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Asymmetric Synthesis of the Highly Potent Anti-Metastatic Prostacyclin Analogue Cicaprost and Its Isomer Isocicaprost

Marco Lerm, Hans-Joachim Gais,* Kejun Cheng, and Cornelia Vermeeren

Contribution from the Institut für Organische Chemie der Rheinisch-Westfälischen Technischen Hochschule (RWTH) Aachen, Prof.-Pirlet-Str. 1, D-52056 Aachen, Germany

Received March 31, 2003; E-mail: Gais@RWTH-Aachen.de

Abstract: An asymmetric synthesis of the anti-metastatic prostacyclin analogue cicaprost and a formal one of its isomer isocicaprost by a new route are described. A key step of these syntheses is the coupling of a chiral bicyclic C6−C14 ethynyl building block with a chiral C15−C21 ω-side chain amide building block with formation of the C14−C15 bond of the target molecules. A highly stereoselective reduction of the thereby obtained C6−C21 intermediate carrying a carbonyl group at C15 of the side chain was accomplished by the chiral oxazaborolidine method. The chiral phosphono acetate method was used for the highly stereoselective attachment of the α-side chain to the bicyclic C6−C21 intermediate carrying a carbonyl group at C6. Asymmetric syntheses of the bicyclic C6−C14 ethynyl building blocks were carried out starting from achiral bicyclic C6−C12 ketones by using the chiral lithium amide method. In the course of these syntheses, a new method for the introduction of an ethynyl group at the α-position of the carbonyl group of a ketone with formation of the corresponding homopropargylic alcohol was devised. Its key steps are an aldol reaction of the corresponding silyl enol ether with chloral and the elimination of a trichlorocarbinol derivative with formation of the ethynyl group. In addition, a new aldehyde to terminal alkyne transformation has been realized. Its key steps are the conversion of an aldehyde to the corresponding 1-alkenyl dimethylaminosulfoxonium salt and the elimination of the latter with a strong base. Two basically different routes have been followed for the synthesis of the enantiomerically pure C15−C21 ω-side chain amide building block. The first is based on the chiral oxazolidinone method and features a highly stereoselective alkylation of (4*R*)-*N*-acetyl-4-benzyloxazolidin-2-one, and the second encompasses a malonate synthesis of the racemic amide and its efficient preparative scale resolution by HPLC on a chiral stationary phase containing column.

Introduction

Prostacyclin (**1**) (Figure 1), which was discovered in the vascular endothelium by Vane et al.,[1] is the most potent endogenous vasodilator that affects both the systemic and pulmonary circulation.[1−7] It prevents vascular smooth muscle proliferation and inhibits blood platelet adhesion and aggregation. Prostacyclin has been shown to interfere with steps of the metastatic cascade as for example tumor cell-blood interaction and tumor cell adhesion.[8,9] These features make prostacyclin an attractive drug for a therapy of solid tumor metastasis[9] and of cardiovascular diseases, in particular of peripheral vascular obstruction, major contributors to human morbidity and mortality.[10] However, its medicinal application is severely hampered by short chemical and metabolic half-lifes, which are mainly due to the facile hydration of its enol ether moiety and the rapid enzymatic modification of both side chains. Thus, intensive efforts have been made to find stable and potent analogues in a quest for drug candidates.[3,5,6] These investigations led to the finding of the carbacyclin derivative iloprost (**2**)[11,4] and of the prostacyclin derivative beraprost (**3**),[12] which are chemically stable and pharmacologically highly potent prostacyclin receptor agonists. Iloprost and beraprost have already been marketed as ilomedin and procycline, respectively, for the treatment of peripheral vascular diseases,[13,14] and both are being currently studied in clinical trails for the treatment of patients with primary pulmonary hypertension, an increasingly common and fatal disease.[15,16] Although beraprost and iloprost are orally active, their relatively short biological half-life and insufficient oral availability require frequent oral or invasive administration.[17]

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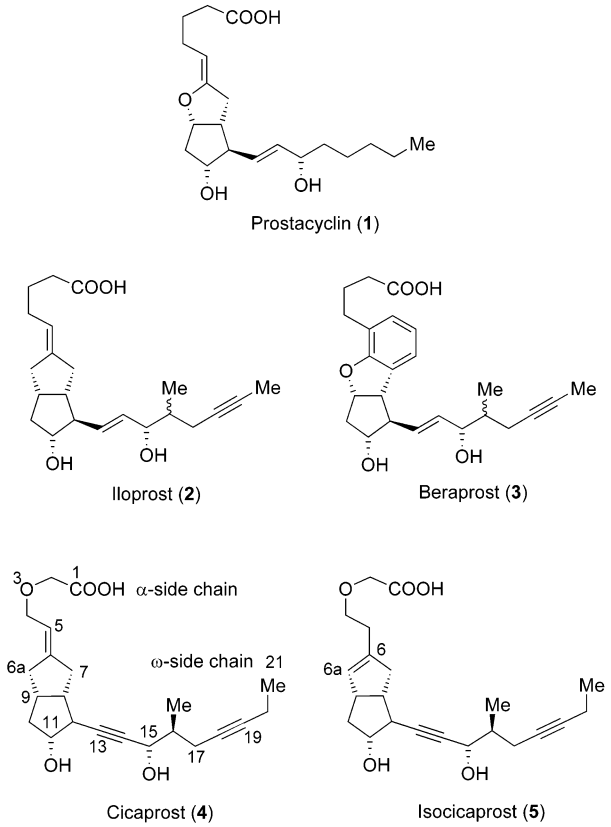

Figure 1. Prostacyclin and its analogues (prostacyclin numbering).

These deficiencies of both prostacyclin analogues led to the development of the carbacyclin derivative cicaprost (**4**).[18−22] Of all of the prostacyclin analogues known, cicaprost seems to hold the most promising prospects. It is not only the most potent and prostacyclin receptor selective analogue but also has a long lasting oral activity and a high oral availability.[23,24] The high oral activity and metabolic stability of cicaprost are due to the special structures of its side chains. The oxygen atom of the α-side chain prevents its degradation via β-oxidation and the two triple bonds in combination with the methyl group at C16 not only add to the metabolic stability of the molecule but also contribute to its high biological activity. These features make cicaprost an attractive candidate for example for the treatment of pulmonary hypertension at an acceptable dosing regimen. The most interesting feature of cicaprost, however, is its strong inhibitory effect in a series of spontaneously metastasizing rodent tumors upon oral administration.[25−28] It has been shown to interfere with several steps of metastasis including tumor cell-platelet interaction and the extravasation, adaptation and intravasation of tumor cells. Because cicaprost is also active on already established metastases as for example of tumors in an advanced stage of growth or those residing after surgery, it may be a candidate for an adjuvant therapy after tumor surgery.[29−31]

Intrigued by the exceptional potential medicinal prospects of cicaprost, we have been engaged in a program aimed at its asymmetric synthesis. Included was its isomer, the isocarbacyclin derivative isocicaprost (**5**),[32] which is expected to have a similar chemical and metabolic stability as cicaprost.[33] Preliminary biological studies showed isocicaprost to be a strong inhibitor of blood platelet aggregation.[32] Future tests will have to show whether isocicaprost exhibits similar anti-metastatic effects as cicaprost. Surprisingly, only a few studies have been conducted directed toward the asymmetric synthesis of cicaprost and isocicaprost. Skuballa et al. disclosed in 1986 in a communication the first asymmetric synthesis of cicaprost[18] and a second one was described by Shibasaki et al. in a full paper in 1988.[20] Finally, a synthesis of isocicaprost had been reported by Skuballa et al. in 1990 in the patent literature.[32] A key feature of the syntheses of cicaprost and isocicaprost is the coupling of a chiral bicyclic C4−C13(C6−C13) building block with a chiral C14−C21 ω-side chain building block with formation of a C4−C21(C6−C21) intermediate carrying a C13−C15 α-bromo-enone moiety.[34] After reduction of the carbonyl group of these intermediates, the C13−C14 triple bond was generated by elimination of HBr. Although these syntheses are imaginative and efficient, the methods applied for joining of the two building blocks with the stepwise generation of the C13−C14 triple bond seem to be not trivial. In addition, lengthy sequences are required for the attainment of the key bicyclic C4−C13(C6−C13) building blocks in enantiomerically pure form. Thus, we were seeking asymmetric syntheses of both cicaprost and isocicaprost by a new and more concise route, which would also allow an easy access to other ω-side chain modified derivatives. The later aspect is of particular importance because the biological activity of carbacyclin and isocarbacyclin derivatives is strongly dependent on the structure of the ω-side chain.[3,5] Herein, is presented a detailed account of the investigations which led to a fully stereocontrolled asymmetric synthesis of cicaprost and isocicaprost by a new and flexible strategy which also features a new method for the introduction of an ethynyl group at α-position of a carbonyl group and a new aldehyde to terminal alkyne transformation.

Results and Discussion

Retrosynthetic Analysis. A key feature of our retrosynthetic analysis of cicaprost is the coupling of a chiral bicyclic C6−

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(34) Because of clarity the prostacyclin numbering is used for cicaprost, isocicaprost and all building blocks througout this paper except in the experimental part where the numbering of the compounds follows the nomenclature rules.

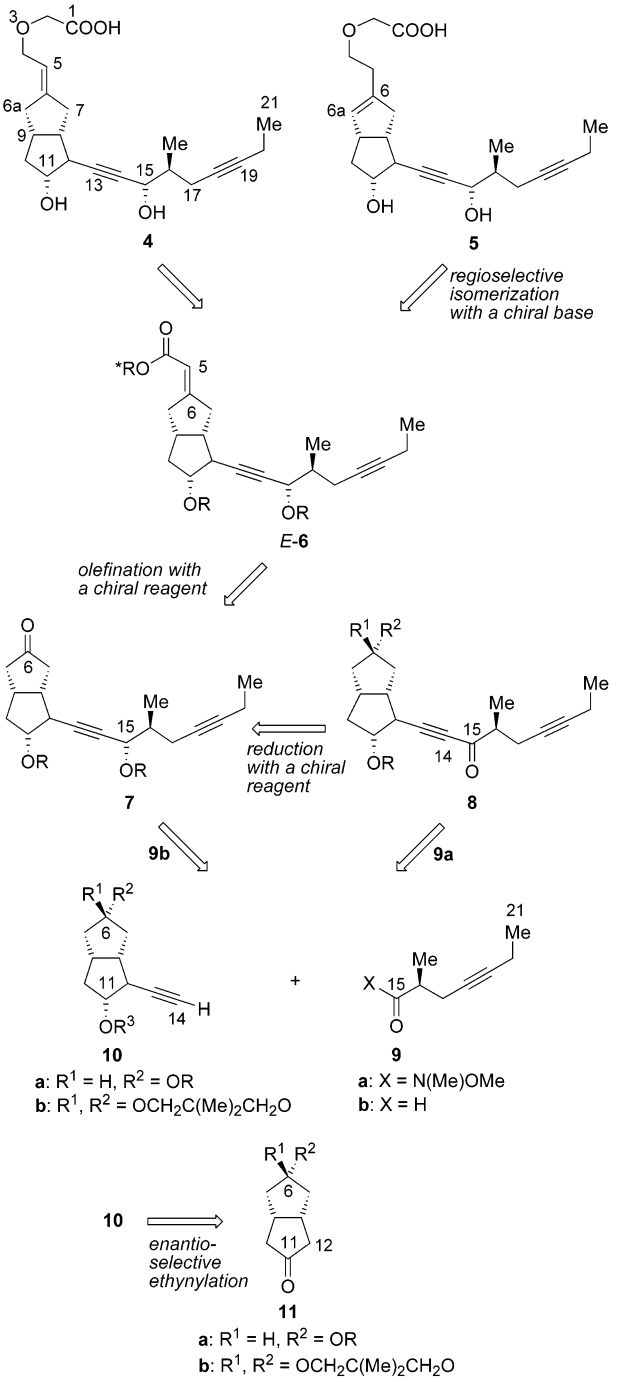

Figure 2. Retrosynthetic analysis of cicaprost and isocicaprost.

C14 building block carrying a C13−C14 ethynyl group with a chiral C15−C21 ω-side chain building block with formation of the C14−C15 bond of the target molecules (Figure 2). It was hoped that this strategy would not only allow an efficient joining of the two building blocks but also provide a high degree of flexibility in regard to the synthesis of derivatives with different ω-side chains. Thus, the retrosynthetic analysis identified the alkyne **10** as the bicyclic building block and the amide **9a**, or alternatively the aldehyde **9b**, as the ω-side chain building block. We selected achiral bicyclic ketones **11a** and **11b** as starting material for the synthesis of alkyne **10** because of their ready availability from *cis*-bicyclo[3.3.0]-octan-2,5-dione on large scale.[35−37] The two ketones, which carry different functionalities at C6 being equivalent to a carbonyl group, were chosen in order to provide synthetic flexibility in the crucial introduction of the ethynyl group (vide infra). The synthetic plan required an enantioselective ethynylation of ketone **11** at C12. We planned to use as key step for this transformation an enantioselective deprotonation of **11** with a chiral lithium amide with formation of the corresponding lithium enolate.[37−41] Because methods for the ethynylation of lithium enolates or enol ethers at the β-position are scarce,[42,43] and most likely only ill-suited in the present case, a new method would perhaps have to be developed. The lithium acetylide of alkyne **10** should be acylated[44,45] with amide **9a** with formation of ketone **8** which has to be stereoselectively reduced to give, after some functional group manipulations and the establishment of the carbonyl group at C6, the protected hydroxy ketone **7**. Alternatively, a stereoselective hydroxy alkylation of the lithium acetylide of **10** with aldehyde **9b** can be envisaged, which could give, after similar group manipulations, more directly **7**. Because the asymmetric induction provided by the substrates **8**, **9**, and **10** in these steps is expected to be low, a chiral reducing reagent[46−48] and a chiral auxiliary,[49] respectively, would have to be applied. A similar situation will be faced in the attachment of the α-side chain, which requires an *E*-stereoselective olefination of the carbonyl group of ketone **7**. Two different methods can be envisioned for the *E*-stereoselective generation of the C5−C6 double bond of the target molecule. The first would involve a diastereoselective olefination of ketone **7** with a chiral phosphono acetate with formation of ester *E*-**6**, a method previously developed in our and other laboratories for the stereoselective olefination of chiral and prochiral ketones of this type.[19,40,50,51] The second would include a diastereoselective conversion of ketone **7** by using a chiral lithiomethyl sulfoximine to give an *E*-configured alkenyl sulfoximine and the subsequent replacement of the sulfoximine group by a protected hydroxymethyl group through a nickel catalyzed cross-coupling reaction, a method which we have previously developed for the stereoselective olefination of ketones of this type.[52−55] Particularly appropriate, however,

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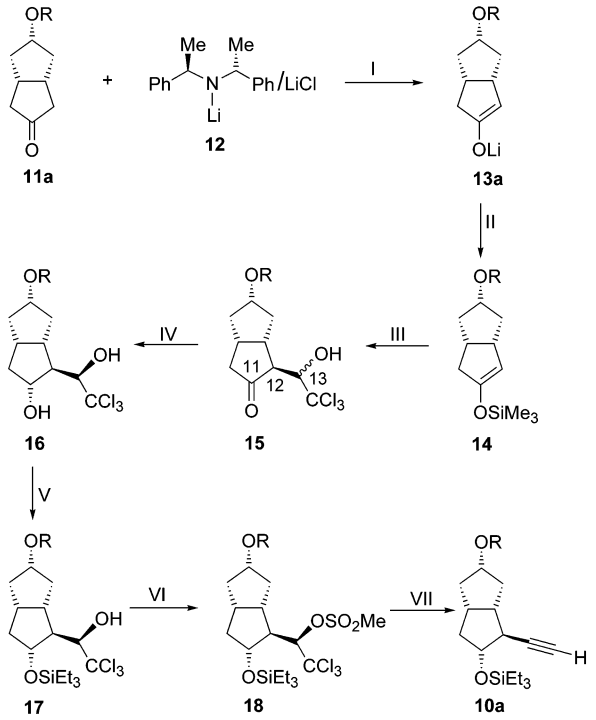
Scheme 1. Asymmetric Synthesis of the Bicyclic Alkyne **10a** (R = Si*t*-BuPh$_2$)[a]



[a] Reagents and conditions: (I) THF, −105 °C. (II) Me_3SiCl, −105 °C → −78 °C. (III) $TiCl_4$, CCl_3CHO, CH_2Cl_2, −78 °C. (IV) $NaBH_4$, EtOH, −45 °C. (V) Et_3SiCl, imidazole, DMF, rt. (VI) $MeSO_2Cl$, DABCO, THF, rt. (VII) *n*-BuLi, THF, −20 °C; H_2O.

for the development of a joint route to both cicaprost and isocicaprost would be the first method because a regioselective isomerization[33,37] of the bicyclic α,*β*-unsaturated ester *E*-**6** could also give, at a late stage of the synthesis, an ultimate precursor for the synthesis of isocicaprost.

