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Catalytic Enantioselective Synthesis of (−)-Prostaglandin E\textsubscript{1} Methyl Ester Based on a Tandem 1,4-Addition–Aldol Reaction

Leggy A. Arnold, Robert Naasz, Adriaan J. Minnaard, and Ben L. Feringa*
Department of Organic and Molecular Inorganic Chemistry, Stratingh Institute, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands
feringa@chem.rug.nl
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Catalytic enantioselective 1,4-additions and tandem 1,4-addition–aldol reactions of dialkylzinc reagents to cyclopentene-3,5-dione monoacetal in the presence of an in situ generated Cu(OTf)\textsubscript{2}/chiral phosphoramidite catalyst result in highly functionalized cyclopentane building blocks with ee’s up to 97%. A new synthesis of cyclopentene-3,5-dione monoacetal is presented as well as its use in a tandem 1,4-addition–aldol protocol for the catalytic asymmetric total synthesis of (−)-PGE\textsubscript{1} methyl ester. This synthesis represents a new approach to this class of natural products. By using only 3 mol % of an enantiomerically pure catalyst in the key step, the absolute configurations at three stereocenters of the basic structure of the PGE\textsubscript{1} are established at once.

Introduction

Prostaglandins (PGs) belong to the family of polyoxygenated fatty acids that are produced by a cytooxygenase enzyme system widely distributed in mammalian tissue.\textsuperscript{1} Their biological functions are restricted locally because of the rapid metabolism, but nevertheless, their pharmacological effects are so diverse that they have become the subjects of intensive research for the past decades.\textsuperscript{2} Several synthetic prostaglandin derivatives are currently used as drugs, but their synthesis is often still the subject of considerable improvement and innovation.\textsuperscript{3} Synthetic routes are largely based on three strategies, the Corey synthesis,\textsuperscript{4} the two-component coupling,\textsuperscript{5} and the three-component coupling,\textsuperscript{6} although a number of other approaches have been reported.\textsuperscript{7} The latter method, developed by Noyori,\textsuperscript{8} is particularly attractive because of the limited number of steps in this convergent synthetic approach. The key step of this route is the tandem 1,4-addition–enolate-trapping reaction (Scheme 1). The optimally active enone 1 is treated with a functionalized cuprate prepared from chiral vinyl iodide 2 and the in situ generated enolate is trapped with aldehyde 3 as electrophile.\textsuperscript{9} This sequence provides a convenient way to introduce simultaneously the α and ω side chains necessary for the elaborations into (−)-PGE\textsubscript{1} 5.

The versatility of organocopper reagents\textsuperscript{10} and the possibility of enolate trapping resulting in α-functionalization\textsuperscript{11} (exemplified in Scheme 1), makes the 1,4-addition one of the most versatile carbon–carbon bond formation reactions in organic synthesis.\textsuperscript{12} In the past decade, considerable progress has been achieved in the development of a catalytic enantioselective 1,4-addition to enones.\textsuperscript{13} In the copper-catalyzed 1,4-addition of dialkylzinc reagents to enones, full stereocontrol has been observed using phosphoramidites as simple chiral ligands for copper.\textsuperscript{14} The reaction of 6, 7-, and 8-membered 2-cyloalkenones and (functionalized) dialkylzinc (R\textsubscript{2}Zn) reagents gave, in the presence of 1 mol % of an in situ prepared catalyst based on Cu(OTf)\textsubscript{2} and phosphoramidates, a wide variety of functionalized cyclopentanes. Such transformations are commonly observed in the decoupling of aldol reactions of dialkylzinc reagents.\textsuperscript{15} Formaldehyde giving the aldol as a sole product of a Cu(OTf)\textsubscript{2} catalyzed reaction has also been observed in the aldol reactions of dialkylzinc with enones.\textsuperscript{16} The catalytic enantioselective 1,4-addition–aldol reaction is known to be an effective method for the asymmetric catalytic total synthesis of many natural products.\textsuperscript{17}

The formaldehyde based aldol reaction provides a straightforward method for the catalytic total synthesis of 4 and is accomplished using 3 mol % of an enantiomerically pure catalyst in the key step (Scheme 1).


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Synthesis of (−) Prostaglandin E₁ Methyl Ester

**Scheme 1**

![Scheme 1](attachment:image.png)

a chiral oxazoline group. Recently, Hoveyda²³ reported ee values up to 97% using a chiral peptide-based phosphine ligand L6 in this conjugate addition reaction.

Although these ligands give excellent enantioselectivities in the copper-catalyzed 1,4-addition to 2-cyclopentenone, the isolated yields for the corresponding 1,4-addition products are often moderate compared to those with other enones.²⁴ When the reaction was performed in the presence of an aldehyde, representing a three-component coupling procedure, the yield increased considerably.¹⁹,²⁰,²⁴ Despite the fact that 2-cyclopentenone is frequently used as a model substrate, it is as such less suitable as a starting material for natural products including the prostaglandins. In the search for a suitable prochiral enone as starting material for the total synthesis of this class of natural products, we focused on cyclopentene-3,5-dione monoacetals because of the following reasons:

1. These compounds represent easy accessible highly functionalized prochiral 2-cyclopentenones.
2. The acetal functionality can be readily converted into a ketone or alcohol.
3. These enones are more sterically demanding than 2-cyclopentenone, which increases the steric interaction with the catalyst.
4. The two oxygen atoms of the acetal might induce an electronic interaction with the catalyst during the tandem 1,4-addition−aldol reaction, giving rise to a higher selectivity.

We report here a new synthesis of cyclopentene-3,5-dione monoacetals and their application as substrate for highly enantioselective catalytic tandem 1,4-addition−aldol reaction. Furthermore, we illustrate the practicality of this new methodology in a short total synthesis of (−)-PGE₁ methyl ester including full experimental details.²⁵ The new features of this strategy are the application of a catalytic three-component coupling, the use of only achiral starting materials, and the observation that the enantioselective introduction of the three stereocenters with absolute stereocontrol is possible in a single key step.

