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Fully Stereocontrolled Total Syntheses of the Prostacyclin Analogues 16*S*-Iloprost and 16*S*-3-Oxa-Iloprost by a Common Route, Using Alkenylcopper-Azoalkene Conjugate Addition, Asymmetric Olefination, and Allylic Alkylation

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Abstract: In this article we describe fully stereocontrolled total syntheses of 16*S*-iloprost (16*S*-**2**), the most active component of the drugs Ilomedin and Ventavis, and of 16*S*-3-oxa-iloprost (16*S*-**3**), a close analogue of 16*S*-**2** having the potential for a high oral activity, by a new and common route. The key steps of this route are (1) the establishment of the complete C13−C20 ω side chain of the target molecules through a stereoselective conjugate addition of the alkenylcopper derivative **9** to the bicyclic C6−C12 azoalkene **10** with formation of hydrazone **8**, (2) the diastereoselective olefination of ketone **7** with the chiral phosphoryl acetate **39**, and (3) the regio- and stereoselective alkylation of the allylic acetate **43** with cuprate **42**. These measures allowed the 5*E*,15*S*,16*S*-stereoselective synthesis of 16*S*-**2** and 16*S*-**3**, a goal which had previously not been achieved. Azoalkene **10** was obtained from the achiral bicyclic C6−C12 ketone **11** as previously described by using as key step an enantioselective deprotonation. The configuration at C16 of ω-side chain building block **9** has been installed with high stereoselectivity by the oxazolidinone method and that at C15 by a diastereoselective oxazaborolidine-catalyzed reduction of the C13−C20 ketone **23** with catecholborane. Surprisingly, a high diastereoselectivity in the reduction of **23** was only obtained by using 2 equiv of oxazaborolidine **24**. Application of substoichiometric amounts of **24** resulted in irreproducible diastereoselectivities ranging from very high to nil.

1. Introduction

Prostacyclin (**1**) (Figure 1) is the most potent endogenous inhibitor of blood platelet aggregation and a strong vasodilator.[1] These features make prostacyclin per se an attractive drug for a therapy of cardiovascular diseases. However, the medicinal application of prostacyclin is severely hampered by its chemical and metabolic instability as indicated by a half-life of only 3 min under physiological conditions.

Intensive efforts to find stable and potent analogues[2] led the Schering group to the imaginative and highly successful design of the carbocyclic prostacyclin analogue iloprost (**2**).[1c,3] Replacement of the O atom at the 6a position of **1** by a methylene group, the introduction of a methyl group at C16, and a triple bond at C18,C19 conveyed high chemical stability and biological activity, respectively, to iloprost.[4] Iloprost has already been approved as Ilomedin for the treatment of peripheral arterial occlusive disease, severe thrombo-angiitis obliterans involving a high risk of amputation, and Raynaud's disease.[5] Moreover, iloprost has recently found approval as Ventavis for the treatment of pulmonary arterial hypertension, a highly debilitating and potentially fatal disease.[6,7] However, Ilomedin and Ventavis are not single isomer drugs. They contain approximately 1:1 mixtures of 16*S*-**2** and its *R*-configured isomer 16*R*-**2**, which has, however, a much lower biological activity than 16*S*-**2**.[1c,8,9] For example, 16*R*-**2** is 20 times less potent than 16*S*-**2** in inhibiting collagen-induced platelet aggregation.[8,9] Although the synthesis of iloprost developed by the Schering group provides access to the drug in sufficient quantities, it is

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(4) Because of clarity the prostacyclin numbering is used for iloprost, 3-oxa-iloprost, and all building blocks through out this paper except in the experimental part where the numbering of the compounds follows the nomenclature rules.

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10.1021/ja0558037 CCC: $30.25

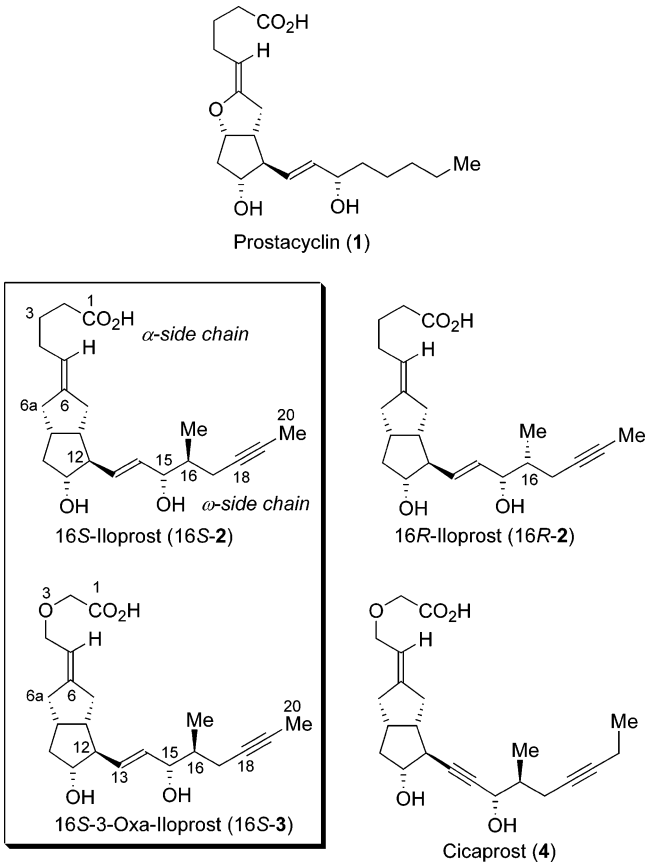

Figure 1. Prostacyclin and its carbocyclic analogues 16*S*-iloprost, 16*S*-3-oxa-iloprost, 16*R*-iloprost, and cicaprost.

nonstereoselective in regard to the configurations at C5, C15, and C16, all three of which are crucial to its biological activity.[1c,3] It finally gives after the separation and discarding of the less active C5 and C15 isomers a practically nonseparable 1:1 mixture of 16*S*-**2** and 16*R*-**2**.[1c,3] Thus the development of a fully stereocontrolled synthesis of 16*S*-**2**, the most active component of the drugs Ilomedin and Ventavis, would be of considerable importance. Although iloprost is orally active, it has only a relatively short duration of action because of a rapid metabolization,[1c,f−h] the key step of which is the β-oxidation of the α-side chain leading to the formation of the inactive tetranoriloprost. Therefore, Ilomedin and Ventavis have to be administered by intravenous infusion and inhalation, respectively. To alleviate the considerable costs, efforts, and possible complications associated with an intravenous delivery it would be highly desirable to have in addition to iloprost an analogue thereof at the disposal, which not only has a similar biological profile but also a long lasting oral activity. A most attractive candidate that should meet these criteria is 16*S*-3-oxa-iloprost (16*S*-**3**). The O atom in the 3 position of 16*S*-**3** will provide for a higher metabolic stability, since the β-oxidation of the α-side chain is impeded and the 16*S*-configuration is expected to ensure a high biological activity. These expectations are born out by the high metabolic stability[1f] of the antimetastatic 3-oxa-carbacyclin derivative cicaprost (**4**)[10,11] and the much higher biological activity of the 16*S*-configured iloprost (16*S*-**2**) as compared to the 16*R*-configured isomer 16*R*-**2**.[8,9] In 1982, a synthesis of 3-oxa-iloprost had been disclosed in patents.[12] This synthesis, however, which closely parallels that of iloprost until a late stage, is nonstereoselective concerning C5, C15, and C16. It finally yields a nearly 1:1 mixture of 16*S*-**3** and 16*R*-**3**, both of which are difficult to separate. Because of (1) the considerable medicinal importance of iloprost, (2) the potential medicinal prospects of 3-oxa-iloprost,[13] and (3) the deficiencies of the existing syntheses, we were seeking fully stereocontrolled syntheses of 16*S*-**2** and 16*S*-**3**, a goal which had not been achieved yet, by a new route which would give, by a diversion at a late stage, access to both prostacyclin analogues. Herein we describe fully stereocontrolled total syntheses of 16*S*-**2** and 16*S*-**3** by a new and common route,[14] the key elements of which are the attachment of the complete ω-side chain to the bicyclo-[3.3.0]octane skeleton through the conjugate addition of an alkenylcopper compound to an azoalkene and the construction of the α-side chains via an asymmetric olefination and a stereoselective allylic alkylation.

2. Results and Discussion

2.1. Retrosynthetic Analysis. The first key feature of our retrosynthetic analysis of 16*S*-**2** and 16*S*-**3** is the coupling of a bicyclic C6−C12 building block, the azoalkene **10**,[14] with a C13−C20 ω-side chain building block, the alkenylcopper compound **9**, with the formation of the C12−C13 bond of the

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(13) Biological studies of 16*S*-**3** have not been reported. It has been briefly stated, without giving any details, that 3-oxa-iloprost shows a decreased receptor affinity as compared to iloprost (Stürzebecher, S.; Haberey, M.; Müller, B.; Schillinger, E.; Schröder, G.; Skuballa, W.; Stock, G.; Vorbrüggen, H.; Witt, W. *Prostaglandins* **1986**, *31*, 95−109). However, it appears that the underlying experiments were done with the 1:1 mixture of 16*S*-**3** and 16*R*-**3**, the 16*R*-isomer of which is expected to have a significantly lower receptor affinity than the 16*S*-isomer.[8,9]