Asymmetric Synthesis of the Bicyclic C6−C14 Ethynyl Building Block 10a. The enantioselective deprotonation of ketone **11a** with the LiCl containing chiral lithium amide **12**[56] and the treatment of the lithium enolate **13a** with $ClSiMe_3$ afforded the silyl enol ether **14** in 92% yield after column chromatography (Scheme 1).[37] Because **14** is slowly hydrolyzed on silica gel with formation of ketone **11a**, the chromatographic separation of **14** and the amine, derived from **12**, is carried out as rapidly as possible. The ee-value of **14**, determined indirectly at a later stage of the synthesis (vide infra), was 94%. According to the synthetic plan, an ethynylation of **14** at the *β*-position was now required. Surprisingly, only a few methods have been described for the ethynylation of lithium enolates or enol ethers in the literature, and these methods are apparently restricted to derivatives having no protons at the α- and the α'-position.[42,43] Thus, we have devised a new stepwise method which is based on the facile elimination of trichlorocarbinol derivatives with formation of alkynes.[57,58] Aldol reaction of the enol ether **14** with chloral in the presence of $TiCl_4$[59,60] gave ketone **15** with ≥ 98% de with respect to C12 and with 60% de with respect to C13. The configuration of **15** at C12 was determined by ^{1}H NMR spectroscopy at a later stage intermediate and that of C13 of the major diastereomer of **15** was tentatively assigned as depicted. Reduction of the major diastereomer of ketone **15** with $NaBH_4$ furnished the trichlorocarbinol **16** with ≥ 98% de with respect to C11 in 75% overall yield, based on **14**, after column chromatography. As hoped for, the formation of the C12−C13 bond and the reduction of the carbonyl group both had occurred with high diastereoselectivities. Silylation of diol **16** with Et_3SiCl selectively gave the silyl ether **17** in 79% yield together with 12% of the corresponding disilyl ether. A quantitative conversion of alcohol **17** to the mesylate **18** was achieved upon treatment with $MeSO_2Cl$ and DABCO in THF.[61] Interestingly, the use of NEt_3 as base and CH_2Cl_2 as solvent saw only an incomplete conversion of alcohol **17** to the mesylate. Elimination of mesylate **18** with 3.5 equiv of *n*-BuLi cleanly afforded alkyne **10a** in 90% yield after aqueous work-up. Alkyne **10a** had an ee-value 94%, which was determined indirectly at a later stage of the synthesis (vide infra). ^{1}H NMR spectroscopy of alkyne **10a** in combination with NOE experiments confirmed the configurations of C11 and C12. In particular, the observation of strong NOE's between 10-H*β* and 12-H*β* and between 11-Hα, 8-Hα and 9-Hα was instrumental in the assignment of the configuration (Figure 3).

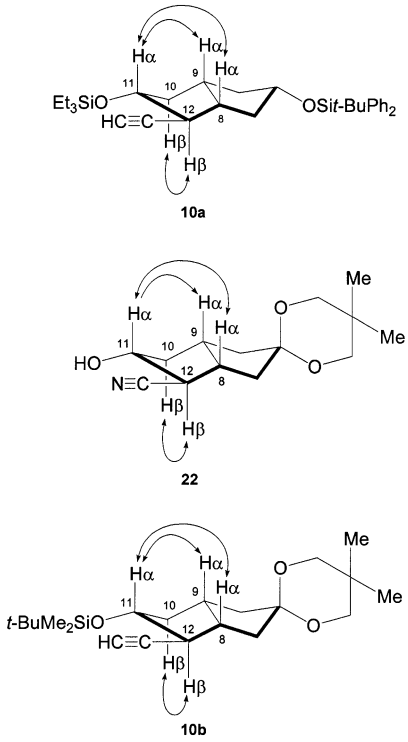


Figure 3. Selected NOEs of **10a**, **10b**, and **22**.

Asymmetric Synthesis of the Bicyclic C6−C14 Ethynyl Building Block 10b. Having developed an asymmetric synthesis of alkyne **10a** from ketone **11a**, we were interested in an asymmetric synthesis of alkyne **10b** from ketone **11b** (cf. Figure 2). In contrast to **10a**, the alkyne **10b** already contains a

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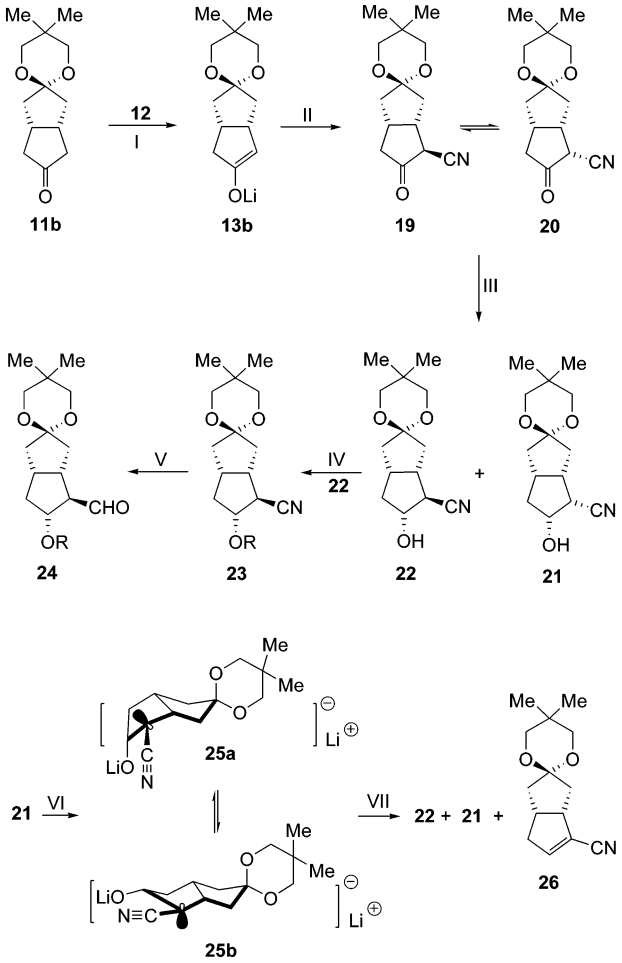
Scheme 2. Asymmetric Synthesis of the Bicyclic Aldehyde **24** (R = Si*t*-BuMe$_2$)[a]



[a] Reagents and conditions: (I) THF, −105 °C. (II) TsCN, THF, first −105 °C and then −78 °C. (III) $NaBH_4$, EtOH, −40 °C. (IV) *t*-BuMe_2SiCl, imidazole, DMF, rt. (V) DIBALH, toluene, −78 °C → rt; EtOH, H_2O. (VI) LDA, THF, first −105 °C and then −78 °C. (VII) Aqueous NaCl, −78 °C.

protected carbonyl group at C6, which is required for the attachment of the α-side chain at a later stage of the synthesis. The method used for the synthesis of alkyne **10a** from ketone **11a** is, however, not well-suited for the synthesis of **10b** from **11b**. It turned out that the acetal group of the silyl enol ether derived from **11b** is not compatible with $TiCl_4$,[37] required for its aldol reaction with chloral. Thus, we envisioned a synthesis of alkyne **10b** from ketone **11b** via the aldehyde **24** (Scheme 2). Aldehyde **24** is an important intermediate in the synthesis of cicaprost (**4**)[18] and iloprost (**2**)[4,11] by Skuballa et al. Although high-yielding syntheses of aldehyde **24** from ketone **11b** have been developed,[62−66] they all use a microbial kinetic resolution of an advanced racemic intermediate for its attainment in enantiomerically pure form. We felt that a perhaps more direct asymmetric synthesis of **24** could be developed on the basis of the enantioselective deprotonation methodology through a cyanation of the lithium enolate derived from ketone **11b** in

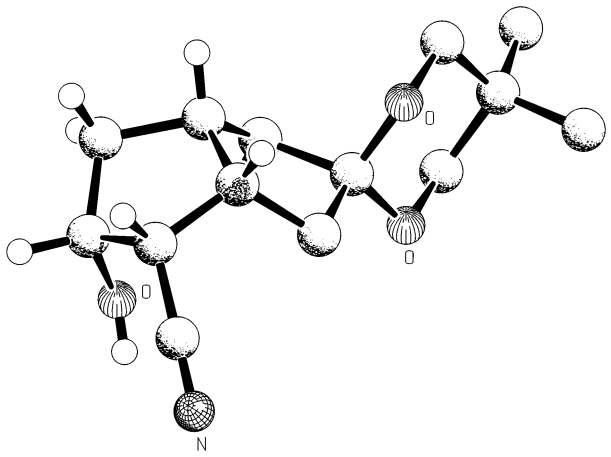


Figure 4. Structure of nitrile **21** in the crystal.

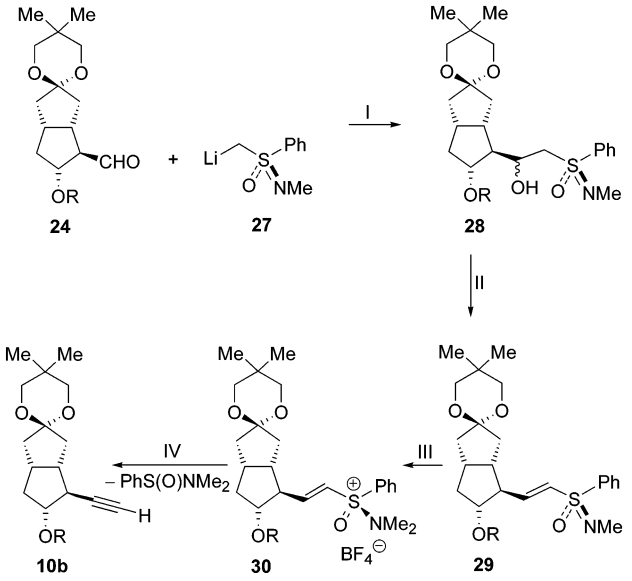
combination with a selective reduction of the cyano group to the aldehyde group at a later stage. Therefore, ketone **11b** was enantioselectively deprotonated with the LiCl containing lithium amide **12** and the lithium enolate **13b**[37] was cyanated through treatment with 2 equiv of TsCN[67] in THF. Crucial to the success of the transformation was the addition of **13b** to the solution of the cyanating reagent. The thereby formed α-cyano ketones **19** and **20** were not isolated[68] but reduced directly with $NaBH_4$ to furnish after chromatography a mixture of the hydroxy nitriles **22** and **21** in a ratio of 3.6:1 in 95% yield. Separation of the nitriles by column chromatography or, more efficiently, by preparative HPLC afforded nitrile **22** in 69% yield and nitrile **21** in 19% yield. According to GC analysis, the nitrile **22** had an ee-value of 92%. Hence, nitrile **21** must have also had an ee-value of 92%. Although the structure of nitrile **21** was determined by X-ray crystal structure analysis (Figure 4), the configuration of the isomeric nitrile **22** was revealed by NOE experiments. The assignment of the configuration of **22** rests on the observation of strong NOE's between 10-Hβ and 12-Hβ and between 11-Hα, 8-Hα, and 9-Hα (cf Figure 3).

In concluding the synthesis of aldehyde **24**, the alcohol **22** (92% ee) was silylated, which gave the silyl ether **23** in 98% yield. Reduction of nitrile **23** (92% ee) with DIBALH[69,70] in toluene or hexane afforded aldehyde **24** with 92% ee in 85% yield after column chromatography.

To make the synthesis of aldehyde **24** from nitrile **22** more efficient, a recycling of the unwanted epimeric nitrile **21** was attempted. We envisioned a double deprotonation of **21** with formation of the dianion **25b**, followed by a protonation. It was speculated that the dianion **25a** formed first from **21** would isomerize to the diastereomeric dianion **25b** and that its protonation would preferentially lead to **22**. The structure of doubly lithiated β-hydroxy nitriles is not known. However, given the large contribution of the polar inductive-field effect to the stabilization of a negative charge by the cyano group,[71,72] it seems not unreasonable to assume that the anionic C-atoms of **25a** and **25b**[73] are pyramidalized and endowed with a low barrier

(62) Skuballa, W.; Dahl, H. German patent DE 3638757 A1 1988; *Chem. Abstr.* **1989**, *110*, 7940.
(63) Dahl, H. German Patent DE 3816801 A1 1989; *Chem. Abstr.* **1990**, *113*, 23 512.
(64) Harre, M.; Westermann, J. German Patent DE 3835162 A1 1990; *Chem. Abstr.* **1990**, *113*, 31889.
(65) Petzold, K.; Dahl, H.; Skuballa, W.; Gottwald, M. *Liebigs Ann.* **1990**, 1087.
(66) Mori, K.; Tsuji, M. *Tetrahedron* **1986**, *42*, 435.
(67) Kahne, D.; Collum, D. B. *Tetrahedron Lett.* **1981**, *22*, 5011.
(68) NMR spectroscopy of a crude mixture of **19** and **20** indicated the presence of the corresponding enol as a third equilibrium component.
(69) For a review, see: Winterfeldt, E. *Synthesis* **1975**, 617.
(70) Hayashi, M.; Yoshiga, T.; Oguni, N. *Synlett* **1991**, 479.
(71) For a review, see: Bradamante, S.; Pagani, G. A. *Adv. Carbanion Chem.* **1996**, *2*, 189.
(72) For a review, see: Boche, G. *Angew. Chem.* **1989**, *101*, 286; Boche, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 277.

