DISSERTATIONES CHIMICAE UNIVERSITATIS TARTUENSIS
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# STEREOSELECTIVE SYNTHESIS OF TETRAHYDROFURAN AND TETRAHYDROPYRAN DERIVATIVES BY USE OF ASYMMETRIC HORNER-WADSWORTH-EMMONS AND RING CLOSURE REACTIONS

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**LAURI VARES**

TARTU UNIVERSITY
PRESS

The study has been carried out at the Royal Institute of Technology in Stockholm, Sweden, the Technical University of Denmark in Lyngby, Denmark, the Tallinn Technical University in Tallinn, Estonia, and the National Institute of Chemical Physics and Biophysics in Tallinn, Estonia.

Dissertation is accepted for the commancement of the degree of Doctor of Philosophy (in organic chemistry) on September 6, 2000 by the Doctoral Committee of the Department of Chemistry, University of Tartu.

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*To Kadri and my parents*

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## List of Original Papers

This thesis is based on the following papers, referred to in the text by Roman numbers I-VI.

I **Reagent Control of Geometric Selectivity and Enantiotopic Group Preference in Asymmetric Horner-Wadsworth-Emmons Reactions with *meso*-Dialdehydes.**
Tullis, J. S.; Vares, L.; Kann, N.; Norrby, P.-O.; Rein, T.
*J. Org. Chem.* **1998**, *63*, 8284.

II **Asymmetric Horner-Wadsworth-Emmons Reactions with Meso-Dialdehydes: Scope, Mechanism, and Synthetic Applications.**
Rein, T.; Vares, L.; Kawasaki, I.; Pedersen, T. M.; Norrby, P.-O.; Brandt, P.; Tanner, D.
*Phosphorus, Sulfur and Silicon* **1999**, *144-146*, 169.

III **A Versatile Stereocontrolled Approach to Chiral Tetrahydrofuran and Tetrahydropyran Derivatives via Sequential Asymmetric Horner-Wadsworth-Emmons and Palladium-Catalyzed Ring Closure Reactions.**
Vares, L.; Rein, T.
*Org. Lett.* **2000**, *2*, 2611.

IV **A Versatile Stereocontrolled Approach to Chiral Tetrahydrofuran and Tetrahydropyran Derivatives by Use of Horner-Wadsworth-Emmons and Ring Closure Reactions.**
Vares, L.; Kann, N.; Rein, T.
Manuscript

V **Progress Towards the Total Synthesis of Mucocin.**
Vares, L.; Rein, T.
Manuscript

VI **Appendix: Supplementary Material.**
Vares, L.

# List of Abbreviations

| | |
|---|---|
| Ac | acetyl |
| AD | asymmetric dihydroxylation |
| AE | asymmetric epoxidation |
| aq | aqueous |
| Bn | benzyl |
| Bu | butyl |
| Bz | benzoyl |
| CAN | ceric ammonium nitrate |
| CSA | camphorsulfonic acid |
| Cy | cyclohexyl |
| DMAP | 4-dimethylaminopyridine |
| dba | dibenzylidene acetone |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DIBALH | diisobutylaluminum hydride |
| DMSO | dimethyl sulfoxide |
| DPP | diphenylphosphinyl |
| dppb | 1,4-*bis*(diphenylphosphino)butane |
| dppe | 1,2-*bis*(diphenylphosphino)ethane |
| d.r. | diastereomeric ratio |
| *ee* | enantiomeric excess |
| Et | ethyl |
| FG | functional group |
| HMPA | hexamethylphosphoramide |
| HWE | Horner-Wadsworth-Emmons |
| KHMDS | potassium hexamethyldisilazide |
| L | ligand |
| LDA | lithium diisopropylamide |
| LG | leaving group |
| Me | methyl |
| MOM | methoxymethyl |
| MTPA | Mosher's acid |
| NaHMDS | sodium hexamethyldisilazide |
| n.d. | not determined |
| NMMO | 4-methylmorpholine-4-oxide |
| NOE | nuclear Overhauser effect |
| Nu | nucleophile |
| PG | protective group |
| Ph | phenyl |
| Piv | pivaloyl |
| PKR | parallel kinetic resolution |

| | |
|---|---|
| Pr | propyl |
| pyr. | pyridine |
| quant. | quantitative yield |
| RT | room temperature |
| TBAF | tetrabutylammonium fluoride |
| TBDMS | *t*-butyldimethylsilyl |
| TBDPS | *t*-butyldiphenylsilyl |
| TES | triethylsilyl |
| Tf | trifluoromethanesulfonyl |
| TFAA | trifluoroacetic anhydride |
| TFE | trifluoroethyl |
| THF | tetrahydrofuran |
| THP | tetrahydropyran |
| TIPS | triisopropylsilyl |
| TLC | thin layer chromatography |
| Tr | trityl |
| Ts | *p*-toluenesulfonyl |

# Foreword

This thesis summarizes roughly four and a half years of my studies from 1996 up to now. The work has been carried out in quite a number of different universities and laboratories. After spending eight months at the Royal Institute of Technology in Stockholm I followed my supervisor to the Technical University of Denmark near Copenhagen at the end of 1996. Almost two years in Denmark was the longest stay in one laboratory and perhaps also the most fruitful period in terms of scientific results. Meanwhile, in the spring of 1998, I had a chance to work for three months in the lab of Prof. Paul Helquist at the University of Notre Dame in USA. There I was involved in studies directed towards the total synthesis of a group of potent cytotoxic agents, the iejimalides. Since these studies are not directly connected to my other work, the results are not included in this thesis. The results from the Swedish-Danish period were written up in the form of a Licentiate Thesis in the fall of 1998, and successfully defended at the Royal Institute of Technology in Stockholm in December [1]. This degree was very important for me in itself, but also served as a prerequisite to be able to defend a Ph.D. degree in Estonia. After moving back to Tallinn at the end of 1998, I continued my studies and work towards the Ph.D. degree, first at the Institute of Chemistry at Tallinn Technical University and then from the late summer of 1999 at the National Institute of Chemical Physics and Biophysics.

This thesis consists of two major parts: the first part (pages 12-84) is intended to describe the general features presented in the articles which form the second part of the thesis.

The first part starts with a short description of the major goals of the study, followed by a general introduction to asymmetric synthesis, since this is the major theme of the thesis. The importance of tetrahydrofuran and tetrahydropyran derivatives, as well as general routes to these compounds are also briefly discussed. Chapter 2 is completely devoted to the Horner-Wadsworth-Emmons reaction; after a short historical overview the results obtained in my thesis work are discussed. An attempt has also been made to rationalize the observed stereochemistry of the products in the light of the postulated reaction mechanism. In Chapter 3, I focus on the synthesis of tetrahydrofuran and tetrahydropyran derivatives. Selected fundamentals of different types of ring-closure reactions are first discussed which should be useful for better understanding the chemistry presented in the second half of this Chapter and in Papers II, III and IV. The fourth Chapter is devoted to mucocin and annonaceous acetogenins in general. The studies towards the total synthesis of mucocin is discussed in context with published studies by other authors. Finally, preliminary results in extending our strategies to preparation of N-heterocycles have been summarized in Chapter 5,

and the main conclusions as well as some possible future perspectives are presented in Chapter 6.

The second part consists of five papers and one appendix. The first full paper contains most of the fundamental studies directed towards the optimization of the asymmetric HWE reactions. My contribution to this paper has been discussed in Chapter 2 in this thesis. In Papers II-V, the main focus is the synthesis of THF/THP derivatives from HWE products via different ring-closure methods. More specifically, Paper II describes the approach to THP derivative via an intramolecular epoxide opening approach (Section 3.2.3. in this thesis), and Paper III describes a palladium(0) catalyzed intramolecular allylic substitution approach leading from HWE products to THF/THP derivatives. Paper IV is a full paper describing in detail, besides the other ring-closure methods, also the hetero-Michael addition approach (Section 3.2.2.). The studies towards the total synthesis of mucocin are presented in Paper V and also discussed in Section 4.4. Finally, the initial results towards the synthesis of piperidines, as well as some selected results which may form a basis for future publications, are presented in the form of supplementary material.

In addition, various parts of the studies have been presented at several scientific conferences. The more important ones have been an American Chemical Society meeting in San Francisco [2], two *Organikerdagarna* meetings in Sweden [3], and the 25th Estonian Chemistry Days in Tallinn [4]. Furthermore, results presented at The International Conference on Phosphorus Chemistry in Cincinnati in 1998, directly lead to Paper II.

# 1. Introduction

## *1.1. The major goals of the study*

In general, there are two major goals in this work: (a) to study auxiliary-controlled asymmetric HWE reactions with acyclic and cyclic *meso*-dialdehydes as substrates, and (b) to study the substrate-controlled conversions of HWE products from acyclic dialdehydes into different THF/THP or piperidine derivatives (Figure 1), which could be used as building blocks in natural product synthesis.

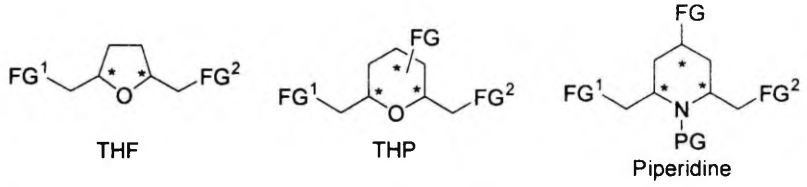



**Figure 1.** The general types of THF's and THP's which are the main subject of the study in this thesis (an asterisk indicates the chiral center).

## *1.2. General introduction to asymmetric synthesis*

The whole world around us is chiral. Most organic compounds are also chiral. Many biological systems recognize the members of a pair of enantiomers as different substances[1] which elicit different responses. Therefore chemists working with pharmaceuticals, perfumes, cosmetics, flavors, pesticides, just to name few, require an access to enantiomerically pure compounds. How do we obtain enantiomerically pure compounds? Historically, the answer to this question has been to isolate them from the natural sources. However, even if the target compound is available from nature, often the isolation is not economical or may even lead to the extermination of the host species.

If the goal is to obtain an enantiomerically pure compound, one has several options to choose from: find a plant or a bacterium that will make it for you, synthesize the molecule in racemic form and resolve it in some way, start with a appropriate chiral natural compound (chiral pool approach),[2] or use an asymmetric synthesis. There are different factors to consider when evaluating these alternatives: the cost of starting materials and reagents, the length of the synthetic sequence, the amount of material required etc. Each of these alternatives have their scope and the choice

(1) To illustrate, the enantiomers can be considered as a pair of hands — similar, but still different.

(2) Be aware that not always the natural compounds are enantiomerically pure. See e.g.: Mori, K. *Acc. of Chem. Res.* **2000**, *33*, 102.

can be very case dependent. For the purposes of biological evaluation, it is often needed to obtain both enantiomers, implying that the resolution might be the choice. However, for the production of a single enantiomer, the resolution approach wastes half of the material unless the unwanted enantiomer can be recycled in some way and the chiral pool and enzyme/microorganism approach is often restricted to the production of one enantiomer only. In these cases asymmetric synthesis is the method of choice.

In modern terms, asymmetric synthesis has been defined as follows [5]:

> **Asymmetric synthesis** is a reaction or a reaction sequence that creates a new stereogenic unit in a controlled by means of a chiral reagent or auxiliary.

In general, methods for asymmetric synthesis can be divided in three major categories:

(a) *De novo* asymmetric synthesis;
(b) Asymmetric induction;
(c) Substrate control.

*(a) De novo asymmetric synthesis.* This is a process where achiral or racemic starting materials in certain circumstances are converted into chiral non-racemic products. Some process of this type must have been responsible for the original favoring of one enantiomeric series of certain natural products (like amino acids). Researchers have been struggling for decades to explain how life acquired this bias, without success. Perhaps the most popular recent contender has been rays of circularly polarized light from supernovae [6]. Another candidate has been the weak nuclear force which governs the radioactive decay of a neutron (which is in the nucleus of an atom) into a proton and an electron, and this force has a handedness: the decay always produces an electron with a left-handed spin. Since this weak nuclear force is the only chiral fundamental force in nature, it has been tempting to link it to handedness of biomolecules [7]. Generally, *de novo* processes are rare and do not at present have practical use in enantioselective synthetic routes.

*(b) Asymmetric induction.* This term refers to the synthesis where a prochiral substrate or functional group is converted into a chiral isomerically enriched product by use of a chiral reagent used either in stoichiometric or catalytic amounts. In case of a (stoichiometric amount of) covalently bound chiral auxiliary, the term *auxiliary controlled* asymmetric synthesis is also used. The use of a chiral catalyst would be the most desirable, since a small amount of chiral auxiliary can produce a large amount of enantiopure product.

*(c) Substrate control.* As the term indicates, the *substrate controlled* reactions are (diastereoselective) reactions in which the formation of the new chiral center is controlled by the chirality already present in the same molecule.

The reactions where stereoselectivity is achieved follows one of two paths: thermodynamic or kinetic control. These two categories are described in Figure 2. In diastereoselective reactions, either kinetic or thermodynamic control is possible, whereas in enantioselective reactions, the products are isoenergetic and only kinetic control is possible. These terms will be used when describing certain reaction paths in this thesis.

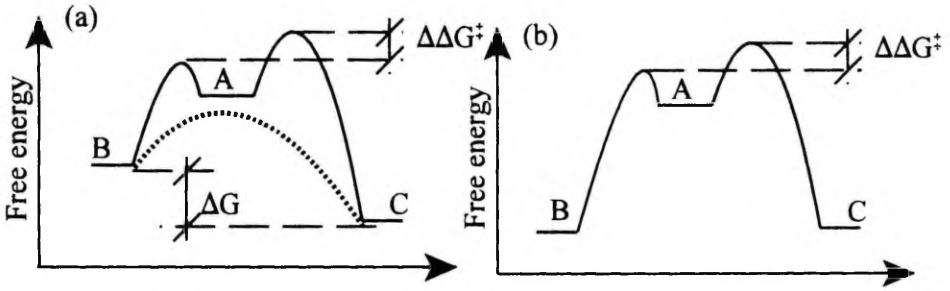



**Figure 2.** (a) Conversion of **A** into a mixture of **B** and **C** under *thermodynamic control*. The products **B** and **C** may equilibrate via **A** or by another route (dotted line). (b) Conversion of **A** into **B** and **C** under *kinetic control.*

### *1.3. Importance of THF/THP subunits*

There are several classes of biologically active natural products containing THF/THP subunits (Figure 3). The most important ones are: annonaceous acetogenins,[3] cytotoxic macrolides [8] and polyether antibiotics [9]. Most of the compounds belonging to one of these classes show a broad range of biological activity, a property which makes them commercially attractive. For example, polyether antibiotics show considerable antimicrobial activity, whereas many representatives of macrolides exhibit exceedingly potent cytotoxicity against human tumor cells. Acetogenins, in turn, show insecticidal, fungicidal, anthelmintic and cancerostatic effects.

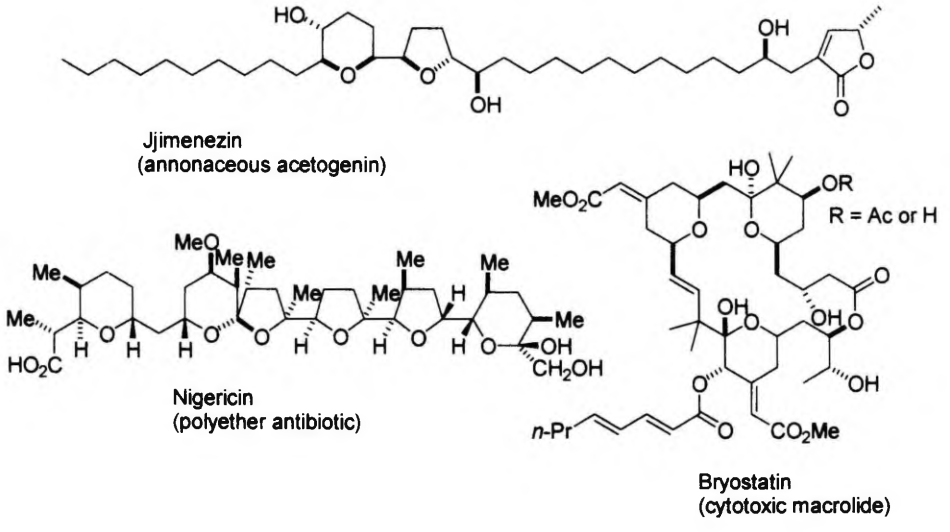
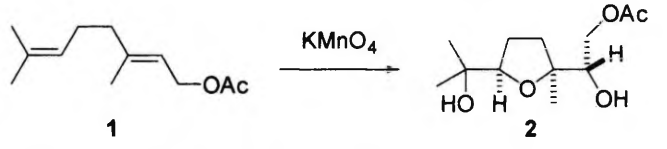



**Figure 3.** Bioactive natural products containing THP and/or THF units.

(3) See Section 4.1. in this thesis.

### *1.4. Selected previously reported strategies for synthesis of THF/THP derivatives*

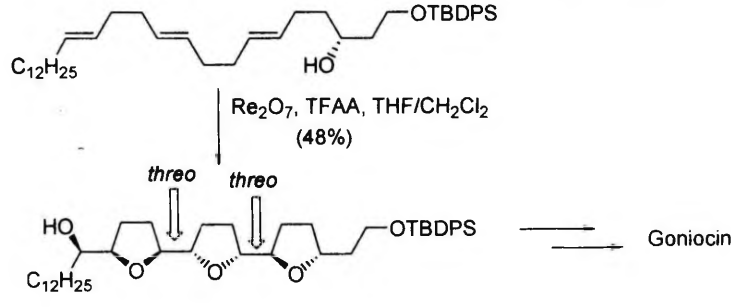
The stereocontrolled preparation of THF and THP units for valuable natural products has stimulated the development of many novel synthetic methods (for a reviews, see [10]). Historically, the first reported THF synthesis dates back to 1924 when Kötz and Steche oxidized 1,5-diene **1** to THF derivative **2** by potassium permanganate (Scheme 1, [11]). However, it took more than 40 years to elucidate the correct structure of the product [12].




**1** **2**

**Scheme 1.** The first known THF synthesis.

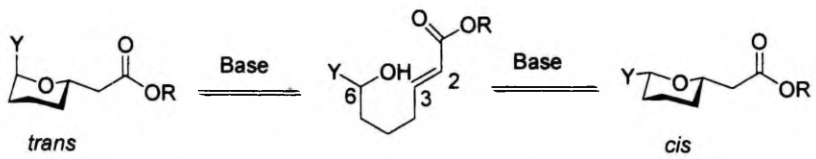
*Oxidative cyclization.* In recent years, after the introduction of milder rhenium-based oxidizing agents [13], oxidative cyclization has gained considerably attention. Monocyclization reactions with simple bis- and trishomoallylic alcohols lead consistatly to *trans*-THF and THP products, respectively [13a,14]. This methodology has also been efficiently applied for the sythesis of compounds bearing adjacent THF rings. Sinha et al. [15] prepared all three adjacent THF rings of acetogenin goniocin in a single polycylization step with very high diastereoselectivity (Scheme 2). The chirality of a hydroxy-substituted stereocenter is used to control the configuration of other six stereogenic carbinol centers. It is only very recently that certain rules have been devised to predict and explain the observed stereochemistry in these cyclization reactions [16]. It was found that the first THF ring is always produced with *trans*-configuration (provided that the hydroxyl is the only strong coordination site for rhenium). If the two vicinal oxygen-substituted stereocenters formed in the first cyclization step have a *threo*-relationship, then the next cyclization produces a *cis*-THF ring, otherwise, the next ring will have a *trans*-configuration.




**Scheme 2.** Oxidative polycyclization of hydroxy diene.

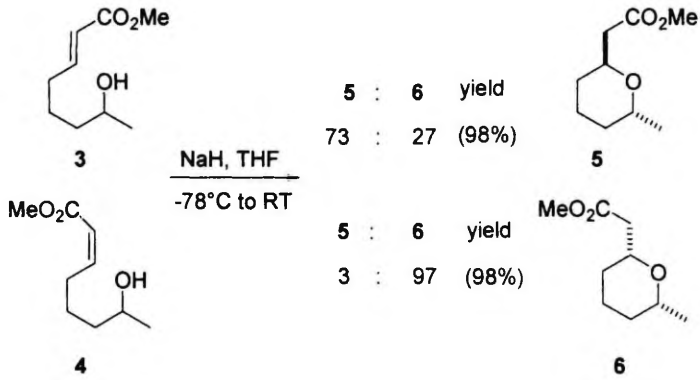
*Epoxide opening route.* In general, opening of an epoxide by attack of an internal nucleophilic oxygen has been one of the most widely used methods for the synthesis of saturated O-heterocycles (for a selected examples, see ref. [17] and Scheme 40). This methodology has gained its popularity because epoxidation of alkenes can be performed highly stereoselectively using methods developed by Sharpless, Katsuki and Jacobsen (for a general discussion on AE, see [18]) or by taking advantage of chirality which is already present in the molecule. Opening of epoxides usually occurs without any loss in stereochemical purity and in most cases with clean inversion of stereochemistry via a $S_N2$ type reaction (for a review, see [19]). Specific examples where the epoxide opening route has been applied for the THF and THP fragments of mucocin are discussed in Section 4.1.2.

*Hetero-Michael addition.* Conceptually one of the simplest routes to THF's and THP's is an intramolecular hetero-Michael addition of the type shown in Scheme 3. In case of disubstituted THF's and THP's, the reaction is usually thermodynamically controlled and the *cis*-disubstituted THF or THP derivative (with both substituents equatorial) becomes almost the exclusive product when the reaction reaches equilibrium [20]. It therefore follows that the configuration at C-3 will be induced by the configuration of the center containing the secondary alcohol moiety (C-6 in Scheme 3). However, the formation of highly substituted THF's and THP's may never reach equilibrium and mixtures of *cis*- and *trans*-products are often obtained [21].



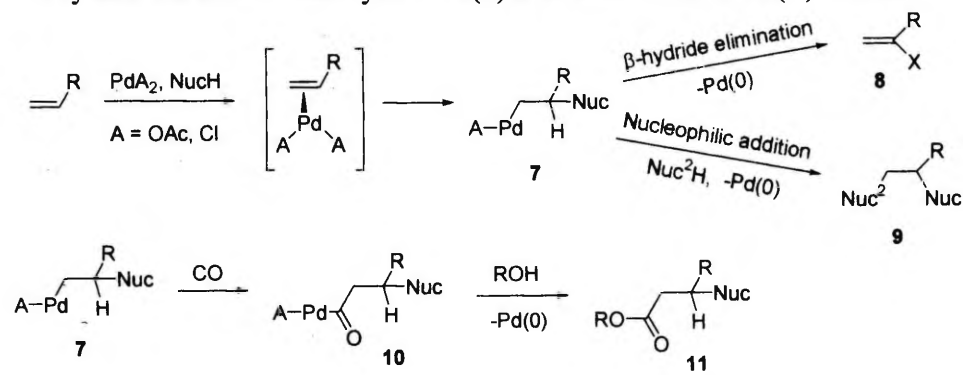

**Scheme 3.** Stereochemistry of the hetero-Michael addition reaction giving a THP product.

It has been also found that the double bond geometry of the Michael acceptor can control the diastereoselectivity in these type of cyclizations [22,23]. Cyclization of (*E*)-alkene **3** (Scheme 4) afforded a 73:27 mixture of *trans*- and *cis*-isomers, whereas (*Z*)-alkene **4**, under the same reaction conditions, afforded almost exclusively *cis*-isomer **6**.




**Scheme 4.** (*E*)-alkene vs (*Z*)-alkene in hetero-Michael addition.

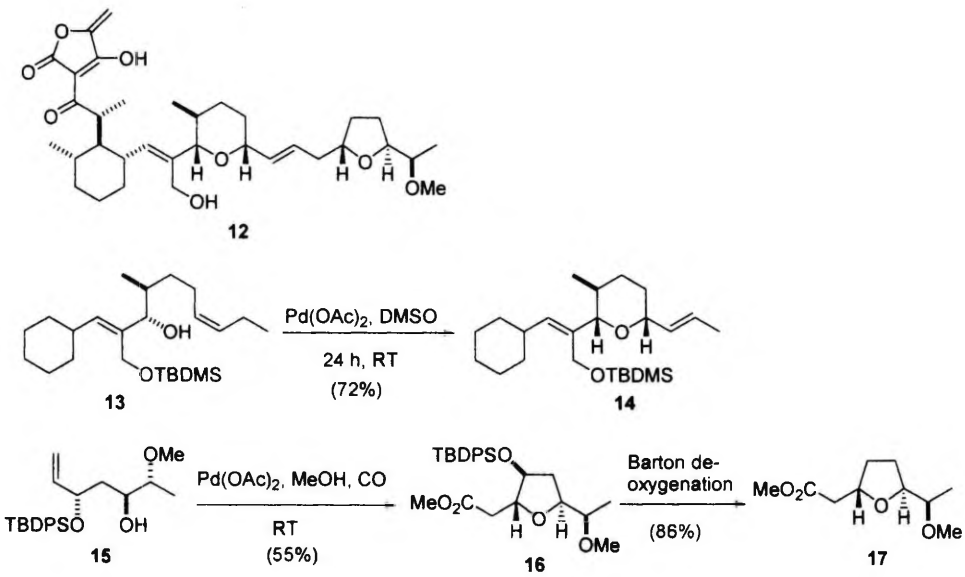
*Pd(II)-promoted nucleophilic addition to alkenes.* Pd(II)-compounds coordinate to alkenes to form π-complexes.[4] The decrease in the electron density of the alkenes by coordination to electrophilic Pd(II) permits the attack by various nucleophiles on coordinated alkenes (Scheme 5). The attack of a nucleophile with accompanying formation of a carbon-palladium σ-bond to form **7** is called a palladation of the alkene. However, the product **7** is very unstable and undergoes rapid decomposition. Depending on the reaction conditions, either β-hydride elimination or trapping of the alkyl-Pd(II) intermediate with a nucleophile takes place. If the reaction is performed under CO atmosphere in an alcoholic solvent, then CO insertion to intermediate **7** takes place followed by alcoholysis to form the ester derivative **11**. Palladium(II) is required to activate the alkene, but palladium(0), formed from reductive elimination, is the product of the reaction. The system can be made catalytic if Pd(0) is oxidized back to Pd(II) in situ.




**Scheme 5.** Pd(II)-promoted reactions of nucleophiles with alkenes.

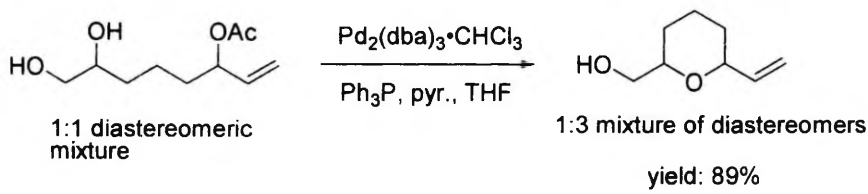
(4) See [82a] pp 16-55.

Among the several studies on applying this strategy in practice (for a selected examples, see [24]), I chose the Sammelhack's approach to tetranomycin **12**, as an example of this approach (Scheme 6, [25]). By choosing the conditions favoring β-hydride elimination (DMSO, argon atmosphere), THP unit **14** could be made from hydroxyalkene **13**. Reaction of $Pd(OAc)_2$ with hydroxyalkene **15**, in turn, performed in DMSO under CO atmosphere, gave the desired *trans*-THF unit **16**.




**Scheme 6.** Semmelhack's approach to tetranomycin.

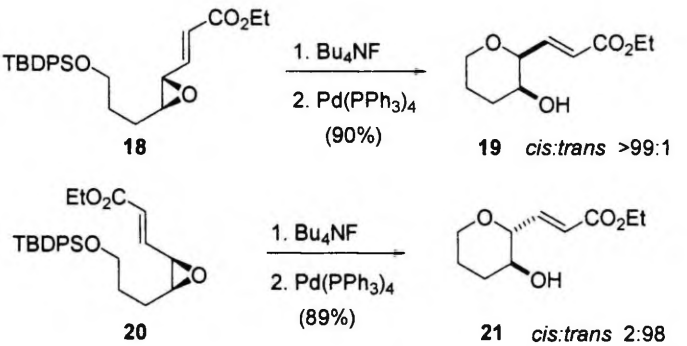
*Pd(0)-catalyzed allylic substitution – ring-closure.* Intramolecular Pd(0)-catalyzed allylic substitution has been reported previously for the synthesis of THF and THP derivatives only in very few cases.[5] Initial studies were done by Trost et al. in 1988 [26]. Using allyl acetates containing a remote vicinal diol unit as substrates, Trost attempted to control the ring size formed, without considering any stereochemical aspects (Scheme 7).




**Scheme 7.** The first THP synthesis via a Pd(0)-catalyzed intramolecular allylic substitution.

(5) See Paper III, footnote 5.

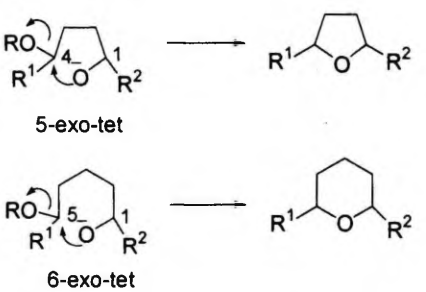
Another example of a similar kind is Hirama's synthesis of *cis*- and *trans*-2,3-disubstituted tetrahydropyrans, where he used allylic epoxides as π-allyl precursors (Scheme 8, [27]). The ammonium alkoxides, removed after removing the silyl protective group with $Bu_4NF$, are good nucleophiles in the subsequent Pd(0)-catalyzed allylic etherification. The *trans*-epoxide **18** gives exclusively *cis*-THP derivative **19**, while *cis*-epoxide **20** gives *trans*-tetrahydropyran derivative **21**.




**Scheme 8.** Hirama's syntheses of 2,3-substituted THP derivatives.

The mechanistic and stereochemical aspects of these type of reactions will be discussed in detail in Section 3.1.1.

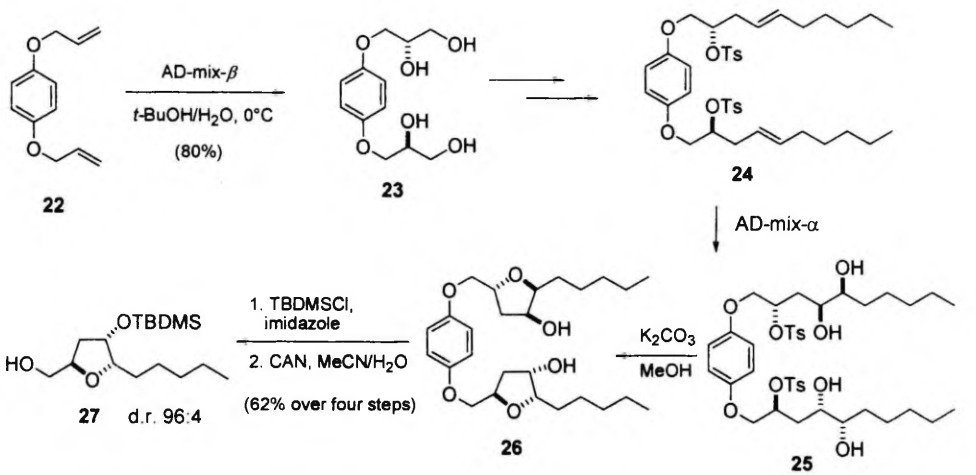
*Intramolecular $S_N2$-reaction.* Intramolecular cyclization by a nucleophilic attack on C-4 or C-5 by an alkoxide gives a THF or THP compound, respectively (Scheme 9).




**Scheme 9.** Intramolecular $S_N2$ type cyclization (see also Baldwin's rules in Section 3.1.2.).

A good example of this methodology is Wang's synthesis of THF derivative **27** [28], which has a characteristic substitution pattern found in many natural products (Scheme 10, for other selected examples, see [29]). The stereochemistry has been set in two different asymmetric dihydroxylation reactions (from **22** to **23** and from **24** to **25**); ring closure is induced by a weak base ($K_2CO_3$) and proceeds via a $S_N2$ mechanism with inversion of configuration. Treatment of **26** with ceric ammonium

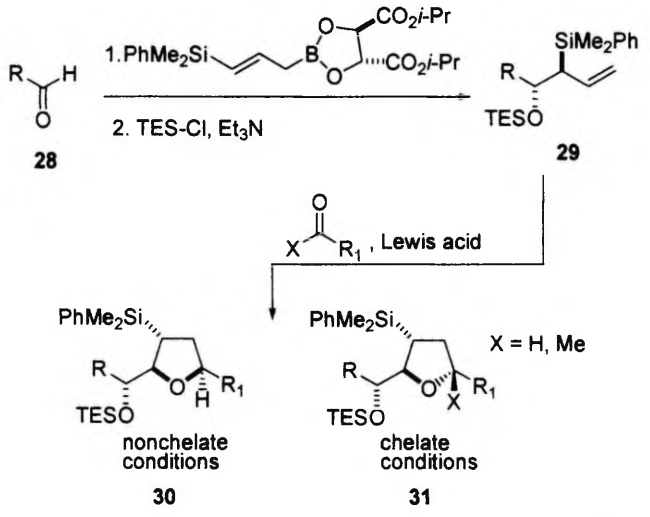
nitrate (after protecting the hydroxy groups) released two equivalents of THF product **27**.




**Scheme 10.** Wang's synthesis of THF derivative **27**.

*Miscellaneous other routes.* Numerous other routes exist for stereoselective synthesis of THF's and THP's — reduction of bicylic ketals and spiro compounds (for a review, see [30], for a recent examples, see [31]), olefin metathesis reactions (see e.g. [38,32]), intramolecular oxa-Diels-Alder reactions (see e.g. [33]), radical cyclizations (see e.g. [34,98g]), just to name few.

Very recently Roush et al. [35] published a convergent route to 2,3,5-trisubstituted tetrahydrofurans via a three-component coupling (Scheme 11). After allylboration of the first aldehyde **28**, the chiral, nonracemic allylsilanes **29** are coupled with a second aldehyde or ketone with Lewis acid catalysis to give tetrahydrofurans **30** or **31** with excellent selectivity. The 2,5-stereochemistry is controlled by operating under nonchelate (**30**) or chelate (**31**) conditions.



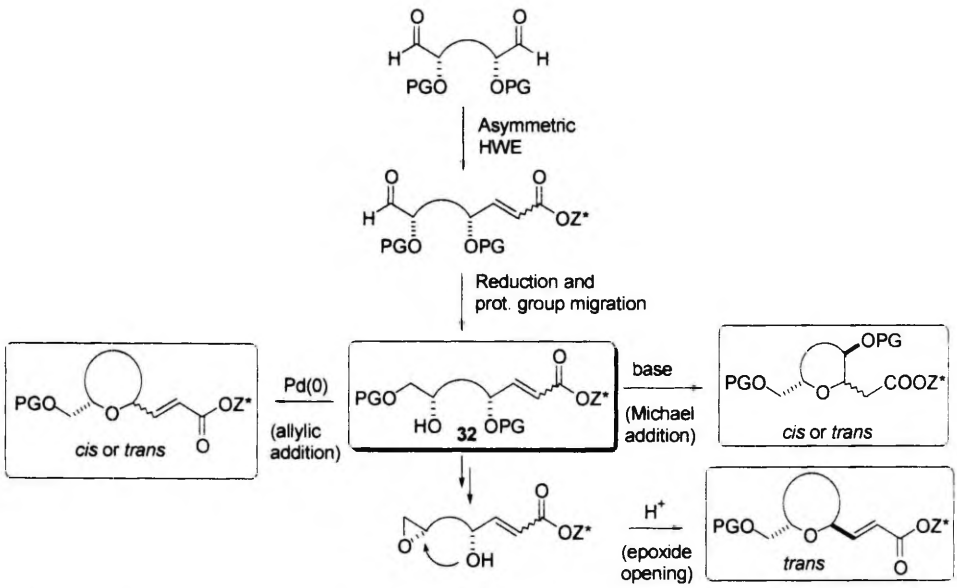

**Scheme 11.** Roush strategy to 2,3,5-trisubstituted THF's.

There has been some debate whether to include also the sugar derivatives in reviews on THP's and THF's since the distinction between a sugar derivatives and pyrans is becoming increasingly vague. Generally, the sugars have been treated separately, but nevertheless these derivatives are being used to a greater extent in total synthesis and a number of *C*-glycosidation procedures have general utility in the synthesis of tetrahydropyrans [36].[6]

(6) A *C*-glycoside (i.e. carbon-glycoside) results when the anomeric oxygen of a glycoside is replaced by a carbon atom.

### *1.5. Our general strategy for THF/THP synthesis.*

Our planned strategy for the synthesis of THF's and THP's studied in this thesis is envisioned in Scheme 12. The α-oxygen-substituted *meso*-dialdehyde is first desymmetrized via an asymmetric HWE reaction. The product obtained is then converted into the key intermediate **32**, which can undergo different ring-closure reactions to form various THF or THP derivatives.




**Scheme 12.** General strategy for the synthesis of O-heterocycles studied in this thesis.

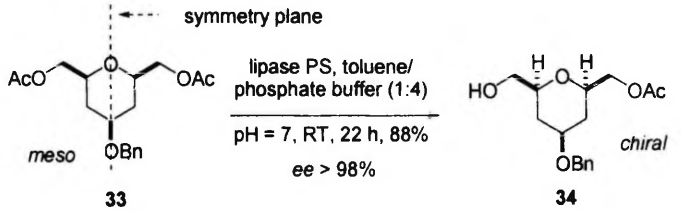
The stereochemistry set in the asymmetric HWE reactions serves as a basis for the synthesis of enantiopure THF and THP derivatives. The use of different methods for ring-closure would enable us to synthesize different THF/THP derivatives even from the very same HWE product, making the overall strategy more versatile. When the opposite enantiomer of the chiral auxiliary is used in the asymmetric HWE reaction, opposite enantiomers of THF/THP products are also readily available.

# 2. Studies of asymmetric HWE reactions[I,III,IV]

## *2.1. General background*

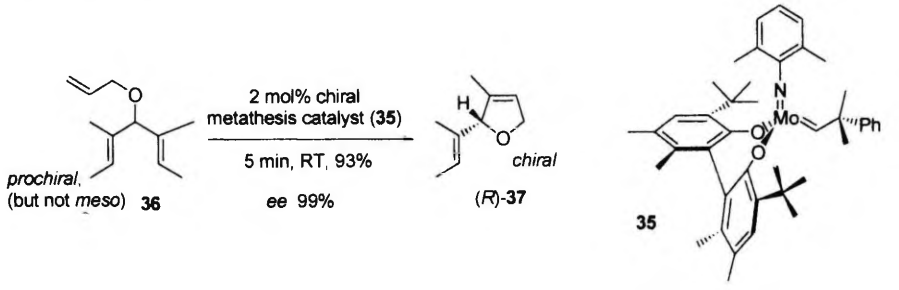
### 2.1.1 Desymmetrization of *meso*-compounds

Since *meso*-dialdehydes have been used as a substrates in my studies of asymmetric HWE reactions, a short discussion on *meso* compounds in general is in place. The desymmetrization of the *meso*-compounds[7] can be viewed as a type of kinetic resolution where the two substrate enantiomers are present in the same molecule. An example of desymmetrization of a *meso*-substrate is shown in Scheme 13, where the *meso*-diacetate **33** is converted into the chiral compound **34** in high chemical and optical yield by the use of enzyme catalysis [37]. As one can see, the absolute configuration of three stereocenters has been set in one single transformation, making this type of desymmetrization reactions very attractive from a synthetic point of view.




**Scheme 13.** Desymmetrization of a *meso*-compound via lipase catalysis.

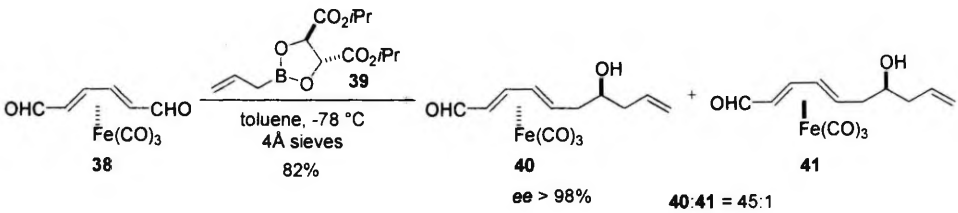
Hoveyda et al. [38] have reported an interesting catalytic enantioselective desymmetrization of dienes that can serve as precursors to dihydrofurans (Scheme 14). Chiral molybdenum metathesis catalyst **35** is efficiently employed to convert the achiral diene **36** into the chiral dihydrofuran **37** in excellent optical and chemical yield.




**Scheme 14.** Catalytic enantioselective desymmetrization of diene.

(7) The descriptor *meso* refers to a stereoisomer that contains two or more stereogenic units, but which is achiral because of a symmetry plane.

The work by Roush and Park [39] illustrated below is of particular interest because it involves the use of a *meso*-dialdehyde as a substrate. Allylboration of the *meso*-dialdehyde diene-$Fe(CO)_3$ complex **38** with chiral borane reagent **39** proceeded with excellent enantio- and diastereoselectivity (Scheme 15). (For a review on iron tricarbonyl diene complexes in stereoselective synthesis, see [40]).

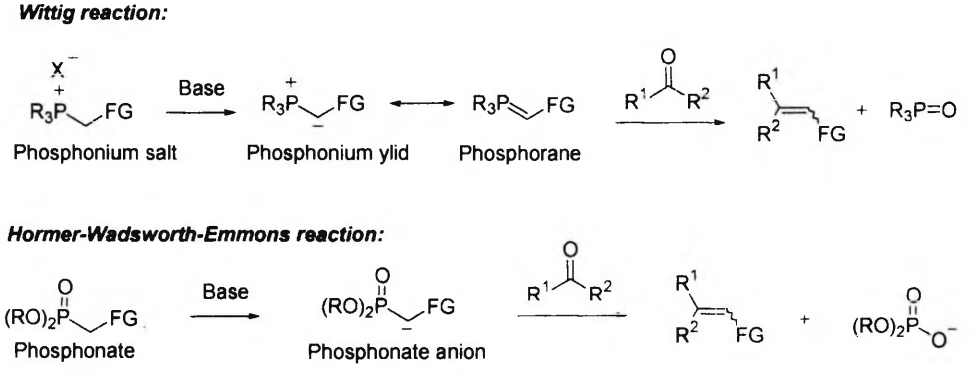



**Scheme 15.** Asymmetric allylboration of the *meso*-dialdehyde **38**.

The remaining aldehyde group in **40** could be used for another stereoselective nucleophilic addition, where the now chiral substrate can serve itself as a directing group for a second nucleophile. This possibility for two-directional functionalization gives to *meso*-substrates even an additional synthetic versatility.

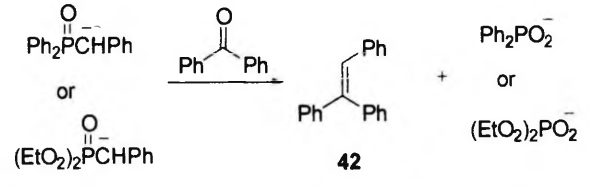
### 2.1.1. Brief history of Wittig reactions

Georg Wittig discovered in the early 1950s [41] that phosphonium ylides react with ketones and aldehydes to form alkene products (Scheme 16). This landmark discovery started a new era in alkene synthesis and lead to the nomination of Georg Wittig as a Nobel prize laureate in 1979. Several modifications of the Wittig reaction have been discovered since then. Perhaps the best known is the Horner-Wadsworth-Emmons (HWE) reaction which takes place between a phosphonate anion and a carbonyl compound yielding an olefin and a phosphate ion (Scheme 16).




**Scheme 16.** The general Wittig- and Horner-Wadsworth-Emmons reactions.

Historically, Horner and co-workers were the first to react phosphoryl-stabilized carbanions with aldehydes and ketones to produce olefins [42]. In these studies, benzylic carbanions were found to combine with benzophenone to give **42** in good yields (Scheme 17). Wadsworth and Emmons expanded this work further and popularized this method to the synthetic community [43]. There has been some confusion as to whom to give the credit for this class of reactions, as the names "Horner", "Wadsworth", "Emmons", "Wadsworth-Emmons", and "Horner-Wittig" have appeared quite regularly.




**Scheme 17.** The first Horner and Horner-Wadsworth-Emmons reactions.

Following the example set by an excellent review [44], the phosphonate mediated reactions will be referred to as the "Horner-Wadsworth-Emmons" (HWE) reaction while the phosphine oxide variant will be called the "Horner" reaction. Other phosphonic acid derivatives (phosphonic bisamides and phosphinoamidates) are commonly also referred to as HWE reagents (Figure 4).

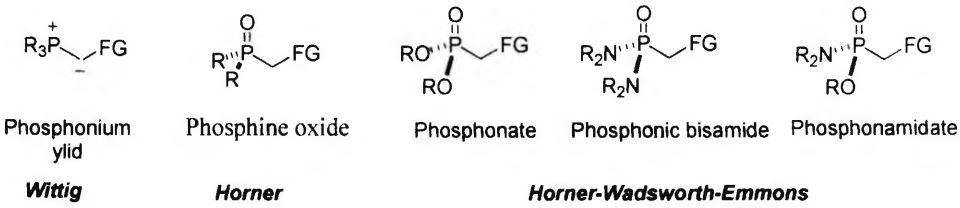



**Figure 4.** Different Wittig-type reagents used in alkene synthesis. FG = H, alkyl, aryl, or a functional group.

When comparing the synthetic utility of Wittig, Horner, and Horner-Wadsworth-Emmons reactions, the HWE reaction has several advantages over the 'classical' Wittig reaction. If an introduction of a simple alkenyl chain is in question, then the Wittig reaction is usually the method of choice, but in many other cases the use of a HWE reaction may be more rational. The main advantages of the HWE reactions are:

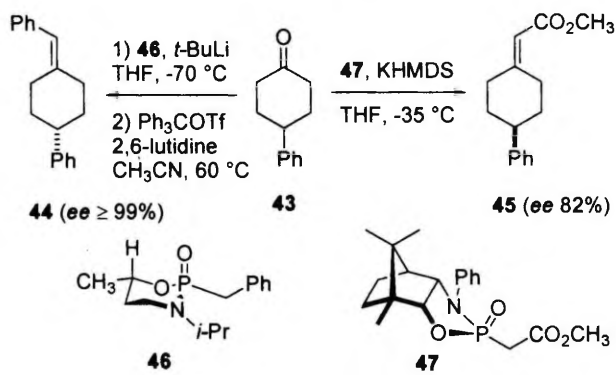
- ☺ the HWE reagents are more reactive (more nucleophilic). This enables milder reaction conditions which in turn often results in a fewer side reactions and higher yields;
- ☺ the particular choice of reaction conditions (base/solvent) or R groups on phosphorus often enables one to obtain selectively either the (*Z*)- or the (*E*)-alkene as a product;
- ☺ the easier work-up procedure, since the by-product (phosphate ion) is water soluble;
- ☺ the synthesis of trisubstituted alkenes is easier, since the corresponding phosphonates can be alkylated in the α-position more easily than Wittig reagents.

The main disadvantage associated with HWE reactions is the need to carry an anion-stabilizing group on the carbon α to phosphorus. The Horner phosphine oxides do not need to carry an anion-stabilizing group, but on the other hand they are more sensitive to oxygen and the intermediate diastereomeric β-hydroxy phosphine oxides usually have to be isolated and purified prior to their stereospecific decomposition to alkenes. Since in this work only the HWE reaction has been studied, the other Wittig-type reactions will not be discussed in further detail.

### 2.1.3. Asymmetric HWE reactions

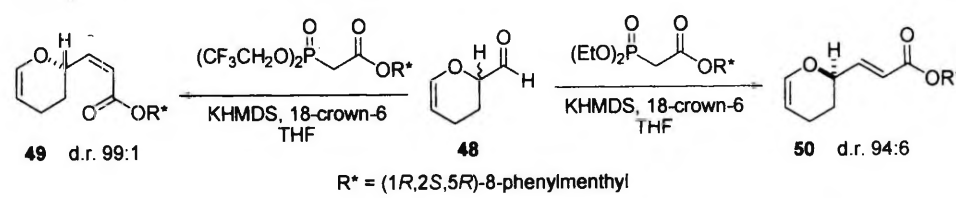
Despite of the fact that no new $sp^3$ stereocenter is formed in HWE (or other Wittig-type) reactions, asymmetric induction can still be achieved if the substrate contains either a prostereogenic unit apart from the resulting carbonyl group, or an enantiotopic set of stereogenic units (for a review on asymmetric HWE reactions, see [45]).

The field of the asymmetric Wittig-type reactions is still a rather undeveloped area, even though the non-asymmetric versions of such reactions have a profound importance in synthetic organic chemistry [44]. Most of the studies on asymmetric HWE reactions have been done by using ketones, particularly 4-substituted cyclohexanones, as a substrates. Denmark [46] has shown that the phosphonamidates **46** and **47** can be used for the preparation of differently functionalized dissymmetric alkenes with high *ee* (Scheme 18).



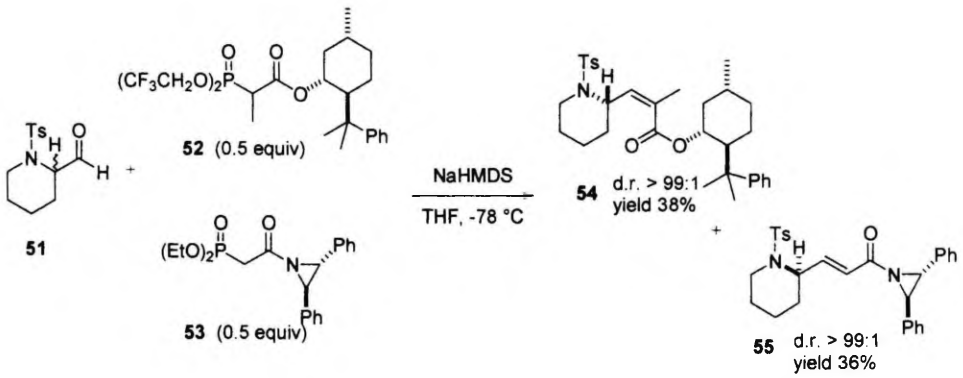

**Scheme 18.** Asymmetric HWE reactions with phosphonamidates.

Kinetic resolution may be obtained if a chiral racemic carbonyl compound is reacted with an enantiopure HWE reagent. The first highly selective example of kinetic resulution using racemic aldehydes was reported by Rein and Reiser [47]. It was found that in the reactions with racemic aldehyde **48**, an appropriate choice of chiral phosphonate gave access to either (*Z*)-alkene **49** or (*E*)-alkene **50** in good to excellent diastereoselectivity (Scheme 19).




**Scheme 19.** First kinetic resolution of a racemic aldehyde by an asymmetric HWE reaction.

The major drawback with the kinetic resolution approach is that only half of the racemic starting material is converted into nonracemic product. To make the process more efficient Vedejs and Chen have recently introduced the concept of *parallel kinetic resolution* (PKR) [48], an interesting strategy by which both enantiomers of a racemate can be converted to useful products via simultaneous reaction with two different chiral reagents. Rein, Pedersen and coworkers [49] have applied this strategy in asymmetric HWE reactions (Scheme 20).

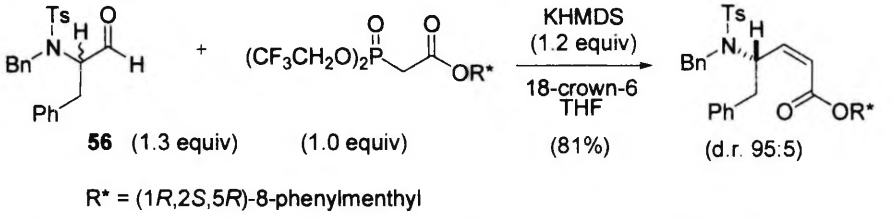



**Scheme 20.** Parallel kinetic resolution of racemic aldehyde **51**.

Simultaneous reaction of a racemic aldehyde **51** with one (*Z*)-selective (**52**) and one (*E*)-selective (**53**) phosphonate affords one (*Z*)- and one (*E*)-product with opposite absolute configuration at the allylic stereocenter, each one in essentially complete diastereoselectivity. The products (alkenes **54** and **55**) are easily separable by flash chromatography due to their somewhat different polarity. It is also noteworthy to mention that PKR reactions can in favorable cases afford increased selectivities compared to the individual kinetic resolutions. PKR reactions should prove particulary useful for synthetic applications in which the both obtained products can be of further utility in the same context, either as a building blocks for two different subunits of the same target or for providing access to both enantiomeric series of the same subunit of a given target.

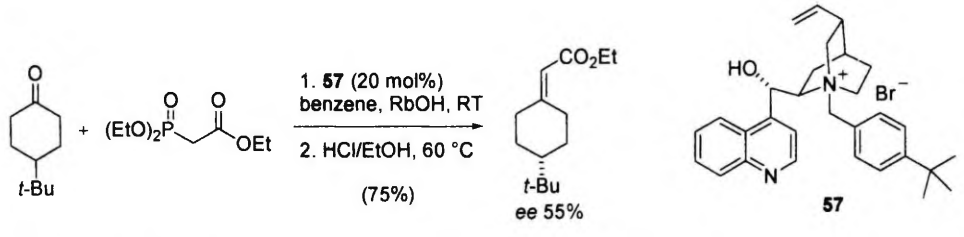
The same authors have also efficiently combined the PKR with enantioconvergent palladium-catalyzed substitution [50]. First a reaction of a racemic monoaldehyde with two different chiral phosphonates simultaneously converts all racemic starting material into useful chiral products. The mixture of product isomers can then be transformed into one single diastereomeric product by use of a palladium catalyzed substitition reaction (see Section 3.1.1.3. for details on palladium reactions).

Another efficient variant of the kinetic resolution is a process called *dynamic kinetic resolution*. If reaction conditions can be found under which the substrate undergoes rapid racemization, then it is theoretically possible to obtain quantitative yield of a single product using equimolar amounts of substrate and reagent. Rein and Reiser [51] have demonstrated the use of protected α-amino aldehydes (e.g. **56**) as substrates in dynamic kinetic resolutions (Scheme 21).



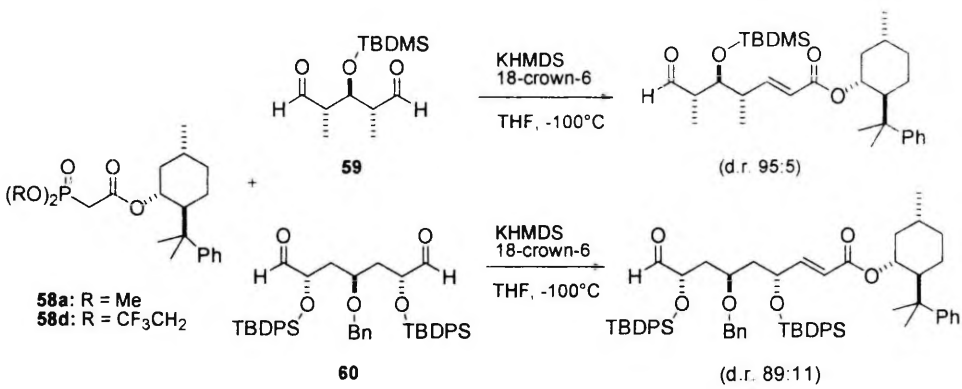

**Scheme 21.** Dynamic kinetic resolution of racemic aldehyde by asymmetric HWE reaction.

It would be very desirable to develop a catalytic version of the asymmetric HWE reaction. However, this task has proven to be very challenging, and only one such attempt has been published so far. Arai et al. [52] have demonstrated that quaternary ammonium salts (such as **57**) can be used as phase transfer catalysts to achieve moderate asymmetric induction in HWE reactions (Scheme 22). Although the catalytic turnover and enantiomeric excess are rather low, the work will hopefully stimulate a further progress in this field.



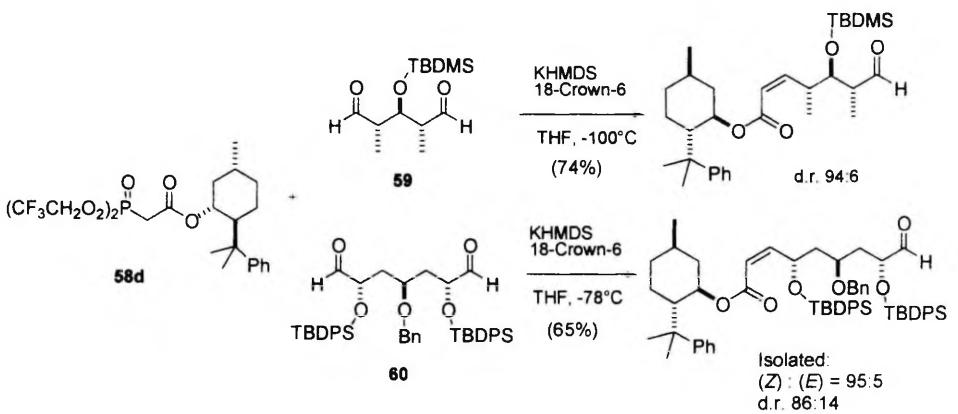

**Scheme 22.** First catalytic asymmetric HWE reaction.

If a compound containing two enantiotopic carbonyl groups is used as the substrate, a chiral Wittig-type reagent might give selective reaction at one of the carbonyl groups, a process which leads to asymmetric induction by 'desymmetrization' of the substrate. Our group has previously investigated asymmetric HWE reactions between chiral phoshonate **58a** and *meso*-dialdehydes **59** and **60**, and obtained (*E*)-monoaddition products with good diastereoselectivity (Scheme 23, [53]).




**Scheme 23.** Initial results with *meso*-dialdehydes as substrates in asymmetric HWE reactions leading to (*E*)-alkenes.

Subsequent work [54] showed that if phosphonate **58d** was used instead of **58a**, the monoaddition products were obtained with high (*Z*)-selectivity and high levels of asymmetric induction from dialdehydes **59** and **60** (Scheme 24).

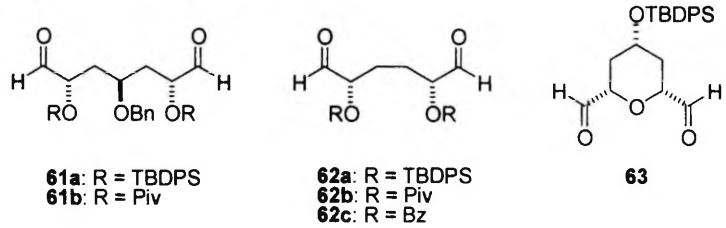



**Scheme 24.** Initial results with *meso*-dialdehydes as substrates in asymmetric HWE reactions leading to (*Z*)-alkenes.

These initial results shown in Schemes 23 and 24 served as a starting point for my attempts to develop and improve the asymmetric HWE reactions with *meso*-dialdehydes.

## 2.2. Meso-dialdehydes[I,III,IV]

In this work three structurally different types of dialdehydes (**61**, **62**, and **63**) have been prepared and tested in asymmetric HWE reactions (Figure 5).



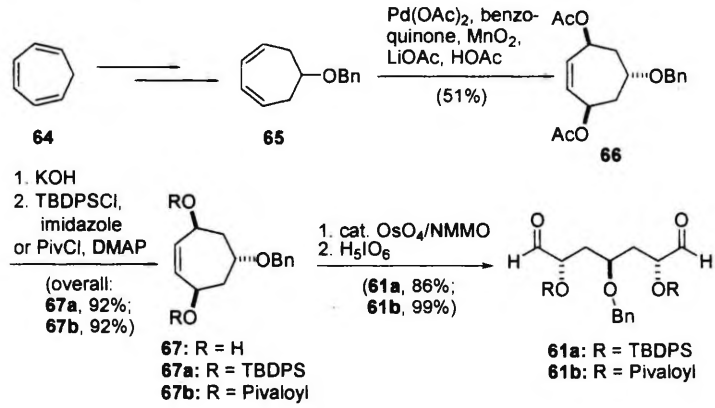

**61a**: R = TBDPS
**61b**: R = Piv

**62a**: R = TBDPS
**62b**: R = Piv
**62c**: R = Bz

**63**

**Figure 5.** Different types of *meso*-dialdehydes used in this work.

Dialdehydes **61** were synthesized in four steps from 6-(benzyloxy)-1,3-cycloheptadiene **35** [55], which in turn is accessible from 1,3,5-cycloheptatriene (Scheme 25). The relative stereochemistry in the three stereocenters in **61** was controlled by a palladium catalyzed *cis*-diacetoxylation developed by Bäckvall et al. [56]. This particular stereochemical outcome has been rationalized in Scheme 26.




