TOTAL SYNTHESIS OF INSECT ANTIFEEDANT

DRIMANE SESQUITERPENES

Promotor: dr. Ae. de Groot, hoogleraar in de bio-organische chemie

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TOTAL SYNTHESIS OF INSECT ANTIFEEDANT DRIMANE SESQUITERPENES

Proefschrift
ter verkrijging van de graad van doctor
in de landbouw- en milieuwetenschappen,
op gezag van de rector magnificus,
dr. H.C. van der Plas,
in het openbaar te verdedigen
op dinsdag 23 maart 1993
des namiddags te vier uur in de Aula
van de Landbouwuniversiteit te Wageningen

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Stellingen

1. Bij de interpretatie van de verkregen meetresultaten zien Devadas *et al.* een allyl-type uitwisseling over het hoofd tijdens de katalytische reductie van 12-methoxy-10-dodecynzuur met tritium gas.

B. Devadas, S.P. Adams en J.I. Gordon, *J. Label. Compd. Radiopharm.*, **1991**, 29, 157.

2. De verwachting van Nakatani *et al.* dat de (Z)-configuratie in α-hydroxymethyleen cyclopentanon de stereochemie van het overeenkomstige (Z)-enoltriflaat zou bepalen is niet terecht en niet in overeenstemming met literatuurgegevens.

K. Nakatani, K. Arai, K. Yamada en S. Terashima, *Tetrahedron*, **1992**, 48, 3045.

3. Het is zeer onwaarschijnlijk, dat de door Brochet en medewerkers genoemde assistentie van Al^{3+} ionen bij de omzetting van furyloxiranen in furylaceetaldehyden bij het gebruik van het mineraal sepioliet is opgetreden.

C. Brochet, J.L. Syssa, Z. Mouloungui, M. Delmas en A. Gaset, *Synthetic Commun.*, **1991**, 21, 1735.

4. Uit de door Yoshikawa *et al.* vermelde gegevens is ook af te leiden dat guaiaan-type sesquiterpenen, welke geisoleerd werden uit de wortelstokken van *Alisma orientale*, wel op een enzymatische wijze uit germacreen C gevormd zijn.

M. Yoshikawa, S. Hatakeyama, N. Tanaka, Y. Fukuda, N. Murakami en J. Yamahara, *Chem. Pharm. Bull.*, **1992**, 40, 2582.

5. De selectieve transformatie van ginkgolide C in het biologisch aktievere ginkgolide B door Weinges *et al.* is door Corey en medewerkers ten onrechte niet geciteerd in hun publikatie.

K. Weinges en H. Schick, *Liebigs Ann. Chem.*, **1991**, 81.
E.J. Corey, K. Srinivas Rao en A.K. Ghosh, *Tetrahedron Lett.*, **1992**, 33, 6955.

6. De verklaring, die Wiltberger *et al.* geven voor de afgeknotte absorptie piek van J-aggregaten van een geconcentreerde dispersie van een cyanine kleurstof, is aan bedenkingen onderhevig.

M. Wiltberger, R. Sharma, P. Martic en T.L. Penner, *Langmuir*, **1992**, 8, 2639.

7. De titels en trefwoorden van publikaties in chemische tijdschriften beloven vaak meer dan ze waar maken.

8. Het verdient aanbeveling om veranderingen in een hoofdtype terpeenkoolstofskelet niet weer te geven met de algemene term "omgelegd".

A. Ulubelen, G. Topcu en N. Tan, *Phytochemistry*, **1992**, 31, 3637.

9. De reactievergelijking, die Bhaskar Kanth en Periasamy geven ter verklaring van de selectieve reductie van carbonzuren met natriumboorhydride en jodium, is onjuist.

J.V. Bhaskar Kanth en M. Periasamy, *J. Org. Chem.*, **1991**, 56, 5964.

10. Alleen bij postzegelverzamelaars met een ruimere beurs vindt de sluipwesp de witte vlieg.

Bijzondere postzegel, uitgegeven op 16-2-1993 vanwege 75 jaar Landbouwuniversiteit Wageningen.

Stellingen behorende bij het proefschrift **"Total Synthesis of Insect Antifeedant Drimane Sesquiterpenes".**

Wageningen, 23 maart 1993. B.J.M. Jansen.

Die Grundlage der Chemie ist Erfahrung,
wozu wir durch Beobachtungen und Versuchen gelangen.
Aus der Erfahrung leitet der Chemiker
durch richtige Vernunftschlüsse
eine Theorie her, welche alle einzelne Tatsachen
zu einem wissenschaftlichen Ganzen,
oder zu einem Systeme verknüpft.

J.W. Döbereiner, "Lehrbuch der allgemeine Chemie",
Jena, 1811, Vorwort.

Aan Ria, Linda en Esther

1 VOORWOORD

Op deze plaats wil ik iedereen bedanken die heeft bijgedragen aan het totstandkomen van dit proefschrift, temeer omdat de wijze van samenwerking en de contacten altijd uiterst prettig waren. Enkele personen wil ik echter graag met name noemen.

Prof.dr. Aede de Groot ben ik zeer erkentelijk voor de grote interesse waarmee hij het verloop van het onderzoek volgde en voor de zeer snelle en kritische beoordeling van het manuscript.
Rob Peperzak, co-auteur van een aantal publikaties, heeft een waardevolle bijdrage geleverd aan hoofdstuk 5 van dit proefschrift.
Gaarne wil ik de inzet vermelden van Frits Bakelaar en Ingrid Boerrigter, tijdens hun HBO-stage, en van Hans Westerbeek, Huub Sengers, André de Haan, Anja Haaksma en Coby Kreuger in het kader van hun ingenieursstudie.
Het analyseren van de vele verbindingen zou niet mogelijk geweest zijn zonder de hulp van Beb van Veldhuizen en Herman Holterman (NMR), Cees Landheer, Willem Combé en Cees Teunis (MS), Maarten Posthumus (GCMS) en Hugo Jongejan (micro analyses). Voor de snelle, bekwame en prettige wijze waarop de gevraagde gegevens werden aangedragen wil ik hen allen bedanken.
Op chromatografisch gebied gaat mijn dank uit naar Pim Melger (GC) en naar Gerrit Lelieveld, die de honderden dunnelaag silicagelplaten vervaardigde, die in dit onderzoek verbruikt werden.
Jurrie Menkman ben ik dank verschuldigd voor de vervaardiging van de vele tekeningen en Hedy D'hondt van de afdeling Tekstverwerking voor de bijzondere typografische zorg, die zij aan dit proefschrift besteed heeft.
Henk Swarts heeft de laatste plooitjes glad gestreken, waarvoor mijn dank.
Tevens is dit een goed moment om de niet met name genoemde (ex)-medewerkers van de vakgroep Organische Chemie te danken voor de vriendschap en de collegialiteit gedurende vele jaren.

Ria, Linda en Esther, jullie hebben ervoor gezorgd dat het schrijven onbelemmerd doorgang kon vinden door het gedogen van enorme hoeveelheden paperassen op alle mogelijke en onmogelijke plaatsen in huis.

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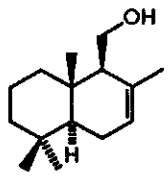
1 STRUCTURE, BIOSYNTHESIS, OCCURRENCE, BIOLOGICAL ACTIVITY AND MODE OF ACTION OF DRIMANE SESQUITERPENOIDS

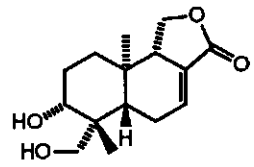
1.1 Structure and occurrence

Extracts of the bark of several *Drimys* species have been used for a long time in the treatment of disease and in food and crop protection.[1] In Southern Chile these extracts were used for the treatment of dermatitis, cattle ringworm, and stomach-ache.[2]
This led to the investigation of the chemical constituents in these barks and in 1948 Appel *et al.* were able to isolate a sesquiterpene alcohol from the bark of *Drimys winteri* Forst, which was named 'drimenol'.[3,4] After numerous experiments the structure and the absolute configuration of drimenol was elucidated in 1956 [5] (see figure 1.1). It was the first bicyclic sesquiterpene with the structure and absolute configuration characteristic for the A,B ring system of many di- and triterpenes; and thus it may be considered as the missing biogenetic link between the lower and higher terpenes.[6]

Figure 1.1



Drimenol



Iresin

The absolute configuration of drimenol was opposite that of iresin, a sesquiterpene isolated from the Mexican shrub *Iresine celosioides*, and characterized a few years before by Djerassi *et al.*[7,8] The stereochemistry of iresin was later on confirmed by a total synthesis from the ketone depicted in figure 1.2.[9]

Figure 1.2

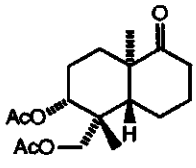
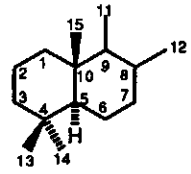
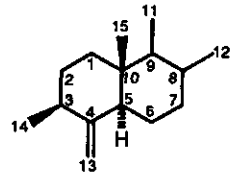


Figure 1.3



Drimane

Figure 1.4



Rearranged Drimane

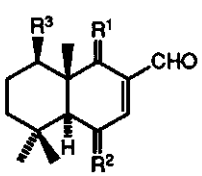
The name *drimane* was proposed for the saturated hydrocarbon with the structure and absolute configuration as depicted in figure 1.3.[5] Iresin has an *ent*-drimane skeleton. The numbering of the carbon skeleton follows the system established by Djerassi.[8a]
The carbon atoms 11 and 12 are very often oxidized but oxidation at other positions is also frequently observed. A few examples of rearranged drimanes are known.[10,11] In these compounds a migration of one of the methyl groups from C-4 to C-3 has occurred and a characteristic exocyclic double bond remains at C-4 as indicated in figure 1.4.

Many drimanes have been isolated from Cannellaceae, a small family of plants consisting of nine species, grouped into four genera.[3,11-24] Of these, *Winterana*, and *Cinnamodendron* are endemic to South America, *Warburgia* to East Africa and *Cinnamosma* to Madagascar. Some drimanes have been isolated from botanically related species.[10,25,26]
Another rich source of drimanes is the cosmopolitan plant *Polygonum hydropiper* L (Polygonaceae). This plant is also known as marsh pepper because of its habitat and hot taste experienced on chewing the leaves.[27-31]
The systematic investigations of the active compounds of the Hepaticeae also revealed some drimanes, especially in the liverwort genus *Porella*.[32-37]
Some remarkable drimanic alcohols were isolated from the neutral fractions of the volatiles of Greek *Nicotiana tabacum* L.[38,39] The biogenetic origin of these compounds is not clear but they may be genuinely biosynthesized from a farnesyl-precursor.
The occurrence of drimanes [40] is not limited to higher plants. They have been isolated from several fungi such as *Penicillium purpurogenum* Stoll,[41] and *P. brevicompactum*,[42] *Mycocalia reticulata* Petch,[43] *Lactarius uvidus* Fries,[44] *Cryptoporous volvatus* ,[45] *Aspergillus oryzae*,[46] *A. variecolor*,[47a] and *A. parasitious*,[47b] *Fomes annosus*,[48] *Alternaria brassicae* Saccardo,[49] *Perenniporia medullaepanis* Aj 8345,[50] and *Phoma asparagi* Sacc.[51]
Drimanes are also found in molluscs belonging to the subclass Opistobranchia. The molluscs have lost their shell during their evolution and so they lack the usual mechanical defensive system and yet few predators are known since a chemical defense mechanism is employed. The drimanes used for this purpose are closely related to the ones first isolated from terrestrial plants.
Drimanic constituents have been isolated from several *Dendrodoris* species, *e.g.*, *D. limbata*,[52] *D. grandiflora*,[53] *D. nigra*, and *D. tuberculosa*.[54] Nudibranchs of the genera *Hypselodoris*,[55a] *Cadlina*,[56] and *Chromodoris* [57] also contain drimanes. Drimanes are sometimes found in sponges [55b] and there is a possibility that these molluscs concentrate metabolites from their sponge diet.[55a] In some cases biosynthetic experiments with [^{14}C]mevalonic acid have shown that nudibranchs make their own drimanes.[52c,52d,53]
The drimanes discussed so far are gathered in the tables 1.1 up to and including 1.4.

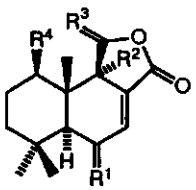
Table 1.1 Isolated drimanes

	Compound	R^1	R^2	R^3	R^4	Ref.
1	Warburganal	ßCHO,OH	H_2	H	-	17
2	Polygodial	ßCHO,H	H_2	H	-	30, 31
3	Isotadeonal	αCHO,H	H_2	H	-	31, 28
4	Polygonic acid	ßCOOH,H	H_2	H	-	27
5	Cinnamodial	ßCHO,OH	ßOAc,H	H	-	14, 15
6	Mukaadial	ßCHO,OH	αOH,H	H	-	22a
7	Pu'ulenal	(E)-CH(OAc)	H_2	H	-	57
8	p-Coumaroyloxy-polygodial	ßCHO,H	H_2	-[1]	-	20
9	Capsicodendrin[2]	ßCHO,OH	ßOAc,H	H	-	18
10	Cinnamolide	H_2	H	H_2	H	14a
11	Cinnamosmolide	ßOAc,H	OH	H_2	H	14a
12	Bemarivolide	ßOAc,H	H	H_2	H	15
13	Pereniporin B	ßOH,H	OH	H_2	H	50
14	11-Ethoxy-cinnamolide	H_2	H	αOEt,H	H	27
15	9-Hydroxy cinnamolide	H_2	OH	H_2	H	22b
16	11-Hydroxy-1-p-coumaroyloxy-cinnamolide [3]	H_2	H	αOH,H	-[1]	20

[1] $-O_2CCH{=}CHC_6H_4OH$. [2] Isolated as a tetramer.
[3] The authors named it (erroneous) valdiviolide.



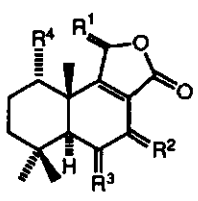
1-9



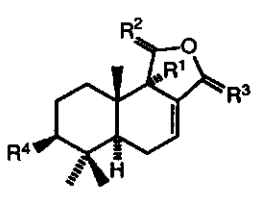
10-16

	Compound	R^1	R^2	R^3	R^4	Ref.
17	Confertifolin	H_2	H_2	H_2	H	12
18	Valdiviolide	αOH,H	H_2	H_2	H	13
19	Fuegin	αOH,H	αOH,H	H_2	H	13
20	Fragrolide	H_2	H_2	O	H	15
21	Winterin	O	H_2	H_2	H	13
22	Purpuride	H_2	H_2	H_2	-[4]	41
23	Bemadienolide	H_2	H,	Δ,H		15
24	Drimenin	H	O	H_2	H	12
25	3-Acetoxydrimenin	H	O	H_2	ßOAc	19
26	Isodrimeninol	H	αOH,H	H_2	H	29
27	Drimeninol	H	ßOH,H	H_2	H	34
28	---[5]	H	αOAc,H	ζOMe,H	H	54
29	Di(7-drimen-11-oxy)-11,12-epoxy-7-drimene	H	ζ [6],H	ζ [6],H	H	5c
30	Olepupuane	H	OAc	αOAc,H	H_2	54
31	Acetoxyolepupuane	H	OAc	αOAc,H	ßOAc,H	53
32	---	H	OR^7	H_2	H_2	52a
33	Euryfuran	Δ		H_2	H_2	55

[4] N-acetyl-L-valinyl = $O_2CCH(iPr)NHCOMe$. [5] Presumably obtained by allylic methanolysis of olepupuane (30). [6] 7-Drimen-11-oxy. [7] R = acyl residues from several fatty acids of different unsaturated degree.



17-23



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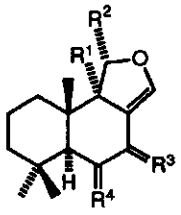
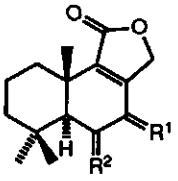


30-33

	Compound	R^1	R^2	R^3	R^4	Ref.
34	Isodrimenin	H_2	H_2	-	-	12
35	Ugandensolide	αOH,H	βOAc,H	-	-	15
36	Acetoxyisodrimenin	H_2	βOAc,H	-	-	18
37	Futronolide[8]	αOH,H	H_2	-	-	18
38	Epoxyisodrimenin	H,  ,H		-	-	32
39	Hydroxyisodrimenin	H_2	βOH,H	-	-	26b
40	Ketodihydrodrimenin	O	H_2	-	-	43
41	Hydroxydihydrodrimenin	βOH,H	H_2	-	-	43
42	Dihydroxy-dihydrodrimenin	βOH,H	αOH,H	-	-	43
43	Drimanol	βCH_3,H	βCH_3,OH	H_2	H_2	40
44	Drimanediol	βCH_2OH,H	βCH_3,OH	H_2	H_2	40
45	Drimanetriol	βCH_2OH,H	αCH_3,OH	αOH,H	H_2	48
46	Albicanol	βCH_2OH,H	CH_2	H_2	H_2	56b
47	Albicanylacetate	βCH_2OAc,H	CH_2	H_2	H_2	56b
48	Cryptoporic acid A	βCH_2OR^9,H	CH_2	H_2	H_2	45a
49	Drim-9(11)-en-8β-ol	CH_2	αCH_3,OH	H_2	H_2	46
50	Drim-9(11)-en-8α-ol	CH_2	βCH_3,OH	H_2	H_2	46
51	Isoalbrassitriol	βCH_2OH,OH	αCH_3,OH	H_2	H_2	49
52	Uvidin D	βCH_2OH,H	βCH_3,H	βOH,H	O	44b
53	Drimenon	CH_3,	A,CH_3	O	H_2	39

[8] The structure for this compound in ref. 13 is incorrect.
[9] R = -CH(CO_2Me)CH(CO_2Me)CH_2CO_2H (ether of isocitric acid).



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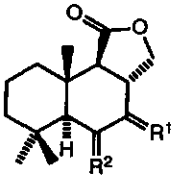
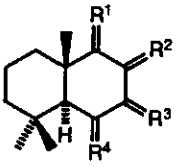


40-42



43-53

	Compound	R^1	R^2	R^3	R^4	Ref.
54	Drimenol	ßCH_2OH,H	H_2	H	H	5a
55	Albrassitriol	ßCH_2OH,OH	=OH,H	H	H	49
56	Deoxy uvidin B	ßCH_2OH,H	O	OH	H	49
57	Drim-7-enyl-glyceride	ßCOR^{10},H	H_2	H	H	56c
58	Drim-7-enyl-glyceride acetate	ßCOR^{11},H	H_2	H	H	56c
59	Uvidin E	ßCH_2OH,H	O	H	OH	44b
60	Uvidin A	ßCH_2OH,H	O	H	-	44a
61	Uvidin B	ßCH_2OH,H	O	OH	-	44a
62	Uvidin C	ßCH_2OH,H	ßOH,H	H	-	44b
63	Dihydrocinnamolide	H_2	CH_3	H	-	34
64	Pebrolide	ßOBz^{12},H	CH_2OAc	OH	-	42a
65	Altiloxin A	H	-	-	-	51
66	Altiloxin B	Cl	-	-	-	51
67	Astellolide A	CH_2OAc	OBz^{12}	CH_2OAc	-	47a
68	Astellolide B	CH_2OAc	O-p-OH-Bz^{12}	CH_2OAc	-	47a
68a	Parasiticolide A	CH_2OAc	OBz^{12}	CH_2OAc	-	47b
69	Pereniporin A	For structures see Figure 1.5				50
70	Cryptoporic acid B					45a
71	Cryptoporic acid C					45a
72	Cryptoporic acid D					45a
73	Cryptoporic acid E					45b

[10] R = $OCH_2CH(OH)CH_2OH$. [11] R = $OCH_2CH(OH)CH_2OAc$. [12] Bz = benzoyl.

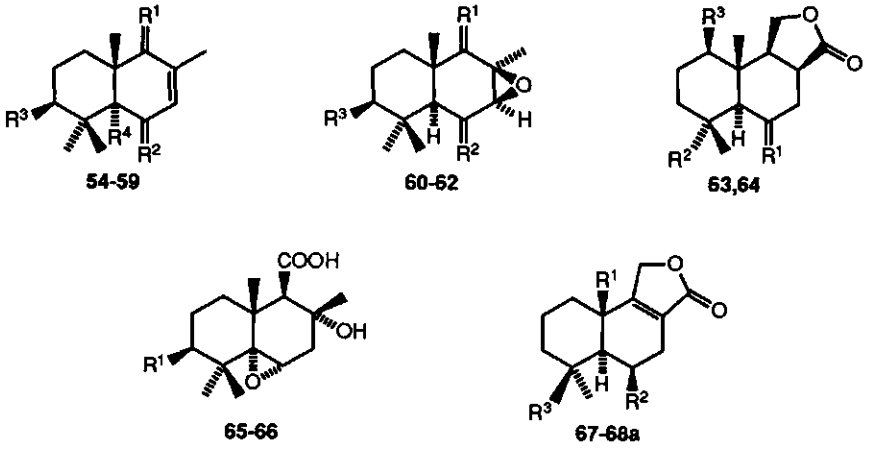


Figure 1.5

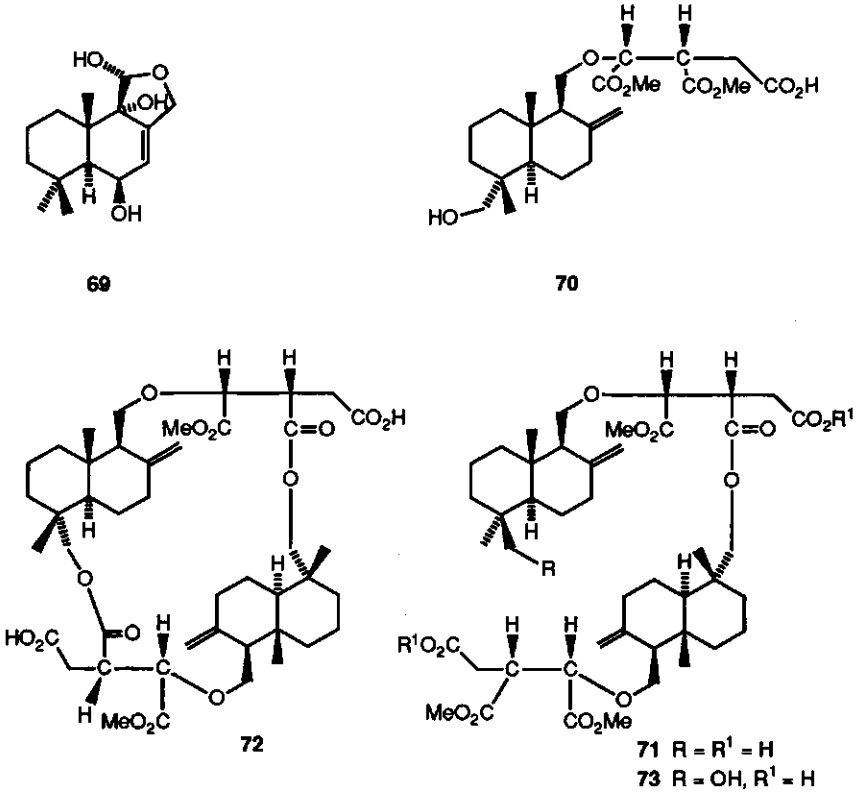
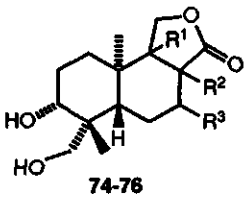


Table 1.2 *Ent*-Drimanes

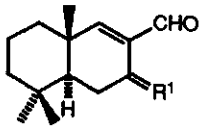
	Compound	R^1	R^2	R^3	Ref.
74	Iresin	βH	Δ		7,8
75	Isoiresin	Δ		H	8
76	Dihydroiresin	βH	βH	H	9



74-76

Table 1.3 *Nor*-Drimanes

	Compound	R^1	Ref.
77	Polygonone	O	27
78	Polygonal	αOH,H	29
79	Isopolygonal	βOH,H	27

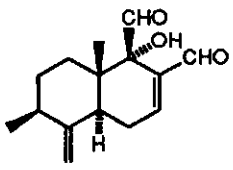


77-79

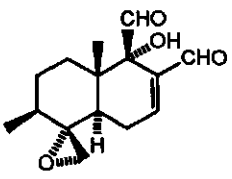
Table 1.4 Rearranged drimanes

	Compound		Ref.
80	Muzigadial	For structures see figure 1.6	21,24
81	4,13-α-Epoxy muzigadial		21
82	Coloratadienolide		10

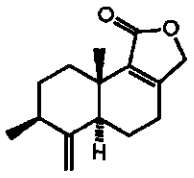
Figure 1.6



80



81

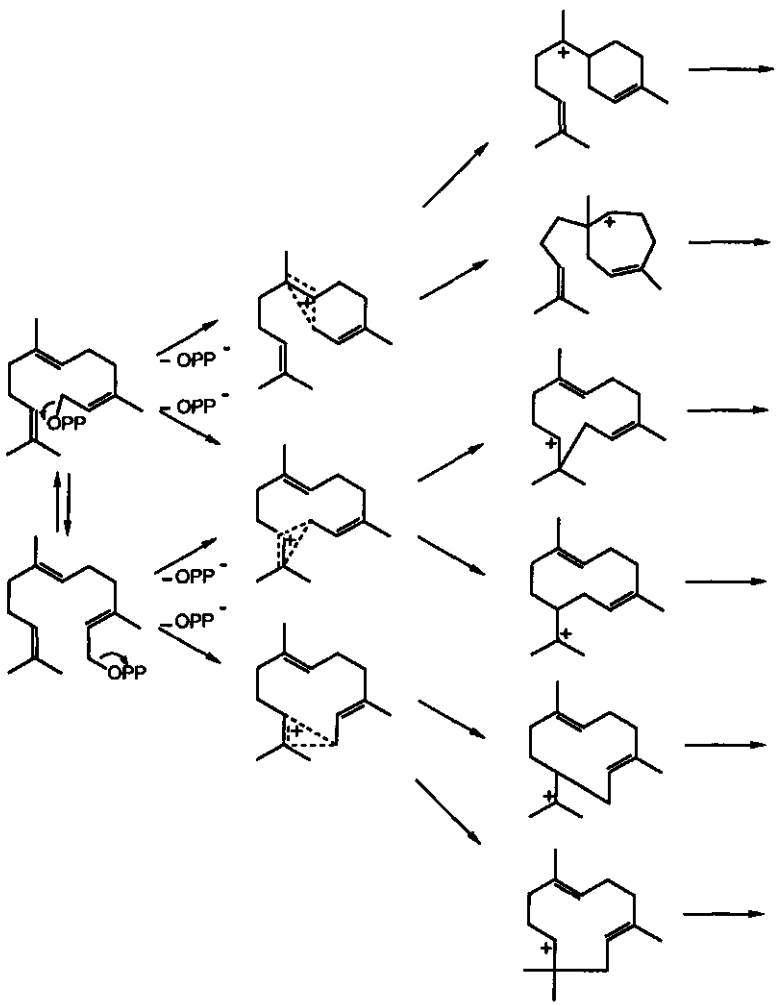


82

1.2 Biosynthesis

The numerous structural classes of sesquiterpenes are derived from farnesylpyrophosphate (FPP) through a series of appropriate cyclizations and rearrangements.[58]
Most cyclizations are initiated by an enzyme-mediated solvolysis of the pyrophosphate group in *cis*- or *trans*-FPP whereby an incipient or actual carbocation is formed at the tail position of the farnesyl chain [59] (see figure 1.7).

Figure 1.7

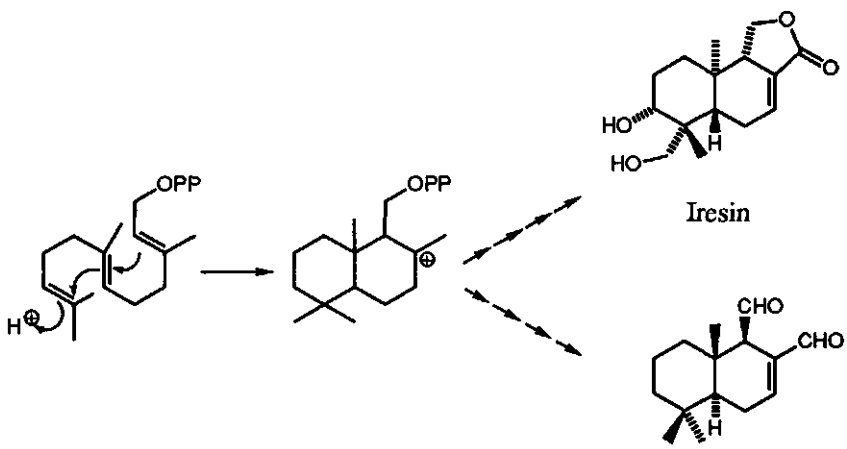


Cyclization of cis- and trans-farnesylpyrophosphate

These cations lead to six possible monocyclic carbocations from which the so-called primary skeletal sesquiterpenes are obtained either through loss of a proton from the adjacent carbon atoms, or *via* attack of a hydroxide ion. When rearrangements or intramolecular additions take place in the cations, then the so-called secondary skeletal sesquiterpenes are formed.

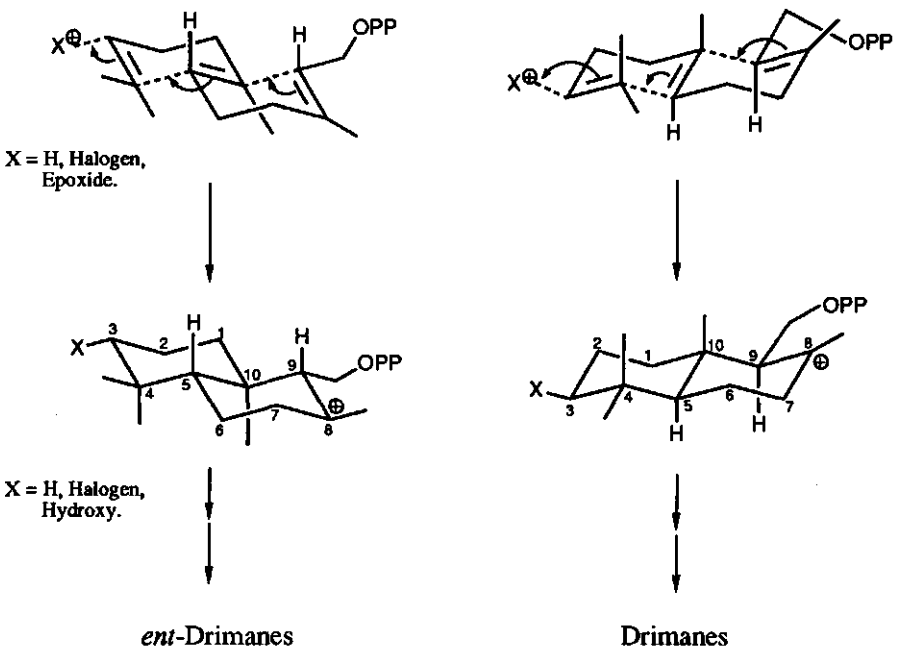
A small number of bicyclic sesquiterpenes, including drimanes, arise from a cyclization which is initiated by an electrophilic attack, mostly by a proton, on the double bond at the head position of FPP or onto the corresponding epoxide (see figure 1.8). [60] This mode of cyclization, which is uncommon for the sesquiterpenes is much more prevalent for the di- and triterpenes.[6b]

Figure 1.8



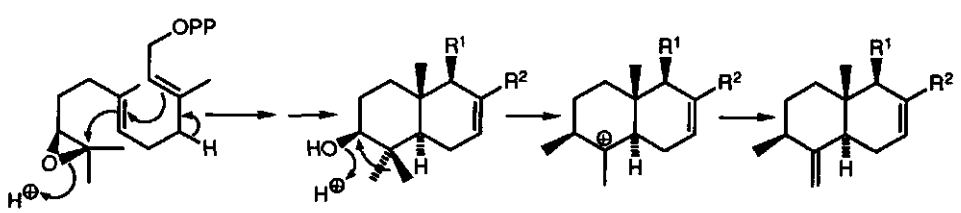
The relative positions of the double bonds in the conformation assumed by the FPP chain determines the structure and the stereochemistry of the final product. The *trans* ring junction is consistent with the stereoelectronic requirements of a concerted mechanism in which the sequential addition of the *non* conjugated double bonds take place. The chair-chair conformation of the polyenic chain during the cyclization can, in principle, exist in two enantiomeric forms from which the two enantiomeric drimane skeletons are derived. Examples of both stereotypes are found in nature although not in the same plant (see figure 1.9).

Figure 1.9



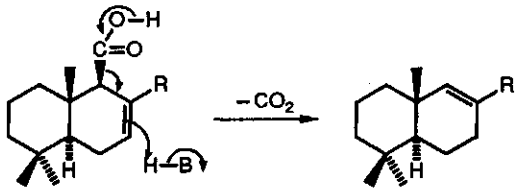
The hydroxyl group at C-3 probably originates from proton attack on an epoxide. It is reasonable to assume that protonation of this hydroxyl group, followed by loss of a molecule of water and rearrangement of the resulting carbocation, accounts for the biogenesis of the rearranged drimanes (see figure 1.10). Till now only a few compounds of this type are isolated (see table 1.4).

Figure 1.10



The co-occurrence of bicyclic *nor*-sesquiterpenes of the drimane class in some plants may arise through decarboxylation of drimanic carboxylic acids (see figure 1.11).[28]

Figure 1.11



1.3 Biological activity of drimanes

Drimanes can be held responsible for a wide variety of biological activities, including antibacterial, antifungal, anticomplemental, antifeedant, plant-growth regulatory, cytotoxic, phytotoxic, piscicidial, and molluscicidal properties. Moreover, the very hot taste of several biologically active drimanes to humans and their skin-irritating properties have attracted much attention.

1.3.1 Antifungal and antibacterial activity

In screening East African plants used in folk medicine Taniguchi *et al.* found several possessing antimicrobial activity.[1b] The plant materials were collected mainly on the basis of information gathered from native people especially from the 'Bwana Mganga', Swahili for 'medicine man'.[61] In particular the species of the genus *Warburgia* (Canellaceae) showed broad activity. The extracts were fractionated and bioassayed [62] leading to the isolation of the antimicrobial principles which were identified as the sesquiterpene dialdehydes polygodial **2**, warburganal **1**, muzigadial **80**, and isotadeonal **3**. The results of several bioassays are gathered in table 1.5.[11,24,26,63-66]

Polygodial **2** proved to be the most potent antifungal compound tested. It killed the cells of *S. cerevisiae* within ten minutes when treated with a fungicidal concentration of 50 μg/ml.[65] The related synthetic compounds **a** and **b** (see figure 1.12) were also tested, but they were devoid of activity.

Pereniporin A **69**, a metabolite of *Perenniporia medullaepanis*, showed a remarkable effect on the growth of *B. subtilis* (MIC 6.25 μg/ml) but it was inactive against Gram-negative bacteria (MIC > 100 μg/ml).[50] Cinnamolide **10** was active against *T. rubrum* (MIC > 20 μg/ml), *T. menthagrophytes* (MIC < 10 μg/ml), and *M. gypseum* (MIC 20 μg/ml).[14b]

Table 1.5 Antimicrobial activity of drimanic dialdehydes

Microorganisms tested	MIC (μg/ml)			
	Polygodial (2)	Warburganal (1)	Muzigadial (80)	Isotadeonal (3)
Staphylococcus aureus	> 100	> 100	> 100	> 100[1])
Escherichia coli	> 100[1])	> 100	> 100	> 100[1])
Pseudomonas aeruginosa	> 100	> 100	> 100	> 100[1])
Saccharomyces cerevisiae	0.78	3.13	1.56	> 100
Hansenula anomala	1.56	12.5	25	> 100
Candida utilis	1.56	3.13	3.13	> 100
Sclerotinia libertiana	1.56	3.13	3.13	> 100
Mucor mucedo	6.25	25	25	> 100
Rhizopus chinensis	12.5	100	100	> 100
Aspergillus niger	25	50	50	> 100
Penicillium crustosum	25	50	50	> 100
Trichophyton mentagrophytes		2	3	> 100
Bacillus subtilis	> 100[1])	> 100	> 100	> 100

[1]) An earlier research stated a somewhat lower value for the minimum inhibitory concentration.[26]

Figure 1.12

a **b**

1.3.2 Plant-growth regulatory activity

A few drimanes were examined for plant-growth regulatory properties. Polygodial **2** completely inhibited germination of rice in husk at a concentration of 100 ppm. [29,33,34] It also inhibited the root elongation of rice plants at a concentration of 100 ppm, but at a concentration of less than 25 ppm a dramatic promotion of root elongation was observed.[33,34] Rice seed (*Oryza sativa*) germination was also inhibited by cryptoporic acid A **48**, which produces the characteristic bitterness of the fungus *Cryptoporous volvatus*, at a 200 ppm concentration.[45a] Polygonal **78** is also active but at a much higher

concentration of 500 ppm.[29] The influence of drimenol **54** and confertifolin **17** was investigated on cuttings of *Tradescantia virginiana* L. *f. albiflora* B. with regard to elongation growth and the increase, in dry weight, of adventitious roots.[67,68] A 10^{-7} molar solution of drimenol **54** proved as active as indole-3-acetic acid (auxin) or N^6-furfuryladenine (kinetin). Confertifolin **17** showed a somewhat higher production and elongation of the roots, but it was not significant compared with exogenous auxin or kinetin. The root elongation of lettuce was completely inhibited by pereniporin A **69** at 100 ppm.[50] Altiloxin A **65** and B **66** also had little effect on the root elongation of lettuce.[51] The root production of asparagus on the other hand was diminished by 50 percent at a concentration of 10 ppm.[51] The germination of wheat seed (*Triticum aestivum* var. Norman, Graminaceae) was only slightly reduced by polygodial **2** and warburganal **1** at a concentration of 0.1%. A higher concentration improved the inhibition but the germinated seeds had twisted leaves instead of normal ones.[69]

1.3.3 Cytotoxic activity

Some drimane-type sesquiterpenes showed cytotoxicity in anti-cancer screens. Cinnamodial **5** and capsicodendrin **9**, a tetrameric conjugate of cinnamodial, had an ED_{50} of 2.2, and 2.9 μg/ml, respectively, in the P-388 lymphocytic leukemia test system *in vitro*. Cinnamosmolide **11** possessed an ED_{50} of 1.2 μg/ml in the Eagle's 9KB carcinoma of the nasopharynx cell culture system. However, these compounds were devoid of *in vivo* activity in the P-388 test system.[18] The drimanic dialdehyde warburganal **1** was active at a concentration of 0.01 μg/ml against KB.[28] The metabolites of *Perenniporia medullaepanis*, pereniporin A **69**, and B **13** were cytotoxic for Friend leukemia cells (F5-5) at 130, and 3.91 μg/ml, respectively, in the bioassay reported by Morioka.[70]
As part of a general attempt to study structure-activity relationships for unsaturated dialdehydes from natural sources several compounds were investigated in the Salmonella-microsome assay (strains TA 98, TA 2637 and TA 100). Polygodial **2** and isotadeonal **3** showed no mutagenic activity at the highest *non*-toxic concentration. Unfortunately other drimanic compounds were not tested.[71]

1.3.4 Taste, skin-irritant properties and anticomplemental activity

The leaves of *Warburgia* species are sometimes used locally as spices in food in East Africa.[1c,d] The fruit of *Drimys lanceolata* are said to have been used as a substitute for pepper in Tasmania.[72] In Japan the pungent hot tasting *tade-jiru* is made from squeezed *Polygonum hydropiper* L. leaves.[66] Some liverworts are also known for this pungency.[33,36] It turned out that the drimanic aldehydes polygodial **2**, warburganal **1**, muzigadial **80**, cinnamodial **5**, and polygonal **78**, a *nor*-drimane, were responsible for

this phenomenon.[28,73] The *nor*-drimane is fairly weak in comparison with the other compounds.[29] The bitterness of the fungus *Cryptoporous volvatus* is caused by cryptoporic acid A **49**, an albicanylether of isocitric acid.[45a]

Polygodial **2** has been reported on several occasions to display skin irritant properties.[23,30,36] When guinea pigs were sensitized to polygodial **2** by using intradermal injections in Freund's[74] complete adjuvant they showed a high response when the skin was treated with polygodial **2**, the primary sensitizer. Moreover, related compounds, *e.g.*, warburganal **1**, having the same configuration, also showed an allergic contact dermatitis (ACD) and it was observed that the reaction was halved when a racemic mixture of warburganal was used, so the allergenic response was stereospecific to enantiomers.[75]

Several constituents of *P. hydropiper* L. leaves and seeds were tested for their anticomplemental properties. Polygodial **2**, and polygonic acid **4** showed an IC_{50} of 10 μg/ml, and 250 μg/ml, respectively. It is surprising that the usually active drimanes, like warburganal **1**, and muzigadial **80**, showed no activity.[27]

1.3.5 Piscicidal and molluscicidal properties

Muzigadial **80** and warburganal **1** were tested as potential helicocides (snail-killers) because the extract of the bark of *Warburgia ugandensis* has been known for some time to have molluscicidal activity. A simple snail test was chosen because it could give a lead to agents useful for controlling the dangerous schistosomes and bilharzia.[76] *Biomphalaria pfeifferi* and *B. glabratus* are killed within two hours by a 5 ppm solution and *Lymnaca natalensis* is killed within two hours by a 10 ppm solution of these two compounds.[77] Treatment of killie fish, *Oryzia latipes*, with polygodial **2** at 0.4 ppm killed them within 30 minutes.[33,69] After an injection of 2 mg of polygodial **2** into the hepatopancreas of the nudibranch *Dendrodoris limbata* suffering of the animal was evident and death occurred between 3 and 16 hours.[52c]

1.3.6 Antifeedant activity

The insect antifeedant activity of the drimanes has been reviewed recently and will not be repeated here in full detail.[78] Seed treatment with appropriate chemicals to protect crops against pests is preferred to foliar or soil treatments as it is generally cheaper than soil application and, since the pesticide is confined to the small area where it is needed, it has less effect on other soil organisms. For this purpose polygodial **2** was used in laboratory and field tests to control slugs (*Deroceras reticulatum*) and wheat bulb flies (*Delia coarctata*) in winter wheat,[79,80] where its effect was marginal on clay loam soil but obvious on peaty loam soil though still inferior to commercial pesticides. It showed no toxicity towards slugs.

Nudibranchs, softbodied and apparently unprotected molluscs, employ some drimanes as defensive chemicals to escape from predators. These drimanes are often derived from a dietary source predominantly, if not exclusively, of sponges. However, the biosynthetic ability of a nudibranch to elaborate its own chemical defense has been shown by incorporation experiments with [2-^{14}C]mevalonic acid, dibenzylethylenediamine salt.[56c] On injection into the hepatopancreas, it gave rise to labelled polygodial **2** and labelled sesquiterpenoid esters **32**.[52d,53] The latter should be regarded as products of further metabolism of polygodial **2** as a result of a detoxication process.[52d]

Polygodial **2**, and olepupuane **30** inhibited feeding of the Pacific damsel fish (*Dascyllus aruanus*) with ED_{50}'s of 15-20 μg/mg of pellet.[54] Polygodial **2** also inhibited feeding of the marine fish *Chromis chromis* and the fresh water fish *Carassius carassius* (ED_{50} 10 μg/mg of pellet).[52b] The glyceride **57**, found in some British Columbia nudibranchs was active against the tide pool sculpin *Oligocottus maculosus* at a level of 18 μg/mg of pellet.[56c] Albicanyl acetate **47**, and 6ß-acetoxyolepupuane **31** showed antifeedant properties in a standard goldfish (*Carassius auratus*) bioassay with ED_{50} of 5-10 μg/mg of pellet.[56b]

On Chinese cabbage leaves, treated with polygodial **2** or warburganal **1**, at a concentration of 0.05%, *ca.* 125 ppm compound/leaf, few *Myzus persicae* settled and few nymphs were deposited.[69,81] The transmission of potato virus Y, beet yellow virus, and barley yellow dwarf virus was therefore reduced, even by aphid variants highly resistant to insecticides.[82,83] Field trials with wintersown barley, treated three times with polygodial **2** at 50 g/ha in early autumn showed diminished damage caused by BYD virus and an improved yield of 136%.

Warburganal **1**, and muzigadial **80** inhibited the feeding of larvae of two species of African armyworm, the monophagous *Spodoptera exempta* and the polyphagous *S. littoralis* at a concentration of 0.1 ppm in a regular leaf disk method.[77] Polygodial **2**, and ugandensidial **5** were also antifeedants for these insects but less active.[1c,17,84] The drimane dialdehydes turned out not to be uniformly active against all insects but showed some species specificity. Activity was also observed against *S. frugiperda, Heliothis armigera*, and *H. virescens*.[69,85] Polygodial **2** was active against diamond moth larvae down to 0.1% and it inhibited food intake by fifth-instar larvae of *Pieris brassicae* at a concentration of 200 ppm.[86]

1.3.7 Phytotoxicity

Some drimanes are potentially valuable crop protecting agents due to their aphid antifeedant activity. For that reason polygodial **2**, warburganal **1**, and cinnamolide **10** were further investigated because primary studies had suggested a possible phytotoxicity.[82b] When treated with a concentration of 0.1% the leaves of Chinese cabbage

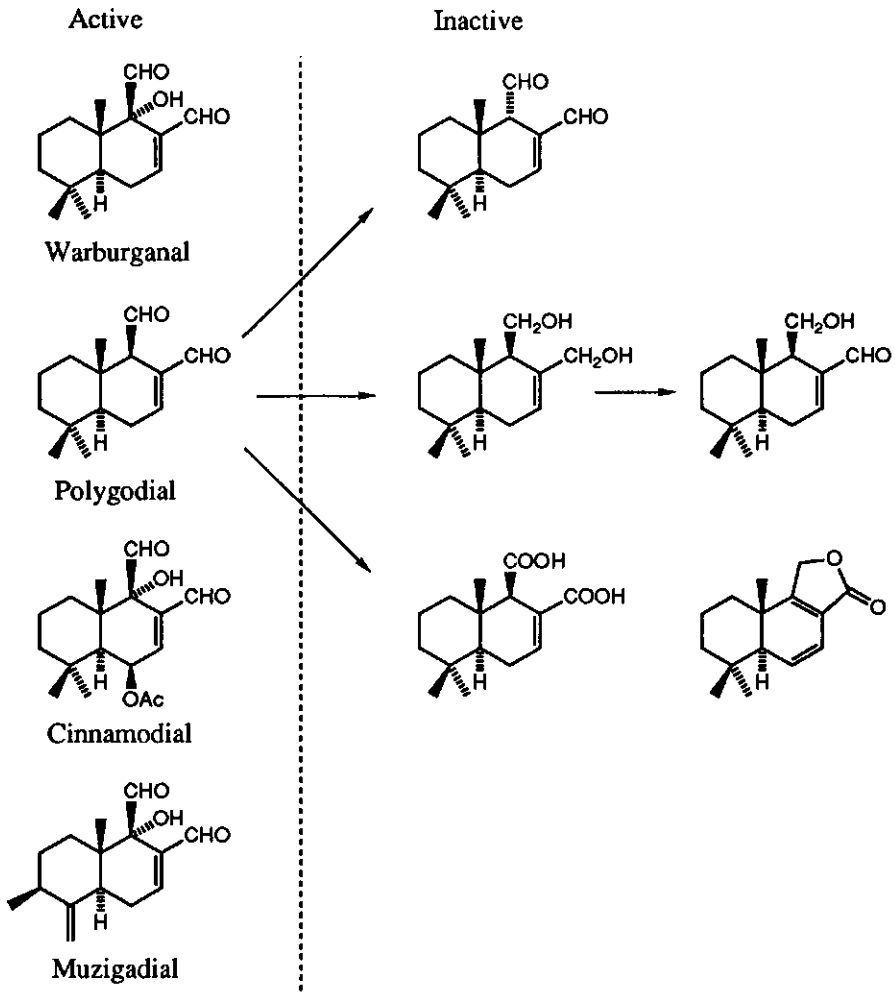
(*Brassica campestris* var. Chinensis) showed slight pitting over the entire surface with some dry patches. Potato leaves (*Solanum tuberosum*) were scorched and yellowed, but the leaves of sugar beet (*Beta vulgaris*) were unharmed.[69] The earlier claim of phytotoxicity for *unnatural* polygodial was not confirmed so the racemates, which are more readily available by synthesis, can be employed in the development of *drimane* type antifeedants.[82b] Altiloxin A **65**, and B **66**, isolated from the culture filtrate of *Phoma asparagi* Sacc., are phytotoxic metabolites responsible for the stem blight disease on asparagus.[51]

1.3.8 Mode of action of biologically active drimanes

Since the drimanic dialdehydes are among the most active drimanes they are frequently used to investigate the mode of action at the molecular level. *Ma* has studied the influence of warburganal **1** on the receptor response of *Spodoptera exempta* to the stimulant activity of sucrose- or *meso*-inositol solutions.[87] Brief treatment with warburganal **1** greatly reduced the excitability of the receptors, but when it was mixed with L-cysteine or dithiothreitol no decrease in excitability was observed.[17] *Ma* suggested that the enal moiety of warburganal **1** may act as an -SH acceptor. Thiol groups have been detected in the chemoreceptor membranes of insects, thus an interference of warburganal **1** with the stimulus transduction process in the chemoreceptor cell seemed likely.[88] Additional evidence for this hypothesis was derived from the fact that the mercaptide forming organomercurial, in *p*-(chloromercuri)benzoate, gave a qualitatively similar reaction to warburganal.[63] Further investigations revealed that the active antifeedants all taste hot and spicy to the human tongue whereas all inactive derivatives are devoid of hot taste (see figure 1.13).[1c,73,77]

Figure 1.13

Structure and antifeedant activity correlation

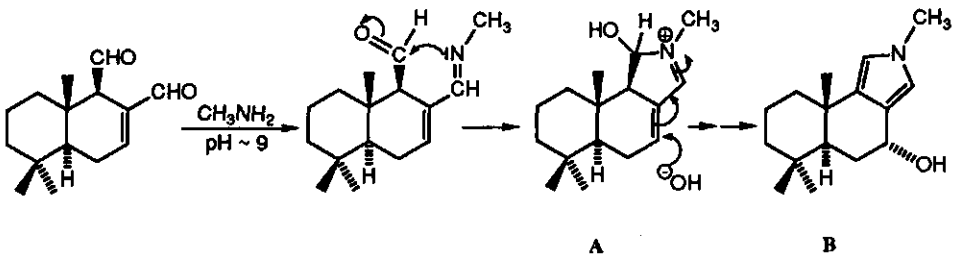


From figure 1.13 it can be concluded that an enal and a 9ß-aldehyde group are required for activity. Mild treatment with base inverted the 9ß-aldehyde into a 9α-aldehyde group with concomitant loss of activity and hotness. The enhanced activity of the 9α-hydroxy compounds suggested an involvement of this functionality with the best fit of the molecule on the sensilla. Similar conditions were found by Sterner *et al.* in a structure-activity relationship study with regard to the mutagenicity of unsaturated dialdehydes.[71]

The antifungal activity of polygodial **2** was studied by Taguchi *et al.* The yeast *Saccharomyces cerevisiae* was the most susceptible organism among those tested, so the mode of action on this yeast was carefully investigated. A variety of physiological effects due to polygodial **2**, *e.g.*, inhibition of growth, alcohol fermentation, and papain activity appeared to result from its irreversible reaction with the sulfhydryl groups.[63,64] However, in a biomimetic reaction, the inactive *epi*-polygodial **3** also had a high reactivity with the sulfhydryl group of L-cysteine.

Based on kinetic data, Sodano *et al.* proposed that the biological activity of the enal aldehydes is primarily related to their ability to form adducts with amino groups rather than sulfhydryl groups on the receptors.[89] Similar reactivity was observed for both polygodial **2** and *epi*-polygodial **3** in a reaction with thiols, while the reaction with substrates possessing both amino and sulfhydryl groups was dependent upon the stereochemistry of the C-9 aldehyde group, the 9ß-isomer exhibiting the higher reactivity. With amines or amino acids a remarkable difference in reactivity was observed, the 9α-isomer was practically unreactive. They were able, under biomimetic conditions, to obtain NMR evidence for their proposed mechanism (see figure 1.14).[90]

Figure 1.14

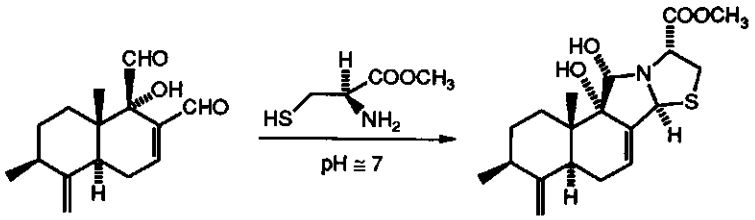


After reaction with a model amine, *i.e.*, methylamine, one single product, the pyrrole B, was observed which, because of its instability was only examined by NMR spectroscopy. The inactive 9α-isomer cannot form intermediates of type A due to the greater distance between the C-9 axial aldehyde and the enal moiety. The distance, measured on Dreiding stereomodels was in agreement with this supposition.[84b] Several other suitable enal aldehydes were also investigated and gave rise to the same observations.[91]

The biological mechanism of hot tasting and antifeedant activity of 1,4- dialdehydes may also result from covalent binding to primary amino groups [84b] of the chemoreceptive sites rather than from Michael addition of membrane sulfhydryl groups,[87] even though both are available at the receptor site.[93] A model study of the reaction of muzigadial **80**

with L-cysteine methyl ester *in vitro* is in agreement with this (see figure 1.15).[92]
Cell permeability studies revealed that polygodial **2** preferentially damaged the cell membrane and caused an appreciable amount of leakage
proteins and saccharides. A decrease in cellular dry weight was also observed. The permeability changes were supported by microscopic evidence; the structural integrity of the cell membrane was markedly disrupted by polygodial.[65,66,94]
However, the polygodial binding site in the cell membrane is not yet established.

Figure 1.15



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2 SYNTHETIC STUDIES ON DRIMANES. A LITERATURE SURVEY

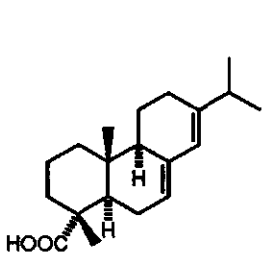
2.1 Introduction

The antifeedant activity of some drimane sesquiterpenes has greatly stimulated the development of general synthetic routes to this class of compounds. Total synthesis is a necessity since, in most cases, only minute amounts of material are available from natural sources. During these synthetic approaches towards drimanes many intermediates have been produced with a drimane-like structure. This has provided knowledge about the functional groups responsible for the activity at a molecular level and may well lead to the discovery of simple biologically active compounds with possibilities for commercial development. Numerous syntheses have appeared within the last twenty years and a rough division can be based on the starting materials and/or reaction types.[1] Synthesis has been accomplished by the transformation of other natural products or by total synthesis; whereby the decalin skeleton has been formed by biomimetic polyolefin cyclizations, Robinson annulations, Diels-Alder cycloadditions, or a metathesis transannular ene sequence.

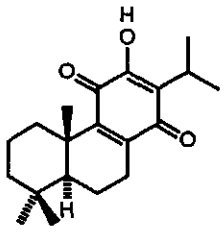
2.2 Synthesis of drimanes by transformations of natural products

Among the published total syntheses of drimanes very few have led to optically active compounds unless the starting material is a product from the chiral pool. The natural products used are abietic acid **83**, royleanone **84**, glycyrrhetinic acid **85**, methyl-14,15-dinor-7-labden-13-oxo-17-oate **86**, levopimaric acid **87**, manool **88**, confertifolin **17**, and drimenol **54** (for structures see figure 2.1).
In most of these compounds superfluous carbon atoms are removed *via* ozonolysis at a suitable stage of the total synthesis.

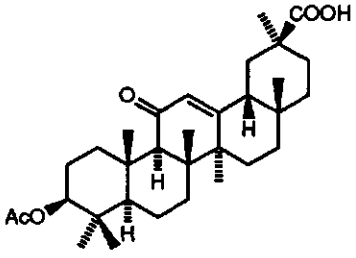
Figure 2.1



83
Abietic acid

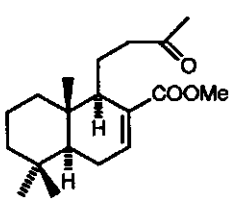


84
Royleanone

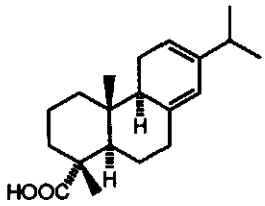


85
Glycyrrhetinic acid

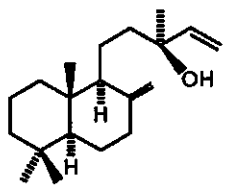
Figure 2.1 (cont.)



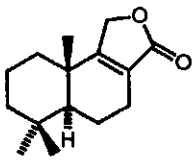
86



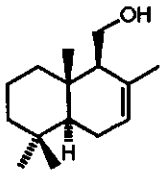
87
Levopimaric acid



88
Manool

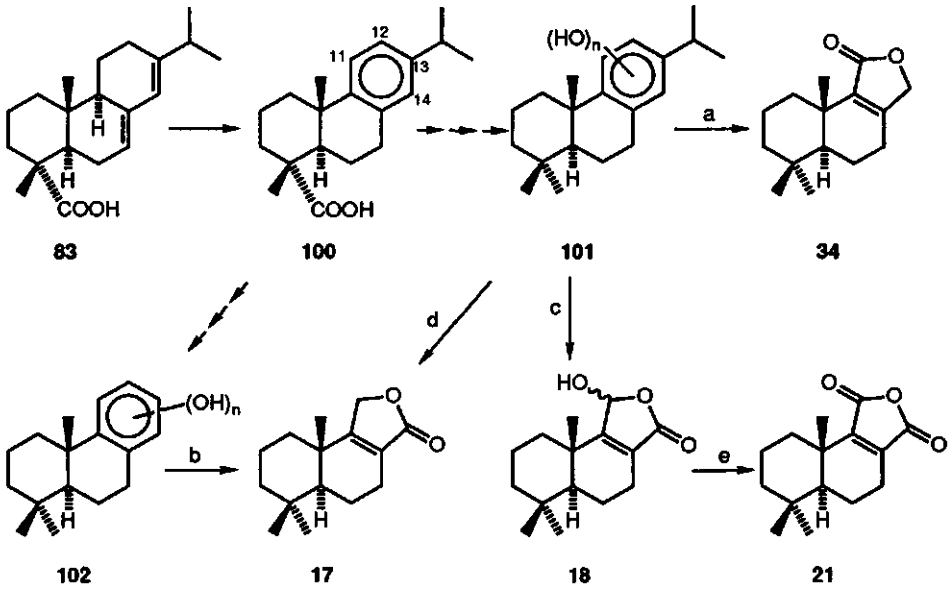


17
Confertifolin



54
Drimenol

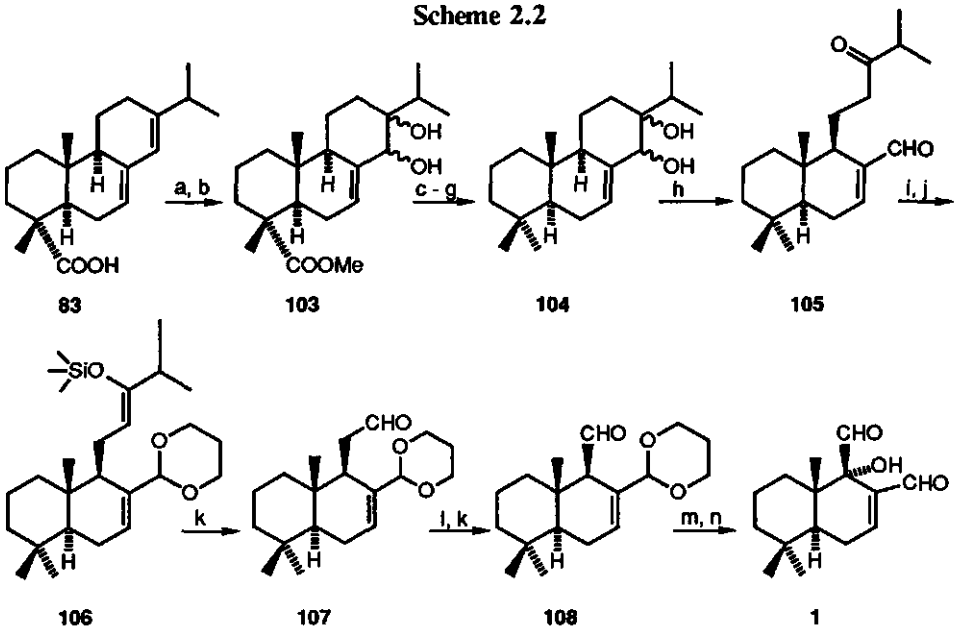
Scheme 2.1



Reagents: *a*, O_3, $NaBH_4$ (11,12-dihydroxy compound); *b*, O_3, $NaBH_4$ (13,14-dihydroxy compound); *c*, O_3, Na_2SO_3 (14-hydroxy compound); *d*, O_3, $NaBH_4$; *e*, CrO_3.

In the course of their studies on the chemical conversion of (-)-abietic acid to biologically active compounds, Akita and Oishi achieved short but low yielding syntheses for several drimanic sesquiterpenes (see scheme 2.1).[2] (-)-Abietic acid **83** was converted into the phenolic dehydroabietane derivatives **101** and **102** [3] which were cleaved by ozone.[4] The mode of cleavage was determined by the substitution pattern of the hydroxyl group(s) in the aromatic ring. Subsequent reduction with the appropriate reagents afforded the drimanes (+)-isodrimenin **34**, (+)-confertifolin **17**, (+)-valdiviolide **18**, and (+)-winterin **21**.

Scheme 2.2



83 **103** **104** **105**

106 **107** **108** **1**

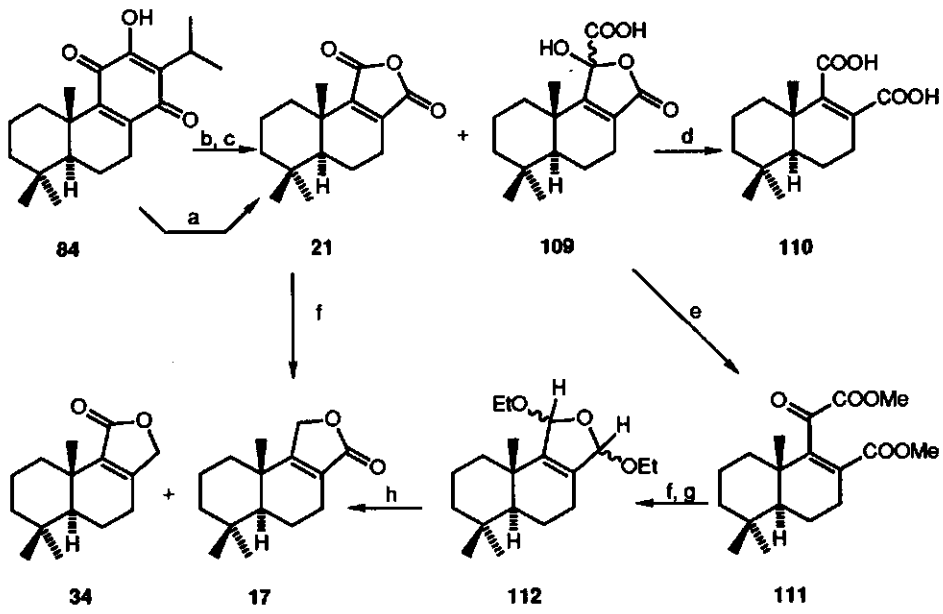
Reagents: *a*, OsO_4, Me_3NO; *b*, CH_2N_2; *c*, DHP, H^+; *d*, $LiAlH_4$; *e*, PCC; *f*, H_2O, H^+; *g*, H_2NNH_2, KOH; *h*, $Pb(OAc)_4$; *i*, trimethylene glycol, H^+; *j*, LDA, HMPA, TMSiCl; *k*, O_3, Me_2S; *l*, LDA, TMSiCl; *m*, LDA, MoO_5.HMPA. pyr.; *n*, H_2O, H^+.

Ohno *et al.* reported the first synthesis of natural (-)-warburganal **1** also starting from (-)-abietic acid **83** by a 15 steps sequence with an overall yield of 8% (see scheme 2.2).[5] The regioselective hydroxylation of the double bond of the C-ring was significantly improved to 86% when a catalytic amount of osmium tetroxide and trimethylamine-*N*-oxide as co-oxidant was used. The acid function was esterified and the required *gem*-dimethyl group was introduced in a straightforward manner in 50% yield. Oxidative cleavage of the diol with lead tetraacetate afforded the keto aldehyde **105**.

The aldehyde function was selectively protected as its acetal. The requisite C-9 aldehyde group was introduced by degradation of the C-9 substituent *via* the successive ozonolysis of two silyl enol ethers. The enolate of aldehyde **108** was then oxidized with the MoO_5. HMPA.pyr. complex and removal of the protective group afforded (-)-warburganal **1**.

The abietane royleanone **84**, easily available from the roots of several *Salvia* species, was used as the starting material for the synthesis of (+)-winterin **21**, (+)-isodrimenin **34**, and (+)-confertifolin **17** (see scheme 2.3).[6]
Several intermediates, previously used in the synthesis of (±)-warburganal **1** and (±)-polygodial **2**, were also produced. A total decomposition of royleanone **84** was observed with a variety of oxidation methods, *i.e.*, potassium permanganate, ozonolysis, *Jones'* reagent, etc., but *Hooker's* oxidation [7] followed by treatment with periodic acid produced (+)-winterin **21**, although in a poor yield of 10%. In contrast, the ozonolysis[2] of 12-*O*-methylroyleanone gave a clean reaction-product from which **109** was isolated in 80% yield together with a 10% yield of (+)-winterin **21**.

Scheme 2.3

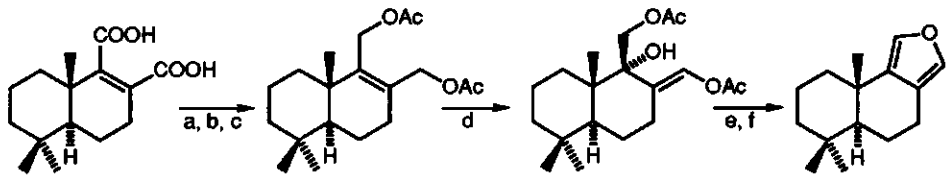


Reagents: *a*, H_2O_2, Na_2CO_3, H_2O, then EtOH, H_5IO_6; *b*, dimethyl sulfate, K_2CO_3; *c*, O_3, CH_2Cl_2, then H_2O_2, NaOH; *d*, $Pb(OAc)_4$; *e*, CH_2N_2; *f*, $LiAlH_4$; *g*, H_5IO_6, EtOH; *h*, H_2O, H^+, acetone.