**Results and Discussion**

The preparation of monoacetals of cyclopentene-3,5-dione has been described only in few cases in the literature.²⁶ The reported syntheses are not generally applicable, which encouraged us to develop a new procedure for their preparation. Treatment of commercial

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available cyclopentene-3,5-dione 6 with different alcohols in the presence of boron trifluoride gave the corresponding cyclopentene-3,5-dione monoacetals 7a–e summarized in Table 1. The reactions were stopped after a certain conversion to avoid the formation of side products. The reaction of 6 with methanol was stopped after 50% conversion, and the acetal 7a could be isolated in 26% yield (Table 1, entry 1). An interesting observation was made, namely the formation of 4-ethoxy-4-methoxy-2-cyclopenten-1-one in 7% yield. The EtO fragment of this compound originates from BF\textsubscript{3} \cdot \text{Et}\textsubscript{2}O. The acetals 7b and 7c were obtained in 29% and 25% yield at conversions of 58% and 45%, respectively (Table 1, entries 2 and 3). The acetalization of 6 with 2,2-diphenyl-1,3-propanodiol gave 71% conversion after 3 h at 0 °C and 50% yield of 7d (Table 1, entry 4). Employing a different purification method\textsuperscript{27} instead of column chromatography improved the isolated yield to 64%. The reaction of 6 and pinacol in the presence of BF\textsubscript{3} \cdot \text{Et}\textsubscript{2}O afforded 7e in 29% yield (76% conversion) after 3 days at room temperature (Table 1, entry 5). In addition, 6% yield of the diacetal was obtained. In the case of 2-propanol and benzyl alcohol, no acetal formation was observed even after 2 days at room temperature (Table 1, entries 6 and 7).

**Catalytic Asymmetric 1,4-Addition.** The monoacetals 7b and 7d were employed in the 1,4-addition with dialkylzinc reagents catalyzed by different chiral copper complexes. The copper catalyst was prepared in situ using 2 mol % Cu(OTf)\textsubscript{2} and 4 mol % phosphoramidite L\textsubscript{1} or L\textsubscript{7} (for structures of ligands, see Scheme 2 and Figure 3). The reactions were carried out in toluene at \(-45 °C\), and the results are summarized in Table 2. Full conversions were reached in all reactions after 16 h affording the corresponding substituted ketones in moderate yields (31–40%). The 1,4-addition of diethylzinc to 7b in the presence of 2 mol % Cu(OTf)\textsubscript{2}/L\textsubscript{1} catalyst afforded 8 in 31% isolated yield (Table 2, entry 1). Unfortunately, no separation of the enantiomers was achieved by chiral HPLC. Derivatization with optically pure (1S,2S)-diphenylethylenediamine\textsuperscript{28} was also unsuccessful. From the formation of 8, 8a and 8b were

<table>
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<th>entry</th>
<th>alcohol</th>
<th>time (h)</th>
<th>T (°C)</th>
<th>convn\textsuperscript{a} (%)</th>
<th>acetal</th>
<th>yield\textsuperscript{b} (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>methanol</td>
<td>1.5</td>
<td>0</td>
<td>50</td>
<td>7a</td>
<td>26 (+7)\textsuperscript{c}</td>
</tr>
<tr>
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<td>2,2-dimethyl-1,3-propanediol</td>
<td>1.5</td>
<td>0</td>
<td>58</td>
<td>7b</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>ethylene glycol</td>
<td>1.5</td>
<td>0</td>
<td>45</td>
<td>7c</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>2,2-diphenyl-1,3-propanediol</td>
<td>3</td>
<td>0</td>
<td>71</td>
<td>7d</td>
<td>50 (64)\textsuperscript{d}</td>
</tr>
<tr>
<td>5</td>
<td>pinacol</td>
<td>72</td>
<td>25</td>
<td>76\textsuperscript{e}</td>
<td>7e</td>
<td>29 (6)\textsuperscript{f}</td>
</tr>
<tr>
<td>6</td>
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<td>25</td>
<td>0</td>
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<tr>
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<td>benzyl alcohol</td>
<td>48</td>
<td>25</td>
<td>0</td>
<td>7f</td>
<td></td>
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</tbody>
</table>

\textsuperscript{a} Determined by \textsuperscript{1}H NMR after 3 h. \textsuperscript{b} Isolated yield. \textsuperscript{c} 4-Ethoxy-4-methoxy-2-cyclopenten-1-one. \textsuperscript{d} Purification by different purification procedure.\textsuperscript{27} \textsuperscript{e} Diacetal. \textsuperscript{f} After 3 d at room temperature.


\textsuperscript{27} See the Experimental Section.

\textbf{FIGURE 1.} Different ligands used for the catalytic asymmetric 1,4-addition of diethylzinc to 2-cyclopentenone.
isolated in 42% combined yield (Figure 2). Similar products, formed by an aldol reaction between a zinc enolate prepared by a 1,4-addition and an enone, have been reported.\(^{(29)}\) NMR analysis identified these diastereomers, which differ in the configuration of the tertiary alcohol. The presence of these products shows the different reactivity between the five-membered-ring zinc enolate and the six-membered-ring zinc enolate.\(^{(20,30)}\) In the case of the copper-catalyzed 1,4-addition of diethylzinc to 2-cyclohexenone, the formation of this type of products was not detected even at elevated temperature.

