STUDIES TOWARDS THE TOTAL SYNTHESIS OF INSECT ANTIFEEDANT CLERODANES

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STUDIES TOWARDS THE TOTAL SYNTHESIS OF INSECT ANTIFEEDANT CLERODANES

Proefschrift
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op gezag van de rector magnificus,
dr. H.C. van der Plas,
in het openbaar te verdedigen
op vrijdag 9 juni 1989
des namiddags te vier uur in de aula
van de Landbouwuniversiteit te Wageningen.

Stellingen

1. De conclusie van Ley *et al.*, dat het door hen gesynthetiseerde fragment van azadirachtine een vrijwel even sterke vraatvergallende werking heeft als azadirachtine zelf, kan niet worden afgeleid uit de door hen vermelde gegevens.
   S.V. Ley, D. Santafianos, W.M. Blaney en M.S.J. Simmonds, Tetrahedron Lett., **28**, 221 (1987).

2. De clerodaan naamgeving heeft behoefte aan duidelijke afspraken, gezien het feit dat Piers en Wai racemische totaalsyntheses van ent-clerodanen beschrijven.
   E. Piers en J.S.M. Wai, J. Chem. Soc., Chem. Commun., 1245 (1988).

3. De door Utaka *et al.* gesuggereerde trans selectieve reductie van 3,4,4a,5-tetrahydro-4aβ-methylnaftaleen-1(2H),7(6H)-dion is aan bedenkingen onderhevig.
   M. Utaka, Y. Fujii en A. Takeda, Chem. Lett., 1103 (1986).

4. Kobayashi *et al.* suggereren met de titel van hun artikel een multigram schaal synthese van leukotrieen B_4, terwijl ze een subgram schaal synthese beschrijven.
   Y. Kobayashi, T. Shimazaki en F. Sato, Tetrahedron Lett., **28**, 5849 (1987).

5. De door Khuroo *et al.* aangedragen gegevens, bij de structuuropheldering van "3α-hydroxy-drimmanyl-8-methanoaat", zijn niet met elkaar verenigbaar.
   M.A. Khuroo, M.A. Qureshi, T.K. Razdan en P. Nichols, Phytochem., **27**, 3541 (1988).

6. Het door Springett en Adams gepostuleerde mechanisme voor de biogenese van "1-cyano-2,3-epithiopropaan" is aan bedenkingen onderhevig.
   M.B. Springett en J.B. Adams, J. Sci. Food Agric., **46**, 211 (1988).

7. Aan de door Atta-ur-Rahman *et al.* beschreven resultaten van de NOE-difference experimenten bij de structuuropheldering van de configuratie op C-20 van tubotaiwine moet geen waarde worden gehecht.
   Atta-ur-Rahman, K.A. Alvi en A. Muzaffar, Planta Med., 325 (1986).

8. Het is onwaarschijnlijk dat Wu en Jean Burnell, bij de omzetting van een acetaal tot een 1,3-cyclopentadion eenheid, de gehydrolyseerde uitgangsstof nauwelijks terug kunnen vinden bij de GC-MS analyse.
   Y.-J. Wu en D. Jean Burnell, Tetrahedron Lett., **29**, 4369 (1988).

9. De wijze waarop Sakai en Ozaki het begrip "protopectinase" gebruiken schept geen duidelijkheid over de werking van het enzym, aangezien de structuur van protopectine per definitie zeer veelomvattend is.
   T. Sakai en Y. Ozaki, Agric. Biol. Chem., **52**, 1091 (1988).

10. Martin-Alvarez *et al.* gaan er bij de analyse van whisky monsters ten onrechte aan voorbij dat er wel meer dan drie goedkope, echte whisky merken bestaan.
    P.J. Martin-Alvarez, M.D. Cabezudo, J. Sanz, A. Herranz, P. de la Serna en C. Barro, J. Sci. Food Agric., **45**, 347 (1988).

11. Een goede formulering van stellingen getuigt meer van kwaliteit op journalistiek gebied dan van kwaliteit op gebied van wetenschappelijk onderzoek.

Stellingen behorende bij het proefschrift " *studies towards the total synthesis of insect antifeedant clerodanes* " door Jan Vader. Wageningen, 9 juni 1989.

VOORWOORD

Bij de voltooiing van dit proefschrift wil ik graag iedereen bedanken, die heeft bijgedragen aan de totstandkoming ervan. Velen die werkzaam zijn (geweest) op de vakgroep Organische chemie wil ik danken voor de stimulerende discussies, technische hulp, verrichting van deel-onderzoeken, hulp op spectroscopisch gebied en hulp bij het verzorgen van tekst en tekeningen van dit proefschrift. De volgende personen wil ik graag met name noemen voor hun bijdragen.

Aede de Groot, voor de mogelijkheid die hij mij heeft geboden dit onderzoek onder zijn enthousiaste leiding uit te voeren, voor zijn voortdurende belangstelling en voor de snelle en kritische beoordeling van manuscripten.

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Lucas Doddema, Rob Peperzak en Hubert Sengers, voor hun belangrijke bijdragen aan dit onderzoek.

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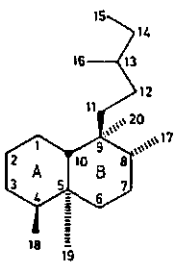
1. STRUCTURE, NOMENCLATURE, BIOSYNTHESIS, OCCURRENCE AND BIOLOGICAL ACTIVITY

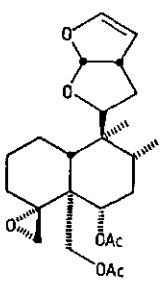
1.1 STRUCTURE

The term clerodane refers to a group of compounds with the general structure **1**[1]. One of the first clerodanes was isolated in 1937 from the Indian bhat tree, *clerodendron infortunatum*. From that time it took a quarter-century untill the structure was elucidated. This compound was called clerodin and the corresponding subgroup of diterpenes was called clerodanes.

Figure 1.1



1



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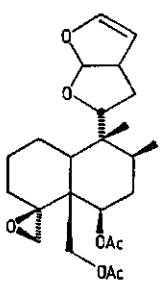
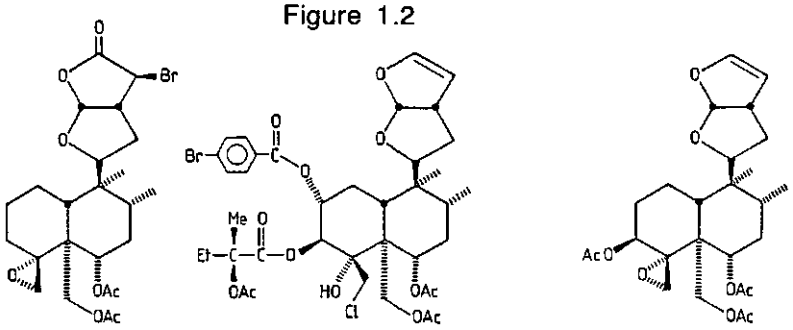


3

The determination of the structure of clerodin was based on chemical evidence and mass spectrometric work[2]. Moreover, the heavy-atom derivative, clerodin bromo-lactone **4** was subjected to an X-ray study[3]. Unfortunately, the clerodin bromo-lactone was erroneously presented as its antipodal structure. This lead to the conclusion that clerodin should be represented by structure **3**.

In the following decade, however, some clerodanes were isolated and characterized with an antipodal chirality as compared to structure **3**. Especially the doubly established absolute configuration of the heavy-atom containing clerodendrin A derivative **5**[4] gave rise to some doubt about the earlier proposed absolute configuration of clerodin. Furthermore the comparison of the O.R.D. and C.D. curves of derivatives of clerodendrin A with those of derivatives of cholestenone confirmed these doubts[5].

Figure 1.2



4 5 6

Caryoptin **6** and clerodin had been shown physico-chemically to share a common chirality. However, the absolute structure of caryoptin, determined by the C.D. exciton method[6], was antipodal to the supposed absolute structure of clerodin determined by the X-ray method and attempts were made to explain away these contradictions.
In 1978 Harada and Uda compared the C.D. spectra of derivatives of clerodin, caryoptin and clerodendrin A and concluded that the originally reported structures for clerodin and caryoptin were antipodal to the naturally occurring compounds **2** and **6**[7]. This conclusion was at the same time confirmed by a new X-ray study of the clerodin bromolactone **4**, in which the earlier X-ray results were verified and the conclusion was drawn that a very unfortunate error had been made during the preparation (copying?) of the diagrams and stereoformulae in the original reports[8].

1.2 NOMENCLATURE

After the isolation and characterization of clerodin **2**, many similar diterpenes were isolated and this class of diterpenes was initially called: clerodanes. As described in chapter 1.1, the initially proposed absolute structure **3** later showed to be the enantiomer of the naturally occurring clerodin **2**. So a nomenclature problem arose. According to the Rowe nomenclature[1], the skeleton as represented in structure **1** is referred to as an ent-clerodane. Thus, the naturally occurring clerodanes should be called ent-clerodanes, which could lead to some confusion. Therefore, Rogers *et al.*[8] proposed to introduce the name neo-clerodane for the naturally occurring clerodanes. So the neo-clerodane in this new

nomenclature is synonymous to the ent-clerodane in the old nomenclature. In the same way ent-neo-clerodane is synonymous to clerodane. However, Piozzi[9] suggested to adopt the old Rowe nomenclature in which the biogenetic relation between the ent-clerodanes and the ent-labdanes is clearly established (see chapter 1.3). According to the proposal of Rogers the neo-clerodanes would be related biogenetically to the ent-labdanes.

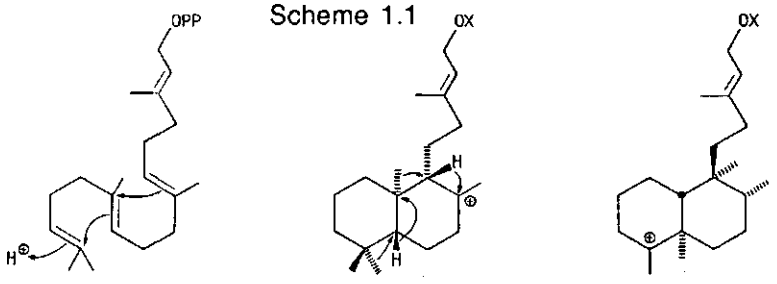
One of the drawbacks of the Rowe/Piozzi nomenclature is the laziness of many researchers with respect to prefixes. According to this nomenclature, the omission of the prefix may suggest a wrong absolute structure, whereas the omission of prefixes according to the Rogers nomenclature suggests nothing about the chirality, because the term clerodane is non-existing.

For reasons of readability and because of the fact that all synthetic compounds described in this thesis are racemates, the prefixes will be omitted and the term clerodane either refers to skeleton **1** or to racemates.

1.3 BIOSYNTHESIS

The biosynthetic precursor of the clerodanes (see scheme 1.1) is the geranyl-geranyl pyrophosphate **7**. Proton initiated cyclization may lead to the intermediate **8**, which can be seen as an ent-labdane. Successive methyl and hydride shifts probably proceed in a concerted manner in which the migrating group is usually positioned anti to the leaving group as indicated in structure **8**. The result of these shifts is the ion **9** with a trans-clerodane skeleton. This mechanism seems very likely, especially for the low oxygenated clerodanes like kolavenol[10].

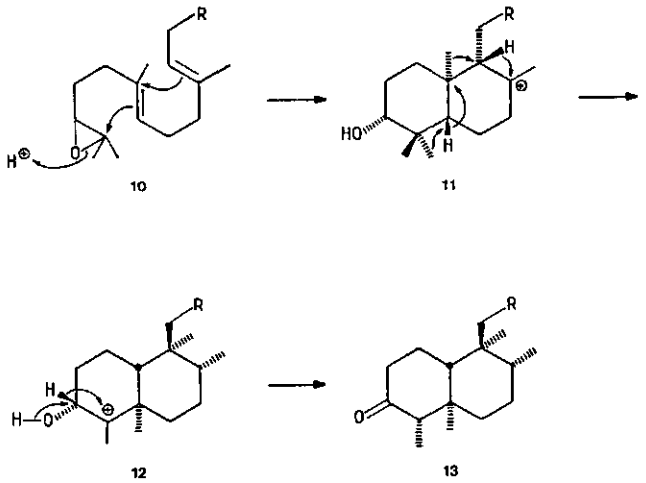
Scheme 1.1



7 8 9

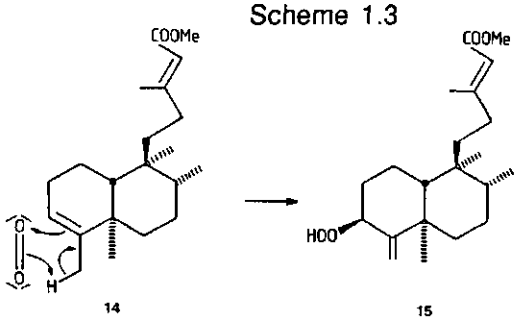
Clerodanes with oxygenated functions in the A-ring may very well originate from the epoxyde **10** as indicated in scheme 1.2[11].

Scheme 1.2



Recently Singh and Singh isolated the hydroperoxyclerodane **15**[12], which has a β-hydroperoxy substituent at C_3. They suggest that this compound arises from the "ene" reaction of oxygen and methyl kolavenoate **14** (see scheme 1.3). The result of such an "ene" reaction is a β-oxygenated carbon atom in contrast to the acid-catalyzed-epoxyde-ring-opening-initiated-cyclization reaction, as described in scheme 1.2, which results in an α-oxygenated carbon atom as in compound **12**.

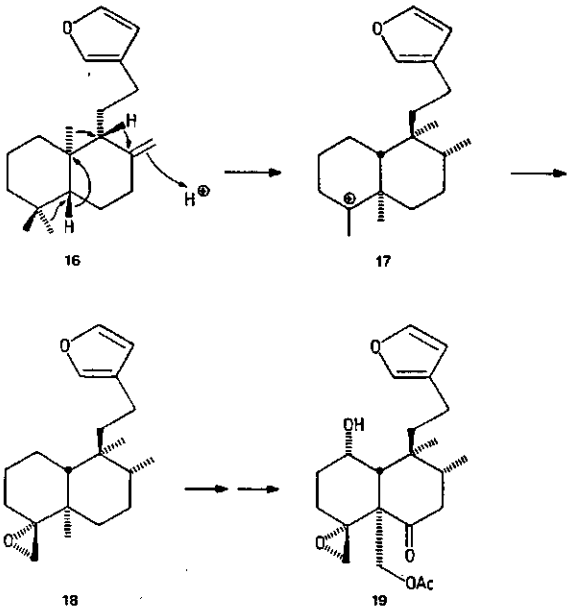
Scheme 1.3



Piozzi and coworkers have postulated a biogenetic pathway for the trans-clerodanes, found in several species of the genus Teucrium of the family

of the Labiatae[13]. They postulate that the ent-furyllabdane **16** is the biogenetic precursor for a series of trans-clerodanes found in Teucrium species. Protonation of the ent-furyllabdane followed by the successive methyl and hydride shifts, as indicated in scheme 1.4, would lead to the carbocation **17**. The biological transformation of this carbocation to the epoxyde **18** seems likely to occur. On the other hand the biotransformation of the epoxyde **18** to fruticolone **19** obviously requires more fantasy. So they propose the formation of the furan ring **prior** to the cyclization to the clerodane skeleton and they suggest that further oxidation reactions at the A/B ring system take place **after** the clerodane skeleton is formed.

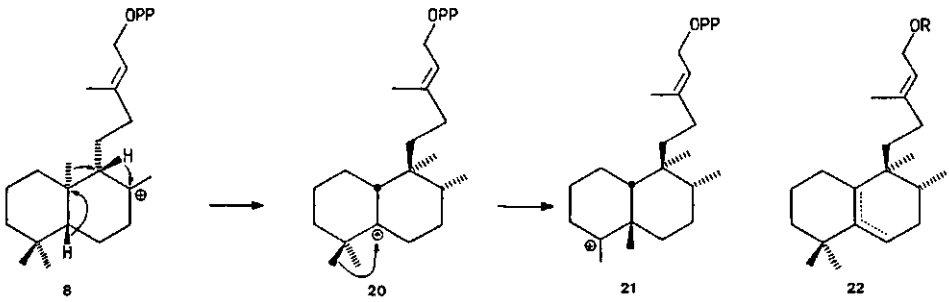
Scheme 1.4



Clerodanes with a cis A/B ring junction have also been isolated. They are found in some Labiatae genera, but especially in some Solidago species (Compositae) in which both cis- and trans-clerodanes are found[14]. The formation of cis-clerodanes (scheme 1.5) cannot be explained by a fully concerted process. Migration of the α-methyl in carbocation **20** will lead to the trans-clerodanes and migration of the β-methyl will result in a cis-clerodane.

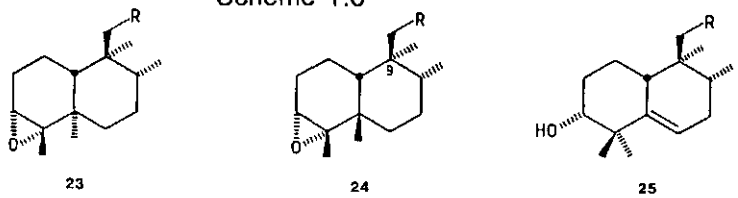
Some natural products are found in which this last α- or β-methyl shift has not taken place at all, thus leading to a class of half rearranged diterpenes[15], the chettaphanes **22**. This last methyl shift is probably the most striking feature in the biosynthesis of the cis- and trans-clerodanes.

Scheme 1.5



In vitro studies of the acid catalyzed rearrangements of some di- and trinor-labdane epoxydes[16] and some pimarane epoxydes[17] indicate that migration of the angular methyl group could actually occur. Also the angular hydride shift is observed leading to a carbocation of type **20**. Further rearrangement to the clerodane skeleton did not occur because this would lead to strong diaxial interaction with the C_9 α-methyl group. This unfavorable diaxial interaction was elegantly shown by McCrindle and coworkers[18]. Treatment of either a trans-clerodane-3,4-epoxyde **23** or a cis-clerodane-3,4-epoxyde **24** with boron trifluoride affords mainly a product **25**, in which a reverse methyl shift has taken place.

Scheme 1.6



Finally, the natural occurrence of quite a few 19-norclerodanes should be mentioned. The formation of these compounds is explained by decarboxylation of clerodane[19] or chettaphane[15d] type precursors, by a retro-Prins reaction initiated by the opening of the C_4-C_{18} epoxyde[20] or by a retroaldolic splitting of formaldehyde in clerodanes having a C_6-carbonyl group[9].

1.4 OCCURRENCE

At present over 500 clerodanes are known and several of these have useful biological activities. They have been isolated from numerous species of many plant families[20,21]. Piozzi has already twice reviewed[9,13] the chemistry of furo-clerodane diterpenes from species of the genus Teucrium (Labiatae). However, the natural occurrence of clerodanes is not limited to plants. They have also been found in micro-organisms and marine animals. Some 17-norclerodanes have been isolated form the fungus Oidiodendron truncatum[22]. Some half and fully rearranged clerodanes have been found from species of the sponge Agelas[23] and have shown to possess antimicrobial activity. Some clerodane-like compounds were isolated from the sponge Dysidea amblia[24].

1.5 BIOLOGICAL ACTIVITY

Clerodanes can be held responsible for a wide variety of biological activities. Some clerodanes show inhibitory effects on the growth of micro-organisms[22,23], the contractive responses of smooth muscles and the enzymic reactions of Na,K-ATPase[23b].

A few piscicidal clerodanes are known[25], for example maingayic acid and callicarpone. The latter compounds were isolated from the leaves of callicarpa plants, which had been used to stupefy fish in the Caroline and Philippine Islands.

Clerodanes with anti-peptic-ulcer activity have been isolated from the Thai medicinal herb plan-noi, Croton subbyratus[26].

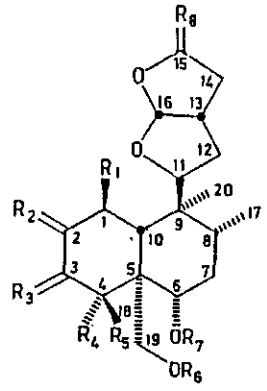
Psychotropic clerodanes have been isolated from the hallucinogenic Mexican plant, Salvia divinorum[27].

The search for antitumor compounds from the Panamanian plant, Rondeletia panamensis, has afforded two cytotoxic clerodanes[28].

The best known and best established bioactivity is the insect-antifeedant activity[29]. Being well aware of the incompleteness, only a few studies with respect to the structure-activity relationship will be described here. The fact that the studies partially overlap is considered to be an advantage, because it allows some tentative conclusions about steric and functional group requirements.

The compounds discussed here have the general formula **26**.

Figure 1.3



26

	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	Double bonds	Activity
a	H	H,αOH	H,βO$_2$CC(OAc)(Me)(Et)	O	CH_2	Ac	Ac	H	7-8 and 14-15	300[1] 200[3]
b	H	H,αOH	H,βO$_2$CC(OAc)(Me)(Et)	O	CH_2	Ac	Ac	H	14-15	200[1]
c	H	H_2	H_2	O	CH_2	Ac	Ac	H	14-15	80[1] 50[2,3]
d	H	H,αOH	H,βOH	O	CH_2	H	H	H	7-8 and 14-15	> 1000[1]
e	H	H,αOH	H,βOH	O	CH_2	H	H	H_2	7-8	> 1000[1]
f	H	H,αOH	H,βO$_2$CC(OAc)(Me)(Et)	O	CH_2	Ac	Ac	H_2	7-8	500[1]
g	H	H,αOH	H,βO$_2$CC(OAc)(Me)(Et)	O	CH_2	Ac	Ac	H,OMe	7-8	15[1]
h	H	H,αOAc	H,βO$_2$CC(OAc)(Me)(Et)	O	CH_2	Ac	Ac	H	7-8 and 14-15	> 1000[1]
i	H	H,αOH	H,βOH	OH	Me	H	H	H	7-8 and 14-15	> 1000[1]
j	H	H,αOH	H,βOH	OH	Me	H	H	H_2	7-8	> 1000[1]
k	H	H_2	H,αOAc	O	CH_2	Ac	Ac	H	14-15	200[2,3]
l	H	H_2	H_2	O	CH_2	Ac	Ac	H,OEt		200[2]

Figure 1.3 (continued)

m	H	H_2	H,αOAc	O	CH_2	Ac	Ac	H,OEt		> 1000[2]
n	H	H_2	H_2	O	CH_2	Ac	Ac	H_2		50[2,3]
o	H	H_2	H,αOAc	O	CH_2	Ac	Ac	H_2		80[2,3]
p	H	H_2	H_2	O	CH_2	Ac	Ac	H,OH		50[2,3]
q	H	H_2	H,αOAc	O	CH_2	Ac	Ac	H,OH		200[2,3]
r	H	H_2	H,αOAc	O	CH_2	Ac	Ac	O		500[2]
s	H	H_2	H_2	O	CH_2	Ac	Ac	O		50[2]
t	H	H_2	H,αOH	O	CH_2	H	H	H_2		> 1000[2]
u	H	H_2	H,αO-C(Me)$_2$-R_6	O	CH_2	C(Me)$_2$-O-R_3	H	H_2		> 1000[2]
v	H	H_2	H_2	O	CH_2	H	H	H_2		> 1000[2]
w	H	H_2	H_2	O	CH_2	C(Me)$_2$-R_7	C(Me)$_2$-R_6	H_2		> 1000[2]
x	H	H_2	H,αOH	OH	Me	H	H	H_2		> 1000[2]
y	H	H_2	H,αO-C(Me)$_2$-OR_4	O-C(Me)$_2$-OR_3	Me	C(Me)$_2$-R_7	C(Me)$_2$-R_6	H_2		> 1000[2]
z	H	H_2	H_2	OH	Me	H	H	H_2		> 1000[2]
aa	H	H_2	H,αOH	O	CH_2	Ac	Ac	H	14-15	200[3]
ab	H	H_2	H,αOH	O	CH_2	Ac	Ac	H_2		100[3]
ac	H	H_2	H,βOAc	O	CH_2	Ac	Ac	H	14-15	200[3]
ad	H	H_2	H,βOAc	O	CH_2	Ac	Ac	H_2		100[3]
ae	O_2CCH(Me)(Et)	H_2	H,βOH	O	CH_2	Ac	Ac	H_2		300[4]
af	H	H,βOH	H,βO_2CCHMe$_2$	O	CH_2	Ac	Ac	H_2		30[4]
ag	H	H_2	H,βO_2CCHMe$_2$	O	CH_2	Ac	Ac	H_2		3[4]
ah	H	H,βOH	H,βO_2CCHMe$_2$	O	CH_2	Ac	Ac	H,OEt		30[4]
ai	H	H,βOH	H,βO_2CCH(Me)(Et)	O	CH_2	Ac	Ac	H_2		30[4]
aj	H	H,βOAc	H,βO_2CCHMe$_2$	O	CH_2	Ac	Ac	H_2		30[4]
ak	H	H,αOH	H,βO_2CCH(Me)(Et)	O	CH_2	Ac	Ac	H,OEt		30[4]
al	H	H,αOH	H,βO_2CCH(Me)(Et)	O	CH_2	Ac	Ac	H,OH		3[4]
am	H	H,αOAc	H,βO_2CCH(Me)(Et)	O	CH_2	Ac	Ac	H_2		30[4]
an	H	H,αOH	H,βO_2CCH(Me)(Et)	O	CH_2	Ac	Ac	H_2		0.03[4]
ao	H	H,αOH	H,βO_2CCH(Me)(Et)	O	CH_2	Ac	Ac	H	14-15	0.3[4]
ap	H	O	H,βO_2CCH(Me)(Et)	O	CH_2	Ac	Ac	O		> 750[4]
aq	OH	H_2	H,βOH	OH	Me	H	H	H_2		> 750[4]

Figure 1.3 (continued)

	Name	Activity			Name	Activity
a	clerodendrin A	300[1]	200[3]	w	saponified 14,15-dihydroclerodin 6,19-acetonide	> 1000[2]
b	clerodendrin B	200[1]		x	saponified 18-seco-14,15-dihydrocaryoptin	> 1000[2]
c	clerodin	80[1]	50[2,3]	y	saponified 18-seco-14,15-dihydrocaryoptin 3,4-6,19-diacetonide	> 1000[2]
d	saponified clerodendrin A	> 1000[1]		z	saponified 18-seco-14,15-dihydroclerodin	> 1000[2]
e	saponified dihydroclerodendrin A	> 1000[1]		aa	3-desacetylcaryoptin	200[3]
f	14,15-dihydroclerodendrin A	500[1]		ab	3-desacetyl-14,15-dihydrocaryoptin	100[3]
g	14-hydro-15-methoxyclerodendrin A	15[1]		ac	3-epicaryoptin	200[3]
h	2-acetylclerodendrin A	> 1000[1]		ad	3-epi-14,15-dihydrocaryoptin	100[3]
i	saponified 18-seco-clerodendrin A	> 1000[1]		ae	ajugareptonsin	300[4]
j	saponified 18-seco-14,15-dihydroclerodendrin A	> 1000[1]		af	ivain I	30[4]
k	caryoptin	200[2,3]		ag	ivain II	3[4]
l	15-ethoxy-14-hydroclerodin	200[2]		ah	ivain III	30[4]
m	15-ethoxy-14-hydrocaryoptin	> 1000[2]		ai	ivain IV	30[4]
n	14,15-dihydroclerodin	50[2,3]		aj	2-acetylivain I	30[4]
o	14,15-dihydrocaryoptin	80[2,3]		ak	15-ethoxy-14-hydroajugapitin	30[4]
p	14-hydro-15-hydroxyclerodin	50[2,3]		al	14-hydro-15-hydroxyajugapitin	3[4]
q	14-hydro-15-hydroxycaryoptin	200[2,3]		am	2-acetyl-14,15-dihydroajugapitin	30[4]
r	14-hydrocaryoptin-15-one	500[2]		an	14,15-dihydroajugapitin	0.03[4]
s	14-hydroclerodin-15-one	50[2]		ao	ajugapitin	0.3[4]
t	saponified 14,15-dihydrocaryoptin	> 1000[2]		ap	14-hydroajugapitin-2,15-dione	> 750[4]
u	saponified 14,15-dihydrocaryoptin 3,19-acetonide	> 1000[2]		aq	saponified 18-seco-ajugapitin	> 750[4]
v	saponified 14,15-dihydroclerodin	> 1000[2]				

[1] tested in a choice test with larvae in 3rd or 4th instar of the tabacco cut worm, Spodoptera Litura; concentration at which 100% antifeedant activity was achieved[33];

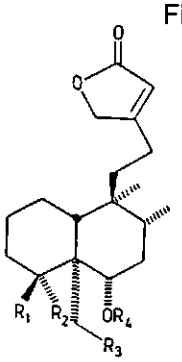
[2] see 1; except 90-100% activity[34];

[3] see 1[35];

[4] tested in a choice test with newly ecdysed 5th instar larvae of the Egyptian cotton leafworm, Spodoptera Littoralis; concentration at which less than 50% relative to the control was eaten at the time that 50% of the control was eaten[36].

Studies in the ajugarin series **27** showed that the ajugarins I, II and III have about the same antifeedant activity[34], whereas the ajugarins IV[35] and V[36] showed no antifeedant activity.

Figure 1.4



27

	R_1	R_2	R_3	R_4
I	CH_2	O	OAc	Ac
II	CH_2	O	OAc	H
III	CH_2OH	CH	OAc	Ac
IV	H	CO_2Me	H	Ac
V	CH_2	O	H	Ac

Some racemic cis- en trans-decalines were synthesized and tested to show at the best a quite limited antifeedant activity[37,38,39]. The same remarks can be made about some synthetic furans[40,41,42] and butenolides[33]. Keeping this in mind the following conclusions are drawn tentatively.

The only compound bearing a substituent at C_1 mentioned here is ajugareptonsin **26ae**. Its activity moderate, which is probably due to ringdistortion[33].

The introduction of a β-hydroxyl or a β-acetate at C_2 lowers the activity somewhat as can be seen by comparing ivain II **26ag**, ivain I **26af** and 2-acetylivain I **26aj**. An α-hydroxyl substituent may enhance the activity. This may be concluded by an indirect comparison. An α-hydroxyl compound is much more active than a β-hydroxyl compound (compare 14,15-dihydroajugapitin **26an** with ivain IV **26ai**). This increase is much greater than the decrease by the introduction of a β-hydroxyl substituent. Acetylation of the α-hydroxyl group lowers the activity drastically (compare 14,15-dihydroajugapitin **26an** with 2-acetyl-14,15-dihydro-ajugapitin **26am** or clerodendrin A **26a** with 2-acetylclerodendrin A **26h**).

