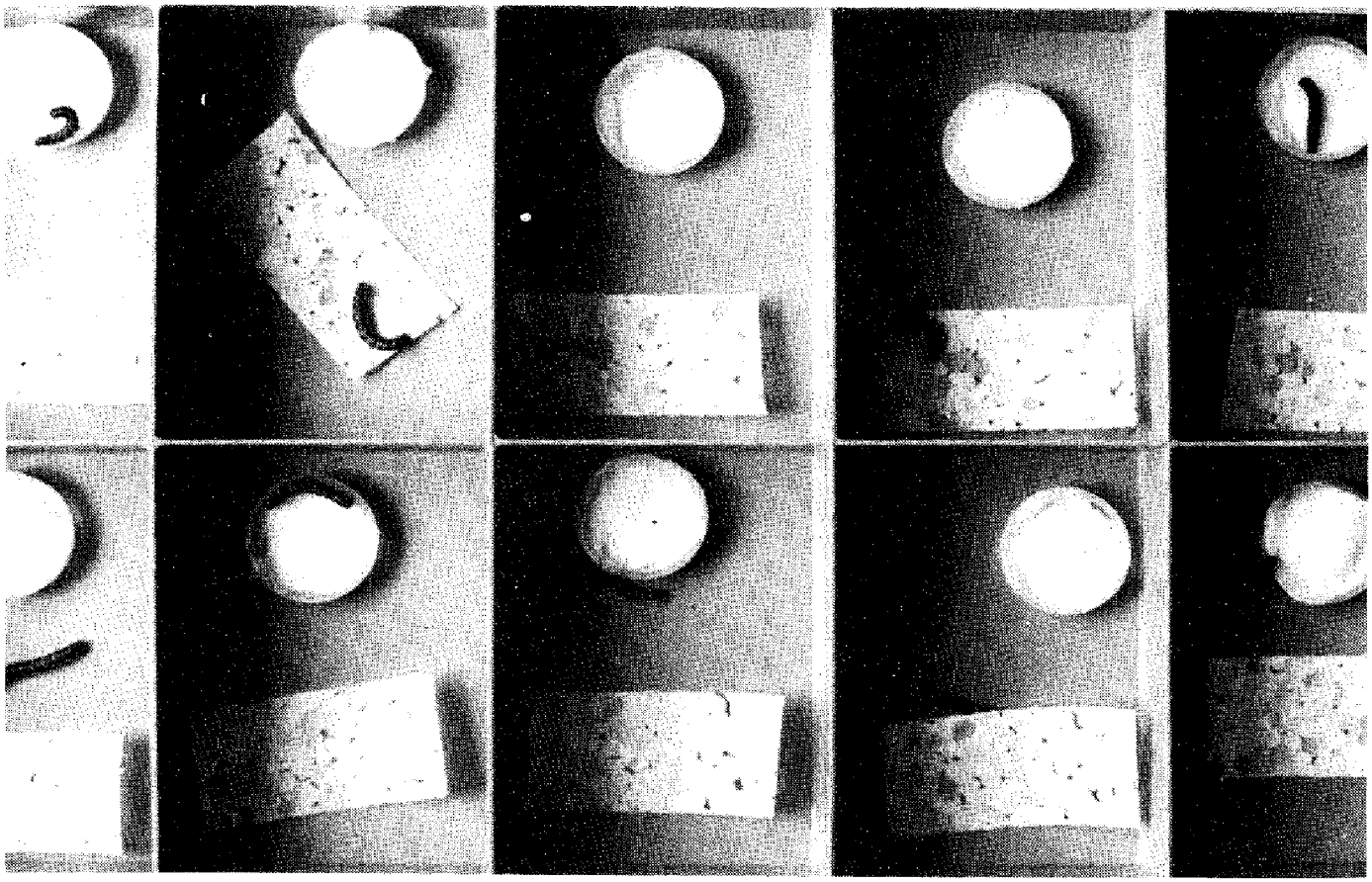
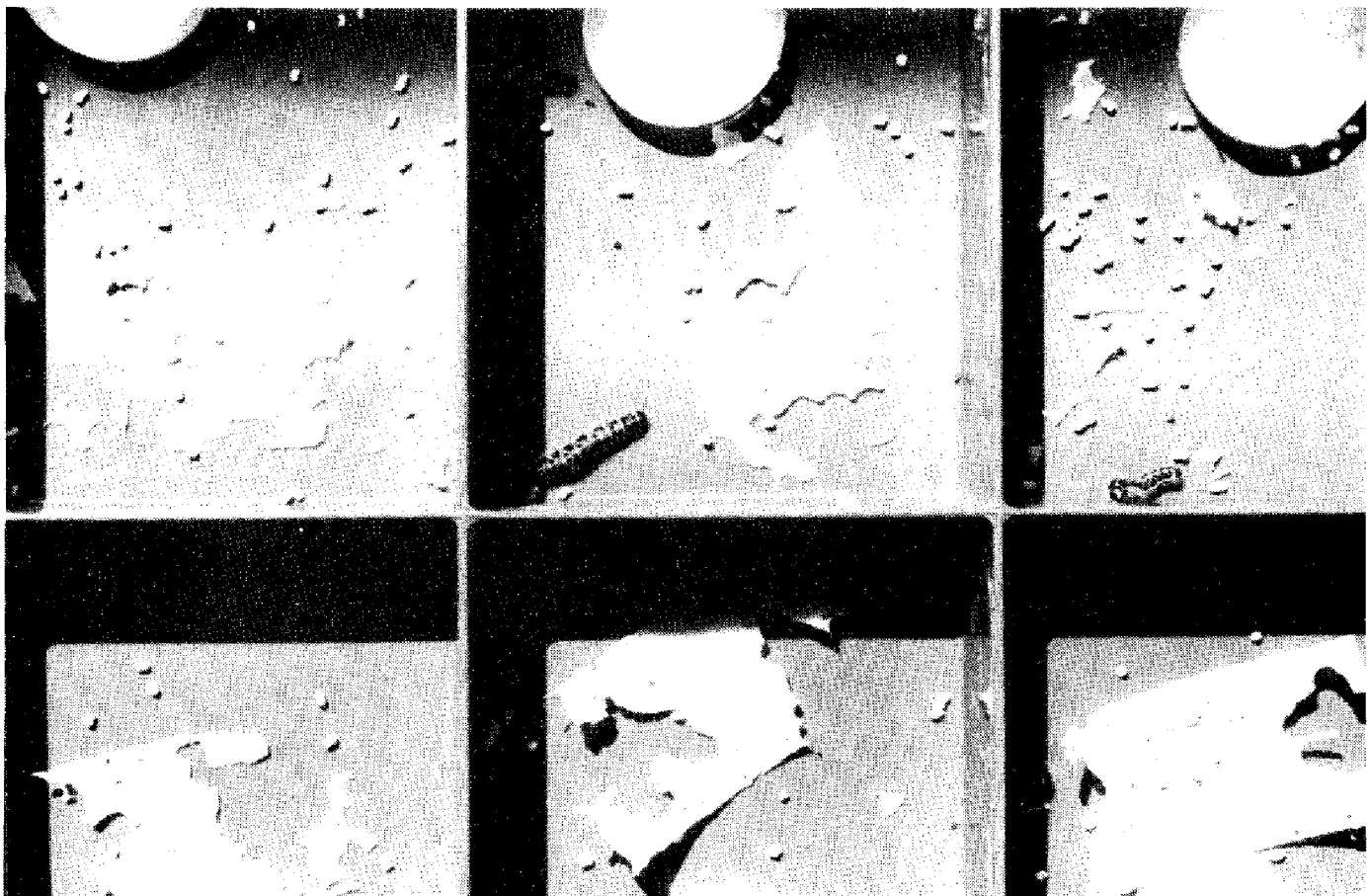
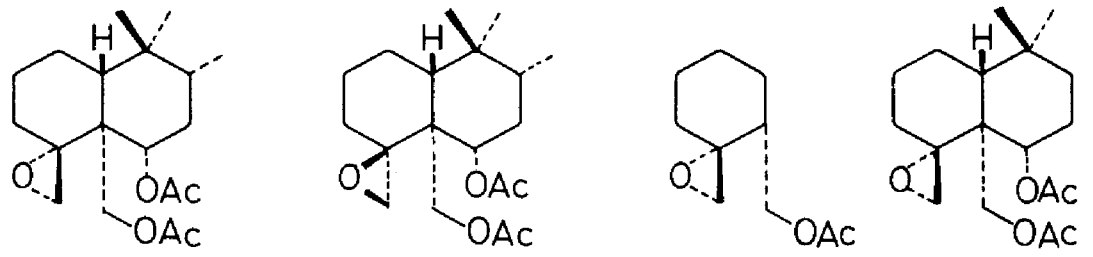