Much to our delight, the use of 2-cyclopentenone with an additional acetal functionality increases the enantioselectivity of the Cu(OTf)\(_2\)/L\(_1\)-catalyzed 1,4-addition dramatically. The reaction of 7d and diethylzinc afforded 9 in 40% yield and 90% ee (Table 1, entry 2). Using L\(_7\) (Figure 3) instead of L\(_1\) as ligand for copper, no asymmetric induction was observed and 9 was isolated in 37% yield (Table 2, entry 3). The 1,4-addition of dibutylzinc to 7d in the presence of Cu(OTf)\(_2\)/L\(_7\) afforded 10 in 32% yield and 5% ee (Table 2, entry 4). In contrast, catalyst Cu(OTf)\(_2\)/L\(_1\) gave in the same reaction 10 in 37% yield with an ee of 94% (Table 2, entry 5). In all cases, the 1,4-addition suffers from considerable side product formation (vide supra) resulting in modest isolated yields.

### Table 2. Catalytic Enantioselective 1,4-Addition with Cyclopentene-3,5-dione Monoacetals

<table>
<thead>
<tr>
<th>entry</th>
<th>enone</th>
<th>R'(_2)Zn</th>
<th>ligand</th>
<th>product</th>
<th>yield(^{a}) (%)</th>
<th>ee(^{b}) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7b</td>
<td>Et(_2)Zn</td>
<td>L(_1)</td>
<td>8</td>
<td>31 (42)(^{c})</td>
<td>d</td>
</tr>
<tr>
<td>2</td>
<td>7d</td>
<td>Et(_2)Zn</td>
<td>L(_1)</td>
<td>9</td>
<td>40</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>7d</td>
<td>Et(_2)Zn</td>
<td>L(_7)</td>
<td>9</td>
<td>37</td>
<td>0</td>
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<td>7d</td>
<td>Bu(_2)Zn</td>
<td>L(_7)</td>
<td>10</td>
<td>32</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>7d</td>
<td>Bu(_2)Zn</td>
<td>L(_1)</td>
<td>10</td>
<td>37 (94)</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\) Isolated yield. \(^{b}\) Determined by chiral HPLC. \(^{c}\) Side product, see: Figure 2. \(^{d}\) No separation by chiral HPLC.

![Figure 2](image-url) Side products formed in the catalytic enantioselective 1,4-addition of diethylzinc to 7b.

**Catalytic Tandem 1,4-Addition – Aldol Reaction.** To circumvent the formation of 8a and 8b (Figure 2), an aldehyde (more reactive than a ketone in an aldol reaction) was added to the reaction mixture from the start. This tandem 1,4-addition–aldol reaction procedure, trapping the intermediate zinc enolate, was first reported by Noyori.\(^{(24)}\) The reaction was carried out using enone 7d, p-bromobenzaldehyde, and dibutylzinc at −45 °C. We were very pleased to find that only 2 mol % of the catalyst, prepared in situ from Cu(OTf)\(_2\) and ligand L\(_1\), was sufficient to obtain the \(\alpha\)-hydroxy ketones 11a and 11b with three consecutive stereocenters in 64% yield (Scheme 3 and Table 3, entry 14).

Under these reaction conditions, virtually one stereoisomer out of the possible four diastereomers was formed. A ratio of 97:3 between 11a trans-threo and 11b trans-erythro was detected by \(^1\)H NMR based on different absorptions of H\(_1\) (4.77 ppm 11a and 5.11 ppm 11b). COSY-NMR and \(^1\)H NMR was used to assign the relative configurations of the two compounds. The coupling constant for 11a and 11b was \(J_{2,3} = 7.2 \text{ Hz}\). This value is typical for a trans configuration of H\(_2\) and H\(_3\) (Scheme 4).\(^{(31)}\) In addition, 11a and 11b have different coupling constants for their H\(_1\) and H\(_2\). The large difference is probably due to strong hydrogen bonding between the hydroxy and carbonyl group, thus preventing free rota-

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![Figure 3](image-url) Different phosphoramidite ligands.

**Scheme 3**

![Scheme 3](image-url)
synthesis of absolute stereochemistry was realized with the total and cis-erythro products are formed. The proof of the complexes one, there is no significant difference between the two competing reaction via transition state $12b$ addition that involves transition state $12a$ and the acetal functionality are less severe for the interactions between the aromatic ring of the aldehyde exclusively under these reaction conditions. The steric was given by NOESY-NMR measurements. No cis-threo gives product $11a$, which was formed almost, which can be easily under these reaction conditions. The steric interactions between the aromatic ring of the aldehyde and the acetal functionality are less severe for the addition that involves transition state $12a$ than for the competing reaction via transition state $12b$. The chiral copper complex is presumed to have no influence in the aldol bond formation step. In the case of 2-cyclopentenone, there is no significant difference between the two diastereomeric transition states leading to a 50:50 mixture of trans-threo/trans-erythro using various copper complexes.

To explore the scope of the reaction, different monoacetals, aldehydes, and dialkylzinc reagents were used in the catalytic asymmetric tandem 1,4-addition—aldol reaction. In all cases, ratios (trans-threo/trans-erythro) exceeding 95:5 for the corresponding hydroxy ketones were found. To facilitate the ee determination of the tandem 1,4-addition—aldol products, it is necessary to remove the stereocenter associated with the hydroxy functionality. Therefore, oxidation to the corresponding diketone was performed using PCC (pyridinium chlorochromate). The results are summarized in Table 3.

