VRIJE UNIVERSITEIT

DESIGN AND SYNTHESIS OF RATJADONE ANALOGUES

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. T. Sminia,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de faculteit der Exacte Wetenschappen
op donderdag 15 december 2005 om 13.45 uur
in de aula van de universiteit,
De Boelelaan 1105

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Voor Henrique

Cover picture: *Center:* 3D representation (including molecular orbital total charge density energy surface) of the minimized energy structure of compound **201** as calculated by CambridgeSoft Chem3D (Mechanics calculations). *Left top:* NOE relations in compound **94a**, indicating all-*cis* conformation. *Right top:* Diene-controlled asymmetric HDA reaction furnishing key compound **94**. *Left bottom:* Mechanism of SeO_2-mediated allylic oxidation. *Right bottom:* Catalytic asymmetric HDA reaction affording compound **183**.

„In this house, we OBEY the laws of thermodynamics!“

- Homer Simpson -

Contents

Abbreviations

AD	asymmetric dihydroxylation
ax.	axial
BINOL	1,1´-binaphth-2,2´-ol
borsm	based on recovered starting material
Cp	cyclopentadienyl
CRM1/*crm1*	chromosome region maintenance
DET	diethyl tartrate
DMP	Dess-Martin periodinane
eq.	equatorial *or* equivalent
GAP	GTPase-activating protein
GDP	guanosine diphosphate
GI_{50}	concentration at which cell growth is inhibited 50%
GTP	guanosine triphosphate
HDA	hetero Diels-Alder
HIV	human immunodeficiency virus
HMDS	hexamethyldisilazane, hexamethyldisilazide
HPV	human papilloma virus
HOMO	highest occupied molecular orbital
IC_{50}	concentration at which cell growth is inhibited 50%
LC_{50}	concentration at which letality is 50%
LMB	leptomycin B
MDM2	murine double minute 2

NES	nuclear export sequence
NLS	nuclear localization sequence
NPC	nuclear pore complex
RanBP	Ran-binding protein
RCC	regulator of chromosome condensation
SAR	structure-activity relationships
TGI	concentration at which tumor growth is completely inhibited
THP	tetrahydropyran, -yl

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Introduction

1 Introduction

1.1 General introduction

Natural products play a key role in modern drug development. According to a recent survey, up to 40% of al current trade drugs are natural products, or compounds derived or otherwise inspired by them.[1-6] Considering the fact that these compounds constitute less than 1% of all screened compounds, it is clear that their success rate in terms of the probability to find activity is much higher than for fully synthetic compounds. This is hardly surprising, since natural products are in essence already optimized structures being the result of millions of years of evolution. The fact that many biologically active natural products with a certain native target also bind to human proteins can be rationalized by the occurence of a limited number of protein folding types in nature.[7,8] These are conserved amino acid sequences in proteins that fold in a particular manner, quite independent of the rest of the protein. Through recombination and mutation of folding sequences, new proteins evolve. This theory provides a strong argument not only for natural products research, but for synthesis of derivatives and analogues of natural products as well.

Another argument for natural products as starting points for drug development is the observation that they commonly fit Lipinski's rule of five,[9*] an important tool to estimate bioavailability on the basis of structure, equally well as current trade drugs.[10]

* Based on an analysis of orally available drugs, Lipinski and co-workers postulated the now famous "rule of five". The rule states that, in order to be orally available, drug-like compounds should have: (a) not more than 5 hydrogen bond donors (-OH and –NH groups); (b) not more than 10 hydrogen bond acceptors (notably O and N); (c) a molecular weight under 500, and (d) a log P value under 5.

Synthetic drugs are often rich in five- and six-membered nitrogen-containing aromatic heterocycles and therefore relatively rigid. These substructures are much less common in natural products, which are often more or less flexible structures in dynamic equilibria. Some of nature's strategies to limit conformational freedom in principally linear compounds like polyketides are e.g. formation of medium and large rings (macrocycles)[11] or formation of tetrahydropyran (THP) and -furan rings. In some cases, the stereochemistry of methyl substituents on a linear polyketide chain may govern the overall conformation of the molecule through 1,3-allylic strain or *syn*-pentane interactions.[12] All of the above structural elements impose a preferred conformation on the molecule, but still leave it quite flexible. This is in accordance with the currently accepted "hand-and-glove" model for receptor-substrate binding rather than the earlier "key-and-lock" model.[13]

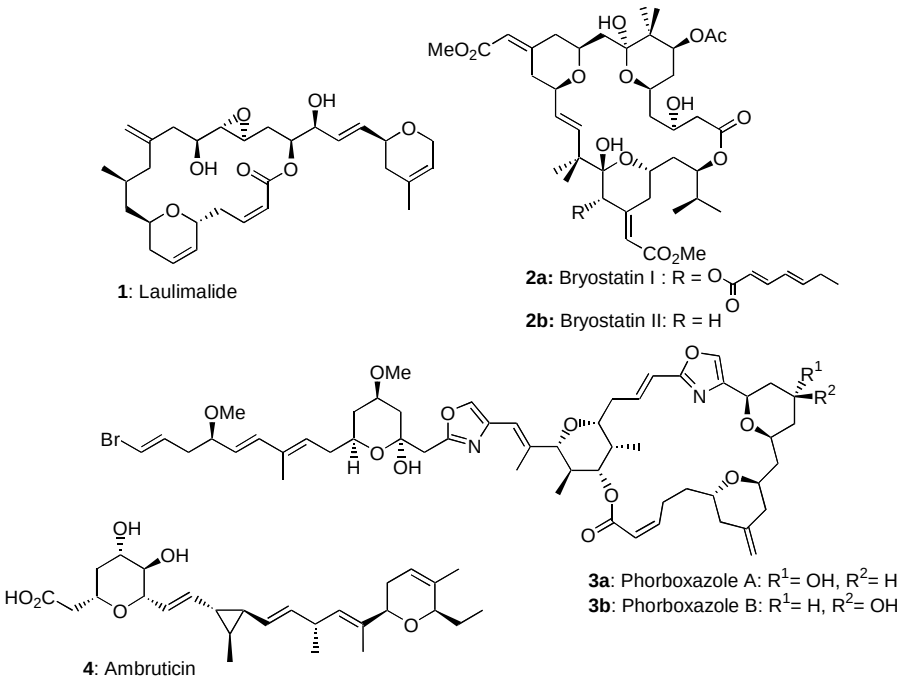


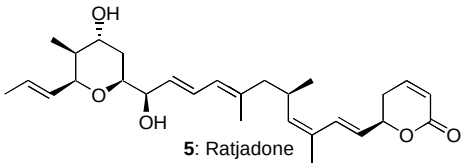
Figure 1.1. THP-containing biologically active natural products.

Tetrahydropyran (THP) rings are common structural motifs in biologically active natural products,[14] including laulimalide (**1**), bryostatins I (**2a**) and II (**2b**), phorboxazoles A (**3a**)

and B (**3b**), and ambruticin (**4**, see Fig. 1.1). Such compounds are mainly of polyketide origin and the THP rings result from cyclization through two oxygen functionalities in a 1,5-relationship.

1.2 Ratjadone and the leptomycin family

A THP-containing polyketide natural product with exceptionally high biological activity is ratjadone (**5**, Fig. 1.2). It was isolated from the myxobacterium *Sorangium cellulosum* present in a soil sample collected in Cala Ratjada (Mallorca, Spain) by Höfle and Reichenbach and co-workers in 1995.[15,16] It was originally selected for its modest antifungal activity against *Mucor hiemalis*, *Phytophthora drechsleri*, *Ceratocystis ulmi*, and *Monilia brunnea*, but was soon shown to possess very strong cytotoxic properties, with IC_{50} values in the picomolar range for a variety of mammalian cell lines.[15,16]



5: Ratjadone

Figure 1.2. Ratjadone.

Ratjadone is a member of a group of structurally similar compounds generally referred to as the leptomycin family, after its most prominent representative, leptomycin B (**6**). Other members include callystatin A,[17,18] the kasuza- and anguinomycins, leptolstatin,[19] and the leptofuranins[20,21] (Fig. 1.3). Recently, Höfle and co-workers isolated several other ratjadones from another strain of *Sorangium cellulosum* and named these ratjadones B-D (Fig. 1.3), while renaming the original ratjadone to ratjadone A.[22] For the sake of simplicity, ratjadone A will be referred to in this thesis as ratjadone.

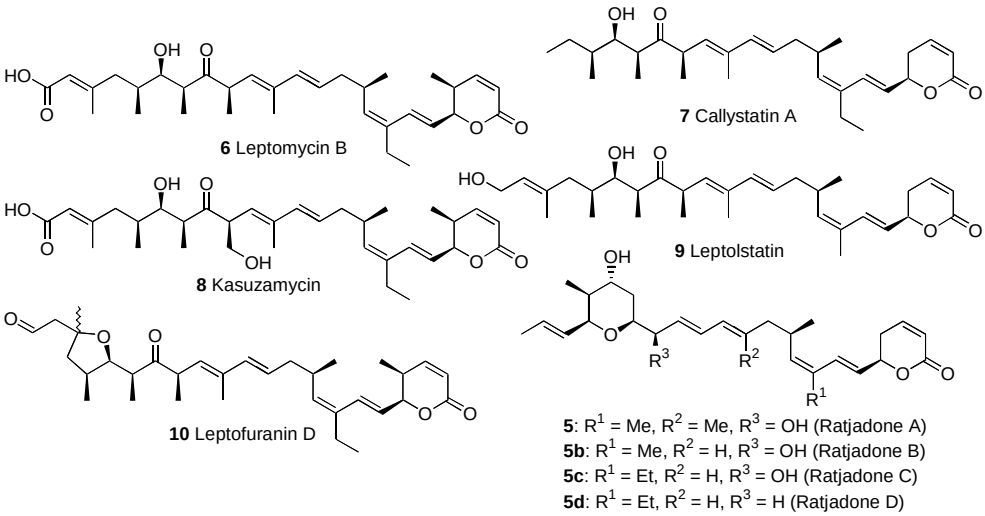


Figure 1.3. Members of the leptomycin family, including the ratjadones.

1.2.1 Inhibition of nuclear export of proteins

Leptomycin B (LMB, **6**) was demonstrated to inhibit the function of the *crm1* gene, which was shown to be required for maintaining correct chromosome structure in the fission yeast *Schizosaccharomyces pombe*.[23] Later, the corresponding CRM1 protein was found to have a much broader function, namely nuclear export of proteins, many of which are essential for cell growth. As a result, the cell cycle is arrested in the G1 phase upon exposure to LMB (**6**). There are two main routes for the export of proteins from the cell nucleus to the cytosol. The first involves proteins carrying nuclear localization sequences (NLS), rich in basic amino acids, and this route is responsible for a major part of subcellular distribution of proteins. The second route concerns proteins carrying nuclear export sequences (NES) rich in leucine. CRM1/exportin 1 was shown to be a receptor for NES in both higher and lower eukaryotes.

Nuclear export of NES-carrying proteins by CRM1 is regulated by the GTPase Ran (see Fig. 1.4), which exists primarily in the GTP-bound state in the nucleus due to the high GTP/GDP ratio and the action of the nucleotide exchange factor RCC1.[24] CRM1, RanGTP

and a NES-carrying cargo protein associate to form a complex, which is transported from the nucleus to the cytoplasm through the nuclear pore complex (NPC). There, the complex is rapidly dissociated by the action of RanBP1 and RanBP2.[25] In addition, the cytoplasmic protein RanGAP stimulates the GTPase activity of Ran and thus converts it to its GDP-bound state, preventing reassociation of the complex.[26] The cargo protein is released into the cytoplasm and CRM1 and RanGDP are shuttled back to the nucleus.

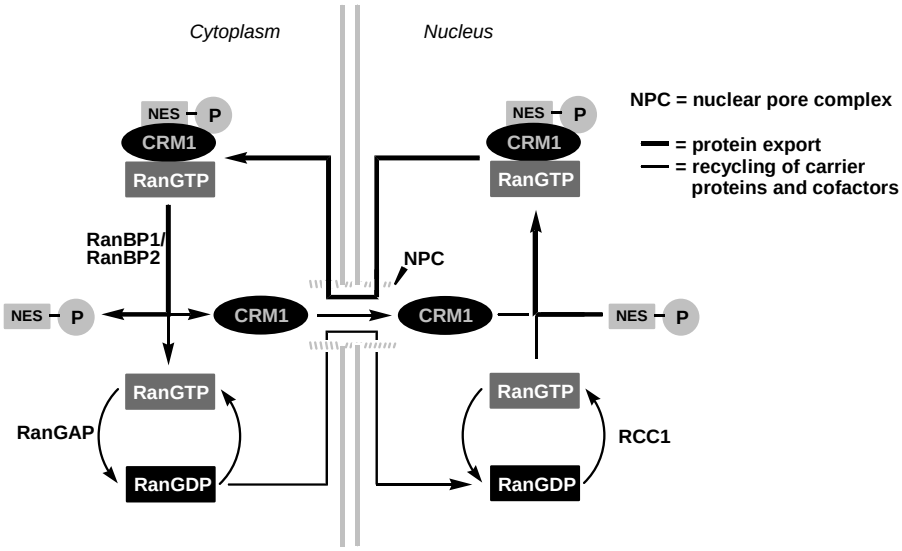


Figure 1.4. RanGTP-dependent nuclear export of proteins by CRM1.

It has been suggested that leptomycin B inhibits the CRM1 protein of *S. pombe* by covalent bonding through Michael addition of Cys529 to the α,β-unsaturated lactone moiety.[27] Cys529 lies in the "central conserved region", which is thought to be involved in NES binding.[28] This hypothesis is supported by the fact that *Saccharomyces cerevisiae* (whose wild-type CRM1 protein contains a serine residue instead of cysteine), and a Cys529Ser mutant of *S. pombe*, are insensitive to leptomycin B. Serine residue hydroxyl groups typically do not react with α,β-unsaturated carbonyl compounds under physiological conditions. Indirect evidence was supplied by the strongly decreased activity of a leptomycin B derivative that is a nitromethane Michael adduct of the natural product and therefore not a Michael acceptor anymore.[27] Also, a synthetic octadecapeptide representing amino acid residues 513-530 of human CRM1 was shown to form an adduct with LMB by

mass spectrometry. A similar octadecapeptide, in which only the Cys residue was substituted by a Ser residue, did not display such adduct formation in the mass spectrometric analysis.[27] Recently, ratjadone and some of its minor natural derivatives were also shown to inhibit nuclear export, and covalent binding to *S. pombe* CRM1 protein through Michael addition was proven.[22]

Thus, the extremely high activity of the members of the leptomycin family can be related to covalent binding of the CRM1 cysteine residue to the α,β-unsaturated lactone in a Michael-type addition. Interestingly, LMB does not react with cysteine-containing compounds such as L-cysteine or glutathione under physiological conditions.[27] Therefore, Kudo *et al.* propose that the molecule initially binds to the CRM1 protein in a non-covalent manner, thereby facilitating Michael addition of the cysteine residue thiol group to the α,β-unsaturated lactone by proximity effects.[27]

Because of this dramatic and selective activity, leptomycin B (which is available by fermentation) has become an important tool in cell biology, and possible therapeutic applications of these compounds have also been suggested.[29] A possible basis for such an application is the effect of CRM1 on the activity of the p53 tumor suppressor protein. The p53 protein marks an important checkpoint in the cell cycle, as it screens the DNA for aberrations and abnormal proliferation.[29] Detection of such an abnormality leads to a cascade of cellular events and eventually to apoptosis. Inactivation of p53 is an important criterium for the development of cancer. Indeed, in more than half of all human tumors, the *P53* gene is mutated. In the majority of cancers in which the *P53* gene is not mutated, p53 activity is compromised in a different manner, such as downregulation of transcription or translation, or through excessive export of p53 from the cell nucleus, where the majority of cellular events concerning the cell cycle take place, to the cytosol.[29] In addition, degradation of p53 takes place in the cytoplasm, e.g. under the influence of the MDM2 oncoprotein or the HPV (human papilloma virus, an oncovirus) E6 protein.[30] Since the p53 protein carries an NES sequence,[31] regulation of CRM1 would be expected to influence the activity of p53 in the cell nucleus. Indeed, it has been demonstrated that p53 activity in the cell nucleus increases considerably upon treatment with leptomycin B.[30] Accumulation of p53 in the nucleus frequently results in apoptosis rather than growth arrest in cancer cells, especially in comparison with many other tissues.[29] It has been suggested that non-

genotoxic activation of p53 (such as that caused by treatment with leptomycin family members) may be particularly effective, whilst avoiding typical side effects caused by current cancer therapeutics.[29]

The obvious drawback to pharmaceutical application of compounds of the leptomycin family is their inherent cytotoxicity. A wide variety of other essential cellular processes are also compromised as a consequence of inhibition of CRM1. Therapeutic effects may, however, occur at subtoxic concentrations. Additionally, there may be a selectivity towards cancer cells. However, preliminary clinical trials with leptomycin B were halted due to secondary effects and problems with pharmacokinetic studies.[29] Nevertheless, the use of these compounds has been suggested for topical application for the treatment of tumors.[29]

Other protein substrates for CRM1 that are of clinical interest include the HIV-1 Rev protein[32] and the influenza ribonucleoprotein complex,[33] as well as other viral proteins.[34]

1.2.2 Williams' synthesis of (-)-ratjadone

Ratjadone has been the object of several total synthesis efforts, which will be discussed in the coming sections. In 2001, Williams et al. reported the total synthesis of the unnatural isomer (-)-ratjadone (**5a**).[35] The synthesis strategy involves an aldol-based reacion sequence to THP fragment **12**, followed by connection to linear C3-C14 fragment **13** and subsequent elaboration to (-)-ratjadone **5a**.

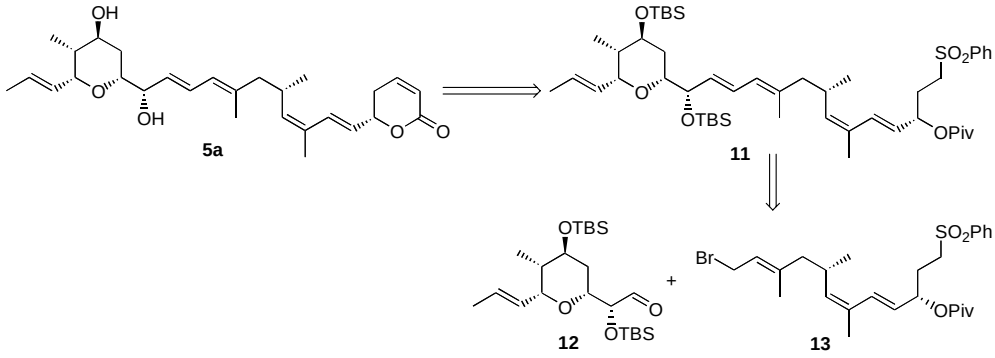
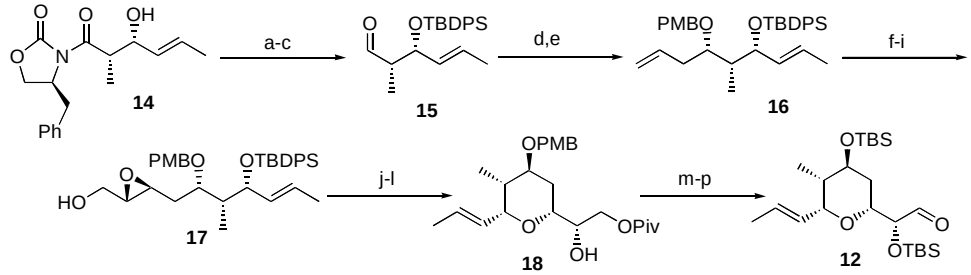


Figure 1.5. Retrosynthesis of Williams' total synthesis of (-)-ratjadone **5a**.

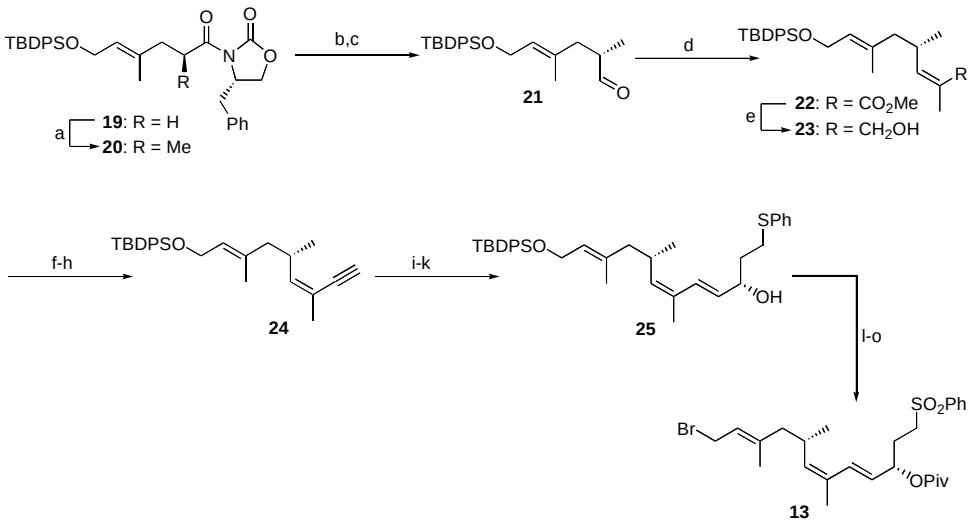
The forward synthesis commenced with conversion of known Evans' aldol product **14** to aldehyde **15** by TBDPS protection, reductive cleavage of the chiral auxiliary and subsequent Swern oxidation (Scheme 1.1). Brown asymmetric allylation using *B*–allyldiisocampheyl-borane followed by PMB protection then furnished **16**. The terminal olefin was converted to an aldehyde by selective Sharpless dihydroxylation and subsequent *in situ* vicinal diol cleavage. Wittig reaction followed by DIBAL-H reduction afforded an allylic alcohol, which was was subjected to Sharpless asymmetric epoxidation to give epoxide **17**. After protection of the primary alcohol as a pivaloate, TBDPS cleavage followed by treatment with acid triggered intramolecular epoxide opening to give **18**. Cleavage of the PMB protective group was then followed by double TBS protection. Reductive cleavage of the pivaloate followed by Dess-Martin oxidation[36] finally furnished THP building block **12**.



Scheme 1.1. (a) TBDPSCl, imidazole, CH_2Cl_2; (b) $LiBH_4$, Et_2O, H_2O, 84% over two steps; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 98%; (d) *B*-allyldiisocampheylborane, Et_2O, -78°C, 91%; (e) PMB trichloroacetimidate, CSA, CH_2Cl_2, 67%; (f) AD-mix α, *t*BuOH, H_2O, then $NaIO_4$, aq. THF, quant.; (g) $MeOC(O)CH=PPh_3$, CH_2Cl_2, 88%; (h) DIBAL-H, CH_2Cl_2, -78°C, 96%; (i) (+)-DET, $Ti(OiPr)_4$, 4Å sieves, *t*BuOOH, CH_2Cl_2, 98%; (j) PivCl, py, CH_2Cl_2, 95%; (k) TBAF, THF, 40°C, 82%; (l) CSA, CH_2Cl_2, 90 %; (m) CAN, CH_3CN, H_2O, quant.; (n) TBSCl, imidazole, DMAP, DMF, 91%; (o) DIBAL-H, CH_2Cl_2, -78°C, 99%; (p) DMP, $NaHCO_3$, CH_2Cl_2, 93%.

Synthesis of linear fragment **13** started with alkylation of known Evans' amide **19**[37] to give **20** in a 11:1 mixture of isomers favoring the desired 2'*S* isomer. Reductive cleavage of the auxiliary followed by Swern oxidation[38] afforded **21**. Still-Gennari reaction[39] and subsequent DIBAL-H reduction then furnished allylic alcohol **23**, which was subject to Swern oxidation,[38] giving an aldehyde that was converted to alkyne **24** using the Corey-

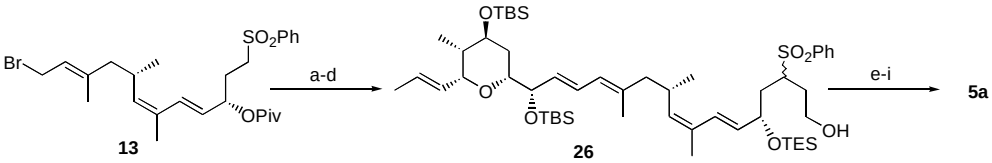
Fuchs[40] procedure. Wipf hydrozirconation followed by transmetallation to the organozinc reagent[41] and subsequent reaction with 3-phenylthiopropionaldehyde produced **25** as a mixture of diastereomers. After Dess-Martin oxidation[36], a Terashima reduction[42,43] introduced the desired *S*-configuration in **25** (5:1 mixture of diastereomers). Then, the thioether was converted to the sulfone and the free alcohol was protected as a pivaloate. Cleavage of the TBDPS ether and conversion of the resulting alcohol to the corresponding bromide then completed the synthesis of linear fragment **13**.



Scheme 1.2. (a) NaHMDS, THF, -78°C, then MeI, 81%, (2'*S*:2'*R* = 11:1); (b) $LiBH_4$, MeOH, Et_2O, 87%; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 94%; (d) $(CF_3CH_2O)_2P(O)CHMeCO_2Et$, KHMDS, 18-crown-6, THF, 99%; (e) DIBAL-H, Et_2O, -78°C, 98% (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (g) CBr_4, PPh_3, CH_2Cl_2; (h) *n*BuLi, THF, -78°C, 85% over three steps; (i) $Cp_2Zr(H)Cl$, CH_2Cl_2, 23°C, then Me_2Zn, -65°C, then 3-phenylthiopropionaldehyde, -65→0°C, 92%; (j) DMP, $NaHCO_3$, CH_2Cl_2, 84%; (k) $LiAlH_4$ (2.0 eq.), (-)-*N*-Me-ephedrine (2.0 eq.), *N*-ethylaniline (4.0 eq.), Et_2O, -78°C, 98%; (l) $(NH_4)_6Mo_7O_{24}$, H_2O_2, aq. EtOH, 0°C, 90%; (m) PivCl, py, DMAP, CH_2Cl_2, quant.; (n) TBAF, THF, quant.; (o) MsCl, collidine, CH_2Cl_2, then LiBr, THF, 82%.

The two main fragments **12** and **13** were now coupled by conversion of bromide **13** to the corresponding tributylphosphonium salt and Wittig reaction with **12**. Exchange of the pivaloate protective group for TES was followed by α-deprotonation of the sulfone and

subsequent reaction with ethylene oxide, installing the final two atoms of the (-)-ratjadone carbon skeleton. After Dess-Martin oxidation[36] of the primary alcohol, acidic cleavage of the TES ether afforded a lactol, which was then oxidized to the corresponding lactone. Basic elimination of the sulfone and cleavage of the TBS protective groups under mild conditions finally afforded (-)-ratjadone **5a**.



Scheme 1.3. (a) PBu_3, then **12**, toluene, then KO*t*Bu/THF, 0°C, 72%; (b) DIBAL-H, CH_2Cl_2, -78°C, 89%; (c) TESCl, py, CH_2Cl_2, 94%; (d) *n*BuLi, THF, HMPA, then ethylene oxide, 78%; (e) DMP, $NaHCO_3$, CH_2Cl_2; (f) PPTS, EtOH, 0°C; (g) TPAP, NMO, 4Å sieves, CH_2Cl_2, 86% over three steps; (h) DBU, toluene, 87%; (i) HF•py, py, THF, 76%.

1.2.3 Kalesse' synthesis of (+)-ratjadone

Shortly before Williams published his synthesis, Kalesse and co-workers reported their total synthesis of the natural isomer (+)-ratjadone (**5**). Kalesse used a much more elegant and convergent strategy (see retrosynthesis in Fig. 1.6) that employs a Heck coupling and a Wittig reaction to connect A (THP ring, **28**), B (chain, **29**), and C (lactone, **30**) fragments.[44,45] THP fragment **28** was constructed in a fashion similar to Williams' synthesis, but more efficiently. The synthesis of aldehyde **31** was achieved in analogy to the corresponding enantiomeric, PMB-protected aldehyde in the Williams' synthesis. A vinyloguous Mukaiyama aldol reaction[46] then afforded ester **32** in a single step, whereas a multistep procedure was required for the comparable transformation in the Williams'synthesis.

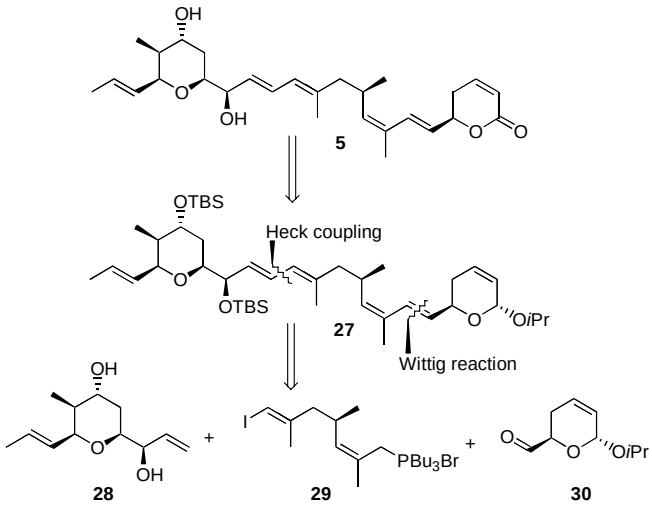
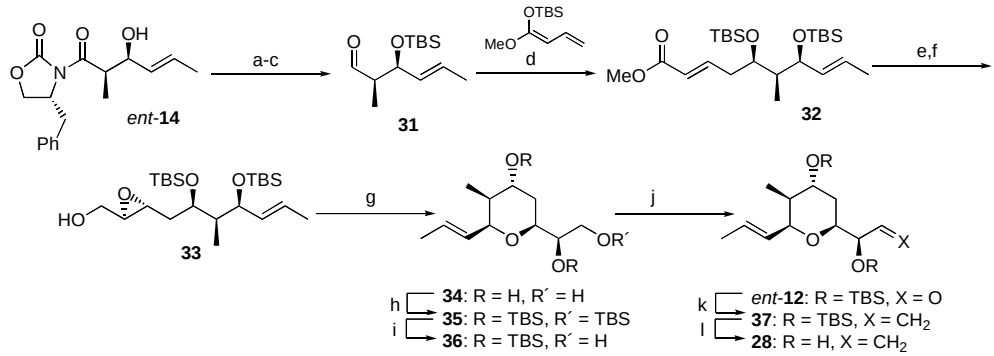


Figure 1.6. Retrosynthetic analysis of Kalesse's total synthesis of (+)-ratjadone

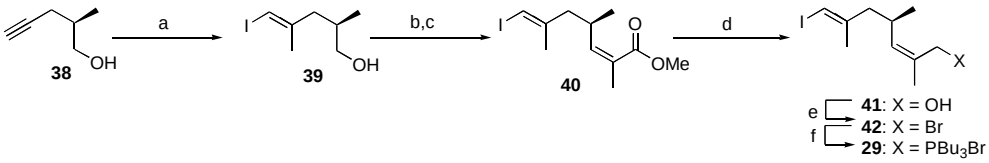
A more efficient and simpler protective group strategy in the following transformation reduces the number of steps in comparison with the Williams' synthesis. Construction of aldehyde *ent*-**12** from Evans' aldol *ent*-**14** required only 11 reaction steps in the Kalesse synthesis, compared to 17 steps for the enantiomeric species in the Williams' synthesis (Scheme 1.4).



Scheme 1.4. (a) MeONHMe•HCl, $AlMe_3$, CH_2Cl_2, -20→25°C; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, -78°C; (c) DIBAL-H, THF, -78°C, 83% over three steps; (d) $B(C_6F_5)_3$, CH_2Cl_2/Et_2O 9:1, -78°C, dr > 19:1, 80%; (e) DIBAL-H, THF, -78°C; (f) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 0°C, 85% over two steps; (g) (i) TBAF, THF, 88%; (ii) amberlyst-15, THF, 93%; (h) TBSOTf, CH_2Cl_2, -78°C, 87%; (i) HCl, $CHCl_3$, 97%; (j) DMP, CH_2Cl_2, 0°C, 92%; (k) Tebbe reagent, THF, 0°C, 95%; (l) TBAF, THF, quant.

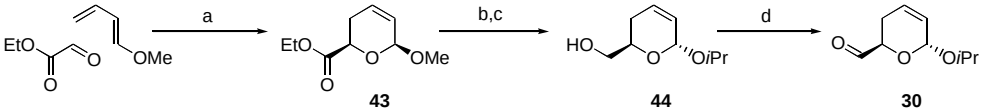
Treatment of aldehyde *ent*-**12** with Tebbe reagent furnished the required alkene **37**, and its unprotected form **28** was available by standard desilylation.

The B fragment **29** was constructed in a relatively short sequence from known alkyne **38**, which is available in five steps from commercial Roche ester [methyl (*S*)-3-hydroxy-2-methyl-propionate].[47] Carbometallation using the $Cp_2ZrCl_2/AlMe_3$ combination according to the Negishi protocol afforded vinylic iodide **39**. Dess-Martin oxidation and subsequent Still-Gennari reaction provided ester **40**, and DIBAL-H reduction followed by a two-step conversion of the resulting alcohol **41** to the corresponding tributylphosphonium bromide furnished B fragment **29**. The strength of this part of the synthesis is that protective groups are not required.



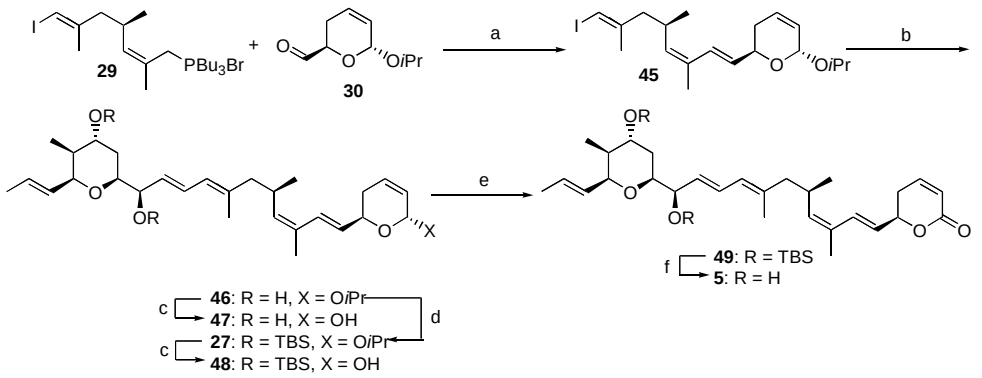
Scheme 1.5. (a) Cp_2ZrCl_2, $AlMe_3$, I_2, CH_2Cl_2, THF, -15→25°C, 83%; (b) DMP, CH_2Cl_2, 0°C, 81%; (c) $(CF_3CH_2O)_2P(O)CHMeCO_2Et$, KHMDS, 18-crown-6, THF, -78°C, 85%; (d) DIBAL-H, CH_2Cl_2, -78°C, 77%; (e) CBr_4, PPh_3, CH_3CN; (f) PBu_3, CH_3CN, 87% over two steps.

The carbon skeleton of the C fragment **30** was constructed in a single step by a $Ti(OiPr)_4$-catalyzed hetero Diels-Alder reaction between 1-methoxy-1,3-butadiene and ethyl glyoxylate.[48] The ester function of **43** was then reduced and the equatorial methyl acetal was converted to the more stable axial isopropyl acetal **44**. Subsequent Swern oxidation afforded the required aldehyde **30**.



Scheme 1.6. (a) $Ti(OiPr)_4$, (+)-BINOL, 4Å mol. sieves, CH_2Cl_2, 65%; (b) $LiAlH_4$, Et_2O, 0°C; (c) PPTS, *i*PrOH; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 77% over three steps.

The B and C fragments were efficiently connected by a Wittig reaction to give **45**. Heck reaction (which was shown to be the most efficient palladium-catalyzed cross-coupling reaction in preliminary studies) of **45** with alkene **37** afforded the desired coupling product **27** in 45% yield. However, when unprotected alkene **28** was used, the coupling reaction proceeded in 80% yield. Subsequent reprotection of the two free hydroxyl groups furnished **27**. After hydrolysis of the isopropyl acetal and oxidation of **48** to the lactone, the synthesis of (+)-ratjadone **5** was completed by mild hydrolysis of the TBS ethers.



Scheme 1.7. (a) KO*t*Bu, toluene, 0°C, 76%; (b) $Pd(OAc)_2$, Bu_4NBr, Cs_2CO_3, Et_3N, DMF, 80% with **28**, 45% with **37**; (c) PPTS, H_2O/acetone, 83%; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 83%; (e) MnO_2, CH_2Cl_2, py, 77%; (f) HF•py, THF, py, 76%.

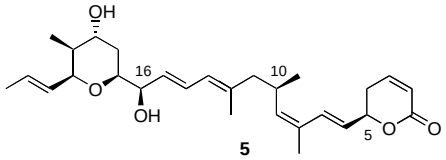
In conclusion, Kalesse's total synthesis of (+)-ratjadone features the efficient asymmetric synthesis of three fragments that are connected by two efficient coupling reactions. The specific planning of the synthesis limits the requirement for protective groups. This in turn reduces the number of steps and increases efficiency.

1.2.4 SAR studies of ratjadone

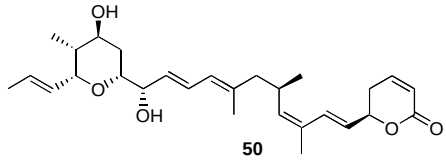
In a later study, Kalesse et al. published limited SAR data based on the biological evaluation of a small library of synthetic ratjadone analogues.[49] These compounds were mainly diastereomers, which were derived from connection of both enantiomers of

fragments **28**, **29**, and **30** in analogy to the total synthesis described above. The structures and activities of the tested compounds are shown in Table 1.1.

Table 1.1: Growth inhibition and LC_{50} values for compounds **5** and **50-54** against different cell lines (values in ng ml^{-1})



5



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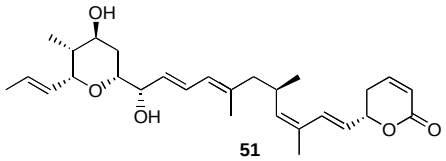

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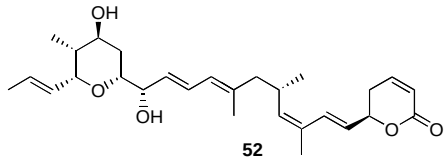

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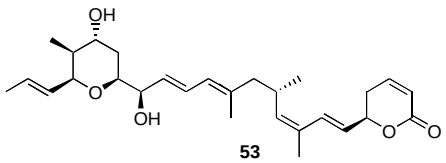

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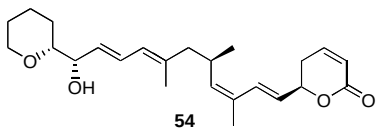


54

Compound	Cell line HM02			Cell line HEPG2			Cell line MCF7		
	GI_{50}	TGI*	LC_{50}	GI_{50}	TGI*	LC_{50}	GI_{50}	TGI*	LC_{50}
5	0.36	2.3	90	0.8	>100	>100	1.1	>100	>100
50	<5.0	24	250	13	>500	>500	16	>500	>500
51	17.0	>100	>100	85	>100	>100	25	>100	>100
52	>100	>100	>100	>100	>100	>100	>100	>100	>100
53	70	>100	>100	>100	>100	>100	75	>100	>100
54	5.0	140	>500	58	>500	>500	100	>500	>500

* TGI: concentration at which a complete inhibition of cell growth was observed.

This study shows that the stereochemistry at C10 is very important (10*R*:10*S* = 1:200), and it was suggested that it has a major influence on the overall conformation of the molecule by minimization of allylic and homoallylic strain. Indeed, such factors often govern conformation of open-chain compounds.[12] This suggestion was confirmed by modelling studies. The configuration at C5, which is extremely important in callystatin A (5*R*:5*S* =

1:350),[50] does not have such a pronounced influence in ratjadone (5*R*:5*S* = 1:20). Also, the absolute stereochemistry of the THP ring is relatively unimportant. Indeed, omission of all THP substituents only leads to minor loss of activity. This is somewhat surprising, since the presence of hydroxy and keto functionalities at the correct positions in the left-hand side of callystatin A are of major importance for the activity.[51] It should, however, be noted that although activity may be retained in this compound, the pharmalogical profile might differ significantly from natural ratjadone.

In addition, the fact that compounds lacking a complete lactone functionality show a complete loss of tumor growth inhibition demonstrates that the α,β-unsaturated lactone is crucial for the biological activity. Finally, replacement of the hydroxyl group at C16 by a keto function results in a major loss of biological activity, indicating that this functionality is important for receptor binding.

1.3 Aim of the project

We recognized a linear terpenoid-like structure in the polyene chain of ratjadone and decided to employ our experience in the application of bifunctional terpenoid building blocks in total synthesis to construct ratjadone analogues with terpenoid-derived polyene spacers.

We considered two different approaches to such compounds. Initially, the use of a one-carbon elongated farnesol derivative as a C5-C17 fragment was explored. Preliminary studies following this strategy showed that it had some complications mainly due to difficulties in synthesis and instability of aldehydes of type **56**, limiting efficiency and flexibility.

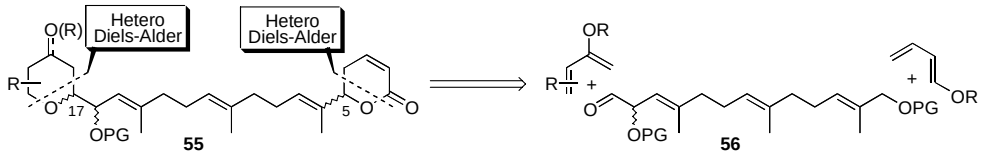


Figure 1.7. Retrosynthetic analysis of ratjadone analogues based on C1-elongated farnesol derivatives

In an alternative approach, bifunctional derivatives of geraniol and nerol (**59**) were considered as C7-C14 fragments and connected to preconstructed C1-C6 (**60**) and C15-C24 (**58**) fragments.

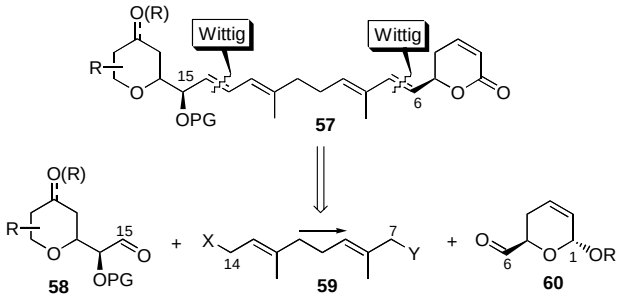


Figure 1.8. Retrosynthetic analysis of ratjadone analogues based on geraniol/nerol derivatives. Numbering is based on ratjadone numbering.

This strategy is similar to the convergent total synthesis strategy of Kalesse, and combines three building blocks of comparable size, *i.e.* A (THP ring, **58**), B (chain, **59**), and C (lactone, **60**) fragments. The possibility for diversity enhancement is increased, since not only the THP fragment can be varied, but also the polyene chain, by varying source (geraniol vs. nerol) and orientation of the bifunctional terpene derivative (Fig. 1.9).

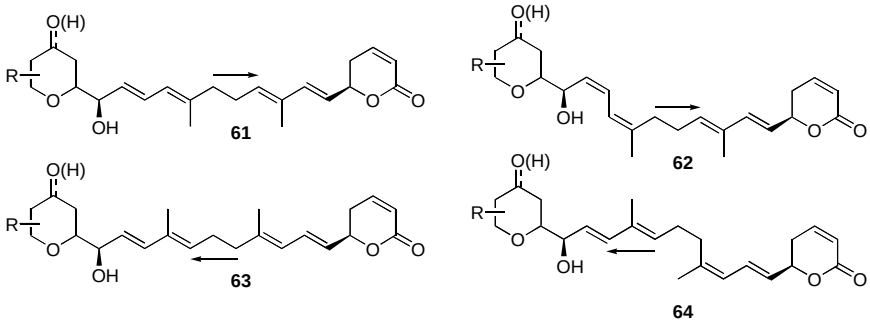


Figure 1.9. Different ratjadone mimics, varying in terpene source (geraniol (left) vs. nerol (right)) and orientation (→ vs. ←).

Kalesse et al. suggested a 3D structure in which the C1-C9 and C11-C24 moieties are perpendicular, imposed by C10 stereochemistry (due to allylic strain and *syn*-pentane interactions, Fig. 1.10) to rationalize the extreme difference in activity between natural (+)-ratjadone and its 10*S* isomer.[49] We calculated the minimum energy conformations for compounds **61**-**64** (with the same THP ring as natural ratjadone) and found that compound **61** in the low energy region adopts a very similar conformation as the natural product. It was therefore decided that the target ratjadone analogues should have a geraniol-derived terpenoid fragment in the same orientation as in **61** (Fig. 1.9).

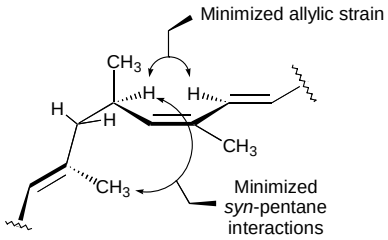


Figure 1.10. Twisted conformation of ratjadone chain governed by allylic strain and *syn*-pentane interactions suggested by Kalesse.[49,52]

Altogether, the route suggested in Fig. 1.8 can be deemed the most promising route with respect to accessability and variability. In combination with versatile new and existing routes to each of the components, this strategy should provide access to a wide variety of ratjadone analogues.

1.4 References

1. Newman, D.J.; Cragg, G.M.; Snader, K.M. *J. Nat. Prod.* **2003**, *66*, 1022-1037.
2. Rouhi, A.M. *Chem. Engin.* **2003**, 77-107.
3. Wessjohann, L.A.; Ruijter, E. *Top. Curr. Chem.* **2004**, *243*, 137-184.
4. Wessjohann, L.A.; Ruijter, E.; Garcia-Rivera, D.; Brandt, W. *Mol. Div.* **2004**, *9*, 171-186.
5. Henkel, T.; Brunne, R.M.; Mueller, H.; Reichel, F. *Angew. Chem.* **1999**, *111*, 688-691; *Angew. Chem. Int. Ed.* **1999**, *38*, 643-647.
6. Feher, M.; Schmidt, J., M. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 218-227.
7. Breinbauer, R.; Manger, M.; Scheck, M.; Waldmann, H. *Curr. Med. Chem* **2002**, *9*, 2129-2145.

