The Total Synthesis of Insect Antifeedant (–)-Dihydroclerodin Starting from R-(–)-Carvone

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

Promotor: dr. B. J. M. Jansen, universitair docent,

Co-promotor: leerstoelgroep bio-organische chemie

T. M. Meulemans

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proefschrift
ter verkrijging van de graad van doctor
op gezag van de rector magnificus
van Wageningen Universiteit,
dr. C. M. Karssen,
in het openbaar te verdedigen
op woensdag 10 mei 2000
des namiddags te vier uur in de aula.

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Stellingen bij het proefschrift van Tommi M. Meulemans

1. Stellingen betekenen niks zonder bronvermelding.
bron: T. M. Meulemans zaterdagmorgen bij het lezen van de krant.

2. Het zoeken naar werk kost onnodig veel tijd door het ontbreken van de discipline in de titel van de vacatures.
Bron: Intermediair, Volkskrant

3. Statistiek zou een vereist vak moeten zijn voor journalisten en nieuwslezers.

4. Het refereren naar internetpagina's getuigt niet van het vertrouwen dat je werk na een jaar nog gelezen wordt.

5. De stap voor een bioloog naar de chemie wordt als veel groter ervaren dan de stap voor een chemicus naar de biologie.

6. Goed literatuuronderzoek verdient zichzelf terug.

7. Dat Hagiwara *et al.* naar de Groot en Luteijn verwijzen voor de reductie van enon **14** met Li/NH_3 is op zijn minst raar te noemen.
bron: (a) Hagiwara, H.; Inome, K.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 757-764. (b) Luteijn, J. M.; de Groot, A. *J. Org. Chem.* **1981**, *46*, 3448-3452.

8. De vergelijking van de door Drewes *et al.* geïsoleerde verbindingen met warburganal is onterecht en het lijkt erop dat Drewes mee wil liften met de bekendheid van dit drimaan sesquiterpeen.
bron: Drewes, S. E.; Horn, M. M.; Connolly, J. D.; Bredenkamp, B. *Phytochemistry* **1998**, *47*, 991-996.

9. De als nieuw aangemerkte clerodanen, geïsoleerd door Ohno *et al.*, zijn hoogst waarschijnlijk chemische producten die gevormd zijn tijdens de extractie met ethanol.
bron: Ohno, A.; Kizu, H.; Tomimori, T. *Chem. Pharm. Bull.* **1996**, *44*, 1540-1545.

10. Het is onjuist om aan te nemen dat er geen racemisatie op zal treden op C5 gedurende de Robinson annulering van dihydrocarvon.
bron: Beauhaire, J.; Durcot, P.-H.; Simon, I. *Synth. Comm.* **1995**, *25*, 3015-3025.

11. De waarde die door Chen *et al.* wordt toegekend aan de resultaten van moleculair modelling bij het opheldelen van de structuur van het clerodaan lupilin F is onjuist.
bron: (a) Chen, H.; Liu, D. Q.; Zhang, L. X.; Xia, Z. H.; Yang, L.; Liu, Z. L.; Tan, R. X. *Indian J. Chem.* **1999**, *38B*, 743-745. (b) Boneva, I. M.; Mikhova, B. P.; Papanov, P. Y.; Duddeck, H.; Spassov, S. L. *Phytochemistry* **1990**, *29*, 2931-2933.

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10 mei 2000

Voorwoord

Op de reis van carvon naar dihydroclerodin, beschreven in dit boek, hebben veel mensen meegereisd. Deze zou ik graag op deze pagina bedanken.
Allereerst Aede de Groot voor de vele discussies over hoe nu verder en zijn enthousiasme gedurende de hele reis.
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Andre Stork voor het synthetiseren van verbinding **246** en **203**.
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Elbert, Harm en Pim voor het in stand houden van de GC apparatuur.
Cyril, Mareen, Havier, Elena, Cindy en Fliur voor hun werk aan dit project als student, PhD of gastmedewerker.
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Marina bedank ik speciaal voor het lezen en nakijken van dit proefschrift en de vele discussies thuis over hoe je iets opschrijft en voor het fotograferen en ontwerpen van de kaft. En natuurlijk Pim die zeer lief was tijdens het schrijven van dit proefschrift.

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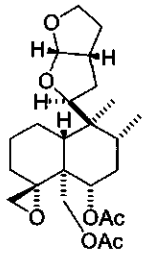
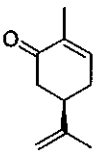
Introduction



dihydroclerodin (**1**)

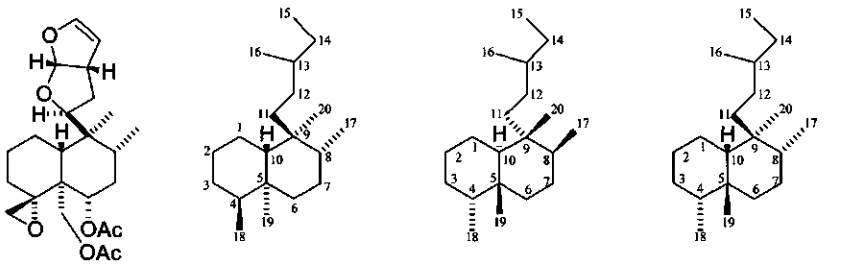


R-(–)-carvone (**2**)

1.1 Dihydroclerodin, Structure, Nomenclature

Dihydroclerodin (**1**) is a natural diterpene (C_{20}) which belongs to the family of clerodanes, a subclass of the diterpenes. It has been first isolated from the *Caryopteris divaricata*[1] and many years later from the *Scutelaria discolor*[2] and the *Ajuga parviflora*[3]. The name of the family of clerodanes is derived from clerodin (**3**) which was isolated from the Indian Bath tree (*Clerodendron infortunatum*) and characterized by Barton *et al.* in 1961.[4] The nomenclature of clerodanes is confusing because a mistake was made in the determination of the absolute stereochemistry of a bromolactone derived from clerodin (**3**), and this compound was published[5] as its enantiomer. The revision of its absolute stereochemistry[6] has led to the nomenclature; *neo*-clerodanes for those compounds with the same absolute stereochemistry as clerodin (**3**) and *ent-neo*-clerodanes for those compounds enantiomeric to clerodin (**3**). A further classification of the clerodanes has led to a division in *cis*- and *trans*-clerodanes, depending on the stereochemistry of the decalin ring junction.

figure 1.1[7]



clerodin (**3**) | *neo-trans*-clerodane skeleton | *ent-neo-trans*-clerodane skeleton | *neo-cis*-clerodane skeleton

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1 Hosozawa, S.; Kato, N.; Munakata, K. *Phytochemistry* **1973**, *12*, 1833-1834.

2 Ohno, A.; Kizu, H.; Tomimori, T. *Chem. Pharm. Bull.* **1996**, *44*, 1540-1545.

3 Beauchamp, P. S.; Bottini, A. T.; Caselles, M. C.; Dev, V.; Hope, H.; Larter, M.; Lee, G.; Mathela, C. S.; Melkani, A. B.; Millar, P. D.; Miyatake, M.; Pant, A. K.; Raffel, R. J.; Sharma, V. K.; Wyatt, D. *Phytochemistry* **1996**, *43*, 827-834.

4 Barton, D. H. R. C., H. T.; Cross, A. D.; Jackman, L. M.; Martin-Smith, M. *J. Chem. Soc.* **1961**, 5061-5073.

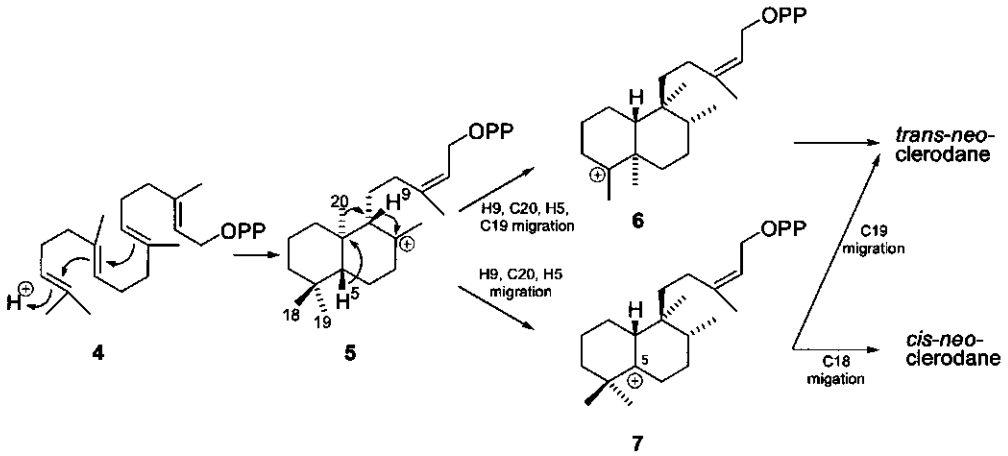
5 Paul, I. C.; Hamor, T. A.; Monteath Robertson, J. *J. Chem. Soc.* **1962**, 4133-4145.

6 (a) Harada, N.; Uda, H. *J. Am. Chem. Soc.* **1978**, *100*, 8022-8024. (b) Rogers, D.; Unal, G. G.; Williams, D. J.; Ley, S. V.; Sim, G. A.; Joshi, B. S.; Ravindranath, K. R. *J. Chem. Soc., Chem. Comm.* **1979**, 97.

7 Throughout this thesis the clerodane numbering according to figure 1.1 will be used in all discussions.

The biosynthesis of clerodanes starts with geranylgeranyl pyrophosphate (**4**), which is first cyclized to an *ent*-labdane skeleton. In the *ent*-labdane carbocation **5** a number of hydride and methyl shifts then leads to the *trans*- and *cis*-clerodanes.[8] The *trans*-clerodanes can be formed by a concerted migration of H9, C20, H5 and C19 or via a stepwise process in which first a concerted migration of H9, C20 and H5 takes place, leaving a carbocation at C5, followed by a shift of C19 at the end of the pathway. Via a similar stepwise process the *cis*-clerodanes can be formed, when C18 migrates in the last step. The pathways depicted in scheme 1.1 explain the configuration of the majority of the clerodanes.

scheme 1.1



1.2 Antifeedant

Of the relatively few clerodanes that were tested for biological activity, many were found to possess interesting activities, which vary from antifeedant to antiviral, antitumor, antibiotic, antipeptic ulcer, and piscicidal activity.[9] Probably the best known is the insect antifeedant activity, an activity of the clerodanes that stops insects from eating the plant without killing the insect directly. Dihydroclerodin is found to possess a high insect antifeedant activity against the Egyptian cotton leafworm (*Spodoptera littoralis*),[10] larvae of the tobacco cut leafworm (*Spodoptera litura*),[11] and larvae of the African armyworm (*Spodoptera exempta*).[10] Recently an extensive review about the antifeedant activities of clerodanes has been written by klein

[8] Wilson, S. R.; Neubert, L. A.; Huffman, J. C. *J. Am. Chem. Soc.* **1976**, *98*, 3669-3674.

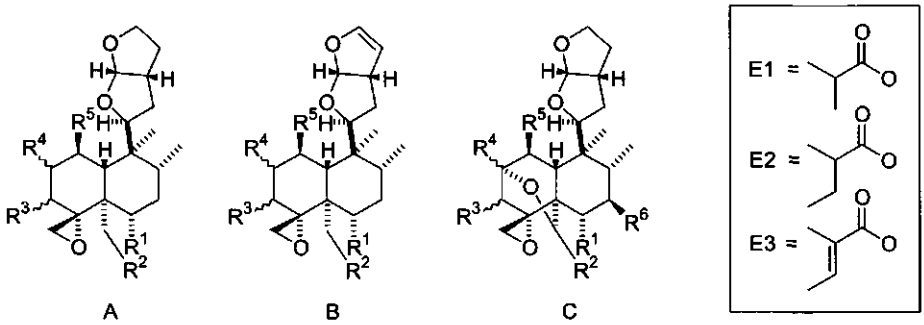
[9] Merrit, A. T.; Ley, S. V. *Nat. Prod. Reports* **1992**, *9*, 243-287.

[10] Blaney, W. M.; Simmonds, M. S. J.; Ley, S. V.; Jones, P. S. *Entomol. Exp. Appl.* **1988**, *46*, 267-274.

[11] (a) Hozokawa, S.; Kato, N.; Munakata, K. *Agric. Biol. Chem.* **1974**, *38*, 823-826; (b) Hozokawa, S.; Kato, N.; Munakata, K.; Chen, Y. L. *Agric. Biol. Chem.* **1974**, *38*, 1045-1048.

Gebbinck.[12] In the table below the antifeedant activity of several clerodanes possessing a hexahydrofuro[2,3-*b*]furan moiety as in structure A and C (figure 1.2) is depicted. For comparison with similar structures possessing an unsaturated furofuran moiety, the activities of clerodanes with structure B are also shown in the table. The activity of clerodanes with a hexahydrofuro[2,3-*b*]furan moiety is comparable to that of their 14,15-unsaturated analogs.

figure 1.2



Name	R^1	R^2	R^3	R^4	R^5	R^6	test A[d] conc.[e] AI[f]	test B[g] conc. AI	test C[h] conc. AI	test D[i] conc. AI	test E[j] conc. AI	ref.
dihydro-clerodin (1)[a]	OAc	OAc	H	H	H	H	100 95%	100 47%	100 94%	50 100%	100 37%	10, 11
clerodin (3)[b]	OAc	OAc	H	H	H	H	100 74%	100 78%	100 76%	50 100%	---	10, 11
3β-hydroxy-ajugavensin[a]	OAc	OAc	β-OH	H	E3	H	100 0%	---	---	---	---	13
ajugareptansin[a]	OAc	OAc	β-OH	H	E2	H	100 40%	---	---	---	---	13
14,15-dehydro-ajugareptansin[b]	OAc	OAc	β-OH	H	E2	H	100 92%	---	---	---	---	13
ivain I[a]	OAc	OAc	β-E1	β-OH	H	H	100 60%	---	---	---	---	14
ivain II[a]	OAc	OAc	β-E1	H	H	H	100 75%	---	---	---	---	14
ivain IV[a]	OAc	OAc	β-E2	β-OH	H	H	100 79%	---	---	---	---	14

[12] (a) klein Gebbinck, A. E. PhD thesis, Wageningen University, **1999**; (b) klein Gebbinck, A. E.; B. J. M. Jansen; de Groot, A. to be published in Phytochemistry.

[13] Bremner, P. D.; Simmonds, M. S. J.; Blaney, W. M.; Veitch, N. C. *Phytochemistry* **1998**, *47*, 1227-1232.

[14] Belles, X.; Camps, F.; Coll, J.; Piulachs, M. D. *J. Chem. Ecol.* **1985**, *11*, 1439-1445.

2-acetyl-ivain I[a]	OAc	OAc	β-E1	α-OAc	H	H	100 79%	---	---	---	---	14
dihydro-ajugapitin[a]	OAc	OAc	β-E2	α-OH	H	H	100 80%	---	---	---	---	14
ajugapitin[b]	OAc	OAc	β-E2	β-OH	H	H	100 92%	---	---	---	---	14
dihydro-caryoptin[a]	OAc	OAc	α-OAc	H	H	H	---	---	---	80 100%	---	11
caryoptin[b]	OAc	OAc	α-OAc	H	H	H	---	---	---	200 100%	---	11
dihydro-caryoptinol[a]	OAc	OAc	α-OH	H	H	H	---	---	---	100 100%	---	11
caryoptinol[b]	OAc	OAc	α-OH	H	H	H	---	---	---	200 100%	---	11
dihydro-jodrellin T[c]	OAc	OAc	H	H	E3	H	100 63%	---	---	---	---	15, 16
scutegalin A[c]	OAc	E3	H	H	H	E3	100 41%	---	---	---	---	16

(**a**) structure A figure 1.2; (**b**) structure B figure 1.2; (**c**) structure C figure 1.2; (**d**) test A activities against larvae of the Egyptian cotton leafworm (*Spodoptera littoralis*) measured in a two-choice feeding assays; (**e**) concentrations are in ppm[12] (**f**) AI is Antifeedant Index[12] (**g**) test B activities against larvae of the fall armyworm (*Spodoptera frugiperda*) measured in a two-choice feeding assays; (**h**) test C activities against larvae of the African armyworm (*Spodoptera exempta*) measured in a two-choice feeding assays; (**i**) test D activities against larvae of the tobacco cut leafworm (*Spodoptera litura*) measured in a two-choice feeding assays; (**j**) test E activities against larvae of the cotton bollworm (*Heliothis amigera)* measured in a two-choice feeding assay

[15] Cole, M. D.; Anderson, J. C.; Blaney, W. M.; Fellows, L. L.; Ley, S. V.; Sheppard, R. N.; Simmonds, M. S. J. *Phytochemistry* **1990**, *29*, 1793-1796.

[16] Rodriguez, B.; Delatorre, M. C.; Rodriguez, B.; Bruno, M.; Piozzi, F.; Savona, G.; Simmonds, M. S. J.; Blaney, W. M.; Perales, A. *Phytochemistry* **1993**, *33*, 309-315.

1.3 Synthesis of clerodanes

During the last two decades a number of clerodanes has been synthesized, starting with the synthesis of annonene in 1979.[17] Since 1987[18] also optically active clerodanes have been synthesized. The clerodanes syntheses can be divided into two main groups; *cis*- and *trans*-clerodanes. In this review, the total syntheses of *trans*- and *cis*-clerodanes starting from 1989[19] will be discussed.

***Trans*-clerodanes, a synthesis survey**

In 1992 Piers *et al.*[20] reported the total synthesis of optically active (–)-kolavenol (**18**) and (–)-agelasine B (**21**) starting from cyclohexanone **8**. A conjugate addition of trimethylstannyl cuprate to cyclohexanone **8**, followed by capturing the copper enolate with methyl iodide gave a cyclohexanone, which was converted into enone **9** by oxidation with DDQ of the kinetic trimethyl silyl ether. Now the carbon atoms for the second ring were introduced by a conjugate addition of cuprate **10**. Ring closure was carried out by converting the chloride into a iodide, which then easily underwent an intramolecular nucleophilic substitution reaction by the enolate to give *cis*-decalin **11**. Reduction of the carbonyl group and the trimethylstannyl function with Li/NH_3 gave alcohol **12**. Oxidation of the hydroxyl group followed by equilibration with sodium methoxide at C8 and C10 gave the *trans*-decalone **13**.[21] A nitrile was introduced at C9 by an addition of tosylmethyl isocyanide to the carbonyl group and the second substituent at C9 was introduced by α-alkylation of this nitrile to give **14**. Reduction of the nitrile group by DIBALH gave an aldehyde which was reduced by a Wolf-Kishner reaction to a methyl group. The MOM group was removed by Me_2BBr, and during this reaction the exocyclic double bond partly isomerized to the endocyclic position. Complete isomerization of the exocyclic double bond to the endocyclic position was accomplished by treatment with acid. The introduction of **16** via a $Pd(dba)_2$ and triphenylarsine catalyzed coupling reaction proceeded in high yield to give **17**. Removal of the silyl protecting group yielded (–)-kolavenol (**18**). Treatment of the silyl ether **17** with Ph_3PBr_2 gave the allylic bromide. Alkylation of adenine **19** with the allylic bromide at N1 gave the desired salt **20** besides the product obtained by alkylation at N2. Separation of these two isomers, followed by electrochemical deprotection of the N-methoxy group finally led to (–)-agelasine B (**21**).

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[17] Takahashi, S.; Kusumi, T.; Kakisawa, H. *Chem. Lett.* **1979**, 515-518.

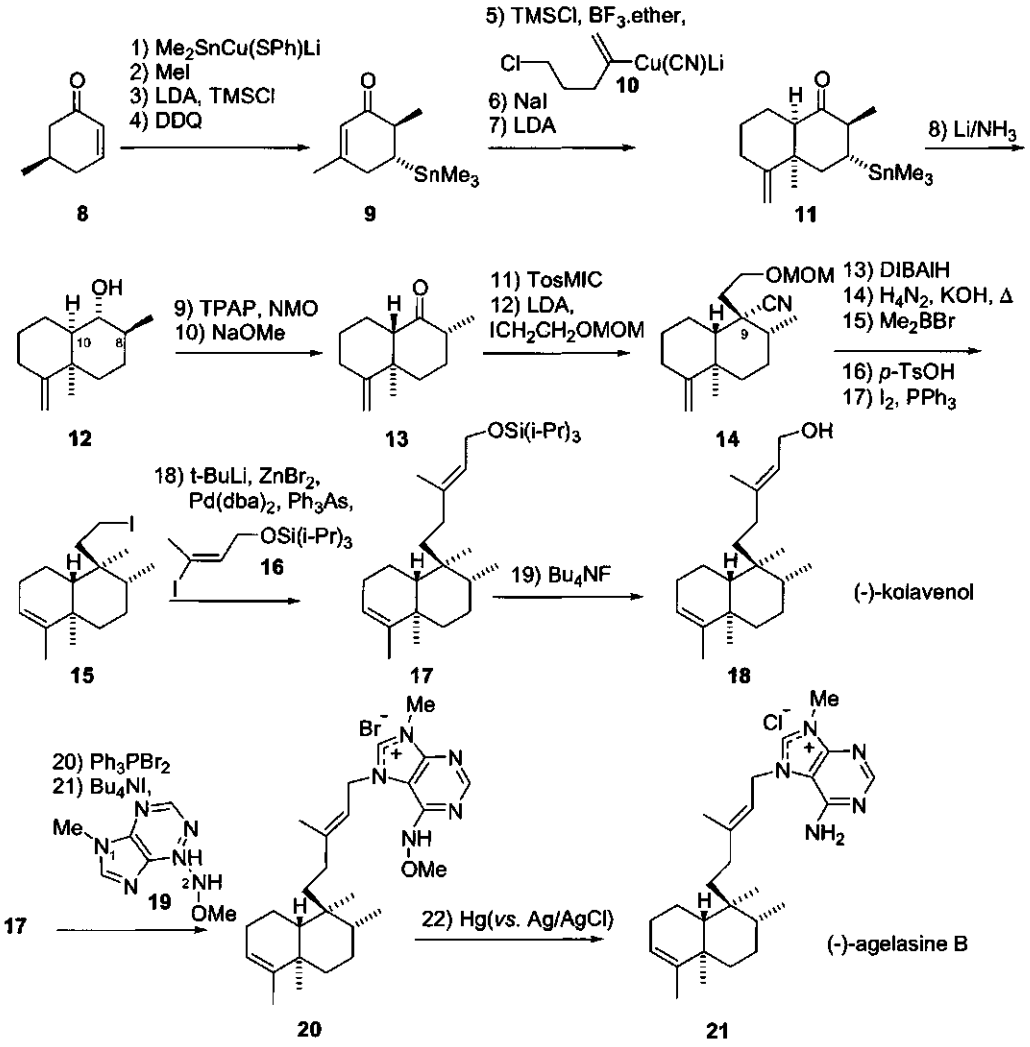
[18] Lio, H.; Monden, M.; Okada, K.; Tokoroyama, T. *J. Chem. Soc., Chem. Commun.* **1987**, 358-359.

[19] For older reviews see:(a) Vader, J. PhD thesis , Wageningen Agricultural University, **1989**; (b) Luteijn, J. M. PhD thesis, Wageningen Agricultural University, **1982**; (c) de Groot, A.; van Beek, T. A. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 1-18; (d) Sarma, A. S. *J. Scientific & Ind. Res.* **1987**, *46*, 492-504; (e) Tokoroyama, T. *Yuki Gosei Kagaku Kyokaishi* **1993**, *51*, 1164-1177 (in Japanese).

[20] Piers, E.; Roberge, J. Y. *Tetrahedron Lett.* **1992**, *33*, 6923-6926.

[21] Piers, E.; Roberge, J. Y. *Tetrahedron Lett.* **1991**, *32*, 5219-5222.

scheme 1.2



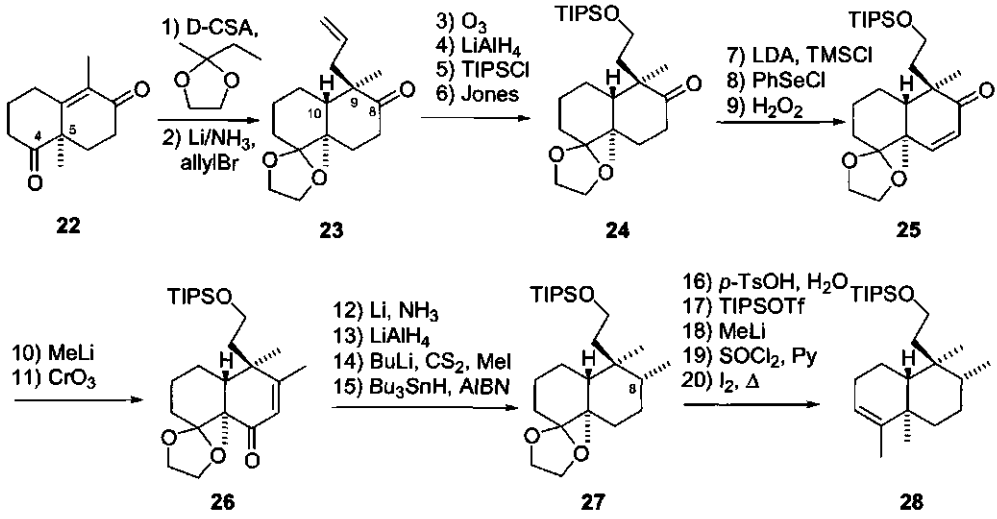
In 1994 Hagiwara *et al.*[22] synthesized the antibacterial clerodane, 16-hydroxycleroda-3,13(14)Z-dien-15,16-olide (**31**) starting from the optically active diketone **22** which could be obtained in 99% optical purity using D-β-phenylanaline as a catalyst in the Robinson annulation. Protection of the carbonyl group at C6, followed by reduction of the enone system with Li/NH_3 and capturing of the enolate with allylbromide gave **23** with the desired stereochemistry at C10 and C9.[23] Ozonolysis of the double bond followed by reduction gave a diol. The hydroxyl group at C8 was oxidized again after protection of the primary alcohol in the side chain to yield **24**. Hagiwara used a lengthy nine step procedure to achieve the introduction of an equatorial methyl

[22] Hagiwara, H.; Inome, K.; Uda, H. *J. Chem. Soc., Perkin Trans. I* **1995**, 757-764.

[23] Hagiwara, H.; Uda, H. *J. Org. Chem.* **1988**, *53*, 2308-2311.

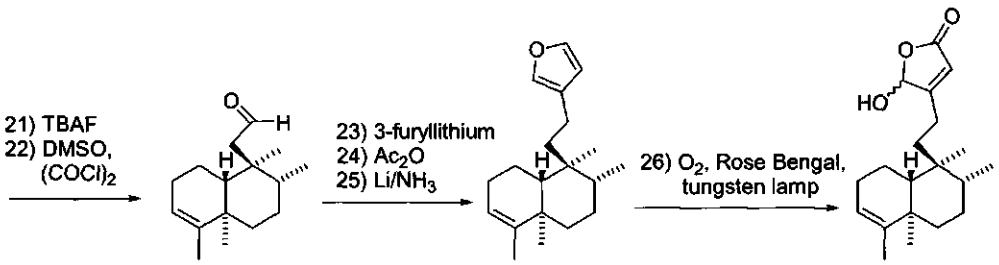
group at C8. First ketone **24** was converted to enone **25** by introduction of a phenylselenyl group, followed by oxidation and elimination. Addition of methyllithium, followed by oxidative rearrangement yielded the transposed enone **26**. Now the enone was reduced with Li/NH_3, but this reduction was not completely selective and gave a mixture of the α- and β-methyl group at C8, which had to be separated. The desired ketone was reduced and the resulting alcohol was converted into the xantogenate ester. This xantogenate ester was then reduced with tributyltin hydride to yield **27**. In my opinion a much shorter route is possible when ketone **24** will be submitted to a Wittig olefination, followed by a Pd/C catalyzed reduction to give the desired stereochemistry at C8 as is shown in the synthesis of (–)-ilimaquinone (scheme 1.4).[24] Deprotection of the carbonyl group in **27** was not selective and the hydroxyl group in the side chain had to be protected again as its silyl ether. Methyllithium was added to the carbonyl group, followed by elimination of the tertiary hydroxyl group with thionyl chloride to yield a mixture of double bond isomers. Refluxing in xylene with a catalytic amount of iodine was necessary to isomerize the obtained mixture completely into compound **28**. After deprotection of the primary hydroxyl group, a Swern oxidation gave aldehyde **29**. Addition of 3-furyllithium to this aldehyde gave, in high yield, a mixture of alcohols. This mixture of alcohols was converted into their acetates, and reductive removal of these acetates with Li/NH_3 yielded annonene **30**. Photochemical oxidation of the furan moiety to a γ-hydroxybutenolide gave 16-hydroxycleroda-3,13(14)*Z*-dien-15,16-olide (**31**).

scheme 1.3



[24] Bruner, S. D.; Radeke, H.; Tallarico, J. A.; Snapper, M. L. *J. Org. Chem.* **1995**, *60*, 1114-1115.

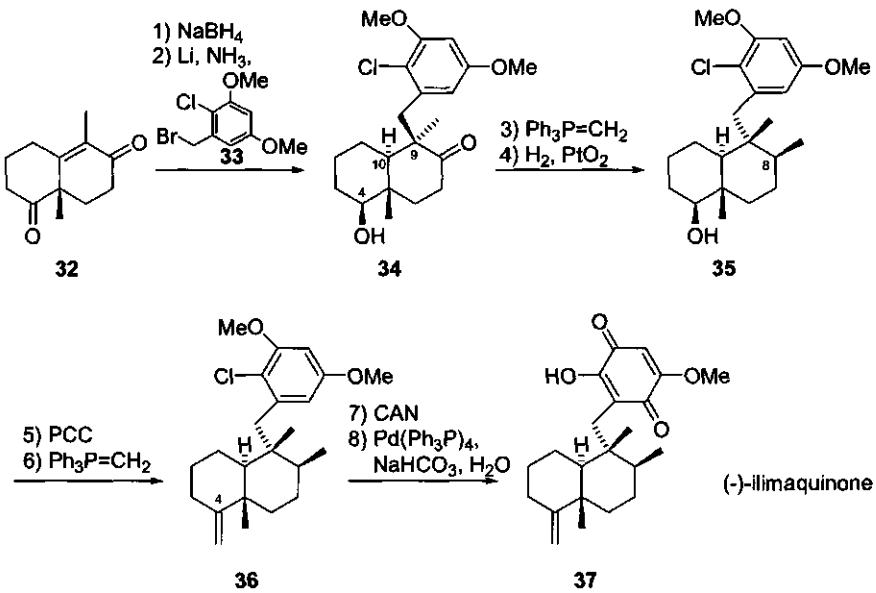
scheme 1.3 (continued)



29 **30** **31**

In the same year Bruner *et al.*[24] reported the total synthesis of (–)-ilimaquinone (**37**) which is a sesquiterpene quinone, but resembles the *ent-neo*-clerodane structure. In this total synthesis they started with the enantiomer **32** of the diketone used by Hagiwara (scheme 1.3). The carbonyl group at C4 is selectively reduced with $NaBH_4$. Then the upper part of the sesquiterpene is introduced by a substitution reaction on benzylbromide **33** by the lithium enolate obtained by reduction of the enone with Li/NH_3. In this reaction the desired configurations at C9 and C10 were obtained. The carbonyl group at C8 in **34** was submitted to a Wittig olefination, and the thus obtained exocyclic double bond at C8 was reduced with hydrogen by a PtO_2 catalyzed reduction into the desired β-methyl group. Oxidation of the hydroxyl group at C4, followed by a Wittig olefination reaction gave the exocyclic double bond. Oxidation by ceric ammonium nitrate of the benzyl group in **36** yielded the chloromethoxyquinone that could be converted to (–)-ilimaquinone (**37**) by a palladium mediated exchange of the chloride by a hydroxyl group.

scheme 1.4



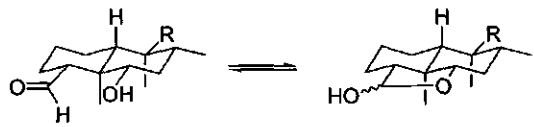
Also in 1995, Goldsmith *et al.*[25] succeeded in the total synthesis of ajugarin IV (**48**) and annonene (**54**), using the Diels-Alder approach that was published earlier in studies towards the synthesis of ajugarin I.[26] In ajugarin IV the C19 is not oxidized which made the synthesis less complicated. A *trans*-decalin system **40** was obtained after a Diels-Alder reaction between **38** and **39** and isomerization at C10. Hydrolysis of the acetate and acidic treatment yielded a methoxy acetal at C6. The desired configuration at C8 was obtained after a Pd/C catalyzed reduction of the C7-C8 double bond. A Wittig olefination at C9 afforded the exocyclic double bond at C9, which gave aldehyde **42** after hydroboration, followed by oxidation. After allylation at C9 from the desired β-side, the aldehyde was reduced by a Wolf-Kishner reaction to a methyl group. The C12-C13 double bond was ozonolyzed, and after reduction and mesylation transformed into the thiophenyl ether **43**. The methoxy acetal was hydrolyzed, and the resulting ketone was reduced to diol **44**. After oxidation of the sulfide, a series of reactions was performed to invert the configuration at C4. The primary hydroxyl group at C18 was tosylated and eliminated under basic conditions to yield an exocyclic double bond. The hydroxyl group at C6 was protected before the double bond was treated with disiamylborane to the hydroxymethyl group with the desired configuration at C4. This hydroxyl group was protected as its silyl ether. Now the finishing of the side chain was undertaken by performing a Michael addition to **46** and subsequent elimination of the phenylsulfonyl group to give **47**. The phenylsulfonyl group was reductively removed to finish the synthesis of the side chain. The construction of the correct functional groups in the lower part of the molecule was performed next. Deprotection and

[25] Goldsmith, D. J.; Deshpande, R. *Synlett* **1995**, 495-497.

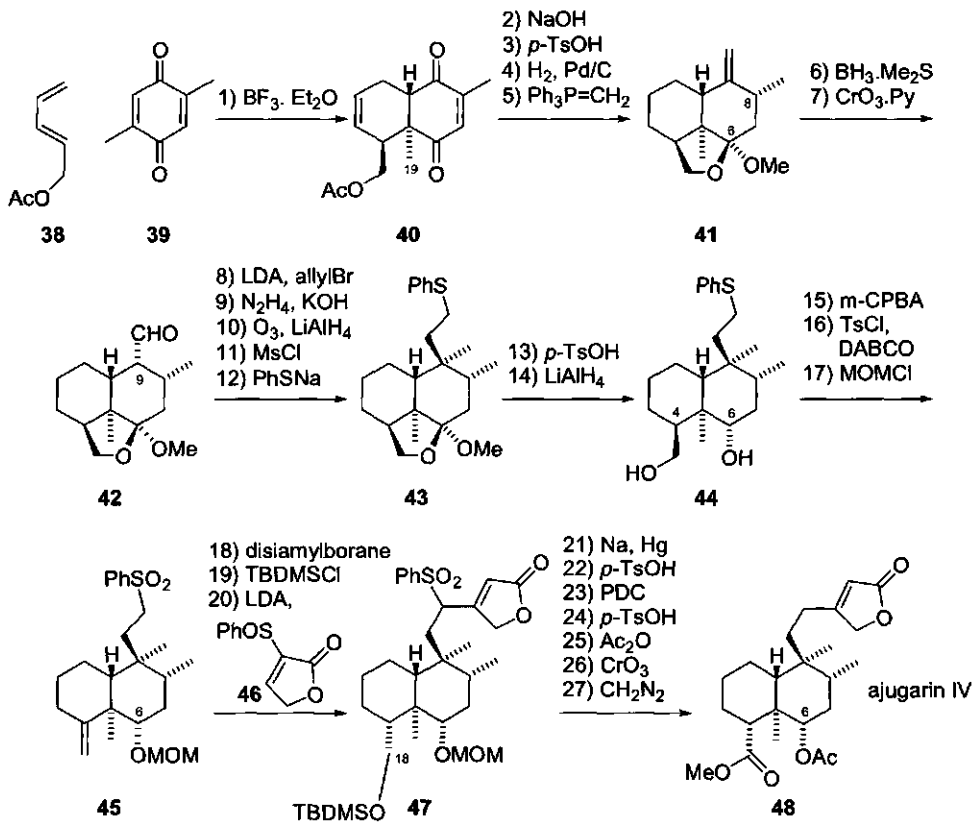
[26] Goldsmith, D. J.; Srouji, G.; Kwong, C. *J. Org. Chem.* **1978**, *43*, 3182-3188.

oxidation of the hydroxyl group at C18 yielded an aldehyde. The hydroxyl group at C6 was deprotected and acetylated. Now the aldehyde was further oxidized to an acid and esterified with diazomethane to yield ajugarin IV. In the last steps of this synthesis no hemiacetal formation was mentioned, as is described figure 1.3, which is somewhat surprising since in the synthesis reported in this thesis (chapter 5) this hemiacetal formation proved to be very rapid.[27]

figure 1.3



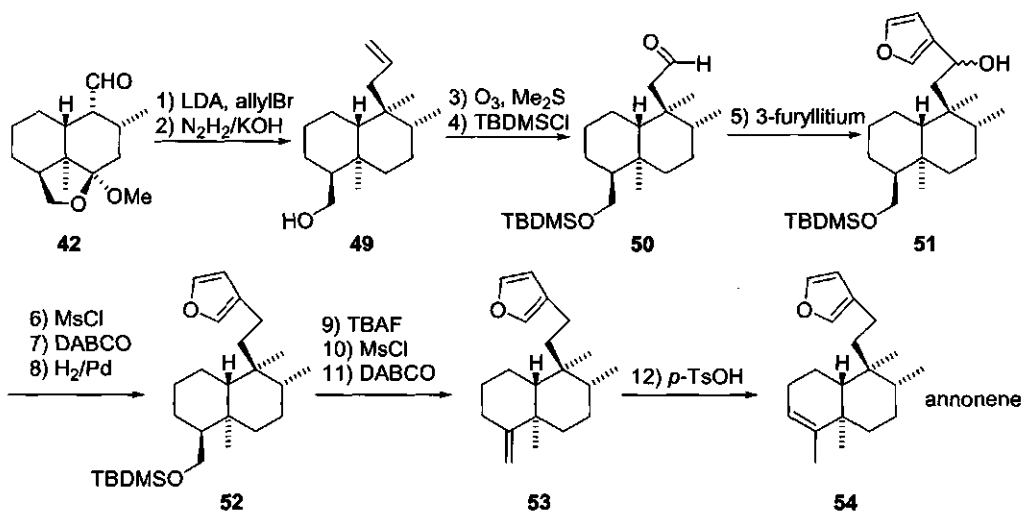
scheme 1.5



[27] The lack of an experimental part and yields in the publication about the synthesis of ajugarin IV and annonene by Goldsmith is a shortcoming.

For the synthesis of annonene (**54**) (scheme 1.6) a modified procedure was followed starting from aldehyde **42**. This aldehyde was α-allylated and reduced by a Wolf-Kishner reduction at 210°C, which also caused opening and reduction of the methoxy acetal to yield compound **49**. After ozonolysis of the double bond and protection of the hydroxyl group, 3-furyllithium was added to the aldehyde to give alcohol **51**. The allylic hydroxyl group was mesylated and eliminated under basic conditions, and the formed double bond was reduced to give **52**. Now the hydroxyl at C18 was deprotected and mesylated, followed by elimination under basic conditions to yield an exocyclic double bond. Isomerization to the endo position by acidic treatment yielded annonene (**54**).

scheme 1.6

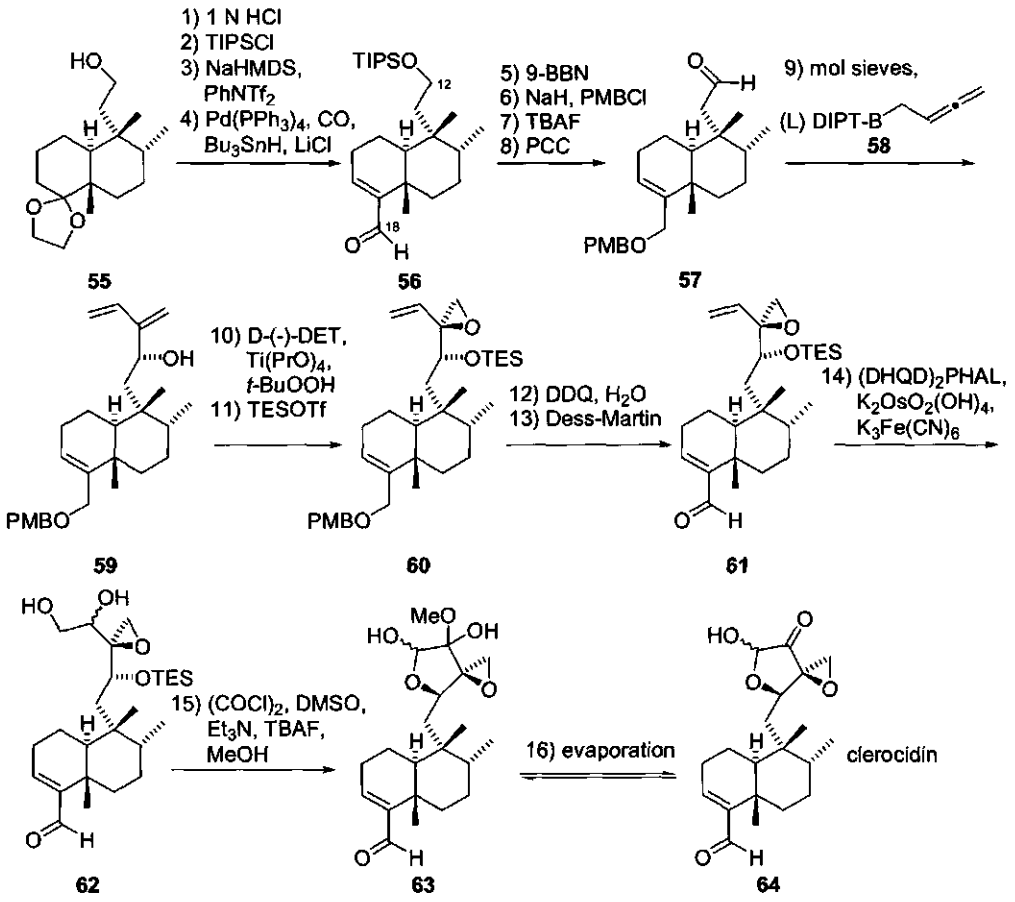


Xiang *et al.*[28] published the total synthesis of clerocidin, a clerodane with a challenging structure in the upper part. For the construction of the decalin part they followed the route of Takahashi.[17] The insertion of C18 was achieved by treatment of the enol triflate with tributyltin hydride under a CO atmosphere and Pd(0) catalysis to obtain the α,β-unsaturated aldehyde **56**. The aldehyde was reduced to a hydroxyl group and protected as its p-methoxybenzyl ether. After removal of the silyl protecting group at C12 this hydroxyl group was oxidized to give aldehyde **57**. The upper part of the molecule is now constructed via a novel enantioselective Brown homoallenyl boration of **57** with **58** to yield **59**. In this reaction a diastereomeric excess of 71% was obtained. A Sharpless asymmetric epoxidation and protection of the C12 hydroxyl group as its silyl ether gave **60**. Deprotection of the hydroxyl group at C18, followed by oxidation with PCC to an aldehyde yielded **61**. Dihydroxylation of the terminal olefin gave a mixture of diols **62**, which was oxidized by Swern's method to an α-keto aldehyde, and in situ desilylation of the C12

[28] Xiang, A. X.; Watson, D. A.; Ling, T. T.; Theodorakis, E. A. *J. Org. Chem.* **1998**, *63*, 6774-6775.

hydroxyl group, gave rise to the cyclized product **63** upon methanolic workup. Dissolving of **63** in methylene chloride and evaporation of the solvent gave clerocidin (**64**).

scheme 1.7

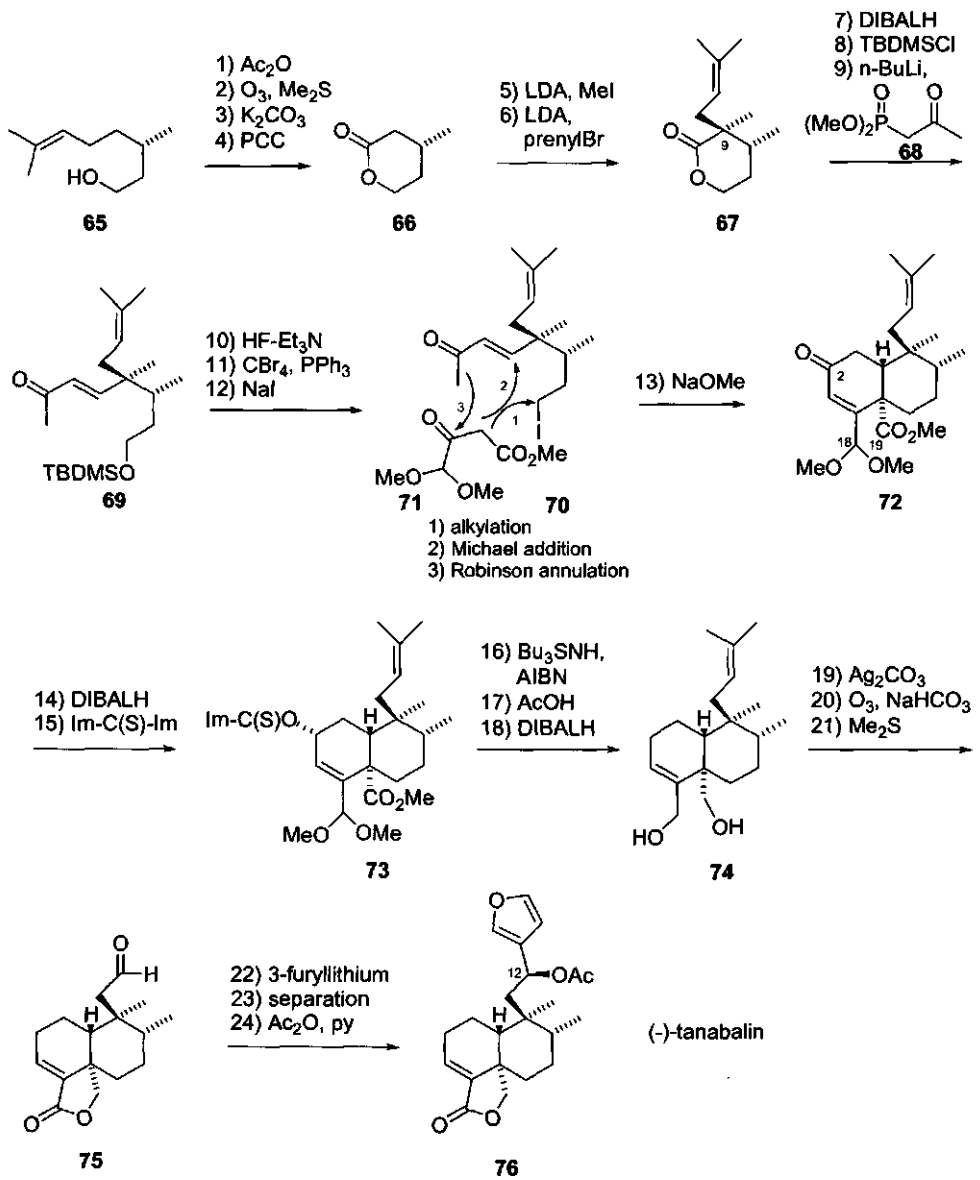


Recently, Watanabe *et al.*[29] published the total synthesis of (–)-tanabalin (**76**) starting from (–)-citronellol (**65**), which was converted into lactone **66** following standard procedures. Alkylation of the enolate of lactone **66**, first with methyl iodide and then with prenyl bromide, gave the desired configuration at C9. Reductive opening of lactone **67** gave an aldehyde which, after protection of the hydroxyl group, was submitted to a Wittig olefination to yield **69**. Removal of the silyl protecting group and substitution of the resulting hydroxyl group with a bromide, followed by substitution of the bromide with a iodide gave **70**. Now the key step of this approach, an elegant tandem intramolecular alkylation-intramolecular Robinson annulation, yielded decalin **72**. In this one pot reaction a *trans*-decalin, with an oxidized C19, C18, and C2, was obtained in good yield. Reduction of the carbonyl group at C2 and conversion of the resulting hydroxyl group

[29] Watanabe, H.; Onoda, T.; Kitahara, T. *Tetrahedron Lett.* **1999**, *40*, 2545-2548.

into its thiocarbamate followed by treatment with tributyltin hydride yielded a methylene at C2. Acid hydrolysis of the methoxy acetal followed by reduction gave diol **74**. Oxidation with Fetizon reagent gave the ring closed γ-lactone. Selective ozonolysis of the double bond, followed by addition of dimethylsulfide gave aldehyde **75**, which was submitted to an addition of 3-furyllithium. Separation of the 1:1 mixture at C12 and subsequent acetylation of the desired diastereoisomer gave (–)-tanabalin (**74**).

