Chapter 7

Total synthesis of prostaglandin E\textsubscript{1} methyl ester using a catalytic asymmetric tandem 1,4-addition-aldol reaction

7.1 Introduction

Prostaglandins (PGs) belong to the family of eicosanoids. These are oxygenated metabolites of 20 carbon unsaturated fatty acids and are produced by two cyclooxygenase enzyme systems widely distributed in mammalian tissue.\textsuperscript{1} Starting from C\textsubscript{20} unsaturated fatty acids (arachidonic, dihomogammalinolenic and eicosapentaenoic acid) the endoperoxides PGG and PGH are formed in the presence of oxygen. Theses intermediates are isomerized or reduced by various enzymes to several types of eicosanoids (Scheme 7.1).\textsuperscript{2,7}

![Scheme 7.1 Biosynthesis of prostaglandins.](image)

The structure of PGs comprises a five membered ring with two side-chains. The side-chain with the acid functionality is called the α side-chain and the other the ω side-chain (Scheme 7.2). The PGs, divided in different types, were discovered in the 1930s by Euler\textsuperscript{3} and isolated in 1957.\textsuperscript{4} Depending on the different substitution pattern of the five membered ring alphabetical designations are made (A, B, C,…). The different numerical subscripts represent the different pairs of side-chains (Scheme 7.3).

![Scheme 7.2 Prostanoic acid.](image)
The structure of a PGE₁ is indicated by the highlighted structural elements. Further members of the eicosanoids are the postacyclins and the thromboxanes (Scheme 7.4).

All these eicosanoids play important regulatory roles in many normal cellular functions. They are found in the phospholipids of cell membranes. In contrast to hormones they do not circulate nor are they stored in tissues. Rather they are synthesized locally on demand, perform a tissue-specific function and are rapidly inactivated by metabolic enzymes afterwards. The half-life time in the body is a few minutes for PGE₁ and a few seconds for PGI₂. Their pattern of action is diverse. The PGE₁ members have a great impact on the cardiovascular system (decrease in blood pressure), nervous system (increase in body temperature), reproductive system (induction of abortion), respiratory system (inhibition of bronchial secretion) and cause a general increase of hormone secretion. Inspired by the fascinating properties of the eicosanoids intensive research started in the 1960’s. Three major problems with the use of natural PGs as drugs have been encountered: (1) chemical instability, (2) rapid metabolism, and (3) incidence of numerous side effects. These results triggered the synthesis of PG analogs which are not affected by the major problems mentioned before. Although countless analogs have been synthesized during the last decades and many now reside in the clinical statutes, only a few of these are marketed. They are used as antiulcer, antihypertensive and antiglaucoma drugs and play an important role in the field of fertility control. From the academic point of view eicosanoids are still one of the most intensively studied class of natural products and every year hundreds, perhaps
thousands of papers are published about these compounds in general (bio)chemical, medical, and biological journals and journals like Prostaglandines & Therapeutics, Prostaglandins, Prostaglandins Research Studies, Prostaglandines & other Lipid Mediators, Advances in Prostaglandin, Thromboxane and Leukotriene Research and so one.\footnote{[7]}

### 7.2 The synthesis of PGs

The first main contributions in this field are those from Corey. Although many precursors have been used for the synthesis of PGs, the bicycloheptane precursor (Corey’s lactone) is one of the most successful building blocks which is also used for the industrial production of PG analogs.\footnote{[8],[9]} The commercially available lactone can be converted into the dialdehyde 7.3 and in the classical approach side chains 7.1 and 7.2 were introduced by Wittig and Wittig-Horner reactions (Scheme 7.5).\footnote{[10]}

![Scheme 7.5 Corey’s PG synthesis.](image)

A second very powerful synthesis of (racemic) prostaglandin analogs is based on the two component coupling.\footnote{[11]} The key step is a conjugate addition reaction of an \textit{in situ} formed cuprate from 7.5 to substituted enone 7.4 (Scheme 7.6). The optically pure precursor (R)-7.4 for the stereoselective synthesis can be obtained by an enzymatic resolution.\footnote{[12]} Recently a resolution-racemization process giving up to 80% yield of the optical pure enone has been developed by Godfroid.\footnote{[13]}

![Scheme 7.6 Two-compound coupling.](image)

Related is the three component coupling method developed by Noyori,\footnote{[14]} which is one of the most elegant approaches because of the shortness of this convergent synthetic route. The key step of this method is the conjugate addition-aldol reaction connecting both side-chains in one step (Scheme 7.7).
A closer look into the three-component coupling method is necessary here in order to understand the motivation of the following investigation.

### 7.3 The three-component coupling method

Isobe and Stork\(^\text{15}\) first used the conjugate addition-aldol reaction for the total synthesis of PGF\(_{2\alpha}\). In this procedure only formaldehyde could be used as electrophile. A modification was developed by Suzuki and Noyori\(^\text{16}\). The use of a stoichiometric amount of a Gilman cuprate and an excess of tributylyphoshine allowed the application of functionalized aldehydes as electrophiles (Scheme 7.8).

In detail, the α-iodoalkene 7.6 undergoes a halogen-metal exchange reaction by treatment with \(t\)-BuLi at low temperature. Addition of CuI gives the corresponding organocopper compound which is complexed with P(Bu)\(_3\). This copper reagent reacts with enone 7.7 in a 1,4-addition fashion giving enolate 7.8 which undergoes an aldol reaction with methyl 7-oxoheptanoate 7.9 to give the corresponding hydroxy ketone 7.10 in 83% overall yield. In the subsequent years a large research effort concerning the total synthesis of PGs in Noyori’s group resulted in numerous examples and major improvements.\(^\text{17}\)

### 7.4 The challenge

The challenge of this part of the investigation is to utilize the catalytic asymmetric tandem 1,4-addition-aldol reaction of diorganozinc reagents to cyclopenten-3,5-dione monoacetals
A total synthesis of prostaglandin E1 methyl ester using a catalytic asymmetric tandem 1,4-addition-aldol reaction

for the total synthesis of a PGE₁ methyl ester. The reason for the choice of a PGE and not one of the other PGs is the biological importance of PGEs and PGFs. Furthermore, PGEs are one of the most difficult PGs to synthesize and PGFs can be synthesized from PGEs. The reason for the choice of a prostaglandin as target molecule in general is the outstanding challenge for a catalytic asymmetric version of the cuprate (zincate) supported three component coupling and the academic and medical importance of these natural products.

7.5 Approach I

The retrosynthetic analysis is illustrated in Scheme 7.9. The initial approach towards the catalytic asymmetric total synthesis of PGE₁ methyl ester is reminiscent of the three component coupling reaction. Therefore unsaturated organozinc reagent 7.13, functionalized aldehyde 7.12 and enone 7.11 are envisioned to react in the presence of a chiral copper catalyst in a tandem 1,4-addition-aldol reaction affording PGE₁ methyl ester.

Scheme 7.9 Retrosynthetic analysis of PGE₁ methyl ester (I).

7.5.1 Dialkenylzinc reagents

Dialkenylzinc reagents represent an essentially unexplored class of organometallics. The only isolated and fully characterized dialkenylzinc compound is the colorless liquid divinylzinc. This compound can either be synthesized by transmetallation of divinylmercury with zinc metal¹⁸ or via the Grignard route from zinc chloride and vinylmagnesium bromide.¹⁹ In the former method the handling of divinylmercury requires the utmost care, but gives the product in high yield, whereas the more familiar Grignard method largely affords varying low yields. This compound is thermally unstable in solution and becomes even more unstable in pure form or in the presence of metal salts.²⁰,²¹ Because of these properties chemistry using divinylzinc is less explored and is limited to addition reactions to aldehydes.¹⁹,²² On the other hand, alkenylzinc halides, synthesized from alkenyllithium reagents²³ and ZnI₂ at -100°C, have been used intensively in addition and substitution reactions.²⁴ These compounds were used in situ and are not applicable in the asymmetric catalytic 1,4-addition.²⁵

The successful use of dialkylzinc reagents synthesized by boron-zinc exchange reaction makes this salt-free route also attractive for the synthesis of dialkenylzincs. In 1991
the first stereoselective synthesis of dialkenylzincs reagents using trialkenylboron compounds as precursors as well as their applications in the 1,2-addition to aldehydes was published by Srebnik (Scheme 7.10).26

\[
\begin{align*}
\text{Et} & \quad \text{Et} \\
\text{B} & \quad \text{B} \\
\text{Et} & \quad \text{Et} \\
\end{align*}
+ \quad \begin{align*}
\text{Et}_2\text{Zn} & \quad \text{Et}_2\text{Zn} \\
\text{ZnEt}_{2-x} & \quad \text{ZnEt}_{2-x} \\
\end{align*}
\xrightarrow{\text{Et}}
\begin{align*}
\text{Et} & \quad \text{Et} \\
\text{B} & \quad \text{B} \\
\text{Et} & \quad \text{Et} \\
\end{align*}
+ \quad \begin{align*}
\text{Et} & \quad \text{Et} \\
\text{Et} & \quad \text{Et} \\
\text{Et} & \quad \text{Et} \\
\text{Et} & \quad \text{Et} \\
\end{align*}
\]

**Scheme 7.10** Synthesis of dialkenylzincs reagents starting from a trialkenylboron compound.

The nature of these compounds was not clear and an equilibrium between a dialkenylzinc and an alkenyl-alkylzinc species was presumed. In fact, the equilibrium of the “mixed” organozinc species was discussed earlier20 as well as the synthesis of alkyl-alkenyl zinc compounds synthesized from vinyllithium and ethylzinc chloride.27 One year later an asymmetric version of the 1,2-addition to aldehydes was developed.28,29 It was reported that the equilibrium gives exclusively the alkenyl-alkyl zinc species at 0°C (Scheme 7.11).

\[
\begin{align*}
\text{Zn} & \quad \text{Me} \\
\text{Zn} & \quad \text{Zn} \\
\end{align*}
\xrightarrow{\text{Me}}
\begin{align*}
\text{ZnMe}_{2} & \quad \text{ZnMe}_{2} \\
\end{align*}
+ \quad \begin{align*}
\text{ZnMe}_{2} & \quad \text{ZnMe}_{2} \\
\end{align*}
\]

**Scheme 7.11** Equilibrium between dialkenylzinc and alkenyl-alkylzinc species.

### 7.5.2 Synthesis of an alkenyl-alkyl zinc reagent and its application in the catalytic 1,4-addition

Because of their successful application as nucleophiles in the 1,2-addition, alkenyl-alkylzinc reagents were synthesized and used as nucleophiles in the catalytic 1,4-addition. 7.16 was prepared according to a literature procedure (Scheme 7.12).22

\[
\begin{align*}
2 \text{C}_6\text{H}_{13} & \quad \text{BH}_3\text{Me}_2\text{S} \\
\text{C}_6\text{H}_{13} & \quad \text{C}_6\text{H}_{13} \\
\text{Cy}_2\text{BH} & \quad \text{Cy}_2\text{BH} \\
\end{align*}
\xrightarrow{0^\circ \text{C}, 3 \text{h}}
\begin{align*}
\text{Cy}_2\text{BH} & \quad \text{Cy}_2\text{BH} \\
\end{align*}
\]

**Scheme 7.12** Synthesis of ethyl[(E)-1-octenyl]zinc 7.16.

First 7.15 was prepared stereoselectively using 1-octyne and dicyclohexylborane 7.14, which was prepared from cyclohexene and BH₃•Me₂S.30 1H-NMR measurements confirmed the formation of 7.15. Treatment with neat Et₂Zn at 0°C for 3 h gave, after evaporation of the excess of Et₂Zn, 7.16 as identified by ¹H-NMR.
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The reaction of 7.16 and 2-cyclohexenone 7.17 in the presence of 2 mol% Cu(OTf)₂/L₂ afforded no product after one day at −30°C. Even upon rising the temperature of the reaction mixture to 0°C for an additional 18 h no product formation was observed.

Preparing 7.16 in situ by combining 7.15 and Et₂Zn (1M hexane) and using this solution in the catalytic 1,4-addition to 7.17 gave 7.18 as the only product in 20% yield (Scheme 7.14).

From the investigation with alkenyl-alkylzinc reagents the following conclusion can be drawn. Compound 7.16 can be synthesized and its application in 1,2-addition to aldehydes proceeds without complication. However, its use in catalytic 1,4-additions was not successful. First of all it should be investigated whether 7.16 and related compounds can undergo a 1,4-addition in general (as a cuprate reagent). If this is the case, the use of substoichiometric amounts of a copper catalyst will establish if 7.16 can be used under the catalytic conditions of the 1,4-addition. A further possibility to use unsaturated organozinc compounds in the catalytic 1,4-addition is the application of dialkynylzinc reagents.

### 7.5.3 Dialkynylzinc reagents
Dialkynylzinc reagents are, in contrast to dialkenylzinc compounds, stable and well-characterized molecules. They are colorless solids that decompose above 200°C without melting. They are not soluble except in very strongly donating solvents like DMF and DMSO. Because of the insolubility and the difficulties to determine their molecular weight it was suggested that they are associated as linear polymers. They can be synthesized by transmetalation from the corresponding alkynyllithium, alkynyl-alkyltellurium ortrialkynylaluminium compounds or by direct metallation of 1-alkynes with organozinc reagents. They have been used in Pd- and Ni-catalyzed cross-coupling methods and the synthesis of ketones starting from acid chlorides, as well as in the addition reaction to 5,6-dihydropyridinium ions and in the catalytic asymmetric 1,2-addition to aldehydes.
7.5.4 Synthesis of dialkynylzinc reagent and its application in the catalytic 1,4-addition
Di(1-octynyl)zinc 7.19 was prepared according to a literature procedure. The reaction of 7.17 and 7.19 in the presence of 2 mol% Cu(OTf)2/L2 afforded no product after one day at −30°C (Scheme 7.15). After four days at 0°C the formation of 7.20 could be detected in 19% yield.

\[
\text{7.17} + \text{Zn}(\equiv\text{C}_6\text{H}_{13})_2 \xrightarrow{2 \text{ mol}\% \text{ Cu}(\text{OTf})_2 / 4 \text{ mol}\% \text{ L2}} \text{toluene, −30°C, 1d} \rightarrow \text{no conversion}
\]

Scheme 7.15 Catalytic conjugate addition of di(1-octynyl)zinc to 2-cyclohexenone at −30°C.

It is evident from these results that approach I, using unsaturated organozinc species in the catalytic conjugate addition, does not work. A different strategy has to be invented for the asymmetric catalytic 1,4-addition-aldol reaction of diorganozinc reagents to cyclopenten-3,5-dienone monoacetals for the synthesis of PGE1.

7.6 General outline of the following approaches II-V

We have shown that the ω side-chain, apparently, cannot be introduced with an unsaturated diorganozinc reagent in an asymmetric catalytic 1,4-addition to enone 7.11, but that functionalized dialkylzinc reagents can be applied (chapter 4). Introducing the α-chain with a saturated diorganozinc reagent is the basic idea for the approaches II-V (Figure 3, C).

For the following approaches the structure of the PGE1 A is turned 180° resulting in B (Figure 3) which interchanges both the α,ω side-chains and the 5-ring oxygen functionalities.

Figure 3 Alternative views of prostaglandin E1.

7.7 Approach II

7.7.1 Retrosynthetic analysis of PGE1 methyl ester (II)

The retrosynthetic outline of approach II is illustrated in Scheme 7.16. In this approach the hydroxy- and ketone functionality of the five membered ring of PGE1 methyl ester would be realized by a reduction and deacetalization step from 7.23. The Δ13,14 double bond of the
PGE$_1$ methyl ester would be established by an elimination of the hydroxy functionality of 7.23. Furthermore, 7.23 would be obtained from the tandem 1,4-addition-aldol reaction of 7.11, 7.21 and 7.22. The stereogenic center of C-15 is already present in silyl ether 7.22. This would ensure no complication of the hydroxy functionality during the synthesis.

Scheme 7.16 Retrosynthetic analysis of PGE$_1$ methyl ester (II).

### 7.7.2 Synthesis of aldehyde (+/-)-7.22a and (+/-)-7.22b

For the initial experiments racemic 7.24 was prepared. Protection as the silyl ether was carried out according to the literature.$^{40}$ The oxidation of the triple bond was realized using a hydroboration-oxidation protocol. The overall yield of (+/-)-7.22a and (+/-)-7.22b was 50% and 52% respectively (Scheme 7.17).

Scheme 7.17 Synthesis of (+/-)-7.22a and (+/-)-7.22b.

