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Asymmetric Synthesis of 3-Oxa-15-deoxy-16-(*m*-tolyl)-17,18,19,20-tetranorisocarbacyclin and Its Neuroprotective Analogue 15-Deoxy-16-(*m*-tolyl)-17,18,19,20-tetranorisocarbacyclin Based on the Conjugate Addition–Azoalkene–Asymmetric Olefination Strategy

Marc van de Sande and Hans-Joachim Gais*[a]

Abstract: A fully stereocontrolled synthesis of 3-oxa-15-deoxy-16-(*m*-tolyl)-17,18,19,20-tetranorisocarbacyclin (3-oxa-15-deoxy-TIC, **7b**) and a formal one of 15-deoxy-16-(*m*-tolyl)-17,18,19,20-tetranorisocarbacyclin (15-deoxy-TIC, **7a**) are described. 15-Deoxy-TIC is specific for the neuronal prostacyclin receptor (IP_2) and exhibits neuroprotective activities, and the new 3-oxa-15-deoxy-TIC is expected to be metabolically more stable than 15-deoxy-TIC. The syntheses of **7a** and **7b** are based on the convergent conjugate addition–azoalkene–asymmetric olefination strategy. Key building blocks are the readily available bicyclic azoalkene **14** and the alkenylcopper derivative **15**. The stereoselective conjugate addition of **15** to **14** gave hydrazone **13**, which was stereoselectively converted to the bicyclic ketone **11**. The key steps for the construction of the α side chain of **7a** and **7b** and the regioselective introduction of the endocyclic $\Delta^{6,6a}$ double bond are: 1) a highly selective asymmetric olefination of ketone **11** with the chiral Horner–Wadsworth–Emmons reagent **28** and 2) a regioselective deconjugation of the α,β-unsaturated ester (*E*)-**10** with the chiral lithium amide **29**, which gave the β,γ-unsaturated ester *anti*-**9** with high selectivity. The homoallylic alcohol **8** served at a late stage as the joint intermediate in the syntheses of **7a** and **7b**. While an etherification of **8** furnished, after hydrolysis and deprotection, 3-oxa-15-deoxy-TIC, its alkylation afforded alcohol **37**, the known precursor for the synthesis of 15-deoxy-TIC.

Keywords: asymmetric synthesis · isocarbacyclins · medicinal chemistry · olefination · prostacyclin receptor

Introduction

Evidence has been provided which suggests that prostacyclin (**1**)[1–3] is not only an important hemostasis regulator but also that it plays an important role in the central nervous system.[4–6] Studies of prostacyclin are severely hampered, however, by its short chemical and metabolic half-lifes. The synthesis of a number of chemically stable prostacyclin agonists, including carbacyclin (**2a**),[7–13] (16*S*)-iloprost (**3a**),[12–15] cicaprost (**4a**),[12,13,16,17] isocarbacyclin (**5a**),[12,13,18–23] (15*R*)-16-(*m*-tolyl)-17,18,19,20-tetranorisocarbacyclin ((15*R*)-TIC, **6a**),[24] and 15-deoxy-16-(*m*-tolyl)-17,18,19,20-tetranorisocarbacyclin (15-deoxy-TIC, **7a**),[25,26] has significantly aided investigations of the neuronal functions of **1**. They revealed a widespread expression of two different prostacyclin receptors in the brain: the IP_1 receptor, also found in the peripheral system, and the IP_2 receptor, apparently expressed only in the neuronal system.[27–41] While isocarbacyclin (**5a**) exhibits similar binding affinities for both IP_1 and IP_2 subtypes, iloprost (**3a**) is specific for the IP_1 receptor and (15*R*)-TIC (**6a**) for the IP_2 receptor.[28] Recently, it was found that 15-deoxy-TIC (**7a**) has an even higher affinity and specificity for the IP_2 receptor than (15*R*)-TIC (**6a**).[25,31] In agreement with the binding studies, iloprost (**3a**) is a very potent vasodilator and inhibitor of blood platelet aggregation, while isocarbacyclins **6a** and **7a** exhibit only very weak inhibitory effects on platelet aggregation.[32] Most interestingly, the IP_2-specific (15*R*)-TIC (**6a**) and 15-deoxy-TIC (**7a**), the methyl esters of which are able to cross the blood–brain barrier, but not iloprost (**3a**) show, besides an inhibition of oxygen-induced apoptosis of neuronal cells, a neuroprotective effect on transient ischemia and an improvement of learning as

[a] Dipl.-Chem. M. van de Sande, Prof. Dr. H.-J. Gais
Institut für Organische Chemie
Rheinisch-Westfälischen Technischen Hochschule (RWTH) Aachen
Landoltweg 1, 52056 Aachen (Germany)
Fax: (+49) 241-809-2665
E-mail: Gais@RWTH-Aachen.de

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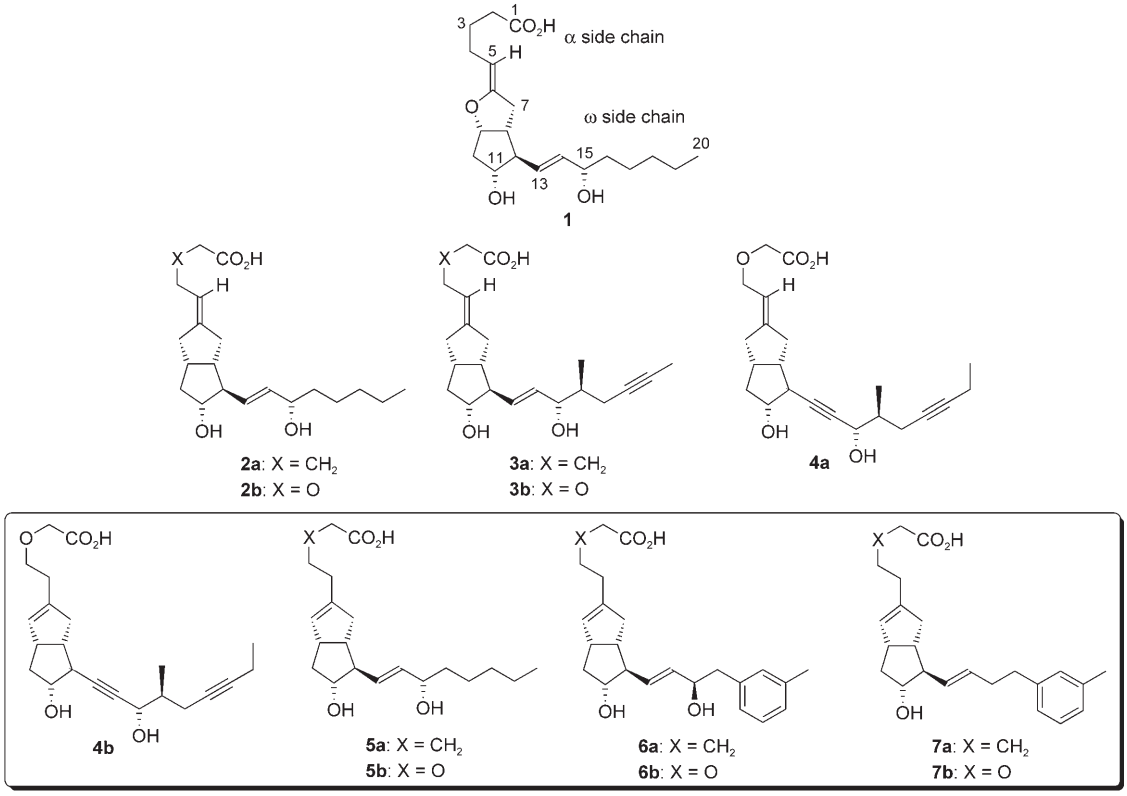


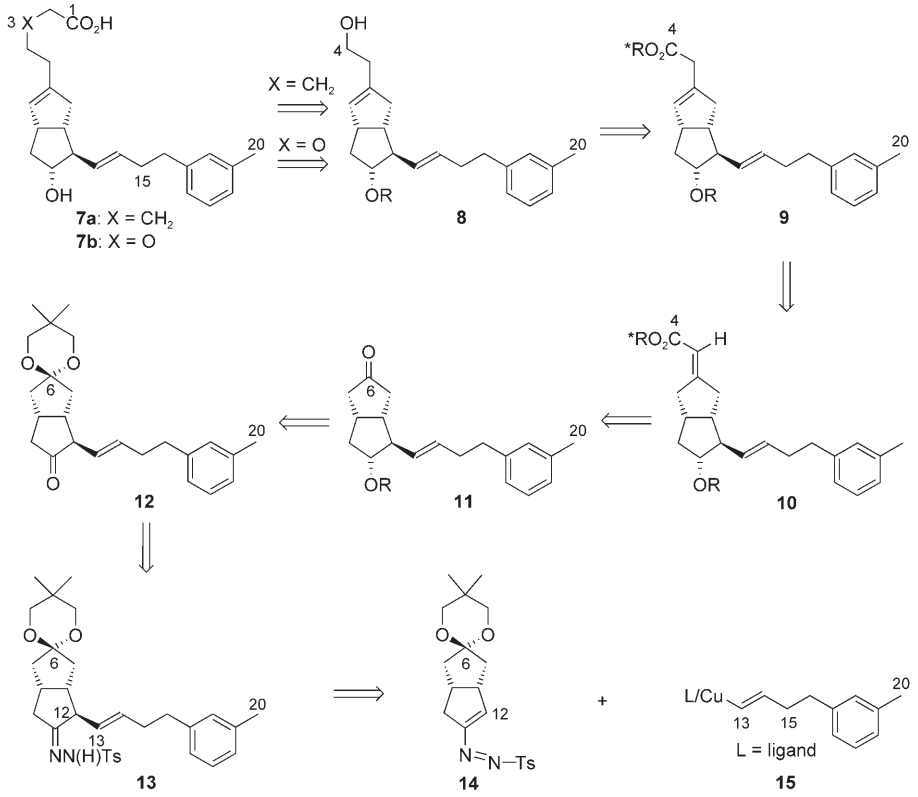
well as memory impairments in a rat model of Alzheimer's disease.[31,34,36] The difference in the prevention of neuronal cell death by (15*R*)-TIC (**6a**) and 15-deoxy-TIC (**7a**) is well correlated with the difference in their binding potency for the IP_2 receptor.[32] Thus, there is hope that the design and synthesis of new ω-side-chain-modified isocarbacyclin derivatives as specific targets for the IP_2 receptor will contribute to the elucidation of the neuronal functions of prostacyclin. The IP_2 receptor could, perhaps, be a novel target for the development of prostacyclin-derived agents for the treatment of neurodegenerative diseases and brain disorders,[42–51] a topic that will gain increasing importance in the future because of the aging world population.[52]

As carbacyclin (**2a**), iloprost (**3a**), and isocarbacyclin (**5a**) are rapidly metabolized by β-oxidation of the α side chain,[53–55] (15*R*)-TIC (**6a**) and 15-deoxy-TIC (**7a**) are expected to also suffer such a metabolization. However, the metabolic degradation of the α side chain of carbacyclins and isocarbacyclins can be prevented by the introduction of an oxygen atom at the β-position, as shown by the examples of 3-oxa-iloprost (**3b**),[15,56,57] cicaprost (**4a**),[16,17,56,58] 3-oxa-carbacyclin (**2b**),[59–62] 3-oxa-isocarbacyclin (**5b**),[62,63] and isocicaprost (**4b**).[17] Thus, the new 3-oxa derivatives 3-oxa-(15*R*)-TIC (**6b**) and 3-oxa-15-deoxy-TIC (**7b**) would be interesting synthetic targets, as they are expected to have a much higher metabolic stability than **6a** and **7a**, respectively. Because of the IP_2-specific drug-like action of **6a** and **7a** and the current strong interest in the discovery of new neuroprotective drugs, it would be desirable to develop a new route to isocarbacyclins that would enable a fully stereocontrolled synthesis of both isocarbacyclin and 3-oxa-isocarbacyclin derivatives carrying the various ω side chains. Although imaginative and yielding, the known syntheses of isocarbacyclins do not allow all of these criteria to be met.[12,13,18–26] The most challenging aspects of the synthesis of isocarbacyclins are, besides the control of the absolute configuration, the construction of the bicyclic ring system, the regioselective introduction of the $\Delta^{6,6a}$ double bond, and the variability in regard to the ω side chain, the structure of which is crucial for biological activity.

We have recently developed a new general strategy for the fully stereocontrolled synthesis of carbacyclins and 3-oxa-carbacyclins including **2a**, **3a**, **2b**, and **3b**.[11,15] This strategy features the establishment of the complete ω side chain through a conjugate addition of the corresponding chiral alkenylcopper building block to a chiral bicyclic azoalkene building block, and uses an asymmetric olefination as the key step for the construction of the α side chain. Herein, we describe the fully stereocontrolled synthesis of both the known 15-deoxy-TIC (**7a**) and the new 3-oxa-15-deoxy-TIC (**7b**) based on the conjugate addition–azoalkene–asymmetric olefination strategy. We thus show that this strategy is also well suited for the asymmetric synthesis of isocarbacyclin (**5a**), 3-oxa-isocarbacyclin (**5b**), and their derivatives. The 15-deoxy-TICs **7a** and **7b** were selected as primary targets because of their higher potency and expected higher metabolic stability than **6a**, respectively.