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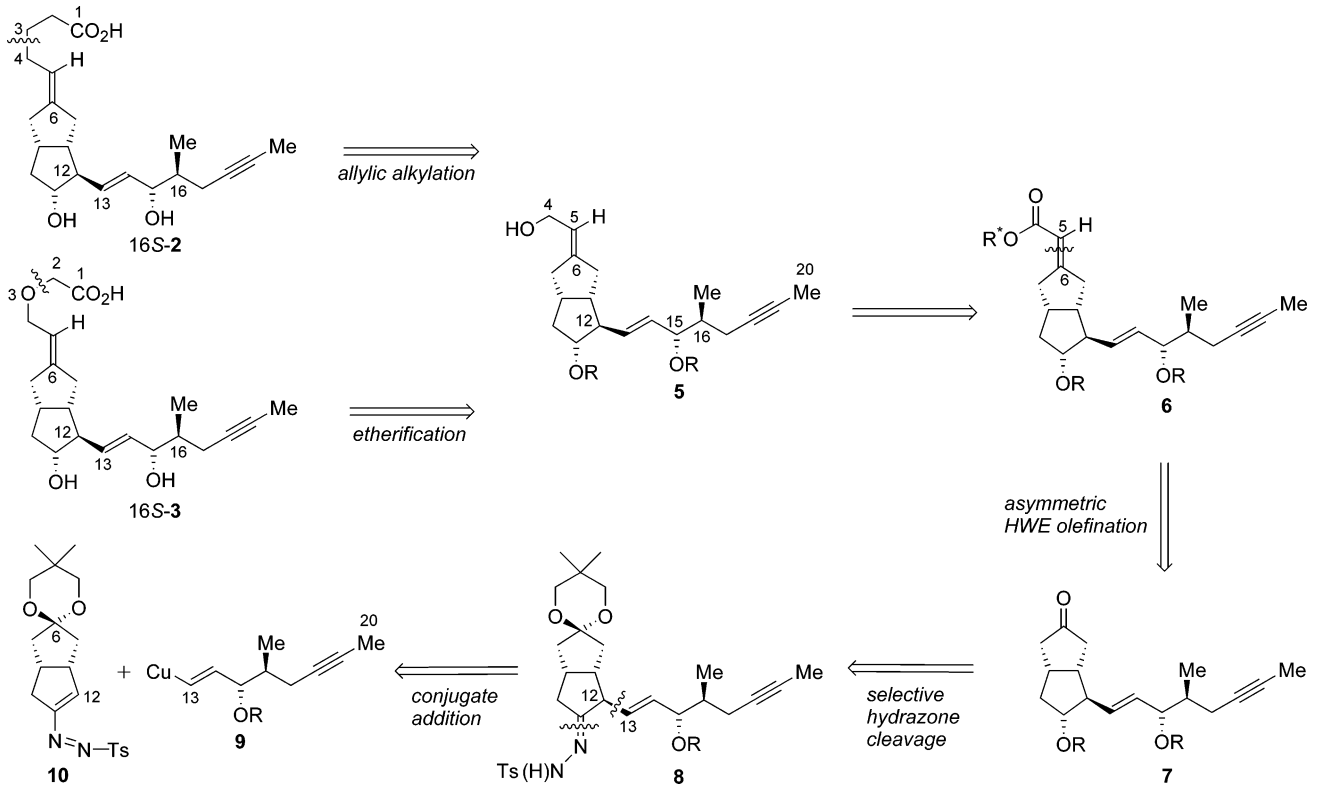
Scheme 1. Retrosynthetic Analysis of 16*S*-Iloprost and 16*S*-3-Oxa-Iloprost



target molecules (Scheme 1). This measure should not only allow the stereoselective attachment of the ω-side chain to the bicyclo[3.3.0]octane skeleton from the convex side in one step but also provide a high degree of flexibility in regard to the synthesis of derivatives with other ω-side chains which are crucial to the biological activity of prostacyclin analogues.[2]

The known syntheses of 16*S*/*R*-**3**[12] and 16*S*/*R*-**2**[1c,3] start from a C6−C13 building block and feature a stepwise construction of the ω-side chain, which renders the stereoselective generation of C15 and C16 difficult. We had previously carried out an asymmetric synthesis of 13,14-dinor-*inter*-*p*-phenylene carbacyclin, a prostacyclin (**1**) analogue which carries a 1,4-disubstituted phenyl group instead of the C13−C14 double bond by connecting the complete ω-side chain to the bicyclo[3.3.0]-octane skeleton through the conjugate addition of the corresponding arylcopper compound to azoalkene **10**.[14] Thus it was hoped that a stereoselective conjugate addition of the alkenylcopper derivative **9** to azoalkene **10** could also be achieved with formation of hydrazone **8**. However, nothing was known about the reactivity and stereoselectivity of azoalkene **10** and azoalkenes in general toward alkenylcopper reagents. Despite their potential for a nucleophilic derivatization of ketones at the α-position only little is known about the reactivity of azoalkenes toward organocopper reagents.[15] Furthermore, since **9** has to be enantio- and diastereomerically pure, it was of considerable importance to see whether such a conjugate addition could be efficiently carried out by using the two building blocks in a ratio of approximately 1:1. A critical step of Scheme 1 could be the conversion of hydrazone **8** to ketone **7** because of the requirement of a selective cleavage of the hydrazone group in the presence of the acetal group. The second key feature of the retrosynthesis of 16*S*-**2** and 16*S*-**3** is the Horner−Wadsworth−Emmons (HWE) olefination of **7** with a chiral phosphoryl acetate, which should stereoselectively give ester *E*-**6**. An asymmetric HWE olefination of this type[16a,b,17] had been successfully applied in the synthesis of cicaprost (**4**),[11,17] 3-oxa-carbacyclin,[16c,d] and 3-oxa-isocarbacyclin.[16d]

The allylic alcohol **5** was planned to be the point of digression of the retrosynthesis of 16*S*-**2** and 16*S*-**3**. An etherification of **5** should give 16*S*-**3**.[10a,11,16] We envisioned as the third new key feature of the retrosynthesis of 16*S*-**2** the establishment of the α-side chain through a copper-mediated allylic alkylation of a derivative of **5** with a suitable functionalized C1−C3-organocopper building block. Here the critical point could be the achievement of both a high α-regioselectivity and a complete retention of configuration of the double bond in the alkylation. Literature was ambiguous as to the feasibility of such a transformation.[18] Generally the regio- and stereoselectivity of the allylic alkylation with organocopper reagents are strongly dependent on the structure of the allylic substrate, the leaving

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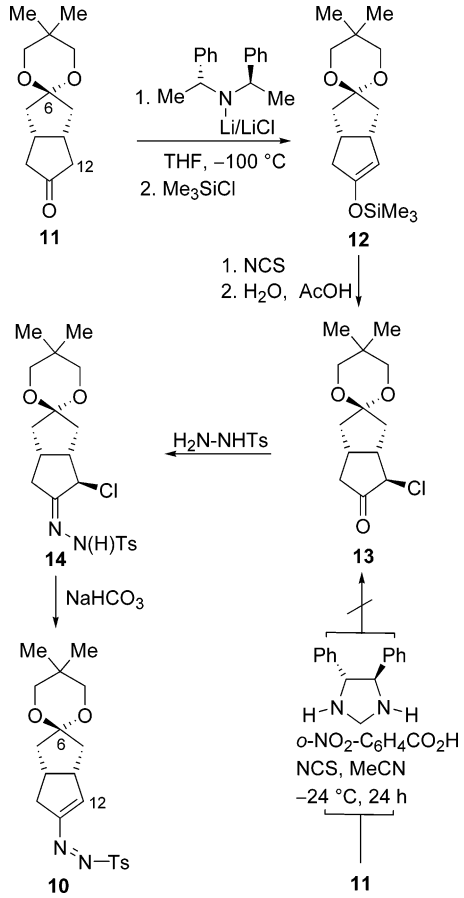
Scheme 2. Asymmetric Synthesis of Azoalkene **10**



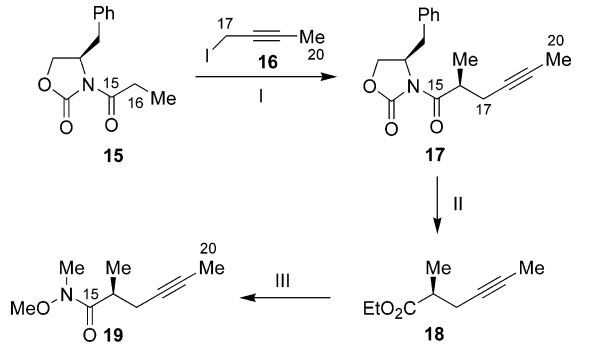
group, and the reagent thus making predictions in the present case difficult.

2.2. Asymmetric Synthesis of the C6−C12 Azoalkene. Azoalkene **10** with 95% enantiomeric excess (ee) was obtained from ketone **11**, which is readily available on large scale,[19,20] in four steps via **12**, **13**, and **14** in 55% overall yield (Scheme 2) as described previously.[14]

The key step of the synthesis is the enantioselective deprotonation of the meso-configured ketone **11** with the *R,R*-configured chiral LiCl-complexed lithium amide, which is readily available on large scale.[21] The synthesis of the chloro ketone **13** through a catalytic enantioselective chlorination of ketone **11** by using the *R,R*-configured imidazolidine derivative (20 mol %), *o*-$NO_2-C_6H_4CO_2H$ (50 mol %) and *N*-chlorosuccinimide (NCS) (2 equiv) according to a recently reported method[22] was not possible. Formation of **13** could not be detected and ketone **11** was recovered.

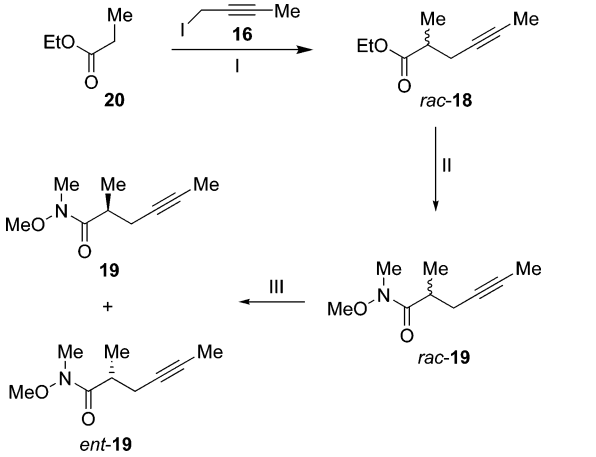
2.3. Asymmetric Synthesis of the C13−C20 Alkenylstannane. The development of an efficient synthesis of the enantio- and diastereomerically pure ω-side chain building block **9** was now of particular importance. It was planned to generate the alkenylcopper compound **9** from stannane **27** (Scheme 5, vide infra) by using the well-established tin−lithium exchange.[23] Thus, a retrosynthetic analysis of **27** identified a C15−C20 subunit, the chiral *N*-methoxyamide **19**, and a C13−C14 subunit, the lithiated stannane **22**. The joining of both subunits should give ketone **23** without effecting its stereochemical integrity.[11,24] A stereoselective reduction of **23** would deliver alcohol **26**. Previous results suggested that a highly diastereoselective reduction of ketone **23** with an achiral reducing reagent would be difficult to achieve.[25] Thus a chiral reducing reagent had to be applied. An oxazaborolidine-catalyzed reduction with a borane[26,27] was chosen since this method had already been successfully employed in our and other laboratories for the

Scheme 3. Asymmetric Synthesis of Amide **19**[a]



[a] Reagents and conditions: (I) (a) 1.35 equiv of $NaN(SiMe_3)_2$, THF, **15**, −78 °C; (b) 1.35 equiv of **16**, −78 °C, 2 h; (c) AcOH, −78 °C. (II) EtOH, $Ti(OEt)_4$, reflux, 10 h. (III) (a) 1.55 equiv of $[Me(OMe)NH_2]Cl$, **18**, 3.1 equiv of *i*-PrMgCl, THF, −20 °C; (b) H_2O, NH_4Cl, −20 °C; (c) preparative HPLC.

Scheme 4. Synthesis and Chromatographic Resolution of Amide *rac*-**19**[a]



[a] Reagents and conditions: (I) (a) LDA, THF, −78 °C; (b) **16**. (II) See Scheme 3. (III) HPLC, Daicel Chiralcel AD column (250 × 50 mm), *n*-hexane/*i*-PrOH, 95:5, 500 mg of *rac*-**19**/per injection.