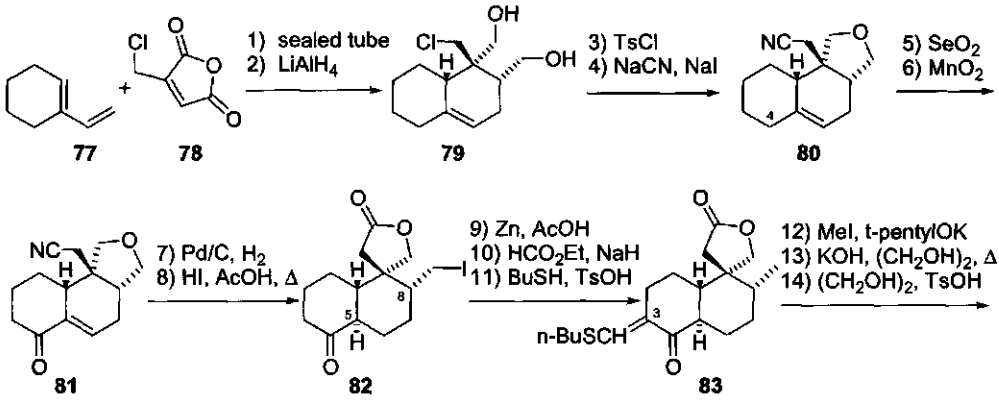
scheme 1.8



***Cis*-clerodanes, a synthesis survey**

The C5 epimer of annonene, the *cis*-clerodane 15,16-epoxy-*cis*-clero-3,13(16),14-triene (**88**), was synthesized by Tokoroyama *et al.*[30] The decalin system was obtained via a Diels-Alder reaction of **77** and **78**.[31] Reduction of the anhydride function yielded diol **79**, which upon treatment with tosyl chloride cyclized to a tetrahydrofuranyl moiety. The chloride was then substituted in situ with sodium iodide, and subsequently substituted with sodium cyanide to give nitrile **80**. Selective allylic oxidation on the C4 position could be accomplished in a moderate yield of 30-50% using SeO_2. The obtained hydroxyl group was further oxidized to give enone **81**. Catalytic reduction with palladium and hydrogen yielded a *trans*-decalin system. Opening of the tetrahydrofuranyl ring by hydroiodic acid and concomitant hydrolysis of the cyano group gave lactone **82**. Reduction of the iodide gave the methyl group at C8. Angular methylation at C5 was achieved in good yield, after protection of the C3 position as a butylthiomethylene group, by using a large excess of potassium t-pentyloxide and methyl iodide. This methylation only gave the *cis* fused decalin system. Deprotection of C3 by alkaline hydrolysis, and protection of the carbonyl group at C4 yielded lactone **84**. Addition of 3-furyllithium to the lactone, followed by immediate reduction gave a diol, which was acetylated to give **85**. Reductive removal of the acetate group at C12, followed by oxidation of the C20 hydroxyl group gave aldehyde **86**. Reduction of the aldehyde, and deprotection of the carbonyl group at C4 yielded ketone **87**. Olefination of this carbonyl group was achieved by the use of Nozaki's reagent and after isomerization of the exocyclic double bond the *cis*-clerodane **88** was obtained. The synthesis of compound **89** was published earlier by Tokoroyama *et al.*[32] and was mentioned as a suitable starting material for a shorter synthesis of **88**.

scheme 1.9

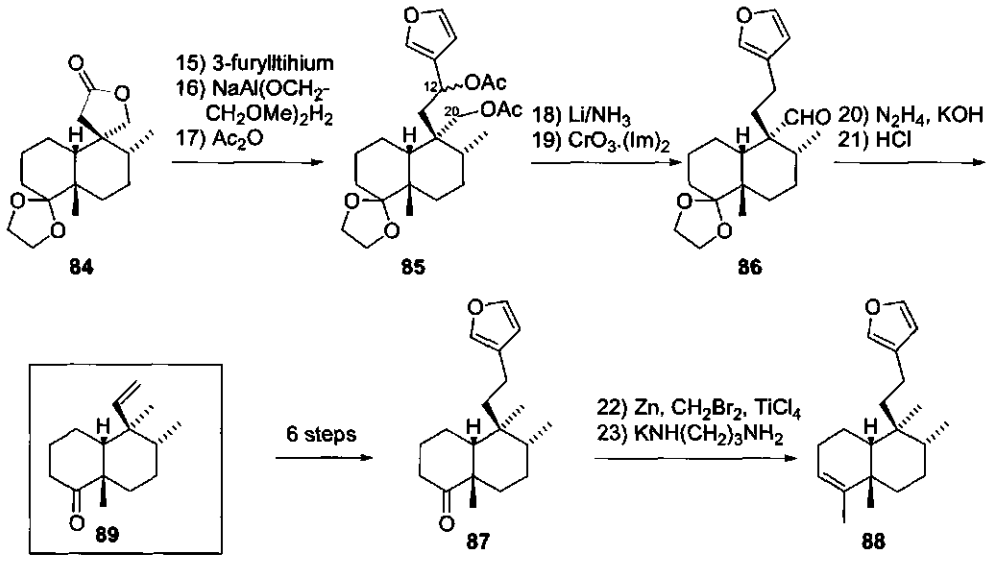


[30] Tokoroyama, T.; Kanazawa, R.; Yamamoto, S.; Kamikawa, T.; Suenaga, H.; Miyabe, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1720-1728.

[31] Tokoroyama, T.; Matsuo, K.; Kubota, T. *Tetrahedron* **1978**, *34*, 1907-1913.

[32] Tokoroyama, T.; Tsukamoto, M.; Asada, T.; Lio, H. *Tetrahedron Lett.* **1987**, *28*, 6645-6648.

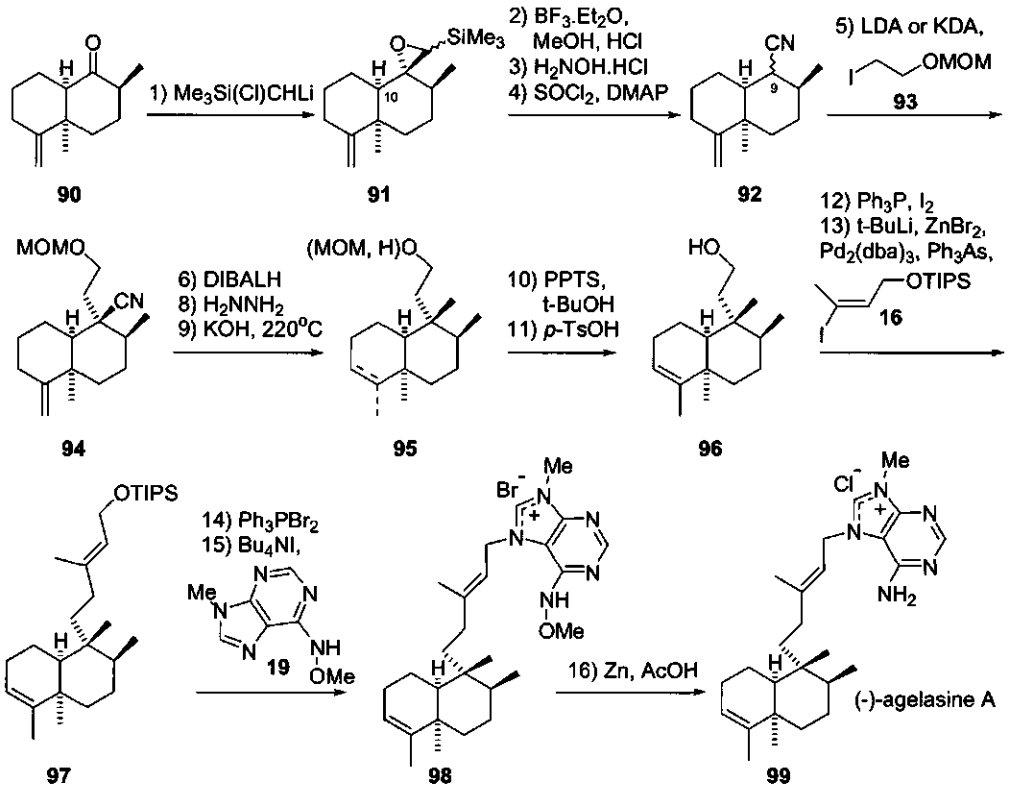
scheme 1.9 (continued)



In 1995 Piers *et al.*[33] reported the total synthesis of (–)-agelasine A (**99**), in which they used the *cis*-decalin system **12** mentioned in scheme 1.2. Oxidation of the hydroxyl group in **12** yielded ketone **90** (scheme 1.10). Addition of trimethylsilyl chloromethyl lithium to this decalone gave a C11 epimeric mixture of epoxides without epimerization of the configuration at C10. These epoxides were opened with BF_3•etherate to a mixture of aldehydes, and these aldehydes were converted to a mixture of nitriles **92** via dehydration of their oximes. The two nitriles (α and β) were separated, and separately treated with a base followed by addition of alkyliodide **93**. In both alkylations compound **94** was obtained but for abstraction of the β proton at C9 the potassium variant of LDA was necessary to obtain good results. The reduction of the nitrile to a methyl group was performed by reduction with DIBALH to an aldehyde, followed by conversion into a hydrazone and heating in the presence of potassium hydroxide. In this reaction a mixture of the protected and deprotected hydroxyl group together with a mixture of the exo- and endocyclic double bond isomers **95** were obtained. Treatment of this mixture with PPTS, to remove the MOM group completely, followed by treatment with anhydrous *p*-TsOH to isomerize the exocyclic double bond to the endo position, gave alcohol **96** in 74% overall yield from **94**. Finishing of the synthesis of (–)-agelasine A (**99**) was carried out in a similar manner as for the synthesis of (–)-agelasine B (**21**) in scheme 1.2.

[33] Piers, E.; Breau, M. L.; Han, Y.; Plourde, G. L.; Yeh, W.-L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 963-966.

scheme 1.10



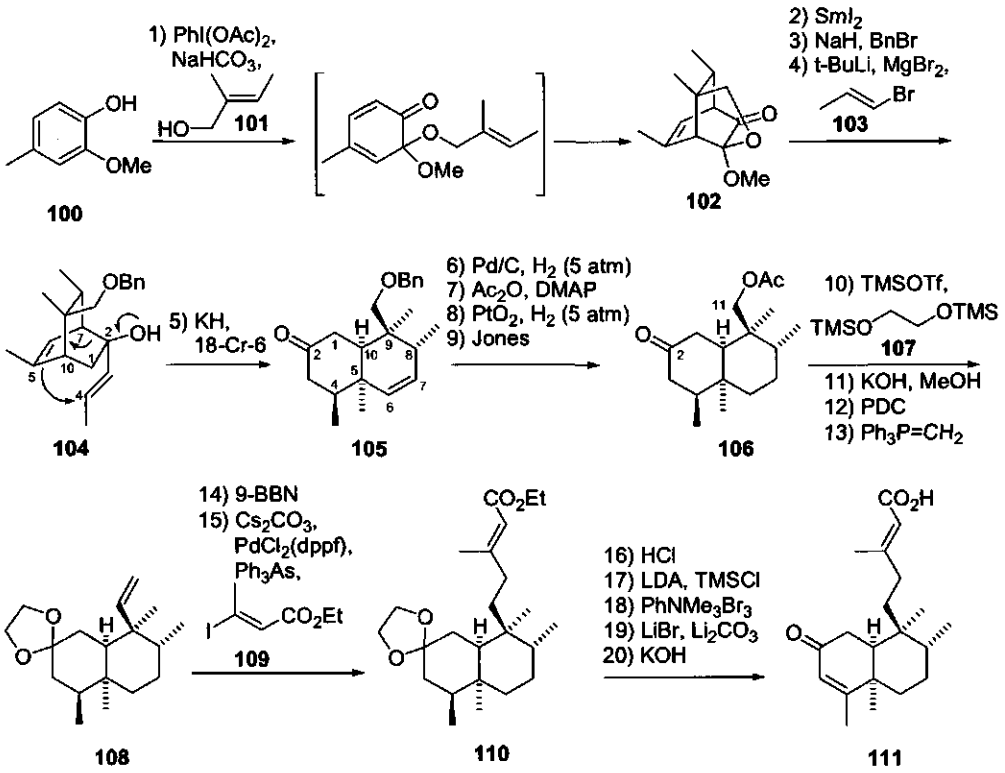
Liao *et al.*[34] reported the synthesis of (±)-(13E)-2-oxo-5α-*cis*-17α,20α-cleroda-3,13-dien-15-oic acid (**111**), a clerodane isolated by Avila *et al.*[35] Oxidation of phenol **100** in the presence of **101** gave an intermediate acetal, which contained the diene and dienophile, that underwent a Diels-Alder reaction to the tricyclic compound **102**. Reductive opening of the methoxy acetal was achieved by SmI_2, and the obtained hydroxyl group was protected as its benzyl ether. Addition of *trans*-1-propenyllithium in the presence of $MgBr_2$ gave almost selectively the endo adduct **104**. Treatment of this alcohol with potassium hydride gave via an anionic oxy-cope rearrangement the *cis*-decalin **105**. Removal of the benzyl group and reduction of the C6-C7 double bond, could not be achieved in one step. Therefore first the benzyl ether was reduced and protected as its acetate. Now catalytic reduction with platinum and hydrogen, followed by oxidation of some overreduced product gave ketone **106**. Protection of the carbonyl group at C2, followed by hydrolysis of the acetate, and oxidation of the hydroxyl group yielded an aldehyde at C11. A Wittig olefination to this aldehyde yielded compound **108**. Hydroboration of the double bond, and a consecutive palladium catalyzed cross-coupling reaction gave the complete clerodane skeleton **110**. The

[34] Lee, T.-H.; Liao, C.-C. *Tetrahedron Lett.* **1996**, *37*, 6869-6872.

[35] Avila, D.; Medina, J. D. *Phytochemistry* **1991**, *30*, 3474-3475.

carbonyl group at C2 was hydrolyzed and selectively converted to a silylenol ether. Bromination of this silylenol ether, followed by dehydrobromination gave the desired enone. In the last step the ethyl ester was hydrolyzed to give the *cis*-clerodane acid **111**, but its ^{1}H and ^{13}C-NMR spectra were different from the natural product that was proposed by Avila. For further proof the acid **111** was converted again to its ethyl ester and this structure was elucidated by X-ray diffraction as being the ester of **111**. This means that the structure of the product found by Avila should be revised.

scheme 1.11

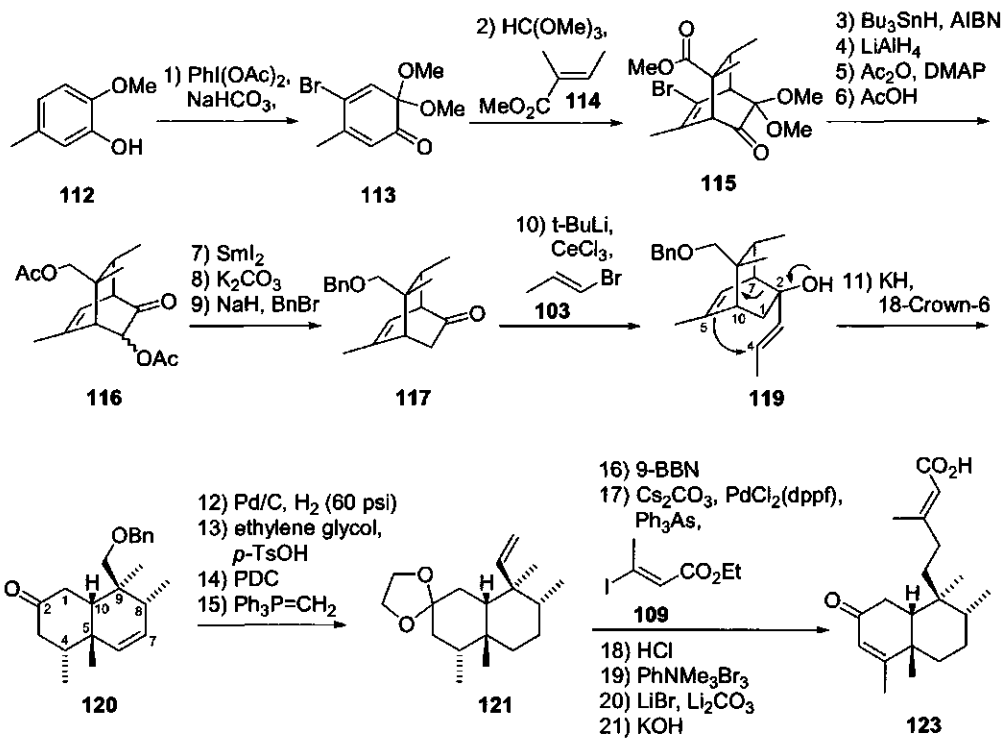


In 1998 Liao *et al.*[36] reported the synthesis of *cis*-clerodane **123** possessing the most common decalin skeleton in *cis*-clerodanes. A similar approach as described in scheme 1.11 was used. The intermolecular Diels-Alder led to the configuration at C9 and C8 as is depicted in compound **105**, but instead an intramolecular Diels-Alder would lead to the opposite configuration at C9 and C8. The intramolecular Diels-Alder product **115** was obtained in good yield by a Diels-Alder reaction of methyl triglate (**114**) and the masked o-benzoquinone **113**, which was stabilized by a bromo substituent. The bromide was removed with tributyltin hydride, and the resulting compound was reduced to a diol, and protected as its diacetate. Acid hydrolysis

[36] Liu, W.-C.; Liao, C.-C. *Synlett* **1998**, 912-914.

of the methoxy acetal yielded ketone **116**. The α-keto acetate was reduced by SmI_2, and the second acetate was hydrolyzed, and the hydroxyl group was protected with benzyl bromide to give **117**. Addition of propenyllithium gave the endo adduct **119**, and an anionic oxy-Cope rearrangement yielded the *cis*-decalin **120**. In contrast to the reduction of compound **105**, now the reduction of the benzyl protecting group and the C6-C7 double bond could be achieved in one step. The finishing of the synthesis was achieved in the similar way as in scheme 1.11 to obtain the *cis*-clerodane acid **123**.

scheme 1.12



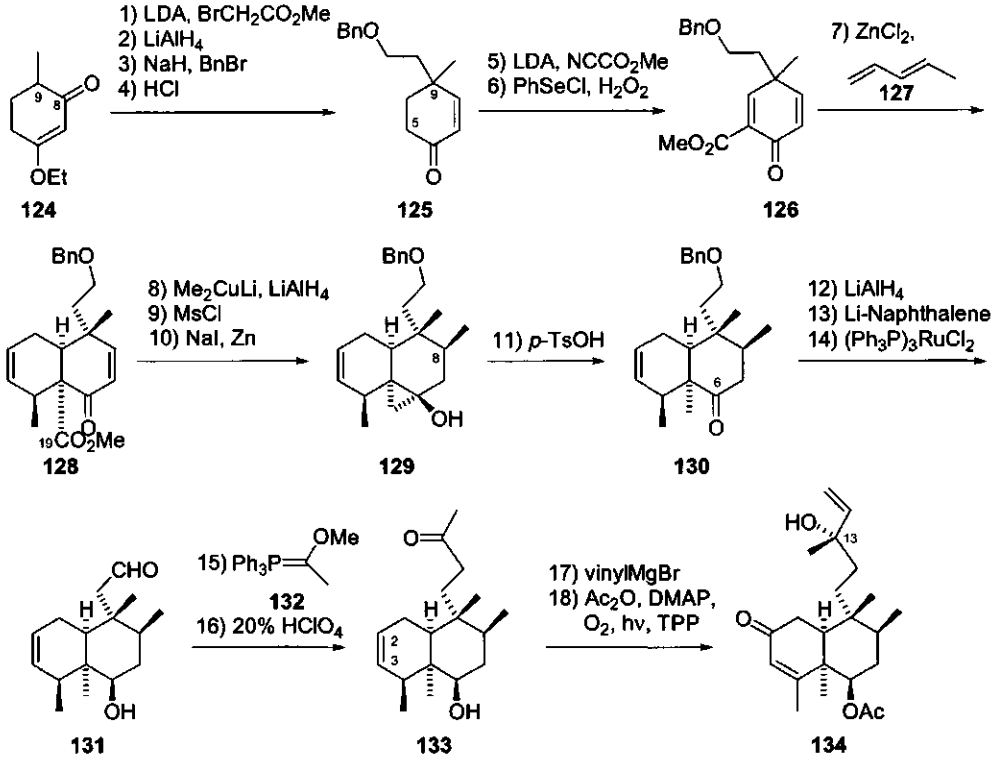
Liu *et al.*[37] reported the synthesis of (±)-6β-acetoxy-2-oxokolavenool (**134**) starting with the Diels-Alder of dienone **126**[38] and *trans*-piperylene (**127**). Mono protected diketone **124** was treated with base, followed by alkylation with methyl bromo acetate at C9. Reduction of the methyl ester in the side chain and the carbonyl group at C8 gave a diol. The primary alcohol in the side chain was selectively protected with a benzyl group. Now the enol ether was hydrolyzed by hydrochloric acid, and subsequent dehydration gave enone **125**. The methyl ester at C5 was introduced by formation of an enolate with LDA followed by addition of methylcyanoformate.

[37] Liu, H.-J.; Shia, K.-S. *Tetrahedron* **1998**, *54*, 13449-13458.

[38] Liu, H. J.; Shia, K. S.; Han, Y.; Wang, Y. *Synlett* **1995**, 545-546.

Treatment of this compound with phenylselenium chloride in pyridine and subsequent oxidation of the phenylselenyl group, followed by elimination gave dienone **126**. A Diels-Alder of **126** and **127** occurred from the less hindered side opposite to the benzyl protected side chain to give the *cis*-decalin **128**. The methyl group at C8 was introduced by a conjugate addition, and in the same flask $LiAlH_4$ was added to reduce the methyl ester while the carbonyl group was still protected as its enolate. Mesylation of the primary hydroxyl group at C19, and treatment of this mesylate with NaI and zinc gave cyclopropanol **129**. Opening of the cyclopropane ring yielded ketone **130**. Reduction of the carbonyl group, and reductive cleavage of the benzyl ether gave a diol which could be selectively oxidized to aldehyde **131**. A Wittig olefination by methoxy enol ether **132**, followed by hydrolysis of the methoxy enol ether yielded ketone **133**. Addition of vinylmagnesium bromide to the carbonyl group gave an inseparable 1:1 mixture of diols. Photooxygenation of the C2-C3 double bond and in the same flask acetylation yielded the desired *cis*-clerodane **134** and its C13 epimer, which could be separated by high performance liquid chromatography (HPLC).

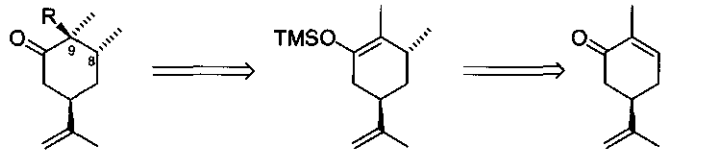
scheme 1.13



1.4 The strategy in the synthesis of dihydroclerodin, and the scope of this thesis

The total synthesis of clerodane insect antifeedants is a topic in our research group for a long time. In 1982 Luteijn *et al.* attempted the synthesis of ajugarin I which ultimately ended in the synthesis of 4-epi-ajugarin I.[39] In 1989 Vader *et al.* studied the synthesis of the furofuran part, as well as the decalin part, of clerodanes like clerodin.[40] In our strategy towards the synthesis of dihydroclerodin we have chosen to accomplish the coupling of the upper part and the decalin in an early stage of the total synthesis, for two reasons. The early introduction of the hexahydrofuro[2,3-*b*]furan moiety gives the opportunity to study the stereochemistry at C9, C11, C13, and C16 in an early stage of the synthesis, so if necessary other routes can be chosen. This is especially important for the stereochemistry at C11, because it is known that when this configuration is correct, the configurations at C13 and C16 can be adjusted relatively easy. Second, because it was assumed that the hexahydrofuro[2,3-*b*]furan moiety would be resistant to probably all the reaction conditions that will be necessary in the later stages of the synthesis. Another important feature in our strategy was the use of R-(–)-carvone as a homochiral starting material. This would give the opportunity to synthesize an optically active clerodane. From previous work in our laboratories was known that a conjugate addition of a methyl group at C8 could be captured as its silyl enol ether **135**. This enol ether was studied for the introduction of functional groups at C9 that can be converted into side chains as encountered in clerodanes. The results of these studies are described in chapter 2.

scheme 1.14



135 R-(–)-carvone (**2**)

The coupling of the hexahydrofuro[2,3-*b*]furan moiety, can result in a mixture of diastereoisomers especially when racemic fragments are used. However, the synthesis of an optically active hexahydrofuro[2,3-*b*]furan fragment seemed possible starting from butylester **145-(3S)** which could be obtained in high optical purity using an enzymatic transesterification reaction developed by Franssen *et al.* in our group.[41] Several other methods for the synthesis of hexahydrofuro[2,3-*b*]furan moiety were investigated as well, and these studies are described in chapter 3.

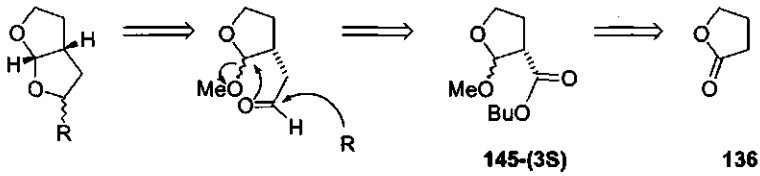
---

[39] (a) Luteijn, J. M. PhD thesis, Wageningen Agricultural University, **1982**; (b) Luteijn, J. M.; de Groot, A. *Tetrahedron Lett.* **1982**, *23*, 3421-3424.

[40] Vader, J. PhD thesis, Wageningen Agricultural University, **1989**.

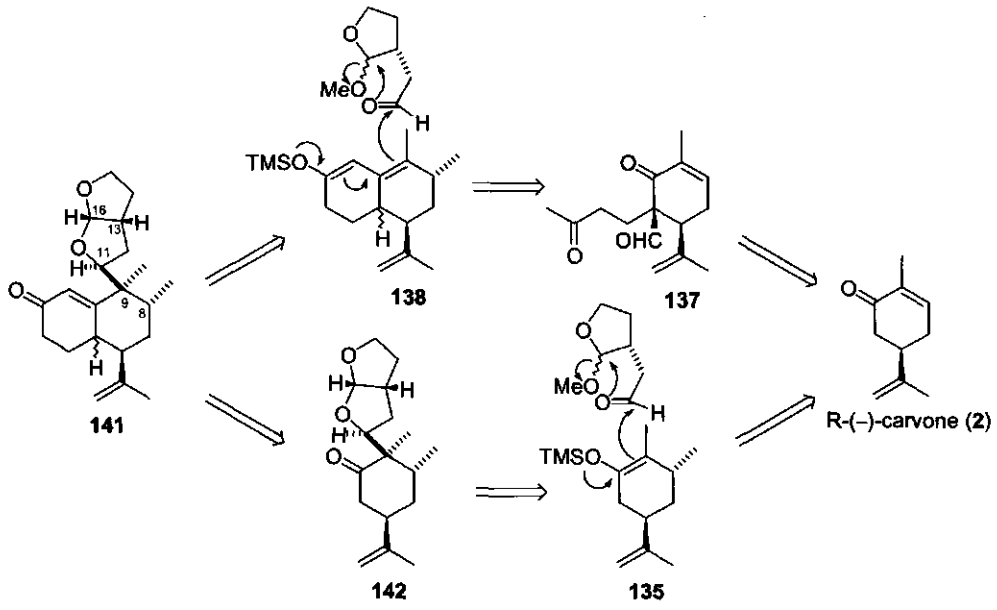
[41] Franssen, M. C. R.; Jongejan, H.; Kooijman, H.; Spek, A. L.; Nuno, L. F. L.; Mondril, N. L. F. L. C.; Dossantos, P. M. A. C. B.; de Groot, A. *Tetrahedron Asymm.* **1996**, *7*, 497-510.

scheme 1.15



The synthesis of an optically active decalone seemed possible starting from R-(–)-carvone (**2**) which possesses the desired absolute configuration for the synthesis of dihydroclerodin. For the synthesis of a decalin system two reaction sequences were investigated. The first reaction sequence consists of the annulation of carvone followed by the introduction of the methyl group at C8 and the side chain at C9 (scheme 1.16). The second method starts with the introduction of the methyl group at C8 and the side chain at C9, followed by the annulation of the second ring. In the second approach the substituents are introduced first which results in a heavily substituted cyclohexanone. It was expected that the annulation of these compounds would be more difficult and would need special attention. Both approaches could lead to decalone **141** and they will be described in chapter 4.

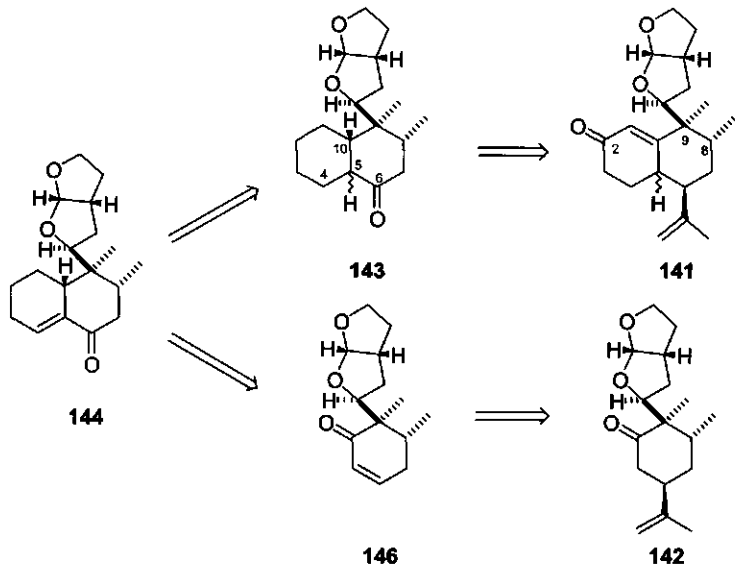
scheme 1.16



Starting from compound **141** several ways for the construction of ketone **143** and **144** can be imagined but none of them could be investigated since enone **141** was not obtained, despite several attempts which are also described in chapter 4.

The isopropenyl in carvone has two functions, first as a chiral handle during the introduction of the methyl group at C8 and the side chain at C9, and second as a protecting group for a carbonyl function (at C6) or a double bond.[42] A second possibility for the construction of enone **144** can be found starting from ketone **142**. Ozonolysis of ketone **142**, followed by a Criegee rearrangement could give enone **146**,[43] which offers several possibilities for the construction of decalin **144**. All these possibilities have to lead to the correct stereochemistry at C10. To achieve the correct stereochemistry, two reaction sequences have been investigated, which will be described in chapter 5.

scheme 1.17



A conjugate addition to enone **144** and trapping of the enolate with formaldehyde should give the desired functionalities and stereochemistry at C5.[44] Reduction of the carbonyl group at C6 and acetylation should give diacetate **147**. In the last part of the synthesis the introduction of the epoxide at C4 has to be accomplished. In earlier studies it was shown that epoxide formation via epoxidation of an exocyclic double bond at C4 gave a mixture in favor of the undesired epoxide.[39,44] Addition of an oxidizing reagent leads to a preferential approach from the β-side, therefore we assumed that the addition of bromine to this double bond would also come from the

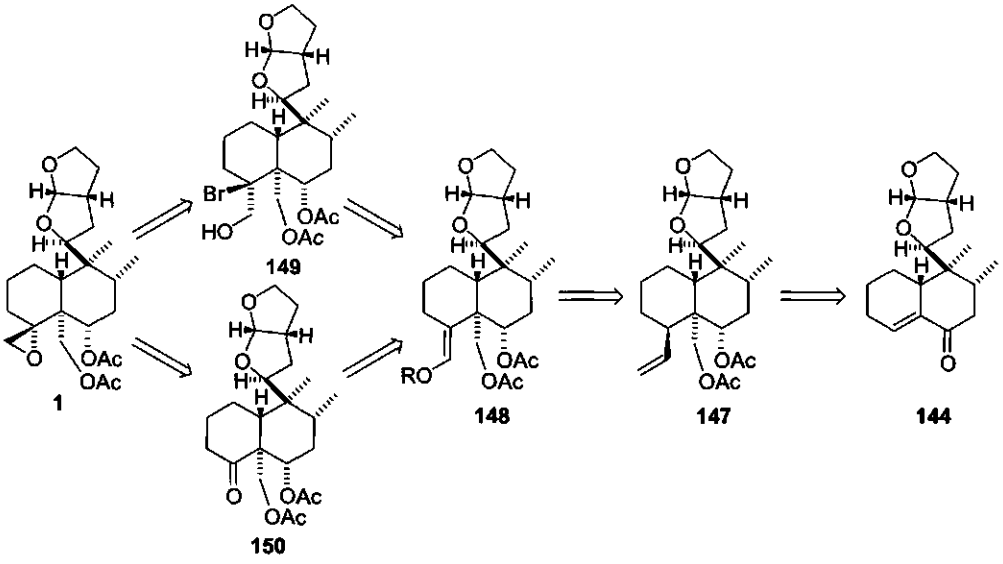
[42] (a) Verstegen-Haaksma, A. A.; Swarts, H. J.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **1994**, *50*, 10095-10106; (b) Schreiber, S. L.; Liew, W.-F. *Tetrahedron Lett.* **1983**, *24*, 2363-2366.

[43] Schreiber, S. L. *J. Am. Chem. Soc.* **1980**, *102*, 6165-6166.

[44] Jones, P. S.; Ley, S. V.; Simpkins, N. S.; Whittle, A. J. *Tetrahedron* **1986**, *42*, 6519-6534.

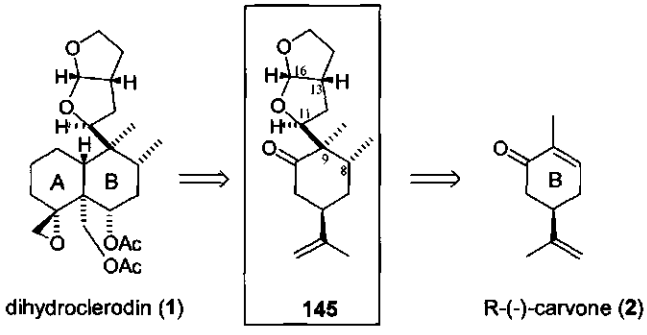
β-side. Using this stereoselectivity we reasoned that bromination of **148**, followed by reduction would give bromohydrine **149** that by treatment with a base could be transformed into the desired epoxide. Another approach involved the ozonolysis of the exocyclic double bond at C4 into ketone **150**. This carbonyl could then be subjected to a Corey epoxidation, which probably would take place from the β-side, to yield the desired epoxide of dihydroclerodin. The synthesis of enone **144**, the introduction of the substituents at C4, C5 and their final transformation into dihydroclerodin is described in chapter 5.

scheme 1.18



2

Enantioselective synthesis of highly functionalized cyclohexanones starting from R-(–)-carvone[45]



dihydroclerodin (**1**) **145** R-(-)-carvone (**2**)

[45] Meulemans, T. M.; Stork, G. A.; Jansen, B. J. M.; de Groot, A. *Tetrahedron Lett.* **1998**, *39*, 6565-6568.

2.1 Introduction[46]

Copper (I) catalyzed conjugate addition of methylmagnesium iodide to enones leads to enolates that can be captured as their silyl enol ethers and a catalyzed Mukaiyama aldol reaction then allows the clean introduction of a second substituent. When these two reactions are applied to one of the enantiomers of carvone, highly functionalized chiral cyclohexanones are obtained that are excellent starting compounds for the total synthesis of enantiomerically pure natural products.[47,48] Carvone is especially useful in such total syntheses because the isopropenyl group determines the stereochemistry of the 1,4-conjugate addition and the stereochemical outcome of the Mukaiyama aldol reaction. In this way the configurations at C2 and C3 in the carvone derived intermediates are fixed, and the isopropenyl group can then be removed without further consequences for the stereochemical integrity of the compound. This isopropenyl group can be transformed by ozonolysis into a hydroxyl group,[49] an acetate,[49] a double bond,[50] or a carbonyl group[51] for further functionalization of the cyclohexane ring.

Using this strategy, it is possible to make useful synthons for the total synthesis of clerodanes. Not only the highly functionalized ring B of clerodanes can be constructed in a few reaction steps (see scheme 2.1) but starting from R-(–)- or S-(+)-carvone both types of natural occurring clerodanes can be obtained without the necessity of separation of enantiomers. We investigated several examples of copper (I) catalyzed conjugate additions of methylmagnesium iodide to R-(–)-carvone, followed by trapping of the enolate as its trimethylsilyl enol ether and the subsequent introduction of a functionalized side chain via a Lewis acid catalyzed Mukaiyama aldol reaction.

2.2 Synthesis of highly functionalized cyclohexanones

The efficiency of trityl perchlorate ($TrClO_4$)[52] or trityl hexachloroantimonate ($TrCl_6Sb$)[53] as a catalyst for the Mukaiyama aldol reaction has been published in the literature,[54,55,56] but to our knowledge this Mukaiyama addition never has been used for the preparation of highly substituted cyclohexanones. In Table 2.1 several functional groups are mentioned that were introduced using a standard procedure with $TrClO_4$ as a Lewis acid catalyst.

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[46] Throughout this thesis the clerodane numbering according to figure 1.1 will be used in all discussions.

[47] Murai, A.; Tanimoto, N.; Sakamoto, N.; Masamune, T. *J. Am. Chem. Soc.* **1988**, *110*, 1985-1986.

[48] Verstegen-Haaksma, A. A.; Swarts, H. J.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **1994**, *50*, 10073-10082.

[49] Schreiber, S. L.; Liew, W.-F. *Tetrahedron Lett.* **1983**, *24*, 2363-2366.

[50] Schreiber, S. L. *J. Am. Chem. Soc.* **1980**, *102*, 6165-6166.

[51] Swarts, H. J.; Verstegen-Haaksma, A. A.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **1994**, *50*, 10083-10094.

[52] This catalyst can easily and cheaply be prepared (ref 59) and can be stored at 20°C for only a few weeks.

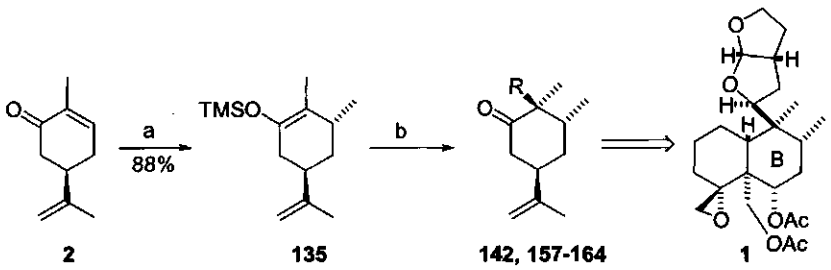
[53] This catalyst is for sale and can be stored at 5°C for months.

[54] Mukaiyama, T.; Kobayashi, S.; Murakami, M. *Chem. Lett.* **1984**, 1759-1762.

[55] Marczak, S.; Michalak, K.; Urbanczyk-Lipkowska, Z.; Wicha, J. *J. Org. Chem.* **1998**, *63*, 2218-2223.

[56] Baranovsky, A. V.; Jansen, B. J. M.; Meulemans, T. M.; de Groot, A. *Tetrahedron* **1998**, *54*, 5623-5634.

