THE TOTAL SYNTHESIS OF 3β-HYDROXYNAGILACTONE F

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STELLINGEN

1 Het door Gold et al. uit Phanerochaete chrysosporium geïsoleerde waterstofperoxide-afhankelijke lignine-afbrekend enzym wordt door de auteurs ten onrechte een oxygenase genoemd.
M. Kuwahara, J.K. Glenn, M.A. Morgan en M.H. Gold, FEBS Letters, 1984, 169, 247.

2 De schematische voorstelling van het enzym-substraat complex, gepubliceerd door Sammes et al. en door Angelino, biedt weinig perspektief.
S.A.G.F. Angelino, Chemisch Magazine, 1984, 201.
P.G. Sammes, S. Smith en G.T. Woolley, J.Chem.Soc., Perkin Trans I, 1984, 2603.

3 Voor de regioselectieve formylering, die door Lallemand et al. wordt gevonden, is een plausibele verklaring te geven.
D. Guillerm, G. Boussac, J. Lalande, P. Lemaitre en J.-Y. Lallemand, Synth. Commun., 1981, 11, 627.

4 De opmerking van Hart et al. over het gebruik van methanol in plaats van ethanol/HCl voor de $NaBH_4$ reductie van imides is niet terecht.
D.A. Burnett, J.-K. Choi, D.J. Hart en Y.-M. Tsai, J.Amer.Chem. Soc., 1984, 106, 8201.

5 De vorming van de β-seleno-γ-lactonen, die Clive et al. vinden in hun mechanistisch onderzoek naar de cyclofunctionalisering van onverzadigde carbonzuren onder invloed van fenylselenenyl chloride wordt ten onrechte niet toegelicht.
D.L.J. Clive, C.G. Russell, G. Chittattu en A. Singh, Tetrahedron, 1980, 36, 1399.

6 De in het computergebruik veel gebezigde term compatible moet met de nodige scepsis worden bekeken.

7 Voor het door Kende et al. gesignaleerde verschil in de productsamenstelling van de transpositionele allyloxidatie, die door hem en andere auteurs wordt gevonden, wordt de mogelijke invloed van de substituenten niet onderkend.
A.S. Kende, B. Roth en I. Kubo, Tetrahedron Lett., 1982, 23, 1751.

8 Het mechanisme. dat door Tanikaga et al. wordt aangegeven voor de vorming van dieenesters uit 2-gesulfinyleerde α,β-onverzadigde esters,is twijfelachtig.
R. Tanikaga, Y. Nozaki, M. Nishida en A. Kaji, Bull.Chem.Soc.Jap., 1984, 57, 729.

J.T.A. Reuvers Wageningen, 1 mei 1985

The total synthesis of 3β-hydroxynagilactone F.

Aan mijn ouders
Voor Bertine

CONTENTS

GENERAL INTRODUCTION

The nor- and bisnorditerpenoid dilactones, isolated from different species of the *Podocarpaceae* form a class of compounds which exhibit a remarkable number of physiological activities. Among these activities are plant-growth regulatory activity, insecticidal and fungicidal activity. Moreover, some members show cytotoxic activity *in vitro* against cells derived from both human carcinoma of nasopharynx (KB) and P-388 murine leukemia. *In vivo* anti-tumor activity against P-388 leukemia in mice has been reported.

In order to study this wide range of biological activities, an efficient total synthesis of the diterpenoid dilactones is required. In addition to the synthesis of the natural products the synthetic route designed should render the synthesis of derivatives possible. The second stage would be a thorough investigation into the structure-activity relations of the natural products and synthetic derivatives. Systematic evaluation of these results and those reported in the literature might lead to a better understanding of the physiological activities at molecular/receptor level. This thesis deals with the investigations aiming at the development of synthetic routes towards this class of natural products, leading to the total synthesis of one member *i.e.* 3β-hydroxynagilactone F.

Parts of this thesis have been published:

- "Functionalized dienes *via* thermolysis of allylic sulfoxides", Ae. de Groot, B.J.M. Jansen, J.T.A. Reuvers, and E.M. Tedjo, *Tetrahedron Lett.*, 1981, **22**, 4137.
- "Synthesis of δ-substituted δ-lactones", J.T.A.Reuvers and Ae. de Groot, *Synthesis*, 1982, 1105.
- "Stereoselective synthesis of ±-octahydronaphthalene-1(2*H*)-ones *via* homogeneous hydrogenation of ±-tetrahydronaphthalenones", J.T.A. Reuvers and Ae. de Groot, *J.Org.Chem.*, 1984, **49**, 1110.
- "The stereoselective synthesis of an intermediate in the total synthesis of diterpene mono- and dilactones", J.T.A. Reuvers, J.B.P.A. Wijnberg, and Ae. de Groot, *Recl.Trav.Chim.Pays-Bas*, 1984, **104**, 16.

LIST OF ABBREVIATIONS

Ac	acetyl
m-CPBA	*meta*-chloroperbenzoic acid
DDQ	2,3-dichloro-4,5-dicyano-quinone
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DPH	dihydropyran
HMPA	hexamethylphosphoric triamide
Im	imidazole
LDA	lithium diisopropylamide
Me	methyl
MED	2-Methyl-2-ethyl-1,3-dioxolane
MSA	mesitylenesulfonic acid
NBS	N-bromosuccinimide
Ph	phenyl
PhH	benzene
pyr.HBr.Br_2	pyridinium bromide perbormide
THF	tetrahydrofuran
TLC	thin layer chromatography
TSOH	*para*-toluenesulfonic acid

1 OCCURRENCE, STRUCTURE, BIOSYNTHESIS AND BIOLOGICAL ACTIVITY OF DITERPENOID DILACTONES

1.1 OCCURRENCE AND STRUCTURE

In 1968 Takahashi published the structure of a norditerpenoid dilactone isolated from the wood of *Podocarpus macrophyllus* D. Don[1,2]. Since then more than 40 nor- and bisnorditerpenoid dilactones have been isolated from 17 species of *Podocarpus* plants (see Table 1.1, p.2). The genus *Podocarpus* includes 80 species, ancient gymnosperms growing in scattered parts in the tropical and subtropical areas of eastern Asia and the southern hemisphere[3]. The compounds are isolated from different parts of the plants, *i.e.* wood, leaves, roots, bark and seeds and they may have chemotaxonomical significance[4]. More important however is the wide range of biological activities these diterpenoid dilactones display (see chapter 1.3).

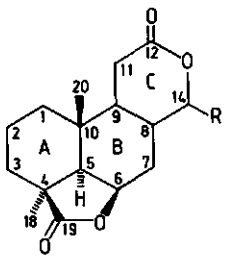


figure 1.1

All lactones possess the same basic ring system, shown in figure 1.1, and the general features are: the *trans*-fused AB ring system; ring C is made up of a δ-substitued δ-lactone and a γ-lactone is annellated to the AB ring system. All of the known diter-

penoid dilactones can be classified into 3 subgroups, depending upon the structure of the BC ring system:

type A: 8(14),9(11)-dienolide (Table 1.2, p.3),

type B: 7α,8α-epoxy-9(11)enolide (Table 1.3, p.4) and

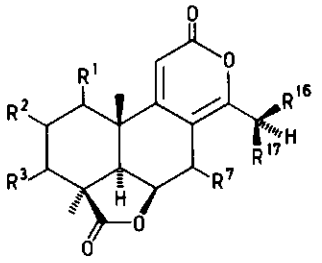
type C: 7(8),9(11)-dienolide (Table 1.4, p.6)[5,49].

Within each subgroup the structures differ in the oxidation state of ring A and B and in the substituent R attached to C-14. Besides the diterpenoid dilactones from *Podocarpus* species some metabolites with the same carbonskeleton were isolated from an unidenti fied species of *Acrostalagmus* fungus[32] and from the fungii *Asper gillus Wentii*[31] and *Oidiodendron truncatum*[26]. The compound LL-Z1271α (49) isolated from *Acrostalagmus* has a methoxy group at the

Table 1.1 Plantsources of the diterpenoid dilactones

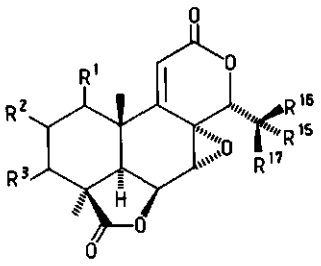
Podocarpus	*sellowii*	Klotzsch
P	*nagi*	(Thunberg) Pilger
P	*macrophyllus*	D. Don
P	*hallii*	Kirk
P	*nubigena*	Lindley
P	*nivalis*	Hook
P	*lambertii*	Klotzsch
P	*gracilor*	Pilger
P	*neriifolius*	D. Don
P	*salignus*	D. Don
P	*nakaii*	(Hayata) Li et Keng
P	*milanjianus*	Rendl
P	*purdieanus*	Hooker
P	*polystachus*	R. Br.
P	*philippinensis*	Foxworthy
P	*andinus*	Peoppigg ex Endlicher
P	*elatus*	R. Br.

Table 1.2. Dilactones of type A



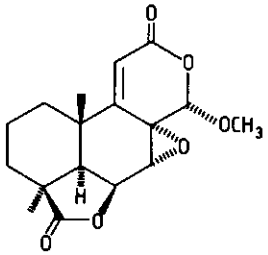
no.	Compound name	R 1	2	3	7	16	17
1	sellowin C[6]	-	-	β OH	β OH	CH_3	CH_3
2	nagilactone A[7]	β OH	-	-	β OH	CH_3	CH_3
3	inumakilactone E[8]	β OH	-	-	β OH	CH_2OH	CH_3
4	1-deoxy-2α-hydroxy-nagilactone A[9]	-	α OH	-	β OH	CH_3	CH_3
5	nagilactone B[7]	β OH	β OH	-	β OH	CH_3	CH_3
6	3 -hydroxy-nagilactone A[10]	β OH	-	β OH	β OH	CH_3	CH_3
7	1-deoxy-2 ,3 -epoxy nagilactone A[11]	-	β -O-		β OH	CH_3	CH_3
8	nagilactone C[7]	β -O-		β OH	β OH	CH_3	CH_3
9	nagilactone D[7]	β -O-		β OH	-	H	CH_3
10	15-methoxycarbonyl-nagilactone D[9]	β -O-		β OH	-	CH_3	$COOCH_3$
11	hallactone A[22]	β -O-		β OH	-	CH_3	CH_3
12	15-hydroxy-nagilactone D[10]	β -O-		β OH	-	OH	CH_3
13	1,2-deoxy-1,2-dihydroxy-nagilactone D[10]	β OH	β OH	β OH	-	H	CH_3
14	urbalactone[12]	-	β OH	β OH	-	CH_3	CH_3

Table 1.3 Dilactones of type B

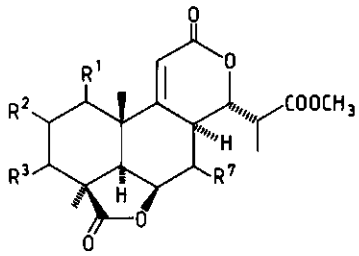


		R					
no.	Compound name	1	2	3	15	16	17
15	nagilactone G[13]	-	-	-	-	CH_3	CH_3
16	salignone H[14]	-	-	-	-	CH_2OH	CH_3
17	salignone H'[15]	-	Δ		-	CH_2OH	CH_3
18	salignone D[16]	-	-	-	-		$CH{=}CH_2$
19	salignone F[15]	-	-	-	OH	CH_2OH	CH_3
20	salignone G[15]	-	βOH	-	-	CH_3	CH_3
21	nagilactone E[17]	-	-	βOH	-	CH_3	CH_3
22	2β,3β-epoxypodolide[18]	-	β-O-		-	CH_3	CH_3
23	sellowin B[6]	-	β-O-		-		CH CH_2
24	sellowin A[6]	-	β-O-		-	CH_3	CH_2OH
25	podolactone A[19,20b]	-	β-O-		OH	CH_2OH	CH_3
26	podolactone C[20,21]	-	β-O-		OH	CH_3	$CH_2S(O)CH_3$
27	hallactone B[22]	-	β-O-		OH	CH_3	$CH_2S(O)_2CH_3$
28	inumakilactone A[2,8]	β-O-		βOH	-	CH_3	OH
29	inumakilactone B[23]	β-O-		βOH	-		CH CH_2
30	podolactone B[19,20b]	β-O-		βOH	OH	CH_3	$COOCH_3$
31	milanjilactone A[24]	Δ		-	-	CH_3	CH_3
32	podolide[25]	-	Δ		-	CH_3	CH_3
33	salignone E[20]	-	Δ		-	CH_2OH	CH_3
34	podolactone D[20]	-	Δ		OH	CH_3	$CH_2S(O)CH_3$
35	dihydropodolide[18]	-	-	-	-	CH_3	CH_3

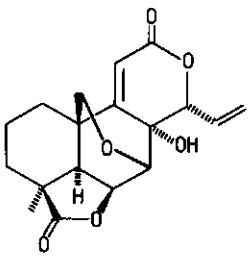
Table 1.3 continued



36 7α,8α-epoxy-LL-Z1271α[26],*iii*



no.	compound name	R
37	salignone B[15]	R^1=R^7=βOH, R^2=R^3=H*ii*
38	salignone C[15]	R^1=R^7=βOH, R^2, R^3=β-O-*ii*
39	salignone J[27]	R^1=H, R^2, R^3=β-O-*ii*, R^7=H



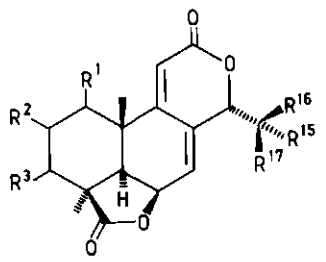
40 salignone A[14],*ii*

i *Also isolated as a glucoside*[8].

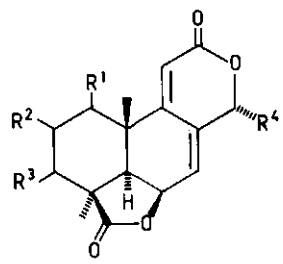
ii *Structures in ring B derived from the 7α,8α-epoxide.*

iii *Isolated from the fungus Oidiodendrum truncatum*[26].

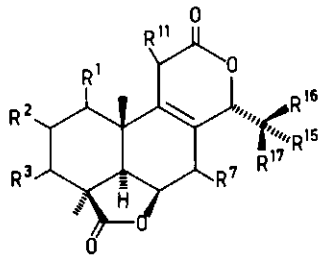
Table 1.4 Dilactones of type C



		R					
no.	compound name	1	2	3	15	16	17
41	nagilactone F[17]	-	-	-	-	CH_3	CH_3
42	3 -hydroxynagilactone F[11]	-	-	βOH	-	CH_3	CH_3
43	nubilactone A[28]	β-O-		βOH	-	CH_3	$COOCH_3$
44	ponalactone A[29]	β-O-		βOH	-	CH_3	CH_3 *i*
45	milanjilactone B[24]	Δ		-	-	CH_3	CH_3
46	podolactone E[30]	β-O-		βOH	-		$CH{=}CH_2$



47	wentilactone A[31]	R^1, $R^2{=}\beta$-O-, $R^3{=}\beta$OH, $R^4{=}H$ *ii*
48	wentilactone B[31]	$R^3{=}\beta$OH, $R^1{=}R^2{=}R^4{=}H$ *ii*
49	LL-Z1271α[32]	$R^1{=}R^2{=}R^3{=}H$, $R^4{=}OCH_3$ *iii, iv*
52	LL-Z1271γ[32]	$R^1{=}R^2{=}R^3{=}H$, $R^4{=}OH$ *iii*



50	inumakilactone C[23]	R^1, R^2=β-O-, R^3=βOH, R^7=αOH, R^{11}=OH, R^{15}=H, R^{16}=OH, R^{17}=CH_3
51	inumakilactone D[33]	R^1, R^2=β-O-, R^3=βOH, R^7=αOH, R^{11}=H, R^{15}=H, R^{16}=OH, R^{17}=CH_3

i *Also isolated as a glucoside*[29].

ii *Isolated from the fungus Aspergillus Wentii*[31].

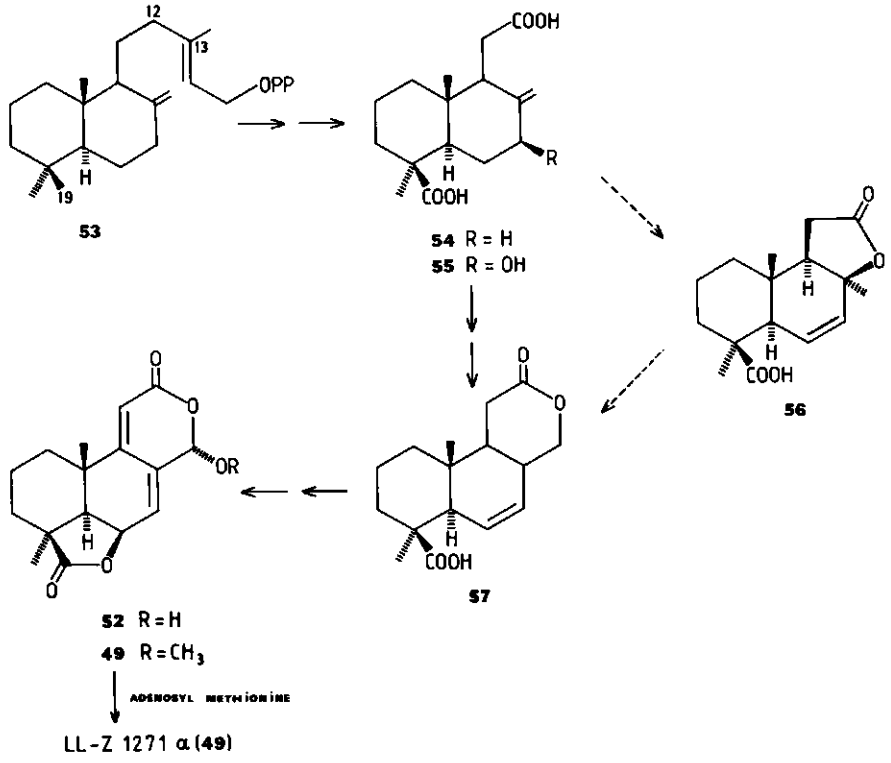
iii *Isolated from an unidentified species of Acrostalgmus*[32].

iv *Isolated from the fungus Oidiodendron truncatum*[26].

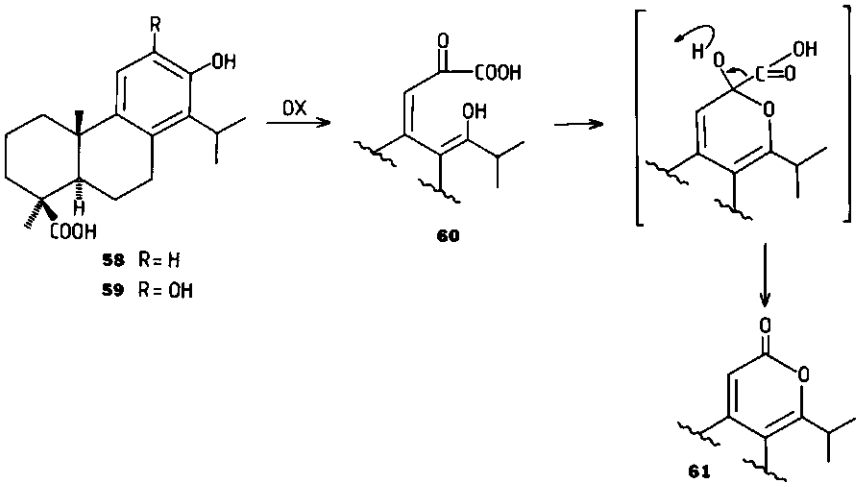
the δ-position of ring C, as has the 7α,8α-epoxy derivative 36 isolated from *Oidiodendron truncatum*. The compounds 47 and 48 found in *Aspergillus Wentii* have no substituent at all at the C-14-position.

1.2 BIOSYNTHESIS

The biosynthesis leading to the fungal metabolite 49 has been published in the literature[34,35]. In a biosynthetic study in the *Acrostalagmus* species Kakisawa and Sato[34] postulated a pathway (see scheme 1.1) which involves the diterpenoid precursor labdadienol 53 formed by a proton initiated cyclization of geranylgeranylpyrophosphate[35]. Conversion of 53 into acrostalic acid 54 by oxidative cleavage between C-12 and C-13 is accompanied by oxidation of C-19. Acid 54 can be oxidized to 55 and transformed into lactone 57 *via* proton initiated cyclization and dehydration.



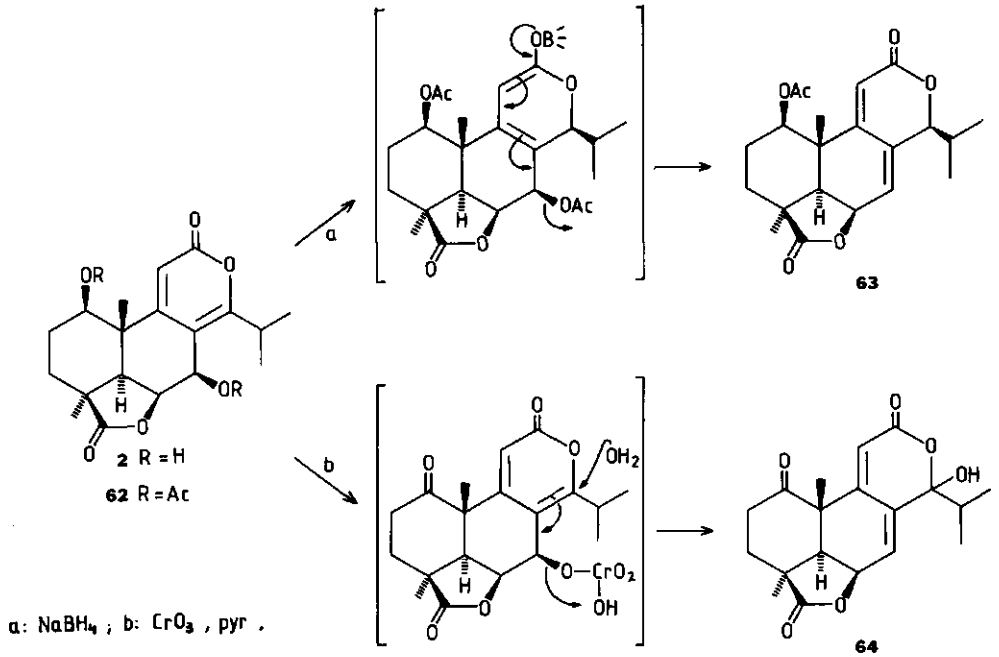
scheme 1.1



scheme 1.2

A second cyclization and oxidation then gives the product LL-Z1271γ (52). Methylation gives the metabolite LL-Z1271α (49). This pathway is strongly supported by the isolation of three metabolites acrostalidic acid (57) acrostalic acid (54) and isoacrostalidic acid (56) occurring in this scheme besides the lac-tones LL-Z1271α (49), LL-Z1271γ (52) and the diacid LL-Z1271β (55).

The group of diterpenoid dilactones isolated from species of *Podocarpaceae* are thought to be derived from totarol or totaroloic acid (58)[36]. Hydroxylation of totaroloic acid (58) to compound 59 and subsequent meta-pyrocathechase type fission, which is known from catechol metabolism, produces a diketo acid 60 which cyclizes and decarboxylates to give an α-pyron, an intermediate for type A dilactones (see scheme 1.2)[7]. Chemical conversions on nagilactone A (an A type dilactone) clearly indicate possible biochemical pathways to type B and C. Hayashi found that treatment of nagilac-



scheme 1.3

tone A diacetate (62) with sodium borohydride affords a dilactone 63 of type C, thus establishing the chemical correlation of types

A and C, although this chemical reduction gives the C-14 epimer of the naturally occurring diterpenoid dilactones (see scheme 1.3)[7]. Oxidation of nagilactone A (2) with CrO_3 gives a product 64 that also has the 7(8),9(11)-dienolide structure. Type C dilactones may be transformed into type B dilactones *via* α-epoxidation.

1.3 BIOLOGICAL ACTIVITY OF DITERPENOID DILACTONES

1.3.1 Insect toxicity

The nor- and bisnorditerpenoid dilactones show a wide range of biological activities[5,37]. Inumakilactone A (28) possesses strong termiticidal activity and is held responsible for the termite resistance of Inumaki wood (*Podocarpus macrophyllus* D. Don) from which it was isolated by Saeki[38].

Observations of Russell and Dugdale that *Podocarpus* plants are host to only a few monophagous insects initiated an investigation on the insect moulting hormone activity in *Podocarpus nivalis* Hook and *Podocarpus hallii* Kirk. This research revealed that leaf material from these plants incorporated into the diet of larvae of the housefly (*Musca domestica* L.), of the codling moth (*Laspeyresia pomonella*) and of the light-brown apple moth (*Epiphyas postvittana*) showed toxic effects. Complete mortality was ascertained for the larvae of the housefly[39]. Examination of the extracts of leaf material resulted in the isolation of nagilactone C (8), responsible for the activity. This compound proved to be lethal at a level of 50 ppm. Recent investigations on housefly larval development, pupation and adult emergence revealed a strong toxicity of nagilactone D (9) with a LD_{50} value of 1 ppm (LD_{50}= lethal dosis for 50% mortality) while 11 other dilactones tested were 10-100 times less active[40,41]. Podolactones A (25) and E (46) and hallactone A (11) were also tested by topical application to larvae and adults, but no mortality resulted. This reveals that the compounds do not possess contact toxicity. The two possible explanations for the activity are toxicity by oral ingestion or antifeedant activity.

1.3.2 Anti-tumor activity

Podolide (32) is known to have antitumor activity *in vivo* against P-388 leukemia in mice and cytotoxicity *in vitro* towards cells of human carcinoma of nasopharynx (KB) and P-388 murine leukemia[25]. Comparable strong cytotoxicity and antileukemia activity was reported for nagilactones B to G (5,8,9,21,41 and 15) and milanjilactones A (31) and B (45). All of them exhibited IC_{50} values of 10^{-3}-10^{-4} mM against cultures of all the aforementioned cancer cells[21].

1.3.3 Plant-growth regulatory activity

One of the most studied features of the diterpene dilactones is the plant-growth inhibitory activity. Systematic studies of the activities of a number of dilactones revealed strong inhibition of expansion and mitosis of plant cells[19a,43,44]. The three bioassays examined are growth inhibition of hook segments from etiolated dwarf peas (Sasse[45]), competitive inhibition in indolyl-3-acetic acid-induced elongation of segments of *Avena coleoptile* (Hayashi[46]) and inhibition of the growth of Jerusalem artichoke tuber tissue[46,47]. The results of the first two bioassays are gathered in Table 1.5 (p.12).

The conclusion that can be drawn from these facts is that dilactones of all three types show inhibitory activity. Hayashi reported on the inhibitory activity of nagilactones A to D at concentrations of 10-100 μM but the reverse, *i.e.* promoting, activity was observed at lower concentrations (10-100 nM)[17]. Sasse reported on the physiological effects in some other bioassays thus establishing the inhibition of growth of many other plant tissues. It appears that the more active compounds have an epoxy group in ring A as well as a relatively small non-polar side chain at C-14. Some interpretations of structure-activities with relation to ring A epoxy substituents must be revised since revised structures are reported for dilactones with such epoxides[20b,44]. In addition the α,β-unsaturated δ-lactone appears to be most essential for activity; the saturated derivatives are completely inactive[44].

1.3.4 Activity of the fungal metabolites

The tetranorditerpenoid dilactones isolated from some fungi exhibit activity against fungal infections. Moreover significant plant growth inhibition is observed[34,35]. The latter effect is comparable with those of the dilactones discussed (*vide supra*). LL-Z1271α (49) possesses activity against a form of ringworm infections in guinea pigs[32].

Table 1.5 Inhibitory activity of lactones

	Hook segment[i] % of control growth at[44]		Avena coleoptile segment[46] conc. of lactones (μM) for 50% growth inhibition[ii]	
Compound No	1 μM	10 μM	IAA:1.7 μM	IAA:170 nM
type A				
5	-	81	70	70
2	-	79	50	70
8	89	53	60	40
9	72	15	3.0	2.0
type B				
26	100	70	-	-
34	98	60	-	-
30	82	60	-	-
21	-	-	5.0	1.0
25	88	37	-	-
28	66	34	3.0	1.0
29	47	10	2.0	1.0
type C				
44	-	-	3.0	1.0
46	38	-	0.1	0.1
50	102	0	inactive	inactive

i Etiolated dwarf peas.

ii Competitive inhibition in indoleacetic acid (IAA)-induced elongation at given IAA concentrations.

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49. Although it may appear somewhat confusing the notations of type, ring and the names, all three with capital letters, is consistent with the literature.

2 SYNTHETIC STUDIES ON DITERPENOID DILACTONES

2.1 CHEMICAL REACTIVITY AND INTERCONVERSIONS OF DILACTONES

A great number of reports on the isolation and structure determination of diterpenoid dilactones have appeared in the literature. The publications which deal with their reactivity mostly concern the preparation of simple derivatives for structure elucidation and reactions aiming at stereochemical correlation with dilactones of known structure. The functional groups in these compounds turn out to be unusually stable towards common reagents. This may be due to stereochemical shielding of the functional groups and to the poor solubility of the dilactones in organic solvents[1,2].

The β-epoxides in ring A of some dilactones of type B are susceptible to acidic hydrolysis, this in contrast with the

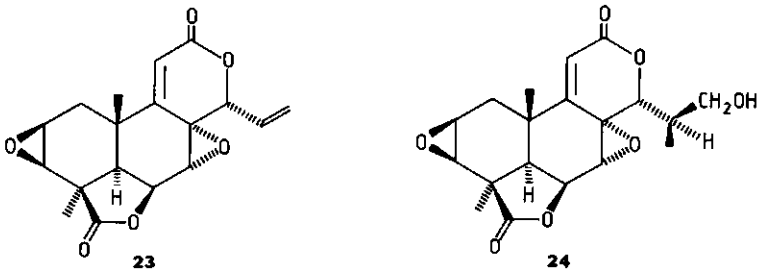
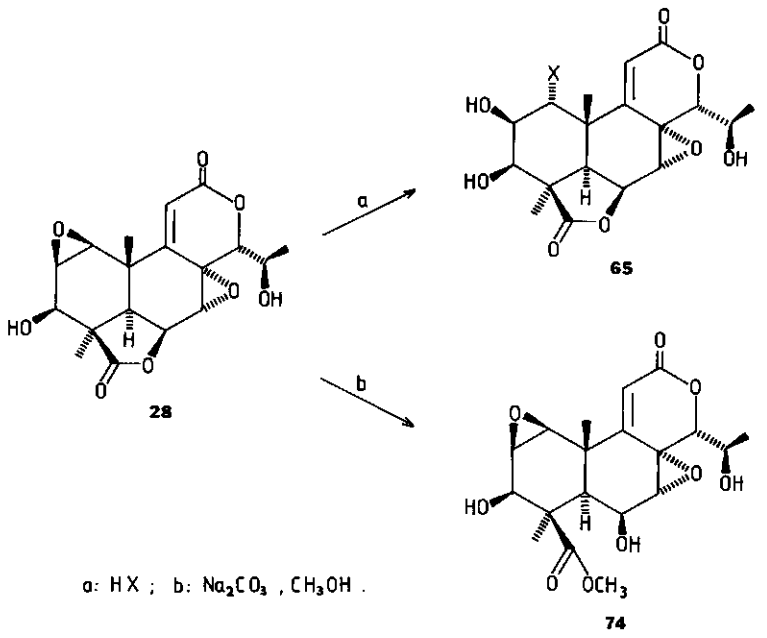
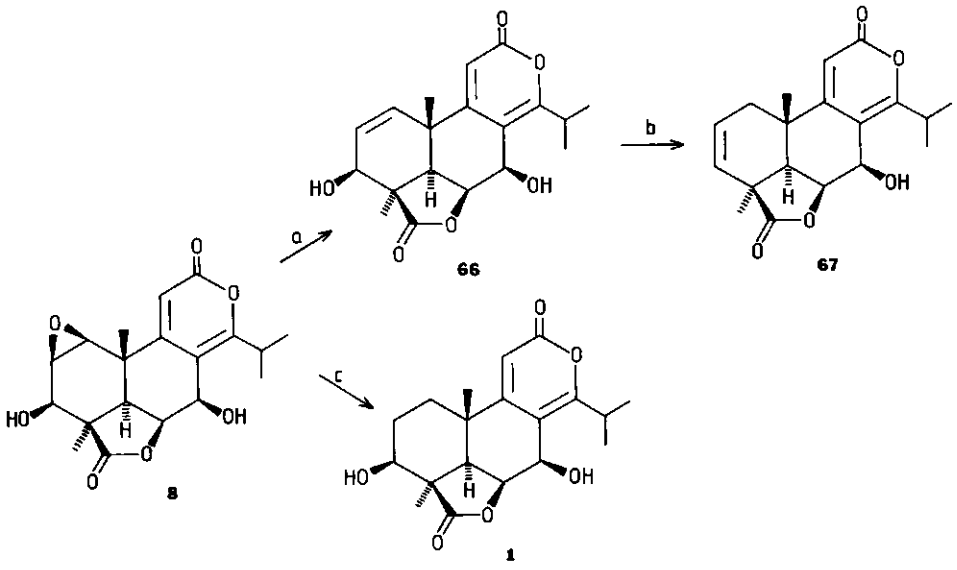


figure 2.1

α-epoxy group in ring B. For instance sellowin A (24) and B (23) (see figure 2.1) and inumakilactone A (28) are reported to give epoxide cleavage to halohydrins in diluted hydrochloric or bromic acid[2,3](scheme 2.1). Inumakilactone A was reported to afford a halohydrin with a 1β-halo-2α-hydroxy configuration. In this report the α-configuration was assigned to the epoxy group. In 1975 however Godfrey and Waters published their results of an X-ray



scheme 2.1



scheme 2.2

analysis of inumakilactone A (28)[4], which showed unambiguously that the epoxy group was in a β-position. This implicated that the structures of the halohydrins formed after epoxy cleavage had to be corrected to the 1α-halo-2β-hydroxy derivatives 65 (scheme 2.1). Interestingly attempted opening of the epoxide in nagilactone C (8) (structure in scheme 2.2) with trifluoroacetic acid failed whereas sellowin B (23) gave a diol mono-trifluoroacetate.

Because structures of a number of other dilactones had been assigned by analogy to inumakilactone A these had to be modified in the same manner (*e.g.* inumakilactone B (29) and C (50), podolactone B (30), nagilactone C (8) and D(9)).

The ring A epoxide in nagilactone C (8) could be deoxygenated to an allylic alcohol 66 by employing a chromium (II) reagent $Cr(ClO_4)_2$, ethylenediamine, DMF (scheme 2.2)[6]. Brown and Sanchez reported on the deoxygenation of nagilactone C (8) to the dilactone 1. Instead of the above mentioned ethylenediamine complex they used $Cr(ClO_4)_2$ or Zn-Cu as reducing agents. In this manner sellowin C (1) was structurally correlated to nagilactone C(8) in one step[2]. The allylic alcohol 66 was subjected to hydrogenation with palladium on charcoal. This resulted in a complex reaction mixture and 67, with a 2,3-double bond, could only be isolated as pure compound after extensive purification. The olefinic protons H-2 and H-3 appeared in the ^1H NMR at 5.88 ppm as a broad triplet. These values are consistent with those of the 2,3 olefinic protons of podolide (32) (structure in figure 2.2).

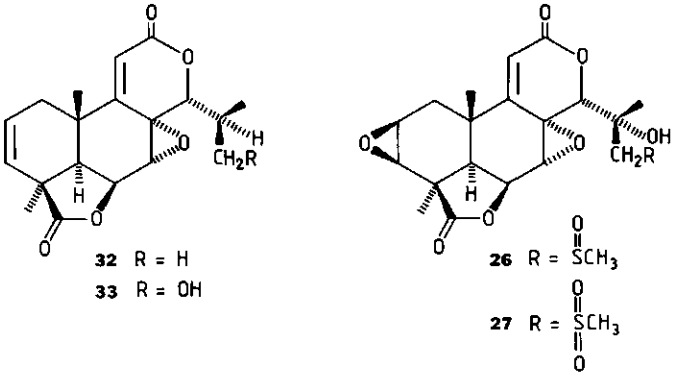
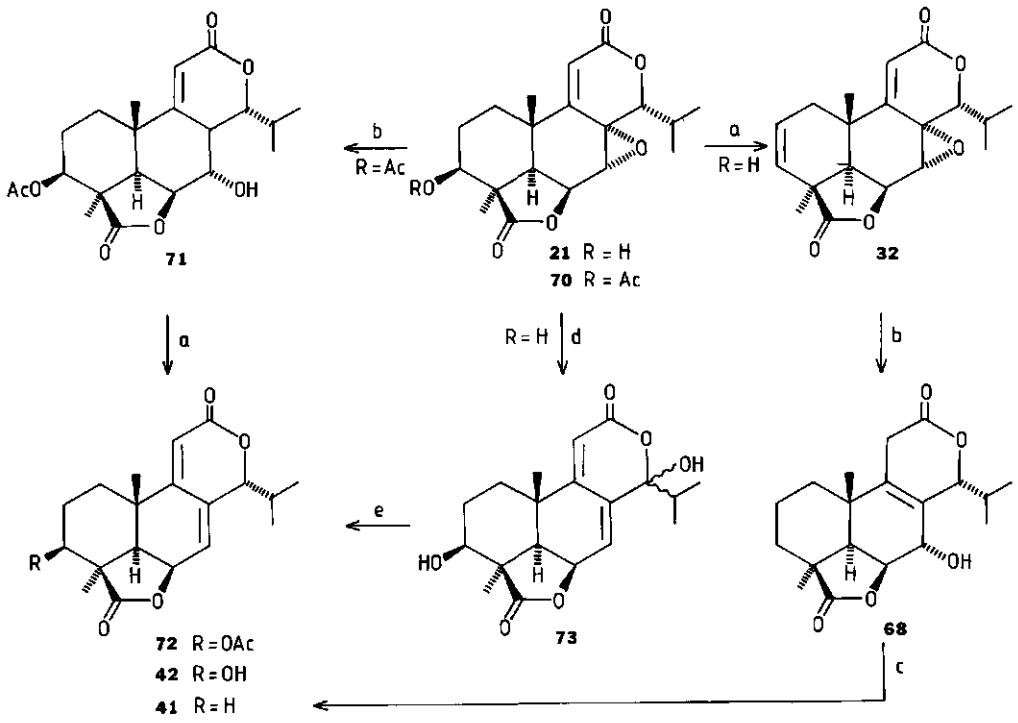


figure 2.2

Correlation of podolide (32) and salignone E (33) (see figure 2.2.) with the natural dilactones 2β,3β-epoxypodolide (22) and sellowin A (24) failed because epoxidation with *m*-CPBA occurs at the less hindered side to produce the corresponding α-epoxides[5].