**Scheme 25.** Preparation of dialdehydes **61**.

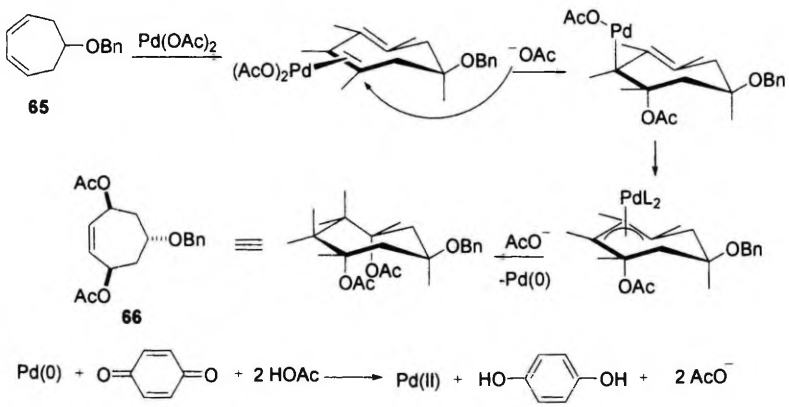
The initial acetoxypalladation of the olefin takes place with *trans* stereochemistry. The second acetoxylation occurs again on the face opposite the palladium, giving the *cis*-diacetate **66** as product.[8,9] The benzoquinone serves as a reoxidant for

(8) However, as evidenced by NMR on the crude product, the Pd-catalyzed diacetoxylation was not completely stereoselective. Fortunately, the other product isomers (ca. 15%) could be cleanly removed by flash chromatography.

(9) See also Section 3.1.1. in this thesis.

palladium(0) to palladium(II), which is then ready to enter the catalytic cycle again (Scheme 26). The motivation for using different oxygen-protecting groups (R in **61**) was twofold: to gain some insight into the influence of different protecting groups on the outcome of the asymmetric HWE reactions and to extend the utility of the HWE products. The alkenes **67a** and **67b**, obtained from the diol **67**, were converted into the dialdehydes **61a** and **61b** respectively, via a dihydroxylation/oxidative cleavage sequence in high to excellet yield. Dialdehyde **61a** is quite stable and allows chromatographic purification and storage in the freezer at least several months, whereas the compound **61b** is more labile and should be prepared shortly before use.

A conversion of diacetate **66** into the corresponding dialdehyde was also attempted. Unfortunately, ozonolysis of **66** didn't give the dialdehyde cleanly, and the two step dihydroxylation/oxidative cleavage procedure failed due to a facile acetyl-group migration in the diol obtained after $OsO_4$-catalyzed dihydroxylation.

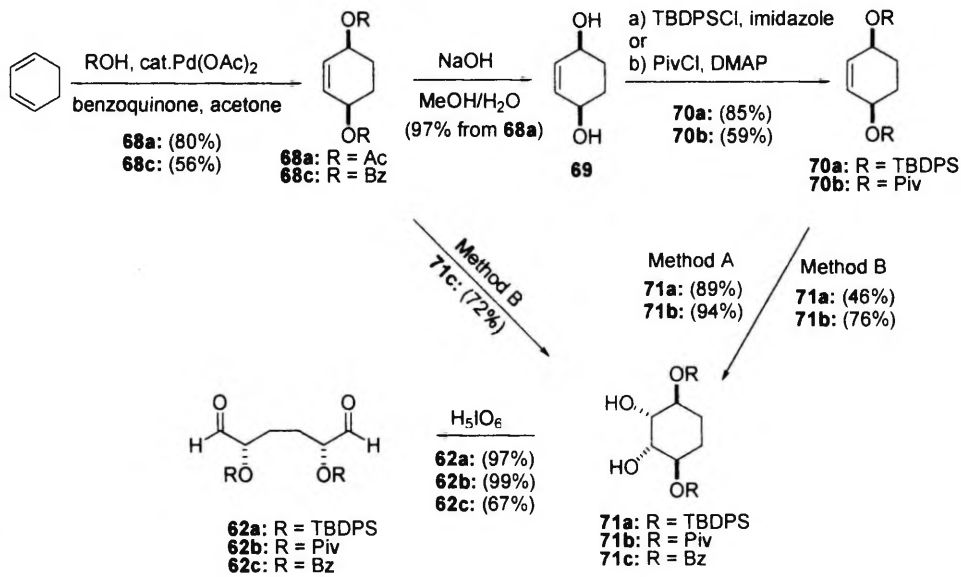



**Scheme 26.** Stereochemistry of Pd(II) catalyzed diacetoxylation and reoxidation of Pd(0) to Pd(II) necessary for a catalytic cycle.

Dialdehydes **62** were prepared in five steps from 1,3-cyclohexadiene (Scheme 27). The synthetic scheme is analogous to that of dialdehydes **61**. A Pd(II)-catalyzed diacyloxylation was performed again according to the procedure developed by Bäckvall et al. [57]. The mechanism of this reaction is similar to that of diene **65** in Scheme 26. A 1,3-cyclohexadiene is much more reactive in diacyloxylation reactions compared to diene **65**, and also enables the direct incorporation of benzoyloxy groups (**68c**).[10] A small amount of undesired *trans*-isomer was obtained, but this was successfully removed by chromatography at the stage of the

(10) The direct incorporation of pivaloyloxy groups, however, unfortunately failed.

protected diols **68c** or **70a,b** respectively.[11,12] The dibenzoyloxy derivative **68c** was directly dihydroxylated and subsequently cleaved to the dialdehyde **62c**. However, this dialdehyde was obtained together with a minor byproduct and it did not perform well in asymmetric HWE reactions. Dihydroxylation of the cyclohexene derivatives **70** worked smoothly by using a $RuCl_3/NaIO_4$ catalytic system (method A [58]), whereas the use of the more commonly employed catalytic system $OsO_4$/NMMO made the reaction very sluggish (incomplete conversion even after 3 days at ca. 60 °C). Oxidative cleavage of diols **71** with periodic acid gave the dialdehydes **62a** and **62b** in almost quantitative yield. Dialdehyde **62a** is a white crystalline compound and can be stored in the freezer several months without any detectable decomposition. Dialdehyde **62b**, however, was obtained as a colorless oil and can be stored only some days in the freezer without decomposition.

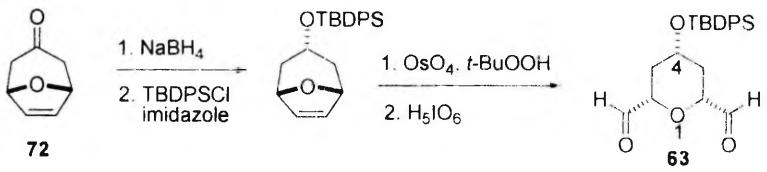



**Scheme 27.** Synthesis of dialdehydes **62**. (Method A: cat. $RuCl_3/NaIO_4$; method B: cat. $OsO_4$/NMMO).

Dialdehyde **63** was prepared according to the route developed in our group by Nina Kann [54] in four steps from bicyclic ketone **72** as illustrated in Scheme 28.

(11) The amount of *trans*-isomer observed: ca. 7% (**68c**), ca. 14% (**68a**).

(12) Undesired *trans*-isomer could be removed at the stage of diol **71a**.

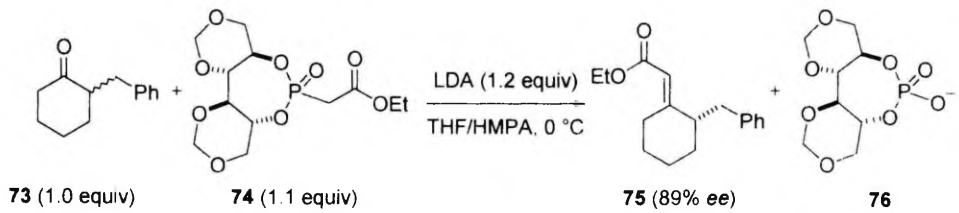



**Scheme 28.** Preparation of cyclic dialdehyde **63**.

## *2.3 Chiral phosphonates*

In principle, there are two conceptually different ways in which the chiral phosphonates can be designed: a) the chiral auxiliary (or the chirality) is placed in such a way that in the asymmetric HWE reaction it is transferred into the product, and the two product isomers are diastereomers to each other, or b) the chiral auxiliary (or just an asymmetric center) will not be incorporated into the olefinic product, but instead will remain in the phosphate ion, and the two product isomers formed are enantiomers.

An example of the latter alternative is shown in Scheme 29. The chiral phosphonate **74** (derived from mannitol) is reacted with an equimolar amount of racemic 2-benzylcyclohexanone **73** in the presence of base to provide the (*S,E*)-alkene **75** and a phosphonate anion **76**.[13]

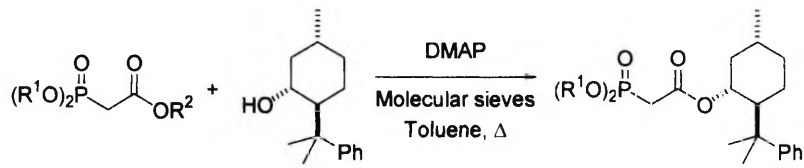



**Scheme 29.** Asymmetric HWE reaction with chiral phosphonate **74**.

The disadvantages of using this type of chiral phosphonate reagents are the difficulties in recycling the chiral auxiliary and in separating the two product enantiomers (in case the minor enantiomer is also formed in detectable amounts). Therefore, we have preferred investigating and using the other type of phosphonates, where the chiral auxiliary will be incorporated into the olefinic product during the HWE reaction, the diastereomeric product isomers are more easily separated, and the chiral auxiliary can be easily recycled.

(13) This is another example of a *dynamic kinetic resolution* (see page 31). The small excess of base rapidly equilibrates the substrate enantiomers during the reaction, and theoretically all the substrate can be converted into a single product.

In this work, phosphonates **58a-e**, bearing (1*R*,2*S*,5*R*)-8-phenylmenthol[14] as a chiral auxiliary, have been used.[15] 8-Phenylmenthol has been used earlier in asymmetric HWE reactions; e.g. reagent **58a** has given useful levels of diastereoselectivity in reactions with a prochiral monoketone and with some structurally related chiral ketones [59]. Useful to high diastereoselectivities have also been obtained in various other types of reactions by using 8-phenylmenthol as a chiral auxiliary; e.g. Diels-Alder reactions [60], free radical and Ti(II) alkoxide-mediated cyclization reactions [61], Grignard additions [62], Michael-type additions [63], [2,3]-Wittig rearrangements [64], alkylations of *N*-benzoylalanine esters [65], iodocarbocyclizations [66], ene reactions [67], and nitro-aldol condensations [68]. In addition, titanocene (8)-phenylmenthol complex has been recently used as a chiral catalyst in enantioselective opening of *meso*-epoxides [69]. The 8-phenylmenthol unit was incorporated into the non-chiral phosphonates by a simple transesterification reaction (Scheme 30).




**77a:** $R^1 = R^2 = Me$
**77b:** $R^1 = R^2 = Et$
**77c:** $R^1 = i\text{-Pr}$, $R^2 = Me$
**77d:** $R^1 = CF_3CH_2$, $R^2 = Me$
**77e:** $R^1 = o\text{-Tolyl}$, $R^2 = Et$

**78**

**58a:** $R^1 = Me$ (93%)
**58b:** $R^1 = Et$ (86%)
**58c:** $R^1 = i\text{-Pr}$ (93%)
**58d:** $R^1 = CF_3CH_2$ (89%)
**58e:** $R^1 = o\text{-Tolyl}$ (100%)

**Scheme 30.** Preparation of chiral phosphonates bearing 8-phenylmenthol as a chiral auxiliary.

Unfortunately, only one enantiomer of 8-phenylmenthol (i.e. **78**) is readily available. However, we expect that the nor-analogue **79**, which differs from the 8-phenylmenthol in lacking the methyl substituent in the cyclohexyl ring and is commercially available in both enantiomeric forms, will give very similar results in asymmetric HWE reactions [70]. Therefore we have prepared the chiral phosphonate **80**, which can be used as a substitute when the opposite HWE product enantiomer is required in some specific synthetic application (Scheme 31).[16]

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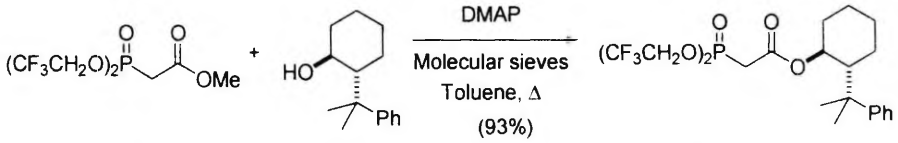
(14) Prepared in multigram scale in five steps from commercially available (*R*)-pulegone according to the following procedure: Ort, O. *Org. Synth.* **1987**, *65*, 203.

(15) Phosphonate **58e** was prepared in our group by Dr. I. Kawasaki.

(16) The cost of 8-phenylmenthol **78** is still considerably lower compared to the nor-analog **79**, and therefore we have preferred it for extensive methodology studies.




77d 79 80

**Scheme 31.** Preparation of chiral phosphonate **80**.

## *2.4. Results of asymmetric HWE reactions*

Being encouraged by the initial results obtained in our group primarily by Nina Kann ([52,54], see Section 2.1.3. for details), we have performed a more thorough study of reactions between chiral phosphonates **58a-e** and structurally different *meso*-dialdehydes bearing α-oxygen substituents. The motivation for using dialdehydes **61**, **62** and **63** was twofold: (i) the use of different oxygen protecting groups would give information about the influence of different OR groups on the reaction selectivity; (ii) the expected chiral monoaddition products are potentially useful chiral building blocks for many classes of natural products. Furthermore, varying the oxygen protective groups would hopefully enable us to perform different synthetic sequences with the expected monoaddition HWE products, since different OR groups possess different reactivities in subsequent conversions.

### 2.4.1. Asymmetric HWE reactions with *meso*-dialdehyde 61[1]

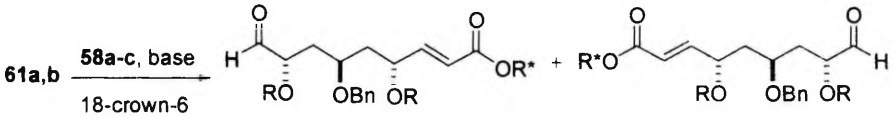
Our first goal was to find the optimum conditions for the synthesis of (*E*)-alkenes **81a** and **81b** from dialdehydes **61a** and **61b**, respectively. The reaction conditions chosen were expected to favor kinetic control in the initial addition step, by increasing the relative rate of the subsequent elimination (KHMDS as a base in combination with 18-crown-6, low temperature [71]). When phosphonates **58a-c** were used, almost exclusively (*E*)-alkenes were obtained (Table 1).

The silyl-protected dialdehyde **61a** behaved similarly with all three (*E*)-selective phosphonate reagents (entries 1-3). Even though the initial diastereomeric ratios ranged from 87:13 to 91:9, the product was obtained as a single diasteromer after flash chromatography, in synthetically useful yields.[17] The slightly lower yield with the diisopropyl phosphonate (entry 3) is probably due to incomplete conversion. The essentially complete (*E*)-selectivity observed with **58a** was

(17) The separation was successful if Amicon silica was used, whereas the use of Merck silica did not enable separation of the diastereomers (see paper I, footnote 23 for further details).

somewhat surprising, since nonasymmetric HWE reactions with dimethyl phosphonoacetates often give (*Z*)-products under similar reaction conditions.

**Table 1.** Reactions of phosphonates **58a-c** with dialdehydes **61**.[a]




R* = (1*R*,2*S*,5*R*)-8-phenylmenthyl
Series a: R = TBDPS
Series b: R = Pivaloyl

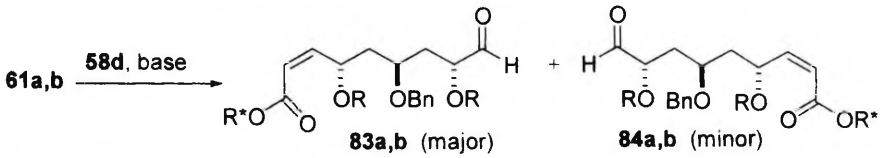
| Entry | Phosphonate | Substrate | Temp. (°C) | Product | Yield[b] (%) | d.r.[c] | Yield of bisadd. (%) |
|---|---|---|---|---|---|---|---|
| 1 | **58a** | **61a** | -78 | **81a** | 65[d] | ≥98:2 (87:13) | n.d. |
| 2 | **58b** | **61a** | -78 | **81a** | 60[d] | ≥98:2 (88:12) | n.d. |
| 3 | **58c** | **61a** | -78 | **81a** | 46[d] | ≥98:2 (91:9) | n.d. |
| 4 | **58a** | **61b** | -90 | **81b** | 10 | 82:18 | 65[e] |
| 5 | **58b** | **61b** | -90 | **81b** | 62 | 95:5 | 35[e] |
| 6 | **58c** | **61b** | -90 | **81b** | 65 | 94:6 | 26[e] |

[a] General reaction conditions: 1.2-1.3 equiv of dialdehyde, 1.1-1.3 equiv of phosphonate, 1.0 equiv of KHMDS, 5 equiv of 18-crown-6, ca. 0.02 M in THF, 6-17 h. [b] Yield of isolated monoaddition product. [c] Ratio (**81a,b**:**82a,b**) in the isolated product. If different, the ratio in the crude product is given in parantheses. The ratios of geometric isomers were in all entries: (*E*):(*Z*) ≥98:2. [d] The isolated product also contained small amounts of unreacted dialdehyde: entry 1, 6%; entry 2, 6%; entry 3, 3%. [e] Mixture of bisaddition products.

The pivaloyl-protected dialdehyde **61b** is somewhat more reactive compared to **61a** and the reactions can be run at even lower temperatures (-90 °C) and for shorter reaction times (after 6 h all starting material was usually consumed). High diastereoselectivities and synthetically useful yields were obtained in the reactions with the diethyl- and diisopropyl phosphonates (entries 5 and 6), whereas the dimethyl phosphonate performed poorly with this substrate (entry 4). The byproducts in all these reactions were the bisaddition compounds, which are formed when the remaining aldehyde group in the monoadditions product (**81** and **82**) immediately reacts further with the phosphonate anion.

Access to the (*Z*)-alkenes was achieved by using the bis(trifluoroethyl)-phosphonate **58d** (Table 2). Under optimized conditions both dialdehyde substrates afforded (*Z*)-monoaddition products with excellent diastereo- and geometric selectivity (entries 2-4) in good yields. The results obtained with dialdehyde **61a** indicate that the specific choice of reaction conditions is very important: although the use of KHMDS/18-crown-6 as a base is often the most efficient with other substrates, the result of the reaction between **61a** and **58d** was greatly improved when 18-crown-6 was omitted (see entries 2 and 3). In case of the pivaloyl-protected dialdehyde **61b** the use of our 'standard' base system (KHMDS/18-crown-6) afforded **83b** as the only detectable monoaddition diastereomer by $^1$H NMR spectroscopy (entry 4). Omitting 18-crown-6 caused a dramatic drop in yield and selectivity with this dialdehyde (results not included in this table).

**Table 2.** Reactions of phosphonate **58d** with dialdehydes **61**.[a]



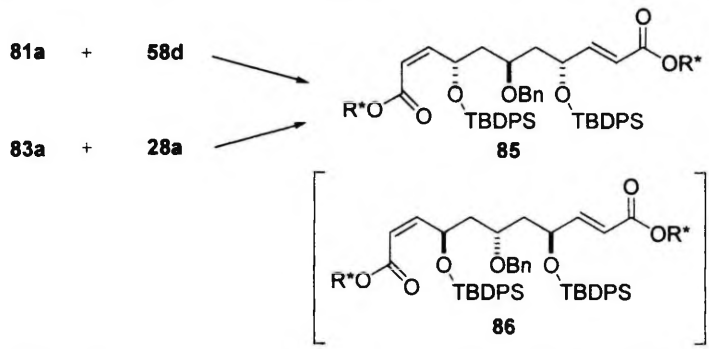

R* = (1*R*,2*S*,5*R*)-8-phenylmenthyl
Series a: R = TBDPS
Series b: R = Pivaloyl

| Entry | Phosphonate | Substrate | Temp. (°C) | Product | Yield[b] (%) | d.r.[c] | Yield of bisadd. (%) |
|---|---|---|---|---|---|---|---|
| 1 | **58d** | **61a** | -78 | **83a** | 61[d] | 84:16 | 24[d] |
| 2 | **58d**[f] | **61a** | -78 | **83a** | 76 | 98:2 | n.d. |
| 3 | **58d**[g] | **61a** | -78 | **83a** | 60 | 96:4 | n.d. |
| 4 | **58d** | **61b** | -90 | **83b** | 62 | ≥98:2 | 29[e] |

[a] General reaction conditions: 1.2-1.3 equiv of dialdehyde, 1.1-1.3 equiv of phosphonate, 1.0 equiv of KHMDS, 5 equiv of 18-crown-6, ca. 0.02 M in THF, 6-17 h. [b] Yield of isolated monoaddition product. [c] Ratio (**83a,b**:**84a,b**) in the isolated product. The ratios of geometric isomers were in all entries: (*Z*):(E) ≥98:2. [d] Some (*Z*,*E*)-bisaddition product (yield 7%) was obatined in the same fraction as the monoaddition products. The (*Z*,*Z*)-bisaddition product was isolated separately (yield 17%). [e] Mixture of bisaddition products. [f] No 18-crown-6 was used. [g] NaHMDS was used as base, no 18-crown-6.

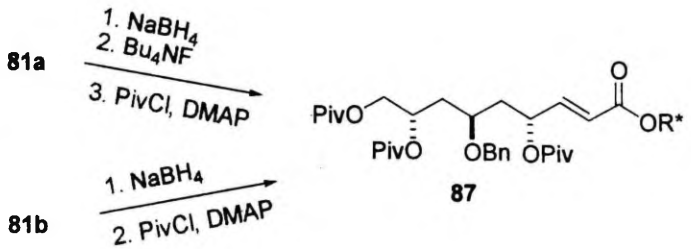
The absolute configuration of the compounds **81b**, **83a** and **83b** were assigned on the basis of the known absolute configuration of compound **81a** [54]. The indicated configuration of compound **83a** was determined as follows: both monoaddition products **81a** and **83a** were converted to the same (*Z*,*E*)-bisaddition product **85** by reaction with phosphonates **58d** and **58a**, respectively (Scheme 32).

If (*Z*)-alkene **83a** would not have had the indicated stereochemistry, but opposite, then compound **86** instead of **85** would have been obtained from the reaction between **83a** and **58a**. Bisaddition compounds **85** and **86** are diastereomers and are distinguishable by NMR spectroscopy.[18]




**Scheme 32.** Assigning the absolute configuration of compound **83a** (see text).

The absolute configuration of the pivaloyl-protected (*E*)-product **81b** was assigned by correlation with the silyl-protected (*E*)-product **81a**. Both (*E*)-monoaddition compounds were converted to the derivative **87** as shown in Scheme 33. Based on NMR analysis, the same diastereomer of **87** was produced in both cases, indicating that the both (*E*)-alkenes have the same absolute configuration. The pivaloyl (*Z*)-alkene **83b** was correlated with **81b** in a similar manner as **83a** was correlated with **81a** (vide supra).




**Scheme 33.** Assigning the absolute configuration of compound **81b** (see text).

A general conclusion from these correlations is that in the asymmetric HWE reactions with dialdehydes **61**, (*E*)- and (*Z*)-selective phosphonates attack opposite enantiotopic carbonyl groups in the dialdehyde. An attempt to rationalize the observed stereochemical outcome of these asymmetric HWE reactions is made in Section 2.5.2.

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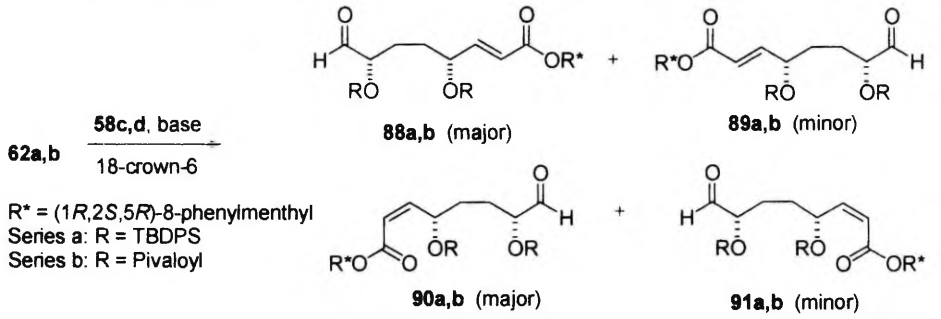
(18) A small amount of bisaddition product **86** was detected in the reaction between **81a** and **58d**, because **81a** contained ca. 10% of **82a**.

### 2.4.2. Asymmetric HWE reactions with *meso*-dialdehydes 62[III,IV]

We applied the best conditions found for the asymmetric HWE reactions with dialdehydes **61** to dialdehydes **62**. The results obtained are summarized in Table 3.

**Table 3.** Asymmetric HWE reactions with dialdehydes **62**.[a]




| Entry | Phosphonate | Substrate | Temp. (°C) | Product | Yield[b] (%) | d.r.[c] | Yield of bisadd. (%) |
|---|---|---|---|---|---|---|---|
| 1 | **58c** | **62a** | -78 | **88a** | 61[d] | 95:5 | 36 |
| 2 | **58d**[e] | **62a** | -78 | **90a** | 88 | ≥98:2 | n.d. |
| 3 | **58c** | **62b** | -85 | **88b** | 55 | 98:2 | 44 |
| 4 | **58d** | **62b** | -85 | **90b** | 71 | ≥98:2 | 25 |

[a] General reaction conditions: 1.2-1.3 equiv of dialdehyde, 1.1-1.3 equiv of phosphonate, 1.0 equiv of KHMDS, 5 equiv of 18-crown-6, ca. 0.02 M in THF, 3-12 h. [b] Yield of isolated monoaddition product. [c] Ratio of **88a,b**:**89a,b** or **90a,b**:**91a,b**, respectively. The ratios of geometric isomers were in all entries: (*Z*):(E) ≥98:2. [d] Yield after reduction of the monoaddition product to the alcohol. [e] NaHMDS was used as a base, no 18-crown-6.

The (*Z*)-alkene products **90a** and **90b** were obtained in high yields with essentially complete geometric- and diastereoselectivity by using bis(trifluoroethyl)-phosphonate **58d**. (*E*)-alkenes **88a** and **88b**, in turn, were obtained with good to excellent levels of asymmetric induction and moderate yields by using the bis(triisopropyl)phosphonate **58c**. The considerable amount of bisaddition products isolated in entries 1 and 3 indicate that some further modification of the reaction conditions might lead to an increased yield of the (*E*)-monoaddition products. In order to assign the absolute configuration of the pivaloyl-protected monoaddition products **88b** and **90b**, two diastereomeric of Mosher esters [72] were prepared from each of the two alkenes (Figure 6). Analysis of the $^1$H NMR spectra of the Mosher esters indicated that the absolute configurations of the HWE products **88b** and **90b** match the absolute configurations of the

corresponding HWE products obtained from dialdehyde **61** (see Paper III for further details). The absolute configurations of the silyl-protected compounds **88a** and **90a** are tentatively assigned by analogy with compounds **81a/83a** and **88b/90b**.

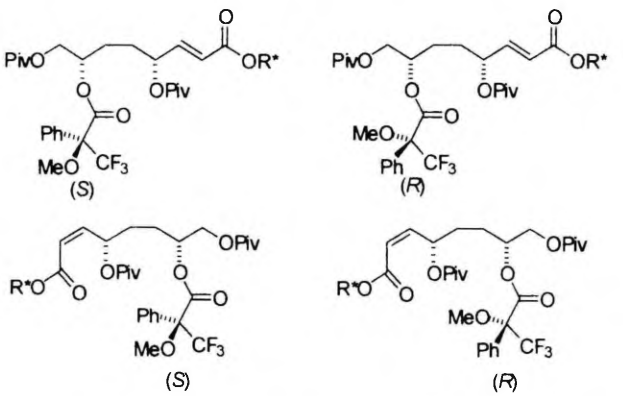
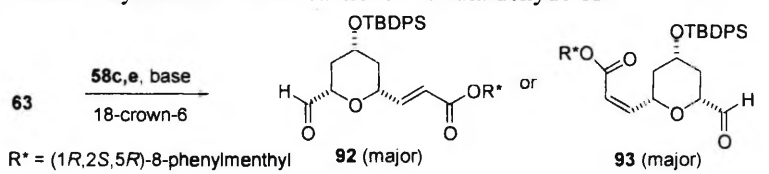



**Figure 6.** Mosher esters prepared for absolute configuration assignments. (The descriptors (*S*) and (*R*) refer to the configuration of the MTPA moiety).

### 2.4.3. Asymmetric HWE reactions with *meso*-dialdehyde 63[IV]

*Meso*-dialdehyde **63** differs from the acyclic dialdehydes **61** and **62** by having a cyclic tetrahydropyran framework. A lot of effort was put into optimizing the reaction conditions with this cyclic dialdehyde, but unfortunately even the best results of the asymmetric HWE reactions remained relatively poor (Table 4).

**Table 4.** Asymmetric HWE reactions with dialdehyde **63**.[a]




| Entry | Phosphonate | Substrate | Time (h) | Product | Yield[b] (%) | d.r.[c] | Yield of bisadd. (%) |
|---|---|---|---|---|---|---|---|
| 1 | **58c** | **63** | 3 | **92** | 35 | ≥98:2 | 53 |
| 2 | **58e** | **63** | 16 | **93** | 39 | ≥98:2 | 50 |

[a] General reaction conditions: 1.2-1.3 equiv of dialdehyde, 1.1-1.3 equiv of phosphonate, 1.0 equiv of KHMDS, 5 equiv of 18-crown-6, ca. 0.02 M in THF, -78 °C. [b] Yield of isolated monoaddition product. [c] The ratios of geometric isomers were in both entries: (*Z*):(E) ≥98:2.

The main problem with this dialdehyde seems to be the formation of large amounts of bisaddition products which, in turn, is a measure of relatively poor geometric and/or diastereoselectivity. However, the monoaddition products (**92** and **93**) were obtained with essentially complete diastereo- and geometric selectivity. The possible explanation for this could be that once **92** or **93** are formed, they are unreactive, whereas other possible monoaddition product isomers react immediately further to form bisaddition products. The diarylphosphonate **58b** was found to be the best for the synthesis of (*Z*)-product **93**. An inspiration for using **58e** came from Ando [73] who recently introduced the corresponding nonchiral phosphonate **77e** as highly (*Z*)-selective in nonasymmetric HWE reactions. However, reagent **58e** performed very poorly in reactions with dialdehyde **61a**, and afforded predominantly (*E*)-alkene products in asymmetric HWE reactions with α-amino aldehydes ([74], see also Paper II).

The use of the cyclic dialdehyde **63** opens a direct route to 2,6-*cis*-THP derivatives, and therefore improving the yields of monoaddition products would be of great importance. One alternative to try would be to modify the substitution pattern at C-4 in the *meso*-dialdehyde, to see if this might improve the selectivities.

## *2.5. Mechanistic aspects of asymmetric HWE reactions*

To fully understand the stereochemical aspects of the HWE reactions which will be discussed in Section 2.5.2, some basic concepts of nucleophilic addition reactions are described preceedingly in following section.

### 2.5.1. The Felkin-Anh and the Cram-chelate model

The formulation of models that successfully predict the stereochemical outcome of reactions at trigonal carbon centers has been a major preoccupation in synthesis design. Currently, the Felkin-Anh model is widely employed to interpret the contributions of torsional, steric, and electronic factors from the stereogenic center α to the reacting carbonyl (see structures in Figure 7). Felkin concluded that transition states **94** and **95** were the most important. (For a more detailed discussions about the Felkin-Anh and other related models, see [75]).

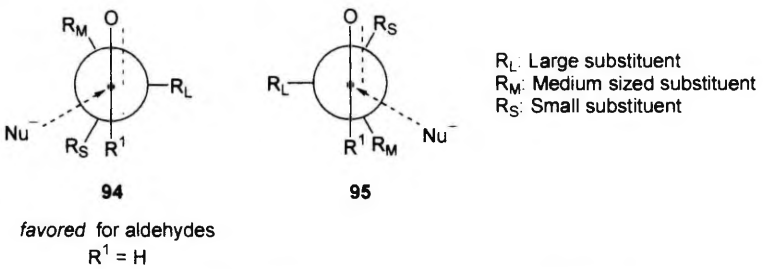


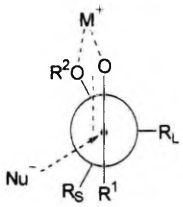

**Figure 7.** Nucleophilic addition according to the Felkin-Anh model.

The use of these structures to predict the stereoselectivity is referred to as the *Felkin-Anh model.*[19] When $R_M$ is similar in size to $R_S$, there is little difference between the destabilizing $R_M \leftrightarrow O$, $R_S \leftrightarrow O$ interactions or the destabilizing $R_S \leftrightarrow R^1$, $R_M \leftrightarrow R^1$ interactions, and modest to poor selectivity is predicted. As $R_M$ or $R^1$ increases in bulk, the increased $R_M \leftrightarrow R^1$ destabilizing interaction in **95** will favor **94**. However, the interactions of the incoming nucleophile (which approaches the carbonyl at a Nu → C=O angle close to 107° [76]) with the medium and small substituents will also have an important influence on the stereodifferentiation. In the case of aldehydes (where $R^1$ = H), these interactions with the incoming nucleophile will presumably dominate.

If chelation between the carbonyl group and one of the substituents of the α-stereocenter can occur, the substrate will be locked into the single rotamer **96**

(19) The term *Felkin-Anh-Eisenstein* model has also been used.

(Figure 8). Chelation places this substituent ($R^2O$ in the example shown) eclipsed with the carbonyl. When this substituent equates with the medium sized substituent in the open-chain (Felkin-Anh) model, the relative stereochemical outcome is the same. Otherwise, the complementary diastereomer, usually referred to as the Cram-chelation product,[20] predominates [77]. The cyclic model applies mainly for α-alkoxy carbonyls (5-membered chelate), whereas β-alkoxy carbonyls (6-membered chelate) are less selective in most cases.

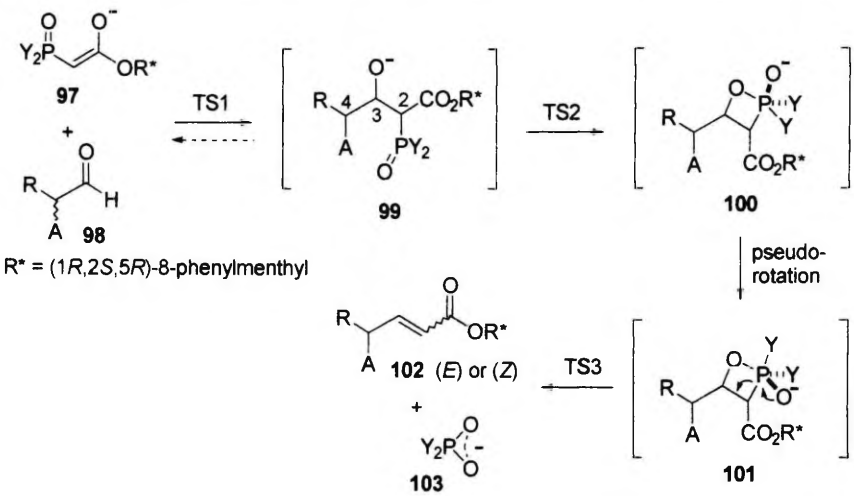



96

**Figure 8.** Addition of nucleophiles to chelated carbonyl compounds.

### 2.5.2. General mechanism and origin of stereochemistry

In spite of the wide synthetic use, the detailed mechanism and the origin of the (*Z*)/(*E*) selectivity of HWE reactions have remained unclear for many years. Only very recently have more thorough theoretical studies on this topic appeared [78]. The generally accepted mechanism of the HWE reaction is shown in Scheme 34.




**Scheme 34.** The general mechanism for the HWE reaction.

(20) Sometimes also referred to as the *anti*-Felkin-Anh product.

The reaction starts with formation of oxyanion **99**, which then ring-closes to form oxaphosphetane **100**, and the subsequent elimination of dialkylphosphate **103** affords an alkene product **102**. Computational studies have shown that transition states one (TS1) and two (TS2) are relatively close in energy, while TS3 has substantially lower energy and has very little influence on the reaction outcome (Figure 9). Whether the formation of oxyanion **99** is reversible or not depends on the relative energies of TS1 and TS2 which, in turn, are dependent on several factors (e.g. the solvent polarity, the nature of the counterion, steric factors in both reactants). The computational studies by Brandt and Ando have also indicated that TS1 should favor (*Z*)-products while TS2 will favor the formation of (*E*)-products.

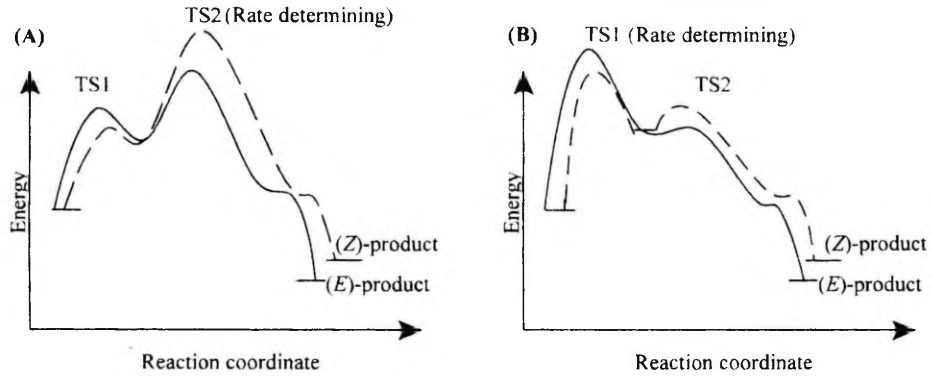



**Figure 9.** Schematic representation of the postulated energy profile for HWE reaction: (A) in the case of (*E*)-selective phosphonate reagent, and (B) in the case of (Z)-selective phosphonate reagent (see text for discussion).

When *meso*-dialdehydes are used as substrates in asymmetric HWE reactions, then two new stereocenters are formed adjacent to the preexisting stereocenter in intermediate **99**. Since the substrate contains two enantiotopic carbonyl groups, eight different diastereomeric forms of **99** are theoretically possible. It has been postulated that three different factors determine the relative rates of formation of different diastereomers of **99**: (i) the chiral auxiliary determines the absolute configuration at C-2 by controlling the facial preference in addition to the phosphonate enolate anion; (ii) the structure of Y determines the relative stereochemistry at C-2 and C-3 (and ultimately the alkene geometry of the product); (iii) the α-stereocenter in the substrate determines the relative stereochemistry at C-3 and C-4. All these three controlling factors have to act together in order to favor only one diastereomer of **99** which is the precursor of the final product. Recent studies [79] based on NMR analysis have shown that the Li-enolate of **58a** has (*E*)-enolate geometry. It is reasonable to assume that other chiral phosphonates used in this work also form predominantly or exclusively (*E*)-enolates (Figure 10). All the asymmetric HWE reactions with substrates

containing α-heteroatom (oxygen or nitrogen) substituents studied in our group to date follow the same pattern: the major products observed experimentally are the ones which would arise if TS1 follows the Felkin-Anh-Einsestein (FAE) model (see Section 2.5.1). Due to the fact that the chiral auxiliary (8-phenylmenthyl) is efficiently

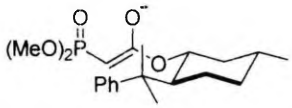
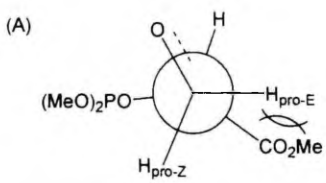
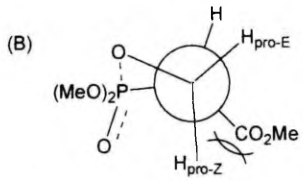



**Figure 10.** Postulated favored structure of the phosphonate anion.

blocking the *Re* face of the phosphonate enolate, oxyanions **99** possessing (2*S*)-configuration are strongly favored in TS1. The postulated intermediate diastereomers **104** and **105**, which give rise to observed products **81** and **83**, respectively, are shown in Scheme 35. So why does the group $R^1$ in the phosphonate induce the observed relative sterochemistry at C-2/C-3? This remains without a clear answer to date. The computational studies have shown that in the case of the (*E*)-selective phosphonate reagent (Figure 9, graph A) TS2 is the rate determining. In TS2, the pro-(*E*)-species is substantially lower in energy compared to the pro-(*Z*)-species (which is destabilized due to interaction(s) between the ester group and the pro-(Z)-substituent, Figure 11, structure B).



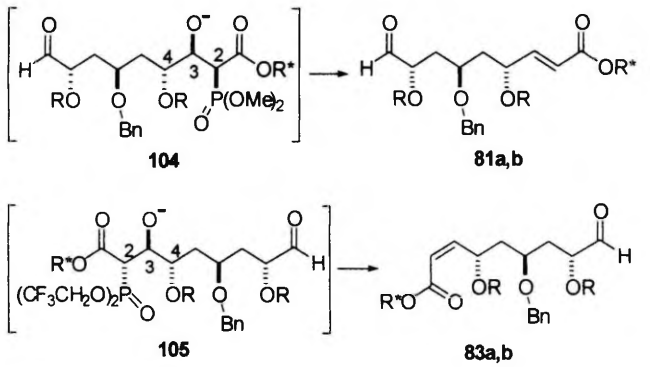

The lowest transition state (TS1) found leading to oxyanion. Note a close steric interaction between the ester group and the pro-*(E)*-aldehyde substituent.




The lowest transition state (TS2) leading to the oxaphosphetane. This transition state will generally favor the formation of *(E)*-products.

**Figure 11.** Postulated transition states in the HWE reaction between formaldehyde and the anion of $(MeO)_2OPCH_2CO_2Me$ [78a].

However, in the case of (*Z*)-selective phosphonates, TS2 can at most have only a marginal influence on the product distribution and TS1 becomes the rate determining step. In TS1, a non-hydrogen substituent in the aldehyde can more easily adopt the pro-(*Z*) position, due to larger steric crowding with the $CO_2R$ group in the pro-(*E*) orientation (Figure 11, structure A). This situation is especially pronounced for trifluoroethyl reagents, where a C-H···O hydrogen bond stabilizes pro-(Z)-species of TS1 particularly well.

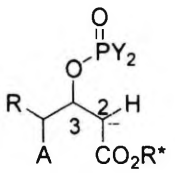



**Scheme 35.** Postulated intermediate diastereomers leading to (*E*)- and (*Z*)-alkenes **81a,b** and **83a,b**, respectively

The possibility for tautomerization of intermediate **99** has also been evaluated [78a]. It turned out that intermediate **99** might have long enough lifetime to enable reversible proton transfer from C-2 to the oxygen at C-3 to form a hydroxy enolate, which may affect the overall reaction selectivity under certain conditions.

A pseudorotation of rather short lived intermediate **100** converts it to **101**. Attack of oxygen on the tetrahedral phosphorus in oxyanion **99** takes place at one face of the tetrahedron, one OR group (the one which is trans to the reacting face) and the attacking oxygen ending up in the apical positions (see [78a] for additional details). It is well known that in five-coordinated phosphorus, the anionic oxygen does not go to an apical position [80], thus the pseudorotation takes place by using the anionic oxygen as a pivot.[21] Although the pseudorotamer **101** is not a stationary point, it is still of very low energy and is very probably a part of the reaction path. Any event on the reaction path after formation of **100** will be unable to influence the reaction rate. An influence on the reaction selectivity, on the other hand, is possible, but only if any subsequent isomeric intermediates can interconvert (e.g., via C2-C3 bond rotation in **106**, Figure 13). However, the computational studies show that this intermediate, if it exists at all, is very short-lived, and the possibility for isomerization through C2-C3 bond rotation is minimal.

(21) The consequence of the pseudorotation is that in **101** the carbon substituent and one OR group on phosphorus are apical, while the other three substituents are equatorial.




**106**

**Figure 13.** Intermediate **106** (lays somewhere between **101** and **102** on the reaction path).

Norrby, Brandt and Rein [81] have recently devised a new method for creating a transition-state force field, based on quantum chemical normal-mode analysis, and used this to rationalize successfully the product selectivities in a set of asymmetric HWE reactions. In all cases in which high selectivities were observed experimentally, the modeling predicted the correct major product isomer and also gave a good estimate of the level of selectivity. One of the long term goals of this work is to produce a tool for rapid screening of potential reagent-substrate combinations, to evaluate new reactants before actually synthesizing them.

To summarize, the results from the asymmetric HWE reactions studied in this thesis can be rationalized by using the three postulated selectivity controlling factors (vide supra), but in spite of the recently published mechanistic studies, several questions remain to be answered and further studies are needed to fully understand the mechanistic details and the origin of the selectivities.

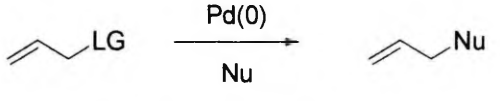
# 3. The synthesis of THF and THP derivatives

## *3.1. Selected fundamentals*

### 3.1.1 Pd(0)-catalyzed allylic substitution

Among the transition metals used for allylic substitutions, palladium is the most widely employed [82]. The important advantages of palladium include the high tolerance to many functional groups, relatively easy handling (lower sensitivity to oxygen and moisture), and lower toxicity compared to many other transition metals. Also, the π-allyl complexes (vide infra) can be formed from a wide variety of starting materials, and these complexes are reactive towards different nucleophiles. Other transition metals which can be used for allylic substitutions are nickel, platinum, tungsten, molybdenum, cobalt, rhodium and iron [83].

The basic process of allylic substitution is illustrated in Scheme 36 where the leaving group (LG) at the allylic position is replaced by an incoming nucleophile. The most commonly used substrates for Pd(0)-catalyzed allylic substitution are allylic acetates, but a wide range of leaving groups function effectively (among others carbonates, carbamates, phosphates, oxiranes, halides, sulfones, amines). The variety of nucleophiles used is also very wide. The most common ones are 'soft' carbanions such as malonate anion, but nitrogen based nucleophiles, oxygen nucleophiles, phosphorus nucleophiles, silicon nucleophiles, vinyl boranes, hydrides (borohydrides, aluminohydrides and formates), tetraphenylborate, organometallics (dialkylzincs, Grignards, organoaluminum reagents, organozirconium reagents, organotin reagents) have all been successfully applied as well.

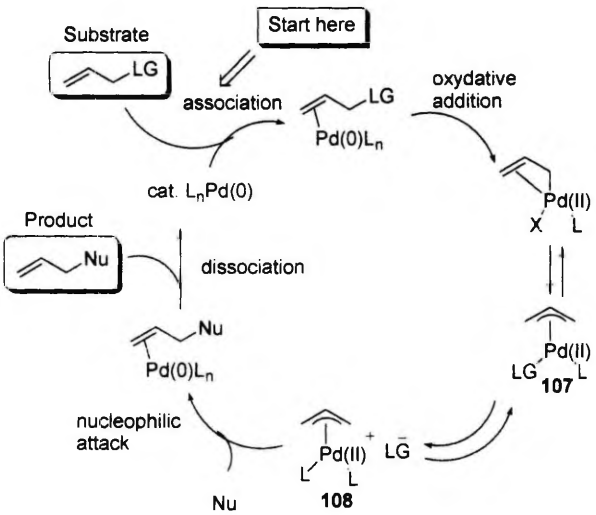



**Scheme 36.** Palladium catalyzed allylic substitution.

#### *3.1.1.1. Mechanism*

It is believed that the mechanism of the palladium catalyzed allylic substitution involves the initial coordination of palladium(0) to the alkene, followed by an oxidative addition, a process which usually goes with clean inversion, to initially give a $\eta^1$-allyl complex which is in equilibrium with the $\eta^3$-allyl complex (**107**) and is rarely detected. In contrast, the $\eta^3$-allyl complexes are rather stable and can often be isolated if desired. However, in the presence of excess ligand, equilibrium concentrations of the cationic $\eta^3$-allyl complex (**108**) are generated. It is known

that in case of bidentate phosphine ligands, the cationic complex is favored. The cationic complex is very reactive towards nucleohiles, and the nucleophilic addition generally occurs at one end of the allylic system to afford the palladium(0) complex of the product alkene. Dissociation of palladium(0) liberates the product and regenerates the active palladium catalyst, as shown in Scheme 37. In addition to nucleophilic addition, the π-allyl compex **107** can also undergo several other transformations like transmetallation, carbonylation, hydrogenolysis and elimination. Sometimes these reactions are competitive with each other, and the chemoselectivity depends on the reactants and reaction conditions.




**Scheme 37.** Mechanism for the palladium catalyzed allylic substitution.

### *3.1.1.2. The geometry of allyl complexes*

For the planar allyl complex (**109**, Figure 14), the substituents which are *syn* to the substituent at C-2 are traditionally termed as 'syn', whereas the substituents *anti* to the hydrogen at C-2 are labeled as 'anti' [84]. In case of a monosubstituted allyl complex (Figure 12), the *syn*-isomer **110** is in most cases favored over the corresponding *anti*-isomer **111** due to sterical requirements. However, some bidentate planar ligands, such as 2,9-disubstituted-1,10-phenantroline, can induce a preference for the *anti*-isomer (**111**) by destabilizing the *syn* configuration (**110**) via the selective interference between methyl substituent on bidentate planar ligand and *syn* substituents of $\eta^3$-allyl square-planar complex [85].

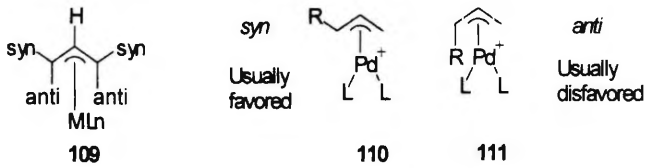



**Figure 12.** Allyl complex **109**, and geometry of monosubstituted allyl complexes.

In disubstituted allyl complexes the *syn,syn*-geometry is usually favored (Figure 13), and for more highly substituted allyl complexes, a similar geometrical preference is observed. The isomeric forms may equilibrate via different processes: a π–σ–π rearrangement (vide infra), apparent allyl rotation [22] [83,86], or a $S_N2$ type displacement of $PdL_2$ at an allylic complex by another $PdL_2$ species [83].

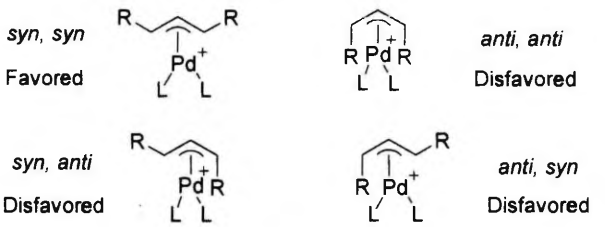



**Figure 13.** Geometry of disubstituted allyl complexes.

### *3.1.1.3. Stereochemical aspects*

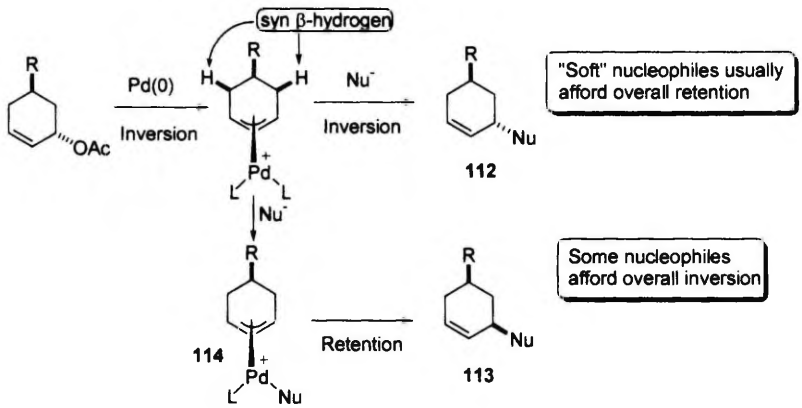
The stereochemistry of the Pd-catalyzed allylic substitution has been studied extensively.[23] In the first step, palladium displaces the leaving group with inversion. The subsequent reaction with 'soft'[24] carbon nucleophiles proceeds by inversion to give **112** (Scheme 38). Overall, this accounts for the observed net retention of stereochemistry. With 'hard', more strongly basic carbon nucleophiles and π-allyl complexes having adjacent hydrogens, proton abstraction may occur which leads to protodemetallation, affording a diene and palladium(0). When the

(22) There is some debate over the exact mechanism of this process, but a general observation is the apparent rotation of the π-allyl group relative to the ligands on palladium.

(23) See [82a] pp 292-297, and references cited therein.

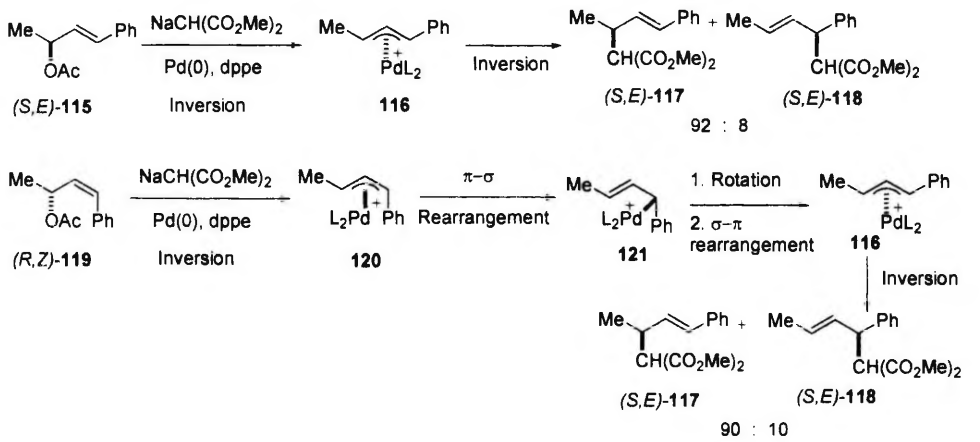
(24) 'Soft' nucleophiles are commonly defined as those derived from conjugate acids whose $pK_a < 25$, and 'hard' nucleophiles from conjugate acids whose $pK_a > 25$. For a more detailed discussion, see e.g.: Isaacs, N. S. *Physical Organic Chemistry,* Longman Scientific & Technical: Essex, 1987, pp 239-242 and references cited therein.

π-allyl cannot eliminate to a diene, attack apparently occurs at the metal center. Reductive elimination of the σ–π-complex (**114**) results in replacement of the metal with retention of configuration. Thus overall inversion is observed, to give product **113** in Scheme 38. However, exceptions do exist, and these guidelines for the stereochemical outcome should by no means be taken as a rules. A good example of an exception, where the stereochemistry of the first step of the Pd(0)-catalyzed allylic substitution is changed by precoordination of the catalyst to a neighboring $Ph_2P$ group, was recently reported by Farthing and Kocovský [87]. With nucleophiles capable of inducing *syn* β-hydrogen elimination, the relative rates of β-hydrogen elimination and reductive elimination will determine which product is formed. Nitrogen and oxygen nucleophiles can displace the metal by either mechanism (by inversion or by retention) with comparable facility [88].




**Scheme 38.** Retention vs. inversion of configuration in Pd(0) catalyzed allylic substitution.

There are also differences in the stereochemical outcome involving (*E*)- or (*Z*)-allylic compounds. Whilst (*E*)-allyl compounds afford overall retention of stereochemistry for soft nucleophiles (e.g. (*S*,*E*)-**115** to (*S*,*E*)-**117**), (*Z*)-allyl compounds often react with overall inversion of configuration accompanied by (*Z*)- to (*E*)-isomerization [89] (Scheme 39).[III] (For a recent example of Pd(0)-catalyzed allylic alkylations without (*Z*)- to (*E*)-isomerization, see [90]). In case of the (*Z*)-allyl acetate **119**, oxidative addition of palladium generates the π-allyl complex **120**, which has the sterically disfavored *anti* form. Complex **120** rearranges via a process called π–σ–π rearrangement (isomerization), where the palladium in $\eta^1$-complex **121** is rotated from the front side to the rear side to give the favored *syn* complex **116**, which has the same configuration as that formed from the (*S*,*E*)-acetate **115**. Finally, the (*S*,*E*)-malonates **117** and **118** are obtained in similar ratios.




**Scheme 39.** (*E*)-Allyl actetates vs (*Z*)-allyl acetates in Pd(0)-catalyzed allylic substitutions.

### 3.1.2. Baldwin's rules

Baldwin studied many nucleophilic, homolytic, and cationic ring closing processes and found a pattern of reactivity which was predictable (Figure 15, [91]). These so-called 'Baldwin's rules' are based on the stereochemical and stereoelectronic requirements and the angles of approach allowed for bringing together two reactive centers when they are connected by a tether of atoms. If the length and nature of the chain (tether) linking the terminal atoms (e.g. O and Y, Figure 15) attains this geometry, ring formation is possible (favored) and the reaction is predicted to proceed. If the proper geometry cannot be attained, ring formation is difficult (disfavored) and competitive alternative processes are usually dominating. Baldwin classified ring closures into two categories: *exo* (the electron flow of the reaction is external to the ring being formed) and *endo* (the electron flow is within the ring being formed). Baldwin further classified reactions according to the hybridization of the atoms accepting the electrons in the ring closing process. If the atom being attacked is $sp^3$ hybridized, the reaction is termed tet (tetrahedral). Attack at a $sp^2$ atom is termed trig (trigonal), and attack at a sp hybridizied atom is dig (digonal).

Baldwin's rules are useful when planning routes to cyclic derivatives (e.g. THF's and THP's) via ring closure reactions. The approach should be planned in such a way that the ring closure falls into a 'favored' category (Figure 14). For example, the hetero-Michael additions described in Paper IV (see Scheme 47) will proceed via a 6-*exo*-trig mode and should therefore be favored. Exceptions however exist.

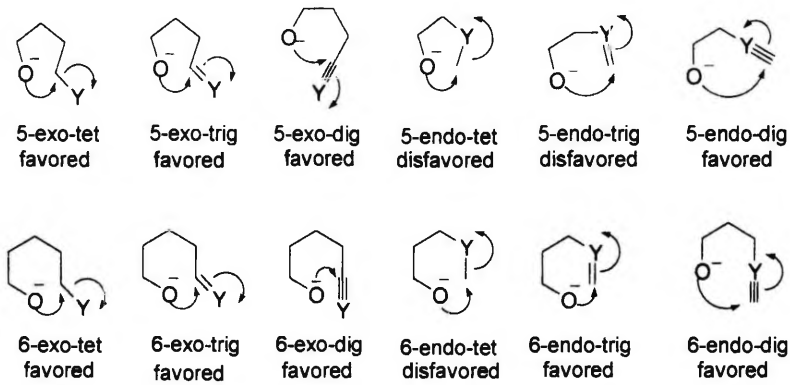
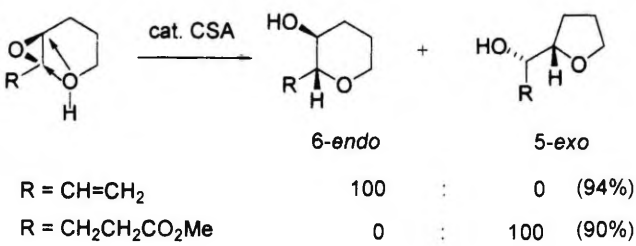



**Figure 14.** Baldwin's rules and categories of ring closure to form furanes and pyranes.

For example, Nicolau [92] has shown that the 6-*endo* mode of epoxide opening can be activated over 5-*exo* by modifying the substitution pattern adjacent to the epoxide in such a way that the C-6 position becomes allylic (Scheme 40).