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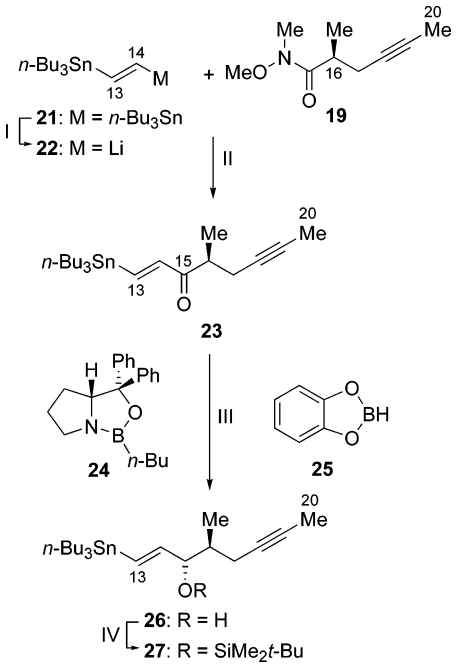
(24) For a review on the synthesis of ketones from *N*-methoxy-*N*-methylamides, see: Mentzel, M.; Hoffmann, H. M. R. *J. Prakt. Chem.* **1997**, *339*, 517−524.
(25) We had previously developed a less yielding synthesis of ketone **13** starting from methyl (*S*)-3-hydroxy-2-methylpropanoate via methyl (*S*)-3-iodo-2-methylpropanoate,[26a] the methyl analogue of **18**, and amide **19**. The reduction of **23** with $Li[BH(CH(Me)CH_2Me]$ in THF gave a mixture of **26** and **30** in a ratio of 1:3: Cheng, K.; Gais, H.-J., unpublished results.
(26) (a) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1997**, *38*, 7511−7514. (b) Corey, E. J.; Helal, C. J. *Angew. Chem*. **1998**, *110*, 2092−2118; *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 1986−2012.
(27) Itsuno, M. *Org. React.* **1998**, *52*, 395−576.

Scheme 5. Synthesis of Alkenylstannane **27**[a]



[a] Reagents and conditions: (I) **21**, *n*-BuLi, THF, −78 °C. (II) (a) **22**, **19,** THF, −78 °C; (b) NH_4Cl/H_2O, −78 °C. (III) (a) 2 equiv of **24**, 2 equiv of **25**, toluene, −78 °C, 12 h; (b) MeOH, −78 °C to room temperature; (c) HPLC. (IV) (a) 2,6-Lutidine, CH_2Cl_2, −10 °C; (b) *t*-$BuMe_2SiOSO_2CF_3$, −10 °C.

highly diastereoselective reduction of structurally related unsaturated ketones.[11,26a]

2.1.1. Synthesis of the C15−C20 Amide. The synthesis of the C15−C20 subunit **19** of the C13−C20 building block **27** was carried out by using the oxazolidinone method[28] for the selective generation of the stereogenic center (Scheme 3). The benzyl-substituted oxazolidinone **15**[28,29] was selected as the starting material. It had given a high selectivity in the synthesis of the homologous C15−C21 amide, which served as the side chain building in the synthesis of cicaprost (**4**).[11] Deprotonation of **15** with $NaN(SiMe_3)_2$ and treatment of the corresponding sodium enolate with iodide **16**,[30] which was prepared from the commercially available 2-butyne-1-ol,[31] gave the substituted oxazolidinone **17** with 92% diastereomeric excess (de) in 70% yield. Treatment of oxazolidinone **17** with $Ti(OEt)_4$ in refluxing EtOH[11,28b] furnished ester **18** with 92% ee (gas chromatography, GC) in 68% yield. Finally, amidation of ester **18** with MeO(Me)NMgCl, which was prepared in situ from $[MeO(Me)NH_2]Cl$ and 2 equiv of *i*-PrMgCl in THF,[24] afforded amide **19** in 93% yield. High-performance liquid chromatography (HPLC) and GC analysis showed the amide to have an ee value of 92%. Thus no partial racemization of **19** had occurred during the reaction sequence. Preparative HPLC of amide **19** (10 g) with 92% ee on a Daicel Chiralcel AD column (250 mm × 50 mm) allowed the ready separation of *ent*-**19** and **19** (500 mg of **19**/*ent*-**19** per injection) and furnished amide **19** with ≥99% ee in 95% yield.

The direct transamidation of **17** upon treatment with $[MeO(Me)NH_2]Cl/AlMe_3$[28c] with formation of **19** was not efficient. Besides **19** (34%), the corresponding amide resulting from an attack of the hydroxylamine derivative at the endocyclic carbonyl group of **17** was also obtained (30%) (for details, see Scheme S1 Supporting Information Available).[28c,d]

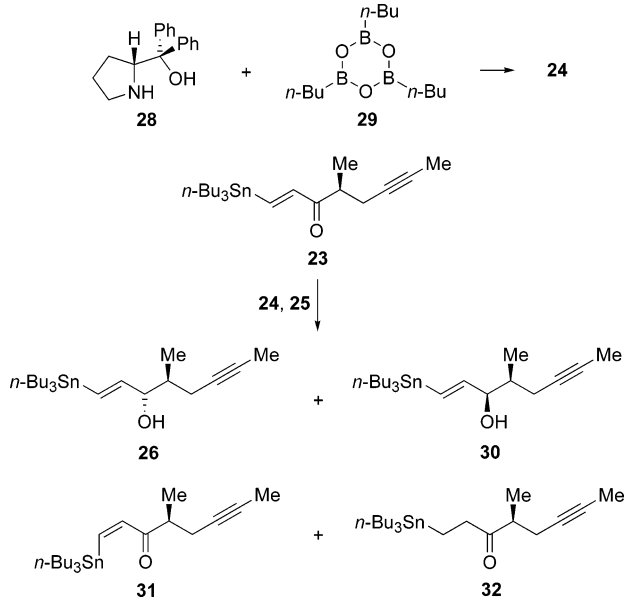
Although amide **19** could be efficiently synthesized from oxazolidinone **15** and iodide **16**, the ready preparative scale separation of **19** and *ent*-**19** by HPLC on a chiral stationary phase led us to consider, as an alternative, a synthesis of *rac*-**19** and its chromatographic resolution.[11] The racemic ester *rac*-**18** was prepared from ester **20** and iodide **16** in 50% yield (Scheme 4).[32] Amidation of *rac*-**18** with MeO(Me)NMgCl gave amide *rac*-**19** in 90% yield. The resolution of *rac*-**19** on a 3.6-g scale by HPLC on a Daicel Chiralcel AD column (250 mm × 50 mm) readily (500 mg of *rac*-**19** per injection) afforded **19** with ≥99% ee in 47% yield and *ent*-**19** with ≥99% ee in 47% yield.[33]

Chain elongation of amide **19** upon reaction with the alkenyllithium derivative **22**,[34] which was prepared through Sn/Li exchange of bisstannane **21** with *n*-BuLi, afforded ketone **23** with ≥99% ee in 75% yield (Scheme 5). HPLC analysis of **23** showed that the synthesis of the ketone was not accompanied by a partial racemization.

Oxazaborolidine **24**[26] was selected as catalyst for the diastereoselective reduction of ketone **23** with catecholborane (**25**). The reduction was carried out by the slow addition of a toluene solution of the ketone, which was treated with molecular sieve (4 Å) prior to the reduction experiment, to a solution of 2 equiv of freshly distilled **25** and 2 equiv of freshly prepared catalyst **24** in toluene at −78 °C. Thereby a mixture of the diastereomeric alcohols **26** and **30** (Scheme 6, vide infra) in a ratio of 95:5 could be reproducibly isolated in 90% yield after chromatography. For comparison purposes, a 1:1-mixture of **26** and **30** (vide infra) was prepared through reduction of ketone **23** with $NaBH_4$ in EtOH at room temperature. The diastereomeric alcohols were readily and quantitatively separated by preparative HPLC. Thus HPLC of alcohol **26** of 90% de gave the alcohol of ≥99% de in 81% yield. The relative and absolute configurations of alcohols **26** and **30** had been previously determined by calculation of their CD spectra and comparison with the experimental CD spectra.[35] Inversion of the configuration of alcohol **30** upon treatment with PPh_3, $PhCO_2H$, and diethyl azodicarboxylate[36] afforded a mixture of the corresponding regioisomeric allylic C15 and C13 benzoates in a ratio of 80:

(28) (a) Evans, D. A.; Starr, J. T. *J. Am. Chem. Soc*. **2003**, *125*, 13531−13540. (b) Evans, D. A.; Ellman, J. A.; Dorow, R. L. *Tetrahedron Lett*. **1987**, *23*, 1123−1126. (c) Evans, D. A.; Bender, S. L. *Tetrahedron Lett*. **1986**, *27*, 799−802. (d) Romo, D.; Rzasa, R. M.; Shea, H. A.; Park, K.; Langenhan, J. M.; Sun, L.; Akhiezer, A.; Liu, J. O. *J. Am. Chem. Soc*. **1998**, *120*, 12237−12254.
(29) (a) Tyrell, E.; Tsang, M. W. H.; Skinner, G. A.; Fawcett, J. *Tetrahedron* **1996**, *52*, 9841−9852. (b) Ho, G.-J.; Mature, D. J. J. *Org. Chem*. **1995**, *60*, 2271−2273.
(30) For a report on the alkylation of *ent*-**16** with 1-bromo-2-butyne without giving details about the diastereoselectivity, see: Savignac, M.; Durand, J.-O.; Genêt, J.-P. *Tetrahedron: Asymmetry* **1994**, *5*, 717−722.
(31) Lange, G. L.; Gottardo, C. *Synth. Commun*. **1990**, *20*, 1473−1479.
(32) For a synthesis of the corresponding racemic acid, see: Wakita, H.; Matsumoto, K.; Yoshiwara, H.; Hosono, Y.; Hayashi, R.; Nishiyama, H.; Nagase, H. *Tetrahedron* **1999**, *55*, 2449−2474.
(33) For laborious resolutions of the corresponding acid with chiral amines, see: (a) Wakita, H.; Yoshiwara, H.; Kitano, Y.; Nishiyama, H.; Nagase, H. *Tetrahedron: Asymmetry* **2000**, *11*, 2981−1989. (b) Skuballa, W.; Vorbrüggen, H. In *Advances in Prostaglandin, Thromboxane, and Leukotriene Research*; Samuelsson, B., Paoletti, R., Ramwell, P., Eds.; Raven Press: New York, 1983; Vol. 11, pp 299−305.
(34) Corey, E. J.; Wollenberg, R. H. *J. Am. Chem. Soc*. **1974**, *96*, 5581−5583. (b) Renaldo, A. F.; Labadie, L. W.; Stille, J. K. *Org. Synth*. **1989**, *67*, 86−97.
(35) Voloshina, E. N.; Raabe, G.; Fleishhauer, J.; Kramp, G. J.; Gais, H.-J. *Z. Naturforsch*. **2004**, *59a*, 124−132.
(36) Mitsunobu, O. *Synthesis* **1981**, 1−28.