Results and Discussion

Retrosynthesis: The retrosynthetic analysis of **7a** and **7b** called for a stereoselective conjugate addition of the C13–C20 alkenylcopper derivative **15** to the C6–C12 bicyclic azoalkene **14** with the formation of hydrazone **13** and its chemo- and stereoselective conversion to ketone **11** (Scheme 1).

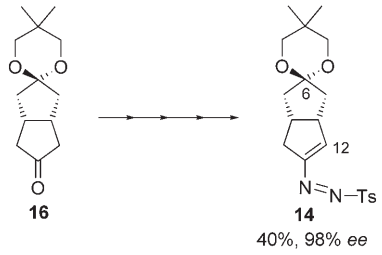


Scheme 1. Retrosynthetic analysis of 15-deoxy-TIC and 3-oxa-15-deoxy-TIC based on the conjugate addition–azoalkene–asymmetric olefination strategy. Ts = *p*-toluenesulfonyl (tosyl).

The regioselective establishment of the $\Delta^{6,6a}$ double bond and the construction of the α side chains of **7a** and **7b** should be accomplished by an asymmetric Horner–Wadsworth–Emmons (HWE) olefination of ketone **11** with a chiral HWE reagent, leading to the *E*-configured α,β-unsaturated ester **10**. Because of the highly stereoselective olefination of similar bicyclic ketones carrying, however, different ω side chains, we were confident of achieving a similarly efficient transformation of ketone **11**.[11,15,17,60–62] The next crucial stereochemical step would be the regioselective deconjugation of ester **10** with the formation of the β,γ-unsaturated ester **9**. We had previously realized the regioselective deconjugation of structurally analogous esters by using a chiral lithium amide.[17,21] Alcohol **8** was planned to serve at a late stage as a joint intermediate in the synthesis of **7a** and **7b**. The etherification and alkylation of the allyl alcohol **8** should give 15-deoxy-TICs **7a** and **7b**, respectively. While the etherification of **8** should pose no problems, its alkylation with a corresponding homoenolate could perhaps be more difficult to achieve.[64]

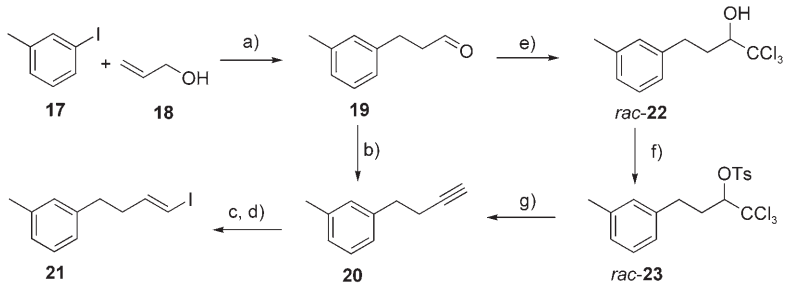
Synthesis of the C6–C12 and C13–C20 building blocks: Azoalkene **14** of 98% enantiomeric excess (*ee*) was synthesized in four steps by starting from the achiral bicyclic ketone **16** (Scheme 2) in 40% overall yield as described previously.[11,15,65] It was planned to synthesize the C13–C20 alkenylcopper building block **15** through an iodine–lithium–copper exchange of the alkenyl iodide **21** (Scheme 3). The required alkyne **20** was obtained from aldehyde **19** following two different routes. The palladium-catalyzed addition of the aryl iodide **17** to allyl alcohol **18** afforded aldehyde **19** in 80% yield.[66] The conversion of aldehyde **19** into alkyne **20** was accomplished through the reaction with lithiated trimethylsilyl diazomethane,[67] which furnished the alkyne in 84% yield.

The alternative and less expensive route to **20** started with the treatment of aldehyde **19** with Cl_3CCO_2H/Cl_3CCO_2Na in DMF,[68] which gave trichlorocarbinol *rac*-**22**. The tosylation of crude *rac*-**22** with TsCl in the presence of DABCO afforded tosylate *rac*-**23**. Finally, elimination of the crude trichloro tosylate *rac*-**23** upon treatment with an excess of MeLi[67] afforded alkyne **20** in 79% overall yield based on aldehyde **19**.



Scheme 2. Asymmetric synthesis of azoalkene **14**.[11,15,65]

The alkenyl iodide **21** was stereoselectively synthesized through the hydrozirconation of alkyne **20** with $Cp_2Zr(H)Cl$[69,70] and treatment of the corresponding alkenylzirconium derivative with an excess of iodine.[69,70] Thereby, the *E*-configured alkenyl iodide **21** was obtained in 76%

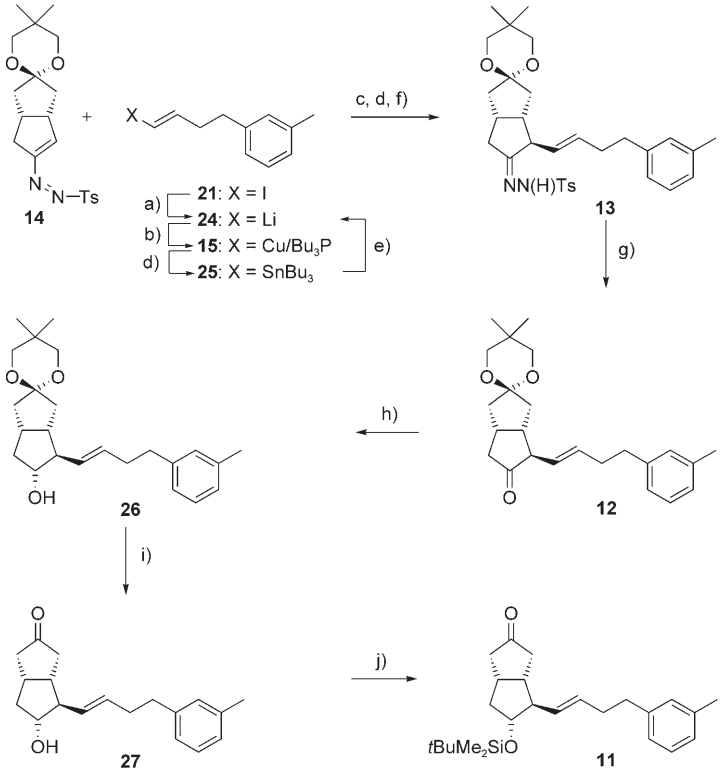


Scheme 3. Synthesis of the alkenyl iodide **21**. a) $Pd(OAc)_2$, $NaHCO_3$, Bu_4NCl, DMF, 30 °C; b) $(CH_3)_3SiCHN_2$, *n*BuLi, THF, −78 °C to RT; c) $Cp_2Zr(H)Cl$, CH_2Cl_2, RT; d) I_2, CH_2Cl_2, RT; e) Cl_3CCO_2H/Cl_3CCO_2Na, DMF, RT; f) TsCl, NEt_3, DABCO, CH_2Cl_2, RT; g) MeLi, THF, −78 °C to RT. Cp = cyclopentadienyl; DABCO = 1,4-diazabicyclo[2.2.2]octane.

yield. ^{1}H NMR spectroscopic analysis showed the iodoalkene to be free of the corresponding *Z* isomer.[71]

Alkenylcopper–azoalkene conjugate addition: The stereoselective conjugate addition of the alkenylcopper derivative **15** to the azoalkene **14** is a key step in the synthesis of **7a** and **7b**. Treatment of iodoalkene **21** with *n*BuLi afforded the alkenyllithium derivative **24**, which was converted to the alkenylcopper derivative **15** upon treatment with one equivalent of CuI and 2.6 equivalents of Bu_3P (Scheme 4). We had previously shown that alkenyl- and arylcopper reagents readily react with azoalkene **14** in the presence of the phosphane by a 1,4-addition.[11,15,65] Accordingly, reaction of azoalkene **14** with two equivalents of **15** cleanly afforded the diastereomerically pure hydrazone **13** in 79% yield. Quenching of the reaction mixture with 2.9 equivalents of Bu_3SnCl enabled the isolation of stannane **25** in 54% yield based on iodide **21**. Thus, because of the quantitative conversion of stannane **25** to the alkenyllithium derivative **24** upon treatment with *t*BuLi in THF at −78 °C, the excess of iodide **21** used in the synthesis of **13** can be recycled.

The chemoselective cleavage of hydrazone **13** was accomplished by its treatment with 1.05 equivalents of $(PhSeO)_2O$ in the presence of seven equivalents of cyclohexene, which serves as a radical scavenger.[11,15,72] Because of the instability of the thus-formed ketone **12**, it was not further purified but stereoselectively reduced with $NaBH_4$, which afforded the diastereomerically pure alcohol **26** in 61% overall yield based on hydrazone **13**. The deprotection of acetal **26** with TsOH in acetone/water gave ketone **27** in 94% yield. The subsequent protection of the hydroxy group of **27** furnished the silyl ether **11** in 93% yield.

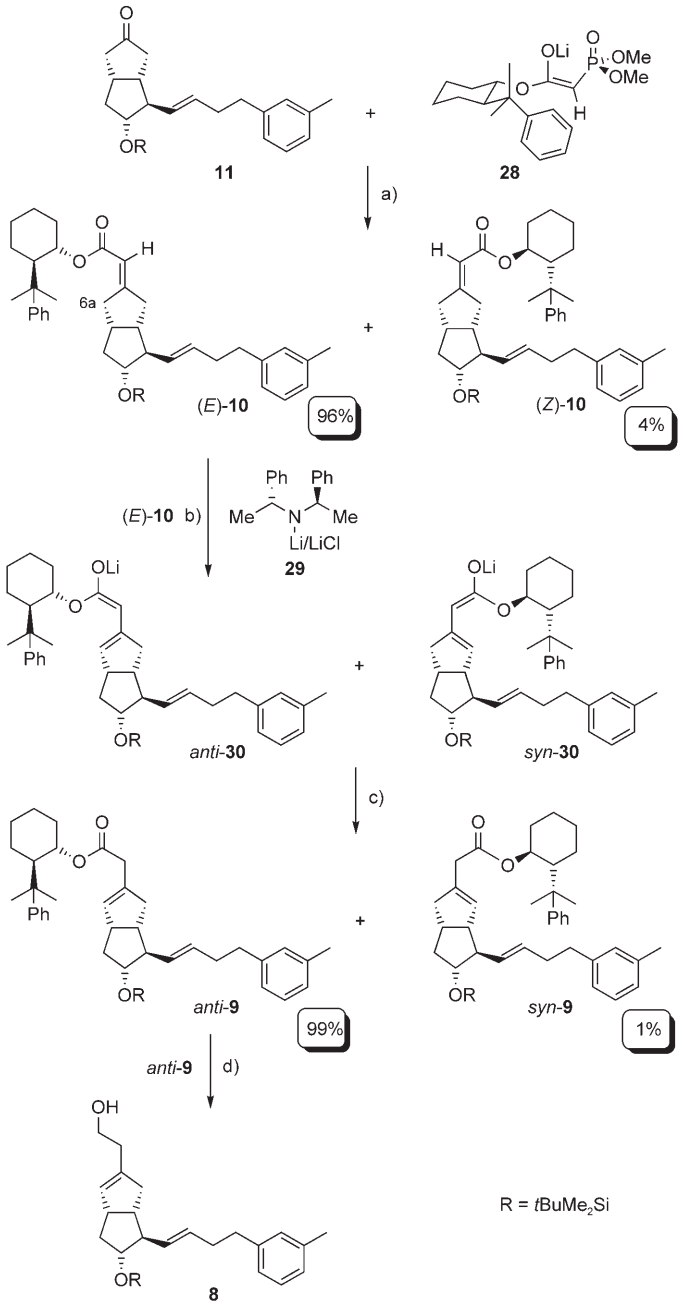


Scheme 4. Conjugate addition of the alkenylcopper compound **15** to azoalkene **14**. a) **21** (2 equiv), *n*BuLi (2 equiv), THF, −78 °C, 3 h; b) CuI (2 equiv), Bu_3P (5.2 equiv), THF, −78 °C, 10 min; c) **14** (1 equiv), THF, −78 °C, 45 min; d) Bu_3SnCl (2.9 equiv); e) *t*BuLi, THF, −78 °C; f) aqueous NH_4Cl; g) cyclohexene (7.4 equiv), $(PhSeO)_2O$, THF, RT; h) $NaBH_4$, EtOH, 0 °C; i) H_2O, TsOH, acetone, RT; j) $tBuMe_2SiCl$, imidazole, DMF, RT.

Regioselective introduction of the $\Delta^{6,6a}$ double bond: It was planned to regioselectively establish the $\Delta^{6,6a}$ double bond and O–C5 moiety of **7b** as well as the $\Delta^{6,6a}$ double bond and C4,C5 moiety of **7a** through an asymmetric HWE reaction of ketone **11** with a chiral phosphonoacetate,[11,15,17,60–62] followed by a regioselective deconjugation of the corresponding α,β-unsaturated ester.[17,62]

The reaction of ketone **11** with ten equivalents of the chiral phosponate **28**[11,15,17,60–62] in THF at −62 °C for seven days afforded a mixture of the two diastereomeric esters (*E*)-**10** and (*Z*)-**10** in a ratio of 96:4 (Scheme 5). Separation of the esters by preparative HPLC gave (*E*)-**10** with ≥99% diastereomeric excess (*de*) in 79% yield and (*Z*)-**10** with ≥99% *de* in 2% yield. The excess of **28** was recovered almost quantitatively.