Scheme 3. Synthesis of the Bicyclic Alkyne **10b** from Aldehyde **24** and Sulfoximine **27** (R = Si*t*-BuMe$_2$)[a]

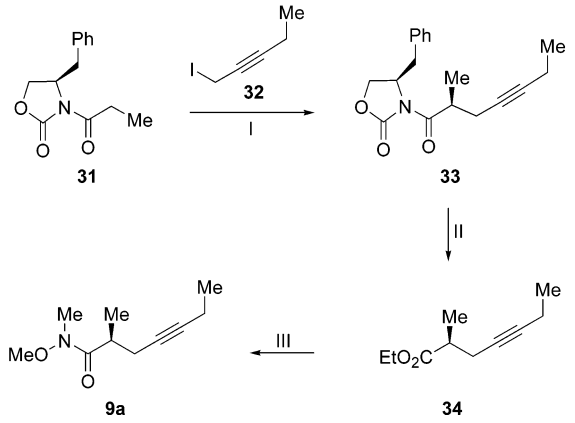


[a] Reagents and conditions: (I) THF, −78 °C → rt. (II) *n*-BuLi, $MeSO_2Cl$, Et_3N; DBU, −78 °C → rt. (III) Me_3OBF_4, CH_2Cl_2, rt. (IV) LiN(H)*t*-Bu, THF, −78 °C.

toward inversion.[72,74] To this end, nitrile **21** was treated with 2.8 equiv of LDA followed by a protonation of dianion **25** with H_2O. This delivered a mixture of nitriles **22** and **21** in a ratio of 1:1 in 90% yield. HPLC of the mixture of both nitriles afforded nitrile **22** in 37% yield and nitrile **21** in 36% yield. GC analysis showed the nitrile **22** to have an ee-value of ≥99% ee. The sample of the nitrile **21** used in the recycling experiment had been recrystallized (90% recovery) prior to its use. This measure obviously raised its ee-value to ≥ 99%. Therefore, the nitrile **21** obtained in the epimerization experiment also was of ≥ 99% ee. Under the conditions used, the dianion **25** was sufficiently stable and its elimination with formation of the unsaturated nitrile **26** (5%) could largely be suppressed. The use of other reagents for the protonation of **25** as for example methyl salicylate and MeOH saw no change of the ratio of the hydroxy nitriles.

A mild method was now required for the conversion of the aldehyde **24** to the alkyne **10b** (Scheme 3), because of its propensity for β-elimination. Although the successive treatment of aldehyde **24** with CBr_4/PPh_3 and *n*-BuLi[75] gave alkyne **10b** in only 30% yield, that with $[Ph_3PCHBr_2]Br$/KO-*t*Bu[76] furnished the alkyne in 90% yield. However, the presence of large amounts of phosphorus compounds rendered the isolation and purification of **10b** difficult. Because of our failure to achieve the desired aldehyde-alkyne conversion by other reagents including lithiotrimethylsilyldiazomethane,[77] a new sulfoximine based conversion was investigated. We have recently described a facile elimination of 1-alkenyl aminosulfoxonium salts with formation of alkynes, which presumably proceeds via formation of alkylidenecarbenes.[78] It was tempting to see whether this elimination could be used as a key step of an alternative synthesis of alkyne **10b** from aldehyde **24**. Synthesis of the alkenyl sulfoximine **29** from aldehyde **24** require an addition of a lithiomethylsulfoximine to the aldehyde followed by an elimination.[79] To this end, aldehyde **24** was treated with the lithiomethylsulfoximine **27**, which gave alcohol **28** as a mixture of diastereomers in essentially quantitative yield. As anticipated, no β-elimination of **24** was observed. Mesylation of alcohol **28** with $MeSO_2Cl$ and NEt_3 and the subsequent in situ elimination of the corresponding mesylate with DBU furnished the *E*-configured alkenyl sulfoximine **29** in 95% yield. Methylation of sulfoximine **29** with Me_3OBF_4 afforded the dimethylaminosulfoxonium salt **30** in essentially quantitative yield. Finally, elimination of salt **30** with LiN(H)*t*-Bu gave alkyne **10b** in 89% overall yield, based on **29**. $PhS(O)NMe_2$, H_2N*t*-Bu and $LiBF_4$ were also formed, which could easily be separated. For the synthesis of **29**, the enantiomerically pure sulfoximine **27**[80] was used to avoid the formation of a mixture of diastereomers of **29**, which might have complicated its NMR spectroscopic analysis. Although it has not been investigated, the conversion of **24** into alkyne **10b** should also be possible by using *rac*-**27**. According to GC analysis, alkyne **10b** had an ee-value of 92%. The configurations of C11 and C12 of alkyne **10b** were determined by ^{1}H NMR spectroscopy in combination with NOE experiments. Instrumental for the assignment of the configurations were the observation of strong NOEs between 10-Hβ and 12-Hβ, and between 11-Hα, 8-Hα and 9-Hα (cf Figure 3).

Scheme 4. Asymmetric Synthesis of the ω-Side Chain Building Block **9a**[a]



[a] Reagents and conditions: (I) (a) **31**, $NaN(SiMe_3)_2$, THF, −78 °C; (b) **32**, −78 °C. (II) EtOH; $Ti(OEt)_4$, reflux. (III) (a) $[Me(OMe)NH_2]Cl$, *i*-PrMgCl, THF; (b) **34**, −19 °C; (c) HPLC.

Synthesis of the C15−C21 Amide Building Block. Asymmetric Synthesis. With the synthesis of the two key bicyclic building blocks accomplished, we opted for the acylation−reduction route for the synthesis of the alcohol **7** (cf. Figure 2). This route requires the enantiomerically pure amide **9a** as the ω-side chain building block. A precursor for amide **9a** is the ester **34**[48] (Scheme 4) which had been synthesized previously by the following routes: (1) from methyl (*S*)-3-hydroxy-2-methyl propionate and 1-bromobutyne,[48] (2) through pent-2-

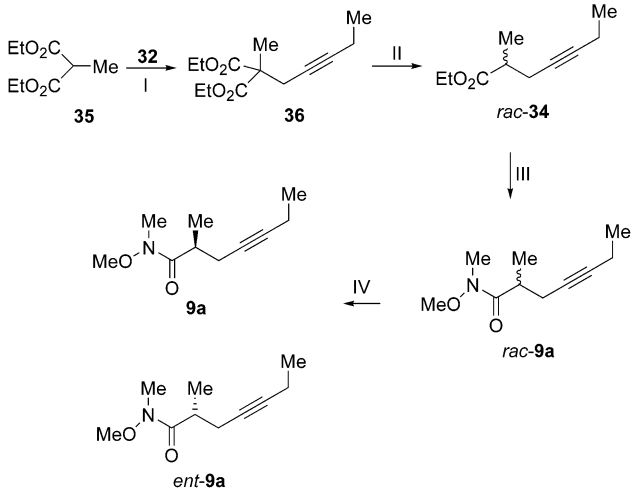
(73) For a recent computational study of the position of metalation of lithiated nitriles, see: Carlier, P. R.; Madura, J. D. *J. Org. Chem.* **2002**, *67*, 3832.
(74) Boehme, W. R.; Schipper, E.; Scharpf, W. G.; Nichols, J. *J. Am. Chem. Soc.* **1958**, *80*, 5488.
(75) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.
(76) Michel, P.; Rassat, A. *Tetrahedron Lett.* **1999**, *40*, 8575.
(77) (a) Ohira, S.; Okai, K.; Moritani, T. *J. Chem. Soc., Chem. Commun.* **1992**, 721. (b) Conversion of **24** to **10b** with dimethyl (diazomethy)phosphonate (Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521) was not studied.
(78) Gais, H.-J.; Reddy, L. R.; Woo, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 10 427.
(79) Gais, H.-J.; Hainz, R.; Müller, H.; Bruns, P. R.; Giesen, N.; Raabe, G.; Runsink, J.; Nienstedt, S.; Decker, J.; Schleusner, M.; Hachtel, J.; Loo, R.; Woo, C.-W.; Das, P. *Eur. J. Org. Chem.* **2000**, 3973.
(80) Gais, H.-J.; Brandt, J. *Tetrahedron: Asymmetry* **1997**, *8*, 909.

ynylation of a chiral iron acetyl complex[81] and of (4*R*,5*S*)-*N*-acetyl-4-methyl-5-phenyl-oxazolidin-2-one,[21] and (3) by resolution.[18] These routes, however, are not very practical either because of nontrivial steps, moderate yields and selectivities or lengthy sequences. Nevertheless, the oxazolidinone route seemed to hold the most prospects for the development of a more efficient synthesis of **34**. The benzyl substituted oxazolidinone **31**[82a] was selected in anticipation[82b] of a higher selectivity and yield. Deprotonation of oxazolidinone **31** with $NaN(SiMe_3)_2$ and treatment of the resulting sodium enolate with iodide **32**, prepared from commercially available 2-pentyne-1-ol,[21] gave the substituted oxazolidinone **33** with 97% de in 93% yield. Thus, pent-2-ynylation of **31** proceeded much more efficiently than that of *N*-acetyl-4-methyl-5-phenyl-oxazolidin-2-one, which proceeded with only 80% de and 62% yield.[21] At this stage of the synthesis of the **9a**, the 1.5% of the unwanted diastereoisomer of **33** could neither be separated by HPLC nor by crystallization. Treatment of oxazolidinone **33** with $Ti(OEt)_4$ in refluxing EtOH gave ester **34** with 97% ee (GC) in 81% yield. Finally, amidation of ester **34** with MeO(Me)NMgCl, prepared in situ from $[MeO(Me)NH_2]Cl$ and 2 equiv of *i*-PrMgCl in THF,[83,84] afforded amide **9a** in 92% yield. HPLC analysis showed the amide to have an ee-value of 97%. Preparative HPLC of amide **9a** (10 g) with 97% ee on a Daicel Chiralcel AD column (250 × 50 mm) allowed the ready separation of *ent*-**9a** (900 mg of **9a** per injection) and furnished amide **9a** with ≥ 99% ee in 90% yield.

Symmetric Synthesis and Chromatographic Resolution. Although amide **9a** could be efficiently synthesized from oxazolidinone **31** and iodide **32**, all three steps required carefully defined reaction conditions to achieve a high diastereoselectivity and to avoid a partial racemization. The facile preparative scale separation of **9a** and *ent*-**9a** by HPLC on a chiral stationary phase containing column led us to consider, as an alternative, the attainment of **9a** through synthesis of the racemic amide *rac*-**9a** and its chromatographic resolution. The racemic ester *rac*-**34** was efficiently prepared by malonate synthesis (Scheme 5).[85] Thus, deprotonation of malonate **35** with 1.05 equiv of LDA and treatment of the resulting lithium enolate with iodide **32** (1.3 equiv) afforded the substituted malonate **36** in 91% yield. Deethoxycarbonylation[86] of malonate **36** with LiCl in DMSO and water furnished the racemic ester *rac*-**34** in 75% yield. Finally, amidation of *rac*-**34** with MeO(Me)NMgCl gave amide *rac*-**9a** in 92% yield. The separation of *rac*-**9a** on a 4.2 g scale by HPLC on a Daicel Chiralcel AD column (250 × 50 mm) readily (750 mg of *rac*-**9a** per injection) afforded **9a** with ≥ 99% ee in 47% yield and *ent*-**9a** with ≥ 99% ee in 47% yield. Interestingly, a HPLC separation of ester *rac*-**34** by using this chiral stationary phase failed.

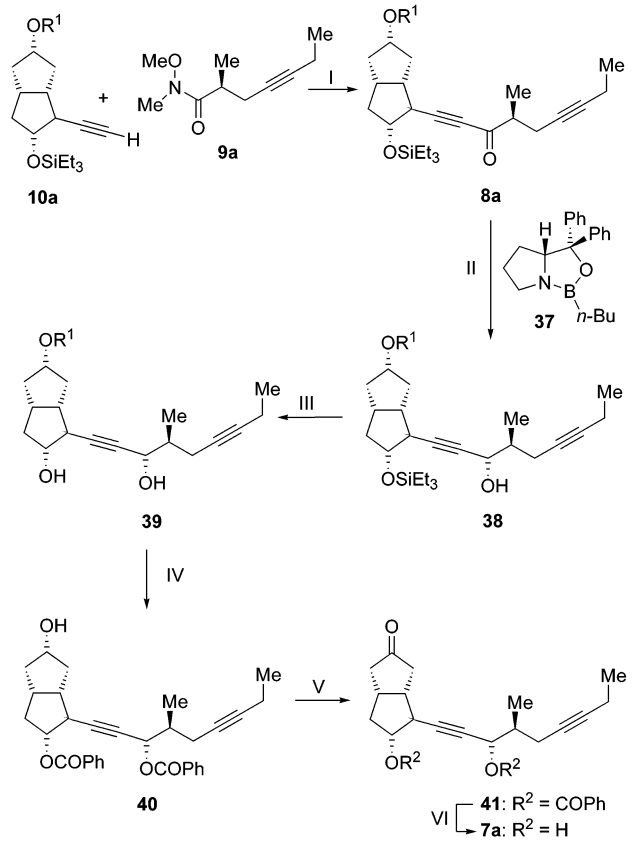
Synthesis of the C6−C21 Ketone Intermediate. Coupling of the C6−C14 Alkyne 10a With the C15−C21 Amide. With the building blocks **9a**, **10a**, and **10b** in hand, their coupling was required next. Special attention had to be paid to the potential configurational lability of C16 of ketone **8a** (cf. Figure 2) in the presence of a base. Coupling[44] of the alkyne **10a** with the amide **9a** was thus carried out as follows (Scheme 6). Alkyne **10a** in THF was treated at −78°C with 1 equiv of *n*-BuLi in hexane and the solution was warmed to room temperature to ensure a complete deprotonation of the alkyne. The solution

Scheme 5. Synthesis of Amide **9a** through Malonate Synthesis of the Racemate and Resolution[a]



[a] Reagents and conditions: (I) (a) LDA, THF, −78 °C; (b) **32**. (II) LiCl, DMSO, H_2O, reflux. (III) $[Me(OMe)NH_2]Cl$, *i*-PrMgCl, THF −19 °C. (IV) HPLC.

Scheme 6. Coupling of the Bicyclic Building Block **10a** with the ω-Side Chain Building Block **9a** (R^1 = Si*t*-BuPh$_2$)[a]



[a] Reagents and conditions: (I) (a) **10a**, *n*-BuLi, THF, −78 °C → 0 °C; (b) **9a**, −19 °C. (II) Catecholborane, **37**, CH_2Cl_2, −78 °C. (III) Aqueous HCl, THF, rt. (IV) (a) PhCOCl, pyridine, 0 °C → rt; (b) NBu_4F, THF, rt. (V) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −60 °C. (VI) NaOH, MeOH, rt.

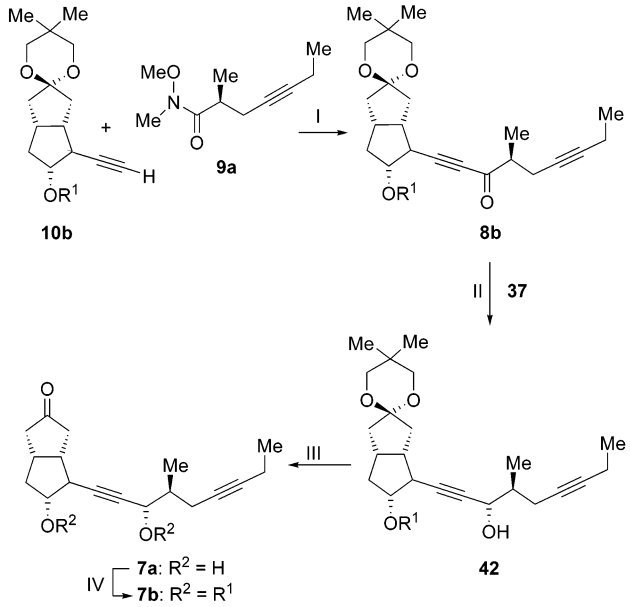
(81) Bodwell, G. J.; Davies, S. G. *Tetrahedron: Asymmetry* **1991**, *2*, 1075.
(82) (a) Evans, D. A.; DiMare, M. *J. Am. Chem. Soc.* **1986**, *108*, 2476. (b) Evans, D. A.; Ennis, M. D.; Mahtre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
(83) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989.
(84) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U. H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461.
(85) The malonate synthesis of the racemic acid was cursory described in a footnote of ref 18.
(86) Krapcho, A. P.; Gadamasetti, G. *J. Org. Chem.* **1987**, *52*, 1880.

was then cooled to −78°C and transferred via cannula to a −19 °C cold solution of 1.15 equiv of amide **9a** with ≥ 99% ee in THF. Quenching of the reaction mixture after 2 h with aqueous NH_4Cl and purification by chromatography furnished ketone **8a** in 92% yield. Alkyne **10a** was recovered in 8% yield. Under these conditions formation of the C16 epimer of **8a** could be completely avoided.