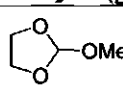
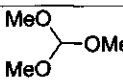
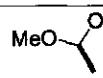
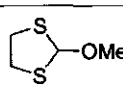
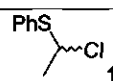
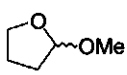
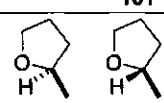
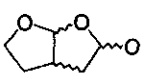
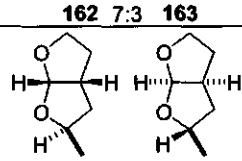
scheme 2.1



2 **135** **142, 157-164** **1**

(**a**) MeMgI, $CuBr{\cdot}Me_2S$, TMSCl; (**b**) $TrClO_4$, reagent (table 2.1)

table 2.1

Entry	Reagent	Product R	Reaction time	Isolated Yield
1	H_2CO (g)	$TMSOCH_2$– **157**	20 min	71%[a]
2	 **151**	 **158**	20 min	75%
3	 **151**	 **159**	72 h	49%
4	 **152**	 **160**	20 min	90% 96%[b]
5	 **153**	 **161**	4 h	40%[c] 86%[d]
6	 **154**	 **162** 7:3 **163**	20 min	80%
7	 **156**	 **142** 1:1 **164**	78 h	75%

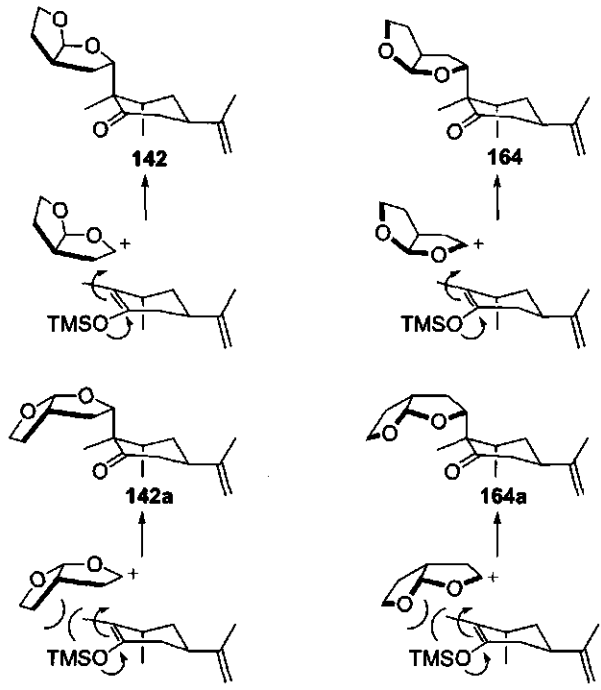
(**a**) quenched with Et_3N; (**b**) $ZnCl_2$, CH_2Cl_2, 0°C; (**c**) RT; (**d**) i) CH_2Cl_2, $SnCl_4$, –78°C, ii) silica, Et_3N.

The products were obtained in good yield but adaptations of the general procedure proved to be necessary to get high yields. In entry 1 the product was captured as its silyl ether by adding triethylamine to the cold solution. The reactions in entry 2 and 4 were surprisingly fast probably due to the relatively high stability of the intermediate carbocation. For entry 5 and 6 mixtures of threo and erythro isomers were found. For entry 3, 5 and 7 the reactions were rather slow

probably due to steric hindrance. After two days at –78°C only 10% of compound **161** was formed in entry 5. By raising the temperature to room temperature the conversion was complete after 4 hours, but in low yield. The use of $SnCl_4$ gave a better yield of 86%. In entry 7 racemic 2-methoxy-hexahydro-furo[2,3-*b*]furan was used, so in principle the formation of eight diastereoisomers is possible. To our surprise only two were formed in a one to one mixture. Compound **164** could be completely separated from its diastereoisomer **142** by crystallization from diisopropyl ether. Compound **142** was obtained as an oil after evaporation of the solvent.

The diastereoselectivity of the Mukaiyama reaction in entry 7 can be explained by an approach of the silylenol ether to the less hindered convex side of both enantiomers of the hexahydrofuro[2,3-*b*]furan cation, which leads to the formation of diastereoisomers **142** and **164** (scheme 2.2). In an approach of the silylenol ether to the concave side of the hexahydrofuro[2,3-*b*]furan cation, serious steric hindrance would be developed between the substituents on the silylenol ether and C14 and C15 of the hexahydrofuro[2,3-*b*]furan moiety, and for this reason the diastereoisomers **142a** and **164a** are not formed.

scheme 2.2

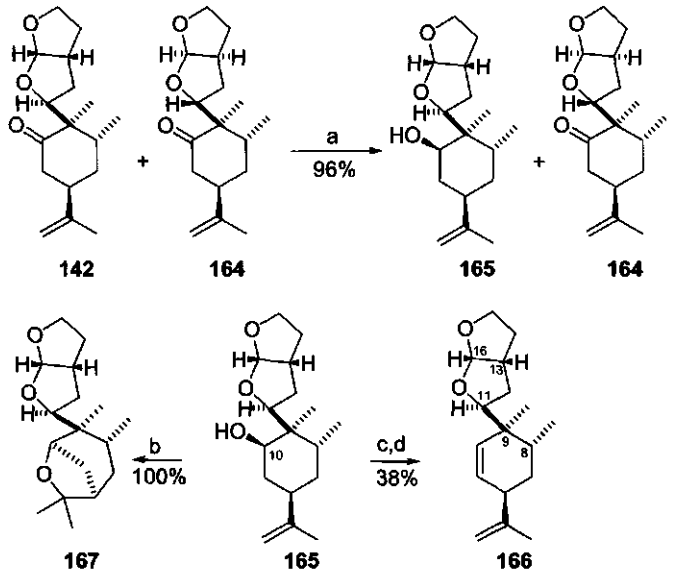


The structure of **164** was determined by X-ray crystallography,[57] but for the oily **142** some transformations had to be performed to obtain a crystalline product suitable for X-ray

[57] X-ray crystallography was performed by Veldman, N.; Menzer, S.; Spek, A. L. Bijvoet Center for Biomolecular Research, Department of Crystal and Structural Chemistry, Utrecht University.

analysis. First the mixture of the two diastereoisomers was treated at –78°C with Li-selectride. In this reaction only ketone **142** was reduced to give alcohol **165**, but ketone **164** was unaffected even at room temperature. This big difference in reactivity was also observed in the reduction of the diastereomeric mixture of **162** and **163**. The configuration at C10 is nicely shown by treatment of the obtained alcohol with a trace of acid, which gives the ether **167** in quantitative yield.[58] Alternatively, elimination of this hydroxyl group could be achieved by transforming it to the mesylate, followed by treatment with LiBr and Li_2CO_3 in DMF at 100°C, to give crystalline **166** in 37% overall yield. Structure elucidation by X-ray crystallography showed that **166** had the desired natural stereochemistry at C8, C9, C11, C13, and C16.[57]

scheme 2.3



(a) i) Li-selectride, ii) H_2O_2; **(b)** HBr; **(c)** MsCl, pyridine; **(d)** LiBr, Li_2CO_3.

2.4 Conclusions

The enantioselective synthesis of highly functionalized cyclohexanones starting from R-(–)-carvone, following the procedure described in this chapter, can be achieved in good yield with different substituents. The introduction of the hexahydrofuro[2,3-*b*]furan moiety is remarkably diastereoselective, and can serve as a good starting point for the synthesis of dihydroclerodin. The absolute stereochemistry in compound **142** is the same as in dihydroclerodin as was determinated by X-ray crystallography.

[58] Reduction of ketone **162**, followed by acid treatment yielded a similar ether bridge (see experimental).

2.4 Experimental

General: All reagents were purchased from Aldrich or Across, except for carvone which was a generous gift of Quest International, and were used without further purification unless otherwise stated. Melting points are uncorrected, NMR experiments were conducted with Bruker AC-E 200 or DPX 400 instruments; signals are reported in ppm (δ). HRMS data were obtained with a Finnigan MAT 95 spectrometer. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Solvents were freshly distilled by common practice. Product solutions were dried over $MgSO_4$ prior to evaporation of the solvent under reduced pressure by using a rotary evaporator. For flash chromatography, Merck Kieselgel silica 60 (230-400 Mesh ASTM) was used with mixtures of ethyl acetate and petroleum ether bp 40-60°C as eluens (10% EA/PE means 10 volume percent of ethyl acetate in petroleum ether). Reactions were monitored by GC with a DB-17 column (30 m x 0.25 mm i.d.) or by TLC on silica gel plates and visualization of compounds was accomplished by UV detection and by spraying with basic $KMnO_4$ or by acidic anisaldehyde solution. Ozone was generated by a Fisher ozone generator 502.

(((3*R*,5*R*)-5-Isopropenyl-2,3-dimethyl-1-cyclohexen-1-yl)oxy)(trimethyl)silane (135).

To a mechanically stirred solution of $CuBr{\bullet}Me_2S$ (3.68 g, 17.9 mmol), HMPA (50 mL, 285 mmol), and dry THF (400 mL) at –60°C, was added freshly prepared MeMgI (150 mL, 3M solution in ether), and stirred for 1 h. After this period R-(–)-carvone (**2**) (42.0 g, 280 mmol), and trimethylsilylchloride (60 g, 553 mmol) were added at –78°C, and stirring was continued for an additional 6 h at this temperature, followed by addition of Et_3N (55 mL). Stirring was continued for an additional 1 h while the temperature rose to rt. After this period water (500 mL) was added. The aqueous phase was extracted three times with ether. The combined organic layers were washed with brine, dried, and evaporated. The residue was filtered over a short column of silica to give **135** (58.6 g, 246 mmol, 88%) as a colorless oil. ^1H NMR ($CDCl_3$, 200 MHz) δ 0.16 (s, 9H), 0.99 (d, J = 8.2 Hz, 3H), 1.51 (m, 2H), 1.53 (s, 3H), 1.73 (s, 3H), 1.98 (m, 2H), 2.18 (m, 1H), 2.39 (m, 1H), 4.71 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 0.6 (q, 3C), 14.6 (q), 19.6 (q), 20.7 (q), 33.5 (d), 35.1 (t), 35.7 (t), 37.1 (d), 108.6 (t), 115.9 (s), 142.4 (s), 149.4 (s). IR ν_{max} (neat) 3082, 1684, 1644, 1251, 1188 cm^{-1}. $[\alpha]^{20}_D$ + 72.7 (c 2.7, $CHCl_3$).

(2*R*,3*R*,5*R*)-5-Isopropenyl-2,3-dimethyl-2-(((trimethylsilyl)oxy)methyl)cyclohexanone (157).

To a stirred solution of **135** (0.95 g, 4.0 mmol) in CH_2Cl_2 (20 mL) at –78°C, was added dropwise triphenylmethyl perchlorate[59] (0.16 g, 0.4 mmol) dissolved in CH_2Cl_2 (15 mL). Then dried ($CaCl_2$) formaldehyde gas, prepared by heating paraformaldehyde under a flow of N_2 at 180°C, was purged through the stirred solution for 10 min. After this period the reaction was quenched by addition of Et_3N (0.5 g, 5.0 mmol), followed by addition of a saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried, and evaporated. The remaining oil was purified by

[59] Dauben, H. J.; Honnen, L. R.; Harmon, K. M. *J. Org. Chem.* **1960**, *25*, 1442-1445.

flash chromatography (5% EA/PE) to give **157** (0.76 g, 2.8 mmol, 71%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.02 (s, 9H), 0.84 (d, J = 7.2 Hz, 3H), 0.89 (s, 3H), 1.58 (m, 1H), 1.69 (s, 3H), 1.92 (m, 1H), 2.10-2.54 (m, 4H), 3.59 (d, J = 9.7 Hz, 1H), 3.69 (d, J = 9.7 Hz, 1H), 4.65 (bs, 1H), 4.72 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ –0.7 (q, 3C), 15.9 (q), 16.3 (q), 21.1 (q), 33.0 (t), 33.5 (d), 40.2 (d), 43.4 (t), 53.7 (s), 67.2 (t), 110.1 (t), 147.4 (s), 214.2 (s).

(2*R*,3*R*,5*R*)-2-(1,3-Dioxolan-2-yl)-5-isopropenyl-2,3-dimethylcyclohexanone (158).

To a stirred solution of 2-methoxy-[1,3]dioxolan (10.5g, 101 mmol) and **135** (23.0 g, 96.6 mmol) CH_2Cl_2 (50 mL) at –78°C, was added dropwise triphenylmethyl perchlorate (0.99 g, 2.89 mmol) dissolved in CH_2Cl_2 (60 mL). The reaction mixture was stirred for 20 min at –78°C. (Samples for monitoring the reaction were diluted using ether with Et_3N). After this period the reaction was quenched by addition of a saturated aqueous $NaHCO_3$ solution (150 mL). The aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried, and evaporated. The remaining oil was distilled (140°C, 0.05 mmHg) to give **158** (17.2 g, 72.5 mmol, 75%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (d, J = 7.2 Hz, 3H), 0.96 (s, 3H), 1.59 (m, 1H), 1.72 (s, 3H), 2.16 (m, 1H), 2.30-2.62 (m, 4H), 3.91 (m, 4H), 4.73 (s, 1H), 4.76 (m, 1H), 5.35 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.6 (q), 16.6 (q), 20.6 (q), 33.4 (t), 36.2 (d), 40.8 (d), 44.7 (t), 56.4 (s), 65.2 (t), 65.6 (t), 105.1 (d), 109.8 (t), 147.6 (s), 211.6 (s). IR ν_{max} (neat) 3081, 1710, 1645, 1089 cm^{-1}.

(2*R*,3*R*,5*R*)-2-(Dimethoxymethyl)-5-isopropenyl-2,3-dimethylcyclohexanone (159).

To a stirred solution of trimethyl orthoformate (0.51g, 4.8 mmol) and **135** (0.95 g, 4.0 mmol) CH_2Cl_2 (35 mL) at –78°C, was added dropwise triphenylmethyl perchlorate (0.16 g, 0.48 mmol) dissolved in CH_2Cl_2 (20 mL). The reaction mixture was stirred for 72 h at –78°C. After this period the reaction was quenched by addition of a saturated aqueous $NaHCO_3$ solution (20 mL). The aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried, and evaporated. The remaining oil was purified by flash chromatography (20% EA/PE) to give **159** (0.47 g, 1.96 mmol, 49%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.85 (d, J = 7.2 Hz, 3H), 0.97 (s, 3H), 1.46 (m, 1H), 1.76 (s, 3H), 2.02 (ddd, J = 18.6, 10.8, 4.5 Hz, 1H), 2.23-2.62 (m, 4H), 3.41 (s, 3H), 3.57 (s, 3H), 4.57 (s, 2H), 4.63 (bs, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.9 (q), 16.2 (q), 20.8 (q), 33.5 (t), 34.9 (d), 40.6 (d), 44.1 (t), 57.7 (d), 58.0 (s), 59.7 (d), 108.9 (d), 109.7 (t), 147.6 (s), 211.8 (s).

(2*S*,3*R*,5*R*)-2-(1,3-Dithiolan-2-yl)-5-isopropenyl-2,3-dimethylcyclohexanone (160).

a) A suspension of $ZnCl_2$ (2.0 g, 15 mmol) in toluene was dried under Dean Stark condition for 4 h. This suspension was cooled and then added to a stirred mixture of **135** (7.13 g, 30 mmol), and 2-ethoxy-1,3-dithiolan[60] (4.5 g, 30 mmol) in CH_2Cl_2 at 0°C. Stirring was continued for 4 h. After this period the reaction was quenched by addition of Et_3N (5 mL), followed by a saturated aqueous $NaHCO_3$ solution (50 mL). The aqueous phase was extracted three times with CH_2Cl_2.

[60] a) PhD thesis Sicherer-Roetman, A., Wageningen Agricultural University, 1984; b) Tanimoto, S.; Miyake, T.; Okano, M. *Bull. Inst. Chem. Res.* **1977**, *55*, 276-281.

The combined organic layers were washed with brine, dried, and evaporated. The remaining solid was recrystallized from pentane to give **160** (7.8 g, 28.9 mmol, 96%) as white crystals. mp 38.0°-38.5°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.92 (d, J = 7.2 Hz, 3H), 1.11 (s, 3H), 1.57 (m, 1H), 1.72 (s, 3H), 2.08-2.67 (m, 7H), 3.20 (m, 2H), 4.75 (m, 2H), 5.38 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.7 (q), 16.9 (q), 20.6 (q), 32.8 (t), 38.9 (t), 39.5 (t), 40.6 (d), 41.0 (d), 43.2 (t), 57.5 (s), 59.1 (d), 109.9 (t), 147.1 (s), 211.9 (s).

b) To a stirred solution of 2-ethoxy-1,3-dithiolan (0.73 g, 4.4 mmol) and **135** (0.95 g, 4.0 mmol) CH_2Cl_2 (30 mL) at –78°C, was added dropwise triphenylmethyl perchlorate (16 g, 0.40 mmol) dissolved in CH_2Cl_2 (15 mL). The reaction mixture was stirred for 20 min at –78°C. After this period the reaction was quenched by addition of a saturated aqueous $NaHCO_3$ solution (25 mL). The aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried, and evaporated. The remaining oil was purified by flash chromatography (20% EA/PE) to give **160** (0.97 g, 3.59 mmol, 90%) as white crystals.

(2*S*,3*R*,5*R*)-5-Isopropenyl-2,3-dimethyl-2-((1*)-1-(phenylsulfanyl)ethyl)cyclohexanone (161).

To a stirred solution of **135** (1.0 g, 4.4 mmol), and ((1-chloroethyl)sulfanyl)benzene (0.8 g, 4.4 mmol) in dry CH_2Cl_2 (20 mL) at –78°C was added $SnCl_4$ (0.52 mL, 4.4 mmol). Stirring was continued for 15 min, followed by addition of Et_3N (5 mL) and silica (10 g). After this period the reaction mixture was filtered, and the filter was washed extensively with CH_2Cl_2. The CH_2Cl_2 was evaporated to yield **161** (1.15 g, 3.8 mmol, 86%) as a mixture of two diastereoisomers (7:3). The mixture was separated by flash chromatography (20% EA/PE) the major isomer was obtained pure. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.84 (d, J = 7.3 Hz, 3H), 0.97 (s, 3H), 1.07 (d, J = 6.9 Hz, 3H), 1.48 (m, 1H), 1.64 (s, 3H), 1.96 (ddd, J = 13.9, 13.9, 4.3 Hz, 1H), 2.27 (m, 2H), 2.50 (m, 1H), 2.79 (m, 1H), 3.74 (q, J = 6.7 Hz, 1H), 4.63 (bs, 1H), 4.69 (bs, 1H), 7.15-7.43 (m, 5H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.6 (q), 16.2 (q), 18.0 (q), 20.7 (q), 32.6 (t), 37.1 (d), 41.0 (d), 43.3 (t), 50.2 (d), 56.6 (s), 109.8 (t), 127.4 (d), 129.2 (d, 2C), 132.9 (d, 2C), 135 6 (s), 147.4 (s), 213.6 (s). MS m/z (relative intensity) 302 (32), 137 (100), 123 (16), 109 (39), 83 (35), 55 (22), 41 (14). HRMS calcd for $C_{19}H_{26}OS$ (M^+) 302.1704, found 302.1710 (σ=0.0964 mmu).

2-Methoxytetrahydrofuran (155).[61]

To a well stirred solution of 2,3-dihydrofuran (35 g, 500 mmol) and dry MeOH (15.5 g, 500 mmol) in CH_2Cl_2 (50 mL) at 0°C was added one drop of trimethylsilyliodide. (The reaction is very exothermic without solvent the reaction mixture will explode.) The reaction is finished immediately (by GC, column 50°C), and the solvent is evaporated carefully, followed by distillation at atmospheric pressure bp 103°-105°C to give **155** (33.7 g, 331 mmol, 66%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.85 (m,4H), 3.28 (s, 3H), 3.83 (m, 2H), 4.95 (dd, J = 3.8, 1.6 Hz, 1H).

[61] This compound is also for sale but expensive.

(2*R*,3*R*,5*R*)-5-Isopropenyl-2,3-dimethyl-2-((2*S*)-tetrahydro-2-furanyl)cyclohexanone (162), (2*R*,3*R*,5*R*)-5-Isopropenyl-2,3-dimethyl-2-((2*R*)-tetrahydro-2-furanyl)cyclohexanone (163).

To a stirred solution of 2-methoxy-tetrahydrofuran (**155**) (14.2g, 139 mmol) and **135** (30.0 g, 126 mmol) CH_2Cl_2 (200 mL) at –78°C, was added dropwise triphenylmethyl perchlorate (2.16 g, 6.3 mmol) dissolved in CH_2Cl_2 (100 mL). The reaction mixture was stirred for 20 min at –78°C. After this period the reaction was quenched by addition of a saturated aqueous $NaHCO_3$ solution (100 mL). The aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were washed with, water, brine, dried, and evaporated. The remaining oil was distilled (0.03 mbar, 108°C) to give a 7:3 diastereoisomeric mixture of **162** and **163** (26.3g, 111 mmol, 88%) as a colorless oil. An analytical sample of **162** and **163** was obtained after purification by flash chromatography (10% EA/PE).

(162) ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.87 (s, 3H), 0.89 (d, J = 7.2 Hz, 3H), 1.38-1.91 (m, 5H), 1.72 (s, 3H), 2.17-2.65 (m, 5H), 3.75 (m, 2H), 4.34 (dd, J = 7.6, 7.6 Hz, 1H), 4.74 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.8 (q), 16.8 (q), 20.6 (q), 26.1 (t), 26.3 (t), 33.1 (t), 36.7 (d), 40.7 (d), 44.8 (t), 56.5 (s), 68.7 (t), 79.8 (d), 109.6 (t), 147.6 (s), 213.7 (s).

(163) ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.91 (d, J = 7.5 Hz, 3H), 0.94 (s, 3H), 1.49-2.17 (m, 6H), 1.75 (s, 3H), 2.29-2.60 (m, 3H), 2.74 (dd, J = 12.7, 12.7 Hz, 1H), 3.80 (m, 2H), 4.44 (dd, J = 8.0, 6.5 Hz, 1H), 4.77 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.1 (q), 16.6 (q), 20.6 (q), 25.7 (t), 26.4 (t), 33.3 (t), 37.7 (d), 40.8 (d), 43.2 (t), 55.2 (s), 68.6 (t), 82.4 (d), 109.7 (t), 147.7 (s), 213.9 (s).

(2*R*,3*R*,5*R*)-2-((2*S*,3a*R*,6a*S*)-Hexahydrofuro[2,3-*b*]furan-2-yl)-5-isopropenyl-2,3-dimethyl-cyclohexanone (142),
(2*R*,3*R*,5*R*)-2-((2*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-2-yl)-5-isopropenyl-2,3-dimethyl-cyclohexanone (164).

To a stirred solution of (±)-2-methoxyhexahydrofuro[2,3-*b*]furan[62] (16.0 g, 110 mmol) and **135** (22.0 g, 92.3 mmol) CH_2Cl_2 (150 mL) at –78°C, was added dropwise triphenylmethyl perchlorate (3.4 g, 10 mmol) dissolved in CH_2Cl_2 (150 mL). The reaction mixture was stirred for 78 h at –78°C until **135** was not detectable anymore on TLC (Samples for monitoring the reaction were diluted using ether with Et_3N). After this period the reaction was quenched by addition of a saturated aqueous $NaHCO_3$ solution (100 mL). The aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried, and evaporated. The residue was distilled (Kugelrohr 0.01 mmHg, oven temperature 110°C). The mixture of two diastereoisomers were separated via crystallization from diisopropylether. After two recrystallizations the diastereoisomers were completely separated, yielding crystalline **164** (9.1 g, 32.7 mmol, 35 %) as white crystals. mp 120°C, $[\alpha]^{20}_D$ + 65.7 (c 2.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.89 (s, 3H), 0.89 (d, J = 7.0 Hz, 3H), 1.52 (m, 1H), 1.69 (bs, 3H), 1.69 (m, 2H), 1.92-2.16 (m, 4H), 2.33 (m, 1H), 2.55 (m, 1H), 2.71 (d, J = 12.6 Hz, 1H), 2.82 (m, 1H), 3.87 (m,

[62] For the synthesis of this compound see chapter 3.

2H), 4.63 (dd, J = 9.6, 6.2 Hz, 1H), 4.75 (m, 2H), 5.66 (d, J = 5.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.4 (q), 16.7 (q), 20.4 (q), 32.6 (t), 33.0 (t), 33.1 (t), 36.8 (d), 40.4 (d), 41.9 (d), 43.3 (t), 54.3 (s), 68.0 (t), 82.6 (t), 109.0 (d), 109.4 (t), 147.4 (s), 213.4 (s).

Compound **142** (11.0 g, 39 mmol, 40 %) was obtained as a colorless oil (90% purity). An analytical sample of **142** was obtained after purification by flash chromatography (20% EA/PE). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.82 (s, 3H), 0.84 (d, J = 5.0 Hz, 3H), 1.45 (ddd, J = 13.4, 6.8, 5.2 Hz, 1H), 1.50-2.31 (m, 7H), 1.67 (bs, 3H), 2.48 (m, 2H), 2.80 (m, 1H), 3.87 (dd, J = 8.6, 4.6 Hz, 2H), 4.70 (m, 3H), 5.69 (d, J = 10.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.8 (q), 16.7 (q), 20.5 (q), 32.6 (t), 32.9 (t), 33.0 (t), 36.2 (d), 40.5 (d), 42.6 (d), 44.8 (t), 56.0 (s), 67.8 (t), 80.3 (d), 109.5 (d), 109.7 (t), 147.4 (s), 213.2 (s).

(1*R*,2*S*,3*R*,5*R*)-2-((2*S*,3a*R*,6a*S*)-Hexahydrofuro[2,3-*b*]furan-2-yl)-5-isopropenyl-2,3-dimethylcyclohexanol (165).

To a stirred solution of **142** (0.94 g, 3.4 mmol) in THF (30 mL) was added dropwise lithium tri-*sec*-butylborohydride (1 M in THF, 5 mL) at –78°C. The reaction mixture was allowed to come to rt and stirred for an additional 8 h. After this period the reaction mixture was cooled down to –10°C and an aqueous solution of NaOH (1 M, 10 mL) and an aqueous solution of H_2O_2 (30%, 8 mL) were added slowly, followed by 2 h vigorous stirring. Water (20 mL) was added and then the aqueous phase was extracted three times with ether. The combined organic layers were carefully washed with an aqueous solution of Na_2SO_3 and brine, dried, and evaporated. The residue was purified by flash chromatography (30% EA/PE) to give **165** (0.91g, 3.25 mmol, 96%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (s, 3H), 0.99 (d, J = 7.4 Hz, 3H), 1.38 (m, 1H), 1.60-2.40 (m, 10H), 1.76 (bs, 3H), 2.78 (m, 1H), 3.71 (dd, J = 10.2, 5.1 Hz, 1H), 3.88 (m, 2H), 4.41 (dd, J = 10.7, 5.5 Hz, 1H), 4.76 (m, 2H), 5.65 (d, J = 5.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.4 (q), 16.5 (q), 21.0 (q), 32.8 (t), 33.1 (d), 33.4 (t), 34.6 (t), 35.2 (t), 38.2 (d), 42.1 (s), 42.4 (d), 68.3 (t), 74.1 (d), 80.1 (d), 107.9 (d), 108.9 (t), 149.7 (s).

(2*S*,3a*R*,6a*S*)-2-((1*S*,4*R*,6*R*)-4-Isopropenyl-1,6-dimethyl-2-cyclohexen-1-yl)hexahydro-furo[2,3-*b*]furan (166).

To a stirred solution of **165** (0.91 g, 3.25 mmol) in pyridine (5 mL) and CH_2Cl_2 (5 mL) was added MsCl (0.6 mL, 5 mmol) at 0°C. The reaction mixture was stirred overnight at rt, followed by addition of water (50 mL). The aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (30% EA/PE) to give the mesylate (0.49 g, 1.37 mmol, 42%) as a colorless oil.

To a solution of the mesylate (400 mg, 1.12 mmol) in dry DMF (20 mL) were added LiBr (0.5 g) and Li_2CO_3 (0.5 g). The reaction mixture was heated at 100°C for 36 h. Then cooled to rt and poured into water (20 mL). The aqueous phase was extracted thee times with petroleum ether. The combined organic layers were washed two times with brine, dried, and evaporated. The residue was purified by flash chromatography (5% EA/PE) to give **166** (290 mg, 1.24 mmol, 90%) as white crystals. For X-ray analysis the crystals were recrystallized from hexane to afford

almost colorless needles. mp 68-70°C. $[\alpha]^{20}_D$ + 114 (c 3.3, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz) δ 0.81 (d, *J* = 6.3 Hz, 3H), 0.96 (s, 3H), 1.35-2.18 (m, 7H), 1.72 (s, 3H), 2.61 (m, 1H), 2.77 (m, 1H), 3.86 (m, 2H), 4.12 (dd, *J* = 10.2, 5.9 Hz, 1H), 4.63 (bs, 1H), 4.77 (bs, 1H), 5.60 (s, 2H), 5.68 (d, *J* = 5.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.9 (q), 18.3 (q), 22.1 (q), 29.4 (d), 30.7 (t), 32.9 (t), 34.0 (t), 41.2 (d), 41.2 (s), 42.4 (d), 68.1 (t), 84.9 (d), 109.0 (d), 111.2 (t), 129.3 (d), 132.5 (d), 148.2 (s). MS m/z (relative intensity) 113 (100), 69 (45). HRMS calcd for $C_{17}H_{26}O_2$ (M^+) 262.1932, found 262.1932 (σ=0.057 mmu).

(2*S*,3a*R*,6a*S*)-2-((1*R*,3*R*,4*S*,5*R*)-3,4,7,7-Tetramethyl-6-oxabicyclo[3.2.1]oct-4-yl)hexahydro-furo[2,3-*b*]furan (167).

To a stirred mixture of **165** (71.0 mg, 0.25 mmol) in butanone (2 mL) was added one drop of HBr (57%) at rt. The reaction was finished immediately, and water was added followed by extraction with ether. The combined organic layers were washed with brine, dried, and evaporated, to give **167** (71.0 mg, 0.25 mmol, 100%). ^1H NMR ($CDCl_3$, 200 MHz) δ 0.65 (s, 3H), 0.92 (d, *J* = 6.7 Hz, 3H), 1.16 (s, 3H), 1.19 (m, 1H), 1.36 (s, 3H), 1.60-2.12 (m, 9H), 2.75 (m, 1H), 3.87 (m, 3H), 4.22 (dd, *J* = 10.4, 5.0 Hz, 1H), 5.67 (d, *J* = 5.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.1 (q), 17.7 (q), 22.8 (q), 30.3 (q), 32.5 (t), 32.7 (t), 33.2 (t), 33.6 (d), 35.1 (t), 41.8 (d), 41.9 (d), 43.0 (s), 68.2 (t), 81.6 (s), 81.9 (d), 87.1 (d), 109.1 (d).

(1*R*,2*S*,3*R*,5*R*)-5-Isopropenyl-2,3-dimethyl-2-((2*S*)-tetrahydro-2-furanyl)cyclohexanol.

To a stirred solution of a 7:3 mixture of **162** and **163** (5.0 g, 21.2 mmol) in dry THF (150 mL) at –78°C was added Li-selectride (40 mL, 1M solution in THF, 40 mmol). The temperature was allowed to come to rt, and stirring was continued overnight. After this period the reaction was quenched by addition of an aqueous solution of NaOH (20mL, 4M), followed by water (40 mL), then the reaction mixture was cooled to 5°C and an aqueous solution of H_2O_2 (15 mL, 37%) was added slowly. Stirring was continued for 3 h, followed by addition of ether. The layers were separated. The aqueous phase was extracted thee times with ether. The combined organic layers were washed two times with brine, dried, and evaporated. The residue was purified by flash chromatography (10% EA/PE) to give first the unreacted ketone **163** (1.4 g, 5.9 mmol, 93%) followed by **(1*R*,2*S*,3*R*,5*R*)-5-Isopropenyl-2,3-dimethyl-2-((2*S*)-tetrahydro-2-furanyl)cyclo-hexanol** (3.4 g, 14.3 mmol, 96%). ^1H NMR (C_6D_6, 200 MHz) δ 1.00 (d, *J* = 6.9 Hz, 3H), 1.02 (s, 3H), 1.42 (m, 1H), 1.52-191 (m, 6H), 1.76 (s, 3H), 2.16 (ddd, *J* = 12.6, 12.6, 4.4 Hz, 1H), 2.25 (m, 1H), 2.50 (m, 1H), 3.52 (m, 2H), 3.66 (ddd, *J* = 8.2, 7.0, 7.0 Hz, 1H), 4.20 (dd, *J* = 7.8, 7.8 Hz, 1H), 4.88 (m, 1H), 4.94 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.5 (q), 17.0 (q), 21.1 (q), 26.3 (t), 27.6 (t), 33.3 (d), 33.5 (t), 35.6 (t), 38.4 (d), 42.5 (s), 67.0 (t), 74.5 (d), 81.2 (d), 108.7 (t), 149.8 (s).

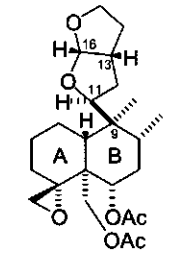
(1*R*,3*R*,4*R*,5*R*)-3,4,7,7-Tetramethyl-4-((2*S*)-tetrahydro-2-furanyl)-6-oxabicyclo[3.2.1]octane.

To a stirred mixture of **(1*R*,2*S*,3*R*,5*R*)-5-Isopropenyl-2,3-dimethyl-2-((2*S*)-tetrahydro-2-furanyl)cyclohexanol** (280 mg, 1.18 mmol) in butanone (2 mL) was added one drop of HBr (57%) at rt. The reaction was finished immediately, and water was added followed by extraction

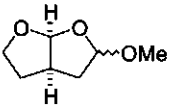
with ether. The combined organic layers were washed with brine, dried, and evaporated, to give **(1*R*,3*R*,4*R*,5*R*)-3,4,7,7-Tetramethyl-4-((2*S*)-tetrahydro-2-furanyl)-6-oxabicyclo[3.2.1]octane** (280 mg, 1.18 mmol, 100%) ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.68 (s, 3H), 0.94 (d, J = 6.8 Hz, 3H), 1.19 (s, 3H), 1.21 (m, 1H), 1.38 (s, 3H), 1.62-2.22 (m, 9H), 3.71-3.95 (m, 4H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.0 (q), 17.8 (q), 22.9 (q), 25.5 (t), 26.4 (t), 30.3 (q), 32.4 (t), 33.9 (d), 35.3 (t), 41.9 (d), 43.1 (s), 68.1 (t), 81.5 (s), 82.5 (d), 87.4 (d).

3

The synthesis of 2-methoxy-hexahydrofuro[2,3-*b*]furan



dihydroclerodin (**1**)



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3.1 Introduction[63]

The introduction of the hexahydrofuro[2,3-*b*]furan fragment in dihydroclerodin (**1**) is an essential element in its total synthesis. Few methods have been published for the introduction of a furofuran moiety in clerodanes, and all make use of a suitable functional group on ring B as a starting point. These syntheses require several steps to obtain the furofuran skeleton with all its chiral centers in the desired configuration. Below a short literature review is given and an alternative strategy for the synthesis of the hexahydrofuro[2,3-*b*]furan moiety of dihydroclerodin is formulated.

In the synthesis of model compound **173a**, Kojima *et al.*[64] constructed the furofuran moiety at the end of the synthesis. The epoxidation of the double bond in compound **168** gave a 92:8 mixture in favor of the desired epoxide (scheme 3.1). Addition of difuryllithium cuprate to this mixture yielded a mixture of two alcohols (92:8) in quantitative yield, which could be separated. Hydrolysis of the protecting acetonide, followed by bromination of the furanyl group in methanol and potassium acetate yielded a mixture of 13,14-unsaturated dimethoxy acetals **170**, which was reduced with Raney-Nickel to the saturated mixture. Acid treatment of these dimethoxy acetals gave a hexahydrofuro[2,3-*b*]furanyl hemiacetal **171**, which was treated with acetic anhydride to give a triacetate as a mixture of C15 epimers. The C15 acetate could be selectively hydrolyzed to give **172**, and this hemiacetal was oxidized to give a mixture of perhydrofuro[2,3-*b*]furanones, **173a** and **173b**. According to the authors, these two compounds are epimeric at C11 and this epimerization should have taken place during the acidic hydrolysis of the acetal acetate.[65] At the end of the report the synthesis of a model compound with methyl groups at C8 and C9 was announced, but up to now this synthesis has not been published.

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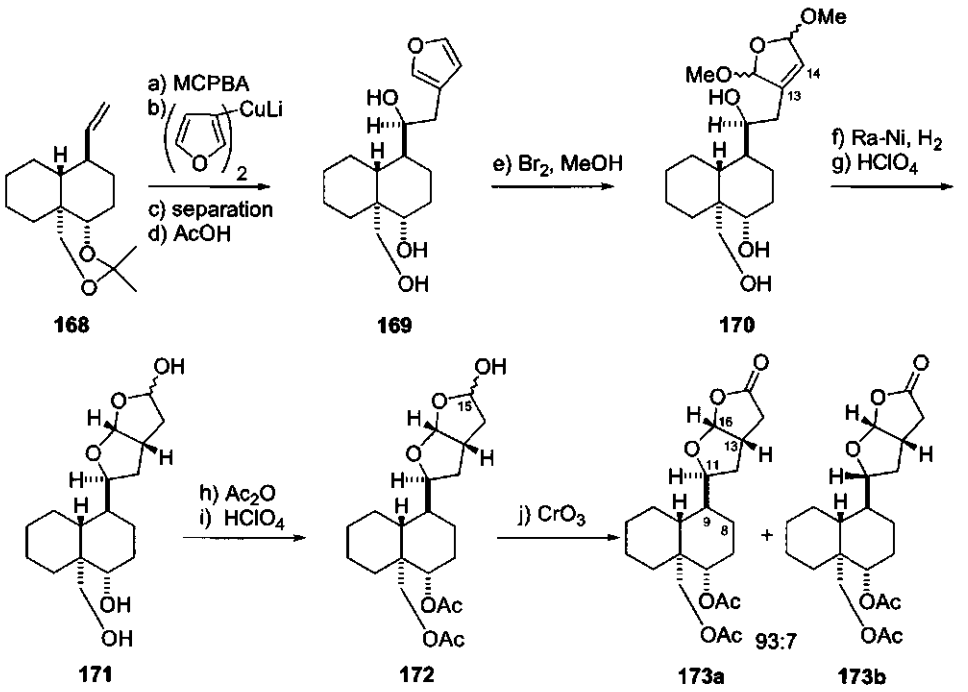
[63] Throughout this thesis the clerodane numbering according to figure 1.1 will be used in all discussions.

[64] Kojima, Y.; Kato, N. *Tetrahedron* **1981**, *37*, 2527-2538.

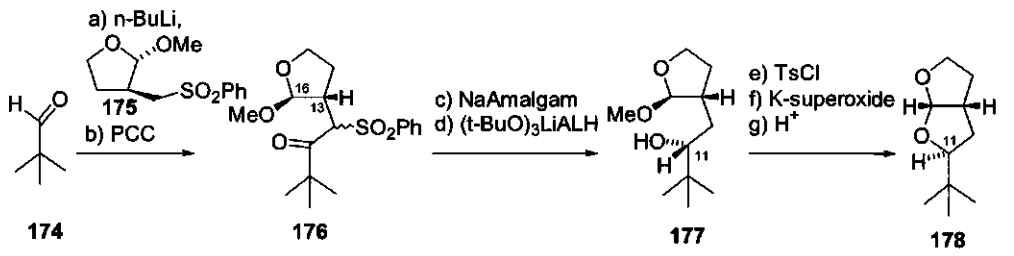
[65] In my opinion the epimerization at C11 is unlikely, it is more probable that an epimeric mixture at C13 and C16 has been obtained. This can either be better explained by a non selective hydrogenation of the C13-C14 double bond, or as was also observed by Vader *et al.* in ref 67, by acidic treatment of the furofuran hemiacetal. In that reaction epimerization at C13 can occur via intermediate enols or enol ethers as shown in scheme 3.8. It should be noted that interpretation of the NMR recordings of these compounds is difficult due to the acetal epimers at C15 and C16.

scheme 3.1



The synthesis of hexahydrofuro[2,3-*b*]furanyl model compounds by Vader *et al.*[66] starts with an addition of **175** to pivaldehyde, and oxidation of the obtained mixture of alcohols to ketone **176** (scheme 3.2). In this ketone the phenylsulfonyl group was reductively removed, but in the subsequent reduction of the carbonyl group to alcohol **177**, the undesired configuration at C11 was obtained. Tosylation of this hydroxyl group, followed by a nucleophilic substitution with potassium superoxide had to be performed to invert the configuration. Next the compound with the natural configuration at C11 was converted into **178** by an acid catalyzed cyclization.

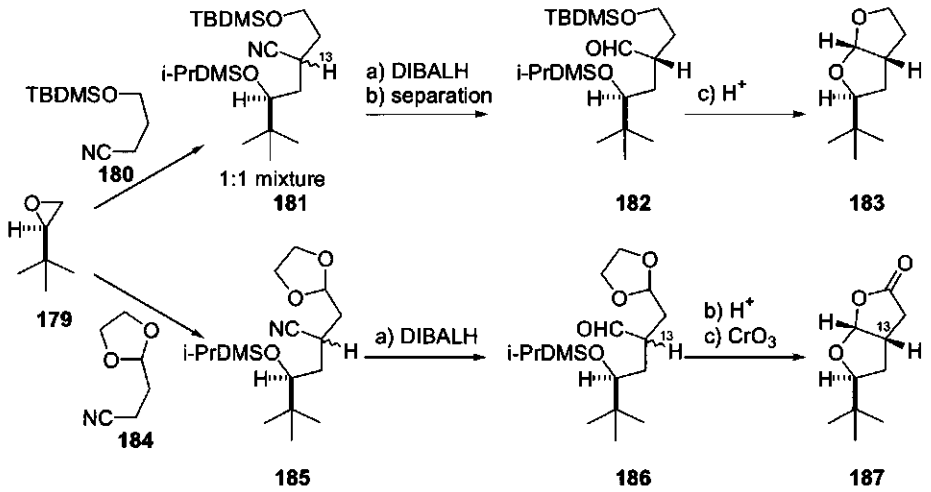
scheme 3.2



[66] Vader, J.; Koopmans, R.; de Groot, A.; van Veldhuizen, A.; van de Kerk, S. *Tetrahedron* **1988**, *44*, 2663-2674.

Later on Vader *et al.*[67] synthesized the hexahydrofuro[2,3-*b*]furan fragment using a shorter route (scheme 3.3). Addition of the lithiated **180** to epoxide **179** gave the nitriles **181** as a 1:1 mixture. Reduction of the nitriles gave a separable 1:1 mixture of aldehydes **182**. After separation, the desired diastereoisomer was converted into **183** by an acid catalyzed cyclization. The other stereoisomer could be partly isomerized at C13 with t-BuOK to give a 7:2 mixture of the desired aldehyde **182** and its epimer. Using a similar method, also perhydrofuro[2,3-*b*]furanone **186** was synthesized. Addition of lithiated **183** yielded again a mixture of nitriles **184**, which was reduced to a mixture of aldehydes **185**. Treatment of this aldehyde with acid afforded a mixture of furofuran hemiacetals, which by elongated acid treatment and subsequent oxidation gave the desired *trans*-isomer **186** together with just a trace of its *cis*-epimer.

scheme 3.3

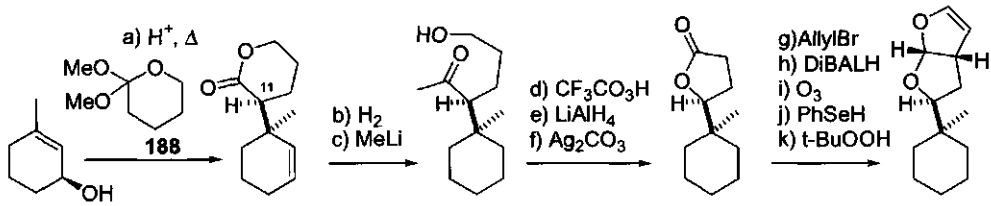


In the synthesis of model compound **192** by Bouchard *et al.*[68] a stereospecific Claisen rearrangement is used as the key step to obtain the C9/C11 bond with the desired configuration at C11. In model compound **190** the double bond was reduced, and next a careful addition of MeLi at –78°C to the lactone, gave ketone **191**. A Baeyer-Villiger oxidation followed by reduction yielded a diol, in which the primary hydroxyl group was selectively oxidized and cyclized to γ-butyrolactone **191**. Compound **191** was then alkylated by allylbromide using LDA as a base. Reduction of the lactone to the hemiacetal, followed by ozonolysis of the double bond afforded a mixture of lactols. Phenyl selenylation and oxidation-elimination of the selenide gave the clerodin model **192** in a reasonable yield.

[67] Vader, J.; Sengers, H.; de Groot, A. *Tetrahedron* **1989**, *45*, 2131-2142.

[68] Bouchard, H.; Renard, P. Y.; Lallemand, J. Y. *Tetrahedron Lett.* **1991**, *32*, 5953-5956; *ibid.* 5957-5958.

scheme 3.4



187 **189** **190** **191** **192**

The feasibility of selective application of oxidations, brominations, reductions, acidic and basic conditions during the synthesis of the furofuran moiety at the end of total syntheses of clerodanes, is questionable and depends on the functionalities in the decalin part of the compounds in question. In that respect the methods described by Kojima, Vader (scheme 3.2), and Bouchard are probably not suitable for the synthesis of fully oxidized clerodanes like dihydroclerodin. Furthermore, the stereochemistry at C11 may be difficult to control, since it has only been studied for simple model compounds.