Treatment of **109** with lead tetraacetate in benzene led to the drimane derivative **110**, used in the synthesis of other drimanes. Keto diester **111** was reduced to a triol which was cleaved by periodic acid in ethanol to a mixture of diacetals **112**. Hydrolysis of this mixture led to (+)-confertifolin **17** (67% yield) and (+)-isodrimenin **34** (3% yield). When **21** was reduced with lithium aluminum hydride, a mixture of **17** and **34** was also obtained but with a reversed product ratio of 1:9.

The drimane (+)-euryfuran **33** was synthesized in 40% overall yield starting from the diacid **110** as described in scheme 2.4 [8]

Scheme 2.4



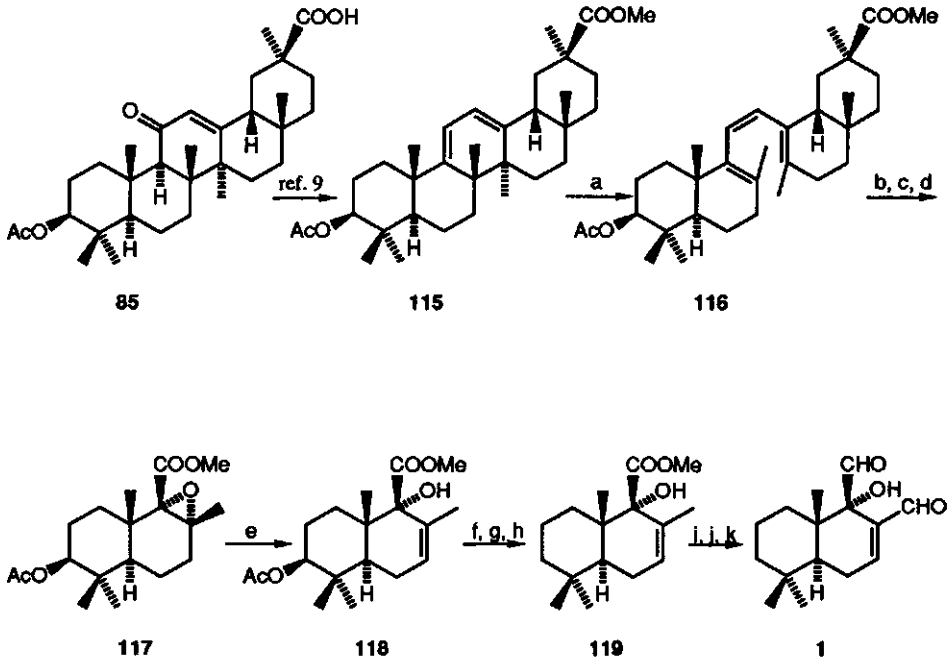
110 **113** **114** **33**

Reagents: *a*, CH_2N_2; *b*, $LiAlH_4$; *c*, Ac_2O, pyr.; *d*, hν, O_2, Bengal rose, then Na_2SO_3; *e*, *p*-TsOH, silica gel; *f*, LiOH, then H_2O, H^+.

Photo-oxidation of the diacetate **113** and subsequent reduction of the oxygenated intermediate led to the 9α-hydroxy diacetate **114**. Treatment with *p*-toluenesulfonic acid in the presence of silica gel followed by hydrolysis with lithium hydroxide and acidification gave (+)-euryfuran **33**.

Glycerrhetinic acid **85** is easily converted [9] in good yield into the diene **115**, which was used by Falck *et al.*[10] for the synthesis of (-)-warburganal **1** in an overall yield of 14% (see scheme 2.5).

Scheme 2.5

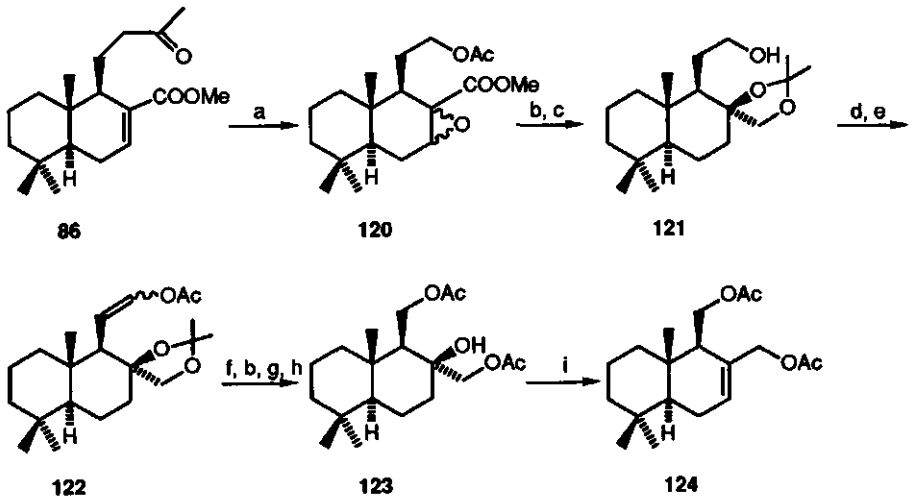


Reagents: *a*, hν, EtOH; *b*, *m*-CPBA; *c*, O_3, Me_2S; *d*, CH_2N_2; *e*, HI, EtOH; *f*, NaOMe, MeOH; *g*, PhOC(S)Cl, pyr.; *h*, Bu_3SnH; *i*, SeO_2; *j*, $LiAlH_4$; *k*, DMSO, oxalyl chloride, Et_3N.

Irradiation of **115** furnished the triene **116** which after epoxidation, exhaustive ozonolysis, and esterification gave the desired chiral building block **117**. The epoxide **117** was readily isomerized with hydroiodic acid to the allylic alcohol **118**. The acetoxy group was removed by methanolysis and *Barton's* reduction procedure. Consecutive allylic oxidation, ester reduction, and *Swern* oxidation of the primary alcohols yielded (-)-warburganal **1**.

Methyl-14,15-dinor-7-labden-13-oxo-17-oate **86** was obtained from the hexane extract of *Halimium viscosum* and transformed into the diacetoxy derivative **124**, already shown to be a pivotal compound in the synthesis of (-)-polygodial **2** and (-)-warburganal **1** [11] (see scheme 2.6).

Scheme 2.6

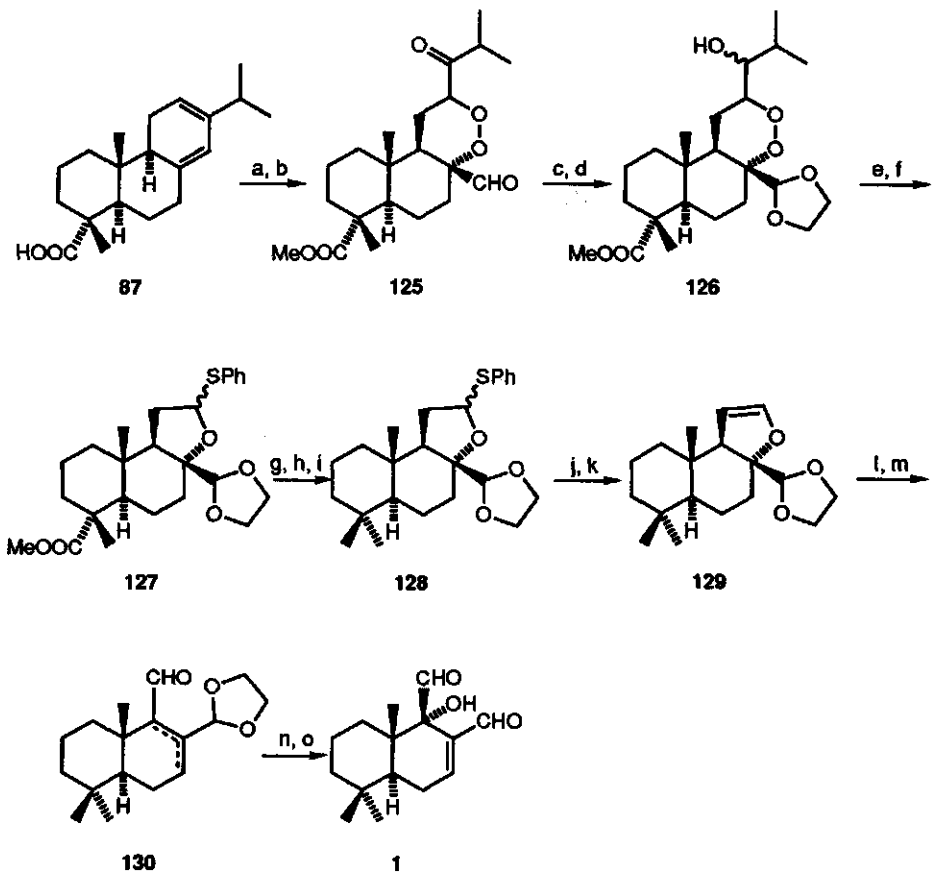


Reagents: *a*, CH_2N_2; *m*-CPBA; *b*, $LiAlH_4$; *c*, DMP, *p*-TsOH; *d*, CrO_3, pyr.; *e*, Ac_2O, Et_3N, DMAP; *f*, O_3, Me_2S; *g*, MeOH, *p*-TsOH; *h*, Ac_2O, pyr.; *i*, $POCl_3$, pyr.

The dinor-labdenoate **86** was oxidized with *m*-CPBA over long periods (up to 15 days) to yield **120** as a mixture of epoxides. A triol was obtained after reduction of **120** and its 1,2-glycol protected. The sidechain with the remaining hydroxy group was degraded *via* ozonolysis of the enol acetate **122**. Finally, dehydration of **123** with phosphorus oxychloride in pyridine led to **124** in an overall yield of 8%.[12]

A major pine resin acid is levopimaric acid **87**. Its isolation from the inexpensive oleorosin is straightforward [13] and thus it is an attractive chiral starting material. Ayer and Talamas used this acid for a synthesis of (-)-warburganal **1** in an overall yield of 2.7% in 15 steps (see scheme 2.7) [14].

Scheme 2.7



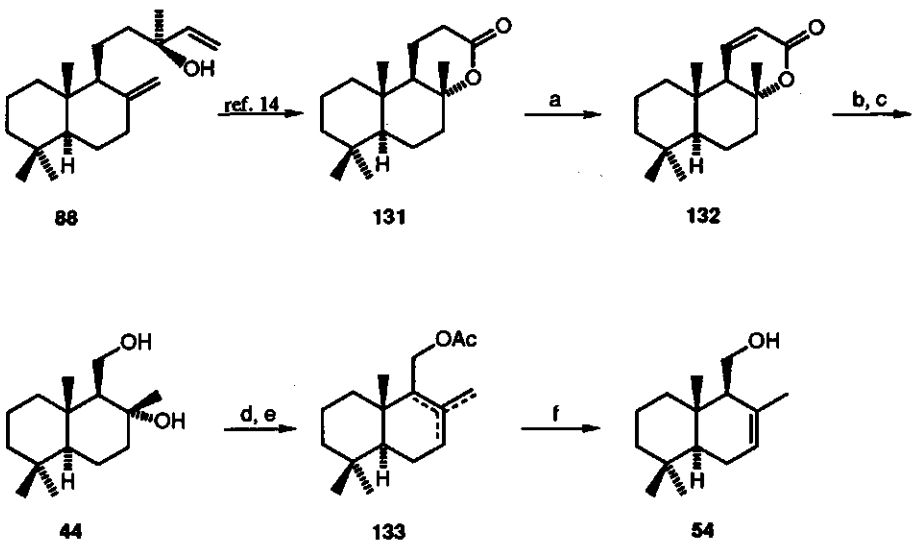
Reagents: *a*, hν, O_2, rose Bengal; *b*, O_3, Me_2S; *c*, ethylene glycol, *p*-TsOH; *d*, $NaBH_4$; *e*, NaOMe, MeOH; *f*, PhSH, TFA; *g*, $LiAlH_4$; *h*, *i*-$PrSO_2Cl$; *i*, $LiEt_3BH$; *j*, *m*-CPBA; *k*, $P(OMe)_3$, xylene, reflux; *l*, O_3, EtOAc, then $P(OMe)_3$; *m*, DBU; *n*, KH, THF, then MoO_5.HMPA.pyr.; *o*, *p*-TsOH, acetone.

Photo-oxygenation followed by ozonolysis was used to oxidize the diene moiety in **87**. An elegant base induced fragmentation of the alcohols **126** led to the removal of four of the unwanted carbon atoms. Reaction of the thus obtained intermediate with thiophenol gave a mixture of the hemithioacetals **127**. The transformation of the C-4 carbomethoxyl group into a methyl group was modified and performed in a modestly improved yield of 65%. Oxidation of the hemithioacetals and subsequent heating gave the enol ether **129**, permitting degradation *via* ozonolysis.The enolate of **130**, formed with potassium

hydride in tetrahydrofuran, was oxidized with the MoO_5.HMPA.pyr complex. Removal of the protecting group with acid in acetone gave (-)-warburganal **1**.

The degradation of the readily available (+)-manool **88** provided an entry to drimanic sesquiterpenes as depicted in schemes 2.8, and 2.9.
Pelletier *et al.*[15] transformed **88** into (+)-ambreinolide **131** [16] and dehydrogenation with DDQ in boiling dioxane afforded now the double bond at C-11 in compound **132**, which on exhaustive ozonolysis and reduction with Red-Al gave rise to (+)-drimane-8,11-diol **44** in 34% yield.[16]

Scheme 2.8

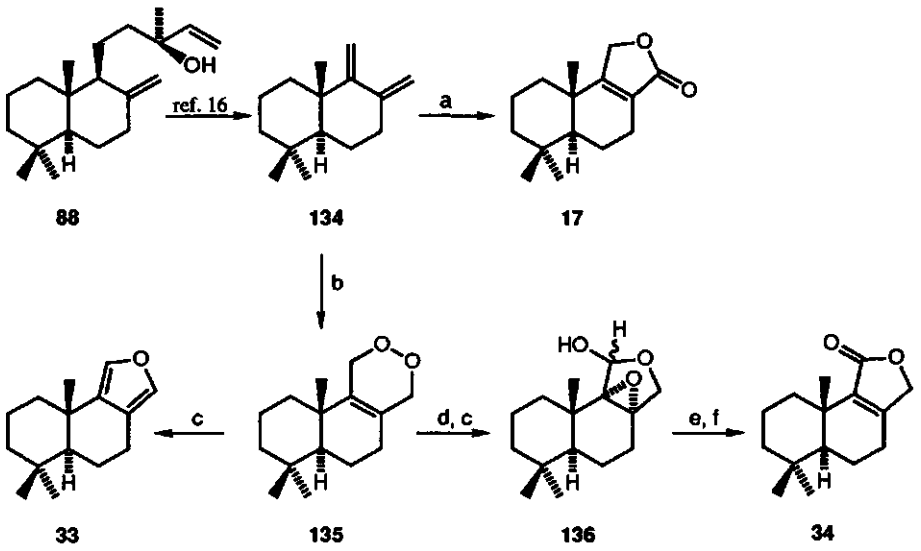


Reagents: *a*, DDQ, dioxane; *b*, O_3, CH_2Cl_2; *c*, Red-Al; *d*, Ac_2O, pyr.; *e*, $POCl_3$, pyr.; *f*, KOH, MeOH.

Dehydration after protection of the primary alcohol function of **44** afforded a mixture of unsaturated acetates **133**. Hydrolysis with base gave a mixture of alcohols from which (-)-drimenol **54** was isolated in 40% yield.

The degradation of the sidechain of manool **88** *via* a Norrish type II cleavage to diene **134** was achieved by Nakano *et al.*[17] (see scheme 2.9).

Scheme 2.9

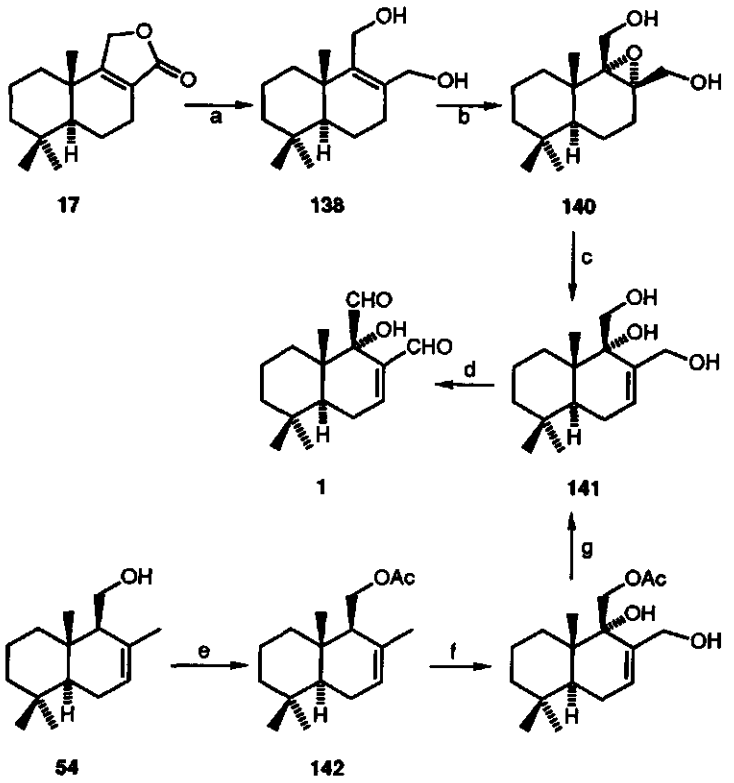


Reagents: *a*, hν, O_2, rose Bengal, CH_2Cl_2, MeOH; *b*, hν, O_2, *meso*-TPP, CCl_4; *c*, $FeSO_4$; *d*, *m*-CPBA; *e*, CrO_3, pyr.; *f*, $Fe(CO)_5$, DMF.

Photo-oxygenation of **134** in dichloromethane containing 5% methanol furnished (+)-confertifolin **17** in 20% yield and 36% of the unreacted diene **134**. When, however, the diene was irradiated in the presence of *meso*-tetraphenylporphine in carbon tetrachloride the endoperoxide **135** was isolated in 65% yield. This endoperoxide proved not to be an intermediate in the formation of **17** since it was unchanged under the above-mentioned irradation conditions. The endoperoxide **135** was, however, rearranged in good yield to (+)-euryfuran **33** by various reagents. When it was oxidized with *m*-CPBA, the epoxide could be rearranged to the epoxylactol **136**, which on oxidation followed by deoxygenation with pentacarbonyliron afforded (+)-isodrimenin **34** in 22% yield, based on manool.[18]

(+)-Confertifolin **17** and (-)-drimenol **54**, both isolated in large quantities from the bark of *Drimys winteri* Forst were obvious starting materials for the synthesis of (-)-warburganal **1** (see scheme 2.10).[21,22]

Scheme 2.10

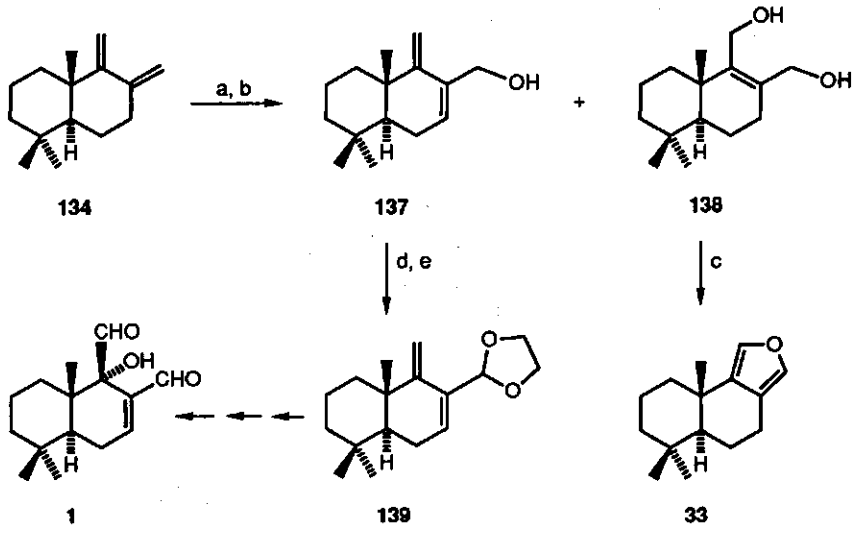


Reagents: *a*, $LiAlH_4$; *b*, *m*-CPBA; *c*, Et_2NLi; *d*, DMSO, TFAA; *e*, Ac_2O, pyr.; *f*, SeO_2; *g*, KOH, MeOH.

The diol **138** was epoxidized to a 7:3 mixture of α- and ß-epoxides from which the α-epoxide **140** could be separated in 65% yield. Treatment of **140** with lithium diethylamide led to the triol **141**, which afforded (-)-warburganal **1** on oxidation by the *Swern* procedure in 13% overall yield.[21] The same triol **141** was obtained starting from (-)-drimenol **54** as indicated in Scheme 2.10 in 28% overall yield.[22] The necessary allylic oxidation of **142** was improved later on by using a catalytic amount of selenium dioxide and a suitable co-oxidant.[23,24]

Oxidation of the diene **134** (see scheme 2.9) with thallium(III) acetate in acetic acid gave a mixture of acetates, which yielded the corresponding alcohols **137** and **138** in 14% and 17% respectively (see scheme 2.11).[19]

Scheme 2.11



Reagents: *a*, $Tl(OAc)_3$; *b*, K_2CO_3, MeOH; *c*, PCC; *d*, PDC; *e*, trimethylene glycol, *p*-TsOH, benzene.

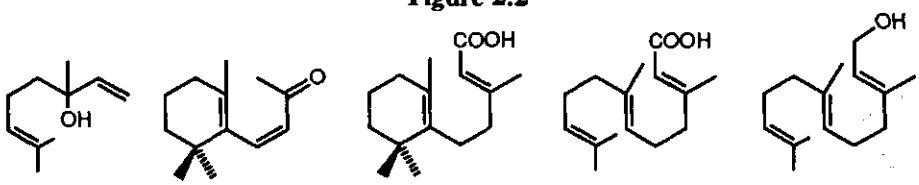
Oxidation of **137** and protection of the aldehyde function afforded **139**. This had been synthesized previously as its racemate and converted into warburganal **1**.[20]. (+)-Eury-furan **33** was obtained in 72% yield after oxidation of the unsaturated diol **138** with pyridinium chlorochromate.

2.3 Synthesis of drimanes by biomimetic polyolefin cyclizations

The biogenetically patterned cyclization of acyclic polyenes or polyene-epoxides has provided an elegant synthetic route to sesquiterpenes of the bicyclofarnesol class.[25-27] Because of its higher efficiency the epoxide cyclization route may prove advantageous even in the synthesis of the deoxy analogs.[27a]

Starting materials for the biomimetic polyolefin cyclizations were linalool **89**, ß-ionone **90**, *mono*-cyclofarnesic acid **91**, farnesic acid **92** and farnesol **93** (see figure 2.2).

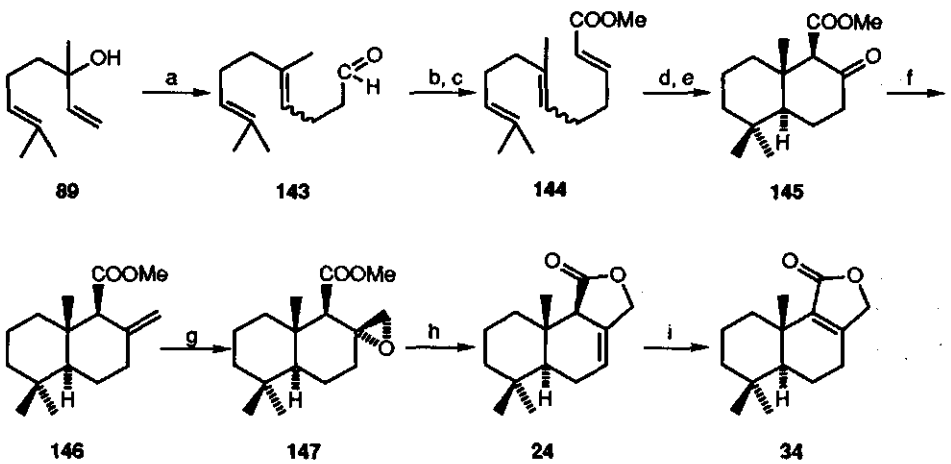
Figure 2.2



89 Linalool | **90** β-Ionone | **91** *mono* Cyclo-farnesic acid | **92** Farnesic acid | **93** Farnesol

Linalool **89** was used as starting material for the synthesis of ketoester **145** which was transformed into (±)-drimenin **24** and (±)-isodrimenin **34** as indicated in scheme 2.12.[28]

Scheme 2.12

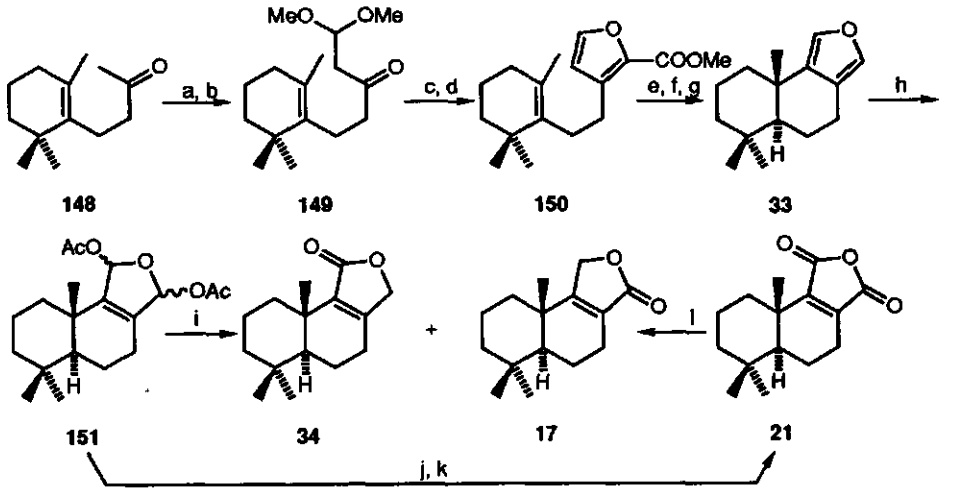


Reagents: *a*, Ethyl vinyl ether; *b*, malonic acid; *c*, MeOH, H^+; *d*, HCOOH, H_2SO_4; *e*, CrO_3; *f*, Ph_3PCH_3Br, $NaNH_2$, toluene; *g*, *m*-CPBA, CH_2Cl_2; *h*, *p*-TsOH; *i*, MeONa, MeOH.

Eschenmoser established that the *trans* configuration of the Δ^2 double bond in **144** was the only requirement for the production of compound **145**.[29] The ester **146** was also transformed into the (±)-acid, which could be resolved to its enantiomers *via* the diastereoisomeric salts with α-phenylethylamine in ethanol.[30,31]

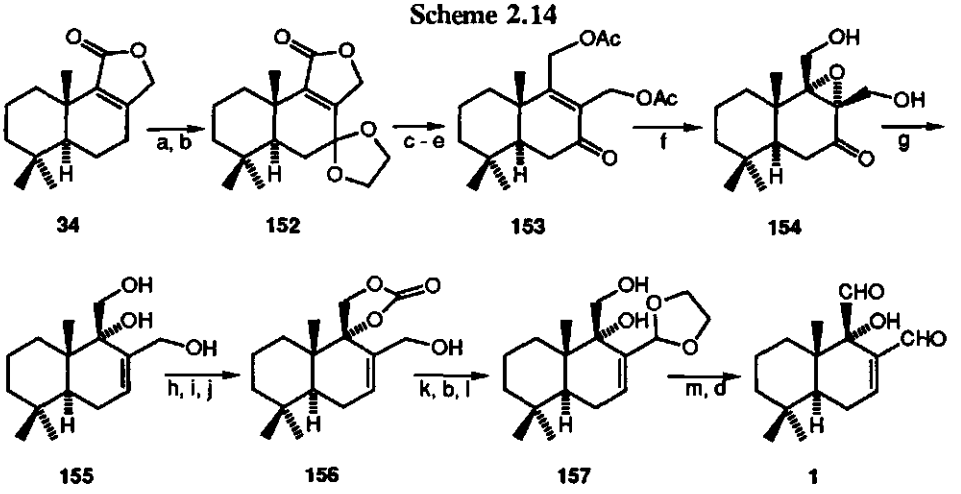
A large scale synthesis of (±)-confertifolin **17** and (±)-isodrimenin **34** was achieved starting from dihydro-ß-ionone **148**, which was obtained from ß-ionone **90** by partial reduction with Raney Ni (see scheme 2.13).[32]

Scheme 2.13



Reagents: *a*, NaOMe, HCOOEt; *b*, MeOH, pyr., HBr; *c*, $ClCH_2COOMe$; *d*, *p*-TsOH; *e*, $SnCl_4$, CH_2Cl_2; *f*, KOH; *g*, Cu, quinoline, Δ; *h*, $Pb(OAc)_4$; *i*, Δ, 170 °C; *j*, KOH, H_2O; *k*, CrO_3; *l*, $NaBH_4$.

Scheme 2.14

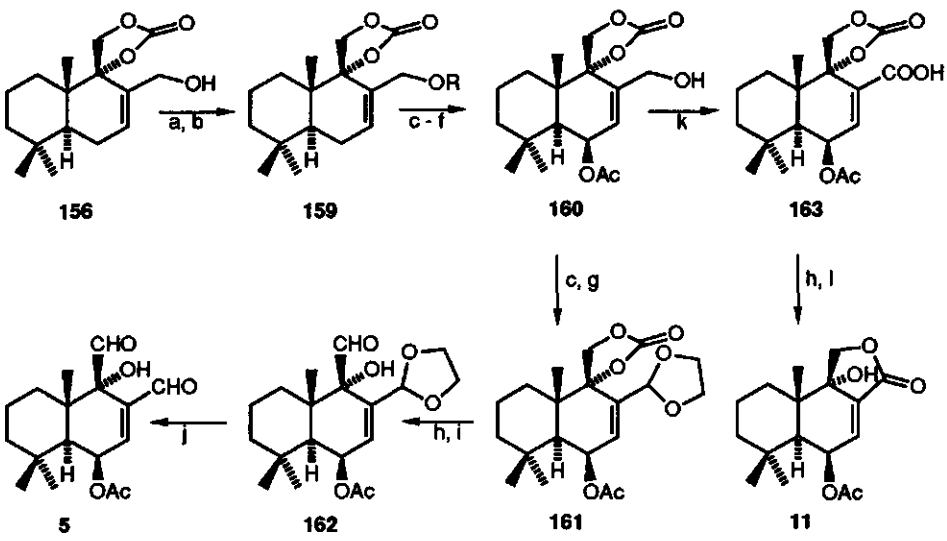


Reagents: *a*, CrO_3, HOAc; *b*, ethylene glycol, *p*-TsOH; *c*, $LiAlH_4$; *d*, H_2O, H^+; *e*, Ac_2O, pyr.; *f*, H_2O_2, NaOH; *g*, N_2H_4, HOAc; *h*, *t*-BDMSiCl, DMF; *i*, *N,N'*-carbonyldiimidazole; *j*, MeOH, H^+; *k*, CrO_3; *l*, NaOH; *m*, DMSO, DCC.

The cyclization was performed with the furanic ester **150** and after saponification and decarboxylation (±)-euryfuran **33** was obtained. Further transformations of the furan ring afforded (±)-confertifolin **17**, (±)-isodrimenin **34**, and (±)-winterin **21**.

The total synthesis of (±)-warburganal **1** was accomplished using the so prepared (±)-isodrimenin **34** as is shown in scheme 2.14.[28b,32,33] Allylic oxidation of isodrimenin **34** and protection of the resulting keto function gave **152**. The unsaturated diacetate **153** was obtained after reduction of the lactone moiety and acetylation of the diol. Epoxidation of **153** with hydrogen peroxide in sodium hydroxide solution gave exclusively the α-epoxide **154**, thus securing the correct stereochemistry at C-9. A *Wharton* rearrangement followed by a series of protection, deprotection, and oxidation reactions as indicated in scheme 2.14 finally gave (±)-warburganal **1** in an overall yield of 32% from (±)-isodrimenin and 9% from ß-ionone. Later it was shown (see Scheme 2.30) that the direct oxidation of the triol could also be achieved in a moderate yield.
The intermediate **156** was also used to synthesize (±)-cinnamodial **5** and (±)-cinnamosmolide **11** (see scheme 2.15).[34]

Scheme 2.15

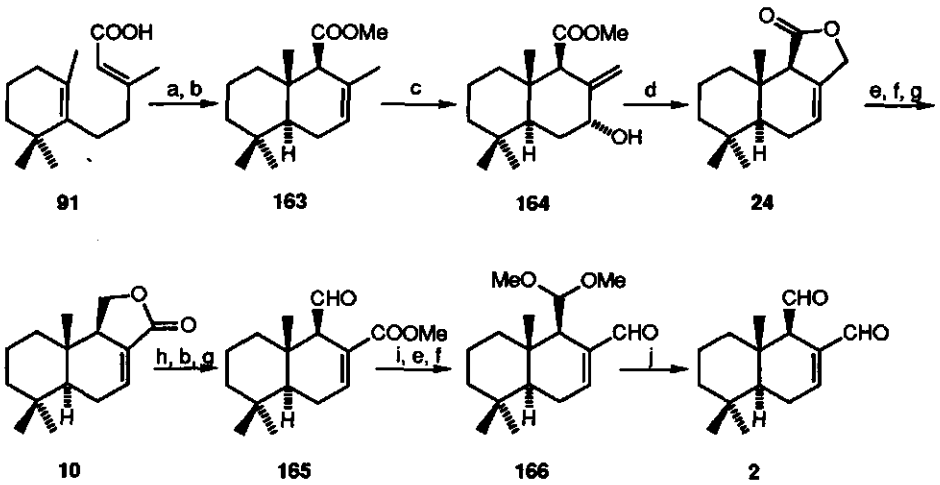


Reagents: *a*, MeOH, H^+; *b*, trichloroethoxycarbonylchloride, pyr.; *c*, CrO_3, HOAc; *d*, $Zn(BH_4)_2$; *e*, Ac_2O, pyr., DMAP; *f*, Zn, HOAc; *g*, ethylene glycol, *p*-TsOH; *h*, NaOH, H_2O; *i*, DMSO, pyr., TFA; *j*, *p*-TsOH, acetone; *k*, CrO_3, large excess.

The allylic alcohol in **156** was first protected as its trichloroethoxycarbonate **159** which allowed selective deprotection. The required acetate group in **160** was introduced *via* allylic oxidation followed by reduction and acetylation. (±)-Cinnamodial **5** was prepared from **160** as described for (±)-warburganal **1** in an overall yield of 14% (see Scheme 2.14). Oxidation of **160** with an excess of *Jones'* reagent afforded the acid **163**, which after hydrolysis and reacetylation gave (±)-cinnamosmolide **11** in an overall yield of 31%.

Kitahara *et al.* have synthesized several drimanes starting from *mono*-cyclofarnesic acid **91**,[35-37] derived from farnesic acid **92** by acid-catalyzed cyclization.[26]

Scheme 2.16

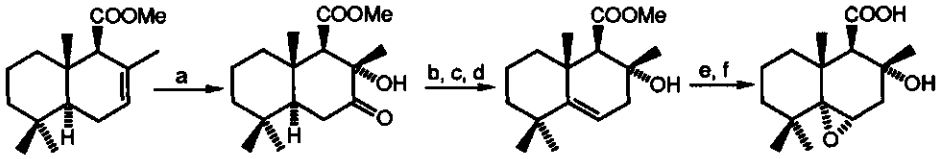


Reagents: *a*, $SnCl_4$; *b*, CH_2N_2; *c*, hν, O_2, rose Bengal; *d*, H_2O, H^+; *e*, $LiAlH_4$; *f*, MnO_2; *g*, CrO_3, pyr.; *h*, NaOH; *i*, $HC(OMe)_3$, *p*-TsOH; *j*, oxalic acid.

Photo-oxidation of methyl drimenate **163** afforded in moderate yield **164**, which was cyclized with acid to (±)-drimenin **24**. Reduction and subsequent oxidation yielded the lactone (±)-cinnamolide **10**, which was converted into (±)-polygodial **2** as depicted in scheme 2.16.

Methyl bicyclofarnesoate **163** was also used as starting material for the synthesis of the phytotoxic metabolite altiloxin A **65**, a drimane with an unusual substitution pattern.[38]

Scheme 2.17



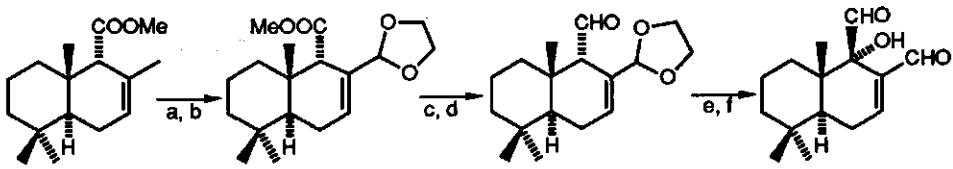
163 167 168 65

Reagents: *a*, $KMnO_4$, $NaHCO_3$; *b*, PhSeCl, EtOAc; H_2O_2; *c*, ethanedithiol, BF_3; *d*, *n*-Bu_3SnH; *e*, *m*-CPBA; *f*, DBU, 165°C.

The ketol **167** was obtained from **163** by dihydroxylation and oxidation with potassium permanganate. Treatment of **167** with phenylselenylchloride followed by oxidation with hydrogen peroxide converted the ketol into an α,ß-unsaturated ketone, from which the ketone function was removed *via* reduction of the thioacetal. Epoxidation of **168** proceeded stereoselective and hydrolysis of the ester function by heating at 165°C with DBU then gave (±)-altiloxin A **65**.

The first synthesis of (±)-warburganal **1**, which was reported by Ohsuka and Matsukawa,[39] made use of methyl-9-*epi*-bicyclofarnesoate **169**, obtained in low yield (5%) by an acid-catalyzed cyclization of methyl farnesoate (see scheme 2.18).

Scheme 2.18



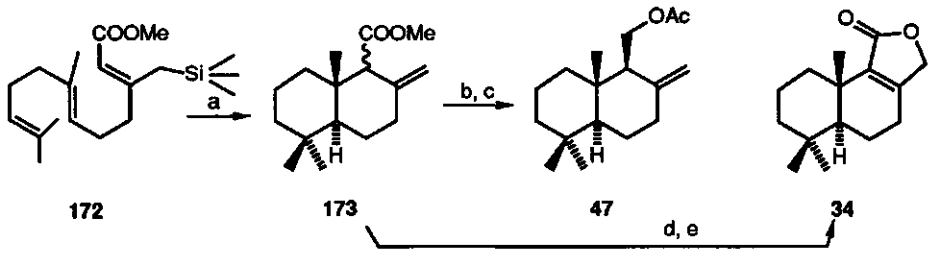
169 170 171 1

Reagents: *a*, SeO_2; *b*, ethylene glycol, *p*-TsOH; *c*, $LiAlH_4$; *d*, CrO_3, pyr.; *e*, LiHMDS, MoO_5. HMPA. pyr.; *f*, H_2O, H^+.

The more abundant methyl bicyclofarnesoate **163** could not be used as starting material because complex mixtures were obtained in the allylic oxidation. The α position of the ester function is also a problem in this approach. Elaboration of this ester function according to scheme 2.18 finally yielded compound **171**, which also had the aldehyde function in the α position. The deprotonation of **171**, necessary for the oxidative introduction of the 9α-hydroxyl group, turned out to be difficult and proceeded in a rather low yield (25%).

Weiler *et al.* used the allylsilane **172** in an electrophilic cyclization to achieve a regioselective alkene formation in good yield (see scheme 2.19).[40]

Scheme 2.19



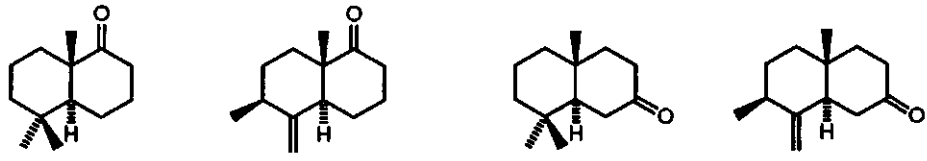
Reagents: *a*, $SnCl_4$, -56°C; *b*, $LiAlH_4$; *c*, Ac_2O, pyr.; *d*, *m*-CPBA; *e*, LDA.

The cyclization reaction was quite solvent and temperature dependent. With stannic chloride at -56°C in dichloromethane a 95% yield of the 1α- and 1ß-isomers were obtained in a 1:4 ratio. After reduction of **173** and acetylation (±)-albicanylacetate **47** was isolated in 75% overall yield. The lactone (±)-isodrimenin **34** was also synthesized from **173** in 60% yield as shown in scheme 2.19.

2.4 Synthesis of drimanes from *trans*-decalones

The appropriate *trans*-decalones **94-97** for the syntheses of drimanes were obtained *via* Robinson annulations (see figure 2.3).

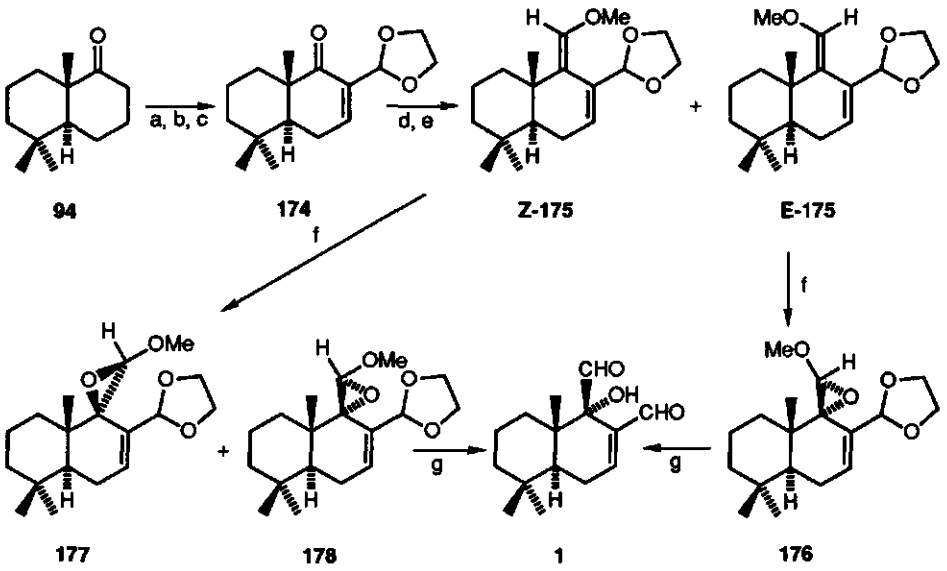
Figure 2.3



The readily available trimethyldecalone **94** had been used as starting material for various drimanes like warburganal **1**, isotadeonal **2**, confertifolin **17**, valdiviolide **18**, euryfuran **33**, and isodrimenin **34**. The synthetic strategies all employ a formylation reaction to introduce the required C-12 carbon atom and a nucleophilic addition of an appropriate reagent to the C-9 keto function to complete the drimane skeleton.

Kende *et al.*[41], and Goldsmith *et al.*[20] reported a total synthesis of (±)-warburganal **1**, based on this approach (see scheme 2.20 and 2.21, respectively).

Scheme 2.20

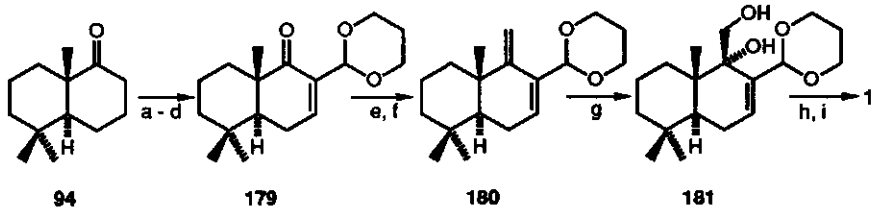


Reagents: *a*, NaH, HCOOEt; *b*, DDQ; *c*, ethylene glycol, *p*-TsOH; *d*, $Me_3Si(MeO)$-CHLi; *e*, KH, THF; *f*, *m*-CPBA; *g*, H_2O, H^+.

The addition of [methoxy(trimethylsilyl)methyl]lithium to the hindered carbonyl function of **174** gave a diastereoisomeric mixture of alcohols which underwent elimination of trimethylsilanol to afford a 1:3 mixture of (E)- and (Z)-enol ethers **175**. Upon epoxidation, the (E)-isomer **175** gave exclusively the α-epoxide which could be hydrolyzed to (±)-warburganal **1** in 13% overall yield.
Epoxidation of (Z)-**175** gave a 4:1 mixture of the ß- and α-epoxides **177** and **178**, respectively, which led after hydrolysis to a corresponding 4:1 mixture of (±)-*epi*-warburganal and (±)-warburganal **1**. Moreover, hydrolysis of (E)-**175** and (Z)-**175** under more vigorous conditions afforded (±)-isotadeonal **3**.

Goldsmith *et al.* used a modified reaction sequence to obtain **179** in which the C-11 carbon atom was introduced *via* addition of methyllithium (see scheme 2.21).[20]

Scheme 2.21

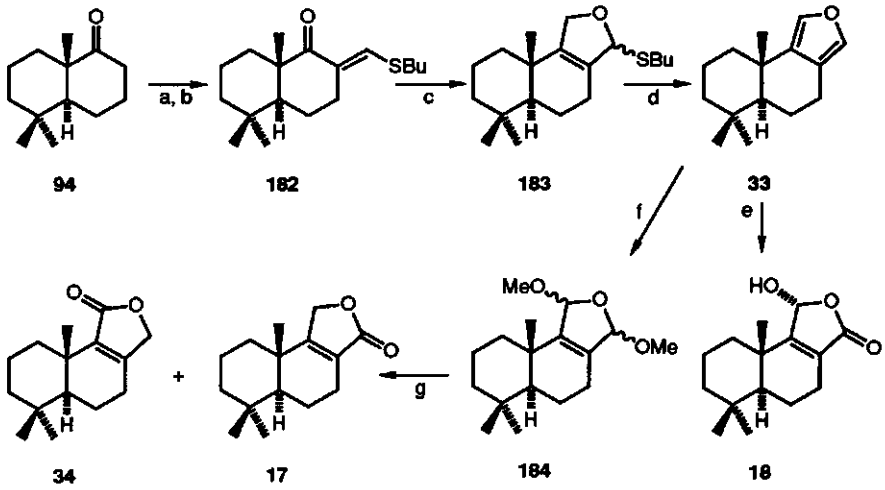


Reagents: *a*, HCOOEt, NaH; *b*, PhSeCl, pyr.; *c*, H_2O_2; *d*, trimethylene glycol, *p*-TsOH; *e*, CH_3Li; *f*, $MeO_2CNSO_2NEt_3$; *g*, OsO_4, pyr.; *h*, DMSO, pyr., TFA; *i*, *p*-TsOH, acetone.

Dehydration employing *Burgess'* reagent [42] gave the diene **180**, which upon hydroxylation, *Swern* oxidation, and hydrolysis yielded (±) warburganal **1** in an overall yield of 15%.

The furan annulation method reported by Spencer [43] *et al.* was used to synthesize (±) euryfuran **33** and some other drimanes as shown in scheme 2.22.[44]

Scheme 2.22

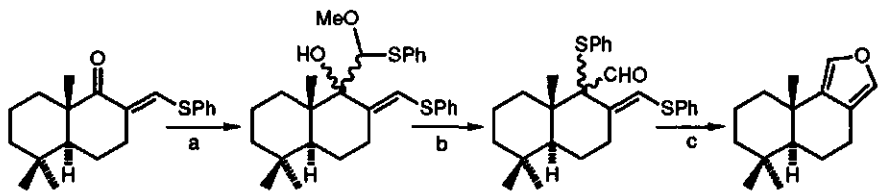


Reagents: *a*, HCOOEt, NaH; *b*, *n*-BuSH, *p*-TsOH; *c*, $(H_3C)_2S{=}CH_2$; *d*, $HgSO_4$; *e*, O_2, hυ, eosin; *f*, Br_2, MeOH; *g*, H_2O, H^+.

Treatment of the *n*-butylthiomethylene derivative **182** with trimethylsulphonium methylide gave, *via* rearrangement of the intermediate epoxide, the dihydrofuran **183**, which on brief treatment with mercury(II) sulfate afforded a 70% yield of (±)-euryfuran **33**. Photo-oxygenation of **33** gave (±)-valdiviolide **18** in 60% as well as the unnatural 11ß-hydroxy isomer. Oxidation of **33** with bromine in methanol followed by hydrolysis afforded (±)-confertifolin **17** in 75% yield together with the regioisomer (±)-iso-drimenin **34** in 10% yield.

[Methoxy(phenylthio)methyl]lithium and [(phenylthio)methyl]lithium were used by de Groot *et al.* to introduce the requisite functionality at C-9 as is shown in schemes 2.23, 2.24, and 2.25.

Scheme 2.23



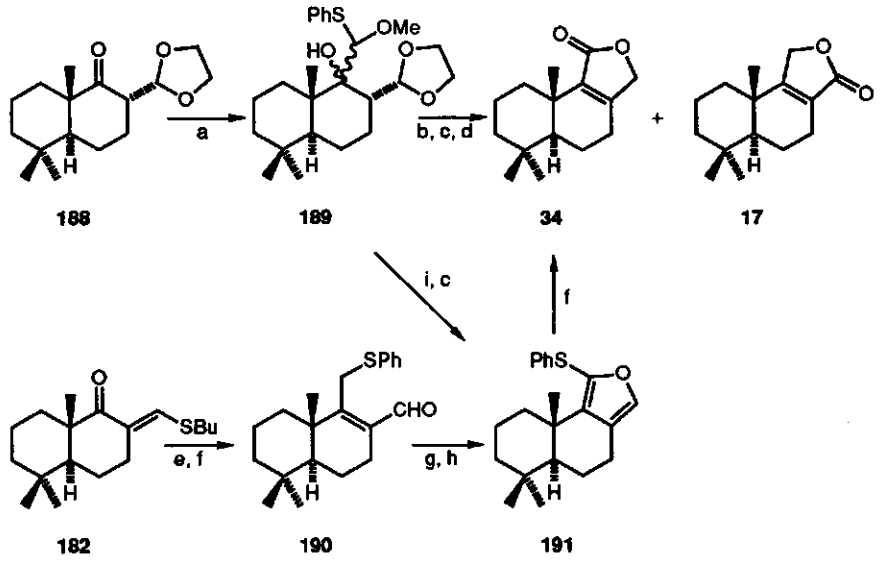
185 **186** **187** **33**

Reagents: *a*, PhS(MeO)CHLi; *b*, $SOCl_2$, pyr.; *c*, $LiAlH_4$.

Addition of [methoxy(phenylthio)methyl]lithium to **185** gave a diastereoisomeric mixture of **186**. These adducts could be rearranged to α-(phenylthio)aldehydes **187**.[45] After reduction a spontaneous cyclization to (±)-euryfuran **33** was observed in an overall yield of 55% based on **94**.[46]

Addition of [methoxy(phenylthio)methyl]lithium to the keto acetal **188** gave a mixture of stereoisomers **189**. Hydrolysis to a mixture of hydroxy dialdehydes followed by acid-catalyzed cyclization gave a 1:3 mixture of (±)-isodrimenin **34** and (±)-confertifolin **17**.[47] Rearrangement of **189** followed by mercury(II)-assisted hydrolysis afforded the (phenylthio)furan **191** which gave (±)-isodrimenin **34** after further hydrolysis in 45% overall yield from **188**. Drimanic lactones were also synthesized regioselectively *via* the addition of [(phenylthio)methyl]lithium to the *n*-butylthiomethylene derivative **182**. The adducts were hydrolysed directly to the γ-(phenylthio)-α,β-unsaturated aldehyde **190**. Oxidation to the sulfoxide, followed by a *Pummerer* type reaction, also led to the (phenylthio)furan **191**. After hydrolysis the lactone (±)-isodrimenin **34** was obtained in 30% overall yield.

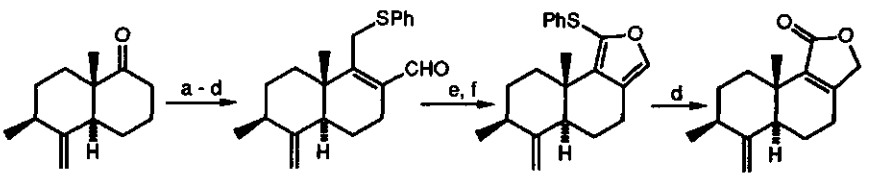
Scheme 2.24



Reagents: *a*, PhS(MeO)CHLi; *b*, $HgCl_2$, HgO, H_2O; *c*, H_2O, H^+; *d*, *p*-TsOH, benzene, Δ; e, $PhSCH_2Li$; *f*, H_2O, $HgCl_2$, H^+; *g*, $NaIO_4$; *h*, Ac_2O, 110°C; *i*, $SOCl_2$, pyr.

The *trans*-decalone **95** [48] was used for the synthesis of the rearranged drimane (±)-colorata-4(13),8-dienolide **82** *via* the same regioselective lactone annulation as shown in scheme 2.25.[47a]

Scheme 2.25

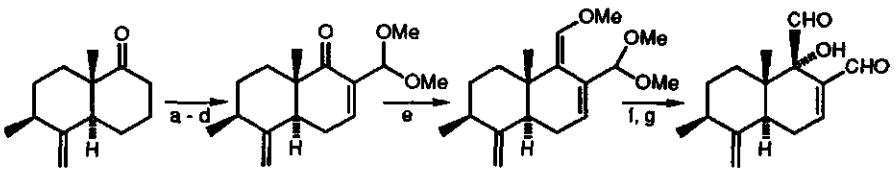


95 192 193 82

Reagents: *a*, HCOOEt, NaH; *b*, *n*-BuSH, *p*-TsOH, benzene; *c*, $PhSCH_2Li$; *d*, H_2O, H^+, $HgCl_2$; *e*, $NaIO_4$; *f*, Ac_2O, 110°C.

This same ketone **95** was used by Bosch, Meinwald *et al.* for a stereoselective total synthesis of (±)-muzigadial **80** (see scheme 2.26).[49]

Scheme 2.26



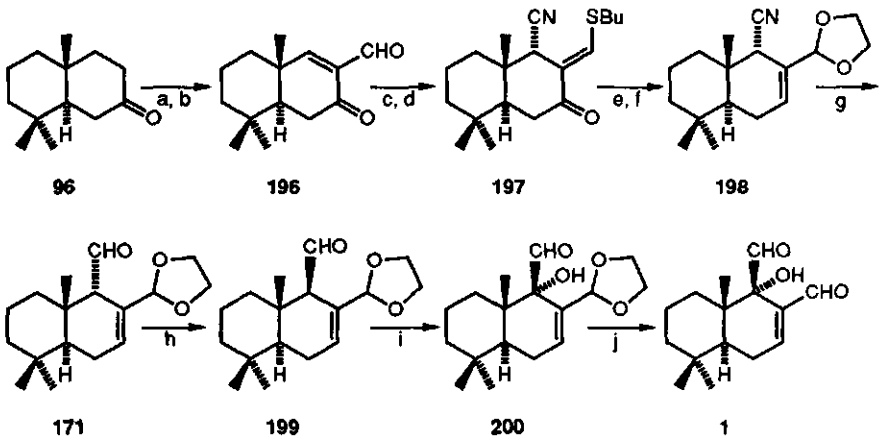
95 194 195 80

Reagents: *a*, HCOOEt, NaH; *b*, PhSeCl, pyr.; *c*, H_2O_2; *d*, $HC(OMe)_3$, *p*-TsOH; *e*, LDA, $Ph_2P(O)CH_2OCH_3$; *f*, OsO_4, TBHP, Et_4NOH, *t*-BuOH; *g*, H^+, H_2O, acetone.

trans-Decalone **95** was transformed into the protected dienol ether **195** as indicated and selective oxidation of the dienol ether was achieved in a subtle way using a catalytic amount of osmium tetroxide with *tert*-butyl hydroperoxide as the oxidant. Hydrolysis of the resulting hydroxy aldehyde afforded (±)-muzigadial **80** in 11% overall yield.

The *trans*-decalones **96** and **97** were used by de Groot *et al.* in a total synthesis of (±)-warburganal **1**, (±)-polygodial **2**, (±)-isotadeonal **3**, and (±)-muzigadial **80**.[50] Subsequently the chiral *trans*-decalones **96** and **97** were synthesized starting from (R)- and (S)-carvone, respectively.[51] The carbonyl group at C-7 made it possible to introduce a formyl group at C-8 and *via* conjugate addition a cyano group at C-9. Later it was used for the introduction of the $\Delta^{7,8}$ double bond (see scheme 2.27).

Scheme 2.27

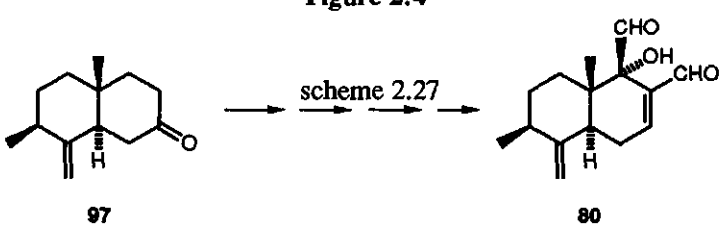


Reagents: *a*, NaH, HCOOEt; *b*, PhSeCl, pyr.; H_2O_2; *c*, KCN; *d*, *n*-BuSH, *p*-TsOH; *e*, $NaBH_4$; H_2O, H^+, $HgCl_2$; *f*, ethylene glycol, *p*-TsOH; *g*, DIBAH; *h*, KO-*t*-Bu, HO-*t*-Bu; *i*, LDA, MoO_5.HMPA.pyr.; *j*, H_2O, H^+.

For the conversion of **171** into warburganal it was necessary to prepare an enolate which could be oxidized to introduce the 9α-hydroxyl group. It turned out that deprotonation of **171** was very difficult, probably due to the steric crowding around the 9ß proton. A nearly quantitative epimerization succeeded after a 10 min treatment at reflux temperature with an excess of potassium *tert*-butoxide in *tert*-butyl alcohol. After this crucial epimerization, the ß-aldehyde **199** was easily deprotonated and subsequently oxidized as had been demonstrated in other syntheses.[5,28a] After hydrolysis (±)-warburganal **1** was obtained in 38% overall yield. (±)-Polygodial **2** was obtained from the intermediate **199** and (±)-isotadeonal **3** from **171** in 44% and 50% overall yield, respectively.

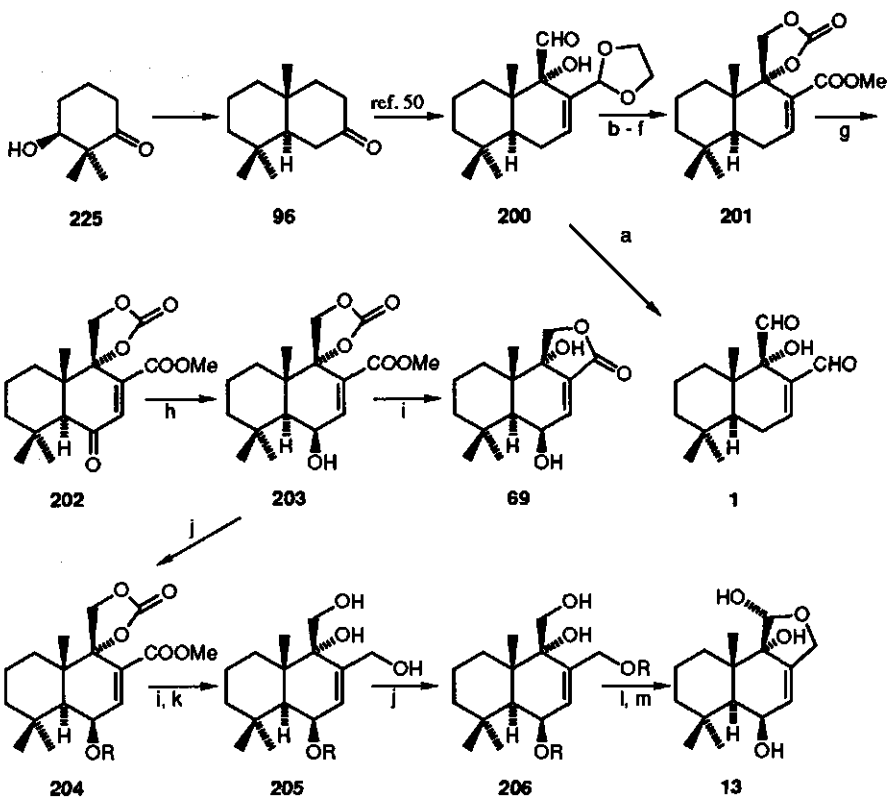
The same procedure was used to synthesize (±)-muzigadial **80** from the *trans*-decalone **97** in 24% overall yield (see figure 2.4).[50]

Figure 2.4



Mori and coworkers have synthesized (-)-warburganal **1** starting from (S)-3-hydroxy-2,2-dimethylcyclohexanone *via* **96** according to the procedure depicted in scheme 2.27.[52] The intermediate **200** was also used to synthesize (-)-pereniporin A **69** and (-)-pereniporin B **13** as shown in scheme 2.28.[53]

Scheme 2.28



Reagents: *a*, H_2O, H^+; *b*, $NaBH_4$; *c*, 1,1′-carbonyldiimidazole; *d*, *p*-TsOH, acetone; *e*, $NaClO_2$, NaH_2PO_4; *f*, CH_2N_2; *g*, CrO_3, HOAc; *h*, $NaBH_4$, $CeCl_3$; *i*, NaOH, H_2O; *j*, *t*-$BuMe_2SiCl$, *k*, LDA, Red-Al; *l*, DMSO, pyr., TFA, DCC; *m*, TBAF.

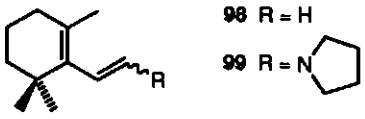
Conversion of **200** into the unsaturated ester **201** was followed by allylic oxidation and reduction to the alcohol **203**. Alkaline hydrolysis followed by acidification gave (-)-pereniporin B **69** in 1.8% overall yield. In order to prepare pereniporin A **13** from **203** reversal of the oxidation state of C-11 and C-12 was necessary. However, all

attempts under conventional conditions to reduce **204** to the triol **205** were in vain and resulted in the reductive removal of the tertiary hydroxy group. The reductive elimination could be avoided when the tertiary alcohol was protected as its lithium salt during the reduction procedure. The so obtained triol **205** was transformed into (-)-pereniporin A **13** in a straightforward manner as depicted in scheme 2.28.

2.5 Synthesis of drimanes by a Diels-Alder approach

The use of the Diels-Alder reaction to construct an appropriately functionalized decalin in a concise manner is especially attractive. In the Diels-Alder approach various 1-vinyl-2,6,6-trimethylcyclohex-1-enes were used (see figure 2.5).

Figure 2.5



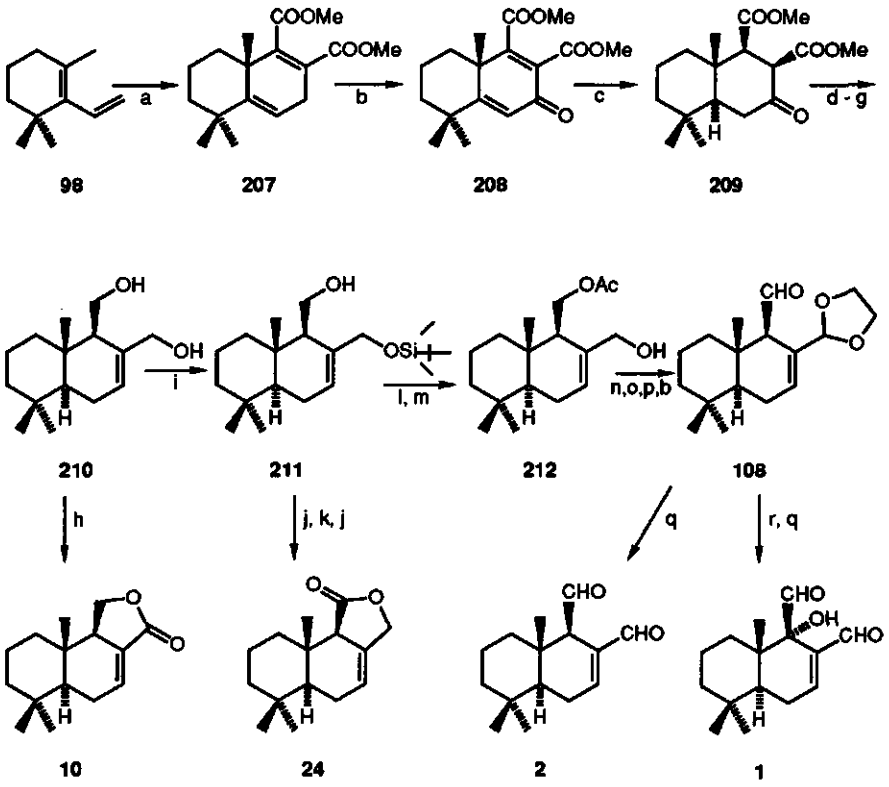
This concept was first used by Brieger [54] in his synthesis of (±)-winterin **21**. Improvements of the initial process were introduced later and several drimanes have now been synthesized following this approach.[55,56]

Nakanishi *et al.* used the Diels-Alder reaction in an efficient total synthesis of (±)-warburganal **1**, (±) polygodial **2**, (±)-cinnamolide **10**, and (±)-drimenin **24** as is shown in scheme 2.29.[28a]

The reaction of dimethyl acetylenedicarboxylate with the diene **98** provided the diester **207**. The stereoselective catalytic *trans* reduction of the $\Delta^{5,6}$ olefinic bond in **207** was achieved with difficulty since normally *cis*-fused reduction products are obtained. Several solutions for this problem are currently available, all are based on the construction of a conjugated system preceding the catalytic reduction. In this case the problem was solved *via* allylic oxidation of **207** to the dienone **208**, which gave the desired *trans*-fused ketone **209** upon reduction. Ketone **209** was converted by standard reactions into the diol **210**. The exposed allylic alcohol reacted more readily than the hindered primary alcohol so a single lactone, (±)-cinnamolide **10**, was obtained upon oxidation in an overall yield of 18%. After selective protection of the allylic hydroxy group the more hindered alcohol was oxidized and the lactone (±)-drimenin **24** was formed in 12% overall yield. A sequence of protection, deprotection, and oxidation steps led to the monoprotected dialdehyde **108**, which afforded (±)-polygodial **2** in 21%

overall yield after hydrolysis. Compound **108** was hydroxylated by the *Vedejs'* procedure and hydrolysis of the acetal gave (±)-warburganal **1** in 16% overall yield.