It was to be expected that a highly diastereoselective reduction of ketone **8a** with an achiral reducing reagent with formation of the (*S*)-configured alcohol **38** would be difficult to achieve (vide infra). Thus, a chiral reducing reagent had to be applied and we selected the oxazaborolidine-catalyzed reduction with a borane.[46,47] This method had already been successfully employed for a highly diastereoselective reduction of a structurally related ketone carrying a bulky silyl group instead of the bicyclooctanyl group.[47] Because it has been reported that the enantioselectivity of oxazaborolidine-catalyzed reduction of ketones with boranes can critically be dependent on the purity of the catalyst, the pure oxazaborolidine **37** was prepared from *n*-butylboroxine and 1 equiv of (*R*)-α,α-diphenyl-2-pyrrolidinemethanol in refluxing C_6D_6.[87] The reduction of ketone **8a** was carried out through addition of catecholborane to a mixture of the ketone and 20 to 30 mol % of **37** in CH_2Cl_2 at −78 °C. Thereby, the alcohol **38** could be reproducibly isolated with ≥ 99% de in regard to C15 in 88% yield after column chromatography. The selectivity of the reduction was determined by ^{1}H NMR spectroscopy. For comparison purposes a 1:1 mixture of **38** and its 15*R*-diastereomer was prepared through reduction of ketone **8a** with $NaBH_4$ in EtOH at −40 °C. The use of wet EtOH as a quenching reagent in the reduction of ketone **8a** produced a partial desilylation of the silyl ether **38** with formation of diol **39** in 77% yield and **38** in 18% yield. Desilylation of the disilyl ether **38** with diluted aqueous HCl in THF also selectively afforded diol **39**. Diol **39** was isolated in 93% overall yield based on **8a**. To establish a carbonyl group at C6 of **39** the diol was dibenzoylated and the corresponding dibenzoate was deprotected at the silyloxy group through treatment with NBu_4F, which gave the alcohol **40** in 86% overall yield, based on **38**. Oxidation of alcohol **40** with DMSO, $(COCl)_2$ and NEt_3[88] afforded ketone **41** in 89% yield. Finally, hydrolysis of dibenzoate **41** with 1 N NaOH in MeOH furnished the dihydroxy ketone **7a**[18] in 90% yield. ^{1}H NMR spectroscopy of **8a**, **40**, and **41** revealed the admixture of approximately 3% of the respective diastereomers, having the opposite configurations at C6, C8, C9, C11, and C12 (Supporting Information, Scheme S10), which are derived from *ent*-**10a**. This result shows that the starting alkyne **10a** had an ee-value of 94%. An unequivocal ^{1}H NMR spectroscopic assignment of the minor diastereomer of ketone **8a** and thus of the minor diastereomers of **38**, **39**, **40**, **41**, and **7a** was made possible by the synthesis of the enantiomer of the minor diastereomer of **8a** through coupling of alkyne **10a** of 94% ee with the enantiomeric amide *ent*-**9a** of ≥ 99% ee (Supporting Information, Scheme S11).

Coupling of the C6−C14 Alkyne 10b With the C15−C21 Amide. In keeping with the strategy outlined in Figure 2, we wanted to evaluate whether the acetal protected alkyne **10b** could serve as the starting material for a more concise synthesis of diol **7a** (Scheme 7). To this end, the two building blocks **9a** and **10b** were coupled by following the same procedure used in the synthesis of ketone **8a**. Thus, the lithium acetylide derived from **10b** with 92% ee was treated with 1.15 equiv of amide **9a** (≥ 99% ee) in THF at −19 °C, and the reaction mixture was quenched with aqueous NH_4Cl at this temperature. Thereby, ketone **8b** was obtained in 92% yield after chromatography. As in the case of the synthesis of ketone **8a**, the reaction temperature had to be kept at −19 °C to avoid a partial epimerization at C16 and, at the same time, to provide for a sufficiently high reaction rate. According to ^{1}H NMR spectroscopy at higher temperatures the coupling step was accompanied by a partial epimerization at C16.

Scheme 7. Coupling of the Bicyclic Building Block **10b** with the ω-Side Chain Building Block **9a** (R^1 = Si*t*-BuMe_2)[a]



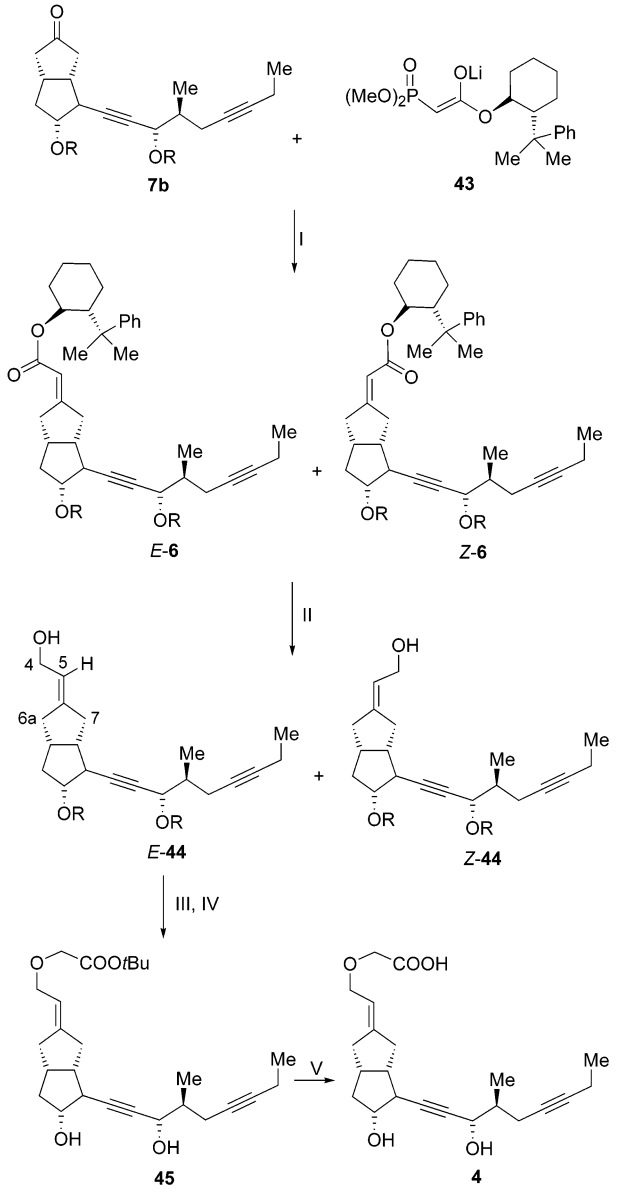
[a] Reagents and conditions: (I) (a) **10b**, *n*-BuLi, THF, −78 °C → rt; (b) **9a**, THF, −19 °C. (II) Catecholborane, **37**, CH_2Cl_2, −78 °C, HPLC. (III) Acetone, TsOH, H_2O, rt. (IV) *t*-BuMe_2SiCl, imidazole, DMF, rt.

The reduction of ketone **8b** with catecholborane in the presence of 9 mol % of **37** in toluene or CH_2Cl_2 at −78 °C gave alcohol **42** with 95% de in regard to C15 in 98% yield. Alcohol **42** contained 2.5% of its 15*R*-diastereomer and 4% of the diastereomer having the opposite configurations at C8, C9, C11, and C12 (Supporting Information, Scheme S12), which arose from the use of alkyne **10b** with 92% ee as starting material. All three diastereomers were readily detected by ^{1}H NMR spectroscopy. Preparative HPLC of **42** at a 5 g scale on a Daicel Chiralcel OD column (250 × 20 mm) allowed for the ready separation of the two minor diastereomers and gave alcohol **42** as a single diastereomer (≥ 99% de) in 90% yield. Treatment of acetal **42** with TsOH in acetone resulted in a cleavage of all three protecting groups and afforded the dihydroxy ketone **7a** which upon silylation with *t*-BuMe_2SiCl furnished the disilyl ether **7b**[18] in 95% overall yield, based on **42**.

Assignment of the Configuration at C15. Crucial to the synthesis of cicaprost and isocicaprost was the determination of the configuration of the alcohols **38** and **42**. NMR spectroscopy had revealed the identity of ketone **7a** obtained by the

(87) (a) 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. (b) Jones; T. K.; 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.
(88) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

Scheme 8. Attachment of the α-Side Chain to Ketone **7b** via Reaction with the Chiral Phosphate **43** (R = Si*t*-BuMe$_2$)[a]



[a] Reagents and conditions: (I) THF, first 6 d, at −62 °C then 15 h at −30 °C and finally 30 min at room temperature. (II) DIBALH, THF, 0 °C, HPLC. (III) NBu_4HSO_4, 50%, NaOH, $BrCH_2COOtBu$, CH_2Cl_2, rt. (IV) NBu_4F, THF, rt. (V) NaOH, MeOH, rt.

two different routes depicted in Schemes 6 and 7. Alcohols **38** and **42** were assigned the 15*S*-configuration in agreement with the reduction of similar ynones with catecholborane/**37** and on the basis of its NMR data in comparison with those of a reference sample.[46−48]

Attachment of the α-Side Chain and Completion of the Synthesis of Cicaprost. Continuation of the synthetic plan called for a diastereoselective conversion of ketone **7b** to the *E*-configured α,*β*-unsaturated ester *E*-**6** (Scheme 8). Although ketone **7b** is chiral, the asymmetric induction it provides in diastereoselective olefination reactions with achiral phosphono acetates is low. Thus, the situation encountered in the olefination of **7b** may be compared to that of the enantioselective olefination of the achiral ketones **11a** and **11b**. We and others had previously introduced the dimethylphosphono acetates derived from 8-phenylmenthol, 8-phenylneomenthol, and 8-phenylnormenthol to solve stereoselectivity problems of this type.[18,37,50,51] We selected for the present case the dimethylphosphono acetate derived from (1*S*,2*R*)-8-phenylnormenthol because of the ready availability of this alcohol in enantiomerically pure form.[89] Treatment of ketone **7b** (≥ 99% de) with 4.5 equiv of the lithium salt **43**[37] in THF first at −62 °C for 6 d, then at −30 °C for 15 h, and finally at room temperature for 30 min gave a mixture of the diastereomeric esters *E*-**6** and *Z*-**6** in a ratio of 95:5 in 99% yield after aqueous work up and column chromatography. Although the *E*- and *Z*-configured esters could be readily separated by preparative HPLC (vide infra), the mixture of the esters *E*-**6** and *Z*-**6** was reduced with DIBALH in THF to give a 95:5 mixture of the allylic alcohols *E*-**44** and *Z*-**44**.[18] Separation of the allylic alcohols by column chromatography or, more efficiently, by preparative HPLC afforded the allylic alcohol *E*-**44** in 84% total yield, based on *E*-**6**. 8-Phenylnormenthol was recovered in 86% yield. It is important to note that during the separation of the allylic alcohols the minor diastereomeric allylic alcohols resulting from the use of the alkynes **10a** and **10b** with only 92% ee and 94% ee, respectively, were also separated (Supporting Information, Scheme S13). The *E*-configuration of the double bond of *E*-**44** 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 cicaprost was completed following the route previously described.[18,20,37] Thus, etherification of alcohol *E*-**44** (≥ 99% de) through treatment with excess $BrCH_2COOt$-Bu under phase transfer conditions in the presence of 50% aqueous NaOH and the subsequent desilylation of the corresponding disilyl ether with Bu_4NF gave the dihydroxy ester **45** in 91% total yield, based on *E*-**44**. Finally, the hydrolysis of ester **45** with NaOH in MeOH furnished cicaprost (**4**) with ≥ 99% de and ≥ 99% ee in 94% yield.

Formal Asymmetric Synthesis of Isocicaprost. The synthetic plan also called for a synthesis of isocicaprost (**5**) from ester *E*-**6** (Scheme 9). This first required a regioselective shift of the double bond of *E*-**6** with formation of the isomeric ester **47**. On the basis of previous results with the isomerization of an ester carrying a different *ω*-side chain, we envisioned a regioselective deprotonation of ester *E*-**6** with amide **12** resulting in the selective formation of the lithium enolate **46** followed by a regioselective protonation at the α-position.[37] Deprotonation of the *E*-configured ester *E*-**6** (≥ 99% de) with 2 equiv of **12** in THF at −105 °C gave the lithium enolate **46** whose protonation with aqueous $NaHCO_3$ at −78 °C afforded the *β*,*γ*-unsaturated ester **47** with ≥ 99% de (^{1}H NMR) in 98% yield after chromatography. Although a chiral base was used for the deprotonation of *E*-**6**, previous results with the deprotonation of a similar esters suggest that an achiral lithium amide could be used as well.[37,90,91] Deprotonation of α,*β*-unsaturated esters including *E*-**6** with lithium amides is perhaps an intramolecular process following the coordination of the lithium amide to the carbonyl O-atom of the ester group.[92−94] Reduction of ester **47** with $LiAlH_4$ in THF afforded alcohol **48** in an nonoptimized yield of 59%. Since the conversion of alcohol **48** to isocicaprost

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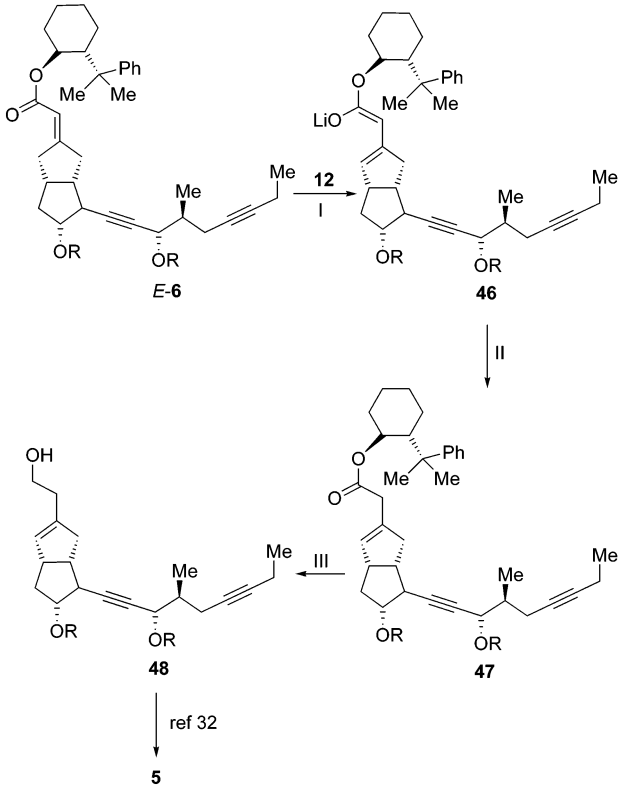
Scheme 9. Formal Asymmetric Synthesis of Isocicaprost (R = Si*t*-BuMe$_2$)[a]



[a] Reagents and conditions: (I) THF, −105 °C. (II) Aqueous $NaHCO_3$, −78 °C. (III) $LiAlH_4$, THF, −20 °C, HPLC.