8. Breinbauer, R.; Vetter, I.R.; Waldmann, H. *Angew. Chem.* **2002**, *114*, 3002-3015; *Angew. Chem. Int. Ed.* **2002**, *41*, 2878-2890.
9. Lipinski, C.A.; Lombardo, F.; Dominy, B.W.; Feeney, P.J. *Adv. Drug Delivery Rev.* **1997**, *46*, 3-25.
10. Lee, M.-L.; Schneider, G. *J. Comb. Chem.* **2001**, *3*, 284-289.
11. Nubbemeyer, U. *Top. Curr. Chem.* **2001**, *216*, 125-196.
12. Hoffmann, R.W. *Angew. Chem.* **2000**, *112*, 2134-2150; *Angew. Chem. Int. Ed.* **2000**, *39*, 2054-2070.
13. Koshland, D.E.J. *Angew. Chem. Int. Ed.* **1994**, *33*, 2375 - 2378.
14. Ruijter, E.; Schültingkemper, H.; Wessjohann, L.A. *J. Org. Chem.* **2004**, *70*, 2820-2823.
15. Schummer, D.; Gerth, K.; Reichenbach, H.; Höfle, G. *Liebigs Ann. Org. Bioorg. Chem.* **1995**, 685-688.
16. Gerth, K.; Schummer, D.; Höfle, G.; Irschik, H.; Reichenbach, H. *J. Antibiot.* **1995**, *48*, 973-976.
17. Kobayashi, M.; Higuchi, K.; Murakami, N.; Tajima, H.; Aoki, S. *Tetrahedron Lett.* **1997**, *38*, 2859-2862.
18. Murakami, N.; Wang, W.; Aoki, M.; Tsutsui, Y.; Higuchi, K.; Aoki, S.; Kobayashi, M. *Tetrahedron Lett.* **1997**, *38*, 5533-5536.
19. Abe, K.; Yoshida, M.; Horinouchi, S.; Beppu, T. *J. Antibiot.* **1993**, *46*, 728-734.
20. Hayakawa, Y.; Sohda, K.; Furihata, K.; Kuzuyama, T.; Shin-ya, K.; Seto, H. *J. Antibiot.* **1996**, *49*, 974-979.
21. Hayakawa, Y.; Sohda, K.; Seto, H. *J. Antibiot.* **1996**, *49*, 980-984.
22. Köster, M.; Lykke-Andersen, S.; Elnakady, Y.A.; Gerth, K.; Washausen, P.; Höfle, G.; Sasse, F.; Kjems, J.; Hauser, H. *Exp. Cell Res.* **2003**, *286*, 321-331.
23. Adachi, Y.; Yanagida, M. *J. Cell Biol.* **1989**, *108*, 1195-1207.
24. Bischoff, F.R.; Ponstingl, H. *Nature* **1991**, *354*, 80-82.
25. Kehlenbach, R.H.; Dickmanns, A.; Kehlenbach, A.; Guan, T.; Gerace, L. *J. Cell Biol.* **1999**, *145*, 645-657.
26. Bischoff, F.R.; Klebe, C.; Kretschmer, J.; Wittinghofer, A.; Ponstingl, H. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 2587-2591.
27. Kudo, N.; Matsumori, N.; Taoka, H.; Fujiwara, D.; Schreiner, E.P.; Wolff, B.; Yoshida, M.; Horinouchi, S. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 9112-9117.
28. Askjaer, P.; Jensen, T.H.; Nilsson, J.; Englmeier, L.; Kjems, J. *J. Biol.Chem.* **1998**, *273*, 33414-3342.
29. Lain, S.; Lane, D. *Eur. J. Cancer* **2003**, *39*, 1053-1060 and references cited therein.
30. Freedman, D.A.; Levine, A.J. *Mol. Cell. Biol.* **1998**, *18*, 7288-7293.
31. Stommel, J.M.; Marchenko, N.D.; Jimenez, G.S.; Moll, U.M.; Hope, T.J.; Wahl, G.M. *EMBO J.* **1999**, *18*, 1660-1672.

32. Wolff, B.; Sanglier, J.-J.; Wang, Y. *Chem. Biol.* **1997**, *4*, 139-147.
33. Watanabe, K.; Takizawa, N.; Katoh, M.; Hoshida, K.; Kobayashi, N.; Nagata, K. *Virus Res.* **2001**, *77*, 31-42.
34. *Nuclear Export of Viral RNAs*; Current Topics in Microbiology and Immunology, Vol. 259; Hauber, J. and Vogt, P.K. Eds.; Springer-Verlag, Germany, 2002.
35. Williams, D.R.; Ihle, D.C.; Plummer, S.V. *Org. Lett.* **2001**, *3*, 1383-1386.
36. Dess, D.B.; Martin, J.C. *J. Org. Chem.* **1983**, *48*, 4155-4156.
37. Evans, D.A.; Rieger, D.L.; Jones, T.K.; Kaldor, S.W. *J. Org. Chem.* **1990**, *55*, 6260-6268.
38. Mancuso, A.J.; Swern, D. *Synthesis* **1981**, 165-196.
39. Still, W.C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405-4408.
40. Corey, E.J.; Fuchs, P.L. *Tetrahedron Lett.* **1972**, *13*, 3769-3772.
41. Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197-5200.
42. Terashima, S.; Tanno, N.; Koga, K. *J. Chem. Soc. Chem. Commun.* **1980**, *21*, 1026-1027.
43. Terashima, S.; Tanno, N.; Koga, K. *Chem. Lett.* **1980**, 981-984.
44. Christmann, M.; Bhatt, U.; Quitschalle, M.; Claus, E.; Kalesse, M. *Angew.Chem.* **2000**, *112*, 4535-4538; *Angew. Chem. Int. Ed.* **2000**, *39*, 4364-4366.
45. Bhatt, U.; Christmann, M.; Quitschalle, M.; Claus, E.; Kalesse, M. *J. Org. Chem.* **2001**, *66*, 1885-1893.
46. Christmann, M.; Kalesse, M. *Tetrahedron Lett.* **2001**, *42*, 1269-1272.
47. Baker, R.; Brimble, M.A. *Tetrahedron Lett.* **1986**, *27*, 3311-3314.
48. Quitschalle, M.; Christmann, M.; Bhatt, U.; Kalesse, M. *Tetrahedron Lett.* **2001**, *42*, 1263-1266.
49. Kalesse, M.; Christmann, M.; Bhatt, U.; Quitschalle, M.; Claus, E.; Saeed, A.; Burzlaff, A.; Kasper, C.; Haustedt, L.O.; Hofer, E.; Scheper, T.; Beil, W. *Chembiochem* **2001**, *2*, 709-714.
50. Murakami, N.; Sugimoto, M.; Nakajima, T.; Kawanishi, M.; Tsutsui, Y.; Kobayashi, M. *Bioorg. Med. Chem.* **2000**, *8*, 2651-2661.
51. Murakami, N.; Sugimoto, M.; Kobayashi, M. *Bioorg. Med. Chem.* **2001**, *9*, 57-68.
52. Kalesse, M.; Christmann, M. *Synthesis* **2002**, 981-1003.

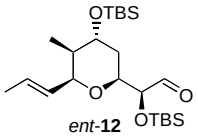
2

Synthesis of the ratjadone analogue A fragment

2 Synthesis of the ratjadone analogue A fragment

2.1 Retrosynthesis

The C15-C24 polyketide domain, or the A fragment, represents the greatest challenge from a synthetic point of view, containing five stereocenters and a six-membered ring. The ideal building block would be aldehyde *ent*-**12**, also featured in Kalesse´s total synthesis of ratjadone (Fig. 2.1).[1,2]



ent-**12**

Figure 2.1. THP fragment building block ***ent*-12**.

In this synthesis, the required linear precursor was synthesized by sequential Evans asymmetric aldol and vinylogous Mukaiyama aldol reactions[3] followed by epoxidation, and then cyclized by intramolecular epoxide opening. Although this is an effective and elegant route for total synthesis, it requires the use of an expensive chiral auxiliary [(*R*)-4-benzyloxazolidin-2-one] and is limited with respect to variation of the substituents on the ring. For our study towards ratjadone analogues, a method was required that would provide rapid access to structurally varied THPs. However, few general synthetic methods to substituted THPs are known. Two methods that have been employed for the synthesis of complex THP systems are the hetero Diels-Alder reaction and Prins-type cyclizations. The former is a Lewis acid-mediated formal [4+2] cycloaddition, and the latter is a cationic

cyclization of a species derived from a hemiacetal of a homoallylic alcohol and an aldehyde (see Fig 2.2).

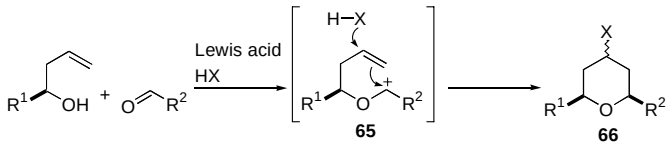
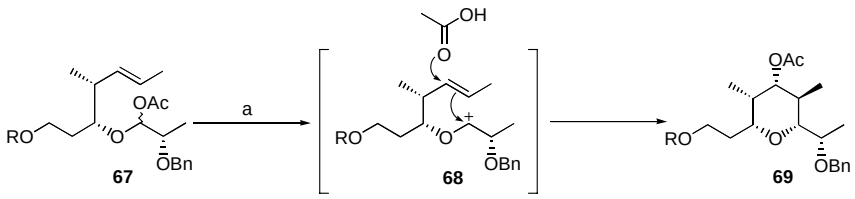


Figure 2.2. Prins cyclization

Recently, the Prins cyclization and related reactions have attracted significant attention from the synthetic community.[4-13] The original Prins cyclization involved a reaction between an aldehyde and a homoallylic alcohol, but recently variations involving e.g. preconstructed hemiacetal acetates have been described.[6,13] Such reactions have been successfully employed in the total and partial synthesis of natural products. An important advantage of this methodology is the possibility to construct tetrahydropyrans from readily available starting materials, namely simple aldehydes and homoallylic alcohols, which are available in enantiomerically pure form by Brown allylation (or crotylation). In some cases, yields and diastereoselectivities of Prins(-type) cyclizations are somewhat disappointing, although cases have been described where both yield and diastereoselectivity are excellent.[6,13] A major drawback of this type of reaction is the formation of side products, probably arising from an oxonia-Cope-type rearrangement,[6,12] especially when substituents at the 2- or 6-position stabilize the cationic intermediate.

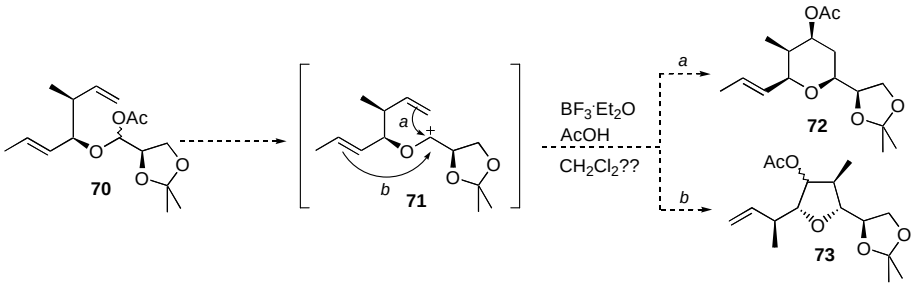


Scheme 2.1. Rychnovsky's synthesis of a pentasubstituted tetrahydropyran towards phorboxazoles. (a) cat. BF_3•Et_2O, AcOH, 52%.

Rychnovsky and co-workers described the synthesis of the C22-C26 THP segment of the phorboxazoles (cf. Fig. 1.1) by a stereoselective Prins cyclization of hemiacetal acetate **67**

(Scheme 2.1).[13] The resulting THP **69** shows significant similarity to the desired THP fragment for ratjadone analogs.

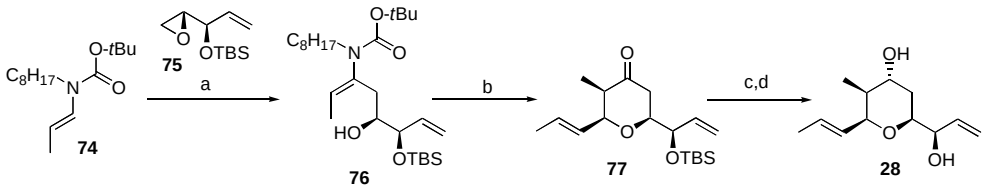
In order to construct such a fragment, cyclization precursor **70** would be required (Scheme 2.2). Hemiacetal acetate **70** would be available through asymmetric crotylation of crotonaldehyde and subsequent esterification with known (*R*)-(2*O*,3*O*-isopropylidene)glyceric acid, followed by DIBAL-H reduction and subsequent acetylation in analogy to Rychnovsky´s synthesis.[13]



Scheme 2.2. Hypothetical Prins-type cyclization of hemiacetal acetate **70**; divergent reaction pathways leading to a tetrahydropyran (*a*) and tetrahydrofuran (*b*) product.

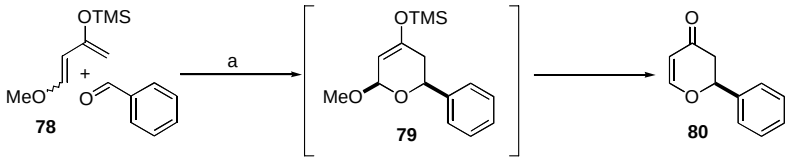
However, the important difference with the phorboxazole fragment lies in the presence of the propenyl substituent. Here, in addition to the THP Prins cyclization path (*a*) leading to **72**, an alternative cationic cyclization (*b*) to form THF compound **73** is possible. Such THF-forming Prins cyclizations are well-known reactions. Also, the propenyl substituent makes the cationic intermediate prone to oxonia-Cope-type rearrangements.[6,11] Therefore, this route was considered unlikely to be successful and was abandoned.

During the preparation of this manuscript, Cossey and Funk described the construction of THP fragment **28** (an intermediate in Kalesse's total synthesis of ratjadone) via a Prins-type cyclization of enecarbamate **76** (Scheme 2.3).[14] This strategy is based on an alternative bond construction, and employs a variation of the Prins cyclization that had not been previously described in literature. Obviously, this route provides very fast and efficient access to **28**.



Scheme 2.3. (a) *t*BuLi, -78°C→-50°C, 1.1 h, then **75**, BF_3•Et_2O, -78°C, 3 h, 62%; (b) CH_3CH=$CHCHO$, $InCl_3$, CH_2Cl_2, 84%; (c) Al(*i*Bu)$_3$, hexanes, -30°C, 1.5 h, 95% (ax./eq. = 48:52); (d) TBAF, THF, 100%.

Another excellent method for the construction of multiply substituted THPs is the hetero Diels-Alder (HDA) reaction. The HDA reaction is formally analoguous to the well-known Diels-Alder reaction, with the difference that one (or more) of the carbon atoms of either the diene or the dienophile is substituted by a heteroatom. Many variations of the HDA reaction have been described.[15] The version that is relevant to this study is the Lewis acid-catalyzed reaction between an electron-rich diene (often activated by oxygen substituents) and an aldehyde (see example Scheme 2.4). In the early 1980s, Danishefsky and co-workers first demonstrated the synthetic potential of this reaction.[16-18] This work mainly concerned reactions between Danishefsky's diene [1-methoxy-3-(trimethylsilyloxy)buta-diene, **78**] (or derivatives) and aromatic aldehydes.



Scheme 2.4. (a) various Lewis acids.

The possibility to construct a substituted THP system (typically a dihydro-γ-pyrone) by forming a carbon-carbon and a carbon-oxygen bond in a single step contributed to the popularity of the HDA reaction. Up to three stereocenters can be formed in the reaction (as well as a fourth one after desilylation, and a fifth one by induction), and different groups have pursued development of a catalytic asymmetric version. Danishefsky and co-workers reported the first example.[19] More recently, several other chiral Lewis acid catalysts were developed, including aluminum[20,21] and boron[22,23] complexes (Fig. 2.3).

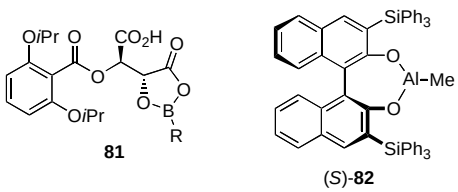
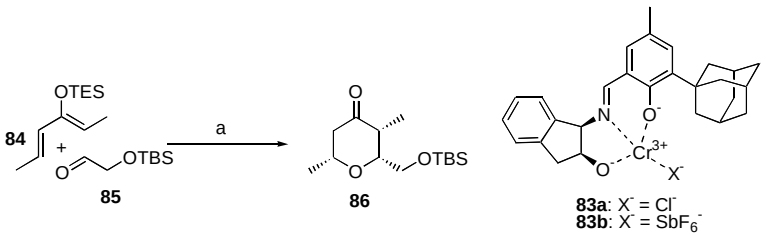


Figure 2.3. Aluminum- and boron-based asymmetric HDA catalysts

Most of these, however, require doubly activated dienes such as Danishefsky's diene **78** as substrate, which limits their applicability substantially. Only Jacobsen's recently developed Cr(III) catalysts **83a** and **83b** (Scheme 2.5) accept monoactivated dienes as substrates.[24] The applicablity of these catalysts was demonstrated by the catalytic asymmetric construction of di- or tetrahydropyran building blocks in the total synthesis of natural products.[25-27] Catalysts **83a** and **83b** were also shown to induce high stereoselectivities in inverse electron demand HDA reactions.[28,29]

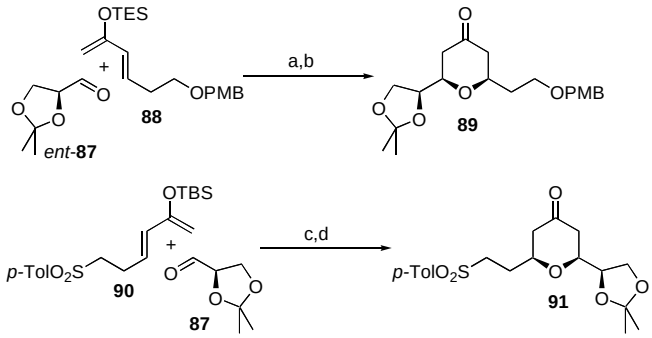


Scheme 2.5. (a) (i) Mol. Sieves 4 Å, **83a** or **b** (0.5-3 mol%); (ii) AcOH, TBAF, THF, 97% (>99% ee, >95% de).

Paterson and Lockhurst recently demonstrated that this catalyst may also be applied in more complex systems, using a catalytic asymmetric HDA reaction for the construction of a phorboxazole A fragment.[30] However, applicability still seems to be limited, depending on the nature of the aldehyde and steric bulk of either of the substrates.

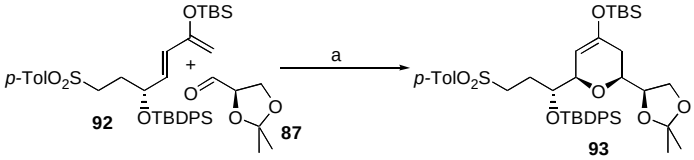
Especially α,β-unsaturated aldehydes lack reactivity and typically require doubly activated dienes as reaction partners.[17] Their incorporation is highly desirable, since the resulting exocyclic vinyl group provides the THP-building block with a handle for metathetic connection or macrocyclization procedures. Unfortunately, to the best of our knowledge, no

diastereo- or enantioselective HDA reaction of α,β-unsaturated aldehydes with monoactivated dienes has been described so far.



Scheme 2.6. Cink and Forsyth´s synthesis towards phorboxazole A[31]; (a) BF_3•Et_2O, Et_2O, -78°C; (b) TBAF, TsOH, THF, 60% over two steps; Synthesis of medium-sized ring ethers by Mujica et al.[32]: (c) BF_3•Et_2O, Et_2O, -25°C, 82%; (d) TBAF, THF, 98%.

Another means of controlling the stereochemical outcome of the HDA reaction is the use of enantiomerically pure starting materials. After a first observation by Danishefsky,[18] several examples of asymmetric HDA reactions with enantiomerically pure chiral aldehydes have been described (Scheme 2.6).[31,32] Martin et al. have demonstrated a synergistic effect between a chiral aldehyde and a chiral diene (Scheme 2.7).[33]



Scheme 2.7. (a) BF_3•Et_2O, Et_2O, -15°C, 74%.

Hu et al. described an asymmetric HDA reaction using a chiral diene and a chiral Co(II) salen catalyst.[34] Similary, Jacobsen and co-workers reported match/mismatch effects when using chiral aldehydes and catalysts **83a** and **83b** (or enantiomers).[35]

We considered the use of an HDA reaction for the construction of the ratjadone THP fragment and analogues, envisioning ketone **94** as a precursor for building block *ent*-**12**. There are two possible retrosynthetic disconnections to form ketone **94** by HDA reaction (*a* and *b*, Fig. 2.4).

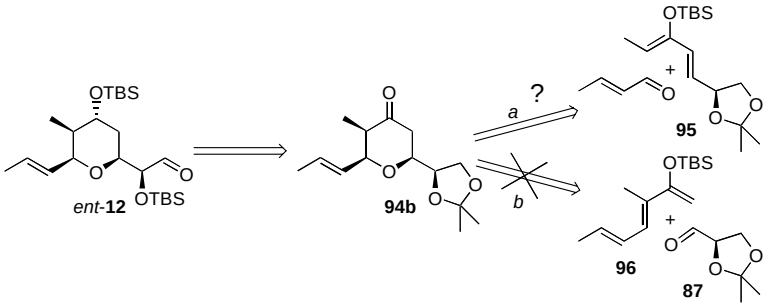


Figure 2.4. Possible retrosynthetic routes to **94** using HDA reactions

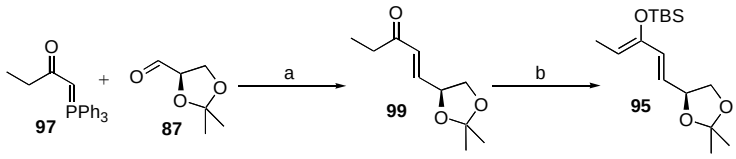
Since aldehyde **87** is known to induce stereochemistry in similar HDA reactions,[18,31,32] route *b* was initially considered promising. Preliminary studies soon showed that silyloxytriene **96** is unable to react as a diene in HDA reactions, presumably due to delocalization of electrons in the conjugated system. Therefore, route *a* was explored further.

Unfortunately, α,β-unsaturated aldehydes are notoriously bad dienophiles in HDA reactions. Also, no previous examples of diene-controlled asymmetric HDA reactions were found in literature. A synergistic effect between a chiral aldehyde and a chiral diene has been described. However, the similar reaction using a chiral aldehyde as the sole source of chirality produced a similar result, which makes the contribution to stereochemical induction by the chiral diene unclear.[33]

Also, it was difficult to predict which of the two expected all-*cis* diastereomers would dominate in such a diene-controlled HDA reaction. Since Kalesse and co-workers reported that absolute stereochemistry of the substituents in this fragment only has limited impact on the biological activity,[36] and because this project is diversity- rather than target-oriented, we decided to further pursue this route in order to construct various THP fragments for ratjadone analogues.

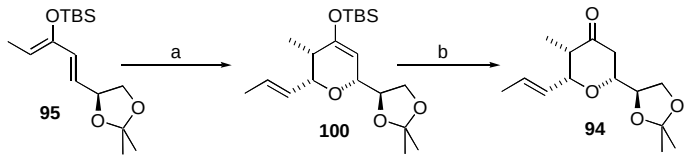
2.2 Synthesis of THP fragments of ratjadone analogues

We started with the construction of silyloxydiene **95**. The chirality is derived from aldehyde **87**, which can be prepared in two straightforward steps from inexpensive mannitol. Efficient large-scale procedures to **87** have been described.[37,38] The other required component is ylide **97**, available by α´-alkylation of (triphenylphosphoranylidene)-acetone (**98**).[39] Wittig reaction between aldehyde **87** and ylide **97** affords the required enone **99**. Subsequent treatment with TBSOTf in the presence of Et_3N readily yields diene **95** without loss of enantiomeric purity.



Scheme 2.8. (a) CH_2Cl_2, rt, 42%; (b) TBSOTf, Et_3N, Et_2O, 0°C, 88%.

The subsequent hetero Diels-Alder reaction between diene **95** and crotonaldehyde (Scheme 2.9) was performed according to the conditions described by Mujica et al.[32]



Scheme 2.9. (a) $CH_3CH{=}CHCHO$ (1.5 eq.), $BF_3{\bullet}Et_2O$ (1.5 eq.), Et_2O, -30°C, 97%; (b) AcOH (2.5 eq), TBAF (1.5 eq.), THF, 87%.

With some minor modifications (1.0 eq. diene, 1.5 eq. aldehyde, 1.5 eq. $BF_3{\bullet}Et_2O$, 1.5 h at -30°C), the reaction proceeded in excellent yield (97%,) in a 4:1 mixture of diastereomers, which was obtained without further purification.

Thus, the complete skeleton of the desired building block including introduction of four chiral centers was achieved in only three steps from known, easily available compounds. The crude diastereomeric mixture was then desilylated by treatment with TBAF in the presence of AcOH to prevent partial epimerization at C3. The resulting isomers **94a** and **94b** were readily separated by flash chromatography (**94a**:**94b** = 4:1). Both diastereomers were assigned the all-*cis* configuration of the ring substituents based on ^{1}H NMR coupling constants.

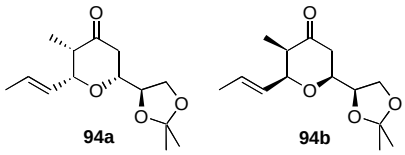
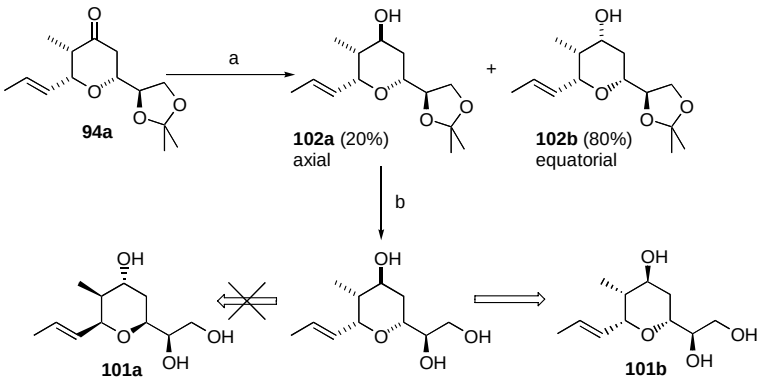


Figure 2.5. Two all-*cis* diastereomers **94a** and **94b**.

Since X-ray analysis to unambiguously assign the absolute configuration was not possible because the compounds are oils, it was decided to further convert the main isomer **94a**. If it would have the desired (2*S*,3*R*,6*S*) configuration, the reaction sequence described below (Scheme 2.10) would afford triol **101a**, a known compound from Kalesse´s total synthesis of (+)-ratjadone.[2] This transformation required selective reduction of the ketone function to the axial alcohol. Cink and Forsyth described a similar case, where reduction with K−Selectride® was most successful.[31] Thus, the ketone function of **94a** was reduced with K−Selectride® to give a 1:4 mixture of axial alcohol **102a** and equatorial alcohol **102b** (in quantitative yield), which were easily separated by flash chromatography. Other reduction methods were investigated (see below), but none led to a higher yield of axial alcohol **102a**. The relative stereochemistries of alcohols **102a** and **102b** were assigned by ^{1}H NMR shifts and coupling constants, and further confirmed for **102a** by NOESY. Subsequent removal of the isopropylidene group furnished triol **101b**, which was shown to be not identical to **101a** by comparison of ^{1}H NMR spectra.[2]



Scheme 2.10. (a) K-Selectride, THF, -78°C (100%, eq.:ax. = 80:20); (b) PPTS, acetone/H_2O 1:1, 58%.

A rationale for the observed diastereoselectivity of the HDA reaction leading to **94** may be provided by considering the approach of the aldehyde dienophile to diene **95**. Figure 2.6 shows a Newman projection of the C3-C2 bond in **95**, suggesting that the dienophile is more likely to approach the diene from the sterically less hindered top face. A (pseudo-) concerted, disrotatory reaction mechanism would then preferentially lead to **94a**.

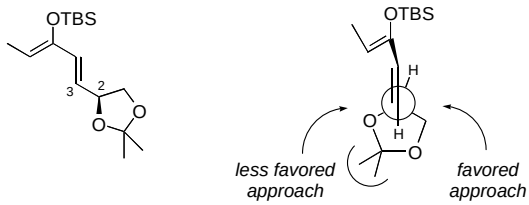
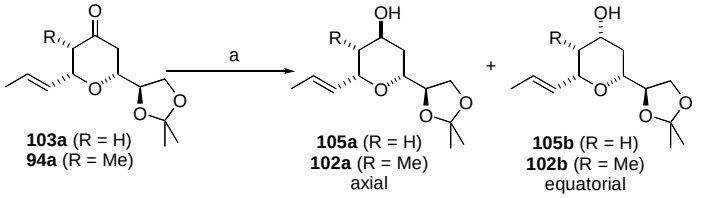


Figure 2.6. Sterically more favorable approach of the dienophile to diene **95**.

In contrast to the K-Selectride® reduction of **94a**, the reduction of ketone **103** (lacking the methyl substituent at the 3-position of the THP ring, synthesis v.i.) with K-Selectride® primarily afforded the axial alcohol **105a**, whereas reduction of a similar compound with an ethyl α-substituent (**104a**) under the same conditions furnished exclusively the equatorial alcohol .



Compound	*R* =	*Ratio ax.:eq.*
103a	H	89:11
94a	Me	20:80
104a	Et	<5:>95

Scheme 2.11. (a) K-Selectride®, THF.

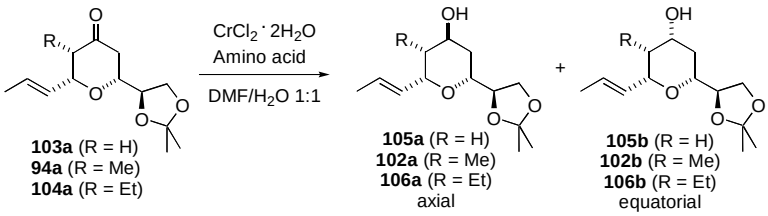
Cr(II) amino acid complexes have been successfully employed in the diastereoselective reduction of ketones.[40-42] In cooperation with Dr. K. Micskei of Debrecen University, Hungary, reduction of ketones **103a**, **94a**, and **104a** (with an ethyl substituent in 3-position, synthesis v.i.) with Cr(II) amino acid complexes were investigated.[†] Complexes of Cr(II) with several achiral (IDA, NTA and EDTA) and chiral (L-valine, L-histidine) amino acids were tested (Table 2.1).[‡]

The results in Table 2.1 clearly demonstrate that reductions of THP-4-ones with Cr(II) amino acid complexes depend strongly on α-substitution of the ketone. In the absence of α−substituents (ketone **103a**), most of the employed complexes successfully reduced the ketone to the corresponding alcohols. With ketone **94a**, which carries a methyl substituent in 3-position, only the Cr(II) NTA complex was successful, possibly indicating that a delicate balance between reactivity and limited steric hindrance is required here. Ketone **104a**, with an ethyl substituent, was not reduced by any of the complexes.

[†] This part of the work was performed in Dr. Micskei's laboratory at Debrecen University. This short research visit was financed by a DAAD/PPP Ungarn program.

[‡] Typical procedure: A mixture of H_2O (15 ml) and DMF (15 ml) was degassed by bubbling Ar through the solution for at least 30 min. $Cr(OAc)_2 \bullet H_2O$ (10 eq. with respect to the ketone) was added, followed by an amino acid (10 (IDA, NTA, EDTA) or 20 (L-Val, L-His) eq.) and an appropriate amount of 2N aq. NaOH. Ar was bubbled through the mixture continuously. When all Cr(II) was in solution, the ketone (~50 mg) was added. The reaction vessel was closed under Ar overpressure and the mixture was stirred overnight. The mixture was diluted with Et_2O and washed five times with H_2O and once with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was analyzed by ^1H NMR to determine the ax./eq. ratio.

Table 2.1. Reduction of THP-4-ones with Cr(II) amino acid complexes

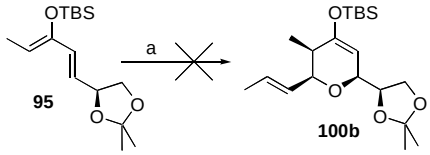


Amino acid	pH	Ratio ax./eq. (conversion, %)		
		103a (R = H)	**94a** (R = Me)	**104a** (R = Et)
IDA	6.0	47:61	n.r.[a]	n.r.
NTA	4.6	46:51	39:55	n.r.
EDTA	5.0	40:54	n.r.	n.r.
L-Val[c]	9.5	38:59	n.t.[b]	n.t.
L-His[c]	9.3	38:61	n.t.	n.t.

[a] n.r.: No reaction; [b] n.t.: Not tested; [c] two amino acids coordinated to each Cr(II) ion.

The most remarkable observation made during these reductions is the fact that the observed diastereoselectivity is relatively independent of both the amino acid and the ketone; it is typically 40:60 (ax./eq.). Indeed, for ketone **94a**, this means an increase of the ax./eq. ratio with respect to the K-Selectride® reduction. However, since the isolated yield was not quantitative and the reaction is somewhat more difficult to perform than K-Selectride® or $NaBH_4$ reduction, this method was not further exploited.

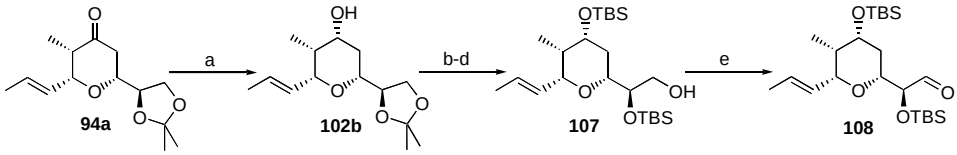
Thus, the main product does not have the same absolute stereochemistry as the corresponding ratjadone fragment when the (*S*)-isomer of diene **95** is used, nor is selective reduction of the ketone to the required axial alcohol efficient. We attempted to improve the diastereomeric ratio by subjecting diene **95** and crotonaldehyde to a catalytic asymmetric HDA reaction using Jacobsen´s HDA catalyst **83a**.[24] Unfortunately, no reaction was observed, not even at higher temperature and longer reaction time. This may be caused either by poor reactivity of the α,β-unsaturated aldehyde or mismatch effects of the chiral diene and the catalyst, as was also described by Jacobsen and co-workers.[35]



Scheme 2.12. (a) crotonaldehyde, mol. sieves 4 Å, **83a** (3 mol%), no reaction.

However, the described route provides rapid and efficient access to highly functionalized THP ring systems with defined stereochemistry. Thus, it is suitable for the construction of A ring analogues of ratjadone, but not immediately useful for the original ratjadone A fragment, which is not mandatory for activity anyway.[36]

Reduction of ketone **94a** with $NaBH_4$ afforded exclusively equatorial alcohol **102b** in quantitative yield. Because of the excellent availability of this compound, it was used for further synthetic studies. The isopropylidene group was efficiently removed by treatment with 1.0 eq. of PPTS in MeOH. Other methods ($Zn(NO_3)_2 \bullet 4H_2O$, CH_3CN; PPTS, acetone/H_2O) were also successful but required long reaction times (> 7 d).

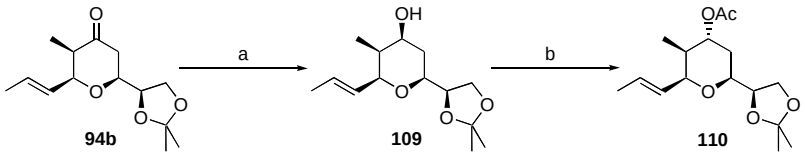


Scheme 2.13. (a) $NaBH_4$, MeOH, 100%; (b) PPTS, MeOH, 88%; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, -78°C, 99%; (d) HCl, $CHCl_3$, 91%; (e) Dess-Martin periodinane, CH_2Cl_2, 84%.

Subsequent transformation to aldehyde **108** was achieved in analogy to Kalesse´s total synthesis of (+)-ratjadone.[1,2] Triple TBS protection followed by selective cleavage of the primary TBS ether (HCl, $CHCl_3$) furnished alcohol **107**. Dess-Martin oxidation[43] resulted in adequately protected aldehyde **108**.

Attempts were also made to construct the original A ring building block *ent*-**12** from **94b**. Ketone **94b** was smoothly converted to the corresponding equatorial alcohol **109**. Then, the

C4 stereocenter had to be inverted. In a first study, Mitsunobu inversion[44] was accompanied by β-elimination, as well as the formation of a third, unidentified product. The desired inversion product **110** was obtained in a modest 33% yield, and was still contaminated with large quantities of diisopropyl hydrazinedicarboxylate. With a larger amount of **110** in hand, aldehyde *ent*-**12** would be available in analogy to **108**. Unfortunately, repetition of the Mitsunobu reaction on preparative scale failed.



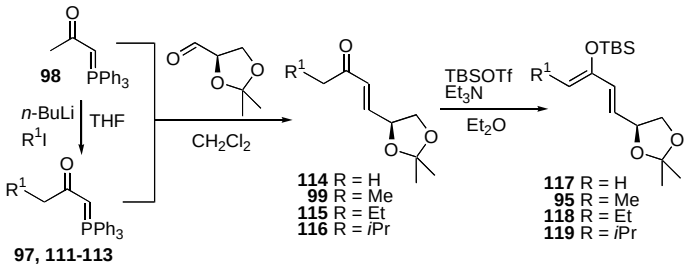
Scheme 2.14. (a) $NaBH_4$, MeOH, quant.; (b) DIAD, Ph_3P, AcOH, THF, 33%.

In order to investigate the scope and exploit the efficiency of the described HDA methodology, a number of derivatives of ketone **94** were synthesized.

β-Keto ylides **111-113** were obtained by alkylation of ylide **98** with the appropriate alkyl iodides after deprotonation with *n*-BuLi (Table 2.2).[39] Enones **114-117** were obtained by Wittig reaction of aldehyde **87** with ylides **98, 97, 111,** and **112**, respectively, as summarized in Table 2.1. In all cases, only the *E*-enone was isolated, the *Z*-product was either absent or present as a minor impurity that was easily removed by flash chromatography. This in contrast to a literature report, where **114** was formed in a 3:1 *E*/*Z* ratio.[34] Yields of this step varied and were sometimes mediocre. This is probably caused by difficulties in the purification of the β-keto ylides. Enones **99** and **114-116** were smoothly converted to the corresponding TBS enol ethers **95** and **117-119**.

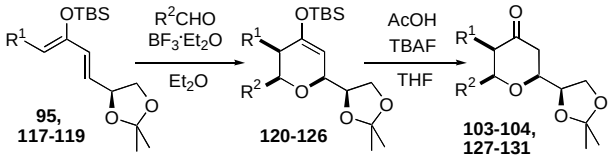
Hu et al. reported that treatment of **117** with BF_3•Et_2O resulted in decomposition.[34] Whereas we found this to be true at room temperature, BF_3•Et_2O-mediated decomposition of silyloxydienes **95** and **117-119** was not observed at temperatures below -20°C. Thus, dienes **95** and **117-119** were subjected to BF_3•Et_2O-mediated HDA reaction with crotonaldehyde or cinnamaldehyde between -20°C and -35°C. The resulting dihydropyrans were desilylated to give tetrahyropyran-4-ones (Table 2.3).

Table 2.2. Synthesis of silyloxydienes



Entry	Ylide	R^1 =	Ylide yield (%)	Enone	Enone yield (%)	Diene	Diene yield (%)
1	**98**	H	---	**114**	80	**117**	95
2	**97**	Me	94	**99**	42	**95**	88
3	**111**	Et	88	**115**	43	**118**	93
4	**112**	*i*Pr	100	**116**	54	**119**	46
5	**113**	*i*Bu	95	---	---	---	---

Table 2.3: HDA reactions and desilylation

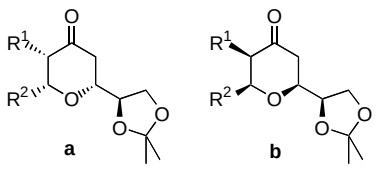


Entry	Diene	R^1 =	R^2 =	HDA product	THP-4-one	Yield (% over two steps)
1	**117**	H	CH_3CH=CH	**120**	**103**	78
2	**117**	H	PhCH=CH	**121**	**127**	85
3	**95**	Me	PhCH=CH	**122**	**128**	85
4	**118**	Et	CH_3CH=CH	**123**	**104**	84
5	**118**	Et	PhCH=CH	**124**	**129**	72
6	**119**	*i*Pr	CH_3CH=CH	**125**	**130**	77
7	**119**	*i*Pr	PhCH=CH	**126**	**131**	69

Yields (Table 2.3) and diasteromeric ratios (Table 2.4) of the HDA products range from good to excellent. The isolated tetrahydropyran-4-ones **103**, **104**, and **127-131** were typically mixtures of the two isomers that have all-*cis* configuration of the ring substituents, as was the case for **94**. This was confirmed by NOE spectroscopy for **131a** and based on analogy of ^{1}H NMR coupling constants for the other tetrahydropyran-4-ones. Diastereomeric ratios are summarized in Table 2.4.

In case of **131**, a minor amount (~5%) of a third isomer (**131c**, thought to be a compound with a *trans* relationship of the 2- and 6-substituents) could also be isolated. Its ^{1}H NMR spectrum displays many similarities with **131a** and **131b**, but the proton at 6-position shows a significant downfield shift with respect to the two major compounds. Third isomeric products were also observed for **103** and **127**, but these were inseparable from **103b** and **127b**, respectively. Amounts of these isomers never exceeded 5%.

Table 2.4: Diastereoselectivity of diene-controlled asymmetric HDA reactions

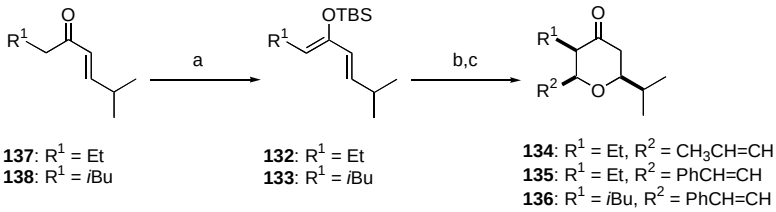


Entry	R^1 =	R^2 =	HDA product	
			Nr.	Ratio a:b
1	H	CH_3CH=CH	**103**	2:1
2	H	PhCH=CH	**127**	1.6:1
3	Me	CH_3CH=CH	**94**	4:1
4	Me	PhCH=CH	**128**	10:1
5	Et	CH_3CH=CH	**104**	7:1
6	Et	PhCH=CH	**129**	8:1
7	*i*Pr	CH_3CH=CH	**130**	7:1
8	*i*Pr	PhCH=CH	**131**	4:1

HDA reaction of diene **117** with ethyl glyoxylate under various conditions, including Co(II) salen catalysis, has been reported to afford not only both *cis* diastereomers, but both *trans* isomers as well.[34] These results suggest that the products arise from a tandem Mukaiyama-Michael-type addition, rather than a (pseudo-)concerted [4+2] cycloaddition. The HDA reactions described in this study employ α,β-unsaturated aldehydes (which are

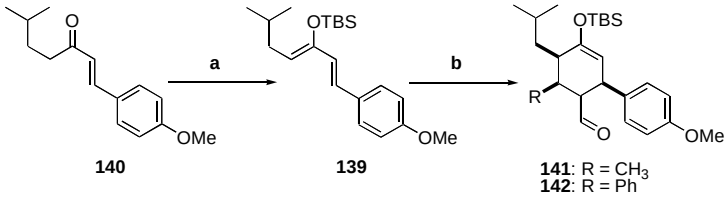
typically less reactive than ethyl glyoxylate), and generally afford only the all-*cis* isomers. Thus, these reactions presumably proceed through a more selective (pseudo-)concerted [4+2] cycloaddition mechanism.

Further evidence for the exclusive formation of the all-*cis* products was supplied by HDA reaction of achiral dienes **132** and **133** (i.e. with an isopropyl group instead of the dimethyldioxolane substituent) with crotonaldehyde or cinnamaldehyde (Scheme 2.15). Here, only one pair of (enantiomeric) diastereomers of the desilylated HDA products **134-136** was formed. The all-*cis* configuration was confirmed by NOE spectroscopy for **135** and based on analogy of ^{1}H NMR coupling constants for the other tetrahydropyran-4-ones **134** and **136**. Dienes **132** and **133** were derived from ketones **137** and **138**, which were obtained by Wittig reaction of ylides **111** and **113** with isobutyraldehyde.



Scheme 2.15. (a) TBSOTf, Et_3N, Et_2O; (b) R^2CHO, BF_3•Et_2O, Et_2O; (c) AcOH, TBAF, THF.

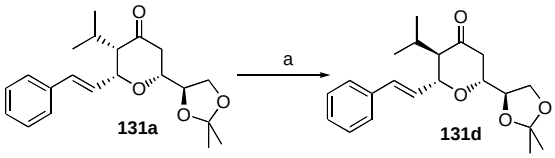
Interestingly, reaction of diene **139** (derived from ketone **140**), which has an aromatic ring conjugated to the diene system, with crotonaldehyde and cinnamaldehyde gave the classical Diels-Alder adducts **141** and **142** as the sole isolated products, rather than the expected HDA products (Scheme 2.16).



Scheme 2.16. (a) TBSOTf, Et_3N, Et_2O; (b) RCH=CHCHO, BF_3•Et_2O, Et_2O, -30°C.

A possible rationalization for this observation is a decrease in the HOMO energy of the diene through conjugation to the aromatic ring.

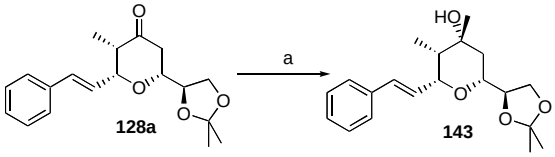
An expansion of the applicability of the current methodology would be the selective base-catalyzed epimerization at C3. Especially in the case of a bulky substituent, the equatorial position should be favored over the axial. Indeed, when **131a** was treated with base, it was slowly converted to **131d** (Scheme 2.17). The product was shown to be different from **131a**, **131b** and **131c** by ^{1}H and ^{13}C NMR, showing coupling constants typical for a *trans*-relationship of the C2 and C3 substituents.



Scheme 2.17. (a) KOtBu, MeOH, 2 d (53%).

Even though the recovery rate needs to be improved, the isomerization provides easy access to related tetrahydropyran-4-ones with different relative configuration.

Another method to increase diversity within this strategy is nucleophilic addition to the ketone function. As an example, **128a** was reacted with MeMgBr to afford a single diastereomer of tertiary alcohol **143** (Scheme 2.18). The excellent stereoselectivity is presumably caused by the adjacent axial methyl group, which makes equatorial attack unfavorable.



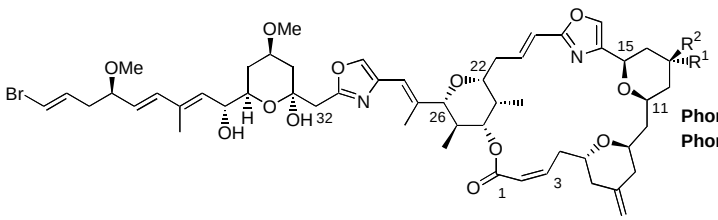
Scheme 2.18. (a) MeMgBr, THF (52%).

Also in this case, the yield needs to be optimized. However, this reaction demonstrates that the described tetrahydro-γ-pyrones can be easily and selectively modified by nucleophilic addition.

Despite the fact that the described HDA reactions display a stereoselectivity preference opposite to the one desired for the ratjadone THP segment, its efficiency combined with the typically good stereocontrol spurred us to apply this methodology to a system in which it would lead to the desired absolute stereochemistry in the THP ring. Such a system was recognized in the phorboxazoles.

2.3 Synthesis of the phorboxazole C22-C26 THP ring

Phorboxazoles A (**3a**) and B (**3b**, see Fig. 2.7) are macrocyclic marine natural products isolated by Searle and Solinski[45] from the sponge *Phorbas* sp.. They show remarkable cytotoxicity (mean GI_{50} <0.79 nM) against the full US NCI panel of 60 human cancer cell lines. The phorboxazoles cause cell cycle arrest in the S phase by a thus far unknown mechanism. Such a mode of action would be complementary in cancer therapy to e.g. microtubule-stabilizing agents such as paclitaxel or the epothilones.[46,47] This extraordinary biological activity, combined with the challenging structure and restricted access to natural material have attracted great interest in the synthetic community, culminating in total syntheses by the groups of Forsyth,[48] Evans,[49-51] and Smith,[52] and several other groups reported partial syntheses.[13,53-58] Several approaches made use of asymmetric HDA methodology, including aldehyde-[31] and catalyst-controlled[30] variants.



Phorboxazole A (**3a**): R^1= OH, R^2= H
Phorboxazole B (**3b**): R^1= H, R^2= OH

Figure 2.7. Structures of phorboxazoles A and B.