3.2 Syntheses of 2-methoxy-hexahydrofuro[2,3-*b*]furan

For the reasons mentioned above we wanted to investigate a different approach for the total synthesis of dihydroclerodin, and its hexahydrofuro[2,3-*b*]furan moiety. This moiety, being an acetal, is assumed to be stable under most of the reaction conditions that have to be applied for the construction of the decalin part of the molecule. This stability opens up the opportunity for an early introduction of this fragment in the total synthesis. We have developed a method for the introduction of the complete hexahydrofuro[2,3-*b*]furan moiety in ring B of dihydroclerodin, as described in chapter 2. Addition of silylenol ether **135** to racemic 2-methoxy-hexahydrofuro[2,3-*b*]furan (**156**) yielded only two of the eight possible diastereoisomers. The use of optically pure **156** in this reaction will even give all chiral centers in the desired configuration without the need of separation. However, only one method is published for the enantioselective synthesis of **156** in seven steps and in low overall yield.[69] Also the reported syntheses of racemic furofurans are not really suitable for the big scale applications that will be necessary in the beginning of a multistep total synthesis.[70]

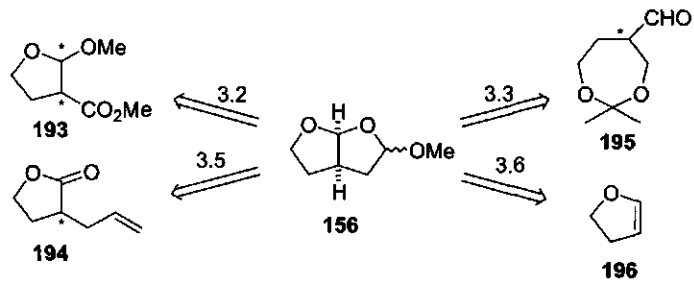
Therefore the synthesis of 2-methoxy-hexahydrofuro[2,3-*b*]furan (**156**) is investigated. It is important to develop a synthesis for **156** which can be applied on a reasonable scale, starts from cheap chemicals, and uses simple procedures. With these conditions in mind, three methods were investigated (scheme 3.5). Three of these methods start from compounds that can be

[69] Petit, F.; Furstoss, R. *Synthesis* **1995**, 1517-1520.

[70] Pezechk, M.; Brunetiere, A. P.; Lallemand, J. Y. *Tetrahedron Lett.* **1986**, *27*, 3715-3718.

obtained in an enantiomerically pure form, but all three methods were studied using the racemic starting materials.

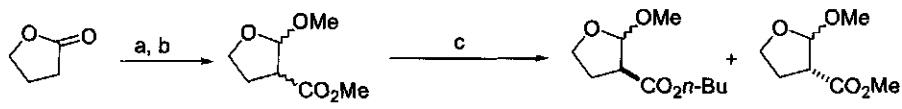
scheme 3.5



3.2.1 Synthesis of 2-methoxy-hexahydrofuro[2,3-*b*]furan from methyl 2-methoxytetrahydro-3-furancarboxylate

For the enantioselective synthesis of **156**, methyl 2-methoxytetrahydro-3-furancarboxylate (**193**) is a suitable intermediate, not only because it has been used before in our laboratory, but also the ester group provides a handle for its enantioselective transesterification. The enzymatic transesterification of **193** using *Candida rugosa* lipase and butanol resulted in a mixture of R-methyl- and S-butylesters that could be separated by preparative gas chromatography. The S-butylester possesses the desired configuration for the synthesis of the hexahydrofuro[2,3-*b*]furan moiety of dihydroclerodin (scheme 3.6).[71]

scheme 3.6[71]



136 **193** **145-(3S)** **193-(3R)**

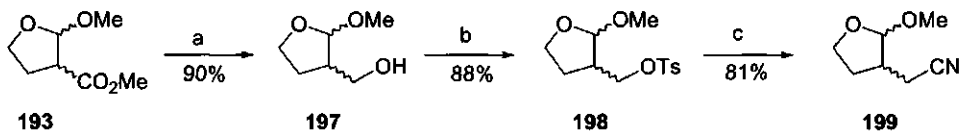
(a) NaH, HCO_2Me; **(b)** MeOH, HCl; **(c)** *Candida rugosa*, n-BuOH

A synthesis of **156** was developed starting from racemic methyl 2-methoxytetrahydro-3-furancarboxylate (**193**) (scheme 3.7). This synthesis started with reduction of ester **193** to give alcohol **197** in quantitative yield.[66] Tosylation of this alcohol, and substitution of the tosylate with cyanide gave nitrile **199** in 71% yield over two steps. For the conversion of this nitrile into **156**, two pathways A and B were investigated. In path A the reduction of the nitrile by DIBALH was performed to obtain aldehyde **200**, which on its turn could be converted into **156** under acidic

[71] Franssen, M. C. R.; Jongejan, H.; Kooijman, H.; Spek, A. L.; Nuno, L. F. L.; Mondril, N. L. F. L. C.; Dossantos, P. M. A. C. B.; de Groot, A. *Tetrahedron Asymm.* **1996**, *7*, 497-510.

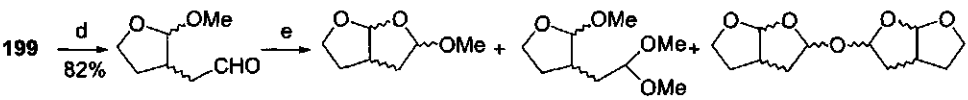
conditions. However, during the treatment of **200** with acid, numerous side products were obtained, which were difficult to separate from the desired **156**.[72] In reaction path B the nitrile **199** was first saponificated, and the carboxylate was then treated with acid to give lactone **203** in high yield. Reduction of **203** by DIBALH and immediate capturing of the intermediate by a reaction with methanol and boron trifluoride etherate, at low temperature and for a short reaction time, gave **156** in a reasonable yield. When longer reaction times were applied, the overreduced hexahydrofuro[2,3-*b*]furan **204** was formed as the product of a BF_3 assisted Meerwein-Ponndorf-Verley reduction[73] (figure 3.1). The minor side products formed in path B were removed by distillation, which gave almost pure **156** in a reasonable yield (62%). These two methods for the synthesis of **156** have three drawbacks. First, the isolation of optically active **145-(3S)** has to be performed by preparative gas chromatography, which makes it time consuming in large scale syntheses. Second, the syntheses are rather long with overall yields of 20 and 34%. Third, racemization is theoretically possible in the acid catalyzed reaction steps.

scheme 3.7



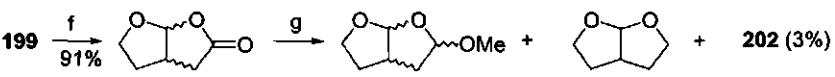
193 **197** **198** **199**

Path A: (Overall yield from **193** to **156** is ~20%)



200 **156** (~40%) **201** (~6%) **202** (14%)

Path B: (Overall yield from **193** to **156** is 34%)



202 (3%)

203 **156** (62%) **204** ~12%

(a) $LiAlH_4$; **(b)** TsCl, Py; **(c)** NaCN; **(d)** DIBALH; **(e)** TMSI, MeOH; **(f)** i) NaOH, ii) HCl; **(g)** i) DIBALH, ii) BF_3•etherate, MeOH

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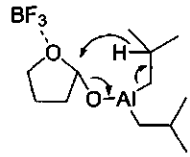
[72] The easy opening of the hexahydro[2,3-*b*]furan moiety to compounds like **201** was already observed by Kojima *et al.* in Kojima, Y.; Kato, N. *Tetrahedron Lett.* **1980**, *21*, 5033-5036.

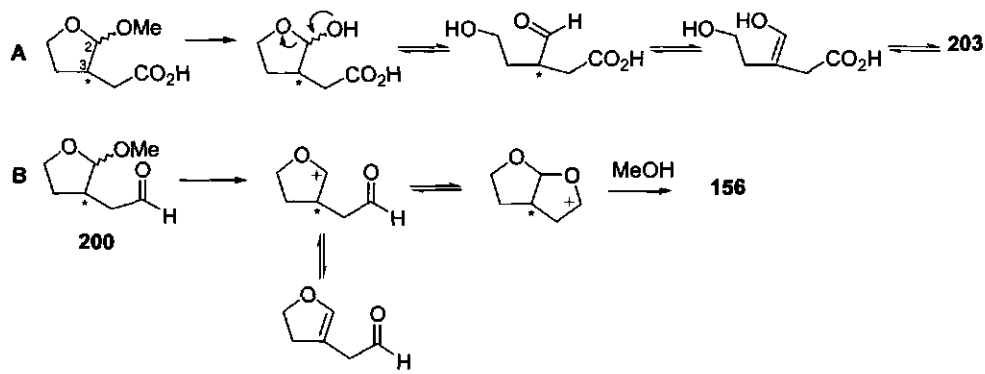
[73] Kiyooka, S.-I.; Shirouchi, M. *J. Org. Chem.* **1992**, *57*, 2-4.

figure 3.1



Since these syntheses were performed with racemic **193**, it was not possible to see if any racemization had occurred during the conversion of **199** into **203** or **200** into **156**. The acetal in **199** is stable to treatment with NaOH in water, but during the lactonization under acidic conditions, there is a competition between the intramolecular lactonization and the formation of a hemiacetal by reaction with water, and at that point racemization may occur. Racemization is possible when C3 becomes sp^2 hybridized. This can occur by opening of the tetrahydrofuran fragment to give an aldehyde at C2, which then can equilibrate C3 (scheme 3.8, A). A second possibility for racemization can occur when a carbocation at C2 is formed. Now deprotenation at C3 becomes possible to give an enolether (scheme 3.8, B). It does not seem very likely that racemization will occur during the conversion of **200** into **156** because the desired reaction is very quick, performed at low temperature, and the cation at C2 is stabilized by the neighboring oxygen atom.

scheme 3.8

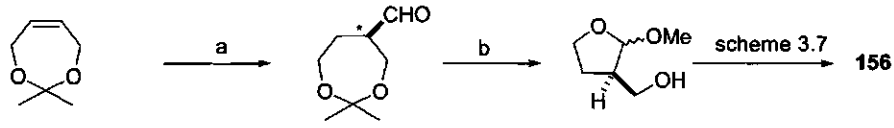


3.2.2 Enantioselective synthesis of (2-Methoxy-tetrahydrofuran-3-yl)-methanol

Recently, an enantioselective route was published[74] to prepare alcohol **197** without the necessity of a time consuming separation, however a rather low ee of 69% and the use of a stoichiometric amount of the rather expensive (R,S)-3,3'-Me_2-BINAPHOS as chiral auxiliary (scheme 3.9) makes this reaction not very attractive for the use in our synthesis.

[74] Horiuchi, T.; Ohta, T.; Shirakawa, E.; Nozaki, K. R. A.; Takaya, H. *J. Org. Chem.* **1997**, *62*, 4285-4292.

scheme 3.9



205 **195** **197-(3R)**

(a) H_2/CO, Rh(acac)$(CO)_2$, R,S-3,3'-Me_2-BINAPHOS; **(b)** I_2, MeOH

3.2.3 Synthesis of 2-methoxy-hexahydrofuro[2,3-*b*]furan from 3-allyldihydro-2(3*H*)-furanone

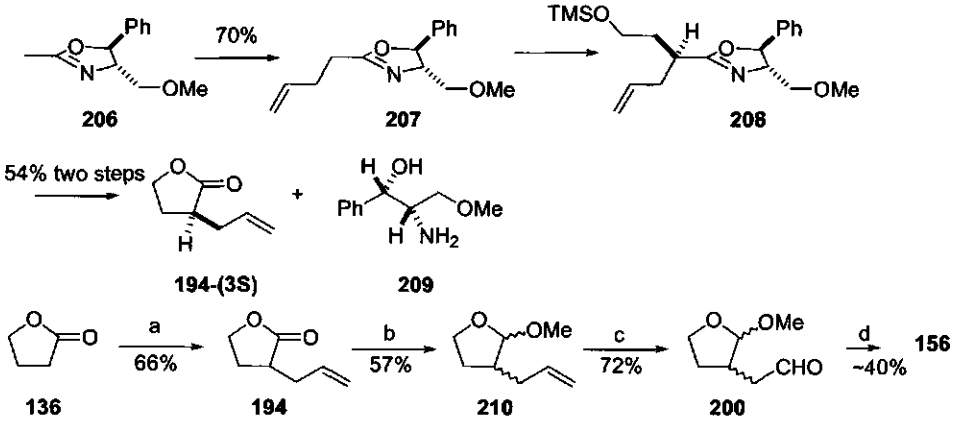
3-Allyldihydro-2(3*H*)-furanone (**194**) also seemed a good intermediate for the synthesis of **156**, especially because it was synthesized in 86% ee by Meyers *et al.*[75] Therefore the synthesis of **156** starting from racemic **194** was investigated.

Racemic lactone **194** was obtained by treatment of γ-butyrolactone with LDA followed by addition of allylbromide.[76] Reduction of the lactone by DIBALH gave a hemiacetal which could be converted into a mixture of methoxy acetals by treatment with MeOH in the presence of HCl. Ozonolysis of the allylic double bond and subsequent reduction of the ozonide by triphenylphosphine gave aldehyde **200** in a reasonable yield. This aldehyde could be transformed into **156** as shown in scheme 3.7. There are however two major drawbacks in this reaction pathway. First, the conversion of aldehyde **200** into acetal **156** proceeds in a moderate yield of 40% with the risk of racemization. Second, the costs will be high because of the low overall yield of 6% , and the use of the expensive starting compound **206**.

[75] Meyers, A. I.; Yamamoto, Y.; Mihelich, E. D.; Bell, R. A. *J. Org. Chem.* **1980**, *45*, 2792-2796.

[76] Herrmann, J. L.; Schlessinger, R. H. *J. Chem. Soc., Chem. Commun.* **1973**, 711-712.

scheme 3.10

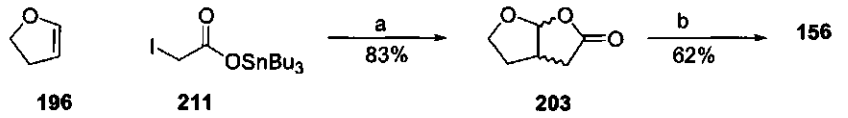


(a) LDA, allylbromide; (b) i) DIBALH, ii) MeOH, HCl; (c) i) O_3, ii) PPh_3; (d) TMSI, MeOH

3.2.4 Synthesis of racemic 2-methoxy-hexahydrofuro[2,3-*b*]furan from 2,3-dihydrofuran

The synthesis of racemic **156** could also be achieved in two steps starting from 2,3-dihydrofuran **196** and the easily prepared iodostannyl ester **211**. This radical reaction, published by Kraus *et al.*[77], could be easily scaled up to 100 gram, and proceeded in the high yield of 88%. The transformation of **203** into **156** is already described in § 3.2.1. The high yield, the cheap and easily available starting materials, and the short synthesis, makes this an interesting and useful reaction path for the preparation of racemic **156** on a large scale.

scheme 3.11



(a) AIBN, Δ; (b) i) DIBALH, ii) BF_3•etherate, MeOH

3.3 Conclusions

It is rather difficult to compare the methods that are discussed above because all methods have their own drawbacks. The introduction of a hexahydrofuro[2,3-*b*]furan moiety early in the reaction sequence of the total synthesis, requires the preparation of at least 50 gram of the natural

[77] Kraus, G. A.; Landgrebe, K. *Tetrahedron Lett.* **1984**, *25*, 3939-3942.

enantiomer of **156**. The use of an expensive chiral auxiliary in stoichiometric amounts and/or low overall yields makes routes laborious and/or expensive. For these reasons, the method discussed in § 3.2.2 and § 3.2.3 were abandoned. The best route to obtain enantiopure **156** is probably via ester **145-(3S)**, because of the reasonable overall yield (20-34%). The enzymatic preparation of ester **145-(3S)** can be done on a 10 g scale but the separation of the butyl- and methyl esters by preparative gas chromatography is time consuming.

The method of Kraus *et al.*[77] is very interesting, because it is short, gives a high yield, and can be carried out on a large scale. The only drawback is that is gives a racemate. This drawback could be circumvented as was shown in chapter 2, where the reaction of racemic **156** with the optically active enolether of *R*-(–)-carvone (ring B) gave only two diastereoisomers that could easily be separated. Although the most elegant approach would be to use optically active **156**, it proved to be much less laborious to use racemic **156**, and to separate the two diastereoisomers. Therefore this became the method of choice for our total synthesis of dihydroclerodin.

3.4 Experimental[78]

(±)-*cis*-,*trans*-(2-Methoxytetrahydro-3-furanyl)methyl 4-methylbenzenesulfonate (198).

To a stirred solution of **(±)-*cis*-,*trans*-**(2-methoxytetrahydro-3-furanyl)methanol **(197)**[66] (37.5 g, 284 mmol) in pyridine (75 mL) and $CHCl_3$ (75 mL) was added *p*-toluenesulfonyl chloride (81 g, 425 mmol) in small portions. After addition, the reaction mixture was stirred for an additional 2 h. Then water was added and the aqueous phase was extracted three times with $CHCl_3$. The combined organic layers were washed with brine and dried. After evaporation of the solvents, the last traces of pyridine were removed by azeotropic distillation with toluene. The remaining oil **198** (71 g, 249 mmol, 88%) was not purified any further. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.49 (m, 1H), 2.05 (m, 1H), 2.34 (s, 3H), 2.47 (m, 1H), 3.17 (s, 0.9H, *cis*) and 3.26 (s, 2.1H, *trans*), 4.75-4.18 (m, 4H), 4.75 (d, J = 1.1 Hz, 0.7H, *trans*), 4.80 (d, J = 4.6 Hz, 0.3H, *cis*), 7.34 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) (*trans*) δ 21.6 (q), 26.3 (t), 44.9 (d), 54.7 (q), 65.9 (t), 70.1 (t), 105.9 (d), 127.9 (d, 2C), 129.9 (d, 2C), 132.7 (s), 145.0 (s); (*cis*) δ 21.6 (q), 26.3 (t), 43.2 (d), 54.4 (q), 66.4 (t), 69.4 (t), 103.1 (d), 127.9 (d, 2C), 129.9 (d, 2C), 132.7 (s), 145.0 (s).

(±)-*cis*-,*trans*-(2-Methoxytetrahydro-3-furanyl)acetonitrile (199).

To a stirred solution of **198** (70 g, 245 mmol) in DMF (800 mL) was added NaCN (24 g, 490 mmol). The reaction mixture was heated at 70°C for 18 h. After this period the reaction mixture was poured into water (500 mL). The aqueous phase was extracted five times with ether. The combined organic layers were washed with brine and dried. After careful evaporation of the solvents, the residue was distilled under reduced pressure. First DMF was collected at 10 mbar, followed by **199** (28.1 g, 200 mmol, 81%) as a *cis*/*trans* mixture (bp 0.1 mbar, 79-82°C)

[78] See chapter 2, for general experimental.

(distillation was done from a water bath to prevent the temperature to rise above 100°C because above this temperature the product decomposed). An analytical sample of the *cis*- and *trans*-compound **199** was obtained after purification by flash chromatography (20% EA/PE). ^{1}H NMR ($CDCl_3$, 200 MHz) (*cis*) δ 1.30 (m, 1H), 2.10 (m, 1H), 2.42 (m, 3H), 3.29 (m, 3H), 3.90 (m, 2H), 4.82 (d, J = 3.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) (*cis*) δ 16.8 (t), 28.9 (t), 40.4 (d), 54.8 (q), 66.6 (t), 103.4 (d), 119.1 (s). ^{1}H NMR ($CDCl_3$, 200 MHz) (*trans*) δ 1.63 (m, 1H), 2.15-2.51 (m, 4H), 3.28 (s. 3H), 3.92 (m, 2H), 4.71 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) (*trans*) δ 20.2 (t), 29.1 (t), 41.9 (d), 54.7 (q), 66.0 (t), 107.5 (d), 118.1 (s).

(±)-*cis*-,*trans*-(2-Methoxytetrahydro-3-furanyl)acetaldehyde (200).

To a stirred solution of **199** (5.0 g, 35.5 mmol) in dry ether (60 mL) was slowly added a freshly prepared solution of DIBALH (11.0 mL, 61.7 mmol) in dry ether (60 mL) at 0°C. Stirring was continued for an additional h. After this period acetic acid (3.5 mL, 46 mmol) dissolved in water (100 mL) was added and the aqueous phase was extracted four times with ether. The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution, brine and dried. After careful evaporation of the solvents, **200** was obtained as a 7:3 mixture of *cis*- and *trans*-**200** as colorless oil (4.2 g, 29.2 mmol, 82%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.50 (m, 1H), 2.03-2.74 (m, 4H), 3.27 (s, 0.9H) and 3.30 (s, 2.1H), 3.90 (m, 2H), 4.67 (d, J = 0.89 Hz, 0.7H), 4.91 (d J = 4.4 Hz, 0.3H), 9.74 (t, J = 1.2 Hz, 0.7H), 9.77 (s, 0.3H). IR ν_{max} (neat) 2724 (CHO), 1725 (CHO) cm^{-1}.

(±)-2-Methoxyhexahydrofuro[2,3-*b*]furan (156).

To a stirred solution of **200** (4.0 g, 27.7 mmol) in dry CH_2Cl_2 (30 mL) and CH_3OH (0.2 g, 5.9 mmol) at 0°C was added one drop of TMSI. Stirring was continued for 3 h. After this period a saturated aqueous $NaHCO_3$ solution (5 mL) was added and the aqueous phase was extracted two times with CH_2Cl_2. The combined organic layers were washed with brine and dried. After careful evaporation of the solvents, a crude mixture of **156**, **201** and **202** was obtained. Distillation by Kugelrohr (3 mmHg, oven temperature 80°C) afforded **156** (1.90 g, 11.1 mmol, 40%), and **201** (1.8 mmol, 6%), according to NMR. This mixture could not be separated by flash chromatography. The remaining residue crystallized upon standing, and **202** was recrystallized from diisopropylether as a 3:1 mixture of two diastereoisomers, as a white powder (0.96 g, 4.0 mmol, 14%). NMR data of **156** are in accordance with the literature.[69]

The major diastereoisomer of **202** was separated from the mixture by flash chromatography (30% PE/EA). mp 90°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.75 (m, 4H), 2.04 (m, 2H), 2.25 (m, 2H), 2.80 (m, 2H), 3.81-4.01 (m, 4H), 5.40 (d, J = 5.8 Hz, 2H), 5.81 (d, J = 5.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 32.7 (t), 39.0 (t), 41.0 (d), 66.9 (t), 100.2 (d), 111.0 (d). HRMS calcd for $C_6H_9O_2$ 113.0603, found 113.0602 (m/e 242 was found but of to little intensity for HRMS measurement).

(±)-Tetrahydrofuro[2,3-*b*]furan-2(3*H*)-one (203).

A well stirred emulsion of **199** (9.6 g, 68.0 mmol) in an aqueous solution of NaOH (5M, 20 mL) was refluxed for 2.5 h until a clear solution was formed. The reaction mixture was cooled to rt,

followed by washing of the aqueous phase with ether (25 mL). Then the aqueous phase was acidified with concentrated HCl until pH 1, and stirred for an additional 1.5 h. After this period the aqueous phase was extracted five times with ethyl acetate. The combined organic layers were washed with brine and dried. After careful evaporation of the solvents, the residue was distilled under reduced pressure (Kugelrohr 0.2 mmHg, oven temperature 80°C) to give **203** (7.89 g, 61.6 mmol, 91%). NMR data are in accordance with the literature.[69]

(±)-2-Methoxyhexahydrofuro[2,3-*b*]furan (156).

To a stirred solution of **203** (10.0 g, 78 mmol) in dry toluene (40 mL) was slowly added DIBALH (1.5 M in toluene, 55 mL, 82 mmol) at –78°C. After addition, the reaction mixture was stirred for an additional 1.5 h at –78°C, followed by addition of dry MeOH (2.9 g, 90 mmol) together with BF_3-etherate (21 mL, 167 mmol) as quick as possible without raising the temperature above –60°C (~10 min). The reaction mixture was stirred for an additional 5 min and then poured into a large beaker with water (100 mL) and $NaHCO_3$ (50 g, 0.60 mol). The resulting slurry was stirred for 2 h, allowing the $NaHCO_3$ to react with the excess of BF_3•etherate. After this period, the aqueous phase was extracted three times with ether. The combined organic layers were washed with brine, and dried. After careful evaporation of the solvents a colorless oil was distilled (Kugelrohr 3 mmHg, oven temperature 80°C) and afforded **156** (7.0 g, 49 mmol, 62%) as a 1:2 mixture of diastereoisomers, along with the overreduced hexahydrofuro[2,3-*b*]furan **204** (1.1 g, 9.6 mmol, 12%). Further purification proved to be unnecessary. NMR data of **156** are in accordance with the literature.[69]

(**204**) ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.65 (m, 2H), 2.02 (m, 2H), 2.78 (m, 1H), 3.80 (m, 4H), 5.62, (d, J = 5.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 32.4 (t), 42.3 (d), 67.9 (t), 109.3 (d).

(±)-3-Allyldihydro-2(3*H*)-furanone (194).

To a stirred solution of diisopropylamine (10.0 g, 99 mmol) in dry THF (100 mL) was added n-BuLi (40 mL, 2.5 M in hexane, 100 mmol) at –10°C. Stirring was continued for an additional 30 min. Then the reaction mixture was cooled to –78°C. At this temperature γ-butyrolactone **136** (4.0 g, 60 mmol) was added slowly to the reaction mixture and stirred for an additional 1 h. After this period allylbromide (7.8 mL, 90 mmol) was slowly added at –78°C, and stirring was continued for 3 h, while the temperature was raised to –30°C. The reaction mixture was then quenched by addition of a saturated aqueous solution of NH_4Cl (10 mL), followed by extraction of the aqueous phase three times with ether. The combined organic layers were washed with an aqueous solution of HCl (4M, 10 mL), brine, and dried. After careful evaporation of the solvents, the residue was distilled under reduced pressure (bp. 57°-60°C, 1 mmHg) to give **194** as a colorless oil (5.0 g, 39.7 mmol, 66%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.98 (m, 1H), 2.29 (m, 2H), 2.61 (m, 2H), 4.27 (m, 2H), 5.13 (m, 2H), 5.78 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.7 (t), 34.3 (t), 38.8 (d), 66.5 (t), 117.7 (t), 134.4 (d), 178.8 (s).

(±)-3-Allyl-2-methoxytetrahydrofuran (210).

To a stirred solution of **194** (6.0 g, 47.2 mmol) in dry ether (90 mL) was added DIBALH (11.2 mL, 62.0 mmol) dissolved in dry ether (30 mL) at –78°C. After addition, stirring was continued for 2.5 h, followed by addition of $Na_2SO_4 \cdot H_2O$ (42 g) and ether (200 mL). Stirring was continued overnight, followed by addition of $MgSO_4$ (5 g). Then the reaction mixture was filtered over a glassfilter and the filter was washed thoroughly with ether. After careful evaporation of the solvent the remaining crude hemiacetal was dissolved in dry MeOH (10 mL) followed by addition of HCl gas (traces). After 15 min an aqueous solution of NaOH (15 mL, 4M) was added. Then the aqueous phase was extracted four times with ether. The combined organic layers were washed with brine and dried. After careful evaporation of the solvents, the residue was distilled under reduced pressure (bp. 38°-39°C, 2 mmHg) to give a 7:3 mixture of *cis*-and *trans*-**210** as a colorless oil (3.81 g, 26.8 mmol, 57%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.56 (m, 1H), 1.89-2.38 (m, 4H), 3.31 (s, 3H), 3.89 (m, 2H), 4.67 (s, 0.7H), 4.76 (d, J = 3.8 Hz, 0.3H), 5.03 (m, 2H), 5.76 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) (*trans*) δ 29.6 (t), 36.8 (t), 44.6 (d), 54.6 (q), 66.5 (t), 109.0 (d), 116.2 (t), 136.3 (d). ^{13}C NMR ($CDCl_3$, 50 MHz) (*cis*) δ 29.0 (t), 32.8 (t), 43.8 (d), 54.6 (q), 66.5 (t), 104.7 (d), 115.3 (t), 137.3 (d).

(±)-*cis*-,*trans*-(2-Methoxytetrahydro-3-furanyl)acetaldehyde (200).

A stirred solution of **210** (8.9 g, 62.7 mmol) in CH_2Cl_2 (350 mL) was purged through with ozone at –78°C until a pale bleu color appeared. Then nitrogen was purged through, followed by addition of PPh_3 (21.0 g, 80.2 mmol) at –78°C. The reaction mixture was allowed to come to rt and stirred overnight. After this period the solvent was evaporated and the residue was distilled quickly under reduced pressure (bp. 42°-45°C, 5 mmHg) yielding **200** as a *cis/trans* mixture as a colorless oil (6.5 g, 45.1 mmol, 72%). NMR data are in accordance with **200** obtained after reduction of nitrile **199**.

Tributyl((iodoacetyl)oxy)stannane (211)[79].

A mixture of iodoacetic acid (50 g, 269 mmol) and bistributylstannyl oxide (75.6 mL, 147.8 mmol) was heated for 10 min at 100°C. The condensed water was removed. The reaction mixture was then allowed to cool, followed by extraction with a mixture of petroleum ether (100 mL) and ethyl acetate (100 mL). The extract was dried with Na_2SO_4 and filtered. After evaporation of the solvents the crude stannyl ester was recrystallized from a mixture of EA/PE (15%, 400 mL) at –20°C, yielding **211** as white crystals (123 g, 259 mmol, 96%). NMR data are in accordance with the literature.[80]

(±)-Tetrahydrofuro[2,3-*b*]furan-2(3*H*)-one (203).[77]

A stirred solution of **211** (190 g, 0.40 mol), 2,3-dihydrofuran (84 g, 1.20 mol), and 5 mol % AIBN (3.28 g, 20 mmol) in benzene (1000 mL) was refluxed for 6 h. After this period the

[79] Anderson, H. H. *J. Org. Chem.* **1957**, *22*, 147-148.

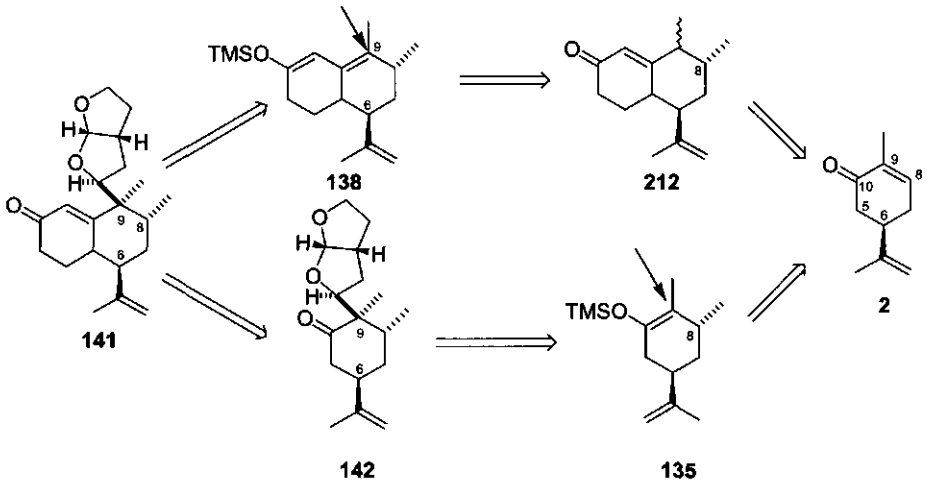
[80] Kraus, G. A.; Landgrebe, K. *Tetrahedron* **1985**, *41*, 4039-4046.

solvents were evaporated and the residue was washed three times with cold PE. The remaining solvent in the residue was evaporated. The reaction was repeated once more and the combined crude products were purified by distillation (Kugelrohr 0.04 mmHg, oven temperature 100°-110°C) to yield **203** as a colorless oil (84.6 g, 0.66 mol, 83%). NMR data are in accordance with the literature.[69]

4.1 Introduction[81]

The construction of the decalin moiety in clerodanes via Robinson annulation has been widely used, and the Wieland-Miescher ketone has been applied as starting material in many low-oxidized clerodane syntheses.[82] In the Wieland-Miescher ketone, C19 is not oxidized, so other Robinson annulations were studied for the construction of more functionalized clerodane skeletons.[83] A problem in the synthesis of natural clerodanes is also the introduction of chirality. It seemed to us that the latter problem could be solved by using carvone as a starting material and therefore we investigated several varieties of the Robinson annulation with functionalized carvone derivatives. In Chapter 2 we have shown that starting from R-(–)-carvone, cyclohexanones could be synthesized that are functionalized with the hexahydrofurofuran moiety as it is present in dihydroclerodin. It might be possible to use the same method for the introduction of the hexahydrofuro[2,3-*b*]furan moiety into the dienol silyl ether **213** (scheme 4.1), and therefore the possibilities to synthesize this compound starting from R-(–)-carvone, were investigated.

scheme 4.1



[81] Throughout this thesis the clerodane numbering according to figure 1.1 will be used in all discussions.

[82] (a) Tokoroyama, T.; Fujimori, K.; Shimizu, T.; Yamagiwa, Y.; Monden, M.; Iio, H. *Tetrahedron* **1988**, *44*, 6607-6622; (b) Kende, A. S.; Roth, B. *Tetrahedron Lett.* **1982**, *23*, 1751-1754; (c) Takahashi, S.; Kusumi, T.; Kakisawa, H. *Chem. Lett.* **1979**, 515-518; (d) Kawano, H.; Itoh, M.; Katoh, T.; Terashima, S. *Tetrahedron Lett.* **1997**, *38*, 7769-7772; (e) Takao, K.; Kobayashi, S. *Tetrahedron Lett.* **1997**, *38*, 6685-6688; (f) Almstead, J. I.; Demuth Jr., T. P.; Ledoussal, B. *Tetrahedron: Asymm.* **1998**, *9*, 3179-3183; (g) Sharma, A. S.; Gayan, A. K. *Tetrahedron* **1985**, *41*, 4581-4592; (h) Sarma, A. S.; Chattopadhyay, P. *J. Org. Chem.* **1982**, *47*, 1727-1731; (i) Bruner, S. D.; Radeke, H.; Tallarico, J. A.; Snapper, M. L. *J. Org. Chem.* **1995**, *60*, 1114-1115.

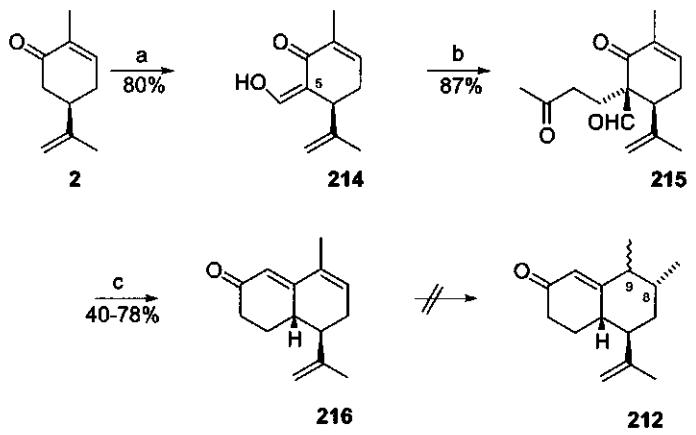
[83] Luteijn, J. M.; van Doorn, M.; de Groot, A. *Tetrahedron Lett.* **1980**, *21*, 4127-4128.

A second possible route to functionalized decalins might be opened up via Robinson annulation of ketones that already contain the necessary hexahydrofuro[2,3-*b*]furanyl and methyl substituents. Therefore also the annulation of heavily substituted carvone derived ketones like **142** was investigated.

4.2 Annulation reactions of β-keto aldehydes with methyl vinyl ketone

In a first attempt to synthesize the decalin system of dihydroclerodin, R-(–)-carvone was formylated using NaH and ethylformate to activate C5 for a Michael addition. Methyl vinyl ketone entered the molecule antiperiplanar to the isopropenyl and gave diketone **137** in high yield. The annulation and simultaneous deformylation of this compound with KOH yielded the dienone **215** in 78% yield.[84] Next, a methyl group needed to be introduced at C8 and the position at C9 needed to be activated for the introduction of the hexahydrofuro[2,3-*b*]furan moiety. For the 1,6-conjugate addition several Cu(I)-salts were studied (CuBr•Me_2S, CuI) but no 1,6-addition products were obtained, only small amounts of 1,4- and 1,2-addition products were observed.[85,86] It seems that the methyl group at C9 and/or the isopropenyl group at C6 hinder the 1,6-addition.[87] To our knowledge, also no examples are known in literature of 1,6-additions to a dienone with a methyl group at the 5-position of the dienone system like in our system.

scheme 4.2



(a) NaH, HCO_2Et; **(b)** Et_3N, KOH, methyl vinyl ketone, 0°C; **(c)** KOH, MeOH

[84] After we had finished this work the same annulation to carvone was published, Beauhaire, J.; Ducrot, P.-H.; Simon, I. *Synth. Comm.* **1995**, *25*, 3015-3025.

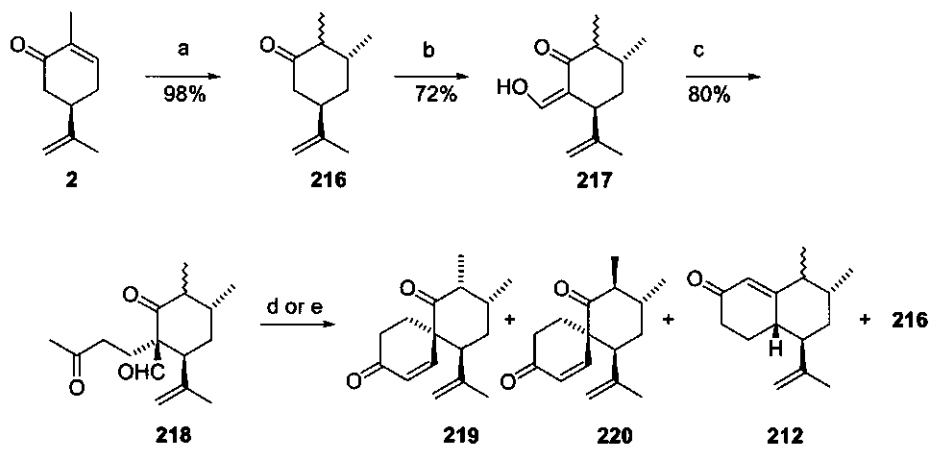
[85] Jansen, B. J. M.; Kreuger, J. A.; de Groot, A. *Tetrahedron* **1989**, *45*, 1447-1452.

[86] Marshall, J. A.; Roebke, H. *J. Org. Chem.* **1966**, *31*, 3109-3113.

[87] Marshall, J. A. R., R. A.; Hirsch, L. K.; Phillippe, M. *Tetrahedron Lett.* **1971**, *41*, 3795-3798.

An obvious alternative reaction path would be to introduce the methyl group first, followed by Robinson annulation, so that the 1,6-addition could be avoided (scheme 4.3). The same method was chosen as in the previous reaction path, except that now the methyl group was introduced first by a 1,4-addition in high yield. No big difference in reaction time and yield was observed for the formylation of **216** compared with the formylation of carvone. The Michael addition was performed at room temperature instead of at 0°C as in the previous scheme and also proceeded in good yield. The annulation however gave at the most a 20% yield of decalone **212**, together with the retro-Michael product **216** and traces of the spiro compounds **219**, **220**. An explanation for the failure of this annulation can be found in the steric hindrance which occurs during the ring closure. A clear 1,3-diaxial interaction of the methyl group at C8 and the incoming side chain will hinder the ring closure, and the competing retro-Michael addition prevails (see § 4.3). When neutral Knoevenagel conditions were used, **218** was smoothly converted into a 2:7 mixture of diastereoisomeric spiro compounds **219** and **220** in 70% yield, and almost no retro-Michael reaction or decalin formation was observed under these reaction conditions. Apparently the decalin formation encounters steric problems and since an aldehyde group offers an alternative reaction possibility, this becomes the route of choice.

scheme 4.3



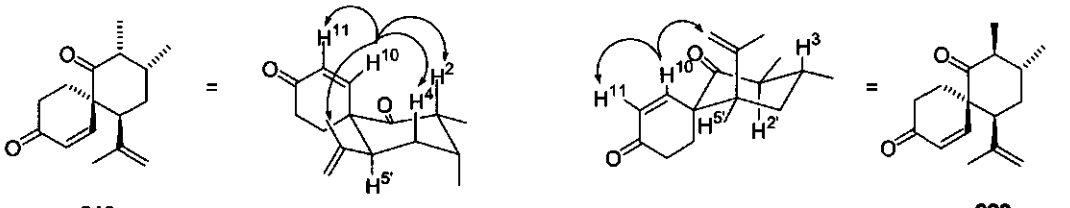
2 **216** **217** **218** **219** **220** **212**

(a) MeMgI, CuBr•Me_2S **(b)** NaH, HCO_2Et; **(c)** Et_3N, KOH, methyl vinyl ketone, rt; **(d)** KOH, MeOH; **(e)** pyrrolidine, AcOH, pH 7

The structure of compound **219**, **220** were elucidated by 2D-NMR. A clear NOE difference interaction was observed between H10 and H2, H4, H11 and the CH_3 at the isopropenyl group, which suggests structure **219** as drawn in figure 4.1. The equatorial position of the isopropenyl group was further proven by the coupling constants of H5', which were 13.6 Hz and 3.5 Hz respectively, indicating an axial-axial and an axial-equatorial coupling. In compound **220** a clear NOE difference was observed between H10 and H11 and the CH_2 of the

isopropenyl group, but no NOE difference was observed for H2 and H4. This indicated an axial position of the isopropenyl group, which was supported by the small coupling constants of H5'.[88]

figure 4.1

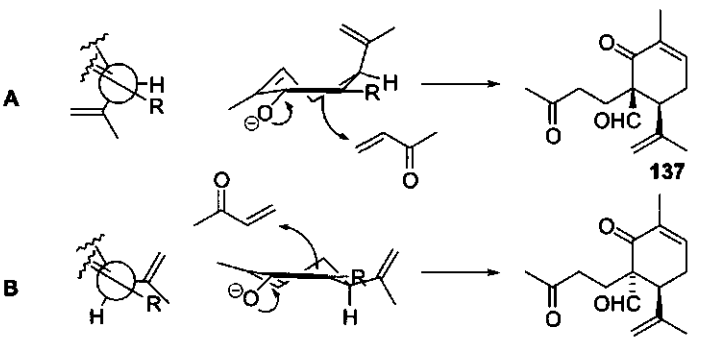


219 **220**

4.3 Steric considerations around the Robinson annulation

The Michael addition of methyl vinyl ketone to carvone is rather selective. This can be explained by assuming that in the transition state the preferred conformation is such that the isopropenyl and the R group are in a *trans* quasi di-axial relationship and that the bulkiness of these groups determines the preferred approach of the methyl vinyl ketone. This is depicted as pathway A (figure 4.2) in which there is less steric hindrance between the isopropenyl and group R (CHO) than in pathway B.[89] A similar selectivity was found in the alkylation reactions of carvone by Gesson *et al.*[90]

figure 4.2[91]



137

[88] The signal of H4 gives an small multiplet, $W_{1/2}$ ~8 Hz.

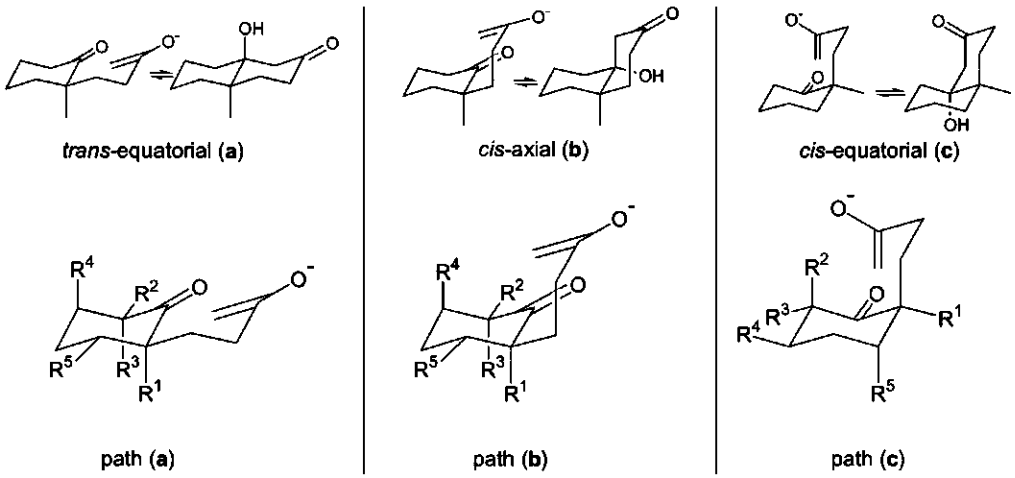
[89] Tomioka showed a similar model Tomioka, K.; Yasuda, K.; Kawasaki, H.; Koga, K. *Tetrahedron Lett.* **1986**, *27*, 3247-3250.