A highly regioselective deconjugation of the unsaturated ester (*E*)-**10** was achieved through deprotonation with the chiral lithium amide **29**[11,15,65] in THF at −105 °C, followed by a regioselective protonation of the lithium enolates *anti*-**30** and *syn*-**30** at the α-position. Thereby, a mixture of the two isomeric esters *anti*-**9** and *syn*-**9** was obtained in a ratio of 99:1 in 89% yield. Separation of the esters by preparative HPLC afforded pure *anti*-**9** in 82% yield and pure *syn*-**9** in 1% yield.



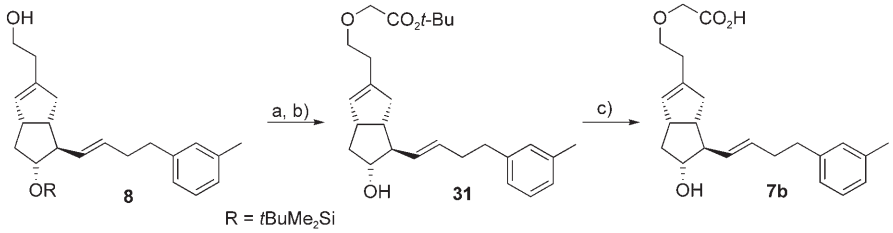
Scheme 5. Regioselective establishment of the $\Delta^{6,6a}$ double bond and α side chain of **7a** and **7b**. a) THF, −62 °C, 7 d, HPLC; b) THF, −105 °C; c) aq. $NaHCO_3$, HPLC; d) DIBAL-H, THF, 0 °C to RT. DIBAL-H = diisobutylaluminum hydride.

Because of the highly enantioselective deprotonation of the prochiral bicyclic ketone **16** with the chiral base **29**, which is the first step of the synthesis of azoalkene **14** (see Scheme 2), we also applied this base for the selective deprotonation of ester (*E*)-**10** at the 6a-methylene group. Evidence has been provided, however, suggesting that an achiral lithium amide would also cause a regioselective deprotonation of ester (*E*)-**10**.[62] The high selectivity of the formation of the lithium enolate *anti*-**30** in the deprotonation of (*E*)-**10** with **29** is perhaps not a reflection of the chirality of the base, but due to its prior coordination to the carbonyl group followed by an intramolecular deprotonation at the *syn* position.[73] Finally, the reduction of ester *anti*-**9** with DIBAL-H afforded the homoallylic alcohol **8** in 88% yield.

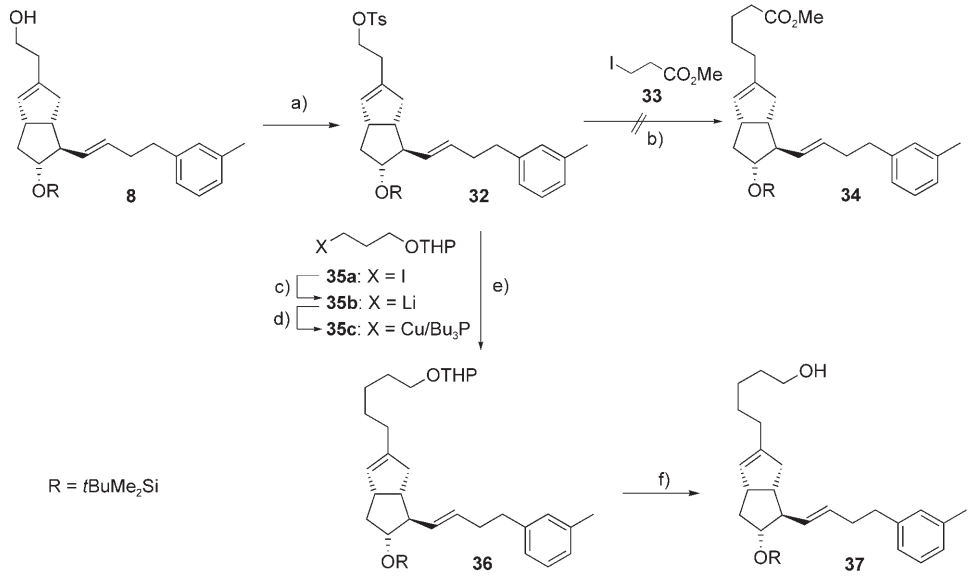
Synthesis of 3-oxa-15-deoxy-TIC (7b): The synthesis of **7b** from alcohol **8** was completed by its etherification with *tert*-butyl 2-bromoacetate in the presence of aqueous NaOH,[11,15–17,62] followed by deprotection of the corresponding silyl ether, which gave ester **31** in 89% yield (Scheme 6). The hydrolysis of ester **31** with aqueous NaOH in MeOH followed by careful acidification with NaH_2PO_4 to pH 4 furnished 3-oxa-15-deoxy-TIC (**7b**) in 98% yield.

Formal synthesis of 15-deoxy-TIC (7a): The homoallylic alcohol **8** was designed to function as the late-stage intermediate in the synthesis of both **7a** and **7b**. Thus, an alkylation of **8** en route to **7a** was required. Tosylate **32** was prepared from alcohol **8** in 90% yield (Scheme 7). The alkylation of tosylate **32** with the functionalized copper reagent **33**,[74] which was prepared from the corresponding organozinc iodide,[75,76] with formation of ester **34** could not be accomplished. Treatment of **32** with **33** led to an almost quantitative recovery of **32**. Thus, an alternative route involving alkylation of **32** with the copper reagent **35c** was envisioned. The alkylcopper derivative **35c** required for the alkylation of **32** was prepared from iodide **35a**[77] via the alkyllithium derivative **35b**.[78] The treatment of tosylate **32** with four equivalents of the alkylcopper reagent **35c**[79] afforded the ether **36** in 82% yield. The selective deprotection of the THP ether **36** was achieved through treatment with an excess of freshly prepared $MgBr_2$ in Et_2O,[80,81] which gave alcohol **37** in 64% yield after preparative HPLC.

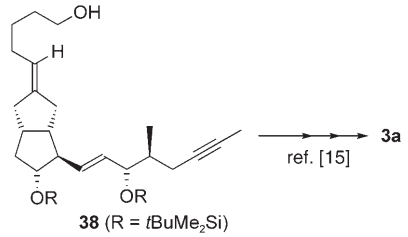
As a two-step oxidation of alcohol **37** to 15-deoxy-TIC (**7a**) via the corresponding aldehyde had recently been described,[26] its preparation represents a formal asymmetric synthesis of **7a**. In our previously described asymmetric synthesis of iloprost (**3a**) and isocarbacyclin (**5a**) from alcohols **38** and **39**, respectively, (Scheme 8) we had already success-

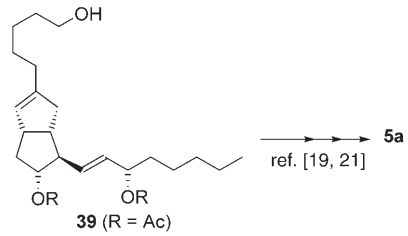


Scheme 6. Completion of the synthesis of 3-oxa-15-deoxy-TIC (**7b**). a) $BrCH_2CO_2tBu$, aq NaOH, Bu_4NHSO_4, CH_2Cl_2; b) Bu_4NF, THF; c) NaOH, MeOH, NaH_2PO_4, pH 4.



Scheme 7. Formal synthesis of 15-deoxy-TIC (**7a**). a) TsCl, NEt_3, DABCO, CH_2Cl_2, RT; b) Zn (1 equiv), dibromoethane (0.036 equiv), $ClSiMe_3$ (0.036 equiv); **33** (0.97 equiv), THF; CuCN (0.80 equiv), LiCl (1.7 equiv), THF; **32**; c) *t*BuLi (2 equiv), Et_2O, *n*-pentane, −78 °C, 1 h; d) CuI (1 equiv), Bu_3P (2.6 equiv), Et_2O, −78 to −40 °C; e) **32** (0.25 equiv), Et_2O, −40 to 0 °C, 2 h; f) $MgBr_2$, Et_2O. THP = tetrahydropyranyl.





Scheme 8. Application of the two-step oxidation of primary alcohols to carboxylic acids in the synthesis of iloprost and isocarbacyclin.

fully applied such a two-step oxidation by using DMSO/NEt_3/pyr·SO_3 and Ag_2O.[15,19,21]

Conclusion

We have developed a fully stereocontrolled convergent synthesis of 3-oxa-15-deoxy-TIC and a formal one of 15-deoxy-TIC based on a conjugate addition–azoalkene–asymmetric olefination strategy. The key step of these syntheses is the conjugate addition of the alkenylcopper derivative **15** to the azoalkene **14**. Because of the successful conjugate addition of several alkenyl- and arylcopper derivatives to the azoalkene (Figure 1), it is to be expected that this strategy will allow for the synthesis of a broad range of ω-side-chain-modified isocarbacyclins, which will be required for the further investigation of the neuronal-specific IP_2 receptor and the development of a prostacyclin-derived neuroprotective agent.

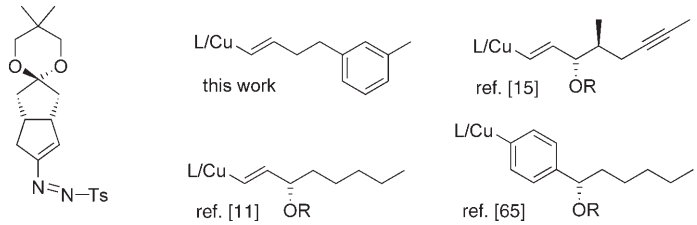


Figure 1. Alkenyl- and arylcopper derivatives used in conjugate addition to the bicyclic azoalkene.

Experimental Section

General methods: All reactions were carried out under an argon atmosphere in absolute or dry solvents with syringe and Schlenk techniques in oven-dried glassware. THF, Et_2O, and *n*-pentane were distilled under argon from lead/sodium in the presence of benzophenone. CH_2Cl_2 was distilled from CaH_2. Dry DMF was obtained from commercial sources and stored over molecular sieves. CuI from commercial sources was dried by heating to 200 °C in high vacuo for 10 min prior to use. Bulk solvents for chromatography and extraction were distilled prior to use. Reagents were obtained from commercial sources and used without further purification unless otherwise stated. *n*BuLi and *t*BuLi were standardized by titration with diphenylacetic acid. Molecular sieves (4 Å) were activated prior to use by heating at 200 °C for 4 h in vacuo (0.01 mbar). Bis[(*R*)-1-phenylethyl]ammonium chloride[82] with ≥99 % *ee* and (1*S*,2*R*)-2-(2-phenylpropan-2-yl)cyclohexyl-2-(dimethoxyphosphoryl) acetate[62] with ≥98 % *ee* were prepared according to the literature. TLC was performed on Merck precoated plates (silica gel 60 F_{254}, layer thickness 0.2 mm), and chromatography was performed with Merck silica gel 60 (0.040–0.063 mm) in the flash mode with a nitrogen pressure of 0.2 bar. Preparative HPLC was carried out with a Dynamax SD-1 pump by using Varian 320 UV/Vis and Knauer refractive index (RI) detectors on Kromasil Si-100 and Chiralpak AD columns. GC analyses were run on Varian 3800, Chrompack CP-9000, and Carlo Erba Mega instruments. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300, or a Varian Inova 400 instrument. Chemical shifts are reported relative to TMS ($\delta = 0.00$ ppm) as internal standard. The following abbreviations are used to designate the multiplicity of the peaks in ^1H NMR spectra: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = 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 attached proton test (APT) pulse sequence. Assignments in the ^1H NMR spectra were made by gradient multiple quantum (GMQ) COSY and het-

eronuclear correlation spectroscopy (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 $\tilde{\nu} \geq 800\ cm^{-1}$ are listed, vs = very strong, s = strong, m = medium, w = weak. LRMS were recorded on a Finnigan SSQ 7000 instrument by using either electron-impact ionization (EI, 70 eV) or chemical ionization (CI, CH_4, or isobutane). Only peaks of $m/z \geq 80$ and an intensity of 5%, except decisive ones, are listed. HRMS were recorded on a Varian MAT 95 mass spectrometer. 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 grams per 100 mL. Elemental analyses were performed by the Institut für Organische Chemie Microanalytical Laboratory.