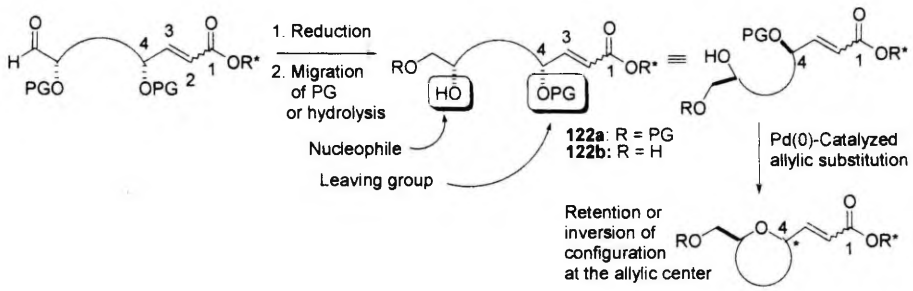



**Scheme 40.** 6-*Endo* vs 5-*exo* epoxide opening.

## *3.2. The synthesis of THF/THP derivatives from acyclic HWE products*[II,III,IV]

### 3.2.1. Via palladium catalysis[III]

Previously reported examples of THF/THP synthesis via an intramolecular Pd(0)-catalyzed allylic substitution is briefly discussed in Section 1.4. The synthetic sequence developed in this thesis offers stereochemical versatility, since depending on the double bond geometry, which is controlled in the asymmetric HWE reaction, the allylic substitution can occur with retention or inversion of stereochemistry (for mechanistic details, see Section 3.1.1.3.). In order to perform a Pd(0)-catalyzed intramolecular allylic substitution reaction to form a THF or THP ring, the presence of a good leaving group in the allylic position and a suitably placed nucleophile are needed (Scheme 41).




**Scheme 41.** A strategy for the synthesis of THF/THP derivatives via a Pd(0)-catalyzed intramolecular allylic substitution.

Since the pivaloyloxy group is a good leaving group in Pd(0)-catalyzed substitutions, all HWE products obtained from the pivaloyl-protected dialdehydes **61b** and **62b** already have a good leaving group at the allylic position. In order to fulfil the other prerequisite for the ring closure, one needs to convert the other pivaloylate to a hydroxyl group. In priciple, there are at least two different ways to do so: after reduction of the remaining aldehyde group to an alcohol one can either induce pivaloyl migration from the secondary alcohol to the adjacent primary alcohol (**122a**) or selectively hydrolyze the non-allylic pivaloyl ester to give **122b**. Both of those alternatives were tested in practice.

Different reagent combinations were tested for the reduction/PG-migration sequence. Reduction of the formyl group with $NaBH_4$ followed by treatment with

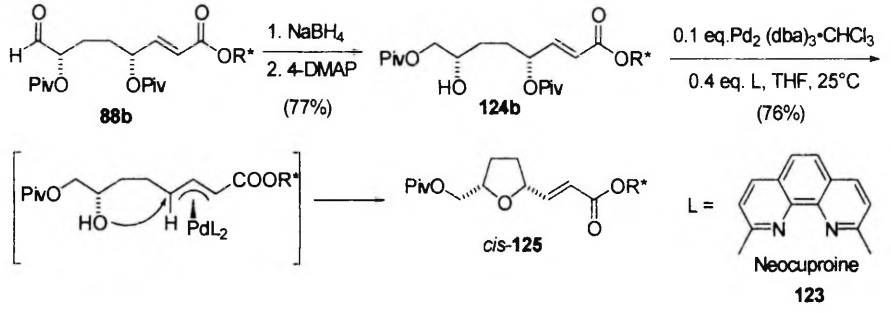
imidazole, DMAP or $Et_3N$ all afforded a roughly 2:1 mixture[25] of the desired secondary alcohol (**122a**) and a corresponding (non-migrated) primary alcohol, which can be recovered and reused. However, when $LiBH_4$ was used as reducing agent, a ca. 2:1 mixture of secondary and primary alcohols was obtained directly as product, implying that the $LiBH_4$ acts as an inducer for the pivaloyl group migration as well.[26] On the other hand, by regio- and chemoselective hydrolysis with LiOH, compound **122b** can be obtained in ca. 60-70% yield, if the reaction is carefully followed on TLC and stopped in time.

In the palladium catalyzed ring closure step, several different ligands for palladium were tested. Use of triphenylphosphine gave predominantly an undesired diene via a β-hydrogen elimination path, and the use of dppb did not give the desired allylic substitution product either. Addition of bases (pyridine, triethylamine, DBU), to increase the strength of the nucleophile, gave at best only ca. 10% of the desired product. However, somewhat surprisingly, using phenantroline based ligands instead of phosphine ligands afforded the desired products in moderate to high yields. The best ligand for these systems (among the ligands tested) turned out to be neucuproine (2,9-dimethyl-1,10-phenantroline, **123**). Normally, the reaction is greatly accelerated in the presence of π-accepting ligands such as phosphines or phosphites, and not by ligands which are only able to function as a σ-donors (e.g. alkylamine-based ligands). The π-acceptor ligands withdraw electron density from the metal, which in turn increases the positive charge character of the allyl unit, rendering it more susceptible to nucleophilic attack. Even though phosphine ligands are the most commonly employed in Pd(0)-catalyzed allylic substitutions, an examples do exist where phenantroline ligands have been found to be superior [85]. As a general rule, also supported by this study, the particular choice of ligand for palladium in allylic substitution reactions can be crucial, and is often rather case dependent.

When the (*E*)-alkene **92b** (Scheme 42) was treated with Pd(0) in the presence of neocuproine, THF derivative **125** formed in 76% yield after chromatography with clean pverall retention of configuration at the allylic stereocenter.

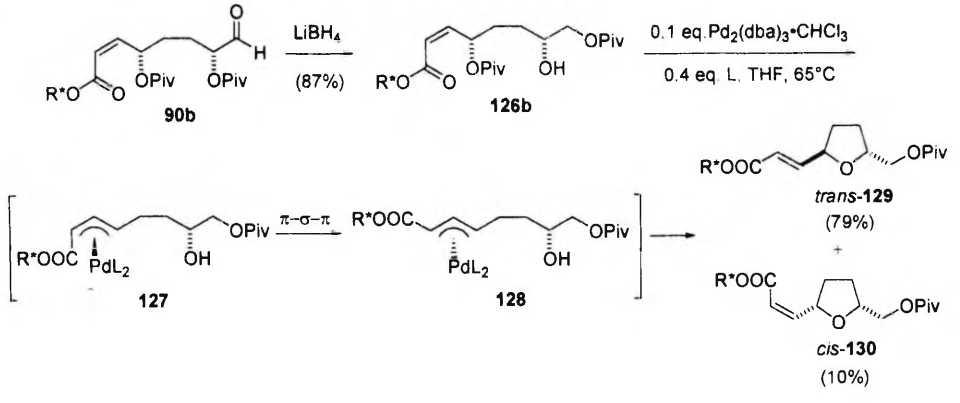
(25) This is probably the product composition at the state of thermodynamic equilibrium.

(26) The yields reported for the reduction/protecting group migration sequences are corrected for recovered primary alcohol.



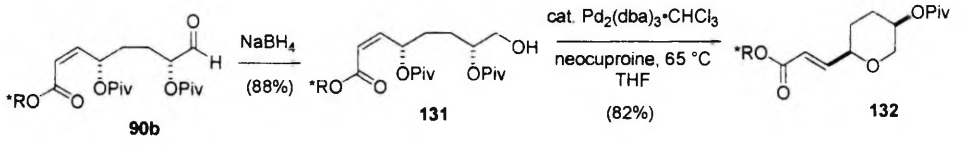

**Scheme 42.** Synthesis of *cis*-THF derivative **125**.

In case of the (*Z*)-alkene **126b** (Scheme 43), the ring-closure reaction did not proceed at room temperature and elevated temperature was needed. The extra energy is probably needed to initially form the disfavored *syn,anti*-palladium-complex **127**, which rearranges to the more stable *syn,syn*-complex **128** via a π–σ–π path (see Section 3.1.1.3. for mechanistic details). The ring-closure reaction then gives the THF derivative **129** as the main product. The product was obtained with overall inversion of stereochemistry at the allylic stereocenter, accompanied by (*Z*)- to (*E*)-isomerization, which is consistent with the suggested π–σ–π rearrangement. However, ca. 10% of *cis*-THF derivative **130**, which is formed when the Pd-complex **127** ring-closes directly, was also isolated. There is a possibility that by further ligand screening reaction conditions might be found where one could selectively force the reaction to proceed either via the π–σ–π path, to give cleanly compound **129**, or via direct nucleophilic attack on the *syn,anti*-intermediate (**127**), leading cleanly to compound **130**; this remains to be demonstrated in practice, however.




**Scheme 43.** Synthesis of *trans*-THF derivative **129**.

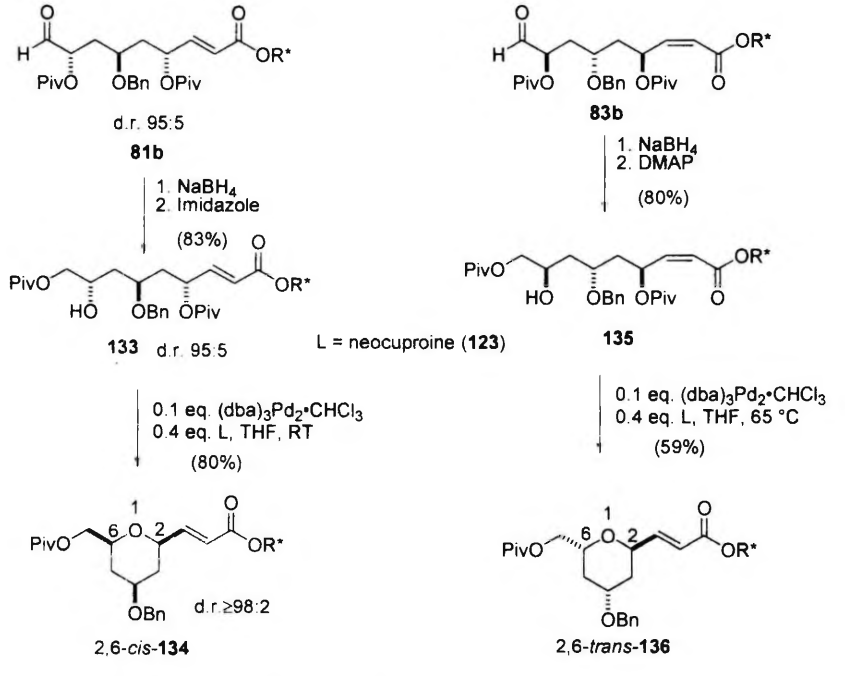
When $NaBH_4$ was used to reduce the HWE product **90b** instead of $LiBH_4$, the primary alcohol **131** is isolated in good yield (Scheme 44). When this primary alcohol was treated with Pd(0) in the presence of neucuproine, THP derivative **132** was obtained in good yield. Only the indicated product isomer was isolated, implying that the reaction proceeds cleanly via a π–σ–π rearrangement. The possibility to prepare both THF and THP derivatives from the same HWE product adds additional versatility to the developed methodology.




**90b** **131** **132**

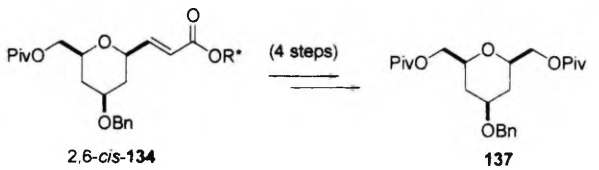
**Scheme 44.** Synthesis of 2,5-THP derivative **132**.

The alkenes **81b** and **83b**, also obtained from asymmetric HWE reactions (see Section 2.4.1.), can be converted into THP derivatives in a similar manner as shown in Scheme 45. It is noteworthy that the ring-closed product **134** was obtained in diastereomerically pure form, even though the starting material contained 5% of a minor diastereomer.




**Scheme 35.** *Trans*- and *cis*-THP's from (*E*)- and (*Z*)-HWE products respectively.

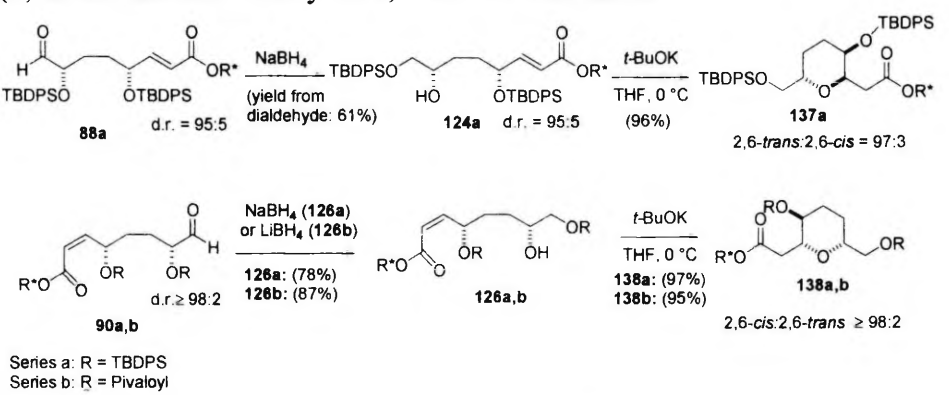
The assignments of relative sterochemistry of THF derivatives **125** and **129** and THP derivative **136** are based on NOE experiments. The stereochemistry of THP derivative **134** was proven after its conversion to compound **137** (Scheme 46), which turned out to be a *meso*-compound as expected.




**Scheme 46.** Assigning the relative configuration for compound **152**.

### 3.2.2. Via hetero-Michael addition[IV]

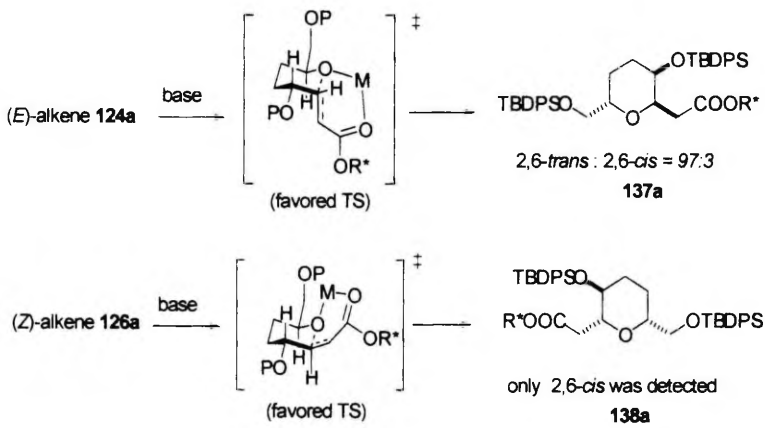
The HWE products obtained from the dialdehyde of the type **32** could be readily converted into trisubstituted THP's via a hetero-Michael addition reaction (Scheme 47). The intermediates **124a** and **126a,b** were first obtained via a reduction/protecting group migration sequence. The migration of the bulky silyl group from the secondary hydroxyl to the primary occured during treatment with borohydride, affording a ca. 5:1 mixture of the corresponding secondary and primary alcohols.[xxv,xxvi,27] Subsequent treatment of **124a** and **126a,b** with potassium *tert*-butoxide afforded the trisubstituted THP's in excellent yield. While the ring-closure of (*E*)-alkene **124a** gave predominantly the 2,6-*trans*-THP as product, the (*Z*)-alkene afforded cleanly the 2,6-*cis*-THP derivative.




**Scheme 47.** Hetero-Michael addition reactions from HWE products.

(27) It is interesting to note, that the use of hydride source ($LiBH_4$ or $NaBH_4$) in combination with *i*-PrOH/THF resulted much faster protective group migration during the reduction compared to MeOH/THF solvent mixture. However, this ei very preliminary observation and was not explored further in any detail.

Assignments of relative configurations of hetero-Micahel products **137a** and **138a** are based on comparison of their $^{13}C$ NMR spectra with literature data.[28] We believe that the stereochemical outcome in these ring-closure reactions primarily depends on the alkene geometry of the intermediates **124a** and **126a,b**. In principle, the difference in relative stereochemistry between the auxiliary and the other stereocenters might also influence the observed stereochemical outcome in the hetero-Michael additions, but based on previous studies by Banwell [22] and Martín [23], the former factor is probably more important than the latter. The proposed transition states leading from the (*E*)- and (*Z*)-alkenes to 2,6-*trans*- and 2,6-*cis*-THP derivatives, respectively, are shown in Scheme 48. Thermodynamically, the 2,6-*cis* product is favored in both cases implying that at least the formation of the 2,6-*trans* alkene proceeds via kinetic control. Upon longer reaction time and higher temperature the *trans*/*cis* ratio in **137a** dropped significantly, probably due to *trans* to *cis* equilibration, supporting the suggestion that the initial product formation occurs via kinetic control.

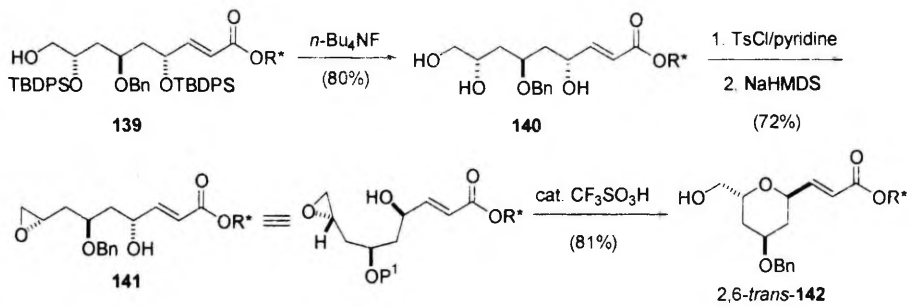



**Scheme 48.** Transition states leading to *trans*- and *cis*-THP's from (*E*)- and (*Z*)-alkenes respectively.

(28) For details, see Paper IV, footnote 45.

### 3.2.3. Via epoxide opening[11]

The third alternative for converting the products from the asymmetric HWE reactions into THF/THP derivatives is via an intramolecular epoxide opening approach. The reduced HWE product **139** obtained by reduction of **81a**[29] (Section 2.3.3.) could be converted into epoxide **141** by three simple transformations: desilylation, selective tosylation and epoxide formation (Scheme 49). Our initial attempts to induce the epoxide opening by activating the nucleophile at allylic position with base failed, leading to the recovery of starting material (in case of $Et_3N$ and DBU), or liberation of chiral auxiliary (when KHMDS was used). However, activation of an epoxide instead of nucleophile, with a catalytic amount of triflic acid, afforded the 2,6-*trans*-THP derivative **142** as the single product.[30] The stereochemistry of the product differs from the ones achieved via palladium catalysis (Section 3.2.1.), thus further extending the utility of the HWE products.



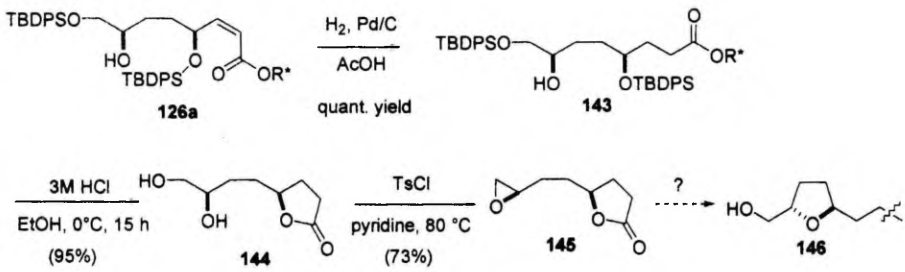

**Scheme 49.** THP synthesis via an intramolecular epoxide opening.

When starting from a related (*Z*)-alkene, a similar synthetic sequence initially failed, since from the desilylation reaction with TBAF only the chiral auxiliary (8-phenylmenthol) was isolated. However, after studying this approach further we succeeded in isolating lactone **144** in high yield when compound **143** was desilylated under acidic conditions (Scheme 50). The tosylation of the primary hydroxyl in **144** was sluggish, but after heating the reaction mixture at 80 °C in the presence of excess TsCl, the epoxide **145** formed directly. Conversion of epoxide

(29) Even though having no importance in this context, we were somewhat surprised to see very little PG migration in this reduction. The reason for this might be the use of MeOH/THF as solvent system (see footnote xxvii), or the particular nature of the substrate.

(30) The relative configuration of **142** has been proven by NOE experiments.

**145** into the corresponding *trans*-THF derivative has not yet been attempted, but after chemoselective lactone opening this might be possible.[31]




**Scheme 50.** Possible synthetic route to THF derivative **146** from the (*Z*)-HWE product **126a**.

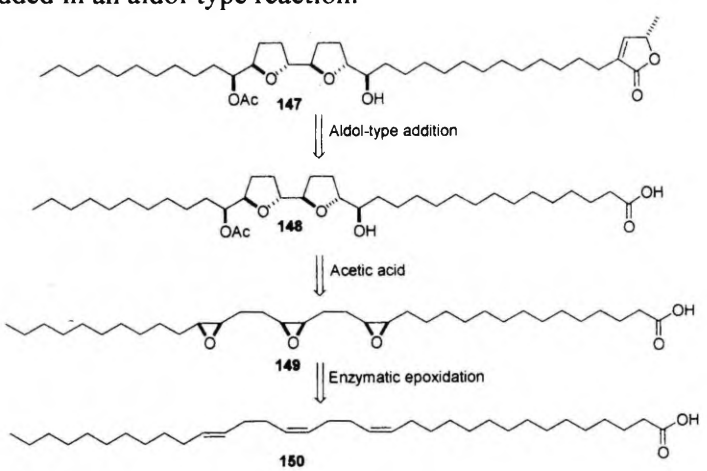
(31) Hydrogenating the reduced (*Z*)-HWE product **126a** before the acidic desilylation might not be necessary. This particular substrate **143** was used because of some specific application studies of the proposed THF product.

# 4. Annonaceous Acetogenins

## *4.1. General overview*

The Annonaceous Acetogenins are an interesting class of bioactive natural products found only in the tropical plant family called Annonaceae [93]. Chemically, they are derivatives of long-chain fatty acids, with THF and butenolide moieties as common structural features. They offer a wide range of biological activities such as anthelmintic, antimalarial, antimicrobial, antiprotozoal, and cytotoxic antitumor, and they show special promise for becoming a new type of antitumor and pesticidal agents.

The tropical plant family Annonaceae consists of 130 genera and 2300 different species. These plants grow around the world in the equatorial region, mostly in the rain forests, but also in arid areas and savannas. The natural products are isolated from all parts of the plants such as seeds, stem bark, leafs or roots. However, despite of its relatively large size, the plant family is chemically one of the least explored. The first isolation and characterization of an acetogenin, the in vivo active antileukemic (P-388) agent uvaracin in 1982 [94] raised wider interest in this family. Since then, the discovery rate of new Annonaceous acetogenins has grown each year, and by the end of 1998 350 acetogenins from 37 species were isolated. The biosynthesis of Annonaceous acetogenins seems to follow the polyene/polyepoxide/polyether pathway, and is similar to the biosynthesis of polyether structures in general [95]. Cole [94] has postulated the biosynthesis of uvaricin **147** as follows (Scheme 51): enzymatic oxidation of trienoic acid **150** affords the corresponding trisepoxide **149**, which in turn forms the THF core (**148**) by addition of acetic acid. To build up the butenolide, a three carbon fragment is added in an aldol-type reaction.

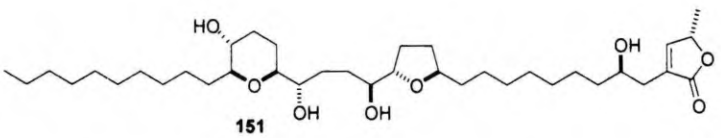



**Scheme 51.** Uvaracin **147**, and its proposed biosynthetic pathway.

The mode of action of the Annonaceous acetogenins is rather well established. They selectively inhibit cancerous cells by causing blockage of mitochondrial complex I (NADH-ubiquinone oxidoreductase), and through the inhibition of plasma membrane NADH oxidase. These actions decrease ATP production and thereby induce apoptosis (programmed cell death). In addition, it has recently been shown that acetogenins also inhibit cancer cells that are multidrug resistant [96] and combat efficiently pesticide-resistant German cockroaches. Thus, they obstruct biological resistance.

### 4.1.1. Mucocin

Mucocin **151** (Figure 15), recently isolated by McLaughlin and coworkers from the leaves of *Rollinia mucosa* (Jacq.) Baill (Annonaceae), was the first acetogenin reported that contains a THP ring [97]. This compound shows very selective inhibitory effects against lung cancer (A-549) and pancreatic cancer (PACA-2) solid tumor lines. Its selective potency was up to 10,000 times that of the known antitumor agent adriamycin. The remarkable biological activity and the unusual structural features have made mucocin a popular target of synthetic studies.

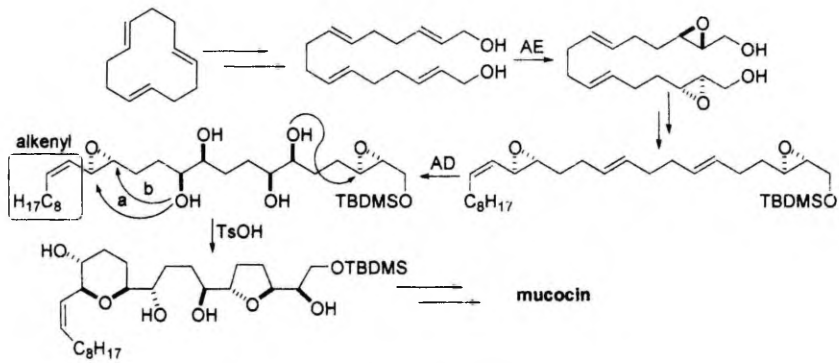


151

**Figure 15.** The structure of mucocin.

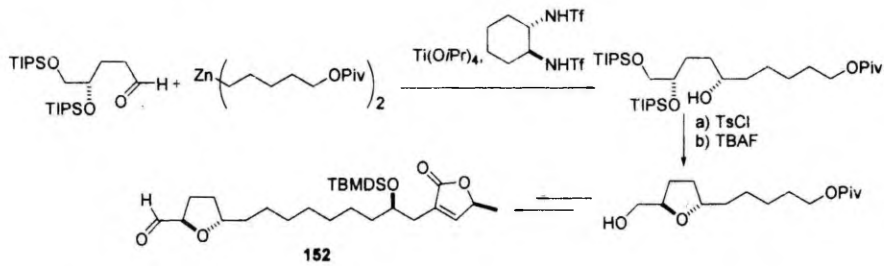
### 4.1.2 Previous synthetic studies directed towards mucocin

Since the discovery in 1995, mucocin has been a subject of intense synthetic studies [98]. The first total synthesis of mucocin was achieved by Keinan and coworkes in 1998 [98c]. Their synthesis starts from cyclododecatriene and relies heavily on the well established Sharpless asymmetric allylic epoxidation and asymmetric dihydroxylation reactions as key steps (Scheme 52). According to the Baldwin rules (see Section 3.1.2.), formation of the 6-membered ring via a 6-*endo* hydroxy epoxide opening (route a, Scheme 52) is disfavored in comparison with the alternative 5-*exo* ring closure (route b). However, the introduction of the alkenyl substituent reverted the regioselectivity and promoted formation of the THP ring rather than the THF ring.



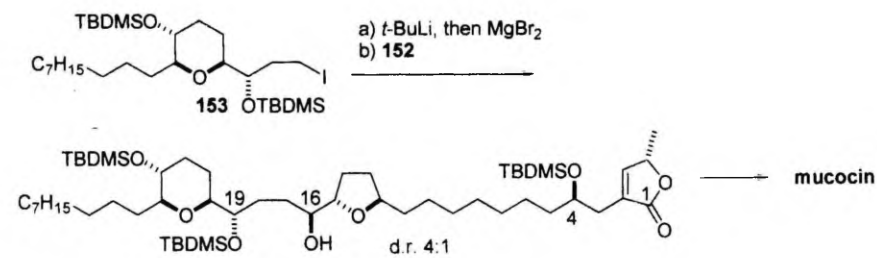

**Scheme 52.** The key steps of the first mucocin synthesis.

Koert [98a] has developed a strategy where the THP and THF fragments are prepared separately and then coupled by using organometallic chemistry. The synthesis of the THP fragment relied on AD and AE reactions. The THF fragment, in turn, was prepared by using a Lewis acid catalyzed organozinc addition to an aldehyde followed by an intramolecular Williamson reaction (Scheme 53).



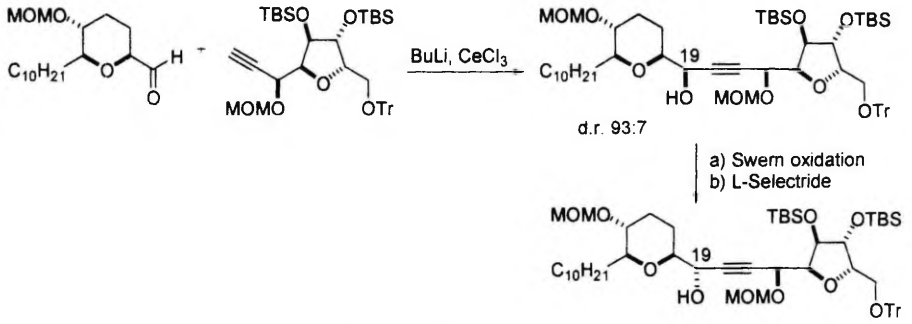

**Scheme 53.** Synthesis of right-hand fragment of mucocin by Koert.

The THP and THF fragments were coupled by addition of the metalated THP fragment **153** to the THF fragment **152**, as shown in Scheme 54. The stereoselectivity of the coupling reaction was 4:1 favoring the desired epimer at C-16. After the iodine-lithium exchange in **153**, transmetalation to magnesium was crucial for the success of the reaction.



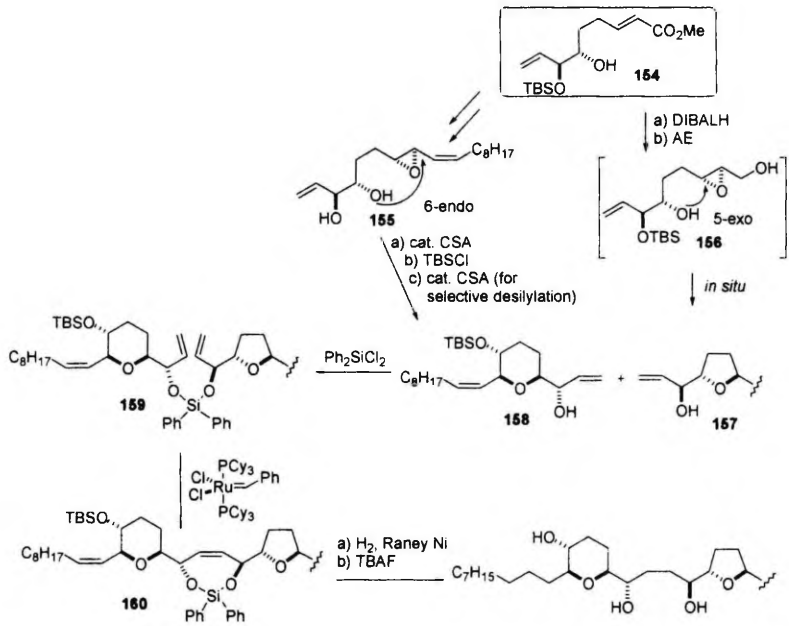

**Scheme 54.** Procedure for joining the left and right hand fragments of mucocin by Koert.

To obtain high stereoselectivity in these types of coupling reactions has often been a source of difficulties. Takahashi [98b], who has used chiral carbohydrate building blocks for the construction of all three key subunits (THF, THP and butenolide) of mucocin, initially obtained predominantly the undesired stereochemistry at C-19 when coupling the THP and THF fragments (Scheme 55). The desired stereochemistry was achieved via an oxidation/reduction sequence.




**Scheme 55.** Coupling of the THP and THF fragments of mucocin by Takahashi.

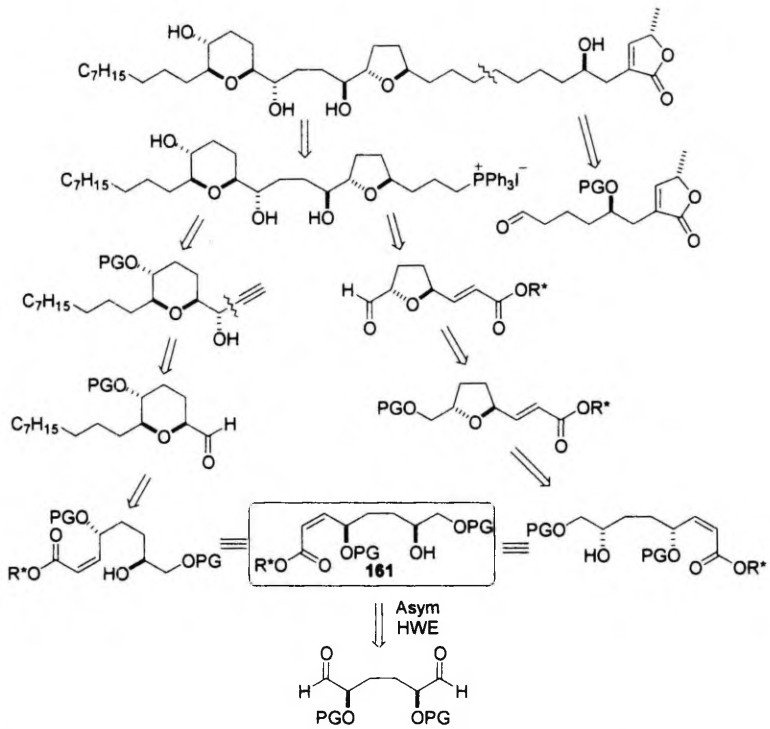
An interesting silicon-tethered cross-coupling technique has been introduced by Evans (Scheme 56, [98d-g]). The THF (**157**) and THP (**158**) fragments, which are both allylic alcohols, were first temporarily tethered together by a silyl group to afford bis-alkoxysilane **159**. A ring-closing metathesis reaction, using the Grubbs catalyst [99], tied the THF and THP fragments together, followed by release of the silylketal to afford a main subunit of mucocin. Interestingly, the THF and THP fragments were both prepared from the common intermediate **154**, by selectively activating the 6-*endo* epoxide opening (**155**) for the THP synthesis over the normally favored 5-*exo* (**156**) opening.




**Scheme 56.** The mucocin synthesis by Evans.

### *4.4. Our synthesis of mucocin subunits*[v]

Combining the asymmetric HWE reaction with different ring closure methods makes it an efficient strategy for the synthesis of key subunits of mucocin. According to the retrosynthetic analysis (Scheme 57), both the THF and THP subunits can be prepared from a common HWE product **161**, by using different methods for the ring closure. The THP unit can be made via a hetero-Michael reaction, and the THF unit via a Pd(0)-catalyzed allylic substitution reaction. The plan is then to connect the THP and THF subunits by use of nucleophilic additions to aldehydes. The butenolide fragment will be incorporated at the final stage because of its instability towards epimerization [100].

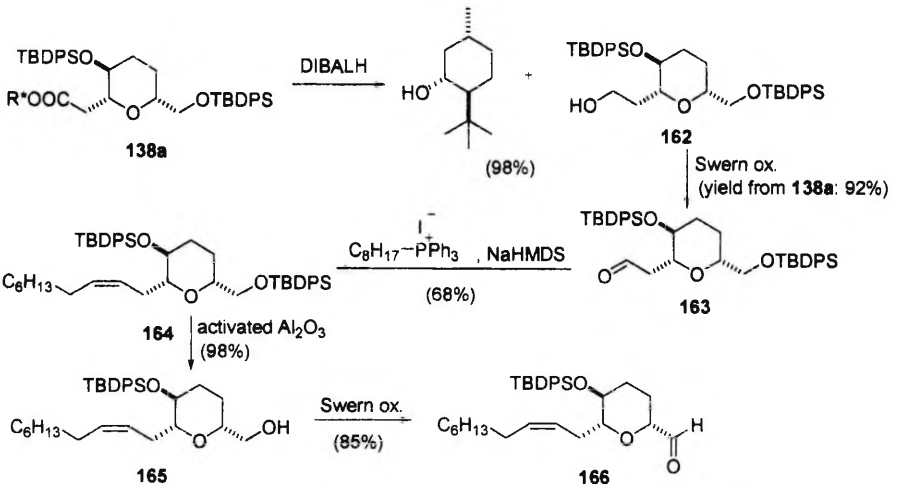



**Scheme 57.** General retrosynthetic scheme for the synthesis of mucocin.

Our studies indicate that the THP fragment **166**[32] can be efficiently synthesized from the hetero-Michael product **138a**[33] in five straightforward steps (Scheme 58). Reduction of the Michael product **138a** liberates the chiral auxiliary, which can be recycled, and alcohol **162** in high yields. An attempt to stop the reduction at the aldehyde stage gave lower yield of the aldehyde **163** than the two step reduction/oxidation sequence. The alkyl side chain was introduced by using a standard Wittig olefination reaction. Fortunately, selective mono-deprotection of bis-silyl ether **164** was possible, and afforded exclusively the primary alcohol **165**. Activated alumina was chosen as reagent for the deprotection [101] after thorough literature studies. The more common desilylation methods (TBAF, acidic or bacic hydrolysis) have shown poor to modest regioselectivities in these types of deprotections (for a review on selective desilylations, see [102]). After Swern oxidation, the THP fragment (**166**) of mucocin is completed and ready for coupling with a nucleophile.

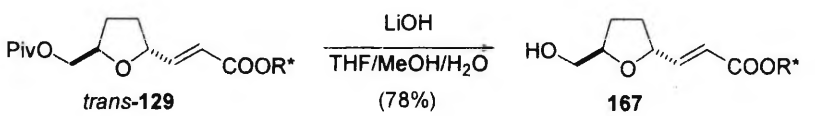
(32) Both **166** and **167** were obtained with correct relative, but opposite absolute configuration. See paper V footnote 10 for more details.

(33) For the synthesis of **138a**, see Section 3.2.2.




**Scheme 58.** Synthesis of THP fragment of mucocin.

The THF fragment can be derived from THF derivative **129** via a chemoselective hydrolysis, as shown in Scheme 59.

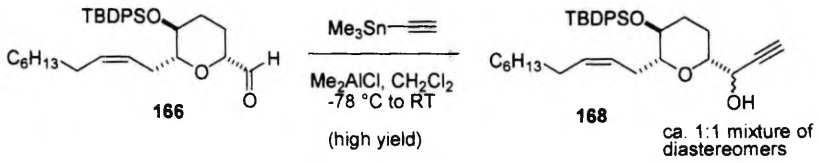



**Scheme 59.** Chemoselective hydrolysis of THF derivative **129**.

### *4.5. Coupling of the THF and THP fragments*

Coupling the THP and THF fragments would complete the main fragment of mucocin and introduce two new carbinol stereocenters. As already noted in Section 4.1.2., to obtain the desired configuration in analogous systems has proven troublesome in many cases (see an example, see [103]). Also somewhat surprisingly, there is no thorough study of nucleophilic additions to these types of systems. In order to obtain the desired configurations for mucocin, the nucleophilic additions to the THP- and THF-aldehydes both have to follow the Cram-chelate path (see Section 2.5.1.). Evans et al. [104] reported recently an exceptional chelating ability of dimethylaluminum chloride and methylaluminum dichloride in the stannylacetylene additions to β-alkoxy aldehydes. Our initial attempts to add a two carbon fragment to the THP subunit **166** and set the desired

stereochemistry at C-19 in mucocin by use of tributylstannylacetylene as a nucleophile gave, at best, only traces of the desired product. However, when trimethylstannylacetylene was used as a nucleophile instead, the two carbon fragment was added in high yield, but unfortunately the product was a ca. 1:1 mixture of two diastereomers (Scheme 60). By further modifying the reaction conditions and/or combination of reagents used, we hope to induce a stronger chelation control and obtain the desired product in high diastereoselectivity.

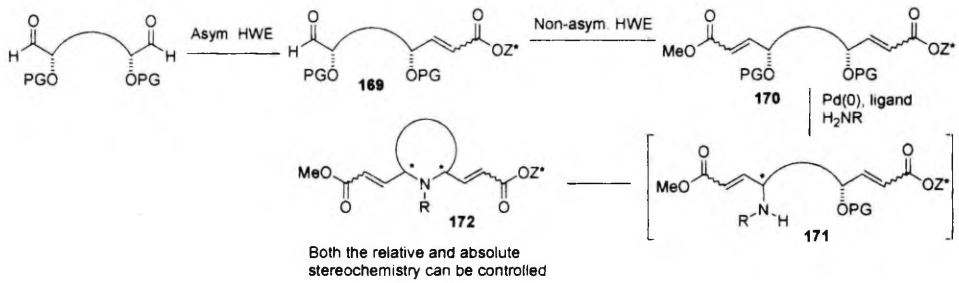



**Scheme 60.** Initial attempt of nucleophilic addition to aldehyde **166**.

# 5. Synthesis of N-heterocycles

Synthesis of N-heterocycles from the products obtained from asymmetric HWE reactions would be a tempting extension of the studies on O-heterocycles presented earlier in this thesis. Also from the point of view of applications, novel methods for the preparation of pyrrolidine and piperidine derivatives might lead to increased interest from pharmaceutical companies, due to the more frequent occurrance of such structures in drugs or potential drugs compared to THF/THP derivatives.

One might envision a strategy for synthesis of N-heterocycles based on the use of two sequential HWE reactions followed by a double Pd(0)-catalyzed allylic substitution reaction, as outlined in Scheme 61.



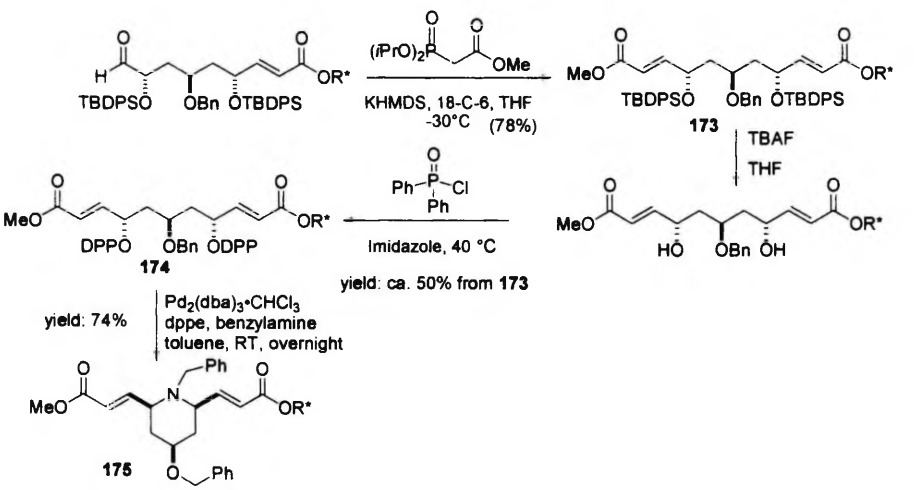

**Scheme 61.** General route to N-heterocycles.

The *meso*-dialdehyde is first desymmetrized via an asymmetric HWE reaction to give mono-HWE product **169**. The remaining aldehyde in **169** is then reacted with a non-chiral phosphonate to afford the bis-HWE product **170**. Treating **170** with Pd(0) in the presence of a suitable ligand and a primary amine as the nucleophile should first lead to allylic substitition at the more reactive center (**171**). The secondary amine in **171** can now act as an internal nucleophile in a second allylic substitution, leading to N-heterocycle **172**.[34] This strategy would enable us to control the relative configurations at the stereocenters in the ring by forcing the allylic substitutions to proceed either with overall retention (from an (*E*)-alkene), or overall inversion (from a (*Z*)-alkene) of configuration.

Based on our experiences from the THF/THP syntheses, we hoped that a bis-HWE product of the type **170**, derived from the pivaloyl-protected *meso*-dialdehyde **61b**, would be a good substrate for this double allylic substitution. Unfortunately, even

(34) Differentiation of the side chains relies on the difference in reactivity between the two end groups.

after numerous attempts to increase the reactivity by using different combinations of N-nucleophiles and ligands, we were unable to introduce any nitrogen nucleophile into the system. Our next intention was then to test different leaving groups to see if this might solve our problem. One potential candidate we chose was a diphenylphosphinyloxy group, which has previously shown good results in asymmetric HWE reactions [50] and in certain types of Pd(0)-catalyzed allylic substitution reactions [105]. In order to test this leaving group in our system, we prepared the bis-HWE product **174** by simply replacing the silyl groups in compound **173** by DPP-groups as shown in Scheme 62. The following treatment of **174** with Pd(0), in the presence of dppe as ligand and benzylamine as nucleophile, afforded cleanly piperidine derivative **175** as the single isolated product. This example shows very clearly the feasibility of the overall strategy and encourages us to continue the studies on the subject.




**Scheme 62.** The synthesis of piperidine derivative **175**.

# 6. Concluding remarks and future perspectives

The work presented in this thesis has further demonstrated the utility of asymmetric HWE reactions in organic synthesis. It has been shown that α-oxygen substituted acyclic *meso*-dialdehydes are generally good substrates for chiral auxiliary mediated asymmetric HWE reactions. Unfortunately, only one enantiomer of the chiral auxiliary used [(8)-phenylmenthol] is readily available, which sets limits when applying the methods to the total synthesis of natural products. Therefore our group has already started to study the utility of new types of chiral auxiliaries, of which both enantiomers are readily available, in asymmetric HWE reactions. It would also be very desirable to replace the stoichiometric chiral auxiliary with a chiral catalyst.

In addition, this work has demonstrated that the products obtained from the asymmetric HWE reactions can be easily converted to useful building blocks for natural product synthesis. Efficient routes to THF and THP derivatives have been established by using either a Pd(0)-catalyzed substitution, a hetero-Michael addition reaction, or an opening of a terminal epoxide as a ring-closure reaction. Furthermore, it has been shown that the THF and THP derivatives obtained are directly applicable to the total synthesis of the natural product mucocin. Preliminary studies also indicate that the use of nitrogen nucleophiles instead of oxygen nucleophiles in the Pd(0)-catalyzed allylic substitutions, either in an intramolecular or intermolecular manner, can give access to substituted piperidines. Nitrogen heterocycles of these types have attracted considerable interest e.g. in the pharmaceutical industry. The area of asymmetric Wittig-type reactions as well as the possibilities for preparation of oxygen- and nitrogen-heterocycles, are still far from fully explored, which gives hope for substantial future improvements.

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**Tetrahüdrfuraanide ja tetrahüdropüraanide stereoselektiivne süntees kasutades asümmeetrilist Horner-Wadsworth-Emmons ja tsükliseerimise reaktsioone**

## Kokkuvõte

See töö on asümmeetrilisest sünteesist. Uuriti stereoselektiivseid meetodeid tetrahüdrofuraani (THF) ja tetrahüdropuraani derivaatide sünteesiks kasutades asümmeetrilist Horner-Wadsworth-Emmons (HWE) reaktsiooni ja erinevaid tsükliseerimise meetodeid.

Töö esimses pooles on demonstreeritud asümmeetrilise Horner-Wadsworth-Emmons (HWE) reaktsiooni edukat kasutamist orgaanilises sünteesis. Reaktsioonid α-O asendatud *meso*-dialdehüüdide ja kiraalsete fosfanaatreagentide vahel toimusid väga kõrge asümmeetrilise induktsiooni ning mõõduka kuni hea saagisega. Fosfanaatreagendi väike strukturaalne varieerimine võimaldas sünteesida kas (*E*)- või (*Z*)-alkeene ülikõrge geomeetrilise selektiivsusega. Lisaks sellele võimaldas tsüklilise *meso*-dialdehüüdi kasutamine substraadina asümmeetrilistes HWE reakstioonides saada 2,6-*cis* tetrahüdropuraani derivaate ühes etaps.

Töö teine osa on pühendatud erinevate tsükliseerimise meetodite uurimisele, mis võimaldaksid konverteerida asümmeetrilise HWE reaktiooni produktid THF/THP derivaatideks. Leiti kolm efektiivset meetodit HWE produktide tsükliseerimiseks: a) Pd(0)-katalüüsitud allüülne asendusreaktsioon, b) hetero-Michael'i liitumisreaktsioon, ja c) terminaalse epoksiidi avamine. Erinevate tsüliseerimise meetodite kasutamine võimaldab saada erinevaid THF/THP derivaate isegi samast asümmeetrilise HWE reaktsiooni produktist — see muudab väljatöötatud metodoloogia paidlikuks.

Samuti õnnestus tänu N-nukleofiili kasutamisele Pd(0)-katalüüsitud allüülses asendusreakstioonis, sisemolekulaarse O-nukleofiili asemel, sünteesida asendatud piperidiini derivaat.

Töö lõpuosas on näidatud kuidas saab väljatöötatud meetodeid efektiivselt kasutada bioaktiivse atsetogeniini — mukotsiini sünteesis.

# Abstract

The main theme in this thesis is asymmetric synthesis. The work has been focused on the synthesis of tetrahydrofuran and tetrahydropyran derivatives by use of an asymmetric Horner-Wadsworth-Emmons reaction followed by a ring closure as key steps.

In the first part of the thesis, an asymmetric version of the Horner-Wadsworth-Emmons (HWE) reaction has been studied. The reactions between α-oxygen substituted *meso*-dialdehydes and chiral phosphonate reagents containing (-)-8-phenylmenthol as a chiral auxiliary gave high to excellent levels of asymmetric induction and moderate to high yields. By slight variation of the structure of the phosphonate reagent, either (*E*)- or (*Z*)-alkenes were obtained with essentially complete double bond selectivity. In addition, the use of cyclic *meso*-dialdehyde, as substrate for asymmetric HWE reactions, enabled the synthesis of 2,6-*cis*-THP derivatives in a single step.

In the second part of the thesis, methods for converting the products from the asymmetric Horner-Wadsworth-Emmons reactions to tetrahydrofuran and tetrahydropyran derivatives have been studied. These conversions were achieved in three different ways: a) via Pd(0)-catalyzed intramolecular allylic substitution, b) via intramolecular hetero-Michael addition, and c) via intramolecular opening of a terminal epoxide. Furthemore, the use of intermolecular nitrogen nucleophile, instead of intramolecular oxygen nucleophile in the Pd(0)-catalyzed allylic substitution, gave access to substituted piperidines.

Finally, the methods developed were applied to the synthesis of the tetrahydrofuran and tetrahydropyran subunits of mucocin, an acetogenin with potentially useful biological activity.



Keywords: asymmetric synthesis, Horner-Wadsworth-Emmons reaction, *meso*-dialdehyde, phosphonate, chiral auxuliary, 8-phenylmenthol, desymmetrization, double bond selectivity, diastereoselectivity, enantioselectivity, tetrahydropyran, tetrahydrofuran, palladium catalysis, hetero-Micahel addition, epoxide opening, total synthesis, mucocin, piperidine.

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# Publications

# I

Tullis, J. S.; Vares, L.; Kann, N.; Norrby, P.-O.; Rein, T.
Reagent Control of Geometric Selectivity and Enantiotopic Group Preference in Asymmetric Horner-Wadsworth-Emmons Reactions with *meso*-Dialdehydes.
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# Reagent Control of Geometric Selectivity and Enantiotopic Group Preference in Asymmetric Horner−Wadsworth−Emmons Reactions with *meso*-Dialdehydes†

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Results from asymmetric Horner−Wadsworth−Emmons reactions between chiral phosphonate reagents **3a**−**d**, which contain (1*R*,2*S*,5*R*)-8-phenylmenthol as a chiral auxiliary, and *meso*-dialdehydes **6** and **14** are presented. It was found that both the geometric selectivities and the levels of asymmetric induction depended on the structure of the phosphonate (i.e., the alkyl group $R^1$ in the phosphoryl unit) and to a certain extent also on the reaction conditions. Furthermore, the nature of the protecting group used on the α-oxygen substituent in dialdehydes **14** influenced the outcome somewhat. By an appropriate choice of reagent and conditions, either (*E*)- or (*Z*)-monoaddition products could be obtained geometrically pure and with good to excellent diastereoselectivities, in synthetically useful yields. Analyses of the absolute configurations of the products showed that the (*E*)-selective reagents (**3a**−**c**) and the (*Z*)-selective phosphonate **3d** reacted at opposite enantiotopic carbonyl groups in the substrates. A mechanistic model which accounts for the products formed is presented.

## Introduction

Selective reaction of only one of two enantiotopic groups in a bifunctional substrate is a powerful strategy[1] for asymmetric synthesis, as witnessed by the increasing attention such processes have received in recent years; a variety of examples, using both enzymatic[2] and non-enzymatic[3] reactions, has been reported. Based on this concept, reaction types in which no additional $sp^3$ stereocenter is created at any of the bond-forming sites can also be used for asymmetric synthesis, since asymmetric induction is achieved by "desymmetrization" of the substrate. One such class of reactions is asymmetric Wittig-type reactions, an area which in recent years has been studied by a number of research groups,[4] with several examples of highly selective transformations being reported. In the vast majority of asymmetric Wittig-type reactions studied so far, however, monocarbonyl compounds have been utilized as substrates; only in a few cases[4f,n,q,bb] have prochiral diketones been employed, and prior to our first report[4m] the possibility

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(4) For a review, see: (a) Rein, T.; Reiser, O. *Acta Chem. Scand.* **1996**, *50*, 369−379. See also: (b) Li, A.-H.; Dai, W.-M.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341−2372. (c) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161−3195. (d) Nicolaou, K. C.; Härter, M. W.; Gunzner, J. L.; Nadin, A. *Liebigs Ann./Recueil* **1997**, 1283−1302. For selected examples, see: (e) Tömösközi, I.; Janszo, G. *Chem. Ind. (London)* **1962**, 2085−2086. (f) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 4929−4932. (g) Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *J. Am. Chem. Soc.* **1984**, *106*, 5754−5756. (h) Gais, H.-J.; Schmiedl, G.; Ball, W. A.; Bund, J.; Hellmann, G.; Erdelmeier, I. *Tetrahedron Lett.* **1988**, *29*, 1773−1774. (i) Rehwinkel, H.; Skupsch, J.; Vorbrüggen, H. *Tetrahedron Lett.* **1988**, *29*, 1775−1776. (j) Hanessian, S.; Beaudoin, S. *Tetrahedron Lett.* **1992**, *33*, 7655−7658. (k) Denmark, S. E.; Chen, C.-T. *J. Am. Chem. Soc.* **1992**, *114*, 10674−10676. (l) Narasaka, K.; Hidai, E.; Hayashi, Y.; Gras, J.-L. *J. Chem. Soc., Chem. Commun.* **1993**, 102−104. (m) Kann, N.; Rein, T. *J. Org. Chem.* **1993**, *58*, 3802−3804. (n) Tanaka, K.; Ohta, Y.; Fuji, K.; Taga, T. *Tetrahedron Lett.* **1993**, *34*, 4071−4074. (o) Rein, T.; Kann, N.; Kreuder, R.; Gangloff, B.; Reiser, O. *Angew. Chem.* **1994**, *106*, 597−599; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 556−558. (p) Furuta, T.; Iwamura, M. *J. Chem. Soc., Chem. Commun.* **1994**, 2167−2168. (q) Mandai, T.; Kaihara, Y.; Tsuji, J. *J. Org. Chem.* **1994**, *59*, 5847−5849. (r) Denmark, S.; Rivera, I. *J. Org. Chem.* **1994**, *59*, 6887−6889. (s) Rein, T.; Kreuder, R.; von Zezschwitz, P.; Wulff, C.; Reiser, O. *Angew. Chem.* **1995**, *107*, 1099−1102; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1023−1025. (t) Rein, T.; Anvelt, J.; Soone, A.; Kreuder, R.; Wulff, C.; Reiser, O. *Tetrahedron Lett.* **1995**, *36*, 2303−2306. (u) Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1996**, *37*, 1077−1080. (v) Tanaka, K.; Otsubo, K.; Fuji, K. *Tetrahedron Lett.* **1996**, *37*, 3735−3738. (x) Kumamoto, T.; Koga, K. *Chem. Pharm. Bull.* **1997**, *45*, 753−755. (y) Gais, H.-J.; Schmiedl, G.; Ossenkamp, R. K. L. *Liebigs Ann./Recueil* **1997**, 2419−2431. (z) Dai, W.-M.; Wu, J.; Huang, X. *Tetrahedron: Asymmetry* **1997**, *8*, 1979−1982. (aa) Mendlik, M. T.; Cottard, M.; Rein, T.; Helquist, P. *Tetrahedron Lett.* **1997**, *38*, 6375−6378. (bb) Tanaka, K.; Watanabe, T.; Ohta, Y.; Fuji, K. *Tetrahedron Lett.* **1997**, *38*, 8943−8946. (cc) Kreuder, R.; Rein, T.; Reiser, O. *Tetrahedron Lett.* **1997**, *38*, 9035−9038. (dd) Mizuno, M.; Fujii, K.; Tomioka, K. *Angew. Chem.* **1998**, *110*, 525−527; *Angew. Chem., Int. Ed.* **1998**, *37*, 515−517. (ee) Arai, S.; Hamaguchi, S.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 2997−3000.

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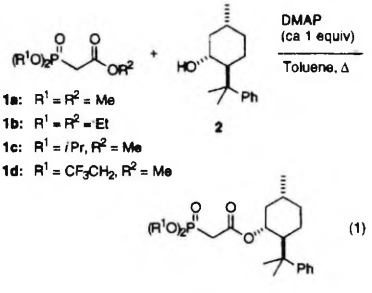
of using dialdehyde substrates[5] had not been investigated. From the viewpoint of synthetic efficiency, this alternative is appealing since the reaction product directly can take part in an additional chain-extending reaction involving the unreacted aldehyde, as exemplified in Scheme 1. Thus, relatively complex chiral structures should be quickly accessible from nonchiral precursors.

In this paper, we report results from an extension of our earlier[6] studies of asymmetric Horner–Wadsworth–Emmons (HWE) reactions[7] with dialdehydes and demonstrate that complementary product selectivities are possible by an appropriate choice of reagent: by slight structural variation in the chiral phosphonate, either (*E*)- or (*Z*)-alkenes can be obtained as products, with both high geometric selectivity and good to excellent levels of asymmetric induction. Furthermore, the (*E*)- and (*Z*)-selective reagents are complementary also in the sense that they react with opposite enantiotopic group preference.

## Results

**Choice and Preparation of Chiral Phosphonate Reagents.** For our initial studies, we chose to examine reactions between suitable model dialdehyde substrates and the chiral phosphonates **3a**–**d**, derived from (1*R*,2*S*,5*R*)-8-phenylmenthol (eq 1). Reagent **3a** has earlier been shown to give useful levels of diastereoselectivity in reactions with a prochiral monoketone[4h,y] and with some structurally related chiral ketones.[4h,i] Furthermore, we felt that incorporation of a chiral auxiliary in the anion-stabilizing functionality rather than in the phosphorus-based functional group could give larger synthetic versatility, since choice of different alkyl groups $R^1$ in the reagent then might enable control of the alkene geometry in the product. This expectation was realized in practice.