[90] Gesson, J.-P.; Jacquesy, J.-C.; Renoux, B. *Tetrahedron* **1989**, *45*, 5853-5866.

[91] The ▬ in figure 4.2 is a double bond.

The ring closure is a sensitive reaction, and steric factors largely control this reaction. Small differences in substituents can give a different outcome in reaction products as is nicely illustrated by Nussbaumer.[92] The outcome of the ring closure reaction can be predicted using the three chair like intermediates depicted in figure 4.3. When all three pathways have steric interactions or when unlikely conformations will be necessary during the ring closure, the ring closure does not take place, under standard basic conditions. The *trans*-equatorial pathway (**a**) leads to the thermodynamic more stable *trans*-decalin and this is the preferred pathway when there is no substituent or a very small substituent (CN), at the angular position (R^1). When R^1 is increased in size from H, CN to CHO, CH_3 or CO_2CH_3 path (**a**) becomes unfavorable for the cyclization.[92,96,97] Steric hindrance between R^4 and the enolate gives rise to a clear 1,3-diaxial interaction in path (**b**) and can prevent the reaction following this path. An axial position of a large substituent in position of R^5 and an axial position of the enolate gives an unlikely conformation of the cyclohexanone and can prevent cyclization following path (**c**).

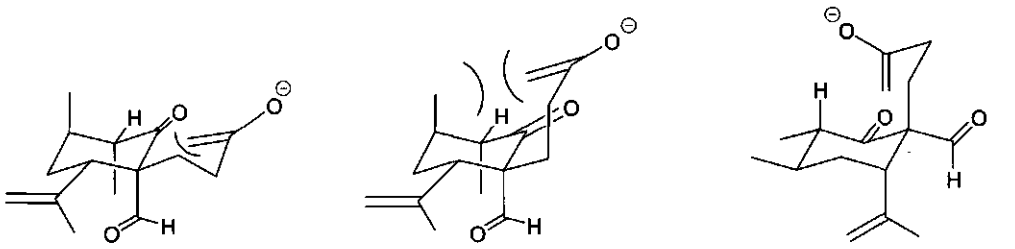
figure 4.3



These considerations can be used to explain the results of the reaction described in scheme 4.3. As can be seen in figure 4.4, the steric hindrance between the aldehyde group (R^1) and the enolate will prevent cyclization along path (**a**), the steric hindrance between the methyl group (R^4) and the enolate will prevent path (**b**), and the axial position of the isopropenyl group (R^5) and the enolate will prevent cyclization along path (**c**). Consequently cyclization takes place with the aldehyde to give the spiro compounds **219,220**.

[92] Nussbaumer, C. *Helv. Chim. Acta* **1990**, *73*, 1621-1636.

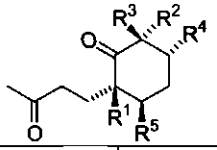
figure 4.4



trans-equatorial (**a**) *cis*-axial (**b**) *cis*-equatorial (**c**)

More data about the cyclization reaction of the Robinson annulation are collected in table 4.1. In this table we see that most reactions that are performed in good yield have no or little steric hindrance following one of the pathways. Also can be observed that when R^1 is a nitrile and Knoevenagel conditions are applied, the annulation is performed in reasonable to good yield, even when there is some steric hindrance in all three pathways. The Knoevenagel conditions for ring closure usually imply higher temperatures so moderate steric hindrance can be overcome. Furthermore, the nitrile can not, as the aldehyde does, serve as an alternative place for ring closure to give spiro compounds like **219**. Knoevenagel conditions not only catalyze ring closure, but when R^1 is a nitrile also a Michael reaction can take place under these conditions. This means that the retro-Michael products can react again with methyl vinyl ketone to give a higher yield of the annulated product.

table 4.1



	R^1	R^2	R^3	R^4	R^5	(a)[k]	(b)[k]	(c)[k]	Yield[a].(%)
1	CHO	CH_3	-	-	i-Propenyl	–[b]	+	–[d]	40-78
2	CN	CH_3	-	-	i-Propenyl	+[e]	+	–[d]	85[93]
3	CHO	CH_3	H	CH_3	i-Propenyl	–[b]	–[c]	–[d]	low
4	CHO	H	CH_3	CH_3	i-Propenyl	–[b]	–[c]	–[d]	low
5	CN	CH_3	H	CH_3	i-Propenyl	+[e]	–[c]	–[d]	82[93]
6	CN	H	CH_3	CH_3	i-Propenyl	–[f]	–[c]	–[d]	---[94,93]
7	CN	CH_3	CH_3	H	i-Propenyl	–[f]	+	–[d]	94[93]
8	CN	CH_3	CH_3	CH_3	i-Propenyl	–[f]	–[c]	–[d]	O, 84[i,93]
9	CN	CH_3	CO_2Et	H	H	–[f]	+	±[g]	~81[95]
10	CN	CO_2Et	CH_3	H	H	–[f]	+	±[g]	~81
11	H	CH_3	CH_3	H	H	+	+	±[g]	good[92]
12	CO_2Me	H	H	H	H	–[b]	+	±[h]	good[96]
13	CH_3	H	H	H	H	–[b]	+	±[g]	60[97]
14	CN	CH_3	H	H	H	+[e]	+	±[g]	good[92]
15	CN	H	CH_3	H	H	–[f]	+	±[g]	good[92]
16	CH_3	H	H	i-Propenyl	H	–[b]	–[h,c]	+	90[98]
17	CH_3	H	H	i-Propenyl	CN	–[b]	–[h,c]	+	90[98]
18	CH_3	H	H	H	CH_3	–[b]	+	±	80[99]
19	CHO	CH_3	H	H	i-Propenyl	–[b]	+	–[d]	~80[84]
20	CHO	H	CH_3	H	i-Propenyl	–[b]	+	–[d]	~80[84]

(a) All yields are obtained under standard basic conditions, using KOH or MeONa as a base, unless stated otherwise; (b) Steric hindrance between R^1 and enolate; (c) Steric hindrance between R^4 and enolate; (d) 3-Oxobutyl group and isopropenyl group are in the axial position, so this conformation is not very likely; (e) Steric hindrance between H/CN and enolate is not very large; (f) Steric hindrance between R^3 and enolate, and little steric interaction between R^1 and the enolate; (g) 3-Oxobutyl group is in the axial position, so this conformation is not very likely; (h) R^1 and isopropenyl group are in the axial position, so this conformation is not very likely; (i) Yield obtained using Knoevenagel conditions for ring closure; (k) Pathways see figure 4.3 and figure 4.4. – indicates that the ring closure reaction will not prefer to follow this path, + indicates that the ring closure reaction can follow this path, ± indicates that the ring closure reaction can follow this path but if possible will choose an other path.

---

[93] Jansen, B. J. M.; Hendrikx, C. C. J.; Masalov, N.; Stork, G. A.; Meulemans, T. M.; Macaev, F. Z.; de Groot, A. accepted *Tetrahedron* **2000**.

[94] This compound is not formed, only entry 5 was observed.

[95] Meyer, W. L.; Goodwin, T. E.; Hoff, R. J.; Sigel, C. W. *J. Org. Chem.* **1977**, *42*, 2761-2769.

[96] Spencer, T. A.; Schmiegel, K. K.; Williamson, K. L. *J. Am. Chem. Soc.* **1963**, *85*, 3785-3793.

[97] Marshall, J. A.; Fanta, W. I. *J. Org. Chem.* **1964**, *29*, 2501-2505.

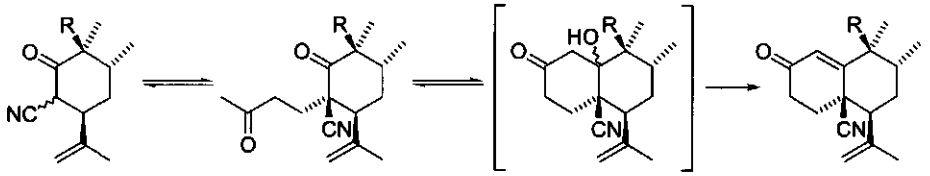
[98] Verstegen-Haaksma, A. A.; Swarts, H. J.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **1994**, *50*, 10073-10082.

[99] Duhamel, P.; Dujardin, G.; Hennequin, L.; Poirier, J. M. *J. Chem. Soc., Perkin Trans. I* **1992**, 387-396.

4.4 Annulation reactions of α-cyano ketones with methyl vinyl ketone

In recent experiments in our laboratory we have investigated several α-cyano ketones derived from carvone as chiral synthons for the synthesis of clerodanes.[93] The Michael addition of methyl vinyl ketone to the highly substituted cyclohexanones **224a-c** still can be realized using standard basic conditions, but the ring closure of **225a-c** under strongly basic conditions (1 eq. NaOMe in benzene), results in a retro-Michael reaction. However, in all cases the ring closure could be achieved using Knoevenagel conditions. In these reactions the intermediate β-hydroxyl ketones were not, or could not be isolated and the reaction proceeded smoothly to the enones **226a-c**. In all cases the stereoselectivity of the Michael addition was determined by the isopropenyl group (figure 4.2), and so the final ring closed product had the cyano group, the isopropenyl group and the R-substituent at C9 in a *cis*-relationship, which makes these compounds unsuitable as intermediates for the synthesis of *trans*-clerodanes.

scheme4.4

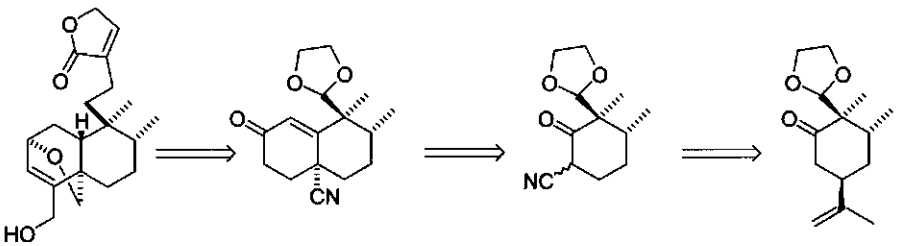


224a R=dioxolanyl
224b R=furofuranyl
224c R=methyl

225a-c **226a-c**

This stereochemical result was not unexpected and these reactions were carried out in the first place to establish the scope of the annulation reaction. Nevertheless these reactions were studied also to develop suitable routes for the synthesis of ring A bridged clerodanes like brevifloralactone (**223**)[100] and for this purpose also the α-cyano ketones without an isopropenyl substituent were investigated (scheme 4.5).

scheme 4.5

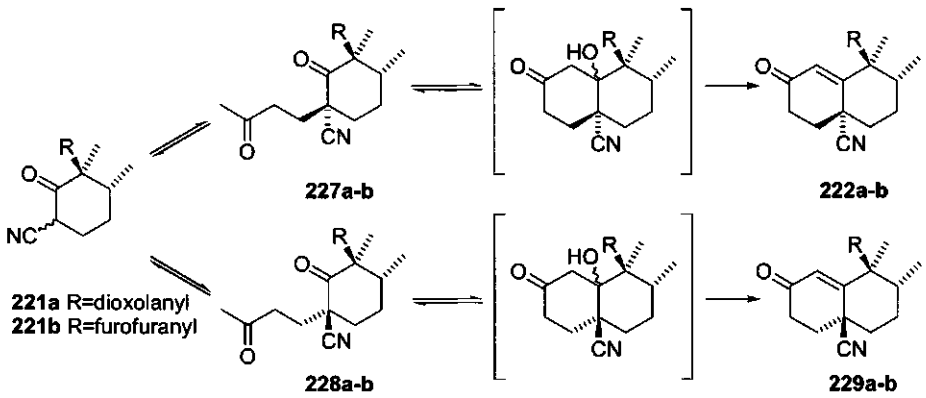


223 **222a** **221a** **158**

[100] Cuevas, G.; Collera, O.; Garcia, F.; Gardenas, J.; Maldonado, E.; Ortega, A. *Phytochemistry* **1987**, *26*, 2019-2021.

It was reasoned that removal of the isopropenyl group would make the R group in compounds **221a-b** the determining factor in the stereoselectivity of the Michael addition. The large R group, which will be in an equatorial position, brings the methyl group at C9 in an axial position and in this way it will block the approach of methyl vinyl ketone from the α-side. The final ring closed product then will have the cyano group and the R group in a *trans*-relationship as is found in *trans*-clerodanes.

scheme 4.6



However, it turned out that a mixture of Michael addition products was obtained. In the case when R=dioxolanyl these products could be separated and both isomers were subjected to Knoevenagel ring closure conditions. The desired isomer **227a** gave a smooth reaction to the cyclized product **222a**. The other isomer **228a** gave, after a much longer reaction time, a mixture of **222a** and **229a**. The obtained mixture of **227b** and **228b** (R=hexahydrofuro[2,3-*b*]furanyl) could not be separated, but when it was submitted to Knoevenagel conditions only enone **222b** was formed. The outcome of these two reactions strongly suggest that under Knoevenagel conditions a retro-Michael-Michael reaction can take place. This was confirmed by an experiment in which an excess of ethyl vinyl ketone was added to the cyclization reaction of compound **228a** under Knoevenagel conditions. Together with the cyclized compounds **222a** and **229a**, a small amount of the ethyl vinyl ketone adduct was found.[101] A one pot reaction for the addition-cyclization-dehydration was carried out with the ketones **224c** and **221a-b**. It proved indeed possible to obtain the enones in good yield and with the desired stereochemistry. In practice it turned out that a higher overall yield could be obtained in a two step procedure, first a Michael addition under basic conditions followed by a ring closure under Knoevenagel conditions. Separation of the diastereomeric mixture of the two Michael adducts was not necessary, because during ring closure a retro-Michael-Michael addition will epimerize the

[101] This compound did not give any ring closed product, probably because the ethyl vinyl ketone addition product is too much hindered for ring closure, because of the extra methyl group in the molecule.

configuration at C5, and almost only the *trans*-related decalin was obtained. An explanation for the different speed of ring closure can be given according to the reasoning followed in § 4.3.

4.4 Conclusions

Several attempts did not lead to a suitable synthesis of decalin **212** in good yield. It was therefore decided to first introduce the hexahydrofuro[2,3-*b*]furan moiety in ring B and to study the annulation of compound **142** (scheme 4.1). It ultimately turned out that only α-cyano ketones could be annulated in good yield but with the wrong stereochemistry at C5 for the synthesis of dihydroclerodin. Removal of the isopropenyl group and annulation of the resulting α-cyano ketones solved these stereochemical problems but at the same time it closed the possibility to introduce a functional group at C6. Therefore other annulation methods, which are described in chapter 5, were investigated for the synthesis of dihydroclerodin.

4.5 Experimental[102]

(5*S*)-6-(Hydroxymethylene)-5-isopropenyl-2-methyl-2-cyclohexen-1-one (214).

To a stirred suspension of NaH (6.0 g, 50% in mineral oil, 160 mmol) in dry ether (250 mL) was slowly added a solution of R-(–)-carvone (20.0 g, 133 mmol) and ethylformate (20.0 g, 270mmol). After addition of ~5 mL, no gas was evolved, therefore EtOH (0.5 mL) was added to start the reaction. After the reaction had started the remaining solution of carvone was added dropwise. Stirring was continued for an additional 12 h. After this period the reaction was quenched by addition of EtOH (5 mL), followed by water (50 mL). After separation of the two phases the organic layer was extracted twice with an aqueous solution of NaOH (100 ml, 0.5 M). The combined aqueous layers were acidified with an aqueous solution of HCl (4 M) until pH 1. The acidic aqueous phase was extracted three times with ether. The combined organic layers were washed two times with brine, dried, and evaporated, to give **214** (19.6g, 109 mmol, 82%). $[\alpha]_D$ –9.73 (c = 4.3); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.69 (s, 3H), 1.85 (s, 3H), 2.38-2.46 (m, 2H), 3.26 (t, *J* = 7.2 Hz, 1H), 4.77 (q, *J* = 0.8 Hz, 1H), 4.84 (q, *J* = 1.6 Hz, 1H), 6.49 (ddd, *J* = 1.4, 3.0, 4.4 Hz, 1H), 7.45 (brs, 1H), 14.50 (brs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.4 (q), 19.6 (q), 29.1 (t), 41.8 (d), 109.7 (s), 113.7 (t), 134.6 (s), 141.2 (d), 145.6 (s), 169.2 (d), 189.3 (s); IR ν_{max} (neat) 3419, 3077, 2929, 2888, 1644, 1627, 1570, 1377, 1208, 1050, 898 cm^{-1}; MS m/z (relative intensity) 178 (M^+, (70), 163 (21), 135 (25), 109 (100), 91 (30), 41 (14), 39 (20); HRMS calcd for $C_{11}H_{14}O_2$ (M^+) 178.0994, found 178.0991.

(1*S*,6*S*)-6-Isopropenyl-3-methyl-2-oxo-1-(3-oxobutyl)-3-cyclohexene-1-carbaldehyde (137)

To a stirred solution of **214** (19.5 g, 109 mmol) and Et_3N (15 g, 148 mmol) in ethyl acetate (250 mL) at 0°C was added methyl vinyl ketone (10.5 g, 150 mmol) followed by three pellets of KOH. Stirring was continued for an additional 3.5 h followed by addition of an aqueous solution of HCl

[102] See chapter 2, for general experimental.

(1 M). The aqueous phase was extracted three times with ether. The combined organic layers were washed two times with brine, dried, and evaporated, to give **137** (25.1g, 94.8 mmol, 87%) as a smelly yellow oil. The product was not purified any further and used in the next reaction. $[\alpha]_D$ –68.6 (c = 4.5); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.63 (s, 3H), 1.77 (t, J = 1.6 Hz, 3H), 2.07 (s, 3H), 2.03-2.43 (m, 5H), 2.70-2.79 (m, 1H), 2.81-2.84 (m, 1H), 4.62 (s, 1H), 4.79 (t, J = 1.3 Hz, 1H), 6.85 (t, J = 1.6 Hz, 1H), 9.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.6 (q), 22.3 (q), 25.9 (t), 28.4 (t), 29.7 (q), 37.8 (t), 49.2 (d), 60.1 (s), 115.1 (t), 134.5 (s), 142.8 (d), 143.7 (s), 198.4 (s), 202.6 (d), 207.2 (s); IR ν_{max} (tetra) 3087, 2977, 2929, 2851, 1727, 1669, 1659, 1435,1360, 1295, 1165, 1074, 1040, 904, 854, 839 cm^{-1}; MS m/z (relative intensity) 248 (11), 220 (22), 163 (17), 162 (37), 161 (20), 149 (51), 147 (32), 135 (13), 121 (82), 109 (13), 107 (10), 105 (13), 91 (22), 82 (100), 77 (16), 55 (13), 43 (50), 41 (17), 39 (15); HRMS calcd for $C_{15}H_{20}O_3$ (M^+) 248.1416, found 248.1416.

(4a*S*,5*R*)-5-Isopropenyl-8-methyl-4,4a,5,6-tetrahydro-2(3*H*)-naphthalenone (215).

To a stirred solution of **137** (2.0 g, 8.0 mmol) in MeOH at 0°C was added an aqueous solution of KOH (8.0 g in 10 mL H_2O). After stirring for 1 h, water was added. The aqueous phase was extracted three times with ether. The combined organic layers were washed with brine, dried, and evaporated. The residue was distilled under reduced pressure (Kugelrohr 0.02 mmHg, oven temperature 170°C), to give **215** (1.27g, 6.28 mmol, 78%) as a slightly yellow oil which crystallized upon standing, mp 70-71°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.49 (m, 1H), 1.70 (s, 3H), 1.84 (s, 3H), 1.98-2.49 (m, 7H), 4.82 (m, 2H), 5.95 (bs, 1H), 5.14 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.1 (q), 19.3 (q), 27.7 (t), 31.8 (t), 37.8 (t), 38.0 (d), 48.7 (d), 113.5 (t), 122.0 (d), 131.7 (s), 136.7 (d), 145.8 (s), 159.1 (s), 200.8 (s).

(3*R*,5*R*)-5-Isopropenyl-2,3-dimethylcyclohexanone (216).

To a mechanically stirred solution of CuBr•Me_2S (1.1 g, 5.1 mmol), HMPA (15 mL), and dry THF (120 mL) at –78°C, was added freshly prepared MeMgI (45 mL, 3M solution in ether). After addition stirring was continued for an additional 1 h, followed by addition of R-(–)-carvone (12.0 g, 80.0 mmol) at –78°C. Stirring was continued for 4 h. After this period the reaction was quenched by addition of an aqueous solution of HCl (150 mL, 1 M). The aqueous phase was extracted three times with ether. The combined organic layers were washed with brine, dried, and evaporated. The residue was distilled under reduced pressure (13 mmHg, 99°-100°C), to give **216** (12.1 g, 77.8 mmol, 97 %) as a colorless oil and as a mixture of diastereoisomers. An analytical sample of **216** was obtained after purification by flash chromatography (10% EA/PE).

Major isomer: ^{1}HNMR ($CDCl_3$, 200 MHz) δ 0.79 (d, J = 7.2 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H), 1.70 (s, 3H), 1.78-1.90 (m, 3H), 2.12-2.34 (m, 4H), 4.72 (brs, 1H), 4.73 (brs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.7 (q), 13.7 (q), 20.3 (q), 36.0 (d), 37.5 (t), 40.8 (d), 46.4 (t), 48.1 (d), 109.5 (t), 147.4 (s), 212.6 (s); IR ν_{max} (neat) 3083, 2962, 2924, 2871, 1710, 1447, 1379, 986, 902 cm^{-1}; MS m/z (relative intensity) 166 (75), 123 (28), 109 (31), 97 (45), 96 (25), 95 (88), 83 (46), 69 (100), 55 (22), 41 (45); HRMS calcd for $C_{11}H_{18}O$ (M^+) 166.1358, found 166.1353.

Minor isomer: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.99 (d, J = 6.2 Hz, 3H), 1.04 (d, J = 6.6 Hz, 3H), 1.78-1.90 (m, 3H), 2.12-2.34 (m, 4H), 4.70 (brs, 1H), 4.79 (brs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.2 (q), 12.8 (q), 21.6 (q), 34.7 (d), 34.9 (t), 40.5 (d), 43.8 (t), 51.3 (d), 111.4 (t), 147.3 (s), 212.7 (s); IR ν_{max} (neat) 3077, 2971, 2924, 2870, 1715, 1447, 1380, 1228, 1167, 986, 894 cm^{-1}; MS m/z (relative intensity) 166 (78), 151 (11), 123 (21), 109 (27), 97 (35), 96 (30), 95 (83), 83 (47), 69 (100) 55 (32), 41 (37); HRMS calcd for $C_{11}H_{18}O$ (M^+) 166.1358, found 166.1355.

(3*S*,5*R*)-2-(Hydroxymethylene)-3-isopropenyl-5,6-dimethylcyclohexanone (217).

The formylation was performed in a similar way as for compound **214**. After stirring for 24 h **216** (4.5 g, 27.1 mmol) was converted to give a 7:2 mixture of diastereoisomers **217** (4.1 g, 20.9 mmol, 77%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (d, J = 7.0 Hz, 0.6H), 0.96 (d, J = 6.2 Hz, 2.4H), 1.06 (d, J = 7.2 Hz, 0.6H), 1.17 (d, J = 7.0 Hz, 2.4H), 1.35-2.00 (m, 4H), 1.78 (s, 3H), 3.07 (m, 1H), 4.52 (bs, 1H), 4.88 (bs, 1H), 8.69 (d, J = 1.6 Hz, 1H), 14.61 (d, J = 1.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.6 (q), 20.0 (q), 21.5 (q), 30.3 (d), 33.2 (t), 40.1 (d), 42.3 (d), 109.5 (s), 113.9 (t), 148.4 (s), 185.1 (s), 192.0 (d). HRMS calcd for $C_{12}H_{18}O_3$ (M^+) 194.1307, found 194.1303.

(1*S*,4*R*,6*S*)-6-Isopropenyl-3,4-dimethyl-2-oxo-1-(3-oxobutyl)cyclohexanecarbaldehyde (218).

Michael addition of methyl vinyl ketone was performed at rt following a similar procedure as for compound **137**. After stirring for 18 h **217** (3.7 g, 19.2 mmol) was converted to give **218** (4.9 g, 18.6 mmol, 97%) as a mixture of two diastereoisomers and as a white solid. An analytical sample was recrystallized from diisopropylether, to give colorless crystals. mp 40°-42°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.04 (d, J = 5.8 Hz, 3H), 1.06 (d, J = 6.4 Hz, 3H), 1.64 (s, 3H), 1.61-2.30 (m, 8H), 2.04 (s, 3H), 2.62 (m, 1H), 4.36 (bs, 1H), 4.86 (m, 1H), 10.15 (d, J = 0.8 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.5 (q), 20.6 (q), 24.5 (q), 29.2 (t), 30.0 (q), 32.7 (t), 34.2 (d), 37.8 (t), 48.2 (d), 50.9 (d), 60.2 (s), 114.0 (t), 144.8 (s), 205.1 (d), 206.9 (s), 214.5 (s). HRMS calcd for $C_{16}H_{24}O_3$ (M^+) 264.1725, found 264.1726.

(4a*S*,5*R*,7*R*)-5-Isopropenyl-7,8-dimethyl-4,4a,5,6,7,8-hexahydro-2(3*H*)-naphthalenone (212).

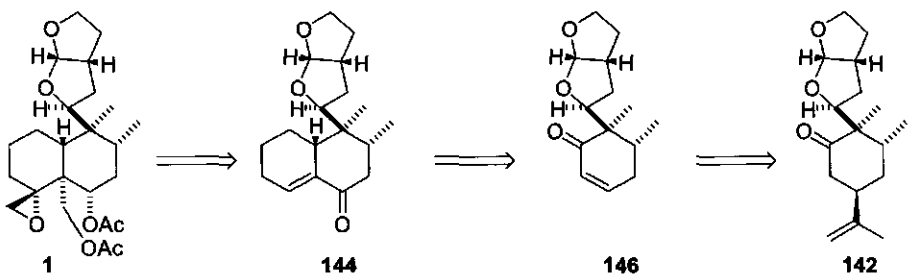
The Robinson annulation of **218** was performed following the same procedure as for **9**. After stirring for 12 h **218** (5.0 g, 18.9 mmol) was converted, to give a 7:3 mixture of diastereoisomers **212** (0.83 g, 3.8 mmol, 20%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.55 (d, J = 7.1 Hz, 0.9H), 0.73 (d, J = 7.1 Hz, 2.1H), 0.82 (d, J = 6.8 Hz, 0.9H), 1.00 (d, J = 7.3 Hz, 2.1H), 1.01-2.48 (m, 10H), 1.48 (bs, 0.9H), 1.46 (bs, 2.1H), 4.56 (m, 2H), 5.61 (bs, 0.3H), 5.66 (d, J = 2.0 Hz, 0.7H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.1 (q), 15.4 (q), 18.3 (q), 18.4 (q), 19.9 (q), 21.2 (q), 26.0 (t), 26.6 (t), 31.9 (t), 34.7 (d), 35.5 (d), 35.6 (t), 35.6 (d), 36.4 (t), 38.7 (t), 40.6 (d), 42.0 (d), 45.2 (d), 47.0 (d), 47.2 (d), 112.3 (t), 112.4 (t), 124.1 (d), 126.5 (d), 146.5 (s), 146.6 (s), 168.1 (s), 168.9 (s), 199.9 (s), 200.0 (s).

(2*R*,3*R*,5*S*,6*R*)-5-Isopropenyl-2,3-dimethylspiro[5.5]undec-7-ene-1,9-dione (219)
(2*S*,3*R*,5*S*,6*R*)-5-Isopropenyl-2,3-dimethylspiro[5.5]undec-7-ene-1,9-dione (220).

To a stirred solution of pyrrolidone (0.69 ml, 8.3 mmol) and acetic acid (~0.5 ml) of pH 7, was added **218** (2.0 g, 7.6 mmol). The reaction mixture was refluxed for 30 min. After this period the reaction mixture was added to water (50 mL).The aqueous phase was extracted three times with ether. The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (20% EA/PE), to give first the **219** (0.30 g, 1.2 mmol, 16%) (isopropenyl is in equatorial position). mp 140-141°C. ^{1}H NMR (C_6D_6, 400 MHz) δ 0.70 (d, J = 7.2 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H), 1.23 (ddd, J = 14.1, 3.5, 2.2 Hz, 1H), 1.51 (bs, 3H), 1.89 (m, 2H), 2.01 (ddd, 13.9, 13.9, 4.8 Hz, 1H), 2.22 (m, 1H), 2.33 (dd J = 13.6, 3.5 Hz, 1H), 2.43 (m, 2H), 3.14 (ddd, J = 17.3, 14.1, 5.5 Hz, 1H), 4.64 (s, 1H), 4.78 (bs, 1H), 6.00 (d, 10.4 Hz, 1H), 6.59 (dd, J = 10.4, 2.2 Hz, 1H). ^{13}C NMR (C_6D_6, 100 MHz) δ 12.6 (q), 13.7 (q), 21.8 (q), 29.1 (t), 34.4 (t), 35.8 (t), 36.9 (d), 46.2 (d), 51.7 (d), 55.1 (s), 115.0 (t), 130.5 (d), 144.7 (s), 146.4 (d), 197.5 (s), 207.6 (s). $[\alpha]^{20}_D$ + 69.2 (c 0.45, $CDCl_3$). Anal. calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.74; H, 9.24; followed by the **220** (1.07 g, 4.35 mmol, 57%) (isopropenyl is in axial position). mp 97-98°C. ^{1}H NMR (C_6D_6, 400 MHz) δ 0.83 (d, J = 6.4 Hz, 3H), 1.13 (d, J = 6.4 Hz, 3H), 1.28-1.97 (m, 6H), 1.50 (s, 3H), 2.25 (m, 2H), 2.39 (m, 1H), 4.57 (s, 1H), 4.86 (s, 1H), 6.17 (d, J = 10.6 Hz, 1H), 7.19 (d, J = 10.6 Hz, 1H). ^{13}C NMR (C_6D_6, 100 MHz) δ 12.6 (q), 20.9 (q), 24.9 (q), 32.2 (t), 33.4 (t), 33.6 (t), 35.4 (d), 47.1 (d), 50.1 (d), 51.6 (s), 114.2 (t), 130.3 (d), 144.8 (s), 151.7 (d), 196.5 (s), 212.2 (s). $[\alpha]^{20}_D$ + 0.6 (c 3.89, $CDCl_3$). Anal. calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.58; H, 9.29.

5

The total synthesis of Dihydroclerodin and Lupulin-C[103]



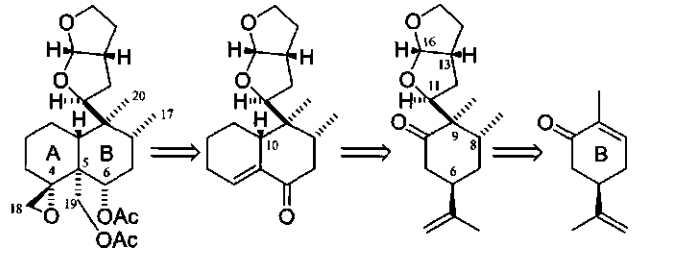
1 144 146 142

[103] Meulemans, T. M.; Stork, G. A.; Macaev, F. Z.; Jansen, B. J. M.; de Groot, A. *J. Org. Chem.* **1999**, *64*, 9178-9188.

5.1 Introduction[104]

The total synthesis of the natural enantiomer of dihydroclerodin and lupulin C, starting from R-(–)-carvone will be described in this chapter. The new strategy in which the methyl group at C8 was introduced first, followed by the diastereoselective Mukaiyama addition of the hexahydrofuro[2,3-*b*]furan moiety, allowed the establishment of the correct configuration at C9, C11, C13, and C16 as was described in Chapter 2. For the annulation of ketone **142**, the Robinson annulation was investigated first. This reaction did not give good results due to too much steric hindrance as was described in Chapter 4. Next, the isopropenyl group was removed and ring A had to be annulated with the correct stereochemistry at C10. In the last stage of the synthesis the characteristic functionalities at C5, C6, and C4 were introduced. The results of these efforts are described in this chapter.

scheme 5.1



dihydroclerodin (**1**) **144** **142** R-(-)-carvone (**2**)

5.2 Annulation of ring A via a 1,4-addition

For the introduction of ring A, additions of alkyllithium or alkylmagnesium reagents to ketone **142** were studied but they failed, most likely owing to steric hindrance of the large hexahydrofuro[2,3-*b*]furan moiety in combination with the other substituents. To reduce the steric congestion it was decided to remove the isopropenyl group in this stage of the synthesis. The isopropenyl has transferred the chirality from C6 to C8 and C9 in the desired sense and as such, it is not necessary anymore. Elimination of the isopropenyl was done by reaction with ozone followed by treatment of the ozonide with $Cu(OAc)_2$ and $FeSO_4$[105] to give enone **146**, which only could be obtained after workup using acidic and basic conditions to break the strong complexation between the metal ions and compound **146**.

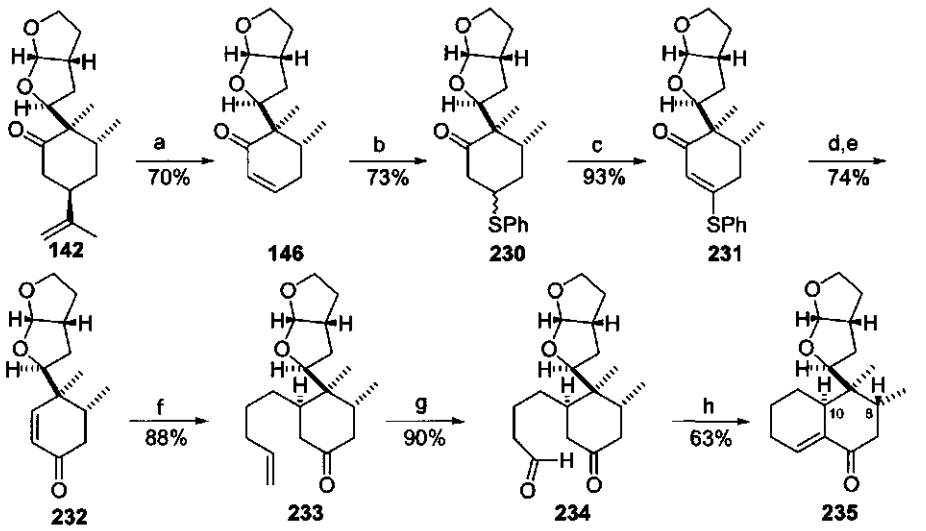
For the construction of ring A, a four carbon fragment had to be introduced at C10 and for that reason a 1,3-enone transposition of **146** into **232** was undertaken to set the stage for a 1,4-

[104] Throughout this thesis the clerodane numbering according to figure 1.1 will be used in all discussions.

[105] Schreiber, S. L. *J. Am. Chem. Soc.* **1980**, *102*, 6165-6166.

addition. It had been shown by Ley *et al.*[106] that a copper (I) catalyzed conjugate addition gives the desired stereochemistry at C10, when a 1,3-dithiolan-2-yl substituent instead of a hexahydrofuro[2,3-*b*]furan substituent is present in the molecule at C9. The 1,3-dithiolan-2-yl moiety probably gives a large complex with the cuprate which blocks the β-side (axial) of the molecule so that a second equivalent of the cuprate can react from the desired α-side (equatorial). We had observed the complexing capability of the hexahydrofuro[2,3-*b*]furan moiety in the treatment of the ozonide with $Cu(OAc)_2$ and $FeSO_4$ before, and therefore reasoned that this complexation might also be expected in the 1,4-addition, causing a similar effect as had been observed for the 1,3-dithiolan-2-yl moiety.

scheme 5.2



(**a**) i) O_3, ii) $Cu(OAc)_2$, $FeSO_4$; (**b**) PhSH, Et_3N; (**c**) trichloroisocyanuric acid; (**d**) $LiAlH_4$; (**e**) *p*-TsOH; (**f**) pent-4-enylMgBr, $CuBr{\bullet}Me_2S$; (**g**) i) O_3, ii) Ph_3P; (**h**) PPTS, Δ.

To achieve the 1,3-transposition of enone **146,** thiophenol was added, followed by chlorination using trichloroisocyanuric acid[107] and concomitant dehydrochlorination,[108] to give compound **231** in high yield. Reduction of the ketone in **231** and hydrolysis of the intermediate then gave the transposed enone **232** in 74% yield. The 1,4-addition of 4-pentenylmagnesiumbromide to enone **232** using $CuBr{\bullet}Me_2S$ as a catalyst gave only one adduct in 88% yield. The configuration at C10 was determined in the cyclized decalin **235,** which was

[106] Jones, P. S.; Ley, S. V.; Simpkins, N. S.; Whittle, A. J. *Tetrahedron* **1986**, *42*, 6519-6534.

[107] Mura, A. J.; Bennet, D. A.; Cohen, T. *Tetrahedron Lett.* **1975**, *50*, 4433-4436.

[108] (a) de Groot, A. ; Peperzak, R. M.; Vader, J. *Synth. Commun.* **1987**, *17*, 1607-1616; (b) Bukuzis, P.; Bakuzis, M. L. F. *J. Org. Chem.* **1981**, *46*, 235-239.

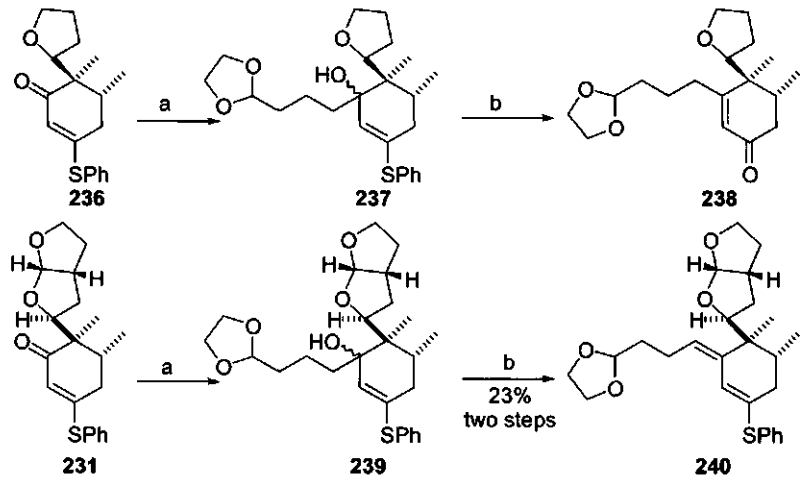
obtained after ozonolysis of the double bond followed by aldol condensation (scheme 5.2). The stereochemistry of **235** was elucidated by NMR, where no NOE between H-10 and H-8 could be detected, whereas a clear NOE was observed between H-10 and both the methyl groups at C8 and C9, which is indicative for an α-position of this proton. This meant that the 1,4-addition to enone **232** had occurred from the β-side, to yield the undesired configuration at C10. Apparently the hexahydrofuro[2,3-*b*]furan moiety does not show the same effect as the 1,3-dithiolan-2-yl moiety did in the synthesis of ajugarin I.[106]

5.3 Annulation of ring A via a 1,2-addition

Based on our experiences in the annulation of ring A via a 1,4-addition, it was expected that also other reagents would approach enones like **232** from the β-side, because the methyl at C9 blocks the approach from the α-side. Therefore a reaction sequence was planned in which a four carbon fragment was introduced first at C10 followed by addition of hydrogen at the C5, C10 double bond.

First, the 1,2-addition of a C_4 fragment to model compound **236** was studied. For this compound the planned addition to the enone sulfide, followed by hydrolysis gave the desired enone **238** in 50% yield (scheme 5.3).[109] However, the 1,2-addition of a C_4 fragment to **231** went poorly and the planned hydrolysis of the intermediate gave the highly stable diene sulfide **240** in low yield as a product of dehydration. Hydrolysis of this diene sulfide could not be achieved. Apparently the larger hexahydrofuro[2,3-*b*]furan moiety in compound **231** makes this reaction sequence unfavorable.

scheme 5.3



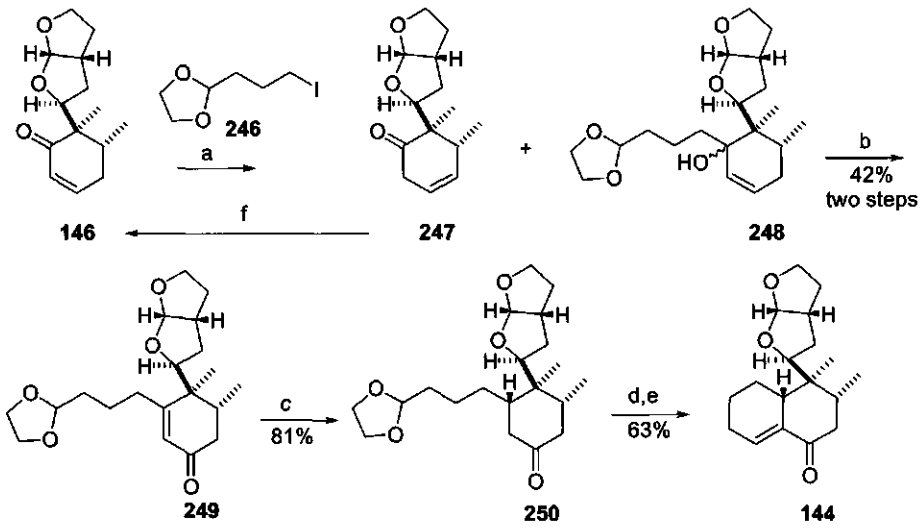
(a) 2-(3-iodo-propyl)-[1,3]dioxolan, *t*-BuLi; (b) PPTS

[109] This work was done by Moreno-Dorado, F. J. (PhD student form the Department of Organic Chemistry, University of Cádiz, Spain) during his stay at our laboratory.

In contrast to the failure of the 1,2-addition to ketone **142**, and the poor yield of the 1,2-addition to **231**, the 1,2-addition of 3-(1,3-dioxolan-2-yl)-propyllithium to the less hindered enone **146** could be accomplished to give a mixture of alcohols in an acceptable isolated yield of 42% (scheme 5.4). Due to the basic character of **146** the deconjugated derivative of enone **146** was obtained in 25% yield as the major side product.[110] This deconjugated enone could be used again for the 1,2-addition after reconversion to **146** by treatment with MeONa. The mixture of alcohols **248** was submitted to an oxidative rearrangement[111] to yield the transposed enone **249**.

Catalytic hydrogenation of enone **249** with H_2 and Pd/C afforded one product in 81% yield, and again the elucidation of the stereochemistry at C10 was done in the cyclized decalin **144**, which was obtained after deprotection of **250** to the aldehyde and subsequent aldol condensation.[112] The correct configuration of C10 in **144** could be concluded from NMR-studies where now a clear NOE between H-10 and H-8 was observed.

scheme 5.4



(a)2-(3-iodo-propyl)-[1,3]dioxolan, *t*-BuLi; (b) PCC; (c) Pd/C, H_2; (d) PPTS, H_2O; (e) PPTS, Δ.

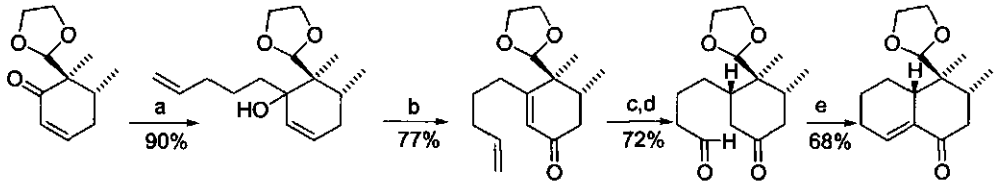
[110] To prevent this base catalyzed isomerization the less basic organocerium reagent was studied in the addition reaction, but this did not yield the addition product due to the low reactivity of the organocerium reagent.

[111] Ziegler, F. E.; Wallace, O. B. *J. Org. Chem.* **1995**, *60*, 3626-3636.

[112] PPTS was used as a catalyst for the aldol condensation, because the more acidic *p*-TsOH yielded many side products (see also note 120).