Substitution at C_3 by an α-hydroxyl, an α-acetate and a β-acetate group.gives a slight decrease of activity. This can be seen by the comparison of (14,15-dihydro) clerodin **26c** (**26n**) with (14,15-dihydro)

3-desacetylcaryoptin **26aa** (**26ab**), (14,15-dihydro) caryoptin **26h** (**26o**) and (14,15-dihydro) 3-epicaryoptin **26ac** (**26ad**).

The spiroepoxyde at C_4 does not seem to be an absolute requisite for evoking antifeedant activity. Hydrolysis of the epoxyde in ajugarin I **27** results in ajugarin III, a compound with an equal activity. On the other hand, the stereochemistry of the spiroepoxyde does seem to be important. This conclusion can be drawn from the results with the synthetic decalines[37,39]. Moreover reductive cleavage of the epoxyde in dihydroclerodin **26n** results in a drastic decrease of the activity[43].

The angular α-acetoxymethyl at C_5 is probably essential. From the ajugarin series **27** this conclusion seems to be justified, since saponification of the acetate results in the disappearance of the activity. The α-acetate at C_6 seems to be less essential, since the ajugarins I and II **27** are equally active. From the "clerodin" series **26**, the last three conclusions cannot be drawn so clearly. Inactive compounds are obtained when both the acetates at C_6 and C_{19} are saponified, alone or in combination with the reduction of the epoxyde.

It does not seem to be important whether the bond between C_7 and C_8 is saturated or unsaturated (compare clerodendrin A **26a** and clerodendrin B **26b**).

Much can be said about the furofuran moiety, although not everything is clear yet. Let us first consider the enolether and the fully saturated furofuran. Comparison of clerodendrin A **26a**, clerodin **26c**, caryoptin **26h** and ajugapitin **26ao** with their respective dihydrocompounds **26f**, **26n**, **26o** and **26an**, shows that except in the case of clerodendrin A, the dihydrocompounds are at least as active as the unsaturated ones.

The hemiacetals of clerodin **26p**, caryoptin **26q** and ajugapitin **26al** are at the best equally active as the dihydrocompounds.

The methyl acetal of clerodendrin A **26g** is much more active than either the saturated **26f** or the unsaturated **26a** compound. It is very regrettable that no more methyl acetals were prepared and tested, because in contrast to the methyl acetal, the ethyl acetals of clerodin **26l**, caryoptin **26m**, ivain **26ah** and ajugapitin **26ak** are at best equally active as the saturated compounds **26n**, **26o**, **26af** and **26an**.

Finally, the clerodin lactone **26s** is equally active as clerodin itself **26c** or the dihydroderivative **26n**. However, caryoptin lactone **26r** is slightly

less active than caryoptin itself **26h** and quite less active than dihydrocaryoptin **26o**.

In a recent study Blaney *et al.*[43] compared the antifeedant activities of a number of compounds against larvae of three different Spodoptera and two different Heliothis species. The compounds tested were mainly in the "clerodin" series and differed in the furanoid side chain. Clerodin **26c** and dihydro-clerodin **26n** were generally found to be the most active compounds.

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2. REPORTED TOTAL SYNTHESES OF CLERODANES

2.1 INTRODUCTION

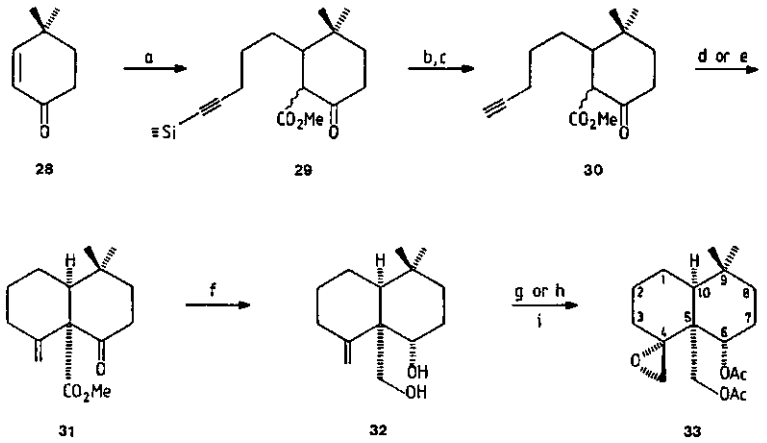
A number of synthetic studies dealing with the synthesis of clerodanes has been carried out during the last decade. These studies can be discerned in *i* the syntheses of synthons and modelcompounds, *ii* the syntheses of low oxygenated cis- and trans-clerodane skeletons and *iii* the total syntheses of highly oxygenated antifeedant clerodanes.
The synthons claimed to be useful for the syntheses of clerodanes[1], will not be discussed in detail in this thesis. The more successful studies on modelcompounds and the most significant details of the clerodane total syntheses will be discussed in this chapter.

2.2 MODEL STUDIES

In 1979 Jackson and Ley synthesized the cis-decalin **33**[2] as outlined in scheme 2.1. The key step in this approach was the Lewis-acid catalyzed cyclization of **30** to the cis-decalin **31**. Another interesting feature of this study was the stereospecific epoxidation of the dihydroxy alkene **32** either by a Sharpless oxidation or a mCPBA oxidation. A mCPBA oxidation of the diacetate of **32** gave the same stereospecific epoxidation. This high stereo-specificity was probably due to the α-methyl at C_9 *.

* The clerodane numbering is used in the text, whereas the IUPAC numbering is used in the experimental.

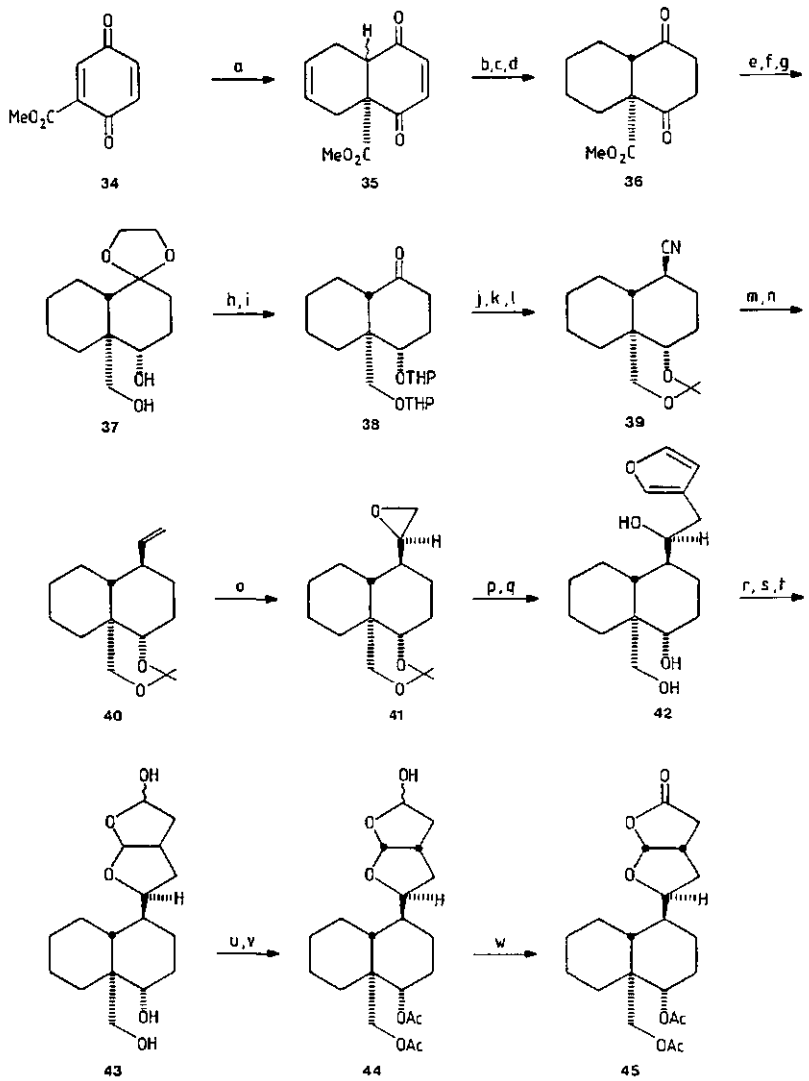
Scheme 2.1



a Me_3Si-C≡C-$(CH_2)_3$-MgI.CuI; then $ClCO_2Me$; 60%; b $AgNO_3$; c KCN; 89%; d ZnI_2, toluene, Δ; e $SnCl_4$; 100%; f $LiAlH_4$; 89%; g mCPBA; h $VO(acac)_2$, tBuOOH; i py, Ac_2O, DMAP; 79%.

In 1980 Kojima and Kato reported the synthesis of the clerodin homologs **44** and **45**[3a,b]. Their synthesis was especially directed towards the construction of the furofuran part of clerodin. It started with a Diels-Alder reaction, resulting in cis-decalin **35**, which was epimerized later on to trans-decalin **36**. One of the key steps was the stereospecific epoxidation of the alkene **40**. Application of a previously developed methodology for the conversion of an oxirane into a hydroxy-perhydrofuro[2,3b]-furan[3c] afforded the clerodin homolog **44**.

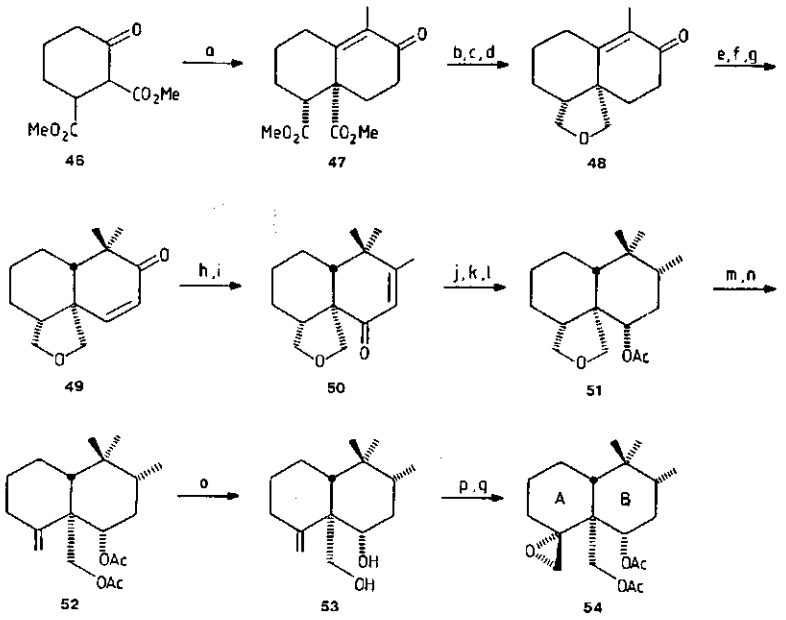
Scheme 2.2



a CH_2=CH-CH=CH_2, $SnCl_4$; 91%; b Zn-AcOH; 97%; c MeONa, MeOH; 90%; d H_2/Pd-C; 77%; e $NaBH_4$; 88%; f TsOH, $(CH_2OH)_2$; 95%; g $LiAlH_4$; 88%; h TsOH, AcOH-H_2O; then KOH; 69%; i TsOH, DHP; 89%; j tBuOK, tBuOH, TosMiC; 75%; k TsOH, MeOH; l TsOH, $Me_2C(OMe)_2$; 91%; m DiBAl-H; n Ph_3P=CH_2; 76%; o mCPBA, Na_2HPO_4; 80%; p (3-furyl)$_2$CuLi.(3-furyl)Li.Me_2S; 92%; q AcOH-H_2O; r Br_2, MeOH; s H_2/Ra-Ni; t $HClO_4$; 77%; u Ac_2O, py, DMAP; v $HClO_4$; 100%; w CrO_3.2py.

The synthesis of the trans-decalin **54** by Luteijn and de Groot was published in 1981 (see scheme 2.3)[4]. The synthesis started with a Robinson annelation of the vicinal diester **46** with ethyl vinyl ketone, resulting in the cis-vicinal diester **47**, which was subsequently transformed into the cyclic ether **48**. The cyclic ether moiety was carried on through the steps, necessary for the introduction of the substituents in the B ring and ultimately was transformed into the acetoyl alkene **52**. Direct epoxidation of the alkene diacetate **52** afforded a 1:1 mixture of epimeric oxiranes. Stereospecific Sharpless oxidation of the alkene diol **53** and subsequent acetylation afforded the decalin **54**.

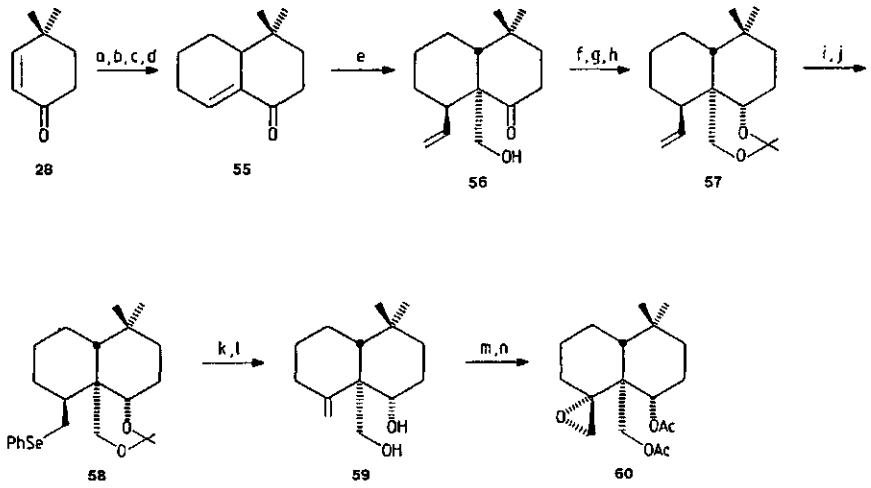
Scheme 2.3



a EVK, triton B, MeOH; 85%; b $HC(OMe)_3$, $BF_3.OEt_2$; c $LiAlH_4$; d H_3O^+, Δ; 84%; e Li, NH_3; then MeI; 94%; f Br_2, AcOH; g LiBr, Li_2CO_3, DMF, Δ; 94%; h MeLi; 97%; i PCC; 95%; j H_2/Pd-C; 97%; k $NaBH_4$, iPrOH; l Ac_2O, py, DMAP; 82%; m py.HCl, Ac_2O, Δ; 80%; n DBN, Δ; 75%; o $LiAlH_4$; 96%; p $VO(acac)_2$, tBuOOH; q Ac_2O, py, DMAP; 77%.

Ley and coworkers synthesized the very similar decalin **60**[5] via a completely different route (see scheme 2.4). The key step in their approach was the conjugated addition of vinylcuprate to the enone **55** followed by trapping of the resulting enolate with formaldehyde to give the trans-decalin **56**.

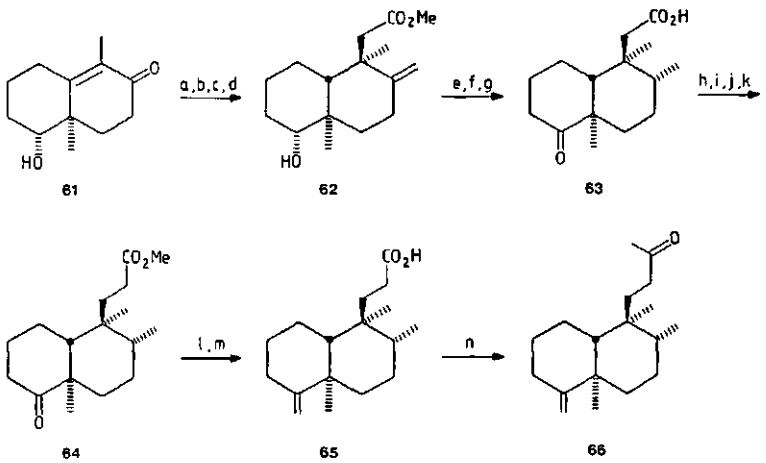
Scheme 2.4



a pent-4-enyl-MgBr.CuBr.Me_2S; 100%; b O_3; 91%; c NaOH, MeOH; d benzene, Δ; 73%; e $(CH_2{=}CH)_2$-CuMgBr; then CH_2O; 63%; f $Ph_2tBuSiCl$, imidazole, DMF; 98%; g $LiAlH_4$; then H_3O^+; 77%; h $Me_2C(OMe)_2$, TsOH, benzene, Δ; 99%; i O_3; then $NaBH_4$; 86%; j NPSP, nBu_3P; 89%; k O_3; 92%; l CF_3CO_2H, CH_3CN-H_2O; 99%; m tBuOOH, $VO(acac)_2$, n Ac_2O, py, DMAP; 53%.

Sharma and Gayen presented the synthesis of the dinorclerodane **66** (see scheme 2.5)[6], based on a reductive alkylation and Wittig reactions for the construction of the desired skeleton.

Scheme 2.5

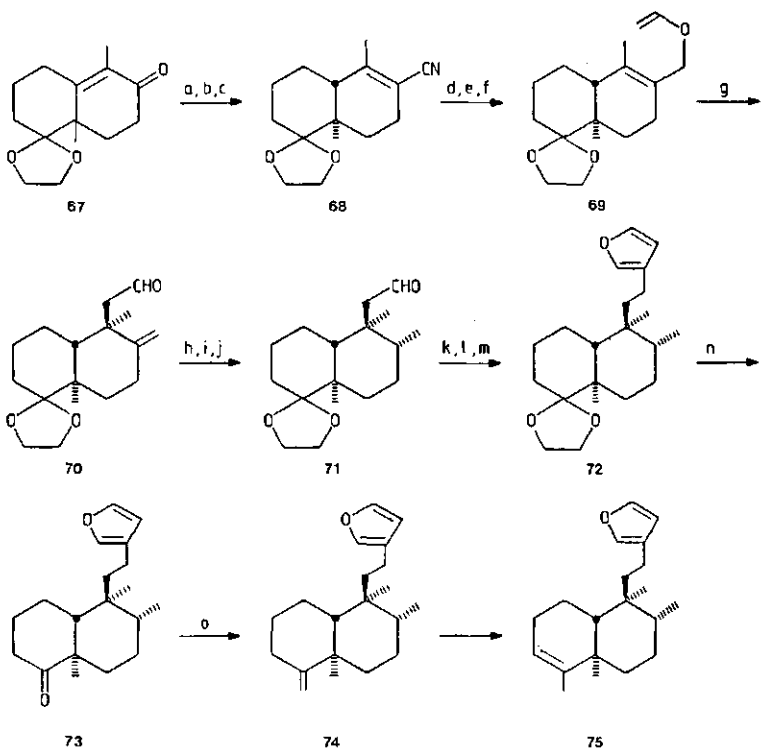


a Li/NH_3; then $BrCH_2$-CO_2Et; b KOH; c CH_2N_2; 50%; d $Ph_3P{=}CH_2$; 50%; e H_2/Pd-C, DMF; 54%; f PCC; 95%; g KOH, MeOH-H_2O; 90%; h NaOH; i $(COCl)_2$; j CH_2N_2; k AgOBz, TEA, MeOH; 50%; l $Ph_3P{=}CH_2$; 50%; m KOH; n MeLi, TMCS; 50%.

2.3 TOTAL SYNTHESES OF CLERODANES

The first total synthesis of a clerodane was published in 1979 by Takahashi *et al.*[7]. The low oxygenated clerodane, annonene **75**, was synthesized from the mono-protected Wieland-Miescher ketone **67** (see scheme 2.6). Due to the lack of steric and regio control, the yields of the steps c and i were low. An elegant step in this sequence was the Claisen rearrangement of the vinyl ether **69** to the aldehyde **70**. The ketone **73** was subjected to a Wittig reaction resulting in the alkene **74**, which had previously been transformed into annonene **75**.

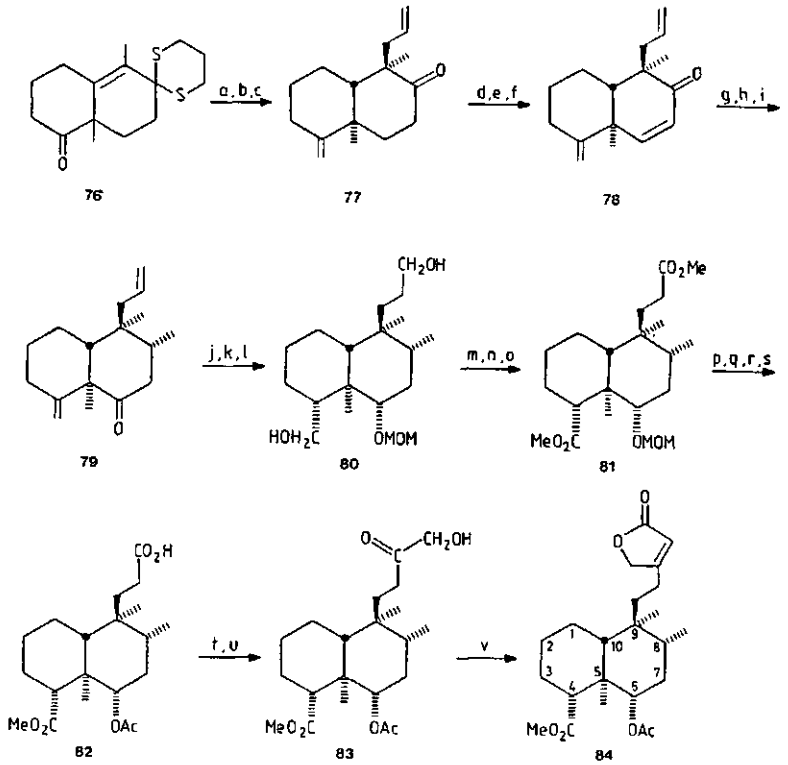
Scheme 2.6



a Li/NH_3; b KCN, AcOH; c $SOCl_2$, py; 42%; d DiBAl-H; e $NaBH_4$; 60%; f CH_2=CH(OEt), $Hg(OAc)_2$; 73%; g 200°C; 70%; h $NaBH_4$; i H_2/Pd-C; 42%; j PCC; k 3-furyl-Li; l Ac_2O; m Ca/NH_3; 77%; n H_3O^+; 100%; o Ph_3P=CH_2; 78%.

The second reported total synthesis of a clerodane, the synthesis of ajugarin IV **84**, was published in 1982 by Kende *et al.*[8], starting from the keto dithiane **76**. The methoxycarbonyl group at C_4 was introduced by a Wittig reaction on the carbonyl group, thermodynamically controlled hydroboration, oxydation and esterification at suitable stages in the synthesis. The carbonyl at C_8 was used to functionalize C_6 and to introduce the butenolide side-chain at C_9 in several steps. The selective saponification of one of the ester functions in compound **81** is remarkable. The chain elongation of the carboxylic acid **82** to the hydroxy-ketone **83** and the reaction of the latter with ketenylidene triphenylphosphorane are noteworthy too.

Scheme 2.7

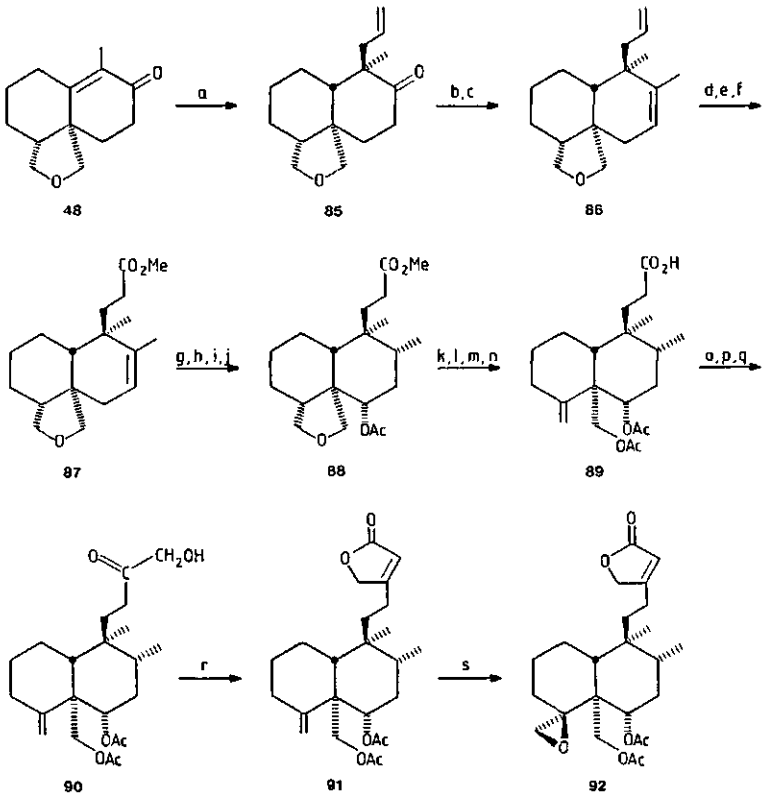


a $Ph_3P{=}CH_2$; b $HgCl_2$, $CdCO_3$; c Li/NH_3; then $CH_2{=}CH{-}CH_2Br$; 70%; d TMCS; e NBS; f LiBr, Li_2CO_3, DMF, Δ; 90%; g MeLi; 100%; h $CrO_3.2py$; 55%; i Li/NH_3; 100%; j $LiAlH_4$; 83%; k CH_3OCH_2Cl, iPr_2NEt; 100%; l Sia_2BH, THF, Δ; then H_2O_2; m PDC; n $NaClO_2$; o CH_2N_2; 53%; p 1.1 eq KOH, MeOH, Δ; 90%; q H_3O^+; 100%; r Ac_2O, TEA, DMAP; s $NaHCO_3$, H_2O; 95%; t $(COCl)_2$; u $(TMSO)_2$-C=CH(OTMS); then H_3O^+; 56%; v $Ph_3P{=}C{=}C{=}O$; 86%.

The total synthesis of 4-epi-ajugarin **92** was reported by Luteijn and de Groot in 1982[9]. The starting material for this synthesis was again the cyclic ether **48**. Although the synthesis of 4-epi-ajugarin was developed independently from the synthesis of ajugarin IV by Kende *et al*, the two strategies show some resemblance. The enone **48** was reductively allylated and subsequently subjected to an alkylative carbonyl transposition. The major difference is of course the oxygenated angular methyl group at C_5. The cyclic ether was transformed in one step into an alkene acetate as in compound **89**, which was efficiently transformed

into compound **91**. Epoxidation of the alkene with mCPBA proceeded in a stereospecific manner to give the oxirane **92**, with an unnatural configuration at C_4. Attempts to synthesize the natural ajugarin I unfortunately failed.

Scheme 2.8

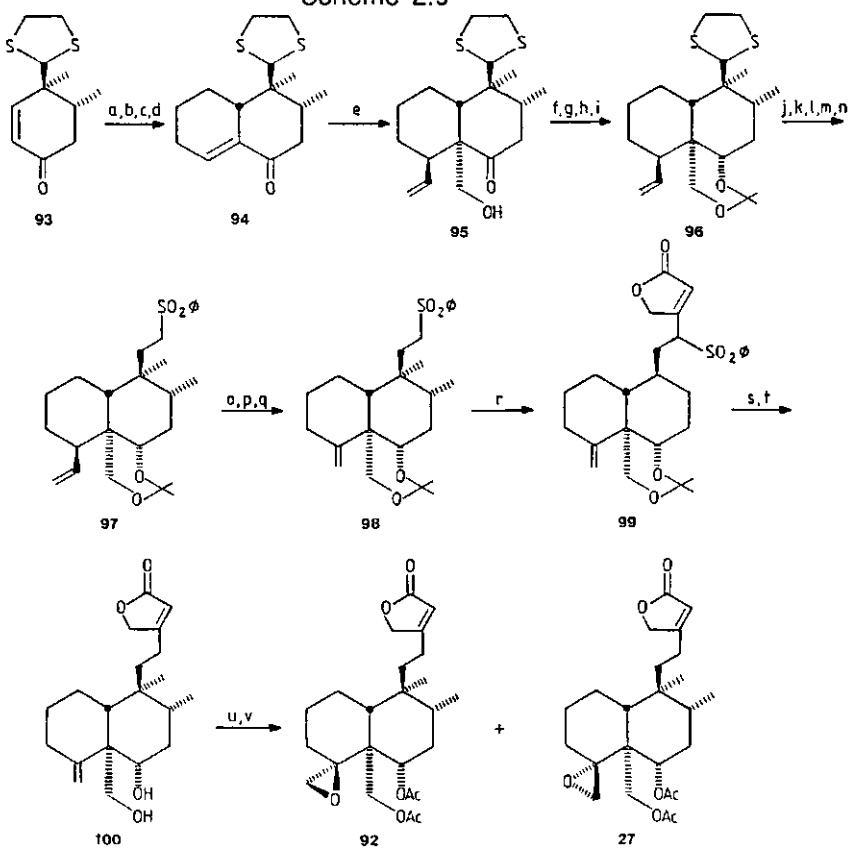


a Li/NH_3; then CH_2=CH-CH_2Br; 78%; b MeLi; 92%; c $BF_3.OEt_2$, benzene, Δ; 93%; d 9-BBN; then H_2O_2; 83%; e Jones ox.; 95%; f CH_2N_2; 100%; g CrO_3, AcOH; 39%; h H_2/Pd-C; 96%; i $Li(tBuO)_3AlH$; j Ac_2O, py, DMAP; 77%; k Ac_2O, py.HBr, Δ; 66%; l KOH, H_2O-MeOH; m Ac_2O, py, DMAP; n py, H_2O; o KOH; then $(COCl)_2$; p CH_2N_2; q SO_2, H_2O; 73%; r Ph_3P=C=C=O; 87%; s mCPBA; 85%.

In 1983 the total synthesis of ajugarin I was reported by Ley and coworkers[10] (see scheme 2.9). Their synthetic approach was partly based upon the methodology developed for the synthesis of model compound **60** (see scheme 2.4). The side-chain with its butenolide ring was completed

via hydrolysis of the dithiolane in **96** and conversion of the resulting aldehyde to the sulfone **97**. The sulfone **98** was lithiated and treated with ethyl 4-*tert*-butyldimethylsilyloxy-but-2-ynoate, subjected to fluoride induced cyclization and reductive desulfonation. Subsequent hydrolysis of the acetonide gave the ene diol **100**, which was oxidized with mCPBA and subsequently acetylated to afford a mixture of 4-epi-ajugarin I **92** and ajugarin I **27** in a ratio of 3:1.