3-*m*-Tolylpropanal (19): Allyl alcohol **18** (24 mL, 351 mmol) was added to a suspension of $NaHCO_3$ (49.7 g, 592 mmol) and Bu_4NCl (70.9 g, 255 mmol) in DMF (200 mL). After the mixture had been stirred at room temperature for 10 min, $Pd(OAc)_2$ (681 mg, 3.03 mmol) was added. Then a solution of the iodide **17** (30 mL, 234 mmol) in DMF was added dropwise at 30 °C over a period of 45 min to the orange suspension, which turned black during the addition. According to GC analysis, iodide **17** was consumed after 18 h. The mixture was left to cool to room temperature and the excess of **18** was removed in vacuo. Water (100 mL) and *n*-pentane (100 mL) were added and the mixture was stirred for 30 min. After this time, the mixture was filtered through Celite and the aqueous phase was extracted with *n*-pentane (3 × 100 mL). The combined organic phases were washed with water (100 mL) and dried ($MgSO_4$). Concentration in vacuo and purification by chromatography (*n*-hexane/EtOAc 6:1) afforded aldehyde **19** (27.7 g, 80%) as a colorless oil. $R_f = 0.57$ (*n*-hexane/EtOAc 4:1); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.31$ (s, 3H; CH_3), 2.71 (dt, $J = 1.4$, 7.5 Hz, 2H; CH_2CHO), 2.89 (t, $J = 7.5$ Hz, 2H; CH_2CH_2CHO), 6.93–7.02 (m, 3H), 7.16 (t, $J = 7.8$ Hz, 1H), 9.76 ppm (t, $J = 1.4$ Hz, 1H; CHO); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.3$ (d), 28.0 (u), 45.2 (u), 125.0 (d), 126.8 (d), 128.2 (d), 128.8 (d), 137.9 (u), 140.0 (u), 201.2 ppm (d); IR (neat): $\tilde{\nu} = 3103$ (w), 3022 (m), 2922 (m), 2862 (m), 2823 (m), 2722 (m), 1724 (vs), 1608 (m), 1590 (w), 1489 (m), 1450 (w), 1408 (w), 1387 (w), 1356 (w), 1277 (w), 1172 (w), 1095 (w), 1056 (w), 907 (w), 884 (w), 848 cm^{-1} (w); MS (EI, 70 eV): m/z (%): 148 (100) $[M]^+$, 120 (13), 119 (22), 117 (15), 115 (15), 106 (66), 105 (98), 103 (18), 92 (55), 91 (60); HRMS (EI, 70 eV): m/z: calcd for $C_{10}H_{12}O$: 148.088815 $[M]^+$; found: 148.088846.

1,1,1-Trichloro-4-*m*-tolylbutan-2-ol (*rac*-22): Cl_3CCO_2Na (61.2 g, 331 mmol) was added in portions at 0 °C to a stirred solution of Cl_3CCO_2H (54.2 g, 331 mmol) and aldehyde **19** (25 g, 169 mmol) in DMF (180 mL). After the mixture had been stirred for 1 h, it was left to warm to room temperature and stirring was continued for 3 h. GC analysis showed the consumption of the aldehyde. Then water (250 mL) was added and the aqueous phase was extracted with *n*-pentane (4 × 80 mL). The combined organic phases were dried ($MgSO_4$), and the solvent was removed in vacuo. The resulting crude alcohol was used for the next step without further purification. Purification of a small amount of the crude alcohol by chromatography (*n*-hexane/EtOAc 8:1) gave alcohol *rac*-**22** as a colorless solid. $R_f = 0.35$ (*n*-hexane/EtOAc 7:1); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.91$–2.01 (m, 1H), 2.31–2.41 (m, 1H), 2.33 (s, 3H; CH_3), 2.67–2.77 (m, 1H), 2.91–2.99 (m, 1H), 3.04–3.09 (m, 1H; OH), 3.97 (ddd, $J = 1.9$, 5.7, 10.0 Hz, 1H; *CH*OH), 7.00–7.06 (m, 3H), 7.19 ppm (t, $J = 7.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.3$ (d), 31.8 (u), 32.94 (u), 81.9 (d), 104.0 (u), 125.2 (d), 126.8 (d), 128.2 (d), 129.1 (d), 137.9 (u), 140.4 ppm (u); IR (neat): $\tilde{\nu} = 3447$ (m, br), 3021 (m), 2967 (m), 2927 (m), 2863 (m), 2250 (w), 1712 (w), 1608 (m), 1488 (w), 1452 (m), 1384 (w), 1265 (w, br), 1161 (w), 1086 (m), 1008 (w), 909 cm^{-1} (s); MS (EI, 70 eV): m/z (%): 270 (3), 268 (10), 266 (10) $[M]^+$, 195 (16), 131 (10), 119 (10), 106 (13), 105 (100), 91 (6); elemental analysis calcd (%) for $C_{11}H_{13}Cl_3O$ (267.58): C 49.38, H 4.90; found: C 49.45, H 4.93; HRMS (EI, 70 eV): m/z: calcd for $C_{11}H_{13}Cl_3O$: 266.003199 $[M]^+$; found: 266.003204.

1,1,1-Trichloro-4-*m*-tolylbutan-2-yl 4-methylbenzenesulfonate (*rac*-23): TsCl (57.9 g, 304 mmol) was added at room temperature to a stirred solution of the crude alcohol *rac*-**22**, NEt_3 (23 mL, 304 mmol), and DABCO (7.62 g, 67.9 mmol) in CH_2Cl_2 (200 mL). After 2.5 h, GC analysis showed the complete consumption of the alcohol. Then water (80 mL) and Et_2O (200 mL) were added and the mixture was stirred for 30 min. The organic phase was washed with 5 M HCl (50 mL), and the combined aqueous phases were extracted with Et_2O (3 × 100 mL). The combined organic phases were washed successively with 2.5 M HCl (100 mL) and water (100 mL) and were then dried ($MgSO_4$). Concentration in vacuo gave the crude tosylate *rac*-**23**, which was used without purification in the next step. Purification of a small amount of the crude tosylate by chromatography (*n*-hexane/EtOAc 8:1) gave tosylate *rac*-**23** as a colorless oil. $R_f = 0.43$ (*n*-hexane/EtOAc 7:1); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.16$–2.28 (m, 1H), 2.32 (s, 3H; CH_3), 2.44 (s, 3H; CH_3), 2.44–2.53 (m, 1H), 2.68–2.77 (m, 1H), 2.79–2.88 (m, 1H), 5.12 (dd, $J = 2.5$, 8.8 Hz, 1H; *CH*OTs), 6.96 (d, $J = 7.5$ Hz, H), 6.97 (s, 1H), 7.02 (d, $J = 7.5$ Hz, 1H), 7.18 (t, $J = 7.5$ Hz, 1H), 7.34 (d, $J = 8.2$ Hz, 2H), 7.86 ppm (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.3$ (d), 21.6 (d), 31.7 (u), 33.7 (u), 88.3 (d), 98.6 (u), 125.2 (d), 126.9 (d), 127.7 (d), 128.3 (d), 129.0 (d), 129.5 (d), 133.8 (u), 138.0 (u), 139.7 (u), 144.9 ppm (u); IR (neat): $\tilde{\nu} = 3065$ (w), 2941 (m), 2864 (w), 2257 (w), 1589 (m), 1491 (w), 1453 (w), 1371 (s), 1177 (vs), 1096 (m), 1028 (m), 936 (s), 910 (s), 851 (s), 812 cm^{-1} (m); MS (EI, 70 eV): m/z (%): 424 (4), 422 (11), 420 (11) $[M^+]$, 247 (8), 176 (17), 141 (25), 139 (65), 131 (17), 119 (15), 118 (100), 105 (26); elemental analysis calcd (%) for $C_{18}H_{19}Cl_3O_3S$ (421.77): C 51.26, H 4.54; found: C 51.33, H 4.58; HRMS (EI, 70 eV) calcd for $C_{18}H_{19}Cl_3O_3S$ $[M]^+$: 420.012051; found: 420.012028.

1-(But-3-ynyl)-3-methylbenzene (20):

From tosylate rac-**23**: MeLi (500 mL, 1.6 M in hexanes, 800 mmol) was added dropwise at −78 °C to a stirred solution of the crude tosylate *rac*-**23** in THF (200 mL). After the mixture had been stirred at −78 °C for 1 h, it was warmed to room temperature and saturated aqueous NH_4Cl (50 mL) was added. Then water (60 mL) and Et_2O (100 mL) were added and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (*n*-hexane) gave alkyne **20** (21.3 g, 148 mmol) as a colorless liquid.

From aldehyde **19**: *n*BuLi (24 mL, 1.6 M in hexanes, 38 mmol) was added at −78 °C to a solution of $(CH_3)_3SiCHN_2$ (20 mL, 2.0 M in hexanes, 40 mmol) in THF (40 mL). After the mixture had been stirred for 20 min, a solution of aldehyde **19** (4.85 g, 32.7 mmol) in THF (15 mL) was added. After stirring for 1 h at −78 °C, the mixture was left to warm to room temperature and saturated aqueous NH_4Cl (40 mL) was added. The aqueous phase was extracted with Et_2O (5 × 40 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (*n*-hexane) gave alkyne **20** (3.96 g, 84%) as a colorless liquid. $R_f = 0.65$ (*n*-hexane/EtOAc 2:1); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.94$ (t, $J = 2.7$ Hz, 1H; C≡CH), 2.31 (s, 3H; CH_3), 2.44 (dt, $J = 2.7$, 7.6 Hz, 2H; CH≡CCH_2), 2.78 (t, $J = 7.6$ Hz, 2H; CH≡CCH_2CH_2), 6.99–7.01 (m, 3H), 7.17 ppm (t, $J = 7.7$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.5$ (u), 21.3 (d), 34.7 (u), 68.7 (d), 83.7 (u), 125.2 (d), 126.9 (d), 128.1 (d), 129.0 (d), 137.7 (u), 140.1 ppm (u); IR (neat): $\tilde{\nu} = 3297$ (vs), 3022 (s), 2924 (vs), 2862 (s), 2117 (m), 1609 (s), 1590 (m), 1488 (s), 1451 (s), 1431 (m), 1378 (w), 1339 (w), 1251 (m, br), 1172 (w), 1093 (w), 1040 (w), 880 (m), 844 cm^{-1} (m); MS (EI, 70 eV): m/z (%): 144 (41) $[M]^+$, 129 (54), 106 (11), 105 (100), 103 (12); elemental analysis calcd (%) for $C_{11}H_{12}$ (144.21): C 91.61, H 8.39; found: C 91.41, H 8.48; HRMS (EI, 70 eV): m/z: calcd for $C_{11}H_{12}$ $[M]^+$: 144.093004; found: 144.092963.

(*E*)-1-(4-Iodobut-3-enyl)-3-methylbenzene (21): Alkyne **20** (1.14 g, 7.91 mmol) was added at room temperature to a stirred suspension of $Cp_2Zr(H)Cl$ (2.03 g, 7.88 mmol) in CH_2Cl_2 (20 mL). After the suspension had been stirred for 10 min, a clear solution was formed and a solution of iodine (2.07 g, 8.16 mmol) in CH_2Cl_2 (50 mL) was added. Then the mixture was stirred for 15 min and saturated aqueous $NaHSO_3$ (20 mL) was added. The mixture was filtered through Celite and the organic phase was washed with saturated aqueous NaCl (10 mL). The aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (*n*-hexane) afforded alkene **21** as a colorless oil. $R_f = 0.62$ (*n*-hexane); ^1H NMR (400 MHz, C_6D_6): $\delta = 1.87$–1.94 (m, 2H; CH_2CH=CHI), 2.13 (s, 3H; CH_3), 2.28 (t, $J = 7.8$ Hz, 2H; CH_2CH$_2$CH=CHI), 5.64

(dt, $J=1.5$, 14.6 Hz, 1H; CH=C*H*I), 6.29 (dt, $J=7.1$, 14.6 Hz, 2H; C*H*=CHI), 6.74 (s, 1H), 6.76 (d, $J=7.6$ Hz, 1H), 6.89 (d, $J=7.6$ Hz, 1H), 7.08 ppm (t, $J=7.6$ Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6): $\delta=21.3$ (d), 34.7 (u), 37.8 (u), 75.4 (d), 125.5 (d), 126.9 (d,), 128.3 (d), 129.2 (d), 137.7 (u), 140.8 (u), 145.5 ppm (d); IR (neat): $\tilde{\nu}=3415$ (w), 3045 (s), 3016 (s), 2921 (vs), 2854 (s), 1935 (w), 1860 (w, br), 1677 (w), 1606 (s), 1487 (s), 1450 (s), 1378 (w), 1339 (w), 1277 (w), 1238 (m), 1205 (s), 1136 (m), 1092 (m), 1041 (m), 940 (vs), 879 (m), 834 cm^{-1} (w); MS (CI, isobutane): *m*/*z* (%): 329 (5) $[M+57]^+$, 273 (6) $[M+1]^+$, 147 (12), 146 (12), 145 (100), 105 (6); elemental analysis calcd (%) for $C_{11}H_{13}I$ (272.13): C 48.55, H 4.82; found: C 48.69, H 4.84.