**1a**: $R^1 = R^2 = Me$
**1b**: $R^1 = R^2 = Et$
**1c**: $R^1 = i$Pr, $R^2 = Me$
**1d**: $R^1 = CF_3CH_2$, $R^2 = Me$



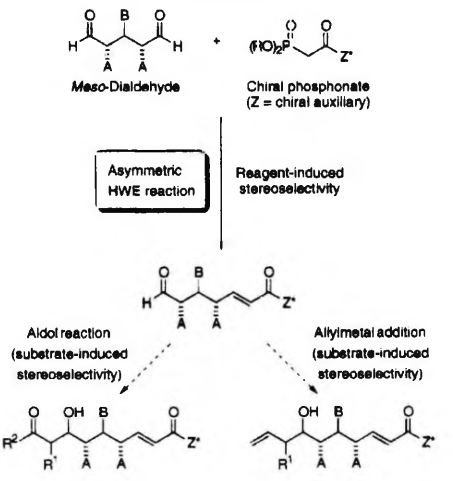

(1)

**3a**: $R^1$ = Me (see ref. 8)
**3b**: $R^1$ = Et (81%)
**3c**: $R^1 = i$Pr (see ref. 8)
**3d**: $R^1 = CF_3CH_2$ (89%)

A procedure for preparation of the chiral phosphonates **3a** and **3c** by transesterification of the achiral precursors **1a** and **1c** with 8-phenylmenthol (**2**) has previously been reported by Takano and co-workers.[8] In the same manner, we prepared[4o] reagents **3b** and **3d** in good yields from the corresponding known phosphonates **1b** and **1d**.[9]

**Choice and Preparation of Model Substrates.** As our model dialdehyde substrates, we chose compounds **6**[10] and **14**. The motivation for this choice was 2-fold: (i) reactions with these substrates would give information on the influence of different types of α-substituents ($CH_3$ or RO) in the dialdehyde on the reaction selectivity; (ii) the expected chiral monoaddition products are potentially useful synthetic intermediates, as they correspond to partial structures of a number of natural products of biomedical interest. Thus, the products expected from dialdehyde **6** match subunits of several strongly cytotoxic macrolides,[11] whereas products derived from dialdehydes of type **14** can be envisioned as building blocks for polyene/polyol macrolide antibiotics.[12]

**Scheme 1**




(5) For examples of the use of *meso*-dialdehydes as substrates for other types of asymmetric transformations, see: (a) Yamazaki, Y.; Hosono, K. *Tetrahedron Lett.* **1988**, *29*, 5769–5770. (b) Roush, W. R.; Park, J. C. *Tetrahedron Lett.* **1990**, *31*, 4707–4710. (c) Wang, Z.; Deschênes, D. *J. Am. Chem. Soc.* **1992**, *114*, 1090–1091. (d) Ward, D. E.; Liu, Y.; Rhee, C. K. *Synlett* **1993**, 561–563. (e) Ward, D. E.; Liu, Y. D.; Rhee, C. K. *Can. J. Chem.* **1994**, *72*, 1429–1446. (f) Roush, W. R.; Wada, C. K. *J. Am. Chem. Soc.* **1994**, *116*, 2151–2152. (g) Oppolzer, W.; De Brabander, J.; Walther, E.; Bernardinelli, G. *Tetrahedron Lett.* **1995**, *36*, 4413–4416. (h) De Brabander, J.; Oppolzer, W. *Tetrahedron* **1997**, *53*, 9169–9202. (i) Oppolzer, W.; Walther, E.; Balado, C. P.; De Brabander, J. *Tetrahedron Lett.* **1997**, *38*, 809–812.

(6) Part of this work has been described in an earlier communication; see ref 4m.

(7) (a) Horner, L.; Hoffman, H.; Wippel, H. G. *Chem. Ber.* **1958**, *91*, 61–63. (b) Horner, L.; Hoffman, H.; Wippel, H. G.; Klahre, G. *Chem. Ber.* **1959**, *92*, 2499–2505. (c) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733–1738. For reviews discussing general aspects of the HWE reaction, see: (d) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87–99. (e) Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73–253. (f) Walker, B. J. In *Organophosphorus Reagents in Organic Synthesis*; Cadogan, J. I. G., Ed.; Academic Press: New York, 1979; pp 155–205. (g) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927. (h) Kelly, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 730–817. See also ref 4d.

(8) Hatakeyama, S.; Satoh, K.; Sakurai, K.; Takano, S. *Tetrahedron Lett.* **1987**, *28*, 2713–2716. In our hands, stoichiometric amounts of DMAP were in some cases required for the reactions to give good yields.

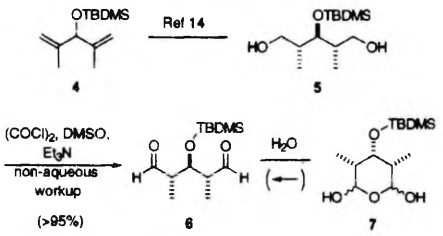
(9) Compound **1b** is commercially available. Phosphonate **1d** was prepared according to the procedure of Still: Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405–4408.

(10) After our initial report on asymmetric HWE reactions with **6**, this dialdehyde has also been used as substrate in group-selective asymmetric aldol reactions; see refs 5g and 5h.

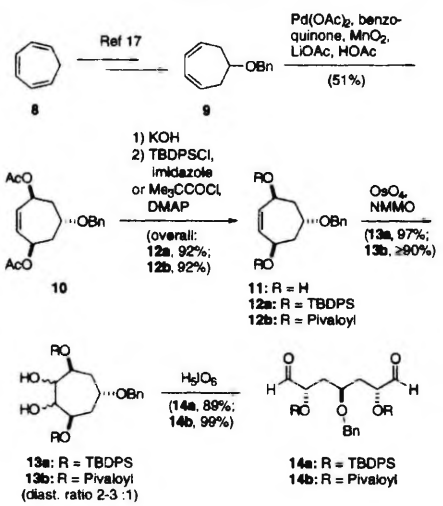
(11) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041–2114.

(12) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021–2040.

**Scheme 2**




**Scheme 3**

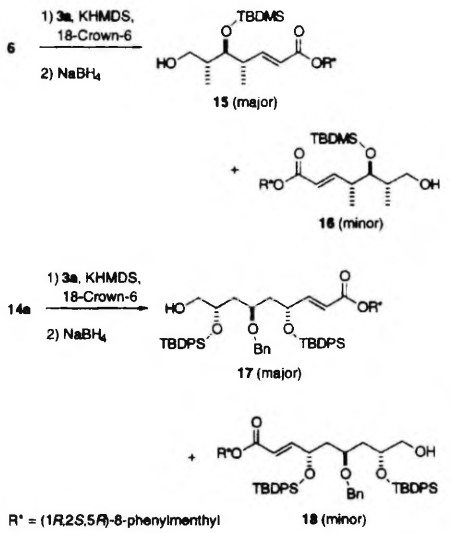



Diol **5**, the immediate precursor of dialdehyde **6**, was obtained by double hydroboration of diene **4**,[13] as described by Harada and co-workers.[14] Compound **6** could be prepared in pure form by Swern oxidation[15] of **5** if water was carefully excluded during the workup (Scheme 2). In the presence of water, the cyclic hydrate **7** was isolated as the major product,[16] and it proved difficult to regenerate **6** once the hydrate had been formed. Dialdehyde **6** is stable in solution for some time, if stored protected from water; we recommend, however, that it is freshly prepared for use.

The other model substrates, dialdehydes **14**, were synthesized in five steps from 6-(benzyloxy)-1,3-cycloheptadiene (**9**) which, in turn, is accessible from 1,3,5-cycloheptatriene[17] (Scheme 3). The relative stereochemistry of the three stereocenters in **14** was controlled by a palladium-catalyzed cis-diacetoxylation[18] of diene **9** to give diacetate **10**.[19] To gain some insight into the influence of different oxygen-protecting groups R in **14** on the outcome of the asymmetric HWE reactions, the *tert*-butyldiphenylsilyl-protected substrate **14a**, and the pivaloyl-protected **14b** were then prepared from **10** by straightforward transformations.[20]

Diols **13a** and **13b** were both formed as diastereomeric mixtures, but upon treatment with periodic acid, both diastereomers of each compound were cleanly converted to the desired dialdehyde. Dialdehyde **14a** is quite robust and stable enough to be purified by chromatography without detectable epimerization. Compound **14b**, however, is more sensitive, and is best prepared fresh immediately prior to use.

**Scheme 4**




**Asymmetric HWE Reactions.** To investigate the influence of reactant stoichiometry and reaction temperature, we first studied reactions between dimethylphosphonate **3a** and dialdehydes **6** and **14a** (Scheme 4, Table 1). Conditions which were expected to favor kinetic control in the initial addition step, by increasing the relative rate of the subsequent elimination, were chosen [potassium hexamethyldisilazide (KHMDS) as base in combination with 18-crown-6, low temperature].[21] In these initial experiments, the crude reaction product was reduced with $NaBH_4$ to facilitate separation of the products from both bis-addition products and remaining unreacted dialdehyde.

Somewhat to our surprise, essentially only (*E*)-products were obtained from both substrates, although nonasymmetric HWE reactions with dimethyl phosphonates often give (*Z*)-products under similar reaction conditions. These initial experiments demonstrated that (*E*)-alkenes **15**[22] and **17**[22] could be obtained in reasonable yields and

(13) For experimental details regarding the preparation of **4** and **5**, see Supporting Information.

(14) (a) Harada, T.; Matsuda, Y.; Uchimura, J.; Oku, A. *J. Chem. Soc., Chem. Commun.* **1990**, 21–22. (b) Harada, T.; Inoue, A.; Wada, J.; Uchimura, J.; Tanaka, S.; Oku, A. *J. Am. Chem. Soc.* **1993**, *115*, 7665–7674. For an enzyme-catalyzed desymmetrization of **5** by group-selective esterification, see: Chenevert, R.; Courchesne, G. *Tetrahedron: Asymmetry* **1995**, *6*, 2093–2096.

(15) Mancuso, A.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.

(16) Harada, T.; Kagamihara, Y.; Tanaka, S.; Sakamoto, K.; Oku, A. *J. Org. Chem.* **1992**, *57*, 1637–1639.

(17) Schink, H. E.; Petterson, H.; Bäckvall, J.-E. *J. Org. Chem.* **1991**, *56*, 2769–2774.

(18) Bäckvall, J.-E.; Byström, S. E.; Nordberg, R. E. *J. Org. Chem.* **1984**, *49*, 4619–4631.

**Table 1. Reactions of Phosphonate 3a with Dialdehydes 6 and 14a[a]**

| entry | substrate (equiv) | temp (°C) | product | yield[b] (%) | diaster ratio[c] | yield of bis-addition (%) |
|---|---|---|---|---|---|---|
| 1 | **6** (2.0) | −78 | **15** | 88 | 87:13 | 5 |
| 2 | **6** (2.1) | −100 | **15** | 87 | 90:10 | – |
| 3 | **6** (1.2) | −78 | **15** | 36 | 97:3 | 48 |
| 4 | **6** (1.3) | −100 | **15** | 77 | 91:9 | 6 |
| 5 | **14a** (2.0) | −78 | **17** | 68 | 87:13 | – |
| 6 | **14a** (2.0) | −100 | **17** | 50 | 89:11 | – |
| 7 | **14a** (1.2) | −78 | **17** | 60[d] | 88:12 | [e] |
| 8 | **14a** (1.2) | −100 | **17** | 49 | 91:9 | – |

[a] General reaction conditions: 1.1 equiv of phosphonate, 1.0 equiv of KHMDS, 5 equiv of 18-crown-6, ca. 0.02 M in THF, 2.5–15 h. [b] Isolated yield of product judged as ≥95% pure by NMR and TLC, unless otherwise noted. [c] Ratio in isolated product; ratios in crude products were within ±2% of these values. Entries 1–4: ratio **15**:**16**; entries 5–8: ratio **17**:**18**. Geometric ratios were ≥98:2. [d] Another product, tentatively assigned as being the product of silyl group migration from the secondary to the primary hydroxyl, was isolated in 18% yield. [e] Although small amounts of bis-addition product were detected in the crude product, none were isolated after chromatography.

diastereoselectivities even when close to equimolar amounts of substrate and reagent were used (compare entries 2 and 4, 5 and 7). In addition, the reaction temperature turned out to be an important parameter, as expected. With the more reactive substrate **6**, reaction at −78 °C gave considerable amounts of bis-addition product (entry 3); this was largely suppressed by performing the reaction at −100 °C (entry 4). On the other hand, the slightly lower yields obtained from dialdehyde **14a** at the lower reaction temperature presumably resulted from incomplete conversion due to this substrate being more sterically hindered (compare entries 6 and 8 with 5 and 7).

We then embarked on a more extensive study of reactions involving dialdehydes **6**, **14a**, and **14b**. Depending on the synthetic objective, it is desirable that either (*E*)- or (*Z*)-alkenes can be prepared with high selectivity in the asymmetric HWE reactions. For this reason, we investigated the utility of reagents **3a**–**d** containing different alkyl groups $R^1$ in the phosphoryl unit. It is known from standard nonasymmetric HWE reactions[7,21] that the alkene geometry of the product often can be controlled by an appropriate choice of $R^1$ and reaction conditions. The results obtained in reactions with **6** (Scheme 5, Table 2) demonstrated that selective preparation of either (*E*)- or (*Z*)-products was indeed possible.

Phosphonates **3a**–**c** all gave essentially exclusive formation of (*E*)-products. However, the structure of

**Scheme 5**

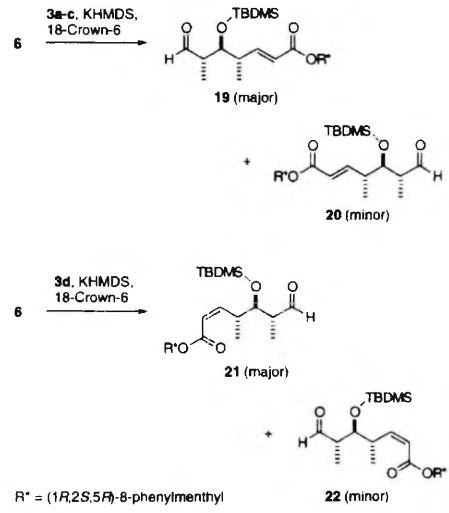



**Table 2. Reactions of Phosphonates 3a–d with Dialdehyde 6[a]**

| entry | phosphonate | temp (°C) | product | yield[b] (%) | diaster ratio[c] | yield of bis-addition (%) |
|---|---|---|---|---|---|---|
| 1 | **3a** | −100 | **19** | 53 | 95:5[d] | [e] |
| 2 | **3b** | −90 | **19** | 25[f] | ca. 95:5[d] | 38[f] |
| 3 | **3c** | −90 | **19** | 2[f] | ca. 97:3[d] | 12[f] |
| 4 | **3d** | −100 | **21** | 74 | ≥98:2[g] | [h] |
| 5 | **3d** | −90 | **21** | 83 | ≥98:2 | – |
| 6 | **3d** | −78 | **21** | 76 | ≥98:2 | [e] |
| 7 | **3d** | 0[i] | **21** | 38[f] | ≥98:2 | 36[f] |

[a] General reaction conditions: 1.1 equiv of dialdehyde, 1.1 equiv of phosphonate, 1.0 equiv of KHMDS, 5 equiv of 18-crown-6, ca. 0.02 M in THF, 6–22 h. [b] Isolated yield of product judged as ≥95% pure by NMR and TLC, unless otherwise noted. [c] Ratio in isolated product; ratios in crude products were within ±2% of these values. Entries 1–3: ratio **19**:**20**; entries 4–7: ratio **21**:**22**. Geometric ratios were ≥98:2, unless stated otherwise. [d] Small amounts of another isomer, assigned as an epimer, were also present in the isolated product: entry 1, 3%; entry 2, 9%; entry 3, 4% (see Supporting Information). [e] Not determined. [f] (*E*)-Mono- and (*E*,*E*)-bis-addition products were obtained in the same fraction after chromatography. [g] The isolated product also contained 6% of another isomer, assigned as an epimer; this was not present in the crude, but was formed during chromatography (see Supporting Information). [h] Reaction time 2 h. [i] After chromatography, the (*Z*)-monoaddition product **21** (38% yield) and the (*E*,*Z*)-bis-addition product **28** (25% yield; see Chart 1) were obtained in the same fraction. In separate fractions, the (*Z*,*Z*)- and (*E*,*E*)-bis-addition products were isolated, in 9% and 2% yield, respectively.

$R^1$ did influence the yield of monoaddition product strongly: the dimethylphosphonate **3a** was clearly superior to the diethyl and diisopropyl analogues. Use of **3a** in combination with KHMDS/18-crown-6 gave the (*E*)-monoaddition product **19**[22,23] in 53% yield with a diastereomer ratio of 95:5 (entry 1).

The (*Z*)-selective reagent **3d** proved to be even more efficient than the (*E*)-selective reagents **3a**–**c** in its reactions with **6**. Together with KHMDS/18-crown-6 as

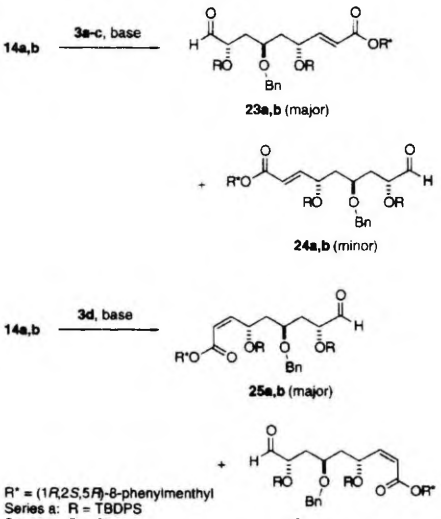
(19) Diacetate **10** was assigned as *meso*-(3*R*,5*s*,7*S*)-5-(benzyloxy)-3,7-diacetoxycyclohept-1-ene on the basis of $^1$H NMR data, by comparison with the known[18] compound *meso*-(3*R*,5*s*,7*S*)-5-methoxy-3,7-diacetoxycyclohept-1-ene. As evidenced by NMR on the crude product, the Pd-catalyzed diacetoxylation was not completely stereoselective. However, the other product isomers could be cleanly removed by use of the MPLC system described by Baeckström: Baeckström, P.; Stridh, K.; Li, L.; Norin, T. *Acta Chem. Scand., Ser. B* **1987**, *41*, 442–447.

(20) Dihydroxylation of diacetate **10** gave a complex mixture of regioisomeric products, presumably due to facile acyl group migration in the initially formed diol. In contrast, dihydroxylation of bis-pivalate **12b** proceeded more cleanly. Upon chromatographic purification, acyl migration sometimes occurred also with diols **13b**; however, if the crude diastereomeric mixture of diols **13b** was directly cleaved with $H_5IO_6$, excellent yields of isomerically pure dialdehyde **14b** were reproducibly obtained. Oxidative cleavage of the alkenes **12** by ozonolysis was also attempted, but in our hands the two-step osmylation/periodic acid protocol gave much cleaner products.

(21) Thompson, S. K.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 3386–3388, and references therein.

(22) For details regarding how structure assignments for the HWE product isomers have been made, and how isomer ratios have been determined, see Supporting Information.

**Scheme 6**




base, reagent **3d** gave the (*Z*)-product **21**[22,23] in high yield, with excellent geometric selectivity and as a single detectable diastereomer (entry 5). The temperature dependence of this reaction was investigated to some extent: reactions at −78 °C and lower afforded good yields of monoaddition product, but a reaction performed at 0 °C gave a much reduced yield due to formation of substantial amounts of bisaddition products.

The reactions with the α-oxygenated substrates **14a** and **14b** (Scheme 6, Table 3) followed similar general trends as the reactions with **6**, although there are some differences worth noting.

Reagents **3a**−**c** all gave high (*E*)-selectivities in reactions with both **14a** and **14b**. The diastereoselectivities observed for the (*E*)-product **23a**[22,23] were similar for all three reagents (entries 1−3); although the amount of unreacted dialdehyde was not determined, the slightly lower yield observed in the reaction with the diisopropyl phosphonate **3c** may well be due to incomplete conversion. On the other hand, in reactions with the more reactive, pivaloyl-protected substrate **14b**, the dimethyl phosphonate **3a** performed poorly (entry 7), whereas both **3b** and **3c** gave **23b**[22,23] in much better yields and diastereoselectivities (entries 8 and 9). Thanks to the fact that the diastereomers of **23a** could be separated under optimized chromatography conditions, diastereomerically pure **23a** was obtained in a synthetically useful yield, even though the diastereoselectivity in the crude product was slightly lower than for **23b**.

The bis(trifluoroethyl)phosphonate **3d** provided access to the (*Z*)-products **25a**[22,23] and **25b**[22,23] with excellent levels of asymmetric induction and in good yields. The reactions with aldehyde **14a** proved to be special cases: both KHMDS and NaHMDS alone gave better results than our "standard" base system KHMDS/18-crown-6 (entries 4−6). The reaction between **3d** and **14b**, however, gave best selectivities under the standard conditions (entry 10).

**Determination of Absolute Configurations.** The assignments of absolute configurations for compounds **15** and **19** are based on $^1$H NMR analyses of both diastereomers of the Mosher ester derivative **27** (Chart 1), according to the method introduced by Mosher and Dale and extended by Kakisawa and co-workers.[24] Compound **21** is assigned the indicated absolute configuration based on a correlation with **19**: both **19** and **21** were converted to the same mono-(*Z*)/mono-(*E*)-diastereomer **28** by reaction with **3d** and **3a**, respectively. On the basis of NMR analysis, the products from these two reactions were identical, which, in turn, implies that the monoaddition products **19** and **21** must have been formed by reaction at enantiotopic carbonyl groups in **6**. In contrast, if the (*E*)- and (*Z*)-monoaddition products were formed via reaction at the same carbonyl group, further reaction of the (*Z*)-product with **3a** would have given the diastereomeric mono-(*Z*)/mono-(*E*)-isomer **29** as product.

The assignments of absolute configurations for the products from dialdehydes **14** have been made on the basis of similar investigations. The (*E*)-product **23a** was converted to both diastereomers of the Mosher ester derivative **30**, and NMR analysis[24] of these compounds gave the assigned absolute configuration. The pivaloyl-protected (*E*)-product **23b** was correlated with **23a** by conversion of both compounds to derivative **31**; based on NMR analysis, the same diastereomer of **31** was produced in both cases. The (*Z*)-products **25a** and **25b** were correlated with **23a** and **23b**, respectively, by conversion to the mono-(*Z*)/mono-(*E*)-bisaddition products: **23a** and **25a** both formed **32a**, and **23b** and **25b** both gave **32b**.

## Discussion

Our results show that the structure of the group R$^1$ in the chiral phosphonates **3** controls not only the (*E*)/(*Z*)-selectivity of the asymmetric HWE reactions but also which enantiotopic carbonyl group in the dialdehyde substrate reacts faster,[25] both of which factors contribute to giving these reactions increased synthetic versatility.

The bis(trifluoroethyl) reagent **3d** was found to give (*Z*)-products with excellent diastereoselectivities in good yields from all three substrates studied. The results obtained with **14a** show that the specific choice of reaction conditions is important: although the use of KHMDS/18-crown-6 as base often is the most efficient

(23) In general, the (*E*)- and (*Z*)-monoaddition products could be separated by flash chromatography. It also proved possible to separate the (*E*)-diastereomers **23a** and **24a** (Scheme 6, vide infra) by chromatography, if Amicon silica (see Experimental Section) was used; however, we have not yet found conditions which enable complete separation of other diastereomeric products (i.e., **19**/**20**, **23b**/**24b**, **25a**/**26a**). Some of the HWE products showed tendencies to undergo slight epimerization during chromatography, but this could be suppressed by use of appropriate conditions: compounds **19** and **21** could be chromatographed on Merck silica (see Experimental Section) if the silica was deactivated by elution with EtOAc or EtOAc/MeOH prior to chromatography; compounds **23b** and **25b** could be chromatographed on Amicon silica without detectable epimerization, whereas use of the Merck silica caused some epimerization. The silyl-protected products **23a** and **25a** did not undergo observable epimerization on either type of silica.

(24) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096, and references therein. For further details regarding the preparation and NMR analyses of compounds **27** and **30**, see Supporting Information.

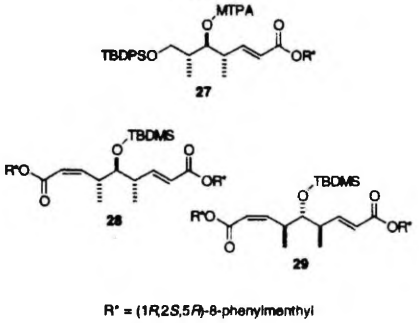
(25) We have found the same general trend to be valid also in kinetic/dynamic resolutions of racemic monoaldehydes by reaction with phosphonates **3a**−**d**; see refs 4o, 4s, and 4t.

**Table 3. Reactions of Phosphonates 3a–d with Dialdehydes 14a and 14b[a]**

| entry | phosphonate | substrate | temp. (°C) | product | yield[b] (%) | diast. ratio[c] | yield of bis addition (%) |
|---|---|---|---|---|---|---|---|
| 1 | **3a** | **14a** | −78 | **23a** | 65[d] | ≥98:2 (87:13) | *e* |
| 2 | **3b** | **14a** | −78 | **23a** | 60[d] | ≥98:2 (88:12) | *e* |
| 3 | **3c** | **14a** | −78 | **23a** | 46[d] | ≥98:2 (91:9) | *e* |
| 4 | **3d** | **14a** | −78 | **25a** | 61[f] | 86:14 | 24[f] |
| 5 | **3d**[g] | **14a** | −78 | **25a** | 76 | 98:2 | h |
| 6 | **3d**[i] | **14a** | −78 | **25a** | 60 | 96:4 | h |
| 7 | **3a** | **14b** | −90 | **23b** | 10 | 82:18 | 65[i] |
| 8 | **3b** | **14b** | −90 | **23b** | 62 | 95:5 | 35[j] |
| 9 | **3c** | **14b** | −90 | **23b** | 65 | 94:6 | 26[i] |
| 10 | **3d** | **14b** | −90 | **25b** | 62 | ≥98:2 | 29[j] |

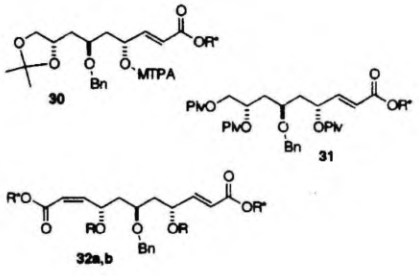
[a] General reaction conditions: 1.1–1.3 equiv of dialdehyde, 1.05–1.2 equiv of phosphonate, 1.0 equiv of KHMDS, 5 equiv of 18-crown-6, ca. 0.02 M in THF, 6–17 h. [b] Isolated yield of product judged as ≥95% pure by NMR and TLC, unless otherwise noted. [c] Ratio in isolated product. If different, the ratio in the crude product is given in parentheses. Entries 1–3: ratio **23a**:**24a**; entries 4–6: ratio **25a**:**26a**; entries 7–9: ratio **23b**:**24b**; entry 10: ratio **25b**:**26b**. Geometric ratios were ≥98:2, unless stated otherwise. [d] The isolated product also contained small amounts of unreacted dialdehyde: entry 1, 6%; entry 2, 6%; entry 3, 3%. [e] After chromatography, (*E*,*E*)-bis-addition product and the minor (*E*)-monoaddition diastereomer **24a** were obtained as a mixture; the yield of bis-addition product was not determined. [f] Some (*Z*,*E*)-bis-addition product **32a** (7% yield; see Chart 2) was obtained in the same fraction as the monoaddition product. The (*Z*,*Z*)-bis-addition product was isolated separately (17% yield). [g] Only KHMDS (no 18-crown-6) used as base. [h] Not determined. [i] NaHMDS used as base. [j] Mixture of bis-addition products.

**Chart 1**




R* = (1*R*,2*S*,5*R*)-8-phenylmenthyl

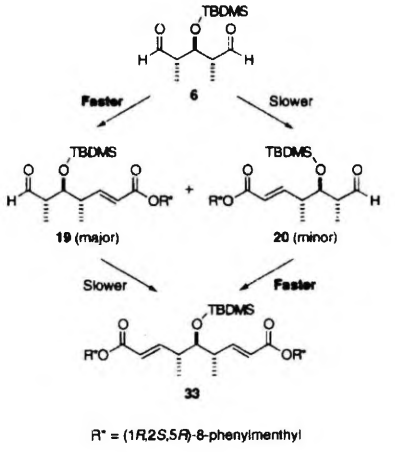
**Chart 2**




R* = (1*R*,2*S*,5*R*)-8-phenylmenthyl
Series a: R = TBDPS
Series b: R = Pivaloyl

with other substrates, the particular reaction between **3d** and **14a** gave best results if the crown ether was omitted. The (*E*)-selective reagents **3a**–**c**, on the other hand, generally performed best in combination with KHMDS/18-crown-6. Depending on the substrate, either **3a** or **3b** proved to be the most efficient reagent, the diisopropyl phosphonate **3c** seemingly being too sterically hindered to be generally useful. By choosing the appropriate reagent, (*E*)-products were obtained with di-

**Scheme 7**



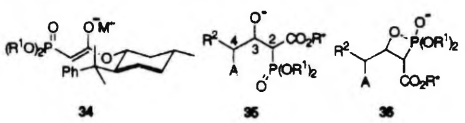

R* = (1*R*,2*S*,5*R*)-8-phenylmenthyl

astereoseletivities ≥ 95:5 and in synthetically useful yields. An additional factor to take into account is the choice of protecting group in α-oxygenated substrates: although substrates **14a** and **14b** gave the same overall trends in their reactions, the structure of the protecting group clearly influenced both the yields and selectivities of the reactions.[26]

As demonstrated by the results obtained in reactions with **6** (Table 1), the diastereoselectivity observed for the monoaddition product depends on the reaction stoichiometry. This outcome is to be expected, since increased conversion to the bisaddition product (e.g., **33**, Scheme 7) should increase the ratio between the diastereomeric monoaddition products (the ratio **19**:**20** in the example shown), due to the minor monoaddition diastereomer reacting faster in the second step.[27,28]

(26) A topic worthy of future investigation is whether the use of another protecting group would enable a change in the mechanism by which the α-stereocenter in the substrate influences the reaction stereochemistry (see mechanistic discussion below, and also ref 4cc); such a change could, in turn, enable complementary preparation of other product diastereomers.

**Mechanism.** Recent results from computational studies, using both high level *ab initio* calculations[29] and molecular mechanics methods,[30] fully support our previously reported working model[4a,cc] for rationalizing the stereochemical outcome of these asymmetric HWE reactions. This analysis is based on the postulate that phosphonates **3** form (*E*)-enolates[31] **34** under the reaction conditions used, an assumption which is reasonable based on previous studies.[32,33] Since two new stereocenters are formed at the bond-forming sites (C2 and C3) in the intermediates, and the substrate contains two enantiotopic carbonyl groups, eight different diastereomeric forms of the intermediate oxyanion **35** are theoretically possible. Our computational studies indicate that for reactions involving phosphonates **3a**–**c**, which normally are (*E*)-selective, the transition states for oxyanion formation (TS1) and for ring closure to the oxaphosphetane **36** (TS2) are close in energy, making it necessary to include appropriate models of both transition states



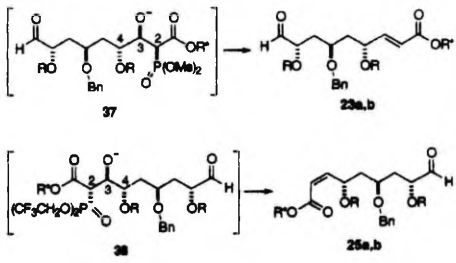
**34** **35** **36**

when analyzing reaction stereoselectivities. In reactions with trifluoroethyl phosphonate **3d**, on the other hand, the initial addition step will be irreversible, and it will be sufficient to model diastereomeric forms of TS1.

The particular diastereomeric intermediates which according to our modeling studies are the precursors of the main product isomers are illustrated in Schemes 8 and 9. The formation of these intermediates is rationalized as follows. The chiral auxiliary efficiently blocks the Re-face of the phosphonate enolate **34**. Diastereomers of TS1 leading to oxyanions with (2*R*)-configuration are therefore prohibitively high in energy, leading to a very high preference for oxyanions with (2*S*)-configuration.

The configuration at the former aldehyde carbonyl carbon, C3, is mainly controlled by the stereochemistry at C4, the former aldehyde α-carbon. The effect can be interpreted as a formal Felkin–Anh–Eisenstein[34,35] (FAE) or anti-FAE effect in TS1, depending on the substituents

**Scheme 8**



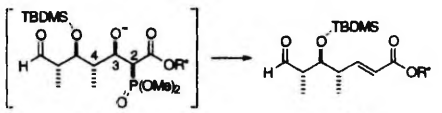
**37** **23a,b**



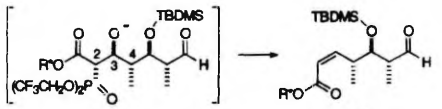
**38** **25a,b**

R* = (1*R*,2*S*,5*R*)-8-phenylmenthyl
Series a: R = TBDPS
Series b: R = Pivaloyl

**Scheme 9**



**39** **19**



**40** **21**

R* = (1*R*,2*S*,5*R*)-8-phenylmenthyl

at C4, but is in fact even more pronounced in the tighter TS2. The overall effect is that oxyanion diastereomers with an unfavorable relative configuration at C3/C4 will revert to starting material instead of proceeding to product.

This analysis also explains the, at first perhaps puzzling, observation that the major (*E*)- and (*Z*)-products have opposite absolute configuration at the allylic stereocenter. Since the favored absolute configuration at C2 always is the same, but the configuration at C3 is controlled by the one at C4, it automatically follows that reactions at opposite enantiotopic aldehyde groups must lead to intermediates with opposite relative configuration at C2/C3 and therefore to products with opposite alkene geometry.[36]

(27) Schreiber, S. S.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525–1529, and references therein.

(28) This expectation rests on the assumption that the unreacted aldehyde carbonyl groups in the monoaddition diastereomers show relative reactivities similar to the corresponding enantiotopic carbonyl groups in the dialdehyde substrate.

(29) Brandt, P.; Norrby, P.-O.; Martin, I.; Rein, T. *J. Org. Chem.* **1998**, *63*, 1280–1289.

(30) (a) Norrby, P.-O. In *Transition State Modelling for Catalysis*; Truhlar, D., Morokuma, K., Eds.; ACS Symposium Series, in press. (b) Norrby, P.-O.; Brandt, P.; Rein, T., manuscript in preparation. At present, modeling tools are available for reactions involving phosphonates containing simple alkyl groups (e.g., **3a**–**c**). Work toward the design of parameter sets which will allow modeling of trifluoroethyl reagents is in progress.

(31) Note that the designation of the geometry of enolate **34** as (*E*) or (*Z*) depends on whether a counterion is considered as being bonded to the anionic oxygen or not, and if so, on the CIP priority of that counterion relative to carbon.

(32) Gais and co-workers have reported[4h] that the lithium enolate formed from **3a** has (*E*)-geometry. We are presently studying the stuctures of enolates derived from reagents **3b**–**d**, as well as the dependence of the enolate ratios on the reaction conditions; these studies will be reported upon separately.

(33) (a) Bottin-Strzalko, T.; Corset, J.; Froment, F.; Pouet, M.-J.; Seyden-Penne, J.; Simmonin, M.-P. *J. Org. Chem.* **1980**, *45*, 1270–1276. (b) Seyden-Penne, J. *Bull. Soc. Chim. France* **1988** (II), 238–242, and references therein.

(34) (a) Chérest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205–2208. (b) Anh, N. T.; Eisenstein, O.; Lefour, J.-M.; Trân Huu Dâu, M. E. *J. Am. Chem. Soc.* **1973**, *95*, 6146–6147. (c) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61–70. (d) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145–162. (e) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 2819–2820. (f) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353–3361. For excellent discussions of different models for diastereoselection in nucleophilic additions to carbonyl compounds, see: (g) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151–4157. (h) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322–4343. (i) Gung, B. W. *Tetrahedron* **1996**, *52*, 5263–5301.

(35) Evans has introduced[34h] a stereochemical model which rationalizes the merged influence of α- and β-substituents in aldol-type additions to substituted aldehydes, including α-methyl-β-alkoxy-aldehydes. However, from substrates containing α- and β-substituents in an anti relationship (as in dialdehyde **6**), the Evans model also predicts formation of FAE-type products.

It should also be noted that the favored relative configuration at C3/C4 cannot easily be predicted from empirical rules. However, our recently developed molecular mechanics method[30] has been able to rationalize the product pattern.

## Conclusions

In this paper, we have demonstrated that when *meso*-dialdehydes **6** and **14** are used as substrates in asymmetric HWE reactions, either (*E*)- or (*Z*)-monoaddition products can be obtained with high geometric selectivity by slight structural variation in the phosphoryl group of the chiral reagent. By an appropriate choice of chiral reagent and reaction conditions, both (*E*)- and (*Z*)-products are obtained with good to excellent diastereoselectivities and in synthetically useful yields; these results show that both α-methyl and α-oxygen substitution in the substrate enable high selectivities to be obtained. The reactions with dialdehydes **14** also show that the choice of oxygen protecting groups in the substrate can be used for fine-tuning the outcome.

Furthermore, (*E*)- and (*Z*)-products are formed with opposite enantiotopic group preference. Thus, when applying these reactions in synthesis, both enantiomeric series of a projected synthetic intermediate can be accessed using the same enantiomer of the chiral auxiliary, as long as the alkene geometry of the product is of no consequence for the particular application at hand.

The stereochemical outcome of these reactions is in all cases consistent with a mechanistic model in which the product stereochemistry is determined by the combined influence of the chiral auxiliary, the alkyl group in the phosphonate unit, and the α-stereocenters in the dialdehyde substrate. In particular, this model explains why reactions at opposite enantiotopic carbonyl groups in the substrate give products having opposite alkene geometry.

Our continuing studies in this area are aimed at further improvement and generalization of this methodology through (1) the design of even more efficient chiral reagents, (2) investigations of mechanistic details, and (3) studies of reactions with new substrates. The products obtained from the asymmetric HWE reactions have projected utility in synthetic approaches to various natural products, and several such synthetic applications are under active investigation.

## Experimental Section

**General.** All reactions were performed in oven-dried or flame-dried glassware. Commercial reagents were used as received, unless otherwise indicated. Solvents were generally distilled before use. Potassium hexamethyldisilazide [KN(SiMe$_3$)$_2$, KHMDS] was purchased as a stock solution (0.5 M in toluene) and titrated according to the method of Ireland and Meissner.[37] 18-Crown-6 was recrystallized from anhydrous acetonitrile and dried under vacuum. Toluene, $CH_2Cl_2$, hexane, $Et_3N$, and pyridine were distilled from $CaH_2$. THF was distilled from sodium/benzophenone ketyl. $Pd(OAc)_2$ was recrystallized from acetic acid, and benzoquinone was recrystallized from ethanol. Dialdehydes **6** and **14b** were freshly prepared just before use. Cooling below −78 °C was effected by use of either EtOH/liquid $N_2$ or an immersion cooler. TLC analyses were performed on Merck aluminum-backed F254 silica gel plates, using UV light and phosphomolybdic acid for visualization. Drying of organic phases obtained from extractive workup was generally done with $MgSO_4$. Flash chromatography was performed as described by Still and co-workers[38] and medium-pressure liquid chromatography (MPLC) as described by Baeckström and co-workers,[19] in both cases using either Merck silica gel 60 (230–400 mesh) or Amicon Matrex 60 Å silica gel (35–70 μm). NMR spectra were recorded in $CDCl_3$ unless otherwise indicated, using $CHCl_3$ (δ 7.24 ppm) and $CDCl_3$ (δ 77.0 ppm) as internal references for $^1$H and $^{13}$C, respectively. (1*R*,2*S*,5*R*)-8-Phenylmenthol was prepared according to a literature procedure.[39] Tropone[40] and 1,3-cycloheptadien-6-ol[41] are intermediates in the synthetic route to diene **9** and were prepared according to literature procedures. Stereochemical descriptors for the *meso* compounds reported here have been assigned in accordance with a recent treatise.[42]

**(Diethoxyphosphoryl)acetic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (3b).** Prepared from triethyl phosphonoacetate (**1b**) and (1*R*,2*S*,5*R*)-8-phenylmenthol (**2**) in 81% yield, in analogy with the published procedure[8] for preparation of **3a**. $^1$H NMR (400 MHz, selected data) δ 7.24–7.16 (m, 4 H), 7.08–7.03 (m, 1 H), 4.77 (ddd [app td], $J$ = 10.8, 4.4 Hz, 1 H), 4.08–3.91 (m, 4 H), 2.31 (dd, $J$ = 21.3, 14.4 Hz, 1 H), 2.02 (dd, $J$ = 21.3, 14.4 Hz, 1 H), 0.81 (d, $J$ = 6.5 Hz, 3 H); $^{13}$C NMR (100 MHz) δ 165.1 (d, $J$ = 5.8 Hz), 151.8, 127.9 (2 C), 125.4 (2 C), 125.1, 75.1, 62.4 (d, $J$ = 5.7 Hz, 2 C), 50.3, 41.3, 39.5, 34.5, 33.9 (d, $J$ = 133 Hz), 31.3, 29.2, 26.3, 23.2, 21.8, 16.3 (d, $J$ = 6.1 Hz, 2 C). Anal. Calcd for $C_{22}H_{35}O_5P$: C, 64.37; H, 8.59. Found: C, 63.97; H, 8.51.

**[Bis(2,2,2-trifluoroethoxy)phosphoryl]acetic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl ester (3d).** Prepared from methyl bis(trifluoroethyl) phosphonoacetate (**1d**) and (1*R*,2*S*,5*R*)-8-phenylmenthol in 89% yield, according to the same procedure as was used for **3b**. $^1$H NMR (400 MHz, selected data) δ 7.30–7.23 (m, 4 H), 7.17–7.07 (m, 1 H), 4.82 (ddd [app td], $J$ = 10.7, 4.4 Hz, 1 H), 4.48–4.20 (m, 4 H), 2.27 (dd, $J$ = 20.7, 15.9 Hz, 1 H), 2.25 (dd, $J$ = 20.4, 15.9 Hz, 1 H), 1.27 (s, 3 H), 1.17 (s, 3 H), 0.86 (d, $J$ = 6.4 Hz, 3 H); $^{13}$C NMR (100 MHz) δ 164.0 (d, $J$ = 5.8 Hz), 151.9, 128.1 (2 C), 125.3 (2 C), 125.1, 122.4 (app quartet of m, one $J$ = ca 277 Hz, 2 C), 75.9, 62.4 (app quartet of m, one $J$ = ca. 40 Hz, 2 C), 50.1, 41.2, 39.3, 34.4, 33.4 (d, $J$ = 144 Hz), 31.2, 30.0, 26.1, 22.2, 21.7. Anal. Calcd for $C_{22}H_{29}O_5FP$: C, 50.97; H, 5.64. Found: C, 50.81; H, 5.66.

***meso*-(2*R*,3*r*,4*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-2,4-dimethylpentanedial (6).** To a solution of oxalyl chloride (136 μL, 1.55 mmol) in $CH_2Cl_2$ (8 mL) at −78 °C under argon was added dropwise a solution of DMSO (147 μL, 2.07 mmol) in $CH_2Cl_2$ (1 mL). After 30 min, a solution of **5**[14] (136 mg, 0.518 mmol) in $CH_2Cl_2$ (1 mL) was added dropwise followed, after 30 min, by triethylamine (722 μL, 5.18 mmol). The reaction mixture was stirred at −78 °C for 1 h and then warmed slowly to 0 °C during 1 h. After 30 min of stirring at 0 °C, the solution was diluted with dry toluene (25 mL), filtered through a dried glass frit, and concentrated. The residue was dissolved in dry hexane (25 mL), filtered again, and concentrated yielding 131 mg (quantitative crude yield) of **6** as a pale yellow oil which due to its limited stability was used without further purification in the HWE reactions: $^1$H NMR (250 MHz) δ 9.73 (d, $J$ = 2.1 Hz, 2H), 4.28 (t, $J$ = 5.1 Hz, 1H), 2.59 (qdd, $J$ = 7.1, 5.1, 2.0 Hz, 2H), 1.08 (d, $J$ = 7.1 Hz, 6H), 0.84 (s, 9H), 0.06 (s, 6H); $^{13}$C NMR (62.5 MHz) δ 203.4, 74.2, 50.8, 25.7, 18.0, 10.5, −4.5.

(36) We have observed the same general trend in all asymmetric HWE reactions studied by us to date. A similar argumentation is used by Fuji and co-workers when analyzing the results of asymmetric HWE reactions between a chiral phosphonate and a group of *meso*-diketones; see ref 4bb.

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(39) Ort, O. *Org. Synth.* **1987**, *65*, 203–214.

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***meso*-(3*R*,5*s*,7*S*)-5-(Benzyloxy)-3,7-diacetoxycycloheptene (10).** Diene 9[17] (1.00 g, 5.0 mmol) was added neat to a solution of palladium(II) acetate (56 mg, 0.25 mmol), lithium acetate dihydrate (2.55 g, 25 mmol), and benzoquinone (108 mg, 1.0 mmol) in glacial acetic acid (10 mL). After addition of $MnO_2$ (869 mg, 10 mmol), the resulting slurry was stirred at room temperature. The reaction was followed by TLC until all starting material had been consumed (2−3 days) and then worked up by addition of water and hexane/EtOAc 1/1. The resulting emulsion was filtered through Celite, the phases were separated, and the aqueous phase was extracted with three portions of hexane/EtOAc 1/1. The combined organic phases were washed with water, 2 M NaOH, and water again and then dried and concentrated to give 1.42 g of a yellowish brown oil. Purification was effected by MPLC (0−100% EtOAc in hexanes), yielding 811 mg (51%) of **10** as a colorless oil: $^1$H NMR (250 MHz) $\delta$ 7.42−7.23 (5H), 5.76 (dd, $J$ = 10.8, 2.3 Hz, 2H), 5.7 (s, 2 H), 4.65 (s, 2H), 3.92 (tt, $J$ = 5.6, 2.7 Hz, 1H), 2.22 (ddd, $J$ = 13.4, 5.6, 2.3 Hz, 2H), 1.86 (ddd, $J$ = 1.4, 10.8, 2.7 Hz, 2H), 2.05 (s, 6H); $^{13}$C NMR (62.5 MHz) $\delta$ 169.9, 138.3, 132.5, 128.2, 127.5, 127.3, 71.7, 70.0, 68.8, 36.6, 21.1. Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 67.83; H, 6.85.

***meso*-(1*R*,4*S*,6*s*)-6-(Benzyloxy)cyclohept-2-ene-1,4-diol (11).** To a solution of diacetate **10** (111 mg, 0.35 mmol) in MeOH (1.5 mL) at 0 °C was added dropwise an aqueous solution of KOH (98 mg, 1.75 mmol, in 1.5 mL of water). The resulting pale yellow solution was stirred at 0 °C until no starting material was detected by TLC (ca. 30 min). The reaction mixture was neutralized with 2 M $H_2SO_4$ and diluted with water. Extractive workup ($CH_2Cl_2$), drying, and concentration gave 82 mg of a white solid. Purification by flash chromatography (hexanes/EtOAc 1/1) gave 76 mg (93%) of white crystalline **11**: $^1$H NMR (400 MHz, DMSO) $\delta$ 7.37−7.23 (m, 5H), 5.55 (s, 2H), 4.79 (d, $J$ = 4.7, 2H), 4.53 (s, 2H), 4.50−4.41 (m, 2H), 3.83−3.75 (m, 1H), 2.02 (ddd, $J$ = 13.3, 5.2, 2.4 Hz, 2H), 1.55 (ddd, $J$ = 13.4, 11.1, 2.5 Hz, 2H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ 139.0, 136.1, 128.3, 127.4, 127.3, 73.2, 69.1, 64.1, 40.0. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.88; H, 7.61.

***meso*-(3*R*,5*s*,7*S*)-5-(Benzyloxy)-3,7 bis-((*tert*-butyldiphenylsilyl)oxy)cyclohept-1-ene (12a).** To a solution of diol **11** (0.816 g, 3.35 mmol) and imidazole (1.14 g, 16.75 mmol) in dry DMF (30 mL) under argon was added *tert*-butyldiphenylsilyl chloride (2.1 mL, 8.05 mmol). The reaction mixture was stirred for 24 h at room temperature and then diluted with brine and extracted with ethyl acetate. Drying ($Na_2SO_4$) and concentration of the combined organic extracts followed by flash chromatography (hexanes/EtOAc 99/1) afforded 2.432 g (99%) of **12a** as a colorless oil: $^1$H NMR (400 MHz) $\delta$ 7.72−7.64 (m, 8H), 7.44−7.23 (m, 15H), 7.00−6.93 (m, 2H), 5.78 (s, 2H), 4.75 (d, $J$ = 9.9 Hz, 2H), 3.89 (s, 2H), 3.67−3.60 (m, 1H), 2.02 (ddd [app br dd], $J$ = 12, 4 Hz, 2H), 1.78 (ddd [app br t], $J$ = 12 Hz, 2H), 1.09 (s, 18H); $^{13}$C NMR (100 MHz) $\delta$ 138.9, 135.8, 134.3, 134.0, 129.5, 128.0, 127.9, 127.5, 127.0, 72.6, 67.5, 69.0, 40.1, 27.0, 26.49, 19.2. Anal. Calcd for $C_{46}H_{54}O_3Si_2$: C, 77.70; H, 7.65. Found: C, 77.48; H, 7.62.

***meso*-(1*R*,2*S*,3*R*,5*s*,7*S*)-5-(Benzyloxy)-3,7-bis((*tert*-butyldiphenylsilyl)oxy)cycloheptane-1,2-diol and *meso*-(1*R*,2*S*,3*S*,5*s*,7*R*)-5-(Benzyloxy)-3,7-bis-(*tert*-butyldiphenylsilyl)oxy)cycloheptane-1,2-diol (13a; mixture of the two *meso* diols).** To a solution of silyl ether **12a** (321 mg, 0.45 mmol) and *N*-methylmorpholine *N*-oxide (53 mg, 0.45 mmol) in 5 mL of THF were added *tert*-butyl alcohol (2.5 mL) and $H_2O$ (1.2 mL), followed by 115 $\mu$L of a 2.5 weight-% solution of $OsO_4$ in *tert*-butyl alcohol (0.009 mmol). The pale yellow solution was stirred for 30 h at room temperature and then quenched with 5 mL of 10% $Na_2S_2O_4$. Dilution with brine followed by extraction (EtOAc), drying, and concentration followed by flash chromatography (hexanes/EtOAc 88/12) afforded 325 mg of a mixture of diastereomeric diols **13a** (97%) as a colorless oil. The diastereomeric mixture was normally used as such for preparation of the dialdehyde **14a**; isomerically pure samples of the separate diastereomeric diols could be obtained by chromatography, however. Faster eluting isomer ($R_f$ = 0.42, hexanes/EtOAc 8/2): $^1$H NMR (250 MHz) $\delta$ 7.75−7.60 (m, 8H), 7.46−7.20 (m, 15H), 6.97−6.90 (m, 2H), 4.06 (br d, $J$ = 10.2 Hz, 2H), 3.91 (s, 2H), 3.65 (br s, 2H), 3.53−3.43 (m, 1H), 3.10 (br d, $J$ = 4.9 Hz, 2H), 2.15 (ddd, $J$ = 14.4, 10.1, 4.1 Hz, 2H), 1.68 (ddd, $J$ = 14.4, 5.8, 2.8 Hz, 2H), 1.06 (s, 18H); $^{13}$C NMR (62.5 MHz) $\delta$ 138.6, 135.9, 133.6, 133.3, 129.8, 128.1, 127.7, 127.2, 74.7, 71.4, 70.6, 69.6, 34.8, 27.0, 19.2. Anal. Calcd for $C_{46}H_{56}O_5Si_2$: C, 74.15; H, 7.58. Found: C, 74.37; H, 7.78. Slower eluting isomer ($R_f$ = 0.28, hexanes/EtOAc 8/2): $^1$H NMR (250 MHz) $\delta$ 7.75−7.65 (m, 8H), 7.50−7.20 (m, 15H), 7.08−7.00 (m, 2H), 4.21 (br td, $J$ = 7, 3 Hz, 2H), 4.01 (br dd, $J$ = 5.9, 2.2 Hz, 2H), 3.96 (s, 2H), 3.70−3.58 (m, 1H), 2.94 (d, $J$ = 2.4 Hz, 2H), 1.97 (ddd, $J$ = 14.7, 6.4, 3.2 Hz, 2H), 1.88 (ddd, $J$ = 14.7, 7.6, 4.8 Hz, 2H), 1.11 (s, 18H); $^{13}$C NMR (62.5 MHz) $\delta$ 138.3, 135.9, 133.9, 133.3, 129.9, 128.2, 127.9, 127.8, 127.4, 74.7, 71.0, 70.2, 69.7, 36.2, 27.1, 19.4. Anal. Calcd for $C_{46}H_{56}O_5Si_2$: C, 74.15; H, 7.58. Found: C, 74.50; H, 7.82.

***meso*-(2*R*,4*s*,6*S*)-4-(Benzyloxy)-2,6-bis(*tert*-butyldiphenylsilyl)oxy)heptanedial (14a).** To a solution of diols **13a** (412 mg, 0.552 mmol) in THF (10 mL) was added a solution of $H_5IO_6$ (125 mg, 0.552 mmol) in THF (10 mL). The reaction mixture became cloudy after a few minutes. After 2.5 h at room temperature, 20 mL of pH 7 phosphate buffer was added, and the solution was extracted with ethyl acetate. Drying and concentration followed by flash chromatography (hexanes/EtOAc 9/1) yielded 365 mg (89%) of **14a** as a pale beige oil: $^1$H NMR (400 MHz) $\delta$ 9.50 (d, $J$ = 1.7 Hz, 2H), 7.68−7.58 (m, 8H), 7.46−7.22 (m, 15H), 7.11−7.05 (m, 2H), 4.15 (ddd [app td], $J$ = 6.0, 1.5 Hz, 2H), 4.06 (s, 2H), 3.75−3.67 (m, 1H), 2.02 (ddd [app td], $J$ = 14.6, 6.2 Hz, 2H), 1.78 (ddd, $J$ = 14.6, 6.0, 4.9 Hz, 2H), 1.11 (s, 18H); $^{13}$C NMR (100 MHz, some signals in the aromatic region overlap) $\delta$ 202.2, 137.8, 135.8, 135.8, 132.9, 132.8, 130.1, 128.2, 127.8, 127.7, 127.4, 76.0, 72.1, 70.1, 38.3, 26.9, 19.3. Anal. Calcd for $C_{46}H_{54}O_5Si_2$: C, 74.35; H, 7.32. Found: C, 74.12; H, 7.16.

***meso*-(3*R*,5*s*,7*S*)-5-(Benzyloxy)-3,7-bis((2,2-dimethylpropionyl)oxy)cyclohept-1-ene (12b).** To a solution of diol **11** (442 mg, 1.39 mmol) and DMAP (170 mg, 1.39 mmol) in dry pyridine (25 mL) under argon was added pivaloyl chloride (520 $\mu$L, 4.22 mmol). The reaction mixture was stirred for 16 h at reflux. After cooling and concentration, the residue was purified by flash chromatography (hexanes/EtOAc 95/5) to afford 555 mg (99%) of **12b** as white solid: $^1$H NMR (400 MHz) $\delta$ 7.39−7.21 (m, 8H), 5.71 (br dd, $J$ = 11, 3 Hz, 2H), 5.66 (s, 2H), 4.63 (s, 2H), 3.9 (tt [app septet], $J$ = 5.8, 2.9 Hz, 1H), 2.18 (ddd, $J$ = 13.4, 5.8, 2.7 Hz, 2H), 1.89 (ddd, $J$ = 13.4, 10.7, 2.7 Hz, 2H), 1.18 (s, 18H); $^{13}$C NMR (100 MHz) $\delta$ 177.2, 138.3, 132.5, 128.2, 127.5, 127.3, 71.6, 70.0, 68.5, 38.4, 36.7, 27.0. Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.61; H, 8.49.

***meso*-(1*R*,2*S*,3*R*,5*s*,7*S*)-5-(Benzyloxy)-3,7-bis((2,2-dimethylpropionyl)oxy)cycloheptane-1,2-diol and *meso*-(1*R*,2*S*,3*S*,5*s*,7*R*)-5-(Benzyloxy)-3,7-bis(2,2-dimethylpropionyl)oxy)cycloheptane-1,2-diol (13b; mixture of the two *meso* diols).** To a solution of bis-pivaloyl ester **12b** (557 mg, 1.38 mmol) and *N*-methylmorpholine *N*-oxide (162 mg, 1.38 mmol) in 16 mL of THF were added *tert*-butyl alcohol (8 mL) and $H_2O$ (4 mL), followed by 325 $\mu$L of a 2.5 wt % solution of $OsO_4$ in *tert*-butyl alcohol (0.026 mmol). The reaction mixture was stirred for 4 h at room temperature and then quenched with 7 mL of 10% $Na_2S_2O_4$. Dilution with brine followed by extraction (EtOAc), drying, and concentration afforded an essentially quantitative yield of a crude mixture of diols **13b** as a colorless oil. This diastereomeric mixture could be used in the preparation of dialdehyde **14b** without further purification. Alternatively, isomerically pure samples of the separate diol diastereomers could be obtained by flash chromatography[38] (hexanes/EtOAc 7/3). Faster eluting isomer ($R_f$ = 0.36, hexanes/EtOAc 7/3): $^1$H NMR (400 MHz) $\delta$ 7.33−7.22 (m, 5H), 5.19 (dm, $J$ = 10.1 Hz, 2H), 4.49 (s, 2H), 4.03 (br s, 2H), 3.82 (tt, $J$ = 6.5, 4.4 Hz, 1H), 2.81 (br s, 2H), 2.37 (ddd, $J$ = 14.3, 10.1, 4.6 Hz, 2H), 1.94 (ddd, $J$ = 14.3, 6.4, 3.1 Hz, 2H), 1.18 (s, 18H); $^{13}$C NMR (100 MHz) $\delta$ 177.9, 138.2, 128.3, 127.5, 73.2, 71.0, 70.5, 70.3, 38.8, 31.9, 27.0. Slower eluting

isomer ($R_f$ = 0.22, hexanes/EtOAc 7/3): $^1$H NMR (400 MHz) δ 7.31–7.24 (m, 5H), 5.15 (ddd [app td], $J$ = 6.4, 4.4 Hz, 2H), 4.54 (s, 2H), 3.91 (d, $J$ = 6.4 Hz, 2H), 3.71 (tt, $J$ = 7.8, 2.9 Hz, 1H), 3.44 (br s, 2H), 2.30 (ddd, $J$ = 15.0, 7.6, 4.3 Hz, 2H), 1.95 (ddd, $J$ = 15.0, 6.1, 3.05 Hz, 2H), 1.17 (s, 18H); $^{13}$C NMR (100 MHz) δ 178.1, 137.6, 128.4, 127.8, 127.7, 73.5, 71.8, 70.4, 70.2, 38.7, 35.1, 27.0. Anal. Calcd for $C_{24}H_{36}O_7$: C, 66.03; H, 8.31. Found: C, 66.02; H, 8.37.

***meso*-(2*R*,4*s*,6*S*)-4-(Benzyloxy)-2,6-bis(2,2-dimethylpropionyl)oxy)heptanedial (14b).** To a solution of diols **13b** (147 mg, 0.339 mmol) in THF (4 mL) was added a solution of $H_5IO_6$ (77.2 mg, 0.339 mmol) in THF (4 mL) at 0 °C. The ice bath was removed after 15 min; the reaction mixture then became cloudy in 10 min. After 1.5 h at room temperature, 3 mL of pH 7 phosphate buffer and 10 mL of brine were added. The solution was extracted with EtOAc, dried, and concentrated, and the residue was dissolved in $CHCl_3$ (2 mL) and filtered through a plug of cotton, affording 147 mg (99%) of a colorless oil after concentration. Dialdehyde **14b** was used in HWE reactions without further purification: $^1$H NMR (400 MHz) δ 9.48 (s, 2H), 7.37–7.27 (m, 5H), 5.13 (dd, $J$ = 9.8, 3.7 Hz, 2H), 4.38 (s, 2H), 3.69 (tt [app sept], $J$ = 7.9, 4.0, 1H), 2.18 (ddd, $J$ = 15.0, 7.9, 3.4 Hz, 2H), 1.95 (ddd, $J$ = 15.0, 9.5, 4.0 Hz, 2H), 1.22 (s, 18H); $^{13}$C NMR (100 MHz) δ 197.5, 177.8, 137.1, 128.6, 128.1, 75.3, 72.2, 71.5, 38.7, 34.0, 27.0.