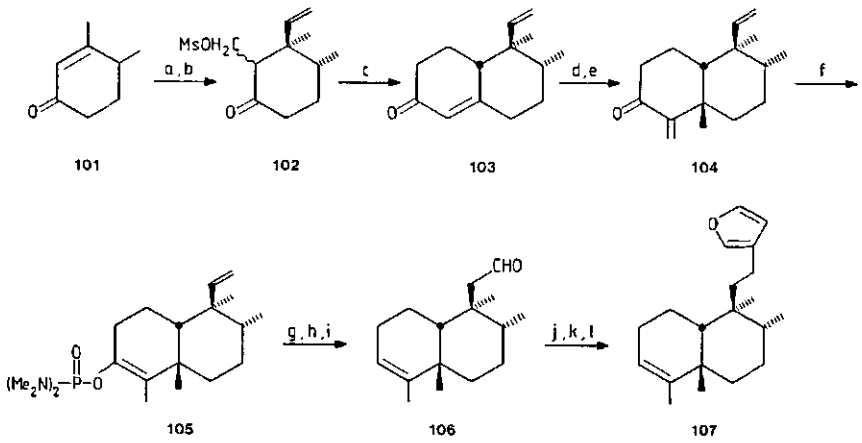
Scheme 2.9



a $(CH_2{=}CH\text{-}CH_2\text{-}CH_2)CuMgBr$; 92%; b $BH_3.SMe_2$; then H_2O_2; 96%; c py.SO_3, DMSO; 71%; d CSA, benzene, Δ; e $(CH_2{=}CH)_2CuMgBr$; then CH_2O; 52%; f $Ph_2tBuSiCl$, imidazole, DMF; g $LiAlH_4$; h H_3O^+; 68%; i acetone, $CuSO_4$; 95%; j $Tl(OCOCF_3)_3$; 69%; k $PhSO_2CH(SiMe_3)(Li)$; l Ac_2O, py, DMAP; m TBAF; 96%; n $LiEt_3BH$; 96%; o O_3; then $NaBH_4$; 100%; p NPSP, nBu_3P; 75%; q O_3; 84%; r nBuLi, $tBuMe_2SiO\text{-}CH_2\text{-}C{\equiv}C\text{-}CO_2Et$; then TBAF; 46%; s Na/Hg, MeOH, Na_2HPO_4; t H_3O^+; 75%; u mCPBA; v Ac_2O, py, DMAP.

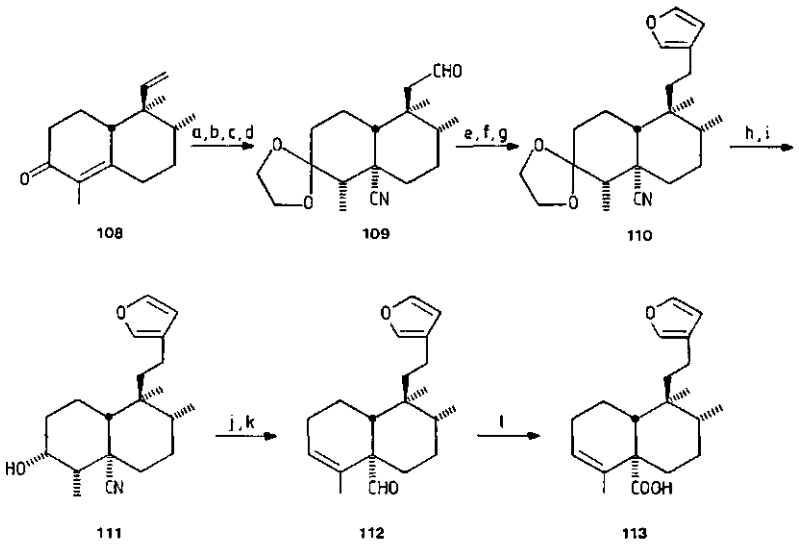
In 1983 Tokoroyama *et al.* presented[11] methods for the syntheses of low oxygenated cis-clerodanes (see scheme 2.10) and trans-clerodanes (see scheme 2.11). Important steps in these syntheses are *i* the stereospecific addition of the vinylmagnesiumbromide-Cu(I)-tri-n-butylphosphine complex to the enone **101**[12], followed by trapping the of enolate with formaldehyde; *ii* the stereospecific annelation; *iii* the cis-selective conjugate addition of dimethyl-copper lithium to the cyclic enone **103**, followed by trapping of the enolate with formaldehyde, ultimately leading to the cis-clerodane **107**, and *iiii* the trans-selective hydrocyanation of the enone **108**, ultimately leading to the trans-clerodane maingayic acid **113**.

Scheme 2.10



a $(CH_2=CH)MgBr.(nBu_3P.CuI)_4$; then CH_2O; 40-70%; b MsCl, TEA; 93%; c $Ac\text{-}CH_2\text{-}CO_2Me$, MeONa, MeOH, benzene, Δ; 69%; d Me_2CuLi; then CH_2O; 46%; e MsCl, TEA; then DBU; 80%; f L-selectride; then $(Me_2N)_2POCl$, HMPA; 51%; g thexyl-borane; then H_2O_2; h Li/Et_2NH, tBuOH; 56%; i $(COCl)_2$, DMSO, TEA; 60%; j 3-furyl-Li; k Ac_2O, py; 99%; l Li/NH_3; 76%.

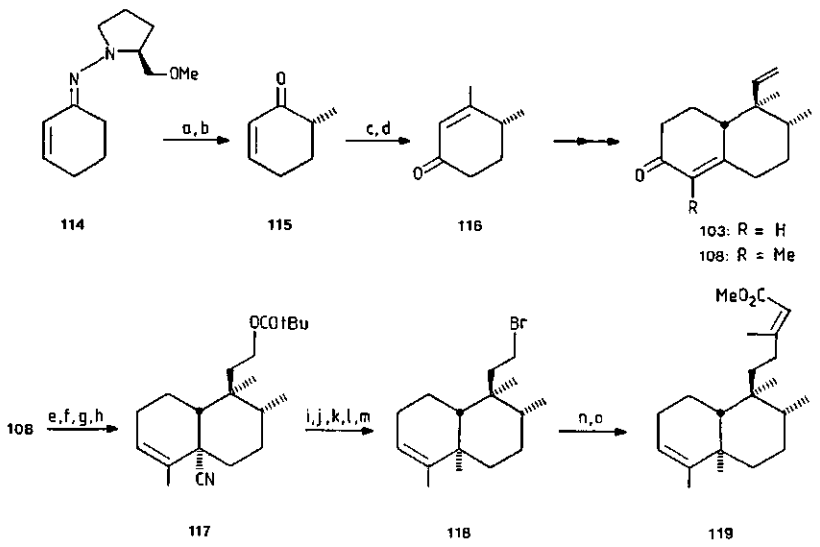
Scheme 2.11



a Et_2AlCN; 83%; b $(CH_2OH)_2$, TsOH, benzene, Δ; 93%; c B_2H_6; then H_2O_2; 56%; d CrO_3, py; 75%; e 3-furyl-Li; f Ac_2O, py; g Li/NH_3; h H_3O^+; 64%; i L-selectride; j $POCl_3$, py; 70%; k DiBAl-H; 94%; l $NaClO_2$, NaH_2PO_4, tBuOH, H_2O, $Me_2C{=}CH(Me)$; 21%.

Four years later Tokoroyama and coworkers reported the enantioselective synthesis of the enones **103** and **108**[13] (see scheme 2.12). The starting material in these syntheses was cyclohexenone, which was converted into the SAMP-hydrazone **114**. Enantioselective alkylation was achieved by using methyl tosylate as the methylating agent. The optically pure enone **115** was converted via the optically pure enone **116** into the enones **103** en **108**. The latter compound was used for the synthesis of (-)-methyl kolavenoate, as an example of the first asymmetric clerodane synthesis.

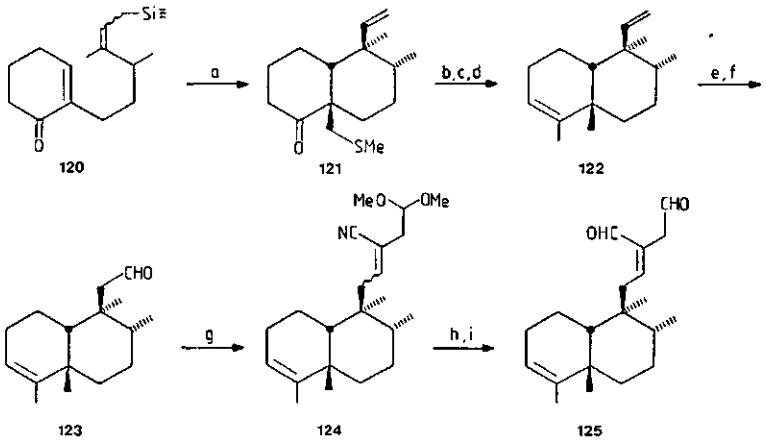
Scheme 2.12



a LDA, then TsOMe; b MeI, then H_3O^+; c MeLi; d PCC; e Et_2AlCN; f L-Selectide; 83%; g $Me_2CHCMe_2BH_2$, then H_2O_2; h tBuCOCl, py, then $POCl_3$; i DiBAl-H; j AcOH, H_2O; k NH_2NH_2, KOH, $(CH_2OH)_2$, Δ; l MSCl, TEA; m LiBr; n LiC≡CH.EDA, DMSO; 71% o $ZrCl_2$ $(n\text{-}C_5H_5)_2$, Me_3Al, then $ClCO_2Me$; 31%.

In 1987 the same research group realized the synthesis of the anti-fungal cis-clerodane, linaridial, **125** via a totally different route[14]. The key step in this approach was the stereocontrolled cyclization of the allyl silane **120** and trapping of the enolate with chloromethyl methylsulfide in a one-pot reaction. The resulting cis-decalin **121** offers many opportunities for the synthesis of cis-clerodanes, which was illustrated by a formal total synthesis of the clerodane **107** and the total synthesis of linaridial **125**.

Scheme 2.13



a $TiCl_4$, $ClCH_2SMe$, CH_2Cl_2, O°C; 77%; b Ra/Ni, EtOH; c CH_2Br_2-Zn-$TiCl_4$, THF; d $KNH(CH_2)_3/NH_2$-$(CH_2)_3$-NH_2; e $Me_2CHCMe_2BH_2$; then H_2O_2; f $(COCl)_2$, DMSO, CH_2Cl_2; then TEA; g $(EtO)_2POCH(CN)$-CH_2-$CH(OMe)_2$), NaH; h DiBAl-H, Et_2AlCl, toluene; i H_3O^+; 73%.

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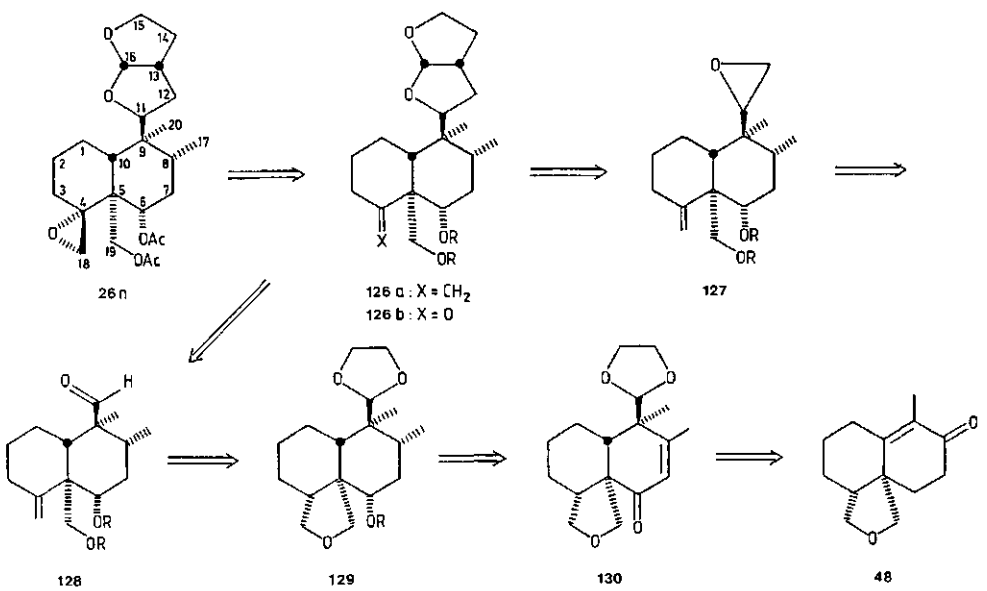
3. SYNTHETIC PLAN TO DIHYDROCLERODIN

3.1 INTRODUCTION

The clerodanes with the strongest antifeedant activities are characterized by epoxy diacetate groups in the decalin part of the molecule and furofuran sidechains. Therefore dihydroclerodin **26n** with the perhydrofuro[2,3b]furan sidechain was chosen as the target molecule for a total synthesis. If possible a route which allows some flexibility, especially with respect to the sidechain should be developed. The strategy for the synthesis of dihydroclerodin **26n** is outlined in scheme 3. The introduction of the epoxy diacetate groups can probably be best postponed to one of the last steps of the synthesis. The epoxide should be synthesized either by a Sharpless oxidation of the alkene diol **126a** (R=H)[1,2] or by ozonolysis of the alkene **126a** (R≠H) followed by a reaction of the ketone **126b** with a sulfur ylide. In both cases the correct stereochemistry of the spiroepoxide may be expected.

Scheme 3



An oxirane function as in **127** or an aldehyde function as in **128** were considered to be useful precursors for the construction of the perhydrofurofuran rings as in **126**. This required the development of new methods for the conversion of aldehydes and oxiranes into furofurans, preferrably with good steric control on the off template C_{11} and with possibilities for control of the configuration at C_{13} and C_{16}. The succesful procedures for these tranformations are described in chapters 5 and 6. The conversion of an epoxide into a furofuran-lactone as in clerodin lactone **26s** is also described in chapter 6.

The cyclic ether **129** may be considered as a suitable precursor for the synthesis of the aldehyde **128**. A cyclic ether as used by Luteijn[1] may serve as a protecting group as long as the rather demanding transformations at C_6 - C_9 have to be performed. Renewed investigations for the conversion of this cyclic ether **129** into the alkene **128** proved to be necessary, as will be described in chapter 7.3.

The synthesis of compound **129** from the enone **130** would require two stereoselective reductions and possibly a protection of the resulting equatorial alcohol. For these transformations some precedents are found again in the work of Luteijn[1].

The γ-dioxolanyl-α,β-unsaturated ketone **130** should be synthesized from the enone **48**. Several methods and sequences are available for the reduction of C_{10}, the dioxolanisation of C_9, the methylation of C_8 and the oxidation of C_6. The problems connected with these transformations and the solutions for these problems will be discussed in chapter 4.

3.2 REFERENCES

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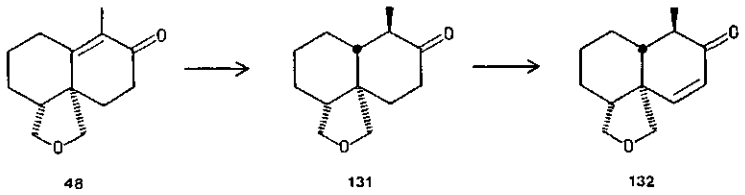
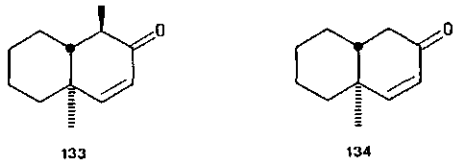
4 THE SYNTHESIS OF THE γ-DIOXOLANYL-α,β-UNSATURATED KETONE

4.1 INTRODUCTION

As outlined in our retrosynthetic plan (chapter 3) for the synthesis of clerodanes, there was a need for an efficient route to the γ-dioxolanyl-α,β-unsaturated ketone **130** starting from the enone **48**.
In the investigated approaches for such a conversion, the enone **48** was first converted into the enone **132**. The enones **133** and **134** were sometimes used as modelcompounds to study some of the required transformations. Several sequences for the introduction of the dioxolanyl group at C_9, the introduction of a methylgroup at C_8 and the oxidation at C_6 have been investigated.

Scheme 4.1





4.2 THE SYNTHESES OF THE STARTING ENONES

Birch reduction of the enone **48**[1] with lithium in ammonia afforded the trans ketone **131** in a quantitative yield. The conversion of this ketone **131** into the enone **132** was somewhat more troublesome. Bromination of **131** with bromine in acetic acid followed by dehydrobromination with

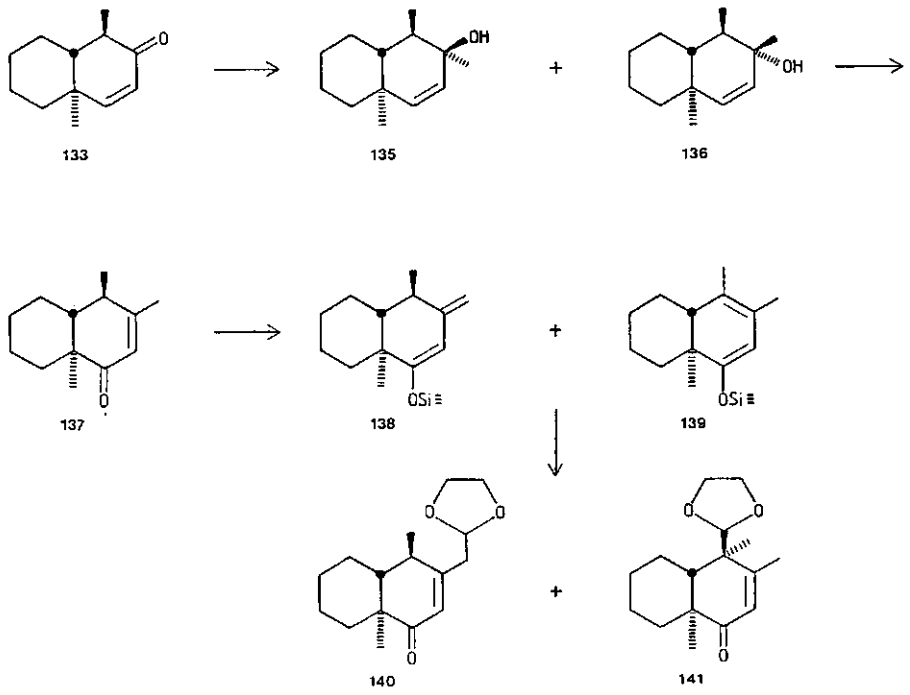
lithium bromide/lithium carbonate in hot dimethylformamide gave varying yields, from 30-70%, moreover the resulting mixtures were separated only with difficulty. Modifications of this method suffered from the same drawbacks. Better and reproducable results were obtained when the ketone **131** was deprotonated under kinetic control and treated with phenylselenyl chloride. Oxidation of the α-phenylselenoketone with either hydrogen peroxide or sodium *meta*-periodate and spontaneous selenoxide syn elimination gave the enone **132** in 71% overall yield.
The unsaturated ketone **133** was prepared in the same way from the corresponding saturated ketone in 60% overall yield.
The enone **134**[2] was synthesized from its corresponding saturated ketone by treatment with pyridinium bromide perbromide in glacial acetic acid, followed by dehydrobromination with lithium bromide/lithium carbonate in dimethylformamide at 120°C.

4.3 THE γ-ALKYLATION OF AN α,β-UNSATURATED KETONE

An elegant and straightforward method for the functionalisation of C_9 could be the γ-alkylation of an α,β-unsaturated ketone via its silyldienolether[3]. This reaction was first explored with the enone **137**, which was prepared from the enone **133** in two steps by an alkylative 1,3-carbonyl transposition[4]. Addition of methyl lithium to the enone **133** afforded the <u>axial</u> alcohol **135** in 38% yield and the <u>equatorial</u> alcohol **136** in 41% yield. The configurations of the tertiary allylic alcohols **135** and **136** were confirmed by the downfield shifts in the ^{1}H-NMR spectra caused by Siever's reagent (tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium). Oxidation of the alcoholmixture with pyridinium chlorochromate in dichloromethane gave the enone **137** in 76% yield. It should be mentioned that the oxidation of the <u>axial</u> alcohol **135** is much faster than the oxidation of the <u>equatorial</u> alcohol **136**. Thermodynamically controlled silylation[5] of the enone **137** gave a mixture of the exocyclic silyldienolether **138** and the endocyclic silyldienolether **139**. Alkylation of this mixture with 2-methoxy-1,3-dioxolan in ethyl acetate promoted by zinc chloride[6] in refluxing ethyl acetate gave a mixture of the dioxolanylated enones **140** and **141** in a combined yield of 48%. According to the ^{1}H-NMR and the GC-MS data the

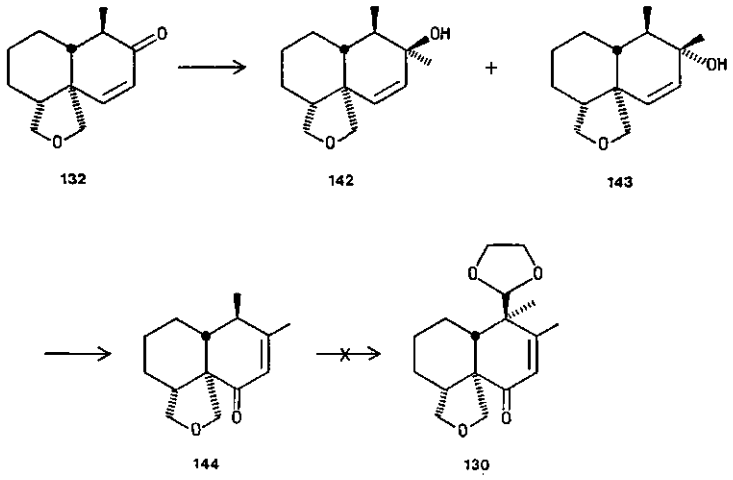
mixture consisted of ca. 25% of the enone **140** and ca. 75% of the desired enone **141**. Unfortunately the mixture could not be separated by column chromatography. The silylation under kinetic control and subsequent alkylation with 2-methoxy-1,3-dioxolan afforded the enone **140** as the only product.

Scheme 4.2



The results of this approach for the functionalisation of C_9 were not very decisive. Nevertheless this reaction sequence was studied with the enone **132** (see scheme 4.3). Treatment of this enone with methyl lithium gave the axial alcohol **142** and the equatorial alcohol **143** both in 50% yield. Oxidation of the alcoholmixture afforded the enone **144** in 90% yield. Attempts to alkylate the thermodynamical silyldienolether from **144** with 2-methoxy-1,3-dioxolan failed in our hands.
So, the approach to synthesize the enone **130** from the enone **132** by: *i* methyl lithium addition, *ii* oxidation and *iii* dioxolanisation proved unsuccessful.

Scheme 4.3



132 142 143

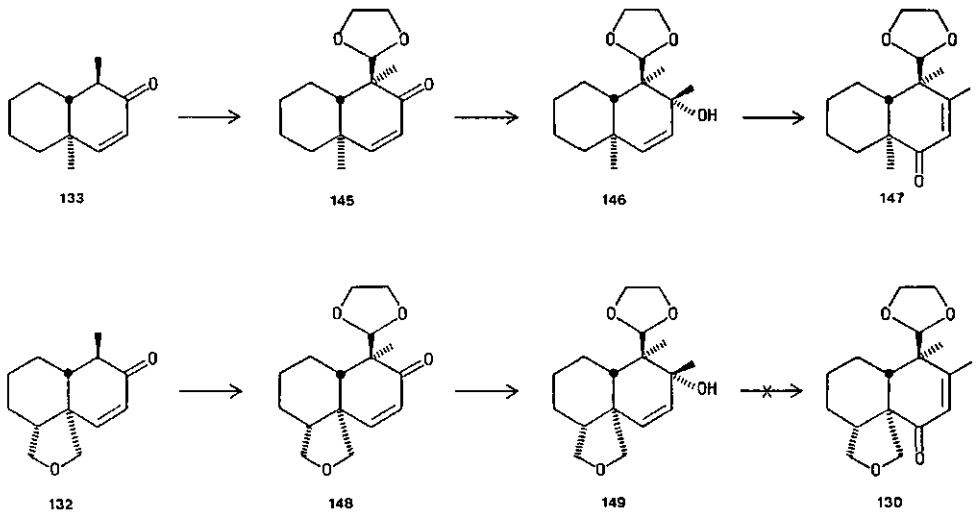
144 130

4.4 THE α'-ALKYLATION OF AN α,β–UNSATURATED KETONE

The conversion of the enone **132** into the enone **130** may also be started with the α'-alkylation of the enone **132** via its silyldienolether. The principal advantages of such an approach as compared with the approach in the previous chapter are: *i* no isomeric silyldienolethers can be formed and *ii* no γ/α selectivity is required. Problems might be expected with the alkylative carbonyl transposition[7].

This reaction sequence (see scheme 4.4) was first explored with the enone **133**. Deprotonation of this compound and subsequent quenching with chlorotrimethylsilane gave the cross silyldienolether, which was treated with 2-methoxy-1,3-dioxolan and zinc chloride in refluxing ethyl acetate to give the enone **145** in 51% yield. Subsequent addition of methyl lithium gave the equatorial alcohol **146**. The oxidation of **146** with pyridinium dichromate in dimethylformamide was slow, nevertheless the desired γ-dioxolanyl-α,β–unsaturated ketone **147** could be obtained in 42% yield. In this way the synthesis of the enone **147** from the enone **133** was accomplished in 19% overall yield. Although this yield was not very high, it was considered sufficient to justifiy the application of this methodology to the enone **132** (see scheme 4.4).

Scheme 4.4



Dioxolanisation of the enone **132** via its cross silyldienolether afforded the enone **148** in 27% yield. The stereochemistry of this dioxolanyl compound was confirmed by a crystal structure determination[8], because the equatorial position of the dioxolan group had to be established firmly. Addition of methyl lithium to the enone **148** gave the tertiary allylic alcohol **149** in a quantitative yield. The stereochemistry of C_8 of the formed alcohol was not proven rigorously, but it was tentatively assumed that β-attack had taken place, resulting in the equatorial alcohol. The attempted oxidation of this compound to the enone **130**, using a number of oxidizing agents unfortunately failed.

So, the approach for the synthesis of the enone **130** from the enone **132** via: *i* dioxolanisation, *ii* methyl lithium addition and *iii* oxidation was unsuccessful too, despite of the fact that some success was obtained for the modelcompound.

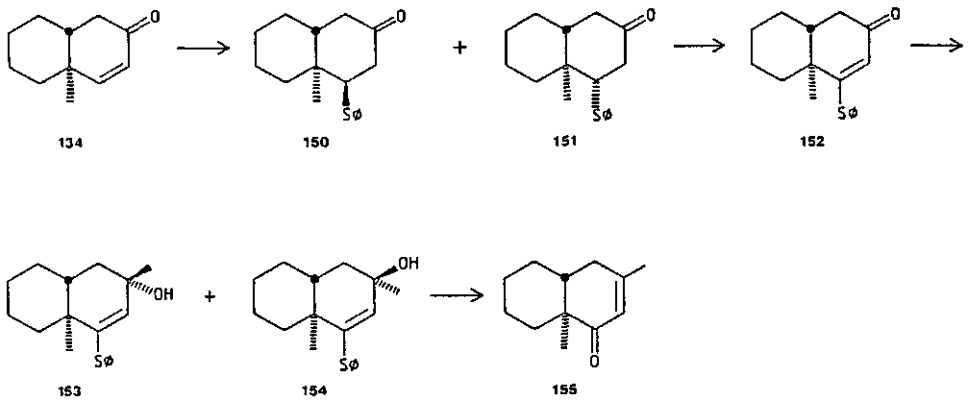
4.5 THE α'-ALKYLATION OF A γ-PHENYLTHIO-α,β-UNSATURATED KETONE

The synthesis of the γ-dioxolanyl-α,β-unsaturated ketone **130** could not be effectuated by the approaches described in the two previous chapters. So another approach was set up, inspired by the work of Bakuzis and Bakuzis[9] and the work of Trost and Stanton[10]. In this sequence first the oxidation of C_6 was investigated followed by the introduction of the

dioxolan group, and the methyl lithium addition was planned as the last step. The conversion of an α,β-unsaturated ketone into a β-phenylthio-α,β–unsaturated ketone was studied in a somewhat broader context[11]. The triethylamine catalyzed addition of thiophenol[9] to the enone **134** gave a mixture of the sulfides **150** and **151**, after stirring for four days at roomtemperature. The axial sulfide was formed predominantly, indicating that the equilibration of the β– phenylthio substitutent is very slow under these conditions. It was found that addition of sodium thiophenolate to the same reaction mixture and stirring overnight gave 6% of the axial sulfide **150** and 78% of the equatorial sulfide **151**. The next step was the oxidation of **150** and **151** to the β-phenylthio-α,β-unsaturated ketone **152**, which can be considered as a half protected β-diketone. This transformation could be achieved by a chlorination/dehydrochlorination reaction. It has been suggested that the initial chlorination takes place on the sulfur atom, the chlorine atom then shifts to the β-carbon atom and finally eliminates spontaneously.

No problems were encountered with the chlorination/elimination of the axial β-phenylthio ketone **150**. The enone sulfide **152** was formed in a rather clean reaction. No significant formation of the enone **134** was observed as a result of the elimination of axial phenylsulfenyl chloride, this in contrast to the findings of Bakuzis and Bakuzis[9]. The important consequence of this observation is that the equilibration of an axial sulfide to an equatorial sulfide is not a prerequisite for a successful chlorination/elimination reaction. Application of the chlorination reaction to the equatorial sulfide **151** also gave the enone sulfide **152**. The yield of this reaction, carried out with 10% excess N-chlorosuccinimide in benzene/ether (2/1) at roomtemperature was 71%. The use of a greater excess N-chlorosuccinimide gave rise to chlorinated byproducts. Better results and much faster reactions were generally observed when trichloroisocyanuric acid (chloreal)[12] was used as the chlorinating agent. The reaction of the sulfide **151** with 15% excess chloreal in bezene (ether (2/1) at 0°C gave the unsaturated sulfide **152** in 75% yield. The addition of methyl lithium gave a mixture of the tertiary allylic alcohols **153** and **154** in a quantitative yield. The mixture of alcohols was subjected to a mild hydrolysis procedure, e.g. 1.5 equivalent of mercury(II)chloride in aqueous acetone, to give the expected enone **155** in 94% yield.