Both phorboxazole A and B feature a 25-membered macrocycle and a linear side chain. They contain two oxazole rings and no less than four tetrahydropyran rings, three of which are embedded in the macrocycle. Most probably, these substituted THP rings play a prominent role in the overall conformation of the macrocycle. Synthetically, they constitute the major challenge in these molecules. Recently, Paterson and Lockhurst elegantly showed that Jacobsen´s catalytic asymmetric hetero Diels-Alder (HDA) methodology[24] may be employed to combine two advanced intermediates (forming the C11-C15 THP ring), leading to formation of the major part of the macrocylic skeleton.[30] Indeed, the HDA reaction may be the most efficient method for the stereocontrolled construction of THP rings. However, no examples of catalytic asymmetric HDA reaction in the synthesis of sterically demanding systems such as the phorboxazole C22-C26 THP ring have been described to date. Therefore, we decided to employ our diene-controlled asymmetric HDA methodology for the fast and efficient synthesis of phorboxazole C20-C32 fragment **144**, previously reported by Paterson and Luckhurst in their synthesis of an advanced C4-C32 fragment.[30] Our retrosynthetic analysis of **144** is shown in Fig. 2.8.

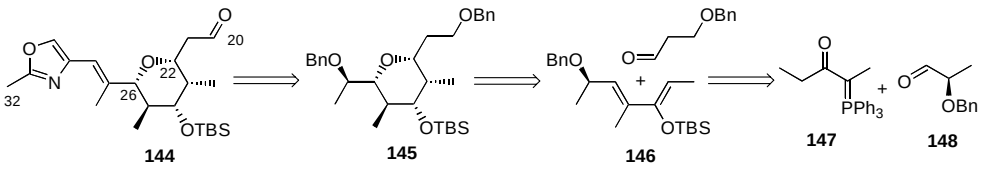
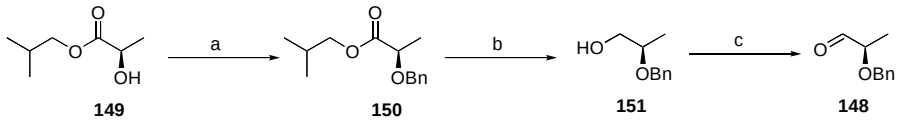


Figure 2.8. Retrosynthetic analysis C20-C32 segment of phorboxazoles.

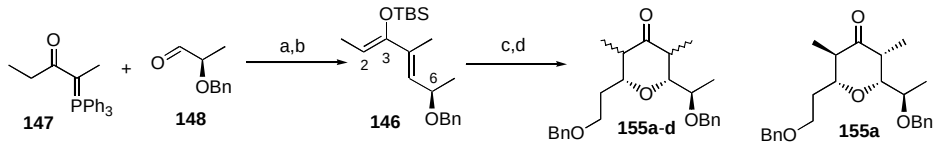
The key step is the diene-controlled HDA reaction between diene **146** and 3-benzyloxypropionaldehyde, leading to the all-*cis* HDA product. Absolute stereochemistry is induced by the C27 stereocenter (derived from D-lactate), which disappears in a later step. Thus, absolute stereochemistry can be switched simply by starting with the other lactate enantiomer (traceless induction). The C24 and C25 stereocenters are to be set by hydrolysis of the intermediate TBS enol ether and subsequent borohydride reduction, respectively, placing both substituents in the thermodynamically favored equatorial position.

The synthesis commenced with a Wittig reaction between known ylide **147**[59,60] and D-lactate-derived aldehyde **148**. The latter was synthesized from commercially available isobutyl D-lactate (**149**) in three straightforward steps (Scheme 2.19).



Scheme 2.19. (a) NaH, BnBr, DMF, 99%; (b) $LiAlH_4$, THF, 100%; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 74%.

Aldehyde **148** was then used in a Wittig reaction with ylide **147**.[60] The resulting enone **152** (not shown) was not converted to the corresponding TBS enol ether under standard conditions (TBSOTf, Et_3N, 0°C), probably due to the presence of an additional methyl group at the ketone α-position. However, subsequent addition of one equivalent of NaHMDS to the reaction mixture at low temperature afforded the desired diene **146** in quantitative yield (2*E*/2*Z* = 9:1). The key BF_3•Et_2O-mediated HDA reaction between diene **146** and 3-benzyloxypropionaldehyde (**153**, obtained by Swern oxidation[61] of commercially available 3-benzyloxypropanol) led to a mixture of diastereomeric products in reasonable yield.

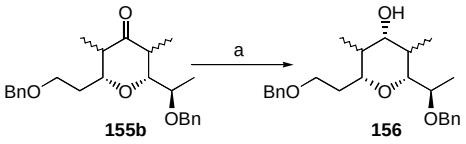


Scheme 2.20. (a) CH_3CN, r.t., 14 h, 75%; (b) TBSOTf, Et_3N, Et_2O, then NaHMDS, -78→0°C, 100%, 2*E*/2*Z* = 9:1; (c) 1.5 eq. 3-benzyloxypropionaldehyde, 1.5 eq. BF_3•Et_2O, Et_2O, -40°C, 2 h, 63%; (d) 2.5 eq. AcOH, 1.5 eq. TBAF, THF, r.t., 1 h, 65%.

The crude mixture of HDA products **154** (not shown) was desilylated (AcOH, TBAF) to give ketones **155** in 14:66:8:12 mixture of diastereomers (**155a-d**), of which the latter two were not separated. The two additional isomers (with respect to the HDA reactions

described earlier in this chapter) may be derived from the ~10% of 5*Z*-diene in **146**. Isomer **155a** was assigned the (3*R*,5*R*) configuration as shown in Scheme 2.20 by NOE spectroscopy. Unfortunately, the configuration of the other diastereomers could not be determined unequivocally.

Borohydride reduction of **155b** led to the exclusive formation of a single diastereomer, presumably the equatorial alcohol **156**.



Scheme 2.21. (a) $NaBH_4$, MeOH, 0°C, 1 h, 72%.

2.4 Conclusion

In conclusion, a versatile, unprecedented diene-controlled asymmetric HDA between α,β-unsaturated aldehydes and monoactivated chiral dienes was developed, affording compounds that can be easily converted to highly substituted stereodefined THP building blocks for the construction of analogues of ratjadone and other natural products.

2.5 Experimental section

General. All commercial reagents were purchased from Fluka, Merck or Aldrich and used without further purification, unless otherwise stated. All oxygen- and water-sensitive reactions were carried out in oven-dried glassware under argon. THF was distilled from potassium/benzophenone ketyl, Et_2O was distilled from sodium/potassium/benzophenone ketyl, and CH_2Cl_2 was distilled from calcium hydride. Other dry solvents were purchased from Fluka. Flash chromatography was performed using silica gel 60 (230-400 mesh, Merck). Thin-layer chromatography (TLC) was performed using silica plates (Merck, silica gel 60 F_{254}) and developed using Cer-MOP reagent [molybdatophosphoric acid (5.0 g), cerium (IV) sulfate (2.0 g), and concentrated H_2SO_4 (16 ml) in water (200 ml)]. Optical rotations were measured using a 1 ml cell with 1 dm path length on a Jasco DIP-1000 digital polarimeter. IR spectra were recorded as $CHCl_3$ solutions or as thin films between NaCl plates on a Bruker IFS 28. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on

Varian Mercury VX 300 and VX 400 spectrometers using TMS as internal standard. Chemical shifts δ are reported in parts per million (ppm), coupling constants *J* are given in Hertz (Hz). High resolution ESI mass spectra were obtained from a Bruker Apex 70e Fourier transform ion cyclotron resonance mass spectrometer equipped with a 7.0 Tesla superconducting magnet and an external electrospray ion source (Agilent, off axis spray).

General procedure for α´-alkylation of 1-triphenylphosphoranylidenepropan-2-one (98): To a solution of **98** (1.0 eq.) in THF (0.125 M) was added at -78°C *n*-BuLi (1.6 M in hexane, 1.4 eq.). The mixture was stirred at -78°C for 1 h, then the appropriate alkyl iodide (1.4 eq.) was added and the mixture was allowed to warm to room temperature over night. The solvent was removed in vacuo, the residue was taken up in CH_2Cl_2 and the mixture was washed three times with H_2O, dried (Na_2SO_4), filtered and concentrated in vacuo. The off-white solid residue was washed with three portions of ice-cold ether and dried in vacuo to give the alkylated ylides as colorless or slightly brown solids, which were used immediately in the next reaction without further purification.

General procedure for Wittig reactions: To a solution of an ylide in CH_2Cl_2 was added an aldehyde and the mixture was stirred 24-48 h at room temperature. The solvent was removed *in vacuo* and the residue was extracted several times with EtOAc/hexane 1:4. The combined extracts were concentrated *in vacuo* and purified by flash chromatography.

General procedure for the synthesis of TBS enol ethers: To a solution of a ketone (1.0 eq.) in Et_2O was added at 0°C Et_3N (1.2 eq.) and then TBSOTf (1.1 eq.). The mixture was stirred for 1 h at 0°C, then quenched by addition of sat. aq. $NaHCO_3$ and extracted three times with *t*BuOMe. The combined organic fractions were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a slightly yellow oil. The crude product was purified by flash chromatography on a small, Et_3N-neutralized column to give the TBS enol ethers.

General procedure for hetero Diels-Alder (HDA) reactions: To a solution of a diene in Et_2O was added at -30°C crotonaldehyde or cinnamaldehyde (1.5 eq.) and then BF_3•Et_2O (1.5 eq.). The mixture was stirred at -20°C to -30°C for 1.5-4 h and then quenched by addition of Et_3N (3 eq.). The mixture was diluted with H_2O (50 ml) and extracted with *t*BuOMe (3 x 35 ml). The combined organic fractions were washed with brine (50 ml), dried (Na_2SO_4), filtered and concentrated in vacuo to give the crude HDA products, which were analyzed by ^{1}H NMR for identity and diastereomeric ratio of the products and used in the next step without further purification.

General procedure for desilylation of TBS enol ethers: To a solution of a TBS enol ether in THF were added at 0°C acetic acid (2.5 eq.) and TBAF•3H_2O (1.5 eq.). The mixture was stirred at room temperature until the starting material had been fully consumed (TLC). The mixture was diluted with sat. aq. $NaHCO_3$ (50 ml) and extracted with *t*BuOMe (3 x 35 ml). The combined organic fractions were dried (Na_2SO_4), filtered, concentrated in vacuo and purified by flash chromatography.

***E*-(2*S*)-1,2-isopropylidenedioxy-3-hexen-5-one 114:** 1-Triphenylphosphoranylidenepropan-2-one (**98**, 6.37 g, 20.0 mmol) and (*R*)-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde (3.00 g, 23.0 mmol) were reacted over 48 h according to the general procedure for Wittig reactions. The residue was purified by flash chromatography (column dimensions: 25 x 3 cm, EtOAc/PE = 1:4) to give **114** (2.725 g, 16.0 mmol, 80%) as a colorless oil. $[\alpha]^{26}_D$ = +41.6 (c = 1.02, $CHCl_3$). IR (film): 3423 (broad), 2989, 2938, 2882, 1682, 1641, 1424, 1374, 1363, 1259, 1217, 1064, 979, 832 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.42 (s, 3H), 1.47 (s, 3H), 2.29 (s, 3H), 3.69 (dd, *J* = 8.20, 7.33 Hz, 1H), 4.21 (dd, *J* = 8.20, 6.45 Hz, 1H), 4.68 (dddd, *J* = 7.33, 6.45, 5.86, 1.18 Hz, 1H), 6.32 (dd, *J* = 15.83, 1.18 Hz, 1H), 6.70 (dd, *J* = 15.83, 5.86 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 25.3, 26.1, 27.0, 68.5, 74.7, 109.8, 130.7, 143.1, 197.5. R_f =0.24 (EtOAc/*n*-hexane = 1:6)

***E*-(2*S*)-1,2-isopropylidenedioxy-3-hepten-5-one 99:** Ylide **98** (7.96 g, 25.0 mmol), *n*-BuLi (1.6M in hexane, 21.88 ml, 35.0 mmol) and methyl iodide (2.16 ml, 4.91 g, 35.0 mmol) were reacted according to the general procedure for alkylation of ylide **98** to give **97** (6.44 g, 29.4 mmol, 78%) as a colorless solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.18 (t, *J* = 7.6 Hz, 3H), 2.33 (dq, *J* = 1.2, 7.6 Hz, 2H), 7.40-7.80 (m, 16H). Ylide **97** (6.44 g, 29.4 mmol) and (*R*)-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde (3.00 g, 23.0 mmol) were reacted over 48 h according to the general procedure for Wittig reactions. The residue was purified by flash chromatography (column dimensions: 25 x 3 cm, EtOAc/PE = 1:5) to give **99** (1.521 g, 8.16 mmol, 42%) as a colorless oil. $[\alpha]^{25}_D$ = +47.8 (c = 1.68, $CHCl_3$). IR ($CHCl_3$): 3674, 3027, 3013, 2982, 2941, 2903, 2883, 1714, 1459, 1409, 1380, 1354, 1275, 1231, 1179, 1116, 1086, 1041, 981 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.11 (t, *J* = 7.33 Hz, 3H), 1.42 (s, 3H), 1.46 (s, 3H), 2.60 (q, *J* = 7.33 Hz, 2H), 3.68 (dd, *J* = 8.21, 7.33 Hz, 1H), 4.19 (dd, *J* = 8.21, 6.43 Hz, 1H), 4.67 (dddd, *J* = 7.33, 6.43, 5.86, 1.56 Hz, 1H), 6.35 (dd, *J* = 15.83, 1.56 Hz, 1H), 6.73 (dd, *J* = 15.83, 5.86 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 7.8, 25.7, 26.4, 33.9, 68.8, 75.1, 110.1, 130.0, 141.9, 200.5. R_f = 0.51 (EtOAc/*n*-hexane = 1:4)

***E*-(2*S*)-1,2-isopropylidenedioxy-3-octen-5-one 115:** Ylide **98** (15.92 g, 50.0 mmol), *n*-BuLi (1.6M in hexane, 43.8 ml, 70.0 mmol) and ethyl iodide (5.60 ml, 70.0 mmol) were reacted according to the general procedure for alkylation of ylide **98** to give **111** (15.27 g, 44.1 mmol, 88%) as a slightly brown solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.97 (dt, *J* = 0.3, 7.3 Hz, 3H), 1.69 (dq, *J* = 0.3, 7.3 Hz, 2H), 2.30 (ddt, *J* = 0.3, 1.2, 7.3 Hz, 2H), 7.40-7.78 (m, 16H). Ylide **111** (3.46 g, 10.0 mmol) and (*R*)-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde (1.95 g, 15.0 mmol) were reacted over 48 h according to the general procedure for Wittig reactions. The residue was purified by flash chromatography (column dimensions: 15 x 4 cm, EtOAc/PE = 1:6) to give **115** (845 mg, 4.26 mmol, 43%) as a slightly yellow oil. $[\alpha]^{25}_D$ = +40.0 (c = 2.26, $CHCl_3$). IR ($CHCl_3$): 3675, 3511, 3329 (broad), 3027, 3012, 2990, 2967, 2936, 2876, 1698, 1681, 1639, 1457, 1384, 1375, 1256, 1230, 1185, 1063, 978, 862 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.94 (t, *J* = 7.33 Hz, 3H), 1.42 (s, 3H), 1.46 (s, 3H), 1.65 (m, *J* = 7.33 Hz, 2H), 2.55 (t, *J* = 7.33 Hz, 2H), 3.68 (dd, *J* = 8.21, 7.33 Hz, 1H), 4.19 (dd, *J* = 8.21, 6.74 Hz, 1H), 4.67 (dddd, *J* = 7.33, 6.74, 5.86, 1.56 Hz, 1H), 6.35 (dd, *J* = 15.83, 1.56 Hz, 1H), 6.72 (dd, *J* = 15.83, 5.86 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 13.7, 17.3, 25.6, 26.4, 42.5, 68.7, 75.0, 109.9, 129.9, 141.8, 199.6. R_f = 0.34 (EtOAc/ PE = 1:6).

***E*-(2*S*)-1,2-isopropylidenedioxy-7-methyl-3-octen-5-one 116:** Ylide **98** (19.10 g, 60.0 mmol), *n*-BuLi (1.6M in hexane, 52.5 ml, 84.0 mmol) and isopropyl iodide (8.40 ml, 84.0 mmol) were reacted according to the general procedure for alkylation of ylide **98** to give **112** (21.59 g, 59.9 mmol, 100%) as a slightly brown solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.90 (m, 1H), 0.96 (d, *J* = 6.5 Hz, 6H), 2.19 (m, 2H), 7.42-7.70 (m, 16H). Ylide **112** (7.21 g, 20.0 mmol) and (*R*)-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde (3.90 g, 30.0 mmol) were reacted over 48 h according to the general procedure for Wittig reactions. The residue was purified by flash chromatography (column dimensions: 16 x 4 cm, EtOAc/PE = 1:6) to give **116** (2.28 g, 10.7 mmol, 54%) as a slightly yellow oil. $[\alpha]^{25}_D$ = +40.3 (c = 1.59, $CHCl_3$)**.** IR ($CHCl_3$): 3675, 3514, 3026, 2989, 2960, 2935, 2872, 1692, 1636, 1466, 1455, 1383, 1374, 1339, 1304, 1229, 1195, 1171, 1154, 1062, 978, 859 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.94 (d, *J* = 7.45 Hz, 6H), 1.42 (s, 3H), 1.46 (s, 3H), 2.12 (m, 1H), 2.44 (d, *J* = 6.75 Hz, 2H), 3.68 (dd, *J* = 8.21, 7.33 Hz, 1H), 4.19 (dd, *J* = 8.21, 6.45 Hz, 1H), 4.67 (ddd, *J* = 7.33, 6.45, 5.86, 1.17 Hz, 1H), 6.34 (dd, *J* = 15.83, 1.17 Hz, 1H), 6.71 (dd, *J* = 15.83, 5.86 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.5, 24.8, 25.6, 26.4, 49.6, 68.7, 75.0, 109.9, 130.2, 141.8, 199.3**.** R_f = 0.49 (EtOAc/*n*-hexane = 1:6).

***E*-(2*S*)-5-*tert*-Butyldimethylsilyloxy-1,2-isopropylidenedioxy-3,5-hexadiene 117:** Ketone **114** (2.04 g, 12.0 mmol) Et_3N (2.99 ml, 2.19 g, 21.6 mmol) and TBSOTf (3.31 ml, 3.81 g, 14.4 mmol) were reacted according to the general procedure for the synthesis of TBS enol ethers. The crude product was purified by flash chromatography on a small, Et_3N-neutralized column (column dimensions 20 x 1.5 cm, EtOAc/PE = 1:20) to give **117** (3.25 g, 11.4 mmol, 95%) as a colourless oil. $[\alpha]^{25}_D$ = +17.1 (c = 2.25, $CHCl_3$). IR

($CHCl_3$): 3689, 3024, 3015, 2929, 2857, 1725, 1601, 1226, 1204, 839 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.18 (s, 6H), 0.97 (s, 9H), 1.40 (s, 3H), 1.44 (s, 3H), 3.50 (dd, *J* = 8.19, 7.51 Hz, 1H), 4.01 (dd, *J* = 8.19, 6.25 Hz, 1H), 4.23 (s, 1H), 4.24 (s, 1H), 4.49 (dddd, *J* = 7.51, 7.03, 6.25, 1.56 Hz, 1H), 5.84 (dd, *J* = 15.22, 7.03 Hz, 1H), 6.05 (dd, *J* = 15.22, 1.56 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = -4.8, -4.7, 18.2, 25.7, 25.8, 26.5, 69.5, 76.2, 96.5, 109.2, 127.5, 130.7, 154.1. R_f = 0.91 (EtOAc/*n*-hexane = 1:6). HRMS: calcd. for $C_{15}H_{28}O_4Si$ $(M+Na+O^{\S})^+$ 323.1649 found 323.1648.

3*E*,5*Z*-(2*S*)-5-*tert*-Butyldimethylsilyloxy-1,2-isopropylidenedioxy-3,5-heptadiene 95: Ketone **99** (720 mg, 3.91 mmol), Et_3N (1.00 ml, 729 mg, 7.20 mmol) and TBSOTf (1.10 ml, 1.27 g, 4.8 mmol) were reacted according to the general procedure for the synthesis of TBS enol ethers. The crude product was purified by flash chromatography on a small, Et_3N-neutralized column (column dimensions 20 x 1.5 cm, EtOAc/PE = 1:20) to give **95** (1.08 g, 3.62 mmol, 92%) as a colourless oil. $[\alpha]^{25}_D$ =+10.4 (c = 1.15, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.11 (s, 3H), 0.12 (s, 3H), 1.01 (s, 9H), 1.40 (s, 3H), 1.42 (s, 3H), 1.64 (d, *J* = 7.03 Hz, 3H), 3.58 (dd, *J* = 8.19, 7.51 Hz, 1H), 4.09 (dd, *J* = 8.21, 6.15 Hz, 1H), 4.54 (m, 1H), 4.89 (d, J = 7.03 Hz), 5.72 (dd, *J* = 15.24, 7.63 Hz, 1H), 6.10 (d, *J* = 15.24 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = -3.7, −3.6, 11.8, 18.4, 25.8, 25.9, 26.6, 69.5, 76.7, 109.2, 110.9, 124.8, 131.7, 148.3. R_f = 0.60 (EtOAc/*n*-hexane = 1:8).

3*E*,5*Z*-(2*S*)-5-*tert*-Butyldimethylsilyloxy-1,2-isopropylidenedioxy-3,5-octadiene 118: Ketone **115** (1.29 g, 6.50 mmol), Et_3N (1.62 ml, 1.18 g, 11.7 mmol) and TBSOTf (1.79 ml, 2.06 g, 7.80 mmol) were reacted according to the general procedure for the synthesis of TBS enol ethers. The crude product was purified by flash chromatography on a small, Et_3N-neutralized column (column dimensions 20 x 1.5 cm, EtOAc/PE = 1:20) to give **118** (1.89 g, 6.04 mmol, 93%) as a colourless oil. $[\alpha]^{25}_D$ = +11.4 (c = 1.74, $CHCl_3$). IR ($CHCl_3$): 3688, 3025, 3014, 2933, 1723, 1253, 1226, 1205, 1069, 838 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.10 (s, 3H), 0.12 (s, 3H), 0.95 (t, *J* = 7.33 Hz, 3H) 1.00 (s, 9H), 1.40 (s, 3H), 1.43 (s, 3H), 2.11 (m, 2H), 3.59 (dd, *J* = 8.21, 7.63 Hz, 1H), 4.09 (dd, *J* = 8.21, 6.15 Hz, 1H), 4.54 (m, 1H), 4.89 (t, J = 7.04 Hz), 5.72 (dd, *J* = 15.24, 7.62 Hz, 1H), 6.10 (d, *J* = 15.24 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = -3.64, -3.58, 14.0, 18.5, 19.5, 26.00 (3C), 26.7, 69.5, 76.6, 109.1, 118.6, 125.0, 131.7, 146.5. R_f = 0.21 (EtOAc/*n*-hexane = 1:40). HRMS: calcd. for $C_{17}H_{32}O_3Si$ $(M + Na + O)^+$ 351.1962 found 351.1972.

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§ All silyl enol ethers described here show the M+Na+O peak in exact mass measurements; this peak is probably caused by formation of an oxidation side product, which also seems to be the main decomposition product of these compounds.

3*E*,5*Z*-(2*S*)-5-*tert*-Butyldimethylsilyloxy-1,2-isopropylidenedioxy-7-methyl-3,5-octadiene 119: Ketone **116** (1.061 g, 5.00 mmol), Et_3N (1.248 ml, 911 mg, 9.00 mmol) and TBSOTf (1.378 ml, 1.586 g, 6.00 mmol) were reacted according to the general procedure for the synthesis of TBS enol ethers. The crude product was purified by flash chromatography on a small, Et_3N-neutralized column (column dimensions 20 x 1.5 cm, EtOAc/PE = 1:20) to give **119** (1.517 g, 4.65 mmol, 93%) as a colourless oil. $[\alpha]^{25}_D$ = +13.8 (c = 1.61, $CHCl_3$). IR ($CHCl_3$): 1718 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.11 (s, 3H), 0.13 (s, 3H), 0.95 (d, *J* = 6.74 Hz, 6H) 1.00 (s, 9H), 1.39 (s, 3H), 1.42 (s, 3H), 2.69 (m, 1H), 3.59 (dd, *J* = 8.21, 7.63 Hz, 1H), 4.08 (dd, *J* = 8.21, 6.15 Hz, 1H), 4.52 (m, 1H), 4.64 (d, J = 9.68 Hz), 5.70 (dd, *J* = 15.25, 7.63 Hz, 1H), 6.07 (d, *J* = 15.25 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = -3.8, -3.7, 18.4, 22.8, 22.8, 25.0, 25.87, 25.94, 26.6, 69.5, 76.7, 109.2, 124.2, 125.2, 132.2, 145.3. R_f = 0.62 (EtOAc/*n*-hexane = 1:10). HRMS: calcd. for $C_{18}H_{34}O_3Si$ $(M+Na+O)^+$ 365.2119 found 365.2122.

(2*R*,6*R*)-6-((4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2-*E*-propenyl-tetrahydropyran-4-one 103: Diene **117** (1.42 g. 5.00 mmol), crotonaldehyde (618 µl, 523 mg, 7.50 mmol) and BF_3•Et_2O (950 µl, 1.06 g, 7.50 mmol) were reacted at -30°C for 1.5 h according to the general procedure for HDA reactions to give crude **120** (1.69 g, 4.76 mmol, 95%) as a slightly yellow oil. TBS enol ether **120** (1,69 g, 4.76 mmol), acetic acid (680 µl, 715 mg, 11.9 mmol) and TBAF•$3H_2O$ (2.25 g, 7.14 mmol) were reacted according to the general procedure for desilylation of TBS enol ethers to give a slightly yellow oil, which was purified by flash chromatography (column dimensions 30 x 2.5 cm, EtOAc/PE = 1:6) to give a total of 943 mg (3.92 mmol, 78% over two steps) of three diastereomers of **103** in a 6.1:3.1:1.0 ratio, the two major components being the two all-*cis* isomers. The major isomer was isolated in pure form, but the two minor components were inseparable. Characterization data below are for the major product. **Major product 103a:** $[\alpha]^{24}_D$ = +24.8 (c = 1.50, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.35 (s, 3H), 1.41 (s, 3H), 1.72 (dd, *J* = 6.64, 0.78 Hz, 3H), 2.39 (dd, *J* = 14.44, 11.71 Hz, 1H), 2.40 (d, *J* = 7.81 Hz, 2H), 2.58 (m, 1H), 3.58 (ddd, *J* = 11.71, 6.25, 2.73 Hz, 1H), 3.93 (dd, *J* = 8.20, 4.29 Hz, 1H), 4.05-4.17 (m, 3H), 5.54 (ddq, *J* = 15.22, 6.25, 1.56 Hz, 1H), 5.74 (dqd, *J* = 15.22, 6.64, 0.78 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 17.6, 24.9, 26.5, 43.6, 47.6, 66.7, 77.4, 77.45, 77.53, 109.6, 128.5, 129.8, 206.2. R_f = 0.42 (EtOAc/*n*-hexane = 1:4). HRMS: calcd. for $C_{13}H_{20}O_4$ $(M+Na)^+$ 263.1254 found 263.1254. **Minor isomer 26b:** R_f = 0.31 (EtOAc/*n*-hexane = 1:4). HRMS: calcd. for $C_{13}H_{20}O_4$ $(M+Na)^+$ 263.1254 found 263.1255.

(2*R*,6*R*)-6-((4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2-(*E*-2-phenylethenyl)tetrahydro-pyran-4-one 127: Diene **117** (1.42 g. 5.00 mmol), cinnamaldehyde (944 µl, 991 mg, 7.50 mmol) and BF_3•Et_2O (950 µl, 1.06 g, 7.50 mmol) were reacted at -30°C for 1.5 h according to the general procedure for HDA reactions to give crude **121** (2.34 g, containing excess cinnamaldehyde) as a slightly yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.17 (s, 3H), 0.18 (s, 3H), 0.93 (s, 9H), 1.37 (s, 3H), 1.45 (s, 3H), 2.08 (ddd, *J* = 16.78, 5.86, 3.12 Hz,

1H), 2.24 (m, 1H), 3.95-4.09 (m, 2H), 4.21-4.31 (m, 2H), 5.00 (t, *J* = 1.56 Hz, 1H), 6.25 (dd, *J* = 16.00, 5.86 Hz, 1H), 6.61 (d, *J* = 16.00 Hz, 1H), 7.22-7.59 (m, 5H). TBS enol ether **121** (2.34 g, max. 5 mmol), acetic acid (715 µl, 751 mg, 12.5 mmol) and TBAF•$3H_2O$ (2.37 g, 7.50 mmol) were reacted according to the general procedure for desilylation of TBS enol ethers to give a slightly yellow oil, which was purified by flash chromatography (column dimensions 30 x 2.5 cm, EtOAc/PE = 1:5) to give a total of 1289 mg (4.26 mmol, 85% over two steps) of three diastereomers of **127** in a 1.6:1.0:0.29 ratio, the two major components being the two all-*cis* isomers. The major isomer was isolated in pure form, but the two minor components were inseparable. Characterization data below are for the major product. **Major product 127a:** $[\alpha]^{25}_D$ = +41.9 (c = 1.45, $CHCl_3$). IR ($CHCl_3$): 3675, 3502, 3026, 3012, 2990, 2934, 2891, 1719, 1626, 1496, 1454, 1383, 1373, 1228, 1203, 1156, 1069, 967, 845 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.357(s, 3H), 1.43 (s, 3H), 2.45 (dd, *J* = 14.44, 11.71 Hz, 1H), 2.51 (m, 2H), 2.62 (dd, *J* = 14.44, 1.17 Hz, 1H), 3.66 (ddd, *J* = 8.98, 6.24, 2.74 Hz, 1H), 3.96 (dd, *J* = 8.59, 4.68 Hz, 1H), 4.13 (dd *J* = 8.59, 6.64 Hz , 1H), 4.20 (dt, *J* = 6.25, 5.07 Hz, 1H), 4.31 (m, 1H), 6.22 (dd, *J* = 16.00, 6.25 Hz, 1H), 6.60 (d, *J* = 16.00 Hz, 1H), 7.23-7.39 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 25.2, 26.7, 43.8, 47.8, 66.8, 77.57, 77.65, 77.68, 109.8, 126.4, 127.5, 128.0, 128.5, 131.4, 135.8, 205.6. R_f = 0.33 (EtOAc/*n*-hexane = 1:4). HRMS: calcd. for $C_{18}H_{22}O_4$ $(M+Na)^+$ 325.1410 found 325.1408. **Minor isomer 127b:** R_f = 0.24 (EtOAc/*n*-hexane = 1:4). HRMS: calcd. for $C_{18}H_{22}O_4$ $(M+Na)^+$ 325.1410 found 325.1410.

(2*R*,3*S*,6*R*)-6-((4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-methyl-2-*E*-propenyltetrahydro-pyran-4-one

94: Diene **95**(1.64 g. 5.50 mmol), crotonaldehyde (680 µl, 578 mg, 8.25 mmol) and BF_3•Et_2O (1045 µl, 1.17 g, 8.25 mmol) were reacted at -30°C for 1.5 h according to the general procedure for HDA reactions to give crude **100** (1.97 g, 5.34 mmol, 97%) as a slightly yellow oil. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.16 (s, 3H), 0.18 (s, 3H), 0.93 (s, 9H), 0.99 (d, *J* = 6.74 Hz, 3H), 1.35 (s, 3H), 1.42 (s, 3H), 1.71 (d, *J* = 6.45 Hz, 3H), 1.93 (m, 1H), 3.89 (dd, *J* = 6.45, 5.86 Hz, 1H), 3.97-4.03 (m, 2H), 4.10 (dt, *J* = 4.10, 1.76 Hz, 1H), 4.15 (dt, *J* = 6.74, 1.76 Hz, 1H), 4.80 (d, *J* = 1.76 Hz, 1H), 5.47 (ddd, *J* = 15.54, 5.86, 1.76 Hz, 1H), 5.66 (ddq, *J* = 15.54, 6.45, 1.17 Hz). TBS enol ether **100** (1.92 g, 5.21 mmol), acetic acid (745 µl, 782 mg, 13.0 mmol) and TBAF•$3H_2O$ (2.47 g, 7.82 mmol) were reacted according to the general procedure for desilylation of TBS enol ethers to give a slightly yellow oil, which was purified by flash chromatography (column dimensions 30 x 2.5 cm, EtOAc/PE = 1:4) to give a total of 1150 mg (4.52 mmol, 84% over two steps) of the two all-*cis* diastereomers of **94** in a 4:1 ratio. **Major isomer 94a:** $[\alpha]^{25}_D$ = +37.0 (c = 1.02, $CHCl_3$). IR ($CHCl_3$): 3026, 3011, 2988, 2936, 2883, 2455, 1712, 1455, 1382, 1373, 1230, 1202, 1151, 1069, 968, 929, 844 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.13 (d, *J* = 7.04 Hz, 3H), 1.36 (s, 3H), 1.41 (s, 3H), 1.73 (d, *J* = 6.45 Hz, 3H), 2.36-2.46 (m, 2H), 2.55 (dd, *J* = 14.66, 11.14 Hz, 1H), 3.57 (ddd, *J* = 11.14, 6.25, 3.23 Hz, 1H), 3.95 (m, 1H), 4.09-4.17 (m, 3H), 5.54 (ddq, *J* = 15.24, 5.86, 1.47 Hz, 1H), 5.74 (dqd, *J* = 15.24, 6.45, 1.17 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 11.1, 17.8, 25.0, 26.6, 40.2, 50.0, 66.7, 77.5, 77.6, 79.4, 109.5, 127.1, 128.2, 210.2. HRMS: calcd. for $C_{14}H_{22}O_4$ $(M+Na)^+$ 277.1410 found 277.1411.

Minor isomer 94b: $[\alpha]^{25}_D$ = +24.1 (c = 1.07, $CHCl_3$). IR ($CHCl_3$): 3026, 3012, 2988, 2936, 2883, 1712, 1675, 1455, 1382, 1373, 1228, 1203, 1155, 1069, 969, 847 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.13 (d, *J* = 7.03 Hz, 3H), 1.38 (s, 3H), 1.45 (s, 3H), 1.73 (d, *J* = 6.64 Hz, 3H), 2.17 (dd, *J* = 14.83, 3.12, 1.17 Hz, 1H), 2.40 (qdd, *J* = 7.03, 3.12, 1.17 Hz, 1H), 2.63 (dd, *J* = 14.83, 11.71 Hz, 1H), 3.75 (ddd, *J* = 11.71, 4.68, 3.12 Hz, 1H), 3.96 (dd, *J* = 8.58, 6.25 Hz, 1H), 4.05 (dd, *J* = 8.58, 6.64 Hz, 1H), 4.15 (m, 1H), 4.23 (m, 1H), 5.45 (ddq, *J* = 15.54, 5.86, 1.76 Hz, 1H), 5.75 (dqd, *J* = 15.54, 6.45, 1.18 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 11.2, 18.0, 25.3, 26.1, 39.0, 50.2, 65.0, 76.5, 76.7, 79.5, 109.6, 127.1, 128.3, 210.4. HRMS: calcd. for $C_{14}H_{22}O_4$ $(M+Na)^+$ 277.1410 found 277.1411.

(2*R*,3*S*,6*R*)-6-((4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-methyl-2-(*E*-2-phenylethenyl)-tetrahydropyran-4-one 128: Diene **95** (597 mg. 2.00 mmol), cinnamaldehyde (378 µl, 396 mg, 3.00 mmol) and BF_3•Et_2O (380 µl, 426 mg, 3.00 mmol) were reacted at -20°C for 4 h according to the general procedure for HDA reactions to give crude **122** (944 mg, containing excess cinnamaldehyde) as a slightly yellow oil. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.18 (s, 3H), 0.20 (s, 3H), 0.94 (s, 9H), 1.04 (d, *J* = 6.95 Hz, 1H), 1.38 (s, 3H), 1.43 (s, 3H), 2.07 (m, 1H), 3.95 (dd, *J* = 6.40, 5.68 Hz, 1H), 4.05 (s, 1H), 4.07 (d, *J* = 1.46 Hz, 1H), 4.23 (dt, *J* = 7.59, 1.65 Hz, 1H), 4.36 (m, 1H), 4.84 (d, *J* = 1.46 Hz, 1H), 6.16 (dd, *J* = 16.10, 5.31 Hz, 1H), 6.61 (d, *J* = 16.10 Hz, 1H), 7.20-7.59 (m, 5H). TBS enol ether **122** (944 mg, max. 2.00 mmol), acetic acid (286 µl, 300 mg, 5.00 mmol) and TBAF•$3H_2O$ (947 mg, 3.00 mmol) were reacted according to the general procedure for desilylation of TBS enol ethers to give a slightly yellow oil, which was purified by flash chromatography (column dimensions 30 x 2.5 cm, EtOAc/PE = 1:5) to give a total of 540 mg (1.71 mmol, 85% over two steps) of the two all-*cis* diastereomers of **128** in a 10:1 ratio. **Major isomer 128a:** $[\alpha]^{26}_D$ = +20.2 (c = 1.28, $CHCl_3$). IR ($CHCl_3$): 3674, 3028, 3011, 2989, 2937, 2887, 1714, 1636, 1578, 1496, 1383, 1373, 1231, 1069, 968, 844 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.40 (d, *J* = 7.42 Hz), 1.36 (s, 3H), 1.43 (s, 3H), 2.49 (ddd, *J* = 14.83, 3.12, 1.18 Hz, 1H), 2.53 (m, 1H), 2.61 (dd, *J* = 14.83, 11.32 Hz, 1H), 3.66 (ddd, *J* = 11.32, 3.12, 2.73 Hz, 1H), 4.00 (dd, *J* = 8.59, 5.68 Hz, 1H), 4.14-4.23 (m, 2H), 4.40 (ddd, *J* = 4.68, 2.73, 1.56 Hz, 1H), 6.12 (dd, *J* = 16.00, 5.46 Hz, 1H), 6.64 (dd, *J* = 16.00, 1.17 Hz, 1H), 7.24-7.59 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 11.3, 25.0, 26.6, 40.1, 50.0, 66.7, 77.6, 77.7, 79.4, 109.8, 125.6, 126.4, 127.8, 128.5, 131.4, 136.2, 210.2. R_f = 0.19 (EtOAc/*n*-hexane = 1:6). HRMS: calcd. for $C_{19}H_{24}O_4$ $(M+Na)^+$ 339.1567 found 339.1563. **Minor isomer 128b:** IR ($CHCl_3$): 3674, 3028, 3012, 2990, 2937, 1711, 1495, 1454, 1415, 1383, 1373, 1230, 1174, 1070, 846 cm^{-1}. TLC: R_f = 0.12 (EtOAc/*n*-hexane = 1:6). HRMS: calcd. for $C_{19}H_{24}O_4$ $(M+Na)^+$ 339.1567 found 339.1563.

(2*R*,3*S*,6*R*)-6-((4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-ethyl-2-*E*-propenyl-tetrahydropyran-4-one 104: Diene **118** (1.72 g. 5.50 mmol), crotonaldehyde (680 µl, 578 mg, 8.25 mmol) and BF_3•Et_2O (1045 µl, 1.17 g, 8.25 mmol) were reacted at -30°C for 1.5 h according to the general procedure for HDA reactions to give

crude **123** (2.01 g, 5.27 mmol, 96%) as a slightly yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.18 (s, 6H), 0.92 (s, 9H), 0.91-0.96 (m, 3H), 1.35 (s, 3H), 1.42 (s, 3H), 1.40-1.46 (m, 1H), 1.58-1.65 (m, 1H), 1.72 (dt, *J* = 6.45, 1.17 Hz, 3H), 1.84 (m, 1H), 3.86 (dd, *J* = 6.75, 5.86 Hz, 1H), 3.96-4.05 (m, 2H), 4.09-4.13 (m, 2H), 4.88 (d, *J* = 1.47 Hz, 1H), 5.49 (ddq, *J* = 15.24, 5.86, 1.46 Hz, 1H), 5.68 (dqd, *J* = 15.24, 6.45, 1.17 Hz). TBS enol ether **123** (1.93 g, 5.05 mmol), acetic acid (723 µl, 759 mg, 12.6 mmol) and TBAF•3H_2O (2.39 g, 7.58 mmol) were reacted according to the general procedure for desilylation of TBS enol ethers to give a slightly yellow oil, which was purified by flash chromatography (column dimensions 30 x 2.5 cm, EtOAc/PE = 1:5) to give a total of 1184 mg (4.41 mmol, 84% over two steps) of the two all-*cis* diastereomers of **104** in a 7:1 ratio. **Major isomer 104a:** $[\alpha]^{24}_{D}$ = -54.0 (c = 1.13, $CHCl_3$). IR ($CHCl_3$): 3466 (broad), 3026, 3012, 2970, 2937, 2878, 1712, 1604, 1457, 1373, 1229, 1069, 967, 845 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.83 (t, *J* = 7.04 Hz, 3H), 1.35 (s, 3H), 1.40 (s, 3H),1.61-1.77 (m, 2H), 1.73 (d, *J* = 6.64 Hz, 3H), 2.22 (ddd, *J* = 10.93, 4.68, 3.12 Hz, 1H), 2.42-2.48 (m, 2H), 3.56 (m, 1H), 3.94 (m, 1H), 4.09-4.15 (m, 3H), 5.46 (ddq, *J* = 15.61, 5.85, 1.56 Hz, 1H), 5.72 (dqd, *J* = 15.61, 6.64, 1.18 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 11.6, 18.0, 18.9, 25.2, 26.7, 41.1, 58.0, 66.9, 77.7, 77.9, 80.0, 109.6, 127.3, 128.0, 209.8. R_f = 0.47 (EtOAc/*n*-hexane = 1:6). **Minor isomer 104b:** $[\alpha]^{24}_{D}$ = +45.1 (c = 1.09, $CHCl_3$). IR ($CHCl_3$): 3446 (broad), 3025, 2969, 2936, 2878, 1718, 1610, 1457, 1383, 1229, 1069, 968, 855 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.83 (t, *J* = 7.40 Hz, 3H), 1.38 (s, 3H), 1.45 (s, 3H), 1.62-1.74 (m, 2H), 1.72 (dt, *J* = 6.64, 1.17 Hz, 3H), 2.18 (ddd, *J* = 14.44, 3.12, 1.17 Hz, 1H), 2.22 (m 1H), 2.57 (dd, *J* = 14.05, 11.71 Hz, 1H), 3.73 (ddd, *J* = 11.71, 4.68, 3.12 Hz, 1H), 3.96 (dd, *J* = 8.59, 6.24 Hz, 1H), 4.05 (dd, *J* = 8.59, 6.64 Hz, 1H), 4.14 (dt, *J* = 4.68, 1.17 Hz, 1H), 4.23 (ddd, *J* = 6.64, 6.24, 4.68 Hz, 1H), 5.50 (ddq, *J* = 15.22, 5.85, 1.56 Hz, 1H), 5.72 (dqd, *J* = 15.22, 6.63, 1.18 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 11.6, 18.0, 18.8, 25.3, 26.2, 39.9, 58.1, 65.0, 76.7, 76.8, 78.0, 109.7, 127.4, 128.0, 209.9. R_f = 0.40 (EtOAc/*n*-hexane = 1:6).

(2*R*,3*S*,6*R*)-6-((4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-ethyl-2-(*E*-2-phenylethenyl)-tetrahydropyran-4-one 129: Diene **118** (350 mg. 1.12 mmol), cinnamaldehyde (184 µl, 193 mg, 1.46 mmol) and BF_3•Et_2O (143 µl, 160 mg, 1.12 mmol) were reacted at -20°C for 2.5 h according to the general procedure for HDA reactions to give crude **124** (494 mg, 1.11 mmol, 99%) a slightly yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.19 (s, 3H), 0.20 (s, 3H), 0.94 (s, 9H), 0.92-0.96 (m, 3H), 1.38 (s, 3H), 1.46 (s, 3H), 1.52-1.66 (m, 2H), 1.99 (m, 1H), 3.93 (dd, *J* = 6.74, 5.57 Hz, 1H), 4.05 (d, *J* = 0.88 Hz, 1H), 4.07 (d, *J* = 2.05 Hz, 1H), 4.19 (ddd, *J* = 7.03, 2.05, 1.76 Hz, 1H), 4.36 (m, 1H), 4.91 (d, *J* = 1.76 Hz, 1H), 6.21 (dd, *J* = 16.13, 5.28 Hz, 1H), 6.61 (dd, *J* = 16.13, 1.47 Hz), 7.28-7.46 (m, 5H). TBS enol ether **124** (489 mg, 1.10 mmol), acetic acid (314 µl, 5.50 mmol) and TBAF•3H_2O (431 mg, 1.65 mmol) were reacted according to the general procedure for the desilylation of a TBS enol ether. The product was purified by flash chromatography (column dimensions: 32 x 3 cm, EtOAc/PE = 1:5) to give a total of 270 mg (0.82 mmol, 74% over two

steps) of the two all-*cis* diastereomers of **129** in a 8:1 ratio. **Major isomer 129a:** $[\alpha]^{24}_D$ = -8.4 (c = 1.34, $CHCl_3$). IR ($CHCl_3$): 3026, 2988, 2966, 2936, 2878, 1714, 1496, 1456, 1382, 1373, 1260, 1229, 1175, 1069, 844 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.84 (t, *J* = 7.42 Hz, 3H), 1.38 (s, 3H), 1.43 (s, 3H), 1.66-1.79 (m, 2H), 2.34 (m, 1H), 2.48-2.57 (m, 2H), 3.64 (m, 3H), 3.99 (dd, *J* = 8.20, 4.69 Hz, 1H), 4.15 (dd, *J* = 8.20, 6.24 Hz, 1H), 4.20 (dt, 6.25, 4.69 Hz, 1H), 4.38 (m, 3H), 6.13 (dd, *J* = 16.00, 5.47 Hz, 1H), 6.63 (dd, *J* = 16.00, 1.17 Hz, 1H), 7.23-7.39 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 11.6, 19.1, 25.1, 26.7, 41.0, 57.9, 66.8, 77.7, 78.0, 79.8, 109.7, 125.8, 126.3, 127.7, 128.4, 130.9, 136.1, 209.4. R_f = 0.36 (EtOAc/*n*-hexane = 1:6). HRMS: calcd. for $C_{20}H_{26}O_4$ $(M+Na)^+$ 353.1723 found 353.1717. **Minor isomer 129b:** $[\alpha]^{24}_D$ = +24.9 (c = 1.45, $CHCl_3$). IR ($CHCl_3$): 3674, 3419 (broad), 3026, 3012, 2975, 2933, 2877, 1715, 1495, 1450, 1382, 1228, 1109, 967, 843 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.84 (t, *J* = 7.41 Hz, 3H), 1.40 (s, 3H), 1.48 (s, 3H), 1.70-1.78 (m, 2H), 2.23 (ddd, *J* = 14.44, 2.74, 1.18 Hz, 1H), 2.35 (m, 1H), 2.65 (dd, *J* = 14.44, 11.71 Hz, 1H), 3.80 (dddd, *J* = 11.71, 5.86, 4.30, 2.74 Hz, 1H), 4.03 (dd, *J* = 8.58, 6.25 Hz, 1H), 4.09 (dd, *J* = 8.58, 6.64 Hz, 1H), 4.28 (dt, 6.24, 4.68 Hz, 1H), 4.38 (m, 1H), 6.15 (dd, *J* = 16.00, 5.47 Hz, 1H), 6.65 (dd, *J* = 16.00, 1.17 Hz, 1H), 7.23-7.39 (m, 5H). R_f = 0.24 (EtOAc/*n*-hexane = 1:6).