When performing the same 1,2-addition to an enone with a 1,3-dioxolan-2-yl moiety at C9, yields up to 90% were obtained in the 1,2-addition. Further conversion of this compound yielded decalin **245** (scheme 5.5).[113]

scheme 5.5



241 **242** **243** **244** **245**

(a) 1-pentenebromide, *t*-BuLi; **(b)** PCC; **(c)** i) O_3, ii) PPh_3; **(d)** Pd/C, H_2; **(e)** PPTS

5.4 Synthesis of dihydroclerodin and lupulin C

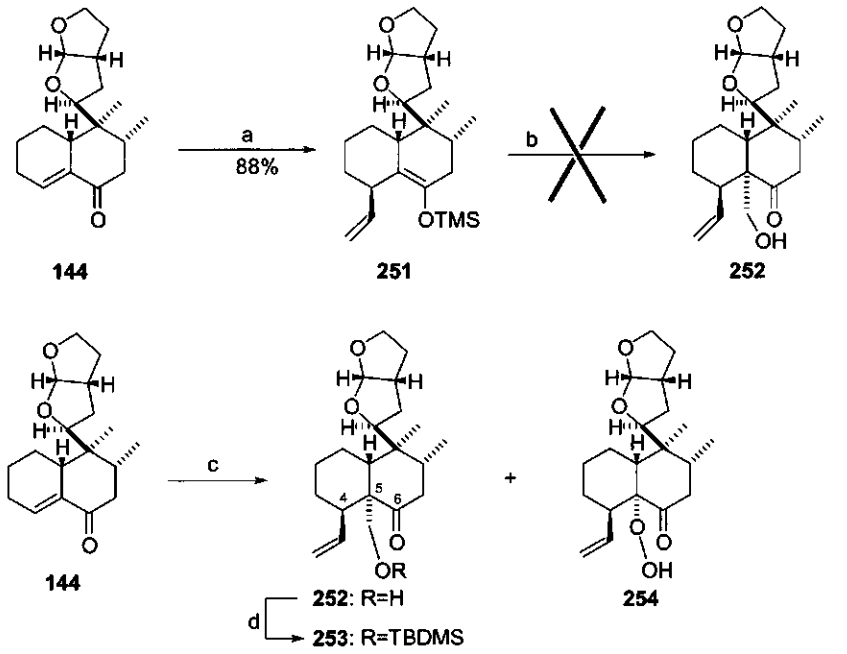
With the top side of the decalin finished, we turned our attention to the introduction of the two additional carbons of the clerodane skeleton following the procedure of Ley.[106] The conjugate addition of vinyl magnesiumbromide to **144** and trapping of the enolate with a solution of monomeric formaldehyde in THF[114] introduced the necessary fragments with the desired stereochemistry at C5 in 51% yield. Exclusion of oxygen proved to be very important in this reaction, because when oxygen is not fully excluded the hydroperoxy **254** was obtained as the major product.[115] Another approach, in which the conjugate addition of vinyl magnesium bromide was captured as its silyl enol ether gave **251** in 88% yield. But the trityl perchlorate catalyzed Mukaiyama reaction of the silyl enol ether with formaldehyde did not give the desired product **252**.

[113] This work was done by Zhernosek, E. V. (Institute of Bio-Organic Chemistry, Belarussian Academy of Sciences, Minsk, Belarus) during her stay at our laboratory.

[114] Schlosser, M.; Jenny, T.; Guggisberg, Y. *Synlett* **1990**, 704.

[115] For similar fast trapping of enolates by oxygen: (a) Koreeda, M.; You, Z. *J. Org. Chem.* **1989**, *54*, 5195-5198; (b) Gallagher, T. F.; Adams, J. L. *J. Org. Chem.* **1992**, *57*, 3347-3353.

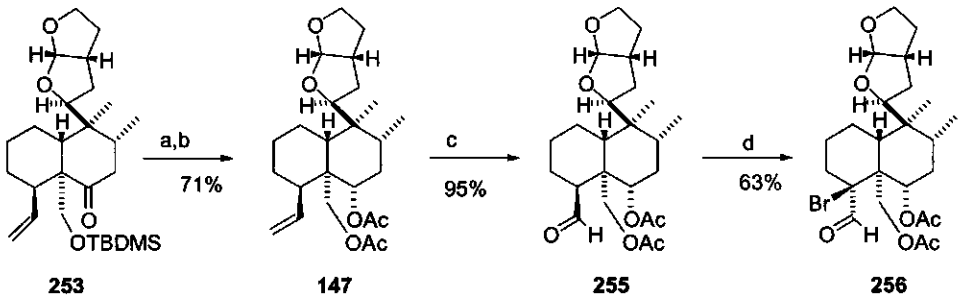
scheme 5.6



(**a**) i) vinylMgBr, CuBr•Me_2S, ii) TMSCl; (**b**) $TrClO_4$, CH_2O (g); (**c**) i) vinylMgBr, CuBr•Me_2S, ii) CH_2O; (**d**) TBDMSiCl, imidazole;

The hydroxymethyl group in **252** was protected as its *t*-butyldimethylsilyl ether **253** to prevent hydroxyl directed reduction of the carbonyl group. Now reduction of the carbonyl group with $LiAlH_4$ yielded the deprotected diol with the correct configuration at C6.

scheme 5.7

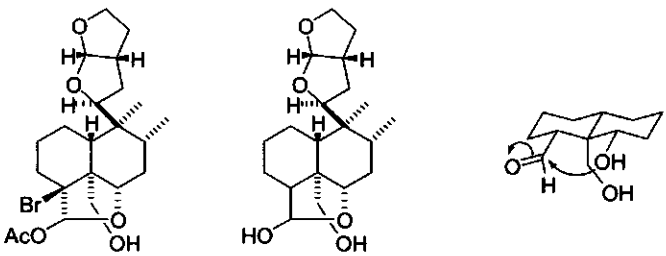


(**a**) i) $LiAlH_4$, ii) H_3O^+; (**b**) Ac_2O, DMAP; (**c**) i) O_3, ii) Ph_3P; (**d**) Pyrolidone•HBr•Br_2.

The final transformation of the vinyl substituent at C4 into an epoxide with the correct stereochemistry proved to be the last problem, that only could be solved after major efforts. From the literature[106] and from our own experience[116] it was concluded that the direct oxidation of an exocyclic double bond at C4 would probably give the wrong configuration of the epoxide. The hydroxyl directed epoxidation with $VO(acac)_2$ seemed more promising in this respect, but its chemoselectivity was questionable, and therefore the route to construct the epoxide via a bromohydrine as intermediate was investigated first.

The two hydroxyl groups that were obtained after the reduction of **253** were transformed into their acetates, as they are present in the natural product, this to avoid extra protection-deprotection steps. The double bond was ozonolyzed to yield aldehyde **255** in 95 % yield, and bromination of this aldehyde gave a 1:4 epimeric mixture with the axial bromine **256** as the major product in 63% yield (scheme 5.5). The idea was to reduce the α-bromoaldehyde to an α-bromohydrine, which upon treatment with base should cyclize to the desired epoxide. However, the alcohol, obtained after reduction of **256** with $NaBH_4$, immediately reacted with the acetates to give a mixture of transposed acetates. An attempt to remove the acetates by treatment with MeONa before the reduction, yielded immediately the ring closed product **257** in 75% yield. An acetonide as protecting group proved to be no solution, owing to the instability of the acetonide group under the bromination conditions and the hemiacetal **258** was isolated as the main product.

figure 5.1



257 **258**

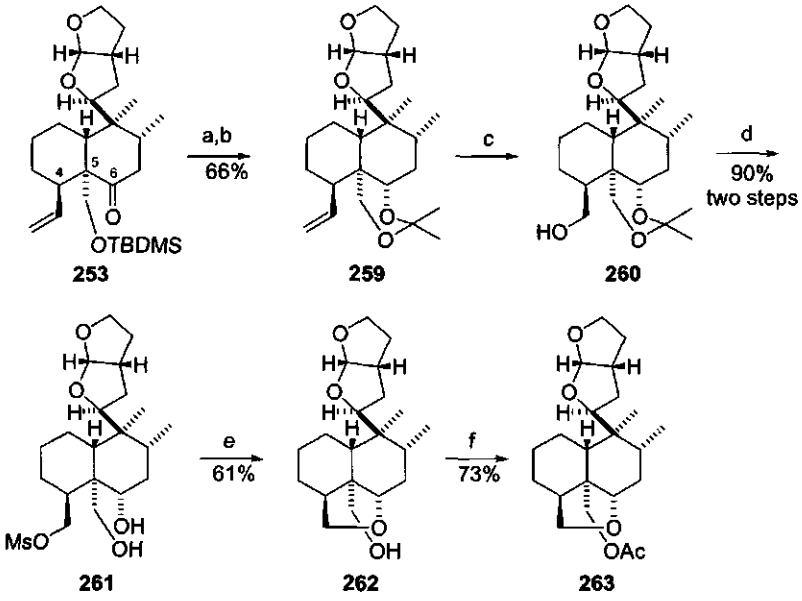
Since this approach did not open an easy route to the desired epoxide, the synthesis of an exocyclic methylene at C4 was investigated, in order to epoxidize this double bond either by $VO(acac)_2$ or by *m*-CPBA. A third possibility to obtain the desired epoxide might be created by ozonolysis of this exocyclic methylene group to a carbonyl group, which then could be submitted to a Corey epoxidation.

To obtain the exocyclic methylene group the vinyl group was ozonolyzed and the ozonide was reduced with $NaBH_4$ to yield alcohol **260**. The acetonide in **260** was not very stable and decomposed in $CDCl_3$ during NMR recording to give a triol. Elimination of the hydroxyl group in **260** through conversion into a phenylselenide or via its mesylate was investigated, but

[116] Luteijn, J. M.; de Groot, A. *Tetrahedron Lett.* **1982**, *23*, 3421-3424.

formation of the selenide failed and formation of the mesylate yielded the deprotected diol mesylate **261** which under elimination conditions gave **262** in 61% isolated yield.

scheme 5.8



(**a**) $LiAlH_4$; (**b**) MeO_2CMe_2, PPTS; (**c**) i) O_3, ii) $NaBH_4$; (**d**) pyridine, MsCl; (**e**) LiBr, Li_2CO_3, 100°C; (**f**) Ac_2O, pyridine, DMAP.

Finally, **260** was transformed into the xanthate ester **264** so that a Chugaev elimination[117] could be tried and this elimination indeed yielded the exomethylene **265** in 74% yield. It was difficult to follow this Chugaev reaction by TLC, because of similar R_f values of **264**, **265**, and several side products. Heating at reflux in n-dodecane for 48 h proved to be necessary to finish the reaction. Careful deprotection of the acetonide **265** with aqueous trifluoroacetic acid gave the diol **266**.

The hydroxyl directed epoxidation using $VO(acac)_2$ gave no epoxidation of the exocyclic double bond, even after 48 hours at room temperature, but left the hexahydrofuro[2,3-*b*]furan moiety intact. Only after heating for 48 h in CH_2Cl_2 the starting material decomposed but no epoxide was detected by NMR. However, using *m*-CPBA in a buffered solution yielded a 1:1 mixture of two epoxides, and acetylation of this mixture gave dihydroclerodin (**1**) and 4-*epi*-dihydroclerodin (**267**), which could be separated easily. NMR-spectroscopy and the recording of an optical rotation of $[\alpha]_D$ −10[118] proved that the natural enantiomer of dihydroclerodin had been

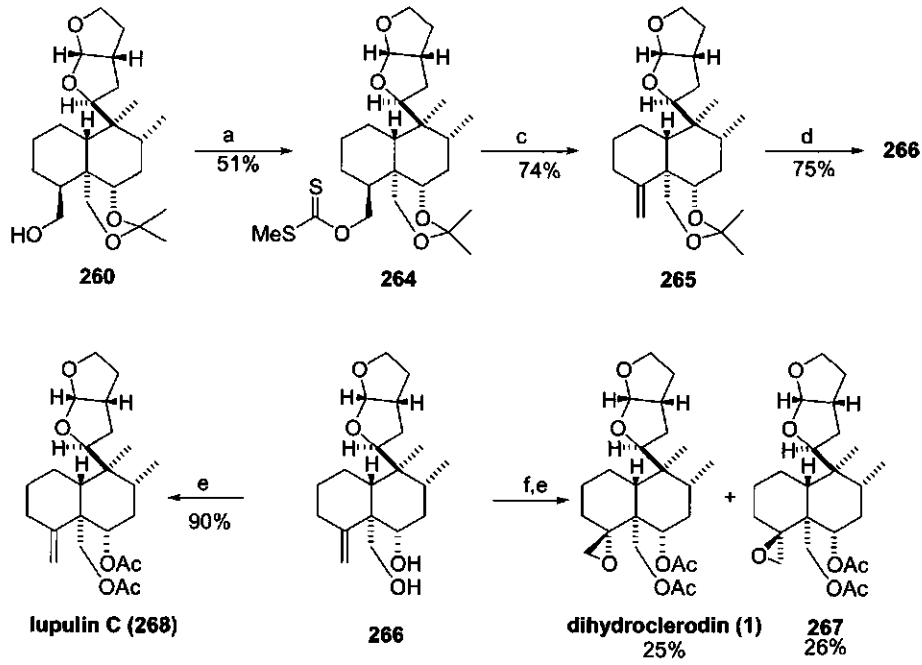
[117] Tschugaeff, L. (Chugaev) *Chem. Ber.* **1899**, *32*, 3332-3335.

[118] $[\alpha]_D$ −10.9 ($CDCl_3$), Beauchamp, P. S.; Bottini, A. T.; Caselles, M. C.; Dev, V.; Hope, H.; Larter, M.; Lee, G.; Mathela, C. S.; Melkani, A. B.; Millar, P. D.; Miyatake, M.; Pant, A. K.; Raffel, R. J.; Sharma, V. K.; Wyatt,

synthesized. Acetylation of diol **266** yielded the natural clerodane lupulin C (**268**), a compound isolated from *Ajuga lupulina*.[119] However, the reported fragment peaks are not in accordance with the ones we found, the most abundant fragment peak that was reported in the literature is *m/e* 111, but the hexahydrofuro[2,3-*b*]furan fragment has a mass of 113, which is the most abundant signal in our mass spectrum. Unfortunately the ^{1}H- and ^{13}C-NMR spectra we recorded were in deuterobenzene, and the reported recordings in the literature were taken in deuterochloroform, so proper comparison was not possible.

A Corey epoxidation was investigated to see whether the selectivity of the epoxide formation could be improved. For this purpose lupulin C (**268**) was successively treated with ozone and PPh_3 to yield a carbonyl group at C4. This ketone (**150**) was submitted to a reaction with trimethylsulfoniumylide, but during this reaction the acetates were removed and no epoxide was obtained.

scheme 5.9



(**a**) i) O_3, ii) $NaBH_4$; (**b**) i) NaH, CS_2, ii) MeI; (**c**) 216°C; (**d**) CF_3CO_2H; (**e**) Ac_2O, pyridine, DMAP; (**f**) *m*-CPBA.

D. *Phytochemistry* **1996**, *43*, 827-834; and $[\alpha]_D$ –20 ($CHCl_3$), Barton, D. H. R.; Cheung, H. T.; Cross, A. D.; Jackman, L. M.; Martin-Smith, M. *J. Chem. Soc.* **1961**, 5061-5073; $[\alpha]_D$ –12.8 (C_2H_5OH), Akiko, O.; Haruhisa, K.; Tsuyoshi, T. *Chem. Pharm. Bull.* **1996**, *44*, 1540-1545.

[119] Chen, H.; Tan, R. X.; Liu, Z. L.; Zhang, Y. *J. Nat. Prod.* **1996**, *59*, 668-670.

5.5 Conclusions

The first total synthesis of dihydroclerodin has been achieved in an overall yield of 0.35% in 18 steps. Characteristic for our approach is the early introduction of the hexahydrofuro[2,3-*b*]furanyl substituent in a remarkably diastereoselective Mukaiyama reaction. In the course of this total synthesis the hexahydrofuro[2,3-*b*]furan moiety has proven to be a stable fragment that, being an acetal, survived nearly all the applied reaction conditions.[120] A good solution was found for the annulation of ring A with the correct stereochemistry at C10 via the selective catalytic reduction of enone **249**. The introduction of the functional groups at C5 and especially at C4 is still susceptible of improvement.

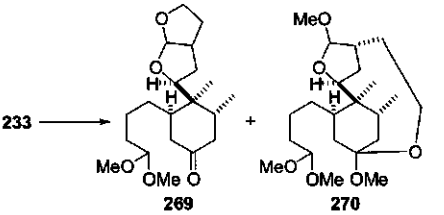
It was observed that in many transformations the yields were clearly lower compared to similar reactions with a 1,3-dioxolan-2-yl substituent at C9. This may explain why the promising results of some reactions which were described in the literature with other substituents at C9, did not give good results in our compounds. The only case in which the hexahydrofuro[2,3-*b*]furan moiety seems to have a beneficial influence is in the final epoxidation, where a better yield of the natural epoxide was obtained in comparison with similar reactions in the literature.[106,116]

5.6 Experimental[121]

((5*R*,6*R*)-6-((2*S*,3a*R*,6a*S*)-Hexahydrofuro[2,3-*b*]furan-2-yl)-5,6-dimethyl-2-cyclohexen-1-one (146).

A stirred solution of **142** (12.5 g, 45 mmol) in CH_2Cl_2 (300 mL) and MeOH (250 mL) at –78°C was purged through with ozone until a pale blue color appeared. Then nitrogen was purged through to remove the excess of ozone, followed by addition of $FeSO_4 \cdot 7H_2O$ (12.5 g, 45 mmol) and $Cu(OAc)_2 \cdot H_2O$ (17.7 g, 90 mmol). The reaction mixture was allowed to come to rt and stirred overnight. After this period the reaction mixture was concentrated to 100 mL, followed by addition of aqueous HCl (4 M, 150 mL). The aqueous phase was extracted three times with ether. The combined organic layers were washed with an aqueous solution of NaOH (4 M) and brine, dried, and evaporated. The residue was purified by flash chromatography (30% EA/PE) to give **146** (7.3 g, 31 mmol, 70%) as a colorless oil. $[\alpha]^{20}_D$ –36.5 (c 2.55, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.91 (s, 3H), 0.95 (d, J = 4.7 Hz, 3H), 1.38 (ddd, J = 13.4, 6.8, 3.1 Hz, 1H), 1.65 (m, 1H), 1.89-2.17 (m, 3H), 2.48 (m, 1H), 2.88 (m, 2H), 3.82 (m, 2H), 4,45 (dd, J = 8.8, 6.6 Hz, 1H), 5.67

[120] It should be noted that acidic reaction conditions have to be treated with care as was demonstrated by the isolation of compound **270** in reaction of the ozonide of **233** with PPh_3 and MeOH. See also note 112.



[121] See chapter 2, for general experimental.

(d, J = 5.0 Hz, 1H), 5.88 (ddd, J = 10.0, 2.8, 1.2 Hz, 1H), 6.77 (dddd, J = 10.0, 5.3, 2.8, 1.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.6 (q), 16.3 (q), 31.7 (t), 32.8 (t), 33.0 (t), 34.8 (t), 42.6 (d), 53.0 (s), 67.7 (t), 80.0 (d), 109.6 (d), 128.8 (d), 147.7 (d), 202.2 (s). MS m/z (relative intensity) 124 (100), 113 (90), 109 (51), 69 (78), 67 (14), 55 (13), 41 (11). HRMS calcd for $C_{14}H_{20}O_3$ (M^+) 236.1412, found 236.1413 (σ=0.083 mmu).

(2*R*,3*R*)-2-((2*S*,3a*R*,6a*S*)-Hexahydrofuro[2,3-*b*]furan-2-yl)-2,3-dimethyl-5-(phenylsulfanyl)-cyclohexanone (231).

To a stirred solution of **146** (10.4 g, 43.8 mmol) in pentane (300 mL) and THF (100 mL) were added thiophenol (5.5 g, 50 mmol) and Et_3N (1 mL). The reaction mixture was stirred for 27 h, followed by evaporation of the solvents. The residue was purified by flash chromatography (first 10% EA/PE, then 30% EA/PE) to give a mixture of the α- and β-phenylsulfide **230** (11.02 g, 31.8 mmol, 73%) as a colorless and slightly smelly oil. The mixture **230** (9.0 g, 26 mmol) was dissolved in ether (100 mL) and benzene (100 mL), and trichloroisocyanuric acid (2.0 g, 8.67 mmol) was added in three portions within 5 minutes, at 0°C (ice-salt bath). The reaction mixture was stirred for no more than 5 minutes. Then K_2CO_3 (5 g) was added, followed by filtration over silica. The solvents were evaporated under reduced pressure at 0°C. The residue was purified by flash chromatography (20% EA/PE) to give **231** (8.3 g, 24.1 mmol, 93%) as a colorless oil. ^{1}H NMR ($CDCl_3$), 200 MHz) δ 0.91 (s, 3H), 0.96 (d, J = 4.6 Hz, 3H), 1.40 (ddd, J = 13.4, 6.8, 3.4 Hz, 1H), 1.65 (m, 1H), 2.02-1.93 (m, 2H), 2.21 (dd, J = 18.3, 2.8 Hz, 1H), 2.54 (m, 1H), 2.81 (m, 1H), 3.09 (ddd, J = 18.3, 5.1, 2.1 Hz, 1H), 3.87 (m, 2H), 4.44 (dd, J = 8.3, 6.9 Hz, 1H), 5.40 (d, J = 2.1 Hz, 1H), 5.69 (d, J = 5.0 Hz, 1H), 7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.9 (q), 16.2 (q), 32.7 (t), 32.8 (t), 35.0 (d), 35.1 (t), 42.5 (d), 52.0 (s), 67.6 (t), 80.1 (d), 109.5 (d), 119.8 (d), 128.0 (s), 129.7 (d, 2C), 130.0 (d, 2C), 135.4 (d), 163.6 (s), 198.1 (s). MS m/z (relative intensity) 126 (14), 113 (100), 71 (21), 69 (54), 67 (11), 55 (16), 41 (11), 32 (80), 31 (100), 30 (14). HRMS calcd for $C_{20}H_{24}O_3S$ (M^+) 344.1446, found 344.1445 (σ=0.12 mmu).

(4*S*,5*R*)-4-((2*S*,3a*R*,6a*S*)-Hexahydrofuro[2,3-*b*]furan-2-yl)-4,5-dimethyl-2-cyclohexen-1-one (232).

To a stirred suspension of $LiAlH_4$ (1.0 g, 26.3 mmol) in dry ether (150 mL) was added **231** (8.3 g, 24.1 mmol) dissolved in dry ether (50 mL). The reaction mixture was stirred for 30 min at rt. After this period water (50 mL) was added. The aqueous phase was extracted three times with ether. The combined organic layers were washed with brine, dried, and evaporated. The residue was dissolved in $CHCl_3$ (100 mL), followed by addition of *p*-TsOH (0.5 g). The reaction mixture was stirred overnight. After this period $CHCl_3$ (100 mL) was added and the mixture was washed twice with an aqueous solution of NaOH (4M, 10 mL) and brine (10 mL), dried, and evaporated. The residue was purified by flash chromatography (30% EA/PE) to give **232** (4.2 g, 17.8 mmol, 74%) as white crystals. mp 90°C. $[\alpha]^{20}_D$ −12.6 (c 3.02, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.94 (d, J = 6.6 Hz, 3H), 1.13 (s, 3H), 1.61-1.75 (m, 3H), 1.98-2.30 (m, 4H), 2.84 (m, 1H), 3.88 (m, 2H), 4.17 (dd, J = 9.9, 6.5 Hz, 1H), 5.73 (d, J =5.0 Hz, 1H) 5.97 (d, J = 10.3 Hz, 1H), 6.89 (d, J = 10.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.5 (q), 16.4 (q), 32.8 (t), 34.3 (d), 34.7 (t),

42.0 (t), 42.4 (d), 42.5 (s), 68.4 (t), 83.1 (d), 109.0 (d), 129.1 (d), 155.1 (d), 199.5 (s). Anal. calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.09; H, 8.57.

((3*R*,4*S*,5*R*)-4-((2*S*,3a*R*,6a*S*)-Hexahydrofuro[2,3-*b*]furan-2-yl)-3,4-dimethyl-5-(4-pentenyl)-cyclohexanone (233).

To a stirred solution of CuBr•Me_2S (1.5 g, 7.3 mmol) in THF (80 mL) and HMPA (5 mL) was added dropwise a freshly prepared solution of pent-4-enylmagnesium bromide in ether (50 mL, 30 mmol) at –78°C. The reaction mixture was stirred for 1.5 h at –78°C, followed by addition of **232** (1.82 g, 7.71 mmol) dissolved in THF (20 mL) and TMSCl (2 mL). The reaction mixture was stirred for 5 h. After this period water (10 mL) was added slowly, followed by an aqueous solution of HCl (4M, 20 mL). The aqueous phase was extracted three times with ether. The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (30% EA/PE) to give **233** (2.07 g, 6.76 mmol, 88%) as white crystals. mp 109°C. $[\alpha]^{20}_D$ –24.0 (c 1.03, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (s, 3H), 0.95 (d, J = 6.8 Hz, 3H), 1.11-1.20 (m, 2H), 1.38-1.78 (m, 5H), 1.90-2.25 (m, 6H), 2.41 (d, J = 6.6 Hz, 2H), 2.62 (dd, J = 14.4, 4.8 Hz, 1H), 2.78 (m, 1H), 3.85 (m, 2H), 4.17 (dd, J = 11.1, 5.2 Hz, 1H), 4.94 (m, 2H), 5.65 (d, J = 5.3 Hz, 1H), 5.76 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.2 (q), 17.8 (q), 26.9 (t), 28.3 (t), 32.6 (t), 33.6 (t), 34.0 (t), 35.9 (d), 40.1 (s), 41.4 (d), 42.5 (t), 43.6 (d), 46.6 (t), 68.3 (t), 83.9 (d), 108.6 (d), 114.7 (t), 138.4 (d), 212.9 (s). Anal. calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 73.52 ; H, 9.92.

4-((1*R*,2*S*,3*R*)-2-((2*S*,3a*R*,6a*S*)-hexahydrofuro[2,3-*b*]furan-2-yl)-2,3-dimethyl-5-oxocyclo-hexyl)butanal (234).

A solution of **233** (2.1 g, 6.76 mmol) in CH_2Cl_2 (80 mL) at –78°C was purged through with ozone until a pale blue color appeared. Then nitrogen was purged through, followed by addition of Ph_3P (2.1 g, 8.0 mmol). The reaction mixture was allowed to come to rt and stirred overnight. Then the solvent was evaporated. The residue was purified by flash chromatography (60% EA/PE) to give aldehyde **234** (1.87 g, 6.1 mmol, 90%) as white crystals. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.86 (s, 3H), 0.92 (d, J = 6.7 Hz, 3H), 1.06-2.22 (m, 11H), 2.39 (m, 4H), 2.59 (dd, J = 14.2, 4.6 Hz, 1H), 2.76 (m, 1H), 3.82 (m, 2H), 4.11 (dd, J = 11.1, 5.2 Hz, 1H), 5.62 (d, J = 5.1, 1H), 9.67 (bs, 1H).

(3*R*,4*S*,4a*S*)-4-((2*S*,3a*R*,6a*S*)-Hexahydrofuro[2,3-*b*]furan-2-yl)-3,4-dimethyl-3,4,4a,5,6,7-hexahydro-1(2*H*)-naphthalenone (235).

A solution of **234** (0.9 g, 2.9 mmol) in benzene (40 mL) and PPTS (50 mg) was refluxed under Dean Stark conditions for 4 h. The reaction mixture was cooled down, followed by addition of a saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous phase was extracted three times with ether. The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (20% EA/PE) to give **235** (0.53 g, 1.8 mmol, 63%) as a colorless oil. $[\alpha]^{20}_D$ –35.1 (c 1.50, $CHCl_3$). ^{1}H NMR (C_6D_6, 400 MHz) δ 0.75 (s, 3H), 0.93 (d, J = 6.8 Hz, 3H), 1.20-1.30 (m, 2H), 1.37 (m, 1H) 1.50-1.76 (m, 5H), 1.98-2.05 (m, 2H), 2.13 (ddq, J

= 7.1, 2.6, 7.1 Hz, 1H), 2.33 (m, 1H), 2.33 (dd, J = 17.5, 2.7 Hz, 1H), 2.43 (ddd, J = 14.8, 7.5, 3.8 Hz, 1H), 3.10 (dd, J =17.5, 6.1 Hz, 1H), 3.64 (m, 2H), 4.12 (dd, J = 10.8, 5.4 Hz, 1H), 5.60 (d, J = 5.1 Hz, 1H), 7.15 (m, 1H). ^{13}C NMR (C_6H_6, 100 MHz) δ 17.7 (q), 20.9 (q), 23.1 (t), 24.2 (t), 26.3 (t), 33.1 (t), 33.6 (d), 34.5 (t), 39.3 (s), 41.8 (d), 42.3 (d), 44.2 (t), 68.2t, 82.9 (d), 108.4 (d), 135.5 (d), 138.0 (s), 198.0 (s). MS m/z (relative intensity) 178 (32), 113 (100), 69 (40), 32 (15), 31 (17). HRMS calcd for $C_{18}H_{26}O_3$ (M^+) 290.1882, found 290.1881 (σ=0.09 mmu).

2-(3-Iodopropyl)-1,3-dioxolane (246).[122]

A well stirred suspension of 4-chlorobutyryl chloride (28 mL, 250 mmol), palladium on barium sulfate (5% Pd) (3.5 g, 1.6 mmol Pd) in dry toluene (200 mL), purged through with hydrogen and then heated in an oil bath of 130°C. The reaction was followed by capturing the hydrogen chloride that evolved during the reduction, and leading this gas through a stirred solution of phenolphthalein in water (250 mL), followed by titration with a solution of NaOH (1M in water). After no more hydrogen chloride evolved (4h, 210 mL NaOH solution), the reaction mixture was cooled to rt and the catalyst was filtered through hy-flo, and the filter was washed with dry toluene. To the filtered solution was added ethylene glycol (40 mL, 717 mmol) and sulfuric acid (0.5 mL, 95-97%), followed by refluxing under Dean Stark conditions for 4 h. After this period, the reaction mixture was cooled, and washed with a saturated aqueous $NaHCO_3$ solution (150 mL) and with brine (10 mL) and dried. After filtration the toluene was evaporated under atmospheric pressure, and the remaining residue was distilled (bp. 96-98°C / 26 mm Hg) to give 2-(3-chloro-propyl)-[1,3]dioxolan (19.2 g, 128 mmol, 51%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.82 (m, 4H), 3.54 (t, J = 6.4 Hz, 2H), 3.88 (m, 4H), 4.87 (t, J = 3.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.9 (t), 30.9 (t), 44.8 (t), 64.8 (t, 2C), 103.7 (d).

A stirred solution of 2-(3-chloro-propyl)-1,3-dioxolane (19.0 g, 126 mmol) and sodium iodide (25.2 g, 168 mmol) in dry acetone (200 mL) was heated to reflux temperature for 18h. After this period the reaction mixture is cooled and the acetone is evaporated under reduced pressure. The residue is dissolved in toluene (100 mL) and ethylene glycol (5 mL), and p-TsOH (0.5 g) are added, followed by refluxing under Dean Stark for 3 h. After this period, the reaction mixture was cooled, and washed with a saturated aqueous $NaHCO_3$ solution (50 mL), with brine (10 mL), dried, and evaporated. The residue was distilled from a water bath (bp. 55-56°C / 0.1 mm Hg) to give **246** (22.7 g, 93.7 mmol, 74%).^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.69 (m, 2H), 1.90)m, 2H), 3.16 (t, J = 6.9 Hz, 2H), 3.87 (m, 4H), 4.81 (t, J = 4.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 6.7 (t), 27.9 (t),34.5 (t), 64.0 (t, 2C), 103.4 (d).

(2*S*,3a*R*,6a*S*)-2-((1*S*,2*E*,6*R*)-1,6-Dimethyl-2-(4-pentenylidene)-4-(phenylsulfanyl)-3-cyclohexen-1-yl)hexahydrofuro[2,3-*b*]furan (240)

A solution of 1-pentenyllithium was prepared by adding *t*-BuLi (1.5M in pentane, 4.0 mL, 6.0 mmol) to a degassed solution of 5-bromo-1-pentene (0.45 g, 3.0 mmol) in dry ether (20 mL) at –

[122] Pleshakov, M. G.; Vasil´ev, A. E.; Sarycheva, I. K.; Preobrazhenskii, N. A. *J. Gen. Chem. U.S.S.R.* **1961**, *31*, 1433-1435.

78°C under argon. The temperature was allowed to raise to rt and the reaction mixture was stirred for an additional 45 min. The fresh prepared lithium reagent was added to a stirred solution of **231** (300 mg, 0.87 mmol) in dry ether (5 mL) at –78°C. After addition the reaction mixture was stirred for an additional 1 h at –78°C and then quenched with water (15 mL). The aqueous phase was extracted three times with ether and the combined organic layers were washed with brine, dried, and evaporated. The residue was dissolved in CH_3Cl (30 mL) and a trace of PPTS was added. The resulting reaction mixture was stirred overnight, followed by addition of water (15 mL). The aqueous phase was extracted three times with ether and the combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (20% EA/PE) to give **240** (80 mg, 0.20 mmol, 23%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.77 (d, J = 7.0 Hz, 3H), 0.87 (s, 3H), 1.37 (ddd, J = 13.2, 6.4, 2.7 Hz, 1H), 1.66 (m, 1H), 1.77-2.22 (m, 8H), 2.75 (m, 2H), 3.84 (m, 2H), 4.26 (dd, J = 9.1, 6.4 Hz, 1H), 4.92-5.03 (m, 2H), 5.26 (bt, J = 6.8 Hz, 1H), 5.64 (d, J = 4.9 Hz, 1H) 5.77 (m, 1H), 6.54 (d, J = 2.2 Hz, 1H), 7.31 (m, 5H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.3 (q), 15.9 (q), 26.6 (t), 32.9 (t), 33.5 (t), 34.0 (t), 34.3 (d), 35.1 (t), 42.2 (d), 43.8 (s), 67.8 (t), 81.5 (d), 109.5 (d), 115.0 (t), 125.8 (d), 127.2 (d), 127.7 (d), 129.0 (d, 2C), 131.6 (d, 2C), 132.9 (s), 134.0 (s), 136.2 (s), 138.1 (d).

(4*S*,5*R*)-4-((2*S*,3a*R*,6a*S*)-Hexahydrofuro[2,3-*b*]furan-2-yl)-3-(3-(1,3-dioxolan-2-yl)propyl)-4,5-dimethyl-2-cyclohexen-1-one (249).

A solution of 3-(1,3-dioxolan-2-yl)-propyllithium was prepared by adding *t*-BuLi (1.5M in pentane, 33 mL, 49.5 mmol) to a degassed solution of 2-(3-iodo-propyl)-1,3-dioxolane (**246**) (6.0 g, 24.8 mmol) in dry ether (80 mL) at –78°C under argon. The temperature was allowed to raise to rt and the reaction mixture was stirred for an additional 45 min. The fresh prepared lithium reagent was added to a stirred solution of **146** (4.0 g, 17 mmol) in dry ether (80 mL) at –78°C. After addition the reaction mixture was stirred for an additional 3 h at –78°C and then quenched with water (30 mL). The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were washed with brine, dried, and evaporated. The residue was dissolved in CH_2Cl_2 (100 mL) and DMF (4 mL), followed by addition of PCC (8.0 g, 37 mmol) in three portions at 0°C. The reaction mixture was stirred overnight at rt. After this period ether (200 mL) was added and the reaction mixture was filtered over a short path of silica. The filter was washed extensively, followed by evaporation of the solvents. The residue was purified by flash chromatography (first 20% EA/PE, then 60% EA/PE) to give **247** (1.0 g, 4.2 mmol, 25%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 086 (d, J = 4.8 Hz, 3H), 0.91 (s, 3H), 1.47 (ddd, J = 13.2, 6.9, 3.3 Hz, 1H), 1.58-2.12 (m, 4H), 2.74 (m, 2H), 2.84 (m, 1H), 3.85 (m, 2H), 4.75 (dd, J = 8.6, 6.9 Hz, 1H), 5.58 (m, 1H), 5.65 (d, J = 4.9 Hz, 1H), 5.77 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.6 (q), 17.2 (q), 32.9 (t), 33.3 (t), 39.4 (t), 40.5 (d), 42.7 (d), 56.2 (s), 67.7 (t), 80 4 (d), 109.4 (d), 121.7 (d), 133.1 (d), 211.2 (s). MS m/z (relative intensity) 166 (15), 151 (11), 124 (16), 113 (100), 109 (16), 83 (12), 69 (68), 67 (18), 41 (20). HRMS calcd for $C_{14}H_{20}O_3$ (M^+) 236.1412, found 236.1410 (σ=0.059 mmu).

Followed by **249** (2.5 g, 7.1 mmol, 42%) as a colorless oil. $[\alpha]^{20}_D$ + 43.2 (c 2.57, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz) δ 089 (d, *J* = 6.9 Hz, 3H), 1.02 (s, 3H), 1.3-2.3 (m H), 2.68-2.89 (m, 3H), 3.77-3.92 (m, 6H), 4.12 (dd, *J* = 10.6, 5.6 Hz, 1H), 4.79 (t, *J* = 4.0 Hz, 1H) 5.60 (d, *J* = 5.0 Hz, 1H), 5.86 (bs, 1H). IR: 2954, 2878, 1666, 1140, 1016 cm^{-1}.

(3*S*,4*S*,5*R*)-4-((2*S*,3a*R*,6a*S*)-Hexahydrofuro[2,3-*b*]furan-2-yl)-3-(3-(1,3-dioxolan-2-yl)propyl)-4,5-dimethylcyclohexanone (250).

To a stirred suspension of Pd/C (10%) (690 mg) in THF (100 mL) saturated with hydrogen was added a solution of **249** (2.7 g, 7.7 mmol) in THF. The reaction mixture was stirred under hydrogen for 20 h. Then the Pd/C was filtered and washed with ethyl acetate. The solvents were evaporated, and the residue was purified by flash chromatography (60% EA/PE) to give **250** (2.2 g, 6.2 mmol, 81%) as a colorless oil. ^1H NMR ($CDCl_3$, 200 MHz) δ 088 (d, *J* = 6.8 Hz, 3H), 0.99 (s, 3H), 1.38-2.26 (m, 15H), 2.39 (dd, *J* = 14.8, 3.9 Hz, 1H), 2.85 (m, 1H), 3.82 (m, 6H), 4.22 (dd, *J* = 11.1, 5.7 Hz, 1H), 4.79 (t, *J* = 4.4 Hz, 1H), 5.63 (d, *J* = 5.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.7 (q), 17.2 (q), 22.1 (t), 30.6 (t), 32.3 (t), 32.8 (t), 33.9 (t), 36.5 (d), 40.3 (s), 41.4 (d), 42.1 (d), 42.7 (t), 46.0 (t), 64.8 (t, 2C), 68.3 (t), 84.7 (d), 104.3 (d), 108.2 (d), 211.5 (s). MS m/z (relative intensity) 240 (28), 123 (17), 113 (100), 73 (33), 71 (22), 69 (53), 55 (14), 32 (47), 31 (57). HRMS calcd for $C_{20}H_{32}O_5$ (M^+) 352.2250, found 352.2246 (σ=0.026 mmu). IR ν_{max} (neat) 2950, 2876, 1717, 1140, 1097, 1018 cm^{-1}.

(3*R*,4*S*,4a*R*)-4-((2*S*,3a*R*,6a*S*)-Hexahydrofuro[2,3-*b*]furan-2-yl)-3,4-dimethyl-3,4,4a,5,6,7-hexahydro-1(2*H*)-naphthalenone (144).

A solution of **250** (1.5 g, 4.3 mmol) in THF (25 mL), water (20 mL), and PPTS (0.5 g) was refluxed for 12 h. Then cooled down to rt, followed by addition of a saturated aqueous $NaHCO_3$ solution (3 mL). After the THF was evaporated, the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried, and evaporated. The residue was treated with PPTS as described for compound **235** yielding **144** (0.78 g, 2.68 mmol, 63%) as a colorless oil. $[\alpha]^{20}_D$ –52.7 (c 1.0, $CHCl_3$). ^1H NMR (C_6D_6, 400 MHz) δ 0.70 (d, *J* = 6.8 Hz, 3H), 0.85 (s, 3H), 1.22 (ddd, *J* = 12.8, 5.6, 1.5 Hz, 1H), 1.27-1.41 (m, 2H), 1.57-1.82 (m, 5H), 1.95 (m, 2H), 2.07 (m, 1H), 2.14 (dd, *J* = 17.5, 10.8 Hz, 1H), 2.42, (m, 1H), 2.48 (dd, *J* = 17.5, 5.9 Hz, 1H) 2.59 (m, 1H), 3.72 (m, 2H), 4.12 (dd, *J* = 11.2, 5.6 Hz, 1H), 5.69 (d, 5.0 Hz, 1H), 7.22 (m, 1H). ^{13}C NMR (C_6D_6, 100 MHz) δ 12.3 (q), 17.4 (q), 22.4 (t), 24.1 (t), 24.9 (t), 33.0 (d), 40.5 (s), 42.5 (d), 42.6 (d), 44.8 (t), 68.3 (t), 84.1 (t), 108.6 (d), 138.0 (s), 138.3 (d), 198.0 (s).

(((3*R*,4*S*,4a*R*,8*R*)-4-((2*S*,3a*R*,6a*S*)-Hexahydrofuro[2,3-*b*]furan-2-yl)-3,4-dimethyl-8-vinyl-2,3,4,4a,5,6,7,8-octahydro-1-naphthalenyl)oxy)(trimethyl)silane (251).

To a solution of CuBr•Me_2S (150 mg, 0.75 mmol), HMPA (0.9 mL), and dry THF (30 mL) under argon was added vinylMgBr (1 M in THF, 2.5 mL, 2.5 mmol) at –78°C. The reaction mixture was stirred for 0.5 h at –78°C, followed by addition of **144** (234 mg, 0.81 mmol) dissolved in THF (3 mL). After addition, trimethylsilylchloride was added (1.0 mL) and the reaction mixture

was stirred for an additional 1 h at –78°C. After this period triethylamine (2.0 mL) was added and the reaction mixture was stirred for an addition 30 min. After this period water (20 mL) was added and the aqueous phase was extracted three times with ether. The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (10% EA/PE) to give **251** (259 mg, 0.71 mmol, 88%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.13 (s, 9H), 0.81 (s, 3H), 0.90 (d, J = 6.6 Hz, 3H), 1.08 (m, 1H), 1.29-2.22 (m, 13H), 2.80 (m, 1H), 3.62 (m, 1H), 3.83 (m, 2H), 4.15 (dd, J = 10.4, 4.6 Hz, 1H), 4.86-4.99 (m, 2H), 5.64 (d, J = 5.0 Hz, 1H), 5.78 (ddd, J = 17.1, 9.9, 6.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 0.7 (q, 3C), 13.1 (q), 16.8 (q), 22.7 (t), 30.2 (t), 31.6 (t), 33.0 (t), 34.0 (d), 35.7 (t), 37.1 (d), 38.4 (d), 39.5 (s), 42.1 (d), 68.1 (t), 84.6 (d), 108.7 (d), 113.7 (t), 117.6 (s), 141.3 (s), 141.9 (d).

(3*R*,4*S*,4a*R*,8*R*,8a*S*)-4-((2*S*,3a*R*,6a*S*)-Hexahydrofuro[2,3-*b*]furan-2-yl)-8a-(((*tert*-butyl-(dimethyl)silyl)oxy)methyl)-3,4-dimethyl-8-vinyloctahydro-1(2*H*)-naphthalenone (253).

To a degassed solution of CuBr•Me_2S (100 mg, 0.5 mmol), HMPA (0.3 mL), and dry THF (20 mL) under argon was added vinylMgBr (1 M in THF, 2.5 mL, 2.5 mmol) at –78°C. The reaction mixture was stirred for 1.5 h at –78°C, followed by addition of **144** (237 mg, 0.82 mmol) dissolved in THF (3 mL). After addition, the reaction mixture was stirred for an additional 1 h. Then a freshly prepared oxygen free solution of formaldehyde in THF (15 mL) was added quickly.[123] Stirring was continued for no more than 10 min. Then the reaction was quenched in an aqueous NH_4Cl solution (60 mL), followed by vigorous extraction with ethyl acetate (three times). The combined organic layers were washed with brine, dried, and evaporated. The residue was dissolved in DMF (5 mL), *tert*-butyl-dimethylsilylchloride (0.3 g, 2.0 mmol) and a trace of imidazole. The reaction mixture was stirred for 12 h at rt. After this period water (10 mL) was added and the aqueous phase was extracted three times with ether. The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (20% EA/PE) to give **253** (190 mg, 0.41 mmol, 51%). $[\alpha]^{20}_D$ + 89.5 (c 2.95, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz) δ –0.01 (s, 3H), 0.01 (s, 3H), 0.84 (s, 9H), 0.88 (d, J = 7.1 Hz, 3H), 0.96 (s, 3H), 1.40-2.42 (m, 14H), 2.82 (m, 1H), 2.97 (m, 1H), 3.86 (m, 2H), 3.95 (s, 2H), 4.20 (dd, J = 11.6, 5.8 Hz, 1H), 5.03 (m, 2H), 5.63 (d, J = 5.1 Hz, 1H), 5.90 (ddd, J = 17.1, 9.8, 6.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ –5.7 (q, 2C), 15.4 (q), 17.9 (q), 18.3 (s), 21.4 (t), 22.5 (t), 22.6 (t), 22.8 (q, 3C), 32.8 (t, 2C), 33.8 (d), 40.0 (s), 41.2 (d), 42.2 (d), 42.3 (d), 46.2 (t), 56.2 (s), 63.9 (t), 68.2 (t), 85.9 (d), 108.5 (d), 116.2 (t), 138.8 (d), 213.1 (s). MS m/z (relative intensity) 405 (11), 113 (100), 83 (21), 75 (21), 71 (42), 57 (21), 55 (22), 43 (19), 41 (16). HRMS calcd for $C_{23}H_{37}O_4Si$ (M^+–57) 405.2461, found 405.2460 (σ=0.113 mmu).