### 7.7.3 Tandem 1,4-addition-aldol reaction with β-silyloxy aldehydes

First, initial experiments were carried out with rac-7.22, 7.11 and diethylzinc in the presence of a 2 mol% Cu(OTf)$_2$/L$_2$ catalyst (Scheme 7.18). Diethylzinc was used instead of the functionalized zinc reagent 7.21 to simplify this approach in the first instance. Optically pure ligand L$_2$ was used to achieve a fast and clean reaction. The asymmetric induction of this reaction is expected to be high but the main interest was the synthetic realization of approach II (Scheme 7.16).
7.7.4 Formation of the Δ13,14 double bond of a PGE1 methyl ester analog (I)

The next step is the formation of the Δ13,14 double bond. The diastereomeric mixture of 7.24 (four diastereomers) was converted into 7.26 to facilitate an elimination reaction in the presence of Al₂O₃ (Scheme 7.19).⁴¹

**Scheme 7.19 Mesylation of compound 7.24.**

The reaction of 7.24 (mixture of 7.24a/b) with MsCl in the presence of triethylamine at 0°C afforded 7.26 in 48% yield (Scheme 7.19). This compound was not stable and decomposed after 6 h at room temperature. In solution (NMR-tube) it was stable for 18 h. Direct elimination of 7.26 would result in the formation of the α,β unsaturated ketone.⁴¹ To avoid enone formation reduction of the ketone was carried out first. Unfortunately, the reduction of 7.26 with NaBH₄ in methanol at 0°C gave only a complex reaction mixture.

7.7.5 Formation of the Δ13,14 double bond of a PGE1 methyl ester analog (II)

In this approach a reduction of ketone 7.25 (used instead of 7.24 because of a higher stability of TBDMS against acid and base) was carried out first before converting the hydroxy group into a mesylate because of the instability of ketone 7.26. Direct reduction would lead to a
compound with two secondary alcohol groups. To discriminate between them a protection step was carried out first.

The diastereomeric mixture of 7.25 was protected as its acetate with acetic anhydride in the presence of pyridine affording 7.27 in 70% yield (Scheme 7.20).

![Scheme 7.20 Protection of compound 7.25 as its acetate.](image)

In the course of the purification of compound 7.27 two other products were isolated in minor amounts and characterized by $^1$H-NMR. Compound 7.28 (4% yield) was identified as an unsaturated ketone formed by an elimination reaction and compound 7.29 (3% yield) was identified as an enol acetate, formed under the basic conditions from 7.27 in the presence of acetic anhydride.

The next step was the stereoselective reduction of the ketone functionality of 7.27. The conversion was realized using sodium borohydride in methanol at 0°C giving 7.30 and 7.31 as a separable mixture in 45% and 20% yield respectively (Scheme 7.21). The full stereocontrol of the reduction of similar systems has been reported in the literature.16b

![Scheme 7.21 Reduction of compound 7.27.](image)

The protection of the hydroxy functionality connected to the five membered-ring is required prior to subsequent elimination of the acetate. Protection as $t$-butyldimethylsilyl ether was chosen for the simultaneous deprotection of two silyl ethers at the end of the total synthesis. The reaction was carried out under standard reaction conditions affording 7.32 in 67% yield. 42
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At this stage of the synthesis, the acetate in 7.32 had to be cleaved and the hydroxy group had to be converted into a mesylate to carry out the elimination reaction, which would establish the $\Delta^{13,14}$ double bond of the $\omega$ side-chain. The hydrolysis of acetate 7.32 was carried out under a variety of reaction conditions, summarized in Table 7.1.

Table 7.1 Cleavage of the acetate 7.32.

<table>
<thead>
<tr>
<th>entry</th>
<th>Conditions</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\text{K}_2\text{CO}_3$, MeOH, H$_2$O, r.t., 24h</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>NaOMe, MeOH, H$_2$O, r.t., 24h</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>KCN, EtOH, H$_2$O, r.t., 24h</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>NH$_3$, MeOH, H$_2$O, r.t., 24h</td>
<td>46</td>
</tr>
<tr>
<td>5</td>
<td>HCl, THF, r.t., 24h</td>
<td></td>
</tr>
</tbody>
</table>

The stability of the acetate 7.32 was remarkable. Under the conditions described no hydrolysis of the ester was observed. The starting material could be recovered or deacetalization took place. A possible explanation for this behavior could be the inaccessibility of the acetate because of the $t$-butyldimethylsilyloxy groups.

7.7.6 Formation of the $\Delta^{13,14}$ double bond of a PGE$_1$ methyl ester analog (III)

Taking the stability of acetate 7.32 to advantage, a selective protection of an intermediate diol was investigated, which might reduce the number of steps of the synthesis. 7.25 was reduced stereoselectivity using zinc borohydride because of the higher reactivity, higher selectivity and better solubility in THF or ether in comparison with sodium borohydride. The reaction of 7.25 with zinc borohydride in ether at $-30^\circ$C afforded 7.33a/7.33b in 75% yield (Scheme 7.23).
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*Scheme 7.23* Reduction of compound 7.27.

Note 7.25 was used as a diastereomeric mixture (65:35 ratio see section 7.7.3). The compounds 7.33a and 7.33b could be separated by column chromatography in 26% and 47% yield respectively. Using one equivalent of TBDMSCl in the presence of imidazole in DMF at 50°C, 7.33a was converted into the mono protected product 7.34 in 88% yield (Scheme 7.24).

*Scheme 7.24* Selective protection of 7.33a.

The next step is the elimination reaction to introduce the Δ₁³,₁₄ double bond. For this purpose 7.34 was treated with MsCl in the presence of Et₃N. The mesylate was formed (detected by TLC and NMR) but the elimination with DBU in refluxing toluene gave a complex reaction mixture. At this point the decision was made to drop approach II because of the difficulties to establish the crucial alkene moiety by this elimination method.

### 7.8 Approach III

#### 7.8.1 Retrosynthetic analysis of PGE₁ methyl ester (III)

The retrosynthetic analysis of approach III is illustrated in Scheme 7.25. The hydroxy- and ketone functionality of the five membered ring of PGE₁ methyl ester would be established by the cleavage of the acetate and acetal from 7.37. The allylic alcohol moiety in the ω side-chain of PGE₁ methyl ester would be established by an allylic transposition reaction. A similar reaction has been used for the synthesis of PGs.⁷¹ The alkene moiety of 7.37 would be introduced by an oxidative elimination of selenium compound 7.36 with a subsequent esterification. For this purpose α-phenylselenium aldehyde 7.35 would be used as electrophile in the tandem 1,4-addition-aldol reaction together with 7.11 and 7.21.
7.8.2 Tandem 1,4-addition-aldol reaction with α-phenylselenium aldehyde 7.35

For this initial reaction the same simplifications were applied as described in 7.7.3 (diethylzinc instead of 7.21, optically pure L2 to guarantee a fast and clean catalysis). The main efforts regarding this tandem 1,4-addition-aldol reaction with 7.11, 7.35 (synthesized according to literature48) and diethylzinc in the presence of 2 mol% Cu(OTf)2/L2 were focused on the chemical transformations and not on the asymmetric induction.

\[
\text{Scheme 7.26 Catalytic asymmetric 1,4-addition-aldol reaction using aldehyde 7.35.}
\]

The reaction of 7.11, 7.35 and diethylzinc afforded products 7.38/7.39 in 67% yield with a ratio of 93:7. The selectivity in the aldol step was higher in this case than for the β-silyloxy aldehydes (7.7.3). The reaction was performed at 0°C because no conversion was observed at −30°C. At this higher reaction temperature the formation of the elimination products 7.38/7.39 was observed (see section 6.4.1). The two products could be separated by column chromatography.

7.8.3 Transformation of 7.38 into a PGE1 analog

The formation of elimination product 7.38 had not been taken into account in the retrosynthetic analysis of approach III (Scheme 7.25). Therefore a different manipulation of 7.38 was carried out to obtain the hydroxy- and ketone functionality of the five membered ring of PGE1 analog.49 The reaction of 7.38 and NaBH4 in the presence of CeCl3 gave no
conversion of the starting material.\textsuperscript{50} The second attempt involved the use of DIBAL-H.\textsuperscript{51} Although no reaction took place at \(-80^\circ C\), the reduction proceeded at room temperature with full conversion of 7.38 after 5 h (Scheme 7.27).

![Scheme 7.27 Reduction of compound 7.38a.](image)

The reduction of 7.38 afforded, after purification by column chromatography, compound 7.40 in 34\% yield and compound 7.41 in 23\% yield. The formation of the acetal of 7.40 from 7.38 has been described for similar reactions.\textsuperscript{52} The desired product, the cyclic hydroxy ketone, was not formed because of a subsequent elimination reaction resulting in the formation of 7.40 and 7.41. This means that instead of converting 7.38 into a suitable structure, one of the important carbonyl functionalities was removed during this reaction.

7.8.4 Formation of the alkene moiety with 7.38

Although the manipulation of 7.38 was not successful according to Scheme 7.27 an attempt was carried out to introduce the alkene moiety. 7.38 was oxidized under basic conditions to obtain an allylic alcohol (Scheme 7.28).

![Scheme 7.28 Attempted oxidative elimination of 7.38a.](image)

The reaction of 7.38 and hydrogen peroxide in the presence of pyridine afforded a complex reaction mixture as indicated by TLC and NMR spectroscopy.

At this point, approach III was also canceled because of the difficulties establishing the proper substitution pattern of the five membered ring and the introducting of the alkene moiety.
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7.9 Approach IV

7.9.1 Retrosynthetic analysis of PGE1 methyl ester (IV)

The retrosynthetic analysis of approach IV is illustrated in (Scheme 7.29).

![Scheme 7.29 Retrosynthetic analysis of PGE1 methyl ester (IV).](image)

The hydroxy and ketone functionality of the five membered ring of PGE1 methyl ester would be realized by the cleavage of the acetal from 7.44. The allylic alcohol moiety in the ω side-chain of PGE1 methyl ester would be established by the stereoselective reduction of the unsaturated ketone of 7.44. Compound 7.44 would be obtained from the corresponding hydroxy enol ether 7.43 by liberation of the ketone functionality and a subsequent elimination reaction. The tandem 1,4-addition-aldol product 7.43 would be obtained by using 7.11, 7.21 and aldehyde 7.42 in the presence of a Cu(OTf)2/L2 catalyst (Scheme 7.29).

7.9.2 Synthesis of aldehyde 7.42

The synthesis of aldehyde 7.42 started with the preparation of ethyl-3-oxo-octanoate 7.45 according to the literature in 56% yield. Subsequent conversion of 7.45 to 7.46 was realized in the presence of triethyl orthoformate under acidic conditions in 84% yield. Reduction of 7.46 to alcohol 7.47 proceeded quantitatively using LiAlH4 and subsequent oxidation, using manganese oxide, gave the desired aldehyde 7.42 in 56% yield. The overall yield of this sequence was 27%.
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Scheme 7.30 Synthesis of aldehyde 7.42.

7.9.3 Tandem 1,4-addition-aldol reaction with aldehyde 7.42

For this initial reaction the same simplifications were applied for the same reasons as described in section 7.7.3. The tandem 1,4-addition-aldol reaction was carried out with 7.11, 7.42 and diethylzinc in the presence of 2 mol% Cu(OTf)₂/L₂ (Scheme 7.31).

Scheme 7.31 Tandem 1,4-addition-aldol reaction using aldehyde 7.42.

The reaction of 7.11, 7.42 and diethylzinc in the presence of a chiral copper catalyst gave no conversion after one day at −20°C. Even at elevated temperature no conversion was seen and we do not have a proper explanation for this behavior. Therefore no further investigations were made along the lines of approach IV.

7.10 Approach V

The retrosynthetic analysis of approach V is illustrated in Scheme 7.32. The preparation of PGE₁ methyl ester would involve cleavage of the acetal and an allylic transposition from 7.50. To carry out the allylic transposition, conversion of the diol 7.50 to the corresponding diacetate would be necessary. 7.50 would be afforded by protodesilylation⁶⁵ and stereoselective reduction of 7.49. The tandem 1,4-addition of 7.11, 7.48 and 7.21 would afford 7.49 in the presence of a chiral copper catalyst.
7.10.1 Retrosynthetic analysis of aldehyde 7.48 (I)

The only synthesis known for compounds like 7.48 is a six step route with good to moderate yields in each step. Unfortunately no information about the E:Z ratio of the aldehyde was reported, which is crucial for the total synthesis of PGE1. Therefore a new method was developed focusing particularly on high E:Z ratios. The retrosynthetic analysis is illustrated in Scheme 7.33.

The double bond of enal 7.48 would be introduced selectively by a Pd-catalyzed reaction of diallyl carbonate with the corresponding keto silyl enol ether (Scheme 7.33).

7.10.2 Synthesis of aldehyde 7.51

For the synthesis of 7.51 three suitable procedures are known.

1. The conjugate addition reaction of a silyl metal species to an unsaturated ester with a subsequent reduction to the aldehyde.
2. The reaction of metallated enamines, which can undergo a silylation and alkylation reaction to the corresponding 3-oxosilanes.
3. Silylation of a vinylborane with subsequent oxidation to the aldehyde.
The aldehyde 7.51 was prepared according to path 3 using a literature procedure (Scheme 7.34). Disiamylborane \([(\text{Sia})_2\text{BH}]\) was prepared from 2-methyl-2-butene and BH$_3$•Me$_2$S and used for the hydroboration of 1-octyne at 0°C. The solution of 7.54 was added to a concentrated solution of TMPLi 7.53 at room temperature with a subsequent addition of TMSCl, which caused an immediate precipitation of LiCl. The reaction mixture was treated with 3 N NaOH solution and H$_2$O$_2$ and 7.51 was isolated by distillation in 29% overall yield.

An alternative synthesis of 7.51 was inspired by the direct silylation of enones and enals with R$_3$SiSiR$_3$ catalyzed by CuOTf. The reaction of 2-octenal and hexamethyldisilane in the presence of CuOTf/Bu$_3$P afforded, however, a complex reaction mixture.

### 7.10.3 Synthesis of aldehyde 7.48 (I)

This synthesis is illustrated in Scheme 7.35. Aldehyde 7.51 was converted into its silyl enol ether 7.56 followed by a Pd-catalyzed reaction with diallyl carbonate.

The reaction of 7.51, hexamethyldisilazane and TMSI afforded 7.56 in 51% yield. Applying 7.56 in the Pd-catalyzed reaction with diallyl carbonate gave a complex reaction mixture after 2h in refluxing CH$_3$CN in our hands. This is a remarkable observation as Tsuji reported successful application of slightly different starting materials. An explanation for the complex reaction mixture cannot be given.
7.10.4 Retrosynthetic analysis of aldehyde 7.48 (II)

A new approach is outlined in Scheme 7.36 in which 7.48 would be obtained from 7.60 by oxidation. The synthesis of 7.60 would be possible with a 1,4-O→sp² C silyl migration reaction starting from 7.59 in the presence of t-BuLi. Magriotis investigated this reaction." The use of 7.57 would afford 7.58 using a Corey reductive iodination reaction.

![Scheme 7.36 Retrosynthetic analysis of 7.48 (II).](image)

7.10.5 Synthesis of aldehyde 7.48 (II)

The synthesis of 7.48 is illustrated in Scheme 7.37. Commercially available 2-octyn-1-ol 7.57 was converted to 7.58 by the Blanchette modification of the Corey reductive iodination. In this process bis(2-methoxyethoxy)aluminium hydride (Red-Al®) was used as the reductive reagent. The aluminium hydride species reacted first with the hydroxy functionality giving a trisalkoxy aluminium compound, which underwent an intramolecular hydride addition reaction to the corresponding cyclic organoaluminium species. The addition of iodine gave compound 7.58 in 94% yield after hydrolysis. This mechanism explains why the reduction proceeds with 100% cis selectivity. Using chlorodimethylphenylsilane, allylic alcohol 7.58 was converted to the silyl ether 7.59 in excellent yield. This compound underwent a 1,4-O→sp² C silyl migration using two equivalents of t-BuLi. The corresponding (Z)-vinylsilane 7.60 was obtained in 74% yield. Subsequently, Swern oxidation gave the unsaturated aldehyde 7.48 with a E:Z ratio of 6:94. The overall yield of this sequence was 51%.

![Scheme 7.37 Synthesis of 7.48 (II).](image)

7.11 Synthesis of a PGE₁ analog using aldehyde 7.48

The initial experiment with aldehyde 7.48 was carried out with 2-cyclopentenone 7.61 and diethylzinc in the presence of 2 mol% of a Cu(OTf)₂/L₂ catalyst (Scheme 7.38). Diethylzinc
and 7.61 were used instead of the functionalized zinc reagent 7.21 and enone 7.11 to simplify this approach in the first instance. Optically pure ligand L2 was used to achieve a fast and clean reaction. The asymmetric induction of this reaction is expected to be low but the main interest is the synthetic realization of this approach.

![Scheme 7.38 Tandem 1,4-addition-aldol reaction with 7.61 and 7.48.]

The reaction of 7.61, 7.11 and diethylzinc in the presence of a chiral copper catalyst afforded 7.62a/7.62b in 78% yield in a ratio of 1:1 after one day at −30°C. From this result it can be concluded that the presence of the acetal in 7.11 is of crucial importance for the high selectivity in the aldol step.

The next step is the protodesilylation reaction of a vinylsilane, which was investigated by Nozaki. In the publication the following conclusions were made:

a) The presence of phenyl, allyl or alkoxy group on the silicon atom facilitate the cleavage of vinylsilanes.

b) Suitably located hydroxy groups in the molecule facilitate the cleavage of sp² C-Si bond.