In the tandem 1,4-addition—aldol reaction with monoacetals $7a$–$e$, catalyzed by Cu(OTf)$_2$ and different phosphoramidites, good yields were obtained for the corresponding aldol products $11a$ and $13a$–$21a$. Oxidations with PCC provide the diketones $11c$ and $13c$–$17c$ in yields up to 76% with excellent ee values. In the presence of 2 mol % of Cu(OTf)$_2$ and 4 mol % of ligand $L1$, enone $7b$, Et$_2$Zn, and benzaldehyde gave the $\beta$-hydroxy ketone $13a$ in 67% yield and after oxidation diketone $13c$ with 87% ee (Table 3, entry 1). For the reaction with Bu$_2$Zn, similar results were found (Table 3, entry 2). Changing the solvent from toluene to CH$_2$Cl$_2$ slowed the reaction (40% conversion after 36 h) and resulted in an ee of 84% for $14c$ (Table 3, entries 10 and 12). Performing the reaction at lower temperature (−30 °C instead of −45 °C), the enantioselectivity decreased from 87% to 83% (Table 3, entries 1 vs 4). For various phosphoramidite ligands, the following results were achieved: for ligand $L8$ (Figure 3), 70% conversion of $7b$ after 36 h and 38% ee for diketone $14c$ (Table 3, entry 5); the ligands $L9$ and $L7$ (Figure 3) gave 62% and 93% conversion of $7b$ after 36 h and 56% ee and 13% ee for $14c$, respectively (Table 3, entries 6 and 7); bidentate ligand $L3$ (Figure 1) gave 59% conversion of $7b$ after 36 h and 5% ee for $14c$ (Table 3, entry 8); and TADDOL-derived phosphoramidite $L2$ (Figure 1) gave no conversion at all (Table 3, entries 9).

Using monocetal $7d$, diethylzinc or dibutylzinc, and benzaldehyde in this reaction gave ee values of 94% for $15c$ and $16c$ (Table 3, entries 10 and 12). Performing the reaction at lower temperature (−60 °C) has no influence.

**TABLE 3. Catalytic Enantioselective Tandem 1,4-Addition—Aldol Reaction of Dialkylzinc Compounds to Cyclopentene-3,5-dione Monoacetals in the Presence of Aldehydes**

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<th>enone</th>
<th>$R'_2$Zn</th>
<th>ligand</th>
<th>$R''$CHO</th>
<th>aldol</th>
<th>conv$^a$ (%)</th>
<th>yield$^b$ (%)</th>
<th>diketone</th>
<th>ee$^c$ (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>$7b$</td>
<td>Et</td>
<td>$L1$</td>
<td>C$_6$H$_5$</td>
<td>$13a$</td>
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<td>$13c$</td>
<td>87</td>
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<td>$7b$</td>
<td>Bu</td>
<td>$L1$</td>
<td>C$_6$H$_5$</td>
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$^a$ Determined by $^1$H NMR. $^b$ Isolated yield. $^c$ Determined by chiral HPLC DAICEL CHIRALPAK AD. $^d$ Reaction carried out in CH$_2$Cl$_2$. $^e$ Reaction temperature −30 °C. $^f$ Reaction temperature −60 °C. $^g$ Oxidation with PCC and NMO/RuCl$_2$(PPh$_3$)$_3$. $^h$ Crude tandem product identified by NMR; purification by column chromatography resulted in the formation of elimination product. $^i$ See text.
on the enantioselectivity (Table 3, entry 11). Furthermore, different aldehydes were used as electrophiles. In the case of p-bromobenzaldehyde, the corresponding hydroxy ketones 17a and 11a were isolated in 69% and 64% yield using Et2Zn and Bu2Zn, respectively (Table 3, entries 13 and 14). After oxidation, excellent ee values of 96% for diketone 17c and 97% for 11c were obtained. Applying butanal resulted in the corresponding hydroxy ketone in 65% yield, but attempts to oxidize 18a with PCC or NMO/RuCl3(PPh3)3 to determine the ee value gave a complex reaction mixture (Table 3, entry 15). A reduction strategy as it was used for the ee determination of 35 (vide infra) offers a solution (Scheme 7). Enone 7e was also successfully applied in the tandem 1,4-addition–aldol reaction. The tandem product 19a was obtained in 54% yield (Table 3, entry 16). Like compound 18a, 19a gave a complex reaction mixture during attempts to oxidize it to the corresponding diketone. The application of enones 7a and 7c resulted in the formation of the crude tandem 1,4-addition–aldol products 20a and 21a (Table 3, entries 17 and 18) but during purification by column chromatography an elimination reaction occurred (Table 4). The formation of these elimination products was also observed using reaction temperatures above –30 °C. Performing the tandem 1,4-addition–aldol reaction at 0 °C gave these products exclusively. To establish an ee determination method that is applicable for these elimination products a protocol comprising a reduction/elimination and oxidation reaction was used. Part of this protocol was actually developed for the synthesis of 2-cyclohexenones. Applying this protocol to the elimination products resulted in the formation of 23 in all cases. The results are given in Table 4.

The elimination product 20a resulting from the copper-catalyzed tandem 1,4-addition–aldol reaction of diethylzinc to 7c in the presence of benzaldehyde was obtained in 75% yield after column chromatography (Table 3, entry 17, and Table 4, entry 1). Reduction of 20a with LiAlH4 and subsequent acid workup gave 22 in 65% yield. Oxidation with PCC afforded 23 in 68% yield and 70% ee. Compound 21d was obtained in 64% yield after column chromatography, and after conversion to 23 an ee value of 76% was measured (Table 3, entry 18, and Table 4, entry 2). Furthermore, a control experiment was carried out to make sure that epimerization does not occur applying this protocol. For this purpose, 13a was treated with acid undergoing an elimination reaction and 13d was obtained in quantitative yield (Table 3, entry 1, and Table 4, entry 3). The reduction/elimination and oxidation reaction gave 23 with an ee of 87%, confirming that no epimerization took place during these conversions (Table 3, entry 1, and Table 4, entry 3).

From these experiments using different phosphoramidite ligands, cyclopentene-3,5-dione monoacetals, aldehydes, and dialkylzinc reagents, the following conclusions can be drawn. The catalyst prepared in situ from Cu(O Tf)2 and L1 gave the highest asymmetric induction in these reactions. The nature of the acetal has a strong influence on the stability of the tandem products. The compounds with the 2,2-dimethyl- and 2,2-diphenyl-substituted 1,3-dioxane acetal functionality are quite stable resulting only in up to 10% elimination product after column chromatography. The tandem products with the 1,3-dioxolanes and acyclic acetal functionality, in contrast, are converted completely during purification by column chromatography (SiO2 and Al2O3). Furthermore, the enantioselectivity of the tandem 1,4-addition–aldol reaction was influenced by the nature of the acetal functionality. The use of dioxolane 7c and dimethoxy acetal 7a gave enantioselectivities of 70% and 76%, respectively, whereas for the dioxane acetals 7d and 7b ee values of 97% and 87% were found for the products of the tandem 1,4-addition–aldol reaction. On the basis of these results, 7d was used as starting material for the natural product synthesis.