(**5**) by the same procedure used for the synthesis of cicaprost from alcohol *E*-**44** had already been described,[32] the attainment of **48** represents a formal asymmetric synthesis of isocicaprost.

Conclusion

In this article, we report an asymmetric synthesis of cicaprost from the achiral bicyclic ketones **11a** (15 steps, 19% yield) and **11b** (11 steps, 22% yield) and the amide **9a**. Ketones **11a** (3 steps, 70%) and **11b** (2 steps 90%) are accessible from commercially available bicyclo[3.3.0]octan-2,5-dione on large scale. The same route leading to cicaprost also allowed diversion of a late stage intermediate to achieve a formal asymmetric synthesis of isocicaprost. The key step of these syntheses is the coupling of a bicyclic C6−C14 building block carrying a C13−C14 ethynyl group with a C15−C21 amide building block. It is this step, which should also permit the synthesis of further ω-side chain modified analogues of cicaprost and isocicaprost. Because of the particular structures of the key intermediates, chiral reagents had to be employed for the diastereoselective reduction of the C15 carbonyl group and the diastereoselective olefination of the C6 carbonyl group. This was accomplished with high stereoselectivities by using the chiral oxazaborolidine/borane and chiral phosphono acetate methods. In the course of the asymmetric synthesis of alkyne **10a** from the silyl enol ether **14**, we have devised a new route for the introduction of an ethynyl group at the α-position of a ketone with formation of the corresponding homopropargylic alcohol. Preliminary results with other ketones by using an acetal protection of the carbonyl group give hope that this sequence can be developed into a general method.[95] Whether the same holds true for the new sulfoximine based conversion of an aldehyde to a terminal alkyne, used in the synthesis of alkyne **10b** from aldehyde **24**, remains to be shown.

The ω-side chain building block **9a** was synthesized by two different routes. The first utilizes the chiral oxazolidinone method for the generation of the stereogenic center of the target molecule and the second relies on a malonate synthesis of the racemate and a chromatographic resolution. In our view, the malonate-resolution route to **9a**, if combined with a racemization of *ent*-**9a**, should offer some advantages over the asymmetric synthesis because of the problems associated with the one stereogenic center in α-position to the carbonyl group.

Experimental Section

General. All reactions were carried out under an argon atmosphere in absolute solvents with syringe and Schlenk techniques in oven-dried glassware. THF and Et_2O were distilled under argon from lead/sodium in the presence of benzophenone, and CH_2Cl_2 was distilled from CaH_2. Bulk solvents for column chromatography and extraction were distilled prior to use. Reagents and DMF including catecholborane were obtained from commercial sources and used without further purification unless otherwise stated. *n*-BuLi was standardized by titration with diphenylacetic acid. (*R*,*R*)-Bis-(phenylethyl)amine hydrochloride[96] with ≥ 99% ee and (1*S*,2*R*)-8-phenylnormenthol[89] with ≥98% ee were prepared according to the literature. Oxazaborolidine **37** was prepared from (*R*)-α,α-diphenyl-2-pyrrolidinemethanol and 0.33 equiv of pure *n*-butylboroxine (NMR) in refluxing C_6D_6 (7 d) by using a Dean−Stark trap whose sidearm contained activated molecular sieve.[87] According to NMR spectroscopy the thus prepared sample of **37** was free of the starting materials. TLC was performed on E. Merck precoated plates (silica gel 60 F_{254}, layer thickness 0.2 mm), and column chromatography was performed with E. Merck silica gel 60 (0.040−0.063 mm) in the flash mode with a nitrogen pressure of 0.2 to 1.0 bar. HPLC was carried out with a Dynamax SD-1 pump by using Varian 320 UV/VIS and Knauer RI detectors. GC analyses were run on Varian 3800, Chrompack CP-9000 and Carlo Erba Mega instruments. Melting points were determined with a Büchi 535 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR 300, a Varian Mercury 300, a Varian Inova 400 or a Varian Unity 500 instrument. Chemical shifts are reported relative to TMS (δ 0.00 ppm) as internal standard. The following abbreviations are used to designate the multiplicity of the peaks in ^{1}H NMR spectra: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad and combinations thereof. Peaks in the ^{13}C NMR spectra are denoted as "u" for carbons with zero or two attached protons or as "d" for carbons with one or three attached protons, as determined from the APT pulse sequence. Assignments in the ^{1}H NMR spectra were made by GMQCOSY, GNOE, and HETCOR experiments and those in the ^{13}C NMR spectra were made by DEPT experiments. IR spectra were recorded on a Perkin-Elmer PE 1759 FT instrument. Only peaks of ν > 1000 cm^{-1} are listed, s = strong, m = medium, w = weak. Low resolution mass spectra were recorded on a Varian MAT 212 mass spectrometer using either electron impact ionization (EI, 70 eV) or chemical ionization (CI, CH_4, isobutane or NH_3). Only peaks of *m*/*z* >80 and an intensity >10%, except decisive ones, are listed. High resolution mass spectra were recorded either on a Varian MAT 95 mass spectrometer or on a Micromass LCT Spectrometer (ESI, TOF). Optical rotations were measured with a Perkin-Elmer model 241 polarimeter at approximately 22 °C. Specific rotations are in grad·mL/dm·g, and *c* is in g/100 mL. Elemental analyses were performed by the Institut für Organische Chemie Microanalytical Laboratory.

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(−)-(1*S*,3a*S*,6a*S*,5*S*)-5-(*tert*-Butyl-diphenyl-silanyloxy)-1-(2,2,2-trichloro-1-hydroxy-ethyl)-hexahydro-pentalen-2-one (15). To a solution of chloral (790 mg, 5.3 mmol) in CH_2Cl_2 (20 mL) was added $TiCl_4$ (0.55 mL, 5.0 mmol) at ambient temperature, and the mixture was stirred at ambient temperature for 5 min. Then the mixture was cooled to −78 °C, and a solution of the silyl enol ether **14** (1.8 g, 4.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise. After the mixture was stirred for 1 h at −78 °C, saturated aqueous $NaHCO_3$ (20 mL) was added and the mixture was warmed to ambient temperature. The aqueous phase was separated and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (hexanes/EtOAc, 5:1) afforded ketone **15** (1.58 g, 75%) with ≥ 98% de as a colorless solid and 380 mg of a 7:3 mixture of 13-*epi*-**15** and ketone **11a**.

15: R_f 0.20 (hexanes/EtOAc, 5:1); mp 87 °C; $[\alpha]_D$ −15.8 (*c* 1.25, Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03 (s, 9 H, *t*-Bu), 1.62 (m, 1 H), 1.85−2.05 (m, 3 H), 2.53−2.74 (m, 3 H), 3.24−3.34 (m, 2 H), 3.71 (d, J = 5.2 Hz, 1 H, OH), 4.40 (m, 1 H, CHOSi), 4.77 (d, J = 5.2 Hz, 1 H, C*H*OH), 7.32−7.45 (m, 6 H, Ph), 7.60−7.65 (m, 4 H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.82 (u), 26.80 (d), 36.10 (d), 37.31 (d), 42.88 (u), 43.22 (u), 45.45 (u), 56.87 (d), 76.66 (d), 81.27 (d), 102.71 (u), 127.35 (d), 129.41 (d), 133.42 (u), 133.50 (u), 135.50 (d), 219.90 (u); IR (KBr): ν 3348 (s), 3071 (m), 3047 (m), 3012 (w), 2957 (s), 2932 (s), 2901 (m), 2857 (s), 1724 (s), 1471 (m), 1428 (m), 1386 (m), 1360 (w), 1309 (w), 1252 (w), 1177 (m), 1107 (s), 1020 (m) cm^{-1}; MS (EI) *m*/*z* (relative intensity, %): 471 (M^+ − HOCl, 37), 470 (28), 469 (100), 468 (27), 467 (95), 417 (14), 416 (18), 415 (64), 414 (28), 413 (99), 377 (22), 237 (11), 235 (57), 234 (10), 233 (81), 219 (16), 217 (42), 200 (15), 199 (84), 197 (39), 193 (10), 191 (14), 183 (16), 181 (31), 179 (18), 175 (11), 173 (17), 157 (22), 155 (25), 153 (17), 151 (13), 139 (14), 136 (11), 135 (23), 121 (11), 105 (23), 91 (11), 81 (26). Anal. Calcd for $C_{26}H_{31}Cl_3O_3Si$ (525.97): C, 59.37; H, 5.94. Found: C, 59.40; H, 5.80.

13-*epi*-15: R_f 0.50 (hexanes/EtOAc, 5:1) (together with **11a**) ^{1}H NMR (400 MHz, $CDCl_3$) (partial data): δ 2.22−2.30 (m, 1 H), 2.70−2.78 (m, 1 H), 3.19 (m, 1 H), 4.12 (dd, J = 8.5, J = 3.5 Hz, 1 H, C*H*OH), 4.40 (m, 1 H, CHOSi), 5.18 (d, J = 8.5 Hz, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.06 (u), 27.07 (d), 35.56 (d), 41.34 (u), 43.01 (u), 45.02 (d), 45.78 (u), 54.73 (d); 76.87 (d), 84.42 (d), 102.90 (u), 127.73 (d), 129.82 (d), 133.67 (u), 133.73 (u), 135.80 (d), 135.85 (d), 219.93 (u)

(1*R*,2*R*,3a*R*,5*S*,6a*S*)-5-(*tert*-Butyl-diphenyl-silanyloxy)-1-(2,2,2-trichloro-1-hydroxy-ethyl)-octahydropentalen-2-ol (16): To a solution of chloral (14.4 g, 97.7 mmol) in CH_2Cl_2 (200 mL) was added $TiCl_4$ (9 mL, 82.1 mmol) at ambient temperature. After stirring the mixture at ambient temperature for 5 min, it was cooled to −78 °C, and a solution of the silyl enol ether **14** (10 g, 22.2 mmol) in CH_2Cl_2 (20 mL) was added within 2 min. After the mixture was stirred for 2 h at −78 °C, saturated aqueous $NaHCO_3$ (200 mL) was added and the mixture was warmed to ambient temperature. The mixture was filtered through a pad of Celite and the residue was washed with Et_2O (200 mL). The aqueous phase was extracted with Et_2O (3 × 100 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue containing **15** was dissolved in a 1:1 mixture of Et_2O/EtOH (500 mL) and the solution was cooled to −45 °C. Then $NaBH_4$ (6.1 g, 161 mmol) was added and the suspension was stirred for 16 h at −45 °C. After the mixture was warmed to ambient temperature, it was concentrated in vacuo and the residue was dissolved in Et_2O (400 mL). The solution was washed with water (300 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (hexanes/EtOAc, 1:1) provided diol **16** (8.84 g, 75%) as a colorless, sticky wax. R_f 0.45 (hexanes/EtOAc, 1:1); $[\alpha]_D$ −19.8 (*c* 0.65, $CDCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (s, 9 H, *t*-Bu), 1.58−1.90 (m, 5 H), 2.12−2.38 (m, 3 H), 2.50−2.65 (m, 2 H), 3.97 (d, J = 6.0 Hz, 1 H, CH(O*H*)CCl_3), 4.02 (m, 1 H, C*H*OH), 4.27 (m, 1 H, CHOSi), 4.40 (d, J = 6.0 Hz, 1 H, $CHCCl_3$), 7.31−7.44 (m, 6 H, Ph), 7.62−7.68 (m, 4 H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.00 (u), 26.96 (d), 36.25 (d), 37.95 (d), 41.03 (u), 41.24 (u), 43.08 (u), 55.22 (d), 76.64 (d), 77.06 (d), 81.11 (d), 103.54 (u), 127.28 (d), 129.30 (d) 129.33 (d), 133.77 (u), 133.88 (u), 135.53 (d); IR ($CHCl_3$): ν 3623 (w), 3444 (w), 3017 (s), 2929 (s), 2857 (m), 1223 (s), 1209 (s), 1107 (m), 1022 (m) cm^{-1}; MS (CI, isobutane) *m*/*z* (relative intensity, %): 531 (34), 530 (33), 529 (100), 528 (36), 527 (M^+ + H, 97), 495 (15), 493 (30), 491 (14), 456 (11), 99 (20). Anal. Calcd for $C_{26}H_{33}Cl_3O_3Si$ (527.98): C, 59.15; H, 6.30. Found: C, 58.81; H, 6.04.

(−)−(1*S*,2*R*,3a*R*,5S,6a*S*)-5-(*tert*-Butyl-diphenyl-silanyloxy)-1-ethynyl-2-(triethyl-silanyloxy)-octahydro-pentalene (10a): To a solution of mesylate **18** (450 mg, 0.59 mmol) in THF (4 mL) was added *n*-BuLi (1.5 mL, 1.6 M in hexanes, 2.4 mmol) dropwise at −20 °C. After the mixture was stirred at −20 °C for 20 min, it was warmed to ambient temperature. Then the mixture was stirred for 60 min, and saturated aqueous NaCl (0.25 mL) was added. The mixture was diluted with Et_2O (25 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (hexanes/Et_2O, 1:25) afforded alkyne **10a** (281 mg, 90%) as a colorless oil. R_f 0.60 (hexanes/EtOAc, 10:1); $[\alpha]_D$ −11.4 (*c* 0.77, Et_2O); ^{1}H NMR (400 MHz, C_6D_6): δ 0.65−0.75 (dq, J = 8.0, J = 4.5 Hz, 6 H, SiCH_2Me), 1.09 (t, J = 8.0 Hz, 9 H, $SiCH_2$*Me*), 1.18 (s, 9 H, *t*-Bu), 1.50−1.73 (m, 3 H), 1.79−1.95 (m, 3 H), 1.99−2.11 (m, 2 H), 2.31 (m, 1 H), 3.07 (dt, J = 8.5, J = 2.5 Hz, 1 H, C*H*C≡CH), 4.07−4.14 (m, 1 H, $CHOSiEt_3$), 4.19−4.26 (m, 1 H, CHOSi*t*-$BuPh_2$), 7.21−7.25 (m, 6 H, Ph), 7.73−7.79 (m, 4 H, Ph). ^{13}C NMR (100 MHz, C_6D_6): δ 5.37 (u), 7.18 (d), 19.28 (u), 27.14 (d), 37.40 (d), 40.89 (u), 42.33 (u), 42.64 (u), 46.27 (d), 46.95 (d), 69.53 (u), 77.19 (d), 79.76 (d), 87.04 (u), 127.74 (d), 129.66 (d), 129.70 (d), 134.28 (u), 134.47 (u), 136.02 (d); IR (neat): ν 3308 (m), 3070 (w), 3049 (w), 2955 (s), 2876 (s), 1461 (m), 1427 (m), 1374 (m), 1263 (w), 1239 (m), 1141 (s), 1113 (s), 1035 (s), 1017 (s) cm^{-1}; MS (CI, isobutane) *m*/*z* (relative intensity, %): 521 (22), 520 (48), 519 (M^+ + H, 100); MS (EI) *m*/*z* (relative intensity, %): 489 (M^+ − Et, 7), 463 (4), 462 (11), 461 (28), 331 (13), 329 (15), 315 (11), 314 (29), 313 (100), 302 (11), 301 (39), 285 (11), 253 (39), 234 (10), 233 (49), 199 (25), 135 (14), 131 (43), 91 (16), 87 (11). Anal. Calcd for $C_{32}H_{46}O_2Si_2$ (518.88): C, 74.07; H, 8.94. Found: C, 73.91; H, 8.98.