Because of the first conclusion the aldehyde 7.48 was provide with a phenylidimethylsilyl substituent instead of the cheaper trimethylsilyl substituent and fortunately a hydroxy group is present in 7.62 from the subsequent aldol reaction.

Unfortunately, a complex reaction mixture was obtained in the reaction of 7.62 in the presence of Bu₄NF in THF/DMSO at 80°C. A possible reason for this behavior could be the presence of the hydroxy ketone, which can undergo an elimination reaction.

On the basis of this observation it was decided to reduce the ketone functionality of 7.62 using Zn(BH₄)₂ in ether at room temperature (Scheme 7.39). The yield of the tandem 1,4-addition-aldol reaction and reduction over two steps was 76%. The reduction proceeded with high stereoselectivity (92:8). Note that 7.62 was used as a 50:50 mixture of diastereomers. The compounds 7.63a and 7.63b showed still the same ratio and could be separated by column chromatography.
The following step is the protodesilylation. The reaction of 7.63a and Bu₄NF in THF/DMSO at 80°C afforded, much to our delight, 7.64 in 85% yield.

![Scheme 7.40 Protodesilylation of 7.63a.](image)

At this stage of the synthesis 7.64 was converted into diacetate 7.65 in order to test the 1,3-allylic transposition reaction to form product 7.66 (Scheme 7.41). This reaction has been extensively studied and has been used several times in the synthesis of PGs, and is known to proceed with retention of configuration. Furthermore, it is an equilibrium reaction and the driving force for the conversion is believed to be the decrease of steric hindrance in the formed product.

![Scheme 7.41 Synthesis of a PGE₁ analog 7.67.](image)

Under standard esterification conditions 7.64 was converted into 7.65 in 74% yield. Treatment of 7.65 with 5 mol% Pd(CH₃CN)₂Cl₂ in THF at room temperature catalyzed the allylic transposition reaction giving 7.66 in 93% yield. In this allylic transposition reaction no detectable equilibrium was recognized as indicated by full conversion (TLC). The last step of this model total synthesis was the ester cleavage to obtain 7.67. This reaction proceeded in the presence of K₂CO₃ in MeOH in 79% yield.

### 7.12 Synthesis of PGE₁ methyl ester

The PGE₁ analog 7.67 has been successfully synthesized. In this section we report a synthesis of a PGE₁ methyl ester using the cascade of reactions used to prepare 7.67.
7.12.1 Synthesis of functionalized organozinc reagent 7.21

The functionalized zinc reagent 7.21 was prepared following a Knochel procedure. The synthesis is illustrated in Scheme 7.42.

![Scheme 7.42 Synthesis of functionalized zinc reagent 7.21.](image)

Commercially available 6-heptenoic acid 7.68 was converted to the methyl ester 7.69 in 94% yield. Subsequent hydroboration of the double bond gave a functionalized borane, which underwent a borane-zinc exchange reaction in presence of neat Et₂Zn. After evaporation of the excess of Et₂Zn, ester functionalized zinc reagent 7.21 was obtained in 85% yield.

7.12.2 Synthesis of PGE₁ methyl ester (part I)

The total synthesis of PGE₁ methyl ester began with the enantioselective catalytic 1,4-addition-aldol reaction with enone 7.11, aldehyde 7.48 and the functionalized zinc reagent 7.21 in the presence of 3 mol% of a Cu(OTf)₂/L₂ catalyst affording compound 7.70 in 60% yield as an inseparable mixture of two diastereomers (threo:erythro ratio 83:17 according to ¹H-NMR). Subsequently, stereoselective reduction (95%) with Zn(BH₄)₂ afforded 7.71 as a single diastereomer in 39% overall yield and 94% ee (as determined by chiral HPLC after separation by column chromatography). The synthesis of 7.71 is illustrated in Scheme 7.43.

![Scheme 7.43 Tandem 1,4-addition-aldol reaction with 7.11, 7.21 and 7.48.](image)
7.12.3 The protodesilylation of 7.71

The protodesilylation of 7.71 in THF/DMSO in the presence of Bu₄NF at 80°C was accompanied by hydrolysis of the methyl ester to give a mixture of 7.72 and 7.73. Nozaki had already noticed the hydrolysis of esters under the reaction conditions of the protodesilylation but gave no explanation for this phenomenon. Subsequent esterification with acetic anhydride in pyridine gave diacetates 7.74 and 7.75 in 30% and 37% overall yield, respectively. The reactions are illustrated in Scheme 7.44.

A reason for the hydrolysis of the ester functionality is probably the presence of water in the THF solution of Bu₄NF (5 wt% water). This problem might be solved by the addition of another ester first to remove the water by hydrolysis.

The reaction was carried out as follows: To a solution of Bu₄NF in THF/DMSO was added methylpropionate as a “sacrificial” ester and the mixture was heated at 80°C until no further ester hydrolysis was detected (GC measurement, 2 h). Subsequently, 7.71 was added and after 20 min the silyl group was completely removed and 7.72 was obtained in 75% yield. The corresponding acid 7.73 could not be detected.

7.12.4 Investigation of the removal of the acetal without elimination of the hydroxy ketone

The next crucial step is the removal of the acetal function without elimination of the 3-hydroxy ketone to the corresponding enone. In the introduction of this chapter we reported the chemical instability of PGEs and the 3-hydroxy ketone functionality is the most unstable part of these compounds. The problem is illustrated in Scheme 7.45.
A total synthesis of prostaglandin E<sub>1</sub> methyl ester using a catalytic asymmetric tandem 1,4-addition-aldol reaction

Scheme 7.45 Deacetalization of 7.72.

To investigate this reaction 7.72 was chosen as model compound. The goal of this investigation was to obtain 7.76 as the only product. Different methods have been used to realize this manipulation and the results are summarized in Table 7.2.

Table 7.2 Deacetalization of 7.72 using different methods

<table>
<thead>
<tr>
<th>entry</th>
<th>method</th>
<th>ratio 7.76/7.77</th>
<th>ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH, HCl</td>
<td>full conversion (0:100)</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>acetone, Dowex 50x80, H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>full conversion (0:100)</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>AcOH 80%</td>
<td>complex reaction mixture (TLC)</td>
<td>77</td>
</tr>
<tr>
<td>4</td>
<td>citric acid, MeOH, H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>No conversion</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>SiO&lt;sub&gt;2&lt;/sub&gt;, H&lt;sub&gt;2&lt;/sub&gt;SO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>No conversion</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>CeCl&lt;sub&gt;3&lt;/sub&gt;*7 H&lt;sub&gt;2&lt;/sub&gt;O, NaI, CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>No conversion</td>
<td>79</td>
</tr>
<tr>
<td>7</td>
<td>PdCl&lt;sub&gt;2&lt;/sub&gt;(CH&lt;sub&gt;3&lt;/sub&gt;CN)&lt;sub&gt;2&lt;/sub&gt;, acetone, H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>complex reaction mixture (TLC)</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>cat. (NH&lt;sub&gt;4&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;Ce(NO&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;6&lt;/sub&gt;, buffer, CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>9:1, full conversion</td>
<td>81</td>
</tr>
</tbody>
</table>

The acid-catalyzed cleavage of acetals is the most general procedure. Using HCl in MeOH or an acidified resin (Dowex) gave 7.77 as the only product (Table 7.2, entries 1 and 2). In the presence of aqueous acetic acid a complex reaction mixture was obtained. The reason for this is not clear (Table 7.2, entry 3). Slightly acidic conditions with citric acid and acidified silica led to no conversion at all (Table 7.2, entries 4 and 5). The Lewis acid CeCl<sub>3</sub> in CH<sub>3</sub>CN in the presence of NaI was also not effective (Table 7.2, entry 6) and PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub> in aqueous acetone gave a complex reaction mixture (Table 7.2, entry 7). The solution was found with the application of a catalytic amount of (NH<sub>4</sub>)<sub>2</sub>Ce(NO<sub>3</sub>)<sub>6</sub> in a buffered solution together with CH<sub>3</sub>CN (Table 7.2, entry 7). Under these conditions acetal cleavage without significant elimination was realized. The products 7.76/7.77 were obtained in a ratio of 9:1 with full conversion of 7.72.

7.12.5 Synthesis of PGE<sub>1</sub> methyl ester (part II)

The total synthesis of PGE<sub>1</sub> methyl ester was continued with the protodesilylation of 7.71 with Bu$_4$NF in THF/DMSO at 80°C using sacrificial methylpropionate and subsequent
esterification affording 7.74 in 71% yield over two steps. The allylic transposition of 7.74 catalyzed by PdCl$_2$(CH$_3$CN)$_2$ gave 7.78 in 63% yield. The reaction proceeds with retention of configuration to give the 15S stereocenter. The reactions are illustrated in Scheme 7.46.

![Scheme 7.46 Protodesilylation and allylic transposition of 7.71.](image)

The final steps comprise two deprotections. First, the cleavage of the acetoxy groups giving 7.79 and then the investigated acetal cleavage giving the PGE$_1$ methyl ester in 41% yield over two steps. The reactions are outlined in Scheme 7.47.

![Scheme 7.47 Final steps of the synthesis of the PGE$_1$ methyl ester.](image)

The reaction of 7.78 with K$_2$CO$_3$ in methanol afforded 7.79 in 90% yield. The PGE$_1$ methyl ester was obtained from 7.79 by treatment with a catalytic amount of (NH$_4$)$_2$Ce(NO$_3$)$_6$ in a HCl-borate buffered aqueous solution and CH$_3$CN (pH = 7.5). Full conversion was achieved with only a minor amount of the elimination product. Unfortunately, the isolated yield after column chromatography was only 45%. Elimination in contact with SiO$_2$ afforded significant amounts of the elimination product during purification.

With this new catalytic synthetic route PGE$_1$ methyl ester was synthesized in seven steps and 7% overall yield with 94% optical purity.
**Dicyclohexyl[(E)-1-octenyl]borane (7.15).**
Prepared according to a literature procedure.\(^{30}\) \(^1\)H-NMR (300 MHz) \(\delta = 6.71 \text{ (dt, } J = 18.2 \text{ Hz, } J = 7.3 \text{ Hz, } 1H), 6.18 \text{ (d, } J = 18.2 \text{ Hz, } 1H), 2.19 \text{ (q, } J = 7.3 \text{ Hz, } 2H), 1.79-1.64 \text{ (m, } 6H), 1.52-1.40 \text{ (m, } 6H), 1.31-1.13 \text{ (m, } 20H), 0.85 \text{ (t, } J = 7.5 \text{ Hz, } 3H).\)

**Ethyl[(E)-1-octenyl]zinc (7.16).**
Crude reaction mixture, in the presence of dicyclohexyl(ethyl) borane. Prepared according to a literature procedure.\(^{22}\) \(^1\)H-NMR (300 MHz) \(\delta = 5.94 \text{ (m, } 1H), 5.51 \text{ (m, } 1H), 1.98 \text{ (q, } J = 7.2 \text{ Hz, } 2H), \text{ absorption of dicyclohexyl(ethyl)borane} 0.31 \text{ (m, } 2H).\)

**1-(1-Octynyl)-2-cyclohexen-1-ol (7.20).**
A solution of Cu(OTf)\(_2\) (3.6 mg, 0.01 mmol) and \(\text{L2} \) (10.6 mg, 0.02 mmol) in freshly distilled toluene (9 ml) was stirred under a nitrogen atmosphere at ambient temperature for 1 h. \(\text{7.17} \) (97 \(\mu\)l, 1 mmol) was added and after cooling to \(-30^\circ\text{C}\) \(\text{7.19} \) (1M in toluene, 1 ml) was added. After four days at \(0^\circ\text{C}\) the reaction mixture was poured into 25 ml of NH\(_4\)Cl (aq) and diluted with ether (25 ml). The organic layer was separated, and the aqueous layer was extracted two times with diethyl ether (20 ml). The combined organic layers were dried over MgSO\(_4\), filtered and concentrated \textit{in vacuo}. Purification by column chromatography (SiO\(_2\) pentane: diethyl ether, 3:1, \(R_f = 0.45\)) gave 34 mg (19%) of \(\text{7.20} \) as a colorless oil. \(^1\)H-NMR (200 MHz) \(\delta = 5.71 \text{ (m, } 2H), 2.15 \text{ (t, } J = 7.0 \text{ Hz, } 2H), 1.74-1.68 \text{ (m, } 6H), 1.54 \text{ (s, } 1\text{H(OH))}, 1.47-1.40 \text{ (m, } 2H), 1.34-1.15 \text{ (m, } 6H), 0.83 \text{ (t, } J = 6.6 \text{ Hz, } 3H); \) \(^{13}\)C-NMR (200 MHz) \(\delta = 131.1, 129.1, 84.5, 83.8, 65.3, 38.2, 31.3, 28.6, 28.5, 24.7, 22.5, 19.2, 18.7, 14.0; \) Ms (Cl) for C\(_{14}\)H\(_{22}\)O: \(m/z = 206 \text{ (M)}^+\).

**3-\{(Trimethylsilyl)oxy\}octanal (7.22a).**
Under an argon atmosphere, BH\(_3\)\*Me\(_2\)S (1M in THF, 35 ml) was added to a solution of cyclohexene (70 mmol, 7.1 ml) in THF (30 ml). After stirring for 2 h at \(0^\circ\text{C}\) a white solid was formed. To this solution 3-(trimethylsilyloxy)-1-octyne\(^{40}\) (7 g, 35 mmol) in THF (10 ml) was added and the mixture was stirred for an additional 2 h at \(0^\circ\text{C}\). The reaction mixture was allowed to warm to room temperature to complete hydroboration and the product was oxidized at \(0^\circ\text{C}\) by the addition of H\(_2\)O\(_2\) (15% in water, 27 ml), maintaining the pH of the reaction mixture at 7-8 by the addition of 3 N NaOH (aq). The reaction mixture was diluted with diethyl ether (50 ml) and the organic layer was separated. The aqueous layer was extracted two times with diethyl ether and the combined organic layers were dried over MgSO\(_4\), filtered and concentrated \textit{in vacuo}. Purification by column chromatography (SiO\(_2\) diethyl ether/pentane, 1:20, \(R_f = 0.42\)) gave 4.54 g (61%) of \(\text{7.22a} \) as a colorless oil. \(^1\)H-NMR (300 MHz) \(\delta = 9.77 \text{ (t, } J = 2.4 \text{ Hz, } 1H), 4.15 \text{ (m, } J = 5.5 \text{ Hz, } 1H), 2.51 \text{ (m, } 2H), 1.48 \text{ (m, } 2H), 1.28 \text{ (m, } 6H), 0.87 \text{ (t, } J = 7.0 \text{ Hz, } 3H), 0.10 \text{ (s, } 9H); \) \(^{13}\)C-NMR (200 MHz) \(\delta = 202.2, 68.1, 51.1, 37.8, 31.7, 25.1, 22.5, 14.0, 0.3; \) Ms (EI) for C\(_{11}\)H\(_{24}\)O\(_2\)Si: \(m/z = 216 \text{ (M)}^+\).
3-\{[\textit{tert-Benzyl(dimethyl)silyl}]oxy\}octanal (7.22b).
Prepared according 7.22a; Purification by column chromatography (SiO\textsubscript{2} diethyl ether/pentane, 1:100 ether/pentane, R\textsubscript{f} = 0.35) gave 5.61 g (52\%) of 7.22b as colorless oil; bp\textsubscript{0.7} = 93\degree C. \textsuperscript{1}H-NMR (200 MHz) \(\delta = 7.97\) (t, \(J = 2.6\) Hz, 1H), 4.15 (m, \(J = 5.8\) Hz, 1H), 2.51 (m, \(J = 2.8\) Hz, 2H), 1.71-0.80 (m, 20H), 0.04 (d, \(J = 5.0\) Hz, 6H); \textsuperscript{13}C-NMR (200MHz) 202.3, 68.3, 50.8, 37.8, 31.8, 30.2, 25.7, 24.8, 22.6, 13.9, -4.5, -4.7; Ms (EI) for C\textsubscript{14}H\textsubscript{30}O\textsubscript{2}Si: m/z = 258 (M)+.