Fig. 9.2 Experimental set-up at the end of the test.



9.3 RESULTS.

The compounds 17-19[10] were tested for antifeedant activity.



17 18 19 20

The activity of 17-19 is summarized in table 9.2.

Table 9.2 Antifeedant activities for the compounds 17-19.

Concentration (ppm)		1000	500	250	100	50	25
17 + 0.250M sucrose	*S. littoralis*	-					
	S. exigua	-					
	P. brassicae	++++	++++	++++	++++	+++	++
18 + 0.250M sucrose	*S. littoralis*	-					
	P. brassicae	++++	+++				
19 + 0.250M sucrose	*P. brassicae*	-					

Degrees of antifeedant activity: ++++ = 100-95%, +++ = 95-75%, ++ = 75-50%, + = 50-25%, - = 25-0%.

No antifeedant activity for *S. littoralis* and *S. exigua* was observed at concentrations of 1000 ppm. Compound 17, however, exhibi-

ted strong antifeedant activity against *P. brassicae*; even at 25 ppm 50% inhibition of feeding was observed. The relation of the spiro epoxide with the antifeedant activity was clearly demonstrated by compound 18. The activity of this compound was only 1/10 of the activity of 17. The cyclohexane derivative 19 showed no activity at all, despite the presence of the spiro epoxide and one acetate group.

Shortly after we obtained these results, Ley *et al.*[11] reported the synthesis of the *trans* decalin 20. Except for the methyl group at C-8, this molecule is identical to 17. On testing 20 for antifeedant activity in *Locusta migratoria*, a 70% inhibition of feeding was observed at a concentration of 100 ppm.

9.4 CONCLUSIONS.

It is clear from the results mentioned above that the epoxy diacetate group plays an important role in the antifeedant activity of the clerodanes. A marked difference, however, is that 17 showed no activity against *S. littoralis*, whereas ajugarin I shows complete inhibition of feeding at 300 ppm when tested with the same insect. Obviously the presence of a butenolide containing side chain is required to extend the antifeeding activity of the epoxy diacetate group. One may also speculate what the effect of other side chains which contain polar groups would be on the activity.

Finally, one may wonder if Kojima and Kato are not in error by seeking the antifeedant activity of the clerodanes exclusively in the furofuran unit of the molecule. It must be taken into consideration that the furofuran ring and the epoxy diacetate groups have a unique synergistic effect, thus leading to the strong antifeedant activity of *e.g.* clerodin[12].

9.5 REFERENCES AND NOTES.

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b. Hosozawa, S., Kato, N., Munakata, K., *ibid.*, (1974), *38*, 823.
c. Hosozawa, S., Kato, N., Munakata, K., Chen, Y.-L., *ibid.*, (1974), *38*, 1045.

2 a. Kojima, Y., Kato, N., Tetr. Lett., (1979), 4667.
b. Agric. Biol. Chem., (1981), *44*, 855.

c. Tetr. Lett., (1980), 5033.
d. Tetrahedron (1981), *37*, 2527.

3 Kubo, I., Lee, Y.-W., Balogh-Nair, V., Nakanishi, K., Chapya, A., J. Chem. Soc., Chem. Commun, (1976), 949.

4 For reviews see Hanson, J.R. in Terpenoids and steroids, Specialist Periodical reports, The chemical Society, London, vol. 9 and preceeding volumes.

