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Catalytic Enantioselective Synthesis of (−)-Prostaglandin E_1 Methyl Ester Based on a Tandem 1,4-Addition−Aldol Reaction

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Catalytic enantioselective 1,4-additions and tandem 1,4-addition−aldol reactions of dialkylzinc reagents to cyclopentene-3,5-dione monoacetals in the presence of an in situ generated $Cu(OTf)_2$/chiral phosphoramidite catalyst result in highly functionalized cyclopentane building blocks with ee's up to 97%. A new synthesis of cyclopentene-3,5-dione monoacetals is presented as well as its use in a tandem 1,4-addition−aldol protocol for the catalytic asymmetric total synthesis of (−)-PGE_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_1 are established at once.

Introduction

Prostaglandins (PGs) belong to the family of polyoxygenated fatty acids that are produced by a cyclooxygenase enzyme system widely distributed in mammalian tissue.[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.[2] Several synthetic prostaglandin derivatives are currently used as drugs, but their synthesis is often still the subject of considerable improvement and innovation.[3] Synthetic routes are largely based on three strategies, the Corey synthesis,[4] the two-component coupling,[5] and the three-component coupling,[6] although a number of other approaches have been reported.[7] The latter method, developed by Noyori,[8] is particular 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 optically 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.[9] This sequence provides a convenient way to introduce simultaneously the α and ω side chains necessary for the elaborations into (−)-PGE_1 **5**.

The versatility of organocopper reagents[10] and the possibility of enolate trapping resulting in α-functionalization[11] (exemplified in Scheme 1), makes the 1,4-addition one of the most versatile carbon−carbon bond formation reactions in organic synthesis.[12] In the past decade, considerable progress has been achieved in the development of a catalytic enantioselective 1,4-addition to enones.[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.[14] The reaction of 6-, 7-, and 8-membered 2-cycloalkenones and (functionalized) dialkylzinc (R_2Zn) reagents gave, in the presence of 1 mol % of an in situ prepared catalyst based on $Cu(OTf)_2$ and phosphoramid-

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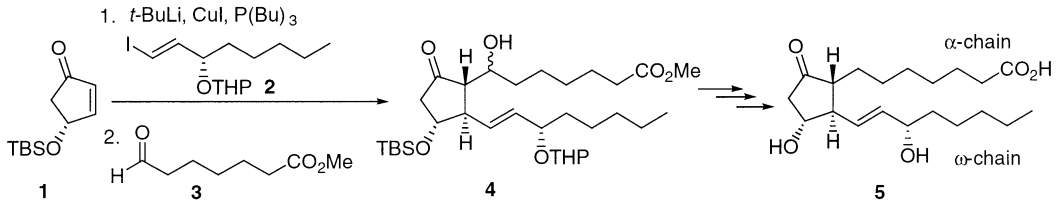
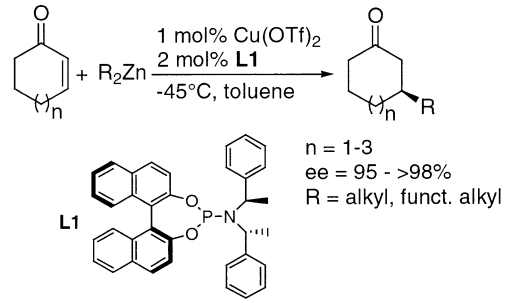
SCHEME 1



SCHEME 2



ite **L1**, the corresponding 1,4-addition products in high yields and with ee's up to >98% (Scheme 2).[15]

On the basis of this methodology, catalytic routes are now available to enantiomerically pure products embedding cyclohexane and larger rings in their structure.[16] In addition to the enantioselective copper-catalyzed 1,4-addition of organozinc reagents, a highly enantioselective rhodium-catalyzed conjugate addition of aryl- and alkenylboronic acids to enones has been developed by Hayashi.[17] For cyclic and acyclic enones, ee's between 92 and 99% have been found in the presence of 1.5 mol % of a $[Rh(OH)((S)\text{-binap})]_2$ catalyst. For example, 3-phenylcyclopentanone was obtained in 95% yield and 98% ee.

In contrast, the enantioselective copper-catalyzed 1,4-addition of dialkylzinc reagents to 2-cyclopentenone remained a major challenge, particularly because chiral cyclopentane structures are ubiquitous in natural products such as prostaglandins. Surprisingly, the use of phosphoramidite **L1** as ligand for $Cu(OTf)_2$ in the 1,4-addition of diethylzinc to 2-cyclopentenone resulted in hardly any selectivity at all (10% ee).[16a] Employing TADDOL[18]-based phosphoramidite ligand **L2**, up to 62% ee was obtained for the corresponding 1,4-addition product when the reaction was run in the presence of molecular sieves (Figure 1).[19] Under the same conditions, chiral bidentate phosphoramidite ligand **L3** gave an enantioselectivity of 83%.[20] Chan[21] reached 89% ee using the diphosphite ligand **L4** in the 1,4-addition of diethylzinc to 2-cyclopentenone, whereas Pfaltz[22] enhanced the enantioselectivity to 94% using phosphite **L5** containing a chiral oxazoline group. Recently, Hoveyda[23] 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 (−)-PGE_1 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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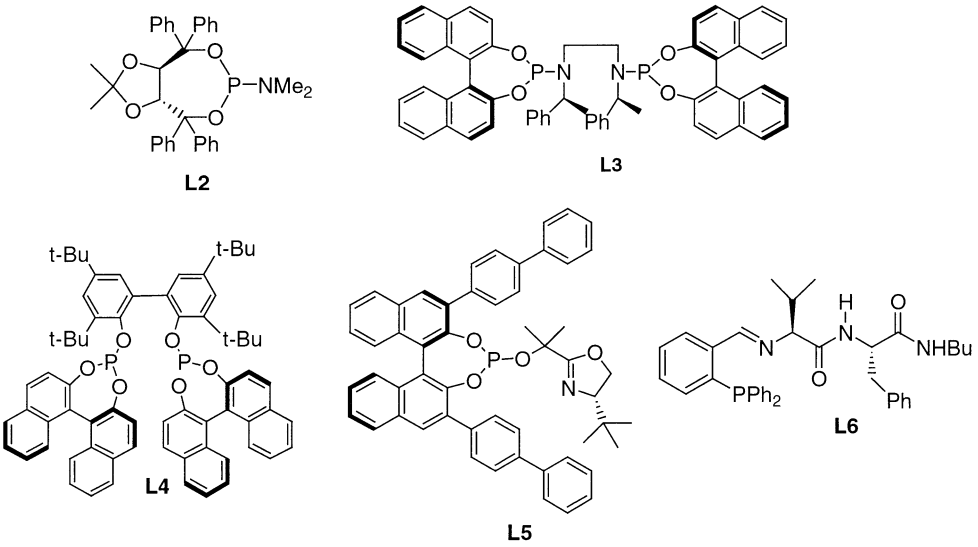
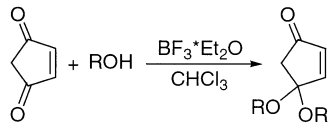


FIGURE 1. Different ligands used for the catalytic asymmetric 1,4-addition of diethylzinc to 2-cyclopentenone.