Scheme 6. Oxazaborolidine-Catalyzed Reduction of Ketone **23** with Borane **25**



20. Hydrolysis of the mixture of the benzoates without prior separation gave alcohol **26** with ≥99% ee in 56% overall yield (for details, see Scheme S2 Supporting Information Available).

Silylation of alcohol **26** with *t*-BuMe_2SiOSO_2CF_3 furnished the silyl ether **27** in 98% yield. Interestingly, the silylation of **26** with *t*-BuMe_2SiCl in DMF in the presence of imidazol was not only much slower but was also accompanied by a partial destannylation of **27**, which led to the formation of the derivative of **27**, carrying a H-atom instead of the stannyl group, as a side product.

2.1.2. Substoichiometric Oxazaborolidine-Catalyzed Reduction of Ketone 23. Much to our surprise, reproducible high diastereoselectivities in the reduction of ketone **23** with **24** and **25** were only obtained when 2 equiv of catalyst **24** were applied. The use of sub stoichiometric amounts of **24** (0.10−0.35 equiv) and 1.1−2.0 equiv of **25** in toluene or CH_2Cl_2 at −78 °C gave in our hands widely differing and nonreproducible diastereoselectivities ranging from very high (98:2) to almost nil (55:45) (for details, see Table S1 and Scheme S3, Supporting Information Available). In all reductions experiments of **23** with less than stoichiometric amounts of catalyst **24** to various extend the formation of the *Z*-configured ketone **31**, and the saturated ketone **32** was observed (Scheme 6). Reduction of **23** with **25** in the absence of **24** was much slower and gave a nearly 1:1 mixture of **26** and **30**.

It had been described that the enantioselectivity of oxazaborolidine-catalyzed reduction of ketones with boranes can be crucially dependent on the water content of the system and the presence of starting materials or intermediates of the synthesis of the catalyst.[37] Thus in all reduction experiments of **23**, catalyst **24** was freshly prepared from 1 equiv of the amino alcohol **28** and 0.333 equiv of the pure borinane **29** in refluxing toluene followed by a distillation.[37b] According to ^{1}H, ^{13}C, and ^{11}B NMR spectroscopic analyses the thus obtained oxazaborolidine **24** was pure and contained neither starting material nor *n*-butylboronic acid or any intermediate of the synthesis of **24**, all of which have been previously identified as possible sources of low enantioselectivity in reductions catalyzed by **24**.[37] Furthermore all solvents were rigorously dried including a final treatment with activated molecular sieve (4 Å). Similarly, the solution of ketone **23** was dried with activated molecular sieve, which was removed prior to the reaction with **24** and **25**. Finally the commercial catecholborane (**25**), the ^{11}B NMR spectrum of which indicated the presence of two further unidentified BH group containing boranes, was purified by distillation.

In all experiments with substoichiometric amounts of **24**, the borane **25** was slowly added to a solution of **23** and **24** in order to suppress a noncatalyzed reduction. However, all of the above measures that were taken to obtain a reproducible high diastereoselectivity in the reduction of ketone **23** in the presence of substoichiometric amounts of **25** were unsuccessful. At present we have no rationalization for the apparently irregular variation of the selectivities in the substoichiometric reductions of **23** with **24** and **25**. It seems interesting to note that in a recently described oxazaborolidine-catalyzed reduction of a chiral alkynone with BH_3 a significantly lower diastereoselectivity was observed when substoichiometric amounts of the catalyst were employed.[38,39]

2.4. Conjugate Addition of the C13−C20 Alkenylcopper Derivative 9 to the C6−C12 Azoalkene 10. With the required building blocks **10** and **27** in hand, their coupling was the next and crucial step according to the synthetic plan. Special attention had to be paid to the generation of a reactive derivative of the alkenylcopper compound **9** and its conjugate addition to azoalkene **10** by using nearly equimolar amounts of the two building blocks. Because of the easiness of preparation, we opted for the alkenylcopper-*n*-Bu_3P complex **9a** (Scheme 7) instead of a corresponding cuprate containing a nontransferable organic ligand.[18a]

Treatment of alkenylstannane **27** with *n*-BuLi afforded the alkenyllithium derivative **33** which upon reaction with 0.275 equiv of [CuI(*n*-Bu_3P)]$_4$[40] furnished the alkenylcopper derivative **9a**. The conjugate addition was achieved through reaction azoalkene **10** with 1.1 equiv of **9a** in the presence of 0.275 equiv of [CuI(*n*-Bu_3P)]$_4$, which afforded hydrazone **8** in 84% yield as a single diastereomer at C12. Quenching of the reaction mixture with *n*-Bu_3SnCl allowed a recovery of the 0.1 equiv of excess **9a** as stannane **27** in 60% yield. The configuration of **8** at the CN-double bond, which has not been determined, is arbitrary depicted as *E*.

The crucial chemoselective cleavage of hydrazone **8** was accomplished upon treatment with 1.05 equiv of $(PhSeO)_2O$ in the presence of 20 equiv of cyclohexene.[41] Thereby ketone **34** was isolated in 70% yield. The reduction of ketone **34** with

(37) (a) Jones, K. T.; Mohan, J. J.; Xavier, L. C.; Blacklock, T. J.; Mathre, D. J.; Sohar, P.; Jones, E. T. T.; Reamer, R. A.; Roberts, F. E.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 763−769. (b) Mathre, D. J.; Jones, T. K.; Xavier, L, C.; Blacklock, T. J.; Reamer, R. A.; Mohan, J. J.; Jones, E. T. T.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751−762. (c) Tschaen, D. M.; Abramson, L.; Cai, D.; Desmond, R.; Dolling, U.-H.; Frey, L.; Karady, S.; Shi, Y.-J.; Verhoeven, T. R. *J. Org. Chem.* **1995**, *60*, 4324−4330.

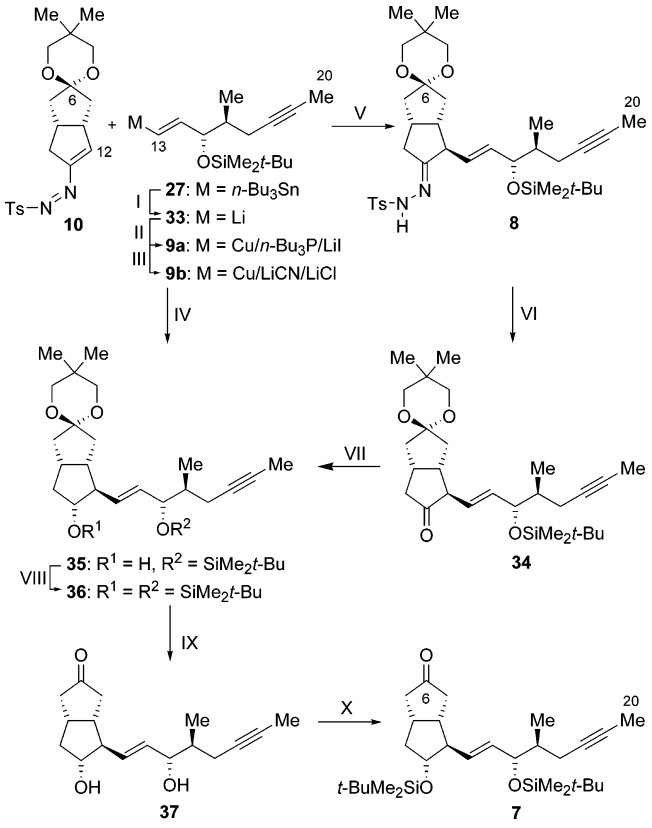
(38) (a) Trost, B. M.; Gunzner, J. L.; Dirat, O.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 10396−10415.

(39) For further examples, see: (a) Parker, K. A.; Ledeboer, M. W. *J. Org. Chem.* **1996**, *61*, 3214−3217. (b) Rodriguez, A.; Nomen, M.; Spur, B. W.; Godfroid, J.-J. *Eur. J. Org. Chem.* **1999**, 2655−2662. (c) Gais, H.-J.; Kramp, G. J., unpublished results.

(40) Suzuki, M.; Noyori, R. In *Organocopper Reagents*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, 1994; pp. 182−216.

(41) (a) Barton, D. H. R.; Okano, T.; Parekh, S. I. *Tetrahedron* **1991**, *47*, 1823−1836. (b) Barton, D. H. R.; Choi, S.-Y.; Liu, W.; Smith, J. A. *Mol. Online* **1998**, *2*, 22−28.

Scheme 7. Conjugate Addition of the Alkenylcopper Derivative **9** to Azoalkene **10**[a]



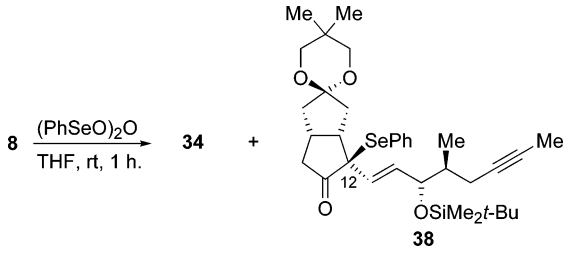
[a] Reagents and conditions: (I) 1.1 equiv of *n*-BuLi, THF, −78 °C, 1 h. (II) **33**, 0.275 equiv of $[CuI(n\text{-}Bu_3P)]_4$, THF, −78 °C, 30 min. (III) **33**, 1.2 equiv of CuCN, 2.4 equiv of LiCl, THF, −78 °C. (IV) (a) 1.1 equiv of **9b**, **10**, THF, −78 °C; (b) 2 equiv of Bu_3SnCl, THF, −78 °C; (c) H_2O, NH_4Cl, THF, −78 °C to room temperature; (d) 1.05 equiv of $(PhSeO)_2O$, 20 equiv of cyclohexene, THF, room temperature; (e) 6 equiv of $NaBH_4$, EtOH, 0 °C; (f) H_2O, NH_4Cl, 0 °C to room temperature. (V) (a) 1.1 equiv of **9a**, **10**, 0.275 equiv of $[CuI(n\text{-}Bu_3P)]_4$, THF, −78 °C, 1 h; (b) 2 equiv of Bu_3SnCl, −78 °C, 30 min; (c) NH_4Cl/NH_3 (9:1), −78 °C to room temperature. (VI) 20 equiv of cyclohexene, 1.05 equiv of $(PhSeO)_2O$, THF, room temperature, 1 h. (VII) 2 equiv of $NaBH_4$, EtOH, 0 °C, 3 h. (VIII) (a) 2,6-Lutidine, CH_2Cl_2, −10 °C; (b) $t\text{-}BuMe_2SiOSO_2CF_3$, −10 °C. (IX) *p*-TsOH, acetone/water, room temperature, 24 h. (X) $t\text{-}BuMe_2SiCl$, imidazol, DMF, room temperature.