5 Hosozawa, S., Kato, N., Munakata, K., Agric. Biol. Chem., (1974), *38*, 823.

6 Asakawa, Y., Toyota, M., Takemoto, T., Kubo, I., Nakanishi, K., Phytochemistry, (1980), *19*, 2147.

7 Jackson, W.P., Ley, S.V., J. Chem. Soc., Perkin I, (1981), 516.

8 Ascher, K.R.S., Meisner, J., Entomologia exp. appl., (1973), *16*, 101.

9 The lamellae containing the epoxy acetate 19 were dried at room temperature for 24h. to prevent evaporation of the compound.

10 The epoxy acetate 19 was prepared by Mr. F. Hofman during his doctoral study. The synthesis of this compound was carried out in an analogous way as described for 17, starting from perhydroisobenzofuran. The compound was admixed with 30% of the 2-β acetate. Unfortunately no satisfactory elementary analysis of this compound could be obtained.

11 Ley, S.V., Simpkins, N.S., and Whittle, A.J., J. Chem. Soc., Chem. Commun., (1981), 1001.

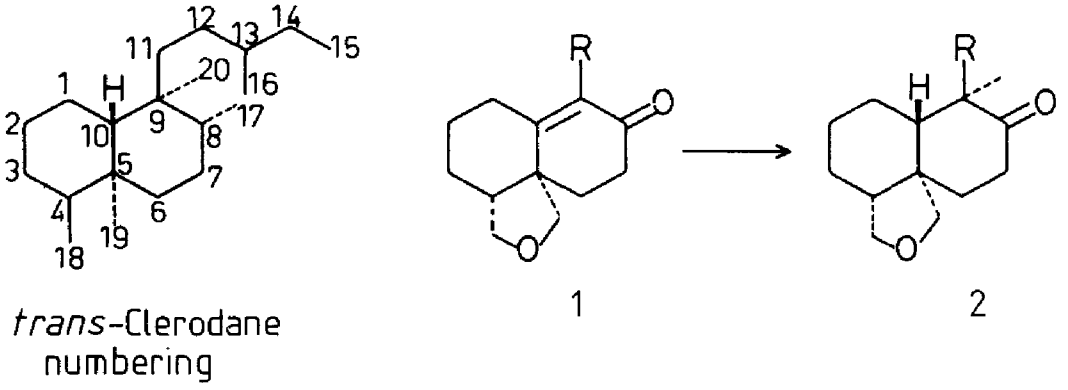
12 For a review on insect antifeedants, see Chapman, R.F., Bull. Ent. Res. (1974), *64*, 339.

10 GENERAL DISCUSSION.

During the investigations described in this thesis considerable progress has been made in the approach to the total synthesis of clerodane type diterpenes.

With the synthesis of enone 1, a versatile intermediate in the total synthesis of these compounds was obtained. Reductive alkylation of 1 afforded a *trans* fused A/B ring system, while at the same time the side chain precuror at C-9 (R) could be introduced in a stereospecific way (scheme 10.1).

Scheme 10.1



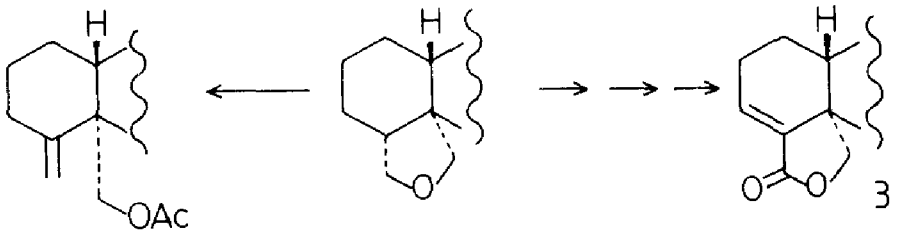
trans-Clerodane numbering

1 2

The transformation of the oxidized functionalities at C-18 and C-19 into a cyclic ether, proved to be a unique protection against a variety of reagents. The rapid and efficient transformation of this group into functionalities frequently encountered in clerodanes could readily be effectuated.

The construction of an α,β-unsaturated lactone (as in 3), starting from the cyclic ether 2, was achieved by ruthenium tetroxide oxidation, followed by the introduction of a double bond in ring A (scheme 10.2).

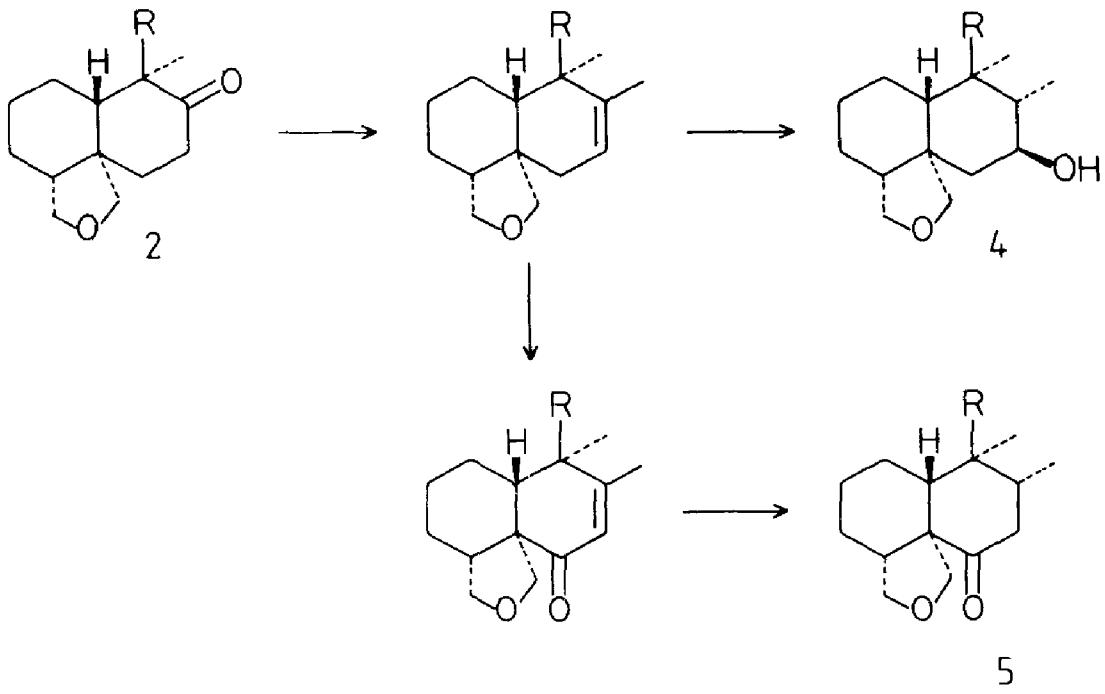
Scheme 10.2



More interesting is the regiospecific cleavage of the ether moiety by pyridinium hydrochloride or pyridinium hydrobromide. This method opens up routes to the synthesis of the insect antifeedant clerodanes like ajugarin I and clerodin (see also scheme 10.4).