An interesting interconversion is that of nagilactone E (21) to nagilactone F (41) *via* podolide (32) (scheme 2.3). Dehydration of



a: $POCl_3$, pyr ; b: Pd/C, H_2 ; c: CH_3SO_2Cl , pyr ; d: Al_2O_3 , PhH ; e: $NaBH_4$, EtOH.

scheme 2.3

the 3β-hydroxyl group of 21 with phosphorus oxychloride in refluxing pyridine affords a product identical in every respect to podolide (32). Hydrogenation of 32 gives a mixture of products from which a tetrahydro derivative 68 was obtained in 65% yield. This compound 68 was then dehydrated with methanesulfonyl chloride in pyridine to nagilactone F (41)[6]. Hydrogenation of nagilactone E acetate (70) produces a 7α-hydroxy-9(11)-enolide 71 which can be

dehydrated with phosphorus oxychloride to 3β-hydroxynagilactone F acetate (72).

Other functional group transformations were established by Hayashi. Treatment of nagilactone E (21) with alumina in refluxing benzene gave 73 in a moderate yield. Reduction of this compound with sodium borohydride afforded 3β-hydroxynagilactone F (42) (scheme 2.3)[6]. The interconversions of type A into type C dilactones were described previously (see chapter 1.2); this was illustrated by the conversion of nagilactone A diacetate 62 into dilactone 63. The product, however, had the epimeric configuration at C-14. This epimeric structure could be assigned because the compound lacked an allylic ($J_{7,14}$= 2.0Hz) and a homoallylic ($J_{6,14}$= 2.0Hz) coupling in the ^{1}H NMR, both characteristic of type C dilactones.

The γ- as well as the δ-lactone can be opened by alkali. On treatment with sodium carbonate in methanol the γ-lactone of inumakilactone A (28) opens preferentially to give the trihydroxy ester 74 (scheme 2.1)[8]. This reaction was also observed for some of the other dilactones[9].

Furthermore some simple transformations of the sidechain at C-14 have been studied, which simplified the structure elucidation of newly isolated diterpenoid dilactones. An example of such a reaction is the oxidation of the sulfoxide group in the side chain of podolactone C (26) with *m*-CPBA to the sulfone *i.e.* hallactone B (27)[10] (see figure 2.2).

2.2 SYNTHESIS OF DITERPENOID DILACTONES

2.2.1 Introduction

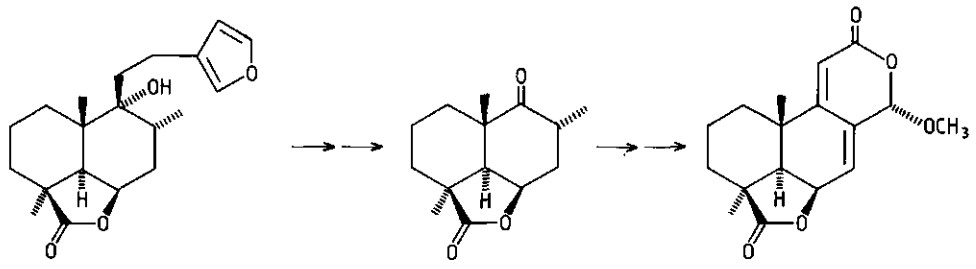
Until August 1984 two total syntheses of LL-Z1271α, the metabolite isolated from *Acrostalagmus* species, had been published, one by Adinolfi *et al.*(see chapter 2.2.2) and another by Welch *et al.* (chapter 2.2.3). Both syntheses started with a suitable AB ring system in which the γ-lactone was constructed first; the carbonyl group at C-9 served as a starting point for the annellation of the

δ-lactone.

In 1982 Hayashi published the first total synthesis of a norditerpenoid dilactone: nagilactone F (41). This synthesis started from the natural product, (S)-(+)-podocarpic acid, a resin acid of which structure and absolute configuration have been established and which is commercially available.

2.2.2 Synthesis of LL-Z1271α by Adinolfi and coworkers

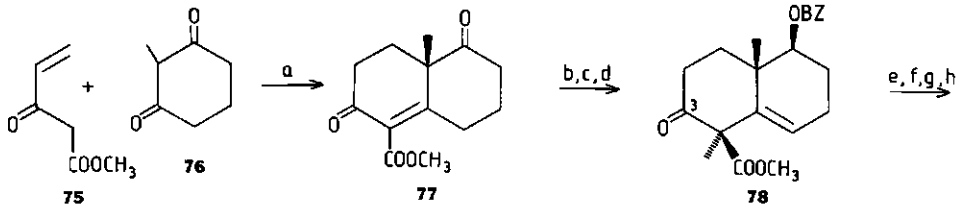
In 1973 Adinolfi and coworkers published a synthesis of the antibiotic LL-Z1271α (49)[12]. As starting material they chose the ketolactone 84, which was easily obtained by degradation of marrubiin, a diterpene lactone isolated from *Marrubium vulgare* (scheme 2.4). The preparation of 84 was accomplished one year earlier when Adinolfi succeeded in the total synthesis of marrubiin[13].



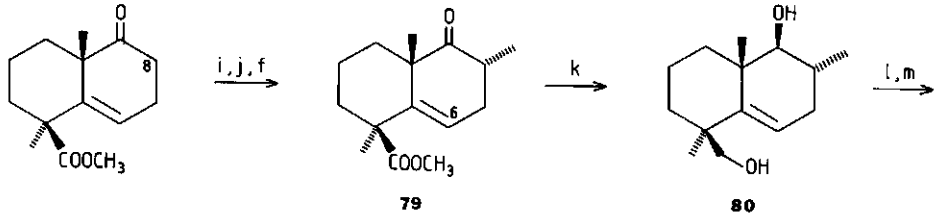
scheme 2.4

The route to ketalactone 84 started with the Robinson annellation of 2-methylcyclohexanedione-1,3 (76) with Nazarov's reagent 75 to product 77 (scheme 2.5). The keto function at C-9 in the

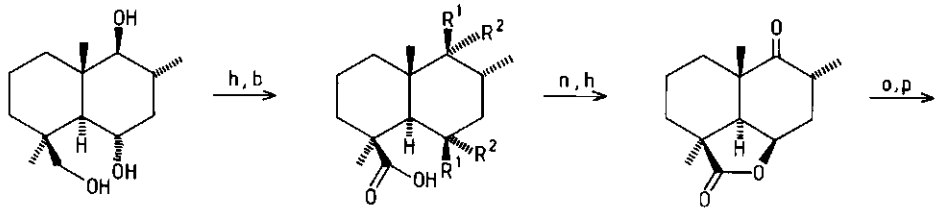
a: KF, CH_3OH; b: $NaBH_4$, EtOH, c: PhCOCl, pyr. ; d: t-BuOK, CH_3I ; e: $(CH_2SH)_2$, BF_3; f: RaNi ; g: KOH, CH_3OH ; h: Jones ox. ; i: NaH, HCOOEt ; j: n-BuSH, TsOH ; k: $LiAlH_4$, Et_2O ; l: B_2H_6 ; m: H_2O_2 ; n: Et_3N, ClCOOEt ; o: Br_2 ; p: DBN, Δ ; q: LiC≡C-OEt, THF; r: H_2SO_4, EtOH ; s: SeO_2, HOAc ; t: HCl, CH_3OH.



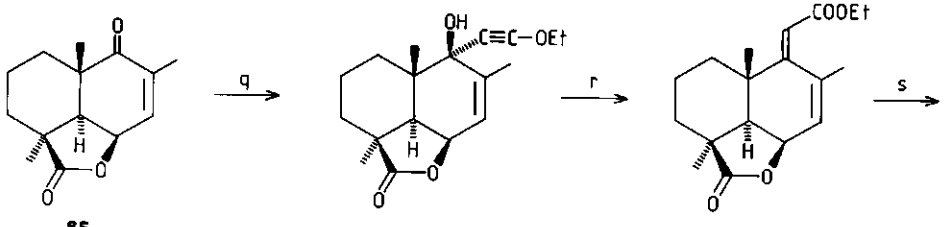
75 76 77 78



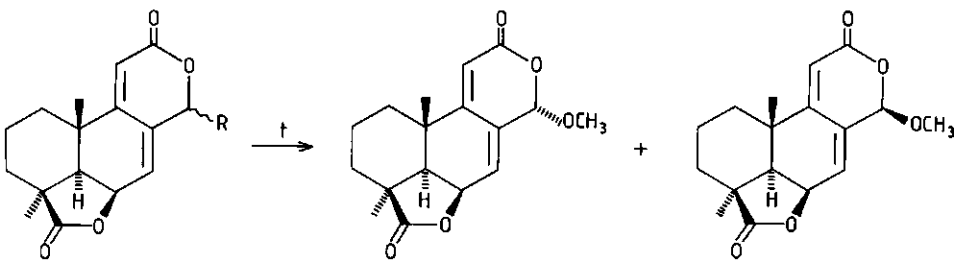
79 80



81 82 R^1, R^2 = O
83 R^1 = OH, R^2 = H 84



85 86 87



88 R = α-OAc
89 R = β-OAc
52 R = α-OH

LL-Z1271α (49) : 90

1 : 2,5

scheme 2.5

bicyclic diketoester 77 was selectively reduced into the β-alcohol with sodium borohydride and subsequent treatment with benzoylchloride in pyridine afforded the benzoate. This benzoate could be methylated according to Pelletier[14] to the keto ester benzoate 78 in which the methylgroup has the desired equatorial position. The functionality in ring A was removed by conversion of the carbonyl at C-3 of 78 into a dithioketal and subsequent desulfurization with Raney Nickel. The further transformation into the C-8 methylated 79 is outlined in scheme 2.5.

The next target was the introduction of the hydroxyl group at C-6 and concomitant formation of the required *trans* ring fusion Hydroboration of 79 also gave partial reduction of the ester function. Therefore the keto ester 79 was reduced with $LiAlH_4$ to the diol 80 and hydroboration of this diol gave a triol 81 with the desired ring fusion buth with the wrong stereochemistry of the hydroxyl group at C-6. In order to prepare the 6β-hydroxy derivative the triol had to be oxidized with CrO_3 to the diketo acid 82. Sodium borohydride then afforded the dihydroxy acid 83 with the desired stereochemistry at C-6. Lactonization of 83 gave a 9β-hydroxylactone which had to be oxidized again to the corresponding keto lactone 84, the degradation product of marrubiin. Intermediate 84 was transformed to 85 *via* bromination-dehydrobromination.

The annellation of the δ-lactone was conducted in the following manner. Addition of lithium ethoxyacetylide to 85 in THF introduced the side at C-9, and the acid catalized Meyer-Schuster rearrangement of the ethynylcarbinol 86 resulted in formation of the unsaturated ester lactone 87. Oxidation of this lactone with selenium dioxide in acetic acid gave a mixture of lactol LL-Z1271γ (52) and two epimeric acetyllactols 88 and 89. Treatment of this mixture with HCl in methanol gave LL-Z1271α (49) and the C-14 epimeric methyl derivative 90 in a ratio of 1:2.5 respectively.

Adinolfi succeeded in synthesizing LL-Z1271α *via* the route outlined above, although the stereospecificity of the last reaction is rather low. Moreover the stereoselective hydroxylation at C-6 could only be accomplished *via* a rather tedious reaction sequence of oxidations and reductions which is unattractive.

2.2.3 Synthesis of LL-Z1271α by Welch et el.

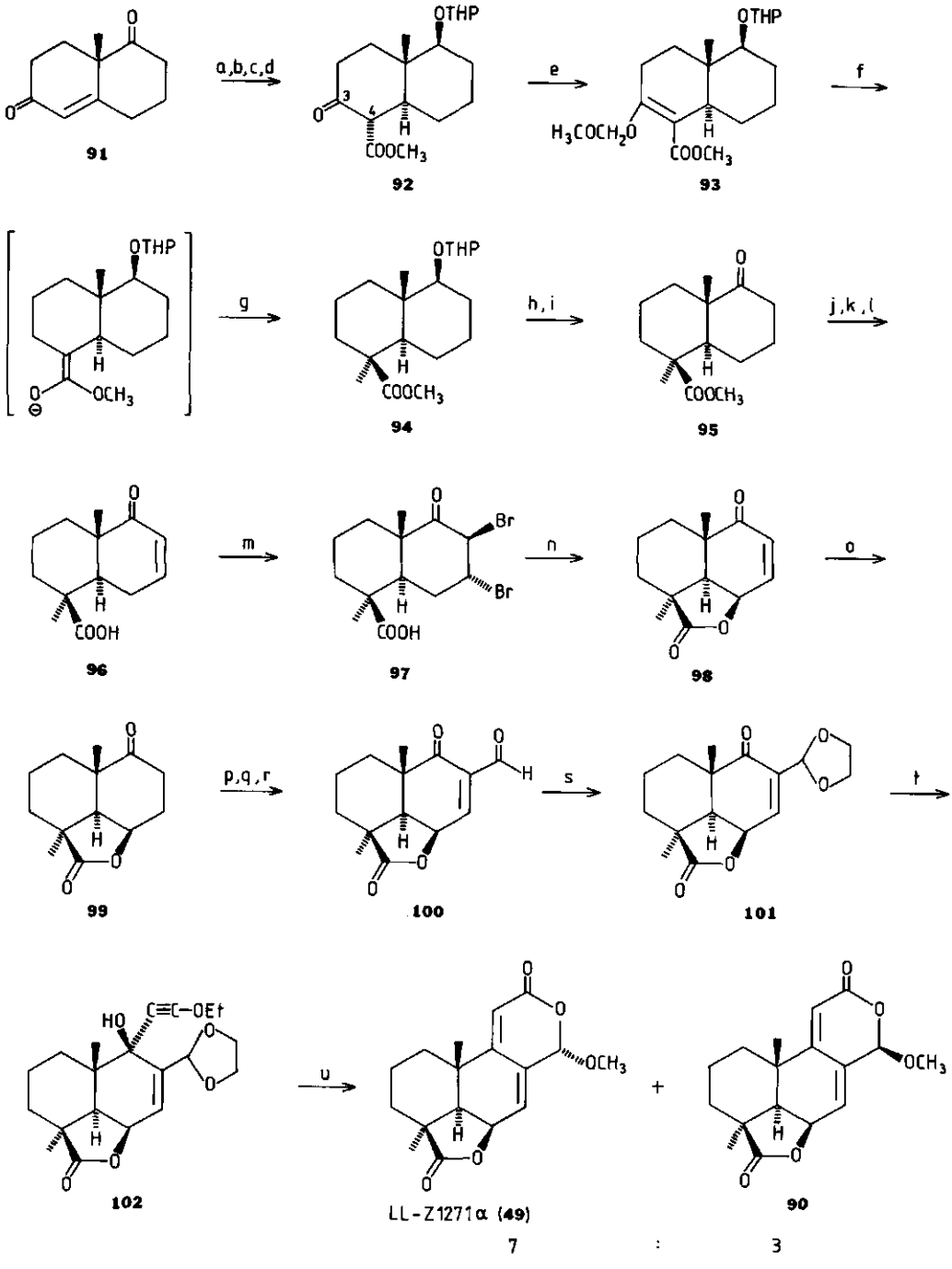
A second total synthesis of LL-Z1271α was published in 1977 by Welch and coworkers[15]. The approach started with the Wieland-Miescher diketone 91. The C-9 carbonyl group was reduced and the resulting alcohol was protected as a THP-ether (scheme 2.6). This compound was reduced with lithium in ammonia and the resulting enolate treated with CO_2 and diazomethane to give 92. In this manner the *trans* ring fusion was secured together with the introduction of the ester function at C-4.

Since methylation of keto ester 92 was known to give a product with the wrong stereochemistry at C-4, it was obvious that an alternative route for the construction of 95 had to be designed. This problem was tackled knowing that exocyclic enolates are alkylated from the less hindered α-side. Hence the carbonyl function at C-3 in 92 was transformed into the enol ether 93. Reductive elimination of the enol ether by lithium in ammonia and quenching of the resulting exocyclic ester enolate with methyl iodide gave the THP-ether 94. Hydrolysis of the THP-ether and Jones oxidation of the resulting hydroxyl group gave keto ester 95.

Welch intended to functionalize position 6 *via* the introduction of a double bond (bromination-dehydrobromination) followed by allylic bromination with NBS. This bromide would then be displaced by the carboxylate of the corresponding acid 96, thus forming the γ-lactone 98. Instead of the allylic bromination however formation of the dibromide 97 took place and this compound cyclized to the γ-lactone 98 upon treatment with potassium carbonate in DMF. Subsequent hydrogenation using Wilkinson's catalyst $[RhCl(Ph_3P)_3]$ afforded the saturated lactone 99[18].

Approximately the same strategy, as used by Adinolfi was followed for the δ-lactone annellation. This route is further outlined in scheme 2.6.

Welch succeeded in solving the problem of the stereochemistry at C-4 and the *trans* ring fusion by a very elegant method, but a consequence of its application is the loss of the carbonyl group in ring A. The product distribution in his last step to LL-Z1271α was better than in Adinolfi's approach.



91 **92** **93** **94** **95** **96** **97** **98** **99** **100** **101** **102** **90**

scheme 2.6

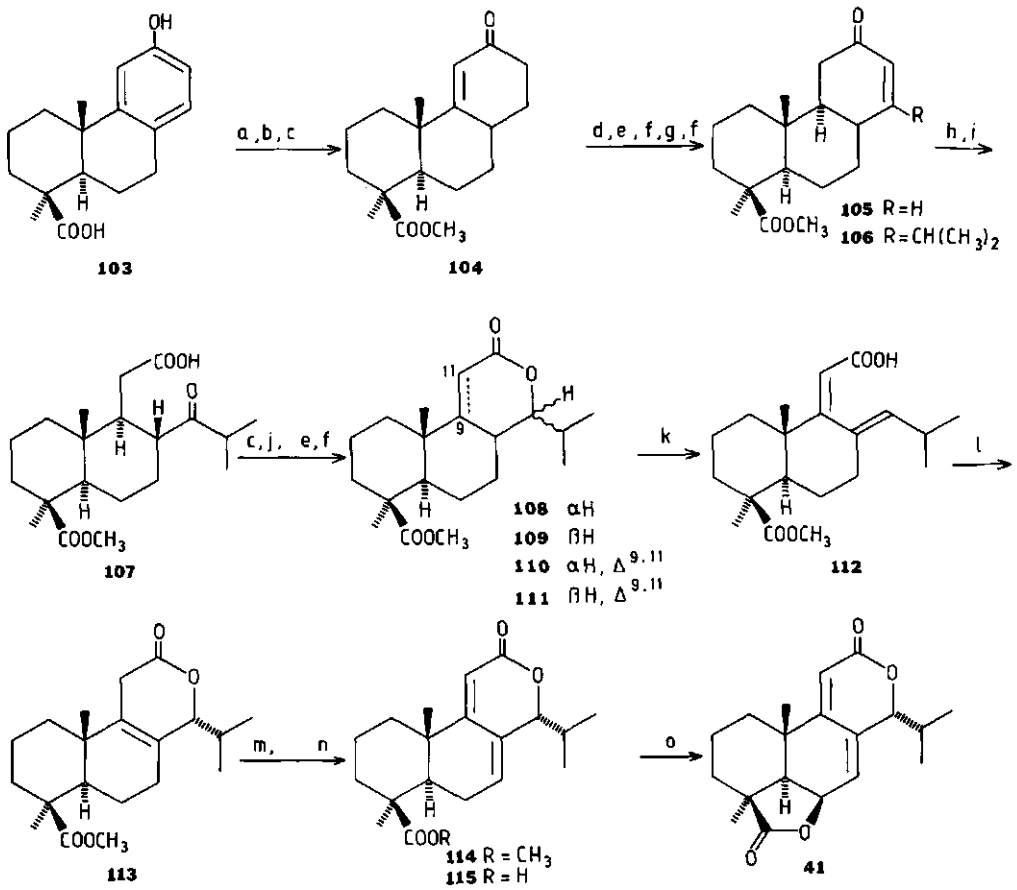
a: $NaBH_4$, EtOH ; b: DHP, CH_2Cl_2 , HCl ; c: Li , NH_3 , CO_2 ; d: CH_2N_2 ; e: NaH, HMPA, CH_3OCH_2Cl; f: Li , NH_3 , DME ; g: CH_3I ; h: TsOH , CH_3OH ; i: Jones ox; j: n-PrSLi, HMPA ; k: Br_2 , HOAc ; l: $CaCO_3$, DMA ; m: Br_2 , CH_2Cl_2 ; n: K_2CO_3 , DMF ; o: $RhCl(Ph_3P)_3$, H_2 , PhH ; p: NaH, HCOOEt, DME ; q: LDA , THF, PhSeCl ; r: m-CPBA , THF ; s: $(CH_2OH)_2$, THF, H_2SO_4; t: LiC≡C-OEt , THF ; u: H_2SO_4 , CH_3OH.

2.2.4 Total synthesis of nagilactone F by Hayashi et al.

In 1982 Hayashi published the first total synthesis of a norditerpenoid dilactone: nagilactone F[16]. As starting material he chose the resin acid (4S)-(+)-podocarpic acid 103. Important features of this compound are the correct stereochemistry at C-4, the *trans* fusion of the AB ring system and the absolute configuration which is the same as in nagilactone F. The major problem was the transformation of the BC ring system to the dienolide lactone moiety. The total synthesis is outlined in scheme 2.7.

Birch reduction of ring C in 103 and esterification with diazomethane gave the enone 104 which was conveniently transformed into enone 105. The isopropyl group at C-14 was introduced through the Michael type addition of lithium diisopropyl cuprate. The resulting enolate was quenched with phenylselenenyl chloride, and oxidative elimination of this group yielded enone 106. Ozonolysis of 106 followed by Jones oxidation afforded the keto carboxylic acid 107. Reduction of the keto group of 107 and subsequent cyclization gave two epimeric lactones 108 and 109, which were converted into the 9(11)-unsaturated lactones 110 and 111 in the same way as described for enone 106 (*vide supra*). Treatment of both enolides 110 and 111 with potassium *t*-butoxide in DMSO afforded ring opening to the same diene carboxylic acid 112.

This diene carboxylic acid 112 could be transformed exclusively to the 8(9)-enolide 113 upon irradiation of a solution in ethanol using a mercury lamp. Coumpound 113 was characterized by comparison with a degradation product of the natural nagilactone F (41) which had the same structure. Dehydrogenation of 113 with DDQ gave the 7(8),9(11)-dienolide 114 in poor yield. Hydrolysis of 114



a: Li, NH_3, t-BuOH; b: H_3O^+ ; c: CH_2N_2 ; d: Pd/C, H_2 ; e: LDA ; f: PhSeCl, H_2O_2 ;
g: $(i\text{-}Pr)_2CuLi$; h: O_3 ; i: Jones ox. ; j: B_2H_6 ; k: t-BuOK, DMSO ; l: hν, EtOH;
m: DDQ, BF_3 ; n: H_2SO_4 ; o: $Pb(OAc)_4$, hν.

scheme 2.7

afforded the corresponding acid 115. The last step in this approach was the lactonization achieved through allylic oxidation with lead (IV) acetate in benzene and concomitant ring closure to nagilactone F (41).

In particular the problem of the stereochemistry of the alkyl substituent at C-14 was elegantly solved by Hayashi in his total synthesis of nagilactone F.

Hayashi succeeded in converting nagilactone E (21) into nagilactone F (41) (see chapter 2.1). This procedure supplied a quantity of nagilactone F, sufficient for degradation to important intermediates used in the total synthesis (*vide supra*).

2.3 SYNTHETIC PLAN TO 3β-HYDROXYNAGILACTONE F

The diterpenoid dilactones isolated from various species of the *Podocarpaceae* and some fungii have been investigated extensively from the biological point of view. Most dilactones with interesting biological activities have some functionality in ring A. The published total syntheses of dilactones however were directed towards LL-Z1271α and nagilactone F which both have an unsubstituted ring A.

Hayashi started his total synthesis of nagilactone F (41) with Podocarpic acid, which lacks a functionality in ring A. This implicates that no other dilactones of type C can be prepared by interconversions *via* functional group transformations. As no other natural products resembling podocarpic acid but with a functionalized ring A are available in large quantities the applicability of this route is seriously limited.

The two approaches to the synthesis of LL-Z1271α, outlined in sections 3.2.2 and 3.2.3 are not concerned with the stereospecific introduction of a C-14 alkyl substituent or with the maintenance of a functional group in ring A. Considerable adjustment of these approaches would be necessary to obtain both of these structural features.

We initiated the investigations into the total synthesis of ring A functionalized diterpenoid dilactones with 3β-hydroxynagilactone F (42) as target molecule. This dilactone has been isolated from the root bark of *Podocarpus nagi* (Thunberg) Pilger[17]. The 3β-hydroxyl group in ring A leaves the possibility to convert this dilactone to dilactones with other substitution paterns. The retrosynthetic plan is outlined briefly in scheme 2.8.

Robinson annellation of a suitable diketone 76 (ring B) with Nazarov's reagent 75 gives the bicyclic product 77. Some important

structural features are already present in this compound, *i.e.* the C-4 ester function required for the construction of the γ-lactone, a functionalized ring A and a carbonyl at C-9 which can be used for the annellation of the δ-lactone. Introduction of the C-4 methyl group in 77 proceeds stereoselectively and yields the 5(6)-unsaturated product. Stereoselective hydrogenation of the double bond to the *trans*-fused intermediate 116 is known to proceed with moderate results and is one of the problems which had to be solved in this approach.

Starting from this compound 116, two routes lead to the synthesis of diterpenoid dilactones of type C. Route I starts with the synthesis of the γ-lactone followed by annellation of the δ-lactone. Then a functional group transformation should afford 42. In the second approach (route II) the δ-lactone is annellated first and subsequently functional group transformations have to be performed in order to activate position 6. Ring closure to the γ-lactone then should complete the synthesis of 42.

In chapter 3 a new method for the δ-lactone annellation is described. Chapter 4 deals with stereoselective synthesis of the *trans*-fused bicyclic intermediate 116. In chapter 5 our efforts to persue route I are described and finally the total synthesis of 3β-hydronagilactone F is outlined in full detail in chapter 6.

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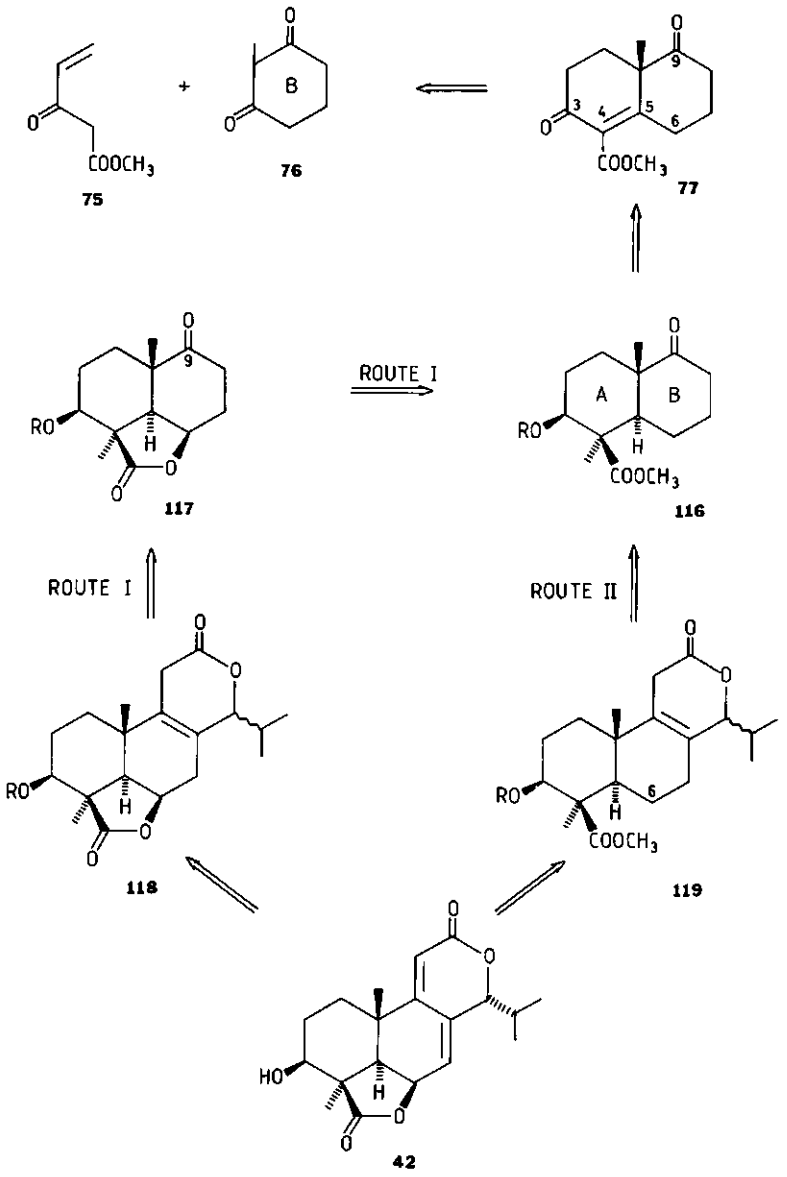
COOCH3
75
B
76
77
3
4
5
6
9
ROUTE I
RO
H
117
A
B
116
ROUTE I
ROUTE II
118
119
HO
42

scheme 2.8

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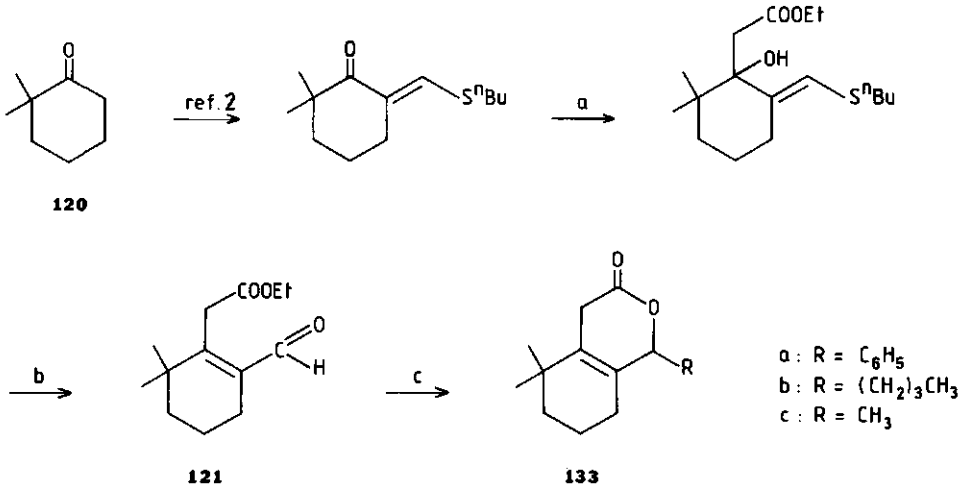
3 INVESTIGATIONS INTO THE SYNTHESIS OF THE BC RING SYSTEM OF NORDITERPENOID DILACTONES

3.1 ANNELLATION OF THE δ-LACTONE MOIETY

3.1.1 Introduction

As part of our strategy towards the synthesis of 3β-hydroxy-nagilactone F we required an efficient method for the annellation of a δ-lactone starting from a keto function. A first approach in this context was published some years ago by Peterse and De Groot (scheme 3.1)[1]. Upon application of this method to the bicyclic

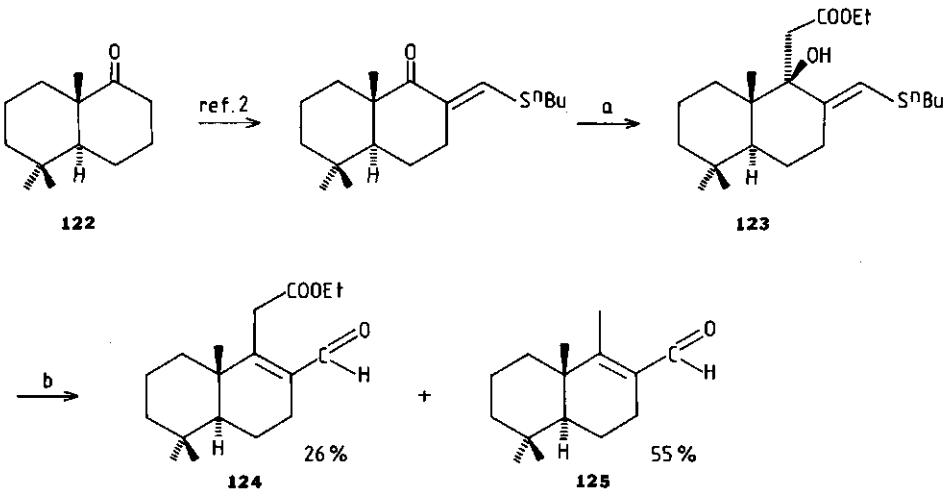


a: $LiCH_2COOEt$, THF; b: H^+/Hg^{2+}; c: RLi, THF.

scheme 3.1

intermediate 122 it appeared that one of the reactions did not proceed in a satisfactory manner. The introduction of the *n*-butylthiomethylene group was achieved according to a literature

procedure[2] and the addition of the lithium enolate of ethylacetate, formed by the action of LDA on ethylacetate in THF, proceeded to yield compound 123 in 95%. Unfortunately, the hydrolysis of the addition product 123 gave the desired aldehyde 124 in a very poor yield (26%) (scheme 3.2)[3]. The main product turned out

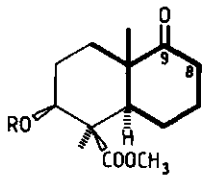


a: $LiCH_2COOEt$, THF ; b : H^+ / Hg^{2+} .

scheme 3.2

to be the aldehyde 125, which was formed *via* hydrolysis of the ester function and subsequent decarboxylation. Moreover conversion of the aldehyde 121 into lactone 133b yielded a reaction mixture which always contained an amount of the starting material 121. Obviously the lithium reagent acts as a base and as a nucleophile.

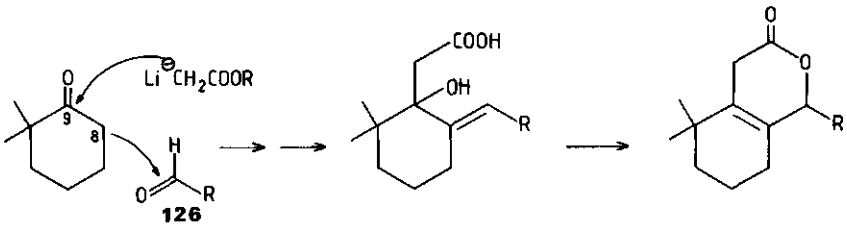
These facts led to the design of a new route for the lactone annellation. As model compound for the AB ring system was chosen 2,2-dimethylcyclohexanone 120, marked with thick lines in figure 3.1[4]. The side chain at C-8 can be introduced *via* an aldol condensation, and therefore the choice of aldehyde determines the nature of this substituent. Subsequently the addition of a suitable nucleophilic reagent on the carbonyl group furnishes the



116

figure 3.1

second side chain at C-9. Cyclization then gives the desired δ-lactones (scheme 3.3).



120 **132** **133**

scheme 3.3

3.1.2 The annellation of δ-substituted δ-lactones

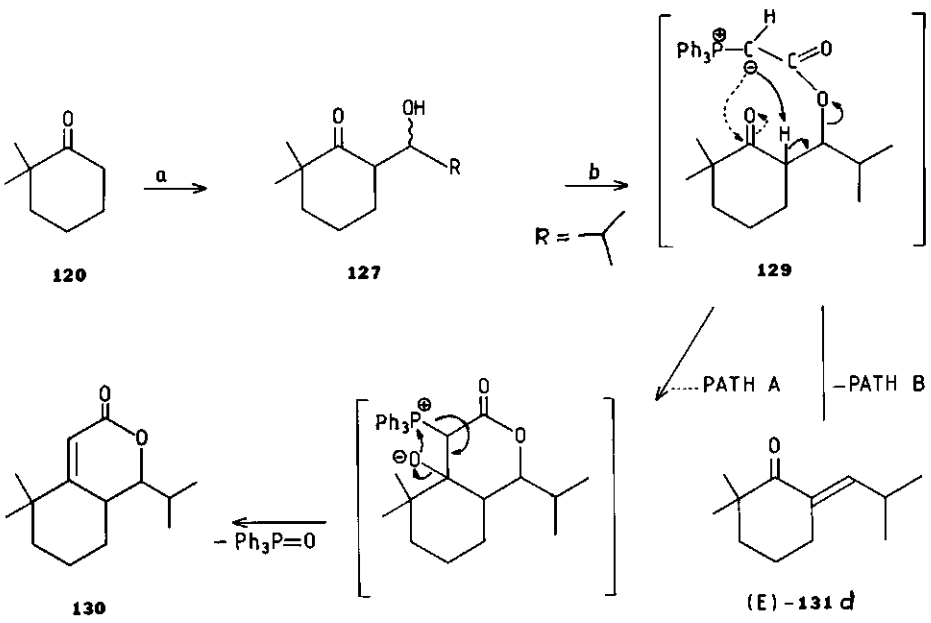
The starting material 2,2-dimethylcyclohexanone 120 was synthesized according to Ireland and Marshall[5]. Aldol condensation of the lithium enolate of 120, formed with LDA in THF at -78°C, with aldehydes 126 was performed at -78°C and furnished mixtures of *erythro* and *threo* β-hydroxy ketones 127 (see figure 3.2). The relative amounts of both isomers in the reaction of cyclic eno-

threo **127** erythro **127**

figure 3.2

lates were found to vary with reaction time and temperature[6]. At low temperature and after a short reaction time the kinetically determined product is formed, in this case the *threo* aldol, while after equilibration, *i.e.* prolonged reaction time, an increased amount of the *erythro* isomer is formed. Heng and Smith established that in the case of aldol condensation of cyclohexanone, the absence of β-alkyl substituents increased the amount of the *erythro* product[7]. These facts are in good agreement with the results obtained in the aldol condensation of 120, *i.e.* the formation of an excess of the *erythro* ketols. Further proof of this stereoselectivity has been obtained (*vide infra*).