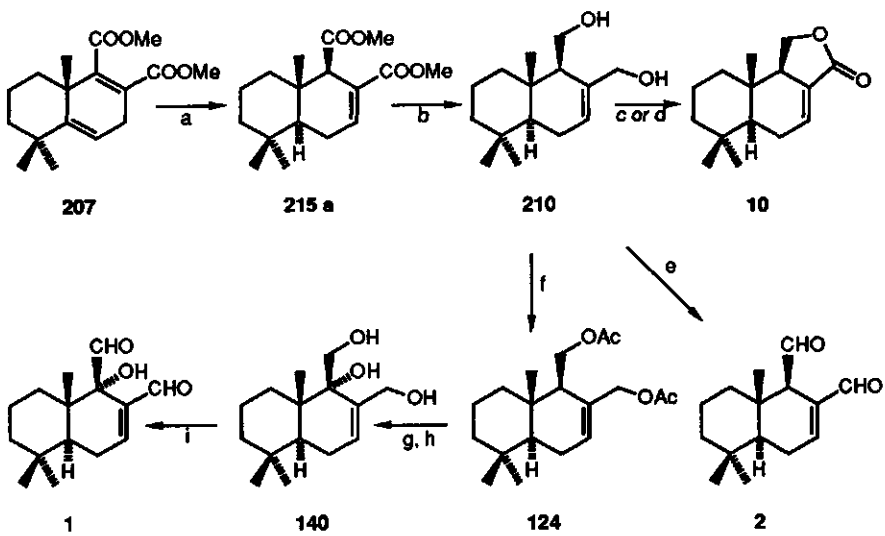
Scheme 2.29



Reagents: *a*, Dimethyl acetylenedicarboxylate, 110°C, neat; *b*, CrO_3, pyr.; *c*, H_2, Pd on C; *d*, $NaBH_4$; *e*, MsCl, Et_3N; *f*, DBU; *g*, $LiAlH_4$; *h*, CrO_3; *i*, *t*-$BuMe_2SiCl$, imidazole; *j*, PCC; *k*, TBAF; *l*, Ac_2O, pyr.; *m*, HOAc, H_2O; *n*, MnO_2; *o*, trimethylene glycol, *p*-TsOH; *p*, KOH, MeOH; *q*, H_2O, H^+, acetone; *r*, LDA, MoO_5.HMPA.pyr.

The *trans*-fused decalin skeleton was obtained from **207** by Ley *et al. via* hydrogenation under isomerizing conditions.[11,57,58] The use of various protecting groups could be avoided by a careful choice of oxidation reagents (see scheme 2.30).

Scheme 2.30



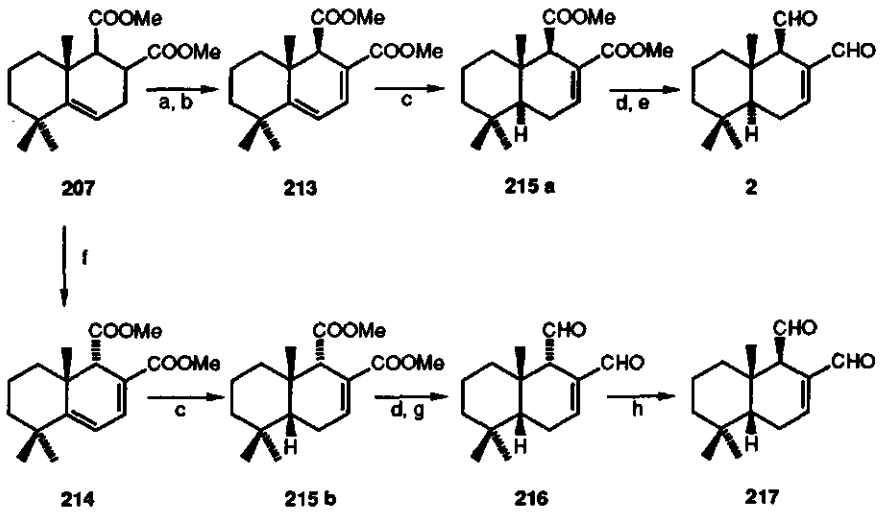
Reagents: *a*, H_2, Pd on C, trace of HCl; *b*, $LiALH_4$; *c*, $BaMnO_4$, 20 equivalents; *d*, Ag_2CO_3 on celite; *e*, DMSO, NEt_3, oxalyl chloride; *f*, Ac_2O, pyr.; *g*, SeO_2; *h*, K_2CO_3, MeOH; *i*, DMSO, NEt_3, TFAA.

Although direct introduction of the 9α-hydroxy group failed with the diol **210**, the corresponding diacetate **124** was easily oxidized by selenium dioxide. Deprotection led to the triol **140**, which provided (±)-warburganal **1** on oxidation by *Swern's* protocol.

An analogous approach was used by Lallemand *et al.*[59] In this case the isomerization of the diester **207** to the conjugated dienic diester **213** was effected by a separate treatment of **207** with lithium diisopropylamide followed by kinetic protonation (see Scheme 2.31). Under thermodynamic conditions the more stable 9α-isomer **214** was obtained, which gave rise to the *cis*-fused diester **215b** upon hydrogenation. Reduction followed by oxidation using the *Swern* procedure, led to the *cis*-fused dialdehyde **216**.

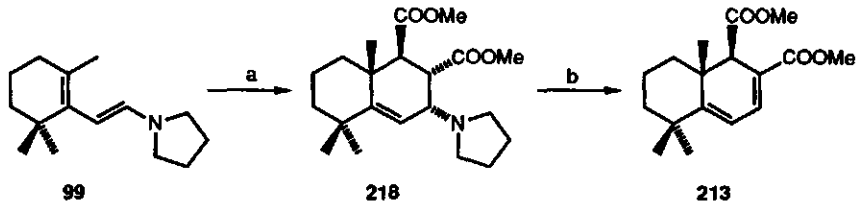
The diester **213** was also prepared *via* a Diels-Alder reaction of the dienamine **99** with dimethyl fumarate. Elimination of pyrrolidine from **218** afforded **213** in a one-pot procedure in 81% yield as depicted in scheme 2.32.[60]

Scheme 2.31



Reagents: *a*, LDA, -78°C; *b*, H_2SO_4, H_2O, -78°C; *c*, H_2, Pd on C; *d*, $LiAlH_4$; *e*, DMSO, NEt_3, oxalyl chloride; *f*, DBU, toluene, reflux; *g*, DMSO, NEt_3, TFAA; *h*, DBN, benzene, reflux.

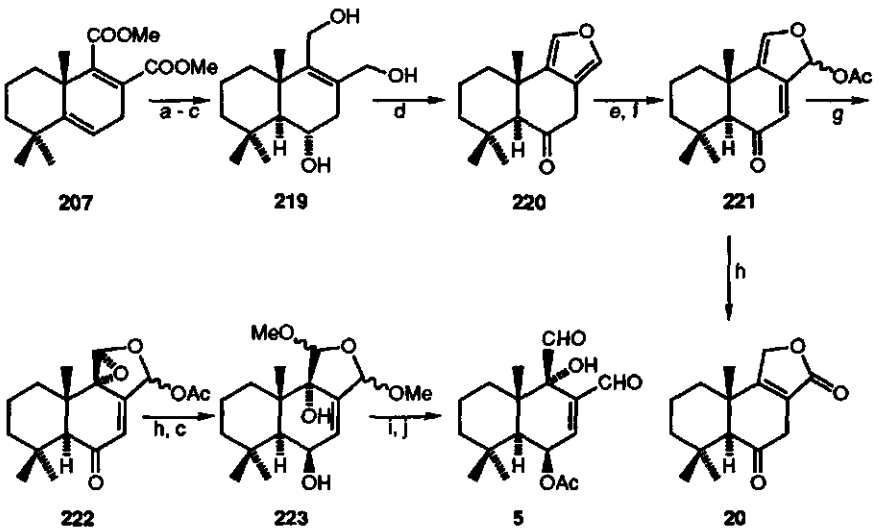
Scheme 2.32



Reagents: *a*, Dimethyl fumarate, xylene, 140°C; *b*, Ac_2O, reflux.

The diester **207** was chosen by White *et al.* as the starting material to introduce an oxygen functionality at C-6 (see scheme 2.33).[61]

Scheme 2.33

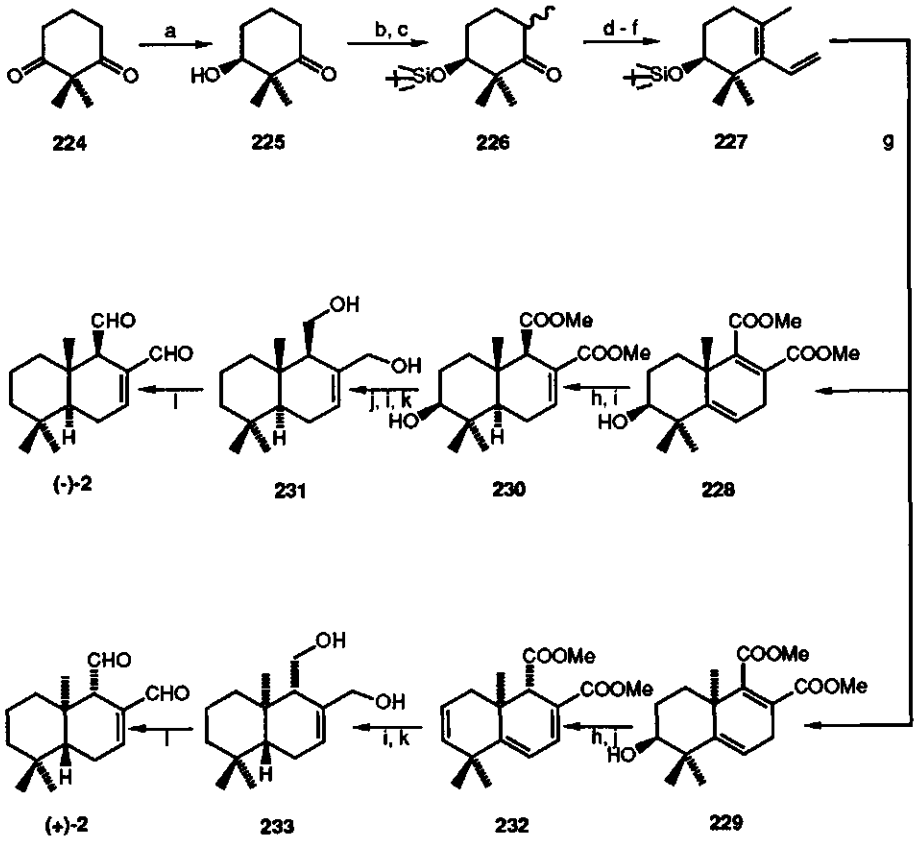


Reagents: *a*, Borane, THF; *b*, H_2O_2, NaOH; *c*, DIBAH; *d*, PCC; *e*, $Pb(OAc)_4$, benzene; *f*, DBU; *g*, *m*-CPBA; *h*, MeOH, HCl; *i*, H_2O, HCl; *j*, Ac_2O, DMAP, pyr.

The Diels-Alder adduct **207** was treated with diborane to give a hydroxy diester after alkaline oxidation. Contrary to an earlier assignment this product was shown to possess a *trans* ring fusion.[28a] To firmly establish the configuration of this hydroxy diester, it was correlated with a substance of known stereochemistry, (±)-isodrimenin **34**. Reduction of the diester with diisobutylaluminum hydride immediately followed by PCC oxidation afforded the keto furan **220**. The furan ring was oxidized and the intermediate diacetate was treated with base to provide the dienone **221**, which led to (±)-fragrolide **20** upon hydrolysis in 33% overall yield. Epoxidation of **221** yielded an α-epoxy compound which was transformed into a suitable protected dialdehyde moiety upon treatment with acidified methanol. Reduction of the keto function in **223** followed by acetylation of the 6ß-hydroxy group gave rise to (±)-cinnamodial **5** in 11% overall yield.

To prove the hypothesis that the phytotoxicity of the synthetic racemate (±)-polygodial **2** might be due to the unnatural enantiomer, Mori *et al.* have developed a synthesis of both enantiomers,[62] see scheme 2.34. The dione **224** was chosen as the starting material because reduction using baker's yeast yielded the (S)-hydroxy compound **225** in good yield. The required diene **227** was obtained by a straightforward

Scheme 2.34

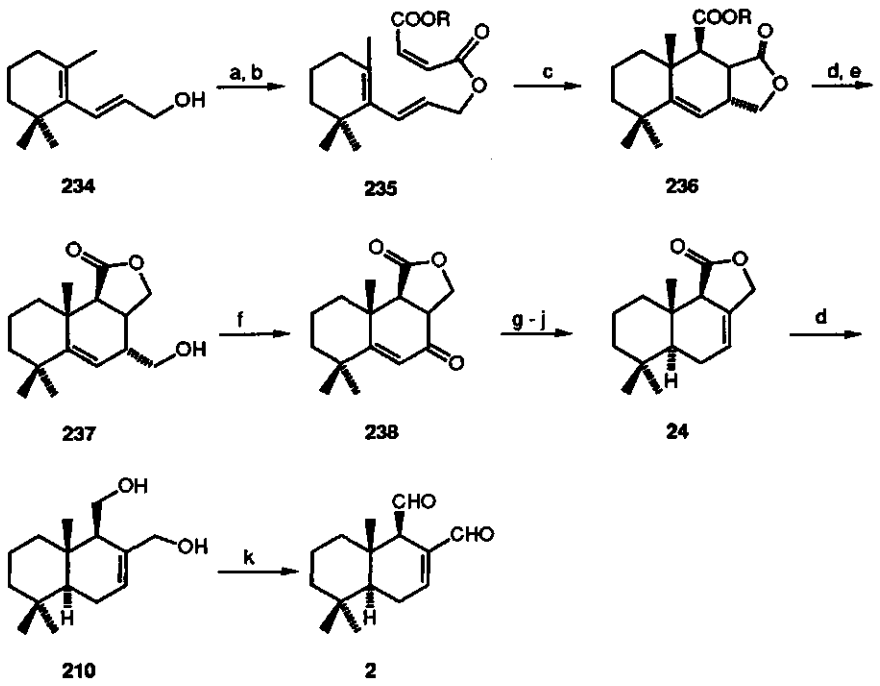


Reagents: *a*, Baker's yeast; *b*, *t*-$BuMe_2SiCl$, imidazole, DMF; *c*, LDA, MeI; *d*, sodium acetylide; *e*, $CuSO_4$, xylene, reflux; *f*, H_2, Pd on $CaCO_3$; *g*, dimethyl acetylenedicarboxylate; *h*, DBU; *i*, H_2, Pd on C; *f*, MsCl, DMAP; *k*, $LiAlH_4$; *l*, DMSO, NEt_3, oxalyl chloride.

method in 50% yield. The Diels-Alder reaction was not diastereoselective but yielded a mixture of **228** and **229** in 33% and 35% respectively. Reduction of diester **228** to the *trans*-fused compound **230** succeeded using an adaptation of the method of Lallemand.[59] The natural (-)-polygodial **2** was finally obtained in an overall yield of 3.0%. The unnatural (+)-polygodial was synthesized *via* a slightly modified route in an overall yield of 2.9%.

An *intra*molecular Diels-Alder approach was studied by Wu *et al.*[63] ß-Ionone was treated with sodium hypobromite and then reduced to give the dienol **234**, which was esterified with maleic anhydride to set the stage for the Diels-Alder reaction which finally proceeded in refluxing xylene (see scheme 2.35).

Scheme 2.35



Reagents: *a*, Maleic anhydride; *b*, CH_2N_2; *c*, xylene, reflux; *d*, $LiAlH_4$; *e*, *p*-TsOH, benzene; *f*, CrO_3; *g*, H_2, Pd on C; *h*, $NaBH_4$; *i*, MsCl, pyr.; *j*, DMSO, 100°C, 2h; *k*, DMSO, NEt_3, oxalyl chloride.

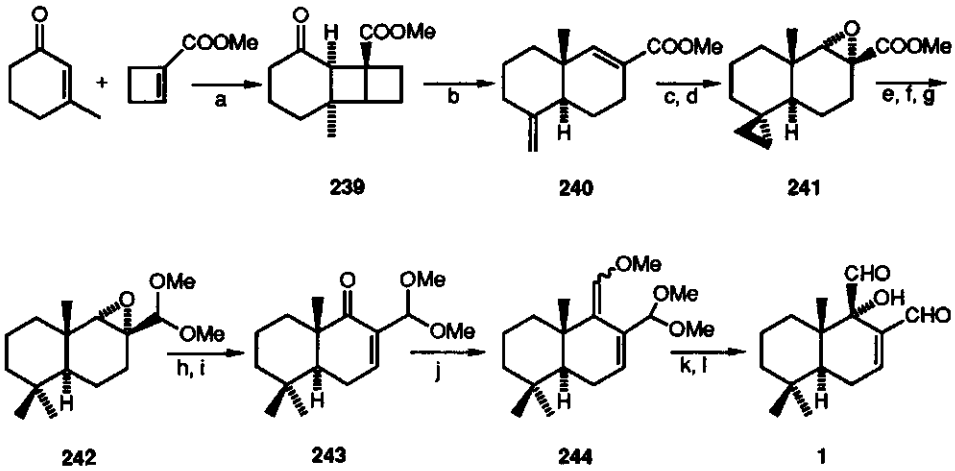
The lactone ring of **236** had to be opened to enable the elimination of the extra carbon atom. Under vigorous conditions the lactone ring could be opened but it recyclized spontaneously on standing. This problem was solved by selective reduction of the lactone functionality followed by an acid-catalyzed cyclization to **237**. This intermediate was transformed into (±)-drimenin **24** in a straightforward manner. Reduction of (±)-drimenin **24** with lithium aluminum hydride afforded the diol **210**, which had been used frequently for the synthesis of drimanes.[28a,57,59,62]

Substrate **235**, suited for the *intra*molecular Diels-Alder reaction, was also synthesized as its (-)-menthyl ester to effect asymmetric induction. Cycloaddition yielded a mixture of the two possible diastereoisomers from which the desired product was easily isolated by recrystallization, with an optical purity of 100% diastereoisomeric excess.

2.6 Synthesis of drimanes via a metathesis transannular ene sequence

A transannular ene reaction was used by Wender *et al.* to construct a suitable *trans*-fused decalin system for drimane synthesis.[64] With 2-substituted enones the [2+2] photo-cycloaddition gave no satisfactory results so the requisite substituent at C-9 had to be introduced afterwards (see scheme 2.36).

Scheme 2.36



Reagents: *a*, hν; *b*, Ph_3PCH_2; *c*, CH_2I_2, Zn, Cu; *d*, 3,5-$(NO_2)_2C_6H_3CO_3H$; *e*, H_2, PtO_2, HOAc; *f*, DIBAH; *g*, $HC(OMe)_3$, H^+; *h*, MICA; *i*, PDC; *j*, $Ph_2PCH(OMe)Li$; *k*, OsO_4; *l*, H_2O, H^+, acetone.

The [2+2] photo-cycloadduct **239** was converted under special reaction conditions (sodium *tert*-amylate in toluene) into the unsaturated ester **240** *via* a Wittig reaction followed by the ene reaction. The *gem*-dimethyl groups were introduced *via* a cyclo-propanation-hydrogenolysis sequence. Epoxidation of the double bond and conversion of the ester function into a protected aldehyde then provided **242**. Eliminative ring opening of the epoxide introduced the $\Delta^{7,8}$ double bond. The keto acetal **243** was transformed into the enol ether **244** by reaction with an excess of [(diphenylphosphino)methoxy-methyl]lithium. Osmylation and hydrolysis gave (±)-warburganal **1** in 13% yield.

2.7 References

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(*b*) S.V. Ley, 'Recent Advances in the Chemistry of Insect Control', Royal Society of Chemistry Special Publication 53, 1985, 307.
(*c*) S.V. Ley, 'Synthesis of Insect Antifeedants', Pest. Sci. Biotechnol., Proc. Int. Congr. Pest. Chem., 6th, 1986, R. Greenhalgh, T.R Roberts, Eds., 25, Blackwell, Oxford UK., 1987.
(*d*) Ae. de Groot and T.A. van Beek, *Recl. Trav. Chim. Pays-Bas*, 1987, **106**, 1.
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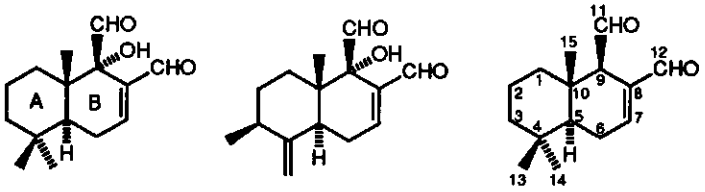
3 SYNTHETIC PLANS TO DRIMANIC SESQUITERPENES

3.1 Introduction

Warburganal **1***, muzigadial **2**, and polygodial **3** are the drimanes with the strongest antifeedant activities and therefore these compounds were chosen as the main target molecules in our investigations.
The main characteristic of these drimanes is an enal aldehyde moiety in ring B of the decalin system (see also chapter 1).

Figure 3.1



1 **2** **3**

It was our intention to develop a general synthetic method for these compounds taking into account the specific problems connected with the *exo*cyclic double bond of muzigadial **2**. Especially the oxidation reaction required for the introduction of the C-9 hydroxy function in muzigadial **2** was estimated to be delicate.

3.2 Synthesis based on *trans*-1-decalones

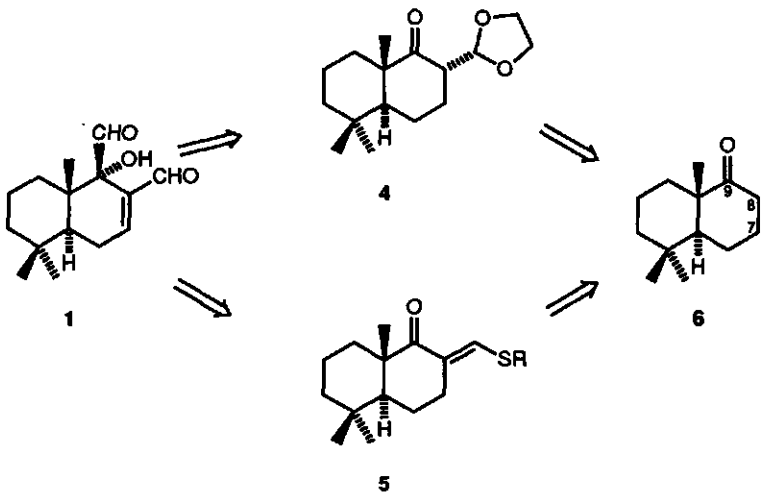
The first synthetic plan to warburganal **1** and polygodial **3** was based on *trans*-decalone **6** [1] as starting material. This *trans*-decalone **6** is readily available and the carbonyl group at C-9 should allow an easy introduction of the required functionalized carbon atoms at C-8 and C-9.

* In order to make a clear distinction between the review in the chapters 1 and 2 and our own work, the numbering of the compounds in the chapters 3 to 7 starts again with compound number 1 and does not correspond with the numbering in the chapters 1 and 2.

** To avoid confusion and to allow direct comparison between the various structures, the numbering system of the drimane sesquiterpenes is used throughout the discussion. In the experimental part, however, the numbering corresponding to the IUPAC rules is used.

The C-8 aldehyde function can be introduced as a hydroxymethylene group by formylation of *trans*-decalone **6**. This rather sensitive functional group has to be protected and the *n*-butylthiomethylene derivative **5** and the monoacetal **4** were selected to serve this purpose.[2]

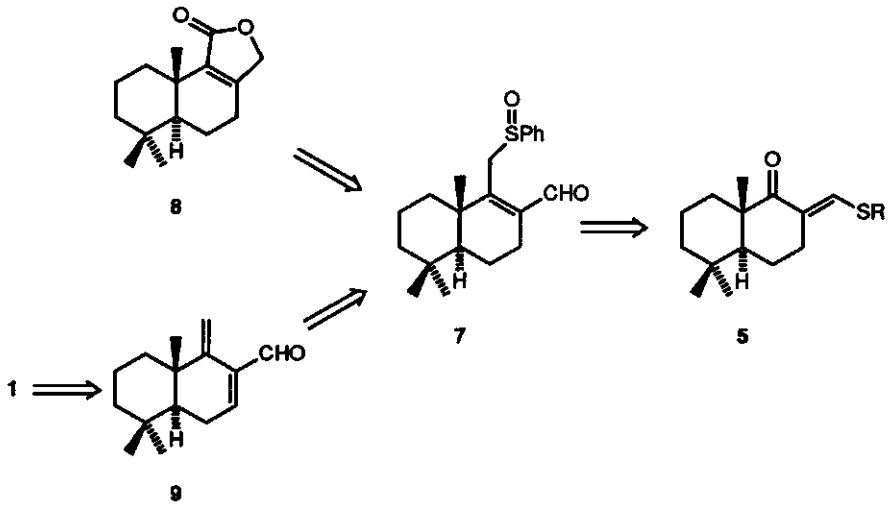
Scheme 3.1



The carbonyl group at C-9 now enables functionalization for instance by nucleophilic addition of suitable organometallic reagents. The hetero atom stabilized organolithium compounds [(phenylthio)methyl]lithium and [methoxy(phenylthio)methyl]lithium were examined for their suitability to serve as an aldehyde precursor. Finally an oxidation procedure should introduce the $\Delta^{7,8}$ double bond (see scheme 3.1).

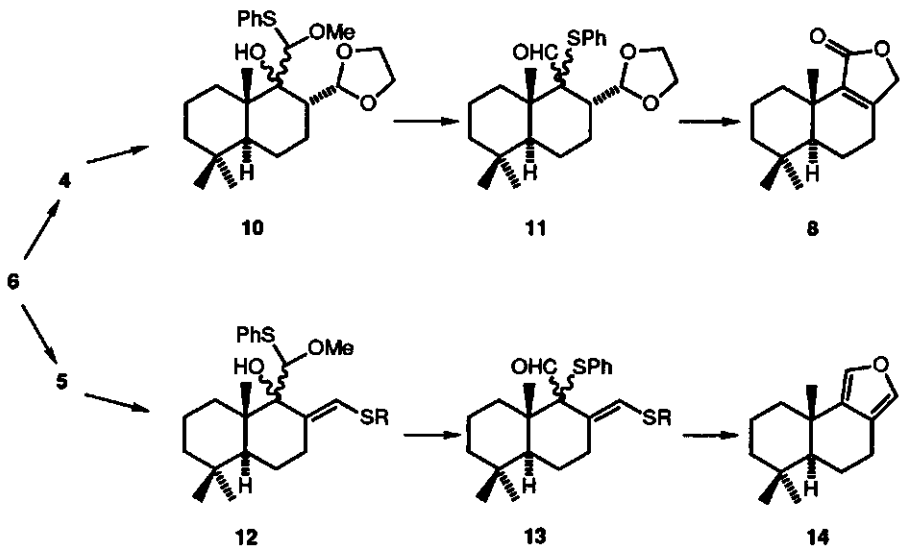
The syntheses based on the addition of [(phenylthio)methyl]lithium to *n*-butylthiomethylene ketones are described in chapter 4. A crucial intermediate in this approach towards warburganal **1** and other drimanes proved to be sulfoxide **7**. Via this intermediate a new regiospecific annulation method for butenolides like **8** was developed. A new type of thermal elimination of sulfenic acid from this sulfoxide [3] led to dienes like **9**. This diene was used as an intermediate in an earlier described synthesis of warburganal **1** (see scheme 3.2).

Scheme 3.2



The addition of [methoxy(phenylthio)methyl]lithium to carbonyl compounds [4] and the rearrangement of the adducts is the topic of chapter 5. The addition as well as the rearrangement was applied to both ketoacetal **4** and *n*-butylthiomethylene ketone **5**. Further transformations have led to new annulation procedures for furans like **14** and lactones like **8** (see scheme 3.3).

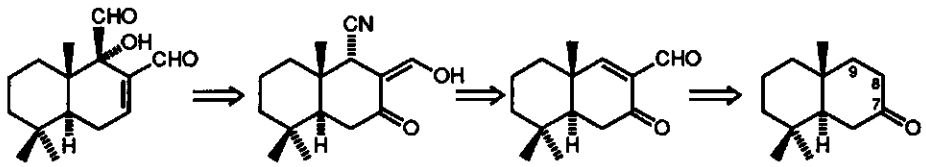
Scheme 3.3



3.3 Syntheses based on *trans*-2-decalones

Although several new annulation procedures for lactones and furans were developed, the syntheses of the principal target molecules had met with limited success. Therefore we turned our attention to the easily accessible *trans*-2-decalone **17** as starting compound.[5] The retrosynthetic plan towards the total synthesis of warburganal **1** is outlined briefly in scheme 3.4.

Scheme 3.4

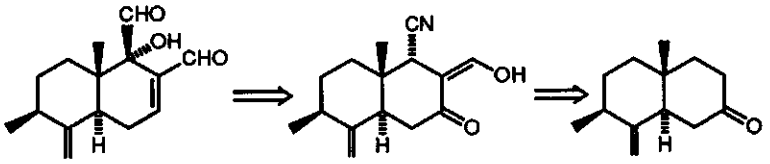


1 **15** **16** **17**

The carbonyl function at C-7 in *trans*-decalone **17** is ideally located for the introduction of the necessary functionalized carbon atoms at C-8 and at C-9 and it can be used later on for the construction of the $\Delta^{7,8}$ double bond. Functional group transformations and epimerization at C-9 will finally complete the total synthesis of warburganal **1**.

A synthesis of muzigadial **2** along these lines should start from *trans*-decalone **19**, so all the reaction conditions should have to be compatible with the presence of an *exo*cyclic double bond in the molecule (see scheme 3.5). The chemistry connected with this approach is described in chapter 6.

Scheme 3.5

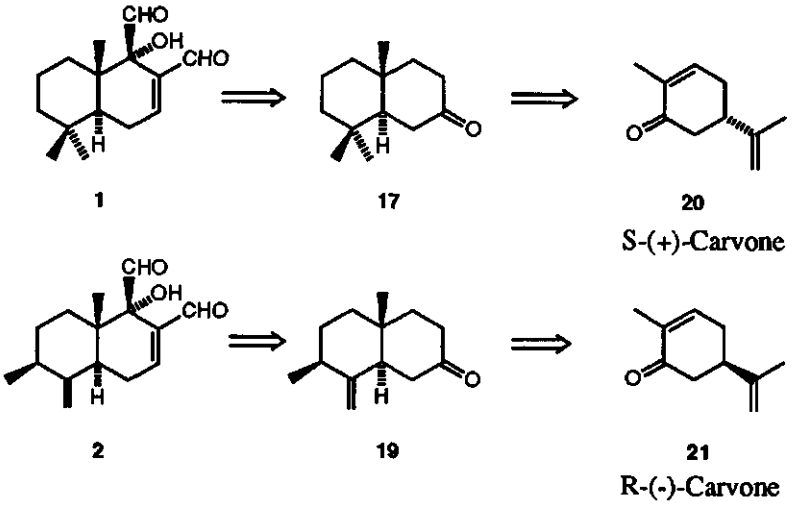


2 **18** **19**

In connection with the supposed differences in the physiologically properties of the enantiomers of the drimanes **1**, **2**, and **3** it was desirable to synthesize the pure enantiomers. Therefore a protocol was established for the synthesis of the enantiomeri-

cally pure *trans*-decalones **17** and **19** starting from (+)- and (-)-carvone **20** and **21** respectively. This is described in chapter 7 (see scheme 3.6).

Scheme 3.6



3.4 References and notes

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4 Although we were aware of the stereochemical outcome of the nucleophilic additions, nevertheless it was decided to examine these reactions.
Intermediates, obtained by rearrangements of *e.g.*, sulfoxides might be suitable for the synthesis of the target molecules.

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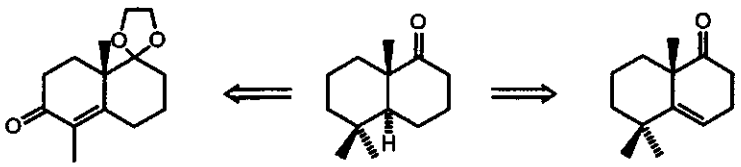
4 REGIOSPECIFIC ANNULATION OF BUTENOLIDES

Total synthesis of (±)-isodrimenin and (±)-colorata-4(13),8-dienolide.

4.1 Introduction

As indicated in chapter 3, our first attempts towards the syntheses of drimanes started from *trans*-decalone **6**. The obvious possibilities in this ketone for the introduction of functionalized carbon atoms at C-8 and C-9 made this choise to an easy one.
A slight drawback was the lack of a procedure for large scale production of **6**. Seemingly obvious procedures for the preparation of this ketone, *i.e.*, reductive alkylation of **22** or catalytic hydrogenation of **23**, turned out to be unattractive in this respect.

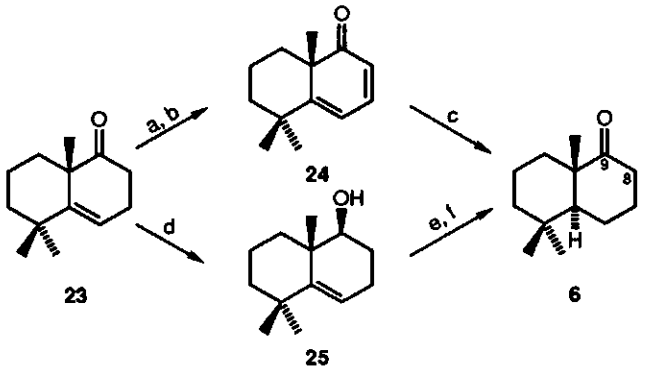
Scheme 4.1



22 **6** **23**

On a larger scale the reductive alkylation of **22** gave mixtures of reduced and alkylated products that required extensive chromatographic purification.[1] The catalytic hydrogenation of **23** has been investigated extensively, but only complex mixtures resulting from *non*-specific hydrogenation and overreduction were obtained.[2]
Recently, two new approaches to the synthesis of *trans*-1-decalones have been developed, suitable for reasonable scale production (scheme 4.2). A stereoselective catalytic reduction of the olefinic double bond in **23** to the *trans*-fused ring system in **6** was possible in high yield after extension of the unsaturated system [3] to the dienone **24**.[4]
Another method first required the reduction of the carbonyl group in **23** to the *equatorial* hydroxy group in **25**, after which a stereoselective catalytic *trans*-reduction of the olefinic double bond was achieved. Reoxidation of the hydroxy group afforded **6** in good yield.[5]

Scheme 4.2



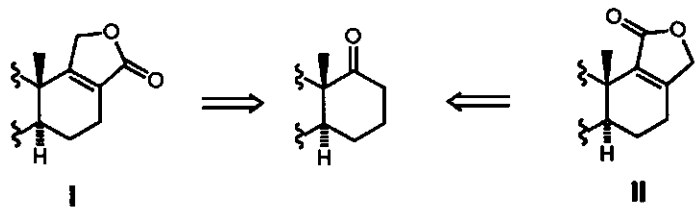
Reagents: *a*, Br_2, HOAc; *b*, LiBr, Li_2CO_3; *c*, $[Ph_3P]_3RhCl$, H_2; *d*, Li(*t*-BuO)$_3$AlH; *e*, PtO_2, H_2; *f*, CrO_3, H_2SO_4.

In this chapter the attempts are described in which [(phenylthio)methyl]lithium [6] is used to introduce a functionalized carbon atom at C-9 by nucleophilic addition on derivatives of *trans*-decalone **6**.

4.2 A general procedure for the annulation of butenolides

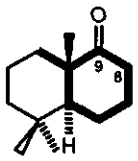
The regiospecific annulation of butenolides forms part of the problems in the total synthesis of, for instance, triptolide and congeners,[7] of a number of drimane sesquiterpenes [8] and eventually of spongianes [9] and scalaranes.[10] Recently an efficient procedure was described for the construction of butenolides of type I, starting from a ketone [7b] (see figure 4.1).

Figure 4.1



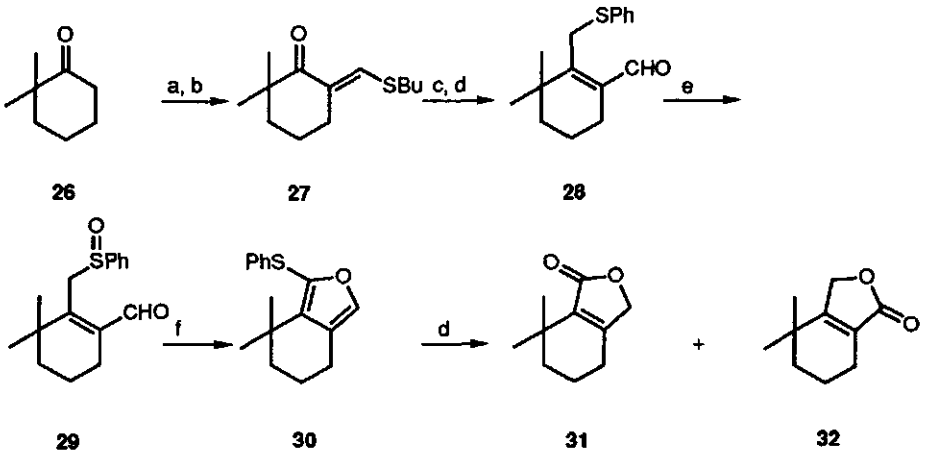
Synthesis of butenolides with the opposite regiochemistry (type II), frequently found in natural products, starting from the same type of ketone, are less known. Therefore we have developed a new method for the regiospecific annulation of butenolides of this type.[11] The procedure was tried out starting with 2,2-dimethylcyclohexanone **26**, marked with thick lines in figure 4.2, as model compound for the *trans*-decalone **6**.

Figure 4.2



The starting material, 2,2-dimethylcyclohexanone **26**, was synthesized according to the procedure of Ireland and Marshall.[12] Formylation of **26** with ethyl formate and sodium hydride as base afforded the hydroxymethylene derivative, which was converted into the (*n*-butylthio)methylene compound **27** in 90% yield. The required functionalized carbon atom is thus properly protected against nucleophilic attack.

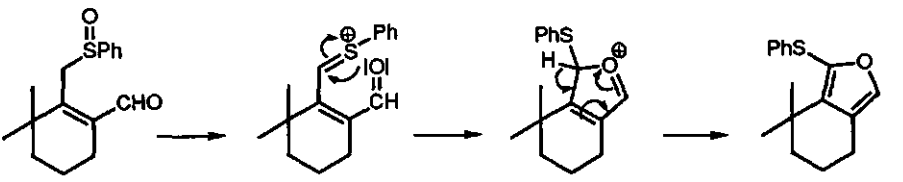
Scheme 4.3



Reagents: *a*, NaH, HCOOEt; *b*, *n*-BuSH, *p*-TsOH, benzene; *c*, $PhSCH_2Li$; *d*, H_2O, HCl, $HgCl_2$; *e*, $NaIO_4$; *f*, Ac_2O, 110°C.

The addition of [(phenylthio)methyl]lithium, formed by the action of *n*-butyllithium on thioanisole in the presence of 1,4-diazabicyclo[2,2,2]octane (DABCO), proceeded well to yield the adduct in good yield. A mercuric chloride assisted hydrolysis with dilute hydrochloric acid gave the γ-(phenylthio)-α,ß-unsaturated aldehyde **28**.[13] Oxidation of sulfide **28** with sodium *meta*periodate in aqueous methanol [14] afforded sulfoxide **29**. This sulfoxide was prepared to achieve a higher oxidation level at the sulfur-bearing carbon atom which is not only required for the butenolides but also for warburganal **1** and polygodial **3**. A Pummerer-type reaction of this sulfoxide **29** by heating in acetic anhydride at 110°C resulted in the formation of (phenylthio)furan **30** (see scheme 4.4).

Scheme 4.4



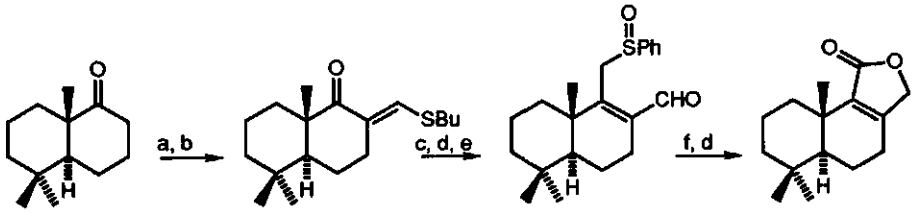
29 **30**

It was expected and hoped for that the sulfoxide would undergo a normal Pummerer reaction to afford an aldehyde function. In this particular situation the Pummerer-type intermediate is intercepted by the neighbouring carbonyl group which results in the formation of a nicely stabilized carbonium ion. Deprotonation of this intermediate then gives (phenylthio)furan **30**. The hydrolysis of this (phenylthio)furan **30** is complete in 4 h at reflux temperature, but up to 10 percent of the other regioisomeric butenolide **32** was isolated. Hydrolysis at room temperature took a week but only the desired regioisomer **31** was formed under these conditions. The overall yield of the annulation procedure was 46% based on ketone **26**. ^{1}H NMR spectra of **31** and **32** strongly supported the structures. The methylene protons adjacent to the oxygen atom in **32** showed a distinct homoallylic spin-spin coupling of 2 Hz at δ 4.70, this in contrast to the spectrum of **31**, which showed a sharp singulet at δ 4.61.

4.3 The synthesis of (±)-Isodrimenin

Having established a useful method for the annulation of butenolides starting from a ketone our attention was focussed on the synthesis of the drimane (±)-isodrimenin **8** [15] and the rearranged drimanic lactone (±)-colorata-4(13),8-dienolide **44**.[16] The lactone (±)-isodrimenin **8** was easily synthesized from *trans*-decalone **6** by application of the above mentioned procedure (see scheme 4.5).

Scheme 4.5



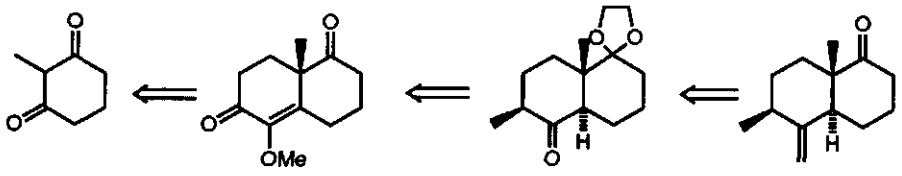
Reagents: *a*, NaH, HCOOEt; *b*, *n*-BuSH, *p*-TsOH, benzene; *c*, $PhSCH_2Li$; *d*, H_2O, HCl, $HgCl_2$; *e*, $NaIO_4$; *f*, Ac_2O, 110 °C.

The introduction of the (*n*-butylthio)methylene moiety was achieved according to the literature [17] and the addition of [(phenylthio)methyl]lithium to the (*n*-butylthio)methylene ketone **33** proceeded to give the adduct in a nearly quantitative yield. The unpurified adduct was hydrolyzed immediately with dilute hydrochloric acid in the presence of mercuric chloride at reflux temperature to afford the γ-(phenylthio)-α,ß-unsaturated aldehyde derivative in 66% yield based on **6**. The oxidation of the sulfide with sodium *meta*periodate gave rise to sulfoxide **7**, which upon heating in acetic anhydride gave regiospecifically the (phenylthio)furan derivative. Hydrolysis with diluted hydrochloric acid and mercuric chloride gave the drimane lactone (±)-isodrimenin **8** in an overall yield of 36%.[18]

4.4 The synthesis of (±)-colorata-4(13),8-dienolide

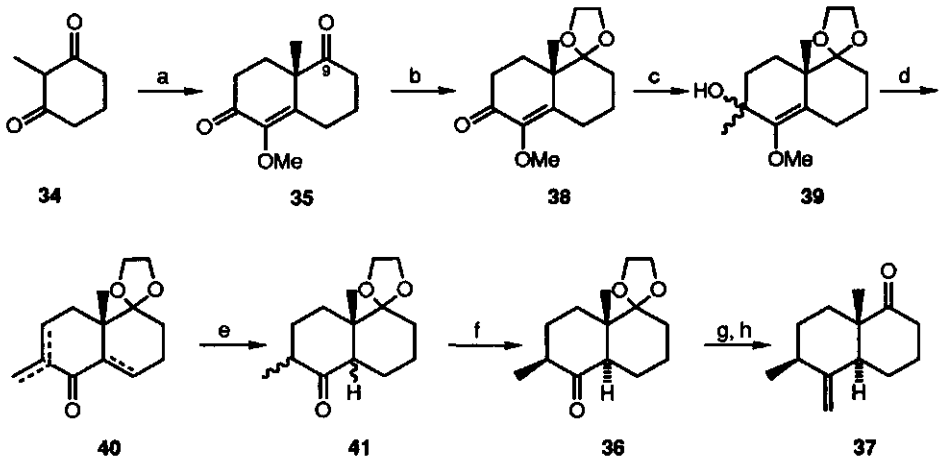
The rearranged drimane (±)-colorata-4(13),8-dienolide **44** [16] was our next goal. Therefore an efficient route to *trans*-decalone **37** had to be developed first and this was achieved starting from the commercially available 2-methyl-cyclohexane-1,3-dione **34**. The retrosynthetic pathway is outlined in scheme 4.6.

Scheme 4.6



Access to intermediate **35** from **34** is known in the literature,[19] but the yield, ranging from 30 to 70% is not easily reproducible. In order to circumvent this problem, we looked for an adaptation to the literature procedures and this was found by refluxing 1,4-dimethoxy-butan-2-one[20] in xylene with tri-*n*-propylamine as base.

Scheme 4.7



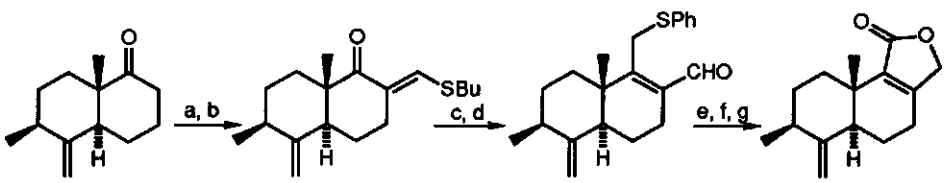
Reagents: *a*, 1,4-Dimethoxy-butan-2-one, tri-*n*-propylamine, xylene, reflux; *b*, *p*-TsOH, MED; *c*, MeLi; *d*, *p*-TsOH, benzene; *e*, H_2, Pd on C; *f*, MeOH, MeONa; *g*, Ph_3PCH_2; *h*, H_2O, HCl.

This gave *in situ* the required 1-methoxy-but-3-en-2-one which underwent a Robinson annulation reaction with 2-methyl-cyclohexane-1,3-dione **34** to the methoxyenone derivative **35** in 55% yield. The C-9 carbonyl function in this product was then selectively protected using 2-methyl-2-ethyl-1,3-dioxolane (MED) [21] at room temperature for seven days to afford monoacetal **38** in 97% yield. Reaction of **35** with MED at 50°C or with ethylene glycol in refluxing benzene afforded after 4 h only a 40-45% yield of monoacetal **38**, due to decomposition of the methoxyenone **35**. The addition of methyl-lithium to **38** gave a nearly quantitative yield of the two possible diastereoisomeric alcohols **39**. The acid catalyzed dehydration of **39** was rather troublesome due to the facile hydrolysis of the acetal function. The use of waterfree *p*-toluenesulfonic acid in dry benzene circumvented this problem because in this way, after dehydration, just the one molecule of water was provided which is necessary for the hydrolysis of the methoxy enol ether. In this way a mixture of unsaturated ketones **40** was obtained with the double bonds in the indicated positions.[22] This crude mixture was hydrogenated at

atmospheric pressure with palladium on carbon as the catalyst to afford again a mixture of saturated ketones **41**. This mixture finally could be equilibrated to pure **36** using sodium methanolate in methanol. Although it might not seem very satisfactory to continue the sequence from **38** to **36** without purification and thorough identification of all the intermediates, it did give a good and reproducible yield of 73% of one single compound **36**. The reaction at 50°C of **36** with 2.5 equivalents of methylenetriphenylphosphorane, formed with sodium hydride in dimethyl sulfoxide from methyltriphenylphosphonium iodide [23], gave a 80% yield of the methylene ketal, which after hydrolysis afforded the desired *trans*-fused bicyclic methylene ketone **37**.[24a] The overall yield of 31%, based on 2-methyl-cyclohexane-1,3-dione **34**, is fully comparable with another synthesis of **37**, which was published later on.[24b] The equilibration of **41** performed with sodium methanolate in methanol, can be omitted because an equilibration takes place under the conditions of the Wittig reaction.

Starting from **37** the established procedure was carried out for the construction of the butenolide moiety and no serious problems were encountered in the synthesis.

Scheme 4.8



37 **42** **43** **44**

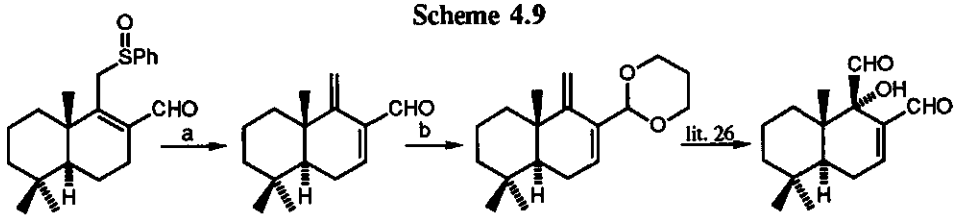
Reagents: *a*, NaH, HCOOEt; *b*, *n*-BuSH, *p*-TsOH, benzene; *c*, $PhSCH_2Li$; *d*, H_2O, HCl, $HgCl_2$; *e*, $NaIO_4$; *f*, Ac_2O, 110 °C.

It should be mentioned that the hydrolysis steps in the sequence required some care. These hydrolyses must be carried out at room temperature to prevent isomerization of the *exo* cyclic 4(13)-double bond. Under these circumstances it took about four weeks to achieve complete conversion of the (phenylthio)furan into the butenolide **44**. After one week the conversion was about 65%. The rearranged drimanic lactone (±)-colorata-4(13),8-dienolide **44** was obtained in 25% yield based on **37**. The ^1H NMR and IR spectra of **44** were in complete agreement with those of the natural product which were kindly provided by professor R.E. Corbett.[16]

4.5 A formal total synthesis of (±)-warburganal

In chapter 4.2 it was mentioned that one of the intentions of the Pummerer reaction of sulfoxide **29** was to achieve a higher oxidation state at the sulfur-bearing carbon atom. An alternative way to achieve this goal is *via* elimination of phenylsulfenic acid from this same sulfoxide **29** followed by selective oxidation of the resulting diene.
The feasibility of such an approach was based on earlier work from our own laboratory [11,25] and on the results of Goldsmith *et al.* [26] who had shown that the selective osmylation and further oxidation of diene **46** to (±)-warburganal **1** can be performed in good yield.

Scheme 4.9



7 **45** **46** **1**

Reagents: *a*, K_2CO_3, toluene, reflux; *b*, propane-1,3-diol, *p*-TsOH, benzene.

The elimination of phenylsulfenic acid from sulfoxide **7** proceeded well at the reflux temperature of toluene in the presence of potassium carbonate to give the diene aldehyde **45** in 90% yield. Acetal formation with **45** was achieved with propane-1,3-diol to afford the propylene acetal **46** in quantitative yield. Since this compound has already been converted into warburganal **1**, our approach constitutes a formal route to (±)-warburganal **1** from ketone **6**.[27]

4.6 Experimental section

Melting points, which were determined on a C. Reichert, Vienna, apparatus, and boiling points are uncorrected.
^{1}H NMR spectra were recorded on a Hitachi Perkin-Elmer R-24B (60 MHz) or a Varian EM-390 (90 MHz) or a Bruker AC 200E (200 MHz) spectrometer.
Chemical shifts are reported in the δ scale as parts per million (ppm) downfield from the internal tetramethylsilane (TMS) in chloroform-*d* as the solvent unless otherwise stated.
^{13}C NMR spectra were recorded on a Varian XL-100 (25.2 MHz) or a Bruker AC 200E (50.33 MHz) or a Bruker CXP-300 (75.46 MHz) in the pulse FT mode using chloroform-*d* as solvent and tetramethylsilane as internal standard.

Mass spectral data and accurate mass measurements were obtained from an AEI-MS-902 equipped with a VG ZAB console or from a VG Micromass 7070F.
Infrared spectra were recorded on a Hitachi EPI-G3 spectrometer. Elemental analysis were performed on a Carlo Erba elemental analyser 1106.
Optical rotations were measured on a Bellinghan and Stanley polarimeter.
GLC analysis were carried out on a Varian 3700 chromatograph provided with a 2 m glass column packed with 3 % SP-2250 on Chromosorb W. Flash chromatography [28] was carried out on Merck Silica gel 60 (230-400 mesh ASTM) and column chromatography on Merck silica gel 60 (70-230 mesh ASTM).
Light petroleum refers to petroleum ether bp 40-60°C. The solvents for column chromatography were always distilled prior to usage.
For all dry reactions performed under a steady stream of nitrogen the equipment was dried in an oven at 150°C for several hours and allowed to cool in an atmosphere of dry nitrogen. Dry tetrahydrofuran (THF) was obtained by distillation of the commercial material from sodium hydride. Dry benzene was obtained by storage of benzene over sodium wire. Hexane and ether were dried by storage of the distilled solvent over sodium wire and other dry solvents were obtained by storage of distilled material over molecular sieves.
Aqueous solutions were usually extracted three times with ether. The combined organic extracts were washed with brine and dried on magnesium sulfate prior to filtration and evaporation of the solvent under reduced pressure.

5,5,8aß-Trimethyl-6,7,8,8a-tetrahydronaphthalen-1(5H)-one (24)

To a solution of 17.44 g (90.8 mmol) of ketone **23** [29] in glacial acetic acid (100 mL) was added dropwise a solution of 14.53 g (90.8 mmol) of bromine in glacial acetic acid (40 mL) at room temperature under nitrogen. After 45 min the solution was poured into ice water (250 mL) and the aqueous layer was extracted with ether. The organic layer was washed with water, saturated aqueous sodium bicarbonate solution and brine and dried. Evaporation of the solvent gave the crude bromide which was then dissolved in dimethylformamide (100 mL) and 8.7 g (100 mmol) of lithium bromide and 11.1 g (150 mmol) of lithium carbonate were added. The suspension was stirred at 120°C for 30 min under nitrogen, cooled, poured into water (300 mL), and worked up as usual. The residual yellow solid was chromatographed over silica gel (eluent light petroleum-ethyl acetate 19:1) and yielded 14.15 g (82 %) of the dienone **24**, mp 44-45°C.
^{1}H NMR 1.19 (s, 3H), 1.26 (s, 3H), 1.38 (s, 3H), 1.1-2.5 (6H), 5.89 (d, J=10 Hz, 1H), 6.17 (d, J=7 Hz, 1H), 6.98 (dd, J=7,10 Hz, 1H); IR (KBr) 1665, 1620; MS *m/e* (%) 190 (100, M^+), 175 (58), 147 (73), 134 (56), 122 (75), 121 (75), 91 (76), 69 (56), 41 (73); HRMS, calcd for $C_{13}H_{18}O$ (M^+) *m/e* 190.1358, found *m/e* 190.1357; Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.13; H, 9.51.

5,5,8aß-Trimethyl-3,4,4aα,5,6,7,8,8a-octahydronaphthalen-1(2H)-one (6)

To a solution of 12.5 g (65.8 mmol) of dienone **24** in a mixture of 1:1 methanol-benzene (300 mL) was added 850 mg (0.93 mmol) of Wilkinson's catalyst. This mixture was hydrogenated in a hydrogen atmosphere at a pressure of 30 psi. The reaction mixture was evaporated and purified by flash chromatography on silica gel (eluent light petroleum-ethyl acetate 19:1). There was obtained 10.98 g (86%) of ketone **6** as a light yellow oil which solidified on standing, mp 41-42°C.
^{1}H NMR 0.91 (s, 3H), 0.95 (s, 3H), 1.16 (s, 3H), 1.0-2.9 (13H); IR (KBr) 1705; MS *m/e* (%) 194 (61, M^+), 179 (53), 176 (11), 161 (50), 151 (20), 150 (21), 123 (83), 111 (65), 95 (84), 69 (88), 41 (100); HRMS, calcd for $C_{13}H_{22}O$ (M^+) *m/e* 194.1671, found *m/e* 194.1670; Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.43; H, 11.41.

5,5,8aß-Trimethyl-1,2,3,5,6,7,8,8a-octahydronaphthalen-1ß-ol (25)

A solution of 55.3 g (288 mmol) of ketone **23** [29] in dry THF (100 mL) was dropped into a stirred solution of 292.5 g (1150 mmol) of lithium tri-*tert*-butoxyaluminohydride in dry THF (1000 mL) at 0°C. The reaction mixture was stirred for 5 h at room temperature and then cooled to 0°C and water (200 mL) was dropped in. The precipitate was filtered, washed with THF and the combined filtrate was concentrated *in vacuo*. The residue was dissolved in chloroform and the solution was washed with 4 N sulfuric acid (100 mL), saturated sodium bicarbonate solution (100 mL) and brine (100 mL), dried and evaporated to give a crystalline material which was recrystallized from light petroleum bp 40-60°C. The yield was 50.8 g (91%) of **25**, mp 115-117°C.
^{1}H NMR 1.05 (s, 3H), 1.15 (s, 6H), 1.2-2.3 (11H), 3.50 (dd, J=8,11 Hz, 1H), 5.40 (t, J=3 Hz, 1H); IR (KBr) 3620, 3450, 1640; MS *m/e* (%) 194 (7, M^+), 179 (6), 176 (28), 161 (21), 150 (57), 135 (100), 123 (8), 121 (8), 119 (8), 107 (15), 105 (13); HRMS, calcd for $C_{13}H_{22}O$ (M^+) *m/e* 194.1671, found *m/e* 194.1673. Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.29; H, 11.32.

5,5,8aß-Trimethyl-3,4,4aα,5,6,7,8,8a-octahydronaphthalen-1(2H)-one (6)

To a solution of 20.36 g (104.9 mmol) of **25** in glacial acetic acid (200 mL) was added 0.95 g (4.2 mmol) of PtO_2. This mixture was hydrogenated overnight in a hydrogen atmosphere at a pressure of 30 psi. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was dissolved in chloroform (200 mL) and the solution was washed with saturated sodium bicarbonate solution (100 mL) and brine (100 mL), dried and evaporated to afford an oil which slowly crystallized on standing. The crude alcohol, **5,5,8aß-trimethyl-trans-perhydronaphthalen-1ß-ol**, mp 71-73°C; ^{1}H NMR 0.85 (s, 6H), 0.90 (s, 3H), 1.0-1.9 (14H),

3.15 (dd, J=4,9 Hz, 1H), was dissolved in acetone (200 mL) and to the solution was added Jones reagent [30] at 0°C until the orange colour persisted. The excess reagent was destroyed by the addition of a few drops of 2-propanol. The solution was decanted from the green precipitate, which was washed with acetone (5 x 25 mL). The combined acetone solution was concentrated *in vacuo* and the residue was dissolved in ether, washed with 4 N sulfuric acid (100 mL) and brine (50 mL), dried and evaporated to give 19.85 g (97%) of yellowish crystals of ketone **6**, mp 40-42°C. The spectroscopic properties of this compound were identical to those of the sample prepared before.

3,3-Dimethyl-2[(phenylthio)methyl]-1-cyclohexene-1-carboxaldehyde (28)

To a stirred solution of 15.75 g (140.6 mmol) of DABCO and 17.41 g (140.6 mmol) of thioanisole in dry THF (200 mL) at 0°C in a nitrogen atmosphere was added dropwise a solution of 140.6 mmol of *n*-butyllithium in hexane (100.0 mL). The solution was stirred for 45 min at room temperature cooled again to 0°C and a solution of 26.6 g (117.0 mmol) of (*n*-butylthio)methylene ketone **27** [12] in THF (50 mL) was added dropwise over 20 min. After 3 h the reaction mixture was poured into a saturated aqueous ammonium chloride solution (200 mL) and worked up as usual. The residue was dissolved in ethanol (250 mL) and to this solution was added 33.9 g (125 mmol) of mercuric chloride dissolved in 4 N hydrochloric acid (35 mL) and stirred overnight. The precipitate was filtered, washed with ethanol (3 x 25 mL) and the filtrate was concentrated *in vacuo*. The residue was dissolved in ether (500 mL) and washed with brine (200 mL) and dried. The solvent was evaporated and the crystalline residue was recrystallized from pentane to afford 27.4 g (90%) of **28**, mp 51-51.5 °C.
^{1}H NMR 1.26 (s, 6H), 1.4-1.8 (4H), 2.1-2.3 (2H), 3.96 (s, 2H), 7.3 (br s, 5H), 10.28 (s, 1H); IR (KBr) 1675, 1620, 1585; MS *m/e* (%) 260 (15, M^+), 150 (100), 137 (27), 107 (21), 81 (20); HRMS, calcd for $C_{16}H_{20}OS$ (M^+) *m/e* 260.1235, found *m/e* 260.1239; Anal. Calcd for $C_{16}H_{20}OS$: C, 73.80; H, 7.74. Found: C, 73.56; H, 7.79.
2,4-DNPH, mp 179-180°C. Anal. Calcd for $C_{22}H_{24}N_4O_4S$: C, 59.98; H, 5.49. Found: C, 59.79; H, 5.66.

3,3-Dimethyl-2[(phenylsulfinyl)methyl]-1-cyclohexene-1-carboxaldehyde (29)

A solution of 5.06 g (19.5 mmol) of **28** in methanol (200 mL) and water (20 mL) was added to a solution of 4.57 g (21.4 mmol) of $NaIO_4$ in methanol (400 mL) and water (40 mL) and stirred overnight. The precipitate was filtered and washed with methanol (3 x 50 mL). The filtrate was concentrated *in vacuo* and the residue was dissolved in chloroform (300 mL). The solution was washed with water (50 mL), brine (50 mL), dried and evaporated to give 4.84 g (90%) of crystalline **29**. An analytical sample was obtained after recrystallization from diisopropyl ether, mp 145-146°C.

^{1}H NMR 1.16 (s, 3H), 1.22 (s, 3H), 1.6-1.8 (4H), 2.2-2.6 (2H), 3.98 (q_{AB}, δ_A 3.70, δ_B 4.23, J_{AB} =13 Hz, 2H), 7.6 (5H), 9.80 (s, 1H).
Anal. Calcd for $C_{16}H_{20}O_2S$: C, 69.53; H, 7.29. Found: C, 69.53; H, 7.36.

7,7-Dimethyl-1-phenylthio-4,5,6,7-tetrahydroisobenzofuran (30)

A solution of 2.58 g (9.3 mmol) of **29** in acetic anhydride (20 mL) was stirred for 90 min at 110°C under nitrogen. After cooling, the reaction mixture was poured into aqueous 4 N NaOH (100 mL) and stirred for 30 min. Work-up as usual followed by flash chromatography on silica gel (eluent light petroleum-ethyl acetate 99.9:0.1) afforded 1.76 g (73%) of **30** as an oil.
^{1}H NMR 1.28 (s, 6H), 1.5-1.8 (4H), 2.3-2.6 (2H), 7.1 (5H), 7.22 (s, 1H); MS *m/e* (%) 258 (68, M^+), 243 (100), 105 (8), 91 (9), 81(7), 77 (8); HRMS, calcd for $C_{16}H_{18}OS$ (M^+) *m/e* 258.1076, found *m/e* 258.1071.

7,7-Dimethyl-4,5,6,7-tetrahydroisobenzofuran-1(3H)-one (31)

To a solution of 1.56 g (6.0 mmol) of **30** in methanol (100 mL) and water (6 mL) was added a solution of 1.08 g (4.0 mmol) of mercuric chloride in methanol (100 mL) and 4 N HCl (6 mL). This reaction mixture was stirred at room temperature until the hydrolysis was complete (1 to 5 days). The precipitate was filtered and washed with methanol (3 x 25 mL).
The methanol was evaporated *in vacuo* and the residue was dissolved in ether. Work-up as usual and flash chromatography on silica gel (eluent light petroleum-ethyl acetate 9:1) yielded 0.90 g (90%) of **31** as an oil.
^{1}H NMR 1.22 (s, 6H), 1.5-2.4 (6H), 4.59 (s, 2H); IR (film) 1770, 1630; MS *m/e* (%) 166 (95, M^+), 151 (100), 138 (17), 137 (18), 123 (68), 121 (30), 95 (44), 93 (48), 91 (19), 79 (18), 77 (18); HRMS, calcd for $C_{10}H_{14}O_2$ (M^+) *m/e* 166.0994, found *m/e* 166.0994. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.35; H, 8.52.

7,7-Dimethyl-4,5,6,7-tetrahydroisobenzofuran-3(1H)-one (32)

Hydrolysis of 0.774 g (3 mmol) of **30** at reflux temperature afforded after work-up as described for **31** a mixture of **31** and **32**, which was separated into the two isomeric lactones by careful chromatography on silica gel (eluent light petroleum-ethyl acetate 19:1).
31: 0,29 g (58%), oil, and **32**: 0.15 g (30%), white solid mp 39-40°C.
^{1}H NMR 1.17 (s, 6H), 1.5-2.4 (6H), 4.70 (t, J=2 Hz, 2H); IR (KBr) 1765, 1670; MS *m/e* (%) 166 (52, M^+), 151 (43), 138 (9), 137 (19), 123 (37), 121 (100), 97 (63), 95 (36), 93 (45), 79 (30), 77 (19), 70 (67); HRMS, calcd for $C_{10}H_{14}O_2$ (M^+) *m/e* 166.0994, found *m/e* 166.0992. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.38; H, 8.54.