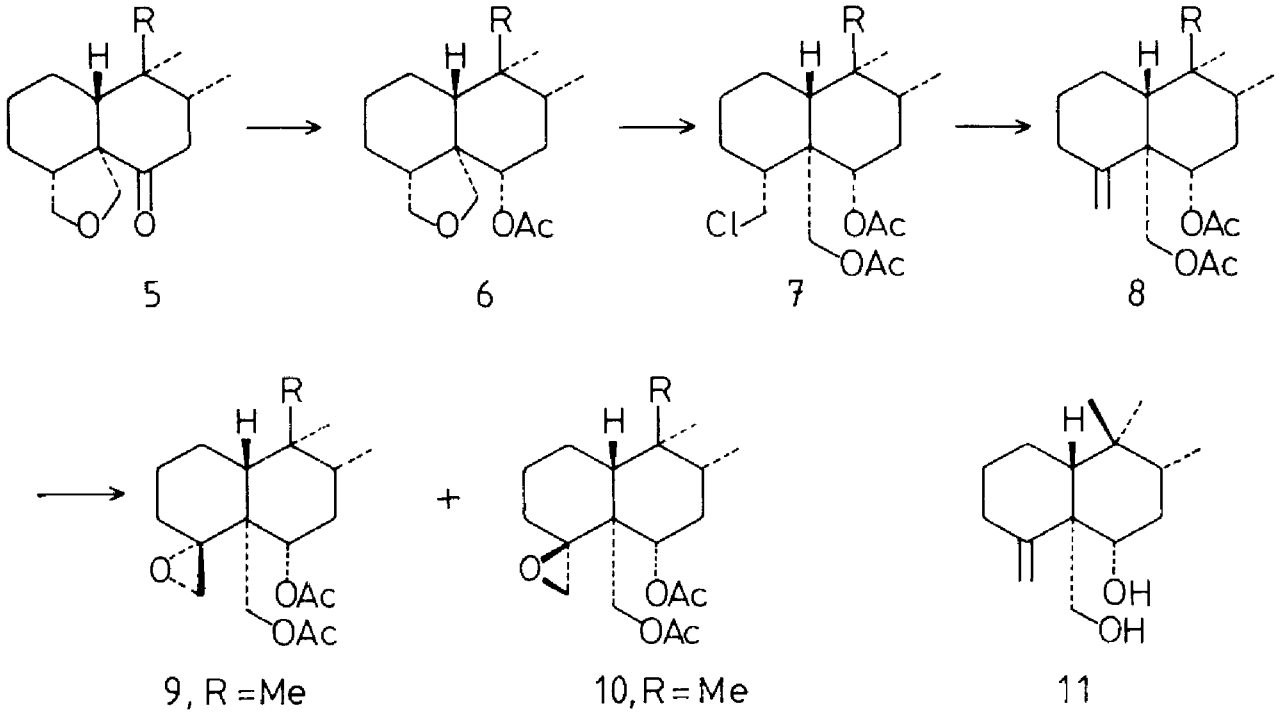
Two different methods were developed for the stereospecific introduction of the equatorial methyl at C-8. These methods involve the simultaneous oxidation of C-6 and C-7 in compounds 4 and 5 respectively (scheme 10.3). Up to the time of writing no other methods for the stereospecific introduction of the C-8 methyl have been described in the literature.

Scheme 10.3



Starting from the ketone 5, model compounds for the study of structure-activity relationships of the insect antifeedant clerodanes could be synthesized. Reduction of 5 and subsequent acetylation, afforded the acetate 6. Ether cleavage with pyridine hydrochloride then gave the chlorodiacetate 7, which in turn was dehydrohalogenated to the olefin 8. The isomeric epoxides 9 and 10 were obtained on epoxidation of olefin 8 (scheme 10.4).

Scheme 10.4

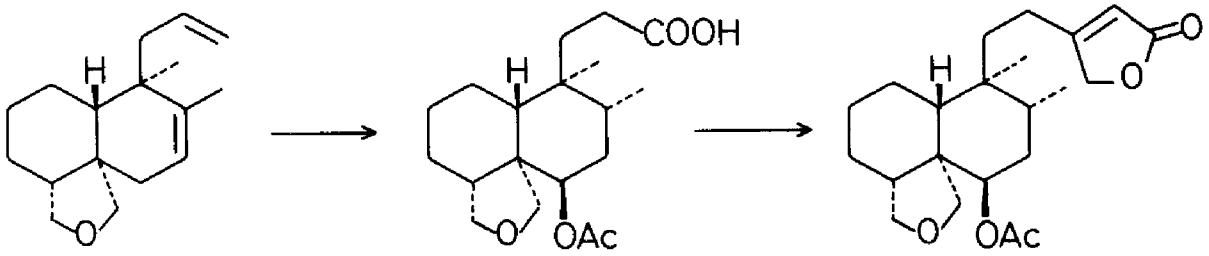


Epoxide 9 could be synthesized in a stereospecific way *via* a vanadium catalysed epoxidation of the diol 11.

These partial clerodane structures possessing epoxy diacetate functions are of interest for structure-activity relationship studies since there is a debate in the literature about which part of the clerodane molecule is the active center for insect antifeedant activity. Entomological tests of these compounds make it clear that at least part of the activity is situated in the epoxy diacetate moiety of the molecule.