Scheme 4.5

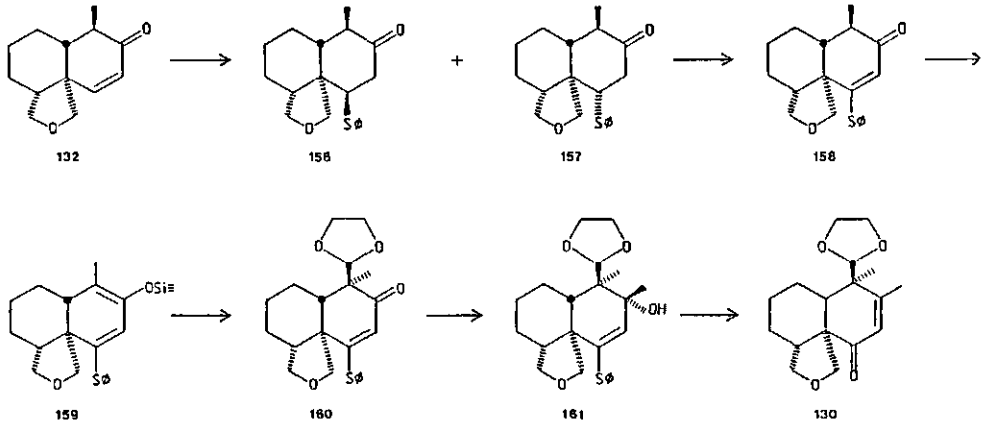


134 150 151 152

153 154 155

With this newly developed alkylative 1,3-carbonyl transposition[13] in hand, a third attempt was made to synthesize the enone **130**. Treatment of the enone **132** with one equivalent of thiophenol and one equivalent of sodium thiophenolate gave rise to the axial sulfide **156**. Surprisingly only minimal epimerization at C_6 was observed under the applied conditions. The oxidation of **156** with N-chlorosuccinimide gave the desired β-phenylthio-α,β-unsaturated ketone **158** in 50% yield. This reaction could be accomplished in 83% yield using chloreal as the chlorinating agent. At this stage the important alkylation reaction with 2-methoxy-1,3-dioxolan was studied. It was anticipated that the silyldienolether would have an enhanced reactivity with electrophiles, compared to the silyldienolethers form the enones **132** and **144**, as a result of the mesomeric donating effect of the sulfide substituent. Indeed the dioxolanisation reaction could be performed in dichloromethane without external heating. However the reaction depended very strongly on the concentration of the reactants and after numerous experiments the reaction could be performed in 60% yield. Subsequent addition of methyl lithium gave the equatorial alcohol **161** in a quantitative yield. In contrast to the rapid and clean hydrolysis of the methyl lithium adducts from the compounds **152** and **158** with mercury(II)chloride in aqueous acetone, the tertiary alcohol **161** gave rise to numerous unidentified products together with a small amount of the desired enone **130** in a slow reaction. Treatment of the alcohol **161** with a catalytic amount of *p*-toluenesulfonic acid monohydrate in chloroform gave, besides some dehydratated and deformylated products, the enone **130** in 63% yield.

Scheme 4.6



In summary it may be concluded that starting from the enone **48** the oxidation of C_6, the stereoselective introduction of the dioxolan function at C_9 and the introduction of a methyl group at C_8 has been realized, giving rise to the promising intermediate **130** for the synthesis of clerodanes.

4.6 EXPERIMENTAL

Boiling points and melting points are uncorrected. NMR spectra were recorded on Varian EM-390 and Bruker CXP-300 spectrometers. Chemical shifts are reported in ppm downfield relative to tetramethylsilane (δ scale), exept for the silyl compounds in which case the methyl groups attached to the silyl atom were used as intramolecular internal standard. $CDCl_3$ was used as a solvent unless stated otherwise. Mass spectral data and accurate mass measurements were obtained using AEI-MS-902 and VG Micromass 7070F spectrometers. Elemental analyses were carried out using a Carlo Erba Elemental Analyser 1106. Flash chromatography was preformed on silica gel 230-400 mesh. Other silica gel used was 70-230 mesh. Light petroleum refers to petroleum ether b.p. 40-60°C. Aqueous solutions were usually extracted three times with ether. Combined organic extracts were washed with brine and dried on magnesium sulfate prior to filtration and evaporation of the solvent under reduced pressure.

3aβ,4,5,6,6aβ,7,9,10-Octahydro-7β-methyl-1H-naphtho[1,8aα-c]furan-8(3H)-one (**131**)

Lithium (1.4 g, 200 mmol) was added in small peaces to ammonia (600 mL, distilled from sodium) at -78°C under nitrogen. The mixture was stirred for 30 min and a solution of the enone **48** (10.30 g, 50 mmol) and water (0.90 mL, 50 mmol) in dry tetrahydrofuran (100 mL) was added dropwise. The reaction mixture was refluxed for 30 min. Ammonium chloride was added and the ammonia was allowed to evaporate. Water and ether were added. The ether layer was separated and the water layer was extracted two more times with ether. Further work up as usual afforded a residue, which was taken up in acetone (40 mL). To this solution at 0°C was added Jones reagent untill the oxidation was complete. Work up as usual afforded the ketone **131** (10.34 g, 99%) as a white solid, mp 68-69°C. An analytic sample was prepared by recrystallisation from light petroleum; mp 70-71°C. Elemental analysis: calc. for $C_{13}H_{20}O_2$: 74.96% C, 9.68% H; found: 74.68% C, 9.69% H.

^{1}H-NMR: 0.97 (d, J=6 Hz, 3H), 1.1-2.7 (m, 13H), 3.58 (d, J=8 Hz, 1H), 3.8-4.2 (m, 3H). MS: m/e (%): 208 (100), 180 (5), 163 (17), 151 (23), 136 (23), 124 (34), 107 (25). Calc. for $C_{13}H_{20}O_2$: 208.1463; found 208.1472.

3aβ,4,5,6,6aβ,7-Hexahydro-7β-methyl-1H-naphtho[1,8aα-c]furan-8(3H)-one (**132**)

Diisopropylamine (12.5 mL, 89 mmol) was added dropwise to a solution of n-butyl lithium (60 mL of a 15% solution in hexane) in dry tetrahydrofuran (250 mL) at -78°C under nitrogen. The solution was stirred for 10 min and a solution of the ketone **131** (17.3 g, 83 mmol) in tetrahydrofuran (50 mL) was added dropwise in 30 min. The mixture was stirred for 10 more min and a solution of phenylselenyl chloride (18.0 g, 94 mmol) in tetrahydrofuran (50 mL) was dropped to the reaction mixture in 10 min. Stirring was continued for 10 min and the mixture was worked up as usual. The resulting residue was dissolved in acetone (700 mL) and water (100 mL). Sodium bicarbonate (10.8 g) and sodium *meta*-periodate (36 g) were added succesively. The reaction mixture was stirred for 2 h, filtered and concentrated. Addition of water and extraction with ether, followed by the usual work up afforded a residue. Flash chromatography on silica gel with light petroleum/ether (2/1) as the eluant afforded the enone **132** (13.25 g, 77%). Recrystallization from light petroleum afforded the pure enone **132** (12.2 g, 71%): mp 67-69°C. Elemental analysis: calc. for $C_{13}H_{18}O_2$: 75.69% C, 8.80% H; found: 75.36% C, 8.71% H.

^{1}H-NMR: 1.09 (d, J=6 Hz, 3H), 1.1-2.3 (m, 9H), 3.6-3.8 (m, 2H), 4.0-4.3 (m, 2H), 5.92 (d, J=10 Hz, 1H), 7.05 (d, J=10 Hz, 1H). MS: m/e (%): 206 (100), 178 (49), 176 (49), 161 (46), 157 (52), 143 (52), 130 (45), 105 (45), 91 (49). Calc. for $C_{13}H_{18}O_2$: 206.1307; found: 206.1312.

4a,5,6,7,8,8aβ–Hexahydro-1β,4aα–dimethyl-naphthalen-2(1H)-one (**133**)
Diisopropylamine (3.2 mL, 23 mmol) was dropped to a solution of n-butyl lithium (15 mL of a 15% solution in hexane) in dry tetrahydrofuran (50 mL) at -78°C under nitrogen. The mixture was stirred for 10 min and a solution of 3,4,4a,5,6,7,8,8aβ–octahydro-1β,4aα–dimethyl-naphthalen-2(1H)-one (3.40 g, 19 mmol) in dry tetrahydrofuran (15 mL) was added dropwise in 30 min. The mixture was stirred for 10 more min and a solution of phenylselenyl chloride (4.35 g, 23 mmol) in tetrahydrofuran (20 mL), was quickly dropped to the reaction mixture. The temperature was allowed to rise to roomtemperature and the reaction mixture was diluted with light petroleum (150 mL). The organic layer was successively washed with 2 N hydrochloric acid, saturated aqueous sodium bicarbonate and brine. Drying and evaporation of the solvents gave a residue, which was dissolved in dichloromethane (100 mL). Hydrogen peroxide (7.5 mL of 30% solution in water, 73 mmol) was added to the solution at 0 °C and the resulting suspension was stirred for 2 h. The reaction mixture was poured into saturated aqueous sodium bicarbonate and further worked up as usual. Chromatography on silica gel eluting with light petroleum/ether (10/1) afforded the enone **133** (2.02 g, 60%) as a colourless oil.
^{1}H-NMR: 1.09 (s, 3H), 1.11 (d, J=6 Hz, 3H), 1.3-1.8 (m, 9H), 2.1-2.5 (m, 1H), 5.80 (d, J=10 Hz, 1H), 6.65 (d, J=10 Hz, 1H). MS: m/e (%): 178 (88), 163 (40), 150 (23), 135 (38), 122 (100). Calc. for $C_{12}H_{18}O$: 178.1358; found: 178.1350.

4a,5,6,7,8,8aβ–Hexahydro-4aα–methyl-naphthalen-2(1H)-one (**134**)[2]
3,4,4a,5,6,7,8,8aβ–Octahydro-4aα–methyl-naphthalen-2(1H)-one (6.64 g, 40 mmol) was dissolved glacial acetic acid (50 mL). Pyridinium bromide perbromide (12.8 g, 40 mmol) was added portionwise. The reaction mixture was taken up in water and extracted three times with ether. The combined organic layers were washed with saturated aqueous sodium bicarbonate and brine. Drying, filtration and evaporization of the volatiles afforded a residue, which was dissolved in dimethylformamide (40 mL). Lithium bromide (6.0 g) and lithium carbonate (8.0 g) were added and the suspension was heated to 120°C for 2 h. Cooling and work up as usual afforded a residue which was chromatographed on silica gel with light petroleum/ether (6/1) as the eluant to give the enone **134** (4.07 g, 62%) as a colourless oil.
^{1}H-NMR: 1.05 (s, 3H), 1.2-1.8 (m, 9H), 2.1-2.3 (m, 2H), 5.82 (d, J=10 Hz, 1H), 6.72 (d, J=10 Hz, 1H).

1,2,4a,5,6,7,8,8aβ-Octahydro-1β,2α,4aα-trimethyl-naphthalen-2β-ol (**135**) and 1,2,4a,5,6,7,8,8aβ-octahydro-1β,2β,4aα-trimethyl-naphthalen-2α-ol (**136**)

The enone **133** (1.42 g, 8.0 mmol) was dissolved in dry ether (20 mL) and cooled to -78°C. Methyl lithium (6 mL of a 1.8 M solution in ether, 10.8 mmol) was added and the temperature was allowed to rise to roomtemperature. Water was added and the reaction mixture was worked up as usual. Chromatography on silica gel eluting with light petroleum/ether (10/1-5/1) afforded the allylic alcohol **135** (586 mg) as a colourless oil.

^{1}H-NMR (CCl_4): 0.84 (s, 3H, C_{4a}-Me), 0.87 (d, J=8 Hz, 3H, C_1, Me), 1.16 (s, 3H, C_2-Me), 1.3-1.9 (m, 11H), 5.37 (s, 2H).

^{1}H-NMR (CCl_4 + Eu(fod)$_3$): 1.52 (s, 3H, C_{4a}-Me), 1.3-3.0 (m, 11H), 2.77 (d, J=6 Hz, 3H, C_2-Me), 3.44 (s, 3H, C_2-Me), 6.29 (d, J=9 Hz, 1H), 7.52 (d, J=9 Hz, 1H).

MS: m/e (%): 194(10), 180 (14), 179 (100), 176 (37), 161 (34), 98 (33), 85 (33). Calc. for $C_{13}H_{22}O$: 194.1671; found: 194.1676.

Further elution gave 632 mg allylic alcohol **136** as a white solid (mp 99-100 °C from hexaan)

^{1}H-NMR (CCl_4): 0.86 (d, J=7 Hz, 3H, C_1-Me), 0.93 (s, 3H, C_{4a}-Me), 1.02 (s, 3H, C_2-Me), 1.0-1.9 (m, 11H), 5.28 (s, 2H).

^{1}H-NMR (CCl_4+Eu(fod)$_3$): 1.42 (s, 3H, C_{4a}-Me), 1.4-2.1 (m, 10H), 1.93 (d, J=7 Hz, 3H, C_1-Me), 2.54 (s, 3H, C_2-Me), 3.3-3.7 (dq, J_1=7 Hz, J_2=11 Hz, 1H), 5.89 (d, J=10 Hz, 1H), 6.92 (d, J=10 Hz, 1H).

MS: m/e (%): 194 (17), 180 (13), 179 (100), 176 (9), 161 (17), 98(29).Calc. for $C_{13}H_{22}O$: 194.1671; found: 194.1672.

4aβ,5,6,7,8,8a-Hexahydro-3,4β,8aα-trimethyl-naphthalen-1(4H)-one (**137**)

The alcoholmixture **135** and **136** (1.16 g, 6.0 mmol) was dissolved in dry dichloromethane (5 mL). This solution was added to a suspension of pyridinium chlorochromate (2.62 g) in dichloromethane (20 mL). The alcohol **135** was oxidized within 1 h. Stirring was continued overnight and pyridinium chlorochromate (0.4 g) was added and stirring was continued for 6 more h to complete the oxidation of alcohol **136**. The reaction mixture was diluted with ether and filtered through a short column with silica gel. Concentration and chromatography on silica gel eluting with light petroleum/ether (6/1) afforded the enone **137** (876 mg, 76%) as a colourless oil.

^{1}H-NMR: 1.01 (s, 3H), 1.13 (d, J=7 Hz, 3H), 1.0-2.1 (m,10H), 1.91 (br s, 3H), 5.79 (br s, 1H). MS: m/e (%): 192 (52), 177 (49). 94 (100). Calc. for $C_{13}H_{20}O$: 192.1514; found: 192.1507.

4β-(1,3-Dioxolan-2-yl)-4aβ,5,6,7,8,8a-hexahydro-3,4α,8aα-trimethyl-naphthalen-1(4H)-one (**141**) from enone (**137**)
A solution of the enone **137** (291 mg, 1.5 mmol), trimethylchlorosilane (0.29 ml) and triethylamine (0.42 mL) in dimethylformamide (10 mL) was heated at 120°C for 24 h under nitrogen. The solution was cooled and aqueous sodium bicarbonate was added. Work up as usual afforded the silyldienolethers **138** and **139** (330 mg). 2-Methoxy-1,3-dioxolan (0.20 mL, 2.1 mmol) and zinc chloride (2.6 mL of a 10% solution in ethyl acetate) were added and the mixture was refluxed for 2 h under nitrogen. The solution was cooled and aqueous sodium bicarbonate was added. Work up as usual and chromatography on silica gel eluting with light petroleum/ether (4/1-2/1) afforded the starting enone **130** (45 mg) and the γ-dioxolanyl-α,β-unsaturated ketones **141** and **140** (194 mg, 48%). From ^{1}H-NMR and GC-MS data the ratio was determined to be 3:1.

3-[(1,3-Dioxolan-2-yl)-methyl]-4aβ,5,6,7,8,8a-hexahydro-4β,8aα-dimethyl-naphthalen-1(4H)-one (**140**)
Diisopropylamine (0.54 mL, 3.9 mmol) was dropped to a solution of n-butyl lithium (2.6 mL of a 15% solution in hexane) in dry tetrahydrofuran (10 mL) at 0°C under nitrogen. The enone **137** (581 mg, 3.0 mmol) was dissolved in dry tetrahydrofuran (8 mL) and added dropwise in 30 min. Stirring was continued for 5 min and trimethylchlorosilane (0.60 mL, 4.7 mmol) and triethylamine (0.25 mL) were added successively. The reaction mixture was taken up in diluted aqueous sodium bicarbonate and worked up as usual. A mixture of the crude silyldienolether **138** (786 mg, 3.0 mmol), 2-methoxy-1,3-dioxolan (0.40 mL, 4.2 mmol) and zinc chloride (5.2 mL of a 10% solution in ethyl acetate, 4.2 mmol) was refluxed for 90 min. The reaction mixture was cooled, worked up as usual and chromatographed on silica gel with light petroleum/ether (4/1→2/1) as the eluant to afford the γ-dioxolanyl-α,β-unsaturated ketone **140** (573 mg, 72%).
^{1}H-NMR: 1.02 (s, 3H), 1.13 (d, J=7 Hz, 3H), 1.1-2.8 (m, 12H), 3.7-4.0 (m, 4H), 4.97 (t, J=5 Hz, 1H), 5.84 (br s, 1H). MS: m/e (%): 264 (1.8), 192 (0.4), 191 (0.4), 95 (1), 73 (100), 45 (9).

3,3aβ,4,5,6,6aβ,7,8-Octahydro-7β,8α-dimethyl-1H-naphtho[1,8aα-c]furan-8β-ol (**142**) and 3,3aβ,4,5,6,6aβ,7,8-octahydro-7β,8β-dimethyl-1H-naphtho[1,8aα-c]furan-8α-ol (**143**)
The enone **132** (0.52 g, 2.5 mmol) was dissolved in dry ether (20mL) at -78°C under nitrogen. Methyl lithium (2 mL of a 1.5 N solution in ether) was added and the reaction mixture was stirred for 4 h. Aqueous ammonium chloride was added and the reaction was worked up as usual to give the allylic alcohols **142** and **143** (0.56 g) in the ratio 1/1.

Separation of the isomeric alcohols could be effected by chromatography on silica gel and elution with light petroleum/ether (2/1). The alcohol **142** was obtained as a colourless oil.
^{1}H-NMR: 0.97 (d, J=7 Hz, 3H), 1.12 (s, 3H), 1.0-1.9 (m, 10H), 3.4-3.7(m, 2H), 3.9-4.1 (m, 2H), 5.56 (d, J=10 Hz, 1H), 5.92 (d, J=10 Hz, 1H). MS: m/e (%): 222 (8), 207 (27), 205 (17), 204 (100), 159 (53), 149 (34). Calc. for $C_{14}H_{22}O_2$: 222.1620; found: 222.1623.
The alcohol **143** was obtained as a white solid (mp 67-68°C)
^{1}H-NMR: 0.91 (d, J=6 Hz, 3H), 1.13 (s, 3H), 1.0-1.9 (m, 10H), 3.4-3.6 (m, 2H), 3.9-4.1 (m, 2H), 5.45 (d, J=10 Hz, 1H), 5.78 (d, J=10 Hz, 1H). MS: m/e (%): 222 (15), 207 (61), 205 (18), 204 (97), 159 (100), 149 (55). Calc. for $C_{14}H_{22}O_2$: 222.1620; found 222.1619.

3aβ,4,5,6,6aβ,7-Hexahydro-7β,8-dimethyl-1H-naphtho[1,8aα-c]furan-10(3H)-one (**144**) from the alcoholmixture **142** and **143**.
The alcohol mixture **142** and **143** (0.56 g, 2.5 mmol) was dissolved in dry dichloromethane (10 ml) and pyridinium chlorochromate (1.05 g, 4.9 mmol) was added. The reaction mixture was stirred for 6 h at roomtemperature, diluted with ether and decanted. Further work up as usual, filtration over a short silica gel column and recrystallization from light petroleum afforded the enone **144** (0.50 g, 90%) as a white solid (m.p. 58-60°C).
^{1}H-NMR: 1.11 (s, 3H), 1.91 (br s, 3H), 1.0-2.6 (m, 9H), 3.4-4.2 (m, 4H), 5.76 (br s, 1H). MS: m/e (%): 220 (95), 205 (6), 191 (29), 135 (25), 123 (12), 97 (50), 96 (100). Calc. for $C_{14}H_{20}O_2$: 220.1463; found: 220.1466.

1β-(1,3-Dioxolan-2-yl)-4a,5,6,7,8,8aβ-hexahydro-1α,4aα-dimethyl-naphthalen-2(1H)-one (**145**)
This compound was prepared in the same way as the enone **140**. The α'-dioxolanyl-α,β-unsaturated ketone **145** was obtained as a colourless oil in 51% yield.
^{1}H-NMR: 1.13 (s, 3H), 1.24 (s, 3H), 1.1-2.3 (m, 9H), 3.7-4.0 (m, 4H), 4.94 (s,1H), 5.90 (d, J=10 Hz, 1H), 6.70 (d, J=10 Hz, 1H).

1β-(1,3-Dioxolan-2-yl)-1,2,4a,5,6,7,8,8aβ-octahydro-1α,2β,4aα-trimethyl-naphthalen-2α-ol (**146**).
The enone **145** (294 mg, 1.2 mmol) was dissolved in dry ether (10 mL) at 0°C under nitrogen. Methyl lithium (2 ml of a 1.8 N solution in ether) was added and the reaction mixture was stirred for 1 h. Work up as usual, chromatography on silica gel eluting with light petroleum/ether (2/1) and recrystallization from light petroleum afforded the alcohol **146** (274 mg, 88%) as a white solid (m.p. 97-98°C).

^{1}H-NMR: 0.91 (s, 3H), 1.04 (s, 3H), 1.38 (s, 3H), 1.2-1.9 (m, 9H), 3.24 (br s, 1H), 3.9-4.1 (m, 4H), 4.76 (s, 1H), 5.24 (d, J=10 Hz, 1H), 5.30 (d, J=10 Hz, 1H). MS: m/e (%): 266 (0.7), 251 (12), 176 (41), 161 (28), 73 (100). Calc for $C_{16}H_{26}O_3$: 266.1882; found: 266.1890.

4β-(1,3-Dioxolan-2-yl)-4aβ,5,6,7,8,8a-hexahydro-3,4α,8aα-trimethyl-naphthalen-1(4H)-one (**147**)
The allylic alcohol **146** (129 mg, 0.48 mmol) and pyridinium dichromate (600 mg, 1.6 mmol) were dissolved in dry dimethylformamide (5 mL). The reaction mixture was stirred for 24 h at roomtemperature, taken up in water and extracted with light petroleum. Further work up as usual and chromatography on silica gel eluting with light petroleum/ether (4/1→2/1) gave the enone **147** (54 mg, 42%) as a colourless oil.
^{1}H-NMR: 1.16 (s, 3H), 1.26 (s, 3H), 1.99 (br s, 3H), 1.0-2.1 (m, 9H), 3.7-4.0 (m, 4H), 4.86 (s, 1H), 5.83 (br s, 1H). MS: m/e (%): 264 (5), 192 (1.3), 191 (0.3), 177 (3), 135 (2), 95 (2), 91 (3), 73 (100), 45 (19).

7β-(1,3-Dioxolan-2-yl)-3aβ,4,5,6aβ,7-hexahydro-7α-methyl-1H-naphtho[1,8aα-c]furan-8(3H)-one (**148**).
The enone **132** (412 mg, 2 mmol) was silylated and subsequently dioxolanylated, as described for the synthesis of **140**, to give the enone **148** (150 mg, 27%) and starting material (70 mg, 17%). The enone **148** was recrystallized in diisopropylether (mp: 133-135°C).
^{1}H-NMR: 1.11 (s, 3H), 1.2-2.1 (m, 7H), 2.6-2.9 (m, 1H), 3.5-4.3 (m, 8H), 5.10 (s, 1H), 5.97 (d, J=10 Hz, 1H), 6.97 (d, J=10 Hz, 1H). MS: m/e(%): 278 (7), 263 (1), 233 (3), 206 (3), 205 (2), 175 (5), 161 (9), 73 (100). Calc for $C_{16}H_{22}O_4$: 278.1518; found: 278.1523.

7β-(1,3-Dioxolan-2-yl)-3,3aβ,4,5,6,6aβ,7,8-octahydro-7α,8β-dimethyl-naphtho[1,8aα-c]furan-8α-ol (**149**)
Methyl lithium addition to enone **148**, in the same way as described for **135** and **136**, afforded the alcohol **149** in a quantitative yield as a white solid (mp: 133-135°C from diisopropyl-ether).
^{1}H-NMR: 0.82 (s, 3H), 1.43 (s,3H), 1.1-2.2 (m, 8H), 3.25 (br s, 1H), 3.4-4.1 (m, 8H), 4.82 (s, 1H), 5.33 (d, J=10Hz, 1H), 5.68 (d, J=10Hz, 1H). MS: m/e (%): 294 (1), 279 (9), 276 (2), 204 (32), 167 (22), 159 (35), 73 (100). Calc. for $C_{17}H_{26}O_4$: 294.1831; found: 294.1837.

3,4,4a,5,6,7,8,8aβ-octahydro-4aα-methyl-4β-phenylthio-naphthalen-2(1H)-one (**150**) and 3,4,4a,5,6,7,8,8aβ-octahydro-4aα-methyl-4α-phenylthio-naphthalen-2(1H)-one (**151**)
The enone **134** (492 mg, 3.0 mmol), thiophenol (0.30 mL, 3.0 mmol) and triethylamine (0.20 mL) were dissolved in dry tetrahydrofuran (10 mL).

The reaction mixture was stirred at ambient temperature under nitrogen. After 4 h the axial sulfide was exclusively formed. Sodium thiophenolate (2 mmol) in tetrahydrofuran (5 mL) was added and the reaction mixture was stirred overnight. The mixture was diluted with ether, washed with aqueous 4 N sodium hydroxide and further worked up as usual. Chromatography on silica gel with light petroleum/ether (9/1) as the eluant afforded the axial sulfide **150** (46 mg, 6%) and the equatorial sulfide **151** (643 mg, 78%).

150: mp: 88-90°C (from hexane).

^{1}H-NMR: 1.18 (s, 3H), 1.2-2.8 (m, 13H), 3.34 (dd, J_1=5 Hz, J_2=3 Hz, 1H), 7.2-7.5 (m, 5H). MS: m/e (%): 274 (100), 165 (71), 164 (70), 122 (70), 110 (75), 95 (47), 81 (31). Calc. for $C_{17}H_{22}OS$: 274.1391; found: 274.1400

151: mp: 97-98°C (from hexane).

^{1}H-NMR: 1.09 (s, 3H), 1.2-2.5 (m, 11H), 2.6-2.8 (m, 2H), 3.06 (dd, J_1=10 Hz, J_2=7 Hz, 1H), 7.2-7.5 (m, 5H). MS: m/e (%): 274 (100), 165 (72), 122 (30), 110 (59), 95 (42), 81 (42). Calc. for $C_{17}H_{22}OS$: 274.1391; found: 274.1394.

4a,5,6,7,8,8aβ-Hexahydro-4aα-methyl-4-phenylthio-naphthalen-2(1H)-one (**152**)

The sulfide **151** (436 mg, 1.6 mmol) was dissolved in benzene (16 mL) and ether (8 mL) at 0°C. Chloreal (142 mg, 0.60 mmol) was added and the mixture was stirred for 1 h. Evaporation of the solvents and chromatography on silica gel with light petroleum/ether (4/1) as the eluant afforded the unsaturated sulfide **152** (325 mg, 76%) as a white solid (mp 93-95°C). Calc. for $C_{17}H_{20}OS$: 74.95% C, 7.40% H; found: 74.91% C, 7.44% H.

^{1}H-NMR: 1.35 (s, 3H), 1.3-2.3 (m, 11H), 5.26 (s, 1H), 7.4-7.5 (m, 5H). MS: m/e (%): 272 (63), 257 (8), 239 (27), 176 (100). Calc. for $C_{17}H_{20}OS$: 272.1235; found: 272.1238.

4a,5,6,7,8,8a-Hexahydro-3,8aα-dimethyl-naphthalen-1(4H)-one (**155**)

The unsaturated sulfide **152** (136 mg, 0.50 mmol) was dissolved in dry ether (10 mL) at -78 °C under nitrogen and methyl lithium was added (0.65 ml of a 1.6 M solution in ether, 1.0 mmol). The reaction mixture was stirred for 90 min without cooling, aqueous ammonium chloride was added and the mixture was worked up as usual. The rather unstable mixture of the alcohols **153** and **154** was obtained in a quantitative yield.

^{1}H-NMR (CCl_4): 1.03 (s, 1.5H), 1.10 (s, 3H), 1.14 (s, 1.5H), 1.0-2.5 (m, 12H), 5.04 (s, 1H), 7.1-7.5 (m, 5H).

The crude alcohol mixture was dissolved in acetone (10 mL). Water (20 drops) and mercury(II)chloride (204 mg, 0.75 mmol) were added. The mixture was stirred for 10 min and the formed mercury salts were filtered off. Work up as usual and chromatography on silica gel eluting

with light petroleum/ether (20/1) gave the enone **155** (64 mg, 94%) as a colourless oil.
^{1}H-NMR: 0.98 (s, 3H), 1.1-2.1 (m, 11H), 1.90 (br s, 3H), 5.74 (br s, 1H). MS: m/e (%): 178 (52), 163 (52), 82 (100). Calc. for $C_{12}H_{18}O$: 178.1358; found 178.1352.

3aβ,4,5,6,6aβ,7,9,10-Octahydro-7β-methyl-10β-phenylthio-1H-naphtho[1,8aα-c]furan-8(3H)-one (**156**).
Thiophenol (12.3 mL, 120 mmol) was dropped to a suspension of sodium hydride (1.8 g of a 80% dispersion in mineral oil, 60 mmol) in dry tetrahydrofuran (200 ml) under nitrogen. The mixture was stirred additionally for 20 min and the enone **132** (11.62 g, 56 mmol) in tetrahydrofuran (100 mL) was added dropwise. The reaction mixture was stirred overnight, diluted with ether and washed with aqueous 0.1 N sodium hydroxide. Further work up as usual and flash chromatography on silica gel eluting with light petroleum/ether (3/1) afforded the axial sulfide **156** (15.29 g, 86%) as a white solid (mp 136-138°C from light petroleum/ether).
^{1}H-NMR (300 MHz): 1.05 (d, J=6 Hz, 3H), 1.2-1.6 (m, 3H), 1.8-1.9 (m, 3H), 2.0-2.1 (m, 2H), 2.68 (dd, J_1=15 Hz, J_2=2.5 Hz, 1H), 2.88 (m+dd, J_1=15 Hz, J_2=5.5 Hz, 2H), 3.67 (d, J=8 Hz, 1H), 3.76 (dd, J_1=5.5 Hz, J_2=2.5 Hz, 1H), 4.0-4.2 (m, 3H), 7.2-7.5 (m, 5H). MS: m/e (%): 316 (96), 207 (91), 206 (93), 110 (100). Calc for $C_{19}H_{24}O_2S$: 316.1497; found: 316.1496
Further elution with light petroleum/ether (2/1) afforded the equatorial sulfide **157** (0.86 g, 5%) as a white solid.
^{1}H-NMR (300 MHz): 1.02 (d, J=7 Hz, 3H), 1.4-2.0 (m, 7H), 2.13 (dq, J_1=7 Hz, J_2=12 Hz, 1H), 2.6-2.8 (m, 3H), 3.29 (dd, J_1=4.5 Hz, J_2=13 Hz, 1H), 3.74 (dd, J_1=4 Hz, J_2=9 Hz, 1H), 4.02 (d, J=10 Hz, 1H), 4.10 (d, J=10 Hz, 1H), 4.35 (t, J=8 Hz, 1H), 7.3-7.4 (m, 3H), 7.4-7.5 (m, 2H). MS: m/e (%): 316 (100), 207 (75), 206 (30), 110 (17). Calc for $C_{19}H_{24}O_2S$: 316.1497; found: 316.1495.

