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Development of a Common Fully Stereocontrolled Access to the Medicinally Important and Promising Prostacyclin Analogues Iloprost, 3-Oxa-Iloprost and Cicaprost

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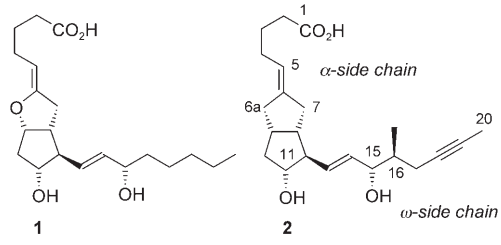
Dedicated to Professor Dieter Enders on the occasion of his 60th birthday

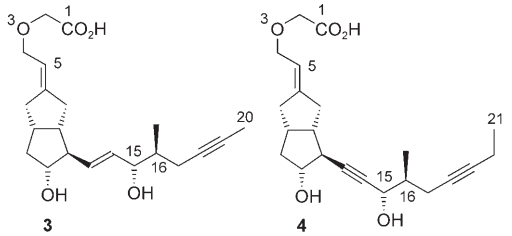
Abstract: We describe new fully stereocontrolled syntheses of the prostacyclin analogues iloprost (**2**), the most active component of the drugs Ilomedin and Ventavis, and 3-oxa-iloprost (**3**), a derivative that is expected to have a significantly higher metabolic stability than **2** perhaps allowing an oral application. The syntheses are based on the same strategy and chiral bicyclic building block as used in the synthesis of cicaprost (**4**), the third most potent analogue that exhibits, besides prostacyclin-like activities, antimetastatic activities. Reaction of the enantiopure C6–C13 bicyclic aldehyde **17** with $Cl_3CCOOH/Cl_3CCOONa$ afforded trichlorocarbinol **24** which was converted via mesylate **25** to the C6–C14 bicyclic alkyne **9**. The palladium-catalysed hydrostannylation of alkyne **9** gave with high regio- and stereoselectivity the alkenylstannane **26**, Sn/Li exchange of which afforded the *E*-configured alkenyllithium derivative **8**. Coupling of the C6–C14 building block **8** with the enantiopure C15–C20 building block, the *N*-methoxyamide **7**, gave the C6–C20 bicyclic ketone **6** in high yield without epimerisation at C16. The configuration at C15 of iloprost (**2**) and 3-oxa-iloprost (**3**) was established through a highly diastereoselective reduction of ketone **6** with catecholborane and the chiral oxazaborolidine **28** which furnished alcohol (15*S*)-**29**. The highly stereoselective conversions of alcohol (15*S*)-**29** to iloprost (**2**) and 3-oxa-iloprost (**3**), which include as key stereoselective steps an olefination with a chiral phosphonoacetate and a copper-mediated allylic alkylation, have already been described.

Keywords: alkenylstannane · asymmetric synthesis · carbacyclins · medicinal chemistry · prostacyclin

Introduction

Iloprost (**2**),[1–3] 3-oxa-iloprost (**3**)[3–7] and cicaprost (**4**)[8–10] are biologically highly potent and chemically stable analogues of prostacyclin (**1**)[11] which have been designed and developed by the Schering group headed by Vorbrüggen and Skuballa. Prostacyclin plays an important role in the vascular and central nervous system and in inflammation. Its





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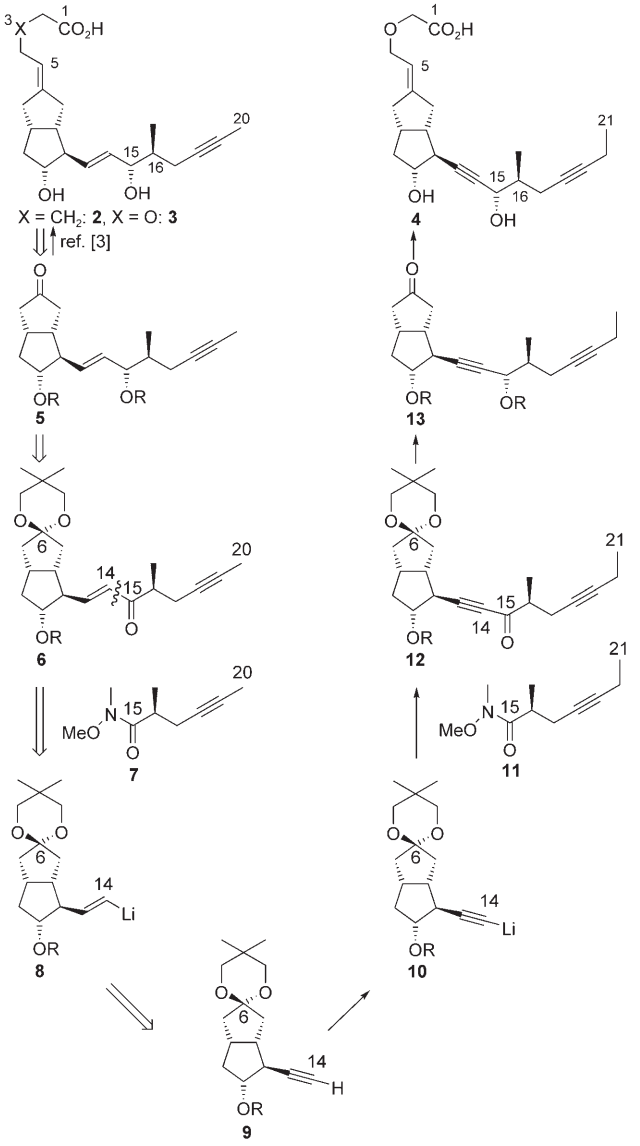
medicinal application is, however, severely hampered by short chemical and metabolic half-lives. Iloprost (**2**) has already been approved as both Ilomedin for the treatment of severe thrombo-angiitis obliterans with a high risk of amputation as well as Raynaud's disease[12] and as Ventavis for the treatment of pulmonary arterial hypertension, a highly debilitating and potentially fatal disease.[13] Iloprost, however, has to be administered by infusion or inhalation because of its relatively low oral activity. 3-Oxa-iloprost (**3**) is expected to have a significantly higher metabolic stability than iloprost (**2**) because enzymatic β-oxidation by the oxygen atom at the 3-position is prevented, which could perhaps allow oral application. Finally cicaprost (**4**) exhibits not only a much higher biological and oral activity than iloprost (**2**) but also exhibits a strong inhibitory effect in a series of spontaneously metastasising rodent mammary tumours.[8d,14]

Structure–activity studies have revealed that the biological activity of iloprost (**2**), 3-oxa-iloprost (**3**) and cicaprost (**4**) is strongly dependent on the 5*E* configuration of the exocyclic double bond and on the configurations at C15 and C16, the 5*E*,15*S*,16*S* diastereomers being the most active ones.[12a,5–7] Thus the development of fully stereocontrolled syntheses of iloprost (**2**), 3-oxa-iloprost (**3**) and cicaprost (**4**) is of considerable importance. For economic reasons it would be particularly attractive to have an access to all three prostacyclin analogues based on one convergent strategy and by using the same or similar building blocks. Although the syntheses of iloprost (**2**),[1,2] 3-oxa-iloprost (**3**)[4] and cicaprost (**4**)[8a,9] developed by the Schering group fulfil these criteria, they are not fully stereocontrolled giving in the case of iloprost (**2**) and 3-oxa-iloprost (**3**) mixtures of diastereomers in regard to the configurations of the exocyclic double bond, C15 and C16. Because of this deficiency Ilomedin and Ventavis are not single isomer drugs but mixtures of iloprost (**2**) and its less active 16*R* diastereomer. We have recently developed a fully stereocontrolled synthesis of cicaprost (**4**)[10] by a new route. Now we describe herein the fully stereocontrolled syntheses of iloprost (**2**) and 3-oxa-iloprost (**3**) based on the same strategy, methodologies and starting material as used in the synthesis of cicaprost.