(*E*)-*N*′-{(3a′*S*,4′*R*,6a′*R*)-5,5-Dimethyl-4′-[(*E*)-4-*m*-tolylbut-1-enyl]dihydro-1′*H*-spiro([1,3]dioxane-2,2′-pentalene)-5′-(3′*H*,6′*H*,6a′*H*)ylidene}-4-methylbenzenesulfonohydrazide (13) and (*E*)-tributyl(4-*m*-tolylbut-1-enyl)-stannane (25): *n*BuLi (0.48 mL, 1.6 M in hexanes, 0.768 mmol) was added at −78 °C under argon to a solution of iodide **21** (209 mg, 0.768 mmol) in THF (3 mL). After the yellow solution of **24** had been stirred for 3 h, a precooled solution (−78 °C) of CuI (146 mg, 0.768 mmol) and Bu_3P (0.50 mL, 1.997 mmol) in THF (3 mL) was added by a double-ended needle. The solution of **15** was stirred for 10 min, and a precooled solution (−78 °C) of azoalkene **14** (150 mg, 0.384 mmol) in THF (4 mL) was added by a double-ended needle. Then the mixture was stirred for 45 min at −78 °C and Bu_3SnCl (0.30 mL, 1.106 mmol) was added. After the mixture had been stirred for 45 min, H_2O (2 mL) was added and the mixture was left to reach ambient temperature. Then, saturated aqueous NH_4Cl (3 mL) was added and the organic phase was washed with saturated aqueous NH_4Cl (3×5 mL). Subsequently, the combined aqueous phases were extracted with Et_2O (5×10 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (*n*-hexane/Et_2O 1:1) afforded hydrazone **13** (162 mg, 79%) as a colorless solid and a mixture of **25** and Bu_3P. Chromatography (*n*-hexane/EtOAc 20:1) gave stannane **25** (182 mg, 0.418 mmol) as a colorless oil.

Hydrazide ***13***: $[\alpha]_D=-24.4$ ($c=1.03$ in THF); $R_f=0.30$ (*n*-hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, [D$_8$]THF): $\delta=0.88$ (s, 3H; CH_3CCH_3), 0.90 (s, 3H; CH_3CCH_3), 1.55–1.61 (m, 1H), 1.73–1.78 (m, 1H), 2.08–2.61 (m, 10H), 2.29 (s, 3H; CH_3), 2.35 (s, 3H; CH_3), 2.91–2.94 (m, 1H; CHC=N), 3.35 (s, 2H; OCH_2), 3.39 (s, 2H; OCH_2), 5.29–5.44 (m, 2H; HC=CH), 6.94–6.96 (m, 2H), 6.99 (s, 1H), 7.11 (t, $J=7.6$ Hz, 1H), 7.26 (d, $J=8.7$ Hz, 2H), 7.78 (d, $J=8.7$ Hz, 2H), 8.91 ppm (s, 1H; NH); ^{13}C NMR (100 MHz, [D$_8$]THF): $\delta=21.4$ (d), 21.5 (d), 22.5 (d), 22.6 (d), 30.4 (u), 33.6 (u), 35.4 (u), 36.8 (u), 38.7 (u), 39.80 (d), 42.3 (u), 47.1 (d), 53.7 (d), 72.1 (u), 72.6 (u), 110.7 (u), 126.0 (d), 126.9 (d), 128.6 (d), 128.7 (d), 129.4 (d), 129.7 (d), 130.7 (d), 131.1 (d), 138.0 (u), 138.1 (u), 142.5 (u), 143.3 (u), 167.1 ppm (u); IR (KBr): $\tilde{\nu}=3736$ (w), 3675 (m, br), 3447 (vs, br), 3238 (s), 3021 (w), 2952 (s), 2862 (m), 1638 (m), 1601 (m), 1545 (w), 1496 (w), 1463 (w), 1399 (m), 1331 (s), 1292 (m), 1216 (w), 1165 (vs), 1114 (s), 1040 (w), 1015 (w), 988 (w), 962 (w), 911 (m), 882 (w), 813 cm^{-1} (m); MS (EI, 70 eV): *m*/*z* (%): 536 (3) $[M]^+$, 415 (18), 382 (25), 381 (100), 378 (5), 365 (7), 296 (11), 295 (60), 280 (6), 278 (5), 262 (17), 261 (92), 237 (22), 213 (15), 189 (8), 177 (6), 174 (19), 167 (8), 156 (8), 154 (10), 147 (7), 145 (9), 143 (5), 138 (7), 133 (9), 132 (9), 131 (16), 130 (6), 129 (7), 128 (11), 119 (18), 118 (8), 117 (8), 115 (6), 107 (7), 106 (11), 105 (72), 103 (7), 95 (7), 92 (19), 91 (46), 81 (7); elemental analysis calcd (%) for $C_{31}H_{40}N_2O_4S$ (536.27): C 69.37, H 7.51, N 5.22; found: C 69.22, H 7.32, N 5.21.

Stannane ***25***: $R_f=0.52$ (*n*-hexane); ^{1}H NMR (400 MHz, C_6D_6): $\delta=0.79$ (s, 6H; $C(CH_3)_2$), 1.48–1.55 (m, 2H; OH), 1.81–2.18 (m, 5H), 2.19 (s, 3H; Me), 2.22–2.35 (m, 3H), 2.50–2.63 (m, 2H; CH=CHCH$_2$C*H*$_2$), 3.29–3.31 (m, 4H; $C(CH_2O)_2$), 3.47–3.53 (m, 1H; C*H*OH), 5.18 (dd, $J=8.4$, 15.3 Hz, 1H; C*H*=CHCH$_2$), 5.48 (dt, $J=6.7$, 15.3 Hz, 1H; CH=C*H*CH$_2$), 6.90–6.93 (m, 3H), 7.13 ppm (t, $J=7.4$ Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6): $\delta=21.4$ (d), 22.5 (d), 29.9 (u), 34.9 (u), 35.8 (d), 36.2 (u), 38.6 (u), 40.8 (u), 41.2 (u), 44.12 (d), 58.5 (d), 71.8 (u), 71.9 (u), 78.1 (d), 110.4 (u), 125.8 (d), 126.7 (d), 128.3 (d), 129.6 (d), 131.1 (d), 133.0 (d), 137.6 (u), 141.8 ppm (u); IR ($CHCl_3$): $\tilde{\nu}=2924$ (vs), 1600 (w), 1456 (m), 1077 (w), 988 (w), 875 cm^{-1} (w); MS (EI, 70 eV) *m*/*z* (%): 383 (17), 381 (15), 380 (20), 379 (100) $[M-57]^+$, 378 (40), 377 (74), 376 (31), 375 (43), 327 (5), 323 (27), 321 (21), 320 (8), 319 (12), 269 (5), 267 (18), 266 (7), 265 (29), 264 (11), 263 (20), 262 (6), 261 (9), 211 (5), 177 (6), 145 (11), 143 (5), 120 (9), 119 (8), 116 (5), 105 (12); HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{23}H_{40}Sn$: 379.144706 $[M-C_4H_9]^+$; found: 379.144708.

(3a′*S*,4′*R*,6a′*R*)-5,5-Dimethyl-4′-[(*E*)-4-*m*-tolylbut-1-enyl]tetrahydro-1′*H*-spiro([1,3]-dioxane-2,2′-pentalen)-5′(3′*H*)-one (12): $(PhSeO)_2O$ (2.86 mg, 2.79 mmol) was added in portions to a stirred solution of hydrazone **13** (1.43 g, 2.67 mmol) and cyclohexene (2 mL, 19.7 mmol) in THF (10 mL). After the mixture had been stirred for 45 min at room temperature, saturated aqueous $NaHCO_3$ (2 mL) and *n*-pentane (10 mL) were added. The aqueous phase was extracted with Et_2O (3×10 mL). The combined organic phases were dried ($MgSO_4$) and the volatiles were removed in vacuo. The crude ketone **12** was not purified but directly used for the next step.

(3a′*S*,4′*R*,5′*R*,6a′R)-5,5-Dimethyl-4′-[(*E*)-4-*m*-tolylbut-1-enyl]hexahydro-1′*H*-spiro([1,3]-dioxane-2,2′-pentalen)-5′-ol (26): $NaBH_4$ (420 mg, 11.1 mmol) was added in portions at 0 °C to a solution of the crude ketone **12** in EtOH (10 mL). After the mixture had been stirred for 90 min at 0 °C, saturated aqueous NH_4Cl (5 mL), saturated aqueous NaCl (10 mL), and Et_2O (10 mL) were added. The aqueous phase was extracted with Et_2O (3×10 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (*n*-hexane/Et_2O 2:1) afforded alcohol **26** (606 mg, 61% based on hydrazone **13**) as a colorless oil. $[\alpha]_D=+21.5$ ($c=0.99$ in THF); $R_f=0.44$ (*n*-hexane/Et_2O 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.94$ (s, 3H; $C(CH_3)_2$), 0.97 (s, 3H; $C(CH_3)_2$), 1.33–1.46 (m, 1H), 1.73–1.82 (m, 3H; OH), 1.99–2.26 (m, 5H), 2.27–2.46 (m, 3H), 2.32 (s, 3H; CH_3), 2.57–2.74 (m, 2H; CH=CHCH$_2$C*H*$_2$), 3.45 (s, 2H; $C(CH_2O)_2$), 3.47 (s, 2H; $C(CH_2O)_2$), 3.54–3.64 (m, 1H; C*H*OH), 5.20 (dd, $J=8.0$, 15.2 Hz, 1H; C*H*=CHCH$_2$), 5.52 (dt, $J=6.7$, 15.2 Hz, 1H; CH=C*H*CH$_2$), 6.92–7.02 (m, 3H), 7.16 ppm (t, $J=7.4$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=21.4$ (d), 22.5 (d), 22.6 (d), 30.0 (u), 34.4 (u), 35.3 (d), 35.7 (u), 37.8 (u), 40.4 (u), 40.9 (u), 43.8 (d), 58.3 (d), 72.0 (u), 72.0 (u), 77.9 (d), 110.2 (u), 125.6 (d), 126.5 (d), 128.1 (d), 129.3 (d), 131.6 (d), 132.2 (d), 137.7 (u), 141.7 ppm (u); IR (neat): $\tilde{\nu}=3421$ (m, br), 2950 (vs), 2860 (s), 2243 (w), 1608 (m), 1468 (m), 1395 (w), 1327 (m), 1257 (m), 1219 (m), 1177 (w), 1114 (s), 1041 (m), 1015 (m), 968 (m), 908 (m), 875 cm^{-1} (w); MS (EI, 70 eV): *m*/*z* (%): 371 (6), 370 (22) $[M]^+$, 353 (19), 352 (70), 297 (17), 267 (9), 266 (30), 265 (33), 255 (7), 251 (9), 238 (7), 237 (5), 224 (14), 209 (9), 208 (31), 185 (6), 183 (13), 181 (23), 179 (12), 169 (7), 168 (13), 167 (22), 161 (24), 157 (11), 155 (6), 154 (12), 151 (6), 147 (6), 145 (13), 144 (11), 143 (10), 141 (8), 135 (11), 133 (14), 131 (22), 129 (16), 128 (47), 122 (9), 121 (7), 119 (33), 118 (11), 117 (6), 107 (7), 106 26), 105 (100), 96 (5), 94 (13), 93 (6), 91 (19), 83 (10), 82 (6), 81 (11); HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{24}H_{34}O_3$: 370.250795 $[M]^+$; found: 370.250789.

(3a*S*,4*R*,5*R*,6a*R*)-5-Hydroxy-4-[(*E*)-4-*m*-tolylbut-1-enyl]hexahydropentalen-2(1*H*)one (27): TsOH (approximately 5 mg) was added to a solution of alcohol **26** (600 mg, 1.62 mmol) in acetone (5 mL) and water (2 mL). After the mixture had been stirred for 2 d at room temperature, saturated aqueous $NaHCO_3$ (2 mL) and Et_2O (20 mL) were added successively. The aqueous phase was extracted with Et_2O (3×10 mL) and the combined extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (*n*-hexane/Et_2O 1:2) gave ketone **27** (433 mg, 94%) as a colorless oil. $[\alpha]_D=-19.3$ ($c=1.06$ in THF); $R_f=0.41$ (*n*-hexane/Et_2O 1:6); ^{1}H NMR (300 MHz, C_6D_6): $\delta=1.14$–1.26 (m, 1H), 1.58 (s, 1H; OH), 1.73–2.15 (m, 8H), 2.19 (s, 3H; CH_3), 2.24–2.29 (m, 2H; CH=CHCH$_2$C*H*$_2$), 2.53–2.58 (m, 2H; CH=CHC*H*$_2$), 3.50–3.58 (m, 1H; C*H*OH), 5.04 (ddt, $J=1.2$, 8.2, 15.2 Hz, 1H; C*H*=CHCH$_2$), 5.34 (dt, $J=6.7$, 15.2 Hz, 1H; CH=C*H*CH$_2$), 6.89–6.94 (m, 3H), 7.11–7.16 ppm (m, 1H); ^{13}C NMR (75 MHz, C_6D_6): $\delta=21.4$ (d), 34.9 (d), 35.0 (u), 36.1 (u), 41.6 (u), 42.5 (u), 43.1 (d), 45.8 (u), 58.3 (d), 77.1 (d), 126.0 (d), 127.0 (d), 128.5 (d), 129.8 (d), 131.6 (d), 132.0 (d), 137.9 (u), 141.9 (u), 217.7 ppm (u); IR ($CHCl_3$): $\tilde{\nu}=3431$ (s, br), 3100 (w), 3015 (s), 2924 (vs, br), 1732 (vs), 1608 (s), 1488 (w), 1451 (m), 1403 (m), 1334 (w), 1290 (w), 1247 (w), 1165 (m), 1093 (m), 970 (s), 881 cm^{-1} (w); MS (EI, 70 eV): *m*/*z* (%): 284 (11) $[M]^+$, 266 (20), 161 (5), 145 (9), 144 (20), 143 (5), 135 (6), 131 (10), 119 (6), 118 (12), 106 (35), 105 (100), 91 (11); HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{19}H_{24}O_2^+-C_4H_9$: 284.177630; found: 284.177635.