4-Ethyl-3-\{1-hydroxy-3-\{(trimethylsilyl)oxy\}octyl\}-8,8-diphenyl-6,10-dioxaspiro[4.5]decan-2-one (7.24).
A solution of Cu(OTf)\textsubscript{2} (3.6 mg, 0.01 mmol) and L\textsubscript{2} (10.6 mg, 0.02 mmol) in freshly distilled toluene (9 ml) was stirred under a nitrogen atmosphere at ambient temperature for 1 h. 7.11 (153 mg, 0.5 mmol) and 7.22a (108 mg, 0.5 mmol) were added and the mixture was cooled to -45\degree C. After adding Et\textsubscript{2}Zn (1.1M in toluene, 0.5 ml) the reaction mixture was stirred for 18 h and poured into NH\textsubscript{4}Cl (aq) (25 ml) and diluted with ether (25 ml). The organic layer was separated, and the aqueous layer was extracted two times with diethyl ether (20 ml). The combined organic layers were dried over MgSO\textsubscript{4} filtered and concentrated \textit{in vacuo}. Purification by column chromatography (SiO\textsubscript{2} diethyl ether/pentane, 1:5, R\textsubscript{f} = 0.35) gave 184 mg (67\%) of 7.24 as a colorless oil (mixture of threo:erythro ratio: 75/25). \textsuperscript{1}H-NMR (200 MHz) \(\delta = 7.49-7.04\) (m, 10H), 4.59 (d, \(J = 12.0\) Hz, 2H), 4.33 (d, \(J = 12.0\) Hz, 1H), 4.21 (d, \(J = 12.0\) Hz, 1H), 3.98 (m, 2H), 3.56 (s, 1H, (OH erythro)), 3.37 (d, \(J = 2.0\) Hz, 1H, (OH threo)), 3.19 (d, \(J = 18.0\) Hz, 1H, (erythro)), 3.17 (d, \(J = 18.0\) Hz, 1H, (threo)), 2.49 (d, \(J = 18.0\) Hz, 1H, (erythro)), 2.46 (d, \(J = 18.0\) Hz, 1H, (threo)), 2.32 (m, 1H), 2.07 (m, 2H), 1.78-1.28 (m, 11H), 0.88 (t, \(J = 7.0\) Hz, 3H), 0.77 (m, 3H), 0.12 (s, 9H); \textsuperscript{13}C-NMR (500MHz) \(\delta = 214.2, 143.6, 143.3, 128.6, 128.4, 128.1, 126.8, 126.4, 126.3, 103.7, 73.7 (e), 71.0 (t), 70.8 (e), 70.6 (t), 68.6, 68.5 (e), 68.1 (t), 58.8 (e), 58.7 (t), 49.1 (t), 49.0 (e), 45.7 (t), 44.8 (e), 40.7, 37.9 (e), 36.6 (t), 32.0 (e), 31.9 (t), 25.5, 24.6, 22.6, 20.7 (t), 20.6 (e), 14.0, 12.6, 0.5 (e), 0.3 (t). threo (t), erythro (e); Ms (EI) for C\textsubscript{33}H\textsubscript{48}O\textsubscript{5}Si: m/z = 552 (M)+.

1-(1-Ethyl-3-oxo-8,8-diphenyl-6,10-dioxaspiro[4.5]decan-2-yl)-3-\{(trimethylsilyl)oxy\}octyl methanesulfonate (7.26).
To a solution of 7.24 (127 mg, 0.23 mmol) and Et\textsubscript{3}N (350 \textmu l, 5 mmol) in THF (5 ml) was added MsCl (77 \textmu l, 1 mmol) at 0\degree C. The reaction mixture was stirred for 3 h, poured into NH\textsubscript{4}Cl (aq) (25 ml) and diluted with ether (25 ml). The organic layer was separated, and the aqueous layer was extracted two times with diethyl ether (20 ml). The combined organic layers were dried over MgSO\textsubscript{4} filtered and concentrated \textit{in vacuo}. Purification by column chromatography (SiO\textsubscript{2} diethyl ether/pentane, 2:5, R\textsubscript{f} = 0.43) gave 70 mg (48\%) of 7.26 as a colorless oil which decomposed upon standing; \textsuperscript{1}H-NMR (300 MHz) \(\delta = 7.41\) (m, 2H), 7.28-7.16 (m, 8H), 7.04 (m, 2H), 5.09 (m, 1H, threo), 5.02 (m, 1H, erythro), 4.61 (d, \(J = 11.0\) Hz, 2H), 4.28 (d, \(J = 11.0\) Hz, 1H), 4.16 (d, \(J = 11\) Hz, 1H), 3.76 (m, 1H), 3.23 (d, \(J = 18.0\) Hz, 1H), 2.95 (d, \(J = 18.0\) Hz, 1H), 2.49 (d, \(J = 18.0\) Hz, 1H), 2.46 (d, \(J = 18.0\) Hz, 1H), 2.41 (d, \(J = 18.0\) Hz, 1H), 2.32 (m, 1H), 2.07 (m, 2H), 1.78-1.28 (m, 11H), 0.88 (t, \(J = 7.0\) Hz, 3H), 0.77 (m, 3H), 0.12 (s, 9H); \textsuperscript{13}C-NMR (500MHz) \(\delta = 214.2, 143.6, 143.3, 128.6, 128.4, 128.1, 126.8, 126.4, 126.3, 103.7, 73.7 (e), 71.0 (t), 70.8 (e), 70.6 (t), 68.6, 68.5 (e), 68.1 (t), 58.8 (e), 58.7 (t), 49.1 (t), 49.0 (e), 45.7 (t), 44.8 (e), 40.7, 37.9 (e), 36.6 (t), 32.0 (e), 31.9 (t), 25.5, 24.6, 22.6, 20.7 (t), 20.6 (e), 14.0, 12.6, 0.5 (e), 0.3 (t). threo (t), erythro (e); Ms (EI) for C\textsubscript{33}H\textsubscript{48}O\textsubscript{5}Si: m/z = 552 (M)+.
17.5 Hz, 1H), 2.98 (s, 3H, threo), 2.97 (s, 3H, erythro), 2.38 (d, \( J = 17.5 \) Hz, 1H), 2.32 (m, 1H, 2.14 (m, 1H), 1.86 (m, 1H), 1.66 (m, 1H), 1.48-1.11 (m, 10H), 0.86 (t, \( J = 7.0 \) Hz, 3H), 0.73 (t, \( J = 7.0 \) Hz, 3H), 0.12 (s, 9H, threo), 0.09 (s, 9H, erythro); \(^{13}\)C-NMR (200MHz) 215.1, 142.7, 128.6, 128.1, 126.9, 124.5, 124.7, 107.2, 106.9(e), 79.2, 68.7, 53.2, 47.9, 47.4, 39.3, 34.6, 31.5, 29.2, 24.6, 23.2(e), 22.5, 21.8(e), 14.0, 10.2, 9.3, 1.9; erythro (e); Ms (EI) for C\(_{34}\)H\(_{50}\)O\(_7\)SSi: m/z = 630 (M)+.

3-(3-[[tert-Butyl(dimethyl)silyloxy]-1-hydroxyoctyl)-4-ethyl-8,8-diphenyl-6,10-dioxaspiro[4.5]decan-2-one (7.25).

A solution of Cu(OTf)\(_2\) (14.4 mg, 0.04 mmol) and L\(_2\) (42.4 mg, 0.08 mmol) in freshly distilled toluene (20 ml) was stirred under a nitrogen atmosphere at ambient temperature for 1 h. 7.11 (612 mg, 2 mmol) and 7.22b (516 mg, 2 mmol) were added and the mixture was cooled to -45°C. After adding Et\(_2\)Zn (1.1M in toluene, 2 ml) the reaction mixture was stirred for 18 h and poured into NH\(_4\)Cl (aq) (25 ml) and diluted with ether (25 ml). The organic layer was separated, and the aqueous layer was extracted two times with diethyl ether (20 ml). The combined organic layers were dried over MgSO\(_4\), filtered and concentrated \textit{in vacuo}. Purification by column chromatography (SiO\(_2\) diethyl ether/pentane, 1:60, Rf = 0.27) gave 764 mg (65%) of 7.25 as a colorless oil (mixture of threo:erythro ratio: 65/35). \(^{1}\)H-NMR (500 MHz) \( \delta = 7.49-7.07 \) (m, 10H), 4.61 (d, \( J = 12.0 \) Hz, 2H), 4.35 (d, \( J = 12.0 \) Hz, 1H), 4.23 (d, \( J = 12.0 \) Hz, 1H), 4.13 (m, 1H (t)), 3.98 (m, 1H (e)), 3.53 (s, 1H, (OH, (t)), 3.38 (s, 1H, (OH, (e)), 3.17 (d, \( J = 18.0 \) Hz, 1H), 2.51 (m, 1H), 2.40 (m, 1H, 2.22 (m, 1H), 2.06 (m, 1H), 1.76-1.68 (m, 1H), 1.59-1.49 (m, 2H), 1.39-1.23 (m, 8H), 0.90 (m, 12H), 0.78 (t, \( J = 7.5 \) Hz, 3H), 0.11 (s, 3H), 0.09 (s, 3H); \(^{13}\)C-NMR (500MHz) \( \delta = 213.8 \) (t), 231.7 (e), 143.7, 143.4, 128.6 (t), 128.4 (e), 128.4 (e), 128.1 (t), 126.9, 126.4 (t), 126.2 (e), 103.6, 73.4 (e), 71.0 (t), 70.8 (e), 70.7 (t), 70.5, 68.6 (e), 68.0 (t), 58.9 (e), 58.6 (t), 49.1 (t), 49.0 (e), 45.7 (t), (e), 41.0 (e), 39.6 (t), 37.8 (e), 36.1 (t), 32.0 (e), 31.9 (t), 25.8 (t), 25.3 (e), 24.4, 22.6 (e), 22.5 (t), 20.6, 17.9, 14.1 (t), 14.0 (e), 12.7 (e), 12.6 (t), -4.1 (e), -4.6, -4.8 (t); Ms (EI) for C\(_{36}\)H\(_{54}\)O\(_5\)Si: m/z = 595 (M)+.

3-[[tert-Butyl(dimethyl)silyloxy]-1-(1-ethyl-3-oxo-8,8-diphenyl-6,10-dioxaspiro[4.5]decan-2-yl)octyl acetate (7.27).

To a solution of 7.25 (650 mg, 1.1 mmol) and DMAP (20 mg) in pyridine (10 ml) was added Ac\(_2\)O (2 ml, 22 mmol) at 0°C. The reaction mixture was stirred for 3 h, poured in NH\(_4\)Cl (aq) (25 ml) and diluted with ether (25 ml). The organic layer was separated, and the aqueous layer was extracted two times with diethyl ether (20 ml). The combined organic layers were dried over MgSO\(_4\), filtered and concentrated \textit{in vacuo}. Purification by column chromatography (SiO\(_2\) diethyl ether/pentane, 1:8, Rf = 0.17) gave 490 mg (70%) of 7.27, 14 mg (4%) of 7.28 (Rf = 0.34) and 18 mg (4%) of 7.29 (Rf = 0.30) as colorless oils. \(^{1}\)H-NMR (300 MHz) \( \delta = 7.42-7.02 \) (m, 10H), 5.21 (m, 1H), 4.56 (d, \( J = 12.0 \) Hz, 2H), 4.26 (d, \( J = 12.0 \) Hz, 1H), 4.13 (d, \( J = 12.0 \) Hz, 1H), 3.61 (m, 1H), 3.13 (d, \( J = 19.0 \) H, 1H), 2.49-2.28 (m, 2H), 2.03-1.90 (m, 5H), 1.71-1.54 (m, 1H), 1.45-1.20 (m, 10H), 0.88-
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$0.75 (m, 12H), 0.66 (t, J = 7.5 Hz, 3H), -0.01 (s, 3H), -0.03 (s, 3H); ^{13}\text{C-NMR (500MHz)} \delta = 211.0, 170.4, 143.4, 143.1, 128.6 (t), 128.4 (e), 128.1, 126.9, 126.3, 103.4, 69.6 (t), 69.0 (e), 70.8, 70.4 (t), 70.0 (e), 68.6, 56.2 (t), 56.4 (t), 50.3 (t), 50.6 (e), 40.5, 44.8, 40.1, 37.5 (t), 36.4 (e), 31.8, 25.8, 32.0, 24.1 (t), 24.8 (e), 22.6, 21.1, 20.0 (t), 18.0 (e), 14.0, 12.5 (t), 12.6 (e), -4.2 (t), -4.5 (e), -4.8 (t), -4.5 (e); Ms (EI) for C$_{38}$H$_{56}$O$_{6}$Si: m/z = 636 (M)$^+$.}

$3-((E)-3-[(\text{tert-Butyl}(\text{dimethyl)}\text{silyl})\text{oxy}])\text{octylidene}-4$-$\text{ethyl-8,8}$-$\text{diphenyl-6,10-dioxaspiro[4.5]decan-2-one (7.28).}$

$^{1}\text{H-NMR (200 MHz)} \delta = 7.49-7.05 (m, 10H), 6.77-6.64 (m, 1H), 4.61-4.30 (m, 4H), 3.77 (m, J = 6.0 Hz, 1H), 3.13 (m, 1H), 2.88 (d, J = 18.0 Hz, 1H), 2.58 (d, J = 18.0 Hz, 1H), 2.29 (m, 2H), 1.90-1.73 (m, 2H), 1.41-1.19 (m, 9H), 0.95-0.56 (m, 15H), 0.07-0.03 (m, 6H); ^{13}\text{C-NMR (200MHz)} \delta = 201.3, 144.2, 143.9, 141.5, 135.2, 128.5, 128.3, 127.6, 128.1, 127.1, 127.6, 126.5, 124.4, 103.9, 71.6, 70.0, 68.6, 47.6, 44.9, 44.7, 37.8 (t), 37.6 (e), 37.5, 31.9, 25.8 (t), 25.2 (e), 24.8, 22.6, 23.6, 18.1, 14.1, 11.9, -4.5.$

$3-([\text{tert-Butyl}(\text{dimethyl)}\text{silyl})\text{oxy}]-\text{1-(1-ethyl-3-hydroxy-8,8}$-$\text{diphenyl-6,10-dioxaspiro[4.5]dec-2-yl})\text{octyl acetate (7.31).}$

To a solution of NaBH$_4$ (36 mg, 1 mmol) in 5 ml MeOH was added $7.27$ (305 mg, 0.48 mmol) at 0°C. The reaction mixture was stirred for 4 h, poured into NH$_4$Cl (aq) (25 ml) and diluted with ether (25 ml). The organic layer was separated, and the aqueous layer was extracted two times with diethyl ether (20 ml). The combined organic layers were dried over MgSO$_4$, filtered and concentrated in vacuo. Purification by column chromatography (SiO$_2$ diethyl ether/pentane, 1:2, $R_f = 0.36$) gave 61mg (20%) of $7.31$ and 138 mg (45%) of $7.30$ ($R_f = 0.29$) as colorless oils. $^{1}\text{H-NMR (300 MHz)} \delta = 7.42-7.01 (m, 10H), 5.20 (m, 1H), 4.53-4.26 (m, 4H), 3.58 (m, 1H), 2.67 (m, 1H), 2.16 (s, 3H), 2.04 (s, 3H), 1.82 (m, 1H), 1.64-1.23 (m, 11H), 0.85 (m, 12H), 0.70-0.61 (m, 3H), 0.06-0.01 (m, 6H); ^{13}\text{C-NMR (200MHz)} \delta = 170.4, 167.6, 153.6, 143.8, 141.5, 128.6, 128.5, 128.1, 126.4, 126.1, 109.1, 108.0, 70.5, 70.4, 69.5, 68.8, 51.1, 50.6, 49.1, 48.5, 44.7, 38.9, 21.2, 37.3 (t), 36.2 (e), 32.2, 25.9, 24.2, 22.6, 21.8, 21.5, 22.1, 14.0, 12.3, -4.1, -4.9.$

$3-([\text{tert-Butyl}(\text{dimethyl)}\text{silyl})\text{oxy}]-1-(\text{1-ethyl-3-hydroxy-8,8}$-$\text{diphenyl-6,10-dioxaspiro[4.5]dec-2-yl})\text{octyl acetate (7.31).}$

To a solution of NaBH$_4$ (36 mg, 1 mmol) in 5 ml MeOH was added $7.27$ (305 mg, 0.48 mmol) at 0°C. The reaction mixture was stirred for 4 h, poured into NH$_4$Cl (aq) (25 ml) and diluted with ether (25 ml). The organic layer was separated, and the aqueous layer was extracted two times with diethyl ether (20 ml). The combined organic layers were dried over MgSO$_4$, filtered and concentrated in vacuo. Purification by column chromatography (SiO$_2$ diethyl ether/pentane, 1:2, $R_f = 0.36$) gave 61mg (20%) of $7.31$ and 138 mg (45%) of $7.30$ ($R_f = 0.29$) as colorless oils. $^{1}\text{H-NMR (300 MHz)} \delta = 7.42-7.01 (m, 10H), 5.20 (m, 1H), 4.53-4.26 (m, 4H), 3.58 (m, 1H), 2.67 (m, 1H), 2.16 (s, 3H), 2.04 (s, 3H), 1.82 (m, 1H), 1.64-1.23 (m, 11H), 0.85 (m, 12H), 0.70-0.61 (m, 3H), 0.06-0.01 (m, 6H); ^{13}\text{C-NMR (200MHz)} \delta = 170.4, 167.6, 153.6, 143.8, 141.5, 128.6, 128.5, 128.1, 126.4, 126.1, 109.1, 108.0, 70.5, 70.4, 69.5, 68.8, 51.1, 50.6, 49.1, 48.5, 44.7, 38.9, 21.2, 37.3 (t), 36.2 (e), 32.2, 25.9, 24.2, 22.6, 21.8, 21.5, 22.1, 14.0, 12.3, -4.1, -4.9.$
3-\{[tert-Butyl(dimethyl)silyl]oxy\}-1-(1-ethyl-3-hydroxy-8,8-diphenyl-6,10-dioxaspiro[4.5]dec-2-yl)octyl acetate (7.30).

\[1H-NMR\ (300\ MHz) \ \delta = 7.44-7.04\ (m, 10H), 5.28\ (m, 1H), 4.56\ (m, 2H), 4.15\ (m, 1H), 3.67\ (m, 1H), 2.74\ (m, 1H), 2.35\ (d, \ J = 9.0\ Hz, 1H), 2.21\ (d, \ J = 9.0\ Hz, 1H), 2.00\ (s, 3H), 1.89-1.73\ (m, 3H), 1.51-1.24\ (m, 11H), 0.86\ (m, 12H), 0.68-0.59\ (m, 3H), 0.08-0.02\ (m, 6H); \[13C-NMR\ (200MHz) \ \delta = 170.4, 143.7, 143.4, 128.6, 128.5, 128.1, 126.9, 126.4, 126.2, 107.6, 70.6, 71.6, 71.1, 70.6, 69.5, 68.5, 56.6, 56.4, 50.6, 50.3, 44.8, 42.6, 41.9, 40.5, 40.1, 38.7, 37.6, 36.6, 32.0, 31.8, 25.9, 24.8, 24.1, 22.6, 21.2, 20.5, 18.0, 14.0, 12.5, -4.3, -4.4, -4.6; Ms (CI) for C\textsubscript{36}H\textsubscript{58}O\textsubscript{6}Si: m/z = 638 (M)+.\]

3-\{[tert-Butyl(dimethyl)silyl]oxy\}-1-(3-\{[tert-Butyl(dimethyl)silyl]oxy\}-1-ethyl-8,8-diphenyl-6,10-dioxaspiro[4.5]dec-2-yl)octyl acetate (7.32).