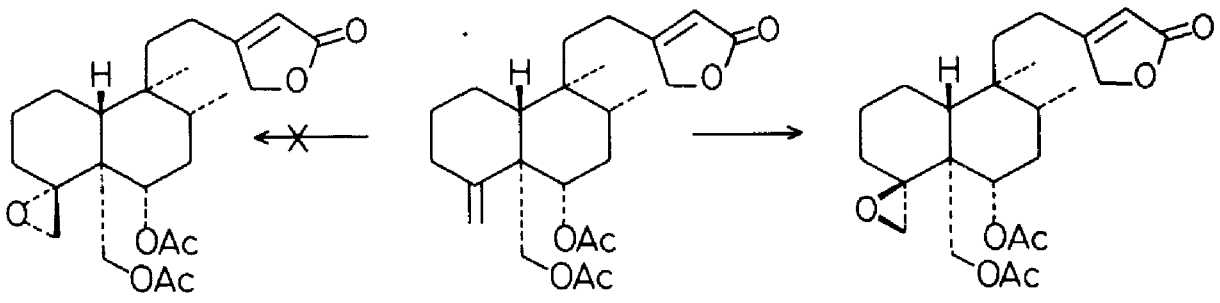
In order to synthesize the insect antifeedant ajugarin I (12) we focussed our attention on the construction of the butenolide containing side chain at C-9. An efficient method was developed to transform an allyl substituent at C-9 into the clerodane side chain. This method was tested for a number of model compounds, as is illustrated in scheme 10.5.

Scheme 10.5



A combination of the above described model syntheses in the same molecule should lead to the total synthesis of ajugarin I. It proved possible to construct a molecule (13) possessing five of the six chiralities of ajugarin I. Unfortunately the introduction of the epoxide at C-4 with *m*-chloroperbenzoic acid afforded the opposite stereochemistry at this center, as compared to ajugarin I. This led to structure 14 (scheme 10.6).

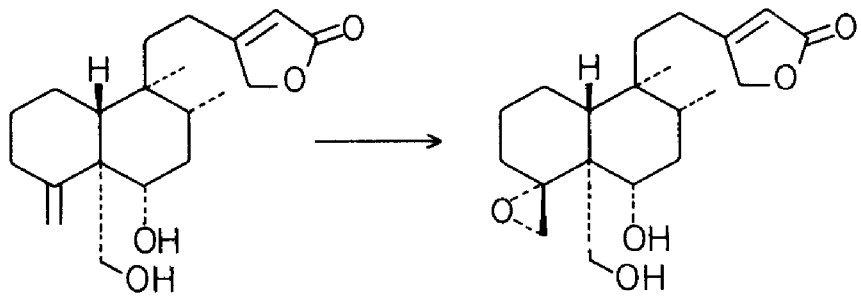
Scheme 10.6



12 13 14

The vanadium catalysed epoxidation of diol 15 however, is expected to afford the reverse stereochemistry at C-4 (*vide supra*). Subsequent acetylation of the epoxydiol 16 would then afford ajugarin I (scheme 10.7).

Scheme 10.7



15 16

Owing to the lack of material at the end of the long sequence of reactions the latter transformations could not be studied in full detail. We have an indication, however, that probably a small amount of ajugarin I was formed.

It may be expected that the total synthesis of clerodanes *via* the intermediates described in this thesis will be possible in the near future. At the same time several important model compounds may be obtained to study structure-activity relationships of the antifeedant clerodanes in greater detail.

SAMENVATTING.

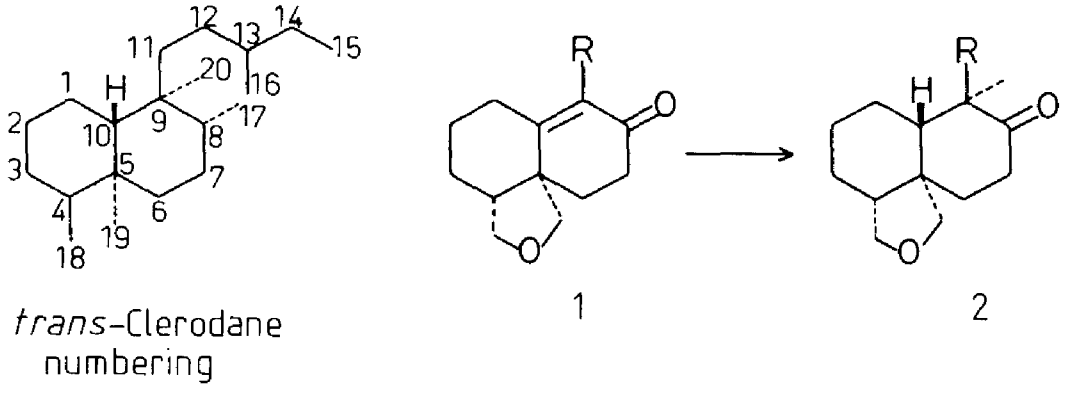
Het in dit proefschrift beschreven onderzoek had tot doel een methode te ontwikkelen voor de totaalsynthese van clerodaan type diterpenen. Deze methode moest tevens toepasbaar zijn om ook de belangrijke fysiologisch actieve clerodanen te kunnen synthetiseren.

In hoofdstuk 1 wordt een overzicht gegeven van de nomenclatuur, de biosynthese, het vóórkomen en de biologische activiteit van de clerodanen.

De diverse studies naar de synthese van clerodanen welke in de literatuur verschenen zijn, worden in hoofdstuk 2 kort weergegeven.

In hoofdstuk 3 wordt het onderzoek naar een algemeen toepasbaar synthon voor clerodaan totaalsynthese beschreven. Na enige inleidende experimenten blijkt dat de vorming van een cyclische ether in een octalon systeem, weergegeven met formule 1, een unieke methode is voor de bescherming van geoxideerde functies op C-18 en C-19. Reductieve alkylering van 1 gaf een *trans* verknoopt A/B ring systeem, terwijl tegelijkertijd de zij-keten op C-9 op een stereospecifieke wijze ingevoerd kon worden (schema 1).