(2*R*,3*S*,6*R*)-6-((4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-isopropyl-2-*E*-propenyl-tetrahydropyran-4-one 130: Diene **119** (725 mg. 2.00 mmol), crotonaldehyde (247 µl, 210 mg, 3.00 mmol) and BF_3•Et_2O (380 µl, 426 mg, 3.00 mmol) were reacted at -20°C for 2.5 h according to the general procedure for HDA reactions to give crude **125** a slightly yellow oil which was used immediately in the next step. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.17 (s, 3H), 0.19 (s, 3H), 0.93 (s, 9H), 0.89-1.03 (m, 6H), 1.35 (s, 3H), 1.41 (s, 3H), 1.72 (dt, *J* = 6.16, 1.17 Hz, 3H), 1.84 (m, 1H), 2.01 (m, 1H), 3.85 (dd, *J* = 7.62, 5.86 Hz, 1H), 4.00-4.12 (m, 4H), 4.98 (d, *J* = 1.76 Hz, 1H), 5.50 (ddq, *J* = 15.54, 5.28, 1.47 Hz, 1H), 5.66 (dqd, *J* = 15.54, 6.45, 0.88 Hz). TBS enol ether **125** (max. 865 mg, max. 2.00 mmol), acetic acid (286 µl, 300 mg, 5.00 mmol) and TBAF•$3H_2O$ (947 mg, 3.00 mmol) were reacted according to the general procedure for the desilylation of a TBS enol ether. The product was purified by flash chromatography (column dimensions: 25 x 2 cm, EtOAc/PE = 1:5) to give a total of 434 mg (1.54 mmol, 77% over two steps) of the two all-*cis* diastereomers of **130** in a 4:1 ratio. **Major isomer 130a:** $[\alpha]^{25}_D$ = +41.9 (c = 0.87, $CHCl_3$). IR ($CHCl_3$): 3688, 3460 (broad), 3026, 3011, 2964, 2934, 2875, 1717, 1601, 1457, 1383, 1374, 1231, 1069 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.94 (d, *J* = 7.64 Hz, 6H), 1.35 (s, 3H), 1.40 (s, 3H), 1.73 (ddd, *J* = 6.45, 1.47, 1.17 Hz, 3H), 2.18 (m, 1H), 2.37 (dd, *J* = 14.95, 11.14 Hz, 1H), 2.44 (d, *J* = 6.74 Hz, 1H), 2.57 (ddd, *J* = 14.95, 2.93, 0.88 Hz, 1H), 3.66 (m, 1H), 3.96 (m, 1H), 4.11 (m, 2H), 4.18 (m, 1H), 5.53 (ddq, *J* = 15.22, 5.86, 1.76 Hz, 1H), 5.70 (dqd, 15.22, 6.45, 1.47 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.9, 21.0, 23.2, 25.3, 25.7, 26.2, 42.8, 61.7, 65.0, 76.2, 76.8, 80.2, 109.7, 127.1, 128.2, 209.1. R_f = 0.44 (EtOAc/*n*-hexane = 1:6). **Minor isomer 130b:** $[\alpha]^{26}_D$ = +46.8 (c = 1.78, $CHCl_3$). IR ($CHCl_3$): 3670, 3496 (broad), 3027, 2965, 2934, 2875, 1712, 1599, 1456, 1418, 1382, 1373, 1231, 1155, 1070, 971, 849 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.94 (d, *J* = 6.64 Hz,

3H), 0.97 (d, *J* = 6.24 Hz, 3H), 1.38 (s, 3H), 1.44 (s, 3H), 1.73 (ddd, *J* = 6.64, 1.56, 1.17 Hz, 3H), 2.20 (m, 1H), 2.31 (ddd, *J* = 14.83, 3.13, 1.17Hz, 1H), 2.47 (dd, *J* = 14.83, 11.71 Hz, 1H), 3.75 (ddd, *J* = 11.71, 4.69, 3.12 Hz, 1H), 3.95 (dd, *J* = 8.19, 6.63 Hz, 1H), 4.05 (dd, *J* = 8.19, 6.63 Hz, 1H), 4.18-4.21 (m, 2H), 5.54 (ddq, *J* = 15.22, 5.86, 1.56 Hz, 1H), 5.75 (dqd, *J* = 15.22, 6.64, 1.17 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 17.8, 20.9, 23.1, 25.2, 25.6, 26.1, 42.8, 61.6, 64.9, 76.2, 76.8, 80.2, 109.7, 127.2, 128.3, 209.4. R_f = 0.33 (EtOAc/*n*-hexane = 1:6).

(2*R*,3*S*,6*R*)-6-((4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-isopropyl-2-(*E*-2-phenylethenyl)tetrahydro-pyran-4-one 131: Diene **119** (725 mg. 2.00 mmol), cinnamaldehyde (378 µl, 396 mg, 3.00 mmol) and BF_3•Et_2O (380 µl, 426 mg, 3.00 mmol) were reacted at -20°C for 4 h according to the general procedure for HDA reactions to give crude **126** as a slightly yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.20 (s, 3H), 0.21 (s, 3H), 0.94 (s, 9H), 0.96 (d, *J* = 7.02 Hz, 3H), 1.03 (d, *J* = 7.03 Hz, 3H), 1.37 (s, 3H), 1.44 (s, 3H), 1.97-2.03 (m, 2H), 3.91 (dd, 7.41, 5.46 Hz, 1H), 4.06-4.13 (m, 3H), 4.36 (m, 1H), 5.02 (d, *J* = 1.95 Hz, 1H), 6.22 (dd, *J* = 16.00, 1.56 Hz, 1H), 6.60 (dd, *J* = 16.00, 4.69 Hz, 1H), 7.22-7.58, (m, 5H). TBS enol ether **126** (max. 2.00 mmol), acetic acid (286 µl, 300 mg, 5.00 mmol) and TBAF•3H_2O (947 mg, 3.00 mmol) were reacted according to the general procedure for desilylation of TBS enol ethers to give a slightly yellow oil, which was purified by flash chromatography (column dimensions 30 x 2.5 cm, EtOAc/PE = 1:6) to give a total of 472 mg (1.37 mmol, 69% over two steps) of the two all-*cis* diastereomers of **131** in a 4:1 ratio, accompanied by a small amount of a third, unidentified diastereomer and some desilylated diene, the latter two being inseparable. **Major isomer 131a:** $[\alpha]^{25}_D$ = +10.2 (c = 0.40, $CHCl_3$). IR ($CHCl_3$): 3687, 3499, 3025, 3013, 2964, 2934, 2874, 1784, 1732, 1603, 1452, 1230, 1213, 1169, 1090 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.93 (d, *J* = 6.64 Hz, 3H), 0.99 (d, *J* = 6.44 Hz, 3H), 1.38 (s, 3H), 1.43 (s, 3H), 2.22 (m, 1H), 2.27 (ddd, *J* = 7.03, 3.12, 1.17 Hz, 1H), 2.44 (dd, *J* = 14.83, 11.51 Hz, 1H), 2.61 (ddd, *J* = 14.83, 3.13, 1.17 Hz, 1H), 3.66 (ddd, *J* = 11.51, 6.44, 3.12, Hz, 1H), 4.00 (m, 1H), 4.17 (m, 1H), 4.41 (ddd, *J* = 5.27, 3.12, 1.76 Hz, 1H), 6.18 (dd, *J* = 16.00, 5.27 Hz, 1H), 6.64 (dd, *J* = 16.00, 1.56 Hz), 7.23-7.39 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.0, 23.4, 25.1, 25.8, 26.7, 43.8, 62.0, 66.8, 77.5, 77.8, 80.0, 109.7, 126.2, 126.6, 127.6, 128.5, 129.8, 136.3, 208.7. R_f = 0.34 (EtOAc/*n*-hexane =1:6). HRMS: calcd. for $C_{21}H_{28}O_4$ $(M+Na)^+$ 367.1880 found 367.1874. **Minor Isomer 131b:** $[\alpha]^{25}_D$ = +16.7 (c = 1.165, $CHCl_3$). IR ($CHCl_3$): 3670, 3408 (broad), 3027, 3011, 2964, 2934, 2874, 1711, 1603, 1495, 1455, 1366, 1229, 1072, 909, 848 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.96 (d, *J* = 7.02 Hz, 3H), 0.98 (d, *J* = 6.63 Hz, 3H), 1.40 (s, 3H), 1.48 (s, 3H), 2.23 (m, 1H), 2.32 (ddd, *J* = 7.03, 3.12, 1.17 Hz, 1H), 2.35 (ddd, *J* = 14.83, 3.12, 1.17 Hz, 1H), 2.56 (dd, *J* = 14.83, 11.71 Hz, 1H), 3.82 (ddd, *J* = 11.71, 4.29, 3.12 Hz, 1H), 4.03 (dd, *J* = 8.19, 6.64 Hz, 1H), 4.08-4.15 (m, 2H), 4.27 (td, 6.64, 4.29 Hz, 1H), 4.43 (m, 1H), 6.21 (dd, *J* = 16.00, 5.47 Hz, 1H), 6.68 (dd, *J* = 16.00, 1.56 Hz, 1H), 7.24-7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.0, 23.3, 25.3, 25.9, 26.1, 42.7, 62.0, 65.0, 76.5, 76.8, 80.0, 109.9, 126.4, 126.8, 127.7, 128.6, 130.1, 136.5, 209.2. R_f = 0.22 (EtOAc/*n*-hexane =1:6).

(2*R*,3*S*,4*R*,6*R*)-6-((4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-methyl-2-*E*-propenyl-tetrahydropyran-4-ol 102b: To a solution of **94a** (53.6 mg, 0.211 mmol) in MeOH (5.0 ml) at 0°C was added $NaBH_4$ (16 mg, 0.422 mmol). The reaction was stirred overnight at room temperature, after which the reaction was complete as judged by TLC. The volume was reduced *in vacuo* and the mixture was diluted with sat. aq. NH_4Cl (5 ml) and water (15 ml) and extracted with *t*BuOMe (3 x 25 ml). The combined organic fractions were dried (Na_2SO_4), filtered, concentrated *in vacuo*, and purified by flash chromatography (20 x 1.5 cm, EtOAc/PE = 1:3) to give **102b** (54.2 mg, 0.211 mmol, 100%) as a colorless oil. $[\alpha]^{25}_D$ = -20.5 (c = 1.375, $CHCl_3$). IR ($CHCl_3$): 3609, 3207 (broad), 3025, 3012, 2987, 2933, 1455, 1382, 1372, 1228, 1205, 1149, 1068, 1032, 969, 845 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.87 (d, *J* = 6.64 Hz, 3H), 1.35 (s, 3H), 1.41 (s, 3H), 1.42 (m, 3H), 1.86-1.91 (m, 2H), 3.32 (ddd, *J* = 11.32, 7.03, 2.34 Hz, 1H), 3.86 (pseudo d, *J* = 5.46 Hz, 1H), 3.91-3.98 (m, 2H), 4.00 (dt, *J* = 5.86, 5.07 Hz, 1H), 4.08 (m, 1H), 5.44 (ddq, *J* = 15.22, 5.46, 1.56 Hz, 1H), 5.65 (dqd, *J* = 15.22, 6.64, 1.56 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 5.3, 18.0, 25.4, 26.8, 31.5, 39.5, 67.1, 70.7, 76.8, 77.7, 79.3, 109.2, 126.6, 129.4. R_f = 0.30 (EtOAc/*n*-hexane = 1:2). HRMS: calcd. for $C_{14}H_{24}O_4$ $(M + Na)^+$ 279.1567 found 279.1564.

(2*R*,3*S*,4*S*,6*R*)-6-((4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-methyl-2-*E*-propenyl-tetrahydropyran-4-ol 102a: To a solution of ketone **94a** (51.4 mg, 0.202 mmol) in THF (5 ml) was added at -78°C K-Selectride® (1M in THF, 303 µl, 0.303 mmol). The mixture was stirred at that temperature for 30 min, allowed to warm to -30°C over a period of 2.5 h and then quenched by addition of 0.2N aq. NaOH (3 ml) and 30% aq. H_2O_2 (0.5 ml). The mixture was diluted with H_2O and extracted with *t*BuOMe (3 x 20 ml). The combined organic fractions were dried (Na_2SO_4), filtered, concentrated in vacuo and purified by flash chromatography (column dimensions 25 x 1.5 cm, EtOAc/PE = 1:3) to give axial alcohol **102a** (10.5 mg, 0.041 mmol, 20%) and equatorial alcohol **102b** (41.5 mg, 0.162 mmol, 80%, characterization see above) as colourless oils. ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.92 (d, *J* = 7.13 Hz, 3H), 1.35 (s, 3H), 1.41 (s, 3H), 1.50-1.68 (m, 3H), 1.70 (ddd, *J* = 6.40, 1.46, 1.10 Hz, 3H), 3.74 (dd, *J* = 14.09, 6.95 Hz, 1H), 3.85-4.11 (m, 4H), 4.38 (m, 1H), 5.42 (ddq, *J* = 15.37, 5.86, 1.46 Hz, 1H), 5.66 (dqd, *J* = 15.37, 6.40, 1.28 Hz, 1H). R_f = 0.38 (EtOAc/*n*-hexane = 1:2). HRMS: calcd. for $C_{14}H_{24}O_4$ $(M + Na)^+$ 279.1567 found 279.1564.

(2*R*,4*S*,6*R*)-2-((4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-*E*-propenyltetrahydropyran-4-ol 105b: To a solution of ketone **103** (31.2 mg, 0.128 mmol) in MeOH (5 ml) was added $NaBH_4$ (10 mg, 0.26 mmol) and the mixture was stirred for 1.5 h at rt. The volume was reduced to ±1 ml *in vacuo* and the residue was diluted with Et_2O (75 ml), washed with sat. aq. NH_4Cl (25 ml) and brine (25 ml), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give **105b** (32 mg, 0.132 mmol, quant.; 4*S*:4*R* = 91:9) as a colorless oil. ^1H

NMR ($CDCl_3$, 200 MHz): δ = 1.35 (s, 3H), 1.41 (s, 3H), 1.71 (d, *J* = 6.4 Hz, 3H), 1.88 (m, 1H), 1.97 (m, 1H), 2.17 (m, 1H), 3.30 (m, 1H), 3.75-3.90 (m, 2H), 3.95 (m, 1H), 4.01 (m, 1H), 4.08 (m, 1H), 5.50 (m, 1H), 5.68 (m, 1H) ppm.

(2*R*,4*R*,6*R*)-2-((4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-*E*-propenyltetrahydropyran-4-ol 105a: To a solution of ketone **103** (112 mg, 0.466 mmol) in THF (10 ml) was added at -78°C K-Selectride® (1 M solution in THF, 699 µl, 0.699 mmol). The mixture was stirred for 2 h at −78°C. The reaction was quenched by addition of 30% aq. H_2O_2 (0.5 ml) and 1N NaOH (3 ml), and diluted with H_2O (20). The mixture was extracted with *t*BuOMe (3 × 15 ml). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (column dimensions 25 × 2 cm, EtOAc/PE = 1:2) to give **105a** (27 mg, 0.111 mmol, 24%; 4*R*:4*S* = 89:11) as a colorless oil. $[\alpha]^{27}_D$ = + 11.1 (c = 1.35, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.35 (s, 3H), 1.42 (s, 3H), 1.53-1.66 (m, 2H), 1.69 (d, *J* = 7.03 Hz, 3H), 1.69-1.73 (m, 1H), 1.87 (dd, *J* = 14.05, 3.12 Hz, 1H), 3.78 (ddd, *J* = 11.71, 7.02, 1.95 Hz, 1H), 3.91 (dd, *J* = 8.20, 5.47 Hz, 1H), 4.00 (td, *J* = 6.64, 5.47 Hz, 1H), 4.09 (dd, *J* = 8.20, 6.25 Hz, 1H), 4.26 (m, 1H), 4.32 (m, 1H), 5.47 (ddq, *J* = 15.22, 6.25, 1.56 Hz, 1H), 5.69 (dqd, *J* = 15.22, 6.64, 1.18 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 17.8, 25.2, 26.6, 34.5, 38.4, 64.1, 67.2, 72.3, 72.6, 78.0, 109.4, 127.3, 131.6 ppm. R_f = 0.40 (EtOAc/*n*/hexane = 1:2).

(2*R*,3*S*,4*S*,6*R*)-6-((1*R*)-1,2-dihydroxyethyl)-3-methyl-2-*E*-propenyl-tetrahydropyran-4-ol 101b: To a solution of **102a** (10.5 mg, 0.041 mmol) in acetone/water 1:1 (1.0 ml) was added PPTS (1.0 mg, 0.0041 mmol). The mixture was stirred for 2 d at room temperature, then diluted with brine and extracted three times with tBuOMe. The combined organic fractions were dried ($NaSO_4$), filtered, concentrated *in vacuo*, and purified by flash chromatography (20 x 1 cm, CH_2Cl_2/MeOH = 20:1) to give **101b** (5.1 mg, 0.024 mmol, 58%) as a colorless oil. IR ($CHCl_3$): 3675, 3606, 3416 (broad), 3025, 3011, 2967, 2925, 2884, 1712, 1673, 1601, 1450, 1436, 1379, 1230, 1203, 1076, 1050, 1006, 969, 933, 883 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.91 (d, *J* = 7.03 Hz, 3H), 1.65-1.78 (m, 3H), 1.71 (dd, *J* = 6.63, 1.17 Hz, 3H), 2.46 (bs, 1H), 2.65 (bs, 1H), 3.67 (m, 3H), 3.94-4.03 (m, 2H), 4.41 (m, 1H), 5.41 (ddq, *J* = 15.22, 6.24, 1.56 Hz, 1H), 5.66 (dqd, *J* = 15.22, 6.63, 1.17 Hz, 1H). HRMS: calcd. for $C_{11}H_{20}O_4$ $(M + Na)^+$ 239.1254 found 239.1251.

(2*R*,3*S*,4*R*,6*R*)-6-((*R*)-1,2-Dihydroxyethyl)-3-methyl-2-*E*-propenyltetrahydropyran-4-ol 107b: To a solution of acetonide **102b** (277 mg, 1.09 mmol) in MeOH (20 ml) was added PPTS•H_2O (274 mg, 1.09 mmol). The mixture was stirred for 3 d at rt. The mixture was diluted with brine (50 ml) and extracted with *t*BuOMe (3 × 50 ml). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by flash chromatography (column dimensions 25 × 2 cm, CH_2Cl_2/MeOH = 10.1)

afforded **107b** (192 mg, 0.89 mmol, 82 %) as a viscous, turbid oil, accompanied by the starting material (43 mg, 0.17 mmol, 16%). The yield based on recovered starting material is therefore 97%. $[a]^{21}_{D} = -22.3$ (c = 1.14, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.88 (d, *J* = 7.03 Hz, 3H), 1.50-1.70 (m, 3H), 1.71 (d, *J* = 6.24 Hz, 3H), 1.92 (t, *J* = 6.64 Hz, 1H, OH), 2.30, (bs, 1H, OH), 2.60 (bs, 1H, OH), 3.56 (ddd, *J* = 11.71, 4.29, 2.73 Hz, 1H), 3.68-3.73 (m, 2H), 3.79 (dd, *J* = 11.31, 5.46 Hz, 1H), 3.87 (d, *J* = 5.07 Hz, 1H), 3.97 (dt, *J* = 11.32, 4.68 Hz, 1H), 5.44 (ddq, *J* = 15.62, 5.47, 1.57 Hz, 1H), 5.65 (dqd, *J* = 15.61, 6.64, 1.17 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 5.32, 17.98, 30.44, 39.47, 63.48, 70.58, 73.41, 77.50, 79.49, 126.93, 129.25 ppm. R_f = 0.57 (CH_2Cl_2/MeOH = 9:1).

(2*R*,3*S*,4*R*,6*R*)-4-*tert*-Butyldimethylsilyloxy-6-((*R*)-1,2-bis(*tert*-butyldimethylsilyloxy)-ethyl)-3-methyl-2-*E*-propenyltetrahydropyran 107a: To a solution of triol **107b** (131 mg, 0.606 mmol) and 2,6-lutidine (421 µl, 389 mg, 3.63 mmol) in CH_2Cl_2 (15 ml) was added at -78°C TBSOTf (626 µl, 721 mg, 2.73 mmol). The mixture was allowed to warm to rt and the reaction was quenched by addition of sat. aq. $NaHCO_3$ (10 ml).. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 15 ml). The combined organic extracts were washed with dilute aq. NH_4Cl (20 ml) and brine (25 ml), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by flash chromatography (column dimensions 25 × 2 cm, EtOAc/PE = 1:50) afforded **107a** (334 mg, 0.597mmol, 99%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.02 (s, 3H), 0.03 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H), 0.07 (s, 3H), 0.09 (s, 3H), 0.84 (d, *J* = 7.03 Hz, 3H), 0.88 (s, 9H), 0.89 (s, 18H), 1.51-1.61 (m, 2H), 1.70 (d, *J* = 6.64 Hz, 3H), 1.70-1.74 (m, 1H), 3.42 (dt, *J* = 10.14, 4.30 Hz, 1H), 3.55 (d, *J* = 5.47 Hz, 2H), 3.77 (q, *J* = 5.07 Hz, 1H), 3.81-3.89 (m, 2H), 5.43 (ddq, *J* = 15.61, 5.47, 1.17 Hz, 1H), 5.64 (dq, *J* = 15.61, 6.24 Hz, 1H) ppm. R_f = 0.76 (EtOAc/*n*-hexane = 1:20).

(2*R*,3*S*,4*R*,6*R*)-4-*tert*-Butyldimethylsilyloxy-6-((*R*)-1-(*tert*-butyldimethylsilyloxy)-2-(hydroxy)ethyl)-3-methyl-2-*E*-propenyltetrahydropyran 107: Concentrated aq. HCl (10 ml) and $CHCl_3$ (50 ml) were mixed in a separatory funnel and shaken exhaustively for 5 min. The organic phase (5 ml) was then poured on tris TBS ether **107a** (368 mg, 0.658 mmol) and the mixture was stirred for 20 h at rt. The mixture was diluted with sat. aq. $NaHCO_3$ (50 ml) and extracted with $CHCl_3$ (3 × 25 ml). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by flash chromatography (column dimensions 30 × 3 cm, EtOAc/PE = 1:12) afforded **107** (267 mg, 0.600 mmol, 91%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.05 (s, 3H), 0.10 (s, 3H), 0.10, (s, 6H), 0.85 (d, *J* = 7.02 Hz, 3H), 0.88 (s, 9H), 0.89 (s, 9H), 1.40 (t, *J* = 6.25 Hz, 1H), 1.69 (d, *J* = 6.25 Hz, 3H), 1.73-1.78 (m, 2H), 2.47 (dd, *J* = 8.98, 2.73 Hz, 1H, OH), 3.41 (ddd, *J* = 11.71, 6.63, 2.34 Hz, 1H), 3.62 (d, *J* = 6.25 Hz, 2H), 3.65-3.73 (m, 1H), 3.85-3.89 (m, 2H), 5.43 (ddq, *J* = 15.61, 5.47, 1.56 Hz, 1H), 5.62 (dq, *J* = 15.61, 6.64 Hz, 1H) ppm. ^{13}C

NMR ($CDCl_3$, 100 MHz): δ = -4.8, -4.7, -4.4, -3.6, 5.5, 17.8, 18.0, 18.1, 25.6, 25.8, 32.5, 40.3, 65.3, 71.3, 74.0, 78.1, 79.6, 126.5, 129.8 ppm. R_f = 0.38 (EtOAc/*n*-hexane = 1:10).

(2*R*,3*S*,4*R*,6*R*)-4-*tert*-Butyldimethylsilyloxy-6-((*S*)-1-(*tert*-butyldimethylsilyloxy)-1-(formyl)methyl)-3-methyl-2-*E*-propenyltetrahydropyran 108: To a solution of alcohol **107** (133 mg, 0.300 mmol) in CH_2Cl_2 (5 ml) was added Dess-Martin periodinane (153 mg, 0.360 mmol) and the mixture was stirred for 2 h at rt. The mixture was diluted with sat. aq. $NaHCO_3$ (50 ml) and extracted with *t*BuOMe (3 × 50 ml). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (column dimensions: 25 × 2 cm, EtOAc/PE = 1:15) to give **108** (111 mg, 0.250 mmol, 83%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.04 (s, 6H), 0.10 (s, 6H), 0.85 (d, *J* = 7.02 Hz, 3H), 0.88 (s, 9H), 0.93 (s, 9H), 1.45 (ddd, *J* = 12.49, 4.69, 2.34 Hz, 1H), 1.66 (dd, *J* = 12.49, 11.71 Hz, 1H), 1.70 (d, *J* = 6.64 Hz, 3H), 1.75 (dd, *J* = 6.63, 6.24 Hz, 1H), 3.63 (ddd, *J* = 11.71, 5.07, 2.34 Hz, 1H), 3.84-3.89 (m, 2H), 4.09 (d, *J* = 5.07 Hz, 1H), 5.42 (ddq, *J* = 15.61, 5.46, 1.56 Hz, 1H), 5.64 (dq, *J* = 15.61, 6.64 Hz, 1H) ppm. R_f = 0.58 (EtOAc/*n*-hexane = 1:10). HRMS calcd. for $C_{23}H_{46}O_4Si_2$ $(M+Na)^+$ 465.2827 found 465.2835.

(2*S*,3*R*,4*S*,6*S*)-6-((4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-methyl-2-*E*-propenyltetrahydropyran-4-ol 109: To a solution of **94b** (762 mg, 3.00 mmol) in MeOH (15 ml) at 0°C was added $NaBH_4$ (113 mg, 3.00 mmol). The reaction was stirred overnight at room temperature, after which the reaction was complete as judged by TLC. The volume was reduced *in vacuo* and the mixture was diluted with sat. aq. NH_4Cl (50 ml) and brine (100 ml) and extracted with *t*BuOMe (3 × 100 ml). The combined organic fractions were dried (Na_2SO_4), filtered, concentrated *in vacuo*, and purified by flash chromatography (25 × 2.5 cm, EtOAc/PE = 1:2) to give **109** (664 mg, 2.59 mmol, 86%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.88 (d, *J* = 7.02 Hz, 3H), 1.36 (s, 3H), 1.43 (s, 3H), 1.49 (t, *J* = 11.71 Hz, 1H), 1.57 (ddd, *J* = 12.49, 4.30, 2.73 Hz, 1H), 1.70 (dd, *J* = 6.25, 1.17 Hz, 3H), 1.91 (m, 1H), 3.51 (ddd, *J* = 11.71, 5.85, 2.73 Hz, 1H), 3.83 (d, *J* = 8.20, 6.64 Hz, 1H), 3.86 (d, *J* = 6.24 Hz, 1H), 3.94 (ddd, *J* = 11.70, 5.07, 4.69 Hz, 1H), 4.01 (dd, *J* = 8.20, 6.64 Hz, 1H), 4.19 (td, *J* = 6.64, 5.85 Hz, 1H), 5.48 (ddq, *J* = 15.22, 6.24, 1.56 Hz, 1H), 5.67 (dqd, *J* = 15.22, 6.64, 1.17 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 5.3, 18.0, 25.4, 26.4, 29.5, 39.8, 65.3, 70.7, 76.1, 77.1, 79.5, 109.4, 126.9, 129.5 ppm. R_f = 0.32 (EtOAc/*n*/hexane = 1:2).

(2*S*,3*R*,4*R*,6*S*)-4-Acetoxy-6-((4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-methyl-2-*E*-propenyltetrahydropyran 110: To a solution of alcohol **109** (128 mg, 0.50 mmol), Ph_3P (197 mg, 0.75 mmol, acetic acid (43 µl, 45 mg, 0.75 mmol) in THF (5 ml) was added DIAD (145 µl, 152 mg, 0.75 mmol). The mixture was stirred for 5 h and quenched by addition of sat. aq. NH_4Cl. The mixture was extracted with

*t*BuOMe (3 × 25 ml) and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (column dimensions 30 × 2 cm, EtOAc/PE = 1:10→1:4) to afford the desired acetate **110** (49 mg, 0.163 mmol, 33 %), accompanied by the elimination product (39 mg, 0.163 mmol, 33%) and a third, unidentified product (21 mg). **Acetate 110:** ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.96 (d, *J* = 7.02 Hz, 3H), 1.36 (s, 3H), 1.43 (s, 3H), 1.70 (d, *J* = 6.25 Hz, 3H), 1.71-1.81 (m, 2H), 3.82 (ddd, *J* = 12.49, 5.46, 2.73 Hz, 1H), 3.85 (dd, *J* = 8.58, 6.64 Hz, 1H), 3.99 (dd, *J* = 8.58, 6.64 Hz, 1H), 4.16 (td, *J* = 6.64, 5.46 Hz, 1H), 4.27 (d, *J* = 5.85 Hz, 1H), 4.98 (m, 1H), 5.43 (ddq, *J* = 15.22, 6.25, 1.56 Hz, 1H), 5.69 (dqd, *J* = 15.22, 6.64, 1.18 Hz, 1H) ppm. R_f = 0.49 (EtOAc/*n*/hexane = 1:4). **Elimination product 110a:** ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.37 (s, 3H), 1.43 (s, 3H), 1.55 (s, 3H), 1.71 (dd, *J* = 6.63, 1.17 Hz, 3H), 1.78 (m, 1H), 1.99-2.06 (m, 1H), 3.64 (ddd, *J* = 10.92, 6.64, 3.12 Hz, 1H), 3.73 (dd, *J* = 8.19, 7.42 Hz, 1H), 4.00 (dd, *J* = 8.19, 6.64 Hz, 1H), 4.18 (dt, *J* = 7.02, 6.64 Hz, 1H), 4.45 (d, *J* = 8.20 Hz, 1H), 5.34 (ddq, *J* = 15.22, 8.58, 1.56 Hz, 1H), 5.55 (dd, *J* = 6.24, 1.17 Hz, 1H), 5.77 (dq, *J* = 15.22, 6.63 Hz, 1H) ppm. R_f = 0.66 (EtOAc/*n*/hexane = 1:4).

2-Methyloct-3-en-5-one 137: Ylide **111** (3.46 g, 10.0 mmol, see synthesis of **115**) was reacted with isobutyraldehyde (1.10 ml, 962 mg, 12.0 mmol) were reacted according to the general procedure for Wittig reactions. The residue was purified by flash chromatography (column dimensions 12 x 4 cm, EtOAc/PE = 1:4) to give **137** (210 mg, 1.50 mmol, 15%) as a slightly yellow oil. IR (film): 2962, 2933, 2873, 1696, 1675, 1628, 1465, 1457, 1363, 1303, 1271, 1196, 1131, 1058, 982, 776, 742 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.94 (t, *J* = 7.42 Hz, 3H), 1.07 (d, *J* = 7.02 Hz, 6H), 1.64 (m, 2H), 2.46 (m, 1H), 2.52 (t, *J* = 7.42 Hz), 6.05 (dd, *J* = 16.00, 1.56 Hz, 1H), 6.79 (dd, *J* = 16.00, 6.63 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 13.8, 17.7, 21.3, 31.0, 41.9, 127.3, 152.9, 200.7. R_f = 0.50 (EtOAc/*n*-hexane = 1:10).

2,8-Dimethylnon-3-en-5-one 138: Ylide **98** (17.5 g, 55.0 mmol), *n*-BuLi (1.6M in hexane, 41.8 ml, 77.0 mmol) and isobutyl iodide (8.90 ml, 14.2 g, 77.0 mmol) were reacted according to the general procedure for alkylation of ylide **98** to give **113** (19.5 g, 52.1 mmol, 95%) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83-0.98 (m, 7H), 1.57 (m, 2H), 2.32 (t, *J* = 7.81 Hz, 2H), 7.42-7.72 (m, 16H). Ylide **113** (5.62 g, 15.0 mmol) was reacted with isobutyraldehyde (20.5 ml, 1.62 g, 22.5 mmol) were reacted according to the general procedure for Wittig reactions. The residue was purified by flash chromatography (column dimensions 10 x 5.5 cm, EtOAc/PE = 1:20) to give **138** (915 mg, 5.44 mmol, 36%) as a slightly yellow oil. IR ($CHCl_3$): 3026, 3011, 2961, 2931, 2871, 2455, 1688, 1661, 1624, 1467, 1409, 1386, 1367, 1339, 1295, 1272, 1233, 1191, 1078, 982, 950 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.91 (d, *J* = 6.25 Hz, 6H), 1.08 (d, *J* = 7.02 Hz, 6H), 1.47-1.63 (m, 3H), 2.47 (m, 1H), 2.54 (t, *J* = 7.81 Hz, 2H), 6.04 (dd, *J* = 16.00, 1.56 Hz, 1H), 6.79 (dd, *J* = 16.00, 6.63 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.3, 22.4, 27.8, 31.1, 33.1, 38.2,

127.2, 152.9, 201.0. R_f = 0.36 (EtOAc/*n*-hexane = 1:20). HRMS: calcd. for $C_{11}H_{20}O$ $(M + Na)^+$ 191.1406 found 191.1404.

4-(*tert*-Butyldimethylsilyloxy)-7-methyl-3*Z*,5*E*-octadiene 132: Ketone **137** (190 mg, 1.35 mmol), Et_3N (220 µl, 164 mg, 1.62 mmol) and TBSOTf (340 µl, 394 mg, 1.49 mmol) were reacted according to the general procedure for the synthesis of TBS enol ethers. The crude product was purified by flash chromatography on a small, Et_3N-neutralized column (column dimensions 20 x 3 cm, EtOAc/PE = 1:100) to give **132** (230 mg, 0.90 mmol, 67%) as a colourless oil. IR ($CHCl_3$): 3670, 3413 (broad), 2957, 2930, 2883, 2857, 1706, 1689, 1621, 1471, 1463, 1387, 1362, 1255, 1098, 1078, 1005, 985, 939, 839 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.10 (s, 3H), 0.95 (t, *J* = 7.41 Hz, 3H), 1.00 (d, *J* = 6.63 Hz, 6H), 1.00 (s, 9H), 2.10 (m, 2H), 2.32 (m, 1H), 4.65 (dd, *J* = 7.41, 7.03 Hz, 1H), 5.74-5.81 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = -3.5, 14.3, 18.5, 19.4, 22.6, 26.1, 30.9, 115.3, 125.6, 136.0, 147.4. R_f = 0.62 (EtOAc/*n*-hexane = 1:100). HRMS: calcd. for $C_{15}H_{30}OSi$ $(M+H)^+$ 255.2139 found 255.2138.

5-(*tert*-Butyldimethylsilyloxy)-2,8-dimethyl-3*E*,5*Z*-nonadiene 133: Ketone **138** (910 mg, 5.41 mmol), Et_3N (2.09 ml, 1.52 g, 6.49 mmol) and TBSOTf (1.37 ml, 1.57 g, 5.95 mmol) were reacted according to the general procdure for the synthesis of TBS enol ethers. The crude product was purified by flash chromatography on a small, Et_3N-neutralized column (column dimensions 20 x 1.5 cm, EtOAc/PE = 1:20) to give **133** (1.47 g, 5.22 mmol, 96%) as a colourless oil. IR ($CHCl_3$): 3669, 3027, 2958, 2930, 2857, 1714, 1623, 1471, 1387, 1362, 1299, 1258, 1094, 1005, 986, 939, 839 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.10 (s, 3H), 0.89 (t, *J* = 6.15 Hz, 3H), 0.99 (s, 9H), 1.00 (d, *J* = 6.63 Hz, 6H), 1.53-1.59 (m, 1H), 1.96 (m, 2H), 2.32 (m, 1H), 4.70 (dd, *J* = 7.41, 7.03 Hz, 1H), 5.68-5.83 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = -3.4, 18.6, 22.6, 22.6, 26.1, 28.9, 30.9, 35.2, 112.1, 125.7, 135.9, 145.4. R_f = 0.90 (EtOAc/*n*-hexane = 1:20). HRMS :calcd. for $C_{17}H_{34}OSi$ $(M+Na+O)^+$ 321.2220 found 321.2222.

3-Ethyl-2-*E*-propenyl-6-isopropyltetrahydropyran-4-one 134: Diene **132** (62 mg, 0.24 mmol), crotonaldehyde (27 µl, 22 mg, 0.32 mmol) and BF_3•Et_2O (30 µl, 34 mg, 0.24 mmol) were reacted according to the general procedure for HDA reactions to give TBS enol ether **134a**. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.17 (s, 3H), 0.18 (s, 3H), 0.89 (d, *J* = 7.04 Hz, 3H), 0.90 (d, *J* = 7.04 Hz, 3H), 0.93 (s, 9H), 1.08 (dd, *J* = 6.74, 2.05 Hz, 3H), 1.43-1.84 (m, 2H), 1.72 (dd, 6.45, 1.17 Hz, 3H), 2.47 (m, 1H), 3.98 (m, 1H), 4.08 (m, 1H), 4.67 (d, *J* = 1.76 Hz, 1H), 5.55 (ddd, 15.24, 6.16, 1.47 Hz, 1H), 5.72 (dqd, 15.24, 6.16, 1.18 Hz, 1H). TBS enol ether **134a** (60 mg, 0.18 mmol), TBAF (70 mg, 0.27 mmol), and AcOH (51 µl, 54 mg, 0.90 mmol) were reacted according to the general procedure for the desilylation of TBS enol ethers to give **134** (12 mg, 0.06 mmol, 23%) as a colorless oil. IR ($CHCl_3$): 3025, 3014, 2965, 2933, 2876, 2855, 1698 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.82 (dd, *J* = 7.62, 7.33 Hz, 3H), 0.94 (d, *J* = 6.75 Hz, 3H), 0.98 (d, *J* = 6.75, 3H), 1.65 (m, 2H), 1.73 (ddd, *J* = 6.45, 1.47, 1.17 Hz, 3H), 1.86 (m, 1H), 2.19 (m, 1H), 2.22 (ddd, *J* = 14.07, 1.46, 1.17 Hz, 1H), 2.39 (dd, *J* = 14.07, 11.44 Hz, 1H), 3.34 (ddd, *J* = 11.43, 5.86, 2.64 Hz, 1H), 4.07 (m, 1H), 5.47 (ddq, *J* = 15.24, 5.57, 1.76 Hz, 1H), 5.76 (dqd, *J* = 15.24, 6.45, 1.47 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 11.7, 17.8, 18.0, 18.4, 18.9, 33.3, 41.5, 58.1, 79.6, 82.0, 127.4, 128.0, 211.6. R_f = 0.25 (EtOAc/*n*-hexane = 1:20). HRMS: calcd. for $C_{13}H_{22}O_2$ $(M+Na)^+$ 233.1512 found 233.1510.

3-Ethyl-2-(*E*-2-phenylethenyl)-6-isopropyltetrahydropyran-4-one 135: Diene **132** (102 mg, 0.40 mmol), cinnamaldehyde (65 µl, 69 mg, 0.52 mmol) and BF_3•Et_2O (51 µl, 57 mg, 0.40 mmol) were reacted according to the general procedure for HDA reactions to give TBS enol ether **135a**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.19 (s, 3H), 0.20 (s, 3H), 0.91-0.97 (m, 9H), 0.94 (s, 9H), 1.53 (m, 1H), 1.65 (m, 1H), 1.81 (m, 1H), 1.96 (m, 1H), 4.04 (m, 1H), 4.32 (m, 1H), 4.72, (d, *J* = 1.46 Hz, 1H), 6.26 (dd, *J* = 15.83, 5.28 Hz, 1H), 6.64 (dd, *J* = 15.83, 1.46 Hz, 1H), 7.21-7.44 (m, 5H). TBS enol ether **135a** (142 mg, 0.37 mmol), TBAF (145 mg, 0.56 mmol), and AcOH (106 µl, 111 mg, 1.85 mmol) were reacted according to the general procedure for the desilylation of TBS enol ethers to give **135** (70 mg, 0.26 mmol, 64%) as a colorless oil. IR ($CHCl_3$): 3691, 3568, 3527, 3029, 2962, 2935, 2876, 1713, 1602, 1496, 1465, 1416, 1283, 1229, 1203, 1178, 938, 828 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.83 (t, *J* = 7.63 Hz, 1H), 0.98 (d, *J* = 6.74 Hz, 3H), 1.04 (d, *J* = 6.74 Hz), 1.73 (m, 2H), 1.91 (m, 1H), 2.29 (ddd, *J* = 14.07, 2.93, 1.18 Hz, 1H), 2.32 (m, 1H), 2.45 (dd, *J* = 14.07, 11.44 Hz, 1H), 3.41 (ddd, *J* = 11.44, 5.86, 2.93 Hz, 1H), 4.32 (ddd, *J* = 4.98, 2.64, 1.76 Hz, 1H), 6.15 (dd, *J* = 16.12, 4.98 Hz, 1H), 6.68 (dd, *J* = 16.12, 1.76 Hz, 1H), 7.22-7.41 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 11.7, 17.9, 18.4, 19.2, 33.3, 41.6, 57.9, 79.2, 82.0, 126.3, 126.5, 127.5, 128.4, 130.5, 136.4, 211.0. R_f = 0.35 (EtOAc/*n*-hexane = 1:10). HRMS: calcd. for $C_{18}H_{24}O_2$ $(M + Na)^+$ 295.1669 found 295.1666.

3-Isobutyl-2-(*E*-2-phenylethenyl)-6-isopropyltetrahydropyran-4-one 136: Diene **133** (599 mg, 2.12 mmol), cinnamaldehyde (321 µl, 337 mg, 2.55 mmol) and BF_3•Et_2O (269 µl, 301 mg, 2.12 mmol) were reacted according to the general procedure for HDA reactions to give TBS enol ether **136a**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.18 (s, 3H), 0.20 (s, 3H), 0.84 (d, *J* = 5.57 Hz, 3H), 0.86 (d, *J* = 5.57 Hz, 3H), 0.93 (d, *J* ≈ 7 Hz, 3H), 0.94 (s, 9H), 0.95 (d, *J* ≈ 7 Hz), 1.24 (m, 1H), 1.52 (m, 1H), 1.70 (m, 1H), 1.80 (m, 1H), 2.00 (m, 1H), 4.06 (m, 1H), 4.32 (ddd, *J* = 5.57, 2.64, 1.17 Hz, 1H), 4.61 (d, *J* = 1.76 Hz, 1H), 6.20 (dd, *J* = 16.12, 5.57 Hz), 6.63 (dd, *J* = 16.12, 1.17 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = -4.4, -4.0, 17.9, 23.2, 25.8, 27.0, 33.2, 38.5, 42.5, 77.4, 78.8, 101.4, 126.2, 127.1, 128.3, 128.96, 129.03, 129.3, 137.1, 154.3. TBS enol ether **136a** (850 mg, 2.05 mmol), TBAF (803 mg, 3.07 mmol), and AcOH (586 µl, 616 mg, 10.3 mmol) were reacted according to the general procedure for the desilylation of TBS enol ethers to give **136** (460 mg, 1.53 mmol, 72%) as a colorless oil. IR ($CHCl_3$): 3674, 3523 (broad), 3083, 3027, 3009, 2961, 2935,

2872, 1705, 1627, 1599, 1577, 1496, 1469, 1449, 1413, 1386, 1368, 1295, 1261, 1243, 1186, 1125, 1101, 1059, 969, 908, 838 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.87 (d, *J* = 5.86 Hz, 1H), 0.88 (d, *J* = 6.16 Hz, 1H), 0.98 (d, *J* = 6.75 Hz, 3H), 1.04 (d, *J* = 6.74 Hz), 1.41 (m, 2H), 1.68 (m, 1H), 1.91 (m, 1H), 2.28 (ddd, *J* = 13.78, 2.64, 1.17 Hz, 1H), 2.45 (dd, *J* = 13.78, 11.43 Hz, 1H), 2.51 (m, 1H), 3.39 (ddd, *J* = 11.43, 6.16, 2.64 Hz, 1H), 4.31 (ddd, *J* = 4.98, 2.35, 1.76 Hz, 1H), 6.11 (dd, *J* = 16.12, 4.99 Hz, 1H), 6.68 (dd, *J* = 16.12, 1.76 Hz, 1H), 7.22-7.42 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.0, 18.5, 21.2, 23.78 26.0, 33.3, 34.9, 41.8, 54.6, 79.5, 82.4, 126.3, 126.5, 127.5, 128.4, 130.5, 136.5, 211.0. R_f = 0.50 (EtOAc/*n*-hexane = 1:10). HRMS: calcd. for $C_{20}H_{28}O_2$ $(M+Na)^+$ 323.1982 found 323.1981.

1-(4-Methoxyphenyl)-6-methylhept-1-en-3-one 140: Ylide **113** (5.62 g, 15.0 mmol, see synthesis of **37**) and 4-methoxybenzaldehyde (2.74 ml, 3.06 g, 22.5 mmol) were reacted according to the general procedure for Wittig reactions. The residue was purified by flash chromatography (column dimensions 10 x 5.5 cm, EtOAc/PE = 1:8) to give **140** (1.62 g, 6.99 mmol, 47%) as off-white crystals. IR ($CHCl_3$): 3028, 3012, 2959, 2935, 2870, 2840, 1680, 1648, 1600, 1573, 1511, 1465, 1422, 1368, 1331, 1307, 1285, 1253, 1173, 1137, 1112, 1079, 1033, 976, 823 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.93 (d, *J* = 6.16 Hz, 6H), 1.53-1.66 (m, 3H), 2.64 (m, 2H), 3.84 (s, 3H), 6.63 (dd, 16.12, 1.76 Hz, 1H), 6.91 (m, 2H), 7.49-7.54 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.5, 27.9, 33.4, 39.0, 55.4, 114.3, 123.9, 127.1, 129.1, 141.9, 161.3, 200.6. R_f = 0.35 (EtOAc/*n*-hexane = 1:8). HRMS: calcd. for $C_{15}H_{20}O_2$ $(M + Na)^+$ 255.1356 found 255.1354.

3-(*tert*-Butyldimethylsilyloxy)-1-(4-methoxyphenyl)-6-methyl-1*E*,3*Z*-heptadiene 139: Ketone **140** (1.60 g, 6.88 mmol), Et_3N (1.14 ml, 835 mg, 8.26 mmol) and TBSOTf (1.74 ml, 2.00 g, 7.57 mmol) were reacted according to the general method for the synthesis of TBS enol ethers to give **139** (2.35 g, 6.79 mmol, 99%) as a colorless solid. IR ($CHCl_3$): 3021, 3009, 2956, 2930, 2857, 1717, 1683, 1597, 1573, 1512, 1464, 1422, 1387, 1362, 1330, 1303, 1290, 1256, 1172, 1094, 1033, 1004, 987, 901, 837 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.15 (s, 6H), 0.92 (d, *J* = 6.75 Hz, 6H), 1.04 (s, 9H), 1.62 (m, 1H), 2.03 (dd, *J* = 7.33, 7.04 Hz, 2H), 3.80 (s, 3H), 4.91 (dd, *J* = 7.32, 6.63 Hz, 1H), 6.44 (d, *J* = 15.83 Hz, 1H), 6.59 (d, *J* = 15.83 Hz, 1H), 6.84 (d, *J* = 8.79 Hz, 2H), 7.30 (d, *J* = 8.79 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = -3.4, 18.6, 22.6, 26.2, 28.9, 35.4, 55.2, 113.9, 114.6, 125.5, 126.2, 127.3, 129.9, 148.8, 158.8.

4-(*tert*-Butyldimethylsilyloxy)-5-isobutyl-6-methyl-2-(4-methoxyphenyl)cyclohex-3-ene-1-carboxaldehyde 141: Diene **139** (600 mg, 1.73 mmol), crotonaldehyde (160 µl, 190 mg, 2.25 mmol) and BF_3•Et_2O (220 µl, 240 mg, 1.73 mmol) were reacted at -30°C for 3 h according to the general procedure for HDA reactions and purified by flash chromatography (column dimensions: 25 x 3 cm, EtOAc/PE = 1:10) to give Diels-Alder product **141** (325 mg, 0.78 mmol, 45%) as a slightly yellow oil. IR ($CHCl_3$): 3699,

3025, 3010, 2957, 2931, 2857, 1717, 1662, 1610, 1513, 1464, 1386, 1362, 1302, 1253, 1179, 1035, 908, 836 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.15 (s, 3H), 0.15 (s, 3H), 0.85-0.97 (m, 9H), 0.93 (s, 9H), 1.35 (m, 2H), 1.87 (m, 1H), 2.06 (m, 1H), 2.33 (m, 2H), 3.75 (m, 1H), 3.77 (s, 3H), 4.65 (d, *J* = 2.93 Hz, 1H), 6.80 (d, *J* = 8.79 Hz, 2H), 7.03 (d, *J* = 8.79 Hz, 2H), 9.62 (d, *J* = 4.10 Hz, 1H). R_f = 0.53 (EtOAc/*n*-hexane = 1:10). HRMS: calcd. for $C_{25}H_{40}O_3Si$ $(M + Na)^+$ 439.2639 found 439.2639.