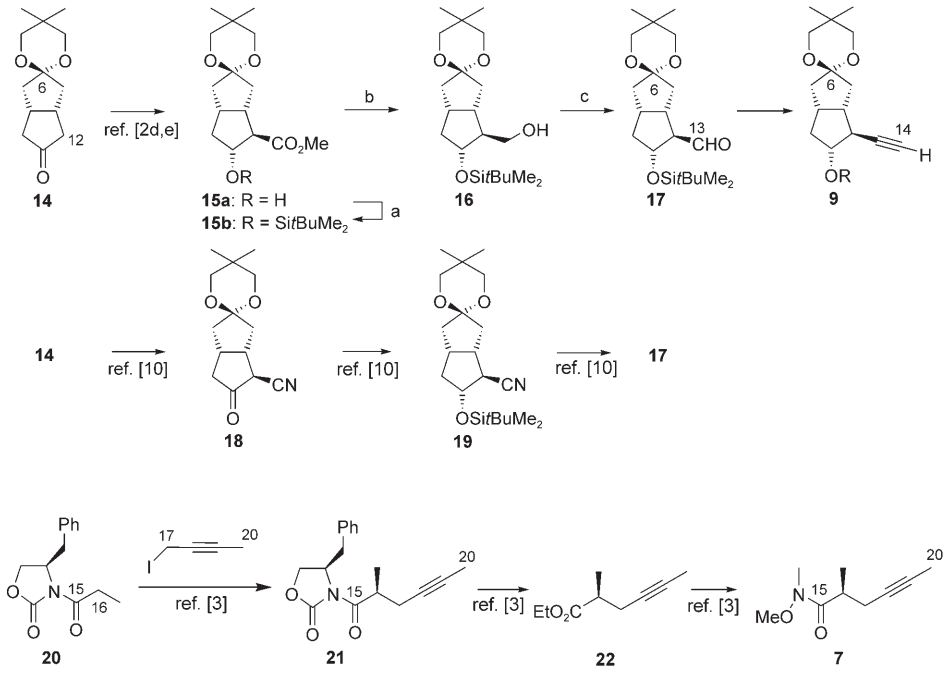
Scheme 1. Retrosynthesis of iloprost (**2**) and 3-oxa-iloprost (**3**), and synthesis of cicaprost (**4**).[10]

Results and Discussion

Retrosynthesis of iloprost and 3-oxa-iloprost: Our synthesis of cicaprost (**4**)[10] has the following key features (Scheme 1). First, the chiral C6–C14 lithioalkyne building block **10** is joined to the chiral C15–C21 amide building block **11** to generate the C14−C15 bond and form the ketone **12**. Secondly, the configuration of C15 of **4** is established through a diastereoselective reduction of **12** with a chiral reducing reagent. Thirdly, the C1–C5 α-side chain is stereoselectively constructed by diastereoselective olefination of ketone **13** with a chiral Horner–Wadsworth–Emmons (HWE) reagent.[9a,10,15]

The first key starting material, the bicyclic alkyne **9** had been synthesised from the enantiopure aldehyde **17**[10] (Scheme 2). This aldehyde can be obtained from the readily available achiral ketone **14**[2d,16,17] either through an enantioselective synthesis via ketone **18** and nitrile **19** using a chiral base for the desymmetrisation[3,10,18] or through a racemic synthesis[2d] via esters **15a** and **15b** and alcohol **16** in combination with an efficient microbiological kinetic resolution of *rac*-**15a**.[2e] In particular, the second route to **17** has been optimised for large-scale synthesis. The second key starting material, the *N*-methoxyamide **11**, was obtained in an enantiopure form through both an enantioselective synthesis using the oxazolidinone method and by a racemic synthesis in combination with an efficient preparative-scale resolution by chiral HPLC.[10]

Based on this strategy for the synthesis of cicaprost (**4**), a retrosynthesis of iloprost (**2**) and oxa-iloprost (**3**) was developed featuring a joining of the C6–C14 lithioalkene building



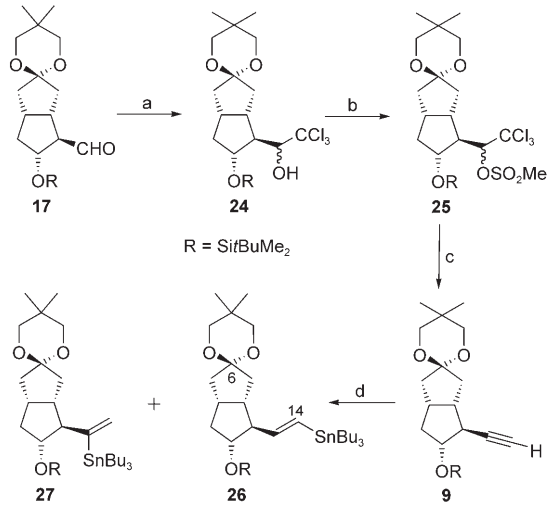
Scheme 2. Synthesis of aldehyde **17** and *N*-methoxyamide **7**. Reagents and conditions: a) $ClSitBuMe_2$, DMF, imidazole; b) $HAl(iBu)_2$, CH_2Cl_2, 0 °C; c) SO_3·pyridine, Me_2SO, NEt_3.

block **8** and the C15–C20 amide building block **7** to generate the C14−C15 bond and form the ketone **6**, and a diastereoselective reduction of **6** with a chiral reducing reagent followed by deprotection and protection to give ketone **5** (cf. Scheme 1). The 5*E* stereoselective conversion of ketone **5** to iloprost (**2**) and 3-oxa-iloprost (**3**) by a highly diastereoselective olefination reaction with a chiral HWE reagent and a highly regio- and diastereoselective allylic alkylation has already been realised (vide infra).[3]

We recently reported on the fully stereocontrolled syntheses of **2** and **3** by a different route which, however, gives no access to cicaprost.[3] In the context of this synthesis we had already developed an efficient synthesis of the enantiopure *N*-methoxyamide **7** by using the same methods applied in the synthesis of the enantiopure amide **11** (cf. Scheme 2). Thus alkylation of oxazolidinone **20** with butynyl iodide gave the substituted oxazolidinone **21** (70%, 92% *de*), the esterification of which afforded ester **22** (68%). Amidation of ester **22** furnished amide **7** (93%) which was purified to give ≥99% *ee* (95%) by preparative chiral HPLC. Alternatively amide **7** with ≥99% *ee* was prepared through a racemic synthesis of *rac*-**7** in combination with an efficient preparative-scale resolution by chiral HPLC.