**Catalytic Enantioselective Synthesis of Prostaglandin E1 Methyl Ester**. The results of the asymmetric 1,4-addition–aldol reactions of diorganozinc reagents to cyclopentene-3,5-dione monoacetals enabled us to employ the optimal conditions for the asymmetric synthesis of a prostaglandin. The initial approach we followed for this catalytic asymmetric total synthesis is reminiscent of the three-component coupling reaction introduced by Noyori (Scheme 1). However, the application of the required dialkenylzinc reagents, corresponding to the organocopper reagents in Scheme 1, did not lead to product formation. These reagents can be prepared, like dialkylzinc reagents, by a boron–zinc exchange reaction in a

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**TABLE 4. Conversion of the Elimination Products to the Corresponding Diketone 23**

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>R'</th>
<th>aldon product</th>
<th>elimination product</th>
<th>yield (%)</th>
<th>ee (%)</th>
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<td>Et</td>
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<td>20d</td>
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<td>CH2C(CH3)2CH2</td>
<td>Et</td>
<td>13a</td>
<td>13d</td>
<td>67</td>
<td>87</td>
</tr>
</tbody>
</table>

*a* Isolated yield based on cyclopentene-3,5-dione monoacetal. *b* Determined by chiral HPLC.

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salt-free procedure from organoboranes. Using this type of reagent in a model 1,4-addition with 2-cyclohexenone in the presence of an in situ generated catalyst from Cu(OTf)$_2$/L$_1$, no product was formed after 24 h at $-20^\circ$C. Employing an in situ generated mixed alkylalkenylnzinc reagent, it was found that only the saturated carbon nucleophile was transferred to the enone.

These results indicate that the $\omega$ side chain, apparently, cannot be introduced using an unsaturated diorganozinc reagent in a catalytic asymmetric 1,4-addition protocol. This is the reason for the new approach outlined in the retrosynthetic analysis in Scheme 4.

The preparation of PGE$_1$ methyl ester 28 would involve cleavage of the acetal and an allylic transposition starting from 27. To carry out the allylic transposition, conversion of the diol 27 to the corresponding diacetate would be necessary. Protodesilylation$^{39}$ and stereoselective reduction of 26 could afford 27. Formation of 26 would involve the tandem 1,4-addition–aldol reaction of 7d, 24, and 25 in the presence of a chiral copper catalyst. In this new three-component coupling approach, the saturated $\alpha$-chain of the PGE$_1$ methyl ester would be introduced with a functionalized zinc reagent and the $\omega$-chain via an unsaturated aldehyde involving the simultaneous presence of an enone and enal. To discriminate between them, 25 is equipped with a silyl substituent, exploiting the fact that 3-substituted enones are not reactive under the condition of the catalytic 1,4-addition.$^{40}$ The phenyldimethylsilyl group is chosen because of its easier removal in comparison with other silyl groups. For the synthesis of aldehyde 25, a protocol described by Magriotis for similar compounds was followed (Scheme 5).$^{39}$

Commercially available 2-octyn-1-ol was converted in a stereoselective manner to 30 by the Masamune modification$^{41}$ of the Corey reductive iodination.$^{42}$ This procedure proceeds with 100% cis selectivity because of the intramolecular coordination of the aluminum center with the hydroxy functionality. Using chlorodimethylphosphinylsilane, allylic alcohol 30 was converted to the silyl ether 31 in excellent yield. This compound underwent a 1,4-O→sp3C silyl migration using 2 equiv of $t$-BuLi.$^{29}$ The corresponding (Z)-vinylsilane 32 was obtained in 74% yield. Subsequently, Swern oxidation gave the unsaturated aldehyde 25 with an E/Z ratio of 6:94. The overall yield of this sequence was 51%.

The zinc reagent 24 was prepared following a Knochel procedure (Scheme 6).$^{43}$ Therefore, commercially available 6-heptenoic acid 33 was converted to the methyl ester 34. Subsequently, hydroboration of the olefin gave the functionalized borane, which underwent a borane–zinc exchange reaction in the presence of neat Et$_2$Zn. After evaporation of the excess of Et$_2$Zn, the corresponding functionalized zinc reagent 24 was obtained in high yield.

For the total synthesis of PGE$_1$ methyl ester enone 7d, aldehyde 25 and the functionalized zinc reagent 24 were converted in a catalytic enantioselective 1,4-addition–aldol procedure (Scheme 7).

In the presence of 3 mol % of an in situ generated chiral Cu(OTf)$_2$/L$_1$ catalyst, compound 26 was obtained in 60% yield as a mixture (not separable at this stage) of diastereomers with high stereoselectivity (trans/threo/trans-erythro ratio 83:17). Reduction of the ketone moiety proceeded with 95% stereoselectivity using Zn(BH$_4$)$_2$ in ether at $-30^\circ$C. All diastereomers (79% yield) could be isolated by column chromatography, and the major diastereomer 35 was obtained in 63% yield with an ee of 88%.