5,5,8aß-Trimethyl-1-[(phenylsulfinyl)methyl]-3,4,4aα,5,6,7,8,8a-octahydronaphthalene-2-carboxaldehyde (7)

The (*n*-butylthio)methylene ketone **33**[17], 8.92 g (30.3 mmol), was treated with [(phenylthio)-methyl]lithium[31] in the same way as described for (*n*-butylthio)methylene ketone **27**. After work-up 9.16 g (92%) of **5,5,8aß-trimethyl-1-[(phenylthio)methyl]-3,4,4aα,5,6,7,8,8a-octahydronaphthalene-2-carboxaldehyde** was obtained, mp 55-57°C.
^{1}H NMR 0.88 (s, 3H), 0.96 (s, 3H), 1.14 (s, 3H), 1.2-2.1 (9H), 2.27 (2H), 3.91 (q_{AB}, δ_A 3.67, δ_B 4.12, J_{AB}=12 Hz, 2H), 7.24 (br *s*, 5H), 9.97 (s, 1H); MS *m/e* (%) 328 (38, M^+), 299 (7), 218 (100), 203 (29), 175 (11), 105 (14), 91 (11), 81(13); HRMS, calcd for $C_{12}H_{28}OS$ (M^+) *m/e* 328.1863, found *m/e* 328.1863. Anal. Calcd for $C_{12}H_{28}OS$: C, 76.78; H, 8.59. Found: C, 76.72; H, 8.61.
2,4-DNPH, mp 173-175°C. Anal. Calcd for $C_{27}H_{32}N_4O_4S$: C, 63.75; H, 6.34. Found: C, 63.54; H, 6.25.

This γ-(phenylthio)-α,ß-unsaturated aldehyde was oxidized with $NaIO_4$ as described for **28**. After the usual work-up 9.6 g (92%) of sulfoxide **7** was obtained, mp 139-140°C.
^{1}H NMR 0.90 (s, 3H), 0.95 (*s*, 3H), 1.13 (s, 3H), 1.3-2.6 (11H), 3.93 (q_{AB}, δ_A 3.58, δ_B 4.25, J_{AB}=13 Hz, 2H), 7.55 (m, 5H), 9.95 (s, 1H). Anal. Calcd for $C_{21}H_{28}O_2S$: C, 73.21; H, 8.19. Found: C, 73.19; H, 8.01.

6,6,9aß-Trimethyl-4,5,5aα,6,7,8,9,9a-octahydronaphtho[1,2-c]furan-1(3H)-one (Isodrimenin) (8)

A solution of 2.41 g (7.0 mmol) of sulfoxide **7** in acetic anhydride was treated as described for sulfoxide **29** and afforded 1.80 g (79%) of **6,6,9aß-trimethyl-1-(phenylthio)-4,5,5aα,6,7,8,9,9a-octahydronaphtho[1,2-*c*]furan** as an oil.
^{1}H NMR 0.89 (s, 3H), 0.95 (s, 3H), 1.21 (s, 3H), 1.3-1.9 (9H), 2.6-3.0 (2H), 7.1 (5H), 7.21 (s, 1H); MS *m/e* (%) 326 (100, M^+), 311 (62), 201 (41), 105 (7), 91 (13), 81 (4), 77 (7), 69 (35); HRMS, calcd for $C_{21}H_{26}OS$ (M^+) *m/e* 326.1703, found *m/e* 326.1708.

This (phenylthio) furan was hydrolyzed as described for (phenylthio) furan **30**. After work-up 1.17 g (90%) of the lactone isodrimenin was obtained, mp 88-90°C.
^{1}H NMR 0.90 (s, 3H), 0.95 (s, 3H), 1.18 (s, 3H), 1.2-2.5 (11H), 4.58 (s, 2H); IR (KBr) 1760, 1670; MS *m/e* (%) 234 (28, M^+), 219 (100), 189 (11), 163 (19), 151 (54), 123 (26), 95 (11), 91 (18), 81 (13), 79 (12), 77 (11); HRMS, calcd for $C_{15}H_{22}O_2$ (M^+) *m/e* 234.1620, found *m/e* 234.1615. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.88; H, 9.37.

5-Methoxy-8aß-methyl-3,4,8,8a-tetrahydronaphtalene-1(2H),6(7H)-dione (35)

A solution of 28.35 g (225 mmol) of 2-methyl-cyclohexane-1,3-dione **34** and 33.0 g (250 mmol) of 1,4-dimethoxy-2-butanon[20] in *p*-xylene (400 mL) was treated with tri-*n*-propylamine (20 mL) and refluxed for 48 h in a nitrogen atmosphere. The reaction mixture was diluted with ether (400 mL) and washed with 4 N HCl (50 mL), saturated sodium bicarbonate solution (100 mL) and brine (50 mL), dried on magnesium sulfate and evaporated to give a dark brown residue, which crystallized on standing. Recrystallization from diisopropyl ether afforded 25.7 g (55%) of **35**, mp 74-76°C.
Another 5.0 g (11%) of crystals were obtained after flash chromatography on silica gel (eluent light petroleum-ethyl acetate 3:2) of the mother liquor.
^{1}H NMR 1.43 (s, 3H), 1.6-3.2 (10H), 3.63 (s, 3H); IR (KBr) 1720, 1680, 1620; MS *m/e* (%) 208 (70, M^+), 193 (2), 180 (11), 177 (25), 165 (100), 152 (75), 138 (71), 137 (83), 124 (32), 123 (40), 109 (31), 79 (42); HRMS, calcd for $C_{12}H_{16}O_3$ (M^+) *m/e* 208.1099, found *m/e* 208.1100. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.39; H, 7.82.

5'-Methoxy-8'aß-methyl-3',4',8',8'a-tetrahydro-spiro[1,3-dioxolane-2,1'(2'H)-naphthalen]-6'(7'H)-one (38)

A solution of 28.08 g (135 mmol) of methoxy enone **35** in 2-methyl-2-ethyl-1,3-dioxolane (MED) (100 mL) was treated with glycol (1 mL) and 100 mg of *p*-toluenesulfonic acid monohydrate for 7 days at room temperature. Ether (300 mL) was added and the solution was washed with saturated sodium bicarbonate solution (100 mL) and brine (100 mL). The solution was dried on $MgSO_4$, filtered and evaporated to afford 31.5 g of crude **38**. Recrystallization from a 1:1 mixture of light petroleum bp 40-60°C and diisopropyl ether gave 29.95 g (88%) of **38**, mp 68°C.
^{1}H NMR 1.29 (s, 3H), 1.5-3.2 (10H), 3.50 (s, 3H), 3.93 (br s, 4H); IR (KBr) 1675, 1615, 1450;MS *m/e* (%) 252 (8, M^+), 237 (1), 221 (4), 100 (5), 99 (100), 91 (5), 77 (8), 55 (18); HRMS, calcd for $C_{14}H_{20}O_4$ (M^+) *m/e* 252.1362, found *m/e* 252.1361. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.62; H, 7.99. Found: C, 66.94; H, 7.90.

5'-Methoxy-6ξ,8'aß-dimethyl-3',4',6',7',8',8a'-hexahydro-spiro-[1,3-dioxolane-2,1'(2'H)-naphthalen]-6'-ol (39)

A solution of methyllithium in ether (80 mL, 120 mmol) was added dropwise with stirring to a solution of 25.2 g (100 mmol) of ketone **38** in ether (250 mL) at 0°C under nitrogen. After 60 min water (15 mL) was added and the reaction mixture was worked up as usual to afford 26.8 g (100%) of a colourless oil. According to GC and ^{1}H NMR this oil proved to be a 1:1 mixture of two stereoisomeric alcohols **39**.

^{1}H NMR 1.18, 1.22, 1.32, 1.38 (s, total 6H), 3.64 (s, 3H), 3.93 (br s, 4H); IR (film) 3610, 3400, 1605, 1455; MS *m/e* (%) 268 (2, M^+), 253 (1), 250 (8), 219 (4), 151 (18), 121 (7), 99 (100), 95 (6), 93 (2); HRMS, calcd for $C_{15}H_{24}O_4$ (M^+) *m/e* 268.1674, found *m/e* 268.1674.

6'ß,8'aß-Dimethyl-2',3',4',4'aα,6',7',8',8'a-octahydro-spiro[1,3-dioxolane-2,1'(5'H)-naphthalen]-5'-one (36)

A solution of 1.9 g (10 mmol) of *p*-toluenesulfonic acid monohydrate in benzene (500 mL) was refluxed for 1 h under a Dean-Stark water separator in a nitrogen atmosphere.
A solution of 25.2 g (94 mmol) of **39** in dry benzene (100 mL) was added and refluxed for 90 min. The reaction mixture was worked up as usual to afford 22.2 g (100%) of an oil, which consisted of three isomers **40** according to GCMS analysis.
This unpurified isomeric mixture was dissolved in ethanol (250 mL) and 1.0 g of Pd on carbon (10%) was added and then stirred vigorously in an atmosphere of hydrogen. After 90 min the uptake of hydrogen stopped and the mixture was filtered. The filtrate was concentrated to provide 22.2 g (99%) of crude **41**. According to GCMS this mixture consisted of two isomeric compounds (M^+) *m/e* 238 and was not purified.
The isomeric ketones **41** were dissolved in methanol (250 mL) and treated with a solution of 5.0 g (93 mmol) of sodium methanolate in methanol (100 mL). After 16 h the reaction mixture was concentrated and worked up as usual to provide crude ketone **36**, which was purified by bulb to bulb distillation at 0.3 torr to yield 16.33 g (73%) of crystalline ketone **36**, mp 50-51°C.
^{1}H NMR 0.87 (s, 3H), 0.99 (d, J=6 Hz, 3H), 1.3-1.9 (6H), 2.0-2.4 (3H), 2.6 (1H), 3.92 (br s, 4H); ^{13}C NMR 14.5 (q), 15.6 (q), 20.0 (t), 21.6 (t), 29.6 (t), 30.2 (t), 31.6 (t), 44.5 (d), 48.1 (s), 54.8 (d), 65.4 (t), 112.0 (s), 200.5 (s); IR (KBr) 1710, 1460; MS *m/e* (%) 238 (12, M^+), 223 (1), 112 (100), 99 (96), 86 (58); HRMS, calcd for $C_{14}H_{22}O_3$ (M^+) *m/e* 238.1569, found *m/e* 238.1569. Anal. Calcd for $C_{14}C_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.53; H, 9.41.

6ß,8aß-Dimethyl-5-methylene-3,4,4aα,5,6,7,8,8a-octahydronaphthalen-1(2H)-one (37)

To anhydrous DMSO (100 mL) was added 2.10 g (70 mmol) of sodium hydride as a 80% dispersion in oil and the slurry was heated at 65° until evolution of hydrogen ceased. The mixture was cooled to room temperature and a solution of 28.28 g (70 mmol) of methyltriphenylphosphonium iodide in DMSO (200 mL) was added dropwise and the mixture stirred for 30 min. A solution of 14.28 g (60 mmol) of keto acetal **36** in DMSO (50 mL) was added dropwise and the reaction mixture heated at 50°C for 3 h. The cooled mixture was poured into water (500 mL) and extracted with pentane (4 x 200 mL) and the combined organic extracts were washed with water (200 mL) and brine (2 x 50 mL) and dried. The solvent

was evaporated and the residue was purified by flash chromatography (eluent light petroleum-ether 9:1) to give 11.33 g (80%) of light yellow crystals of **6'ß,8'ß-dimethyl-5'-methylene-3',4,4'aα,5',6',7',8',8a'-octahydro-spiro[1,3-dioxolane-2,1'(2)'-naphthalene]**, mp 40-42°C. ^{1}H NMR 0.82 (s, 3H), 1.00 (d, J=6 Hz, 3H), 1.2-2.4 (12H), 3.88 (br s, 4H), 4.60 (br s, 1H), 4.70 (br s, 1H); ^{13}C NMR 14.8 (q), 18.5 (q), 22.5 (t), 23.9 (t), 30.5 (t), 30.6 (t), 32.4 (t), 38.4 (d), 44.9 (s), 47.5 (d), 65.1 (t), 65.3 (t), 103.8 (t), 113.1 (s), 154.6 (s); IR (KBr) 1645, 1455; MS *m/e* (%) 236 (4, M^+), 221 (2), 181 (5), 174 (16), 161 (7), 112 (19), 99 (100), 86 (30), 73 (12), 55 (10); HRMS, calcd for $C_{15}H_{24}O_2$ (M^+) *m/e* 236.1776, found *m/e* 236.1775; Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.05; H, 10.25.

To a solution of 10.90 g (46.2 mmol) of the above-mentioned acetal in methanol (50 mL) were added water (5 mL) and concentrated hydrochloric acid (1 mL) and stirred for 4 h at room temperature. The methanol was evaporated *in vacuo* at 20°C and the residue was worked up as usual to give after recrystallization from pentane 10.6 g (98%) of ketone **36** as white crystals, mp 47-48°C.
^{1}H NMR 0.97 (s, 3H), 1.05 (d, J=6 Hz, 3H), 1.5-2.7 (12H), 4.70 (d, J=0.9 Hz, 1H), 4.82 (d, J=0.9 Hz, 1H); ^{13}C NMR 16.7 (q), 18.1 (q), 23.7 (t), 25.6 (t), 31.9 (t), 33.0 (t), 37.1 (t), 38.1 (d), 50.4 (s), 51.5 (s), 105.1 (t), 152.2 (s), 215.2 (s); IR (KBr) 1705, 1640; MS *m/e* (%) 192 (62, M^+), 177 (13), 159 (11), 137 (100), 135 (30), 121 (66), 109 (77), 93 (65), 77 (33), 41 (75); HRMS, calcd for $C_{13}H_{20}O$ (M^+) *m/e* 192.1514, found *m/e* 192.1513. Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 80.91; H, 10.46.

2-[(Butylthio)methylene]-6ß,8aß-dimethyl-5-methylene-3,4,4aα,5,6,7,8,8a-octahydro-naphthalen-1(2H)-one (42)

A solution of 9.6 g (50 mmol) of ketone **37** and 7.4 g (100 mmol) of ethyl formate in dry ether (100 mL) was added dropwise to a dispersion of 1.65 g (55 mmol) of a 80% dispersion in oil of sodium hydride in dry ether (250 mL) at room temperature and stirred overnight. Water (50 mL) was added and the reaction mixture was extracted three times with 2 N sodium hydroxide (100 mL). The combined aqueous extracts were acidified and worked up as usual to furnish 10.0 g (91%) of **2-(hydroxymethylene)-6ß,8aß-dimethyl-5-methylene-3,4,4aα, 5,6,7,8,8a- octahydronaphthalen-1(2H)-one** as a yellow oil.
^{1}H NMR 0.85 (s, 3H), 1.04 (d, J=6 Hz, 3H), 1.2-2.6 (10H), 4.58 (d, J=0.9 Hz, 1H), 4.80 (d, J=0.9 Hz, 1H), 8,52 (s, 1H), 14.50 (br s, 1H); IR (film) 1640, 1630, 1580; MS *m/e* (%) 220 (45, M^+), 192 (20), 191 (22), 177 (19), 135 (48), 107 (26), 91 (92), 77 (63), 69 (28), 67 (42), 55 (100); HRMS, calcd for $C_{14}H_{20}O_2$ (M^+) *m/e* 220.1463, found *m/e* 220.1461.

To a solution of 9.90 g (45.0 mmol) of the above-mentioned formyl decalone in benzene (250 mL) was added 4.5 g (50 mmol) of 1-butanethiol and 100 mg of *p*-toluenesulfonic acid

monohydrate and the mixture was refluxed for 60 min in a Dean-Stark apparatus. The reaction mixture was poured into a saturated aqueous sodium bicarbonate solution (200 mL) and worked up as usual to provide a crystalline residue, which was recrystallized from pentane to afford 12.1 g (92%) of **42** as light yellow crystals, mp 55-55.5°C.
^{1}H NMR 0.87 (s, 3H), 0.93 (t, J=6 Hz, 3H), 1.06 (d, J=6 Hz, 3H), 1.2-2.7 (14H), 2.85 (t, J=6 Hz, 2H), 4.70 (d, J=0.9 Hz, 1H), 4.84 (d, J=0.9 Hz, 1H), 7.57 (br s, 1H); IR (KBr) 1665, 1640; MS *m/e* (%) 292 (30, M^+), 253 (100), 203 (10), 175 (12), 161 (24), 159 (11), 129 (12); HRMS, calcd for $C_{18}H_{28}OS$ (M^+) *m/e* 292.1861, found *m/e* 292.1857. Anal. Calcd for $C_{18}H_{28}OS$: C, 73.92; H, 9.65. Found: C, 74.38; H, 9.57.

6ß,8aß-Dimethyl-5-methylene-1-[(phenylthio)methyl]-3,4,4aα,5,6,7,8,8a-octahydronaphthalene-2-carboxaldehyde (43)

The γ-(phenylthio)-α,ß-unsaturated aldehyde **43** was prepared in the same way as described for aldehyde **28**. Starting from 11.5 g (39.4 mmol) of (*n*-butylthio)methylene ketone **42** there was obtained 11.7 g (91%) of aldehyde **43** as white crystals, mp 89-90°C.
^{1}H NMR 0.93 (s, 3H), 1.07 (d, J=6 Hz, 3H), 1.5-2.6 (10H), 3.95 (q_{AB}, δ_A 3.75, δ_B 4.15, J_{AB} =11 Hz, 2H), 4.63 (d, J=0.9 Hz, 1H), 4.81 (d, J=0.9 Hz, 1H), 7.31 (br s, 5H), 10.21 (s, 1H). IR (KBr) 1695, 1620, 1605; MS *m/e* (%) 326 (27, M^+), 216 (100), 173 (93), 105 (17), 91 (19), 81 (16), 79 (16); HRMS, calcd for $C_{21}H_{26}OS$ (M^+) *m/e* 326.1704, found *m/e* 326.1707. Anal. Calcd for $C_{21}H_{26}OS$: C, 77.25; H, 8.03. Found: C, 76.93; H, 7.80.
2,4-DNPH, mp 103-105°C; Anal. Calcd for $C_{27}H_{30}N_4O_4S$: C, 64.01; H, 5.97. Found: C, 63.86; H, 5.82.

7ß,9aß-Dimethyl-6-methylene-4,5,5aα,6,7,8,9,9a-octahydronaphtho[1,2-c]furan-1(3H)-one (Colorata-4(13),8-dienolide) (44)

The oxidation of the sulfide **43** with $NaIO_4$ was performed as previously described. Starting from 11.4 g (35 mmol) of **43** there was obtained 11.0 g (92%) of a rather unstable oil, which was most conviently directly converted into **7ß,9aß-dimethyl-6-methylene-1-(phenylthio)-4,5,5aα,6,7,8,9,9a-octahydronaphtho[1,2-c]furan** as described for sulfoxide **29**, yield 6.46 g (62%).
^{1}H NMR 0.95 (s, 3H), 1.04 (d, J=6 Hz, 3H), 1.2-2.9 (10H), 4.62 (d, J=0.9 Hz, 1H), 4.80 (d, J=0.9 Hz, 1H), 7.1-7.2 (5H), 7.22 (s, 1H); MS *m/e* (%) 324 (100, M^+), 309 (54), 200 (19), 199 (15), 105 (6), 91 (14), 81 (4), 77 (9); HRMS, calcd for $C_{21}H_{24}OS$ (M^+) *m/e* 324.1546; found *m/e* 324.1551.
The above-mentioned (phenylthio)furan was hydrolyzed as described for **30**. After 5 days at room temperature there was obtained from 4.86 g (15.0 mmol) of the (phenylthio)furan 2.12 g (61%) of colorata-4(13),8-dienolide **44**, mp 101-103°C.

^{1}H NMR 0.93 (s, 3H), 1.06 (d, J=6 Hz, 3H), 1.1-2.5 (10H), 4.62 (br s, 2H), 4.80 (br s, 2H); ^{1}H NMR (C_6D_6) 0.90 (s, 3H), 0.96 (d, J=6Hz, 3H), 1.1-1.9 (8H), 2.7-2.9 (2H), 3.87 (s, 2H), 4.54 (d, J=0.9 Hz, 1H), 4.80 (d, J=0.9 Hz, 1H); IR (KBr) 1770, 1680, 1655, 1460, 1350, 1150, 1130, 1120, 1020, 900; MS *m/e* (%) 232 (96, M^+), 217 (100), 204 (18), 203 (21), 189 (22), 162 (28), 151 (29), 150 (23), 107 (33), 105 (30), 91 (42), 79 (38), 77 (28); HRMS, calcd for $C_{15}H_{20}O_2$ (M^+) *m/e* 232.1463, found *m/e* 232.1453. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.50; H, 8.75.

1-Methylene-5,5,8aß-trimethyl-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-2-carboxaldehyde (45)

A solution of 344 mg (1.0 mmol) of sulfoxide **7** in toluene (25 mL) was refluxed for 2 h in the presence of 140 mg (1.0 mmol) of potassium carbonate. After cooling, the reaction mixture was poured into water (25 mL) and worked up as usual to furnish 188 mg (86%) of **45** as an oil.

^{1}H NMR 0.87 (s, 3H), 0.90 (s, 3H), 0.91 (s, 3H), 1.2-1.7 (10H), 1.85 (1H), 2.40 (2H), 5.13 (s, 1H), 5.90 (s, 1H), 6.72 (t, J=2 Hz, 1H), 9.53 (s, 1H); ^{13}C NMR 18.5 (t), 19.8 (q), 21.6 (q), 25.7 (t), 32.4 (q), 33.2 (s), 36.5 (t), 37.4 (s), 41.8 (t), 47.6 (d), 109.4 (t), 136.4 (s), 149.2 (s), 152.2 (d), 193.6 (d); IR (film) 1690, 1645, 1620; MS *m/e* (%) 218 (44, M^+), 203 (33), 189 (91), 175 (24), 147 (21), 133 (53), 119 (57), 105 (100), 91 (36), 56 (27); HRMS, calcd for $C_{15}H_{22}O$ (M^+) *m/e* 218.1671, found *m/e* 218.1671.

2-(1-Methylene-5,5,8aß-trimethyl-1,4,4aα,5,6,7,8,8a-octahydro-2-naphthalenyl)-1,3-dioxane (46)

A solution of 109 mg (0.5 mmol) of aldehyde **45** in benzene (20 mL) was heated under reflux with a waterseparator in the presence of 10 mg of *p*-toluenesulfonic acid and glycol (1 mL) for 3 h. The reaction mixture was poured into an aqueous saturated sodium bicarbonate solution (25 mL) and worked up as usual to afford acetal **46**. The crude acetal **46** was purified by flash chromatography (eluent light petroleum-ethyl acetate 19:1) to yield 116 mg (84%) of **46** as an oil.

^{1}H NMR 0.81 (s, 3H), 0.84 (s, 3H), 0.86 (s, 3H), 1.1-2.3 (11H), 3.9 (2H), 4.1 (2H), 4.91 (s, 1H), 5.04 (s, 1H), 5.09 (s, 1H), 6.20 (dd, J=1.7,2.5 Hz, 1H); ^{13}C NMR 18.7 (t), 20.5 (q), 21.8 (q), 23.7 (t), 25.6 (t), 32.5 (q), 33.0 (s), 37.1 (t), 37.4 (s), 41.9 (t), 47.6 (d), 67.1 (t), 67.3 (t), 101.0 (d), 104.6 (t), 128.6 (d), 133.0 (s), 153.2 (s); IR (film) 1640, 1610, 1450; MS *m/e* (%) 276 (61, M^+), 261 (50), 133 (17), 119 (20), 105 (28), 91 (30), 87 (100), 79 (16), 77 (18), 55 (21), 41 (44); HRMS, calcd for $C_{18}H_{28}O_2$ (M^+) *m/e* 276.2089, found 276.2089.

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31 E.J. Corey and D. Seebach, *J. Org. Chem.*, 1966, **31**, 4097.

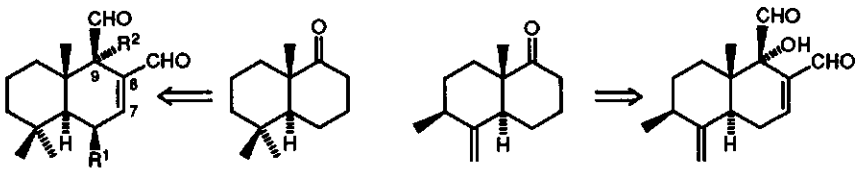
5 [METHOXY(PHENYLTHIO)METHYL]LITHIUM, A VERSATILE REAGENT

The Synthesis of (±)-Isodrimenin, (±)-Euryfuran, (±)-Confertifolin, and 1-Benzothiophenes.

5.1 Introduction

The drimanes like warburganal **1**,[1] muzigadial **2**,[2] polygodial **3**,[3] and cinnamodial **47**,[4] which exhibit insect antifeedant activity, all possess a $\Delta^{7,8}$-ene-11,12-dialdehyde functionality.[5] In the more potent substances **1** and **47** this functionality is further made up with a 9α-hydroxy group. An analogous array of functional groups is found in the rearranged drimane antifeedant muzigadial **2** (see figure 5.1).

Figure 5.1



1 R^1 = H , R^2 = OH
3 R^1 = R^2 = H
47 R^1 = OAc , R^2 = OH

6 **37** **2**

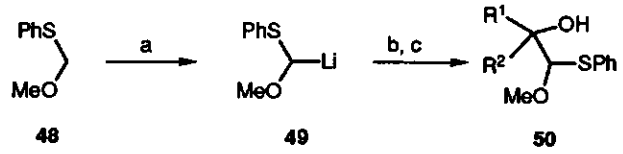
As mentioned before in chapter 3 the intention to use the *trans*-decalones **6** or **37** for the total synthesis of this type of compounds gave rise to look for a nucleophile that enables the introduction of a masked aldehyde group. [Methoxy(phenylthio)methyl]lithium[6] was selected for this purpose and its use in synthesis was examined.[7]

5.2 A synthesis of α-sulfenylated aldehydes

Methoxy(phenylthio)methane **48** was easily prepared from chloromethyl methyl ether and thiophenol on a large scale. A suspension of sodium thiophenolate, formed with sodium hydride in tetrahydrofuran at 0°C, was quenched with two equivalents of chloromethyl methyl ether to furnish a quantitative yield of methoxy(phenylthio)methane **48**. Due to the carciogenic character of chloromethyl methyl ether another synthesis of **48** was developed by Vatele using thiophenol and dimethoxy methane in the presence of boron trifluoride diethyl etherate.[8]
Lithiation of the O,S-acetal **48** occurred cleanly and without attendant decomposition, by employing *n*-butyllithium in tetrahydrofuran below -30°C. The addition of this lithiated

species **49** to *ketones* proceeded smoothly at -78°C and gave the adducts **50a-e** in high yield (see table 5.1 and scheme 5.1).

Scheme 5.1

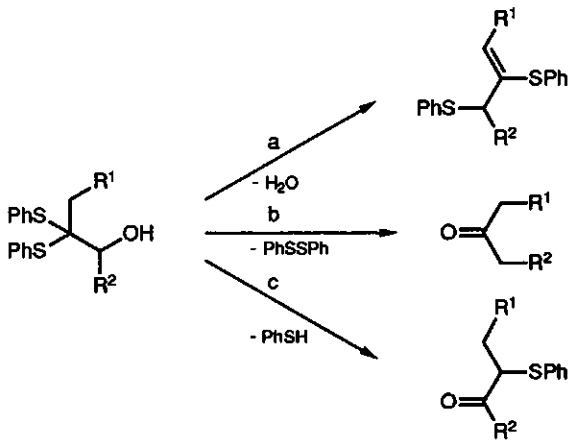


48 **49** **50**

Reagents: *a*, *n*-Buli, -30°C, THF; *b*, R^1R^2CO, THF, -78°C; *c*, H_2O, NH_4Cl.

From the literature it was known that α-(hydroxy)-bis(phenylthio) compounds rearrange under the influence of acid or thionyl chloride in pyridine,[9,10] to afford reasonable yields of ketones, α-(phenylthio) ketones or α-(phenylthio)phenylthio enol ethers.

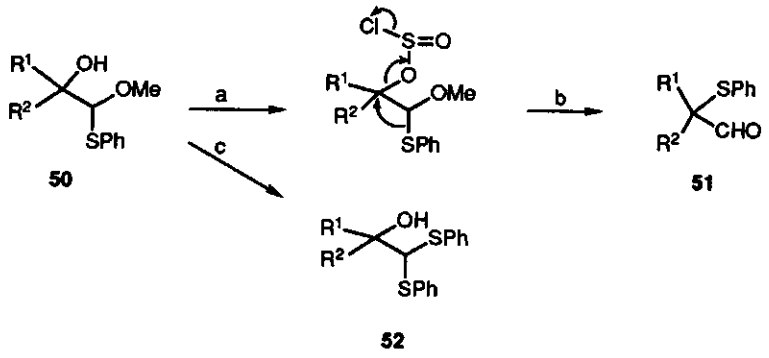
Scheme 5.2



Reagents: *a*, $SOCl_2$, pyridine; *b*, CF_3COOH; *c*, *p*-TsOH, benzene.

Heating of **50** in the presence of a catalytic amount of *p*-toluenesulfonic acid in acetic acid gave low yields (20-30%) of hydroxy compounds **52** and many unidentified products. To circumvent this problem a transformation of the hydroxy group in **50** into a better leaving group was practized using thionyl chloride in pyridine at 0°C.

Scheme 5.3



Reagents: *a*, $SOCl_2$, pyridine, 0°C; *b*, H_2O; *c*, *p*-TsOH, acetic acid.

Under these conditions a rapid reaction was observed and the corresponding α-(phenylthio)aldehydes **51a-e** were obtained in high yields. Obviously, the methoxy group modifies the results of the rearrangement. This is due to the stability of α-methoxy carbocations which facilitates the migration of the phenylthio group.

Table 5.1 α-Hydroxyaldehyde *O*-Methyl *S*-Phenyl Acetals **50** and α-(Phenylthio)aldehydes **51** prepared.

Carbonyl compound		Adduct 50	Aldehyde 51
R^1R^2CO		yield (%)	yield (%)
a	$R^1=R^2=CH_3$	92	93
b	$R^1=R^2=C_2H_5$	88	95
c	$R^1=CH_3;R^2=C_2H_5$	98*	93
d	$R^1=CH_3;R^2=C_6H_5$	96*	90
e	$R^1=R^2=(CH_2)_5$	93	83
f	$R^1=(CH_3)_2CH;R^2=H$	95*	-
g	$R^1=C_6H_5;R^2=H$	89*	-

* Diastereoisomeric mixture

Adducts of [methoxy(phenylthio)methyl]lithium **49** with *aldehydes* could be obtained simply and in high yield as well, but the rearrangement of these adducts **50 f,g** did not give satisfactory results under the above-mentioned conditions. Later on it was shown by Otera *et al.* that exposure of the adducts **50 f,g** to methanesulfonyl chloride and triethylamine provided the α-sulfenylated aldehydes in good yields.[11]

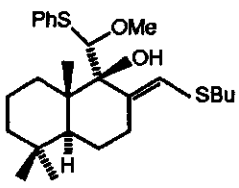
Having achieved a synthesis of α-(phenylthio)aldehydes from simple carbonyl compounds we turned our attention to the ketone derivatives which were used as starting material in the total synthesis of drimane sesquiterpenes. These results are gathered in table 5.2.

The addition of **49** to α-oxo acetals, α,ß-unsaturated ketones and (aryl- or alkylthio)methylene ketones was straightforward and the adducts were obtained in high yields. The separation of diastereoisomeric mixtures of the adducts was not always possible, but this did not prove to be a serious drawback for further transformations. The addition of **49** to the *mono*-protected oxo aldehyde **58** gave the deprotected aldehyde **67** as reaction product, the hydrolysis of the acetal could not be prevented.

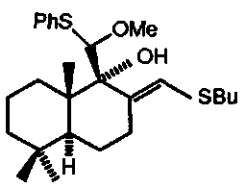
The rearrangement of the adducts mentioned in table 5.2 was usually performed at the lower reaction temperature of -30°C (entries 4, 5, 8, 9, 10). The adducts of the *mono*-cyclic (*n*-butylthio)methylene ketones and the adducts of the cyclohexenones rearranged spontaneously or upon heating with or without acid (entries 1, 2, 3, 6, 7). In entry 1 and 2 the adducts could not be isolated at all, only the rearranged products were isolated.

The rearrangement of the epimers of the adducts **63, 64, 67** and **10** gave more information about the mechanism of this reaction. The diastereoisomeric mixture of adducts **63** could be separated by column chromatography into two fractions **63a** and **63b** which were treated with thionyl chloride in pyridine at -30°C to afford the aldehydes **72a** and **72b**, respectively (see figure 5.2).

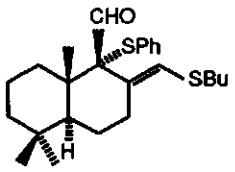
Figure 5.2



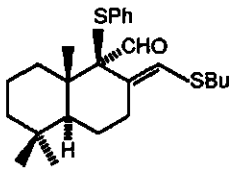
63 a



63 b

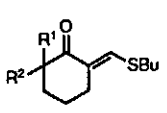
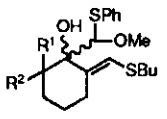
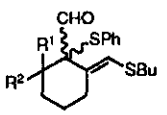
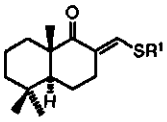
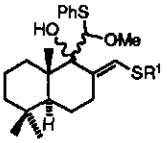
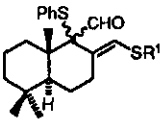
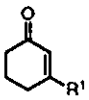
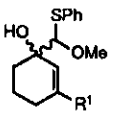
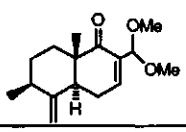
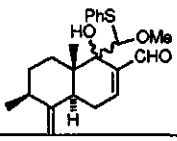
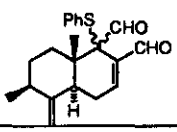
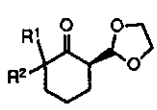
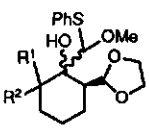
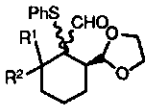
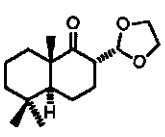
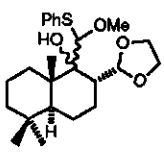
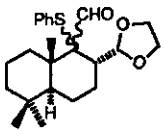


72 a



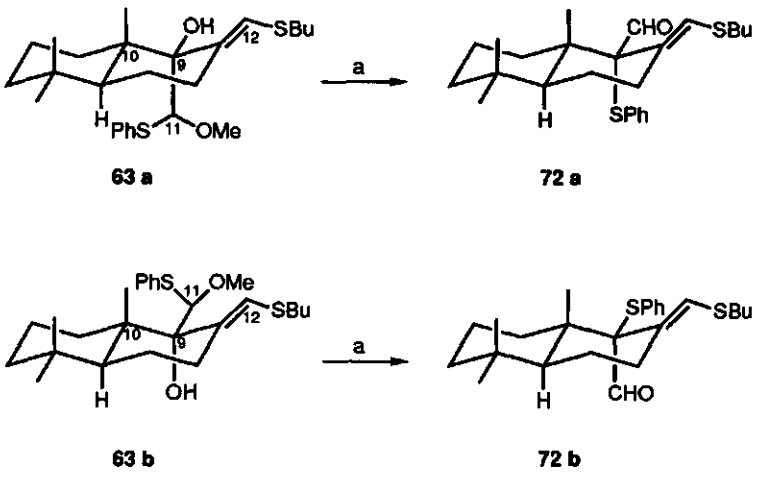
72 b

Table 5.2 α-Hydroxyaldehyde *O*-Methyl *S*-Phenyl Acetals, and α-(Phenylthio)aldehydes.

Entry	R^1	R^2	Substrate	Adduct	yield (%)	α-(phenylthio)aldehyde	yield (%)
							
1	H	H	53	60	-a)	69	80
2	H	Me	54	61	-a)	70	85
3	Me	Me	27	62	80	71	82
							
4	Bu	-	33	63	88	72	61
5	Ph	-	55	64	94	73	91
							
6	H	-	56	65	76	74	75
7	Me	-	57	66	-a)	75	86
							
8	-	-	58	67	70	76	70
							
9	Me	Me	59	68	84	77	86
							
10	-	-	4	10	85	11	75

a) Unstable compound

Scheme 5.4

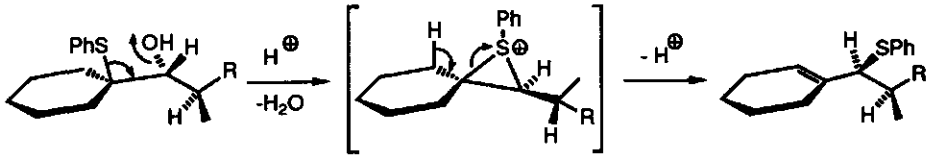


Reagents: *a*, $SOCl_2$, pyridine, -30°C.

In both cases only one (phenylthio)aldehyde was formed and none of the epimeric (phenylthio)aldehyde was obtained. This not only proved that the fractions **63a** and **63b** were epimeric at C-9, but also revealed that the rearrangement was stereospecific. For stereochemical reasons it was assumed that the nucleophilic attack occurred preferably from the α-side in *trans*-decalones such as **33**, hence the epimers **63a**, which were obtained in the highest yield, had resulted from α-attack of [methoxy(phenylthio)methyl]lithium. This was confirmed by 2D NOE NMR spectroscopy which revealed a short distance between the hydroxyl proton and the protons of the methyl group on C-10 and between the hydroxyl proton and the olefinic proton at C-12. NOE's between the proton on C-11 and the protons of the C-10 methyl group or the olefinic proton were absent. Consequently, the structures of the epimers **63a** and **63b** were assigned as indicated in scheme 5.4

Recently, sulphur participation in the synthesis of allyl sulphides from alcohols by phenylthio migration has been reported.[12] A stereospecific [1,2] migration of the phenylthio group, with inversion at the carbon atom bearing the leaving hydroxyl group was observed.

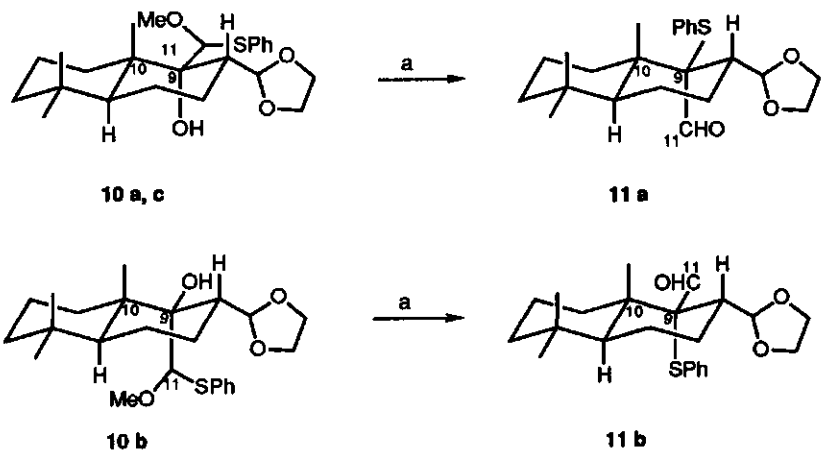
Scheme 5.5



A similar participation of sulphur in the rearrangement of the epimers **63a** and **63b** resulted in an inversion at C-9 and gave rise to the aldehydes **72a** and **72b**, respectively. This was again confirmed by the 2D NOE spectrum of **72a**. The same stereospecificity was observed in the rearrangement of the epimers of **64** and **67**.

The mixture of diastereoisomers **10** could be separated into three fractions **10a, b, c** with R_f values of 0.37, 0.22 and 0.15, respectively, on silica gel TLC using petroleum ether-diethyl ether 95:5 as eluent. These compounds were isolated in 27%, 25%, and 18% yield, respectively.

Scheme 5.6



Reagents: *a*, $SOCl_2$, pyridine, -30°C.

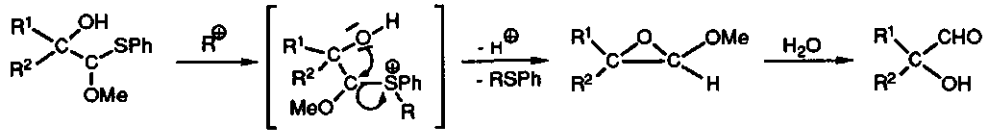
The rearrangement of the stereoisomers **10a** and **10c** gave the same α-(phenylthio)aldehyde **11a**. The rearrangement of isomer **10b** afforded α-(phenylthio)aldehyde **11b**. In all three rearrangements none of the C-9 epimeric α-(phenylthio)aldehydes could be isolated. In this case, it may be concluded that the isomers **10a** and **10c** and the isomer **10b** are epimeric at C-9 and that the rearrangements again are stereospecific.

The 2D NOE spectra of **10a** and **10b** indicated the positions of the substituents at C-9 although such evidence is not conclusive. The 2D NOE spectra of **11a** and **11b** showed in addition the relative positions of the aldehyde and the phenylthio groups to be as indicated in scheme 5.6.

5.3 Synthesis of 1-Benzothiophenes from α-(phenylthio)aldehydes

With a range of adducts of [methoxy(phenylthio)methyl]lithium with ketones and α-sulfenylated aldehydes now in hand the synthetic possibilities of these compounds were further investigated. One idea was to perform an intramolecular nucleophilic substitution of the phenylthio group after alkylation of the latter to develop a general method for the conversion of a ketone into a α-hydroxy aldehyde (see scheme 5.7).

Scheme 5.7



50

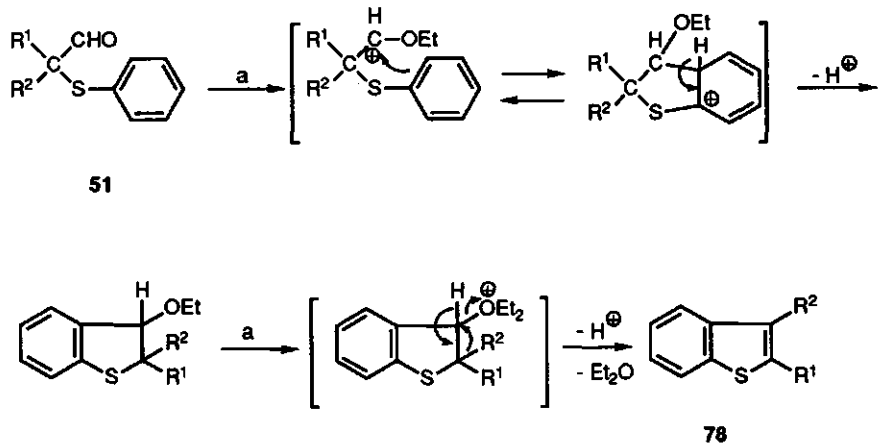
Upon treatment with triethyloxonium tetrafluoroborate in dichloromethane at room temperature the adducts **50a-e** gave a rapid reaction. The NMR spectra of the products showed only alkyl groups and some aromatic protons, hence an intramolecular electrophilic aromatic substitution had to be considered. Moreover three equivalents of alkylating reagent were necessary for a complete conversion, indicating a possible rearrangement of the adducts **50a-e** into the α-sulfenylated aldehydes **51a-e** first.

Indeed, these aldehydes **51a-e** also reacted very fast under the above-mentioned reaction conditions to afford the same products which were identified as 1-benzothiophenes **78a-e** (see scheme 5.8).

In the case of the unsymmetrical aldehydes **51c** and **51d**, two isomeric cyclization products can be expected, however, the reaction led predominantly to the 1-benzothiophenes **78c** and **78d**, respectively, reflecting the migratory aptitude in this kind of rearrangement. Less than 5% of the isomeric 1-benzothiophenes were obtained and these isomers could be removed by column chromatography. As mentioned before the adducts **50a-e** could also be cyclized directly, to the 1-benzothiophenes **78a-e**.

However, the yields were somewhat lower and unidentified byproducts hampered the purification.

Scheme 5.8



Reagents: *a*, TOF, CH_2Cl_2.

This method for the synthesis of 1-benzothiophenes will be a valuable addition to existing literature procedures.[13]

Table 5.3 1-Benzothiophenes **78** prepared.

1-Benzothiophenes **78**				
	R^1	R^2	Yield (%)	Lit.
a	CH_3	CH_3	85	13b
b	C_2H_5	C_2H_5	88	13c
c	CH_3	C_2H_5	90	13c
d	CH_3	C_6H_5	82	--
e	$-(CH_2)_5-$		85	13d

5.4 Synthesis of annulated butenolides

5.4.1 Methoxy[(phenylthio)methyl]lithium adducts as starting material

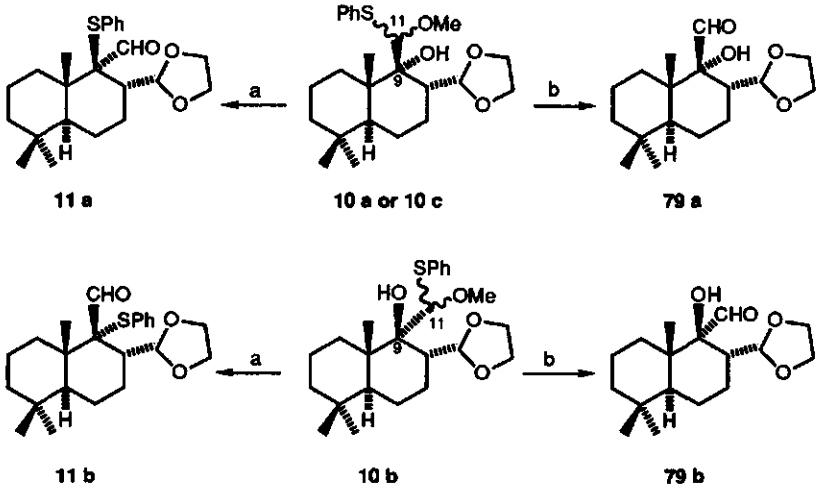
The addition of [methoxy(phenylthio)methyl]lithium to the protected formylated ketones followed by rearrangement of the adducts provided a series of precursors with a correct oxidation level at C-11 and C-12. The possibilities of conversion of the adducts **10** into drimanes were investigated first.

As mentioned before, the mixture of adducts **10** could be separated into three isomers **10a, 10b** and **10c**, respectively. The adducts **10a** and **10c** proved to be epimeric at C-11 and **10b** proved to be a C-9 epimer of **10a** and **10c**. Mild hydrolysis of **10a** and **10b** or **10c**, using an aqueous acetone solution of mercuric chloride and mercuric oxide at room temperature, gave the isomeric *mono*-protected dialdehydes **79a** and **79b**, respectively (see scheme 5.9).

The orientation of the *aldehyde* group in **79a** and **79b** reflects the side of attack of [methoxy(phenylthio)methyl]lithium on the carbonyl group of **4**. Compound **79a**, the major isomer, results from an attack from the ß-side and the minor isomer **79b** arises from an attack from the α-side.

Just the reverse position of the aldehyde function was obtained via rearrangement of the adducts **10** under the influence of thionyl chloride in pyridine (see scheme 5.6 and scheme 5.9).

Scheme 5.9

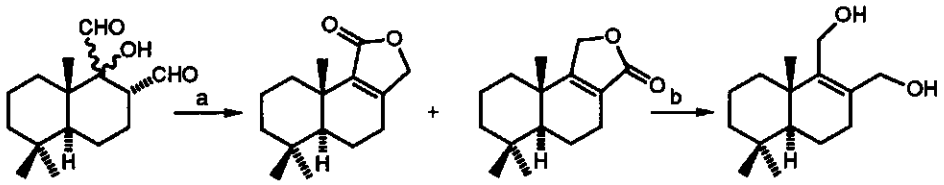


Reagents: *a*, $SOCl_2$, pyridine, -30°C; *b*, $HgCl_2$, HgO, acetone, water.

Consequently it is possible to synthesize just that type of aldehyde with a definite stereochemistry, required for a planned total synthesis.

Further hydrolysis of **79a** and **79b** to the dialdehydes **80a** and **80b** was achieved with 4 N hydrochloric acid at reflux temperature. Both hydroxy dialdehydes **80a** and **80b** could be transformed into the same mixture of isodrimenin **44** (20%) and confertifolin **81** (60%) by treatment with a catalytic amount of *p*-toluenesulfonic acid in refluxing benzene. This mixture was separated with difficulty and the best way to proceed turned out to be its reduction to the diol **82**, a well-known intermediate in the synthesis of drimanes.[14]

Scheme 5.10

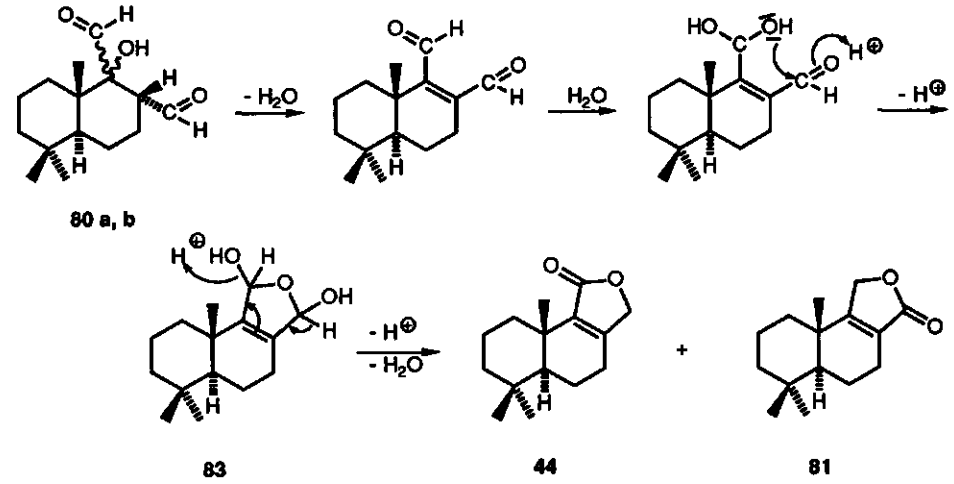


80 a, b **44** **81** **82**

Reagents: *a*, *p*-TsOH, benzene; *b*, $LiAlH_4$.

A mechanism such as that outlined in scheme 5.11 may be operating during the acid catalyzed cyclization of **80a** and **80b**. A comparable mixture of butenolides has been obtained previously in similar situations in which intermediates such as **83** were involved.[15]

Scheme 5.11

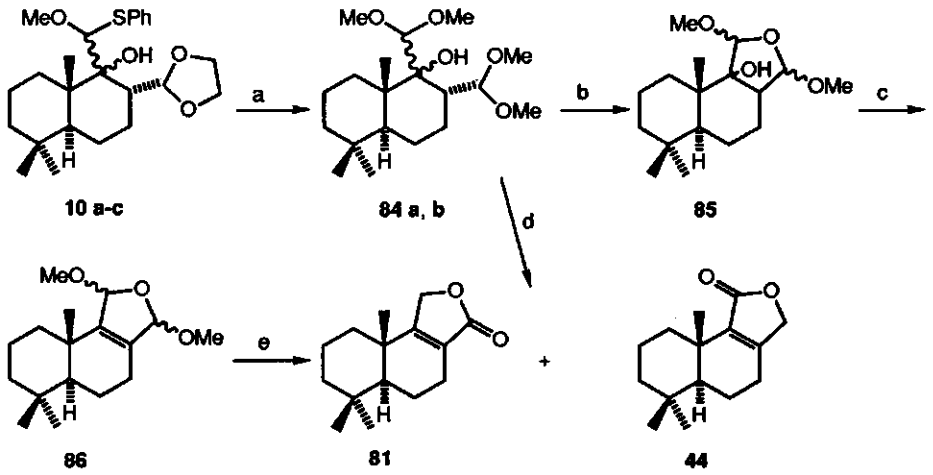


80 a, b

83 **44** **81**

The methanolysis of the adducts **10a**, **10b**, and **10c** was investigated also. Treatment of **10a** or **10c** with mercuric chloride and yellow mercuric oxide in methanol at room temperature afforded in good yield the tetramethoxy compound **84a**.

Scheme 5.12



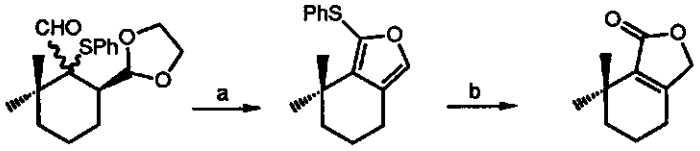
Reagents: *a*, $HgCl_2$, HgO, MeOH; *b*, MeOH, *p*-TsOH, reflux; *c*, $SOCl_2$, pyridine; *d*, *p*-TsOH, benzene, reflux; *e*, HCl, H_2O, acetone.

Compound **84b** was obtained starting with **10b**. Upon heating in benzene in the presence of some *p*-toluenesulfonic acid the familiar mixture of isodrimenin **44** and confertifolin **81** was obtained again with the latter in excess (see scheme 5.12).
When **84a** was treated in methanol with a catalytic amount of *p*-toluenesulfonic acid at reflux temperature, it was converted into **85**. The isomeric mixture **85** was dehydrated with thionyl chloride in pyridine to give the diacetal **86**, still as a mixture of stereoisomers. When **86** was hydrolyzed with hydrochloric acid in acetone the lactone confertifolin **81** could be isolated in 75% yield.[15b]

5.4.2 α-(Phenylthio)aldehydes as starting material

The conversion of the α-(phenylthio)-ß-(1,3-dioxolan-2-yl) aldehydes **77**, **11a** and **11b** were investigated next. The diastereoisomeric mixture of **77** was hydrolyzed with hydrochloric acid to afford one single product, which proved to be (phenylthio)furan **30** (see scheme 5.13). Upon hydrolysis with acid and mercuric chloride lactone **31** was obtained in good yield.[16]

Scheme 5.13

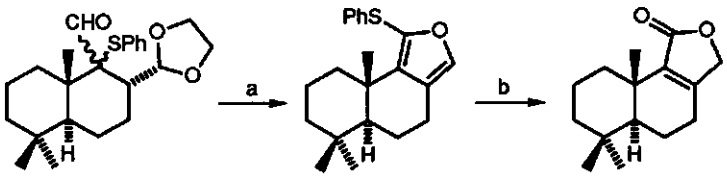


77 30 31

Reagents: *a*, HCl, acetone; *b*, $HgCl_2$, HCl, H_2O.

When this hydrolysis procedure was applied to the compounds **11a** and **11b** the known (phenylthio)furan **87** was obtained in about 80% yield, which could be transformed into the drimanic lactone isodrimenin **44** as was demonstrated before in chapter 4.

Scheme 5.14

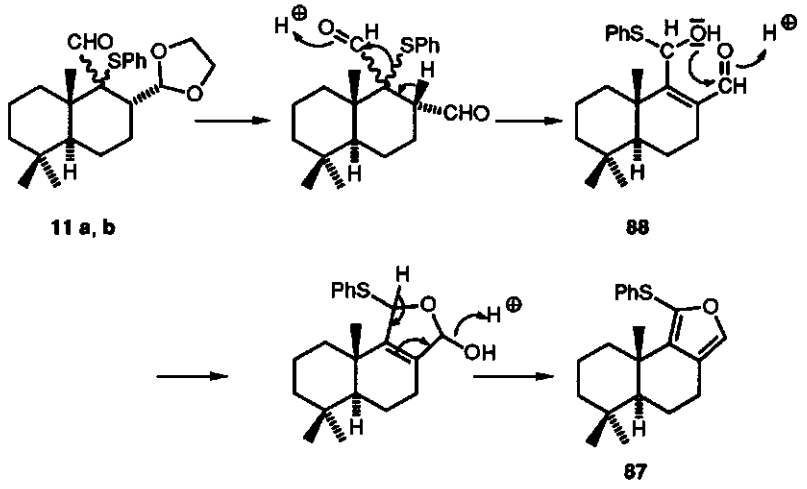


11 a, b 87 44

Reagents: *a*, HCl, acetone; *b*, $HgCl_2$, HCl, H_2O.

The acid-catalyzed cyclization may be rationalized as depicted in scheme 5.15.

Scheme 5.15



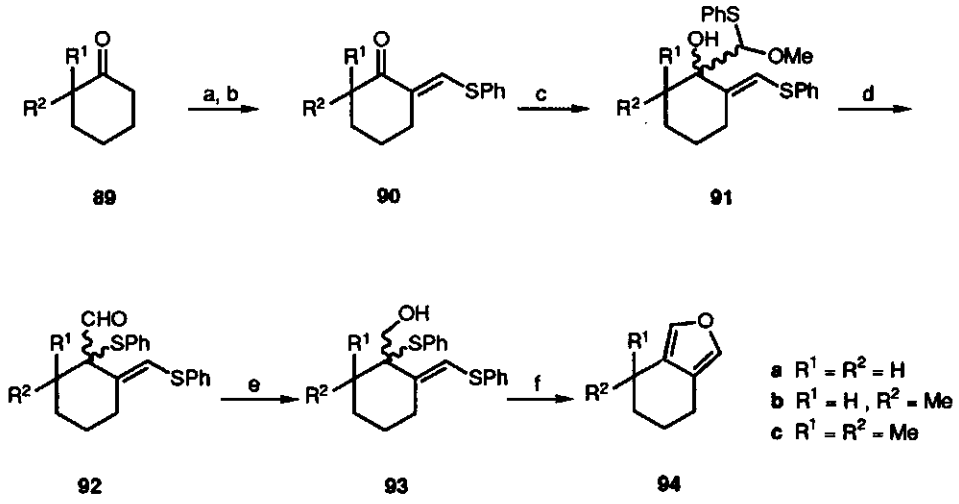
11 a, b 88 87

After hydrolysis of the acetal function a proton catalyzed [1,2] migration of the phenylthio group may occur to give the intermediate **88**. Cyclization followed by the loss of water gives rise to the furan **87**.

5.5 A new approach to annulated furans. The total synthesis of (±)-euryfuran

The array of functional groups present in the compounds **69-73** seemes suited for a conversion into annulated *c*-furans when brought to the correct oxidation level. When this should be possible, a new route to the drimane euryfuran **14** would be feasible. The reactions were tried out for simple ketones first as depicted in scheme 5.16. The ketones were formylated and the aldehyde function was protected as its (phenylthio)methylene derivative. The *phenylthio* group was used as protective group in **90** in stead of the more usual *n-butylthio* group to avoid the formation of mixed disulfides in the last step of the sequence, which facilitated the purification of the furans.

Scheme 5.16

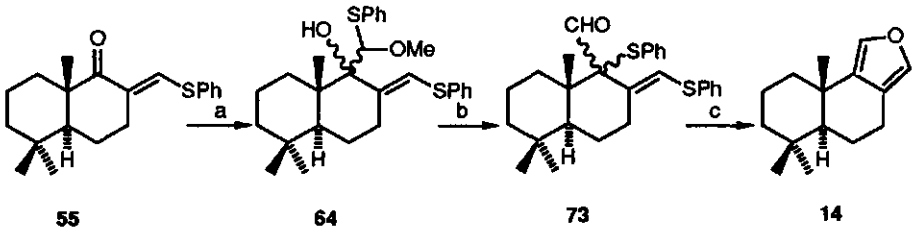


Reagents: *a*, NaH, HCOOEt; *b*, PhSH, *p*-TsOH, benzene; *c*, PhSCH(OMe)Li; *d*, H_2O, HCl; *e*, $LiAlH_4$; *f*, $CuCl_2$, collidine.

Addition of [methoxy(phenylthio)methyl]lithium to **90** gave a diastereoisomeric mixture of relatively unstable adducts **91**. Complete or partial rearrangement of these adducts occurred during the isolation and purification procedure, therefore the purification was omitted and the crude adducts were directly treated with acid to effect a complete

conversion into the aldehydes **92**. These aldehydes were also not particulary stable and reduction to the alcohols **93** directly followed by treatment with cupric chloride in collidine [17] proved to be the best procedure for the preparation of the furans **94**. The furans were obtained in overall yields of about 30%. These modest isolated yields were partly due to losses which occurred during the isolation procedure.
For the preparation of (±)-euryfuran, compound **64** was prepared as described previously. The adduct **64** could be separated into two stable diastereoisomers **64a** and **64b** which were epimeric at C-9. Rearrangement of both adducts **64a** and **64b** and reduction of the aldehydes **73** were again performed in one continuous operation since these intermediates again showed a limited stability. The alcohols were not isolated either because a spontaneous cyclization took place to afford (±)-euryfuran **14** (see scheme 5.17).[18]

Scheme 5.17



Reagents: *a*, PhSCH(OMe)Li; *b*, $SOCl_2$, pyridine; *c*, $LiAlH_4$.

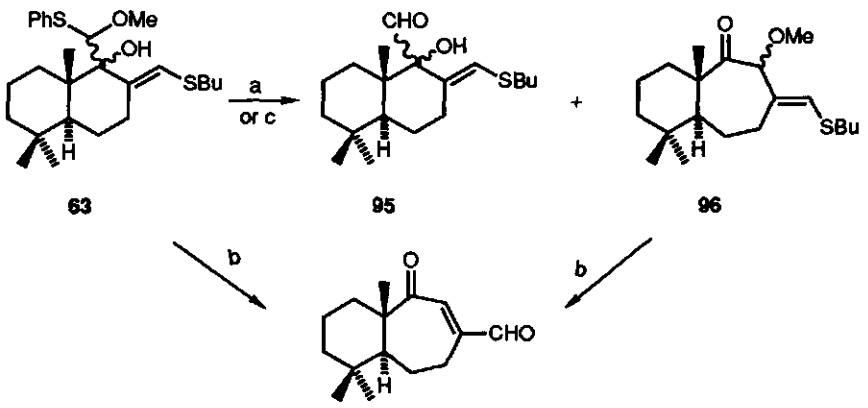
When the (*n-butyl*thio)methylene ketone **33** was used as starting material, the rearranged aldehydes **63** and the alcohols therefrom were stable compounds and treatment with cupric chloride in collidine was necessary to convert the (*n-butyl*thio)methylene alcohol into (±)-euryfuran **14**.

5.6 Ring expansion of some [methoxy(phenylthio)methyl]lithium adducts

In the course of our work directed to the total synthesis of drimanic lactones an unexpected ring expansion was observed when the hydrolysis of the adducts **63** was performed with assistance of mercuric chloride. Normal hydrolysis of the adduct of [methoxy(phenylthio)methyl]lithium and α-(1,3-dioxolan-2-yl) ketones, *e.g.*, **59** and **4**, afforded the expected hydroxy aldehydes without any rearranged products (see scheme 5.9). Mild hydrolysis with water assisted by mercuric chloride and mercuric oxide of the same type of adducts of α-(*n*-butylthio)methylene ketones, *e.g.*, **63**, however, gave mixtures.

Besides the expected hydroxy aldehyde **95** an unexpected rearranged product was isolated which could be identified as the ring expanded ketone **96**. Upon hydrolysis with mercuric chloride and hydrochloric acid at room temperature **96** was the sole product. When the hydrolysis of **63** was performed at reflux temperature in the presence of mercuric chloride and hydrochloric acid, the ring expanded γ-oxo-α,ß-unsaturated aldehyde **97** was isolated as the sole product.

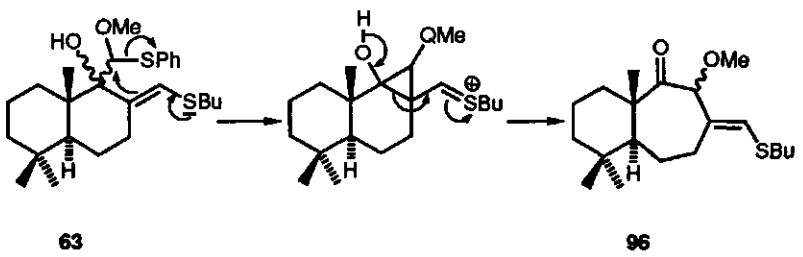
Scheme 5.18



Reagents: *a*, $HgCl_2$, HgO (yellow), H_2O, acetone; *b*, $HgCl_2$, HCl, H_2O, acetone, 60°C; *c*, $HgCl_2$, HCl, H_2O, acetone, room temperature.

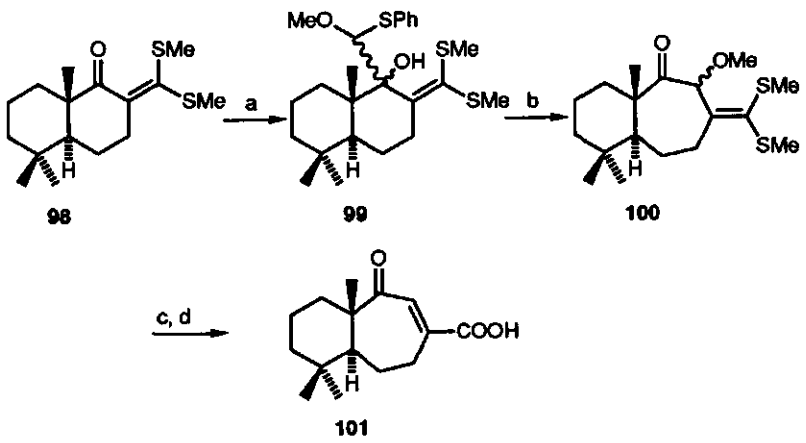
These results can be explained by a mechanism wherein an anchimeric assistance of the (*n*-butylthio)methylene group compensates the positive charge induced by the mercuric chloride promoted cleavage of the carbon-sulphur bond. Similar results were found in related compounds.[19,20,21]

Scheme 5.19



The same type of rearrangement frustrated the attempts to produce annulated lactols as indicated in scheme 5.20. For this purpose the *trans*-decalone **6** was converted into the ketone dithioacetal **98**.[22] Subsequent addition of [methoxy(phenylthio)methyl]lithium afforded a mixture of diastereoisomeric adducts **99**. The hydrolysis of these adducts gave results, comparable with those observed for **63** and the ring expanded ketone **100** was isolated in 70% yield. Further, hydrolysis of **100** could be accomplished in 65% yield by treatment with mercuric chloride and hydrochloric acid in methanol to give an esterified product which was hydrolyzed with potassium hydroxide into the γ-oxo-α,ß-unsaturated carboxylic acid **101**.

Scheme 5.20



Reagents: *a*, PhSCH(OMe)Li; *b*, $HgCl_2$, HCl, acetone, reflux; *c*, $HgCl_2$, HCl, MeOH, reflux; *d*, KOH.

5.7 Experimental section

General experimental conditions were as described in chapter 4.

1-Methoxy-2-methyl-1-(phenylthio)-propan-2-ol (50a).