**General Procedure for the Asymmetric HWE Reactions.** To a solution of the chiral phosphonate (**3a–d**; 1.05–1.2 equiv) and 18-crown-6 (if applicable; 5 equiv) in THF (ca 0.02 M with respect to the phosphonate) at −78 °C under argon was added 1.0 equiv of KHMDS (0.5 M in toluene). After 30 min the resulting grayish slurry was transferred via cannula to a precooled solution of the dialdehyde[43] (**6**, **14a** or **14b**; Table 1: 1.2–2.1 equiv, Tables 2 and 3: 1.1–1.3 equiv). The reaction mixture was stirred for the indicated time at the appropriate reaction temperature (monitoring by TLC) and then quenched with acetic acid (1 M in MeOH or THF). After 5 min, pH 7 phosphate buffer was added, and the reaction was slowly warmed to room temperature. After dilution with water, extractive workup (ethyl acetate), drying, and concentration gave the crude condensation products. Purification by flash chromatography or MPLC[19] using EtOAc in hexanes as eluent afforded the products as colorless oils.[23]

**General Procedure for Reduction of the HWE Products.** The crude condensation product was dissolved in MeOH or *i*-PrOH (THF was sometimes added to increase solubility) at 0 °C, and $NaBH_4$ (5–10 equiv) was added. After stirring at 0 °C until the reaction was finished (monitoring by TLC), the reaction mixture was diluted with water and extracted with $CH_2CH_2$. Drying, concentration, and purification by flash chromatography (EtOAc in hexanes) gave the alcohols as colorless oils.

**(*E*)-(4*S*,5*S*,6*R*)-5-(*tert*-(Butyldimethylsilyl)oxy)-7-hydroxy-4,6-dimethylhept-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (15).** Prepared from **3a** and **6** in 77% overall yield; (*E*):(*Z*) = 98:2, diastereomeric ratio **15**:**16** = 91:9.[23] **15**: $^1$H NMR (250 MHz, selected data) δ 7.27–7.19 (m, 4H), 7.13–7.06 (m, 1H), 6.72 (dd, $J$ = 15.8, 7.7 Hz, 1H), 5.21 (dd, $J$ = 15.7, 1.3 Hz, 1H), 4.84 (ddd [app td], $J$ = 10.7, 4.3 Hz, 1H), 3.61–3.53 (br m, 2H), 3.57 (dd [app t], $J$ = 5.1 Hz, 1H), 2.56–2.43 (m, 1H), 2.31 (br s, 1H), 2.00 (ddd, $J$ = 12.1, 10.7, 3.3 Hz, 1H), 1.84–1.73 (m, 1H), 1.28 (s, 3H), 1.19 (s, 3H), 1.00 (d, $J$ = 6.9 Hz, 3H), 0.90 (d, $J$ = 6.8 Hz, 3H), 0.89 (s, 9H), 0.84 (d, $J$ = 6.5 Hz, 3H), 0.09 (s, 3H), 0.06 (s, 3H); $^{13}$C NMR (100 MHz) δ 165.7, 151.6, 150.4, 127.9, 125.4, 124.9, 121.5, 79.8, 74.3, 65.7, 50.6, 41.72, 39.8, 38.0, 34.6, 31.3, 27.2, 26.7, 26.0, 25.7, 21.8, 18.2, 15.6, 15.6, −4.09, −4.12. Anal. Calcd for $C_{31}H_{52}O_4Si$: C, 72.04; H, 10.14. Found: C, 71.81; H, 10.13. **16**: $^1$H NMR (250 MHz, selected data assigned from a mixture (91:9) of diastereomers **15** and **16**) δ 6.70 (dd, $J$ = 15.8, 7.4 Hz, 1H), 5.18 (dd, $J$ = 15.8, 1.4 Hz, 1H).

(43) The opposite mode of addition (i.e., adding a precooled solution of the aldehyde to the phosphonate enolate) gave identical results, if the transfer was performed rapidly.

**(*E*)-(4*R*,6*R*,8*S*)-6-(Benzyloxy)-4,8-bis((*tert*-butyldiphenylsilyl)oxy)-9-hydroxynon-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl ester (17).** Prepared from **3a** and **14a** in 60% overall yield; (*E*):(*Z*) = 98:2, diastereomeric ratio **17**:**18** = 89:11.[23] **17**: $^1$H NMR (400 MHz, selected data) δ 6.62 (dd, $J$ = 15.6, 5.9 Hz, 1H), 5.45 (dd, $J$ = 15.6, 1.1 Hz, 1H), 4.83 (ddd [app td], $J$ = 10.7, 4.3 Hz, 1H), 4.21 (app br q, $J$ = 5.8 Hz, 1H), 4.07 (d, $J$ = 11.1 Hz, 1H), 4.01 (d, $J$ = 11.1 Hz, 1H), 3.77–3.70 (m, 1H), 3.46 (ddd, $J$ = 11.6, 5.7, 3.5 Hz, 1H), 3.31 (ddd, $J$ = 11.6, 7.23, 4.3 Hz, 1H), 3.24 (dddd [app quintet], $J$ = ca 6 Hz, 1H), 1.27 (s, 3H), 1.24 (s, 3H), 1.05 (s, 9H), 1.02 (s, 9H), 0.87 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, some signals in the aromatic region overlap) δ 165.5, 150.8, 149.3, 138.2, 135.9, 135.7, 133.8, 133.6, 133.5, 133.2, 129.9, 129.8, 128.2, 127.9, 127.82, 127.76, 127.65, 127.57, 127.5, 127.4, 125.6, 125.2, 120.8, 74.5, 72.6, 71.6, 69.99, 69.95, 66.2, 50.7, 42.8, 41.8, 40.1, 38.7, 34.5, 31.3, 28.5, 27.04, 26.98, 25.0, 21.8, 19.3. Anal. Calcd for $C_{64}H_{80}O_6Si_2$: C, 76.76; H, 8.05. Found: C, 76.54; H, 7.96. **18**: $^1$H NMR (400 MHz, selected data assigned from a mixture (89:11) of diastereomers **17** and **18**) δ 6.41 (dd, $J$ = 15.6, 6.1 Hz, 1H), 5.34 (dd, $J$ = 15.6, 1.1 Hz, 1H).

**(*E*)-(4*S*,5*S*,6*S*)-5-(*tert*-(Butyldimethylsilyl)oxy)-4,6-dimethyl-7-oxo-hept-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (19).** Prepared from **3a** and **6** in 53% yield; (*E*):(*Z*) = 98:2, diastereomeric ratio **19**:**20** = 95:5.[23,44] **19**: $^1$H NMR (250 MHz, selected data) δ 9.73 (d, $J$ = 2.5 Hz, 1H), 7.27–7.19 (m, 4H), 7.14–7.05 (m, 1H), 6.68 (dd, $J$ = 15.8, 7.7 Hz, 1H), 5.20 (dd, $J$ = 15.8, 1.3 Hz, 1H), 4. 82 (ddd [app td]), $J$ = 10.7, 4.3 Hz, 1H), 3.81 (dd [app t], $J$ = 4.6 Hz, 1H), 2.52–2.39 (m, 2H), 2.01 (ddd, $J$ = 12.1, 10.6, 3.4 Hz, 1H), 1.28 (s, 3H), 1.19 (s, 3H), 1.05 (d, $J$ = 7.1 Hz, 3H), 0.97 (d, $J$ = 6.9 Hz, 3H), 0.87 (s, 9H), 0.84 (d, $J$ = 6.5 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H); $^{13}$C NMR (62.5 MHz) δ 204.3, 165.6, 151.7, 149.2, 127.9, 125.4, 124.9, 122.2, 77.2, 74.4, 50.5, 50.2, 41.7, 41.6, 39.7, 34.6, 31.3, 27.5, 26.6, 25.9, 25.4, 21.8, 18.1, 15.5, 11.7, −4.2, −4.4. Anal. Calcd for $C_{31}H_{50}O_4Si$: C, 72.32; H, 9.79. Found: C, 72.06; H, 9.74. **20**: $^1$H NMR (250 MHz, selected data assigned from a mixture (95:5) of diastereomers **19** and **20**) δ 6.66 (dd, $J$ = 16, 7 Hz, 1H), 5.17 (dd, $J$ = 16, 1.5 Hz, 1H).

**(*Z*)-(4*R*,5*R*,6*R*)-5-(*tert*-(Butyldimethylsilyl)oxy)-4,6-dimethyl-7-oxo-hept-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (21).** Prepared from **3d** and **6** in 83% yield; (*Z*):(*E*) = 98:2, diastereomeric purity = 98:2. **21**: $^1$H NMR (400 MHz, selected data) δ 9.74 (d, $J$ = 2.7 Hz, 1H), 7.25–7.20 (m, 4 H), 7.13–7.09 (m, 1H), 6.11 (dd, $J$ = 11.6, 10.0 Hz, 1H), 5.18 (dd, $J$ = 11.5, 0.6 Hz, 1H), 4.79 (ddd [app td], $J$ = 10.7, 4.3 Hz, 1H), 3.81 (dd, $J$ = 5.8, 3.2 Hz, 1H), 3.82 (m, 1H), 2.47 (qdd, $J$ = 7.0, 5.8, 2.7 Hz, 1H), 1.98 (ddd, $J$ = 12.3, 10.6, 3.2 Hz, 1H), 1.28 (s, 3H), 1.21 (s, 3H), 1.08 (d, $J$ = 7.1 Hz, 3H), 1.00 (d, $J$ = 6.9 Hz, 3H), 0.89 (s, 9 H), 0.84 (d, $J$ = 6.5 Hz, 3H), 0.09 (s, 3H), 0.05 (s, 3H); $^{13}$C NMR (100 MHz) δ 204.4, 165.1, 151.5, 149.9, 127.8, 125.4, 125.0, 120.4, 77.2, 73.9, 51.5, 50.5, 41.8, 39.7, 36.6, 34 6, 31.3, 26.9, 26.7, 25.8, 25.4, 21.6, 18.2, 17.6, 11.3, −4.1, −4.4. Anal. Calcd for $C_{31}H_{50}O_4Si$: C, 72.32; H, 9.79. Found: C, 72.14; H, 9.63.

**(*E*)-(4*R*,6*R*,8*S*)-6-(Benzyloxy)-4,8-bis((*tert*-butyldiphenylsilyl)oxy)-9-oxonon-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (23a).** Prepared from **3a** and **14a** in 65% yield:[45] (*E*):(*Z*) = 98:2, diastereomeric ratio **23a**:**24a** = 98:2 (in the crude product, this diastereomer ratio was 89:11, but the diastereomers could be separated by chromatography[23]). **23a**: $^1$H NMR (400 MHz, selected data) δ 9.45 (d, $J$ = 1.7 Hz, 1H), 7.65–7.53 (m, 8 H).

(44) The sample also contained 3% of an isomer tentatively assigned as being epimeric at the carbon α to the aldehyde carbonyl; see Supporting Information for details.

(45) The sample obtained after flash chromatography also contained 6% of unreacted dialdehyde **14a**; this could be removed, with good material recovery, by a second chromatography. Alternatively, it was easily removed by chromatography after $NaBH_4$ reduction of the HWE product.

7.43–7.18 (m, 19H), 7.07–7.01 (m, 3H), 6.68 (dd, $J$ = 15.6, 6.1 Hz, 1H), 5.44 (dd, $J$ = 15.6, 1.2 Hz, 1H), 4.82 (ddd [app td], $J$ = 10.6, 4.3 Hz, 1H), 4.28 (app br q, $J$ = 6.2 Hz, 1H), 4.08 (ddd [app td], $J$ = 6.0, 1.8 Hz, 1H), 4.03 (d, $J$ = 11.1 Hz, 1H), 3.99 (d, $J$ = 11.0 Hz, 1H), 3.54 (dddd [app br quintet], $J$ = ca 5 Hz, 1H), 1.26 (s, 3H), 1.23 (s, 3H), 1.08 (s, 9H), 1.04 (s, 9H), 0.86 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (100 MHz, some signals overlap) $\delta$ 202.1, 165.5, 150.9, 149.1, 138.2, 135.97, 135.95, 135.92, 135.8, 133.6, 133.3, 133.0, 132.9, 130.2, 129.9, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 125.6, 125.5, 125.3, 121.1, 76.0, 74.6, 72.1, 70.3, 70.1, 50.7, 43.0, 41.8, 40.2, 38.2, 34.6, 31.4, 28.4, 27.1, 25.2, 21.9, 19.4. Anal. Calcd for $C_{64}H_{78}O_6Si_2$: C, 76.91; H, 7.87. Found: C, 76.63; H, 7.77. A sample enriched in diastereomer **24a** was obtained from a different experiment. **24a**: $^1$H NMR (400 MHz, selected data assigned from a mixture (87:13) of diastereomers **23a** and **24a**) $\delta$ 9.42 (d, $J$ = 1.8 Hz, 1H), 6.41 (dd, $J$ = 15.6, 6.1 Hz, 1H), 5.38 (dd, $J$ = 15.6, 1.4 Hz, 1H).

**(*Z*)-(4*S*,6*S*,8*R*)-6-(Benzyloxy)-4,8-bis((*tert*-butyldiphenylsilyl)oxy)-9-oxonon-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (25a).** Prepared from **3d** and **14a**, using only KHMDS as base (i.e., no 18-crown-6), in 76% yield; (*Z*):(*E*) = 98:2, diastereomeric ratio **25a**:**26a** = 98:2. **25a**: $^1$H NMR (400 MHz, selected data) $\delta$ 9.41 (d, $J$ = 2.5 Hz, 1H), 7.66–7.51 (m, 8H), 7.44–7.01 (m, 22H), 5.95 (dd, $J$ = 11.6, 8.1 Hz, 1H), 5.44 (ddd [app br quartet], $J$ = ca 6 Hz, 1H), 4.75 (dd, $J$ = 11.6, 1.1 Hz, 1H), 4.56 (ddd [app td], $J$ = 10.6, 4.2 Hz, 1H), 4.26 (d, $J$ = 11.2 Hz, 1H), 4.23 (ddd [app td], $J$ = 6.4, 2.5 Hz, 1H), 4.11 (d, $J$ = 11.0 Hz, 1H), 3.75–3.66 (m, 1H), 1.12 (s, 3H), 1.10 (s, 12H), 1.00 (s, 9H), 0.89 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, some signals overlapping) $\delta$ 201.8, 164.3, 151.5, 151.1, 138.5, 135.8, 134.0, 133.7, 133.3, 133.2, 129.93, 129.87, 129.7, 129.6, 128.1, 127.8, 127.7, 127.6, 127.4, 127.2, 125.4, 124.9, 118.5, 76.5, 73.9, 72.1, 69.6, 67.8, 50.4, 42.1, 41.7, 39.8, 39.6, 34.5, 31.3, 27.3, 27.0, 26.6, 25.4, 21.9, 19.4, 19.2. Anal. Calcd for $C_{64}H_{78}O_6Si_2$: C, 76.91; H, 7.87. Found: C, 77.17; H, 7.58. A sample enriched in diastereomer **26a** was obtained from a different experiment. **26a**: $^1$H NMR (400 MHz, selected data assigned from a mixture (86:14) of diastereomers **25a** and **26a**) $\delta$ 9.38 (d, $J$ = 2.3 Hz, 1H), 6.00 (dd, $J$ = 11.6, 7.9 Hz, 1H), 4.93 (dd, $J$ = 11.7, 1.3 Hz, 1H).

**(*E*)-(4*R*,6*R*,8*S*)-6-(Benzyloxy)-4,8-bis((2,2-dimethylpropionyl)oxy)-9-oxonon-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (23b).**[46] Prepared from **3b** and **14b** in 62% yield; (*E*):(*Z*) = 98:2, diastereomeric ratio **23b**:**24b** = 95:5.[23] **23b**: $^1$H NMR (400 MHz, selected data) $\delta$ 9.47 (s, 1H), 7.38–7.17 (m, 9H), 7.11–7.02 (m, 1H), 6.49 (dd, $J$ = 15.8, 5.3 Hz, 1H), 5.50 (dddd, $J$ = 9.3, 5.0, 3.5, 1.3 Hz, 1H), 5.41 (dd, $J$ = 15.8, 1.5 Hz, 1H), 5.17 (dd, $J$ = 9.7, 3.5, 1H), 4.83 (ddd [app td], $J$ = 10.7, 4.3 Hz, 1H), 4.41 (d, $J$ = 10.6 Hz, 1H), 4.35 (d, $J$ = 10.5 Hz, 1H), 3.59 (dddd [app septet], $J$ = 4 Hz, 1H), 1.26 (s, 3H), 1.21 (s, 3H), 1.23 (s, 9H), 1.19 (s, 9H), 0.84 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (50 MHz, some peaks in the aliphatic region overlap) $\delta$ 197.3, 177.8, 177.0, 165.0, 151.3, 144.4, 137.3, 128.6, 128.2, 128.1, 127.9, 125.4, 125.1, 122.1, 75.3, 74.7, 72.6, 71.8, 69.1, 50.4, 41.6, 39.9, 38.8, 34.5, 34.1, 31.2, 27.1, 26.6, 25.9, 21.7. **24b**: $^1$H NMR (400 MHz, selected data assigned from a mixture (95:5) of diastereomers **23b** and **24b**) $\delta$ 6.13 (dd, $J$ = 15.8, 4.5 Hz, 1H), 5.28 (dd, $J$ = 15.8, 1.7 Hz, 1H).

**(*Z*)-(4*S*,6*S*,8*R*)-6-(Benzyloxy)-4,8-bis((2,2-dimethylpropionyl)oxy)-9-oxonon-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (25b).**[46] Prepared from **3d** and **14b** in 62% yield; (*Z*):(*E*) = 98:2, diastereomeric ratio **25b**:**26b** = 98:2. **25b**: $^1$H NMR (250 MHz, selected data) $\delta$ 9.48 (s, 1H), 7.38–7.16 (m, 9H), 7.13–7.04 (m, 1H), 6.24 (dddd, $J$ = 9.3, 7.5, 3.3, 1.3 Hz, 1H), 5.79 (dd, $J$ = 11.6, 7.4 Hz, 1H), 5.20 (dd, $J$ = 10.2, 3.4 Hz, 1H), 5.04 (dd, $J$ = 11.6, 1.4 Hz, 1H), 4.82 (ddd [app td], $J$ = 10.7, 4.3 Hz, 1H), 4.60 (d, $J$ = 11.1 Hz, 1H), 4.40 (d $J$ = 11.1 Hz, 1H), 3.75–3.65 (m, 1H), 1.21 (s, 9H), 1.14 (s, 9H), 0.86 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (125 MHz, some peaks in the aliphatic region overlap) $\delta$ 197.6, 177.7, 177.4, 164.4, 151.5, 146.7, 137.9, 128.4, 128.1, 127.9, 127.7, 125.4, 125.0, 120.9, 75.5, 74.4, 72.3, 71.7, 69.8, 50.5, 41.7, 39.7, 38.8, 34.6, 31.3, 27.7, 27.1, 26.6, 25.2, 21.8. A sample enriched in diastereomer **26b** was obtained from a different experiment. **26b**: $^1$H NMR (250 MHz, selected data) $\delta$ 9.46 (s, 1H), 5.82 (dd, $J$ = 11.5, 7.5 Hz, 1H).

(46) Due to their limited stability, aldehydes **23b** and **25b** did not give satisfactory elemental analyses. The corresponding alcohols, obtained after $NaBH_4$ reduction, were fully characterized, however: see Supporting Information for details.

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**Supporting Information Available:** Additional experimental and characterization data (31 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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II

Rein, T.; Vares, L.; Kawasaki, I.; Pedersen, T. M.;
Norrby, P.-O.; Brandt, P.; Tanner, D.
Asymmetric Horner-Wadsworth-Emmons Reactions
with Meso-Dialdehydes: Scope, Mechanism, and Synthetic Applications.
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# Asymmetric Horner-Wadsworth-Emmons Reactions with *Meso*-Dialdehydes: Scope, Mechanism, and Synthetic Applications

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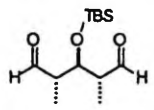
Asymmetric Horner-Wadsworth-Emmons reactions between chiral phosphonate reagents and various *meso*-dialdehydes have been investigated. A mechanistic model useful for rationalizing the experimentally observed stereoselectivities is presented. Furthermore, strategies for applying these reactions to the stereocontrolled preparation of chiral heterocyclic building blocks have been developed.

*Keywords:* asymmetric Horner-Wadsworth-Emmons reaction; chiral phosphonate; desymmetrization; *meso*-dialdehyde; chiral heterocycles

## INTRODUCTION

In recent years, the area of asymmetric Wittig-type reactions has received increasing attention.[1] We have studied several aspects of such reactions,[2] including the use of *meso*-dialdehydes (e.g., 1-3) as substrates in asymmetric Horner-Wadsworth-Emmons (HWE) reactions.[2b]

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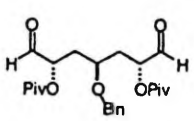


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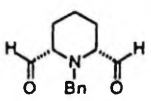
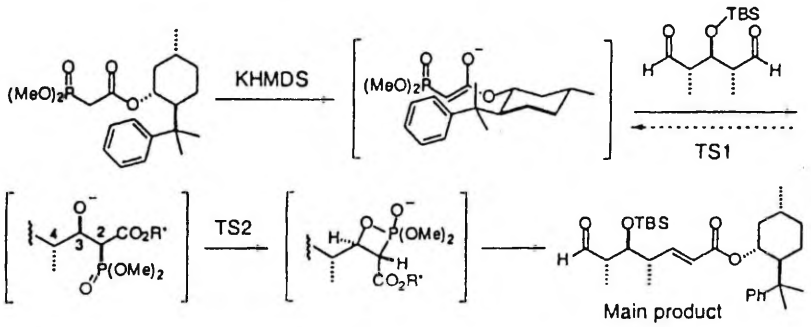



3

## RESULTS

### Mechanism

We have recently investigated the mechanistic details of these HWE reactions both by *ab initio* calculations on simplified models[13] and by molecular mechanics modelling of the actual systems.[14] Our current mechanistic model for the stereoselectivity in the asymmetric HWE reactions is illustrated by the example in Scheme 1.




Key factors:

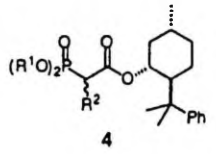
| | |
|---|---|
| *Chiral auxiliary* | -> Absolute configuration at C(2) |
| *R group in $(RO)_2P(=O)$* | -> Relative stereochemistry at C(2)/C(3) |
| *Substrate α-stereocenters* | -> Relative stereochemistry at C(3)/C(4) |

SCHEME 1. Factors determining product stereochemistry.

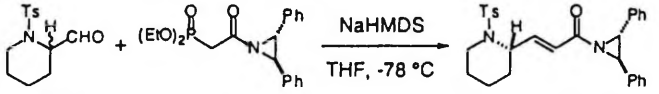
These studies indicate that the relative energies of the oxyanion and oxaphosphetane intermediates involved depend strongly on both reactant structures and reaction conditions. An interesting observation is that C-H···O hydrogen bonding between one of the alkoxy groups on phosphorus and the developing oxyanion can stabilize (*Z*)-selective forms of the transition state for the initial addition step. As illustrated in Scheme 1, several different factors combine to selectively favor one single diastereomeric form of the intermediates out of the eight theoretically possible. The chiral auxiliary controls from which face of the phosphonate enolate the reaction takes place. Our experimental studies have shown that the structure of the substituents on phosphorus controls the overall geometric selectivity, and that the influence of the substrate stereocenters depends on the specific reaction conditions. It is also clear that the whole reaction path (i.e, both the initial addition step and the subsequent ring closure) must be taken into consideration in the molecular mechanics modelling.

## New Reagents

Our modelling studies serve as a basis for the design and evaluation of new chiral reagents. The most efficient reagents we have used to date are the ones of type **4**, which contain 8-phenylmenthol as a chiral auxiliary. We are presently investigating reagents of type **5**, which have shown promising results in initial kinetic resolutions of racemic monoaldehydes, as exemplified below.



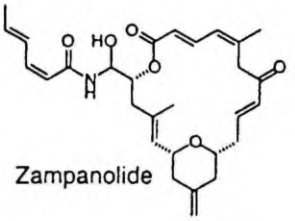
4



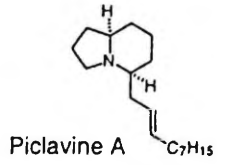

(Racemic; 2.2 equiv) 5 82%, (*E*):(*Z*) = 96:4, d.r.(*E*) = 90:10

## Application in synthetic approaches to chiral heterocycles

A range of natural products with interesting and potentially useful biological activity, e.g. zampanolide[5] and piclavine A,[6] contain heterocyclic substructures which might be derived from asymmetric HWE reactions with *meso*-dialdehyde substrates.

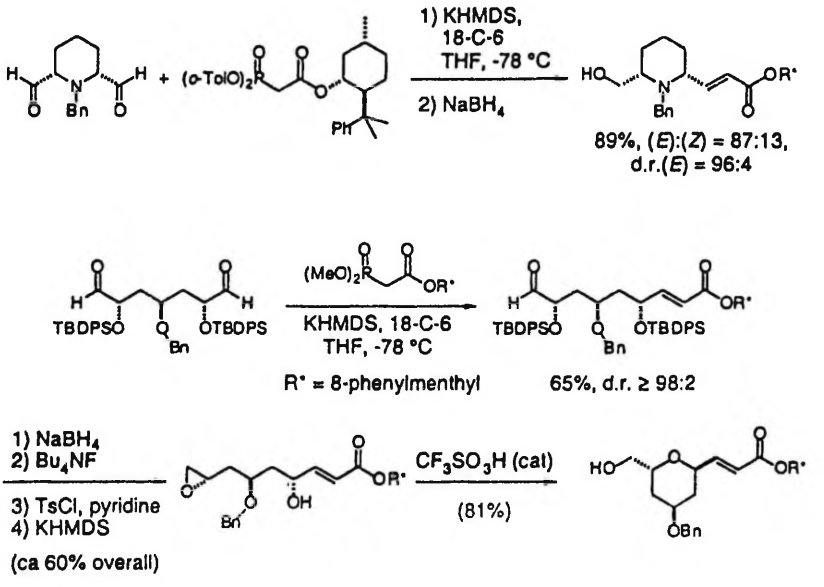


Zampanolide



Piclavine A

We have recently developed general strategies, based on asymmetric HWE reactions, which can be applied to the preparation of appropriately functionalized chiral heterocyclic building blocks (Scheme 2). In one approach, a cyclic *meso*-dialdehyde is desymmetrized to give a chiral HWE product, while an alternative strategy utilizes an asymmetric HWE reaction followed by a stereospecific ring closure to the heterocycle. By using reactions which proceed with either overall retention or inversion of stereochemistry in the ring closure step, the latter strategy enables construction of either *cis*- or *trans*-substituted derivatives, respectively.




SCHEME 2. Examples of strategies for synthesis of heterocyclic building blocks via asymmetric HWE reactions.

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# III

Vares, L.; Rein, T.
A Versatile Stereocontrolled Approach to Chiral Tetrahydrofuran and Tetrahydropyran Derivatives via Sequential Asymmetric Horner-Wadsworth-Emmons and Palladium-Catalyzed Ring Closure Reactions.
*Org. Lett.* 2000, *2*, 2611.

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# A Versatile Stereocontrolled Approach to Chiral Tetrahydrofuran and Tetrahydropyran Derivatives via Sequential Asymmetric Horner–Wadsworth–Emmons and Palladium-Catalyzed Ring Closure Reactions

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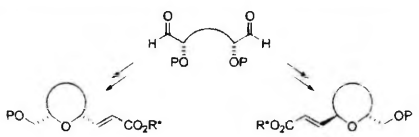
**Received May 31, 2000**

## ABSTRACT




**An approach to chiral tetrahydrofuran and tetrahydropyran derivatives is reported which is based on the sequential use of an asymmetric Horner–Wadsworth–Emmons desymmetrization of a *meso*-dialdehyde and a palladium-catalyzed intramolecular allylic substitution. The strategy is versatile in that either a *cis*- or a *trans*-relation between the stereocenters adjacent to the ring oxygen can be obtained.**

The development of stereoselective syntheses of substituted tetrahydrofuran (THF) and tetrahydropyran (THP) derivatives is an important challenge because of the frequent occurrence of such oxacycles as substructures in biologically active substances, such as the annonaceous acetogenins[1] and several groups of macrolides.[2] The need for appropriately functionalized synthetic building blocks has motivated the development of many different synthetic approaches.[3] In this Letter, we describe a stereochemically versatile approach to certain

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(1) For a review, see: Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504.

(2) For a review, see: Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041.

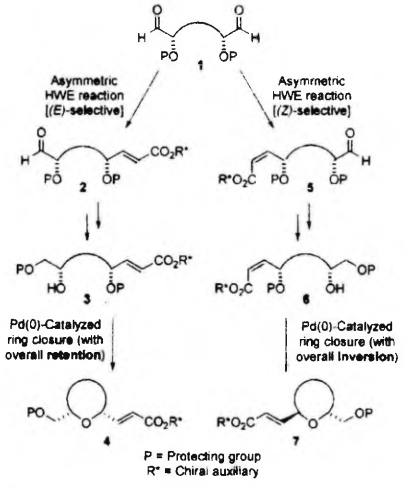
(3) For reviews, see: (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (b) Harmange, J.-C.; Figadère, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711. Selected recent examples: (c) Berninger, J.; Koert, U.; Eisenberg-Höhl, C.; Knochel, P. *Chem. Ber.* **1995**, *128*, 1021, and references therein. (d) Ramirez, M. A.; Padrón, J. M.; Palazón, J. M.; Martin, V. S. *J. Org. Chem.* **1997**, *62*, 4584, and references therein. (e) Sinha, S. C.; Keinan, E.; Sinha, S. C. *J. Am. Chem. Soc.* **1998**, *120*, 9076, and references therein. (f) Ley, S. V.; Brown, D. S.; Clase, J. A.; Fairbanks, A. J.; Lennon, I. C.; Osborn, H. M. I.; Stokes, E. S. E.; Wadsworth, D. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2259. (g) Morimoto, Y.; Iwai, T.; Kinoshita, T. *J. Am. Chem. Soc.* **1999**, *121*, 6792. (h) Pilli, R. A.; Riatto, V. B.; Vencato, I. *Org. Lett.* **2000**, *2*, 53. (i) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2000**, *2*, 461.

10.1021/ol006135r CCC: $19.00 
**Published on Web 08/04/2000**

THF and THP derivatives which is based on the sequential use of an asymmetric Horner–Wadsworth–Emmons (HWE) reaction[4] and an intramolecular palladium-catalyzed allylic substitution.[5] An attractive feature of this approach is the fact that as a result of the stereospecificity of the Pd(0)-catalyzed reaction, control of the alkene geometry in the HWE product translates into control of the relative configuration of the ring-closed product.

We have recently reported that *meso*-dialdehydes of type **1** can be efficiently desymmetrized by use of asymmetric HWE reactions[4g] to give either (*E*)-alkenes **2** or (*Z*)-alkenes **5** with good to excellent levels of geometric selectivity and asymmetric induction. The protective group P can be chosen so that the PO group can act as a leaving group in a Pd(0)-catalyzed allylic substitution[6] (Scheme 1). After reduction

**Scheme 1**




of the unreacted formyl group in the HWE product, migration of the one protective group P which is adjacent to the primary alcohol will give compounds **3** and **6**, respectively, in which the stage is now set for a Pd(0)-catalyzed ring closure in which the liberated secondary OH group can act as the nucleophile. In general, (*E*)-allylic substrates are known to undergo Pd(0)-catalyzed substitution with O-nucleophiles with overall *retention* of configuration; (*Z*)-allylic compounds, on the other hand, might undergo a $\pi-\sigma-\pi$ rearrangement of the intermediate palladium complex before the nucleophilic attack takes place, resulting in overall *inversion* of configuration and simultaneous conversion of the (*Z*)-alkene to an (*E*)-alkene.[7] We therefore anticipated a possibility for versatility of stereocontrol: whereas (*E*)-substrates **3** would give *cis*-products **4**, ring closure of (*Z*)-substrates **6** could provide access to *trans*-products **7**. Precedence for ring closure by Pd(0)-catalyzed allylic substitution with an oxygen nucleophile does exist,[5] but the opportunities for simultaneously controlling the stereochemistry to obtain, at will, either retention or inversion of configuration appear to be previously unexplored.

To apply this strategy to the preparation of THF derivatives, we investigated asymmetric HWE reactions with *meso*-dialdehyde **8**[8] (Scheme 2). Pivaloyl protective groups were chosen because allylic carboxylates are known to be good precursors of $\eta^3$-allylpalladium complexes. To our delight, asymmetric HWE reactions between **8** and phosphonates **9** gave essentially complete geometric selectivities as well as excellent diastereoselectivities.[9,10]

Subsequent reduction of the aldehyde functionalities in **10** and **14**, followed by acyl group migration, gave **12** and **16**, respectively.[11] When compound **12** was treated with catalytic amounts of $Pd_2(dba)_3$ in the presence of neocuproine,[12] it readily ring-closed at room temperature to give the 2,5-*cis*-disubstituted THF derivative **13**,[13] with complete retention of configuration at the allylic stereocenter.

The (*Z*)-alkene **16**, on the other hand, required elevated temperatures (refluxing THF) under otherwise similar condi-

(4) For a review, see: Rein, T.; Reiser, O. *Acta Chem. Scand.* **1996**, *50*, 369. Selected recent examples: (b) Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1996**, *37*, 1077. (c) Kumamoto, T.; Koga, K. *Chem. Pharm. Bull.* **1997**, *45*, 753. (d) Dai, W.-M.; Wu, J.; Huang, X. *Tetrahedron: Asymmetry* **1997**, *8*, 1979. (e) Mizuno, M.; Fujii, K.; Tomioka, K. *Angew. Chem.* **1998**, *110*, 525; *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 515. (f) Vaulont, I.; Gais, H.-J.; Reuter, N.; Schmitz, E.; Ossenkamp, R. K. L. *Eur. J. Org. Chem.* **1998**, 805. (g) Tullis, J. S.; Vares, L.; Kann, N.; Norrby, P.-O.; Rein, T. *J. Org. Chem.* **1998**, *63*, 8284. (h) Arai, S.; Hamaguchi, S.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 2997. (i) Tanaka, K.; Watanabe, T.; Shimamoto, K.-Y.; Sahakitpichan, P.; Fuji, K. *Tetrahedron Lett.* **1999**, *40*, 6599. (j) Pedersen, T. M.; Jensen, J. F.; Humble, R. E.; Rein, T.; Tanner, D.; Bodmann, K.; Reiser, O. *Org. Lett.* **2000**, *2*, 535.

(5) For selected examples of use of an intramolecular Pd(0)-catalyzed allylic substitution as the ring-closing step in approaches to oxygen heterocycles, see: (a) Trost, B. M.; Tenaglia, A. *Tetrahedron Lett.* **1988**, *29*, 2927. (b) Suzuki, T.; Sato, O.; Hirama, M.; Yamamoto, Y.; Murata, M.; Yasumoto, T.; Harada, N. *Tetrahedron Lett.* **1991**, *32*, 4505. (c) Mizuguchi, E.; Achiwa, K. *Chem. Pharm. Bull.* **1997**, *45*, 1209. (d) Fournier-Nguefack, C.; Lhoste, P.; Sinou, D. *Tetrahedron* **1997**, *53*, 4353. (e) Trost, B. M.; Asakawa, N. *Synthesis* **1999**, 1491. (f) Labrosse, J.-R.; Poncet, C.; Lhoste, P.; Sinou, D. *Tetrahedron: Asymmetry* **1999**, *10*, 1069.

(6) For a general reference, see: Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley & Sons: New York, 1995; pp 290–340.

(7) For examples, see: (a) Hayashi, T.; Yamamoto, A.; Hagihara, T. *J. Org. Chem.* **1986**, *51*, 723. (b) Sugiura, M.; Yagi, Y.; Wei, S.-Y.; Nakai, T. *Tetrahedron Lett.* **1998**, *39*, 4351.

(8) See Supporting Information for details on how compound **8** was prepared.

(9) Both geometric selectivities and diastereomer ratios for the HWE products were determined by $^1$H NMR spectroscopy. The absolute configurations of compounds **12** and **16** were assigned on the basis of NMR analyses of the corresponding Mosher esters (see Supporting Information for details).

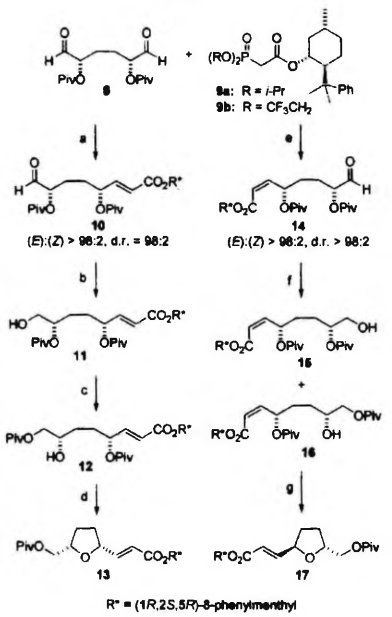
(10) From the reaction between **8** and **9a**, bisaddition products were also isolated in ca. 40% yield, which explains the modest yield of compound **10**.

(11) Depending on the specific conditions used, varying ratios between the secondary alcohols (**12**, **16**, **20**, and **23**) and the isomeric primary alcohols (**11**, **15**, **19**, and **22**, respectively) could be obtained from reduction of the corresponding HWE products. The primary alcohols could be separated and converted to mixtures of secondary/primary, thereby increasing the overall yield of the desired secondary alcohols to ca. 70% after one iteration (see Supporting Information for details).

(12) Neocuproine = 2,9-dimethyl-1,10-phenanthroline

(13) Assignments of relative configuration in the ring-closed products are based on NOE experiments on compounds **13**, **17**, and **24**. The assignment for compound **21** is based on $^{13}$C NMR analysis of a derivative (see Supporting Information for details).

**Scheme 2**[a]



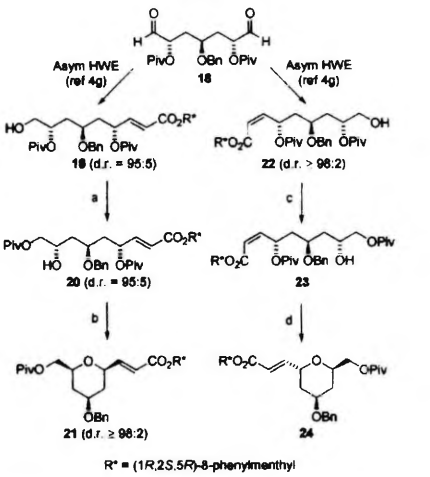

[a] Reaction conditions: (a) 1.3 equiv of **8**, 1.1 equiv of **9a**, 1.0 equiv of KHMDS, 5 equiv of 18-crown-6, THF, −85 °C; 55%; (b) $NaBH_4$, MeOH/THF, 0 °C; 85%; (c) DMAP, EtOH, 75 °C; 63% **12**, 27% recovered **11** (see footnote 11); (d) $Pd_2(dba)_3{\cdot}CHCl_3$ (0.05 equiv), neocuproine (0.2 equiv), THF, 25 °C; 76%; (e) 1.3 equiv of **8**, 1.1 equiv of **9b**, 1.0 equiv of KHMDS, 5 equiv of 18-crown-6, THF, −85 °C; 71%; (f) $LiBH_4$, *i*-PrOH/THF, 0 °C; 49% **16**, 38% **15** (see footnote 11); (g) $Pd_2(dba)_3{\cdot}CHCl_3$ (0.15 equiv), neocuproine (0.4 equiv), THF, 65 °C; 79%.

tions for the ring closure to occur. The major product was the 2,5-*trans*-disubstituted THF derivative **17**,[13] containing an (*E*)-alkene, an outcome which is completely consistent with the anticipated $\pi-\sigma-\pi$ rearrangement. Use of phosphine ligands in place of neocuproine in reactions with **16** caused elimination to form a diene to prevail over the desired ring closure.

Starting from compounds **19** and **22**, which are available via asymmetric HWE desymmetrization of *meso*-dialdehyde **18** followed by $NaBH_4$ reduction,[4g] THP derivatives **21** and **24** were synthesized using a similar approach (Scheme 3).

Pivaloyl group migration afforded the secondary alcohols **20** and **23** from **19** and **22**, respectively.[11] When the (*E*)-alkene **20** was subjected to the ring closure conditions, we were pleased to see that the desired 2,6-*cis*-THP derivative **21** could be obtained diastereomerically pure, even though the starting material **20** contained minor amounts (ca. 5%) of another isomer. Ring closure of the (*Z*)-alkene **23** gave, as expected, the 2,6-*trans*-derivative **24**, in analogy to the formation of compound **17** from **16**.

**Scheme 3**[a]




[a] Reaction conditions: (a) imidazole, EtOH, 75 °C; 59% **20**, 28% recovered **19** (see footnote 11); (b) $Pd_2(dba)_3{\cdot}CHCl_3$ (0.1 equiv), neocuproine (0.4 equiv), THF, 25 °C; 80%; (c) DMAP, EtOH, 75 °C; 48% **23**, 42% recovered **22** (see footnote 11); (d) $Pd_2(dba)_3{\cdot}CHCl_3$ (0.15 equiv), neocuproine (0.4 equiv), THF, 50 °C; 59%

To summarize, we have demonstrated efficient stereocontrolled routes for the preparation of various functionalized THF and THP derivatives, using a strategy involving an asymmetric HWE reaction in sequence with a palladium-catalyzed intramolecular allylic substitution as key steps. The relative configuration of the stereocenters adjacent to the ring oxygen is controlled by the combined influence of the geometric selectivity of the HWE reaction and the stereospecificity of the palladium-catalyzed process, while the absolute configuration is controlled in the asymmetric HWE reaction. We are currently investigating possible extensions of this strategy to the preparation of other heterocyclic and carbocyclic systems.

**Acknowledgment.** We thank the Danish Technical Science Research Council (STVF), the Danish Natural Science Research Council (SNF), the Swedish Natural Science Research Council (NFR), the Swedish Institute, the Salén Foundation (Sweden), the Royal Institute of Technology, the Estonian Science Foundation (Grant 4230), the Estonian Ministry of Education (Grant 0350315s98), and the Nordic-Baltic Scholarship Scheme for financial support. Dr Ivar Martin, Institute of Chemistry at Tallinn Technical University, and Professor Paul Helquist, University of Notre Dame, are acknowledged for helpful discussions and continuous support. We are grateful to Professor Christian Pedersen and Mr. Torben M. Pedersen, Technical University of Denmark, and Professor Tõnis Pehk, National Institute of Chemical Physics and Biophysics, Tallinn, for skilful assistance with

NMR experiments. Mrs. Nonka Sevova, University of Notre Dame, is gratefully acknowledged for assistance with HRMS analyses.

**Supporting Information Available:** Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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# IV

Vares, L.; Kann, N.; Rein, T.
A Versatile Stereocontrolled Approach to Chiral Tetrahydrofuran and Tetrahydropyran Derivatives by Use of Horner-Wadsworth-Emmons and Ring Closure Reactions.
Manuscript

# A Versatile Stereocontrolled Approach to Chiral Tetrahydrofuran and Tetrahydropyran Derivatives by Use of Horner-Wadsworth-Emmons and Ring Closure Reactions

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An approach to chiral to tetrahydrofuran and tetrahydropyran derivatives via an asymmetric Horner-Wadsworth-Emmons and sequential cyclization reactions is presented. The approach is both stereochemically and structurally versatile since three different cyclization methods can be employed starting from the same HWE product: (i) palladium-catalyzed substitution, (ii) hetero-Michael addition, or (iii) epoxide opening. The asymmetric HWE reaction controls the absolute configuration of the ultimate product, whereas the relative configuration is controlled by the combined influence of the geometric selectivity in the HWE reaction and the stereochemistry of the respective cyclization method. In addition, the use of a cyclic meso-dialdehydes as a substrates for HWE reaction, enables the synthesis of chiral 2,6-cis-THP derivatives is a single step.

## Introduction

Compounds containing tetrahydrofuran (THF) and tetrahydropyran (THP) subunits are receiving considerable attention because of frequent occurrance in bioactive natural products, such as annonaceous acetogenins,[1] polyether

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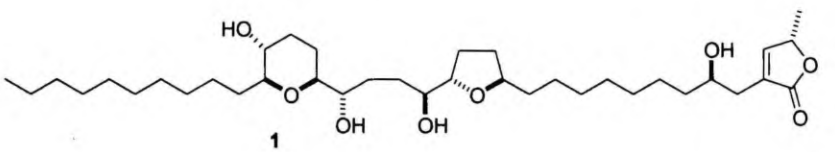
(1) For a recent review, see: Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504.

antibiotics,[2] and several groups of macrolides. The range of biological activities of these type of compounds is very wide including among others antibiotic,[2] antimicrobal,[1] cytotoxic,[3] pesticidal,[1] antimalarial,[1] and antiviral[4] effects. For example, the studies on aceteogenins, a growing class of natural products found in the tropical plant family annonaceae, have grown remarkably in recent years. Structurally, acetogenins are derivatives of long-chain fatty acids containing THF and/or THP and butenolide moieties. Several representatives of acetogenins are potent cytotoxic agents by selectively inhibiting the cancerous cells by the blockage of mitochondrial complex I (NADH-ubiquinone oxidoreductase), and by the inhibition of plasma membrane NADH oxidase. For example, mucocin (**1**) exhibits up to 10000 times more selective inhibitory effect against A-548 (lung cancer) and PACA-2 (pancreatic cancer) cell lines compared to the known antitumor agent adriamycin.[5]

**Chart 1**




**1**

The need for appropriately functionalized builing blocks, such as those shown in Chart 2, has motivated the development of many different synthetic approaches.[6] Among earlier reported methods for preparing functionalized THF's and THP's, some of the more frequently used are acid-induced ring-closure of an epoxy alcohol,[7] intramolecular hetero-Michael addition,[8] metal-catalyzed oxidative

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(2) Wesley, J. W. *Polyether Antibiotics: Naturally Occurring Acid Ionophores*; Marcel Dekker: New York, 1982; Vols. I and II.

(3) Corley, D. G.; Herb, R.; Moore, R. E.; Scheuer, P. J.; Paul, V. J. *J. Org. Chem.* **1998**, *53*, 3644.

(4) Sakemi, S.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *Tetrahedron Lett.* **1986**, *27*, 4287.

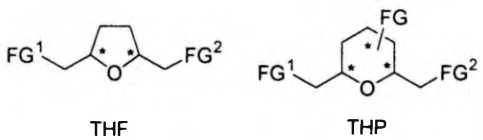
(5) Shi, G.; Alfonso, D.; Fatope, M. O.; Zeng, L.; Gu, Z.-M.; Zhao, G.-X.; He, K.; MacDougal, J. M.; McLaughlin, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 10409.

(6) For reviews, see: (a) Elliott, M. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4175. (b) Harmange, J.-C.; Figadère, B. *Tetrahedron: Asymm.* **1993**, *4*, 1711. (c) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309.

(7) For selected examples, see: (a) Li, K.; Vig, S.; Uckun, F. M. *Tetrahedron Lett.* **1998**, *39*, 2063. (b) Ley, S. V.; Brown, D. S.; Clase, J. A.; Fairbanks, A. J.; Lennon, I. C.; Osborn, H. M. I.; Stokes (née Owen), E. S. E.; Wadsworth, D. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2259. (c) Maguire, R. J.; Thomas, E. J. *J.*

cyclization of a hydroxy-alkene,[9] reduction of bicyclic ketals,[10] oxabicyclic systems,[11] or spiro compounds,[12] and intramolecular Williamson-type reactions.[13].

**Chart 2**




In this paper, we describe a stereochemically versatile approach to *cis*- and *trans*-substituted THF and THP derivatives of the types shown above which is based on sequential use of an asymmetric Horner-Wadsworth-Emmons (HWE) reaction followed by a ring closure reaction via either: (i) an intramolecular Pd(0)-catalyzed allylic substitution, (ii) a hetero-Michael addition, or (iii) intramolecular opening of a terminal epoxide (Scheme 1). The fact that the use of different

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*Chem. Soc., Perkin Trans. 1* **1995**, 2487. (d) Fotsch, C. H.; Chamberlin, A. R. *J. Org. Chem.* **1991**, *56*, 4141. (e) Iqbal, J.; Pandey, A.; Chauhan, B. P. S. *Tetrahedron* **1991**, *47*, 4143. (f) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5335. (g) Bartlett, P. A.; Chapuis, C. *J. Org. Chem.* **1986**, *51*, 2799.

(8) For selected examples, see: (a) Betancort, J. M.; Martín, V. S.; Padrón, J. M.; Palazón, J. M.; Ramírez, M. A.; Soler, M. A. *J. Org. Chem.* **1997**, *62*, 4570, and references therein. (b) Ramírez, M. A.; Padrón, J. M.; Palazón, J. M.; Martín, V. S. *J. Org. Chem.* **1997**, *62*, 4584. (c) Paterson, I.; Arnott, E. A. *Tetrahedron Lett.* **1998**, *39*, 7185. (d) Takagi, R.; Sasaoka, A.; Kojima, S.; Ohkata, K. *Heterocycles* **1997**, *45*, 2313. (e) Banwell, M. G.; Bui, C. T.; Pham, H. T. T.; Simpson, G. W. *J. Chem. Soc., Perkin Trans. 1* **1996**, 967.

(9) For examples using Pd(II), see: (a) Semmelhack, M. F.; Epa, W. R.; Cheung, A. W.-H.; Gu, Y.; Kim, C.; Zhang, N.; Lew, W. *J. Am. Chem. Soc.* **1994**, *116*, 7455, and references therein. For recent examples using Re(VII), see: (b) Towne, T. B.; McDonald, F. E. *J. Am. Chem. Soc.* **1997**, *119*, 6022. (c) Kennedy, R. M.; Tang, S. *Tetrahedron Lett.* **1992**, *33*, 3729. (d) Sinha, S. C.; Keinan, E.; Sinha, S. C. *J. Am. Chem. Soc.* **1998**, *120*, 9076. (e) Sinha, S. C.; Sinha, A.; Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1997**, *119*, 12014. (f) Morimoto, Y.; Iwai, T.; Kinoshita, T. *J. Am. Chem. Soc.* **1999**, *121*, 6792, and references therein.

(10) Kotsuki, H. *Synlett* **1992**, 97, and references therein.

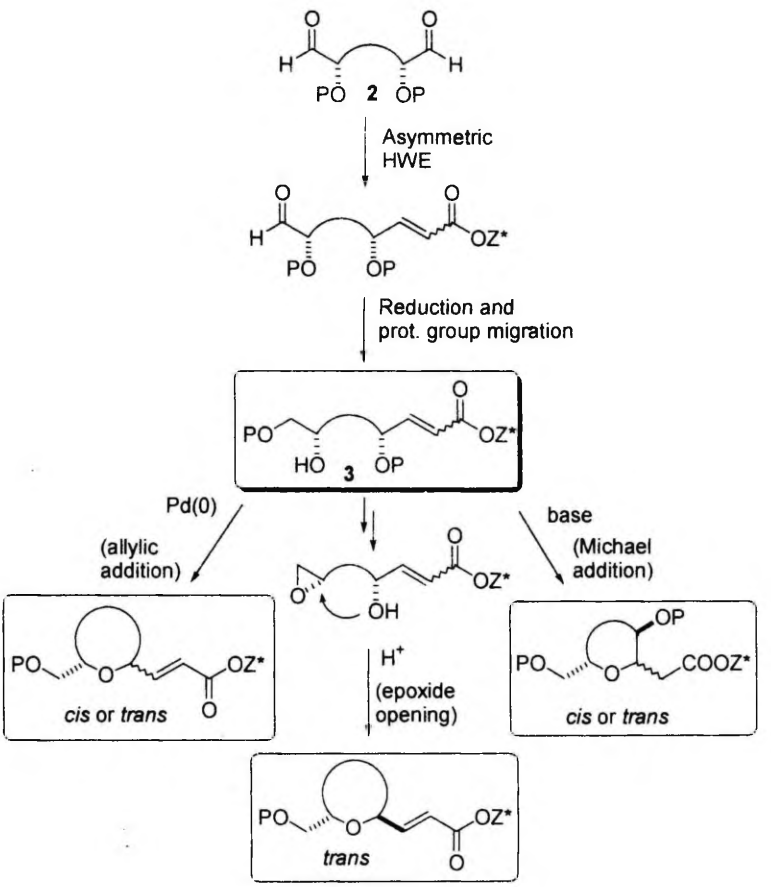
(11) Molander, G. A.; Swallow, S. *J. Org. Chem.* **1994**, *59*, 7148.

(12) (a) Oikawa, M.; Ueno, T.; Oikawa, H.; Ichihara, A. *J. Org. Chem.* **1995**, *60*, 5048. (b) Crimmins, M. T.; Rafferty, S. W. *Tetrahedron Lett.* **1996**, *37*, 5649.

(13) For recent examples, see: (a) Berninger, J.; Koert, U.; Eisenberg-Höhl, C.; Knochel, P. *Chem. Ber.* **1995**, *128*, 1021, and references cited therein. (b) Wang, Z.-M.; Shen, M. *J. Org. Chem.* **1998**, *63*, 1414.

cyclization methods leads to different THF or THP derivatives from the same HWE product makes makes the overall strategy more versatile. In addition, the use of a cyclic *meso*-THP-dialdehyde as substrate for an asymmetric HWE reaction, enables the synthesis of 2,6-*cis*-THP's in a single step.

**Scheme 1**




We have recently reported that α-oxygen substituted *meso*-dialdehydes of type **2** can be efficiently desymmetrized by use of asymmetric HWE reactions, giving either (*E*)- or (*Z*)-alkene as product with an essentially full control of geometric selectivity and with good to excellent levels of asymmetric induction.[14] The key intermediate **3**, obtained after reduction of the unreacted formyl group

(14) (a) Tullis, J. S.; Vares, L.; Kann, N.; Norrby, P.-O.; Rein, T. *J. Org. Chem.* **1998**, *63*, 8284. (b) Vares, L.; Rein, T. *Org. Lett.* **2000**, *2*, 2611.

accompanied by protective group migration to the adjacent primary hydroxyl, can directly afford a THF or THP derivative via either a Pd(0)-catalyzed allylic substitution or a hetero-Michael addition reaction, in both cases with the liberated secondary OH group acting as an internal nucleophile (Scheme 1). Control of the alkene geometry in **3** translates into control of the relative configuration of the ring-closed product, a fact which makes this approach attractive (Scheme 2). Generally, (*E*)-allylic substrates are known to undergo Pd(0)-catalyzed allylic substitution with O-nucleophiles with overall *retention* of configuration (**6**); (*Z*)-allylic compounds, on the other hand, might undergo a $\pi-\sigma-\pi$ rearrangement of the intermediate palladium complex before the nucleophilic attack takes place, resulting in overall *inversion* of configuration (**7**).[15] In hetero-Michael additions the (*Z*)-alkene substrates normally afford *cis* product (**9**) both in case of kinetic and thermodynamic control, whereas (*E*)-alkene substrates, under conditions of kinetic control, can give predominantly *trans* product (**8**).[16] In case of the terminal epoxide opening route, a few additional steps are needed to convert the intermediate **3** into an epoxide, which is subsequently opened via a $S_N2$ reaction by the allylic alcohol to form the corresponding oxacycle.

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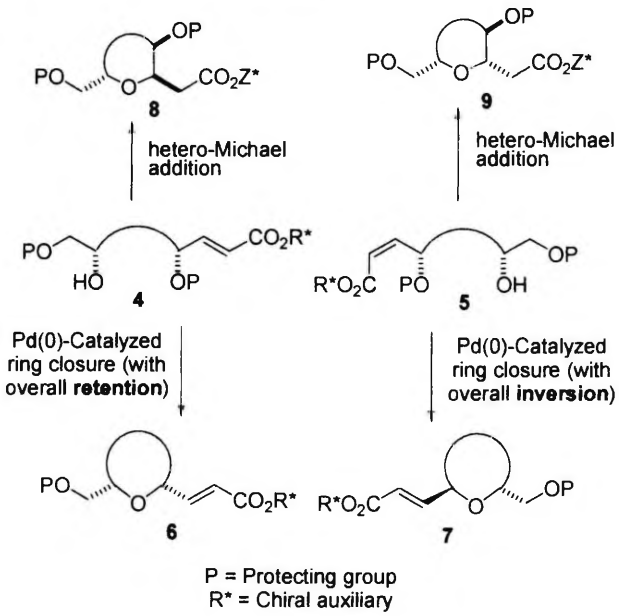
(15) (a) Hayashi, T.; Yamamoto, A.; Hagihara, T. *J. Org. Chem.* **1986**, *51*, 723. (b) Sugiura, M.; Yagi, Y.; Wei, S.-Y.; Nakai, T. *Tetrahedron Lett.* **1998**, *39*, 4351.

(16) (a) Banwell, M. G.; Bui, C. T.; Pham, H. T. T.; Simpson, G. W. *J. Chem. Soc., Perkin Trans. 1* **1996**, 967. (b) Betancort, J. M.; Martín, V. S.; Padrón, J. M.; Palazón, J. M.; Ramírez, M. A.; Soler, M. A. *J. Org. Chem.* **1997**, *62*, 4570. (c) Ramírez, M. A.; Padrón, J. M.; Palazón, J. M.; Martín, V. S. *J. Org. Chem.* **1997**, *62*, 4584.

**Scheme 2**

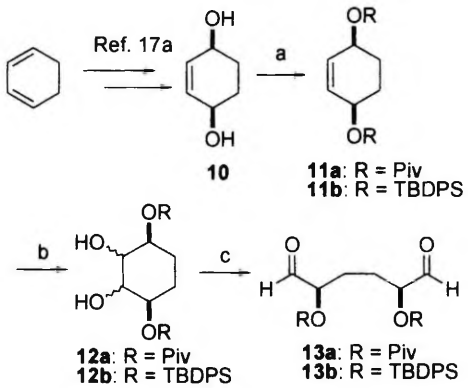



## Results and Discussion

**Choice and Preparation of Substrates.** We chose the α-oxygen substituted *meso*-dialdehydes **13**, **18** and **36**[14a] as substrates for asymmetric HWE reactions for two reasons: from earlier work we know that dialdehydes of type **33** can perform well in asymmetric HWE reactions,[14a] and the expected HWE products have an appropriate framework to form five- or six-membered oxygen heterocycles with the desired substitution patterns. The hydroxyl protective groups on the *meso*-dialdehydes have particular importance by enabling the respective ring-closure to be performed. Pivaloyl protective groups were chosen (in *meso*-dialdehydes **13a** and **36a**), because they have earlier given good results in asymmetric HWE reactions and allylic carboxylates are known to be good precursors for $\eta^3$-allylpalladium complexes. Even though the silyloxy groups are not suitable for Pd(0)-catalyzed substitutions due to their inability to function as leaving groups, their choice was motivated because they could be efficiently employed on route to hetero-Michael additions and epoxide opening reactions and they are superior to pivalates in many occasions where selective deprotection is needed. Furthemore, the silyl-protected meso-dialdehyde **36b** has given good selectivities in asymmetric HWE reactions, and the ability of silyl groups to migrate from one oxygen to another is well known. The dialdehydes **13a** and **13b** were prepared in

three simple steps from the known *cis*-2-cyclohexene-1,4-diol (**10**) which, in turn, is accessible from 1,3-cyclohexadiene[17] (Scheme 3). The protected diols **11** were dihydroxylated in high yield using $RuCl_3/NaIO_4$, whereas the more conventional $OsO_4$/NMMO oxidation system gave ca. 45% (**12b**) and 75% (**12a**) conversions even after several days at 50 °C. The desired dialdehydes were obtained in essentially quantitative yield after oxidative cleavege with periodic acid.