In a recent paper Bohlman described a very elegant method for the conversion of α-hydroxy ketones into butenolides[8]. An attempt to extend the method to the conversion of β-hydroxy ketones into unsaturated δ-lactones 130 failed. Probably the hydroxyl group attacks the ketenylidene triphenylphosphorane[9] 128 to afford the

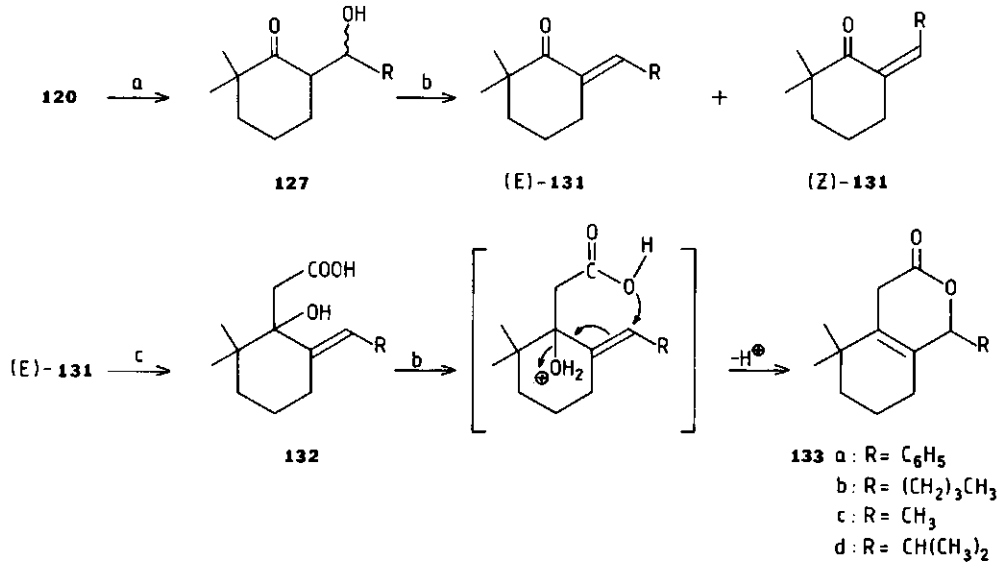


120 127 129 130 (E)-131 d

a : LDA , THF , -78° , R—CHO (126) ; b : $Ph_3P=C=C=O$ (128) , PhH .

scheme 3.4

intermediate phosphorous ylide 129. Instead of an intramolecular Wittig reaction to a δ-lactone (scheme 3.4, path A), an elimination takes place with the ylide acting as the base (scheme 3.4, path B). The product of this reaction is the stable enone (*E*)-131d, isolated in a 45% yield. Because of the relative instability of the β-hydroxy ketones 127 these compounds were converted into the alkylidene ketones by elimination of H_2O, and another way of introducing the two carbon moiety at C-9 was chosen (scheme 3.5).



a : LDA, THF, R-CHO ; b : TsOH , PhH ; c : $LiCH_2COOLi$, THF, HMPA .

scheme 3.5

The *trans* elimination of H_2O from the β-ketols was performed by refluxing in benzene with a catalytic amount of *p*-toluenesulfonic acid. After work up the reaction mixtures were purified by column chromatography yielding the (*Z*)- and (*E*)-isomers of enones 131. The main products resulting from this dehydration were the (*E*)-isomers 131. This confirms the statement that the *erythro* β-ketols were formed in excess during the aldol condensation (Table 3.1)[7].

The introduction of the side-chain at C-9 can be performed *via*

Table 3.1. Yields of the subsequent reactions of scheme 3.4.

120 ⟶ (*E*)-131 + (*Z*)-131			(*E*)-131 ⟶ 132 ⟶ 133	
a R=C_6H_5 [i]	E : Z = 100:0	80%	84%	98%
b R=$(CH_2)_3CH_3$	E : Z = 89:11	74%	81%	83%
c R=CH_3	E : Z = 87:13	81%	84%	80%
d R=$CH(CH_3)_2$	E : Z = 82:18	60%	79%	96%

i) prepared according to Johnson[12].

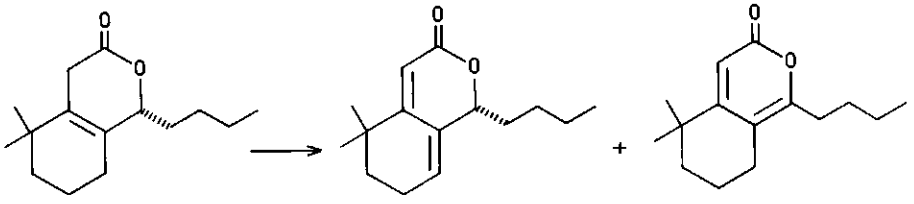
an 1,2-addition of an organometallic reagent to the alkylidene ketones. The dianion of acetic acid (dilithio acetate[10]) can be regarded as a hard nucleophile[11] and therefore seemed to offer good perspectives. The products formed are indeed the β-hydroxy-γ,δ-unsaturated carboxylic acids 132. In all cases, ^{1}H NMR investigation of the crude reaction mixtures revealed the presence of only small amounts (<10%) of the 1,4-addition products[13]. Refluxing the 1,2-adducts 132 in benzene with a catalytic amount of p-toluenesulfonic acid resulted in cyclization to the desired lactones 133[14] *via* a vinylogous intramolecular substitution (S_Ni'). The overall yields of this reaction sequence starting with ketone 120 were approximately 50%.

The question now arose whether this method could be used on bicyclic ketones. In chapter 5 and 6 the method is applied to bicyclic ketones 116 and 117 (see scheme 3.7). It is demonstrated that the method is useful, but in addition its applicability appeared to be limited.

3.2 CONVERSION OF THE 8(9)-ENOLIDE INTO THE 7(8),9(11)-DIENOLIDE

3.2.1 Introduction

Now that a useful method for the annellation of the δ-lactone 8(9)-enolide had become available we focussed our attention to the conversion of the 8(9)-enolide into the 7(8),9(11)-dienolide



133b 134 135

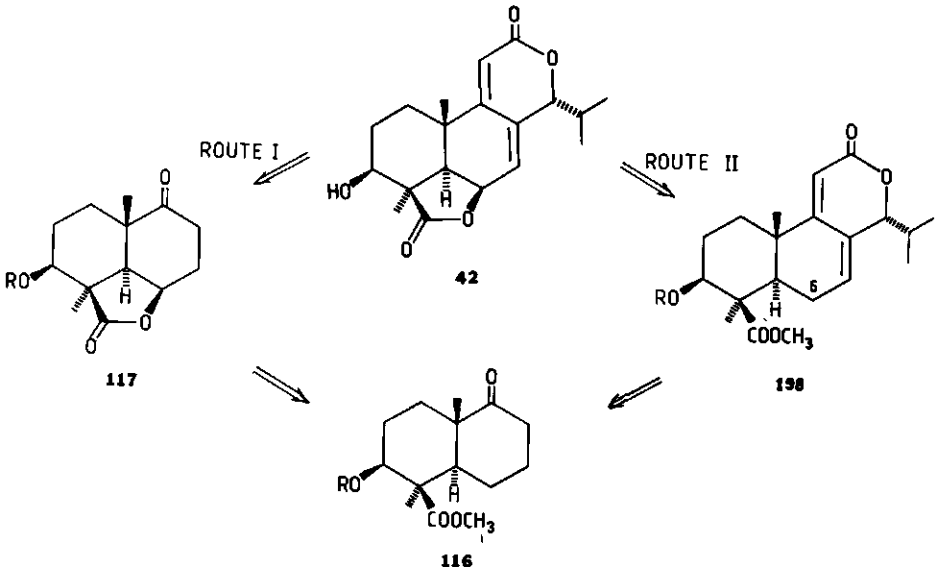
scheme 3.6

134. It is obvious from literature data that the formation of the 8(14),9(11)-dienolide 135 may be a competitive reaction (scheme 3.6).

In the retrosynthetic plan two possible routes to diterpenoid dilactones remain, starting with 116 (scheme 3.7).

Route I: Primary construction of the γ-lactone followed by δ-lactone annellation (chapter 5).

Route II: primary annellation of the δ-lactone followed by ring closure to the γ-lactone (chapter 6).



117 42 198 116

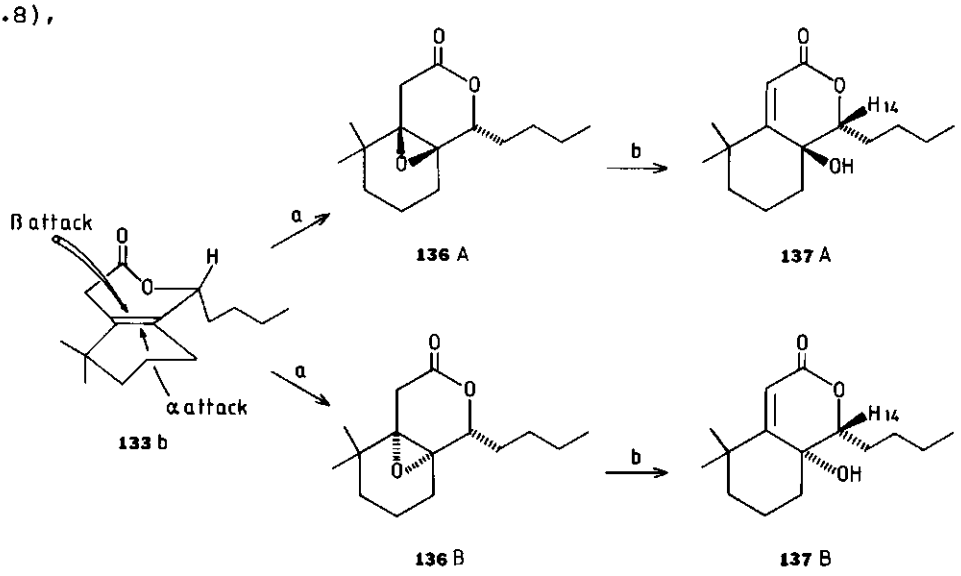
scheme 3.7

In the first approach both dienolides 134 and 135 lead to diterpenoid dilactones of type C and type A respectively. In the second case only the 7(8),9(11)-dienolide 134 can lead to the synthesis of dilactones of type C because the 6 position must be activated for the formation of the γ-lactone. No easy way of achieving this is obvious in the case of the 8(14),9(11)-dienolide 135.

In the following sections the attempts to bring about the regiospecific transformation of 133 into 134 are outlined.

3.2.2 Epoxidation of the 8(9) double bond

The initial approach towards the conversion of the 8(9)-unsaturated lactone to the 7(8),9(11)-dienolide proceeded through epoxidation, ring opening to a hydroxy derivative and dehydration. The epoxidation of 133b was performed with *m*-CPBA in chloroform and resulted in a mixture of epoxides 136 A and 136 B in a 2.5:1 ratio respectively and in a quantitative yield. Examination of a Dreiding model of the starting material showed that the main product has the relative configuration of compound 136 A (scheme 3.8),



a : m-CPBA , CH_3OH ; b : LDA , THF.

scheme 3.8

resulting from an attack of *m*-CPBA on the less hindered β-face of the molecule[15]. The two isomeric epoxides 136 A and 136 B were not separable and therefore the mixture was treated with LDA in THF to give opening of the epoxides. The two isomeric hydroxy derivatives 137 A and 137 B which were formed could be separated using column chromatography on silica gel, yielding 59% of 137 A and 24% of 137 B respectively.

The tentative assignment of the structures was strongly supported by ^{1}H NMR studies on the two hydroxy derivatives with a ^{1}H NMR lanthanide shift reagent (LSR), to wit Eu(fod)$_3$:tris (6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato) europium. The Δδ-values of the hydrogen atoms of the methyl groups, of H-11 and H-14 (see figure 3.3, $\Delta\delta = \delta$[with Eu(fod)$_3$] - δ[without

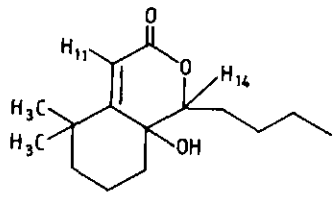


figure 3.3

Eu(fod)$_3$]) were determined for both isomers. The reagent/substrate ratio was 4.2:1 and the Δδ values of the hydrogen atoms are

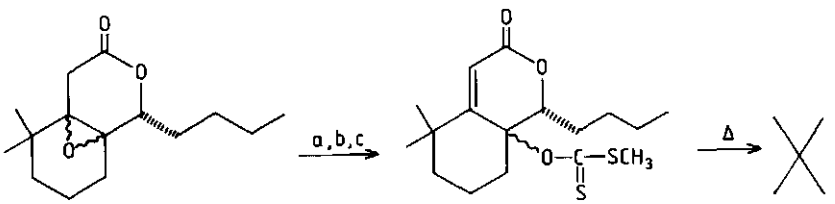
Table 3.2. ^{1}H NMR lanthanide shift experiment with 137A *and* 137B.

		δ ppm	δ[+Eu(fod)$_3$]ppm	Δδ ppm
137A	H_{11}	5.85	7.56	1.71
	H_{14}	4.22	5.70	**1.48**
	CH_3	1.18	1.46	0.28
	CH_3	1.30	1.96	0.66
137B	H_{11}	5.85	7.54	1.69
	H_{14}	3.90	4.83	**0.93**
	CH_3	1.18	1.43	0.25
	CH_3	1.32	1.85	0.53

gathered in Table 3.2. In both cases the complexation of europium will take place with the three oxygen atoms present in the molecule, *i.e.* of the hydroxyl group and of the lactone. It is obvious that the europium complexes on that side of the molecule to which the hydroxyl group is attached. Therefore the shifts of both H-11 and the methyl groups must be approximately the same whereas the shift of H-14 must be different. In 137 A the distance between H-14 and europium is small, this in contrast with 137 B where H-14 and europium are attached to the opposite sides of the molecule. A larger distance to europium gives rise to a smaller shift[16], and this is in good agreement with the experimental $\Delta\delta$ values.

The hydroxy derivatives were subjected to a dehydration by refluxing in benzene with a catalytic amount of *p*-toluenesulfonic acid. Unfortunately this resulted in both cases in a mixture of 7(8),9(11)-dienolide 134 and the 8(14),9(11)-dienolide 135. A ratio of 1:1 was obtained for 137 A and 4:1 for 137 B. The overall transformation of 133 b *via* the epoxides 136 A and B leads to a mixture of 5:4 of 134 and 135.

An attempt was made to eliminate the hydroxyl group *via* a xanthate (scheme 3.9)[17]. The reaction product was rather complex, however, and therefore this route was not investigated further.



136 **138**

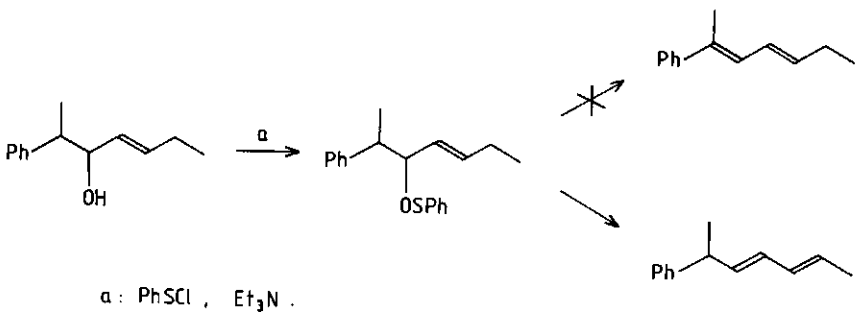
a: LDA, THF ; b: CS_2, THF; c: CH_3J.

scheme 3.9

The fact that a three reaction sequence was necessary in this epoxidation method led to the exploration of other, shorter, routes for the desired conversion.

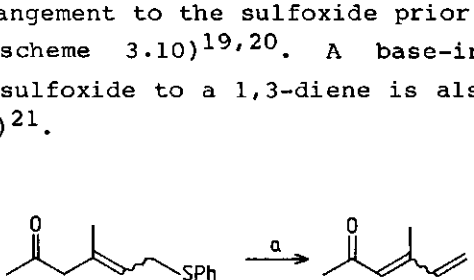
3.2.3 Sulfenylation and oxidative elimination

In a second approach the thermal elimination of allylic sulfoxides to 1,3-dienes was studied. This type of reaction has not been used extensively in organic synthesis, although recently some papers were published in which this type of reaction is applied, *e.g.* in the synthesis of the sex pheromone 8(*E*),10(*E*)-dodecadiene-1-ol of a codling moth (*Laspeyresia Pomonella* L)[18]. These studies revealed that the elimination of the allylic sulfoxide preferentially occurs through the *cis* elemination of the sulfoxide and not *via* the sulfenate ester. Even sulfenate esters formed by treatment



scheme 3.10

of an allylic alcohol with a sulfenylating agent give a 2,3 - sigmatropic rearrangement to the sulfoxide prior to elimination to the 1,3-diene (scheme 3.10)[19,20]. A base-induced vinylogous elimination of a sulfoxide to a 1,3-diene is also reported in one case (scheme 3.11)[21].



scheme 3.11

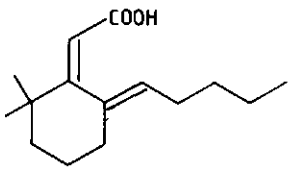
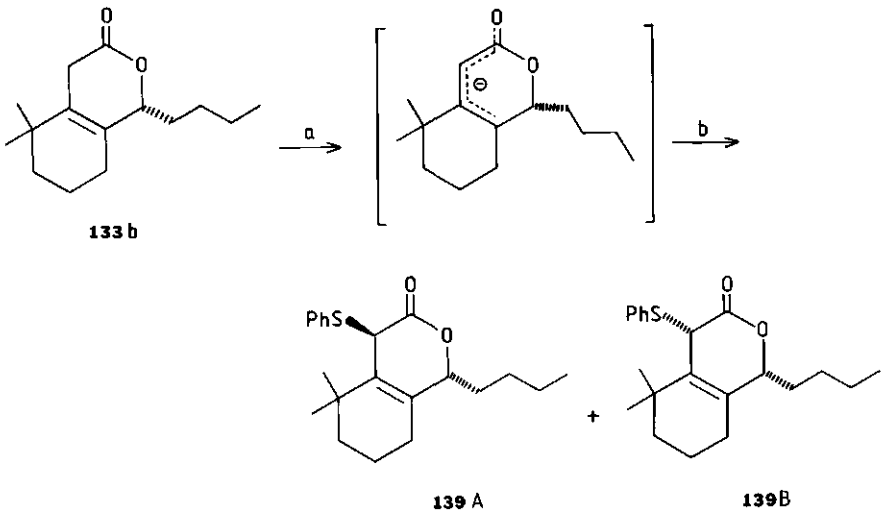


figure 3.4

In order to study this reaction in compound 133b this δ-lactone had to be sulfenylated (scheme 3.12). The anion of 133b was formed by reaction with a base at low temperature because it is known from the work of Hayashi[22] that base-treatment of the lactone at room temperature affords a ring opening to dienoic acid 140 (figure 3.4). Reaction of 133b with LDA in THF at -78°C gave a solution of the corresponding anion which was added dropwise to a solution of phenylsulfenyl chloride, diphenyl disulfide or phenyl phenylthiosulfonate (the inverse quench procedure, described by Trost *et al.*[23]).



133b **139A** **139B**

a : LDA , THF ; b : PhSCl or PhSSPh or $PhSSO_2Ph$.

scheme 3.12

Sulfenylation performed with phenylsulfenylchloride proceeded not only with the formation of the desired sulfide, but also with

sulfenylation of the diisopropyl amine present in the reaction mixture. The product of this side reaction is diisopropylphenylthioamine and the hydrogen chloride which is liberated protonates the preformed anion of 133b. The main product was therefore the starting material, and only minor quantities of the sulfides 139A and 139B could be isolated (entry 1, Table 3.3).

Another sulfenylation performed with diphenyldisulfide proceeded incompletely and sluggishly (entry 2, Table 3.3). After six hours at -78°C the reaction mixture still contained starting material.

After these two fruitless attempts phenyl phenylthiosulfonate was tried as sulfenylating agent. The reactivity of this reagent lies between that of phenylsulfenyl chloride and diphenyldisulfide. Under the reaction conditions used in these experiments this reagent gave useful results (entry 3, Table 3.3). No starting material remained and the total yield of the two isomeric sulfides 139A and 139B was 78%. The structures of the sulfides could be assigned after conversion of the corresponding sulfoxides, which cannot be isolated, into the allylic hydroxy derivatives 137A and 137B, the structures of which had been established in the previous section (*vide supra*).

In 1965 Johnson and McCants published an overview of oxidation methods used in the synthesis of sulfoxides from sulfides[24]. Oxidation of a mixture of the sulfides 139A and 139B with 1 equivalent of *m*-CPBA in methanol yielded a rather complex reaction mixture which consisted of some starting material (18% of 139B), 37% of an allylic hydroxy derivative and 20% of mixture which consists of the 7(8),9(11)-dienolide and probably the epoxide

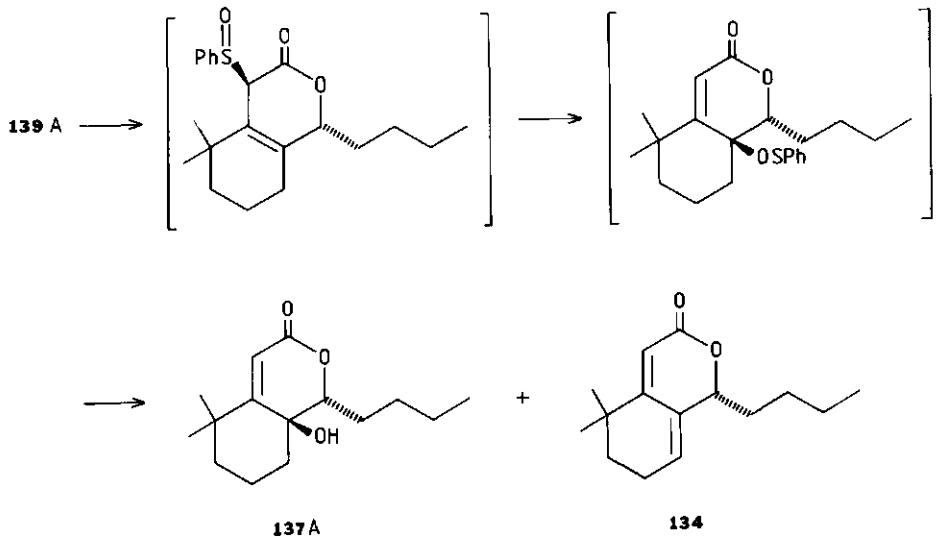
Table 3.3. Results of the sulfenylation of lactone 133.

Entry	lactone 133	sulfide 139A	sulfide 139B	totalyield	reactiontime
1 PhSCl	78%	16%	6%	100%	1 h
2 PhSSPh	10%	26%	34%	70%	6 h
3 $PhSSO_2Ph$	-	55%	23%	78%	45 min

obtained by epoxidation of the 8(9)-double bond. The latter compound however could not be isolated in pure form.

The hydroxy compound was identified as 137B by comparison with the ^{1}H NMR spectra of the allylic hydroxy derivatives, obtained after the ring opening of the epoxides 136A and 136B (section 3.2.2). Obviously the sulfoxides obtained after oxidation react in two different ways. The elimination to the 1,3-diene occurs, but also a 2,3 -sigmatropic rearrangement to a sulfenate ester which decomposes into the hydroxy derivative upon the action of a nucleophile[25]. When the sulfoxide is attached in a β-fashion to C-11, the rearrangement must produce the β-sulfenate and this gives rise to the β-hydroxy derivative.

Oxidation of the sulfide 139A did indeed give the dienolide 134 and the hydroxy compound 137A as main products. Careful TLC examination of the reaction mixture revealed that no trace of 137B was present (scheme 3.13). This rearrangement can be used in the ^{1}H NMR assignment of both sulfides 139A and 139B.



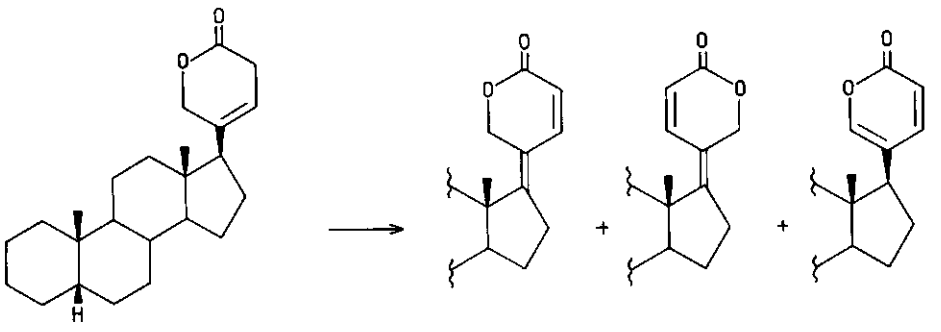
scheme 3.13

Because of the rather complex nature of the reaction product and the low chemospecificity of the conversion the *m*-CPBA oxidation was abandoned.

Instead the sodium periodate oxidation was investigated. Reaction of a mixture of 139A and 139B with one equivalent of oxidant in aqueous methanol at room temperature gave a sluggish and incomplete transformation. The reaction conditions were therefore adapted and the optimum yield of 68% was obtained using 6 equivalents of sodium perjodate at reflux temperature. The optimum ratio 7(8),9(11)-dienolide 134 to 8(14),9(11)-dienolide 135 was 7 to 3. Because mixtures of the two isomeric sulfides were used initially, it was not sure whether one of the isomers would produce 134 and the other 135 or *vice versa*. Therefore two additional experiments were performed with the individual isomers. This revealed that the influence of the stereochemistry of the sulfides on the regiochemistry of the elimination is negligible. Sulfide 139A gave 74% of 134 and 26% of 135, while sulfide 139B gave 67% of 134 and 33% of 135. The results obtained from the oxidation-elimination sequence were not unambiguous. Therefore no conclusions could be drawn with respect to the mechanism, *i.e* whether vinylogous elimination of the sulfoxide occurs or whether a 2,3 -sigmatropic rearrangement to sulfenate ester occurs followed by elimination to the product[19,26].

3.2.4 Dehydrogenation with DDQ

The final possibility considered was the dehydrogenation of 133b with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[27].



141 **142** **143** **144**

scheme 3.14

Yoshii and co-workers found during their synthesis of bufadienolides that treatment of the precursor 141 with DDQ in refluxing dioxane using *p*-toluenesulfonic acid as the catalyst predominantly produced the compounds 142 and 143[28]. This contrasted remarkably with the findings of Sarel *et al.*[29], who stated that under the same reaction conditions the exclusive product was dienolide 144 (scheme 3.14). An additional dehydrogenation of an 8(9)-enolide to the 7(8),9(11)-dienolide was published by Hayashi who explored this reaction with DDQ and with BF_3-etherate as catalyst in his total synthesis of nagilactone F (41)[22]. He obtained the desired product in only a poor yield however.

Although not all results gathered from the literature were encouraging the same reaction was nevertheless tried on the model lactone. As catalyst was tried BF_3-etherate and also *p*-toluenesulfonic acid. The ratios 134 to 135 were *ca.* 1:2 and 3:2 in the respective cases. These results show that also the dehydrogenation with DDQ is not regiospecific and proceeds with the concommitant formation of the undesired 8(14),9(11)-dienolide. The advantage of this method is however, that it is a one step conversion.

3.2.5 Concluding remarks

In the foregoing sections an overview is given of the methods explored for the conversion of the 8(9)-unsaturated lactone 133 into the desired 7(8),9(11)-dienolide 134. All the methods suffer from the fact that besides compound 134 also the 8(14),9(11)-dienolide is formed in varying amounts (see Table 3.4). The results obtained on the model compound reveal that the sulfenylation-oxidative elimination or the dehydrogenation with DDQ in dioxane and *p*-toluenesulfonic acid as catalyst offer the best perspectives.

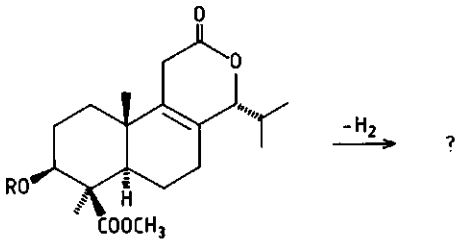
It must be stated, however, that these results only give an indication which method can best be applied to the bicyclic intermediate 116 to which the 8(9)-enolide is annellated (scheme 3.15). The stereochemical outcome of the methods remain uncertain. This is due to the fact that the conformation in the model compound is flexible and can change in the different stages of the

Table 3.4. Overview of the dehydrogenation methods

Entry	8(14),9(11)-dienolide	7(8),9(11)-dienolide	overall yield
elimination of H_2O	45%	55%	60%
elimination of PhSOH[i]:			
A mixture of 139 A/B	31-	69-	68%
B 139A	26-[ii]	74-[ii]	-
C 139B	33-[ii]	67-[ii]	-
Dehydrogenation (DDQ):			
A with BF_3-Et_2O	67-[ii]	33-[ii]	-
B *p*-TsOH	30-	70-	88%

i Oxidation of sulfide with sodium periodate.
ii The product composition was determined by ^1H NMR.

reaction sequence. This in contrast with the tricyclic intermediate which has a rather rigid structure because of the *trans* ring junction.



scheme 3.15

3.3 EXPERIMENTAL SECTION

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM-390 or a Hitachi Perkin-Elmer R-24B spectrometer. The line positions for the ^{1}H NMR spectra are given in the δ-scale as parts per million (ppm) downfield from the internal tetramethylsilane in chloroform-*d* as the solvent, unless otherwise stated. The following abbreviations are used to describe the ^{1}H NMR spectral bands: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), double doublet (dd) and broad (br). ^{13}C NMR spectra were recorded on a Bruker CXP-300 spectrometer operating at 75.460 MHz, in the pulse FT mode using chloroform-*d* as solvent and tetramethylsilane as the internal standard (p.126).

Mass spectral data and exact massa measurements were obtained with an AEI-MS-902 or an VG MM 70-70F. GC analyses were carried out on a Varian 3700 provided with a 2-m glass-column packed with 3% SP-2250 on chromosorb W.

For all dry reactions performed under a nitrogen atmosphere the equipment was dried in an oven at 150°C for several hours and then allowed to cool in an atmosphere of dry nitrogen. Dry tetrahydrofuran was obtained by destillation of the commercial material from sodium hydride. Dry benzene was obtained by storage of commercial benzene (*p.a.*) over sodium wire. Other dry solvents were obtained by storage of distilled material over molecular sieves. The solvents for column chromatography were distilled prior to usage.

Extracts were dried with anhydrous sodium sulfate prior to filtration and evaporation of the solvent under reduced pressure. The numbering according to the IUPAC rules is utilized in the experimental section.

Diastereomeric 6-(1[1]-Hydroxyalkyl)-2,2-dimethyl-cyclohexanones 127. *General Procedure.*

To a stirred solution of 22 mmol of *n*-butyllithium in hexane (14.7 mL) at 0°C was added dropwise, over 10 min, a solution of 2.42 g (24 mmol) of diisopropylamine in 75 mL of dry tetrahydrofuran under nitrogen. After 15 min the solution was cooled to -78°C and then a solution of 2.539 (20 mmol) of 120 in 25 mL of dry tetrahydrofuran was added dropwise over 10 min. The solution was stirred for another 0.5h and then a solution of 22 mmol of aldehyde in 20 mL of dry tetrahydrofuran was added dropwise. Stirring is continued for 45 min, 5.5 mL of 4N hydrochloric acid was added and the mixture was allowed to warm to room temperature. This mixture was poured into water and extracted with ether (3x100 mL). The organic layer was washed with water and brine and dried.

Evaporation of the solvent *in vacuo* afforded the crude product 127 . These compounds were somewhat unstable and were used immediately without further purification.

2-Alkylidene-6,6-dimethylcyclohexanones 131. *General Procedure.*

The crude product 127 was dissolved in 100 mL of dry benzene and 100 mg (0.5 mmol) of *p*-toluenesulfonic acid was added. The mixture was refluxed with a Dean-Stark apparatus for 1.5h. After cooling the reaction mixture was poured into saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with ether (2x50 mL) and the combined organic layers were washed with brine and dried. The solvent was removed under reduced pressure and the residue chromatographed on 75 g of silica gel with petroleum ether (40-60°C)/ether (24:1) to afford the isomeric alkylideneketones (*E*)-131 and (*Z*)-131 as oils of moderate stability.

(*E*)-131a: mp 76-77°C (lit.[12]: mp 79-80°C); ^{1}H NMR: 1.17 (s,6H), 1.7 (m,4H), 2.7 (m,2H), 7.3 (m,5H).

(*E*)-131b: oil; ^{1}H NMR: 0.7-1.6 (m,7H), 1.10 (s,6H), 1.7 (m,4H), 2.1 (m,2H), 2.4 (m,2H), 6.39 (m,1H); M.S. (70eV), *m/e* (%) 194 (M^+,13), 179(11), 69(100); calcd for $C_{13}H_{22}O$ M^+ 194.1671, found M^+ 194.1670.

(*Z*)-131b: oil; ^{1}H NMR: 0.7-1.6 (m,7H), 1.08 (s,6H), 1.7 (m,4H), 2.1 (m,2H), 2.4 (m,2H), 5.45 (m,1H); M.S. (70eV), *m/e* (%) 194 (M^+,100), 179(81), 69(90); calcd for $C_{13}H_{22}O$ M^+ 194.1671, found M^+ 194.1668.

(*E*)-131c: oil; ^{1}H NMR: 1.11 (s,6H), 1.6-1.8 (m,7H), 2.45 (m,2H), 6.50 (m,1H); M.S. (70eV), *m/e* (%) 152(M^+,12), 109(57), 69(100); calcd for $C_{10}H_{16}O$ M^+ 152.1201, found M^+ 152.1201.

(*Z*)-131c: oil; ^{1}H NMR: 1.08 (s,6H), 1.6-1.8 (m,7H), 2.4 (m,2H), 5.60 (m,1H); M.S. (70eV), *m/e* (%) 152(M^+,51), 109(77), 69(100); calcd for $C_{10}H_{16}O$ M^+ 152.1201, found M^+ 152.1203.

(*E*)-131d: oil; ^{1}H NMR: 0.98 (d,6H), 1.09 (s,6H), 1.7 (m,4H), 2.4 (m,3H), 6.21 (m,1H); M.S. (70eV), *m/e* (%) 180(M^+,52), 165(38), 69(100); calcd for $C_{12}H_{20}O$ M^+ 180.1514, found M^+ 180.1509.

(*Z*)-131d: oil; ^{1}H NMR: 0.96 (d,6H), 1.08 (s,6H), 1.6 (m,4H), 2.4 (m,3H), 5.22 (m,1H); M.S. (70eV), *m/e* (%) 180(M^+,70), 165(100), 69(60); calcd for $C_{12}H_{20}O$ M^+ 180.1514; found M^+ 180.1509.

Attempted Lactonization of 127d *with Ketenylidene Triphenylphosphorane* 128.

A mixture of 0.40 g (2.0 mmol) of 127d and 0.6 g (2.0 mmol) of 128 in 50 mL

of dry benzene was refluxed under nitrogen for 50h until the starting material had disappeared. The reaction mixture was poured into water, the layers separated and the aqueous layer extracted with ether (2x50 mL). The combined organic layers were washed with brine and dried. After evaporation of the solvent *in vacuo* the crude product was chromatographed on 30 g of silica gel. Besides some minor unidentified compounds, 0.18 g (45%) of (*E*)-131d could be isolated.

2-Alkylidene-6,6-dimethyl-1-hydroxycyclohexaneacetic Acids 132. *General Procedure.*

To a stirred solution of 25 mmol of *n*-butyllithium in 16.7 mL of hexane at 0°C was added dropwise, over 10 min, a solution of 2.64 g (26 mmol) of diisopropylamine in 50 mL of dry tetrahydrofuran under nitrogen. After 15 min 5.92 g (33 mmol) of hexamethylphosphoric triamide[30] was added at once. The solution was cooled to -20°C and then a solution of 0.67 g (11 mmol) of acetic acid in 60 mL of dry tetrahydrofuran was added dropwise over 10 min. This mixture was stirred at 50°C for a period of 1.5h and then cooled to -78°C. A solution of 10 mmol of the alkylidene ketone (*E*)-131 in 10 mL of dry tetrahydrofuran was added dropwise and this solution was stirred for 16h under nitrogen during which time it was allowed to warm to room temperature. The mixture was poured into 1N hydrochloric acid and extracted with chloroform (3x50 mL). The organic layer was washed with water and brine and dried. After removal of the solvent *in vacuo* the residue was chromatographed on 50 g of silica gel with ether to afford the condensation product 132. An analytical sample was prepared by crystallization from pentane.

132a: mp 118.5-119.0°C; ^{1}H NMR: 0.99 (s,6H), 1.3-1.8 (m,4H), 1.8-2.8 (m,2H), 2.79 (dd,2H), 6.45 (s,1H), 7.1 (m,5H), 7.5 (br s,2H, exchanges with D_2O); M.S. (70eV), *m/e* (%) 274 (M^+,3), 256(40), 142(100), 105(96). Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.42; H, 8.20.

132b: mp 28-29°C; ^{1}H NMR: 0.8-2.5 (m,15H), 0.88 (s,3H), 0.93 (s,3H), 2.72 (dd,2H), 5.36 (t,1H), 6.5 (br s,2H, exchanges with D_2O); M.S. (70eV), *m/e* (%) 254 (M^+,4), 236(18), 179(100), 69(46). Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.71; H, 10.38.

132c: mp 97-100°C; ^{1}H NMR: 0.88 (s,3H), 0.93 (s,3H), 1.3-1.9 (m,4H), 1.60 (d,3H), 2.0-2.5 (m,2H), 2.73 (dd,2H), 6.5 (br s,2H, exchanges with D_2O); M.S. (70eV), *m/e* (%) 212 (M^+,13), 194(54), 43(100). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.08; H, 9.58.