A three-necked flask equipped with a magnetic stirring bar, a nitrogen inlet adaptor and a dropping funnel was dried and kept under nitrogen. The flask was charged with 5.4 g (35 mmol) of methoxy(phenylthio)methane [6] in dry THF (75 mL) and cooled between -30° and -40°C. A solution of 1.5 M *n*-butyllithium in hexane (23.3 mL, 35 mmol) was

added slowly and the reaction mixture was stirred at -35°C for 30 min. The yellow solution was cooled to -78°C and a solution of 2.04 g (35 mmol) of acetone in dry THF (20 mL) was added. The reaction mixture was stirred for another 30 min at -78°C and then quenched with a saturated aqueous ammonium chloride solution (30 mL). The reaction mixture was worked up as usual to afford after purification by flash chromatography on silica gel (eluent light petroleum-ether 9:1) 6.83 g (92%) of alcohol **50a** as a colourless oil, n_D^{20} 1.5440.
^{1}H NMR 1.30 (s, 6H), 2.84 (br s, 1H), 3.35 (s, 3H), 4.43 (s, 1H), 7.1-7.5 (5H); MS *m/e* (%) 212 (20, M^+), 165 (8), 154 (26), 153 (33), 110 (45), 103 (100), 71 (54), 59 (23); HRMS, calcd for $C_{11}H_{16}O_2S$ (M^+) *m/e* 212.0871, found *m/e* 212.0869.

2-Ethyl-1-methoxy-1-(phenylthio)-butan-2-ol (50b).

Compound **50b** was prepared in the same way as described for **50a**. Flash chromatography on silica gel (eluent light petroleum - ether 9:1) afforded 7.39 g (88%) of alcohol **50b** as a colourless oil, n_D^{20} 1.5360.
^{1}H NMR 0.90 (t, *J*=6 Hz, 6H), 1.70 (q, *J*=6 Hz, 4H), 2.38 (br s, 1H), 3.32 (s, 3H), 4.66 (s, 1H), 7.2-7.5 (5H); MS *m/e* (%) 240 (11, M^+), 179 (28), 154 (47), 153 (23), 131 (100), 110 (83), 73 (40), 57 (96); HRMS, calcd for $C_{13}H_{20}O_2S$ (M^+) *m/e* 240.1184, found *m/e* 240.1186.

1-Methoxy-2-methyl-1-(phenylthio)-butan-2-ol (50c).

Compound **50c** was obtained as described before to give a diastereoisomeric mixture, which was separated by flash chromatography on silica gel (eluent light petroleum-ether 9:1).
Major diastereomer, R_f 0.30 (hexane-ether 9:1), isolated in 53% yield as an oil, n_D^{20} 1.5380.
^{1}H NMR 0.96 (t, *J*=6 Hz, 3H), 1.27 (s, 3H), 1.70 (q, *J*=6 Hz, 2H), 2.50 (s, 1H), 3.42 (s, 3H), 4.60 (s, 1H), 7.2-7.5 (5H); MS *m/e* (%) 226 (4, M^+), 195 (1), 194 (2), 179 (5), 165 (12), 154 (28), 153 (28), 117 (96), 118 (45), 109 (15), 85 (40), 43 (100); HRMS, calcd for $C_{12}H_{18}O_2S$ (M^+) *m/e* 226.1029, found *m/e* 226.1030.
Minor diastereomer, R_f 0.25 (hexane-ether 9:1), isolated in 45% yield as an oil, n_D^{20} 1.5377.
^{1}H NMR 0.93 (t, *J*=6 Hz, 3H), 1.27 (s, 3H), 1.70 (dq, *J*=2,6 Hz, 2H), 2.40 (s, 1H), 3.42 (s, 3H), 4.56 (s, 1H), 7.2-7.5 (5H); MS *m/e* (%) 226 (4, M^+), 195 (1), 194 (2), 179 (5), 165 (12), 154 (28), 153 (28), 117 (96), 110 (45), 109 (15), 85 (40), 43 (100); HRMS, calcd for $C_{12}H_{18}O_2S$ (M^+) *m/e* 226.1029, found *m/e* 226.1030.

1-Methoxy-2-phenyl-1-(phenylthio)-propan-2-ol (50d)

Compound **50d** was obtained as described before to provide a diastereoisomeric mixture, which was separated by flash chromatography on silica gel (eluent light petroleum-ether 19:1).

Major diastereomer, R_f 0.30 (hexane-ether 19:1), isolated in 81% yield as a colourless oil, n_D^{20} 1.5866.

^{1}H NMR 1.68 (s, 3H), 2.95 (s, 1H), 3.35 (s, 3H), 4.64 (s, 1H), 7.22 (s, 5H), 7.2-7.4 (5H); MS *m/e* (%) 274 (2, M^+), 165 (6), 154 (32), 153 (100), 133 (55), 121 (30), 110 (19), 105 (43), 77 (17), 43 (28); HRMS, calcd for $C_{16}H_{18}O_2S$ (M^+) *m/e* 274.1028, found *m/e* 274.1028.

Minor diastereomer, R_f 0.38 (hexane-ether 19:1), isolated in 15% yield as a colourless oil, n_D^{20} 1.5859.

^{1}H NMR 1.65 (s, 3H), 2.98 (s, 1H), 3.30 (s, 3H), 4.64 (s, 1H), 7.1-7.5 (10H); MS *m/e* (%) 274 (2, M^+), 165 (6), 154 (32), 153 (100), 133 (55), 121 (30), 110 (19), 105 (43), 77 (17), 43 (28); HRMS, calcd for $C_{16}H_{18}O_2S$ (M^+) *m/e* 274.1028, found *m/e* 274.1029.

1-[Methoxy(phenylthio)methyl]-cyclohexan-1-ol (50e)

Compound **50e** was obtained in 93% yield as an oil, n_D^{20} 1.5562.

^{1}H NMR 1.4-1.8 (10H), 2.35 (s, 1H), 3.35 (s, 3H), 4.45 (s, 1H), 7.1-7.5 (5H); MS *m/e* (%) 252 (12, M^+), 154 (31), 153 (11), 143 (100), 111 (42), 110 (40), 99 (11), 55 (38); HRMS, calcd for $C_{14}H_{20}O_2S$ (M^+) *m/e* 252.2284, found *m/e* 252.1189.

1-Methoxy-3-methyl-1-(phenylthio)-butan-2-ol (50f)

A diastereomeric mixture was obtained starting with 2-methyl-propanal. The separation of the isomers was performed by flash chromatography on silica gel (eluent light petroleum-ether 9:1).

Major isomer, R_f 0.15 (hexane-ether 9:1), was obtained in 55% yield as an oil, n_D^{20} 1.5390.

^{1}H NMR 0.90 (d, J=6 Hz, 3H), 0.94 (d, J= 6 Hz, 3H), 1.7-2.2 (1H), 2.45 (br s, 1H), 3.25-3.45 (1H), 3.47 (s, 3H), 4.49 (d, J=6 Hz, 1H), 7.1-7.5 (5H); MS *m/e* (%) 226 (18, M^+), 153 (42), 117 (100), 110 (79), 99 (41), 85 (24), 73 (31), 45 (51); HRMS, calcd for $C_{12}H_{18}O_2S$ (M^+) *m/e* 226.1029, found *m/e* 226.1030.

Minor isomer. R_f 0.21 (hexane-ether 9:1), was obtained in 40% yield as an oil, n_D^{20} 1.5398.

^{1}H NMR 0.85 (d, J=6 Hz, 3H), 0.90 (d, J=6 Hz, 3H), 1.7-2.2 (1H), 2.40 (br s, 1H), 3.15-3.40 (1H), 3.40 (s, 3H), 4.45 (d, J=6 Hz, 1H), 7.1-7.5 (5H); MS *m/e* (%) 226 (15, M^+), 153 (35), 117 (100), 99 (38), 85 (25), 73 (29), 45 (50); HRMS, calcd for $C_{12}H_{18}O_2S$ (M^+) *m/e* 226.1029, found *m/e* 226.1028.

α-[Methoxy(phenylthio)methyl]-benzenemethanol (50g)

The reaction of benzaldehyde with [methoxy(phenylthio)methyl]lithium afforded a diastereomeric mixture of **50g**, which was separated by flash chromatography on silica gel (eluent light petroleum-ether 9:1).

Major isomer, R_f 0.28 (hexane-ether 9:1), was isolated in 67% yield as an oil, n_D^{20} 1.5840.

^{1}H NMR 3.15 (br s, 1H), 3.45 (d, J=5 Hz, 1H), 3.50 (s, 3H), 4.60 (d, J=5 Hz, 1H), 7.15 (s, 5H), 7.28 (br s, 5H); MS *m/e* (%) 260 (3, M^+), 154 (19), 153 (100), 151 (11), 119 (52), 110 (30), 91 (56), 77 (14); HRMS, calcd for $C_{15}H_{16}O_2S$ (M^+) *m/e* 260.0871, found *m/e* 260.0875.

Minor isomer, R_f 0.36 (hexane-ether 9:1), was obtained in 22% yield as an oil, n_D^{20} 1.5842.

^{1}H NMR 3.0 (br s, 1H), 3.40 (s, 3H), 4.62 (s, 2H), 7.2-7.5 (10H); MS *m/e* (%) 260 (3, M^+), 199 (36), 153 (100), 151 (9), 119 (32), 110 (30), 105 (36); HRMS, calcd for $C_{15}H_{16}O_2S$ (M^+) *m/e* 260.0871, found *m/e* 260.0870.

2-Methyl-2-(phenylthio)-propanal (51a)

A solution of 2.12 g (10 mmol) of adduct **50a** in pyridine (20 mL) was cooled to 0°C and 1.5 mL of thionyl chloride was added dropwise. The reaction mixture was stirred for 30 min at 0°C and then poured onto crushed ice. Acidification was performed with concentrated hydrochloric acid (15 mL). The reaction mixture was worked up as usual and the residue was purified by chromatography on silica gel (eluent light petroleum-ether 19:1) to give 1.67 g (93%) of aldehyde **51a** as an oil, n_D^{20} 1.5524.

^{1}H NMR 1.30 (s, 6H), 7.25 (br s, 5H), 9.23 (s, 1H); MS *m/e* (%) 180 (23, M^+), 151 (100), 123 (15), 111 (17), 110 (20), 109 (18); HRMS, calcd for $C_{10}H_{12}OS$ (M^+) *m/e* 180.0609, found *m/e* 180.0610.

2,4-DNPH, mp 153-154°C. Anal. Calcd for $C_{16}H_{16}N_4O_4S$: C, 53.32; H, 4.48. Found: C, 53.58; H, 4.47.

2-Ethyl-2-(phenylthio)-butanal (51b)

Compound **51b** was prepared as described for **51a**. Rearrangement of 2.40 g (10 mmol) of **50b** afforded 1.98 g (95%) of **51b** as a colourless oil, n_D^{20} 1,5478.
^{1}H NMR 0.92 (t, J=7 Hz, 6H), 1.70 (q, J=7 Hz, 4H), 7.1-7.4 (br s, 5H), 9.23 (s, 1H); MS *m/e* (%) 208 (28, M^+), 179 (100), 123 (26), 110 (42), 109 (17); HRMS, calcd for $C_{12}H_{16}OS$ (M^+) *m/e* 208.0922, found *m/e* 208.0911.
2,4-DNPH, mp 144-145°C. Anal. Calcd for $C_{18}H_{20}N_4O_4S$: C, 55.66; H, 5.19. Found: C, 55.65; H, 5.09.

2-Methyl-2-(phenylthio)-butanal (51c)

Rearrangement of 2.26 g (10 mmol) of adduct **50c** as described before provided 1.80 g (93%) of **51c** as a colourless oil, n_D^{20} 1.5501.
^{1}H NMR 1.00 (t, J=7 Hz, 3H), 1.27 (s, 3H), 1.72 (dq, J=1,7 Hz, 2H), 7.2-7.3 (br s, 5H), 9.35 (s, 1H); MS *m/e* (%) 194 (18, M^+), 166 (12), 165 (100), 123 (22), 111 (9), 110 (24), 109 (17), 87 (7), 55 (18); HRMS, calcd for $C_{11}H_{14}OS$ (M^+) *m/e* 194.0766, found *m/e* 194.0769.
2,4-DNPH, mp 126-127°C. Anal. Calcd for $C_{17}H_{18}N_4O_4S$: C, 54.53; H, 4.85. Found: C, 54.53; H, 4.87.

2-Phenyl-2-(phenylthio)-propanal (51d)

Compound **51d** was obtained as white crystals in 90% yield, mp 75°C.
^{1}H NMR 1.54 (s, 3H), 7.1-7.5 (10H), 9.56 (s, 1H); MS *m/e* (%) 242 (11, M^+), 213 (100), 133 (19), 110 (33), 109 (16), 103 (39); HRMS, calcd for $C_{15}H_{14}OS$ (M^+) *m/e* 242.0754, found *m/e* 242.0765. Anal. Calcd for $C_{15}H_{14}OS$: C, 74.34; H, 5.82. Found: C, 74.58; H, 5.87.
2,4-DNPH, mp 202-203°C. Anal. Calcd for $C_{21}H_{18}N_4O_4S$: C, 59.70; H, 4.29. Found: C, 59.85; H, 4.15.

1-(Phenylthio)-cyclohexane-1-carboxaldehyde (51e)

Rearrangement of **50e** in the usual way afforded aldehyde **51e** as a colourless oil in 83% yield, n_D^{20} 1.5702.
^{1}H NMR 1.1-2.0 (10H), 7.25 (br s, 5H), 9.15 (s, 1H); MS *m/e* (%) 220 (22, M^+), 191 (100), 123 (24), 110 (31), 81 (72); HRMS, calcd for $C_{13}H_{16}OS$ (M^+) *m/e* 220.0922, found *m/e* 220.0924.
2,4-DNPH, mp 194-195°C. Anal. Calcd for $C_{19}H_{20}N_4O_4S$: C, 56.98; H, 5.03. Found: C, 56.96; H, 5.13.

1-[Bis(phenylthio)methyl]-cyclohexan-1-ol (52)

A solution of 500 mg (1.98 mmol) of **50e** in acetic acid (5 mL) was treated with 100 mg of *p*-toluenesulfonic acid and stirred overnight. The reaction mixture was diluted with ether (50 mL) and washed with water (5x20 mL) and brine (20 mL), dried and the solvent evaporated. The residue was chromatographed on silica gel (eluent light petroleum-ether 19:1) to furnish 250 mg (37%) of **52** [$R_1=R_2=(CH_2)_5$] as an oil.
^{1}H NMR 1.5-2.0 (10H), 2.50 (1H), 4.30 (s, 1H), 7.15 (br s, 10H); MS *m/e* (%) 330 (12, M^+), 232 (39), 221 (100), 171 (9), 123 (82), 121 (16), 111 (47), 110 (30), 109 (18), 93 (30), 55 (50); HRMS, calcd for $C_{19}H_{22}OS_2$ (M^+) *m/e* 330.1112, found *m/e* 330.1118.

2-[(Phenylthio)methylene]-5,5,8aß-trimethyl-3,4,4aα,5,6,7,8,8a-octahydronaphthalen-1(2H)-one (55)

5,5,8a-Trimethylnaphthalen-1(2H)-one **6** was formylated as described.[23] The formyl ketone was converted into **55** following the procedure of *Ireland* and *Marshall*.[24] The (phenylthio)methylene ketone **55** was obtained in 92% yield as a white crystalline compound, mp 65-66°C.
^{1}H NMR 0.92 (s, 3H), 0.95 (s, 3H), 1.11 (s, 3H), 1.2-2.6 (11H), 7.25 (br s, 5H), 7.55 (t, *J*=2.5 Hz, 1H); IR (KBr) 1690, 1610; MS *m/e* (%) 314 (100, M^+), 205 (56), 177 (36), 137 (67), 95 (40), 81 (33), 69 (29); HRMS, calcd for $C_{20}H_{26}OS$ (M^+) *m/e* 314.1705, found *m/e* 314.1705. Anal. Calcd for $C_{20}H_{26}OS$: C, 76.38; H, 8.33. Found: C, 76.49; H, 8.58.

2α-(1,3-Dioxolan-2-yl)-5,5,8aß-trimethyl-3,4,4aα,5,6,7,8,8a-octahydronaphthalen-1(2H)-one (4)

5,5,8a-Trimethylnaphthalen-1(2H)-one **6** was formylated as described.[23] The formyl ketone was converted into **4** in the following way. A solution of 3.95 g (17.8 mmol) of the formyl ketone in benzene (100 mL) was treated with 1.29 g (19.4 mmol) of ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid at reflux temperature for 14 h in a Dean-Stark apparatus. The reaction mixture was cooled and triethylamine (1 mL) was added. The benzene solution was washed with water (50 mL) and brine (25 mL), dried and evaporated *in vacuo*. The residue was chromatographed on silica gel (eluent light petroleum-ether 6:1) to give 3.78 g (80%) of **4** as white crystals, mp 72-74°C.
^{1}H NMR 0.94 (s, 3H), 0.96 (s, 3H), 1.20 (s, 3H), 1.2-2.0 (10H), 2.0-2.3 (1H), 2.7-3.0 (1H), 3.95 (br s, 4H), 5.15 (d, *J*=4 Hz, 1H); MS *m/e* (%) 266 (5, M^+), 251 (1), 238 (2), 223 (4), 195 (1), 141 (5), 129 (4), 123 (4), 109 (2), 99 (3), 95 (2), 73 (100);

HRMS, calcd for $C_{16}H_{26}O_3$ (M^+) *m/e* 266.3799, found *m/e* 266.3800. Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.03; H, 10.01.

6,6-Dimethyl-2-(1,3-dioxolan-2-yl)-cyclohexanone (59)

The *mono*-protected formyl ketone **59** was prepared as described for compound **4**, starting from 2,2-dimethyl-cyclohexanone in 87% yield.
^{1}H NMR 1.05 (s, 3H), 1.20 (s, 3H), 1.4-2.3 (7H), 3.88 (s, 4H), 5.15 (d, *J*=4 Hz, 1H); IR (film) 1710, 1455; MS *m/e* (%) 198 (17, M^+), 183 (2), 73 (100), 70 (28), 55 (16), 45 (38); HRMS, calcd for $C_{11}H_{18}O_3$ (M^+) *m/e* 198.1256, found *m/e* 198.1250.

2-[(*n*-Butylthio)methylene]-6,6-dimethyl-1-[methoxy(phenylthio)methyl]-cyclohexan-1-ol (62)

This compound was obtained as white crystals, mp 48-50°C, in 80% yield following the general procedure.
^{1}H NMR 0.99 (s, 3H), 1.02 (s, 3H), 1.2-1.9 (11H), 2.2-2.6 (2H), 2.70 (t, *J*=6 Hz, 2H), 2.82 (s, 1H), 3.32 (s, 3H), 5.00 (s, 1H), 6.02 (s, 1H), 7.2-7.5 (5H); MS *m/e* (%) 380 (1, M^+), 239 (16), 227 (100), 153 (17), 121 (15), 110 (16), 95 (27); HRMS, calcd for $C_{21}H_{32}S_2O_2$ (M^+) *m/e* 380.1843, found *m/e* 380.1845. Anal. Calcd for $C_{21}H_{32}S_2O_2$: C, 66.27; H, 8.48. Found: C, 66.43; H, 8.64.

2-[(*n*-Butylthio)methylene]-1-[methoxy(phenylthio)methyl]-5,5,8aß-trimethylperhydronaphthalen-1-ol (63)

The epimers **63** were obtained as described before by addition of [methoxy(phenylthio)-methyl]lithium to the (*n*-butylthio)methylene ketone **33**.[15b] The epimers were separated in two fractions **63a** and **63b** by flash chromatography on silica gel (eluent light petroleum-ether 98:2).
Epimers **63a** (1ß-OH) were obtained in 53% yield as white crystals, mp 116-117°C.
^{1}H NMR 0.85 (s, 3H), 0.86 (s, 3H), 0.97 (s, 3H), 1.0-2.0 (14 H), 2.16 (dd, *J*=3,12 Hz, 2H), 2.70 (t, *J*=7 Hz, 2H), 2.95 (s, 1H), 3.30 (s, 3H), 5.14 (s, 1H), 5.97 (br s, 1H), 7.1-7.2 (3H), 7.3-7.5 (2H); MS *m/e* (%) 448 (0.1, M^+), 416 (1), 306 (30), 295 (42), 249 (88), 221 (61), 217 (35), 189 (65), 110 (100); HRMS, calcd for $C_{26}H_{40}O_2S_2$ (M^+) *m/e* 448.2469, found *m/e* 448.2463. Anal. Calcd for $C_{26}C_{40}O_2S_2$: C, 69.59; H, 8.98. Found: C, 69.41; H, 8.94.
Epimers **63b** (1α-OH) were obtained in 35% yield as a colourless oil.
^{1}H NMR 0.82 (s, 3H), 0.91 (s, 6H), 1.0-2.0 (18H), 2.67 (t, *J*=7 Hz, 2H), 3.0 (s, 1H), 3.33 (s, 3H), 5.17 (s, 1H), 6.03 (s, 1H), 7.1-7.3 (3H), 7.4-7.6 (2H); IR (film) 3570,

1580, 1460, 1440, 1100, 1080, 980; MS *m/e* (%) 448 (0.1, M^+), 416 (0.1), 338 (3), 295 (72), 249 (50), 221 (94), 189 (81), 110 (100); HRMS, calcd for $C_{26}H_{40}O_2S_2$ (M^+) *m/e* 448.2469, found *m/e* 448.2470.

1-[Methoxy(phenylthio)methyl]-2-[(phenylthio)methylene]-5,5,8aß-trimethylperhydronaphthalen-1-ol (64)

The epimers **64** were prepared as described before. Evaporation of the solvent *in vacuo* after work-up afforded an oil, which was chromatographed on silica gel (eluent light petroleum-ether 99:1). The epimers **64** were separated in two fractions **64a** and **64b**, respectively.

Epimers **64a** (1ß-OH) were obtained in 55% yield as an oil.

^{1}H NMR 0.91 (s, 3H), 0.92 (s, 3H), 1.06 (s, 3H), 1.0-2.0 (9H), 2.21 (dd, J=3,15 Hz, 2H), 2.80 (1H), 3.36 (s, 3H), 5.16 (s, 1H), 6.30 (d, J=1.5 Hz, 1H), 7.1-7.4 (10H); MS *m/e* (%) 436 [$(M-32)^+$,2], 358 (6), 326 (64), 315 (12), 249 (53), 221 (36), 189 (45), 110 (100), 109 (36); HRMS, calcd for $C_{27}H_{32}OS_2$ $(M-32)^+$ *m/e* 436.1894, found *m/e* 436.1896, FD, M^+=468.

Epimers **64b** (1α-OH) were obtained in 39% yield as an oil.

^{1}H NMR 0.88 (s, 3H), 0.96 (s, 3H), 1.00 (s, 3H), 1.0-2.1 (10H), 2.8 (1H), 3.0 (1H), 3.40 (s, 3H), 5.23 (s, 1H), 6.43 (s, 1H), 7.1-7.5 (10H); MS *m/e* (%) 436 [2, $(M-32)^+$], 358 (5), 326 (83), 315 (25), 249 (88), 221 (35), 189 (45), 110 (100); HRMS, calcd for $C_{27}H_{32}OS_2$ $(M-32)^+$ *m/e* 436.1894, found *m/e* 436.1900, FD, M^+=468.

1-[Methoxy(phenylthio)methyl]-cyclohex-2-en-1-ol (65)

A mixture of diastereoisomeric **65** was obtained following the general procedure in 75% yield.

Major isomer, oil, 44% yield.

^{1}H NMR 1.5-2.1 (6H), 2.60 (br s, 1H), 3.46 (s, 3H), 4.58 (s, 1H), 5.6-6.1 (2H), 7.1-7.6 (5H); MS *m/e* (%) 250 (1, M^+), 218 (1), 206 (11), 190 (7), 189 (9), 153 (100), 141 (16), 110 (25), 109 (33), 97 (16), 81 (50); HRMS, calcd for $C_{14}H_{18}O_2S$ (M^+) *m/e* 250.1028, found *m/e* 250.1023.

Minor isomer, oil, 31% yield.

^{1}H NMR 1.5-2.1 (6H), 2.55 (br s, 1H), 3.46 (s, 3H), 4.61 (s, 1H), 5.6-6.1 (2H), 7.1-7.4 (5H); MS *m/e* (%) 250 (1, M^+), 153 (47), 141 (100), 140 (17), 110 (13), 109 (20), 81 (54), 67 (12); HRMS, calcd for $C_{14}H_{18}O_2S$ (M^+) *m/e* 250.1028, found *m/e* 250.1027.

6ß,8aß-Dimethyl-1-hydroxy-5-methylene-1-[methoxy(phenylthio)methyl]-1,4,4aα,-5,6,7,8,8a-octahydronaphthalene-2-carboxaldehyde (67)

The epimers **67** were prepared as described before starting with the ketone **58**.[19] The epimers were separated by flash chromatography on silica gel (eluent light petroleum-ethyl acetate 19:1).

Major epimers (1ß-OH), yield 47%.

^{1}H NMR 0.80 (s, 3H), 1.09 (d, J=6 Hz, 3H), 1.2-2.1 (7H), 2.40 (dd, J=4,7 Hz, 2H), 3.38 (s, 3H), 4.70 (br s, 1H), 4.85 (br s, 1H), 5.18 (s, 1H), 6.92 (dd, J=4.5,5 Hz, 1H), 7.2-7.5 (5H), 9.54 (s, 1H).

Minor epimers (1α-OH), yield 19%.

^{1}H NMR 0.80 (s, 3H), 1.10 (d, J=6 Hz, 3H), 1.5-2.1 (7H), 2.50 (dd, J=4,9 Hz, 2H), 3.30 (s, 3H), 4.68 (br s, 1H), 4.85 (br s, 1H), 5.18 (s, 1H), 6.91 (dd, J=4.5,5 Hz, 1H), 7.2-7.5 (5H), 9.48 (s, 1H).

6,6-Dimethyl-2-(1,3-dioxolan-2-yl)-1-[methoxy(phenylthio)methyl]-cyclohexan-1-ol (68)

The stereoisomers **68** were prepared as described before and were separated by column chromatography on silica gel (eluent light petroleum-ether 19:1).

68a, yield 16%, R_f 0.29 (light petroleum-ether 19:1), oil.

^{1}H NMR 0.90 (s, 6H), 1.3-2.0 (6H), 2.48 (dd, J=6,9 Hz, 1H), 3.40 (s, 3H), 3.65 (s, 1H), 3.7-4.1 (4H), 4.91 (s, 1H), 5.06 (br s, 1H), 7.2-7.7 (5H); MS *m/e* (%) 352 (0.2, M^+), 243 (31), 199 (9), 153 (16), 110 (13), 109 (9), 93 (6), 73 (100); HRMS, calcd for $C_{19}H_{28}O_4S$ (M^+) *m/e* 352.1708, found *m/e* 352.1712.

68b, yield 20%, R_f 0.17 (light petroleum-ether 19:1), mp 99-100°C.

^{1}H NMR 1.00 (s, 3H), 1.17 (s, 3H), 1.3-2.1 (7H), 3.34 (s, 3H), 3.7-4.1 (4H), 4.26 (s, 1H), 5.09 (d, J=7 Hz, 1H), 5.20 (s, 1H), 7.2-7.7 (5H); MS *m/e* (%) 352 (0.1, M^+), 243 (38), 199 (5), 153 (10), 110 (11), 109 (6), 73 (100).

Anal. Calcd for $C_{19}H_{28}O_4S$: C, 64.73; H, 8.01. Found C, 64.77; H, 7.72.

68c, yield 48%, R_f 0.11 (light petroleum-ether 19:1), oil.

^{1}H NMR 1.02 (s, 3H), 1.16 (s, 3H), 1.3-2.2 (7H), 2.50 (ddd, J=3,7,9 Hz, 1H), 3.30 (s, 3H), 3.90 (br s, 4H), 5.03 (s, 1H), 5.45 (d, J=3 Hz, 1H), 7.2-7.5 (5H); MS *m/e* (%) 352 (0.1, M^+), 243 (26), 149 (15), 153 (15), 110 (7), 109 (7), 73 (100); HRMS, calcd for $C_{19}H_{28}O_4S$ (M^+) *m/e* 352.1708, found *m/e* 352.1705.

2α-(1,3-Dioxolan-2-yl)-1-[methoxy(phenylthio)methyl]-5,5,8aß-trimethyl-1,2,3,4,-4aα,5,6,7,8,8a-decahydronaphthalen-1-ol (10)

The epimers **10** were obtained from **4** as described before. Evaporation of the solvent gave an oil, which was chromatographed on silica gel (eluent light petroleum-ether 19:1).

10a, yield 18%, R_f 0.37 (light petroleum-ether 19:1), mp 116-118°C.

^{1}H NMR 0.85 (s, 3H), 0.90 (s, 3H), 0.95 (s, 3H), 1.3-1.9 (11H), 2.56 (dd, J=4,11 Hz, 1H), 3.4 (s, 3H), 3.72 (s, 1H), 3.7-3.9 (4H), 4.93 (s, 1H), 5.02 (d, J=2 Hz, 1H), 7.2-7.5 (5H); MS *m/e* (%) 388 (0.3, M^+-32), 311 (12), 279 (2), 189 (3), 153 (5), 110 (19), 109 (6), 73 (100); MS (FD) 420; HRMS, calcd for $C_{23}H_{32}O_3S$ (M^+-32) *m/e* 388.2072, found *m/e* 388.2060. Anal. Calcd for $C_{24}H_{36}O_4S$: C, 68.53; H, 8.63. Found: C, 68.75; H, 8.81.

10b, yield 24%, R_f 0.22 (light petroleum-ether 19:1), mp 114-115°C.

^{1}H NMR 0.90 (s, 6H), 1.22 (s, 3H), 1.1-2.4 (12H), 3.34 (s, 3H), 3.8-4.1 (4H), 4.36 (s, 1H), 5.09 (d, J=7 Hz, 1H), 5.38 (s, 1H), 7.2-7.7 (5H). MS *m/e* (%) 388 (0.5, M^+-32), 311 (12), 279 (2), 267 (4), 189 (2), 153 (6), 110 (19), 109 (8), 73 (100); MS (FD) 420; HRMS, calcd for $C_{23}H_{32}O_3S$ (M^+-32) *m/e* 388.2072, found *m/e* 388.2069. Anal. Calcd for $C_{24}H_{36}O_4S$: C, 68.53; H, 8.63. Found: C, 68.21; H, 8.77.

10c, yield 27%, R_f 0.15 (light petroleum-ether 19:1), oil.

^{1}H NMR 0.87 (s, 3H), 0.90 (s, 3H), 1.27 (s, 3H), 1.0-2.0 (11H), 2.3-2.8 (1H), 3.27 (s, 3H), 3.35 (s, 1H), 3.7-3.9 (4H), 5.01 (s, 1H), 5.40 (d, J=2 Hz, 1H), 7.2-7.7 (5H); MS *m/e* (%) 420 (0.05, M^+), 388 (0.4), 311 (14), 267 (11), 153 (6), 110 (15), 109 (6), 73 (100); MS (FD) 420; HRMS, calcd for $C_{24}H_{36}O_4S$ (M^+) *m/e* 420.2334, found *m/e* 420.2355; calcd for $C_{23}H_{32}O_3S$ (M^+-32) 388.2072, found *m/e* 388.2073.

2-[(*n*-Butylthio)methylene]-1-(phenylthio)-cyclohexane-1-carboxaldehyde (69)

The adduct **60** was prepared by addition of [methoxy(phenylthio)methyl]lithium to the ketone **53**. Evaporation of the solvent and purification by column chromatography (eluent light petroleum-ether 19:1) did not give the adduct **60**, but rather the rearranged α-(phenylthio)aldehyde **69** as an oil in 80% yield.

^{1}H NMR 0.9-1.2 (3H), 1.5-2.0 (10H), 2.0-2.2 (2H), 2.72 (t, J=7 Hz, 2H), 5.59 (s, 1H), 7.2-7.4 (5H), 9.49 (s, 1H); MS *m/e* (%) 320 (1, M^+), 291 (1), 211 (43), 155 (100), 110 (5), 77 (3); HRMS, calcd for $C_{18}H_{24}OS_2$ (M^+) *m/e* 320.1269, found *m/e* 320.1258.

2-[(*n*-Butylthio)methylene]-6-methyl-1-(phenylthio)-cyclohexane-1-carboxaldehyde (70)

The adduct **61** was prepared as described for **60** to yield a rather unstable product, which was rearranged immediately by acidification of the THF solution. The crude aldehyde was purified by flash chromatography (eluent light petroleum-ether 19:1) to afford the aldehyde **70** in 85% yield as a mixture of stereoisomers.
Major isomer, yield 56%, colourless oil.
^{1}H NMR 1.05 (d, J=6 Hz, 3H), 0.8-2.0 (14H), 2.6-2.7 (2H), 5.78 (s, 1H), 7.1-7.3 (5H), 9.63 (s, 1H); MS *m/e* (%) 334 (0.4, M^+), 305 (0.3), 277 (8), 245 (3), 225 (82), 169 (100); HRMS, calcd for $C_{19}H_{26}OS_2$ (M^+) *m/e* 334.1425, found *m/e* 334.1428.
Minor isomer, yield 29%, colourless oil.
^{1}H NMR 0.95 (d, J=6 Hz, 3H), 0.8-2.0 (14H), 2.7-2.8 (2H), 5.80 (s, 1H), 7.1-7.3 (5H), 9.48 (s, 1H); MS *m/e* (%) 334 (1, M^+), 305 (1), 277 (8), 245 (3), 225 (82), 169 (100).

2-[(*n*-Butylthio)methylene]-6,6-dimethyl-1-(phenylthio)-cyclohexane-1-carboxaldehyde (71)

The adduct **62** was dissolved in dioxane and treated with a few drops of concentrated hydrochloric acid. After 2 h, the reaction mixture was poured into water and extracted with ether. The extract was washed with water and brine, dried and evaporated. The residue was purified by column chromatography (eluent light petroleum-ether 9:1) to afford aldehyde **71** in 82% yield as a colourless oil.
^{1}H NMR 1.00 (s, 3H), 1.10 (s, 3H), 1.1-1.9 (11H), 2.50 (dd, J=6,10 Hz, 2H), 2.75 (t, J=7 Hz, 2H), 5.78 (s, 1H), 7.1-7.5 (5H), 9.48 (s, 1H); MS *m/e* (%) 348 (1, M^+), 291 (1), 239 (100), 183 (92), 135 (56), 110 (96); HRMS, calcd for $C_{20}H_{28}OS_2$ (M^+) *m/e* 348.1581, found 348.1573.

2-[(*n*-Butylthio)methylene]-1-(phenylthio)-5,5,8aß-trimethyl-1,2,3,4,4aα,5,6,7,8,8a-decahydronaphthalene-1-carboxaldehyde (72)

The rearrangement of epimers **63a** was performed at -30°C as described before. The crude product was purified by flash chromatography on silica gel (eluent light petroleum-ether 97:3) to afford (phenylthio)aldehyde **72a** in 61% yield as a colourless oil.
^{1}H NMR 0.87 (s, 3H), 0.94 (s, 3H), 1.02 (s, 3H), 1.0-2.0 (16H), 2.1-2.8 (2H), 2.80 (t, J=6 Hz, 2H), 5.78 (s, 1H), 7.1-7.4 (5H), 9.37 (s, 1H); IR (film) 1700, 1605, 1480; MS *m/e* (%) 416 (0.1, M^+), 359 (1), 326 (7), 306 (100), 250 (11), 235 (7), 233 (7), 110 (32); HRMS, calcd for $C_{25}H_{36}OS_2$ (M^+) *m/e* 416.2207, found *m/e* 416.2201.

The rearrangement of epimers **63b** was performed as described. Purification of the crude product by flash chromatography on silica gel (eluent light petroleum-ether 98:2) afforded (phenylthio)aldehyde **72b** in 58% yield as an oil.
^{1}H NMR 0.83 (s, 3H), 0.87 (s, 3H), 1.16 (s, 3H), 0.9-1.0 (3H), 1.2-2.2 (13H), 2.65 (t, J=6 Hz, 2H), 2.70 (dd, J=6,11 Hz, 2H), 5.80 (s, 1H), 7.2-7.3 (3H), 7.3-7.4 (2H), 9.66 (s, 1H); IR (film) 1705, 1610, 1475; MS *m/e* (%) 416 (0.1, M^+), 359 (0.5), 326 (8), 306 (100), 250 (12), 235 (4), 233 (3), 110 (25); HRMS, calcd for $C_{25}H_{36}OS_2$ (M^+) *m/e* 416.2207, found *m/e* 416.2210.

1-(Phenylthio)-2-[(phenylthio)methylene]-5,5,8aß-trimethyl-1,2,3,4,4aα,5,6,7,8,8a-decahydronaphthalene-1-carboxaldehyde (73)

The rearrangement of epimers **64a** was performed at -35°C to yield 91% of aldehyde **73** as an unstable oil.
^{1}H NMR 0.84 (s, 3H), 0.90 (s, 3H), 1.00 (s, 3H), 1.1-2.0 (9H), 2.50 (dd, J=6,9 Hz, 1H), 2.70 (dd, J=2,6 Hz, 1H), 6.10 (s, 1H), 7.1-7.5 (10H), 9.36 (s, 1H).

1-(Phenylthio)-cyclohex-2-ene-1-carboxaldehyde (74)

The rearrangement of **65** was performed in acetone with 1 N hydrochloric acid (3 mL) at room temperature. Compound **74** was obtained as a colourless oil in 75% yield.
^{1}H NMR 1.5-2.1 (6H), 5.52 (d, J=11 Hz, 1H), 6.02 (ddd, J=3,6,8 Hz, 1H), 7.1-7.3 (5H), 9.33 (s, 1H); IR (film) 1705, 1610, 1480; MS *m/e* (%) 218 (8, M^+), 189 (100), 147 (3), 123 (2), 110 (21), 109 (14), 79 (26); HRMS, calcd for $C_{13}H_{14}OS$ (M^+) *m/e* 218.0765, found *m/e* 218.0762.

3-Methyl-1-(phenylthio)-cyclohex-2-ene-1-carboxaldehyde (75)

The addition of [methoxy(phenylthio)methyl]lithium to 3-methyl-cyclohex-2-en-1-one **57** was performed as described before. The rearrangement of the adduct occurred during flash chromatography on silica gel (eluent light petroleum-ether 9:1). Aldehyde **75** was obtained as white crystals, mp 61-62°C, in 86% yield.
^{1}H NMR 1.5-1.8 (4H), 1.75 (s, 3H), 1.9-2.1 (2H), 5.25 (br s, 1H), 7.35 (br s, 5H), 9.30 (s, 1H); MS *m/e* (%) 232 (5, M^+), 204 (17), 203 (100), 123 (69), 122 (8), 110 (16), 109 (13), 95 (32), 93 (39), 77 (15); HRMS, calcd for $C_{14}H_{16}OS$ (M^+) *m/e* 232.0922, found *m/e* 232.0927. Anal. Calcd for $C_{14}H_{16}OS$: C, 72.37; H, 6.94. Found: C, 72.21; H, 6.90.
2,4-DNPH, mp 157-158°C. Anal. Calcd for $C_{20}H_{20}N_4O_4S$: C, 58.24; H, 4.89. Found: C, 58.33; H, 4.97.

6ß,8aß-Dimethyl-5-methylene-1-(phenylthio)-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-1,2-dicarboxaldehyde (76)

The rearrangement was performed as previously described. Compound **76** was obtained as an oil in 70% yield.
^{1}H NMR 0.87 (s, 3H), 1.10 (d, *J*=6 Hz, 3H), 1.4-2.5 (8H), 4.73 (br s, 1H), 4.92 (br s, 1H), 6.92 (t, *J*=6 Hz, 1H), 7.1-7.5 (5H), 8.70 (s, 1H), 9.68 (s, 1H); MS *m/e* (%) 340 (4, M^+), 322 (21), 311 (14), 263 (28), 231 (70), 230 (62), 215 (60), 131 (55), 110 (100), 105 (84), 91 (88), 77 (61); HRMS, calcd for $C_{21}H_{24}O_2S$ (M^+) *m/e* 340.1497, found *m/e* 340.1502.

6,6-Dimethyl-2-(1,3-dioxolan-2-yl)-1-(phenylthio)-cyclohexane-1-carboxaldehyde (77)

The rearrangement of a mixture of diastereomers **68** was performed at -20°C following the procedure described before. A mixture of isomers was obtained which was separated by column chromatography on silica gel (eluent light petroleum-ether 19:1).
Major isomer, R_f 0.20 (light petroleum-ether 9:1), yield 61%, oil.
^{1}H NMR 1.17 (s, 3H), 1.22 (s, 3H), 1.4-2.0 (6H), 2.20 (1H), 3.80 (br s, 4H), 5.49 (d, *J*=3 Hz, 1H), 7.2-7.3 (3H), 7.5-7.6 (2H), 9.44 (s, 1H); MS *m/e* (%) 320 (2, M^+), 292 (0.4), 291 (0.5), 276 (0.4), 258 (2), 211 (22), 73 (100); HRMS, calcd for $C_{18}H_{24}H_{24}O_3S$ (M^+) *m/e* 320.1446, found *m/e* 320.1457.
Minor isomer, R_f 0.25 (light petroleum-ether 9:1), yield 25%, oil.
^{1}H NMR 1.10 (s, 3H), 1.30 (s, 3H), 1.4-2.0 (6H), 2.65 (ddd, *J*=4,7,12 Hz, 1H), 3.5-3.9 (4H), 4.82 (d, *J*=4 Hz, 1H), 7.2-7.3 (3H), 7.6-7.7 (2H), 9.56 (s, 1H); MS *m/e* (%) 320 (7, M^+), 291 (2), 258 (5), 243 (1), 211 (17), 153 (6), 121 (4), 110 (4), 109 (5), 73 (100); HRMS, calcd for $C_{18}H_{24}O_3S$ (M^+) *m/e* 320.1446, found *m/e* 320.1451.

2α-(1,3-Dioxolan-2-yl)-1-(phenylthio)-5,5,8aß-trimethyl-1,2,3,4,4aα,5,6,7,8,8a-decahydronaphthalene-1-carboxaldehyde (11)

A solution of 1.50 g (3.6 mmol) of adduct **10a** or **10c** in pyridine (1.5 mL) was cooled to -30°C and thionyl chloride (0.15 mL) was added dropwise. The reaction mixture was stirred for 40 min at -30°C and then water (50 mL) was added. Work-up as usual afforded the crude aldehyde **11a** which was purified by flash chromatography on silica gel (eluent light petroleum-ether 19:1). In both reactions, the same aldehyde **11a** was obtained as a colourless oil in 70-75% yield, R_f 0.40 (light petroleum-ether 9:1).
^{1}H NMR 0.88 (s, 3H), 0.89 (s, 3H), 1.24 (s, 3H), 1.1-2.0 (11H), 2.43 (dd, *J*=13,4 Hz, 1H), 3.8-3.9 (4H), 5.80 (d, *J*=1.5 Hz, 1H), 7.15-7.30 (3H), 7.35-7.45 (2H), 9.60 (s, 1H); MS *m/e* % 388 (48, M^+), 359 (0.5), 326 (6), 279 (11), 237 (7), 189 (11), 110

(5), 109 (5), 73 (100); HRMS, calcd for $C_{23}H_{32}O_3S$ (M^+) *m/e* 388.2072, found *m/e* 388.2071.

The same procedure was performed for the rearrangement of adduct **10b**, which gave a 72% yield of aldehyde **11b** as a colourless oil, R_f 0.33 (light petroleum-ether 9:1).
^1H NMR 0.85 (s, 3H), 0.95 (s, 3H), 1.07 (s, 3H), 1.2-1.9 (10H), 2.70 (2H), 3.5-3.9 (4H), 4.85 (d, *J*=4 Hz, 1H), 7.1-7.3 (3H), 7.6-7.7 (2H), 9.39 (s, 1H); MS *m/e* (%) 388 (15, M^+), 359 (0.5), 326 (10), 279 (5), 189 (10), 110 (4), 109 (4), 73 (100); HRMS, calcd for $C_{23}H_{32}O_3S$ (M^+) *m/e* 388.2072, found *m/e* 388.2070.

2,3-Dimethyl-benzo[*b*]thiophene (78a)

A solution of 0.72 g (4 mmol) of α-(phenylthio)aldehyde **51a** in dichloromethane (20 mL) was added to a stirred solution of 1.9 g (10 mmol) of triethyloxonium tetrafluoroborate in dichloromethane (20 mL) at room temperature. Then, water (25 mL) was added and stirring was continued for 5 min. Usual work-up of the reaction mixture afforded the crude benzo[*b*]thiophene **78a**, which was purified by flash chromatography on silica gel (eluent light petroleum-ether 99:1) to afford 550 mg (85%) of compound **78a** as a colourless oil, n_D^{20} 1.6160.
^1H NMR 2.22 (s, 3H), 2.43 (s, 3H), 7.2-7.4 (2H), 7.5-7.8 (2H); MS *m/e* (%) 162 (100, M^+), 161 (43), 147 (97), 128 (20), 115 (13), 77 (7); HRMS, calcd for $C_{10}H_{10}S$ (M^+) *m/e* 162.0503, found *m/e* 162.0505.

2,3-Diethyl-benzo[*b*]thiophene (78b)

Compound **78b** was obtained as a colourless oil in 88% yield, n_D^{20} 1,5923.
^1H NMR 1.20 (t, *J*=6 Hz, 3H), 1.33 (t, *J*=6 Hz, 3H), 2.80 (q, *J*=6 Hz, 2H), 2.87 (q, *J*=6 Hz, 2H), 7.1-7.4 (2H), 7.5-7.8 (2H); MS *m/e* (%) 190 (58, M^+), 175 (100), 161 (17), 160 (12), 147 (17), 142 (10), 115 (12); HRMS, calcd for $C_{12}H_{14}S$ (M^+) *m/e* 190.0816, found *m/e* 190.0813.

3-Ethyl-2-methyl-benzo[*b*]thiophene (78c)

Thiophene **78c** was obtained as an oil in 90% yield, n_D^{20} 1.6020.
^1H NMR 1.12 (t, *J*=6 Hz, 3H), 2.42 (s, 3H), 2.72 (q, *J*=6 Hz, 2H), 7.1-7.3 (2H), 7.5-7.8 (2H); MS *m/e* (%) 176 (51, M^+), 162 (13), 161 (100), 147 (6), 134 (4), 128 (18), 115 (11), 77 (4); HRMS, calcd for $C_{11}H_{12}S$ (M^+) *m/e* 176.0655, found *m/e* 176.0652.

2-Methyl-3-phenyl-benzo[*b*]thiophene (78d)

Compound **78d** was obtained in 82% yield as an oil, n_D^{20} 1.6570.
^{1}H NMR 2.50 (s, 3H), 7.2-7.3 (2H), 7.40 (br s, 5H), 7.4-7.6 (1H), 7.7-7.8 (1H); MS *m/e* (%) 224 (100, M^+), 223 (34), 222 (9), 221 (24), 208 (7), 191 (5), 189 (7), 178 (8), 147 (36); HRMS, calcd for $C_{15}H_{12}S$ (M^+) *m/e* 224.0660, found 224.0656.

7,8,9,10-Tetrahydro-6H-benzo[*b*]cyclohepta[*d*]thiophene (78e)

Compound **78e** was obtained in 85% yield as white crystals, mp 74-75°C.
^{1}H NMR 1.6-2.0 (6H), 2.8-3.0 (4H), 7.1-7.3 (2H), 7.5-7.8 (2H); MS *m/e* (%) 202 (100, M^+), 201 (23), 174 (20), 173 (67), 161 (25), 160 (33), 148 (24), 147 (35); HRMS, calcd for $C_{13}H_{14}S$ (M^+) *m/e* 202.0816, found 202.0813. Anal. Calcd for $C_{13}H_{14}S$: C, 77.17; H, 6.98. Found: C, 76.88; H, 7.05.

2α-(1,3-Dioxolan-2-yl)-1α-hydroxy-5,5,8aß-trimethyl-1,2,3,4,4aα,5,6,7,8,8a-decahydronaphthalene-1ß-carboxaldehyde (79a)

To a solution of 535 mg (1.27 mmol) of adduct **10a** in acetone (25 mL) and water (5 mL) were added 600 mg (2.8 mmol) of yellow mercuric oxide and 755 mg (2.8 mmol) of mercuric chloride and stirred for 1 h. The precipitated mercuric salts were filtered and the filtrate was diluted with water (200 mL) and worked up as usual to yield crude **79a**, which was purified by flash chromatography on silica gel (eluent light petroleum-ether 85:15). The *mono*-protected dialdehyde **79a** was obtained in 83% yield (312 mg) as white crystals, mp 83-84°C.
^{1}H NMR 0.87 (s, 3H), 0.90 (s, 3H), 1.23 (s, 3H), 1.2-2.0 (11H), 2.50 (ddd, *J*=4,6,10 Hz, 1H), 3.66 (s, 1H), 3.82 (br s, 4H), 4.63 (d, *J*=6 Hz, 1H), 9.78 (s, 1H); IR (KBr) 3450, 1720, 1460, 1200; MS *m/e* (%) 296 (5, M^+), 278 (0.3), 267 (12), 249 (1), 234 (5), 205 (2), 178 (4), 73 (100); HRMS, calcd for $C_{17}H_{28}O_4$ (M^+) *m/e* 296.1987, found *m/e* 296.1988. Anal. Calcd for $C_{17}H_{28}O_4$: C, 75.58; H, 10.99. Found: C, 75.67; H, 11.20.

2α-(1,3-Dioxolan-2-yl)-1ß-hydroxy-5,5,8aß-trimethyl-1,2,3,4,4aα,5,6,7,8,8a-decahydronaphthalene-1α-carboxaldehyde (79b)

This compound was obtained as described for **79a**. Hydrolysis of adduct **10b** afforded **79b** as crystals in 78% yield, mp 110°C.
^{1}H NMR 0.82 (s, 3H), 0.95 (s, 3H), 1.32 (s, 3H), 1.2-2.2 (11H), 2.40 (dd, *J*=6,11 Hz, 1H), 3.20 (s, 1H), 3.80 (br s, 4H), 5.40 (br s, 1H), 9.33 (s, 1H); IR (KBr) 3460,

1715, 1455, 1210; MS *m/e* (%) 296 (5, M^+), 278 (1), 267 (10), 249 (1), 234 (8), 178 (5), 73 (100); HRMS, calcd for $C_{17}H_{28}O_4$ (M^+) *m/e* 296.1987, found *m/e* 296.1990. Anal. Calcd for $C_{17}H_{28}O_4$: C, 75.58; H, 10.99. Found: C, 75.62; H, 11.01.

1α-Hydroxy-5,5,8aß-trimethyl-1,2,3,4,4aα,5,6,7,8,8a-decahydronaphthalene-1ß,2α-dicarboxaldehyde (80a)

To a solution of 976 mg (2.3 mmol) of adduct **10c** in acetone (50 mL) and water (5 mL) were added 1.15 g (5.3 mmol) of yellow mercuric oxide and 1.40 gr (5.2 mmol) of mercuric chloride and the mixture was stirred for 1 h at room temperature. Hydrochloric acid (4 N, 4 mL) was then added and the reaction mixture was refluxed for 1 h. The reaction mixture was filtered and water (150 mL) was added. Usual work-up yielded 420 mg (71%) of dialdehyde **80a**.
^{1}H NMR 0.90 (s, 3H), 0.94 (s, 3H), 1.13 (s, 3H), 1.2-1.9 (9H), 2.05 (2H), 3.08 (dd, *J*=5,14 Hz, 1H), 3.72 (s, 1H), 9.53 (s, 1H), 9.90 (s, 1H); IR (KBr) 3500, 1720, 1460, 1200; MS *m/e* (%) 252 (19, M^+), 234 (23), 223 (87), 205 (21), 177 (68), 123 (34), 121 (19), 109 (34), 107 (23), 102 (42), 95 (68), 81 (53), 69 (100); HRMS, calcd for $C_{15}H_{24}O_3$ (M^+) *m/e* 252.1725, found *m/e* 252.1731.

1ß-Hydroxy-5,5,8aß-trimethyl-1,2,3,4,4aα,5,6,7,8,8a-decahydronaphthalene-1α,2α-dicarboxaldehyde (80b)

When the adduct **10b** was treated as described before for **10c**, the dialdehyde **80b** was obtained in 73% yield as a solid, dimeric product, mp 122-125°C.
^{1}H NMR 0.87 (s, 6H), 1.10 (s, 3H), 1.1-1.6 (7H), 1.7-2.0 (2H), 2.20 (dd, *J*=6,11 Hz, 1H), 4.06 (s, 1H), 4.80 (s, 1H), 5.15 (d, *J*=6 Hz, 2H), 5.60 (s, 1H); IR (KBr) 3600-3200, 1450, 1080, 980; MS *m/e* (%) 252 (17, M^+), 234 (32), 223 (67), 206 (14), 205 (18), 177 (59), 137 (31), 123 (56), 109 (44), 107 (25), 102 (36), 95 (72), 81 (58), 69 (100); HRMS, calcd for $C_{15}H_{24}O_3$ (M^+) *m/e* 252.1724, found *m/e* 252.1730. Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.40; H, 9.72.

6,6,9aß-Trimethyl-4,5,5aα,6,7,8,9,9a-octahydronaphtho[1,2-*c*]furan-1(3H)-one (44)
6,6,9aß-Trimethyl-4,5,5aα,6,7,8,9,9a-octahydronaphtho[1,2-*c*]furan-3(1H)-one (81)

A solution of 412 mg (1.63 mmol) of dialdehyde **80a** and 10 mg (0.06 mmol) of *p*-toluenesulfonic acid in benzene (150 mL) was refluxed for 5 h. The solvent was evaporated *in vacuo* after the usual work-up procedure and the residue was purified by chromatography on silica gel (eluent light petroleum-ether 3:2) to afford 305 mg (80%) of a mixture of **44** and **81**. Flash chromatography on silica gel (eluent light petroleum-

ether 8:2) of this mixture afforded lactone **44** (isodrimenin), 75 mg (20%) and lactone **81** (confertifolin), 225 mg (60%). When the same procedure was carried out with dialdehyde **80b**, the same mixture of **44** and **81** was obtained in 86% yield.
Isodrimenin **44**, mp 89-90°C.
^{1}H NMR 0.90 (s, 3H), 0.95 (s, 3H), 1.18 (s, 3H), 1.2-2.5 (11H), 4.58 (s, 2H); MS *m/e* (%) 234 (28, M^+), 219 (100), 151 (50), 123 (25); HRMS, calcd for $C_{15}H_{22}O_2$ (M^+) *m/e* 234.1620, found *m/e* 234.1618.
Confertifolin **81**, mp 120-122°C.
^{1}H NMR 0.92 (s, 3H), 0.95 (s, 3H), 1.16 (s, 3H), 1.1-2.0 (9H), 2.2-2.4 (2H), 4.69 (ddd, J= 0.75,2,3 Hz, 2H); MS *m/e* (%) 234 (17, M^+), 219 (100), 189 (26), 151 (56), 123 (18), 77 (20); HRMS, calcd for $C_{15}H_{22}O_2$ (M^+) *m/e* 234.1620, found *m/e* 234.1615. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.86; H, 9.37.

5,5,8aß-Trimethyl-3,4,4aα,5,6,7,8,8a-octahydronaphthalene-1,2-dimethanol (82)

To a solution of 150 mg (0.64 mmol) of a mixture of confertifolin **81** and isodrimenin **44** in dry ether (20 mL) was added 100 mg (2.6 mmol) of lithium tetrahydridoaluminate and the mixture was refluxed under nitrogen for 1 h. The excess lithium tetrahydridoaluminate was destroyed by addition of 3 drops of water, 3 drops of 4 N sodium hydroxide and 12 drops of water. The mixture was dried with $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel (eluent light petroleum-ether 1:4). Diol **82** was obtained in 90% yield as white crystals, mp 82-84°C.
^{1}H NMR 0.87 (s, 3H), 0.92 (s, 3H), 1.00 (s, 3H), 1.1-2.0 (11H), 2.16 (dd, J=4.5,9 Hz, 2H), 2.85 (br s, 2H), 4.08 (d, J= 3 Hz, 2H), 4.15 (d, J=2 Hz, 2H); IR (KBr) 3600, 3400, 1420, 1210, 1000; MS *m/e* (%) 238 (0.5, M^+), 220 (78), 207 (33), 205 (30), 190 (51), 189 (100), 177 (29), 149 (44), 137 (44), 123 (49), 109 (64), 107 (47), 105 (36), 95 (62), 93 (33), 91 (31), 81 (50), 69 (60); HRMS, calcd for $C_{15}H_{26}O_2$ (M^+) *m/e* 238.1933, found *m/e* 238.1935, calcd for $C_{15}H_{24}O$ (M^+-18) *m/e* 220.1827, found 220.1835. Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.67; H, 11.20.

1ß,2α-Di[bis(methoxy)methyl]-5,5,8aß-trimethyl-1,2,3,4,4aα,5,6,7,8,8a-decahydronaphthalen-1α-ol (84a)

A solution of 289 mg (0.68 mmol) of adduct **10a** or **10c** in absolute methanol (10 mL) was treated with 400 mg (1.47 mmol) of mercuric chloride and 325 mg (1.50 mmol) of yellow mercuric oxide at room temperature. After 2 h the precipitated mercuric salts were filtered and the filtrate was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent light petroleum-ether 9:1) to afford 183 mg (78%) of **84a** as a rather unstable oil.

^{1}H NMR 0.83 (s, 3H), 0.86 (s, 3H), 0.96 (s, 3H), 1.1-1.9 (11H), 2.0-2.3 (1H), 3.27 (s, 6H), 3.42 (s, 3H), 3.53 (s, 3H), 4.00 (br s, 1H), 4.22 (br s, 1H), 4.72 (d, J= 2 Hz, 1H); MS *m/e* (%) 344 (0.05, M^+), 343 (0.1), 312 (0.7), 281 (3), 269 (11), 238 (21), 237 (100), 177 (16), 75 (99); HRMS, calcd for $C_{19}H_{35}O_4$ (M^+-1) *m/e* 343.2484, found *m/e* 343.2502.

1α,2α-Di[bis(methoxy)methyl]-5,5,8aß-trimethyl-1,2,3,4,4aα,5,6,7,8,8a-decahydronaphthalen-1ß-ol (84b)

A solution of 300 mg (0.7 mmol) of adduct **10b** was treated as described before for adduct **10a** and provided 190 mg (84%) of **84b** as an unstable oil.
^{1}H NMR 0.87 (s, 3H), 0.90 (s, 3H), 1.08 (s, 3H), 1.1-1.9 (10H), 2.0-2.4 (2H), 3.25 (s, 3H), 3.35 (s, 3H), 3.38 (s, 3H), 3.55 (s, 3H), 4.47 (s, 1H), 4.63 (1H), 4.80 (d, J=7 Hz, 1H).

Confertifolin (81) and isodrimenin (44)

A solution of 150 mg (0.44 mmol) of **84a** or **84b** and 10 mg of *p*-toluenesulfonic acid in benzene (25 mL) was refluxed under nitrogen. After 1 h the reaction mixture was worked up. The residue was purified by flash chromatography (eluent light petroleum-ether 4:1) and afforded 83 mg (81%) of a mixture of **81** and **44** in a ratio of 3:1.

1,3-Dimethoxy-9b-hydroxy-6,6,9aß-trimethyl-1,3,3a,4,5,5aα,6,7,8,9,9a,9b-dodecahydronaphtho[1,2-*c*]furan (85)

A solution of 246 mg (0.72 mmol) of **84a** in absolute methanol (25 mL) was refluxed for 2 h in the presence of a catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was neutralized with a few drops of triethyl amine and worked up as usual. The residue was purified by flash chromatography on silica gel (eluent light petroleum-ether 17:3) to afford four diastereomers **85**.
Isomer **a**, R_f 0.45 (light petroleum-ether 9:1), yield 65%, oil.
^{1}H NMR 0.85 (s, 3H), 0.87 (s, 3H), 1.00 (s, 3H), 1.0-2.2 (10H), 2.90 (br s, 1H), 3.50 (s, 3H), 3.52 (s, 3H), 4.96 (d, J=7 Hz, 1H), 5.15 (s, 1H).
Isomer **b**, R_f 0.16 (light petroleum-ether 9:1), yield 10%, oil.
^{1}H NMR 0.87 (s, 3H), 0.88 (s, 6H), 1.0-2.0 (9H), 2.30 (1H), 3.36 (s, 3H), 3.47 (s, 3H), 4.65 (s, 1H), 4.73 (d, J=6 Hz, 1H).
Isomer **c** and **d**, R_f 0.30 (light petroleum-ether 9:1), yield 19%, oil.
^{1}H NMR 0.76, 0.80, 0.81, 0.90 and 0.93 (s, total 9H), 1.0-2.1 (10H), 3.0 (br s, 1H), 3.25, 3.33, 3.50 and 3.80 (s, total 6H), 4.76 (d, J=4 Hz, 1H), 4.95 (s, 1H).

1,3-Dimethoxy-6,6,9aß-trimethyl-1,3,4,5,5aα,6,7,8,9,9a-decahydronaphtho[1,2-*c*]-furan (86)

A solution of 245 mg (0.82 mmol) of **85a** in pyridine (5 mL) was cooled to -40°C and thionyl chloride (0.2 mL) was added and stirred for 30 min. The reaction mixture was poured into water and worked up as usual to afford 228 mg (99%) of **86** as an oil.
^{1}H NMR 0.86 (s, 3H), 0.91 (s, 3H), 1.08 (s, 3H), 1.1-1.9 (9H), 2.0-2.3 (2H), 3.26 (s, 3H), 3.31 (s, 3H), 5.66 (d, J=3 Hz, 1H), 5.72 (br s, 1H); MS *m/e* (%) 280 (13, M^+), 279 (24), 265 (16), 248 (59), 233 (15), 219 (100), 156 (15), 143 (47), 105 (34); HRMS, calcd for $C_{17}H_{28}O_3$ (M^+) *m/e* 280.2038, found 280.2028.

7,7-Dimethyl-1-(phenylthio)-4,5,6,7-tetrahydroisobenzofuran (30)

A solution of 113 mg (0.35 mmol) of acetal **77** in acetone (5 mL) was treated with 1 N hydrochloric acid (0.5 mL) overnight. The reaction mixture was neutralized with solid sodium bicarbonate, diluted with ether (50 mL), dried and evaporated. The residue was purified by flash chromatography on silica gel (eluent light petroleum-ether 98:2) to afford 90 mg (99%) of (phenylthio)furan **30**. The spectroscopic data were in agreement with those reported in chapter 4.

1-(Phenylthio)-6,6,9aß-trimethyl-4,5,5aα,6,7,8,9,9a-octahydronaphtho[1,2-*c*]furan (87)

A solution of 167 mg (0.43 mmol) of acetal **11a** in acetone (10 mL) was treated with 1 N hydrochloric acid (1 mL) overnight. The reaction mixture was neutralized with solid sodium bicarbonate, diluted with ether (100 mL), dried and evaporated. The residue was purified by flash chromatography on silica gel (eluent light petroleum-ether 98:2) to give 129 mg (92%) of **87** as an oil.
^{1}H NMR: 0.91 (s, 3H), 0.95 (s, 3H), 1.10 (s, 3H), 1.3-1.9 (9H), 2.6-3.0 (2H), 7.1 (5H), 7.21 (s, 1H); MS *m/e* (%) 326 (100, M^+), 311 (57), 201 (40), 105 (7), 69 (35); HRMS, calcd for $C_{21}H_{26}OS$ (M^+) *m/e* 326.1703, found *m/e* 326.1704.

A solution of 192 mg (0.49 mmol) of acetal **11b** in acetone afforded 140 mg (87%) of (phenylthio)furan **87** when treated as described above.

2-[(Phenylthio)methylene]-cyclohexanone (90a)

Compound **90a** was prepared following the procedure of Ireland and Marshall [24] in 86% yield as an oil, bp 140-142°C (0.5 torr).
^{1}H NMR 1.5-1.9 (4H), 2.2-2.5 (4H), 7.1-7.4 (5H), 7.63 (dd, J=2,2 Hz, 1H).

6-Methyl-2[(phenylthio)methylene]-cyclohexanone (90b)

2-Methylcyclohexanone was formylated as described. The formyl ketone was converted into **90b** following the procedure of Ireland and Marshall [24] in 92% yield, bp 145-150°C (0.1 torr).
^{1}H NMR 1.04 (d, J=6 Hz, 3H), 1.3-1.9 (4H), 2.1-2.5 (3H), 7.1-7.3 (5H), 7.60 (dd, J=2,2 Hz, 1H).

6,6-Dimethyl-2-[(phenylthio)methylene]-cyclohexanone (90c)

Compound **90c** was prepared by alkylation of **90b**. A solution of 11.6 g (50 mmol) of **90b** in *tert*-butyl alcohol (50 mL) was dropped into a stirred solution of 12.32 g (110 mmol) of commercial potassium *tert*-butoxide in *tert*-butyl alcohol (200 mL) at room temperature. After 30 min the red solution was treated with 32.8 g (160 mmol) of methyl iodide and stirred overnight. The reaction mixture was concentrated and poured into water and worked up as usual. The residue was distilled and afforded 10.68 g (87%) of **90c** as an oil, bp 145-147°C (0.05 torr).
^{1}H NMR 1.13 (s, 6H), 1.7-1.9 (4H), 2.4-2.7 (2H), 7.1-7.3 (5H), 7.55 (dd, J=2,2 Hz, 1H).

1-(Phenylthio)-2-[(phenylthio)methylene]-cyclohexanemethanol (93a)

The addition of [methoxy(phenylthio)methyl]lithium (40 mmol) to the ketone **90a** (30 mmol) was performed as previously described. The ethereal solution, obtained by usual work-up procedures, was concentrated to yield crude adduct **91a**, an unstable oil, which was dissolved in a mixture of dioxane (50 mL) and 2 N hydrochloric acid (20 mL). This mixture was stirred for 30 min and water (250 mL) and ether (100 mL) were then added. The organic phase was separated and the water phase was extracted with ether. The combined extracts were washed with brine and dried. The resulting solution of the (phenylthio)aldehyde **92a** was concentrated and added to a suspension of 10 mmol of lithium tetrahydridoaluminate in ether (50 mL) at 0°C. This reaction mixture was stirred for 30 min and then water (0.2 mL), 4 N sodium hydroxide (0.2 mL) and again water (0.6 mL) were added. After stirring for another 30 min, the solution was dried over

sodium sulfate overnight and filtered. The solvent was evaporated and the residue was purified by column chromatography on silica gel to afford the alcohol **93a**, a rather unstable compound, in 50% yield.
^{1}H NMR 1.1-1.8 (6H), 2.42 (br s, 1H), 2.5-2.7 (2H), 3.54 (q_{AB}, δ_A 3.47, δ_B 3.54, 2H), 5.61 (s, 1H), 7.0-7.2 (5H), 7.2-7.4 (5H).