4-(*tert*-Butyldimethylsilyloxy)-5-isobutyl-6-phenyl-2-(4-methoxyphenyl)cyclohex-3-ene-1-carboxaldehyde 142: Diene **139** (600 mg, 1.73 mmol), cinnamaldehyde (260 µl, 270 mg, 2.08 mmol) and BF_3•Et_2O (220 µl, 240 mg, 1.73 mmol) were reacted at -30°C for 3 h according to the general procedure for HDA reactions and purified by flash chromatography (column dimensions: 30 x 3 cm, EtOAc/PE = 1:8) to give Diels-Alder product **142** (315 mg, 0.66 mmol, 38%) as a slightly yellow oil. IR ($CHCl_3$): 3669, 3025, 3012, 2957, 2930, 2857, 2359, 2341, 1710, 1601, 1513, 1463, 1362, 1304, 1253, 1204, 1179, 1035, 834 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.18 (s, 3H), 0.21 (s, 3H), 0.50 (d, *J* = 6.45 Hz, 3H), 0.73 (d, *J* = 6.45 Hz), 0.84-0.97 (m, 3H), 0.94 (s, 9H), 1.35 (m, 2H), 1.32 (m, 1H), 2.28 (m, 1H), 3.05 (m, 1H), 3.56 (m, 1H), 4.70-4.87 (m, 1H), 3.80 (s, 3H), 4.72 (d, *J* = 2.64 Hz, 1H), 6.85 (d, *J* = 8.80 Hz, 2H), 7.09 (d, *J* = 8.50 Hz, 2H), 7.14-7.24 (m, 5H), 9.46 (d, *J* = 4.39 Hz, 1H). R_f = 0.47 (EtOAc/*n*-hexane = 1:8). HRMS: calcd. for $C_{30}H_{42}O_3Si$ $(M + Na)^+$ 501.2795 found 501.2794.

(2*R*,3*R*,6*R*)-6-((4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-isopropyl-2-(*E*-2-phenylethenyl)-tetrahydropyran-4-one (131d): To a solution of **131a** (89.4 mg, 0.260 mmol) in MeOH (5.0 ml) was added KO*t*Bu (1M in THF, 0.026 ml, 0.026 mmol) and the mixture was stirred for 2 days at room temperature. TLC analysis indicated that the starting material was fully converted. The mixture was diluted with sat. aq. NH_4Cl (15 ml) and brine (15 ml) and extracted with *t*BuOMe (3 x 25 ml). The combined organic fractions were dried (Na_2SO_4), filtered, concentrated *in vacuo*, and purified by flash chromatography (20 x 1.5 cm, EtOAc/PE = 1:6) to give **131d** (47.4 mg, 0.138 mmol, 53%) as a colorless oil. $[\alpha]^{24}_D$ = +12.4 (c = 2.06, $CHCl_3$). IR ($CHCl_3$): 3523 (broad), 3026, 3011, 2987, 2960, 2935, 2878, 1712, 1496, 1449, 1383, 1373, 1311, 1258, 1228, 1204, 1155, 1071, 984, 967, 845 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.00 (d, *J* = 7.02 Hz, 3H), 1.07 (d, *J* = 7.02 Hz, 3H), 1.35 (s, 3H), 1.42 (s, 3H), 2.07 (m, 1H), 2.39 (ddd, *J* = 10.14, 1.57, 0.78 Hz, 1H), 2.49 (ddd, *J* = 14.44, 11.32, 1.17 Hz, 1H), 2.59 (dd, *J* = 14.44, 3.12 Hz, 1H), 3.67 (ddd, *J* = 11.32, 6.25, 3.12 Hz, 1H), 3.91 (dd, *J* = 8.20, 4.40 Hz, 1H), 4.11-4.22 (m, 3H), 6.21 (dd, *J* = 16.00, 8.20 Hz, 1H), 6.64 (d, *J* = 16.00 Hz, 1H), 7.24-7.45 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 18.1, 20.4, 25.0, 25.7, 26.6, 44.8, 59.9, 66.7, 77.5, 77.6, 81.4, 109.8, 126.6, 127.7, 128.2, 128.6, 133.6, 136.0, 206.8. R_f = 0.51 (EtOAc/*n*-hexane = 1:4). HRMS: calcd. for $C_{21}H_{28}O_4$ $(M+Na)^+$ 367.1880 found 367.1877.

(2*R*,3*S*,4*R*,6*R*)-3,4-Dimethyl-6-((4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(*E*-2-phenylethe-nyl)-tetrahydropyran-4-ol 143: To a solution of ketone **128a** (158.2 mg, 0.50 mmol) in THF (10 ml) at -78°C was added MeMgBr (3 M solution in Et_2O, 1.00 ml, 3.00 mmol). The mixture was stirred for 15 min. at −78°C, then warmed to room temperature and quenched by addition of sat. aq. NH_4Cl (25 ml). The mixture was extracted with *t*BuOMe (3 x 25 ml) and the combined organic fractions were washed with brine (30 ml), dried (Na_2SO_4), filtered, concentrated *in vacuo* and purified by flash chromatography (column dimensions 25 x 2 cm, EtOAc/PE = 1:3) to give **47** (82.3 mg, 0.248 mmol, 50%) as a colorless oil. $[\alpha]^{26}_D$ = +17.1 (c = 1.07, $CHCl_3$). IR ($CHCl_3$): 3670, 3599, 3458 (broad), 3027, 3010, 2987, 2935, 2885, 1713, 1636, 1600, 1576, 1495, 1455, 1382, 1373, 1230, 1202, 1150, 1111, 1069, 947, 916, 886, 844 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.98 (d, *J* = 7.03Hz, 3H), 1.37 (s, 3H), 1.44 (s, 3H), 1.47 (s, 3H), 1.57-1.72 (m, 3H), 3.45 (ddd, *J* = 11.32, 6.63, 2.73 Hz, 1H), 4.00-4.06 (m, 2H), 4.12 (m, 1H), 4.27(m,1H), 6.12 (dd, *J* = 16.00, 4.68 Hz, 1H), 6.56 (dd, *J* = 16.00, 1.56, 1H), 7.21-7.38 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 7.8, 25.3, 26.7, 27.1, 37.2, 44.7, 49.4, 66.9, 70.9, 76.0, 77.6, 78.0, 109.4, 126.3, 127.4, 128.5, 129.0, 129.7, 136.9. R_f = 0.36 (EtOAc/*n*-hexane =1:2). HRMS: calcd. for $C_{20}H_{28}O_4$ $(M + Na)^+$ 355.1880 found 355.1881.

2-Bromopentan-3-one 147a: Bromine (17.7 ml, 55.1 g, 345 mmol) was added to a solution of 3-pentanone (36.6 ml, 29.7 g, 345 mmol) in acetic acid (48 ml) and H_2O (72 ml) and reacted according to reference[59] to give 2-bromopentan-3-one (**147a**, 32.0 g, 194 mmol, 56%) after distillation. ^1H NMR (400 MHz, $CDCl_3$) δ = 1.12 (t, *J* = 7.42 Hz, 3H), 1.75 (d, *J* = 6.63 Hz, 3H), 2.61 (dq, *J* = 17.95, 7.42 Hz, 1H), 2.87 (dq, *J* = 17.95, 7.42 Hz, 1H), 4.42 (q, *J* = 6.63 Hz, 1H) ppm.

2-(Triphenylphosphoranylidene)pentan-3-one 147: 2-Bromopentan-3-one (**147a**, 32.0 g, 194 mmol) was added to a solution of PPh_3 (48.5 g, 185 mmol) in benzene and the mixture was reacted according to reference[59] to give crude **147** as a slightly brown solid that was used in the next step without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ = 1.15 (t, *J* = 7.41 Hz, 3H), 1.65 (d, *J* = 16.00 Hz, 3H), 2.42 (q, *J* = 7.41 Hz, 2H), 7.40-7.70 (m, 15H) ppm.

Isobutyl (*R*)-2-benzyloxypropanoate 150: Commercially available isobutyl D-lactate (**149**, 7.51 ml, 7.31 g, 50.0 mmol) was added at 0°C to a suspension of NaH (60% dispension in mineral oil, 2.00 g, 50.0 mmol) in DMF (100 ml). The mixture was stirred for 5 min. at 0°C and benzyl bromide (5.92 ml, 8.55 g, 50.0 mmol) was added. The mixture was stirred for 1.5 h at rt, quenched by addition of H_2O (50 ml) and extracted with PE (5 × 75 ml). The combined organic fractions were washed with H_2O (100 ml) and sat. aq. NH_4Cl (100 ml), dried (Na_2SO_4), filtered and concetrated *in vacuo* to give crude **150** (11.68 g, 49.4 mmol,

99%) as a colorless oil that was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.95 (d, *J* = 7.03 Hz, 6H), 1.45 (d, *J* = 7.02 Hz, 3H), 1.98 (m, 1H), 3.91-4.00 (m, 2H), 4.07 (q, *J* = 7.02 Hz, 1H), 4.45 (d, *J* = 11.71 Hz, 1H), 4.72 (d, *J* = 11.71 Hz, 1H), 7.28-7.39 (m, 5H) ppm. R_f = 0.71 (EtOAc/*n*-hexane = 1:4).

(*R*)-2-Benzyloxypropanol 151: Isobutyl (*R*)-2-benzyloxypropanoate (**150**, 11.68 g, 49.4 mmol) was added at 0°C to a suspension of $LiAlH_4$ (1.88 g, 49.4 mmol) in THF (100 ml). The mixture was stirred for 5 min. at 0°C, quenched by addition of sat.aq. NH4Cl (300 ml), and extracted with *t*BuOMe (3 × 250 ml). The combined organic fractions were washed with brine (300 ml), dried (Na_2SO_4), filtered and concetrated *in vacuo* to give crude **151** (8.20 g, 49.3 mmol, 100%) as a colorless oil that was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.19 (d, *J* = 6.24 Hz, 3H), 2.02 (dd, *J* = 8.20, 4.30 Hz, 1H, O<u>H</u>), 3.48-3.54 (m, 1H), 3.60-3.65 (m, 1H), 3.66-3.73 (m, 1H), 4.49 (d, *J* = 11.32 Hz, 1H), 4.66 (d, *J* = 11.32 Hz, 1H), 7.27-7.38 (m, 5H) ppm. R_f = 0.23 (EtOAc/*n*-hexane = 1:4).

(*R*)-2-Benzyloxypropanal 148: DMSO (3.91 ml, 4.30 ml, 55.0 mmol) was added at -78°C to a solution of oxalyl chloride (2.40 ml, 3.49 g, 27.5 mmol) in CH_2Cl_2 (125 ml). The mixture was stirred for 10 min. at -78°C and (*R*)-2-benzyloxypropanol (**151**, 4.16 g, 25.0 mmol) was added dropwise. The mixture was stirred for an additional 20 min. at -78°C and Et_3N (10.40 ml, 7.59 g, 75.0 mmol) was added. The mixture was allowed to warm to room temperature, quenched by addition of sat. aq. NH_4Cl (200 ml) and extracted with CH_2Cl_2 (3 × 150 ml). The combined organic fractions were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (column dimensions 30 × 4 cm, EtOAc/PE = 1:4) afforded **148** (3.02 g, 18.4 mmol, 74%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.34 (d, *J* = 7.02 Hz, 3H), 3.90 (qd, *J* = 7.03, 1.56 Hz, 1H), 4.60 (d, *J* = 11.71 Hz, 1H), 4.66 (d, *J* = 11.71 Hz, 1H), 7.29-7.38 (m, 5H), 9.76 (d, *J* = 1.56 Hz, 1H) ppm. R_f = 0.50 (EtOAc/*n*-hexane = 1:4).

(*R*)-(4*E*)-6-(Benzyloxy)-4-methylhept-4-en-3-one 152: To a solution of 2-(triphenylphospho-ranylidene)pentan-3-one (**147**, 10 g, 28 mmol) in acetonitrile (100 ml) was added (*R*)-2-benzyloxypropanal (**148**, 3.02 g, 18.38 mmol) and Et_3N (1.70 ml, 1.24 g, 12.29 mmol). The mixture was stirred overnight at rt. The solvent was removed *in vacuo* and the residue was extracted with several portions of EtOAc/*n*-hexane 1:4. The extracts were concentrated *in vacuo* and the residue was purified by flash chromatography (column dimensions: 30 × 3.5 cm, EtOAc/PE = 1:6) to give **152** (3.22 g, 13.87 mmol, 75%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.09 (t, *J* = 7.42 Hz, 3H), 1.31 (d, *J* = 6.64 Hz, 3H), 1.76 (d, *J* = 1.17 Hz, 3H), 2.68 (q, *J* = 7.42 Hz, 2H), 4.40 (dq, *J* = 8.20, 6.64 Hz, 1H), 4.42 (d, *J* = 12.10 Hz, 1H), 4.52 (d, *J* = 11.71

Hz, 1H), 6.51 (dd, *J* = 8.19, 1.17 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 8.5, 11.5, 20.2, 30.3, 70.6, 71.5, 127.5, 128.1, 128.3, 137.0, 138.1, 142.7, 202.2 ppm. R_f = 0.81 (EtOAc/*n*-hexane = 1:4).

(*R*)-(2Z,4E)-6-Benzyloxy-3-(*tert*-butyldimethylsilyloxy)hepta-2,4-diene 146: To a solution of ketone **152** (1.39 g, 6.00 mmol) and Et_3N (1.25 ml, 911 mg, 9.00 mmol) in Et_2O (30 ml) was added at 0°C TBSOTf (1.65 ml, 1.90 g, 7.20 mmol). The mixture was stirred for 2 h at 0°C, but TLC analysis indicated that no reaction had taken place. The mixture was cooled to -78°C and NaHMDS (1 M solution in THF, 6.00 ml, 6.00 mmol) was added. The mixture was allowed to warm to rt, diluted with sat. aq. NH_4Cl (100 ml), and extracted with *t*BuOMe (3 × 100 ml). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on a Et_3N-neutralized column (column dimensions: 20 × 2 cm, EtOAc/PE = 1:50) to give **146** (2.09 g, 6.02 mmol, 100%) as a colorless oil (2*Z*:2*E* = 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.11 (s, 3H), 0.12 (s, 3H), 1.01 (s, 9H), 1.27 (d, *J* = 6.24 Hz, 3H, 1.66, *J* = 7.03 Hz, 3H), 1.74 (d, *J* = 0.78 Hz, 3H), 4.32 (dq, *J* = 8.98, 6.24 Hz, 1H), 4.32 (d, *J* = 11.71 Hz, 1H), 4.55 (d, *J* = 11.71 Hz, 1H), 5.01 (q, *J* = 7.03 Hz, 1H), 5.73 (d, *J* = 8.97 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = -3.7, -3.6, 11.9, 13.9, 18.4, 21.6, 26.0, 69.9, 71.2, 105.4, 127.3, 127.6, 128.3, 128.5, 134.3, 138.9, 151.1 ppm. R_f = 0.89 (EtOAc/*n*-hexane = 1:8).

3-Benzyloxypropanal 153: DMSO (3.91 ml, 4.30 ml, 55.0 mmol) was added at -78°C to a solution of oxalyl chloride (2.40 ml, 3.49 g, 27.5 mmol) in CH_2Cl_2 (125 ml). The mixture was stirred for 10 min. at -78°C and commercially available 3-benzyloxypropanol (4.16 g, 25.0 mmol) was added dropwise. The mixture was stirred for an additional 20 min. at -78°C and Et_3N (10.40 ml, 7.59 g, 75.0 mmol) was added. The mixture was allowed to warm to room temperature, quenched by addition of sat. aq. NH_4Cl (200 ml) and extracted with CH_2Cl_2 (3 × 150 ml). The combined organic fractions were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (column dimensions 30 × 4 cm, EtOAc/PE = 1:4) afforded **153** (3.99 g, 24.3 mmol, 97%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.71 (td, *J* = 6.25, 1.95 Hz, 2H), 3.82 (t, *J* = 6.25 Hz, 2H), 4.54 (s, 2H), 7.27-7.37 (m, 5H), 9.80 (t, *J* = 1.95 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 43.8, 63.7, 73.1, 127.6, 127.7, 128.3, 137.8, 201.1 ppm. R_f = 0.49 (EtOAc/*n*-hexane = 1:4).

2-(1-Benzyloxyethyl)-6-(2-benzyloxyethyl)-3,5-dimethyltetrahydropyran-4-one 155: To a solution of diene **146** (693 mg, 2.00 mmol) and 3-benzyloxypropanal (**153**, 394 mg, 2.40 mmol) in Et_2O (20 ml) was added at −30°C BF_3•Et_2O (304 µl, 341 mg, 2.40 mmol). The mixture was stirred for 5 h between -30°C and -15°C. Et_3N (665 µl, 486 mg, 4.80 mmol) was added, the mixture was diluted with H_2O (50 ml) and sat. aq. NH_4Cl (100 ml), and extracted with *t*BuOMe (3 × 100 ml). The combined organic fractions were dried

(Na_2SO_4), filtered, and concentrated *in vacuo* to give the crude diastereomeric mixture of HDA product **154**. To a solution of crude silyl enol ether **154** (max. 2.00 mmol) in THF (20 ml) was added acetic acid (286 µl, 300 mg, 5.00 mmol) followed by TBAF•$3H_2O$ (947 mg, 3.00 mmol) and the mixture was stirred overnight at rt. The mixture was diluted with sat. aq. NH_4Cl (100 ml) and extracted with *t*BuOMe (3 × 100 ml). The combined organic fractions were washed with sat. aq. $NaHCO_3$ (100 ml) and brine (100 ml), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (column dimensions: 35 × 2.5 cm, EtOAc/PE = 1:8) to give four diastereomeric products (**155a-d**) in a 14:66:8:12 ratio (the latter two, **155c** and **155d**, being inseparable; their configurations could not be determined) in a total yield of 647 mg (1.63 mmol, 82% over two steps). The former isomer (**155a**) was determined to have the (3x,5x) configuration, and may be derived (at least partially) from the *E*-diene. The configuration of major product **155b** could not be determined unequivocally. **Isomer 155a**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.98 (d, *J* = 6.64 Hz, 3H), 1.05 (d, *J* = 7.02 Hz, 3H), 1.27 (d, *J* = 5.85 Hz, 3H), 1.79 (ddt, *J* = 14.44, 9.76, 5.07 Hz, 1H), 2.08 (dtd, *J* = 14.44, 7.42, 2.34 Hz, 1H), 2.46 (dq, *J* = 10.54, 6.64 Hz, 1H), 2.83 (qd, *J* = 7.03, 2.34 Hz, 1H), 3.37 (ddd, *J* = 10.54, 9.76, 2.34 Hz, 1H), 3.38 (dd, *J* = 8.59, 2.34 Hz, 1H), 3.59 (dq, *J* = 8.59, 5.85 Hz, 1H), 3.67 (dd, *J* = 7.42, 5.07 Hz, 2H), 4.36 (d, *J* = 11.70 Hz, 1H), 4.49 (d, *J* = 12.10 Hz, 1H), 4.53 (d, *J* = 11.71 Hz, 1H), 4.65 (d, *J* = 11.71 Hz, 1H), 7.27-7.36, (m, 10H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 9.2, 11.4, 16.7, 34.5, 46.1, 46.3, 66.6, 70.4, 72.6, 73.2, 80.3, 82.0, 127.63, 127.64, 127.67, 128.39, 128.40, 138.1, 138.3, 212.7 ppm. R_f = 0.67 (EtOAc/*n*-hexane = 1:4). **Isomer 155b**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.97 (*J* = 6.63 Hz, 3H), 1.13 (d, *J* = 7.03 Hz, 3H), 1.30 (d, *J* =6.63 Hz, 3H), 1.67-1.74 (m, 1H), 1.94-2.01 (m, 1H), 2.43 (qd, *J* = 7.03, 2.34 Hz, 1H), 2.52 (dq, *J* = 10.54, 6.64 Hz, 1H), 3.42 (dd, *J* = 10.53, 2.34 Hz, 1H), 3.57-3.70 (m, 3H), 3.81 (ddd, *J* = 8.58, 4.29, 2.34 Hz, 1H), 4.48 (s, 2H), 4.55 (d, *J* = 12.10 Hz, 1H), 4.59 (d, *J* = 12.10 Hz, 1H), 7.28-7.35 (m, 10H) ppm. R_f = 0.57 (EtOAc/*n*-hexane = 1:4).

2-(1-Benzyloxyethyl)-6-(2-benzyloxyethyl)-3,5-dimethyltetrahydropyran-4-ol 156: To a solution of ketone **155b** (198 mg, 0.50 mmol) in MeOH (10 ml) was added at 0°C $NaBH_4$ (37 mg, 1.00 mmol) and the mixture was stirred for 1 h at 0°C. The mixture was quenched by addition of sat. aq. NH_4Cl (10 ml), diluted with brine (50 ml) and extracted with *t*BuOMe (3 × 30 ml). The combined organic fractions were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give **156** (144 mg, 0.36 mmol, 72%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.89 (d, *J* = 7.02 Hz, 3H), 0.91 (d, *J* = 7.03 Hz, 3H), 1.28 (d, *J* = 5.86 Hz, 3H), 1.63-1.71 (m, 1H), 1.81-1.92 (m, 2H), 2.30 (m, 1H), 3.16 (dd, *J* = 9.37, 2.34 Hz, 1H), 3.44-3.64 (m, 4H), 3.91 (td, *J* = 5.07, 4.69 Hz, 1H), 4.36 (d, *J* = 10.93 Hz, 1H), 4.48 (d, *J* = 11.71 Hz, 1H), 4.53 (d, *J* = 12.10 Hz, 1H), 4.66 (d, *J* = 11.31 Hz, 1H), 7.28-7.37 (m, 10H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 8.3, 8.4, 16.9, 32.9, 35.3, 38.6, 67.2, 70.6, 73.0, 73.2, 73.5, 76.7, 83.0, 127.6 (2C), 127.66 (2C), 127.67 (2C), 128.31 (2C), 128.34 (2C), 138.29, 138.32 ppm.

2.6 References

1. Christmann, M.; Bhatt, U.; Quitschalle, M.; Claus, E.; Kalesse, M. *Angew.Chem.* **2000**, *112*, 4535-4538; *Angew. Chem. Int. Ed.* **2000**, *39*, 4364-4366.
2. Bhatt, U.; Christmann, M.; Quitschalle, M.; Claus, E.; Kalesse, M. *J. Org. Chem.* **2001**, *66*, 1885-1893.
3. Christmann, M.; Kalesse, M. *Tetrahedron Lett.* **2001**, *42*, 1269-1272.
4. Zhang, W.-C.; Li, C.-J. *Tetrahedron* **2000**, *56*, 2403-2411.
5. Miranda, P.O.; Díaz, D.D.; Padrón, J.I.; Bermejo, J.; Martín, V.S. *Org. Lett.* **2003**, *5*, 1979-1982.
6. Rychnovsky, S.D.; Marumoto, S.; Jaber, J.J. *Org. Lett.* **2001**, *3*, 3815-3818.
7. Keh, C.C.K.; Namboodiri, V.V.; Varma, R.S.; Li, C.-J. *Tetrahedron Lett.* **2002**, *43*, 4993-4996.
8. Keck, G.E.; Covel, J.A.; Schiff, T.; Yu, T. *Org. Lett.* **2002**, *4*, 1189-1192.
9. Hu, Y.; Skalitzky, D.J.; Rychnovsky, S.D. *Tetrahedron Lett.* **1996**, *37*, 8679-8682.
10. Dobbs, A.P.; Martinovic, S. *Tetrahedron Lett.* **2002**, *43*, 7055-7057.
11. Crosby, R.C.; Harding, J.R.; King, C.D.; Parker, G.D.; Willis, C.L. *Org. Lett.* **2002**, *4*, 577-580.
12. Crosby, R.C.; Harding, J.R.; King, C.D.; Parker, G.D.; Willis, C.L. *Org. Lett.* **2002**, *4*, 3407-3410.
13. Rychnovsky, S.D.; Thomas, C.R. *Org. Lett.* **2000**, *2*, 1217-1220.
14. Cossey, K.N.; Funk, R.L. *J. Am. Chem. Soc.* **2004**, *126*, 12216-12217.
15. Boger, D.L.; Weinreb, S.M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press, San Diego, 1987.
16. Larson, E.R.; Danishefsky, S. *Tetrahedron Lett.* **1982**, *23*, 1975-1978.
17. Danishefsky, S.; Kerwin, J.F.J. *J. Org. Chem.* **1982**, *47*, 3183-3184.
18. Danishefsky, S.; Kobayashi, S.; Kerwin, J.F. *J. Org. Chem.* **1982**, *47*, 1981-1983.
19. Bednarski, M.; Maring, C.; Danishefsky, S. *Tetrahedron Lett.* **1983**, *24*, 2451-2454.
20. Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1989**, *111*, 789-790.
21. Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310-312.
22. Gao, Q.; Maruyama, T.; Mouri, M.; Yamamoto, H. *J. Org. Chem.* **1992**, *57*, 1951-1952.
23. Gao, Q.; Ishihara, K.; Maruyama, T.; Mouri, M.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 979-988.
24. Dosseter, A.G.; Jamison, T.F.; Jacobsen, E.N. *Angew. Chem.* **1999**, *111*, 2549-2552; *Angew.Chem.Int.Ed.* **1999**, *38*, 2398-2400.
25. Thompson, C.F.; Jamison, T.F.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2001**, *123*, 9974-9983.
26. Thompson, C.F.; Jamison, T.F.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2000**, *122*, 10482-10483.
27. Chavez, D.E.; Jacobsen, E.N. *Angew. Chem.* **2001**, *113*, 3779-3782; *Angew.Chem. Int. Ed.* **2001**, *40*, 3667-3670.
28. Chavez, D.E.; Jacobsen, E.N. *Org. Lett.* **2003**, *5*, 2563-2565.

29. Gademann, K.; Chavez, D.E.; Jacobsen, E.N. *Angew. Chem.* **2002**, *114*, 3185-3187; *Angew. Chem. Int. Ed.* **2002**, *41*, 3059-3061.
30. Paterson, I.; Luckhurst, C.A. *Tetrahedron Lett.* **2003**, *44*, 3749-3754.
31. Cink, R.D.; Forsyth, C.J. *J. Org. Chem.* **1997**, *62*, 5672-5673.
32. Mujica, M.T.; Alfonso, M.M.; Galindo, A.; Palenzuela, J.A. *J. Org. Chem.* **1998**, *63*, 9728-9738.
33. Martin, M.; Afonso, M.M.; Galindo, A.; Palenzuela, J.A. *Synlett* **2001**, 117-119.
34. Hu, Y.-J.; Huang, X.-D.; Yao, Z.-J.; Wu, Y.-L. *J. Org. Chem.* **1998**, *63*, 2456-2461.
35. Joly, G.D.; Jacobsen, E.N. *Org. Lett.* **2002**, *4*, 1795-1798.
36. Kalesse, M.; Christmann, M.; Bhatt, U.; Quitschalle, M.; Claus, E.; Saeed, A.; Burzlaff, A.; Kasper, C.; Haustedt, L.O.; Hofer, E.; Scheper, T.; Beil, W. *Chembiochem* **2001**, *2*, 709-714.
37. Earle, M.J.; Abdur-Rashid, A.; Priestley, N.D. *J. Org. Chem.* **1996**, *61*, 5697-5700.
38. Schmid, C.R.; Bryant, J.D.; Dowlatzedah, M.; Phillips, J.L.; Prather, D.E.; Schantz, R.D.; Sear, N.D.; Vianco, C.S. *J. Org. Chem.* **1991**, *56*, 4056-4058.
39. Schuda, P.F.; Ebner, C.B.; Potlock, S.J. *Synthesis* **1987**, *12*, 1055-1057.
40. Patonay, T.; Hajdu, C.; Jek, J.; Lévai, A.; Micskei, K.; Zucchi, C. *Tetrahedron Lett.* **1999**, *40*, 1373-1374.
41. Gyarmati, J.; Hajdu, C.; Dinya, Z.; Micskei, K.; Zucchi, C.; Pályi, G. *J. Organomet. Chem.* **1999**, *586*, 106-109.
42. Micskei, K.; Hajdu, C.; Wessjohann, L.A.; Mercs, L.; Kiss-Szikszai, A.; Patonay, T. *Tetrahedron: Asymmetry* **2004**, *15*, 1735-1744.
43. Dess, D.B.; Martin, J.C. *J. Org. Chem.* **1983**, *48*, 4155-4156.
44. Mitsunobu, O. *Synthesis* **1981**, 1-28.
45. Searle, P.A.; Molinski, T.F. *J. Am. Chem. Soc.* **1995**, *117*, 8126-8131.
46. Wessjohann, L.A. *Angew. Chem.* **1997**, *109*, 738-742.
47. He, L.; Orr, G.A.; Horwitz, S.B. *Drug Discov. Today* **2001**, *6*, 1153-1164.
48. Forsyth, C.J.; Ahmed, F.; Cink, R.D.; Lee, C.S. *J. Am. Chem. Soc.* **1998**, *120*, 5597-5598.
49. Evans, D.A.; Fitch, D.M.; Smith, T.E.; Cee, V.J. *J. Am. Chem. Soc.* **2000**, *122*, 10033-10046.
50. Evans, D.A.; Cee, V.J.; Smith, T.E.; Fitch, D.M.; Cho, P.S. *Angew. Chem.* **2000**, *112*, 2633-2636; *Angew. Chem. Int. Ed.* **2000**, *39*, 2533-2536.
51. Evans, D.A.; Fitch, D.M. *Angew. Chem.* **2000**, *112*, 2636-2640; *Angew. Chem. Int. Ed.* **2000**, *39*, 2536-2540.
52. Smith, A.B., III; Minbiole, K.P.; Verhoest, P.R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942-10953.
53. Williams, D.R.; Clark, M.P.; Emde, U.; Berliner, M.A. *Org. Lett.* **2000**, *2*, 3023-3026.
54. Huang, H.; Panek, J.S. *Org. Lett.* **2001**, *3*, 1693-1696.
55. Wolbers, P.; Misske, A.M.; Hoffmann, H.M.R. *Tetrahedron Lett.* **1999**, *40*, 4527-4530.
56. Pattenden, G.; Plowright, A.T. *Tetrahedron Lett.* **2000**, *41*, 983-986.

57. Greer, P.B.; Donaldson, W.A. *Tetrahedron* **2002**, *58*, 6009-6018.

58. White, J.D.; Kranemann, C.L.; Kuntiyong, P. *Org. Lett.* **2001**, *3*, 4003-4006.

59. Tan, C.-H.; Holmes, A.B. *Chem. Eur. J.* **2001**, *7*, 1845-1854.

60. Kraus, G.A.; Choudhury, P.K. *Synth. Commun.* **2001**, *15*, 2230-2230.

61. Mancuso, A.J.; Swern, D. *Synthesis* **1981**, 165-196.

3

Synthesis of the ratjadone analogue B fragment

3 Synthesis of the ratjadone analogue B fragment

3.1 Retrosynthesis

The substituted THP and dihydro-α-pyrone ring systems of ratjadone are connected by a linear tetraene chain with methyl substituents at various positions. Radioactive labeling studies showed that this chain (like the rest of the molecule) is derived from polyketide metabolism (acetate and propionate residues).[1] However, we recognized that this segment of ratjadone also resembles linear terpenoids, such as geraniol **157**, nerol **158**, and farnesol **159**. These compounds are derived from isoprenoid metabolism and formed from head/tail coupling of the basic building blocks dimethylallyl pyrophosphate (DMAPP) **160** and isopentenyl pyrophosphate (IPP) **161**, and are available from natural sources in large quantities.

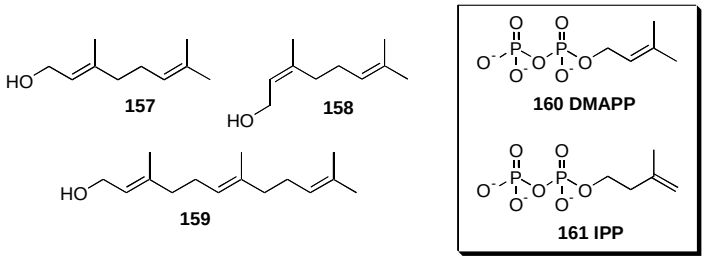


Figure 3.1. DMAPP, IPP, and simple linear isoprenoids.

The incorporation of e.g. geraniol into ratjadone analogues would contribute ten of the total number of twenty-eight carbon atoms of the ratjadone skeleton, and is therefore highly desirable from an atom economy point of view.

In order to construct a building block that can serve as a connection between the other two fragments, functionalization of e.g. a geraniol derivative at the terminal *E*-methyl group is required. Although many selective allylic oxidation methods are known, only the SeO_2 oxidation (and its catalytic variations) selectively functionalize terminal *E*-methyl groups, and only when the *Z* substituent is not larger than a methyl group. This chemo- and regioselectivity is inherent to the mechanism of the reaction (Fig. 3.2).[2]

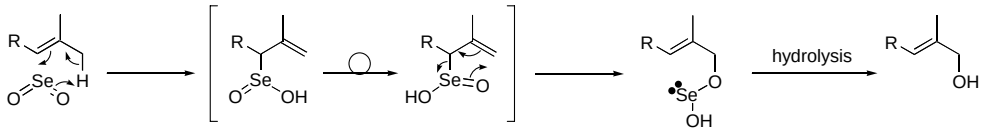


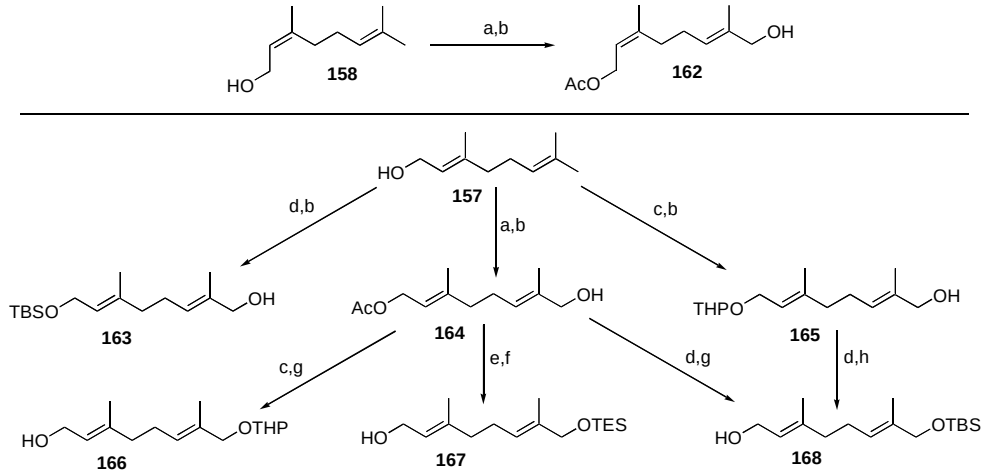
Figure 3.2. Mechanism of the SeO_2 oxidation.

Since the stoichiometric version of the SeO_2 oxidation suffers from complications such as the large amount of red selenium formed during the reaction and high toxicity of selenium compounds, it is often replaced (especially in large-scale procedures) by a catalytic version using a stoichiometric oxidant (typically *t*BuOOH), which was first described by Sharpless and co-workers.[3] Several procedures have been described in literature, varying in stoichiometry, reaction temperature and time, and additives. An efficient procedure has been developed in our group.[4]

A major drawback of this methodology is the fact that the reaction typically does not proceed to completion. Instead, there seems to be an optimum in the yield of the desired allylic alcohol. An increase in reaction time and/or temperature, or the amount of stoichiometric oxidant or SeO_2 does not result in an increase of the yield of the desired alcohol, but rather in formation of the corresponding aldehyde, which is only a minor side product under optimal conditions. A typical optimal yield of the desired alcohol is 50%, the major part of the remainder being the starting material. Therefore, yields in literature reports are often based on recovered starting material. It should be mentioned that these problems have (at least partly) been overcome by using alternative selenium catalysts, which are, however, expensive and not yet commercially available.

3.2 Synthesis

We performed the catalytic SeO_2 oxidation using several protected geraniol and nerol derivatives **162-168**. The yield is not only dependent on reaction conditions, but also on the nature of the protective group. The yield of the reaction seems to increase with the polarity of the protective group, ranging from 11% for geranyl TBS ether to 54% (42% alcohol + 12% aldehyde) for geranyl acetate. The reason for this observation is unclear. The reaction also proceeds quite well with THP-protected geraniol or nerol, but later selective cleavage of the THP ether in the presence of other protective groups such as Ac or TBS proved troublesome.

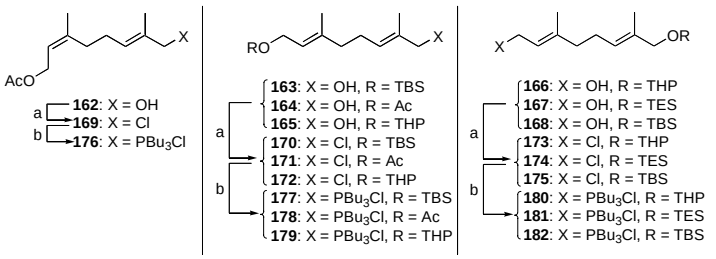


Scheme 3.1. (a) Ac_2O, py, 87% from **158**, quant. from **157**; (b) cat. SeO_2, tBuOOH, CH_2Cl_2, 11-54% (see text and Experimental section); (c) DHP, cat. PPTS, CH_2Cl_2, quant. for **165**, quant. for **166**; (d) TBSCl, imidazole, CH_2Cl_2, 100% from **157**, 99% from **164**, 89% from **165**; (e) TESCl, imidazole, CH_2Cl_2, quant.; (f) $LiAlH_4$, THF, 0°C, 100%; (g) K_2CO_3, MeOH, 68% for **166**, 94% for **168**; (h) $MgBr_2 \bullet Et_2O$, Et_2O, 37% (+ 14% starting material).

For example, treatment of the ω-OTBS ether of **165** with various Lewis acids (LiBr, $ZnBr_2$, $SnCl_2$) in MeOH or Et_2O or PPTS in MeOH led either to no reaction, simultaneous cleavage of both protective groups or decomposition. Only reaction with $MgBr_2 \bullet Et_2O$ led to selective cleavage of the THP ether to give **165**, albeit in poor yield (37%, along with 14%

starting material). Thus, a number of monoprotected ω-hydroxylated geraniol and nerol derivatives were synthesized using standard reaction conditions.

Since the terpenoid building blocks were to be connected to the other fragments by Wittig reaction with the phosphonium salt functionality being part of the terpenoid building block, the free alcohol was required to be transformed into a leaving group. Literature often reports the use of Appel-type reactions[5,6] or bromide displacement of mesylates[7] to generate bromides in similar cases, we chose to employ the corresponding chlorides. Studies in our group have shown that such allylic chlorides are sufficiently electrophilic to be displaced by nucleophilic phosphines such as tri-*n*-butylphosphine. The advantage of such chlorides over the corresponding bromides lies mainly in their higher stability. They are stable under flash chromatography conditions and therefore can be obtained in pure form; this is not possible for the corresponding bromides, which are, in addition, often contaminated by significant amounts of chloride. For these reasons, the chlorides can be analyzed unambiguously. Finally, the chlorides remain stable upon storage at -20°C (decomposition takes place over weeks at room temperature), whereas the bromides are sometimes unstable.



Corey-Kim reaction	
Product	***Yield (%)***
169	63
170	63
171	77
172	37
173	52
174	54
175	77

Scheme 3.2. (a) NCS, Me_2S, CH_2Cl_2, -78→-10°C, 37-77%; (b) PBu_3, 70°C, 3h, no solvent, quant.

The Corey-Kim reaction[8] proved to be an efficient and reliable method to generate the allylic chlorides. The functionalized allylic alcohols were converted to the corresponding chlorides in reasonable to excellent yields using this procedure. The allylic chlorides were

transformed into the corresponding tributylphosphonium salts by treatment with 1.0 eq. of tri-*n*-butylphosphine at 70°C fo 3h (no solvent).

3.3 Conclusion

Despite its limitations, the catalytic selenium dioxide oxidation provides a unique possibility to rapidly generate α,ω-bifuctional terpenoids. The resulting alcohols are reliably transformed to the corresponding chlorides, which are stable, isolable compounds. Treatment with tributylphosphine affords the phosphonium salts required for connection to the other segments quantitatively.

3.4 Experimental section

General. All commercial reagents were purchased from Fluka, Merck or Aldrich and used without further purification, unless otherwise stated. All oxygen- and water-sensitive reactions were carried out in oven-dried glassware under argon. THF was distilled from potassium/benzophenone ketyl, Et_2O was distilled from sodium/potassium/benzophenone ketyl, and CH_2Cl_2 was distilled from calcium hydride. Other dry solvents were purchased from Fluka. Flash chromatography was performed using silica gel 60 (230-400 mesh, Merck). Thin-layer chromatography (TLC) was performed using silica plates (Merck, silica gel 60 F_{254}) and developed using Cer-MOP reagent [molybdatophosphoric acid (5.0 g), cerium (IV) sulfate (2.0 g), and concentrated H_2SO_4 (16 ml) in water (200 ml)]. Optical rotations were measured using a 1 ml cell with 1 dm path length on a Jasco DIP-1000 digital polarimeter. IR spectra were recorded as $CHCl_3$ solutions or as thin films between NaCl plates on a Bruker IFS 28. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Varian Mercury VX 300 and VX 400 spectrometers using TMS as internal standard. Chemical shifts δ are reported in parts per million (ppm), coupling constants *J* are given in Hertz (Hz). High resolution ESI mass spectra were obtained from a Bruker Apex 70e Fourier transform ion cyclotron resonance mass spectrometer equipped with a 7.0 Tesla superconducting magnet and an external electrospray ion source (Agilent, off axis spray).

10-Hydroxyneryl acetate 162: To a cooled (0°C) mixture of pyridine (16.1 ml, 15.8 g, 200 mmol) and acetic anhydride (16.1 ml, 17.5 g, 170 mmol) was added nerol (15.4 g, 100 mmol). The mixture was stirred for 2 h at 0°C, diluted with EtOAc (100 ml), and washed with 1N aq. HCl (2 × 50 ml), H_2O (2 × 50 ml), and

brine (50 ml). The organic fraction was dried (Na_2SO_4), filtered, and concentrated *in vacuo*, giving **162a** (17.0 g, 86.6 mmol, 87%) as a colorless oil that was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.60 (s, 3H), 1.68 (s, 3H), 1.77 (d, *J* = 1.18 Hz, 3H), 2.06-2.14 (m, 4H), 4.55 (dd, *J* = 7.33, 0.59 Hz, 2H), 5.09 (tq, *J* = 5.57, 1.47 Hz, 1H), 5.36 (t, *J* = 7.33 Hz, 1H) ppm. A mixture of neryl acetate (**162a**, 17.0 g, 86.6 mmol), SeO_2 (2.41 g, 21.8 mmol), 70% aq. *t*BuOOH (12.3 ml, 93.5 mmol) and CH_2Cl_2 (150 ml) was stirred for 2 h at 0°C. The solvent was removed *in vacuo*, and toluene (100 ml) was added and removed *in vacuo*. This process was repeated three times in order to remove excess *t*BuOOH. The residue was purified by flash chromatography (column dimensions: 30 × 4 cm, EtOAc/PE = 1:4→1:2) to give **162** (4.14 g, 19.5 mmol, 23%) as a colorless oil, accompanied by the starting material (10.8 g, 55.1 mmol). The yield based on recovered starting material is therefore 65%. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.65 (s, 3H), 1.75 (d, *J* = 1.01 Hz, 3H), 2.03 (s, 3H), 2.12-2.14 (m, 4H), 3.97 (s, 2H), 4.55 (d, *J* = 7.18 Hz, 1H), 5.30-5.37 (m, 2H) ppm.

***tert*-Butyldimethylsilyl 10-hydroxygeranyl ether 163**: To a solution of imidazole (1.56 g, 23.3 mmol) and geraniol (3.27 g, 21.2 mmol) in CH_2Cl_2 (25 ml) was added at 0°C TBSCl (3.35 g, 22.2 mmol). The mixture was stirred 2 h at rt, diluted with sat aq. NH_4Cl (50 ml), and extracted with CH_2Cl_2 (3 × 50 ml). The organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*, giving TBS geranyl ether (**163a**, 5.67 g, 21.1 mmol, 100 %) as a colorless oil that was pure as judged by ^{1}H NMR and used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.07 (s, 6H), 0.91 (s, 9H), 1.60 (s, 3H), 1.62 (s, 3H), 1.68 (d, *J* = 0.78 Hz, 3H), 2.00-2.02 (m, 2H), 2.08-2.10 (m, 2H), 4.19 (d, *J* = 5.86 Hz, 2H), 5.09 (tdd, *J* = 7.03, 1.56, 1.17 Hz, 1H), 5.30 (tt, *J* = 6.64, 1.17 Hz, 1H) ppm. A mixture of SeO_2 (117 mg, 1.05 mmol), 70% aq. *t*BuOOH (7.79 ml, 59.2 mmol) and CH_2Cl_2 (50 ml) was stirred for 40 min at rt. Then, TBS geranyl ether (**163a**, 5.67 g, 21.1 mmol) was added and the mixture was stirred for 24 h at rt. The solvent was removed *in vacuo*, and toluene (25 ml) was added and removed *in vacuo*. This process was repeated three times in order to remove excess *t*BuOOH. The residue was purified by flash chromatography (column dimensions: 25 × 3.5 cm, EtOAc/PE = 1:10) to give **163** (659 mg, 2.32 mmol, 11%) as a colorless oil, as well as a significant amount of unreacted starting material. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.07 (s, 6H), 0.91 (s, 9H), 1.63 (s, 3H), 1.67 (s, 3H), 2.03-2.06 (m, 2H), 2.13-2.19 (m, 2H), 3.99 (d, *J* = 4.68 Hz, 2H), 4.19 (d, *J* = 6.25 Hz, 2H), 5.30 (td, *J* = 6.24, 1.17 Hz, 1H), 5.38 (td, *J* = 7.03, 1.17 Hz, 1H) ppm.

10-Hydroxygeranyl acetate 164: To a cooled (0°C) mixture of pyridine (8.05 ml, 7.91 g, 100 mmol) and acetic anhydride (8.03 ml, 8.73 g, mmol) was added geraniol (8.77 ml, 7.71 g, 50 mmol). The mixture was stirred for 2 h at 0°C and poured into ice water (200 ml). The mixture was extracted with EtOAc (3 × 100 ml). The combined organic fractions were washed with 1N aq. HCl (2 × 100 ml), H_2O (2 × 100 ml), and brine (100 ml), dried (Na_2SO_4), filtered, and concentrated *in vacuo*, giving **164a** (9.99 g, quant.) as a

colorless oil that was used in the next step without further purification. R_f = 0.80 (EtOAc/*n*/hexane = 1:4) A mixture of SeO_2 (277 mg, 2.5 mmol), 70% aq. *t*BuOOH (18.5 ml, 140 mmol) and CH_2Cl_2 (75 ml) was stirred for 30 min at rt. Then, geranyl acetate (**164a**, max. 50 mmol) was added and the mixture was stirred for 24 h at rt. The solvent was removed *in vacuo*, and toluene (50 ml) was added and removed *in vacuo*. This process was repeated three times in order to remove excess *t*BuOOH. The residue was purified by flash chromatography (column dimensions: 28 × 4 cm, EtOAc/PE = 1:4→1:2) to give **164** (4.41 g, 20.8 mmol, 42% over two steps) as a colorless oil, accompanied by the corresponding aldehyde (1.22 g, 5.81 mmol, 12%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.38 (bs, 1H, O<u>H</u>), 1.67 (s, 3H), 1.71 (s, 3H), 2.06 (s, 3H), 2.10 (dd, *J* = 7.42, 7.03 Hz, 2H), 2.18 (dt, *J* = 7.42, 7.02 Hz, 2H), 4.00 (s, 2H), 4.59 (d, *J* = 7.03 Hz, 2H), 5.34 (td, *J* = 7.03, 1.17 Hz, 1H), 5.37 (t, *J* = 7.03 Hz) ppm. R_f = 0.22 (EtOAc/*n*−hexane = 1:3).