132d: mp 91.5-92.0°C; ^{1}H NMR: 0.88 (d,3H), 0.90 (s,3H), 0.93 (s,3H), 0.99 (d,3H), 1.4-1.8 (m,4H), 1.8-2.8 (m,3H), 2.74 (dd,2H), 5.20 (d,1H), 7.5 (br s,2H, exchanges with D_2O). M.S. (70eV), *m/e* (%) 240 (M^+,1), 222(8), 179(100). Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 70.19; H, 10.30.

*1-Alkyl-5,5-dimethyl-3-oxo-3,4,5,6,7,8-hexahydro-1*H*-2-benzopyrans* 133. *General Procedure*.

A mixture of 5 mmol of 132 and 100 mg (0.5 mmol) *p*-toluenesulfoniC, acid in 50 mL of dry benzene was refluxed with a Deans-Stark apparatus for 2h. After cooling the mixture was poured into saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with ether (2x25 mL) and the combined organic layers were washed with brine and dried. The solvent was evaporated under reduced pressure and the residual crude product purified by column chromatography (50 g of silica gel; petroleum ether (40-60°C)/ether; 19:1) to afford the lactone 133.

133a: mp 99.0-99.5°C; ^{1}H NMR: 1.07 (s,6H), 1.3-1.9 (m,6H), 3.01 (q,2H), 5.51 (s,1H), 7.2 (m,5H); M.S. (70eV), *m/e* (%) 256 (M^+,30), 142 (27), 105(100). Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.95; H, 8.11.

133b: mp 49.5-50.0°C; ^{1}H NMR: 0.8-2.1 (m,15H), 1.00 (s,3H), 1.02 (s,3H), 2.98 (q,2H), 4.6 (m,1H); M.S. (70eV), *m/e* (%) 236 (M^+,15), 179(100), 85(48). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 75.94; H, 10.21.

133c: mp 38.5-39.5°C; ^{1}H NMR: 1.01 (s,6H), 1.3-1.9 (m,6H), 1.41 (d,3H), 2.96 (q,2H), 4.80 (q,1H); M.S. (70eV), *m/e* (%) 194 (M^+, 40), 43(100). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.17; H, 9.31.

133d: mp 32.0-32.5°C; ^{1}H NMR: 0.82 (d,3H), 1.01 (s,6H), 1.09 (d,3H), 1.3-1.9 (m,6H), 2.93 (q,2H), 4.48 (q,1H); M.S. (70eV), *m/e* (%) 222 (M^+,7), 179(100). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.51; H, 9.82.

*Diastereomeric 1-Butyl-5,5-dimethyl-9,10-epoxy-3-oxo-3,4,5,6,7,8-hexahydro-1*H*-2-benzopyran* 136.

To a stirred solution of 0.714 g (3.0 mmol) of 133b in 10 mL of chloroform was added dropwise at 0°C a solution of 0.880g of 70% *m*-chloroperbenzoic acid (3.6 mmol) in 30 mL of chloroform. The mixture was stirred for 17h during which time the solution was allowed to warm to room temperature. Then a solution of

1.0 g (4 mmol) of sodium thiosulfate and 1.0 g (12 mmol) of sodium bicarbonate in 15 mL of water was added and stirring was continued for another 0.5h. The two layers were separated and the aqueous layer was extracted with chloroform (2x30 mL). The combined organic layers were washed with brine, dried and filtered. Evaporation of the solvent under reduced pressure afforded 0.756 g (3.0 mmol) of a white solid which consisted of two diastereoisomeric epoxides 136A and 136B in a ratio of 2.5 to 1 respectively[31]. The epoxides were not separable and therefore the mixture was used in the following reaction.

136: ^{1}H NMR: 0.8-2.0 (m,15H), 1.03 (s,3H), 1.05 (s,3H), 2.88 (dd,2H)[31], 4.32 (m,1H); M.S. (70eV), *m/e* (%) 252(M^+,9), 236(6), 234(7), 177(30), 151(100), 138(82), 123(98), 95(96), Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.39; H, 9.59. Found: C, 71.59; H, 9.65.

*1α-Butyl-5,5-dimethyl-9β-hydroxy-3-oxo-3,5,6,7,8,9-hexahydro-1*H*-2-benzopyran* 137A *and* *1α-Butyl-5,5-dimethyl-9α-hydroxy-3-oxo-3,5,6,7,8,9-hexahydro-1H-2-benzopyran* 137B.

To 1 mL of a 15% solution of *n*-butyllithium in hexane (1.5 mmol) was added dropwise over a period of 10 min a solution of 0.18 g (1.8 mmol) of diisopropylamine in dry tetrahydrofuran at 0°C under nitrogen. After stirring for 0.5h the solution was cooled to -78°C and then a solution of 0.330g (1.31 mmol) of 136 in 20 mL of dry tetrahydrofuran was added dropwise. The solution was stirred for another hour and then the reaction was quenched with 1N hydrochloric acid at -78°C and this mixture was allowed to warm to room temperature. The mixture was extracted with ether (4x50 mL) and the combined organic layers were washed with brine and dried. Evaporation of the solvent afforded a residue which was chromatographed on 35 g of silica gel with petroleum ether (40-60°C)/ether (1:3).

The first compound isolated was identified as 137B a white solid (79 mg, 24%): mp 110.5-112.0°C; ^{1}H NMR: 0.8-2.2 (m,15H), 1.19 (s,3H), 1.38 (s,3H), 2.8 (br s,1H, exchanges with D_2O), 3.85 (br d,1H), 5.75 (s,1H),; M.S. (70eV), *m/e* (%) 252(M^+,0), 234(3), 177(6), 166(74), 151(100), 123(43); calcd for $C_{15}H_{22}O_3$ M^+-H_2O 234.1620, found M^+ 234.1621.

The second material eluted was identified as 137A as a white solid (195 mg, 59%): mp 124.0-126.0 °C; ^{1}H NMR: 0.8-2.2 (m,15H), 1.19 (s,3H), 1.38 (s,3H), 2.7 (br s,1H, exchanges with D_2O), 4.15 (br s,1H), 5.75 (s,1H); M.S. (70eV), *m/e* (%) 252(M^+,0), 234(3), 177(16), 166(80), 151(100), 123(40); Calcd for $C_{15}H_{22}O_3$

M^+-H_2O 234.1620, found 234.1625.

*1-Butyl-5,5-dimethyl-3-oxo-3,5,6,7-tetrahydro-1*H*-2 benzopyran* 134 *and 1-Butyl-5,5-dimethyl-3-oxo-5,6,7,8-tetrahydro-3*H-2-benzopyran 135.

A: A solution of 60 mg (0.28 mmol) of 137A was refluxed in 20 mL of benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid. After 16h the reaction mixture was poured into a saturated aqueous sodium bicarbonate solution and the aqueous layer was extracted with ether (2x20 mL). The combined organic layers were washed with brine and dried. Evaporation of the solvent afforded a mixture of 134 and 135 which were separated by column chromatography on 25 g of silica gel. Elution with petroleum ether (40-60°C)/ether (7:3) afforded 20 mg (33%) of 134 as a colourless oil: ^{1}H NMR: 0.7-2.1 (m,11H), 1.14 (s,3H), 1.18 (s,3H), 2.2-2.6 (m,2H), 4.88 (m,1H), 5.78 (br s,1H), 5.99 (m,1H); M.S. (70eV), *m/e* (%) 234(M^+,8), 177(100); calcd for $C_{15}H_{20}O_2$ M^+ 234.1620, found 234.1629. Further elution gave 20 mg (33%) of 135 as a colourless oil: ^{1}H NMR: 0.7-2.0 (m,1H), 1.22 (s,6H), 2.2-2.7 (m,4H), 6.12 (s,1H); M.S. (70eV), *m/e* (%) 234(M^+,25), 206(37), 191(35), 163(100); calcd for $C_{15}H_{20}O_2$ M^+ 234.16200; found 234.1622.

B: The same reaction was performed with 137B yielding a mixture which consisted of 80% of 135 and 20% of 134, as was estimated by integration of the ^{1}H NMR of the crude product.

Attempted Formation of 138.

To a solution of 5.6 mmol of *n*-butyllithium in 3.8 mL of hexane at 0°C was added dropwise a solution of 600 mg (5.95 mmol) of diisopropylamine in dry tetrahydrofuran under nitrogen. After 15 min the solution was cooled to -78°C and then a solution of 1.30 g (5.15 mmol) of 136 in 15 mL of dry tetrahydrofuran was added dropwise. After stirring for 45 min a solution of 460 mg (6 mmol) of carbon disulfide in 10 mL of dry tetrahydrofuran was added dropwise. The solution turned orange. Stirring was continued for another 0.5h. The reaction mixture was quenched with methyliodide at -78°C and the solution allowed to warm to room temperature. Careful TLC examination of the product revealed a rather complex mixture of compounds. Therefore this reaction was not investigated further.

Sulfenylation of Lactone 133b. *General Procedure.*

To a solution of 6.6 mmol of *n*-butyllithium in 4.4. mL of hexane was added dropwise over a period of 15 min at 0°C a solution of 750 mg (7.4 mmol) of diisopropylamine in 20 mL of dry tetrahydrofuran under nitrogen. After stirring for 0.5h the solution was cooled to -78°C and then a solution of 1.42 g (6.0 mmol) of 133b in 20 mL of dry tetrahydronfuran was added dropwise over 15 min The solution turned orange and was stirred for another 0.5h at -78°C. This cooled solution was then added dropwise to a solution of 7 mmol of sulfenylating agent in 25 mL of dry tetrahydrofuran which was cooled (-78°C). Stirring was continued for 45 min to 6h (see Table 3.3). The solution decolourized. The reaction mixture was warmed to room temperature, then poured into water and extracted with ether (3x50 mL). The organic layer was washed with water and brine and dried. Evaporation of the solvent afforded the crude product. Columnd chromatography on 50 g of silica gel with petroleum ether (40-60°C)/ether (19:1) gave the pure compounds. The yields are gathered in Table 3.3.

*1α-Butyl-5,5-dimethyl-3-oxo-4β-phenylthio-3,4,5,6,7,8-hexahydro-1*H*-2-benzopyran* 139A: ^{1}H NMR: 0.7-2.2 (m,15H), 1.05 (s,3H), 1.26 (s,3H), 4.23 (s,1H), 5.17 (m,1H), 7.2-7.7 (m,5H); M.S. (70eV), *m/e* (%) 344(M^+,5), 235(100), 85(92); calcd for $C_{21}H_{26}O_2S$ M^+ 344.1810, found M^+ 344.1805.

*1α-Butyl-5,5-dimethyl-3-oxo-4α-phenylthio-3,4,5,6,7,8-hexahydro-1*H*-2-benzopyran* 139B: ^{1}H NMR: 0.7-2.2 (m,15H), 1,01 (s,3H), 1.27 (s,3H), 4.06 (s,1H), 4.41 (br d,1H), 7.1-7.6 (m,5H); M.S. (70eV), *m/e* (%) 344(M^+,3), 235(58), 85(100), 57(44). Anal. Calcd for $C_{21}H_{26}O_2S$: C, 73.21; H, 8.19. Found: C, 73.33; H, 8.00.

Oxidation of 139A *and* 139B *with m-Chloroperbenzoic Acid.*

To a solution of 0.5 g of 139 (0.83 mmol 139A and 0.62 mmol 139B) in 10 mL of methanol was added 1.4 mmol of *m*-chloroperbenzoic acid. After stirring for 20h the reaction mixture was poured into saturated aqueous sodium bicarbonate solution and extracted with dichloromethane (3x25 mL). The organic layer was washed with brine and dried. Removal of the solvent *in vacuo* afforded a crude product which was chromatographed on 40 g of silica gel using petroleum ether (40-60°C)/ether (9:1). The following compounds could be isolated in order of elution: 90 mg (18%) of 139B, 130 mg (37%) of 137B and 90 mg (20%) of a mixture of 134 and a final compound, presumably an epoxy sulfide as deduced from ^{1}H NMR

data. This product could not be obtained in pure form.

Oxidation of 139A *with m-Chloroperbenzoic Acid.*

To a solution of 46 mg (0.13 mmol) of 139A in 1 mL of methanol was added 32 mg of 85% *m*-chloroperbenzoic acid (0.16 mmol). The same procedure as described above was used. The crude product was examined by ^{1}H NMR which revealed that 29% of 134 and 35% of 137A were present. Moreover 36% of the same unknown compound as mentioned above was present.

Oxidation of Sulfides 139 *with Sodium Perjodate.*

A: To a solution of 1.025 g of 139 (2.06 mmol of 139A and 0.92 mmol of 139B) in 25 mL of methanol and 5 mL of water was added 3.83 g (17.8 mmol) of sodium periodate. This mixture was refluxed for 6h and then the reaction mixture was poured into water and extracted with ether (4x50 mL). The organic layer was washed with water and brine and dried. Evaporation of the solvent under reduced pressure afforded an oil which was chromatographed on 50 g of silica gel with petroleum ether (40-60°C)/ether (9:1). The first compound eluted was 330 mg (47%) of 134 and the second was 147 mg (21%) of 135.

B: The same procedure was used for the oxidation of 139A. This afforded 134 and 135 in a ratio of 74% to 26%.

C: The same procedure was used for the oxidation of 139B. This afforded 134 and 135 in a ratio of 67% to 33%.

Dehydrogenation of Lactone 133b *with DDQ.*

A. To a solution of 183 mg (0.76 mmol) of 133b in 15 mL of dioxane and 443 mg (1.95 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was added 1 mL (8 mmol) of boron trifluoride etherate. This reaction mixture was refluxed for 20h. The mixture was poured into saturated aqueous sodium bicarbonate and extracted with ether (3x50 mL). The organic layer was washed with water and brine and dried. Evaporation of the solvent *in vacuo* afforded a crude product (85%) which consisted of 8% starting material, 36% of 134 and 41% of 135 according to ^{1}H NMR.

B: The same procedure was used as described above using 113 mg (0.51 mmol) of 133b in 20 mL of dioxane, 231 mg (1.02 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone and 194 mg (1.02 mmol) of *p*-toluenesulfonic acid. The crude product (100 mg, 88%) consisted of 59% of 134 and 29% of 135 according to ^{1}H NMR spectral data.

3.4 REFERENCES AND NOTES

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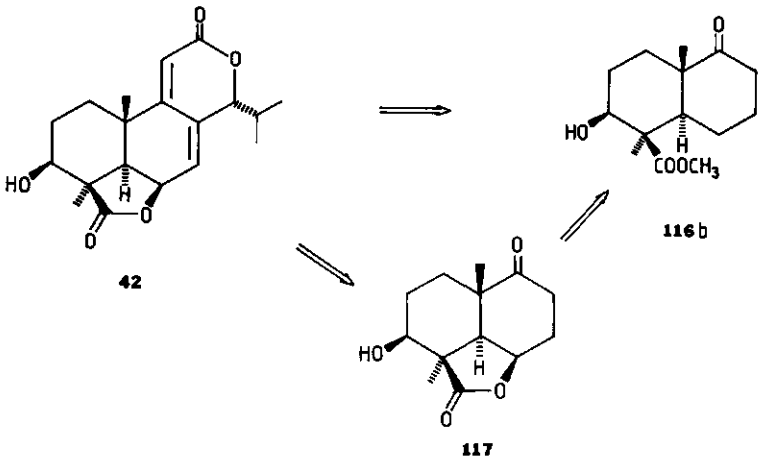
30. This reaction must be conducted in a well-ventilated hood; the chemist should wear rubber gloves because hexamethylphosphoramide is a severe carcinogen.

31. In the ^{1}H NMR two dd signals appear in a ratio of 2.5 to 1 as was determined by ^{1}H NMR integration.

4 THE STEREOSELECTIVE SYNTHESIS OF 4,4,10-TRISUBSTITUTED *TRANS*-FUSED NAPHTHALENONES AS INTERMEDIATES IN THE TOTAL SYNTHESIS OF 3β-HYDROXYNAGILACTONE F AND OTHER NATURAL PRODUCTS

4.1 INTRODUCTION

The retrosynthetic plan to the synthesis of 3β-hydroxynagilactone F (42) is outlined in section 2.2.5 (scheme 2.8). The *trans*-fused bicyclic ketone 116b (scheme 4.1) is a key intermediate in the approaches to this norditerpenoid dilactone in this thesis.



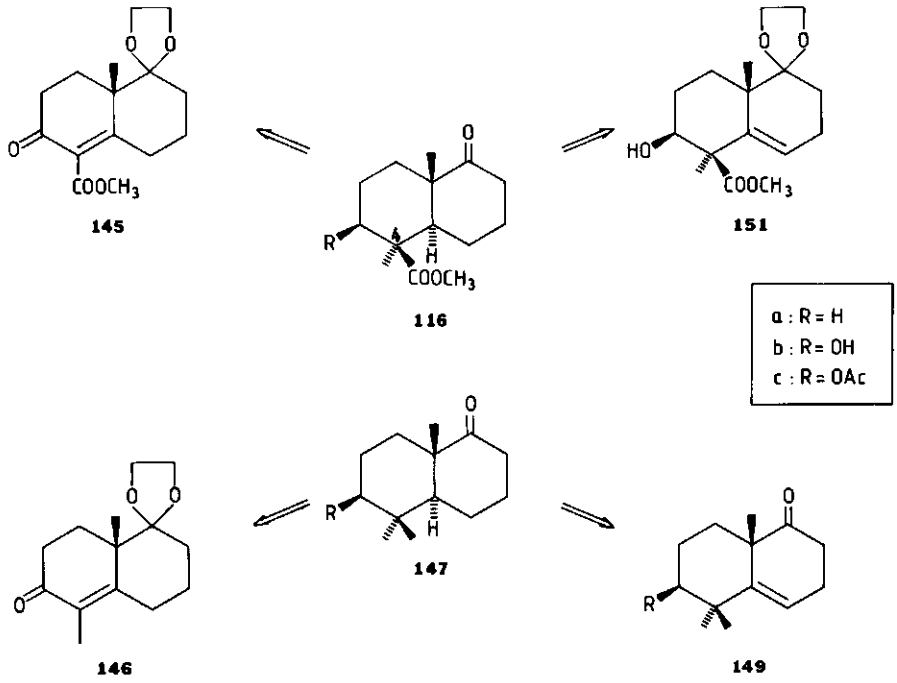
scheme 4.1

The investigations described in this chapter concern the stereoselective synthesis of the compounds 116. In addition the method is extended to the synthesis of the 4,4,10-trimethyl analogue 147a, a suitable starting material for the synthesis of drimane sesquiterpenes such as isodrimenin[1] and the insect antifeedant Warburganal[2].

The obvious procedures for the preparation of 116b and 147a, *i.e.* reductive alkylation of 145 and 146 or catalytic hydrogena-

tion of 151 and 149, turned out te be unattractive (scheme 4.2). Reductive alkylation of 146 gave good results in small-scale preparations, but on a larger scale mixtures of reduced and alkylated products were obtained, that required extensive purification. Reductive alkylation of 145 did not seem very promising since dissolving metal reduction of 145 gave mixtures of *cis*- and *trans*-fused reduction products and moreover methylation of the *trans*-fused enolate anion afforded a product with the epimeric configuration at C-4[5]. The methods developed for the synthesis of intermediates used in the total synthesis of LL-Z1271$^{\alpha}$ are not applicable as such (see chapter 2).

The catalytic hydrogenation of 149a and 149b has been investigated extensively, but only complex mixtures resulting from non-specific hydrogenation and overreduction were obtained[3b,6]. In addition the catalytic hydrogenation of 151 was troublesome and turned out to be irreproducible (scheme 4.2)[7].

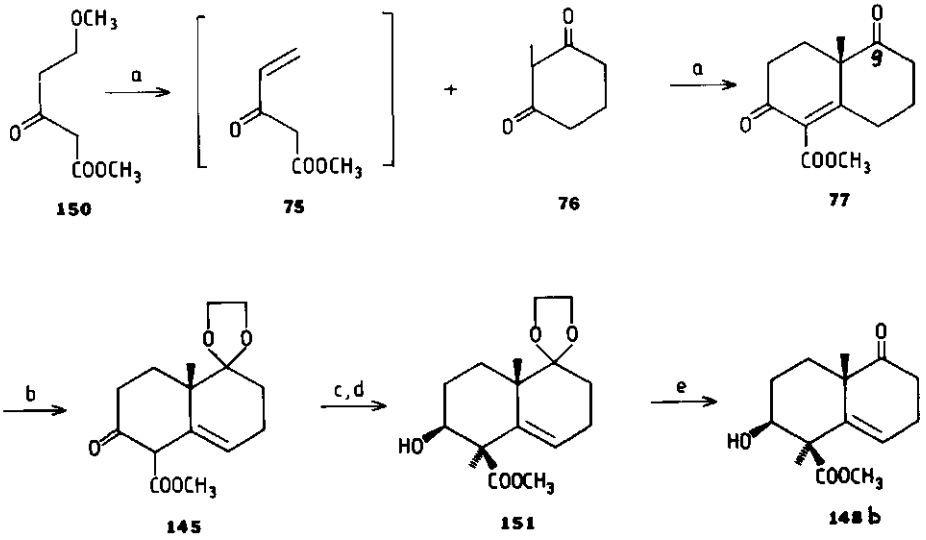


scheme 4.2

In this chapter a synthesis of 116 and 147 is described using compounds 148b, 149a and 149c as precursors. Extension of the unsaturated system in ring B followed by homogeneous catalytic hydrogenation proved to be a useful approach for the stereoselective reduction of the diene system. A stereoselective hydrogenation of the 5(6)-double bond in 149 and 151 can be achieved *via* this detour.

4.2 SYNTHESIS OF THE *TRANS*-FUSED AB RING SYSTEM

The starting compound 148b was prepared as outlined in scheme 4.3. The procedures published in the literature were used for the



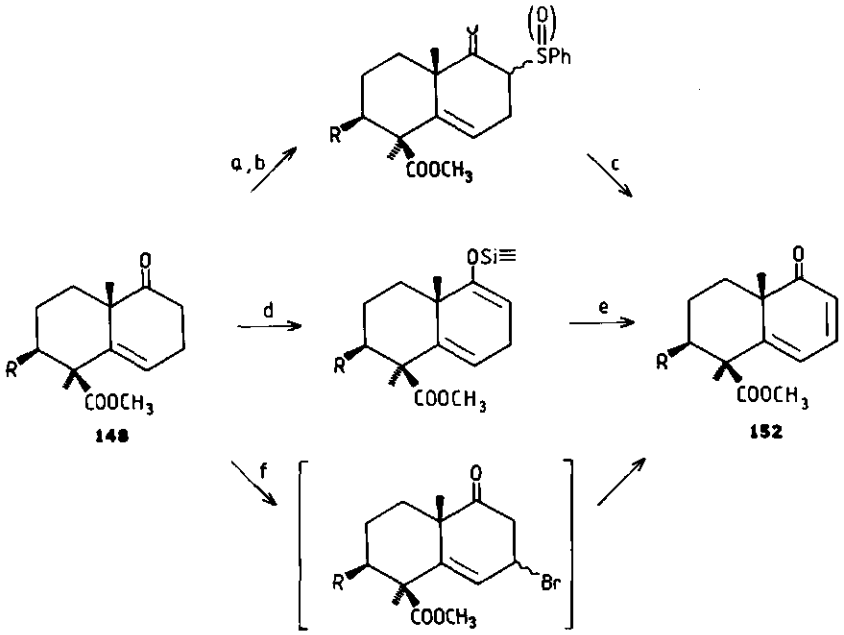
a : TsOH , PhH ; b : MED , TsOH ; c: t-BuOK , CH_3I ; d: $NaBH_4$, CH_3OH ; e: $H_3O^{\oplus}$, CH_3OH .

scheme 4.3

subsequent conversions, although some modifications were introduced which increased the overall yield. Refluxing methyl 5-methoxy-3-oxopentanoate 150 in benzene with a catalytic amount of

p-toluenesulfonic acid gives *in situ* the Nazarov reagent 75 which undergoes a Robinson annellation with 2-methyl-cyclohexane-1,3-dione 76 to the diketo ester 77. The C-9 carbonyl function in this product is then selectively protected, using 2-methyl-2-ethyl-1,3-dioxolane (MED) to afford the monoacetal 145. Methylation of 145 with potassium *t*-butoxide and methyliodide yielded 151 with the correct configuration at C-4. Subsequently sodium borohydride reduction of the C-3 carbonyl group and hydrolysis of the C-9 dioxolane group furnished the desired keto ester 148b in an overall yield of *ca.* 50%.

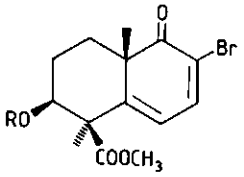
Initial attempts for the introduction of the double bond, *i.e.* sulfenylation, oxidation to the corresponding sulfoxide and elimination[8], DDQ dehydrogenation[9] or NBS bromination and dehydrobromination[10] proved to be quite laborious or irreproducible (scheme 4.4), and therefore were rejected. In the case of the one step reaction with NBS, varying amounts of the desired product



a : LDA , $PhSSO_2Ph$; b : $NaIO_4$; c: K_2CO_3 , $PhCH_3$, Δ ; d: LDA , $ClSi(CH_3)_3$; e : DDQ , collidine ; f: NBS , CCl_4.

scheme 4.4

152b, the starting material 148b and the bromodienone 155a (figure 4.1) were obtained. Especially the exothermic character of the reaction proved to be troublesome when scaling up the reaction was endeavoured.

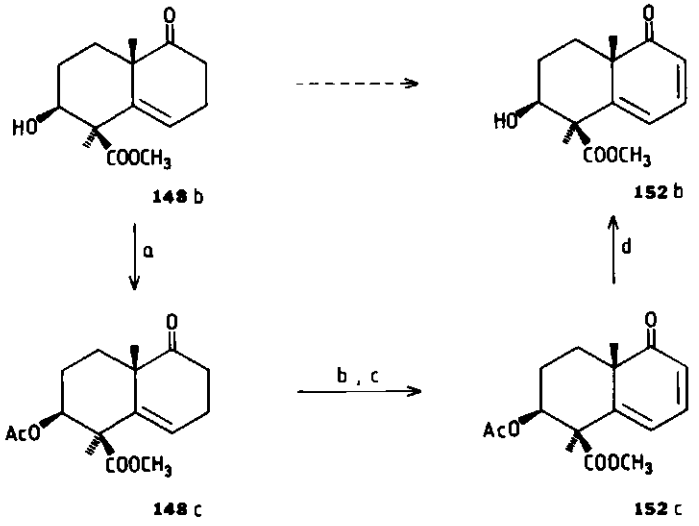


a : R= H
b : R= Ac

155

figure 4.1

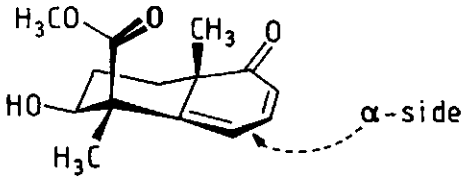
A convenient way for the extension of the unsaturated system proceeded through bromination followed by dehydrobromination to afford 152c. The best results were obtained, when the C-3 hydroxyl group of 148b was protected as acetate prior to bromination. After dehydrobromination small quantities (<10%) of the unsaturated bromide 155b were isolated in addition (*vide supra*). Saponification of the acetate group at C-3 gave 152b in an overall yield of 79%, starting from 148b (scheme 4.5).



a : Ac_2O , pyr , DMAP ; b : Br_2 , HOAc ; c : LiBr , Li_2CO_3 , DMF , Δ ;
d : K_2CO_3 , H_2O , CH_3OH.

scheme 4.5

When dienone 152b was hydrogenated with palladium on carbon at 45 psi hydrogen pressure this resulted in the formation of a 1:1 mixture of the *cis*- and *trans*-fused reduction products 156b and 116b respectively[11]. When this compound 152b was hydrogenated with Wilkinson's catalyst $[(Ph_3P)_3RhCl]$ at 24 psi however the products obtained were the desired *trans*-fused keto ester 116b and the unsaturated keto ester 148b in a ratio of *ca.* 1:2 (scheme 4.6). It is assumed that this catalyst complexes with the substrate prior to the hydrogen transfer. This complexation is likely to take place from the less hindered α-side of the molecule thus giving rise to the *trans*-fused AB ring system. The β-side is shielded by the axial angular C-10 methyl group and the axial C-4 ester group (figure 4.2).

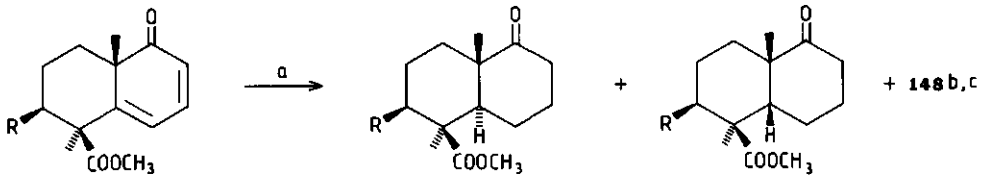


152 b

figure 4.2

A reduction was performed at higher hydrogen pressure (150 psi) to minimize the formation of 148b. In addition to a decrease in the amount of 148b, however, a noteworthy side reaction led to the formation of the *cis*-fused keto ester 156b. When the pressure was increased to 230 psi both the formation of 148b and the *cis*-fused ketone 156b increased. Obviously the hydrogen pressure influences the regio- and stereoselectivity of the hydrogenation, and therefore a series of hydrogenations was performed at increasing pressure (see Table 4.1, Method A). The optimum pressure appeared to be approximately 60 psi, but a considerable amount of the unsaturated compound 148b was still formed.

Besides this effect of the hydrogen pressure it is known from the literature that oxygen has an effect on the catalyst in that



152 b,c **116** b,c **156** b,c

a : $RhCl(Ph_3P)_3$, H_2.

b : R = OH
c : R = OAc

scheme 4.6

Table 4.1 Hydrogenation of 152b with $RhCl(Ph_3P)_3$

entry	pressure psi	percentage of 116b	148b	156b	Method
1	24	37	63		A[i]
2[ii]	44	62	38		A
3	55	80	20		A
4	60	87	13		A
5	70	~73	~27	<10	A
6	150	70	20	10	A
7	230	30	40	30	A
8	130	52	36	12	B[iii]
9	130	100			C[iv]

i Method A: The substrate and catalyst are dissolved in contact with air in ca. 10 min. prior to hydrogenation.

ii In this run the acetate 152c was hydrogenated. The acetate group became partially hydrogenated to the hydroxyl group, so in the runs 1 and 3-7 the hydroxy dienone 152b was hydrogenated.

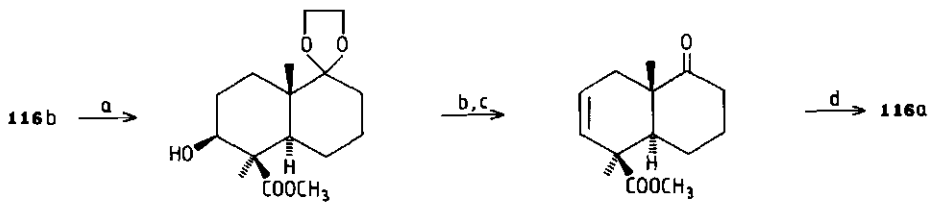
iii Method B: The substrate and catalyst are dissolved under a nitrogen atmosphere prior to hydrogenation.

iv Method C: The substrate and catalyst are dissolved and then stirred in contact with air for 1 hour prior to hydrogenation.

it accelerates the catalytic hydrogenation[13]. The effect of exclusion of oxygen (entry 8, Table 4.1) was an increase in the amount of the unsaturated compound 148b, contrary to what was desired.

In another run therefore (entry 9, Table 4.1), the solution of substrate 152b and catalyst was stirred for one hour in contact with air, prior to the hydrogenation. This did indeed result in hydrogenation with a high degree of regio- and stereoselectivity. The dienones 152b and 152c were hydrogenated under these conditions to the *trans*-fused keto esters 116b and 116c respectively in a yield of 80% (Method C).

The stereochemistry of the *trans*-fused keto ester 116b was assigned by ^1H NMR spectroscopic data. In addition 116b was converted into the saturated keto ester 116a a known compound, described by Welch *et al.* (see scheme 4.7)[14].



a : MED , p-TsOH , $(CH_2OH)_2$; b : $POCl_3$, pyr. ; c : $H_3O^{\oplus}$, CH_3OH ; d : Pd/C , H_2

scheme 4.7

For this purpose compound 116b had to be dehydrated and subsequently hydrogenated to the saturated keto ester 116a. It proved necessary to protect the C-9 carbonyl group prior to dehydration in order to avoid the formation of the chlorinated products 158 and 159 (figure 4.3).

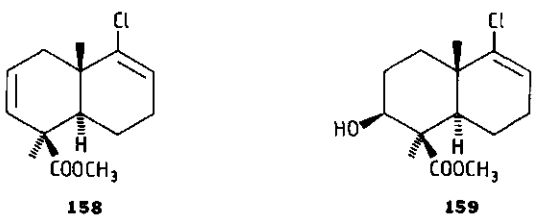
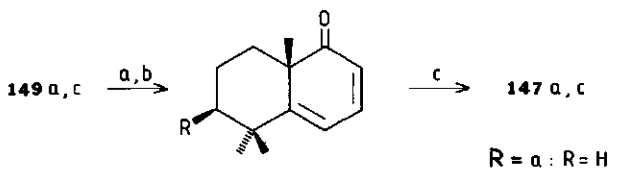


figure 4.3

The method for the synthesis of the *trans*-fused bicyclic ketone 116 outlined above was also applied for the synthesis of ketones 147a and 147c (scheme 4.8). The dienones 157a and 157c were prepared in the same manner, as described for the dienones 152, starting from the ketones 149a and 149b[15] (*vide supra*). When these dienones were hydrogenated with Wilkinson's catalyst at 28 psi hydrogen pressure the desired *trans*-fused bicyclic ketones 147a and 147c were isolated in approximately 80% yield. Small quanti-



scheme 4.8

ties (<5%) of partly hydrogenated products were formed and no *cis*-fused reduction products could be detected. The α,β-unsaturated ketone was isolated as a minor side product when low concentrations of catalyst were used. An attempted stereoselective hydrogenation of 157 with palladium on carbon gave a 1:1 mixture of *cis*- and *trans*-fused reduction products. This is comparable with the results obtained with dienone 152. The assignment of the configurations of 147a and 147c was based on the fact, that their spectroscopic data were identical with those reported in the literature[3b,6].

An attempt to hydrogenate 148b directly using Wilkinson's catalyst, even at 1200 psi hydrogen pressure, was unsuccesful. The bromo dienone 155a (figure 4.1) could not be hydrogenated either. These two examples again illustrate the general feature of this catalyst in that triply substituted olefins are generally not or at best only sluggishly hydrogenated[13]. The reactivity of this type of olefin is sometimes increased by the presence of a second conjugated double bond and/or an electron-withdrawing substituent. In this case extension of the unsaturated system in 147 and 116 to

a dienone system in 152 and 157 clearly enhances the reducibility in homogeneous hydrogenations. Both double bonds can be reduced using method A but the greater steric hindrance in keto ester 152 becomes evident from the isolation of 148b in reasonable amounts, whereas in the hydrogenation of 157 only traces of 149 were found.

4.3 EXPERIMENTAL SECTION

General experimental conditions were as described in chapter 3.

Methyl 2,5-Dioxo-4aβ-methyl-2,3,4,4a,5,6,7,8-octahydronaphthalene-1-carboxylate (77)[17].

A solution of 23.9 g (149 mmol) of methyl 5-methoxy-3-oxo-pentanoate 150[16] in 50 mL of anhydrous benzene was added to a suspension of 20.7 g (164 mmol) of 2-methylcyclohexane-1,3-dione 76[18] and 0.50 g of *p*-toluene sulfonic acid in 600 mL of anhydrous benzene, and this mixture was refluxed for 76 hours while water was removed using a Deans Stark apparatus. The cooled benzene solution was washed with saturated aqueous sodium bicarbonate and the aqueous layer was extracted with ether (2x150 mL). The combined organic layers were washed with water, brine and dried. The solvent was evaporated under reduced pressure to afford a light yellow oil, which was crystallized from disopropyl ether-methanol to give 18.5 g of the diketoester 77. Seeding of the concentrated mother liquor and subsequent crystallisation gave an additional 8.5 g of 77 (total yield of 82%): mp 69-70°C (lit.[7] mp 70-71°C); ^{1}H NMR: 1.48 (s,3H), 1.6-2.8 (m,10H), 3.78 (s,3H).

Methyl 5,5-(Ethylenedioxy)-2-oxo-4aβ-methyl-2,3,4,4a,5,6,7,8-octahydronaphthalene-1-carboxylate (145).

The procedure of Bauduin and Pietrasanta[19] was employed for the protection of the carbonyl function at C-5. An amount of 20.6 g (87.1 mmol) of diketo ester 77 was dissolved in 75 mL of 2-methyl-2-ethyl-1,3-dioxolane. Glycol (1.5 mL) and 200 mg of *p*-toluene sulfonic acid were added and the mixture was stirred at room temperature for 4 days. TLC examination revealed that the reaction was complete. The reaction mixture was poured into saturated aqueous sodium bicarbonate and extracted with ether (3x150 mL). The combined organic layers were washed with water and brine and dried. The solvent was evaporated,

and the residual light yellow oil was crystallized from diisopropyl ether methanol to give 15.8 g of keto ester acetal 145. The mother liquor was chromatographed on 100 g of silica gel. Elution with petroleum ether (40-60°C)/ether (1:3) gave an additional 4.2 g of the product. The total yield ws 82%: mp 121-122°C (lit.[7] mp 120-122°C); ^{1}H NMR: 1.38 (s,3H), 1.8-2.7 (m,10H), 3.76 (s,3H), 3.93 (s,4H).

Methyl 5,5-(Ethylenedioxy)-1α,4aβ-dimethyl-2β-hydroxy-1,2,3,4,4a,5,6,7 -octahydronapthalene-1β-carboxylate (151).