TABLE 1. Monoacetalization of 6 in the Presence of $BF_3 \cdot Et_2O$



6 7a-e

entry	alcohol	time (h)	*T* (°C)	convn[a] (%)	acetal	yield[b] (%)
1	methanol	1.5	0	50	**7a**	26 (+7)[c]
2	2,2-dimethyl-1,3-propanediol	1.5	0	58	**7b**	29
3	ethylene glycol	1.5	0	45	**7c**	25
4	2,2-diphenyl-1,3-propanediol	3	0	71	**7d**	50 (64)[d]
5	pinacol	72	25	76[f]	**7e**	29 (6)[e]
6	isopropyl alcohol	48	25	0[f]		
7	benzyl alcohol	48	25	0[f]		

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

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 $BF_3 \cdot Et_2O$. 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-propanediol gave 71% conversion after 3 h at 0 °C and 50% yield of **7d** (Table 1, entry 4). Employing a different purification method[27] instead of column chromatography improved the isolated yield to 64%. The reaction of **6** and pinacol in the presence of $BF_3 \cdot Et_2O$ 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 % $Cu(OTf)_2$ and 4 mol % phosphoramidite **L1** or **L7** (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 % $Cu(OTf)_2$/**L1** 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 (1*S*,2*S*)-diphenylethylenediamine[28] was also unsuccessful. Apart from the formation of **8**, **8a** and **8b** were

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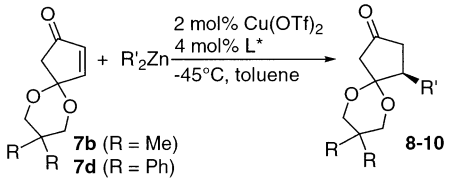
(27) See the Experimental Section.

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



entry	enone	R'_2Zn	ligand	product	yield[a] (%)	ee[b] (%)
1	**7b**	Et_2Zn	**L1**	**8**	31 (42)[c]	*d*
2	**7d**	Et_2Zn	**L1**	**9**	40	90
3	**7d**	Et_2Zn	**L7**	**9**	37	0
4	**7d**	Bu_2Zn	**L7**	**10**	32	5
5	**7d**	Bu_2Zn	**L1**	**10**	37	94

[a] Isolated yield. [b] Determined by chiral HPLC. [c] Side product, see: Figure 2. [d] No separation by chiral HPLC.

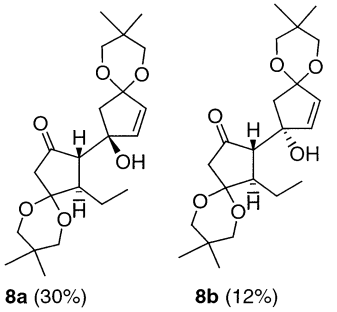


FIGURE 2. Side products formed in the catalytic enantioselective 1,4-addition of diethylzinc to **7b**.

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 $Cu(OTf)_2$/**L1**-catalyzed 1,4-addition dramatically. The reaction of **7d** and diethylzinc afforded **9** in 40% yield and 90% ee (Table 1, entry 2). Using **L7** (Figure 3) instead of **L1** 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 $Cu(OTf)_2$/**L7** afforded **10** in 32% yield and 5% ee (Table 2, entry 4). In contrast, catalyst $Cu(OTf)_2$/**L1** 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.

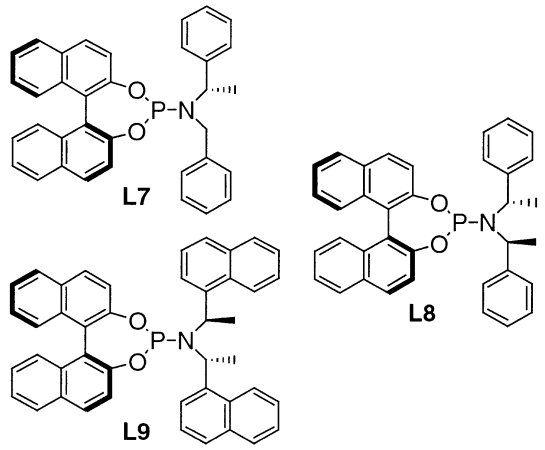
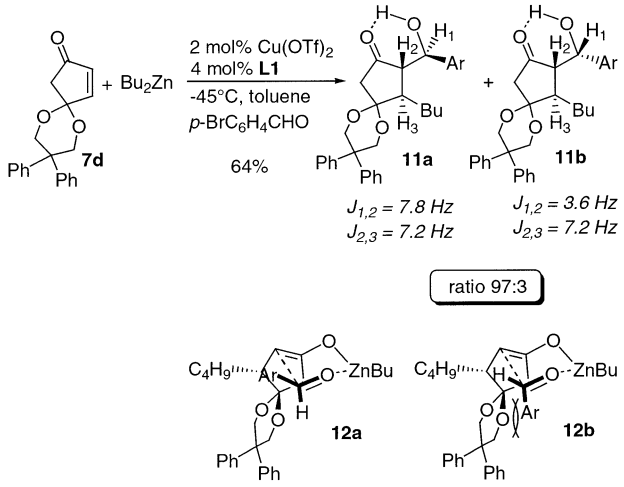


FIGURE 3. Different phosphoramidite ligands.