$^{38}$Oppolzer, W.; Rudolph, R. N. Helv. Chim. Acta 1995, 78, 670. (b) For the Pd(II)-mediated allylic acetate transposition in a catalytic enantioselective 1,4-addition–aldol reaction of 7d, 24, and 25 in the presence of a chiral copper catalyst. In this new three-component coupling approach, the saturated $\alpha$-chain of the PGE$_1$ methyl ester would be introduced with a functionalized zinc reagent and the $\omega$-chain via an unsaturated aldehyde involving the simultaneous presence of an enone and enal. To discriminate between them, 25 is equipped with a silyl substituent, exploiting the fact that 3-substituted enones are not reactive under the condition of the catalytic 1,4-addition. The phenyldimethylsilyl group is chosen because of its easier removal in comparison with other silyl groups. For the synthesis of aldehyde 25, a protocol described by Magriotis for similar compounds was followed (Scheme 5).$^{39}$


94%. In the next step, the silyl substituent was removed using Bu$_4$NF in THF/DMSO to give compound 27. This comprises a novel protection and deprotection sequence for enones/enals suitable for the catalytic 1,4-addition with dialkylzinc reagents. The cleavage of vinyl carbon–silicon bonds with Bu$_4$NF was developed by Nozaki. However, under the normal reaction conditions, hydrolysis of the ester moiety of compound 27 was observed caused by water in the commercial THF solution of Bu$_4$NF. Adding first sacrificial methyl propionate to remove the water by hydrolysis and only afterward gave the desilylated compound 27 as the only product. Diacetylation of crude 27 afforded 36 in 71% yield over two steps. The 1,3-allylic transposition of 36 with a catalytic amount of Pd(CH$_3$CN)$_2$Cl$_2$ in THF proceeded with reasonable yield (63%) and full retention of configuration to provide allylic acetate 37 with the required stereochemistry. After deacetylation in the presence of K$_2$CO$_3$ in MeOH, compound 38 was obtained in excellent yield. The final step comprises the mild deprotection of the ketone functionality to provide the labile $\beta$-hydroxy ketone moiety of the prostaglandin E$_1$. This conversion was realized using a catalytic amount of (NH$_4$)$_2$Ce(NO$_3$)$_6$ under nearly neutral conditions. In this way ($\text{(-)}$)-PGE$_1$ methyl ester 28, in all respects identical with an independent sample, was obtained in 7% overall yield with 94% optical purity in 7 steps from 7d.

Conclusions. A new general synthesis of rather labile cyclopentene-3,5-dione monoacetals with yields up to 64% was introduced. Furthermore, we demonstrated that these compounds could be successfully applied as substrates for the catalytic enantioselective 1,4-addition and, in particular, for the catalytic enantioselective tandem 1,4-addition–aldol reaction. In the presence of 2 mol % of the in situ generated catalyst Cu(OTf)$_2$/phosphoramidite L$_1$, enantioselectivities up to 94% could be obtained for the 1,4-addition products, whereas 97% ee was achieved in the tandem 1,4-addition–aldol reaction. In the latter procedure, excellent stereoselectivity is also observed in the subsequent aldol step achieving nearly complete stereocontrol in the formation of the consecutive stereocenters, which provides an efficient route to enantiomerically pure multifunctional cyclopentanones. In addition, it was shown that the stability toward elimination of the tandem 1,4-addition–aldol products depends strongly on the nature of the acetal moiety; 1,3-dioxolanes and acyclic monoacetals of cyclopentene-3,5-dione undergo elimination even during purification by column chromatography, whereas 2,2-disubstituted 1,3-dioxane monoacetals can be purified without any difficulties. The versatility of this catalytic methodology was demonstrated.

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SCHEME 7

$^a$ Key: (a) 3 mol % Cu(OTf)$_2$, 6 mol % L$_1$, toluene, $-45^\circ$C, 18 h; (b) Zn(BH$_4$)$_2$, ether, $-30^\circ$C, 3 h; (c) (1) 3 equiv of Bu$_4$NF (1 M in THF), methyl propionate, DMSO, 80 $^\circ$C, 20 min, (2) Ac$_2$O, DMAP, pyridine, 20 min; (d) 5 mol % Pd(CH$_3$CN)$_2$Cl$_2$, THF, 3 h; (e) K$_2$CO$_3$, MeOH, 18 h; (f) (NH$_4$)$_2$Ce(NO$_3$)$_6$, MeCN, borate–HCl buffer (pH = 8), 60 $^\circ$C, 2 h.

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(46) The analytical and spectral data (TLC, HPLC, $^1$H NMR, $^{13}$C NMR, CD, MS) (a)$_{PGE1}$$beta$ $\delta$ 51 (c 1.0, CH$_3$OH) of 28 were identical with those of authentic material (Sigma) (a)$_{PGE1}$$beta$ $\delta$ 54 (c 1.0, CH$_3$OH).
strated in the application as the key step in a short asymmetric synthesis of a PGE₁ methyl ester comprising a new route to this natural product. We showed in this synthesis that except for 3 mol % of an enantiomerically pure catalyst, only achiral materials are required to prepare an PGE₁ methyl ester in a highly effective manner.

**General Considerations.** Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Toluene, diethyl ether, and THF were distilled from sodium/benzophenone ketyl and stored under nitrogen. DCM, hexane, pentane, and CHCl₃ were distilled from P₂O₅ and MeOH from MeONa. BF₃·Et₂O, benzylic alcohol, and triethylamine were distilled before use. Cu(OTf)₂ was dried before use. Enantiomeric ratios were determined by chiral HPLC (DAICEL CHIRALPAK AD) in comparison with racemic material. Spectra are referenced internally to the residual resonance in CDC₁₃ (δ 7.24 ppm) for hydrogen and (δ = 77 ppm) for carbon atoms. Chemical shifts (δ) are denoted as part per million (ppm) starting from downfield to upfield.

**General Procedure for the Acetalization of 2-Cyclopentene-1,3-dione (7a–e).** To a cooled solution (0 °C) of cyclopentene-3,5-dione (1.92 g, 20 mmol) and BF₃·Et₂O (20 mmol for diol). After being stirred for 18 h. After complete conversion, the reaction mixture was poured into 25 mL of NH₄Cl (aq), 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. Column chromatography (SiO₂) ether/pentane) gave the corresponding acetals.