To a solution of imidazole (272 mg, 4 mmol) and 7.30 (688 mg, 1 mmol) in DMF (5 ml) was added TBDMSCl (181 mg, 1.2 mmol). The reaction mixture kept at 50 °C for 14 h, poured into NH\textsubscript{4}Cl (aq) (25 ml) and diluted with ether (25 ml). The organic layer was separated, and the aqueous layer was extracted two times with diethyl ether (20 ml). The combined organic layers were dried over MgSO\textsubscript{4}, filtered and concentrated in vacuo. Purification by column chromatography (SiO\textsubscript{2} diethyl ether/pentane, 1:12, Rf = 0.40) gave 507 mg (67%) of 7.32 as a colorless oil. \[1H-NMR\ (300\ MHz) \ \delta = 7.45-7.01\ (m, 10H), 5.19\ (m, 1H (t)), 5.07\ (m, 1H (e)), 4.46\ (d, \ J = 12.0\ Hz, 2H), 4.25\ (d, \ J = 12.0\ Hz, 2H), 4.11\ (m, 1H), 3.56\ (m, 1H), 2.15\ (m, 1H), 1.97\ (s, 3H), 2.03-1.92\ (m, 1H), 1.79-1.70\ (m, 2H), 1.60-1.20\ (m, 12H), 0.85-0.81\ (m, 21H), 0.61\ (t, \ J = 6.0\ Hz, 3H), 0.03-0.05\ (m, 12H); \[13C-NMR\ (200MHz) \ \delta = 170.4, 143.9, 128.5, 128.2, 128.1, 126.7, 126.1, 106.4, 106.3, 70.7\ (t), 70.5\ (e), 70.2\ (t), 70.0\ (e), 69.8, 69.5, 68.5, 55.3\ (t), 54.9\ (e), 48.6, 44.7, 41.1\ (t), 40.9\ (e), 40.6, 38.0\ (t), 36.3\ (e), 32.0, 31.9, 26.0, 25.8, 24.6\ (t), 24.1\ (e), 22.7\ (t), 22.6\ (e), 21.2, 18.0\ (t), 17.8\ (e), 20.6, 14.0, 12.4\ (t), 12.2\ (e), -3.8, -4.7, -4.2, -4.5; Ms (Cl) for C\textsubscript{44}H\textsubscript{72}O\textsubscript{6}Si\textsubscript{2}: m/z = 753 (M)+.\]

3-\{[tert-Butyl(dimethyl)silyl]oxy\}-1-hydroxyoctyl)-4-ethyl-8,8-diphenyl-6,10-dioxaspiro[4.5]decan-2-ol (7.33a).

Under argon atmosphere, a solution of 7.27 (595 mg, 1 mmol) in ether (5 ml) was treated with Zn(BH\textsubscript{4})\textsubscript{2} (5 ml, 0.3 M in diethyl ether) at -30°C. After stirring for 1 h at the same temperature the reaction mixture was quenched with NH\textsubscript{4}Cl (aq) into a beaker (250 ml) and stirred for 30 min. The reaction mixture was diluted with diethyl ether (50 ml) and the organic layer was separated. The aqueous layer was extracted two times with diethyl ether and the combined organic layers were dried over MgSO\textsubscript{4}, filtered and concentrated in vacuo. Purification by column chromatography (SiO\textsubscript{2} diethyl ether/pentane, 5:4, Rf = 0.23), gave 123 mg (26%) of 7.33a and 290 mg (47%) of 7.33b (Rf = 0.18) as a colorless oils. \[1H-NMR\ (300\ MHz) \ \delta = 7.42-7.02\ (m, 10H), 5.28\ (m, 1H), 4.56\ (m, 2H), 4.35\ (m, 1H), 3.67\ (m, 1H), 2.74\ (m, 1H), 2.35\ (d, \ J = 9.0\ Hz, 1H), 2.21\ (d, \ J = 9.0\ Hz, 1H), 2.00\ (s, 3H), 1.89-1.73\ (m, 32.0, 31.9, 26.0, 25.8, 24.6\ (t), 24.1\ (e), 22.7\ (t), 22.6\ (e), 21.2, 18.0\ (t), 17.8\ (e), 20.6, 14.0, 12.4\ (t), 12.2\ (e), -3.8, -4.7, -4.2, -4.5; Ms (Cl) for C\textsubscript{44}H\textsubscript{72}O\textsubscript{6}Si\textsubscript{2}: m/z = 753 (M)+.\]
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10H), 4.54-4.30 (m, 4H), 4.15 (m, 1H), 3.68 (m, 1H), 3.51 (m, 1H), 2.55 (m, 1H), 2.31-2.11 (m, 2H), 1.70-1.42 (m, 6H), 0.83 (m, 12H), 0.69 (t, J = 7.2 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H); 13C-NMR (200MHz) δ = 144.2, 143.7, 128.6, 128.1, 126.8, 126.5, 126.1, 107.7, 74.3, 73.3, 71.8, 70.1, 68.9, 58.1, 50.3, 44.8, 41.1, 38.3, 37.9, 32.0, 25.8, 24.3, 22.6, 22.1, 17.9, 14.0, 12.8, -3.9, -4.7.

3-(3-[(tert-Butyl(dimethyl)silyl)oxy]-1-hydroxyoctyl)-4-ethyl-8,8-diphenyl-6,10-dioxaspiro[4.5]decan-2-ol (7.33b).

1H-NMR (300 MHz) δ = 7.42-7.02 (m, 10H), 4.54-4.31 (m, 4H), 4.17-4.13 (m, 1H), 3.95-3.90 (m, 2H), 3.74 (s, 1H), 2.55 (d, J = 7.0 Hz, 1H), 2.30-2.12 (m, 2H), 1.77-1.44 (m, 8H), 1.31-1.12 (m, 6H), 0.83 (m, 12H), 0.67 (t, J = 7.2 Hz, 3H), 0.04 (s, 3H), 0.02 (s, 3H); 13C-NMR (200MHz) δ = 144.2, 143.7, 128.6, 128.5, 128.0, 126.8, 126.5, 126.1, 107.7, 72.2, 71.8, 70.2, 70.0, 69.0, 58.0, 50.3, 44.8, 39.5, 38.1, 35.6, 31.8, 25.8, 25.6, 22.6, 22.0, 17.9, 14.0, 12.7, -4.6, -4.8; Ms (CI) for C36H56O5Si: m/z = 596 (M)+.

3-[(tert-Butyl(dimethyl)silyl)oxy]-1-(3-[(tert-butyl(dimethyl)silyl)oxy]-1-ethyl-8,8-diphenyl-6,10-dioxaspiro[4.5]dec-2-yl)-1-octanol (7.34).

To a solution of imidazole (190 mg, 2.8 mmol) and 7.33a (518 mg, 0.86 mmol) in 5 ml DMF was added TBDMSCl (90 mg, 0.5 mmol). The reaction mixture kept at 50° C for 14 h, poured into NH4Cl (aq) (25 ml) and diluted with ether (25 ml). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (20 ml) two times. The combined organic layers were dried over MgSO4, filtered and concentrated in vacuo. Purification by column chromatography (SiO2 diethyl ether/pentane, 1:12, Rf = 0.26) gave 310 mg (88%) of 7.34 as a colorless oil. 1H-NMR (300 MHz) δ = 7.37-7.06 (m, 10H), 4.45 (d, J = 7.0 Hz, 2H), 4.26 (m, 3H), 3.83 (m, 1H), 3.73 (s, 1H (OH)), 2.22 (m, 1H), 1.97 (m, 1H), 1.75-1.21 (m, 14H), 0.83 (m, 21H), 0.68 (t, J = 6.5 Hz, 3H), 0.03 (m, 12H); 13C-NMR (200MHz) δ = 144.1, 128.6, 128.3, 128.1, 126.7, 126.1, 107.0, 71.1, 69.9, 69.6, 67.8, 57.1, 49.1, 44.8, 40.7, 40.5, 37.9, 32.0, 25.9, 24.4, 22.6, 21.3, 17.9 (t), 17.7 (e), 14.0, 12.6, -3.8, -4.2, -4.6; Ms (CI) for C42H70O5Si2: m/z = 711 (M)+.

2-(Phenylselenyloctanal (7.35).

To a solution of PhSeBr (5.9 g, 20 mmol) in 150 ml CH2Cl2, was added dropwise morpholine (4.4 ml, 50 mmol). After 15 min, octanal (3.3 g, 25 mmol) was added and the reaction mixture was stirred for an additional hour. After filtration the reaction mixture was concentrated in vacuo. Purification by column chromatography (SiO2 diethyl ether/pentane, 1:35, Rf = 0.45) gave 2.5 g (40%) of 7.35 as yellow oil. 1H-NMR (200 MHz) δ = 9.31 (m, 1H), 7.46-7.42 (m, 2H), 7.27-7.16 (m, 3H), 3.54 (m, 1H), 1.78-1.20 (m, 10H), 0.81 (t, 3H); 13C-NMR (200 MHz) δ = 193.0,
135.7, 129.2, 128.7, 126.0, 52.9, 31.5, 28.8, 27.9, 27.6, 22.5, 13.9. Ms (EI) for C_{14}H_{20}OSe: m/z = 283 (M)^{+}.

4-Ethyl-3-(3-hydroxy-2,2-diphenylpropoxy)-5-[1-hydroxy-2-(phenylselenyl)octyl]-2-cyclopenten-1-one (7.39).

A solution of Cu(OTf)\textsubscript{2} (3.6 mg, 0.01 mmol) and L\textsubscript{2} (10.6 mg, 0.02 mmol) in freshly distilled toluene (9 ml) was stirred under a nitrogen atmosphere at ambient temperature for 1 h. 7.11 (153 mg, 0.5 mmol) and 7.35 (141 mg, 0.5 mmol) were added and the mixture was cooled to -45°. After adding Et\textsubscript{2}Zn (1.1M in toluene, 1 ml) the reaction stirred for 18 h and poured into NH\textsubscript{4}Cl (aq) (25 ml) and diluted with ether (25 ml). The organic layer was separated, and the aqueous layer was extracted two times with diethyl ether (20 ml). The combined organic layers were dried over MgSO\textsubscript{4}, filtered and concentrated in vacuo. Purification by column chromatography (SiO\textsubscript{2} diethyl ether/pentane, 2:5, Rf = 0.44) gave 189 mg (61%) of 7.38 and 14 mg (5%) 7.39 (Rf = 0.39) as colorless oils (mixture of threo:erythro 93/7). 1H-NMR (200 MHz) δ = 7.48 (m, 2H), 7.34-7.13 (m, 13H), 5.37 (s, 1H), 4.82 (s, 1H (OH)), 4.63 (d, J = 9.6 Hz, 1H), 4.51 (d, J = 9.6 Hz, 1H), 4.32 (m, 2H), 3.80 (m, 1H), 3.70 (m, 1H), 3.16 (m, 1H), 2.71 (m, 1H), 2.45 (m, 1H), 1.98 (m, 1H), 1.78 (m, 1H), 1.48-1.22 (m, 11H), 0.83 (t, J = 6.3 Hz, 3H), 0.47 (t, J = 7.2 Hz, 3H); 13C-NMR (200 MHz) δ = 208.0, 191.0, 142.2, 135.2, 133.6, 128.9, 128.6, 128.5, 127.8, 127.3, 127.2, 127.0, 140.7, 74.6, 74.3, 66.4, 52.4, 52.3, 51.1, 44.6, 34.2, 31.6, 29.1, 28.2, 22.5, 22.4, 14.0, 8.5.

4-Ethyl-3-(3-hydroxy-2,2-diphenylpropoxy)-5-[1-hydroxy-2-(phenylselenyl)octyl]-2-cyclopenten-1-one (7.38).

1H-NMR (200 MHz) δ = 7.51 (m, 2H), 7.30-7.08 (m, 13H), 5.27 (s, 1H), 4.63 (d, J = 9.6 Hz, 1H), 4.44 (d, J = 9.6 Hz, 1H), 4.27 (m, 2H), 4.08 (d, J = 2.1 Hz, 1H (OH)), 3.80 (m, 1H), 3.20 (m, 1H), 2.48 (m, 1H), 2.34 (m, 1H), 1.67-1.13 (m, 13H), 0.80 (t, J = 6.0 Hz, 3H), 0.50 (t, J = 7.5 Hz, 3H); 13C-NMR (200 MHz) δ = 207.4, 190.8, 142.1, 134.3, 130.3, 128.9, 128.5, 128.4, 127.8, 127.2, 127.1, 127.0, 104.6, 76.0, 74.6, 66.3, 52.2, 51.1, 50.9, 44.6, 31.7, 29.6, 29.2, 28.1, 22.6, 22.5, 14.1, 8.8; NOESY/COSY; Ms (CI) for C_{36}H_{44}O_{4}Se: m/z = 619 (M)^{+}.

1-(1-Ethyl-8,8-diphenyl-6,10-dioxaspiro[4.5]dec-3-en-2-yl)-2-(phenylselenyl)-1-octanol (7.40).

To a solution 7.38a (100 mg, 0.16 mmol) in 10 ml ether was added 1 ml DIBAL-H (1M in diethyl ether). The reaction mixture was stirred for 5 h, poured into NH\textsubscript{4}Cl (aq) (25 ml) and diluted with ether (25 ml). The organic layer was separated, and the aqueous layer was extracted two times with diethyl ether (20 ml). The combined organic layers were dried over MgSO\textsubscript{4}, filtered and concentrated in vacuo. Purification by column chromatography (SiO\textsubscript{2} diethyl ether/pentane, 1:3, Rf = 0.48) gave 33 mg (34%) of 7.41a and 15 mg (23%) of 7.41b (Rf = 0.17) as colorless oils. 1H-NMR (300 MHz) δ = 7.55 (m, 2H), 7.42-7.08 (m, 13H), 6.47 (d, J =
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6.1 Hz, 1H), 5.89 (dd, J = 6.1 Hz, J = 3.6 Hz, 1H), 4.55-4.32 (m, 4H), 3.68 (m, 1H), 3.18 (m, 1H), 3.00 (m, 1H), 2.85 (d, J = 3.6 Hz, 1H (OH)), 1.91-1.08 (m, 13H), 0.90-0.77 (m, 3H); ¹³C-NMR (300 MHz) δ = 164.8, 144.3, 143.8, 136.3, 134.7, 129.5, 129.1, 128.8, 128.6, 128.3, 128.2, 127.6, 126.9, 126.7, 126.6, 126.3, 110.5, 75.6, 70.0, 69.9, 68.7, 53.2, 52.2, 50.0, 49.2, 48.9, 44.9, 31.7, 30.6, 29.2, 27.8, 22.6, 22.1, 14.1, 12.4; Ms (CI) for C₃₆H₄₄O₃Se: m/z = 604 (M)+.

5-Ethyl-4-[1-hydroxy-2-(phenylselenyl)octyl]-2-cyclopenten-1-one (7.41).

1H-NMR (300 MHz) δ = 7.65 (dd, J = 5.8 Hz, J = 2.2 Hz, 1H), 7.53-7.47 (m, 2H), 7.30-7.22 (m, 3H), 6.12 (dd, J = 5.8 Hz, J = 1.8 Hz, 1H), 3.47 (m, 1H), 3.27 (m, 1H), 3.02 (m, 1H), 2.39 (d, J = 4.4 Hz, 1H (OH)), 1.86-1.29 (m, 13H), 0.89-0.82 (m, 6H); ¹³C-NMR (300 MHz) δ = 211.0, 164.8, 134.7, 134.6, 129.4, 128.4, 128.2, 75.6, 53.2, 49.2, 48.9, 31.6, 29.2, 29.0, 28.4, 23.1, 22.6, 14.1, 10.3; HRMS calcd for C₂₁H₃₀O₂Se 394.141, found 394.136.