3aβ,4,5,6,6aβ,7-hexahydro-7β-methyl-10-phenylthio-1H,naphtho[1,8aα-c]furan-8(3H)-one (**158**)
The saturated sulfide **156** (6.6 g, 20.9 mmol) was dissolved in benzene (200 mL) and ether (100 mL) at 0°C under nitrogen. Chloreal (1.78 g, 7.7 mmol) was added and the reaction mixture was stirred for 30 min. Evaporation of the solvents and flash chromatography on silica gel eluting with light petroleum/ether (3/1) afforded the unsaturated sulfide **158** (5.4 g, 83%) as a white solid (mp 149-150°C from *tert*-butyl methyl ether).
^{1}H-NMR: 1.10 (d, J=6 Hz, 3H), 1.2-2,2 (m, 8H), 2.8-3.1 (m, 1H), 3.7-4.0 (m, 2H), 4.2-4.6 (m, 2H), 5.30 (s, 1H), 7.4-7.5 (m, 5H). MS: m/e (%): 314 (100), 289 (25), 205 (33). Calc. for $C_{19}H_{22}O_2S$: 314.1341; found: 314.1340.

7β-(1,3-Dioxolan-2-yl)-3aβ,4,5,6,6aβ,7-hexahydro-7α-methyl-10-phenylthio-1H-naphtho[1,8aα-c]furan-8(3H)-one (**160**)

A solution of the enone **158** (8.34 g, 26.6 mmol) was added dropwise at 0°C under nitrogen to a solution of lithiumdiisopropylamide (28.6 mmol). After stirring for 30 min. chlorotrimethylsilane (3.8 mL, 30.0 mmol) and triethylamine (2 mL) were added successively. Work up as usual afforded the crude silyldienolether **159**. Successive addition of 2-methoxy-1,3-dioxolan (5 mL, 52.5 mmol), dry dichloromethane (15 mL, distilled from calcium hydride) and dry zinc chloride (5.0 g), stirring for 2 h and direct flash chromatography on silica gel eluting with light petroleum/ether (2/1) afforded starting material (0.92 g, 11%) and the acetal **160** (6.14 g, 60%) as a white solid (mp 167-169°C, from *tert*-butyl methyl ether). Elemental analysis: calc. for $C_{22}H_{26}O_4S$: 68.36% C, 6.78% H; found: 68.24% C, 6.81% H.

^{1}H-NMR: 1.11 (s, 3H), 1.2-2.2 (m, 6H), 2.7-3.1 (m, 2H), 3.5-4.0 (m, 6H), 4.1-4.6 (m, 2H), 4.99 (s, 1H), 5.32 (s, 1H), 7.3-7.6 (m, 5H). MS: m/e (%): 386 (33), 314 (85), 175 (61), 73 (100). Calc for $C_{22}H_{26}O_4S$: 386.1552; found: 386.1540.

7β-(1,3-Dioxolan-2-yl)-3aβ,4,5,6,6aβ,7-hexahydro-7α,8-dimethyl-1H-naphtho[1,8aα-c]furan-10(3H)-one (**130**)

The ketone **160** (1.21 g, 3.1 mmol) was treated with excess methyl lithium in dry tetrahydrofuran at 0°C to afford the rather unstable tertiary alcohol **161** in a quantitative yield.

^{1}H-NMR (CCl_4): 0.89 (s, 3H), 1.37 (s, 3H), 1.1-2.8 (m, 8H), 3.20 (br s, 1H), 3.4-4.5 (m, 8H), 4.81 (s, 1H), 5.14 (s, 1H), 7.3-7.6 (m, 5H).

The crude alcohol was dissolved in chloroform (30 mL) and a catalytic amount of *p*-toluenesulfonic acid monohydrate was added.

The reaction mixture was stirred for 2 h, neutralized and worked up. Flash chromatography on silica gel with light petroleum/ether (2/1) as the eluant afforded the enone **130** (0.58 g, 63%) as a white solid (mp 87-88°C, from light petroleum/ether). Elemental analysis: calc. for $C_{17}H_{24}O_4$: 69.83% C, 8.27% H; found 70.26% C, 8.66% H.

^{1}H-NMR: 1.05 (s, 3H), 1.87 (br s, 3H), 1.1-2.5 (m, 8H), 3.3-4.2 (m, 8H), 4.84 (s, 1H), 5.82 (br s, 1H). MS: m/e (%): 292 (23), 219 (67), 172 (29), 73 (100). Calc. for $C_{17}H_{24}O_4$: 292.1674; found: 292.1673.

3a,β,4,5,6,6aβ,7-Hexahydro-7β,8-dimethyl-1H-naphtho[1,8aα-c]furan-10(3H)-one (**144**) from the sulfide **158**

The unsaturated sulfide **158** (157 mg, 0.50 mmol) was treated with methyl lithium in the same way as described for the synthesis of **142** and **143** to give a mixture of tertiary allylic alcohols in a quantitative yield. Hydrolysis with mercuric(II)chloride, as described for **155**, resulted in the enone **144** (680 mg, 62%) after chromatography on silica gel and elution with light petroleum/ether (2/1).

4.7 REFERENCES AND NOTES

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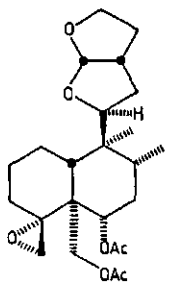
5. THE STEREOSELECTIVE SYNTHESIS OF PERHYDRO-FURO[2,3b]FURANS FROM CARBONYLCOMPOUNDS.

5.1 INTRODUCTION

As outlined in the synthetic plan in chapter 3, synthetic methods for the construction of the furofuran side chain were required. Many furopyran[1] and furofuran[2] syntheses have been reported during the last decade, however none of these were suitable for our purposes, so we had to develop new methods. Useful precursors for the furofuran moiety would probably be: aldehydes, carboxyl derivatives and/or oxiranes. The principal modelcompounds used to study the conversion of such precursors were therefore pivalaldehyde, pivaloyl chloride and *tert*-butyloxirane. In this chapter the stereoselective synthesis of 2-substituted perhydrofuro[2,3b]furans **163** from carbonyl compounds like **162** is described.

With carbonyl compounds as starting materials, the introduction of a functionalized methylene-perhydrofuran was investigated via the addition of a stabilized carbanion to the carbonyl group of **162**. To this extent the dithiane **164** and the sulfones **165**, **166** and **167** were chosen as reagents, likely to lead to positive results.

Figure 5.1



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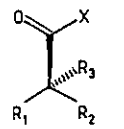
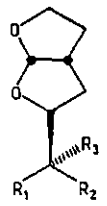
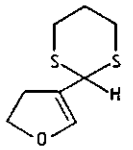


X = H, OMe, Cl

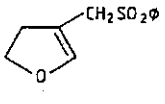
162



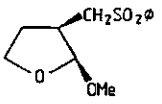
163



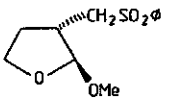
164



165



166



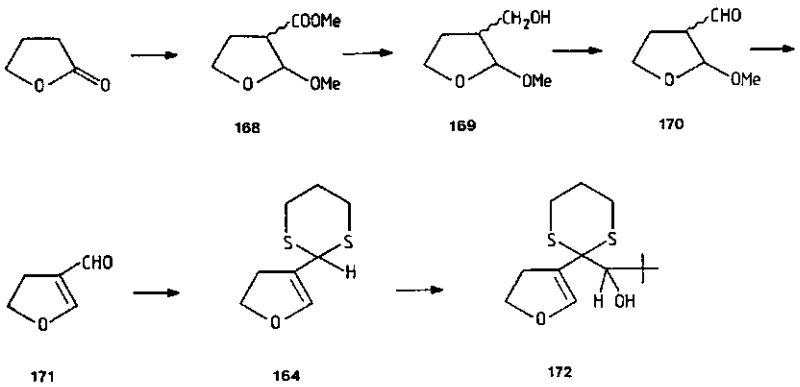
167

In view of the stereochemical problems to be expected in the built-up of a furofuran side chain in dihydroclerodin **26n**, the symmetrical dithiane **164** seemed to be the reagent to be preferred, followed by the sulfone **165**. In the sulfone-acetals **166** and **167** an influence of the asymmetric centres in these reagents has to be taken into account as an additional difficulty. The syntheses of **164-167** was set up starting from γ-butyrolactone.

5.2 VIA 3-(1,3-DITHIAN-2-YL)-4,5-DIHYDROFURAN

The dithiane **164** was synthesized in five steps from γ-butyrolactone. By a modification of the procedure of Korte and Machleidt[3] this was converted into a mixture of acetal-esters **168** in 53% yield (scheme 5.1). The esters **168** were reduced quantitatively to the alcohols **169**, and subsequent Swern oxidation[4] resulted in a mixture of the aldehydes **170** and **171**. Treatment of this mixture with triethylamine in refluxing benzene gave the rather labile aldehyde **171** in 48% yield. The dithiane **164** was obtained in 55% yield by reaction of the aldehyde **171** with 1,3-propanedithiol[5].

Scheme 5.1

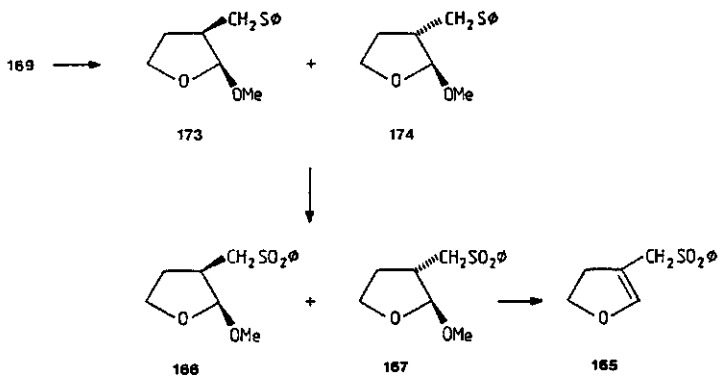


Reaction of the lithiated dithiane **164** with 2,2-dimethylpropanal (pivalaldehyde) in tetrahydrofuran at -78°C in the presence of hexamethylphosphoric triamide gave the adduct **172** in 80% yield. Attempts at cyclization of **172** to a furofuran ring, using a number of acidic catalysts, were unsuccessful, and removal of the dithiane moiety with Raney Nickel failed as well.

5.3 VIA 3-[(PHENYLSULFONYL)-METHYL]-4,5-DIHYDROFURAN

The synthesis of perhydrofuro[2,3b]furans from the dithiane **164** having failed, the attention was focussed on the allylic sulfone **165**[6]. The latter was synthesized from the mixture of alcohols **169** in three steps (scheme 5.2). The alcohols **169** were converted into the sulfides **173** and **174** by reaction with diphenyldisulfide and tri-n-butylphosphine in pyridine[7]. Separation of the diastereoisomeric sulfides was effectuated by means of flash chromatography. Oxidation of the sulfides **173** and **174** with oxone® in buffered methanol[8] yielded the corresponding sulfones almost quantitatively. The unsaturated sulfone **165** was obtained in yields up to 68% by treatment of sulfone **166** and/or **167** with *p*-toluenesulfonic acid in refluxing benzene. However, it proved to be impossible to isolate any stable product from the reactions carried out between pivalaldehyde and lithiated **165**.

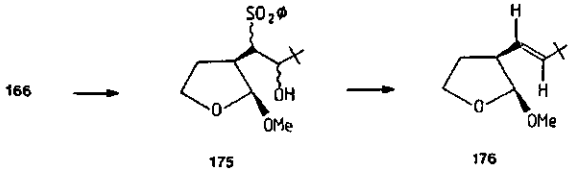
Scheme 5.2



5.4 VIA 2-METHOXY-3-[(PHENYLSULFONYL)-METHYL]-PERHYDROFURANS

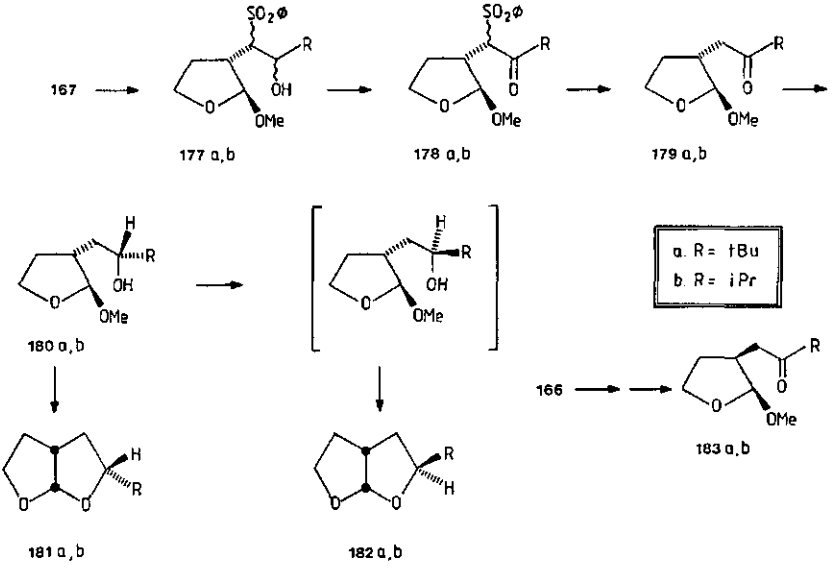
Since the experiments with the dihydrofurans **164** and **165** had been unsuccessful, the sulfone-acetals **166** and **167** remained to be investigated. A disadvantage of the use of these sulfone-acetals was illustrated by the addition of the lithiated sulfone-acetal **166** to pivalaldehyde[9], which yielded a complex mixture of the stereoisomeric alcohols **175**. Apart from that, elimination of the hydroxyl group took place during the reductive desulfonation, and the alkene **176** was obtained in 85% yield (scheme 5.3).

Scheme 5.3



In order to circumvent both problems, the β-ketosulfone **178a** was synthesized both by oxidation of the hydroxyl group in the adduct **177a**, and by addition of the dilithiated sulfone-acetal **167** to pivaloyl chloride[10] (scheme 5.4). Both routes gave yields of about 70%.

Scheme 5.4



Reductive desulfonation of **178a** with sodium amalgam in buffered methanol[11] yielded the ketone **179a**, as expected. Similarly, the ketone **179b** was obtained from the trans-sulfone **167**. Starting from the cis-sulfone **166** the corresponding ketones **183a** and **183b** were prepared, following the same procedures.

Upon experimenting with a number of reducing agents on the ketones **179a**, **179b**, **183a** and **183b**, it was found that nearly complete stereoselective reduction of the carbonyl group in **179a** and **179b** could be achieved by reaction with lithium tri-*tert*-butoxyaluminohydride in tetrahydrofuran at 0 °C. Thus, the ketone **179a** yielded the alcohol **180a,** after which ring closure to the furofuran **181a** was achieved by brief treatment of **180a** with acid (yield 95%, calc. from **179a**). Upon determination of the structure of this furofuran (*vide infra*), it appeared that the relative stereochemistry of the substituent at C_2 and the acetal proton is opposed to that observed for dihydroclerodin.
Inversion of the configuration at the neopentylic carbon atom C_2 was effectuated via tosylation of the alcohol **180a** followed by a nucleophilic substitution reaction with potassium superoxide[12]. Subsequently, the furofuran **182a** was obtained by acid catalyzed cyclization (yield 52%, calc. from the ketone **179a**), and proved to possess the same relative stereochemistry as dihydroclerodin (*vide infra*).
The corresponding 2-isopropyl-perhydrofuro[2,3b]furans **181b** and **182b** were synthesized following the same route as described for **181a** and **182a**, respectively. A selectivity, similar to the reactions carried out with the trans compounds **179a** and **179b**, could not be achieved in the reduction of the cis compounds **183a** and **183b**.

5.5 THE STRUCTURES OF 2-*tert*-BUTYL-PERHYDROFURO[2,3b]FURANS

The structures of the compounds **181a** and **182a** were elucidated by means of ^{1}H-NMR, viz. by combining the results of double resonance measurements and of the 2D-NOE spectra of the respective compounds. The 2D-NOE (300 MHz) proton spectra of **181a** and **182a** are shown in Fig. 5.2 and 5.3, respectively, in combination with the normal spectra.

Figures 5.2

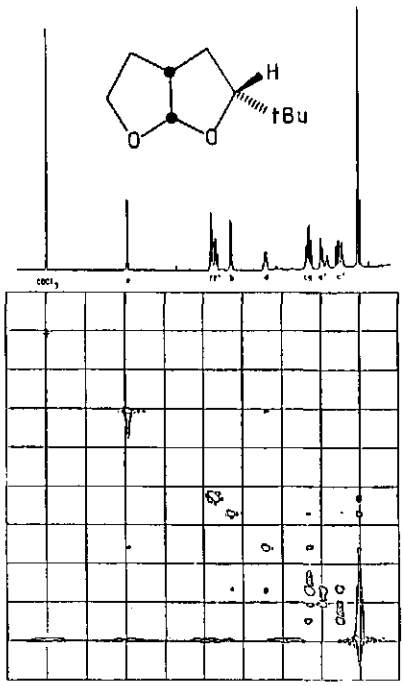
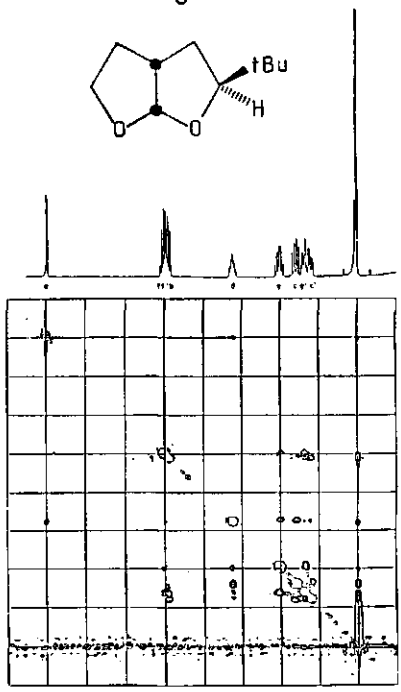


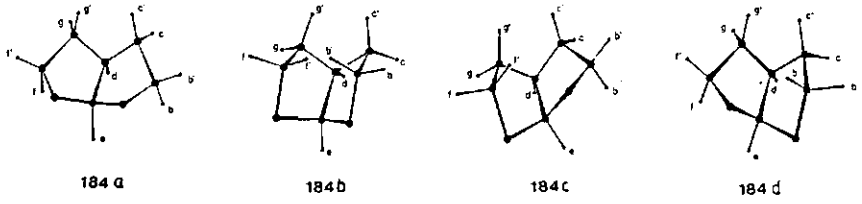
Figure 5.3



In the cis-fused unsubstituted perhydrofuro[2,3b]furan **184** (see Fig. 5.4), molecular models show four conformations to be possible. Interconversions between these geometries appear not to occur at room temperature (in the case of the 2-isopropyl- and the 2-*tert*-butylperhydrofuro[2,3b]furans).

Of the four conformations, two (**184a** and **184b**) have C_s symmetry; the remaining two (**184c** and **184d**) possess no symmetry elements, but each is the mirror image of the other. Upon substitution of the proton in the b or b' position, a total of eight possible conformations is obtained.

Figure 5.4



184 a 184 b 184 c 184 d

The molecular structure of compound **181a**.

Assignment of the ^{1}H-signals in the spectrum of compound **181a** was based on direct evidence (as for the t-Bu protons, H_e, H_d, the set H_b, H_f, $H_{f'}$, the set H_c, $H_{c'}$,H_g, $H_{g'}$), on the results obtained upon irradiation of the various multiplets,and on the 2D-NOE spectrum, and is indicated in Fig. 5.2. The 2D-NOE spectrum shows the protons H_e and H_d to be spatially near, so there can be no doubt about the cis junction of the rings. Also, a strong NOE is observed between H_d and H_c, between H_d and H_g, and between H_b and H_c. NOE's between H_d and $H_{c'}$, between H_d and $H_{g'}$, and between H_b and $H_{c'}$, are conspicuously absent.

Further, upon irradiation of the resonance frequency of H_e, the H_d multiplet turns into a regular quartet (relative intensities 1:3:3:1).

The only condition under which this deceptively simple pattern can occur is when of the four protons H_c, $H_{c'}$, H_g, and $H_{g'}$ three have very nearly identical couplings with H_d, while the fourth coupling constant is zero. Measurements of the torsion angles in a Dreiding molecular model of **184c**, and application of the Karplus relation showed this to be a real possibility. It should be noted that the equality of three of the four coupling constants (the fourth being zero) completely rules out the ring geometries of C_s symmetry, **184a** and **184b**. This is corroborated by the value of the coupling constant J_{de} (5.2 Hz), which appears too small for the torsion angle of zero degrees corresponding to a symmetrical structure. Actually, the value found fits the torsion angle measured in models of **184c** and **184d** very well. Further, the results of the double resonance experiments showed the coupling constants J_{cd}, $J_{c'd}$, and J_{gd} to be nearly equal (ca 9.0 Hz), while $J_{g'd}$ proved to be close to zero, as was confirmed by the simple observation that the $H_{g'}$ multiplet does not change upon irradiation on the H_d multiplet. As in geometry **184d** the coupling constant $J_{c'd}$ would be expected to be zero, this leads to the conclusion that structure **184c** is the correct representation of the geometry of the rings, while the 2D-NOE spectrum proves the t-Bu group to occupy the pseudo equatorial position (a strong NOE between H_b and H_c being present). Compound **181a** thus has to structure **184c** (see Fig. 5.4), with the t-Bu group in the b' position.

It should be noted that the multiplet originating from H_b has the form of a quartet (relative intensities 1:1:1:1); this now can only come about under circumstances in which either $J_{bc}=2J_{bc'}$ or $J_{bc'}=2J_{bc}$. Estimation of torsion

angles and correlation of the data obtained with the Karplus relation shows that the only condition under which either of these two possibilities (viz. the latter, J_{bc}=4.5 Hz, $J_{bc'}$ 9.9 Hz) can be realized is when compound **181a** has geometry **184c**.

The molecular structure of compound **182a**.

The assignment of the ^{1}H-signals in the spectrum of compound **182a** was carried out in the same way as for compound **181a** and is indicated in Fig. 5.3.

For compound **182a** as well, the 2D-NOE spectrum shows the protons H_e and H_d to be spatially near, proving a cis junction between the rings.

As opposed to the results obtained with compound **181a**, irradiation of the resonance frequency of H_e yields direct evidence that the basic structure of the rings in **182a** his C_s symmetry, witnessing the fact that here the H_d multiplet turns into a triplet-like structure, which could be fully reproduced starting from the following coupling constants: J_{cd}=J_{gd}=9.2 Hz, $J_{c'd}$=2.2 Hz, and $J_{g'd}$=3.2 Hz (the difference between $J_{c'd}$ and $J_{g'd}$ being due to an asymmetry induced in the molecule caused by repulsion between H_b, and $H_{f'}$, *vide infra*). Measurement of the torsion angles in Dreiding models of **184a** and **184b**, and correlation of the values obtained with the Karplus relation shows geometry **184b** to be by far the most probable possibility. This is confirmed by the magnitude of the coupling constants $J_{b'c}$ (9.9 Hz) and $J_{b'c'}$ (6.0 Hz).

In Fig. 5.3 it is seen that a strong NOE is observed between H_d and H_c, between H_d and H_g, and between $H_{b'}$ and $H_{c'}$. The NOE's between H_d and $H_{c'}$, and between H_d and $H_{g'}$ are weak, while a NOE between $H_{b'}$ and H_c is absent. These data inevitably lead to the "closed" symmetric geometry **184b**, the proximity of $H_{b'}$ and $H_{c'}$ showing the t-Bu group to occupy the (least hindered) pseudo equatorial position. The axial position of $H_{b'}$ is confirmed by the values of the coupling constants $J_{b'c}$ and $J_{b'c'}$ (*vide supra*). However, as noted before, due to a repulsive interaction between $H_{b'}$, and $H_{f'}$ a twist is induced in the molecule, as can be inferred from the fact that in **182a** the coupling constant J_{de} has almost the same value as in **181a** (4.9 and 5.2 Hz, respectively), indicating about the same torsion angles between the respective C-H bonds. Were **182a** to have a fully symmetrical geometry, the torsion angle would be zero and J_{de} consequently would be expected to be larger (and the coupling constants

$J_{c'd}$ and $J_{g'd}$ would be equal). This deformation from symmetry can take place in two directions (yielding torsion angles between the bonds to H_d and H_e that have the same absolute magnitude, but opposed signs); however, the values found for the coupling constants $J_{c'd}$ (2.2 Hz) and $J_{g'd}$ (3.2 Hz) show the torsion angle between the bonds to H_d and $H_{c'}$ to be about 30° smaller than the torsion angle between the bonds to H_d and $H_{g'}$. Deformation of the symmetric geometry in this direction will be favoured over the alternative, as in the former case there will be less steric interaction between the t-Bu group and H_c.
In summary, compound **182a** is concluded to have structure **184b** (see Fig. 5.4), with the t-Bu group in the b position.

The molecular structure of compounds **181b** and **182b.**
The structural analysis of the iso-propyl compounds was carried out in the same way as for the *tert*-butyl compounds **181a** and **182a**. As the line of reasoning and the results obtained were the same as for the t-Bu derivatives, i.e. compound **181b** proved to have geometry **184c** (with the i-Pr group in the pseudoequatorial b' position), and compound **182b** has geometry **184b** (with the i-Pr group in the pseudo equatorial b position), no details will be given here, except for the following two remarks.
Both in **181b** and in **182b** the rotation of the i-Pr group is (within the ^{1}H-NMR time scale) fully hindered, witnessing the fact that the two methyl groups within the iso-propyl group have clearly different chemical shifts. Therefore, the normal i-Pr coupling pattern is not observed; instead, each of the methyl groups splits into a doublet.
As in the t-Bu derivative **182a**, the structure of **182b** appears to deviate from C_s symmetry, albeit to a lesser extent. This can be inferred from the facts that a coupling J_{de} of 5.1 Hz is found.

5.6 EXPERIMENTAL

For general experimental details see chapter 4.6.

Methyl 2-methoxy-perhydrofuran-3-carboxylate (**168**)
To a mechanically stirred suspension of 80% sodium hydride (31.5 g, 1.05 mol) in ether (1 L) was added dropwise a mixture of methyl formate (60 g, 1.0 mol) and γ-butyrolactone (86 g, 1.0 mol). Stirring was continued for

20 h. The solid material was filtered off and washed with hexane and ether, after which it was suspended in dry methanol (300 mL). A solution of hydrogen chloride (67.7 g) in dry methanol (400 mL) was added dropwise and the reaction mixture was stirred for 1 h. After careful neutralization with sodium hydroxide, the reaction mixture was filtered and the filtrate was concentrated carefully. Water was added and the mixture was worked up as usual to afford 93.9 g of the crude ester. Vacuum distillation (88-92°C, 13 mm Hg) afforded the esters **168** (85.6 g, 53%) as a colourless oil.
^{1}H-NMR: 2.1-2.3 (m, 2H), 2.9-3.1 (m, 1H), 3.37 (s, 3H), 3.75 (s, 3H), 3.8-4.2 (m, 2H), 5.1-5.2 (m, 1H). The mass spectra of both isomers were identical: m/e (%): 159 (0.4), 145 (3),129 (23), 100 (33), 69 (100), 59 (15).

2-Methoxy-perhydrofuran-3-methanol (**169**)
The esters **168** (40.0 g, 250 mmol) were dissolved in dry ether (100 mL) and added dropwise to a mechanically stirred suspension of $LiAlH_4$ (6.13 g, 188 mmol) in ether (600 mL). After refluxing for 3 h the mixture was cooled and water (6 mL), 4 N sodium hydroxide (6 mL) and water (18 mL) were added successively. The mixture was dried by adding magnesium sulfate directly. After filtration the solvent was evaporated carefully to yield the alcohols **169** (32.8 g, 99%) as a colourless oil.
^{1}H-NMR: 1.3-2.5 (m, 3H), 2.9-3.2 (m, 1H), 3.36 (s, 3H), 3.4-3.6 (m, 2H), 3.7-4.0 (m, 2H), 4.9-5.0 (m, 1H). MS: m/e (%): cis: 104 (21), 101 (67), 71 (79), 61(100), 44 (81), 31 (44); trans: 131 (2), 104 (19), 101 (47), 71 (56), 61 (100), 44 (71), 31 (27).

4,5-Dihydrofuran-3-carbaldehyde (**171**)
To a stirred solution of oxalyl chloride (7.4 mL, 85 mmol) in dry dichloromethane (150 mL) at -78°C under nitrogen, was added dropwise dimethylsulfoxide (13 mL, 185 mmol) in dichloromethane (30 mL). After stirring for 5 min the alcohols **169** (10.2 g, 77 mmol) in dichloromethane (60 mL) were added dropwise. Stirring was continued for 15 more min and triethylamine (54 mL, 390 mmol) was added dropwise. The stirred reaction mixture was slowly warmed to roomtemperature, water was added and the mixture was extracted three times with dichloromethane. The combined organic extract was washed with brine and dried. The solvent was evaporated and the residue was filtered through a short column of silica gel. The filtrate was concentrated and the residue, still containing some triethylamine, was dissolved in benzene. The solution was refluxed and the condensed vapor was led through a column filled with molecular sieves 4 Å. After 48 h the mixture was cooled and concentrated. Flash chromatography on silica gel eluting with light petroleum/ether (3/1) afforded the aldehyde **171** (3.64 g, 48%) as white

crystals; mp 49-51°C. No satisfactory elemental analysis could be obtained, due to the instability of this compound.
^{1}H-NMR: 2.80 (br t, J=10 Hz, 2H), 4.65 (t, J=10 Hz, 2H), 7.47 (br s, 1H), 9.65 (s, 1H). MS: m/e (%): 98 (100), 97 (35), 69 (48), 41 (60), 39 (57).