Synthesis of the alkenylstannane 26: Aldehyde **17** was prepared as depicted in Scheme 2.[2d] Silylation of the hydroxy ester **15a** gave the silyl ether **15b** (98%) which was reduced to the alcohol **16** (97%). Finally, oxidation of alcohol **16** afforded the labile aldehyde **17** in 93% yield. Alkyne **9** has previously been synthesised from aldehyde **17** either by Wittig reaction with dibromomethyltriphenylphosphonium bromide followed by elimination of the corresponding dibromoalkene with potassium *tert*-butylate or by olefination with *S*-lithiomethyl-*N*-methylphenylsulfoximine that includes an addition–elimination reaction followed by α-elimination of the corresponding vinyl dimethylaminosulfoxonium salt with lithium *tert*-butylamide.[10] Although both routes give alkyne **9** in high yields, an alternative method was sought that uses commercially available or less expensive reagents and gives no phosphorus- or sulfur-based reaction products. Based on previous results with a structurally related aldehyde,[10] the trichloroacetic acid/sodium trichloroacetate addition–elimination method was selected.[19] Thus treatment of aldehyde **17** with $Cl_3CCOOH/Cl_3CCOONa$ in dimethylformamide (DMF) gave trichlorocarbinol **24** as a mixture of diastereomers in a ratio of 2:1 in 87% yield (Scheme 3). Mesylation of alcohol **24** with $MeSO_2Cl$ and 1,4-diazabicyclo[2.2.2]octane (DABCO) in CH_2Cl_2 afforded mesylate **25** as a mixture of diastereomers in a ratio of 2:1 in 80% yield. Reaction of mesylate **25** with four equivalents of *n*BuLi in THF at −20 °C furnished the enantiopure alkyne **9** in 86% yield, which was easily purified by column chromatography.

It was planned to selectively generate the *E*-configured alkenyllithium derivative **8** from the corresponding alkenyl-

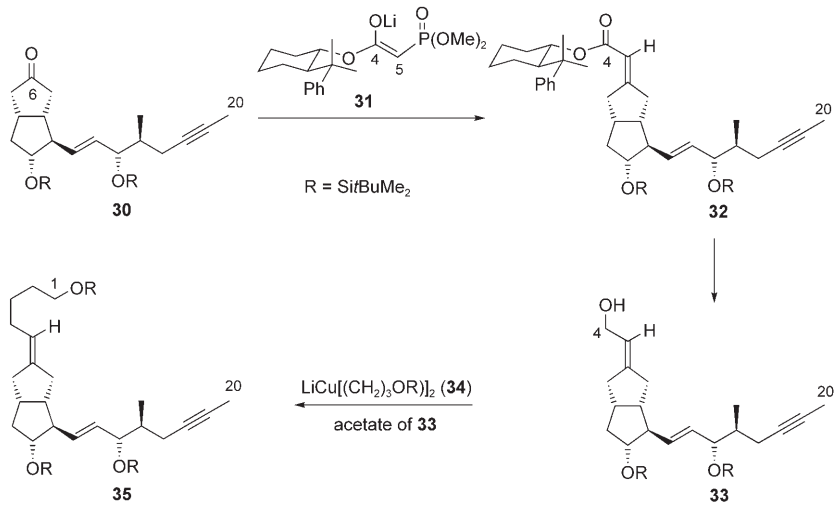


Scheme 3. Synthesis of the alkenylstannane **26**. Reagents and conditions: a) 1) 1.5 equiv Cl_3CCOOH, $Cl_3CCOONa$, DMF, 5 °C; 2) NH_4Cl, RT; b) 1) 4.2 equiv DABCO, 2.5 equiv $MeSO_2Cl$, CH_2Cl_2, RT; 2) 2 N HCl, NaCl, RT; c) 1) 4.0 equiv *n*BuLi, THF, −20 °C to RT; 2) NH_4Cl, RT; d) Bu_3SnH, $[PdCl_2(PPh_3)_2]$, THF, RT.

stannane **26** by a Sn/Li exchange reaction. Thus a regio- and stereoselective synthesis of stannane **26** from alkyne **9** was required. The palladium-catalysed addition of Bu_3SnH (1.2 equiv)[20a,b] to alkyne **9** in THF at room temperature using $[PdCl_2(PPh_3)_2]$ (0.02 equiv) as precatalyst gave a mixture of the isomeric alkenylstannanes **26** and **27** in a ratio of 94:6 in 94% yield. Preparative HPLC afforded stannane **26** in 80% and stannane **27** in 6% yield. Formation of the *Z* isomer of **26** was not observed. The high selectivity of the addition reaction may be attributed to the steric bulk of the substituents at the propargylic position.[20c]

Coupling of the building blocks: Treatment of the alkenylstannane **26** with *n*BuLi in THF at −78°C delivered the *E*-configured alkenyllithium derivative **8**, the reaction of which with amide **7** at −78°C gave ketone **6** in 88% yield (Scheme 4). Epimerisation of ketone **6** at C16 was not observed under these conditions. The alkenylstannane **26** was recovered in 8% yield. It was expected that stereoselective reduction of ketone **6** would be difficult to achieve with an achiral reducing reagent because of the low degree of asymmetric induction provided by C16. Thus a chiral reducing reagent had to be used and based on previous results for the stereoselective reduction of structurally related ketones[3,10] the oxazaborolidine method[21,22] was selected. Treatment of a mixture of catecholborane (1.5 equiv) and oxazaborolidine **28** (1.5 equiv) with ketone **6** in toluene at −78°C led to the formation of a mixture of alcohols (15*S*)- and (15*R*)-**29** in a ratio of 95:5. Column chromatography gave alcohol (15*S*)-**29** in 75% yield and alcohol (15*R*)-**29** in 5% yield. Ketone **6** was recovered in 17% yield. A similar reduction of the recovered ketone **6** increased the yield of alcohol (15*S*)-**29** to 87%. The use of only 0.3 equivalents of **28** in the reduction of ketone **6** led to a much reduced reaction rate and a lower diastereoselectivity of only 85:15. We previously observed a similar decrease in diastereoselectivity for the reduction of a structurally related ketone upon application of substoichiometric amounts of **28** and catecholborane.[3]

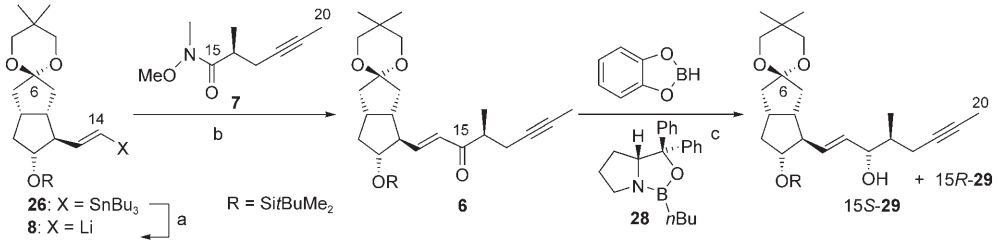
The attainment of (15*S*)-**29** represents a formal fully stereocontrolled total syntheses of iloprost (**2**) and 3-oxa-iloprost (**3**) since this alcohol has already been converted via ketone **30** to the target molecules.[3] The key stereoselective steps in the syntheses of iloprost (**2**) and 3-oxa-iloprost (**3**) from ketone **30** are 1) a highly diastereoselective olefination of the ketone with the chiral HWE reagent **31** with formation of the 5*E*-configured alkene **32** and 2) a highly regio- and stereoselective allylic alkylation of the acetate of the allyl alcohol **33** with the C1–C3 organocuprate **34** with formation of alkene **35** (Scheme 5).



Scheme 5. Final key steps in the formal stereoselective syntheses of **2** and **3**.[3]

Conclusion

The three carbocyclic analogues of prostacyclin, iloprost, 3-oxa-iloprost and cicaprost, which are important and promising medicinal substrates, are accessible by fully stereocontrolled routes based on a common synthetic strategy and similar building blocks, a goal which had not been attained previously.



Scheme 4. Coupling of the building blocks **7** and **8** and stereoselective reduction of ketone **6**. Reagents and conditions: a) *n*BuLi, THF, −78°C; b) 1) **7**, THF, −78°C; 2) NH_4Cl, H_2O, RT; c) **28**, catecholborane, toluene, −78°C.