6-Methyl-1-(phenylthio)-2-[(phenylthio)methylene]-cyclohexanemethanol (93b)

Compound **93b** was obtained following the procedure described for **93a**, yield 48%.
Major isomer, ^{1}H NMR 0.90 (d, J=6 Hz, 3H), 1.1-1.3 (2H), 1.4-1.9 (3H), 2.08 (s, 1H), 2.2-2.5 (2H), 3.80 (q_{AB}, δ_A 3.71, δ_B 3.89, 2H), 5.50 (s, 1H), 7.1-7.5 (10H).
Minor isomer, ^{1}H NMR 1.12 (d, J=6 Hz, 3H), 1.4-2.1 (5H), 2.01 (s, 1H), 2.4-2.8 (2H), 3.81 (q_{AB}, δ_A 3.66, δ_B 3.97, 2H), 5.60 (s, 1H), 7.0-7.3 (5H), 7.3 (s, 5H).

6,6-Dimethyl-1-(phenylthio)-2-[(phenylthio)methylene]-cyclohexanemethanol (93c)

Alcohol **93c** was obtained as described for **93a** in 69% yield as an oil.
^{1}H NMR 0.96 (s, 3H), 1.06 (s, 3H), 1.1-2.0 (4H), 2.30 (br s, 1H), 2.45 (t, J=6 Hz, 2H), 3.64 (br s, 2H), 5.50 (s, 1H), 7.1-7.4 (10H).

4,5,6,7-Tetrahydroisobenzofuran (94a)

The rather unstable alcohol **93a** was dissolved in THF. To this solution were added 2 equivalents of cupric chloride and 4 equivalents of collidine and the reaction mixture was refluxed for 2 h. The precipitated salts were filtered and the filtrate was diluted with ether, washed with 2 N hydrochloric acid, water and brine and dried. The solvent was evaporated and the residue was purified by column chromatography on silica gel (eluent pentane) to afford a 70% yield of **94a**, an unstable oil.
^{1}H NMR 1.50-1.90 (4H), 2.30-2.60 (4H), 6.98 (s, 2H); MS *m/e* (%) 122 (100, M^+), 121 (19), 94 (51), 93 (35), 91 (25), 81 (16), 79 (35), 77 (25); HRMS, calcd for $C_8H_{10}O$ (M^+) *m/e* 122.0732, found *m/e* 122.0730.

4-Methyl-4,5,6,7-tetrahydroisobenzofuran (94b)

Following the procedure as described above, furan **94b** was obtained in 74% yield as an unstable oil.
^{1}H NMR 1.18 (d, J=6 Hz, 3H), 1.50-2.00 (4H), 2.30-2.60 (3H), 7.05 (br s, 2H); MS *m/e* (%) 136 (80, M^+), 122 (8), 121 (100), 108 (12), 107 (12), 93 (22), 91 (24), 79 (18), 77 (26); HRMS, calcd for $C_9H_{12}O$ (M^+) *m/e* 136.0888, found *m/e* 136.0889.

4,4-Dimethyl-4,5,6,7-tetrahydroisobenzofuran (94c)

Furan **94c** was obtained as described before as a colourless oil in 66% yield.
^{1}H NMR 1.20 (s, 6H), 1.40-2.00 (4H), 2.50 (ddd, J=6,7,1 Hz, 2H), 6.97 (t, J=1 Hz, 1H), 7.08 (br s, 1H); MS *m/e* (%) 150 (28, M^+), 135 (100), 107 (9), 105 (9), 91 (18), 79 (14), 77 (10); HRMS, calcd for $C_{10}H_{14}O$ (M^+) *m/e* 150.1045, found *m/e* 150.1048.

6,6,9aß-Trimethyl-4,5,5aα,6,7,8,9,9a-octahydronaphtho[1,2-*c*]furan (14) Euryfuran

A solution of 700 mg (1.6 mmol) of (phenylthio) aldehydes **73** in dry ether (5 mL) was added dropwise to a solution of 40 mg (1.1 mmol) of lithium tetrahydroaluminate in dry ether (100 mL) at 0°C under nitrogen. The reaction mixture was stirred for 15 min and then 5 drops of water, 5 drops of 4 N sodium hydroxide and a further 10 drops of water were added. The mixture was stirred for 1 h and magnesium sulfate was added and left overnight. The mixture was filtered and the solvent evaporated *in vacuo*. The residue was set aside at room temperature for 2 h, which was sufficient time for the complete transformation of the reduced product into euryfuran **14**. Flash chromatography on silica gel (eluent pentane) afforded **14** in 80% yield as a colourless oil.
^{1}H NMR 0.94 (s, 3H), 0.97 (s, 3H), 1.23 (s, 3H), 1.3-2.1 (9H), 2.4-2.8 (2H), 7.05 (br s, 2H); IR (film) 2900, 1460, 1430, 1380, 900; MS *m/e* (%) 218 (37, M^+), 203 (100), 185 (4), 175 (10), 147 (16), 135 (9), 133 (12), 107 (5), 105 (9), 91 (15), 69 (52); HRMS, calcd for $C_{15}H_{22}O$ (M^+) *m/e* 218.1671, found *m/e* 218.1669.

2-[(*n*-Butylthio)methylene]-1-hydroxy-5,5,8aß-trimethyl-1,2,3,4,4aα,5,6,7,8,8a-decahydronaphthalene-1-carboxaldehyde (95)
and
4-[(*n*-butylthio)methylene]-3-methoxy-1ß,8,8-trimethyl-*trans*-bicyclo[5.4.0]undecan-2-one (96)

A solution of 245 mg (0.55 mmol) of a diastereomeric mixture **63**, 262 mg (1.21 mmol) of yellow mercuric oxide and 328 mg (1.21 mmol) of mercuric chloride in aceton (18 mL) and water (2 mL) was stirred for 15 min at room temperature. Dilute hydrochloric acid was added and the mixture extracted with ether. The ethereal solution was washed with brine and then dried and evaporated. The residue was purified by chromatography (eluent light petroleum-ether 19:1) to afford 88 mg (50%) of compound **95**.
^{1}H NMR 0.90 (s, 3H), 0.98 (s, 6H), 1.1-2.0 (17H), 2.67 (t, J=6 Hz, 2H), 2.90 (1H), 3.67 (s, 1H), 6.25 (s, 1H), 10.10 (s, 1H); IR (film) 3420, 2870, 1700, 1600, 1460, 1340; MS *m/e* (%) 324 (6, M^+), 296 (100), 282 (8), 281 (7), 268 (13), 205 (13), 194 (31), 179 (26), 163 (13), 161 (15), 137 (24), 123 (38), 111 (42), 95 (31), 81 (23), 69

(26), 55 (23); HRMS, calcd for $C_{19}H_{32}O_2S$ (M^+) *m/e* 324.2123, found *m/e* 324.2124.
The rearranged ketone **96** was eluted next, 77 mg (42%).
^1H NMR 0.87 (s, 3H), 0.93 (s, 3H), 1.20 (s, 3H), 1.2-2.6 (18H), 2.65 (t, J=6 Hz, 2H), 3.30 (s, 3H), 4.82 (s, 1H), 6.18 (s, 1H); IR (film) 1700, 1605, 1460, 1380, 1100, 1080, 980; MS *m/e* (%) 338 (7), 310 (7), 295 (3), 221 (100), 189 (67), 95 (20), 91 (16), 85 (31), 83 (27); HRMS, calcd for $C_{20}H_{34}O_2S$ (M^+) *m/e* 338.2280, found *m/e* 338.2278.

***trans*-2-Oxo-1ß,8,8-trimethylbicyclo[5,4,0]undec-3-ene-4-carboxaldehyde (97)**

A solution of 112 mg (0.25 mmol) of adducts **63** and 408 mg (1.1 mmol) of mercuric chloride in acetone (20 mL) and 1 N hydrochloric acid (4 mL) was refluxed for 4 h.
The reaction mixture was cooled and solid sodium bicarbonate was added. The mixture was filtered and the solvent was evaporated *in vacuo*. Water (100 mL) was added and the solution was extracted with ether. The combined extracts were washed with water and brine, dried and evaporated. The residue was purified by flash chromatography on silica gel (eluent light petroleum-ether 9:1) to afford 50 mg (85%) of unsaturated oxo aldehyde **97** as an oil.
^1H NMR 0.92 (s, 3H), 0.95 (s, 3H), 1.25 (s, 3H), 1.1-2.1 (9H), 2.50 (2H), 6.62 (d, J=2 Hz, 1H), 9.58 (s, 1H); IR (KBr) 2730, 1695, 1645, 1080, 890; MS *m/e* (%) 234 (100, M^+), 219 (10), 218 (10), 217 (8), 208 (10), 206 (10), 205 (8), 192 (16), 178 (69), 165 (92), 137 (42), 123 (92), 111 (62), 110 (82), 109 (69), 97 (51), 95 (53), 69 (65); HRMS, calcd for $C_{15}H_{22}O_2$ (M^+) *m/e* 234.1620, found *m/e* 234.1622.

The aldehydes **95** and the ring-enlarged ketones **96** were also transformed into keto aldehyde **97** when treated as described for compound **63**.

***trans*-2-[Bis(methylthio)methylene]-5,5,8aß-trimethyl-perhydronaphthalen-1-one (98)**

A solution of lithium bis(trimethylsilyl)amide was generated at 10°C under nitrogen by addition of butyllithium (11 mL, 15.5 mmol) to a solution of 2.5 g (15.5 mmol) of hexamethyldisilazane in dry THF (20 mL). The solution was cooled to -78°C and 2.7 mL (15.5 mmol) of hexamethylphosphoric triamide (HMPA) was added. A solution of 2.8 g (15.5 mmol) of ketone **6** in dry THF (10 mL) was added dropwise and the mixture was stirred for 20 min at -78°C. A solution of 1.18 g (15.5 mmol) of carbon disulfide in dry THF (10 mL) was then added and the temperature of the solution was allowed to rise to 0°C over 2 h. The solution was cooled to -78°C and a solution of 15.5 mmol of bis(trimethylsilyl)amide in dry THF (10 mL) was added.
The solution was stirred for another 0.5 h and then 2 mL (15.5 mmol) of methyl iodide

was added at -78°C and the reaction mixture was slowly warmed to room temperature and stirred overnight. The solution was poured into water and extracted with ether. The ether extracts were washed with water and brine and dried. The solvent was evaporated and the residue was purified by chromatography on silica gel (eluent light petroleum-ether 98:2) to afford 3.25 g (70%) of component **98** as a colourless oil.
^{1}H NMR 0.91 (s, 6H), 1.04 (s, 3H), 1.1-1.8 (9H), 2.0-2.3 (1H), 2.25 (s, 3H), 2.30 (s, 3H), 3.30 (ddd, *J*=2,4,7 Hz, 1H); MS *m/e* (%) 298 (66, M^+), 283 (58), 255 (79), 251 (29), 207 (19), 161 (100), 147 (74), 133 (100), 85 (55); HRMS, calcd for $C_{16}H_{26}OS_2$ (M^+) *m/e* 298.1426, found *m/e* 298.1425.

trans-2-[Bis(methylthio)methylene]-1-[methoxy(phenylthio)methyl]-5,5,8aß-trimethyl-perhydronaphthalen-1-ol (99)

The addition of [methoxy(phenylthio)methyl]lithium to ketone **98** was performed as described before. The diastereoisomers **99** were separated by flash chromatography on silica gel (eluent light petroleum-ether 96:4).
Epimers **99a**, R_f 0.30 (hexane-ether 19:1) were obtained in 44% yield as an oil.
^{1}H NMR 0.86 (s, 3H), 0.90 (s, 3H), 1.00 (s, 3H), 1.1-2.0 (9H), 2.30 (s, 3H), 2.34 (s, 3H), 2.50 (ddd, *J*=3,7.5,13 Hz, 1H), 3.33 (s, 3H), 3.60 (dt, *J*=13,3 Hz, 1H), 5.00 (s, 1H), 7.12 (s, 1H), 7.2-7.4 (3H), 7.5-7.7 (2H); MS *m/e* (%) 452 (0.01, M^+), 405 (0.2), 373 (0.4), 343 (0.6), 341 (1), 299 (100), 295 (44), 267 (45), 234 (14), 187 (18), 177 (24), 161 (17), 153 (19), 145 (14), 110 (16), 109 (18); FD *m/e* 452 (M^+).
Epimers **99b** were obtained in 35% yield as a white solid, mp 93-95°C.
^{1}H NMR 0.83 (s, 3H), 0.90 (s, 3H), 0.93 (s, 3H), 1.1-1.8 (9H), 2.0 (1H), 2.32 (s, 3H), 2.43 (s, 3H), 3.50 (s, 3H), 3.50 (ddd, *J*=2,5,12 Hz, 1H), 5.40 (s, 1H), 6.82 (s, 1H), 7.1-7.3 (3H), 7.3-7.5 (2H); MS *m/e* (%) 452 (0.01, M^+), 405 (0.2), 373 (0.7), 343 (2), 299 (100), 295 (37), 267 (25), 234 (18), 187 (12), 177 (15), 153 (15), 110 (47), 109 (17); FD *m/e* 452 (M^+). Anal. Calcd for $C_{24}H_{36}O_2S_3$: C, 63.67; H, 8.02. Found: C, 63.43; H, 8.16.

trans-4-[Bis(methylthio)methylene]-3-methoxy-1ß,8,8-trimethyl-bicyclo[5,4,0]undecan-2-one (100)

A solution of 171 mg (0.35 mol) of epimers **99b** and 0.57 g (2.1 mmol) of mercuric chloride in acetone (30 mL) and 1 N hydrochloric acid (6 mL) was refluxed for 2 h. The mixture was cooled and solid sodium bicarbonate was added. The reaction mixture was filtered and the solvent was evaporated *in vacuo*. Water was added and the solution was extracted with ether. The ether extracts were washed with water and brine, dried and evaporated. The residue was chromatographed on silica gel (eluent light petroleum-ether 19:1). Compound **100** was obtained as a 6:1 mixture of two epimers in 75% yield as a colourless oil.

^{1}H NMR 0.88 (br s, 6H), 1.20 (s, 3H), 1.2-2.0 (11H), 2.29, 2.30 and 2.34 (s, 6H), 3.08 (1H), 3.34 and 3.36 (s, 3H), 4.83 and 5.15 (s, 1H); MS *m/e* (%) 342 (0.3, M^+), 314 (2), 299 (26), 295 (36), 267 (100), 251 (10), 235 (16), 219 (25), 187 (26), 177 (51), 175 (20), 161 (26), 145 (31), 91 (23); HRMS, calcd for $C_{18}H_{30}O_2S_2$ (M^+) *m/e* 342.1688, found *m/e* 342.1683.
The epimers **99a** afforded upon hydrolysis the same mixture of isomers **100**.

trans-2-Oxo-1ß,8,8-trimethylbicyclo[5,4,0]undec-3-ene-4-carboxylic acid (101)

To a solution of 200 mg (0.58 mmol) of **100** in methanol (15 mL) was added 238 mg (0.88 mmol) of mercuric chloride and 4 N hydrochloric acid (5 mL). The solution was then refluxed for 24 h. The mixture was filtered and the solvent evaporated. The crude product was dissolved in methanol (10 mL) and 0.8 g (14 mmol) of potasssium hydroxide was added. The reaction mixture was stirred overnight at room temperature and then poured into water. The solution was extracted with ether (100 mL). The aqueous layer was acidified with 4 N hydrochloric acid (5 mL) and extracted with three portions of ether (100 mL). The ethereal solution was washed with brine, dried and evaporated, leaving a white solid, which was recrystallized from pentane. Acid **101** was obtained in 75% yield as a white crystalline compound, mp 152-154°C.
^{1}H NMR 0.92 (s, 3H), 0.95 (s, 3H), 1.26 (s, 3H), 1.3-1.7 (8H), 1.7-1.9 (1H), 2.50 (2H), 7.03 (s, 1H); ^{13}C NMR 17.4 (q), 18.4 (t), 22.0 (q), 22.8 (t), 29.7 (t), 32.6 (q), 33.9 (s), 36.9 (t), 41.4 (t), 48.9 (d), 52.1 (s), 138.0 (s), 138.1 (d), 172.9 (s), 211.4 (s); IR (KBr) 3300-2700, 1690, 1685, 1610; MS *m/e* (%) 250 (58, M^+), 235 (15), 232 (5), 222 (11), 217 (6), 207 (14), 123 (81), 112 (100), 109 (58), 95 (48), 82 (60), 69 (74); HRMS, calcd for $C_{15}H_{22}O_3$ (M^+) *m/e* 250.1569, found *m/e* 250.1572. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.86; H, 8.97.

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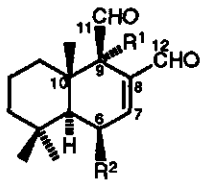
6 A NEW STEREOSELECTIVE APPROACH FOR THE TOTAL SYNTHESIS OF DRIMANE SESQUITERPENES

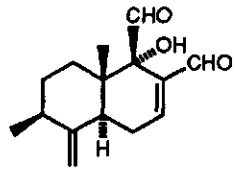
6.1 Introduction

Phytochemical studies of *Warburgia* Engl., a small genus restricted in distribution to East and Eastern Central Africa, revealed the presence of a number of drimane sesquiterpenes.[1] These compounds have attracted particular attention because of their potent insect antifeedant activity.[2] With regard to biological activity, warburganal **1**, polygodial **3**, mukaadial **102**, ungandensidial **47**, and muzigadial **2** are probably the most interesting compounds. In addition to their antifeedant activity, they are also molluscicidal,[3] antifungal,[4] and inhibit plant growth.[5]

Figure 6.1



1 R^1 = OH, R^2 = H
3 R^1 = R^2 = H
47 R^1 = OH, R^2 = OAc
102 R^1 = R^2 = OH

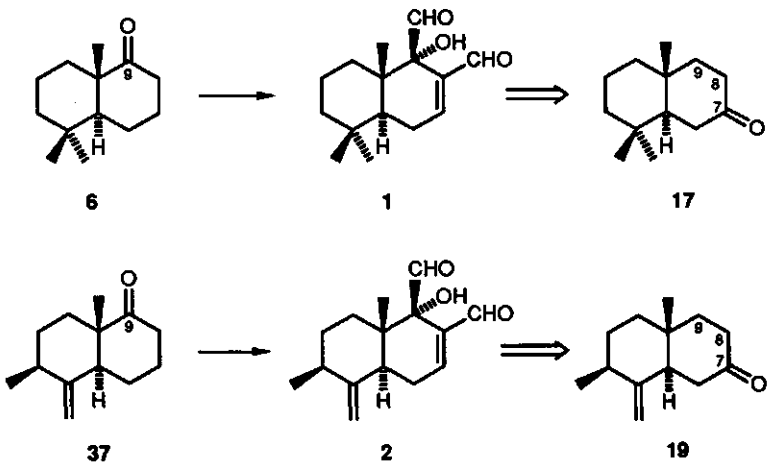


2

A common structural feature in these compounds is the presence of a 7,8-ene-11ß,12-dialdehyde functionality and, except for polygodial **3**, a 9α-hydroxy group. An analogous set of functionalities is found in the rearranged drimane muzigadial **2** as depicted in figure 6.1

A variety of methods was used for the total synthesis of the above-mentioned drimanes.[6] The *trans*-decalones **6** and **37**, with a carbonyl group at C-9, have turned out to be versatile intermediates in several syntheses of **1** [6a-q] and **2**.[6u] In all these cases the 9α-hydroxy group was introduced *via* oxidation of an exocyclic double bond or an enol ether in one of the final steps of the synthesis using osmiun tetroxide or *m*-CPBA as the oxidizing reagent. A total synthesis of muzigadial **2**, with its exocyclic double bond in ring A, along these lines, seems risky since it remains speculative until the final steps in such an approach whether the required selectivity in these oxidation reactions can be achieved. Recently it was shown in the first synthesis of muzigadial **2** that selective osmylation of an enol ether in the presence of the exocyclic 4,13-double bond can be accomplished under careful controlled conditions.[6u]

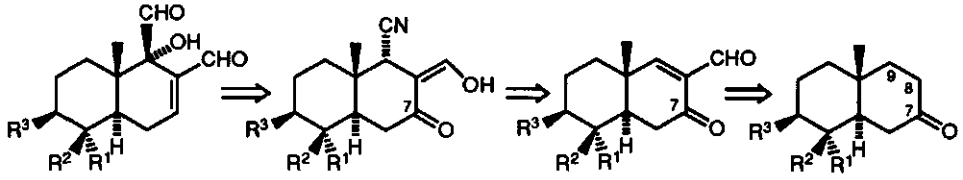
Scheme 6.1



Although we also have investigated a total synthesis of muzigadial **2** from **37** [7] we finally decided to develope a new and possibly general route for the synthesis of warburganal **1**, polygodial **3**, and especially muzigadial **2** in which the necessity of highly selective oxidation reactions could be avoided.

This new approach was found starting from the *trans*-decalones **17** and **19**, respectively (see scheme 6.1). These *trans*-decalones, with the carbonyl function at C-7, are easily accessible and the carbonyl group is ideally located for the introduction of the necessary functionalized carbon atoms at C-8 and at C-9 and it can be used later on for the introduction of the $\Delta^{7,8}$ double bond (see scheme 6.2).

Scheme 6.2



1 $R^1 = R^2 = CH_3$, $R^3 = H$
2 $R^1, R^2 = CH_2$, $R^3 = CH_3$
103 $R^1 = R^2 = R^3 = H$

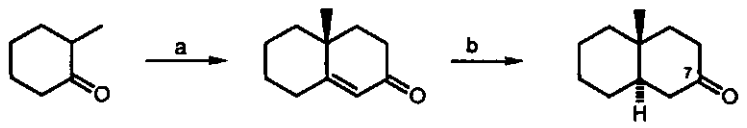
To test the possibilities of this synthetic plan the reaction sequence was first worked out for the syntheses of (±)-*dinor* drimanes. When the approach had proven its use it was

applied to the synthesis of the insect antifeedants (±)-polygodial **3**, (±)-warburganal **1**, and (±)-muzigadial **2**.

6.2 The synthesis of *trans*-decalones 106 and 17

The ketone 4,4a,5,6,7,8-hexahydro-4a-methylnaphthalen-2(3H)-one **105**, obtained from 2-methylcyclohexanone **104** and methyl vinyl ketone in reasonable yield,[8] was the starting material for **106** and **17**. Upon reduction with lithium in liquid ammonia [9] the desired *trans*-fused decalone **106** was obtained in 80% yield from **105**.

Scheme 6.3

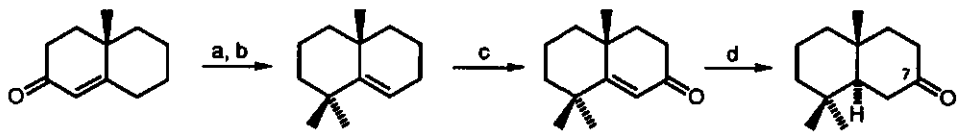


104 **105** **106**

Reagents: *a*, Methyl vinyl ketone, H_2SO_4, benzene; *b*, Li, NH_3, *t*-BuOH.

The *trans*-decalone **17** was synthesized from **105** partly *via* known procedures partly *via* adapted procedures.

Scheme 6.4



105 **107** **108** **17**

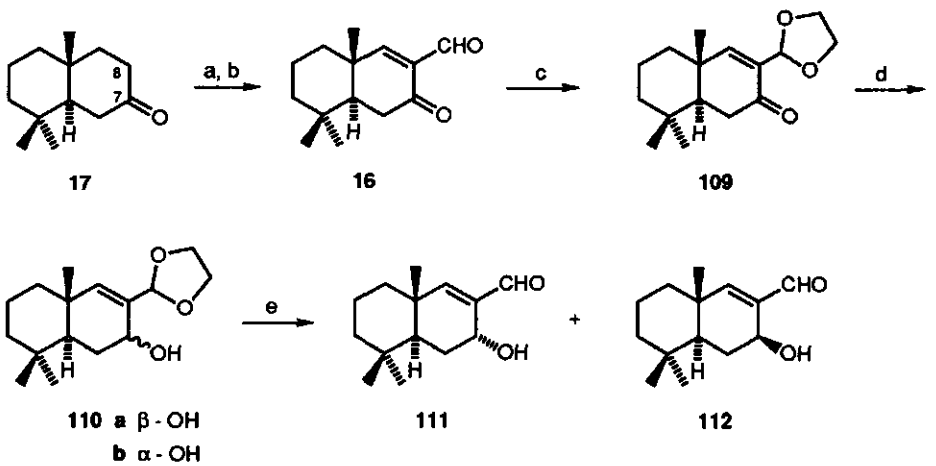
Reagents: *a*, KO-*t*-Bu, HO-*t*-Bu; CH_3I; *b*, H_2NNH_2, KOH, diethylene glycol; *c*, Na_2CrO_4, HOAc, Ac_2O; *d*, Li, NH_3, *t*-BuOH.

The required *gem* dimethyl group in **17** was introduced by dimethylation of **105** using methyl iodide as methylation reagent and potassium *tert*-butoxide as base.[10] The ketone function was reduced *via* Wolff-Kishner reduction to afford **107** in almost quantitative yield. The oxidation of C-7 was achieved *via* an allylic oxidation with sodium chromate in acetic acid at 35°C.[11] Although the reaction was very slow, the yield of **108** was quite good (85%). After reduction with lithium in liquid ammonia the *trans*-decalone **17** was obtained in an overall yield of 55% in four steps from **105**, which is comparable with other syntheses.[12]

6.3 Synthesis of (±)-Polygonone, (±)-Isopolygonal and (±)-Polygonal

The continuing study of the chemical constituents of *Polygonum hydropiper* L. has led to the isolation of several drimanic sesquiterpenes and some drimane-type *nor*sesquiterpenes, *e.g.*, polygonone **16**, isopolygonal **112**, and polygonal **111**.[13] With the *trans*-decalone **17** in hand a synthesis of the above-mentioned compounds was undertaken as depicted in scheme 6.5. Formylation of **17** occurred at C-8 exclusively to afford in 92% yield the 8-(hydroxymethylene) derivative. Dehydrogenation either with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or with benzeneselenyl chloride and hydrogen peroxide [14,60] gave rise to the unsaturated ketoaldehyde (±)-polygonone **16** in 96% yield.

Scheme 6.5



Reagents: *a*, NaH, HCOOEt; *b*, DDQ, dioxane or PhSeCl, pyridine; H_2O_2; *c*, ethylene glycol, *p*-TsOH, benzene; *d*, $LiAlH_4$; *e*, H_2O, HCl, acetone.

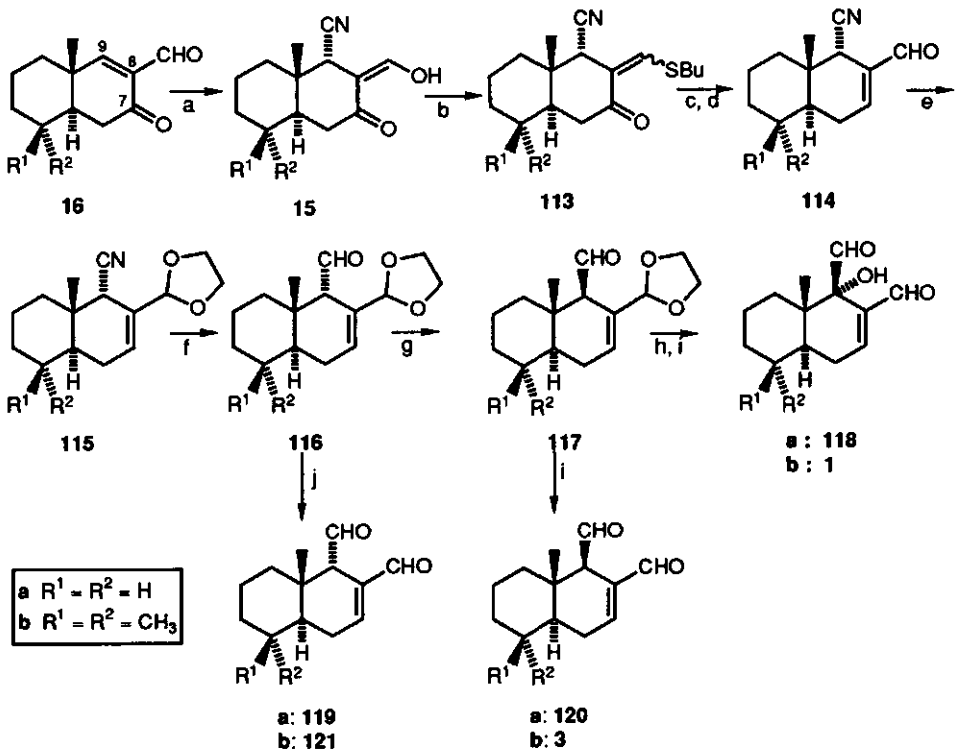
To protect the aldehyde against reduction, it was converted into the 1,3-dioxolan-2-yl derivative **109** in an almost quantitative yield. After reduction with lithium aluminum hydride in ether, two epimeric alcohols **110** were obtained. Purification by flash chromatography on silica gel afforded the alcohol **110a** with the equatorial hydroxy group in 83% yield and the alcohol **110b** with the axial hydroxy group in 5% yield. The assignments of the configuration at C-7 were based on the multiplicity of H-7 in the ^1H NMR spectra. A doublet of doublets with J=8.0 and 6.9 Hz required an α-oriented proton in **110a**. A dd with J=2.8 and 1.0 Hz in **110b** correspond with a ß-oriented proton at C-7. The stereochemical outcome of the reduction was not changed when sodium borohydride or lithium tri-*tert*-butoxyaluminum hydride was used. Mild

hydrolysis of the dioxolan function with dilute hydrochloric acid afforded (±)-isopolygonal **112** and (±)-polygonal **111**. The spectroscopic properties of these synthetic materials were in agreement with those reported.[13]

6.4 Synthesis of (±)-Isotadeonal, (±)-Polygodial, (±)-Warburganal and the (±) 13,14-dinor Congeners

The conversion of the unsaturated keto aldehyde functionality in **16a** into a 7,8-ene-11ß,12-dialdehyde was investigated next. The unsaturated keto aldehyde **16a** [15] smoothly

Scheme 6.6



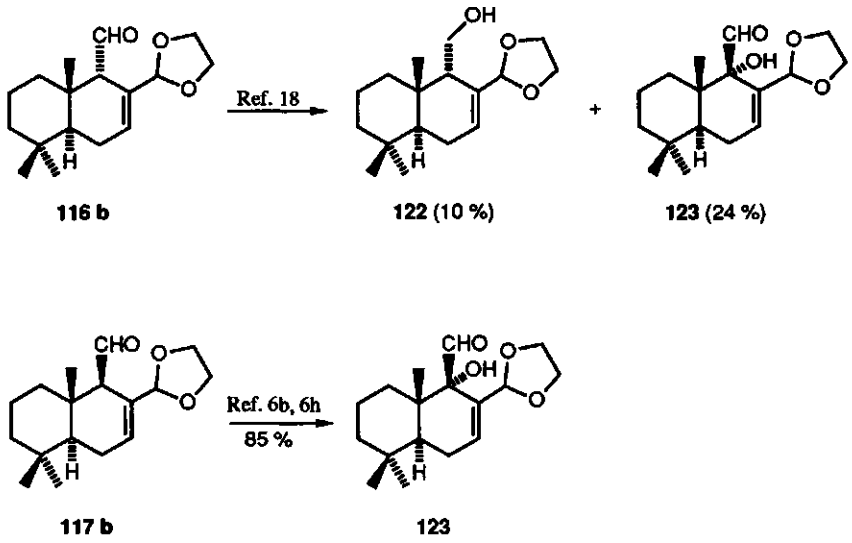
Reagents: *a*, KCN, dioxane; *b*, *n*-BuSH, *p*-TsOH, benzene; *c*, $NaBH_4$; *d*, $HgCl_2$, HCl, methanol; *e*, ethylene glycol, *p*-TsOH, benzene; *f*, DIBAH, toluene, -80°C; *g*, KO-*t*-Bu, HO-*t*-Bu; *h*, LDA, MoO_5.HMPA.pyr.; *i*, HCl, H_2O, acetone; *j*, *p*-TsOH, acetone.

underwent a conjugate addition of a cyanide anion [16] to afford in very good yield the 9α-nitrile **15a**. The conversion of the ß-formyl ketone moiety in this molecule into the protected α,ß-unsaturated aldehyde **115a** was performed *via* sodium borohydride reduction of the (*n*-butylthio)methylene derivative **113a** followed by a mercuric chloride assisted hydrolysis [17] and protection of the aldehyde group of **114a** as its ethylene acetal. The conversion of **16a** into the protected nitrile **115a** could be accomplished in 65% overall yield without extensive purification of the intermediates. The nitrile group in **115a** was reduced with diisobutylaluminum hydride to give the 9α-aldehyde **116a**. Hydrolysis of the acetal functionality with *p*-toluenesulfonic acid in acetone afforded (±)-13,14-dinorisotadeonal **119**.

The α-hydroxylation of 8-(1,3-dioxolan-2-yl)-9α-aldehyde **116a** was performed in conformity with a literature procedure in which the enolate of the aldehyde **116b** was oxidized in a rather low 24% yield.[18]

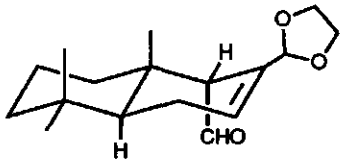
In contrast, the epimer **117b**, with an exposed α-proton at C-9 and a relatively hindered aldehyde group (see figure 6.3), is easily deprotonated and subsequently oxidized as was shown by Nakanishi *et al.*[6b] and by Ohno *et al.*[6h] in their syntheses of warburganal.

Figure 6.2

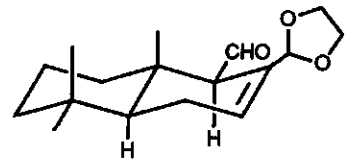


In our hands this deprotonation-oxidation procedure either gave the desired product **118** in very low yield (2-5%) or failed completely. This may be due to the steric crowding around the 9ß-proton so that nucleophilic attack of the so-called *non*-nucleophilic base lithium diisopropylamide (LDA) on the carbonyl function of the relatively exposed 9ß-aldehyde group is the preferred reaction (see figure 6.3).

Figure 6.3



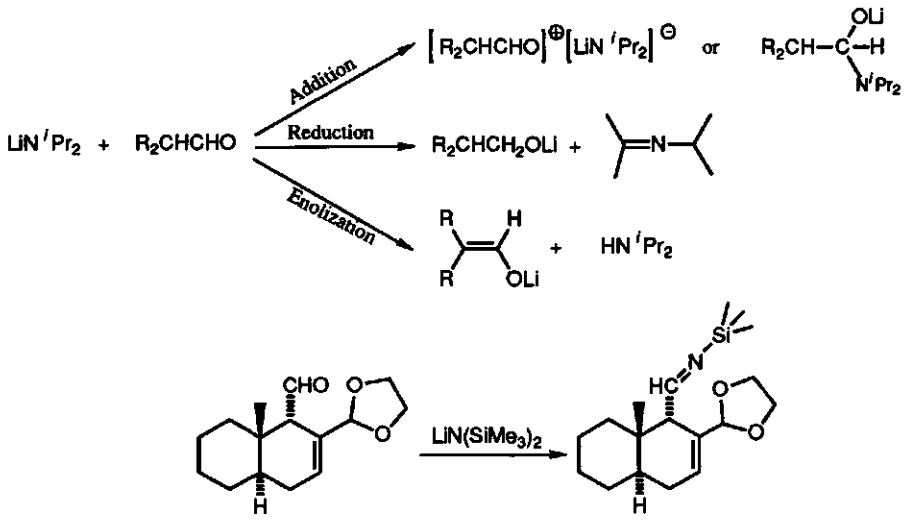
116 b



117 b

The reduction product **122** found by Ohsuka *et al.*[18] as a byproduct in this reaction is in agreement with this supposition. Its formation was explained by a Cannizarro-type reaction although the corresponding carboxylic acid derivative was not isolated. The ability of lithium diisopropylamide (LDA) to transfer a hydride ion as is shown in scheme 6.7 to explain the formation of the appropriate alkoxide, should not be excluded.[19]

Scheme 6.7

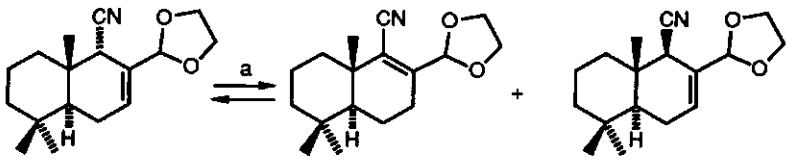


116 a **124**

Further evidence for this type of reaction was aquired by changing the lithium diisopropylamide (LDA) for lithium bis(trimethylsilyl)amide. In this case the N-trimethylsilylaldimine **124** was isolated, thus demonstrating the nucleophilic attack of this base on the exposed 9α-aldehyde group.[20]

Faced with these difficulties it was decided to try to prepare the 9ß-aldehyde **117b** *via* epimerization of the 9α-nitrile **115b**, followed by reduction.

Scheme 6.8



115 b **125** **126**

Reagents: *a*, KO-*t*-Bu, HO-*t*-Bu.

This epimerization of **115b** was investigated under a variety of reaction conditions but there was always isolated a mixture of the isomers **115b**, **125** and **126**, which could be separated by flash column chromatography. Upon prolonged treatment with base the nitrile **115b** was isomerized completely into the α,ß-unsaturated nitrile **125**. Unfortunately the reduction of **125** as well as **126** failed in our hands.

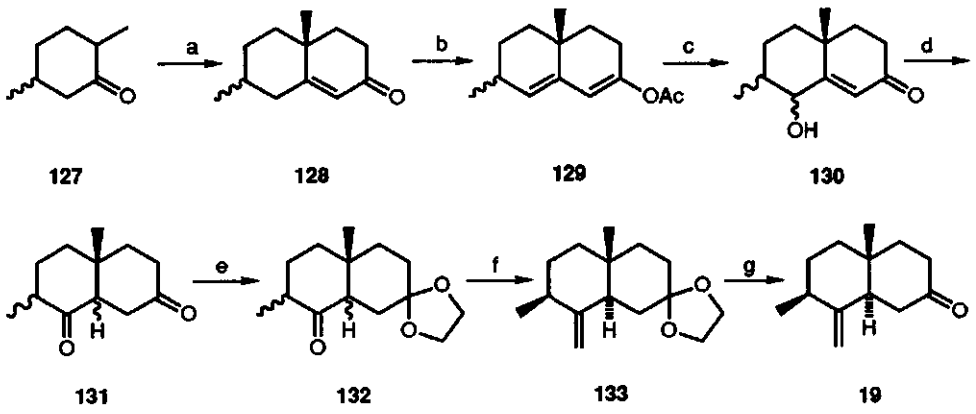
Therefore, the attention was focussed again on the transformation of the 9α-aldehyde **116a** and finally it was discovered that a complete epimerization could be accomplished by a *ten*-minutes treatment of **116a** with a *five*fold excess of potassium *tert*-butoxide in refluxing *tert*-butylalcohol.

The resulting 8-(1,3-dioxolan-2-yl)-9ß-aldehyde **117a** was easily deprotonated now and the enolate smoothly underwent an oxidation upon treatment with oxodiperoxymolybdenium (pyridine) hexamethylphosphoramide (MoOPH). Hydrolysis afforded (±)-13,14-dinor warburganal **118**. (±)-Dinorpolygodial **120** was obtained by hydrolysis of **117a** and (±)-dinorisotadeonal **119** from **116a**. With this procedure firmly established our attention was turned towards the synthesis of (±)-warburganal **1**, (±)-polygodial **3**, and (±)-isotadeonal **121** starting from the unsaturated keto aldehyde **16b** (see scheme 6.6). Without any troubles the procedure was repeated for **16b** and (±)-polygodial **3** was obtained in an overall yield of 30% and (±)-warburganal **1** in 27% overall yield. (±)-Isotadeonal **121** was synthesized in 35% overall yield after hydrolysis of **116b**.

6.5 Synthesis of *trans*-decalone 19

The synthesis of *trans*-decalone **19**, necessary for the preparation of muzigadial **2**, was achieved before in our laboratory and proved to be suitable for production on a good scale.[21]

Scheme 6.9



Reagents: *a*, MVK, H_2SO_4, benzene; *b*, Ac_2O, Me_3SiCl, NaI; *c*, $KHSO_5$; *d*, HBr, ether; *e*, MED, *p*-TsOH; *f*, DMSO, NaH, Ph_3PCH_3I; *g*, H_2O, HCl, acetone.

Robinson annulation of 2,5-dimethylcyclohexanone **127** with methyl vinyl ketone [8] afforded the bicyclic enone **128** as a diastereoisomeric mixture. This mixture was converted into its dienol acetate **129** with acetic anhydride, promoted by trimethylsilyl iodide generated *in situ* from trimethylsilyl chloride and sodium iodide.[22]

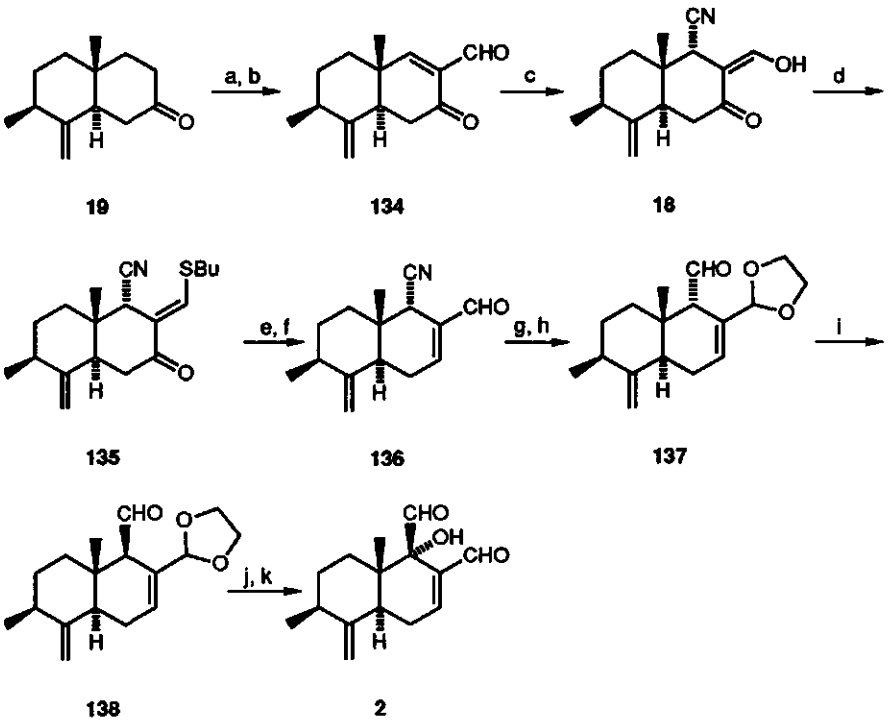
Oxidation of **129** with potassium peroxymonosulfate (Oxone [R]) gave a mixture of the hydroxy enones **130** which were easily isomerized upon treatment with hydrobromic acid in ether into the diketones **131**, again as a stereoisomeric mixture. The exposed keto function at C-7 was protected selectively by trans-acetalization with 2-methyl-2-ethyl-1,3-dioxolane (MED) [23] in quantitative yield. This was a marked improvement of the conventional acid-catalyzed acetalization with ethylene glycol. Wittig reaction of **132** with methylenetriphenylphosphorane [24] afforded one, single product **133**. This ment that the expected epimerization indeed had occurred under the basic reaction conditions at both asymmetric centers adjacent to the carbonyl group.

Mild hydrolysis of **133** gave *trans*-decalone **19** in an overall yield of 35%, based on the Robinson annulation product **128**.

6.6 Synthesis of (±)-Muzigadial

Since all the reaction conditions and reagents used for the conversion of **17** into (±)-warburganal **1** are compatible with the presence of an *exo* cyclic double bond in the molecule, the transformation of **19** into (±)-muzigadial **2** was expected to be straightforward and indeed no serious problems were encountered in the synthesis.

Scheme 6.10



19 134 18

135 136 137

138 2

Reagents: *a*, NaH, HCOOEt; *b*, PhSeCl, pyridine; H_2O_2; *c*, KCN, dioxane; *d*, *n*-BuSH, *p*-TsOH, benzene; *e*, $NaBH_4$; *f*, H_2O, HCl, $HgCl_2$; *g*, ethylene glycol, *p*-TsOH, benzene; *h*, DIBAH; *i*, KO-*t*-Bu, HO-*t*-Bu; *j*, LDA, MoO_5.HMPA.pyr.; *k*, HCl, acetone.

The hydrolysis of the reduced (*n*-butylthio)methylene compound (**135→136**) must be carried out at room temperature to prevent isomerization of the exocyclic olefinic bond. The key transformation in this sequence, notably the epimerization of the 9α-aldehyde **137** to the 9ß-aldehyde **138** was performed in almost quantitative yield although the monitoring of this reaction with TLC was deceiving since both epimers have the same R_f values. (±)-Muzigadial **2** was obtained *via* this *ten*-step procedure in an overall yield of 24% from **19**.

This novel approach is a valuable addition to the known methods for the synthesis of the insect antifeedant drimanic sesquiterpenes.[6,25] It enables the use of 7-oxo decalines as starting compounds and the method is compatible with sensitive functional groups in the starting compounds.

6.7 Experimental section

General experimental conditions were as described in chapter 4.

4aß,8,8-Trimethyl-2,3,4,4a,5,6,7,8-octahydronaphthalene (107)

To a solution of 112 g (1000 mmol) of potassium *tert*-butoxide in *tert*-butyl alcohol (1000 mL) was added dropwise a solution of 66.5 g (400 mmol) of enone **105** [8] in *tert*-butyl alcohol (100 mL) at room temperature. After stirring for 30 min 270 g (1200 mmol) of methyl iodide was added dropwise in 10 min at 0°C and the reaction mixture was left at room temperature. After 2 hours the reaction mixture was filtered and the filtrate was concentrated *in vacuo* and worked up as usual to afford an oily residue which gave after distillation at 15 torr 67 g (88%) of **1,1,4aß-trimethyl-3,4,4a,5,6,7-hexahydronaphthalen-2(1H)-one**, bp 127-130°C.
^{1}H NMR 1.00 (s, 3H), 1.23 (s, 6H), 1.4-2.2 (m, 8H), 2.4-2.7 (m, 2H), 5.60 (t, J=3 Hz, 1H); MS *m/e* (%) 192 (57, M^+), 177 (12), 164 (70), 149 (100), 121 (43); HRMS, calcd for $C_{13}H_{20}O$ (M^+) *m/e* 192.1514, found *m/e* 192.1512.

This ketone, 63.5 g (330 mmol), was treated with hydrazine hydrate (300 mL) in diethylene glycol (1000 mL) at 150°C. After 5 hours the excess of hydrazine hydrate was distilled off and 100 g of potassium hydroxide was added. After 5 hours at 180°C the reaction mixture was poured into water (2000 mL) and worked up as usual. The residual oil was distilled at 15 torr to yield 53.5 g (91%) of alkene **107**, bp 122-125°C.
^{1}H NMR 1.04 (s, 3H), 1.08 (s, 3H), 1.17 (s, 3H), 1.3-2.3 (m, 12H), 5.40 (t, J=3 Hz, 1H); MS *m/e* (%) 178 (30, M^+), 163 (100), 121 (21), 109 (21), 108 (45), 107 (40), 95 (31), 93 (38); HRMS, calcd for $C_{13}H_{22}$ (M^+) *m/e* 178.1722, found *m/e* 178.1721.

4aß,8,8-Trimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one (108)

A solution of 44.5 g (250 mmol) of alkene **107** in acetic acid (500 mL) and acetic anhydride (250 mL) was treated with 100 g (600 mmol) of sodium chromate at 35°C.
After 72 h the reaction mixture was poured into 1000 g of crushed ice and extracted with 7 portions of hexane. The combined extracts were washed with water (100 mL) and 4 N aqueous potassium hydroxide solution (250 mL), brine (100 mL), dried on magnesium sulfate and evaporated. The residue was distilled at 15 torr to give 38.5 g (80%) of enone **108**, bp 132-135°C.
^{1}H NMR 1.15 (s, 3H), 1.19 (s, 3H), 1.35 (s, 3H), 1.4-2.7 (m, 10H), 5.95 (s, 1H); IR (film) 1670, 1615; MS *m/e* (%) 192 (100, M^+), 177 (17), 164 (31), 149 (50), 136 (60), 135 (25), 123 (94), 122 (60), 121 (31), 95 (25); HRMS, calcd for $C_{13}H_{20}O$ (M^+) *m/e* 192.1514, found *m/e* 192.1516.

4aß,8,8-Trimethyl-3,4,4a,5,6,7,8,8aα-octahydronaphthalen-2(1H)-one (17)

A solution of 28.8 g (150 mmol) of enone **108** and 20 mL of *tert*-butyl alcohol in dry ether (200 mL) was added dropwise to a solution of 2.55 g (360 mgrat) of lithium in liquid ammonia (750 mL). After stirring for 15 min the excess of lithium was destroyed by adding solid ammonium chloride. The ammonia was allowed to evaporate and the residue was worked up as usual to afford 25.2 g (87%) of ketone **17**, bp 128-130°C (15 torr).

^{1}H NMR 0.75 (s, 6H), 1.03 (s, 3H), 1.2-2.0 (m, 9H), 2.0-2.2 (m, 4H); IR (film) 1710; MS *m/e* (%) 194 (90, M^+), 179 (38), 165 (9), 161 (16), 123 (100), 122 (34), 111 (30), 109 (34), 95 (25), 83 (51); HRMS, calcd for $C_{13}H_{22}O$ (M^+) *m/e* 194.1671, found *m/e* 194.1675.

3-Oxo-5,5,8aß-trimethyl-3,4,4aα,5,6,7,8,8a-octahydronaphthalene-2-carboxaldehyde (16)

A suspension of 0.72 g (15 mmol) of sodium hydride in mineral oil was added to dry ether (100 mL) under nitrogen. A solution of 2.52 g (13 mmol) of ketone **17** and 1.93 g (26 mmol) of ethyl formate in dry ether (25 mL) was added dropwise at room temperature. After 2 hours the reaction mixture was poured into water (50 mL) and extracted twice with ether (50 mL). The combined etheral solutions were extracted with 2 N aqueous potassium hydroxide. The combined aqueous fase was acidified with concentrated hydrochloric acid and extracted twice with ether. The extracts were dried and evaporated *in vacuo* to afford 2.66 g (92%) of **3-(hydroxymethylene)-4aß,8,8-trimethyl-3,4,4a,5,6,7,8,8aα-octahydronaphthalen-2(1H)-one.**

^{1}H NMR 0.90 (s, 9H), 1.4-2.7 (m, 11H), 8.43 (s, 1H), 14.37 (br s, 1H); IR (film) 3300, 1650, 1590; MS *m/e* (%) 222 (38, M^+), 124 (73), 123 (25), 109 (100), 81 (18), 69 (23), 55 (14); HRMS, calcd for $C_{14}H_{22}O_2$ (M^+) *m/e* 222.1622, found *m/e* 222.1620.

This (hydroxymethylene) ketone was added to an ice-cold solution of 2.49 g (13 mmol) of benzeneselenyl chloride and 1.19 g (15 mmol) of pyridine in dichloromethane (100 mL). The reaction mixture was stirred for 1 hour and washed with 4 N aqueous hydrochloric acid (20 mL) and brine (50 mL). The dichloromethane solution was cooled in ice, and 30% hydrogen peroxide (1.5 mL) was added in three portions with intervals of 15 min. The reaction mixture was washed with brine and dried on magnesium sulfate and evaporated. The residue was purified by flash chromatography on silica gel (eluent light petroleum-ether 4:1) to give 2.75 g (96%) of **16** as a yellow oil, which crystallized upon standing, mp 48-50°C.

^{1}H NMR 0.97 (s, 3H), 0.99 (s, 3H), 1.20 (s, 3H), 1.3-1.9 (m, 7H), 2.50 (dd, J=5.2,

1.5 Hz, 2H), 7.34 (s, 1H), 10.07 (s, 1H); IR (KBr) 1705, 1685, 1605; MS *m/e* (%) 220 (18, M^+), 205 (12), 192 (33), 124 (88), 109 (100), 81 (14), 69 (19); HRMS, calcd for $C_{14}H_{20}O_2$ (M^+) *m/e* 220.1463, found *m/e* 220.1460. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.50; H, 9.18.

3-(1,3-Dioxolan-2-yl)-4aß,8,8-trimethyl-4a,5,6,7,8,8aα-hexahydronaphthalen-2(1H)-one (109)

A solution of 2.20 g (10 mmol) of aldehyde **16** in benzene (100 mL) was treated with 1.24 g (20 mmol) of ethylene glycol and 50 mg of *p*-toluenesulfonic acid at reflux temperature under a Dean-Stark water separator. After 60 min the reaction mixture was cooled, diluted with ether (100 mL) and washed with a saturated aqueous sodium hydrogen carbonate solution (25 mL), dried and evaporated. The residue was purified by flash chromatography on silica gel (eluent light petroleum-ether 3:2) to yield 2.40 g (91%) of crystalline **109**, which was recrystallized from methanol, mp 74-75°C.
^{1}H NMR 0.87 (s, 3H), 0.90 (s, 3H), 1.10 (s, 3H), 1.2-2.0 (m, 7H), 2.2-2.7 (m, 2H), 3.9 (br s, 4H), 5.62 (s, 1H), 6.87 (s, 1H); IR (KBr) 1675, 1610; MS *m/e* (%) 264 (22, M^+), 249 (51), 219 (76), 149 (41), 141 (46), 140 (100), 109 (64), 73 (86); HRMS, calcd for $C_{16}H_{24}O_3$ (M^+) *m/e* 264.1725, found *m/e* 264.1719. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.74; H, 9.38.

3-(1,3-Dioxolan-2-yl)-4aß,8,8-trimethyl-1,2,4a,5,6,7,8,8aα-octahydronaphthalen-2ß-ol (110a) and **3-(1,3-dioxolan-2-yl)-4aß,8,8-trimethyl-1,2,4a,5,6,7,8,8aα-octahydronaphthalen-2α-ol (110b)**.

To a solution of 114 mg (3 mmol) of lithium tetrahydridoaluminate in dry ether (100 mL) was added dropwise 2.12 g (8.0 mmol) of ketone **109** in dry ether (10 mL). After 30 min there were added ten drops of water, ten drops of an aqueous 4 N potassium hydroxide solution, and ten drops of water, respectively. The reaction mixture was dried on magnesium sulfate and the solvent evaporated. The residue was purified by flash chromatography on silica gel (eluent light petroleum-ether 7:3) to afford 1.77 g (83%) of the alcohol **110a** as a colourless oil, R_f 0.30 (hexane-ether 7:3).
^{1}H NMR 0.88 (s, 6H), 1.05 (s, 3H), 1.1-1.8 (8H), 2.15 (ddd, J=1,7,6 Hz, 1 H), 3.50 (s, 1H), 4.0 (4H), 4.52 (dd, J=7,8 Hz, 1H), 5.22 (s, 1H), 5.70 (s, 1H); MS *m/e* (%) 266 (55, M^+), 251 (4), 248 (6), 233 (8), 193 (19), 143 (23), 141 (11), 128 (30), 73 (100); HRMS, calcd for $C_{16}H_{26}O_3$ (M^+) *m/e* 266.1882, found *m/e* 266.1889.
The alcohol **110b** was eluted next, 106 mg (5%), R_f 0.20 (hexane-ether 7:3), mp 143-145°C.
^{1}H NMR 0.85 (s, 3H), 0.93 (s, 3H), 0.94 (s, 3H), 1.2-1.9 (9H), 2.99 (s, 1H), 4.0

(4H), 4.40 (dd, J=3,1 Hz, 1H), 5.17 (s, 1H), 5.67 (s, 1H); MS *m/e* (%) 266 (13, M^+), 251 (2), 248 (13), 233 (15), 193 (23), 163 (5), 161 (4), 143 (12), 128 (11), 109 (8), 99 (16), 91 (5), 73 (100); HRMS, calcd for $C_{16}H_{26}O_3$ (M^+) *m/e* 266.1882, found *m/e* 266.1886. Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.10; H, 9.99.

3α-Hydroxy-5,5,8aß-trimethyl-3,4,4aα,5,6,7,8,8a-octahydronaphthalene-2-carboxaldehyde (111) (Polygonal)

A solution of 90 mg (0.34 mmol) of alcohol **110b** in acetone (3 mL) was treated with 0.5 N hydrochloric acid (0.5 mL). The mixture was stirred for 30 min and then poured into water and worked up as usual to afford a white solid. Recrystallization from hexane gave 68 mg (90%) of polygonal **111**, mp 139-140°C.
^{1}H NMR 0.89 (s, 3H), 0.97 (s, 3H), 1.03 (s, 3H), 1.1-2.0 (9H), 2.67 (s, 1H), 4.63 (dd, J=4,1 Hz, 1H), 6.52 (s, 1H), 9.62 (s, 1H); IR (KBr) 3600, 3450, 1675, 1605; MS *m/e* (%) 222 (3, M^+), 207 (3), 204 (94), 193 (31), 190 (14), 189 (100), 75 (32), 161 (29), 135 (24), 133 (26), 119 (27), 109 (29), 105 (34), 99 (27), 91 (32); HRMS, calcd for $C_{14}H_{22}O_2$ (M^+) *m/e* 222.1620, found *m/e* 222.1620. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.65; H, 10.04.

3ß-Hydroxy-5,5,8aß-trimethyl-3,4,4aα,5,6,7,8,8a-octahydronaphthalene-2-carboxaldehyde (112) (Isopolygonal)

The hydrolysis of 1.18 g (4.44 mmol) of acetal **110a** was performed as described above. The residue was purified by flash chromatography on silica gel (eluent light petroleum-ether 7:3) to give 921 mg (94%) of isopolygonal as a colourless oil.
^{1}H NMR 0.92 (s, 3H), 0.93 (s, 3H), 1.15 (s, 3H), 1.1-1.8 (8H), 2.16 (dd, J=7, 12 Hz, 1H), 3.68 (s, 1H), 4.65 (dd, J=7,8 Hz, 1H), 6.46 (s, 1H), 9.39 (s, 1H); IR (KBr) 3600, 3450, 1675, 1610; MS *m/e* (%) 222 (28, M^+), 207 (18), 204 (44), 193 (42), 189 (50), 174 (28), 160 (22), 136 (21), 134 (32), 132 (24), 125 (100), 122 (48), 111 (52), 109 (72), 99 (52); HRMS, calcd for $C_{14}H_{22}O_2$ (M^+) *m/e* 222.1620, found *m/e* 222.1619. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.75; H, 10.00.

2-(Hydroxymethylene)-8aß-methyl-*trans*-perhydro-3-oxonaphthalene-1α-carbonitrile (15a)

To a solution of 7.67 g (35 mmol) of compound **16a** in dioxane (100 mL) and water (10 mL) was added a solution of 2.47 g (38 mmol) of potassium cyanide in dioxane (10 mL) and water (1 mL). The reaction mixture was stirred at room temperature for

30 min and then the dioxane was evaporated. The residue was treated with 4 N aqueous potassium hydroxide (20 mL) and extracted with ether. The basic aqueous solution was acidified with concentrated hydrochloric acid (5 mL) and extracted with ether. The ethereal solution was washed with brine and dried. The ether was evaporated and the residue was recrystallized from diisopropyl ether to afford 7.28 g (95%) of **15a** as white crystals, mp 141-142°C.
^{1}H NMR 0.96 (s, 3H), 1.2-2.4 (11H), 3.18 (s, 1H), 8.80 (s, 1H), 11.67 (br s, 1H); IR (KBr) 2220, 1645, 1600; MS *m/e* (%) 219 (86, M^+), 125 (29), 124 (31), 109 (12), 96 (100), 95 (63), 81 (46), 67 (16); HRMS, calcd for $C_{13}H_{17}NO_2$ (M^+) *m/e* 219.1259, found *m/e* 219.1260. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.81. Found: C, 71.49; H, 7.75.

2-(Hydroxymethylene)-5,5,8aß-trimethyl-*trans*-perhydro-3-oxonaphthalene-1α-carbonitrile (15b)

Compound **15b** was prepared from **16b** as described for **15a**. Recrystallization from diisopropyl ether gave 7.90 g (91%) of white crystalline nitrile **15b**, mp 88-94°C.
^{1}H NMR 0.94 (s, 3H), 0.96 (s, 3H), 1.00 (s, 3H), 1.3-1.9 (6H), 1.75 (dd, J=7,11 Hz, 1H), 2.44 (ddd, J=7,11,18 Hz, 2H), 3.06 (s, 1H), 8.77 (s, 1H), 11.70 (br s, 1H); IR (KBr) 2220, 1645, 1595; MS *m/e* (%) 247 (100, M^+), 232 (9), 205 (12), 151 (12), 124 (98), 123 (98), 109 (76), 96 (13), 81 (24), 69 (74); HRMS, calcd for $C_{15}H_{21}NO_2$ (M^+) *m/e* 247.1572, found *m/e* 247.1572. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56. Found: C, 72.96; H, 8.50.

2-(*E*)-[(Butylthio)methylene]-8aß-*trans*-perhydro-3-oxonaphthalene-1α-carbonitrile (113a)

A solution of 6.57 g (30 mmol) of **15a** in benzene (100 mL) was treated with 1-*n*-butanethiol (4 mL) and 25 mg of *p*-toluenesulfonic acid at reflux temperature for 3 h in a Dean-Stark apparatus. After cooling the reaction mixture was washed with an aqueous sodium bicarbonate solution (50 mL), with water (50mL), and with brine (25 mL) and dried. The benzene was evaporated and the residue was purified by flash chromatography on silica gel (eluent light petroleum-ether 7:3) to provide 8.03 g (92%) of compound **113a** as an oil.
^{1}H NMR 0.97 (s, 3H), 0.9-2.5 (18H), 2.95 (t, J=6 Hz, 2H), 3.33 (s, 1H), 7.94 (s, 1H); IR (film) 2210, 1660, 1540; MS *m/e* (%) 291 (24, M^+), 276 (2), 234 (100), 201 (8), 95 (36); HRMS, calcd for $C_{17}H_{25}NOS$ (M^+) *m/e* 291.1657, found *m/e* 291.1657.

2-(*Z*)-[(Butylthio)methylene]-8aß-*trans*-perhydro-3-oxonaphthalene-1α-carbonitrile (113a)

This isomer of the nitril **113a** described above was isolated in 6% yield as second fraction in the purification procedure.
^{1}H NMR 0.97 (s, 3H), 0.9-2.5 (18H), 2.77 (t, J=7 Hz, 2H), 3.33 (s, 1H), 7.15 (s, 1H); IR (film) 2220, 1655, 1540; MS *m/e* (%) 291 (24, M^+), 276 (3), 234 (100), 201 (8), 95 (36); HRMS, calcd for $C_{17}H_{25}NOS$ (M^+) *m/e* 291.1657, found *m/e* 291.1655.

2-(*E*)-[(Butylthio)methylene]-5,5,8aß-trimethyl-*trans*-perhydro-3-oxonaphthalene-1α-carbonitrile (113b)

Nitrile **113b** was prepared from **15b** as described for **113a**. Crystallization from a mixture of diisopropyl ether and hexane (3:7) afforded 9.10 g (95%) of white crystals, mp 75-76°C.
^{1}H NMR 0.91 (s, 3H), 0.93 (s, 3H), 1.00 (s, 3H), 0.9-2.1 (14H), 2.40 (ddd, J=6, 12,18 Hz, 2H), 2.95 (t, J=7 Hz, 2H), 3.24 (s, 1H), 7.96 (s, 1H); IR (KBr) 2220, 1645, 1595; MS *m/e* (%) 319 (68, M^+), 304 (5), 286 (10), 277 (7), 262 (68), 259 (8), 197 (16), 182 (18), 173 (6), 123 (100), 109 (10), 97 (9), 81 (9); HRMS, calcd for $C_{19}H_{29}NOS$ (M^+) *m/e* 319.1970, found *m/e* 319.1964. Anal. Calcd for $C_{19}H_{29}NOS$: C, 71.24; H, 9.15. Found: C, 71.13; H, 9.18.

2-Formyl-8aß-methyl-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-1α-carbonitrile (114a)

To a solution of 7.28 g (25 mmol) of **113a** in methanol (50 mL) was added 0.29 g (7.5 mmol) of sodium borohydride at 0°C. The reaction mixture was stirred for 15 min, and the methanol was evaporated. Ether (200 mL) was added to the residue, and the solution was washed with water and with brine and dried. The ether was evaporated and the reduction product was hydrolyzed without further purification.
^{1}H NMR 0.87 (s, 3H), 0.93 (t, J=6 Hz, 3H), 1.1-1.9 (15H), 2.52 (br s, 1H), 2.73 (t, J=7 Hz, 2H), 3.65 (s, 1H), 4.43 (ddd, J=2,6,8 Hz, 1H), 6.35 (d, J=2 Hz, 1H); IR ($CHCl_3$) 3600, 3450-3300, 2220, 1470, 1460; MS *m/e* (%) 293 (36, M^+), 275 (85), 218 (44), 203 (36), 185 (22), 96 (100), 81 (35); HRMS, calcd for $C_{17}H_{27}NOS$ (M^+) *m/e* 293.1813, found *m/e* 293.1811.
This reduction product was dissolved in methanol (75 mL) and 4 N aqueous hydrochloric acid (25 mL), and 8.13 g (30 mmol) of mercuric chloride were added. The reaction mixture was stirred at room temperature for 16 h and then filtered. The methanol was evaporated and ether (200 mL) was added. The ethereal solution was washed with

saturated sodium bicarbonate solution (25 mL), with brine (50 mL) and dried. The ether was evaporated and the residue was purified by column chromatography on silica gel (eluent light petroleum-ether 3:1) to give 4.62 g (91%) of **114a** as white crystals, mp 123-124°C.

^{1}H NMR 0.80 (s, 3H), 1.0-2.4 (11H), 3.23 (s, 1H), 6.94 (dd, J=3,4 Hz, 1H), 9.42 (s, 1H); IR (KBr) 2220, 1690, 1650; MS *m/e* (%) 203 (15, M^+), 96 (100), 81 (35); HRMS, calcd for $C_{13}H_{17}NO$ (M^+) *m/e* 203.1310, found *m/e* 203.1307. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43. Found: C, 77.01; H, 8.60.

2-Formyl-5,5,8aß-trimethyl-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-1α-carbonitrile (114b)

Compound **114b** was prepared from **113b** as described for **114a** to yield 5.10 g (88%) of **114b** as a white crystalline compound, mp 91-92°C.