3-(1,3-Dithian-2-yl)-4,5-dihydrofuran (**164**)
To a solution of the aldehyde **171** (724 mg, 7.4 mmol) in dry chloroform (30 mL) at 0°C under nitrogen, was added 1,3-propanedithiol (750 µL, 7.5 mmol) and boron trifluoride etherate (90 µL, 0.73 mmol). The solution was stirred for 1 h and poured into diluted aqueous sodium bicarbonate. The water layer was extracted with dichloromethane. The combined organic extract was washed with brine, dried, filtered and concentrated. Flash chromatography on silica gel eluting with light petroleum/ether (10/1) afforded the dithiane **164** (762 mg, 55%) as white crystals. An analytical sample was obtained by recrystallization in light petroleum/ether; mp 71-73°C. Elemental analysis: calc. for $C_8H_{12}OS_2$: 51.02% C, 6.42% H; found: 50.57% C, 6.47% H.
^{1}H-NMR: 1.7-2.3 (m, 2H), 2.73 (br t, J=9 Hz, 2H), 2.8-3.0 (m, 4H), 4.37 (t, J=9 Hz, 2H), 4.80 (br s, 1H), 6.45 (br s, 1H). MS: m/e (%): 188 (100), 155 (22), 114 (25). Calc. for $C_8H_{12}OS_2$: 188.0330; found: 188.0330.

1-(1,3-Dithian-2-yl)-1-(4,5-dihydrofuryl)-3,3-dimethyl-butan-2-one (**172**)
The dithiane **164** (110 mg, 0.59 mmol) and hexamethylphosphoric triamide (100 µL) were dissolved in dry tetrahydrofuran (5 mL) under nitrogen. The solution was cooled to -78°C and 15% n-butyl lithium in hexane (420 µL) was added. The mixture was stirred for 15 min and pivalaldehyde (60 µL, 0.55 mmol) in tetrahydrofuran (2 mL) was added. The solution was stirred for 30 min and quenched with aqueous ammonium chloride. The reaction mixture was allowed to warm up to roomtemperature and the usual work up afforded a residue (220 mg), which was purified by flash chromatography on silica gel gel with light petroleum/ether (9/1) as the eluant to give the dithiane **164** (16 mg) and the dithiane **172** (129 mg, 85%).
^{1}H-NMR: 1.11 (s, 9H), 1.8-2.1 (m, 3H), 2.6-3.1 (m, 6H), 3.53 (s, 1H), 4.47 (br t, J=10 Hz, 2H), 6.62 (br s, 1H). MS: m/e (%): 274 (16), 259 (13), 187 (100). Calc. for $C_{13}H_{22}O_2S_2$: 274.1061; found: 274.1062.

2β-Methoxy-3β-[(phenylthio)-methyl]-perhydrofuran (**173**) and
2α-Methoxy-3β-[(phenylthio)-methyl]-perhydrofuran (**174**)
Tri-n-butylphosphine (59 mL, 0.24 mol) was added dropwise to a stirred solution of the alcohol mixture **169** (19.5 g, 0.15 mol) and diphenyl disulfide (64.0 g, 0.29 mol) in pyridine (200 mL) at roomtemperature. The

reaction mixture was stirred for 20 h, taken up in ether (700 mL) and washed with 2 N sodium hydroxide. The water layer was extracted twice with ether. The combined organic extracts were washed with brine, dried and concentrated. The residue was dissolved in light petroleum (200 mL) and set aside to crystallize in a refrigerator. The mixture was filtered and the crystals were washed with cold light petroleum. The filtrate was concentrated and chromatographed on silica gel eluting with light petroleum/ether (20/1) as the eluant to give the cis-sulfide **173** (5.83 g), the trans-sulfide **174** (10.16 g) and a mixed fraction of **173** and **174** (13.86 g) as colourless oils. The total yield was 29.85 g (90%).
173: ^{1}H-NMR : 1.6-2.5 (m, 3H), 3.06 (t, J=7 Hz, 2H), 3.31 (s, 3H), 3.7-4.1(m, 2H), 4.81 (d, J=4 Hz, 1H), 7.1-7.4 (m, 5H). MS: m/e (%): 224 (17), 192 (20), 123 (40), 115 (15), 83 (100), 55 (83). Calc. for $C_{12}H_{16}O_2S$: 224.0871; found: 224.0869.
174: ^{1}H-NMR : 1.5-2.4 (m, 3H), 2.9-3.0 (m, 2H), 3.33 (s, 3H), 3.9-4.1 (m, 2H), 4.86 (s, 1H), 7.1-7.4 (m, 5H). MS: m/e (%): 224 (22), 123 (42), 83 (30), 55 (100). Calc. for $C_{12}H_{16}O_2S$: 224.0871; found: 224.0870.

2β-Methoxy-3β-[(phenylsulfonyl)-methyl]-perhydrofuran (**166**) and
2α-Methoxy-3β-[(phenylsulfonyl)-methyl]-perhydrofuran (**167**)
A mixture of the sulfides **173** and **174** (23.09 g, 103 mmol) was dissolved in methanol (200 mL) and sodium bicarbonate (50.4 g, 600 mmol) was added. To the resulting suspension, a suspension of oxone® (123 g, 400 mmol $KHSO_5$) in water (400 mL) was added in 2 h. The solids were filtered off and the filtrate was extracted four times with dichloromethane (150 mL). The combined organic organic extract was washed with brine, dried, filtered and concentrated. Flash chromatography on silica gel eluting with light petroleum/ether (1/1) afforded the cis-sulfone **166** (3.56 g), the trans-sulfone **167** (7.39 g) and a mixed fraction of **166** and **167** (14.62 g). The total yield was 25.57 g (97%)
166: ^{1}H-NMR: 1.5-2.7 (m, 3H), 3.21 (s, 3H), 3.1-3.6 (m, 2H), 3.8-4.0 (m, 2H), 4.75 (d, J=4 Hz, 1H), 7.5-7.7 (m, 3H), 7.9-8.0 (m, 2H). MS: m/e (%): 256 (0.2), 225 (5), 115 (22), 83 (83), 55 (100). Calc. for $C_{12}H_{16}O_4S$: 256.0770; found: 256.0777.
167: ^{1}H-NMR: 1.5-2.7 (m, 3H), 3.0-3.3 (m, 2H), 3.29 (s, 3H), 3.8-4.0 (m, 2H), 4.78 (br s, 1H), 7.6-7.7 (m, 3H), 7.9-8.0 (m, 3H). MS: m/e (%): 225 (2), 115 (22), 83 (46), 55 (100). Calc. for $C_{12}H_{15}O_4S$ (M-H): 255.0691; found: 255.0705.

3-[(Phenylthio)-methyl]-4,5-dihydrofuran (**165**)
A mixture of the sulfones **166** and **167** (14.62 g, 57 mmol) and *p*-toluenesulfonic acid monohydrate (100 mg) were dissolved in benzene (100 mL). The solution was refluxed and the condensed vapor was led through a column filled with molecular sieves 4 Å. After refluxing for 24

h the mixture was cooled, poured into diluted aqueous sodium bicarbonate and worked up as usual. After flash chromatography eluting with light petroleum/ether (1/1) and recrystallization in ether, the sulfone **165** (8.65 g, 68%) was obtained as a white solid ; mp 94°C. Elemental analysis: calc for $C_{11}H_{12}O_3S$: 58.91% C, 5.39% H; found: 58.62% C, 5.65% H.
^{1}H-NMR: 2.66 (br t, J=9 Hz, 2H), 3.87 (s, 2H), 4.34 (t, J=10 Hz, 2H), 6.09 (br s, 1H), 7.5-7.6 (m, 3H), 7.9-8.0 (m, 2H). MS: m/e (%): 224 (5), 83 (100), 55 (11).

(E)-1-(2β-Methoxyperhydrofur-3β-yl)-3,3-dimethyl-1-butene (**176**)
Cis-sulfone **166** (995 mg, 3.9 mmol) was dissolved in dry tetrahydrofuran (40 mL) and cooled at -78°C under nitrogen. A solution of 15% n-butyl lithium in hexane (2.7 mL) was added to the solution. The mixture was stirred for 15 min and pivalaldehyde (380 μL, 3.5 mmol) in tetrahydrofuran (5 mL) was added dropwise. After stirring for 2 h the reaction mixture was quenched with aqueous ammonium chloride. The mixture was allowed to warm to roomtemperature and worked up as usual. Flash chromatography on silica gel eluting with light petroleum/ether (1/1) afforded the diastereomeric alcohols **175** (1.222 g, 92%). A sample of this alcohol mixture (717 mg, 2.1 mmol) was dissolved in dry methanol (30 mL) at -15°C. Disodium hydrogen phosphate (1.60 mg) and 5% sodium amalgam (5.12 g) were added and the reaction mixture was stirred for 24 h and concentrated. The residue was stirred up in ether and decanted. This procedure was repeated three times. Water was added to the organic solution and the layers were separated. The water layer was extracted twice withn ether.Further work up as usual afforded the alkene **176** (439 mg, 85%) as a colourless oil, which was analyzed without further purification.
^{1}H-NMR: 1.02 (s, 9H), 1.7-2.1 (m, 2H), 2.4-2.8 (m, 1H), 3.31 (s, 3H), 3.7-4.1 (m, 2H), 4.72 (d, 1H), 5.33 (dd, J_1=7 Hz, J_2=16 Hz, 1H), 5.58 (d, J=16 Hz, 1H). MS: m/e (%): 183 (0.4), 153 (11), 124 (44), 109 (100). Calc. for $C_{11}H_{19}O_2$ (M-H): 183.1385; found: 183.1390. Calc. for $C_{10}H_{17}O$ (M-OMe): 153.1279; found:153.1278.

1-Phenylsulfonyl-1-(2α-methoxyperhydrofur-3β-yl)-3,3-dimethylbutan-2-one (**178a**)
A The sulfone **167** (1.08 g, 4.2 mmol) was dissolved in dry tetrahydrofuran (10 mL) at -78°C under nitrogen. A 15% solution of n-butyl lithium in hexane (2.9 mL) was added and the solution was stirred for 15 min. Pivalaldehyde (430 μL, 4.0 mmol) in tetrahydrofuran (5 mL) was added dropwise. After stirring for 15 min the reaction mixture was quenched with diluted aqueous ammonium chloride. Work up as usual afforded a residue (1.40 g), which was dissolved in dry dichloromethane (25 mL). Pyridinium chlorochromate (200 g, 9.3 mmol) was added and the

mixture was stirred for 20 h. As the conversion was not yet complete, additional pyridinium chlorochromate (1.0 g, 4.06 mmol) was added and the slurry was stirred for 5 more h. Ether was added and the suspension was filtered through a short silica gel column. Concentration and chromatography on silica gel with light petroleum/ether (2/1) as the eluant gave the β-keto sulfones **178a** (0.98 g, 73%).
MS*i*: m/e (%): 309 (1.6), 199 (23), 167 (27), 141 (29), 139 (61), 83 (56), 57 (100). MS *ii*: m/e (%): 309 (0.8), 199 (17), 167 (32), 141 (29), 139 (61), 83 (65), 57 (100).

B A 15% solution of n-butyl lithium (4.3 mL) in hexane was dropped to a solution of the sulfone **167** (1.08 g, 4.2 mmol) in dry tetrahydrofuran (5 mL) at -78°C under nitrogen. The mixture was stirred for 20 min and pivaloyl chloride (350 µL, 2.8 mmol) in tetrahydrofuran (5 mL) was added dropwise. The reaction mixture was stirred for 2 h and quenched with aqueous ammonium chloride. Work up as usual and flash chromatography as described under A afforded β-keto sulfones **178a** (696 mg, 72%).

1-(2α-Methoxyperhydrofur-3β-yl)-3,3-dimethylbutan-2-one (**179a**)
To a solution of a mixture of the β-keto sulfones **178a** (1.50 g, 4.6 mmol) in tetrahydrofuran (5 mL) and methanol (20 mL) at roomtemperature, was added disodium hydrogen phosphate (2.65 g) and 5% sodium amalgam (8.2 g). The suspension was stirred for 1 h and concentrated. The residue was stirred up in ether and decanted. This procedure was repeated three times. Water was added and the layers were separated. Further work up as usual and flash chromatography on silica gel eluting with light petroleum/ether (5/1) afforded the ketone **179a** (884 mg, 96%) as a colourless oil.
^{1}H-NMR: 1.10 (s, 9H), 1.2-1.6 (m, 1H), 2.1-2.6 (m, 4H), 3.30 (s, 3H) 3.90 (t, J=7 Hz, 2H), 4.63 (s, 1H). MS: m/e (%): 200 (1), 169 (29), 100 (100), 83 (85), 57 (95). Calc. for $C_{11}H_{20}O_3$: 200.1412; found: 200.1412.

1-(2α-Methoxyperhydrofur-3β-yl)-3-methylbutan-2-one (**179b**)
The ketone **179b** was prepared as described for ketone **179a**, by addition of the dilithiated sulfone **167** to methyl isobutyrate and subsequent desulfonation to give the ketone **179b** in 60% yield, as a colourless oil.
^{1}H-NMR: 1.08 (d, 6H), 1.0-1.6 (m, 2H), 2.1-2.8 (m, 3H), 3.30 (s, 3H), 3.90(t, J=7 Hz, 2H), 4.64 (s, 1H). MS: m/e (%): 186 (0.3), 185 (1.6), 155 (48),143 (58), 126 (25), 111 (33), 100 (49), 83 (100), 71 (92). Calc. for $C_{10}H_{18}O_3$:186.1256; found: 186.1241. Calc. for $C_{10}H_{17}O_3$ (M-H): 185.1178; found: 185.1172.

1-(2α-Methoxyperhydrofur-3β-yl)-3,3-dimethylbutan-2-ol (**180a**)
The ketone **179a** (884 mg, 4.4 mmol) was dissolved in tetrahydrofuran (5 mL) at 0°C. Lithium tri-*tert*-butoxyaluminohydride (6.7 mmol) was added, the mixture was stirred for 30 min and diluted with ether (30 mL). Subsequent careful additions of water (1 mL), 4 N sodium hydroxide (1 mL) and water (4 mL) to the well stirred reaction mixture were followed by adding magnesium sulfate directly to the resulting mixture. Filtration and evaporation of the solvents afforded the alcohol **180a** (883 mg, 99%) as a colourless oil. The diastereomeric purity was 97%.
^{1}H-NMR (CCl_4): 0.83 (s, 9H), 1.3-1.6 (m, 3H), 2.0-2.3 (m, 3H), 3.15(t, J=6 Hz, 1H), 3.26 (s, 3H), 3.7-3.9 (m, 2H), 4.62 (d, J=2 Hz, 1H). MS: m/e (%): 201 (1), 171 (14), 145 (15), 113 (100), 87 (43), 69 (47). Calc. for $C_{11}H_{21}O_3$ (M-H): 201.1491; found: 201.1493.

1-(2α-Methoxyperhydrofur-3β-yl)-3-methylbutan-2-ol (**180b**)
The alcohol **180b** was prepared from the ketone **179b** as described for **180a**. The alcohol **180b** was obtained as a colourless oil in 95% yield and with a 93% diastereomeric purity.
^{1}H-NMR (C_6D_6): 0.92 (d, 3H), 0.94 (d, 3H), 1.1-2.6 (m, 8H), 3.37 (s, 3H), 3.8-4.0 (m, 2H), 4.86 (d, J=2 Hz, 1H). MS: m/e (%): 187 (2), 157 (38),133 (50),113 (94), 73 (100), 69 (68). Calc. for $C_{10}H_{19}O_3$ (M-H): 187.1334; found:187.1337.

2α-*tert*-Butyl-2β,3,3aβ,4,5,6aβ-hexahydrofuro[2,3b]furan (**181a**)
The ketone **179a** (468 mg, 2.3 mmol) was dissolved in tetrahydrofuran (10 mL) at 0°C. Lithium tri-*tert*-butoxyaluminohydride (1.2 g, 4.7 mmol) was added and the mixture was stirred for 2 h. After careful addition of 4 N hydrochloric acid (2 mL) the mixture was stirred for 30 min. Work up as usual and flash chromatography on silica gel eluting with light petroleum/ether (6/1) gave the furofuran **181a** (376 mg, 95%) as a colourless oil.
^{1}H-NMR: 0.92 (s, 9H), 1.2-1.4 (m, 1H), 1.6-1.7 (m, 1H), 1.9-2.0 (m, 2H), 2.8-2.9 (m, 1H), 3.52 (dd, J_1=5 Hz, J_2=10 Hz, 1H), 3.8-4.0 (m, 2H), 5.62 (d, J=5 Hz, 1H). MS: m/e (%): 169 (0.5), 155 (1), 113 (100), 69 (92). Calc. for $C_{10}H_{17}O_2$ (M-H):169.1228; found: 169.1227.

2α-Isopropyl-2β,3,3aβ,4,5,6aβ-hexahydrofuro[2,3b]furan (**181b**)
The furofuran **181b** was prepared from the ketone **179b** in the same way as described for **181a**. The furofuran **181b** was obtained as a colourless oil in quantitative yield.
^{1}H-NMR: 0.88 (d, 3H), 0.99 (d, 3H), 1.1-1.4 (m, 2H), 1.6-2.1 (m, 3H), 1.7-3.0 (m, 1H), 3.3-4.0 (m, 3H), 5.63 (d, J=5 Hz, 1H). MS: m/e (%): 156 (0.1), 155

(3), 113 (92), 69 (100), 56 (34), 55 (34). Calc. for $C_6H_9O_2$ (M-iPr): 113.0603; found: 113.0591.

2β-*tert*-Butyl-2α,3,3aβ,4,5,6aβ-hexahydrofuro[2,3b]furan (**182a**)
The alcohol **180a** (883 mg, 4.4 mmol) and triethylamine (610 µL, 4.4 mmol) were dissolved in dry dichloromethane (20 mL). To this solution 4-dimethylaminopyridine (1.07 g, 8.8 mmol) and *p*-toluenesulfonyl chloride (1.67 g, 8.8 mmol) were added successively. The reaction mixture was stirred for 20 h and adsorbed on silica gel. Flash chromatography on silica gel eluting with light petroleum/ether (5/1) gave the corresponding tosylate (1.328 g, 3.7 mmol), which was dissolved in dry dimethylsulfoxide (5 mL) and dry 1,2-dimethoxyethane (5 mL). The mixture was kept below 35°C, when 18-crown-6 (2.5 g, 9.5 mmol) and potassium superoxide (1.32 g, 18.6 mmol) were added. The cloudy mixture was stirred for 1 h and water, sodium borohydride (1.4 g, 37 mmol) and 4 N hydrochloric acid were successively, **carefully** added. The acidic solution was stirred for 15 min and poured into saturated aqueous sodium bicarbonate. Work up as usual and flash chromatography on silica gel eluting with light petroleum/ether (7/1) yielded the furofuran **182a** (396 mg, 53%) as a colourless oil.
^{1}H-NMR: 0.87 (s, 9H), 1.5-2.3 (m, 4H), 2.6-3.0 (m, 1H), 3.7-4.0 (m, 3H), 5.68 (d, J=5 Hz, 1H). MS: m/e (%): 169 (0.1), 155 (3), 113 (100), 69 (90). Calc. for $C_{10}H_{17}O_2$ (M-H): 169.1228; found: 169.1230.

2β-Isopropyl-2α,3,3aβ,4,5,6aβ-hexahydrofuro[2,3b]furan (**182b**)
The furofuran **182b** was prepared as described for **182a** from the alcohol **180b**. The furofuran **182b** was obtained as a colourless oil in 40% yield.
^{1}H NMR: 0.84 (d, 3H), 0.97 (d, 3H), 1.1-1.3 (m, 2H), 1.6-1.8 (m, 2H), 2.0-2.2 (m, 1H), 2.7-3.0 (m, 1H), 3.5-4.0 (m, 3H), 5.70 (d, J=5 Hz, 1H). MS: m/e (%): 156 (0.1), 155 (3), 113 (97), 69 (100), 56 (35), 55 (35). Calc. for $C_6H_9O_2$ (M-iPr): 113.0603; found: 113.0596.

1-(2β-Methoxyperhydrofur-3β-yl)-3,3-dimethylbutan-2-one (**183a**)
The ketone **183a** was prepared as described for the ketone **179a**, by addition of the dilithiated sulfone **167** to pivaloyl chloride and subsequent desulfonation to give the ketone **183a** as a colourless oil in 61% overall yield.
^{1}H-NMR: 1.14 (s, 9H), 1.5-1.8 (m, 1H), 1.9-3.0 (m, 4H), 3.27 (s, 3H), 3.7-4.1 (m, 2H), 4.90 (d, J=4 Hz, 1H). MS: m/e (%): 200 (0.7), 199 (0.7), 169 (23),143 (93), 100 (19), 83 (100), 57 (53). Calc. for $C_{11}H_{20}O_3$: 200.1412; found: 200.1416.

1-(2β-Methoxyperhydrofur-3β-yl)-3-methylbutan-2-one (**183b**)

The ketone **183b** was prepared as described for the ketone **179a**, by addition of the dilithiated sulfone **167** to methyl isobutyrate and subsequent desulfonation to give the ketone **183b** as a colourless oil in 32% overall yield.

^{1}H-NMR: 1.07 (d, 6H), 1.2-2.2 (m, 2H), 2.4-2.9 (m, 3H), 3.23 (s, 3H), 3.6-4.0 (m, 2H), 4.86 (d, J=4 Hz, 1H). MS: m/e (%): 186 (0.3), 185 (1.8), 155 (40), 143 (50), 126 (21), 111 (35), 100 (47), 83 (100), 71 (93). Calc. for $C_{10}H_{18}O_3$: 186.1256; found: 186.1256.

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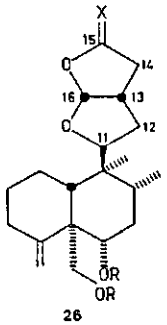
6. THE STEREOSELECTIVE SYNTHESES OF FURO[2,3b]FURANS FROM OXIRANES

6.1 INTRODUCTION

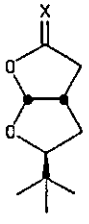
In our investigations towards the synthesis of clerodanes, methods for the introduction of the furofuran side chain were required (see chapter 3). Preferrably such a method should allow some flexibility with respect to the oxidation level of this side chain, for this may vary to some extend without having a dramatic effect on the bioactivity [compare clerodin **26c**, dihydroclerodin **26n** ($X=H_2$), clerodin hemiacetal **26p** (X=H,OH) and clerodin lactone **26s** (X=O); see chapter 1.5][1].

In the previous chapter the conversion of carbonyl compounds into 2-substituted perhydrofuro[2,3b]furans was described[2,3]. In this chapter the stereoselective synthesis of substituted perhydrofuro[2,3b]furans **185n** ($X=H_2$), perhydrofuro[2,3b]furanols **185p** (X=H,OH) and perhydrofuro[2,3b]furanones **185s** (X=O) from oxiranes **186** is described. The principal advantage of an approach to synthesize a furofuran side chain from an oxirane instead of a carbonyl compound would be the steric control at the off template carbon atom C-11 (see chapter 3). Once fixed this configuration is preserved during the construction of the furofuran unit and moreover this configuration might direct the stereochemistry at C-13 and C-16 in the desired direction.

Figure 6.1



26



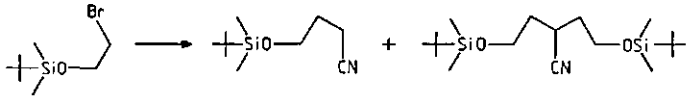
185

186

6.2 THE SYNTHESES OF PERHYDROFURO[2,3b]FURANS FROM α-LITHIO-NITRILES.

The nitrile **188** was considered to be a useful reagent for the conversion of oxiranes into perhydrofuro[2,3b]furans. It was synthesized in two steps from 2-bromoethanol. The hydroxyl group was protected as its *tert*-butyldimethylsilyl ether[4] to give **187** in 91% yield. The reaction of lithiated acetonitrile with **187** gave the desired nitrile **188** in 68% yield together with the dialkylated nitrile **189** in 25% yield (see scheme 6.1).

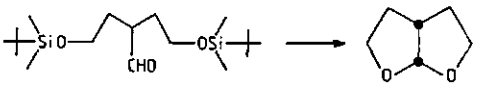
Scheme 6.1



187 188 189

The nitrile **189** was reduced with diisobutylaluminium hydride to give the aldehyde **190** in 90% yield. Acid catalyzed cyclization furnished the unsubstituted furo[2,3b]fufan **191** in 20% (unoptimized) yield.

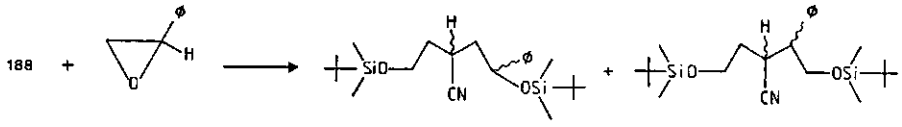
Scheme 6.2



190 191

The reaction of lithiated **188** with styrene oxide did not proceed in a regiospecific manner. After trapping of the intermediate alcoholate with *tert*-butyldimethylsilyl chloride, the nitriles **192** and **193** were formed in the ratio of 3:1 in a combined yield of 71% (see scheme 6.3). Trapping of the intermediate alcoholate was necessary in order to prevent the formation of γ-hydroxy nitriles, γ-lactimes and γ-lactones[5].

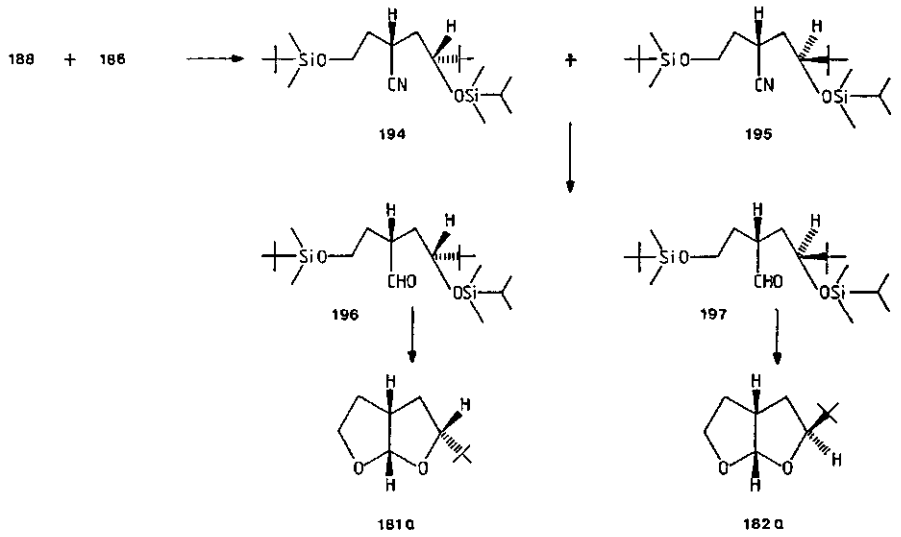
Scheme 6.3



192 193

The reaction of lithiated **188** with *tert*-butyloxirane **186** proceeded in a regiospecific manner and the trapping of the alcoholate with isopropyldimethylsilyl chloride afforded the nitriles **194** and **195** in 81% yield. Trapping of the alcoholate with *tert*-butyldimethylsilyl chloride failed, probably due to the large steric hindrance[6]. The diastereomeric mixture of of the nitriles **194** and **195** was reduced with diisobutylaluminium hydride to give the corresponding mixture of the aldehyde **196** in 41% yield and its diastereoisomer **197** in 51% yield. Acid treatment of the aldehyde **196** gave exclusively the furofuran **181** and likewise the aldehyde **197** gave the furofuran **182**. Under these circumstances the cleavage of the silyl ethers and the subsequent cyclization evidently were faster reactions then the isomerization of the aldehydes and/or the furofurans.

Scheme 6.4



Potential stages for base-catalyzed isomerization, aiming at an ultimately increased yield of the desired furofuran **182**, are the nitrile and/or the aldehyde stage. Treatment of the original 3:4 mixture of the nitriles **194** and **195** with potassium *tert*-butoxide in refluxing *tert*-butyl alcohol improved the ratio to 1:4.

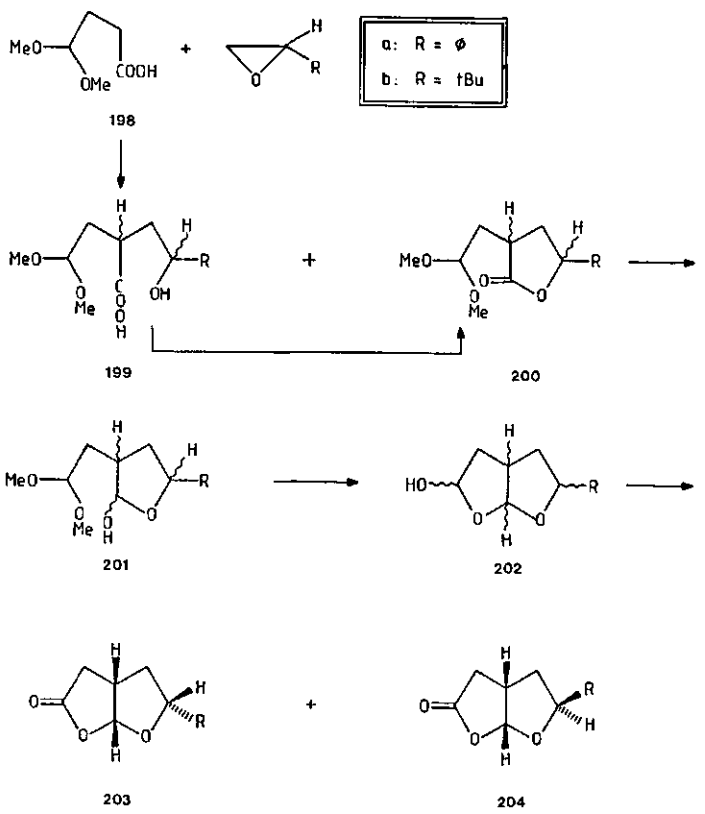
Unfortunately these nitriles could not be seperated by column chromatography, this in contrast to the aldehydes **196** and **197**. Separation of the isomeric aldehydes and equilibration of the unwanted aldehyde **196** with potassium *tert*-butoxide in *tert*-butyl alcohol resulted in a 1:2 mixture of **196**:**197**. In this way the aldehyde **197** was synthesized from the mixture of the nitriles **194** and **195** in 75% overall yield. Acid catalyzed cleavage of the silyl ethers and subsequent cyclization gave the desired *tert*-butylperhydrofuro[2,3b]furan **182**, with the relative stereochemistry of the natural clerodanes, in 95% yield.