10-Hydroxygeranyl THP ether 165: To a mixture of geraniol (87 ml, 77.1 g, 500 mmol) and DHP (50 ml, 46.3 g, 550 mmol) was added $AlCl_3$•H_2O (1.21 g, 5.00 mmol). The mixture was stirred 5 h at rt, eluted over a short silica column with EtOAc/PE = 1:10 and concentrated *in vacuo*, giving geranyl THP ether (**165a**) in quantitative yield, as a colorless oil that was pure as judged by ^{1}H NMR and used in the next step without further purification. A mixture of SeO_2 (1.55 g, 14.0 mmol), 70% aq. *t*BuOOH (79 ml, 600 mmol) and CH_2Cl_2 (500 ml) was stirred for 30 min at rt. Then, geranyl THP ether (**165a**, 47.7 g, 200 mmol) was added and the mixture was stirred for 24 h at rt. Toluene (120 ml) was added and the solvent was removed *in vacuo*. The residue was taken in Et_2O (300 ml), washed with 0.2 N NaOH (3 × 100 ml), and brine (150 ml), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (column dimensions: 25 × 6 cm, EtOAc/PE = 1:10) to give **165** (13.3 g, 52.4 mmol, 26%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.48-1.85 (m, 6H), 1.67 (s, 3H), 1.68 (s, 3H), 2.05-2.10 (m, 2H), 2.15-2.19 (m, 2H), 3.49-3.54 (m, 1H), 3.86-3.92 (m, 1H), 3.99 (s, 2H), 4.02 (dd, *J* = 11.71, 7.42 Hz, 1H), 4.24 (dd, *J* = 11.71, 6.64 Hz, 1H), 5.35 (ddd, *J* = 7.41, 6.64, 1.17 Hz, 1H), 5.37 (td, *J* = 6.64, 1.17 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.8, 16.4, 19.6, 25.5, 25.8, 30.7, 39.2, 62.2, 63.6, 68.8, 97.7, 120.8, 125.3, 134.9, 139.5 ppm.

10-(Tetrahydropyran-2-yl)oxygeraniol 166: To a solution of 10-hydroxygeranyl acetate (**164**, 5.80 g, 27.3 mmol) and PPTS•H_2O (690 mg, 2.7 mmol) in CH_2Cl_2 (135 ml) was added DHP (4.63 g, 55.0 mmol).The mixture was stirred for 5 h at rt, diluted with Et_2O (200 ml), washed with brine (125 ml), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give crude **166a** (8.25 g, 27.8 mmol, quant.) that was pure as judged by TLC and ^{1}H NMR and used in the next step without further purification. K_2CO_3 (459 mg, 3.32 mmol), was added at rt to a solution of 10-(tetrahydropyran-2-yl)oxygeranyl acetate (**166a**, 4.76 g, 16.6 mmol) in MeOH (10 ml) and the mixture was stirred overnight at rt. The mixture was diluted with EtOAc (250 ml) and washed with 1N aq. NH_4Cl (100 ml), H_2O (100 ml), and brine (100 ml), dried ($MgSO_4$),

filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (column dimensions 25 × 4 cm, EtOAc/PE = 1:4) to give **166** (2.88 g, 11.32 mmol, 68%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.34-1.77 (m, 6H), 1.46 (s, 2 × 3H), 1.83-2.00 (m, 4H), 2.86 (bs, 1H, O<u>H</u>), 3.22-3.33 (m, 1H), 3.61-3.72 (m, 2H), 3.86-3.93 (m, 3H), 5.12-5.20 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 13.5, 15.6, 18.9, 24.9, 25.4, 38.6, 58.4, 61.4, 72.3, 96.5, 123.9, 127.2, 131.5, 137.4 ppm.

10-Triethylsilyloxygeraniol 167: Triethylsilyl chloride (9.23 ml, 8.29 g, 55.0 mmol) was added in at 0°C to a solution of 10-hydroxygeranyl acetate (**164**, 10.61 g, 50.0 mmol) and imidazole (4.43 g, 65.0 mmol) in CH_2Cl_2 (250 ml) and the mixture was stirred for 2 h at rt. After dilution with CH_2Cl_2 (250 ml), the mixture was washed with H_2O (200 ml), sat. aq. NH_4Cl (200 ml) and brine (250 ml). The organic fraction was dried (Na_2SO_4), filtered, and concentrated *in vacuo*, affording **167a** (16.9 g, quant.) as a colorless oil that was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.61 (q, *J* = 8.00 Hz, 6H), 0.96 (t, *J*= 8.00 Hz, 9H), 1.61 (s, 3H), 1.71 (s, 3H), 2.06 (s, 3H), 2.09 (m, 2H), 2.16 (m, 2H), 4.00 (s, 2H), 4.59 (d, *J* = 7.03 Hz, 2H), 5.37 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 4.4, 6.7, 13.4, 16.4, 21.0, 25.7, 39.1, 61.3, 68.2, 118.3, 123.8, 134.7, 142.0, 171.1 ppm. R_f = 0.80 (EtOAc/*n*/hexane = 1:4).To a solution of **167a** (max. 50.0 mmol) in THF (250 ml) was added at 0°C $LiAlH_4$ (1.88 g, 50.0 mmol) and the mixture was stirred for 10 min. at 0°C. The mixture was diluted with sat. aq. NH_4Cl (500 ml) and extracted with with *t*BuOMe (3 × 300 ml). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give crude **167** (14.28 g, 50.2 mmol, 100% over two steps) as a colorless oil that was pure as judged by TLC, ^{1}H and ^{13}C NMR. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.59 (q, *J* = 7.81 Hz, 6H), 0.95 (t, *J*= 7.81 Hz, 9H), 1.60 (s, 3H), 1.66 (s, 3H), 1.93 (bs, 1H), 2.05 (m, 2H), 2.15 (m, 2H), 3.98 (s, 2H), 4.11 (d, *J* = 7.02 Hz, 2H), 5.37 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 4.3, 6.7, 13.4, 16.1, 25.7, 39.1, 59.1, 68.2, 123.6, 124.1, 134.5, 138.9 ppm. R_f = 0.40 (EtOAc/*n*/hexane = 1:4)

10-*tert*-Butyldimethylsilyloxygeraniol 168: ***From 164***: *tert*-Butyldimethylsilyl chloride (3.29 g, 21.8 mmol) was added in one portion at 0°C to a solution of 10-hydroxygeranyl acetate (**164**, 4.41 g, 20.8 mmol) and imidazole (1.56 g, 22.8 mmol) in CH_2Cl_2 (50 ml) and the mixture was stirred for 15 min. at rt. After dilution with sat aq. NH_4Cl (50 ml) the phases were separated and the aqueous phase was extracted one more time with CH_2Cl_2 (50 ml). The combined organic fractions were washed with brine (50 ml), dried (Na_2SO_4), filtered, and concentrated *in vacuo*, affording **168a** (6.70 g, 20.5 mmol, 99%) as a colorless oil that was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.06 (s, 6H), 0.91 (s, 9H), 1.59 (s, 3H), 1.71 (s, 3H), 2.06 (s, 3H), 2.09 (m, 2H), 2.15 (m, 2H), 4.00 (s, 2H), 4,58 (d, *J* = 7.13 Hz, 2H), 5.35-5.36 (m, 2H) ppm. R_f = 0.77 (EtOAc/PE = 1:4). To a solution of **168a** (6.69 g, 20.5 mmol) in MeOH (150 ml) was added K_2CO_3 (567 mg, 4.10 mmol) and the mixture was stirred for 45 min. at rt. The volume was reduced *in vacuo* and the mixture was diluted with sat. aq. NH_4Cl (100 ml) and brine

(200 ml) and extracted with with *t*BuOMe (3 × 150 ml). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give **168** (5.51 g, 19.4 mmol, 94%) as a colorless oil that was used in the next step without further purification.

From 165: *tert*-Butyldimethylsilyl chloride (791 mg, 5.25 mmol) was added in one portion at 0°C to a solution of 10-hydroxygeranyl THP ether (**165**, 1.27 g, 5.00 mmol) and imidazole (374 mg, 5.50 mmol) in CH_2Cl_2 (10 ml) and the mixture was stirred for 2 h at 0°C. After dilution with *t*BuOMe (50 ml), the mixture was washed with sat. aq. NH_4Cl (25 ml), sat. aq. $NaHCO_3$ (25 ml) and brine (25 ml). The organic fraction was dried (Na_2SO_4), filtered, and concentrated *in vacuo*, affording **168b** (1.65 g, 4.47 mmol, 89%) as a colorless oil that was used in the next step without further purification. ^{1}H NMR (MHz): δ = 0.06 (s, 6H), 0.91 (s, 9H), 1.51-1.58 (m, 4H), 1.59 (s, 3H), 1.68 (s, 3H), 1.70-1.76 (m, 1H), 1.81-1.86 (m, 1H), 2.07 (m, 2H), 2.16 (m, 2H), 3.49-3.53 (m, 1H), 3.86-3.92 (m, 1H), 4.00 (s, 2H), 4.02 (dd, *J* = 12.10, 7.42 Hz, 1H), 4.24 (dd, *J* = 12.10, 6.64 Hz, 1H), 4.62 (m, 1H), 5.35-5.38 (m, 2H) ppm. To a solution of THP ether **168b** (737 mg, 2.00 mmol) in Et_2O (40 ml) was added $MgBr_2$•Et_2O (1.55 g, 6.00 mmol) and the mixture was stirred overnight at rt. The mixture was diluted with sat. aq. $NaHCO_3$ (100 ml) and extracted with with *t*BuOMe (3 × 75 ml). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The product was purified by flash chromatography (column dimensions: 25 × 2.5 cm, EtOAc/PE = 1:4) to give **168** (211 mg, 0.741 mmol, 37%) as a colorless oil, accompanied by the starting material (107 mg, 0.29 mmol, 14 %). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.06 (s, 6H), 0.91 (s, 9H), 1.59 (s, 3H), 1.68 (s, 3H), 2.06 (m, 2H), 2.15 (m, 2H), 4.00 (s, 2H), 4.15 (d, *J* = 5.85 Hz, 2H), 5,36 (t, *J* = 5.85 Hz), 5.42 (t, *J* = 7.03 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = -5.1, 13.6, 16.3, 18.5, 25.8, 26.0, 39.2, 59.4, 68.5, 123.4, 123.7, 134.5, 139.4 ppm. R_f = 0.37 (EtOAc/PE = 1:4). R_f = 0.16 (EtOAc/*n*-hexane = 1:6).

10-Chloroneryl acetate 169: To a solution of NCS (421 mg, 3.15 mmol) in CH_2Cl_2 (15 ml) was added at −10°C Me_2S (251 µl, 214 mg, 3.44 mmol). The mixture was stirred for 10 min. at -10°C, and the resulting white suspension was cooled to -78°C. 10-Hydroxygeranyl acetate (**162**, 608 mg, 2.87 mmol) was added and the mixture was stirred for 1 h at -10°C. After dilution with sat. aq. NH_4Cl (100 ml), the mixture was extracted with CH_2Cl_2 (3 × 50 ml). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The product was purified by flash chromatography (column dimensions: 25 × 2 cm, EtOAc/PE = 1:10) to give **169** (415 mg, 1.80 mmol, 63%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.74 (d, *J* = 0.88 Hz, 3H), 1.77 (s, 3H), 2.05 (s, 3H), 2.15-2.16 (m, 4H), 4.01 (s, 2H), 4.55 (d, *J* = 7.04 Hz, 2H), 5.39 (td, *J* = 7.03, 1.17 Hz, 1H), 5.50 (m, 1H) ppm.

***tert*-Butyldimethylsilyl 10-chlorogeranyl ether 170**: To a solution of NCS (588 mg, 4.40 mmol) in CH_2Cl_2 (25 ml) was added at -10°C Me_2S (351 µl, 298 mg, 4.80 mmol). The mixture was stirred for 10 min. at -10°C, and the resulting white suspension was cooled to -78°C. *tert*-Butyldimethylsilyl

10−hydroxygeranyl ether (**163**, 1.14 g, 4.00 mmol) was added and the mixture was stirred for 1 h at -10°C. After dilution with sat. aq. NH_4Cl (20 ml) and H_2O (50 ml), the mixture was extracted with CH_2Cl_2 (1 × 75 ml) and Et_2O (2 × 75 ml). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The product was purified by flash chromatography (column dimensions: 25 × 2 cm, EtOAc/PE = 1:40) to give **170** (760 mg, 2.51 mmol, 63%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.08 (s, 6H), 0.91 (s, 9H), 1.63 (s, 3H), 1.74 (d, *J* = 0.78 Hz, 3H), 2.03-2.07 (m, 2H), 2.14-2.19 (m, 2H), 4.00 (s, 2H), 4.19 (d, *J* = 6.24 Hz, 2H), 5.30 (tt, *J* = 6.24, 1.17 Hz, 1H), 5.51 (t, *J* = 7.03 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = -4.9, 14.2, 16.4, 18.5, 26.1, 26.3, 38.7, 52.5, 60.3, 124.7, 130.2, 131.6, 135.9 ppm. R_f = 0.76 (EtOAc/PE = 1:20).

10-Chlorogeranyl acetate 171: To a solution of NCS (586 mg, 4.40 mmol) in CH_2Cl_2 (25 ml) was added at −10°C Me_2S (351 µl, 298 mg, 4.80 mmol). The mixture was stirred for 10 min. at -10°C, and the resulting white suspension was cooled to -78°C. 10-Hydroxygeranyl acetate (**164**, 849 mg, 4.00 mmol) was added and the mixture was stirred for 1 h at -10°C. After dilution with sat. aq. NH_4Cl (150 ml), the mixture was extracted with CH_2Cl_2 (3 × 100 ml). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The product was purified by flash chromatography (column dimensions: 25 × 2.5 cm, EtOAc/PE = 1:15) to give **171** (714 mg, 3.09 mmol, 77%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.71 (s, 3H), 1.74 (s, 3H), 2.06 (s, 3H), 2.10 (m, 2H), 2.17 (m, 2H), 4.01 (s, 2H), 4.59 (d, *J* = 7.14 Hz, 2H), 5.34 (m, 1H), 5.50 (m, 1H) ppm. R_f = 0.37 (EtOAc/*n*-hexane = 1:10).

10-Chlorogeranyl tetrahydropyran-2-yl ether 172: To a solution of NCS (734 mg, 5.50 mmol) in CH_2Cl_2 (25 ml) was added at -10°C Me_2S (439 µl, 373 mg, 6.00 mmol). The mixture was stirred for 10 min. at −10°C, and the resulting white suspension was cooled to -78°C. 10-Hydroxygeranyl tetrahydropyran-2-yl ether (**165**, 1.27 g, 5.00 mmol) was added and the mixture was stirred for 1 h at -10°C. After dilution with sat. aq. NH_4Cl (50 ml), the phases were separated and the aqueoues phase was extracted with Et_2O (2 × 50 ml). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The product was purified by flash chromatography (column dimensions: 25 × 3 cm, EtOAc/PE = 1:20) to give **172** (510 mg, 1.87 mmol, 37%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.50-1.88 (m, 6H), 1.68 (s, 3H), 1.73 (d, *J* = 0.73 Hz, 1H), 2.05-2.11 (m, 2H), 2.15-2.22 (m, 2H), 3.48 (m, 1H), 3.86 (m, 1H), 4.01 (s, 2H), 4.02 (dd, *J* = 11.89, 7.50 Hz, 1H), 4.24 (dd, *J* = 11.89, 7.32 Hz, 1H), 4.62 (dd, *J* = 4.02, 2.93 Hz, 1H), 5,37 (ddd, *J* = 7.32, 6.40, 1.10 Hz, 1H), 5.51 (t, *J* = 6.40 Hz, 1H) ppm.

10-(Tetrahydropyran-2-yl)oxygeranyl chloride 173: To a solution of NCS (706 mg, 5.29 mmol) in CH_2Cl_2 (25 ml) was added at -10°C Me_2S (422 µl, 359 mg, 5.77 mmol). The mixture was stirred for 10 min.

at -10°C, and the resulting white suspension was cooled to -78°C. 10-(Tetrahydropyran-2-yl)oxygeraniol (**166**, 1.22 g, 4.81 mmol) was added and the mixture was stirred for 1 h at -10°C. After dilution with sat. aq. NH_4Cl (50 ml), the phases were separated and the aqueoues phase was extracted with Et_2O (2 × 50 ml). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give crude **173** (1.24 g, 4.54 mmol, 94%) as a yellow oil. The product was purified by flash chromatography (column dimensions: 25 × 3 cm, EtOAc/PE = 1:20) to give **173** (682 mg, 2.50 mmol, 52%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.51-1.94 (m, 6H), 1.66 (s, 3H), 1.73 (d, *J* = 1.17 Hz, 3H), 2.07-2.21 (m, 4H), 3.50 (m, 1H), 3.82-3.91 (m, 2H), 4.08-4.11 (m, 3H), 4.60 (dd, *J* = 3.82, 2.93 Hz, 1H), 5.40 (td, *J* = 7.04, 1.17 Hz, 1H), 5.45 (td, *J* = 8.21, 1.17 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.0, 16.0, 19.5, 25.4, 30.6, 38.9, 40.9, 62.0, 72.6, 97.2, 120.3, 126.5, 132.2, 142.03 ppm.

10-Triethylsilyloxygeranyl chloride 174: To a solution of NCS (1.469 g, 11.0 mmol) in CH_2Cl_2 (100 ml) was added at -10°C Me_2S (877 µl, 745 mg, 12.0 mmol). The mixture was stirred for 10 min. at -10°C, and the resulting white suspension was cooled to -78°C. 10-Triethylsilyloxygeraniol (**167**, 2.845 mg, 10.0 mmol) was added and the mixture was stirred for 1 h at -10°C. After dilution with sat. aq. NH_4Cl (300 ml), the mixture was extracted with CH_2Cl_2 (3 × 200 ml). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give crude **174** (3.018 g, 9.96 mmol, 100%) as a colorless oil. The product, which was estimated ~90% pure by ^{1}H NMR, was used in the next step without further purification, since flash chromatography under various conditions resulted in significant loss of material. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.61 (q, *J* = 7.81 Hz, 6H), 0.96 (t, *J* = 7.81 Hz, 9H), 1.61 (s, 3H), 1.73 (s, 3H), 2.10 (m, 2H), 2.16 (m, 2H), 4.00 (s, 2H), 4.10 (d, *J* = 7.80 Hz, 2H), 5.37 (t, *J* = 6.25 Hz, 1H), 5.45 (t, *J* = 8.00 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 6.7, 13.4, 16.0, 25.5, 29.5, 38.9, 41.0, 68.6, 120.5, 123.6, 134.7, 142.4 ppm. R_f = 0.72 (EtOAc/*n*-hexane = 1:6).

10-*tert*-Butyldimethylsilyloxygeranyl chloride 175: To a solution of NCS (105 mg, 0.788 mmol) in CH_2Cl_2 (5 ml) was added at -10°C Me_2S (63 µl, 53 mg, 0.859 mmol). The mixture was stirred for 10 min. at -10°C, and the resulting white suspension was cooled to -78°C. 10-*tert*-Butyldimethylsilyloxygeraniol (**168**, 204 mg, 0.716 mmol) was added and the mixture was stirred for 1 h at -10°C. After dilution with sat. aq. NH_4Cl (25 ml), the mixture was extracted with CH_2Cl_2 (3 × 25 ml). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The product was purified by flash chromatography (column dimensions: 25 × 2 cm, EtOAc/PE = 1:40) to give **175** (168 mg, 0.555 mmol, 77%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.06 (s, 6H), 0.91 (s, 9H), 1.59 (s, 3H), 1.73 (d, *J* = 1.28 Hz, 3H), 2.09-2.17 (m, 4H), 4.00 (s, 2H), 4.10 (d, *J* = 8.05 Hz, 2H), 5.35 (m, 1H), 5.45 (td, *J* = 8.59, 1.28 Hz, 1H) ppm.

3.5 References

1. Schummer, D.; Gerth, K.; Reichenbach, H.; Höfle, G. *Liebigs Ann. Org. Bioorg. Chem.* **1995**, 685-688.
2. Sharpless, K.B.; Lauer, R.F. *J. Am. Chem. Soc.* **1972**, *94*, 7154-7155.
3. Umbreit, M.A.; Sharpless, K.B. *J. Am. Chem. Soc.* **1977**, *99*, 5526-5528.
4. Scheid, G.O., Ph.D. Thesis, Faculty of Exact Sciences, Vrije Universiteit Amsterdam, 2002.
5. Christmann, M.; Bhatt, U.; Quitschalle, M.; Claus, E.; Kalesse, M. *Angew.Chem.* **2000**, *112*, 4535-4538; *Angew. Chem. Int. Ed.* **2000**, *39*, 4364-4366.
6. Bhatt, U.; Christmann, M.; Quitschalle, M.; Claus, E.; Kalesse, M. *J. Org. Chem.* **2001**, *66*, 1885-1893.
7. Williams, D.R.; Ihle, D.C.; Plummer, S.V. *Org. Lett.* **2001**, *3*, 1383-1386.
8. Corey, E.J.; Kim, C.U.; Takeda, M. *Tetrahedron Lett.* **1972**, *13*, 4339-4342.

4

Synthesis of the ratjadone analogue C fragment

4 Synthesis of the ratjadone analogue C fragment

4.1 Retrosynthesis

A suitable building block representing the C1-C6 fragment of ratjadone should be aldehyde **30**, in which the sensitive lactone functionality is protected as an isopropyl acetal (Fig. 4.1). This is a known compound, employed in several total syntheses, including not only Kalesse´s total synthesis of ratjadone,[1,2] but also syntheses of callystatin A[3-6] and fostriecin[7].

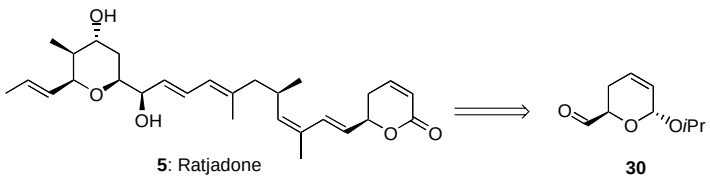
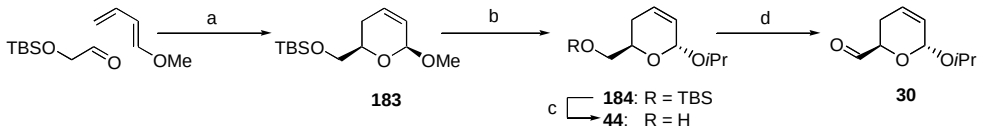


Figure 4.1. Ratjadone and its C ring building block **30**.

The strategies employed to obtain compound **30** (or derivatives) are diverse, and include methods involving catalytic asymmetric hetero Diels-Alder reactions[4], Brown asymmetric allylation and subsequent acrylation of the resulting alcohol followed by RCM[8], and vinyl Grignard addition to a glycidol derivative followed by transacetalization and RCM[3]. Jacobsen and co-workers demonstrated that their chiral HDA catalyst can also be used to construct a similar compound.[9] We chose to employ an eclectic approach, combining efficient literature procedures to achieve an optimal process.

4.2 Synthesis

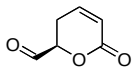
Commercially available (*tert*-butyldimethylsilyloxy)acetaldehyde and 1-methoxy-1,3-butadiene were subjected to a Jacobsen catalytic asymmetric HDA reaction,[9] affording **183** in very good yield with only 0.5 mol% of catalyst **83a**, even in larger scale procedures. Subsequently, the equatorial methyl acetal was converted to the more stable axial isopropyl acetal.[2] Interestingly, this axial isopropyl acetal is used as a protective group in nearly all syntheses of complex molecules carrying an α,β-unsaturated δ-lactone, even in cases where the lactone is formed.[7] The reason for this is probably the sensitivity of this lactone moiety to both basic and acidic conditions, as well as its incompatibility with a variety of other reagents and conditions.



Scheme 4.1. (a) **83a** (0.5 mol%), crushed 4Å mol. sieves, 88%; (b) PPTS, *i*PrOH; (c) TBAF, THF, 61% over two steps; (d) DMP, CH_2Cl_2, 96%.

The inversion of the acetal was accompanied on some occasions with partial desilylation. This is not a problem, since the next reaction is the cleavage of the TBS ether under standard conditions (TBAF, THF). Because of concerns about possible partial epimerization at C5, the basic conditions of the Swern oxidation[10] were deemed inappropriate for conversion to aldehyde **30**. Instead, Dess-Martin oxidation[11] was employed to obtain the required aldehyde **30** in excellent yield.

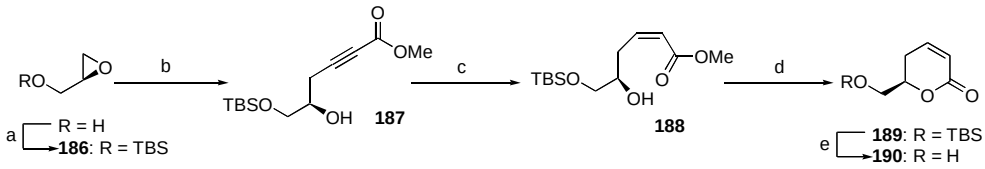
In preliminary studies, we attempted to use unprotected lactone **185**. At this point in time, it was still unclear if this was a useful building block. Reports that avoid the use of the lactone and similar compounds as building blocks and use protected lactols instead are quite recent and were not available at the beginning of our study.



185

Figure 4.2. Unprotected C ring building block **185**.

Commercially available (*S*)-glycidol was protected as a TBS ether. TBS ether **186** was treated with lithiated methyl propiolate at -78°C in the presence of BF_3•Et_2O to facilitate epoxide opening. It should be noted that in our hands none of the desired product was obtained when the literature procedure[12] was followed (alkyne, then *n*-BuLi, then BF_3•Et_2O, then epoxide), whereas when the order of addition was changed to a more logical sequence (alkyne, then *n*-BuLi, then epoxide, then BF_3•Et_2O), the desired product **187** was obtained in up to 88% yield (vs. 65% reported). Selective hydrogenation of the alkyne to the desired *Z*-alkene **188** was achieved with Lindlar catalyst in EtOAc. Ring closure to δ-lactone **188** then proceeded smoothly by treatment with PPTS in refluxing benzene. Cleavage of the TBS ether was achieved by treatment with TBAF in the presence of AcOH.



Scheme 4.2. (a) TBSCl, imidazole, CH_2Cl_2, 83%; (b) methyl propiolate, *n*-BuLi, THF, -78°C, then **186**, then BF_3•Et_2O, 84%; (c) H_2 (1 atm), Lindlar catalyst, EtOAc, 93%; (d) PPTS, benzene, Δ, 85%; (e) TBAF, AcOH, THF, 57%.

Thus, we were able to obtain (*R*)-6-hydroxymethyl-5,6-dihydro-α-pyrone **190**, but further conversion to aldehyde **185** was unsuccessful under various conditions (Swern, Dess-Martin). The apparent instability of this aldehyde is the probable reason that this compound is not used in any synthesis of a complex natural product. The only report of the use of this compound for a total synthesis is that of (+)-goniothalamin and (−)-argentilactone by Tsubuki et al., who generated the aldehyde *in situ* by Swern oxidation and used it immediately in the subsequent Wittig reaction.[13] Even in this case, the yield did not exceed 37%.

Boger and co-workers also attempted to use fragment **185** in their total synthesis of fostriecin.[7] They were, however, not successful, and protected the lactone as an axial isopropyl acetal for further conversions. These findings indeed suggest that protection of such lactones is necessary for multistep syntheses, since the presence of the unprotected lactone is incompatible with a wide variety of conditions commonly used in organic synthesis. The only reported example of a synthesis where such a lactone is present in its unprotected form over a longer sequence of reactions is the elegant total synthesis of fostriecin by Chavez and Jacobsen.[14] In syntheses of compounds of the leptomycin family, the main problem seems to be the combination of the unsaturated lactone and the tetraene chain.

4.3 Conclusion

The synthesis of (*R*)-6-hydroxymethyl-5,6-dihydro-α-pyrone was achieved in four steps, including nucleophilic ring opening of a protected glycidol derivative, Lindlar hydrogenation, acid-catalyzed cyclization, and desilylation. Unfortunately, the corresponding aldehyde proved to be extremely unstable, rendering this route impractical if not useless for the synthesis of complex molecules. Various groups reported the use of isopropyl acetal **30** in the synthesis of 6-substituted 5,6-dihydro-α-pyrones.[1-6] This compound was obtained via a new reaction sequence featuring a very efficient catalytic asymmetric HDA reaction using Jacobsen's HDA catalyst **83a**.[9] Subsequent transacetalization, desilylation, and Dess-Martin oxidation[11] afforded the required building block **30**. This four step sequence not only provides the desired fragment in good overall yield, but also does not require enantiomerically pure starting materials, and uses only a very small amount (0.5 mol%) of catalyst **83a**.

4.4 Experimental section

General. All commercial reagents were purchased from Fluka, Merck or Aldrich and used without further purification, unless otherwise stated. All oxygen- and water-sensitive reactions were carried out in oven-

dried glassware under argon. THF was distilled from potassium/benzophenone ketyl, Et_2O was distilled from sodium/potassium/benzophenone ketyl, and CH_2Cl_2 was distilled from calcium hydride. Other dry solvents were purchased from Fluka. Flash chromatography was performed using silica gel 60 (230-400 mesh, Merck). Thin-layer chromatography (TLC) was performed using silica plates (Merck, silica gel 60 F_{254}) and developed using Cer-MOP reagent [molybdatophosphoric acid (5.0 g), cerium (IV) sulfate (2.0 g), and concentrated H_2SO_4 (16 ml) in water (200 ml)]. Optical rotations were measured using a 1 ml cell with 1 dm path length on a Jasco DIP-1000 digital polarimeter. IR spectra were recorded as $CHCl_3$ solutions or as thin films between NaCl plates on a Bruker IFS 28. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Varian Mercury VX 300 and VX 400 spectrometers using TMS as internal standard. Chemical shifts δ are reported in parts per million (ppm), coupling constants *J* are given in Hertz (Hz). High resolution ESI mass spectra were obtained from a Bruker Apex 70e Fourier transform ion cyclotron resonance mass spectrometer equipped with a 7.0 Tesla superconducting magnet and an external electrospray ion source (Agilent, off axis spray).

(2*S*,6*R*)-6-*tert*-Butyldimethylsilyloxymethyl-2-methoxy-5,6-dihydropyran 183: To a mixture of *tert*-butyldimethylsilyloxyacetaldehyde (9.10 g, 52.2 mmol), 1-methoxy-1,3-butadiene (4.06 g, 47.9 mmol), and crushed molecular sieves 4Å (1.30 g) was added (*R*,*R*)-Jacobsen HDA catalyst (116 mg, 0.24 mmol). The mixture was stirred for 24 h at rt, after which the starting material was fully consumed as judged by TLC. The product was purified by flash chromatography (column dimensions: 30 × 5 cm, EtOAc/PE = 1:10) to give **183** (10.90 g, 42.2 mmol, 88%) as a slightly brown oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.07 (s, 6H), 0.90 (s, 9H), 2.06-2.10 (m, 2H), 3.47 (s, 3H), 3.65 (dd, *J* = 10.15, 6.24 Hz, 1H), 3.75 (dd, *J* = 10.15, 5.85 Hz, 1H), 3.85 (m, 1H), 5.02 (m, 1H), 5.64 (dd, *J* = 10.15, 1.56 Hz, 1H), 5.97 (dtd, *J* = 10.15, 6.25, 1.56 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = -5.2, -5.1, 18.4, 26.0, 26.8, 55.2, 65.4, 72.5, 97.5, 126.7, 128.2 ppm. R_f = 0.64 (EtOAc/*n*−hexane = 1:6).

(2*R*,6*R*)-6-*tert*-Butyldimethylsilyloxymethyl-2-isopropoxy-5,6-dihydropyran 184: To a solution of **183** (4.58 g, 17.6 mmol) in *i*PrOH (125 ml) was added PPTS (442 mg, 1.76 mmol). The mixture was stirred at rt overnight, diluted with brine (500 ml) and extracted with *t*BuOMe (3 × 250 ml). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The product was purified by flash chromatography (column dimensions: 25 × 4 cm, EtOAc/PE = 1:10) to give **184** (4.76 g, 16.6 mmol, 94%) as a colorless oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.07 (s, 6H), 0.90 (s, 9H), 1.17 (d, *J* = 6.25 Hz, 3H), 1.25 (d, *J* = 6.25 Hz, 3H), 1.97 (m, 2H), 3.62 (dd, *J* = 10.54, 4.68 Hz, 1H), 3.71 (dd, *J* = 10.54, 5.85 Hz, 1H), 3.99-4.06 (m, 2H), 5.09 (s, 1H), 5.71 (m, 1H), 6.00 (m, 1H) ppm. R_f = 0.61 (EtOAc/*n*/hexane = 1:10).

(2*R*,6*R*)-6-Hydroxymethyl-2-isopropoxy-5,6-dihydropyran 44: To a solution of **184** (4.76 g, 16.6 mmol) in anhydrous THF (100 ml) was added TBAF•$3H_2O$ (5.51 g, 17.5 mmol) and the mixture was stirred for 1.5 h at rt. After dilution with sat. aq. NH_4Cl (300 ml), the mixture was extracted with *t*BuOMe (3 × 150 ml). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The product was purified by flash chromatography (column dimensions: 25 × 4 cm, EtOAc/PE = 1:3) to give **44** (1.85 g, 10.7 mmol, 65%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.18 (d, *J* = 6.24 Hz, 3H), 1.25 (d, *J* = 6.25 Hz, 3H), 1.89 (dddd, *J* = 17.56, 5.46, 3.51, 1.56 Hz, 1H), 2.14 (dddt, *J* = 17.56, 11.32, 2.34, 1.95 Hz, 1H), 2.33 (dd, *J* = 5.85, 5.46 Hz, 1H, O<u>H</u>), 3.61 (m, 1H), 3.71 (m, 1H), 4.00 (heptet, *J* = 6.25 Hz, 1H), 4.08 (m, 1H), 5.11 (s, 1H), 5.72 (dtd, *J* = 10.15, 2.73, 1.56 Hz, 1H), 6.00 (dd, *J* = 10.15, 5.85 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.97, 23.83, 26.04, 65.14, 66.64, 69.41, 92.64, 125.56, 127.94 ppm. R_f = 0.21 (EtOAc/*n*/hexane = 1:4).

(2*R*,6*R*)-6-Formyl-2-isopropoxy-5,6-dihydropyran 30: To a solution of **44** (86 mg, 0.50 mmol) in anhydrous CH_2Cl_2 (3 ml) was added Dess-Martin periodinane (254 mg, 0.60 mmol) and the mixture was stirred for 1 h at rt, after which the starting material was fully consumed as judged by TLC. The reaction mixture was transferred to a flash column (column dimensions) and eluted with CH_2Cl_2/*t*BuOMe (20:1), affording **30** (81.4 mg, 0.48 mmol, 96%) as a colorless, somewhat volatile liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.21 (d, *J* = 6.25 Hz, 3H), 1.25 (d, *J* = 6.25 Hz, 3H), 2.12-2.29 (m, 2H), 4.07 (heptet, *J* = 6.25 Hz, 1H), 4.43 (dd, *J* = 11.31, 4.29 Hz, 1H), 5.21 (d, *J* = 1.17 Hz, 1H), 5.76 (m, 1H), 6.02 (m, 1H), 9.74 (s, 1H) ppm.

(*S*)-*tert*-Butyldimethylsilyl glycidyl ether 186: To a solution of imidazole (1.22 g, 18.0 mmol) and (*S*)-glycidol (995 µl, 1.11 g, 15.0 mmol) in CH_2Cl_2 (15 ml) was added at 0°C *tert*-butyldimethylsilyl chloride (2.49 g, 16.5 mmol). The mixture was stirred for 2 h at rt and quenched by addition of sat. aq. NH_4Cl. The mixture was extracted three times with CH_2Cl_2 and the combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*, affording **186** (2.35 g, 12.5 mmol, 83 %) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.06 (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 2.62 (dd, *J* = 5.15, 2.67 Hz, 1H), 2.76 (dd, *J* = 5.08, 4.11 Hz, 1H), 3.07 (dddd, *J* = 4.76, 4.111, 3.19, 2.76 Hz, 1H), 3.64 (dd, *J* = 11.92, 4.76 Hz, 1H), 3.84 (dd, *J* = 11.92, 3.19 Hz, 1H) ppm.

Methyl (*R*)-6-*tert*-butyldimethylsilyloxy-5-hydroxyhex-2-ynoate 187: To a solution of methyl propiolate (6.23 ml, 5.88 g, 70.0 mmol) in THF (80 ml) was added slowly at -78°C *n*-BuLi (1.6 M in hexane, 43.8 ml, 70.0 mmol). (Caution! If the reaction temperature exceeds ~-55°C, decomposition takes place!) The solution was stirred for 20 min. at -78°C and a solution of *tert*-butyldimethylsilyl glycidyl ether (**186**, 8,74

g, 46.4 mmol) in THF (30 ml) was added at -78°C. The mixture was stirred for an additional 20 min. at −78°C and BF_3•Et_2O (8.87 ml, 9.94 g, 70.0 mmol) was added dropwise. The mixture was stirred for 2 h at −78°C. The reaction was quenched by addition of sat.aq. NH_4Cl (15 ml) and extracted with Et_2O (3 × 50 ml). The combined organic fractions were washed with sat aq. $NaHCO_3$ (2 × 50 ml), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by flash chromatography (column dimension: 25 × 4 cm, EtOAc/PE = 1:4) yielded **187** (10.7 g, 39.2 mmol, 84%) as a slightly yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.00 (s, 6H), 0.81 (s, 9H), 2.48 (d, *J* = 7.38 Hz, 2H), 3.49-3.66 (m, 2H), 3.68 (s, 3H), 3.72-3.79 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = <-5.0 18.0, 23.0, 25.6, 52.4, 65.2, 69.4, 74.1, 85.8, 153.8 ppm.

Methyl (*R*)-6-*tert*-butyldimethylsilyloxy-5-hydroxyhex-2*Z*-enoate 188: To a solution of alkyne **187** (10.32 g, 37.9 mmol) in EtOAc (200 ml) was added Lindlar catalyst (1.2 g). The mixture was stirred for 5 h under a 1 bar H_2 atmosphere. The mixture was filtered over Celite and the filtrate was washed with sat. aq. $NaHCO_3$ (100 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product contained the desired product (*E*/*Z* > 1:20) in pure form as judged by ^{1}H NMR, but it was further purified (to remove traces of palladium) by flash chromatography (column dimensions: 25 × 5 cm, EtOAc/PE = 1:4) to give **188** (9.63 g, 35.1 mmol, 93%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.00 (s, 6H), 0.83 (s, 9H), 2.64-2.89 (m, 2H), 2.93 (bs, 1H, O<u>H</u>), 3.43-3.61 (m, 2H), 3.62 (s, 3H), 3.64-3.72 (m, 1H), 5.81 (dt, *J* = 11.52, 1.58 Hz, 1H), 6.26 (dt, *J* = 11.52, 7.46 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 18.0, 25.6, 32.4, 66.7, 71.0, 120.6, 146.2, 166.6 ppm.

(*R*)-6-(*tert*-butyldimethylsilyloxy)methyl-5,6-dihydro-α-pyrone 189: To a solution of hydroxy ester **188** (274 mg, 1.00 mmol) in benzene (5 ml) was added PPTS (25 mg, 0.10 mmol) and the mixture was heated to reflux for 5.5 h. The mixture was allowed to cool to room temperature, diluted with Et_2O (50 ml) and washed with H_2O (25 ml) and brine (25 ml). The combined organic fractions were dried ($MgSO_4$), filtered, concentrated *in vacuo*, and purified by flash chromatography (column dimension: 25 × 2 cm, EtOAc/PE = 1:2) to give **189** (206 mg, 0.85 mmol, 85%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.08 (s, 6H), 0.89 (s, 9H), 2.32-2.63 (m, 2H), 3.81 (d, *J* = 5.05 Hz, 1H), 4.46 (m, 1H), 6.00 (dt, *J* = 9.68, 1.21 Hz, 1H), 6.90 (ddd, *J* = 9.58, 5.55, 2.95 Hz, 1H) ppm.

(*R*)-6-hydroxymethyl-5,6-dihydro-α-pyrone 190: To a solution of TBS ether **189** (1.21 g, 5.00 mmol) in THF (25 ml) was added TBAF•$3H_2O$ (1.74 g, 5.50 mmol). The mixture was stirred for 16 h at rt. The mixture was concentrated *in vacuo*, and purified by flash chromatography (column dimension: 25 × 2.5 cm, CH_2Cl_2/MeOH = 10:1) to give **190** (365 mg, 2.85 mmol, 57 %) as a colorless oil that crystallized upon

storage. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.32 (m, 1H), 2.62 (m, 1H), 3.75 (dd, *J* = 12.31, 4.69 Hz, 1H), 3.90 (dd, *J* = 12.31, 3.23 Hz, 1H), 4.56 (m, 1H), 6.04 (dd, *J* = 9.67, 2.05, 1H), 6.94 (ddd, *J* = 9.67, 6.16, 2.25 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = <-5.0, 25.1, 63.1, 78.3, 120.1, 145.7, 164.0 ppm.

4.5 References

1. Christmann, M.; Bhatt, U.; Quitschalle, M.; Claus, E.; Kalesse, M. *Angew.Chem.* **2000**, *112*, 4535-4538; *Angew. Chem. Int. Ed.* **2000**, *39*, 4364-4366.
2. Bhatt, U.; Christmann, M.; Quitschalle, M.; Claus, E.; Kalesse, M. *J. Org. Chem.* **2001**, *66*, 1885-1893.
3. Crimmins, M.T.; King, B.W. *J. Am. Chem. Soc.* **1998**, *120*, 9084-9085.
4. Kalesse, M.; Quitschalle, M.; Khandavalli, C.P.; Saeed, A. *Org. Lett.* **2001**, *3*, 3107-3109.
5. Vicario, J.L.; Job, A.; Wolberg, M.; Mueller, M.; Enders, D. *Org. Lett.* **2002**, *4*, 1023-1026.
6. Kalesse, M.; Chary, K.P.; Quitschalle, M.; Burzlaff, A.; Kasper, C.; Scheper, T. *Chem. Eur. J.* **2003**, *9*, 1129-1136.
7. Boger, D.L.; Ichikawa, S.; Zhong, W. *J. Am. Chem. Soc.* **2001**, *123*, 4161-4167.
8. Cossy, J.; Pradaux, F.; BouzBouz, S. *Org. Lett.* **2001**, *3*, 2233-2235.
9. Dosseter, A.G.; Jamison, T.F.; Jacobsen, E.N. *Angew. Chem.* **1999**, *111*, 2549-2552; *Angew. Chem. Int. Ed.* **1999**, *38*, 2398-2400.
10. Mancuso, A.J.; Swern, D. *Synthesis* **1981**, 165-196.
11. Dess, D.B.; Martin, J.C. *J. Org. Chem.* **1983**, *48*, 4155-4156.
12. Takano, S.; Shimazaki, Y.; Y., I.; Ogasawara, K. *Tetrahedron Lett.* **1990**, *31*, 3619-3622.
13. Tsubuki, M.; Kanai, K.; Honda, T. *Heterocycles* **1993**, *35*, 281-288.
14. Chavez, D.E.; Jacobsen, E.N. *Angew. Chem.* **2001**, *113*, 3779-3782; *Angew. Chem. Int. Ed.* **2001**, *40*, 3667-3670.

5

Connection of the fragments

5 Connection of the fragments

5.1 Retrosynthesis

The connection of A, B, and C fragments was envisioned to be achieved through two Wittig reactions, the phosphonium salt being present on the terpenoid fragment in both occasions and the aldehyde moiety on the A and C fragments. There are, obviously, two approaches to construct the full skeleton: (i) B + C → BC → ABC (right to left) and (ii) A + B → AB → ABC (left to right).

Since the synthesis of fragment A requires the highest number of steps, the former route can be considered more efficient in terms of convergence. The latter route, however, provides a viable alternative, because, at this stage of the synthesis, the available amount of A and C building blocks were comparable.

5.2 Right to left route

Aldehyde **30** was reacted with terpene-derived phosphonium salts **176** and **179** (using the procedure of the corresponding Wittig reaction in Kalesse's total synthesis of (+)-ratjadone[1,2]) to give coupling products **191** and **192** (differing in protective group and 12,13 double bond geometry (ratjadone numbering)) in reasonable to good yield. However, neutralization of the slightly acidic silica with Et_3N prior to flash chromatography proved essential, and neglecting this resulted in a loss of up to 75% of the product.