(3a*S*,4*R*,5*R*,6a*R*)-5-(*tert*-Butyldimethylsilyloxy)-4-[(*E*)-4-*m*-tolylbut-1-enyl]hexahydropentalen-2(1*H*)-one (11): Imidazole (210 mg, 3.09 mmol) and *t*BuMe$_2$SiCl (200 mg, 1.33 mmol) were added to a solution of alcohol **27** (115 mg, 0.404 mmol) in DMF (6 mL). The solution was stirred at room temperature for 16 h. Filtration of the mixture through silica gel (*n*-hexane/EtOAc 4:1) afforded silyl ether **11** (150 mg, 93%) as a colorless oil. $[\alpha]_D=-17.1$ ($c=1.03$ in THF); $R_f=0.56$ (*n*-hexane/EtOAc 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.02$ (s, 6H; $SiCH_3$), 0.87 (s, 9H; $SiC(CH_3)_3$), 1.37–1.46 (m, 1H), 2.05–2.21 (m, 4H), 2.24–2.41 (m, 4H), 2.31 (s, 3H; CH_3), 2.49–2.70 (m, 4H), 3.84–3.91 (m, 1H; CHOSi), 5.26 (dd, $J=8.2$, 15.1 Hz, 1H; OCHCHC*H*=CH), 5.49 (dt, $J=6.8$, 15.1 Hz, 1H; OCHCHCH=C*H*), 6.93–7.00 (m, 3H), 7.15 ppm (t, $J=7.7$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-4.7$ (d), 18.0 (u), 21.3 (d), 25.74 (d), 34.5 (u), 35.2 (d), 35.8 (u), 42.2 (u), 42.7 (d), 42.9 (u), 45.9 (u), 57.9 (d), 78.9 (d), 125.2 (d), 126.3 (d), 127.9 (d), 129.0 (d), 131.0 (d), 131.3 (d), 137.5 (u), 141.5 (u), 219.0 ppm (u); IR ($CHCl_3$): $\tilde{\nu}=3461$ (w), 3016 (m), 2930 (vs), 2856 (s), 174 (vs), 1608 (m), 1466 (m), 1404 (m), 1384 (m), 1363 (m), 1252 (s), 1122 (s), 1003 (m), 969 (m), 940 (w), 898 (s), 838 cm^{-1} (s); MS (CI, CH_4): *m*/*z* (%): 399 (7) $[M+1]^+$, 397 (8), 384 (6), 383 (21), 355 (5), 343 (7), 342 (28), 341 (100) $[M-C_4H_9]^+$, 296 (7), 295 (28), 281 (28), 268 (21), 267 (94), 249 (11), 209 (9), 131 (39), 105 (11); HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{25}H_{38}O_2Si$: 341.193684 $[M-C_4H_9]^+$; found: 341.193670.

(*E*)-[(1*S*,2*R*)-2-(2-Phenylpropan-2-yl)cyclohexyl]-2-{(3a*S*,4*R*,5*R*,6a*S*)-5-(*tert*-butyldimethylsilyloxy)-4-[(*E*)-4-*m*-tolylbut-1-enyl]hexahydropentalen-2(1*H*)ylidene} acetate ((*E*)-10): *n*BuLi (4.8 mL, 1.6 M in hexanes, 7.70 mmol) was added at −78 °C to a solution of (1*S*,2*R*)-2-(2-phenylpropan-2-yl)cyclohexyl-2-(dimethoxyphosphoryl) acetate (2.99 g, 8.10 mmol) in THF (7 mL). Subsequently, the mixture was warmed to room temperature and then cooled to −62 °C. The solution of **28** was slowly treated with a precooled (−78 °C) solution of ketone **11** (323 mg, 0.81 mmol) in THF (7 mL). After the mixture had been stirred for 7 d at −62 °C, saturated aqueous NH_4Cl (10 mL) was added at −62 °C. Then the mixture was warmed to ambient temperature and the aqueous phase was extracted with Et_2O (5×15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (*n*-hexane/EtOAc 10:1) afforded a mixture of esters (*E*)-**10** and (*Z*)-**10** (441 mg, 85%) in a ratio of 96:4. Preparative HPLC (Kromasil Si-100, 250 mm×30 mm; *n*-hexane/EtOAc 98:2; 20 mL min^{-1}; UV: 254 nm, RI) gave (*E*)-**10** (410 mg, 79%) and (*Z*)-**10** (10 mg, 2%) as colorless oils.

*Ester (E)-**10***: $[\alpha]_D=+28.6$ ($c=1.00$ in CH_2Cl_2); $R_f=0.86$ (*n*-hexane/EtOAc 4:1); ^{1}H NMR (300 MHz, C_5D_5N): $\delta=0.00$ (s, 3H; $SiCH_3$), 0.01 (s, 3H; $SiCH_3$), 0.85 (s, 9H; $SiC(CH_3)_3$), 0.89–1.26 (m, 5H), 1.13 (s, 3H; $C(CH_3)_2$), 1.31–1.55 (m, 4H), 1.39 (s, 3H; $C(CH_3)_2$), 1.90–2.17 (m, 5H), 2.18 (s, 3H; CH_3), 2.27–2.41 (m, 4H; CH=CHC*H*$_2$), 2.57–2.74 (m, 2H; CH=CHCH$_2$C*H*$_2$), 2.82–2.92 (m, 1H), 2.94–3.03 (m, 1H), 3.71 (q, $J=8.4$ Hz, 1H; CHOSi), 4.88 (dt, $J=4.3$, 10.4 Hz, 1H; CO_2CHCH_2), 5.27–5.35 (m, 2H; CO_2CH=C, OCHCHC*H*=CH), 5.55 (dt, $J=6.6$, 15.3 Hz, 1H; OCHCHCH=C*H*), 6.95–7.03 (m, 3H), 7.09–7.19 (m, 2H), 7.26–7.33 ppm (m, 4H); ^{13}C NMR (75 MHz, C_5D_5N): $\delta=-4.6$ (d), −4.6 (d), 18.1 (u), 21.2 (d), 24.7 (u), 25.6 (d), 25.8 (d), 25.9 (u), 27.2 (u), 27.5 (d), 33.8 (u), 34.8 (u), 36.1 (u), 38.5 (d), 39.5 (u), 39.9 (u), 39.9 (u), 42.6 (u), 44.4 (d), 51.1 (d), 57.2 (d), 73.4 (d), 78.5 (d), 113.8 (d), 125.0 (d), 125.7 (d), 125.8 (d), 126.7 (d), 128.2 (d), 128.4 (d), 129.5 (d), 131.1 (d), 132.5 (d), 137.7 (u), 142.0 (u), 151.65 (u), 165.4 (u), 166.4 ppm (u); IR ($CHCl_3$): $\tilde{\nu}=3017$ (w), 2932 (m), 2857 (m), 1698 (m), 1655 (w), 1605 (w), 1493 (w), 1467 (w), 1369 (w), 1252 (w), 1217 (s), 1125 (m), 1029 (m), 965 (w), 908 (w), 839 cm^{-1} (m); MS (CI, CH_4): *m*/*z* (%): 641 (2) $[M+1]^+$, 584 (5), 583 (9) $[M-C_4H_9]^+$, 439 (5), 426 (6), 425 (19), 423 (5), 385 (8), 384 (29), 383 (100), 365 (8), 337 (8), 310 (14), 309 (76), 292 (7), 291 (34), 201 (24), 145 (5), 131 (22), 119 (29), 105 (22); HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{42}H_{60}O_3Si$ $[M-C_4H_9]^+$: 583.360749; found: 583.360850.

(1*S*,2*R*)-2-(2-Phenylpropan-2-yl)cyclohexyl-2-{(3a*S*,5*R*,6*R*,6a*S*)-5-(*tert*-butyldimethylsilyloxy)-6-[(*E*)-4-*m*-tolylbut-1-enyl]-1,3a,4,5,6,6a-hexahydropentalen-2-yl} acetate (*anti*-9): *n*BuLi (1.2 mL, 1.6 M in hexanes, 1.98 mmol) was added at −78 °C to a suspension of bis[(*R*)-1-phenylethyl]ammonium chloride in THF (12 mL). Then the suspension was left to warm to ambient temperature, which led to the formation of a clear, red solution of **29**. Subsequently, the mixture was cooled to −105 °C and a precooled (−78 °C) solution of ester (*E*)-**10** (318 mg, 0.497 mmol) in THF (6 mL) was slowly added. After 15 min, the solution was warmed to −78 °C and stirred for 1.5 h. After this time, saturated aqueous $NaHCO_3$ (2 mL), saturated aqueous NH_4Cl (8 mL), and Et_2O (10 mL) were added successively. The organic phase was washed with H_2O (3×5 mL) and the aqueous phase was extracted with Et_2O (3×20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (*n*-hexane/EtOAc 7:1) gave a mixture of esters *anti*-**9** and *syn*-**9** (287 mg, 90%) in a ratio of 99:1 as a colorless oil. Preparative HPLC (Chiralpak AD, 250 mm×50 mm; *n*-hexane/isopropanol 99:1; 40 mL min^{-1}; UV: 254 nm, RI) afforded *anti*-**9** (261 mg, 82%) and *syn*-**9** (3 mg, 1%) as colorless oils.

Ester anti-***9***: $[\alpha]_D=-28.6$ ($c=1.04$ in CH_2Cl_2); $R_f=0.86$ (*n*-hexane/EtOAc 4:1); ^{1}H NMR (400 MHz, C_6D_6): $\delta=0.06$ (s, 3H; $SiCH_3$), 0.08 (s, 3H; $SiCH_3$), 0.74–0.84 (m, 1H), 0.91–1.03 (m, 3H), 1.00 (s, 9H; $SiC(CH_3)_3$), 1.07 (s, 3H; $C(CH_3)_2$), 1.15–1.28 (m, 1H), 1.32 (s, 3H; $C(CH_3)_2$), 1.36–1.44 (m, 2H), 1.49–1.53 (m, 1H), 1.94–2.01 (m, 2H), 2.05–2.17 (m, 4H), 2.18 (s, 3H; CH_3), 2.27–2.43 (m, 2H; CH=CHC*H*$_2$), 2.52–2.72 (m, 5H), 2.81–2.88 (m, 1H), 3.58–3.65 (m, 1H; CHOSi), 4.93 (dt, $J=4.4$, 10.6 Hz, 1H; $CO_2CH(CH_2)_2$), 5.31 (dd, $J=7.7$, 15.2 Hz, 1H; OCHCHC*H*=CH), 5.37–5.40 (m, 1H; C*H*=C(CH$_2$)$_2$), 5.58 (dt, $J=6.7$, 15.2 Hz, 1H; OCHCHCH=C*H*), 6.92–6.98 (m, 3H), 7.03–7.07 (m, 1H), 7.12–7.21 ppm (m, 5H); ^{13}C NMR (100 MHz, C_6D_6): $\delta=-4.3$ (d), −4.3 (d), 18.3 (u), 21.4 (d), 24.8 (u), 25.3 (d), 26.1 (d), 26.1 (u), 27.2 (u), 27.9 (d), 33.8 (u), 35.3 (u), 36.4 (u), 37.2 (u), 39.9 (u), 40.1 (u), 40.5 (u), 44.1 (d), 45.7 (d), 51.0 (d), 58.0 (d), 74.4 (d), 77.9 (d), 125.1 (d), 125.6 (d), 125.7 (d), 126.7 (d), 128.3 (d), 129.4 (d), 131.3 (d), 132.4 (d), 132.6 (d), 134.4 (u), 137.6 (u), 142.0 (u), 151.6 (u), 169.5 ppm (u); IR ($CHCl_3$): $\tilde{\nu}=$ 3937 (w), 3916 (w), 3890 (w), 3780 (w), 3725 (w), 3681 (w), 3397 (w), 3019 (w), 2929 (vs), 2856 (s), 2674 (w), 1729 (s), 1605 (w), 1496 (w), 1467 (m), 1446 (m), 1368 (w), 1301 (w), 1251 (s), 1118 (s), 1027 (m), 965 (m), 908 (w), 838 cm^{-1} (s); MS (CI, CH_4): *m*/*z* (%): 641 (7) $[M+1]^+$, 640 (5), 639 (14), 625 (6), 584 (14), 583 (33) $[M-C_4H_9]^+$, 508 (8), 440 (5), 439 (14), 426 (5), 425 (12), 407 (5), 385 (5), 384 (23), 383 (81), 366 (5), 365 (20), 337 (5), 310 (13), 309 (34), 308 (5), 307 (10), 291 (8), 263 (5), 249 (10), 202 (17), 201 (100), 145 (8), 133 (5), 132 (10), 131 (87), 120 (8), 119 (79), 106 (5), 105 (64), 91 (10); HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{42}H_{60}O_3Si$: 583.360749 $[M-C_4H_9]^+$; found: 583.360820.