^{1}H NMR 0.90 (s, 3H), 0.97 (s, 3H), 1.00 (s, 3H), 1.3-1.9 (7H), 2.30 (ddd, J=1.5, 3,11 Hz, 1H), 2.50 (dd, J=5,6 Hz, 1H), 3.20 (s, 1H), 7.03 (dd, J=3,5 Hz, 1H), 9.47 (s, 1H); IR (KBr) 2215, 1695, 1605; MS *m/e* (%) 231 (3, M^+), 216 (7), 124 (100), 109 (55), 69 (23); HRMS, calcd for $C_{15}H_{21}NO$ (M^+) *m/e* 231.1623, found *m/e* 231.1626. Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15. Found: C, 78.11; H, 8.82.

2-(1,3-Dioxolan-2-yl)-8aß-methyl-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-1α-carbonitrile (115a)

A solution of 4.06 g (20 mmol) of **114a**, ethylene glycol (5 mL) and 25 mg of *p*-toluenesulfonic acid in benzene (50 mL) was refluxed for 4 h in a Dean-Stark apparatus. The reaction mixture was cooled and diluted with ether (100 mL), and the solution was washed with saturated aqueous sodium bicarbonate solution (50 mL) and worked up as usual. The residue was purified by column chromatography on silica gel (eluent light petroleum-ether 7:3) to afford 4.30 g (87%) of compound **115a** as white crystals, mp 103-104°C.

^{1}H NMR 0.90 (s, 3H), 1.0-2.0 (10H), 2.16 (dd, J=4,12 Hz, 1H), 2.56 (s, 1H), 4.00 (4H), 5.25 (s, 1H), 6.16 (dd, J=3,4 Hz, 1H); IR (KBr) 2220, 1640; MS *m/e* (%) 247 (33, M^+), 232 (8), 207 (8), 151 (18), 138 (29), 125 (33), 96 (27), 86 (31), 81 (24), 73 (100); HRMS, calcd for $C_{15}H_{21}NO_2$ (M^+) *m/e* 247.1572, found *m/e* 247.1577. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56. Found: C, 73.07; H, 8.52.

2-(1,3-Dioxolan-2-yl)-5,5,8aß-trimethyl-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-1α-carbonitrile (115b)

Compound **115b** was prepared from **114b** as described for **115a**. After usual work-up the residue was purified by flash chromatography on silica gel (eluent light petroleum-ether 7:3) to afford 4.95 g (90%) of crystalline **115b**, mp 95-96°C.
^{1}H NMR 0.97 (br s, 9H), 1.3-1.9 (7H), 2.0-2.4 (2H), 2.81 (s, 1H), 3.98 (4H), 5.27 (s, 1H), 6.10 (dd, *J*= 3,4 Hz, 1H); IR (KBr) 2215, 1650; MS *m/e* (%) 275 (23, M^+), 274 (20), 261 (14), 260 (74), 235 (11), 138 (35), 137 (16), 125 (100), 124 (50), 109 (82), 86 (24), 73 (82); HRMS, calcd for $C_{17}H_{25}NO_2$ (M^+) *m/e* 275.1885, found *m/e* 275.1874. Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15. Found: C, 74.43; H, 8.85.

2-(1,3-Dioxolan-2-yl)-8aß-methyl-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-1α-carboxaldehyde (116a)

A solution of 2.47 g (10 mmol) of **115a** in dry toluene (200 mL) was cooled to -80°C under nitrogen, and a solution of 1.5 M diisobutylaluminum hydride in toluene (15 mL, 22.5 mmol) was added dropwise. The reaction mixture was stirred for 60 min at -80°C and then poured into saturated aqueous ammonium chloride solution (250 mL). Usual work-up afforded crude **116a** which was purified by column chromatography on silica gel (eluent light petroleum-ether 7:3) to give 2.13 g (85%) of crystalline **116a**, mp 88-90°C.
^{1}H NMR 0.93 (s, 3H), 1.0-2.3 (11H), 2.70 (d, *J*=5 Hz, 1H), 3.83 (4H), 5.15 (s, 1H), 6.16 (dd, *J*=3,4 Hz, 1H), 9.56 (d, *J*=5 Hz, 1H); IR (KBr) 1720, 1190, 1080, 1030; MS *m/e* (%) 250 (2, M^+), 222 (55), 221 (94), 91 (18), 81 (20), 73 (100); HRMS, calcd for $C_{15}H_{22}O_3$ (M^+) *m/e* 250.1569, found *m/e* 250.1565. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.96; H, 8.86. Found: C, 71.88; H, 8.90.

2-(1,3-Dioxolan-2-yl)-5,5,8aß-trimethyl-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-1α-carboxaldehyde (116b)

Compound **116b** was prepared from **115b** as described for **116a**. The residue obtained after the usual work-up procedures, was purified by flash chromatography on silica gel (eluent light petroleum-ether 7:3) to afford 2.36 g (85%) of white crystalline **116b**, mp 65-66°C.
^{1}H NMR 0.95 (br s, 6H), 0.97 (s, 3H), 1.1-1.9 (7H), 2.12 (ddd, *J*=2,4,12 Hz, 1H), 2.28 (dd, *J*=3,4 Hz, 1H), 2.60 (dd, *J*=2,5 Hz, 1H), 3.80 (4H), 5.14 (s, 1H), 6.18 (dd, *J*=3,5 Hz, 1H), 9.51 (d, *J*=5 Hz, 1H); IR (KBr) 1720; MS *m/e* (%) 278 (3, M^+), 250 (42), 249 (90), 234 (17), 210 (10), 191 (12), 141 (25), 139 (11), 109 (15), 105

(12), 91 (13), 73 (100), 69 (17); HRMS, calcd for $C_{17}H_{26}O_3$ (M^+) *m/e* 278.1882, found *m/e* 278.1873. Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.42. Found: C, 73.09; H, 9.40.

2-(1,3-Dioxolan-2-yl)-8aß-methyl-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-1ß-carboxaldehyde (117a)

To a solution of 2.08 g (18.6 mmol) of potassium *tert*-butoxide in *tert*-butyl alcohol (25 mL) under nitrogen was added 1.00 g (4 mmol) of the 1α-carboxaldehyde **116a**, and the reaction mixture was refluxed for 10 min. The solution was cooled in ice, and water and ether were added. Usual work-up procedure afforded 0.92 g (92%) of **117a** after purification by column chromatography on silica gel (eluent light petroleum-ether 8:2), mp 66-68°C.
^{1}H NMR 1.06 (s, 3H), 1.2-2.2 (11 H), 2.71 (ddd, *J*=3,6,9 Hz, 1H), 3.85 (4H), 5.20 (s, 1H), 6.18 (ddd, *J*=3,6,7 Hz, 1H), 9.63 (d, *J*=6 Hz, 1H); IR (KBr) 1720; MS *m/e* (%) 250 (3, M^+), 222 (100), 221 (61), 91 (15), 81 (18), 73 (30); HRMS, calcd for $C_{15}H_{22}O_3$ (M^+) *m/e* 250.1569, found *m/e* 250.1571. Anal. Calcd for $C_{15}H_{22}O_3$: C, 74.14; H, 9.15. Found: C, 73.80; H, 9.20.

2-(1,3-Dioxolan-2-yl)-5,5,8aß-trimethyl-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-1ß-carboxaldehyde (117b)

Compound **117b** was prepared from **116b** as described for aldehyde **117a**. The crude aldehyde was purified by column chromatography on silica gel (eluent light petroleum-ether 8:2) to provide 1.03 g (93%) of **117b** as white crystals, mp 62-63°C.
^{1}H NMR 0.87 (s, 3H), 0.94 (s, 3H), 1.10 (s, 3H), 1.2-1.8 (7H), 2.15 (ddd, *J*=3,5, 11 Hz, 2H), 2.70 (ddd, *J*=2,3,6 Hz, 1H), 3.85 (4H), 5.16 (s, 1H), 6.18 (ddd, *J*=2,6,9 Hz, 1H), 9.56 (d, *J*=6 Hz, 1H); IR (KBr) 1720; MS *m/e* (%) 278 (2, M^+), 263 (4), 250 (100), 249 (66), 235 (34), 191 (17), 173 (7), 165 (12), 154 (23), 141 (24), 139 (24), 109 (20), 73 (37); HRMS, calcd for $C_{17}H_{26}O_3$ (M^+) *m/e* 278.1882, found *m/e* 278.1882. Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.51; H, 9.43.

1α-Hydroxy-8aß-methyl-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-1ß,2-dicarboxaldehyde (118) (13,14-dinorwarburganal)

A solution of 1.2 mmol of lithium diisopropylamide in dry THF (25 mL) under nitrogen was cooled to -80°C, and a solution of 250 mg (1.0 mmol) of **117a** in dry THF (10 mL) was added. The reaction mixture was stirred for 30 min at -80°C, and 650 mg (1.5 mmol) of MoO_5.HMPA.pyr. complex was added. The solution was stirred for 1 h

and then quenched with saturated aqueous sodium sulfite solution (100 mL) at -80°C. The mixture was worked up as usual, and the residue was purified by column chromatography on silica gel (eluent light petroleum-ether 4:1) to afford 253 mg (95%) of **2-(1,3-dioxolan-2-yl)-1α-hydroxy-8aß-methyl-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-1ß-carboxaldehyde** as white crystals, mp 38-42°C.

^{1}H NMR 1.06 (s, 3H), 1.1-1.8 (10H), 1.90 (ddd, J=2,7,11 Hz, 2H), 4.78 (4H), 5.12 (s, 1H), 6.17 (dd, J=2,3 Hz, 1H), 9.72 (s, 1H); IR (KBr) 3470, 3430, 1715, 1640; MS *m/e* (%) 266 (3, M^+), 251 (1), 248 (2), 237 (100), 193 (43), 175 (9), 73 (20); HRMS, calcd for $C_{15}H_{22}O_4$ (M^+) *m/e* 266.1518, found *m/e* 266.1525. Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.91; H, 8.35.

A solution of 133 mg (0.5 mmol) of the above-mentioned hydroxy acetal in acetone (5 mL) was treated with 1 N hydrochloric acid (1 mL) and stirred for 30 min. The reaction mixture was poured into water and worked up as usual. The residue was purified by flash chromatography on silica gel (eluent light petroleum-ether 7:3) to give 90 mg (82%) of **118** as a colourless oil.

^{1}H NMR 1.00 (s, 3H), 1.15-1.75 (8H), 1.96 (1H), 2.10 (1H), 2.25 (dd, J=4,9 Hz, 1H), 3.70 (br s, 1H), 7.16 (dd, J=2,5 Hz, 1H), 9.40 (s, 1H), 9.67 (s, 1H); IR ($CHCl_3$) 3450, 3415, 1715, 1675, 1640; MS *m/e* (%) 222 (1, M^+), 204 (2), 194 (30), 193 (100), 189 (2), 176 (7), 175 (9), 147 (9), 133 (15), 125 (9), 105 (14), 81 (23); HRMS, calcd for $C_{13}H_{18}O_3$ (M^+) *m/e* 222.1256, found 222.1259. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.31; H, 8.33.

1α-Hydroxy-5,5,8aß-trimethyl-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-1ß,2-dicarboxaldehyde (1) (Warburganal)

Warburganal **1** was prepared as described above for the dinor congener. Oxidation of the enolate of **117b** gave in 91% yield **2-(1,3-dioxolan-2-yl)-1α-hydroxy-5,5,8aß-trimethyl-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-1ß-carboxaldehyde (123)** as white crystals, mp 96-97°C.

^{1}H NMR 0.90 (s, 3H), 0.97 (s, 3H), 1.20 (s, 3H), 1.2-1.7 (6H), 1.92 (1H), 2.1-2.3 (2H), 3.82 (4H), 5.16 (s, 1H), 6.33 (dd, J=2,4 Hz, 1H), 9.83 (s, 1H); IR (KBr) 3480, 3420, 1715, 1675, 1120, 1080, 1040; MS *m/e* (%) 294 (14, M^+), 279 (1), 276 (3), 266 (20), 265 (100), 261 (3), 249 (4), 221 (18), 157 (16), 109 (35), 73 (31); HRMS, calcd for $C_{17}H_{26}O_4$ (M^+) *m/e* 294.1831, found *m/e* 294.1837. Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.51; H, 8.88.

Hydrolysis of the above-mentioned acetal afforded warburganal **1** in 81% yield as white crystals from hexane, mp 96-97°C.

^{1}H NMR 0.93 (s, 3H), 0.99 (s, 3H), 1.08 (s, 3H), 1.2-1.8 (6H), 1,88 (dd, J=5,10 Hz, 1H), 2.38 (ddd, J=3,11,21 Hz, 1H), 2.50 (ddd, J=5,6,21 Hz, 1H), 4.10 (br s, 1H),

7.25 (dd, J=3,6 Hz, 1H), 9.40 (s, 1H), 9.73 (s, 1H); IR (KBr) 3460, 3420, 1720, 1680, 1635; MS *m/e* (%) 250 (8, M^+), 232 (6), 222 (25), 221 (100), 217 (4), 204 (6), 203 (7), 189 (19), 124 (36), 109 (72), 105 (25), 69 (26); HRMS, calcd for $C_{15}H_{22}O_3$ (M^+) *m/e* 250.1569, found *m/e* 250.1578. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.15; H, 8.96.

8aß-Methyl-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-1α,2-dicarboxaldehyde (119) (13,14-dinorisotadeonal)

A solution of 250 mg (1 mmol) of acetal **116a** in acetone (5 mL) and water (1 mL) was treated with 25 mg of *p*-toluenesulfonic acid for 2 h. The reaction mixture was poured into water and worked up as usual. The residue was purified by flash chromatography on silica gel (eluent light petroleum-ether 7:3) to provide 192 mg (93%) of **119** as an oil.
^{1}H NMR 0.87 (s, 3H), 1.1-2.6 (11H), 3.33 (d, J=2 Hz, 1H), 7.00 (dd, J=2,4 Hz, 1H), 9.40 (s, 1H), 9.85 (d, J=2 Hz, 1H); IR (film) 1720, 1685, 1655; MS *m/e* (%) 206 (1, M^+), 191 (1), 188 (1), 179 (12), 178 (100), 173 (1), 163 (16), 149 (16), 147 (18), 121 (13), 109 (11), 105 (12), 95 (17), 91 (18), 81 (17), 79 (11), 67 (12); HRMS, calcd for $C_{13}H_{18}O_2$ (M^+) *m/e* 206.1307, found *m/e* 206.1310. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.40; H, 8.91.

5,5,8aß-Trimethyl-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-1α,2-dicarboxaldehyde (121) (Isotadeonal

Isotadeonal was prepared as described for the 13,14-dinor congener from **116b**. There was obtained 210 mg (90%) of white crystalline **121**, mp 66-67°C.
^{1}H NMR 0.91 (s, 3H), 0.93 (s, 3H), 0.96 (s, 3H), 1.05-1.7 (6H), 1.78 (dd, J=2, 11 Hz, 1H), 2.21 (ddt, J=2,11,21 Hz, 1H), 2.55 (dt, J=5,21 Hz, 1H), 3.25 (dd, J=1.7,2 Hz, 1H), 7.09 (ddd, J=2,5,5 Hz, 1H), 9.40 (s, 1H), 9.85 (d, J=2.5 Hz, 1H); IR (KBr) 1730, 1690, 1650; MS *m/e* (%) 234 (4, M^+), 219 (2), 216 (1), 207 (16), 206 (100), 201 (8), 191 (36), 137 (9), 135 (10), 123 (43), 110 (32), 109 (43), 105 (15), 91 (21), 69 (19), 55 (16); HRMS, calcd for $C_{15}H_{22}O_2$ (M^+) *m/e* 234.1620, found *m/e* 234.1622. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.49; H, 9.61.

8aß-Methyl-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-1ß,2-dicarboxaldehyde (120) (13,14-dinorpolygodial)

To a solution of 250 mg (1 mmol) of **117a** in acetone (10 mL) was added 10 mg (0.06 mmol) of *p*-toluenesulfonic acid at room temperature. The mixture was stirred for

10 min and then poured into saturated aqueous sodium bicarbonate solution (50 mL) and worked up as usual. The residue was purified by flash chromatography on silica gel (eluent light petroleum-ether 4:1) to afford 187 mg (91%) of **120** as a colourless oil.
^{1}H NMR 0.84 (s, 3H), 1.0-2.0 (9H), 2.23 (ddd, J=4,9,12 Hz, 2H), 2.87 (ddd, J=2,4.5,7 Hz, 1H), 7.09 (ddd, J=2,4.5,7 Hz, 1H), 9.47 (s, 1H), 9.55 (d, J=4.5 Hz, 1H); IR ($CHCl_3$) 1720, 1685, 1640; MS *m/e* (%) 206 (3, M^+), 191 (3), 179 (17), 178 (100), 173 (3), 163 (40), 110 (40), 109 (50), 97 (16), 93 (14), 81 (13), 69 (17); HRMS, calcd for $C_{13}H_{18}O_2$ (M^+) *m/e* 206.1307, found *m/e* 206.1309. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.51; H, 8.91.

5,5,8aß-Trimethyl-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-1ß,2-dicarboxaldehyde (3) (Polygodial)

Polygodial **3** was prepared as described for the dinor congener **120** from 278 mg (1 mmol) of **117b**. There was obtained 229 mg (98%) of crystalline polygodial **3**, mp 92-93°C.
^{1}H NMR 0.93 (s, 3H), 0.96 (s, 3H), 0.97 (s, 3H), 1.1-1.6 (6H), 1.85 (1H), 2.43 (2H), 2.83 (1H), 7.13 (ddd, J=2.5,3,6 Hz, 1H), 9.47 (s, 1H), 9.55 (d, J=5 Hz, 1H); IR (KBr) 2850, 2750, 1725, 1700, 1685, 1640; MS *m/e* (%) 234 (4, M^+), 219 (3), 207 (17), 206 (100), 201 (3), 191 (41), 121 (37), 110 (41), 109 (50), 97 (16), 81 (14), 69 (18); HRMS, calcd for $C_{15}H_{22}O_2$ (M^+) *m/e* 234.1620, found *m/e* 234.1618. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.93; H, 9.35.

2-(1,3-Dioxolan-2-yl)-8aß-methyl-N-trimethylsilyl-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-1α-aldimine (124)

A solution of 250 mg (1 mmol) of **116a** in dry THF (10 mL) was added dropwise to a solution of 1.0 M lithium bis(trimethylsilyl)amide (1.5 mL) at 0°C. The reaction mixture was stirred for 30 min and then cooled to -80°C, and 650 mg (1.5 mmol) of MoO_5.HMPA.pyr. complex was added. After 2 h the reaction mixture was quenched with saturated aqueous sodium sulfite solution (100 mL), and then worked up as usual. The residue was purified by column chromatography on silica gel (eluent light petroleum-ether 19:1) to afford 170 mg (53%) of **124** as an unstable oil.
^{1}H NMR 0.08 (s, 9H), 0.93 (s, 3H), 1.00-2.30 (11H), 2.96 (dd, J=1,5 Hz, 1H), 4.0 (4H), 5.15 (s, 1H), 6.03 (ddd, J=1,4,5 Hz, 1H), 8.06 (d, J=5 Hz, 1H); MS *m/e* (%) 321 (0.5, M^+), 306 (8), 248 (5), 221 (7), 91 (18), 81 (12), 73 (100).

2-(1,3-Dioxolan-2-yl)-5,5,8aß-trimethyl-3,4,4aα,5,6,7,8,8a-octahydronaphthalene-1-carbonitrile (125)

To a solution of 275 mg (1 mmol) of **115b** in *tert*-butyl alcohol (5 mL) was added 112 mg (1 mmol) of potassium *tert*-butoxide. The reaction mixture was stirred overnight at room temperature or refluxed for 30 min. After usual work-up the residue was crystallized from diisopropyl ether to afford 250 mg (91%) of **125**, mp 131-131.5°C.
^{1}H NMR 0.90 (s, 3H), 0.94 (s, 3H), 1.16 (s, 3H), 1.2-1.8 (8H), 1.95 (1H), 2.33 (dd, J=2,7 Hz, 2H), 4.00 (4H), 5.63 (s, 1H); IR (KBr) 2210, 1685, 1450, 1230, 1085; MS *m/e* (%) 275 (54, M^+), 260 (100), 232 (5), 138 (11), 137 (18), 99 (28), 173 (67); HRMS, calcd for $C_{17}H_{25}NO_2$ (M^+) *m/e* 275.1885, found 275.1883. Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15. Found: C, 73.92; H, 8.98.

2-(1,3-Dioxolan-2-yl)-5,5,8aß-trimethyl-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-1ß-carbonitrile (126)

A solution of 275 mg (1 mmol) of **115b** in *tert*-butyl alcohol (5 mL) was treated with 22 mg (0.2 mmol) of potassium *tert*-butoxide for 15 min. The reaction mixture was poured into water and worked up as usual to afford a mixture of nitriles. Purification by chromatography on silica gel (eluent light petroleum-ether 19:1) afforded first 100 mg (36%) of **126** as white crystals, mp 110-111°C.
^{1}H NMR 0.90 (s, 3H), 0.93 (s, 3H), 1.10 (s, 3H), 1.1-1.8 (6H), 2.00 (dd, J=3,6 Hz, 1H), 2.13 (2H), 3.13 (dt, J=3,5 Hz, 1H), 3.94 (2H), 4.10 (2H), 5.27 (s, 1H), 6.07 (ddd, J=3,4,5 Hz, 1H); IR (KBr) 2215, 1690, 1450, 1125, 1080; MS *m/e* (%) 275 (25, M^+), 274 (21), 260 (83), 248 (6), 235 (13), 138 (34), 125 (100), 124 (46), 109 (79), 86 (24), 73 (75); HRMS, calcd for $C_{17}H_{25}NO_2$ (M^+) *m/e* 275.1885, found *m/e* 275.1884. Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15. Found: C, 74.44; H, 8.99.

The nitrile **115b** was eluted next, 160 mg (58%).

2,5-Dimethylcyclohexanone (127)

To a solution of concentrated sulfuric acid (75 mL) in water (830 mL) was added 101.6 g (0.79 mol) of 2,5-dimethylcyclohexanol. The mixture was warmed to 45°C, and 162 g (0.55 mol) of potassium bichromate was added in 15 min. The reaction mixture was stirred for another 2 h and then cooled. The solution was diluted with water (500 mL) and extracted with ether. The combined ethereal extracts were washed with 4 N aqueous sodium hydroxide solution (150 mL) and with water and dried on calcium chloride. The solvent was evaporated and the residue was distilled at 10 torr to yield 92 g (92%) of **127**, bp 58-60°C, n_D^{20} 1.4460.

cis, trans-4a,7-Dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one (128)

A solution of 50.4 g (400 mmol) of **127** and 42 g (600 mmol) of methyl vinyl ketone in benzene (400 mL) was treated with concentrated sulfuric acid (1 mL) for 15 min at room temperature. The reaction mixture was refluxed for 16 h in a Dean-Stark apparatus. The solution was diluted with hexane (400 mL) and worked up as usual to afford crude **128**, which was purified by distillation at 10 torr. The yield was 47.3 g (66%), bp 126-132°C. According to GCMS and ^{1}H NMR enone **128** was a 2:1 mixture of two stereoisomers, **128** (trans isomer) [^{1}H NMR (major peaks) 0.91 (d, J=7 Hz, 3H), 1.26 (s, 3H), 5.70 (br s, 1H); MS *m/e* (%) 178 (80, M^+), 150 (60), 136 (100), 135 (45), 121 (69)] and **128** (cis isomer) [^{1}H NMR (major peaks) 1.00 (d, J=6 Hz, 3H), 1.23 (s, 3H), 5.72 (br s, 1H); MS *m/e* (%) 178 (92, M^+), 150 (55), 136 (100), 135 (47), 121 (69)], respectively.

cis, trans-2-Acetoxy-4aß,7-Dimethyl-3,4,4a,5,6,7-hexahydronaphthalene (129)

A solution of 35.6 g (200 mmol) of **128** in acetic anhydride (700 mL) was cooled to 0°C under nitrogen and 120 g (800 mmol) of powdered sodium iodide was added. To this mixture was added dropwise 87 g (800 mmol) of chlorotrimethylsilane and then stirred for 1 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in ether, washed with 2 M aqueous sodium thiosulfate solution, saturated aqueous sodium bicarbonate solution, brine and dried on magnesium sulfate. Filtration and evaporation under reduced pressure afforded the dienol acetate **129**, which was purified by distillation at 1 torr, bp 100-103°C. The yield was 40.5 g (92%) of colourless **129**, which, according to ^{1}H NMR and GLC, was also a 2:1 mixture of the *trans* isomer **129** [^{1}H NMR 0.95 (d, J=7 Hz, 3H), 1.03 (s, 3H), 2.13 (s, 3H), 5.33 (d, J=4 Hz, 1H), 5.73 (br s, 1H)] and the *cis* isomer **129** [^{1}H NMR 0.98 (d, J=6 Hz, 3H), 1.04 (s, 3H), 2.23 (s, 3H), 5.27 (br s, 1H), 5.70 (br s, 1H)].

4aß,7-Dimethyl-8-hydroxy-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one (130)

A solution of 17.6 g (80 mmol) of dienol acetate **129** in methanol (300 mL) was cooled to 0°C and 20.2 g (84 mmol) of solid sodium bicarbonate was added. A solution of 78.6 g (160 mmol) of oxone ^{R} in water (300 mL) was added dropwise and the reaction mixture was stirred for 4 h at room temperature. The precipitate was filtered and the filtrate was worked up as usual after addition of water. The residue, 11.95 g (66%), was used without further purification in the next step.
A sample was purified by flash chromatography on silica gel (eluent light petroleum-ether 4:1) to give the isomers **130**.

4aß,7α-Dimethyl-8ß-hydroxy-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one, 44%.
^{1}H NMR 0.89 (d, J=7 Hz, 3H), 1.1-2.8 (10H), 1.46 (s, 3H), 3.97 (t, J=1.5 Hz, 1H), 5.79 (s, 1H); MS *m/e* (%) 194 (100, M^+), 179 (80), 137 (40), 124 (62), 123 (72), 110 (29), 109 (52).
4aß,7ß-Dimethyl-8ß-hydroxy-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one, 21%.
^{1}H NMR 1.04 (d, J=6 Hz, 3H), 1.2-2.8 (10H), 1.40 (s, 3H), 4.04 (t, J=1.5 Hz, 1H), 5.74 (s, 1H); MS *m/e* (%) 194 (100, M^+), 179 (82), 137 (40), 124 (58), 123 (53), 110 (29), 109 (61).
4aß,7α-Dimethyl-8α-hydroxy-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one, 8%.
^{1}H NMR 0.83 (d, J=7 Hz, 3H), 1.2-2.8 (10H), 1.25 (s, 3H), 4.47 (dd, J=1.5,5 Hz, 1H), 6.13 (d, J=1.5 Hz, 1H); MS *m/e* (%) 194 (65, M^+), 179 (29), 138 (45), 124 (32), 123 (68), 110 (100), 109 (92).
4aß,7ß-Dimethyl-8α-hydroxy-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one, 4%.
^{1}H NMR 0.84 (d, J=6 Hz, 3H), 1.22 (s, 3H), 1.2-2.8 (10H), 3.86 (dd, J=1,8 Hz, 1H), 6.16 (d, J=1.5 Hz, 1H); MS *m/e* (%) 194 (100, M^+), 179 (33), 138 (49), 137 (30), 124 (15), 110 (80), 109 (90).

2,4aß-Dimethyl-naphthalene-1,7-dione (131)

An ethereal solution of crude **130** (10.0 g) was treated with concentrated hydrogen bromide (1.5 mL) for 1 h at room temperature. The reaction mixture was poured into saturated aqueous sodium bicarbonate solution and worked up as usual. The residue (10.0 g) was used in the next step. A sample was purified by flash chromatography on silica gel (eluent light petroleum-ether 7:3) to afford the isomers **131**.
2α,4aß-Dimethyl-7-oxo-3,4,4a,5,6,7,8,8aß-octahydronaphthalen-1(2H)-one, 28%.
^{1}H NMR 1.00 (d, J=6 Hz, 3H), 1.35 (s, 3H), 1.3-1.8 (4H), 1.9-2.4 (5H), 2.44 (m, J=6,7,12 Hz, 1H), 2.6-2.8 (2H); MS *m/e* (%) 194 (70, M^+), 179 (13), 137 (12), 124 (26), 111 (100).
2ß,4aß-Dimethyl-7-oxo-3,4,4a,5,6,7,8,8aα-octahydronaphthalen-1(2H)-one, 60%.
^{1}H NMR 1.00 (s, 3H), 1.06 (d, J=6 Hz, 3H), 1.6-2.0 (6H), 2.0-2.3 (1H), 2.3-2.7 (5H).
^{1}H NMR (C_6D_6) 0.57 (s, 3H), 1.09 (d, J=6 Hz, 3H), 1.1-1.4 (5H), 1.60 (1H), 1.85 (m, J=6,7,12 Hz, 1H), 1.9-2.2 (3H), 2.50 (2H); MS *m/e* (%) 194 (57, M^+), 179 (8), 165 (100), 137 (53).

4'a,7'-Dimethylspiro[1,3-dioxolane-2,2'(8'H)-octahydronaphthalen]-8'-one (132)

To a solution of 9.0 g (46.5 mmol) of a stereoisomeric mixture of **131** in 2-methyl-2-ethyl-1,3-dioxolane (MED) (150 mL) was added one drop of ethylene glycol and 30 mg

of *p*-toluenesulfonic acid monohydrate. The reaction mixture was stirred at room temperature overnight and then triethylamine (1 mL) was added. The reaction mixture was diluted with ether (500 mL), washed with brine, and dried. Evaporation of the solvents afforded an oil, which was purified by flash chromatography on silica gel (eluent light petroleum-ether 4:1). According to GCMS and ^{1}H NMR the resulting colourless oil (10.5 g, 95%) was a mixture of two stereoisomers, which was used without further purification in the next step. A sample was purified again and gave the isomers **132**.

1',3',4',4'a,5',6',7',8'aα-Octahydro-4'aß,7'ß-dimethylspiro[1,3-dioxolane-2,2'(8'H)-naphthalen]-8'-one, yield 73%.

^{1}H NMR 0.77 (s, 3H), 0.99 (d, *J*=6 Hz, 3H), 1.3-1.9 (9H), 2.0 (1H), 2.3 (1H), 2.5 (dd, *J*=6,12 Hz, 1H), 3.92 (br s, 4H); MS *m/e* (%) 238 (12, M^+), 99 (100); HRMS, calcd for $C_{14}C_{22}O_3$ (M^+) *m/e* 238.1569, found *m/e* 238.1570.

1',3',4',4'a,5',6',7',8'aß-Octahydro-4'aß,7'ß-dimethylspiro[1,3-dioxolane-2,2'(8'H)-naphthalen]-8'-one, yield 20%.

^{1}H NMR 0.89 (s, 3H), 0.99 (d, *J*=6 Hz, 3H), 1.3-2.2 (10H), 1.33 (dd, *J*=5,7 Hz, 1H), 2.50 (dd, *J*=6,13 Hz, 1H), 3.92 (br s, 4H); MS *m/e* (%) 238 (12, M^+), 99 (100); HRMS, calcd for $C_{14}H_{22}O_3$ (M^+) *m/e* 238.1569, found 238.1569.

3',4',4'a,5',6',7',8',8'aα-Octahydro-4'aß,7'ß-dimethyl-8'-methylenespiro[1,3-dioxolane-2,2'(1'H)-naphthalene] (133)

To a solution of 2.70 g of a 80% dispersion in oil of sodium hydride (90 mmol) in DMSO (150 mL) was added 36.4 g (90 mmol) of triphenylphosphonium iodide at room temperature and stirred for 30 min. To the red solution was added a solution of 10.3 g (43.3 mmol) of the 4:1 mixture of ketone **132** in DMSO (50 mL) and the reaction mixture was stirred overnight at room temperature. The reaction mixture was poured into water (500 mL) and extracted five times with pentane (100 mL). The combined extracts were washed with water and brine and dried on magnesium sulfate. The residue was used without purification in the next step. A sample was purified by flash chromatography on silica gel (eluent light petroleum-ether 19:1) to give one, single product **133**, yield 75%.

^{1}H NMR: 0.92 (s, 3H), 1.05 (d, *J*=6 Hz, 3H), 1.2-1.8 (10H), 2.1-2.2 (1H), 2.33 (dd, *J*=7,12 Hz, 1H), 3.98 (br s, 4H), 4.52 (s, 1H), 4.78 (s, 1H); MS *m/e* (%) 236 (23, M^+), 99 (100); HRMS, calcd for $C_{15}H_{24}O_2$ (M^+) *m/e* 236.1776, found *m/e* 236.1778.

4aß,7ß-Dimethyl-8-methylene-3,4,4a,5,6,7,8,8aα-octahydronaphthalen-2(1H)-one (19)

The acetal **133** was dissolved in a mixture of acetone (100 mL) and 4 N aqueous hydrochloric acid (15 mL) and stirred at room temperature overnight. The mixture was concentrated at room temperature under reduced pressure and the residue was diluted with ether and worked up as usual. The residue was purified by flash chromatography on silica gel (eluent light petroleum-ether 19:1) to afford 6.65 g (80%) of methylene ketone **19** as a white solid, mp 66-66.5°C.
^{1}H NMR: 0.90 (s, 3H), 1.07 (d, J=6 Hz, 3H), 1.1-1.9 (6H), 1.9-2.5 (6H), 4.50 (br s, 1H), 4.80 (br s, 1H); IR (KBr) 1705, 1640; MS *m/e* (%) 192 (84, M^+), 177 (42), 135 (100), 68 (68); HRMS, calcd for $C_{13}H_{20}O$ (M^+) *m/e* 192.1514, found *m/e* 192.1515. Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.16; H, 10.52.

6ß,8aß-Dimethyl-5-methylene-3,4,4aα,5,6,7,8,8a-octahydro-3-oxonaphthalene-2-carboxaldehyde (134)

A suspension of 1.8 g (60 mmol) of a 80% dispersion in mineral oil of sodium hydride in dry ether (150 mL) was cooled to 0°C. A mixture of 9.95 g (51.8 mmol) of ketone **19** and 8.9 g (120 mmol) of ethyl formate in dry ether (150 mL) was added dropwise over 30 min. The reaction mixture was stirred overnight at ambient temperature and then poured into water (250 mL). The aqueous layer was separated, and the ethereal solution was extracted twice with 4 N aqueous potassium hydroxide (50 mL). The combined alkaline solutions were acidified with concentrated hydrochloric acid and then extracted with ether. The ethereal solution was washed with brine and dried, and the ether was evaporated. The residue was crystallized from methanol to give 10.49 g (92%) of **4aß,7ß-dimethyl-3-(hydroxymethylene)-8-methylene-3,4,4a,5,6,7,8,8aα-octahydronaphthalen-2(1H)-one** as a light yellow crystalline compound, mp 92-93°C.
^{1}H NMR 0.67 (s, 3H), 1.06 (d, J=6 Hz, 3H), 1.2-1.9 (4H), 2.20 (s, 2H), 2.36 (s, 1H), 2.46 (d, J=9 Hz, 1H), 1.8-2.5 (2H), 4.63 (s, 1H), 4.83 (t, J=1.5 Hz, 1H), 8.60 (s, 1H), 14.35 (br s, 1H); IR (KBr) 1650, 1600, 1450; MS *m/e* (%) 220 (100, M^+), 205 (29), 202 (5), 192 (8), 191 (9), 163 (21), 135 (22), 122 (36), 121 (19), 107 (33); HRMS, calcd for $C_{14}H_{20}O_2$ (M^+) *m/e* 220.1463, found *m/e* 220.1469. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 75.91; H, 9.12.

The dehydrogenation of the above-mentioned compound was performed as described for **16**. Compound **134** was obtained as a yellow oil in 93% yield.
^{1}H NMR 1.00 (s, 3H), 1.12 (d, J=6 Hz, 3H), 1.2-2.1 (5H), 2.57 (s, 2H), 2.58 (d, J=12 Hz, 1H), 4.66 (br s, 1H), 4.97 (br s, 1H), 7.60 (s, 1H), 10.13 (s, 1H); IR (film)

1705, 1690, 1610, 1450; MS *m/e* (%) 218 (68, M^+), 203 (11), 190 (100), 175 (45), 121 (95); HRMS, calcd for $C_{14}H_{18}O_2$ (M^+) *m/e* 218.1307, found *m/e* 218.1310.

2-(Hydroxymethylene)-6ß,8aß-dimethyl-5-methylene-*trans*-perhydro-3-oxonaphthalene-1α-carbonitrile (18)

Compound **18** was prepared from **134** as described for **15**. Evaporation of the ethereal solution gave an oily residue, which was purified by column chromatography on silica gel (eluent light petroleum-ether 3:2) to afford 6.52 g (76%) of a colourless oil.
^{1}H NMR 0.80 (s, 3H), 1.13 (d, *J*=6 Hz, 3H), 1.3-2.0 (4H), 2.15 (dd, *J*=3,12 Hz, 2H), 2.50 (s, 1H), 2.58 (1H), 3.28 (s, 1H), 4.72 (br s, 1H), 4.94 (br s, 1H), 8.87 (s, 1H), 14.50 (br s, 1H); IR (film) 2225, 1640, 1590; MS *m/e* (%) 245 (77, M^+), 230 (16), 217 (13), 216 (15), 202 (23), 175 (19), 135 (22), 122 (100), 121 (55), 107 (54); HRMS, calcd for $C_{15}H_{19}NO_2$ (M^+) *m/e* 245.1416, found 245.1419. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7,81; N, 5.71. Found: C, 73.14; H, 7.99; N, 5.80.

2-(*E*)-[(Buthylthio)methylene]-6ß,8aß-dimethyl-5-methylene-*trans*-perhydro-3-oxonaphthalene-1α-carbonitrile (135)

Compound **135** was prepared from **18** as described for **113**. Crystallization of the residue from methanol gave 7.51 g (79%) of **135**, mp 102-103°C.
^{1}H NMR 0.83 (s, 3H), 0.95 (t, *J*=5 Hz, 3H), 1.10 (d, *J*=6 Hz, 3H), 1.3-2.0 (8H), 2.17 (dd, *J*=3,12 Hz, 2H), 2.41 (d, *J*=12 Hz, 1H), 2.50 (s, 1H), 2.97 (t, *J*=6 Hz, 2H), 3.47 (s, 1H), 4.66 (br s, 1H), 4.92 (br s, 1H), 8.00 (s, 1H); IR (KBr) 2225, 1660, 1535; MS *m/e* (%) 317 (38, M^+), 302 (4), 284 (9), 260 (100), 163 (10), 135 (10), 121 (21); HRMS, calcd for $C_{19}H_{27}NOS$ (M^+) *m/e* 317.1813, found 317.1809. Anal. Calcd for $C_{19}H_{27}NOS$: C, 71.88; H, 8.57; N, 4.41. Found: C, 71.74; H, 8.67; N, 4.32.

6ß,8aß-Dimethyl-2-formyl-5-methylene-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-1α-carbonitrile (136)

The reduction of **135** was performed as described for **113**. The intermediate alcohol was not purified, only a small sample was chromatographed on silica gel (eluent light petroleum-ether 4:1).
^{1}H NMR 0.70 (s, 3H), 0.94 (t, *J*=5 Hz, 3H), 1.05 (d, *J*=6 Hz, 3H), 1.1-2.1 (11H), 2.33 (br s, 1H), 2.50 (dd, *J*=2,4 Hz, 1H), 2.70 (t, *J*=6 Hz, 2H), 3.73 (s, 1H), 4.47 (dd, *J*=2,5 Hz, 1H), 4.57 (br s, 1H), 4.80 (br s, 1H), 6.57 (d, *J*=2 Hz, 1H); MS *m/e* (%) 319 (100, M^+), 304 (3), 301 (11), 286 (3), 262 (24), 244 (24), 229 (46), 211 (39),

196 (15), 183 (27), 137 (37), 121 (31); HRMS, calcd for $C_{19}H_{29}NOS$ (M^+) *m/e* 319.1963, found *m/e* 319.1967.
Hydrolysis of the above-mentioned alcohol afforded the aldehyde nitrile **136** as described for **114**. Crystallization of the residue from methanol gave 5.38 g (94%) of **136**, mp 120-121°C.
^{1}H NMR 0.68 (s, 3H), 1.11 (d, J=6 Hz, 3H), 1.1-2.0 (4H), 2.16 (dd, J=4,12 Hz, 2H), 2.50 (2H), 3.42 (s, 1H), 4.77 (br s, 1H), 4.93 (br s, 1H), 7.10 (dd, J=2,4 Hz, 1H), 9.53 (s, 1H); IR (KBr) 2210, 1675, 1650, 1610; MS *m/e* (%) 229 (100, M^+), 214 (38), 200 (23), 186 (20), 122 (45), 107 (36), 93 (21), 91 (20); HRMS, calcd for $C_{15}H_{19}NO$ (M^+) *m/e* 229.1466, found *m/e* 229.1465. Anal. Calcd for $C_{15}H_{19}NO$: C, 78,56; H, 8.35; N, 6.11. Found: C, 78.79; H, 8.51; N, 6.04.

6ß,8aß-Dimethyl-2-(1,3-dioxolan-2-yl)-5-methylene-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-1α-carboxaldehyde (137)

Compound **137** was prepared by acetalization of aldehyde **136** followed by reduction of the 1α-nitrile functionality. The protection of the aldehyde function in **136** was performed as described for **115**. Recrystallization of the residue from methanol afforded 4.97 g (91%) of **6ß,8aß-dimethyl-2-(1,3-dioxolan-2-yl)-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-1α-carbonitrile**, mp 108-110°C.
^{1}H NMR 0.73 (s, 3H), 1.08 (d, J=6 Hz, 3H), 1.3-2.0 (4H), 2.0-2.5 (4H), 3.00 (s, 1H), 4.00 (4H), 4.70 (br s, 1H), 4.87 (br s, 1H), 5.28 (s, 1H), 6.17 (dd, J=3,4 Hz, 1H); IR (KBr) 2225, 1650, 1610, 1455; MS *m/e* (%) 273 (77, M^+), 258 (19), 193 (15), 180 (13), 179 (15), 151 (34), 138 (16), 122 (23), 73 (100); HRMS, calcd for $C_{17}H_{23}NO_2$ (M^+) *m/e* 273.1729, found *m/e* 273.1726. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.46; H, 8.56; N, 4.94.
The reduction of the nitrile functionality was performed with diisobutylaluminum hydride as described for **116**. The residue was purified by crystallization from methanol to give 2.57 g (93%) of **137**, mp 80-81°C.
^{1}H NMR 0.73 (s, 3H), 1.07 (d, J=6 Hz, 3H), 1.5-1.9 (4H), 2.2-2.5 (4H), 2.80 (d, J=5 Hz, 1H), 3.85 (4H), 4.72 (br s, 1H), 4.85 (br s, 1H), 5.17 (s, 1H), 6.27 (dd, J=3,4 Hz, 1H), 9.62 (d, J=5 Hz, 1H); IR (KBr) 1705, 1650, 1610, 1455; MS *m/e* (%) 276 (44, M^+), 248 (38), 247 (100), 213 (69), 188 (38), 185 (37), 73 (66); HRMS, calcd for $C_{17}H_{24}O_3$ (M^+) *m/e* 276.1725, found *m/e* 276.1739. Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.92; H, 8.91.

6ß,8aß-Dimethyl-2-(1,3-dioxolan-2-yl)-5-methylene-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-1ß-carboxaldehyde (138)

Compound **138** was prepared from **137** as described for **117**. The residue was chromatographed on silica gel (eluent light petroleum-ether 3:1) and subsequently recrystallized from methanol to give 994 mg (90%) of white crystalline **138**, mp 59-60°C.
^{1}H NMR 0.90 (s, 3H), 1.07 (d, J=6 Hz, 3H), 1.2-2.2 (8H), 2.88 (ddd, J=3,6,8 Hz, 1H), 3.80 (4H), 4.70 (br s, 1H), 4.88 (br s, 1H), 5.22 (s, 1H), 6.23 (ddd, J=2.5,6,8 Hz, 1H), 9.53 (d, J=6 Hz, 1H); IR (KBr) 1720, 1680, 1645, 1450; MS *m/e* (%) 276 (10, M^+), 248 (100), 247 (76), 232 (10), 213 (10), 173 (15), 171 (21), 105 (14); HRMS, calcd for $C_{17}H_{24}O_3$ (M^+) *m/e* 276.1725, found *m/e* 276.1728. Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.51; H, 8.68.

6ß,8aß-Dimethyl-1α-hydroxy-5-methylene-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-1ß,2-dicarboxaldehyde (2) (Muzigadial)

Muzigadial **2** was prepared from **138** as described for **1**. Oxidation of the enolate of aldehyde **138** with oxodiperoxymolybdenum(pyridine)hexamethylphosphoramide afforded 225 mg (77%) of **6ß,8aß-dimethyl-2-(1,3-dioxolan-2-yl)-1α-hydroxy-5-methylene-1,4,4aα,5,6,7,8,8a-octahydronaphthalene-1ß-carboxaldehyde** as a white solid, mp 106-107°C.
^{1}H NMR 0.97 (s, 3H), 1.04 (d, J=6 Hz, 3H), 1.30-2.30 (7H), 2.57 (1H), 3.85 (4H), 4.70 (br s, 1H), 4.87 (br s, 1H), 5.20 (s, 1H), 6.35 (t, J=4 Hz, 1H), 9.73 (s, 1H); IR (KBr) 3410, 1720, 1680, 1645, 1450, 1260, 1080; MS *m/e* (%) 292 (4, M^+), 277 (1), 274 (3), 264 (19), 263 (100), 221 (10), 219 (25), 135 (10), 73 (10); HRMS, calcd for $C_{17}H_{24}O_4$ (M^+) *m/e* 292.1674, found *m/e* 292.1682. Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 70.05; H, 8.50.
Hydrolysis of the acetal functionality was performed as described to afford 130 mg (87%) of muzigadial **2**, mp 105-106°C.
^{1}H NMR 0.87 (s, 3H), 1.07 (d, J=6 Hz, 3H), 1.3-2.3 (6H), 2.53 (2H), 4.05 (s, 1H), 4.75 (br s, 1H), 4.93 (br s, 1H), 7.23 (dd, J=2,3 Hz, 1H), 9.43 (s, 1H), 9.65 (s, 1H); IR (KBr) 3480, 1725, 1690, 1640, 1260; MS *m/e* (%) 248 (1, M^+), 230 (2), 219 (100), 177 (8), 159 (7), 145 (5), 135 (16), 131 (6), 107 (12); HRMS, calcd for $C_{15}H_{20}O_3$ (M^+) *m/e* 248.1412, found 248.1423; calcd for $C_{15}H_{18}O_2$ (M^+ -18) *m/e* 230.1307, found 230.1305; calcd for $C_{14}H_{19}O_2$ (M^+ -29) *m/e* 219.1385, found 219.1388. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12.Found: C, 72.61; H, 8.15.

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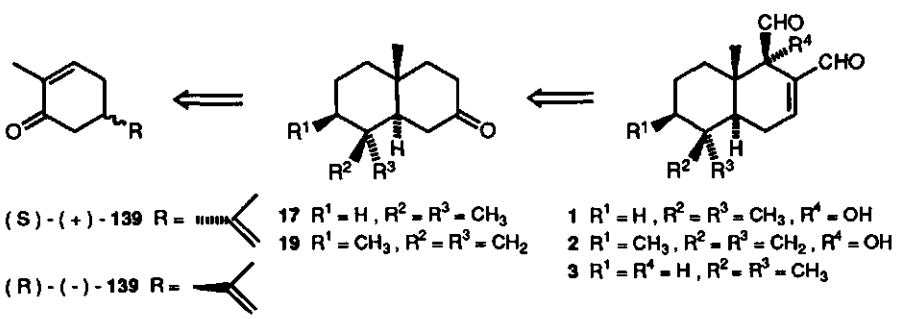
7 CHIRAL INTERMEDIATES FOR THE SYNTHESIS OF (-)-WARBURGANAL, (-)-POLYGODIAL, AND (-)-MUZIGADIAL FROM (+)- AND (-)-CARVONE

7.1 Introduction

Several naturally occurring drimane sesquiterpenes show interesting biological activities as is described in chapter 1 and a large number of syntheses of this important class of natural products have been published recently as is outlined in chapter 2. In most of these syntheses achiral starting compounds were used and racemates were obtained. In a few cases an *enantioselective* reaction was incorporated in the synthetic sequence which led to optically active compounds.[1] In all the other cases the starting material for the optically active drimanes has been a natural product with the correct absolute configuration.[2] With regard to the drimane insect antifeedants, *e.g.*, (-)-polygodial **3**, (-)-warburganal **1**, and (-)-muzigadial **2**, there was a strong necessity for the production of *non*-racemic compounds because of the supposed difference in the physiological effects of the unnatural enantiomer.[3]
In chapter 6 the conversion of the racemic *trans*-decalones **17** and **19** into the racemic antifeedants (±)-polygodial **3**, (±)-warburganal **1**, and (±)-muzigadial **2** was described (see figure 7.1).[4]

Figure 7.1



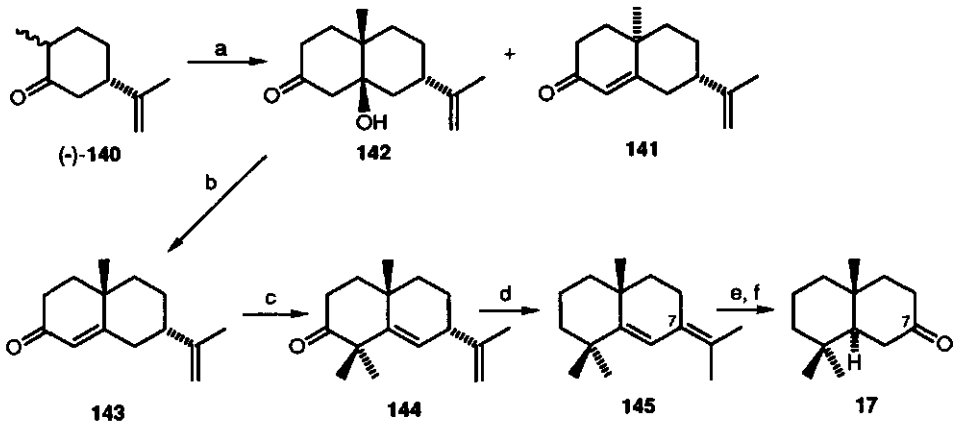
A retrosynthetic analysis of the *trans*-decalones **17** and **19** revealed the possibility to use (S)- and (R)-carvone **139**, respectively, as starting material for these decalones.
Both enantiomers of carvone **139** and dihydrocarvone **140** have been widely used in the enantiospecific synthesis of many sesquiterpenes.[5] In some cases the isopropenyl group in (S)- or (R)-carvone just served as a chiral handle which was removed at a suitable stage in the total synthesis. In other situations the isopropenyl group was converted into

an useful functional group which could be used for further transformations.[6] Both options are incorporated in the conversion of (S)- and (R)-carvone into the chiral *trans*-decalones **17** and **19**, respectively.

7.2 Synthesis of (-)-(4aR,8aS)-3,4,4a,5,6,7,8,8a-Octahydro-4a,8,8-trimethylnaphthalen-2(1H)-one

(S)-(+)-Carvone was first converted into (-)-dihydrocarvone *via* reduction with lithium bronze.[7] The (-)-dihydrocarvone was obtained as a mixture of stereoisomers and this mixture was converted into (-)-*trans*-decalone **17** as depicted in scheme 7.1.

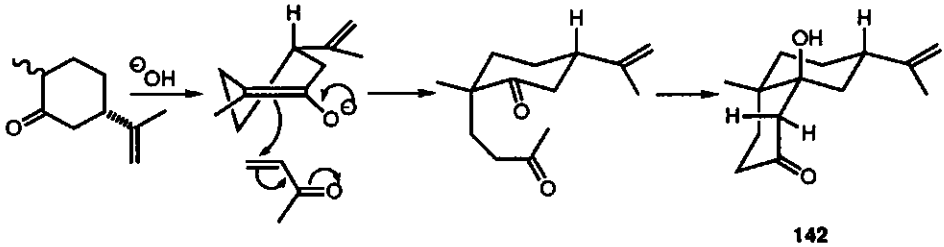
Scheme 7.1



Reagents: *a*, MVK, KOH; *b*, KOH, MeOH; *c*, KO-*t*-Bu, HO-*t*-Bu, CH_3I; *d*, hydrazine monohydrate, KOH, 200°C; *e*, O_3, thiourea; *f*, Li, NH_3, NH_4Cl.

From the literature it was known that both enones **141** and **143** were formed in the base catalyzed Robinson annulation of (-)-dihydrocarvone in protic medium.[8] The separation of these products proved to be rather troublesome and required extensive chromatografic purification.[8,9] It turned out, however, that the dehydration of ketol **142** could be prevented by performing the annulation with potassium hydroxide as base at 0°C in ether as solvent, using a relative short reaction time of one to two hours. This ketol **142** could be separated easily by crystallization from the enone **141**, which was also obtained in the annulation reaction. The production of the ketol **142** as the major product apparently is the result of an axial alkylation of the more stable conformer of the enolate of (-)-dihydrocarvone with the isopropenyl group equatorial. This result is invariably obtained in Michael reactions of such dialkylated cyclohexanones (see figure 7.2).[10]

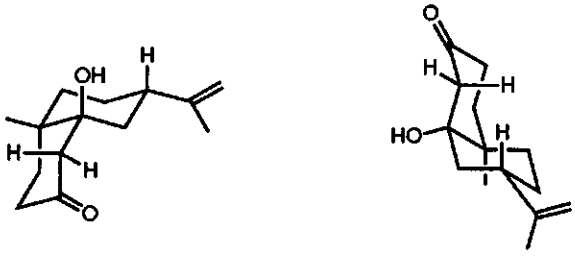
Figure 7.2



142

It was impossible to tune the reaction conditions in such a way that the formation of enone **141** could be prevented. Obviously two isomeric *cis-fused* ketols are formed initially, the *non-steroid* ketol **142** and the *steroid* ketol **142a** (see figure 7.3).

Figure 7.3



142
cis decaline
non steroid

142 a
cis decaline
steroid

It is easily understood that the spatial *trans-diaxial* arrangement of the hydroxyl group and one of the hydrogen atoms in the ketol **142a** facilitates a rapid dehydration to afford the enone **141**. Such a favourable orientation is not present in the most stable conformation of compound **142** and at lower temperatures no dehydration takes place. The isolation of ketol **142** could be accomplished by Kugelrohr distillation of the residue, followed by crystallization. The distillation gave a 25% recovery of (-)-dihydrocarvone and a 72% yield of a mixture of ketol **142** and enone **141**. The ketol could be isolated from this mixture in a total yield of 55% *via* crystallization from hexane followed by column chromatography of the mother liquor. The ketol **142** could be separated easily from the enone **141** which was eluted first in 17% yield.
After the separation ketol **142** was dehydrated [8] and dimethylated [11] to give **144** in 80% yield. When this ketone **144** was submitted to a Wolff-Kishner reduction, a complete isomerization of the olefinic bond from the isopropenyl sidechain to the conjugated

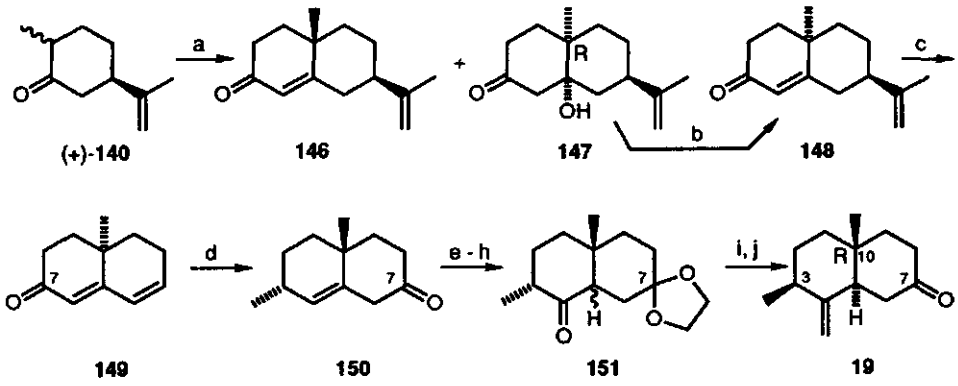
*exo*cyclic position was observed as an accompanying reaction to afford **145**. Selective ozonolysis of the *exo*cyclic double bond in **145** proved possible in good yield. In this way this sequence provided a short route for the conversion of the former chiral handle into the desired carbonyl group at C-7. The α,ß-unsaturated ketone **108** was reduced, using lithium in liquid ammonia and (-)-*trans*-decalone **17** was obtained in an overall yield of 40% based on ketol **142**. Since the racemic **17** has already been converted into (±)-warburganal **1** and (±)-polygodial **3**,[4] this approach constitutes a formal route to (-)-warburganal **1** and (-)-polygodial **3** from (S)-(+)-carvone.

7.3 Synthesis of (+)-(4aR,7S,8aR)-4a,7-Dimethyl-8-methylene-3,4,4a,5,6,7,8,8a--octahydronaphthalen-2(1H)-one

(+)-*trans*-Decalone **19**, the starting material for the synthesis of (-)-muzigadial **2**,[4] was obtained as depicted in scheme 7.2. In order to obtain the desired R configuration at C-10 in *trans*-decalone **19**, the ketol **147** [12] had to have the R configuration at C-10 also, which required the use of (+)-dihydrocarvone as starting material for the Robinson annulation.

Enone **148** was synthesized from (+)-dihydrocarvone as described for its enantiomer **143** (see scheme 7.1). The isopropenyl group in **148** was removed by ozonolysis in methanol at -78°C followed by decomposition of the intermediate methoxy hydroperoxide with cupric acetate and ferrous sulfate [13] to afford the dienone **149**.

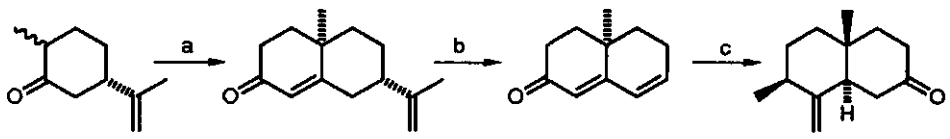
Scheme 7.2



Reagents: *a*, MVK, KOH; *b*, KOH, MeOH; *c*, O_3, $Cu(OAc)_2$, $FeSO_4$; *d*, Me_2CuLi; *e*, Ac_2O, *p*-TsOH; *f*, $KHSO_5$; *g*, HBr, Et_2O; *h*, ethylene glycol, *p*-TsOH, benzene; *i*, Ph_3PCH_3Br, NaH, DMSO; *j*, HCl, H_2O.

Conjugate addition of lithium dimethylcopper gave the deconjugated enone **150** with the two methyl groups in a trans position, the C-3 epimer was formed in trace amounts.
Enol acetylation of enone **150** gave the corresponding dienol acetate which was transformed into keto acetal **151** as previously described (see scheme 6.9).[14] Upon treatment of **151** with methylenetriphenylphosphorane in dimethyl sulfoxide and subsequent hydrolysis of the acetal function the (+)-methylene ketone **19** was obtained in 25% overall yield based on the ketol **147**, thus providing the chiral starting material for the synthesis of (-)-muzigadial **2**.[4]
It should be mentioned that the enone **141**, obtained in a yield of 17% as a byproduct in the Robinson annulation of (-)-dihydrocarvone (see scheme 7.1), can be used for conversion into the dienone **149**. In this way the (+)-decalone **19** can be prepared also from this byproduct (see scheme 7.3).

Scheme 7.3

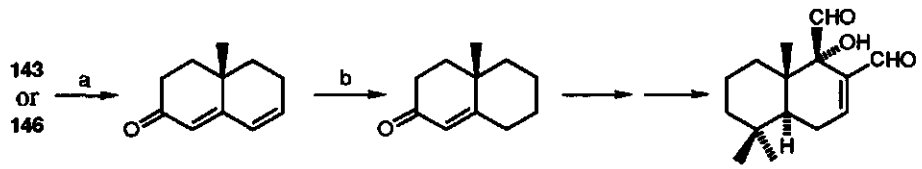


Reagents: *a*, MVK, KOH; *b*, O_3, $Cu(OAc)_2$, $FeSO_4$; *c*, see scheme 7.2.

7.4 Chiral intermediates from (+)- or (-)-dihydrocarvone suited for drimane sesquiterpenes total synthesis

The Robinson annulation product **105**, obtained from 2-methylcyclohexanone and methyl vinyl ketone, was used as starting material in the total synthesis of racemic warburganal **1**.[4] This enone is also easily available from (+)- or (-)-dihydrocarvone as depicted in scheme 7.3 and 7.4.
The enone **146**, obtained as a byproduct in the Robinson annulation of (+)-dihydrocarvone with methyl vinyl ketone and the enone **143**, the major product in the annulation of (-)-dihydrocarvone with methyl vinyl ketone can be converted into the dienone **152** by ozonolyses and subsequent fragmentation of the intermediate methoxy hydroperoxide with cupric acetate and ferrous sulfate (see scheme 7.4).

Scheme 7.4



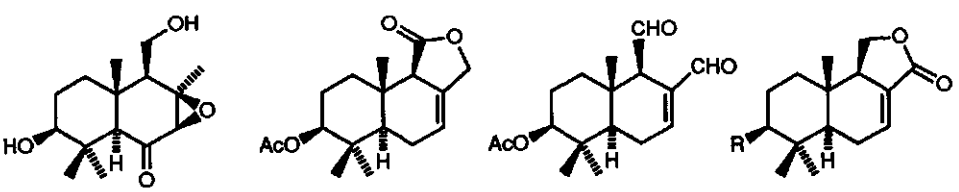
152 105 1

Reagents: *a*, O_3, $Cu(OAc)_2$, $FeSO_4$; *b*, Li-selectride

Selective 1,6 reduction with lithium-selectride in the presence of HMPA gave the (+)-enone **105** in 80% yield. The conversion of **105** into (-)-*trans*-decalone **17** is standard chemistry (see 6.2).

As mentioned before the ketone **144** was smoothly reduced *via* the Wolff-Kishner method with concomitant isomerization of the isopropenyl group into an isopropylidene function. Isomerization of the isopropenyl group of **144** was also observed under the conditions of the Wolff-Kishner reaction in the absence of hydrazine monohydrate, thus with potassium hydroxide in diethylene glycol at 200°C. This isomerization proceeded also in good to moderate yield for derivatives of **144** (see scheme 7.5).[15] This isomerization is of relevance for the synthesis of various 3-oxygenated drimanes like uvidin B **156**,[16] 3ß-acetoxy drimenin **157**,[17] 3ß-acetoxy polygodial **158**,[18] 3ß-hydroxy cinnamolide **159**, [19] and 3ß-acetoxy cinnamolide **160** (see figure 7.4).[19]

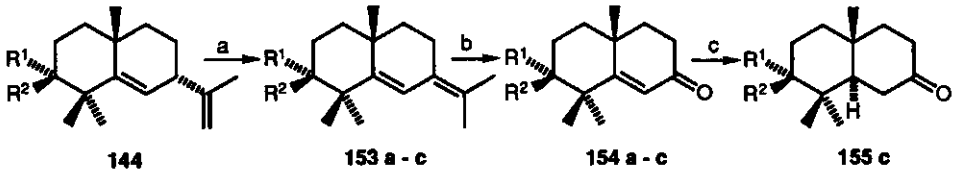
Figure 7.4



156 **157** **158** **159** R = OH
160 R = OAc

When the compounds **144a,b,c** were treated with 3 equivalents of potassium hydroxide in diethylene glycol at 200°C a rapid isomerization was observed and the isomers **153a,b,c** were isolated from the reaction mixture in 54%, 90%, and 91% yield, respectively. Compound **153a** was rather unstable under the strongly basic reaction conditions and therefore it was impossible to continue the isomerization till completeness.

Scheme 7.5



a $R^1 = R^2 = O$

b $R^1 = R^2 =$ 

c $R^1 = H$, $R^2 = OH$

Reagents: *a*, KOH, diethylene glycol, 200°C; *b*, O_3, MeOH, thiourea; *c*, Li, NH_3.

The ozonolysis of **153a,b,c** should be performed immediately after their isolation because of the instability of these dienes. After a few weeks at room temperature the dienes **153a,b** were decomposed to a substantial degree, the hydroxy diene **153c** proved to be a moderately stable compound. After treatment with ozone the intermediate methoxy hydroperoxides were reduced with thiourea to afford the conjugated enones **154a,b,c**. Enone **154c**, upon reduction with lithium in liquid ammonia, gave the (-)-*trans*-decalone **155c**. This ketone is in principle a suitable starting material for the total synthesis of (-)-3ß-acetoxy polygodial **158** along the lines established in this thesis.

7.5 Experimental section

General experimental conditions were as described in chapter 4.

(-)-(4aS,7S,8aS)-8a-Hydroxy-7-isopropenyl-4a-methyl-3,4,4a,5,6,7,8,8a-octahydro-naphthalen-2(1H)-one (142)

A solution of 8.12 g (116 mmol) of methyl vinyl ketone in ether (100 mL) was added over a period of 60 min to a mixture of 15.2 g (100 mmol) of (-)-dihydrocarvone **140** [7] in ether (150 mL) and 2.24 g (40 mmol) of potassium hydroxide in ethanol (10 mL) at 0°C. After the addition was complete, stirring was continued for 60 min. The reaction mixture was washed with water (100 mL) and brine (100 mL) and the ethereal solution was dried. The ether was evaporated and the residue was submitted to Kugelrohr distillation which gave 3.8 g (25%) of recovered (-)-dihydrocarvone **140** and 15.6 g of a mixture of **141** and **142**, which solified and was recrystallized from hexane to yield

7.7 g (35%) of pure **140**. Flash chromatography on silicagel (eluent light petroleum-ethyl acetate 3:1) of the mother liquor yielded 3.5 g (17%) of enone **141** and another 4.4 g (20%) of ketol **142** as a white crystalline solid, mp 109°C, $[\alpha]_D$ - 51.9 (c=1.0, chloroform).
^{1}H NMR 1.20 (s, 3H), 1.70 (s, 3H), 1.2-2.9 (m, 14H), 4.68 (br s, 2H); IR (KBr) 3530, 1700, 1640, 1270, 1200; MS *m/e* (%) 222 (1, M^+), 204 (100), 189 (17), 152 (22), 109 (51), 107 (54), 95 (20), 81 (25); HRMS, calcd for $C_{14}H_{22}O_2$ (M^+) *m/e* 222.1620, found *m/e* 222.1620. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.61; H, 10.01.