Experimental Section

General methods: All reactions were carried out under argon in absolute solvents in oven-dried glassware using syringe and Schlenk techniques. THF, Et_2O and toluene were distilled under argon from lead/sodium in the presence of benzophenone. DMSO, DMF and CH_2Cl_2 were distilled from CaH_2. Reagents were obtained from commercial sources and used without further purification. *n*BuLi was standardised by titration with diphenylacetic acid. Oxazaborolidine **28** was prepared from (*R*)-α,α-diphenyl-2-pyrrolidinemethanol and 0.333 equivalents of *n*-butylboroxine in refluxing toluene (16 h) by using a Dean–Stark trap.[23] TLC was performed on E. Merck precoated plates (silica gel 60 F_{254}, layer thickness 0.2 mm), and flash chromatography was performed with E. Merck silica gel 60 (0.040–0.063 mm) with a nitrogen pressure of 0.2 bar. HPLC was carried out with a Dynamax SD-1 pump using Varian 320 UV/VIS and Knauer RI detectors. ^{1}H and ^{13}C NMR spectra were recorded with Varian VXR 300, Varian Mercury 300 and Varian Inova 400 instruments. Chemical shifts are reported relative to TMS ($\delta = 0.00$ ppm) as internal standard. The following abbreviations have been used to designate the multiplicity of the peaks in ^{1}H NMR spectra: s = singlet, d = doublet, t = triplet, q = quartet, sex = sextet, m = multiplet, b = broad and combinations thereof. Peaks in the ^{13}C NMR spectra are denoted as "u" for carbon atoms with zero or two attached protons or as "d" for carbon atoms with one or three attached protons, as determined from the APT pulse sequence. Peaks in the ^{1}H NMR spectra were assigned by GMQCOSY, GNOE, and HETCOR experiments and those in the ^{13}C NMR spectra by DEPT experiments. IR spectra were recorded with a Perkin-Elmer PE 1759 FT instrument. Only peaks ≥ 800 cm^{-1} are listed: vs = very strong, s = strong, m = medium, w = weak. Low-resolution mass spectra were recorded with a Varian MAT 212 S instrument using either electron impact ionisation (EI, 70 eV) or chemical ionisation (CI, CH_4 or isobutane). Only peaks of $m/z \geq 80$ and an intensity of $\geq 10\%$ except decisive ones are listed. High-resolution mass spectra were recorded either with a Varian MAT 95 mass spectrometer or with a Mircomass 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^{-1} g^{-1} and c is in g per 100 mL.

Methyl (3a′*S*,4′*R*,5′*R*,6a′*R*)-5′-(*tert*-butyldimethylsilyloxy)-5,5-dimethylhexahydro-1′*H*-spiro[[1,3]dioxane-2,2′-pentalene]-4′-carboxylate (15b): Imidazole (1.36 g, 20 mmol) and ClSi*t*BuMe$_2$ (1.66 g, 11 mmol) were added to a solution of alcohol **15a** (2.84 g, 10 mmol) in DMF (50 mL). After the mixture had been stirred at room temperature for 20 h, a half-saturated aqueous solution of $NaHCO_3$ was added. The mixture was extracted with diethyl ether and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (EtOAc/hexanes, 1:4) gave the silyl ether **15b** (3.90 g, 98%) as a colourless oil. $[\alpha]_D = -9.1$ ($c = 1.00$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.02$ (s, 3H), 0.08 (s, 3H), 0.92 (s, 9H), 1.56 (m, 1H), 1.84 (m, 2H), 2.09 (m, 3H), 2.44 (m, 1H), 2.60 (m, 2H), 3.44 (d, $J = 2.0$ Hz, 2H), 3.48 (d, $J = 2.0$ Hz, 2H), 3.70 (s, 3H), 4.28 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -5.1$ (d), −4.8 (d), 18.0 (u), 22.5 (d), 22.6 (d), 25.7 (d), 30.1 (u), 36.2 (d), 38.4 (u), 40.6 (u), 41.8 (u), 42.2 (u), 51.6 (d), 58.9 (d), 72.1 (u), 72.2 (u), 77.6 (d), 109.9 (u), 175.6 (u) ppm; IR (capillary): $\tilde{\nu} = 2954$ (vs), 2887 (s), 2857 (s), 2808 (m), 1736 (m), 1470 (m), 1437 (m), 1391 (m), 1362 (w), 1255 (s), 1205 (m), 1170 (m), 1117 (vs), 1047 (s), 1007 (s), 837 (vs) cm^{-1}; MS (CI, isobutane): m/z (%): 399 (100) [M^++1], 383 (1), 342 (2), 341 (8), 313 (2); MS (EI, 70 eV): m/z (%): 398 (5) [M^+], 341 (100), 313 (2), 309 (5), 297 (5), 255 (30), 235 (8), 223 (10), 207 (8), 181 (6), 161 (11), 149 (35); HRMS: calcd for $C_{21}H_{38}O_5Si$: 398.248853; found: 398.248715.

[(3a′*S*,4′*S*,5′*R*,6a′*R*)-5′-(*tert*-Butyldimethylsilyloxy)-5,5-dimethylhexahydro-1′*H*-spiro[[1,3]dioxane-2,2′-pentalen]-4′-yl]methanol (16): HAl(*i*Bu)$_2$ (10.21 mL, 57.3 mmol) in CH_2Cl_2 (20 mL) was added to a solution of ester **15b** (15.0 g, 37.6 mmol) in CH_2Cl_2 (60 mL) at −78 °C within 1.5 h. After the mixture had been stirred at 0 °C for 2 h, MeOH (10 mL) and aqueous potassium tartrate were added. Then the mixture was filtered through Celite which was washed with CH_2Cl_2 (200 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (EtOAc/hexanes, 1:1) gave alcohol **16** (13.4 g, 97%) as colourless crystals. $[\alpha]_D = -22.0$ ($c = 1.00$ in CH_2Cl_2); $R_f = 0.30$ (hexanes/EtOAc, 3:1); ^{1}H NMR (400 MHz, [D$_8$]THF): $\delta = 0.04$ (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 0.89 (s, 3H), 0.91 (s, 3H), 1.44 (m, 1H), 1.73 (m, 2H), 1.82 (m, 1H), 2.08 (m, 3H), 2.27 (m, 2H), 2.73 (s, 1H), 3.41 (m, 4H), 3.50 (m, 2H), 3.93 (m, 1H) ppm; ^{13}C NMR (100 MHz, [D$_8$]THF): $\delta = -4.7$ (d), −4.4 (d), 18.5 (u), 22.7 (d), 22.7 (d), 26.2 (d), 30.5 (u), 36.8 (d), 39.9 (u), 40.9 (d), 41.3 (u), 42.3 (u), 57.1 (d), 62.7 (u), 72.0 (u), 72.5 (u), 76.4 (d), 110.7 (u) ppm; IR ($CHCl_3$): $\tilde{\nu} = 3362$ (br), 2954 (vs), 2886 (s), 2858 (vs), 1645 (m), 1470 (s), 1392 (m), 1362 (w), 1328 (m), 1255 (vs), 1113 (s), 1044 (s), 1009 (s), 861 (s), 837 (vs) cm^{-1}; MS (CI, isobutane): m/z (%): 371 (100) [M^++1], 370 (2), 369 (2), 314 (2), 313 (17), 295 (2), 285 (2), 209 (2), 133 (2); MS (EI, 70 eV): m/z (%): 370 (4) [M^+], 313 (56), 297 (5), 227 (32), 209 (100), 183 (30), 168 (11), 135 (42); HRMS: calcd for $C_{20}H_{38}O_4Si$: 370.253939; found: 370.253923.