For the methylation of ketone 145, the procedure of Mangoni *et al.*[20] was addapted. A solution of 9.0 g (32.4 mmol) of keto ester 145 in 50 mL of 1:1 of dry benzene and *t*-butanol was added dropwise in 30 min to a stirred solution of 4.10 g (33.5 mmol) of commercial potassium *t*-butoxide in 500 mL of 4:1 dry benzene and *t*-butanol under nitrogen. After being stirred for 15 min at 40°C, the dark red solution was cooled to 0°C in an ice bath. Then 25 mL of methyl iodide was added and the mixture refluxed for 17h. The cooled reaction mixture was poured into water and the layers separated. The aqueous layer was extracted with ether (2x150 mL). The combined organic layers were washed with water and brine and dried. The solvent was evaporated under reduced pressure, and the residual white solid was crystallized from diisopropyl ether-methanol to give 7.05 g of methylated keto ester ketal. The mother liquor was chromatographed on silica gel 50 g, eluent petroleum ether (40-60°C)/ether (3:1) to afford an additional 1.06 g. A total yield of 8.12 g (86%) was obtained: mp 120-121°C (lit.[7], mp 121.5-122.5°C); ^{1}H NMR: 1.25 (s,3H), 1.49 (s,3H), 1.7-2.8 (m,8H), 3.69 (s,3H), 4.0 (br s,4H), 5.59 (dd, *J*=4, 4Hz,1H).

The reduction of the C-2 carbonyl group was performed as described by Pelletier *et al.*[7]. To a suspension of 13.52 g (46.0 mmol) of keto ester in 300 mL of methanol was added portionwise 4.53 g (120 mmol) of sodium borohydride in 3h. After stirring for 17h the methanol was distilled off under reduced pressure and the residue treated with water and chloroform. The layers were separated and the aqueous layer was extracted with chloroform (3x50 mL). The combined organic layers were washed with water and brine and dried. After filtration the solvent was evaporated under reduced pressure affording hydroxy ester ketal 151 as a solid material (12.2 g, 90%). NMR analysis showed a single compound, which was used without further purification in the next step: ^{1}H NMR[7]: 1.07 (s,3H), 1.51 (s,3H), 1.4-2.4 (m,8H), 3.13 (dd, *J*=6, 9Hz,1H), 3.55 (br s,1H, exchanges with D_2O), 3.61 (s,3H), 3.92 (s,4H), 5.79 (dd, *J*=4,

4Hz,1H).

Methyl 5-Oxo-1α,4aβ-dimethyl-2β-hydroxy-1,2,3,4,4a,5,6,7-octahydronaphthalene-1β-carboxylate 148b.

To a solution of 13.6 g (45.9 mmol) of ester ketal 151 in 74 mL of methanol at 0°C was added 5 mL of 4N hydrochloric acid, and this mixture was stired for 4h. The reaction mixture was neutralized with saturated aqueous sodium bicarbonate and most of the methanol distilled off *in vacuo*. The residue was worked up by adding water and chloroform. After separation of the layers the aqueous layer was extracted with chloroform (3x50 mL). The organic layer was washed with water and brine and dried. Evaporation of the solvent afforded an residual solid which was crystallized from diisopropyl ether yielding 6.11 g hydroxy keto ester 148b. The mother liquor was chromatographed on silica gel 50 g, eluent ether/petroleum ether (40-60°C)(3:1) to give an additional 3.79 g 148b (85% total yield): mp 82.5-83.5°C (lit.[7]: mp 83-84°C); ^{1}H NMR: 1.15 (s,3H), 1.56 (s,3H). 1.8-2.8 (m,8H), 3.10 (dd, *J*=6, 9Hz,1H), 3.5 (br s,1H, exchanges with D_2O), 3.70 (s,3H), 5.97 (dd, *J*=5, 6Hz,1H).

Methyl 5-Oxo-2β-acetoxy-1α,4aβ-dimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalene-1β-carboxylate (148c).

To a stirred solution of 6.43 g (25.5 mmol) of keto ester 148b in 25 mL of dry pyridine was added 25 mL of acetic anhydride and 100 mg of dimethylaminopyridine as catalyst. Stirring was continued for another 18h and then the reaction mixture was poured into ice water. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with dichloromethane (4x75 mL). The organic layer was washed with 0.5N hydrochloric acid, saturated aqueous sodium bicarbonate, water and brine and dried. After filtration the solution was concentrated *in vacuo* and the residual solid crystallized from diisopropylether to afford 7.34 g (25.0 mmol) of the acetate 148c (98%): mp 104-105°C (lit[7]. 104-106°C); ^{1}H NMR: 1.20 (s,3H), 1.37 (s,3H), 1.3-2.8 (m,8H), 2.08 (s,3H), 3.64 (s,3H), 4.48 (dd, *J*=4, 11Hz,1H), 6.03 (dd, *J*=5, 6Hz,1H).

Reaction of 148b *with NBS.*

To a solution of 386 mg (1.53 mmol) of 148b in 10 mL of tetra was added 300 mg (1.69 mmol) of N-bromosuccinimide and this mixture was refluxed for 3.5h. This reaction mixture then was allowed to cool to room temperature whereupon the remaining succinimide crystallized and was filtered of with suction. The

filtrate was concentrated *in vacuo* to afford the crude product which was chromatographed on 50 g of silica gel with petroleum ether (40-60°C)/ether (1:1). This resulted in the isolation of 38.5 mg (0.09 mmol, 6%) of hydroxy bromo dienone 155a and 271 mg (1.08 mmol, 71%) of hydroxy dienone 152b.

Methyl 5-Oxo-2β-acetoxy-1α,4aβ-dimethyl-1,2,3,4,4a,5-hexahydronapthalene-1β-carboxylate (152c).

To a solution of 7.34 g (25.0 mmol) of acetate 148c in 100 mL of glacial acetic acid was added dropwise a solution of 4.00 g (25.0 mmol) of bromine in 20.6 mL of glacial acetic acid at room temperature. After 30 min the solution was poured into ice water, and this mixture was extracted with ether (3x100 mL). The organic layer was washed with water, saturated aqueous sodium bicarbonate and brine and dried. Evaporation of the solvent under reduced pressure gave the crude bromide. The crude α-bromo ketone was dissolved in 100 mL of dimethylformamide and then 3.3 g (38 mmol) of lithium bromide and 4.4 g (60 mmol) of lithium carbonate were added. The suspension was stirred in a preheated oil bath at 120°C for 30 min under nitrogen. Then the reaction mixture was cooled, poured into water and after neutralization of the aqueous layer with 1N hydrochloric acid, extracted with ether (3x150 mL). The organic layer was washed with water and brine and dried. Evaporation of the solvent *in vacuo* yielded a crude product which was chromatographed on 150 g of silica gel with ether/petroleum ether (40-60°C)(2:3). The first compound isolated was 0.36 g (4%) of 155b, which was not further characterized but hydrolyzed to bromo hydroxy ketone 155a. The second compound eluted was identified as dienone acetate 152c (6.61 g, 91%): mp 108.0-108.5°C; ^{1}H NMR: 1.21 (s,3H), 1.47 (s,3H), 1.3-2.8 (m,4H), 2.00 (s,3H), 3.66 (s,3H), 4.52 (dd, J=4, 12Hz,1H), 6.03 (d, J=10Hz,1H), 6.41 (d, J=7Hz,1H), 7.10 (dd, J=7, 10Hz,1H); M.S. (70eV), *m/e* (%) 292(M^+,12), 232(32), 173 (100), 172(41), 145(87), 43(93). Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.70; H, 6.95.

Methyl 5-Oxo-1α,4aβ-dimethyl-2β-hydroxy-1,2,3,4,4a,5-hexahydronaphthalene-1β-carboxylate (152b).

To a solution of 6.28 g (21.5 mmol) of acetate 152c in 100 mL of methanol was added at 0°C a solution of 2.09 g (14.5 mmol) of potassium carbonate. After being stirred for 4h, the mixture was poured into ice water, and the aqueous layer extracted with dichloromethane (5x60 mL). The combined organic layers were washed with water (100 mL) and brine and dried. Evaporation of the solvent

under reduced pressure yielded a light yellow solid, which was crystallyzed from diisopropyl ether to afford 4.69 g (18.8 mmol, 87%) of hydroxy dienone 152b: mp 125.0-126.0°C; ^{1}H NMR: 1.14 (s,3H), 1.62 (s,3H), 1.3-2.4 (m,4H), 3.14 (dd, J=6, 11Hz,1H), 3.62 (s,3H), 3.72 (br s,1H, exchanges with D_2O), 5.99 (d, J=10Hz,1H), 6.34 (d, J=6Hz,1H), 7.05 (dd, J=6, 10Hz,1H); M.S. (70eV), *m/e* (%) 250 (M^+,20), 232(5), 218(36), 194(87), 173(41), 162(100), 161(34), 145(49), 133(36). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.98; H, 7.23.

Methyl 5-Oxo-6-bromo-1α,4aβ-dimethyl-2β-hydroxy-1,2,3,4,4a,5-hexahydronephthalene-1β-carboxylate (155a).

Bromo dienone acetate 155b was treated as is described for the synthesis of compound 152b from 152c. This afforded 300 mg (0.9 mmol, 86%) of bromo dienone 155a: mp 154.5-155.5°C; ^{1}H NMR: 1.21 (s,3H), 1.64 (s,3H), 1.3-2.5 (m,4H), 3.18 (dd, J=5, 9Hz,1H), 3.68 (s,3H), 3.70 (br s,1H, exchanges with D_2O), 6.31 (d, J=7Hz,1H), 7.59 (d, J=7Hz,1H); M.S. (70eV), *m/e* (%) 330/328(M^+,19/21), 298/296(35/37), 274/272 (94/100), 273/271(42/40), 242,240 (93/90), 241/239(50/44), 213/211(50/42), 192(32), 172(56), 43(68). Anal. Calcd for $C_{14}H_{17}BrO_4$: C, 51.08; H, 5.21. Found: C, 51.36; H, 5.06.

General Procedures for the Hydrogenation of the Dienones 152b *and* 152c *with Tris(triphenylphosphine)rhodium (I) Chloride.*

Method A.

To a solution of 4 mmol of the dienone in 40 mL of absolute methanol and dry benzene (1:1) was added 200 mg of Wilkinson's catalyst (5 mol %). This mixture was hydrogenated in a hydrogen atmosphere at the indicated pressure (see Table 4.1). The yields obtained after column chromatography on SiO_2 were approximately 80%.

Method B.

To a solution of 4 mmol of the dienone in 40 mL of absolute methanol and dry benzene (1:1) was added 200 mg of Wilkinson's catalyst (5 mol %) under nitrogen and the catalyst was dissolved in *ca.* 10 min prior to hydrogenation. The mixture was hydrogenated at a hydrogen pressure of 130 psi (see Table 4.1).

Method C.

To a solution of 4 mmol of the dienone in 40 mL of absolute methanol and dry benzene (1:1) was added 200 mg of Wilkinson's catalyst (5 mol %). When the

catalyst was dissolved the solution was stirred in contact with air for 1h. The mixture was hydrogenated at a hydrogen pressure of 130 psi. Column chromatography on silica gel afforded 80% of hydroxy keto ester 116b.

Methyl 5-Oxo-2β-acetoxy-1α,4aβ-dimethyl-1,2,3,4,4a,5,6,7,8,8aα-decahydronaphthalene-1β-carboxylate (116c).

The procedure outlined above was used (see Table 4.1): mp 127.5-128.0°C; ^{1}H NMR: 1.08 (s,3H), 1.27 (s,3H), 1.0-2.8 (m,11H), 2.06 (s,3H), 3.72 (s,3H), 4.53 (dd, *J*=5, 13 Hz,1H); M.S. (70eV), *m/e* (%) 268 (M^+,3), 236(52), 226(15), 209(16), 208(100), 193(11). Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.94; H, 8.26.

Metnyl 5-Oxo-1α,4aβ-dimethyl-2β-hydroxy-1,2,3,4,4a,5,6,7,8,8aα-decahydronaphthalene-1β-carboxylate (116b).

The procedure outlined above was used (see Table 4.1): mp 158.0-159.0°C; ^{1}H NMR: 0.98 (s,3H), 1.40 (s,3H), 1.0-2.6 (m,11H), 3.08 (dd, *J*=6, 9Hz,1H), 3.6 (br s,1H, exchanges with D_2O), 3.73 (s,3H); M.S. (70eV), *m/e* (%) 254 (M^+,6), 236(30), 222(22), 204(18), 165(46), 149(24), 125(60), 121(34), 107(45), 95(100). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 66.35; H, 8.80.

Methyl 5-Oxo-1α,4aβ-dimethyl-2β-hydroxy-1,2,3,4,4a,5,6,7,8,8aβ-decahydronaphthalene-1β-carboxylate (156b).

A side product of the hydrogenation of 152b at higher pressure (see Table 4.1): mp 105.5-107.0°C; ^{1}H NMR: 1.10 (s,3H), 1.34 (s,3H), 1.2-2.7 (m,11H), 3.60 (br s,1H, exchanges with D_2O), 3.68 (dd, *J*=5, 9Hz,1H), 3.70 (s,3H); M.S. (70eV), *m/e* (%) 254 (M^+,4), 236(38), 222(16), 204(38), 165(38), 149(40), 121(42), 107(56), 95(100). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 66.26; H, 8.81.

Attempted Dehydration of 116b *with Thionyl Chloride.*

To an ice-cooled solution of 259 mg (1.02 mmol) of 116b in 10 mL of dry pyridine was added 4 mL (50 mmol) of thionyl chloride. After stirring for 64h during which time the solution warmed up to room temperature crushed ice was added and this mixture was extracted with ether (3x50 mL). The organic layer was washed with 1N hydrochloric acid, saturated aqueous sodium bicarbonate and brine and dried. Evaporation of the solvent *in vacuo* afforded the crude product which was chromatographed on 30 g of silica gel with petroleum ether (40-

60°C)/ether (7:3). The first compound, isolated as an oil (50 mg, 20%), was identified as methyl 5-chloro-1α,4aβ-dimethyl-1,4,4a,7,8,8aα-hexahydronaphthalene-1β-carboxylate (158): ^{1}H NMR: 1.01 (s,3H), 1.32 (s,3H), 1.5-2.4 (m,7H), 3.63 (s,3H), 5.69 (m,3H); M.S. (70eV), *m/e* (%) 256/254(M^+,3/8), 219(7), 195(94), 159(62), 115(100). The second material, isolated as a white solid (50 mg, 18%), was identified as methyl 5-chloro-1α,4aβ-dimethyl-2 -hydroxy-1,2,3,4,4a,7,8,8aα-octahydronaphthalene-1β-carboxylate (159): ^{1}H NMR: 0.98 (s,3H), 1.43 (s,3H), 1.2-2.3 (m,9H), 3.13 (dd, *J*=6, 9Hz,1H), 3.35 (br s,1H, exchanges with D_2O), 5.70 (m,1H); M.S. (70eV), *m/e* (%) 274/272 (M^+,0.5/2), 256/254(0.5/2), 159(32), 114(100).

No other products could be isolated.

Methyl 5,5-(Ethylenedioxy)-1α,4aβ-dimethyl-2β-hydroxy-1,2,3,4,4a,5,6,7,8,8aα-decanydronaphthalene-1β-carboxylate (153).

For the protection of the carbonyl function at C-5 of 116b, the procedure described for the synthesis of acetal 145 was employed to give 252 mg (0.85 mmol, 80%) of hydroxy acetal 153: ^{1}H NMR: 0.88 (s,3H), 1.36 (s,3H), 1.1-2.3 (m,11H), 3.11 (dd, *J*=4, 10Hz,1H), 3.15 (br s,1H, exchanges with D_2O), 3.67 (s,3H), 3.90 (br s,4H); M.S. (70eV), *m/e* (%) 298 (M^+,18), 99(100), 86(24); calcd for $C_{16}H_{26}O_5$ M^+ 298.1780, found M^+ 298.1790.

Methyl 5-Oxo-1α,4aβ-dimethyl-1,2,3,4,4a,5,6,7,8,8aα-octahydronaphthalene-1β-carboxylate (154).

To an ice-cooled solution of 252 mg (0.85 mmol) of hydroxy acetal 153 in 10 mL of dry pyridine was added at 0°C 0.5 mL of phosphorus oxytrichloride, and then the solution was refluxed for 1h. The cooled reaction mixture was poured into ice water and extracted with dichloromethane (4x50 mL). The combined organic layers were washed with 1N hydrochloric acid (50 mL), saturated aqueous sodium bicarbonate, and brine and dried. The solution was concentrated *in vacuo*, and the residual oil (112 mg) was dissolved in 5 mL of methanol. Then 0.5 mL of 4N hydrochloric acid was added, and the reaction mixture was stirred for 17h. The reaction mixture was poured into ice water containing 5 mL of saturated aqueous sodium bicarbonate and this aqueous layer was extracted with dichloromethane (4x50 mL). The organic layers were washed with brine and dried. The crude product that was obtained after evaporation of the solvent was chromatographed on silica gel (30 g, eluent ether/petroleum ether (40-60°C), 1:1) and yielded 84 mg (0.36 mmol, 42%) of 154: ^{1}H NMR: 1.07 (s,3H), 1.30

(s,3H), 1.1-2.6 (m,9H), 3.65 (s,3H), 5.60 (m,2H); M.S. (70eV), *m/e* (%) 236 (M^+,26), 193(56), 177(38), 159(100), 133(41), 85(50); calcd for $C_{14}H_{20}O_3$ M^+ 236.1412, found M^+ 236.1420.

Methyl 5-Oxo-1α,4aβ-dimethyl-1,2,3,4,4a,5,6,7,8,8aα-decahydronaphthalene-1β-carboxylate (116a).

To a solution of 70 mg (0.29 mmol) of enone 154 was added 50 mg of palladium on charcoal, and this mixture was hydrogenated at atmospheric pressure for 5h. The catalyst was filtered off and the solution concentrated in vacuo. The crude product (67 mg, 95%) was crystallized from petroleum ether (40-60°C) to give 30 mg of 116a: mp 85-87°C (lit.[4b] mp 87.5-88.5°C); ^1H NMR: 0.97 (s,3H), 1.20 (s,3H), 1.1-2.8 (m,13H), 3.68 (s,3H); M.S. (70eV), *m/e* (%) 238 (M^+,4) 210(27), 151(31), 110(22), 109(100), 101(21), 95(26), 81(23); calcd for $C_{14}H_{22}O_3$ M^+ 238.1569, found M^+ 238.1550. These data are in agreement with those reported in the literature[4b].

5,5,8β-Trimetnyl-5,6,7,8-tetrahydronaphthalene-1(8aH)-one (157a).

The bromination and dehydrobromination of 149a was performed as described for the synthesis of compound 152c. 7.44 g (38.7 mmol) of ketone 149a was used and the crude product was chromatographed on 150 g of silica gel with petroleum (40-60°C)/ether (1:9). The dienone 157a was isolated in an 80% yield as a light yellow solid: ^1H NMR: 1.19 (s,3H), 1.26(s,3H), 1.38(s,3H), 1.1-2.5 (m,6H), 5.89 (d, J=10 Hz,1H), 6.17 (d, J=7Hz,1H), 6.98 (dd, J=7, 10Hz,1H); M.S. (70eV), *m/e* (%) 190 (M^+,100), 175(58), 147(73), 134(56), 122(75), 121(75), 91(76), 69(56), 41(73); calcd for $C_{13}H_{18}O$ M^+ 190.1358, found M^+ 190.1357.

6β-Acetoxy-5,5,8aβ-trimethyl-5,6,7,8-tetrahydronaphthalen-1(8aH)-one (157c).

The procedure described for the synthesis of dienone 157a was employed. The crude dienone 157c (260 mg, 1,05 mmol) was chromatographed on silica gel (50 g, eluent ether/petroleum ether (40-60°C), 1:1). The first material eluted was identified as 6-acetoxy-2-bromo-5,5,8aβ-trimethyl-5,6,7,8-tetrahydronaphthalen-1(8a*H*)-one, a light yellow solid (31 mg, 9.5%): mp 183.0-184.0°C; ^1H NMR: 1.16 (s,3H), 1.26 (s,3H), 1.43 (s,3H), 1.3-2.3 (m,4H), 2.08 (s,3H), 4.54 (dd, J=6, 8Hz,1H), 6.11 (d, J=7Hz,1H), 7.42 (d, J=7Hz,1H); M.S. (70eV), *m/e* (%) 328/326 (M^+,4/5), 268/266(26/28), 229/227(80/86), 187(40), 172(34), 43(100). Anal. Calcd for $C_{15}H_{19}BrO_3$: C, 55.06; H, 5.85. Found: C, 55.24; H, 5.88. The second material eluted was identified as dienone 157c (196 mg, 79%), a light yellow

solid: mp 115.5-116.0°C; ^{1}H NMR: 1.18 (s,3H), 1.28 (s,3H), 1.39 (s,3H), 1.1-2.3 (m,4H), 2.07 (s,3H), 4.55 (dd, *J*=7, 8Hz,1H), 5.94 (d, *J*=10Hz,1H), 6.25 (d, *J*=7Hz,1H), 7.02 (dd, *J*=7, 10Hz,1H); M.S. (70eV), *m/e* (%) 248 (M^+,14), 206(20), 188(55), 173(64), 149(100), 145(72), 43(33). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.62; H, 8.34.

5,5,8aβ-Trimethyl-3,4,4aα,5,6,7,8,8a-octahydronaphthalen-1(2H)-one (147a).

To a solution of 6.0 g (31 mmol) of ketone 157a in 210 mL of a mixture of 1:1 absolute methanol and dry benzene was added 850 mg (0.93 mmol) of Wilkinson's catalyst (3 mol %). This mixture was hydrogenated in a hydrogen atmosphere at a pressure of 28 psi. Column chromatography on silica gel (150 g, eluent ether/petroleum ether (40-60°C), 1:9) yielded 4.81 g (80%) of ketone 147a: ^{1}H NMR: 0.91 (s,3H), 0.95 (s,3H), 1.16 (s,3H), 1.0-2.9 (m,13H). The additional characteristics were identical with those reported in the literature[3b].

6β-Acetoxy-5,5,8aβ-trimethyl-3,4,4aα,5,6,7,8a-octahydronaphthalen-1(2H)-one (147c).

The hydrogenation of 1.0 g (4 mmol) of ketone 157c was performed as outlined above at a pressure of 28 psi. The acetate 147c was obtained in 80% yield (0.81 g): ^{1}H NMR: 0.90 (s,3H), 0.97 (s,3H), 1.18 (s,3H), 1.1-2.8 (m,11H), 2.05 (s,3H), 4.45 (dd, *J*=6, 11Hz,1H). The additional characteristics were identical with those reported in the literature[6].

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5 THE SYNTHESIS OF 3β-HYDROXYNAGILACTONE F: A FIRST APPROACH

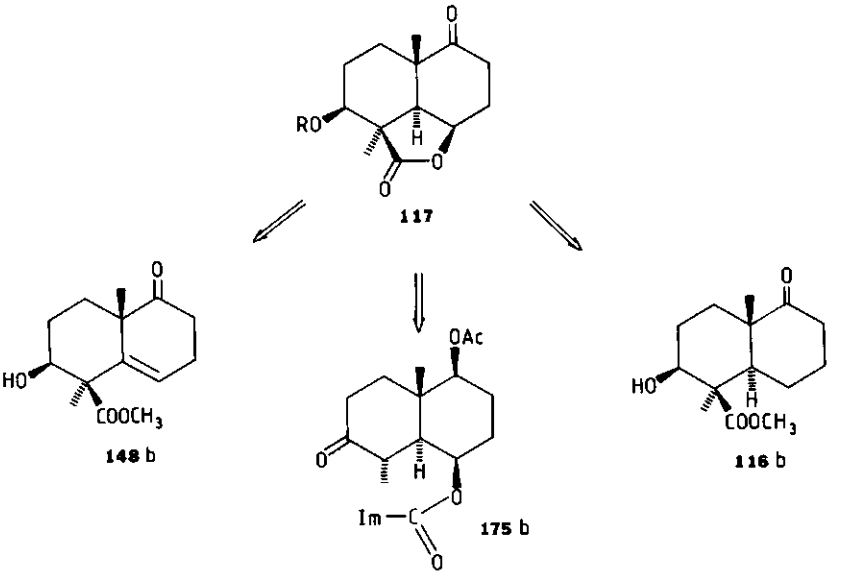
5.1 INTRODUCTION

The γ-lactone 117 seemed a suitable intermediate in the synthesis of 3β-hydroxynagilactone F (42) (see scheme 4.1).

Some approaches towards the synthesis of γ-lactones analogous to 117 have been published in the literature. Two such compounds (84 and 99), which served as intermediates in the total synthesis of LL-Z1271α (49), are described in chapter 2 but both compounds lack a functionality in ring A and hence were not considered for the synthesis of 117.

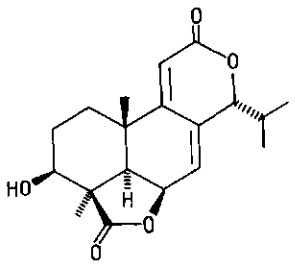
The synthesis of γ-lactones from γ-hydroxy ketones, used in an approach for the synthesis of corticosteroids, was published in 1963[1]. An analogous method was applied to 175b and the results are outlined in section 5.2.1 (scheme 5.1).

Two additional approaches aiming at the synthesis of γ-lactone

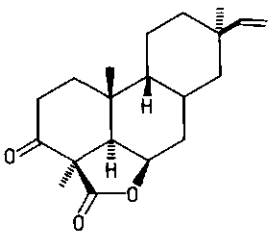


scheme 5.1

117 are outlined in the sections 5.2.2 and 5.2.3, which start from the intermediates 148b and 116b (scheme 5.1). Finally, the method developed for the annellation of a δ-lactone was applied on compound 117 (see section 5.3).



42



160

figure 5.1

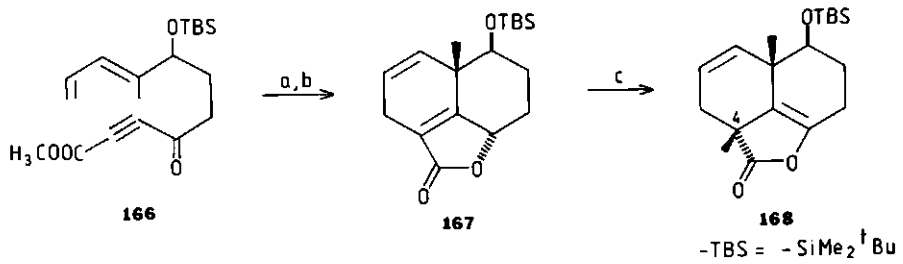
The structure of momilactone A (160) is drawn in figure 5.1[2]. The AB ring system of this natural product, isolated from a cultivated species of rice (*Oryza sativa* L.) shows great similarity to that of diterpenoid dilactones, *e.g.* 3β-hydroxynagilactone F (42)[3]. Therefore the γ-lactone 117, the synthesis of which is outlined in this chapter, might be of interest as intermediate in the total synthesis of momilactone A (160)[4].

5.2 SYNTHESIS OF THE INTERMEDIATE 2*H*-NAPHTHO [1,8-*bc*] FURAN-2,6-(2a*H*)-DIONE

5.2.1 *Approach via γ-hydroxy ketones*

Recently Burk *et al.*[5] published an intramolecular Diels Alder approach for the synthesis of γ-lactones. The cyclization of compound 166 gave a γ-lactone 167 (scheme 5.2). Methylation of this compound however yielded a product 168, which had a configuration at C-4, opposite to the one which was required and therefore this method was rejected.

In the approach of Bucourt *et al.*[1] a γ-hydroxy ketone is converted to a γ-lactone *via* a reaction with diethyl carbonate as

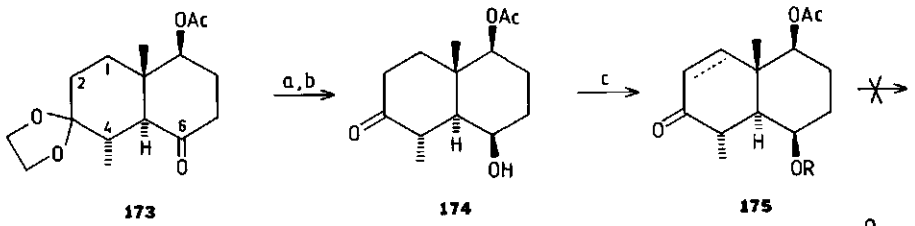


a : $PhCH_3$, Δ ; b: $NaBH_4$; c: LDA , THF , HMPA , CH_3I .

scheme 5.2

carbonyl donor. The stereoselectivety of the methylation of this type of γ-lactones is uncertain (see Burke *et al.*). The presence of the methyl group at C-4 in compound 175 and the axial β-orientation of the γ-hydroxyl group should secure the stereoselective introduction of the carbonyl group of the γ-lactone at C-4.

An efficient route to the selectively protected *trans*-fused dione mono acetal 173 had been developed in connection with research in the field of eudesmane total syntheses[6,7]. Sodium borohydride reduction of the C-6 carbonyl group and subsequent hydrolysis of the dioxolane function afforded the hydroxy ketone 174. The axial β-position could be assigned to the hydroxyl group, since in the ^1H NMR the C-6 hydrogen signal at δ 4.01 has a small half band width ($w_{½}$=8 Hz) due to an axial-equatorial and equatorial-equatorial coupling with the adjacent hydrogen atoms. This compound 174 can serve as starting material for the introduction of the γ-lactone (scheme 5.3)[1].



a: $NaBH_4$, EtOH ; b: H_3O^+ ; c: $Im_2C{=}O$, PhH , Δ . Im =

b : R = $C(=O)$—Im
c : R = H , $\Delta^{1,2}$
d : R = $C(=O)$—Im , $\Delta^{1,2}$

scheme 5.3

The β-hydroxyl group is 175a was transformed into a carbamate by treatment with carbonyldiimadazole. The aim was to cyclize this derivative 175b *via* an intramolecular acylation by attack of an enolate anion, generated at C-4, on the β-carboxyimidazole[8], the β-position of the hydroxyl group securing the desired stereochemistry at C-4. However, several attempts to accomplish ring closure failed. Since deprotonation at C-2 in compound 175b might be a competing reaction, compound 175a was converted into the unsaturated analogue 175c *via* bromination-dehydrobromination[9]. Subsequent reaction with carbonyldiimidazole gave 175d, but all attempts to cyclize 175d were again unsuccessful. Therefore, another possible route was explored which is outlined in the next section.

5.2.2 *Attempted lactonization via the bicyclic 5(6)-unsaturated keto ester*

One of the intermediates in the ultimately successful synthesis of the *trans*-fused keto 116b was the 5(6)-unsaturated keto ester 148b (see chapter 4). This compound seemed to be an attractive substrate for the construction of the γ-lactone, for instance *via* a iodo-[10], a sulfeno[11]- or selenolactonization[12]. Reductive elimination of X (PhS, PhSe, I) in the product 164 would then give 117. Adinolfi *et al.* tried to cyclize the keto acid 161 *via* iodolactonization, but this attempt failed (figure 5.2).

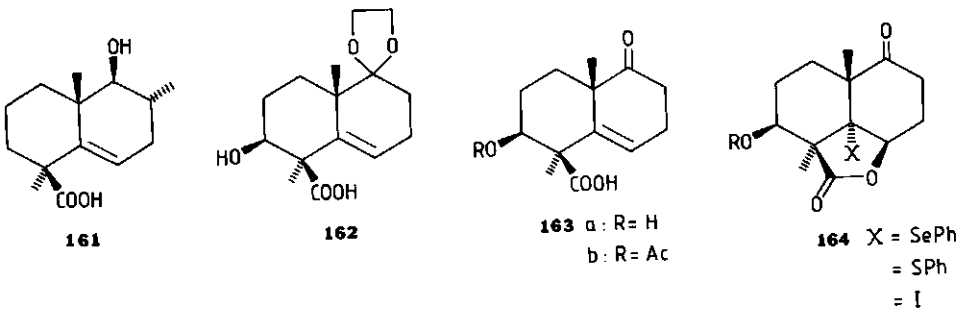
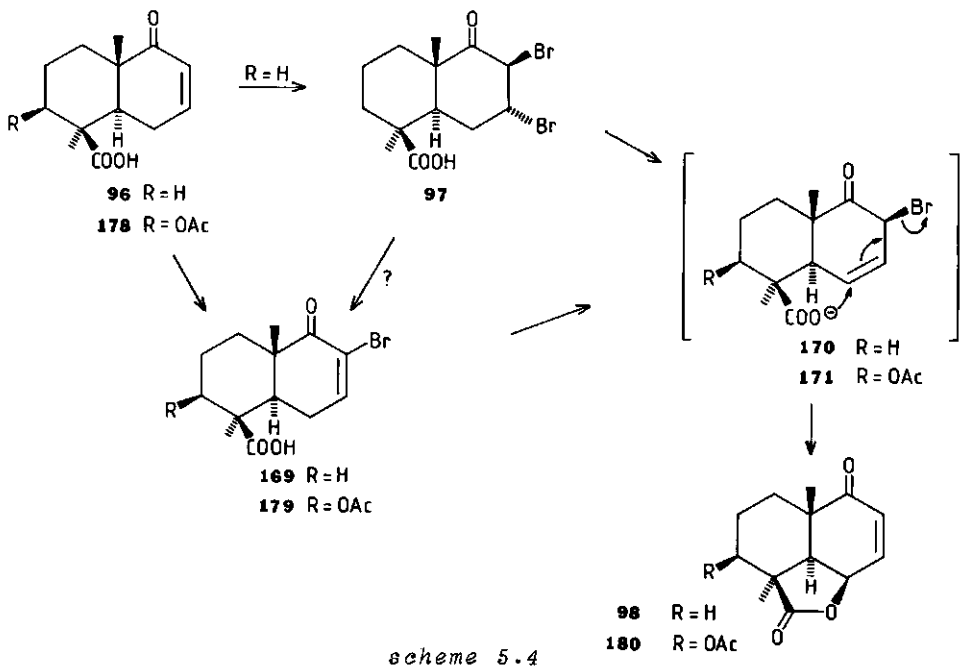


figure 5.2

In view of the Baldwin rules for ring closure[14], this is a disfavoured 5-*endo-trig* process. This will be the case for the sulfeno- and the selenolactonization too.

Nevertheless some endeavours were undertaken to cyclize acetal acid 162 and keto acids 163a and 163b. The acid 162 was obtained by saponification of ester 151 with potassium hydroxide in glycol at 200°C. Subsequent hydrolysis of the dioxolane group afforded 163a. Acetylation of this compound then yielded 163b. The attempted cyclizations were fruitless, and consequently the method was not further investigated.

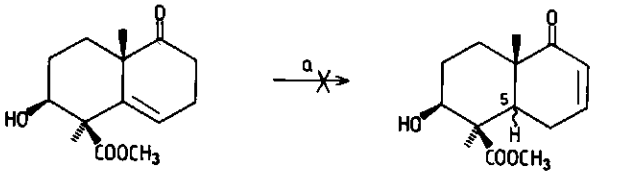
Another approach for the γ-lactonization *via* the 5(6)-unsaturated keto ester 148b was based upon the method, which was used by Welch and coworkers in their total synthesis of LL-Z1271$^{\alpha}$ (41) (scheme 5.4)[16]. This strategy was based upon the bromination of



scheme 5.4

the 7(8)-unsaturated keto acid 96 and subsequent cyclization to the γ-lactone 98. This implicates, that in compound 148b the double bond should be isomerized from the 5(6)- to the 7(8)-position. A potent method for such type of conversions was published

in the literature[17]. Treatment of unconjugated unsaturated ketones with rhodium (I) chloride trihydrate in ethanol at 100°C in a sealed tube gave isomerisation to the more stable α,β-enones in several cases. However, treatment of 148b according to this procedure did not give the desired isomerisation (scheme 5.5).



148 b

176 a: 5α-H
b: 5β-H

a : $RhCl \cdot 3H_2O$, CH_3OH.

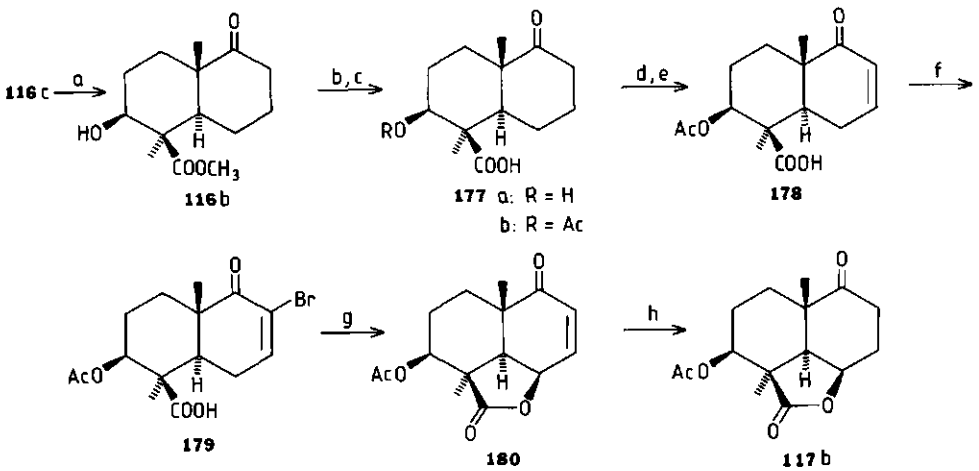
scheme 5.5

The ultimate synthesis of the γ-lactone was achieved *via* the route outlined in scheme 5.6, which starts with the *trans*-fused keto ester 116c (*vide infra*)[16].

5.2.3 *Syntnesis of tne* 2H-*naphtho*[1,8-bc]*furan*-2,6(2a*H*)-*dione*

The starting material 116c, the synthesis of which was described in chapter 4 had to be transformed into the unsaturated acid 178. Therefore 116c was deacetylated[18] and subsequently, the corresponding acid 177a was obtained by ester cleavage of 116b with iodotrimethylsilane[19]. Conversion of acid 177a into the unsaturated derivative 178 by bromination-dehydrobromination was performed on 177b, which was obtained after acetylation of 177a (pyridine, acetic anhydride, DMAP). In order to obtain the dibromide analogue of 97 the acid 178 was treated with pyridinium bromide perbromide. The only product, which could be isolated however was the monobromo acid 179. Yet is was possible to cyclize this compound to the γ-lactone 180 by treatment with anhydrous potassium carbonate in dimethylformamide (scheme 5.6).