(-)-(4aR,7S)-7-Isopropenyl-4a-methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one (141)

This enone **141** was obtained as described above as a yellow oil in 17% yield, $[\alpha]_D$ - 79 (c=1.2, chloroform).
^{1}H NMR 1.25 (s, 3H), 1.74 (s, 3H), 1.0-2.7 (m, 11H), 4.76 (br s, 2H), 5.74 (s, 1H); IR (film) 1675, 1610, 1250, 1225; MS *m/e* (%) 204 (15, M^+), 189 (12), 186 (11), 176 (45), 161 (20), 158 (26), 148 (19), 147 (25), 133 (40), 132 (100), 119 (20), 107 (19), 105 (23), 91 (22), 79 (18); HRMS, calcd for $C_{14}H_{20}O$ (M^+) *m/e* 204.1514, found *m/e* 204.1519. Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.10; H, 10.03.

(+)-(4aS,7S)-7-Isopropenyl-4a-methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one (143)

A solution of 11.8 g (53.2 mmol) of **142** and 6 g of potassium hydroxide in ethanol (100 mL) was stirred overnight at room temperature. The mixture was diluted with water (500 mL) and worked up as usual. The residue was distilled in a Kugelrohr at 0.6 torr. The fraction from 110-120°C was collected to yield 10.1 g (93%) of enone **143** as a colourless oil which solidified on standing. Recrystallization from pentane afforded needles, mp 38-39°C, $[\alpha]_D$ +180.1 (c=1.2, chloroform).
^{1}H NMR 1.25 (s, 3H), 1.70 (s, 3H), 1.0-2.8 (m, 11H), 4.75 (br s, 1H), 4.86 (br s, 1H), 5.80 (s, 1H); IR (KBr) 1670, 1615, 1255, 1235; MS *m/e* (%) 204 (15, M^+), 189 (13), 186 (8), 176 (45), 161 (20), 158 (26), 147 (25), 133 (40), 132 (100), 119 (20), 105 (23); HRMS, calcd for $C_{14}H_{20}O$ (M^+) *m/e* 204.1514, found *m/e* 204.1519. Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.22; H, 9.80.

(-)-(4aS,7S)-7-Isopropenyl-1,1,4a-trimethyl-3,4,4a,5,6,7-hexahydronaphthalen-2(1H)-one (144)

To a solution of 11.4 g (101 mmol) of potassium *tert*-butoxide in *tert*-butyl alcohol (100 mL) was added a solution of 9.38 g (46 mmol) of enone **143** in *tert*-butyl alcohol (20 mL) at room temperature under nitrogen. The mixture was stirred for 30 min and then 8.64 ml (139 mmol) of iodomethane was added. After 3 h the reaction mixture was poured into water (500 mL) and worked up as usual. The residue was distilled in a Kugelrohr at 0.4 torr. The 110-120°C fraction was collected to yield 10.0 g (94%) of **144** as a colourless oil, $[\alpha]_D$ - 65.5 (c=1.0, chloroform).
^{1}H NMR 0.97 (s, 3H), 1.23 (s, 3H), 1.26 (s, 3H), 1.0-2.8 (m, 9H), 1.77 (s, 3H), 4.63 (br s, 1H), 4.84 (br s, 1H), 5.50 (d, *J*=4.5 Hz, 1H); IR (film) 1715, 1610; MS *m/e* (%) 232 (29, M^+), 217 (14), 189 (10), 147 (33), 133 (100), 119 (19), 105 (18), 91 (13); HRMS, calcd for $C_{16}H_{24}O$ (M^+) *m/e* 232.1827, found *m/e* 232.1830. Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.51; H, 10.29.

(-)-(4aR)-2-Isopropylidene-4a,8,8-trimethyl-2,3,4,4a,5,6,7,8-octahydronaphthalene (145)

To a solution of 7.2 g (143 mmol) of hydrazine hydrate and 7.17 g (127 mmol) of potassium hydroxide in diethylene glycol (50 mL) was added 9.28 g (40 mmol) of ketone **144**. The reaction mixture was heated for 3 h at 120°C and then excess of hydrazine hydrate and water was removed by distillation. The temperature was raised to 210°C and hold for 2 h. After cooling the reaction mixture was poured into water (300 mL) and worked up as usual. The residue was purified by flash chromatography on silica gel (eluent light petroleum) and yielded 6.10 g (70%) of diene **145** as a colourless oil, $[\alpha]_D$ - 70.6 (c=1.0, chloroform).
^{1}H NMR 1.17 (br s, 9H), 1.73 (s, 3H), 1.82 (s, 3H), 1.2-1.7 (m, 7H), 2.1-2.5 (m, 3H), 6.33 (s, 1H); IR (film) 1660, 1600; MS *m/e* (%) 218 (100, M^+), 203 (97), 175 (14), 161 (23), 149 (29), 148 (23), 147 (22), 135 (24), 133 (37), 105 (20), 95 (20); HRMS, calcd for $C_{16}H_{26}$ (M^+) *m/e* 218.2034, found *m/e* 218.2033.

(-)-(4aR,8aS)-4a,8,8-Trimethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-2(1H)-one (17)

A solution of 5.0 g (23.0 mmol) of diene **145** in methanol (200 mL) was ozonolyzed at -80°C. The excess ozone was expelled and 2 g of dimethylsulfide was added at -80°C. After stirring for 3 h the temperature was raised to room temperature. The solvents were evaporated and the residue was purified by flash chromatography (eluent light

petroleum-ethyl acetate 19:1) to yield 3.44 g (78%) of **(-)-(4aR)-4a,8,8-trimethyl-4,-4a,5,6,7,8-hexahydronaphthalen-2(3H)-one**, $[\alpha]_D$ -105 (c=1.0, chloroform).
^{1}H NMR 1.13 (s, 3H), 1.20 (s, 3H), 1.33 (s, 3H), 1.4-2.0 (m, 8H), 2.3-2.7 (m, 2H), 5.97 (s, 1H); MS *m/e* (%) 192 (100, M^+), 177 (17), 164 (31), 149 (44), 136 (60), 135 (27), 123 (94), 122 (56), 121 (31), 95 (26); HRMS, calcd for $C_{13}H_{20}O$ (M^+) *m/e* 192.1514, found *m/e* 192.1517. Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.33; H, 10.57.

This enone was dissolved in dry ether (25 mL) and added to a solution of 14.3 g (192 mmol) of *tert*-butyl alcohol and 0.57 g (82 mgrat) of lithium in liquid ammonia (150 mL). The excess of lithium was destroyed after 15 min with solid ammonium chloride and the ammonia was evaporated. Usual work-up afforded 3.14 g (90%) of crystalline ketone **17**, which was recrystallized from pentane, mp 39°C, $[\alpha]_D$ - 12.8 (c=1.0, chloroform).
^{1}H NMR 0.87 (s, 6H), 1.13 (s, 3H), 1.2-1.8 (m, 9H), 2.1-2.6 (m, 4H); IR (KBr) 1720; MS *m/e* (%) 194 (90, M^+), 179 (38), 165 (9), 161 (16), 123 (100), 122 (34), 111 (30), 109 (34), 95 (26), 83 (47); HRMS, calcd for $C_{13}H_{22}O$ (M^+) *m/e* 194.1671, found *m/e* 194.1670. Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.42. Found: C, 80.19; H, 11.33.

(+)-(4aR,7R,8aR)-8a-Hydroxy-7-isopropenyl-4a-methyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-2(1H)-one (147)

This ketol was prepared following the same procedure as described for ketol **142**, starting from (+)-dihydrocarvone **140**. It was obtained in 55% yield as a white crystalline solid, mp 109°C, $[\alpha]_D$ +55.3 (c=1.7, chloroform).
^{1}H NMR 1.22 (s, 3H), 1.70 (s, 3H), 1.2-2.9 (m, 14H), 4.68 (br s, 2H); IR (KBr) 3580, 1705, 1640, 1260, 1200; MS *m/e* (%) 222 (2, M^+), 204 (100), 189 (19), 151 (24), 123 (21), 121 (14), 109 (62), 107 (64), 95 (22), 81 (29), 69 (20), 55 (19), 43 (18), 41 (16); HRMS, calcd for $C_{14}H_{22}O_2$ (M^+) *m/e* 222.1620, found *m/e* 222.1620. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.39; H, 10.00.

(+)-(4aS,7R)-7-Isopropenyl-4a-methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one (146)

This enone **146** was prepared following the procedure for enone **141**, starting from (+)-dihydrocarvone **140**. It was obtained in 15% yield as a yellow oil, $[\alpha]_D$ +80.6 (c=1.8, chloroform).
^{1}H NMR 1.25 (s, 3H), 1.77 (s, 3H), 1.3-2.0 (m, 6H), 2.1-2.4 (m, 5H), 4.77 (br s, 2H), 5.73 (s, 1H); IR (film) 1680, 1620; MS *m/e* (%) 204 (100, M^+), 189 (27), 176

(23), 162 (30), 161 (37), 149 (32), 148 (27), 147 (37), 133 (40), 107 (38); HRMS, calcd for $C_{14}H_{20}O$ (M^+) *m/e* 204.1514, found *m/e* 204.1510. Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.17; H, 9.91.

(-)-(4aR,7R)-7-Isopropenyl-4a-methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one (148)

A solution of 8.88 g (40 mmol) of ketol **147** in ethanol (50 mL) was treated at reflux temperature with 3.14 g (56 mmol) of potassium hydroxide. After 60 min the reaction mixture was poured into water (250 mL) and worked up as usual. The residue was purified by flash chromatography on silica gel (eluent light petroleum-ethyl acetate 19:1) to yield 7.40 g (91%) of enone **148** as an oil, $[\alpha]_D$ -177 (c=2.1, chroloform).
^{1}H NMR 1.30 (s, 3H), 1.73 (s, 3H), 1.3-2.0 (m, 6H), 2.3-2.6 (m, 5H), 4.77 (s, 1H), 4.87 (s, 1H), 5.82 (s, 1H); IR (film) 1670, 1610, 1255, 1235; MS *m/e* (%) 204 (15, M^+), 189 (11), 186 (10), 176 (47), 161 (20), 158 (29), 147 (27), 133 (42), 132 (100), 119 (20), 107 (18), 105 (20), 91 (20); HRMS, calcd for $C_{14}H_{20}O$ (M^+) *m/e* 204.1514, found *m/e* 204.1515. Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.23; H, 10.02.

(-)-(4aR)-4a-Methyl-4,4a,5,6-tetrahydronaphthalen-2(3H)-one (149)

A solution of 6.12 g (30 mmol) of enone **148** in methanol (150 mL) was ozonized at -80°C till the colour of the solution was light blue. The excess of ozone was expelled by nitrogen and 12.0 g (60 mmol) of cupric acetate monohydrate and 8.34 g (30 mmol) of ferrous sulfate heptahydrate were added. The resulting mixture was stirred overnight at room temperature and concentrated *in vacuo*. The residue was dissolved in aqueous 1 N hydrochloric acid (75 mL) and worked up as usual. The residue was purified by flash chromatography (eluent light petroleum-ethyl acetate 9:1) and 3.42 g (67%) of **149** was obtained as an oil, $[\alpha]_D$ - 176 (c=1.0, chloroform).
^{1}H NMR 1.16 (s, 3H), 1.5-2.0 (m, 4H), 2.3-2.6 (m, 4H), 5.66 (s, 1H), 6.16 (br s, 2H); ^{13}C NMR 21.2 (q), 23.5 (t), 33.2 (s), 34.1 (t), 35.9 (t), 36.9 (t), 123.5 (d), 127.7 (d), 137.7 (d), 161.9 (s), 199.7 (s); IR (film) 1670, 1660, 1615; MS *m/e* (%) 162 (75, M^+), 134 (100), 119 (43), 106 (11), 105 (28), 91 (62); HRMS, calcd for $C_{11}H_{14}O$ (M^+) *m/e* 162.1045, found *m/e* 162.1043.

(+)-(4aR,7R)-4a,7-Dimethyl-3,4,4a,5,6,7-hexahydronaphthalen-2(1H)-one (150)

A suspension of 3.44 g (18 mmol) of cuprous iodide in ether (50 mL) was treated with 22.5 mL of a 1.6 molar solution of methyllithium (36 mmol) in ether at 0°C. After 15

min a solution of 2.76 g (18 mmol) of dienone **149** in ether (25 mL) was added and stirred for 15 min. The reaction mixture was poured into water (50 mL) and worked up as usual. The residue was purified by flash chromatography (eluent light petroleum-ethyl acetate 19:1) and 2.79 g (87%) of **150** was obtained as a yellow oil, $[\alpha]_D$ +42 (c=2.4, chloroform).
^{1}H NMR 0.92 (d, *J*=6 Hz, 3H), 1.20 (s, 3H), 1.45-1.90 (m, 6H), 2.0-2.7 (m, 3H), 2.78 (dd, *J*=16,2 Hz, 1H), 3.22 (dt, *J*=16,2 Hz), 5.26 (dd, *J*=3,2 Hz, 1H); ^{13}C NMR 21.0 (q), 24.0 (q), 26.6 (t), 29.7 (d), 34.2 (s), 35.2 (t), 37.9 (t), 38.1 (t), 48.5 (t), 129.5 (d), 137.1 (s), 209.3 (s); IR 1710, 1600; MS *m/e* (%) 178 (100, M^+), 163 (63), 160 (4), 145 (10), 136 (37), 123 (79), 107 (46), 93 (34); HRMS, calcd for $C_{12}H_{18}O$ (M^+) *m/e* 178.1358, found *m/e* 178.1354.

(+)-(4aR,7S,8aR)-4a,7-Dimethyl-8-methylene-3,4,4a,5,6,7,8,8a-octahydronaphthalen-2(1H)-one (19)

Ketone **19** was prepared from 2.51 g (14.1 mmol) of **150** in six steps using standard procedures.[14] The yield was 1.43 g (53%) of crystalline **19**, mp 65-66°C, $[\alpha]_D$ +72 (c=0.25, chloroform).
^{1}H NMR 0.92 (s, 3H), 1.10 (d, *J*=6 Hz, 3H), 1.2-1.9 (m, 8H), 2.1-2.7 (m, 6H), 4.50 (br s, 1H), 4.81 (br s, 1H); IR (KBr) 1705, 1640, 1450; MS *m/e* (%) 192 (84, M^+), 177 (42), 135 (100), 68 (65); HRMS, calcd for $C_{13}H_{20}O$ (M^+) *m/e* 192.1514, found *m/e* 192.1515. Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.18; H, 10.51.

(+)-(4aS)-4a-Methyl-4,4a,5,6-tetrahydronaphthalen-2(3H)-one (152)

This dienone **152** was prepared from enone **143** or enone **146** as described for its enantiomer **149** in 55% yield, $[\alpha]_D$ +187 (c=6.03, chloroform).
^{1}H NMR 1.17 (s, 3H), 1.4-2.0 (m, 4H), 2.3-2.7 (m, 4H), 5.66 (s, 1H), 6.17 (br s, 2H); ^{13}C NMR 21.2 (q), 23.5 (t), 33.2 (s), 34.1 (t), 35.9 (t), 36.9 (t), 123.6 (d), 126.6 (d), 137.7 (d), 161.9 (s), 199.8 (s); IR (film) 1670, 1660, 1615; MS *m/e* (%) 162 (75, M^+), 134 (100), 119 (43), 106 (17), 105 (34), 91 (60); HRMS, calcd for $C_{11}H_{14}O$ (M^+) *m/e* 162.1045, found *m/e* 162.1045.

(+)-(4aS)-4a-Methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one (105)

To a solution of 8.8 mmol of Li-selectride in dry THF (40 mL) and HMPA (8 mL) was added a solution of 1.30 g (8 mmol) of dienone **152** in THF (5 mL) at 0°C. After 60 min the reaction mixture was poured into water (100 mL) and worked up as usual. The residue was purified by flash chromatography on silica gel (eluent light petroleum-ethyl

acetate 4:1) to yield 1.12 g (86%) of **105** as a yellow oil, $[\alpha]_D$ +202 (c=1.0, chloroform).
^{1}H NMR 1.25 (s, 3H), 1.3-2.0 (m, 8H), 2.1-2.5 (m, 4H), 5.73 (s, 1H); IR (film) 1680, 1625; MS *m/e* (%) 164 (100, M^+), 149 (12), 136 (50), 122 (92), 107 (42), 93 (17), 91 (13), 79 (19); HRMS, calcd for $C_{11}H_{16}O$ (M^+) *m/e* 164.1201, found *m/e* 164.1200.

(-)-(4aS,7S)-2,2-(Ethylenedioxy)-7-isopropenyl-1,1,4a-trimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalene (144b)

A solution of 2.0 g (8.6 mmol) of ketone **144a** in benzene (100 mL) was treated with ethylene glycol (5 mL) and 100 mg of *p*-toluenesulfonic acid at reflux temperature for 24 h under a Dean-Stark water-separator. After cooling the mixture was diluted with ether (200 mL) and worked up as usual. The residue was purified by flash chromatography on silica gel (eluent light petroleum-ether 50:1) to yield 1.90 gr (80%) of **144b** as a colourless oil, $[\alpha]_D$ -139 (c=3.7, chloroform).
^{1}H NMR 1.04 (s, 3H), 1.20 (s, 6H), 1.76 (s, 3H), 1.0-2.3 (m, 8H), 2.53-2.75 (m, 1H), 3.91 (br s, 4H), 4.68 (br s, 1H), 4.79 (br s, 1H), 5.37 (d, *J*=5 Hz, 1H); MS *m/e* (%) 276 (2, M^+), 261 (0.3), 133 (1), 119 (1), 105 (1), 100 (5), 99 (100), 91 (1); HRMS, calcd for $C_{18}H_{28}O_2$ (M^+) *m/e* 276.2089, found *m/e* 276.2086.

(-)-(2S,4aS,7S)-7-Isopropenyl-1,1,4a-trimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-ol (144c)

A solution of 1.04 g (4.5 mmol) of ketone **144a** in dry ether (50 mL) was added dropwise to a stirred suspension of 0.14 g (3.67 mmol) of lithium tetrahydroaluminate in dry ether (50 mL). After 60 min water (0.15 mL), aqueous 4 N sodium hydroxide (0.15 mL), and again water (0.5 mL) was added. This mixture was dried on magnesium sulfate, filtered and evaporated to leave a paste-like residue, which was purified by flash chromatography on silica gel (eluent light petroleum-ether 4:1) to give 0.96 g (92%) of alcohol **144c**, $[\alpha]_D$ - 129 (c=2.7, chloroform).
^{1}H NMR 1.05 (s, 3H), 1.16 (s, 6H), 1.76 (s, 3H), 0.9-2.1 (m, 8H), 2.32 (br s, 1H), 2.56-2.78 (m, 1H), 3.25 (dd, *J*=6,9.6 Hz, 1H), 4.58 (br s, 1H), 4.78 (br s, 1H), 5.44 (d, *J*=4.5 Hz, 1H); MS *m/e* (%) 234 (24, M^+), 219 (17), 216 (95), 201 (100), 148 (41), 135 (79), 133 (41), 121 (38), 108 (48), 93 (38); HRMS, calcd for $C_{16}H_{26}O$ (M^+) *m/e* 234.1984, found *m/e* 234.1975. Anal. Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 82.01; H, 11.10.

(-)-(4aS)-7-Isopropylidene-1,1,4a-trimethyl-3,4,4a,5,6,7-hexahydronaphthalen-2(1H)-one (153a)

A solution of 0.90 g (3.9 mmol) of ketone **144a** and 0.68 g (12 mmol) of potassium hydroxide in diethylene glycol (30 mL) was heated under nitrogen at 200°C. After 15 min the reaction mixture was cooled and poured into water (200 mL) and worked up as usual. The residue was purified by flash chromatography on silica gel (eluent light petroleum-ether 24:1) to yield 0.56 g (54%) of a colourless oil, $[\alpha]_D$ - 55.7 (c=1.0, chloroform).
^{1}H NMR 1.03 (s, 3H), 1.27 (s, 6H), 1.73 (s, 3H), 1.80 (s, 3H), 0.8-2.7 (m, 8H), 6.38 (s, 1H); MS *m/e* (%) 232 (100, M^+), 217 (70), 189 (78), 161 (39), 146 (38), 133 (45), 119 (38), 105 (33), 91 (32), 55 (28), 41 (44); HRMS, calcd for $C_{16}H_{24}O$ (M^+) *m/e* 232.1827, found *m/e* 232.1831.

(-)-(4aS)-2,2-(Ethylenedioxy)-7-isopropylidene-1,1,4a-trimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalene (153b)

Acetal **153b** was prepared from 0.98 g (3.6 mmol) of **144b** by the procedure described for **153a**. After usual work-up 0.88 g (90%) of **153b** was obtained as a colourless oil, $[\alpha]_D$ -105 (c=4.0, chloroform).
^{1}H NMR 1.12 (s, 3H), 1.20 (s, 3H), 1.23 (s, 3H), 1.72 (s, 3H), 1.79 (s, 3H), 0.9-2.5 (m, 8H), 3.93 (br s, 4H), 6.38 (s, 1H); MS *m/e* (%) 276 (6, M^+), 99 (100); HRMS, calcd for $C_{18}H_{28}O_2$ (M^+) *m/e* 276.2089, found *m/e* 276.2084.

(-)-(2S,4aS)-7-Isopropylidene-1,1,4a-trimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-ol (153c)

Alcohol **153c** was prepared as described for **153a**. After 120 min the reaction was stopped and worked up as usual to afford 2.65 g (95%) of a colourless oil, $[\alpha]_D$ - 94.6 (c=2.4, chloroform).
^{1}H NMR 1.04 (s, 3H), 1.13 (s, 3H), 1.22 (s, 3H), 1.72 (s, 3H), 1.81 (s, 3H), 0.7-2.5 (m, 9H), 3.29 (dd, *J*=5,10 Hz, 1H), 6.40 (s, 1H); MS *m/e* (%) 234 (100, M^+), 219 (21), 201 (60), 177 (55), 148 (51), 85 (57), 83 (83); HRMS, calcd for $C_{16}H_{26}O$ (M^+) *m/e* 234.1984, found *m/e* 234.1982.

(-)-(4aS)-1,1,4a-Trimethyl-3,4,4a,5-tetrahydronaphthalen-2(1H),7(6H)-dione (154a)

A solution of 1.16 g (5.0 mmol) of **153a** in methanol (50 mL) was ozonized at -80°C till the colour of the solution was light blue. The excess of ozone was expelled by a

stream of nitrogen and 0.21 g (2.8 mmol) of thiourea was added. After being stirred for 3 h at room temperature the reaction mixture was concentrated *in vacuo* and dissolved in water and worked up as usual to give after flash chromatography on silica gel (eluent light petroleum-ether 1:1) 0.67 g (65%) of the dione **154a** as an oil, $[\alpha]_D$ - 23.1 (c=0.45, chloroform).
^{1}H NMR 1.20 (s, 3H), 1.32 (s, 6H), 1.4-3.2 (m, 8H), 5.97 (s, 1H); IR (film) 1715, 1680, 1615; MS *m/e* (%) 206 (100, M^+), 191 (18), 178 (23), 163 (19), 152 (44), 151 (41), 135 (26), 123 (49), 107 (26), 70 (60); HRMS, calcd for $C_{13}H_{18}O_2$ (M^+) *m/e* 206.1307, found *m/e* 206.1303.

(-)-(4aS)-7,7-(Ethylenedioxy)-4a,8,8-trimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one (154b)

The procedure was followed as described for diene **153a**. There was obtained 1.03 g (82%) of the enone **154b** as a colourless oil, $[\alpha]_D$ - 89 (c=2.3, chloroform).
^{1}H NMR 1.10 (s, 3H), 1.27 (s, 3H), 1.38 (s, 3H), 1.4-2.8 (m, 8H), 3.96 (br s, 4H), 5.95 (s, 1H); IR (film) 1680, 1640; MS *m/e* (%) 250 (2, M^+), 235 (4), 99 (100); HRMS, calcd for $C_{15}H_{22}O_3$ (M^+) *m/e* 250.1569, found *m/e* 250.1571.

(-)-(4aR,7S)-7-Hydroxy-4a,8,8-trimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one (154c)

A solution of 1.17 g (5 mmol) of diene **153c** was treated with ozone as described for **153a**. There was obtained 0.92 g (88%) of enone **154c** as an oil, $[\alpha]_D$ - 91.2 (c=2.0, chloroform).
^{1}H NMR 1.10 (s, 3H), 1.21 (s, 3H), 1.34 (s, 3H), 1.2-2.8 (m, 8H), 3.03 (br s, 1H), 3.44 (dd, *J*=6,10 Hz, 1H), 6.00 (s, 1H); IR (film) 3440, 3420, 1685, 1630, 1130; MS *m/e* (%) 208 (41, M^+), 193 (50), 190 (7), 175 (9), 152 (100), 123 (48), 109 (41), 43 (40); HRMS, calcd for $C_{13}H_{20}O_2$ (M^+) *m/e* 208.1463, found *m/e* 208.1460.

(-)-(4aR,7S,8aS)-7-Hydroxy-4a,8,8-trimethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-2(1H)-one (155c)

A solution of 0.83 g (4.0 mmol) of hydroxy enone **154c** and 2.96 g (40 mmol) of *tert*-butyl alcohol in dry ether (100 mL) was added to a solution of 0.083 g (12 mgrat) of lithium in liquid ammonia (100 mL). After 10 min the excess of lithium was destroyed with solid ammonium chloride and the ammonia was allowed to evaporate. After work-up in the usual way there was obtained after flash chromatography (eluent light petroleum-ether 1:1) 0.70 g (83%) of hydroxy ketone **155c**. Recrystallization from

pentane afforded white crystals, mp 93°C, $[\alpha]_D$ - 6.9 (c=3.1, chloroform).
^{1}H NMR 0.80 (s, 3H), 0.94 (s, 3H), 1.13 (s, 3H), 1.2-2.0 (m, 7H), 2.1-2.7 (m, 5H), 3.27 (dd, *J*=6,8 Hz, 1H); IR (KBr) 3440, 3400, 1735; MS *m/e* (%) 210 (100, M^+), 195 (12), 192 (9), 177 (24), 167 (44), 153 (29), 149 (18), 137 (16), 135 (18), 123 (22), 111 (38), 109 (29), 97 (47), 69 (35); HRMS, calcd for $C_{13}H_{22}O_2$: (M^+) *m/e* 210.1620, found *m/e* 210.1617. Anal. Calcd for $C_{13}H_{22}O_2$; C, 74,24; H, 10.55. Found: C, 74.50; H, 10.29.

7.6 References and notes

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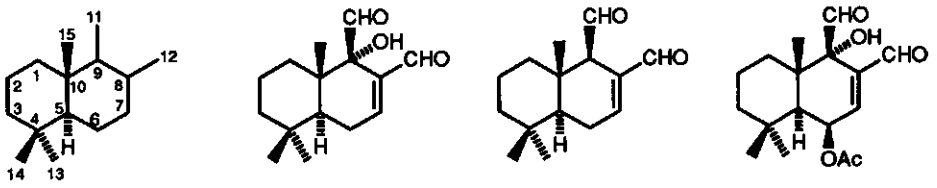
8 SUMMARY

The investigations described in this thesis deal with the total synthesis of sesquiterpenes of the drimane family, named for their widespread occurrence in the stem bark of South American *Drimys* species. These compounds contain the bicyclofarnesol nucleus **1**, which is invariably oxidized at C-11 and/or C-12 and often at other sites as well (see figure 8.1).

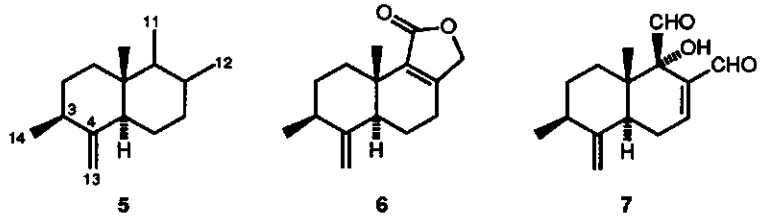
Figure 8.1



1 **2** **3** **4**

A few rearranged drimanes, *e.g.*, (+)-colorata-4(13),8-dienolide **6**, and (-)-muzigadial **7**, are also isolated from natural products. The rearranged bicyclofarnesol nucleus **5** presumably owes its biogenesis to a cation-induced migration of a methyl group from C-4 to C-3 followed by loss of a proton from C-13 to give the exocyclic methylene group (see figure 8.2).

Figure 8.2



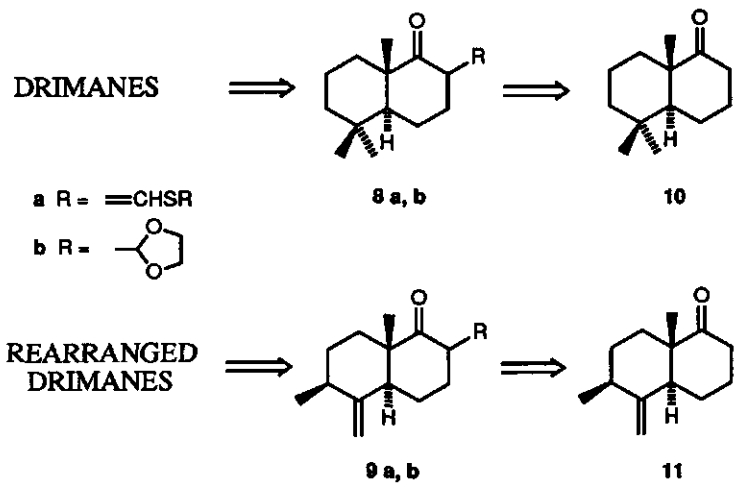
5 **6** **7**

Interest in this class of compounds has been stimulated by the discovery of drimanes exemplified by (-)-warburganal **2**, (-)-polygodial **3**, and (-)-ugandensidial **4**, which exhibit remarkable physiological activities, *e.g.*, antifungal, molluscicidal, cytotoxic, and plant growth regulation. Especially the insect antifeedant activity has attracted much attention, for the application of naturally occurring antifeedants is of potential value for crop protection due to their specificity of action and their usually low mammalian toxicity. A survey of these drimanic sesquiterpenes and their physiological properties is presented in chapter 1.

The common structural feature in these drimanes is the presence of a $\Delta^{7,8}$ ene-11,12ß-dialdehyde functionality which, in the more potent substances, is further completed with a 9α-hydroxyl substituent. This array of functional groups clearly provides a challenging target to synthetic organic chemists, as does the rearranged drimane muzigadial **7** with its additional exocyclic methylene group at C-4 and the chiral center at C-3. Chapter 2 is devoted to a literature survey of synthetic studies towards the total synthesis of drimanes and rearranged drimanes.

From a retrosynthetic analysis of these compounds an approach, starting from the *trans*-decalones **10** and **11** seemed to offer good perspectives, as outlined in scheme 8.1. Both **10** and **11** were synthesized in multigram quantities by approaches developed at our laboratory, as described in chapter 4.

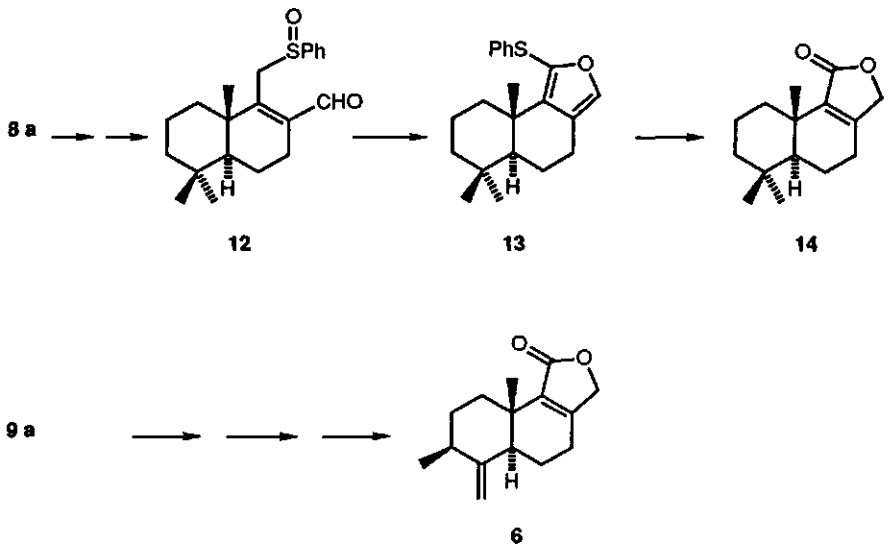
Scheme 8.1



In both decalones the carbonyl function is properly located for the introduction of the necessary functionalized carbon atoms at C-8 *via* Claisen condensation with ethyl formate and at C-9 *via* addition of suitably functionalized nucleophiles.

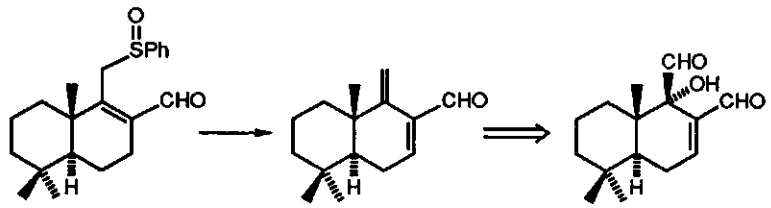
Ketones **8a** and **9a** were obtained in a straightforward manner. Addition of *[(phenylthio)methyl]lithium* to **8a** followed by hydrolysis and oxidation afforded sulfoxide **12**, which in turn gave regiospecifically (phenylthio)furan **13** upon heating in acetic anhydride. Hydrolysis then completed a new approach for the regiospecific annulation of butenolides from ketones of type **10** (see scheme 8.2).

Scheme 8.2



This sequence was also applied to **9a** thus giving rise to the first stereoselective total synthesis of the rearranged drimanic lactone (±)-colorata-4(13),8-dienolide **6**.
Thermolysis of sulfoxide **12** in refluxing toluene gave the unsaturated aldehyde **15**. Since the latter has been converted into (±)-warburganal **2**, this approach allows a synthetic entry to this antifeedant (see scheme 8.3).

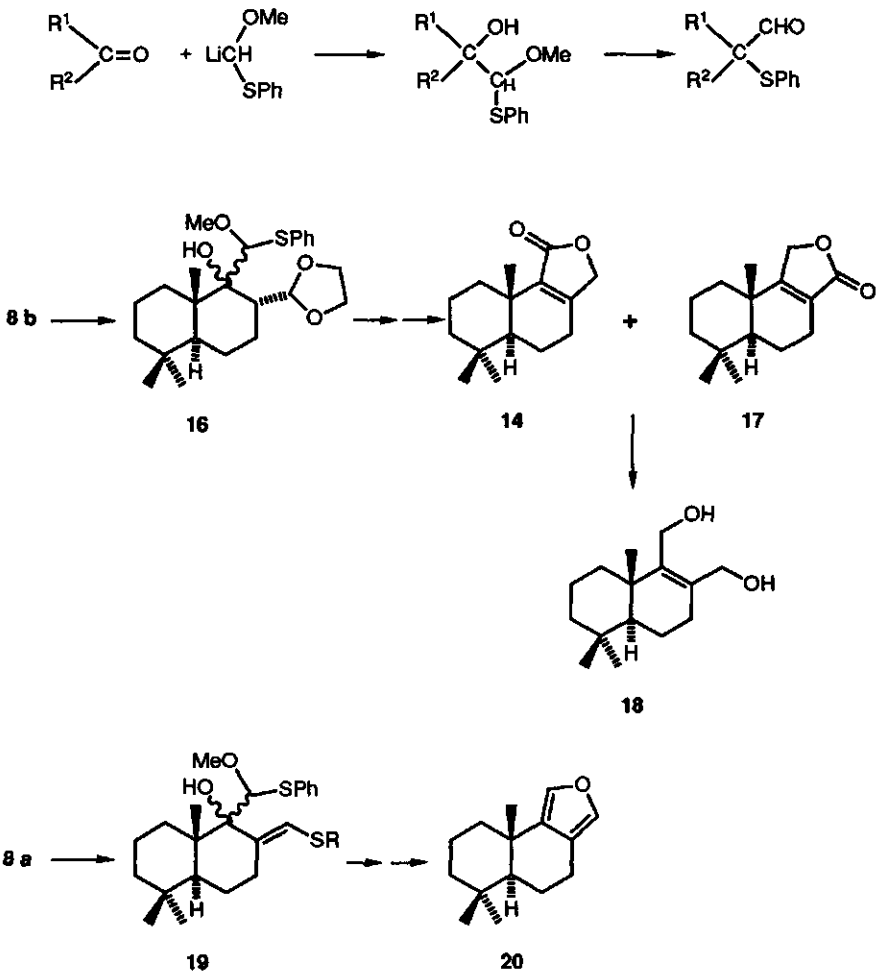
Scheme 8.3



In chapter 5 the promising nucleophile *[methoxy(phenylthio)methyl]lithium* was used to introduce a masked aldehyde group at C-9. The addition of this nucleophile to aldehydes, ketones, α,ß-unsaturated ketones, α-oxo acetals, and (aryl- or alkylthio)methylene ketones was straightforward and the adducts were obtained in high yields. These adducts could be rearranged into α-sulfenylated aldehydes upon treatment with thionyl chloride

and sometimes also with acid. This new rearrangement was developed as a new synthetic method and applied in the synthesis of several drimane sesquiterpenes (see scheme 8.4).

Scheme 8.4



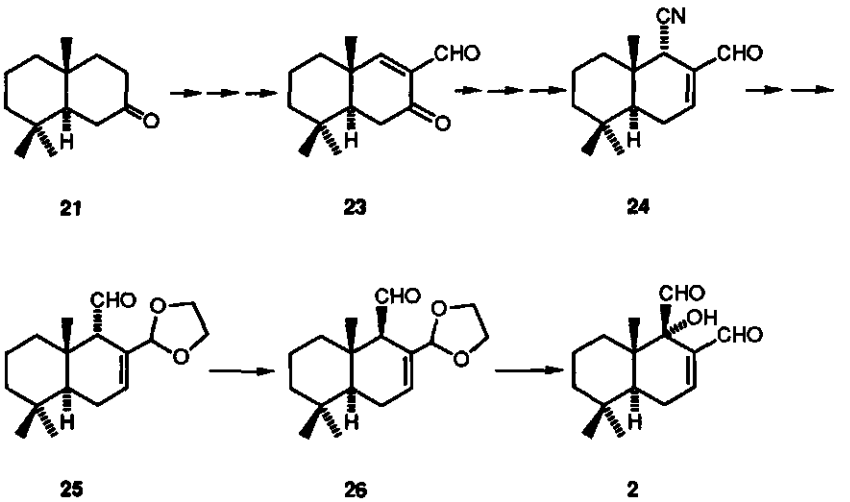
The adducts **16** were subjected to hydrolysis and the lactones **14** and/or **17** were obtained dependent on the conditions used. Mixtures of lactones were separated with difficulty and the best way to proceed turned out to be their reduction into the diol **18**, a well-known intermediate in the synthesis of drimanes such as confertifolin **17** and warburganal **2**.

trans-Decalone **10** was formylated and the aldehyde function was protected as its (phenylthio)methylene derivative **8a** or as its dioxolan **8b**. The adducts **19**, obtained by addition of [methoxy(phenylthio)methyl]lithium to **8a**, rearranged into rather unstable aldehydes and therefore a reduction was performed immediately. A spontaneous cyclization then afforded (±)-euryfuran **20**.

When the adducts **19** were subjected to a mercuric chloride assisted hydrolysis an unexpected ring expansion reaction was observed.

Several drimanes could be synthesized starting from **10** and **11**, but a straight- forward total synthesis of the more biologically active drimanes warburganal **2**, polygodial **3**, and muzigadial **7** proved to be troublesome. Therefore a new concept was taken into consideration starting from the *trans*-decalones **21** and **22**, as is dealt with in chapter 6. Both were synthesized in multigram quantities *via* adaptation of known procedures.

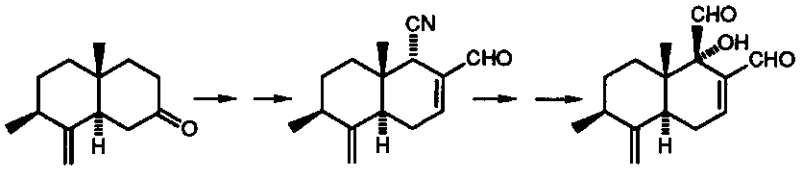
Scheme 8.5



Formylation of **21** and subsequent dehydrogenation afforded the unsaturated keto aldehyde **23**. Addition of HCN then introduced the functionalized C-11 carbon atom and the remaining ß-keto aldehyde was reduced to an unsaturated aldehyde to afford **24**. Protection of the aldehyde group and reduction of the nitrile function then gave the *mono* protected dialdehyde **25**. It turned out that the α-positioned aldehyde group in **25** had to be epimerized before introducing the 9α-hydroxyl group *via* oxidation of the enolate of **25**. This epimerization is a crucial step in this approach and it had to be performed with an excess of potassium *tert*-butoxide in refluxing *tert*-butyl alcohol for just 10 minutes. Subsequent oxidation of the enolate of **26** then afforded (±)-warburganal **2** in a wholly acceptable 38% overall yield (see scheme 8.5).

Since all the reaction conditions and reagents used for the conversion of **21** into (±)-warburganal **2** were compatible with the presence of an exocyclic double bond in the molecule, the transformation of *trans*-decalone **22** into (±)-muzigadial **7** was expected to be straightforward and indeed no serious problems were encountered and (±)-muzigadial **7** was obtained in 24% overall yield (see scheme 8.6).

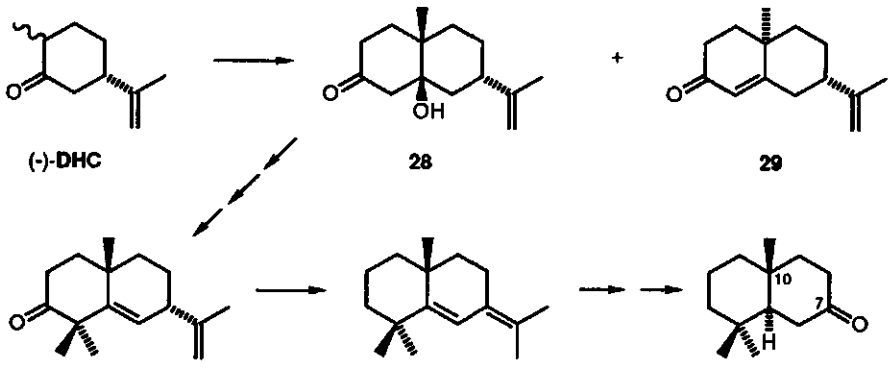
Scheme 8.6



22 **27** **7**

In principle, the natural enantiomers of polygodial **3**, warburganal **2**, and muzigadial **7** are to be preferred over their racemic forms, so a synthesis of the intermediate ketones **21** and **22** in the optically active form was investigated as described in chapter 7.
The synthesis of the chiral *trans*-decalones **21** and **22** was undertaken, using (S)-(+)- and (R)-(-)-carvone as a chiral starting compound, respectively. The isopropenyl group of carvone first served as a chiral handle and was converted afterwards into the desired carbonyl group at C-7. (-)-Dihydrocarvone, obtained from (+)-carvone by lithium bronze reduction, was converted into (-)-*trans*-decalone **21** starting with a conventional Robinson annulation. The ketol **28** could be isolated in pure form *via* crystallization from hexane, leaving the enone 29 in solution.

Scheme 8.7

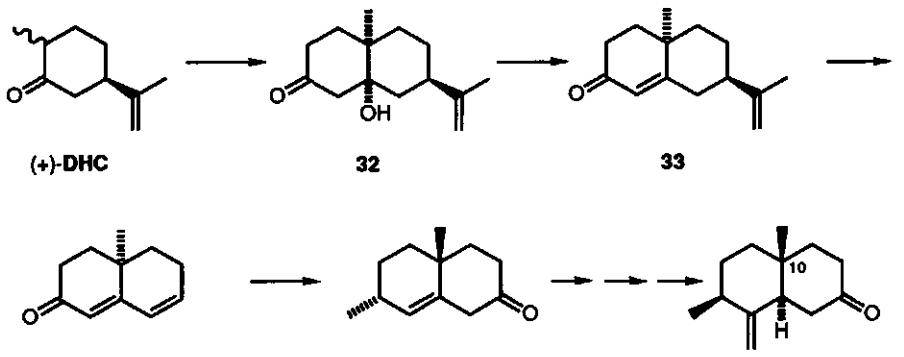


(-)-DHC **28** **29**

30 **31** **(-)-21**

This ketol was transformed into **30**, which upon Wolff-Kishner reduction also gave an isomerization of the double bond in the isopropenyl group as an accompanying reaction. Subsequent selective ozonolysis and reduction with lithium in liquid ammonia then gave the chiral (-)-*trans*-decalone **21** (see scheme 8.7).
(+)-*trans*-Decalone **22**, the starting material for the synthesis of (-)-muzigadial **7**, had to be synthesized starting with (+)-dihydrocarvone in order to obtain the desired R configuration at C-10 (see scheme 8.8).

Scheme 8.8



(+)-DHC **32** **33**

34 **35** (+)-**22**

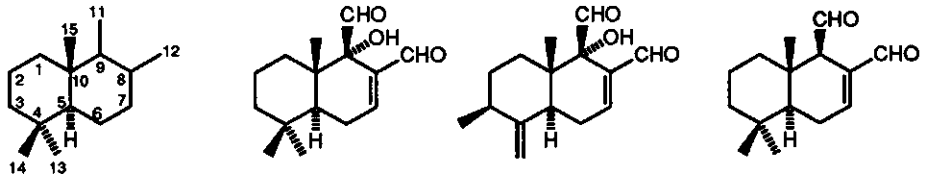
The isopropenyl group of enone **33** was removed by ozonolysis followed by decomposition of the ozonide by cupric acetate and ferrous sulfate to give dienone **34**. Conjugate addition of dimethylcopper lithium then afforded the deconjugated enone **35**, with the methyl groups in a *trans* position. This enone was further elaborated into (+)-*trans*-decalone **22** *via* known procedures, developed at our laboratory.

In summary, starting from easily available ketones efficient syntheses of several drimanic sesquiterpenes were performed. Especially the biologically active compounds (±)-polygodial **3**, (±)-warburganal **2**, and (±)-muzigadial **7** were synthesized straightforward in good yields.

9 SAMENVATTING

In dit proefschrift wordt een onderzoek beschreven waarin de synthese van drimaan sesquiterpenen centraal staat. Deze groep van natuurstoffen komt wijdverbreid voor en veel verbindingen uit deze groep vertonen een breed spectrum aan fysiologische activiteiten, zoals beschreven staat in hoofdstuk 1. Vooral de insektenvraatremmende werking van een aantal drimanen is intrigerend en mede daardoor zijn vooral warburganal **1**, muzigadial **2** en polygodial **3** het onderwerp van onderzoek geweest. Het overzicht van de syntheses van deze verbindingen in hoofdstuk 2 illustreert de wereldwijde belangstelling van synthetici voor bovengenoemde en andere drimaan sesquiterpenen.

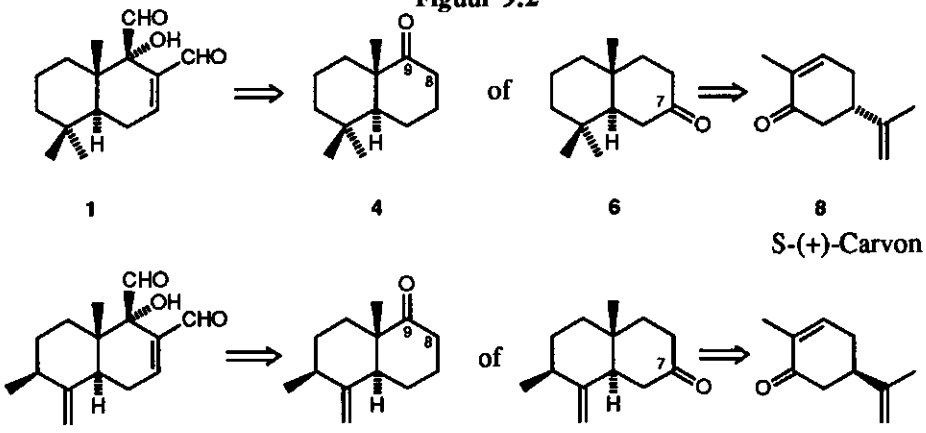
Figuur 9.1



DRIMAAN SKELET **1** **2** **3**

Een retrosynthetische analyse van de doelmoleculen (zie figuur 9.1) toonde aan, dat een opbouw van deze moleculen, uitgaande van de *trans*-decalonen **4** en **5** of **6** en **7**, goede mogelijkheden zou kunnen bieden. Dit is weergegeven in hoofdstuk 3.

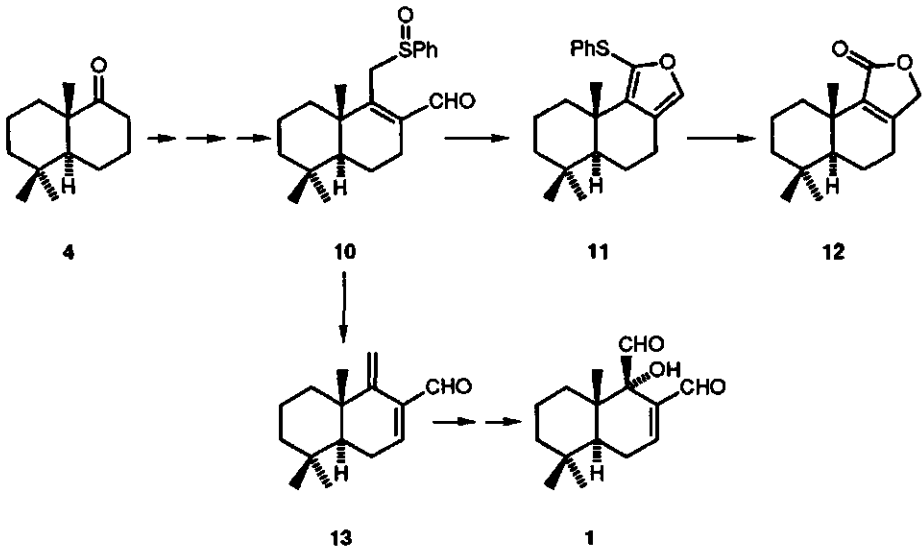
Figuur 9.2



De carbonyl functie in de *trans*-decalonen **4** en **5** kan benut worden om gefunctionaliseerde koolstofatomen in te voeren op C-8 via formylering en op C-9 door een additie van een geschikt nucleofiel. De keto groep in **6** en **7** is eveneens zeer geschikt om de noodzakelijke, gefunctionaliseerde koolstofatomen op C-8, weer via formylering en op C-9, door hydrocyanering, in te voeren. Bovendien kan deze carbonyl groep later dienen voor de invoering van een $\Delta^{7,8}$ dubbele binding. Ook zijn er goede mogelijkheden om **6** en **7** te synthetiseren uitgaande van respectievelijk (S)-(+)-carvon en (R)-(-)-carvon, zodat het uiteindelijk gesynthetiseerde drimaan optisch actief verkregen kan worden.

In hoofdstuk 4 werden de *trans*-decalonen **4** en **5** als uitgangsstof gebruikt. Door formyleren werd op C-8 een hydroxymethyleen groep ingevoerd, welke omgezet werd in een thio enol ether. Door een 1,2 additie van [(fenylthio)methyl]lithium, gevolgd door hydrolyse en oxidatie van het zwavelatoom werd het γ-fenylsulfinyl-α,ß-onverzadigde aldehyde **10** verkregen (zie schema 9.1).

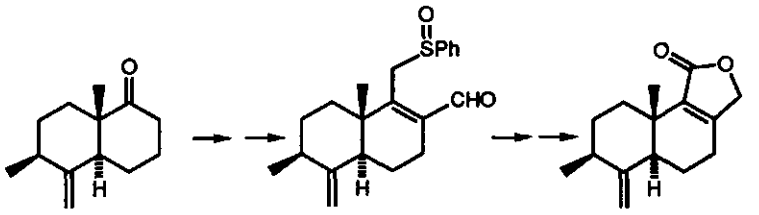
Schema 9.1



Onder Pummerer condities legde **10** om tot het (fenylthio)furaan **11**, dat na hydrolyse het lakton (±)-isodrimenin **12** opleverde. Deze werkwijze bleek algemeen toepasbaar, zodat uit ketonen van het type **4** op een regiospecifieke wijze butenoliden gesynthetiseerd kunnen worden. Eliminatie van fenylsulfeenzuur uit **10** gaf het dieen **13**, een verbinding, die als intermediair voorkomt in een totaal synthese van warburganal **1**. Via dit sulfoxide **10** is dus een synthese van dit insekt antifeedant mogelijk (zie schema 9.1).

Colorata-4(13),8-dienolide **15**, dat een omgelegd drimaan koolstofskelet heeft, werd, uitgaande van keton **5**, gesynthetiseerd (zie schema 9.2).

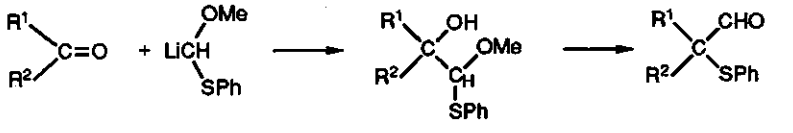
Schema 9.2

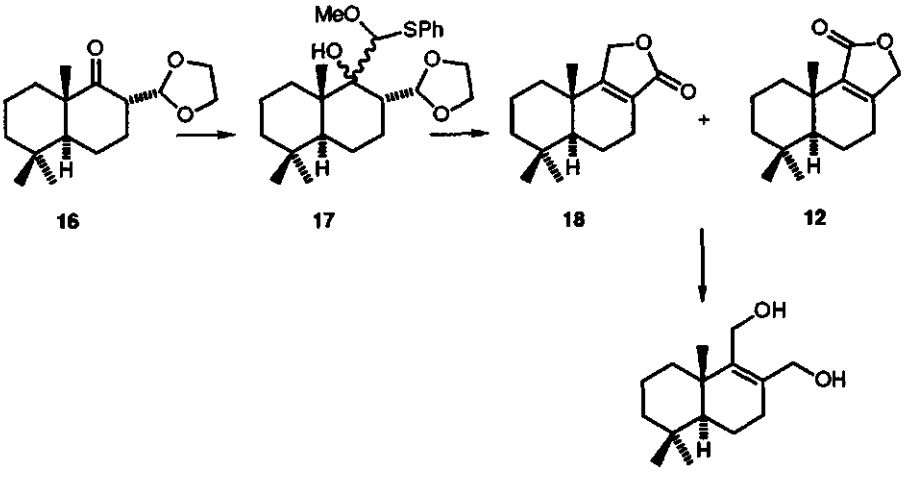


5 **14** **15**

[Fenylthio(methoxy)methyl]lithium is eenvoudig te synthetiseren en het lijkt bij uitstek geschikt om een aldehyde functie in te voeren *via* additie aan carbonyl verbindingen. In hoofdstuk 5 zijn de resultaten vermeld, die met dit reagens zijn verkregen. De additie aan ketonen, aldehyden, α,β-onverzadigde ketonen, α-oxo acetalen en α-(aryl- of alkylthio)methyleen ketonen verliep in hoge opbrengst en de adducten legden om naar α-(fenylthio)aldehyden bij behandelen met thionyl chloride in aanwezigheid van pyridine.

Schema 9.3

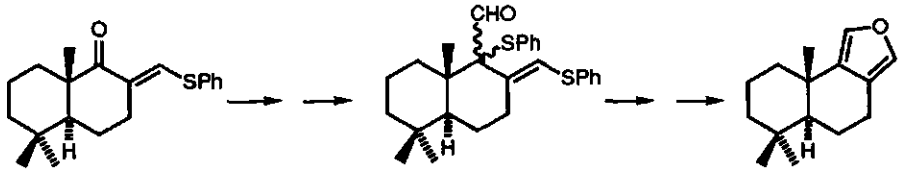




16 **17** **18** **12**

19

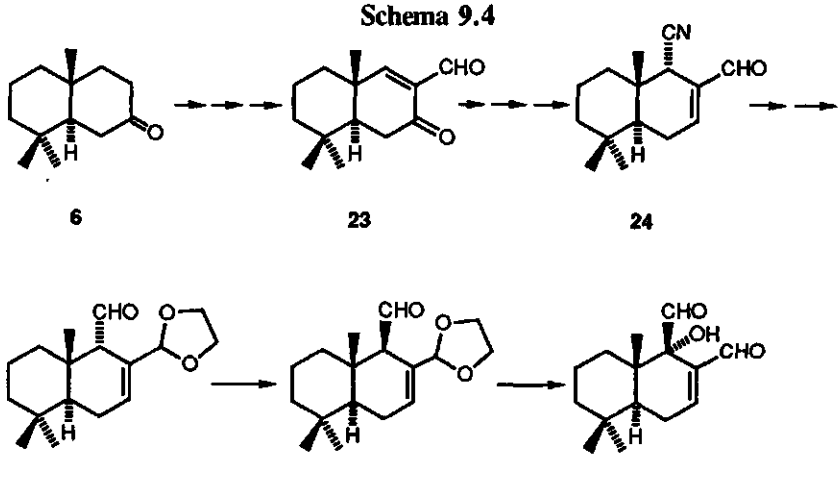
Schema 9.3 (vervolg)



20 **21** **22**

Van deze, nieuw ontwikkelde, methode werd gebruik gemaakt om enkele drimaan sesquiterpenen te synthetiseren, uitgaande van derivaten van keton **4** (zie schema 9.3).
Door formyleren van **4** werd op C-8 een aldehyde groep ingevoerd, welke beschermd werd tegen nucleofiele reagentia door een omzetting in het dioxolaan **16** of in het (fenylthio)methyleen derivaat **20**.
De adducten **17** gaven bij zure hydrolyse een mengsel van **12** en **18**. Hoewel dit mengsel te scheiden was door kolomchromatografie in (±)-isodrimenin **12** en (±)-confertifolin **18**, bleek het doelmatiger dit mengsel te reduceren tot diol **19**, een veel gebruikt intermediair in de totaal synthese van meerdere drimanen.
De adducten van **20** legden om naar tamelijk instabiele aldehyden **21**, en daarom werden deze onmiddellijk gereduceerd. Bij opwerken vond een spontane cyclisatie plaats tot (±)-euryfuran **18**.
Een onverwachte ringverwijding werd waargenomen bij hydrolyse van de adducten **20** in aanwezigheid van kwik (II) chloride.
Hoofdstuk 6 vermeldt de resultaten, die verkregen werden door de synthese van drimanen te beginnen met de *trans*-decalonen **6** en **7**.

Schema 9.4



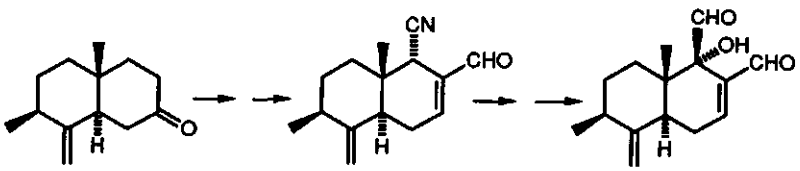
6 **23** **24**

25 **26** **1**

Formylering van **6** gevolgd door dehydrogenering gaf het keto aldehyde **23**. Door additie van HCN gevolgd door reductie van de ß-keto aldehyde functie werd nitril **24** verkregen. Bescherming van de C-8 aldehyde groep gevolgd door reductie van de nitril functie gaf **25**, maar deze verbinding kon niet reproduceerbaar geoxideerd worden. De epimerisatie tot **26** was derhalve van cruciaal belang, omdat het bekend is, dat **26** in warburganal **1** kan worden omgezet. Het bleek mogelijk deze epimerisatie kwantitatief uit te voeren door dit *mono* beschermde dialdehyde **25** gedurende 10 minuten te behandelen met een 5-voudige overmaat kalium-*tert*-butylaat in refluxende *tert*-butyl alcohol. Oxidatie van **26** en hydrolyse gaf (±)-warburganal **1** in 38% totaal opbrengst. (±)-Polygodial **3** werd verkregen door hydrolyse van **26** in een totaal opbrengst van 42%.

Daar alle reagentia en reactieomstandigheden in schema 9.4 verenigbaar zijn met een exocyclische dubbele binding in het molecuul, werd *trans*-decalone **7** gesynthetiseerd en op dezelfde wijze omgezet in (±)-muzigadial **2** in 24% opbrengst (zie schema 9.5).

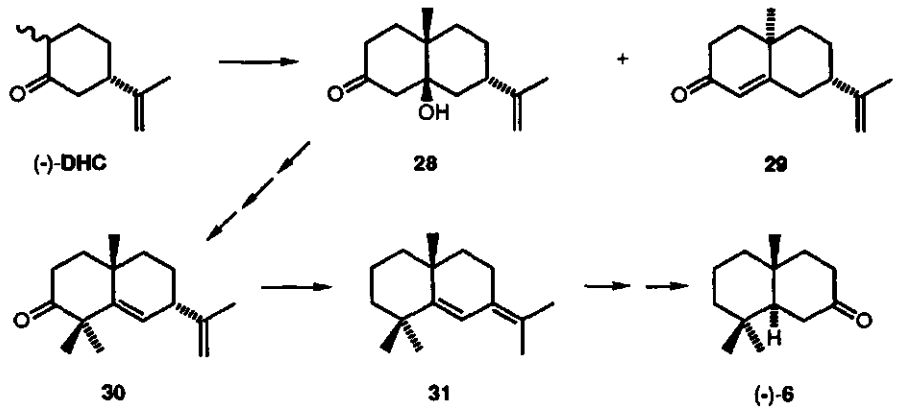
Schema 9.5



7 **27** **2**

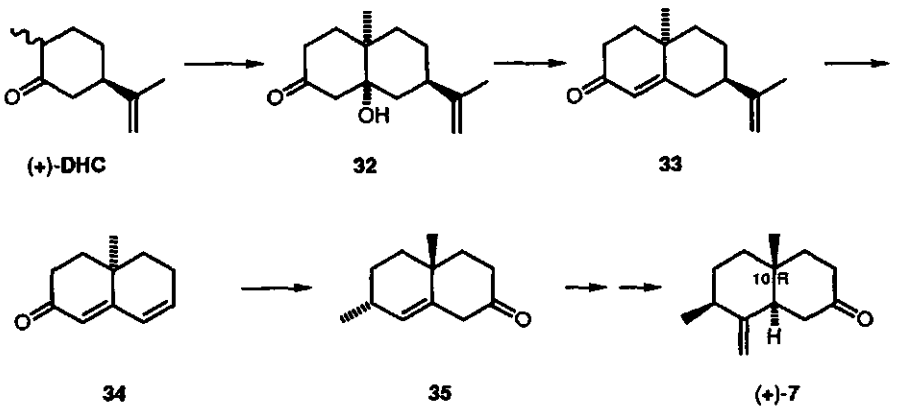
De synthese van de enantiomeerzuivere *trans*-decalonen **6** en **7** is beschreven in hoofdstuk 7, zodat ook de natuurlijk voorkomende enantiomeren van warburganal **1**, muzigadial **2** en polygodial **3** beschikbaar kunnen komen via totaal synthese. De chirale *trans*-decalonen **6** en **7** werden verkregen door uit te gaan van respectievelijk (S)-(+)- en (R)-(-)-carvon. De isopropenyl groep in deze verbindingen werd eerst gebruikt als chiraal handvat en vervolgens omgezet in de gewenste keto functie op C-7.
(-)-Dihydrocarvon, verkregen door lithium brons reductie van (+)-carvon, werd daartoe eerst omgezet in ketol **28**, dat gemakkelijk gezuiverd kon worden door kristallisatie. Ketol **28** kon aldus goed gescheiden worden van eenon **29**, dat in oplossing bleef.
Na dehydratering en dimethylering werd **30** verkregen, dat in één bewerking omgezet werd in **31** onder de condities van de Wolff-Kishner reactie. Ozonolyse en reductie gaf het (-)-*trans*-decalone **6** in 22% totaal opbrengst (zie schema 9.6).

Schema 9.6



(+)-*trans*-Decalone **7**, waaruit (-)-muzigadial gesynthetiseerd kan worden, moet uit (+)-dihydrocarvon gemaakt worden om de gewenste R configuratie op C-10 te krijgen. De isopropenyl groep in **33** werd omgezet in een dubbele binding door ozonolyse gevolgd door oxidatie met koper (II) acetaat en ijzer (II) sulfaat. Na een 1,6 additie van dimethylkoper lithium ontstond het eenon **35**, dat omgezet werd in (+)-**7** in een opbrengst van 14% op een wijze, die eerder ontwikkeld is op ons laboratorium (zie schema 9.7).

Schema 9.7



Samenvattend kan gesteld worden, dat gemakkelijk toegankelijke *trans*-decalonen efficiënt gebruikt zijn om meerdere drimaan sesquiterpenen te synthetiseren.
In het bijzonder werd een goede synthese route ontwikkeld voor de biologische actieve drimanen warburganal **1**, muzigadial **2** en polygodial **3**.

CURRICULUM VITAE

De auteur van dit proefschrift werd op 2 januari 1945 te Wehl geboren.
Na het behalen van het HBS-B diploma aan het Ludgercollege te Doetinchem in 1962, werkte hij tot 1968 op het AKU Research Laboratorium te Arnhem.
Tijdens deze periode werden de avondopleidingen analist (KNCV) en technisch chemicus (PBNA) gevolgd.
Van 1968 tot 1972 was hij werkzaam op het Unilever Research Laboratorium te Duiven.
In 1970 werd de deeltijdstudie MO-A natuur- en scheikunde aan de Rijksuniversiteit Utrecht aangevangen. Deze opleiding werd in 1973 afgesloten met het examen.
Na ruim een jaar verbonden te zijn geweest aan de OLAN te Arnhem als praktijkdocent werd in 1973 een werkkring aanvaard bij de vakgroep Organische Chemie van de Landbouwuniversiteit, eerst als analist en na 1986 als universitair docent.
De scheikunde studie werd voortgezet als deeltijdstudie aan de Rijksuniversiteit Utrecht en het kandidaatsexamen (S1) werd in december 1977 afgelegd. Na een onderbreking van enkele jaren werd de draad weer opgepakt en in februari 1989 werd het doctoraal examen afgelegd met als hoofdvak organische chemie (prof.dr. H.J.T. Bos) en als bijvak geschiedenis der natuurwetenschappen (prof.dr. H.A.M. Snelders).

Het in het proefschrift beschreven onderzoek werd onder leiding van prof.dr. Ae. de Groot uitgevoerd van 1981 tot 1988.
Daarnaast werd een gedeelte van de tijd besteed aan niet in dit proefschrift beschreven onderzoek en aan het begeleiden van studenten in diverse fasen van hun studie.