2-{(3a*S*,5*R*,6*R*,6a*S*)-5-(*tert*-Butyldimethylsilyloxy)-6-[(*E*)-4-*m*-tolylbut-1-enyl]-1,3a,4,5,6,6a-hexahydropentalen-2-yl}ethanol (8): DIBAL-H (1.2 mL, 1.0 M in THF, 1.2 mmol) was slowly added at 0 °C to a stirred solution of ester *anti*-**9** (257 mg, 0.401 mmol) in THF (6 mL). After 30 min, the mixture was left to warm to ambient temperature and stirred for 2 h. Then the mixture was diluted with Et_2O (10 mL) and successively treated with ice (10 mg), saturated aqueous NH_4Cl (3 mL), and saturated aqueous NaCl (10 mL). The aqueous phase was extracted with Et_2O (5× 30 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (*n*-hexane/EtOAc 10:1) gave alcohol **8** (150 mg, 88%) as a colorless oil. $[\alpha]_D=-19.4$ ($c=$ 1.02 in THF); $R_f=0.31$ (*n*-hexane/EtOAc 4:1); ^{1}H NMR (400 MHz, C_6D_6): $\delta=0.08$ (s, 3H; $SiCH_3$), 0.09 (s, 3H; $SiCH_3$), 0.83–0.91 (m, 1H; OH), 1.00 (s, 9H; $SiC(CH_3)_3$), 1.36–1.43 (m, 1H), 2.00–2.17 (m, 6H), 2.16 (s, 3H; CH_3), 2.31–2.42 (m, 3H), 2.59–2.73 (m, 2H; CH=CHCH$_2$C*H*$_2$), 2.82–2.90 (m, 1H), 3.46–3.49 (t, $J=6.6$ Hz, 2H; C*H*$_2$OH), 3.63–3.69 (m, 1H; CHOSi), 5.27–5.28 (m, 1H; C*H*=C(CH$_2$)$_2$), 5.34 (dd, $J=8.0$, 15.3 Hz, 1H; OCHCHC*H*=CH), 5.55 (dt, $J=6.8$, 15.3 Hz, 1H; OCHCHCH=C*H*), 6.92–6.98 (m, 3H), 7.12–7.15 ppm (m, 1H); ^{13}C NMR (100 MHz, C_6D_6): $\delta=-4.3$ (d), −4.3 (d), 18.4 (u), 21.4 (d), 26.1 (d), 34.7 (u), 35.3 (u), 36.5 (u), 40.3 (u), 40.9 (u), 43.8 (d), 45.9 (d), 58.3 (d), 60.8 (u), 78.1 (d), 125.7 (d), 126.7 (d), 128.4 (d), 129.4 (d), 130.3 (d), 131.1 (d), 132.7 (d), 137.6 (u), 138.5 (u), 142.0 ppm (u); IR ($CHCl_3$): $\tilde{\nu}=3357$ (m, br), 3009 (m), 2929 (s), 2875 (s), 1606 (w), 1467 (w), 1382 (w), 1253 (m), 1217 (w), 1115 (m), 1044 (w), 1006 (w), 968 (w), 908 (w), 840 cm^{-1} (m); MS (CI, CH_4): *m*/*z* (%): 427 (15) $[M+1]^+$, 426 (9), 425 (24), 411 (7), 409 (10), 371 (8), 370 (29), 369 (100) $[M-C_4H_9]^+$, 351 (7), 337 (6), 323 (7), 296 (18), 195 (85), 293 (9), 278 (15), 277 (73), 173 (6), 159 (9), 145 (9), 132 (7), 131 (63), 105 (23); HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{27}H_{42}O_2Si$: 369.224984 $[M-C_4H_9]^+$; found: 369.224932.

***tert*-Butyl 2-(2-{(3a*S*,5*R*,6*R*,6a*S*)-5-hydroxy-6-[(*E*)-4-*m*-tolylbut-1-enyl]-1,3a,4,5,6,6a-hexahydropentalen-2-yl}ethoxy)acetate (31)**: Bu_4NHSO_4 (67 mg, 0.12 mmol), $BrCH_2CO_2tBu$ (200 μL, 1.29 mol), and aqueous NaOH (50%, 3 mL) were added successively to a solution of alcohol **8** (96 mg, 0.23 mmol) in CH_2Cl_2. Then the mixture was stirred for 2.5 h at room temperature, and $BrCH_2CO_2tBu$ (200 μL, 1.29 mmol) and aqueous NaOH (50%, 2 mL) were added. After the mixture had been stirred for 12 h, ice (10 g) was added and the aqueous phase was extracted with CH_2Cl_2 (3×25 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in THF (6 mL) and Bu_4NF (1.3 mL, 1.0 M in THF, 1.28 mmol) was added. After the mixture had been stirred for 16 h, Et_2O (20 mL), aqueous NaCl (10 mL), and water (10 mL) were added successively. The aqueous phase was extracted with Et_2O (5×25 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (*n*-hexane/EtOAc 6:1) afforded ester **31** (85 mg, 89%) as a colorless oil. $[\alpha]_D = +4.18$ ($c = 0.98$ in THF); $R_f = 0.21$ (*n*-hexane/EtOAc 4:1); ^{1}H NMR (400 MHz, C_6D_6): $\delta = 1.34$ (s, 9H; $C(CH_3)_3$), 1.34–1.42 (m, 2H; OH), 1.90–1.97 (m, 1H; C*H*CH=CHCH$_2$), 2.08–2.20 (m, 3H), 2.19 (s, 3H; CH_3), 2.26–2.36 (m, 4H; CH=CC*H*$_2$CH$_2$O, CH=CHC*H*$_2$), 2.40–2.47 (m, 1H), 2.52–2.64 (m, 2H; CH=CHCH$_2$C*H*$_2$), 2.83–2.90 (m, 1H), 3.50–3.53 (m, 1H; C*H*OH), 3.55 (t, $J = 6.7$ Hz, 2H; CH=CCH$_2$C*H*$_2$O), 3.82 (s, 2H; OCH_2CO_2), 5.19 (dd, $J = 8.5$, 15.1 Hz, 1H; OCHCHC*H*=CH), 5.33 (d, $J = 1.4$ Hz, 1H; C*H*=C(CH$_2$)$_2$), 5.48 (dt, $J = 6.7$, 15.1 Hz, 1H; OCHCHCH=C*H*), 6.91–6.94 (m, 3H), 7.12–7.16 ppm (m, 1H); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 21.4$ (d), 28.0 (d), 31.8 (u), 35.0 (u), 36.2 (u), 39.8 (u), 40.4 (u), 44.6 (d), 46.1 (d), 58.9 (d), 68.8 (u), 70.1 (u), 77.3 (d), 80.5 (u), 125.8 (d), 126.7 (d), 128.3 (d), 129.6 (d), 129.9 (d), 131.4 (d), 132.7 (d), 137.6 (u), 138.5 (u), 141.8 (u), 169.3 ppm (u); IR ($CHCl_3$): $\tilde{\nu} = 3394$ (m, br), 2925 (vs), 1747 (s), 1667 (w), 1608 (w), 1455 (m), 1393 (w), 1369 (m), 1305 (w), 1229 (m), 1132 (s), 1070 (m), 968 (w), 844 cm^{-1} (w); MS (CI, CH_4): *m*/*z* (%): 427 (2) $[M+1]^+$, 426 (2) $[M]^+$, 381 (6), 371 (8), 370 (7), 369 (15), 354 (24), 353 (100), 352 (18), 351 (9), 305 (6), 295 (6), 294 (6), 293 (12), 278 (18), 277 (83), 276 (7), 159 (6), 145 (9), 132 (5), 131 (48), 105 (6); HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{27}H_{38}O_4$: 352.203845 $[M-C_4H_{10}O]^+$; found: 352.203859.

2-(2-{(3a*S*,5*R*,6*R*,6a*S*)-5-Hydroxy-6-[(*E*)-4-*m*-tolylbut-1-enyl]-1,3a,4,5,6,6a-hexahydropentalen-2-yl}ethoxy)acetic acid (7b): Aqueous NaOH (1 N, 1 mL) was added to a stirred solution of ester **31** (57 mg, 0.134 mmol) in MeOH (2.5 mL). After the mixture had been stirred for 7 h at room temperature, water (3 mL) and saturated aqueous NH_4Cl (3 mL) were successively added. The pH value was adjusted to 4 by addition of NaH_2PO_4 and the solution was extracted with Et_2O (3×20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Removal of residual solvent and *t*BuOH in vacuo (10^{-6} mbar) gave acid **7b** (48 mg, 98%) as a colorless oil. $[\alpha]_D = +4.18$ ($c = 0.98$ in THF); ^{1}H NMR (400 MHz, C_6D_6): $\delta = 1.35$ (br, 1H; OH), 1.40–1.47 (m, 1H), 2.00–2.08 (m, 1H; C*H*CH=CHCH$_2$), 2.12–2.26 (m, 5H), 2.20 (s, 3H; CH_3), 2.28–2.40 (m, 3H), 2.56–2.68 (m, 2H; CH=CHCH$_2$C*H*$_2$), 2.84–2.90 (m, 1H), 3.34–3.43 (m, 2H; CH=CCH$_2$C*H*$_2$O), 3.61 (dt, $J = 6.9$, 8.8 Hz, 1H; C*H*OH), 3.82 (s, 2H; OCH_2CO_2), 5.22 (dd, $J = 8.2$, 15.3 Hz, 1H; OCHCHC*H*=CH), 5.27–5.30 (m, 1H; C*H*=C(CH$_2$)$_2$), 5.54 (dt, $J = 6.7$, 15.3 Hz, 1H; OCHCHCH=C*H*), 6.56 (br, 1H; CO_2H), 6.93–6.97 (m, 3H), 7.14–7.18 ppm (m, 1H); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 21.4$ (d), 31.4 (u), 35.0 (u), 36.2 (u), 39.5 (u), 40.4 (u), 44.6 (d), 46.3 (d), 58.6 (d), 67.8 (u), 70.0 (u), 77.7 (d), 125.8 (d), 126.7 (d), 128.3 (d), 129.6 (d), 130.2 (d), 131.5 (d), 132.5 (d), 137.7 (u), 138.4 (u), 141.9 (u), 173.9 ppm (u); IR ($CHCl_3$): $\tilde{\nu} = 3392$ (m, br), 2924 (vs), 1729 (s), 1609 (m), 1455 (m), 1375 (w), 1218 (w), 1132 (m), 969 (w), 883 cm^{-1} (w). MS (CI, CH_4): *m*/*z* (%): 385 (2) $[M+15]^+$, 370 (4) $[M]^+$, 369 (11), 355 (6), 354 (19), 353 (77), 352 (17), 351 (8), 345 (14), 327 (7), 309 (17), 307 (10), 305 (5), 295 (17), 294 (6), 293 (18), 291 (9), 279 (19), 278 (24), 277 (100), 276 (6), 275 (10), 185 (6), 173 (6), 171 (6), 159 (11), 157 (5), 145 (22), 133 (8), 132 (8), 131 (71), 121 (5), 105 (17); HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{23}H_{30}O_4$: 352.203845 $[M-H_2O]^+$; found: 352.203947.