(3a′*S*,4′*R*,5′*R*,6a′*R*)-5′-(*tert*-Butyldimethylsilyloxy)-5,5-dimethylhexahydro-1′*H*-spiro[[1,3]dioxane-2,2′-pentalene]-4′-carbaldehyde (17): A solution of SO_3–pyridine complex (7.0 g, 44.1 mmol) in DMSO (30 mL) was added to a solution of alcohol **16** (5.45 g, 14.7 mmol) in DMSO (30 mL) and NEt_3 (26.2 mL, 17.8 mmol) at room temperature within 30 min. After the mixture had been stirred for 3 h, water was added and the mixture extracted with diethyl ether. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (hexanes/EtOAc, 1:4) gave aldehyde **17** (5.01 g, 93%) as a colourless oil. $[\alpha]_D = -22.7$ ($c = 0.9$ in CH_2Cl_2); $R_f = 0.65$ (hexanes/EtOAc, 3:1); ^{1}H NMR (400 MHz, [D$_8$]THF): $\delta = 0.04$ (s, 3H), 0.06 (s, 3H), 0.88 (s, 9H), 0.91 (s, 3H), 0.93 (s, 3H), 1.57 (m, 1H), 1.84 (m, 2H), 2.08 (m, 3H), 2.45 (m, 1H), 2.60 (m, 2H), 3.42 (d, $J = 2.8$ Hz, 2H), 3.45 (s, 2H), 4.31 (m, 1H), 9.62 (d, $J = 2.2$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, [D$_8$]THF): $\delta = -4.56$ (d), −4.22 (d), 18.70 (u), 22.86 (d), 22.96 (d), 26.40 (d), 30.73 (u), 37.58 (d), 39.29 (d), 39.40 (u), 41.02 (u), 42.80 (u), 67.30 (d), 72.48 (u), 72.58 (u), 76.22 (d), 110.54 (u), 202.15 (d) ppm; IR (capillary): $\tilde{\nu} = 2953$ (vs), 2857 (s), 2708 (s), 1724 (vs), 1472 (m), 1394 (m), 1362 (m), 1312 (w), 1255 (m), 1117 (vs), 1046 (s), 1005 (m) cm^{-1}; MS (CI, isobutane): m/z (%): 369 (100) [M^++1], 367 (9), 357 (7), 355 (6), 353 (19), 327 (10), 323 (6), 313 (4), 312 (18), 283 (22), 279 (6), 265 (9), 238 (5), 237 (38), 155 (6), 151 (5); MS (EI, 70 eV): m/z (%): 368 (2) [M^+], 340 (3), 311 (41), 236 (15), 225 (94), 219 (38), 207 (29), 133 (70), 127 (100); HRMS: calcd for $C_{20}H_{36}O_4Si$: 368.238288; found: 368.238212.

(*S*)- and (*R*)-1-[(3a′*S*,4′*S*,5′*R*,6a′*R*)-5′-(*tert*-Butyldimethylsilyloxy)-5,5-dimethylhexahydro-1′*H*-spiro[[1,3]dioxane-2,2′-pentalen]-4′-yl]-2,2,2-trichloroethanol (24): $Cl_3CCOONa$ (3.77 g, 20.4 mmol) was added portionwise to a stirred solution of aldehyde **17** (5.00 g, 13.6 mmol) and Cl_3CCOOH (3.32 g, 20.4 mmol) in DMF (15 mL) at 5 °C so as to maintain a temperature of 5 °C. Subsequently the mixture was stirred at 5 °C for 6 h. Then water was added until two clear phases had formed. The aqueous phase was extracted with Et_2O. The combined organic phases were washed with aqueous NH_4Cl, dried ($MgSO_4$) and concentrated in vacuo. Chromatography (hexanes/EtOAc, 5:1) afforded trichlorocarbinol **24** (5.76 g, 87%) as a mixture of diastereomers in a ratio of 2:1 as a colourless oil. Major diastereomer: $R_f = 0.51$ (hexanes/EtOAc, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.06$ (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 0.94 (s, 3H), 0.97 (s, 3H), 1.42–2.67 (m, 9H), 3.45 (s, 2H), 3.48 (s, 2H), 3.97–4.13 (m, 1H), 4.08–4.12 (m, 1H), 5.08 (d, $J = 4.9$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.9$ (d), −3.5 (d), 17.9 (u), 22.5 (d), 22.5 (d), 25.7 (d), 30.0 (u), 34.5 (d), 36.6 (d), 39.8 (u), 40.6 (u), 41.0 (u), 55.0 (d), 71.8 (u), 72.1 (u), 76.8 (d), 81.6 (d), 103.8 (u), 109.7 (u) ppm. Minor diastereomer: $R_f = 0.51$ (hexanes/EtOAc, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.12$ (s, 3H), 0.14 (s, 3H), 0.91 (s, 9H), 0.95 (s, 3H), 0.98 (s, 3H), 1.42–2.67 (m, 9H), 3.47 (s, 2H), 3.50 (s, 2H), 4.16–4.17 (m, 1H), 4.18–4.22 (m, 1H), 5.08 (d, $J = 4.9$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.8$ (d), −3.4 (d), 17.7 (u), 22.4 (d), 22.4 (d), 25.6 (d), 30.0 (u), 36.2 (d), 39.5 (u), 40.6 (u), 40.8 (u), 41.6 (d), 55.0 (d), 71.8 (u), 72.1 (u), 79.0 (d), 86.8 (d), 102.9 (u), 109.2 (u) ppm. Data for the mixture of diastereomers: IR ($CDCl_3$): $\tilde{\nu} = 3401$ (m), 2954 (s), 2859 (s), 1723 (m), 1469 (m), 1394 (w), 1363 (w), 1328 (w), 1255 (m), 1114 (s), 1045 (m), 1006 (m), 911 (m), 838 (m) cm^{-1}; MS (EI, 70 eV): m/z (%): 490 (4), 489 (5), 488 (12), 487 (5) [M^++1], 486 (12) [M^+], 433 (24), 432 (15), 431 (70), 430 (16), 429 (70), 415 (25), 369 (22), 357 (11), 347 (35), 346 (16), 345 (96), 344 (16), 343

(100), 339 (35), 327 (26), 309 (19), 307 (29), 301 (11), 298 (13), 297 (13), 271 (12), 243 (15), 237 (12), 235 (18), 233 (19), 215 (11), 211 (16), 197 (11), 181 (24), 169 (15), 161 (17), 151 (16), 133 (13), 128 (18), 127 (11), 121 (17), 115 (11), 105 (15), 95 (17), 93 (31); MS (CI, isobutane): *m/z* (%): 491 (37), 490 (28), 489 (100), 488 (30), 487 (98) [M^++19], 486 [M^+] (1), 403 (14), 401 (15); HRMS: calcd for $C_{21}H_{37}Cl_3O_4Si$: 486.152673; found: 486.152807.