**Scheme 3**[a]




[a]Reaction conditions: (a) **11a**: PivCl, 4-DMAP, pyr., reflux, 3 h, 59%; **11b**: TBDPSCl, imidazole, DMF, RT, 30 h, 85%. (b) **12a**: cat. $RuCl_3$, $NaIO_4$, MeCN/$H_2O$, 0 °C, 5 min., 94%; **12b**: cat. $RuCl_3$, $NaIO_4$, MeCN/EtOAc/$H_2O$, 0 °C, 80 sec., 89%. (c) $H_5IO_6$, THF, RT, 70-80 min., 99% (**13a**); 97% (**13b**).

The cyclic dialdehyde **18** was prepared in four steps from the bicyclic ketone **14** which, in turn, is accessible from the reductive cycloaddition of α,α,α',α'-tetrabromoacetone and furan (Scheme 4).[18] The alcohols **15**, obtained after the reduction of the carbonyl functionality, are readily separable by flash chromatography. Studies by Hoffmann have shown that the use of L-Selectride® instead of $NaBH_4$ would give exclusively the axial (*endo*) alcohol.[19] The dialdehyde **18**, obtained after the periodic acid cleavage of the diol **17**, is quite stable and can even be purified by flash chromatography if needed.

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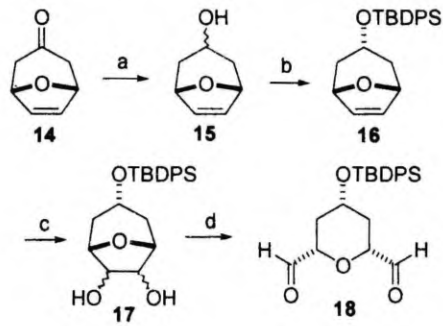
(17) (a) Bäckvall, J.-E.; Granberg, K. L.; Hopkins, R. B. *Acta Chem. Scand.* **1990**, *44*, 492. (b) Bäckvall, J. E.; Byström, S. E.; Nordberg, R. E. *J. Org. Chem.* **1984**, *49*, 4619.

(18) Mann, J.; Barbosa, L.-C. d. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 787.

(19) Lampe, T. F. J.; Hoffmann, H. M. R. *Chem. Commun.* **1996**, 1931.

**Scheme 4**[a]



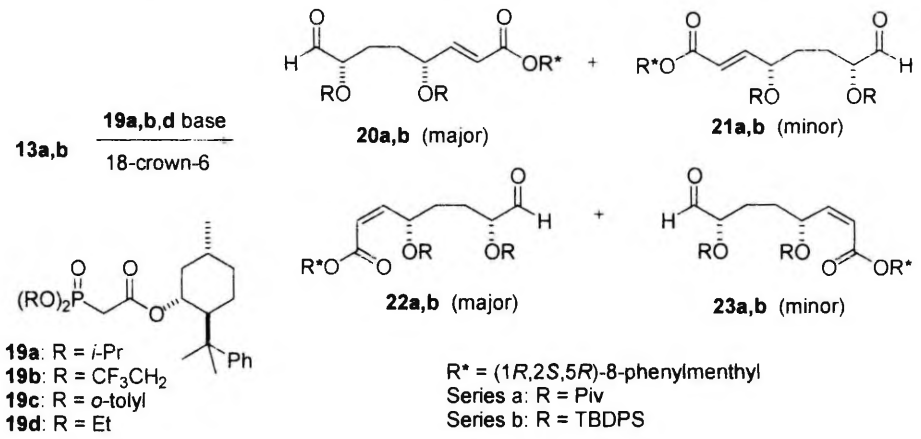

[a]Reaction conditions: (a) $NaBH_4$, MeOH, 0 °C - RT, 4 h, 90%, *endo*:*exo* = 7:3; (b) TBDPSCl, imidazole, DMF, RT, 36 h, 46%; (c) cat. OsO4, $Et_4NOH$, *t*-BuOOH, *t*-BuOH, ether, 0 °C - RT, 29 h, 73%; (d) $H_5IO_6$, THF, RT, 1.5 h, 99%.

**Asymmetric HWE Reactions.** For the synthesis of HWE products **20a**,**b** and **22a**,**b**, we applied the best conditions found earlier[14a] for reactions with dialdehydes **36**.

The (*Z*)-alkene products **22a** and **22b** were obtained in high yields with essentially complete geometric and diastereoselectivity by using bis(trifluoroethyl)phosphonate **19b** (entries 2 and 5, Table 1). The pivaloyl protected-dialdehyde **13a** performed best under our "standard" KHMDS/18-crown-6 base system, the silyl-protected dialdehyde **13b** gave better results when NaHMDS was used as a base without 18-crown-6.

The (*E*)-alkenes, in turn, were obtained with good to excellent levels of asymmetric induction and moderate yields by using bis(diisopropyl)phosphonate **19a** and the KHMDS/18-crown-6 base system (entries 1 and 3). When bis(diethyl)phosphonate **19d** was used instead of **19a**, the diastereoselectivity dropped significantly (entry 4).

**Table 1.** Asymmetric HWE reactions with dialdehydes **13**.[a]




| Entry | Phosphonate | Substrate | Temp. (°C) | Product | Yield[b] (%) | d.r.[c] | Yield of bisadd. (%) |
|---|---|---|---|---|---|---|---|
| 1 | **19a** | **13a** | -85 | **20a** | 55 | **98**:2 | 44 |
| 2 | **19b** | **13a** | -85 | **22a** | 71 | ≥98:2 | 25 |
| 3 | **19a** | **13b** | -78 | **20b** | 61[d] | 95:5 | 36 |
| 4 | **19d** | **13b** | -78 | **20b** | 69 | 80:20 | n.d. |
| 5 | **19b**[e] | **13b** | -78 | **22b** | 88 | ≥98:2 | n.d. |

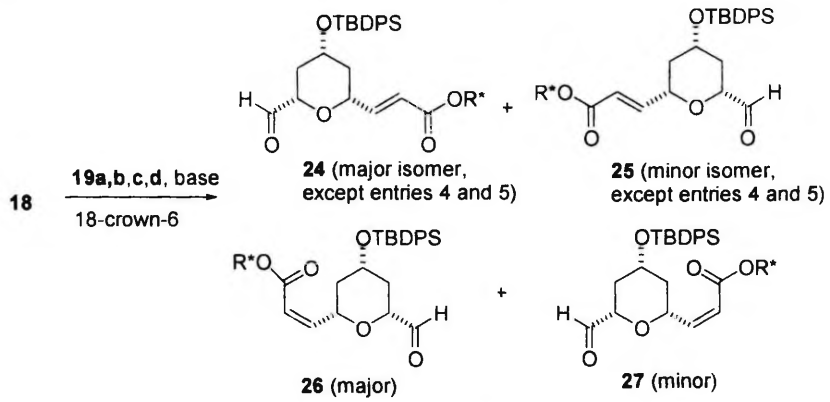
[a] General reaction conditions: 1.2-1.3 equiv of dialdehyde, 1.1-1.3 equiv of phosphonate, 1.0 equiv of KHMDS, 5 equiv of 18-crown-6, ca. 0.02 M in THF, 3-12 h. [b] Yield of isolated monoaddition product. [c] Ratio of **20a,b**:**21a,b** or **22a,b**:**23a,b**, respectively. The ratios of geometric isomers were in all entries: (*Z*):(E) ≥98:2. [d] Yield after reduction of the monoaddition product to the alcohol. [e] NaHMDS was used as a base, no 18-crown-6.

We also explored the possibility to desymmetrize the cyclic dialdehyde **18**, to obatin directly the 2,6-*cis*-THP derivatives **24** and **26** (Table 2). Unfortunately, despite our efforts to optimize the reaction conditions, the results of the asymmetric HWE reactions remained poorer. Both the (*E*)- and (*Z*)-monoaddition products were obtained with essentially complete geometric and diastereoselectivities but in rather low yields (entries 1 and 2). The (*Z*)-product **26** was obtained only by using the bis(*o*-tolyl)phosphonate **19c**, whereas the usually (*Z*)-selective bis(trifluoro)phosphonate **19b** afforded (*E*)-products with poor diastereoselectivity (entries 4 and 5). The use of different solvents (MeCN, EtCN, $CH_2Cl_2$) and base (NaHMDS) did not improve yield and diastereoselectivity of monoaddition products (entries 3-7). We postulate that the switch in selectivity observed in entries 4 and 5 when the base is altered is caused by a change in

mechanism from Felkin-Anh to chelation control in the initial addition of phosphonate anion to the aldehyde.[20] Beside the monoaddition product, large amounts of bisaddition products were isolated which, in turn, could be a measure of relatively poor geometric and/or diastereoselectivity. One possible rationalization of these results could be that once the monoaddition products **24** or **26** are formed, they are relatively unreactive, whereas other possible monoaddition product isomers react faster to form bisaddition products.

(20) For a discussion on HWE reaction mechanism, see: (a) Brandt, P.; Norrby, P.-O.; Martin, I.; Rein, T. *J. Org. Chem.* **1998**, *63*, 1280, and references therein. (b) Ando, K. *J. Org. Chem.* **1999**, *64*, 6815. Similar trend was also observed by Kreuder et al.: (c) Kreuder, R.; Rein, T.; Reiser, O. *Tetrahedron Lett.* **1997**, *38*, 9035.

**Table 2.** Asymmetric HWE reactions with dialdehyde **18**.[a]




R* = (1*R*,2*S*,5*R*)-8-phenylmenthyl

| Entry | Phosphonate | Base | Solvent | Major monoaddition product | Yield[b] (%) | d.r.[c] | Yield of bisadd. (%) |
|---|---|---|---|---|---|---|---|
| 1 | **19c** | KHMDS, 18-crown-6 | THF | **26** | 39 | ≥98:2 | 50 (*E*,*Z*) |
| 2 | **19a**[d] | KHMDS, 18-crown-6 | THF | **24** | 35 | ≥98:2 | 35 (*E*,*E*); 17 (*E*,*Z*) |
| 3 | **19a** | KHMDS | MeCN[e] | **24** | 25 | 89:11 | 23 (*E*,*E*) |
| 4 | **19b** | NaHMDS | THF | **25** | 35 | 41:59 | 62%[f] |
| 5 | **19b** | NaHMDS | $CH_2Cl_2$ | **25** | 24 | 26:74 | 59 (*E*,*E*) |
| 6 | **19d** | KHMDS | EtCN | **24** | 24 | 52:48 | 38 (*E*,*Z*); 37 (*E*,*E*) |
| 7 | **19d** | KHMDS, 18-crown-6 | THF | **24** | 23 | 82:18 | n.d. |

[a] General reaction conditions: 1.2-1.3 equiv of dialdehyde, 1.1-1.3 equiv of phosphonate, 1.0 equiv of base, 5 equiv of 18-crown-6 (if applicable), -78 °C, 16 h, ca. 0.02 M in respective solvent. [b] Yield of isolated monoaddition product. [c] Ratio of major and minor diastereomers, respectively. The ratios of geometric isomers were in both entries: (*Z*):(E) ≥98:2. [d] Reaction time 3 h. [e] Reaction was run at -40 °C. [f] Mixture of bisadition products.

**Pd(0)-Catalyzed Intramolecular Allylic Substitutions.** The reduction of the remaining aldehyde functionalities in HWE products **20a** and **22a**, followed by acyl group migration, afforded intermediates **28a** and **32a**, respectively.[21] Different reagent combinations can be used for the reduction/PG-migration sequence: the use of $NaBH_4$ followed by treatment with imidazole, DMAP or $Et_3N$ all afforded roughly a 2:1 mixture of the desired secondary alcohol **29a** and the corresponding primary alcohol. The use of $LiBH_4$ as reducing agent, however, afforded directly a ca. 2:1 mixture of secondary and primary alcohols as product, implying that $LiBH_4$ acts as an inducer if the pivaloyl group migration as well.

For the Pd(0)-catalyzed allylic substitution, several different ligands for palladium were tested: with dppb, all starting material was recovered, and the use of triphenylphosphine afforded predominantly an undesired diene via a β-hydrogen elimination path. Addition of bases (pyridine, triethylamine, DBU) to increase the nucleophilicity of the hydroxy group gave, at best, only ca. 10% of the desired product. However, somewhat to our surprise,[22] use of phenantroline type ligands afforded the desired ring-closed products in moderate to high yields. Among the tested ligands, 2,9-dimethyl-1,10-phenantroline (neocuproine) turned out to be the best for our system. When the (*E*)-alkene **29a** (Scheme 5) was treated with Pd(0) in the presence of neocuproine, THF derivative **30** formed readily in 76% yield with clean retention of configuration at the allylic stereocenter.

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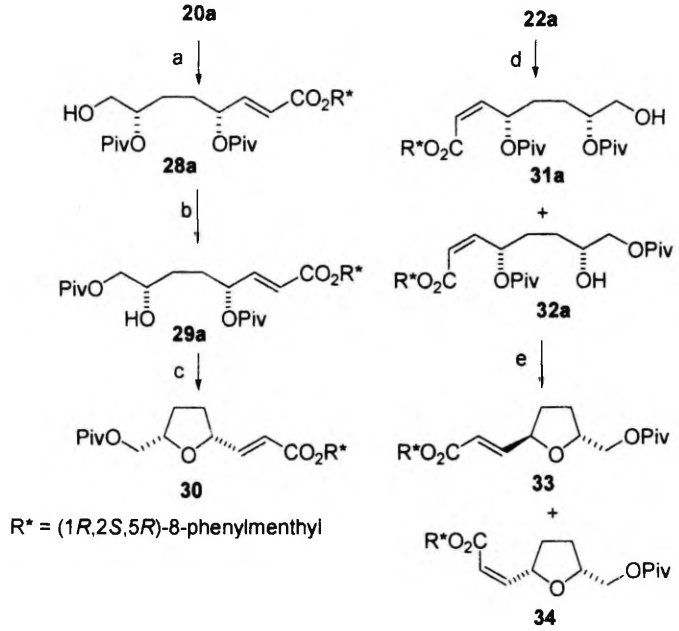
(21) The primary alcohols recovered after the acyl group migration could be separated and converted to mixtures of secondary/primary alcohols again, thereby increasing the overall yield.

(22) Normally, a Pd(0)-catalyzed allylic substitutions are greatly accelerated in the presence of π-accepting ligands such as phosphines or phosphites, and not by ligands which mainly function as σ-donors (like phenantroline based ligands).

**Scheme 5**[a]




[a]Reaction conditions: (a) $NaBH_4$, MeOH/THF, 0 °C, 85%; (b) DMAP, EtOH, 75 °C; 63% **29a**, 27% recovered **28a** (see footnote 21); (c) $Pd_2(dba)_3$•$CHCl_3$ (0.05 equiv), neocuproine (0.2 equiv), THF, 25 °C, 76%; (d) $LiBH_4$, *i*-PrOH/THF, 0 °C; 49% **32a**, 38% **31a** (see footnote 21); (e) $Pd_2(dba)_3$•$CHCl_3$ (0.15 equiv), neocuproine (0.4 equiv), THF, 65 °C; 79% **33**, 10% **34**.

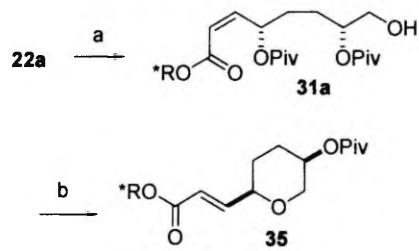
The ring-closure of (*Z*)-alkene **32a** did not proceed at room temperature and heating to 65 °C was needed. The rate determining step in this reaction is presumably the initial formation of the disfavored *syn,anti*-π-allyl palladium-complex, which rearranges to the more stable *syn,syn*-complex via a π–σ–π path.[15] The subsequent nucleophilic attack gives THF derivative **33** as the main product. The product is obtained with overall inversion of configuration at the allylic stereocenter, accompanied by (*Z*)- to (*E*)-isomerization which is consistant with the suggested π–σ–π rearrangement. However, 10% of *cis*-THF derivative **34**,[23] which is formed when the initially formed *syn,anti*-palladium-complex ring-closes directly, was also isolated. It is known that in the case of mono-substituted $\eta^3$-complexes where neocuproine ligand is used for palladium, the *anti*-complex formed from (*Z*)-alkenes undergoes slower rearrangement. The corresponding *syn*-complex is destabilized due to the interference between the methyl substituents on

(23) The (*Z*)-geometry of **34** is proven by NMR, but the 2,5-*cis* configuration is only tentatively assigned.

neocuproine and the *syn*-substituents of $\eta^3$-allyl complex, which favors retation of the (*Z*)-alkene geomentry in the product.[24]

The protective group migration during the reduction of the HWE product **22a** was suppressed by using $NaBH_4$ in MeOH/THF,[27] and the primary alcohol **31a** could be isolated in high yield (Scheme 6). By subjecting alcohol **31a** to the ring-closing conditions (Pd(0)/neocuproine) THP derivative **35** was obtained in good yield. The reaction afforded only the indicated isomer, implying that the allylic substitution proceeded cleanly with inversion of configuration at the allylic stereocenter via a π–σ–π rearrangemant.[25] The preparation of 2,5-*cis*-THP derivative **35** indicates that our methodolgy can be efficiently extended for the synthesis these types of THP's as well.

**Scheme 6**[a]




[a]Reaction conditions: (a) $NaBH_4$, MeOH/THF, 0 °C, 88%; (b) $Pd_2(dba)_3$•$CHCl_3$ (0.05 equiv), neocuproine (0.2 equiv), THF, 65 °C, 82%.

In an analogous manner to the route to THF derivatives **30** and **33** (vide supra), the alkenes **37a** and **40a**, which were obtained from asymmetric HWE reactions with dialdehyde **36a**,[14a] could be converted into THP derivatives **39** and **42** as shown in Scheme 7.[26]

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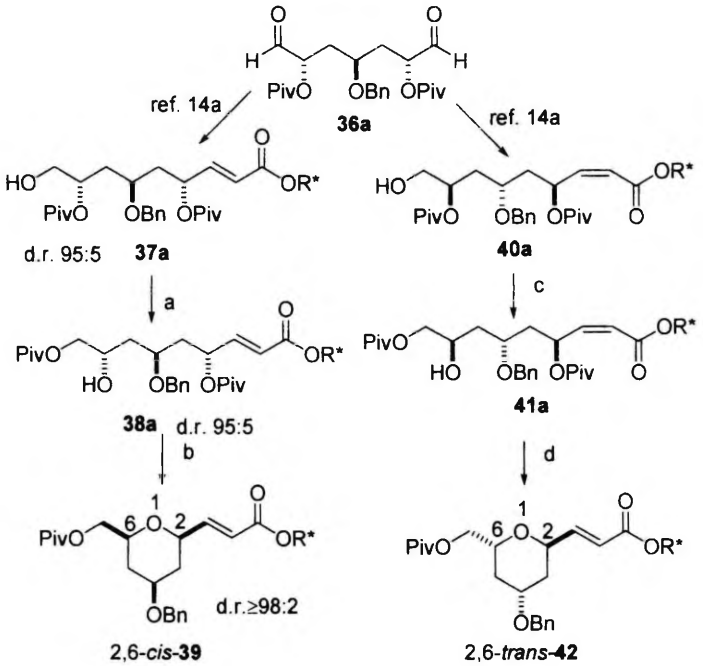
(24) (a) Sjögren, M. P. T.; Hansson, S.; Åkermark, B.; Vitagliano, A. *Organometallics* **1994**, *13*, 1963. (b) Sjögren, M. P. T.; Hansson, S.; Norrby, P.-O.; Åkermark, B.; Cucciolito, M. E.; Vitagliano, A. *Organometallics* **1992**, *11*, 3954.

(25) The (*E*)-geometry of **35** is proven by NMR, but the 2,5-*cis* configuration is only tentatively assigned.

(26) It is noteworthy that the ring-closed product **42** was obtained in diastereomerically pure form, even though the starting material contained 5% of a minor diastereomer.

**Scheme 7**[a]



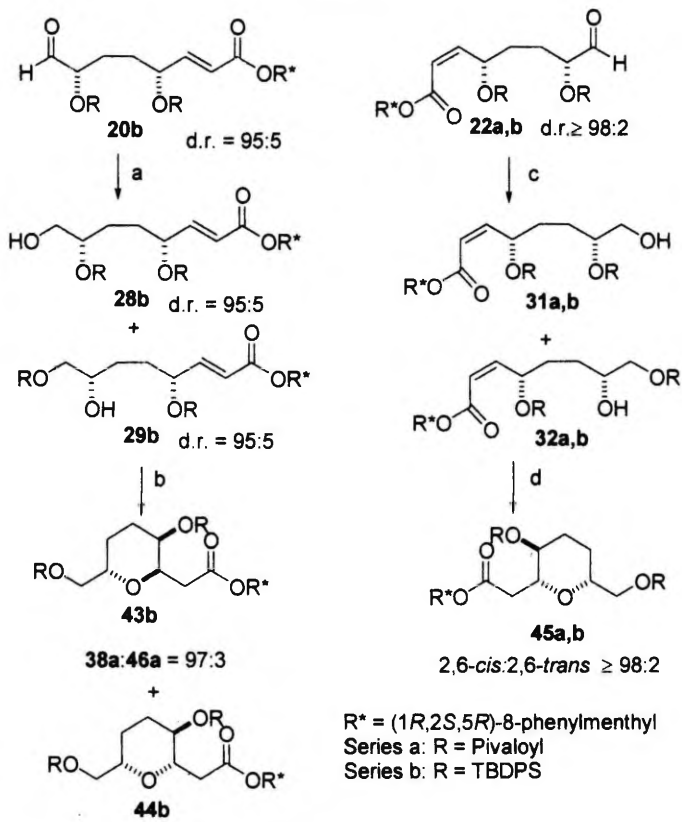

[a]Reaction conditions: (a) imidazole, EtOH, 75 °C; 59% **38a**, 28% recovered **37a** (see footnote 21); (b) $Pd_2(dba)_3$•$CHCl_3$ (0.1 equiv), neocuproine (0.4 equiv), THF, 25 °C, 80%; (c) DMAP, EtOH, 75 °C; 48% **41a**, 42% recovered **37a** (see footnote 21); $Pd_2(dba)_3$•$CHCl_3$ (0.15 equiv), neocuproine (0.4 equiv), THF, 50 °C, 59%.

**Hetero-Michael Additions.** We found that HWE products **20b** and **22a,b** could be readily converted into the trisubstituted THP:s via hetero-Michael addition reaction (Scheme 8). The intermediates **29b** and **32a,b** were obtained from the HWE products by reduction of the remaining formyl group accompanied by migration of one silyl-protective group to the adjacent primary hydroxyl. The bulky silyl protective groups were more prone to migration than pivaloylate esters, and the migration occurred readily even when $NaBH_4$ was used as reducing agent, affording a ca. 5:1 mixture of the corresponding secondary and primary alcohols.[21,21,27] When the (*E*)-alkene **29a** was treated with base (*t*-BuOK), 2,6-*trans*-THP **43b** was predominantly obtained (**43b**:**44b** = 97:3) as product in excellent yield. The (Z)-alkenes **32a,b**, in turn, afforded exclusively 2,6-*cis*-THP:s

(27) It is interesting to note, that the use of either $LiBH_4$ or $NaBH_4$ in combination with *i*-PrOH/THF resulted in much faster protective group migration during the reduction compared to when MeOH/THF was used as solvent mixture. However, this is a very preliminary observation and was not explored further in any detail.

**45a** and **45b** as products under analogous reaction conditions. The difference in stereochemistry could depend on several factors: (i) the difference in alkene geometry; (ii) the difference in relative stereochemistry between the auxiliary and the other stereocenters; (iii) a combination of both of the above. Based on earlier studies by Banwell[16a] and Martín,[16b,c] we believe that the former factor is more important than the latter.

**Scheme 8**[a]

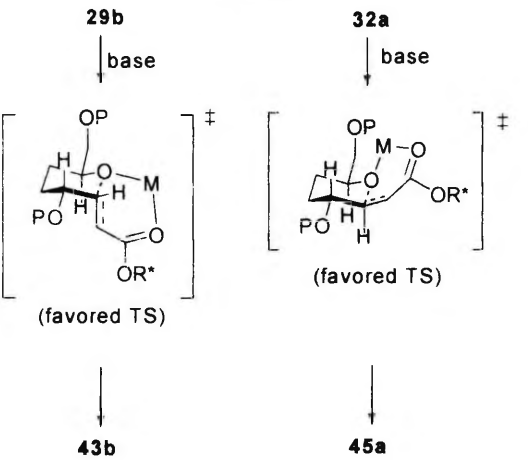



[a]Reaction conditions: (a) $NaBH_4$, *i*-PrOH/THF, 0 °C, overall yield from **13b**: 55% **29b**, 6% **28b** (see footnote 21); (b) *t*-BuOH, THF, 0 °C, 96%; (c) **32a**: $NaBH_4$, *i*-PrOH/THF, 0 °C, 87% (see footnote 21); **32b**: $LiBH_4$, *i*-PrOH/THF, 0 °C, 78% (see footnote 21); (d) *t*-BuOH, THF, 0 °C; 97% (**45a**); 95% (**45b**).

According to the mechanistic model proposed by Martin,[16b] the transition states for the system leading from the (*E*)- and (*Z*)-alkenes to 2,6-*trans*- and 2,6-*cis*-THP derivatives, respectively, are shown in Scheme 9. The 2,6-*cis*-product should be thermodynamically favored in both cases implying that at least the formation of 2,6-*trans* alkene **43b** proceeds via kinetic control. Upon longer reaction time and

higher temperature the *trans/cis* ratio in **43b** dropped significantly due to *trans* to *cis* equilibration, supporting the suggested initial product formation via kinetic control.

**Scheme 9**

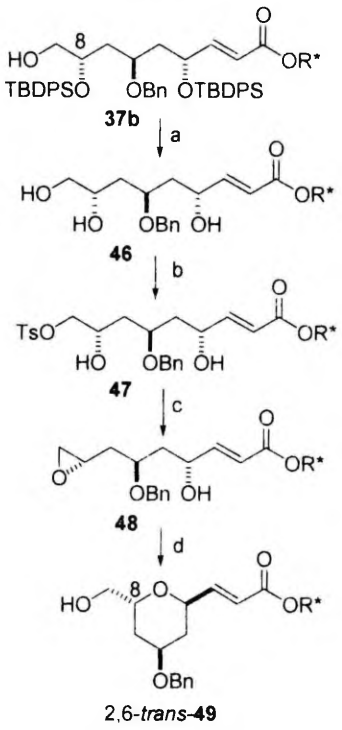



**Epoxide opening.** We also explored the possibilities to convert the reduced HWE product **37b** into a THP derivative via an intramolecular opening of a terminal epoxide by an internal oxygen nucleophile.[28] Normally, the opening of epoxides occurs via a $S_N2$ type mechanism with complete inversion of stereochemistry.[29] While in the case of the Pd(0)-catalyzed allylic substitution one may, by choosing a (*Z*)-alkene substrate, invert the stereochemistry at the allylic stereocenter, the epoxide opening approach instead has the allylic hydroxy group acting as a nucleophile, and the configuration is inverted at the C-8 stereocenter.

(28) Rein, T.; Vares, L.; Kawasaki, I.; Pedersen, T. M.; Norrby, P.-O.; Brandt, P.; Tanner, D. *Phosphorus, Sulfur and Silicon* **1999**, *144-146*, 169.

(29) For a review on epoxide openings, see: Smith, J. K. *Synthesis* **1984**, 629.

**Scheme 10**[a]




R* = (1*R*,2*S*,5*R*)-8-phenylmenthyl

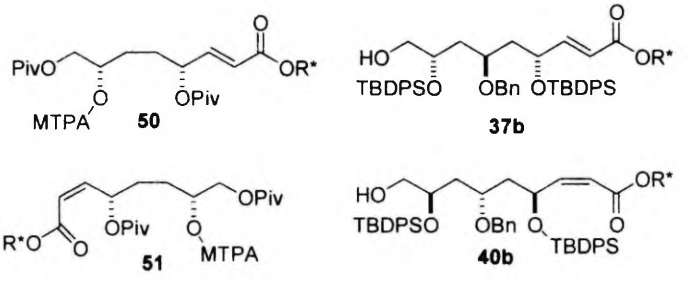
[a]Reaction conditions: (a) *n*-$Bu_4NF$, THF, RT, 80%; (b) TsCl, pyridine, 0 °C, 76%; (c) NaHMDS, THF, 95%; (d) cat. $CF_3SO_3H$, MeCN, 81%.

The primary hydroxy group in triol **46** (Scheme 10), obtained after desilylation of both silyl-protective groups in **37b**,[14a] was regioselectively tosylated in 76% yield by carefully monitoring the reaction by TLC and stopping immediately after disappearance of the starting material. The subsequent treatment with base afforded the terminal epoxide **48** in 95% yield. Our initial attempts to open the epoxide by activating the nucleophile with base failed, but the use of catalytic amount of a triflic acid to activate the epoxide afforded the desired 2,6-*trans*-THP derivative **49** as a single isomer in good yield.[28]

**Determination of Absolute and Relative Configurations.** The absolute configuration assignment for the pivaloyl-protected HWE products **20b** and **22b** are based on $^1$H NMR analyses of both diastereomers of the Mosher ester derivatives **50** and **51** (Chart 3), respectively, according to the method developed

by Mosher and Dale, and extended by Kakisawa et al.[30] The absolute configutations of the silyl-protected HWE products **20b** and **22b** are assigned based on correlation with compounds **20a**/**22a** and **37b**/**40b** (Chart 3).[14a]

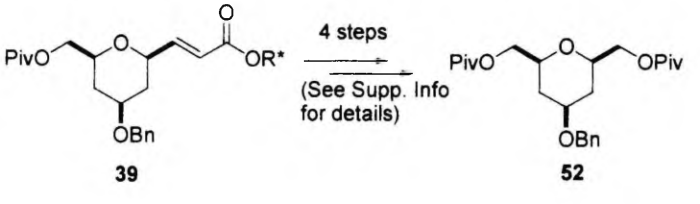
**Chart 3**




The relative configuration assignments of ring-closed products **30**, **33**, **45a**, and **49** are based on NOE experiments. The assignment for compound **39** is based on $^{1}H$ and $^{13}C$ NMR analysis of derivative **52** (Scheme 11), which is *meso* (and not pseudo $C_2$-symmetric) implying that the stereochemistry of **39** is the one shown. The relative configuration assignments of the hetero-Michael products **43b** and **45b** are based on $^{13}C$ NMR analysis.[45]

The absolute configurations of **24** and **26**are tentatively assigned in analogy with the absolute configuration of products obtained from other α-O-dialdehydes.

**Scheme 11**




(30) (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092, and references therein. For experimental details regarding the preparation and NMR analyses of the Mosher esters, see Supporting Information.

## Conclusions

In this paper, we have demonstrated that the sequential use of an asymmetric HWE reaction with a *meso*-dialdehyde and a ring-closure reaction is an efficient and versatile strategy for the synthesis of substituted THF and THP derivatives. In the asymmetric HWE reactions, either (*E*)- or (*Z*)-monoaddition products could be obtained with essentially complete geometric control by slight structural variation in the phosphoryl group of the chiral phosphonate reagent. Both (*E*)- and (*Z*)-products were obtained in good to excellent diastereoselectivities and good yields. When a cyclic THP dialdehyde was used as substrate in asymmetric HWE reactions, the *cis*-THP derivatives could be prepared in a single step, although the yields were only moderate.

Three different methods were employed for converting the products from the asymmetric HWE reactions into THF or THP derivatives: (i) intramolecular Pd(0)-catalyzed allylic substitution, (ii) hetero-Michael addition, or (iii) intramolecular opening of a terminal epoxide. The choice of a particular ring-closure method depends on the structure and configuration of the THF or THP derivative needed. The fact, that different oxacycles can be prepared in few steps makes the overall approach very appealing.

## Experimental Section

**General methods:** All solvents were distilled prior to use. Ether and tetrahydrofuran were destilled from sodium/benzophenone. Dichloromethane and triethylamine were destilled from calcium hydride. All reactions were carried out in oven dried glassware unless water was used as a reaction medium. Commercial reagents were generally used as received. Potassium hexamethyldisilazide (KHMDS) and sodium hexamethyldisilazide (NaHMDS) were purchased as stock solutions (0.5 M or 0.6 M in toluene, respectively), and titrated according to the method of Ireland and Meissner.[31] 18-Crown-6 was recrystallized from anhydrous acetonitrile and dried under vacuum. Cooling below -78 °C was effected by an immersion cooler. TLC analyses were performed on Merck aluminum-backed F254 silica gel plates, using UV light and phosphomolybdic acid for visualization. Drying of organic phases obtained from extractive workup was generally done with $MgSO_4$. Flash chromatography was performed as described by Still and coworkers[32] using either Merck silica gel 60 (230-400 mesh), Amicon Matrex 60Å

(31) Ireland, R. E.; Meissner, R. S. *J. Org. Chem.* **1991**, *56*, 4566.
(32) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

silica gel (35-70 μm), or Chemapol silica gel L 40/100. NMR spectra were recorded in $CDCl_3$ unless otherwise indicated, using $CHCl_3$ (δ 7.26 ppm) and $CDCl_3$ (δ 77.0 ppm) as internal references for $^1H$ and $^{13}C$, respectively. IR spectra were recorded neat as a thin films using AgCl or KBr plates. Microanalyses were perfomed either at the Research Institute for Pharmacy and Biochemistry, Prague, Czech Republic, at the Analytische Laboratorien, Lindlar, Germany, or at the Microanalysis Laboratory, Institute of Physical Chemistry, University of Vienna, Austria. HRMS analyses were perfomed at the Department of Chemistry and Biochemistry, University of Notre Dame, USA.

**Bis-Pivaloyl Ester 11a.** To a solution of diol **10** (1.01 g, 8.85 mmol, 86:14 mixture of *cis*- and *trans*-isomers) and 4-(dimethylamino)pyridine (1.08 g, 8.85 mmol) in 30 mL of dry pyridine, pivaloyl chloride (5.5 mL, 44.25 mmol) was added. The reaction mixture was refluxed for 3 h, diluted with 1 N HCl, and extracted with EtOAc. Drying, concentration, and purification by flash chromatography (2%-6% EtOAc in hexanes) afforded 1.484 g (59%) of *cis*-ester **11a** and 1.01 g (40%) a ca. 1.4:1 mixture of *cis*- and *trans*-isomers. **11a**: ($Rf$ = 0.45 hexanes/EtOAc 9/1,. $^1H$ NMR (250 MHz) δ 5.84 (app d, $J$ = 1.4 Hz, 2H), 5.20-5.13 (m, 2H), 1.94-1.68 (m, 4H), 1.18 (s, 18 H); $^{13}C$ NMR (62.9 MHz) δ 178.0, 130.2, 67.0, 38.6, 27.0, 24.8; IR 2972, 1728, 1480, 1279, 1156, 1035, 1019 $cm^{-1}$.

**Bis-Silyl ether 11b.** To a solution of crude *cis*-2-cyclohexene-1,4-diol[33] **10** (2.2 g, 19.3 mmol, 86:14 mixture of *cis*- and *trans*-isomers) and imidazole (6.56 g, 96.5 mmol) in 190 mL of dry DMF, TBDPSCl (13.3 g, 48.4 mmol) was added. After stirring the reaction mixture for 30 hours at RT, EtOAc was added and the organic layer was washed with water, dried, filtered and concentrated. Purification by flash chromatography (0-10% EtOAc in hexanes) afforded 9.7 g (85%) of bis-silyl ether **11b** as a colorless oil (86:14 mixture of *cis*- and *trans*-isomers).[34] **11b**: ($Rf$ = 0.3 1.6% EtOAc in hexanes); $^1H$ NMR(250 MHz) δ 7.82-7.67 (m, 8H), 7.52-7.31 (m, 12H), 5.65 (br s, 2H), 4.14 (br t, $J$ = 4.8 Hz, 2H), 2.0-1.84 (m, 2H), 1.62-1.45 (m, 2H), 1.15 (s, 18H); $^{13}C$ NMR (62.9 MHz) d 135.7, 134.3, 131.8, 129.4, 127.4, 66.6, 28.2, 26.8, 19.1; IR 2958, 2931, 2857, 1428, 1111, 1082, 701, 506 $cm^{-1}$. Anal. Calcd for $C_{38}H_{46}O_2Si_2$: C, 77.23; H, 7.85. Found: C, 76.98; H, 7.73.

**Diol 12a.** *Method* (a):[35] A solution of alkene **11a** (447 mg, 1.584 mmol) in $CH_3CN$ (26 mL) was cooled to 0 °C. A solution of $RuCl_3$ hydrate (38 mg, ca. 0.17 mmol) and $NaIO_4$ (818 mg, 3.75 mmol) in 5 mL of $H_2O$ was then added to the

(33) Bäckvall, J.-E.; Byström, S. E.; Nordberg, R. E. *J. Org. Chem.* **1984**, *49*, 4619, and references cited therein.

(34) The *cis*- and *trans*-isomrs can be separated by careful flash chromatography (2-8% EtOAc in haxanes).

(35) Shing, T. K. M.; Tam, E. K. W. *Tetrahedron Lett.* **1999**, *40*, 2179.

alkene solution. The reaction mixture was stirred vigorously for 5 min and quenched with 20% aq $Na_2S_2O_3$ (5 mL). The aqueous phase was separated and extracted with EtOAc. Drying, filtration and concentration followed by flash chromatography (25% EtOAc in hexanes) afforded 473 mg (94%) of diol **13a** as a colorless oil which slowly solidified. **12a**: (*Rf* = 0.2 hexanes/EtOAc 3/1). $^1$H NMR (250 MHz) δ 5.00 (br s, 2H), 3.84 (app dd, *J* = 8.2, 2.4 Hz, 2H), 3.20 (br s, 2H), 1.97-1.82 (m, 2H), 1.73-1.56 (m, 2H), 1.20 (s, 18H); $^{13}$C NMR (62.9 MHz) δ 178.5, 72.0, 71.5, 38.8, 27.1, 23.7; IR 3481, 2974, 1732, 1481, 1283, 1156, 734 cm$^{-1}$. Anal. Calcd for $C_{16}H_{28}O_6$: C, 60.74; H, 8.85. Found: C, 61.07; H, 8.87.
*Method* (b): To a solution of pivaloyl ester **11a** (397 mg, 1.407 mmol) and *N*-methyl morpholine *N*-oxide (165 mg, 1.407 mmol) in a mixture of THF, *t*-butanol and $H_2O$ (16 mL, 8 mL and 4 mL respectively), 540 μL of a 2.5 wt.-% solution of $OsO_4$ in *t*- butanol (0.042 mmol) was added. The reaction mixture was stirred for 60 h at 55 °C and then quenched by the addition of $NaS_2O_3$ (5 mL, 20% aq solution). Dilution with brine followed by extraction (EtOAc), drying and concentration afforded 425 mg of a colorless oil. Purification by flash chromatography (4%-40% EtOAc in hexanes) afforded 65 mg (16%) of unreacted alkene **11a** and 340 mg (76%) of diol **12a** as a colorless oil which slowly solidified.

**Diol 12b.** *Method* (a):[36] A solution of alkene **11b** (242 mg, 0.41 mmol) in the mixture of EtOAc (9 mL), $CH_3CN$ (9 mL) and $H_2O$ (2.5 mL) was cooled down to 0 °C. $RuCl_3$ hydrate (6.3 mg, 0.029 mmol) and $NaIO_4$ (131 mg, 0.614 mmol) was then added to the alkene solution. The two phase mixture was vigorously stirred for 80 seconds, and then quenced with 20% aq solution of $Na_2S_2O_3$ (ca. 5 mL). The aqueous phase was separated and extracted with diethyl ether. The combined organic extracts were dried over and concentrated. Flash chromatography (10% EtOAc in hexanes) afforded 215 mg (89%) of diol **12b** as a colorless oil. Only one stereoisomer was detected by $^1$H NMR spectroscopy. **12b**: (R*f* = 0.15 hexanes/EtOAc 9/1); $^1$H NMR(250 MHz) δ 7.73-7.61 (m, 8H), 7.47-7.32 (m, 12H), 4.00-3.85 (m, 4H), 2.29 (br s, 2H), 1.66-1.32 (m, 4H), 1.09 (s, 18H); $^{13}$C NMR (62.9 MHz) δ 135.74, 135.65, 134.0, 133.8, 129.8, 129.7, 127.7, 127.6, 73.7, 71.9, 27.0, 26.7, 19.3; IR 3579, 2931, 2857, 1428, 1105, 701, 501 cm$^{-1}$.
*Method* (b): To a solution of alkene **11b**[37] (2.32 g, 3.92 mmol) and *N*-methyl morpholine *N*-oxide (508 mg, 4.34 mmol) in 14 mL of THF was added *t*-butyl alcohol (7 mL) and $H_2O$ (3.5 mL), followed by solution of $OsO_4$ in *tert*-butyl

(36) Shing, T. K. M.; Tam, E. K. W.; Tai, W.-F.; Chung, I. H. F.; Jiang, Q. *Chem. Eur. J.* **1996**, *2*, 50.

(37) Mixture of *cis*- and *trans*-isomers, 86:14 respectively.

alcohol (2.5 wt.-%, 1.52 mL, 0.118 mmol). The reaction mixture was stirred for 60 h at ca. 45 °C and then quenched with 5 mL 20% $Na_2S_2O_3$. Dilution with brine followed by extraction (EtOAc), drying and concentration, followed by flash chromatography (10% EtOAc in hexanes) afforded 1.12 g (46%) of diol **12b** as a colorless oil. Diol **12b** was obtained as a single steroisomer.

**Dialdehyde 13a.** To a solution of diol **12a** (127 mg, 0.402 mmol) in THF (8 mL) a solution of $H_5IO_6$ (91.6 mg, 0.402 mmol) in THF (8 mL) was added at 0 °C. After 80 min at RT, 5 mL phosphate buffer (pH 7) and 10 mL of brine was added. The solution was extracted with EtOAc, dried and concentrated. The residue was dissolved in $CHCl_3$ (2 mL) and filtered through a plug of cotton, giving 126 mg (99%) of **13a** as a white crystalline compound. Due to its limited stability, the dialdehyde was generally used in HWE reactions without further purification. **13a**: $^1$H NMR (200 MHz) δ 9.47 (d, $J$ = 0.7 Hz, 2H), 5.03-4.87 (m, 2H), 2.04-1.74 (m, 4H), 1.26 (s, 18H); 13C NMR (50.3 MHz) δ 197.8, 177.9, 77.1, 38.8, 27.0, 24.2; IR 3466, 2974, 1732, 1481, 1282, 1151 cm$^{-1}$.

**Dialdehyde 13b.** To a solution of diol **12b** (210 mg, 0.3349 mmol) in THF (7 mL) was added a solution of $H_5IO_6$ (84 mg, 0.368 mmol) in THF (4 mL) at 0 °C. After 70 min at RT 10 mL of brine was added. The solution was extracted with EtOAc, dried and concentrated to give 201 mg (96%) of **13b** as a white crystalline compound. The dialdehyde was used in HWE reactions without further purification. **13b**: $^1$H NMR (200 MHz) δ 9.49 (br d, $J$ = 1.2 Hz, 2H), 7.25-7.68 (m, 20H), 4.04-3.94 (m, 2H), 1.82-1.69 (m, 2H) 1.64-1.52 (m, 2H), 1.09 (s, 18H); $^{13}$C NMR (50.3 MHz) δ 203.2, 135.7, 132.8, 130.0, 127.8, 77.5, 27.4, 26.9, 19.3; IR 2931, 2859, 1737, 1428, 1112, 702, 505 cm$^{-1}$. Anal. Calcd for $C_{38}H_{46}O_4Si_2$: C, 73.27; H, 7.44. Found: C, 73.00; H, 7.43.

**Alcohol 15.** A solution of ketone **14** (10.76 g, 86.7 mmol) in MeOH (150 mL) was cooled to 0 °C. Sodium borohydride was added in portions during 1 h. The reaction mixture was slowly warmed up to RT during 3 h and then quenched with acetic acid (15 mL). Neutralization with 10% $NaHCO_3$, followed by addition of water, extraction ($CH_2Cl_2$) and drying gave 12.8 g of crude **15** as a pale yellow oil. Purification by MPLC[38] (0-8% MeOH in $CH_2Cl_2$) afforded 9.90 g (90%) of **15** as a separable mixture of *endo* and *exo* isomers[39] (*endo*:*exo* ca. 7:3). *Endo* (white solid): $^1$H (400 MHz) δ 6.10-6.08 (m, 2H), 4.80-4.75 (m, 2H), 3.93-3.77 (m, 1H), 2.15-1.95 (br s, 1H), 1.96-1.86 (m, 2H), 1.65-1.53 (m, 2H); $^{13}$C (100 MHz) δ

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(38) Baeckström, P.; Stridh, K.; Li, L.; Norin, T. *Acta Chem. Scand., Ser. B* **1987**, *41*, 442.

(39) Relative configuration is assigned according to analogy with a simial compound: LaBel, N. A.; Maxwell, R. J. *J. Am. Chem. Soc.* **1969**, *91*, 2307.

130.9, 78.0, 64.0, 35.5; IR 3392, 2948, 1257, 1110, 1044, 957, 842, 769, 707 $cm^{-1}$.

**Silyl ether 16.** To a solution of *endo* alcohol **15** (361 mg, 2.86 mmol) and imidazole (974 mg, 14.3 mmol) in DMF (15 mL), was added TBDPSCl (1.79 mL, 6.87 mmol). The reaction mixture was stirred for 36 h. Addition of water, extraction with hexanes, drying and concentration gave 2.2 g of crude **16** as a pale yellow oil. Purification by flash chromatography yielded 485 mg (46%) of **16** in the form of white crystals. **16**: $^1H$ (400 MHz) δ 7.61-7.57 (m, 4H), 7.44-7.32 (m, 6H), 6.35 (d, $J$ = 0.4 Hz, 2H), 4.66 (d, $J$ = 4.0 Hz, 2H), 4.13 (app br t, $J$ = 5 Hz, 1H), 2.01 (ddd, $J$ = 14.8, 5.3, 4.2 Hz, 2H), 1.57 (dd, $J$ = 14.6, 0.8 Hz, 2H), 1.05 (s, 9H); $^{13}C$ NMR (100 MHz) δ 130.5, 129.1, 128.6, 124.3, 122.3, 72.5, 60.4, 30.5, 21.7, 13.8; IR 3436, 2966, 2939, 2853, 1428, 1375, 1107, 1071, 1032, 872, 703 $cm^{-1}$. Anal. Calcd. for $C_{23}H_{28}O_2Si$: C, 75.78; H, 7.74. Found: C, 75.72; H, 7.79.

**Diol 17**:[40] A solution of silyl ether **16** (100 mg, 0.274 mmol) and $Et_4NOH$ (20 μL, 0.0274 mmol; 20% aqueous solution) in *t*-BuOH/diethyl ether (2:1, 900 μL) was coolded to 0 °C before *t*-BuOOH (55 μL, 0.411 mmol) was added dropwise. After 5 min, a 2.5wt.-% solution of $OsO_4$ in *t*-BuOH (56 μL, 0.0055 mmol) was added, and the resulting solution was stirred for 30 min 0 °C, then 5 h at RT. *t*-BuOOH (18 μL), $OsO_4$ (19 μL) and $Et_4NOH$ (10 μL) were added anew, and the mixture was stirred for 24 h at RT. The reaction was cooled to 0 °C, a 20% aqueous solution of $Na_2S_2O_3$ (0.5 mL) was added, and the mixture was stirred for 0.5 h at 0 °C. The solvent was evaporated, 2 mL of acetone was added and the solution was filtered through the celite and evaporated again. Addition of ethanol (3x1 mL), followed by evaporation after each addition, gave 112 mg of crude **17**. Purification by flash chromatography (40% EtOAc in hexanes) yielded 80 mg of **17** (73%) as a colorless oil which solidified upon standing. **17**: $^1H$ NMR (400 MHz) δ 7.61-7.56 (m, 4H), 7.45-7.33 (m, 6H), 4.90-4.85 (m, 2H), 4.15-4.12 (m, 2H), 3.19-3.14 (m, 2H), 4.04-4.00 (m, 1H), 1.84 (dt, $J$ = 14.8, 4.4 Hz, 2H), 1.67 (br dd, $J$ = 14.7, 1.0 Hz, 2H), 1.06 (s, 9H); $^{13}C$ NMR (100 MHz) δ 135.8, 133.4, 129.9, 127.8, 82.5, 74.7, 65.1, 36.4, 27.1, 19.0; IR 3308, 2960, 2928, 2856, 1427, 1106, 1065, 1031, 996, 872, 701 $cm^{-1}$. Anal. Calcd. for $C_{23}H_{30}O_4Si$: C, 69.31; H, 7.59. Found: C, 69.05; H, 7.59.

**Dialdehyde 18**: A solution of periodic acid (87 mg, 0.3813 mmol) in 6 mL of THF was added to a solution of diol **17** (152 mg, 0.3813 mmol) in 6 mL of THF at RT. The reaction mixture was stirred for 1.5 h at RT, then diluted with brine.

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(40) A modification of Noyori's procedure for the dihydroxylation of the corresponding ketone was used. See: Sato, T.; Hayakawa, Y.; Noyori, R. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2515. See also: Wierenga, W.; Evans, B. R.; Woltersom, J. A. *J. Am. Chem. Soc.* **1979**, *101*, 1334, for the dihydroxylation of a similar compound.

Extraction (EtOAc), drying, and concentrating afforded 150 mg (99%) of crude **18** as a pale yellow oil. Dialdehyde was used in HWE reactions without further purification.[41] **18**: $^1$H NMR (400 MHz) δ 9.61 (s, 2H), 7.68-7.59 (m, 4H), 7.48-7.31 (m, 6H), 3.91-3.74 (m, 1H), 3.70 (dd, $J$ = 12.4, 2.5 Hz, 2H), 2.08-1.97 (m, 2H), 1.55-1.39 (m, 2H), 1.08 (s, 9H).

**General procedure for HWE reactions.** To a solution of chiral phosphonate (**19a-d**; 1.1 equiv) and 18-crown-6 (if applicable; 5 equiv) in respective solvent (ca. 0.02 M with respect to the phosphonate) at -78 °C under argon was added 1.0 equiv of KHMDS (0.5 M in tolune) or NaHMDS (0.6 M in toluene). After 30 min the resulting slurry was transferred via cannula to a precooled solution of the dialdehyde (**13a,b**, or **18**). The reaction mixture was stirred for the indicated reaction time at the indicated temperature and quenched with phosphate buffer (pH 7). After dilution with brine, extractive workup (EtOAc), drying and concentration gave the crude reaction products. Purification by flash chromatography (EtOAc in hexanes as an eluent) afforded the products as colorless oils.

**(*E*)-Alkene 20a.** Prepared from **13a** and **19a** in 55% yield. (*E*):(*Z*) ≥ 98:2, diastereomeric ratio = 98:2. **20a**: ($R_f$ = 0.56 hexanes/EtOAc 3/1); $^1$H NMR (250 MHz, selected data) δ 9.47 (d, $J$ = 0.6 Hz, 1H), 7.28-7.16 (m, 4H), 7.13-7.03 (m, 1H), 6.45 (dd, $J$ = 15.7, 5.1 Hz, 1H, C*H*=CHC(O) in major diastereomer), 6.16 (dd, $J$ = 16.0, 4.3 Hz, 1H, C*H*=CHC(O) in minor diastereomer), 5.38 (dd, $J$ = 15.7, 1.6 Hz, 1H), 5.34-5.26 (m, 1H), 4.98-4.90 (m, 1H), 4.85 (ddd [app td], $J$ = 10.7, 4.3 Hz, 1H), 1.27 (s, 9H), 1.21 (s, 9H), 0.86 (d, $J$ = 6.5, 3H); $^{13}$C NMR (62.9 MHz, some signals in the aliphatic region overlap) δ 97.8, 177.9, 177.1, 164.9, 151.4, 143.6, 127.8, 125.3, 124.9, 122.4, 77.2, 74.6, 70.9, 50.3, 41.6, 39.6, 38.9, 38.8, 34.5, 31.2, 29.0, 27.7, 27.1, 26.5, 25.1, 24.1, 21.7; IR 2960, 2928, 1732, 1480, 1280, 1152, 733 cm$^{-1}$. Anal. Calcd for $C_{34}H_{50}O_7$: C, 71.55; H, 8.83. Found: C, 71.50; H, 8.89.

**(*E*)-Alkene 20b.** Prepared from **13b** and **19a**. An approximately 2:1 mixture of mono- and bisaddition products was obtained.[42] **20b**: $^1$NMR (250 MHz, assigned from a 95:5 mixture of diastereomers **20b**:**21b** and bisaddition product) δ 9.44 (d, $J$ = 1.5 Hz, 1H), 7.65-6.98 (m, 25 H), 6.63 (dd, $J$ = 15.6, 5.3 Hz, 1H), 5.56 (dd, $J$ = 15.6, 1.5 Hz, 1H), 4.85 (ddd [app td], $J$ = 10.7, 4.4, 1H), 4.33-4.24 (m, 1H), 4.24-4.12 (m, 1H), 3.98-3.91 (m, 1H), 1.29 (s, 3H), 1.25 (s, 3H), 1.09 (s, 9 H), 1.06 (s, 9H), 0.89 (d, $J$ = 6.4 Hz, 3H). **21b:** $^1$NMR (250 MHz, selected data assingned from a mixture of diastereomers **20b**:**21b** (95:5) and bisaddition

(41) If purification is needed, the dialdehyde is stable during the flash chromatography.

(42) The bisaddition byproduct was readily separated after reduction of the aldehyde moiety in **20b** to the corresponding alcohol..

product) δ 9.43 (d, $J$ = 1.5 Hz, 1H).

**(*Z*)-Alkene 22a.** Prepared from **13a** and **19b** in 71% yield. (*Z*):(*E*) ≥ 98:2, d.r. ≥ 98:2. **22a**: (*Rf* = 0.56 hexanes/EtOAc 3/1; $^1$H NMR (250 MHz, selected data) δ 9.50 (d, $J$ = 0.6 Hz, 1H), 7.27-7.17 (m, 4H), 7.14-7.04 (m, 1H), 6.07 (br q, $J$ = 6 Hz, 1H), 5.81 (dd, $J$ = 11.5, 7.6 Hz, 1H), 5.02 (dd, $J$ = 11.5, 1.4 Hz, 1H), 5.03-4.95 (m, 1H), 4.79 (ddd [app td], $J$ = 10.7, 4.4 Hz, 1H), 1.28 (s, 9H), 1.17 (s, 9H), 0.86 (d, $J$ = 6.5, 3H); $^{13}$C NMR (62.9 MHz) δ 197.9, 178.0, 177.5, 164.4, 151.6, 146.4, 127.8, 125.2, 124.9, 121.2, 77.5, 74.2, 70.9, 50.3, 41.6, 39.5, 38.7, 38.6, 34.4, 31.2, 29.4, 27.9, 27.1, 27.0, 26.4, 24.6, 24.5, 21.7; IR 2962, 2928, 1714, 1480, 1202, 1152 cm$^{-1}$. $[\alpha]_{546}$ +4.0 (c = 8.3, $CHCl_3$). Anal. Calcd for $C_{34}H_{50}O_7$: C, 71.55; H, 8.83. Found: C, 71.55; H, 8.79.

**(*Z*)-alken-22b:** Prepared from **13b** and **19b** in 88% yield. (Z):(E) ≥ 98:2; diastereomeric ratio ≥ 98:2. **22b**: (*Rf* = 0.55 hexanes/EtOAc 8.5/1.5); $^1$H NMR (250 MHz, selected data) δ 9.50 (d, $J$ = 1.54 Hz, 1H), 7.68-7.04 (m, 25H), 5.94 (dd, $J$ = 11.6, 8.0 Hz, 1H), 5.39-5.28 (m, 1H), 4.81 (dd, $J$ = 11.6, 1.3 Hz, 1H), 4.63 (ddd [app td], $J$ = 10.7, 4.3 Hz, 1H), 4.09-4.0 (m, 1H), 1.21 (s, 3H), 1.16 (s, 3H), 1.13 (s, 9H), 1.03 (s, 9H), 0.89 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (125 MHz, some singals overlap) δ 203.3, 164.4, 151.5, 151.4, 135.8, 135.7, 134.0, 133.8, 133.1, 133.0, 129.9, 129.6, 129.5, 127.9, 127.8, 127.7, 127.5, 127.4, 125.3, 125.0, 118.5, 78.0, 73.8, 69.4, 50.4, 41.6, 39.6, 34.5, 32.1, 31.2, 28.0, 27.2, 27.0, 26.6, 25.5, 21.8, 19.4, 19.2; IR 2958, 2858, 1713, 1428, 1198, 1112, 700 cm$^{-1}$. $[\alpha]_{546}$ +14.8 (c = 2.83, $CHCl_3$).

**(*E*)-THP 24.** Prepared from **18** and **19a** in 35% yield. (*E*):(*Z*) ≥ 98:2, d.r. ≥ 98:2. In addition, 18% of (*E*,*Z*)-bisaddition product (R*f* = 0.49 hexanes/EtOAc 9/0.5), and 35% of (*E*,*E*)-bisaddition product (*Rf* = 0.22 hexanes/EtOAc 9/0.5) were also isolated. **23**: (R*f* = 0.08 hexanes/EtOAc 9/0.5); $^1$H NMR (400 MHz, selected data) δ 9.62 (d, $J$ = 0.9 Hz, 1H), 7.70-7.62 (m, 4H), 7.48-7.36 (m, 6H), 7.28-7.15 (m, 4H), 7.04-6.95 (m, 1H), 6.40 (dd, $J$ = 15.9, 4.3 Hz, 1H), 5.44 (dd, $J$ = 15.6, 1.8 Hz, 1H), 4.85 (ddd [app td], $J$ = 10.7, 4.3 Hz, 1H), 3.88-3.79 (m, 1H), 3.74 (dddd, $J$ = 11.9, 4.3, 1.9, 1.9 Hz, 1H), 3.65 (br dd, $J$ = 12.4, 2 Hz, 1H).

**(*Z*)-THP 26.** Prepared from **18** and **19c** in 39% yield. (Z):(E) ≥ 98:2, d.r. ≥ 98:2. In addition, 50% of (*E*,*Z*)-bisaddition product (R*f* = 0.63 hexanes/EtOAc 9/1) was also isolated. **24**: (R*f* = 0.27 hexanes/EtOAc 9/1); $^1$H NMR (250 MHz, selected data) δ 9.53 (d, $J$ = 0.4 Hz, 1H), 7.73-7.62 (m, 4H), 7.49-7.36 (m, 6H), 7.23-7.17 (m, 4H), 7.15-7.04 (m, 1H), 6.02 (dd, $J$ = 11.7, 7.2 Hz, 1H), 5.00 (dd, $J$ = 11.7, 1.4 Hz, 1H), 4.88-4.68 (m, 2H), 4.08-3.91 (m, 1H), 3.67 (dd, $J$ = 12.3, 2.3 Hz, 1H), 1.08 (s, 9H), 0.85 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (62.9 MHz, some signals overlap) δ 200.4, 164.5, 151.4, 147.3, 135.7, 129.8, 128.0, 127.7, 125.3, 125.1,

119.8, 79.4, 74.1, 73.1, 68.6, 50.5, 41.8, 39.5, 35.3, 34.5, 31.4, 29.7, 28.2, 26.9, 26.5, 24.6, 21.7, 19.1.

**General Procedure for Reductions of the HWE Products.** To a solution of aldehyde in 1:1 mixture of MeOH or *i*-PrOH and THF (0.015 M with respect to the aldehyde) $NaBH_4$ or $LiBH_4$ (3-5 equiv) was added at 0 °C. After stirring at 0 °C until the reaction was finished (monitoring by TLC), the reaction mixture was diluted with brine, extracted with EtOAc, dried, filtered, concentrated, and purified by flash chromatography (EtOAc in hexanes) to afford alcohols as colorless oils.