SCHEME 3



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 **L1**, was sufficient to obtain the *β*-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 ^1H NMR based on different absorptions of H_1 (4.77 ppm **11a** and 5.11 ppm **11b**). COSY-NMR and ^1H NMR was used to assign the relative configurations of the two compounds. The coupling constant for **11a** and **11b** was $J_{2,3} = 7.2$ 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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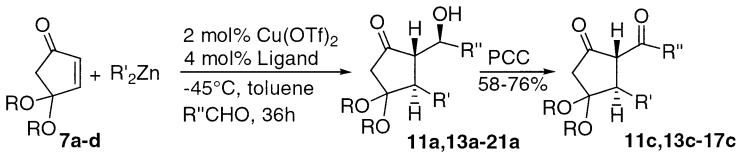
TABLE 3. Catalytic Enantioselective Tandem 1,4-Addition−Aldol Reaction of Dialkylzinc Compounds to Cyclopentene-3,5-dione Monoacetals in the Presence of Aldehydes



entry	enone	R'_2Zn	ligand	R″CHO	aldol	convn[a] (%)	yield[b] (%)	diketone	ee[c] (%)
1	**7b**	Et	**L1**	C_6H_5	**13a**	100	67	**13c**	87
2	**7b**	Bu	**L1**	C_6H_5	**14a**	100	64	**14c**	87
3	**7b**	Bu	**L1**	C_6H_5	**14a**	40	23	**14c**	84[d]
4	**7b**	Bu	**L1**	C_6H_5	**14a**	100	67	**14c**	83[e]
5	**7b**	Bu	**L8**	C_6H_5	**14a**	70		**14c**	38
6	**7b**	Bu	**L9**	C_6H_5	**14a**	62		**14c**	56
7	**7b**	Bu	**L7**	C_6H_5	**14a**	93		**14c**	13
8	**7b**	Bu	**L3**	C_6H_5	**14a**	59		**14c**	5
9	**7b**	Bu	**L2**	C_6H_5	**14a**	0		**14c**	
10	**7d**	Et	**L1**	C_6H_5	**15a**		76	**15c**	94
11	**7d**	Et	**L1**	C_6H_5	**15a**		68	**15c**	94[f]
12	**7d**	Bu	**L1**	C_6H_5	**16a**		69	**16c**	94
13	**7d**	Et	**L1**	*p*-BrC_6H_4	**17a**		69	**17c**	96
14	**7d**	Bu	**L1**	*p*-BrC_6H_4	**11a**		64	**11c**	97
15	**7d**	Et	**L1**	*n*-C_3H_8	**18a**		65	*g*	
16	**7e**	Et	**L1**	C_6H_5	**19a**		54	*g*	
17	**7c**	Et	**L1**	C_6H_5	**20a**		(75)[h]		
18	**7a**	Et	**L1**	C_6H_5	**21a**		(64)[h]		

[a] Determined by ^{1}H NMR. [b] Isolated yield. [c] Determined by chiral HPLC DAICEL CHIRALPAK AD. [d] Reaction carried out in CH_2Cl_2. [e] Reaction temperature −30 °C. [f] Reaction temperature −60 °C. [g] Oxidation with PCC and NMO/$RuCl_2(PPh_3)_3$[34] was unsuccessful. [h] Crude tandem product identified by NMR; purification by column chromatography resulted in the formation of elimination product. [i] See text.

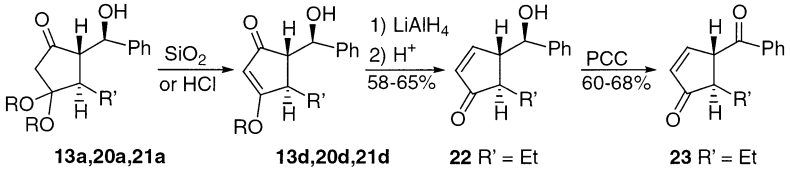
tion of the α-substituent. The coupling constants found were $J_{1,2}$ = 7.8 Hz for **11a** and $J_{1,2}$ = 3.6 Hz for **11b** (Scheme 3). Further proof for the relative configuration was given by NOESY-NMR measurements.[32] No cis-threo and cis-erythro products are formed. The proof of the absolute stereochemistry was realized with the total synthesis of (−)-PGE_1 methyl ester and its comparison with the natural compound (vide infra). The selectivity of the aldol step can be explained by the stability of the different transition states for **11a** and **11b** and can be rationalized in terms of a Zimmerman−Traxler transition-state model (Scheme 4).[33] In our case, transition state **12a** gives product **11a**, which was formed almost exclusively 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.[19,20]

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_2Zn, and benzaldehyde gave the *β*-hydroxy ketone **13a** in 67% yield and after oxidation diketone **13c** with 87% ee (Table 3, entry 1). For the reaction with Bu_2Zn, similar results were found (Table 3, entry 2). Changing the solvent from toluene to CH_2Cl_2 slowed the reaction (40% conversion after 36 h) and resulted in an ee of 84% for **14c** (Table 3, entry 3). When the reaction was performed with diethylzinc at −30 °C instead of −45 °C, the enantioselectivity decreased from 87% to 83% (Table 3, entry 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 monoacetal **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

(31) Kitamura, M.; Miki, T.; Nakano, K.; Noyori, R. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 999.
(32) See the Supporting Information.
(33) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

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



entry	R	R′	aldol product	elimination product	yield[a] (%)	ee of **23**[b] (%)
1	$-CH_2CH_2-$	Et	**20a**	**20d**	75	70
2	CH_3	Et	**21a**	**21d**	64	76
3	$-CH_2C(CH_3)_2CH_2-$	Et	**13a**	**13d**	67	87

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

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 Et_2Zn and Bu_2Zn, 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/$RuCl_2(PPh_3)_3$[34] 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.[35] Applying this protocol to the elimination products resulted in the formation of **23** in all cases. The results are given in Table 4.

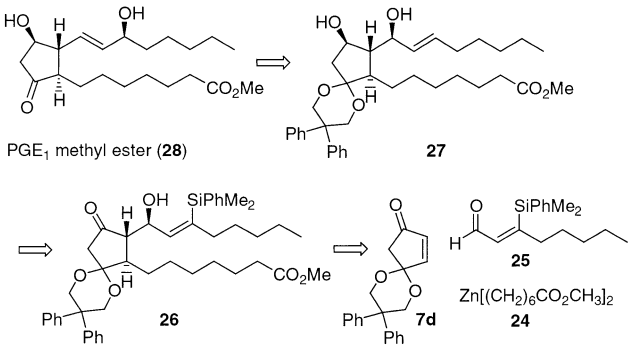
The elimination product **20a** resulting from the copper-catalyzed tandem 1,4-addition−aldol reaction of diethylzinc to **7c** in the presence of benzaldehyde was obtained in 75% yield after column chromatography (Table 3, entry 17, and Table 4, entry 1). Reduction of **20a** with $LiAlH_4$ and subsequent 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 phoshoramidite ligands, cyclopentene-3,5-dione monoacetals, aldehydes, and dialkylzinc reagents, the following conclusions can be drawn. The catalyst prepared in situ from $Cu(OTf)_2$ 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 (SiO_2 and Al_2O_3). 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 E_1 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).[9] 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

(34) Sharpless, K. B.; Akashi, K.; Oshima, K. *Tetrahedron Lett.* **1976**, *17*, 2503.
(35) Gannon, W. F.; House, H. O. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 294.