2-{(3a*S*,5*R*,6*R*,6a*S*)-5-(*tert*-Butyldimethylsilyloxy)-6-[(*E*)-4-*m*-tolylbut-1-enyl]-1,3a,4,5,6,6a-hexahydropentalen-2-yl}ethyl 4-methylbenzenesulfonate (32): TsCl (34 mg, 0.18 mmol) was added to a stirred solution of alcohol **8** (76 mg, 0.18 mmol), NEt_3 (0.04 mL, 0.27 mmol), and DABCO (6.0 mg, 0.05 mmol) in CH_2Cl_2 (2 mL). After the mixture had been stirred for 1.5 h, additional NEt_3 (0.04 mL, 0.27 mmol) and TsCl (20 mg, 0.11 mmol) were added and stirring was continued for 12 h. Then water (5 mL) was added and the organic phase was washed successively with 1 M HCl (2×3 mL) and water (3 mL). The combined aqueous phases were extracted with Et_2O (3×15 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (*n*-hexane/EtOAc 9:1) afforded tosylate **32** (92 mg, 90%) as a colorless oil. $[\alpha]_D = -9.35$ ($c = 0.97$ in THF); $R_f = 0.57$ (*n*-hexane/EtOAc 4:1); ^{1}H NMR (400 MHz, C_6D_6): $\delta = 0.07$ (s, 3H; $SiCH_3$), 0.08 (s, 3H; $SiCH_3$), 1.00 (s, 9H; $SiC(CH_3)_3$), 1.25–1.32 (m, 1H), 1.84 (s, 3H; CH_3), 1.92–2.22 (m, 7H), 2.17 (s, 3H; CH_3), 2.31–2.41 (m, 2H; CH=CHC*H*$_2$), 2.59–2.77 (m, 3H), 3.59 (dt, $J = 6.9$, 9.3 Hz, 1H; CHOSi), 3.99 (t, $J = 6.6$ Hz, 2H; CH_2OSO_2), 5.10–5.11 (m, 1H; C*H*=C(CH$_2$)$_2$), 5.29 (dd, $J = 7.9$, 15.3 Hz, 1H; OCHCHC*H*=CH), 5.52 (dt, $J = 6.5$, 15.3 Hz, 1H; OCHCHCH=C*H*), 6.71 (d, $J = 8.2$ Hz, 2H), 6.92–6.98 (m, 3H), 7.12–7.16 (m, 1H), 7.77 ppm (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (100 MHz, C_6D_6): $\delta = -4.30$ (d), −4.35 (d), 18.3 (u), 21.1 (d), 21.4 (d), 26.1 (d), 30.6 (u), 35.3 (u), 36.4 (u), 40.1 (u), 40.6 (u), 43.6 (d), 45.7 (d), 58.1 (d), 68.3 (u), 77.9 (d), 125.7 (d), 126.7 (d), 128.1 (d), 128.4 (d), 129.4 (d), 129.6 (d), 130.8 (d), 131.1 (d), 132.5 (d), 134.6 (u), 136.2 (u), 137.8 (u), 142.0 (u), 144.1 ppm (u); IR ($CHCl_3$): $\tilde{\nu} = 3378$ (w, br), 2928 (vs), 2856 (s), 1601 (w), 1464 (m), 1364 (s), 1253 (m), 1179 (s), 1112 (s), 968 (s), 908 (m), 837 cm^{-1} (s); MS (CI, CH_4): *m*/*z* (%): 581 (7) $[M+1]^+$, 580 (7) $[M]^+$, 579 (8), 565 (7), 523 (13), 451 (6), 450 (17), 449 (56), 410 (9), 409 (28), 407 (6), 393 (8), 351 (10), 305 (8), 279 (7), 278 (22), 277 (100), 173 (5), 159 (8), 145 (10), 131 (33); HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{34}H_{48}O_4SSi$: 523.233836 $[M-C_4H_9]^+$; found: 523.233846.

2-(3-Iodopropoxy)tetrahydro-2*H*-pyran (35a): A small amount of pyridinium *p*-toluenesulfonate was added to a stirred solution of 3-iodopropanol (10.0 g, 53.7 mmol) and 3,4-dihydro-2*H*-pyran (5.2 mL, 56.5 mmol) in CH_2Cl_2 (80 mL). After the mixture had been stirred for 12 h at room temperature, saturated aqueous NaCl (30 mL) was added. The aqueous phase was extracted with Et_2O (3×30 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (*n*-hexane/EtOAc 10:1) gave iodide **35a** (13.5 g, 93%) as a colorless oil. R_f 0.30 (*n*-hexane/EtOAc 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.50$–1.84 (m, 6H), 2.06–2.12 (m, 2H; C*H*$_2$CH$_2$I), 3.27–3.32 (m, 2H; CH_2I), 3.42–3.47 (m, 1H), 3.49–3.55 (m, 1H), 3.78–3.83 (m, 1H), 3.84–3.89 (m, 1H), 4.59–4.61 ppm (m, 1H; CHO_2); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 3.4$ (u), 19.4 (u), 25.4 (u), 30.5 (u), 33.5 (u), 62.1 (u), 66.7 (u), 98.7 ppm (d); IR (neat): $\tilde{\nu} = 3852$ (w), 3747 (w), 3672 (w), 3648 (w), 3625 (w), 3466 (w), 2940 (vs), 2868 (s), 2361 (m), 2335 (m), 1651 (w), 1559 (w), 1540 (w), 1506 (w), 1438 (m), 1383 (m), 1322 (w), 1279 (w), 1183 (m), 1132 (s), 1075 (s), 1031 (vs), 980 (m), 906 (w), 870 (m), 814 cm^{-1} (w); MS (CI, CH_4): *m*/*z* (%): 271 (0.6) $[M+1]^+$, 270 (4) $[M]^+$, 268 (6), 168 (5), 142 (9), 86 (5), 85 (100); elemental analysis calcd (%) for $C_8H_{15}IO_2$ (270.11): C 35.57, H 5.60; found: C 35.64, H 5.62.

***tert*-Butyldimethyl{(2*R*,3*R*,3a*S*,6a*S*)-5-[5-(tetrahydro-2*H*-pyran-2-yloxy)-pentyl]-3-[(*E*)-4-*m*-tolylbut-1-enyl]-1,2,3,3a,4,6a-hexahydropentalen-2-yloxy}silane (36)**: *t*BuLi (0.11 mL, 1.60 M in hexanes, 0.18 mmol) was added at −78 °C to a solution of iodide **35a** (24 mg, 0.09 mmol) in *n*-pentane/Et_2O (1 mL, 3:2). After the resulting turbid solution of **35b** had been stirred for 5 min at −78 °C, a cold (−78 °C) solution of CuI (17 mg, 0.09 mmol) and Bu_3P (0.06 mL, 0.24 mmol) in Et_2O (1 mL) was added by a syringe. Subsequently, the mixture was warmed to −40 °C to form a clear yellow solution of **35c**. Then a cold (−40 °C) solution of tosylate **32** (13 mg, 0.02 mmol) in Et_2O (1 mL) was added. The solution was left to warm to 0 °C within 2 h, and then saturated aqueous NH_4Cl (1 mL) was added. Subsequently, the organic phase was washed with water (2 mL) and the combined aqueous phases were extracted with Et_2O (5×3 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Preparative HPLC (Kromasil Si-100, 250 mm×30 mm; *n*-hexane/EtOAc, 96:4; UV: 254 nm, RI) gave acetal **36** (10 mg, 82%) as a colorless oil. $[\alpha]_D = -11.93$ ($c = 1.10$ in THF); $R_f = 0.65$ (*n*-hexane/EtOAc 6:1); ^{1}H NMR (400 MHz, C_6D_6): $\delta = 0.09$ (s, 3H; $SiCH_3$), 0.10 (s, 3H; $SiCH_3$), 1.02 (s, 9H; $SiC(CH_3)_3$), 1.24–1.50 (m, 9H), 1.57–1.67 (m, 4H), 1.74–1.85 (m, 1H), 2.00–2.24 (m, 5H), 2.17 (s, 3H; CH_3), 2.30–2.47 (m, 3H), 2.61–2.74 (m, 2H; CH=CHCH$_2$C*H*$_2$), 2.89–2.95 (m, 1H), 3.32–3.38

(m, 1H), 3.40–3.45 (m, 1H), 3.68 (dt, $J=7.1$, 9.3 Hz, 1H; CHOSi), 3.81–3.88 (m, 2H), 4.61 (t, $J=3.4$ Hz, 1H; OCHO), 5.29–5.30 (m, 1H; CHC*H*=C(CH$_2$)$_2$), 5.37 (dd, $J=7.9$, 15.1 Hz, 1H; OCHCHC*H*=CH), 5.59 (dt, $J=6.6$, 15.1 Hz, 1H; OCHCHCH=C*H*), 6.92–6.99 (m, 3H), 7.12–7.16 ppm (m, 1H); ^{13}C NMR (100 MHz, C_6D_6): $\delta=-4.3$ (d), −4.2 (d), 18.4 (u), 19.7 (u), 21.4 (d,), 26.0 (u), 26.1 (d), 26.7 (u), 28.0 (u), 30.1 (u), 31.1 (u), 31.4 (u), 35.3 (u), 36.5 (u), 40.2 (u), 41.1 (u), 43.9 (d), 45.7 (d), 58.3 (d), 61.5 (u), 67.4 (u), 78.1 (d), 98.4 (d), 125.7 (d), 126.7 (d), 128.2 (d), 128.4 (d), 129.4 (d), 131.1 (d), 132.8 (d), 137.6 (u), 141.8 (u), 142.05 ppm (u); IR ($CHCl_3$): $\tilde{\nu}=3025$ (w), 2931 (vs), 2858 (s), 2361 (w), 2335 (w), 1609 (w), 1461 (m), 1358 (w), 1253 (m), 1200 (w), 1119 (s), 1078 (w), 1030 (m), 970 (w), 907 (w), 840 cm^{-1} (m); MS (EI, 70 eV): *m*/*z* (%): 552 (2) [M^+], 496 (17), 495 (48), 420 (5), 411 (15), 403 (15), 319 (16), 158 (13), 157 (5), 145 (20), 131 (26), 119 (6), 105 (37), 91 (8), 86 (5), 85 (100); HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{35}H_{56}O_3Si$: 495.329449 [$M-C_4H_9$]$^+$; found: 495.329473.

5-{(3a*S*,5*R*,6*R*,6a*S*)-5-(*tert*-Butyldimethylsilyloxy)-6-[(*E*)-4-*m*-tolylbut-1-enyl]-1,3a,4,5,6,6a-hexahydropentalen-2-yl}pentan-1-ol (37): 1,2-Dibromoethane (0.08 mL, 0.93 mmol) was added to a stirred suspension of Mg (25 mg, 1.03 mmol) in Et_2O (1.5 mL). After a brief heating of the mixture at reflux, it was stirred at room temperature until all of Mg was consumed (2 h). A solution of acetal **36** (10 mg, 0.018 mmol) in Et_2O (1 mL) was added to the thus-formed solution of $MgBr_2$, followed by the addition of saturated aqueous NH_4Cl (2 μL). After the mixture had been stirred for 1.5 h, it was cooled to 0 °C and saturated aqueous NH_4Cl (1 mL) was added. The organic phase was washed with water (3×2 mL) and the combined aqueous phases were extracted with Et_2O (5×3 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Preparative HPLC (Chiralpak AD, 250 mm×50 mm, 30 mL min^{-1}, 50 mm; *n*-hexane/*i*PrOH 97:3; UV: 254 nm, RI) gave alcohol **37** (5.4 mg, 64%) as a colorless oil. $[\alpha]_D=-15.36$ ($c=1.10$ in THF); $R_f=0.16$ (*n*-hexane/EtOAc 6:1); ^{1}H NMR (400 MHz, C_6D_6): $\delta=0.09$ (s, 3H; SiCH$_3$), 0.11 (s, 3H; SiCH$_3$), 0.53 (t, $J=5.2$ Hz, 1H; OH), 0.86 (s, 9H; SiC(CH$_3$)$_3$), 1.21–1.28 (m, 2H), 1.33–1.50 (m, 5H), 1.97–2.01 (m, 2H; CH=CC*H*$_2$), 2.08–2.25 (m, 4H), 2.17 (s, 3H; CH$_3$), 2.33–2.47 (m, 3H), 2.61–2.74 (m, 2H; CH=CHCH$_2$C*H*$_2$), 2.89–2.96 (m, 1H), 3.31–3.35 (m, 2H; CH$_2$O), 3.69 (dt, $J=7.1$, 9.3 Hz, 1H; CHOSi), 5.30–5.31 (m, H; C*H*=C(CH$_2$)$_2$), 5.38 (dd, $J=7.8$, 15.2 Hz, 1H; OCHCHC*H*=CH), 5.60 (dt, $J=6.6$, 15.2 Hz, 1H; OCHCHCH=C*H*), 6.92–6.99 (m, 3H), 7.12–7.16 ppm (m, 1H); ^{13}C NMR (100 MHz, C_6D_6): $\delta=-4.2$ (d), −4.3 (d), 18.4 (u), 21.4 (d), 26.0 (u), 26.1 (d), 27.9 (u), 31.4 (u), 33.0 (u), 35.3 (u), 36.5 (u), 40.2 (u), 41.1 (u), 43.9 (d), 45.7 (d), 58.3 (d), 62.5 (u), 78.1 (d), 125.7 (d), 126.7 (d), 128.3 (d), 128.4 (d), 129.4 (d), 131.1 (d), 132.8 (d), 137.6 (u), 141.8 (u), 142.0 ppm (u); IR ($CHCl_3$): $\tilde{\nu}=3350$ (w), 2927 (vs), 2857 (s), 1728 (w), 1605 (w), 1461 (m), 1377 (w), 1254 (m), 1217 (w), 1115 (m), 966 (w), 909 (w), 839 cm^{-1} (m); MS (EI, 70 eV): *m*/*z* (%): 413 (9), 412 (33), 411 (100) [$M-C_4H_9$]$^+$, 367 (5), 363 (9), 336 (5), 320 (5), 319 (19), 314 (5), 249 (5), 231 (8), 208 (6), 205 (7), 201 (9), 185 (8), 182 (8), 175 (7), 173 (6), 171 (12), 168 (5), 159 (12), 157 (14), 154 (8), 147 (10), 146 (6), 145 (45), 143 (13), 135 (11), 133 (11), 132 (10), 131 (84), 129 (8), 125 (6), 12 (5), 121 (6), 119 (21), 117 (13), 111 (8), 108 (8), 107 (7), 106 (11), 105 (98), 97 (10), 95 (14), 93 (12), 91 (24), 85 (25), 81 (12); HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{30}H_{48}O_2Si$: 411.271934 [$M-C_4H_9$]$^+$; found: 411.271953.

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