**General Procedure for Protective Group Migration.** To a solution of primary alcohol in EtOH (ca. 0.03 M with respect to alcohol) 4-DMAP or imidazole was added. After refluxing for ca. 15 h, ethanol was evaporated and the mixture of secondary and primary alcohols were separated by flash chromatography.

**Primary Alcohol 28a.** Prepared from **20a** in 85% yield. **28a**: (R*f* = 0.28 hexanes/EtOAc 3/1); $^1$H NMR (250 MHz, selected data) δ 7.27-7.17 (m, 4H), 7.14-7.04 (m, 1H), 6.49 (dd, *J* = 15.7, 5.1 Hz, 1H), 5.39 (dd, *J* = 15.7, 1.6 Hz, 1H), 5.34-5.25 (m, 1H), 4.91-4.80 (m, 1H), 4.85 (ddd [app td], *J* = 10.6, 4.3 Hz, 1H), 3.69 (dd, *J* = 11.9, 4.0 Hz, 1H), 3.61 (dd, *J* = 11.9, 5.8 Hz, 1H), 1.21 (s, 18H), 0.86 (d, *J* = 6.5, 3H); $^{13}$C NMR (62.9 MHz, some signals in the aliphatic region overlap) δ 178.6, 177.2, 165.1, 151.3, 144.1, 127.9, 125.4, 125.0, 122.1, 74.65, 74.56, 71.3, 64.7, 50.4, 41.6, 39.7, 38.9, 34.5, 31.2, 29.5, 27.4, 27.1, 26.6, 25.9, 25.5, 21.7; IR 3504, 2958, 2928, 1731, 1480, 1281, 1157, 1032 cm$^{-1}$.

**Secondary Alcohol 29a.** Prepared from **28a**; 52% of secondary alcohol **29a** and 38% of a 1:2.5 mixture of secondary and primary alcohols (**29a** and **28a**, respectively) was obtained. **29a**: (*Rf* = 0.33 hexanes/EtOAc 3/1). $^1$H NMR (250 MHz, selected data) δ 7.28-7.18 (m, 4H), 7.15-7.06 (m, 1H), 6.52 (dd, *J* = 15.7, 5.1 Hz, 1H), 5.41 (dd, *J* = 15.7, 1.6 Hz, 1H), 5.37-5.28 (m, 1H), 4.86 (ddd [app td], *J* = 10.7, 4.4 Hz, 1H), 4.12 (dd, *J* = 11.3, 3.4 Hz, 1H), 3.97 (dd, *J* = 11.3, 6.8 Hz, 1H), 3.90-3.78 (m, 1H), 1.22 (s, 9H), 1.21 (s, 9H), 0.86 (d, *J* = 6.5 Hz, 3H); $^{13}$C NMR (62.9 MHz) δ 178.7, 177.4, 165.1, 151.4, 144.4, 127.9, 125.4, 125.4, 122.1, 74.7, 71.7, 69.8, 68.4, 50.4, 41.7, 39.7, 38.9, 34.5, 31.3, 29.9, 29.7, 28.6, 27.4, 27.19, 27.15, 26.6, 25.5, 21.8; IR 3522, 2958, 2926, 1732, 1282, 1155 cm$^{-1}$; $[\alpha]_{546}$ +9.8 (c = 1.5, $CHCl_3$).

**Alcohols 29b and 28b.** To a solution of aldehyde **20b** (contains ca 33% E,E-bisaddition product, inseparable by TLC, ratio measured by NMR, total weight 302 mg) in 20 mL of THF/MeOH (1:1), 76 mg (2 mmol) of $NaBH_4$ was added at 0 °C. After stirring at 0 °C for 3 h, the reaction mixture slowly warmed up to RT during an additional 2 h. Dilution with brine, extraction with EtOAc (3x15 mL),

drying and concentration afforded the crude reduction product. The purification by flash cromatography (gradual elution 3% up to 10% EtOAc in hexanes) yielded three fractions: (a) (*E,E*)-bisaddition product (79 mg, 40%); (b) **29b** (d.r. 95:5, 154 mg, 53%) ; and (c) 78:22 mixture of **28b** and **29b** (d.r. 95:5) (22 mg, 8%). **29b:** $^1$H NMR (250 MHz, selected data) δ 7.70-7.57 (m, 8H) and 7.50-7.05 (m, 17H, aromatic), 6.68 (dd, *J* = 15.6, 5.2 Hz, 1H, C*H*=CHC(O)), 5.62 (dd, *J* = 15.6, 1.5 Hz, 1H, CH=C*H*C(O)), 4.86 (ddd [app td], *J* = 10.6, 4.3 Hz, 1H, C*H*OC(O)), 4.35-4.25 (m, 1H), 3.53 (dd, *J* = 10.7, 3.2 Hz, 1H) and 3.38 (dd, *J* = 9.8, 8.0 Hz, 1H, C$H_2$OSi), 1.31 (s, 3H), 1.26 (s, 3H), 1.08 (s, 18H), 0.89 (d, *J* = 6.4 Hz, 3H); $^{13}$C NMR (62.9 MHz) δ 165.6, 150.9, 149.3, 135.8, 135.5, 129.8, 129.7, 127.9, 127.8, 127.6, 127.5, 125.5, 125.2, 121.1, 74.6, 72.1, 71.8, 67.9, 50.6, 41.8, 40.1, 34.5, 32.5, 31.3, 28.1, 27.3, 27.0, 26.8, 25.3, 21.8, 19.3, 19.1; IR 2957, 2930, 2858, 1712, 1428 ,1112, 735, 701, 505 cm$^{-1}$. $[\alpha]_{546}$ +18.53 (c = 1.24, $CHCl_3$); Anal. Calcd for $C_{56}H_{72}O_5Si_2$: C, 76.32; H, 8.23. Found: C, 76.32; H, 8.45. **53**:[43] $^1$NMR (250 MHz, selected data assingned from a mixture (95:5) of diastereomers **29b** and **53**) δ 6.32 (dd, *J* = 15.6, 5.2 Hz, 1H, C*H*=CHC(O)), 5.46 (dd, *J* = 15.6, 1.5 Hz, 1H, CH=C*H*C(O)). **28b:** $^1$NMR (250 MHz, selected data) 6.61 (dd, *J* = 15.6, 5.3 Hz, 1H, C*H*=CHC(O)), 5.53 (dd, *J* = 15.6, 1.4 Hz, 1H, CH=C*H*C(O)).

***cis*-Tetrahydrofuran derivative 30.** Neocuproine hemihydrate (1.3 mg, 0.006 mmol) and $Pd_2(dba)_3$•$CHCl_3$ (1.5 mg, 0.0015 mmol) were dissolved in 1 mL THF and the solution was added via syringe to a solution of alkene **29a** (8.5 mg, 0.015 mmol) in 2 mL of THF. After stirring 45 min at RT, 1 mL 2% aq HCl was added. Filtration through a plug of $MgSO_4$, concentration, and flash chromatograpy of the residue (7.5% EtOAc in hexanes) afforded 5.3 mg (76%) of **30** as a colorless oil. **30**: (*Rf* = 0.48 hexanes/EtOAc 3/1); $^1$H NMR (250 MHz, selected data) δ 7.29-7.20 (m, 4H), 7.17-7.07 (m, 1H), 6.59 (dd, *J* = 15.6, 4.8 Hz, 1H), 5.52 (dd, *J* = 15.6, 1.6 Hz, 1H), 4.84 (ddd [app td], *J* = 10.7, 4.3 Hz, 1H), 4.44 (app br qd, *J* = 4.9, 1.6 Hz, 1H), 4.26-4.16 (m, 1H), 4.14 (dd, *J* = 11.5, 4.0 Hz, 1H), 4.06 (dd, *J* = 11.4, 5.2 Hz, 1H), 1.30 (s, 9H), 0.86 (d, *J* = 6.5 Hz, 3H); $^{13}$C NMR (62.9 MHz, some signals in the aliphatic region overlap) δ 178.5, 165.7, 151.5, 147.3, 127.9, 125.4, 125.0, 120.9, 78.2, 77.2, 74.4, 66.0, 50.5, 41.7, 39.7, 38.8, 34.6, 31.3, 27.6, 27.2, 26.6, 25.7, 21.8; IR 2955, 1714, 1278, 1162 cm$^{-1}$;$[\alpha]_{546}$ -8.4 (c = 0.5, $CHCl_3$). HRMS (EI): calcd for $C_{29}H_{42}O_5$, 470.3032; found, 470.3050.

**Alcohols 31a and 32a.** The reduction of **22a** with $LiBH_4$, according to the general procedure, afforded 49% of secondary alcohol **32a**, and 38% of primary alcohol **31a**, which were readily separated by flash chromatography (12% EtOAc

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(43) Compound **53** is the minor diastereomer which originates from the reaction between **13b** and **19a**.

in hexanes). **32a**: ($R_f$ = 0.4 hexanes/EtOAc 3/1); $^1$H NMR (250 MHz, selected data) δ 7.28-7.18 (m, 4H), 7.16-7.06 (m, 1H), 6.15-6.03 (m, 1H), 5.83 (dd, *J* = 11.5, 7.7 Hz, 1H), 5.05 (dd, *J* = 11.5, 1.3 Hz, 1H), 4.79 (ddd [app td], *J* = 10.7, 4.3 Hz, 1H), 4.15 (dd, *J* = 11.2, 3.3 Hz, 1H), 4.01 (dd, *J* = 11.2, 6.6 Hz, 1H), 3.97-3.86 (m, 1H), 1.23 (s, 9H), 1.17 (s, 9H), 0.86 (d, *J* = 6.5 Hz, 3H); $^{13}$C NMR (62.9 MHz) δ 178.7, 177.7, 164.5, 151.6, 146.9, 127.9, 125.4, 124.9, 121.0, 74.4, 71.4, 70.0, 68.4, 50.4, 47.9, 41.6, 39.6, 38.9, 34.5, 31.3, 30.0, 29.0, 27.8, 27.2, 27.1, 26.5, 25.0, 21.1; IR 3528, 2960, 1732, 1715, 1283, 1202, 1155, 702 cm$^{-1}$; $[\alpha]_{546}$ -1.9 (c = 1.6, $CHCl_3$). **31a**: ($R_f$ = 0.27 hexanes/EtOAc 3/1); $^1$H NMR (250 MHz, selected data) δ 7.25-7.17 (m, 4H), 7.14-7.05 (m, 1H), 6.10-6.00 (m, 1H), 5.81 (dd, *J* = 11.5, 7.6 Hz, 1H), 5.01 (dd, *J* = 11.5, 1.3 Hz, 1H), 4.97-4.87 (m, 1H), 4.79 (ddd [app td], *J* = 10.7, 4.3 Hz, 1H), 3.71 (br dd, *J* = 11.9, 3.2 Hz, 1H), 3.64 (br dd, *J* = 11.9, 6.5 Hz, 1H), 1.23 (s, 9H), 1.17 (s, 9H), 0.85 (d, *J* = 6.5 Hz, 3H); $^{13}$C NMR (62.9 MHz) δ 178.9, 177.7, 164.4, 151.6, 146.9, 127.8, 125.3, 124.9, 120.9, 74.8, 74.2, 71.2, 64.8, 50.4, 41.6, 39.6, 38.9, 38.6, 34.4, 31.2, 29.7, 27.8, 27.1, 27.0, 26.45, 26.36, 24.8, 21.7; IR 3524, 2971, 1728, 1283, 1201, 1156 cm$^{-1}$.

**Alcohols 32b and 31b.** To a solution of aldehyde **22b** (316 mg, 0.359 mmol) in 20 mL THF/*i*-PrOH (1:1), $NaBH_4$ (55 mg, 1.45 mmol) was added at 0 °C. After stirring for 2.5 h at 0 °C, the reaction mixture was diluted with brine, extracted with ethyl acetate, dried and filtered to give the crude reduction product. Purification by flash chromatography (4-8% EtOAc in hexanes) afforded 186 mg (59%) of alcohol **32b** (in which the silyl group has migrated), and 61 mg (19%) of alcohol **31b**.[44] **32b**: $^1$H NMR (250 MHz, selected data) δ 7.70-7.53 (m, 8H), 7.47-7.04 (m, 17H), 5.97 (dd, *J* = 11.7, 8.0 Hz, 1H), 5.41-5.29 (m, 1H), 4.80 (dd, *J* = 11.7, 1.2 Hz, 1H), 4.58 (ddd [app td], *J* = 10.7, 4.3 Hz, 1H), 3.73-3.64 (m, 1H), 3.61 (dd, *J* = 9.8, 3.5 Hz, 1H), 3.45 (dd, *J* = 9.8, 7.3 Hz, 1H), 1.15 (s, 3H), 1.13 (s, 3H), 1.07 (s, 9H), 1.03 (s, 9H), 0.88 (d, *J* = 6.6 Hz, 3H); $^{13}$C NMR (62.9 MHz, some signals overlap) 164.4, 151.7, 151.4, 135.8, 135.5, 134.1, 133.9, 133.2, 129.8, 129.6, 129.5, 127.8, 127.76, 127.5, 127.4, 125.3, 125.0, 118.3, 74.0, 72.1, 69.6, 68.0, 50.4, 41.6, 39.6, 34.5, 33.5, 31.2, 27.9, 27.2, 27.0, 26.9, 26.6, 25.5, 21.8, 19.2; IR 2956, 2930, 2858, 1713, 1428, 1198, 1112, 700 cm$^{-1}$. $[\alpha]_{546}$ +26.3 (c = 1.9, $CHCl_3$). Anal. Calcd for $C_{56}H_{72}O_5Si_2$: C, 76.32; H, 8.23. Found: C, 76.09; H, 8.26. **31b**: $^1$H NMR (250 MHz, selected data) δ 7.72-7.03 (m, 25H), 5.84 (dd, *J* = 11.7, 8.0 Hz, 1H), 5.33-5.22 (m, 1H), 4.76 (dd, *J* = 11.7, 1.3 Hz, 1H), 4.60 (ddd [app td], *J* = 10.7, 4.3 Hz, 1H), 3.84-3.72 (m, 1H), 3.44 (br s, 1H), 3.43 (d, *J* = 2.2

(44) The overall yield of **32b** can be increased by treatment of compound **31b** with $Et_3N$ in ethanol at reflux, which gives a separable ca 4:1 mixture of **32b** and **31b** in good yield.

Hz, 1H), 1.20 (s, 3H), 1.15 (s, 3H), 1.07 (s, 9H), 0.99 (s, 9H), 0.87 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (125 MHz) δ 164.4, 151.8, 151.4, 135.9, 135.8, 135.7, 135.65, 135.5, 134.8, 134.0, 133.9, 133.6, 129.7, 129.54, 129.47, 127.9, 127.74, 127.66, 127.5, 127.4, 125.4, 125.0, 118.2, 74.2, 73.8, 69.6, 65.8, 50.4, 41.7, 39.7, 34.5, 32.8, 31.2, 28.5, 27.2, 27.1, 27.0, 26.6, 25.6, 21.8, 19.4, 19.2; IR 2955, 2945, 2855, 1715, 1195, 1115, 702 cm$^{-1}$.

***trans*-Tetrahydrofuran derivative 34.** Neocuproine hemihydrate (3.4 mg, 0.0155 mmol) and $Pd_2(dba)_3$•$CHCl_3$ (4 mg, 0.0039 mmol) were dissolved in 1 mL THF and the solution added via syringe to a solution of alkene **32a** (22.1 mg, 0.0387 mmol) in 2 mL of THF. After heating to 65 °C for 1.5 h, an additional portion of 2 mg (0.002 mmol) of $Pd_2(dba)_3$•$CHCl_3$ was added. After another 1.5 h at 65 °C, the THF was evaporated and the crude product was purified by flash chromatography (5% EtOAc in hexanes) to give 14.3 mg (78%) of **33** as a colorless oil. In addition, ca. 10% of a compound tentatively assigned as the ring-closed (*Z*)-product **34** was isolated in a separate fraction, together with some dba ligand. **33**: ($Rf$ = 0.53 hexanes/EtOAc 3/1); $^1$H NMR (250 MHz, selected data) δ 7.30-7.20 (m, 4H), 7.17-7.05 (m, 1H), 6.52 (dd, $J$ = 15.6, 4.9 Hz, 1H), 5.49 (dd, $J$ = 17.6, 1.6 Hz, 1H), 4.85 (ddd [app td], $J$ = 10.7, 4.3 Hz, 1H), 4.52 (app br qd, $J$ = 6.7, 1.6 Hz, 1H), 4.26 (br quintet, $J$ = 5.8 Hz, 1H), 4.12 (dd, $J$ = 11.5, 4.2 Hz, 1H), 4.05 (dd, $J$ = 11.5, 5.4 Hz, 1H), 1.22 (s, 9H), 0.86 (d, $J$ = 6.5 Hz, 1H); $^{13}$C NMR (62.9 MHz, some signals in aliphatic region overlap) δ 178.4, 165.6, 151.5, 147.2, 127.9, 125.4, 125.0, 120.8, 78.0, 76.8, 74.5, 50.5, 41.6, 39.7, 38.8, 34.5, 31.5, 31.3, 29.7, 27.9, 27.3, 27.2, 26.6, 25.6; IR 2958, 2924, 1732, 1283, 1156, 700 cm$^{-1}$; $[\alpha]_{546}$ +17.4 (c = 0.7, $CHCl_3$). Anal. Calcd for $C_{29}H_{42}O_5$: C, 74.01; H, 8.99. Found: C, 73.76; H, 9.19. **34**: ($Rf$ = 0.56 hexanes/EtOAc 3/1); $^1$H NMR (500 MHz, selected data) δ 7.27-7.22 (m, 4H), 7.14-7.10 (m, 1H), 6.13 (dd, $J$ = 11.5, 7 Hz, 1H), 5.23 (app br q, $J$ = 7 Hz, 1H), 5.07 (dd, $J$ = 12, 1.5 Hz, 1H), 4.77 (app td, $J$ = 11, 4.5 Hz, 1H), 4.21-4.15 (m, 1H), 4.12 (dd, $J$ = 11.5, 4 Hz, 1H), 4.07 (dd, $J$ = 11.5, 5.5 Hz, 1H), 2.38-2.30 (m, 1H), 1.30 (s, 3H), 1.22 (s, 9H), 0.86 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (125 MHz) δ 178.4, 170.0, 151.4, 150.3, 127.9, 125.4, 125.0, 119.9, 77.2, 76.8, 72.3, 66.2, 50.1, 41.7, 39.7, 38.8, 34.5 ,31.8, 31.3, 28.2, 27.6, 27.2, 26.6, 25.3, 21.8; IR 2955, 2925, 1730, 1710, 1170, 1090 cm$^{-1}$.

**2,5-THP 35.** To a solution of primary alcohol **31a** (35.5 mg, 0.062 mmol) in 3 mL of THF was added $Pd_2(dba)_3$•$CHCl_3$ (6 mg, 0.0058 mmol) and neocuproine hemihydrate (5 mg, 0.023). The reaction mixture was refluxed for 2 h, cooled down to RT and concentrated. Purification by flash chromatography (8% EtOAc in hexanes) afforded 24 mg (82%) of **35** as a white cristalline compound. **35**: ($Rf$ = 0.53 hexanes/EtOAc 3/1); $^1$H (500 MHz, selected data) δ 7.29-7.22 (m, 4H), 7.12-7.08 (m, 1H), 6.55 (dd, $J$ = 15.8, 4.4 Hz, 1H), 5.52 (dd, $J$ = 15.8, 1.6 Hz, 1H),

4.86 (td, $J$ = 10.7, 4.3 Hz, 1H), 4.77 (br s, 1H), 4.01 (br dt, $J$ = 12.7, 1.85 Hz, 1H), 3.89 (br dquintet, $J$ = 10.7, 2 Hz, 1H), 3.61 (dd, $J$ = 12.7, 1.3 Hz, 1H), 1.31 (s, 3H), 1.24 (s, 9H), 1.22 (s, 3H), 0.86 (d, $J$ = 6.6 Hz, 3H); $^{13}$C NMR (125 MHz) δ 178.0, 165.7, 151.4, 146.5, 127.9, 125.4, 124.9, 121.0, 75.5, 74.4, 69.2, 66.4, 50.5, 41.7, 39.8, 38.9, 34.5, 31.3, 27.19, 27.16, 27.13, 26.7, 26.1, 25.8, 21.8; IR 2945, 1720, 1440, 1285, 1185, 700 cm$^{-1}$. $[\alpha]_{546}$ +23.95 (c = 1.67, $CHCl_3$). Anal. Calcd for $C_{29}H_{42}O_5$: C, 74.01; H, 8.99. Found: C, 73.93; H, 8.90.

**Secondary Alcohol 38a.** Prepared from **37a** according to the general procedure; 59% of the secondary alcohol **38a** and 28% of starting material **37a** ($Rf$ = 0.21 hexanes/EtOAc 3/1) were obtained. **38a**: ($Rf$ = 0.35 hexanes/EtOAc 3/1); $^1$H NMR (250 MHz, selected data) δ 7.40-7.18 (m, 9H), 7.13-7.03 (m, 1H), 6.52 (dd, $J$ = 15.8, 5.2 Hz, 1H), 5.58-5.47 (m, 1H), 5.42 (dd, $J$ = 15.6, 1.5 Hz, 1H), 4.85 (ddd [app td], $J$ = 10.7, 4.3 Hz, 1H), 4.57 (d, $J$ = 10.7 Hz, 1H), 4.45 (d, $J$ = 10.7 Hz, 1H), 4.17-3.93 (m, 3H), 3.83-3.68 (m, 1H), 1.23 (s, 9H), 1.22 (s, 9H), 0.86 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (62.9 MHz, some signals in the aliphatic region overlap) δ 178.5, 177.1, 165.1, 151.4, 144.8, 137.5, 128.6, 128.2, 128.0, 127.9, 125.4, 125.0, 121.8, 74.6, 73.2, 72.5, 69.1, 68.4, 66.9, 50.4, 41.6, 39.7, 39.4, 38.8, 37.0, 34.5, 31.2, 27.2, 26.6, 25.6, 21.8; IR 3508, 2960, 2930, 1731, 1281, 1153, 700 cm$^{-1}$; $[\alpha]_{546}$ +9.2 (c = 3.7, $CHCl_3$).

**2,6-*cis*-Tetrahydropyran derivative 38.** Neocuproine hemihydrate (0.9 mg, 0.0042 mmol) and $Pd_2(dba)_3$•$CHCl_3$ (1.1 mg, 0.001 mmol) were dissolved in 1 mL of dry THF and the solution added via syringe to a solution of alkene **38a** (7.2 mg, 0.0104 mmol) in 1.5 mL of THF. After stirring for 50 min at room temperature, the THF was evaporated and the residue was purified by flash chromatograpy (7.5% EtOAc in hexanes) to give 4.9 mg (80%) of **38** as a colorless oil which slowly solidified. **35** ($Rf$ = 0.52 hexanes/EtOAc 3/1): $^1$H NMR (250 MHz, selected data) δ 7.38-7.21 (m, 9H), 7.16-7.06 (m, 1H), 6.52 (dd, $J$ = 15.7, 4.1 Hz, 1H), 5.54 (dd, $J$ = 15.7, 1.8 Hz, 1H), 4.85 (ddd [app td], $J$ = 10.7, 4.3 Hz, 1H), 4.60 (app s, 2H), 4.16 (dd, $J$ = 11.5, 5.8 Hz, 1H), 4.10 (dd, $J$ = 11.5, 4.5 Hz, 1H), 3.88 (dddd, $J$ = 11.8, 4.0, 2.0, 2.0 Hz, 1H), 3.69-3.55 (m, 2H), 1.21 (s, 9H), 0.85 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (62.9 MHz) δ 178.4, 165.6, 151.4, 145.7, 138.2, 128.5, 127.9, 127.7, 127.5, 125.4, 125.0, 120.9, 74.5, 74.0, 73.6, 69.8, 66.4, 50.5, 41.6, 39.7, 38.8, 37.0, 34.5, 34.2, 31.2, 27.7, 27.1, 26.6, 25.8, 25.1, 21.8; IR 2951, 2922, 1726, 1710, 1283, 1176, 700 cm$^{-1}$; $[\alpha]_{546}$ +5.5 (c = 0.6, $CHCl_3$). Anal. Calcd for $C_{37}H_{49}O_6$: C, 75.35; H, 8.37. Found: C, 75.02; H, 8.75.

**Secondary Alcohol 41a.** Prepared from **40a** according to the general procedure; 48% of the secondary alcohol **41a** and 42% of starting material **40a** ($Rf$ = 0.27 hexanes/EtOAc 3/1) was obtained. **41a**: ($Rf$ = 0.47 hexanes/EtOAc 3/1);

$^1$H NMR (500 MHz, selected data) δ 7.48-7.19 (m, 9H), 7.15-7.07 (m, 1H), 6.26-6.16 (m, 1H), 5.85 (dd, *J* = 11.6, 7.6 Hz, 1H), 5.04 (dd, *J* = 11.6, 1.5 Hz, 1H), 4.81 (td, *J* = 10.7, 4.3 Hz, 1H), 4.62 (d, *J* = 11.7 Hz, 1H), 4.56 (d, *J* = 11.7, 1H), 4.14-4.00 (m, 3H), 3.87-3.80 (m, 1H), 0.86 (d, *J* = 6.4 Hz, 3H); $^{13}$C (125 MHz, some signals overlap) δ 178.7, 177.5, 164.6, 151.7, 146.4, 133.3, 128.4, 128.3, 127.93, 127.89, 127.7, 125.4, 125.0, 121.2, 74.7, 74.5, 73.3, 71.6, 69.1, 65.7, 50.4, 41.5, 39.6, 38.7, 38.6, 37.9, 34.6, 31.4, 27.8, 27.2, 27.0, 26.6 24.9, 21.8; IR 3506, 2965, 1725, 1280, 1160, 700 cm$^{-1}$.

**2,6-*trans*-Tetrahydropyran derivative 42.** To a solution of **41a** (50 mg, 0.072 mmol) in 5 mL of THF, neocuproine hemihydrate (6 mg, 0.028 mmol) and $Pd_2(dba)_3$•$CHCl_3$ (7.5 mg, 0.007 mmol) was added at 50 °C. After stirring for 30 min at 50 °C, an additional portion of 4 mg of $Pd_2(dba)_3$•$CHCl_3$ was added. After stirring for another 30 min at 50 °C, the reaction mixture was concentrated and purified by flash chromatography (10% EtOAc in hexanes) to give 25 mg (59%) of **42** as a colorless oil. **42**: (*Rf* = 0.61 hexanes/EtOAc 3/1); $^1$H NMR (250 MHz, selected data) δ 7.41-7.06 (m, 10H), 6.54 (dd, *J* = 16.0, 3.4 Hz, 1H), 5.51 (dd, *J* = 16.0, 2.3 Hz, 1H), 4.87 (ddd [app td], *J* = 10.7, 4.4 Hz, 1H), 4.66 (app td, *J* = 7.9, 2.3 Hz, 1H), 4.57 (d, *J* = 11.2 Hz, 1H), 4.53 (d, *J* = 11.8 Hz, 1H), 4.23 (dd, *J* = 11.6, 7.1 Hz, 1H), 4.09 (dd, *J* = 11.6, 3.7 Hz, 1H), 3.82 (app ddd, *J* = 13.4, 6.8, 3.3 Hz, 1H), 3.82 (app ddd, *J* = 13.9, 9.2, 4.2 Hz, 1H), 1.23 (s, 9H), 0.87 (d, *J* = 6.5 Hz, 3H); $^{13}$C NMR (50.3 MHz, some signals in the aliphatic region overlap) δ 178.3, 165.2, 151.3, 146.7, 138.3, 128.5, 127.9, 127.7, 127.5, 125.5, 125.0, 122.7, 74.6, 70.9, 70.4, 70.1, 69.1, 66.1, 50.6, 41.8, 39.8, 38.8, 34.7, 34.6, 33.4, 31.3, 27.2, 26.7, 25.9, 21.8; IR 2955, 2927, 1713, 1283, 1162, 1094, 700 cm$^{-1}$; $[a]_{546}$ -35.7 (c = 0.8, $CHCl_3$). FAB-HRMS (M + H)+: Calcd for $C_{37}H_{48}O_6$, 589.3529; Found, 589.3526.

**2,6-*trans*-THP derivative 43b.** To a solution of alkene **29b** (24 mg, 0.027 mmol; d.r. 95:5) in 3 mL of THF, *t*-BuOK (5 mg, 0.04 mmol) was added at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and quenched with 1 mL phosphate buffer (pH 7). Extractive workup, followed by flash chromatography (3% EtOAc in hexanes) afforded 23 mg (96%) of **43b** as a colorless oil. According to NMR analysis, the product contained ca. 3% of a minor isomer, tentatively

assigned as the 2,6-*cis*-THP derivative **44b**.[45,46] **43b**: (*Rf* = 0.48 hexanes/EtOAc 9/1); $^1$H (500 MHz, selected data) δ 7.72-7.53 (m, 8H), 7.47- 7.27 (m, 16H), 7.20-7.15 (m, 1H), 4.77 (ddd [app td], *J* = 10.7, 4.3 Hz, 1H), 4.22-4.15 (m, 1H), 3.81 (ddd, *J* = 10, 4.5, 4.5 Hz, 1H), 3.55 (dd, *J* = 9.5, 4.2 Hz, 1H), 3.46-3.40 (m, 1H), 3.29 (dd, *J* = 9.3, 7.5 Hz, 1H), 2.27 (dd, *J* = 14.5, 3 Hz, 1H), 2.16 (dd, *J* = 14.5, 11.5 Hz, 1H), 1.98 (br t, *J* = 9.7 Hz, 1H), 1.33 (s, 3H), 1.22 (s, 3H), 1.07 (s, 9H), 1.02 (s, 9H), 0.70 (d, *J* = 6.5 Hz, 3H); $^{13}$C NMR (125 MHz) δ 171.7, 151.9, 135.74, 135.68, 135.6, 135.5, 129.8, 129.7, 129.6, 127.9, 127.7, 127.62, 127.57, 125.5, 124.9, 74.3, 73.8, 69.2, 68.5, 66.5, 50.4, 41.7, 39.7, 34.5, 31.2, 31.1, 28.2, 27.08, 26.96, 26.88, 26.8, 24.8, 26.5, 21.6, 19.3, 19.2; IR 2930, 2857, 1728, 1428, 1112, 700, 504 cm$^{-1}$. $[\alpha]_{546}$ +24.7 (c = 1.4, $CHCl_3$); Anal. Calcd for $C_{56}H_{72}O_5Si_2$: C, 76.32; H, 8.23. Found: C, 76.08; H, 8.31. **44b:** $^1$H (500 MHz, selected data assigned from a ca. 70:30 mixture of **43b** and **44b**) δ 3.65 (dd, *J* = 10, 4.5 Hz, 1H), 2.70 (dd, *J* = 14.5, 2.6 Hz, 1H). $^{13}$C (125 MHz, selected data assigned from a ca. 70:30 mixture of **43b** and **44b**) δ 171.2, 151.2, 77.2, 74.7, 72.2, 66.4, 50.6, 41.6, 39.9, 34.6.

**2,6-*cis*-THP 45a.** To a solution of alkene **32a** (52 mg, 0.091 mmol) in 2 mL dry ether, *t*-BuOK (10 mg) was added. The reaction mixture was stirred for 10 minutes at RT, and then quenched with 0.5 mL phosphate buffer (pH 7). Extractive workup (EtOAc/brine), drying, and evaporation of solvents afforded 54 mg (ca. 95% pure based on $^1$H NMR, crude yield 99%) tetrahydropyran **45a** as a colorless oil. An analytically pure sample was obtained after purification by flash chromatography in 95% yield (5% EtOAc in hexanes). Only one stereoisomer was detected by $^1$H NMR spectroscopy; the relative stereochemistry was proven by using NOE experiments. **45a**: (*Rf* = 0.72 hexanes/EtOAc 3/1); $^1$H NMR (250 MHz, selected

(45) The stereochemical assignment of the product isomers is based on $^{13}$C NMR analysis. In a separate experiment, performed at higher temperature and for a longer reaction time, a ca. 70:30 mixture of **43b** and **44b** was obtained as product. In compound **43b**, the carbons at C-2 and C-6 give $^{13}$C NMR peaks at 73.8 and 68.5 ppm, respectively, whereas the corresponding carbons in the minor product **44b** give peaks at 79.2 and 72.2 ppm, respectively. In 2,6-*trans*-THP derivatives the carbons at C-2 and C-6 are, on average, shifted upfield by ca. 7.3 ppm compared to the same carbons in the corresponding 2,6-*cis*-THP derivative; see: (a) Pihlaja, K.; Kleinpeter, E. *Carbon-13 NMR Chemical Shifts in Structural and Stereochemical Analysis*; VCH Publishers: New York, 1994, pp 108-114. (b) Eliel, E. L.; Manoharan, M.; Pietrusiewicz, K. M.; Hargrave, K. D. *Org. Magn. Reson.* **1983**, *21*, 94.

(46) We cannot exclude the possibility that the product contains a few percent of the 2,6-*trans*-THP product resulting from ring closure of secondary alcohol obtained from the reduction of **21b**; however, we have only been able to detect product isomers **43b** and **44b**.

data) δ 7.30-7.19 (m, 4H), 7.14-7.06 (m, 1H), 4.82 (ddd [app td], $J$ = 10.7, 4.3 Hz, 1H), 4.36 (ddd [app br td], $J$ = 9.8, 4.6 Hz, 1H), 4.00 (dd, $J$ = 11.4, 5.0 Hz, 1H), 3.93 (dd, $J$ = 11.4, 5.8 Hz, 1H), 3.74 (ddd [app dt], $J$ = 9.9, 2.6 Hz, 1H), 3.62-3.51 (m, 1H), 1.20 (s, 9H), 1.18 (s, 9 H), 0.86 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (62.9 MHz, some signals overlap) δ 178.2, 177.5, 170.4, 151.3, 127.8, 125.4, 125.1, 76.1, 75.1, 74.6, 70.8, 66.0, 50.2, 41.8, 39.7, 38.7, 37.6, 34.5, 31.3, 29.7, 28.5, 27.2, 27.1, 26.6, 25.7, 21.8; IR 2956, 2926, 2870, 1731, 1284, 1153 cm$^{-1}$. $[\alpha]_{546}$ +30.4 (c = 3.7, $CHCl_3$). FAB-HRMS $(M + H)^+$ calcd for $C_{34}H_{52}O_7$ 573.3791, found 573.3794.

**2,6-*cis*-THP 45b.** To a solution of **32b** (212 mg, 0.24 mmol) in 10 mL dry ether, *t*-BuOK (40 mg, 0.356 mmol) was added. The reaction mixture was stirred for 30 minutes at RT, quenched with 2 mL phosphate buffer (pH 7). Extractive workup, followed by flash chromatography (3% EtOAc in hexanes) afforded 206 mg (97%) of **45b** as a colorless oil. Only one stereoisomer was detected. **45b**: (*Rf* = 0.48 hexanes/EtOAc 8.5/1.5); $^1$H NMR (500 MHz, selected data) δ 7.71-7.68 (m, 4H), 7.60-7.57 (m, 4H), 7.48-7.20 (m, 17H),7.13-7.10 (m, 1H), 4.83 (ddd [app td], $J$ = 10.7, 4.4 Hz, 1H), 3.70 (ddd [app td], $J$ = 10.1, 2 Hz, 1H), 3.61 (dd, $J$ = 10, 4.5 Hz, 1H), 3.46-3.39 (m, 1H), 3.36-3.27 (m, 2H), 2.68 (dd, $J$ = 15, 2 Hz, 1H), 1.28 (s, 3H), 1.18 (s, 3H), 1.05 (s, 9H), 0.97 (s, 9H), 0.67 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (50.3 MHz, some signals overlap) δ 171.4, 151.2, 135.9, 135.8, 135.51, 135.45, 134.2, 133.5, 129.8, 129.7, 129.5, 127.8, 127.7, 127.6, 125.5, 125.1, 79.3, 77.6, 77.1, 74.5, 72.1, 66.3, 50.3, 41.7, 39.9, 38.7, 34.5, 32.7, 31.2, 28.0, 27.0, 26.8, 26.1, 21.6, 19.3, 19.2; IR 2956, 2931, 2857, 1725, 1427, 1111, 700 cm$^{-1}$. $[\alpha]_{546}$ +19.3 (c = 1.1, $CHCl_3$). Anal. Calcd for $C_{56}H_{72}O_5Si_2$: C, 76.32; H, 8.23. Found: C, 76.27; H, 8.49.

**Triol 46.** To a solution of bis-silyl ether **37b** (131.7 mg, 0.13 mmol) in 7 mL of dry THF, 525 ml (0.53 mmol) of $Bu_4NF$ solution (1 M in THF) was added. After stirring 2 h at room temperature the reaction mixture was diluted with 10 mL aq sat. sol. of $NH_4Cl$, extracted with $CH_2Cl_2$ (3x20 mL), dried, filtered through the layer of cotton and concentrated. Purification by flash chromatography (3% MeOH in $CH_2Cl_2$ yielded 55 mg (80%) of triol **46** as a colorless oil. **46**: (*Rf* = 0.31 $CH_2Cl_2$/MeOH 19/1); $^1$H NMR (200 MHz, selected data) δ 7.42-7.18 (m, 9H, aromatic), 7.16-7.04 (m, 1H), 6.58 (dd, $J$ = 15.6, 4.4 Hz, 1H), 5.53 (dd, $J$ = 15.6, 1.7 Hz, 1H), 4.85 (ddd [app td], $J$ = 10.7, 4.3 Hz, 1H), 4.63 (d, $J$ = 11.2 Hz, 1H), 4.56 (d, $J$ = 11.2 Hz, 1H), 4.48-4.35 (m, 1H), 4.08-3.88 (m, 2H), 3.64 (dd, $J$ = 11.1, 3.1 Hz, 1H), 3.44 (dd, $J$ = 11.1, 6.7 Hz, 1H), 1.30 (s, 3H), 1.21 (s, 3H), 0.86 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (50.3 MHz) δ 165.7, 151.5, 149.2, 137.6, 128.6, 128.2, 128.1, 127.9, 125.4, 124.9, 120.6, 74.5, 74.2, 71.9, 69.0, 68.1, 66.9, 50.4, 41.7, 39.8, 39.7, 36.5, 34.5, 31.2, 27.2, 26.6, 25.7, 21.8, 20.1; IR 3384, 2952, 1709, 1274, 1092, 700 cm$^{-1}$.

**Diol 47.** To a triol **46** (51 mg, 0.097 mmol) in 200 μL of pyridine, TsCl (27 mg, 0.141 mmol) in 200 μLof pyridine was added via syringe. After 2 hours at 0 °C an additional 18.5 mg of TsCl in 100 μL of pyridine was added. After stirring an additional two hours at 0 °C the reaction mixture was diluted with brine, extracted with $CH_2Cl_2$ (1x10 mL) and ether (2x10 mL), dried, filtered through the layer of cotton and concentrated to give 99 mg pale yellow oil. Flash chromatography (0.5% MeOH/$CH_2Cl_2$ yielded 50.1 mg (76%) of diol **47** as colorless oil. **47**: (*Rf* = 0.18 $CH_2Cl_2$/MeOH 49/1); $^1$H NMR (250 MHz, selected data) δ 7.83-7.75 (m, 2H), 7.41-7.19 (m, 11H), 7.14-7.03 (m, 1H), 6.54 (dd, *J* = 15.6, 4.5 Hz, 1H), 5.51 (dd, *J* = 15.6, 1.7 Hz, 1H), 4.85 (ddd [app td], *J* = 10.7, 4.3 Hz, 1H), 4.56 (s, 2 H), 4.38 (app qd, *J* = 4.1, 1.6 Hz, 1H), 4.13-4.01 (m, 2H), 4.01 (dd, *J* = 10.0, 3.7 Hz, 1H), 3.91 (dd, *J* = 10.0, 6.4 Hz, 1H), 2.44 (s, 3H), 1.30 (s, 3H), 1.21 (s, 3H), 0.86 (d, *J* = 6.5 Hz, 3H); $^{13}$C NMR (50.3 MHz, some signals in the aromatic region overlap) δ 165.6, 151.6, 148.9, 145.1, 137.5, 132.6, 129.9, 128.6, 128.2, 127.9, 125.4, 124.9, 120.7, 74.5, 73.8, 72.2, 68.0, 66.5, 50.5, 41.7, 39.74, 39.70, 36.6, 34.5, 31.3, 27.4, 26.6, 25.6, 21.8, 21.6; IR 3474, 2951, 2924, 1708, 1176, 700 cm$^{-1}$.

**Epoxide 48.** To a solution of tosylate **47** (63 mg, 0.092 mmol) in 6 mL of dry THF, NaHMDS solution (0.585 M in toluene, 190 μl, 0.111 mmol) was added dropwise under argon atmosphere. After stirring the reaction mixture for 10 min at room temperature 0.5 mL of water was added. Filtration through a layer of $MgSO_4$ and silica gel followed by evaporation gave 44 mg (95%) of **48** as colorless oil. No further purification was needed. **48**: (*Rf* = 0.28 hexanes/EtOAc 7/3); $^1$H NMR (250 MHz, selected data) δ 7.42-7.20 (m, 9H, aromatic), 7.16-7.06 (m, 1H), 6.61 (dd, *J* = 15.6, 4.3 Hz, 1H), 5.56 (dd, *J* = 15.6, 1.8 Hz, 1H), 4.86 (ddd [app td], *J* = 10.7, 4.3 Hz, 1H), 4.66 (d, *J* = 11.2 Hz, 1H), 4.53 (d, *J* = 11.2 Hz, 1H), 4.53-4.41 (m, 1H), 3.94 (app ddd, *J* = 13.2, 6.4, 4.0 Hz, 1H), 3.07-2.98 (m, 1H), 2.82 (dd, *J* = 4.9, 4.1 Hz, 1H), 2.74 (br d, *J* = 3.2 Hz, 1H), 2.52 (dd, *J* = 5, 2.7 Hz, 1H), 1.31 (s, 3H), 1.23 (s, 3 H), 0.87 (d, *J* = 6.4 Hz, 3H); $^{13}$C NMR (62.9 MHz, some signals in the aromatic region overlap) δ 165.4, 151.3, 149.0, 137.5, 128.4, 127.8, 127.7, 125.3, 124.7, 120.5, 74.6, 74.2, 71.7, 67.9, 50.3, 49.1, 47.1, 41.5, 39.8, 39.6, 37.0, 34.4, 31.1, 26.9, 26.5, 25.7, 21.6.

**Tetrahydropyran 49.** To a solution of epoxide **48** (20 mg, 0.039 mmol) in 8 mL of acetonitrile, a catalytic amount of triflic acid (0.5% solution in $CH_2Cl_2$, 0.0044 mmol, 100 μL) was added under argon at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and then quenched by adding 70 μL of $Et_3N$. The reaction mixture was warmed up to RT, diluted with water (10 mL), extracted with EtOAc (3x15 mL), dried, filtered through the layer of cotton and contcentrated. Purification by flash chromatograpy (20% EtOAc in hexanes) afforded 16.1 mg

(81%) tetrahydropyran **49** as colorless oil. **49**: (*Rf* = 0.18 hexanes/EtOAc 7/3); $^1$H NMR (250 MHz, selected data) δ 7.39-7.19 (m, 9H), 7.16-7.06 (m, 1H), 6.83 (dd, *J* = 15.8, 4.7 Hz, 1H), 5.43 (dd, *J* = 15.8, 1.9 Hz, 1H), 4.85 (ddd [app td], *J* = 10.7, 4.3 Hz, 1H), 4.55 (d, *J* = 11.8 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 4.40 (br qd, *J* = 5.0, 1.7 Hz, 1H), 4.21-4.09 (m, 1H), 3.87-3.76 (m, 1H), 3.64 (dd, *J* = 11.5, 7.5 Hz, 1H), 3.56 (dd, *J* = 11.5, 3.9 Hz, 1H), 1.29 (s, 3H), 1.20 (s, 3H), 0.86 (d, *J* = 6.4 Hz, 3H); $^{13}$C NMR (50.3 MHz, some signals in the aromatic region overlap) δ 165.5, 151.6, 147.1, 138.3, 128.4, 127.9, 127.6, 127.4, 125.5, 124.9, 120.9, 74.4, 70.6, 70.1, 69.7, 69.4, 64.1, 50.5, 41.7, 39.7, 34.6, 31.4, 31.3, 29.7, 27.3, 26.6, 25.6, 21.8; IR 3453, 2954, 2924, 1710, 1271, 1175, 1094, 700 cm$^{-1}$.

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# V

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Progress Towards the Total Synthesis of Mucocin.
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# Progress Towards the Total Synthesis of Mucocin

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ABSTRACT

A stereocontrolled approach to two different oxacyclic subunits of the annonaceaous acetogenin mucocin from a common intermediate is described. Key features of the synthesis are an asymmetric Horner-Wadsworth-Emmons desymmetrization of a *meso*-dialdehyde and stereoselective ring closure reactions via either an intramolecular Michael addition (to provide the tetrahydropyran unit) or a palladium-catalyzed allylic substitution (to give the tetrahydrofuran unit).

The annonaceous acetogenins constitute a growing class of natural products,[1] which has attracted considerable attention in recent years due to the important biological activities displayed by many of these compounds. Mucocin[2] (**1**), which was isolated from the leaves of *Rollinia Mucosa*, exhibits up to 10000 times more selective inhibitory effect against A-549 (lung cancer) and PACA-2 (pancreatic cancer) cell lines compared to the known antitumor agent adriamycin. Furthermore, mucocin was the first annonaceous acetogenin reported which contains a tetrahydropyran (THP) ring in addition to a tetrahydrofuran (THF) ring. The remarkable biological activity and unusual structural features have made mucocin a popular target for synthetic studies.[3] In this paper, we describe a novel

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(1) (a) Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z.-H.; He, K.; McLaughlin, J. *Nat. Prod. Rep.* **1996**, *13*, 275. (b) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504.

(2) Shi, G.; Alfonso, D.; Fatope, M. O.; Zeng, L.; Gu, Z.-m.; Zhao, G.-x.; He, K.; MacDougal, J. M.; McLaughlin, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 10409.

(3) Total syntheses: (a) Neogi, P.; Doundoulakis, T.; Yazbak, A.; Sinha, S. C.; Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1998**, *120*, 11279. (b) Bäurle, S.; Hoppen, S.; Koert, U. *Angew. Chem. Int. Ed.* **1999**, *38*, 1263. (c) Takahashi, S.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 723; Takahashi, S.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 727. Synthetic studies: (d) Crimmins, M. T.; Rafferty, S. W.

stereoselective approach, by which both the THP and the THF subunits of mucocin can be accessed from a common intermediate.[4]

According to our retrosynthetic analysis (Scheme 1), an intermediate of type **4** might serve a dual purpose: the THP unit **2** could be constructed from **4** via an intramolecular hetero-Michael reaction,[5] whereas a palladium-catalyzed allylic substitution was expected to give access to the THF unit **3**.[6] The intermediate **4** would, in turn, be obtained from a *meso*-dialdehyde **6**, via an asymmetric Horner-Wadsworth-Emmons (HWE) reaction.[7] Dialdehydes of type **6** are readily prepared from *cis*-cyclohexene-1,4-diol **7**.[8] Thus, the synthesis would be highly convergent since two of the oxacyclic rings in the target structure are derived from the same precursor.

In order to realize this plan, the possible choices of protecting groups P in the substrate **6** were dictated by certain criteria. First of all, the *meso*-dialdehyde must be reasonably stable, and well-behaved in the asymmetric HWE reaction. Furthermore, selective unmasking of one of the secondary OH groups in the HWE product **5** must be feasible. In addition, an attractive opportunity would be the use of a protecting group P which allows the substituent PO to be used directly as a leaving group in a Pd-catalyzed allylic substitution. To identify protecting groups which meet the above criteria we have used dialdehydes **6a**[6] and **6b**[5] as key intermediates in our initial studies.

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*Tetrahedron Lett.* **1996**, *37*, 5649. (e) Evans, P. A.; Roseman, J. D. *Tetrahedron Lett.* **1997**, *38*, 5249. (f) Evans, P. A.; Murthy, V. S. *Tetrahedron Lett.* **1998**, *39*, 9627. (g) Evans, P. A.; Murthy, V. S. *Tetrahedron Lett.* **1999**, *40*, 1253.

(4) Interestingly, Evans has reported[3g] a different synthetic approach which also allows preparation of functionalized THP and THF intermediates from a common precursor.

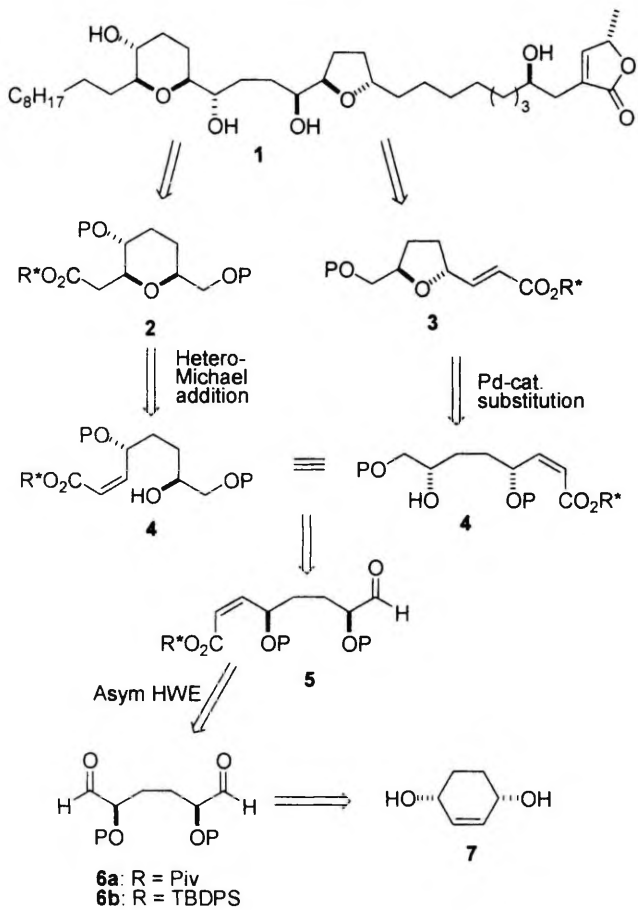
(5) Paper IV.

(6) Vares, L.; Rein, T., *Org. Lett.* **2000**, *2*, 2611.

(7) For a review, see: (a) Rein, T.; Reiser, O. *Acta Chem. Scand.* **1996**, *50*, 369. Selected recent examples: (b) Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1996**, *37*, 1077. (c) Kumamoto, T.; Koga, K. *Chem. Pharm. Bull.* **1997**, *45*, 753. (d) Dai, W.-M.; Wu, J.; Huang, X. *Tetrahedron: Asymmetry* **1997**, *8*, 1979. (e) Mizuno, M.; Fujii, K.; Tomioka, K. *Angew. Chem.* **1998**, *110*, 525; *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 515. (f) Vaulont, I.; Gais, H.-J.; Reuter, N.; Schmitz, E.; Ossenkamp, R. K. L. *Eur. J. Org. Chem.* **1998**, 805. (g) Tullis, J. S.; Vares, L.; Kann, N.; Norrby, P.-O.; Rein, T. *J. Org. Chem.* **1998**, *63*, 8284. (h) Arai, S.; Hamaguchi, S.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 2997. (i) Tanaka, K.; Watanabe, T.; Shimamoto, K.-Y.; Sahakitpichan, P.; Fuji, K. *Tetrahedron Lett.* **1999**, *40*, 6599. (j) Pedersen, T. M.; Jensen, J. F.; Humble, R. E.; Rein, T.; Tanner, D.; Bodmann, K.; Reiser, O. *Org. Lett.* **2000**, *2*, 535.

(8) Bäckvall, J.-E.; Granberg, K. L.; Hopkins, R. B. *Acta Chem. Scand.* **1990**, *44*, 492.

**Scheme 1**

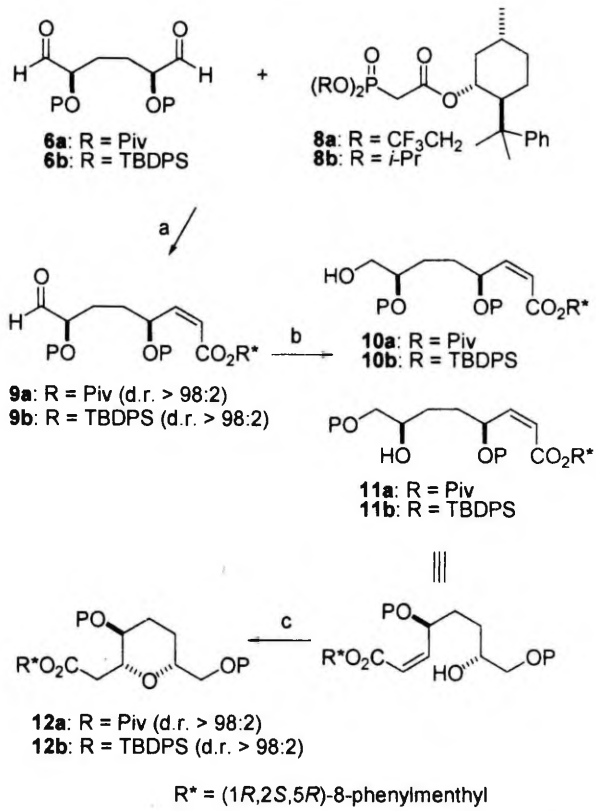



Our route to the functionalized THP derivatives **12**, which possess the desired relative stereochemistry of the THP fragment of mucocin,[9] is shown in Scheme 2. The (*Z*)-alkenes **9a** and **9b** were both obtained in good yield and excellent diastereoselectivity from the respective asymmetric HWE reaction. Reduction of the remaining aldehyde and migration of one protecting group provided

(9) Use of (1*R*,2*S*,5*R*)-8-phenylmenthol (i.e., the most readily available enantiomer) as the chiral auxiliary gives THP fragments **12** and THF fragment **22** with absolute configuration opposite to the one of natural mucocin. However, we expect that use of the nor-analogue 2-(1-methyl-1-phenylethyl)cyclohexanol — which is commercially available in both enantiomeric forms — will give very similar results in the asymmetric HWE reactions; see reference 7f and references therein.

intermediates **11** together with the isomeric alcohols **10**, which could be recycled.[10] Upon treatment with base, THP derivatives **12a** and **12b** were both formed in excellent yields as single detected diastereomers.[5]

**Scheme 2**[a]




[a]Reaction conditions: (a) **9a**: 1.3 equiv **6a**, 1.1 equiv **8a**, 1.0 equiv KHMDS, 5 equiv 18-crown-6, THF, -85 °C; 71% (see footnote 5). **9b**: 1.3 equiv **6b**, 1.1 equiv **8a**, 1.0 equiv NaHMDS, THF, -78 °C; 88%. (b) **11a**/**10a**: $LiBH_4$, *i*-PrOH/THF, 0 °C; 49% **11a**, 38% **10a** (see footnotes 6 and 10). **11b**/**10b**: $NaBH_4$, THF/*i*-PrOH, 0 °C; 59% **11b**, 19% **10b** (see footnotes 5 and 10). (c) *t*-BuOK, $Et_2O$, 25 °C; 95% **12a**, 97% **12b**.

We anticipated that the alkene geometry of the acyclic precursor **4** could be of importance for the stereochemical outcome of the intramolecular Michael

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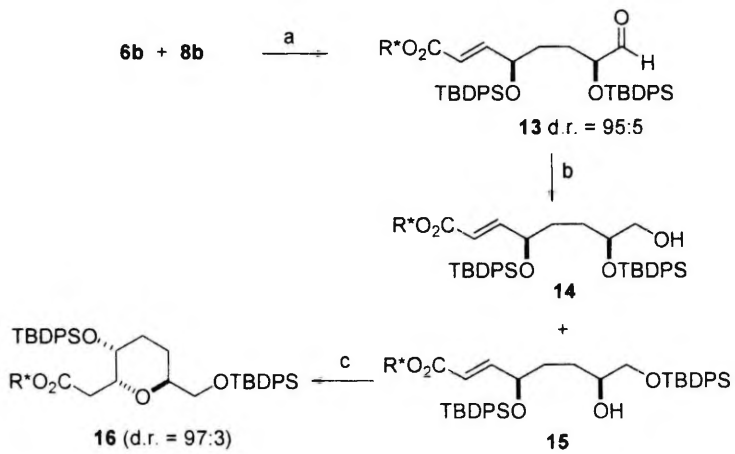
(10) Depending on the specific conditions used, varying ratios between the secondary alcohols **11** and the isomeric primary alcohols **10** could be obtained from **9a,b**. Compounds **10a** and **10b** could be separated and converted to mixtures of **11a**/**10a** and **11b**/**10b**, respectively, thus increasing the overall yield of the desired secondary alcohols (see Paper IV for details).

addition,[5] and the alternative route via the (*E*)-alkene intermediate **13** was therefore investigated as well (Scheme 3). Desymmetrization of **6b** by reaction with the phosphonate **8b** gave the (*E*)-alkene **13**.[11] Reduction and TBDPS migration gave intermediate **15**, which underwent intramolecular Michael addition to give the 2,6-*trans*-THP derivative **16**.[5] Although not relevant for the synthesis of natural mucocin, this approach to 2,6-*trans*-THP derivatives is of interest for analog synthesis. The change in stereochemical outcome between ring closure of **11a,b** on the one hand and **15** on the other hand is in agreement with reported mechanistic models.[12]

**Scheme 3**[a]




[a]Reaction conditions: (a) 1.3 equiv **6b**, 1.1 equiv **8b**, 1.0 equiv KHMDS, 5 equiv 18-crown-6, THF, -82 °C (see footnote11 ). (b) $NaBH_4$, MeOH/THF, 0 °C; overall yields from the reaction of **6b** with **8b** = 53% **15**, ca. 5% **14** (see footnote 10). (c) *t*-BuOK, $Et_2O$, 0 °C; 96%.

Compound **12b** was further transformed to the advanced intermediate **22** (Scheme 4). DIBALH reduction provided a mixture of aldehyde **18** and alcohol **17**, the latter of which was quantitatively converted to **18** by Swern oxidation; the

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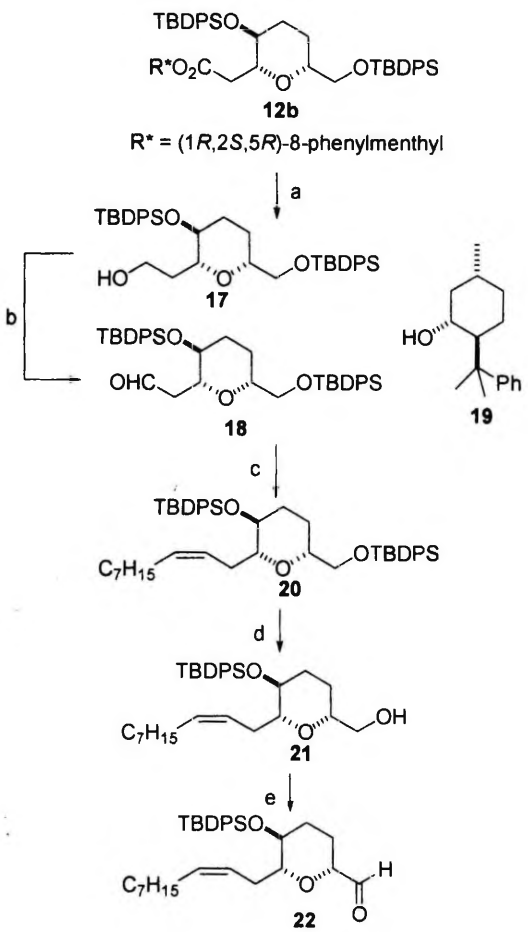
(11) After chromatography, compound **13** was obtained in mixture with some bisaddition product. This byproduct could be easily separated from **14** and **15** after the subsequent step (see Paper IV for details).