SCHEME 4



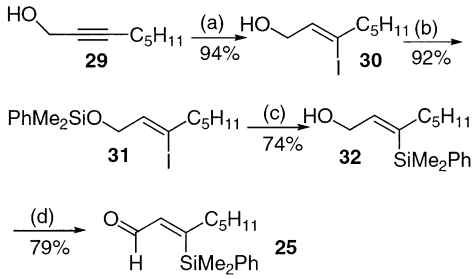
salt-free procedure from organoboranes.[36] Using this type of reagent in a model 1,4-addition with 2-cyclohexenone in the presence of an in situ generated catalyst from Cu(OTf)$_2$/**L1**, no product was formed after 24 h at −20 °C. Employing an in situ generated mixed alkylalkenylzinc reagent,[37] it was found that only the saturated carbon nucleophile was transferred to the enone.

These results indicate that the ω 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[38] 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 α-chain of the PGE$_1$ methyl ester would be introduced with a functionalized zinc reagent and the ω-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]

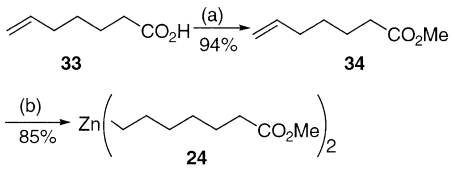
Commercially available 2-octyn-1-ol **29** was converted in a stereoselective manner to **30** by the Masamune modification[41] of the Corey reductive iodination.[42] This

SCHEME 5[a]



[a] Key: (a) (1) Red-Al, THF, 5 h; (2) I_2, −78 °C; (b) DMPSCl, Et_3N, DMAP, CH_2Cl_2, 0 °C; (c) *t*-BuLi, 2 equiv, THF, −78 °C; (d) $(COCl)_2$, Me_2SO, Et_3N, −78 °C.

SCHEME 6[a]



[a] Key: (a) MeOH, *p*-TSA, CCl_4, 10 h; (b) (1) Et_2BH, THF, 0 °C, 3 h, (2) Et_2Zn neat, 0−25 °C, 3 h.

procedure proceeds with 100% cis selectivity because of the intramolecular coordination of the aluminum center with the hydroxy functionality. Using chlorodimethylphenylsilane, allylic alcohol **30** was converted to the silyl ether **31** in excellent yield. This compound underwent a 1,4-O → sp^{2}C silyl migration using 2 equiv of *t*-BuLi.[39] 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_2Zn. After evaporation of the excess of Et_2Zn, 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)$_2$/**L1** 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 of **26** proceeded with 95% stereoselectivity using $Zn(BH_4)_2$ in ether at −30 °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

(36) Srebnik, M. *Tetrahedron Lett.* **1991**, *32*, 2449. For an earlier report dealing with the alkenyl transfer from boron to zinc, see: Molander, G. A.; Zinke, P. W. *Organometallics* **1986**, *5*, 2161.

(37) (a) Oppolzer, W.; Radinov, R. N. *Helv. Chim. Acta* **1992**, *75*, 170. (b) For a stereoselective version, see: Soai, K.; Takahashi, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1257.

(38) (a) For the Pd(II)-mediated allylic acetate transposition in a modified prostaglandin intermediate, see: Grieco, P. A.; Takigawa, T.; Bongers, S. L.; Tanaka, H. *J. Am. Chem. Soc.* **1980**, *102*, 7588. (b) The Pd(II)-catalyzed allylic acetate transposition was first described by: Meyer, K. DOS 2513198 1975; *Chem. Abstr.* **1976**, *84*, 89629s. (c) For a full review of Pd(II)-catalyzed [3,3]-sigmatropic rearrangements, see: Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 579.

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(40) De Vries, A. H. M. *Catalytic Enantioselective Conjugate Addition of Organometallic Reagents*. Ph.D. Thesis, University of Groningen, 1996.

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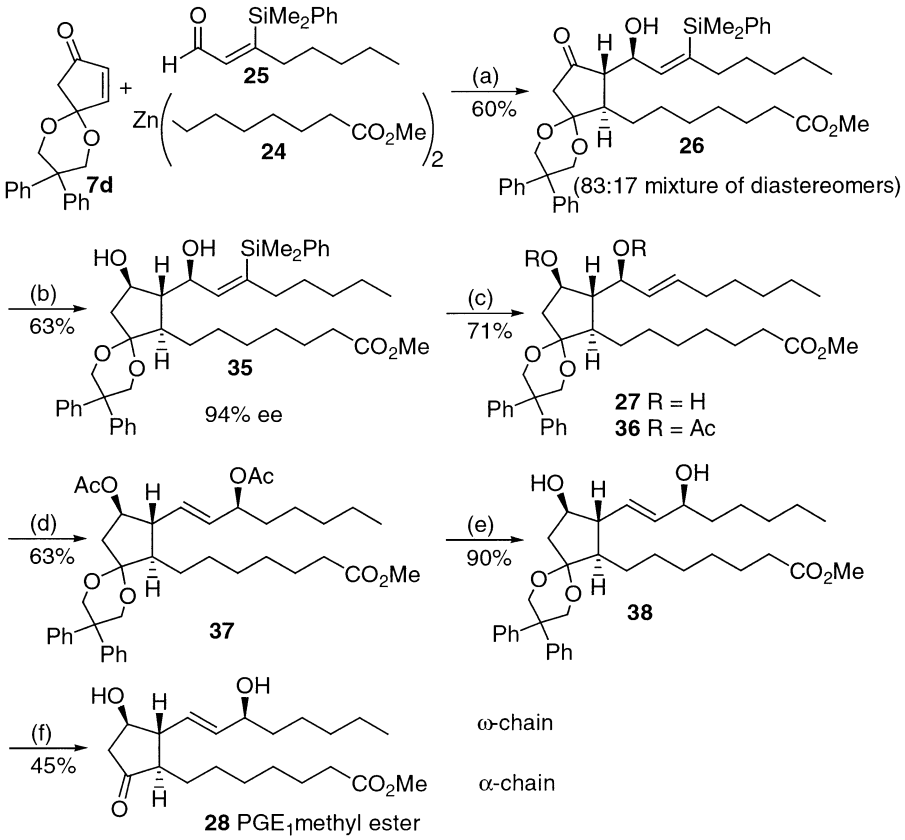
(42) Corey, E. J.; Katzenellenbogen, J. A.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 4245.