6.3 THE SYNTHESES OF PERHYDROFURO[2,3b]FURANOLS AND PERHYDROFURO[2,3b]FURANONES FROM DILITHIO-4,4-DIMETHYLBUTAN-2-OATE.

The carboxylic acid **198** was considered to be a useful reagent for the conversion of oxiranes into 5-substituted furo[2,3b]furan-2-ols and their corresponding furofuranones. The carboxylic acid was obtained by saponification of the methyl ester of **198**[7] followed by careful acidification.

The reaction of dilithiated **198** with styrene oxide afforded a mixture of γ-hydroxy carboxylic acids **199a** and γ-lactones **200a**. This mixture was converted into the lactones **200a** in 49% yield by refluxing it in benzene. Diisobutylaluminium hydride reduction then gave the corresponding lactols **201a** in almost quantitative yield. A subsequent brief treatment of the lactols with acid, followed by oxidation of the furofuranols **202a**[8] gave the furofuranones **203a** and **204a** in 44% and 35% yield respectively. Elongated treatment of the lactols with acid[8] and subsequent oxidation gave these furofuranones **203a** and **204a** in 12% and 76% yield respectively.

Scheme 6.5



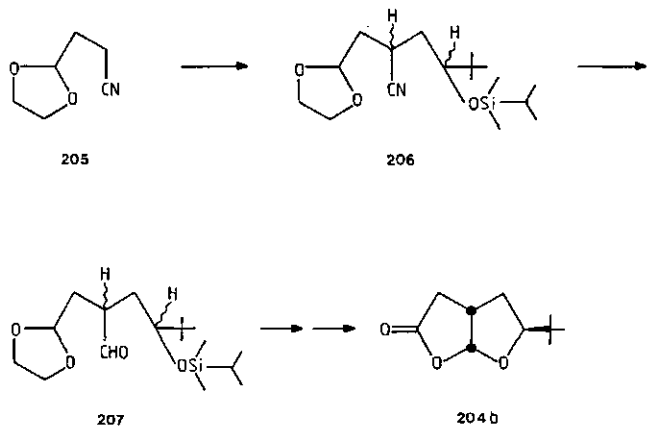
The reaction of dilithiated **198** with *tert*-butyloxirane gave, after cyclization, the lactones **200b** in a disappointingly low yield of 17%. Reduction of these lactones with diisobutylaluminium hydride gave the lactols **201b** in 66% yield. Elongated acid treatment of these lactols and subsequent oxidation gave the 5-*tert*-butylfuro[2,3b]furan-2-ones **203b** and **204b** in 6% and 71% yield respectively.

6.4 THE SYNTHESIS OF 5-*tert*-BUTYL-PERHYDROFURO[2,3b]FURAN-2-ONE FROM 3-(1,3-DIOXOLAN-2-YL)-PROPIONITRILE.

The low yield of the coupling reaction of the dilithiated carboxylate **198** with *tert*-butyloxirane prompted us to study the utility of the nitrile **205**[9] for the stereoselective synthesis of the *tert*-butylfurofuranone **204b**. The lithiated nitrile **205** gave a mixture of the nitriles **206** in 91%

yield, after successive treatment with *tert*-butyloxirane and isopropyldimethylsilyl chloride. The nitriles were reduced with diisobutylaluminium hydride to give the aldehydes **207** in 94% yield. Elongated acid treatment and subsequent oxidation gave the aimed furofuranone **204b** in 72% yield together with a small amount of **203b**.

Scheme 6.6



The easy preparation of substituted nitriles, the high yields in the addition reaction of the lithiated nitriles to oxiranes and the ample possibilities for adjustment of the relative stereochemistry in the intermediates, make this approach very flexible and suitable for incorporation in total syntheses of natural products containing furofurans as structural elements.

6.5 EXPERIMENTAL

For general experimental details see chapter 4.6.

2-Bromo-1-*tert*-butyldimethylsilyloxy-ethane (**187**)
To a mixture of *tert*-butyldimethylsilyl chloride (21.1 g, 140 mmol) and imidazole (12.5 g, 184 mmol) in dimethylformamide (25 mL) was added dropwise 2-bromoethanol (10 mL, 141 mmol). The reaction mixture was stirred overnight, poured into water and extracted twice with light petroleum. The combined organic extracts were washed with brine, dried and filtered. The solvent was evaporated and the residue was submitted to bulb-to-bulb distillation (70-75°C, 2.5 mm Hg) to give the silyl ether **187** (30.4 g, 91%) as a colourless oil.

^{1}H-NMR (CCl_4): 0.00 (s, 6H), 0.84 (s, 9H), 3.27 (t, J=7 Hz, 2H), 3.82 (t, J=7 Hz, 2H). MS: m/e (%): 183 (63), 181 (63), 139 (100), 137 (100). Calc. for $C_4H_{10}BrOSi$ (M-tBu): 180.9685; found: 180.9685.

3-*tert*-Butyldimethylsilyloxy-propionitrile (**188**) and
1,5-Di-*tert*-butyldimethylsilyloxy-pentane-3-carbonitrile (**189**)
Dry acetonitrile (3.5 mL, 67 mmol) in dry tetrahydrofuran (15 mL) was added dropwise to a solution of lithium diisopropylamide (58 mmol) in tetrahydrofuran (150 mL) and hexamethylphosphoric triamide (10 mL, 57 mmol) at -78°C under nitrogen. The mixture was stirred for 30 min and the bromide **187** (11 mL, 50.6 mmol) in tetrahydrofuran (50 mL) was dropped to the solution. The reaction mixture was stirred for 2 h at -78°C, saturated aqueous ammonium chloride was added and the temperature was warmed up to roomtemperature. Extraction with light petroleum, followed by the usual workup gave a residue which was submitted to flash chromatography on silica gel. Elution with light petroleum /ether (40/1) afforded the dialkylated compound **189** (2.258 g, 25%) and the mono-alkylated nitrile **188** (7.270 g, 72%) both as colourless oils. Further purification of the nitrile **188** by distillation in vacuo (110-120°C, 3 mm Hg) gave 6.822 g (68%).
188: ^{1}H-NMR (CCl_4) : 0.00 (s, 6H), 0.85 (s, 9H), 1.7-2.0 (m, 2H), 2.38 (t, J=7 Hz, 2H), 3.67 (t, J=6 Hz, 2H). MS: m/e (%): 184 (2), 144 (4), 143 (13), 142 (100) , 75 (14), 73 (4), 59 (6). Calc. for $C_9H_{18}NOSi$ (M-Me): 184.1158; found: 184.1156.
189: ^{1}H-NMR (CCl_4) : 0.00 (s, 12H), 0.83 (s, 18H), 1.5-1.8 (m, 4H), 2.90 (quintet, J=8 Hz, 1H), 3.73 (t, J=6 Hz, 4H). MS: m/e (%): 342 (4), 302 (5), 301 (14), 300 (54), 147 (57), 73 (100). Calc. for $C_{17}H_{36}NO_2Si_2$ (M-Me): 342.2284; found: 342.2273.

1,5-Di-*tert*-butyldimethylsilyloxy-pentane-3-carbaldehyde (**190**)
The nitrile **189** (3.57 g, 10 mmol) was dissolved in dry toluene (50 mL) at -78°C under nitrogen. Diisobutylaluminum hydride (12 mL of a 1.0 M solution in toluene) was added and the reaction mixture was stirred for 1 h. Water (2 mL) was added and the temperature was raised to roomtemperature and stirred for 15 min.The successive addition of 4 N aqueous sodium hydroxide (2 mL), stirring for 20 min, addition of water (6 mL) and stirring for 20 min resulted in a suspension, which was dried by adding magnesium sulfate. Filtration and evaporation of the solvents gave the crude aldehyde **190** in a quantitative yield. Flash chromatography on silica gel with light petroleum/ether (20/1) as the eluant afforded the pure aldehyde **190** (3.232 g, 90%) as a colourless oil.
^{1}H-NMR (CCl_4): 0.00 (s, 12H), 0.86 (s, 18H), 1.5-2.1 (m, 4H), 2.3-2.6 (m, 1H), 3.62 (t, J=6 Hz, 4H), 9.62 (d, J=2 Hz, 1H).

MS: m/e (%): 303 (0.5), 299 (1.3), 171 (100), 141 (27), 97 (26), 75 (96), 73 (62). Calc. for $C_{14}H_{31}O_3Si_2$ (M-tBu): 303.1812; found: 303.1819.

2,3,3aβ,4,5,6aβ-Perhydrofuro[2,3b]furan (**191**)
The aldehyde **190** (2.642 g, 6.8 mmol) was dissolved in ether (10 mL) and concentrated hydrochloric acid (1 mL) was added. After stirring for 20 h the mixture was diluted with ether and the aqueous layer was removed. The organic layer was washed with saturated aqueous sodium bicarbonate and brine. Work up as usual, flash chromatography on silica eluting with pentane/ether (6/1) and vacuum distillation (50-60°C, 13 mm Hg) gave the pure furofuran **191** (157 mg, 20%) as a colourless oil.
^{1}H-NMR: 1.5-2.0 (m, 2H), 2.0-2.3 (m, 2H), 2.7-3.0 (m, 1H), 3.83 (dd, J_1=5 Hz, J_2=9 Hz, 4H), 5.60 (d, J=5 Hz, 1H). MS: m/e (%): 114 (19), 113 (26), 84 (100), 83 (20), 69 (22), 68 (46), 55 (49). Calc. for $C_6H_{10}O_2$: 114.0681; found:114.0678.

1,5-Di-*tert*-butyldimethylsilyloxy-1-phenyl-pentane-3-carbonitrile (**192**) and
1,5-Di-*tert*-butyldimethylsilyloxy-2-phenyl-pentane-3-carbonitrile (**193**)
A solution of the nitrile **188** (848 mg, 4.3 mmol) and tetramethylethylene-diamine (0.65 mL, 4.3 mmol) in dry ether (10 mL) was added dropwise to a solution of lithium diisopropylamide (4.3 mmol) in ether (15 mL) at 0°C under nitrogen .The mixture was stirred for 15 min.and styrene oxide (0.45 mL, 3.9 mmol) in ether (2 mL) was added. The reaction mixture was stirred for 90 min and *tert*-butyldimethylsilyl chloride (650 mg, 4.3 mmol) in dimethylformamide (20 mL) was added. The reaction mixture was stirred for 90 min, taken up in light petroleum and successively washed with water and brine. Further work up as usual and flash chromatography on silica gel eluting with light petroleum/ether (30/1) afforded the alkylated and silylated compounds **192** and **193** (1.216 g, 71%). GCMS analysis showed four compounds in approximate ratio's of 3 : 1 : 3 : 1.
MS *i* : m/e (%): 418 (4), 378 (8), 377 (21), 376 (70), 302 (7), 286 (5), 244 (21), 147 (20), 143 (14), 117 (12), 101 (12), 75 (37), 73 (100).
MS *ii* : m/e (%): 418 (3), 378 (11), 377 (26), 376 (80), 302 (-), 286 (-), 244 (11), 147 (60), 143 (6), 117 (8), 101 (-), 75 (33), 73 (100).
MS *iii* : m/e (%): 418 (3), 378 (9), 377 (25), 376 (82), 302 (9), 286 (7), 244 (28), 147 (23), 143 (15), 117 (15), 101 (14), 75 (40), 73 (100).
MS *iiii*: m/e (%): 418 (5), 378 (7), 377 (20), 376 (55), 302 (-), 286 (-), 244 (24), 147 (57), 143 (5), 117 (5), 101 (-), 75 (28), 73 (100).

1-*tert*-Butyldimethylsilyloxy-6,6-dimethyl-5-isopropyldimethylsilyloxy-heptane-3-carbonitriles (**194**) and (**195**)

A solution of the nitrile **188** (1.56 g, 7.9 mmol) and tetramethylethylenediamine (1.2 mL, 7.9 mmol) in dry ether (5 mL) was added dropwise to a solution of lithium diisopropylamide (7.8 mmol) in ether (10 mL) at -15°C under nitrogen. The mixture was stirred for 15 min and *tert*-butyloxirane (590 mg, 5.9 mmol) was added. The reaction mixture was stirred for 30 min and isopropyldimethylsilyl chloride (3.0 mL, 19.0 mmol) was added. The reaction mixture was stirred for 90 min, poured into saturated aqueous sodium bicarbonate and further worked up as usual. Flash chromatography on silica gel with light petroleum/ether (40/1) as the eluant gave the nitriles **194** and **195** (1.916 g, 81%), and the starting nitrile **188** (0.563 g).

^{1}H-NMR: 0.0-0.1 (m, 12H), 0.8-1.0 (m, 25H), 1.3-1.8 (m, 4H), 2.5-3.0 (m, 1H), 3.2-3.5 (m, 1H), 3.6-3.8 (m, 2H). MS *i* : m/e (%): 384 (10), 356 (57), 344 (11), 343 (30), 342 (100), 224 (28), 75 (38), 73 (88). MS *ii* : m/e (%): 384 (9), 356 (56), 344 (10), 343 (28), 342 (100), 224 (28), 75 (25), 73 (54).

1-*tert*-Butyldimethylsilyloxy-6,6-dimethyl-5-isopropyldimethylsilyloxy-heptane-3-carbaldehydes (**196**) and (**197**)

A mixture of the nitriles **194** and **195** (1.916 g, 4.8 mmol) was dissolved in dry toluene (10 mL) at -78°C under nitrogen. Diisobutylaluminium hydride (5 mL of a 1.2 M solution in toluene) was added and the reaction mixture was stirred for 20 min. Water (1 mL) was added and the mixture was allowed to adopt roomtemperature. After successive stirring for 30 min, addition of ether (30 mL), addition of 4 N aqueous sodium hydroxide (1 mL), stirring for 30 min, addition of water (3 mL) and stirring for 20 min, the resulting mixture was dried by direct addition of magnesium sulfate. Filtration, evaporation of the solvents and flash chromatography on silica gel with light petroleum/ether (60/1) as the eluant afforded the desired aldehyde **197** (989 mg, 51%) and the unwanted aldehyde **196** (792 mg, 41%). A solution of the aldehyde **196** and potassium *tert*-butoxide (150 mg) in *tert*-butyl alcohol (150 mL) was refluxed for 1 h. The reaction mixture was cooled, poured into aqueous ammonium chloride and worked up as usual. Chromatographic separation gave the aldehyde **197** (460 mg) and the aldehyde **196** (292 mg). So the ultimate yields of de aldehydes **197** and **196** were 75% and 15% respectively.

196:^{1}H-NMR: 0.0-0.1 (m, 12H), 0.8-0.9 (m, 25H), 1.5-1.9 (m, 4H), 2.3-2.5 (m, 1H), 3.29 (dd, J_1=8 Hz, J_2=3 Hz, 1H), 3.60 (t, J=6 Hz, 2H), 9.55 (d, J=2 Hz, 1H). MS: m/e (%): 345 (4), 227 (57), 157 (57), 135 (28), 95 (75), 75 (100), 73 (80).

197:^{1}H-NMR: 0.0-0.1 (m, 12H), 0.8-0.9 (m, 25 H), 1.6-2.0 (m, 4H), 2.3-2.6 (m, 1H), 3.26 (br d, J=9 Hz, 1H), 3.61 (t, J=6 Hz, 2H), 9.51 (d, J=3 Hz, 1H).

MS: m/e (%): 345 (3), 227 (65), 157 (53), 135 (28), 95 (83), 75 (100), 73 (88).

2β-*tert*-Butyl-2a,3,3aβ,4,5,6aβ-hexahydrofuro[2,3b]furan (**182**)
The aldehyde **197** (1.45 g, 3.6 mmol) was dissolved in acetone (40 mL) and 4 N hydrochloric acid (1 mL) was added. The mixture was stirred for 2 h and poured into aqueous sodium bicarbonate. Work up as usual and flash chromatography on silica gel eluting with light petroleum/ether (7/1), gave the *furofuran* **182** (582 mg, 95%). *For physical properties: see ref 1.*

4,4-Dimethoxybutan-1-oic acid (**198**)
Aqueous sodium hydroxide (10 mL of a 1 N solution) was added dropwise to a solution of the methyl ester of **198**[7] (1.34 g, 8.3 mmol) in methanol (11 mL). The reaction mixture was stirred overnight, cooled to 0°C and carefully acidified to pH=4. Work up as usual afforded the crude carboxylic acid **198** (1.22 g, 99%) as a colourless oil, which was used without further purification.
^{1}H-NMR: 1.99 (dt, J_1=6 Hz, J_2=7 Hz, 2H), 2.43 (t, J=7 Hz, 2H), 3.34 (s, 6H), 4.45 (t, J=6 Hz, 1H), 9.4 (br s, 1H). MS: m/e (%): 147 (1), 131 (5), 117 (40), 85 (100), 75 (98), 72 (21). Calc. for $C_6H_{11}O_4$ (M-H): 147.0657; found: 147.0656.

3-(2,2-Dimethoxyethyl)-5-phenyl-4,5-dihydrofuran-2(3H)-one (**200a**)
A solution of n-butyl lithium in hexane (9.0 mL, 1.6 M) was added to a solution of diisopropylamine (1.9 mL, 14 mmol) in dry tetrahydrofuran (25 mL) at -78°C under nitrogen. The mixture was stirred for 10 min and carboxylic acid **198** (1.0 g, 6.8 mmol) in tetrahydrofuran (10 mL) was added dropwise. The mixture was allowed to warm up to 0°C, stirred additionally for 1 h and styrene oxide (0.69 mL, 6.1 mmol) was added dropwise to the solution. The reaction mixture was stirred overnight, water was added and the mixture was carefully acidified to pH=4. Further work up as usual gave a mixture hydroxy acids **199a** and lactones **200a**. This mixture was taken up in benzene (100 mL) and refluxed for 4 h in a Dean-Stark trap. Work up as usual and flash chromatography on silica gel eluting with light petroleum/ether (7/3) afforded the lactone **200a**$_1$ (275 mg, 18%) as a colourless oil.
^{1}H-NMR: 1.6-2.8 (m, 5H), 3.33 (s, 6H), 4.52 (t, J=6 Hz, 1H), 5.56 (t, J=6 Hz, 1H), 7.3 (br s, 5H). MS : m/e (%): 250 (0.6), 249 (1), 235 (3), 219 (14), 218 (42), 187 (12), 186 (10), 115 (28), 105 (22), 75 (100). Calc. for $C_{14}H_{18}O_4$: 250.1205; found: 250.1196.
Further elution afforded the isomeric lactone **200a**$_2$ (474 mg, 31%) as a colourless oil. ^{1}H-NMR: 1.1-2.9 (m, 5H), 3.33 (s, 6H), 4.53 (t, J=6 Hz, 1H), 5.32 (dd, J_1=6 Hz, J_2=11 Hz, 1H), 7.3 (br s, 1H). MS: m/e (%): 250 (3), 249

(3), 235 (9), 219 (9), 218 (2), 187 (9), 115 (21), 75 (100). Calc. for $C_{14}H_{18}O_4$: 250.1205; found: 250.1193.

5-Phenyl-perhydrofuro[2,3b[furan-2-ols (**202a**)
To a solution of the lactones **200a** (797 mg, 3.2 mmol) in dry tetrahydrofuran (10 mL) at -30°C under nitrogen was added dropwise a solution of diisobutylaluminum hydride in toluene (4 mL of a 1.6 M solution). The reaction mixture was stirred for 3.5 h, water (2 mL) was added and the mixture was diluted with ether (50 mL). The resulting suspension was stirred vigorously for 30 min and 7 N potassium hydroxide in water (3 mL) was added. The suspension was stirred for 30 min and dried on magnesium sulfate. Filtration and evaporation of the solvents afforded the crude lactols **201a** (793 mg).
^{1}H-NMR: 1.2-2.6 (m, 5H), 3.28 (s, 6H), 3.6 (br s, 1H), 4.4-4.5 (m, 1H), 4.8-5.5 (m, 2H), 7.2-7.3 (br s, 5H).
The crude lactol mixture was dissolved in tetrahydrofuran (20 mL) and 2 N hydrochloric acid (20 mL) and stirred for 1 h. The reaction mixture was poured into saturated aqueous sodium bicarbonate, worked up as usual and chromatographed on silica gel with light petroleum/ether (1/1) as the eluant to afford the furofuranols **202a** (498 mg, 76%).
^{1}H-NMR: 1.5-2.5 (m, 4H), 2.7-3.1 (m, 1H), 4.5-5.1 (m, 2H), 5.3-5.6 (m, 2H), 7.2-7.3 (m, 5H).

5α-Phenyl-3aβ,4,5,6aβ-tetrahydrofuro[2,3b]furan-2(3H)-one (**203a**) and
5β-phenyl-3aβ,4,5,6aβ-tetrahydrofuro[2,3b]furan-2(3H)-one (**204a**)
A By direct oxidation.
The furofuranol mixture **202a** (58 mg, 0.28 mmol) was dissolved in dichloromethane (5 mL) and pyridinium dichromate (200 mg) was added. The reaction mixture was stirred for 3 d, diluted with ether, filtered and chromatographed on silica gel with light petroleum/ether (2/3) as the eluant to afford the lactone **204a** (20 mg, 35%) as a colourless oil.
^{1}H-NMR: 2.0-2.2 (m, 2H), 2.56 (dd, J_1=4 Hz, J_2=18 Hz, 1H), 2.95 (dd, J_1=10 Hz, J_2=18 Hz, 1H), 3.2-3.5 (m, 1H), 5.17 (dd, J_1=7 Hz, J_2=8 Hz, 1H), 6.26 (d, J=6 Hz, 1H), 7.3 (br s, 5H). MS: m/e (%): 204 (79), 160 (20), 107 (82), 105 (44), 104 (89), 98 (38), 91 (31), 77 (38), 70 (100), 42 (39).
Further elution gave the lactone **203a** (25 mg, 44%), as a colourless oil.
^{1}H-NMR: 1.80 (dt, J_1=9 Hz, J_2=13 Hz, 1H), 2.48 (dd, J_1=18 Hz, J_2=3 Hz, 1H), 2.6-3.0 (m, 2H), 3.1-3.4 (m, 1H), 5.35 (dd, J_1=7 Hz, J_2=9 Hz, 1H), 6.16 (d, J=5 Hz, 1H), 7.3 (br s, 5H). MS: m/e (%): 204 (82), 160 (23), 107 (84), 105 (44), 104 (100), 98 (38), 91 (31), 77 (38), 70 (95), 42 (39).
B By equilibration followed by oxidation.
The lactones **203a** and **204a** can also be synthesized in 12% resp 76% by treatment with 3 N hydrochloric acid/acetone (1/10) for 45 h and subsequent oxididation with pyridinium dichloromate.

5-*tert*-Butyl-3-(2,2-dimethoxyethyl)-4,5-dihydrofuran-2(3H)-one (**200b**)

The lactone **200b** was prepared in the same way from *tert*-butyloxirane as described for **200a**. The lactone **200b** was obtained as a colourless oil in 17% yield.

^{1}H-NMR: 0.94 (s, 9H), 1.5-2.0 (m, 2H), 2.0-2.5 (m, 2H), 2.5-2.9 (m,1H), 3.32 (s, 6H), 3.9-4.3 (m, 1H), 5.51 (t, J=6 Hz, 1H). MS: m/e (%): 199 (2), 198 (5), 155 (5), 113 (43), 97 (67), 84 (100), 75 (20).

5-*tert*-Butyl-perhydrofuro[2,3b]furanols (**202b**)

The lactone **200b** was reduced with diisobutylaluminium and subsequently cyclized with 2 N hydrochloric acid as described for **202a** to give the furofuranol mixture **202b** in 66% yield.

^{1}H-NMR: 0.9 (m, 9H), 1.5-2.3 (m, 4H), 2.7-3.1 (m, 1H), 3.5-4.3 (m, 2H), 5.5-5.9 (m, 2H).

5α-*tert*-Butyl-3aβ,4,5,6aβ-tetrahydrofuro[2,3b]furan-2(3H)-one (**203b**) and

5b-*tert*-Butyl-3aβ,4,5,6aβ-tetrahydrofuro[2,3b]furan-2(3H)-one (**204b**)

Equilibration of the furofuranol mixture **202b** was effectuated by treatment with 8 N hydrochloric acid in acetone for 6 days. Subsequent oxidation as described for the lactones **203a** and **204a** and separation of the isomers afforded the furofuranones **203b** and **204b** as white solids in 6% and 71% yield respectively.

203b: ^{1}H-NMR (300 MHz) : 0.92 (s, 9H), 1.44 (dt, J_1=13 Hz, J_2=11 Hz, 1H), 2.19 (ddd, J_1=13 Hz, J_2=9 Hz, J_3=6 Hz, 1H), 2.50 (dd, J_1=18 Hz, J_2=1 Hz, 1H), 2.75 (dd, J_1=13 Hz, J_2=8 Hz, 1H), 3.0-3.1 (m, 1H), 3.96 (dd, J_1=11 Hz, J_2=6 Hz, 1H), 5.93 (d, J=5 Hz, 1H). MS: m/e (%): 169 (20), 140 (10), 129 (50), 128 (100), 127 (100), 100 (27), 71 (63). Calc. for $C_9H_{13}O_3$ (M-Me): 169.0865; found: 169.0868.

204b white solid, mp: 96-97 °C, (lit[8]: 70-72°C).Elemental analysis: calc. for $C_{10}H_{16}O_3$: 65.19% C, 8.75% H; found: 65.01% C, 8.84% H

^{1}H-NMR (300MHz): 0.92 (s, 9H), 1.63 (ddd, J_1=13 Hz, J_2=6 Hz, J_3=2 Hz, 1H), 1.94 (ddd, J_1=13 Hz, J_2=10 Hz, J_3=9 Hz, 1H), 2.44 (dd, J_1=18 Hz, J_2=4 Hz, 1H), 2.85 (dd, J_1=18 Hz, J_2=10 Hz, 1H), 3.1-3.2 (m, 1H), 3.89 (dd, J_1=11 Hz, J_2=6 Hz, 1H), 6.08 (d, J=6 Hz, 1H). MS: m/e (%): 169 (10), 140 (4), 127 (100), 109 (20), 99 (16), 71 (47). Calc. for $C_9H_{13}O_3$ (M-Me): 169.0865; found: 169.0867.

5,5-Dimethyl-1-(1,3-dioxolan-2-yl)-4-isopropyldimethylsilyloxy-2-carbonitrile (**206**)

To a solution of n-butyl lithium (10.7 mL of a 1.45 M solution in hexane) in dry ether (15 mL) at 0°C was added diisopropylamine (2.2 mL, 15.7 mmol). The solution was stirred for 10 min and a solution of the nitrile

205[9] (1.98 g, 15.6 mmol) and tetramethylethyleendiamine (2.4 mL) in ether (10 mL) was added. The solution was stirred for 30 min and *tert*-butyloxirane (12.0 mmol) in ether (5 mL) was added. The reaction mixture was stirred for 1 h and quenched with isopropyldimethylsilyl chloride (7 mL, 45 mmol). The temperature was raised to roomtemperature and the reaction mixture was stirred additionally for 1 h. Work up as usual and flash chromatography on silica gel eluting with light petroleum/ether (8/1) afforded the nitriles **206** (3.83 g, 91%).
^{1}H-NMR: 0.0 (s, 6H), 0.9-1.0 (m, 16H), 1.4-2.1 (m, 4H), 2.5-3.0 (m, 1H), 3.2-3.6 (m, 1H), 3.8-4.0 (m, 4H), 4.9-5.1 (m, 1H).
MS *i* : 326 (1), 312 (7), 284 (46), 272 (3), 271 (14), 270 (63), 166 (37), 119 (25), 101 (46), 75 (100), 73 (94), 59 (36).
MS *ii* : 326 (1), 312 (4), 284 (35), 272 (4), 271 (8), 270 (46), 166 (38), 119 (26), 101 (39), 75 (100), 73 (92), 59 (36).

5,5-Dimethyl-1-(1,3-dioxolan-2-yl)-4-isopropyldimethylsilyloxy-2-carbaldehyde (**207**)
The nitrile mixture **206** (851 mg, 2.6 mmol) was dissolved in dry toluene (50 mL) and cooled to -40°C under nitrogen. Diisobutylaluminium hydride (2.6 mL of a 1.2 M solution in toluene) was added and the reaction mixture was stirred for 20 min, 4 N aqueous sodium hydroxide (0.5 mL) was added and the suspension was stirred for 1 h! This long period proved necessary to effect complete decomposition of the intermediate aluminates. Work up as usual and flash chromatography on silica gel eluting with light petroleum/ether (8/1) afforded the aldehyde mixture **207** (806 mg, 94%).
^{1}H-NMR: 0.0 (m, 6H), 0.8-0.9 (m, 16H), 1.1-2.1 (m, 4H), 2.2-2.7 (m, 1H), 3.1-3.2 (m, 1H), 3.7-3.9 (m, 4H), 4.82 (t, J=4 Hz, 1H), 9.36 (d, J=4 Hz, 1/2H), 9.47 (d, J=2 Hz, 1/2H).
MS *i* : 287 (2), 274 (1), 273 (4), 155 (12), 101 (8), 75 (54), 73 (100).
MS *ii* : 287 (2), 274 (1), 273 (5), 155 (9), 101 (7), 75 (56), 73 (100).

5β-*tert*-Butyl-3aβ,4,5,6aβ-tetrahydrofuro[2,3b]furan-2(3H)-one (**204b**)
The aldehyde mixture **207** (806 mg, 2.4 mmol) was dissolved in acetone (20 mL), 5 drops 8 N hydrochloric acid were added and the reaction mixture was stirred for 3 days. Work up as usual and subsequent oxidation gave the aimed furofuranone **204b** (324 mg, 72%).

6.6 REFERENCES AND NOTES

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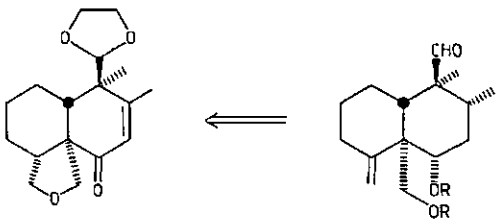
7. THE SYNTHESIS OF THE INTERMEDIATE ALDEHYDE

7.1 INTRODUCTION

As outlined in the synthetic plan (see chapter 3), there was a need for the transformation of **130** into **128** (scheme 7.1). The aldehyde **128** was supposed to be a very promising clerodane precursor, especially since mild and stereoselective methods were developed for the synthesis of furofurans from either aldehydes (see chapter 5) or oxiranes (see chapter 6).