(+)−(3a'*S*,4'*S*,5'*R*,6a'*R*)-[4'-Cyano-octahydro-5,5-dimethyl-spiro-[1,3-dioxan-2,2(1'H)-pentalene]]-5-ol (22) and (+)−(3a'*S*,4'*R*,5'*R*,-6a'*R*)-[4'-Cyano-octahydro-5,5-dimethyl-spiro[1,3-dioxan-2,2'(1'H)-pentalen]]-5-ol (21): To a suspension of (*R*,*R*)-bis-(phenylethyl)amine hydrochloride (1.2 g, 4.6 mmol) in THF (33 mL) was added *n*-BuLi (5.4 mL of 1.6 M in hexanes, 8.6 mmol) at −78 °C. The mixture was warmed to ambient temperature, whereby a clear yellow solution of the lithium amide **12** was formed. Then the mixture was cooled to −105 °C and a solution of ketone **11b** (780 mg, 3.5 mmol) in THF (10 mL) was added within 10 min. After the stirring of the mixture for 60 min at −105 °C, it was transferred into a −105 °C cold solution of TsCN (1.3 g, 7.2 mmol) in THF (20 mL) by means of a double tipped ended needle. After the mixture was stirred first for 20 min at −105 °C and then for 80 min at −78 °C, EtOH (45 mL) and $NaBH_4$ (800 mg, 21 mmol) were added. Then, the mixture was gradually warmed to −40 °C within 4 h. After the mixture was warmed to ambient temperature, the solvents were removed in vacuo (HCN!). The solid residue was dissolved in Et_2O, and the solution was washed with aqueous $NaHCO_3$. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (first hexanes/EtOAc, 4:1, then hexanes/EtOAc, 1:2) or HPLC (Merck Lichrospher, 250 × 20 mm, EtOAc, RI detector). afforded nitrile **22** (610 mg, 69%) with 92% ee (GC: Chrompack Chirasil-Dex-CB (Beta I−CP), 25 m, t_R (*ent*-**22**) = 32.01 min, t_R (**22**) = 32.33 min) and nitrile **21** (169 mg, 19%) as colorless solids. Nitrile **21** was recrystallized from EtOAc (90%).

Epimerization of Nitrile 21: A solution of nitrile **21** (2.0 g, 7.9 mmol) in THF (40 mL) was added dropwise to a solution of freshly prepared LDA (22 mmol) in THF (50 mL) at −78 °C. After the mixture

was stirred for 60 min at this temperature, aqueous NaCl (10 mL) was added, and the mixture was warmed to ambient temperature. The organic phase was dried ($MgSO_4$) and concentrated in vacuo to give a mixture of nitriles **21**, **22**, and **26** in a ratio of 4.5:4.5:1 (GC: CP−Sil 8). HPLC (Merck Lichrospher, 250 × 20 mm, EtOAc, RI detector) afforded nitrile **22** (740 mg, 37%) with ≥ 99% ee (GC), nitrile **21** (720 mg, 36%) and nitrile **26** (93 mg, 5%).

22: mp 95 °C; R_f 0.73 (EtOAc); $[\alpha]_D$ +33.2 (*c* 2.65, $CDCl_3$), ^{1}H NMR (400 MHz, C_5D_5N): δ 0.89 (s, 3 H), 0.91 (s, 3 H), 1.78 (m, 1 H), 2.00 (m, 2 H), 2.05−2.20 (m, 1 H), 2.31 (m, 1 H), 2.55 (m, 1 H), 2.75 (m, 1 H), 3.05 (t, J = 6.6 Hz, 1 H, CHCN) 3.39 (s, 2 H), 3.43 (s, 2 H), 4.46 (m, 1 H, C*H*OH), 7.58 (brs, 1 H, OH);^{13}C NMR (100 MHz, C_5D_5N): δ = 22.36 (d), 22.38 (d), 29.95 (u), 36.18 (d), 38.19 (u), 39.60 (u), 41.52 (u), 43.10 (d), 43.84 (d), 71.37 (u), 72.09 (u), 76.46 (d), 109.65 (u), 122.82 (u); IR (KBr): ν 3450 (s), 2958 (s), 2931 (s), 2911 (s), 2872 (s), 2241 (s), 1481 (s), 1451 (m), 1423 (s), 1397 (m), 1365 (m), 1355 (m), 1336 (m), 1318 (m), 1289 (m), 1265(s), 1247 (s), 1213 (m), 1185 (m), 1176 (m), 1141 (s), 1124 (s), 1106 (s), 1058 (s), 1050 (s), 1018 (s) cm^{-1}; MS (EI, 70 eV) *m*/*z* (relative intensity %): 252 (7), 251 (M^+, 47), 183 (59), 167 (20), 166 (24), 141 (10), 128 (100), 97 (10), 94 (15). Anal. Calcd for $C_{14}H_{21}NO_3$ (251.32): C, 66.91; H, 8.42; N, 5.57. Found: C, 66.64; H, 8.36; N 5.46.

21: Mp 150 °C; R_f 0.63 (EtOAc); $[\alpha]_D$ +11.1 (*c* 3.1, $CDCl_3$); ^{1}H NMR (400 MHz, C_5D_5N): δ 0.87 (s, 3 H), 0.95 (s, 3 H), 1.93 (m, 2 H), 2.19 (m, 1 H), 2.50−2.75 (m, 4 H), 2.89 (m, 1 H), 3.16 (t, J = 4.7 Hz, 1 H, CHCN), 3.40−3.55 (m, 4 H), 4.63 (m, 1 H, C*H*OH), 7.23 (brs, 1 H, OH); ^{13}C NMR (100 MHz, C_5D_5N): δ = 22.32 (d), 22.56 (d), 30.06 (u), 37.38 (u), 38.90 (d), 40.42 (u), 40.80 (d), 41.87 (d), 41.91 (u), 70.90 (u), 72.88 (u), 75.57 (d), 109.39 (u), 120.36 (u).

26: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (s, 3 H), 1.03 (s, 3 H), 1.64 (m, 1 H), 2.02 (m, 1 H), 2.23−2.40 (m, 3 H), 2.73−2.93 (m, 2 H), 3.35−3.54 (m, 5 H), 6.50 (q, J = 2.0 Hz, CH═CCN); ^{13}C NMR (100 MHz, $CDCl_3$) 22.29 (d), 22.54 (d), 30.01 (u), 35.83 (u), 37.42 (d), 40.36 (u), 42.27 (u), 49.40 (d), 71.92 (u), 72.25 (u), 108.33 (u), 116.50 (u), 118.01 (u), 146.99 (d).

(3a*S*,4*R*,5*R*,6a*R*)-5-(*tert*-Butyl-dimethyl-silyloxy)-[octahydro-5,5-dimethyl-spiro[1,3-dioxan-2,2′(1′*H*)-pentalen]]-4-carbaldehyde (25): To a solution of nitrile **23** (1.0 g, 2.7 mmol) in toluene (20 mL) was added DIBALH (1 M in hexanes, 4.0 mmol, 4 mL) at −78 °C. After the mixture was stirred for 3 h at −78 °C, it was warmed to ambient temperature and a 1:1 mixture of EtOH/H_2O (4 mL) was added. Then the mixture was diluted with Et_2O (50 mL) and treated with aqueous NH_4Cl (50 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography afforded aldehyde **25** (860 mg, 85%) as a colorless oil: R_f 0.62 (hexanes/EtOAc, 3:1); ^{1}H NMR (400 MHz, [D$_8$]-THF): δ 0.03 (s, 3 H), 0.05 (s, 3 H), 0.87 (s, 9 H, *t*-Bu), 0.90 (s, 3 H), 0.93 (s, 3 H), 1.56 (m, 1 H), 1.84 (m, 2 H), 2.07 (m, 3 H), 2.44 (m, 1 H), 2.60 (m, 2 H), 3.41 (d, J = 2.8 Hz, 2 H), 3.44 (s, 2 H), 4.29 (m, 1 H, CHOSi), 9.62 (d, J = 2.2 Hz, 1 H, CHO); ^{13}C NMR (100 MHz, [D$_8$]-THF): δ −4.86 (d), −4.50 (d), 18.31 (u), 22.56 (d), 22.65 (d), 25.97 (d), 30.36 (u), 37.14 (d), 38.83 (d), 39.03 (u), 40.59 (u), 42.39 (u), 66.88 (d), 72.08 (u), 72.16 (u), 75.79 (d), 110.11 (u), 201.74 (d).

(−)−(3a′*S*,4′*S*,5′*R*,6a′*R*)-5′-(*tert*-Butyl-dimethyl-silanyloxy)-[4′-(2-((*R*$_S$,*E*)-*N*-methyl-S-phenyl-sulfonimidoyl)-ethenyl)-octahydro-5,5-dimethyl-spiro[1,3-dioxan-2,2′(1′*H*)-pentalene]] (29): To a solution of (*R*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine (169 mg, 1 mmol) in THF (10 mL) was added *n*-BuLi (1.6 M in hexanes, 0.69 mL, 1.1 mmol) at −78 °C. After the mixture was stirred for 30 min at −78 °C, it was warmed to ambient temperature over a period of 30 min to ensure complete formation of salt **27**. Subsequently the mixture was cooled to −78 °C and a solution of aldehyde **25** (368 mg, 1 mmol) in THF (2 mL) was added. After the mixture was stirred for 2 h at −78 °C, it was warmed to ambient temperature over a period of 12 h. Then aqueous NH_4Cl (10 mL) was added, and the aqueous phase was separated and extracted with EtOAc (50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to give alcohol **28** as a 3:2 mixture of diastereomers. Alcohol **28** was dissolved in THF (20 mL), and *n*-BuLi (1.6 M in hexanes, 0.68 mL, 1.1 mmol) was added at −78 °C. After the mixture was stirred for 30 min at −78°C, NEt_3 (0.3 mL, 2.1 mmol) and $MeSO_2Cl$ (0.12 mL, 1.5 mmol) were added. Then the mixture was stirred at −78 °C for 3 h. Subsequently, DBU (0.3 mL, 2 mmol) was added, and the mixture was warmed to ambient temperature. After the mixture was stirred for 12 h at ambient temperature, it was diluted with Et_2O (50 mL) and washed successively with aqueous NH_4Cl, 10% aqueous Na_2CO_3 and water. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (hexanes/EtOAc, 1:2) afforded the alkenyl sulfoximine **29** (495 mg, 95%) as a colorless solid. Mp 88°C, R_f 0.3 (hexanes/EtOAc, 1:1); $[\alpha]_D$ −4.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.28 (s, 3 H, SiMe), −0.12 (s, 3 H, SiMe), 0.65 (s, 9 H, *t*-Bu), 0.91 (s, 3 H), 0.99 (s, 3 H), 1.44 (m, 1 H) 1.83 (m, 2 H), 2.09 (m, 3 H), 2.33 (m, 1 H), 2.45 (m, 2 H), 2.72 (s, 3 H, SO_2Me), 3.45 (m, 4 H), 3.76 (m, 1 H, CHOSi), 6.52 (d, J = 14.8 Hz, 1 H, HC═C*H*S), 6.76 (dd, J = 14.8, J = 9 Hz, 1 H, *H*C═CHS), 7.55 (m, 3 H), 7.88 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.15 (d), −4.68 (d), 17.17 (u), 22.36 (d), 22.56 (d), 25.52 (d), 29.38 (d), 29.98 (u), 35.34 (d), 37.08 (u), 41.05 (u), 41.69 (u), 42.77 (d), 56.69 (d), 71.78 (u), 71.96 (u), 77.92 (d), 109.65 (u), 128.58 (d), 129.07 (d), 130.42 (d), 132.26 (d), 138.87 (u), 147.96 (d); IR (KBr): ν 3060 (w), 2954 (s), 2891 (s), 2856 (s), 2801 (m), 1634 (m), 1472 (s), 1446 (m), 1392 (m), 1360 (w), 1360 (w), 1329 (m), 1313 (w), 1250 (s), 1184 (w), 1116 (s), 1080 (s), 1063 (m), 1038 (m), 1014 (m) cm^{-1}; MS (EI, 70 eV) *m*/*z* (%): 519 (M^+, 5), 464 (13), 463 (33), 462 (100), 221 (11), 212 (14). Anal. Calcd for $C_{28}H_{45}NO_4SSi$ (519.81): C, 64.70; H, 8.73; N 2.69. Found: C, 64.38; H, 8.80; N 2.62.

(−)−(3a*S*,4*S*,5*R*,6a*R*)-5-(*tert*-Butyl-dimethyl-silyloxy)-[4-ethynyl-octahydro-5,5-dimethyl-spiro[1,3-dioxan-2,2′(1′*H*)-pentalene] (10b): The alkenyl sulfoximine **29** (520 mg, 1 mmol) and Me_3OBF_4 (192 mg, 1.3 mmol) were placed in a Schlenk flask. The flask was evacuated and refilled with dry argon (3 times). Then CH_2Cl_2 (30 mL) was added, and the mixture was stirred at ambient temperature for 60 min. Subsequently, water (10 mL) was added, and the mixture was stirred for 15 min. Then, the mixture was extracted with CH_2Cl_2 (30 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The thus obtained salt **30** was dried in vacuo (10^{-3} mbar) for 3 h and subsequently dissolved in THF (50 mL). The solution was cooled to −78 °C and treated with LiN(H)*t*-Bu, which was freshly prepared from *t*-$BuNH_2$ (0.21 mL, 2 mmol) and *n*-BuLi (1.6 M in hexanes, 1.25 mL, 2 mmol) in THF (2 mL). After the mixture was stirred first for 30 min at −78 °C and then for 15 h at ambient temperature, aqueous $NaHCO_3$ (25 mL) was added and stirring was continued for 10 min. The mixture was extracted with Et_2O (100 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (hexanes/EtOAc, 9:1) gave alkyne **10b** (320 mg, 89%) with 92% ee (GC: Macherey-Nagel Lipodex-C, 25 m, t_R (*ent*-**10b**) = 193.07 min, t_R (**10b**) = 195.30 min) as a colorless oil. R_f 0.59 (hexanes/EtOAc, 3:1); $[\alpha]_D$ −1.5 (*c* 5.4, $CDCl_3$); ^{1}H NMR (500 MHz, C_6D_6): δ 0.12 (s, 3 H), 0.19 (s, 3 H), 0.64 (s, 3 H), 0.82 (s, 3 H), 1.01 (s, 9 H), 1.53 (m, 1 H), 1.80 (dd, J = 5.0, J = 13.0 Hz, 1 H), 1.95 (d, J = 2.5 Hz, 1 H, C≡CH), 1.96−2.07 (m, 4 H), 2.28 (m, 1 H), 2.50 (m, 1 H), 2.68 (dt, J = 2.5, J = 8.8 Hz 1 H, C*H*C≡CH), 3.09−3.17 (m, 2 H), 3.22 (s, 2 H), 4.02 (m, 1 H, CHOSi); ^{13}C NMR (100 MHz, C_6D_6): δ −4.53 (d), −4.27 (d), 18.30 (u), 22.26 (d), 22.56 (d), 26.04 (d), 29.80 (u), 35.70 (d), 37.58 (u), 41.30 (u), 41.67 (u), 45.35 (d), 45.51(d), 69.79 (u), 71.50 (u), 71.92 (u), 79.60 (d), 86.72 (u), 109.74 (u); IR (neat): ν 3311 (s), 2955 (s), 2886 (s), 2857 (s), 2738 (s), 2708 (s), 2280 (w), 2115 (w), 1472 (s), 1464 (s), 1435 (m), 1395 (s), 1362 (s), 1352 (s), 1330 (s), 1312 (m), 1284 (m), 1256 (s), 1221 (s), 1210 (m), 1190 (m), 1171 (s), 1118 (s), 1049 (s), 1019 (s), 1007 (s) cm^{-1}; MS (EI, 70 eV) *m*/*z* (relative intensity, %): 364 (M^+, 6), 308 (19), 307 (80), 222 (18), 221 (100),

203 (46), 179 (18), 178 (89), 128 (15), 105 (12). Anal. Calcd for $C_{21}H_{36}O_3Si$ (364.59): C, 69.18; H, 9.95. Found: C, 69.11; H, 9.97.