(43) (a) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117. (b) Langer, F.; Devasagayaraj, A.; Chavant, P.-Y.; Knochel, P. *Synlett* **1994**, 410.

SCHEME 7[a]



[a] Key: (a) 3 mol % $Cu(OTf)_2$, 6 mol % **L1**, toluene, −45 °C, 18 h; (b) $Zn(BH_4)_2$, ether, −30 °C, 3 h; (c) (1) 3 equiv of Bu_4NF (1 M in THF), methyl propionate, DMSO, 80 °C, 20 min, (2) Ac_2O, DMAP, pyridine, 20 min; (d) 5 mol % $Pd(CH_3CN)_2Cl_2$, THF, 3 h; (e) K_2CO_3, MeOH, 18 h; (f) $(NH_4)_2Ce(NO_3)_6$, MeCN, borate−HCl buffer (pH = 8), 60 °C, 2 h.

94%. In the next step, the silyl substituent was removed using Bu_4NF 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_4NF was developed by Nozaki.[44] 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_4NF. Adding first sacrificial methyl propionate to remove the water by hydrolysis and only afterward **35** 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 $Pd(CH_3CN)_2Cl_2$ in THF proceeded with reasonable yield (63%) and full retention of configuration[38] to provide allylic acetate **37** with the required stereochemistry. After deacetylation in the presence of K_2CO_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 β-hydroxy ketone moiety of the prostaglandin E_1. This conversion was realized using a catalytic amount of $(NH_4)_2Ce(NO_3)_6$ under nearly neutral conditions.[45] In this way (−)-PGE_1 methyl ester **28**,[46] in all respect 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 **L1**, 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 demon-

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(46) The analytical and spectral data (TLC, HPLC, ^1H NMR, ^{13}C NMR, CD, MS) $[\alpha]^{23}_D$ −51 (c 1.0, CH_3OH) of **28** were identical with those of authentic material (Sigma) $[\alpha]^{23}_D$ −54 (c 1.0, CH_3OH).

strated in the application as the key step in a short asymmetric synthesis of a PGE_1 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 PGE_1 methyl ester in a highly effective manner.

Experimental Section

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 $CHCl_3$ were distilled from P_2O_5 and MeOH from MeONa. $BF_3{\cdot}Et_2O$, benzyl 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 $CDCl_3$ (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 $BF_3{\cdot}Et_2O$ (2.52 mL, 20 mmol) in chloroform (50 mL) was added the alcohol (40 mmol, 20 mmol for diol). After being stirred for 3 h, the reaction mixture was poured into NH_4Cl (aq) and extracted three times with 25 mL of diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography (SiO_2 ether/pentane) gave the corresponding acetals.

8,8-Diphenyl-6,10-dioxaspiro[4.5]dec-3-en-2-one (7d). Purification by column chromatography (SiO_2 hexane/diethyl ether, 1:1, R_f = 0.43) gave 3.06 g (50%) 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 NH_4Cl (aq) and diluted with CH_2Cl_2 (150 mL). The organic layer was separated, washed with 1 M NaOH solution to remove the cyclopentene-3,5-dione, dried over $MgSO_4$, filtered, and concentrated in vacuo. The unreacted diol can be removed by crystallization from hexane/$CHCl_3$, and **7d** (10.2 g) could be obtained in 64% yield after evaporation of the solvents: mp 75−76 °C; ^{1}H NMR (300 MHz) δ 7.51 (d, J = 6.0 Hz, 1H), 7.41−7.20 (m, 10H), 6.21 (d, J = 6.0 Hz, 1H), 4.65 (d, J = 11.7 Hz, 2H), 4.35 (d, J = 11.7 Hz, 2H), 2.70 (s, 2H); ^{13}C NMR (200 MHz) δ 203.3, 156.5, 143.4, 143.2, 135.1, 128.4, 128.2, 127.6, 126.7, 126.7, 126.4, 104.0, 70.2, 44.4, 44.0; MS (CI) for $C_{20}H_{18}O_3$ m/z = 306 (M^+), 324 ($M + NH_4^+$).

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 a 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 diorganozinc compound (0.6 mL of a 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 into 25 mL of NH_4Cl (aq), the organic layer was separated, and the aqueous layer was extracted two times with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo.

(4*R*)-4-Butyl-8,8-diphenyl-6,10-dioxaspiro[4.5]decan-2-one (10). Purification by column chromatography (SiO_2 pentane/diethyl ether, 3:1, R_f = 0.30) gave 67 mg (37%) of **10** as a colorless liquid: ^{1}H NMR (300 MHz) δ 7.50−7.05 (m, 10H), 4.57 (d, J = 12.0 Hz, 2H), 4.26 (d, J = 11.7 Hz, 2H), 3.06 (d, J = 18.3 Hz, 1H), 2.53−2.05 (m, 4H), 1.59 (m, 1H), 1.25−1.05 (m, 5H), 0.80 (t, J = 7.4 Hz, 3H); ^{13}C NMR (200 MHz) δ 213.3, 143.6, 143.3, 128.7, 128.5, 128.1, 126.9, 126.4, 126.3, 104.7, 70.8, 68.8, 45.9, 44.8, 44.7, 43.3, 30.1, 27.3, 22.9, 13.8; HRMS calcd for $C_{24}H_{28}O_3$ 364.203, found 364.203. The ee was determined by HPLC on a chiral stationary phase (DAICEL CHIRALPAK AD, *i*-PrOH/hexane 10:90, 1 mL/min, rt, t_R = 6.03 min, t_R = 12.77 min).