(*S*)- and (*R*)-1-[(3a′*S*,4′*R*,5′*R*,6a′*R*)-5′-(*tert*-Butyldimethylsilyloxy)-5,5-dimethylhexahydro-1′*H*-spiro[[1,3]dioxane-2,2′-pentalen]-4′-yl]-2,2,2-trichloroethyl methanesulfonate (25): $MeSO_2Cl$ (3.8 g, 48.4 mmol) was added to a stirred solution of trichlorocarbinol **24** (9.44 g, 19.4 mmol) and DABCO (9.12 g, 81.3 mmol) in CH_2Cl_2 (35 mL) within 15 min using a syringe pump. After the mixture had been stirred at ambient temperature for 15 h, water was added. The aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with 2 N HCl and aqueous NaCl, dried ($MgSO_4$) and concentrated in vacuo. Chromatography (hexanes/EtOAc, 5:1) afforded mesylate **25** (8.75 g, 80%) as a mixture of diastereomers in a ratio of 2:1 as a colourless oil. Major diastereomer: R_f=0.36 (hexanes/EtOAc, 5:1); ^{1}H NMR (400 MHz, C_6D_6): δ= 0.16 (s, 3H), 0.33 (s, 3H), 0.71 (s, 3H), 0.82 (s, 3H), 0.99 (s, 9H), 1.49–2.92 (m, 9H), 2.35 (s, 3H), 3.27 (s, 2H), 3.30 (s, 2H), 4.22–4.29 (m, 1H), 5.56 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=−4.7 (d), −3.8 (d), 18.1 (u), 22.3 (d), 22.4 (d), 26.1 (d), 29.1 (u), 36.0 (d), 37.7 (d), 38.4 (d), 38.5 (u), 40.9 (u), 42.6 (u), 55.7 (d), 71.7 (u), 71.9 (u), 76.5 (d), 87.9 (d), 99.6 (u), 109.9 (u) ppm. Minor diastereomer: R_f=0.36 (hexanes/EtOAc, 5:1); ^{1}H NMR (400 MHz, C_6D_6): δ=0.12 (s, 3H), 0.19 (s, 3H), 0.76 (s, 3H), 0.78 (s, 3H), 1.05 (s, 9H), 1.49–2.92 (m, 9H), 2.40 (s, 3H), 3.25 (s, 2H), 3.26 (s, 2H), 4.59 (m, 1H), 5.26 (d, J=2.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=−4.4 (d), −4.2 (d), 22.4 (d), 22.5 (d), 22.9 (u), 26.0 (d), 31.8 (u), 36.7 (d), 38.4 (d), 39.9 (u), 40.1 (u), 41.7 (u), 44.0 (d), 55.4 (d), 71.5 (u), 71.7 (u), 76.3 (d), 87.8 (d), 99.4 (u), 109.7 (u) ppm. Data for the mixture of diastereomers: IR ($CDCl_3$): $\tilde{\nu}$=2953 (s), 2858 (s), 2278 (m), 1469 (m), 1363 (s), 1332 (m), 1255 (m), 1179 (s), 1117 (s), 1036 (m), 935 (m), 860 (s) cm^{-1}; MS (EI, 70 eV): (m/z) (%): 568 (2), 567 (2) [M$^+$+1], 566 (5) [M$^+$], 564 (5), 509 (21), 507 (18), 423 (14), 421 (13), 377 (12), 339 (23), 329 (16), 327 (49), 325 (49), 181 (13), 155 (11), 153 (100); MS (CI, CH_4): *m/z* (%): 570 (12), 569 (40), 568 (32), 567 (90), 566 (35), 565 (100) [M^++1], 564 (14) [M^+], 563 (10), 551 (17), 549 (19), 511 (17), 510 (11), 509 (40), 507 (38), 471 (25), 469 (25), 435 (17), 433 (20), 423 (18), 421 (18), 349 (20), 347 (21), 339 (14), 327 (18), 325 (18), 251 (11), 153 (29); HRMS: calcd for $C_{22}H_{39}Cl_3O_6SSi-C_4H_9$: 507.059799; found: 507.059819.

(−)-*tert*-Butyl[(3a′*S*,4′*S*,5′*R*,6a′*R*)-4′-ethynyl-5,5-dimethylhexahydro-1′*H*-spiro[[1,3]-dioxane-2,2′-pentalen]-5′-yloxy]dimethylsilane (9): *n*BuLi (1.60 M in hexanes, 40 mL, 61.84 mmol) was added to a stirred solution of mesylate **25** (8.75 g, 15.46 mmol) in THF (60 mL) at −20 °C within 15 min using a syringe pump. After the addition was complete, the mixture was stirred at −20 °C for 20 min. The mixture was then warmed to ambient temperature and stirred for a further 1 h. The resulting clear, orange solution was quenched with aqueous NH_4Cl (20 mL) to give a yellow turbid suspension. The aqueous phase was extracted with Et_2O. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Chromatography (hexanes/EtOAc, 3:1) afforded alkyne **9** (4.85 g, 86%) as a colourless oil. The spectroscopic data for compound **9** matched those reported previously.[10]

(+)-*tert*-Butyl{(3a′*S*,4′*S*,5′*R*,6a′*R*)-5,5-dimethyl-4′-[(*E*)-2-(tributylstannyl)-vinyl]hexahydro-1′*H*-spiro[[1,3]dioxane-2,2′-pentalen]-5′-yloxy}dimethylsilane (26) and *tert*-butyl{(3a′*S*,4′*R*,5′*R*,6a′*R*)-5,5-dimethyl-4′-[1-(tributylstannyl)vinyl]hexahydro-1′*H*-spiro[[1,3]dioxane-2,2′-pentalen]-5′-yloxy}-dimethylsilane (27): Bu_3SnH (4.3 mL, 15.96 mmol) was added dropwise to a solution of alkyne **9** (4.85 g, 13.3 mmol) and $[PdCl_2(PPh_3)_2]$ (187 mg, 0.27 mmol) in THF (35 mL) at room temperature within 1.5 h using a syringe pump. During the addition the colour of the mixture changed from yellow to dark-brown and finally to black. After the addition was complete, the mixture was stirred for an additional 20 min. Then the mixture was concentrated in vacuo. Chromatography (hexanes/EtOAc, 30:1) afforded 8.20 g (94%) of a mixture of stannane **26** and its regioisomer **27**. Preparative HPLC (Kromasil Si-100, 250×30 mm; hexanes/EtOAc, 98:2; RI; UV, 254 nm) gave stannanes **26** (6.88 g, 80%) and **27** (520 mg, 6%) as colourless oils. Stannane **26**: $[\alpha]_D$=+1.32 (c=1.06 in $CDCl_3$); R_f=0.70 (hexanes/EtOAc, 10:1); ^{1}H NMR (400 MHz, C_6D_6): δ=0.08 (s, 3H), 0.10 (s, 3H), 0.69 (s, 3H), 0.84 (s, 3H), 0.93–1.02 (m, 24H), 1.35–1.44 (m, 6H), 1.54–1.66 (m, 7H), 1.86 (dd, J=5.5, J=12.9 Hz, 1H), 1.96–2.35 (m, 6H), 2.53 (m, 1H), 3.23–3.28 (m, 4H), 3.77 (dt, J=6.3, J=9.6 Hz, 1H), 6.05 (dd, J=7.1, J=18.9 Hz, 1H), 6.17 (d, J=18.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, C_6D_6): δ=−4.4 (d), −4.3 (d), 9.5 (u), 13.7 (d), 18.1 (u), 22.2 (d), 22.4 (d), 25.9 (d), 27.5 (u), 29.4 (u), 29.7 (u), 35.5 (d), 37.9 (u), 41.3 (u), 41.9 (u), 42.9 (d), 62.5 (d), 71.6 (u), 71.7 (u), 78.9 (d), 110.1 (u), 127.6 (d), 151.5 (d) ppm; IR (neat): $\tilde{\nu}$=2955 (s), 2856 (s), 1597 (m), 1466 (m), 1375 (m), 1329 (m), 1253 (m), 1118 (s), 1045 (m), 992 (m), 963 (w), 940 (w), 909 (m), 838 (s) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 603 (12), 601 (18), 600 (27), 599 (78), 598 (37), 597 (54), 596 (24), 595 (28), 253 (16), 251 (16), 250 (11), 249 (100), 248 (30), 247 (69), 246 (25), 245 (41), 235 (11), 207 (11), 200 (17), 199 (15), 198 (12), 197 (12), 195 (15), 193 (56), 192 (19), 191 (45), 190 (15), 189 (25), 179 (20), 177 (19), 175 (14), 172 (24), 171 (27), 170 (15), 137 (12), 135 (14); MS (CI, CH_4): *m/z* (%): 657 (4), 656 (4) [M^++1], 655 [M^+] (7), 654 (4), 603 (13), 601 (19), 600 (33), 599 (100), 598 (48), 597 (68), 596 (35), 595 (39), 543 (12), 525 (16), 291 (56), 289 (41), 249 (13); HRMS: calcd for $C_{33}H_{54}O_3SiSn-C_4H_9$: 599.294179; found: 599.294088. Stannane **27**: $[\alpha]_D$=−1.34 (c=1.12 in $CDCl_3$). R_f= 0.68 (hexanes/EtOAc, 10:1); ^{1}H NMR (300 MHz, C_6D_6): δ=0.03 (s, 3H), 0.05 (s, 3H), 0.62 (s, 3H), 0.73 (s, 3H), 0.83–0.95 (m, 24H), 1.25–1.33 (m, 6H), 1.50–1.62 (m, 7H), 1.76–1.82 (m, 1H), 1.90–2.35 (m, 6H), 2.62 (t, J=8.8 Hz, 1H), 3.17–3.25 (m, 4H), 3.85 (dt, J=6.4, J=9.4 Hz, 1H), 5.26 (d, J=2.9 Hz, 1H), 5.86 (dd, J=0.7, J=2.9 Hz, 1H) ppm; ^{13}C NMR (75 MHz, C_6D_6): δ=−4.3 (d), −4.0 (d), 10.3 (u), 13.6 (d), 18.0 (u), 22.1 (d), 22.3 (d), 25.9 (d), 27.6 (u), 29.2 (u), 29.6 (u), 35.9 (d), 38.2 (u), 41.3 (u), 41.8 (u), 45.2 (d), 66.7 (d), 71.7 (u), 78.7 (d), 110.1 (u), 127.7 (u), 156.7 (u) ppm; IR (neat): $\tilde{\nu}$=2954 (s), 2856 (s), 1465 (m), 1327 (w), 1253 (m), 1119 (s), 1003 (w), 909 (w), 838 (m) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 656 (1) [M^+], 603 (14), 601 (18), 600 (31), 599 (100), 598 (37), 597 (67), 596 (34), 595 (38), 248 (12), 192 (13), 178 (13), 176 (15), 171 (11), 170 (10); MS (CI, CH_4): *m/z* (%): 657 (4) [M^++1], 656 (5) [M^+] 655 (7), 654 (6), 652 (4), 603 (15), 601 (20), 600 (34), 599 (100), 598 (49), 597 (72), 596 (40), 595 (43), 291 (15), 289 (12); HRMS (ESI, TOF): calcd for $C_{33}H_{65}O_3SiSn$ [M^++H]: 657.3735; found: 657.3725.