**8,8-Diphenyl-6,10-dioxaspiro[4.5]dec-2-en-2-one (7d).** Purification by column chromatography (SiO₂ pentanediethyl ether, 1:1, Rₙ = 0.43) gave 150 mg (69%) of 7d as a white solid. Alternative workup for large-scale reaction (52 mmol) (only starting materials and product present in the crude reaction mixture). The reaction mixture was poured into NH₄Cl (aq) and extracted three times with 25 mL of diethyl ether. The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The unreacted diol can be removed by crystallization from hexane/CHCl₃ (5:1) and CH₂Cl₂ (150 mL). The organic layer was separated, washed with 1 M NaOH solution to remove the cyclopentene-3,5-dione, dried over MgSO₄, filtered, and concentrated in vacuo.

**General Procedure for the 1,4-Addition (8–10).** A solution of Cu(OTf)₂ (3.6 mg, 0.01 mmol) and phosphoramidite (0.02 mmol) in toluene (0.6 mL, 1 M solution in toluene) was added to the reaction mixture was cooled to −45 °C, the diol, and triethylamine were distilled before use. Cu(OTf)₂ was dried before use. Enantiomeric ratios were determined by chiral HPLC (DAICEL CHIRALPAK AD) in comparison with racemic material. Spectra are referenced internally to the residual resonance in CDC₁₃ (δ 7.24 ppm) for hydrogen and (δ = 77 ppm) for carbon atoms. Chemical shifts (δ) are denoted as part per million (ppm) starting from downfield to upfield.

**General Procedure for the Oxidation of a Diketone (11c, 13c–17c).** To hydroxy ketone (0.2 mmol) in CH₂Cl₂ (5 mL) were added molecular sieves (4 Å, 0.5 g) and PCC (215 mg, 1 mmol) at 0 °C. The reaction mixture was stirred for 4 h at room temperature, filtered through silica gel, and evaporated to dryness.

**General Procedure for the 1,4-Addition (8–10).** A solution of Cu(OTf)₂ (3.6 mg, 0.01 mmol) and phosphoramidite (0.02 mmol) in toluene (7 mL) was stirred under nitrogen atmosphere at ambient temperature for 1 h. The cyclopentene-3,5-dione monoacetal (0.5 mmol) was added, and after the reaction mixture was cooled to −45 °C, the diol, and triethylamine were distilled before use. Cu(OTf)₂ was dried before use. Enantiomeric ratios were determined by chiral HPLC (DAICEL CHIRALPAK AD) in comparison with racemic material. Spectra are referenced internally to the residual resonance in CDC₁₃ (δ 7.24 ppm) for hydrogen and (δ = 77 ppm) for carbon atoms. Chemical shifts (δ) are denoted as part per million (ppm) starting from downfield to upfield.

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Synthesis of (−) Prostaglandin E₁ Methyl Ester

with stirring, of 10 mL of water. The resulting reaction mixture was poured into 70 mL of cold aqueous 10% sulfuric acid. 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/hexane, 1:1, Rᵣ = 0.31) gave 124 mg (64%) of 22 as a colorless liquid: ¹H NMR (300 MHz) δ 7.75 (dd, J = 5.7 Hz, J = 2.1 Hz, 1H), 7.37–7.30 (m, 5H), 6.19 (dd, J = 5.4, 2.1 Hz, 1H), 4.60 (dd, J = 6.9, 2.7 Hz, 1H), 2.93 (m, 1H), 2.21 (d, J = 2.1 Hz, OH), 2.07 (m, 1H), 1.35 (m, 2H), 0.67 (t, J = 6.9 Hz, 3H); ¹³C NMR (200 MHz) δ 132.5, 131.2, 130.0, 128.5, 55.2, 48.8, 23.1, 11.0; MS (EI) for C₈H₁₅IO₂ m/z = 216 (M⁺), 234 (M + NH₄⁺).

(45R,5S)-5-Ethyl-4-(R)-hydroxy(phenyl)methyl)-2-cyclopenten-1-one (23). General procedure for the oxidation to a diketone was used in this case: Purification by column chromatography (SiO₂, hexane/diethyl ether, 2:3, Rᵣ = 0.31) gave 23 in 65% yield as yellow oil: ¹H NMR (300 MHz) δ 8.02 (m, 2H), 7.65–7.50 (m, 4H), 6.22 (m, 1H), 4.52 (m, 1H), 2.90 (m, 2H), 1.86 (m, 1H), 1.64 (m, 1H), 0.89 (t, J = 7.2 Hz, 3H); ¹³C NMR (200 MHz) δ 211.5, 164.1, 143.5, 134.7, 133.4, 129.0, 128.5, 116.5, 54.5, 48.9, 23.1, 10.4; MS (EI) for C₁₁H₁₆O₂ m/z = 216 (M⁺), 234 (M + NH₄⁺).

(Z)-3-Iodo-2-octen-1-ol (30). 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 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 resulting 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, Rᵣ = 0.30) gave 40.3 g (94%) of 30 as a light purple colored oil (100% cis): ¹H NMR (300 MHz) δ 7.54 (m, 2H), 7.37 (m, 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 (200 MHz) δ 133.2, 111.0, 67.3, 45.1, 30.4, 28.8, 22.4, 14.0; MS (EI) for C₁₆H₂₅IOSi m/z = 214 (M⁺), 232 (M + NH₄⁺).

(Z)-1-Dimethyl(phenyl)siloxy-3-iodo-2-octene (31). To a solution of 30 (14 g, 59 mmol) in CH₂Cl₂ (300 mL) were added â-BuLi (100 mL, 1.7 M pentane) and phosphoramidite â-PrOH/hexane 2:98, 1 mL/400 mL, 1 h, the reaction mixture was poured into NH₄Cl (aq), and 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, Rᵣ = 0.35) gave 14.8 g (74%) of 32 as a colorless oil (100% cis): ¹H NMR (300 MHz) δ 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 (200 MHz) δ 142.4, 141.4, 139.5, 133.5, 129.0, 128.0, 62.3, 38.3, 31.9, 30.1, 22.5, 14.0, 11.0; MS (EI) for C₁₆H₂₅OSi m/z = 262 (M⁺), 280 (M + NH₄⁺).