General Procedure for the Tandem 1,4-Addition−Aldol Reaction (11a,b, 13a−21a). A solution of $Cu(OTf)_2$ (3.6 mg, 0.01 mmol) and phosphoramidite[47] (0.02 mmol) in toluene (7 mL) was stirred under a nitrogen atmosphere at ambient temperature for 1 h. Cyclopentene-3,5-dione monoacetal (0.5 mmol) and the aldehyde (0.5 mmol) were added. After the reaction mixture was cooled to −45 °C, the dialkylzinc reagent (0.6 mL, 1 M solution in toluene) was added, and stirring at −45 °C was continued for 18 h. After complete conversion, the reaction mixture was poured in 25 mL of NH_4Cl (aq), the organic layer was separated, and the aqueous layer was extracted two times with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo.

(3*S*,4*R*)-4-Butyl-3-[(*R*)-hydroxy(phenyl)methyl]-8,8-diphenyl-6,10-dioxaspiro[4.5]decan-2-one (16a). Purification by column chromatography (SiO_2 pentane/diethyl ether, 2:1, R_f = 0.18) gave 158 mg (69%) of **16a** as a colorless oil which solidified upon standing: ^{1}H NMR (300 MHz) δ 7.33−7.06 (m, 15H), 4.81 (dd, J = 8.1 Hz, J = 1.8 Hz, 1H), 4.54−4.44 (m, 2H), 4.32−4.17 (m, 2H), 3.85 (d, J = 1.8 Hz, 1H(OH)), 3.04 (d, J = 18.0 Hz, 1H), 2.53 (d, J = 17.4 Hz, 1H), 2.44 (t, J = 8.1 Hz, 1H), 2.02 (q, J = 6.6 Hz, 1H), 1.35 (m, 1H), 0.70 (m, 5H), 0.52 (t, J = 6.6 Hz, 3H); ^{13}C NMR (200 MHz) δ 216.3, 143.4, 143.2, 140.9, 129.9, 128.6, 128.4, 128.3, 128.1, 127.9, 126.9, 126.6, 126.4, 104.0, 75.2, 70.1, 68.9, 59.8, 460.8, 45.4, 44.8, 29.6, 27.7, 22.7, 13.8; HRMS calcd for $C_{31}H_{34}O_4$ 477.245, found 477.243.

General Procedure for the Oxidation to a Diketone (11c, 13c−17c). To hydroxy ketone (0.2 mmol) in CH_2Cl_2 (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, diluted with diethyl ether, filtered over Celite, and evaporated to dryness.

(3*R*,4*R*)-3-Benzoyl-4-butyl-8,8-diphenyl-6,10-dioxaspiro-[4.5]decan-2-one (16c). Purification by column chromatography (SiO_2 pentane/diethyl ether, 5:1, R_f = 0.32) gave 64 mg (69%) of **16c** as a colorless oil which solidified upon standing: ^{1}H NMR (300 MHz) δ 8.01 (d, J = 6.0 Hz, 2H), 7.57−7.05 (m, 13H), 4.68 (d, J = 11.6 Hz, 2H), 4.49−4.21 (m, 3H), 3.38 (d, J = 18.0 Hz, 1H), 3.16 (m, 1H), 2.56 (d, J = 16.2 Hz, 1H), 1.55 (m, 1H), 1.32−0.88 (m, 5H), 0.66 (t, J = 6.9 Hz, 3H); ^{13}C NMR (200 MHz) δ 206.6, 194.7, 143.3, 143.0, 137.0, 133.5, 129.4, 128.7, 128.6, 128.1, 127.0, 126.9, 126.3, 103.1, 71.4, 68.6, 62.7, 49.1, 47.6, 45.0, 44.8, 30.2, 27.1, 22.8, 13.7; HRMS calcd for $C_{31}H_{32}O_4$ 468.230, found 648.231. The ee of 94% was determined by HPLC on a chiral stationary phase (DAICEL CHIRALPAK AD, *i*-PrOH/hexane 50:50, 1 mL/min, rt, t_R = 5.11 min, t_R = 10.71 min).

(4*R*,5*S*)-4-Ethyl-5-[(*R*)-hydroxy(phenyl)methyl]-3-methoxy-2-cyclopenten-1-one (21d). Purification by column chromatography (SiO_2 hexane/diethyl ether, 1:1, R_f = 0.18) gave 79 mg (64%) of **21d** as a colorless liquid: ^{1}H NMR (300 MHz) δ 7.35−7.21 (m, 5H), 5.26 (s, 1H), 4.56 (d, J = 9.9 Hz, 1H), 3.79 (s, 3H), 2.38 (m, 2H), 1.20 (m, 1H), 0.90 (m, 1H), 0.43 (t, J = 7.2 Hz, 3H); ^{13}C NMR (200 MHz) δ 208.1, 193.4, 141.4, 128.4, 128.2, 127.0, 130.2, 76.2, 58.9, 55.8, 44.0, 22.6, 8.9; HRMS calcd for $C_{15}H_{18}O_3$ 246.126, found 246.125.

(4*S*,5*R*)-4-Benzoyl-5-ethyl-2-cyclopenten-1-one (22). Under an argon atmosphere, a solution of the aldol product (0.9 mmol) in diethyl ether (10 mL) was added dropwise to a solution of $LiAlH_4$ (34 mg, 0.9 mmol) in diethyl ether (30 mL). After complete addition, the reaction mixture was boiled under reflux for an additional 30 min and allowed to cool to rt. The complex was hydrolyzed, and excess lithium aluminum hydride was destroyed by the cautious addition, dropwise and

(47) Arnold, L. A.; Imbos, R.; Mandoli, A.; de Vries, A. H. M.; Naasz, R.; Feringa, B. L. *Tetrahedron* **2000**, *56*, 2865.

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 $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2 diethyl ether/hexane, 1:1, $R_f = 0.31$) gave 124 mg (64%) of **22** as a colorless liquid: ^{1}H 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); ^{13}C NMR (200 MHz) δ 211.5, 164.1, 142.5, 134.8, 128.7, 128.3, 126.1, 76.5, 54.5, 48.9, 23.1, 10.4; MS (CI) for $C_{114}H_{16}O_2$ m/z = 216 (M^+), 234 ($M + NH_4^+$).