Ethyl 3-oxo-octanoate (7.45). Prepared according to a literature procedure. Purification by distillation (b.p. = 66 °C (0.4 mm) gave 39.1 g (57%) of 7.45 as a colorless liquid. ¹H-NMR (300 MHz, CDCl₃) δ = 4.18 (q, J = 6.9 Hz, 2H), 3.41 (s, 2H), 2.20 (t, J = 6.8 Hz, 2H), 1.55 (q, J = 6 Hz, 2H), 1.25 (m, 9H), 0.87 (t, J = 6.8 Hz, 3H); ¹³C-NMR (200 MHz, CDCl₃): δ = 202.8, 167.1, 61.1, 49.1, 42.8, 31.0, 22.9, 22.2, 13.9, 13.7.

Ethyl (Z)-3-ethoxy-2-octenoate (7.46).

This material was prepared by the procedure of Blaisen and Marie. Ethyl 3-oxo-octanoate (39 g, 209 mmol) was stirred with triethyl orthoformate (35.4 ml, 213 mmol) and six drops of conc. H₂SO₄ for 18 h at room temperature. Purification by distillation (b.p. = 78 °C (0.35 mm) gave 38.6 g (84%) of 7.46 as a colorless liquid. ¹H-NMR (300 MHz, CDCl₃) δ = 4.91 (s, 1H), 4.10 (q, J = 7.0 Hz, 2H), 3.76 (q, J = 7.0 Hz, 2H), 2.67 (m, 2H), 1.51 (m, 2H), 1.46-1.19 (m, 12H), 0.85 (t, J = 6.5 Hz, 3H); ¹³C-NMR (200 MHz, CDCl₃) δ = 176.2, 167.7, 90.5, 63.6, 59.1, 32.1, 31.6, 27.3, 22.4, 14.4, 14.2, 14.0.

(Z)-3-Ethoxy-2-octen-1-ol (7.47).

To a solution of LiAlH₄ (5.13 g, 135 mmol) in 100 ml ether was added a solution of ethyl (Z)-3-ethoxy-2-octenoate (38 g, 177 mmol) in diethyl ether (100 ml) at 0°C. The reaction mixture was stirred at room temperature for 18 h. Slow hydrolysis with Na₂SO₄ (aq) solution (25 ml), and stirring for an additional 3 h gave a white precipitate, which was removed by filtration. The organic phase was dried over MgSO₄, filtered and concentrated in vacuo. This compound was not purified. ¹H-NMR (300 MHz, CDCl₃) δ = 4.62 (t, J = 7.7 Hz, 1H), 4.07 (d, J = 7.7 Hz, 2H), 3.63 (q, J = 7.0 Hz, 2H), 2.21 (t, J = 7.7 Hz, 2H), 1.43 (q, J = 7.4 Hz, 2H), 1.29-1.14 (m, 9H), 0.83 (t, J = 7.0 Hz, 3H).
(Z)-3-Ethoxy-2-octenal (7.42).

To a solution of (Z)-3-ethoxy-2-octen-1-ol (1.95 g, 11.3 mmol) and molecular sieves (30 g, 4 Å) in CH₂Cl₂ (200 ml) was added MnO₂ (30 g) and the reaction mixture was stirred for 18 h. After filtration and evaporation of the solvent compound 7.42 was obtained as a pure colorless liquid in 53% yield. ¹H-NMR (300 MHz, CDCl₃) δ = 9.74 (d, J = 7.7 Hz, 1H), 5.30 (d, J = 8.0 Hz, 1H), 3.83 (q, J = 7.0 Hz, 2H), 2.53 (t, J = 7.7 Hz, 2H), 1.57 (q, J = 7.3 Hz, 2H), 1.33-1.11 (m, 7H), 0.84 (t, J = 7 Hz, 3H); ¹³C-NMR (200 MHz, CDCl₃) δ = 190.4, 180.3, 104.6, 64.3, 31.4, 31.2, 27.9, 22.3, 14.1, 13.9.

3-(Trimethylsilyl)octanal (7.51).

Prepared according to a literature procedure. Purification by distillation (b.p. = 91 °C (20 mm)) gave 5.1 g (29%) of 7.51 as a colorless liquid. ¹H-NMR (200 MHz) 9.81 (t, J = 2.8 Hz, 1H), 2.39 (m, J = 2.8 Hz, 2H), 1.55 (m, 1H), 1.39-.111 (m, 8H), 0.81 (t, J = 7.3 Hz, 3H), 0.02 (s, 9H).

(Z)-1-(Trimethylsilyloxy)-3-(trimethylsilyl)-1-octene (7.56).

To a stirred mixture of 7.51 (7 g, 35 mmol) in hexane (300 ml) and hexamethyldisilazane (9.5 ml, 45 mmol) at −20°C under nitrogen was added TMSI (5.7 ml, 40 mmol) over a period of 15 min. The reaction mixture was stirred under the same conditions for 20 min, at room temperature for 2.5 h and quenched with ice cooled saturated aqueous sodium bicarbonate solution (200 ml). The organic phase was thoroughly washed with water, dried over MgSO₄ and concentrated in vacuo. Purification by distillation (b.p. = 95°C (1 mm)) gave 4.8 g (51%) of 7.56 as a colorless liquid. ¹H-NMR (200 MHz) δ = 6.11 (d, J = 5.8 Hz, 1H), 4.10 (dd, J = 5.8 Hz, J = 6.1 Hz, 1H), 2.16-1.77 (m, 1H), 1.77-1.49-1.08 (m, 8H), 0.81 (t, J = 6.6 Hz, 3H), -0.06 (s, 9H), -0.11 (s, 9H); ¹³C-NMR (200 MHz) δ = 136.1, 112.4, 36.7, 31.8, 29.7, 24.2, 22.7, 14.1, -0.4, -3.0.

(Z)-3-Iodo-2-octen-1-ol (7.58).

Under an argon atmosphere, Red-Al (3.4 M in toluene, 49 g, 338 mmol) was dissolved in diethyl ether (600 ml). To this mechanically stirred solution maintained at 0 °C was added dropwise 2-octyn-1-ol (25 ml, 169 mmol) in ether (50 ml). After 4 h at room temperature, the reaction mixture was re-cooled to 0 °C and quenched by addition of ethyl acetate (16.5 ml, 169 mmol). After the mixture was cooled to −78 °C, iodine (64 g, 254 mmol) was added in one portion and the reaction mixture was allowed to warm to room temperature over 2 h. The reaction mixture was quenched by slow addition of saturated Na₂SO₃ (aq), and the organic layer was separated and washed with Na₂SO₃ (aq), water and saturated NaCl (aq). The resulting organic solution was dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography (SiO₂ diethyl ether/pentane, 1:6, Rf = 0.30) gave 40.3 g (94%) of 7.58 as a light purple colored oil (100% cis). ¹H-NMR (300 MHz, CDCl₃): δ = 5.78 (t, J = 5.9 Hz, 1H), 4.14 (d, J = 5.9 Hz, 2H), 2.44 (t, J = 7.4 Hz, 2H), 1.48 (m, J = 7.0 Hz, 2H), 1.24 (m, 4H), 0.84 (t, J = 6.6 Hz, 3H); ¹³C-NMR (300 MHz, CDCl₃) δ = 136.1, 112.4, 36.7, 31.8, 29.7, 24.2, 22.7, 14.1, -0.4, -3.0.
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\[ \text{PhMe}_{2}SiO\longrightarrow\text{C}_{5}H_{11} \]

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\( \delta = 133.2, 111.0, 67.3, 45.1, 30.4, 28.8, 22.4, 14.0; \text{Ms (Cl) for CsH}_{15}IO: m/z = 254 (M)^{+}, 272 (M + NH}_{4}^{+}). \)

\( (Z)-1\text{-Dimethyl(phenyl)siloxy-3-iodo-2-octene (7.59)}. \)

To a solution of 7.58 (14g, 59 mmol) in CH₂Cl₂ (300 ml) was added Et₃N (8.3 ml, 60 mmol) and a catalytic amount of DMAP. At 0°C chlorodimethylphenylsilane (10 ml, 59 mmol) in CH₂Cl₂ (20 ml) was added over a period of 1 h. After an additional 1 h, the reaction mixture was poured into NH₄Cl (aq) and the organic layer was filtered and concentrated in vacuo. The residue was dissolved in pentane (300 ml) and washed with water, NaCl (aq) and dried over MgSO₄, filtered and concentrated in vacuo. The colorless oil 20.6 g (92 %) was used without further purification. 1H-NMR: 7.60-7.50 (m, 2H), 7.40-7.32 (m, 3H), 5.71 (t, \( J = 5.4 \) Hz, 1H), 4.17 (d, \( J = 5.4 \) Hz, 2H), 2.39 (t, \( J = 6.8 \) Hz, 2H), 1.45 (m, \( J = 6.6 \) Hz, 2H), 1.24 (m, 6H), 0.87 (t, \( J = 6.5 \) Hz, 3H), 0.39 (s, 6H); 13C-NMR: 142.3, 133.9, 133.4, 129.7, 127.8, 108.4, 68.2, 45.0, 31.9, 30.4, 22.4, 14.0, -1.7; Ms (Cl) for C₁₆H₂₅IOSi: m/z = 388 (M)+, 406 (M + NH₄)+.

\( (Z)-3\text{-Dimethyl(phenyl)silyl-2-octen-1-ol (7.60)}. \)

Under argon atmosphere 7.59 (30 g, 77 mmol) was dissolved in THF (400 ml). At -78°C, 2.2 equiv. of t-BuLi (100 ml, 1.7 M pentane) was added dropwise over a period of 10 min and the mixture was stirred for 2h at the same temperature. The reaction mixture was quenched with NH₄Cl (aq) (250 ml), the organic layer was separated, and the aqueous layer was extracted twice with 100 ml of diethyl ether. The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography (SiO₂ diethyl ether/pentane, 1:6, Rf = 0.35) gave 14.8 g (74%) of 7.60 as a colorless oil (100% cis). 1H-NMR (300 MHz, CDCl₃) \( \delta = 7.54-7.50 \) (m, 2H), 7.37-7.28 (m, 3H), 6.21 (t, \( J = 5.7 \) Hz, 1H), 3.94 (d, \( J = 5.7 \) Hz, 2H), 2.19 (t, \( J = 6.9 \) Hz, 2H), 1.41-1.19 (m, 8H), 0.88 (t, \( J = 6.8 \) Hz, 3H), 0.40 (s, 6H). 13C-NMR (300 MHz, CDCl₃) \( \delta = 142.4, 141.4, 139.5, 133.5, 129.0, 128.0, 62.3, 38.3, 31.9, 30.1, 22.5, 14.0, -1.0; \text{Ms (Cl) for C}_{16}H_{26}OSi: m/z = 262 (M)^{+}, 280 (M + NH}_{4}^{+}). \)

\( (Z)-3\text{-Dimethyl(phenyl)silyl-2-octenal (7.48)}. \)

To a solution of (COCl)₂ (3.7 ml, 42 mmol) in THF (20 ml) was added Me₂SO (6 ml, 84 mmol) in CH₂Cl₂ (10 ml) at -78°C, and the resulting solution was stirred for 5 min. To this solution alcohol 7.60 (10 g, 38 mmol) in THF (20 ml) was added slowly and the mixture was stirred for 30 min, followed by the addition of Et₃N (26 ml, 190 mmol) in CH₂Cl₂ (300 ml). The reaction mixture was warmed to room temperature and quenched with NH₄Cl (aq). The organic layer was separated and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography (SiO₂ diethyl ether/pentane, 1:50, Rf = 0.34) gave 7.8 g (79 %) of 7.48 as a bright yellow oil; (mixture of E/Z ratio 79% determined by 1H-NMR); 1H-NMR (300 MHz, CDCl₃) \( \delta = 9.68 \) (d, \( J = 8.5 \) Hz, 1H), 7.50-7.43 (m, 2H), 7.35-7.30 (m, 3H), 6.45 (d, \( J = 8.5 \) Hz,
1H), 2.33 (t, J = 8.0 Hz, 2H), 1.35-1.20 (m, 6H), 0.83 (t, J = 6.7 Hz, 3H), 0.50 (s, 6H); 13C-NMR (300 MHz, CDCl3) δ = 192.8, 170.8, 141.5, 138.9, 133.4, 129.4, 128.0, 39.0, 31.3, 28.6, 22.2, 13.7, -0.70; Ms (Cl) for C16H24OSi: m/z = 260 (M)+, 278 (M + NH4+).

2-{(Z)-3-[Dimethyl(phenyl)silyl]-1-hydroxy-2-octenyl}-3-ethylcyclopentanone (7.62b).
A solution of Cu(OTf)2 (21.6 mg, 0.06 mmol) and L2 (63.6 mg, 0.12 mmol) in freshly distilled toluene (9 ml) was stirred under a nitrogen atmosphere at ambient temperature for 1 h. 7.61 (252 µl, 3 mmol) and 7.48 (780 mg, 3 mmol) were added and the mixture was cooled to -45°C. After adding Et2Zn (1.1M in toluene, 3 ml) the reaction was stirred for 18 h and poured into NH4Cl (aq) (25 ml) and diluted with ether (25 ml). The organic layer was separated, and the aqueous layer was extracted two times with diethyl ether (25 ml). The combined organic layers were dried over MgSO4, filtered and concentrated in vacuo. Purification by column chromatography (SiO2 diethyl ether/pentane, 1:3, Rf = 0.53) gave 457 mg (38%) of 7.62a and 463 mg (41%) of 7.62b (Rf = 0.41) as colorless oils. 1H-NMR (200 MHz) δ = 7.49-7.46 (m, 2H), 7.30-7.28 (m, 3H), 6.93 (d, J = 10 Hz, 1H), 4.42 (m, 1H), 2.45 (d, J = 7.6 Hz, 1H), 1.40-1.00 (m, 6H), 0.84-0.75 (m, 6H), 0.41 (s, 3H), 0.37 (s, 3H); 13C-NMR (300MHz) δ = 221.9, 143.5, 141.8, 139.2, 133.6, 129.0, 127.9, 69.9, 58.9, 39.0, 38.4, 38.3, 31.6, 30.0, 27.7, 26.5, 22.4, 14.0, 11.3, -0.9, -1.0; Ms (Cl) for C23H36O2Si: m/z = 372 (M)+.

2-{(Z)-3-[Dimethyl(phenyl)silyl]-1-hydroxy-2-octenyl}-3-ethylcyclopentanol (7.63a).
Under an argon atmosphere, a solution of 7.62 (1116 mg, 3 mmol) in diethyl ether (40 ml) was treated with Zn(BH4)2 (8 ml, 0.5 M in diethyl ether) at -30°C. After stirring for 3 h at the same temperature the reaction mixture was quenched with NH4Cl (aq) in a beaker (250 ml) and stirred for 30 min. The reaction mixture was diluted with diethyl ether (50ml) and the organic layer was separated. The aqueous layer was extracted two times with diethyl ether and the combined organic layers were dried over MgSO4, filtered and concentrated in vacuo. Purification by column chromatography (SiO2 diethyl ether/pentane, 1:2) gave 395 mg (36%) of 7.63a (Rf = 0.55), 25 mg (3 % yield) of 7.63b (Rf = 0.50), 32 mg (3 % yield) of 7.63b (Rf = 0.25) and 382 mg (34 % yield) of 7.63a (Rf = 0.20) as colorless oils. 1H-NMR (300 MHz) δ = 7.53-7.51 (m, 2H), 7.34-7.32 (m, 3H), 6.14 (d, J = 10.0 Hz, 1H), 4.50 (dd, J =10.0 Hz, J = 3.0 Hz, 1H), 3.93 (q, J = 4.6 Hz,
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1H), 2.16-2.05 (m, 3H), 1.88 (m, 1H), 1.63-1.02 (m, 12H), 0.87 (m, 6H), 0.43 (s, 3H), 0.40 (s, 3H); ¹³C-NMR (200 MHz) δ = 144.3, 140.5, 139.9, 133.7, 129.0, 127.9, 76.9, 71.2, 53.3, 38.2, 37.8, 34.6, 31.7, 30.1, 29.5, 28.4, 22.5, 14.0, 12.3, -0.9, -1.2.

2-{(Z)-3-[Dimethyl(phenyl)silyl]-1-hydroxy-2-octenyl}-3-ethylcyclopentanol (7.63a).