The isolation of bromo acid 179 and its subsequent cyclization to the γ-lactone suggests an alternative mechanism for ring

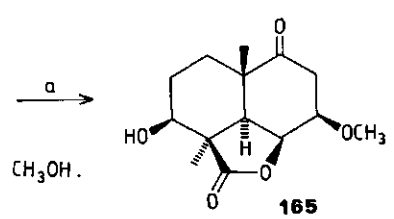


a: K_2CO_3 , H_2O , CH_3OH ; b: TMSiI , $CHCl_3$; c: Ac_2O , pyr., DMAP ;
d: Br_2, HOAc ; e: LiBr , Li_2CO_3 , DMF ; f: pyr.HBr·Br_2 , HOAc ;
g: K_2CO_3 , DMF ; h: $RhCl(Ph_3P)_3$, H_2.

scheme 5.6

closure, compared with that, proposed by Welch. In case of cyclization of bromo acid 179 the double bond deconjugates[20] by action of the base resulting in the formation of an intermediate 171 (scheme 5.4) which cyclizes *via* an intramolecular S_N2' substitution. It is therefore possible that the dibromo acid 97, isolated by Welch is initially dehydrobrominated to the monobromide 169, which then cyclizes as is outlined in scheme 5.4.

The next stage was the conversion of 180 to the saturated hydroxy lactone 117a. Saponification of the acetate function with potassium carbonate in aqueous methanol was performed after hydrogenation of the double bond using Wilkinson's catalyst



a: K_2CO_3, H_2O , CH_3OH.

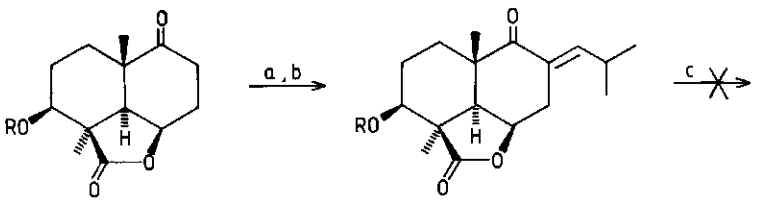
scheme 5.7

$[RhCl(Ph_3P)_3]$. This sequence was necessary since saponification of the acetate group in 180 prior to hydrogenation led to the formation of 165 (scheme 5.7). In the ^1H NMR of the γ-lactones the H-5 resonance at *ca.* 2.0 ppm has a small axial equatorial coupling with H-6 of 5Hz indicating the 1,3-diaxial position of the γ-lactone.

In the following section the attempted annellation of the δ-lactone according to the method, described in chapter 3, is described.

5.3 ATTEMPTED ANNELLATION OF THE δ-LACTONE

Now that a good synthetic route to the γ-lactone 117a was available, the method for the annellation of a δ-lactone as outlined in chapter 3 was applied. The first step in this annellation is the aldol condensation of 117a with isobutyraldehyde. Prior to the formation of the enolate anion with LDA in THF at -78°C, the hydroxyl group was protected as a trimethylsilyl ether. The acetate group present in 117b could not be used since the aldol condensation could not be effected with this protective group[21].



117 a: R= H
c: R= $Si(CH_3)_3$

(E)**181** a: R= H
b: R= THP

a: LDA, THF, -78°, $(CH_3)_2CHCHO$; b: TsOH, PhH ; c: $LiCH_2COOLi$, THF, HMPA.

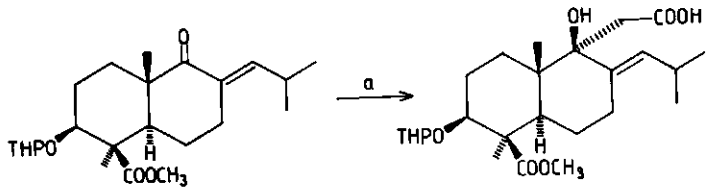
scheme 5.8

Silylation of the hydroxyl group with trimethylsilyl chloride and pyridine in chloroform yielded the silyl ether lactone 117c[22]. The aldol condensation with isobutyraldehyde afforded a β-hydroxy

ketone, which was not purified but dehydrated to the corresponding alkylidene ketone by refluxing in benzene, using *p*-toluenesulfonic acid as catalyst. Under these reaction condition however, the trimethylsilyl ether hydrolyzed to afford the hydroxy derivative (*E*)-181a. The overall yield was 50% (scheme 5.8).

The next step was the addition of dilithio acetate ($LiCH_2COOLi$), performed at the unprotected hydroxy-*γ*-lactone (*E*)-181a[23]. An excess of the nucleophilic reagent was used, since deprotonation of the hydroxyl group also occurs. No 1,2-addition product, but only *ca.* 50% of the starting material could be isolated from the reaction mixture. It was unclear at this point whether the unprotected hydroxyl group or the *γ*-lactone moiety interfered with the addition. To exclude the eventual influence of the deprotonated hydroxyl group during the addition, the hydroxy enone (*E*)-181a was converted into the corresponding THP-ether (*E*)-181b. This was achieved in a quantitative yield by treatment of (*E*)-181a with dihydropyran in dichloromethane and pyridinium *p*-toluenesulfonate as catalyst[24]. Unfortunately the addition of dilithio acetate again failed; no product and no starting material could be isolated at all.

In the next chapter a reaction of dilithio acetate with an alkylidene ester THP-ether is described. This resulted in the formation of the 1,2-addition product in 55% yield (scheme 5.9).



a: $LiCH_2COOLi$, THF, HMPA.

scheme 5.9

From these results, the conclusion could be drawn that the *γ*-lactone moiety was responsible for the failure of this addition.

Since other methods for the introduction of the two carbon atom-moiety (C-11 and C-12) do not proceed in sterically comparable situations or are unattractive for other reasons and

because the addition of dilithio acetate does take place upon the ester in scheme 5.9, the route *via* the γ-lactone was abandoned.

5.4 EXPERIMENTAL SECTION

General experimental conditions were as described in chapter 3.

5β-Acetoxy-8β-hydroxy-1α,4aβ-dimethyl-3,4,4a,5,6,7,8,8aα-octahydronaphthalen-2(1H)-one (174).

A solution of 173[10] (8.55 g, 28.9 mmol) in ethanol (150 mL) was cooled at 0°C and 2.50 g (66 mmol) of sodium borohydride (2.50 g) was added. The reaction mixture was stirred for 1 h at 0°C and 2 h at room temperature. The reaction mixture was then poured into 2% acetic acid solution (100 mL) and extracted with dichloromethane (6x75 mL). The combined extracts were washed with brine, dried and concentrated *in vacuo*. The residual solid was dissolved in a mixture of dioxane (100 mL) and 1N hydrochloric acid solution (20 mL). The solution was stirred for 18h at room temperature, poured into water, and extracted with dichloromethane (4x75 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate and dried. Evaporation of the solvent *in vacuo* gave a white solid which was purified by column chromatography on silica gel (petroleum ether 40-60°C: ethylacetate = 4:1 to 2:1) to afford 5.57 g (76%) of 174: mp 138-140°C; ^{1}H NMR: 1.09 (d, J=7Hz,3H), 1.30 (s,3H), 1.23-2.67 (m,10H), 2.06 (s,3H), 2.74 (m, J=7, 13Hz,1H), 4.01 (m, J=1.5Hz,1H), 4.53 (dd, J=5, 11Hz,1H). M.S. (70eV) *m/e* (%) 254(M^+,5), 194(33), 176(11), 121(31), 93(29), 81(53), 43(100). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found C, 66.40; H, 8.43.

5β-Acetoxy-8β-carbimidazolyloxy-1α,4aβ-dimethyl-3,4,4a,5,6,7,8,8aα-octahydronaphthalen-2(1H)-one (175b).

A mixture of 174 (2.39 g, 9.42 mmol) and 1,1'-carbonyldiimidazole (3.67 g, 22.65 mmol) in dry benzene (100 mL) was refluxed under a nitrogen atmosphere for 72h. The solvent was evaporated *in vacuo* and the residual solid was purified by column chromatography on silica gel with petroleum ether (40-60°C)/ethylacetate (1:1). Recrystallization from diisopropyl ether gave pure 175b (2.10 g, 64%); mp 154-155°C; ^{1}H NMR: 1.07 (d, J=7Hz,3H), 1.23-2.82 (m,10H), 1.50 (s,3H), 2.11 (s,3H), 4.62 (m,1H), 5.28 (m, $W_{\frac{1}{2}}$=6Hz,1H), 7.10 (br

s,1H), 7.42 (br s,1H), 8.14 (br s,1H). M.S. (70eV) *m/e* (%) 348(M^+,5), 237(11), 195(100), 177(76). Anal. Calcd for $C_{18}H_{24}N_2O_5$: C, 62.05; H, 6.94. Found: C, 62.33; H, 7.09.

5β-Acetoxy-8β-hydroxy-1α,4aβ-dimethyl-4a,5,6,7,8,8aα-hexahydronaphthalen-2(1H)-one (175c).

The bromination and dehydrobromination (150°C, 2 h) of hydroxy ketone 174 (2.54 g, 10.0 mmol) was performed as previously described[9]. The workup gave a solid (2.30 g, 91%) which, according to ^{1}H NMR, was pure 175; mp 139.5-141.0°C; ^{1}H NMR: 1.22 (d, *J*=7Hz,3H), 1.39 (s, 3H), 1.33-2.53 (m, 6H), 2.13 (s, 3H), 2.78 (m, *J*=7, 13Hz,1H), 4.12 (t, *J*=1.5Hz,1H), 4.67 (dd, *J*= 5, 11Hz,1H), 5.83 (d, *J*=10Hz,1H), 6.79 (d, *J*=10Hz,1H). M.S. (70eV) *m/e* (%) 252(M^+,4) 192 (21), 174 (18), 148 (24), 123 (100). Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99; Found C, 66.51; H, 8.12.

5β -Acetoxy-8β-carbimidazolyloxy-1α,4aβ-dimethyl-4a,5,6,7,8,8aα-hexahydronaphthalen-2(1H)-one (175d).

The hydroxy α,β-unsaturated keton 175c (1.26 g, 5.0 mmol) was treated with 1,1'-carbonyldiimidazole (1.78 g, 11.0 mmol) as described above to afford 175d (1.30 g, 75%); mp 172-173°C; ^{1}H NMR: 1.20 (d, *J*=7Hz,3H), 1.45 (s,3H), 1.56-2.41 (m,5H), 2.16 (s,3H), 2.64 (m, *J*=7, 13Hz,1H), 4.77 (m,1H), 5.39 (m, $W_{\frac{1}{2}}$=6Hz,1H), 5.92 (d, *J*=10Hz,1H), 6.85 (d, *J*=10Hz,1H), 7.12 (br s,1H), 7.43 (br s,1H), 8.14 (br s,1H). M.S. (70eV) *m/e* (%) 346(M^+,12), 235(12), 193(100), 175(93). Anal. Calcd for $C_{18}H_{22}N_2O_5$: C, 62.41; H, 6.40. Found C, 62.38; H, 6.68.

5,5-(Ethylenedioxy)-1α,4aβ-dimethyl-2β-hydroxy-1,2,3,4,4a,5,6,7-octahydronaphthalene-1β-carboxylic Acid (162).

A solution of 1.20 g (21 mmol) of potassium hydroxide and 1.00 g (3.2 mmol) of the ester 151[15] in a mixture of 20 mL of ethylene glycol and 2 mL of water was heated at 200°C for 1h. After cooling the solution, 40 mL of water was added and this mixture was extracted with ethyl acetate (2x50 mL). The aqueous layer was acidified with concentrated hydrochloric acid and extracted with ethyl acetate (4x50 mL). The combined organic layers were washed with water and brine and dried. Filtration and evaporation under reduced pressure gave the crude product which was crystallized from ethyl acetate to give 0.80 g of the acetal acid 162 (88%): mp 215.0-216.0°C (dec.); ^{1}H NMR: 1.10 (s,3H), 1.48 (s,3H), 1.2-2.6 (m,8H), 3.15 (dd, *J*=6, 9 Hz,1H), 3.88 (s,4H), 5.77 (m,1H), 6.77

(br s,2H, exchanges with D_2O). M.S. (70eV), *m/e* (%) 282(M^+,12), 133(13), 87(74), 86(100).

5-Oxo-1α,4aβ-dimethyl-2β-hydroxy-1,2,3,4,4a,5,6,7-octahydronaphthalene-1β-carboxylic Acid (163a).

To a solution of 1.82 g (6.4 mmol) of 162 in 40 mL of ethanol was added 5 mL of 4N hydrochloric acid. After stirring for 18 h. the reaction mixture was diluted with water and extracted with chloroform (5x50 mL). The combined organic layers were washed with water and brine and dried. After evaporation of the solvent *in vacuo* the product was crystallized from ethyl acetate to afford 1.08 g (70%) of the keto acid 163a: mp 161.0-162.5°C (dec.); ^1H NMR: 1.23 (s,3H), 1.57 (s,3H), 1.2-2.8 (m,8H), 3.20 (dd, *J*=7, 9Hz,1H), 5.97 (m,1H), 7.8(br s,2H, exchanges with D_2O). M.S. (70eV), *m/e* (%) 238(M^+,12), 220(74), 182(88), 163(50), 133(100), 118(76).

5-Oxo-2β-acetoxy-1α,4aβ-dimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalene-1β-carboxylic Acid (163b).

The procedure described for the preparation of 148c was employed. The yield of 163b was 80%: mp 146.0-147.5°C; ^1H NMR: 1.29 (s,3H), 1.42 (s,3H), 2.07 (s,3H), 1.5-2.8 (m,8H), 4.47 (dd, *J*=5, 12Hz,1H), 6.01 (m,1H), 9.6 (br s,1H, exchanges with D_2O). M.S. (70eV), *m/e* (%) 280(M^+,1), 220(20), 192(24), 178(36), 163(22), 133(100), 118(47), 43(95).

Attempted Selenolactonization. General Procedure.

The procedure of Nicolau *et al.* was employed[12a].

A: To a solution of 0.81 mmol of the acid 162 or 163a in 10 mL of dichloromethane was added 1.00 mmol of triethylamine, and this mixture was stirred at ambient temperature for 0.5h under nitrogen. Then the solution was cooled to -78°C and subsequently 0.85 mmol of phenylselenenyl chloride was added at once. The reaction mixture was allowed to warm to room temperature. Stirring was continued for 1h, and then the reaction mixture was concentrated *in vacuo* and the residue was chromatographed on silica gel (30 g) with ether. In both cases the starting material was recovered.

B: The same procedure as outlined in A was used, exept for the addition temperature of the phenylselenyl chloride which was 0°C. The starting material was recovered in these cases as well.

Attempted Sulfenolactonization.

The procedure of Trost *et al.*[11] was employed. To a solution of 0.332 g (0.75 mmol) of lead (IV) acetate and 0.188 g (0.75 mmol) of phenyl phenylthiosulfonate in 5 mL of dry dichloromethane at 0°C under nitrogen was added 0.855 g (7.5 mmol) of trifluoroacetic acid. To this mixture was added dropwise a solution of 0.140 g (0.5 mmol) of the acetate acid 163b in 3 mL of dry dichloromethane. The precipitate which was formed dissolved in *ca* 10 min. After stirring for 1h 30 mL of dichloromethane was added and the organic layer was washed with saturated sodium bicarbonate solution. The organic layer only contained the amount of sulfenylating reagent used in the reaction. After acidifying and extraction of the sodium bicarbonate layer with dichloromethane (3x50 mL) the combined organic layers were washed with brine and dried. Evaporation of the solvent under reduced pressure gave the starting material.

$RhCl_3.3H_2O$ mediated Isomerisation of 148b.

The isomerisation was performed according to the method of Grieco *et al.*[17]. A solution of 0.120 g (0.48 mmol) of the ketone 148b and 0.02 equivalent (2.3 mg) of rhodium chloride trihydrate in 1 mL of dry methanol was heated at 100°C in a sealed tube under nitrogen for 3 h. The reaction mixture was chromatographed on silica gel with petroleum ether (40-60°C)/ether (1:3). The compound isolated was the starting material.

5-Oxo-2β-acetoxy-1α,4aβ-dimethyl-1,2,3,4,4a,5,6,7,8,8aα-decahydronaphthalene-1β-carboxylic Acid (177b).

The acetoxy keto ester 116c was converted into the corresponding hydroxy ester 166b as described previously[9]. To a solution of this hydroxyester (0.626 g, 2.46 mmol) in chloroform (7 mL) was added iodotrimethylsilane[15] (1.5 mL, 10.5 mmol) at room temperature. After stirring for 1h the reaction was complete. The resulting mixture was poured into water (50 mL) and extracted with dichloromethane (4x50 mL). The combined organic layers were washed with a solution of sodium thiosulfate and brine and then dried. Evaporation of the solvent *in vacuo* yielded a light-yellow oil which was crystallized from diisopropyl ether-methanol to afford the hydroxy keto acid 177a (0.466 g, 79%); ^1H NMR: 1.13 (s,3H), 1.49 (s,3H), 1.1-2.8 (m,11H), 3.17 (dd, J=7, 11Hz,1H), 6.15 (br s,2H, exchanges with D_2O). M.S. (70eV) *m/e* (%): 240(M^+,29), 222(70), 194(24), 125(100), 107(55), 95(64); calcd for $C_{13}H_{20}O_4$ M^+ 240.1362; found 240.1363.

The hydroxy keto acid 177a was converted into the corresponding acetate 177b according to the method of Pelletier[9] (0.493 g, 90%); mp 211.5-212.5°C; ^{1}H NMR: 1.16 (s,3H), 1.31 (s,3H), 1.3-2.8 (m,11H), 2.08 (s,3H), 4.22 (dd, J=5, 12Hz,1H). M.S. (70eV) *m/e* (%) 282(M^+,0.6), 222(14), 194(55), 107(95), 43(100). Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found C, 63.83; H, 7.59.

5-Oxo-2β-acetoxy-1α,4aβ-dimethyl-1,2,3,4a,5,8,8aα-octahydronaphthalene-1β-carboxylic Acid (178).

The acetoxy keto acid 177b was converted into the α,β-unsaturated analogue 178 *via* the procedure described previously[9] (2.230 g, 70%); mp 198-200°C(dec.); ^{1}H NMR: 1.10 (s,3H), 1.33 (s,3H), 1.3-2.8 (m,7H), 2.10 (s,3H), 4.60 (dd, J=4, 11Hz,1H), 5.94 (br d, J=11Hz,1H), 6.99 (m,1H), 9.8 (br s,1H, exchanges with D_2O). M.S. (70 eV) *m/e* (%) 280(M^+,8), 220(59), 202(20), 175(32), 107(80), 68(100), 43(58). Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found C, 63.97; H, 7.40.

5-Oxo-2β-acetoxy-6-bromo-1α,4aβ-dimethyl-1,2,3,4,4a,5,8,8aα-octahydronaphthalene-1β-carboxylic Acid (179).

To a solution of 178 (1.877 g, 6.70 mmol) in acetic acid (30 mL) was added pyridinium bromide perbromide (2.030 g, 6.35 mmol). After stirring at room temperature for 16h the mixture was diluted with ice water and extracted with dichloromethane (4x50 mL). The combined extracts were washed with water and brine, dried and concentrated *in vacuo*. The crude product was crystallized from diisopropyl ether-methanol to afford 179 (1.930 g, 80%); mp 190°C (dec); ^{1}H NMR: 1.13 (s,3H), 1.32 (s,3H), 1.2-2.8 (m,7H), 2.09 (s,3H), 4.59 (dd, J=5, 11Hz,1H), 7.39 (dd, J=3, 5Hz,1H), 10 (br s,1H, exchanges with D_2O). M.S. (70eV) *m/e* (%) 360/358 (M^+,5/5.5), 300/298 (31/34), 219 (40), 174 (38), 107 (37), 43 (100); calcd for $C_{15}H_{19}O_5$ (M^+-Br) 279.1232; found 279.1226.

3β-Acetoxy-2aα,5aβ-dimethyl-3,4,5,5a,8aα,8bα-hexahydro-2H-naphtho-[1,8-bc]-furan-2,6(2aH)-dione (180).

To a solution of 179 (1.930 g, 5.4 mmol) in DMF (30 mL) was added anhydrous potassium carbonate (0.500 g, 5.05 mmol) at room temperature. After stirring for 48h, the reaction mixture was poured into water and extracted with dichloromethane (4x50 mL). The organic layer was washed with brine and dried over. Filtration and evaporation of the solvent *in vacuo* gave the crude reaction mixture which was purified by column chromatography on silica gel with

ether/petroleum ether (40-60°C) (3:1) to afford 180 (0.926, 62%); mp 138.5-139.5°C; ^{1}H NMR: 1.42 (s,3H), 1.43 (s,3H), 1.5-2.0 (m,4H), 2.05 (d, J=4Hz,1H), 2.14 (s,3H), 5.05 (m,2H), 6.18 (d, J=10Hz,1H), 6.88 (dd, J=5, 10Hz,1H). M.S. (70eV) *m/e* (%) 278(M^+,0.3), 218(15), 192(19), 159(30), 107(80), 43(100). Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found C, 64.99; H, 6.35.

Deacetylation of 180.

Compound 180 was treated as described for the preparation of 152b (chapter 4). The product which was isolated was 2aα,5aβ-dimethyl-3β-hydroxy-8β-methoxy-3,4,5,5a,7,8,8aα,8bα-octahydro-2*H*-naphtho 1,8-*bc* furan-2,6(2a*H*)-dione (165) in a 40% yield: mp 159.5-160.5°C; ^{1}H NMR: 1.12 (s,3H), 1.53 (s,3H), 2.07 (d, J=5Hz,1H), 1.3-2.0 (m,4H), 2.36 (dd, J_{AB}=18.6Hz, J_{AX}=12Hz,1H), 2.90 (dd, J_{AB}=18.6Hz, J_{BX}=6Hz,1H), 3.47 (s,3H), 3.62 (dd, J=6, 9Hz,1H), 3.6 (s,1H, exchanges with D_2O), 4.26 (octet, J=4, 6, 12Hz,1H), 4.82 (dd, J=4, 5Hz,1H). M.S. (70eV), *m/e* (%) 268(M^+,8), 250(83), 218(21), 181(60), 163(85), 93(100). Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.43; H, 7.74.

3β-Acetoxy-2aα,5aβ-dimethyl-3,4,5,5a,7,8,8aα,8bα-octahydro-2H-naphtho[1,8-bc]-furan-2,6(2aH)-dione (117b).

A solution of 180 (0.657 g, 2.36 mmol) and Wilkinson's catalyst [$RhCl(Ph_3P)_3$] (0.100 g, 0.11 mmol) in dry benzene (25 mL) was hydrogenated in a hydrogenation bomb. After stirring for 48h at 5 atm. of hydrogen at room temperature the reaction mixture was concentrated in the presence of silica gel (2 g) *in vacuo* and the resulting mixture poured on a column of silica gel (50 g) and eluted with Et_2O. After evaporation of the eluent 117b was obtained (0.653 g, 98%) as a white solid; mp 140.0-141.0°C; ^{1}H NMR: 1.33 (s,3H), 1.42 (s,3H), 1.99 (d, J=5Hz,1H), 2.15 (s,3H), 1.6-2.7 (m,8H), 5.05 (m,2H). M.S. (70eV) *m/e* (%) 280(M^+,0.2), 220(31), 161(44), 107(41), 43(100). Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found C, 64.04; H, 7.28.

2aα,5aβ-Dimethyl-3β-hydroxy-3,4,5,5a,7,8,8aα,8bα-octahydro-2H-naphtho[1,8-bc]furan-2,6-(2aH)-dione (117a).

The deacetylation of 117b was performed as described for the synthesis of 152b (chapter 4). The hydroxy lactone 117a was isolated in a quantitative yield, and was used in the next reaction without further purification; ^{1}H NMR: 1.22 (s,3H), 1.53 (s,3H), 2.02 (s, J=5Hz,1H), 1.3-2.7 (m,8H), 3.65 (dd, J=6, 10Hz,1H), 3.6 (br s,1H, exchanges with D_2O), 5.13 (m,1H).

2aα,5aβ-Dimethyl-3β-trimethylsilyloxy-3,4,5,5a,7,8,8aα,8bα-octahydro-2H-naphtho[1,8-bc]furan-2,6-(2aH)-dione (117c).

To a solution of 0.555 g (2.33 mmol) of hydroxy lactone 117a in 30 mL of dry chloroform was added at 0°C, 4.5 mL (55 mmol) of pyridine and 4.5 mL (35 mmol) of trimethylsilyl chloride. After stirring for 17h, during which time the solution was allowed to warm to room temperature, the solvent was evaporated under reduced pressure and the residue stirred with dry ether. After filtration and evaporation, the crude product was chromatographed on 40 g of silica gel with ether to yield 0.500 g (69%) of the silyl ether 117c as a white solid: mp 141.0-143.0°C; ^{1}H NMR: 0.17 (s,9H), 1.39 (s,6H), 1.7 (m,4H), 1.89 (d, J=6Hz,1H), 2.0-2.7 (m,4H), 3.79 (m,1H), 4.94 (m,1H), M.S. (70eV) *m/e* (%) 310 (M^+,5), 295(25), 220(12), 159(28), 129(21), 101(23), 75(100); calcd. for $C_{16}H_{26}O_4Si$ M^+ 310.1600, found M^+ 310.1583.

2aα,5aβ-Dimethyl-3β-hydroxy-7E-2-(methylpropylidene)-3,4,5,5a,7,8,8aα,8bα-octahydro-2H-naphtho[1,8-bc]furan-2,6(2aH)-dione (*E*)-181a .

To a stirred solution of 3.3 mmol of *n*-butyllithium in 2.2 mL of hexane at 0°C was added dropwise over a period of 10 min, a solution of 0.368 g (3.65 mmol) of diisopropylamine in 20 mL of dry tetrahydrofuran. After 15 min stirring at 0°C, the solution was cooled to -78°C and then a solution of 0.685 g (2.21 mmol) of -lactone 117c in 20 mL of dry tetrahydrofuran was added dropwise over 20 min and stirring was continued another 0.5 h. Then a solution of 0.60 g (8.3 mmol) of freshly distilled isobutyraldehyde was added dropwise in 15 mL of dry tetrahydrofuran. Stirring was continued for 1h, 1.5 mL of 4N hydrochloric acid was added at -78°C and the mixture was allowed to warm to room temperature. This mixture was poured into 0.5 N hydrochloric acid and extracted with ether (4x50 mL). The organic layer was washed with water and brine and dried. Evaporation of the solvent afforded the crude -hydroxy ketone, which was used immediately without further purification in the dehydration. The crude product was dissolved in 25 mL of dry benzene and a catalytic amount (50 mg) *p*-toluenesulfonic acid was added. The reaction mixture was refluxed for 2h, using a Deans Stark apparatus, and then poured into saturated sodium bicarbonate solution. The aqueous layer was extracted with ether (2x50 mL) and the combined organic layers were washed with brine and dried. The solvent was removed *in vacuo* and the residue purified by column chromatography (35 g silica gel; eluent ether). This afforded 0.443 g (69%) alkylidene lactone (*E*)-181a as a white solid: mp 145.0-147.0°C; ^{1}H NMR: 1.06 (d, J=7Hz,6H), 1.26

(s,3H), 1.53 (s,3H), 1.3-2.2 (m,4H), 1.87 (d, J=6Hz,1H), 2.4-3.1 (m,2H), 3.2-3.8 (m,2H), 3.7 (br s,1H, exchanges with D_2O), 5.04 (m,1H), 6.73 (dt, J=3, 11Hz,1H). M.S. (70eV), *m/e* (%) 292(M^+,39), 274(100), 139(38); calcd for $C_{17}H_{24}O_4$ M^+ 292.1674, found M^+ 292.1670.

Attempted Addition of Dilithio Acetate to (*E*)-181a.

To a stirred solution of 8.0 mmol of *n*-butyllithium in 5.3 mL of hexane was added dropwise at 0°C, over 10 min, a solution of 0.883 g (8.70 mmol) of diisopropylamine in 25 mL of dry tetrahydrofuran. After stirring for 0.5h at 0°C 1.96 g (10.9 mmol) of hexamethylphosphoric triamide was added at once. The solution was cooled to -20°C and then a solution of 0.219 g (3.65 mmol) of acetic acid in 20 mL of dry tetrahydrofuran was added dropwise over 10 min. This mixture was heated at 50°C for 3h and then cooled to -20°C. A solution of 0.445 g (1.52 mmol) of (*E*)-181a in 25 mL of dry tetrahydrofuran was added dropwise, and this mixture was stirred for 16h under nitrogen during which time it was allowed to warm to room temperature. The mixture was poured into 1N hydrochloric acid and extracted with chloroform (4x50 mL). The organic layer was washed with water and brine and dried. After removal of the solvent *in vacuo* the residue was chromatographed on silica gel (50 g; eluent ether). The only compound which could be isolated was 0.211 g (47%) of the starting material.

Diastereomeric 2aα,5aβ-Dimethyl-7E-(2-methylpropylidene)-3β-[(tetrahydro-2H-pyran-2-yl)oxy]-3,4,5,5a,7,8,8aα,8bα-octahydro-2H-naphtho[1,8-bc]furan-2,6(2aH)-dione (*E*)-181b .

The procedure of Grieco *et al.* was employed. To a solution of 1.476 g (4.80 mmol) of (*E*)-181a in 35 mL of dry dichloromethane was added 225 mg (0.9 mmol) of pyridinium *p*-toluenesulfonate and 1.11 g (13.2 mmol) of dihydropyran. The mixture was stirred at room temperature under a nitrogen atmosphere for 17h. Then 100 mL of dichloromethane was added and the organic layer was washed with water and brine and dried. After evaporation of the solvent *in vacuo* the resulting residue was chromatographed on 100 g of silica gel with petroleum ether (40-60°C)/ether (3:2) to afford 1.787 g (100%) of the THP-ether (*E*)-181b as a colourless oil; ^1H NMR (major resonances): 1.03 (d, J=6Hz 6H), 1.32 (s), 1.37 (s), 1.43 (s), 1.47 (s), 4.7-5.1 (m,2H), 6.7 (dt, J=2, 10Hz,1H).

Attempted Addition of Dilithio Acetate to (*E*)-181c.

The procedure described for the addition of dilithio acetate to (*E*)-181c was employed (*vide supra*). Again no product at all could be isolated, and no starting material remained either.

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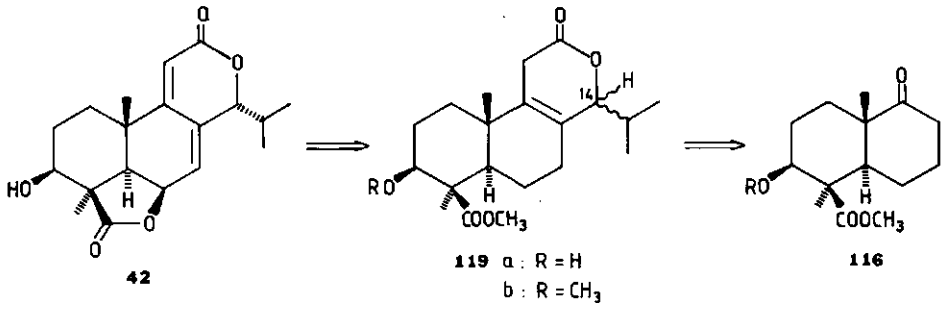
6 THE TOTAL SYNTHESIS OF 3β-HYDROXYNAGILACTONE F

6.1 INTRODUCTION

The approach towards the total synthesis of 3β-hydroxynagilactone F (42), in which the γ-lactone was introduced first, ran up against the inapplicability of the δ-lactone annellation. The second concept based upon the construction of the γ-lactone after annellation of the δ-lactone was therefore explored (*vide infra*). A suitable starting material was the *trans*-fused bicyclic keto ester 116, the synthesis of which is outlined in chapter 4. The -lactone was introduced as previously described in chapter 3, but initially the required stereochemistry of the C-14 alkyl substituent was not obtained. This problem was solved and then the transformation of the BC ring moiety to the desired 7(8),9(11)-dienolide was undertaken. Subsequent cyclization produced the γ-lactone and this compound was further transformed into the natural product. The elaboration of this synthetic plan (scheme 6.1) is outlined in full detail in this chapter.



scheme 6.1

6.2 THE ANNELLATION OF THE δ-LACTONE

6.2.1 Introduction

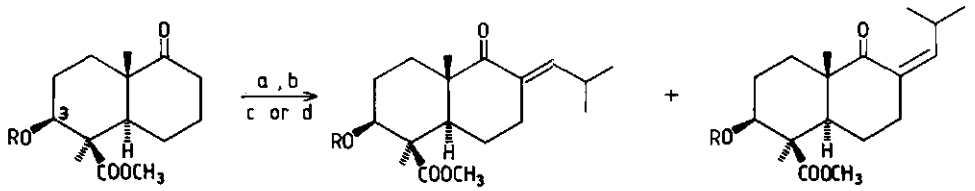
The δ-lactone annellation was explored on the keto ester 116, and the protection of the C-3 hydroxyl group turned out to be a very important aspect in this procedure.

Initially the acetate group was used as a protective group, since it was already present in compound 116c (chapter 4). The aldol condensation with isobutyric aldehyde, however, could not be carried out, because the solution of the anion of 116c gelatinized. Moreover the addition of dilithio acetate was expected to be troublesome. The acetate was put aside as a protective group for these reasons.

A large number of protective groups is available for the hydroxyl function and a proper choice required some consideration. The stability towards acidic and basic media as well as the method of removal are important factors, determining this choice. In additions, the interpretation of the ^1H NMR spectra must stay as unambiguous as possible in these complex compounds.

6.2.2 The silyl ether as the protective group for the 3β-hydroxyl group

The potential of the trimethylsilyl group was investigated

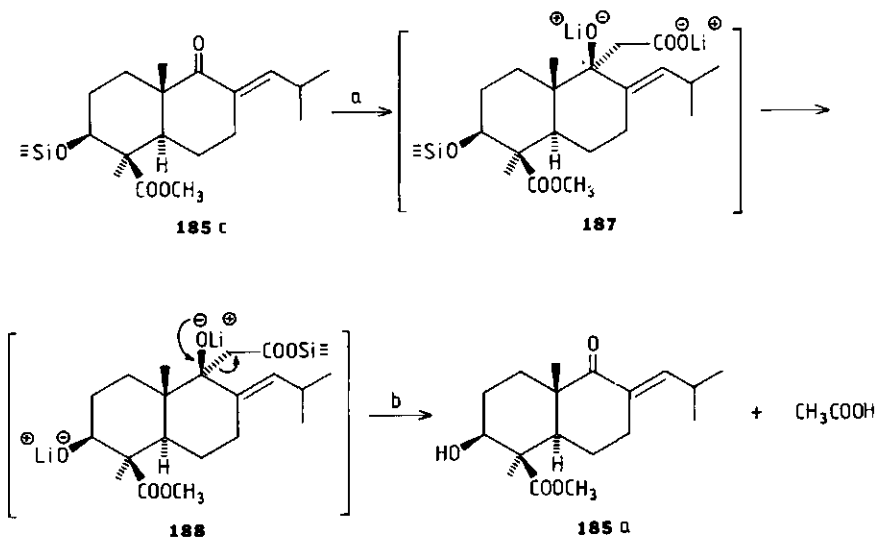


116 d : R = Si≡ **185** a : R = H **186** a : R = H
b : R = THP
c : R = Si≡
116 e : R = CH_3 d : R = CH_3 + d : R = CH_3

a : LDA , THF, -78°, $(CH_3)_2CHCHO$; b: TsOH , PhH ; c: DPH , CH_2Cl_2 , pyr.$H^{\oplus}OTs^{\ominus}$;
d : TMSiCl , pyr., $CHCl_3$.

scheme 6.2

first. The silyl group was introduced as previously described yielding compound 116d, on which the aldol condensation was performed. The subsequent dehydration gave compound 185a in a 73% yield (scheme 6.2). During the dehydration the silyl ether was cleaved and for this reason the hydroxyl group was again protected as a silyl ether. Then the reaction with dilithio acetate was performed and after 40 min at 0°C the reaction mixture was examined with TLC. This revealed that the 1,2-addition product had been formed, although some starting material was still present. After standing overnight, the only detectible product was the hydroxy compound 185a. Assuming that the 1,2-adduct 187 was formed a possible explanation could be that the carboxylate anion of the adduct 187 attacks the silyl group of another molecule. A retro addition then becomes possible, because now a carbonyl stabilized anion of the silyl ester of acetic acid can be split off (scheme 6.3)[2].



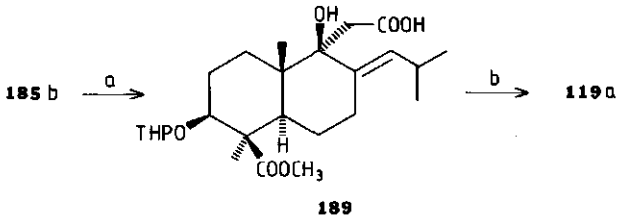
scheme 6.3

To avoid this retro addition the reaction was performed at room temperature in a second run. Quenching of the reaction after 20

min yielded a crude product which consisted of starting material, the hydroxy compound, and the 1,2-addition product. This was determined by TLC examination and ^{1}H NMR spectral data. In order to prevent this silyl migration an attempt was undertaken to prepare a sterically more hindered silyl ether (*e.g.* the *t*-butyldimethylsilyl ether). No reaction occurred however and finally a different protective group was chosen.

6.2.3 The THP-ether as the protective group for the 3β-hydroxyl group

In order to obtain the information whether the γ-lactone or the C-3 hydroxyl group protected as THP-ether was responsible for the failure of the dilithio acetate addition on (*E*)-181b (chapter 5), the enone 185a was converted into the corresponding THP-ether 185b. Subsequently the addition was performed and this gave a 55% yield of the 1,2-adduct. This adduct 189 was not characterized but was cyclized to the δ-lactone 119a by refluxing in benzene containing a catalytic amount of *p*-toluenesulfonic acid (see scheme 6.4). Under these conditions the THP-ether was also cleaved[3]. These results established that the γ-lactone was responsible for the failure of the approach described in chapter 5.