(4*S*,5*R*)-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 (SiO_2 hexane/diethyl ether, 2:3, $R_f = 0.31$) gave **23** in 65% yield as yellow oil: ^{1}H 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); ^{13}C NMR (200 MHz) δ 210.1, 196.4, 159.7, 134.7, 133.9, 129.0, 128.5, 55.2, 48.8, 23.1, 11.0; MS (EI) for $C_{14}H_{14}O_2$ $m/z = 214$ (M^+). The ee was determined by HPLC on a chiral stationary phase (DAICEL CHIRALPAK AD, *i*-PrOH/hexane 2:98, 1 mL/min, rt, $t_R = 20.6$ min, $t_R = 25.0$ min).

(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 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 Na_2SO_3 (aq), and the organic layer was separated and washed with Na_2SO_3 (aq), water, and saturated NaCl (aq). The resulting organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2 diethyl ether/pentane, 1:6, $R_f = 0.30$) gave 40.3 g (94%) of **30** as a light purple colored oil (100% cis): ^{1}H NMR (300 MHz) 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); ^{13}C NMR (200 MHz) δ 133.2, 111.0, 67.3, 45.1, 30.4, 28.8, 22.4, 14.0; MS (CI) for $C_8H_{15}IO$ $m/z = 254$ (M^+), 272 ($M + NH_4^+$).

(Z)-1-Dimethyl(phenyl)siloxy-3-iodo-2-octene (31). To a solution of **30** (14 g, 59 mmol) in CH_2Cl_2 (300 mL) were added Et_3N (8.3 mL, 60 mmol) and a catalytic amount of DMAP. At 0 °C, chlorodimethylphenylsilane (10 mL, 59 mmol) in CH_2Cl_2 (20 mL) was added over a period of 1 h. After an additional 1 h, the reaction mixture was poured into NH_4Cl (aq), and the organic layer was filtered and concentrated in vacuo. The residue was dissolved in pentane (300 mL), washed with water and NaCl (aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. The colorless oil (20.6 g, 92%) of **31** was used without further purification: ^{1}H NMR (300 MHz) δ 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); ^{13}C NMR (200 MHz) δ 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 (CI) for $C_{16}H_{25}IOSi$ $m/z = 388$ (M^+), 406 ($M + NH_4^+$).

(Z)-3-Dimethyl(phenyl)silyl-2-octen-1-ol (32). Under argon atmosphere, **31** (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 2 h at the same temperature. The reaction mixture was quenched with NH_4Cl (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 $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2 diethyl ether/pentane, 1:6, $R_f = 0.35$) gave 14.8 g (74%) of **32** as a colorless oil (100% cis): ^{1}H 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); ^{13}C 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, −1.0; MS (CI) for $C_{16}H_{26}OSi$ $m/z = 262$ (M^+), 280 ($M + NH_4^+$).

(Z)-3-Dimethyl(phenyl)silyl-2-octenal (25). To a solution of $(COCl)_2$ (3.7 mL, 42 mmol) in THF (20 mL) was added Me_2SO (6 mL, 84 mmol) in CH_2Cl_2 (10 mL) at −78 °C, and the resulting solution was stirred for 5 min. To this solution was slowly added alcohol **32** (10 g, 38 mmol) in THF (20 mL), and the mixture was stirred for 30 min, followed by the addition of Et_3N (26 mL, 190 mmol) in CH_2Cl_2 (300 mL). The reaction mixture was warmed to room temperature and quenched with NH_4Cl (aq). The organic layer was separated, and the aqueous layer was extracted two times with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2 diethyl ether/pentane, 1:50, $R_f = 0.34$) gave 7.8 g (79%) of **25** as a bright yellow oil (mixture of *E*/*Z* ratio, 7:93 determined by ^{1}H NMR): ^{1}H NMR (300 MHz) δ 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); ^{13}C NMR (200 MHz) 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 (CI) for $C_{16}H_{24}OSi$ $m/z = 260$ (M^+), 278 ($M + NH_4^+$).

Methyl 6-Heptenoate (34). A mixture of commercially available 6-heptenoic acid (5 mL, 37 mmol), MeOH (7 mL), *p*-toluenesulfonic acid (0.5 g), and CCl_4 (15 mL) was refluxed for 16 h. After cooling, the mixture was diluted with CH_2Cl_2 and washed with $NaHCO_3$ (aq). The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2 diethyl ether/pentane, 1:15, $R_f = 0.78$) gave 4.94 g (94%) of **34** as a colorless oil: ^{1}H NMR (300 MHz) $\delta = 5.82−5.73$ (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 (24). Compound **34** (2.84 g, 20 mmol) was cooled (degassed using a freeze/thaw technique under vacuum/argon) to 0 °C, and $HBEt_2$ [freshly prepared from $BH_3{\cdot}Et_2O$ (2 M in diethyl ether) and BEt_3 (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 organoborane was treated at 0 °C with 2 mL of Et_2Zn (neat) and stirred at room temperature for 2 h. The formed BEt_3 and the excess Et_2Zn were removed under vacuum (0.1 mmHg, 3 h) giving 3 g (85%) of **24** as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.63 (s, 6H), 2.27 (t, $J = 7.8$ Hz, 4H), 1.62−1.47 (m, 8H), 1.28−1.25 (m, 8H), 0.31 (t, $J = 7.8$ Hz, 4H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 174.3, 51.4, 36.0, 34.1, 28.9, 26.1, 24.9, 15.9.

Methyl 7-[(1*R*,2*S*)-2-[(1*R*,2*Z*)-3-[Dimethyl(phenyl)silyl]-1-hydroxy-2-octenyl]-3-oxo-8,8-diphenyl-6,10-dioxaspiro-[4.5]dec-1-yl]heptanoate (26). A solution of $Cu(OTf)_2$ (32.4 mg, 0.09 mmol) and phosphoramidite **L1** (97 mg, 0.18 mmol) in toluene (20 mL) was stirred under a nitrogen atmosphere at ambient temperature for 1 h, whereupon **7d** (918 mg, 3 mmol) and **25** (780 mg, 3 mmol) were added. After the reaction mixture was cooled to −45 °C, **24** (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 into NH_4Cl (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 $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2 diethyl ether/pentane, 2:1, $R_f = 0.35$) gave 1.28 g (60%

yield) of **26** as a colorless oil (mixture of threo/erythro ratio of 83:17): ^{1}H 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 = 10.0 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); ^{13}C NMR (200 MHz) 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 (EI) for $C_{44}H_{58}O_6Si$ m/z = 710 (M^+).