1H-NMR (300 MHz) δ = 7.52-7.49 (m, 2H), 7.35-7.32 (m, 3H), 5.97 (d, J = 10.0 Hz, 1H), 3.94 (dd, J₁ =10.0 Hz, J₂ = 9.5 Hz, 1H), 3.88 (q, J = 7.0 Hz, 1H), 2.19-2.11 (m, 2H), 1.71 (m, 1H), 1.51-1.23 (m, 1H), 1.08 (m, 2H), 0.87 (t, J = 7.0 Hz, 3H), 0.75 (t, J = 7.0 Hz, 3H), 0.42 (s, 3H), 0.41 (s, 3H); ¹³C-NMR (200 MHz) δ = 144.4, 143.1, 139.9, 133.5, 129.2, 128.1, 78.0, 75.3, 57.9, 41.1, 38.4, 32.6, 31.7, 30.2, 28.7, 27.3, 22.5, 14.0, 12.2, -0.8, -0.9; Ms (CI) for C₂₃H₃₈O₂Si: m/z = 374 (M⁺), m/z 392 (NH₄⁺).

2-{(Z)-3-[Dimethyl(phenyl)silyl]-1-hydroxy-2-octenyl}-3-ethylcyclopentanol (7.63b).

1H-NMR (300 MHz) δ = 7.53-7.51 (m, 2H), 7.34-7.32 (m, 3H), 6.15 (d, J = 10 Hz, 1H), 4.35 (m, J = 3.0 Hz, 1H), 3.26 (m, 1H), 2.22-1.06 (m, 16H), 0.89-0.70 (m, 6H), 0.43 (s, 6H); ¹³C-NMR (200 MHz) δ = 144.2, 142.6, 139.9, 133.6, 129.1, 128.0, 75.1, 71.1, 54.3, 39.9, 38.3, 33.5, 31.7, 30.2, 28.0, 27.6, 22.5, 14.0, 12.4, -1.0.

3-Ethyl-2-[(E)-1-hydroxy-2-octenyl]cyclopentanol (7.64).

Under argon atmosphere, a solution of Bu₄NF (4 ml, 1 M THF), DMSO (4 ml) and 7.63a (500 mg, 1.34 mmol) was refluxed for 3 h. After full conversion (indicated by TLC) the mixture was poured into NH₄Cl (aq), diluted with diethyl ether (50 ml) and the organic layer was separated. The aqueous layer was extracted two times with diethyl ether and the combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography (SiO₂ diethyl ether/pentane, 2:3, Rf = 0.60) gave 273 mg (85%) of 7.64 as a colorless oil (mixture ¹H-NMR (300 MHz) δ = 5.70-5.52 (m, 2H), 4.48 (m, 1H), 4.34 (dd, J = 10.2 Hz, J = 4.8 Hz, 1H), 2.66 (OH), 2.37 (t, J = 7.5 Hz, 1H), 2.10-1.02 (m, 15H), 0.86 (t, J = 7.6 Hz, 3H), 0.85 (t, J = 7.6 Hz, 1H); ¹³C-NMR (200 MHz) δ = 131.8, 131.0, 76.8, 73.0, 53.7, 38.4, 34.8, 32.1, 31.3, 29.3, 28.9, 28.5, 22.5, 14.0, 12.4; Ms (EI) for C₁₅H₂₆O₂: m/z = 240 (M⁺).
(E)-1-[2-(Acetyloxy)-5-ethylcyclopentyl]-2-octenyl acetate (7.65).
To a solution of pyridine (2 ml) and 7.64 (240 mg, 1 mmol) was added 2 ml of acetic anhydride at room temperature together with a catalytic amount of DMAP. The reaction mixture was poured in NH₄Cl (aq) after 12 h and extracted two times with ether and the combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography (SiO₂ diethyl ether/pentane, 1:10, Rf = 0.43) gave 237 mg (74%) of 7.65 as a colorless oil (mixture of threo:erythro ratio 50:50). ¹H-NMR (300 MHz) δ = 5.74-5.61 (m, 1H), 5.38-5.05 (m, 3H), 2.02-1.52 (m, 14H), 1.36-1.16 (m, 8H), 0.86 (m, 6H); ¹³C-NMR (200 MHz) δ = 169.8, 169.7, 169.6, 169.5, 169.3, 169.3, 135.4, 135.3, 135.3, 135.3, 127.1, 126.6, 125.9, 125.1, 77.3, 76.9, 76.8, 75.3, 74.7, 74.3, 74.3, 75.1, 54.4, 53.6, 52.3, 50.6, 41.8, 41.7, 41.3, 40.2, 31.6, 31.5, 30.9, 30.8, 30.7, 29.1, 28.9, 28.2, 28.1, 28.0, 27.9, 27.6, 21.9, 20.8, 20.7, 20.6, 20.5, 13.4, 11.8, 11.7, 11.6; Ms (EI) for C₁₉H₃₂O₄: m/z = 324 (M+).

(E)-3-[2-(Acetyloxy)-5-ethylcyclopentyl]-1-pentyl-2-propenyl acetate (7.66).
Bis(acetonitrile)palladium(II) chloride (8.8 mg, 0.034 mmol) was added to a solution of 7.65 (220 mg, 0.68 mmol) in THF (10 ml). The mixture was stirred at room temperature. The reaction was worked up after 3 h by filtration over silica gel (10 g). Evaporation at reduced pressure gave 216 mg (93%) of 7.66 as a colorless liquid. ¹H-NMR (300 MHz) δ = 5.56-5.25 (m, 2H), 5.17-5.05 (m, 1H), 4.77 (m, 1H), 2.07-1.80 (m, 14H), 1.78-0.95 (m, 8H), 0.79 (m, 6H); ¹³C-NMR (200 MHz) δ = 169.1, 168.8, 168.6, 133.5, 132.8, 132.4, 130.8, 130.5, 129.1, 128.6, 125.3, 124.9, 78.5, 78.3, 77.3, 77.2, 75.9, 73.3, 73.2, 73.1, 72.8, 53.3, 53.1, 52.9, 51.3, 51.2, 43.3, 43.2, 43.0, 40.8, 32.8, 30.6, 30.5, 29.9, 29.8, 29.0, 28.8, 28.1, 27.3, 26.9, 26.8, 26.5, 25.4, 25.3, 23.3, 23.2, 20.9, 19.7, 19.5, 12.3, 10.8, 10.6, -0.6; Ms (Cl) for C₁₉H₃₂O₄: m/z = 324 (M+).

3-ethyl-2-[(E)-3-hydroxy-1-octenyl]cyclopentanol (7.67).
Acetate 7.66 (160 mg, 0.5 mmol) was dissolved in MeOH (10 ml) and potassium carbonate (139 mg, 1 mmol) was added. After 3 h full conversion was reached. The reaction mixture was treated with NH₄Cl (aq) and extracted two times with diethyl ether and the combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography (SiO₂ diethyl ether/pentane, 1:10, Rf = 0.45) gave 102 mg (79%) of 7.67 as a colorless liquid. ¹H-NMR (300 MHz) δ = 5.58-5.30 (m, 2H), 4.04-3.67 (m, 2H), 1.97-1.67 (m, 4H), 1.59-0.96 (m, 14H), 0.8 (m, 6H); ¹³C-NMR (200 MHz) δ = 133.9, 133.7, 133.2, 132.9, 132.3, 131.4, 130.5, 130.4, 128.0, 76.5, 76.3, 76.2, 75.57, 74.9, 74.7, 71.9, 71.6, 70.9, 70.4, 64.3, 56.8, 56.7, 56.1, 53.2, 43.1, 42.6, 42.2, 40.9, 40.0, 39.8, 35.6, 35.5, 35.4, 31.9, 31.7, 30.7, 30.6, 30.4, 30.2, 30.2, 30.1, 29.8, 27.8, 27.5, 27.3, 26.7, 26.1, 25.9, 25.8, 25.7, 23.7, 23.6, 21.1, 20.9, 13.6, 12.5, 11.0, 10.8, 10.7, 10.6, -0.54; Ms (Cl) for C₁₅H₂₈O₂: m/z = 240 (M+).

Methyl-6-heptenoate (7.69).
A mixture of commercially available 6-heptenoic acid (5 ml, 37 mmol),
MeOH (7 ml), p-toluenesulfonic acid (0.5 g) and CCl₄ (15 ml) was refluxed for 16 h. After cooling, the mixture was diluted with CH₂Cl₂ and washed with NaHCO₃ (aq). The organic phase was dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography (SiO₂ diethyl ether/pentane, 1:15, Rf = 0.78) gave 4.94 g (94 %) of 7.69 as a colorless oil. ¹H-NMR (300 MHz) δ = 5.82-5.73 (m, 1H), 4.96-4.91 (m, 2H), 3.65 (s, 3H), 2.30 (t, J = 7.3 Hz, 2H), 2.05 (q, J = 7.3 Hz, 2H), 1.62 (m, 2H), 1.41 (m, 2H).

Bis(methyl-6-hepanoate)zinc (7.21).

Compound 7.69 (2.84 g, 20 mmol) was cooled (degassed using a freeze/thaw technique under vacuum/argon) to 0°C and HBEt₂ [freshly prepared from BH₃*Et₂O (2M in diethyl ether) and BEt₃ (1M in THF)] was added via a syringe (1 min). The volatiles were removed after complete conversion (GC) under vacuum (0.1mm Hg, 0°C, 1 h). The resulting organoborane was treated at 0°C with 2 ml of Et₂Zn (neat) and stirred at rt for 2h. The formed BEt₃ and the excess Et₂Zn were removed under vacuum (0.1 mmHg, 3 h) giving 3 g (85%) of 7.21 as a colorless liquid: ¹H-NMR (200 MHz, CDCl₃): δ = 3.63 (s, 6H), 2.27 (t, J = 7.8 Hz, 4H), 1.62-1.47 (m, 4H), 1.28-1.25 (m, 4H), 0.31 (t, J = 7.8 Hz, 4H); ¹³C-NMR (200 MHz, CDCl₃): δ = 174.3, 51.4, 36.0, 34.1, 28.9, 26.1, 24.9, 15.9.

Methyl 7-((1R,2S)-2-((1R,2Z)-3-[dimethyl(phenyl)silyl]-1-hydroxy-2-octenyl)-3-oxo-8,8-diphenyl-6,10-dioxaspiro[4.5]dec-1-yl)heptanoate (7.70).

A solution of Cu(OTf)₂ (32.4 mg, 0.09 mmol) and phosphoramidite L₂ (97 mg, 0.18 mmol) in toluene (20 ml) was stirred under a nitrogen atmosphere at ambient temperature for 1 h. 7.11 (918 mg, 3 mmol) and 7.48 (780 mg, 3 mmol) was added. After cooling the reaction mixture to -45 °C, di(methylheptanoate)zinc (6 ml, 1 M solution in toluene) was added and stirring at -45°C was continued for 18 h. The conversion was determined by TLC. After complete conversion, the reaction mixture was poured in to NH₄Cl (aq) (25 ml), the organic layer was separated, and the aqueous layer was extracted two times with diethyl ether. The combined organic layers were dried over MgSO₄ filtered and concentrated in vacuo. Purification by column chromatography (SiO₂ diethyl ether/pentane, 2:1, Rf = 0.35) gave 1.28 g (60% yield) of 7.70 as a colorless oil (mixture of threo:erythro ratio 83:17). ¹H-NMR (300 MHz) δ = 7.44-7.42 (m, 4H), 7.39-7.12 (m, 9H), 7.01-6.96 (m, 2H), 6.33 (d, J = 10 Hz, 1H) threo, 5.91 (d, J = 10.0 Hz, 1H) erythro, 4.53 (m, 2H), 4.23-4.05 (m, 3H), 3.64 (s, 3H), 3.06 (d, J = 17.0 Hz, 1H), 2.32-1.92 (m, 7H), 1.52-0.79 (m, 19H), 0.35 (s, 3H), 0.33 (s, 3H); ¹³C-NMR (300MHz) δ = 214.4, 174.1, 143.3, 143.1, 142.9, 142.2, 139.3, 133.5, 129.0, 128.5, 128.3, 128.1, 128.0, 127.9, 126.8, 126.2, 103.4, 70.6, 70.1, 68.3, 57.9, 51.3, 47.7, 44.9, 44.6, 38.2, 34.0, 31.7, 29.9, 29.6, 28.9, 27.9, 27.2, 24.9, 22.4, 13.9, -0.9; Ms (El) for C₄₄H₅₈O₆Si: m/z = 710 (M⁺).
Methyl 7-((1R,2R,3S)-2-{(Z)-3-[dimethyl(phenyl)silyl]-1-hydroxy-2-octenyl}-3-hydroxy-8,8-diphenyl-6,10-dioxaspiro[4.5]dec-1-yl)heptanoate (7.71a).
Under argon atmosphere, a solution of 7.70 (1420 mg, 2 mmol) in diethyl ether (40 ml) was treated with Zn(BH₄)₂ (8 ml, 0.5 M in diethyl ether) at −30°C. After stirring for 3 h at the same temperature the reaction mixture was quenched with NH₄Cl (aq) in a beaker (250 ml) and stirred for 30 min. The reaction mixture was diluted with diethyl ether (50 ml) and the organic layer was separated. The aqueous layer was extracted two times with diethyl ether and the combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography (SiO₂ diethyl ether/pentane, 5:4, Rf = 0.35) gave 44 mg (3%) of 7.71a, 55 mg (3.5%) of 7.71b (Rf = 0.33) and 897 mg (63%) of 7.71 (Rf = 0.30) as colorless oils. ¹H-NMR (300 MHz) δ = 7.40-6.99 (m, 15H), 6.24 (d, J = 10.0 Hz, 1H) threo, 6.04 (d, J = 10.0 Hz, 1H) erythro, 4.51-4.44 (m, 2H), 4.33-4.18 (m, 4H), 3.62 (s, 3H), 3.15 (d, J = 5.0 Hz, 1H) OH, 2.23-2.02 (m, 7H), 1.94-1.81 (m, 2H), 1.50-0.76 (m, 19H), 0.37 (s, 3H), 0.35 (s, 3H).

Methyl 7-((1R,2R,3R)-2-{(1S,2Z)-3-[dimethyl(phenyl)silyl]-1-hydroxy-2-octenyl}-3-hydroxy-8,8-diphenyl-6,10-dioxaspiro[4.5]dec-1-yl)heptanoate (7.71b).
¹H-NMR (300 MHz) δ = 7.46-6.99 (m, 15H), 6.18 (d, J = 10 Hz, 1H), 4.52-4.44 (m, 2H), 4.34-4.18 (m, 4H), 3.63 (s, 3H) threo, 3.59 (s, 3H) erythro, 3.16 (m, 1H) OH, 2.23-2.12 (m, 7H), 1.94 (m, 1H), 1.84 (d, J = 6 Hz, 1H) OH, 1.75-0.76 (m, 19H), 0.35 (s, 3H), 0.34 (s, 3H); ¹³C-NMR (200MHz) δ = 174.4, 143.8, 143.7, 143.3, 142.9, 139.6, 133.5, 129.2, 128.6, 128.5, 128.1, 128.0, 127.7, 126.7, 126.4, 108.1, 71.3, 70.6, 69.8, 68.6, 51.6, 51.4, 47.1, 44.8, 40.0, 38.3, 34.1, 31.8, 30.1, 29.7, 28.8, 27.7, 27.4, 25.0, 22.5, 14.1, -1.0; Ms (EI) for C₄₄H₆₀O₆Si: m/z = 712 (M⁺).

Methyl 7-((1R,2R,3R)-2-{(1R,2Z)-3-[dimethyl(phenyl)silyl]-1-hydroxy-2-octenyl}-3-hydroxy-8,8-diphenyl-6,10-dioxaspiro[4.5]dec-1-yl)heptanoate (7.71). Colorless oil; [α]D₂₃=-31° (c = 0.9, CHCl₃); ¹H-NMR (300 MHz) δ = 7.47-6.99 (m, 15H), 6.03 (d, J = 10.0 Hz, 1H), 4.53-4.42 (m, 2H), 4.31-4.24 (m, 2H), 3.94 (m, 2H), 2.44 (d, J = 5.6 Hz, 1H) OH, 2.35-2.04 (m, 6H), 1.57-0.80 (m, 2H), 0.38 (s, 3H), 0.33 (s, 3H); ¹³C-NMR (200MHz) δ = 174.3, 144.0, 143.7, 143.6, 143.2, 139.8, 133.4, 129.2, 128.6, 128.5, 128.1, 128.0, 126.8, 126.4, 126.1, 107.3, 72.9, 72.1, 70.0, 68.7, 56.8, 51.4, 49.2, 44.8, 38.4, 37.8, 34.1, 31.8, 30.2, 29.8, 29.0, 28.6, 27.9, 25.0, 22.5, 14.0, -0.9, -1.0; Ms (EI) for C₄₄H₆₀O₆Si: m/z = 712 (M⁺). The ee of 94 % was determined by HPLC on a chiral stationary phase (DAICEL CHIRALPAK AD, iPrOH:heptane 25:75, 1 ml/min, RT, Tₐ = 4.9 min, Tₑ = 9.0).
A total synthesis of prostaglandin E₁ methyl ester using a catalytic asymmetric tandem 1,4-addition-aldol reaction

Methyl 7-[(1R,2R,3R)-3-hydroxy-2-[(1S,2E)-1-hydroxy-2-octenyl]-8,8-diphenyl-6,10-dioxaspiro[4.5]dec-1-yl]heptanoate (7.74).