$NaBH_4$ furnished alcohol **35** as a single diastereomer at C11 in 76% yield. The synthesis of alcohol **35** has also been carried out without the isolation of hydrazone **8** and ketone **34** in 51% overall yield starting from **10** and **27** by using the cyano cuprate **9b** which was prepared by treatment of **33** with 1.2 equiv of CuCN and 2.4 equiv of LiCl.

Now a cleavage of the protecting groups of **35** with formation of ketone-diol **37** was required. Surprisingly, the reaction of **35** with *p*-TsOH in acetone/water was sluggish. Therefore alcohol **35** was first converted to the bissilyl ether **36** in 98% yield. Treatment of **36** with *p*-TsOH in acetone/water proceeded uneventful and gave diol-ketone **37**, the hydroxy groups of which were silylated to afford ketone **7** in 98% yield. Isolation of **37** is not required for the synthesis of **7** from **36**.

A ^1H NMR spectroscopic analysis of hydrazone **8** indicated the presence of a minor amount of the diastereomer of **8** stemming from the reaction of *ent*-**10**, contained in azoalkene **10** of 95% ee, with **9a**. A chromatographic separation of the minor diasteromer was achieved at the stage of alcohol **35** as

Scheme 8. Cleavage of Hydrazone **8** in the Absence of Cyclohexene



revealed by a HPLC and ^1H NMR spectroscopic analysis of the bissilyl ether **36**.

Crucial for the attainment of a high yield of ketone **34** in the cleavage of hydrazone **8** with $(PhSeO)_2O$ proved to be the presence of a large excess of cyclohexene. In the absence of cyclohexene the selanyl derivative **38** (Scheme 8) was obtained as a single diastereomer (32%) in addition to ketone **34** (30%). The configuration at C12 of **38**, which could not be determined by nuclear Overhauser effect (NOE) experiments, is arbitrarily assigned as depicted. Evidence had been previously presented showing that the cleavage of tosyl hydrazones with $(PhSeO)_2O$ involves the intermediate formation of the tolylsulfonyl and phenylselanyl radicals, which can be trapped with cyclohexene.[41] Thus the formation of **38** can perhaps be ascribed to a reaction of ketone **34** with these radicals which are otherwise efficiently trapped by cyclohexene with formation of the corresponding phenylselenotosylate derivative.

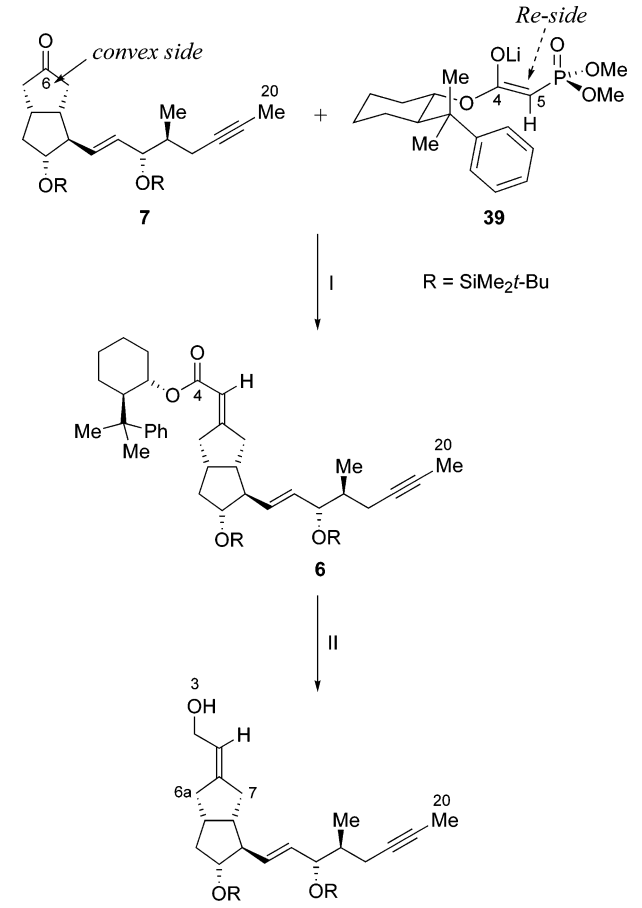
2.5. Asymmetric HWE Olefination of the C6−C20 Ketone 7 and Completion of the Synthesis of 16*S*-3-Oxa-Iloprost. Now the synthetic plan called for a diastereoselective HWE olefination of ketone **7** with formation of the *E*-configured α,β-unsaturated ester *E*-**6** (Scheme 9). We selected the dimethylphosphoryl acetate derived from (1*S*,2*R*)-8-phenylnormenthol[11,16] because of the ready availability of this alcohol in enantiomerically pure form.[42] Treatment of ketone **7** with 6 equiv of the lithium salt **39** in THF at −62 °C for 6 days resulted in a highly selective olefination and gave after aqueous work up and chromatography a mixture of the diastereomeric esters *E*-**6** and *Z*-**6** in a ratio of 98:2 in 89% yield. The excess of the phosphoryl acetate was recovered in almost quantitative yield. Preparative HPLC of the mixture of esters *E*-**6** and *Z*-**6** afforded ester *E*-**6** with ≥99% de in 78% yield and ester *Z*-**6** with ≥99% de in 1% yield.

The high diastereoselectivity of the reaction of **7** with **39** can be rationalized by assuming that (1) a selectivity determining step involving the addition of phosphonate **39** to ketone **7** and (2) a preferred trajectory of approach from the *Re* side of **39** and the convex side of **7**.[16b] Reduction of ester *E*-**6** with $(i\text{-}Bu)_2AlH$ in THF gave the allylic alcohol *E*-**5** in 94% yield and 8-phenylnormenthol in 85% yield. The *E*-configuration of the double bond of *E*-**5** was secured by NOE experiments, which revealed strong NOEs between 6a−H and 4-H and between 5-H and 7-H.

The synthesis of 16*S*-**3** was completed following the route previously used for the synthesis of cicaprost (**4**)[10a,11] and other 3-oxa-analogues of carbacyclins.[16c,d] Thus etherification of alcohol *E*-**5** through treatment with excess $BrCH_2COOt\text{-}Bu$ under phase transfer conditions in the presence of 50% aqueous

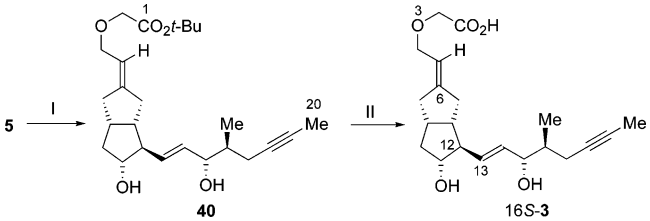
(42) Commins, D. L.; Salvador, J. M. *J. Org. Chem.* **1993**, *58*, 4656−4661.

Scheme 9. Asymmetric HWE Olefination of the Bicyclic Ketone **7**[a]



[a] Reagents and conditions: (I) (a) 6.0 equiv of **39**, THF, −62 °C, 6 d; (b) NH_4Cl, −62 °C to room temperature; (c) HPLC. (II) $(i\text{-Bu})_2AlH$, THF, 0 °C.

Scheme 10. Etherification of the Allylic Alcohol **5** and Completion of the Synthesis of 16*S*-**3**[a]

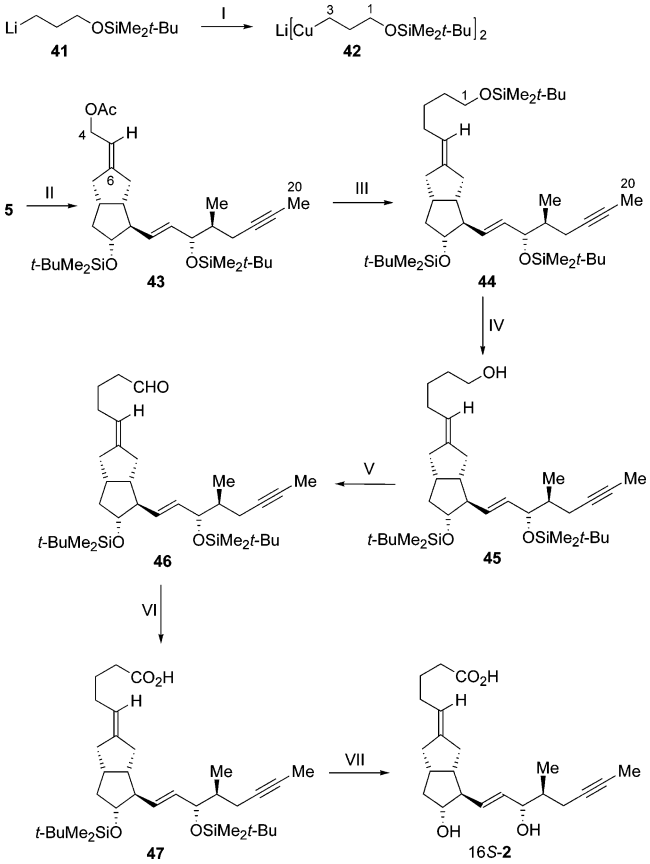


[a] Reagents and conditions: (I) (a) $n\text{-Bu}_4NHSO_4$, 50% NaOH, $BrCH_2COOt\text{-Bu}$, CH_2Cl_2, room temperature; (b) $n\text{-Bu}_4NF$, THF, room temperature. (II) MeOH, 1 N NaOH, NaH_2PO_4, pH 4−5, room temperature.

NaOH and a subsequent desilylation of the corresponding bissilyl ether, which was not isolated, with $n\text{-Bu}_4NF$ gave the dihydroxy ester **40** in 90% overall yield (Scheme 10). Finally, the hydrolysis of ester **40** with NaOH in MeOH and acidification with NaH_2PO_4 to pH 4−5 furnished the enantio- and diastereomerically pure 16*S*-3-oxa-iloprost (16*S*-**3**) in 90% yield. An acidification of the solution of 16*S*-**3** to pH 1 resulted in its partial conversion to a mixture of the corresponding 6-vinyl substituted C6−C6a- and C6−C7-dienes and 2-hydroxyacetic acid.