HPLC Separation of *rac*-9a: Preparative HPLC (Ciralcel AD, 250 × 50 mm, *i*-PrOH/hexanes 5:95, UV: 254 nm, flow 30 mL/min, 750 mg of racemate per injection) of *rac*-**9a** (4.2 g) gave **9a** (2.0 g, 47%) and *ent*-**9a** (2.0 g, 47%) each with ≥ 99% ee (GC). **9a**: $[\alpha]_D$ +15.5 (*c* 4.5, $CDCl_3$); *ent*-**9a**: $[\alpha]_D$ −15.5 (*c* 4.5, $CDCl_3$).

(1*S*,2*R*,3a*R*,5*S*,6a*S*)-1-[5-(*tert*-Butyl-diphenyl-silanyloxy)-2-(triethyl-silanyloxy)-octahydro-pentalen-1-yl]-(4*S*)-methyl-nona-1,6-diyn-3-one (8a): To a solution of alkyne **10a** (1.0 g, 1.9 mmol) in THF (10 mL) was added *n*-BuLi (1.6 M in hexanes, 1.2 mL, 1.9 mmol) at −78 °C. The mixture was warmed to ambient temperature for 10 min, cooled to −78 °C and then transferred to a −19 °C cold stirred solution of amide **9a** (560 mg, 3.1 mmol) in THF (10 mL) by means of a double-tipped ended needle. After the mixture was stirred for 3 h at −19 °C, saturated aqueous NH_4Cl (2 mL) and water (5 mL) were added. Subsequently, the mixture was warmed to ambient temperature, and the aqueous phase was separated and extracted with Et_2O (3 × 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (hexanes/ Et_2O, 20:1) afforded ketone **8a** (1.13 g, 92%) with 94% de (^{1}H NMR: δ (CH_2*Me*) 0.960, δ (CH*Me*) 1.266 (**8a**); δ (CH_2*Me*) 0.958, δ (CH*Me*) 1.275 (**8a'**)) and alkyne **10a** (80 mg, 8%). R_f 0.53 (hexanes/EtOAc, 5:1); $[\alpha]_D$ −25.0 (c 0.92, Et_2O); ^{1}H NMR (500 MHz, C_6D_6): δ 0.61−0.72 (m, 6 H, SiCH_2Me), 0.96 (t, J = 7.4 Hz, 3 H, C≡CCH_2*Me*), 1.08 (t, J = 7.9 Hz, 9 H, SiCH_2*Me*), 1.17 (s, 9 H, *t*-Bu), 1.27 (d, J = 6.8 Hz, 3 H, CH*Me*), 1.46−1.61 (m, 3 H), 1.79−1.89 (m, 2 H), 1.94−2.06 (m, 4 H), 2.19−2.27 (m, 1 H), 2.38−2.44 (m, 1 H), 2.61−2.69 (m, 2 H), 3.21 (t, J = 8.8 Hz, 1 H, $COSiEt_3$−CHC≡C), 4.02−4.08 (m, 1 H, $CHOSiEt_3$), 4.20−4.25 (m, 1 H, CHOSi*t*-$BuPh_2$), 7.23−7.27 (m, 6 H), 7.73−7.77 (m, 4 H). ^{13}C NMR (75 MHz, C_6D_6): δ 5.29 (u), 7.13 (d), 12.72 (u), 14.39 (d), 15.59 (d), 19.28 (u), 22.50 (u), 27.18 (d), 37.69 (d), 40.67 (u), 42.22 (u), 42.95 (u), 46.56 (d), 46.66 (d), 48.30 (d), 76.81 (u), 77.35 (d), 79.38 (d), 81.21 (u), 83.66 (u), 96.78 (u), 128.00 (d), 129.97 (d), 130.03 (d), 134.35 (u), 134.46 (u), 136.22 (d), 188.59 (u); IR (neat): ν 3070 (w), 3048 (w), 2956 (s), 2876 (s), 2203 (s), 1674 (s), 1459 (m), 1427 (m), 1374 (m), 1321 (w), 1264 (w), 1239 (m), 1175 (m), 1140 (s), 1113 (s), 1064 (m), 1019 (s) cm^{-1}; MS (EI, 70 eV) *m*/*z* (relative intensity, %): 640 (M^+, 0.7), 612 (24), 611 (48), 593 (11), 585 (19), 584 (52), 583 (100), 506 (10), 505 (22), 451 (13), 451 (14), 427 (14), 365 (16), 355 (54), 337 (24), 313 (21), 254 (11), 253 (48), 199 (41), 197 (20), 195 (12), 183 (17), 181 (12), 135 (22), 129 (10), 115 (11), 87 (25). Anal. Calcd for $C_{40}H_{56}O_3Si_2$ (641.04): C, 74.94; H, 8.81. Found: C, 75.04; H, 9.14.

(+)−(1*S*,2*R*,3a*R*,5*S*,6a*S*)-1-[5-(*tert*-Butyl-diphenyl-silanyloxy)-2-hydroxy-octa-hydro-pentalen-1-yl]-4(*S*)-methyl-nona-1,6-diyn-3(*S*)-ol (39): To a solution of ketone **8a** (750 mg, 1.16 mmol) in CH_2-Cl_2 (15 mL) was added oxazaborolidine **37** (0.86 M solution in C_6D_6, 0.3 mL, 0.25 mmol). The mixture was cooled to −78 °C, and catecholborane (0.5 mL, 4.7 mmol, diluted with 0.5 mL CH_2Cl_2) was added within 5 min. After the mixture was stirred for 16 h at −78 °C, EtOH (1 mL) was added, and the mixture was warmed to ambient temperature and concentrated in vacuo. Column chromatography first with hexanes/Et_2O, 1:1, afforded the silyl ether **38** (140 mg, 18%) and then with CH_2Cl_2/EtOH, 1:1, gave diol **39** admixed with catechol. The mixture of **39** and catechol was dissolved in Et_2O (50 mL) and the solution was washed with NaOH (2 N, 50 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (CH_2Cl_2/Et_2O, 1:1) afforded diol **39** (480 mg, 77%) as a colorless oil. The silyl ether **38** was dissolved in THF (2 mL) and diluted aqueous HCl (0.5 mL) was added. After the mixture was stirred for 1 h at ambient temperature, it was neutralized with NaOH and extracted with Et_2O (15 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (CH_2Cl_2/Et_2O, 1:1) afforded diol **39** (99 mg, 16%) as a colorless oil. The total yield of diol **39** was 93%. R_f 0.64 (EtOAc); $[\alpha]_D$ +9.2 (*c* 0.8, THF); ^{1}H NMR (300 MHz, C_6D_6): δ 1.00 (t, J = 7.4 Hz, 3 H, C≡CCH_2*Me*); 1.19 (s, 9 H, *t*-Bu); 1.29 (d, J = 6.6 Hz, 3 H, CH*Me*); 1.55−1.64 (m, 2 H); 1.66−1.88 (m, 3 H), 1.94−2.14 (m, 4 H), 2.16−2.30 (m, 2 H), 2.34−2.55 (m, 2 H), 3.04 (dt, J = 9.1, J = 1.2 Hz, 1 H, C*H*Me); 3.75 (d, J = 4.2 Hz, 1 H, C≡CCHO*H*), 3.97 (d, J = 1.5 Hz, 1 H, CHO*H*-CHC≡CCHOH), 4.00−4.15 (m, 1 H, C*H*OH−CHC≡C), 4.17−4.26 (m, 1 H, CHOSi*t*-$BuPh_2$), 4.54 (m, 1H, C≡CC*H*OH), 7.22−7.32 (m, 6 H), 7.74−7.80 (m, 4 H); ^{13}C NMR (100 MHz, C_6D_6): δ 12.80 (u), 14.53 (d), 15.49 (d), 19.29 (u), 22.70 (u), 27.22 (d), 37.08 (d), 40.11 (d), 40.65 (u), 41.24 (u), 42.58 (u), 46.52 (d), 66.26 (d), 77.46 (d), 78.01 (u), 79.45 (d), 81.62 (u), 83.27 (u), 88.57 (u), 128.00 (d), 129.90 (d), 129.94 (d), 134.49 (u), 134.54 (u), 136.20 (d); MS (CI, isobutane) *m*/*z* (relative intensity, %): 529 (M^+ + H, 3), 511 (3); 493 (13); 405 (10), 125 (100). HRMS calcd for $C_{30}H_{35}O_3Si^+$ (M^+ − *t*-Bu) 471.23554, found 471.23568.

(+)-(3a*S*,4*S*,5*R*,6a*S*)-5-Hydroxy-4-((3*S*)-hydroxy-4(*S*)-methyl-nona-1,6-diynyl)-hexahydro-pentalen-2-on (7a): To a solution of diester **41** (170 mg, 0.34 mmol) in MeOH (2.5 mL) was added aqueous NaOH (1 M, 1 mL, 1.0 mmol). After the mixture was stirred at ambient temperature for 3 h, TLC showed a complete conversion of the diester. The mixture was diluted with Et_2O (20 mL) and washed with NaOH (1 M, 5 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (Et_2O/hexanes/MeOH, 20:10:1) afforded diol **7a** (90 mg, 90%) as a colorless oil. R_f 0.5 (EtOAc); $[\alpha]_D$ +38.0 (*c* 1.75, Et_2O); ^{1}H NMR (400 MHz, C_6D_6): δ 1.02 (t, J = 7.4 Hz, 3 H, C≡CCH_2*Me*), 1.29 (d, J = 6.6 Hz, 3 H, CH*Me*), 1.36−1.44 (m, 1 H), 1.93−2.53 (m, 13 H), 3.42 (d, J = 5.2 Hz, 1 H, C≡CCHO*H*), 3.52 (d, J = 6.1 Hz, 1 H, CHO*H*-CHC≡C), 4.12−4.17 (m, 1 H, C*H*OH−CHC≡C), 4.54 (m, 1 H, C≡CC*H*OH). ^{13}C NMR (100 MHz, C_6D_6): δ 12.79 (u), 14.52 (d), 15.46 (d), 22.72 (u), 35.64 (d), 40.09 (d), 41.20 (u), 43.34 (u), 44.88 (d), 45.44 (u), 46.29 (d), 65.99 (d), 77.70 (u), 79.06 (d), 82.50 (u), 83.41 (u), 86.87 (u), 218.52 (u). IR (neat) ν 3397 (s), 2969 (s), 2933 (s), 1732 (s), 1455 (m), 1403 (m), 1322 (w), 1284 (w), 1249 (w), 1171 (w), 1117 (w), 1091 (w), 1023 (m); MS (CI, isobutane) *m*/*z* (relative intensity, %): 289 (M^+ + H, 10), 273 (9), 272 (21), 271 (100), 253 (19). Anal. Calcd for $C_{18}H_{24}O_3$ (288.38): C, 74.97; H, 8.39. Found: C, 74.84; H, 8.76.

(−)-(3a'*S*,4'*S*,5'*R*,6a'*R*)-5'-[(*tert*-Butyl-dimethyl-silanyloxy)]-[(4'-(3-oxo-4*S*-methyl-nona-1,6-diynyl)-octahydro-5,5-dimethyl-spiro-[1,3-dioxan-2,2'(1'*H*)-pentalene]] (8b): To a solution of alkyne **10b** (1.5 g, 4.1 mmol) (92% ee) in THF (20 mL) was added *n*-BuLi (1.6 M in hexanes, 2.55 mL, 4.1 mmol) at −78 °C. The mixture was warmed to ambient temperature for 10 min and then cooled to − 78 °C. Then, the mixture was added to a −19 °C cold solution of amide **9a** (890 mg, 4.8 mmol, ≥99% ee) in THF (10 mL) by means of a double tipped ended needle. After the mixture was stirred for 40 min at −19 °C, aqueous NH_4Cl (10 mL) was added, and the mixture was warmed to ambient temperature. Water was added until two clear phases were formed. The aqueous phase was separated and extracted with Et_2O (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (hexanes/EtOAc, 5:1) afforded ketone **8b** (1.8 g, 90%) with 92% de (^{1}H NMR: δ (CH_2*Me*) 0.960, δ (CH*Me*) 1.266 (**8b**); δ (CH_2*Me*) 0.958, δ (CH*Me*) 1.275 (**8b'**) and alkyne **10b** (120 mg, 0.24 mmol, 8%) both as colorless oils. R_f 0.59 (hexanes/EtOAc, 3:1); $[\alpha]_D$ −2.2 (*c* 2.3, $CDCl_3$); ^{1}H NMR (400 MHz, C_6D_6): δ 0.09 (s, 3 H, SiMe), 0.16 (s, 3 H, SiMe), 0.68 (s, 3 H), 0.80 (s, 3 H), 0.96 (t, J = 7.4 Hz, 3 H, C≡CCH_2*Me*), 0.98 (s, 9 H, *t*-Bu), 1.26 (d, J = 6.8 Hz, 3 H, CH*Me*), 1.44−1.54 (m, 1 H), 1.80 (dd, J = 13.4, J = 4.9 Hz, 1 H), 1.90−2.01 (m, 6 H), 2.18−2.30 (m, 1 H), 2.36−2.46 (m, 2 H), 2.59−2.71 (m, 2 H), 2.79 (t, J = 9.0 Hz, 1 H, CH−C≡CCO), 3.13 (m, 2 H), 3.22 (s, 2 H), 3.98 (m, 1 H, CHOSi);^{13}C NMR (100 MHz, C_6D_6): δ −4.53 (d), −4.48 (d), 12.67 (u), 14.35 (d), 15.57 (d), 18.17 (u), 22.28 (d), 22.44 (d), 22.48 (u), 25.95 (d), 29.83 (u), 35.85 (d), 37.78 (u), 40.73 (u), 41.87 (u), 44.97 (d), 45.59 (d), 48.18 (d), 71.47 (u), 72.03 (u), 76.61 (u), 79.08 (d), 81.23 (u), 83.57 (u), 96.07 (u), 109.62 (u), 188.22 (u). IR (neat): ν

2954 (s), 2857 (s), 2204 (s), 1674 (s), 1472 (m), 1462 (m), 1434 (m), 1394 (m), 1376 (m), 1361 (m), 1351 (m), 1330 (m), 1253 (s), 1221 (m), 1175 (m), 1139 (s), 1118 (s), 1048 (m), 1020 (m), 1001 (m) cm^{-1}; MS (CI, isobutane) *m*/*z* (relative intensity, %): 488 (36), 487 (M^+ + H, 100), 429 (13), 355 (21). Anal. Calcd for $C_{29}H_{46}O_4Si$ (486.76): C, 71.56; H, 9.53. Found: C, 71.75; H, 9.75.