(+)-(*S*,*E*)-1-[(3a′*S*,4′*R*,5′*R*,6a′*R*)-5′-(*tert*-Butyldimethylsilyloxy)-5,5-dimethylhexahydro-1′*H*-spiro[[1,3]dioxane-2,2′-pentalen]-4′-yl]-4-methyloct-1-en-6-yn-3-one (6): *n*BuLi (1.6 M in hexanes, 1.9 mL, 3.05 mmol) was added to a solution of stannane **26** (2.0 g , 3.05 mmol) in THF (15 mL) at −78 °C within 10 min using a syringe pump. After the mixture had been stirred for 1 h at −78 °C, it was added through a double-ended needle to a solution of amide **7** (491 mg, 2.90 mmol) in THF (5 mL) at −78 °C. The mixture was stirred for 1 h at −78 °C and then quenched by the addition of aqueous NH_4Cl (8 mL). Then the mixture was warmed to ambient temperature and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with aqueous NaCl, dried ($MgSO_4$) and concentrated in vacuo. Chromatography (hexanes/EtOAc, 5:1) afforded ketone **6** (1.26 g, 88%) as a colourless oil and stannane **26** (160 mg, 8%). $[\alpha]_D$=+6.79 (c=1.12 in $CDCl_3$); R_f=0.52 (hexanes/EtOAc, 5:1); ^{1}H NMR (400 MHz, C_6D_6): δ=0.02 (s, 6H), 0.76 (s, 3H), 0.80 (s, 3H), 0.95 (s, 9H), 1.16 (d, J=6.9 Hz, 3H), 1.54 (t, J=2.6 Hz, 3H), 1.49–1.57 (m, 1H), 1.78–1.85 (m, 2H), 1.96–2.09 (m, 4H), 2.19–2.33 (m, 2H), 2.47 (q, J=9.1 Hz, 1H), 2.51–2.59 (m, 1H); 2.78 (sex, J= 6.8 Hz, 1H), 3.23 (s, 2H), 3.27 (s, 2H), 3.64 (dt, J=9.1, J=6.0 Hz, 1H), 6.20 (d, J=15.7 Hz, 1H), 6.80 (dd, J=8.9, J=15.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, C_6D_6): δ=−4.5 (d), −4.4 (d), 3.3 (u), 16.5 (d), 18.2 (u), 22.4 (d), 22.5 (d), 22.7 (u), 25.9 (d), 29.9 (u), 35.9 (d), 38.2 (u), 40.7 (u), 42.2 (u), 43.1 (d), 43.9 (d), 57.8 (d), 71.7 (u), 71.9 (u), 76.7 (u), 77.2 (u), 78.6 (d), 110.0 (u), 129.2 (d), 148.4 (d), 199.7 (u) ppm; IR (neat): $\tilde{\nu}$=2954 (s), 2858 (s), 2736 (w), 1694 (m), 1670 (s), 1626 (s), 1467 (m), 1361 (m), 1328 (m), 1255 (s), 1220 (w), 1189 (w), 1119 (s), 1043 (m), 1005 (m), 986 (m), 910 (m), 857 (m), 838 (m) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 474 (1) [M^+], 418 (30), 417 (100), 332 (12), 331 (48), 239 (10), 209 (18), 197 (15), 181 (15), 161 (11), 128 (13), 119 (18), 105 (12); MS (CI, CH_4): *m/z* (%): 476 (4), 475 (11) [M^++1], 474 (3) [M^+], 459 (14), 417 (36), 371 (19), 343

(100), 257 (15); HRMS: calcd for $C_{28}H_{46}O_4Si$: 474.316539; found: 474.316541.