[123] ref. 114, For oxygen free, a cooled solution of THF, paraformaldehyde, and acid was degassed prior to slowly distillation under argon.

(3*R*,4*S*,4a*R*,8*R*,8a*R*)-4-((2*S*,3a*R*,6a*S*)-Hexahydrofuro[2,3-*b*]furan-2-yl)-8a-hydroperoxy-3,4-dimethyl-8-vinyloctahydro-1(2*H*)-naphthalenone (254).

Reaction of **144** with vinyl magnesium cuprate, followed by formaldehyde without exclusion of oxygen

254: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (s, 3H), 0.94 (d, *J* = 7.6 Hz, 3H), 1.48-2.20 (m, 11H), 2.25 (dd, *J* = 13.2, 7.6 Hz, 1H), 2.62 (m, 1H), 2.70 (dd, *J* = 13.2, 5.4 Hz, 1H), 2.88 (m, 1H), 2.88 (m, 1H), 3.38 (m, 1H), 3.90 (m, 2H), 4.16 (dd, *J* = 10.5, 5.9 Hz, 1H), 5.09 (m, 1H), 5.12 (s, 1H), 5.68 (d, *J* = 5.2 Hz, 1H), 5.94 (m, 1H), 9.20 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.7 (q), 18.1 (q), 21.1 (t), 21.9 (t), 25.7 (t), 31.9 (t), 32.8 (t), 33.2 (t), 39.5 (s), 39.7 (d), 42.2 (d, 2C), 46.2 (t), 68.2 (t), 84.8 (d), 87.5 (s), 108.8 (d), 118.4 (t), 135.5 (d), 216.0 (s). IR ν_{max} (neat) 3321.62, 3079.37, 1723.48 cm^{-1}. MS m/z (relative intensity) 113 (100), 126 (17), 86 (11), 83 (13), 69 (60), 67 (11), 55 (18), 49 (19), 43 (11), 41 (15). HRMS calcd for $C_{20}H_{29}O_4$ (M^+–17) 333.2066, found 333.2064 (σ=0.136 mmu).

For structure elucidation compound 254 was treated with TBDMSiCl to give (3*R*,4*S*,4a*R*,8*R*,8a*R*)-4-((2*S*,3a*R*,6a*S*)-hexahydrofuro[2,3-*b*]furan-2-yl)-8a-((*tert*-butyl(dimethyl)silyl)peroxy)-3,4-dimethyl-8-vinyloctahydro-1(2*H*)-naphthalenone.

^{1}H NMR (C_6D_6, 200 MHz) δ 0.17 (s, 3H), 0.21 (s, 3H), 0.70 (d, *J* = 6.8 Hz, 3H), 0.95 (s, 9H), 0.93-1.22 (m, 2H), 1.30 (s, 3H), 1.49-1.90 (m, 9H), 2.10 (dd, *J* =13.3, 3.4 Hz, 1H), 2.22 (m, 2H), 2.97 (dd, 13.3, 13.3 Hz, 1H), 3.61 (m, 2H), 3.81 (m, 1H), 4.04 (dd, *J* = 11.0, 5.8 Hz, 1H), 5.27 (m, 2H), 5.56 (d, *J* = 5.0 Hz, 1H), 6.17 (ddd, *J* = 17.5, 10.7, 5.5 Hz, 1H). ^{13}C NMR (C_6D_6, 200 MHz) δ –5.4 (q), –5.3 (q), 14.2 (q), 17.0 (q), 18.1 (s), 21.1 (t), 23.6 (t), 25.5 (t), 25.9 (q, 3C), 32.6 (t), 32.8 (t), 37.4 (d), 37.6 (d), 40.5 (s), 41.8 (d), 43.2(t), 45. 3 (d), 67.7 (t), 85.1 (d), 89.5 (s), 108.2 (d), 115.7 (t), 138.5 (d), 204.0 (s). IR ν_{max} (neat) 3080.05, 1729.75 cm^{-1}. MS m/z (relative intensity) 407 (15), 113 (100), 95 (17), 83 (27), 81 (18), 75 (56), 69 (69), 55 (20), 43 (16), 41 (17). HRMS calcd for $C_{22}H_{35}O_5Si$ (M^+–C_4H_9) 407.2254, found 407.2253 (σ=0.081 mmu).

(1*S*,3*R*,4*S*,4a*R*,8*R*,8a*S*)-4-((2*S*,3a*R*,6a*S*)-Hexahydrofuro[2,3-*b*]furan-2-yl)-8a-((acetyloxy)methyl)-3,4-dimethyl-8-vinyldecahydro-1-naphthalenyl acetate (147).

To a stirred solution of **253** (94 mg, 21 mmol) in ether (25 mL) was added $LiAlH_4$ (50 mg) at 0°C. The reaction mixture was stirred for 3 h at rt. After this period ice water (5 mL) was added, followed by an aqueous solution of HCl (2M, 10 mL). The aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried, and evaporated to yield the crude diol. A solution of the crude diol in pyridine (5 mL), acetic anhydride (1 mL), and a trace of DMAP was stirred overnight. Then water was added and the aqueous phase was extracted three times with ether. The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (30% EA/PE) to give **147** (67 mg, 0.15 mmol, 71%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.81 (d, *J* = 6.2 Hz, 3H), 0.91 (s, 3H), 1.30-2.15 (m, 14H), 1.90 (s, 3H), 2.03 (s, 3H), 2.80 (m, 2H), 3.73 (m, 2H), 4.04 (dd, *J* = 11.3, 5.4 Hz, 1H), 4.16 (d, *J* = 12.3 Hz, 1H), 4.48 (dd, *J* = 9.8, 4.9 Hz, 1H), 4.87 (d, *J* = 12.3 Hz, 1H), 4.91 (dd, *J* = 16.7, 2.2 Hz, 1H), 5.04 (dd, *J* = 10.1, 2.2 Hz, 1H), 5.57 (d, *J* = 5.1 Hz,

1H), 6.14 (ddd, J = 16.7, 10.1, 10.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.0 (q), 16.5 (q), 20.9 (t), 21.1 (q), 21.2 (q), 22.4 (t), 27.2 (t), 31.9 (t), 32.5 (t, 2C), 35.9 (d), 40.3 (s), 41.4 (d), 41.5 (d), 42.1 (d), 43.9 (s), 61.3 (t), 68.3 (t), 77.0 (d), 85.9 (d), 107.7 (d), 117.3 (t), 137.7 (d), 170.1 (s), 170.7 (s). MS m/z (relative intensity) 260 (17), 187 (12), 113 (100), 69 (14). HRMS calcd for $C_{25}H_{38}O_6$ (M^+) 434.2668, found 434.2659 (6 scans), calcd for $C_{17}H_{24}O_2$ (M^+–174) 260.1776, found 260.1774 (σ=0.096 mmu).

(1*S*,3*R*,4*S*,8*S*,8a*R*)-4-((2*S*,3a*R*,6a*S*)-hexahydrofuro[2,3-*b*]furan-2-yl)-8a-((acetyloxy)methyl)-8-formyl-3,4-dimethyldecahydro-1-naphthalenyl acetate (255).

A solution of **147** (67 mg, 0.15 mmol) was ozonolyzed as described for compound **235** to give **255** (64 mg, 0.15 mmol, 95%). $[\alpha]^{20}_D$ –26.2 (c 3.0, $CHCl_3$). ^{1}H NMR (C_6D_6, 200 MHz) δ 0.59 (d, J = 6.7 Hz, 3H), 0.92 (s, 3H), 1.05-1.78 (m, 11H), 1.70 (s, 3H), 1.74 (s, 3H), 2.11-2.46 (m, 3H), 2.98 (m, 1H), 3.59 (m, 2H), 3.94 (dd, J = 10.3, 5.3 Hz, 1H), 4.00 (d, J = 12.3 Hz, 1H), 5.02 (d, J = 12.3 Hz, 1H), 5.48 (dd, J = 10.4, 5.4 Hz, 1H), 5.56 (d, J = 5.1 Hz, 1H), 9.81 (d, J = 1.5 Hz, 1H). ^{13}C NMR (C_6D_6, 50 MHz) δ 14.8 (q), 16.1 (q), 20.4 (q), 20.5 (q), 21.0 (t), 22.1 (t), 32.3 (t, 2C), 32.5 (t, 2C), 35.9 (d), 40.3 (s), 41.9 (d), 42.1 (d), 43.9 (s), 47.9 (d), 60.5 (t), 67.9 (t), 74.7 (d), 85.7 (d), 107.7 (d), 169.2 (s), 169.5 (s), 202.3 (d). MS m/z (relative intensity) 202 (20), 113 (100), 69 (30), 43 (15). HRMS calcd for $C_{24}H_{35}O_7$ (M^+ –1) 435.2383, found 435.2383 (σ=0.510 mmu). HRMS calcd for $C_{22}H_{32}O_5$ (M^+ –60) 376.2250, found 376.2245 (σ=0.134 mmu).

(1*S*,3*R*,4*S*,4a*R*,8*R*,8a*R*)-4-((2*S*,3a*R*,6a*S*)-Hexahydrofuro[2,3-*b*]furan-2-yl)-8a-((acetyloxy)-methyl)-8-bromo-3,4-dimethyl-8-vinyldecahydro-1-naphthalenyl acetate (256).

To a stirred solution of **255** (35 mg, $8.3\cdot10^{-5}$ mol) in CH_2Cl_2 (5 mL) was added pyrrolidone•HBr•Br_2 (82 mg, $16.5\cdot10^{-5}$ mol). The reaction mixture was stirred for 5 d at rt. After this period CH_2Cl_2 (30 mL) was added, followed by a saturated aqueous $NaHCO_3$ solution (4 mL). The aqueous phase was extracted with CH_2Cl_2 (10 mL). The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (35% EA/PE) to give **256** (26.8 mg, $5.2\cdot10^{-5}$ mol) (63%). $[\alpha]^{20}_D$ + 33.1 (c 1.6, $CHCl_3$). ^{1}H NMR (C_6D_6, 200 MHz) δ 0.54 (d, J = 6.5 Hz, 3H), 0.84 (s, 3H), 1.05-1.89 (m, 11H), 1.59 (s, 3H), 1.79 (s, 3H), 2.00-2.52 (m, 4H), 3.58 (m, 2H), 3.88 (dd, J = 11.1, 5.2 Hz, 1H), 4.09 (d, J = 12.3 Hz, 1H), 4.96 (d, J = 12.3 Hz, 1H), 5.46 (dd, J = 10.2, 3.5 Hz, 1H), 5.52 (d, J = 5.1 Hz, 1H), 9.81 (s, 1H). ^{13}C NMR (C_6D_6, 50 MHz) δ 14.2 (q), 16.0 (q), 20.0 (q), 20.8 (q), 21.8 (t), 22.0 (t), 30.5 (t), 32.2 (t), 32.4 (t), 32.6 (t), 35.93 (d), 40.3 (s), 41.9 (d), 43.5 (d), 50.2 (s), 60.6 (t), 67.9 (t), 77.5 (d), 85.3 (d), 87.5 (s), 107.6 (d), 168.4 (s), 168.9 (s), 188 (d). MS m/z (relative intensity) 113 (100), 69 (16). HRMS calcd for $C_{24}H_{35}O_7$ (M^+ –Br) 435.2383, found 435.2382 (σ=0.325 mmu).

(2*S*,2a*S*,5a*R*,6*S*,7*R*,8a*S*,8b*R*)-6-((2*S*,3a*R*,6a*S*)-Hexahydrofuro[2,3-*b*]furan-2-yl)-2a-bromo-8b-(hydroxymethyl)-6,7-dimethyldecahydro-2*H*-naphtho[1,8-*bc*]furan-2-yl acetate (257).

To a stirred solution of **256** (16 mg, $3.1\cdot10^{-5}$ mol) in MeOH (4 mL) was added MeONa (1.0 M in MeOH, 0.1 mL) at 0°C. After 20 min an aqueous solution of HCl (0.5 M, 10 mL) was added. The aqueous phase was extracted three times with ethyl acetate. The combined organic layers were

washed with brine, dried, and evaporated. The residue was purified by flash chromatography (60% EA/PE) to give **257** (11 mg, $2.3 \cdot 10^{-5}$ mol) (75%). ^{1}H NMR (C_6D_6, CD_3OD, 200 MHz) δ 0.58 (d, *J* = 6.0 Hz, 3H), 0.66 (s, 3H), 0.82-2.52 (m, 16H), 1.90 (s), 3H), 3.54 (m, 2H), 3.90 (dd, *J* = 11.4, 5.7 Hz, 1H), 4.03 (d, *J* = 9.0 Hz, 1H), 4.14 (d, *J* = 9.0 Hz, 1H), 5.20 (m, 1H), 5.48 (d, 5.1 Hz, 1H), 6.00 (s, 1H). ^{13}C NMR (C_6D_6, 50 MHz) δ 13.7 (q), 16.1 (q), 21.3 (q), 22.1 (t), 23.0 (t), 32.2 (t), 32.8 (t), 33.4 (t), 33.5 (t), 35.9 (d), 41.0 (s), 42.2 (d), 43.0 (d), 53.0 (s), 65.9 (t), 68.2 (t), 74.9 (s), 78.9 (d), 84.9 (d), 103.6 (d), 107.9 (d), 168.7 (s). MS m/z (relative intensity) 113 (100), 69 (22). HRMS calcd for $C_{16}H_{23}O_3{}^{79}Br$ (M^+–130) 342.0831, found 342.0823 (σ=0.149 mmu).

(4a*S*,6*R*,7*S*,7a*R*,11*R*,11a*S*)-7-((2*S*,3a*R*,6a*S*)-hexahydrofuro[2,3-*b*]furan-2-yl)-3,3,6,7-tetramethyl-11-vinyloctahydro-4a*H*-naphtho[1,8a-*d*][1,3]dioxine (259).

Reduction of compound **253** was performed as described for compound **147**. To a stirred solution of the crude diol (234 mg, 0.68 mmol) in dry DMF (5 mL) and 2,2-dimethoxy-propane (5 mL) was added a few crystals of PPTS. The reaction mixture was stirred for 0.5 h, followed by addition of a saturated aqueous $NaHCO_3$ solution (5 mL) and water (5 mL). The aqueous phase was extracted three times with ether. The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (20% EA/PE) to give **259** (175 mg, 0.45 mmol, 66%). $[\alpha]^{20}_D$ + 8.8 (c 1.0, $CHCl_3$). ^{1}H NMR (C_6D_6, 200 MHz) δ 0.85 (d, *J* = 5.8 Hz, 3H), 0.96 (s, 3H), 1.05-1.18 (m, 3H), 1.41 (s, 6H), 1.30-2.05 (m, 11H), 2.22 (m, 1H), 3.13 (m, 1H), 3.56 (m, 2H), 3.76 (d, *J* = 12.1 Hz, 1H), 3.84 (dd, *J* = 8.9, 4.2 Hz, 1H), 3.96 (dd, *J* = 11.2, 5.3 Hz, 1H), 4.04 (d, *J* = 12.1 Hz, 1H), 5.06 (dd, *J* = 10.0, 2.5 Hz, 1H), 5.21 (dd, *J* = 16.8, 2.5 Hz, 1H), 5.57 (d, *J* = 5.0 Hz, 1H), 6.12 (ddd, *J* = 16.8, 10.0, 10.0 Hz, 1H). ^{13}C NMR (C_6D_6, 50 MHz) δ 15.5 (q), 18.7 (q), 21.8 (t), 22.6 (t), 26.7 (q), 26.9 (q), 27.4 (t), 32.6 (t, 2C), 32.7 (d), 34.8 (t), 40.1 (d), 40.5 (d), 41.8 (s), 42.0 (d), 44.7 (d), 61.1 (t), 67.9 (t), 73.5 (d), 85 3 (d), 98.6 (s), 108.2 (d), 116.8 (t), 138.9 (d).

(2*R*,2a*R*,5a*R*,6*S*,7*R*,8a*S*,8b*R*)-6-((2*S*,3a*R*,6a*S*)-Hexahydrofuro[2,3-*b*]furan-2-yl)-8b-(hydroxymethyl)-6,7-dimethyldecahydro-2*H*-naphtho[1,8-*bc*]furan-2-ol (258).

Compound **259** (20 mg, $5.1 \cdot 10^{-5}$ mol) was ozonolyzed as described for compound **235** yielding **(4a*S*,6*R*,7*S*,7a*R*,11*S*,11a*R*)-7-((2*S*,3a*R*,6a*S*)-hexahydrofuro[2,3-*b*]furan-2-yl)-3,3,6,7-tetramethyloctahydro-4a*H*-naphtho[1,8a-*d*][1,3]dioxine-11-carbaldehyde**. (18.7 mg, $4.8 \cdot 10^{-5}$ mol, 93%) as a white gum which was used directly in the next reaction. $[\alpha]^{20}_D$ –13.6 (c 1.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (d, *J* = 6.3 Hz, 3H), 0.99 (s, 3H), 1.12-2.21 (m, 14H), 1.33 (s, 3H), 1.45 (s, 3H), 2.78 (m, 1H), 3.37 (brd, *J* = 5.1 Hz, 1H), 3.83 (m, 3H), 4.08 (dd, *J* = 11.1, 5.7 Hz, 1H), 4.15 (d, *J* = 12.4 Hz, 1H), 4.21 (dd, *J* = 12.5, 4.4 Hz, 1H), 5.57 (d, *J* = 5.1 Hz, 1H), 9.92 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.4 (q), 17.2 (q), 21.2 (t), 21.6 (t), 23.4 (t), 26.4 (q), 29.3 (q), 32.3 (t), 32.7 (t), 34.9 (t), 35.2 (d), 40.3 (s), 41.3 (s), 42.0 (d), 42.2 (d), 50.2 (d), 60.2 (t), 68.3 (t), 73.9 (d), 86.5 (d), 98.5 (s), 108.0 (d), 205.7 (s). MS m/z (relative intensity) 334 (25), 222 (10), 220 (15), 113 (100), 69 (22). HRMS calcd for $C_{23}H_{36}O_5$ (M^+) 392.2563, found 392.2552 (σ=0.262 mmu).

To a stirred solution of the aldehyde (18 mg, $4.7 \cdot 10^{-5}$ mol) in CH_2Cl_2 (4 mL) was added pyrrolidone•HBr•Br_2 (36 mg, $7.0 \cdot 10^{-5}$ mol). After 5 min the reaction mixture was filtered through a silica filter, the filter was washed thoroughly with ethyl acetate. The solvents were evaporated to give **258** (12 mg, $3.4 \cdot 10^{-5}$ mol, 73%) as a white powder. ^{1}H NMR (C_6D_6, CD_3OD, 200 MHz) δ 0.69 (d, J = 6.9 Hz, 3H), 0.71 (s, 3H), 0.71-2.05 (m, 17H), 2.27 (m, 1H), 3.37 (dd, J = 11.3, 4.6 Hz, 1H), 3.60 (m, 2H), 3.88 (d, J = 9.0 Hz, 1H), 3.99 (dd, J = 11.4, 5.6 Hz, 1H), 4.19 (dd, J = 11.4, 9.0 Hz, 1H), 5.08 (s, 1H), 5.54 (d, 5.1 Hz, 1H). ^{13}C NMR (C_6D_6, CD_3OD, 50 MHz) δ 13.4 (q), 16.7 (q), 22.5 (t), 23.3 (t), 28.4 (t), 32.4 (t), 32.8 (t), 36.2 (d), 37.3 (t), 41.2 (s), 42.1 (d), 43.8 (d), 50.7 (s), 54.5 (d), 68.1 (t), 68.5 (t), 77.6 (d), 85.2 (d), 104.6 (d), 108.0 (d). MS m/z (relative intensity) 175 (13), 149 (20), 113 (100), 83 (11), 81 (12), 69 (48), 55 (13), 43 (12), 32 (68), 31 (18). HRMS calcd for $C_{20}H_{30}O_4$ (M^+–18) 334.2144, found 334.2148 (σ=0.126 mmu).

((4a*S*,6*R*,7*S*,7a*R*,11*S*,11a*R*)-7-((2*S*,3a*R*,6a*S*)-Hexahydrofuro[2,3-*b*]furan-2-yl)-3,3,6,7-tetramethyloctahydro-4a*H*-naphtho[1,8a-*d*][1,3]dioxin-11-yl)methyl methanesulfonate (261).

A solution of **259** (30 mg, $7.7 \cdot 10^{-5}$ mol) dissolved in MeOH (30 mL) was purged through with ozone at –78°C until a pale blue color appeared. Then nitrogen was purged through, followed by addition of $NaBH_4$ (20 mg). The reaction mixture was allowed to come to rt and stirred for an additional 3 h. After this period water (10 mL) was added. The aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried, and evaporated. The remaining alcohol **260** was dissolved in pyridine (5 mL), followed by addition of MsCl (0.2 mL) at 0°C. The reaction mixture was stirred for 3 h. Then ether (30 mL) was added, followed by water (15 mL). The aqueous phase was extracted three times with ether. The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (60% EA/PE) to give mesylate **261** (30 mg, $6.9 \cdot 10^{-5}$ mol, 90%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.85 (s, 3H), 0.87 (d, J = 6.6 Hz, 3H), 1.16-2.16 (m, 14H), 2.69-2.95 (m, 4H), 3.02 (s, 3H), 3.65 (m, 1H), 3.84 (m, 3H), 4.03 (dd, J = 11.1, 5.4 Hz, 1H), 4.23 (d, J = 11.7 Hz, 1H), 4.39 (dd, J = 9.9, 7.0 Hz, 1H), 4.57 (dd, J = 9.9, 5.6 Hz, 1H), 5.56 (d, J = 5.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.5 (q), 17.0 (q), 21.5 (t), 22.3 (t), 23.3 (t), 32.5 (t), 32.8 (t), 33.4 (d), 35.8 (d), 36.4 (t), 37.5 (q), 40.5 (s), 41.8 (d), 42.1 (d), 45.0 (s), 61.1 (t), 68.3 (t), 70.8 (d), 74.8 (d), 85.9 (d), 107.7 (d).

((2a*S*,5a*R*,6*S*,7*R*,8a*S*,8b*R*)-6-((2*S*,3a*R*,6a*S*)-Hexahydrofuro[2,3-*b*]furan-2-yl)-6,7-dimethyldecahydro-8b*H*-naphtho[1,8-*bc*]furan-8b-yl)methanol (262).

To a solution of **261** (30 mg, $6.9 \cdot 10^{-5}$ mol) in DMF (5 mL) and HMPA (1.0 mL) was added LiBr (30 mg) and Li_2CO_3 (26 mg). The reaction mixture was heated at 100°C for 12 h. Then the reaction mixture was cooled, followed by addition of water (20 mL). The aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (60% EA/PE) to give **262** (15.8 mg, $4.7 \cdot 10^{-5}$ mol, 61%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.83 (s, 3H), 1.03 (d, J = 6.7 Hz, 3H), 1.16-2.20 (m, 15H), 2.35 (m, 1H), 2.81 (m, 1H), 3.14-3.29 (m, 3H), 3.85 (m, 2H), 3.92 (dd, J = 10.7, 5.4 Hz, 1H), 4.08 (d, J = 10.8 Hz, 1H), 4.22 (dd, J = 8.6, 8.6 Hz, 1H), 5.61 (d, J =

5.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.7 (q), 17.8 (t), 19.3 (q), 20.9 (t), 22.5 (t), 32.3 (t), 33.4 (t), 34.4 (t), 35.0 (d), 40.6 (d), 40.9 (d), 41.5 (s), 42.3 (d), 46.6 (s), 64.6 (t), 68.2 (t), 75.7 (t), 86.6 (d), 86.8 (d), 108.1 (d). MS m/z (relative intensity) 113 (100), 69 (37), 55 (11).

((2a*S*,5a*R*,6*S*,7*R*,8a*S*,8b*R*)-6-((2*S*,3a*R*,6a*S*)-Hexahydrofuro[2,3-*b*]furan-2-yl)-6,7-dimethyl-decahydro-8b*H*-naphtho[1,8-*bc*]furan-8b-yl)methyl acetate (263).

For proper structure elucidation alcohol **262** was converted into its acetate **263**.

To a stirred solution of **262** (15 mg, $4.7 \cdot 10^{-5}$ mol) in pyridine (2 mL) and Ac_2O (0.3 mL) was added one crystal of DMAP. The reaction mixture was stirred for 1 h. Then ether (20 mL) was added, followed by water (10 mL). The aqueous phase was extracted three times with ether. The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (40% EA/PE) to give **263** (13 mg, $3.4 \cdot 10^{-5}$ mol, 73%). $[\alpha]^{20}_D$ –16.5 (c 1.3, $CHCl_3$). ^{1}H NMR (C_6D_6, 400 MHz) δ 0.90 (d, J = 6.8 Hz, 3H), 1.03 (s, 3H), 1.24 (m, 4H), 1.42 (m, 1H), 1.62-1.90 (m, 7H), 1.85 (s, 3H), 2.07 (s, 3H), 2.38 (m, 1H), 3.27(dd, J = 12.8, 4.3 Hz, 1H), 3.31 (dd, J = 8.9, 6.7 Hz, 1H), 3.69 (ddd, J = 8.5, 8.5, 4.2 Hz, 1H), 3.77 (ddd, J = 8.5, 8.5, 6.7 Hz, 1H), 3.98 (dd, J = 11.1, 5.1 Hz, 1H), 4.31 (dd, J = 8.5, 8.5 Hz, 1H), 4.40 (d, J = 11.5 Hz, 1H), 4.45 (d, J = 11.5 Hz, 1H), 5.71 (d, J = 5.1 Hz, 1H). ^{13}C NMR (C_6D_6, 100 MHz) δ 16.2 (q), 18.6 (t), 18.7 (q), 20.5 (q), 21.3 (t), 23.1 (t), 32.2 (t), 33.1 (t), 34.3 (t), 34.5 (d), 41.3 (d), 41.6 (s), 41.7 (d), 42.2 (d), 45.3 (s), 67.3 (t), 67.8 (t), 74.7 (t), 85.5 (d), 85.8 (d), 108.0 (d), 170.1 (s). MS m/z (relative intensity) 206 (32), 151 (33), 135 (22), 123 (34), 113 (100), 109 (27), 95 (20), 82 (22), 32 (34), 31 (68). HRMS calcd for $C_{22}H_{33}O_5$ (M^+–1) 377.23287, found 377.2324 (σ=0.139 mmu).

***O*-(((4a*S*,6*R*,7*S*,7a*R*,11*S*,11a*R*)-7-((2*S*,3a*R*,6a*S*)-Hexahydrofuro[2,3-*b*]furan-2-yl)-3,3,6,7-tetramethyloctahydro-4a*H*-naphtho[1,8a-*d*][1,3]dioxin-11-yl)methyl) *S*-methyl dithiocarbonate (264).**

To a stirred solution of the crude alcohol **260** (100 mg, 0.25 mmol) in THF (20 mL) was added sodiumhydride (100 mg, 60% in mineral oil) at 0°C. The reaction mixture was stirred for 2 h, followed by addition of CS_2 (1 mL) and the reaction mixture was stirred for an additional 1.5 h. After this period MeI (0.5 mL) was added and the reaction mixture was allowed to come to rt and stirred overnight. Then ether (20 mL) was added, followed by ice water (10 mL). The aqueous phase was extracted three times with ether. The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (10% EA/PE) to give **264** (61 mg, 0.13 mmol, 51%) as a colorless oil. $[\alpha]^{20}_D$ + 9.7 (c 1.25 CH_2Cl_2). ^{1}H NMR (C_6D_6, 200 MHz) δ 0.91 (d, J = 7.0 Hz, 3H), 1.00 (s, 3H), 1.00-1.82 (m, 12H), 1.48 (s, 3H), 1.49 (s, 3H), 1.95-2.40 (m, 3H), 2.23 (s, 3H), 3.14 (m, 1H), 3.68 (m, 2H), 3.80 (d, J = 12.1 Hz, 1H), 3.98 (m, 2H), 4.09 (d, J = 12.1 Hz, 1H), 4.91 (dd, J = 11.0, 7.8 Hz, 1H), 5.10 (dd, J = 11.0, 4.8 Hz, 1H), 5.64 (d, J = 5.0 Hz, 1H). ^{13}C NMR (C_6D_6, 50 MHz) δ 15.8 (q), 18.38 (q), 18.45 (q), 21.5 (t), 22.6 (t), 23.9 (t), 26.3 (q), 27.4 (q), 27.4 (t), 32.6 (t), 32.6 (d), 32.8 (t), 34.8 (d), 37.7 (d), 40.0 (s), 40.7 (d), 41.9 (d), 41.9 (s), 60.7 (t), 67.9 (t), 73.3 (d), 74.3 (t), 85 3 (d), 98.8 (s), 108.1 (d). MS m/z (relative intensity) 206 (11), 205 (19), 113 (100), 69 (13). HRMS calcd for $C_{25}H_{40}O_5S_2$ (M^+)

484.2317, found 484.2314 (σ=6.453 mmu, 4 scans), HRMS calcd for $C_{23}H_{36}O_4$ (M^+–108) 376.2614, found 376.2610 (σ=0.174 mmu).

(4a*S*,6*R*,7*S*,7a*R*,11a*R*)-7-((2*S*,3a*R*,6a*S*)-Hexahydrofuro[2,3-*b*]furan-2-yl)-3,3,6,7-tetramethyl-11-methyleneoctahydro-4a*H*-naphtho[1,8a-*d*][1,3]dioxine (265).

A solution of **264** (61 mg, 0.13 mmol) in degassed and freshly distilled dodecane (5 mL) was heated for 48 h at reflux temperature (216°C). Then the solvent was evaporated until 1 mL of the volume remained, followed by flash chromatography (10% EA/PE) to give **265** (35 mg, $9.3\cdot10^{-5}$ mol, 74 %) as a colorless oil $[\alpha]^{20}_D$ + 13.2 (c 0.43 CH_2Cl_2). ^{1}H NMR (C_6D_6, 200 MHz) δ 0.80 (d, *J* = 6.8 Hz, 3H), 1.15 (s, 3H), 1.05-1.80 (m, 10H), 1.56 (s, 6H), 2.15-2.39 (m, 5H), 3.66 (m, 2H), 3.96 (d, *J* = 12.1 Hz, 1H), 4.06 (dd, *J* = 11.2, 5.4 Hz, 1H), 4.21 (dd, *J* = 12.3, 5.0 Hz, 1H), 4.22 (d, *J* = 12.1 Hz, 1H), 5.10 (bs, 1H), 5.44 (bs, 1H), 5.62 (d, *J* = 5.0 Hz, 1H). ^{13}C NMR (C_6D_6, 50 MHz) δ 15.0 (q), 17.2 (q), 22.6 (t), 27.9 (q), 28.8 (q), 28.8 (t), 32.6 (t), 33.0 (t), 34.0 (t), 36.2 (d), 36.6 (t), 41.3 (s), 42.3 (d), 45.6 (s), 49.4 (d), 61.1 (t), 68.2 (t), 74.3 (d), 86.0 (d), 99.0 (s), 108.2 (d), 108.4 (t), 153.7 (s). MS m/z (relative intensity) 361 (16), 113 (100), 69 (33). HRMS calcd for $C_{23}H_{36}O_4$ (M^+) 376.2614, found 376.2609 (σ=0.308 mmu).

(1*S*,3*R*,4*S*,4a*R*,8a*R*)-4-((2*S*,3a*R*,6a*S*)-Hexahydrofuro[2,3-*b*]furan-2-yl)-8a-(hydroxymethyl)-3,4-dimethyl-8-methylenedecahydro-1-naphthalenol (266).

To a stirred solution of **265** (35 mg, $9.3\cdot10^{-5}$ mol) in THF (20 mL) and water (10 mL), was added one drop of (10%) trifluoroacetic acid. The reaction mixture was stirred for 4 h. After this period a saturated aqueous $NaHCO_3$ solution (5 mL) was added, followed by evaporation of THF. The aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (60% EA/PE) to give **266** (23 mg, $7.0\cdot10^{-5}$ mmol, 75%) as a colorless oil. $[\alpha]^{20}_D$ + 17.0 (c 0.50 CH_2Cl_2). ^{1}H NMR (C_6D_6, 200 MHz) δ 0.73 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 3H), 1.03-1.88 (m, 11H), 2.09-2.42 (m, 6H), 3.62 (m, 2H), 3.95 (m, 3H), 4.08 (d, *J* = 10.8 Hz, 1H), 5.13 (bs, 1H), 5.40 (bs, 1H), 5.59 (d, *J* = 5.1 Hz, 1H). ^{13}C NMR (C_6D_6, 100 MHz) δ 15.0 (q), 17.0 (q), 23.2 (t), 29.2 (t), 32.8 (t), 33.0 (t), 34.6 (t), 36.2 (d), 37.5 (t), 41.3 (s), 42.4 (d), 49.5 (d), 52.0 (s), 61.1 (t), 68.2 (t), 75.3 (d), 85.6 (d), 108.1 (d), 109.7 (t), 152.8 (s). MS m/z (relative intensity) 113 (100), 69 (34). HRMS calcd for $C_{20}H_{32}O_4$ (M^+) 336.2301, found 336.2290 (σ=0.259 mmu), calcd for $C_{20}H_{30}O_3$ (M^+–18) 318.2195, found 318.2188 (σ=0.337 mmu).

Dihydroclerodin (1) and 4-*epi*-Dihydroclerodin (267).

To a stirred solution of **266** (7.4 mg, $2.2\cdot10^{-5}$ mol) in CH_2Cl_2 (0.5 mL) was added a mixture of Na_2HPO_4 (15 mg) and *m*-CPBA (10 mg) in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred for 4 h. After this period ethyl acetate (10 mL) and water (5 mL) were added. The aqueous phase was extracted two times with ethyl acetate. The combined organic layers were washed with brine, dried, and evaporated. The residue was dissolved in pyridine (0.3 mL), acidic anhydride (0.2 mL), followed by addition of one crystal of DMAP. The reaction mixture was stirred for 4 h, followed by addition of water (5 mL). The aqueous phase was extracted three times with ethyl

acetate. The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (60% EA/PE) to elute first **267** (2.5 mg, $5.7 \cdot 10^{-6}$ mol, 26%) as a colorless oil. $[\alpha]^{20}_D$ + 14.9 (c 0.21, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.85 (d, J = 6.4 Hz, 3H), 0.98 (s, 3H), 1.15 (m, 1H), 1.38-2.25 (m, 13H), 1.96 (s, 3H), 2.05 (s, 3H), 2.55 (d, J = 4.4 Hz, 1H), 2.71 (d, J = 4.4 Hz, 1H), 2.90 (m, 1H), 3.89 (m, 2H), 4.12 (dd, J = 11.3, 5.5 Hz, 1H), 4.31 (d, J = 12.0 Hz, 1H), 4.60 (dd, J = 10.4, 6.2 Hz, 1H), 4.89 (d, J = 12.0 Hz, 1H), 5.65 (d, J = 5.1 Hz, 1H). ^{13}C NMR (C_6D_6, 100 MHz) δ 14.4 (q), 16.7 (q), 21.6 (q), 22.0 (q), 22.2 (t), 23.5 (t), 32.0 (t), 32.5 (t), 32.7 (t), 33.1 (t), 35.8 (d), 40.6 (s), 42.5 (d), 46.0 (s), 46.0 (d), 55.6 (t), 61.4 (s), 62.2 (t), 69.0 (t), 72.3 (d), 86.0 (d), 108.1 (d), 170.4 (s), 171.1 (s). MS m/z (relative intensity) 248 (12), 233 (13), 173 (15), 149 (23), 113 (100), 109 (11), 69 (30). HRMS calcd for $C_{22}H_{33}O_6$ (M^+–43) 393.2277, found 393.2267 (σ=0.164 mmu), followed by **1** (2.4 mg, $5.5 \cdot 10^{-6}$ mol, 25%) as a colorless oil. $[\alpha]^{20}_D$ –9.6 (c 0.22, $CHCl_3$) ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (d, J = 6.5 Hz, 3H), 0.98 (s, 3H), 1.04 (m, 1H), 1.37-1.95 (m, 11H), 1.97 (s, 3H), 2.13 (s, 3H), 2.10-2.23 (m, 3H), 2.24 (d, J = 4.0 Hz, 1H), 2.91 (m, 1H), 3.00 (dd, J = 3.9, 2.3 Hz, 1H), 3.89 (m, 1H), 4.12 (dd, J = 11.3, 5.5 Hz, 1H), 4.37 (d, J = 12.2 Hz, 1H), 4.70 (dd, J = 11.4, 4.8 Hz, 1H), 4.93 (d, J = 12.2 Hz, 1H), 5.66 (d, J = 5.1 Hz, 1H). ^{13}C NMR (C_6D_6, 100 MHz) δ 14.6 (q), 17.0 (q), 21.7 (q), 21.8 (q), 22.6 (t), 25.4 (t), 32.8 (t), 33.0 (t), 33.1 (t), 33.7 (t), 36.4 (d), 40.8 (s), 42.5 (d), 45.9 (s), 48.5 (d), 48.9 (t), 62.1 (t), 65.5 (s), 69.0 (t), 72.3 (d), 85.7 (d), 108.1 (d), 170.7 (s), 171.5 (s). MS m/z (relative intensity) 173 (14), 113 (100), 69 (42), 55 (10), 43 (19). HRMS calcd for $C_{22}H_{33}O_6$ (M^+–43) 393.2277, found 393.2273 (σ=0.278 mmu).

Lupulin-C (268).

A solution of pyridine (0.3 mL), Ac_2O (0.2 mL), **266** (9.0 mg, $2.7 \cdot 10^{-5}$ mol), and a trace of DMAP was stirred for 4 h. Then water (5 mL) was added. The aqueous phase was extracted three times with ether. The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (40% EA/PE) to give lupulin-C (**268**) (10 mg, $2.4 \cdot 10^{-5}$ mol, 90%). $[\alpha]^{20}_D$ 0.0 (c 1.0, $CHCl_3$) ^1H NMR (C_6D_6, 400 MHz) δ 0.67 (d, J = 6.8 Hz, 3H), 1.01 (s, 3H), 1.05 (m, 1H), 1.15-1.89 (m, 11H), 1.83 (s, 3H), 1.88 (s, 3H), 2.18-2.35 (m, 4H), 3.68 (m, 2H), 4.00 (dd, J = 11.2, 5.2 Hz, 1H), 4.23 (d, J = 12.0 Hz, 1H), 4.95 (d, J = 10.0 Hz, 1H), 5.21 (d, J = 12.0 Hz, 1H), 5.40 (dd, J = 10.8, 4.4, 1H), 5.63 (d, J = 5.2 Hz, 1H). ^{13}C NMR (C_6D_6, 100 MHz) δ 14.7 (q), 16.5 (q), 21.1 (q), 21.1 (q), 23.1 (t), 29.2 (t), 32.5 (t), 32.9 (t), 33.2 (t), 34.7 (t), 36.1 (d), 41.3 (s), 42.3 (d), 49.4 (s), 50.4 (d), 61.2 (t), 68.3 (t), 75.8 (d), 85.4 (d), 106.7 (t), 108.0 (d), 152.6 (s), 169.9 (s), 170.0 (s). MS m/z (relative intensity) 113 (100), 69 (18), 43 (13). HRMS calcd for $C_{24}H_{36}O_6$ (M^+) 420.2512, found 420.2510 (σ=0.167 mmu).

(3*R*,4*S*,5*R*)-4-((2*S*,3a*R*,6a*S*)-Hexahydrofuro[2,3-*b*]furan-2-yl)-3-(4,4-dimethoxybutyl)-4,5-dimethylcyclohexanone (269).

(1*S*,2*S*,5*S*,8*S*,10*R*,11*R*)-10-(4,4-Dimethoxybutyl)-4,8-dimethoxy-1,11-dimethyl-3-oxatricyclo-[6.2.2.1^{2,5}]tridecane (270).

A stirred solution of **233** (1.0 g, 3.26 mmol), MeOH (25 mL), and CH_2Cl_2 (25 mL) was purged through with ozone at –78°C until a pale blue color appeared. Then nitrogen was purged through,

followed by addition of dimethylsulfide (2.0 mL)). The reaction mixture was allowed to come to rt and stirred overnight. After this period the solvents were evaporated. The residue was purified by flash chromatography (30% EA/PE) to give first **270** (193 mg, 0.48 mmol, 15%), followed by **269** (622 mg, 1.76 mmol, 54%) as a 1:1 mixture of C16 epimers.

(**270**): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.87 (s, 3H), 0.94 (d, J = 6.8 Hz, 3H), 1.15 (m, 2H), 1.40-1.75 (m, 7H), 1.85-2.23 (m, 4H), 2.40 (m, 2H), 2.63 (dd, J = 14.5, 4.9 Hz, 1H), 3.27 (s, 3H), 3.28 (s, 3H), 3.85 (m, 2H), 4.16 (dd, J = 11.1, 5.2 Hz, 1H), 4.28 (t, J = 5.2 Hz, 1H), 5.64 (d, J = 5.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.6 (q), 17.9 (q), 22.9 (t), 28.9 (t), 32.6 (t), 32.7 (t), 34.0 (t), 35.8 (d), 40.0 (s), 41.4 (d), 42.6 (t), 43.6 (d), 46.6 (t), 52.7 (q), 53.1 (q), 68.3 (t), 83.9 (d), 104.5 (d), 108,7 (d). IR ν_{max} (neat) 1711.33 cm^{-1}. MS m/z (relative intensity) 210 (20), 113 (100), 75 (25), 69 (38), 32 (19). HRMS calcd for $C_{19}H_{30}O_4$ (M^+–32) 322.2144, found 322.2142 (σ=0.03 mmu)

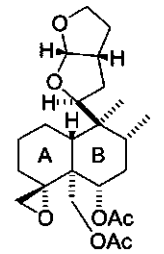
(**269**): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.62/0.63 (s, 3H), 0.85 (d, J = 6.4 Hz, 3H), 1.01-2.31 (m, 17H), 3.25 (s, 3H), 3.28 (s, 3H), 3.296 (s, 3H), 3.303 (s, 3H), 3.85 (m, 3H), 4.33 (t, J = 5.4 Hz, 1H), 4.65 (d, J = 1.6 Hz, 0.5H), 4.81 (d, J = 4.5 Hz, 0.5H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.0 (q), 18.0 (q), 18.2 (q), 22.4 (t), 29.4 (t), 30.2 (t), 30.7 (d), 30.9 (d), 31.5 (t), 32.8 (t), 33.4 (t), 34.2 (d), 35.9 (s), 35.9 (s), 37.3 (t), 37.5 (t), 38.4 (t), 38.5 (t), 41.0 (d), 42.6 (d), 49.2 (q), 52.68 (q),52.72 (q), 54.5(q), 54.7(q), 66.7 (t), 66.9 (t), 77.0 (d), 98.8 (s), 98.9 (s), 104.5 (d), 104.9 (d), 109.5 (d). IR ν_{max} (neat) no carbonyl. MS m/z (relative intensity) 224 (17), 166 (19), 123 (24), 113 (100), 75 (30), 71 (18), 69 (37), 67 (18), 55 (25), 32 (18). HMRS calcd for $C_{22}H_{40}O_6$ (M^+) 400.2825 found 400.2818 (σ=0.16 mmu)

(1*S*,3*R*,4*S*,8a*R*)-4-((2*S*,3a*R*,6a*S*)-hexahydrofuro[2,3-*b*]furan-2-yl)-8a-((acetyloxy)methyl)-3,4-dimethyl-8-oxodecahydro-1-naphthalenyl acetate (150).