2.7. Allylic Alkylation of the C4−C20 Alcohol 5 and Completion of the Synthesis of 16*S*-Iloprost. The retrosynthesis of 16*S*-**2** now demanded for a regio- and stereoselective

Scheme 11. Allylic Alkylation of Acetate **43** with Cuprate **42** and Completion of the Synthesis of 16*S*-**2**[a]



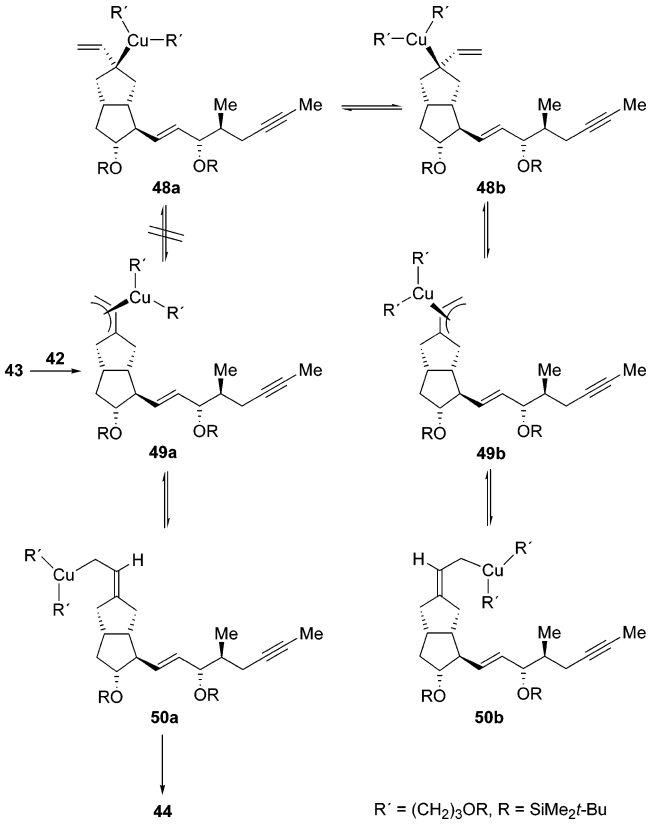
[a] Reagents and conditions: (I) CuI, Et_2O, Me_2S. (II) Ac_2O, THF. (III) **42**, Et_2O. (IV) Alumina, hexanes, H_2O. (V) DMSO, SO_3-pyridine, NEt_3. (VI) $AgNO_3$, EtOH, H_2O, NaOH. (VII) $n\text{-Bu}_4NF$, THF.

alkylation of the allylic alcohol **5** or a derivative thereof with an organocopper C1−C3 building block (Scheme 11). In principle ketones **7** and **37** (cf. Scheme 7) could also serve as starting materials for the synthesis of 16*S*-**2**. However, the Wittig olefination of ketones **7** and **37** with the achiral ylide $Ph_3P{=}CH(CH_2)_3CO_2^-M^+$ proceeds only with low *E*-stereoselectivity because of the insufficient asymmetric induction provided by the ϖ-side chain.[43] For example reaction of the hydroxy ketone **37** with $Ph_3P{=}CH(CH_2)_3CO_2^-M^+$, which had been reported to be more selective than that of the protected ketone **7** (*E*:*Z* = 78:22) and to deliver a mixture of 16*S*-**2** and its *Z* isomer in a ratio of 90:10,[43] gave in our hands a mixture of 16*S*-**2** and its *Z* isomer in a ratio of only 62:38, the separation of which by HPLC afforded 16*S*-**2** in 45% yield and its *Z* isomer in 12% yield (for details, see Scheme S4 Supporting Information Available).

To solve the problem of the stereoselective olefination of ketone **37** the sulfoximine method could be applied.[44] Application of this method would involve a conversion of the ketone to the corresponding 5*E*-configured 6-(phenylsulfonimidoyl)-methylene derivative and its subsequent Ni-catalyzed cross-coupling reaction with a suitably functionalized C1−C4-

(43) Westermann, J.; Harre, M.; Nickisch, K. *Tetrahedron Lett.* **1992**, *33*, 8055−8056.
(44) (a) Erdelmeier, I.; Gais, H.-J.; Lindner, H. J. *Angew. Chem.* **1986**, *98*, 912−914; *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 935−937. (b) Erdelmeier, I.; Gais, H.-J. *J. Am. Chem. Soc.* **1989**, *111*, 1125−1126. (c) Gais, H.-J.; Bülow, G. *Tetrahedron Lett.* **1992**, *33*, 465−468.

Scheme 12. Mechanistic Rationalization of the Allylic Alkylation of Acetate **43** with Cuprate **42**



zinkorganyl. Although the synthesis of the 5*E*-configured alkenylsulfoximine should proceed with high stereoselectivity and yield, the feasibility of a stereoselective cross-coupling reaction has thus far only been demonstrated for bicyclic alkenylsulfoximines of this type carrying an incomplete ω-side chain. Therefore, an allylic alkylation of the late-stage intermediate **5** seemed to be much more attractive provided this transformation can be made to proceed with high regio- and stereoselectivities. Acetate **43** and homocuprate **42**[45a] which was prepared from the lithiumorganyl **41**[45b] were selected as starting materials. Gratifyingly, the allylic alkylation of acetate **43**, which was obtained from alcohol **5** in 96% yield, with homocuprate **42** proceeded with high regio- and diastereoselectivities at C4 and gave the *E*-configured alkene **44** in 82% yield. ^{1}H NMR spectroscopy and HPLC analysis showed alkene **44** to be free of the corresponding *Z* isomer and the regioisomers derived from a substitution of **43** at C6.

The complete retention of the configuration of the exocyclic double bond in the allylic alkylation of acetate **43** is noteworthy. It suggests that the oxidative addition/substitution of acetate **43** upon reaction with cuprate **42** directly leads to the *E*-configured π-allylcopper(III) complex **49a** which suffers an isomerization to the *E*-configured α-σ-allylcopper(III) complex **50a**, the reductive elimination of which gives **44**[46] (Scheme 12). The normally expected oxidative addition/substitution of **43** upon reaction with **42** under formation of the γ-σ-allylcopper(III) complex **48a**[18a] seems not to have taken place. Once formed complex **48a** is expected to give via conformer **48b** the *Z*-configured π-allylcopper(III) complex **49b**, the isomerization of which would generate the *Z*-configured α-σ-allylcopper(III) complex **50b**. A final reductive elimination of **50b** would lead to the formation of the *Z* isomer of alkene **44**, an event which was, however, not observed.

The completion of the synthesis of 16*S*-**2** demanded a chemoselective deprotection of of the primary silyl ether group of **44** in the presence of the two secondary silyl ether groups (cf. Scheme 11). This was achieved upon treatment of ether **44** with water containing neutral alumina in hexanes,[47] which furnished the primary alcohol **45** in 80% yield. Formation of a corresponding diol was not observed. The oxidation of the primary alcohol **45** to acid **47** was carried out without purification of intermediates **46** and **47** by the two-step procedure we[48] and others[49] had successfully used in previous isocarbacylin syntheses. Thus oxidation of alcohol **45** with SO_3/pyridine/DMSO afforded aldehyde **46**, which was oxidized with Ag_2O to acid **47**. The subsequent deprotection of the bissilyl ether **47** upon treatment with *n*-Bu_4NF in THF finally gave the enantio- and diastereomerically pure 16*S*-iloprost (16*S*-**2**) in 59% overall yield based on alcohol **5**.

3. Conclusion

In this article, we report asymmetric total syntheses of 16*S*-iloprost (16*S*-**2**) and 16*S*-3-oxa-iloprost (16*S*-**3**) from the chiral bicyclic azoalkene **10** (4 steps from **11**, 55% yield) and the chiral alkenylstannane **27** (6 steps from **15**, 25% yield) in 11 steps in 12% overall yield and in 7 steps in 25% overall yield, respectively. A diversion at the late-stage intermediate, the allylic alcohol **5**, allowed the synthesis of both 16*S*-**2** and 16*S*-**3**. The key steps of the syntheses are (1) the coupling of a bicyclic C6−C12 building block with a C13−C20 building block through a stereoselective conjugate addition of an alkenylcopper derivative to an azoalkene, (2) the stereoselective olefination of ketone **7** with a chiral phosphoryl acetate, and (3) the regio- and stereoselective allylic alkylation of acetate **43**. The synthesis of 16*S*-**2** from ketone **7** via the ester **6** and the allylic alcohol **5** represents a solution of the long-standing problem of the stereoselective olefination of **7** and related bicyclic ketones. The successful syntheses of 16*S*-**2** and 16*S*-**3** clearly demonstrate the viability of the alkenylcopper-azoalkene route for the synthesis of carbocyclic prostacyclin analogues.

The facile conjugate addition of alkenyl- and arylcopper derivatives to the azoalkene **10** points to an unexplored potential of azoalkenes for the alkylation, arylation and alkenylation of ketones at the α-position,[50] which warrants further studies to determine the scope and limitation of this transformation. Fuchs et al. had already shown that azoalkenes derived from simple cyclic and acyclic ketones readily react with aryl- and alkylcopper reagents.[15a]

The enantio- and diastereomerically pure building blocks **18**, **19**, and **27**, for which efficient syntheses have been developed, could also find application in asymmetric syntheses of beraprost.

(45) (a) Hua, D. H.; Verma, A. *Tetrahedron Lett.* **1985**, 26, 547−550. (b) Tanner, D.; Hagberg, L. *Tetrahedron* **1998**, *54*, 7907−7918.
(46) (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3063−3066. (b) Underiner, T. L.; Paisley, S. D.; Schmitter, J.; Lesheski, L.; Goering, H. L. *J. Org. Chem.* **1989**, *54*, 2369−2374.
(47) Feixas, J.; Capdevila, A.; Guerrero, A. *Tetrahedron* **1994**, *50*, 8539−8550.
(48) (a) Hemmerle, H.; Gais, H.-J. *Angew. Chem.* **1989**, *101*, 362−365; *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 349−351. (b) Bund, J.; Gais, H.-J.; Schmitz, E.; Erdelmeier, I.; Raabe, G. *Eur. J. Org. Chem.* **1998**, 1319−1335.
(49) Mase, T.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.* **1984**, *25*, 5087−5090.
(50) For a recent example, see: Chae, J.; Yun, J.; Buchwald, S. L. *Org. Lett.* **2004**, *6*, 4809−4812.

Beraprost which is an orally active benzoprostacyclin derivative having the same ω-side chain as iloprost has already been approved as Procyclin and Dorner for the treatment of peripheral vascular diseases and primary pulmonary hypertension.[51] However, the Procyclin and Dorner formulations of beraprost consist of mixtures of the four C15/C16 isomers, three of which are much less active.[51a]

The diastereoselective reduction of the chiral C13−C20 ketone **23** with substoichiometric amounts of the oxazaborolidine catalyst and catecholborane gave widely differing diastereoselectivities ranging from very high to nil. Reproducible high selectivities were recorded only in experiments with 2 equiv of the chiral catalyst. Thus, it seems that with certain substrates the stereoselectivity of the oxazaborolidine catalyzed reduction with substoichiometric amounts of the catalyst is influenced by factors which have not yet been fully identified.