189

a: $LiCH_2COOLi$, THF, HMPA ; b: TsOH, PhH.

scheme 6.4

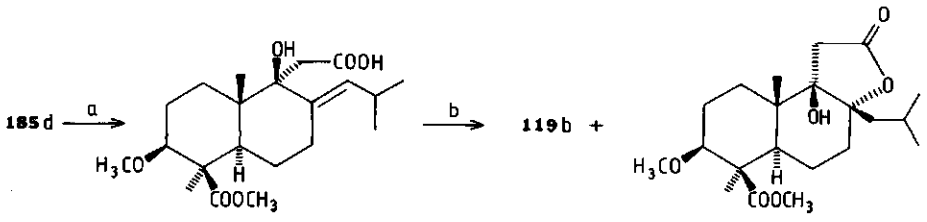
The instability of the THP-ether and the complexity of its ^{1}H NMR spectra made it an unattractive protective group. The methyl ether was therefore ultimately chosen.

6.2.4 The metnyl ether as the protective group for the 3β-hydroxyl group

When the methyl group is introduced the reaction sequence leading to the δ-lactone probably can be performed without the interference of this protective group. Whether the cleavage postponed to a later stage in the total synthesis could be achieved at all without destroying the highly functionalized BC ring system, was not sure at this point. The protection of the C-3 hydroxyl group could not be accomplished easily as was noticed before[4].

The alkylation methods which were endeavoured, *e.g.* potassium hydroxide in dimethyl sulfoxide with methyliodide, sodium hydride in dimethyl sulfoxide with methyliodide, diazomethane, and LDA in THF with methyliodide, did not give the desired conversion[5]. Ultimately the conditions used by Kuhn[6], *e.g.* barium oxide and barium hydroxide in dimethylsulfoxide/dimethylformamide with dimethyl sulfate as the methylating agent, gave the desired result, although in some runs the reactions did not proceed to completion and had to be repeated to obtain a total conversion to the desired methyl ether 116e.

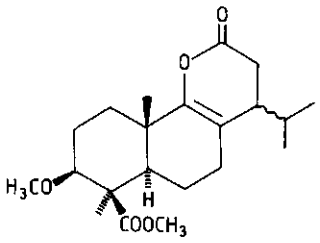
The introduction of the δ-lactone was performed without any difficulty on this properly protected bicyclic keto ester 116e. The aldol condensation and subsequent dehydration resulted in an 8 to 1 mixture of (*E*)-185d and (*Z*)-186d (see scheme 6.2). These enones were separated and the addition of dilithio acetate was performed on 185d, yielding 78% of the 1,2-addition product 190 (scheme 6.5)[7]. The stereochemistry of the product is as indicated in the structure resulting from an α-attack of the nucleophile as



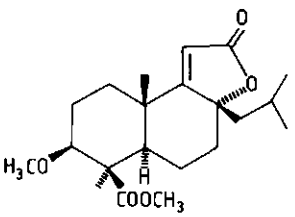
a: $LiCH_2COOLi$, THF, HMPA ; b: TsOH, PhH.

scheme 6.5

is mentioned in the literature. In addition about 10% of the 1,4-addition product was obtained which was not characterized, but transformed into the δ-lactone 191 (figure 6.1).



191



193

figure 6.1

The cyclization of the 1,2-adduct led to the expected δ-lactone albeit in an approximately 1 to 1 mixture of the α- and β-isopropyl isomers 119b. The yield was 63% due to the formation of 20% of the hydroxy γ-lactone 192. Obviously this side product is formed by protonation of the double bond to give the most stable carbonium ion, followed by ring closure *via* an intramolecular attack of the carboxyl group. The probable stereochemistry of this product 192 is depicted in scheme 6.5, since attack of the dilithio acetate occurs from the α-side. In addition examination of a Dreiding model revealed that the ring fusion must be *cis* for steric reasons. The structure assignment of 192 was further supported by its conversion to the dehydrated γ-lactone 193 (figure 6.1). Cyclization of the adduct 190 by sulfuric acid in acetone did not increase the yield of the δ-lactone mixture 119b.

Further investigations into the total synthesis of the diterpenoid dilactone concerned the conversion of the δ-lactone mixture into one isomer and subsequent transformation of the BC ring system into the desired 7(8),9(11)-dienolide. The route *via* sulfenylation and oxidative elimination (chapter 3) was performed initially as is outlined in the next section.

6.3. THE TRANSFORMATION OF THE BC RING SYSTEM *VIA* SULFENYLATION

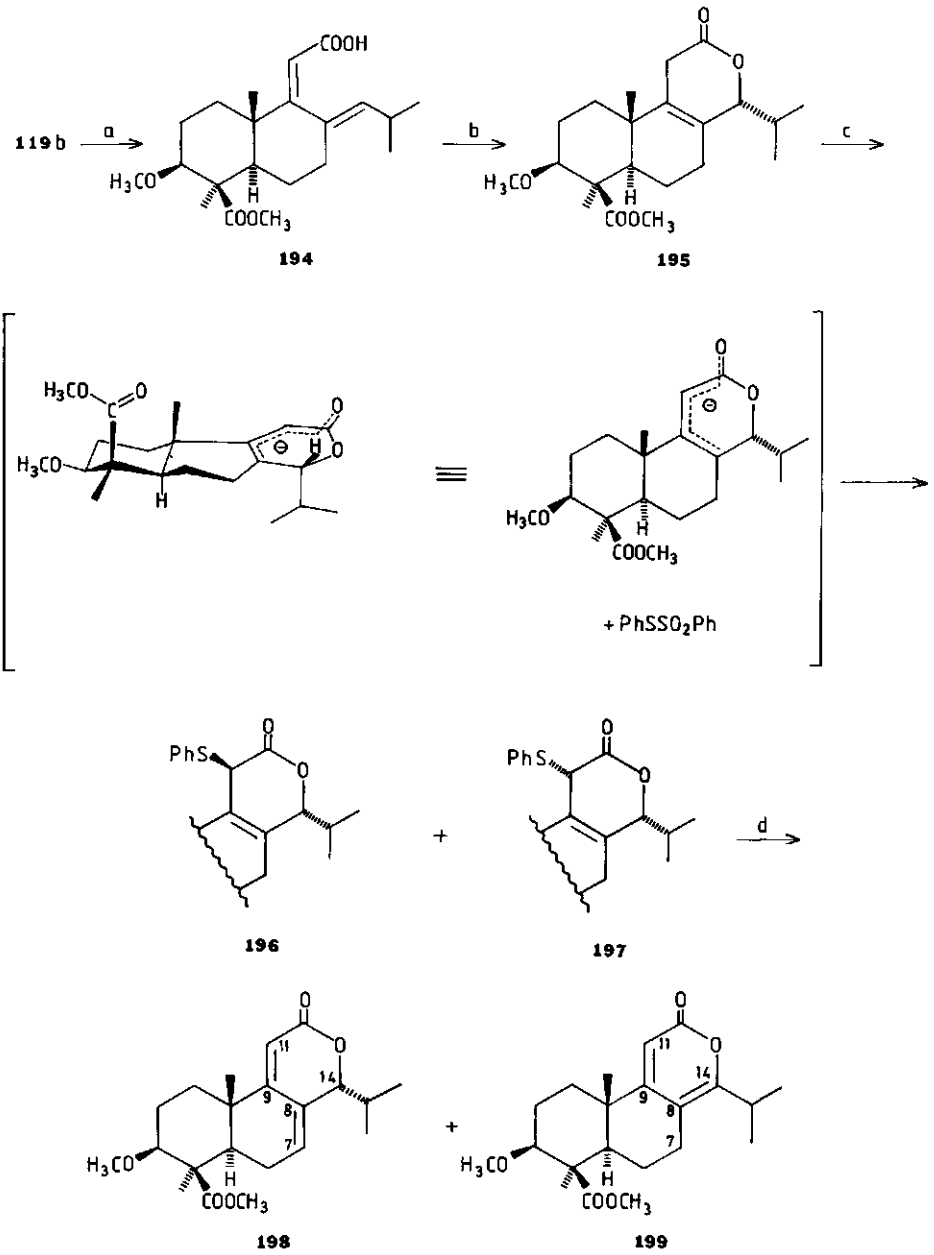
The first step was the isomerisation of the isopropyl group at C-14 from the β-position to the α-position. The reaction sequence developed by Hayashi *et al.* to solve this problem was applied on 119b. Since the α- and β-isomers could not be separated the mixture was treated with 3 equivalents of potassium *t*-butoxide in dimethyl sulfoxide after which the dienoic acid 194 could be isolated. Irradiation of a solution of this acid 194 in ethanol with a high pressure mercury lamp at 0°C gave ring closure to the sterically less hindered α C-14-substituted lactone 195[8] (scheme 6.6, compound 195 is identical to α 119b).

Subsequently this δ-lactone 195 was sulfenylated with benzene phenylthiosulfonate *via* the anion, prepared with LDA in THF at -78°C according to the procedure outlined in chapter 3. Two isomeric sulfides 196 and 197 were obtained in 46 and 17% yield respectively. The most abundant one, 196, was formed by attack of the reagent on the β-face of the molecule[10]. Preliminary experiments with the oxidative eliminations of comparable sulfides had revealed that both isomers gave approximately the same ratio of 7(8),9(11)- and 8(14),9(11)-dienolides, and therefore no correlation could be ascertained between this ratio and the stereochemistry of the sulfides. Consequently the mechanism remained uncertain (see also chapter 3). The oxidative elimination performed on the mixture of the sulfides 196 and 197 unfortunately gave an unfavourable ratio of 1 to 3 of the 7(8),9(11)- and 8(14),9(11)-dienolides (198 and 199) in a total yield of 54% (scheme 6.6).

With the 7(8),9(11)-dienolide 198 in hand the following three transformations had to be performed to obtain the natural product 42.

1) Cleavage of the ester function at C-4.
2) Ring closure to the γ-lactone.
3) Cleavage of the methyl ether.

The first two types of conversions were already encountered in the total synthesis of nagilactone F (41) by Hayashi[9]. The same procedures were therefore planned. The hydrolysis with concentrated



a : KO^{t}Bu , DMSO ; b : hν , EtOH ; c : LDA , THF , -78° , $PhSSO_2Ph$;
d : $NaIO_4$, CH_3OH , H_2O , Δ.

scheme 6.6

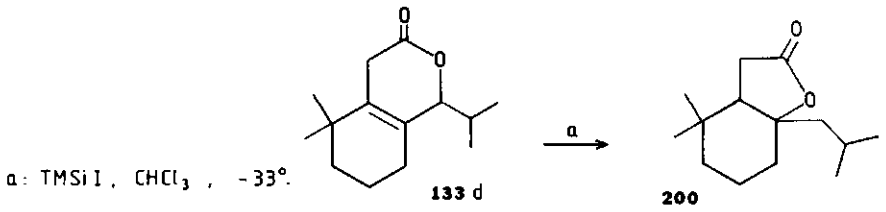
sulfuric acid of ester 198 could not be accomplished however. The difference between these two cases lies in the substituent at C-3. Probably this substituent shields the ester function against hydrolysis. To check the procedure it was also performed on ester 116e, but again, no cleavage could be observed.

No other methods for ester cleavage were attempted at this point on compound 198 for several reasons. First, it is known that podocarpic acid esters are hard to cleave[11] and consequently drastic conditions are required. This will probably lead to undesired side reactions of the reactive 7(8),9(11)-dienolide moiety in 198, obtained *via* sulfenylation and oxidative elimination. Secondly, the last conversions were rather discouraging. Therefore a different sequence for the last transformations in this synthesis was employed.

6.4 THE TOTAL SYNTHESIS OF 3β-HYDROXYNAGILACTONE F

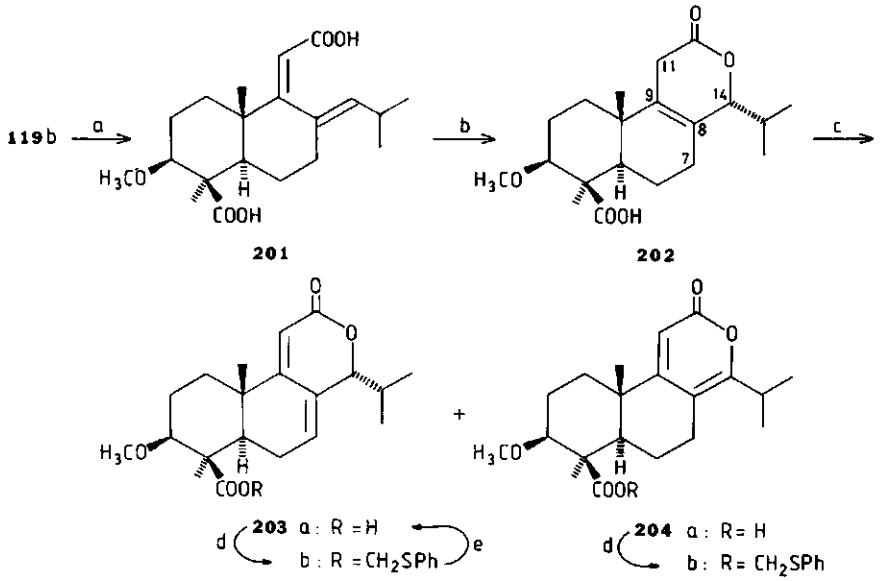
Since cleavage of the ester function in 198 proved to be troublesome this problem was tackled first. A review on esters published by Haslam[11] suggested for instance iodotrimethylsilane, 1,8-diazabicyclo 5.4.0 undec-7-ene (DBU), or lithium *n*-propylmercaptide in HMPA for this conversion. Iodotrimethylsilane used for the cleavage of this type of esters in chapter 5 did not appear to be applicable to the lactone ester 195, since concomitant transformation of the δ-lactone into a γ-lactone occurred. This contrasted with the results of Watt *et al.*[12] who found that a δ-lactone was stable towards iodotrimethylsilane at low temperature (-20°C). In the case of 133d, used as a model compound for the δ-lactone ester 195, transformation to the γ-lactone 200 took place (scheme 6.7), even at low temperature (-33°C). The mechanism of the ring contraction was not elucidated. Moreover an attempted cleavage of ester 116e at this temperature failed. A reaction performed with DBU did not yield the desired product either.

Another possibility for ester cleavage, a reaction with lithium *n*-propylmercaptide in HMPA[13], was performed on ester lactone 195. The obtained product was the diene dicarboxylic acid 201, resul-



scheme 6.7

ting from the desired ester cleavage and concomitant opening of the δ-lactone (scheme 6.8). For this reason the ester cleavage was performed on the diastereomeric mixture of δ-lactones 119b, thus bypassing the opening of the δ-lactones with potassium *t*-butoxide. Irradiation of this diene dicarboxylic acid (201) under the same conditions as previously described (*vide supra*) gave a stereoselective ring closure to the tricyclic acid 202 (scheme 6.8).

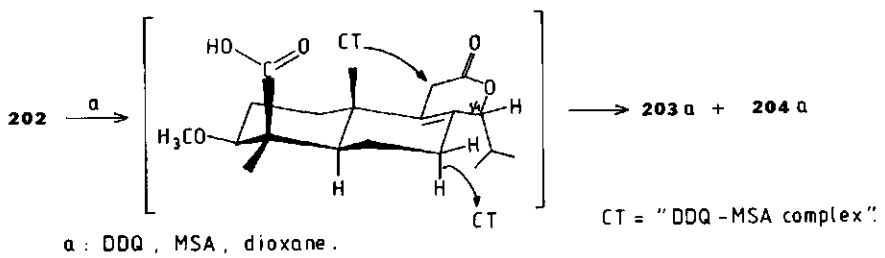


a : n-PrSLi , HMPA ; b : hv , EtOH ; c : DDQ , MSA , dioxane ; d : $PhSCH_2Cl$; e : CF_3COOH.

scheme 6.8

As was mentioned in section 6.3, the sulfenylation sequence for the regioselective introduction of the second unsaturation in 195 was rather unsuccessful. Therefore the alternative dehydrogenation with DDQ, investigated in chapter 3, was tried on the lactone acid 202 Treatment of this compound with DDQ and *p*-toluenesulfonic acid in refluxing dioxane resulted in the formation of a 3 to 4 mixture of the 7(8),9(11)- and 8(14),8(11)-dienolides 203a and 204a (scheme 6.8). This ratio is also unfavourable compared to that obtained in chapter 3. Some attempts were therefore undertaken to optimize this ratio. According to Sarel *et al.*[14] the use of hydrochloric acid as a catalyst at ambient temperature might exclusively give the desired dienolide 203a. A reaction conducted under these conditions failed and reflux temperature proved necessary to obtain complete conversion. However, then the compounds 203a and 204a were present in the crude reaction mixture in only a 2 to 3 ratio. A reaction performed with 2-mesitylenesulfonic acid increased the ratio of the 7(8),9(11)- and 8(14),9(11)-dienolide to 3 to 2.

Considering the mechanism of the dehydrogenation this might be explained as follows[15]. First, acid catalyzed enolisation of 202 occurs followed by hydride abstraction at the C-7 or C-14 position. Probably β-attack of the charge-transfer complex of DDQ and 2-mesitylenesulfonic acid (MSA) is favoured, because of the bulkier MSA in comparison with *p*-toluenesulfonic acid. Consequently hydride abstraction by a second charge-transfer complex then takes place from the α-side of the molecule and therefore in ring B, since hydride abstraction in ring C is prohibited by the α-position of the isopropyl group (scheme 6.9).



scheme 6.9

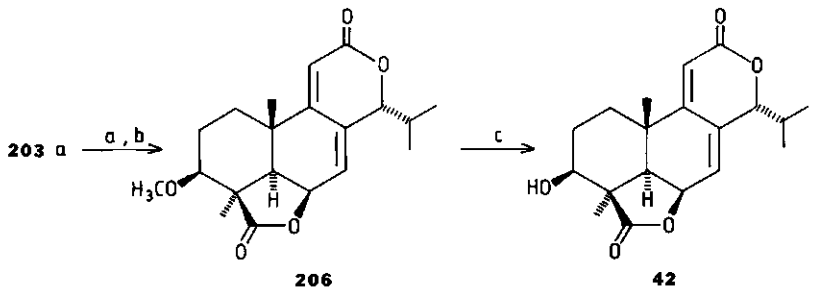
The two dienolide carboxylic acids formed in the dehydrogenation with DDQ were inseparable, this in contrast with the dienolide esters. Protections of the acids as esters was therefore considered, but the esters had to be sufficiently stable and separable on silica gel, and easy to cleave. Phenylthiomethyl esters were ultimately chosen and synthesized according to the preparation of methylthiomethyl esters[16]. Treatment of a 3 to 2 mixture of the potassium salts of the acids 203a and 204a with phenylthiomethyl chloride in the presence of 18-crown-6 and sodium iodide afforded the corresponding esters 203b and 204b in 52 and 24% yield. These esters could indeed be separated by chromatography. Cleavage of ester 203b was performed by treatment with trifluoroacetic acid and afforded the pure carboxylic acid 203a in a 90% yield (scheme 6.8).

The next goal to be attained was ring closure of 203a to the γ-lactone. At first glance the procedure of Hayashi seemed to be suitable, *i.e.* treatment of 203a with lead (IV)acetate under irradiation. It was unexpected and very disappointing to discover that this reaction gave no results at all. The reason for this failure was not clear and adapting the conditions did not improve the results.

The γ-lactonization *via* bromination, described in chapter 5, seemed to offer some perspective, although in this case the regioselectivity of the bromination and the stability of the dienolide might provide serious limitations. Nevertheless the bromination was performed initially on a mixture of 203a and 204a and the crude product was treated with potassium carbonate in dimethylformamide (scheme 6.10). Only 6% of the cyclized product 206, the methyl ether of 3β-hydroxynagilactone F, could be obtained *via* preparative thin layer chromatography. No other identifiable product could be isolated. Repeating these reactions with the pure dienolide acid 203a again gave the product 206 in low yield.

Finally the demethylation, using boron tribromide, was undertaken as the twentythird step[17]. Treatment of 206 with boron tribromide in dichloromethane at -78°C did not result in any cleavage at all. At -24°C in 48h approximately 50% demethylation was

obtained according to ^1H NMR investigation of the crude product. After performing the reaction at 4°C the ^1H NMR spectrum of the product became obscure and no starting material remained. The crude reaction mixture of this last reaction was purified by preparative thin layer chromatography on silica gel and resulted in the isolation of a small amount (<1mg) of the desired natural product in racemic form. The optimum temperature for the ether cleavage is therefore approximately -24°C, at which temperature a good yield can be obtained. This last reaction could not be optimized because no starting material remained. The product obtained was characterized by ^1H NMR, mass measurement, and exact mass.



a: Br_2 , HOAc ; b: K_2CO_3 , DMF ; c: BBr_3 , CH_2Cl_2 , -24°.

scheme 6.10

Going back to the roots of *Podocarpus Nagi* (Thunberg) Pilger where it all started, it appeared that the spectroscopic data of the dilactone synthesized in the way described in this thesis were identical with those of natural 3β-hydroxynagilactone F isolated from the root bark. The same observations as described by Hayashi *et al.*[20] in relation to the stereochemistry of the protons around the dienolide system were made. The same characteristic couplings and relations in ^1H homo spin decoupling experiments were determined.

6.5 EXPERIMENTAL SECTION

General experimental conditions were as described in chapter 3.

Methyl 5-Oxo-1α,4aβ-dimethyl-2β-trimethylsilyloxy-1,2,3,4,4a,5,6,7,8,8aα-decahydronaphthalene-1β-carboxylate (116d).

The method described for the synthesis of 117c (chapter 5) was used for the preparation of 116d (1.72 g, 88%): ^{1}H NMR: 0.08 (s,9H), 1.06 (s,3H), 1.26 (s,3H), 1.3-2.8 (m,11H), 3.19 (dd, *J*=4, 12Hz,1H), 3.62 (s,3H). M.S. (70eV), *m/e* (%) 326(M^+,16), 311(41), 236(43), 129(88), 116(100), 73(94), calcd for $C_{17}H_{30}O_4Si$: M^+ 326.1913; found M^+ 326.1919.

Methyl 5-Oxo-1α,4aβ-dimethyl-2β-hydroxy-6E-(2-methylpropylidene)-1,2,3,4,4a,5,-6,7,8,8aα-decahydronaphthalene-1β-carboxylate (185a).

The introduction of the isobutylidene side chain at C-7 was performed on 116d according to the method described for the synthesis of 181a in chapter 5. The enone 185a was obtained in 73% yield (1.18 g): ^{1}H NMR 0.93 (s,3H), 0.97 (d, *J*=3Hz,3H), 1.04 (d, *J*=3Hz,3H), 1.47 (s,3H), 1.2-3.0 (m,10H), 3.13 (dd, *J*=5, 10Hz,1H), 3.33 (br s,1H, exchanges with D_2O), 3.70 (s,3H), 6.29 (br d, *J*=10Hz,1H). M.S. (70eV), *m/e* (%) 308(M^+,100), 290(27); calcd for M^+ 308.1987; found M^+ 308.1985. In addition *ca.* 20% (estimated by ^{1}H NMR integration) of the (*Z*)-isomer was formed. This compound could not be isolated in pure form and was therefore not characterized further.

Methyl 5-Oxo-1α,4aβ-dimethyl-6E-(2-methylpropylidene)-2β-trimethylsilyloxy-1,2,3,4,4a,5,6,7,8,8aα-decahydronaphthalene-1β-carboxylate (185c).

The method described for the synthesis of 117c (chapter 5) was used, and compound 185c was obtained from 0.431 g (1.40mmol) of 185a in a quantitative yield (0.532 g); ^{1}H NMR: 0.11 (s,9H), 0.94 (d, *J*=1Hz,3H), 1.06 (d, *J*=1Hz,3H), 1.08 (s,3H), 1.34 (s,3H), 1.2-2.8 (m,10H), 3.34 (dd, *J*=4, 12Hz,1H), 3.67 (s,-3H), 6.28 (dt, *J*=1, 10Hz,1H).

Attempted Addition of Dilithio Acetate to 185c.

The addition was performed as previously described for the synthesis of 132 (chapter 3). Silyl enone 185c (0.532 g, 1.21 mmol) was reacted with 1.2 equivalents of dilithio acetate. The only product isolated was the hydroxy enone 185a in 77% yield (0.332 g).

Diastereomeric Methyl 5-Oxo-1α,4aβ-dimethyl-6E-(2-methylpropylidene)-2β-[(tetrahydro-2H-pyran-2-yl)oxy]-1,2,3,4,4a,5,6,7,8,8aα-decahydronaphthalene-1β-carboxylate (185b).

The hydroxy alkylidene ketone 185a (1.476 g, 4.80 mmol) was transformed into the THP ether 185b as previously described for the prtection of 181a (chapter 5). The yield was 1.787 g (95%); ^{1}H NMR (major resonances): 1.06 (s,3H), 1.33 (s) + 1.45 (s)(sH), 3.65 (s) + 3.67 (s)(3H), 4.5-5.0 (m,3H), 6.25 (br d, *J*=9Hz,1H).

Diastereomeric Methyl 5α-Carboxymethyl-1α,4aβ-dimethyl-5β-hydroxy-6E-(2-methylpropylidene)-2β-[(tetrahydro-2H-pyran-2-yl)oxy]-1,2,3,4,4a,5,6,7,8,8aα-decanydronaphthalene-1β-carboxylate (189).

The addition of dilithio acetate was performed as previously described for the preparation of 132 (chapter 3). THP-ether 185b (0.882 g, 2.25 mmol) was treated with 2.6 equivalents of dilithio acetate. After work up and column chromatography 0.560 g (55%) of the 1,2-addition product 189 could be isolated. This product was not charaterized but cyclized to the -lactone 119a.

Methyl 2-Oxo-7α,10aβ-dimethyl-8β-hydroxy-4-(1-methylethyl)-1,4,5,6,6aα,7,8,9,10,10a-decahydro-2H-napnthalene[2,1-c]pyran-7β-carboxylate (119a).

The cyclization of 189 was performed as previously described (chapter 3) for the preparation of 133. The adduct (0.560 g, 1.24 mmol) gave 0.373 g (86%) of 119a;

^{1}H NMR: 0.81 (d, *J*=7Hz,3H), 0.89 (br s,3H), 1.10 (d, *J*=7Hz,3H), 1.46 (s,3H), 1.2-2.3 (m,10H), 2.91 (m,2H), 3.16 (dd, *J*=5, 11Hz,1H), 3.40 (br s,1H, exchanges with D_2O), 3.68 (s,3H), 4.50 (m,1H).

Methyl 5-Oxo-1α,4aβ-dimethyl-2β-methoxy-1,2,3,4,4a,5,6,7,8,8aα-decahydronaphthalene-1β-carboxylate (116e).

To a solution of 4.33 g (17 mmol) of 116b in a mixture of 60 mL of dimethylsulfoxide and 60 mL of dimethylformamide was added at 0°C, 22.5 g (147 mmol) of barium oxide and 12.3 g (39 mmol) of barium hydroxyde octahydrate and subsequently 44.0 g (350 mmol) of dimethylsulfate was added dropwise at 0°C under nitrogen. After stirring for 18h at ambient temperature under nitrogen, 33 mL of a concentrated aqueous ammonia solution was added dropwise in 0.5h, and subsequently 35 mL of 4N hydrochloric acid at 0°C in 0.5h. Then this mixture was poured into water and extracted with ethyl acetate (5x100 mL). The or-

ganic layer was washed with water and brine and dried. Evaporation of the solvent *in vacuo* gave the crude product which was purified by column chromatography to afford the methyl ether 116e in 88% yield[18] (4.01 g) as a white solid: mp 105.0-106.0°C; ^{1}H NMR: 1.05 (s,3H), 1.35 (s,3H), 1.1-2.7 (m,11H), 2.73 (dd, J=5, 11Hz,1H), 3.37 (s,3H), 3.67 (s,3H). M.S. (70eV), *m/e* (%) 268(M^+,3), 236(46), 110(33), 95(26), 712(100), 58(40). Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 67.22; H, 8.83.

Methyl 5-Oxo-1α,4aβ-dimethyl-2β-methoxy-6E-(2-methylpropylidene)-1,2,3,4,4a,5,6,7,8,8aα-decahydronaphthalene-1β-carboxylate (185d) *and Methyl 5-Oxo-1α,4aβ-dimethyl-2β-methoxy-6Z-(2-methylpropylidene)-1,2,3,4,4a,5,6,7,8,8aα-decahydronaphthalene-1β-carboxylate* (186d).

The aldol condensation and dehydration were performed on 7.19 g (26.8 mmol) of 116e as described for the preparation of 181a (chapter 5). The crude product was purified by column chromatography on silica gel (150 g; eluent ether/petroleum ether (40°-60°C), 3:7). The first compound eluted was the (Z)-isomer 186d, a white solid (0.86 g, 10%): mp 104.0-104.5°C; ^{1}H NMR: 0.89 (d,J=7Hz,3H), 0.98 (s,3H), 0.99 (d, J=7Hz,3H), 1.39 (s,3H), 1.1-2.8 (m,10Hz), 2.79 (dd, J=5, 10Hz,1H), 3.40 (s,3H), 3.67 (s,3H), 5.36 (br d, J=10Hz,1H), M.S. (70eV), *m/e* (%) 322(M^+,100), 247(45), 215(23), 187(29), 71(44). Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 71.00; H, 9.32. The second compound obtained was the (E)-isomer 185d as a white solid (6.35 g, 74%): mp 100.0-101.0°C; ^{1}H NMR: 0.97 (d, J=3Hz,3H), 1.02 (s,3H), 1.03 (d, J=3Hz,3H), 1.41 (s,3H), 1.3-2.7 (m,-10H), 2.82 (dd, J=5, 10Hz,1H), 3.40 (s,3H),3.67 (s,3H), 6.29 (br d, J=10Hz,1H). M.S. (70eV), *m/e* (%) 322(M^+,17), 290(37), 247(19), 121(37), 71(100), 55(27), 41(35). Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.99; H, 9.46.

Methyl 5α-Carboxymethyl-1α,4aβ-dimethyl-5β-hydroxy-2β-methoxy-6E-(2-methylpropylidene)-1,2,3,4,4a,5,6,7,8,8aα-decahydronaphthalene-1β-carboxylate (190).

The addition of dilithio acetate was performed as previously described for the preparation of 132 (chapter 3). The methoxy enone 185d (6.35 g, 19.7 mmol) was treated with 1.2 equivalents of dilithio acetate and this afforded, after chromatographic purification on silica gel, 5.86 g (78%) of the 1,2-addition pro-duct 190 as a white solid: mp 210.0-212.0°C; ^{1}H NMR: 0.81 (s,3H), 0.87 (d, J=6Hz, 3H), 0.97 (d, J=6Hz,3H), 1.39 (s,3H), 1.1-2.8 (m,11H), 2.60 (H_A, J_{AB}=13Hz, 1H), 2.90 (H_B,1H), 3.40 (s,3H), 3.63 (s,3H), 5.23 (d, J=9Hz,1H), 8.1 (br s,2H, exchanges with D_2O). M.S. (70eV), *m/e* (%) 382(M^+,20), 364(6), 350(5),

338(9), 323(24), 311(18), 293(29), 237(39), 180(41), 85(59), 71(100). Anal. Calcd for $C_{21}H_{34}O_6$: C, 65.94; H, 8.96. Found: C, 65.72; H, 8.89. In addition o.407 g(5%) of the Michael type addition product was isolated. This product was not characterized but ring closure according to the preparation of 133 (chapter 3) gave 191 (figure 6.1); ^{1}H NMR: 0.93 (m,6H), 0.99 (s,3H), 1.40 (s,3H), 1.2-3.0 (m,14H), 3.42 (s,3H), 3.65 (s, 3H). M.S. (70eV), *m/e* (%) 364(M^+,46), 321(100), 289(84), 229(62), 123(47), 71(69); calcd for $C_{21}H_{32}O_5$ M^+ 364.2250 ; found M^+ 364.2238.

*Diastereomeric Methyl 2-Oxo-7α,10aβ-dimethyl-8β-methoxy-4-(1-methylethyl)-1,4,-5,6,6aα,7,8,9,10,10a-decahydro-2*H*-naphtho[2,1-c]pyran-7β-carboxylate* (119b) *and Methyl 2-Oxo-6α,9aβ-dimethyl-9bβ-hydroxy-7β-methoxy-3aβ-(2-methylpropyl)-1,2,3a,4,5aα,6,7,8,9,9a,9b-dodecahydronaphtho[2,1-b]furan-7β-carboxylate* (192).

The cyclization of 190 (1.026 g, 2.68 mmol) was performed as previously described for the preparation of 133 (chapter 3). Chromatography of the crude product on silica gel afforded as first component 119b (0.615 g, 63%) as a solid which consisted of a diastereomeric mixture of the - and -isomer at C-14; ^{1}H NMR: 0.80 (d, J=6Hz,3H), 0.89 (s) + 0.90 (s),3H , 1.08 (d, J=6Hz,3H), 1.40 (s,3H), 1.2-2.5 (m,10H), 2.76 (dd, J=5, 11Hz,1H), 2.93 (m,2H), 3.40 (s,3H), 3.63 (s,3H), 4.49 (m,1H). The second component which was eluted was the -lactone 192 (0.206 g, 20%) as a white solid: mp 189.0-190.5°C; ^{1}H NMR: 0.93 (s,3H), 0.99 (d, J=6Hz,6H), 1.42 (s,3H), 1.2-2.4 (m,13H), 2.34 (H_a, J_{AB}=17.7Hz,1H), 2.94 (H_B,1H), 2.73 (dd, J=5, 11Hz,1H), 3.40 (s,3H), 3.68 (s,3H). M.S. (70eV), *m/e* (%) 382(M^+,4), 323(8), 293(11), 237(17), 180(25), 85(41), 71(100). Anal. Calcd for $C_{21}H_{34}O_6$: C, 65.94; H, 8.96. Found: C, 66.19; H, 9.10.

*Methyl 2-Oxo-6α,9aβ-dimethyl-7β-methoxy-3aβ-(2-methylpropyl)-2,3a,4,5,5aα,6,7,8,9,9a-decahydro-2*H*-naphtho[2,1-b]furan-7β-carboxylate* (193).

To a solution of 0.324 g (0.85 mmol) of 192 in 5 mL of dry pyridine was added 1.65 g (10.8 mmol) of phosphorous oxychloride and this mixture was stirred at 80°C for 5h. After cooling to room temperature the reaction mixture was poured into water and extracted with dichloromethane (4x50 mL). The combined organic layers were washed with diluted hydrochloric acid and brine and dried. Evaporation of the solvent under reduced pressure gave the crude product which was purified by chromatography on silica gel (50 g, eluent ether). The enolide 193 was obtained as a white solid (0.260 g, 84%): mp 114.5-115.5°C; ^{1}H NMR:

0.89 (d, J=4Hz,3H), 0.98 (d, J=4Hz,3H), 1.07 (s,3H), 1.38 (s,3H), 1.1-2.5 (m,12H), 2.78 (dd, J=5, 10Hz,1H), 3.42 (s,3H), 3.70 (s,3H), 5.66 (s,1H). M.S. (70eV), *m/e* (%) 364(M^+,2), 320(13), 307(19), 215(12), 71(100). Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 68.93; H, 8.93.

Methyl 5E-Carboxymethylene-1α,4aβ-dimethyl-2β-methoxy-6E-(2-methylpropylidene)-1,2,3,4,4a,5,6,7,8,8aα-decahydronaphthalene-1β-carboxylate (194).

The procedure described by Hayashi *et al.*[9] was employed. To a solution of 1.113 g (3.06 mmol) of 119b in dry dimethyl sulfoxide under nitrogen was added at room temperature 0.529 g (4.68 mmol) of potassium *t*-butoxide. After 4h stirring an additional amount of potassium *t*-butoxide (0.320 g, 2.85 mmol) was added and stirring was continued for 18h. Then the mixture was poured into 0.5 N hydrochlorid acid and extracted with chloroform (4x75 mL). The organic layer was washed with brine and dried. After filtration and evaporation of the solvent *in vacuo* the residual oil was chromatagraphed on silica gel (100 g, eluent ether) to afford 194 (0.780 g, 70%) as a white solid: mp 145.0-147.0°C; ^{1}H NMR: 0.92 (d, J=5Hz,3H), 0.95 (s,3H), 0.98 (d, J=5Hz,3H), 1.37 (s,3H), 1.2-2.7 (m,10H), 2.81 (dd, J=5, 12Hz,1H), 3.43 (s,3H), 3.68 (s,3H), 5.07 (d, J= 10Hz,1H), 5.50 (s,1H), 9,5 (br s,1H, exchanges with D_2O). M.S. (70eV), *m/e* (%) 364(M^+,3), 322(21), 321(100), 289(13), 257(6), 229(15). Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 68.89; H, 8.83.

Methyl 2-Oxo-7α,10aβ-dimethyl-8β-methoxy-4α-(1-methylethyl)-1,4,5,6,6a ,7,8,9, 10,10a-decanydro-2H-naphtho[2,1-c]pyran-7β-carboxylate (195).

The procedure of Hayashi *et al.*[9] was employed. A solution of 0.710 g (1.95 mmol) of 194 in 95% ethanol (300 mL) was irradiated with a high-pressure mercury lamp at 0°C for 6h under nitrogen. After evaporation of the solvent *in vacuo* at ambient temperature, the residue was purified on silica gel (eluent ether) to afford 0.552 g (78%) of 195; ^{1}H NMR: 0.80 (d, J=8Hz,3H), 0.89 (s,3H), 1.04 (d, J=8Hz,3H), 1.40 (s,3H), 1.1-2.5 (m,10H), 2.78 (dd, J=5, 11Hz,1H), 2.95 (m,2H), 3.41 (s,3H), 3.65 (s,3H), 4.55 (br q,1H). M.S. (70eV), *m/e* (%) 364(M^+,3), 332(15), 321(39), 289(57), 257(66), 229(59), 73(73), 53(100); calcd for $C_{21}H_{32}O_5$ M^+ 364.2250; found M^+ 364.2236.

Methyl 2-Oxo-7α,10aβ-dimethyl-8β-methoxy-4α-(1-methylethyl)-1α-phenylthio-1,4,5,6,6aα,7,8,9,10,10a-decahydro-2H-naphtho[2,1-c]pyran-7β-carboxylate (197) *and Methyl 2-Oxo-7α,10aβ-dimethyl-8β-methoxy-4α-(1-methylethyl)-1β-phenylthio-*

1,4,5,6,6aα,7,8,9,10,10a-decahydro-2H-naphtho[2,1-c]pyran-7β-carboxylate (196).