(12) (a) Banwell, M. G.; Bui, C. T.; Pham, H. T. T.; Simpson, G. W. *J. Chem. Soc., Perkin Trans. 1* **1996**, 967, and references therein. (b) Betancort, J. M.; Martín, V. S.; Padrón, J. M.; Palazón, J. M.; Ramírez, M. A.; Soler, M. A. *J. Org. Chem.* **1997**, *62*, 4570, and references therein. (c) Ramírez, M. A.; Padrón, J. M.; Palazón, J. M.; Martín, V. S. *J. Org. Chem.* **1997**, *62*, 4584.

chiral auxiliary **19** was also recovered in high yield. A Wittig reaction served to install the required hydrocarbon chain, and selective deprotection of the primary TBDPS group[13] then gave **21** in excellent yield.[14] Subsequent Swern oxidation afforded THP derivative **22** in good yield. We are presently exploring the opportunities to transform THP derivative **12a** to similar advanced intermediates.

**Scheme 4**[a]




[a]Reaction conditions: (a) DIBALH, $CH_2Cl_2$, -78 °C; 59% **17**, 33% **18**, 98% **19**. (b) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, -78 to -50 °C; quant. (c) $C_8H_{17}PPh_3I$, NaHMDS, 0 °C to RT; 68%. (d) $Al_2O_3$; 98%. (e) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, -78 to -50 °C; 85%.

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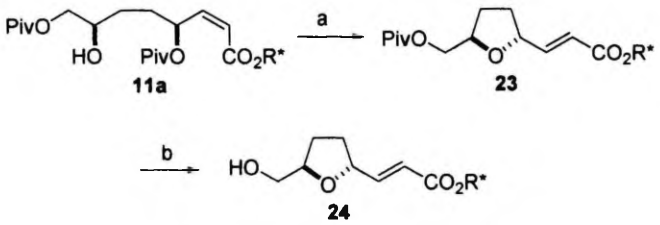
(13) Feixas, J.; Capdevila, A.; Guerro, A. *Tetrahedron* **1994**, *50*, 8539.

(14) According to our synthetic plan, the double bond present in **21** will be hydrogenated at a later stage, simultaneously with hydrogenation of unsaturation present in other fragments, to minimize the overall number of steps.

As illustrated in Scheme 5, THF fragment **24**[9] was obtained in good yield by selective hydrolysis of the primary pivaloyl group in **23**. This intermediate was, in turn, prepared from **11a** by a palladium-catalyzed intramolecular allylic nucleophilic substitution.[6] Thus, both the THF fragment **24** and the THP fragments **12** are available in few steps from a common synthetic precursor. These intermediates are suitably functionalized to allow introduction of an appropriate two-carbon spacer joining the THP and THF fragments, as well as coupling to the butenolide subunit of mucocin.

**Scheme 5**[a]




R* = (1*R*,2*S*,5*R*)-8-phenylmenthyl

[a]Reaction conditions: (a) $Pd_2(dba)_3$•$CHCl_3$ (0.15 equiv), neocuproine hemihydrate (0.4 equiv), THF, 65 °C; 79% (see footnote 6). (b) LiOH, THF/MeOH/$H_2O$; 78%.

To summarize, we have demonstrated that synthetic intermediates corresponding to the THP and THF fragments of mucocin can be prepared by short and efficient routes from a common precursor. Key elements of these routes are asymmetric HWE reactions and stereoselective ring closure reactions. These studies highlight the synthetic utility of the asymmetric HWE reactions, which serve to simultaneously set the absolute stereochemistry of the intermediates, extend the carbon skeleton, and introduce the functionality necessary for the different types of ring closure. Further results of our efforts towards completing the total synthesis of mucocin will be reported in due course.

## Experimental Section

**General.** Commercial reagents were generally used as received. Dichloromethane and triethylamine were destilled from calcium hydride. All reactions were carried out in oven dried glassware unless water was used as a reaction medium.. TLC analyses were performed on Merck aluminum-backed F254 silica gel plates, using UV light and phosphomolybdic acid for visualization. Drying of organic phases obtained from extractive workup was generally done with $MgSO_4$. Flash chromatography was performed as described by Still and

coworkers[15] using either Merck silica gel 60 (230-400 mesh), Amicon Matrex 60Å silica gel (35-70 μm), or Chemapol silica gel L 40/100. NMR spectra were recorded in $CDCl_3$ unless otherwise indicated, using $CHCl_3$ (δ 7.26 ppm) and $CDCl_3$ (δ 77.0 ppm) as internal references for $^1H$ and $^{13}C$, respectively. IR spectra were recorded neat as a thin films using AgCl or KBr plates. Microanalyses were perfomed at the Institute of Physical Chemistry, University of Vienna, Austria. HRMS analyses were perfomed at the Department of Chemistry and Biochemistry, University of Notre Dame, USA.

**Reduction of ester 12b.** To a solution of **12b** (37 mg, 0.042 mmol) in 4 mL $CH_2Cl_2$, a solution of DIBALH (1 M in hexanes, 140 μL) was added at –78 °C. After stirring for 5 h at –78 °C, ca 100 mg of tartaric acid was added and the reaction mixture was warmed up to RT. Extractive workup ($CH_2Cl_2$/brine) and subsequent purification by flash chromatography (5% EtOAc in hexanes) afforded 16.3 mg (59%) of alcohol **17**, 9.0 mg (33%) of aldehyde **18**, and 9.5 mg (98%) of 8-phenylmenthol **19**. **17:** $^1H$ NMR NMR (250 MHz, selected data) δ 7.51-7.58 (m, 8H), 7.49-7.32 (m, 12H), 3.80-3.73 (m, 2H), 3.59-3.36 (m, 5H), 2.23-2.10 (m, 1H), 1.85-1.73 (m, 1H), 1.67-1.4 (m, 3H), 1.33-1.22 (m, 2H), 1.03 (s, 9H), 1.01 (s, 9H); $^{13}C$ NMR (62.9 MHz) δ 135.9, 135.8, 135.5, 134.5, 133.4, 133.3, 129.8, 129.6, 127.7, 127.6, 127.4, 83.7, 77.8, 71.9, 66.6, 62.1, 33.8, 32.6, 27.1, 27.0, 26.7, 19.3, 19.1; IR 2931, 2857, 1428, 1112, 702, 505 $cm^{-1}$. $[\alpha]_{546}$ +29.6 (c = 1.3, $CHCl_3$). FAB-HRMS $(M + H)^+$ calcd for $C_{40}H_{52}O_4Si_2$ 653.3482, found 653.3476. **18:** $^1H$ NMR (500 MHz, selected data) δ 9.70 (app br q, $J$ = 1.5 Hz, 1H), 7.67 (br d, $J$ = 7 Hz, 4H), 7.62-7.59 (m, 4H), 7.47-7.31 (m, 12H), 3.81 (app td, $J$ = 9, 2.5 Hz, 1H), 3.59 (dd, $J$ = 10, 5.5 Hz, 1H), 3.51-3.45 (m, 1H), 3.43 (dd, $J$ = 10, 5 Hz, 1H), 3.39 (ddd, $J$ = 10.5, 9, 4.5 Hz, 1H), 2.84 (app dq, $J$ = 16, 1.5 Hz, 1H), 2.31 (app ddd, $J$ = 16, 9, 3 Hz, 1H), 1.88-1.82 (m, 1H), 1.68-1.48 (m, 3H), 1.03 (s, 9H), 1.00 (s, 9H); $^{13}C$ NMR (125 MHz) δ 202.1, 135.9, 135.8, 135.5, 134.2, 133.6, 133.5, 133.2, 129.9, 129.7, 129.6, 127.8, 127.6, 127.5, 77.9, 77.8, 71.9, 66.4, 46.4, 32.7, 27.4, 27.0, 26.7, 19.3, 19.2; IR 2935, 2860, 1730, 1425, 1110, 702 $cm^{-1}$. $[\alpha]_{546}$ +22.4 (c = 8.1, $CHCl_3$).

**Oxidation of alcohol 17 to aldehyde 18.** To a solution of oxalyl chloride (10 μL, 0.115 mmol) in $CH_2Cl_2$ (2 mL) at –70 °C under argon was added dropwise a solution of DMSO (11 μL, 0.155 mmol) in $CH_2Cl_2$ (0.5 mL). After 30 min, a solution of **17** (25 mg, 0.038 mmol) in $CH_2Cl_2$ (0.5 mL) was added dropwise followed, after an additional 30 min, by $Et_3N$ (55 μL, 0.395 mmol). The reaction mixture was allowed to warm to –50 °C over 45 min and quenched with phosphate buffer (pH 7). Extractive workup (EtOAc/brine), followed by drying and

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(15) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

concentration afforded the crude aldehyde **18** in quantitative yield. The aldehyde was used in the subsequent Wittig reaction without further purification.

**Wittig-product 20.** To a solution of $C_8H_{17}PPh_3I$ (73 mg, 0.145 mmol) in 1 mL of THF was added NaHMDS (0.55 M in toluene, 300 μL, 0.165 mmol) at 0 °C. After 3 min at 0 °C a solution of aldehyde **18** (45 mg, 0.069 mmol) in 0.4 mL of THF was added. The ice-bath was removed and the reaction mixture was stirred for 2 h at RT, and quenched with phosphate buffer (0.5 mL, pH 7). After a few minutes $MgSO_4$ was added, followed by filtration and concentration. Purification by flash chromatography (2% EtOAc in hexanes) afforded 33 mg (68%) of alkene **20** as a colorless oil. **20:** $^1$ NMR (500 MHz, selected data) δ 7.69 (br t, $J$ = 7 Hz, 4H), 7.63 (br t, $J$ = 6.5 Hz, 4H), 7.45-7.31 (m, 12H), 5.52 (app br dt, $J$ = 11, 7.5 Hz, 1H), 5.40 (app dt, $J$ = 11, 7.5 Hz, 1H), 3.67-3.61 (m, 1H), 3.45-3.35 (m, 3H), 3.21 (app td, $J$ = 9, 2 Hz, 1H), 2.77 (app dd, $J$ = 15, 8 Hz, 1H), 1.98 (app br t, $J$ = 7 Hz, 2H), 1.91-1.83 (m, 1H), 1.81-1.76 (m, 1H), 1.05 (s, 9H), 1.00 (s, 9H), 0.88 (br t, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (125 MHz) δ 135.93, 135.90, 135.6, 134.8, 134.7, 133.8, 133.7, 131.0, 129.7, 129.52, 129.48, 127.60, 127.56, 127.53, 127.4, 126.3, 82.5, 77.6, 72.5, 66.8, 32.9, 31.9, 30.1, 29.7, 29.34, 29.26, 27.8, 27.6, 27.0, 26.8, 22.7, 19.3, 19.2, 14.1; IR 2920, 2850, 1412, 1090 cm$^{-1}$. $[\alpha]_{546}$ +23.3 (c = 2.2, $CHCl_3$).

**Tetrahydropyran alcohol 21.** To a solution of bis-silyl ether **20** (13 mg, 0.0174 mmol) in 2 mL of hexane was added 650 mg of activated neutral alumina.[13,16] The slurry was stirred at RT for 18 h. The mixture was diluted with MeOH (3 mL) and filtered through a plug of cotton (the additon of MeOH is essential to remove the product from the alumina). Evaporation of the solvent followed by flash chromatography (5%-12% EtOAc in hexanes) afforded 8.7 mg (98%) of alcohol **21** as a colorless oil. **21:** $^1$H NMR (500 MHz, $CDCl_3$) δ 7.72-7.66 (m, 4H), 7.44-7.41 (m, 2H), 7.41-7.36 (m, 4H), 5.48-5.40 (m, 2H), 3.50 (br d, $J$ = 8.5 Hz, 1H), 3.41-3.34 (m, 3H), 3.24 (app td, $J$ = 9.5, 2.5 Hz, 1H), 2.75 (ddd, $J$ = 15, 6, 2.5 Hz, 1H), 2.20-1.88 (m, 4H), 1.83-1.77 (m, 1H), 1.54-1.44 (m, 1H), 1.43-1.38 (m, 1H), 1.34-1.24 (m, 12H), 1.05 (s, 9H), 0.89 (br t, $J$ = 7Hz, 3H); $^1$H NMR (500 MHz, $C_6D_6$) δ 7.81-7.75 (m, 4H), 7.24-7.20 (m, 6H), 5.76 (app br dt, $J$ = 10.5, 7.5 Hz, 1H), 5.59 (app br dt, $J$ = 10.5, 7.5 Hz, 1H), 5.52 (ddd, $J$ = 13.5, 9.5, 5 Hz, 1H), 3.34 (app td, $J$ = 9.5, 2.5 Hz, 1H), 3.33-3.29 (m, 1H), 3.24 (br dd, $J$ = 11, 7 Hz, 1H), 3.13 (ddd, $J$ = 13, 6.5, 3 Hz, 1H), 3.06-2.98 (m, 1H), 2.24 (app br quintet, $J$ = 7.5 Hz, 1H), 2.15 (app br q, $J$ = 7 Hz, 1H), 1.80-1.75 (m, 1H), 1.70 (br s, 1H), 1.43-1.22 (m, 14H), 1.17 (s, 9H), 0.95-0.86 (m, 2H), 0.90 (br t, $J$ = 7Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 135.92, 135.89, 134.5, 133.6, 131.6, 129.7, 129.6,

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(16) The alumina was activated by heating at 120 °C for 14 h.

127.7, 127.4, 125.8, 82.3, 77 (overlaps with $CDCl_3$, see data recorded in $C_6D_6$ below), 72.3, 65.7, 32.7, 31.9, 30.1, 29.7, 29.3, 29.2, 27.5, 27.0, 26.7, 26.6, 22.7, 19.3, 14.1; $^{13}C$ NMR (125 MHz, $C_6D_6$; some signals in the aromatic region overlap with $C_6D_6$, and two signals in the aliphatic region overlap) δ 136.31, 136.26, 131.7, 130.1, 130.0, 128.3, 126.5, 82.6, 77.8, 72.9, 65.7, 33.3, 32.3, 30.7, 30.2, 29.8, 29.7, 28.0, 27.3, 26.8, 23.1, 19.6, 14.4; IR 3415, 2925, 2850, 1685, 1415, 1093, 702 $cm^{-1}$. $[\alpha]_{546}$ +20.1 (c = 1.4, $CHCl_3$). Anal. Calcd for $C_{32}H_{48}O_3Si$: C, 75.54; H, 9.51. Found: C, 75.24; H, 9.30.

**Tetrahydropyran aldehyde 22.** To a solution of oxalyl chloride (7.5 μL, 0.0866 mmol) in $CH_2Cl_2$ (1 mL) at –74 °C under argon was added dropwise a solution of DMSO (7.5 μL, 0.108 mmol) in $CH_2Cl_2$ (0.4 mL). After 30 min, a solution of **21** (22 mg, 0.043 mmol) in $CH_2Cl_2$ (0.5 mL) was added dropwise followed, after an additional 30 min, by $Et_3N$ (30 μL, 0.3 mmol). The reaction mixture was allowed to warm to –50 °C over 45 min and quenched with phosphate buffer (pH 7). Extractive workup (EtOAc/brine), drying, and concentration followed by flash chromatography (5% EtOAc in hexanes) afforded 18.8 mg (85%) of aldehyde **22** as a colorless oil. Small amount of compound resulting presumambly from the cleavage of the silyl group was also detected. **22**: $^1H$ NMR (500 MHz, $CDCl_3$, selected data) δ 9.55 (br s, 1H), 7.72-7.65 (m, 6H), 7.48-7.30 (m, 4H), 3.73 (dd, $J$ = 12, 1.5 Hz, 1H), 2.80 (ddd, $J$ = 14.5, 6.5, 1 Hz, 1H); 2.75-2.64 (m, 1H), 1.06 (s, 9H), 0.89 (d, $J$ = 7 Hz, 3H); $^{13}C$ (125 MHz) δ 201.8, 135.9 (2C), 134.3, 133.3, 131.9, 129.8, 129.7, 127.7, 127.5, 125.4, 82.7, 80.9, 71.6, 32.4, 31.9, 29.9, 29.6, 29.3, 29.2, 27.5, 27.0, 25.8, 22.7, 19.3, 14.1; IR 3415, 2930, 2855, 1085, 702 $cm^{-1}$.

**Primary alcohol 24.** To a solution of pivaloyl ester **23** (40 mg, 0.085 mmol) in 5 mL of THF 2.4 mL of aq LiOH (0.4 M) was added. After addition of methanol (0.5 mL), the mixture became clear. The reaction mixture was kept at 5 °C for 48 h. Extractive workup (EtOAc/brine), drying, and concentration followed by flash chromatography (20% EtOAc in hexanes) afforded 25.5 mg (78%) of alcohol **24** as a colorless oil. **24:** $^1H$ NMR (500 MHz, selected data) δ 7.28-7.23 (m, 4H), 7.13-7.09 (m, 1H), 6.54 (dd, $J$ = 15.5, 5 Hz, 1H), 5.49 (dd, $J$ = 15.5, 1.5 Hz, 1H), 4.85 (app td, $J$ = 11, 4.5 Hz, 1H), 4.53-4.47 (m, 1H), 4.19-4.13 (m, 1H), 3.69 (dd, $J$ = 11.5, 3.5 Hz, 1H), 3.51 (dd, $J$ = 11.5, 6 Hz, 1H), 1.30 (s, 3H), 1.22 (s, 3H), 0.86 (d, $J$ = 6.5 Hz, 3H); $^{13}C$ NMR (125 MHz) δ 165.6, 151.5, 147.2, 127.9, 125.4, 125.0, 120.9, 79.6, 77.9, 74.5, 64.9, 50.5, 41.7, 39.8, 34.6, 31.9, 31.3, 27.3, 27.2, 26.6, 25.6, 21.8; IR 3415, 2955, 2916, 1722, 1280, 1182, 700 $cm^{-1}$. $[\alpha]_{546}$ +16.7 (c = 1.6, $CHCl_3$). FAB-HRMS $(M - H)^+$ calcd for $C_{24}H_{34}O_4$ 385.2379, found 385.2352.

**Acknowledgment**. We thank the Danish Technical Science Research Council (STVF), the Danish Natural Science Research Council (SNF), the Salén Foundation (Sweden), and the Estonian Science Foundation (grant no 4230) for financial support. We are also grateful to Professor Tõnis Pehk, National Institute of Chemical Physics and Biophysics, Tallinn, for skilful assistance with NMR experiments. Mrs. Nonka Sevova, University of Notre Dame, is gratefully acknowledged for assistance with HRMS analyses.

VI

Appendix:
Vares, L. Supplementary Material.

# Appendix: Supplementary material[1]

Lauri Vares

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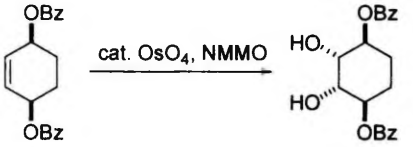
**General methods:** All solvents were distilled prior to use. All reactions were carried out in oven dried glassware unless water was used as a reaction medium. Commercial reagents were generally used as received. TLC analyses were performed on Merck aluminum-backed F254 silica gel plates, using UV light and phosphomolybdic acid for visualization. Drying of organic phases obtained from extractive workup was generally done with $MgSO_4$. Flash chromatography was performed as described by Still and coworkers[2] using either Merck silica gel 60 (230-400 mesh), Amicon Matrex 60Å silica gel (35-70 μm), or Chemapol silica gel L 40/100. NMR spectra were recorded in $CDCl_3$ unless otherwise indicated, using $CHCl_3$ (δ 7.26 ppm) and $CDCl_3$ (δ 77.0 ppm) as internal references for $^1H$ and $^{13}C$, respectively. IR spectra were recorded neat as a thin films using AgCl or KBr plates. HRMS analyses were perfomed at the Department of Chemistry and Biochemistry, University of Notre Dame, USA.

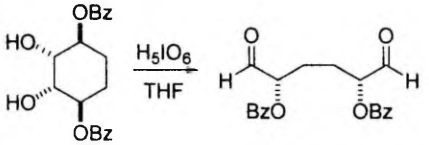



**68c** **71c**

**Diol 71c.** To a solution of alkene **68c**[3] (277 mg, 0.86 mmol) and *N*-methyl morpholine *N*-oxide (161 mg, 1.371 mmol) in a mixture of THF, *t*-butanol and $H_2O$ (13 mL,7 mL and 3 mL respectively), 530 μL of a 2.5 wt.-% solution of $OsO_4$ in *t*- butanol (0.041 mmol) was added. After 8 h at RT 250 μL of $OsO_4$ solution was added and reaction mixture was warmed up to 50 °C. After additional stirring

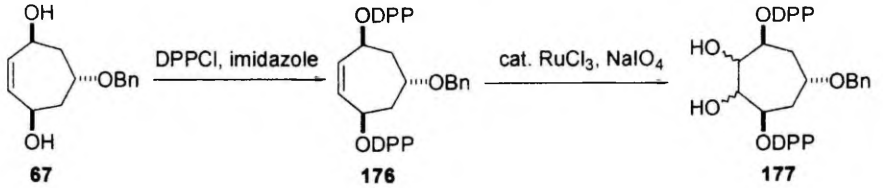
(1) Numbering of compounds is consistant with the numbering in the thesis.
(2) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(3) Bäckvall, J.-E.; Granberg, K. L.; Hopkins, R. B. *Acta Chem. Scand.* **1990**, *44*, 492.

at 50 °C for 2 days, the reaction was quenched by the addition of $NaS_2O_3$ (3 mL, 20% aq solution). Dilution with brine followed by extraction (EtOAc), drying and concentration afforded a crude dihydroxylation product. Purification by flash chromatography (10%-40% EtOAc in hexanes) afforded 44 mg (14%) of starting alkene and 219 mg (71.5%) of diol **71c** as a white crystalline compound. **71c**: (*Rf* = 0.12, hexanes/EtOAc 3/1); $^1$H NMR (250 MHz) δ 8.10-8.04 (m, 4H), 7.63-56 (m, 2H), 7.51-7.43 (m, 4H), 5.40-5.31 (m, 2H), 4.17 (dd, *J* = 8.3, 2.5 Hz, 2H), 3.00 (br s, 2H), 2.21-2.09 (m, 2H), 2.02-1.87 (m, 2H); $^{13}$C NMR (62.5 MHz) δ 166.4, 133.3, 129.9, 129.7, 128.5, 73.0, 71.6, 24.0.



**71c** **62c**

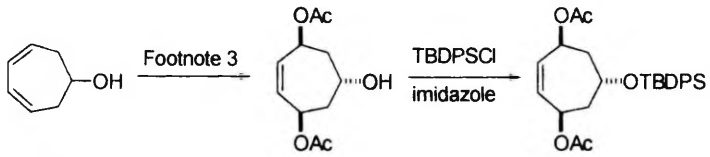
**Dialdehyde 62c.** To a solution of diol **71c** (219 mg, 0.615 mmol) in THF (10 mL) was added a solution of $H_5IO_6$ (141 mg, 0.615 mmol) in THF (10 mL) at 0 °C. After 90 min at RT 4 mL phosphate buffer (pH 7) followed by ca. 5 mL of brine was added. The solution was extracted with EtOAc, dried and concentrated to give 146 mg (67%) of dialdehyde **62c** as a white crystalline compound containing ca. 5% of isomeric aldehyde product. The dialdehyde was used in HWE reactions without further purification. $^1$H NMR (250 MHz) δ 9.42, (s, 2H), 7.86-7.77 (m,4H), 5.08-5.02 (m, 2H), 2.03-1.82 (m, 4H).



**67** **176** **177**

**Diol 177.** To a solution of diol **67** (247 mg, 1.05 mmol) and imidazole (428 mg, 6.3 mmol) in the mixture of $Et_2O$ (8 mL) and $CH_2Cl_2$ (8 mL) DPPCl (600 μL, 3.15 mmol) was added. After stirring the reaction mixture for 12 h at RT, dilution with brine, extraction (EtOAc), drying, and concentration afforded the crude reaction product. Purification by flash chromatography (50% EtOAc in hexane) afforded 427 mg of protected diol **176**. The DPP-protected diol **176** (88 mg, 0.139 mmol) was dissolved in the mixture of EtOAc (1 mL), $CH_3CN$ (1 mL) and $H_2O$ (0.5 mL),

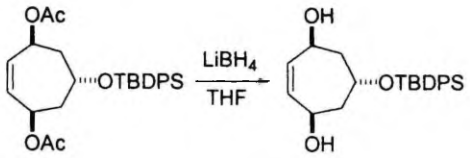
and cooled down to 0 °C. $RuCl_3$ hydrate (2.1 mg, 0.0097 mmol) and $NaIO_4$ (45 mg, 0.21 mmol) was then added to the alkene solution. The two phase mixture was vigorously stirred for 90 seconds, and then quenced with 20% aq solution of $Na_2S_2O_3$ (ca. 5 mL). The aqueous phase was separated and extracted with diethyl ether. The combined organic extracts were dried over and concentrated. Flash chromatography (3-5% MeOH in $CHCl_3$) afforded 57 mg (61%) of diol **177** as a white crystalline compound. Only one stereoisomer was detected by $^1H$ NMR spectroscopy. **177**: (R*f* = 0.21, $CHCl_3$/MeOH 19/1); $^1H$ NMR (500 MHz) δ 7.80-7.72 (m, 8H), 7.54-7.40 (m, 12H), 7.28-7.21 (m, 5H), 4.66-4.60 (m, 2H), 4.54 (br s, 2H), 4.40 (s, 2H), 4.21-4.16 (m, 2H), 3.86 (br t, *J* = 8.5 Hz, 1H), 2.33-2.30 (m, 2H), 2.30-2.26 (m, 2H); $^{13}C$ NMR (125 MHz) δ 138.2, 132.4 (d), 131.8, 131.7, 131.6, 131.5, 131.4, 131.3, 130.2, 128.73, 128.66, 128.63, 128.56, 128.3, 127.6, 127.5, 75.6 (d), 73.7, 69.9, 69.2, 37.9.




**178** **179** **180**

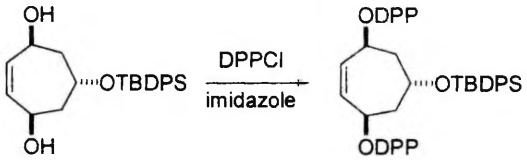
**Silyl-ether 180.** To a solution of alcohol **179** (293 mg, 1.28 mmol), obtained from dienol **178** after diacetoxylation,[4] and imidazole (261 mg, 3.84 mmol) in 3 mL of DMF TBDPSCl (0.5 mL, 1.92 mmol) was added. After stirring for 16 h at RT the reaction mixture was diluted with brine, extracted (EtOAc), dried, and concentrated to give the crude silylation product. Purification by flash chromatography (5% EtOAc in hexanes) afforded 280 mg (47%) of **180** as a colorless oil. $^1H$ NMR (500 MHz) δ 7.73-7.68 (m, 4H), 7.46-7.35 (m, 6H), 5.94 (br d, *J* = 11.5, 2H), 5.67 (br s, 2H), 4.26-4.21 (m, 1H), 2.04 (s, 6H), 1.87 (ddd, *J* = 13, 5.5, 2.5 Hz, 1H), 1.69 (ddd [app td, *J* = 11, 2 Hz, 2H), 1.13 (s, 9H); $^{13}C$ NMR (125 MHz) δ 169.8, 135.9, 134.8, 133.6, 132.8, 129.7, 127.7, 68.7, 67.3, 39.7, 26.9, 21.2, 19.1.

(4) Johnson, C. R.; Bis, S. J. *J. Org. Chem.* **1995**, *60*, 615.



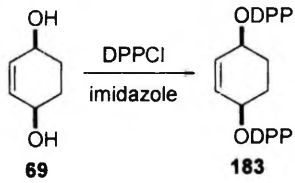

**180** **181**

**Diol 181.** To a solution of diacetat **180** (233 mg, 0.499 mmol) in 8 mL of THF $LiBH_4$ (32 mg, 1.47 mmol) was added. After stirring for 16 h at RT the reaction mixuture was diluted with brine, extracted with EtOAc, dried, concentarted, and subsequent purification by flash chromatography (10%-50% EtOAc in hexanes) afforded 83 mg (44%) of diol **181** as a white crystalline compound. **181**: (*Rf* = 0.33, hexanes/EtOAc 3/1); $^1$H NMR (500 MHz) δ 7.69 (br d, *J* = 7.5 Hz, 4H), 7.47-7.36 (m, 6H), 5.74 (s, 2H), 4.83 (d, *J* = 10.5 Hz, 2H), 4.29 (br s, 1H), 1.82 (br dd, *J* = 13, 5 Hz, 2H), 1.67-1.56 (m, 4H), 1.11 (s, 9H); $^{13}$C NMR (125 MHz) δ 135.75, 135.69, 134.0, 129.8, 127.7, 68.2, 65.9, 43.3, 27.1, 19.3.



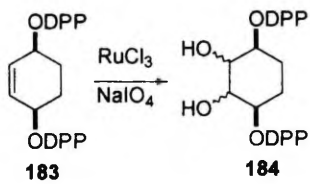

**181** **182**

**Alkene 182.** The diol **181** (82 mg, 0.214 mmol) was dissolved in 2 mL of $CH_2Cl_2$ followed by the addition of imidazole (87 mg, 1.28 mmol) and DPPCl (122 μL, 0.64 mmol). After stirring for 60 min at RT the reaction mixture was concentrated. The purification by flash chromatography (25-75% EtOAc in hexanes) afforded 164 mg (98%) of DPP-protected diol **182** as a white crystalline compound. **182**: (*Rf* = 0.18, hexanes/EtOAc 1/1); $^1$H NMR (500 MHz) δ 7.78-7.69 (m, 8H), 7.57-7.30 (m, 22H), 5.95 (s, 2H), 5.34 (t, *J* = 10 Hz, 2H), 4.24-19 (m, 1H), 2.11 (ddd, *J* = 13.5, 6, 2.5 Hz, 2H), 1.98-1.91 (m, 2H), 0.88 (s, 9H); $^{13}$C NMR (125 MHz) δ 135.8, 133.6, 133.6, 133.3, 132.0, 131.6, 131.5, 131.06, 131.02, 129.6, 128.5, 128.4, 127.6, 71.1 (d, *J* = 6 Hz), 42.0 (d, *J* = 3.9 Hz), 26.9, 20.9, 18.9.



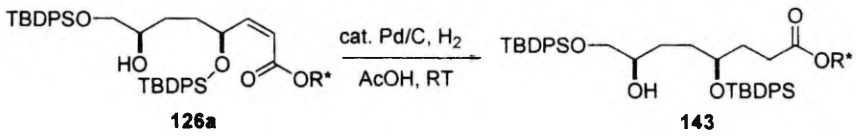
**69** **183**

**Alkene 183.** To a solution of diol **69** (273 mg, 2.39 mmol) in the mixture of $Et_2O$ (4 mL) and $CH_2Cl_2$ (5 mL) imidazole (976 mg, 14.34 mmol) and DPPCl (1.35 mL, 7.18 mmol) was added. After stirring for 25 min at RT the resulting slurry was diluted with $Et_2O$, filtered through the pad of celite, washed with 1 M $H_2SO_4$, 2 M NaOH, water, and brine. The combined organic extracts were dried and concentrated to give 583 mg of crude product. Purification by flash chromatography (3% MeOH in $CH_2Cl_2$) yielded 346 mg (28%) of protected diol **183** as a viscous oil which slowly solidified. **183**: (*Rf*= 0.28, $CH_2Cl_2$/MeOH 32/1); $^1$H NMR (250 MHz) δ 7.86-7.75 (m, 8H), 7.55-7.37 (m, 12H), 5.89 (s, 2H), 4.88-4.77 (m, 2H), 2.19-2.03 (m, 2H), 1.92-1.76 (m, 2H).



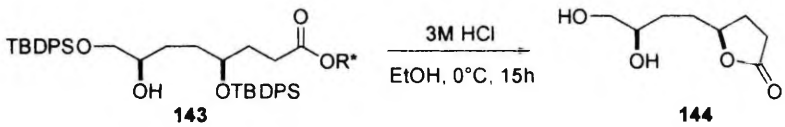
**183** **184**

**Diol 184.** A solution of alkene **183** (123 mg, 0.239 mmol) in the mixture of $CH_2Cl_2$ (1 mL), $CH_3CN$ (1 mL) and $H_2O$ (0.8 mL) was cooled down to 0 °C. $RuCl_3$ hydrate (3.6 mg, 0.016 mmol) and $NaIO_4$ (77 mg, 0.36 mmol) was then added to the alkene solution. The two phase mixture was vigorously stirred for 70 seconds, and then quenced with 20% aq solution of $Na_2S_2O_3$ (ca. 5 mL). The aqueous phase was separated and extracted with $CH_2Cl_2$. The combined organic extracts were dried over and concentrated. Flash chromatography (3-5% MeOH in $CH_2Cl_2$) afforded 83 mg (63%) of diol **184** as a white crystalline compound. Only one stereoisomer was detected by $^1$H NMR spectroscopy. **13**: $^1$H NMR (250 MHz) δ 7.86-7.75 (m, 8H), 7.56-7.38 (m, 12H), 4.54-4.41 (m, 2H), 4.30 (br s, 2H), 4.09 (d, *J* = 5.5 Hz, 2H), 2.07-1.93 (m, 2H), 1.90-1.76 (m, 2H).



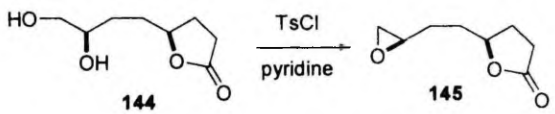

126a 143

**Alcohol 143.** To a solution of alkene **126a** (51 mg, 0.0579 mmol) in 1.5 mL of AcOH was added 23 mg of catalyst (10% Pd on carbon) and stirred under hydrogen atmosphere for 20 h.Then the solution was filtered through the pad of celite and concentrated. The residue (50 mg, 0.0566 mmol, 98%) was a colorless oil, which was spectrospopically pure and needed no further purification. $^1$H NMR (500 MHz, selected data) δ 7.69-7.57 (m, 8H), 7.47-7.16 (m, 16H), 7.07-7.02 (m, 1H), 4.76 (ddd [app td], $J$ = 10.5, 4.5 Hz, 1H), 3.62 (br t, $J$ = 5 Hz, 1H), 3.52-3.44 (m, 1H), 3.48 (dd, $J$ = 10.5, 7.5 Hz, 1H), 3.33 (dd, $J$ = 10.5, 8.5 Hz, 1H), 1.26 (s, 3H), 1.18 (s, 3H), 1.05 (s, 9H), 1.02 (s, 9H), 0.86 (d, $J$ = 6.5 Hz, 3H).




143 144

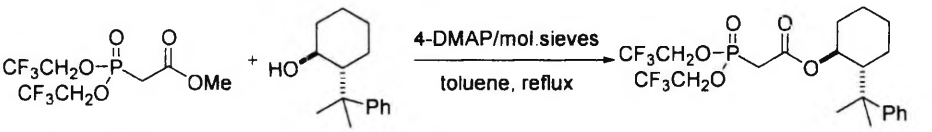
**Lactone 144** :To a solution of bis-silyl ether **143** in 2 mL of EtOH ca. 0.5 mL 3 M HCl was added. After stirring the reaction for 19 h at 50 °C ca. 0.5 g of silica gel was added. Solvents were evaporated and the crude lactone on silica gel was pourned into the partly filled flash chromatography column. Elution of the column with 10% MeOH in $CHCl_3$ afforded 5.5 mg (95%) of a lactone **144** as a colorless oil. **144**: ($Rf$ = 0.26, $CHCl_3$/MeOH 9/1); $^1$H NMR (500 MHz) δ 4.55-4.49 (m, 1H), 3.78-3.72 (m, 1H), 3.67 (dd, $J$ = 11.0, 3.0 Hz, 1H), 3.51-3.44 (m, 1H), 2.80 (ddd, $J$ = 19.0, 9.6, 1.0 Hz, 1H), 2.73 (ddd, $J$ = 19.0, 9.6, 1.0 1H), 2.36 (app sextet, $J$ = 6.4 Hz, 1H), 1.93-1.84 (m, 2H), 1.81-1.72 (m, 1H), 1.70-1.62 (m, 1H), 1.56-1.48 (m, 1H); $^{13}$C NMR (125 MHz) δ 177.2, 81.1, 71.7, 66.7, 32.0, 29.1, 28.8, 28.1.




144 145

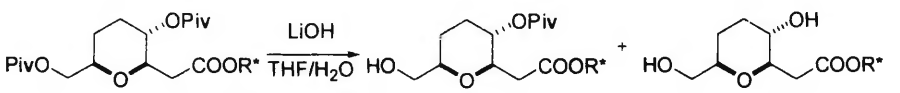
**Epoxide 145.** To a solution of diol **144** (5.5 mg, 0.315 mmol) in 250 μL of pyridine TsCl (30 mg, 0.16 mmol) was added. The reaction mixture was stirred for 12 h at 80 °C, then cooled down, diluted with $CHCl_3$ (ca. 0.2 mL), and subsequent purification by flash chromatography (10-25% EtOAc in hexanes) afforded 3.6 mg

(76%) of epoxide **145** as a colorless oil. **144**: (*Rf* = 0.2, hexanes/EtOAc 3/1); $^1$H NMR (500 MHz) δ 4.57-4.50 (m, 1H), 4.12-4.05 (m, 1H), 3.79 (dd, *J* = 11, 5 Hz, 1H), 3.65 (dd, *J* = 11, 7.5 Hz, 1H), 2.56 (dd, *J* = 9.5, 7 Hz, 2H), 2.38 (sextet, *J* = 6.5 Hz, 1H), 2.19-2.11 (m, 1H), 2.01-1.88 (m, 2H), 1.85-1.78 (m, 1H), 1.61-1.51 (m, 1H); $^{13}$C NMR (125 MHz) δ 176.7, 79.6, 60.1, 47.8, 31.8, 30.8, 28.7, 28.0.




**77d** **79** **80**

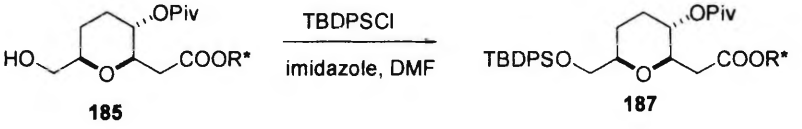
**Phosphonate 80**: Prepared from methyl bis(trifluoroethyl) phosphonoacetate **77d** and chiral alcohol **79** in 93% yield by simple transesterification according to the procedure described in Paper I for phosphonates **58b** and **58d**. **80**: $^1$H NMR (500 MHz, selected data) δ 7.31-7.28 (m, 4H), 7.16-7.11 (m, 1H), 4.81 (ddd [app td], *J* = 10.5, 4.5 Hz, 1H), 4.45-4.27 (m, 4H), 2.27 (ddd, *J* = 26, 20.5, 16 Hz, 2H), 2.12 (app td, *J* = 11.5, 3.5 Hz, 1H), 1.94 (br d, *J* = 13 Hz, 1H), 1.87-1.82 (m, 1H), 1.77-1.67 (m, 2H), 1.30 (s, 3H), 1.18 (s, 3H); $^{13}$C NMR (125 MHz) δ 164.1, 151.9, 128.1, 125.3, 125.1, 123.7, 121.1, 76.3, 62.4 (qd, *J* = 19.6, 5.5 Hz), 62.3 (qd, *J* = 19.6, 5.5 Hz), 50.5, 39.5, 33.4 (d, *J* = 144 Hz), 32.9, 30.0, 26.6, 25.8, 24.6, 22.1; IR 2964, 2918, 1730, 1300, 1268, 1180, 1070, 960 cm$^{-1}$.




**138b** **185** **186**

**Alcohol 185 and Diol 186.** To a solution of bis-pivaloyl ester **138b** (91 mg, 0.159 mmol) in the mixture of THF/MeOH (3/0.5 mL) 2.4 mL 0.4 M LiOH was added. The reaction mixture was stirred for 6 h at room temperature followed by storing in the fridge (at 5 °C) overnight (16 h). The progress of the reaction was carefully followed by TLC analyses (50% EtOAc in hexanes). The reaction mixture was diluted with phosphate buffer (pH 7) followed by extractive workup (EtOAc/brine), drying, and concentartion. Purification by flash chromatography (gradual elution 1.5% up to 75% EtOAc in hexanes) afforded 19.5 mg (21%) of

unreacted starting material **138b** (21%), 32 mg (41%) of alcohol **185**,[5] 16.5 mg (26%) of diol **186**, and 4 mg (10%) of 8-phenylmenthol[6] as a colorless oils. **185**: (*Rf* = 0.13, hexanes/EtOAc 3/1); $^1$H NMR (500 MHz, selected data) δ 7.29-7.21 (m, 4H), 7.13-7.09 (m, 1H), 4.84 (ddd [app td], *J* = 10.5, 4.5 Hz, 1H), 4.37 (br td, *J* = 10, 5 Hz, 1H), 3.72 (td, *J* = 9.5, 2.5 Hz, 1H), 3.54 (br d, *J* = 8.5 Hz, 1H), 3.49-3.41 (m, 2H), 1.30 (s, 3H), 1.22 (s, 3H), 1.20 (s, 9H), 0.85 (d, *J* = 6.5 Hz, 3H); $^{13}$C NMR (125 MHz) δ 177.4, 170.6, 151.2, 127.8, 125.4, 125.2, 77.7, 76.2, 74.6, 70.9, 65.3, 50.2, 41.9, 39.8, 38.7, 37.8, 34.4, 31.2, 28.5, 27.15, 27.06, 26.6, 26.1, 25.8, 21.7; IR 3445, 2955, 2925, 1725, 1280, 1155, 715 cm$^{-1}$. $[\alpha]_{546}$ +28.2 (c = 1.67, $CHCl_3$). FAB-HRMS $(M+H)^+$ calcd for $C_{29}H_{45}O_6$ 489.3216, found 489.3216. **186**: (*Rf* = 0.13, hexanes/EtOAc 1/1); $^1$H NMR (500 MHz, selected data) δ 7.30-7.28 (m, 4H), 7.15 (br quint, *J* = 4 Hz, 1H), 4.83 (ddd [app td], *J* = 10.5, 4.5 MHz, 1H), 3.57-3.51 (m, 1H), 3.44-3.38 (m, 2H), 3.37-3.31 (m, 1H), 3.27-3.21 (m, 1H), 2.28 (dd, *J* = 15, 5 Hz, 1H), 2.12-2.07 (m, 1H), 2.06-2.00 (m, 1H), 1.95 (dd, *J* = 15, 6.5 Hz, 1H), 1.31 (s, 3H), 1.21 (s, 3H), 0.87 (d, *J* = 6.5 Hz, 3H); $^{13}$C NMR (125 MHz) δ 171.2, 151.7, 128.0, 125.4, 125.1, 78.3, 77.6, 74.9, 70.2, 65.5, 50.3, 41.7, 39.7, 38.4, 34.5, 32.1, 31.3, 28.1, 26.55, 26.51, 24.7, 21.8. IR 3418, 2950, 2924, 1710, 1095, 1050 cm$^{-1}$.



**185** **187**

**Silyl-ether 187.** To a solution alcohol **185** (10 mg, 0.02 mmol, includes also ca 15% of unknown by-product) in 1.5 mL of dry DMF imidazole (4 mg, 0.05 mmol) and TBDPSCl (10 μL, 0.036 mmol) was added.. After stirring the reaction mixture at room temperature for 2 days, the extractive workup (EtOAc/brine), drying, evaporation of the solvents followed by the flash chromatography (gradual elution from 2% up to 10% EtOAc in hexanes) afforded 12 mg (80%, or 95% based on pure starting material) of silyl ether **187** as a colorless oil. **187**: (*Rf* = 0.31, hexanes/EtOAc 19/1); $^1$H NMR (500 MHz, selected data) δ 7.62 (td, *J* = 6.5, 1.5 Hz, 4H), 7.42-7.31 (m, 6H), 7.25-7.20 (m, 4H), 7.13-7.08 (m, 1H), 4.81 (td, *J*

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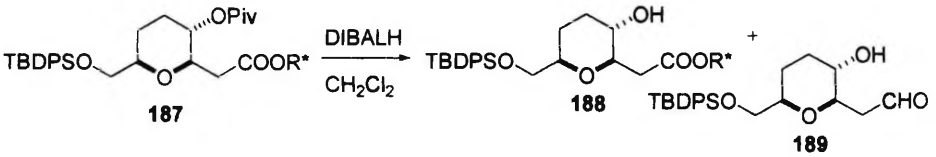
(5) Unfortunately, the alcohol **185** obtained contained also ca 10%-15% of unidentified by-product. However, during the conversion of alcohol **185** into the silyl ether **187**, the by-product remaides unreacted, and was thus easily separated. Characteristic peaks of the by-product: $^1$H NMR (500 MHz) δ 3.96 (br d, *J* = 6 Hz); $^{13}$C NMR (125 MHz) δ 78.3, 74.9, 70.1, 66.1, 41.6.

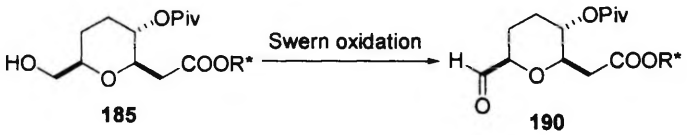
(6) The corresponding carboxylic acid was apparently lost during the workup into the water phase.

= 11, 4 Hz, 1H), 4.37 (td, $J$ = 10, 5 Hz, 1H), 3.73 (td, $J$ = 10, 2.5 Hz, 1H), 3.66 (br d, $J$ = 5 Hz, 1H), 3.50-3.43 (m, 2H), 2.19-2.14 (m, 1H), 2.13 (dd, $J$ = 15, 2.5 Hz, 1H), 1.27 (s, 3H), 1.20 (s, 9H), 1.178 (s, 3H), 1.02 (s, 9H), 0.70 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (125 MHz) δ 177.5, 170.6, 151.2, 135.6, 135.5, 133.5, 129.6, 127.8, 127.6, 125.4, 125.1, 77.5, 76.5, 74.6, 71.3, 66.2, 50.2, 41.7, 39.8, 38.7, 38.0, 34.4, 31.2, 28.7, 27.4, 27.1, 26.8, 26.7, 26.5, 26.4, 21.6, 19.2; IR 2955, 2930, 2855, 1730, 1280, 1160, 1115, 735, 700 cm$^{-1}$.



187 188 189

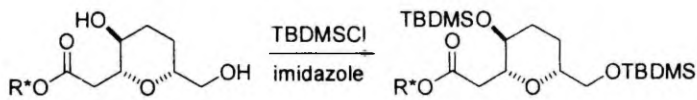
**Alcohol 188 and Alhehyde 189.** To a solution of bis-ester **187** (23 mg, 0.0316 mmol) in 2 mL of $CH_2Cl_2$ 23 μL (0.034 mmol) DIBALH (1.5 M solution in toluene) was added dropwise at -80 °C. After stirring the reaction mixture at -80 °C for 1 h Rochelle salt (ca. 400 mg) was added, and the the slurry was warmed slowly up to room temperature. Extractive workup (EtOAc/brine), drying, concentration followed by flash chromatography afforded 8.2 mg (40%) of alcohol **188**, 3.2g (25%) of aldehyde **189**, and 3.5 mg (48%) of 8-phenylmenthol **78**. **188**: $^1$H NMR (500 MHz, selected data) δ 7.65-7.61 (m, 4H), 7.42-7.32 (m, 6H), 7.28 (app br d, $J$ = 4 Hz, 4H), 7.15-7.10 (m, 1H), 4.81 (td, $J$ = 10.7, 4.3 Hz, 1H), 3.65 (dd, $J$ = 10.0, 4.8 Hz, 1H), 3.46 (dd, $J$ = 10.0, 6.02 Hz, 1H), 3.44-3.39 (m, 1H), 3.39-3.29 (m, 1H), 3.23 (app br td, $J$ = 9.8, 4.1 Hz, 1H), 2.26 (dd, $J$ = 15.3, 5.3 Hz, 1H), 1.29 (s, 3H), 1.18 (s, 3H), 1.03 (s, 9H), 0.79 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (125 MHz) δ 171.4, 151.6, 135.62, 135.56, 133.7, 133.6, 129.5, 127.9, 127.6, 125.5, 125.1, 78.2, 77.6, 74.9, 70.6, 66.5, 50.3, 41.7, 39.7, 38.8, 34.5, 32.4, 31.3, 27.8, 27.7, 26.8, 26.6, 25.1, 21.7, 19.3; **189**: $^1$H NMR (500 MHz, selected data) δ 9.78 (br s, 1H), 7.66 (br d, $J$ = 7.5 Hz, 4H), 7.44-7.35 (m, 6H), 3.68 (br dd, $J$ = 9, 5 Hz, 1H), 3.66-3.60 (m, 1H), 3.55 (dd, $J$ = 10.5, 5 Hz, 1H), 3.34 (br td, $J$ = 10, 4 Hz, 1H), 2.82 (br d, $J$ = 15.5 Hz, 1H), 2.55 (ddd, $J$ = 16, 8, 2.5 Hz, 1H), 1.04 (s, 9H).



185 190

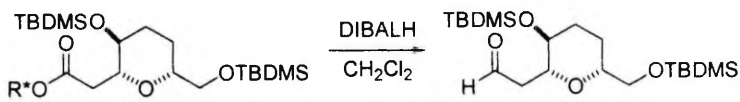
**Aldehyde 190.** To a solution of oxalyl chloride (10 μL, 0.115 mmol) in $CH_2Cl_2$ (2 mL) at –75 °C under argon was added dropwise a solution of DMSO (11 μL,

0.155 mmol) in $CH_2Cl_2$ (0.5 mL). After 30 min, a solution of **185** (20 mg, 0.039 mmol) in $CH_2Cl_2$ (0.5 mL) was added dropwise followed, after an additional 30 min, by $Et_3N$ (55 μL, 0.395 mmol). The reaction mixture was allowed to warm to –50 °C over 45 min and quenched with phosphate buffer (pH 7). Extractive workup (EtOAc/brine), followed by drying and concentration afforded the crude aldehyde **18**. Purification by flash chromatography (5-12% EtOAc in hexanes) afforded 10.5 mg (53%) of aldehyde **190** as a colorless oil. The aldehyde was obtained togetether with a small amount (ca. 10%) of unidentified byproduct. **190**: $^1$H NMR (500 MHz, selected data) δ 9.54 (s, 1H), 7.29-7.21 (m, 4H), 7.13-7.08 (m, 1H), 4.86 (td, $J$ = 10.5, 4.5 Hz, 1H), 4.40 (td, $J$ = 10, 4.5 Hz, 1H), 3.79 (app br qd, $J$ = 10, 2.5 Hz, 2H), 2.15 (dd, $J$ = 15.5, 3 Hz, 1H), 1.30 (s, 3H), 1.21 (s, 9H), 0.86 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (125 MHz) δ 200.7, 177.3, 170.4, 151.2, 127.8, 125.4, 125.2, 80.8, 76.5, 74.8, 70.2, 50.2, 41.8, 39.7, 38.8, 37.7, 34.4, 31.3, 28.3, 27.3, 27.0, 26.6, 25.6, 25.3, 21.8.



**186** **191**

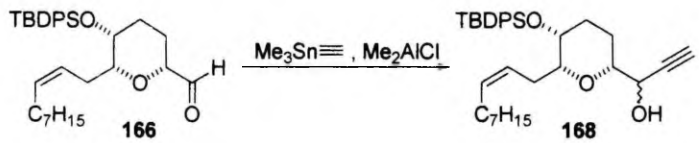
**Bis-silyl ether 191.** To a solution diol **186** (20 mg, 0.049 mmol) in 1 mL of dry DMF imidazole (17 mg, 0.25 mmol) and TBDMSCl (30 mg, 0.2 mmol) was added. After stirring at RT for 16 h, the reaction mixture was diluted with brine, extracted (EtOAc), dried, concentrated, and purified by flash chromatography (2% EtOAc in hexanes) to afford 19 mg (63%) of bis-silyl ether **191** as a colorless oil. $^1$H NMR (500 MHz, selected data) δ 7.29-7.22 (m, 4H), 7.14-7.09 (m, 1H), 4.86 (td, $J$ = 11, 4.5 Hz, 1H), 3.60 (dd, $J$ = 9.5, 4 Hz, 1H), 3.94 (br td, $J$ = 10.5, 2.5 Hz, 1H), 3.37 (dd, $J$ = 9.5, 7 Hz, 1H), 3.35-3.28 (m, 1H), 3.21 (br td, $J$ = 10.5, 4.5 Hz, 1H), 2.46 (dd, $J$ = 14.5, 2.5 Hz, 1H), 1.32 (s, 3H), 1.23 (s, 3H), 0.88 (s, 9H), 0.85 (s, 9H), 0.046 (s, 3H), 0.043 (s, 3H), 0.002 (s, 3H), -0.004 (s, 3H); $^{13}$C NMR (125 MHz) δ 171.5, 151.3, 127.8, 125.5, 125.1, 79.5, 77.3, 74.4, 71.0, 65.8, 50.4, 41.9, 39.9, 38.5, 34.5, 32.9, 31.2, 27.9, 26.8, 26.5, 26.4, 25.9, 25.8, 21.8, 18.3, 17.9, -4.0, -4.7, -5.32, -5.35; IR 2955, 2930, 2958, 1725, 1255, 1095, 838, 775 cm$^{-1}$.



**191** **192**

**Aldehyde 192.** To a solution of ester **191** (18 mg, 0.029 mmol) in 3 mL $CH_2Cl_2$, a solution of DIBALH (1 M in hexanes, 24 μL) was added at –78 °C.

After stirring for 1 h at –78 °C, ca 100 mg of Rochelle salt was added and the reaction mixture was warmed up to RT. Extractive workup ($CH_2Cl_2$/brine) and subsequent purification by flash chromatography (1-4% EtOAc in hexanes) afforded 4.5 mg (39%) of aldehyde **192**, 2.5 mg (37%) of 8-phenylmenthol **78**, and 4 mg (23%) of unreacted ester was recovered. $^1$H NMR (500 MHz, selected data) δ 9.77 (app br q, $J$ = 1.5 Hz, 1H), 3.67 (td, $J$ = 9, 3.5 Hz, 1H), 3.65-3.57 (m, 1H), 3.51-3.40 (m, 2H), 3.36-3.28 (m, 1H), 2.77 (br dd, $J$ = 3.5, 2 Hz, 1H), 2.73 (br dd, $J$ = 3.5, 2 Hz, 1H), 2.48-2.38 (m, 1H), 2.08-2.01 (m, 1H), 1.78 (br d, $J$ = 14.5 Hz, 1H), 0.874 (s, 9H), 0.867 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.031 (s, 3H), 0.029 (s, 3H); $^{13}$C NMR (125 MHz) δ 202.0, 78.1, 77.9, 71.1, 66.0, 46.6, 32.9, 27.6, 25.9, 25.7, 17.91, 17.89, -4.0, -4.8, -5.25, -5.35; IR 2955, 2930, 2863, 1730, 1250, 1105, 835 cm$^{-1}$.




**Alcohol 168.** To a solution of aldehyde **166** (16.4 mg, 0.032) in 1 mL of $CH_2Cl_2$ 167 μL $Me_2AlCl$ (0.16 mmol, 1 M in hexane) and 18 mg trimethylstannylacetylene[7] (0.048 mmol, purity ca. 50%) in 0.25 mL of $CH_2Cl_2$ was added at –84 °C. Reaction was allowed to warm up to RT over 12 h, diluted with brine, extracted (EtOAc), dried and concentrated to give colorless oil as a crude reaction product. Two diasteromeric alcohols were detected by NMR (ratio ca. 55:45). **168 major**: $^1$H NMR (500 MHz) δ 7.73-7.66 (m, 4H), 7.45-7.36 (m, 6H), 5.48-5.40 (m, 2H), 4.35 (br s, 1H), 4.07 (dd, $J$ = 7.5, 2 Hz, 1H), 3.45-3.30 (m, 2H), 3.26 (td, $J$ = 9.5, 2 Hz, 1H), 2.78-2.70 (m, 1H), 2.38 (dd, $J$ = 10.5, 2 Hz, 1H), 2.02-1.91 (m, 2H), 1.87-1.79 (m, 1H), 1.77-1.70 (m, 1H), 1.62-1.52 (m, 2H), 1.52-1.40 (m, 1H), 1.33-1.24 (m, 10H), 1.05 (s, 9H), 0.89 (t, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (125 MHz, selected signals) δ 135.9 (2C), 131.9, 131.7, 129.8, 129.6, 127.7, 127.5, 125.7, 125.4, 82.5, 81.3, 78.5, 74.0, 72.1, 65.5, 32.5, 31.8, 30.0, 29.6, 29.3, 29.2, 27.5, 27.0, 26.7, 26.6, 24.9, 14.1; **168 minor**: $^{13}$C NMR (125 MHz, selected signals) δ 135.9 (2C), 131.9, 131.7, 129.8, 129.6, 127.7, 127.5, 125.7, 125.4, 82.8, 81.4, 79.6, 78.5, 74.0, 65.4, 32.5, 31.8, 30.0, 29.6, 29.3, 29.2, 27.5, 27.0, 26.7, 26.6, 24.9, 14.1.

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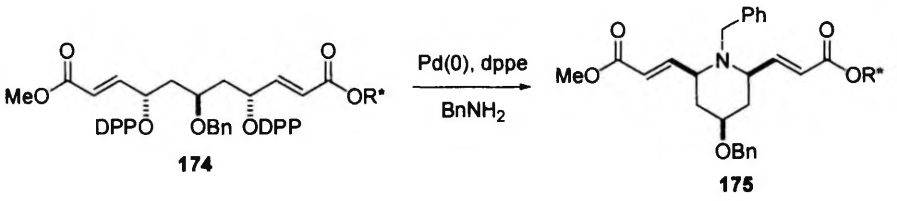
(7) Prepared according to the following procedure: Nozaki, H.Organotin Chemistry. In *Organometallics in Syntheis: A Manual*; John Wiley & Sons: New York, 1996, p 570.




**174** **175**

**Piperidine 175.** Dppe (4.7 mg, 0.012 mmol), $Pd_2(dba)_3$•$CHCl_3$ (3 mg, 0.0029 mmol) and $BnNH_2$ (30 μL, 0.28 mmol) were added to a solution of **174** (27 mg, 0.0298 mmol) in 400 μL of toluene. The reaction mixture was stirred for 1 h at RT, concentrated and purified by flash chromatography (10% EtOAc in hexanes) to afford 14 mg (72%) of piperidine **175** as a slightly brownish oil. **175**: (*Rf* = 0.13, hexanes/EtOAc 9/1); $^1$H NMR (500 MHz, selected signals) δ 7.38-7.05 (m, 15H), 6.78 (dd, *J* = 15.5, 8.5 Hz, 1H), 6.66 (dd, *J* = 15.5, 8.5 Hz, 1H), 5.90 (d, *J* = 16 Hz, 1H), 5.36 (d, *J* = 16 Hz, 1H), 4.84 (ddd [app td], *J* = 10.5, 4.5 Hz, 1H), 4.54 (s, 2H), 3.68 (s, 3), 3.68 (d, *J* = 15 Hz, 1H), 3.59 (d, *J* = 15.5 Hz, 1H), 3.42-3.35 (m, 1H), 3.07 (br t, *J* = 9.5 Hz, 1H), 3.00 (br t, *J* = 9.5 Hz, 1H), 1.27 (s, 3H), 1.21 (s, 3H), 0.86 (d, *J* = 6.5 Hz, 3H); $^{13}$C NMR (125 MHz) δ 166.4, 165.2, 151.4, 151.3, 150.1, 138.4, 137.3, 129.3, 128.4, 128.0, 127.9, 127.6, 127.4, 126.9, 125.5, 124.9, 122.4, 121.2, 74.4, 73.5, 69.8, 61.7, 61.4, 56.1, 51.5, 50.6, 41.7, 39.8, 38.5, 38.4, 34.5, 31.3, 27.1, 26.7, 25.9, 21.8.

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