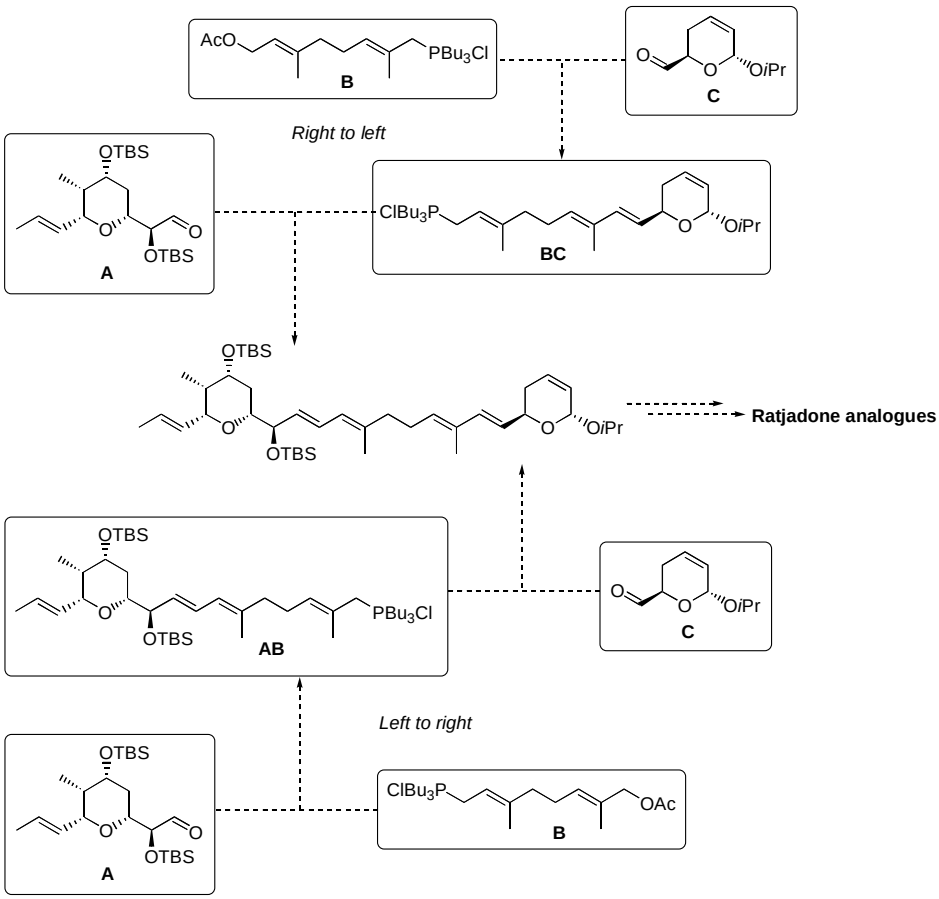
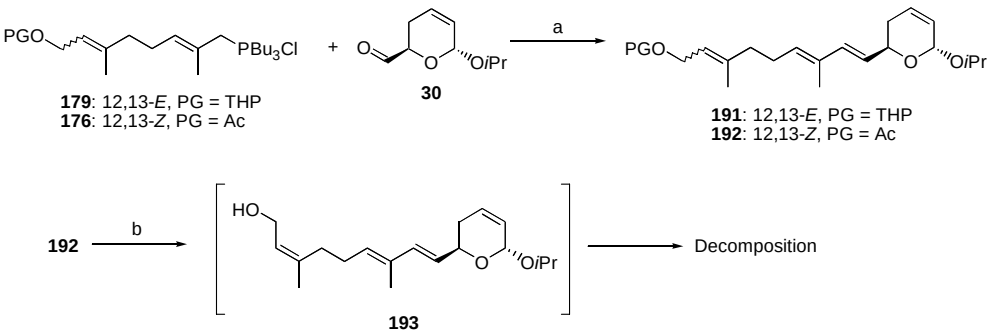


Figure 5.1. Right to left and left to right strategies

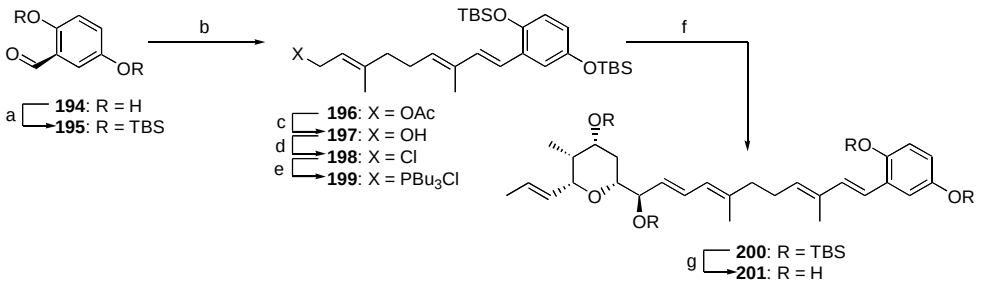
The next task at hand was selective cleavage of the protective group on the terpenoid alcohol in the presence of the acetal function on the C ring. This proved impossible for **191**, which is hardly surprising since a THP ether is also an acetal. The acetate in **192** was considered a more suitable protective group at this position. Indeed, formation of the desired alcohol was observed by TLC analysis upon treatment with K_2CO_3 in MeOH. TLC analysis of the product solution also indicated presence of the desired alcohol **193**, uncontaminated with other compounds. After concentration of the product solution,

however, no product alcohol could be detected, and a mixture of products was formed. After three days, the product mixture converged to a single, unidentified product. A possible explanation for this observation is displacement of the isopropoxy group of the acetal by the newly formed allylic alcohol function. This instability may also be a reason why such intermediates are not found in either Kalesse's[1,2] or Williams'[3] synthesis of ratjadone.



Scheme 5.1. (a) KO*t*Bu, toluene, 0°C, 89% for **191**, 49% for **192**; (b) K_2CO_3, MeOH.

This problem was considered a major reason to abandon this route, since it was inherent to the synthesis planning and could hardly be circumvented. However, it still may be useful for the synthesis of derivatives lacking the acetal functionality at the C ring. Therefore, it was decided to construct a derivative with a 2,5-dihydroxyphenyl C ring. This moiety is easily available and has the advantage that it can be e.g. transformed to a quinone, which is expected to display a similar electrophilicity as the α,β-unsaturated δ-lactone of ratjadone. For this purpose, commercially available 2,5-dihydroxybenzaldehyde (**194**) was protected as a bis-TBS ether and subsequently reacted with terpene-derived phosphonium salt **178**, giving Wittig product **196** in moderate yield. It is unclear why the yield in this case is much lower than in comparable reactions, where the yield is often excellent (90-100%).



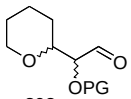
Scheme 5.2. (a) TBSCl, imidazole, DMF, 81%; (b) **178**, KO*t*Bu, toluene, 0°C, 42%; (c) $LiAlH_4$, THF, 0°C, 95%; (d) NCS, Me_2S, CH_2Cl_2, -78→-10°C, 95%; (e) PBu_3; (f) **108**, KO*t*Bu, toluene, 0°C, 98% over two steps; (g) HF•py, py/THF 1:1, 65%.

The acetate group of the Wittig product **196** was cleaved by reduction (treatment with K_2CO_3 in MeOH led to partial cleavage of the phenolic TBS ethers) and the resulting alcohol was converted to tributylphosphonium salt **199** in a two step sequence. Subsequently, a second Wittig reaction with A ring aldehyde **108** afforded tetrakis-TBS ether **200** in excellent yield. The final cleavage of the four TBS ethers was troublesome. Reaction with TBAF in THF led to rapid decomposition of the starting material. When **200** was reacted with TBAF in THF in the presence of AcOH, the phenolic TBS ethers were cleaved smoothly, but cleavage of the remaining two TBS ethers was extremely slow and led to partial decomposition. Fortunately, treatment with HF•py in a 1:1 mixture of pyridine and THF (under similar conditions as the final desilylation in Kalesse's total synthesis of (+)-ratjadone[1,2]) afforded ratjadone analogue **201** in 65% yield.

Attempts to oxidize hydroquinone **201** to the corresponding quinone using DDQ resulted in the formation of an unstable product, presumably the quinone. Possibly, the electrophilic quinone is susceptible to intramolecular attack by the adjacent electron-rich diene, leading to a bicylic structure. This could, however, not be confirmed, since the product was not obtained in pure form.

5.3 Left to right route

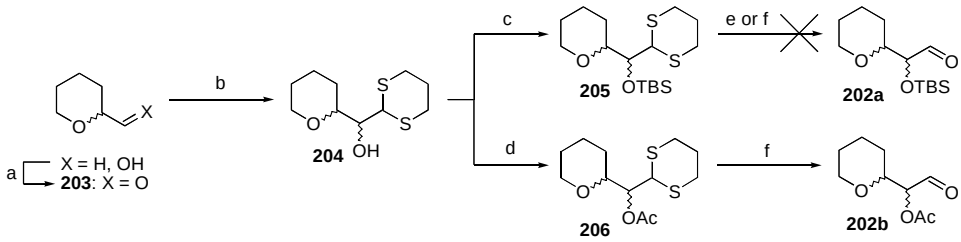
Due to the problems encountered in the right to left route, we decided to pursue the inverse approach. In order to avoid unnecessary wasting of valuable fully functionalized A ring fragment, we decided to carry out some preliminary studies to validate the viability of this approach. Since Kalesse and co-workers reported that ratjadone derivative **54** with a monosubstituted THP ring was still a very active compound (IC_{50} = 5.0 ng ml^{-1}),[4] we considered using a simplified A ring fragment of type **202**.



202

Figure 5.2. Simplified A ring fragment.

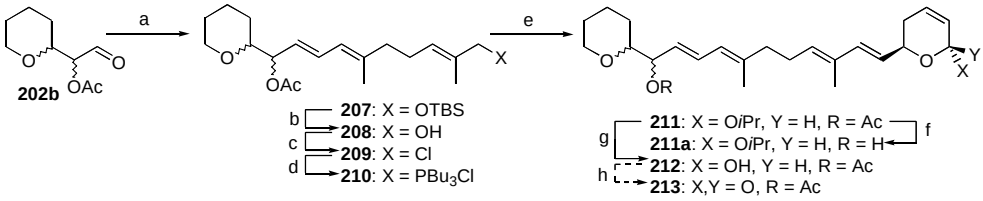
Commercially available (±)-2-(hydroxymethyl)tetrahydropyran was converted to the corresponding volatile aldehyde **203** by Swern oxidation.[5] Aldehyde **203** was then treated with 2-lithio-1,3-dithiane to give **204**. The resulting alcohol function was then protected as a TBS ether (**205**) or an acetate (**206**). Hydrolysis of the thioacetal of **205** under various conditions ($PhI(O_2CCF_3)_2$, CH_3CN/H_2O; MeI, $CaCO_3$, CH_3CN/H_2O) was apparently accompanied with cleavage of the silyl ether.



Scheme 5.3. (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78→0°C, 65% ; (b) 1,3-dithiane, *n*BuLi, THF, -78°C, then **203**, -78→25°C, 70%; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, -78→0°C, 91% (borsm); (d) AcCl, py, 43%; (e) $PhI(O_2CCF_3)_2$, CH_3CN/H_2O 9:1; (f) 50 eq. MeI, $CaCO_3$, CH_3CN/H_2O 2:1, 96% for **202b**.

Whereas the Stork protocol[6] ($PhI(O_2CCF_3)_2$, CH_3CN/H_2O) was also unsuccessful with **206**, treatment with excess MeI and $CaCO_3$ in CH_3CN/H_2O led to clean conversion to the desired aldehyde **202b**.

Simplified A ring fragment **202b** was then connected to terpenoid fragment **182** and the ω−TBS ether was converted to the corresponding tributylphosphonium salt **210** in the familiar three step sequence.

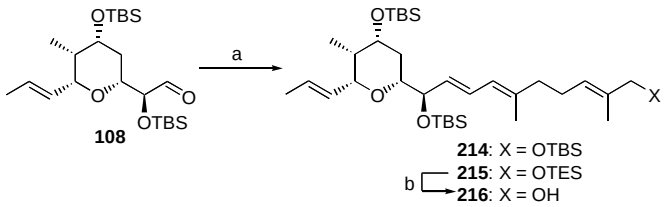


Scheme 5.4. (a) **182**, KO*t*Bu, toluene, 0°C, 77%; (b) TBAF•3H_2O, AcOH, THF, 0°C→rt, 73%; (c) NCS, Me_2S, CH_2Cl_2, -78→-10°C, 86%; (d) PBu_3; (e) **30**, KO*t*Bu, toluene, 0°C, 77% over two steps; (f) K_2CO_3, MeOH, 77%; (g) PPTS, acetone/H_2O 6:1, quant. (h) various conditions, no reaction or decomposition.

Wittig reaction of phosphonium salt **210** and C ring fragment **30** then afforded **211**. The final steps to a simplified ratjadone analogue were cleavage of the acetal and oxidation of the resulting lactol, followed eventually by cleavage of the acetate. It was shown that the acetate group could be selectively cleaved at the stage of **211**. To proceed to the desired ratjadone analogue, the acetal of **211** was smoothly cleaved by treatment with PPTS in an acetone/water mixture. However, subsequent oxidation of hemiacetal **212** to the lactone was unsuccessful under various conditions, including MnO_2 oxidation, TPAP oxidation, and Dess-Martin oxidation.[7] However, the left to right connection strategy proved valid, and since all three fragments were available in sufficient amounts, we decided to move on to the next stage.

With a reliable procedure for the elaboration of the three fragments to the target ratjadone analogues at hand, we started to construct an analogue with a fully functionalized A ring. For this purpose, A ring aldehyde **108** was reacted with terpene-derived phosphonium salts **182** and **181** to give Wittig products **214** and **215**, respectively. Whereas it proved difficult

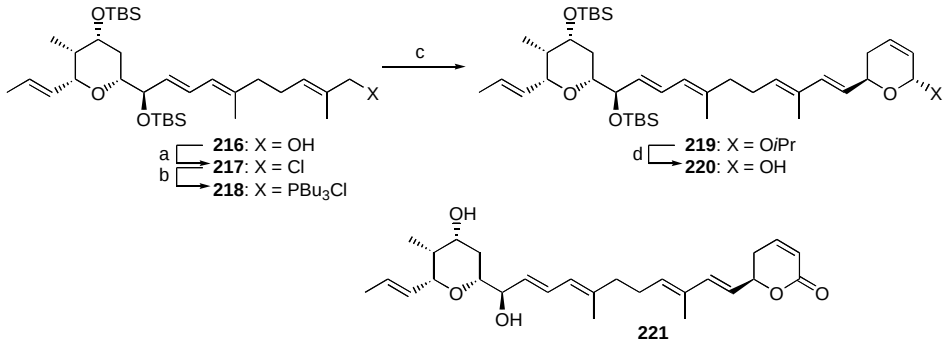
to cleave the primary TBS ether of **214** selectively, the primary TES ether of **215** was readily cleaved under slightly acidic conditions in MeOH.



Scheme 5.5. (a) **182** or **181**, KO*t*Bu, toluene, 0°C,65% with **182**, 100% with **181**; (b) PPTS, MeOH, 66%.

Thus, for the described strategies, the ω-functionalized terpene fragment with acetate protection at the α-position (**178**) and the α-functionalized terpene fragment with TES protection at the ω-position (**181**) proved the best building blocks with respect to synthesis efficiency and orthogonality. The fact that both fragments are derived from the same synthesis route (both are derived from **164**) is an additional advantage.

Alcohol **216** was smoothly converted to tributylphosphonium salt **218** by Corey-Kim reaction[8] and subsequent treatment with PBu_3. Wittig reaction with C ring aldehyde **30** then afforded coupling product **219** in very good yield.



Scheme 5.6. (a) NCS, Me_2S, CH_2Cl_2, -78→-10°C; (b) PBu_3; (c) **30**, KO*t*Bu, toluene, 0°C, 84% over three steps; (d) PPTS, acetone/H_2O 6:1, 99%.

Although hydrolysis of isopropyl acetal **219** was successful, the resulting lactol **220** (mixture of anomers) proved to be unstable. It was therefore not fully characterized, but only used as an intermediate. The subsequent oxidation to the corresponding lactone **221** proved a great challenge. In our hands, a variety of oxidation methods (including Dess-Martin, TPAP, and MnO_2 oxidations) failed, and the desired lactone could not be obtained. In some cases, the starting material decomposed completely within minutes, whereas in other cases, no reaction seemed to take place at all. On some occasions, conversion to a slighty less polar product (TLC analysis) was observed, but mild aqueous workup resulted in a complex mixture of products.

5.4 Conclusion

In summary, the left to right connection strategy provides a reliable way of connecting the three fragments to give the full carbon skeleton of the desired ratjadone analogues. Both a simplified A ring and a fully functionalized one were used. Although the final products could not be obtained, connection of the fragments was very efficient, providing the coupling products in excellent yields. This demonstrates the general validity of the employed strategy.

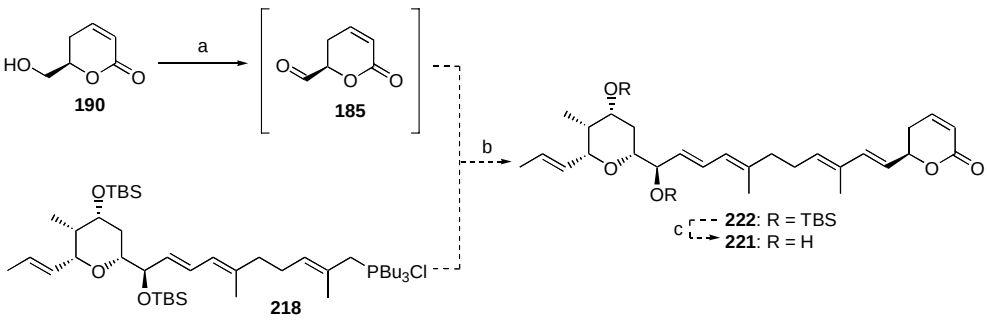
The right to left strategy could not be used for the synthesis of these compounds because of incompatibility of the free allylic alcohol and the acetal functionality. However, this method proved successful in the synthesis of analogues lacking the acetal function in the C ring. As an example, hydroquinone-containing derivative **201** was synthesized.

5.5 Outlook

Although the connection of the ratjadone analogue fragments proceeded very efficiently, the essential oxidation to the lactone failed in our hands, even using literature procedures for similar conversions. This troublesome oxidation might, however, be circumvented by using aldehyde **185**, with the lactone functionality already installed. Although this option

was discarded because of the severe instability of aldehyde **185**, it might be useful when the aldehyde is generated *in situ* by Swern oxidation[5] and the subsequent Wittig reaction is performed at low temperature in a one-pot procedure as described by Tsubuki et al.[9]

By using excess of the lactone fragment **185**, a reasonable yield might be achieved. Furthermore, the many alternative A and B fragments that are available, may be employed in the construction of a small library of ratjadone analogues.



Scheme 5.7. Possible alternative route to ratjadone analogue **221**. (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (b) KOtBu, toluene; (c) HF•py, py/THF.

5.6 Experimental section

General. All commercial reagents were purchased from Fluka, Merck or Aldrich and used without further purification, unless otherwise stated. All oxygen- and water-sensitive reactions were carried out in oven-dried glassware under argon. THF was distilled from potassium/benzophenone ketyl, Et_2O was distilled from sodium/potassium benzophenone ketyl, and CH_2Cl_2 was distilled from calcium hydride. Other dry solvents were purchased from Fluka. Flash chromatography was performed using silica gel 60 (230-400 mesh, Merck). Thin-layer chromatography (TLC) was performed using silica plates (Merck, silica gel 60 F_{254}) and developed using Cer-MOP reagent [molybdatophosphoric acid (5.0 g), cerium (IV) sulfate (2.0 g), and concentrated H_2SO_4 (16 ml) in water (200 ml)]. Optical rotations were measured using a 1 ml cell with 1 dm path length on a Jasco DIP-1000 digital polarimeter. IR spectra were recorded as $CHCl_3$ solutions or as thin films between NaCl plates on a Bruker IFS 28. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Varian Mercury VX 300 and VX 400 spectrometers using TMS as internal standard. Chemical shifts δ are reported in parts per million (ppm), coupling constants *J* are given in Hertz (Hz). High resolution ESI mass

spectra were obtained from a Bruker Apex 70e Fourier transform ion cyclotron resonance mass spectrometer equipped with a 7.0 Tesla superconducting magnet and an external electrospray ion source (Agilent, off axis spray).

THP ether 191: To 10-chlorogeranyl THP ether (**172**, 136 mg, 0.50 mmol) was added tri-*n*-butylphosphine (123 µl, 101 mg, 0.50 mmol) and the mixture was stirred for 3 h at 70°C. The resulting phosphonium salt **179** was dissolved in toluene (4 ml) and the mixture was cooled to 0°C. Aldehyde **30** (61 mg, 0.361 mmol) was added, followed by KO*t*Bu (1 M solution in THF, 650 µl, 0.650 mmol). The mixture was stirred for 15 min. at 0°C, then diluted with H_2O (20 ml) and extracted with *t*BuOMe (3 × 30 ml). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The product was purified by flash chromatography on a Et_3N-neutralized column (column dimensions: 25 × 2 cm, EtOAc/PE = 1:8) to give **191** (126 mg, 0.321 mmol, 89%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.18 (d, *J* = 6.25 Hz, 3H), 1.24 (d, *J* = 6.25 Hz, 3H), 1.51-1.83 (m, 6H), 1.68 (s, 3H), 1.75 (s, 3H), 2.05-2.12 (m, 4H), 2.27 (dt, *J* = 7.80, 7.42 Hz, 2H), 3.49-3.52 (m, 1H), 3.86-3.89 (m, 1H), 4.01 (m, 1H), 4.01 (dd, *J* = 11.71, 6.64 Hz, 1H), 4.24 (dd, *J* = 11.71, 6.25 Hz, 1H), 4.47 (m, 1H), 4.62 (dd, *J* = 3.90, 2.73 Hz, 1H), 5.11 (s, 1H), 5.37 (td, *J* = 6.24, 1.17 Hz, 1H), 5.48 (t, *J* = 6.24 Hz, 1H), 5.59 (dd, *J* = 15.61, 6.24 Hz, 1H), 5.72 (dd, *J* = 10.15, 1.56 Hz, 1H), 5.99 (m, 1H), 6.27 d, *J* = 15.61 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 12.5, 16.5, 19.7, 22.1, 24.0, 25.6, 26.6, 30.8, 31.0, 39.2, 62.3, 63.6, 66.9, 69.3, 93.0, 97.7, 120.8, 125.9, 126.2, 128.4, 132.6, 133.0, 135.8, 139.5 ppm.

Acetate 192: To 10-chloroneryl acetate (**169**, 415 mg, 1.80 mmol) was added tri-*n*-butylphosphine (444 µl, 364 mg, 1.80 mmol) and the mixture was stirred for 3 h at 70°C. The resulting phosphonium salt **176** was dissolved in toluene (15 ml) and the mixture was cooled to 0°C. Aldehyde **30** (340 mg, 2.00 mmol) was added, followed by KO*t*Bu (1 M solution in THF, 2.34 ml, 2.34 mmol). The mixture was stirred for 15 min. at 0°C, then diluted with sat. aq. NH_4Cl (100 ml) and extracted with *t*BuOMe (3 × 50 ml). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The product was purified by flash chromatography on a Et_3N-neutralized column (column dimensions: 25 × 2 cm, EtOAc/PE = 1:10) to give **192** (305 mg, 0.875 mmol, 49%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.18 (d, *J* = 6.04 Hz, 3H), 1.24 (d, *J* = 6.23 Hz, 3H), 1.76 (s, 3H), 1.77 (s, 3H), 2.05 (s, 3H), 2.06-2.26 (m, 6H), 4.02 (heptet, *J* = 6.22 Hz, 1H), 4.48 (m, 1H), 4.55 (d, *J* = 7.32 Hz, 1H), 5.47 (m, 1H), 5.61 (dd, *J* = 15.74, 6.41 Hz, 1H), 5.70-5.75 (m, 1H), 5.99 (m, 1H), 6.27 (d, *J* = 15.74 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 12.4, 21.2, 22.1, 23.5, 24.0, 26.9, 31.0, 31.8, 60.9, 66.9, 69.4, 93.0, 107.5, 119.3, 125.9, 126.6, 128.4, 131.8, 133.5, 135.6, 142.0, 170.8 ppm. R_f = 0.67 (EtOAc/*n*-hexane = 1:4).

2,5-Bis(*tert*-butyldimethylsilyloxy)benzaldehyde 195: To a solution of 2,5-dihydroxy-benzaldehyde (276 mg, 2.00 mmol) and imidazole (408 mg, 6.00 mmol) in DMF (10 ml) was added in one portion at 0°C *tert*-butyldimethylsilyl chloride (724 mg, 4.80 mmol). The mixture was stirred for 2 h at rt, diluted with H_2O (25 ml) and extracted with PE (3 × 50 ml). The combined organic fractions were washed with H_2O (50 ml) and brine (50 ml), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The product was purified by flash chromatography on a Et_3N-neutralized column (column dimensions: 25 × 2.5 cm, EtOAc/PE = 1:20) to give **195** (591 mg, 1.61 mmol, 81%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.18 (s, 6H), 0.25 (s, 6H), 0.97 (s, 9H), 1.01 (s, 9H), 6.76 (d, *J* = 8.98 Hz, 1H), 6.97 (dd, *J* = 8.98, 3.12 Hz, 1H), 7.23 (d, *J* = 3.12 Hz, 1H), 10.39 (s, 1H) ppm. R_f = 0.79 (EtOAc/*n*-hexane = 1:10).

1-Acetoxy-9-(2,5-bis(*tert*-butyldimethylsilyloxy)phenyl)-3,7-dimethyl-2,6,8-nonatriene 196: To 10-chlorogeranyl acetate (**171**, 577 mg, 2.50 mmol) was added tri-*n*-butylphosphine (595 µl, 506 mg, 2.50 mmol) and the mixture was stirred for 3 h at 70°C. The resulting phosphonium salt **178** was dissolved in toluene (25 ml) and the mixture was cooled to 0°C. Aldehyde **195** (591 mg, 1.61 mmol) was added, followed by KO*t*Bu (1 M solution in THF, 2.50 ml, 2.50 mmol). The mixture was stirred for 15 min. at 0°C, then diluted with sat. aq. NH_4Cl (100 ml) and extracted with *t*BuOMe (3 × 100 ml). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The product was purified by flash chromatography on a Et_3N-neutralized column (column dimensions: 30 × 2.5 cm, EtOAc/PE = 1:40) to give **196** (367 mg, 0.674 mmol, 42%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.17 (s, 6H), 0.18 (s, 6H), 0.98 (s, 9H), 1.02 (s, 9H), 1.73 (s, 3H), 1.85 (s, 3H), 2.06 (s, 3H), 2.15 (m, 2H), 2.32 (m, 2H), 4.60 (d, *J* = 6.95 Hz, 2H), 5.38 (m, 1H), 5.59 (m, 1H), 6.56 (dd, *J* = 8.60, 2.74 Hz, 1H), 6.61-6.67 (m, 2H), 6.76 (d, *J* = 16.28 Hz, 1H), 6.96 (d, *J* = 2.74 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = -4.3, -4.2, 12.6, 16.6, 18.3, 18.3, 21.1, 25.8, 25.9, 26.8, 39.2, 61.3, 116.2, 118.5, 119.1, 112.0, 120.9, 129.6, 132.3, 133.2, 134.5, 141.6, 147.1, 149.6, 170.9 ppm. R_f = 0.64 (EtOAc/*n*-hexane = 1:4). HRMS: calcd. for $C_{31}H_{53}O_4Si_2$ $(M+Na)^+$ 567.3296 found 567.3298.

9-(2,5-Bis(*tert*-butyldimethylsilyloxy)phenyl)-3,7-dimethyl-1-hydroxy-2,6,8-nonatriene 197: To a solution of **196** (324 mg, 0.595 mmol) in THF (15 ml) was added at 0°C $LiAlH_4$ (23 mg, 0.595 mmol) and the mixture was stirred for 10 min. at rt. The mixture was diluted with sat. aq. NH_4Cl (25 ml) and brine (25 ml) and extracted with with *t*BuOMe (3 × 75 ml). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The product was purified by flash chromatography on a Et_3N-neutralized (column dimensions: 25 × 2.5 cm, EtOAc/PE = 1:4) to give **197** (284 mg, 0.564 mmol, 95%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.17 (s, 6H), 0.18 (s, 6H), 0.98 (s, 9H), 1.03 (s, 9H), 1.70 (s, 3H), 1.85 (s, 3H), 2.13 (m, 2H), 2.33 (m, 2H), 4.16 (d, *J* = 6.63 Hz, 2H), 5.45 (td, *J* = 6.63, 1.17 Hz, 1H), 5.60 (t, 7.03 Hz, 1H), 6.56 (dd, *J* = 8.59, 2.73 Hz, 1H), 6.59-6.67 (m, 2H), 6.76 (d, *J* = 16.39 Hz, 1H), 6.96

(d, J = 3.12 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = -4.5, -4.4, 12.4, 16.3, 18.1, 18.2, 25.7, 25.8, 26.8, 39.1, 59.3, 116.3, 119.1, 120.0, 120.9, 123.7, 129.7, 132.7, 133.3, 134.5, 139.1, 147.2, 149.7 ppm. R_f = 0.32 (EtOAc/*n*-hexane = 1:4). HRMS :calcd. for $C_{29}H_{50}O_3Si_4$ $(M+Na)^+$ 525.3191 found 525.3192.

9-(2,5-Bis(*tert*-butyldimethylsilyloxy)phenyl)-1-chloro-3,7-dimethyl-2,6,8-nonatriene 198: To a solution of NCS (90 mg, 0.673 mmol) in CH_2Cl_2 (10 ml) was added at -10°C Me_2S (53 µl, 45 mg, 0.729 mmol). The mixture was stirred for 10 min. at -10°C, and the resulting white suspension was cooled to -78°C. Alcohol **197** (282 mg, 0.561 mmol) was added and the mixture was stirred for 1 h at -10°C. After dilution with sat. aq. NH_4Cl (50 ml), the mixture was extracted with CH_2Cl_2 (3 × 50 ml). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The product was purified by flash chromatography (column dimensions: 25 × 2.5 cm, EtOAc/PE = 1:20) to give **198** (281 mg, 0.534 mmol, 95%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.17 (s, 6H), 0.18, (s, 6H), 0.98 (s, 9H), 1.02 (s, 9H), 1.75 (s, 3H), 1.85 (s, 3H), 2.16 (m, 2H), 2.33 (m, 2H), 4.11 (d, J = 8.20 Hz, 2H), 5.49 (m, 1H), 5.58 (m, 1H), 6.56 (dd, J = 8.59, 2.73 Hz, 1H), 6.61-6.69 (m, 2H), 6.76 (d, J = 16.39 Hz, 1H), 6.96 (d, J = 2.73 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = -4.5, -4.3, 12.5, 16.1, 18.1, 18.2, 25.7, 25.8, 26.6, 39.1, 41.0, 116.3, 119.2, 120.1, 120.6, 121.1, 129.7, 132.2, 133.3, 134.7, 142.2, 147.2, 149.7 ppm. R_f = 0.82 (EtOAc/*n*-hexane = 1:4).

Tetrakis TBS ether 200: To chloride **198** (278 mg, 0.529 mmol) was added tri-*n*-butylphosphine (139 µl, 118 mg, 0.582 mmol) and the mixture was stirred for 3 h at 70°C. The resulting phosphonium salt **199** was dissolved in toluene (10 ml) and the mixture was cooled to 0°C. Aldehyde **108** (219 mg, 0.495 mmol) was added, followed by KO*t*Bu (1 M solution in THF, 600 µl, 0.600 mmol). The mixture was stirred for 15 min. at 0°C, then diluted with sat. aq. NH_4Cl (50 ml) and extracted with *t*BuOMe (3 × 50 ml). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The product was purified by flash chromatography on a Et_3N-neutralized column (column dimensions: 25 × 2 cm, EtOAc/PE = 1:40) to give **200** (442 mg, 0.483 mmol, 98%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.04 (s, 6H), 0.05 (s, 3H), 0.09 (s, 3H), 0.14 (s, 3H), 0.17 (s, 3H), 0.19 (s, 6H), 0.86 (d, J = 7.80 Hz, 3H), 0.88 (s, 9H), 0.93 (s, 9H), 0.98 (s, 9H), 1.02 (s, 9H), 1.54-1.60 (m, 2H), 1.70 (d, J = 6.64 Hz, 3H), 1.77 (s, 3H), 1.85 (s, 3H), 2.15 (m, 3H), 2.33 (m, 2H); 3.23 (m, 1H), 3.81-3.86 (m, 2H), 4.27 (m, 1H), 5.44 (ddq, J = 15.22, 5.08, 1.57 Hz, 1H), 5.60-5.67 (m, 3H), 5.89 (d, J = 11.32 Hz, 1H), 6.48 (ddd, J = 15.22, 10.93, 1.17 Hz, 1H), 6.56 (dd, J = 8.59, 3.12 Hz, 1H), 6.59-6.70 (m, 2H), 6.76 (d, J = 16.39 Hz, 1H), 6.96 (d, J = 2.73 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = -4.7, -4.61, -4.55, -4.4 (2C), -4.3 (2C), -4.2, 5.5, 12.5, 16.7, 17.9, 18.11, 18.17, 18.23, 18.27, 25.7(3C), 25.8 (6C), 25.9 (3C), 27.1, 29.8, 39.6, 40.5, 71.8, 75.1, 79.2, 79.8, 116.3, 119.1, 120.1, 120.9, 124.4, 125.8, 126.6, 129.8, 130.4, 131.7, 132.9, 133.4, 134.5, 137.9, 147.2, 149.7 ppm. R_f = 0.73 (EtOAc/*n*-hexane = 1:10). HRMS: calcd. for $C_{52}H_{94}O_5Si_4$ $(M+Na)^+$ 933.6071 found 933.6077.

Hydroquinone 201: To a solution of tetrakis-TBS ether **200** (46.0 mg, 0.0502 mmol) in pyridine (1.5 ml) and THF (1.5 ml) was added HF•py (1.0 ml) and the mixture was stirred for 4 h at rt. The reaction was quenched by addition of sat. aq. $NaHCO_3$ (25 ml), the mixture was brought to pH 4 with 1 N aq. HCl and extracted with *t*BuOMe (3 × 25 ml). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The product was eluted on a small silica column ($CHCl_3$→$CHCl_3$/MeOH = 10:1) to give **201** (14.7 mg, 0.0323 mmol, 65%) as a yellow solid. ^{1}H NMR (acetone-d_6, 400 MHz): δ = 0.82 (d, *J* = 7.02 Hz, 3H), 1.64 (m, 1H), 1.67 (d, *J* = 6.24 Hz, 3H), 1.80 (s, 3H), 1.83 (m, 1H), 1.87 (s, 3H), 2.18 (m, 2H), 2.37 (q, *J* = 7.41 Hz, 2H), 2.86 (s, 1H) 3.34 (ddd, *J* = 11.32, 4.30, 2.34 Hz, 1H), 3.81 (t, *J* = 7.03 Hz, 1H), 3.87-3.92 (m, 2H), 4.15 (m, 1H), 5.45 (ddq, *J* = 15.22, 5.07, 1.56 Hz, 1H), 5.61-5.73 (m, 3H), 5.92 (d, *J* = 10.93 Hz, 1H), 6.52 (m, 2H), 6.70 (d, *J* = 8.58 Hz, 1H), 6.80 (s, 1H), 6.97 (d, *J* = 2.73 Hz, 1H), 7.69 (s, 1H), 7.90 (s, 1H) ppm. ^{13}C NMR (acetone-d_6, 100 MHz): δ = 5.8, 12.6, 16.6, 18.0, 27.6, 30.6, 40.2, 40.7, 71.0, 74.9, 79.7, 80.1, 112.5, 115.7, 117.2, 121.6, 125.72, 126.0, 126.3, 127.7, 131.8, 132.4, 133.2, 134.0, 135.4, 138.1, 148.6, 151.4 ppm. R_f = 0.41 (CH_2Cl_2/MeOH = 9:1).

2-Formyltetrahydropyran 203: To a solution of oxalyl chloride (3.84 ml, 5.59 g, 44.0 mmol) in CH_2Cl_2 (400 ml) was added at -78°C DMSO (6.25 ml, 6.88 g, 88.0 mmol). The mixture was stirred for 10 min. at -78°C and 2-(hydroxymethyl)tetrahydropyran (4.65 g, 40.0 mmol) was added. The mixture was stirred for an additional 20 min at -78°C, Et_3N (27.7 ml, 20.2 g, 200 mmol) was added and the mixture was allowed to warm to room temperature. After dilution with sat. aq. NH_4Cl (500 ml), the mixture was extracted with CH_2Cl_2 (3 × 250 ml). The combined organic fractions were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (column dimensions: 30 × 3 cm, EtOAc/PE = 1:3) afforded **203** (2.97 g, 26.0 mmol, 65%) as a volatile colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.48-1.66 (m, 4H), 1.88-1.97 (m, 2H), 3.58 (ddd, *J* = 11.32, 10.54, 2.73 Hz, 1H), 3.87 (dd, *J* = 11.32, 2.34 Hz, 1H), 4.11 (m, 1H) ppm. R_f = 0.50 (EtOAc/*n*-hexane = 1:2).

(1,3-Dithian-2-yl)-(tetrahydropyran-2-yl)methanol 204: *n*-BuLi (1.6 M in hexane, 9.38 ml, 15 mmol) was added at -78°C to a solution of 1,3-dithiane (1.80 g, 15.0 mmol) in THF (100 ml). The mixture was stirred for 30 min. at -30°C, recooled to -50°C and 2-formyltetrahydropyran (**203**, 1.14 g, 10.0 mmol) was added. The mixture was stirred overnight at 0°C. The reaction was quenched by addition of sat. aq. NH_4Cl (100 ml) and the mixture was extracted with *t*BuOMe (3 × 100 ml). The combined organic fractions were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (column dimensions: 25 × 3 cm, EtOAc/PE = 1:4→1:2) afforded **204** (1.64 g, 7.01 mmol, 70%) as a colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz, minor isomer signals in brackets): δ = 1.24-1.76 (m, 4H), 1.88-2.11 (m, 2H),

2.71-2.95 (m, 4H), 3.21-3.84 (m, 3H), 4.22 (4.14) (d, *J* = 5.86 (6.63) Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, minor isomer signals in brackets): δ = 23.2 (22.9), 25.8 (25.8), 25.9 (25.9), 28.1 (28.2), 28.5 (28.8), 48.6 (48.3), 68.5 (68.7), 74.8 (75.2), 76.2 (76.9) ppm. R_f = 0.24 (EtOAc/*n*-hexane = 1:4).

***tert*-Butyldimethylsilyl (1,3-dithian-2-yl)-(tetrahydropyran-2-yl)methyl ether 205**: To a solution of alcohol **204** (1.64 g, 7.00 mmol) and 2,6-lutidine (975 µl, 900 mg, 8.40 mmol) in CH_2Cl_2 (20 ml) was added dropwise at -78°C TBSOTf (1.77 ml, 2.04 g, 7.70 mmol). The mixture was allowed to warm to room temperature and then quenched by addition of sat.aq. NH_4Cl (25 ml). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 25 ml). The combined organic fractions were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (column dimensions: 25 × 3 cm, EtOAc/PE = 1:15) afforded **205** (1.46 g, 4.17 mmol, 60%) and unreacted alcohol **204** (566 mg, 2.41 mmol, 34%) as a colorless oil. The yield based on recovered starting material was therefore 91%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ =0.07 (s, 3H), 0.15 (s, 3H), 0.91 (s, 9H), 1.34-1.58 (m, 4H), 1.68 (m, 1H), 1.86 (m, 2H), 2.06 (m, 1H), 2.78-3.00 (m, 4H), 3.33-3.38 (m, 2H), 3.70 (dd, *J* = 6.25, 2.73 Hz, 1H), 3.96 (m, 1H), 4.26 (d, *J* = 2.74 Hz, 1H) ppm.

(1,3-Dithian-2-yl)-(tetrahydropyran-2-yl)methyl acetate 206: To a solution of alcohol **204** (2.34 g, 10.0 mmol) in pyridine (2.0 ml) was added at 0°C acetyl chloride (1.07 ml, 1.18 g, 15.0 mmol). The mixture was stirred at 0°C for 2 h. The mixture was diluted with 1N aq. HCl (250 ml) and extracted with *t*BuOMe (3 × 150 ml). The combined organic fractions were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (column dimensions: 30 × 3 cm, EtOAc/PE = 1:4) afforded **206** (1.26 g, 4.31 mmol, 43%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz, signals for minor isomer in brackets): δ = 1.30-1.63 (m, 4H), 1.80-2.10 (m, 2H), 2.17 (2.13) (s, 3H), 2.51-2.99 (m, 4H), 3.38-4.26 (m, 3H), 5.25-5.30 (m, 1H) ppm. R_f = 0.63 (EtOAc/*n*-hexane = 1:2).

2-Acetoxy-2-(tetrahydropyran-2-yl)acetaldehyde 202b: To a mixture of dithiane **206** (947 mg, 3.24 mmol), $CaCO_3$ (1.22 g, 12.2 mmol), CH_3CN (14 ml) and H_2O (7 ml) was added MeI (10.1 ml, 23.0 g, 162 mmol). The mixture was stirred overnight at rt. The mixture was concentrated *in vacuo*. The residue was diluted with sat. aq. NH_4Cl (100 ml) and the mixture was extracted with *t*BuOMe (3 × 100 ml). The combined organic fractions were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (column dimensions: 25 × 2 cm, EtOAc/PE = 1:2) afforded **202b** (582 mg, 3.12 mmol, 96%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz, signals for minor isomer in brackets): δ = 1.47-1.67 (m, 6H), 2.24 (2.20) (s, 3H), 3.43 (t, *J* = 11.32 Hz, 1H), (3.74 (td, *J* = 9.76, 3.90 Hz, 1H)), 3.93-4.02 (m, 2H), 5.00 (4.93) (d, *J* = 3.13 (4.30) Hz, 1H), 9.55 (9.60) (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, signals

for minor isomer in brackets): δ = 20.7, 23.0 (22.9), 25.4 (25.6), 27.0 (27.6), 69.1 (68.7), 76.3 (77.1), 79.9 (80.0), 170.3, 197.3 (196.8) ppm. R_f = 0.41 (EtOAc/*n*-hexane = 1:2).

1-Acetoxy-10-(*tert*-butyldimethylsilyl)oxy-5,9-dimethyl-1-(tetrahydropyran-2-yl)deca-2,4,8-triene 207: To chloride **175** (1.21 g, 4.00 mmol) was added tri-*n*-butylphosphine (987 µl, 809 mg, 4.00 mmol) and the mixture was stirred for 3 h at 70°C. The resulting phosphonium salt **182** was dissolved in toluene (30 ml) and the mixture was cooled to 0°C. A solution of aldehyde **202b** (634 mg, 3.40 mmol) in toluene (10 ml) was added, followed by KO*t*Bu (1 M solution in THF, 4.00 ml, 4.00 mmol). The mixture was stirred for 15 min. at 0°C, then diluted with sat. aq. NH_4Cl (100 ml) and extracted with *t*BuOMe (3 × 100 ml). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The product was purified by flash chromatography on a Et_3N-neutralized column (column dimensions: 30 × 2.5 cm, EtOAc/PE = 1:8) to give **207** (1.14 g, 2.62 mmol, 77%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz, values for minor isomer in brackets): δ = 0.05 (s, 6H), 0.90 (s, 9H), 1.46-1.61 (m, 5H), 1.59 (s, 3H), 1.76 (s, 3H), 1.83 (m, 1H), 2.05-2.17 (m, 1H), 2.09 (2.08) (s, 3H), 3.37-3.46 (m, 2H), 3.99 (s, 2H), 4.00-4.04 (m, 1H), 5.28 (5.22) (dd, *J* = 7.81, 5.46 (8.20, 3.51) Hz, 1H), 5.35 (t, *J* = 7.03 Hz, 1H), 5.54 (5.60) (dd, *J* = 15.22, 7.81 (14.83, 8.19) Hz, 1H), 5.82 (5.85) (d, *J* = 10.54 (10.93) Hz, 1H), 6.51 (6.50) (dd, *J* = 15.22, 10.54 (14.83, 10.93) Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, values for major isomer): δ = -5.1, 13.5, 16.9, 18.5, 21.5, 23.1, 23.2, 25.9, 26.0, 26.2, 27.7, 39.6, 68.4, 68.6, 76.8, 78.7, 123.5, 123.8, 125.1, 130.7, 134.4, 140.5, 170.1 ppm. R_f = 0.76 (EtOAc/*n*-hexane = 1:2).

1-Acetoxy-5,9-dimethyl-10-hydroxy-1-(tetrahydropyran-2-yl)deca-2,4,8-triene 208: To a solution of TBS ether **207** (932 mg, 2.13 mmol) and AcOH (306 µl, 320 mg, 5.34 mmol) in THF (35 ml) was added TBAF•$3H_2O$ (1.01 g, 3.20 mmol). The mixture was stirred for 17 h at rt, then diluted with sat. aq. NH_4Cl (100 ml) and extracted with *t*BuOMe (3 × 100 ml). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The product was purified by flash chromatography on a Et_3N-neutralized column (column dimensions: 30 × 2.5 cm, EtOAc/PE = 2:3) to give **208** (502 mg, 1.56 mmol, 73%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz, values for minor isomer in brackets): δ = 1.32-1.40 (m, 1H), 1.41-1.62 (m, 4H), 1.66 (s, 3H), 1.77 (s, 3H), 1.79-1.87 (m, 1H), 2.09 (2.08) (s, 3H), 2.09-2.18 (m, 4H), 3.37-3.48 (m, 2H), 3.97 (s, 2H), 4.00-4.04 (m, 1H), 5.28 (5.22) (dd, *J* = 7.86, 5.49 (8.05, 3.84) Hz, 1H), 5.38 (t, *J* = 6.22 Hz, 1H), 5.60 (5.55) (dd, *J* = 14.82, 7.87 (15.00, 8.05) Hz, 1H), 5.82 (5.86) (d, *J* = 10.98 Hz, 1H), 6.51 (6.50) (dd, *J* = 14.82, 10.98 (15.00, 10.98) Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, values for minor isomer in brackets): δ = 13.6 (13.6), 16.7 (16.5), 21.3 (21.3), 23.2 (23.0), 25.7 (25.7), 25.9, 27.6 (27.2), 39.4 (39.7), 68.4, 68.5 (68.6), 72.2 (72.1), 76.6 (77.1), 78.6 (78.7), 123.7 (123.7), 124.8 (124.6), 125.1 (124.9), 130.6 (131.1), 134.9, 140.2 (140.1), 170.1 (170.0) ppm. R_f = 0.26 (EtOAc/*n*-hexane = 1:2).

1-Acetoxy-10-chloro-5,9-dimethyl-1-(tetrahydropyran-2-yl)deca-2,4,8-triene 209: To a solution of NCS (73 mg, 0.55 mmol) in CH_2Cl_2 (5 ml) was added at -10°C Me_2S (44 µl, 37 mg, 0.60 mmol). The mixture was stirred for 10 min. at -10°C, and the resulting white suspension was cooled to -78°C. Alcohol **208** (161 mg, 0.50 mmol) was added and the mixture was stirred for 1 h at -10°C. The reaction was quenched by addition of sat. aq. NH_4Cl (5 ml). After dilution with *t*BuOMe (30 ml) and H_2O (15 ml), the phases were separated and the porganic phase was washed with brine (20 ml), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The product was purified by flash chromatography (column dimensions: 20 × 2 cm, EtOAc/PE = 1:6) to give **209** (147 mg, 0.427 mmol, 86%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz, values for minor isomer in brackets): δ = 1.31-1.40 (m, 1H), 1.42-1.60 (m, 4H), 1.73 (s, 3H), 1.76 (s, 3H), 1.79-1.87 (m, 1H), 2.09 (2.08) (s, 3H), 2.11-2.20 (m,4H), 3.21-3.48 (m, 2H), 4.01 (s, 2H), 4.01-4.04 (m, 1H), 5.28 (5.22) (dd, *J* = 8.19, 5.47 (8.19, 3.90) Hz, 1H), 5.50 (t, *J* = 6.64 Hz, 1H), 5.56 (5.62) (dd, *J* = 15.22, 8.20 (15.22, 8.19) Hz, 1H), 5.82 (5.84) (d, *J* = 10.93 Hz, 1H), 6.50 (6.49) (dd, *J* = 15.22, 10.93 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, values for minor isomer in brackets): δ = 14.2, 16.9 (16.6), 21.4 (21.5), 23.1 (23.2), 25.8 (25.9), 26.4, 27.7 (27.4), 39.1, 52.4, 68.6 (68.7), 77.1 (76.7), 78.7 (78.8), 124.0 (124.1), 125.4 (124.9), 129.9 (129.9), 130.5 (131.1), 131.8, 139.7 (139.6), 170.1 (170.0) ppm. R_f = 0.72 (EtOAc/*n*-hexane = 1:2).

11-Acetoxy-1-[(2*R*,6*R*)-2-isopropoxy-5,6-dihydro-2*H*-pyran-6-yl]-3,7-dimethyl-11-(tetra-hydropyran-2-yl)undeca-1,3,7,9-tetraene 211: To chloride **209** (345 mg, 1.00 mmol) was added tri-*n*-butylphosphine (296 µl, 243 mg, 1.20 mmol) and the mixture was stirred for 3 h at 70°C. The resulting phosphonium salt **210** was dissolved in toluene (10 ml) and the mixture was cooled to 0°C. Aldehyde **30** (255 mg, 1.50 mmol) was added, followed by KO*t*Bu (1 M solution in THF, 1.50 ml, 1.50 mmol). The mixture was stirred for 15 min. at 0°C, then diluted with sat. aq. NH_4Cl (100 ml) and extracted with *t*BuOMe (3 × 50 ml). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The product was purified by flash chromatography on a Et_3N-neutralized column (column dimensions: 25 × 2 cm, EtOAc/PE = 1:4) to give **211** (353 mg, 0.770 mmol, 77%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz, values for minor isomer in brackets): δ = 1.18 (d, *J* = 6.25 Hz, 3H), 1.24 (d, *J* = 6.25 Hz, 1H), 1.34-1.52 (m, 5H), 1.75 (s, 3H), 1.76 (s, 3H), 1.84-1.87 (m, 1H), 2.01-2.17 (m, 4H), 2.10 (2.09) (s, 3H) 2.24-2.28 (m, 4H), 3.40-3.47 (m, 2H), 3.98-4.05 (m, 3H), 4.47 (m, 1H), 5.12 (s, 1H), 5.28 (5.22) (dd, *J* = 7.80, 5.46 (8.20, 3.90) Hz, 1H), 5.47 (t, *J* = 6.64 Hz, 1H), 5.56 (5.61) (dd, *J* = 15.22, 7.80 (15.22, 8.20) Hz, 1H), 5.60 (dd, *J* = 15.61, 6.63 Hz, 1H), 5.72 (m, 1H), 5.83 (5.86) (d, *J* = 10.93 Hz, 1H), 5.96-5.6.02 (m, 1H), 6.27 (d, *J* = 15.61 Hz, 1H), 6.51 (6.50) (dd, *J* = 15.22, 10.93 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, values for major isomer): δ = 12.4, 16.9, 21.4, 22.1, 23.2, 24.0, 25.8, 26.7, 27.7, 31.0, 39.5, 66.9, 68.7, 69.3, 77.2, 78.7, 93.0, 123.8, 125.3, 125.9, 126.3, 128.3, 130.6, 132.3, 133.1, 135.7, 140.1, 170.1 ppm. R_f = 0.37 (EtOAc/*n*-hexane = 1:4).