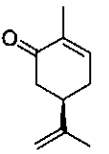
A solution of lupulin C (10 mg, $2.4\cdot10^{-5}$ mol) was ozonolyzed as described for compound **234** to give **150** (5.8 mg, $1.4\cdot10^{-5}$ mol, 57%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.87 (d, J = 6.1 Hz, 3H), 1.03 (s, 3H), 1.42-1.83 (m, 9H), 1.94 (s, 3H), 1.99 (s, 3H), 2.03-2.45 (m, 4H), 2.52 (dd, J = 13.6, 6.6 Hz, 1H), 2.87 (m, 1H), 3.88 (m, 2H), 4.10 (dd, J = 11.3, 5.6 Hz, 1H), 4.42 (d, J = 12.0 Hz, 1H), 4.95 (d, J = 12.0 Hz, 1H), 5.18 (dd, J = 11.6, 5.0 Hz, 1H), 5.63 (d, J = 5.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.6 (q), 16.3 (q), 21.0 (q), 21.1 (q), 22.1 (t), 27.0 (t), 32.1 (t), 32.2 (t), 32.6 (t), 35.8 (d), 40.0 (t), 41.3 (s), 42.1 (d), 49.8 (d), 56.7 (s), 61.3 (t), 68.5 (t), 72.2 (d), 85.2 (d), 107.7 (d), 169.9 (s), 170.3 (s), 208.7 (s). MS m/z (relative intensity) 250 (13), 113 (100), 43 (11). HMRS calcd for $C_{23}H_{34}O_7$ (M^+) 422.2305 found 422.2305 (σ=0.198 mmu). $[\alpha]^{20}_D$ 0.0 (c 0.58, $CHCl_3$)

6

Discussion and outlook



dihydroclerodin (**1**)



R-(–)-carvone (**2**)

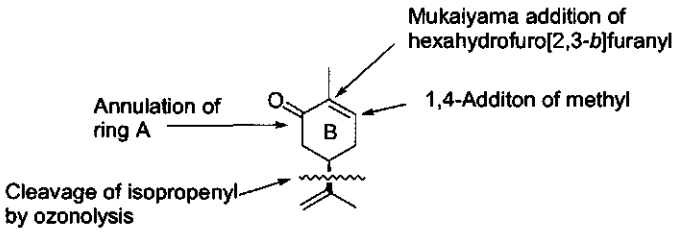
6.1 Why the synthesis of dihydroclerodin?[124]

The total synthesis of clerodane insect antifeedants is a topic in our research group since Luteijn and de Groot attempted the synthesis of racemic ajugarin I, which ultimately ended in the synthesis of 4-*epi*-ajugarin I.[125] The synthesis of the furofuran part, as well as the decalin part, of clerodanes like clerodin was studied by Vader and de Groot.[126] With the knowledge gathered in this research, it was estimated that the synthesis of dihydroclerodin would be feasible within one PhD period.[127] In our approach we have chosen for the synthesis of a clerodane with a hexahydrofuro[2,3-*b*]furanyl group at C9, a chiral center at C11 and a decalin system that is oxidized at C4, C19, and C6. The biological activity of this type of clerodanes is high (see chapter 1) and the complexity of such molecules makes them a real challenge for total synthesis.

6.2 Why carvone as a starting material?

In the last decade, another topic in our research group has been the use of carvone as a homochiral starting material.[128] The availability of both the enantiomers of carvone, makes it an interesting starting material for the synthesis of natural products. Via the enone functionality in carvone substituents can be introduced at the upper part. The isopropenyl group at the lower part has a function as a chiral handle but can also be seen as a disguised functional group. This group is stable towards most reaction conditions, but when necessary it can easily be transformed by ozonolysis into a hydroxyl group,[129] an acetate,[129] a double bond,[130] or a carbonyl group[131]. Starting from carvone the synthesis of ring B in dihydroclerodin can be achieved in a short and highly selective synthesis, as was described in chapter 2.

figure 6.1



[124] Throughout this thesis the clerodane numbering according to figure 1.1 will be used in all discussions.

[125] (a) Luteijn, J. M. PhD thesis, Wageningen Agricultural University, **1982**; (b) Luteijn, J. M.; de Groot, A. *Tetrahedron Lett.* **1982**, *23*, 3421-3424.

[126] Vader, J. PhD thesis, Wageningen Agricultural University, **1989**.

[127] This is four years.

[128] Verstegen-Haaksma, A. A. PhD Thesis, Wageningen Agricultural University, **1994**.

[129] Schreiber, S. L.; Liew, W.-F. *Tetrahedron Lett.* **1983**, *24*, 2363-2366.

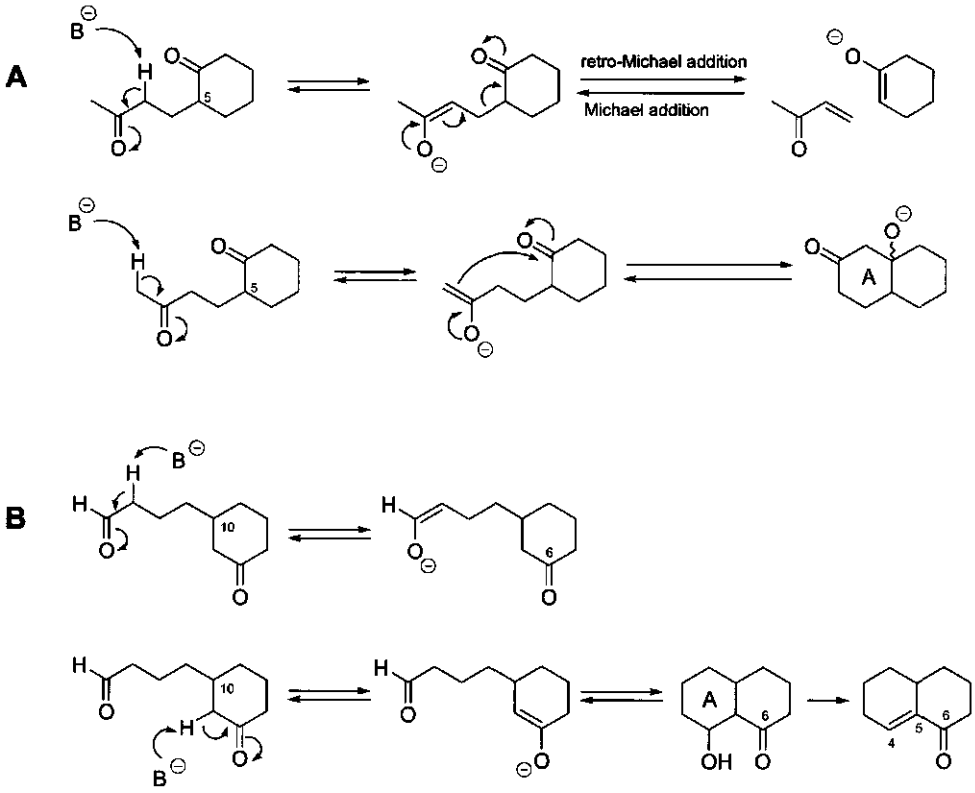
[130] Schreiber, S. L. *J. Am. Chem. Soc.* **1980**, *102*, 6165-6166.

[131] Swarts, H. J.; Verstegen-Haaksma, A. A.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **1994**, *50*, 10083-10094.

6.3 Discussion of the total synthesis

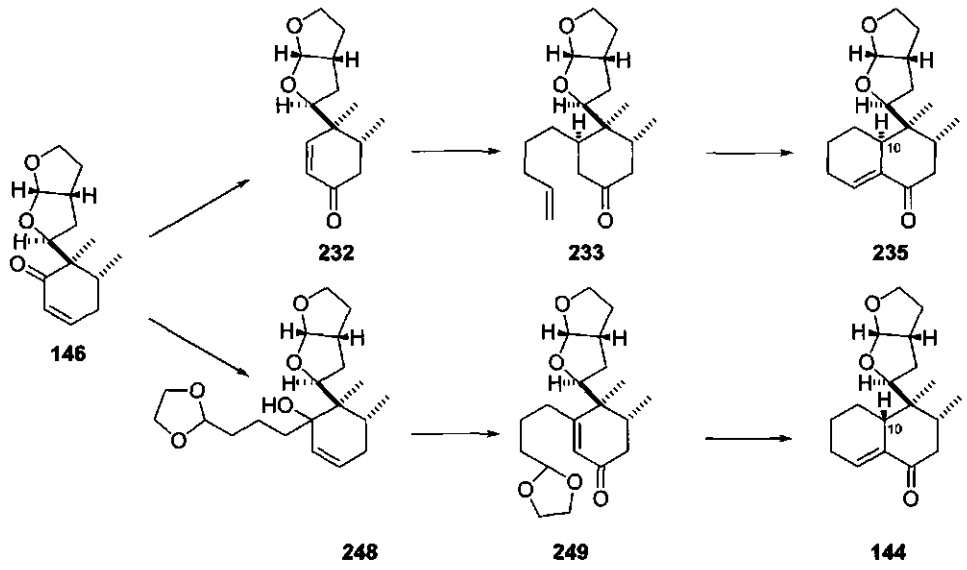
The first enantioselective total synthesis of a clerodane oxidized at C4, C6, C11, C15, C16, and C19 and with a chiral center at C11 is described in this thesis. The introduction of the hexahydrofuro[2,3-*b*]furan moiety via a remarkably diastereoselective Mukaiyama reaction, as is described in chapter 2, is one of the key steps in this total synthesis, and we have shown that an early introduction of the hexahydrofuro[2,3-*b*]furan is a good strategy in the total synthesis of clerodanes. Since the hexahydrofuro[2,3-*b*]furanyl fragment has an acetal function, it was expected that it would survive basic conditions, oxidations, and reductions. And indeed in the course of this total synthesis this group has proven to be stable and survived nearly all the applied reaction conditions. It was also expected that acidic conditions had to be handled with some care and indeed this has proven to give some minor problems. When the hexahydrofuro[2,3-*b*]furanyl group is hydrolyzed under acidic conditions, this group will close again without stereochemical consequences, but when other ring closing reactions are possible, as is the case when a carbonyl function is located at C6 (see note 112, 120), acidic conditions have to be avoided. Despite its stability it was observed that many reactions gave lower yields compared to similar reactions with a 1,3-dioxolan-2-yl substituent at C9. This may also explain why the promising results of some reactions which were described in the literature with other substituents at C9, did not give good results in our compounds. The only case in which the hexahydrofuro[2,3-*b*]furan moiety seems to have a beneficial influence is in the final epoxidation by *m*-CPBA, where a better yield of the natural epoxide was obtained in comparison with similar reactions in the literature. Possibly, a first equivalent of *m*-CPBA complexes to the hexahydrofuro[2,3-*b*]furan moiety and blocks the β-side for reaction, followed by a second equivalent of *m*-CPBA, which reacts with the double bond from the α-side.

figure 6.2



The ring annulation of a highly functionalized cyclohexanone, did not give good results using the Robinson annulation as was described in chapter 4. Two reasons can be pointed out namely, the steric hindrance in the ring closure reaction and the possibility of a retro-Michael reaction. The retro-Michael reaction can occur in a system as depicted in path **A** (figure 6.2), nevertheless an approach via path **A** can be successful when the steric hindrance can be diminished by removal of the isopropenyl group as was shown in § 4.4. But in such an approach there will be no functionality at C6, and an introduction of this functionality after the ring annulation will be very difficult. When there is one additional carbon between the carbonyl group in the side chain and the carbonyl group in the cyclohexanone the retro-Michael reaction is not possible anymore (path **B**, figure 6.2). Therefore this is a better choice for the annulation of ring B in a highly substituted cyclohexanone, as is the case in our system. The ring annulation following path **B** also gives good access for the introduction of functionalities at C4, C5, and C6. Therefore the ring annulation via path **B** is the annulation of choice in our total synthesis of dihydroclerodin.

scheme 6.1

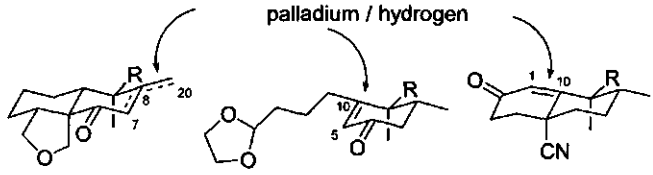


Two reaction sequences were studied for the introduction of a C_4-fagment at C10 (scheme 6.1). In the first reaction sequence a 1,3-enone transposition was performed in enone **146**, followed by a conjugate addition of the C_4-fragment. In this way the synthesis of the decalin system was achieved in an overall yield of 25% calculated from enone **146**, but in the thus obtained decalin system the configuration at C10 was opposite to the one in dihydroclerodin. A good solution was found for the annulation of ring A with the correct stereochemistry at C10 via the selective catalytic reduction of the C5-C10 double bond. Although the yield of the 1,2-addition of the C_4-fragment was not high (42%), the overall yield for the ring annulation is still a reasonable 21%. It should also be noted that when another substituent than the bulky hexahydrofuro[2,3-*b*]furanyl group is present at C9, the yield of the introduction of a C_4-fragment increases up to 90%.

Catalytic reductions of the C9-C17, C8-C20 and C8-C7 double bond in the clerodane skeleton were already reported in literature[132] to occur from the β-side. It was found that in our system the catalytic reductions of the C10-C5 and C1-C10 double bond also occur from the β-side.

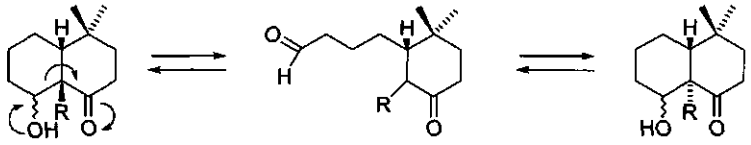
[132] (a) Luteijn, J. M.; de Groot, A. *J. Org. Chem.* **1981**, *46*, 3448-3452; (b) Luteijn, J. M.; de Groot, A. *Tetrahedron Lett.* **1982**, *23*, 3421-3424; (c) Sharma, A. S.; Gayan, A. K. *Tetrahedron* **1985**, *41*, 4581-4592; (d) Bruner, S. D.; Radeke, H.; Tallarico, J. A.; Snapper, M. L. *J. Org. Chem.* **1995**, *60*, 1114-1115; (e) Goldsmith, D. J.; Deshpande, R. *Synlett* **1995**, 495-497.

figure 6.3



The introduction of a substituent at C4 and the angular carbon at C5 via a conjugate addition to **144** followed by capturing of the enolate with monomeric formaldehyde was a tricky reaction. As was described in § 5.3 exclusion of oxygen was very important, and the yield of the reaction was moderate. Jones *et al.*[133] published a similar conjugate addition in the synthesis of ajugarin I with the same moderate yield. Capturing of the enolate after the conjugate addition as its silyl enol ether could be performed in good yield but the introduction of an angular substituent to this silyl enol ether could not be accomplished. A few other methods have been published for the introduction of an angular substituent to similar decalin systems, but only when an enone is situated at the C3-C5 position, a 1,4-addition of a cyano group at C5 was accomplished with the desired configuration for the synthesis of *trans*-clerodanes.[134] Other introductions at C5 lead to *cis*-decalin systems and consequently can not be used for the synthesis of *trans*-clerodanes. Isomerization at C5 can lead to the thermodynamic more stable *trans*-decalin system, when there is a possibility of opening the decalin ring system and closing it again, as was nicely illustrated by Lallemand *et al.* (scheme 6.2).[135]

scheme 6.2



269 R=CO_2Me **270** **271**

In the preparation of the epoxide at C4, some improvement is desirable. The hydroxyl directed epoxidation, using $VO(acac)_2$, of the exocyclic double bond does not give good results in the oxidation of compound **266**. A complexation of the vanadium reagent was observed but no epoxide was formed. The epoxidation by $VO(acac)_2$ and *t*-butyl hydroperoxide gave good results in model compound **273**. Oxidation of the exocyclic double bond in **266** by *m*-CPBA gave a 1:1 mixture of dihydroclerodin and 4-*epi*-dihydroclerodin, and in the epoxidation of **272** into

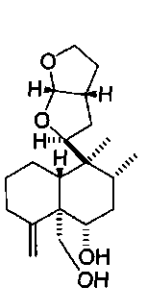
[133] Jones, P. S.; Ley, S. V.; Simpkins, N. S.; Whittle, A. J. *Tetrahedron* **1986**, *42*, 6519-6534.

[134] Tokoroyama, T.; Fujimori, K.; Shimizu, T.; Yamagiwa, Y.; Monden, M.; Lio, H. *Tetrahedron* **1988**, *44*, 6607-6622.

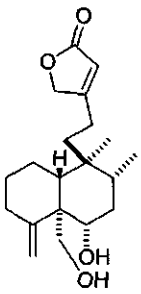
[135] Bouchard, H.; Lallemand, J. Y. *Tetrahedron Lett.* **1990**, *31*, 5151-5152.

ajugarin I, a 3:1 mixture was obtained in favor of 4-*epi*-ajugarin I. The big influence of the upper part of the molecule on reactions at the lower part of the compound is unexpected, as it is rather distant from the reaction center. Nevertheless this phenomenon has been observed in several situations.

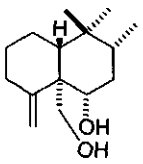
figure 6.4



266



272

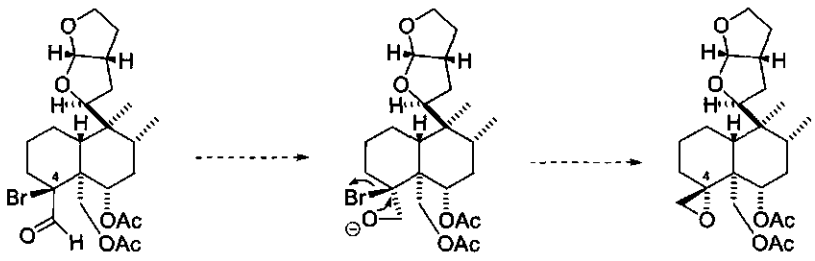


273

Addition at C4 usually occurs from the β-side, as was shown in the conjugate addition to enone **144** and in the α-bromination of aldehyde **255**. We wanted to use this selectivity to synthesize an epoxide by reduction of the α-bromoaldehyde **256** to an α-bromohydrine and subsequent cyclization to dihydroclerodin. The bromination occurred mainly from the β-side, but after reduction of the aldehyde function, the hydroxyl group reacted with the acetate groups to give a mixture of transposed acetates. Other protecting groups of the two hydroxyl groups at C6 and C19 might overcome this problem, but would have to be resistant to bromination, reduction, and basic conditions, and also must be cleaved again after the epoxide formation without demolishing the epoxide group. The use of an acetonide protecting group seemed to be a good candidate but it proved to be vulnerable during the bromination reaction. The use of benzyl ether protecting groups could be good candidates, but it is questionable if they can be prepared in good yield due to the steric congestion of the hydroxyl group at C6. The cleaving of the benzyl protecting groups should be possible because in the palladium catalyzed reduction of the C14-C15 double bond in clerodin by Barton *et al.*[136], no reduction of the epoxide was observed. Due to lack of time we did not investigate other bromination candidates or other protecting groups.

[136] Barton, D. H. R.; Cheung, H. T.; Cross, A. D.; Jackman, L. M.; Martin-Smith, M. *J. Chem. Soc.* **1961**, 5061-5073.

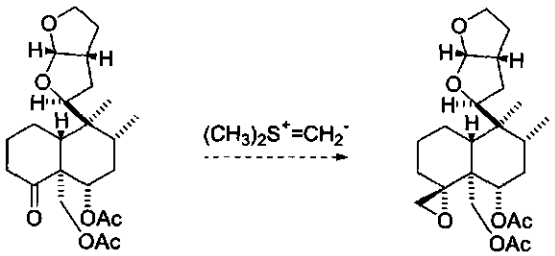
scheme 6.3



256 **274** **1**

Another possibility for the introduction of an epoxide is the Corey epoxidation[137] of a carbonyl group at C4. If the incoming carbene reacts from the β-side the desired epoxide may be obtained. At the end of the synthesis we have studied this reaction briefly but did not obtain any promising results. After the ozonolysis of the exocyclic double bond, a carbonyl group at C4 was obtained, but during the Corey reaction no epoxide formation was observed. This might be due to the steric hindrance at this carbonyl group which leads to enolization instead of addition. Alternatively the two acetate groups may interfere as they can not stand the basic epoxidation conditions.

scheme 6.4



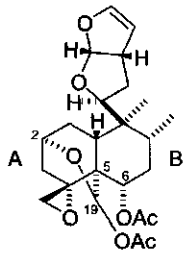
150 **1**

[137] Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353-1364.

6.4 Outlook of the approach, described in this thesis

In this paragraph the further challenges in the synthesis of clerodanes will be discussed. A total synthesis of the highly active clerodane jodrellin can be considered as the most challenging one. In the approach described in chapter 5 there is no easy access to functionalities at C2 in ring A. Therefore the synthesis of clerodanes possessing an ether bridge between the angular C19 and C2 do need an other approach.

figure 6.5



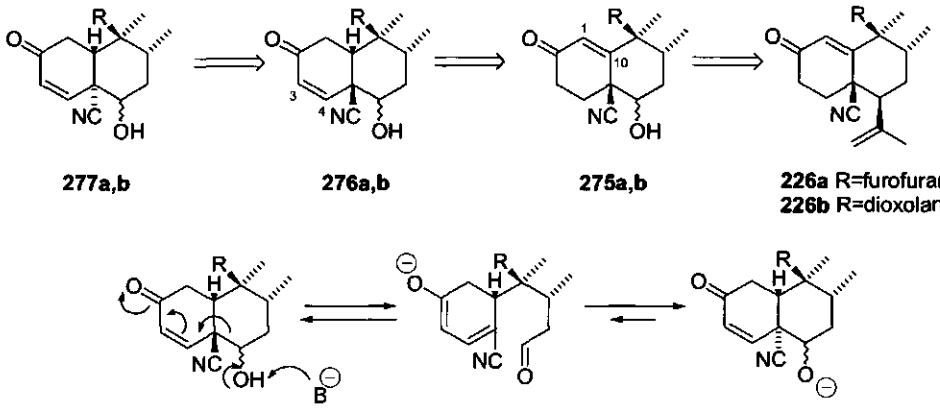
jodrellin

The Robinson annulation described in § 4.4, leads to a decalin system with a functionalized C2, and the desired configuration at C5, but a functionality at C6 in ring B is missing. The challenge will be to maintain the functionality at C6 without getting the wrong configuration at C5. Below two possibilities to solve this problem are briefly described.

Ozonolysis followed by Criegee rearrangement of decalin **226a,b**[138] will give alcohol **275**. Reduction of the C1-C10 double bond from the β-side and introduction of a double bond at the C3-C4 position by selenylation and oxidation-elimination of the selenide should give alcohol **276a,b**. Equilibration of this compound by a retro-aldol-aldol reaction may lead to compound **277a,b** with the nitrile group in the desired position (scheme 6.5). In ring B the C6 position is still functionalized and in ring A, the enone enables the introduction of the necessary functional group at C4. The carbonyl group at C2 is at the right place for the construction of the ether bridge.

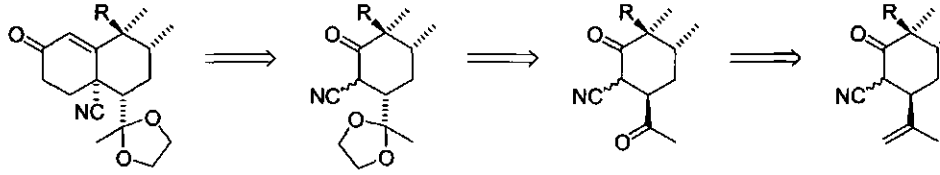
[138] see § 4.4

scheme 6.5



A second approach in which a functional group is maintained at C6 may be realized when the double bond in the isopropenyl group is ozonolyzed to an acetyl group which can be equilibrated to the equatorial position (scheme 6.6). The ring annulation of compound **224a,b** yielded a decalin in reasonable yield[138], and even though the protected acetyl group in compound **279a,b** is more bulky than the isopropenyl group, its interference in the ring closure reaction will be less because of its equatorial position. The Michael addition of methyl vinyl ketone to compound **279a,b** may be somewhat slow but these additions usually can be performed in good yield. In a suitable stage of the synthesis the acetyl group can be converted into an hydroxyl group by a Baeyer Villiger oxidation and the ring A can be functionalized as described in scheme 6.5.

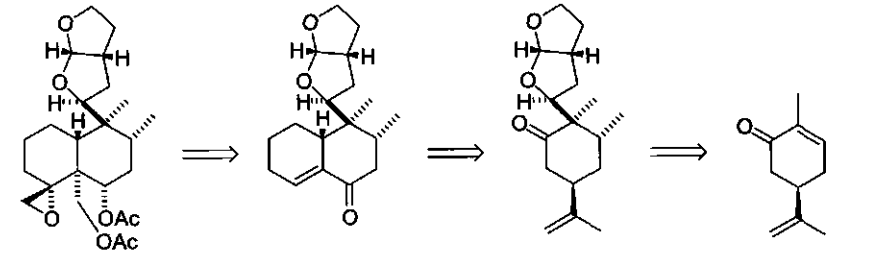
scheme 6.6



In the two approaches mentioned above the choice of substituent R for the upper part depends on the target molecule. For the synthesis of dihydrojodrellin both the dioxolanyl group and the hexahydrofuro[2,3-*b*]furan group can be used. The use of the hexahydrofuro[2,3-*b*]furan group as R substituent will give the possibility to use almost all reaction conditions, because of its stability, as is proven in the synthesis of dihydroclerodin in this thesis. When the dioxolanyl group is used as R substituent, acidic conditions should be avoided, but it is more flexible in syntheses of the upper part of the molecule.

7

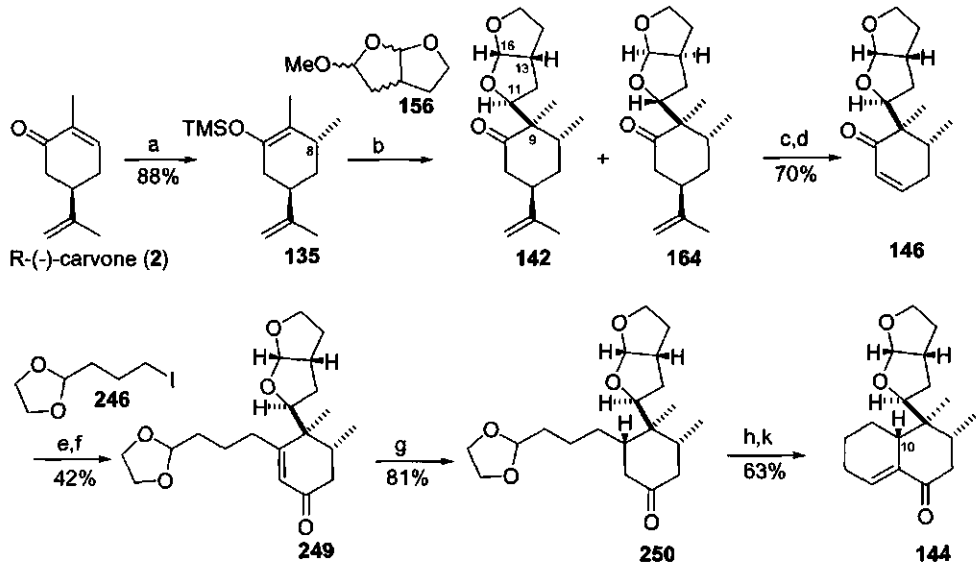
Summary



dihydroclerodin (**1**) **144** **142** R-(–)-carvone (**2**)

The first total synthesis of the natural enantiomer of the insect-antifeedant dihydroclerodin (**1**) and lupulin C (**268**) has been achieved in 18 and 17 steps respectively starting from R-(–)-carvone (**2**). A new strategy was developed in which the hexahydrofuro[2,3-*b*]furan fragment was introduced in the beginning of the synthesis, via a remarkably diastereoselective Mukaiyama reaction of silyl enol ether **135** with 2-methoxy-hexahydrofuro[2,3-*b*]furan (**156**), which gave only two of the possible eight diastereoisomers. After separation of the two diastereoisomers, ketone **142** with the correct configuration at C9, C11, C13, and C16 was obtained in an easy procedure (chapter 2). For the annulation of ketone **142**, the Robinson annulation was investigated first, but this did not give good results due to steric hindrance (chapter 4). To reduce the steric congestion, the isopropenyl group was transformed into a double bond by ozonolysis, followed by treatment of the ozonide with $Cu(OAc)_2$ and $FeSO_4$ to give enone **146**. A 1,2-addition of 3-(1,3-dioxolan-2-yl)-propyllithium to this enone, followed by an oxidative rearrangement yielded enone **249**. Catalytic reduction of this enone with palladium took place from the β-side and thus gave the correct stereochemistry at C10. Deprotection of the aldehyde, followed by an aldol reaction led to decalone **144**.

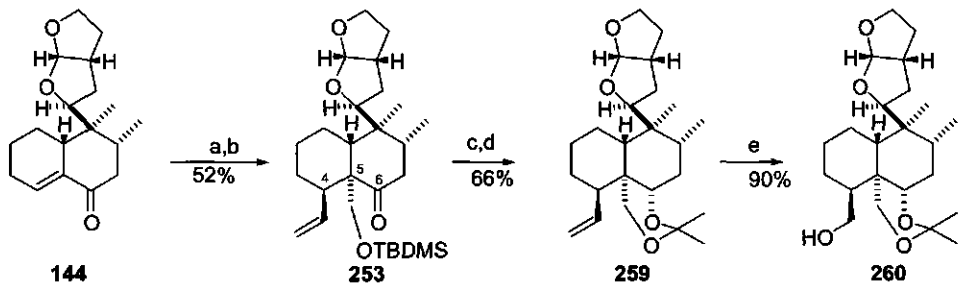
scheme 7.1



(**a**) MeMgI, CuBr•Me_2S, TMSCl; (**b**) $TrClO_4$, **156**; (**c**) separation of diastereoisomers; (**d**) i) O_3, ii) $Cu(OAc)_2$, $FeSO_4$; (**e**) *t*-BuLi, **246**; (**f**) PCC; (**g**) Pd/C, H_2; (**h**) PPTS, H_2O; (**k**) PPTS, Δ.

The conjugate addition of vinylmagnesium bromide to **144** and trapping of the enolate with a solution of monomeric formaldehyde introduced the last carbon atoms of the clerodane skeleton and established the desired stereochemistry at C5. The hydroxyl group was protected as its silyl ether (**253**) to ensure a selective reduction of the carbonyl function to give a diol with the desired configuration at C6. The obtained diol was protected as its acetonide, followed by ozonolysis of the double bond, and subsequent reduction of the ozonide gave alcohol **260**.

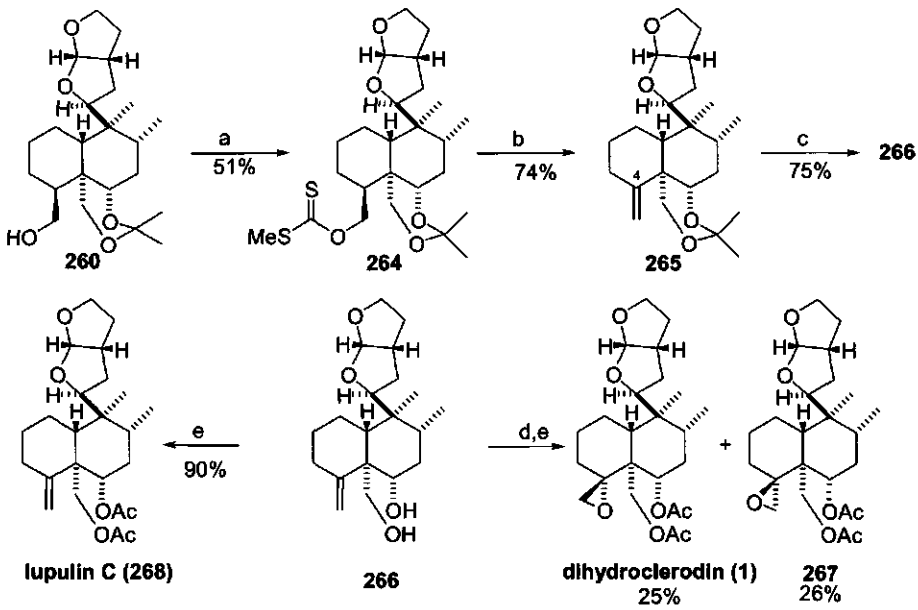
scheme 7.2



(**a**) i) vinylMgBr, $CuBr{\cdot}Me_2S$, ii) CH_2O; (**b**) TBDMSiCl, imidazole; (**c**) $LiAlH_4$; (**d**) MeO_2CMe_2, PPTS; (**e**) i) O_3, ii) $NaBH_4$.

To obtain an exocyclic double bond at C4, the hydroxyl group in compound **260** was transformed into its xanthate ester **264**. Elimination of this ester at 216°C gave the Chugaev elimination to **265**. After careful deprotection of the acetonide, an epoxidation of the double bond by *m*-CPBA was carried out. Acetylation of the hydroxyl groups then gave dihydroclerodin (**1**) and *epi*-dihydroclerodin (**268**) which could be separated by flash column chromatography. The measured $[\alpha]_D$ fitted well with reported optical rotations of dihydroclerodin isolated from natural sources, which proved that we had synthesized the natural enantiomer of dihydroclerodin. Acetylation of diol **266** completed the synthesis of lupulin C (chapter 5).

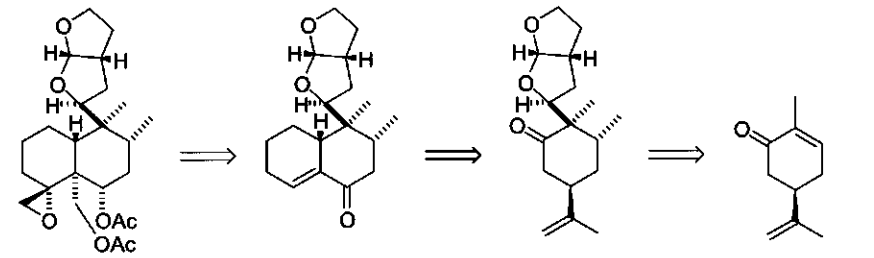
scheme 7.3



(**a**) i) NaH, CS_2, ii) MeI; (**b**) 216°C; (**c**) CF_3CO_2H; (**d**) *m*-CPBA; (**e**) Ac_2O, pyridine, DMAP.
overall yield of 0.35% in 18 steps

8

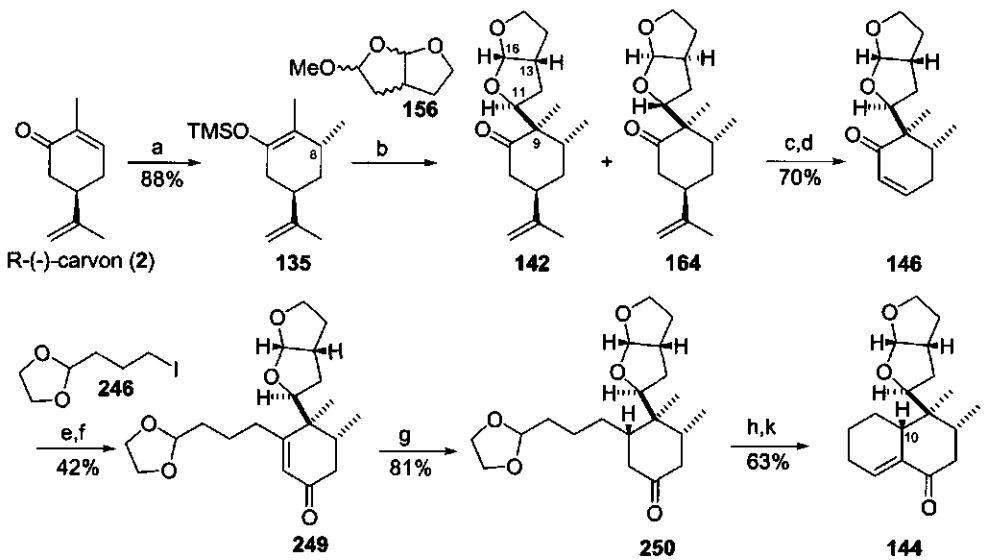
Samenvatting



dihydroclerodin (**1**) **144** **142** R-(–)-carvon (**2**)

In dit proefschrift wordt de eerste totaalsynthese van de insektvraatremmer dihydroclerodin (**1**) en lupulin C (**268**) beschreven, waarbij R-(–)-carvone (**2**) als uitgangsstof diende in de 18- respectievelijk 17-staps totaalsynthese. Een nieuwe strategie is ontwikkeld waarin een opmerkelijk diastereoselectieve Mukaiyama reactie van silyl enol ether **135** met 2-methoxy-hexahydrofuro[2,3-*b*]furan (**156**) de sleutel reactie is. Deze reactie geeft slechts twee van de acht mogelijke diastereomeren en het gewenste keton **142** is gemakkelijk te scheiden van het ongewenste diastereomeer **164**. Het keton **142** heeft de correcte configuratie op C9, C11, C13 en C16 (hoofdstuk 2). Om vanuit keton **142** het bicyclische systeem van dihydroclerodin op te bouwen, werd eerst de Robinson annelering onderzocht, maar door te grote sterische hinder was deze weg niet succesvol (hoofdstuk 4). Om deze sterische hinder te verminderen werd de isopropenyl groep met behulp van ozon, $Cu(OAc)_2$ en $FeSO_4$ omgezet in een dubbele binding en dit leverde enon **146** op. Een 1,2-additie van 3-(1,3-dioxolan-2-yl)-propyllithium aan dit enon, gevolgd door een oxidatieve omlegging, leverde enon **249** op. De katalytische reductie van dit enon met behulp van palladium vond plaats vanaf de β-zijde en dit leidde tot de gewenste configuratie op C10. Ontscherming van het aldehyde, gevolgd door een ring sluiting leverde decalon **144** op.

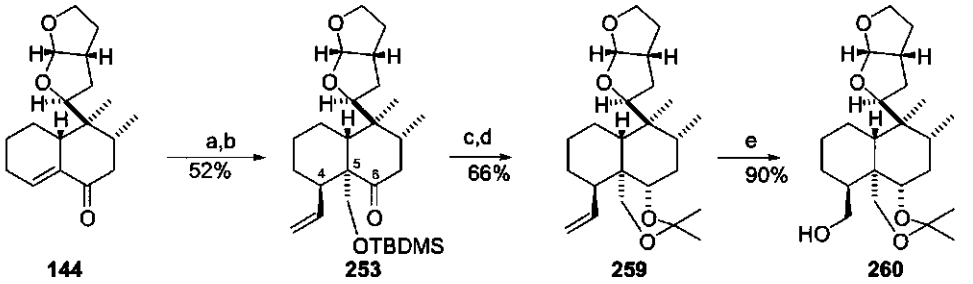
schema 8.1



(**a**) MeMgI, CuBr•Me_2S, TMSCl; (**b**) $TrClO_4$, **156**; (**c**) scheiden van de diastereoisomeren; (**d**) i) O_3, ii) $Cu(OAc)_2$, $FeSO_4$; (**e**) *t*-BuLi, **246**; (**f**) PCC; (**g**) Pd/C, H_2; (**h**) PPTS, H_2O; (**k**) PPTS, Δ.

De laatste koolstofatomen van het clerodaan skelet werden ingevoerd door middel van een geconjugeerde additie van vinylmagnesium bromide aan **144** en het afvangen van het ontstane enolaat met formaldehyde, waarbij de correcte stereochemie op C5 ontstond. De hydroxyl groep werd beschermd als een silyl ether (**253**) om er voor te zorgen dat de carbonyl groep op C6 selectief gereduceerd kon worden tot een alcohol met de gewenste configuratie. Na opwerken werd een diol verkregen, dat beschermd werd als acetonide. Ozonolyse van de vinyl groep in verbinding **259** en reductie van het ozonide met $NaBH_4$ leverde alcohol **260** op.

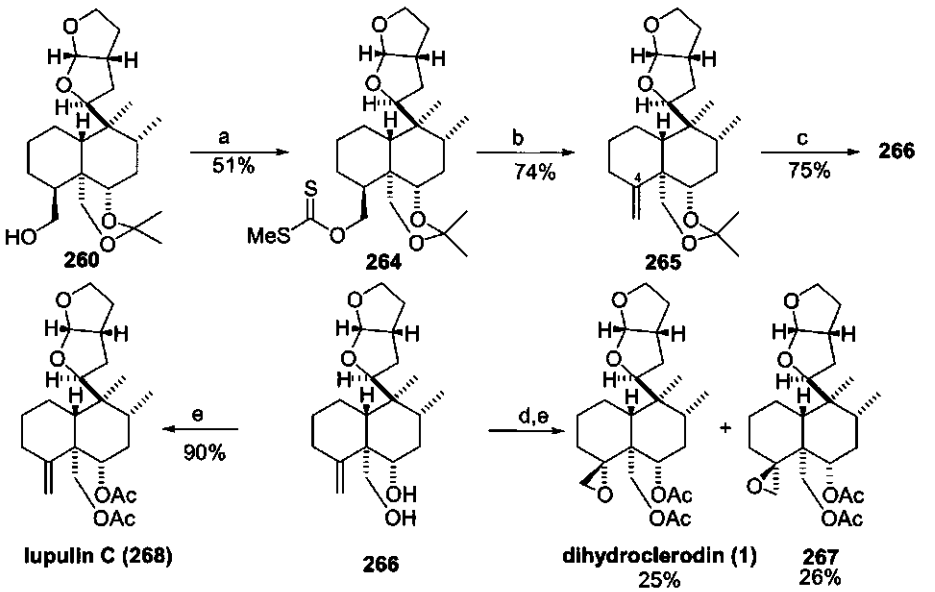
schema 8.2



(**a**) i) vinylMgBr, $CuBr{\bullet}Me_2S$, ii) CH_2O; (**b**) TBDMSiCl, imidazol; (**c**) $LiAlH_4$; (**d**) MeO_2CMe_2, PPTS; (**e**) i) O_3, ii) $NaBH_4$.

Om een exocyclische dubbele band te verkrijgen op C4, werd de hydroxyl groep in **260** omgezet in een xanthaat ester. Eliminatie van deze ester bij een temperatuur van 216°C leidde tot verbinding **265** (Chugaev reactie). Na voorzichtige ontscherming van diol **266** werd de dubbele binding geëpoxideerd met behulp van *m*-CPBA. Na acetylering van de hydroxyl groepen werden dihydroclerodin (**1**) en *epi*-dihydroclerodin (**268**) verkregen in een 1:1 verhouding. De gemeten $[\alpha]_D$ van dihydroclerodin was ongeveer gelijk aan de in de literatuur vermelde optische rotatie van natuurlijk dihydroclerodin en dit betekende dat we inderdaad het natuurlijke enantiomeer van dihydroclerodin gesynthetiseerd hadden. De synthese van lupulin C werd voltooid door acetylering van diol **266** (hoofdstuk 5).

schema 8.3



(**a**) i) NaH, CS_2, ii) MeI; (**b**) 216°C; (**c**) CF_3CO_2H; (**d**) *m*-CPBA; (**e**) Ac_2O, pyridine, DMAP.
totaal opbrengst van 0.35% in 18 stappen

List of abbreviations and terms

See standard list of abbreviations *J. Org. Chem.* 64, **1999**, 21A

α-side	Below the plane of the paper in a quasi planar drawn structure.
β-side	Above the plane of the paper in a quasi planar drawn structure.
	Nomenclature in Organic Chemistry, Pergamon Press, 1979, rule F-6.2.
NMO	N-methylmorpholine N-oxide
TPAP	Tetrapropylammonium perruthenate
PMB	*p*-Methoxybenzyl
Py	Pyridine
Tosmic	Tosylmethyl isocyanide
TBAF	Tetrabutylammonium fluoride
TPP	5,10,15,20-Tetraphenyl-21*H*,23*H*-porphine
disiamylborane	Bis-3-methyl-2-butyl-borane
D-CSA	D-(+)-10-Camphorsulfonic acid
Im	Imidazole
dba	(Dibenzylidene)acetone
DIPT	Diisopropyl tartrate
DET	Diethyl tartrate
$(DHQD)_2PHAL$	Hydroquinidine 1,4-phthalazinediyl diether
dppf	1,1'-Bis(diphenylphosphino)ferrocene

Curriculum Vitae

Tommi Maria Meulemans werd geboren op 26 oktober 1969 te Nijmegen. In 1987 behaalde hij het HAVO-diploma aan de Nijmeegse Scholen Gemeenschap. Na zijn propedeuse HLO te Nijmegen begon hij in 1988 aan zijn studie scheikunde aan de Rijksuniversiteit Groningen. Tijdens de doctoraalfase koos hij voor de afstudeerrichting Organische Chemie. Het doctoraalexamen werd afgelegd in 1993. Van 1995 tot en met 1999 was hij werkzaam als Onderzoeker in Opleiding (OIO) bij de vakgroep organische chemie van Wageningen Universiteit. Daar werd het in dit proefschrift beschreven onderzoek verricht onder leiding van prof. dr. Aede de Groot en dr. Ben Jansen. Vanaf februari 2000 is hij bij diezelfde universiteit werkzaam als post-doc bij de vakgroep industriële microbiologie.