Methyl 7-[(1*R*,2*R*,3*S*)-2-[(*Z*)-3-[Dimethyl(phenyl)silyl]-1-hydroxy-2-octenyl]-3-hydroxy-8,8-diphenyl-6,10-dioxaspiro[4.5]dec-1-yl]heptanoate (35). Under argon atmosphere, a solution of **26** (1420 mg, 2 mmol) in diethyl ether (40 mL) was treated with $Zn(BH_4)_2$ (8 mL, 0.5 M in diethyl ether) at −30 °C. After being stirred for 3 h at the same temperature, the reaction mixture was quenched with NH_4Cl (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 $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2 diethyl ether/pentane, 5:4, R_f = 0.30) gave 897 mg (63%) of **35** as colorless oil: $[\alpha]^{23}_D$ −31 (c = 0.9, $CHCl_3$); ^{1}H 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), 3.63 (s, 3H), 2.44 (d, J = 5.6 Hz, 1H) OH, 2.23−2.04 (m, 6H), 1.57−0.80 (m, 22H), 0.38 (s, 3H), 0.33 (s, 3H); ^{13}C NMR (200 MHz) 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 $C_{44}H_{60}O_6Si$ m/z = 712 (M^+). The ee of 94% was determined by HPLC on a chiral stationary phase (DAICEL CHIRALPAK AD, ^{i}PrOH/heptane 25:75, 1 mL/min, rt, t_R = 4.9 min, t_R = 9.0 min).

Methyl 7-[(1*R*,2*R*,3*R*)-3-(Acetyloxy)-2-[(1*S*,2*E*)-1-(acetyloxy)-2-octenyl]-8,8-diphenyl-6,10-dioxaspiro[4.5]dec-1-yl]heptanoate (36). Under argon atmosphere, a solution of Bu_4NF (6 mL, 1 M THF) was added to a solution of methyl propionate (176 mg, 2 mmol) in DMSO (3 mL), and the reaction mixture was refluxed for 2 h. After addition of a solution of **35** (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 NH_4Cl (aq) and 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 in vacuo. The crude products were dissolved in pyridine (4 mL), and acetic anhydride (2 mL) was added at room temperature together with a catalytic amount of DMAP. After 20 min, the reaction mixture was poured into NH_4Cl (aq) and extracted two times with ether, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2 diethyl ether/pentane, 1:1, R_f = 0.69) gave 282 mg (71%) of **36** as a colorless oil: ^{1}H 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); ^{13}C NMR (200 MHz) 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 $C_{40}H_{54}O_8$ m/z = 662 (M^+).

Methyl 7-[(1*R*,2*R*,3*R*)-3-(Acetyloxy)-2-[(*E*,3*S*)-3-(acetyloxy)-1-octenyl]-8,8-diphenyl-6,10-dioxaspiro[4.5]dec-1-yl]heptanoate (37). Bis(acetonitrile)palladium(II) chloride (18 mg, 0.07 mmol) was added to a solution of **36** (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 (20 g). The solvent was evaporated at reduced pressure. Purification by column chromatography (SiO_2 diethyl ether/pentane, 3:1, R_f = 0.35) gave 167 mg (63%) of **37** as a colorless oil: $[\alpha]_D$ −39.5 (c = 2.6, $CDCl_3$); ^{1}H NMR (300 MHz) δ 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, 8.8 Hz, 1H), 2.27 (m, 1H), 2.19 (t, J = 7.7 Hz, 2H), 2.05 (dd, J = 14.3, 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); ^{13}C NMR (200 MHz) 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 $C_{40}H_{54}O_8$ m/z = 662 (M^+).

Methyl 7-[(1*R*,2*R*,3*R*)-3-Hydroxy-2-[(*E*,3*S*)-3-hydroxy-1-octenyl]-8,8-diphenyl-6,10-dioxaspiro[4.5]dec-1-yl]heptanoate (38). Acetate **37** (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 NH_4Cl (aq) and extracted two times with diethyl ether, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2 diethyl ether/MeOH, 50:1, R_f = 0.41) gave 119 mg (90%) of **38** as a white solid: $[\alpha]_D$ −24.5 (c = 0.9, $CDCl_3$); ^{1}H 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), 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, 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); ^{13}C NMR (200 MHz) 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 $C_{36}H_{50}O_6$ m/z = 578 (M^+).

Methyl 7-[(1*R*,2*R*,3*R*)-3-Hydroxy-2-[(*E*,3*S*)-3-hydroxy-1-octenyl]-5-oxocyclopentyl]heptanoate or Prostaglandin E_1 Methyl Ester (28). Solid cerium ammonium nitrate (18 mg, 0.045 mmol) was added to a solution of **38** (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 60 °C for 2 h. After the mixture was cooled to room temperature, H_2O (5 mL) and 5 mL of ether were added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography (SiO_2 diethyl ether/MeOH, 100:3, Rf = 0.42) gave 26 mg (45%) of **28** as a colorless oil: $[\alpha]_D$ −51 (c = 1.00, CH_3OH); ^{1}H NMR (500 MHz) δ 5.64 (dd, J = 15.0, 7.3 Hz, 1H), 5.51 (dd, J = 15.0, 8.8 Hz, 1H), 4.09 (m, 1H), 4.00 (m, 1H), 3.63 (s, 3H), 2.70 (dd, J = 18.6, 7.3 Hz, 1H), 2.32 (dt, J = 12.1, 8.8 Hz, 1H), 2.26 (t, J = 7.7 Hz, 2H), 2.20 (dd, J = 18.3, 9.9 Hz, 1H), 1.96 (dt, J = 12.1, 5.9 Hz, 1H), 1.60−1.24 (m, 19H), 0.86 (t, J = 6.9 Hz, 3H); ^{13}C NMR (300 MHz) δ 214.6, 174.3, 136.8, 131.8, 73.0, 71.8, 54.8, 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 $C_{36}H_{50}O_6$ m/z 368 (M^+), 386 ($M + NH_4^+$).

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Supporting Information Available: Characterization of compounds **7a**−**c**,**e**, **8**, **8a**,**b**, **9**, **11a**,**b**, **13a**−**15a**, **17a**−**21a**, **11c**, **13c**−**15c**, **17c**, **13d**, and **20d**; NOESY-NMR of compounds **11a**,**b** and **28** and CD spectra of compound **28**; ^{13}C NMR spectra of compounds: **7a**−**e**, **8**−**10**, **11a**,**b**, **13a**−**21a**, **11c**, **13c**−**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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