11-Hydroxy-1-[(2*R*,6*R*)-2-isopropoxy-5,6-dihydro-2*H*-pyran-6-yl]-3,7-dimethyl-11-(tetra-hydropyran-2-yl)undeca-1,3,7,9-tetraene 211a: To a solution of acetate **211** (26.8 mg, 0.058 mmol) in MeOH (1 ml) was added K_2CO_3 (7.7 mg, 0.056 mmol) and the mixture was stirred overnight at rt. The mixture was diluted with sat. aq. NH_4Cl (25 ml) and brine (25 ml), and extracted with *t*BuOMe (3 × 25 ml). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The product was purified by flash chromatography on a Et_3N-neutralized column (column dimensions: 25 × 2 cm, EtOAc/PE = 1:4) to give **211a** (353 mg, 0.770 mmol, 77%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz, values for minor isomer in brackets): δ = 1.18 (d, *J* = 6.25 Hz, 3H), 1.19-1.32 (m, 1H), 1.24 (d, *J* = 6.25 Hz, 1H), 1.41-1.60 (m, 4H), 1.75 (s, 3H), 1.76 (s, 3H), 1.82-1.85 (m, 1H), 2.00-2.17 (m, 4H), 2.21-2.28 (m, 2H), 2.29, (bs, 1H, O<u>H</u>), 3.16 (dd, *J* = 10.93, 7.42 Hz, 1H), 3.37-3.49 (m, 2H), 3.95-4.06 (m, 2H), 4.42-4.50 (m, 1H), 5.11 (s, 1H), 5.48 (m, 1H), 5.59 (5.60) (dd, *J* = 15.61, 6.63 (14.83, 6.63) Hz, 1H), 5.70-5.73 (m, 1H), 5.84 (5.85) (d, *J* = 10.92 Hz, 1H), 5.95-6.02 (m, 1H), 6.27 (d, *J* = 15.61 Hz, 1H), 6.51 (6.50) (dd, *J* = 15.22, 10.92 Hz, 1H) ppm. R_f = 0.56 (EtOAc/*n*-hexane = 1:2).

11-Acetoxy-1-[(2*R*,6*R*)-2-hydroxy-5,6-dihydro-2*H*-pyran-6-yl]-3,7-dimethyl-11-(tetrahydropyran-2-yl)undeca-1,3,7,9-tetraene 212: To a solution of **211** (20.6 mg, 0.045 mmol) in acetone (3 ml) was added a solution of PPTS (10.8 mg, 0.043 mmol) in H_2O (0.5 ml). The mixture was stirred for 16.5 h at rt. The mixture was diluted with sat. aq. $NaHCO_3$ (25 ml) and brine (25 ml) and extracted with *t*BuOMe (3 × 25 ml). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give **212** (20.2 mg, 0.046 mmol, quant.), which was used in following steps without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz, values for minor isomer in brackets): δ = 1.31-1.44 (m, 1H), 1.46-1.57 (m, 4H), 1.75 (s, 3H), 1.76 (s, 3H), 1.78-1.87 (m, 1H), 2.02-2.20 (m, 4H), 2.22-2.29 (m, 2H), 3.38-3.47 (m, 2H), 4.03 (m, 1H), 4.52 (ddd, *J* = 10.54, 6.44, 3.90 Hz, 1H), 5.28 (5.22) (dd, *J* = 7.80, 4.10 (7.80, 5.66) Hz, 1H), 5.44 (s, 1H), 5.48 (t, *J* = 6.44 Hz, 1H), 5.56 (5.64) (dd, *J* = 15.22, 7.81 (14.83, 8.20) Hz, 1H)), 5.60 (dd, *J* = 15.80, 6.44 Hz, 1H), 5.79-5.87 (m, 2H), 6.04-6.07 (m, 1H), 6.31 (d, *J* = 15.80 Hz, 1H), 6.51 (6.50) (dd, *J* = 15.41, 10.73 (14.83, 10.53) Hz, 1H) ppm. R_f = 0.31 (EtOAc/*n*-hexane = 1:2).

Tris TBS ether 214: To chloride **175** (168 mg, 0.555 mmol) was added tri-*n*-butylphosphine (137 µl, 112 mg, 0.555 mmol) and the mixture was stirred for 3 h at 70°C. The resulting phosphonium salt **182** was dissolved in toluene (5 ml) and the mixture was cooled to 0°C. Aldehyde **108** (108 mg, 0.244 mmol) was added, followed by KO*t*Bu (1 M solution in THF, 600 µl, 0.600 mmol). The mixture was stirred for 15 min. at 0°C, then diluted with sat. aq. NH_4Cl (25 ml) and extracted with *t*BuOMe (3 × 25 ml). The combined

organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The product was purified by flash chromatography on a Et_3N-neutralized column (column dimensions: 25 × 2 cm, EtOAc/PE = 1:20) to give **215** (111 mg, 0.159 mmol, 65%) as a colorless oil. $[\alpha]^{23}_D$ = -10.4° (c = 0.89, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.04 (s, 6H), 0.05 (s, 6H), 0.06 (s, 3H), 0.09 (s, 3H), 0.84 (d, *J* = 7.03 Hz, 3H), 0.88 (s, 9H), 0.90 (s, 9H), 0.92 (s, 9H), 1.52-1.63 (m, 2H), 1.59 (s, 3H), 1.70 (d, *J* = 6.64 Hz, 3H), 1.70-1.78 (m, 1H), 1.74 (s, 3H), 2.08 (m, 2H), 2.16 (m, 2H), 3.21 (m, 1H), 3.81-3.84, (m, 2H), 4.00 (s, 2H), (dd, *J* = 5.47, 5.08 Hz, 1H), 5.37 (m, 1H), 5.43 (ddq, *J* = 15.22, 5.47, 1.56 Hz, 1H), 5.58 (dqd, *J* = 15.22, 6.64, 1.17 Hz, 1H), 5.62-5.68 (m, 1H), 5.83 (d, *J* = 10.93 Hz, 1H), 6.46 (ddd, *J* = 14.83, 10.53, 1.17 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = -5.1, -4.5, -4.4, -4.3, -4.2, 5.6, 13.6, 16.7, 18.0, 18.3, 18.4, 18.6, 25.9, 26.0, 26.1, 29.8, 39.7, 40.6, 68.6, 71.8, 75.1, 79.2, 79.8, 123.8, 124.2, 125.6, 126.5 130.3, 131.3, 134.4, 137.9 ppm. R_f = 0.39 (EtOAc/*n*-hexane = 1:20).

TES ether 215: To chloride **174** (1.818 g, 6.00 mmol) was added tri-*n*-butylphosphine (1.628 ml, 1.335 g, 6.60 mmol) and the mixture was stirred for 3 h at 70°C. The resulting phosphonium salt **181** was dissolved in toluene (60 ml) and the mixture was cooled to 0°C. Aldehyde **108** (1.800 g, 4.07 mmol) was added, followed by KO*t*Bu (1 M solution in THF, 6.50 ml, 6.50 mmol). The mixture was stirred for 15 min. at 0°C, then diluted with sat. aq. NH_4Cl (200 ml) and extracted with *t*BuOMe (3 × 150 ml). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The product was purified by flash chromatography on a Et_3N-neutralized column (column dimensions: 30 × 4 cm, EtOAc/PE = 1:40) to give **215** (2.830 g, 4.08 mmol, 100%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.04 (s, 6+3H), 0.09 (s, 3H), 0.61 (q, *J* = 7.81 Hz, 6H), 0.84 (d, *J* = 6.64 Hz, 3H), 0.88 (s, 9H), 0.92 (s, 9H), 0.96 (t, *J* = 7.81 Hz, 9H), 1.57 (m, 2H), 1.61 (s, 3H) 1.70 (d, *J* = 6.25 Hz, 3H), 1.75 (s, 3H), 2.03 (m, 1H), 2.09 (m, 2H), 2.15 (m, 2H), 3.23 (ddd, *J* = 10.54, 4.29, 3.51 Hz, 1H), 3.81-3.86 (m, 2H), 4.00 (s, 2H), 4.26 (m, 1H), 5.32-5.47 (m, 2H), 5.56-5.70 (m, 2H), 5.84 (d, *J* = 10.93 Hz, 1H), 6.47 (ddd, *J* = 15.22, 10.93, 1.56 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = -4.7, -4.63, -4.57, -4.46, 4.45, 5.5, 13.5, 16.6, 17.9, 18.1, 18.3, 25.8, 25.9, 26.0, 29.7, 39.5, 40.5, 68.3, 71.8, 75.1, 79.2, 79.9, 124.2, 124.3, 125.7, 126.7, 130.4, 131.4, 134.5, 138.1 ppm. R_f = 0.47 (EtOAc/*n*-hexane = 1:20).

Alcohol 216: To a solution of TES ether **215** (2.409 g, 3.47 mmol) in MeOH (40 ml) was added PPTS (437 mg, 1.74 mmol) and the mixture was stirred for 4 h at rt. The mixture was diluted with sat. aq. $NaHCO_3$ (100 ml) and brine (200 ml) and extracted with *t*BuOMe (3 × 200 ml). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The product was purified by flash chromatography on a Et_3N-neutralized column (column dimensions: 30 × 4 cm, EtOAc/PE = 1:6) to give **216** (1.375 g, 2.37 mmol, 68%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.04 (s, 6+3H), 0.09 (s, 3H), 0.84 (d, *J* = 7.03 Hz, 3H), 0.88 (s, 9H), 0.92 (s, 9H), 1.54-1.64 (m, 2H), 1.67 (s, 3H) 1.70 (d, *J* = 6.64

Hz, 3H), 1.75 (s, 3H), 2.01 (m, 1H), 2.10 (m, 2H), 2.17 (m, 2H), 3.23 (m, 1H), 3.81-3.86 (m, 2H), 3.99 (s, 2H), 4.26 (t, *J* = 4.69 Hz, 1H), 5.38-5.47 (m, 2H), 5.57-5.70 (m, 2H), 5.84 (d, *J* = 10.92 Hz, 1H), 6.47 (ddd, *J* = 15.22, 10.93, 1.57 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = −4.8, -4.7, -4.6, -4.5, 5.7, 6.6, 13.6, 16.5, 17.8, 18.1, 18.2, 25.76, 25.83, 26.0, 26.9, 29.7, 39.4, 40.4, 68.7, 71.8, 75.0, 79.2, 79.8, 124.4, 125.5, 125.7, 126.6, 130.4, 131.5, 135.0, 137.8 ppm. R_f = 0.33 (EtOAc/*n*-hexane = 1:4).

Chloride 217: To a solution of NCS (413 mg, 3.09 mmol) in CH_2Cl_2 (30 ml) was added at -10°C Me_2S (246 µl, 210 mg, 3.38 mmol). The mixture was stirred for 10 min. at -10°C, and the resulting white suspension was cooled to -78°C. Alcohol **216** (1.084 g, 1.87 mmol) was added and the mixture was stirred for 1 h at -10°C. After dilution with sat. aq. NH_4Cl (150 ml), the mixture was extracted with CH_2Cl_2 (3 × 100 ml). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The product, which was estimated >90% pure by ^{1}H NMR, was used in the next step without further purification, since flash chromatography under various conditions resulted in significant loss of material. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.04 (s, 6+3H), 0.09 (s, 3H), 0.84 (d, *J* = 7.03 Hz, 3H), 0.88 (s, 9H), 0.92 (s, 9H), 1.56 (m, 2H), 1.70 (d, *J* = 6.64 Hz, 3H), 1.74 (bs, 3+3H), 2.10 (m, 2H), 2.17 (m, 2H), 3.22 (m, 1H), 3.81-3.86 (m, 2H), 4.01 (s, 2H), 4.26 (t, *J* = 4.69 Hz, 1H), 5.43 (ddq, *J* = 15.22, 5.46, 1.57 Hz, 1H), 5.51 (t, *J* = 7.03 Hz, 1H), 5.58-5.69 (m, 2H), 5.83 (d, *J* = 10.93 Hz, 1H), 6.46 (ddd, *J* = 15.22, 10.93, 1.57 Hz, 1H) ppm. R_f = 0.77 (EtOAc/*n*-hexane = 1:4).

Tetraene 219: To chloride **217** (max. 1.87 mmol) was added tri-*n*-butylphosphine (508 µl, 417 mg, 2.06 mmol) and the mixture was stirred for 3 h at 70°C. The resulting phosphonium salt **218** was dissolved in toluene (20 ml) and the mixture was cooled to 0°C. Aldehyde **30** (426 mg, 2.50 mmol) was added, followed by KO*t*Bu (1 M solution in THF, 5.00 ml, 5.00 mmol). The mixture was stirred for 15 min. at 0°C, then diluted with sat. aq. NH_4Cl (150 ml) and extracted with *t*BuOMe (3 × 100 ml). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The product was purified by flash chromatography on a Et_3N-neutralized column (column dimensions: 30 × 3 cm, EtOAc/PE = 1:10) to give **219** (1.127 g, 1.58 mmol, 84% over three steps) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.04 (s, 6+3H), 0.09 (s, 3H), 0.84 (d, *J* = 6.64 Hz, 3H), 0.88 (s, 9H), 0.92 (s, 9H), 1.18 (d, *J* = 5.86 Hz, 3H), 1.24 (d, *J* = 6.25 Hz, 3H), 1.56 (m, 2H), 1.70 (d, *J* = 6.25 Hz, 3H), 1.75 (bs, 3+3H), 2.00-2.31 (m, 6H), 3.22 (m, 1H), 3.81-3.86 (m, 2H), 4.01 (m, 1H), 4.26 (dd, *J* = 5.08, 4.68 Hz, 1H), 4.48 (m, 1H), 5.12 (s, 1H), 5.41-5.53 (m, 2H), 5.57-5.74 (m, 4H), 5.84 (m, 1H), 6.00 (m, 1H), 6.28 (d, *J* = 15.61 Hz, 1H), 6.47 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = -4.73, -4.65, -4.59, -4.46, 5.4, 12.3, 16.6, 17.9, 18.1, 18.2, 22.0, 23.9, 25.8, 25.9, 26.7, 29.7, 30.9, 39.4, 40.4, 66.9, 69.3, 71.8, 75.0, 79.2, 79.8, 93.0, 124.4, 125.7, 126.0, 126.4, 126.6, 128.5, 130.4, 131.6, 132.7, 133.2, 135.9, 137.7 ppm. R_f = 0.65 (EtOAc/*n*-hexane = 1:4).

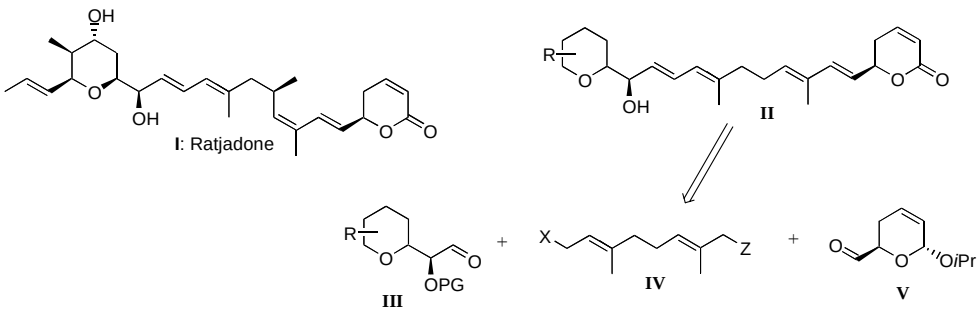
Hemiacetal 220: To a solution of isopropyl acetal **219** (143 mg, 0.20 mmol) in acetone (18 ml) was added a solution of PPTS (50 mg, 0.20 mmol) in H_2O (3 ml). The mixture was stirred overnight at rt. The mixture was diluted with sat. aq. $NaHCO_3$ (50 ml) and brine (100 ml) and extracted with *t*BuOMe (3 × 100 ml). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give crude **220** (133 mg, 0.197 mmol, 99%) as a colorless oil, that was used immediately in subsequent oxidation experiments without further purification. R_f = 0.30 (EtOAc/*n*-hexane = 1:4).

5.7 References

1. Bhatt, U.; Christmann, M.; Quitschalle, M.; Claus, E.; Kalesse, M. *J. Org. Chem.* **2001**, *66*, 1885-1893.
2. Christmann, M.; Bhatt, U.; Quitschalle, M.; Claus, E.; Kalesse, M. *Angew.Chem.* **2000**, *112*, 4535-4538; *Angew. Chem. Int. Ed.* **2000**, *39*, 4364-4366.
3. Williams, D.R.; Ihle, D.C.; Plummer, S.V. *Org. Lett.* **2001**, *3*, 1383-1386.
4. Kalesse, M.; Christmann, M.; Bhatt, U.; Quitschalle, M.; Claus, E.; Saeed, A.; Burzlaff, A.; Kasper, C.; Haustedt, L.O.; Hofer, E.; Scheper, T.; Beil, W. *Chembiochem* **2001**, *2*, 709-714.
5. Mancuso, A.J.; Swern, D. *Synthesis* **1981**, 165-196.
6. Stork, G.; Zhao *Tetrahedron Lett.* **1989**, *30*, 287-290.
7. Dess, D.B.; Martin, J.C. *J. Org. Chem.* **1983**, *48*, 4155-4156.
8. Corey, E.J.; Kim, C.U.; Takeda, M. *Tetrahedron Lett.* **1972**, *13*, 4339-4342.
9. Tsubuki, M.; Kanai, K.; Honda, T. *Heterocycles* **1993**, *35*, 281-288.

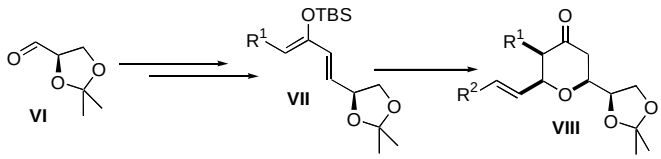
Summary

This thesis describes the development of a flexible synthesis of analogues of the cytotoxic polyketide natural product ratjadone (**I**). The synthesis features combination of three building blocks of comparable size. The retrosynthetic analysis is shown in Scheme I. Ratjadone analogues **II** are to be formed by Wittig connection of two aldehyde fragments (tetrahydropyran fragment **III** and protected lactone fragment **V**) to a central terpene-derived fragment **IV**.



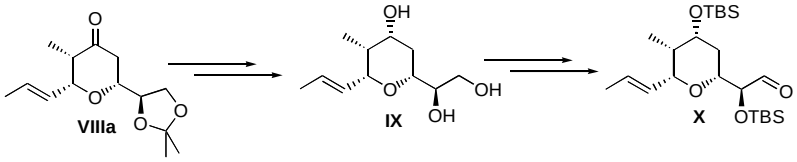
Scheme I. Retrosynthetic analysis of ratjadone analogues.

Fragments **III** were synthesized by a newly developed diene-controlled asymmetric hetero Diels-Alder reaction. Aldehyde **VI** (derived from the sugar mannitol) is the sole source of chirality in the synthesis of these compounds. It is used to construct silyloxydienes **VII**, which reacted efficiently with α,β-unsaturated aldehydes to give, after desilylation, tetrahydropyran-4-ones **VIII** (Scheme II). Typically, only the two isomers with all-*cis* configuration on the ring were formed. The yields of the latter two steps varied from 69-85%, and the diastereoselectivities varied from 1.6:1 to 10:1.



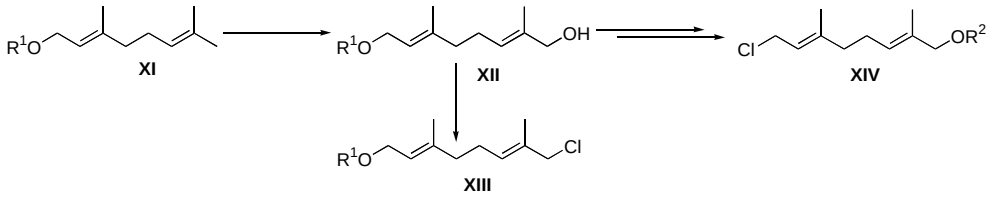
Scheme II. Synthesis of compounds **VIII** *via* hetero Diels-Alder reaction.

Ketone **VIIIa** was then converted in five steps to the adequately protected aldehyde **X**, which was to be used in further steps (Scheme III). The absolute stereochemistry is different from that in the natural product, but this was considered of minor importance with respect to the effiency in rapid diversity generation.



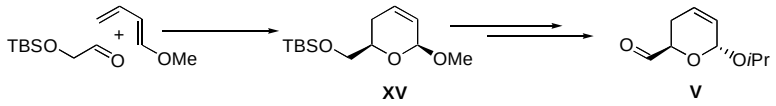
Scheme III. Synthesis of building block **X**.

α,ω-Bifunctionalized terpene derivatives **IV** were synthesized from protected geraniol or nerol by catalytic SeO_2 oxidation. The resulting free alcohol could be activated by conversion to the chloride by Corey-Kim reaction. Alternatively, by protective group manipulations, C1 could be activated (Scheme IV).



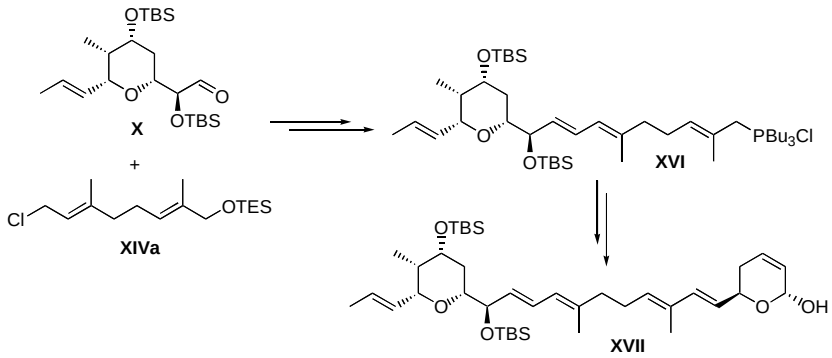
Scheme IV. Synthesis of bifunctionalized terpenoid building blocks.

Lactone fragment **V** was synthesized by making use of Jacobsen's catalytic asymmetric hetero Diels-Alder methodology. Protective group manipulations followed by oxidation afforded desired aldehyde **V** (Scheme V).



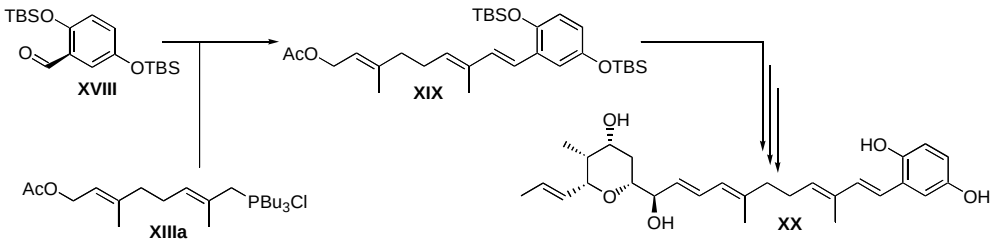
Scheme V. Synthesis of fragment **V**.

The fragments were successfully combined using a standard reaction sequence (deprotection – activation – phosphonium salt formation – Wittig reaction). Although the acetal function at C1 could be hydrolyzed, oxidation to the desired lactone was unsuccessful under a variety of conditions (Scheme VI).



Scheme VI. Connection of fragments **X**, **XIVa**, and **V**.

A (hydro)quinone was considered a reasonable alternative to the lactone ring, and hydroquinone-containing ratjadone analogue **XX** was obtained using a similar strategy as above (Scheme VII).

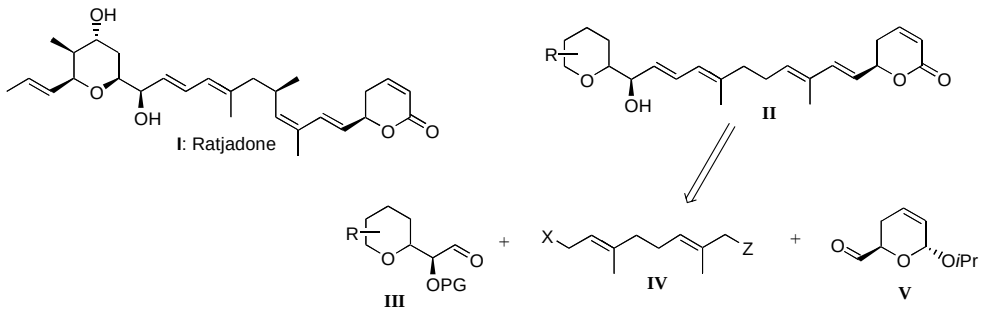


Scheme VII. Synthesis of compound XX.

Samenvatting

(Ontwerp en Synthese van Ratjadon-Analoga)

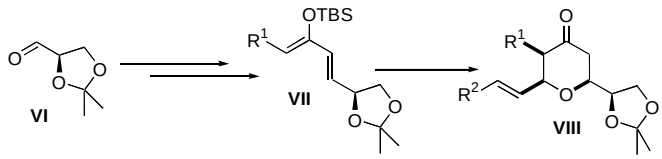
Dit proefschrift beschrijft de ontwikkeling van een flexibele synthese van analoga van de cytotoxische polyketide natuurstof ratjadon (**I**). Uitgangspunt van de synthese is de combinatie van drie bouwstenen van vergelijkbare grootte. De retrosynthetische analyse is weergegeven in Schema I. Ratjadon-analoga **II** zullen worden gevormd door Wittig reactie van twee aldehyde fragmenten (tetrahydropyran-fragment **III** en beschermd lacton-fragment **V**) met een centraal terpenoïde fragment **IV**.



Schema I. Retrosynthetische analyse van ratjadon-analoga.

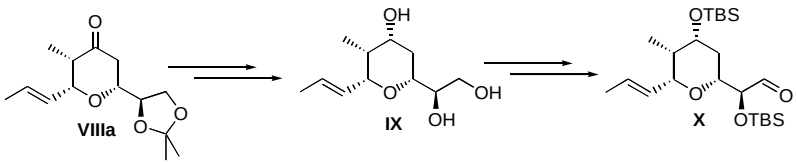
Fragmenten **III** werden gesynthetiseerd door middel van een nieuw ontwikkelde diëen-gecontrolleerde asymmetrische hetero-Diels-Alder reactie. Aldehyde **VI** (afgeleid van de suiker mannitol) is de enige bron van chiraliteit in de synthese van deze verbindingen. Het werd gebruikt voor de bereiding van silyloxydiënen **VII**, die efficiënt reageerden met α,β-onverzadigde aldehydes, leidend tot tetrahydropyran-4-onen **VIII** (Schema II). In het algemeen werden alleen de twee isomeren met de allen-*cis* configuratie op de ring

gevormd. De opbrengst van de laatste twee stappen varieerde van 69-85% en de diastereoselectiviteit varieerde van 1.6:1 tot 10:1.



Schema II. Synthese van verbindingen **VIII** d.m.v. hetero-Diels-Alder reactie.

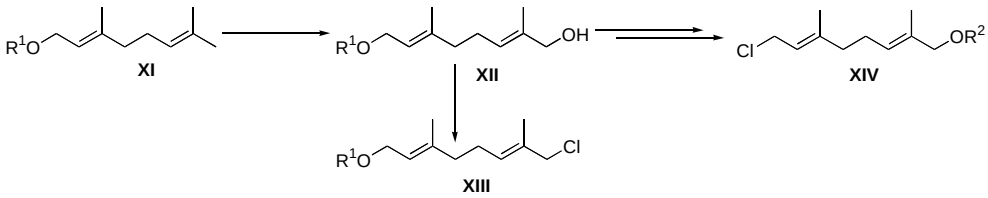
Keton **VIIIa** werd toen in vijf stappen omgezet naar het geschikt beschermde aldehyde **X**, dat verder in de synthese gebruikt zou worden (Schema III). De absolute stereochemie verschilt van die in de natuurstof, maar dit werd van ondergeschikt belang geacht met betrekking tot de efficiëntie van de snelle diversiteitsontwikkeling.



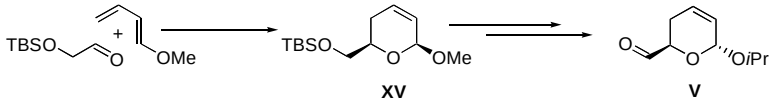
Schema III. Synthese van bouwsteen **X**.

α,ω-Gebifunctionaliseerde terpeen-derivaten **IV** werden gesynthetiseerd vanuit beschermd geraniol of nerol door catalytische SeO_2-oxidatie. De daaruit verkregen vrije alcohol kon worden geactiveerd door omzetting in het chloride door Corey-Kim-reactie. Tevens kon door beschermgroepmanipulaties C1 worden geactiveerd (Schema IV).

Lacton-fragment **V** werd gesynthetiseerd door gebruik te maken van Jacobsen's catalytische asymmetrische hetero-Diels-Alder methodologie. Beschermgroepmanipulaties gevolgd door oxidatie leverden het gewenste aldehyde **V** op (Schema V).

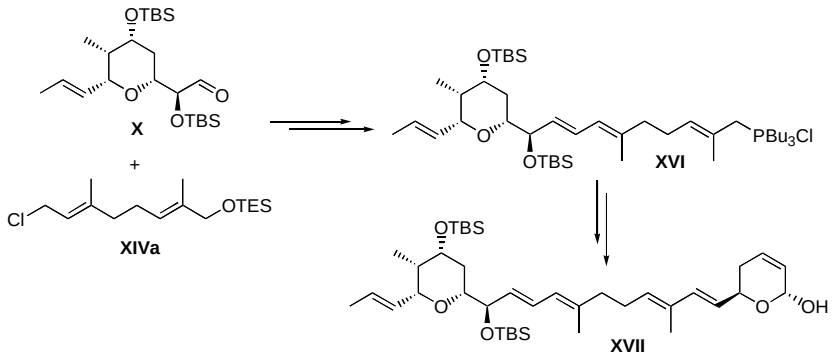


Schema IV. Synthese van gebifunctionaliseerde terpenoïde bouwstenen.



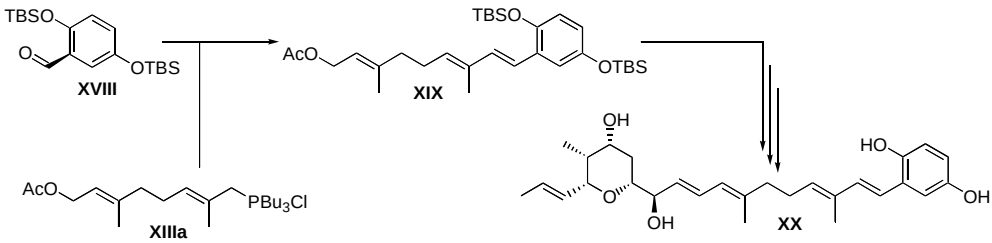
Schema V. Synthese van fragment **V**.

De fragmenten werden op succesvolle wijze aan elkaar bevestigd door middel van een standaard reactie-sequentie (ontscherming – activering – fosfoniumzoutvorming – Wittig reactie). Hoewel de acetaal-functie op C1 kon worden gehydrolyseerd, was oxidatie tot het gewenste lacton onder verschillende omstandigheden niet succesvol (Schema VI).



Schema VI. Verbinding van fragmenten **X**, **XIVa** en **V**.

Een (hydro)quinon werd beschouwd als een redelijk alternatief voor de lactonring en hydroquinon-bevattend ratjadon-analogon **XX** werd verkregen via een soortgelijke strategie als hierboven (Schema VII).

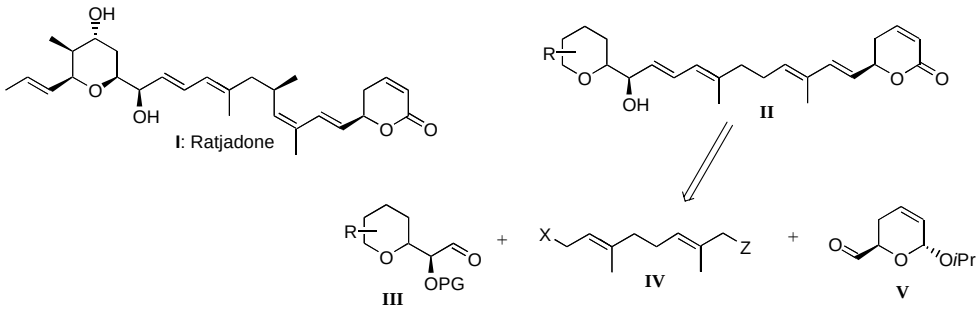


Schema VII. Synthese van verbinding **XX**.

Zusammenfassung

(Entwurf und Synthese von Ratjadon-Analoga)

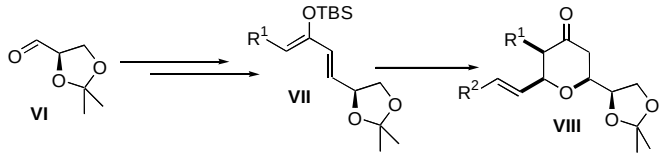
Die vorliegende Dissertationsschrift beschreibt die Entwicklung einer flexiblen Synthese von Analoga des cytotoxischen Polyketid-Naturstoffs Ratjadon (**I**). Ausgangspunkt der Synthese ist die Kombination von drie Bausteine vergleichbarer Größe. Die retrosynthetische Analyse ist in Schema I dargestellt. Ratjadon-Analoga **II** sind hierbei durch eine Wittig Reaktion von zwei Aldehyd-Fragmente (Tetrahydropyran-Fragment **III** und geschütztes Lacton-Fragment **V**) mit einem zentralen Terpenoid-Fragment **IV** zugänglich.



Schema I. Retrosynthetische Analyse von Ratjadon-Analoga.

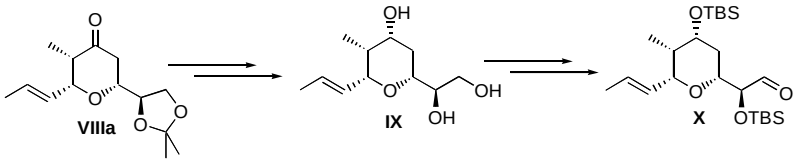
Fragmente **III** wurden mittels eine neu entwickelte Dien-kontrollierten asymmetrischen hetero-Diels-Alder-Reaktion hergestellt. Aldehyd **VI** (abgeleitet von D-Mannit) ist die einzige chiral-Pool-Quelle in der vorgestellten Synthese von Ratjadon-Analoga. Er dient als Ausgangsstoff für die Darstellung der Silyloxydiene **VII**, die ausgezeichnet mit α,β-ungesättigten Aldehyden zu Tetrahydropyran-4-onen **VIII** (Schema II) reagieren. Als

Produkte wurden ausschließlich die Isomere mit *cis*-Konfiguration am Ring gebildet. Die Ausbeuten der letzten beiden Schritte variierten von 69-85% und die Diastereoselektivität zeigte Verhältnisse von 1.6:1 bis 10:1.



Schema II. Synthese von Verbindungen **VIII** mittels hetero-Diels-Alder-Reaktion.

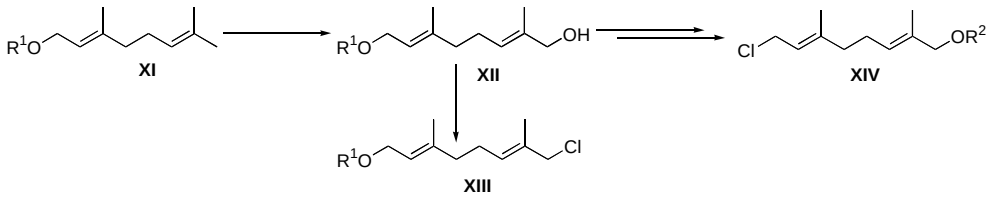
Keton **VIIIa** wurde in fünf Schritten in den geschützten Aldehyd **X** überführt, welcher im weiteren Syntheseverlauf eingesetzt wurde (Schema III). Die absolute Stereochemie unterscheidet sich zwar von der des Naturstoffs, dieser Aspekt kann jedoch im Hinblick auf die Effiziens und Variabilität der Synthese vernachlässigt werden.



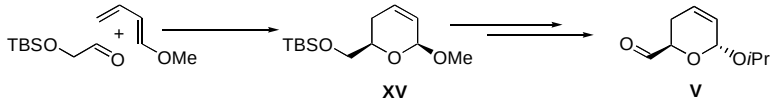
Schema III. Synthese von Baustein **X**.

Mittels SeO_2-Oxidation gelangt man ausgehend von Nerol oder Geraniol zum α,ω-bifunktionalisierten Terpen-Derivat **IV**. Der daraus erhaltene freie Alkohol wurde in einer Corey-Kim-Reaktion in das entsprechende Chlorid überführt. Zusätzlich konnte C1 durch Schutzgruppenmanipulationen aktiviert werden (Schema IV).

Das Lacton-Fragment **V** wurde durch Anwendung der Jacobsen's asymmetrischen hetero-Diels-Alder-Methodologie synthetisiert. Schutzgruppenoperationen und anschließende Oxidation liefern den gewünschten Aldehyd **V** (Schema V).

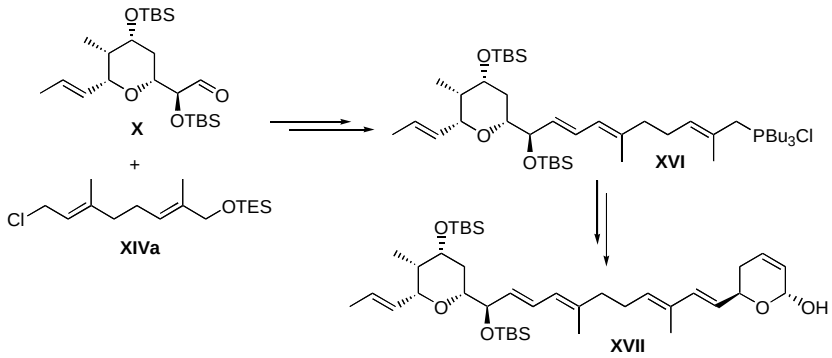


Schema IV. Synthese von bifunktionalisierten Terpenoid-Bausteinen.



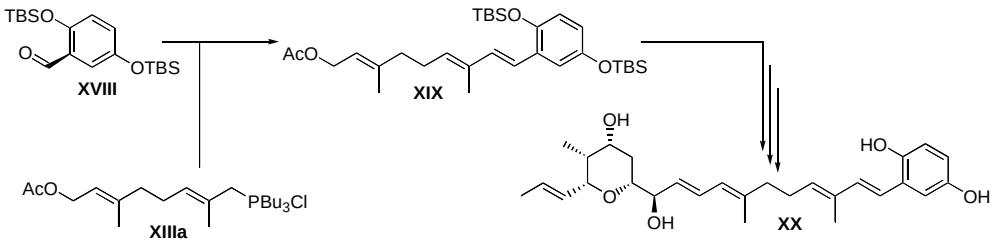
Schema V. Synthese von Fragment **V**.

Die erhaltenen Fragmente wurden abschließend erfolgreich mittels einer Standard-Reaktionssequenz (Entschützung – Aktivierung – Phosphoniumsalzbildung – Wittig-Reaktion) verknüpft. Obwohl die Acetal-Funktion an C1 hydrolysiert werden konnte, war die Oxidation zum gewünschten Lacton unter verschiedene Bedingungen nicht erfolgreich (Schema VI).



Schema VI. Verknüpfung von Fragmenten **X**, **XIVa** und **V**.

(Hydro-)Chinone können weitläufig als Strukturanaloga des Lactonringes betrachtet werden. Ein Ratjadon-Analogon (**XX)** mit einem Chinon anstelle des Lactonringes konnte ebenfalls durch eine ähnliche Strategie wie oben (Schema VII) erfolgreich synthetisiert werden.



Schema VII. Synthese von Verbindung **XX**.

Acknowledgements, Dankwoord, Danksagung

„Wissenschaft und Kunst gehören der Welt an,
und vor ihnen verschwinden die Schranken der Nationalität“

- Johann Wolfgang von Goethe -

De wetenschap is grenzenloos – dat is mij wel duidelijk geworden tijdens het grote avontuur dat mijn promotie-onderzoek is geworden. Hier heb ik dan de gelegenheid om de mensen die mij op deze reis hebben begeleid te bedanken.

Allereerst ben ik natuurlijk mijn promotor dank verschuldigd. Ludger, mein Doktorvater (so ein schönes deutsches Wort), ich möchte Dir recht herzlich danken, daß Du mir die Möglichkeit gegeben hast an so einem anregenden Thema zu arbeiten. Ich danke Dir auch für das Vertrauen und die Verantwortlichkeit die Du mir gegeben hast.
Ook zou ik natuurlijk mijn co-promotor willen bedanken. Romano, al hebben we niet lang nauw samengewerkt, ik heb het contact met jou altijd als zeer aangenaam ervaren. Ik heb jou, net als je groep, de afgelopen jaren zien groeien en ik geloof zeker dat het in de toekomst alleen maar beter zal gaan. Ook heel veel dank voor al je hulp bij de laatste (zware) loodjes.
Tevens zou ik de leden van de leescommisie willen danken voor het kritisch lezen van mijn manuscript.

Ook op het praktische vlak had ik het niet alleen gered, al is het bij één medestrijder gebleven. Heike, Du hast wirklich sehr gute Arbeit geleistet, und eine Menge von deinen Ergebnissen sind in dieser Doktorarbeit (und in einer schönen Publikation) zu lesen. Es

wundert mich nicht daß Du so schnell einen schönen Job gefunden hast. Ich hoffe, es gefällt Dir immer noch, und wünsche Dir alles Gute für die Zukunft.
Op elke werkvloer, zo ook in het lab, zijn het de collega´s die de sfeer maken. De eerste 15 maanden van mijn promotie heb ik het genoegen gehad samen te werken met de zeer gewaardeerde collegae uit het beruchte "bier-is-geen-cola"-tijdperk. André, Kimberly, "Milles", Jeroen, "Wok": een oergezellige groep studenten. De meesten van jullie zijn ook AIO geworden, ik wens jullie heel veel succes. Ook dank aan de collega-AIO´s van het eerste uur: Günther (ik ben je erg gaan waarderen en heb meer over chemie van jou geleerd dan van wie dan ook), Udo, Mieke, Michael, Marco, Henri en twee kleurrijke post-docs: Dr. J. Fred Stevens ("Mens'nkinder'n!") and Dr. Einar Bakstad ("Now I have found the right conditions: reflux in DMF over the weekend!") en de altijd gezellige secretaresse Judith. Ik wens jullie allemaal het beste!

Dann ging es natürlich nach Halle. Ich möchte die viele netten Kollegen der Abteilung NWC des IPB herzlich danken. Ich habe mich immer zu Hause gefühlt im Labor. Besonderer Dank gilt den Kollegen die die Zeit nach der Arbeit angenemher gemacht haben („Eeehh!! Biertje??"). Folgenden Kollegen möchte ich besonders danken für ihre praktische Beiträge: Angela Schaks für die Hilfe im Labor; Dr. Jürgen Schmidt und Martina Lerbs für die Massenspektroskopie; Maritta Süsse für die IR-Messungen; Dr. Andrea Porzel für die 2D-NMR-Messungen und natürlich Elisabeth Kaydamov für die Hilfe bei verschiedensten Sachen. Of course, I would also like to thank all english-speaking fellow PhD students and guests in Halle.

Ook dank aan mijn ouders, Koos en Suzanna. Jullie hebben me zoveel dingen meegegeven zonder welke ik nooit zover was gekomen. Jullie hebben altijd mijn keuzes gerespecteerd en mij gesteund in mijn beslissingen en me altijd een veilige thuishaven geboden.

Lieve Henrique, als laatste natuurlijk al mijn dank aan jou. In elk dankwoord is te lezen dat het niet makkelijk is om een relatie met promovendus te hebben, maar zelden geldt dat als in ons geval. Meer dan tweeënhalf jaar heb je me moeten missen tijdens mijn tijd in Duitsland. Ik ben zo dankbaar dat jij er steeds voor me geweest bent. Zonder jouw begrip en liefde was het me allemaal niet gelukt. Dank je.

Curriculum vitae

Eelco Ruijter was born on September 15th 1977 in Barsingerhorn, the Netherlands. He graduated from high school („VWO") at the Openbare Schoolgemeenschap Schagen in 1995. In March 2000, he obtained his M.Sc. from the Department of Organic and Inorganic Chemistry at the Vrije Universiteit Amsterdam in the group of prof. dr. L.A. Wessjohann on the project "Towards a novel synthesis of the epothilone B northern half". He started his Ph.D. project "Design and synthesis of ratjadone analogues" in the same group in March 2000, soon joining the Wessjohann group to the Department of Bioorganic Chemistry at the Institute of Plant Biochemistry in Halle (Saale), Germany. Since August 2004, he is working as a post-doctoral fellow at the Department of Medicinal Chemistry at Utrecht University.

List of publications:

1. Scheid, G.; Kuit, W.; Ruijter, E.; Orru, R.V.A.; Henke, E.; Bornscheuer, U.; Wessjohann, L.A.: A New Route to Protected Acyloins and Their Enzymatic Resolution with Lipases. *Eur. J. Org. Chem.* **2004**, 5, 1063-1074.

2. Scheid, G.; Ruijter, E.; Konarzycka-Bessler, M.; Bornscheuer, U.T.; Wessjohann, L.A.: Synthesis and resolution of a key building block for epothilones: a comparison of asymmetric synthesis, chemical and enzymatic resolution. *Tetrahedron: Asymm.* **2004**, 15(18), 2861-2869.

3. Ruijter, E.; Schültingkemper, H.; Wessjohann, L.A.: Highly substituted tetrahydropyrones from hetero-Diels-Alder reactions of 2-alkenals with stereochemical induction from chiral dienes. *J. Org. Chem.* **2005**, 70(7), 2820-2823.

4. Zhu, M.; Ruijter, E.; Wessjohann, L.A.: A new scavenger resin for the reversible linking and monoprotection of functionalized aromatic aldehydes. *Org Lett.* **2004**, 6(22), 3921-3924.

5. Wessjohann, L.A.; Ruijter, E.: Strategies for Total and Diversity-Oriented Synthesis of Natural Product(-Like) Macrocycles. *Topics in Current Chemistry,* Volume 243 (**2005**): Natural Product Synthesis I: Targets, Methods, Concepts (Ed: J. Mulzer), 137-184.

6. Wessjohann, L.A.; Ruijter, E.: Macrocycles rapidly produced by multiple multicomponent reactions including bifunctional building blocks (MiBs) *Mol. Divers*. **2005**, 9(1-3), 159-169.

7. Wessjohann, L.A.; Ruijter, E.; Garcia-Rivera, D.; Brandt, W.: What can a chemist learn from nature's macrocycles? – A brief, conceptual view *Mol. Divers.* **2005**, 9(1-3), 171-186.