Schema 1

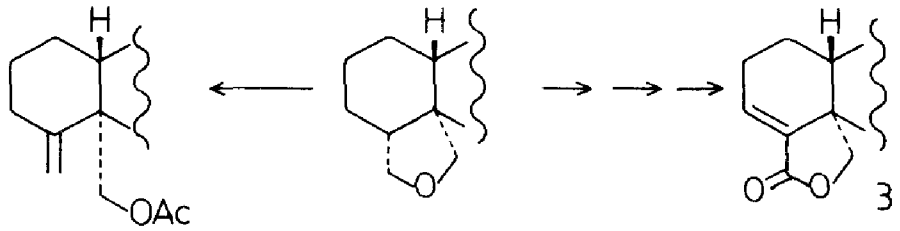


trans-Clerodane numbering

De vorming van een α,β-onverzadigde lacton (zoals in 3), werd op eenvoudige wijze geëffectueerd door ruthenium tetroxide oxidatie

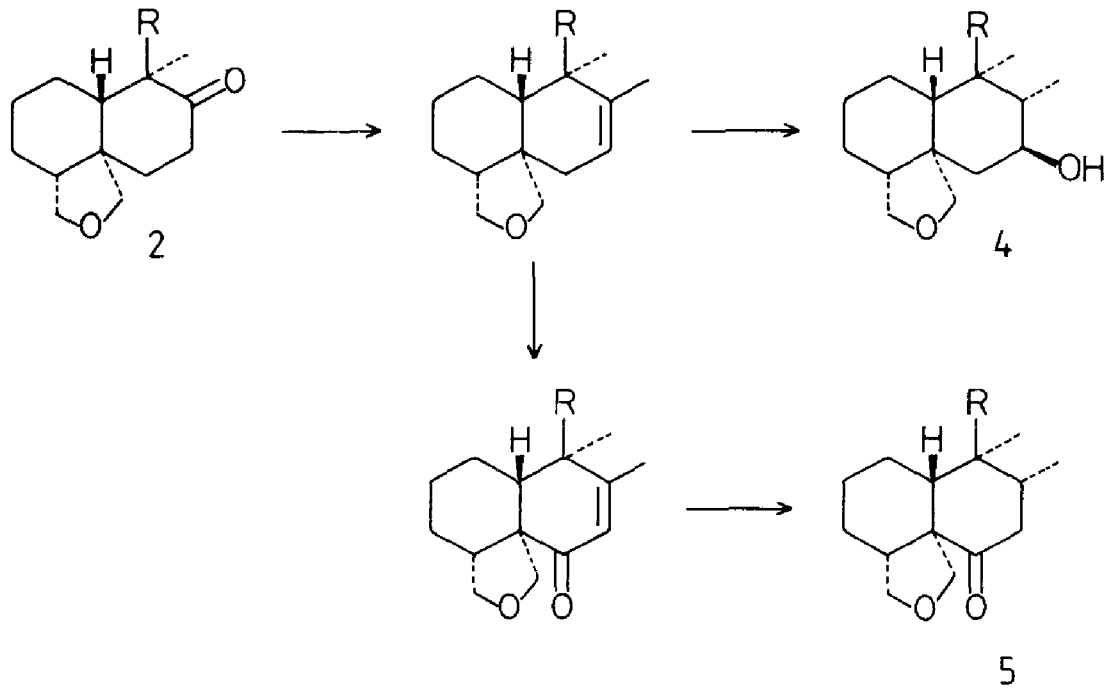
van 2, gevolgd door invoering van de dubbele band in ring A (schema 2).

Schema 2



Interessanter is de regiospecifieke ethersplitsing door pyridine hydrochloride of pyridine hydrobromide. Deze methode, (beschreven in hoofdstuk 5) opent mogelijkheden om "insect antifeedant" clerodanen zoals ajugarin I (12) te synthetiseren (zie ook schema 4).