Under an argon atmosphere, a solution of Bu₄NF (1.5 ml, 1 M THF), DMSO (5 ml) and 7.71 (324 mg, 0.455 mmol) was refluxed for 2 h. After full conversion (TLC indicated two products: ester and acid) the mixture was poured into NH₄Cl (aq), diluted with diethyl ether (50 ml) and the organic layer was separated. The aqueous layer was washed with diethyl ether, and the combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. The crude products were dissolved in pyridine (4 ml) and acetic anhydride (2 ml) together with a catalytic amount of DMAP was added at room temperature. After 12 h the reaction mixture was poured into NH₄Cl (aq) and extracted twice with ethyl ether and the combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography (SiO₂ diethyl ether/pentane, 1:1, Rf = 0.69) gave 90 mg (30%) of 7.74 and 109 mg (37%) of 7.75 (Rf = 0.42) as colorless oils. 1H-NMR (300 MHz) δ 7.39-6.99 (m, 10H), 5.61 (m, 1H), 5.25 (m, 2H), 5.07 (m, 1H), 4.54 (d, J = 12.0 Hz, 1H), 4.44 (d, J = 12.0 Hz, 1H), 4.34 (d, J = 12.0 Hz, 1H), 4.14 (d, J = 12.0 Hz, 1H), 3.62 (s, 3H), 2.37-1.89 (m, 6H), 1.97 (s, 3H), 1.96 (s, 3H), 1.62-0.99 (m, 18H), 0.81 (t, J = 6.5 Hz, 3H); 13C-NMR (200MHz) δ = 174.3, 170.6, 170.0, 143.7, 143.4, 134.4, 128.6, 128.3, 128.1, 126.8, 126.5, 126.2, 126.0, 106.7, 73.3, 72.2, 70.3, 68.2, 51.7, 51.4, 47.6, 44.7, 37.2, 34.1, 32.1, 31.3, 29.7, 28.9, 28.5, 27.7, 27.3, 25.0, 22.4, 21.2, 21.1, 14.0; Ms (EI) for C₄₀H₅₄O₈: m/z = 662 (M⁺).

Methyl 7-[(1R,2R,3R)-3-hydroxy-2-[(1S,2E)-1-(acetyloxy)-2-octenyl]-8,8-diphenyl-6,10-dioxaspiro[4.5]dec-1-yl]heptanoic acid (7.75).

1H-NMR (300 MHz) δ = 7.39-6.99 (m, 10H), 5.61 (m, 1H), 5.25 (m, 2H), 5.07 (m, 1H), 4.54 (d, J = 12 Hz, 1H), 4.44 (d, J = 12 Hz, 1H), 4.34 (d, J = 12 Hz, 1H), 4.14 (d, J = 12 Hz, 1H), 3.62 (s, 3H), 2.37-1.89 (m, 6H), 1.97 (s, 3H), 1.96 (s, 3H), 1.62-0.99 (m, 18H), 0.81 (t, J = 6.5 Hz, 3H); 13C-NMR (200MHz) δ = 179.2, 170.7, 170.1, 143.6, 143.4, 134.5, 128.6, 128.3, 128.1, 126.5, 126.2, 126.0, 106.7, 73.4, 72.2, 70.3, 68.2, 51.7, 47.6, 44.8, 37.2, 34.1, 32.1, 31.3, 29.7, 28.8, 28.5, 27.6, 27.3, 24.8, 22.4, 21.2, 21.1, 14.0; Ms (Cl) for C₃₉H₅₂O₈: m/z = 649 (M⁺).

Methyl 7-[(1R,2R,3R)-3-hydroxy-2-[(1S,2E)-1-hydroxy-2-octenyl]-8,8-diphenyl-6,10-dioxaspiro[4.5]dec-1-yl]heptanoate (7.72):

Under argon atmosphere, a solution of Bu₄NF (6 ml, 1 M THF) was added to a solution of methylpropionate (176 mg, 2 mmol) in DMSO (3 ml) and the reaction mixture was refluxed for 2 h. After adding a solution of 7.71 (0.6 mmol, 427 mg) in DMSO (3 ml), the reaction mixture was heated again for an additional 20 min. After full conversion...
(indicated by TLC) the mixture was poured into NH₄Cl (aq), diluted with diethyl ether (50 ml) and the organic layer was separated. The aqueous layer was extracted two times with diethyl ether and the combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. Purification by column chromatography (SiO₂ diethyl ether/pentane, 2:1, Rf = 0.38) gave 274 mg (79%) of \(7.72\) as a colorless oil. \(^1\)H-NMR (300 MHz) \(\delta = 7.38-7.01\) (m, 10H), 5.68-5.59 (m, 1H), 5.50-5.42 (m, 1H), 4.48 (m, 2H), 4.31 (m, 2H), 4.10 (q, \(J = 6.1\) Hz, 1H), 3.97 (t, \(J = 6.0\) Hz, 1H), 3.62 (s, 3H), 2.17 (m, 4H), 1.95 (m, 2H), 1.67-0.79 (m, 22H); \(^13\)C-NMR (200MHz) \(\delta = 174.4, 143.9, 143.6, 133.0, 131.5, 128.6, 128.4, 128.1, 126.8, 126.5, 126.2, 107.5, 75.2, 71.9, 70.0, 68.8, 57.3, 51.4, 48.8, 44.8, 40.8, 38.2, 34.1, 32.2, 31.4, 29.6, 28.9, 28.8, 27.8, 25.0, 22.5, 14.0; Ms (CI) for C₃₆H₅₀O₆: m/z = 578 (M\(^+\)).

**Methyl 7-\{(1R,2R,3R)-3-hydroxy-2-\{(1S,2E)-1-hydroxy-2-octenyl\}-5-oxocyclopentyl\}heptanoate (7.76).**

Solid cerium ammonium nitrate (18 mg, 0.045 mmol) was added to a solution of \(7.72\) (87 mg, 0.15 mmol) in MeCN (2 ml) and borate-HCl buffer (Merck, pH 8, 2 ml). The pale yellow solution was heated at 60°C for 2 h. After cooling to room temperature, H₂O (5 ml) and diethyl ether (5 ml) was added. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (2x15 ml). The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. TLC (SiO₂ diethyl ether/pentane, 2:1, Rf = 0.65) of the crude product. \(^1\)H-NMR (300 MHz) 5.73 (dd, \(J = 15.3\) Hz, \(J = 6.6\) Hz, 1H), 5.68 (dd, \(J = 15.3\) Hz, \(J = 6.6\) Hz, 1H), 4.31 (m, 1H), 4.07 (m, 1H), 3.61 (s, 3H), 2.70 (dd, \(J = 11.9\) Hz, \(J = 6.2\) Hz, 1H), 2.25-1.91 (m, 5H), 1.56-1.23 (m, 19H), 0.81 (t, \(J = 6.9\) Hz, 3H); \(^13\)C-NMR (200MHz) \(\delta = 214.6, 173.1, 134.6, 131.2, 71.6, 68.6, 53.3, 53.1, 51.4, 46.7, 37.1, 34.0, 32.1, 31.4, 29.4, 28.9, 28.7, 26.1, 24.9, 22.5, 14.0.

**Methyl 7-\{(1R,2S)-2-\{(1S,2E)-1-hydroxy-2-octenyl\}-5-oxo-3-cyclopenten-1-yl\}heptanoate (7.77).**

To a solution of \(7.72\) (87 mg, 0.15 mmol) in MeOH (2 ml) was added 5M HCl (2 ml). The reaction mixture was stirred for 1 h and extracted with CH₂Cl₂ (2x15 ml). The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. TLC (SiO₂ diethyl ether/pentane, 2:1, Rf = 0.69) of the crude product. \(^1\)H-NMR (300 MHz) 7.66 (m, 1H), 6.14 (m, 1H), 3.99 (t, \(J = 7.0\) Hz, 1H), 3.61 (s, 3H), 2.68 (m, 1H), 2.24 (t, \(J = 6.7\) Hz, 2H), 2.09-1.96 (m, 3H), 1.77 (s, 1H (OH)), 1.57-1.24 (m, 18H), 0.81 (t, \(J = 6.9\) Hz, 3H).

**Methyl 7-\{(1R,2R,3R)-3-(acetyloxy)-2-\{(E,3S)-3-(acetyloxy)-1-octenyl\}-8,8-diphenyl-6,10-dioxaspiro[4.5]dec-1-yl\}heptanoate (7.78).**

Bis(acetonitrile)palladium(II) chloride (18 mg, 0.07 mmol) was added to a solution of \(7.74\) (264 mg, 0.4 mmol) in THF (5 ml). The reaction mixture was stirred
at rt for 3 h, whereupon it was filtered over silica gel (20g). The solvent was evaporated at reduced pressure. Purification by column chromatography (SiO2 diethyl ether/pentane, 3:1, Rf = 0.35) gave 167 mg (63%) of 7.78, as a colorless oil; [α]D –39.5° (c 2.6, CDCl3); 1H-NMR (300 MHz) 7.41-6.97 (m, 10H), 5.41 (m, 2H), 5.13 (m, 1H), 4.77 (m, 1H), 4.55 (d, J = 11.7 Hz, 1H), 4.48 (d, J = 11.7 Hz, 1H), 4.29 (d, J = 11.7 Hz, 1H), 4.16 (d, J = 11.7 Hz, 1H), 3.62 (s, 3H), 2.52 (dd, J = 14.3 Hz, J = 8.8 Hz, 1H), 2.27 (m, 1H), 2.19 (t, J = 7.7 Hz, 2H), 2.05 (dd, J = 14.3 Hz, J = 5.7 Hz, 1H), 1.97 (s, 3H), 1.95 (s, 3H), 1.55-0.84 (m, 19H), 0.81 (t, J = 6.6 Hz, 3H); 13C-NMR (200MHz) δ = 174.3, 170.8, 170.2, 143.6, 143.4, 133.1, 131.2, 128.7, 128.1, 126.8, 126.3, 126.1, 105.9, 75.7, 74.1, 70.4, 68.1, 51.7, 51.4, 44.8, 37.4, 34.2, 34.1, 31.5, 29.7, 28.9, 27.7, 26.4, 25.0, 24.7, 22.5, 21.5, 21.0, 14.0; Ms (CI) for C40H54O8: m/z = 662 (M+).

Methyl 7-{(1R,2R,3R)-3-hydroxy-2-[(E,3S)-3-hydroxy-1-octenyl]-8,8-diphenyl-6,10-dioxaspiro[4.5]dec-1-yl}heptanoate (7.79).

Acetate 7.78 (320 mg, 0.46 mmol) was dissolved in MeOH (2 ml) and potassium carbonate (32 mg, 0.23 mmol) was added. The reaction was monitored by TLC and after 3 h full conversion was reached. The reaction mixture was treated with NH4Cl (aq) and extracted two times with diethyl ether and the combined organic layers were dried over MgSO4 filtered and concentrated in vacuo. Purification by column chromatography (SiO2 diethyl ether/MeOH, 50:1, Rf = 0.41) gave 119 mg (90%) of 7.79, as a white solid; [α]D –24,5° (c 0.9, CDCl3). 1H-NMR (300 MHz) 7.41-7.00 (m, 10H), 5.48 (dd, J = 15.0 Hz, J = 6.7 Hz, 1H), 5.36 (dd, J = 15.0 Hz, J = 6.7 Hz, 1H), 4.52 (m, 2H), 4.25 (m, 2H), 4.00 (m, 1H), 3.81 (m, 1H), 3.62 (s, 3H), 2.42 (dd, J = 13.6 Hz, J = 8.4 Hz, 1H), 2.19 (t, J = 7.7 Hz, 2H), 2.04 (m, 2H), 1.64-0.85 (m, 19H), 0.81 (t, J = 6.6 Hz, 3H); 13C-NMR (200MHz) δ = 174.3, 143.7, 143.5, 135.8, 132.9, 128.6, 128.0, 126.8, 126.3, 126.1, 106.2, 74.3, 73.0, 70.3, 68.2, 55.8, 52.6, 51.4, 50.8, 44.8, 39.2, 37.2, 34.1, 31.7, 29.6, 28.8, 27.7, 26.8, 25.1, 24.9, 22.6, 14.0; Ms (CI) for C36H50O6: m/z = 578 (M+).

Methyl 7-{(1R,2R,3R)-3-hydroxy-2-[(E,3S)-3-hydroxy-1-octenyl]-5-oxocyclopentyl}heptanoate or prostaglandin E1 methyl ester 13

Solid cerium ammonium nitrate (18 mg, 0.045 mmol) was added to a solution of 7.79 (87 mg, 0.15 mmol) in MeCN (2 ml) and borate-HCl buffer (Merck, pH 8, 2 ml). The faintly yellow solution was heated at 60ºC for 2h. After cooling to room temperature, H2O (5 ml) and 5 ml of ether is added. The organic layer was separated, and the aqueous layer was extracted with CH2Cl2 (2x15 ml). The combined organic layers were dried over MgSO4 filtered and concentrated in vacuo. Column chromatography (SiO2 diethyl ether/MeOH, 100:3, Rf = 0.42) gave 26 mg (45%) of prostaglandin E1 methyl ester, as a colorless oil; [α]D –51° (c 1.00, CH3OH); 1H-NMR (500 MHz) 5.64 (dd, J = 15.0 Hz, J = 7.3 Hz, 1H), 5.51 (dd, J = 15.0 Hz, J = 8.8 Hz, 1H), 4.09 (m, 1H), 4.00 (m, 1H), 3.63 (s, 3H), 2.70 (dd, J = 18.6 Hz, J = 7.3 Hz, 1H), 2.32 (dt, J = 12.1 Hz, J = 8.8 Hz).
Hz, 1H), 2.26 (t, J = 7.7 Hz, 2H), 2.20 (dd, J = 18.3 Hz, J = 9.9 Hz, 1H), 1.96 (dt, J = 12.1 Hz, J = 5.9 Hz, 1H), 1.60-1.24 (m, 19H), 0.86 (t, J = 6.9 Hz, 3H); COSY NMR; 13C-NMR (300MHz) δ = 214.6, 174.3, 136.8, 131.8, 73.0, 71.8, 54.4, 51.5, 45.8, 37.3, 34.0, 31.6, 29.3, 28.8, 27.6, 26.5, 25.1, 24.8, 22.6, 14.0; Ms (CI) for C36H50O6: m/z = 368 (M+), 386 (M + NH4+).

7.15 References

17 Noyori, R. Asymmetric Catalysis in Organic Synthesis, Wiley&Sons, 1994; Chapter 4.
A total synthesis of prostaglandin E1 methyl ester using a catalytic asymmetric tandem 1,4-addition-aldol reaction


25 The reaction of EtZnCl and 2-cyclohexenone gave racemic product (see section 4.3).


72. The Pd(II)-catalyzed allylic acetate transposition was first described by: Meyer, K. DOS 2513198 (1975); Chem. Abstr. 1976, 84, 89629s.
7.13 Conclusions

We have shown that the application of the asymmetric catalytic tandem 1,4-addition-aldol reaction was successful for the synthesis of PGE\textsubscript{1} methyl ester. Although the first approach was not successful, the fifth one was.

The first approach, using unsaturated organozinc reagents, showed that the application of these reagents is not successful in the enantioselective copper catalyzed 1,4-addition.

The second approach to introduce the double bond of the ω side-chain by elimination was believed to be straightforward but was not successful. Although the β-silyloxy aldehyde reacted in a tandem fashion under the reaction condition the accomplishment of the three oxy-groups at carbons 11, 13 and 15 makes the functionality in the middle (C-13) inaccessible for chemical conversions because of steric hindrance.

The third approach, introducing the double bond by an oxidative elimination of a selenium compound was more reliable but less achievable. The reason was the lower reactivity of the α-selenium aldehyde in contrast to other aldehydes obtaining only the elimination 1,4-addition-aldol products at higher reaction temperatures. The conversion of this product into PGE\textsubscript{1} methyl ester could not be accomplished.

Approach four failed because the aldehyde 7.42 gave no reaction under the tandem 1,4-addition-aldol reaction conditions even at elevated temperatures.

Finally, approach five was successful and because of the structural similarities among PGs this route presents a general catalytic route for their synthesis. Although a few catalytic methods for the synthesis of PGs are available this is the first asymmetric catalytic method using only achiral starting materials except for the chiral catalyst. The advantage of this new total synthesis is the introduction of three consecutive stereocenters in one step (asymmetric catalytic tandem 1,4-addition-aldol reaction). Fortunately, one of the possible 16 diastereomers was obtained in good yield. The chiral information within this tandem product was used for the further transformations making the use of other chiral compounds unnecessary. The overall yield of this synthesis is 7%, which seems quite low considering the fact that the route consists of only 7 steps. The reason is that this synthesis has not been optimized and the purification of PGE\textsubscript{1} methyl ester by column chromatography should be carried out very carefully. Using a short column as Noyori\textsuperscript{17} did for the purification of the PGs will enhance the yield.

7.14 Experimental section

7.14.1 Material

For general information: see Chapter 3.