(Bis(methyl-6-hepanoate)zinc (24). Compound 34 (2.84 g, 20 mmol) was cooled (degassed using a freeze-dry technique under vacuum/argon) to 0 °C, and HBE₃ was freshly prepared in toluene (2 M in diethyl ether) and BET₃ (1 M in THF) were added via a syringe (1 min). The volatiles were removed after complete conversion (GC) under vacuum (0.1 mmHg, 0 °C, 1 h). The resulting organoborate was treated at 0 °C with 2 mL of Et₂Zn (neat) and stirred at room temperature for 2 h. The formed BET₂ and the excess Et₂Zn were removed under vacuum (0.1 mmHg, 3 h) giving 3 g (85%) of 24 as a colorless liquid: ¹H NMR (300 MHz, CDCl₃) δ 0.62–0.53 (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).
yield of 26 as a colorless oil (mixture of three enantiomer ratio of 83:17): 1H NMR (300 MHz) δ 7.39-7.12 (m, 4H), 7.07-7.00 (m, 2H), 6.53 (d, J 5.7 Hz, 1H), 4.56 (d, J 4.0 Hz, 2H), 3.50 (s, 3H), 2.47-2.34 (m, 2H). 13C NMR (150 MHz) δ 171.1, 143.2, 133.5, 133.0, 128.7, 128.4, 128.2, 127.8, 126.4, 126.2, 125.7, 125.2, 124.7, 121.2, 120.8, 120.6, 120.4, 120.0, 119.2, 108.9, 108.7, 107.8, 107.7, 107.6, 106.4, 106.0, 93.7, 74.6, 73.0, 72.4, 72.2, 71.0, 68.2, 56.8, 51.8, 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 C31H52O3 m/z = 446 (M+).

Methyl 7-[1(R),2,3R]-3-Acetyloxy-2-[(1S,2E)-1-(acetyl oxy)-2-octenyl]-8,8-diphenyl-6,10-dioxaspiro[4.5]heptanoate (35). Under argon atmosphere, a solution of 26 (1420 mg, 2 mmol) in diethyl ether (40 mL) was treated with Zn(BH4)2 (8 mL, 0.5 M in diethyl ether) at −23 °C. After being stirred for 3 h at the same temperature, the reaction mixture was quenched with NH4Cl aqueous (250 mL) and stirred for 30 min. The reaction mixture was diluted with diethyl ether (50 mL), and the organic layer was separated, and the aqueous layer was extracted with CH2Cl2 (aq) in a beaker (250 mL) and stirred for 30 min. The reaction mixture was filtered over SiO2, filtered, and concentrated in vacuo.

Purification by column chromatography (SiO2 diethyl ether/pentane, 1:1, vol/vol) gave 119 mg (90%) of 36 as a white solid: 1H NMR (300 MHz) δ 7.41–7.00 (m, 10H), 5.48 (dd, J = 15.0, 6.7 Hz, 1H), 5.36 (dd, J = 15.0, 6.7 Hz, 1H), 5.42 (dd, J = 15.0, 6.7 Hz, 1H). 13C NMR (200 MHz) δ 174.3, 173.0, 170.8, 170.2, 144.6, 134.3, 134.1, 133.8, 132.9, 132.8, 128.5, 128.6, 128.5, 128.1, 128.0, 128.6, 128.4, 126.1, 107.3, 72.9, 72.1, 70.0, 68.2, 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 C31H52O3Si m/z = 712 (M+).

The ee of 94% was determined by HPLC on a chiral stationary phase (DAICEL CHIRALPAK AD, 250 × 4.6 mm, 254 nm, 0.5 mL/min, rt, tR = 4.9 min, tR = 9.0 min).

Methyl 7-[1(R),2,3R,3aS,4aS]-3-Acetyloxy-2-[(1S,2E)-1-(acetoxy)-2-octenyl]-8,8-diphenyl-6,10-dioxaspiro[4.5]dec-1-yl]heptanoate (35). Under argon atmosphere, a solution of Bu4NF (6 mL, 1 M THF) was added to a solution of methyl heptanoate (37). Under argon atmosphere, a solution of 35 was added at room temperature together with Ac2O. After being stirred for 30 min, the reaction mixture was filtered over SiO2, filtered, and concentrated in vacuo. Purification by column chromatography (SiO2 diethyl ether/pentane, 1:1, vol/vol) gave 119 mg (90%) of 38 as a white solid: 1H NMR (300 MHz) δ 7.41–7.00 (m, 10H), 5.48 (dd, J = 15.0, 6.7 Hz, 1H), 5.36 (dd, J = 15.0, 6.7 Hz, 1H), 5.42 (dd, J = 15.0, 6.7 Hz, 1H). 13C NMR (200 MHz) δ 174.3, 173.0, 170.8, 170.2, 144.6, 134.3, 134.1, 133.8, 132.9, 132.8, 128.5, 128.6, 128.4, 126.1, 107.3, 72.9, 72.1, 70.0, 68.2, 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 C31H52O3Si m/z = 712 (M+).

Supporting Information Available: Characterization of compounds 7a–10, 11a–b, 13a–15a, 17a–21a, 11c–13c, 17c, 13d, and 20d; NOESY-NMR of compounds 11a,b and 28 and CD spectra of compound 28. 13C NMR spectra of compounds: 7a–e, 8–10, 11a–b, 13a–21a, 11c–17c, 13d, 20d, 21d, and 22–38. This material is available free of charge via the Internet at http://pubs.acs.org.

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