4. Experimental Section

(+)-(3′a*S*,4′*R*,5′*R*,6′a*R*)-4′-((3*S*,4*S*,*E*)-3-(*tert*-Butyldimethylsilyloxy)-4-methyl-oct-1-en-6-ynyl)-5,5-dimethylhexahydro-1′*H*-spiro[[1,3]-dioxane-2,2′-pentalen]-5′-ol (35). From azoalkene **10** and stannane **27** without isolation of **8** and **34**. *n*-BuLi (0.88 mL, 1.60 M in hexanes, 1.40 mmol) was added at −78 °C to a solution of stannane **27** (762 mg, 1.40 mmol) in THF (4 mL). After the mixture was stirred at −78 °C for 1 h, it was added to a cold solution of CuCN (275 mg, 3.08 mmol) and LiCl (260 mg, 6.13 mmol) in THF (3 mL) at −78 °C via a double-ended needle. The resulting yellow solution was stirred at −78 °C for 30 min. Then a cold solution of azoalkene **10** (500 mg, 1.28 mmol, 95% ee) in THF (4 mL) was added via a double-ended needle. After the mixture was stirred at −78 °C for 1 h, *n*-Bu_3SnCl (0.76 mL, 2.8 mmol) was added. Then the mixture was stirred at −78 °C for 30 min, water (3 mL) was added, and the mixture was warmed to ambient temperature. Subsequently the mixture was diluted with Et_2O (100 mL) and washed with a mixture of saturated aqueous NH_4Cl and concentrated aqueous NH_3 (10:1) (3 × 20 mL). The combined aqueous phases were extracted with Et_2O (3 × 20 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in THF (20 mL), cyclohexene (2.60 mL, 25.61 mmol) was added, and the solution was treated with $(PhSeO)_2O$ (461 mg, 1.28 mmol) at ambient temperature, whereby a gas evolution occurred. The mixture was stirred at ambient temperature for 40 min, cooled to 0 °C, and EtOH (30 mL) added. Then $NaBH_4$ (291 mg, 7.68 mmol) was added at 0 °C. After the mixture was stirred at 0 °C for 2 h, saturated aqueous NH_4Cl (3 mL) was added, and the mixture was warmed to ambient temperature. Then the mixture was concentrated in vacuo, and the residue was dissolved in a mixture of Et_2O (100 mL) and water (10 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (hexanes/EtOAc, 6:1) gave alcohol **35** (330 mg, 51%) as a colorless oil. $[\alpha]_D$ +16.5 (*c* 1.71, $CDCl_3$); R_f 0.36 (hexanes/EtOAc, 3:1); ^{1}H NMR (400 MHz, C_6D_6) δ 0.00 (s, 3 H, $SiCH_3$), 0.02 (s, 3 H, $SiCH_3$), 0.62 (s, 3 H, $CH(CH_3)_2$), 0.67 (s, 3 H, $CH(CH_3)_2$), 0.88 (s, 9 H, $SiC(CH_3)_3$), 0.92 (d, J = 6.9 Hz, 3 H, $CHCH_3$), 1.22 (bs, 1 H, OH), 1.29−1.37 (m, 1 H), 1.48 (t, J = 2.5 Hz, 3 H, $CH_2C{\equiv}CCH_3$), 1.64−1.70 (m, 2 H), 1.80−1.87 (m, 1 H), 1.93−2.02 (m, 4 H), 2.08−2.28 (m, 4 H), 3.15−3.18 (m, 4 H, OCH_2), 3.45 (dt, J = 6.6, J = 9.3 Hz, 1 H, *CH*OH), 3.92 (t, J = 6.3 Hz, 1 H, CHOSi), 5.32−5.36 (m, 2 H, CH=CH); ^{13}C NMR (100 MHz, C_6D_6) δ −4.8 (d), −3.9 (d), 3.2 (d), 15.7 (d), 18.2 (u), 22.2 (d), 22.3 (d), 22.3 (u), 25.9 (d), 29.7 (u), 35.9 (d), 38.8 (u), 39.7 (d), 40.3 (u), 41.3 (u), 43.9 (d), 57.6 (d), 71.7 (u), 71.7 (u), 76.4 (u), 76.76 (d), 78.0 (u), 78.2 (d), 110.2 (u), 132.8 (u), 133.4 (u); IR (neat) ν 3457 (m), 2955 (s), 2858 (s), 2278 (m), 1467 (m), 1393 (m), 1361 (m), 1329 (m), 1253 (m), 1219 (m), 1176 (w), 1113 (s), 1062 (s), 974 (m), 938 (w), 837 (s) cm^{-1}; MS (EI, 70 eV) *m*/*z* (relative intensity, %) 476 (M^+, 0.7), 419 (29), 378 (28), 377 (100), 333 (17), 291 (14), 263 (10), 241 (15), 159 (14); HRMS calcd for $C_{28}H_{48}O_4Si^+$ 476.332189, found 476.332258.

(+)-(*E*)-((1*S*,2*R*)-2-(2-Phenylpropan-2-yl)cyclohexyl)-2-((3a*S*,4*R*,5*R*,-6a*S*)-5-(*tert*-butyldimethylsilyloxy)-4-((3*S*,4*S*,*E*)-3-(*tert*-butyldimethylsilyloxy)-4-methyl-oct-1-en-6-ynyl)hexahydropentalen-2(1*H*)-ylidene)acetate (*E*-6) and (*Z*)-((1*S*,2*R*)-2-(2-Phenylpropan-2-yl)cyclohexyl)-2-((3a*S*,4*R*,5*R*,6a*S*)-5-(*tert*-butyldimethylsilyloxy)-4-((3*S*,4*S*,*E*)-3-(*tert*-butyl-dimethylsilyloxy)-4-methyl-oct-1-en-6-ynyl)hexahydropentalen-2(1*H*)-ylidene)acetate (*Z*-6). To a solution of (1*S*,2*R*)-dimethoxyphosphanyl-2-(2-phenylpropan-2-yl)cyclohexyl 2-(dimethoxyphosphoryl)acetate (1.313 g, 3.56 mmol) in THF (8 mL) was added *n*-BuLi (2.08 mL of 1.6 M in hexanes, 3.32 mmol) at −78 °C. The resulting solution of the lithium salt **39** was warmed to ambient temperature for 15 min and cooled to −62 °C. Then a solution of ketone **7** (300 mg, 0.594 mmol) in THF (3 mL) was added within 10 min. Subsequently the mixture was stirred at −62 °C by using a cryostat for 144 h. Then aqueous NH_4Cl (15 mL) was added at −62 °C, and the mixture was warmed to ambient temperature. The aqueous phase was separated, diluted with water until a clear solution was formed, and extracted with Et_2O (4 × 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Chromatography (hexanes/EtOAC, 10:1) afforded a mixture of esters *E*-**6** and *Z*-**6** (394 mg, 89%) in a ratio of 98:2 (^{1}H NMR δ (CH=CH*CH*OSi) 4.15, δ (CHOCO) 5.38 (*E*-6); δ (CH=CH*CH*OSi) 3.95, δ (CHOCO) 5.42 (*Z*-6) as a colorless oil, ketone **7** (25 mg, 8%) and the phosphoryl acetate (1.06 g, 2.9 mmol). Preparative HPLC (Kromasil Si-100, 30 mm; *n*-hexane/EtOAc, 95:5; UV, 254 nm, RI) gave ester *E*-**6** (348 mg, 78%) with ≥99% de and ester *Z*-**6** (6 mg, 1%) as colorless oils.

E-**6**: $[\alpha]_D$ +17.6 (*c* 0.83, $CDCl_3$); R_f 0.84 (hexanes/EtOAc, 5:1); ^{1}H NMR (400 MHz, C_6D_6) δ 0.04 (s, 3 H, $SiCH_3$), 0.08 (s, 3 H, $SiCH_3$), 0.15 (s, 3 H, $SiCH_3$), 0.17 (s, 3 H, $SiCH_3$), 0.85−1.58 (m, 7 H), 0.97 (s, 9 H, $SiC(CH_3)_3$), 1.04 (s, 9 H, $SiC(CH_3)_3$), 1.12 (d, J = 6.6 Hz, 3 H, $CHCH_3$), 1.17 (s, 3 H, CCH_3), 1.38 (s, 3 H, CCH_3), 1.62 (t, J = 2.5 Hz, 3 H, C°CCH_3), 1.80−1.90 (m, 2 H), 2.00−2.45 (m, 10 H), 2.80−3.08 (m, 2 H), 3.70 (dt, J = 7.1, J = 8.5 Hz, 1 H, CHOSi), 4.14 (t, J = 6.0 Hz, 1 H, CH=CH*CH*OSi), 5.07 (dt, J = 4.4, J = 10.7 Hz, 1 H, CHOCO), 5.38 (m, 1 H, COCH=C), 5.50 (dd, J = 6.0, J = 15.7 Hz, 1 H, CH=*CH*-CHOSi), 5.58 (dd, J = 6.0, J = 15.7 Hz, 1 H, CH-*CH*=CH), 7.14−7.30 (m, 5 H, Ph); ^{13}C NMR (100 MHz, C_6D_6) δ −4.8 (d), −4.6 (d), −4.3 (d), −3.8 (d), 3.2 (d), 15.6 (d), 18.0 (u), 18.2 (u), 22.4 (u), 24.8 (u), 25.4 (d), 25.9 (d), 26.0 (d), 26.1 (u), 27.1 (u), 27.6 (d), 33.9 (u), 38.8 (d), 39.4 (u), 39.7 (u), 39.9 (u), 40.1 (d), 42.6 (u), 44.4 (d), 51.2 (d), 56.3 (d), 73.3 (d), 76.2 (d), 76.4 (u), 77.9 (u), 78.7 (d), 113.8 (d), 124.7 (d), 125.5 (d), 127.9 (d), 132.0 (d), 132.6 (d), 151.5 (u), 165.0 (u), 165.5 (u); IR ($CDCl_3$) ν 2933 (s), 2858 (s), 1706 (s), 1658 (m), 1466 (m), 1368 (m), 1253 (m), 1214 (m), 1124 (s), 1066 (m), 1032 (m), 910 (m), 839 (s) cm^{-1}; MS (CI, CH_4) *m*/*z* (relative intensity, %) 748 (3), 747 (M^+ + 1, 4), 746 (2), 689 (16), 615 (22), 531 (8), 489 (15), 416 (16), 415 (68), 397 (8), 283 (26), 201 (40), 119 (33), 105 (18), 101 (10), 85 (29), 83 (45); HRMS calcd for $C_{46}H_{74}O_4Si_2^+$ C_4H_9 689.442143, found 689.442163.

Z-**6**: R_f 0.84 (hexanes/EtOAc, 5:1); ^{1}H NMR (300 MHz, C_6D_6) δ 0.03 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$), 0.14 (s, 3 H, $SiCH_3$), 0.15 (s, 3 H, $SiCH_3$), 0.85−1.58 (m, 7 H), 0.98 (s, 9 H, $SiC(CH_3)_3$), 1.03 (s, 9 H, $SiC(CH_3)_3$), 1.13 (d, J = 6.6 Hz, 3 H, $CHCH_3$), 1.21 (s, 3 H, CCH_3), 1.42 (s, 3 H, CCH_3), 1.60 (t, J = 2.5 Hz, 3 H, C°CCH_3), 1.80−1.90 (m, 2 H), 2.00−2.45 (m, 10 H), 2.80−3.08 (m, 2 H), 3.64−3.74 (m, 1 H, CHOSi), 4.08 (t, J = 6.0 Hz, 1 H, CH=CH*CH*OSi), 5.02 (dt, J = 6.2, J = 10.4 Hz, 1 H, CHOCO), 5.43−5.54 (m, 3 H, COCH=C, CH=*CH*−CHOSi, CH−*CH*=CH), 7.15−7.27 (m, 5 H, Ph); ^{13}C NMR

(51) (a) Wakita, H.; Yoshiwara, H.; Nishiyama, H.; Nagase, H. *Heterocycles* **2000**, *53*, 1085−1110. (b) Kim, Y. H.; Lee, Y. S. 2004, WO 2004026224; *Chem. Abstr*. **2004**, *140*, 270668. (d) Melian, E.; Balmori, G.; Karen, L. *Drugs* **2002**, *62*, 107−133.