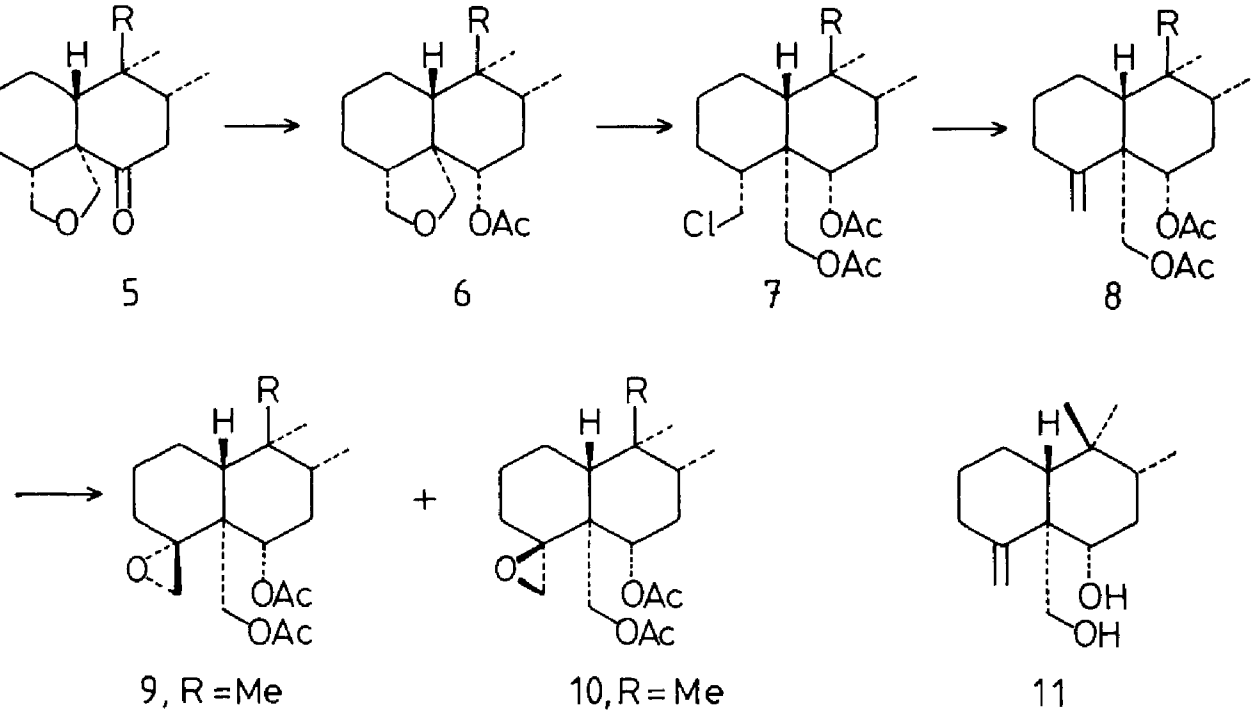
Schema 3



Er werden twee verschillende mogelijkheden ontwikkeld om de equatoriale methylgroep op koolstofatoom 8 te introduceren (hoofdstuk 4). Via deze methodes kunnen tevens C-6 en C-7 in respectivelijk verbinding 4 en 5 geoxideerd worden (schema 3). In de tot op heden verschenen literatuur zijn geen andere methoden beschreven, waarbij de C-8 methyl groep stereospecifiek wordt aangebracht.

Uitgaande van keton 5 kunnen modelverbindingen gesynthetiseerd worden die belangrijk zijn voor het bestuderen van structuuractiviteitsrelaties van de "antifeedant" clerodanen. De synthese van een tweetal model verbindingen wordt in hoofdstuk 5 beschreven.
Reductie van keton 5 gaf, na acetylering, acetaat 6. Ether splitsing met pyridine hydrochloride leidde tot chlorodiacetaat 7. Na dehydrohalogenering van 7 werd 8 verkregen die na epoxidatie de twee isomere epoxides 9 en 10 opleverde (schema 4).

Schema 4

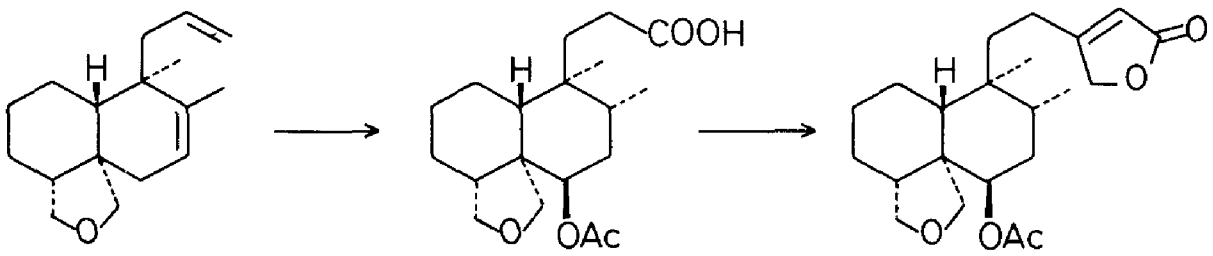


Epoxide 9 kon ook op een stereospecifieke manier gesynthetiseerd worden via de vanadium-gekatalyseerde epoxidatie van diol 11.
De structuur van 9 werd door middel van een röntgenanalyse bevestigd (hoofdstuk 6).

Deze partiële clerodaan structuren welke epoxy-diacetaat functies bevatten, zijn van belang voor structuur-activiteitsrelatie studies. Er is, blijkens de literatuur, een verschil van opvatting tussen diverse auteurs, over welk gedeelte van het clerodaan molecuul verantwoordelijk is voor de "antifeedant" activiteit. Entomologische tests van deze verbindingen, welke in hoofdstuk 9 beschreven zijn, maken duidelijk, dat tenminste een gedeelte van de activiteit uit de aanwezigheid van de epoxydiacetaat groepen verklaard moet worden.

Om het "antifeedant" actieve ajugarin I (12) te synthetiseren werd het onderzoek verder geconcentreerd op het vervaardigen van de butenolide-bevattende zijketen op C-9. In schema 5 wordt weergegeven hoe een allyl substituent omgevormd kan worden in de vereiste zijketen.

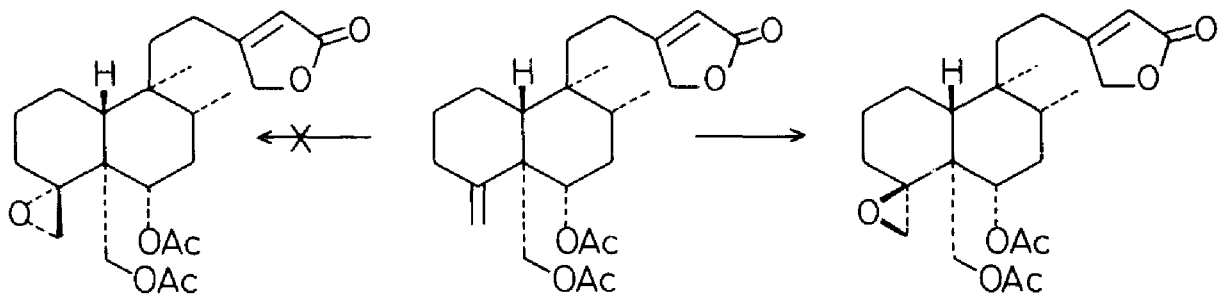
Schema 5



In hoofdstuk 7 wordt beschreven hoe, door toepassing van de hierboven beschreven methodes, ajugarin I synthetisch benaderd kan worden. Aldus komt men vrij snel tot een molecuul (13) waarin reeds vijf van de zes asymmetrische centra van ajugarin I aanwezig zijn.

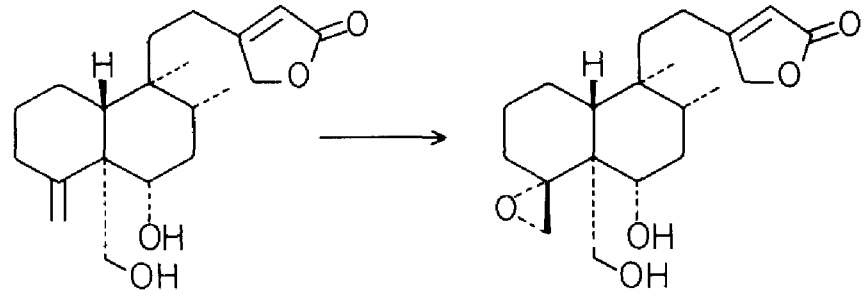
Ongelukkigerwijze leverde de epoxidatie van de dubbele band op C-4 met *m*-chloor perbenzoëzuur de tegenovergestelde stereochemie voor het epoxide, vergeleken met ajugarin I. Dit leidde tot structuur 14 (schema 6).