(+)-(3*S*,4*S*,*E*)-1-[(3a′*S*,4′*R*,5′*R*,6a′*R*)-5′-(*tert*-Butyldimethylsilyloxy)-5,5-dimethylhexahydro-1′*H*-spiro[[1,3]dioxane-2,2′-pentalen]-4′-yl]-4-methyloct-1-en-6-yn-3-ol [(15*S*)-29] and (−)-(3*R*,4*S*,*E*)-1-[(3a′*S*,4′*R*,5′*R*,6a′*R*)-5′-(*tert*-butyldimethylsilyloxy)-5,5-dimethylhexahydro-1′*H*-spiro-[[1,3]dioxane-2,2′-pentalen]-4′-yl]-4-methyloct-1-en-6-yn-3-ol [(15*R*)-29]: A solution of ketone **6** (1.13 g, 2.38 mmol) in toluene (2 mL) was added to a solution of oxazaborolidine **28** (0.8 M solution in toluene, 4.4 mL, 3.6 mmol, 1.5 equiv) and catecholborane (0.4 mL, 3.6 mmol, 1.5 equiv) in toluene (5 mL) within 2.5 h using a syringe pump. After the mixture had been stirred for 1 h at −78 °C, MeOH (5 mL) was added and the mixture was warmed to ambient temperature. The mixture was stirred for a further 30 min and then concentrated in vacuo. Column chromatography (hexanes/EtOAc, 5:1) afforded ketone **6** (196 mg, 17 %), alcohol (15*S*)-**29** (851 mg, 75 %) with ≥99 % *de* and alcohol (15*R*)-**29** (40 mg, 5 %) with ≥99 % *de* as colourless oils. The diastereomeric ratio of (15*S*)- and (15*R*)-**29** was 95:5. Alcohol (15*S*)-**29**: $[\alpha]_D = +7.0$ ($c = 1.02$ in THF); $R_f =$ 0.31 (hexanes/EtOAc, 5:1); ^{1}H NMR (300 MHz, C_6D_6): $\delta = 0.07$ (s, 3H), 0.09 (s, 3H), 0.77 (s, 3H), 0.79 (s, 3H), 0.99 (s, 9H), 1.06 (d, $J = 6.9$ Hz, 3H), 1.51–1.56 (m, 1H), 1.58 (t, $J = 2.6$ Hz, 3H), 1.71–1.80 (m, 1H), 1.86 (dd, $J = 6.0$, $J = 13.7$ Hz, 1H), 1.95 (m, 1H), 2.02–2.19 (m, 5H), 2.26–2.43 (m, 4H), 3.26 (s, 2H), 3.31 (s, 2H), 3.67 (dt, $J = 6.3$, $J = 9.2$ Hz, 1H), 3.97 (m, 1H), 5.54 (t, $J = 5.9$ Hz, 2H) ppm; ^{13}C NMR (75 MHz, C_6D_6): $\delta =$ −4.3 (d), −4.2 (d), 3.4 (d), 16.0 (d), 18.2 (u), 22.5 (d), 22.5 (d), 22.6 (u), 26.1 (d), 29.9 (u), 35.9 (d), 38.7 (u), 39.1 (d), 40.9 (u), 42.0 (u), 43.3 (d), 57.4 (d), 71.9 (u), 72.0 (u), 76.1 (d), 76.8 (u), 78.1 (u), 79.3 (d), 110.4 (u), 132.5 (d), 134.4 (d) ppm; IR (neat): $\tilde{\nu} = 3478$ (m), 2954 (s), 2858 (s), 1467 (m), 1392 (m), 1362 (m), 1329 (m), 1254 (m), 1218 (w), 1117 (s), 1042 (m), 1007 (m), 973 (m), 907 (m), 838 (s) cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 476 (1) [M^+], 420 (26), 419 (89), 333 (32), 328 (12), 327 (41), 291 (12), 275 (24), 251 (11), 242 (18), 241 (95), 225 (37), 223 (35), 213 (24), 211 (27), 209 (14), 200 (13), 199 (63), 197 (29), 195 (12), 193 (11), 187 (23), 185 (18), 184 (16), 183 (81), 181 (23), 177 (17), 171 (21), 169 (36), 168 (14), 167 (16), 161 (24), 159 (65), 157 (30), 143 (39), 143 (31), 135 (12), 133 (27), 131 (35), 129 (25), 128 (27), 121 (59), 119 (52), 117 (26), 115 (14), 109 (30), 107 (36), 105 (54), 95 (34), 93 (36), 91 (32), 81 (48); MS (CI, CH_4): *m*/*z* (%): 478 (3), 477 (11) [M^++1], 476 (4) [M^+], 475 (9), 461 (18), 459 (37), 419 (44), 345 (43), 327 (100), 259 (21), 241 (64); HRMS: calcd for $C_{28}H_{48}O_4Si$: 476.332189; found: 476.332141. Alcohol (15*R*)-**29**: $[\alpha]_D = -16.36$ ($c = 1.1$ in $CDCl_3$); $R_f = 0.28$ (hexanes/EtOAc, 5:1); ^{1}H NMR (300 MHz, C_6D_6): $\delta = 0.08$ (s, 3H), 0.10 (s, 3H), 0.75 (s, 3H), 0.79 (s, 3H), 1.01 (s, 9H), 1.09 (d, $J = 6.9$ Hz, 3H), 1.45–1.50 (m, 1H), 1.56 (t, $J = 2.5$ Hz, 3H), 1.74–1.81 (m, 1H), 1.87 (dd, $J = 6.3$, $J = 13.4$ Hz, 1H), 1.95 (m, 1H), 2.03–2.21 (m, 5H), 2.27–2.46 (m, 4H), 3.26 (s, 2H), 3.31 (s, 2H), 3.67 (dt, $J = 6.3$, $J = 9.2$ Hz, 1H), 4.14 (m, 1H), 5.54 (m, 2H) ppm; ^{13}C NMR (75 MHz, C_6D_6): $\delta = -4.3$ (d), −4.2 (d), 3.3 (d), 14.3 (d), 18.3 (u), 22.4 (d), 22.5 (d), 23.2 (u), 26.1 (d), 29.9 (u), 35.9 (d), 38.7 (u), 39.3 (d), 41.0 (u), 42.0 (u), 43.5 (d), 57.7 (d), 71.9 (u), 72.0 (u), 75.1 (d), 76.7 (u), 78.4 (u), 79.3 (d), 110.4 (u), 132.8 (d), 133.7 (d) ppm; IR (neat): $\tilde{\nu} =$ 3476 (m), 2954 (s), 2858 (s), 1468 (m), 1392 (m), 1362 (m), 1329 (m), 1253 (m), 1218 (m), 1117 (s), 1041 (m), 1009 (m), 970 (m), 908 (m), 838 (s) cm^{-1}; MS (EI, 70 eV): *m*/*z* (%): 476 (1) [M^+], 420 (22), 419 (77), 333 (41), 327 (28), 326 (11), 315 (16), 291 (10), 275 (20), 251 (10), 242 (17), 241 (88), 240 (11), 225 (36), 223 (34), 213 (21), 211 (41), 209 (20), 200 (12), 199 (56), 197 (30), 195 (13), 193 (11), 187 (18), 185 (15), 184 (13), 183 (70), 181 (23), 177 (16), 171 (19), 169 (36), 168 (14), 167 (16), 161 (28), 160 (11), 159 (73), 157 (30), 155 (14), 147 (24), 145 (41), 143 (28), 135 (13), 133 (21), 131 (32), 129 (24), 128 (27), 122 (10), 121 (95), 119 (63), 117 (25), 115 (14), 109 (30), 107 (34), 105 (39), 95 (34), 93 (32), 91 (31), 83 (11), 81 (46); MS (CI, CH_4): *m*/*z* (%): 478 (6), 477 (18) [M^++1], 476 [M^+] (5), 475 (11), 461 (26), 460 (16), 459 (42), 420 (18), 419 (60), 346 (16), 345 (70), 343 (13), 333 (18), 328 (25), 327 (100), 259 (32), 242 (15), 241 (83), 225 (12), 223 (11), 183 (10), 121 (17); HRMS (ESI, TOF): calcd for $C_{28}H_{49}O_4Si$ [M^++H]: 477.3400; found: 474.3400.

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[15] For the sake of clarity the prostacyclin numbering is used for iloprost, 3-oxa-iloprost, cicaprost and all building blocks through out this paper except in the experimental part where the numbering of the compounds follows nomenclature rules.

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