Scheme 7.1



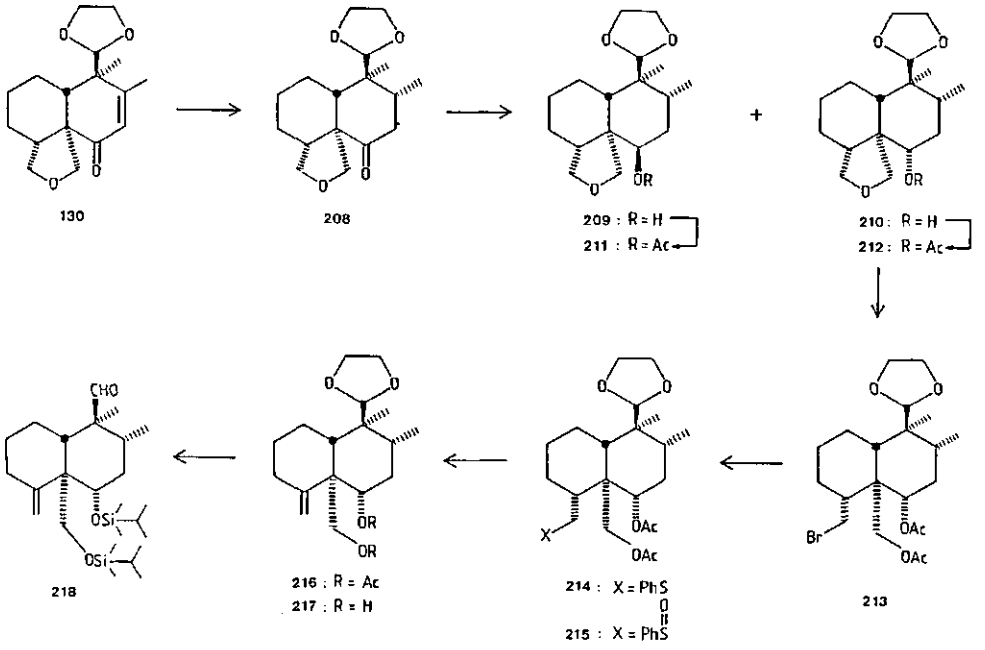
130 128

7.2 STEREOSELECTIVE ENONE REDUCTIONS

The synthesis of the enone **130** was described in chapter 4. At this stage stereoselective reductions of both the double bond and the carbonyl group were required. Luteijn[1] had found in a very similar system that Birch reduction of the double bond did not proceed in a stereoselective manner, this in contrast to the findings of Kende *et al.*[2]. Luteijn had also found that catalytic hydrogenation of the double bond did proceed in the desired stereospecific manner. Therefore the Birch reduction of **130** was not investigated and the enone **130** was hydrogenated using palladium on charcoal as the catalyst to give the ketone **208** in 85% yield. Also in this compound no trace of the isomeric axial methyl compound was detected.
The reduction of the ketone **208** gave the epimeric alcohols **209** and **210**. Reduction with lithium alumino hydride gave the epimeric alcohols **209** and **210** in the ratio 45:55 respectively. This ratio was improved to 30:70 using lithium tri-*tert*-butoxyaluminohydride and even further improvement of this ratio to 10:90 was accomplished using L-selectride®

as the reducing agent. The alcohol mixture was converted into the acetates **211** and **212**, which were easily separated by means of flash chromatography. In this way the desired equatorial acetate **212** was obtained in 87% yield. The structure of this acetate **212** was proven additionally by an X-ray crystal structure[3].

Scheme 7.2



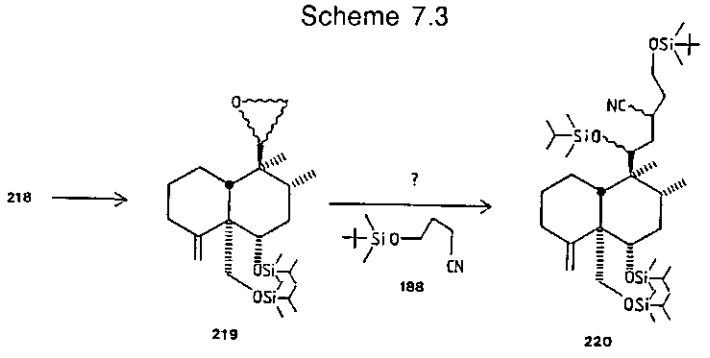
7.3 THE CLEAVAGE OF THE CYCLIC ETHER

Luteijn[1] had found that cleavage of cyclic ethers very similar to **212** could be achieved using pyridinium chloride or pyridinium bromide in refluxing acetic anhydride. Bastiaans[4] had worked out a modification of this method by using the combination of pyridine and acetylbromide in acetic anhydride at elevated temperatures. In this way the conversion of such a cyclic ether into a bromide acetate could be achieved when $70^{o}C \leq T \leq 100^{o}C$. Dehydrobromination and subsequent isomerization of the exocyclic double bond to the endocylic double bond was found when $120^{o}C \leq T \leq 140^{o}C$.

Treatment of the cyclic ether **212** with pyridine/acetyl bromide in acetic anhydride at 70 °C for 16 h gave the bromide diacetate **213** in almost quantitative yield, with the dioxolan group left intact! Attempted dehydrobromination of **213** in hot dimethylformamide and lithium carbonate as proton scavenger did not result in formation of the aimed alkene, but resulted in back formation of the cyclic ether **212**. In order to circumvent this problem the bromide **213** was treated with sodium thiophenolate in dimethylformamide to give the sulfide **214** in almost quantitative yield. Attempted pyrolysis of the corresponding sulfoxide **215** did not give the desired methylene compound **216**, possibly due to the crowded surroundings of the sulfoxide which may have prevented the adoption of the correct conformation necessary for the syn elimination. Therefore the acetate groups in **215** were saponified prior to the pyrolysis. By reacting this way, the sulfide **214** gave a mixture of the cyclic ether **210** (20%) and the desired methylene diol **217** (40%).The overall transformation of the bromide **213** into the alkene **217** was not studied in full detail, due to the limited availability of material at the end of a long sequence of reactions and only a small amount of **217** was obtained. Hydrolysis of the acetal function and protection of the alcohol groups as isopropyldimethylsilyl ethers gave the aldehyde **218** in 94%.

Preliminary experiments on the utility of the aldehyde **218** for the total synthesis of clerodanes indicate that the aldehyde does react with dimethylsulfonium methylide[3], albeit in a low yield and with unknown stereoselectivity. The reaction of the oxirane **219** with the lithiated nitrile **188** was extremely sluggish and no clear indications for the formation of the aimed coupling product **220** were obtained.

Scheme 7.3



7.4 EXPERIMENTAL

For general experimental details see chapter 4.6.

7β-(1,3-Dioxolan-2-yl)-3aβ,4,5,6,6aβ,7,8,9-octahydro-7α,8α-dimethyl-1H-naphtho[1,8aα-c]furan-10(3H)-one (**208**)

The enone **130** (2.212 g, 7.5 mmol) was dissolved in ethanol (30 mL) and triethylamine (1 mL). A catalytic amount of 10 % palladium on charcoal was added and the mixture was hydrogenated at 4.10^5 Pa in a Parr-apparatus overnight. The catalyst was removed by filtration and the solvents were evaporated. Flash chromatography on silica gel eluting with light petroleum/ether (2/1) afforded the ketone **208** (1.966 g, 89%) as a colourless oil which solidified upon standing. Recrystallization in *tert*-butyl methyl ether afforded the pure keton **208** (1.862 g, 85 %) as a white solid. (mp 90-91°C). Elemental analysis: calc. for $C_{17}H_{26}O_4$: 69.35% C, 8.90% H; found: 69.54% C, 9.02% H.

^{1}H-NMR: 0.96 (s, 3H), 1.00 (d, J=6 Hz, 3H), 1.2-1.4 (m, 3H), 1.6-1.8 (m, 2H), 1.8-1.9 (m, 1H), 2.0-2.3 (m,3H), 2.53 (dd, J_1=12 Hz, J_2=5 Hz, 1H), 2.63 (dd, J_1=13 Hz, J_2=12 Hz, 1H), 3.35 (d, J=7 Hz, 1H), 3.7-4.0 (m, 5H), 4.00 (d, J=9 Hz, 1H), 4.09 (d, J=9 Hz, 1H), 4.78 (s, 1H). MS: m/e (%): 294 (2), 276 (1), 204 (3), 127 (2), 73 (100). Calc. for $C_{17}H_{26}O_4$: 294.1831; found: 294.1830.

10α-Acetoxy-7β-(1,3-dioxolan-2-yl)-3,3aβ,4,5,6,6aβ,7,8,9,10-octahydro-7α,8α-dimethyl-1H-naphtho[1,8aα-c]furan (**212**)

The ketone **208** (1.502 g, 5.2 mmol) was dissolved in dry tetrahydrofuran (20 mL) at -20°C and L-selectride® (7 mL of a 1 N solution in tetrahydrofuran) was added dropwise. The mixture was stirred for 4 h, poured into water and worked up as usual. Flash chromatography on silica gel eluting with light petroleum/ether (1/2) afforded an alcohol mixture **209/210** (1.55 g), which was acetylated by treatment with acetic anhydride (4 mL), pyridine (4 mL) and dimethylaminopyridine (100 mg) overnight. The volatiles were evaporated at reduced pressure (50°C, 2 mm Hg) and the residue was chromatographed on silica gel using light petroleum/ether (2/1) as the eluant to afford the axial acetate **211** (167 mg, 10%) as a white solid, mp 151-152°C (from *tert*-butyl methyl ether), elemental analysis: calc. for $C_{19}H_{30}O_5$: 67.42% C, 8.93% H; found: 67.34% C, 8.99% H.

^{1}H-NMR: 0.73 (s, 3H), 0.87 (d, J=7 Hz, 3H), 1.2-2.3 (m, 11H), 2.12 (s, 3H), 3.35 (d, J=8 Hz, 1H), 3.76 (d, J=8 Hz, 1H), 3.8-4.0 (m, 6H), 4.81 (s, 1H), 4.9 (br s, 1H) MS: m/e (%): 338 (0.2), 279 (0.4), 204 (5), 159 (3), 73 (100). Calc for $C_{19}H_{30}O_5$: 338.2093; found: 338.2091.

Further elution gave the equatorial acetate **212** (1494 mg, 87%).as a white solid, mp 131-132°C (from *tert*-butyl methyl ether), elemental analysis: calc. for $C_{19}H_{30}O_5$: 67.42% C, 8.93% H; found: 67.68% C, 9.20% H. ^{1}H-NMR: 0.75 (s, 3H), 0.92 (d, J=7 Hz, 3H), 1.1-2.1 (m, 11H), 2.06 (s, 3H), 3.36 (dd, J_1=8 Hz, J_2=2 Hz, 1H), 3.7-4.1 (m, 7H), 4.77 (1, 1H), 4.83 (dd, J_1=11 Hz, J_2=5 Hz, 1H). MS: m/e (%): 338 (0.3), 279 (0.6), 204 (5), 159 (2), 73 (100). Calc for $C_{19}H_{30}O_5$: 338.2093; found: 338.2085.

1α-Acetoxy-8aα-acetoxymethyl-8α-bromomethyl-4β-(1,3-dioxolan-2-yl)-1,2,3,4,4aβ,5,6,7,8,8a-perhydro-3α,4α-dimethyl-naphthalene (**213**)
A mixture of the equatorial acetate **212** (952 mg, 2.8 mmol), pyridine (1.2 mL, 15 mmol), acetylbromide (1.1 mL, 15 mmol) and acetic acid anhydride (4 mL) was stirred overnight at 70°C. The suspension was cooled, poured into saturated aqueous sodium bicarbonate and extracted three times with ether. The combined organic layers were washed with brine, dried with magnesium sulfate, filtered and concentrated under reduced pressure (2 mm Hg). Flash chromatography on silica gel eluting with light petroleum/ether (5/2) afforded the bromide **213** (1.229 g, 95%) as a colourless oil which solidified upon standing.
^{1}H-NMR: 0.90 (s, 3H), 0.93 (d, J=5 Hz, 3H), 1.0-2.1 (m, 11H), 2.04 (s ,3H), 2.07 (s, 3H), 3.32 (t, J=10 Hz, 1H), 3.8-4.1 (m, 5H), 4.30 (d, J=12 Hz, 1H), 4.75 (s, 1H), 4.81 (d, J=12 Hz, 1Hz), 4.7-4.9 (m, 1H). MS: m/e (%): 462 (0.1), 460 (0.1), 389 (0.2), 387 (0.2), 151 (4), 73 (100). Calc. for $C_{21}H_{32}O_6Br$ (M-H): 459.1383; found: 459.1384.

1α-Acetoxy-8aα-acetoxymethyl-4β-(1,3-dioxolan-2-yl)-1,2,3,4,4aβ,5,6,7,8,8a-perhydro-3α,4α-dimethyl-8α-phenylthiomethyl-naphthalene (**214**)
The bromide **213** (1.229 g, 2.7 mmol) was dissolved in dimethylformamide (5 mL) and a solution of sodium thiophenolate (4 mmol) in dimethylformamide (3 mL) was added. The mixture was stirred overnight, poured into aqueous ammonium chloride and worked up as usual. Flash chromatography on silica gel with light petroleum/ether (5/1→3/1) as the eluants gave the sulfide **214** (1.262 g, 97%) as a white solid.
mp: 93-94°C (from light petroleum/ether 4/1). Elemental analysis: calc. for $C_{27}H_{38}O_6S$: 66.09% C, 7.80% H; found: 66.00% C, 7.94% H.
^{1}H-NMR: 0.90 (d, J=7 Hz, 3H), 0.91 (s, 3H), 1.0-2.1 (m, 17H), 2.79 (dd, J_1=13 Hz, J_2=9 Hz, 1H), 3.57 (dd, J_1=13 Hz, J_2=2 Hz, 1H), 3.7-4.0 (m, 4H), 4.37 (d, J=13 Hz, 1H), 4.6-4.9 (m, 1H), 4.74 (s, 1H), 4.79 (d, J=13 Hz, 1H), 7.2-7.3 (br s, 5H). MS: m/e (%): 490 (17), 446 (1.3), 417 (5), 381 (1), 380 (1), 356 (2), 182 (10), 173 (7), 123 (7), 73 (100). Calc. for $C_{27}H_{38}O_6S$: 490.2389; found: 490.2395.

4β-(1,3-Dioxolan-2-yl)-1,2,3,4,4aβ,5,6,7,8,8a-perhydro-8aα-hydroxymethyl-3α,4α-dimethyl-8-methylene-naphthalen-1α-ol (**217**)

Sodium *meta*-periodate (400 mg) in water (4 mL) was added dropwise to a solution of the sulfide **214** (740 mg, 1.5 mmol) in methanol/dichloromethane (10 mL/1 mL) and the mixture was stirred overnight at roomtemperature. The reaction mixture was filtered, concentrated and worked up as uaual. The crude sulfoxide diacetate **215** was dissolved in methanol (5 mL), potassium hydroxide (1 pellet) was added, the mixture was stirred overnight, poured into aqueous ammonium chloride and worked up as usual. The formed sulfoxide diol was taken up in toluene, refluxed for 6 h, cooled and worked up as usual. Flash chromatography on silica gel eluting with light petroleum/ether (3/1→3/2) gave the cyclic ether **210** (92 mg, 20%) and the alkene diol **217** (167 mg, 40%).

^{1}H-NMR: 0.83 (s, 3H), 0.94 (d, J=6 Hz, 3H), 1.1-2.0 (m, 8H), 2.1-2.3 (m, 2H), 2.93 (dd, J_1=7 Hz, J_2=4 Hz, 1H), 3.16 (d, J=4 Hz, 1H), 3.7-4.1 (m, 7H), 4.72 (s, 1H), 4.97 (br s, 1H), 5.11 (br s, 1H). MS: m/e (%): 296 (0.1), 295 (0.2), 278 (0.5), 248 (3), 223 (0.5), 206 (5), 188 (5), 173 (6), 73 (100). Calc. for $C_{17}H_{26}O_3$ (M-H_2O): 278.1882; found: 278.1880. Calc. for $C_{14}H_{23}O_2$ (M-$C_3H_5O_2$): 223.1698; found: 223.1698.

1,2,3,4,4a,5,6,7,8,8aβ-Perhydro-4α-isopropyldimethylsilyloxy-4aα-isopropyldimethylsilyloxymethyl-1α,2α-dimethyl-5-methylene-naphthalene-1β-carbaldehyde (**218**)

The acetal **217** (167 mg, 0.60 mmol) was dissolved in actone (4 mL) and 1 N hydrochloric acid (1 mL). The reaction mixture was stirred overnight, neutrlized concentrated and worked up as usual. The crude aldehyde diol was dissolved in dimethylformamide (5 mL) and imidazole (340 mg, 5.0 mmol) and isopropyldimethylsilyl chloride (300 µL, 1.9 mmol) were added and the reaction mixture was stirred overnight. The mixture was poured into diluted aqueous sodium bicarbonate, extracted with light petroleum, further worked up as usual and chromatographed on silica gel with light petroleum/ether (30/1) as the eluant. The aldehyde **218** (256 mg, 94%) was obtained as a colourless oil.

^{1}H-NMR: 0.0-0.1 (m, 12H), 0.69 (d, J=6 Hz, 3H), 0.7-0.9 (m, 2H), 0.9-1.0 (m, 15H), 1.2-2.3 (m,10H), 3.92 (d, J=11 Hz, 1H), 3.85 (d, J=11 Hz, 1H), 4.04 (dd, J_1=11 Hz, J_2=6 Hz, 1H), 4.75 (br s, 1H), 4.85 (br s, 1H), 9.09 (s, 1H). MS: m/e (%): 452 (0.1), 409 (0.3), 247 (6), 219 (100), 185 (34), 147 (37), 133 (39), 75 (48), 73 (34). Calc. for $C_{25}H_{48}O_3Si_2$: 452.3141; found: 452.3140.

[1,2,3,4,4a,5,6,7,8,8aβ-Perhydro-4α-isopropyldimethylsilyloxy-4aα-isopropyldimethylsilyloxymethyl-1α,2α-dimethyl-5-methylene-naphthalene-1β-yl]-oxirane (**219**)

To a solution of trimethylsulfonium iodide (204 mg, 1.0 mmol) in dry dimethylsulfoxide (5 mL) and tetrahydrofuran (4 mL) at 0°C was added potassium *tert*-butoxide (112 mg, 1.0 mmol) and the mixture was stirred for 5 min. A solution of the aldehyde **218** (170 mg, 0.38 mmol) in tetrahydrofuran (5 mL) was added dropwise and the reaction mixture was stirred for 30 min. Water was added and the aqueous layer was extracted three times with light petroleum. Further work up as usual and flash chromatography on silica gel with light petroleum/ether (40/1) as the eluant afforded the oxirane **219** (66 mg, 38%) as a colourless oil.

^{1}H-NMR: 0.02 (s, 6H), 0.07 (s, 3H), 0.08 (s, 3H), 0.57 (s, 3H), 0.82 (d, J=6 Hz, 3H), 0.7-0.9 (m, 2H), 0.9-1.0 (m, 12H), 1.1-1.7 (m, 7H), 1.7-2.0 (m, 3H), 2.4-2.6 (m, 3H), 3.86 (d, J=11 Hz, 1H), 3.91 (d, J=11 Hz, 1H), 3.97 (dd, J_1=11 Hz, J_2=5 Hz, 1H), 4.70 (br s, 1H), 4.78 (br s, 1H). MS: m/e (%): 466 (1), 451 (2), 423 (33), 349 (29), 305 (100), 75 (66), 73 (98). Calc. for $C_{26}H_{50}O_3Si_2$: 466.3298; found: 466.3299.

7.5 REFERENCES AND NOTES

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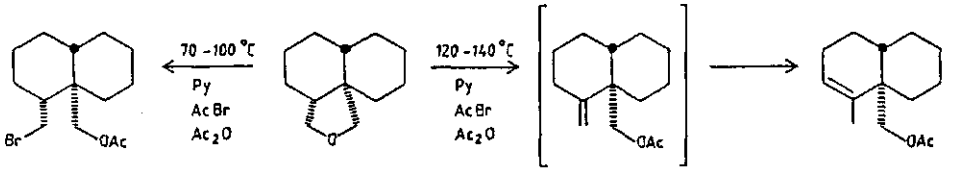

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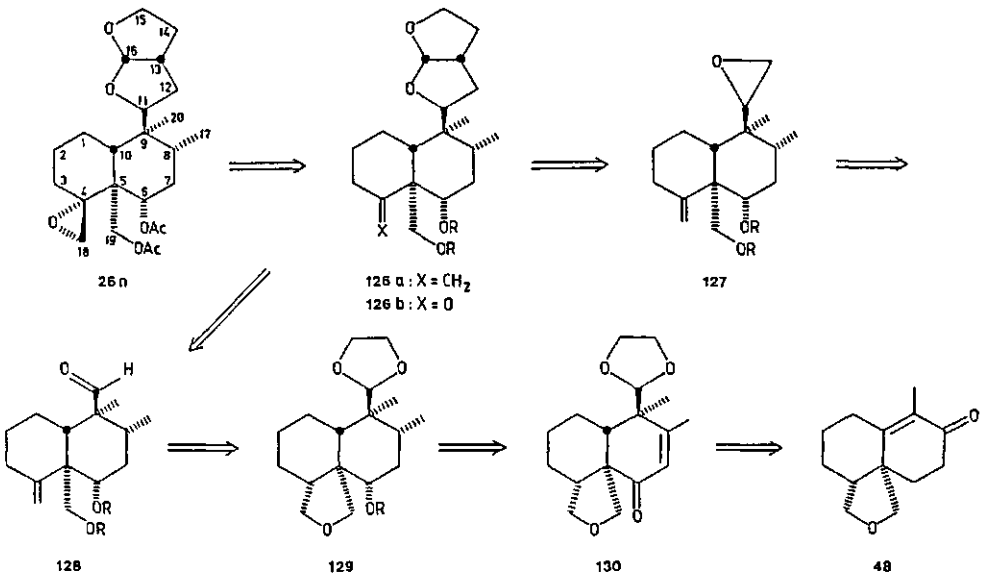
8. SUMMARY

An approach towards the total synthesis of insect antifeedant clerodanes is described in this thesis.
In chapter 1 the structure, nomenclature, occurrence, biosynthesis and physiological activities of the clerodanes are described. A number of structure/activity studies, concerning the insect antifeedant properties of these compounds, is summarized in a tabular form. Such studies have led to the conclusion that for evoking strong antifeedant activity both the furofuran and the decalin part of the molecule are required (de Groot/ Schoonhoven and Ley/Blaney). A literature survey of the most relevant synthetic studies towards the clerodanes is presented in chapter 2.
A retrosynthetic study of the targetmolecule dihydroclerodin **26n** is described in chapter 3. This approach offers some flexibility with respect to the decalin part and the furofuran part of the molecule. According to this synthetic plan the enone **48** has to be converted into the γ-dioxolanyl-α,β-unsaturated ketone **130**. The problems connected with this transformation and the solution for these problems are described in chapter 4.
New methods for the stereoselective synthesis of the furofuran unit had to be developed. Such methods must be applicable on the planned intermediates **127** and/or **128** and therefore had to start from an aldehyde or an oxirane function and had to be compatible with the functional groups present in other parts of these molecules, so strongly oxidizing or electrophilic reactions had to be avoided. Moreover reactions have to be carried out on a neopentylic carbon atom and therefore pivalaldehyde and *tert*-butyloxirane were chosen as the principal model compounds. In chapter 5 stereoselective perhydrofurofuran syntheses, based on the reaction of lithiated sulfones with carbonyl compounds, are described. In chapter 6 stereoselective furofuran syntheses, based on the reaction of lithiated nitriles with oxiranes, are described.
Having appropiate methods for the introduction of a furofuran unit in hand, the aldehyde **128** was considered to be a very promising clerodane precursor. So the enone **130** was converted into the cyclic ether **129** via two stereoselective reductions. Additional prove for the correct stereochemistry of this molecule was obtained by an X-ray crystal structure determination. The subsequent cleavage of the cyclic ether

structure determination. The subsequent cleavage of the cyclic ether proceeded in a remarkable chemo- and regioselective manner to give a bromide diacetate, which was further transformed into the aldehyde **128**. The latter transformation was not studied in full detail owing to the limited availability of material. Nevertheless a small amount of this aldehyde **128** was obtained. Its transformation into dihydroclerodin **26n** will need further investigations.

Scheme 8



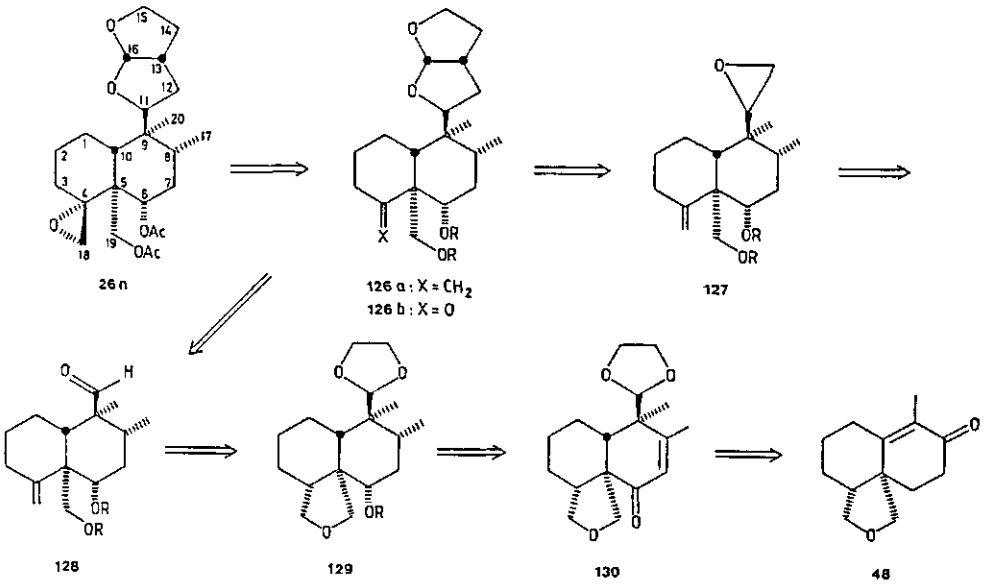
9. SAMENVATTING

In dit proefschrift wordt een benadering voor de totaal synthese van clerodanen met insectenvraat remmende eigenschappen beschreven.
In hoofdstuk 1 zijn de structuur, naamgeving, voorkomen in de natuur, biosynthese en fysiologische activiteiten van de clerodanen weergegeven. Een aantal structuur/activiteit studies over de vraatremmende eigenschappen van deze verbindingen zijn tabellarisch samengevat. Uit dergelijke studies kan de conclusie worden getrokken dat zowel het decaline als het furofuran stuk van het molecuul nodig zijn voor een sterk vraatremmende activiteit (de Groot/Schoonhoven en Ley/Blaney).
In hoofdstuk 2 wordt een literatuur overzicht gegeven van de meest relevante tot nu toe gepubliceerde clerodaan syntheses.
Een retrosynthetische studie van het doelmolecuul, dihydroclerodin **26n**, leidde tot het synthese plan zoals dat beschreven staat in hoofdstuk 3. Dit plan biedt enige flexibiliteit, zowel met betrekking tot het decaline stuk als het furofuran stuk van het molecuul. Volgens dit synthese plan wordt uitgegaan van het enon **48** dat moet worden omgezet in het γ-dioxolanyl-α,β-onverzadigde keton **130**. De problemen bij de hiervoor benodigde transformaties en de daarvoor gevonden oplossing staan beschreven in hoofdstuk 4.
Voor de stereoselectieve synthese van de furofuran eenheid moesten nieuwe methoden ontwikkeld worden. Deze methoden moeten toepasbaar zijn op de geplande intermediairen **127** en **128**. Dit betekent dat de furofuran eenheid gesynthetiseerd moet kunnen worden uitgaande van een aldehyde of een oxiraan en dat daarvoor reagentia en reactieomstandigheden gebruikt moeten worden die verenigbaar zijn met de in **127** en **128** aanwezige functionele groepen. Bovendien zouden de reacties moeten worden uitgevoerd op een neopentyllisch koolstof atoom en derhalve werden pivalaldehyde en *tert*-butyloxiraan als belangrijkste model verbindingen gekozen.
In hoofdstuk 5 worden enkele stereoselectieve perhydrofurofuran syntheses beschreven, gebaseerd op de reactie van gelithieerde sulfonen met carbonyl verbindingen. In hoofdstuk 6 worden enkele stereoselectieve furofuran syntheses beschreven, gebaseerd op de reactie van gelithieerde nitrillen met oxiranen.

Het aldehyde **128** kan worden beschouwd als een veelbelovend intermediair in de totaalsynthese van clerodanen, omdat in principe de ontwikkelde furofuran syntheses op dit molecuul toegepast kunnen worden.

In hoofdstuk 7 staat de synthese van dit aldehyde **128** beschreven, uitgaande van het enon **130**. Dit enon **130** werd door middel van twee stereoselectieve reducties omgezet in de cyclische ether **129**. Een bevestiging van de juiste stereochemie van het molecuul **129** werd verkregen door middel van een kristalstructuur bepaling. De cyclische ether **129** kan vervolgens met een opmerkelijke regio- en chemoselectiviteit worden omgezet in een bromide acetaat, dat uiteindelijk werd omgezet in het aldehyde **128**. De laatstgenoemde omzetting kon niet optimaal onderzocht worden, bij gebrek aan uitgangsstoffen. Desalniettemin werd een geringe hoeveelheid verkregen van het aldehyde **128**. De omzetting van deze verbinding in dihydroclerodin **26n** vereist nog verder onderzoek.

Scheme 9



CURRICULUM VITAE

De auteur van dit proefschrift werd op 9 september 1960 te Wieringermeer geboren. In 1978 werd het ongedeeld atheneum diploma behaald aan de Rijksscholengemeenschap te Schagen.In hetzelfde jaar werd begonnen aan de studie Levensmiddelentechnologie aan de toenmalige Landbouwhogeschool te Wageningen. Het doctoraal examen, met Organiche chemie (prof. dr. Ae. de Groot/dr. J.B.P.A. Wijnberg) als hoofdvak en Levensmiddelen chemie (prof. dr. W. Pilnik/dr. A.G.J. Voragen) als verzwaard hoofdvak, werd afgelegd in juli 1984. Aansluitend hierop werd, onder leiding van prof. dr. Ae. de Groot, het in dit proefschrift beschreven onderzoek verricht. Van 1 augustus 1984 to 1 augustus 1988 geschiedde dit in dienst van de toenmalige stichting Zuiver Wetenschappelijk Onderzoek en van 1 augustus 1988 tot 1 februari 1989 in dienst van de Landbouwuniversiteit.