Schema 6



12 13 14

De vanadium gekatalyseerde epoxidatie van diol 15 zal waarschijnlijk wél tot de goede stereochemie op C-4 leiden (zie boven). Acetylering van het aldus verkregen epoxy diol 16 zal dan ajugarin I geven.



15 16

Echter, aan het einde van de lange reeks synthesestappen, was er slechts zéér weinig van verbinding 16 over. Deze laatste reactie kon daarom nog niet goed bestudeerd worden, hoewel er wél aanwijzingen zijn dat er inderdaad een kleine hoeveelheid ajugarin I gevormd is.

In hoofdstuk 8 wordt ingegaan op de toepassing van de ^{13}C-NMR waarden welke verkregen zijn voor de belangrijkste verbindingen uit dit proefschrift. Deze gegevens kunnen van groot belang zijn voor de correcte toekenning van ^{13}C-NMR waarden in de natuurproducten, zoals aan de hand van enige voorbeelden geïllustreerd wordt.

Hoofdstuk 9 behandelt de reeds hierboven genoemde entomologische tests. In hoofdstuk 10 wordt, op een analoge wijze als in deze samenvatting, een overzicht gegeven van de belangrijkste punten van dit onderzoek.

CURRICULUM VITAE.

Op 7 oktober 1952 ben ik te Aardenburg in Zeeland geboren. Na het behalen van het HBS-B diploma aan de Rijksscholengemeenschap "Koningin Wilhelmina" te Oostburg in 1970 begon ik mijn studie in de chemie aan de Rijksuniversiteit te Utrecht.
In maart 1974 werd het kandidaatsdiploma behaald. Als hoofdvak heb ik organische chemie gedaan onder leiding van Prof. dr. C.A. Salemink. Voor dit onderzoek, de synthese van pyrolyseprodukten van cannabidiol, werd in 1976 een universitaire studieprijs toegekend. Het bijvak toxicologie, onder leiding van Prof. dr. R.A.A. Maes, werd uitgevoerd bij het Rijksinstituut voor de Volksgezondheid en bestond uit het opstellen van residu-analyse methoden voor ureumherbiciden. Na het behalen van het doctoraalexamen in september 1976 heb ik nog gedurende een jaar mijn hoofdvakonderzoek voortgezet, in de functie van "ambtenaar buiten bezwaar van 's rijks schatkist".

Sedert 15 februari 1978 ben ik werkzaam op de afdeling Organische Chemie van de Landbouwhogeschool te Wageningen, waar ik, onder leiding van Prof. dr. Ae. de Groot, het in dit proefschrift beschreven onderzoek heb verricht. Daarnaast besteedde ik een deel van mijn tijd aan het begeleiden van studenten in diverse fasen van hun studie.

STELLINGEN

1 Het mechanisme dat Kurihara *et al.* voorstellen voor de vorming van 8-carbethoxy-3-cyano-7-methyl-6H-pyrazolo[1,5-a][1,3]diazepin-6-one en 8-carbethoxy-3-carbamoyl-7-methyl-6H-pyrazolo[1,5-a][1,3]diazepin-6-one is onwaarschijnlijk.
T. Kurihara, K. Nasu, F. Ishimori en T. Tani, J. Heterocyclic Chem., *18*, 163 (1981).

2 Bunting en Sindhuatmadja laten bij de interpretatie van de kinetiek van de reductie van 5-nitroisochinolium kationen door 1,4-dihydronicotinamides ten onrechte een mogelijke dimerisatie van de 5-nitroisochinolium kationen buiten beschouwing.
J.W. Bunting en S. Sindhuatmadja, J. Org. Chem.,*46*, 4211 (1981).

3 Ten onrechte houden Laredo *et al.* geen rekening met wijzigingen in de defectstructuur door defect-defect interactie. Hierdoor is de toekenning van de ITC piek bij 219 K en de verklaring van de afname van de concentratie van naaste buur dipolen aan grote twijfel onderhevig.
E. Laredo, M. Puma, N. Suarez en D.R. Figueroa, Phys. Rev., B *23*, 3009 (1981).

4 De wijze waarop Gács Baitz *et al.* tot de structuurtoekenning van Teucrin H2 komen is aanvechtbaar.
E. Gács Baitz, L. Radics, G.B. Oganessian en V.A. Mnatsakanian, Phytochemistry, *17*, 1967 (1978).

5 De sterke antifeedant activiteit die Yajima *et al.* voor bergapteen vermelden is niet in overeenstemming met eerdere door hun gevonden resultaten.
T. Yajima, N. Kato en N. Munakata, Agr. Biol. Chem., *41*, 1263 (1977).
S. Hosozawa, N. Kato en K. Munakata, Agr. Biol. Chem., *38*, 832 (1974).

6 De conclusie van Bruijns en Froeling, dat een direct verband tussen de hoogte van de nitraatinname en de concentratie van nitrosaminen ontbreekt, mist de nodige wetenschappelijke onderbouw.
E. Bruijns en P.G.A.M. Froeling, Ned. T. Geneesk., *125*, 1298, (1981).

7 De verteerbaarheid van droge stof in de pens hangt niet zo zeer af van de retentietijd van de vaste en vloeibare fase, zoals Crawford, Jr. *et al.* suggereren, maar is vooral een functie van de pH.
R.J. Crawford, Jr., W.H. Hoover en P.H. Knowlton, J. Animal Sci., *51*, 975 (1980).

8 Bij de huidige werkloosheid dienen geslaagde sollicitanten kansspelbelasting te betalen. De hieruit voortvloeiende gelden dienen *direct* aan de bestrijding van de werkloosheid ten goede te komen.

J.M. Luteijn Wageningen, 12 februari 1982

Investigations into the total synthesis of insect antifeedant clerodanes.