The sulfenylation was performed on lacton 195 (o.359 g, 0.99 mmol) according to the General Procedure described in chapter 3 with benzene phenylthiosulfonate. Column chromatography on silica gel afforded 0.296 g (63%) of a 7 to 3 mixture of 196 and 197. After repeated chromatography 26 mg of 197 was obtained in pure form; ^{1}H NMR: 0.90 (s,3H), 1.06 (d, *J*=6Hz,3H), 1.13 (d, *J*=6Hz,3H), 1.43 (s,3H), 1.1-2.5 (m,10H), 2.85 (dd, *J*=5, 10Hz,1H), 3.43 (s,3H), 3.63 (s,3H), 4.00 (s,1H), 4.20 (br s,1H), 7.60 (m,5H). M.S. (70eV), *m/e* (%) 472(M^+,5), 363(100), 362(48), 321(23), 287(25), 71(71). In addition 60 mg of 196 was obtained in pure form as a white solid: mp 170°C(dec.); ^{1}H NMR: 0.83 (d, *J*=7Hz,3H), 1.16 (d, *J*=7Hz,3H), 1.23 (s,3H), 1.41 (s,3H), 1.1-2.5 (m,10H), 2.77 (dd, *J*=5, 11Hz,1H), 3.41 (s,3H), 3.67 (s,3H), 4.28 (s,1H), 4.93 (br s,1H), 7.4 (m,5H). M.S. (70eV), *m/e* (%) 472(M^+,1), 363(100), 362(56), 321(30), 71(75). Anal. Calcd for $C_{27}H_{36}O_5S$: C, 68.61; H, 7.68. Found: C, 68.08; H, 7.83.

Methyl 2-Oxo-7α,10aβ-dimethyl-8β-methoxy-4α-(1-methylethyl)-4,6,6aα,7,8,9,10,10a-octahydro-2H-naphtho[2,1-c]pyran-7β-carboxylate (198) *and Methyl 2-Oxo-7α,10aβ-dimethyl-8β-methoxy-4-(1-methylethyl)-5,6,6aα,7,8,9,10,10a-octahydro-2H-naphtho[2,1-c]pyran-7β-carboxylate* (199).

The oxidative elimination (chapter 3) was performed on 0.170 g (0.36 mmol) of a 7 to 3 mixture of 196 and 197 using 6 equivalents (0.470 g) of sodium periodate. Purification on silica gel (35 g, eluent ether/petroleum ether(40°-60°C), 3:1) afforded 17 mg (13%) of 198; ^{1}H NMR: 0.93 (d, *J*=7Hz,3H), 1.03 (s,3H), 1.06 (d, *J*=7Hz,3H), 1.38 (s,3H), 1.1-2.6 (m,8H), 2.83 (dd, *J*=4, 10Hz,1H), 3.40 (s,3H), 3.69 (s,3H), 4.73 (m,1H), 5.73 (br s,1H), 6.03 (m,1H). M.S. (70eV), *m/e* (%) 362(M^+,0.3), 287(5), 227(3), 85(89), 83(100); calcd for $C_{21}H_{30}O_5$ M^+ 362.2093; found M^+ 362.2088. The second compound isolated was 199 (53 mg, 41%); ^{1}H NMR: 1.13 (s,3H), 1.19 (d, *J*=6Hz,3H), 1.21 (d, *J*=6Hz,3H), 1.41 (s,3H), 1.2-3.2 (m,11H), 3.40 (s,3H), 3.67 (s,3H), 6.04 (s,1H). M.S. (70eV), *m/e* (%) 362(M^+,60), 334(41), 319(48), 308(46), 71(100), 59(20), 45(84), 43(81); calcd for $C_{21}H_{30}O_5$ M^+ 362.2093; found M^+ 362.2101.

Attempted Hydrolysis of Dienolide Ester 198

The method of Hayashi was employed[9]. The ester 198 (17 mg) was dissolved in 0.3 mL of concentrated sulfuric acid. After 2h standing at room temperature crushed ice was added and this mixture was extracted with chloroform (4x25 mL). The organic layer was washed with brine and dried. Evaporation of the solvent

gave as crude product the starting material in quantitative yield.

4,4-Dimethyl-7a(2-methylpropyl)-perhydrobenzo[b]furan-2-one (200).

Iodotrimethylsilane (0.70 g, 3,5 mmol) was added at -33°C to a solution of 96 mg (0.43 mmol) of 133d in 1 mL of chloroform and this mixture was stirred at ambient temperature for 48h. The reaction mixture was poured into water, extracted with chloroform (3x25 mL), and the organic layer was washed with water, an aqueous solution of 1 g sodium thiosulfate, and brine and dried. Evaporation of the solvent under pressure gave an oil, which was pure 200; ^{1}H NMR: 0.93 (s,3H), 1.00 (d, *J*=7Hz,6H), 1.05 (s,3H), 1.0-2.7 (m,12H); M.S. (70eV), *m/e* (%) 224(M^+,1), 209(3), 181(28), 167(100), 139(35).

5E-Carboxymethylene-1α,4aβ-dimethyl-2β-methoxy-6E-(2-methylpropylidene)-1,2,3,-4,4a,5,6,7,8,8aα-decahydronaphthalene-1β-carboxylic Acid (201).

1-Propanethiol (1.34 g, 17.6 mmol) was added dropwise under nitrogen *via* a syringe to a suspension of 0.141 g (17.6 mmol) of lithium hydride in 8.0 mL of dry HMPA. This mixture was stirred under nitrogen at room temperature overnight. Then a solution of 0.400 g (1.10 mmol) of the ester lactone 119b in 1 mL of dry HMPA was added dropwise and the reaction mixture was stirred an additional 24h. The solution was poured into ice-cold 0.1 N aqueous sodium hydroxide solution and this aqueous layer was washed with dichloromethane (3x50 mL). The the aqueous layer was acidified to pH 2 with concentrated hydrochloric acid and extracted with dichloromethane (5x50 mL). The organic layer was washed with brine and dried. After evaporation of the solvent under reduced pressure there remained a crude product which contained some HMPA. Column chromatography on silica gel (50 g; eluent ether) afforded 0.351 g (91%) of the dienedicarboxylic acid 201 as a white solid: mp 180.0-182.0°C; ^{1}H NMR: 0.92 (d,*J*=5Hz,3H), 1.00 (s,3H), 1.00 (d, *J*=5Hz,3H), 1.42 (s,3H), 1.2-3.0 (m,11H), 3.52 (s,3H), 5.04 (dt, *J*=1, 9Hz,1H), 5.45 (s,1H), 11 (br s,2H, exchanges with D_2O). M.S. (70eV), *m/e* (%) 350(M^+,5), 307(100), 289(19), 229(19). Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.48; H, 8.83.

2-Oxo-7α,10aβ-dimethyl-8β-methoxy-4α-(1-methylethyl)-1,4,5,6,6aα,7,8,9,10,10a-decahydro-2H-naphtho[2,1-c]pyran-7β-carboxylic Acid (202).

The method described for the preparation of 195 was employed on 0.920 g (2.63 mmol) of diene dicarboxylic acid 201 and the lactone 202 was obtained in a quantitative yield; ^{1}H NMR: 0.80 (d, *J*=8Hz,3H), 1.00 (s,3H), 1.10 (d,

J=8Hz,3H), 1.43 (s,3H), 1.1-2.3 (m,10H), 2.90 (m,3H), 3.87 (s,3H), 4.57 (m,1H), 9.5 (br s,1H, exchanges with D_2O). M.S. (70eV), *m/e* (%) 350(M^+,3), 307(23), 289(24), 229(25), 213(20), 184(66), 83(100); calcd for for $C_{20}H_{30}O_5$ M^+ 350.2093; found M^+ 350.2096.

2-Oxo-7α,10aβ-dimethyl-8β-methoxy-4α-(1-methylethyl)-4,6,6aα,7,8,9,10,10a-octahydro-2H-naphtho[2,1-c]pyran-7β-carboxylic Acid (203a) *and 2 Oxo-7α,10aβ-dimethyl-8β-methoxy-4-(1-methylethyl)-5,6,6aα,7,8,9,10,10a-octahydro-2H-naphtho-[2,1-c]pyran-7β-carboxylic Acid* (204a).

To a solution of 0.200 g (0.57 mmol) of 202 in 15 mL of dioxane was added 0.259 g (1.14 mmol) of DDQ and subsequently 0.270 g (1.14 mmol) of 2-mesitylenesulfonic acid. The mixture was refluxed under nitrogen for 5.5h and, after cooling, concentrated *in vacuo* in the presence of 5 g of silica gel. The resulting mixture was poured on a column of silica gel (25 g) and eluted with ether. This afforded 0.200 g of an oil which solidified on treatment with ether. The ether was decanted and 0.120 g (60%) of a mixture of 203a and 204a in a ratio of 3:2 remained. This mixture was inseparable and used as such in the next reaction.

3aα,10bβ-Dimethyl-3β-methoxy-7α-(1-methylethyl)-1,2,3,3a,5a,7,10b,10cα-octahydro-4H,9H-furo[2',3',4':4β,5β]naphtho[2,1-c]pyran-4,9-dione (206).

To a solution of 0.120 g (0.34 mmol) of a mixture of 203a and 204a, containing 0.072 g (0.21 mmol) of 203a, in 5 mL of acetic acid was added 0.230 g pyr.HBr.Br_2 (80%) (0.57 mmol) and this mixture was stirred for 17h at ambient temperature. The reaction mixture was poured into 0.5N hydrochloric acid and extracted with dichloromethane (5x25 mL). The organic layer was washed with water and brine and dried. Evaporation of the solvent afforded the crude product, which was dissolved in 10 mL of dry dimethylformamide. To this solution was added 0.300 g (2.17 mmol) of dry potassium carbonate. After strirring overnight at room temperature under nitrogen, the reaction mixture was poured into water and extracted with dichloromethane (5x20 mL). The organic layer was washed with brine and dried. Evaporation of the solvent afforded an oil, which was purified *via* preparative thin layer chromatography, eluting twice with ether. This afforded 4 mg (6%) of 206; ^1H NMR: 1.00 (d, J=6Hz,3H), 1.20 (d, J=6Hz,3H), 1.30 (s,3H), 1.55 (s,3H), 1.5-2.4 (m,6H), 3.33 (dd, J=6, 14Hz,1H), 3.55 (s,3H), 4.87 (t, J=2Hz,1H), 5.00 (m,1H), 5.77 (br s,1H), 6.15 (m,1H). M.S. (70eV), *m/e* (%) 346(M^+,29), 318(15), 303(30), 286(18), 275(100),

243(53); calcd for $C_{20}H_{26}O_5$ M^+ 346.1780; found M^+ 346.1774.

Phenylthiomethyl 2-Oxo-7α,10aβ-dimethyl-8β-methoxy-4α-(1-methylethyl)-4,6,6aα,7,8,9,10,10a-octahydro-2H-naphtho[2,1-c]pyran-7β-carboxylate (203b) *and Phenylthiomethyl 2-Oxo-7α,10aβ-dimethyl-8β-methoxy-4-(1-methylethyl)-5,6,6aα,7,8,9,10,10a-octahydro-2H-naphtho[2,1-c]pyran-7β-carboxylate* (204b).

To a suspension of 120 mg (0.34 mmol) of a 3 to 2 mixture of 203a and 204a in 15 mL of dry benzene was added 129 mg (1.15 mmol) of potassium *t*-butoxide and this suspension was stirred for 25 min. Then 61 mg (0.23 mmol) of 18-crown-6 was added and stirring was continued for 5 min. Subsequently 34 mg (0.25 mmol) of sodium iodide and a solution of 166 mg (1.15 mmol) of phenylthiomethyl chloride in 3 mL of dry benzene was added and this mixture was refluxed for 10h. After cooling the reaction mixture was poured into water and extracted with dichloromethane (3x25 mL). The organic layer was washed with brine and dried. Evaporation of the solvent afforded a residue which was chromotagraphed on silica gel (30 g; eluent petroleum ether (40°-60°C)/ether, 7:3). The first compound eluted was 84 mg (52%) of 203b; ^{1}H NMR: 0.93 (d, J=7Hz,3H), 1.02 (s,3H), 1.05 (d, J=7Hz,3H), 1.40 (s,3H), 1.2-2.6 (m,8H), 2.83 (dd, J=7, 12Hz,1H), 3.40 (s,3H), 4.70 (m,1H), 5.37 (H_A, J_{AB}=12.6Hz,1H), 5.65 (H_B,1H), 5.68 (s,1H), 5.93 (m,1H), 7.2-7.6 (m,5H). M.S. (70eV), *m/e* (%) 470 (M^+,10), 347(13), 123(100); calcd for $C_{27}H_{34}O_5S$ M^+ 470.2127; found M^+ 470.2120. The second compound eluted was 38 mg (24%) of 204b as a white solid: mp 164.5-166.0°C; ^{1}H NMR: 1.12 (s,3H), 1.16 (d, J=3Hz,3H), 1.23 (d, J=3Hz,3H), 1.40 (s,3H), 1.4-2.8 (m,10H), 2.95 (dd, J=6, 15Hz,1H), 3.42 (s,3H), 5.35 (H_A, J_{AB}=12.1Hz,1H), 5.57(H_B,1H), 6.00 (s,1H), 7.2-7.6 (m,5H). M.S. (70eV), *m/e* (%) 470(M^+,43), 331(100), 303(12), 271(26), 123(27). Anal. Calcd for $C_{27}H_{34}O_5S$: C, 68.90; H, 7.28. Found: C, 68.71; H, 7.39.

Hydrolysis of 203b *with trifluoroacetic acid to* 203a.

The phenylthio ester 203b (0.110 g, 0.23 mmol) was dissolved in 1 mL of trifluoroacetic acid at ambient temperature. After stirring for 15 min the solution was poured into water (50 mL) and extracted with dichloromethane (5x20 mL). The organic layer was washed with brine and dried, filtered and the solvent was evaporated under reduced pressure. The residual oil was crystallized from methanol-diisopropyl ether to afford 52 mg (64%) of 203a. The mother liquour was chromatographed on silica gel (10 g; eluent ether) and afforded an additional 23 mg (28%) product: mp 193.5-194.5°C; ^{1}H NMR: 0.94 (d, J=7Hz,3H),

1.06 (d, J=7Hz,3H), 1.10 (s,3H), 1.45 (s,3H), 1.2-2.7 (m,8H), 2.99 (dd, J=3, 10Hz,1H), 3.58 (s,3H), 4.75 (m,1H), 5.70 (br s,1H), 6.10 (m,1H). M.S. (70eV), *m/e* (%) 348(M^+,5), 346(10). 330(11), 287(100), 227(86), 37(38); calcd for $C_{20}H_{25}O_5$ M^+ 348.1937; found M^+ 348.1934.

3aα,10bβ-Dimethyl-3β-hydroxy-7α-(1-methylethyl)-1,2,3,3a,5a,7,10b,10cα-octahydro-4H,9H-furo[2',3',4':4β,5β]naphtho[2,1-c]pyran-4,9-dione (42) (3β-hydroxynagilactone F).

To a solution of 4 mg of 206 in 1.0 mL of dry dichloromethane at -40°C was added under nitrogen 0.5 mL of 1M boron tribromide solution in dichloromethane. After standing at -24°C for 48h the reaction mixture was poured into saturated aqueous sodium bicarbonate, extracted with dichloromethane (3x25 mL) and washed with brine and dried. Evaporation of the solvent *in vacuo* afforded 4 mg of crude product which consisted of a *ca.* 1 to 1 mixture of product and starting material. A repeated reaction was carried out on the crude product in the same way as described, but the temperature was raised to 4°C and the mixture was allowed to stand for 4 days at this temperature. The same work up procedure afforded the crude product, which was purified by preparative TLC, affording less then 1.0 mg of the desired product; ^{1}H NMR[19]: 0.99 (d, J=6,5Hz,3H), 1.21 (d, J=6.5Hz,3H), 1.24 (s,3H), 1.55 (s,3H), 1.75-1.91 (m,2H), 1.94 (d, J=4.5Hz,H_5), 2.14-2.25 (m,2H), 2.25-2.39 (m,H_{15}), 3.57-3.80 (m,2H*), 4.89 (ddd, J=2.0, 2.0, 2.0Hz,H_{14}),5.11 (ddd, J=4.0, 4.5, 2.0Hz,H_6), 5.78 (d, J=2.0Hz,H_{11}), 6.18 (ddd, J=2.0, 2.0, 4.0Hz,H_7). M.S. (70eV), *m/e* (%) 332(M^+,45), 289(83), 261(100), 243(95), 215(53); calcd for $C_{19}H_{24}O_5$ M^+ 332.1624; found 332.1635.

* 1H exchanges with CD_3OD. The remaining H_3 appears like a double doublet with coupling constants of 7 and 11Hz.

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Table 6.1 ^{13}C *chemical shifts of several compounds described in this thesis*

comp. / C-atom	152b[i]	148b[i]	116b[i]	131d[ii]	185d	190	194	202	195
1	31.1	31.9	31.3		32.5	30.8	35.0	32.0	29.0
2	21.8	22.1	22.2*		22.3*	22.6*	22.9*	23.6	22.7
3	87.0	86.7	87.4		87.7	88.3	87.7	87.7	87.8
4	52.8*	52.0	49.8**		50.0	49.9	50.4	49.0	49.1
5	156.4	142.6	53.5	38.5	50.1	49.7	53.7	52.8	52.8
6	123.9	124.1	22.4*	20.0	21.0*	23.9*	23.9*	19.6	19.7
7	141.2	24.8	26.0	27.4	26.1	25.7	29.3	28.9	29.0
8	119.1	34.8	37.4	133.7	132.4	134.9	132.8	126.0	125.3
9	206.3	214.2	214.5	207.4	206.1	78.6	170.1	132.9	133.8
10	51.4*	48.3	48.9**	43.7	47.3	43.0	42.0	37.5	37.9
11						39.3	110.2	34.6	35.0
12						175.0	172.0	170.4	170.6
14				145.3	146.3	131.5	136.3	86.7	87.8
15				27.1	27.1	26.5	27.0	29.3	32.2
16				22.0	22.3	23.4	23.1	18.0	16.7
17				22.0	21.6	23.1	21.4	14.7	14.8
18	25.0	23.3*	24.4		24.6	25.2	24.9	24.2	23.7
19	173.3	174.4	174.4		174.4	174.4	174.1	174.9	174.4
20	22.5	23.0*	17.0	26.2	17.4	12.9	18.3	19.4	19.4
iii	58.6	58.4	58.3		58.2	58.4	58.2	57.9	58.6
iv	51.8	51.6	51.3		51.2	51.2	51.2		51.2

i the spectrum of the methyl ether was recorded

ii the (E)-isomer was measured

iii the OCH_3 *of the ether group*

192	193	196[vi]	199	198	203a	180	147b[i]	147a	42
32.6	35.9	35.8	36.7	34.3	34.8	25.3	31.2	33.1	29.9
21.9	22.4	22.8	22.7	22.5	23.7	23.8	21.7	18.1	28.8
87.7	87.4	87.7	87.3	87.3	86.7	70.1	87.8	41.6	73.3
49.2	49.6	48.7	49.7	49.6	49.2	42.1	39.7	34.1	45.0
51.0	56.2	52.9	49.1	48.4	49.1	48.5	53.2	53.5	49.7
20.0	20.8	19.9	19.5	25.2	24.5	71.7	20.7	21.0	72.4
39.5	39.8	28.4	23.7	130.7	132.2	136.9	26.3	26.3	121.1
90.6	89.9	132.7	108.0	128.1	127.3	131.8	37.5	37.6	135.4
83.8	182.0	137.4	168.8	162.5	162.0	201.6	215.3	216.0	158.3
41.3	40.2	38.9	38.5	37.5	37.7	46.1	48.8	49.1	35.7
40.9	112.8	45.3	107.0	109.8	110.1				111.8
174.4	172.0	168.4	164.8	165.5	165.4				163.9
35.1	45.3	83.6	163.8	83.7	83.9				83.0
25.2	24.6	28.8	29.1	32.7	32.9				29.8
24.5	24.2	18.5	19.7*	19.3*	19.5				19.7
24.5	24.2	14.9	21.9*	16.1	16.2				15.2
24.1	24.5	23.8	24.4	24.5	23.8	23.4	18.6	22.1	23.5
174.5	174.2	174.5	174.1	174.0	174.9	175.1	16.5	18.6	179.9
12.7	15.8	201.7	19.4*	19.5*	21.4	22.3	28.0	33.1	22.3
58.6	58.6	58.7	58.2	58.3	57.9	*v*	57.6		
51.4	51.5	51.2	51.2	51.4					

iv the OCH_3 of the ester group

v the $O\text{-}CO\text{-}CH_3$ group: 21.1(q), 170.4(s)

vi the -SPh group: 135.0(s), 133.7(2d), 128.8(d)

*, ** *these values may be interchanged in one column*

7 GENERAL DISCUSSION

The investigations described in this thesis deal with the total synthesis of physiologically active nor- and bisnorditerpenoid dilactones (fig.1). The goal was to design a synthetic route for

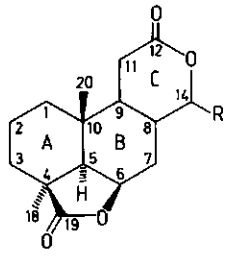
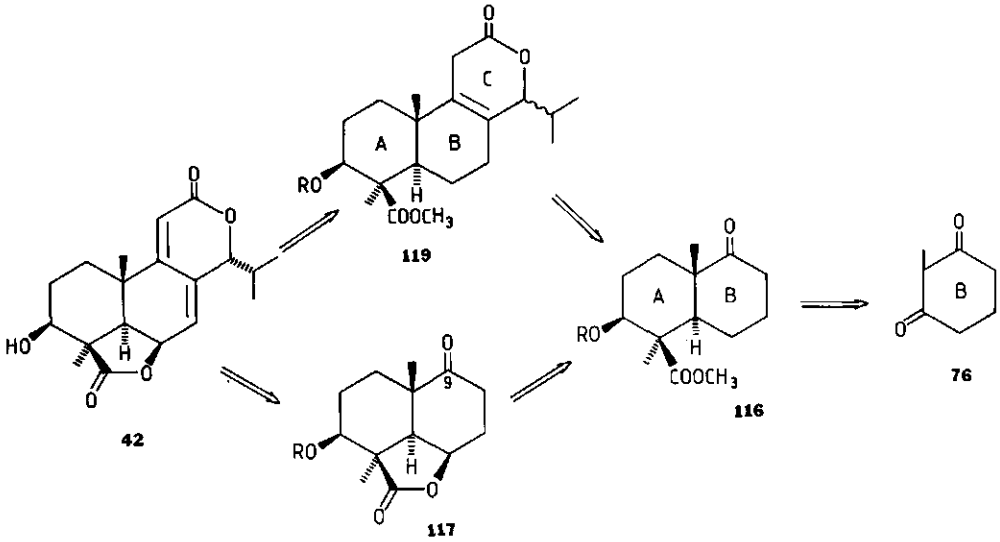


figure 1

this class of natural products and its derivatives. From a retrosynthetic study of 3β-hydroxynagilactone F (42), which was chosen as target molecule, an approach, starting from ring B followed by annellation of ring A and ring C, seemed to offer good perspectives.



scheme 1

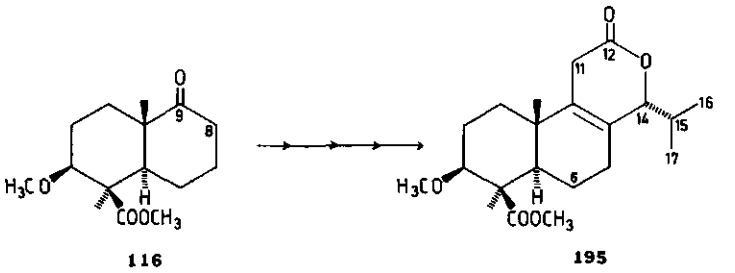
Methylcyclohexanedione was used as starting material, representing ring B, and Robinson annellation with carbomethoxymethylinylketone yielded the AB ring system. This product could be stereoselectively transformed into the *trans*-fused bicyclic ketone 116, a crucial intermediate in the total synthesis. The method which was developed for this transformation was also applied in the synthesis of the trimethyl-analogue of 116, an intermediate, used in the synthesis of natural products, *e.g.* drimane type sequiterpenes.

Starting from 116 two possible routes were explored, which differed in the sequence of introduction of the two lactones varied. The first approach was the synthesis of the tricylic γ-lactone 117 and subsequent annellation of the δ-lactone. Different methods for the synthesis of 117 were investigated and ultimately introduction of a doubel bond, bromination, and cyclization resulted in the formation of the desired -lactone. The carbonyl function at C-9 can serve as handle for the annellation of δ-lactone.

Initially the annellation was investigated using 2,2-dimethylcyclohexanone as a model compound for ring B. Aldolcondensation at C-8, followed by a dehydration, afforded an alkylideneketone. The carbonatomes 11 and 12 were introduced by an addition of dilithio acetate at the carbonyl at C-9. Cyclization of the adduct gave the -lactone. The choice of the aldehyde determines the side-chain at C 14 and the method therefore offers the possibility to vary the diterpenoid dilactones at this position.

This procedure was applied on the tricyclic γ-lactone 117. The results however were very disappointing. The introduction of the alkylidene side-chain could be nicely performed, but the addition of dilithio acetate failed. Once again it appeared that development of a method on a model compound is no guarantee for its applicability on more complicated compounds.

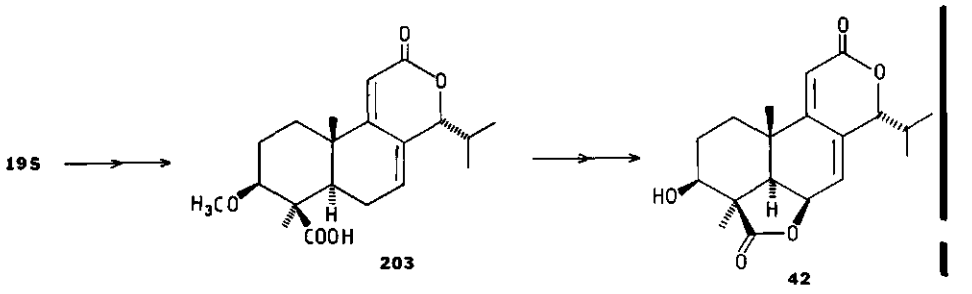
The second approach started with the bicyclic ketone 116 to which the δ-lactone was annellated. Now, this reaction sequence could be performed without any particular problem and afforded the tricyclic product 119, which was however a mixture of the α and β-isomer at C-14.



scheme 2

Treatment with base gave lactone opening to a diene carboxylic acid which upon irradiation stereoselectively afforded the δ-lactone 195 with the correct configuration at C-14. As the γ-lactone had to be introduced in a later stage of the synthesis it was necessary to activate the C-6 position. Regioselective transformation of 195 into the 7(8),9(11)-dienolide is therefore essential.

Some methods have been investigated and the results are outlined in chapter 3. DDQ-dehydrogenation appeared to give the best results when applied on the tricyclic 7(8),9(11)-dienolide. A cyclization, analogous to that used in the synthesis of the γ-lactone 117, was performed on the intermediate 203 and this resulted in the formation of a small amount of the methyl ether of 3β-hydroxynagilactone F. The synthetic and racemic 3β-hydroxynagilactone F (42) could be isolated after treatment of the ether with boron tribromide at low temperature.

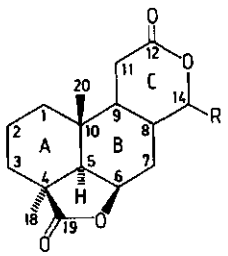


scheme 3

The synthetic route, explored in this thesis leaves the possibility to vary the side chain C-14. Moreover, the substitution patern in ring A can be changed by functional group transformations, performed on the hydroxyl group present in ring A.

SAMENVATTING

De opzet van het in dit proefschrift beschreven onderzoek, was de ontwikkeling van een methode voor de totaalsynthese van norditerpeen dilactonen (fig.1). Deze groep van natuurstoffen, die



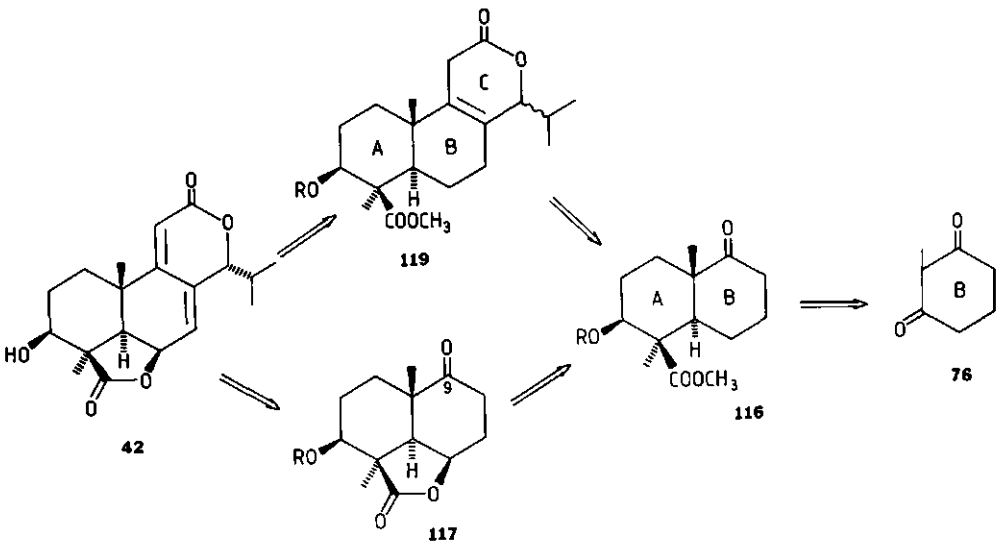
figuur 1

geisoleerd kan worden uit species van de *Podocarpaceae*, vertonen een breed spectrum van fysiologische aktiviteiten, zoals in hoofdstuk 1 is beschreven. Voor een goed inzicht in de werking van dit type verbindingen op moleculair niveau is een uitgebreid onderzoek naar struktuur-aktiviteits relaties noodzakelijk. De syntheseroute zou de mogelijkheid moeten bieden derivaten van deze verbindingen te synthetiseren, zodat veranderingen in de aktiviteit bewerkstelligd kunnen worden.

In hoofdstuk 2 wordt de synthese van een schimmelmetaboliet, LL-Z1271α, beschreven, dat een vergelijkbare struktuur heeft. De δ-alkylsubstituent in ring C van diterpeen dilactonen is bij deze verbinding vervangen door een methoxy groep. Bovendien wordt de totaalsynthese van een norditerpeen dilacton besproken.

Een retrosynthetische studie van 3ß-hydroxynagilacton F, (42), dat als doelmolecuul gekozen werd, toonde aan dat een opbouw van het molecuul, uitgaande van ring B gevolgd door annellering van respectievelijk ring A en ring C goede mogelijkheden bood (schema 1). Robinson annellering van 2-methyl-cyclohexaandion-1,3 (ring B) met carbomethoxymethylvinylketon leverde het AB ringsysteem op. Dit bicyclisch produkt kon vervolgens stereoselectief omgezet worden in het *trans*-verknoopte product 116, dat een cruciaal intermediair is in de totaalsynthese. De methode, die hiervoor ontwikkeld werd, kon ook toegepast worden voor de synthese van het

4,4,10-trimethyldecalon, een intermediair dat gebruikt wordt in de synthese van natuurprodukten, o.a. sesquiterpenen van het drimaan type (hoofdstuk 4).



schema 1

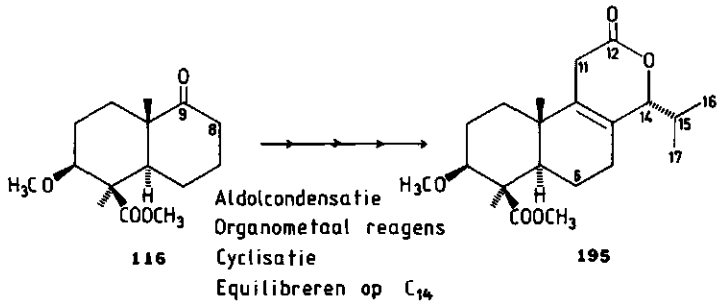
Twee mogelijke routes zijn, uitgaande van dit intermediair, uitgewerkt, waarbij de volgorde van de introduktie van de twee lactonen verschilde. De synthese van het tricyclisch γ-lactone 117, gevolgd door de annellering van het δ-lacton, vormde de eerste benadering. Verschillende methodieken voor de synthese van 117 werden onderzocht; de introduktie van een dubbele binding, bromering van deze dubbele binding en cyclisatie bleek uiteindelijk een goede benadering voor het gewenste γ-lactone. De carbonylfunktie op C-9 kan nu dienen voor de annellering van een δ-lactone.

Deze annellering is aanvankelijk onderzocht aan 2,2-dimethylcyclohexanon, dat als modelsysteem voor ring B werd gebruikt (hoofdstuk 3). Op C-8 kon een aldolcondensatie uitgevoerd worden die, gevolgd door een dehydratatie van het produkt, een alkylideenketon opleverde. Door middel van een additie van het dianion van azijnzuur op de carbonyl groep op C-9 werden de C-atomen C-11 en C-12 geintroduceerd. Cyclisatie van het additie-

produkt leidde vervolgens tot het gewenste δ-lacton. De keuze van het aldehyde bepaalt de zijketen op de δ-positie en deze methode biedt dus de mogelijkheid de substitentop deze positie te varieren.

Deze methode werd toegepast op het tricyclisch γ-lactone 117. De resultaten hiervan waren teleurstellend. De invoering van de alkylideen-zijketen verliep goed, maar de additie van het dianon van azijnzuur bleek niet uitvoerbaar. Hieruit blijkt, dat modelwerk geschikt is om de methodiek te ontwikkelen, maar dat geen garantie voor de toepasbaarheid op gecompliceerdere verbindingen wordt verkregen.

De tweede benadering startte met het bicyclisch keton 116, waaraan eerst het δ-lactone geannelleerd werd. De toe te passen reakties verliepen nu zonder noemenswaardige problemen en leidden tot het tricyclisch produkt 119. Hierin is de stand van de alkylsubstituent op de C-14 positie nog niet eenduidig. Lactonopening tot een dieencarbonzuur, gevolgd door een fotochemische ringsluiting, leverde stereoselectief het δ-lacton 195 op met de correcte

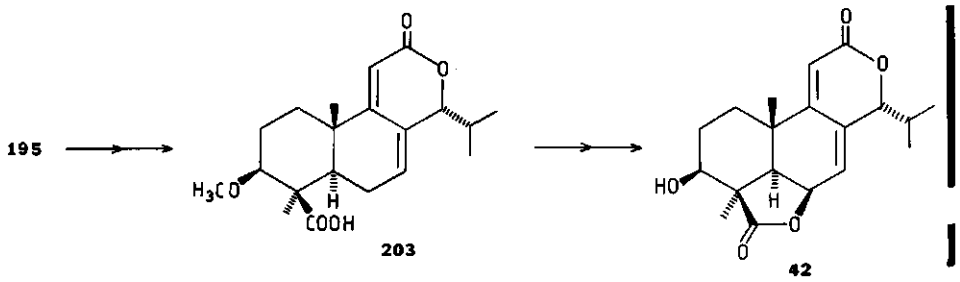


schema 2

stereochemie op C-14. Aangezien in deze benadering het γ-lacton in een later stadium ingevoerd moet worden is het noodzakelijk om de C-6 positie te activeren. Regioselectieve transformatie van 195 naar het 7(8),9(11)-dienolide 203 is daarom essentieel.

In hoofdstuk 3 zijn enige methodieken hiervoor onderzocht en daarvan bleek DDQ-dehydrogenering de beste resultaten te geven. Toepassing van deze methode op 195 gaf verbinding 203 waarna een cyclisatie zoals toegepast in de synthese van lactone 117

resulteerde in de vorming van een geringe hoeveelheid van de methyl ether van 3β-hydroxynagilacton F. Na ethersplitsing met boor tribromide bij lage temperatuur werd het synthetische 3β-hydroxynagilacton F (42) geïsoleerd.



schema 3

De syntheseroute, die in dit proefschrift uitgewerkt is, biedt de mogelijkheid de zijketen op C-14 positie te varieren. Bovendien is het door de aanwezigheid van de 3β-hydroxyl groep mogelijk het substitutiepatroon in ring A te varieren door funktionele groep transformaties toe te passen.

DANKWOORD

Bij de voltooing van dit proefschrift wil ik graag iedereen bedanken, die in de periode waarin dit onderzoek is uitgevoerd, heeft bijgedragen aan de totstandkoming ervan. Zowel de stimulerende discussies als ook feitelijke uitvoering van gedeelten van het onderzoek zijn daarbij van belang geweest. Met name Prof.Dr. Ae. de Groot ben ik zeer erkentelijk voor de mogelijkheid die hij mij heeft geboden, dit onderzoek onder zijn leiding uit te voeren.

Eveneens is een woord van dank op zijn plaats aan hen die de technische ondersteuning van het onderzoek en de uitvoering van analyses ten behoeve van struktuurophelderingen verzorgden.

Last but not least ben ik hen erkentelijk, die aan de totstandkoming van het manuscript en de vormgeving van het proefschrift hun medewerking hebben verleend.

CURRICULUM VITAE

De auteur van dit proefschrift werd op 28 maart 1955 te Groesbeek geboren. Na het behalen van het diploma HBS-B aan het Canisius College te Nijmegen in 1972, begon hij met de studie scheikunde aan de Katholieke Universiteit te Nijmegen. Het kandidaatsexamen (S2) werd in november 1975 afgelegd. Hiervoor werden twee hoofdvakken gedaan en wel farmacochemie (Prof.Dr. J.M. van Rossum, Dr. F. Seutter-Berlage) en organische chemie (Prof.Dr. R.J.F. Nivard, Dr. J.W. Scheeren). Ook werd de onderwijsbevoegdheid verkregen in de scheikunde in augustus 1979.

In maart 1979 werd hij als wetenschappelijk ambtenaar aan het laboratorium voor organische chemie van de Landbouwhogeschool te Wageningen aangesteld, waar hij onder leiding van Prof.Dr. Ae. de Groot het in dit proefschrift beschreven onderzoek verrichtte. Gedurende zijn studie en promotie-onderzoek was hij betrokken bij het onderwijs aan studenten en HBO-B stagiaires.