(75 MHz, C_6D_6) δ −4.7 (d), −4.4 (d), −4.2 (d), −3.6 (d), 3.4 (d), 15.8 (d), 18.2 (u), 18.4 (u), 22.5 (u), 25.0 (u), 26.1 (d), 26.2 (d), 26.3 (d), 27.0 (u), 27.3 (u), 27.6 (d), 34.1 (u), 36.3 (u), 37.5 (d), 40.3 (d), 40.4 (u), 42.1 (u), 43.5 (u), 47.0 (d), 51.6 (d), 57.2 (d), 73.8 (d), 76.4 (d), 76.6 (u), 78.3 (u), 79.2 (d), 113.9 (d), 125.2 (d), 126.0 (d), 128.2 (d), 132.6 (d), 132.7 (d), 151.7 (u), 165.5 (u), 166.7 (u).

(+)-*tert*-Butyl((*E*)-5-((3a*S*,4*R*,5*R*,6a*S*)-5-(*tert*-butyldimethylsilyloxy)-4-((3*S*,4*S*,*E*)-3-(*tert*-butyldimethylsilyloxy)-4-methyl-oct-1-en-6-ynyl)hexahydropentalen-2(1*H*)-ylidene))-pentyloxy)dimethylsilane (44). To a solution of *t*-$BuMe_2SiOCH_2CH_2CH_2I$ (780 mg, 2.60 mmol) in Et_2O (12 mL) was added *t*-BuLi (3.24 mL of 1.60 M in hexanes, 5.18 mmol) at −78 °C. After the mixture was stirred at this temperature for 0.5 h, it was transferred via a double-ended needle to a solution of CuI (246 mg, 1.29 mmol) in Et_2O (10 mL) and Et_2S (2 mL) at −78 °C. The mixture was stirred at −45 °C for 1 h whereby the color of the mixture changed from yellow to greenish-brown. Then a solution of acetate **43** (124 mg, 0.216 mmol) in Et_2O (2 mL) was added within 10 min at −45 °C. The reaction mixture was stirred at −45 °C for 3 h. Then a saturated aqueous NH_4Cl (5 mL) was added, and the mixture was warmed to ambient temperature. The aqueous phase was extracted with Et_2O (3 × 30 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (hexanes/EtOAc, 40:1) gave a mixture of alkene **44** and *t*-$BuMe_2SiO(CH_2)_6OSitBuMe_2$. Preparative HPLC (Kromasil Si-100, 30 mm, *n*-hexane/EtOAc, 98:2, RI) afforded alkene **44** (122 mg, 82%) as a colorless oil. $[\alpha]_D$ +27.8 (*c* 1.05, $CDCl_3$); R_f 0.29 (hexanes/ EtOAc, 50:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00−0.07 (m, 18 H, 3 × $Si(CH_3)_2$), 0.87 (s, 9 H, $SiC(CH_3)_3$), 0.89 (s, 9 H, $SiC(CH_3)_3$), 0.90 (s, 9 H, $SiC(CH_3)_3$), 0.91 (d, J = 6.9 Hz, 3 H, $CHCH_3$), 1.14−1.31 (m, 1 H), 1.31−1.45 (m, 2 H), 1.45−1.59 (m, 2 H), 1.59−1.76 (m, 1 H), 1.78 (t, J = 2.5 Hz, 3 H, $C{\equiv}CCH_3$), 1.88−2.13 (m, 7 H), 2.13−2.28 (m, 2 H), 2.28−2.45 (m, 3 H), 3.61 (t, J = 6.2 Hz, 2 H, CH_2OSi), 3.74 (dt, J = 6.9, J = 8.9 Hz, 1 H, CHOSi), 3.97 (t, J = 6.2 Hz, 1 H, CHOSi), 5.18−5.27 (m, 1 H, C=*CH*−CH_2OC=O), 5.39 (dd, J = 6.2, J = 15.8 Hz, 1 H, CH=*CH*−CHOSi), 5.52 (dd, J = 7.0, J = 15.8 Hz, 1 H, *CH*=CH−CHOSi); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.2 (d), −4.9 (d), −4.6 (d), −4.4 (d), −3.9 (d), 3.5 (d), 15.4 (d), 18.1 (u), 18.2 (u), 18.4 (u), 22.1 (u), 25.9 (d), 26.0 (d), 26.1 (u), 29.2 (u), 32.5 (u), 36.0 (u), 37.8 (d), 38.3 (u), 39.9 (d), 42.6 (u), 44.5 (d), 56.1 (d), 63.2 (u), 76.2 (u), 76.3 (d), 78.1 (u), 78.4 (d), 121.7 (d), 131.6 (d), 132.8 (d), 141.9 (u); IR ($CHCl_3$): ν 2933 (s), 2858 (s), 1667 (w), 1467 (m), 1384 (m), 1254 (s), 1107 (s), 1005 (w), 974 (w), 938 (w), 938 (w), 909 (w), 839 (s) cm^{-1}; MS (EI, 70 eV) *m*/*z* (relative intensity, %) 689 (3), 688 (M^+, 5), 633 (25), 632 (55), 631 (100), 609 (16), 608 (36), 607 (71), 557 (16), 556 (26), 500 (26), 499 (57), 476 (21), 475 (46), 450 (12), 449 (30), 425 (21), 367 (12), 293 (28), 251 (10), 225 (17), 211 (11), 185 (15), 183 (27), 172 (10), 171 (66), 159 (14), 147 (29), 145 (12), 133 (19), 115 (11), 105 (11), 91 (14); HRMS calcd for $C_{40}H_{76}O_3Si_3^+-C_4H_9$ 631.439808, found 631.439840.

(+)-(*E*)-5-((3a*S*,4*R*,5*R*,6a*S*)-5-(*tert*-Butyldimethylsilyloxy)-4-((3*S*,4*S*,*E*)-3-(*tert*-butyldimethylsilyloxy)-4-methyl-oct-1-en-6-ynyl)-hexahydropentalen-2(1*H*)-ylidene)-pentan-1-ol (45). To a solution of the silyl ether **44** (118 mg, 0.171 mmol) in hexanes (18 mL) was added neutral alumina (with 3% of H_2O, 70−230 mesh) (11 g). The mixture was stirred at ambient temperature for 24 h, then filtered, and the alumina washed with hexanes (20 mL) and the organic phase was discarded. Then the alumina was washed subsequently with EtOAc (6 × 20 mL) and MeOH (2 × 20 mL). The combined organic phases were concentrated in vacuo. Purification by column chromatography (hexanes/EtOAc, 9:1) afforded alcohol **45** (78 mg, 80%) as a colorless oil. $[\alpha]_D$ +31.5 (*c* 0.6, $CDCl_3$); R_f 0.20 (hexanes/EtOAc, 6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 3 H, $SiCH_3$), 0.03 (s, 3 H, $SiCH_3$), 0.03 (s, 3 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$), 0.87 (s, 9 H, $SiC(CH_3)_3$), 0.89 (s, 9 H, $SiC(CH_3)_3$), 0.91 (d, J = 6.9 Hz, 3 H, $CHCH_3$), 1.16−1.28 (m, 1 H), 1.35−1.46 (m, 2 H), 1.52 (bs, 1 H, OH), 1.53−1.72 (m, 3 H), 1.78 (t, J = 2.5 Hz, 3 H, $C{\equiv}CCH_3$), 1.90−2.11 (m, 7 H), 2.16−2.25 (m, 2 H), 2.30−2.42 (m, 3 H), 3.64 (t, J = 6.6 Hz, 2 H, CH_2OH), 3.75 (dt, J = 6.9, J = 9.1 Hz, 1 H, CHOSi), 3.97 (t, J = 6.3 Hz, 1 H, CHOSi), 5.18−5.26 (m, 1 H, C=*CH*−CH_2), 5.39 (dd, J = 6.6, J = 15.7 Hz, 1 H, CH=*CH*−CHOSi), 5.51 (dd, J = 7.1, J = 15.7 Hz, 1 H, *CH*=CH−CHOSi); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9 (d), −4.6 (d), −4.4 (d), −3.9 (d), 3.5 (d), 15.4 (d), 18.1 (u), 18.1 (u), 22.0 (u), 25.9 (d), 25.9 (u), 29.1 (u), 32.3 (u), 36.0 (u), 37.6 (d), 38.2 (u), 39.8 (d), 42.6 (u), 44.4 (d), 56.0 (d), 62.8 (u), 76.1 (d), 76.1 (u), 78.0 (u), 78.2 (d), 121.2 (d), 131.4 (d), 132.5 (d), 142.0 (u); IR ($CHCl_3$) ν 3375 (bw), 2931 (s), 2858 (s), 1667 (w), 1467 (m), 1382 (m), 1362 (m), 1254 (m), 1216 (m), 1107 (m), 1008 (m), 975 (m), 938 (w), 909 (w), 838 (s) cm^{-1}; MS (EI, 70 eV) *m*/*z* (relative intensity, %) 574 (M^+, 1), 517 (16), 494 (10), 493 (24), 386 (32), 385 (100), 362 (30), 361 (96), 335 (27), 311 (11), 310 (19), 293 (13), 229 (11), 197 (11), 187 (12), 185 (16), 183 (13), 171 (60), 159 (22), 157 (10), 147 (18), 145 (17), 133 (16), 131 (11), 119 (11), 109 (11), 107 (10), 105 (15), 91 (15), 81 (11); HRMS calcd for $C_{34}H_{62}O_3Si_2^+-C_4H_9$ 517.353328, found 517.353430.

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Supporting Information Available: Schemes S1−S4, Table S1, general information, experimental procedures and spectroscopic data for 16*S*-**2**, *Z*-16*S*-**2**, 16*S*-**3**, **5**, **7**, **8**, **17**, **18**, *rac*-**18**, **19**, *rac*-**19**, **23**, **26**, **27**, **30**, **31**, **32**, **34**, **35**, **36**, **37**, **38**, **40**, **43**, acetate of **45**, **51**, **52**, **53**, and copies of the NMR spectra of 16*S*-**2**, *Z*-16*S*-**2**, 16*S*-**3**, **5**, *E*-**6**, *Z*-**6**, **7**, **8**, **26**, **27**, **30**, **31**, **32**, **34**, **35**, **36**, **38**, **40**, **43**, **44**, **45**, **52**, and **53**. This material is available free of charge via the Internet at http://pubs.acs.org.

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