(−)-(3a'*S*,4'*S*,5'*R*,6a'*R*)-5'-(*tert*-Butyl-dimethyl-silanyloxy)-[(4'-(3*S*-hydroxy-4*S*-methyl-nona-1,6-diynyl)-octahydro-5,5-dimethyl-spiro[1,3-dioxan-2,2'(1' *H*)-pentalene]] (42): To a solution of ketone **8b** (1.57 g, 3.23 mmol) in CH_2Cl_2 (20 mL) was added oxazaborolidine **37** (0.86 M solution in C_6D_6, 0.35 mL, 0.3 mmol). The mixture was cooled to −78 °C and a solution of catecholborane (0.95 mL, 8.9 mmol) in CH_2Cl_2 (5 mL) was added within 60 min by means of a syringe pump. After the mixture was stirred for 4.5 h at −78 °C, MeOH (15 mL) was added at this temperature and the mixture was warmed to ambient temperature and kept at this temperature for 12 h. Concentration in vacuo and purification by column chromatography (hexanes/EtOAc, 3:1) gave alcohol **42** (1.55 g, 98%) with 92% de (^{1}H NMR: δ (CH_2CH_3) 1.24 (**42**); δ (CH_2CH_3) 1.17 (**42'**)) colorless oil. HPLC (Daicel Chiralcel OD 250 × 20 mm, EtOH/hexanes 1:99, RI-detector, flow 6 mL/min, 40 mg per injection) afforded alcohol **42** (1.39 g, 90%) with ≥ 99% de. R_f 0.43 (hexanes/EtOAc, 3:1); $[\alpha]_D$ +20.6 (*c* 1.26, $CDCl_3$), ^{1}H NMR (400 MHz, C_6D_6): δ 0.13 (s, 3 H, SiMe), 0.19 (s, 3 H, SiMe), 0.69 (s, 3 H), 0.82 (s, 3 H), 0.98 (t, *J* = 7.4 Hz, 3 H, C≡CCH$_2$*Me*), 1.02 (s, 9 H, *t*-Bu), 1.24 (d, *J* = 6.8 Hz, 3 H, CH*Me*), 1.50−1.60 (m, 1 H), 1.83 (dd, *J* = 13.1, *J* = 5.3 Hz, 1 H), 1.90 (d, *J* = 5.7 Hz, 1 H, C≡CCHO*H*), 1.95−2.18 (m, 7 H), 2.30−2.55 (m, 4 H), 2.75 (dt, *J* = 8.8, *J* = 1.5 Hz, 1 H, CH−C≡C), 3.14−3.22 (m, 2 H), 3.26 (s, 2 H), 4.02 (m, 1 H, CHOSi), 4.46 (dt, *J* = 6.0, *J* = 1.6 Hz,1 H, C≡CC*H*OH). ^{13}C NMR (100 MHz, C_6D_6): δ −4.43 (d), −4.31 (d), 12.74 (u), 14.49 (d), 15.49 (d), 18.29 (u), 22.32 (d), 22.53 (d), 22.58 (u), 26.05 (d), 29.85 (u), 35.94 (d), 38.18 (u), 39.98 (d), 41.04 (u), 41.72 (u), 45.69 (d), 45.79 (d), 66.14 (d), 71.65 (u), 71.94 (u), 77.78 (u), 79.76 (d), 81.65 (u), 83.12 (u), 88.33 (u), 109.88 (u); IR (neat): ν 3452 (m), 2954 (s), 2857 (s), 1470 (m), 1435 (w), 1393 (w), 1377 (w), 1362 (w), 1329 (m), 1254 (s), 1118 (s), 1019 (m) cm^{-1}; MS (CI, isobutane) *m*/*z* (relative intensity, %): 491 (13), 490 (14), 489 (M^+ + H, 100), 487 (12), 473 (18), 472 (29), 471 (84), 369 (17), 341 (12), 340 (16), 339 (71). Anal. Calcd for $C_{29}H_{48}O_4Si$ (488.77): C, 71.26; H, 9.90. Found: C, 71.14; H, 10.09.

(−)-(*E*,3a*S*,4*S*,5*R*,6a*S*)-{5-(*tert*-Butyl-dimethyl-silanyloxy)-4[(3*S*)-*tert*-butyl-dimethyl-silanyloxy)-4*S*-methyl-nona-1,6-diynyl]-hexahydropentalen-2-ylidene}acetic acid-(2*R*-(1-methyl-1-phenylethyl)-1*S*-cyclohexyl ester (*E*-6): To a solution of (1*S*,2*R*)-dimethoxyphosphanyl-2-(1-methyl-1-phenylethyl)-cyclohexyl acetate (2.9 g, 7.87 mmol) in THF (12 mL) was added *n*-BuLi (1.6 M in hexanes, 4.5 mL, 7.2 mmol) at −78 °C. The solution of **43** thus formed was warmed to ambient temperature for 15 min and cooled to −62 °C. Then a solution of ketone **7b** (910 mg, 1.76 mmol) in THF (5 mL) was added within 10 min. Subsequently the mixture was stirred first for 144 h at −62 °C and then for 15 h at −30 °C. After the mixture was stirred for 30 min at ambient temperature, it was treated with aqueous NH_4Cl (30 mL), and the aqueous phase was separated and diluted with water until a clear solution was formed. The aqueous phase was extracted with Et_2O (4 × 40 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (hexanes/EtOAc, 10:1) afforded a mixture of esters *E*-**6** and *Z*-**6** (1.32 g, 99%) in a ratio of 95:5 (^{1}H NMR: δ (C≡CCHOSi) 4.57, δ (CHOCO) 5.31 (*E*-**6**); δ (C≡CCHOSi) 4.51, δ (CHOCO) 5.40 (*Z*-**6**)) as a colorless oil. HPLC (Chiralcel OD, 250 × 20 mm, hexanes/0.15% *i*-PrOH, UV: 254 nm) gave ester *E*-**6** with ≥ 99% de in 90% yield. R_f 0.52 (hexanes/EtOAc, 10:1); $[\alpha]_D$ −16.7 (*c* 0.72, Et_2O); ^{1}H NMR (400 MHz, C_6D_6): δ 0.10 (s, 3 H), 0.18 (s, 3 H), 0.22 (s, 3 H), 0.30 (s, 3 H), 0.80−1.58 (m, 12 H) 1.00 (s, 9 H), 1.05 (s, 9 H), 1.16 (s, 3 H), 1.30 (d, *J* = 6.8 Hz, 3 H, CH*Me*), 1.37 (s, 3 H), 2.00−2.55 (m, 13 H), 2.80−3.10 (m, 2 H), 4.00 (m, 1 H, C*H*OSi−CHC≡C), 4.57 (dd, *J* = 6.3, *J* = 1.6 Hz, 1 H, C≡CCHOSi), 5.00 (m, 1 H,C═CH), 5.31 (m, 1 H, CHOCO), 7.16−7.31 (m, 5 H); ^{13}C NMR (100 MHz, C_6D_6): δ −4.86 (d), −4.45 (d), 4.38 (d), 3.99 (d), 12.78 (u), 14.56 (d), 15.56 (d), 18.21 (u), 18.45 (u), 22.51 (u), 24.93 (u), 25.49 (d), 26.02 (d), 26.06 (d), 26.24 (u), 27.31 (u), 27.82 (d), 34.07 (u), 38.92 (u), 39.33 (d), 40.03 (u), 40.48 (u), 40.79 (d), 42.39 (u), 45.68 (d), 46.90 (d), 51.38 (d), 66.85 (d), 73.39 (d), 77.72 (u), 79.42 (d), 82.08 (u), 83.15 (u), 87.29 (u), 114.27 (d), 124.98 (d), 125.66 (d), 128.13 (d), 151.64 (u), 164.89 (u), 165.09 (u); IR (neat): ν 3021 (w), 2931 (s), 2857 (s), 1708 (s), 1659 (m), 1496 (w), 1468 (m), 1374 (m), 1323 (w), 1253 (s), 1213 (s), 1188 (m), 1128 (s), 1074 (s), 1030 (m), 1006 (m) cm^{-1}; MS (CI, isobutane) *m*/*z* (relative intensity, %): 761 (12), 760 (M^+ + H, 22), 759 (37), 629 (25), 628 (34), 627 (74), 497 (12), 495 (11), 428 (11), 428 (27), 427 (88), 295 (26), 202 (11), 201 (72), 200 (15), 199 (51), 175 (12), 134 (12), 133 (100), 123 (56), 119 (56), 105 (10). Anal. Calcd for $C_{47}H_{74}O_4Si_2$ (759.26): C, 74.35; H, 9.82. Found: C, 74.36; H, 9.91.

(+)-[(2*E*)-2-[(3a*S*,4*S*,5*R*,6a*S*)-Hexahydro-5-hydroxy-4-[(3*S*,4*S*)-3-hydroxy-4-methyl-1,6-nonadiynyl]-2(1*H*)-pentalenylidene]ethoxy-acetic acid (4): To a solution of ester **45** (220 mg, 0.15 mmol) in MeOH (8 mL) was added 1 N NaOH (3 mL, 3 mmol), and the mixture was stirred for 5 h at ambient temperature. Then water (20 mL) was added to the mixture and its pH value was adjusted first to 5 through addition of solid NaH_2PO_4 and then to 2 through addition of aqueous 1 N HCl. The solution was extracted with Et_2O (6 × 30 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Drying of the residue in vacuo (10^{-3} mbar) afforded cicaprost (**4**) (180 mg, 94%) with ≥ 99% de as a colorless oil. $[\alpha]_D$ +92.0 (*c* 4.15, $CDCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 1.07 (d, *J* = 6.8 Hz, 3 H, CH*Me*), 1.11 (t, *J* = 7.4 Hz, 3 H, C≡CCH$_2$*Me*), 1.14−1.23 (m, 1 H), 1.81−1.90 (m, 1 H, C*H*Me), 2.10−2.56 (m, 12 H), 3.92−4.00 (m, 1 H, C*H*OH−CHC≡C), 4.02−4.16 (m, 4 H, CH_2OCH_2), 4.36 (dd, *J* = 6.4, *J* = 1.7 Hz, 1 H, C≡CC*H*OH), 5.50 (m, 1 H, C═CH), 6.00−6.15 (brs, 3 H, 3 × OH); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 12.75 (u), 14.58 (d), 15.19 (d), 22.46 (u), 35.88 (u), 37.84 (d), 39.07 (u), 39.79 (d), 41.08 (u), 44.99 (d), 46.38 (d), 66.17 (d), 66.55 (u), 68.89 (u), 77.42 (u), 78.16 (d), 81.11 (u), 83.44 (u), 87.62 (u), 117.92 (d), 148.03 (u), 173.47 (u); IR (neat): ν 3398 (s), 2966 (s), 2934 (s), 2245 (w), 1734 (s), 1455 (m), 1431 (m), 1375 (w), 1322 (w), 1245 (m), 1213 (m), 1119 (s), 1095 (s), 1018 (m) cm^{-1}; MS (CI, NH_3) *m*/*z* (relative intensity, %): 392 (M^+ + NH_4, 5), 318 (15), 317 (22), 316 (100), 314 (21), 299 (12), 281 (10).

(3a*S*,5R,6*S*,6a*S*)-{5-(*tert*-Butyl-dimethyl-silanyloxy)-6-[(3*S*,4*S*)-3-*tert*-butyl-dimethyl-silanyloxy)-4-methyl-nona-1,6-diynyl]-1,3a,4,5,6,6a-hexahydropentalen-2-yl}-acetic acid-[(2*R*,1*S*)-2-(1-methyl-1-phenylethyl)-1-cyclohexyl ester] (47): To a suspension of (*R*,*R*)-bis-(phenylethyl)amine hydrochloride (350 mg, 1.33 mmol) in THF (15 mL) was added *n*-BuLi (1.6 M in hexanes, 1.7 mL, 2.7 mmol) at −78 °C. The suspension was warmed to ambient temperature whereby a clear yellow solution of **12** was formed. Then the solution was cooled to −105 °C and a solution of ester *E*-**6** (500 mg, 0.65 mmol) (≥ 99% de) in THF (5 mL) was added slowly along the cold inner side of the flask. After the mixture was stirred for 15 min at −105 °C, it was warmed to −78 °C within 30 min, and stirring was continued for 60 min. Then aqueous $NaHCO_3$ was added at this temperature. The mixture was warmed to ambient temperature and aqueous NH_4Cl (10 mL) was added. Subsequently water was added until two clear phases were formed. The aqueous phase was separated and extracted with Et_2O (20 mL) and pentanes (20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (hexanes/EtOAc, 3:1) provided ester **47** (490 mg, 98%) with ≥ 99% de (^{1}H NMR) as a colorless oil. R_f 0.52 (hexanes/EtOAc, 10:1), ^{1}H NMR (400 MHz, C_6D_6) δ 0.11 (s, 3 H, SiMe), 0.20 (s), 0.205 (s, 3 H, SiMe), 0.29 (s, 3 H, SiMe)), 0.75−1.56 (m, 12 H) 1.00 (s, 9 H, *t*-Bu), 1.03 (s, 9 H, *t*-Bu), 1.11 (s, 3 H), 1.28 (d, *J* = 6.8 Hz, 3 H, CH*Me*), 1.31 (s, 3 H), 1.92−2.10 (m, 5 H), 2.26 (d, 1 H) 2.38−2.64 (m, 6 H), 2.79 (m, 1 H), 3.93 (m, 1 H), 4.53 (dd, *J* = 6.3, *J* = 1.4 Hz, 1 H, C≡CCHOSi), 4.90 (m, 1 H), 5.25 (m, 1 H), 7.05 (m, 1 H), 7.18−

7.23 (m, 4 H), ^{13}C NMR (100 MHz, C_6D_6): δ −4.88 (d), −4.34 (d), −4.29 (d), −3.96 (d), 12.77 (u), 14.57 (d), 15.60 (d), 18.23 (u), 18.44 (u), 22.44 (u), 24.86 (u), 25.23 (d), 26.05 (d), 26.07 (d), 26.14 (u), 27.20 (u), 27.99 (d), 33.79 (u), 36.93 (u), 39.91 (u), 40.08 (u), 40.48 (u), 40.74 (d), 45.85 (d), 46.16 (d), 51.01 (d), 66.87 (d), 74.40 (d), 77.80 (u), 78.13 (d), 81.71 (u), 83.00 (u), 87.49 (u), 125.11 (d), 125.56 (d), 127.69 (d), 131.91 (d), 134.29 (u), 151.62 (u), 169.28 (u); IR (neat): ν 3056 (w), 3032 (w), 2930 (s), 2884 (s), 2856 (s), 2279 (w), 1730 (s), 1496 (w), 1471 (m), 1462 (m), 1449 (m), 1374 (w), 1361 (w), 1339 (w), 1323 (w), 1252 (s), 1120 (s), 1074 (s), 1025 (m), 1005 (m), 939 (w), 905 (m), 838 (s), 815 (m) cm^{-1}; MS (CI, isobutane) *m*/*z* (relative intensity, %): 760 ($M^+ + H$, 11), 759 (17), 427 (11), 202 (17), 201 (100), 119 (33), 105 (17).

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Supporting Information Available: Schemes S10, S11, S12 and S13 referred to in the text, copies of the ^{1}H and ^{13}C NMR spectra of compounds **4**, **7a**, **16**, **23**, **24**, **26**, **29**, **36**, **39**, **40**, **41**, *E*-**44**, **47**, and **48**, data of the crystal structure analysis of **21**, and procedures for the synthesis and analytical data of compounds **7b**, **9a**, *rac*-**9a**, **14**, **17**, **18**, **23**, **33**, **34**, *rac*-**34**, **36**, **38**, **40**, **41**, *E*-**44**, **45**, and **48** (66 pages, print/PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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